Synthesis of new fused heterocyclic systems

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Publication Date:
2010

DOI:
https://doi.org/10.26190/unsworks/23565

SYNTHESIS OF NEW FUSED HETEROCYCLIC SYSTEMS

This thesis is submitted in fulfilment of the degree of

Doctor of Philosophy

By

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Sydney, Australia

August, 2010

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The primary aim of this project was to synthesize novel 4,6-dihydroxyindoles and 5,7-dihydroxyquinolin-2-ones and to study their reactivity. 4,6-Dibenzyloxyindoles were synthesised from 3,5-dibenzyloxyaniline. The synthesis of 3,5-dibenzyloxyaniline was initially attempted using a modified Curtius reaction. However, this method was not efficient due to the requirement of multiple steps and a low yield in the penultimate step. To overcome this, an alternative synthesis starting from phloroglucinol was optimised which gave 3,5-dibenzyloxyaniline in four steps in 84% overall yield.

By employing 3,5-dibenzyloxyaniline, a variety of indoles were prepared using methods such as the Bischler, modified Bischler and Hemetsberger indole syntheses. A one-pot reaction for the synthesis of 2-substituted indoles, 2,3-disubstituted indoles and 3-substituted indoles was investigated. The reactivity studies on 4,6-dibenzyloxyindoles included formylation, bromination, the Mannich reaction, the synthesis of indolylmethanes and biindolyls. Using 4,6-dihydroxyindoles a new class of heterocyclic pyrano[2,3-*g*]indoles was prepared *via* the von Pechmann reaction in 60-73% yield. Pyrano[2,3-*f*]indoles were also prepared from 5-aminoresorcinol employing the Bischler indole synthesis in 62-65% yield. Selected pyranoindoles were tested and found to have anti-cancer and anti-fungal activity in the *in vitro* assays.

The secondary aim of the project was to construct fused heterocyclic systems derived from 4,6-dihydroxyindoles and 5,7-dihydroxyquinolin-2-ones. Furoindoles were synthesised using two different methods. In the first method, the hydroxy group of 4,6-dihydroxyindole at C4 was reacted with α-haloketones to give acyl intermediates which were readily cyclised at C5 by trifluoroacetic acid to give furoindoles in 72-83% yield. In the second method 4-hydroxy-2,3-diphenylindole was used to make a variety of substituted furoindoles in 73-78% yield following a similar method.

Dihydropyranoindoles were prepared in four steps with average yield of 71-77% using a modification of the Hemetsberger indole synthesis. These reactions generated four different kinds of novel dihydropyranoindoles.

5,7-Dihydroxyquinolin-2-ones were synthesised from phloroglucinol in good 73-76% yield over two steps. 5,7-Dihydroxyquinolin-2-ones were reacted further with α-haloketones followed by cyclization in trifluoroacetic acid to give difuroquinolones in 58-86% yield.

Mannich adducts were obtained in 65-67% yield through the reaction of 5,7-dihydroxyquinolin-2-ones with bis(dimethylamino)methane, whereas oxazinoquinolones were obtained in 63-73% yield when 5,7-dihydroxyquinolin-2-ones were reacted with benzylamine and formaldehyde.

Pyrroloquinolines were prepared in a one-step method using indole-7-carbaldehyde and acrylonitrile. This is demonstrated to be a facile method to generate pyrroloquinolines in 70-84% yield.

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ABSTRACT

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ACKNOWLEDGEMENTS

This is by far the most important part of my thesis. I consider myself to be very privileged to have had this opportunity to work with wonderful people. It is with great gratitude that I write these acknowledgements to illustrate my appreciation to some of the most important people in my life.

First of all, I wish to express my heartfelt gratitude to my supervisor, A/Prof Naresh Kumar for allowing me the freedom to pursue and materialize my research ideas and providing consistent encouragement and support. I thank him for his patience, guidance and for the enormous amount of time he spent helping me. The knowledge he has shared will certainly be something I carry with me throughout my career. I could not have imagined having a better advisor than him.

I am exceptionally grateful to Prof. David Black for very friendly discussions, ideas and motivation throughout this project.

I am thankful to all the academic staff of the School of Chemistry for constructive comments, good advice and encouragement. I would like to thank Dr Mohan Bhadbade and Dr. Jim Hook for their helpful discussions with structure elucidation.

I want to express my deepest thanks to all the technical staff at UNSW specially to Adelle Moore and Don Thomas for all their cheerfulness and willingness to help with NMR spectroscopy and Mohan Bhadbade and Don Craig for the X-ray crystal structures. I would like to thank A/Prof. Gary Willett for help in sending samples for mass spectrometry and to Marianne Dick and Ian Stewart at the University of Otago, microanalysis determinations and HRMS analysis, Ms Sally Duck at the Monash University for HRMS analysis. I thank to Dr John Stride for help with scholarship process, Dr Sharifi for technical help, Dr. Ron Haines and Ray Arnold for help with computers, and Ken McGuffin, Anne Ayres and Jodee Anning for help with the

administrative matters, Joseph Antoon for purchasing help and Barry Ward for helping in setting hydrogenation reactions.

I feel fortunate to have worked at UNSW and what made the time at the university so rewarding was the wonderful people I had a chance to work with. Most warmly I will remember Mandar, Wade, Alam, Wai, Frank, Santosh, Samuel, Murat, Ibrahim, Hakan, Ani, Ren, Rick, Shabri, Able, George, Nidup, Fenty, Ruth, Kitty, Rui, Adeline and Miga. This is a wonderful group of people, and I have benefited so much from all of our time together. Thanks to all, for your company and friendship, and for making my postgraduate time at UNSW pleasing and unforgettable. I would like to thank Ika, Muthukumar and Sarovar for their friendship.

I cannot forget the time I spent at the Department of Natural products, National Institute of Pharmaceutical Education and Research (NIPER), India. During this time, I was guided by some of the most inspiring people. These are the people who helped me fall in love with chemistry. I am exceptionally grateful to the academic staff at NIPER and would especially thank Prof. K. K. Bhutani, and Prof. U.C. Banerjee for making the subject interesting and enjoyable.

I thank to my previous supervisors in the pharmaceutical industry, Dr. Kamlesh Padiya for sharing his knowledge of organic synthesis and NMR spectroscopy, and Dr. T Mukhopadhay, H. Sivaramakrishnan, Dr. Rosalind Marita for encouragement. I also thank my teachers, Prof. Vasaikar, Prof. A.C. Chakraborty, Prof. Kulkarni for making science most interesting. I would like to thank Amit Kudale, Sanju Narayan and Deepak Dash for their guidance for PhD admission.

I owe a large debt of gratitude to my parents and my parents-in-laws for their love, support, encouragement, patience and blessings. I give special thanks to Mr Naeem

Shaikh for being a source of inspiration and blessings. I also thank to Vijayraj More, Majid, Sagar and Nafees for their financial help.

I would like to specially thank to Peter, Alam, Mandar, Sabri, Ani and Daniel for proof reading this thesis.

I cannot find words to express my thanks and love to Lubna, my best friend and wife, and my loving son Areesh for all the love and support they have given me. I could not have finished this work without support from them.

The UIPA scholarship from the Australian Government and UNSW during the three and half years is greatly acknowledged.

THANK YOU, to those who have helped with this thesis.

Finally, I dedicate this thesis to my parents.

Presentations and publications

A part of this research has been presented at the following conferences as well as submitted for publication

1. Taj Khan, David StC. Black, Naresh Kumar, Synthesis of Dihydroxyindoles, The Southern Highlands Conference on Heterocyclic Chemistry, Aug **2008**. (Poster presentation)
2. Taj Khan, David StC. Black, Naresh Kumar, Synthesis of Fused Heterocyclic Systems. RACI Natural Products Group Annual One-day Symposium, New Castle University, NSW, Sept **2009**. (Oral presentation)
3. Taj Khan, David StC, Black, Naresh Kumar, Pyranoindole compounds and uses thereof. Australian Provision Patent Application 2009553220, Nov **2009**.
4. Taj Khan, David StC. Black, Naresh Kumar, Synthesis of 4,6-Dihydroxyindoles and Some Fused Heterocycles, Singapore International Chemical Conference-6, Singapore, Dec **2009**. (Poster presentation)

Table of Contents

ABBREVIATIONS

Abs.	absolute
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
AcONa	sodium acetate
a.m.u.	atomic mass unit
Ar	aryl
$BF_3 \cdot OEt_2$	boron trifluoride-diethyl etherate
b.p.	boiling point
conc.	concentrated
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
EI	electron impact
ER	estrogen receptor
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOH	ethanol
h	hour(s)
HCl	hydrochloric acid
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
lit.	literature
M	molar
MALDI	matrix assisted laser desorption ionization
Me	methyl
MeI	methyl iodide
MeO	methoxy
min	minute

mL	milliliter(s)
mmol	milli mol
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser enhancement spectroscopy
$Pd(PPh_3)_4$	tetrakis(triphenylphosphene)palladium(0)
$PdCl_2$(dppf)	dichloro[1,1'-bis(diphenylphosphene)ferrocene]palladium(II)
$PdCl_2(PPh_3)_2$	*trans*-dichlorobis(triphenylphosphene)palladium(II)
PG	protecting group
Ph	phenyl
PPE	polyphosphoric acid ethyl ester
PPh_3	triphenylphosphene
p-TSA	*p*-toluenesulfonic acid
r.t.	room temperature
TBAH	tetrabutylammonium hydroxide
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCl	trimethylsilyl chloride
Ts	*p*-toluenesulfonyl
TsCl	*p*-toluenesulfonyl chloride
UV	ultraviolet spectroscopy

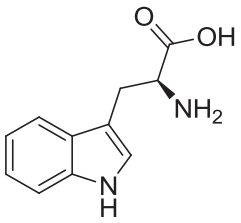
CHAPTER 1

INTRODUCTION

1.1 General introduction:

1.1.1 Indoles and hydroxyindoles:

Indole containing heterocyclic compounds are prevalent in nature, often derived from the essential amino acid tryptophan **1**, and include the neurotransmitter serotonin **2** and the potent anti-cancer compounds vincristine **3** and vinblastine **4**.[1]



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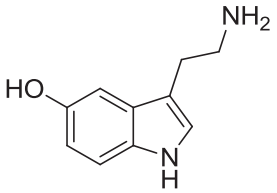

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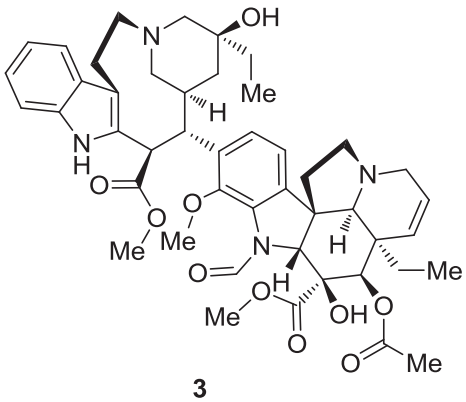

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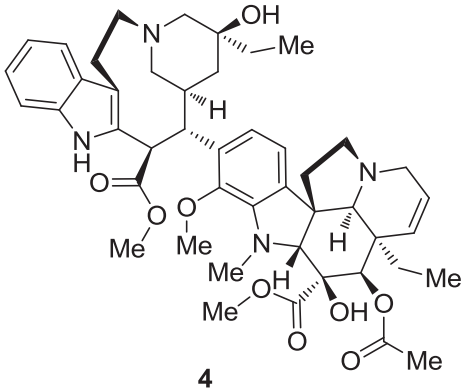

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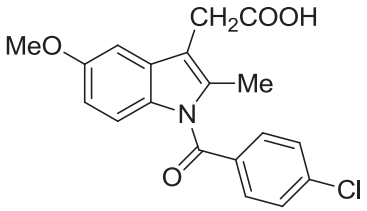
A well known example of a synthetic compound containing an indole skeleton is indomethacin **5**, a potent anti-inflammatory compound.[2]



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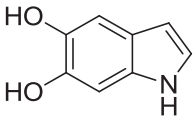
Indoles also occupy an important place in biological chemistry. Regardless of the deep scrutiny that indoles have undergone over the past 100 years, new chemistry of this fascinating heterocycle continues to be revealed.

The generation of 5,6-dihydroxyindole **6**, a precursor of the pigment melanin, has a physiological significance and possibly plays an important role in photoprotection. The indolic melanin precursors have been shown to possess redox properties that could modify some important processes such as the attack of radicals on biomolecules. For example, 5,6-dihydroxyindole **6** and 5,6-dihydroxyindole-2-carboxylic acid **7**, have been shown to inhibit lipid peroxidation and are good scavengers for the peroxynitrite and hydroxyl radicals generated by the Fenton reaction. The Fenton reaction is the iron-salt-dependent decomposition of hydrogen peroxide, generating the highly reactive hydroxyl radical, possibly *via* an oxoiron(IV) intermediate. Addition of a reducing agent, such as ascorbate, leads to a cycle which increases the damage to biological molecules.[3]



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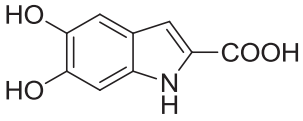

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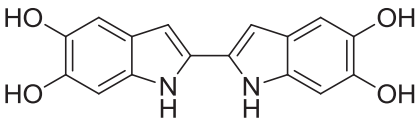
5,6-Dihydroxyindoles are naturally occurring, catechol-containing heterocyclic compounds, which provide the fundamental monomer precursors of eumelanins, the characteristic black insoluble biopolymers found in human skin, hair and eyes.[4]

Chemical or enzymatic oxidation converts the parent 5,6-dihydroxyindole **6** into a black insoluble material virtually indistinguishable from natural pigments. This polymerization reaction proceeds through oligomer intermediates that can be populated at the dimer level by up to four main biindolyls **8**-**11**.[5] In recognition of the importance of eumelanin like polymers, 5,6-dihydroxyindole derived dimers are synthetic targets for new prototypes of bioinspired functional materials. Moreover, 2,2`-biindolyls are of current interest as structural motifs for the preparation of anion sensing architectures.[6] 5,6-Dihydroxyindole based oligomers have recently also been shown to exhibit fluoride-sensing properties.[7]



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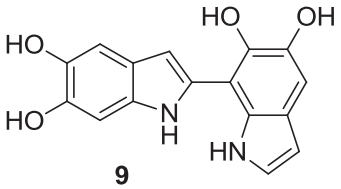

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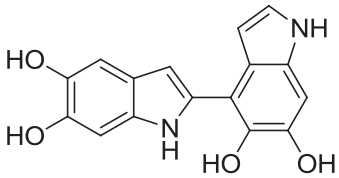

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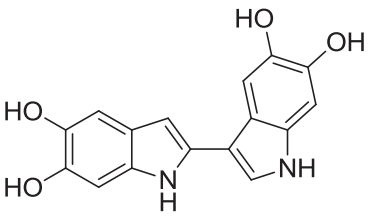

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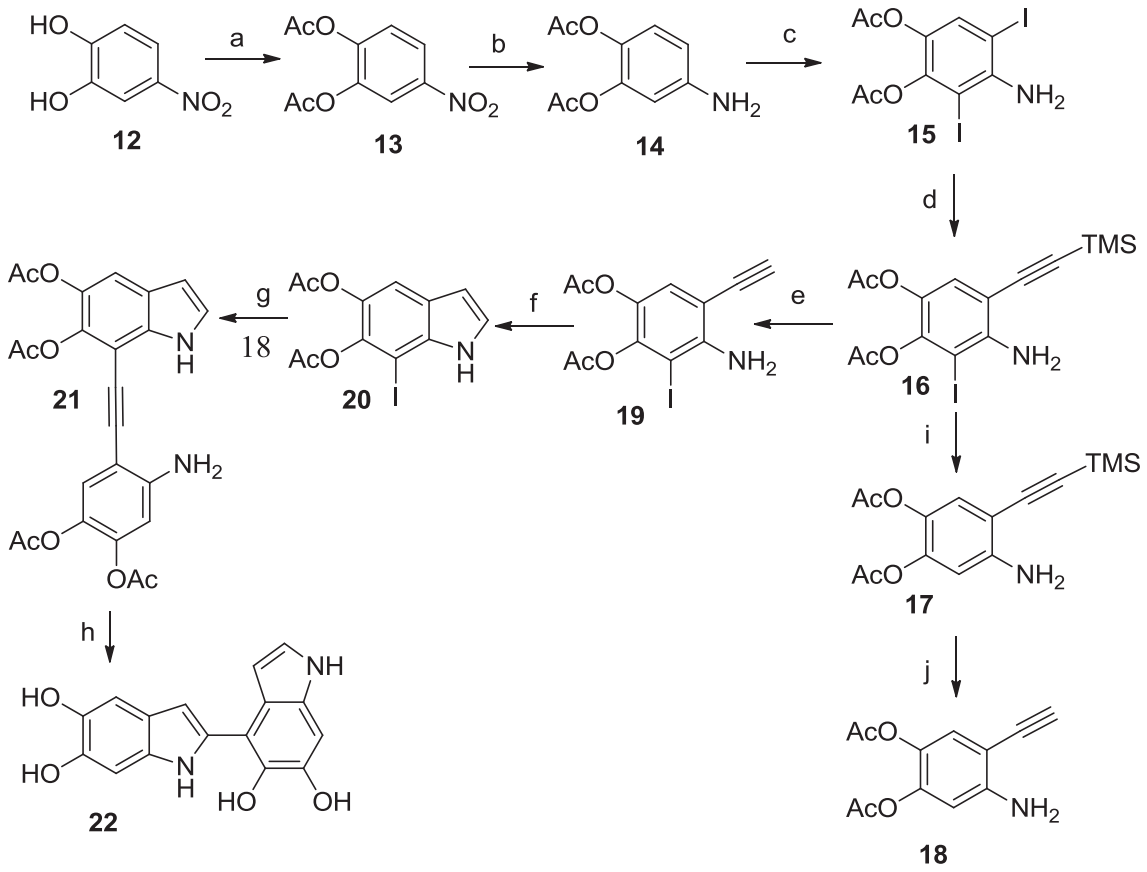
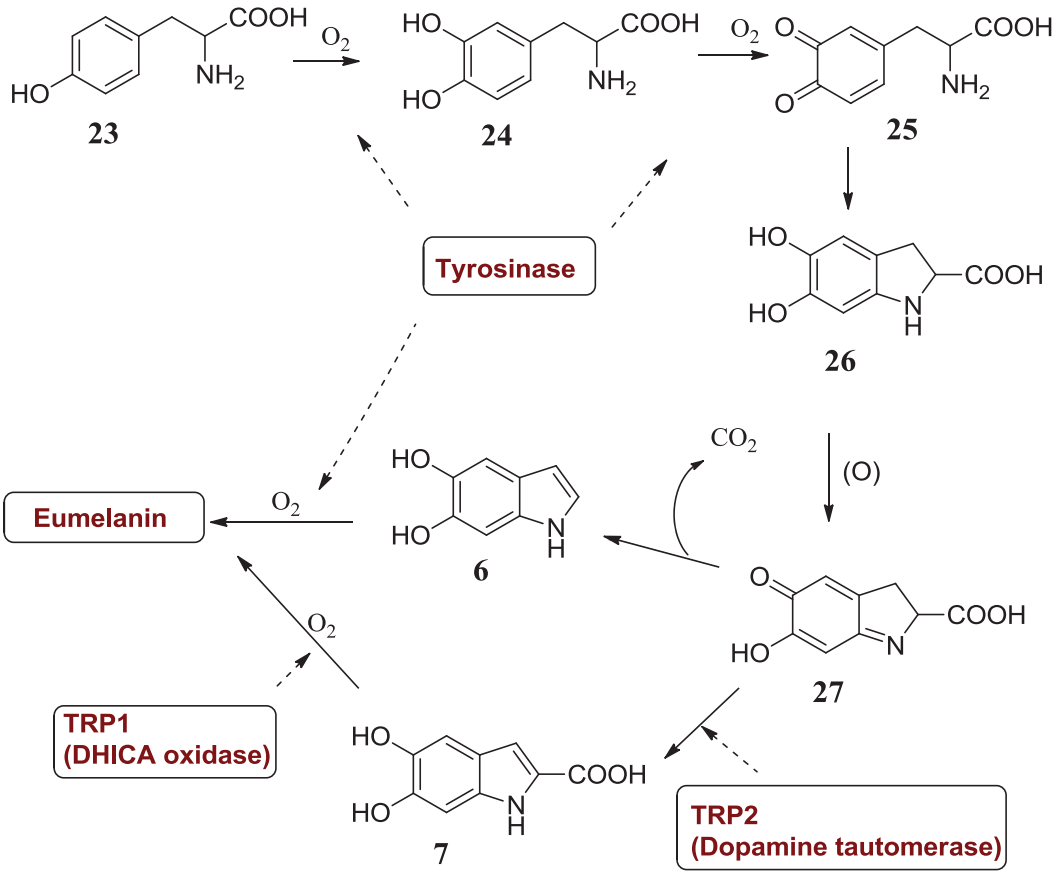
The synthesis of tetrahydroxy-biindoles often requires multiple steps. For example, 2,7`-biindolyl **22**, was synthesised in 10 steps starting from 4-nitrobenzene-1,2-diol **12** (Scheme 1-1).



Reagents and conditions: (a) Ac_2O, pyr, 320W, 6 min; (b) 10% Pd/C, 20 atm H_2, $CHCl_3$, 6 h; (c) $NaClO_2$, NaI, HCl, H_2O/methanol, 1 h; (d) PPh_3, CuI, $(PPh_3)2PdCl_2$, trimethylsilylacetylene, TEA/toluene, Ar atm, 60 °C, 30 min; (e) KF, H_2O/DMF, 30 min; (f) CuI, TEA/toluene, Ar atm, 130 °C, 1.5 h; Ar atm, 60 °C, 1 h; g) PPh_3, CuI, $(PPh_3)2PdCl_2$, 18, TEA/toluene, Ar atm, 60 °C, 1 h; (h) $AlCl_3$, toluene, Ar atm, 110 °C, 3.5 h; (i) Zn, AcOH, 30 min; (j) KF H_2O/DMF, 30 min.

Scheme 1-1

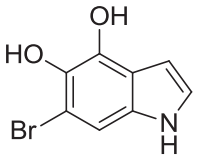
The colour of hair and wool in mammals is mostly determined by the quantity and quality of melanins that are synthesized in follicular melanocytes and transferred to keratinocytes. Mammalian melanins exist in two chemically distinct forms: the brown to black eumelanins and the yellow to reddish pheomelanins. Eumelanins are derived from copolymerization of 5,6-dihydroxyindole (DHI) **6** and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) **7**, which in turn are derived from dopaquinone **25**. The key starting material 3,4-dihydroxyphenylalanine **24** (dopa), is produced from tyrosine by the action of tyrosinase. Dopaquinone **25** undergoes a series of redox reactions leading to eumelanin formation (Scheme 1-2).[8]



Scheme 1-2

Pawelek *et al.*[9] have reported that 5,6-dihydroxyindole **6** is one of the cytotoxic compounds in the melanin biosynthetic pathway, while Heiduschka *et al.*[10] have reported the antioxidant properties of indole **6**. Apart from medicinal properties, 5,6-dihydroxyindoles are reported to be useful in dye composition for dying keratinous fibres, especially human hair.

Ochi *et al.*[11] isolated the brominated dihydroxyindoles **28** and **29** from the mid-intestinal gland of the muricid gastropod *Drupella fragum* and these indoles were found to have antioxidant properties.



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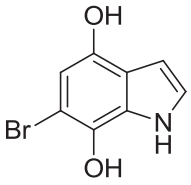

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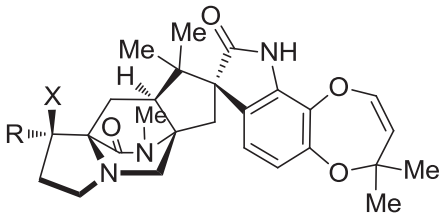
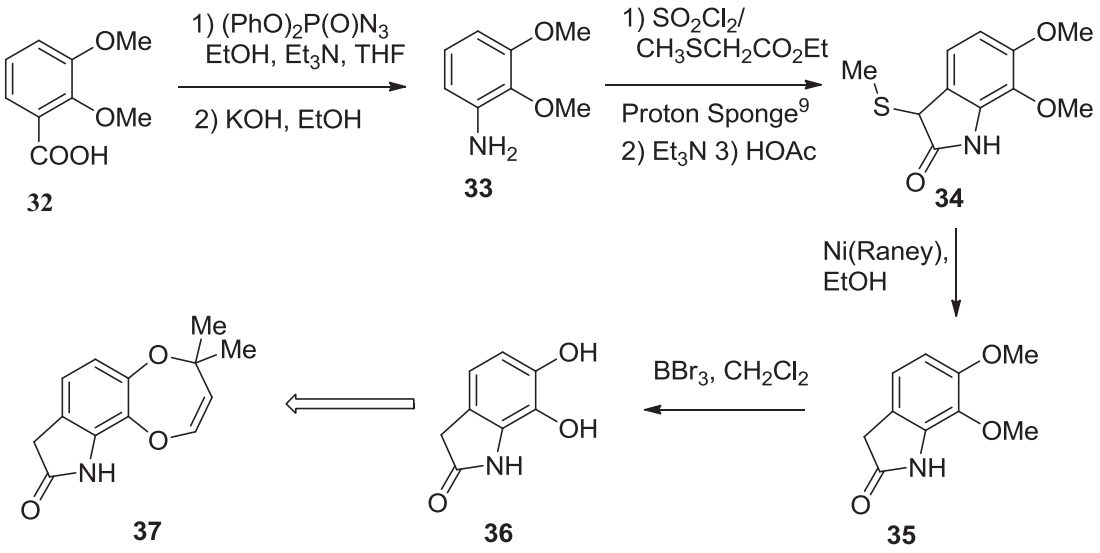
Paraherquamide-A **30** and paraherquamide-B **31** are the alkaloids isolated from *Penicillium paraherquei* and *Penicillium roqueforti* respectively.



30; R = CH_3, X = OH
31; R = H, X = H

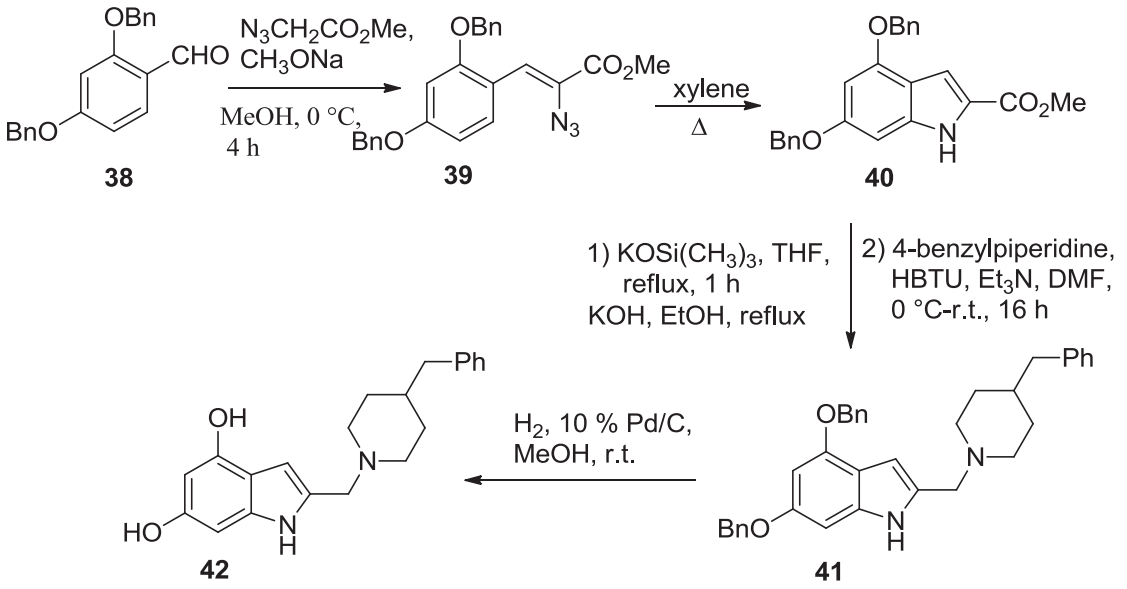
Both of these natural products have potent anthelmintic activity. In particular, they contain the 4,4-dimethyldioxepinooxindole ring system, which can be prepared from the related 6,7-dihydroxyoxindole structure. Savall *et al.*[12] have reported the synthesis of 6,7-dihydroxyoxindole **36** in four steps from 2,3-dimethoxybenzoic acid **32**, which reacted with diphenylphosphoryl azide to afford amine **33**. Amine **33** was converted to indole intermediate **34** by reaction with sulfuryl chloride and ethyl(methylthio)acetate, which was then cyclised to give intermediate **35** using Raney nickel. Demethylation of **35** using boron tribromide in dichloromethane gave dihydroxyoxindole **36**. Dihydroxyoxindole **36** can be converted to 4,4-dimethyldioxepinooxindole **37** (Scheme 1-3).



Scheme 1-3

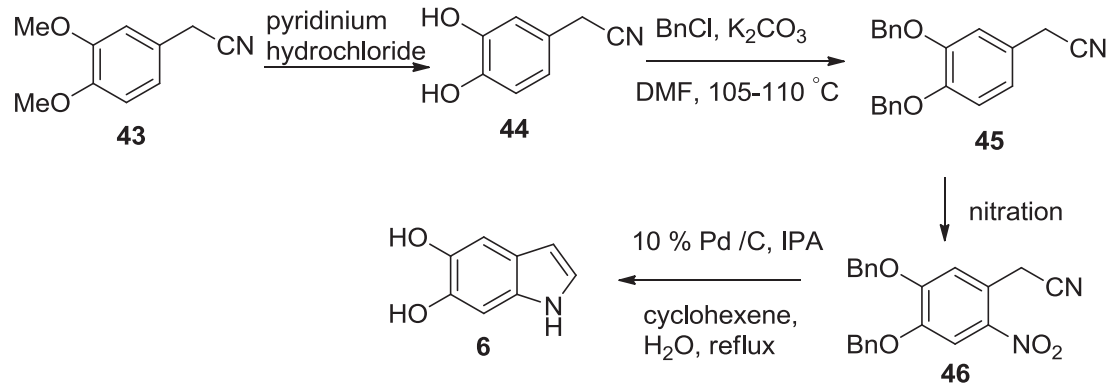
4,4-Dimethyldioxepinooxindole **37** or its precursors are envisaged to be intermediates in the total synthesis of paraherquamide-A **30**.

4,6-Dihydroxyindoles, relevant to the present work have been synthesised from 2,4-dibenzyloxybenzaldehyde **38**. For example, Borza *et al.*[13] have reported the synthesis of 4,6-dihydroxyindoles **42** utilizing the Hemetsberger indole synthesis from 2,4-dibenzyloxybenzaldehyde **38**, which upon reaction with methyl azidoacetate in the presence of sodium methoxide afforded the azidocinnamate **39**. Thermal cyclisation of **39** gave the dibenzyloxyindole **40**, which upon coupling with 4-benzylpiperidine in the presence of potassium trimethylsilanolate, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, triethylamine and potassium trimethylsilanolate gave indole **41**. Standard hydrogenolysis using palladium on carbon gave the target dihydroxyindole **42** (Scheme 1-4).



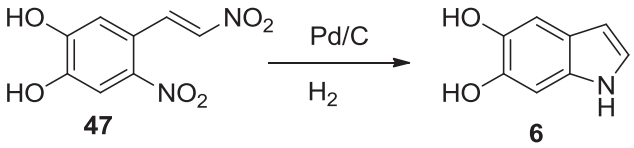
Scheme 1-4

Another method for synthesizing 5,6-dihydroxyindole **6**, reported by Junino *et al.*[14] involves the conversion of 3,4-dimethoxyphenylacetonitrile **43** into 3,4-dihydroxyphenylacetonitrile **44**, which upon reaction with benzyl chloride gave the benzyloxy derivative **45**. The nitro derivative **46** was obtained upon nitration of **45**. 5,6-Dihydroxyindole **6** was obtained by heating **46** with palladium on carbon in cyclohexene (Scheme 1-5).



Scheme 1-5

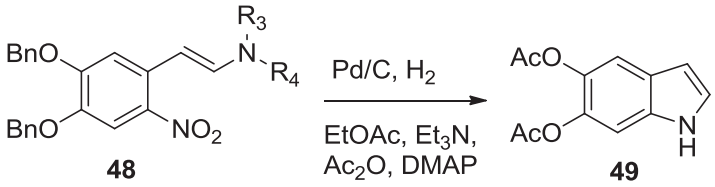
Generally, dihydroxyindole **6** can be obtained by saponification of 5,6-diacetoxyindole or hydrogenolysis of 5,6-dibenzyloxyindole. However, these methods yield only small quantities of the pure **6**. Murphy *et al.*[15] reported the improved synthesis of **6** by reductive cyclisation of (*E*)-4,5-dihydroxy-2-β-dinitrostyrene **47** with palladium catalyst in polar, alcoholic solvents (Scheme 1-6).



47 **6**

Scheme 1-6

Pan *et al.*[16] have reported a one-pot method for the synthesis of 4,5-diacetoxyindole **49** from nitrostyrene **48**, using 4-dimethylaminopyridine, triethylamine and acetic anhydride under hydrogenation conditions (Scheme 1-7).



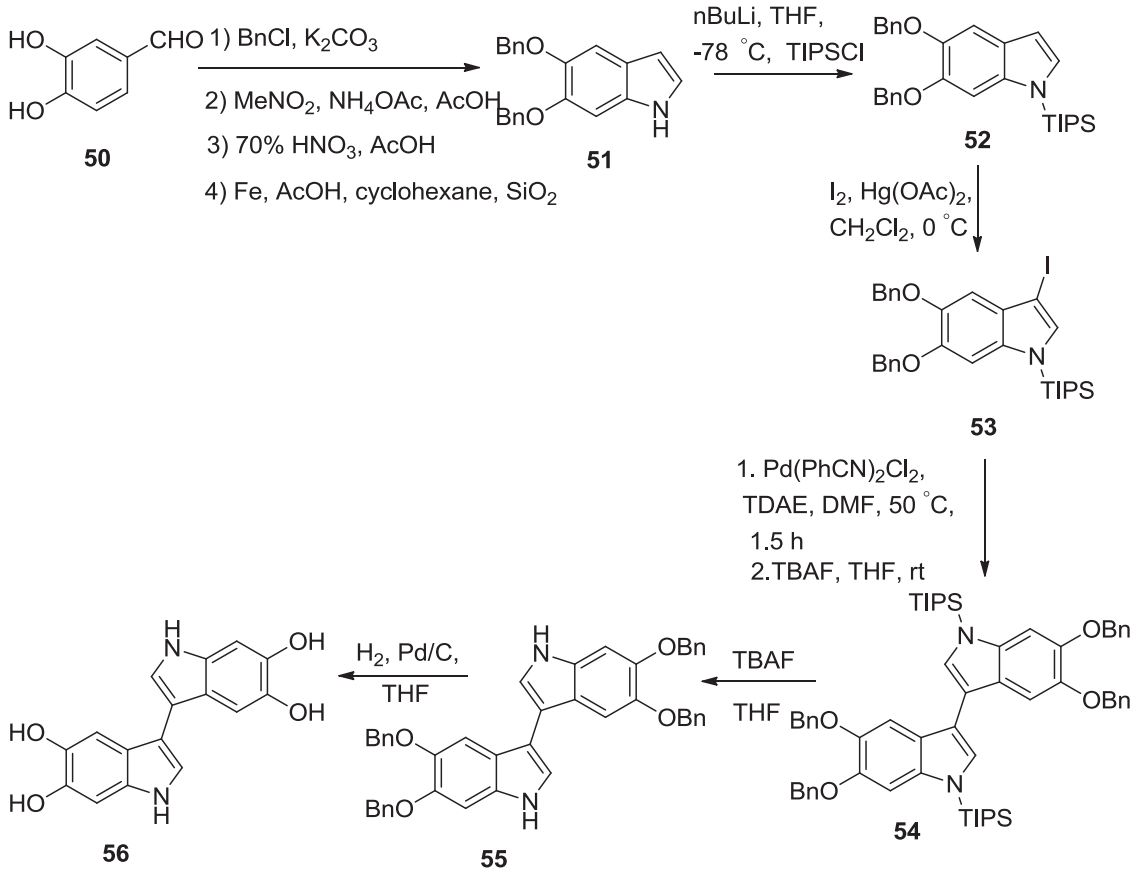
48 **49**

$NR_3\ R_4$ = pyrrole, pyrrolidine, piperidine or morpholine

Scheme 1-7

Mee *et al.*[17] have reported the total synthesis of 3,3`-biindolyl **56**, a potent antioxidant found in beetroot (*Beta vulgaris*), from 3,4-dihydroxybenzaldehyde **50**. Indole **51** was synthesised using the nitrostyrene route previously described in the schemes above. Dibenzyloxyindole **51** was reacted with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane to afford TIPS protected indole **52**, which was converted to the 3-iodoindole derivative **53** by iodine and mercury(II) acetate. Indole **53**, upon reaction with

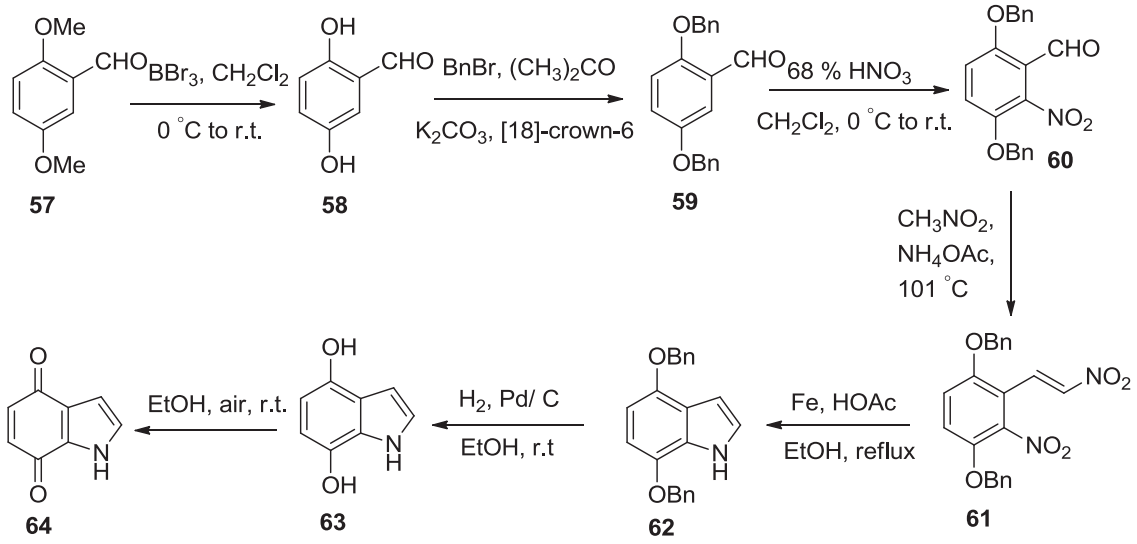
tetrakis(dimethylamino)ethylene and bis(benzonitrile)dichloropalladium, gave dimer **54**. Finally, removal of the TIPS group using tetrabutylammonium fluoride, followed by hydrogenolysis of the benzyloxyindole **55** gave the dihydroxyindole dimer **56** (Scheme 1-8).



Scheme 1-8

The synthesis of 4,7-dihydroxyindole **63** has been reported by Knolker *et al.*[18] It involves demethylation of 2,5-dimethoxybenzaldehyde **57** by boron tribromide to give the corresponding dihydroxybenzaldehyde **58**. Subsequent reaction of aldehyde **58** with benzyl bromide yielded the dibenzyloxy aldehyde **59**, which upon nitration gave the nitro derivative **60**. The nitro derivative **60** was reacted with nitromethane in the presence of ammonium acetate to afford the nitrostyrene derivative **61**, which was

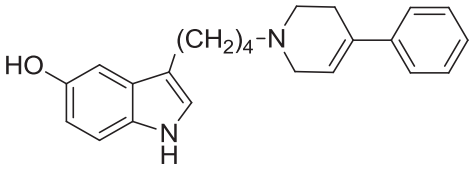
cyclised using an iron and acetic acid mixture to afford the indole **62**. Debenzylation of **62** was achieved by hydrogenolysis using palladium on carbon to afford the dihydroxyindole **63**. This dihydroxyindole was converted to 1*H*-indole-4,7-dione **64** in the presence of air (Scheme 1-9).



Scheme 1-9

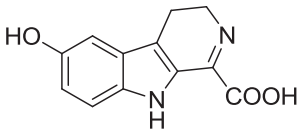
However, the synthesis of 3-substituted and 2,3-disubstituted-4,6-dihydroxyindoles has not yet been reported in the literature.

Many monohydroxyindoles have also been reported for their various biological activities. Roxindole **65** belongs to a class of dopaminergic and serotonergic drugs and was originally developed for the treatment of schizophrenia. However, in clinical trials its anti-psychotic efficacy was found to be only modest but unexpectedly, it was found to produce potent and rapid anti-depressant and anxiolytic effects. As a result, hydroxyindole **65** was instead researched for the treatment of depression. It has also been investigated as a therapy for Parkinson's disease.[19-20]

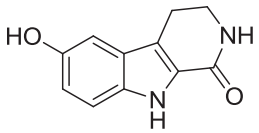


65

Lee *et al.*[21] isolated alkaloids **66-71** from the tropical marine sponge *Hyrtios sp*. In a latter study, these showed potent inhibitory activity against isocitrate lyase of *Candida albicans.*



66



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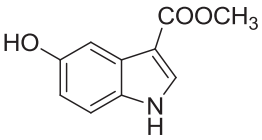

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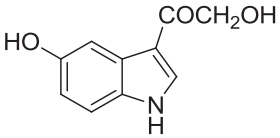

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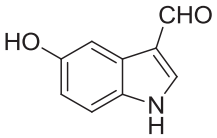

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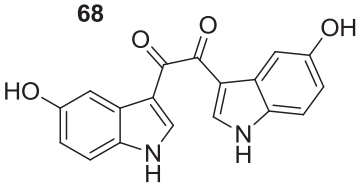
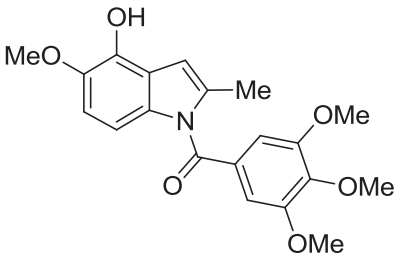


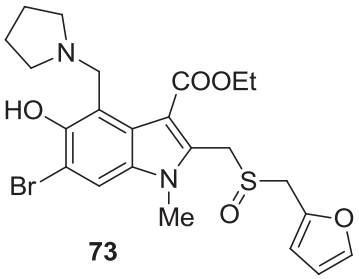
71

Liou *et al.*[22] have reported the anti-proliferative activity of hydroxyindole **72**, with an IC_{50} value of 0.6 μM. It exhibited anti-tubulin activity superior or comparable with that of colchicine, a well known anti-cancer drug.

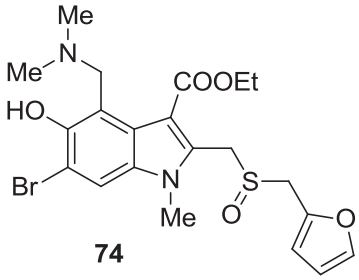


72

Gong *et al.*[23] have reported the anti-viral activities of hydroxyindoles **73** and **74**. Indole **73** showed anti-hepatitis B activity, while indole **74** showed anti-influenza activity.

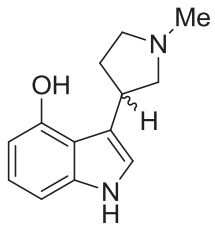


73



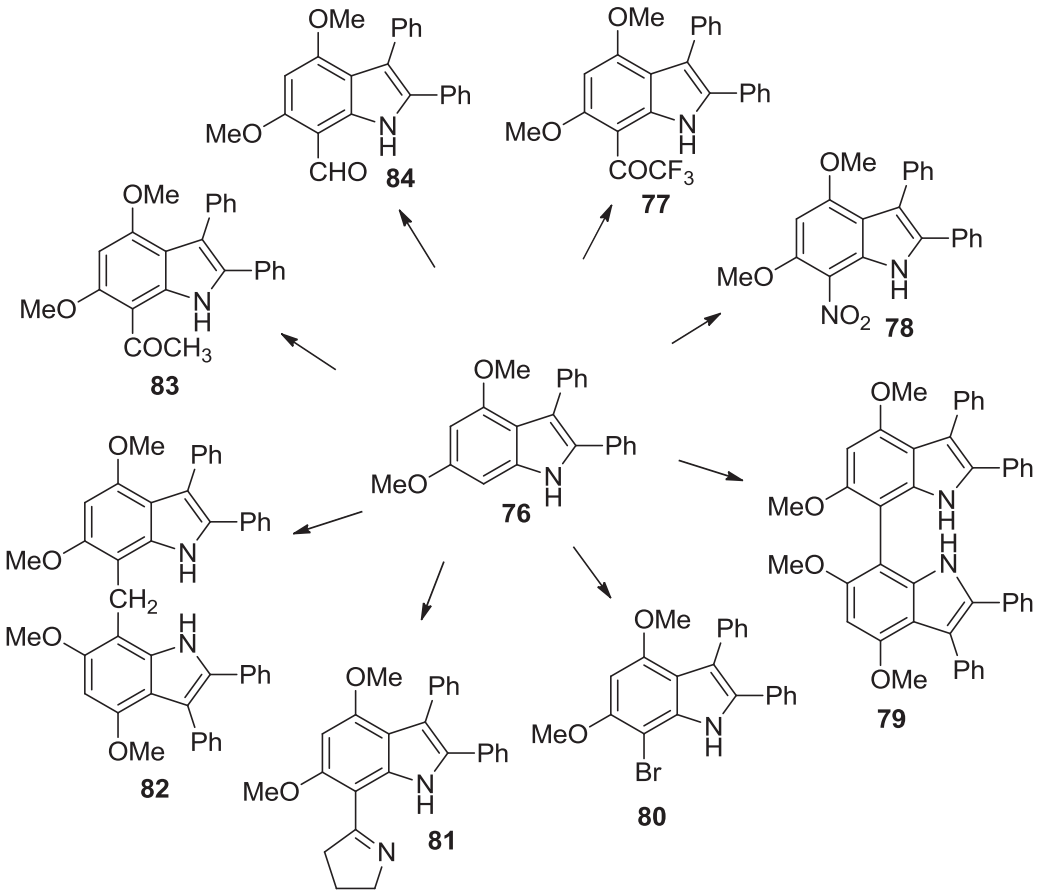
74

The LSD (lysergic acid diethylamide) like activity of the oxygenated tryptamine derivative **75** has been reported by Gerasimov *et al.*[24]



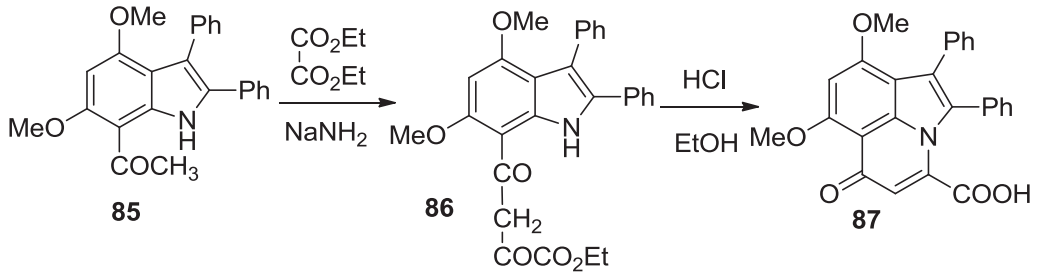
75

Our group has carried out extensive studies on 4,6-dimethoxyindoles and generated a wide range of interesting ring systems based on this scaffold.[25] However, the corresponding 4,6-dihydroxyindole system has been relatively unexplored. The following scheme depicts the synthesis of a range of compounds based on 4,6-dimethoxy-2,3-diphenylindole **76** (Scheme 1-10).[26-36]



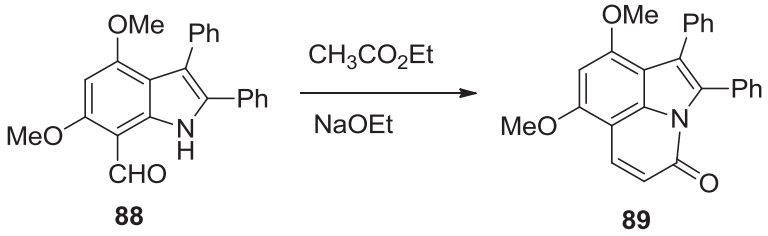
Scheme 1-10

The pyrroloquinolone **87** was obtained by a simple route involving reaction of the 7-acetyl indole **85** with diethyl oxalate and sodamide, followed by acid-catalysed cyclisation of the intermediate glyoxylic ester **86** (Scheme 1-11).[37]



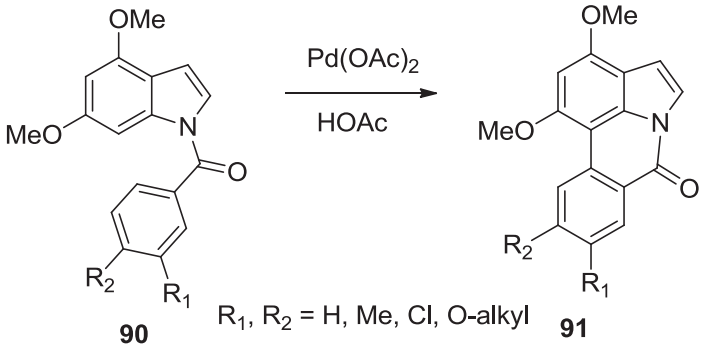
Scheme 1-11

An example of cyclisation between the N1 and C7 position is the synthesis of 4-oxo-4*H*-pyrrolo[3,2,1-*ij*]quinolone **89** from the reaction of 7-carbaldehyde **88** with ethyl acetate and sodium ethoxide (Scheme 1-12).[38]



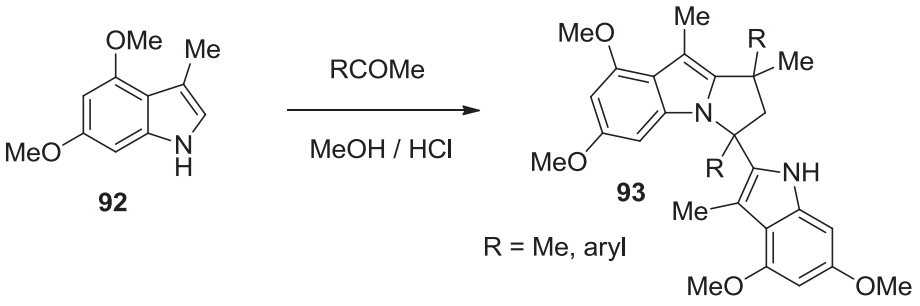
Scheme 1-12

Since the C4 and C6 methoxy groups activate the C7 position, it was envisaged that the biaryl coupling reactions could be directed at C7 in preference to C2. Using this idea, a wide range of *N*-benzoyl-4,6-dimethoxyindoles **90** could be converted directly and into the corresponding pyrrolophenanthridones **91** in good yields (Scheme 1-13).[39]



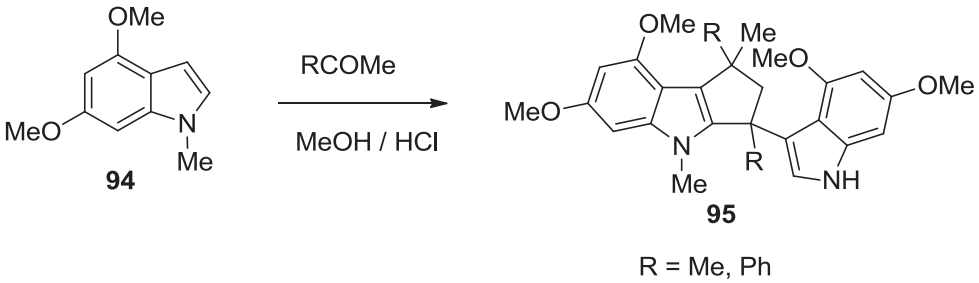
Scheme 1-13

It is known that pyrroles not only combine with aldehydes but also undergo macrocycle formation with methyl ketones. However, acid catalysed reactions of 4,6-dimethoxy-3-methylindole **92** with ketones gave pyrrolo[*a*]indoles **93** (Scheme 1-14).[40]

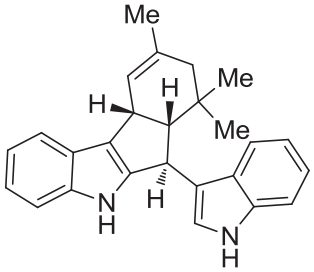


Scheme 1-14

An investigation of the reaction of the related 4,6-dimethoxy-1-methylindole **94** with acetone or acetophenone in methanolic hydrogen chloride yielded cyclopentano[*b*]indoles **95** (Scheme 1-15), which have structural similarities to yuehchukene **96**, an anti-fertility agent isolated from *Murraya paniculata*.[26,41]

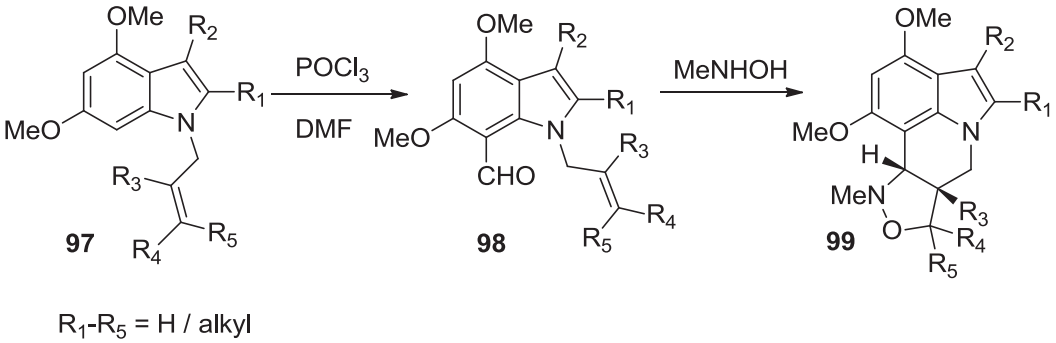


Scheme 1-15



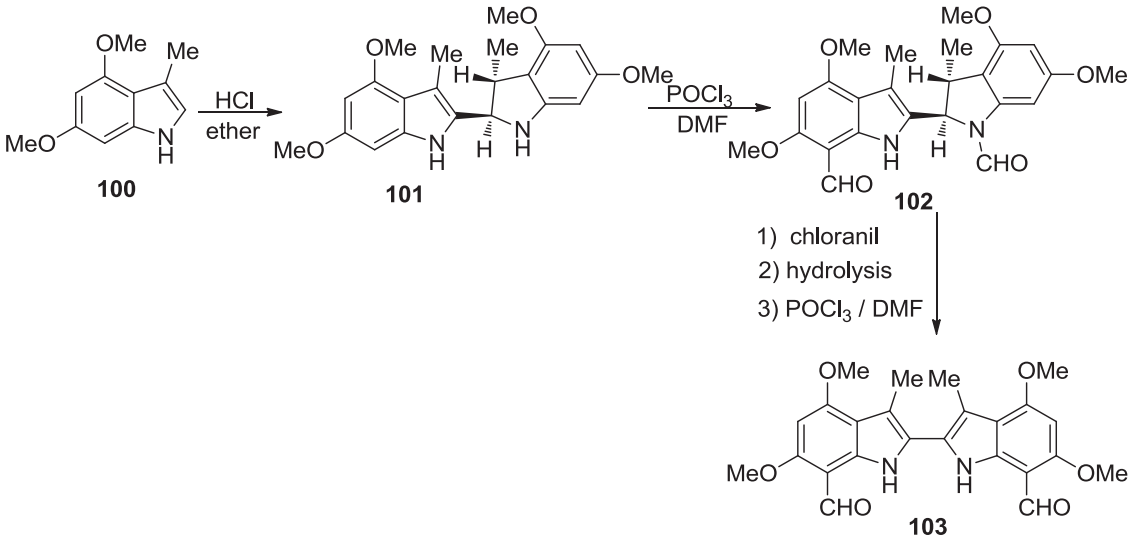
96

The intramolecular 1,3-dipolar cycloaddition of a nitrone to an alkene can also be effected to build a new ring between N1 and C7. *N*-Allylindoles **97** readily undergoes formylation at C7 to give the aldehydes **98**, which on treatment with *N*-methylhydroxylamine afford excellent yields of cycloadducts **99** (Scheme 1-16).[26]



Scheme 1-16

An acid catalysed dimerisation of dimethoxyskatole **100** gave the 2,2′-indole-indoline **101**, which upon formylation gave the dialdehyde **102**. Oxidation of **102** followed by amide hydrolysis and formylation gave the 2,2′-biindolyl-7,7′-dicarbaldehyde **103** (Scheme 1-17).[42]



Scheme 1-17

However, the chemistry of 4,6-dihydroxyindoles have so far been unexplored. The 4,6-dihydroxyindole system has the same oxygenation pattern as that of flavonoids. The biological properties of flavonoids are well documented and range from anti-inflammatory to anti-cancer activities. Genistein has been shown to bind to the estrogen receptors and shows biological activity similar to estradiol, the endogenous estrogen.

The similarity of oxygenation pattern of 3-hydroxyphenyl-4,6-dihydroxyindole (blue) and the flavonoid genistein (black) is shown in Figure 1-1.

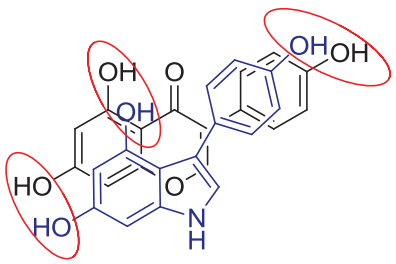
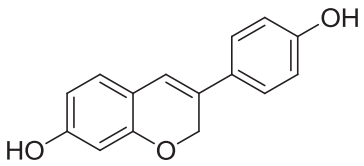


Figure 1-1 Overlap of genistein (black) and 4,6-dihydroxyindole (blue).

Phenoxodiol **104** is an example of an anti-cancer drug candidate based on the isoflavene scaffold and is currently being developed for therapeutic applications. It belongs to a class of drugs which act as multiple signal transduction regulators (MSTRs).[43]

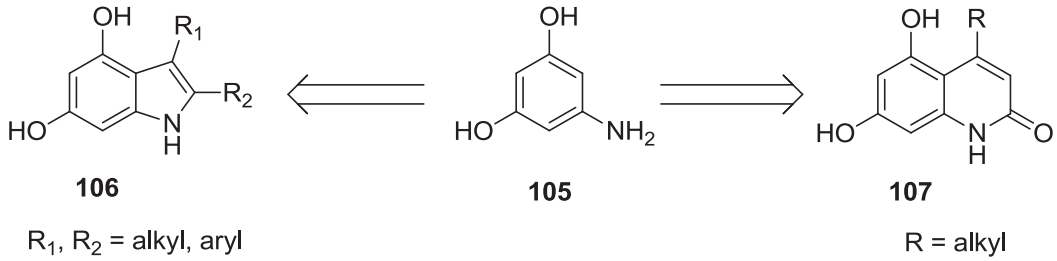


104

Therefore, it would be interesting to prepare 4,6-dihydroxyindoles to investigate their chemical reactivities as well as their biological properties, and to prepare fused heterocycles based on them.

In the case of 4,6-dimethoxyindoles the majority of the reactions in the benzene ring occur at the C7 position and not at C5. The reason for this could be the buttressing effect of the bulky methoxy groups present at C4 and C6, which prevent the incoming reagents from reacting at C5. However, in the case of 4,6-dihydroxyindoles, it would be possible to study the potential reactivity at C5 and to exploit this property to synthesise new fused ring systems.

This approach could also be extended to include the 5,7-dihydroxyquinolone framework, since 4,6-dihydroxyindoles **106** and 5,7-dihydroxyquinolin-2-ones **107** their synthesis involve the common starting material, 3,5-dihydroxyaniline **105** (Scheme 1-18) and discussed in subsequent chapters.

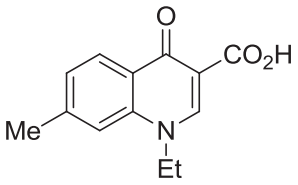


Scheme 1-18

1.1.2. Dihydroxyquinolones:

Quinolones are widely distributed in nature and in synthetic drugs.[44-45] Their biological activities range from anti-cancer[46-47] to anti-microbial.[48-50] A major class of anti-microbials is based on the quinolone nucleus. There is a constant need for research on the development of new anti-microbial agents due to resistance shown by many species of Gram-negative and Gram-positive bacteria.[51-56]

Nalidixic acid **108** and oxolinic acid **109** were the first quinolin-4-ones used as anti-bacterial agents to cure infection caused by Gram-negative bacteria.[57] SAR studies and further research on quinolone anti-microbials led to the development of a significant number of quinolones having a fluorine atom in their nucleus, known as fluoroquinolones, such as ciprofloxacin **110** and norfloxacin **111**, and these compounds possessed better anti-bacterial activity with fewer side effects as compared to the earlier quinolones.[58-60]



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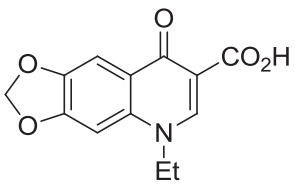

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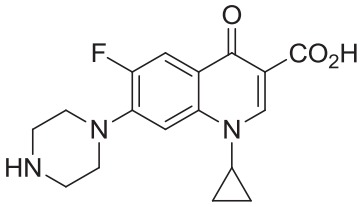

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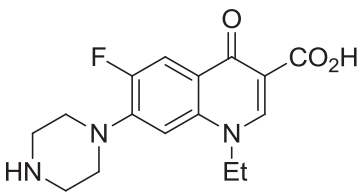


111

Quinolin-2-ones have been reported as anti-cancer,[61-63] anti-viral, anti-protozoal[64] and anti-HIV agents.[65] Apart from their medicinal use, quinolin-2-one based luminescent dyes have found use in analytical application in time-resolved fluoro-immunoassays.[66]

1.2. Aims of the present work:

Although the chemistry of 4,6-dimethoxyindoles and ring systems derived from them has been extensively studied, 4,6-dihydroxyindoles and heterocyclic systems such as pyrano[2,3-*g*]indol-7(1*H*)-one and dihydropyrano[2,3-*e*]indole are not yet reported in the literature. Therefore, the aims of the present work were 1) to investigate various methodologies for the synthesis of a range of 4,6-dihydroxyindoles, 2) to synthesise new fused heterocyclic systems based on the indole scaffold, particularly pyranoindoles, dihydropyranoindoles, furoindoles and pyrroloquinolines, and 3) to develop methodologies for the synthesis of fused heterocycles based on 5,7-dihydroxyquinolin-2-ones.

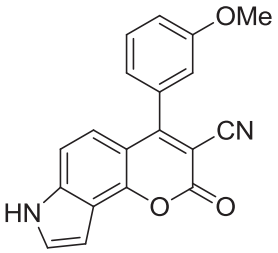
CHAPTER 2

SYNTHESIS OF NOVEL PYRANOINDOLES

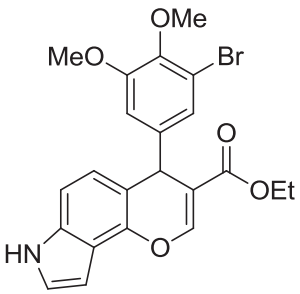
2.1 Introduction:

Indole-based fused-ring systems containing structures related to pyranoindoles have been considered as important heterocycles because they possess interesting biological activities including anti-cancer,[67] anti-inflammatory,[68] antidepressant[69-70] and anti-viral activities.[71]

For example, pyrano[2,3-*e*]indoles **112** and **113** are reported to activate caspases, which are enzymes involved in programmed cell-death or apoptosis. These compounds, by inducing apoptosis, act as anti-cancer agents.[67]

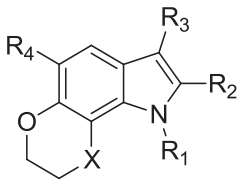


112



113

On the other hand, pyrano[2,3-*e*]indoles **114** and **115** showed anti-ulcerous, anti-inflammatory, analgesic and hepatitis C-inhibitory activities.[72-73] Pyranoindoles are isosteres of furocoumarins, where the furan ring has been replaced by a pyrrole ring, and thus they are also named as pyrrolocoumarins. There have also been some reports of heterocyclic systems incorporate the fusion of a pyrrole ring on to the pyrone ring of coumarins.



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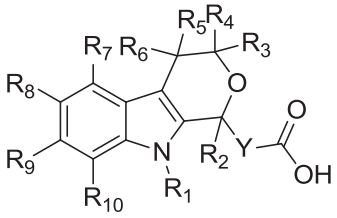
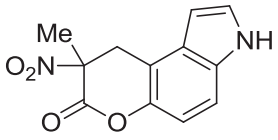


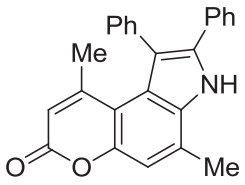
115

R_1-R_{10} alkyl, aryl

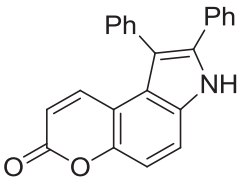
A literature search revealed the existence of only four derivatives of pyrano[3,2-*e*]indoles **116-119**,[74] however, the corresponding pyrano[2,3-*g*]indole **120** system has not yet been reported.



116



117



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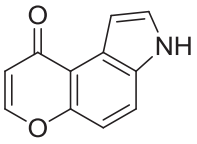

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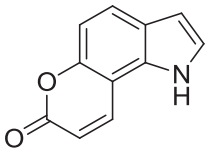


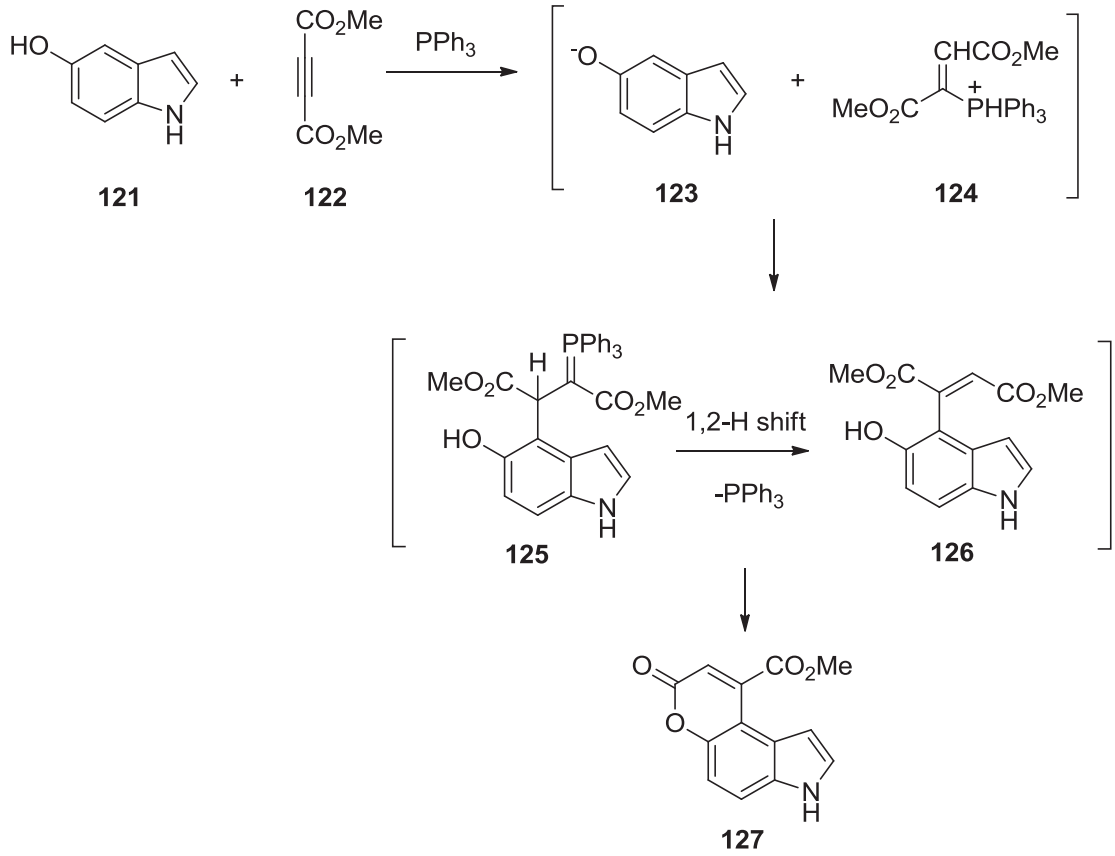
120

Therefore, the development of synthetic routes to the substituted pyrano[2,3-*g*]indole related to **120** is of particular interest.

2.1.1 Known synthetic methods for pyranoindoles:

Various routes are reported in the literature for the synthesis of pyranoindoles. They can be prepared from indoles, in particular hydroxyindoles, followed by the installation of a pyran ring. Another option could be to build the pyran scaffold first, and then constructing the indole nucleus on it. Kontogiorgis *et al.*[75] have reported the synthesis of pyrano[3,2-*e*]indole **127** using a novel method utilizing the reaction of 5-hydroxyindole **121** with dimethyl acetylenedicarboxylate (DMAD) **122** and triphenylphosphine (Scheme 2-1).

The formation of compound **127** proceeds through a series of intermediates. An initial addition of conjugate base **123** to vinyltriphenylphosphonium salt **124** leads, after a few transformations involving a 1,2-H shift and abstraction of triphenylphosphine from the intermediate ylide **125**, to the formation of the substituted indole **126**, which by lactonization affords pyrano[3,2-*e*]indole **127**.

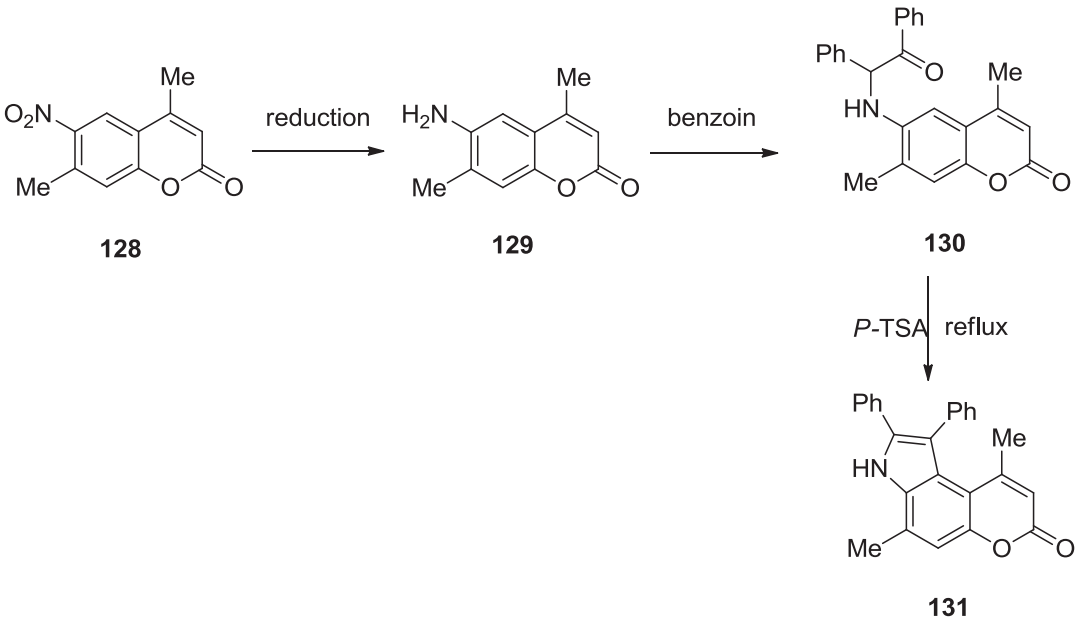


Scheme 2-1

The compounds made using this methodology were tested for their biological activities and exhibited significant anti-inflammatory activity in carrageenan-induced paw oedema and antioxidant activity in the DPPH assay. DPPH (1,1-diphenyl-2-picrylhydrazyl) is a stable free radical that can accept an electron or hydrogen radical and thus be converted into a stable, diamagnetic molecule. DPPH has an odd electron and so has a strong absorption band at 517 nm that can be measured spectrophotometrically.[76]

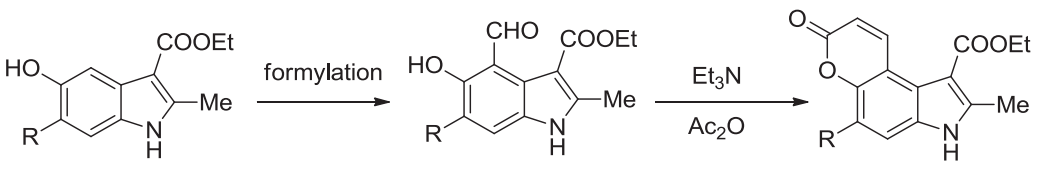
Meyer *et al.*[77] has reported the synthesis of pyrano[3,2-*e*]indole from coumarin wherein the nitrocoumarin **128** was first reduced with tin(II) chloride to give the amine **129**, which upon condensation with benzoin gave the intermediate **130**. Cyclisation of the

aminoketone **130** using *p*-toluenesulfonic acid gave the pyrano[3,2-*e*]indole **131** (Scheme 2-2).



Scheme 2-2

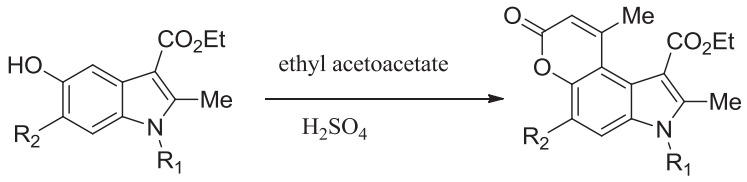
Hiremath *et al.*[78] has reported the synthesis of pyrano[3,2-*e*]indole **134** from 5-hydroxyindoles **132**, which upon formylation gave 4-formylindoles **133**. Subsequent reaction of **133** with triethylamine and acetic anhydride at reflux gave the pyrano[3,2-*e*]indole **134** (Scheme 2-3).



132 **133** **134**

Scheme 2-3

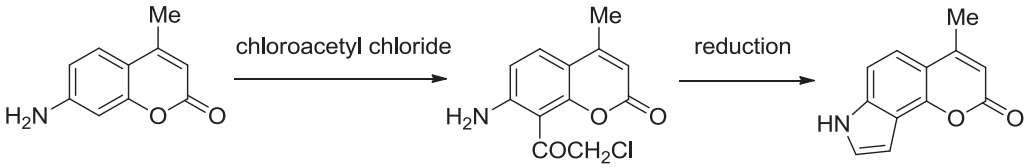
Reaction of *N*-methyl-5-hydroxyindole **135** with ethyl acetoacetate in the presence of sulfuric acid, gave pyrano[3,2-*e*]indole **136** (Scheme 2-4).



135 **136**

Scheme 2-4

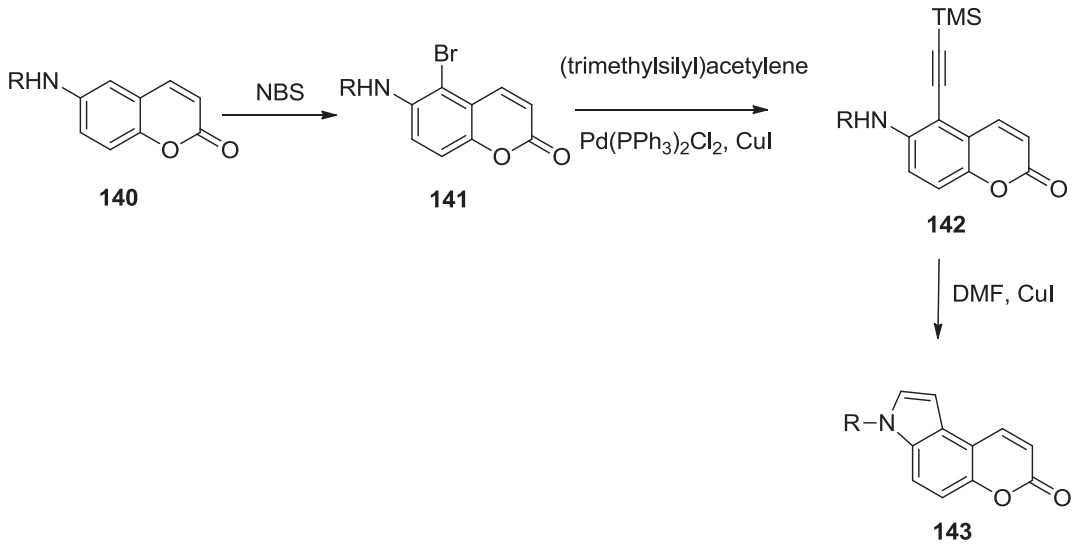
Gonzalez *et al.*[79] have reported the synthesis of pyrano[3,2-*e*]indole **139** from the aminocoumarin **137** by reaction with chloroacetyl chloride to give the intermediate **138**, which upon cyclisation, reduction and dehydration was converted to pyrano[3,2-*e*]indole **139** (Scheme 2-5).



137 **138** **139**

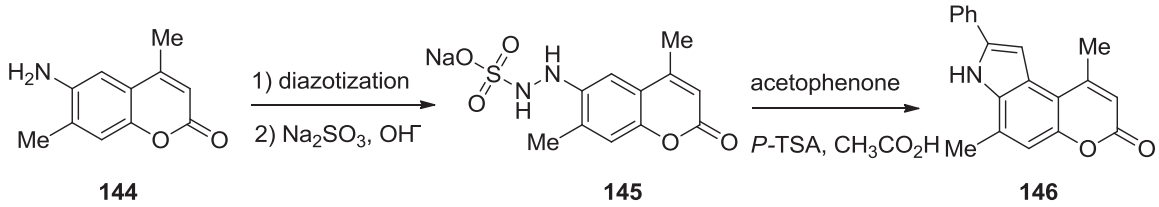
Scheme 2-5

Recently Majumdar *et al.*[80] have reported the synthesis of pyrano[3,2-*e*]indole **143** from the substituted coumarin **140**, which was converted to the bromo derivative **141**, which upon the Stille coupling with (trimethylsilyl)acetylene gave the intermediate **142**. Pyrano[3,2-*e*]indole **143** was obtained by cyclisation with cuprous iodide in *N*,*N*-dimethylformamide (Scheme 2-6).



Scheme 2-6

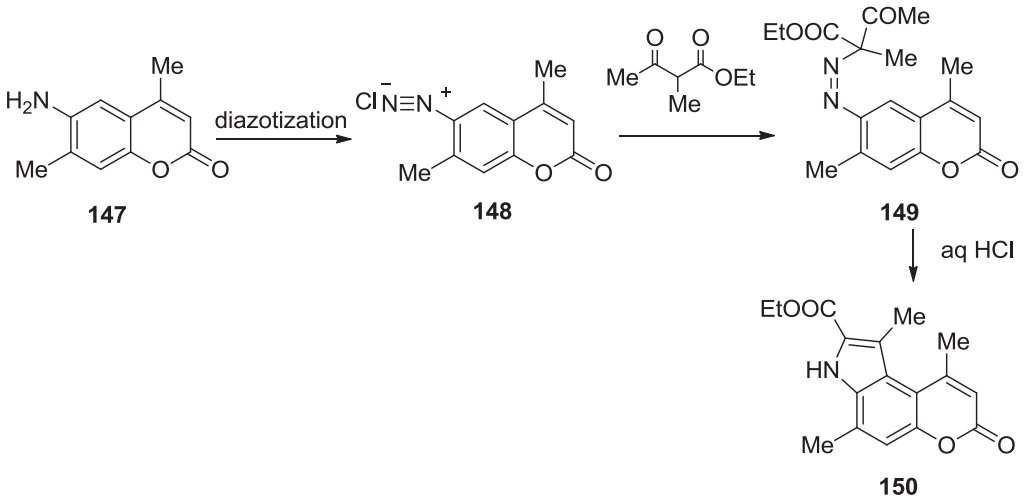
Pyrano[3,2-*e*]indoles can also be prepared by utilization of the Fischer indole synthesis. Suslov *et al.*[81] has reported a scheme for the synthesis of pyrano[3,2-*e*]indole from coumarins, in which the aminocoumarin **144** was diazotized and converted to the diazosulfonate **145**, which was subsequently reacted with acetophenone in the presence of *p*-toluenesulfonic acid to give pyrano[3,2-*e*]indole **146** (Scheme 2-7).



Scheme 2-7

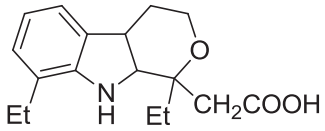
Traven *et al.*[82] have reported a similar synthesis of pyrano[3,2-*e*]indole **150** from the aminocoumarin **147**, which was first diazotised to produce the intermediate diazonium salt **148**, which in turn was coupled with an α-substituted acetoacetate ester to afford

compound **149**, which was cyclised using HCl to give pyrano[3,2-*e*]indole **150** (Scheme 2-8).



Scheme 2-8

Another example of a drug containing a pyrano[3,4-*b*]indole is etodolac **151**, which belongs to a class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs).[68]



151

Pyrano[3,4-*b*]indole **151** was also reported to possess anti-viral activity against HCV NS5B RdRp. The inhibitory activity of this racemate was found to reside in the (*R*) enantiomer (HCV-371). The results of these studies confirmed that pyranoindoles target the NS5B polymerase through interactions at the thumb domain[83] (Figure 2-1).

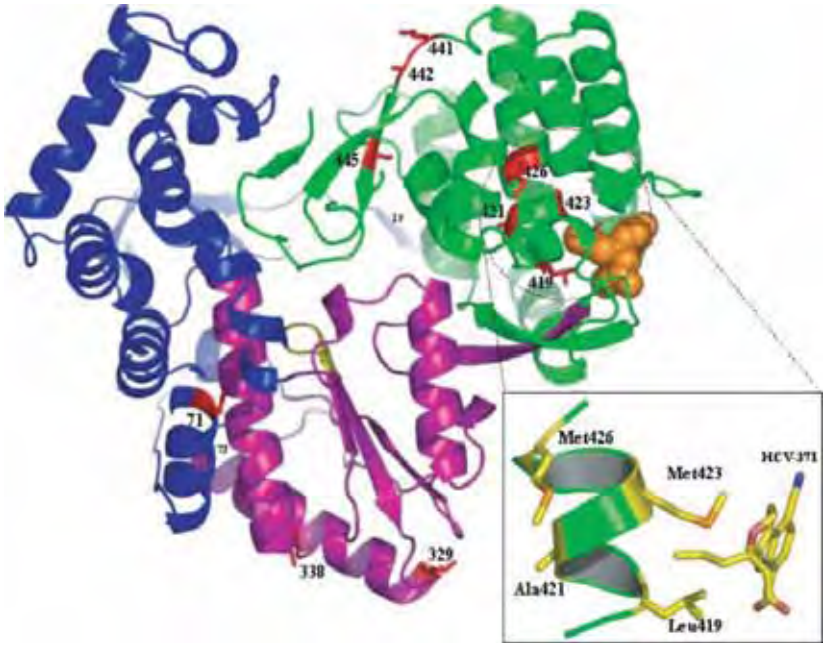


Figure 2-1 Crystal structure showing pyranoindole resistance mutations in a ribbon diagram of HCV NS5B in complex with a pyranoindoles **151**, HCV-371[83]

Given the diverse range of biological activities exhibited by pyranoindoles, and the lack of report of pyrano[3,2-*g*]indoles led us to investigate the synthesis of these types of molecules.

2.2 Results and Discussion:

2.2.1 Synthesis of 4,6-dihydroxyindoles as starting material:

Since there are many potential routes available to make pyranoindoles, the selection depended on the versatility of the method to generate novel skeletons, the availability of the chemicals and the reproducibility of the method.

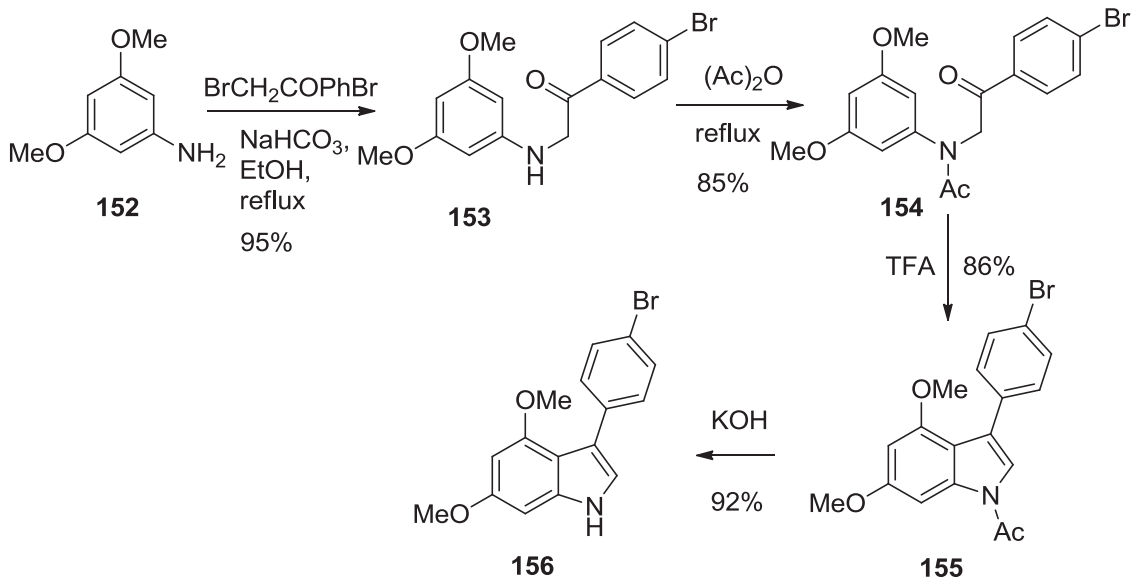
The following two methodologies were chosen for this purpose:

i. Demethylation of 4,6-dimethoxyindoles followed by the installation of the pyrone moiety using the von Pechmann condensation reaction.

ii. Synthesis of the coumarin fragment, followed by installation of the indole moiety using various methods.

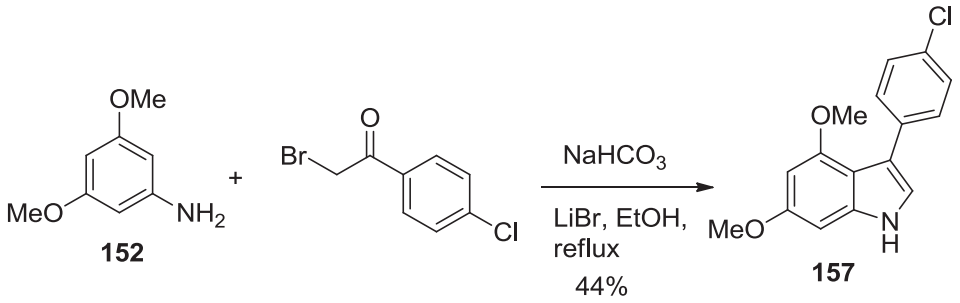
2.2.1.1 Synthesis of 4,6-dimethoxyindoles:

4,6-Dimethoxyindoles were synthesised according to a well established method.[84-85] For 4,6-dimethoxy-3-(4`-bromophenyl)indole 3,5-dimethoxyaniline **152** was heated under reflux with the 2,4`-dibromoacetophenone in ethanol containing sodium bicarbonate to afford the anilinoketone **153**. The presence of base in the reaction mixture is essential to prevent the partial acid catalysed cyclisation of the anilinoketone. The anilinoketone was reacted with acetic anhydride to give the *N*-acetyl derivative **154**, which was cyclised in refluxing trifluoroacetic acid to give *N*-acetylindole **155**. The crude *N*-acetylindole **155** was purified by column chromatography and then deprotected by heating under reflux in the presence of potassium hydroxide in methanol to yield the desired indole **156** (Scheme 2-9).[86]



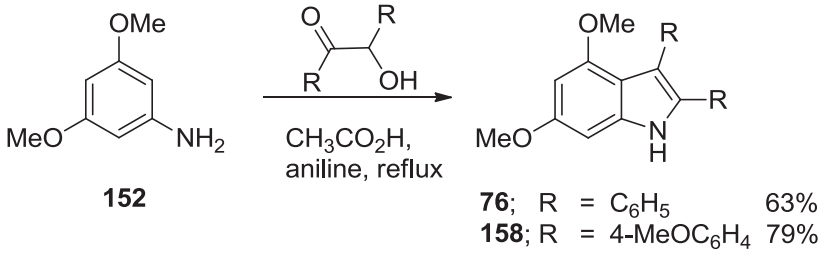
Scheme 2-9

4,6-dimethoxy-3-(4`-chlorophenyl)indole **157** was prepared in 44% yield using a one-pot method by the reaction of 3,5-dimethoxyaniline **152** and 2-bromo-4`-chloroacetophenone in the presence of sodium bicarbonate and lithium bromide in refluxing ethanol (Scheme 2-10).[86]



Scheme 2-10

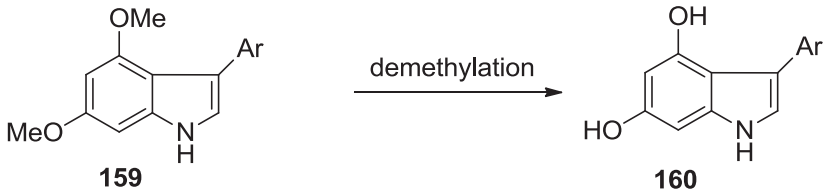
4,6-Dimethoxy-2,3-disubstituted indoles **76** and **158** were prepared using a one-pot method by the reaction of 3,5-dimethoxyaniline **152** with substituted benzoins in 63-79% yield (Scheme 2-11).[87-88]



Scheme 2-11

2.2.1.2 Demethylation of 3-aryl-4,6-dimethoxyindoles:

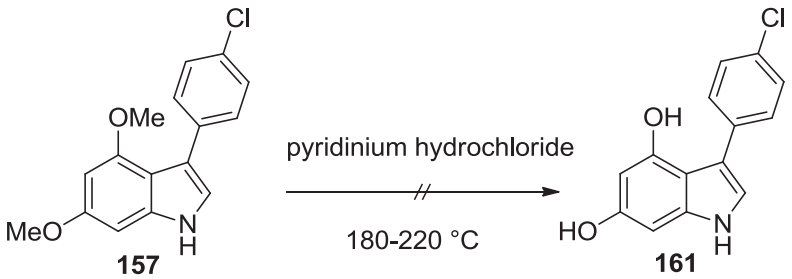
Given the difficulties associated with cyclisation of 3,5-dihydroxyanilinoketone (discussed in Chapter-7), a direct approach would be to access the 4,6-dihydroxyindoles **160** by the demethylation of the corresponding 4,6-dimethoxyindoles **159** (Scheme 2-12).



Scheme 2-12

The available dealkylation techniques of methyl aryl ethers may be classified into those using electrophilic and nucleophilic reagents, *e.g*. aluminium chloride and sodium cyanide respectively.[89]

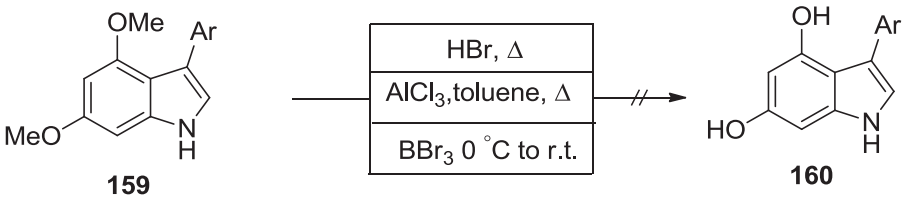
Preliminary demethylation investigations using 3-(4`-chlorophenyl)-4,6-dimethoxyindole **157** and pyridinium hydrochloride under melt conditions were unsuccessful due to several factors such as high temperatures (180-220 °C), extended reaction times, use of excessive amounts of reagent and the difficulty in the work-up of the reaction. In most of the cases the starting material was recovered unchanged (Scheme 2-13).



Scheme 2-13

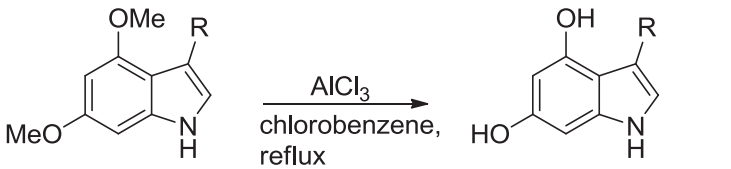
An adaptation of a work-up procedure described by Schmid *et al*[90] was employed where the reaction mixture was treated with 5M hydrochloric acid at 90 °C followed by dilution with water to produce a homogeneous non-viscous solution at room temperature permitting organic solvent extraction. However, this work-up procedure did

not improve the reaction in this case. Further attempts to demethylate **159** using hydrogen bromide and aluminium chloride in toluene or boron tribromide were also unsuccessful. In case of hydrogen bromide, there were formation of multiple products, while in the case of boron tribromide, the starting material was recovered from the reaction mixture (Scheme 2-14).



Scheme 2-14

Gratifyingly, the 4,6-dihydroxyindoles **161-162** were obtained from 4,6-dimethoxyindoles **156-157** by demethylation with aluminium chloride heated under reflux in chlorobenzene (Scheme 2-15).



156; R = 4-BrC_6H_4
157; R = 4-ClC_6H_4

162; R = 4-BrC_6H_4, 71%
161; R = 4-ClC_6H_4, 77%

Scheme 2-15

Demethylation using aluminium chloride proceeded smoothly and the dihydroxy product could be easily isolated.

The ^{1}H NMR spectrum of compound **161** in DMSO-d_6 showed the presence of a singlet at δ 5.94 ppm corresponding to H5, a doublet at δ 6.23 ppm (J = 3.0 Hz) due to H7, another singlet at δ 6.77 ppm corresponding to H2. Doublets at 7.43 and δ 7.72 ppm (J = 9.0 Hz) corresponded to H3`/H5` and H2`/H6` respectively. The NH proton appeared

as a broad singlet at δ 8.83 ppm, while singlets at δ 9.35 and 11.00 ppm were due to the OH protons. The spectrum of the product was consistent with the anticipated structure, as evidenced by the loss of two methoxy signals at δ 3.80 ppm (Figure 2-2).

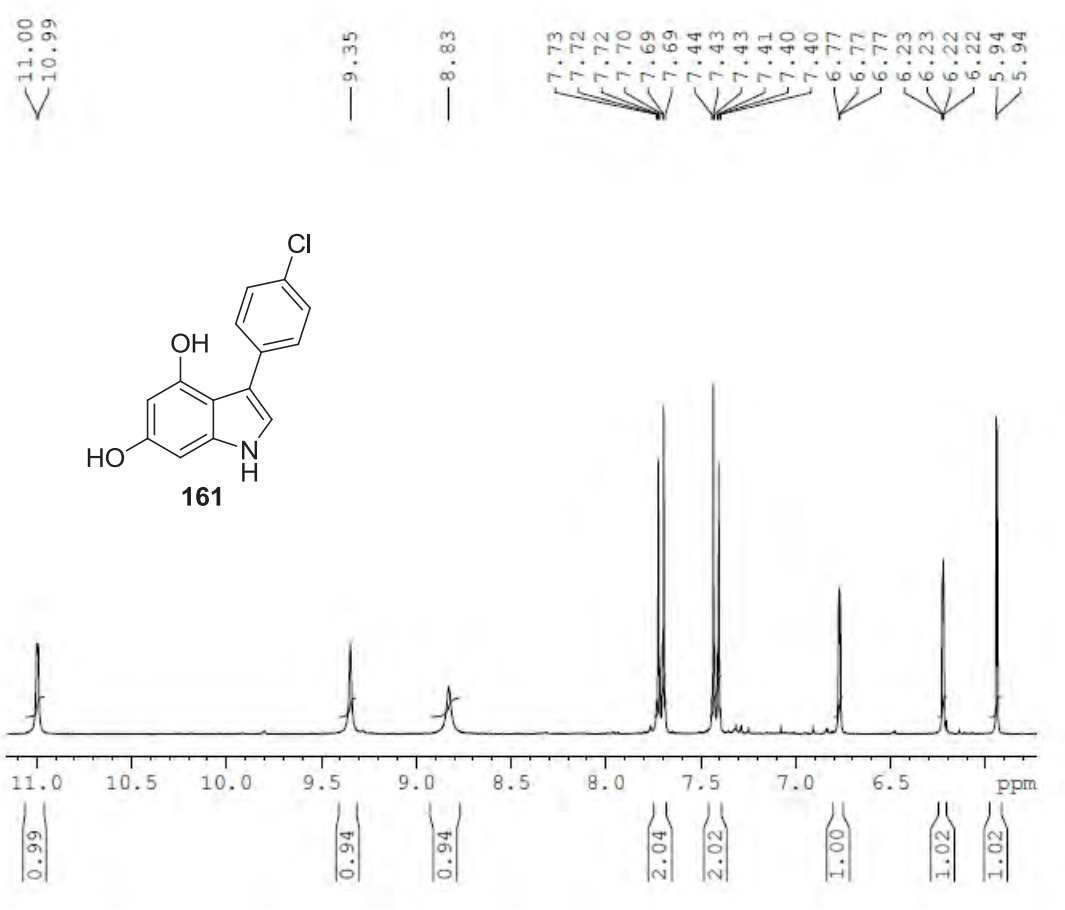


Figure 2-2 ^{1}H NMR spectrum of compound **161** in DMSO-d_6

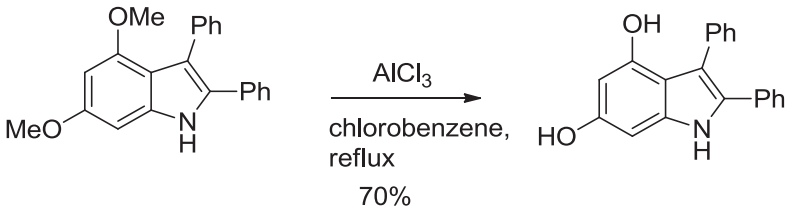
A variety of reaction conditions *e.g.* solvents, reflux time and moles of aluminium chloride were investigated. Moreover, it was found that the reaction was dependent upon several factors. The reaction required anhydrous conditions necessitating the use of fresh anhydrous aluminium chloride, dried chlorobenzene and an inert atmosphere.

The optimal reaction conditions used three equivalents of aluminium chloride in chlorobenzene under reflux for 1 h to give 4,6-dihydroxyindoles in 71-77% yield. The work-up for this reaction simply involved the addition of crushed ice to give a

precipitate, which was washed with water followed by hexane to remove excess chlorobenzene, giving a pure product. However, it was observed that the 4,6-dihydroxyindoles quickly decomposed when exposed to moisture and atmospheric oxygen, so it was necessary to utilise them immediately for further reaction. The slow addition of aluminium chloride was found to be crucial as a single addition of aluminium chloride resulted in decomposition of the desired 4,6-dihydroxyindoles.

2.2.1.3 Demethylation of 2,3-disubstituted-4,6-dimethoxyindoles:

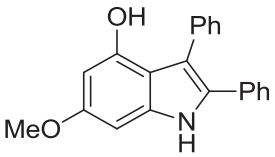
The demethylation of 4,6-dimethoxy-2,3-diphenylindole **76** was equally facile with 3 molar equivalents of aluminium chloride under the conditions described above and the dihydroxy product **163** was obtained in 70% yield (Scheme 2-16).



76 **163**

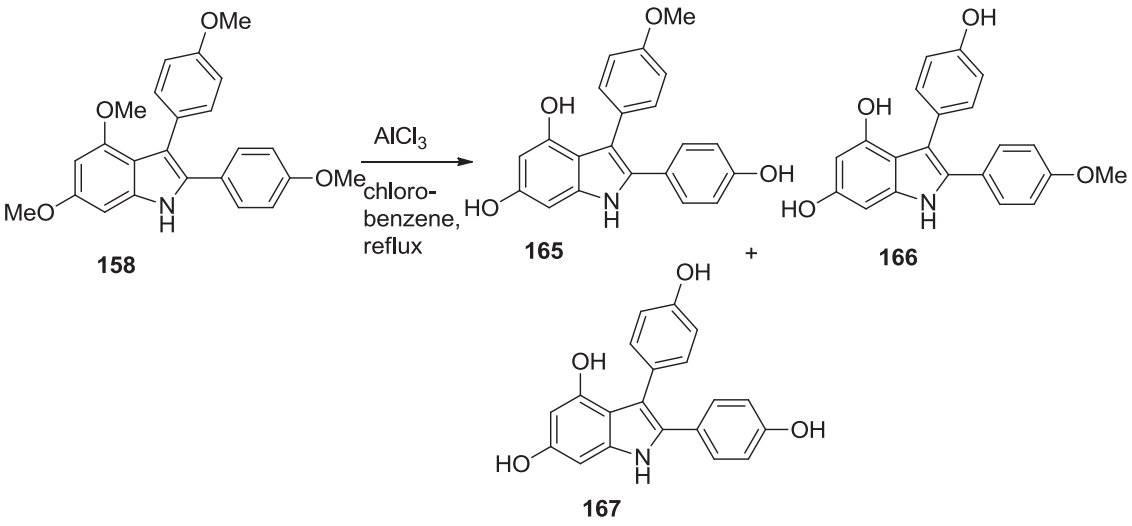
Scheme 2-16

When closely monitoring the reaction by thin layer chromatography, it was noticed that one faster running spot formed as the reaction progressed which was indicative of the mono-demethylated product. Attempted demethylation of 4,6-dimethoxy-2,3-diphenylindole **164** gave a mono demethylated product which was isolated, purified and analysed by ^{1}H ^{13}C NMR and a H-H NOESY experiments, and the structure was consistent with 4-hydroxy-6-methoxy-2,3-diphenyl indole **164**. The chemistry related to this compound will be discussed in Chapter-5.



164

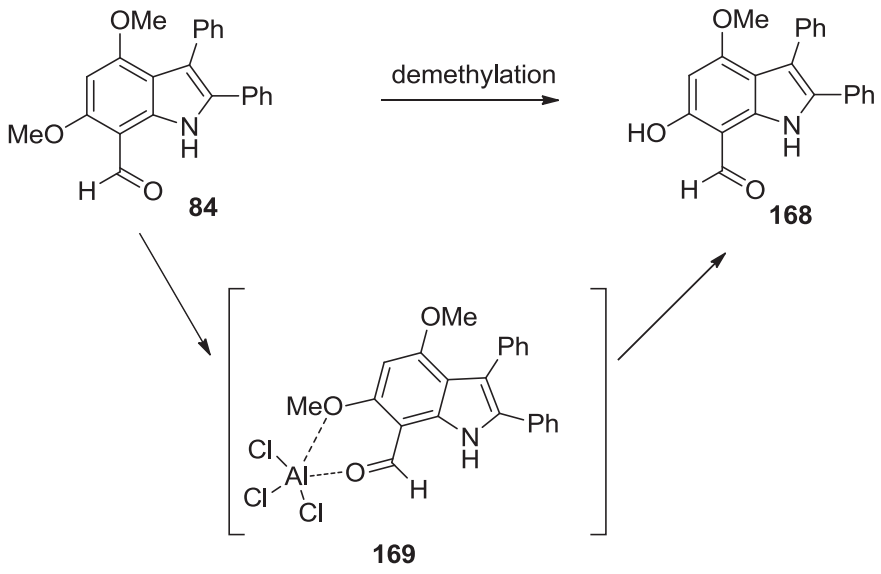
In contrast, the demethylation of 4,6-dimethoxy-2,3-bis(4-methoxyphenyl)indole **158** was unsuccessful even with 6-7 molar equivalents of the aluminium chloride in chlorobenzene and elevated temperatures. It was presumed that the removal of the additional methoxy groups would require harsher conditions. The TLC analysis of this reaction consistently revealed three blue fluorescent spots under a UV light, which could be possibly due to formation of **165-167** (Scheme 2-17). However, all the attempts to separate the individual compounds were unsuccessful.



Scheme 2-17

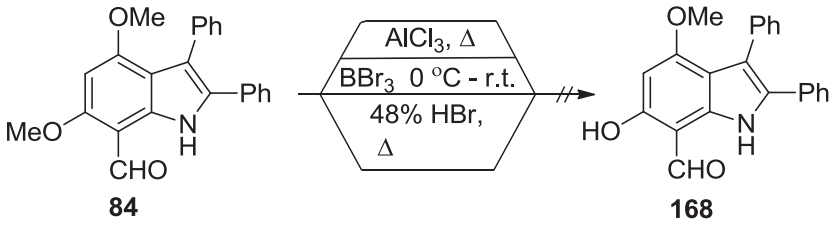
2.2.1.4 Attempted demethylation of 7-formyl-2,3-disubstituted-4,6-dimethoxyindoles:

We were interested to investigate the direct demethylation of 7-formyl-2,3-disubstituted-4,6-dimethoxyindoles such as **84** was due to the potential for new ring connectivity from hydroxy indoles. It was anticipated that demethylation with anhydrous aluminium chloride would selectively provide the monohydroxy compound **168**. This is because the aldehyde substituent at C7 would promote selective demethylation of the adjacent methoxy group *via* coordination to aluminium in the intermediate **169** (Scheme 2-18).



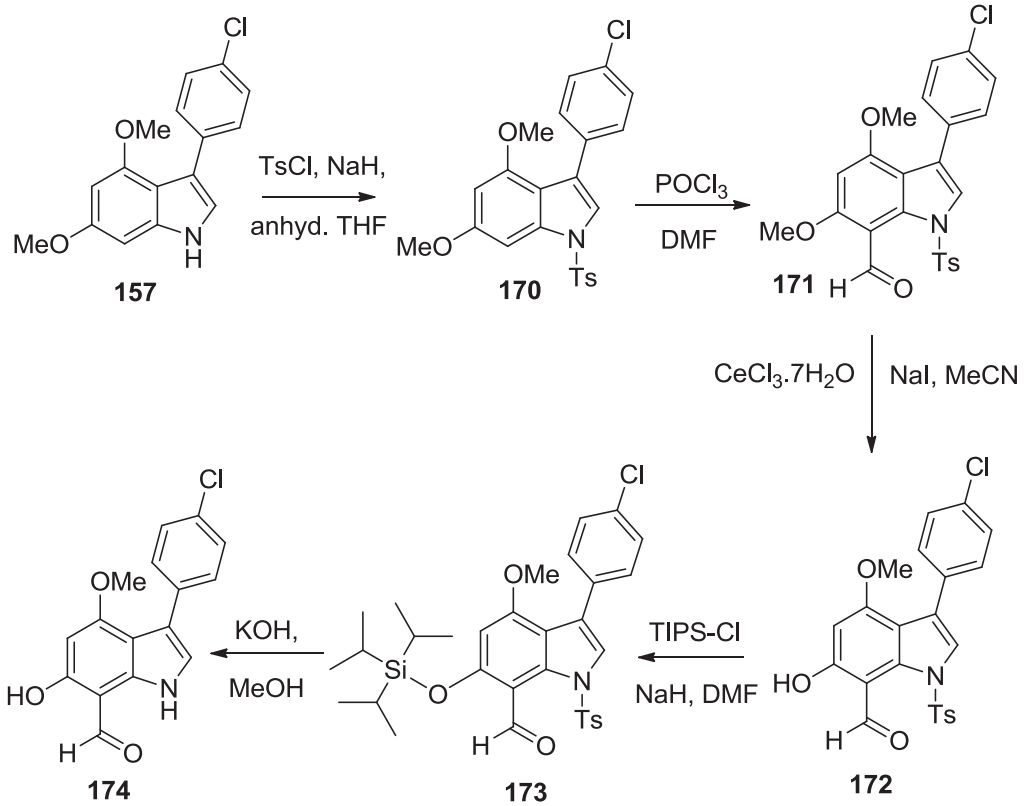
Scheme 2-18

However, attempted demethylation of 7-formyl-2,3-disubstituted-4,6-dimethoxyindoles **84** using aluminium chloride in chlorobenzene, boron tribromide in dichloromethane, or 48% HBr was unsuccessful (Scheme 2-19).



Scheme 2-19

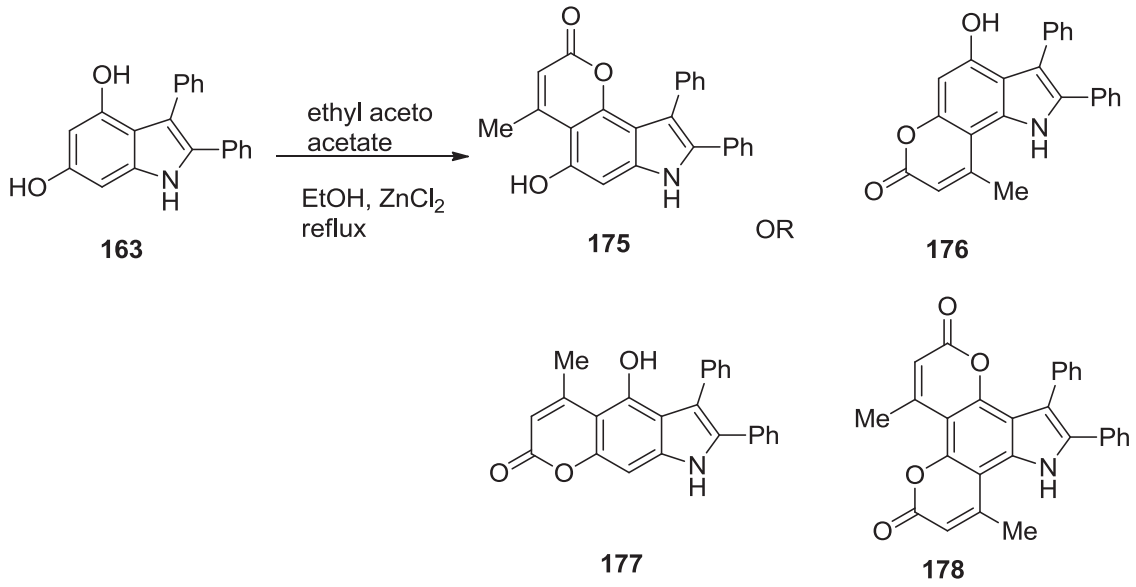
In contrast, previous research in our group has shown that the monodemethylation of *N*-tosyl-3-(4`-chlorophenyl)-4,6-dimethoxyindole-7-carbaldehyde **171** could be accomplished with cerium(III) chloride and sodium iodide. The hydroxyindole aldehyde **174** could thus be obtained from 3-(4`-chlorophenyl)-4,6-dimethoxyindole **157** in five steps with an overall yield of 44% (Scheme 2-20).[91]



Scheme 2-20

2.2.2 Synthesis of pyranoindoles:

With the free phenolic groups present in the 4,6-dihydroxyindoles **161-163**, the investigation of further reactions was now possible. Coumarins can be formed from the reaction of a phenol with a β-ketoester (von Pechmann condensation) under a variety of acidic conditions such as sulfuric acid, boron tribromide or methanesulfonic acid. These conditions appeared to be too strong for the reaction of indoles **161-163** with β-ketoesters, but the milder Lewis acid, zinc chloride, gave the pyranoindoles **176**, **178-185**. These final products, usually were precipitated out of the ethanol, filtered and washed with water (Scheme 2-21).



Scheme 2-21

In principle, the reaction of 4,6-dihydroxyindole **163** with ethyl acetoacetate could lead to four different products due to the presence of two free hydroxyl groups.

i. Reaction with C4-OH followed by cyclisation at C5 to give **175**.

ii. Reaction with C6-OH followed by cyclisation at C7 to give **176**.

iii. Reaction with C6-OH followed by cyclisation at C5 to give **177**.

iv. Reaction with C4-OH and C6-OH followed by cyclisation at C5 and C7 to give **178**.

The ^{1}H NMR spectrum (DMSO-d_6) of the product from the reaction of 3-(4`-chlorophenyl)-4,6-dihydroxyindole and ethyl acetoacetate was consistent with the pyranoindole skeleton as evidenced by loss of one of the protons from the indole ring and appearance of four new signals, namely, a singlet at δ 2.80 ppm for the CH_3 protons, and three singlets at δ 5.99, 6.46 and 7.02 ppm. The NH proton signal appeared at δ 10.86 ppm and the OH proton signal appeared at δ 10.40 ppm (Figure 2-3).

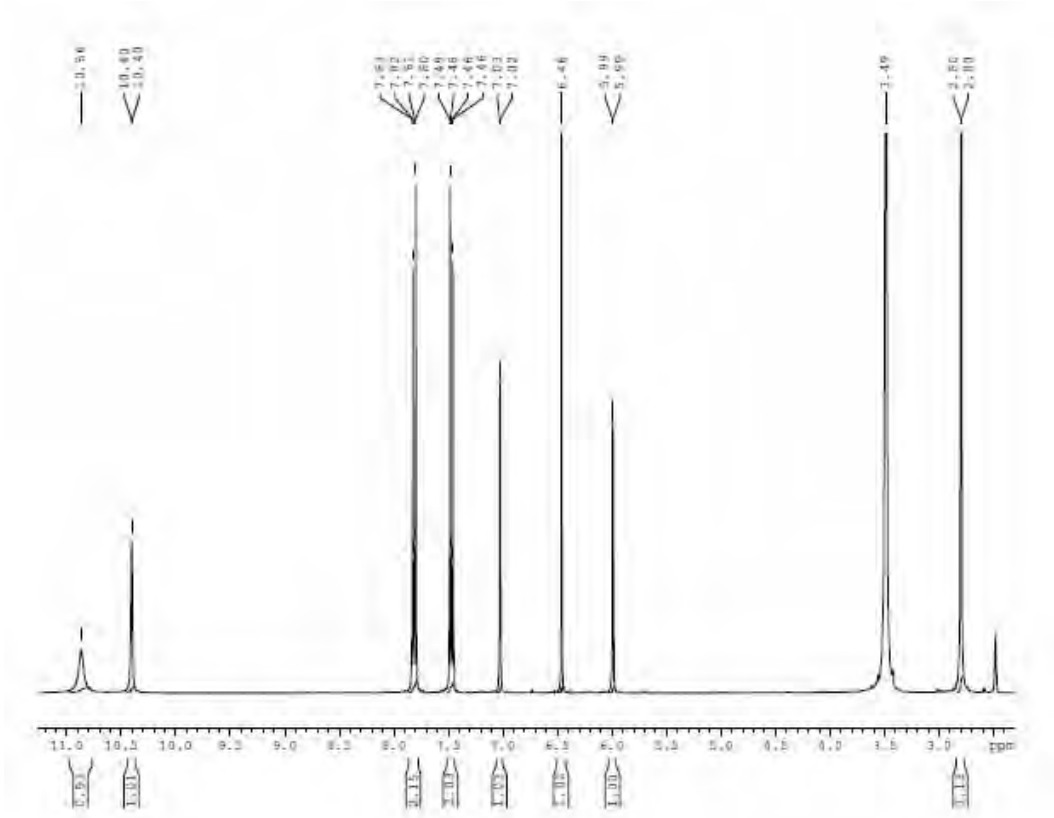


Figure 2-3 ^{1}H NMR (DMSO-d_6) spectrum of the product obtained from the reaction of 3-(4`-chlorophenyl)-4,6-dihydroxyindole and ethyl acetoacetate.

The formation of **178** was ruled out due to the presence of only one methyl proton signal in the ^{1}H NMR spectrum. To investigate the structure further, 2D NMR spectroscopy experiments such as HMBC, HSQC and H-H NOESY were performed, but unfortunately complete structural assignment could not be achieved. Therefore, single crystal X-ray crystallography was necessary to pinpoint the structure.

The hydroxy compound **176** could not be satisfactorily crystallised. Therefore, crystals of O-acetyl derivative was obtained. X-ray crystallography showed the structure to be **176a** (Figure 2-4), indicating that the initial reaction with β-ketoester had taken place at the C6-OH group. The cyclisation then occurred at C7 to give the pyrano[2,3-*g*]indole.

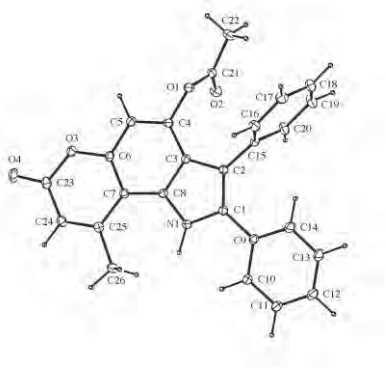
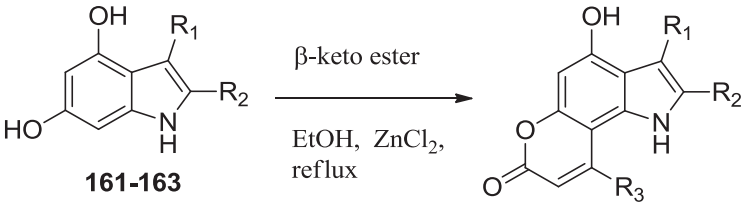


Figure 2-4 ORTEP view of **176a** (O-acetoxy derivative of **176**)

This reaction was found to be quite general and worked well with both 3-aryl-substituted indoles **163** and 2,3-diarylsubstituted indoles **161** and **162**. The reaction could be extended to include phenyl acetoacetate and trifluoromethyl acetoacetate, which gave the corresponding phenyl and trifluoromethyl substituted pyrano[2,3-*g*]indoles. This type of fusion of an indole with a pyrone is not yet reported in the literature. Therefore, this methodology allowed the synthesis of a series of novel pyrano[2,3-*g*]indoles **176**, **179-186** in 60-73% yields (Scheme 2-22).



Scheme 2-22

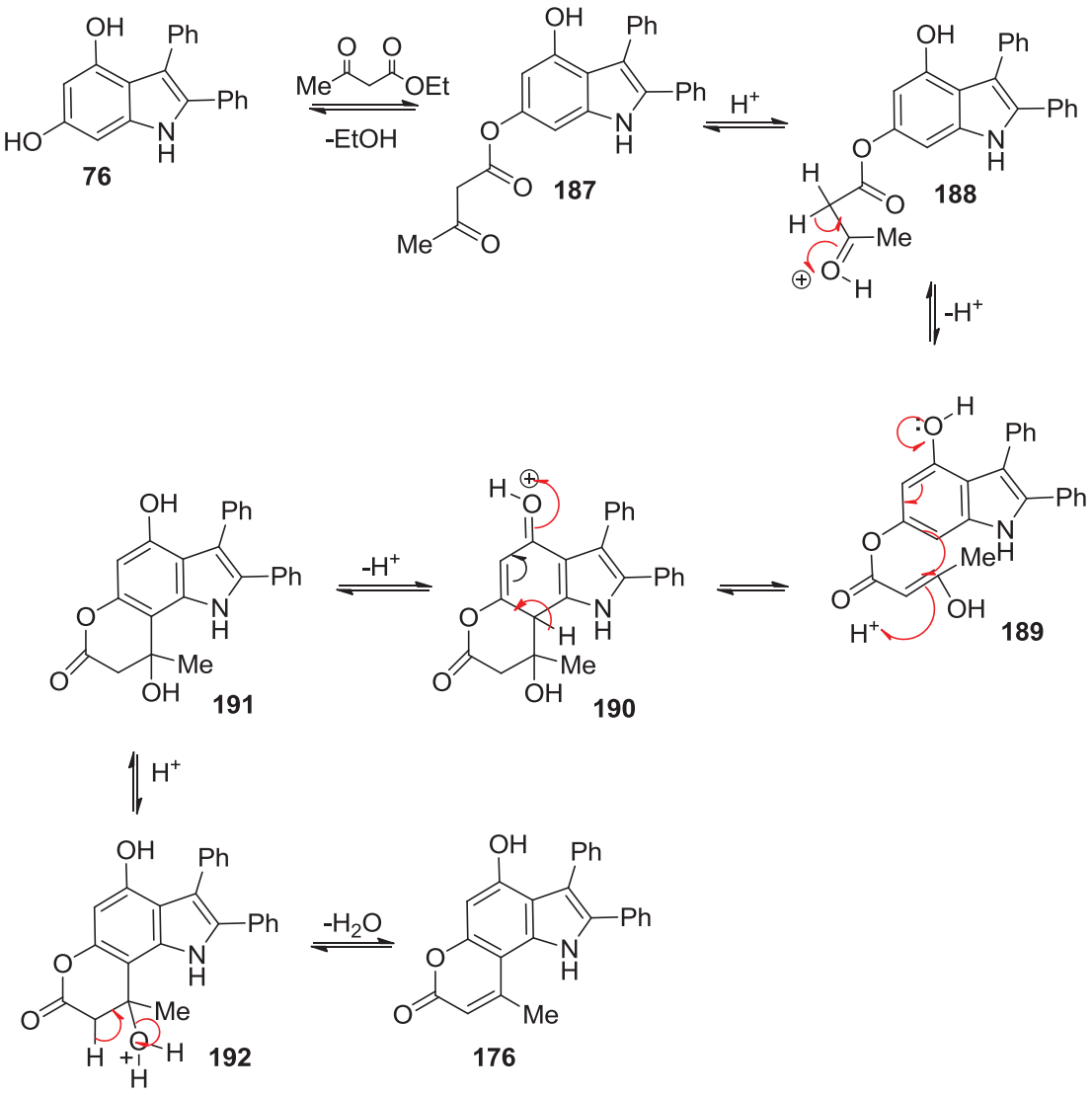
The yield and the nature of the R_1, R_2 and R_3 substituents are depicted in Table 2-1

Table 2-1: Yield and the nature of the R_1, R_2 and R_3 substituents.

Product	R_1	R_2	R_3	Yields (%)
176	C_6H_5	C_6H_5	Me	60
179	C_6H_5	C_6H_5	CF_3	71
180	C_6H_5	C_6H_5	C_6H_5	60
181	4-BrC_6H_4	H	Me	60
182	4-BrC_6H_4	H	CF_3	73
183	4-BrC_6H_4	H	C_6H_5	68
184	4-ClC_6H_4	H	Me	62
185	4-ClC_6H_4	H	CF_3	72
186	4-ClC_6H_4	H	C_6H_5	62

2.2.2.1 Reaction mechanism:

The synthesis of these pyranoindoles, based on the von Pechmann condensation, can be described according to the following mechanism (Scheme 2-23).



Scheme 2-23

The reaction presumably involves the esterification of the C6-OH group to give the acetoacetate ester **187**, which upon acid-catalysed tautomerism leads to the enol **189**. A Michael addition leads to cyclisation and the formation of the coumarin skeleton **191**. Rearomatisation and subsequent acid-induced elimination of water gives the pyrano[2,3-*g*]indole **176**. One of the possible reasons for the selectivity is that C7 is generally more reactive than C5, as evidenced from extensive studies of 4,6-dimethoxyindoles.[26,92] This would be due to the steric buttressing of the 4-hydroxy moiety by the 3-aryl group.

2.2.3 Biological Screening:

2.2.3.1 Anti-cancer screening:

Selected pyranoindoles (**180** and **185**) synthesized in this project were tested against a range of cancer cell lines in an *in vitro* assay. The cancer cell lines used include hepatocarcinoma, small cell lung cancer, large cell lung carcinoma and colorectal cancer. The MTT anti-proliferation assay was used to assess the efficiency of the pyranoindoles to inhibit cell proliferation. The anti-proliferative activity of the pyranoindoles was assessed by determining the concentration that inhibits cellular proliferation by 50% (IC_{50}). The IC_{50} values were determined for each cell line.

Table 2-2 IC_{50} values of pyranoindoles in various cell lines.

Indication		IC_{50} value (μM)	
		180	**185**
Liver	**JHH-1**	22.08	25.09
Lung	**NCI-H2126**	9.97	3.71
Lung	**NCI-H838**	45.68	7.03
Colorectal	**SW620**	16.59	7.06

Cells were seeded in well plates at an appropriate cell density as determined from growth kinetics analysis and cultured for 5 days in the absence and presence of the test compounds. Cell proliferation was assessed after the addition of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) for 3-4 h at 37 °C. This cytotoxicity data establishes the foundation of a preliminary structure-activity relationship analysis and may provide a basis for the further development of pyranoindoles with more potent biological activities (Table 2-2).

2.2.3.2 Anti-microbial screening

In this screening, the compounds were tested against indicator strains (test organisms) such as *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and *Malassezia furfur*. The assay media (nutrient broth with agar medium 13.0 g/L for bacterial strains and malt extract agar medium 25.0 g/L for fungal strains and pH 7.0) were utilized for the test organisms. The test organisms were inoculated in 10 mL assay broth in 50 mL falcon tubes at 30 ºC for bacteria and at 37 ºC for fungi, respectively and incubated overnight. 100 µL of test organisms was added in each assay plate and spread on the agar plates. Paper discs impregnated with samples were applied on the test plates and the plates were incubated for 24-36 h at 30 °C for bacteria and 37 °C for fungi. Clear zone (inhibitory zone) surrounding the test disc indicates the presence of bioactive compound, which inhibits the growth of the test organism selectively.

Disc size: 6.0 mm (width), volume: 20 µL / disc (c = 1.0 mg/mL)

Clear zone (inhibitory zone): * = + - 11 mm (weak activity)

** = 12 - 16 mm (high activity)

*** = 17 - >20 mm (very high activity)

Pyranoindoles were tested for their anti-microbial activity. According to the results, compounds **180**, **184** and **186** showed high activity against the fungal test organism *M. furfur*. However, these compounds did not show any activity against *E. coli* and *C. albicans* in 20 µL/mL (MIC) *in vitro* (Table 2-3).

Table 2-3 IC_{50} values of pyranoindoles.

Compound	*E. coli*	*S. aureus*	*C. albicans*	*M. furfur*
180	-	-	-	**
184	-	-	-	**
186	-	-	-	**
Control ($CHCl_3$)				*

(Clear zone (inhibitory zone): * = + - 11 mm (weak activity)

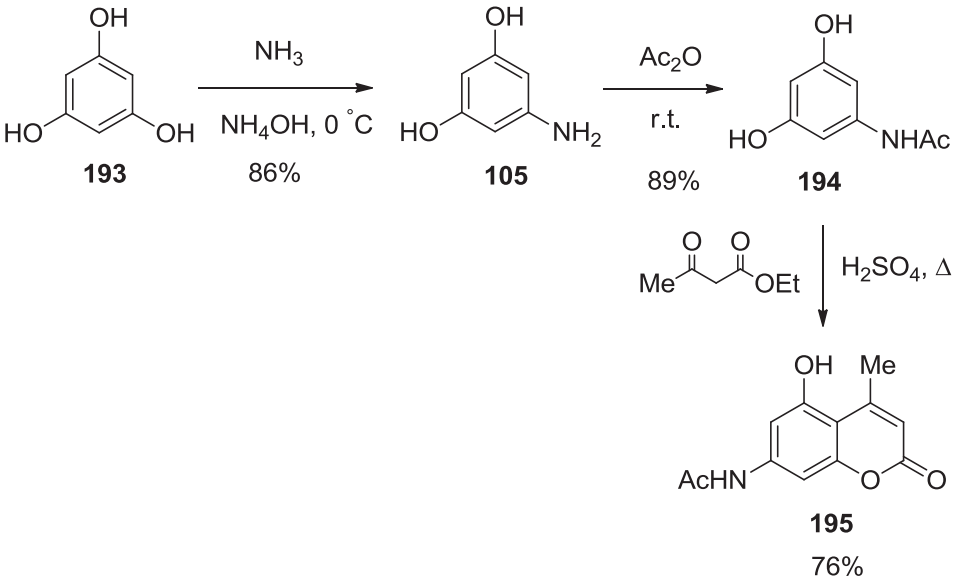
Clear zone (inhibitory zone): ** = 12 - 16 mm (high activity))

2.3 Synthesis of pyrano[2,3-*g*]indoles from phloroglucinol:

2.3.1 Synthesis of *N*-(5-hydroxy-4-methyl-2-oxo-2*H*-chromen-7-yl) acetamide:

An alternative route to pyrano[2,3-*g*]indoles was the synthesis of the aminobenzopyranone nucleus followed by construction of the indole moity.

Therefore, phloroglucinol **193** was reacted with liquid ammonia and ammonium hydroxide to give 5-aminoresorcinol **105** in 86% yield. Reaction of **105** with acetic anhydride gave *N*-(3,5-dihydroxyphenyl) acetamide **194** in 89% yield. The reaction of **194** with ethyl acetoacetate in the presence of sulfuric acid gave *N*-(5-hydroxy-4-methyl-2-oxo-2*H*-chromen-7-yl) acetamide **195** in 72% yield (Scheme 2-24).



Scheme 2-24

The ^{1}H NMR spectrum of compound 195 in DMSO-d_6 showed the presence of a singlet at δ 2.07 ppm corresponding to the COMe protons, and a singlet at δ 2.49 ppm due to the C=C-CH_3 protons, while H3 appeared as a singlet at δ 5.94 ppm, H6 appeared as a doublet at δ 7.00 ppm, and H8 appeared as a singlet at δ 7.16 ppm. The hydroxyl proton appeared as a sharp singlet at δ 10.16 ppm and the NH proton appeared as a broad singlet at δ 10.64 ppm (Figure 2-5).

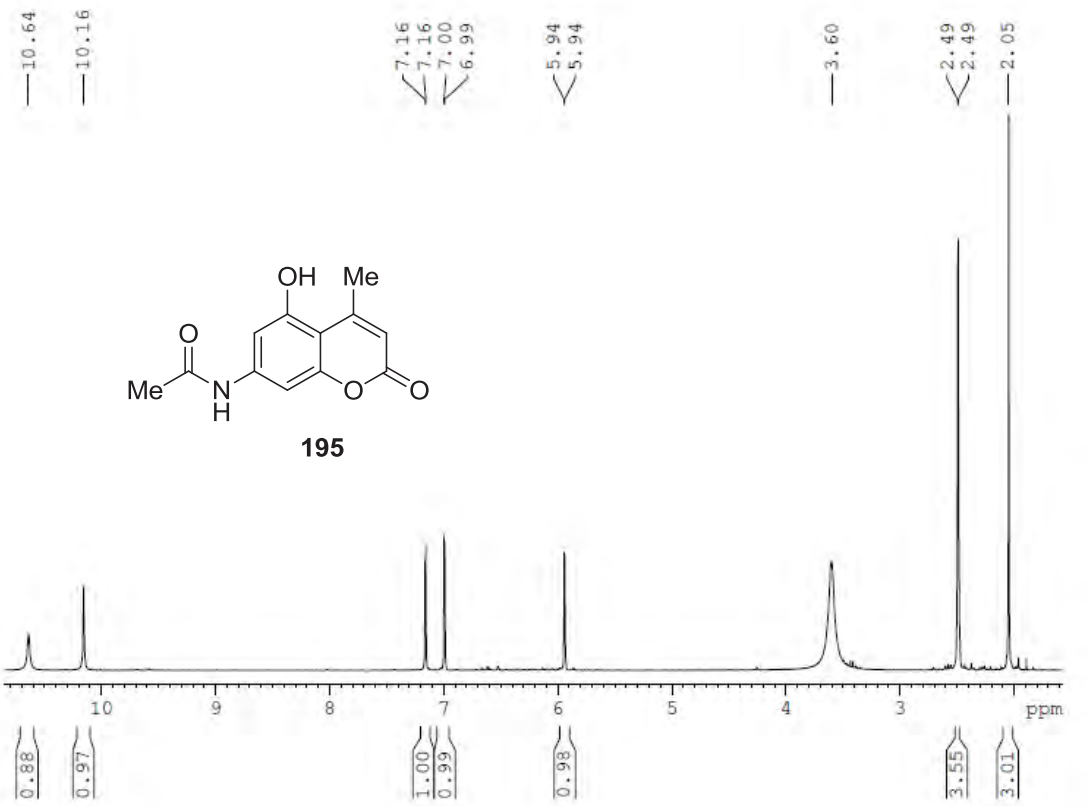
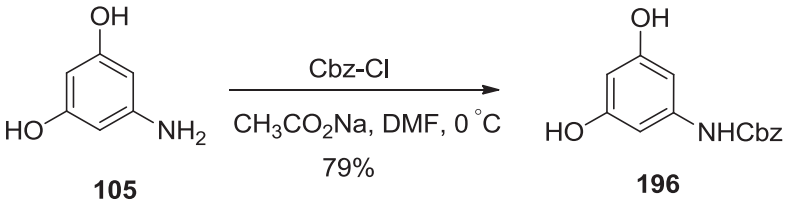


Figure 2-5 ^{1}H NMR spectrum of **195** in DMSO-d_6

The DEPT 135 ^{13}C NMR spectrum showed the presence of five positive peaks. The peaks at δ 23.75 and 24.60 ppm were assigned as CH_3 and CO<u>Me</u> carbons respectively, and three CH peaks at δ 97.57, 101.82 and 111.07 ppm. The ESI^+ mass spectrum also showed a molecular ion peak at *m*/*z* 234.0761, which further supports the formation of the product.

The next step in this approach was the generation of the free amine. However, the attempted removal of the acetoxy group with KOH was futile. This could be because the coumarin system is known to undergo hydrolysis under strong basic conditions.[93-94] Therefore, the acetoxy protected compound was not pursued further.

In another approach, the Cbz was chosen as a protecting group for the primary amine. 5-Aminoresorcinol **105**, upon reaction with Cbz chloride in the presence of sodium acetate, gave the *N*-Cbz protected aminoresorcinol **196** in 79% yield (Scheme 2-25).



Scheme 2-25

The ^{1}H NMR spectrum of compound **196** in DMSO-d_6 showed the presence of a singlet at δ 5.13 ppm corresponding to the CH_2 protons. One *N*-substituted resorcinol aromatic proton appeared as a triplet at δ 6.43 ppm, while the two appeared as a doublet at δ 5.85 ppm. The phenyl ring protons appeared as a multiplet at δ 7.43 ppm, the carbamate NH proton as a broad singlet at δ 9.71 ppm, and the OH protons appeared as a singlet at δ 9.47 ppm (Figure 2-6).

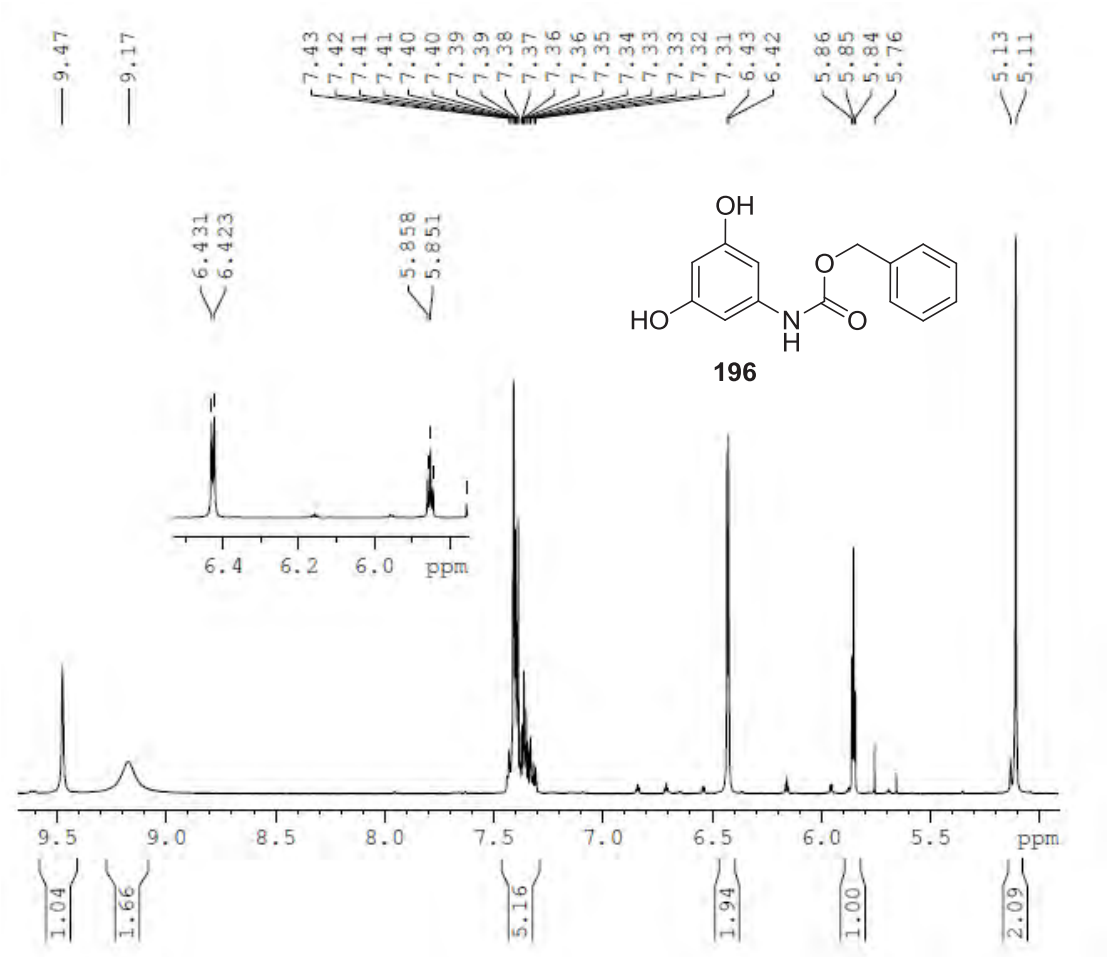
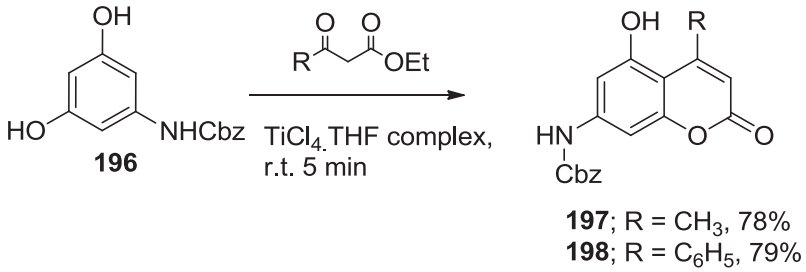


Figure 2-6 ^{1}H NMR spectrum of **196** in DMSO-d_6

2.3.2 Synthesis of *N*-Cbz protected coumarin:

N-Cbz protected resorcinol **196** was reacted with ethyl acetoacetate under the von Pechmann conditions using sulfuric acid as a catalyst. However, no reaction occurred as indicated by TLC analysis and the starting material was recovered from the reaction mixture. The case of another Lewis acid such as $BF_3.OEt_2$ or aluminium chloride was also unsuccessful. However, the $TiCl_4$.THF complex was found to be a good catalyst for this reaction and gave a clean product. The reaction completed within 5 min, and the addition of water gave a precipitate which was sufficiently clean for use in the next step without further purification (Scheme 2-26). The coumarins **197-198** were thus obtained in 78-79% yield.



Scheme 2-26

The ^{1}H NMR spectrum of compound **198** in DMSO-d_6 showed the presence of additional five protons at δ 7.33-7.46 ppm along with the coumarine ring protons (Figure 2-7). The presence of the CH_2 moiety was confirmed by a negative peak at δ 66.53 ppm in the DEPT 135 ^{13}C NMR spectrum.

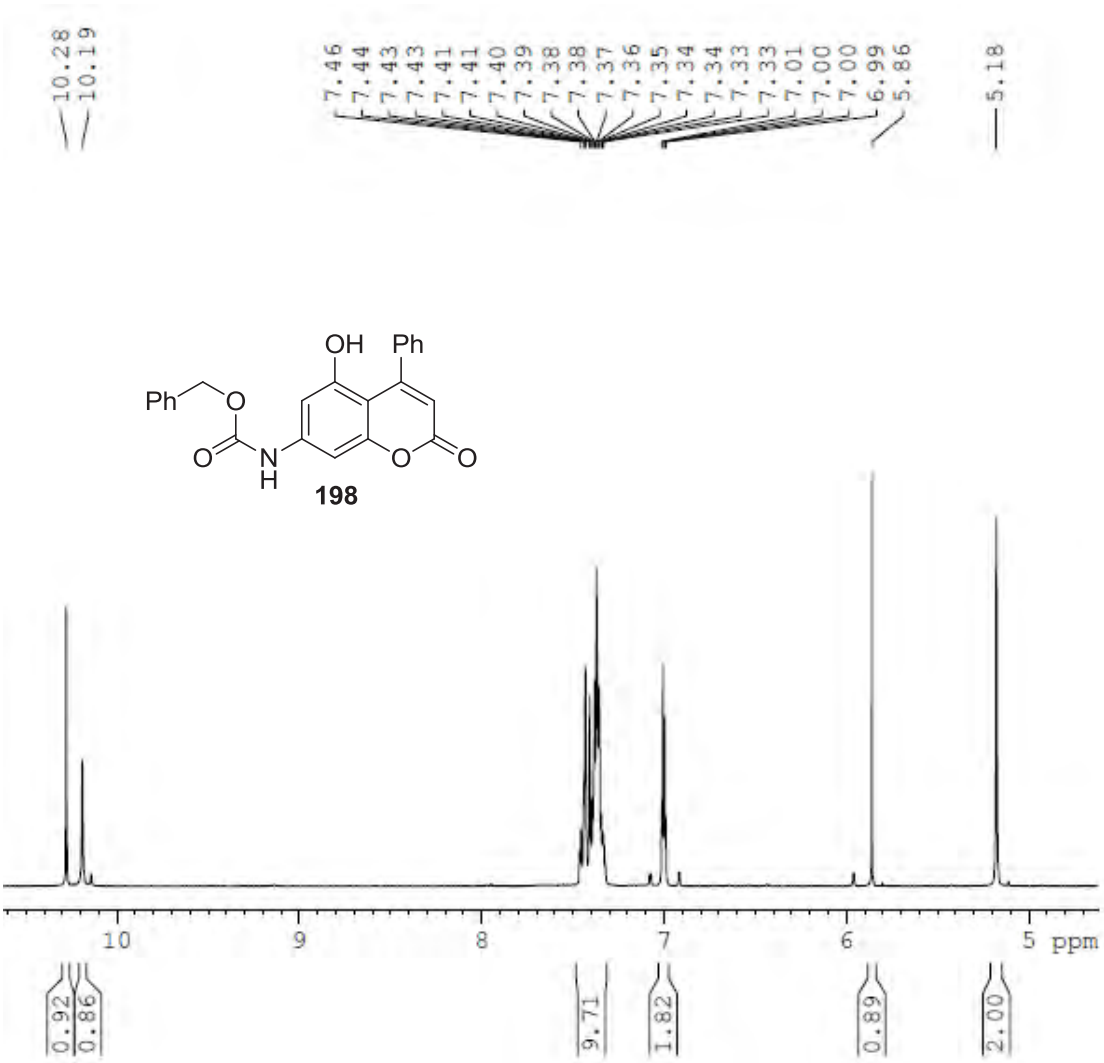
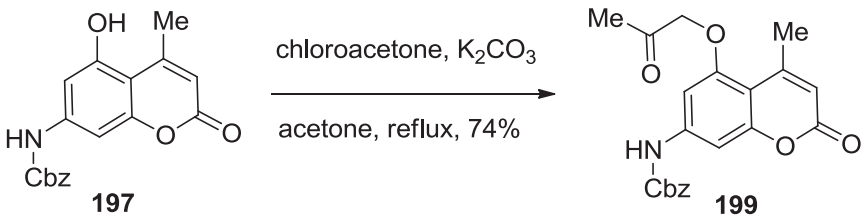


Figure 2-7 ^{1}H NMR spectrum of **198** in DMSO-d_6

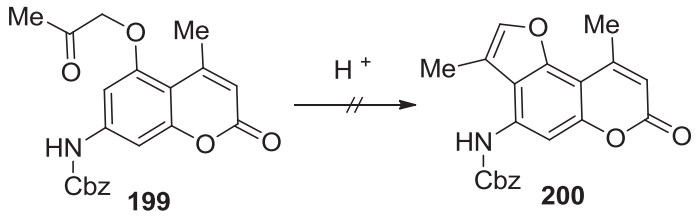
Cbz-protected aminocoumarin **197** was reacted with chloroacetone in the presence of K_2CO_3 to give the intermediate **199** in 78% yield (Scheme 2-27).



Scheme 2-27

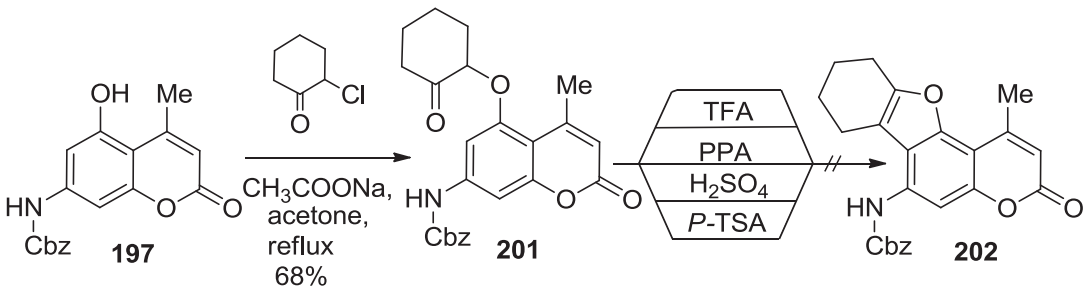
The ^{1}H NMR spectrum of compound **199** in DMSO-d_6 showed the presence of a singlet at δ 2.16 ppm due to the COMe protons, singlets at δ 2.55 and 4.87 ppm were due to C=C-CH_3 and CH_2 protons respectively. Another CH_2 appeared as a singlet at δ 5.16 ppm. The H3 appeared as a singlet at δ 6.04 ppm, while H6 and H8 appeared as doublets at δ 6.90 and 7.09 ppm (J = 3.0 Hz) respectively. The multiplet at δ 7.33-7.43 ppm assigned to the phenyl ring protons. The carbamate NH proton appeared as a singlet at δ 10.17 ppm.

However, all attempts to cyclise this intermediate **199** were proved to be unsuccessful. Only starting material was recovered from the reaction mixture (Scheme 2-28).



Scheme 2-28

Cbz-protected aminocoumarin **197** was reacted with 2-chlorocyclohexanone in the presence of sodium acetate to give the intermediate **201** in 68% yield (Scheme 2-29).

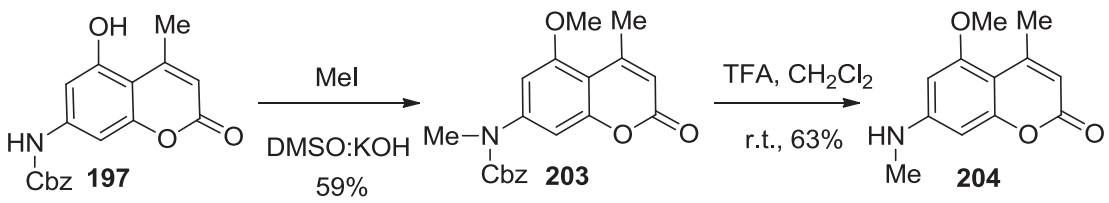


Scheme 2-29

The ^{1}H NMR spectrum of compound **201** in DMSO-d_6 showed the presence of a multiplet at δ 1.83-2.50 ppm due to the CH_2 protons from the cyclohexanone moiety, and a peak at δ 5.15 ppm corresponding to the CH_2 protons. The H3 appeared as a singlet at δ 6.02 ppm, while H6 and H8 appeared as doublet at δ 6.79 and 7.10 ppm (J = 3.0 Hz) respectively. The multiplet at δ 7.32-7.42 ppm was assigned to the phenyl ring protons. The carbamate NH proton appeared as a singlet at δ 10.07 ppm. Compound **201** also exhibited a molecular ion peak at m/z 382.1284 in the ESI$^+$ mass spectrum, which matched with the expected compound.

However, attempts to cyclise **201** with trifluoroacetic acid, polyphosphoric acid, sulfuric acid or *p*-toluenesulfonic acid were unsuccessful. The sole starting material was recovered from the reaction mixture (Scheme 2-29).

In order to exploit the chemistry of the amino substituted coumarins, the deprotection of the Cbz group was crucial. Therefore, removal of the Cbz group was attempted using various methods reported in the literature. In order to facilitate the deprotection of Cbz, an *N*-methylation strategy was adopted, in which coumarin **197** was reacted with iodomethane in the presence of K_2CO_3 in acetone at room temperature to give the methoxy coumarin **203** in 59% yield. Under these conditions, both the phenolic and the amide NH were methylated, as evidenced by the ^{1}H NMR spectrum. Subsequent deprotection using trifluoroacetic acid in dichloromethane at room temperature gave the *N*-methylcoumarin derivative **204** in 63% yield (Scheme 2-30).



Scheme 2-30

The ^{1}H NMR spectrum of compound **204** in DMSO-d_6 revealed the presence of a singlet at δ 2.39 ppm corresponding to the CH_3 protons, and a doublet at δ 2.73 ppm (J = 6.0 Hz) for the CH_3 protons. A singlet at δ 3.77 ppm assigned to the methoxy protons while a singlet at δ 5.67 ppm was assigned to H3. The NMR spectrum also showed the presence of two doublets at δ 5.98 and 6.07 ppm (J = 3.0 Hz) due to H6 and H8, respectively. The NH proton appeared as a quartet at δ 6.62 ppm (Figure 2-8). The IR spectrum showed a strong peak at 3335 cm^{-1} for the NH group. The ESI^{+} mass spectrum showed a molecular ion peak at m/z 220.0966, which matched the anticipated structure.

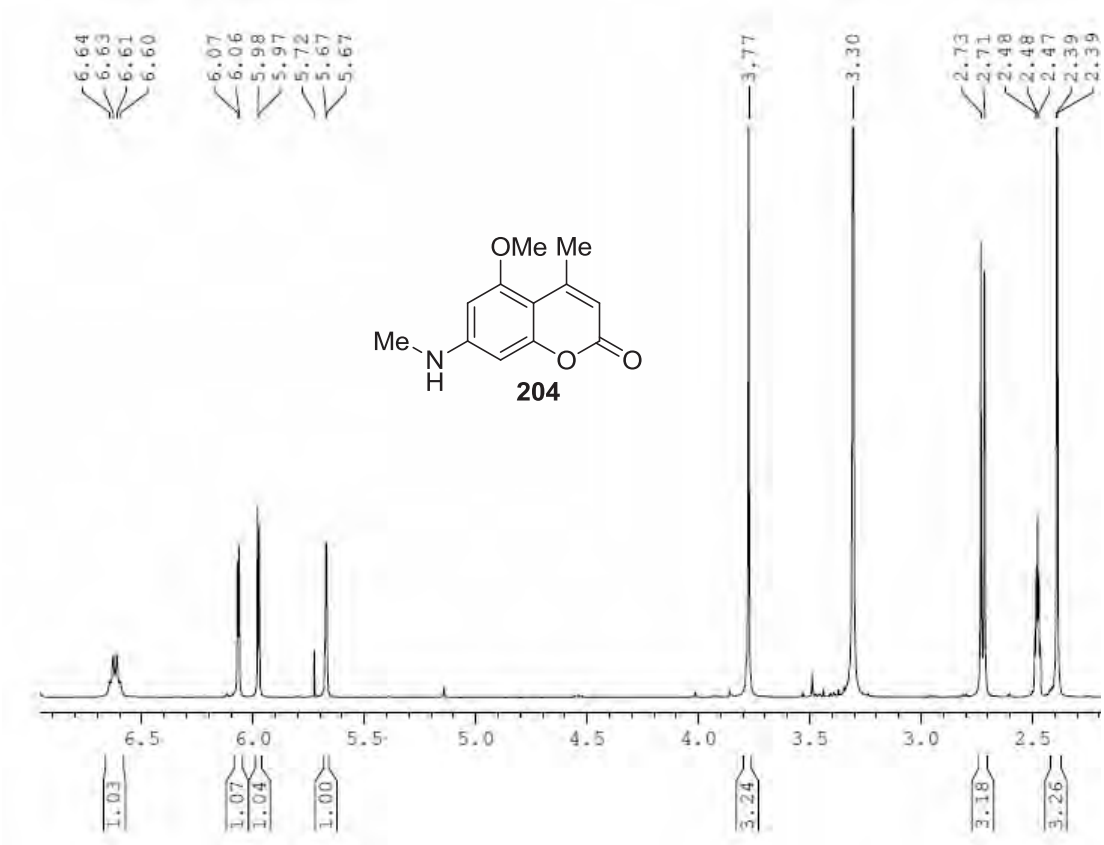
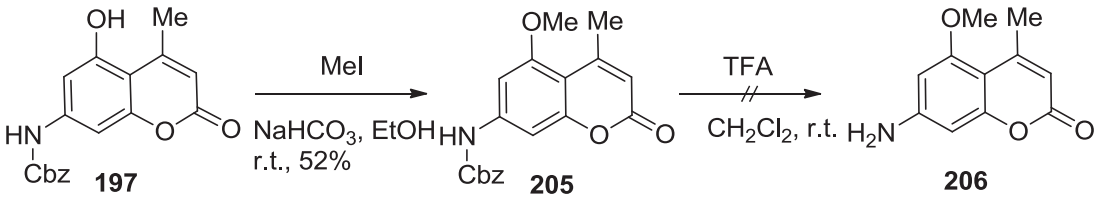


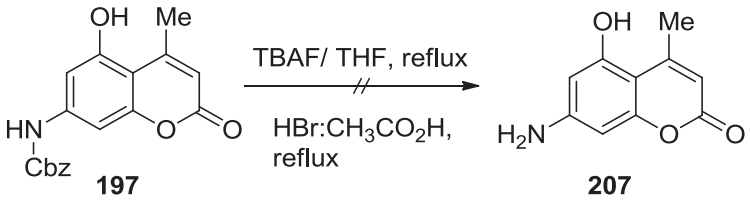
Figure 2-8 ^{1}H NMR spectrum of compound **204** in DMSO-d_6

Interestingly, attempted *N*-methylation of coumarin **197**, using $NaHCO_3$ in place of KOH, gave the compound **205** in 52% yield. However, the deprotection of the Cbz group by trifluoroacetic acid was unsuccessful (Scheme 2-31).



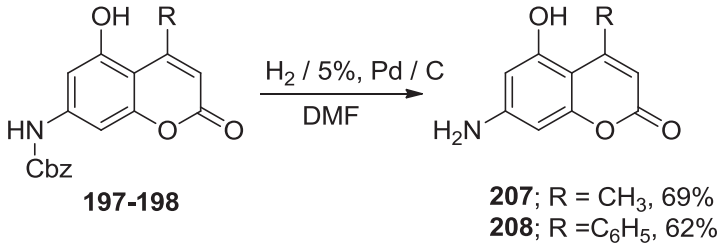
Scheme 2-31

Attempted removal of the Cbz group **197** using tetrabutylammonium fluoride in tetrahydrofuran[95] or HBr in acetic acid[96] was also unsuccessful. The starting material was recovered from the reaction mixture (Scheme 2-32).



Scheme 2-32

Despite various attempts, removal of the Cbz group from coumarin was only successful in the case of methylated coumarin **203** only. Ultimately, deprotection of the Cbz coumarins **197-198** was achieved by hydrogenation using 5% palladium on carbon in *N*,*N*-dimethylformamide in 62-69% yield (Scheme 2-33).



Scheme 2-33

The ^{1}H NMR spectrum of compound **208** in DMSO-d_6 revealed the presence of a singlet at δ 5.46 ppm for H3. The two doublets at δ 5.96 and 6.05 ppm (J = 3.0 Hz) were assigned to H6 and H8 respectively. The NH_2 protons appeared as a broad peak at δ 5.45 ppm (Figure 2-9).

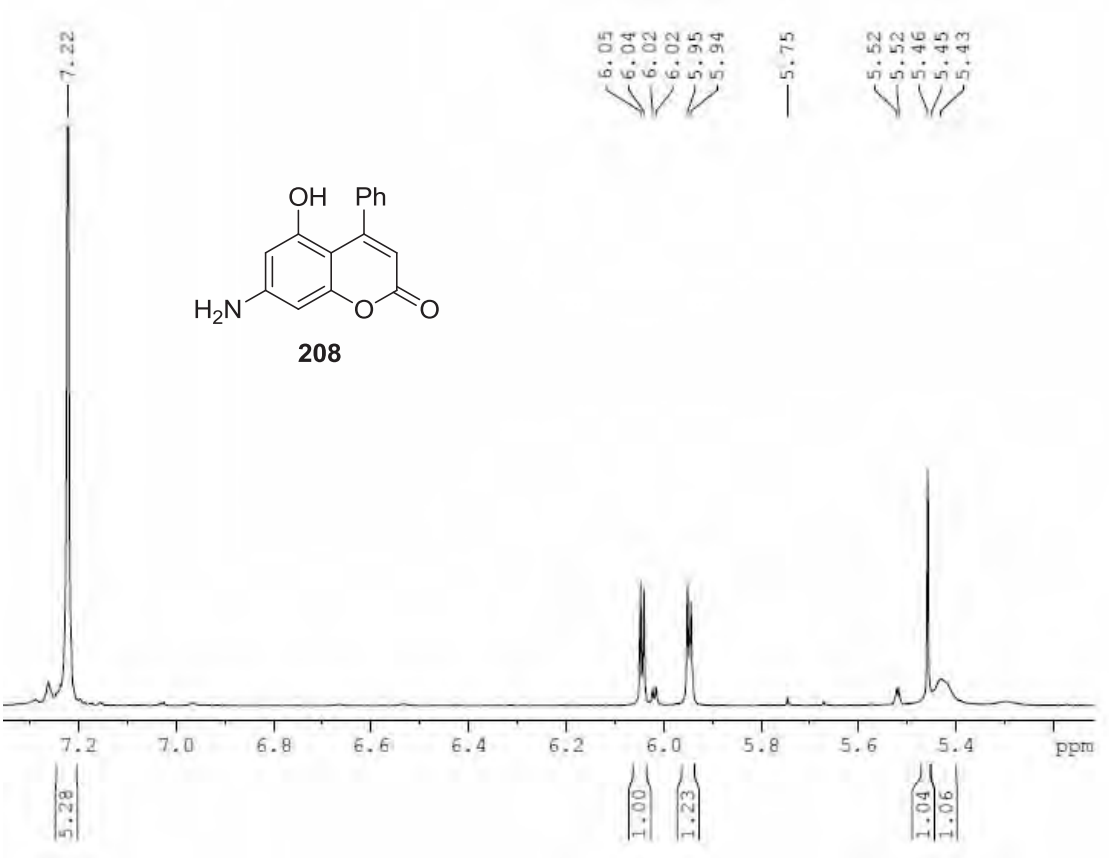
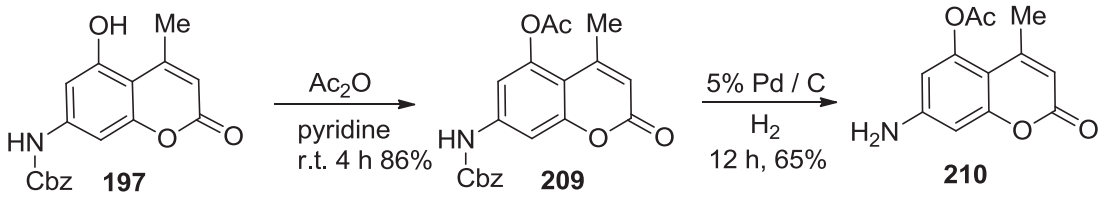


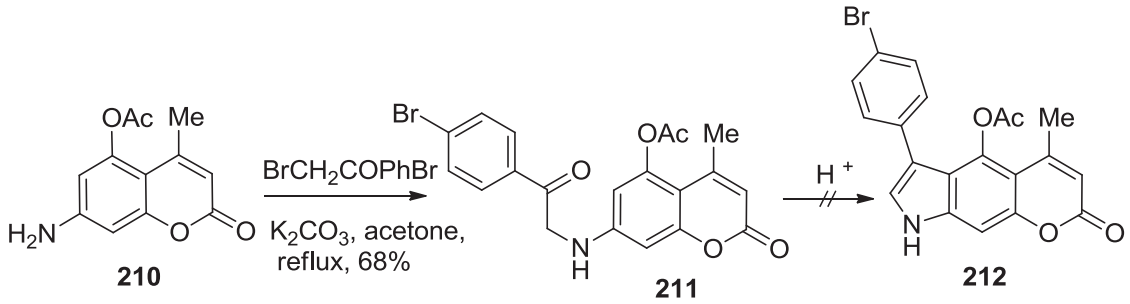
Figure 2-9 ^{1}H NMR spectrum of **208** in DMSO-d_6

It was initially thought that the free hydroxy group from **207** and **208** might interfere with the reactions at the amino group. For this reason, the hydroxy group in compound **197** was protected as an acetoxy group using acetic anhydride in pyridine at room temperature to give **209** in 86% yield. The deprotection of the Cbz group of **209** was achieved by standard hydrogenolysis with 5% palladium on carbon in *N*,*N*-dimethylformamide to give **210** in 65% (Scheme 2-34).



Scheme 2-34

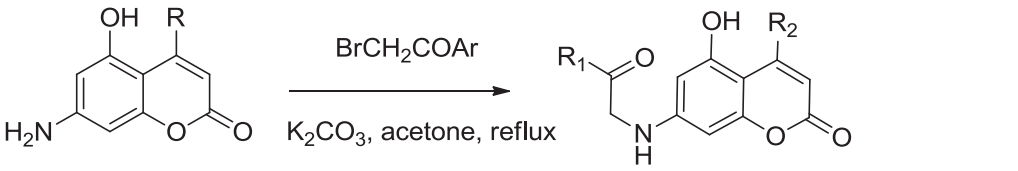
Acetoxy-protected aminocoumarin **210** was reacted with an α-haloketone in the presence of K_2CO_3 in acetone at reflux to give intermediate **211** in 68% yield. However, this intermediate failed to cyclise under a variety of acidic conditions. Only starting material could be recovered from the reaction mixture (Scheme 2-35).



Scheme 2-35

We thus turned to investigate the reactivity of unprotected aminocoumarins **207**-**208**, especially to construct fused heterocycles. Coumarins **207**-**208** were reacted with an α-

haloketones in the presence of potassium carbonate in refluxing acetone to give anilinoketone intermediates **213-216** in 69-77% yield (Scheme 2-36).



207; R = CH_3
208; R = C_6H_5

213; R_1 = 4-ClC_6H_4, R_2 = CH_3, 77%
214; R_1 = 4-BrC_6H_4, R_2 = CH_3, 73%
215; R_1 = 4-ClC_6H_4, R_2 = C_6H_5, 69%
216; R_1 = 4-$MeOC_6H_4$, R_2 = C_6H_5, 77%

Scheme 2-36

The ^{1}H NMR spectrum of compound **216** in DMSO-d_6 revealed the presence of a singlet at δ 3.82 ppm due to the methoxy group while the CH_2 proton appeared as a singlet at δ 4.92 ppm. A singlet at δ 5.46 ppm corresponded to H3. The presence of two doublets at δ 5.86 and 6.13 ppm (J = 3.0 Hz) confirmed the presence of H6 and H8, respectively. The NH and OH protons appeared as a broad peak at δ 6.18 ppm (Figure 2-10). The DEPT 135 ^{13}C NMR spectrum revealed the presence of CH_2 as a negative peak at δ 70.56 ppm. The methoxy carbon peak appeared at δ 56.00 ppm, while protonated carbons from the coumarin ring appeared at δ 93.33, 94.85 and 108.40 ppm.

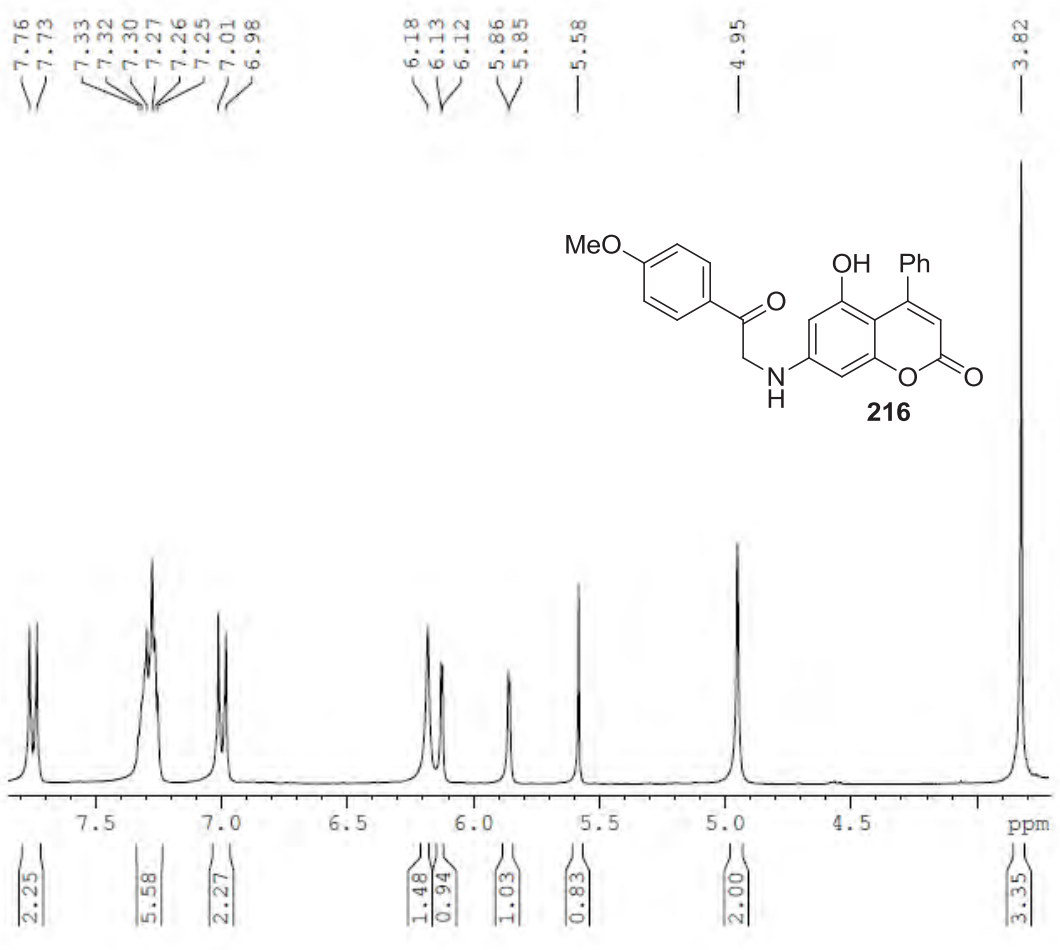
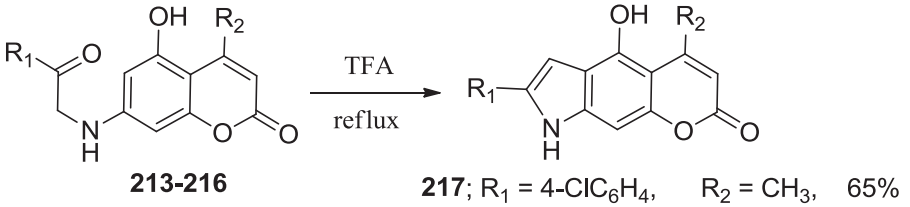


Figure 2-10 ^{1}H NMR spectrum of compound **216** in DMSO-d_6

Cyclisation of intermediate **216** using sulfuric acid or polyphosphoric acid gave multiple spots on the TLC; therefore, milder cyclisation using trifluoroacetic acid was attempted. These conditions gave the pyranoindoles **217-220** in 62-65% yield (Scheme 2-37).



217; R_1 = 4-ClC_6H_4, R_2 = CH_3, 65%
218; R_1 = 4-BrC_6H_4, R_2 = CH_3, 64%
219; R_1 = 4-ClC_6H_4, R_2 = C_6H_5, 62%
220; R_1 = 4-$MeOC_6H_4$, R_2 = C_6H_5, 64%

Scheme 2-37

The ^{1}H NMR spectrum of compound **220** in $CDCl_3$ revealed the presence of a singlet at δ 3.81 ppm corresponding to the methoxy protons. A singlet at δ 6.28 ppm was assigned to H3, and the multiplet at δ 6.96-6.99 ppm was assigned to H6 and H8. The NH proton appeared as a broad singlet at δ 8.39 ppm and the OH proton appeared as a sharp singlet at δ 6.30 ppm. The disappearance of the CH_2 proton signal at δ 4.92 ppm indicated that the cyclisation of **216** to pyrano[2,3-*f*]indole **220** had occurred (Figure 2-11).

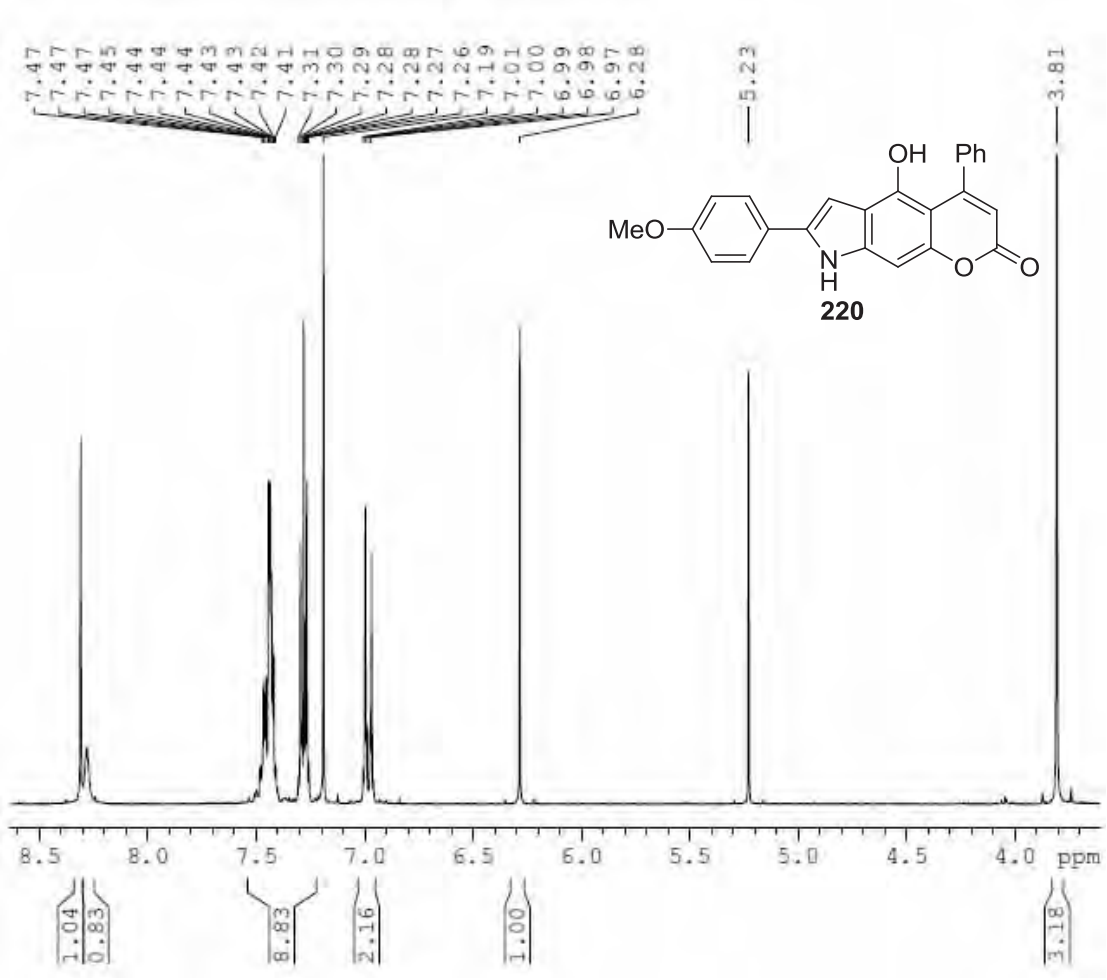
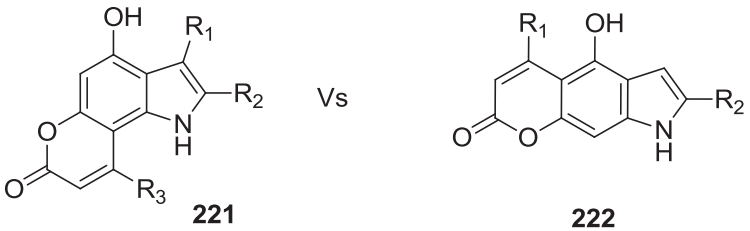


Figure 2-11 ^{1}H NMR spectrum of compound **220** in $CDCl_3$

It is noteworthy that when the synthesis started from 4,6-hydroxyindole the final product obtained was a pyrano[2,3-*g*]indole. However, the route from phloroglucinol *via* coumarin was employed, gave instead the pyrano[2,3-*f*]indoles in good yields.

The general structures of the pyranoindoles synthesized using the two different methodologies, which gave different ring fused systems, are represented in Figure 2-12.

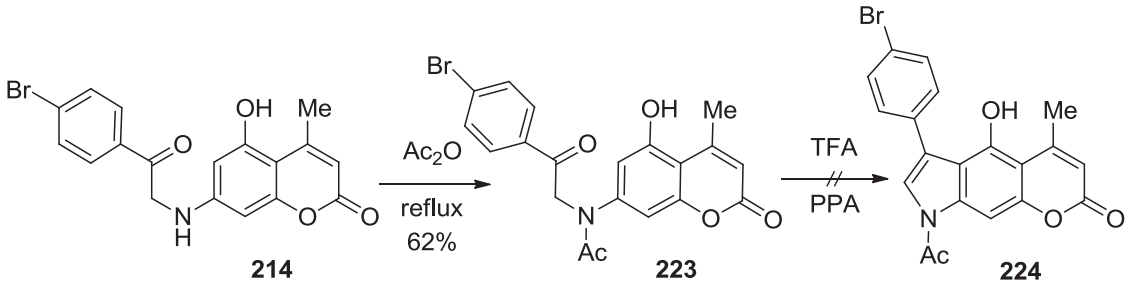


221 pyrano[2,3-*g*]indole

222 pyrano[2,3-*f*]indole

Figure 2-12 Pyranoindoles **221** and **222** synthesized from 4,6-dihydroxyindole phloroglucinol respectively.

In Bischler indole synthesis when NH of anilinoketone is protected it gives 3-substituted indoles.[84] Therefore, after achieving success in the synthesis of a series of 7-arylpyrano[3,2-*f*]indol-2(8*H*)-one, we attempted an alternative cyclisation of **214** to 6-arylpyrano[3,2-*f*]indol-2(8*H*)-one in which indole has a substituent at C3. In this methodology, the anilinoketone **214** was first acetylated using acetic anhydride to give **223** in 62% yield. However, attempted cyclisation of **223** with trifluoroacetic acid or polyphosphoric acid failed to give the expected 6-arylpyrano[3,2-*f*]indol-2(8*H*)-one. Only starting material was recovered from the reaction mixture (Scheme 2-38).


Br
OH
Me
O
N
H
O
O
214
Ac2O
reflux
62%
Br
OH
Me
O
N
Ac
O
O
223
TFA
PPA
Br
OH
Me
N
Ac
O
O
224

Scheme 2-38

2.4 Conclusion:

Novel pyranoindoles were prepared by the von Pechmann condensation of 4,6-dihydroxyindoles and β-ketoesters. In these pyranoindoles, the fusion of indole with pyran was of the [2,3-*g*] type, which has not yet been reported in compounds either from synthetic or natural origin. These novel compounds showed interesting biological activity and were found to possess significant anti-cancer, anti-fungal and anti-bacterial activity in preliminary biological screening.

The chemistry of aminocoumarins to generate fused heterocycles was investigated. Starting with phloroglucinol, a range of pyrano[2,3-*f*]indoles were synthesised *via* the 7-aminocoumarins. Interestingly, with this method pyrano[2,3-*f*]indoles were obtained, while the other route starting from 4,6-dihydroxyindole gave pyrano[3,2-*g*]indoles.

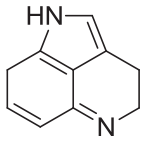
These results demonstrate that by a careful choice of reaction route, different pyranoindoles structures can be obtained.

CHAPTER 3

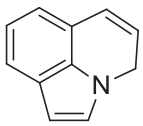
SYNTHESIS OF NOVEL PYRROLOQUINOLINES

3.1 Introduction:

Pyrroloquinolines are considered an important class of natural and synthetic heterocycles. These systems are of interest because, in some of the pyrroloquinolines, the lone pair of electrons on the nitrogen atom is distributed between the quinoline and pyrrole. They are reported for their various biological properties such as anti-viral,[97] neuroprotective,[98] anti-HIV,[99] and immunosuppressant.[100] The different fusions of quinoline and pyrrole that have been reported can be divided into three types. Type-I pyrroloquinolines, consists of the fusion of the pyrrole moiety with both the phenyl as well as pyridine ring of quinoline *e.g.* **225-226**.

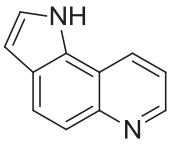


225

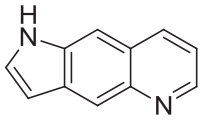


226

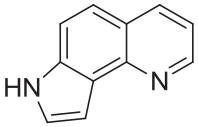
In type-II pyrroloquinolines, the pyrrole moiety is fused with the benzene ring of quinoline, such as **227-229**.



227

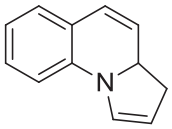


228



229

In type-III pyrroloquinolines, the pyrrole moiety is fused with the pyridine ring of quinoline *e.g*. **230-232**.



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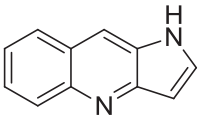
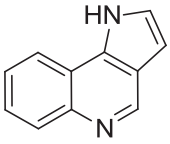


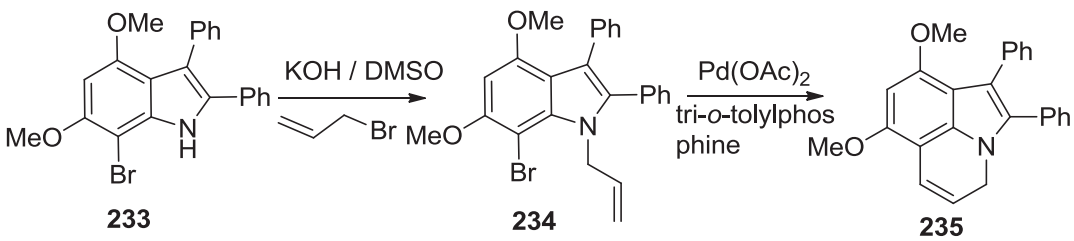
231



232

Type-I fusion:

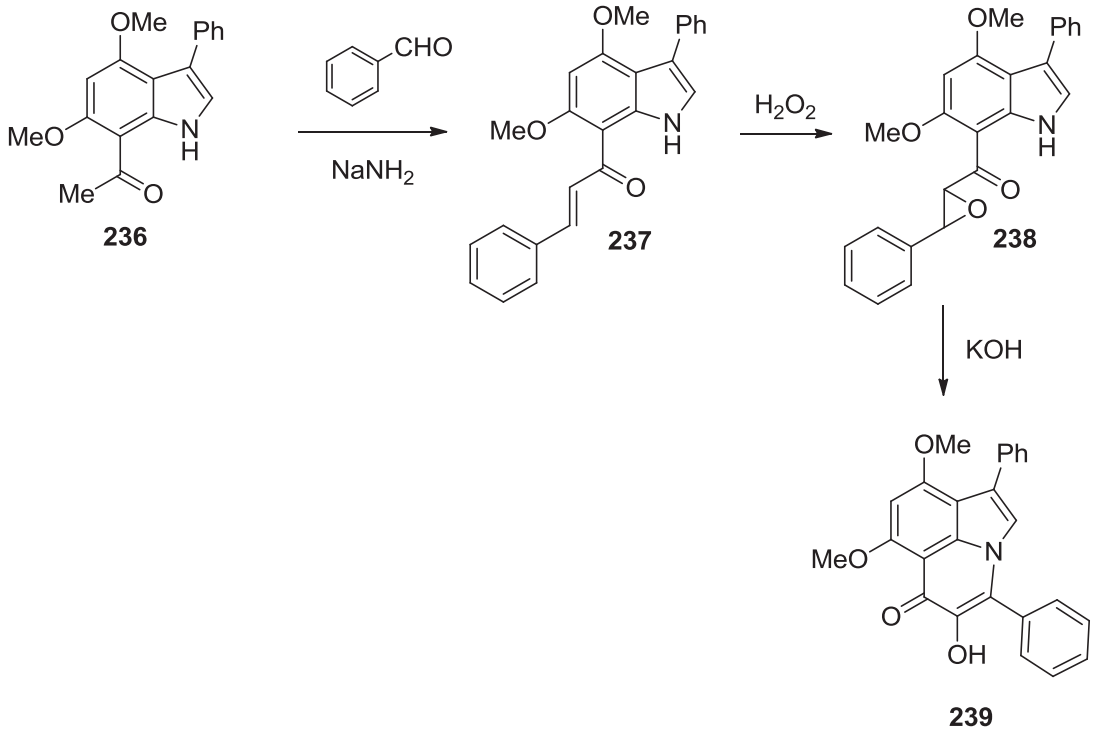
The heterocycles containing this type of fusion have been reported to posses various biological activities *e.g.* Stanton *et al.*[101] have reported the anticonvulsant activity of pyrroloquinolines. Black *et al.*[102] have reported the synthesis of pyrroloquinoline **235** from 7-bromoindole **233**, which was reacted with allyl bromide in the presence of potassium hydroxide to give an intermediate **234**. This intermediate was cyclised using Pd(II)acetate and tri-*o*-tolylphosphine to give pyrroloquinoline **235** (Scheme 3-1).



233 **234** **235**

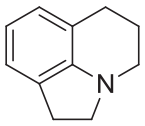
Scheme 3-1

In another study the synthesis of pyrroloquinoline **239** as an indole analogue of flavonol was reported.[29] 7-Acetyl-4,6-dimethoxy-3-phenylindole **236** was converted into 7-indolyl chalcone **237** by reaction with benzaldehyde under basic conditions. Oxidation of the chalcone **237** with alkaline hydrogen peroxide gave the epoxide **238**, which was cyclised to pyrroloquinoline **239** in the presence of potassium hydroxide (Scheme 3-2).



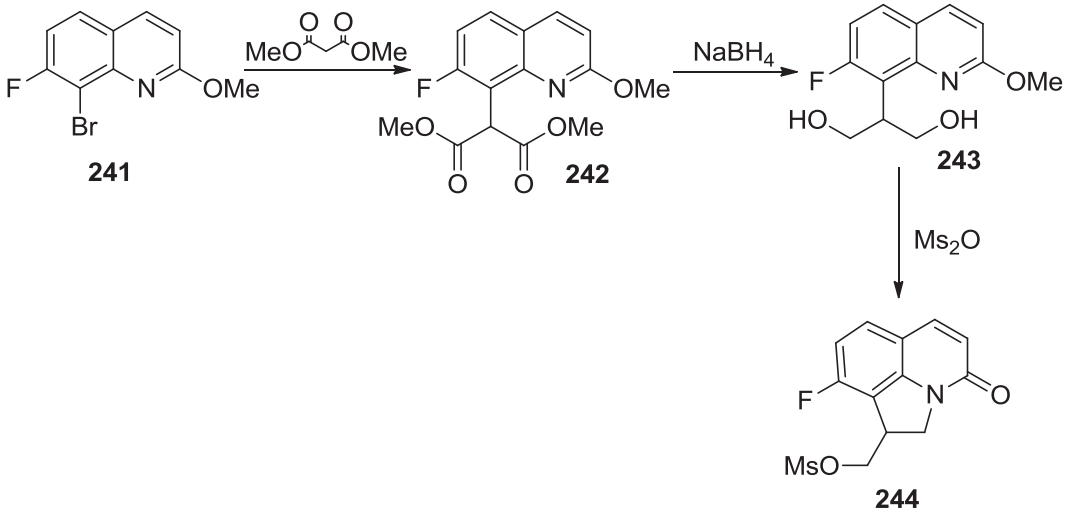
Scheme 3-2

The tricyclic skeleton, 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*] quinoline, appears as a basic structural moiety in alkaloid lilolidine **240**.[103-104]



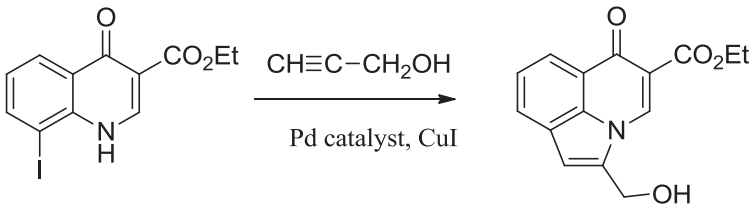
240

This moiety, in varying states of hydrogenation, is found in a large number of alkaloids such as strychnine, aspidospermine, galanthine, lycorine, pulvine, crinine and pyrifoline. Ballell-Pages *et al.*[105] recently reported the synthesis of pyrrolo[3,2,1-*ij*]quinoline **244**. Bromoquinoline **241**, was reacted with dimethyl malonate to give intermediate **242**, which upon reduction with sodium borohydride, gave diol **243**. Using methanesulfonic anhydride, **243** was cyclised to pyrrolo[3,2,1-*ij*]quinoline **244**, which was found to possess anti-tubercular activity (Scheme 3-3).



Scheme 3-3

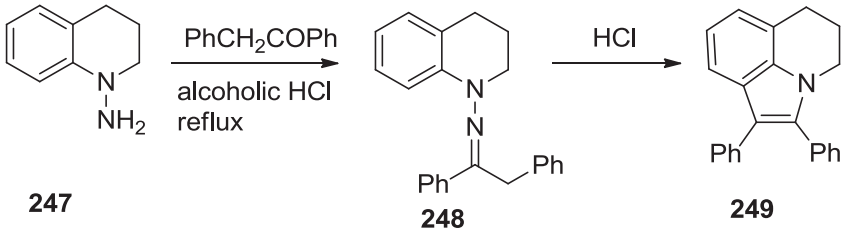
Layek *et al.*[106] have reported a method for preparing pyrroloquinoline **246** from iodoquinolone **245** by the reaction with propargyl alcohol in the presence of Pd catalyst and copper iodide (Scheme 3-4).



245 **246**

Scheme 3-4

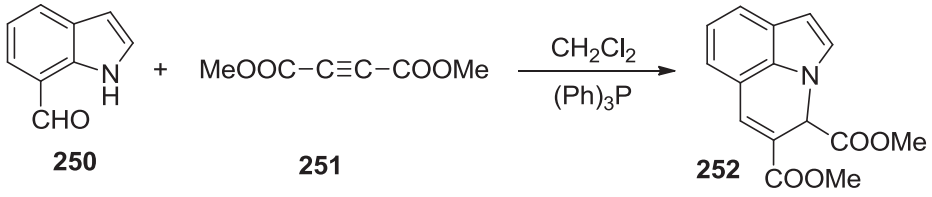
Steck *et al.*[107] have developed a method for preparing pyrroloquinoline **249** based on the Fischer indole synthesis. In this method, 1-aminoquinoline **247** was reacted with deoxybenzoin at reflux with alcoholic hydrochloric acid to give the intermediate **248**, which was cyclised with hydrochloric acid to give pyrroloquinoline **249** (Scheme 3-5).



247 **248** **249**

Scheme 3-5

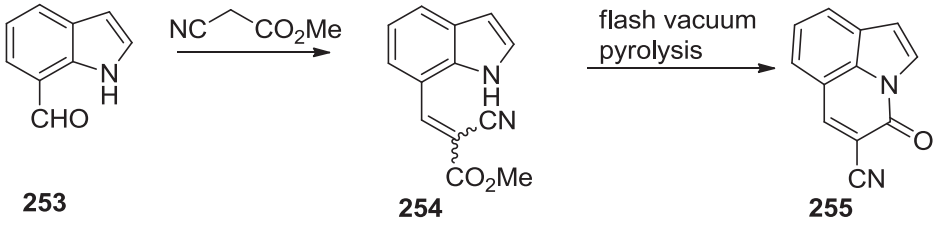
Adib *et al.*[108] have reported the synthesis of pyrroloquinoline **252** by reaction of indole-7-carbaldehyde **250** with dimethyl acetylenedicarboxylate **251** in the presence of triphenylphosphine (Scheme 3-6).



250 **251** **252**

Scheme 3-6

McNab *et al.*[109] have reported the synthesis of pyrroloquinoline **255** by FVP (flash vacuum pyrolysis) of cyanoester **254**, which was prepared from indole-7-carbaldehyde **253** and methylcyanoacetate (Scheme 3-7).

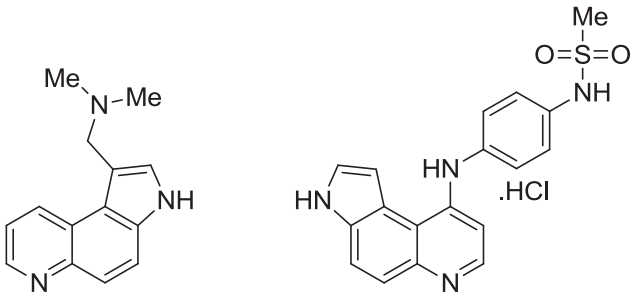


253 **254** **255**

Scheme 3-7

Type-II fusion:

Ferlin *et al.*[110-111] have reported the vasorelaxing activity of pyrroloquinoline **256**, and the anti-cancer activity of pyrroloquinoline **257**.

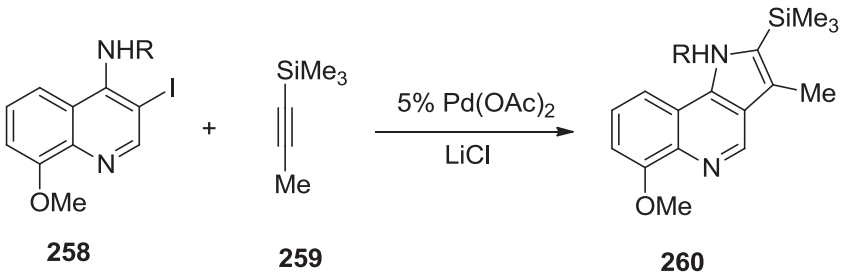


256 **257**

Type-III fusion:

The 2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline ring system is a central core to a number of biologically active molecules. Derivatives from this class possess anti-inflammatory, bradykinin receptor antagonist[112] and anti-cancer activity.[61] Moreover, 2,3-dihydro-1H-pyrrolo[3,2-*c*]quinolines are potential therapeutic agents for peptic ulcer disease by acting as a gastric H^+/K^+ ATPase 'proton pump' inhibitor.[113] Kang *et al.*[114] have

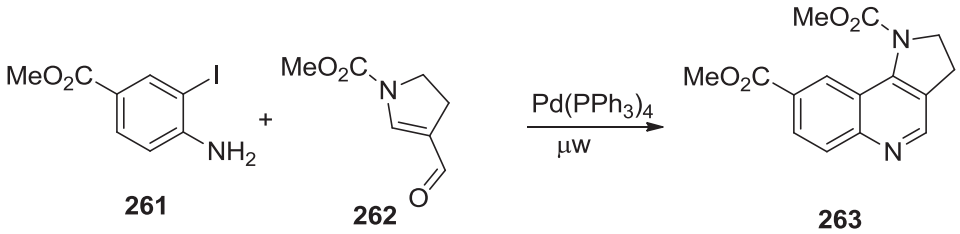
reported the synthesis of 1,2,3-trisubstituted pyrrolo[3,2-*c*]quinoline **260**, by using 4-amino-3-iodoquinoline **258** and prop-1-ynyl-silane **259** (Scheme 3-8).



258 **259** **260**

Scheme 3-8

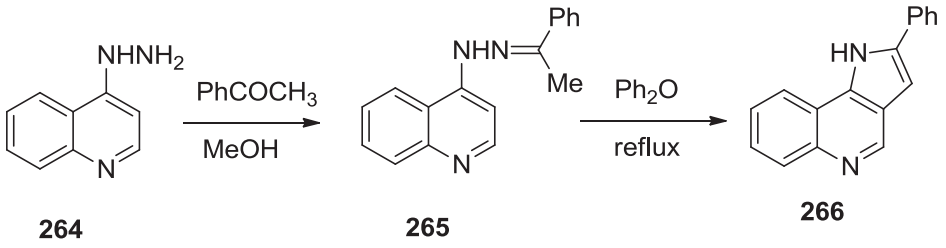
One-pot synthesis of 2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline **263** has been reported by Tomaszewski *et al.*[115] employing iodoaniline **261**, 2,3-dihydro-1*H*-pyrrole **262** and $Pd(PPh_3)_4$ under microwave irradiation. The proposed mechanism involves a Heck-coupling reaction followed by intra molecular Schiff base formation and double bond migration (Scheme 3-9).



261 **262** **263**

Scheme 3-9

Park *et al.*[116] have reported the formation of pyrrolo[3,2-*c*]quinoline **266** by employing the Fischer indole synthesis. In this method, the quinolyl hydrazine **264** was reacted with acetophenone to give **265**, which was refluxed in diphenyl ether to afford pyrroloquinoline **266** (Scheme 3-10).

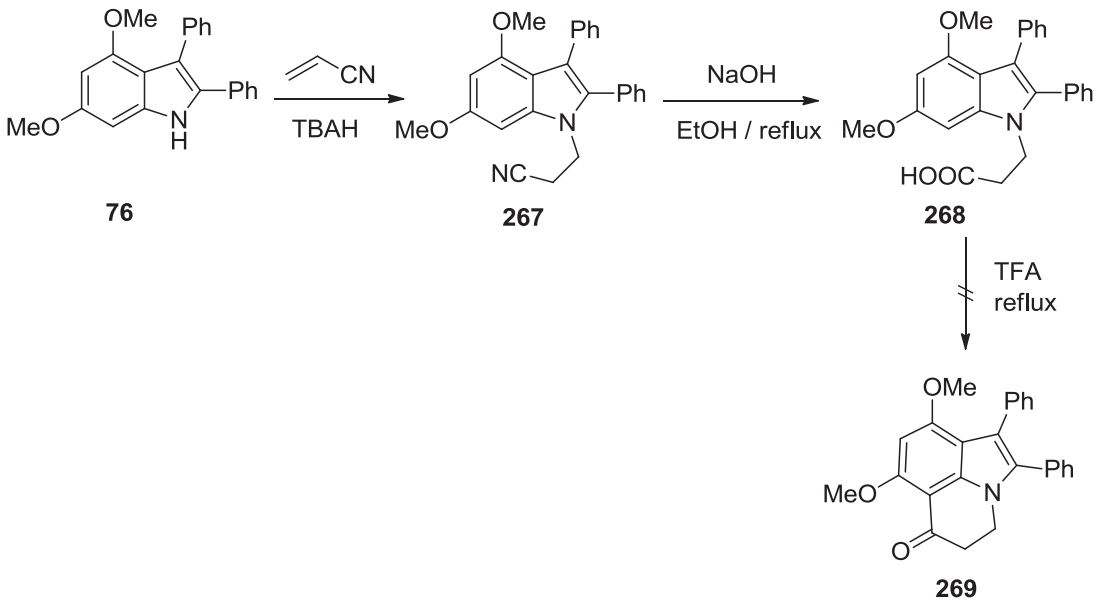


Scheme 3-10

3.2 Results and Discussion:

3.2.1 Attempted synthesis of pyrroloquinolines from 4,6-dimethoxyindoles:

Given the ready access to 4,6-dimethoxyindoles, it was of interest to investigate the synthesis of fused heterocycles from them. 4,6-Dimethoxyindole **76** was reacted with acrylonitrile in the presence of tetrabutylammonium hydroxide to furnish cyanoethyl indole **267** in 71% yield, which in turn was converted to the corresponding acid **268** in 76% yield using sodium hydroxide under reflux conditions[117] (Scheme 3-11).



Scheme 3-11

The ^{1}H NMR spectrum of compound **268** in $CDCl_3$ revealed the presence of two triplets at δ 2.59 and 4.30 ppm corresponding to the two sets of methylene protons, and two singlets at δ 3.64 and 3.83 ppm corresponding to the methoxy groups. The H5 appeared at δ 6.20 ppm as a doublet with coupling constant of 3.0 Hz and H7 appeared as a singlet at δ 6.44 ppm, while the phenyl ring protons appeared as a multiplet at δ 7.05-7.25 ppm (Figure 3-1).

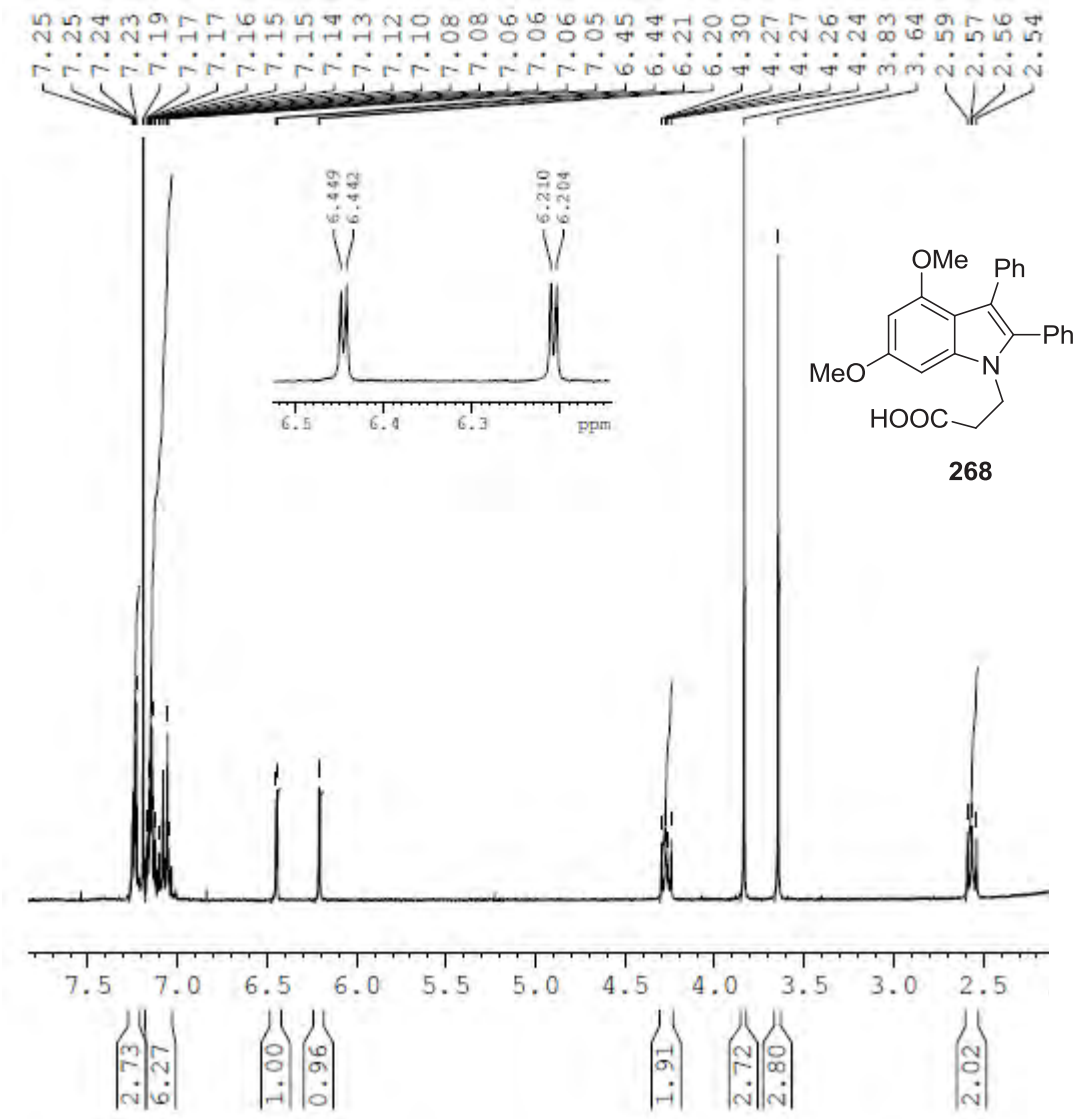
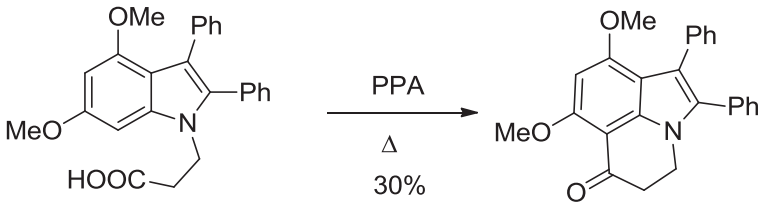


Figure 3-1 ^{1}H NMR spectrum of compound **268** in $CDCl_3$

However, the attempted cyclisation of **268** with trifluoroacetic acid both at room temperature and heating at reflux did not furnish the desired pyrroloquinoline. The starting material was recovered from the reaction mixture.

When **268** was heated with polyphosphoric acid, the desired pyrroloquinoline **269** was obtained in low yield (Scheme 3-12). The use of different acid catalysts and temperature conditions did not improve the yield. Therefore, this approach was not pursued further.



268 **269**

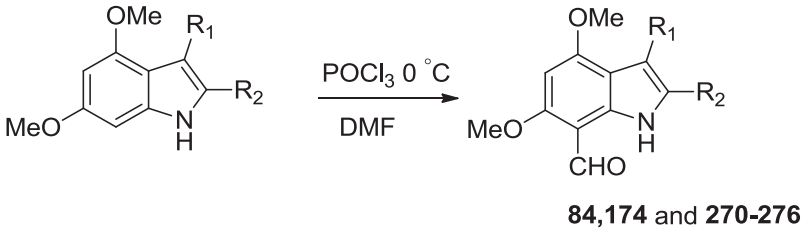
Scheme 3-12

It was decided to investigate an alternative method for the synthesis of pyrroloquinolines.

3.2.2 Synthesis of pyrroloquinolines from 4,6-dimethoxyindole-7-carbaldehyde:

Synthesis of 4,6-dimethoxyindole-7-carbaldehydes:

The 2-substituted indoles required for this strategy were prepared by the Bischler indole synthesis, whereas 3-substituted indoles were prepared by a modified Bischler synthesis, which are previously reported. These indoles were subjected to the Vilsmeier-Haack formylation reaction to yield the corresponding formylindoles (Scheme 3-13).[38,118-123]



84,174 and **270-276**

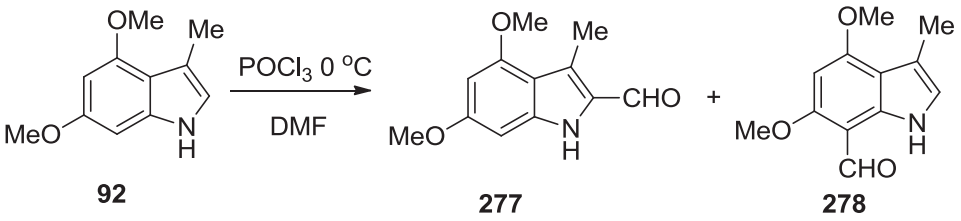
Scheme 3-13

The yield and the nature of the R_1 and R_2 substituents are depicted in Table 3-1

Table 3-1: Yield and the nature of the R_1 and R_2 substituents

Product	R_1	R_2	Yields (%)
84	C_6H_5	C_6H_5	75
174	4-ClC_6H_4	H	78
270	4-MeC_6H_4	H	73
271	naphthyl	H	72
272	C_6H_5	H	71
273	4-BrC_6H_4	H	78
274	H	4-BrC_6H_4	65
275	3,4-$Cl_2C_6H_3$	H	79
276	H	H	59

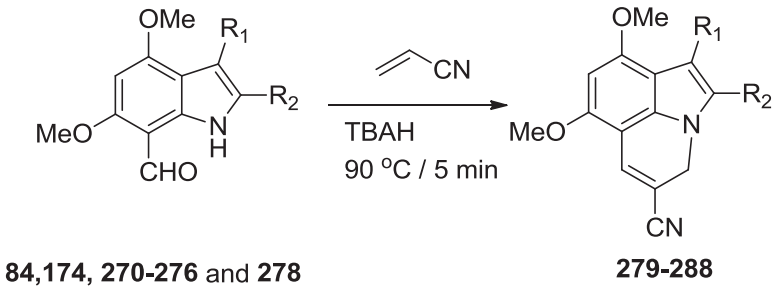
When 3-methylindole **92** was subjected to Vilsmeier-Haack formylation reaction, two isomeric products the 2-formylindole **277** and the 7-formylindole **278**, were obtained (Scheme 3-14).



Scheme 3-14

3.2.3 Synthesis of pyrroloquinolines from 4,6-dimethoxyindoles:

When 4,6-dimethoxyindoles were mixed with acrylonitrile and a few drops of tetrabutylammonium hydroxide, an exothermic reaction was observed. The reaction mixture was stirred at room temperature for 5 min and then heated at 90 °C for 5 min to form pyrrolo[3,2,1-*ij*]quinolines **279-288** (Scheme 3-15).



Scheme 3-15

The yield and the nature of the R_1 and R_2 substituents are depicted in Table 3-2

Table 3-2: Yield and the nature of the R_1 and R_2 substituents.

Product	R_1	R_2	Yields (%)
279	C_6H_5	C_6H_5	82
280	4-ClC_6H_4	H	82
281	C_6H_5	H	75
282	4-MeC_6H_4	H	83
283	naphthyl	H	80
284	H	H	70
285	4-BrC_6H_4	H	84
286	H	4-BrC_6H_4	80
287	3,4-$Cl_2C_6H_3$	H	84
288	Me	H	70

The yield of pyrrolo[3,2,1-*ij*]quinolines ranged from 70-84%. Purification of the product only required passage through a plug of silica gel. Therefore, this strategy can be considered as a useful and a quick route to prepare pyrrolo[3,2,1-*ij*]quinolines in good yields.

The ^{1}H NMR spectrum of compound **285** in $CDCl_3$ matched the expected structure, with a doublet at δ 5.10 ppm (J = 3.0 Hz), and three singlets at δ 6.05, 6.86 and 7.26 ppm corresponding to H2, H5 and H7, respectively. The disappearance of the aldehydic and the NH peaks indicated that a new ring had formed, which connected the nitrogen and C7 of the indole (Figure 3-2). A negative peak at δ 46.07 ppm in the DEPT 135 ^{13}C NMR spectrum signified the presence of a CH_2 group in the molecule. These pyrroloquinolines have a strong fluorescence, and showed two peaks at 254 and 394 nm in their UV absorption spectra. A strong peak in the IR spectrum at 2197 cm^{-1} indicated

the presence of a cyano group. The HRMS spectrum showed an M+1 peak at *m/z* 395.0249, which matched the expected mass of the compound.

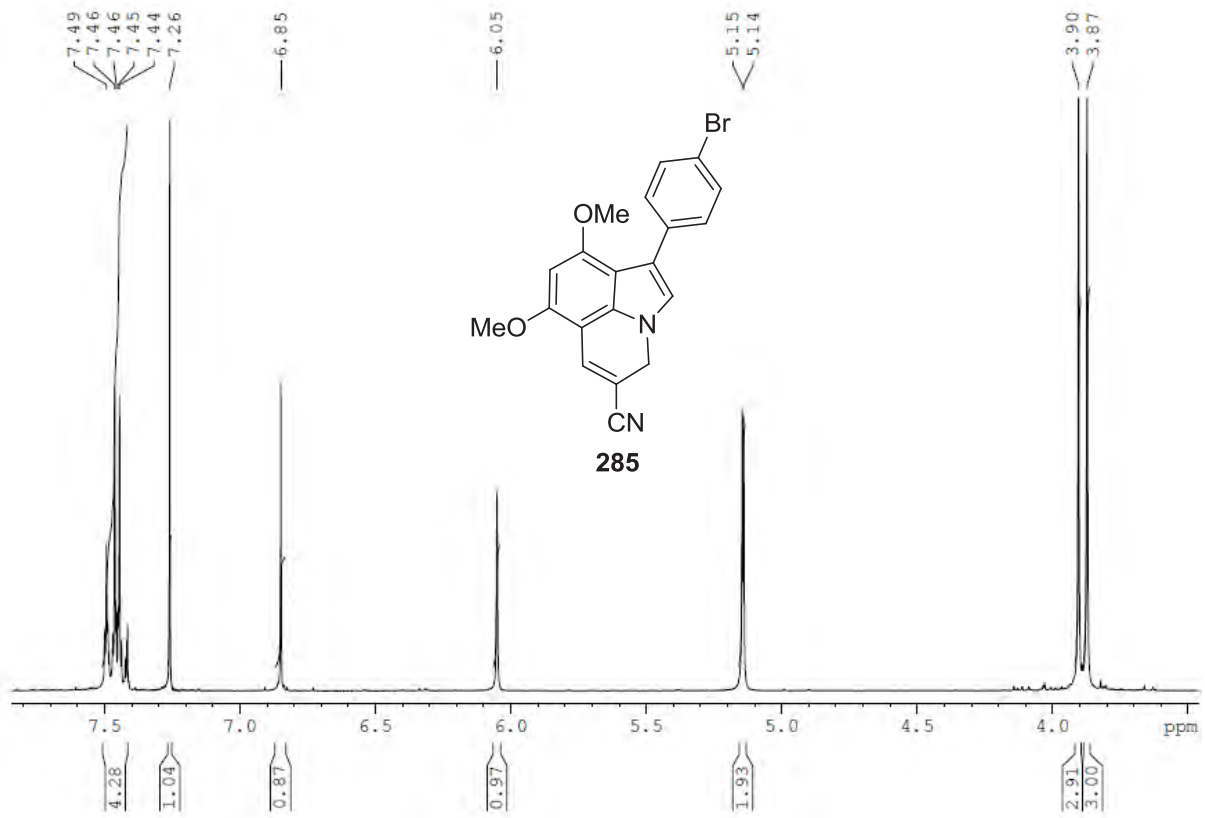
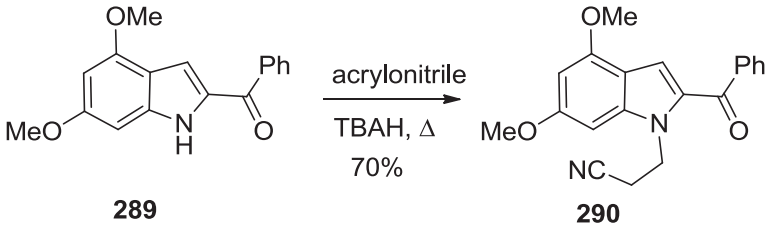


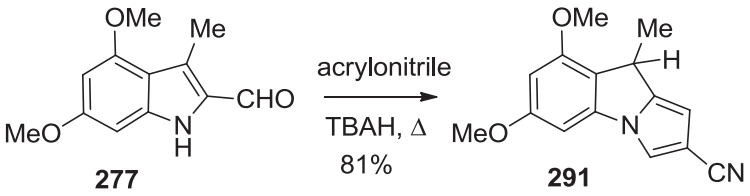
Figure 3-2 ^{1}H NMR spectrum of compound **285** in $CDCl_3$

Reaction of 2-benzoylindole **289** with acrylonitrile gave *N*-cyanoethylindole **290** in 70% yield, which failed to cyclise even after extended heating (Scheme 3-16).



Scheme 3-16

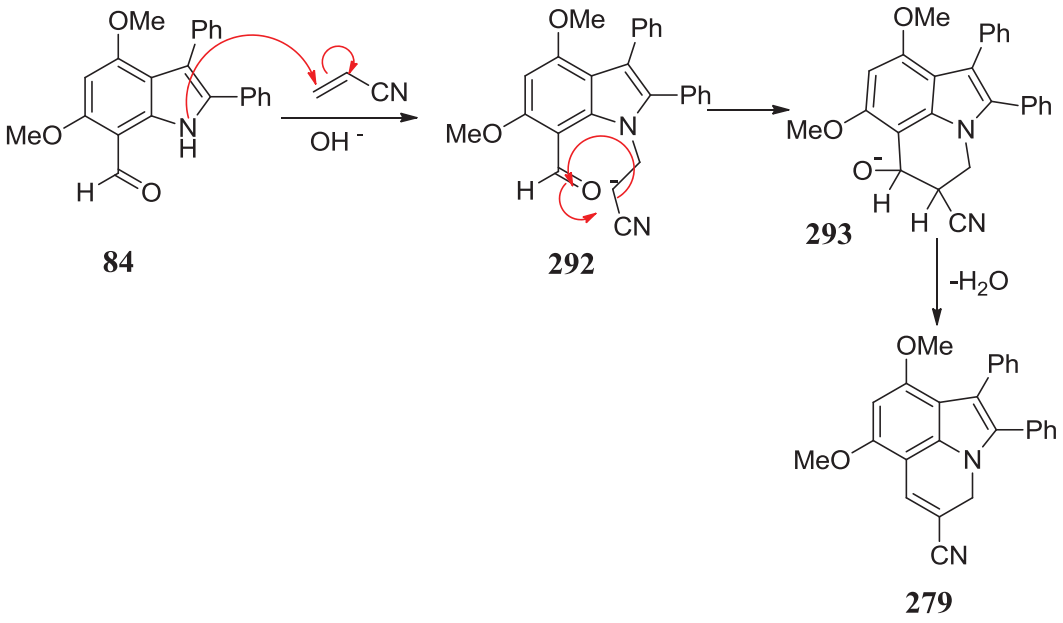
When 3-methylindole-2-carbaldehyde **277** was reacted with acrylonitrile, cyclisation had taken place at the formyl group at C2 to give pyrroloindole **291** in 81% yield. Furthermore, it was noticed that the indole had lost its aromaticity. The ring system of the product favoured pyrrole formation rather than indole. This was evidenced by the ^{1}H NMR spectrum, where the CH_3 protons appeared as a doublet and the C3 proton as a quartet due co-coupling with the methyl protons (Scheme 3-17).



Scheme 3-17

3.2.3.1 Reaction mechanism:

The possible reaction mechanism for the formation of compounds **279-288** can be explained as below (Scheme 3-18).



Scheme 3-18

The reaction follows a Michael addition process where base abstracts a proton from the indole NH **84**, which then attacks the double bond of acrylonitrile to produce carbanion **292**. The intermediate **292** attacks the carbonyl carbon intramolecularly to give oxyanion **293**, which upon dehydration produces pyrroloquinoline **279**.

3.3 Conclusion:

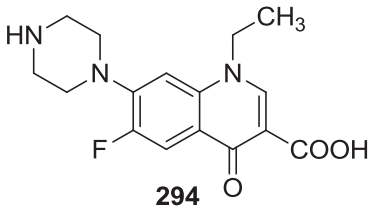
Although several methods are available for preparing pyrroloquinolines, more involve multistep reactions requiring a long reaction time or require transition metal catalysts such as palladium. In this study, a facile method was developed for the synthesis of pyrroloquinolines. This method involves the reaction of indole-7-carbaldehyde and acrylonitrile in the presence of tetrabutylammonium hydroxide. Using this protocol a range of novel pyrroloquinolines has been prepared.

CHAPTER 4

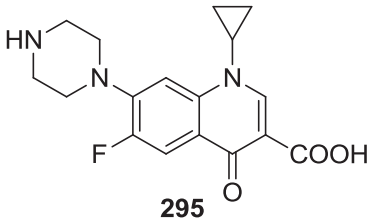
SYNTHESIS AND REACTIVITY OF 5,7-DIHYDROXYQUINOLIN-2-ONES

4.1 Introduction:

There is a great demand for new anti-bacterial agents due to the resistance shown by many micro-organisms against existing anti-bacterial drugs. Quinolones are well known for their anti-bacterial activities and numerous examples have been reported in the literature.[124] Norfloxacin **294** and ciprofloxacin **295** are examples of drugs which contain the quinolone nucleus.

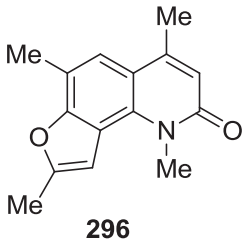


294

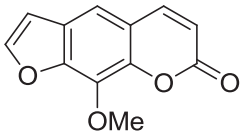


295

Moreover, the quinolones have also been reported for various other biological activities. Bordin *et al.*[125] reported the anti-proliferative activity of furoquinoline **296**, a new isostere of angelicin **299**, characterised by an extremely strong photosensitizing activity. This activity is several times higher than that of the well-known photoinducer, 8-MOP **297** and 4,6,4`-trimethylangdicin **298**. These molecules are also expected to possess fewer side effects compared to the available photochemotherapeutic agents.



296



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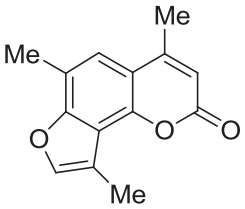
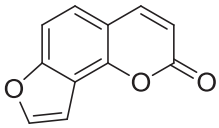
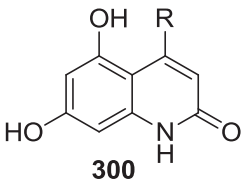


298

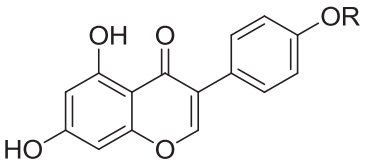


299

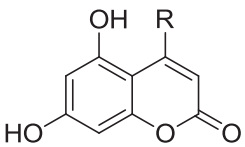
5,7-Dihydroxyquinolin-2-ones **300** have the same oxygenation pattern as that of flavonoids **301** and 5,7-dihydroxycoumarins **302**, which are well-known for their wide-ranging biological properties.



300

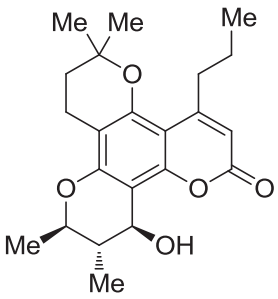


301



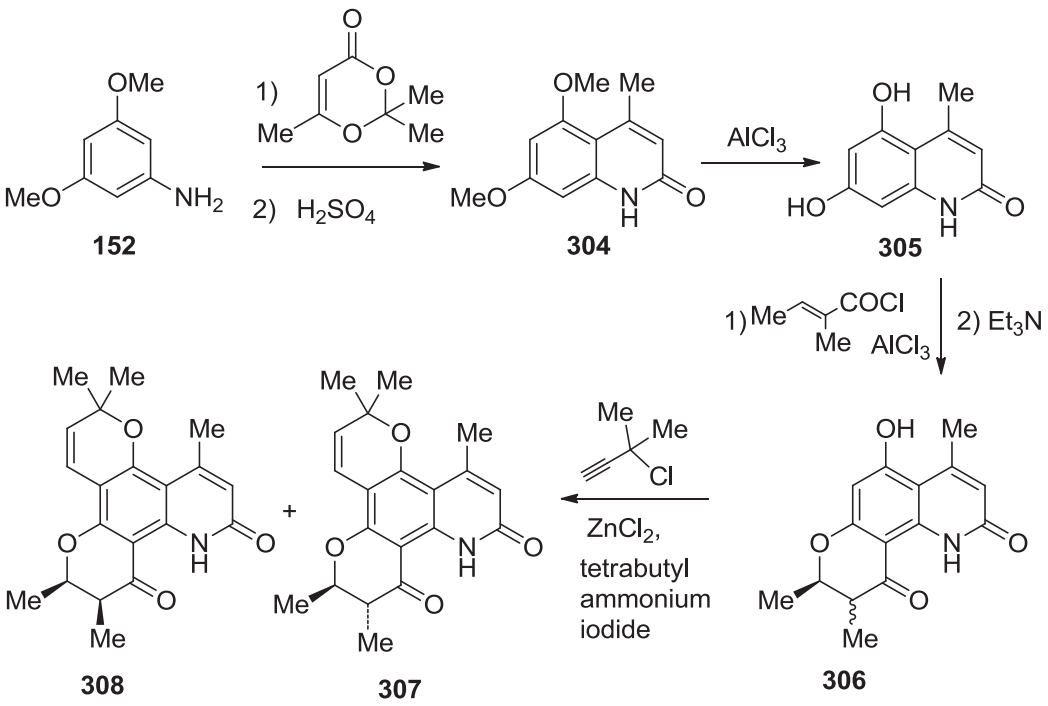
302

Calanolide A **303** is a new, experimental non-nucleoside reverse-transcriptase inhibitor (NNRTI) first isolated from the leaves of *Calophyllum lanigerum*. Calanolide A was initially investigated as a possible anti-cancer agent, but later on it was found to possess potent anti-HIV activity.[126-127]



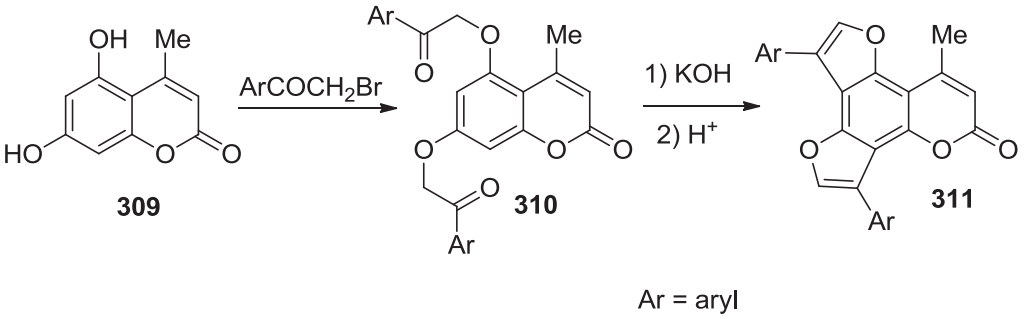
303

Dipyrano-quinolines **307** and **308**, which are isosteres of **303**, also showed potent anti-HIV activity.[128] These compounds were synthesised by the reaction of 3,5-dimethoxyaniline **152** with 2,2,6-trimethyl-4H-1,3-dioxin-4-one to give 5,7-dimethoxyquinolin-2-one **304**, which upon reaction with $AlCl_3$ gave the 5,7-dihydroxyquinolin-2-one **305**. This quinolone **305** was reacted with tigloyl chloride followed by cyclisation to afford the pyrano intermediate **306**, which upon subsequent reaction with alkynyl chloride and cyclisation gave the two isomers **307** and **308** (Scheme 4-1).



Scheme 4-1

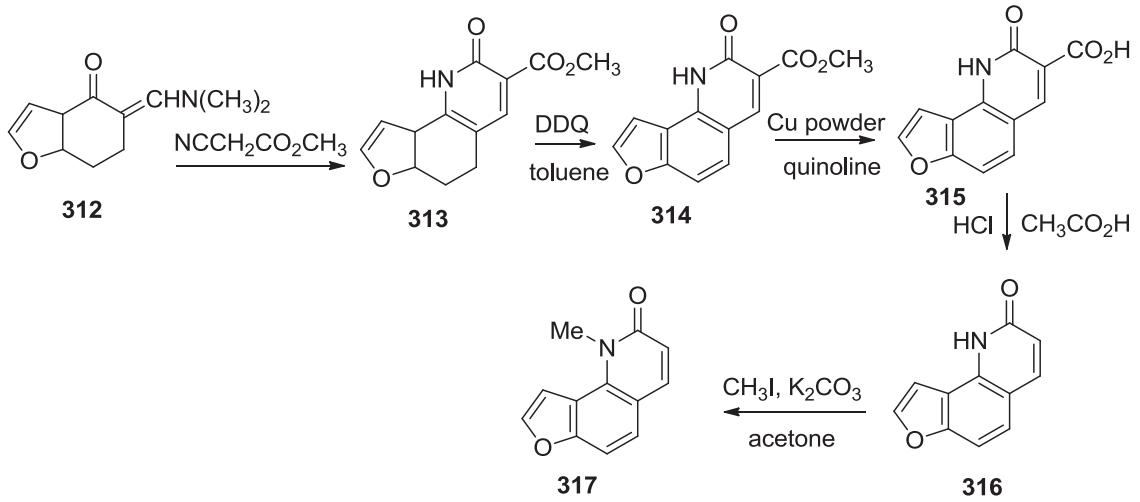
Traven *et al.*[82] have recently reported the synthesis of difurocoumarins **311** wherein dihydroxycoumarin **309** was first reacted with α-haloketones to give the intermediate phenacyl ethers **310**, which were cyclised under basic conditions to produce difurocoumarins **311** (Scheme 4-2). These compounds possess diverse biological activities including treatment of blood disorders and anti-proliferative activity.



Scheme 4-2

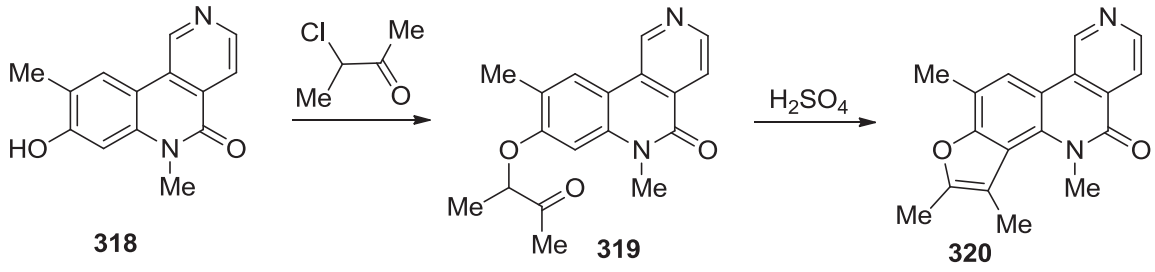
Furoquinolones are reported for various biological activities such as anti-inflammatory and anti-allergic activities.[129] The furoquinolones are structurally similar to the furocoumarins **311**, where the oxygen atom in the six membered ring is replaced by nitrogen. Therefore, it would be interesting to investigate the synthesis and the reactivity of these types of heterocycles. These compounds not only possess photosensitising activity but also anti-proliferative activities. Fossa *et al.*[130] reported the synthesis and biological properties of the some furoquinolones. Photochemotherapeutic activity, with increased anti-proliferative activity of these compounds suggests their potential as a drug for PUVA photochemotherapy and photophoeresis. PUVA is a combination of psoralen (P) and long-wave ultraviolet radiation (UVA) that is used to treat many different skin conditions.

The furoquinolone **317** was synthesised by reacting benzofuranone **312** with methyl cyanoacetate to give the intermediate **313**, which was oxidised using 2,3-dichloro-5,6-dicyanobenzoquinone to furnish the ester **314**. After hydrolysis the resulting acid intermediate **315** was decarboxylated using quinoline and copper powder to afford quinolone **316**, which on *N*-methylation gave the *N*-methylquinolone **317** (Scheme 4-3).



Scheme 4-3

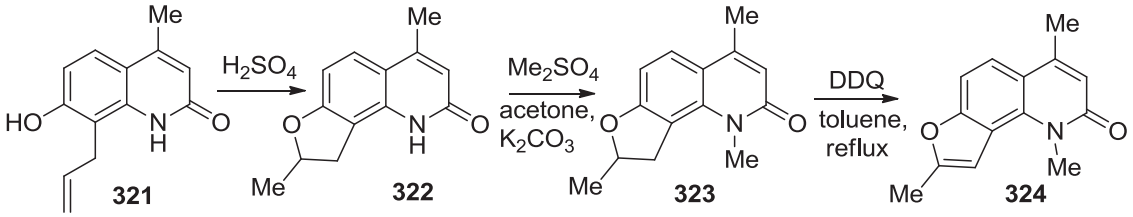
Chilin *et al.*[131] have reported the synthesis of the furoquinolone **320** in which an additional pyridine ring is fused to the quinolone core. In the synthesis of this ring system the appropriate quinolone skeleton was built first followed by installation of the furan moiety. Thus, hydroxyquinolone **318** was first reacted with 3-chloro-2-butanone to give the ether intermediate **319**, which was subsequently cyclised to give the furoquinolone **320** using sulfuric acid (Scheme 4-4).



Scheme 4-4

Marzano *et al.*[132] have reported the synthesis and biological activities of the furoquinolone **324**. To achieve the synthesis of **324**, an alternate route starting with 4-

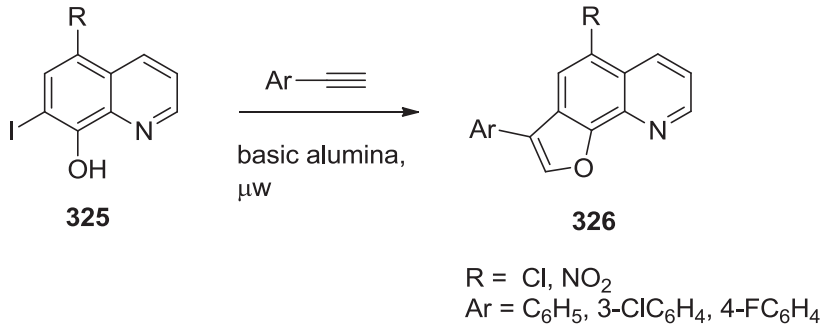
methyl-7-hydroxy-8-allylquinolin-2-one **321** was utilised. The starting quinolone **321** was cyclised using sulfuric acid to give the corresponding dihydro-2-methoxyfuroquinoline **322**. The *N*-methyl derivative **323** was obtained by methylation with methyl iodide, and was oxidised with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to afford the furoquinolone **324** (Scheme 4-5).



Scheme 4-5

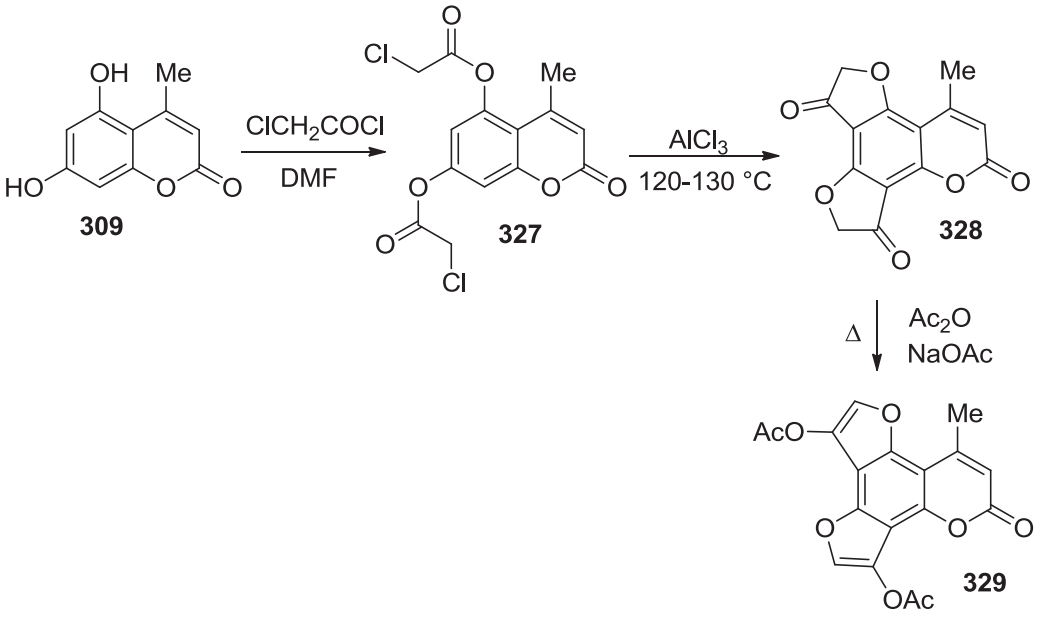
This compound was found to possess anti-proliferative activity demonstrated by the inhibition of DNA synthesis in Ehrlich cells and the inhibition of clonal growth capacity in HeLa cells cultivated *in vitro* with or without ultraviolet-A (UVA) ray activation.

Saha *et al.*[133] have recently reported a method for the synthesis of furoquinolines by a one-pot tandem synthesis using a Sonogashira cross-coupling reaction. In this approach, the hydroxyquinolines **325** were reacted with arylacetylene under microwave irradiation to give the furoquinolines **326** (Scheme 4-6).



Scheme 4-6

In another study, Traven *et al.*[134] developed an alternative method for preparation of furocoumarins using a Fries rearrangement. Dihydroxycoumarin **309** was reacted with chloroacetyl chloride to give the intermediate ester **327**, which upon Fries rearrangement gave the trione intermediate **328**. Subsequent treatment with acetic anhydride and sodium acetate generated the desired furocoumarin **329** (Scheme 4-7).



Scheme 4-7

Furoquinolones are important from a biological point of view and very few methods are available for their synthesis. Hence the main aim of the work described in this chapter was to synthesise 5,7-dihydroxyquinolin-2-one and the fused heterocycles based on them.

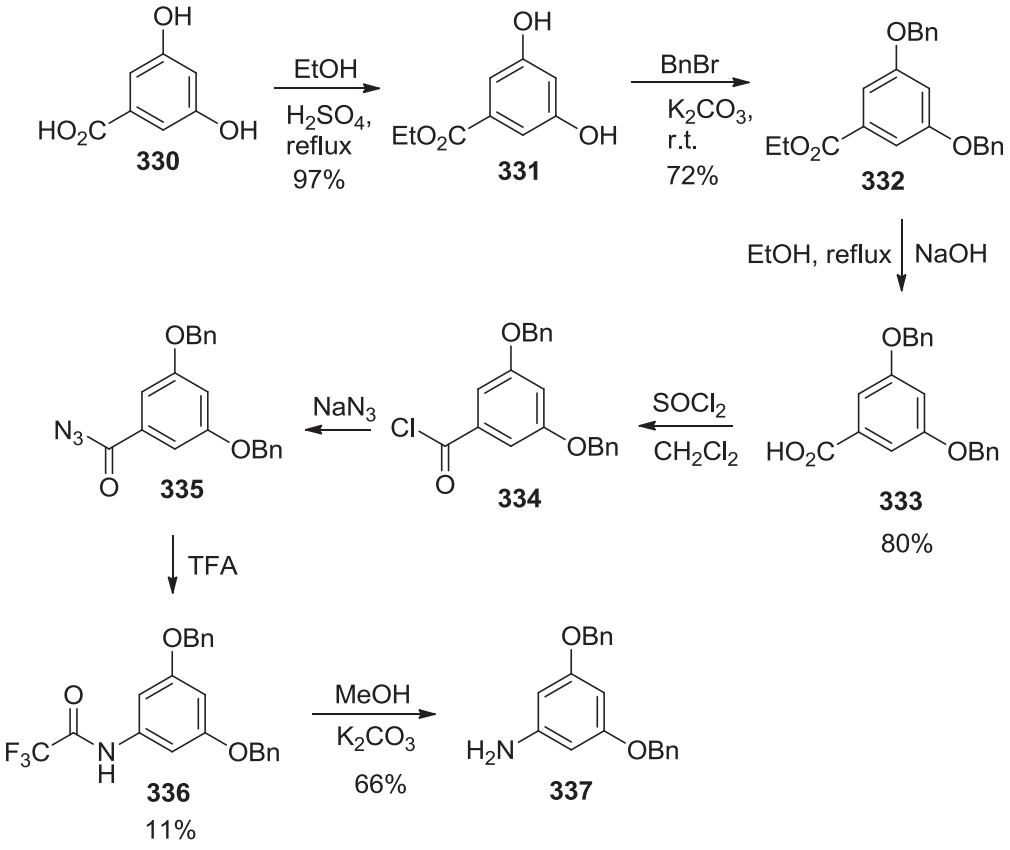
4.2 Results and Discussion:

4.2.1 Synthesis of 5,7-dihydroxyquinolin-2-one:

Three approaches for the synthesis of 5,7-dihydroxyquinolin-2-ones were investigated, and involved the use of three different starting anilines namely, 3,5-dibenzyloxyaniline, 3,5-dimethoxyaniline and 3,5-dihydroxyaniline.

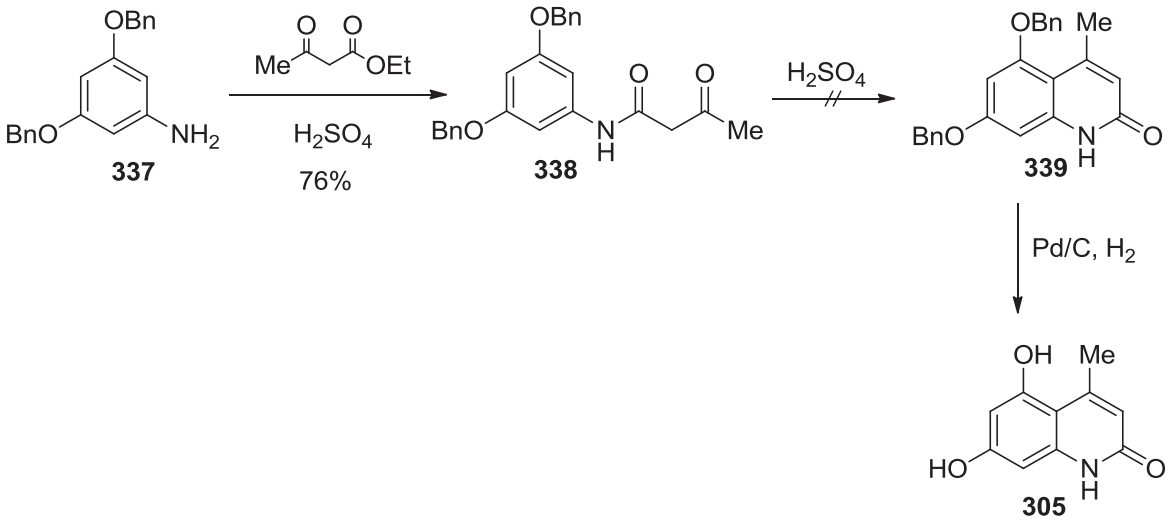
4.2.1.1 Attempted synthesis of 5,7-dihydroxyquinolin-2-ones using 3,5-dibenzyloxyaniline:

The more obvious route to benzyloxy-protected 5,7-dihydroxyquinolin-2-ones started with the protected aniline, 3,5-dibenzyloxyaniline. Thus 3,5-dihydroxybenzoic acid **330** was esterified using ethanol and sulfuric acid to give the ester **331** in 97% yield, and the phenolic hydroxy groups were benzylated to give dibenzyloxybenzoate **332** in 72% yield. Alkaline hydrolysis of the dibenzyloxyester **332** gave the corresponding acid **333** in 80% yield, which was converted to the acid chloride **334** using thionyl chloride followed by reaction with sodium azide to give **335**. Compound **335** was subjected to a modified Curtius reaction[135] to give *N*-(3,5-bis(benzyloxy)phenyl)-2,2,2-trifluoroacetamide **336** in 11% yield, which was converted to 3,5-dibenzyloxyaniline **337** in 66% yield by basic hydrolysis (Scheme 4-8).



Scheme 4-8

It is known that the condensation reaction of aromatic amines with β-ketoesters in the presence of sulfuric acid should give quinolin-2-ones in good yields. However, when the reaction was attempted using 3,5-dibenzyloxyaniline **337**, the intermediate amide **338** was obtained as the sole product in 76% yield (Scheme 4-9).



Scheme 4-9

The ^{1}H NMR spectrum of compound **338** in $CDCl_3$ showed a singlet at δ 2.27 ppm which was assigned to methoxy group, a singlet at δ 3.52 ppm corresponding to the CH_2 group, a singlet at δ 4.99 ppm corresponding to the benzylic methylenes, and a triplet and doublet at δ 6.42 and 6.93 ppm for H4 and H2, respectively. This pattern indicated a substituted dibenxyloxyaniline (Figure 4-1).

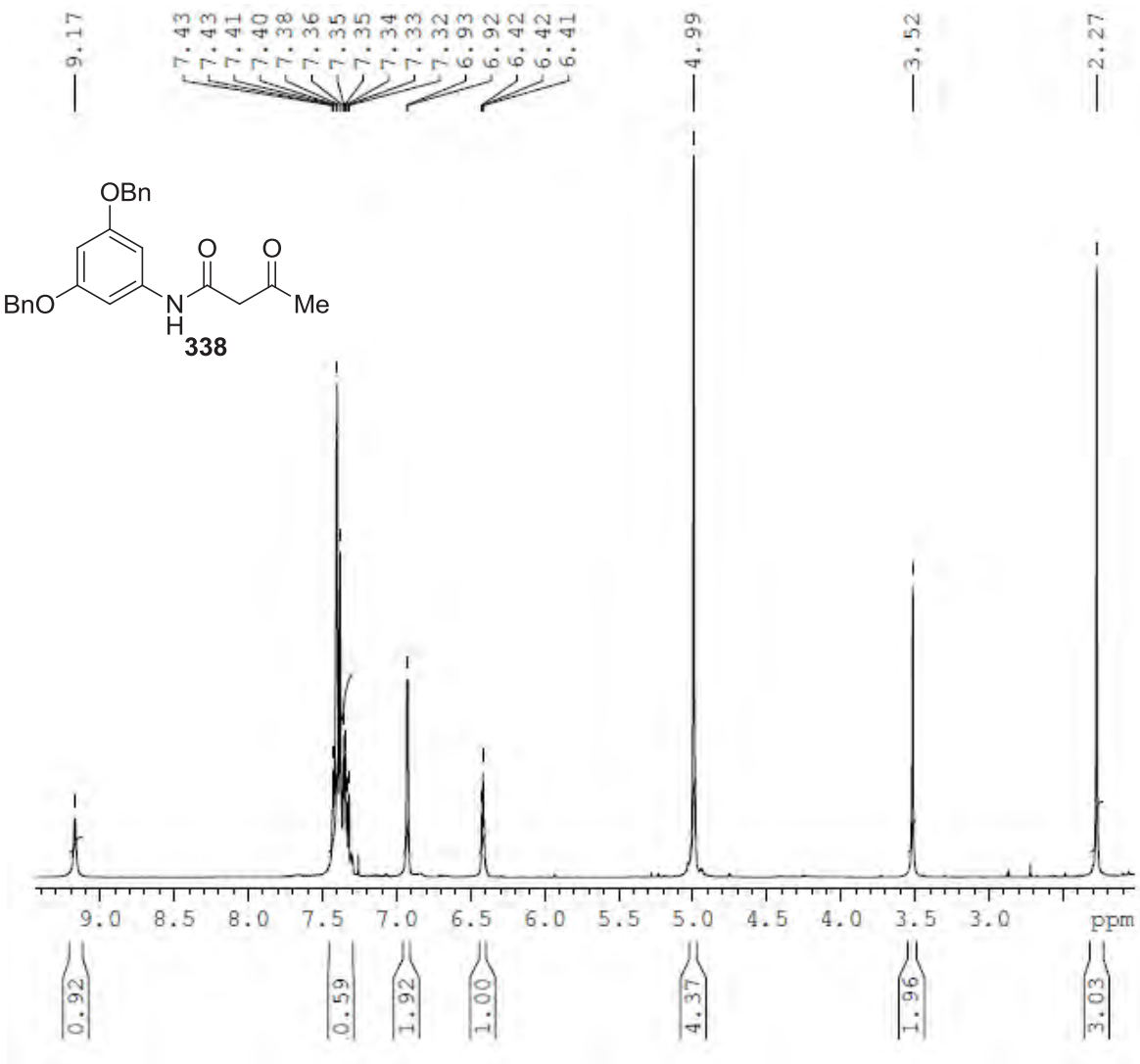


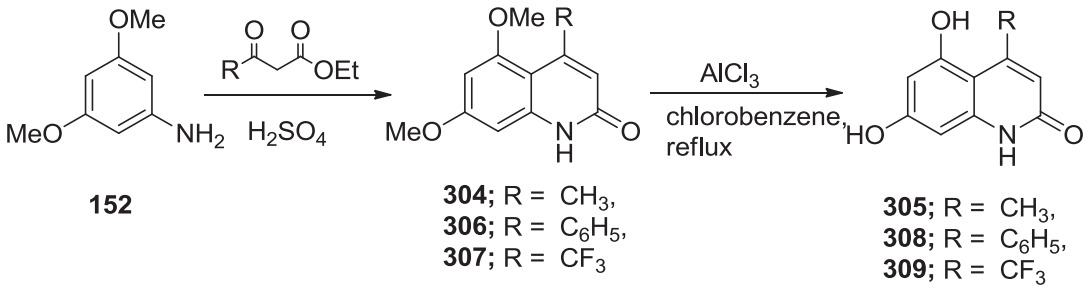
Figure 4-1 ^{1}H NMR spectrum of **338** in $CDCl_3$

The structure of compound **338** was supported by the ^{13}C NMR spectrum. The DEPT 135 ^{13}C NMR spectrum showed the presence of a CH_2 peak one at δ 49.93 ppm for the CH_2 group adjacent to the amide and a second at δ 69.99 ppm the benzyloxy groups. This data indicated that the reaction had stopped at the intermediate **338**, which failed to cyclise. Further attempts to cyclise the intermediate by heating and using other cyclising agents such as *p*-toluenesulfonic acid or trifluoroacetic acid were unsuccessful. In most cases, the starting material was recovered unchanged. When cyclisation was attempted with Conc. sulfuric acid at elevated temperatures, the TLC analysis showed the formation of multiple products. A possible reason for this could be the cleavage of

benzyloxy groups by heat or strong acid. Presumably the steric buttressing effect of the benzyloxy groups at C3 and C5 was a problem.

4.2.1.2 Synthesis of 5,7-dihydroxyquinolin-2-ones using 3,5-dimethoxyaniline:

The synthesis of 5,7-dihydroxyquinolin-2-ones has been reported previously by Gurjar *et al*.[128] When 3,5-dimethoxyaniline **152** was reacted with β-ketoesters in the presence of Conc. sulfuric acid, 5,7-dihydroxyquinolin-2-ones **304**, **306** and **307** were obtained. The corresponding 5,7-dihydroxyquinolin-2-ones **305**, **308** and **309** were obtained by demethylation employing aluminium chloride in chlorobenzene (Scheme 4-10).



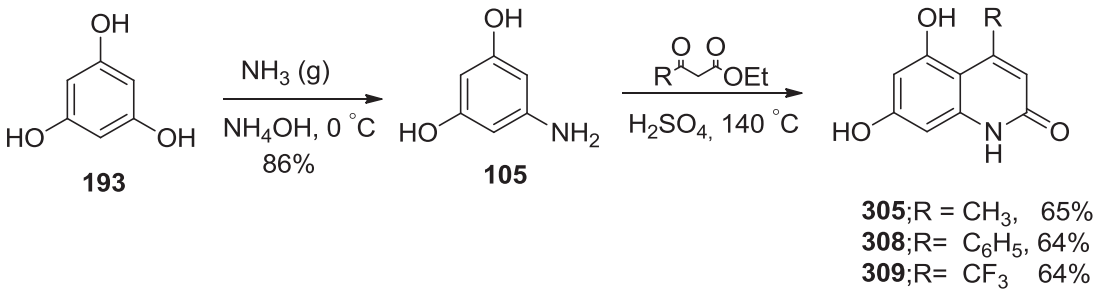
Scheme 4-10

Despite the quick synthesis of 5,7-dihydroxyquinolin-2-ones, the method has drawbacks such as low yield, the use 3 molar equivalents of aluminium chloride, and generally harsh conditions. Therefore, an alternative method to prepare 5,7-dihydroxyquinolin-2-ones was considered.

4.2.1.3 Synthesis of 5,7-dihydroxyquinolin-2-ones using phloroglucinol:

The synthesis of 3,5-dibenzyloxyaniline **337** involved multiple steps with very low yields, especially in the final hydrolysis step. Furthermore, all attempts to cyclise 3,5-dibenzyloxyaniline to 5,7-dibenzyloxyquinolin-2-one were unsuccessful. The second method involved the use of aluminium chloride with heating, a very harsh condition that

gave low yields. Therefore, an alternative method employing the cheaper and readily available starting material phloroglucinol **193** was investigated (Scheme 4-11).



Scheme 4-11

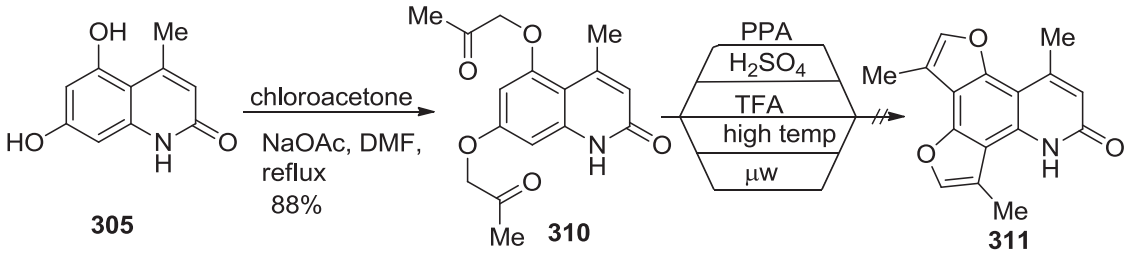
Reaction of phloroglucinol **193** in with saturated aqueous ammonia gave 3,5-dihydroxyaniline **105**. A low temperature was found to be crucial to this reaction. This reaction simply involved dissolving phloroglucinol in aqueous ammonia followed by bubbling of ammonia gas at low temperature, and the desired product **105** was obtained upon evaporation of water in 86% yield.

When 3,5-dihydroxyaniline **105** was reacted with β-ketoesters in the presence of Conc. sulfuric acid, gave 5,7-dihydroxyquinolin-2-ones **305**, **308** and **309** in 64-65% yield.

The ^{1}H NMR spectrum of compound **305** in DMSO-d_6 showed the presence of a singlet at δ 2.47 ppm corresponding to the methyl protons, a singlet at δ 5.84 ppm corresponding to H3, and two doublets at δ 6.09 and 6.15 ppm (J = 3.0 Hz) corresponding to H6 and H8, respectively. Two singlets at δ 9.78 and 10.03 ppm indicated the presence of two free hydroxy groups in the molecule. The NH proton appeared as a singlet at δ 11.10 ppm.

In order to prepare the furoquinolones, 5,7-dihydroxyquinolin-2-one **305** was reacted with chloroacetone in the presence of sodium acetate to afford the intermediate **310** in

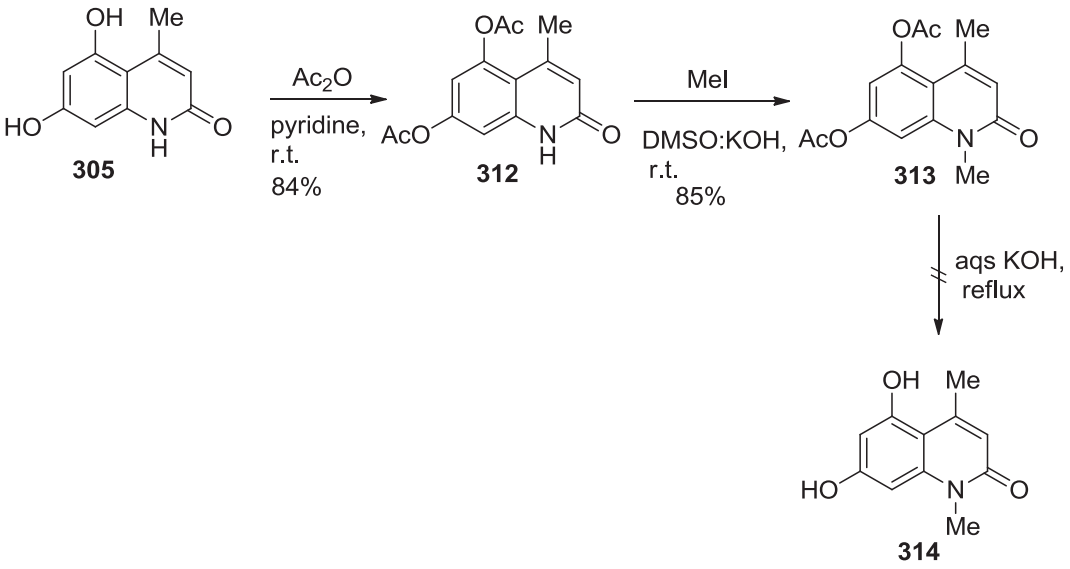
88% yield. When **310** was treated with Conc. sulfuric acid, polyphosphoric acid, trifluoroacetic acid, high temperature or microwave irradiation, none of the desired furoquinolone was produced. Only starting material could be recovered from the reaction mixture (Scheme 4-12).



Scheme 4-12

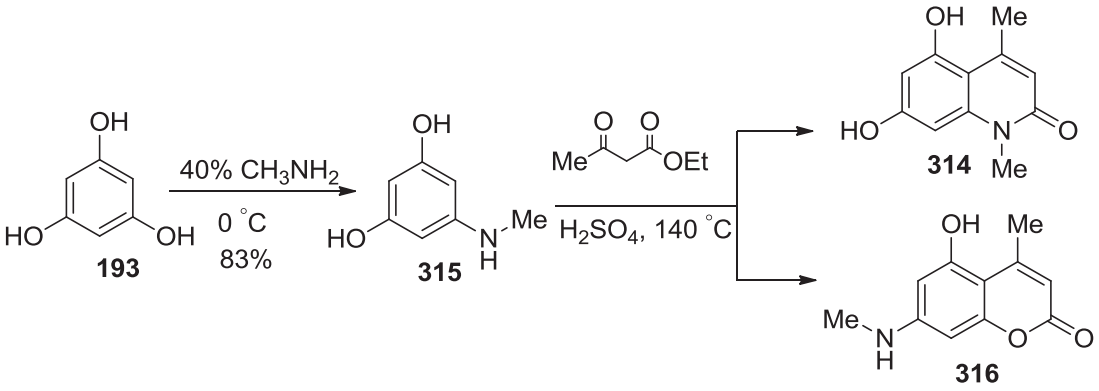
Unfortunately, this methodology also failed to furnish the desired furoquinolone. It was noticed that cyclisation of quinolone acyl ethers to the furoquinolone skeleton was possible in cases where nitrogen was methylated.[131-132] Therefore, this observation was considered to be useful in this study.

In order to prepare the *N*-methylated 5,7-dihydroxyquinolin-2-ones it was essential to block the free hydroxyl groups. For this purpose, the acetoxy group was chosen as the protecting group and acetylation was achieved by reacting **305** at room temperature with acetic anhydride to afford the diacetoxy intermediate **312** in 84% yield. *N*-Methylation was carried out using methyl iodide in the presence of potassium carbonate to afford *N*-methylquinolone **313** in 85% yield. However, deprotection of the acetoxy groups using KOH at reflux gave multiple products. TLC analysis showed that the products had Rf values too close together to separate them using column chromatography. Therefore, this methodology was not pursued further (Scheme 4-13).



Scheme 4-13

The failure of acyl-quinolones to afford furoquinolones led to the search for alternative methods. There were no reports of cyclisation of acyl-quinolones when the NH of quinolones is free. Conversely, there are reports of cyclisation of *N*-methyl-acyl-quinolones.[132] Therefore, *N*-methylation was considered necessary. An alternative strategy for preparing *N*-methylquinolones was the synthesis of *N*-methylated-3,5-dihydroxyaniline. The synthesis of *N*-alkylated aniline was straightforward. The addition of 40% aqueous methylamine solution to phloroglucinol **193** in *N*,*N*-dimethylformamide and water gave the *N*-methylaminoresorcinol **315** in 83% yield. Further reaction of *N*-methylaminoresorcinol **315** with different β-ketoesters in the presence of Conc. sulfuric acid in a von Pechmann reaction yielded the *N*-methylquinolones in 73-76% yield (Scheme 4-14).



Scheme 4-14

This strategy is quite versatile as it allowed an easy access to *N*-alkylated 3,5-dihydroxyaniline **315** and the corresponding *N*-alkylated quinolones. However, two products are possible in this reaction, a quinolone **314** or coumarin **316**.[136]

The ^{1}H NMR spectrum of product from the reaction of **315** and ethyl acetoacetate in DMSO-d_6 showed the presence of the two overlapping methyl peaks at δ 3.41-3.42 ppm, and a singlet at δ 6.00 ppm corresponding to H3. The presence of two doublets at δ 6.21 and 6.23 ppm with a coupling constant of 2.2 Hz, indicative of *meta* coupling, indicated the formation of the second ring fused to *N*-methyaminoresorcinol **315**. A broad peak at δ 10.00 ppm and a sharp singlet at δ 10.20 ppm pointed towards the presence of two free hydroxyl groups in the molecule (Figure 4-2).

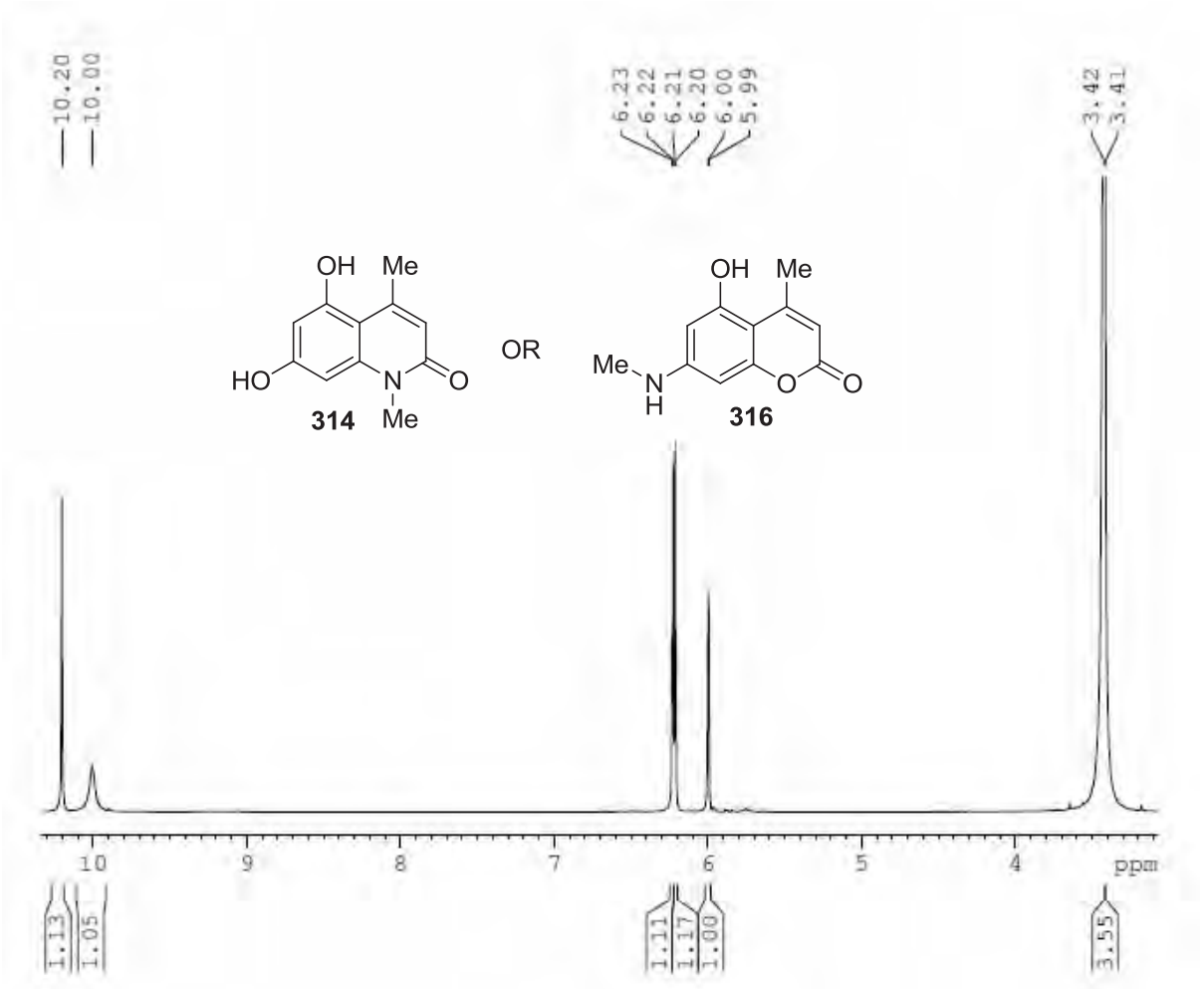
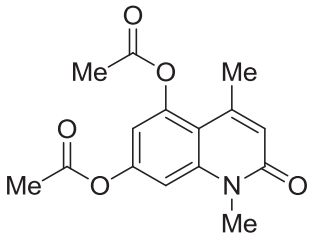


Figure 4-2 ^{1}H NMR spectrum of compound formed upon reaction of **315** with ethyl acetoacetate in DMSO-d_6.

The ^{13}C NMR spectrum of compound showed the presence of peaks at δ 158.61 ppm for the carbon bearing the hydroxyl group and a second peak at δ 160.35 ppm, which could be due to the carbon bearing a free hydroxyl group or carbon bearing an *N*-CH_3 group. The presence of a carbonyl group was confirmed by the presence of a peak at δ 161.36 ppm in the ^{13}C NMR spectrum and a strong peak at 1630 cm^{-1} in the IR spectrum.

The formation of coumarin **316** could not be ruled out by NMR spectroscopy data. Therefore, X-ray crystallography was necessary to elucidate the structure. Crystallization was attempted using different solvents to obtain a single crystal suitable

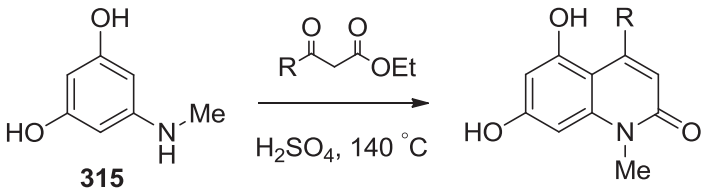
for X-ray crystallography. Unfortunately all attempts to obtain suitable crystals were unsuccessful. Therefore, O-acetylation using acetic anhydride and pyridine was carried out to give the diacetoxy derivative **314a** in crystalline form.



314a

Figure 4-3 ORTEP view of **314a**

X-ray crystallographic analysis revealed the structure to be quinolone **314** rather than the acetoxy derivative of coumarin **316** (Figure 4-3). Using this method, three different 5,7-dihydroxyquinolin-2-ones were prepared in 73-76% yield (Scheme 4-15).

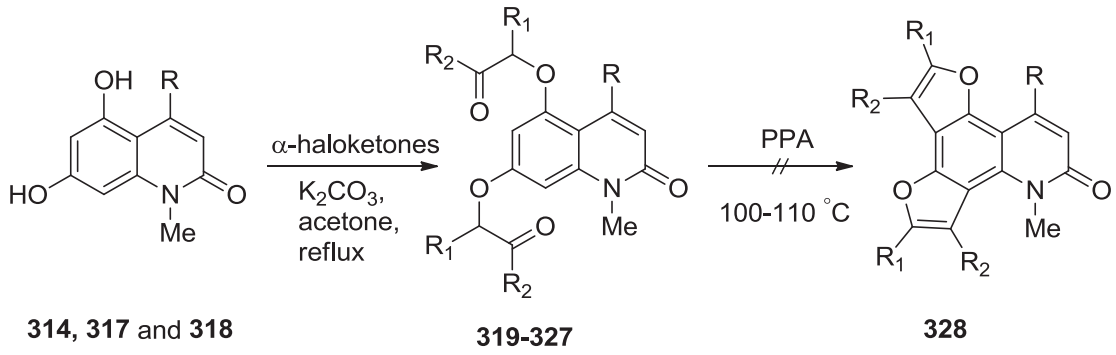


Scheme 4-15

This method provided a facile route to 5,7-dihydroxyquinolin-2-ones and ready access to *N*-protected quinolones. No additional steps were required to protect the NH of the quinolone.

4.2.2 Reactivity studies of 5,7-dihydroxyquinolin-2-ones:

Having successfully synthesised the 5,7-dihydroxy-*N*-methylquinolin-2-ones, it was of interest to study their reactivities. The first reaction attempted was the synthesis of furoquinolones, wherein *N*-methyl-5,7-dihydroxyquinolin-2-one **314**, **317** and **318** were reacted with 2 molar equivalents of α-haloketones in the presence of K_2CO_3 in acetone to give the ketone intermediates **319-327** in 69-84% yields (Scheme 4-16).



Scheme 4-16

The ^{1}H NMR spectrum of compound **319** in $CDCl_3$ showed two singlets at δ 2.27 and 2.29 ppm for the COMe protons, and a singlet at δ 2.65 ppm due to the CH_3 protons at C4. Another singlet at δ 3.60 ppm corresponding to the *N*-CH_3 protons was observed, and the two singlets at δ 4.62 and 4.67 ppm were assigned to the two sets of methylene protons. Two doublets at δ 6.13 and 6.34 ppm (J = 3.0 Hz) corresponded to H6 and H8, respectively (Figure 4-4).

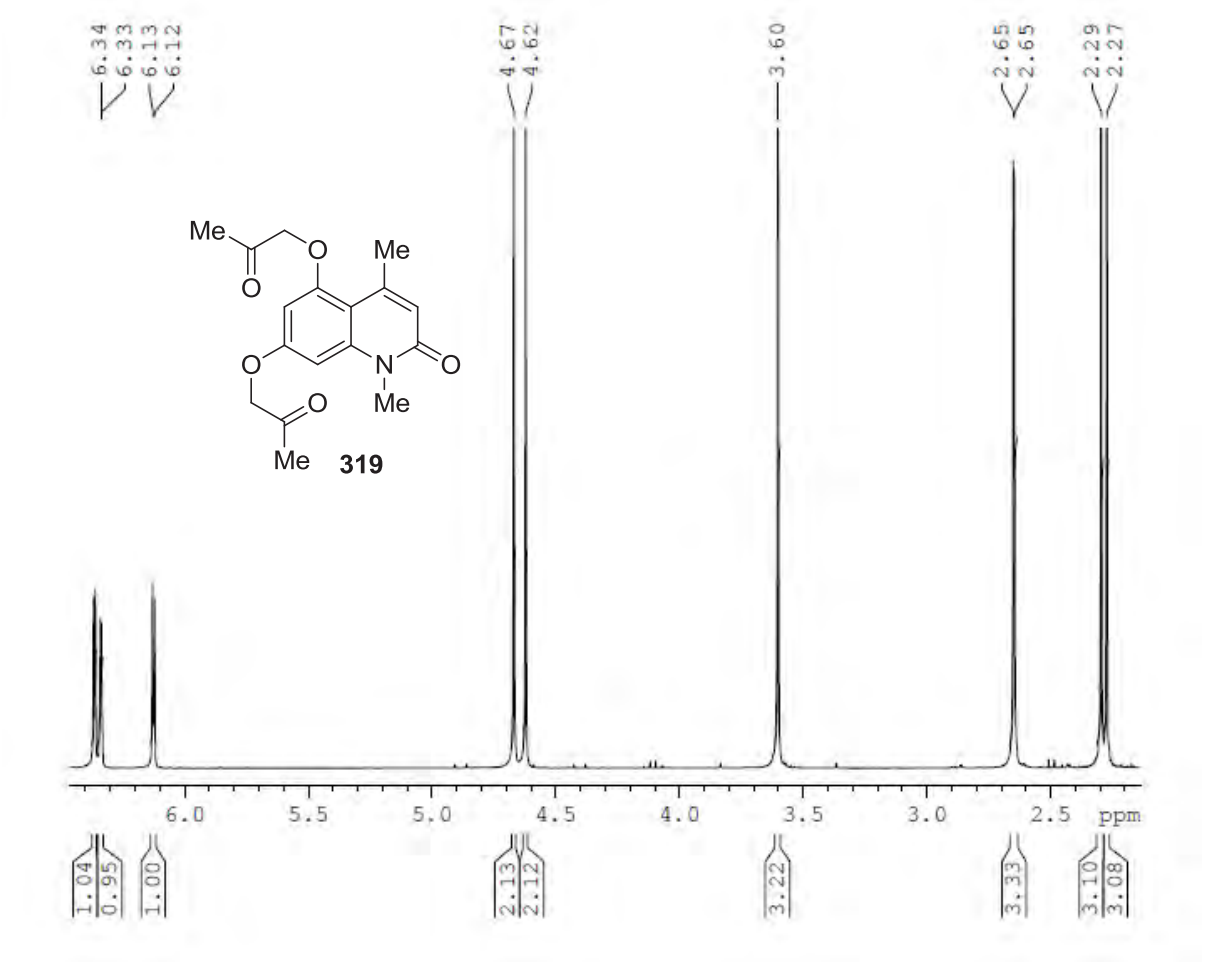


Figure 4-4 ^{1}H NMR spectrum of **319** in $CDCl_3$.

The ^{13}C NMR spectrum showed the presence of two signals at δ 72.77 and 73.27 ppm which appeared as negative signals in the DEPT 135 ^{13}C NMR spectrum, confirming the presence of two CH_2 groups in the molecule.

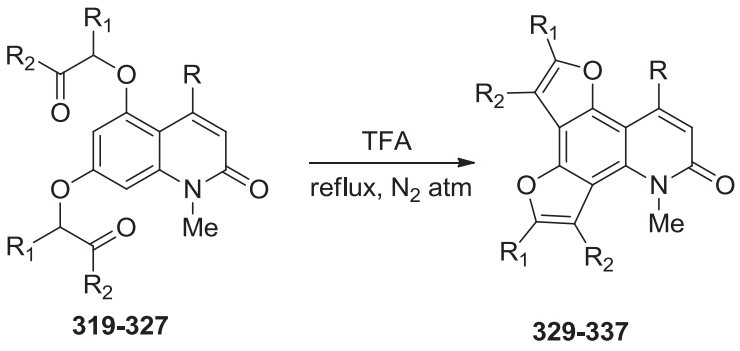
The yield and the nature of the R, R_1 and R_2 substituents are depicted in Table 4-1.

Table 4-1: Yield and the nature of the R, R_1 and R_2 substituents.

Product	R	R_1	R_2	Yields (%)
319	Me	H	Me	80
320	Me	Me	Me	78
321	Me	H	C_6H_5	69
322	CF_3	H	Me	76
323	CF_3	Me	Me	74
324	CF_3	H	C_6H_5	70
325	C_6H_5	H	Me	71
326	C_6H_5	Me	Me	84
327	C_6H_5	H	C_6H_5	69

In order to synthesise the furoquinolones, the quinolone acyl ethers **319-327** were treated with polyphosphoric acid. However, the attempted cyclisation was unsuccessful and only starting material was recovered from the reaction mixture.

Interestingly, when the same intermediates were heated under reflux with trifluoroacetic acid, the furoquinolones **329-337** were formed in 58-86% yield (Scheme 4-17). This was found to be efficient route towards furoquinolones.



319-327 **329-337**

Scheme 4-17

The yield and the nature of the R, R_1 and R_2 substituents are depicted in Table 4-2.

Table 4-2: Yield and the nature of the R_1, R_2 and R_3 substituents.

Product	R	R_1	R_2	Yields (%)
329	Me	H	Me	62
330	Me	Me	Me	61
331	Me	H	C_6H_5	58
332	CF_3	H	Me	65
333	CF_3	Me	Me	58
334	CF_3	H	C_6H_5	61
335	C_6H_5	H	Me	66
336	C_6H_5	Me	Me	86
337	C_6H_5	H	C_6H_5	59

The ^1H NMR spectrum of compound **329** in $CDCl_3$ showed the presence of a overlapping singlet corresponding to the methyl protons on the furan rings at δ 2.46 ppm, another overlapping singlet at δ 2.78 ppm from C4-CH_3 group, and a singlet at δ 6.27 ppm corresponding to H3. The furan ring protons appeared at δ 7.69 and 8.26 ppm. The disappearance of the two CH_2 peaks indicated that the cyclisation had taken place (Figure 4-5).

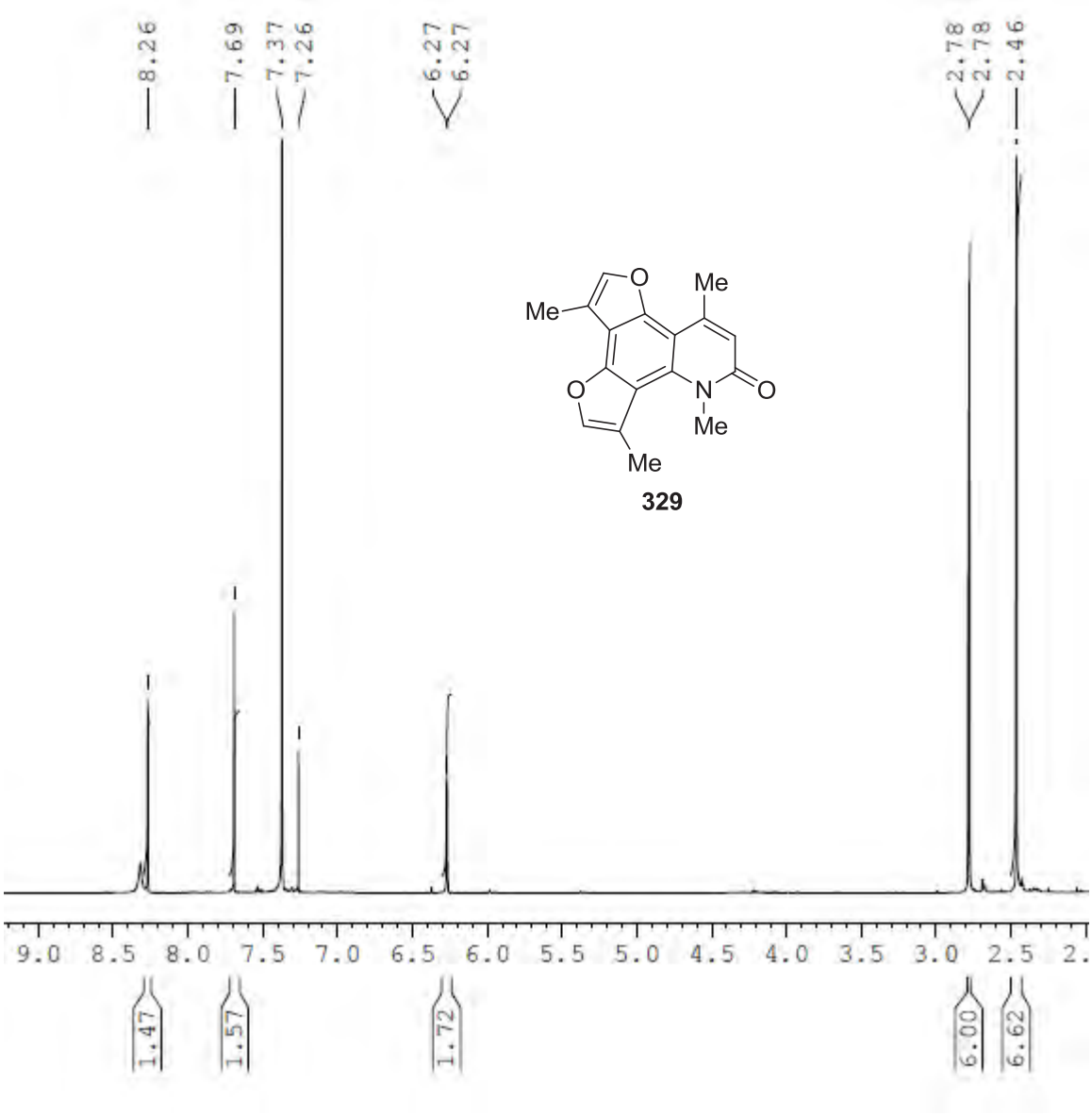
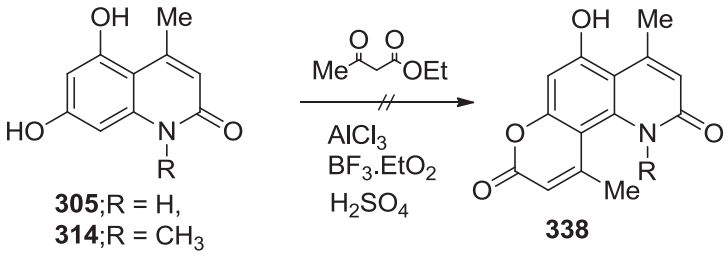


Figure 4-5 ^{1}H NMR spectrum of **329** in $CDCl_3$

4.2.2.1 Attempted synthesis of pyranoquinolones:

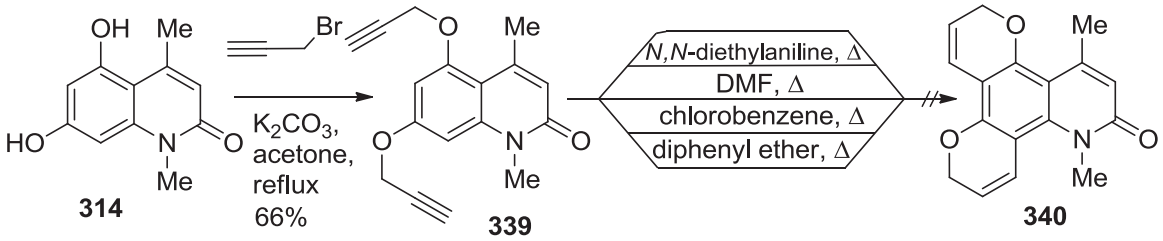
After having successfully reacted 4,6-dihydroxyindoles with ethyl acetoacetate under von Pechmann conditions to generate pyranoindoles as described in Chapter-2, it was of interest to apply the same protocol to 5,7-dihydroxyquinolin-2-ones, as it could generate another type of fused heterocycle. However, when 5,7-dihydroxyquinolin-2-ones **305** and **314** were reacted with ethyl acetoacetate in the presence of Conc. sulfuric acid, no

reaction occurred, as evidenced by TLC analysis. Only starting material was recovered after extended heating with different Lewis acids such as aluminium chloride, $BF_3{\cdot}OEt_2$ or Conc. sulfuric acid (Scheme 4-18).



Scheme 4-18

An alternative strategy was therefore pursued in which 5,7-dihydroxyquinolin-2-ones **314** was reacted with propargyl bromide in the presence of K_2CO_3 under the reflux in acetone, it gave the intermediate **339** in 66% yield (Scheme 4-19).



Scheme 4-19

The ^{1}H NMR spectrum of compound **339** in acetone-d_6 showed the presence of an overlapping singlet at δ 1.54 ppm corresponding to acetylenic protons, a singlet at δ 2.54 ppm corresponding to C4-CH_3 protons, and another singlet at δ 3.58 ppm was assigned to *N*-methyl protons. The methylene protons appeared as two doublets at δ 4.70 and 4.74 ppm. H3 appeared at δ 6.27 ppm as a singlet, while H6 and H8 appeared as doublets at δ 6.42 and 6.52 ppm (J = 3.0 Hz), respectively. The DEPT 135 ^{13}C NMR

spectrum showed two negative peaks at δ 56.43 and 56.82 ppm corresponding to the CH_2 groups in the molecule.

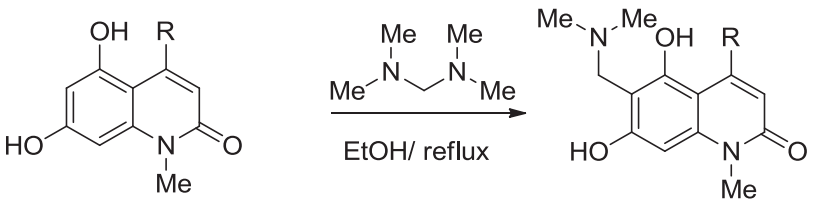
Thermal cyclisation of the propargyloxy intermediate **339** was attempted using various solvents (*N*,*N*-diethylaniline, *N*,*N*-dimethylformamide, chlorobenzene or diphenyl ether) and temperatures but these conditions failed to give the desired pyranoquinolone. Starting material was recovered unchanged from the reaction mixture (Scheme 4-19). The attempted cyclisation conditions of **339** are shown in Table 4-3.

Table 4-3: Cyclisation conditions for **339**.

Solvent	Temp./˚C	Time /h	Result
N,*N*-diethylaniline	reflux	3-6	S.M.
N,*N*-diethylaniline	reflux	12	S.M.
N,*N*-dimethylformamide	reflux	12	S.M.
chlorobenzene	reflux	12	S.M.
diphenyl ether	reflux	12	S.M.

4.2.2.2 Mannich reaction of 5,7-dihydroxyquinolin-2-ones:

When quinolones **314**, **317-318** were heated with the preformed Mannich reagent bis(dimethylamino)methane in ethanol for 1 h, the Mannich adducts were obtained in 65-67% yield (Scheme 4-20).



314; R = CH_3
317; R = C_6H_5
318; R = CF_3

341; R = CH_3 66%
342; R = C_6H_5 68%
343; R = CF_3 65%

Scheme 4-20

The ^{1}H NMR spectrum of compound **343** in acetone-d_6 showed a singlet at δ 2.34 ppm for the *N*-$(CH_3)_2$ protons, a singlet at δ 3.47 ppm corresponding to the *N*-CH_3 protons, and another singlet at δ 3.78 ppm corresponding to the CH_2 protons. Two singlets at 6.31 and 6.59 ppm corresponded to the two aryl protons. The loss of only one proton signal from the quinolone protons indicated that the reaction had taken place at one carbon only (Figure 4-6). The DEPT 135 ^{13}C NMR spectrum showed a negative peak at δ 55.01 ppm corresponding to CH_2 carbon in the molecule.

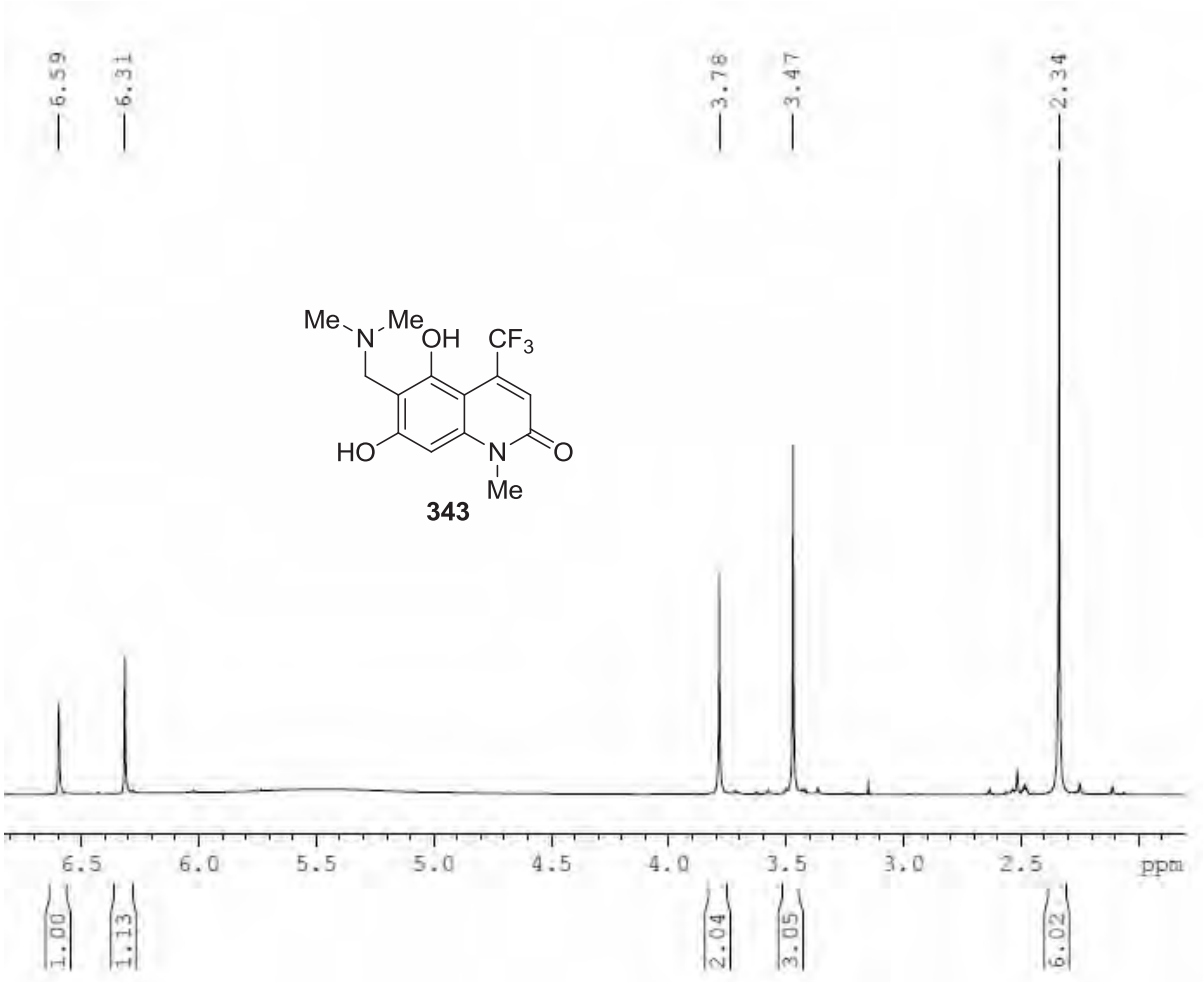
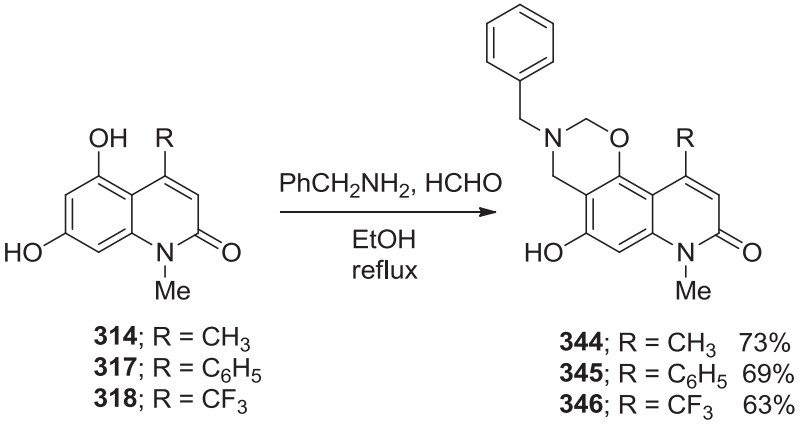


Figure 4-6 ^{1}H NMR spectrum of compound **343** in acetone-d_6.

Interestingly, when quinolones **314**, **317-318** were heated under reflux with formaldehyde and benzylamine, benzoxazinoquinolone were obtained in 63-73% yields (Scheme 4-21).



Scheme 4-21

The ^{1}H NMR spectrum of compound **345** in DMSO-d_6 showed the presence of a singlet at δ 3.52 ppm corresponding to *N*-CH_3 protons, and three singlets at δ 3.69, 3.75 and 4.32 ppm corresponded to *N*-CH_2 and *O*-CH_2 protons. Two singlets at δ 5.98 and 6.50 ppm were due to two aryl protons, while a multiplet at δ 7.24-7.33 corresponded to phenyl ring protons. The loss of only one proton signal from the quinolone protons indicated that the reaction had taken place at one carbon only (Figure 4-7). The DEPT 135 ^{13}C NMR spectrum showed three negative peaks at δ 45.19, 55.13 and 81.39 ppm corresponding to the three CH_2 groups in the molecule.

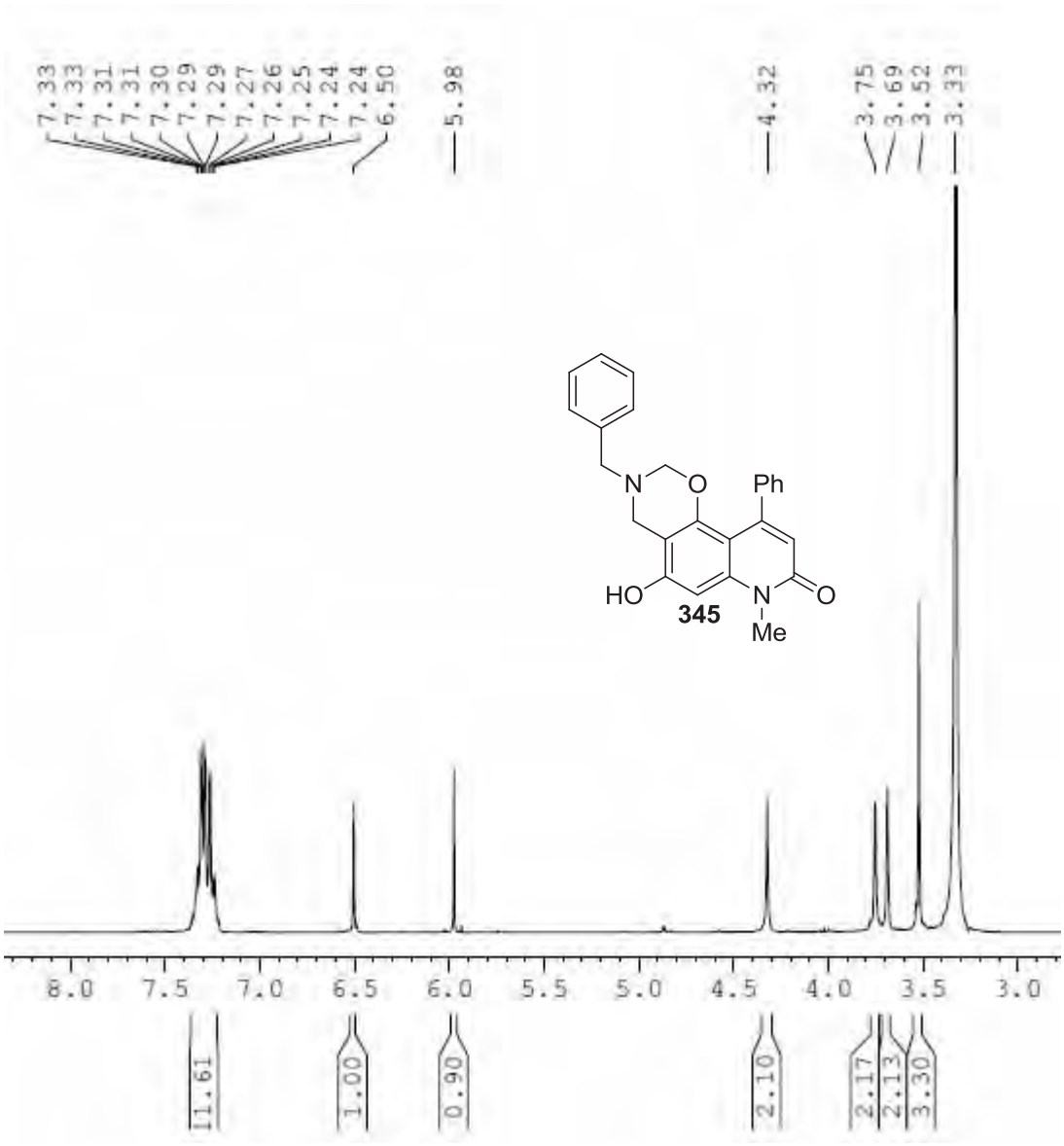
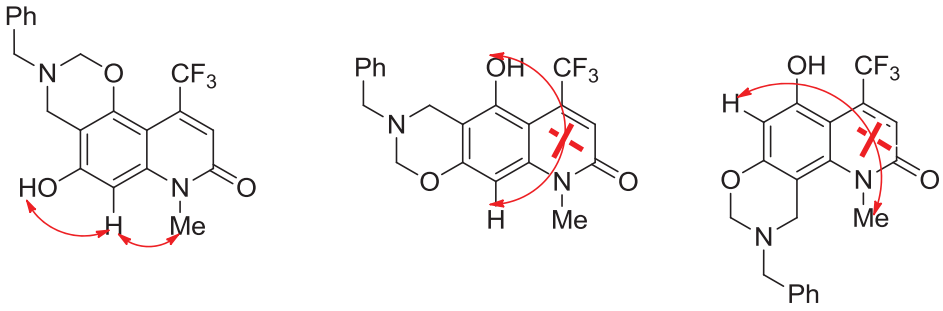


Figure 4-7 ^{1}H NMR spectrum of compound **345** in DMSO-$d_{6.}$

However, there was a likelihood of the formation of one of the products from the three possible structures in all the cases as exemplified by **346**, **346a** and **346b**. Therefore, to determine the exact structure 2D NMR spectroscopy study was performed. Which showed the correlation of H8 with OH and *N*-CH_3 protons, further confirming the structure. As there was correlation of H8 and OH proton therefore, the possibility of the structure **346a** was ruled out, and there was a correlation between H8 and *N*-CH_3 protons therefore, the probability of the structure **346a** was negated.



346 **346a** **346b**

Important H-H NOESY correlations of Mannich adduct of quinolone **318**

4.3 Conclusion:

A series of new fused quinolones has been synthesized. These heterocycles are important from a biological point of view and can be exploited to make other fused heterocycles. Four methods for preparation of 5,7-dihydroxyquinolin-2-ones were investigated. Among these methods, the synthetic route from phloroglucinol and methylamine was found to be the most promising, as it allowed the efficient protection of the NH group at an early stage. It also minimized the number of steps, and could be easily cyclised *via* the acyl ether intermediate to yield furoquinolones as compared to the intermediate with a free NH group in quinolone.

In order to generate the pyranoquinolones, the reaction of 5,7-dihydroxyquinolin-2-ones with a β-ketoesters was attempted but only starting material was recovered. 5,7-Dihydroxyquinolin-2-one was also reacted with propargyl bromide to give o-propargyl intermediates, which failed to cyclise under thermal cyclisation conditions.

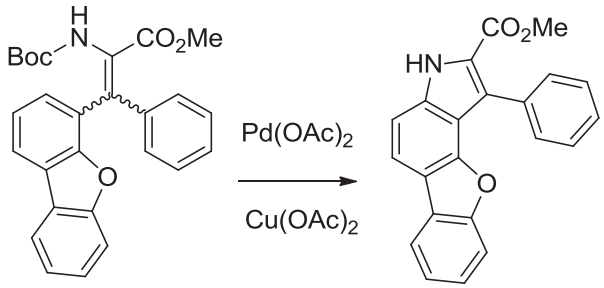
The Mannich reaction of 5,7-dihydroxyquinolin-2-ones was also investigated. Reaction of 5,7-dihydroxyquinolin-2-one with bis(dimethylamino)methane gave the Mannich adducts, whereas reaction with benzylamine and formaldehyde gave the benzoxazinoquinolone.

CHAPTER 5

SYNTHESIS OF NOVEL FUROINDOLES

5.1 Introduction:

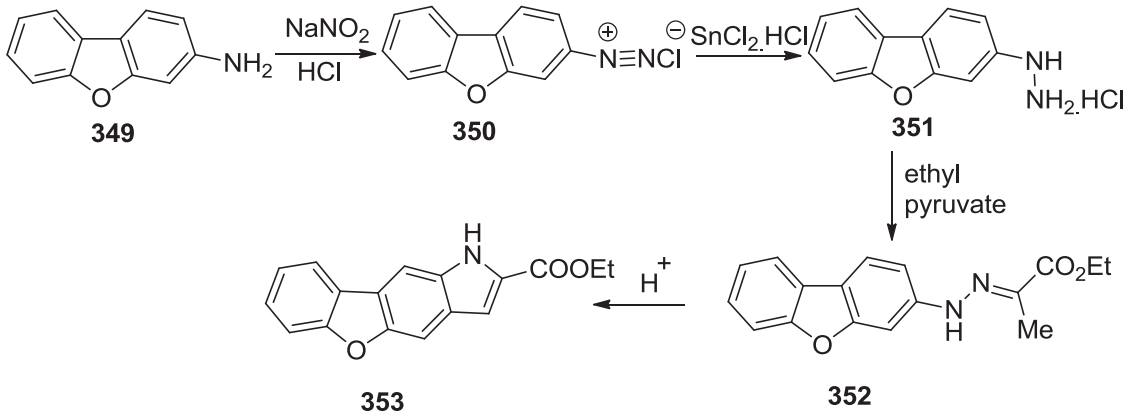
Furoindoles are an important class of heterocycles having various biological activities. Many planar heteroaromatic derivatives have shown anti-proliferative activity *in vitro* and some of them have been reported to possess anti-cancer,[137-138] anti-inflammatory,[139] and anti-allergic activities.[140] Furoindoles consist of a fusion of a furan with an indole. Several types of fused indole-furan systems have been reported.[141-144] The inhibitory effect of furoindole **348** against breast adenocarcinoma (MCF-7) and non-small cell lung cancer (NCI-H460) has been reported by Queiroz *et al.*[145] Furoindole **348** was synthesized from methyl 2-((*tert*-butoxycarbonyl)amino)-3-(dibenzo[*b,d*]furan-4-yl)-3-phenylacrylate **347** (Scheme 5-1).



347 **348**

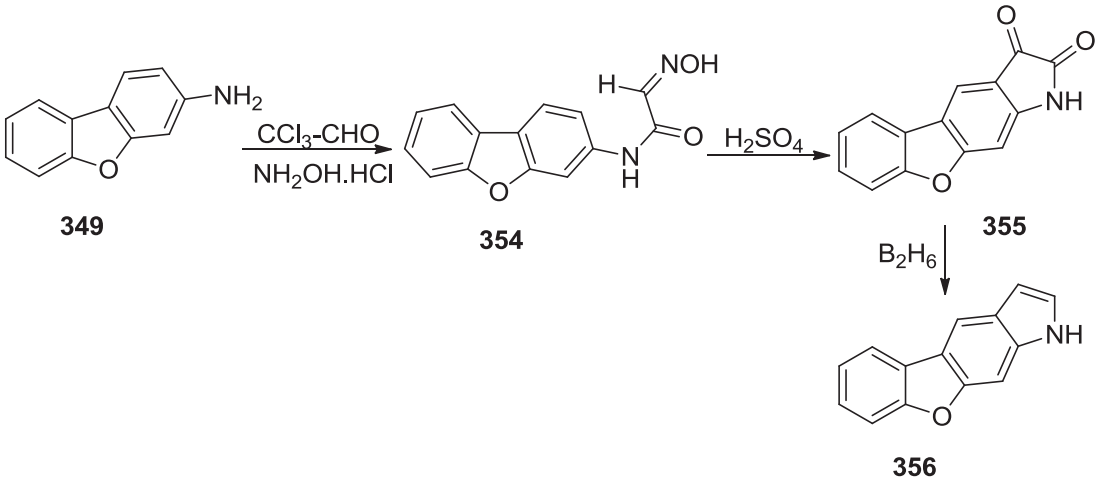
Scheme 5-1

Furoindoles can be synthesized from a furan using the Fischer indole synthesis as reported by Khoshtariya *et al.*[146] The amine **349** was diazotized to give the diazonium compound **350**, which was converted to hydrazone **351**. Subsequent reaction of **351** with ethyl pyruvate gave the intermediate **352**, which was cyclised using acid to give furoindole **353** (Scheme 5-2).



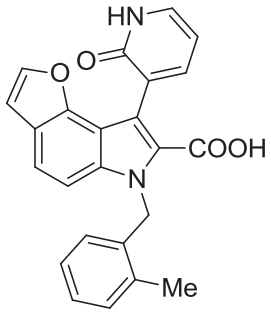
Scheme 5-2

Another route for the synthesis of furoindoles has been reported by Dzhashi *et al.*[147] starting from aminofuran **349**, which was reacted with chloral hydrate and hydroxylamine hydrochloride to give **354**. Acid cyclisation gave the oxindole derivative **355**, which was subsequently reduced to the furoindole **356** using diborane (Scheme 5-3).



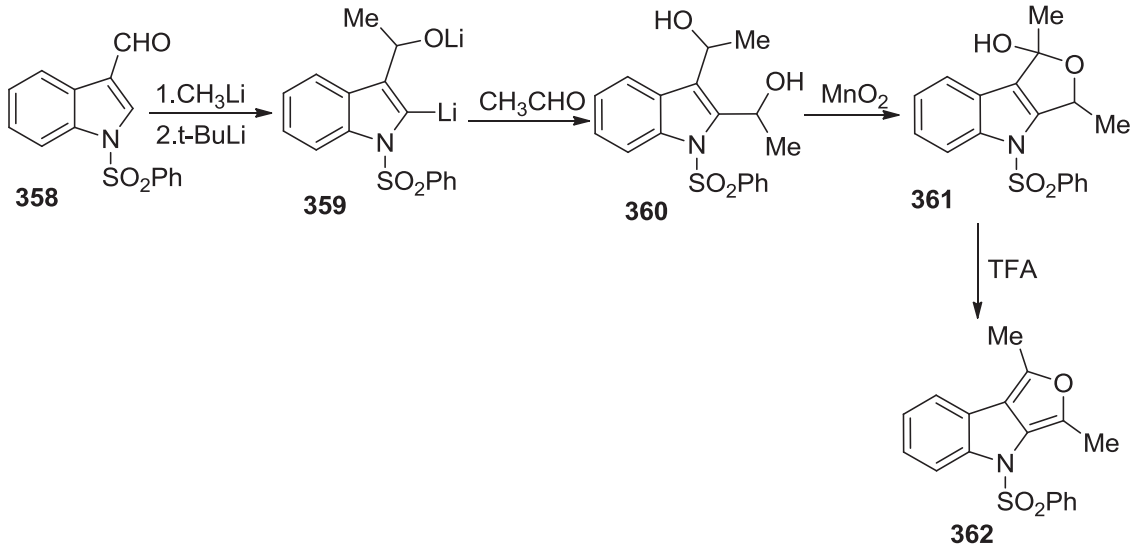
Scheme 5-3

Chen *et al.*[148] have reported the synthesis and anti-viral activity of compound **357** against hepatitis C virus.



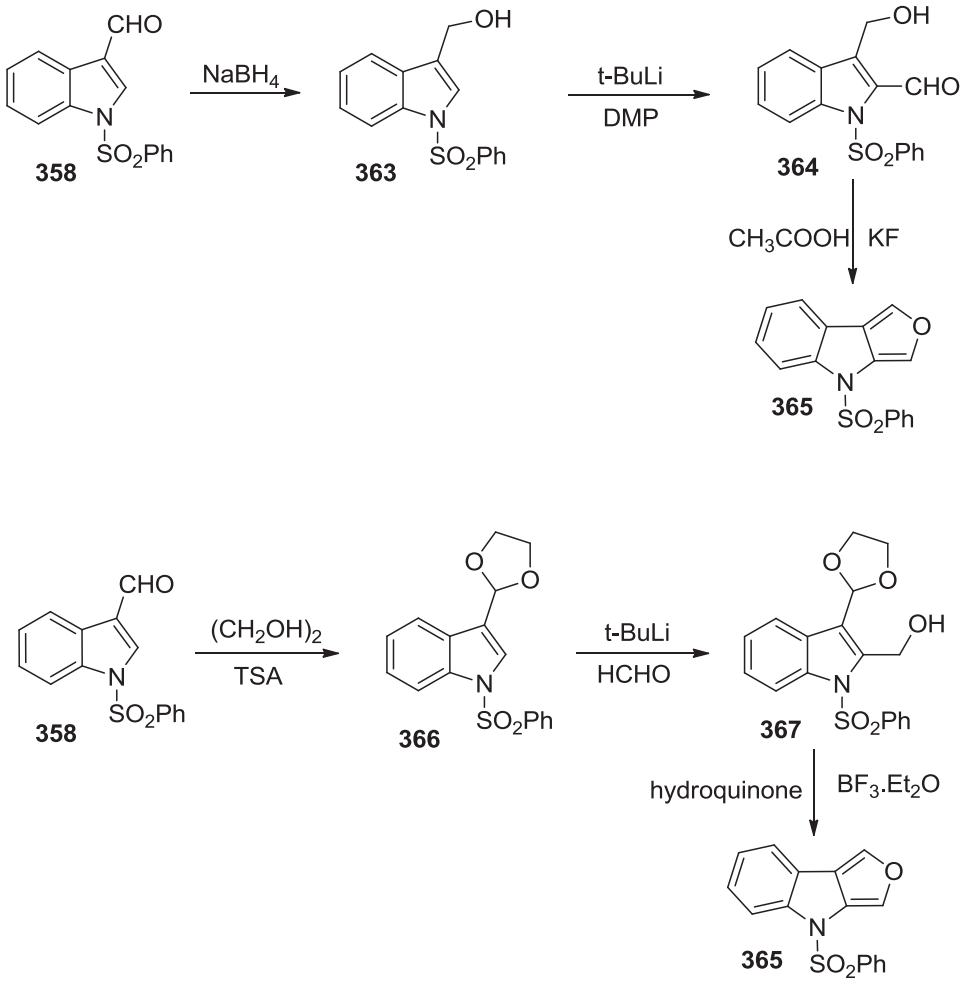
357

The fused heterocycle 4*H*-furo[3,4-*b*]indole has served admirably over the past 20 years as an indole-2,3-quinodimethane synthetic analogue in the Diels-Alder reactions.[149-151] Gribble *et al.*[137] have developed a strategy for constructing the furoindole **362** starting from indole-3-carbaldehyde **358**. Lithiation of **358** yielded **359**, which when reacted with acetaldehyde gave diol **360**. The reaction of **360** with manganese dioxide gave **361**, which was dehydrated by trifluoroacetic acid to yield the desired furoindole **362** (Scheme 5-4).



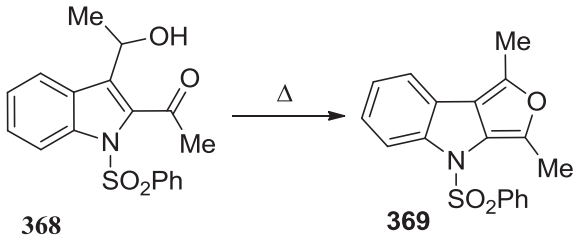
Scheme 5-4

Recently, Gribble *et al.*[152] have published a report on the synthesis of the furoindole **365** using an alternative route, starting from indole-3-carbaldehyde **358**. Reduction of **358** gave alcohol **363**, which after lithiation gave **364**. Cyclisation of **364** with acetic acid and potassium fluoride gave the desired furoindole **365**. In another modification, aldehyde **358** was reacted with ethylene glycol to give **366**. Lithiation of **366** and reaction with formaldehyde gave indole derivative **367**, which was cyclised to furoindole **365** in the presence of boron trifluoride etherate (Scheme 5-5).



Scheme 5-5

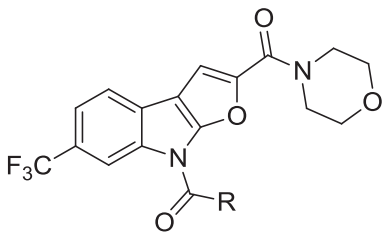
The facile thermal cyclisation of **368**, without acid treatment, to dimethyl analogue **369** is noteworthy (Scheme 5-6). This may be a consequence of the well-known Thorpe-Ingold effect, wherein cyclisation is both kinetically and thermodynamically favoured by alkyl substitution in the open-chain substrate **368**.



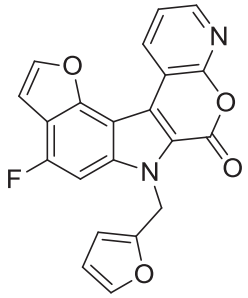
368 **369**

Scheme 5-6

Furoindole **370** has been shown to possess analgesic, anti-inflammatory and anti-pyretic activity.[153] While anti-viral activity of furoindole **371** has been reported by Bennett *et al.*[154]

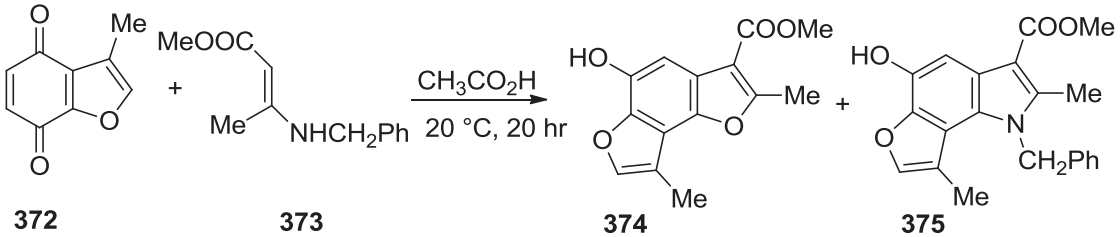


370



371

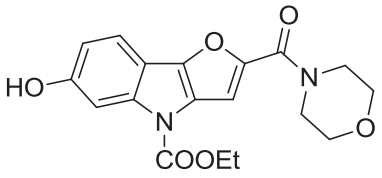
Another synthesis of furoindole **375** using the Nenitzescu reaction of quinone **372**, with the enamine of methyl acetoacetone and benzylamine has been reported by Lyubchanskaya *et al.*[155] (Scheme 5-7).



372 **373** **374** **375**

Scheme 5-7

Kawashima *et al.*[153] have reported the synthesis and anti-inflammatory activity of furoindole **376**.

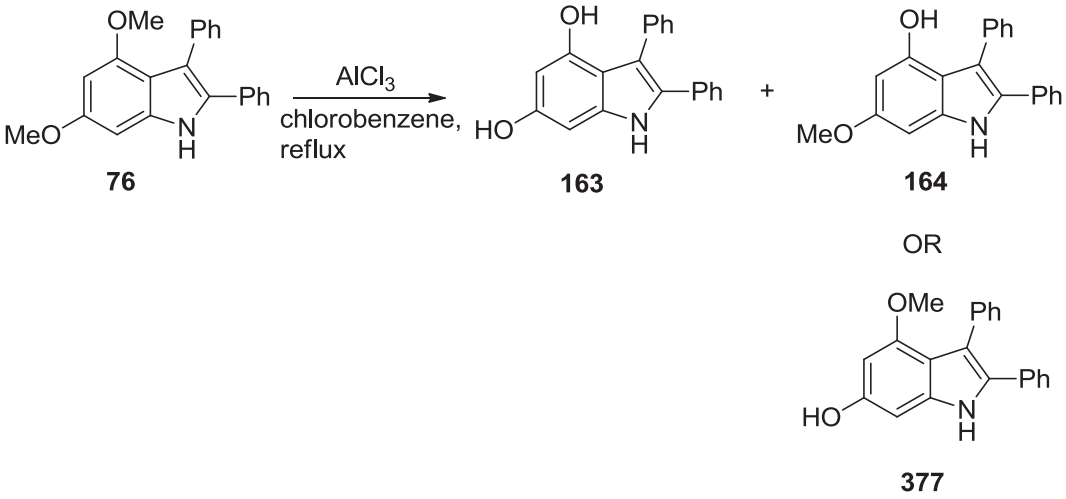


376

5.2 Results and Discussion:

5.2.1 Synthesis of the starting 4-hydroxy-2,3-diphenylindole:

During the synthesis of 4,6-dihydroxyindole **163** (Chapter 2), it was observed that the slow addition of aluminium chloride to indole **76** gave a faster running spot compared to **163**. This product was isolated (Scheme 5-8) and its structure was established on the basis of the ^{1}H, ^{13}C, HSQC and HMBC NMR spectroscopy data.



76 **163** **164** **377**

Scheme 5-8

The ^{1}H NMR spectrum of the demethylation product of **76** in DMSO-d_6 showed the presence of a singlet at δ 3.78 ppm which indicated the presence of one methoxy group in the molecule (Figure 5-1).

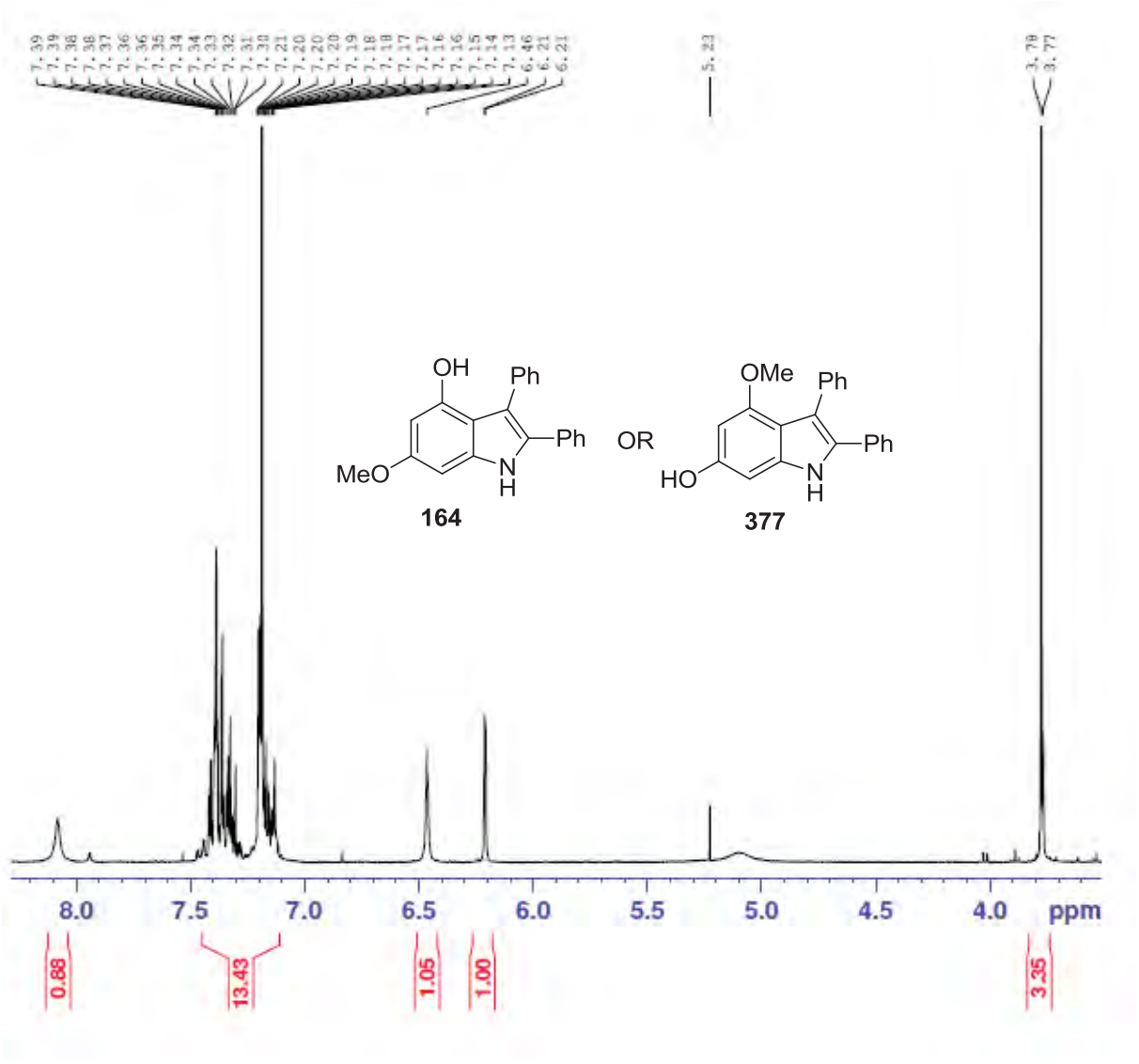
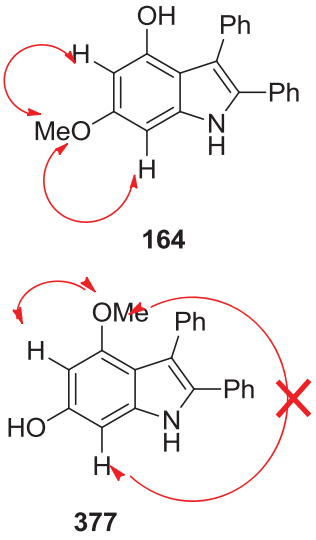


Figure 5-1 ^{1}H NMR spectrum of monohydroxy-diphenylindole in DMSO-d_6

However, it was not clear whether the methoxy group was at C4 or C6 of the indole. Therefore, 2-D NMR analysis was performed. The H-H NOESY spectrum showed a through space correlation of OH (δ 11.10 ppm) with the phenyl ring protons (δ 7.1-7.40 ppm). This observation was consistent with the 4-hydroxy-6-methoxy-2,3-diphenylindole **164** structure.

It seems that the OMe group is displaying the NOE correlations to the H5 and H7, which proves the structure **164** (Figure 5-2).



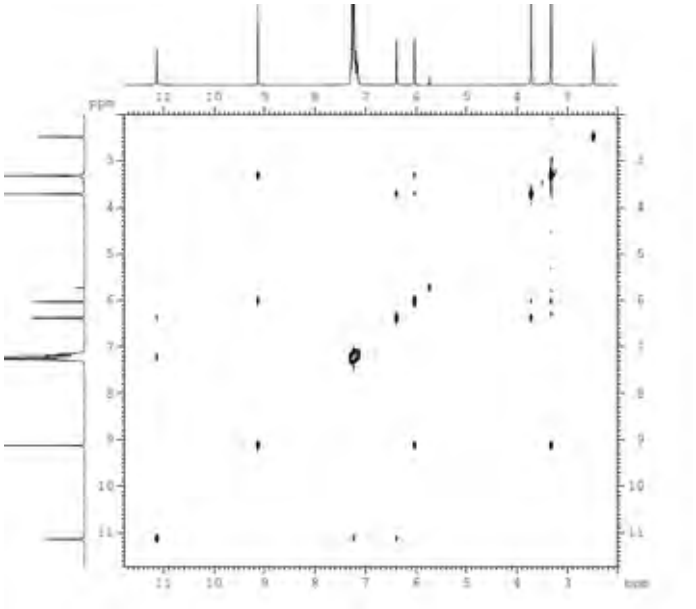
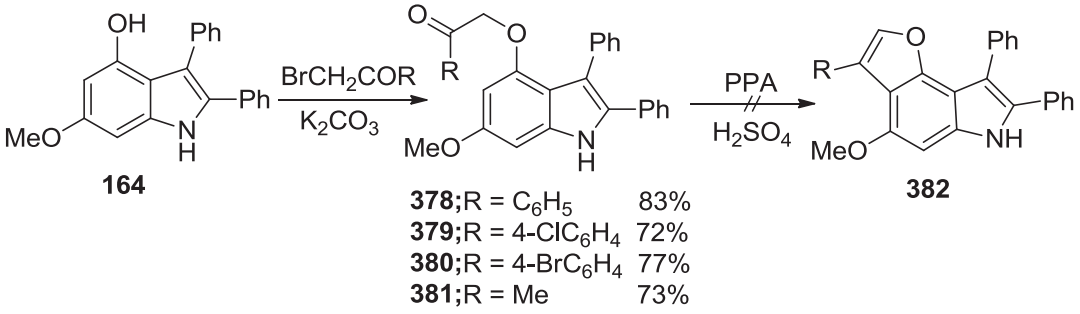


Figure 5-2 H-H NOESY NMR spectrum of Important NOEs for monohydroxyindole

hydroxyindole obtained by demethylation of **76** is shown.

5.2.2 Synthesis of furo[2,3-*e*]indoles:

It was of interest to exploit the reactivity of the hydroxyl group of 4-hydroxy-2,3-diphenylindole to prepare furoindoles. When 4-hydroxy-2,3-diphenylindole **164** was reacted with α-haloketones in the presence of potassium carbonate in refluxing acetone, it gave the intermediates **378-381** in 73-83% yield (Scheme 5-9).



Scheme 5-9

The ^{1}H NMR spectrum of compound **379** in $CDCl_3$ showed the presence of a signal at δ 4.90 ppm corresponding to -CO-CH_2-O protons, two singlets at δ 6.21 and 6.55 ppm for H5 and H7, respectively, and a multiplet at δ 7.09-7.64 ppm corresponding to the aryl protons. The NH proton appeared as a singlet at δ 8.26 ppm (Figure 5-3). The presence of the methylene group in the molecule was confirmed by a negative peak at δ 71.62 ppm in the DEPT 135 spectrum.

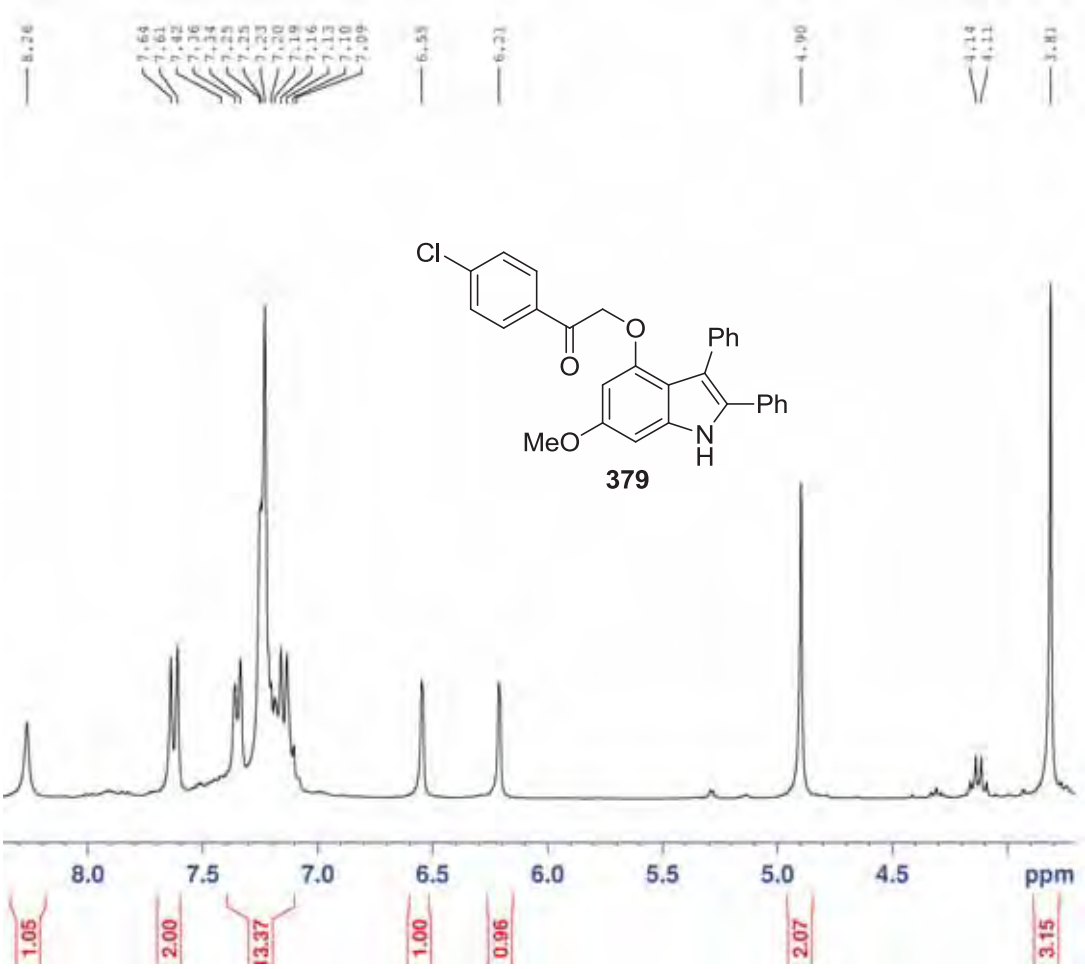
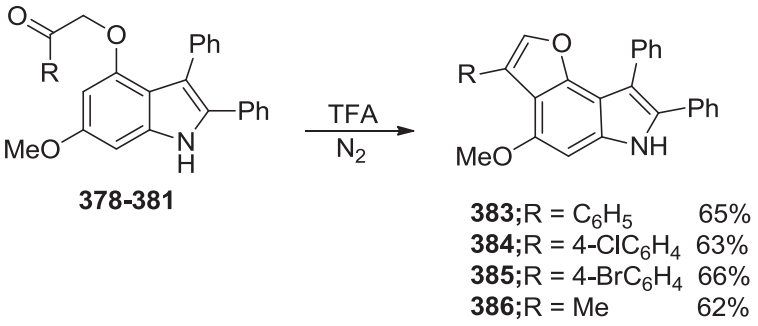


Figure 5-3 ^{1}H NMR spectrum of compound **379** in $CDCl_3$

Several methods were attempted for the cyclisation of acylindoles, including heating with polyphosphoric acid, sulfuric acid or refluxing with trifluoroacetic acid in

dichloromethane. However, the cyclisation was unsuccessful. Interestingly, when the intermediates **378-381** were refluxed with neat trifluoroacetic acid for 24 h under nitrogen atmosphere, the furoindoles **383-386** were obtained in 62-66% yield (Scheme 5-10).



378-381

383;R = C_6H_5 65%
384;R = 4-ClC_6H_4 63%
385;R = 4-BrC_6H_4 66%
386;R = Me 62%

Scheme 5-10

The ^{1}H NMR spectrum of cyclised compound **384** in $CDCl_3$ showed the disappearance of the two signals, one at δ 4.90 ppm corresponding to -CO-CH_2-O and the δ 6.21 ppm corresponding to the ring proton (Figure 5-4).

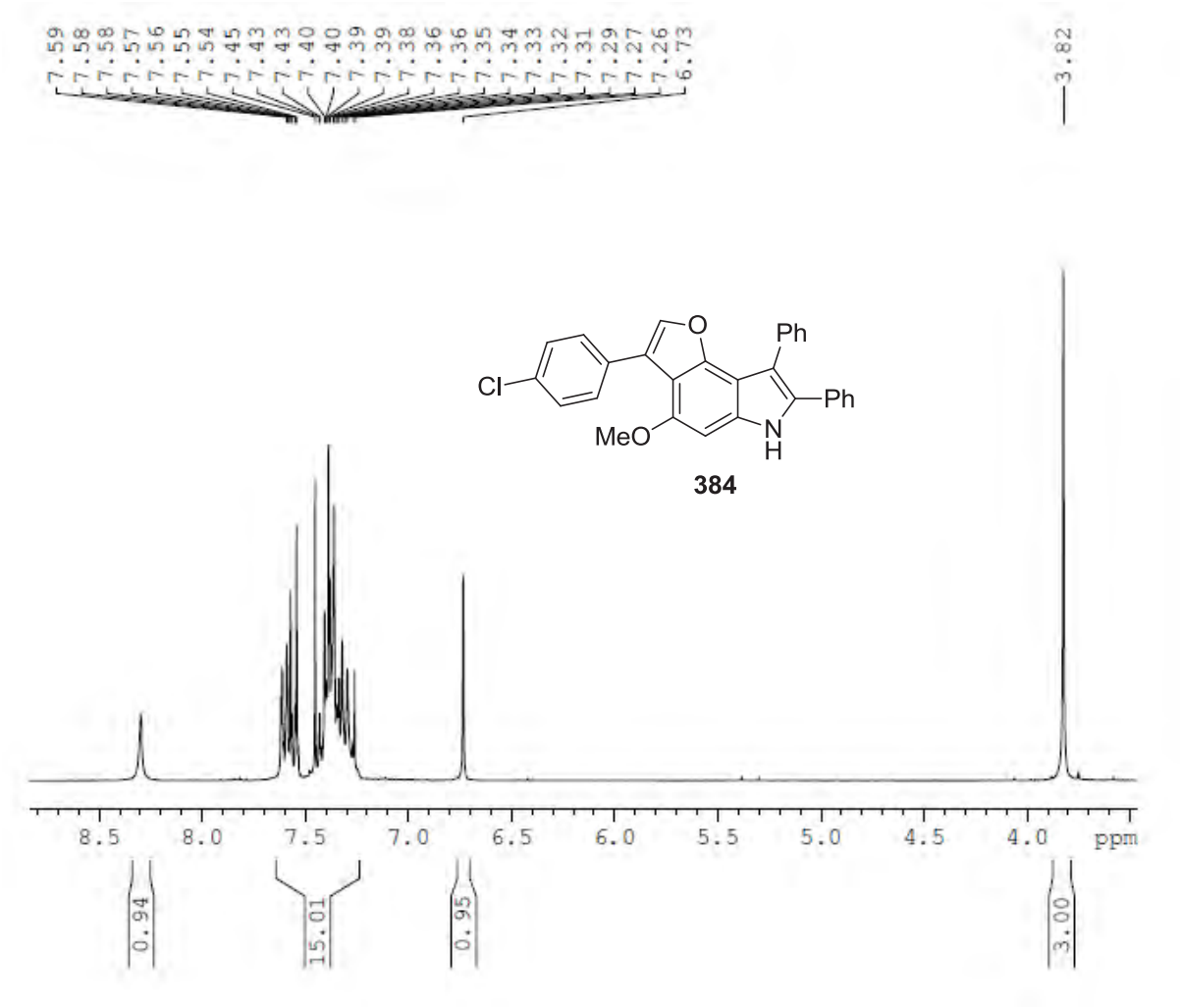


Figure 5-4 ^{1}H NMR spectrum compound **384** in $CDCl_3$.

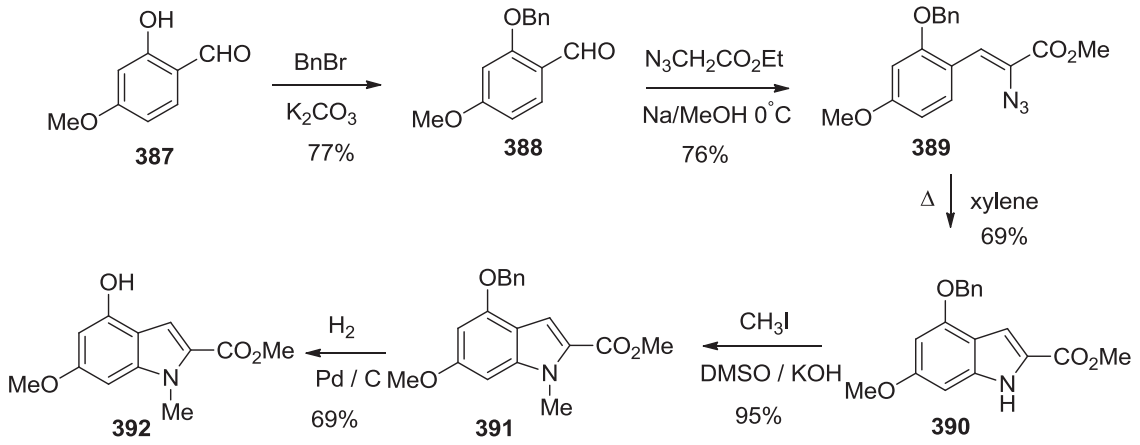
As mentioned previously, the most reactive position in 4,6-dimethoxyindoles is C7. [92] Almost all reactions involving this system are exclusively directed at C7 making it a preferable centre for cyclisation. 4-Hydroxy-6-methoxyindole **164** is an interesting intermediate for the synthesis of furoindoles and the involvement of C5 in a reaction leading to the synthesis of furoindole has not been reported in the literature.

5.2.3 Synthesis of methyl 4-hydroxy-6-methoxy-1-methyl-indole-2-carboxylate:

In order to study the reactivity at 4-OH, the synthesis of 4-hydroxyindole was considered essential. Thus, 4-hydroxyindole **392**, was prepared from 2-hydroxy-4-

methoxybenzaldehyde **387** using the Hemetsberger indole synthesis. The aldehyde **387** was reacted with benzyl bromide to form the benzyloxy derivative **388**. This conversion was necessary because the Hemetsberger methodology involves the use of a strong base, such as sodium methoxide, which would ionise the free hydroxyl intermediate. The benzyloxy aldehyde **388** was treated with sodium methoxide, and methyl azidoacetate was added slowly under anhydrous conditions and maintaining a low temperature, which is crucial for this reaction. When TLC analysis indicated that the starting material has been consumed, the reaction was quenched by addition of crushed ice. The resulting precipitate was washed with water and air-dried to afford azidocinnamate **389**.

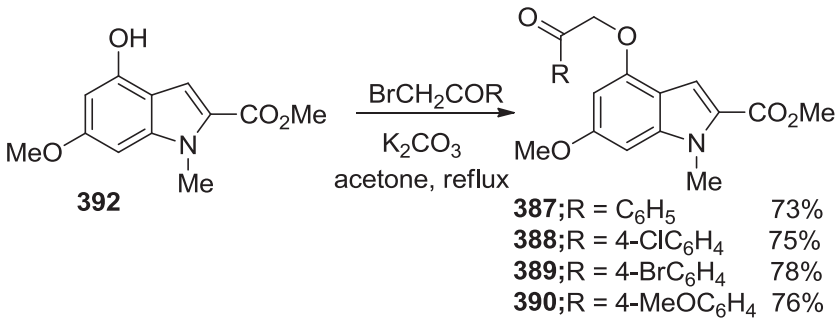
Azidocinnamates are known to decompose rapidly, therefore **389** was used in the subsequent reaction without further purification. The azide **389** was added portion-wise to boiling xylene under a nitrogen atmosphere. The bubbles emerging from the reaction mixture indicated decomposition of the azide and liberation of nitrogen. After the reaction was finished, excess xylene was evaporated under high vacuum, and evaporated under a slow stream of nitrogen to give indole **390** in 69% yield. *N*-Methylation of indole **390** was achieved with methyl iodide and potassium hydroxide to give *N*-methylindole derivative **391**. The benzyloxy group was removed under standard hydrogenolysis conditions to give **392** (Scheme 5-11).



Scheme 5-11

5.2.4 Synthesis of furoindole-2-carboxylate:

4-Hydroxyindole **392** was reacted with α-haloketones in the presence of potassium carbonate in refluxing acetone, to give the intermediates **387-390** in 73-78% yield (Scheme 5-12).



Scheme 5-12

The ^{1}H NMR spectrum of compound **388** in $CDCl_3$ revealed the presence of three singlets at δ 3.78, 3.80 and 3.93 ppm which corresponded to OMe, COOMe and *N*-Me protons respectively. The H5 and H7 appeared as doublets at δ 6.04 and 6.30 ppm woth coupling constant of 3.0 Hz respectively, whereas the indole H3 appeared at δ 7.29 ppm (Figure 5-5).

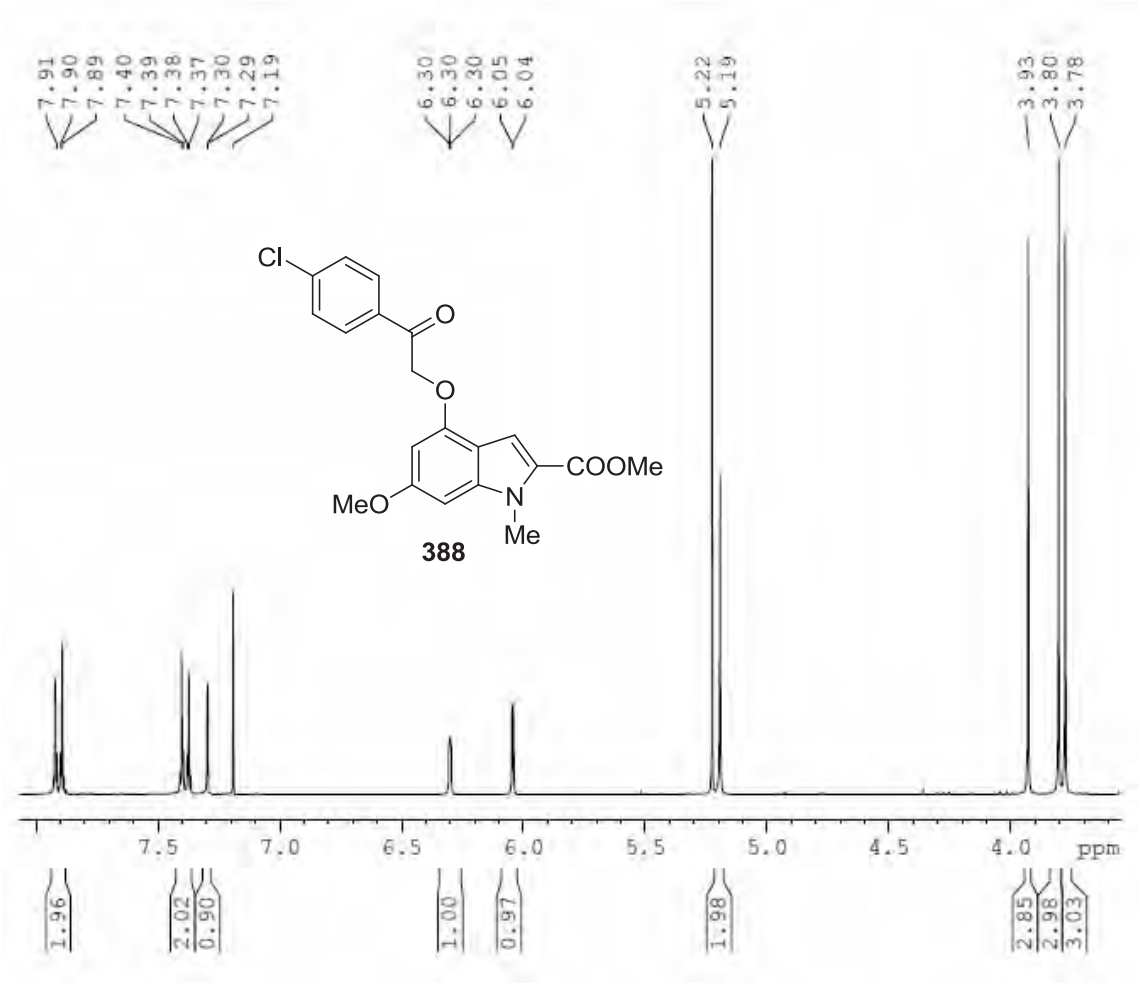
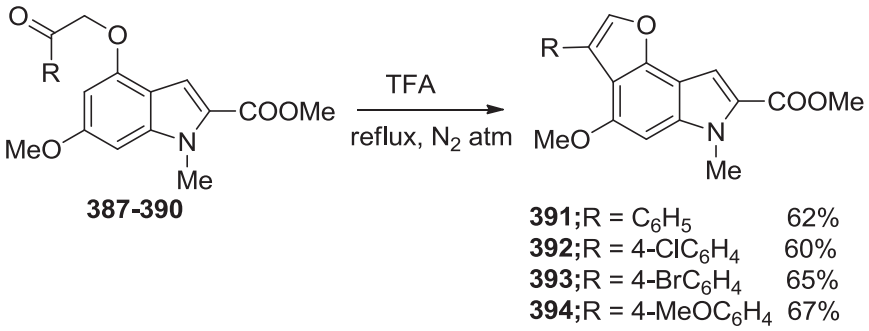


Figure 5-5 ^{1}H NMR spectrum of **388** in $CDCl_3$.

The ^{13}C NMR spectrum of the product showed the presence of an ester carbonyl signal at δ 162.86 ppm and another carbonyl carbon peak at δ 193.84 ppm. A negative peak at δ 71.45 ppm in the DEPT 135 ^{13}C NMR spectrum supported the presence of a CH_2 moiety in the molecule.

These intermediates **387-390** were readily cyclised in refluxing trifluoroacetic acid under a nitrogen atmosphere to give furoindoles **391-394** in 60-77% yield (Scheme 5-13).



Scheme 5-13

The ^{1}H NMR spectrum of compound **392** in $CDCl_3$ revealed the presence of three singlets at δ 3.83, 3.84 and 4.04 ppm which corresponded to the OMe, COOMe and *N*-methyl protons, respectively. The indole ring proton appeared as singlets at δ 6.50 and 7.18 ppm respectively, and the proton from the furan ring at δ 7.18 ppm (Figure 5-6).

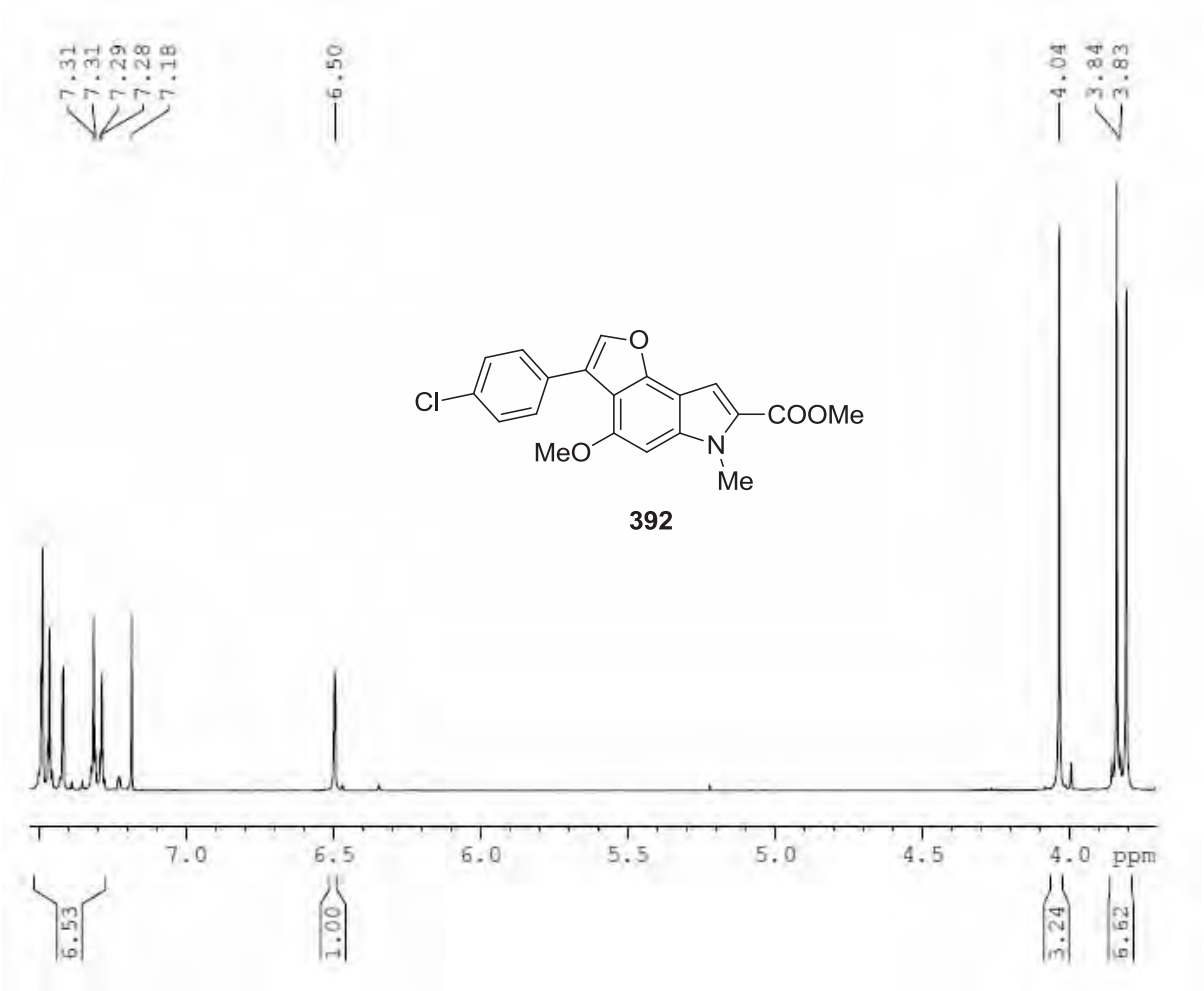


Figure 5-6 ^{1}H NMR spectrum of compound **392** in $CDCl_3$.

The ^{13}C NMR spectrum showed the presence of a carbonyl signal at δ 153.08 ppm. The disappearance of H5 at δ 6.30 ppm in the ^{1}H NMR spectrum and the absence of a negative peak at δ 71.45 ppm in the DEPT 135 ^{13}C NMR spectrum, confirmed the formation of the furoindole.

5.3 Conclusion:

In order to investigate the reactivity of indoles at C5, two different 4-hydroxy-6-methoxyindoles were synthesized and reacted with the α-haloketones, followed by cyclisation with trifluoroacetic acid to give furoindoles. A short and efficient route for the synthesis of diphenyl-6*H*-furo[2,3-*e*]indoles and 6*H*-furo[2,3-*e*]indole-7-carboxylates has been developed.

CHAPTER 6

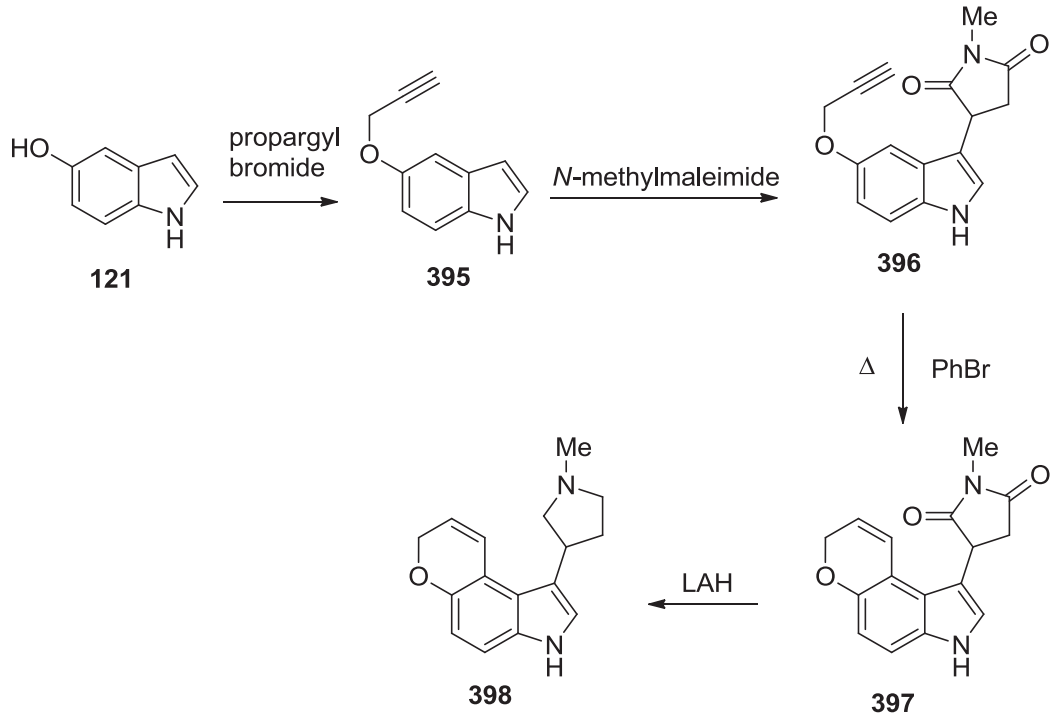
SYNTHESIS OF NOVEL DIHYDROPYRANOINDOLES

6.1 Introduction:

Dihydropyranoindoles are compounds that incorporate an indole and dihydropyran in their ring systems. This ring system has received considerable attention due to its interesting biological properties such as anti-cancer and 5-HT agonist,[156] plasminogen activator inhibitory activities.[157-158]

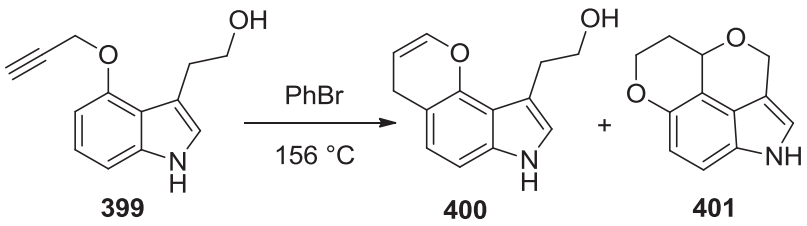
There are two approaches for the construction of these heterocycles. The first is to prepare a hydroxyindole and then install a dihydropyrano moiety on it. The second is to synthesize a pyran scaffold first followed by construction of an indole nucleus using a variety of available methods.

Macor *et al.*[159] have reported the synthesis of the selective 5-HT_2 agonist, dihydropyranoindole **398**, by reaction of 5-hydroxyindole **121** with propargyl bromide to give the propargyloxyindole **395**. Reaction of **395** with *N*-methylmaleimide gave the intermediate **396**, which was cyclised upon heating in bromobenzene to give the indole intermediate **397**. Reduction of **397** gave the desired product **398** (Scheme 6-1).



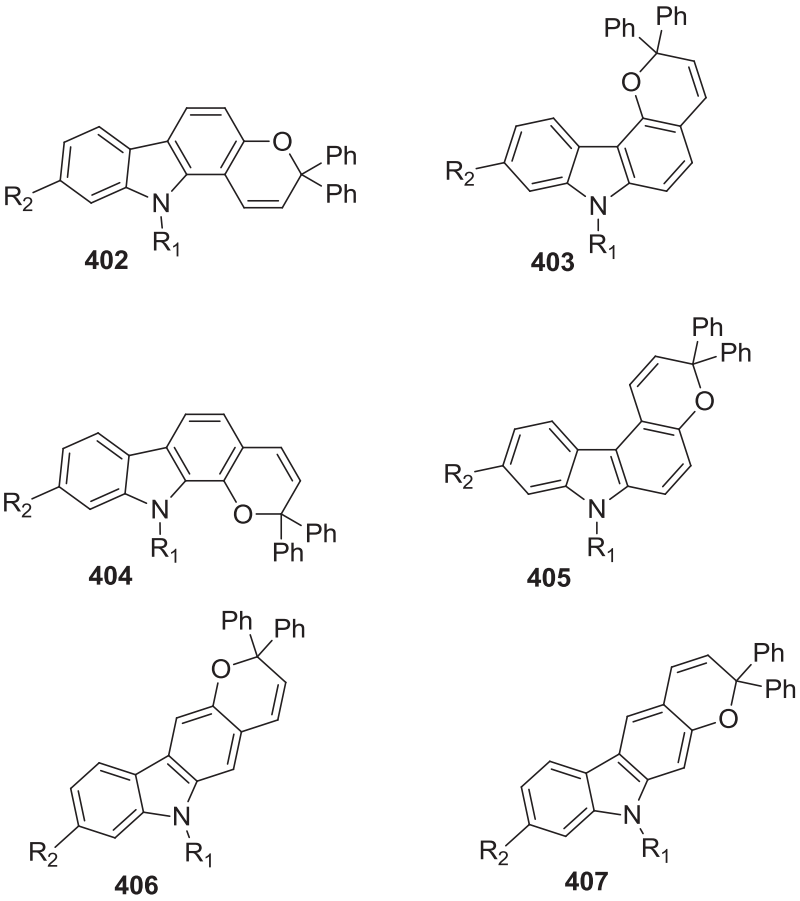
Scheme 6-1

In another study, Macor *et al.*[160] have reported an unusual rearrangement of propargyloxyindole **399** by heating at high temperature in bromobenzene. The major product was found to be **401** and the minor product was dihydropyranoindole **400** (Scheme 6-2).

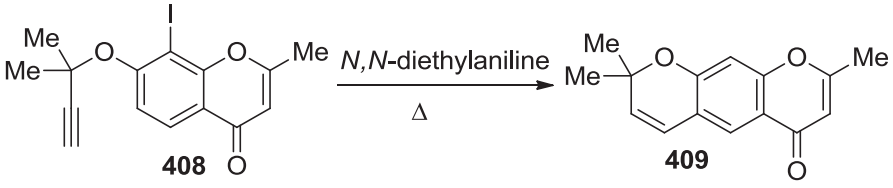


Scheme 6-2

Oliveira *et al.*[161] have reported the synthesis and photochromic properties of compounds **402-407** derived from 2,2-diphenyl-2*H*-1-benzopyrans fused to indoles.

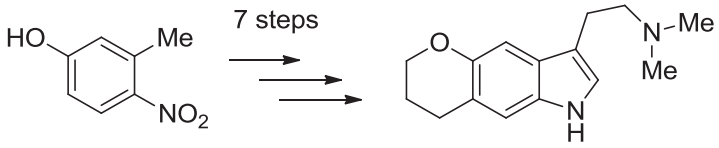


A similar kind of propargyl ether cyclisation of a chromone system has been reported by Ahluwalia *et al.*[162] wherein conversion of propargyl ether **408** to chromone **409** was achieved by heating in *N,N*-diethylaniline (Scheme 6-3).



Scheme 6-3

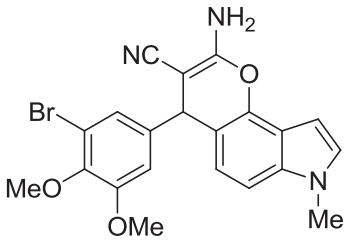
In another study Macor *et al.*[159] synthesized **411** from 3-methyl-4-nitrophenol **410** in 7 steps (Scheme **6**-4).



410 **411**

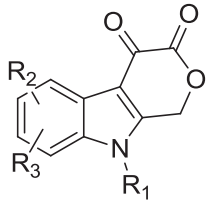
Scheme 6-4

Kemnitzer *et al.*[163] have reported the apoptosis-inducing property of **412**. Apoptosis or programmed cell death is the process for eliminating excessive cells that may threaten tissue homeostasis and organ morphogenesis. Caspase-3, one of the key enzymes involved in apoptosis, was activated by dihydropyranoindole **412**.



412

Elokdah *et al.*[71] have reported the inhibition of the plasminogen activator by dihydropyranoindoles **413**. The inhibition of plasminogen could be a potential target in fibrinolytic disorders such as deep vein thrombosis, coronary heart disease and pulmonary fibrosis.



R_1, R_2 = alkyl
R_3 = phenyl, benzyl

413

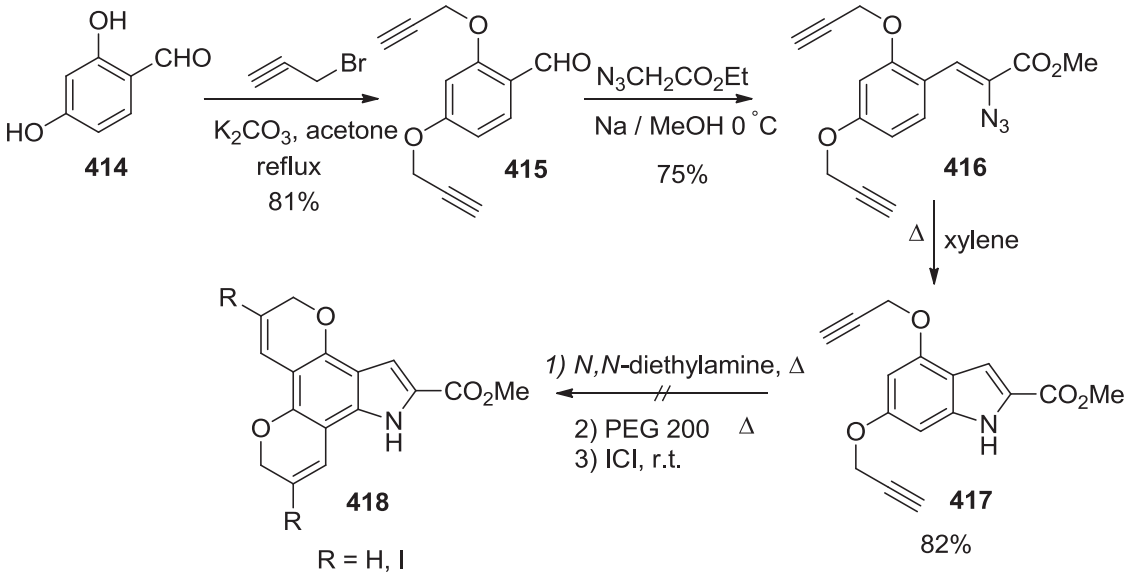
6.2 Results and Discussion:

After having successfully synthesised 4,6-dibenzyloxyindole-2-carboxylate, 4-benzyloxy-6-methoxyindole-2-carboxylate and 4-methoxy-6-benzyloxyindole-2-carboxylate, it was of interest to exploit the chemistry around the hydroxyl group of indoles for the synthesis of fused heterocyclic systems, namely dihydropyranoindoles.

In this study, a slightly different approach was followed. Instead of preparing the 4,6-dimethoxyindoles, converting them to hydroxyindoles and then installing the other heterocycles on the indole scaffold, the hydroxyl groups of the precursor hydroxybenzaldehydes were first reacted with bromoalkynes to yield the propargyloxy substituted benzaldehydes. These precursors were subsequently used for constructing an indole scaffold using the Hemetsberger indole synthesis, and then cyclised to yield the desired dihydropyranoindoles.

6.2.1 Synthesis of 5,9-dihydro-1*H*-dipyrano[2,3-*e*:2',3'-*g*]indole:

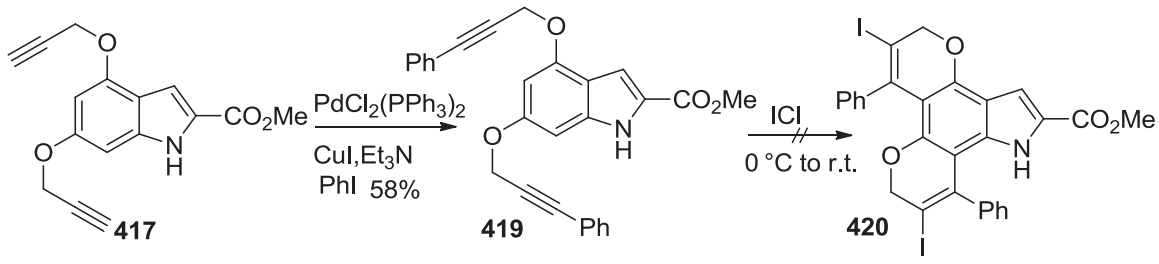
2,4-Dihydroxybenzaldehyde **414** was reacted with propargyl bromide under reflux condition with acetone to afford the propargyl ether **415** in 81% yield. Reaction of **415** with methyl azidoacetate under strongly basic conditions gave azidocinnamate **416** in 75% yield, which was used without any further purification. Heating the azidocinnamate **416** in refluxing xylene gave the indole propargyl ether **417** in 82% yield. However, attempted to cyclisation of this ether by heating in PEG-200 or *N*,*N*-diethylaniline was unsuccessful (Scheme 6-5). In both cases, only the unreacted starting material was recovered from the reaction.



Scheme 6-5

Attempted cyclisation of indole propargyl ether **417** using iodine monochloride showed many spots by TLC analysis and therefore this methodology was not pursued further.

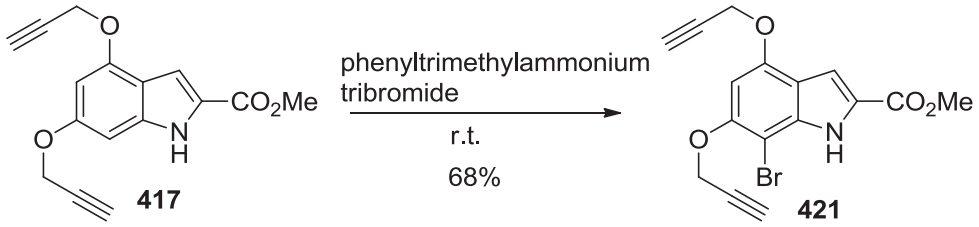
It has been reported that when terminal alkyne proton is replaced by a phenyl group, the cyclisation could proceed readily.[164] To achieve this conversion, the Sonogashira coupling method was used to convert the indole propargyl ether **417** using bromobenzene to the phenyl substituted indole propargyl ether **419** in 58% yield. However, attempted cyclisation of **419** using iodine monochloride was unsuccessful (Scheme 6-6).



Scheme 6-6

The ^{1}H NMR spectrum of compound **419** in acetone-d_6 showed a singlet at δ 3.72 ppm corresponding to the methyl ester protons, and two singlets at δ 4.89 and 5.02 ppm corresponding to the CH_2 groups. The singlets at δ 6.39 and 6.74 ppm corresponded to H5 and H7 respectively, and H3 resonated as a singlet at δ 7.04 ppm. A multiplet corresponding to the phenyl ring protons appeared at δ 7.23-7.32 ppm. The NH proton appeared as a broad singlet at δ 10.71 ppm. The DEPT 135 ^{13}C NMR spectrum supported the expected structure with the loss of two positive signals. It also showed the presence of two negative peaks at δ 57.53 and 57.79 ppm corresponding to two CH_2 groups.

It was postulated that the alkyne triple bonds in propargyloxyindole **417** would react with bromine followed by cyclisation to yield **418**. However, bromination of propargyloxyindole **417** using phenyltrimethylammonium tribromide in carbon tetrachloride instead gave 7-bromoindole derivative **421** in 68% yield, presumably because of the high reactivity of C7[165] (Scheme 6-7).

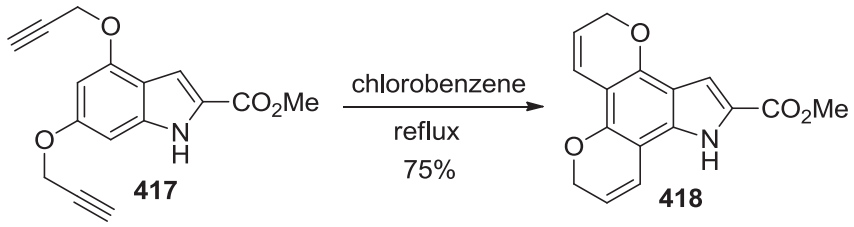


Scheme 6-7

The ^{1}H NMR spectrum of compound **421** in $CDCl_3$ showed the presence of a singlet at δ 3.86 ppm due to the methyl ester protons, and a multiplet at δ 4.75-4.79 ppm for the CH_2 protons. A singlet at δ 6.57 ppm corresponded to H5, while H3 appeared as a doublet at δ 6.37 ppm (J = 2.1 Hz). The NH appeared as a broad singlet at δ 8.80 ppm. The DEPT 135 ^{13}C NMR spectrum showed the presence of two negative peaks at δ

56.77 and 58.85 ppm corresponding to the CH_2 groups, along with the absence of a signal from the protonated carbon due to bromination.

Interestingly, the cyclisation of propargyloxy indole **417** could be achieved by heating at reflux in chlorobenzene, giving the desired tetracyclic system **418** in 75% yield (Scheme 6-8).



Scheme 6-8

The ^1H NMR spectrum of compound **418** in $CDCl_3$ showed the presence of a peak at δ 3.84 ppm corresponding to the methyl ester protons, and multiplets at δ 4.75-4.77 ppm and δ 4.81-4.83 ppm due to the two CH_2 protons. A multiplet at δ 5.53-5.65 ppm corresponded to the H6 and H10; another multiplet was at δ 6.55-6.67 ppm corresponded to H7 and H11, whereas H3 appeared as a broad singlet at δ 7.10 ppm. The NH proton appeared as a broad singlet at δ 8.75 ppm (Figure 6-1).

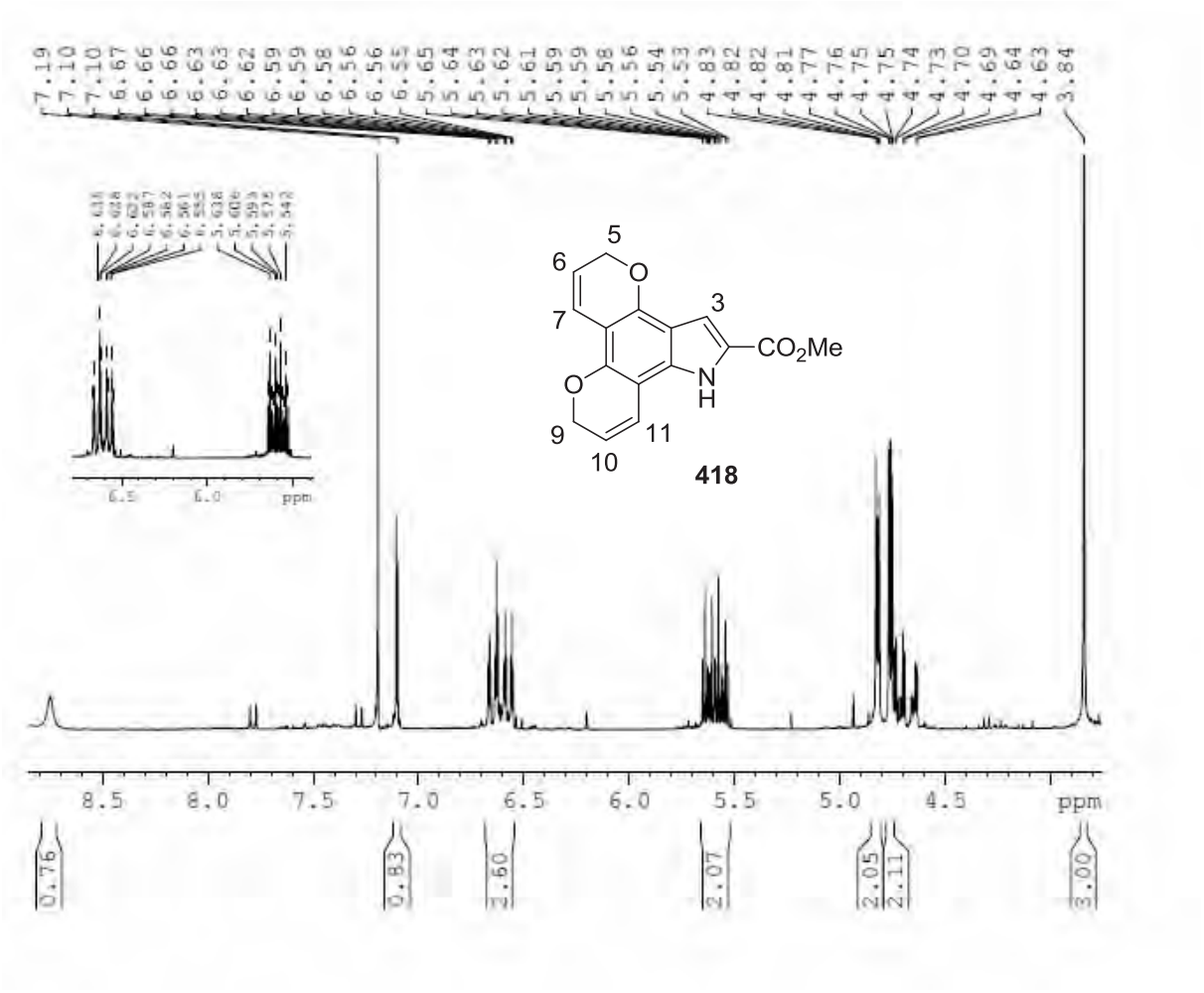


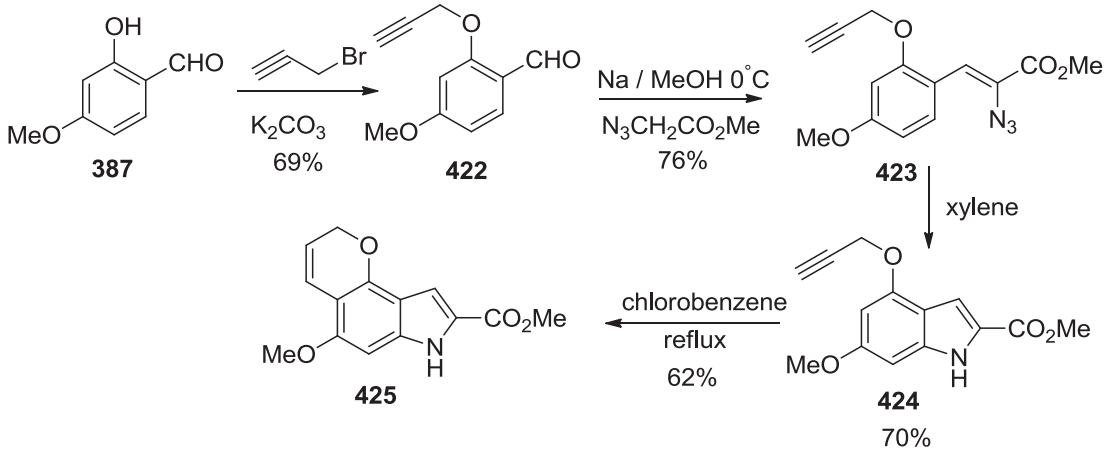
Figure 6-1 ^{1}H NMR spectrum of **418** in $CDCl_{3.}$

The DEPT 135 ^{13}C NMR spectrum supported the anticipated structure, indicating the loss of two CH carbons as a result of cyclisation. The spectrum also showed the presence of two negative peak at δ 64.68 and 64.72 ppm, respectively for the methylene carbons.

6.2.2 Synthesis of 2,7-dihydropyrano[2,3-*e*]indole:

Reaction of 2-hydroxy-4-methoxy benzaldehyde **387** with propargyl bromide in the presence of potassium carbonate gave ether **422** in 69% yield, which was then reacted with methyl azidoacetate under Hemetsberger conditions to give azidocinnamate **423** in 76% yield. Heating the azidocinnamate **423** in refluxing xylene gave the propargyloxy

indole **424** in 70% yield. Indole **424** was then thermally cyclised in chlorobenzene to furnish the desired **2,7**-dihydropyrano[2,3-*e*]indole **425** in 62% yield (Scheme 6-9).



Scheme 6-9

The ^{1}H NMR spectrum of compound **425** in $CDCl_3$ showed the presence of a singlet at δ 3.84 ppm corresponding to the methoxy protons, a singlet at δ 3.91 ppm corresponding to the methyl ester protons, and a doublet at δ 4.88 ppm corresponding to the CH_2 protons. The H3 and H4 appeared as multiplets at δ 5.59-5.65 and 6.75-6.80 ppm, respectively. The H6 appeared as a singlet at δ 6.37 ppm, and H9 appeared as a doublet at δ 7.18 ppm (J = 3.0 Hz) and the NH proton appeared as a broad singlet at δ 8.78 ppm (Figure 6-2).

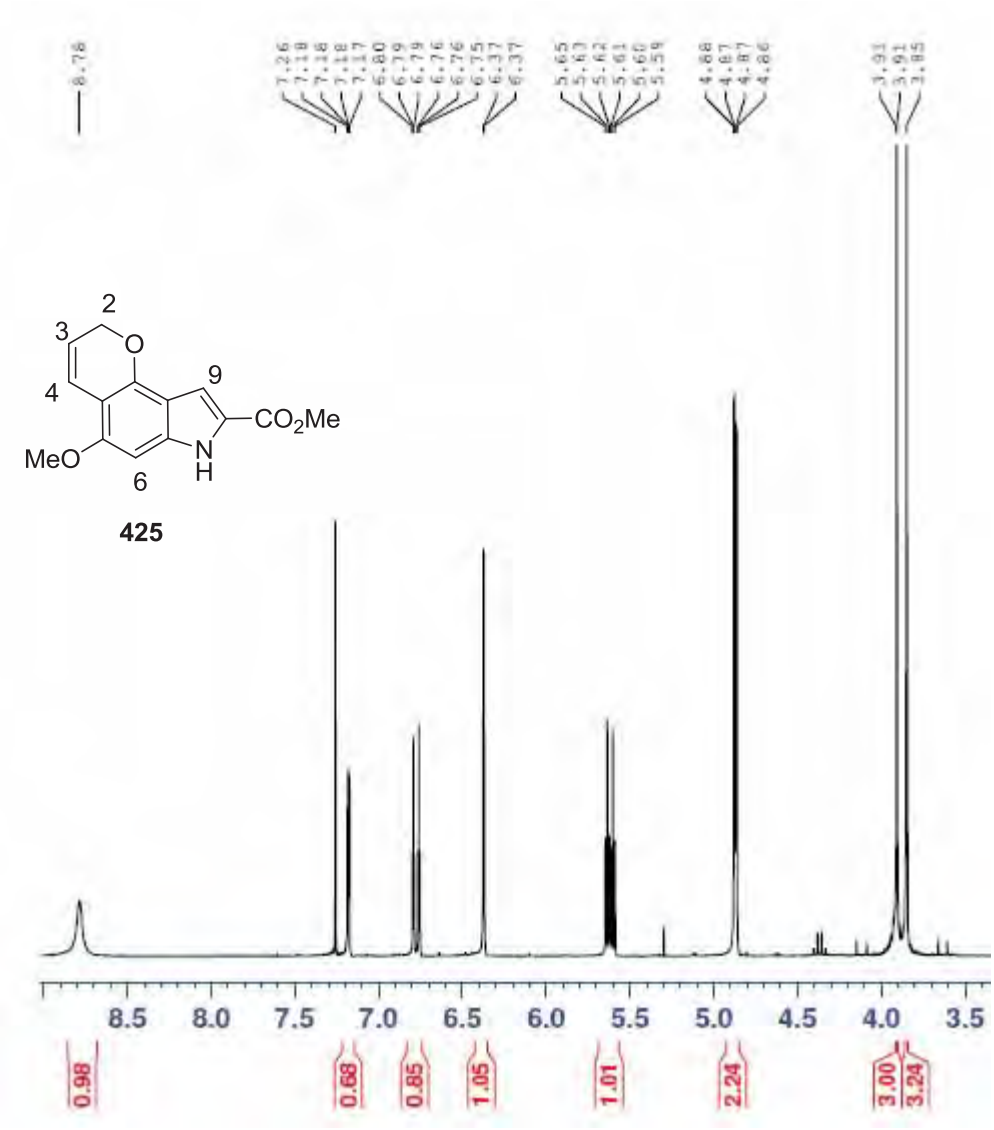


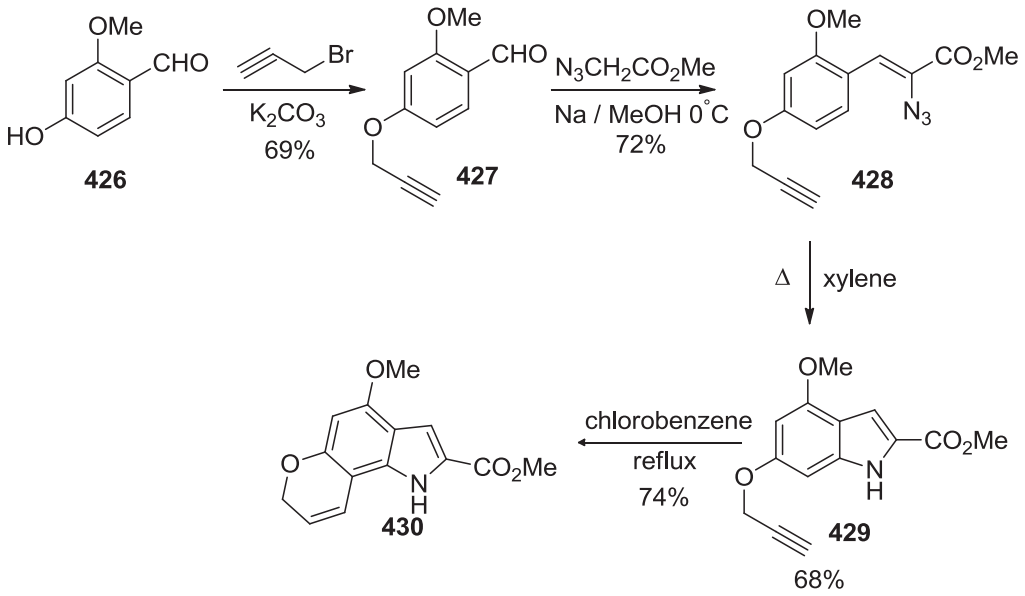
Figure 6-2 ^{1}H NMR spectrum of **425** in $CDCl_3$.

The DEPT 135 ^{13}C NMR spectrum showed the presence of a negative peak at δ 65.40 ppm corresponding to a methylene carbon, along with loss of a signal due to CH as compared to **424** as a result of cyclisation.

6.2.3 Synthesis of 1,7-dihydropyrano[2,3-*g*]indole:

When 4-hydroxy-2-methoxybenzaldehyde **426** was reacted with propargyl bromide in the presence of potassium carbonate, it gave the intermediate ether **427** in 69% yield,

which upon reaction with methyl azidoacetate in strongly basic conditions gave the target azidocinnamate **428** in 72% yield. Heating the azidocinnamate **428** in refluxing xylene gave propargyloxy indole **429** in 68% yield, which was then thermally cyclised in chlorobenzene to afford the desired dihydropyranoindole **430** in 74% yield (Scheme 6-10).



Scheme 6-10

The ^{1}H NMR spectrum of compound **430** in $CDCl_3$ showed a singlet at δ 3.84 ppm corresponding to the methoxy protons, a singlet at δ 3.91 ppm corresponding to the methyl ester protons, and a doublet at δ 4.88 ppm corresponding to the CH_2 protons. The H8 and H9 appeared as multiplets at δ 5.59-5.64 and 6.75-8.89 ppm, respectively. The H5 appeared as a singlet at δ 6.37 ppm. The H3 appeared as a doublet at δ 7.19 ppm (J = 3.0 Hz) and the NH proton resonated as a broad singlet at δ 8.88 ppm (Figure 6-3).

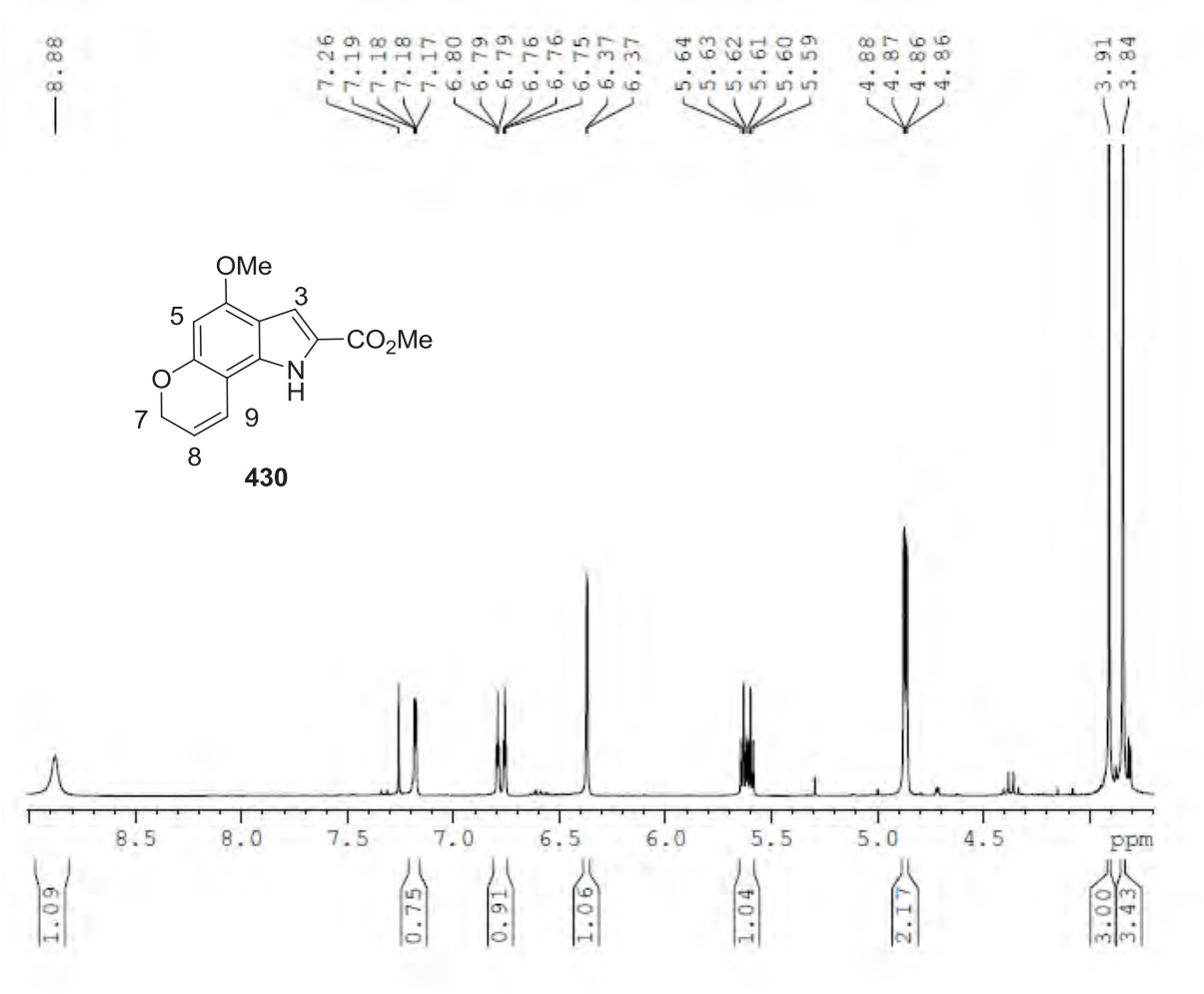


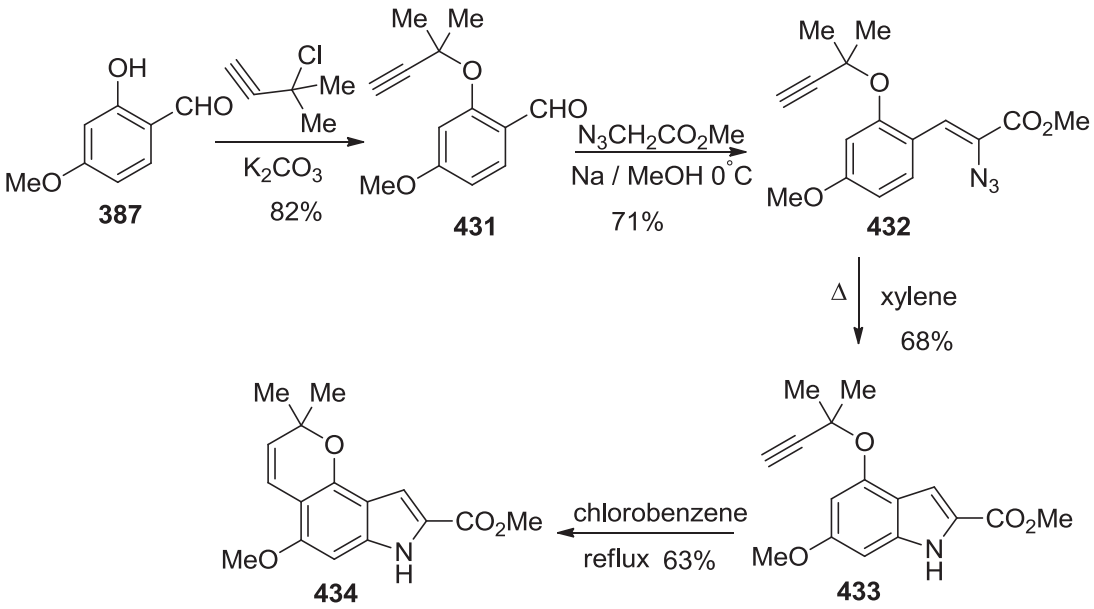
Figure 6-3 ^{1}H NMR spectrum of **430** in $CDCl_3$.

The DEPT 135 ^{13}C NMR spectrum showed negative a peak at δ 65.40 ppm corresponding to the CH_2 group along with loss of a CH signal when compared to **429** as a result of cyclisation.

6.2.4 Synthesis of 2,2-dimethyl-2,7-dihydropyrano[2,3-*e*]indole:

The cyclisation reaction was extended to include substituted alkynes. Reaction of 2-hydroxy-4-methoxybenzaldehyde **387** with 3-chloro-3-methylbut-1-yne in the presence of potassium carbonate gave **431** in 82% yield, which was reacted with methyl azidoacetate under basic conditions to give azidocinnamate **432** in 71% yield. Heating

432 in refluxing xylene gave the propargyloxy indole **433** in 68% yield. Thermal cyclisation of **433** in chlorobenzene gave the desired dihydropyranoindole **434** in 63% yield (Scheme 6-11).



Scheme 6-11

The ^{1}H NMR spectrum of compound **434** in $CDCl_3$ showed a singlet at δ 1.46 ppm corresponding to two CH_3 groups, a singlet at δ 3.85 ppm corresponding to OMe, and a singlet at δ 3.90 ppm corresponding to COOMe. The H3 and H4 appeared as a doublet at δ 5.45 ppm (J = 12.0 Hz) and 6.67 ppm (J = 9.0 Hz), respectively. H6 resonated as a doublet at δ 6.34 ppm (J = 3.0 Hz), while H3 appeared as a doublet at δ 7.24 ppm (J = 3.0 Hz). The NH proton appeared at δ 8.69 ppm as a broad singlet (Figure 6-4).

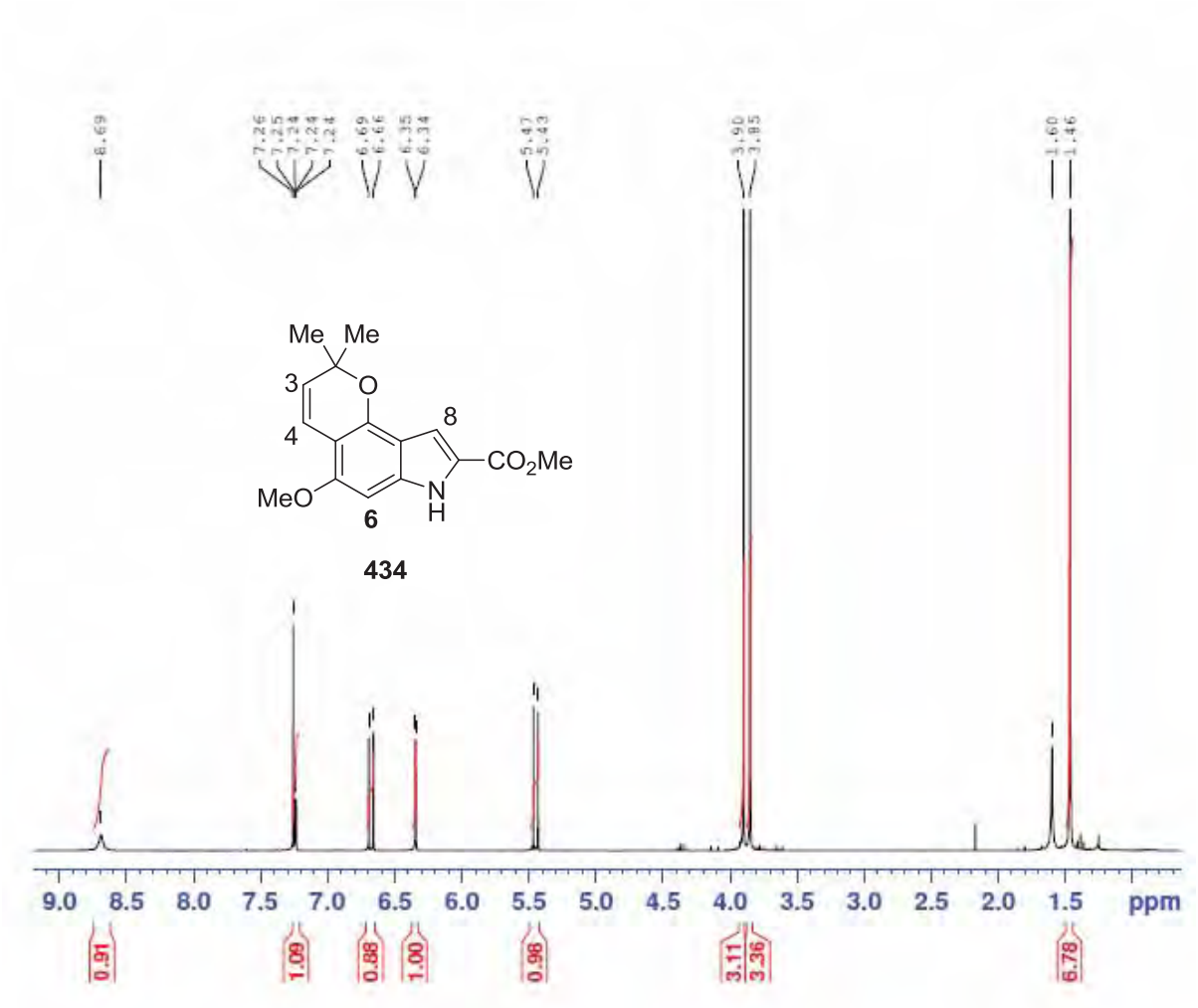
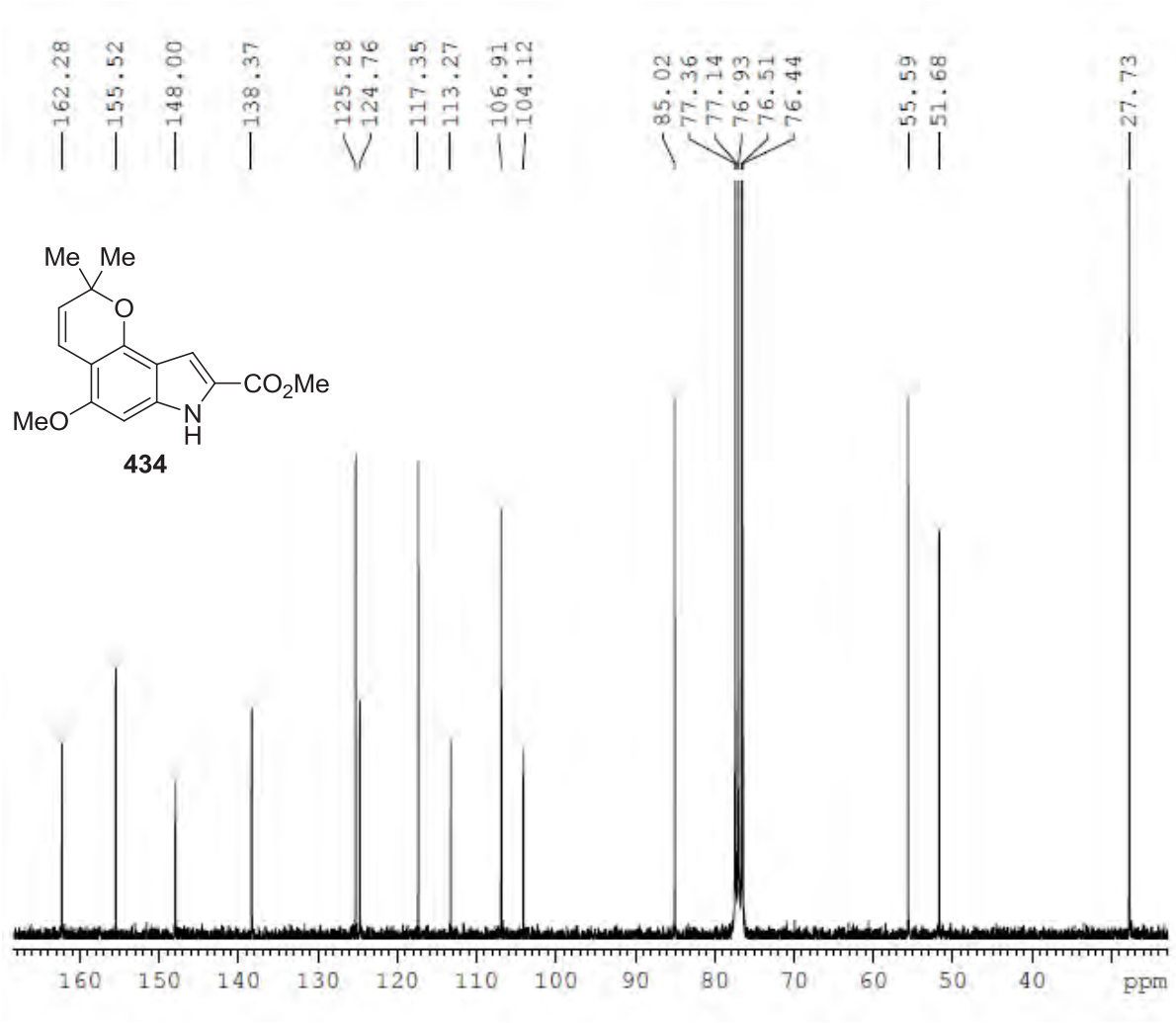


Figure 6-4 ^{1}H NMR spectrum of **434** in $CDCl_3$.

The ^{13}C NMR spectrum of compound **434** in $CDCl_3$ showed a peak at δ 27.73 ppm corresponding to the methyl carbon, a peak at δ 51.68 ppm corresponding to a methyl ester carbon. A methoxy carbon appeared at δ 55.59 ppm while carbonyl carbon appeared at δ 162.28 ppm (Figure 6-5). The DEPT 135 ^{13}C NMR spectrum revealed the presence of three positive peaks at δ 27.73, 55.59 and 51.68 ppm corresponding to CH_3, COOMe and OMe carbons, respectively along with four CH signals at δ 84.99, 106.90, 117.34 and 125.29 ppm corresponding to C6, C8, C4 and C3, respectively The loss of one of the CH signal as compared to **433** indicated that cyclisation did take place.



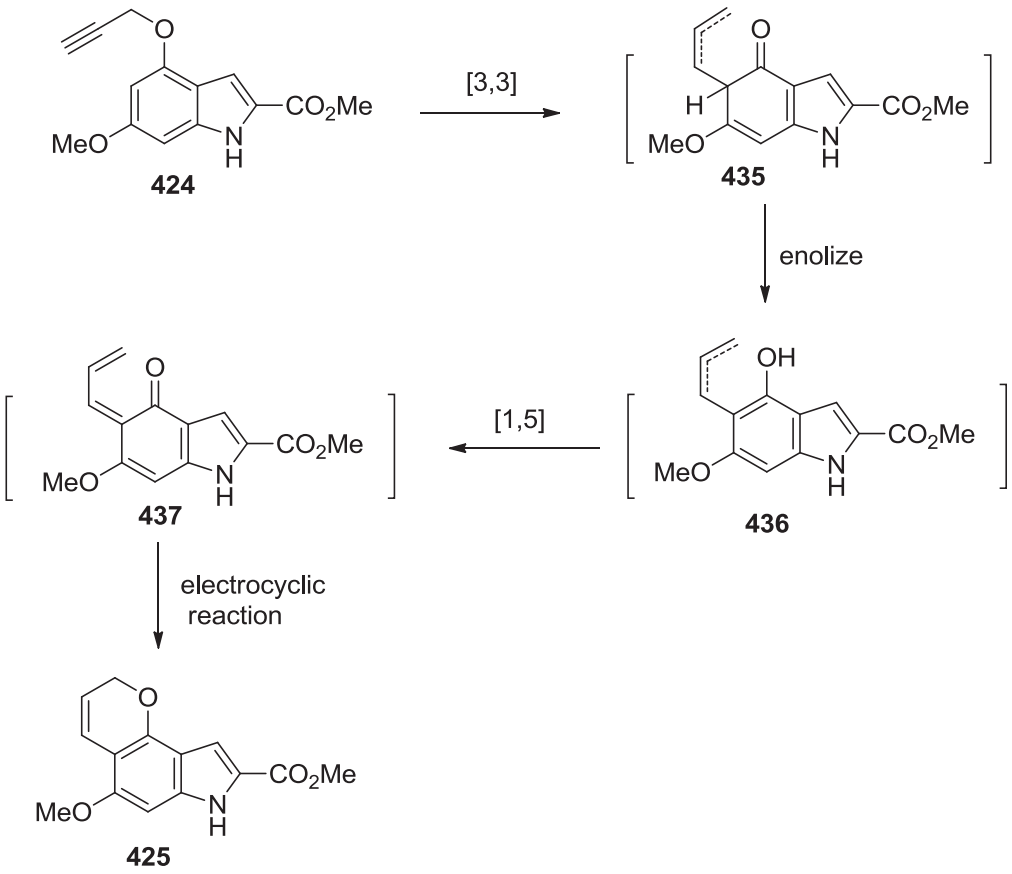
434

Figure 6-5 ^{13}C NMR spectrum compound **434** in $CDCl_3$.

6.2.5 Reaction mechanism:

A possible mechanism of the reaction is follows (Scheme 6-12).

Methyl 6-methoxy-4-(prop-2-ynyloxy)-indole-2-carboxylate **424** undergoes an initial Claisen rearrangement to generate intermediate **435**, which subsequently enolizes to produce 4-hydroxyindole derivative **436**. A [1,5] hydride shift in **436** gives the keto intermediate **437**, which undergoes an electrocyclic ring closing reaction to form methyl-5-methoxy-2,7-dihydropyrano[2,3-*e*]indole-8-carboxylate **425**.


O
MeO
N
H
CO2Me
424
[3,3]
H
435
enolize
OH
436
[1,5]
437
electrocyclic
reaction
425

Scheme 6-12

6.3 Conclusion:

The reactivity of propargyloxy-indole-2-carboxylates towards the synthesis of fused heterocycles was investigated. A short and facile synthetic route for the syntheses of 2,7-dihydropyrano[2,3-*e*]indole, 1,7-dihydropyrano[2,3-*g*]indole and 5,9-dihydro-1*H*-dipyrano[2,3-*e*:2`,3`-*g*]indole has been developed.

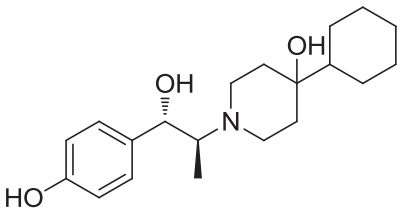
CHAPTER 7

SYNTHESIS AND REACTIVITY OF 4,6-DIBENZYLOXYINDOLES

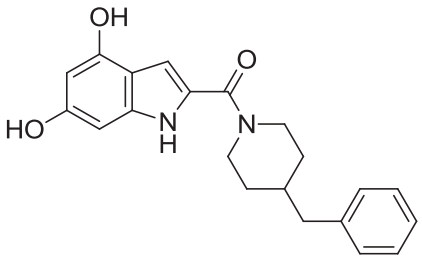
7.1 Introduction:

Molecules with free hydroxyl groups, such as the flavonoids, are generally associated with various types of biological activity. Hydroxyindoles have been considered as important heterocycles because of their biological activity ranging from anti-inflammatory to anti-cancer activity. Furthermore hydroxyindoles are especially interesting because they can possess the same oxygenation pattern as that of flavonoids.

Many other synthetic molecules possessing free hydroxyl groups are also reported to show a wide range of biological activity. For example, traxoprodil **438**, developed by Pfizer, is an excellent example, showing how the presence of hydroxyl groups in a molecule can be correlated with biological activity. This compound has anti-Parkinsonian and anti-stroke activity, and is also a selective NR2B antagonist. Notably, hydroxyindoles, both from natural and synthetic origin have established biological properties.[166-170] Borza *et al.*[13] have reported the synthesis and NMDA receptor antagonistic activity of **439**.

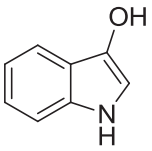


438

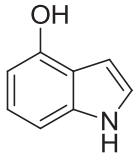


439

The inhibition of the amyloid beta (Aβ) fibril formation and cytotoxicity of hydroxyindoles **440** and **441** have been reported by Cohen *et al*.[171] Indoles **440** and **441**, simple low molecular weight, aromatic compounds were the most effective inhibitors of formation of aggregated structures of Aβ. The results of this study provide experimental support for the paradigm of amyloid inhibition and indicate a platform for the development of novel fibrillization inhibitors.

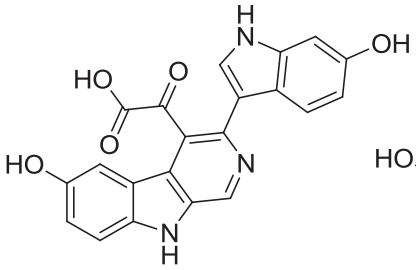


440

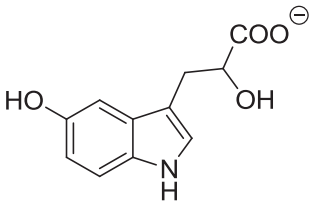


441

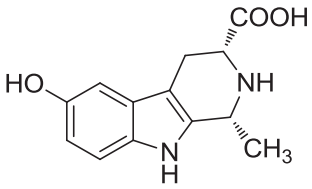
Youssef *et al*.[172] have reported the isolation of hyrtioerectines A-C **442-444**. These alkaloids were isolated from the Red Sea marine sponge, *Hyrtios erectus* and were found to possess cytotoxic activity.



442

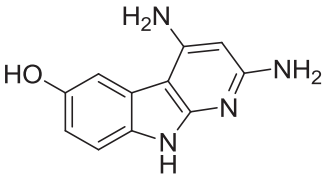


443

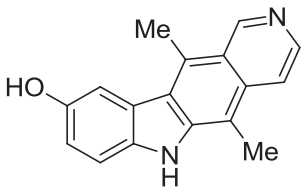


444

Dotzauer *et al*.[173] have reported the synthesis and *in vitro* cytotoxic activity of **445**, a tricyclic analogue of 9-hydroxyellipticine **446**.

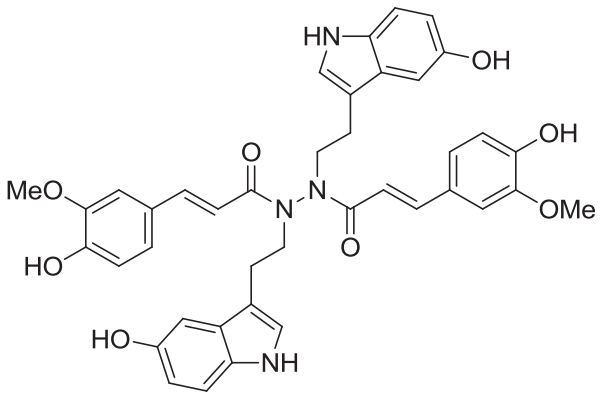


445

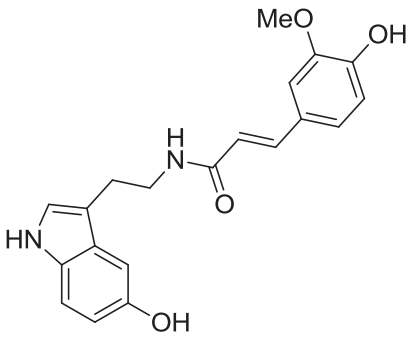


446

Shoeb *et al*.[174] have reported the isolation of the dimeric indole alkaloid, montamine **447** and monomeric alkaloid moschamine **448** from methanol extracts of the seeds of *Centaurea montana*. Compound 447 showed significant anti-cancer activity in colon cancer cell lines (IC_{50} = 43.9 µM), while that of the monomer **448**, was of a moderate level (IC_{50} = 81.0 µM).

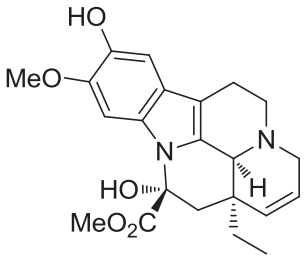


447



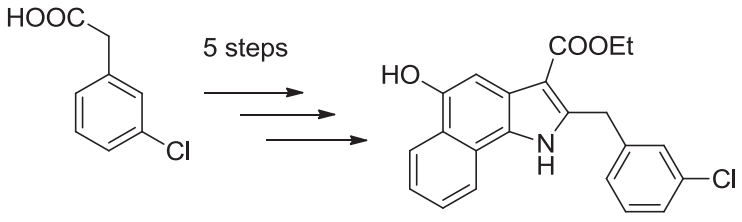
448

Zhang *et al.*[175] have reported the isolation of the indole alkaloid **449** from *Ervatamia* genus.



449

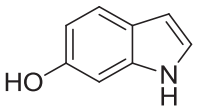
Karg *et al.*[176] have reported the synthesis and leukotriene-inhibitory activity of 2-substituted 5-hydroxyindole **451** from 2-(3-chlorophenyl)acetic acid **450** (Scheme 7-1). Leukotrienes play an established role in the pathophysiology of inflammatory and allergic disorders (*i.e.* asthma and allergic rhinitis) but may also promote cancer and atherosclerosis. Leukotrienes are formed from arachidonic acid, catalysed by the 5-lipoxygenase (5-LOX) enzyme. Hydroxyindole **451** inhibits 5-LOX activity in human neutrophils and recombinant human 5-LOX with IC_{50} values of 0.23 and 0.086 μM, respectively. Notably, it efficiently blocks 5-LOX-product formation in human whole-blood assays (IC_{50} 0.83-1.6 μM) and significantly prevented leukotriene B4 production in pleural exudates of carrageenan-treated rats, associated with reduced severity of pleurisy.



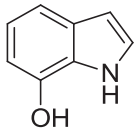
450 **451**

Scheme 7-1

Yamazaki *et al.*[177] have reported the human melanoma-tyrosinase inhibitory activity of 6-hydroxyindole **452** and 7-hydroxyindole **453**.



452

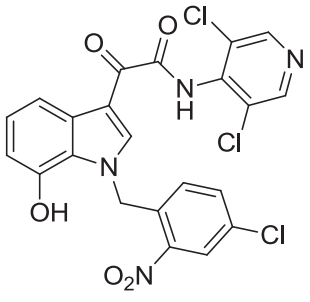


453

These compounds were found to be potent inhibitors of human melanoma tyrosinase with IC_{50} values of 20 and 79 μM respectively.

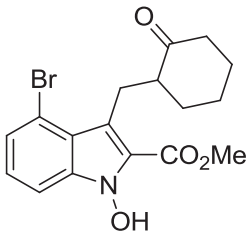
A similar pattern of inhibition was found with these compounds against mouse B16 melanoma tyrosinase, but with some difference from that for HMV-II tyrosinase. Kinetic analysis with HMV-II tyrosinase showed that the inhibition by hydroxyindoles was competitive with respect to the substrate L-DOPA. Melanin formation in HMV-II cells was suppressed by 14% at 10 μM without cytotoxicity. It indicated that 6-hydroxyindole is a potential and useful lead as an anti-melanogenic agent and the position of the phenolic hydroxyl group in a specific heterocyclic ring such as the indole can possibly be optimized to yield more active inhibitors for tyrosinase.

Norbert *et al.*[178] have reported the synthesis and phosphodiesterase inhibitory activity of the 7-hydroxyindole derivative **454**, which indicated its potential in the management of the disorders induced by allergy such as asthma.



454

While studying the total synthesis of natural products, Nicolau *et al*.[179] have investigated the importance of the *N*-hydroxyindole moiety **455** which is one of the most striking structural motifs within the molecular framework of nocathiacin I. Nocathiacin I is a complex thiopeptide antibiotic isolated from *Nocardia sp*. and the fungus *Amicolaptosis sp*, which exhibits remarkably potent *in vitro* and *in vivo* activity against Gram-positive bacteria.

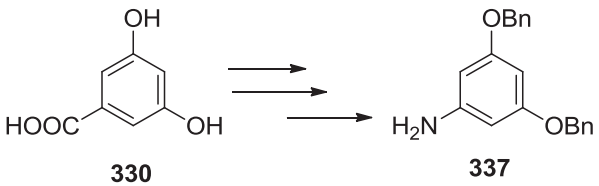


455

7.2 Results and Discussion:

7.2.1 Synthesis of 3,5-dibenzyloxyaniline:

The first approach for the synthesis of 3,5-dibenzyloxyaniline **337**, a key intermediate is shown below (Scheme 7-2) and was described in detail in Chapter 4.

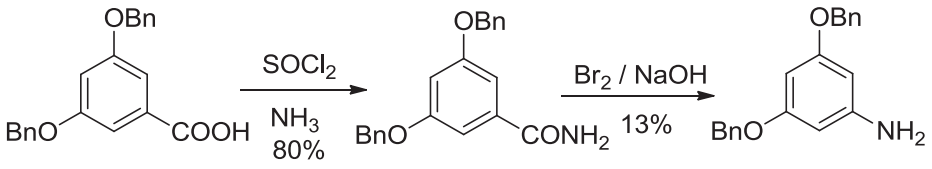


Scheme 7-2

One of the problems associated with this methodology was the poor yield of the terminal step, which involves a modified Curtius reaction. A possible reason for the low

yield could be the involvement of trifluoroacetic acid in the penultimate step in which the benzyloxy group could be cleaved.

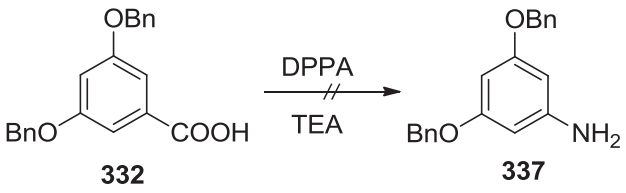
Other methods attempted for the synthesis of 3,5-dibenzyloxyaniline include the Schmidt[180] and Hoffmann reactions.[181-182] The Schmidt reaction was unsuccessful, and only starting material was recovered. In the case of the Hoffmann reaction, TLC analysis showed the conversion of amide **456** to amine **337**. However, the yield was very low, so, this method was not pursued further (Scheme 7-3).



332 **456** **337**

Scheme 7-3

Diphenylphosphoryl azide (DPPA) is known to convert aromatic carboxylic acids into aromatic amines. However, when this reaction was performed using 3,5-dibenzyloxybenzoic acid **332**, with DPPA in *tert*-BuOH and triethylamine, only starting material was recovered from the reaction mixture[183-185] (Scheme 7-4).



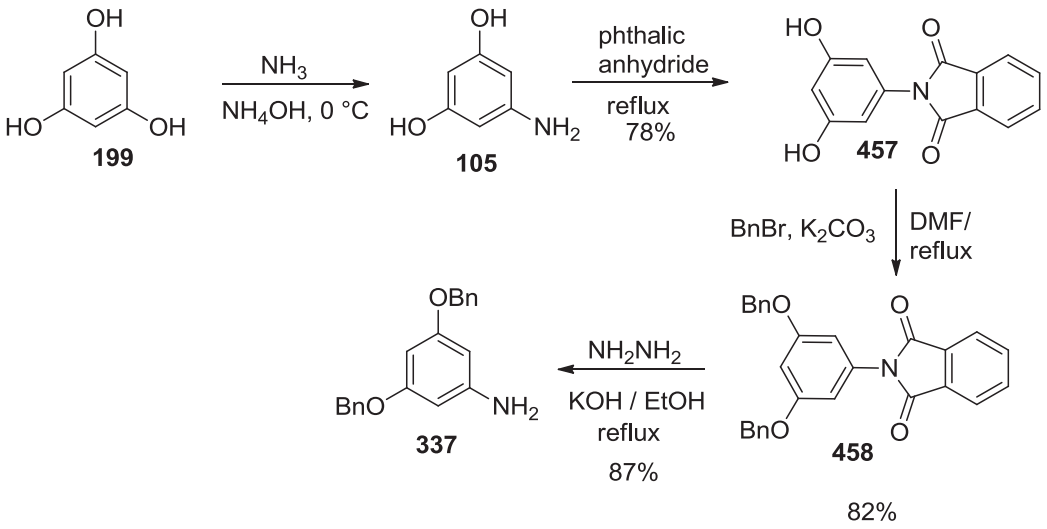
332 **337**

DPPA = Diphenylphosphoryl azide

Scheme 7-4

Therefore, an alternative method for the synthesis of 3,5-dibenzyloxyaniline **337** was attempted starting with phloroglucinol **193**.

Phloroglucinol **193** was reacted with ammonium hydroxide and ammonia gas for 72 h to give 5-aminoresorcinol **105**, and this was refluxed with phthalic anhydride in acetic acid to give *N*-phthalimido-protected resorcinol **457** in 78% yield. Subsequent benzylation using benzyl bromide in the presence of potassium carbonate gave the dibenzyloxy derivative **458** in 82% yield. The removal of the phthalimido group was performed using hydrazine hydrate in refluxing ethanol, to give 3,5-dibenzyloxyaniline **337** in 94% yield (Scheme 7-5).[186]



Scheme 7-5

The ^{1}H NMR spectrum of compound **337** in DMSO-d_6 revealed the presence of a singlet at δ 4.94 ppm corresponding to the CH_2 protons, and aromatic peaks from the substituted aniline appeared as a multiplet at δ 5.82-5.83 ppm. The phenyl ring protons from the benzyloxy group appeared as a multiplet at δ 7.28-7.32 ppm. The NH_2 protons appeared as a singlet at δ 5.04 ppm (Figure 7-1).

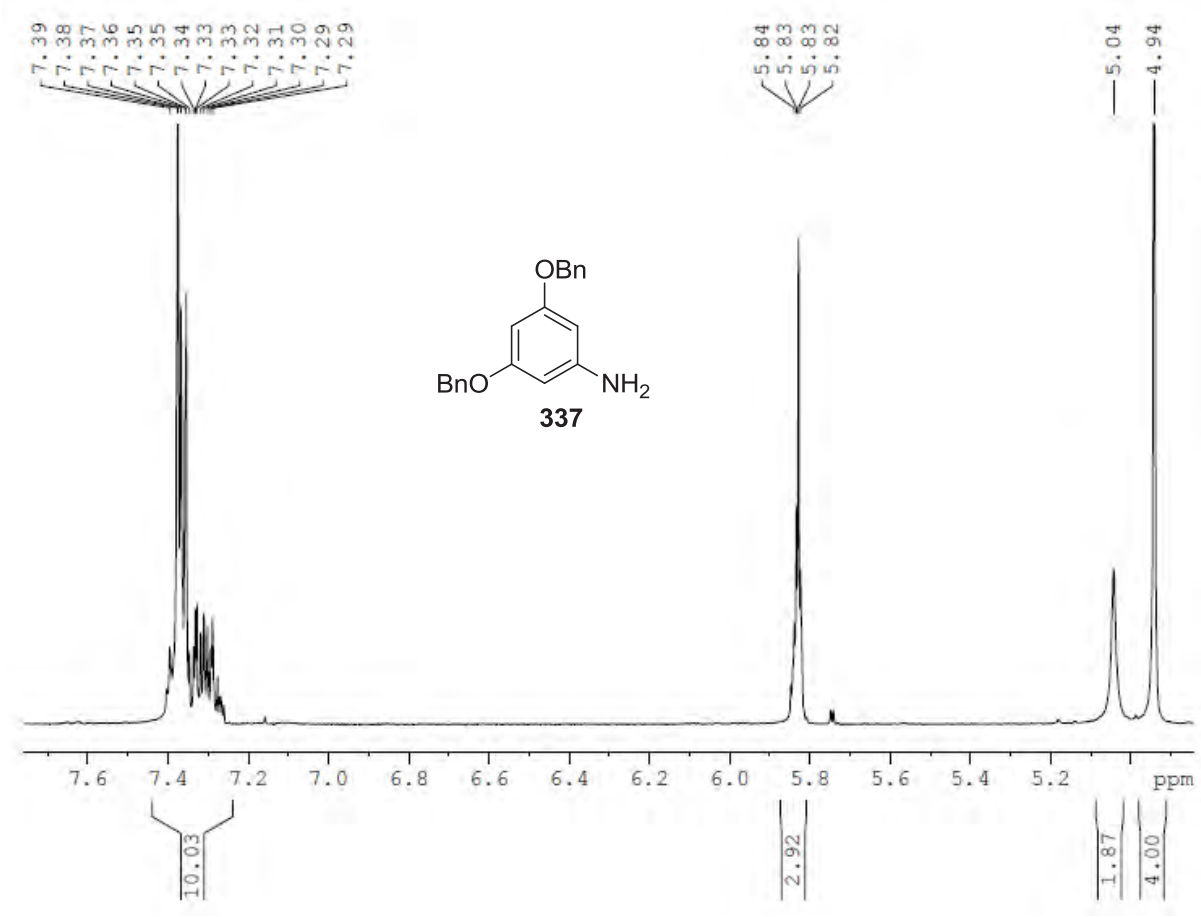
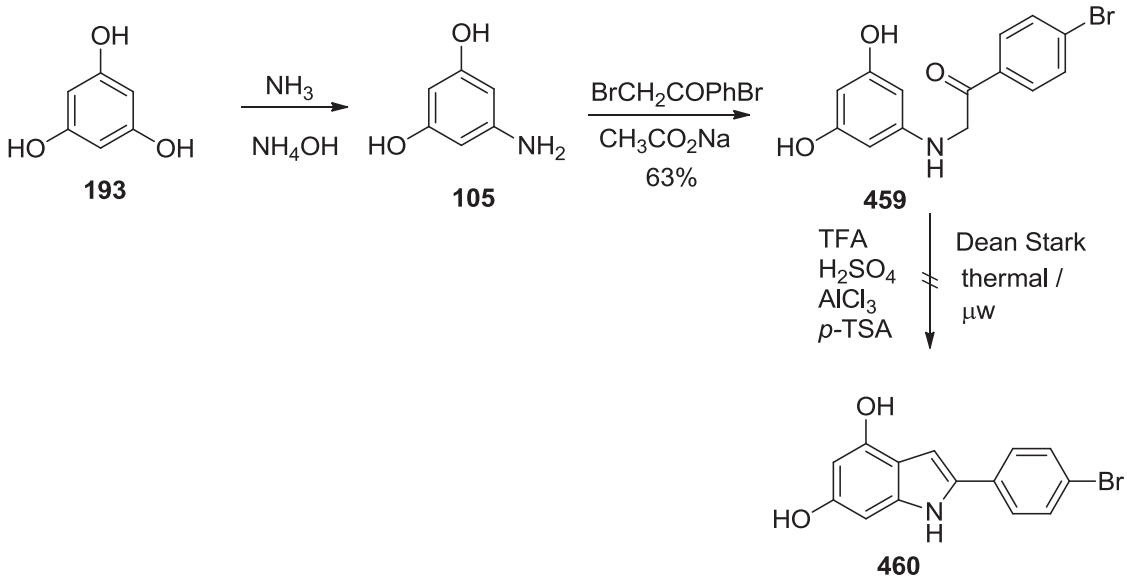


Figure 7-1 ^{1}H NMR spectrum of compound **337** in DMSO-$d_{6.}$

7.2.2 Attempted synthesis of 4,6-dihydroxyindoles:

The synthesis of 4,6-dihydroxyindole **460** was attempted using 5-aminoresorcinol **105**, which was reacted with an α-haloketone in the presence of sodium acetate to give anilinoketone **459** in 63% yield. This finding was encouraging as this synthesis starts with 5-aminoresorcinol, which can be easily obtained using the economical starting material, phloroglucinol. Moreover, 5-aminoresorcinol has two free hydroxyl groups so there was no need of protection-deprotection chemistry. A variety of methods were attempted to cyclise the anilinoketone *e.g.* trifluoroacetic acid, sulfuric acid, aluminium chloride, *p*-toluenesulfonic acid, silicone oil, heating in Dean-Stark apparatus and

microwave heating. Unfortunately, all attempts failed to give the cyclised product (Scheme 7-6). Furthermore, it was noticed that **459** was so unstable that it was readily converted to black polymeric material upon standing at room temperature. This decomposition is probably due to the highly activating free hydroxyl groups present in the anilinoketone.



Scheme 7-6

The ^{1}H NMR spectrum of compound **459** in DMSO-d_6 revealed the presence of a doublet at δ 4.49 ppm (J = 5.6 Hz) corresponding to the CH_2 protons, and peaks from the phenyl ring of the substituted aniline appeared as a multiplet at δ 5.49-5.60 ppm. The OH protons appeared as a sharp singlet at δ 8.73 ppm, and the 4`-bromophenyl protons as two doublets at δ 7.75 and 7.96 ppm respectively (J = 8.6 Hz) (Figure 7-2). The presence of the CH_2 peak was confirmed by a negative peak at δ 50.46 ppm in the DEPT 135 ^{13}C NMR spectrum.

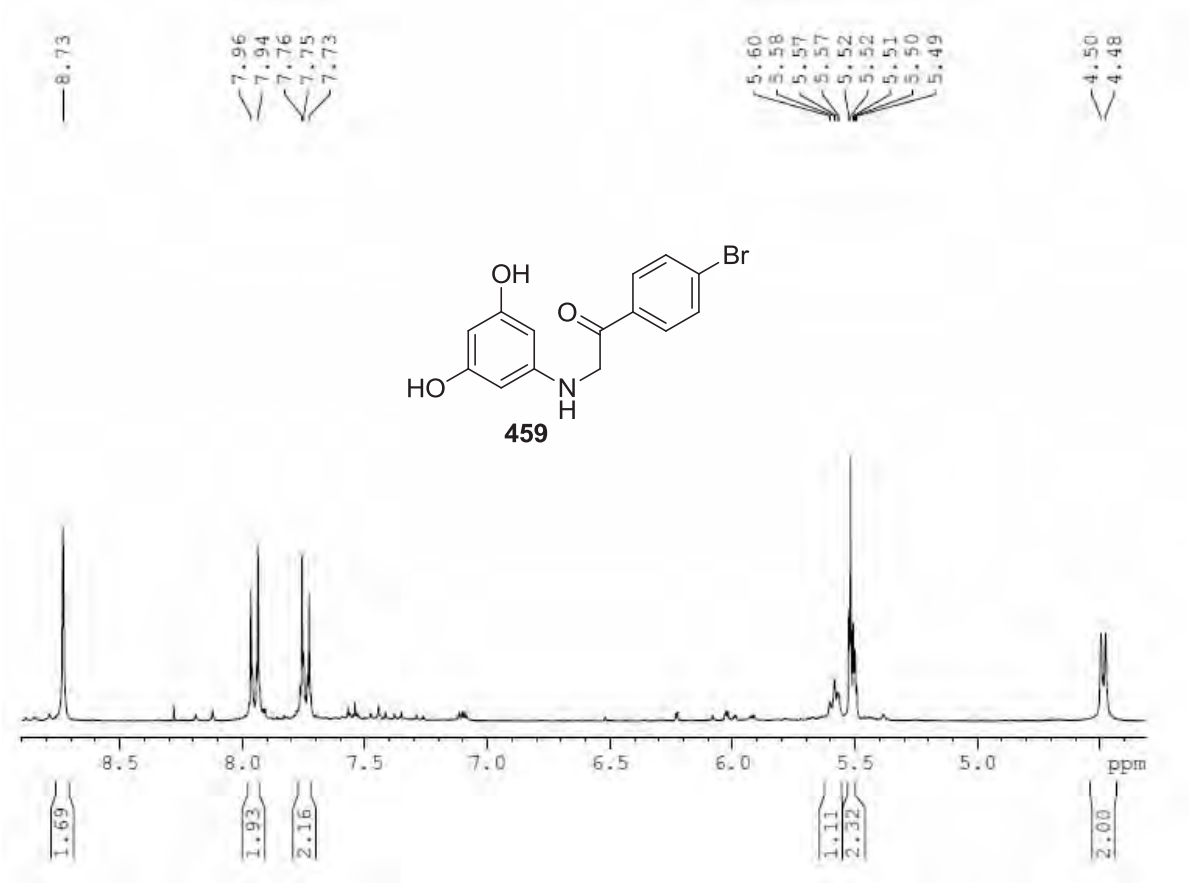
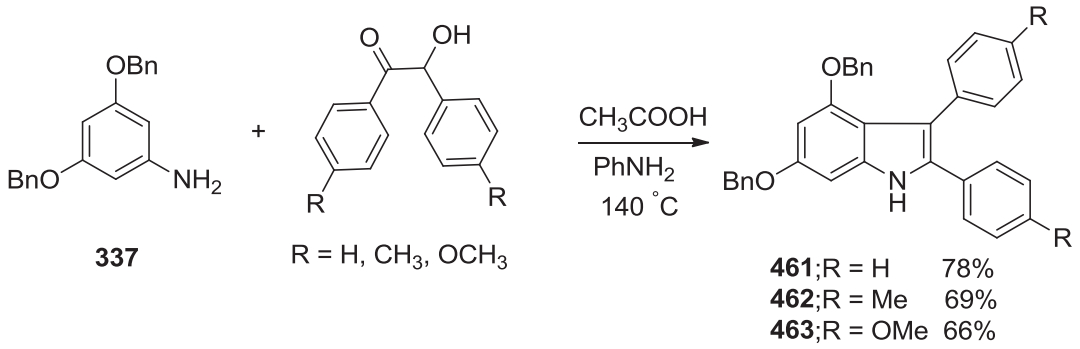


Figure 7-2 ^{1}H NMR spectrum of compound **459** in DMSO-d_6

7.2.3 Synthesis of 2,3-disubstituted indoles:

For the synthesis of 2,3-disubstituted indoles a one-pot method was investigated, in which a mixture of 3,5-dibenzyloxyaniline **337** and benzoin was heated in silicone oil at 140 °C for 1h. Silicone oil was used in the reaction mixture to avoid thermal decomposition by excess heating. After cooling, acetic acid and aniline were added the reaction mixture followed by heating at 140 °C for 4 h to give 4,6-dibenzyloxyindoles **461-463** in 66-78% yield (Scheme 7-7).



Scheme 7-7

The ^{1}H NMR spectrum of compound **463** in $CDCl_3$ revealed the presence of four singlets at δ 3.36, 3.40, 4.55 and 4.69 ppm corresponding to two OMe groups and two CH_2 groups, H5 of the indole appeared at δ 5.99 ppm, and H7 of the indole appeared at δ 6.17 ppm. The NH proton appeared as a broad singlet at δ 7.64 ppm (Figure 7-3). The presence of two CH_2 groups in the molecule was confirmed by negative peaks at δ 69.16 and 70.08 ppm in the DEPT 135 ^{13}C NMR spectrum.

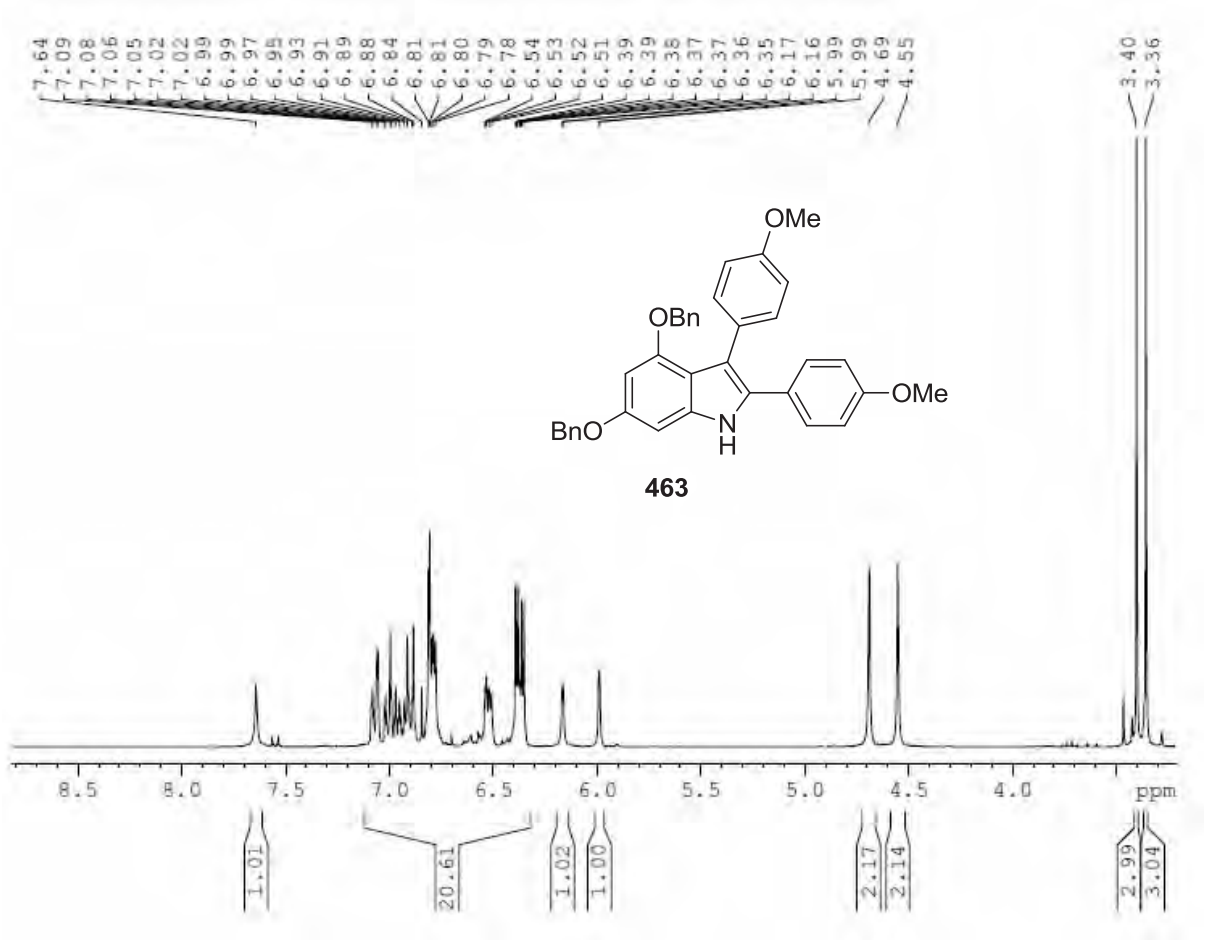
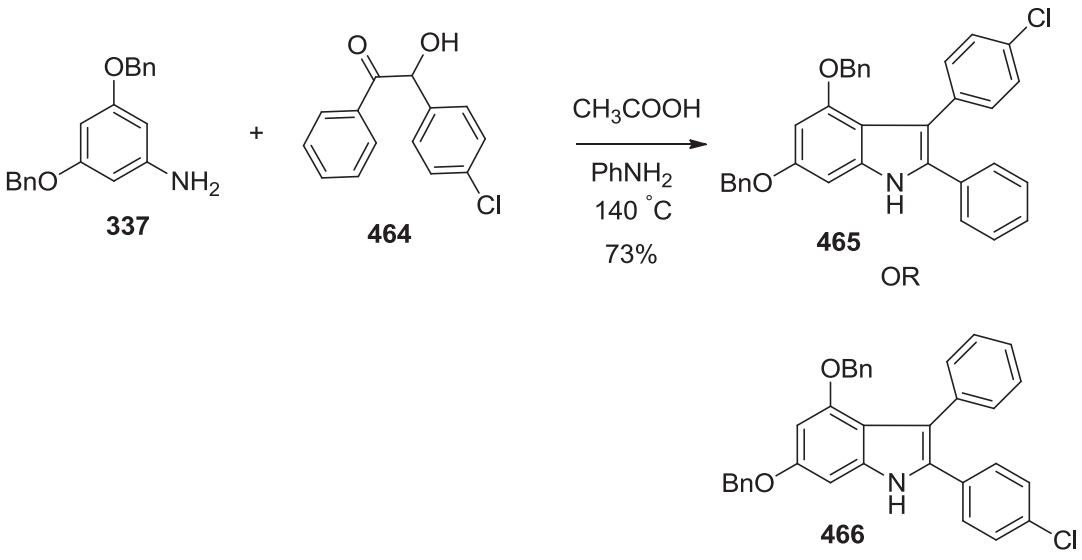


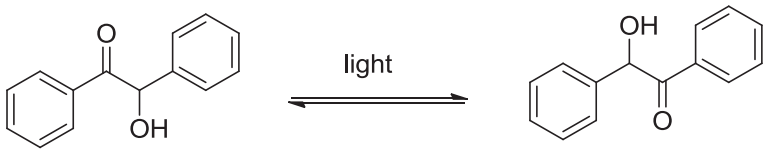
Figure 7-3 ^{1}H NMR spectrum of compound **463** in $CDCl_3$.

Synthesis of 4,6-dibenzyloxy-2,3-diarylindole using **337** and benzoin **464**, led to a surprising result (Scheme 7-8).



Scheme 7-8

It was presumed that when 3,5-dibenzyloxyaniline **337** was reacted with 4-chlorobenzoin **464** under the usual conditions, it would give a product containing the phenyl ring bearing the chloro substituent either on C2 or C3 of the indole (Scheme 7-8). However, TLC analysis showed the presence of only one compound. The ^{1}H NMR spectrum of the product showed that it was a pure compound and had all the signals for the desired indole. However, it was not clear whether the product was **465** or **466**. Benzoins are known to undergo keto-enol tautomerisation. The predominating form should give the corresponding product. Also it is reported that benzoin tautomerises in the presence of light (Scheme 7-9).[187]



467 **468**

Scheme 7-9

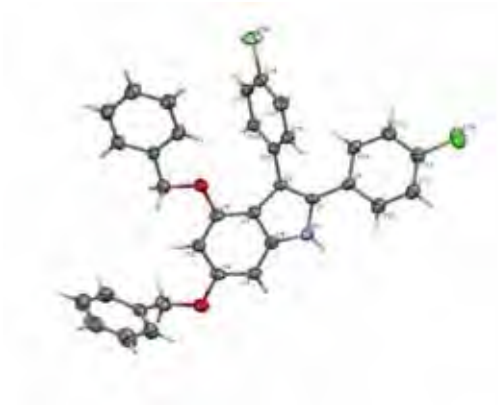


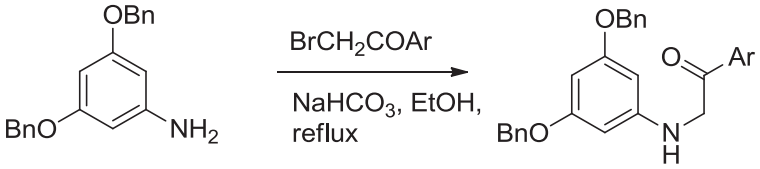
Figure 7-4 ORTEP view of the product obtained from the reaction of **337** and **464**, showing the superimposed structure of two isomers.

It was necessary to determine the true product. X-ray analysis of the product of **337** and **464** was undertaken to ascertain the structure of the possible isomer produced in the

reaction. Interestingly, the crystal structure revealed presence of both the isomers in exactly equal proportion (Figure 7-4). This was evident from the peak heights for the chlorides, which were half in strength (~ 8 eA^{-3}) than the expected height for the fully occupied Cl atom (~ 17 eA^{-3}). Thus this compound contains two isomers (**465** and **466**) that occupy the same positions in the crystal lattice, the only difference is in the chloro substitution; one has it on C18 and the second one on C12.

7.2.4 Attempted synthesis of 2-substituted indoles:

When 3,5-dibenzyloxyaniline **337** was heated at reflux in ethanol with an α-haloketone in the presence of $NaHCO_3$, it gave anilinoketones **469-473** in 68-85% yield (Scheme 7-10).



337 **469-473**

Scheme 7-10

Table 7-1 depicts the nature of the Ar substituents and % yields of anilinoketones **469-473**.

Table 7-1: Yield and the nature of the Ar substituents.

Product	Ar	Yields (%)
469	Me	68
470	C_6H_5	79
471	4-ClC_6H_4	71
472	4-$MeOC_6H_4$	84
473	4-BrC_6H_4	85

The ^{1}H NMR spectrum of compound **473** in $CDCl_3$ revealed the presence of a singlet at δ 4.53 ppm due to the *N*-CH_2 group, and a singlet at δ 5.02 ppm due to the two CH_2 groups of the benzyloxy protons. The aromatic peaks from the benzyl group appeared as a multiplet at δ 7.32-7.44 ppm, the aniline protons proton appeared as a doublet δ 5.98 (*J* = 3.0 Hz), and a triplet at δ 6.10 ppm (*J* = 3.0 Hz), and the 4`-bromophenyl protons appeared as two doublets at δ 7.67 and 7.86 ppm respectively (*J* = 9.0 Hz) (Figure 7-6). The presence of CH_2 groups was confirmed by negative peaks at δ 50.24 and 69.92 ppm in the DEPT 135 ^{13}C NMR spectrum.

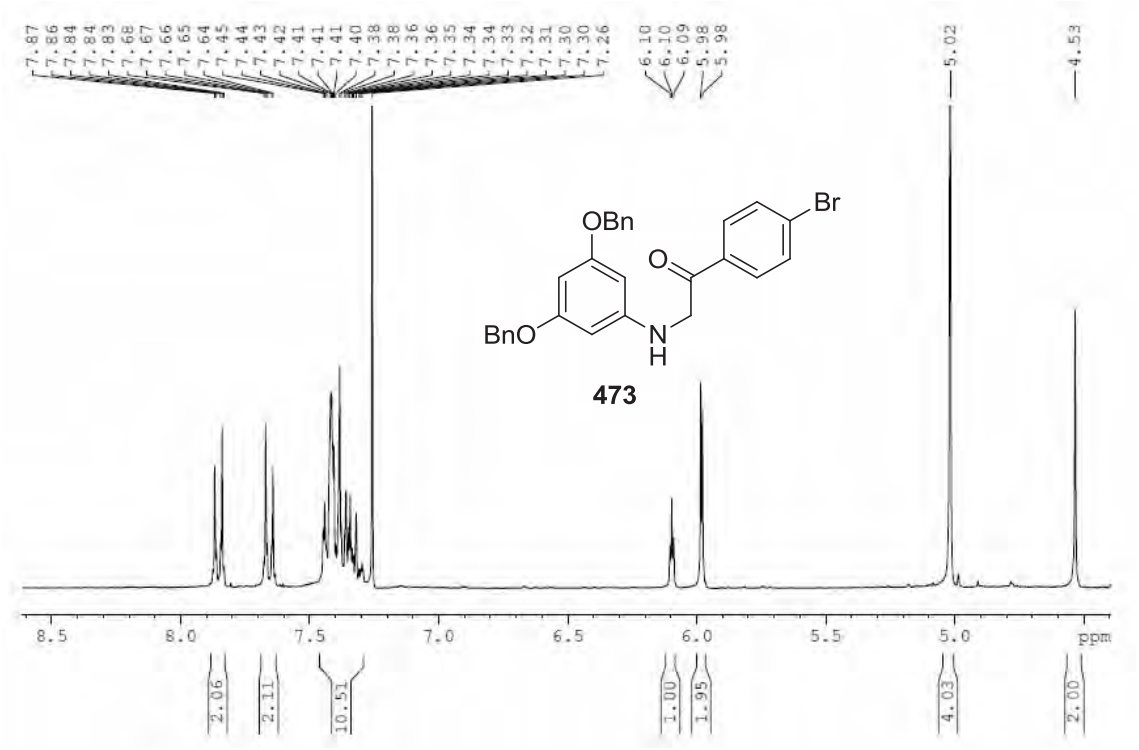
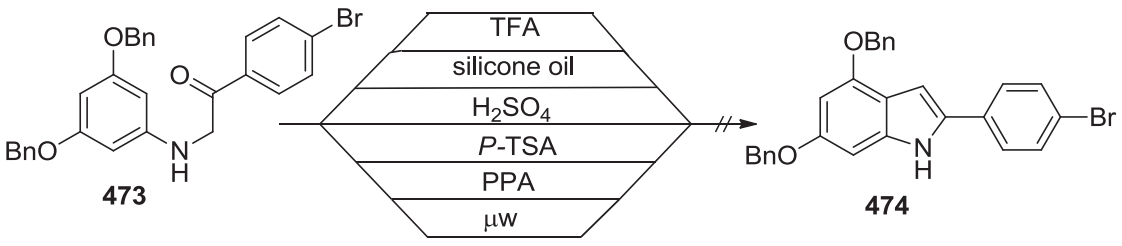


Figure 7-6 ^{1}H NMR spectrum of compound **473** in $CDCl_3$

When cyclisation of anilinoketone **473** was attempted by heating in silicone oil with 3,5-dibenzyloxyaniline hydrochloride, trifluoroacetic acid, sulfuric acid, *p*-toluenesulfonic acid or polyphosphoric acid, all attempts were unsuccessful. Even the reaction under microwave irradiation was not successful. Only starting material was recovered (Scheme 7-11).

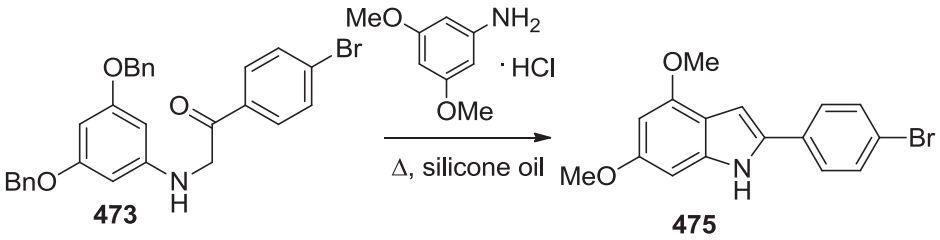


Scheme 7-11

However in some cases the reaction gave a complex mixture and TLC analysis showed the presence of many spots. The ^{1}H NMR spectrum of the crude mixture did not show

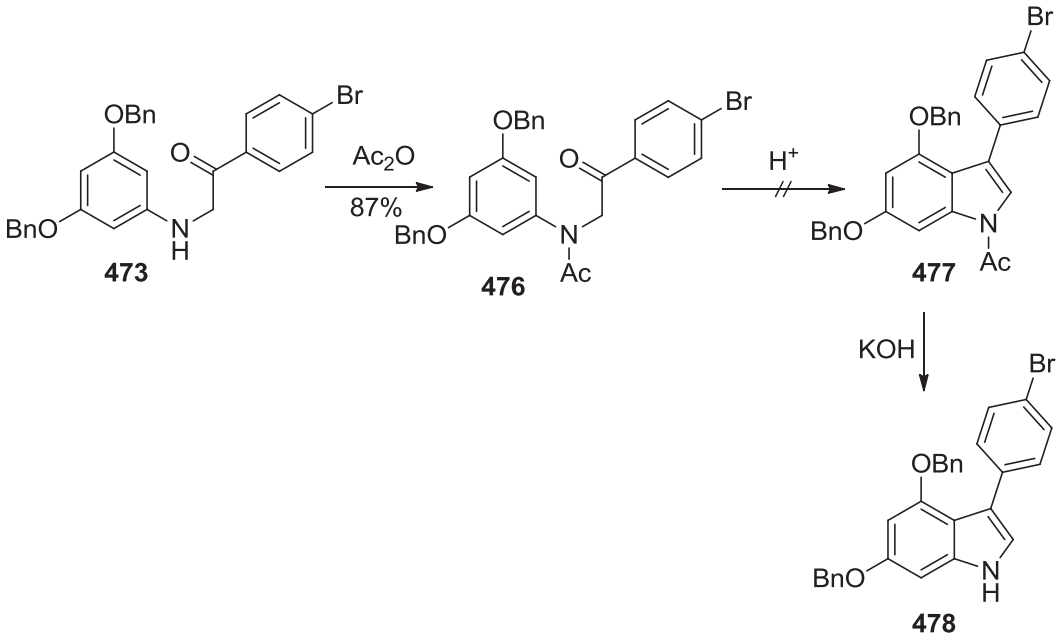
any signals corresponding to an indole. A possible reason for the failure of the anilinoketone to cyclise could be the bulkiness of the two benzyloxy groups which might prevent the reaction from taking place. Another reason could be that overheating and strong acid may cleave benzyloxy groups thus making the system more likely to decompose quickly.

Attempted cyclisation of the anilinoketone **473** using silicone oil and 3,5-dimethoxyaniline hydrochloride, gave 4,6-dimethoxyindole **475** instead of 4,6-dibenzyloxyindole **474**. The disappearance of benzyl proton peaks and the appearance of OMe proton peaks in the ^{1}H NMR spectrum of the product indicated that 3,5-dimethoxyaniline displaced 3,5-dibenzyloxyaniline from 3,5-dibenzyloxyanilinoketone **473** and readily cyclised to give **475** (Scheme 7-12).



Scheme 7-12

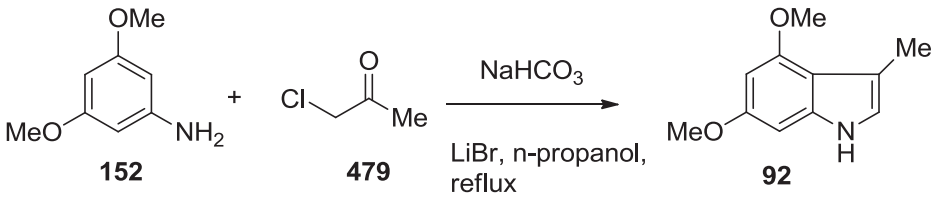
In the Bischler indole synthesis cyclisation of the anilinoketone by acid involves migration of the substituent leading to a 2-substituted indole. When this anilinoketone is protected, it stops migration of the substituent and gives the 3-substituted indole. In order to obtain a 3-substituted indole, anilinoketone **473** was acetylated with acetic anhydride to give *N*-Acetyl-anilinoketone **476** in 87% yield. Attempted cyclisation of *N*-Acetyl-anilinoketone **476**, using a variety of reaction conditions was unsuccessful (Scheme 7-13).



Scheme 7-13

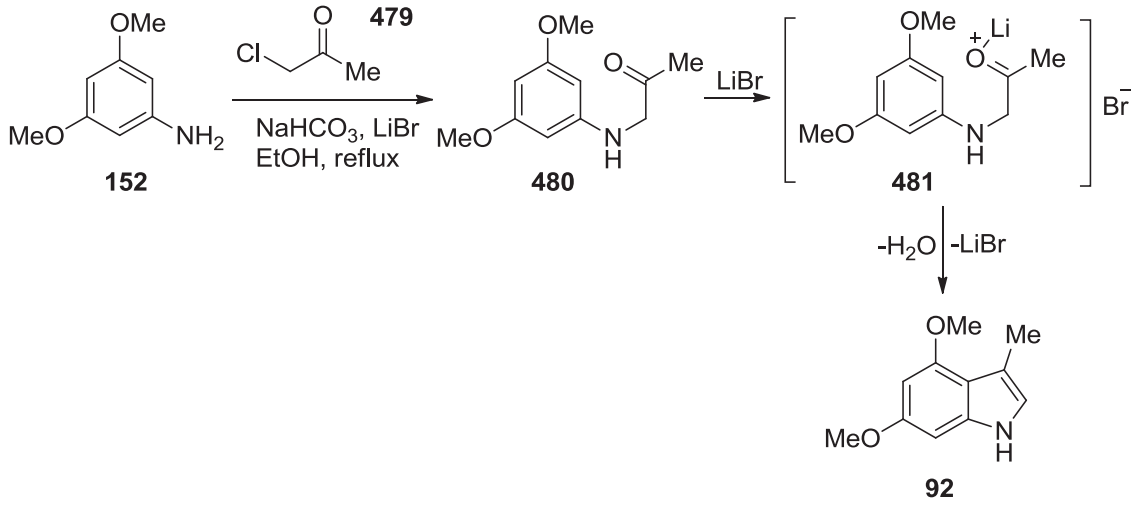
7.2.5 Synthesis of 2-substituted indoles:

Black *et al.*[84] have demonstrated that 3,5-dimethoxyaniline **152** reacts with chloroacetone **479** in the presence of LiBr and $NaHCO_3$ in a one-pot reaction to give 3-methylindole **92** (Scheme 7-14).



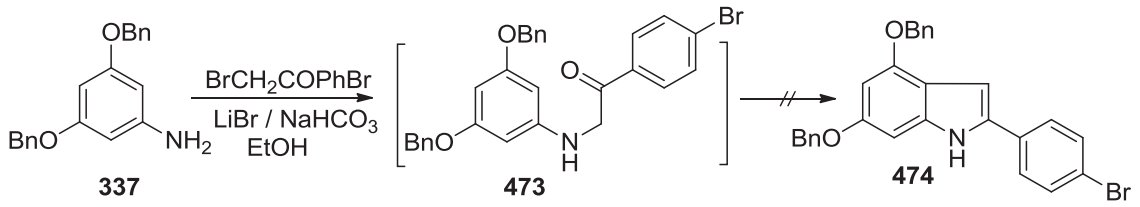
Scheme 7-14

It is assumed that lithium bromide does not only undergo exchange with the chloro group to increase the formation of the anilinoketone **480**, but also acts as a Lewis acid allowing cyclisation at neutral conditions and moderate temperatures, and therefore preventing the rearrangement (Scheme 7-15).[91]



Scheme 7-15

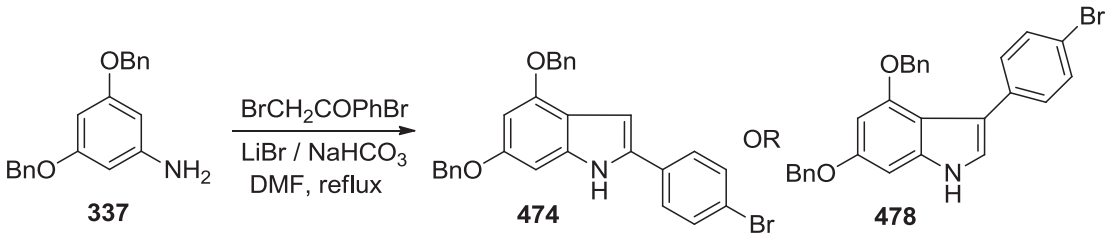
When the same reaction was attempted using 3,5-dibenzyloxyaniline **337**, it was observed that the reaction stopped at the intermediate step, giving anilinoketone **473** in high yield (Scheme 7-16).



Scheme 7-16

Failure of the cyclisation of the one-pot reaction can be caused by the limited solubility of anilinoketone **473**, which precipitated out from the reaction mixture and thus stopping the further reaction. Further heating also failed to affect cyclisation of the anilinoketone. Fortunately cyclisation was successful using *N*,*N*-dimethylformamide as a solvent (Scheme 7-17). A possible explanation of the success using *N*,*N*-dimethylformamide was that the intermediate was highly soluble, while the

anilinoketone was only partly soluble in ethanol, n-propanol and IPA. Another reason is that *N*,*N*-dimethylformamide is an activator of Lewis acids, enhances the Lewis acidity of LiBr and therefore helps in cyclisation.



Scheme 7-17

The ^{1}H NMR spectrum of the product in DMSO-d_6 showed the presence of two singlets at δ 4.91 and 5.05 ppm corresponding to the benzylic CH_2 protons. The three doublets at δ 6.30, 6.38 and 6.78 ppm are characteristic for the indole H5, H7 and H2 or H3 respectively. The phenyl ring protons from the benzyloxy groups appeared as a multiplet at δ 7.13-7.40 ppm, while the NH proton appeared as broad singlet at δ 7.99 ppm. The disappearance of the *N*-CH_2 proton signal indicated that cyclisation had taken place (Figure 7-7).

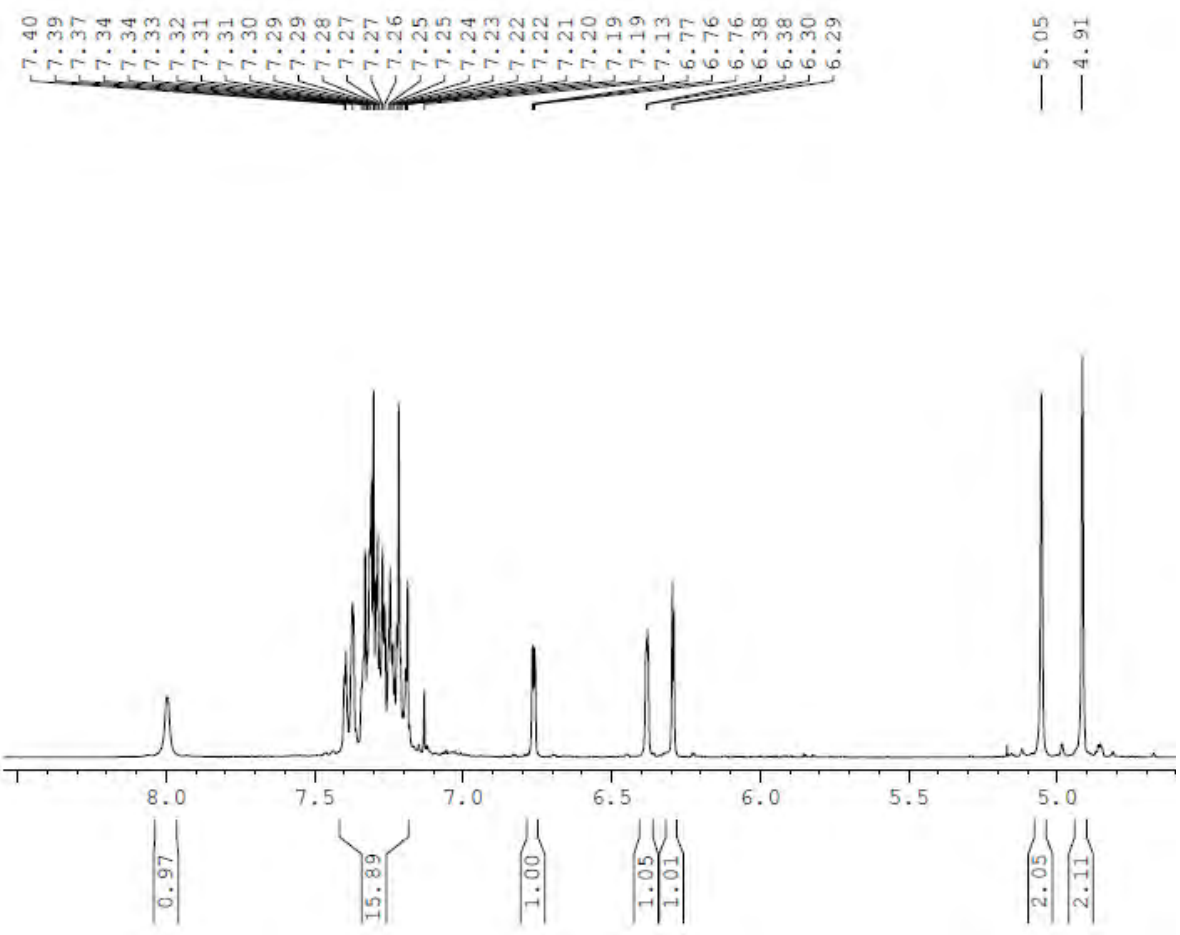


Figure 7-7 ^{1}H NMR spectrum of cyclised product in DMSO-d_6.

The DEPT 135 ^{13}C NMR spectrum of the product also indicated the presence of two negative peaks at δ 68.93 and 69.52 ppm confirming the presence of the two CH_2 groups in the molecule. Although these conditions were expected to give the 3-substituted indoles, it was of interest to determine the exact structure of the molecule as there were slight differences in the ^{1}H NMR signals. Therefore, 2D NMR spectroscopic experiments such as HMBC, HSQC and NOESY were performed to see whether it was a 2-substituted indole or a 3-substituted indole. However, the structural assignment was still not clear. Hence, it became necessary to perform an X-ray crystallographic analysis to determine the exact structure. X-ray quality crystals were obtained from

dichloromethane and X-ray crystal structure analysis indicated the formation of the 2-substituted indole **474** (Figure 7-8).

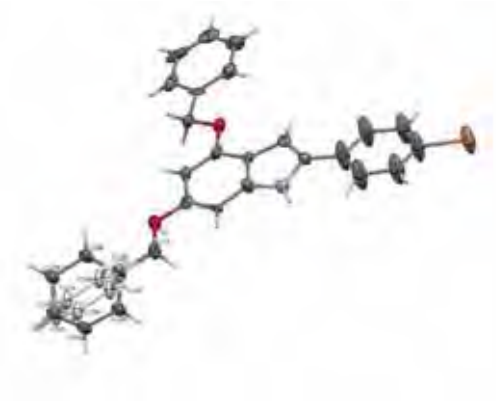
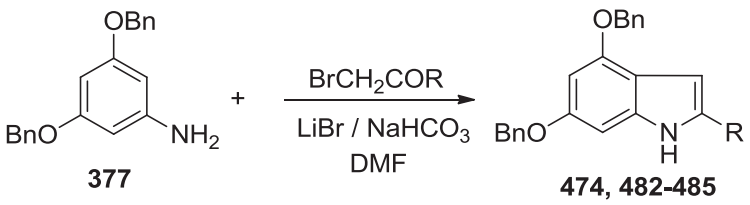


Figure 7-8 ORTEP view of compound **474** showing two orientations of the phenyl ring.

Structure of **474** showed rotational disorder for one of the phenyl rings around C22-C23 bond (Figure 7-8). The two equally occupied orientations of the aromatic ring (C23A–C28A and C23B-C28B) in the crystal lattice, almost perpendicular (82.2 deg.) to each other, were recognized during the structure solution and early cycles of least-squares refinement. The geometry of the six membered ring and anisotropic thermal parameters of both the positions were restrained in the refinement using AFIX and DELU, SIMU options in SHELXL.

Using this protocol, a range of 2-substituted indoles were synthesized (Scheme 7-18).



Scheme 7-18

Table 7-2 depicts the nature of the R substituents and % yields of 2-substituted indoles.

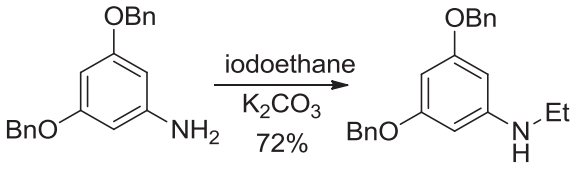
Table 7-2: Yield and the nature of the R substituents.

Product	R	Yields (%)
474	4-BrC_6H_4	74
482	C_6H_5	72
483	4-ClC_6H_4	73
484	4-$MeOC_6H_4$	80
485	Me	76

7.2.6 Synthesis of 3-substituted indoles:

In order to prepare 3-substituted indoles *via* the modified Bischler indole synthesis, it was necessary to block one of the NH protons of 3,5-dibenzyloxyaniline, **337** to prevent rearrangement which leads to the formation of 2-substituted indoles. Therefore, *N*-alkylation was considered as the method of choice, and *N*-ethylation was preferred to *N*-methylation since there was a possibility of the formation the dialkylation product.

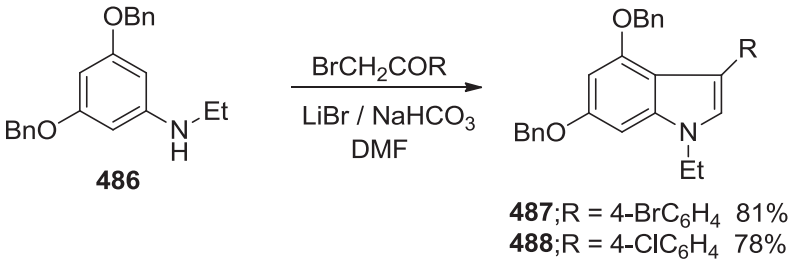
3,5-Dibenzyloxyaniline **337** was reacted with iodoethane in the presence of K_2CO_3 to form 3,5-bis (benzyloxy)-*N*-ethylaniline **486** in 72% yield (Scheme 7-19).



337 **486**

Scheme 7-19

When 3,5-bis(benzyloxy)-*N*-ethylaniline **486** was heated under reflux with an α-haloketone in the presence of $NaHCO_3$ in *N*,*N*-dimethylformamide, gave 3-substituted indoles **487-488** in 75-76% yield (Scheme 7-20).



Scheme 7-20

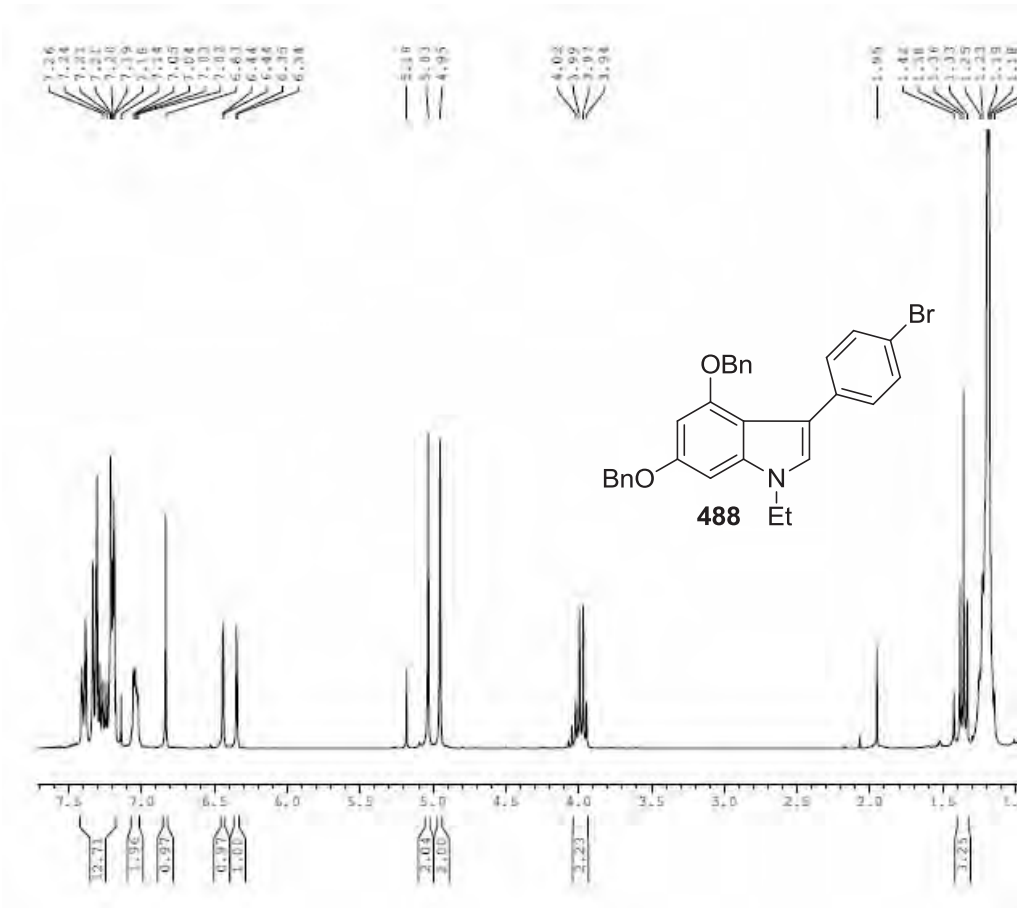
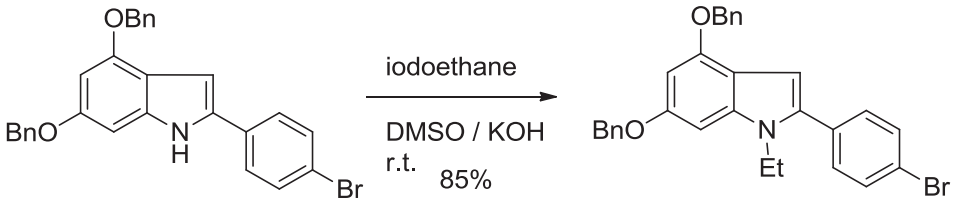


Figure 7-9 ^{1}H NMR spectrum of compound **488** (prepared by one-pot method) in $CDCl_3$.

To confirm whether this method was yielding 2 or 3 substituted indole, *N*-ethylation was performed on 2-(4`-bromophenyl)indole **474** for comparison. Thus **474**, was reacted with iodoethane in the presence of KOH, to give **489** in 85% yield (Scheme 7-21).



474 **489**

Scheme 7-21

When *N*-ethylindole **488** (synthesised from *N*-ethylaniline, **486**) and the product of *N*-ethylation of 2-substituted indole **474** (the structure of which was already established by X-ray crystallography analysis) were examined by co-TLC, the Rf values were found to be different.

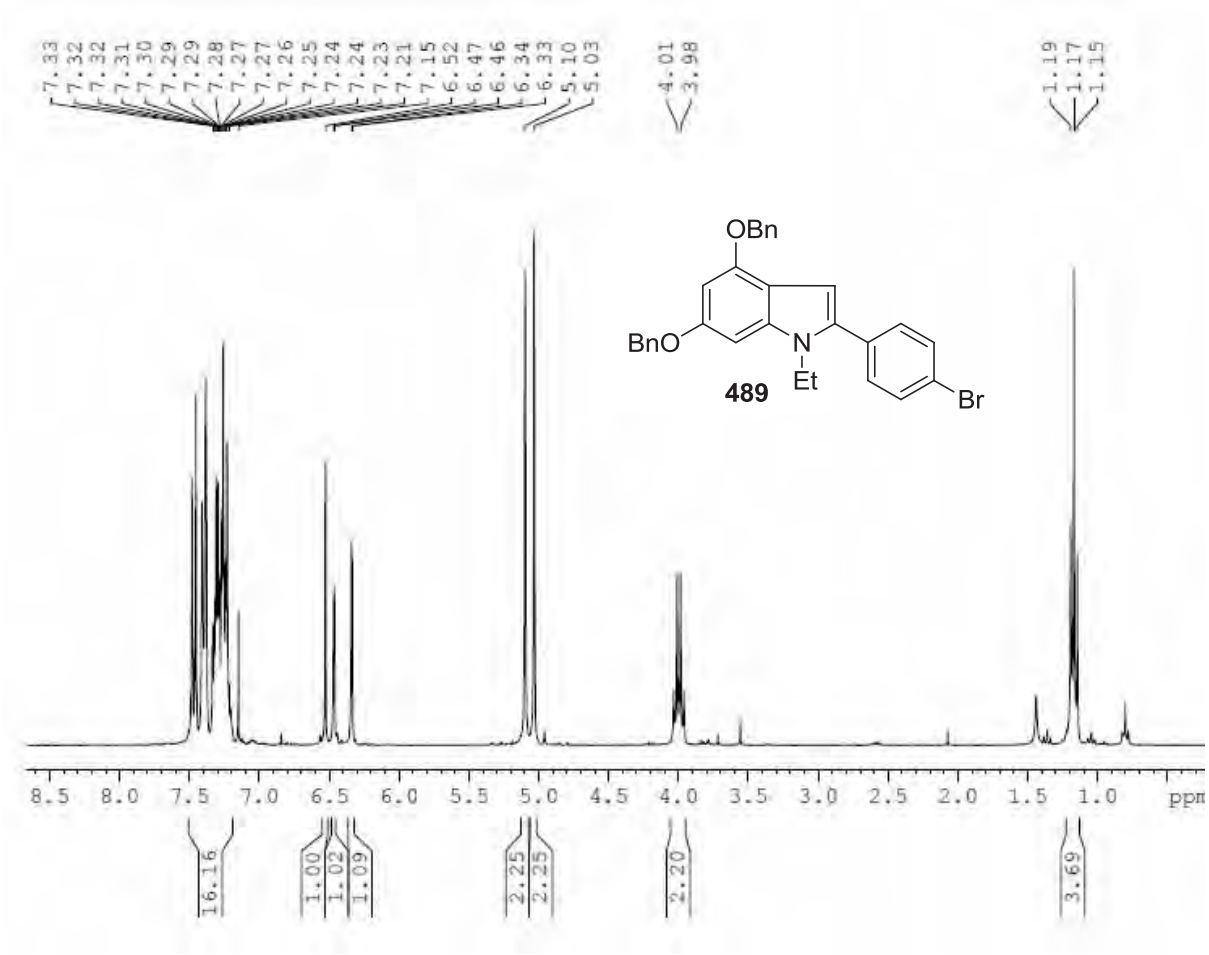
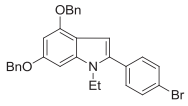
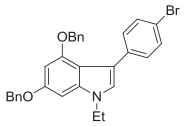


Figure 7-10 ^{1}H NMR spectrum compound **489** in $CDCl_3$.

The ^{1}H NMR spectra ($CDCl_3$) of these compounds were compared and found to have different chemical shifts, especially of the three protons from the indole ring. Table 7-3 shows difference in the chemical shift of these two molecules.

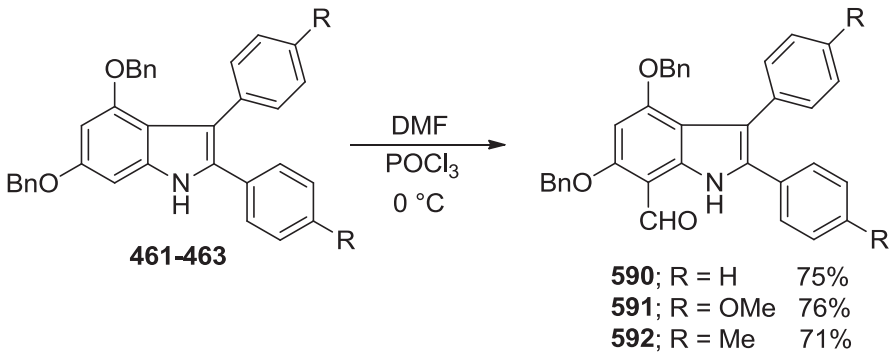
Table 7-3: The comparison of chemical shifts of two indole molecules.

Position of proton		**Position of proton**	
	Chemical shift δ ppm		**Chemical shift δ ppm**
H3	6.52	H2	6.83
H5	6.34 (d, 1H, *J* = 3.0 Hz)	H5	6.35 (d, 1H, *J* = 3.0 Hz)
H7	6.47 (d, 1H, *J* = 3.0 Hz)	H7	6.44 (d, 1H, *J* = 3.0 Hz)

7.2.7 Reactivity studies:

7.2.7.1 Synthesis of indole-7-carbaladehydes:

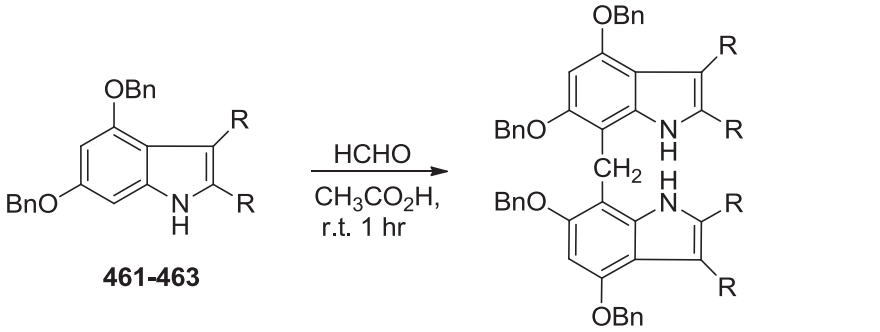
Indoles **461-463** were formylated at C7 to give indole-7-cabaldehyde **490-492** (Scheme 7-22).[118]



Scheme 7-22

7.2.7.2 Synthesis of 7-7`diindolylmethane:

7,7`-Diindolylmethanes have been synthesized from 4,6-dimethoxy-2,3-diarylindoles.[188] It was of interest to perform a similar reaction on 4,6-dibenzyloxyindoles to see the effect of bulky benzyloxy groups as compared to methoxy groups, in positions 4 and 6 of the indoles. When the reaction was performed using 4,6-dibenzyloxyindoles a similar type of 7-7`-diindolylmethane products, **493-495** were formed in 74-87% yield (Scheme 7-23).

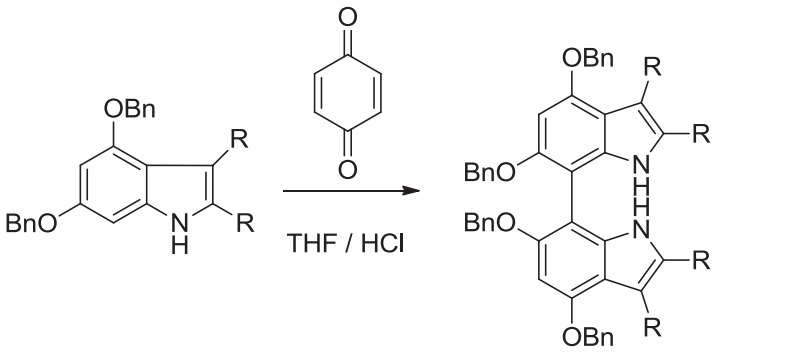


Scheme 7-23

The ^{1}H NMR spectrum of compound **493** in $CDCl_3$ showed two singlets at δ 4.88 and 5.29 ppm corresponding to two the CH_2 groups, and the presence of another singlet at δ 4.54 ppm for the CH_2 group which linking the two indoles. A singlet at δ 6.46 ppm was due to 2 x H5 and the absence of signal corresponding to H7 indicated that the indoles were linked *via* 7 positions. The ^{13}C NMR spectrum showed a signal at δ 19.71 ppm corresponding to an additional methylene moiety apart from the benzyloxy methylene signals. The DEPT 135 ^{13}C NMR spectrum indicated three negative peaks confirming the presence of three CH_2 groups in the molecule.

7.2.7.3 Synthesis of 7,7`-biindolyls:

It has been shown that when 4,6-dimethoxy-2,3-diphenyl indole reacts with 1,4-benzoquinone in the presence of concentrated HCl it gives a 7,7`biindolyl.[92] A similar reaction of 4,6-dibenzyloxyindoles with 1,4-benzoquinone gave the formation of 7,7`-biindolyls, **496-498** in 51-62% yield (Scheme 7-24).



461-463

496; R = C_6H_5 61%
497; R = 4-$MeOC_6H_4$ 62%
498; R = 4-MeC_6H_4 51%

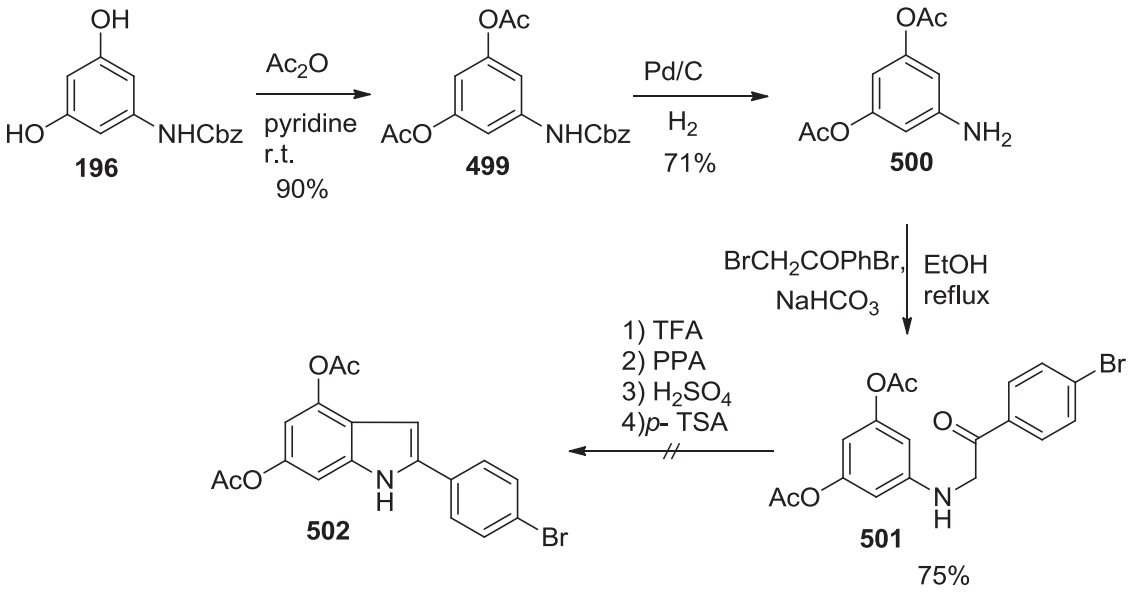
Scheme 7-24

The ^{1}H NMR spectrum of compound **496** in acetone-d_6 showed two singlets at δ 4.97 and 5.02 ppm corresponding to the two CH_2 groups and a singlet at δ 6.61 ppm due to 2 x H5. The absence of a signal corresponding to H7 indicated that the indoles were linked through the 7 position. The DEPT 135 ^{13}C NMR spectrum also indicated two negative peaks at δ 70.41 and 72.61 ppm confirming the presence of two CH_2 groups in the molecule.

7.2.8 Attempted synthesis of 4,6-diacetoxyindole:

When benzyl(3,5-dihydroxyphenyl) carbamate **196** was acetylated, it gave diacetoxy derivative **499** in 90% yield. The *N*-Cbz group from **499** was removed by hydrogenolysis using palladium on carbon at room temperature to give 3,5-

diacetoxyaniline **500** in 71% yield. 3,5-Diacetoxyaniline **500**, reacted with 2,4`-dibromoacetophenone gave anilinoketone **501** in 75% yield (Scheme 7-25).



Scheme 7-25

The examination of the ^{1}H NMR spectrum of compound **501** in $CDCl_3$ showed the presence of two singlets at δ 2.28 ppm corresponding to the two acetoxy groups, and a doublet at δ 7.65 (J = 3.0 Hz) and a triplet at δ 7.86 (J = 3.0 Hz) of substituted aniline protons. The DEPT 135 ^{13}C NMR spectrum also indicated a negative peak at δ 49.86 ppm which was assigned to *N*-CH_2 in the molecule. The HRMS spectrum showed M + Na peak at 428.0104 confirming the formation of anilinoketone **501**.

However, attempts of cyclisation using trifluoroacetic acid, sulfuric acid, polyphosphoric acid or *p*-toluenesulfonic acid were unsuccessful.

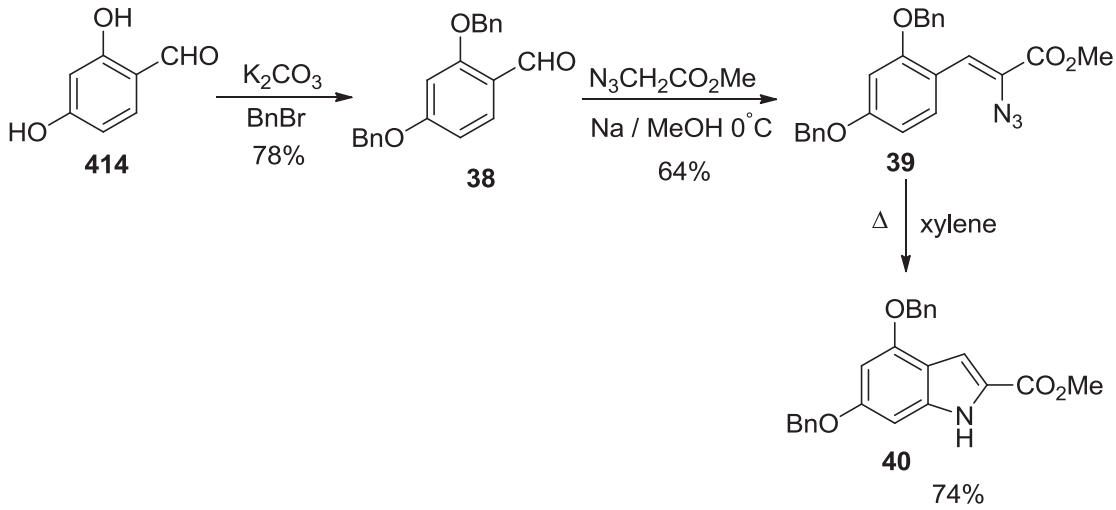
7.2.9 Synthesis of indole-2-carboxylate:

As discussed earlier, the synthesis of 4,6-dihydroxyindoles **161-163** required a long sequence time when a demethylation route was followed. Moreover, the yields

were also not encouraging and reaction required three equivalents of aluminium chloride. Furthermore, the 4,6-dihydroxyindoles **161-163** were unstable, and could not be stored for a long period of time. Thus, it was necessary to synthesize hydroxyl protected indoles in which the protecting groups were easily removable *e.g.* benzyl or acetyl groups. The most straightforward method for synthesizing these indoles was the Hemetsberger indole synthesis.

Synthesis of methyl 4,6-bis(benzyloxy)-indole-2-carboxylate:

2,4-Dihydroxybenzaldehyde **414** was reacted with benzyl bromide in the presence of K_2CO_3 to give 2,4-dibenzyloxybenzaldehyde **38** in 78% yield, which upon reaction with methyl azidoacetate under Hemetsberger conditions gave the azidocinnamate **39** in 64% yield. The crude azidocinnamate was heated in xylene gave **40** in 74% yield (Scheme 7-26).



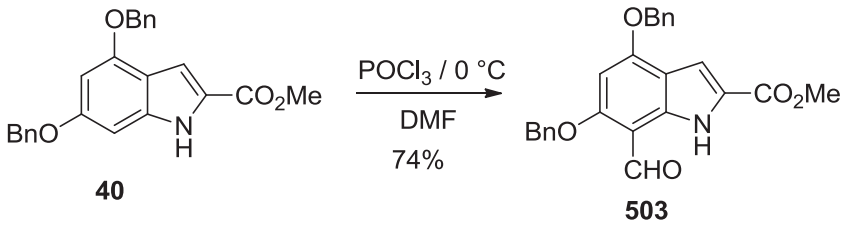
Scheme 7-26

The formation of compound **40** was supported by ^{1}H NMR spectrum and melting point which showed correlation with the data reported in the literature.[189]

7.3 Reactivity studies of 4,6-dibenzyloxyindole-2-carboxylate:

7.3.1 Vilsmeier-Haack formylation:

The 2-substituted-4,6-dimethoxyindoles have been shown to undergo formylation at C7 as well as at C3.[32] Compound **40** was formylated with a mixture of phosphoryl chloride and *N*,*N*`-dimethylformamide to give 7-formylindole **503** in 74% yield (Scheme 7-27).



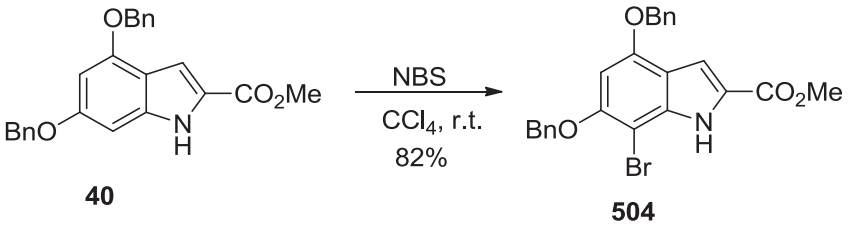
40 **503**

Scheme 7-27

The ^{1}H NMR spectrum of compound **503** in $CDCl_3$ showed a sharp singlet at δ 10.41 ppm corresponding to the presence of CHO. The loss of one proton signal from the indole scaffold indicated that the monoformylation had taken place. The NH proton appeared at δ 10.68 ppm as a broad singlet. The downfield shift of the NH proton from δ 8.72 to 10.68 ppm due to hydrogen bonding in between the NH proton and CHO oxygen, further confirmed the formation of 7-formylindole.

7.3.2 Bromination:

When indole **40** was reacted with *N*-bromosuccinimide in carbon tetrachloride at room temperature, gave the 7-bromoindole derivative **504** in 82% yield (Scheme 7-28).



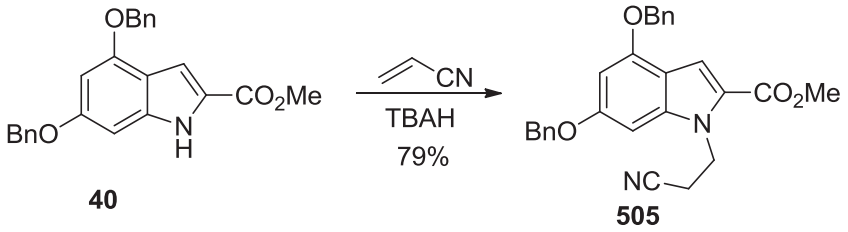
40 **504**

Scheme 7-28

The ^{1}H NMR spectrum of compound **504** in $CDCl_3$ showed peaks corresponding to compound **40** except peak for H7. The disappearance of one of only one peak of indole proton indicated that mono-bromination had taken place. This was also confirmed by the loss of a CH signal in the DEPT 135 spectrum.

7.3.3 Cyanoethylation:

When indole **40** was suspended in acrylonitrile and stirred at room temperature. for 5 min followed by addition of 2 drops of tetrabutylammonium hydroxide, subsequent heating this mixture at 100 °C for 10 min gave the cyanoethyl derivative **505** in 79% yield (Scheme 7-29).



40 **505**

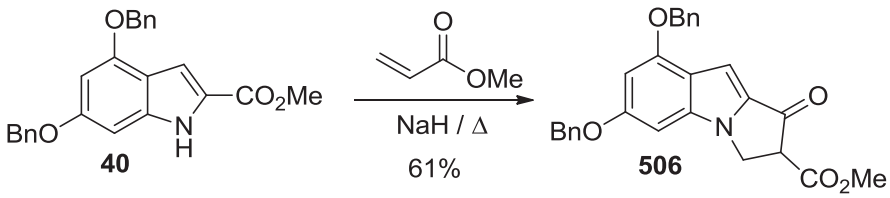
TBAH = Tetrabutylammonium hydroxide

Scheme 7-29

The ^{1}H NMR spectrum of compound **505** in $CDCl_3$ apart from parent indole **40** peaks, showed two triplets at δ 2.86 and 4.75 ppm (J = 6.0 Hz) corresponding to two CH_2CN and the CH_2 group attached to indole nitrogen. The loss of the NH proton signal and appearance of two triplets confirmed the cyanoethylation reaction.

7.3.4 Reaction with methyl acrylate:

When indole **40** was refluxed with methyl acrylate in the presence of sodium hydride, it gave **506** in 61% yield (Scheme 7-30).



Scheme 7-30

The ^{1}H NMR spectrum of compound **506** in $CDCl_3$ showed the CH_2 protons of the five-membered ring as a pair of doublets at δ 4.50 ppm (J = 9.0 Hz, 12.0 Hz) and 4.74 ppm (J = 3.0 Hz, 12.0 Hz) respectively, while the CH proton appeared as a doublet of a doublet at δ 4.22 ppm (J = 6.0 Hz, 9.0 Hz).

7.4 Conclusion:

A one-pot method for the synthesis of 4,6-dibenzyloxyindoles was investigated and using this methodology a series of 2-substituted, 3-substituted and 2,3-disubstituted indoles has been prepared. The reactivities of these indoles in formylation, bromination, oxidative coupling and diindolylmethane formation were investigated.

An efficient synthetic route for preparing 4,6-dibenzyloxyindole-2-carboxylate has been developed and the reactivity of 4,6-dibenzyloxyindole-2-carboxylate in formylation, bromination and cyanoethylation has been investigated.

CHAPTER 8

EXPERIMENTAL

8.1 General information

All reactions requiring anhydrous conditions were performed under an argon atmosphere.

Methanol (MeOH), ethanol (EtOH) and ethyl acetate were obtained from commercial sources. Light petroleum (hexane) was distilled and the fraction b.p. 60-80 °C was used for chromatography. Anhydrous ether and tetrahydrofuran (THF) were distilled from sodium and benzophenone under argon. Anhydrous dichloromethane (DCM) was freshly distilled from calcium hydride under argon. Anhydrous acetonitrile was freshly distilled from phosphorus pentoxide.

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected.

Microanalyses were performed on a Carlo Erba Elemental Analyzer EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand.

NMR spectra were recorded in the designated solvents on a Bruker Avance DPX300 (300 MHz) or a Bruker DMX600 (600 MHz) spectrometer at the designated frequency and were internally referenced to the solvent peaks. ^{1}H NMR spectral data are reported as follows: chemical shift measured in parts per million (ppm) downfield from TMS (δ) multiplicity observed coupling constant (J =) in Hertz (Hz), proton count; assignment.

Multiplicities are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), quintet (p), multiplet (m), doublet of doublets (dd), doublet of doublet of doublets (ddd), broad (br), buried, and combinations of these. ^{13}C NMR chemical shifts are reported in ppm downfield from TMS (δ), and identifiable carbons are given. Acid-free deuterated $CHCl_3$ was obtained by passing the solvent through a short column of anhydrous potassium carbonate immediately prior to use.

Low resolution mass spectrometric analysis was carried out at the Bioanalytical Mass Spectrometry Facility, UNSW, and the spectra were recorded on either

- Q-Star Pulsar API (Applied Biosystems)
- Q-TOF Ultima API (Micromass)
- Voyager DE STR MALDI TOF (Applied Biosystems) mass spectrometers.

High resolution mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI) mass spectrometer at the School of Chemistry, Monash University Melbourne and the School of Chemistry University of Otago, New Zealand. High resolution mass is reported to 4 decimal places and the low resolution mass is reported to 2 decimal places.

Infrared spectra were recorded with a Thermo Nicolet 370 FTIR spectrometer. Ultraviolet-visible spectra were recorded using a Varian Cary 100 Scan spectrometer, and the absorption maxima together with the molar absorptivity (ε) are reported.

Column chromatography was carried out using Merck 230-400 mesh ASTM silica gel. Preparative thin-layer chromatography was carried out on 3 × 200 × 200 mm glass plates coated with Merck $60GF_{254}$ silica gel.

Reactions were monitored using thin-layer chromatography, performed on Merck DC aluminium foil coated with silica gel GF_{254}. Compounds were detected by short and long wavelength ultraviolet light and with iodine vapour.

8.2 Experimental Details:

8.2.1 General Synthetic Procedures:

GP-1: General procedure for the synthesis of anilinoketones:

A mixture of aniline (0.65 mmol), α-haloketone (0.65 mmol) and sodium hydrogen carbonate (0.65 mmol) in EtOH (150 mL) was heated under reflux for 5 h. A yellow precipitate was obtained after cooling to room temperature, which was filtered off and washed with water (100 mL). Recrystallisation from Methanol gave the anilinoketone.

GP-2: General procedure for the synthesis of 2,3-disubstituted indoles:

A mixture of aniline (13 mmol) and benzoin (13 mmol) was heated at 125 °C for 1.5 h. The mixture was cooled to room temperature, aniline (4.3 mmol) and acetic acid (140 mmol) were added and the heating was continued at 125 °C for further 4 h. The mixture was cooled to room temperature and filtered. The product was washed with methanol and dried to yield the 2,3-disubstituted indole.

GP-3: General procedure for the demethylation:

Anhydrous aluminium chloride (3.4 mmol) was added portionwise at room temperature to the solution of methyl ether (1.15 mmol) in chlorobenzene (15 mL). The mixture was heated under reflux at 150 °C. When TLC showed starting material was consumed (~2-3 h), the reaction mixture was allowed to cool at room temperature, and poured on to crushed ice (100 g). The resulting precipitate was filtered and washed with water until

the washings were neutral. The product was then washed with hexane, followed by air drying to yield the phenol.

GP-4: General procedure for the synthesis of pyranoindoles:

A mixture of 4,6-dihydroxyindole (1.15 mmol), β-keto ester (15 mmol) and zinc chloride (1.4 mmol) was heated under reflux in absolute ethanol for 24 h. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered, washed with water and air dried to yield the pyranoindole.

GP-5: General procedure for acetylation:

Hydroxy/amine compound (0.27 mmol) was added to pyridine (3.0 mL) and the mixture was stirred until complete dissolution. Acetic anhydride (0.5 mL) was added dropwise and the reaction mixture was stirred for further 4 h at room temperature. Water (25 mL) was added to the reaction mixture, the resulting precipitate was thoroughly washed with ethanol followed by water to remove unreacted acetic anhydride and acetic acid by-product. The product was dried at 50 °C under vacuum to yield the acetyl derivative.

GP-6: General procedure for the synthesis of *N*-Cbz protected coumarins:

To a mixture of *N*-Cbz protected resorcinol (0.019 mol) and β-keto ester (0.15 mol) was added $TiCl_4$.THF complex (0.019 mol) under nitrogen atmosphere. After stirring for 5 min at room temperature, water (200mL) was added to the reaction mixture and the resulting precipitate was filtered and washed with water to yield the *N*-Cbz protected coumarins.

GP-7: General procedure for the synthesis of acyl coumarins:

A mixture of coumarin (0.61 mmol), α-haloketone (0.61 mmol) and sodium acetate (0.61 mmol) in acetone (50 mL) was heated under reflux overnight. The solvent was evaporated under vacuum. The reaction mixture was diluted with water (50 mL), extracted with Ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine (25 mL) and dried over sodium sulfate. The solvent was evaporated and the product was purified by column chromatography (SiO_2, Ethyl acetate) to give the acyl coumarin.

GP-8: General hydrogenolysis procedure:

After two vacuum/H_2 cycles to remove air from the reaction flask, a stirred mixture of *N*-Cbz/benzyloxy protected compound, 5% Pd/C catalyst (10% w/w) in tetrahydrofuran or *N*,*N*-dimethylformamide (10.0 mL) was hydrogenated at atmospheric pressure and room temperature for 12 h. The reaction mixture was filtered through a pad of Celite ® and the filtrate was concentrated. The resulting product was purified by column chromatography (SiO_2,).

GP-9: General procedure for the synthesis of anilinoketone (coumarins):

A mixture of coumarin (1.04 mmol), α-haloketone (1.04 mmol) and potassium carbonate (1.04 mmol) in acetone (100 mL) was heated under reflux overnight. The solvent was evaporated under vacuum. The reaction mixture was diluted with water (50 mL) and extracted with Ethyl acetate (3 × 50 mL). The combined organic layers washed with brine (50 mL) and dried over sodium sulfate. The solvent was evaporated and the product purified by column chromatography (SiO_2, 50%-60% Ethyl acetate/hexane) to give the anilinoketone.

GP-10: General procedure for the cyclisation of anilinoketone (coumarins):

A solution of anilinoketone (0.29 mmol) in trifluoroacetic acid (10 mL) was heated under nitrogen atmosphere at reflux for 5 h. The reaction mixture was cooled to room temperature, and poured into ice-cold aqueous NaOH (0.2 M, 5.0 mL). To this solution CH_2Cl_2 (25 mL) was added, and the organic layer separated, dried over $MgSO_4$, and evaporated *in vacuo.* The resulting yellow solid was purified by flash chromatography (SiO_2, 30% CH_2Cl_2/hexane) to give the pyranoindole.

GP-11: General procedure for the synthesis of pyrroloquinolines:

Tetrabutylammonium hydroxide (2 drops) was added to a solution of indole-7-carbaldehyde in acrylonitrile. The mixture was stirred at room temperature for 5 min followed by heating under reflux for 10 min. Upon evaporation of excess of the acrylonitrile gave a yellow solid, which was passed through a pad of SiO_2 eluting with 40-50% dichloromethane/hexane to give the pyrroloquinoline.

GP-12: General procedure for the 5,7-dihydroxyquinolin-2-ones:

A mixture of aniline (1.6 mmol) and β-keto ester (6.4 mmol) was heated at 145 ^oC for 30 min followed by cooling to room temperature. Conc. sulfuric acid (1.0 mL) was added dropwise and the mixture was then heated at 145 ^oC for 30 min. After cooling to room temperature, crushed ice (50 g) was added to the reaction mixture, and the resulting precipitate was filtered and washed with distilled water (200 mL) to yield the 5,7-dihydroxyquinolin-2-one

GP-13: General procedure for the synthesis of quinolone ethers:

A mixture of 5,7-dihydroxyquinolin-2-one (0.97 mmol), α-haloketone (1.95 mmol), potassium carbonate (1.95 mmol) and acetone (100 mL) was heated under reflux overnight. Acetone was removed under vacuum and water (100 mL) was added to the residue. The product was extracted with Ethyl acetate (3 × 100 mL), and the combined extract was dried over anhydrous sodium sulfate and concentrated under vacuum. Purification by column chromatography (SiO_2) gave the quinolone ether.

GP-14: General procedure for the synthesis of furoquinolones:

A mixture of quinolone ether (0.26 mmol) and trifluoroacetic acid (10.0 mL) was stirred at reflux for 24 h. The reaction mixture was poured onto crushed ice (100 g) and the precipitated product was filtered, washed with water and air dried to give a solid. The crude product was purified by column chromatography (SiO_2) to give the furoquinolone.

GP-15: General procedure for the Mannich reaction:

A solution of amine (2.42 mmol), formaldehyde (37%, 12.1 mmol) and 5,7-dihydroxy-quinolin-2-one (1.21 mmol) in absolute ethanol (5.0 mL) was heated under reflux for 30 min. The solvent was evaporated under reduced pressure. The brown solid thus obtained was recrystallised from (40% ethyl acetate/hexane) to give the Mannich adduct.

GP-16: General procedure for the synthesis of acyl indoles:

A mixture of indole (0.85 mmol), (0.85 mmol) and potassium carbonate (0.85 mmol) in acetone (50 mL) was heated under reflux overnight. Upon cooling to room temperature the reaction mixture was diluted with water (50 mL), extracted with CH_2Cl_2 (3 × 50

mL). The combined organic phase was washed with brine (25 mL) and dried over sodium sulfate. The solvent was evaporated and the crude product was purified by column chromatography (SiO_2) to give the acyl indole.

GP-17: General procedure for the synthesis of furoindoles:

A solution of acyl indole (0.28 mmol) in trifluoroacetic acid (10 mL) was heated under reflux for 5 h and poured into ice-cold aqueous NaOH (0.2 M, 10 mL), CH_2Cl_2 (25 mL) was added, and the organic layer was separated, dried over $MgSO_4$, evaporated *in vacuo.* The resulting green solid was purified by column chromatography (SiO_2) to give the furoindole.

GP-18: General procedure for the benzylation:

A solution of phenol (0.08 mol), anhydrous potassium carbonate (0.08 moles per hydroxyl group), benzyl bromide (0.08 moles per hydroxyl group), in anhydrous *N*,*N*-dimethylformamide (100 mL) was heated under reflux until TLC analysis showed the disappearance of the starting materials (~9 h). Upon cooling to room temperature, the reaction mixture was diluted with water (300 mL). The resulting precipitate was filtered, washed with water (2 × 250 mL) and air dried to give the benzyloxy product.

GP-19: General procedure for the synthesis of azidocinnamate:

A 250 mL round bottom flask was charged with dry Methanol (40 mL). Sodium chunks (8.7 mmol) were added portion wise to pre-cooled methanol, and the solution was stirred until no more sodium was visible. The reaction flask was cooled to -15 °C and an addition funnel was attached to the reaction flask. The separating funnel was charged with the aryl ether (0.87 mmol) and methyl azidoacetate (8.7 mmol) in Methanol (10 mL). The contents of the funnel were added dropwise to the sodium methoxide solution

over 1 h. Once the addition was completed, the reaction mixture was warmed to 5 °C, where it remained for 2 h. The heterogeneous mixture was poured into ice (200 g) and stirred for 15 min. The aqueous solution was extracted with Et_2O (3 × 200 mL) and the combined extract was dried over sodium sulfate. The solvent was concentrated under reduced pressure to give the azidocinnamate. The crude product was used in the next step without further purification.

GP-20: General procedure for the cyclisation of azidocinnamate:

The azidocinnamate (0.52 mmol) was dissolved in xylene (50 mL) and the reaction mixture was heated under reflux for 6 h. After refluxing for 6 h, the solvent was distilled under reduced pressure, and the remaining residue was extracted with boiling hexane. Upon cooling, the resulting solid was filtered to give indole as a granular solid.

GP-21: General procedure for the synthesis of propagyloxybenzaldehyde:

Propargyl bromide (1.9 mmol/per hydroxyl group) was added to a mixture of potassium iodide (0.8 mmol), potassium carbonate (1.6 mmol/per hydroxyl group) and hydroxybenzaldehyde (1.6 mmol) in acetone. The reaction mixture was heated under reflux with stirring until no more starting material remained (~30 h). The reaction mixture was cooled to room temperature and Et_2O (100 mL) was added. The ethereal solution was washed with NaOH (1N, 3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the propagyloxybenzaldehyde.

GP-22: General procedure for the synthesis of dihydropyranoindoles:

A solution of indole (0.42 mmol) in chlorobenzene (100 mL) was heated under reflux for 12 h. The heating was discontinued and the solvent was reduced to 10 mL under vacuum, followed by drying under slow stream of N_2 to afford a solid. Purification of

the crude product was done using column chromatography (SiO_2) to give the dihydropyranoindole.

GP-23: General procedure for the synthesis of 4,6-dibenzyloxy-2-substituted and 4,6-dibenzyloxy-3-substituted indoles (One-pot method):

A mixture of 3,5-dibenzyloxyaniline **337** (0.65 mmol), α-haloketone (0.65 mmol), sodium hydrogen carbonate (0.65 mmol) and LiBr (0.65 mmol) in *N*,*N*-dimethylformamide (50 mL) was heated under reflux for 6 h. The reaction mixture was cooled to room temperature and water (100 mL) was added. The resulting precipitate was filtered, washed with water (3 × 100 mL) and air dried to give a yellow solid. The crude product was purified by using column chromatography (SiO_2, 30% CH_2Cl_2/hexane) to give the 4,6-dibenzyloxyindole.

GP-24: General procedure for the Vilsmeier Haack formylation of 4,6-dibenzyloxyindoles:

N,*N*-Dimethylformamide (1.0 mL) was cooled in a salt-ice slurry and treated with phosphoryl chloride (0.1 mL, 0.3 mmol) and stirred for 15 min. The resulting solution was then added dropwise, over 5 min, to a cooled and stirred solution of indole (0.2 mmol) in dimethylformamide (3.0 mL). The resulting solution was stirred at room temperature for 1 h. After cooling, the mixture was poured onto crushed ice and basified to high pH with 5 M sodium hydroxide and then extracted with ethyl acetate (3 × 100 mL). The organic extract was washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated to give a pale yellow solid. The crude product was purified *via* column chromatography to give the 4,6-dibenzyloxyindole-7-carbaldehyde.

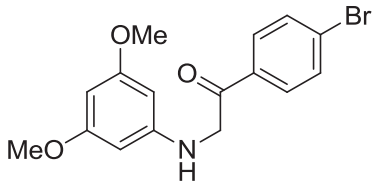
GP-25: General procedure for the synthesis of 7-7′-diindolylmethanes:

A solution of indole (0.24 mmol) in glacial acetic acid (5.0 mL) was warmed at 60 °C, followed by the addition of formaldehyde (37%, 2.0 mL). The mixture was stirred at room temperature for 2 h and the resulting precipitate was filtered off, washed with water and dried to give the 7-7′-diindolylmethane.

GP-26: General procedure for the synthesis of 7,7′-biindolyls:

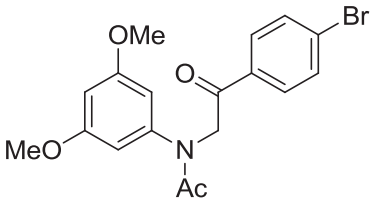
1,4-Benzoquinone (30 mg) was added with stirring to a solution of indole (0.24 mmol in tetrahydrofuran (4.0 mL) containing Conc. hydrochloric acid (2.0 ml). The reaction mixture was stirred at room temperature for 4 h and water (50 mL) was added. The resulting precipitate was filtered, washed with water and air dried to give 7,7-biindolyl.

1-(4-Bromophenyl)-2-[(3,5-dimethoxyphenyl)amino]ethanone (153)



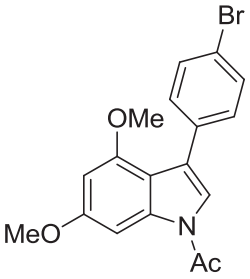
The anilinoketone **153** was prepared from 3,5-dimethoxyaniline **152** (4.1 g, 26.76 mmol), 4-bromophenacylbromide (7.5 g, 27.0 mmol) and sodium bicarbonate (2.6 g, 31.0 mmol) in absolute ethanol (75 mL) according to **GP-1** to yield the *title compound* as a white solid (8.9 g, 95%). M.p. 133-135 °C, *lit*[86] 134-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 6H, OMe), 4.52 (s, 2H, CH_2), 5.90-5.95 (m, 3H, H2′, H4′, H6′), 7.60-7.95 (m, 4H, H2, H3, H5, H6).

_N_-[2-(4-Bromophenyl)-2-oxo-ethyl]-N-(3,5-dimethoxyphenyl)acetamide (154)



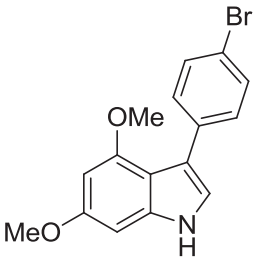
A mixture of acetophenone **153** (5.0 g, 14.27 mmol) and acetic anhydride (10 mL, 105.75 mmol) was heated at 50 °C for 1 h. Water (100 mL) was added and the mixture was stirred overnight at room temperature. The resulting precipitate was filtered, washed with water and dried. Purification by column chromatography (SiO_2, 40% CH_2Cl_2/hexane) to give the *title compound* as a white solid (4.8 g, 85%). M.p. 112-114 °C, *lit*[86] 113-114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00 (s, 3H, OMe), 3.76 (s, 6H, OMe), 4.98 (s, 2H, CH_2), 6.40 (t, *J* = 2.3 Hz, 1H, H4′), 6.50 (d, *J* = 2.3 Hz, 2H, H2′, H6′), 7.56 (d, *J* = 8.7 Hz, 2H, H2, H6), 7.78 (d, *J* = 8.7 Hz, 2H, H3, H5).

1-Acetyl-3-(4′-bromophenyl)-4,6-dimethoxyindole (155)



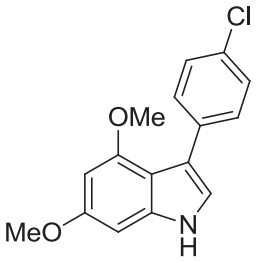
A mixture of ketone **154** (5.0 g, 12.75 mmol) and trifluoroacetic acid (25 mL) was heated at reflux under an argon atmosphere for 2 h. The reaction mixture was cooled to room temperature and poured into ice-cold water (200 mL). The resulting precipitate was filtered, washed with cold water and air dried to give the *title compound* as a white solid (4.10 g, 86%). M.p. 156-158 °C, *lit*[86] 156-158 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.62 (s, 3H, $COCH_3$), 3.74 (s, 3H, OMe), 3.89 (s, 3H, OMe), 6.40 (d, *J* = 1.8 Hz, 1H, H5), 7.14 (s, 1H, H2), 7.41 (d, *J* = 8.7 Hz, 2H, H2′, H6′), 7.49 (d, *J* = 8.7 Hz, 2H, H3′, H5′), 7.76 (d, *J* = 1.8 Hz, 1H, H7).

3-(4'-Bromophenyl)-4,6-dimethoxyindole (156)



A mixture of *N*-acetylindole **155** (10.07 g, 27.0 mmol) and aqueous potassium hydroxide (9.50 g, 169.0 mmol, 20 mL) in methanol (30 mL) was stirred at room temperature for 1 h. The reaction mixture was extracted with dichloromethane (3 x 50 mL) and washed with water (3 x 50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 50% CH_2Cl_2/hexane) to yield the *title compound* as a yellow solid (8.25 g, 92%). M.p.178-179 °C, *lit*[86] 180-181°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H, OMe), 3.84 (s, 3H, OMe), 6.26 (d, *J* = 1.9 Hz, 1H, H5), 6.49 (d, *J* = 1.9 Hz, 1H, H7), 6.99 (d, *J* = 2.3 Hz, 1H, H2), 7.46 (s, 4H, ArH), 8.11 (bs, 1H, NH).

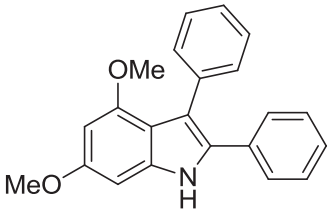
3-(4′-Chlorophenyl)-4,6-dimethoxyindole (157)



A mixture of 3,5-dimethoxyaniline **152** (3.00 g, 19.0 mmol), 4-chlorophenacylbromide (4.50 g, 29.0 mmol), sodium hydrogen carbonate (1.80 g, 20.0 mmol) and lithium bromide (1.75 g, 20.0 mmol) was suspended in propan-2-ol (35 mL) and was heated under reflux for 5 h. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered. The filtrate was concentrated under reduced pressure to yield the brown oil. The crude product was purified by column chromatography (SiO_2, 40% CH_2Cl_2/hexane) to give the *title compound* as a white solid (2.54 g, 44%). M.p. 188-190 °C, *lit*[88]185-187 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.26 (s, 1H,

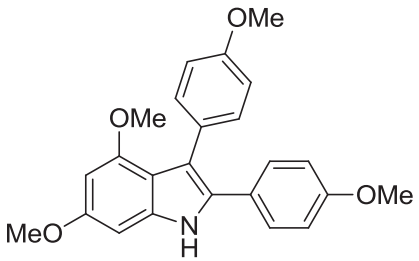
H5), 6.50 (s, 1H, H7), 7.00 (s, 1H, H2), 7.30 (d, *J* = 1.9 Hz, 2H, ArH), 7.51 (d, *J* = 1.9 Hz, 2H, ArH), 8.09 (bs, 1H, NH).

4,6-Dimethoxy-2,3-diphenylindole (76)



The indole **76** was prepared from 3,5-dimethoxyaniline **152** (2.0 g, 13 mmol) and benzoin (2.77 g, 13 mmol) according to **GP-2** to yield the *title compound* as a white solid (2.7 g, 63%). M.p. 240-242 °C, *lit*[86] 240-241 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.65 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.20 (d, *J* = 2.0 Hz, 1H, H5), 6.65 (d, *J* = 2.0 Hz, 1H, H7), 7.25-7.40 (m, 10H, Ar).

4,6-Dimethoxy-2,3-bis(4-methoxyphenyl)indole (158)

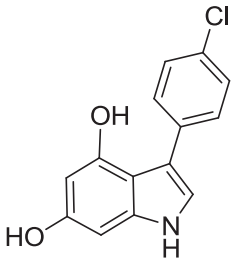


A stream of hydrochloric acid gas was passed into a suspension of 3,5-dimethoxyaniline **152** (9.85 g, 64.3 mmol) in anhydrous diethyl ether (80 mL) for 0.5 h. The resulting slurry was filtered and washed with ether (100 mL) to give 3,5-dimethoxyanilinium hydrochloride as a yellow solid (11.50 g, 94%).

A mixture of 3,5-dimethoxyaniline **152** (2.14 g, 14.0 mmol), anisoin (1.90 g, 7.01 mmol), and 3,5-dimethoxyanilinium hydrochloride (1.60 g, 8.43 mmol) in silicone oil (10 mL) was heated at 130-140 °C for 1 h. After cooling, the mixture was washed with light petroleum (2 x 20 mL), extracted with CH_2Cl_2 (3 x 15 mL) and concentrated under

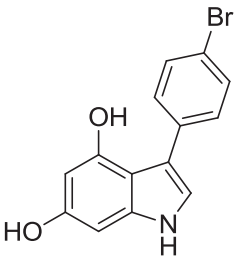
vacuum to yield the *title compound* as a yellow solid (4.30 g, 79%). M.p. 100-101 °C, *lit*[88]102-103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.84 (s, 3H, OMe), 6.21 (d, *J* = 1.9 Hz, 1H, H4), 6.49 (d, *J* = 1.9 Hz, 1H, H7), 6.81 (d, *J* = 9.0 Hz, 2H, ArH), 6.85 (d, *J* = 8.6 Hz, 2H, ArH), 7.20 (d, *J* = 6.7 Hz, 2H, ArH), 7.31 (d, *J* = 6.3 Hz, 2H, ArH), 8.06 (bs, 1H, NH).

4,6-Dihydroxy-3-(4′-chlorophenyl)indole (161)



The indole **161** was prepared from 3-(4-chlorophenyl)-4,6-dimethoxyindole **157** (300 mg, 1.15 mmol) and anhydrous aluminium chloride (460 mg, 3.4 mmol) in chlorobenzene according to **GP-3** to yield the *title compound* as a white solid (193 mg, 71%). M.p. 176-178 °C, *lit*[88]178-180 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.96 (d, *J* = 1.5 Hz, 1H, H5), 6.24 (d, *J* = 1.5 Hz, 1H, H7), 6.78 (d, *J* = 1.1 Hz, 1H, H2), 7.41 (d, *J* = 8.6 Hz, 2H, ArH), 7.71 (d, *J* = 8.6 Hz, 2H, ArH), 8.81 (s, 1H, OH), 9.3 3 (s, 1H, OH), 10.98 (bs, 1H, NH).

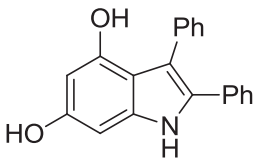
4,6-Dihydroxy-3-(4′-bromophenyl)indole (162)



The indole **162** was prepared from 3-(4-bromophenyl)-4,6-dimethoxyindole **156** (300 mg, 0.9 mmol) in chlorobenzene (15.0 mL) and anhydrous aluminium chloride (350 mg, 2.7 mmol) according to **GP-3** to yield the *title compound* as a white solid (210 mg, 77%). M.p. 151-152 °C *lit*[88] 152-154 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.95 (d, *J* = 1.5 Hz, 1H, H5), 6.24 (d, *J* = 1.5 Hz, 1H, H7), 6.78 (bs, 1H, H2), 7.54 (d, *J*

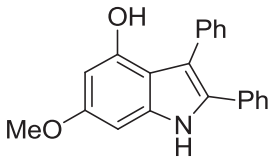
= 8.6 Hz, 2H, ArH), 7.64 (d, *J* = 8.6 Hz, 2H, ArH), 9.35 (bs, 1H, OH), 10.98 (bs, 1H, NH).

4,6-Dihydroxy-2,3-diphenylindole (163)



The indole **163** was prepared from 4,6-dimethoxy-2,3-diphenylindole **76** (300 mg, 0.91 mmol) in chlorobenzene (15.0 mL), and anhydrous aluminium chloride (2.02 g, 2.7 mmol) according to **GP-3** to yield the *title compound* as a brown solid. (190 mg, 70%) M.p. 260-261 °C *lit*[88]263 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.12 (d, *J* = 1.9 Hz, 1H, H5), 6.46 (d, *J* = 1.9 Hz, 1H, H7), 7.12-7.42 (m, 10H, ArH), 7.87 (bs, 1H, OH), 10.15 (bs, 1H, NH).

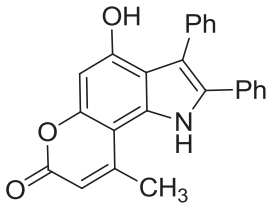
4-Hydroxy-6-Methoxy-2,3-diphenylindole (164)



The indole **164** was prepared from 4,6-dimethoxy-2,3-diphenylindole **76** (4.0 g, 0.012 mol) in chlorobenzene (150 mL), and aluminium chloride (4.75 g, 0.036 mol) according to **GP-3**. Upon column chromatography (SiO_2, 40% Ethyl acetate/hexane), the first fraction gave the *title compound* as a white solid (1.8 g, 47%). The other fraction gave 4,6-dihydroxy-2,3-diphenylindole **163** as a brown solid (1.3 g, 35%). M.p. 200 °C (dec.); UV (MeOH): λ_{max} 261 nm (ε 22,144 $cm^{-1}M^{-1}$), 322 (14,049); IR (KBr): ν_{max} 3520, 3329, 3052, 2964, 2938, 2839, 1637, 1602, 1586, 1555, 1499, 1460, 1447, 1438, 1362, 1324, 1292, 1198, 1140, 1086, 1072, 1031, 834, 814, 805, 766, 755, 716, 697, 650, 620, 566, 533, 450 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (s, 3H, O-CH_3),

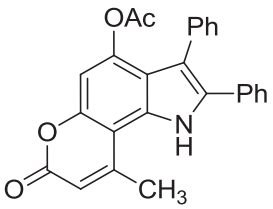
6.01 (bs, 1H, H5), 6.38 (bs, 1H, H7), 7.13-7.28 (m, 10H, ArH), 9.15 (s, 1H, OH), 11.12 (s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 55.38 (O-CH_3), 85.96 (ArCH), 94.90 (ArCH), 112.33 (ArC), 114.01 (ArC), 125.99 (2 × ArCH), 126.86 (ArCH), 127.58 (2 × ArCH), 127.98 (2 × ArCH), 128.57 (2 × ArCH), 131.63 (ArCH), 133.34 (ArC), 136.85 (ArC), 138.69 (ArC), 152.52 (ArC), 157.07 (ArC); HRMS *m/z:* Calcd. for $C_{21}H_{17}NO_2$ $[M + 1]^+$ 316.1259. Found 316.1331.

4-Hydroxy-9-methyl-2,3-diphenylpyrano[2,3-*g*]indol-7-one (176)



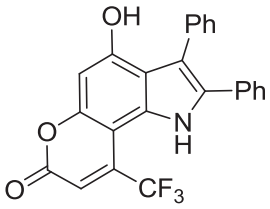
The pyranoindole **176** was prepared from indole **163** (200 mg, 1.15 mmol), ethyl acetoacetate (2.33 mL, 15 mmol) and zinc chloride (190 mg, 1.4 mmol) according to **GP-4** to give the *title compound* as a white solid (146 mg, 60%). M.p. 310-311 °C (dec.); UV (MeOH) λ_{max} 203 nm (ε 15,083 cm^{-1} M^{-1}), 250 (10,789), 309 (7266); IR (KBr) ν_{max}: 3395, 3194, 1650, 1593, 1569, 1401, 1120, 769, 585 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.837 (s, 3H, CH_3), 6.01 (s, 1H, ArH), 6.43 (s, 1H, ArH), 7.21-7.31 (m, 10H, ArH), 10.4 (bs, 1H, NH), 10.59 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 22.46 (CH_3), 94.95 (ArCH), 100.35 (ArC), 108.33 (ArCH), 115.38 (ArC), 115.46 (ArC), 126.49 (2 × ArCH), 127.62 (2 × ArCH), 128.45 (2 × ArCH), 129.41 (2 × ArCH), 131.68 (2 × ArCH), 132.36 (ArC), 132.96 (ArC), 135.68 (ArC), 144.03 (ArC), 153.47 (ArC), 153.77 (ArC), 156.29 (ArC), 160.62 (C=O); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{24}H_{17}NO_3$ $[M + 1]^+$ 368.1208. Found 368.1283.

9-Methyl-7-oxo-2,3-diphenyl-1,7-dihydropyrano[2,3-*g*]indol-4-yl acetate (176a)



The pyranoindole **176a** was prepared from pyranoindole **176** (100 mg, 0.27 mmol), pyridine (3.0 mL) and acetic anhydride (0.5 mL) according to **GP-5** to give the *title compound* as white crystals (81 mg, 73%). M.p. 260-262 °C; UV (MeOH) λ_{max} 203 nm (ε 24,131cm^{-1} M^{-1}), 250 (17,300), 308 (11,738); IR (KBr) $\nu_{max:}$ 3424, 3070, 1731, 1625, 1595, 1574, 1446, 1202, 1149, 1092, 1061, 767, 698, 685cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.46 (s, 3H, $COCH_3$), 2.93 (s, 1H, CH_3), 6.33 (s, 1H, ArH), 6.92 (s, 1H, ArH), 7.195-7.409 (m, 10H, ArH), 10.95 (s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 19.89 (OCO<u>C</u>H$_3$), 22.43 (CH_3), 104.40 (ArCH), 105.43 (ArC), 112.47 (ArCH), 114.07 (ArC), 119.07 (ArC), 127.19 (2 × ArCH), 128.17 (2 × ArCH), 128.38 (2 × ArCH), 129.43 (2 × ArCH), 131.51 (2 × ArCH), 131.72 (ArC), 132.66 (ArC), 134.72 (ArC), 137.18 (ArC), 146.56 (ArC), 151.30 (ArC), 153.35 (ArC), 160.19 (C=O), 168.78 (<u>C</u>OCH$_3$); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{26}H_{19}NO_4$ [M + 1]$^{+}$ 410.1314. Found 410.1380.

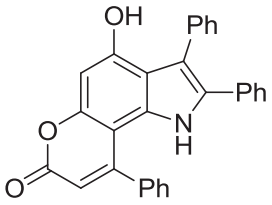
4-Hydroxy-2,3-diphenyl-9-(trifluoromethyl)pyrano[2,3-*g*]indol-7-one (179)



The pyranoindole **179** was prepared from indole **163** (100 mg, 6.6 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate (0.77 mL, 5.28 mmol) and zinc chloride (500 mg, 4.8 mmol) according to **GP-4** to yield the *title compound* as a white solid (98 mg, 71%). M.p. 290-292 °C; UV (MeOH): λ_{max} 261 nm (ε 21,601 cm^{-1} M^{-1}), 329 (11032), 467 (13,769); IR (KBr) ν_{max}: 3461, 3200, 3081, 1692, 1570, 1505, 1446, 1355, 1279, 699

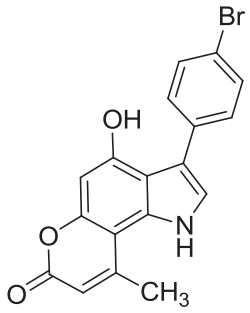
cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.60 (s, 1H, H8), 6.77 (s, 1H, H5), 7.24-7.35 (m, 10H, ArCH), 9.50 (s, 1H, OH), 10.99 (bs, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 93.28 (ArC), 96.04, (ArCH), 115.89 (ArCH), 116.14 (ArC), 123.12 (CF_3), 126.96 (2 × ArCH), 127.85 (2 × ArCH), 128.17 (2 × ArCH), 128.63 (2 × ArCH), 128.97 (2 × ArCH), 129.56 (ArC), 131.69 (ArC), 131.88 (ArCH), 134.65 (ArC), 135.21 (ArC), 141.21 (ArCH), 155.17 (ArC), 158.06 (ArC), 159.34 (C=O); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{24}H_{14}F_3NO_3$ $[M + 1]^+$ 422.0926. Found 422.0996.

4-Hydroxy-2,3,9-triphenylpyrano[2,3-*g*]indol-7-one (180)



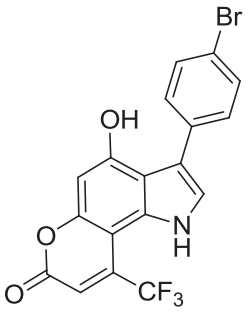
The pyranoindole **180** was prepared from indole **163** (100 mg, 0.33 mmol), ethyl 3-oxo-3-phenylpropanoate (1.0 mL, 5.28 mmol) and zinc chloride (50 mg, 3.9 mmol) according to **GP-4** to give the *title compound* as a white solid (85 mg, 60%). M.p. 305-306 °C (dec.); UV (MeOH) λ_{max} 254 nm (ε 34,620 cm^{-1} M^{-1}), 331 (20,204), 422 (38,567); IR (KBr) ν_{max}: 3474, 1685, 1623, 1446, 1102, 968, 800, 695 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.02 (s, 1H, ArH), 6.44 (s, 1H, ArH), 7.21-7.95 (m, 15 H, ArH), 10.5 (bs, 1H, NH), 10.59 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 94.96 (ArCH), 100.37 (ArC), 108.33 (ArCH), 115.47 (ArC), 127.62 (2 × ArCH), 128.44 (2 × ArCH), 128.94 (3 × ArCH), 129.41 (3 × ArCH), 129.62 (2 × ArCH), 131.68 (3 × ArCH), 131.80 (ArC), 132.97 (ArC), 133.23 (ArC), 135.01 (ArC), 136.04 (ArC), 144.03 (ArC), 144.07 (ArC), 153.48 (ArC), 156.28 (ArC), 160.61 (C=O); HRMS *m/z*: Calcd. for $C_{29}H_{19}NO_3$ $[M]^+$ 429.1365. Found 429.1093.

3-(4-Bromophenyl)-4-hydroxy-9-methylpyrano[2,3-*g*]indol-7-one (181)



The pyranoindole **181** was prepared from indole **162** (100 mg, 0.33 mmol), ethyl acetoacetate (0.68 mL, 5.2 mmol) and zinc chloride (84 mg, 6.33 mmol) according to **GP-4** to give the *title compound* as a white solid (73 mg, 60%). M.p. 290-291 °C; UV (MeOH) λ_{max} 263 nm (ε 18,929 cm^{-1} M^{-1}), 325 (20,036), 404 (17,721); IR (KBr) ν_{max}: 3472, 3230, 1679, 1670, 1606, 1592, 1544, 1267, 1068, 1004, 825, 799, 685 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.82 (s, 3H, CH_3), 6.01 (s, 1H, ArH), 6.62 (s, 1H, ArH), 7.07 (bs, 1H, ArH), 7.65 (d, *J* = 10.9 Hz, 2H, ArH), 7.93 (d, *J* = 10.9 Hz, 2H, ArH), 10.43 (s, 1H, OH) 10.81 (bs, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 22.33 (CH_3), 94.89 (ArCH), 99.23 (ArCH), 100.73 (ArC), 108.48 (ArCH), 117.45 (ArC), 120.83 (ArC), 128.35 (2 × ArCH), 131.36 (ArC), 131.87 (2 × ArCH), 133.88 (ArC), 136.78 (ArC), 153.53 (ArC), 153.89 (ArC), 154.94 (ArC), 160.77 (C=O); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{18}H_{12}BrNO_3$ $[M + 1]^+$ 370.0001. Found 370.0071.

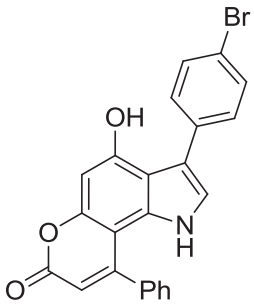
3-(4-Bromophenyl)-4-hydroxy-9-(trifluoromethyl)pyrano[2,3-*g*]indol-7-one (182)



The pyranoindole **182** was prepared from indole **162** (300 mg, 0.995 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate (2.32 mL, 15.9 mmol) and zinc chloride (162 mg, 1.19 mmol) according to **GP-4** to give the *title compound* as a yellow solid (306 mg, 73%). M.p. 258-260 °C; UV (MeOH): λ_{max} 264 nm (ε 11,605 cm^{-1} M^{-1}); 331 (9,771), 448 (5,795); IR(KBr) ν_{max}: 3511, 3365, 1707, 1606, 1592, 1284, 1192, 1164, 1111, 829, 705 cm^{-1};

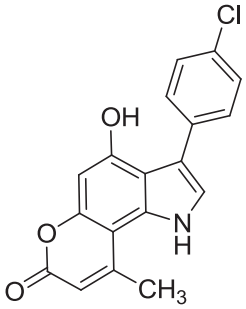
^{1}H NMR (300 MHz, DMSO-d_6): δ 6.31 (s, 1H, ArH), 7.02 (s, 1H, ArH), 7.59-7.77 (m, 4H, ArH), 8.36 (bs, 1H, ArH), 9.89 (bs, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 94.91 (ArCH), 102.09 (ArC), 110.12 (ArC), 112.35 (ArCH), 123.04 (CF_3), 124.07 (ArCH), 124.50 (ArC), 127.34 (2 × ArCH), 132.25 (2 × ArCH), 135 (ArC), 137 (ArC), 143.32 (ArC), 148.65 (ArC), 155.16 (ArC), 151.16 (ArC), 164.96 (C=O); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{18}H_9BrF_3NO_3$ $[M]^+$ 422.9634. Found 422.9718.

3-(4-Bromophenyl)-4-hydroxy-9-phenylpyrano[2,3-*g*]indol-7-one (183)



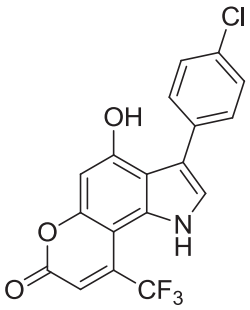
The pyranoindole **183** was prepared from indole **162** (100 mg, 0.23 mmol), ethyl 3-oxo-3-phenylpropanoate (0.7 mL, 3.68 mmol) and zinc chloride (36 mg, 0.27 mmol) according to **GP-4** to give the *title compound* as a white solid (97 mg, 68%). M.p. 288-289 °C; UV (MeOH) λmax 266 nm (ε 23,610 cm^{-1} M^{-1}), 331 (20,204), 422 (16,450); IR (KBr) ν_{max}: 3450, 3239, 1682, 1609, 1362, 1090, 821, 784, 707, 503 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.14 (s, 1H, ArH), 6.61 (s, 1H, ArH), 7.05 (bs, 1H, ArH), 7.1 (d, *J* = 8.64 Hz, 2H, ArH), 7.49 (d, *J* = 8.64 Hz, 2H, ArH), 7.5-7.7 (m, 5H, ArH), 8.1 (s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 95.12 (ArCH), 98.34 (ArC), 98.41 (ArCH), 109.24 (ArCH), 117.21 (ArC), 125.03 (ArCH), 126.14 (2 × ArCH), 128.16 (2 × ArCH), 129.40 (2 × ArCH), 129.75 (2 × ArCH), 130.25 (ArC), 130.33 (ArC), 132.31 (ArC), 132 (ArC), 133 (ArC), 135 (ArC), 154.31 (ArC), 155.82 (ArC), 160.62 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{23}H_{14}BrNO_3$ $[M + 1]^+$ 432.0157. Found 432.0131.

3-(4-Chlorophenyl)-4-hydroxy-9-methylpyrano[2,3-*g*]indol-7-one (184)



The pyranoindole **184** was prepared from indole **161** (100 mg, 0.3 mmol), ethyl acetoacetate (0.6 mL, 4.8 mmol) and zinc chloride (60 mg, 0.45 mmol) according to **GP-4** to give the *title compound* as a white solid (66 mg, 62%). M.p. 296-298 °C; UV (MeOH) λmax 261 nm (ε 26,101cm^{-1} M^{-1}), 250 (29,589), 402 (19,893); IR (KBr) ν_{max}: 3476, 3241, 1670, 1607, 1594, 1376, 1269, 1166, 1113, 842, 801, 695 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.80 (s, 3H, CH_3), 5.99 (bs, 1H, ArH), 6.46 (s, 1H, ArH), 7.02 (bs, 1H, ArH), 7.49 (d, *J* = 9.0 Hz, 2H, ArH), 7.83 (d, *J* = 9.0 Hz, 2H, ArH), 10.4 (s, 1H, OH), 10.86 (bs, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 22.34 (CH_3), 94.87 (ArCH), 99.16 (ArCH), 100.71 (ArC), 108.44 (ArCH), 117.43 (ArC), 128 (2 × ArCH), 128.94 (2 × ArCH), 130.96 (ArC), 132.29 (ArC), 133.82 (ArC), 136.73 (ArC), 153.73 (ArC), 153.85 (ArC), 154.92 (ArC), 160.84 (C=O); HRMS (TOF-ESI) m/*z*: Calcd. for $C_{18}H_{12}ClNO_3$ $[M + 1]^+$ 326.0506. Found 326.0578.

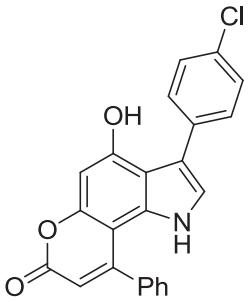
3-(4-Chlorophenyl)-4-hydroxy-9-(trifluoromethyl)pyrano[2,3-*g*]indol-7-one (185)



The pyranoindole **185** was prepared from indole **161** (300 mg, 0.995 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate (2.32 mL, 15.9 mmol) and zinc chloride (162 mg, 1.19 mmol) according to **GP-4** to give the *title compound* as a yellow solid (271 mg, 72%). M.p. 260-261 °C; UV (MeOH) λ_{max} 202 nm (ε 14,213cm^{-1} M^{-1}), 264 (11032), 331 (9778), 448 (6557); IR (KBr) ν_{max}: 3515, 1704, 1595, 1692, 1518, 1282, 1163, 1115, 832, 711, 509 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.14 (s, 1H, H2), 6.63 (s,

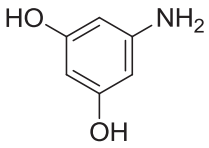
1H, H8), 7.07 (s 1H, H5), 7.30 (d, *J* = 8.64 Hz, 2H, ArH), 7.51 (d, *J* = 8.64 Hz, 2H, ArH), 8.00 (s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 95.85 (ArCH), 102.04 (ArC), 112.04 (ArCH), 122.16 (ArC), 123.03 (CF_3), 124.07 (ArCH), 127.51 (2 × ArCH), 129.26 (2 × ArCH), 130.35 (ArC), 132.73 (ArC), 134.04 (ArC), 135.99 (ArC), 136.53 (ArC), 152.80 (ArC), 155.80 (ArC), 159.24 (C=O); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{18}H_9ClF_3NO_3$ $[M + 1]^+$ 380.0223. Found 380.0302.

3-(4-Chlorophenyl)-4-hydroxy-9-phenylpyrano[2,3-*g*]indol-7-one (186)



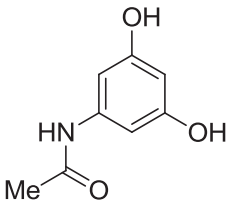
The pyranoindole **186** was prepared from indole **161** (300 mg, 1.15 mmol), ethyl 3-oxo-3-phenylpropanoate (3.5 mL, 18.53 mmol) and zinc chloride (189 mg, 1.38 mmol) according to **GP-4** to give the *title compound* as a white solid (238 mg, 62%). M.p. 296-298 °C; UV (MeOH) λ_{max} nm (ε cm^{-1} M^{-1}), 266 (23,610), 331 (20,204), 422 (16,450); IR (KBr) ν_{max}: 3450, 3239, 1682, 1609, 1362, 1090, 821, 784, 707, 503 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.14 (s, 1H, H2), 6.63 (s, 1H, H8), 7.07 (bs, 1H, H5), 7.3 (d, *J* = 8.64 Hz, 2H, ArH), 7.51 (d, *J* = 8.64 Hz, 2H, ArH), 7.6-7.8 (m, 5H, ArH), 8.00 (s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 95.14 (ArCH), 98.37 (ArC), 98.44 (ArCH), 109.21 (ArCH), 117.23 (ArC), 126.12 (2 × ArCH), 127.03 (ArCH), 128.18 (2 × ArCH), 129.43 (2 × ArCH), 129.78 (2 × ArCH), 130.31 (ArC), 132.34 (ArC), 133 (ArC), 134 (ArC), 137 (ArC), 154.12 (ArC), 154.34 (ArC), 155.81 (ArC), 160.64 (C=O); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{23}H_{14}ClNO_3$ $[M]^+$ 387.0582. Found 387.0662.

5-Aminoresorcinol (105)



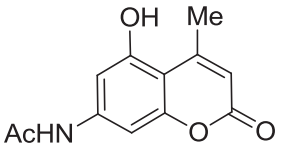
Aqueous ammonia solution (400 mL) was added over a 3 min period to phloroglucinol **193** (50 g, 0.4 mol) while stirring and cooling. Upon completion of the addition, a stream of ammonia was bubbled through the reaction mixture for 30 min. The cooling bath was removed and stirring was continued at room temperature for 46 h. Vacuum concentration of the clear solution gave the *title compound* as a white solid (43.10 g 86%). M.p. 150-151 °C, *lit*[190] 150 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.71 (s, 2H, NH_2), 5.40 (s, 3H, ArH), 9.11 (s, 2H, OH).

***N*-(3,5-Dihydroxyphenyl)acetamide (194)**



Acetic anhydride (5.0 mL, 0.088 mol) was added drop-wise to a solution of 3,5-dihydroxyaniline **105** (1.0 g, 0.008 mol) in dioxane (15 mL) in such a manner that the internal temperature did not exceed 50 °C. The mixture was subsequently stirred for 2 h and light petroleum (50 mL) was added, whereupon the product precipitated as a white solid (1.20 g, 89%). M.p. >200 °C, *lit*[190] °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.95 (s, 3H, $COCH_3$), 5.85 (bs, 1H, ArH), 6.10 (bs, 2H, ArH), 9.14 (s, 2H, OH), 9.61 (s, 1H, NH).

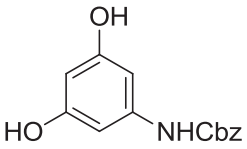
***N*-(5-Hydroxy-4-methyl-2-oxo-2H-chromen-7-yl)acetamide (195)**



A mixture of *N*-(3,5-dihydroxyphenyl)acetamide **194** (500 mg, 2.99 mmol) and ethyl acetoacetate (3.2 mL, 24 mmol)

was heated at 140 °C for 30 min. The reaction mixture was cooled, and Conc. sulfuric acid (1.0 mL) was added. The resulting mixture was stirred at 140 °C for 30 min. Crushed ice (100 g) was added to the reaction mixture which gave a white precipitate, which was filtered, washed with water (2 × 100 mL) and recrystallised from methanol to yield the *title compound* as a white solid (503 mg, 72%). M.p. 278-280 °C; UV (MeOH): λ_{max} 210 nm (ε 21,203 $cm^{-1}M^{-1}$), 261 (9,366), 323 (12,185); IR (KBr): ν_{max} 3312, 3118, 2800, 2700, 1834, 1710, 1669, 1635, 1613, 1549, 1512, 1444, 1334, 1305, 1167, 1101, 1083, 1033, 1004, 955, 858, 828, 768, 751, 663, 565, 543 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.04 (s, 3H, $COCH_3$), 2.49 (s, 3H, CH_3), 5.93 (s, 1H, H3), 6.99 (d, *J* = 3.0, 1H, H6), 7.15 (d, *J* = 3.0 Hz, 1H, H8), 10.15 (s, 1H, OH), 10.63 (s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 23.75 (CH_3), 24.60 ($CO\underline{C}H_3$), 97.57 (ArCH), 101.82 (ArCH), 104.94 (ArC), 111.07 (ArCH), 142.88 (ArC), 154.89 (ArC), 155.77 (ArC), 157.49 (ArC), 160.24 (C=O), 169.43 (NH$\underline{C}$=O); HRMS *m/z:* Calcd. for $C_{12}H_{11}NO_4$ $[M + 1]^+$ 234.0688. Found 234.0761.

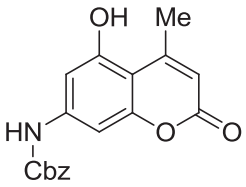
Benzyl (3,5-dihydroxyphenyl) carbamate (196)



Benzyl chloroformate (34 mL, 0.2 mol) was added dropwise with cooling at 15-20 °C to a mixture of 3,5-dihydroxyaniline **105** (25 g, 0.2 mol), and sodium acetate (24.6 g, 0.3 mol), *N*,*N*-dimethylformamide (200 mL) and dioxane (50 mL). The mixture was stirred for 1 h at 20-25 °C, diluted with ethyl acetate (250 mL) and the precipitated sodium chloride was filtered off. The filtrate was concentrated under reduced pressure and the residue was crystallised from methanol to give white needles (41.30 g, 79%). M.p. 150-152 °C, *lit*[190] 152-153 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.09 (s, 2H, CH_2), 5.85 (t, *J* = 3.0 Hz,

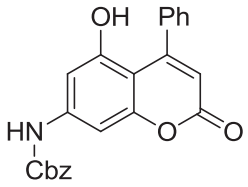
1H, ArH), 6.42 (d, *J* = 3.0 Hz, 2H, ArH), 7.34-7.39 (m, 5H, ArH), 9.14 (s, 2H, OH), 9.47 (s, 1H, NH).

Benzyl (5-hydroxy-4-methyl-2-oxo-chromen-7-yl) carbamate (197)



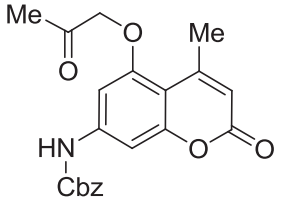
The coumarin **197** was prepared from benzyl (3,5-dihydroxyphenyl)carbamate **196** (5.0 g, 0.019 mol), ethyl acetoacetate (20 mL, 0.15 mol) and $TiCl_4$.THF complex (5.0 g, 0.019 mol) according to **GP-6**. The resulting crude product was crystallised from methanol to yield the *title compound* as a white solid (4.90 g, 78%). M.p. 223-224 °C (dec.); UV (MeOH): λ_{max} 215 nm (ε 26,682 $cm^{-1}M^{-1}$), 250 (7,865), 325 (14,430); IR (KBr): ν_{max} 3268 (br), 1704, 1662, 1552, 1509, 1424, 1333, 1096, 1061, 1006, 1029, 836, 766, 693, 575, 546, 463 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.48 (s, 3H, CH_3), 5.15 (s, 2H, CH_2), 5.93 (s, 1H, H3), 6.88 (d, *J* = 3.0 Hz, 1H, H6), 7.04 (d, *J* = 3.0 Hz, 1H, H8), 7.33-7.43 (m, 5H, ArH), 10.09 (s, 1H, NH), 10.66 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 23.75 (CH_3), 66.52 (CH_2), 101.03 (ArCH), 104.52 (ArCH), 110.87 (ArCH), 128.54 (ArCH), 128.63 (2 × ArCH), 128.84 (2 × ArCH), 136.60 (ArC), 142.97 (ArC), 151.03 (ArC), 153.43 (NHC=O), 154.95 (ArC), 155.92 (ArC), 156.79 (ArC), 160.04 (C=O); HRMS *m/z:* Calcd. for $C_{18}H_{15}NO_5$ $[M + 1]^+$ 326.0950. Found 326.1024.

Benzyl (5-hydroxy-2-oxo-4-phenyl-chromen-7-yl)carbamate (198)



The coumarin **198** was prepared from benzyl (3,5-dihydroxyphenyl)carbamate **196** (5.0 g, 0.019 mol), ethyl 3-oxo-3-phenylpropanoate (28.8 mL, 0.15 mol) and $TiCl_4$.THF complex (5.0 g, 0.019 mol) according to **GP-6**. The resulting crude product was crystallised from methanol to yield the *title compound* as a white solid (5.91 g, 79%). M.p. 200-201 °C (dec.); UV (CH_3CN): λ_{max} 215 nm (ε 30,650 $cm^{-1}M^{-1}$), 253 (10,178), 329 (10,449); IR (KBr): ν_{max} 3273 (br), 1686, 1613, 1542, 1498, 1426, 1374, 1288, 1150, 1011, 949, 841, 775, 729, 696 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 5.18 (s, 2H, CH_2), 5.86 (s, 1H, H3), 6.99-7.01 (m, 2H, H6 and H8), 7.33-7.47 (m, 10H, ArCH), 10.19 (bs, 1H, NH), 10.28 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 66.53 (CH_2), 96.83 (ArCH), 101.07 (ArCH), 102.93 (ArCH), 127.66 (2 × ArCH), 127.80 (2 × ArCH), 128.26 (ArCH), 128.54 (ArCH), 128.62 (2 × ArCH), 128.84 (2 × ArCH), 136.58 (ArC), 137.02 (ArC), 139.65 (ArC), 143.56 (ArC), 153.41 (NHC=O), 155.87 (ArC), 156.14 (ArC), 156.79 (ArC), 160.04 (C=O); HRMS *m/z:* Calcd. for $C_{23}H_{17}NO_5$ $[M]^+$ 387.1107. Found 387.1179.

Benzyl (4-methyl-2-oxo-5-(2-oxopropoxy)-chromen-7-yl)carbamate (199)

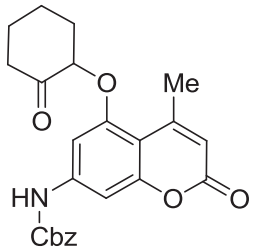


The acyl coumarin **199** was prepared from coumarin **197** (200 mg, 0.61 mmol), chloroacetone (0.1 mL, 0.61 mmol) and sodium acetate (50 mg, 0.61 mmol) in acetone (50 mL) according to **GP-7** to give the *title compound* as a white solid (175 mg, 74%). M.p. 265-266 °C; UV (MeOH): λ_{max} 213 nm (ε 16,878 $cm^{-1}M^{-1}$), 325 (7,391); IR (KBr): ν_{max} 3297, 2929, 2356, 2141, 1713, 1692, 1616, 1573, 1536,

1494, 1460, 1447, 1302, 1219, 1116, 1097, 1066, 1042, 1016, 990, 831, 735, 698, 564, 460 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.16 (s, 3H, $COCH_3$), 2.58 (s, 3H, CH_3), 4.87 (s, 2H, O-$\underline{CH_2}$Ph), 5.16 (s, 2H, O-CH_2), 6.04 (s, 1H, H3), 6.89 (bs, 1H, H6), 7.09 (bs, 1H, H8), 7.33-7.43 (m, 5H, ArH), 10.17 (s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 23.74 (CH_3), 26.73 ($COCH_3$), 66.63 (O-$\underline{CH_2}$Ph), 73.26 ($\underline{CH_2}CO$), 96.81 (ArCH), 98.44 (ArC), 101.02 (ArCH), 110.86 (ArCH), 128.55 (2 × ArCH), 128.63 (ArCH), 128.86 (2 × ArCH), 136.52 (ArC), 142.97 (ArC), 153.43 ($O\underline{CO}CH_2$), 154.23 (ArC), 155.88 (NHC=O), 159.81 (ArC), 160.22 (C=O), 202.86 ($CH_2\underline{CO}CH_3$); HRMS *m/z:* Calcd. for $C_{21}H_{19}NO_6$ $[M + 1]^+$ 382.1212. Found 382.1284.

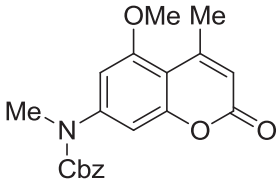
Benzyl (4-methyl-2-oxo-5-((2-oxocyclohexyl)oxy)-chromen-7-yl)carbamate (201)

The acyl coumarin **201** was prepared from coumarin **197** (200 mg, 0.61 mmol), 2-chlorocyclohexanone (0.2 mL, 0.61 mmol) and sodium acetate (50 mg, 0.61 mmol) in acetone (50 mL) according to **GP-7** to give the *title compound* as a white solid (178 mg, 68%). M.p. 242-244 °C; UV (MeOH): λ_{max} 214 nm (ε 33,124 $cm^{-1}M^{-1}$), 322 (7,374); IR (KBr): ν_{max} 3296, 3115, 2929, 2864, 2361, 1742, 1726, 1696, 1613, 1570, 1539, 1494, 1443, 1385, 1362, 1243, 1226, 1125, 1094, 1061, 1076, 907, 846, 832, 768, 738, 711 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.46-2.49 (m, 9H, cyclohexyl), 2.50 (s, 3H, CH_3), 5.15 (s, 2H, O-$\underline{CH_2}$Ph), 6.02 (s, 1H, H3), 6.78 (d, *J* = 3.0 Hz, 1H, H6), 7.09 (d, *J* = 3.0, 1H, H8), 7.32-7.42 (m, 5H, ArH), 10.07 (s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 23.39 (CH_3), 24.14 (CH_2), 27.50 (CH_2), 29.19 (CH_2), 40.01 (CH_2), 66.60 (O-$\underline{CH_2}$Ph), 81.27 (ArC), 98.14 (CH), 98.93 (ArCH), 105.42 (ArCH), 111.97 (ArCH), 128.50 (2 × ArCH), 128.55 (ArCH), 128.86 (2 × ArCH), 136.53 (ArC), 142.95



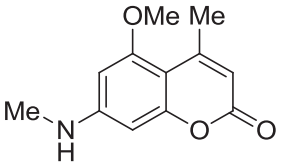
(ArC), 153.39 (CO), 154.34 (ArC), 155.82 (ArC), 156.77 (ArC), 159.93 (NHCO), 206.35 (CO); HRMS *m/z*: Calcd. for $C_{24}H_{23}NO_6$ $[M + 1]^+$ 422.1525. Found 422.1598.

Benzyl (5-methoxy-4-methyl-2-oxo-chromen-7-yl)(methyl)carbamate (203)



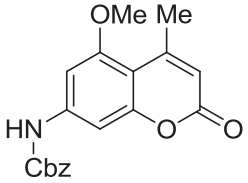
Dimethyl sulfoxide (25 mL) was added to powdered potassium hydroxide (70 mg, 1.22 mmol) and the mixture was stirred at room temperature for 10 min followed by the adiition of the coumarin **197** (200 mg, 0.61 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was cooled briefly in ice. Iodomethane (60 µL, 0.61 mmol) was added, and the reaction mixture stirred at room temperature for a further 1 h. After diluting with water, the mixture was extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water, dried ($MgSO_4$), and concentrated to yield the *title compound* as a white solid (129 mg, 59%). M.p. 132-134 °C; UV (MeOH): λ_{max} 215 nm (ε 29,757 $cm^{-1}M^{-1}$), 243 (10,378), 312 (14,473); IR (KBr): ν_{max} 3023, 2935, 2074, 1878, 1716, 1606, 1553, 1499, 1451, 1328, 1218, 1072, 1027, 965, 913, 837, 743, 705, 648, 624, 603, 556, 543, 471 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 3H, CH_3), 3.36 (s, 3H, N-CH_3), 3.78 (s, 3H, O-CH_3), 5.21 (s, 2H, CH_2), 6.05 (s, 1H, H3), 6.80 (s, 2H, H6 and H8), 7.36 (s, 5H, ArH) ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 24.06 (CH_3), 37.06 (N-CH_3), 55.70 (O-CH_3), 67.83 (CH_2), 103.74 (ArCH), 105.01 (ArCH), 107.98 (ArC), 113.62 (ArCH), 128.10 (2 × ArCH), 128.23 (ArCH), 128.50 (2 × ArCH), 135.90 (ArC), 146.23 (ArC), 153.73 (ArC), 154.68 (ArC), 155.36 (NHC=O), 157.91 (ArC), 160.48 (C=O); HRMS *m/z*: Calcd. for $C_{20}H_{19}NO_5$ $[M + 1]^+$ 354.1263. Found 354.1335.

5-Methoxy-4-methyl-7-(methylamino)-chromen-2-one (204)



Benzyl(5-methoxy-4-methyl-2-oxo-2H-chromen-7-yl)(methyl)carbamate **203** (200 mg, 0.5 mmol) was suspended in dichloromethane (50 mL) to this trifluoroacetic acid (15 mL) was added and stirred at room temperature for 5 h. solvents were evaporated using vacuum. The resulting solid was purified by column chromatography (SiO_2, 50% Ethyl acetate/hexane) to yield the *title compound* as a white solid (79 mg, 63%). M.p. 220-222 °C; UV (MeOH): λ_{max} 209 nm (ε 15,330 $cm^{-1}M^{-1}$), 246 (7,161), 364 (15,483); IR (KBr): ν_{max} 3343, 3090, 2982, 2926, 2359, 1809, 1681, 1622, 1592, 1565, 1496, 1477, 1454, 1430, 1241, 1215, 1196, 1098, 1056, 1029, 1039, 857, 834, 801, 769, 717, 624, 551, 515 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.38 (s, 3H, CH_3), 2.72 (d, J = 6.0 Hz, 3H, NH-CH_3), 3.77 (s, 3H, O-CH_3), 5.66 (s, 1H, H3), 5.97 (bs, 1H, H6), 6.06 (bs, 1H, H8), 6.61 (d, J = 3.0 Hz, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 23.95 (CH_3), 29.27 (N-CH_3), 56.00 (O-CH_3), 90.30 (ArCH), 92.46 (ArCH), 100.36 (ArC), 107.26 (ArCH), 153.67 (ArC), 154.85 (ArC), 157.55 (ArC), 159.22 (ArC), 160.66 (C=O); HRMS *m/z*: Calcd. for $C_{12}H_{13}NO_3$ $[M + 1]^+$ 220.0895. Found 220.0966.

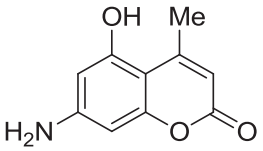
Benzyl-(5-methoxy-4-methyl-2-oxo-chromen-7-yl) carbamate (205)



To a mixture of coumarin **197** (200 mg, 0.61 mmol) and sodium hydrogen carbonate (103 mg, 1.22 mmol in ethanol (50 mL) was added iodomethane (60 µL, 0.61 mmol) and the mixture was stirred at room temperature for 24 h. Ethanol was evaporated under vacuum. The reaction mixture was diluted with water (100 mL) and extracted with ethyl

acetate (3 × 100 mL). The organic layer was washed with water, dried ($MgSO_4$), and concentrated to yield the *title compound* as a white solid (119 mg, 52%). M.p. 196-198 °C; UV (MeOH): λ_{max} 215 nm (ε 29,757 $cm^{-1}M^{-1}$), 243 (10,378), 312 (14,473); IR (KBr): ν_{max} 3298, 2946, 1711, 1627, 1608, 1577, 1531, 1499, 1452, 1439, 1383, 131356, 1307, 1193, 1116, 1090, 1058, 1026, 999, 837, 735, 695 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.48 (s, 3H, CH_3), 3.80 (s, 3H, O-CH_3), 5.17 (s, 2H, O-CH_2), 6.01 (s, 1H, H3), 7.07-7.09 (m, 2H, H6 and H8), 7.33-7.43 (m, 5H, ArH), 10.20 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 24.06 (CH_3), 55.70 (O-CH_3), 67.83 (CH_2), 103.74 (ArCH), 105.01 (ArCH), 107.98 (ArC), 113.62 (ArCH), 128.10 (2 × ArCH), 128.23 (ArCH), 128.50 (2 × ArCH), 135.90 (ArC), 146.23 (ArC), 153.73 (ArC), 154.68 (ArC), 155.36 (NHC=O), 157.91 (ArC), 160.48 (C=O); HRMS *m/z*: Calcd. for $C_{19}H_{17}NO_5$ $[M + 1]^+$ 340.1107. Found 340.1182.

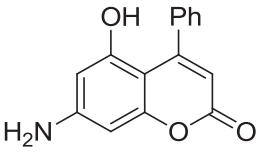
7-Amino-5-hydroxy-4-methyl-chromen-2-one (207)



The aminocoumarin **207** was prepared from benzyl (5-hydroxy-4-methyl-2-oxo-2H-chromen-7-yl) carbamate **197** (2.0 g, 6.15 mmol), 10% Pd/C catalyst (200 mg) in *N*,*N*-dimethylformamide (50 mL) according to **GP-8** to yield the *title compound* as a white solid (812 mg, 69%). M.p. 260-261 °C (dec.); UV (MeOH): λ_{max} 210 nm (ε 12,720 $cm^{-1}M^{-1}$), 271 (4,316), 355 (6,551); IR (KBr): ν_{max} 3349, 3221, 2926, 1670, 1611, 1609, 1459, 1396, 1289, 1216, 1178, 1092, 1073, 928, 829, 544, 463 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.40 (s, 3H, CH_3), 5.59 (s, 1H, H3), 5.89 (d, *J* = 3.0 Hz, 1H, H6), 5.92 (bs, 2H, NH_2), 5.97 (d, *J* = 3.0 Hz, 1H, H8), 10.11 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 23.76 (CH_3), 92.21 (ArCH), 97.01 (ArCH), 99.83 (ArC), 106.46 (ArCH), 153.18 (ArC), 155.48 (ArC),

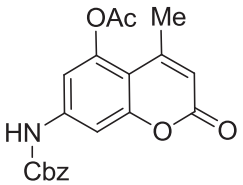
157.35 (ArC), 157.98 (ArC), 160.90 (C=O); HRMS *m/z*: Calcd. for $C_{10}H_9NO_3$ $[M + 1]^+$ 192.0582. Found 192.0656.

7-Amino-5-hydroxy-4-phenyl-chromen-2-one (208)



The aminocoumarin **208** was prepared from benzyl (5-hydroxy-4-methyl-2-oxo-2H-chromen-7-yl)carbamate **198** (2.0 g, 5.16 mmol), 10% Pd/C catalyst (200 mg) in *N*,*N*-dimethylformamide (50 mL) according to **GP-8** to yield the *title compound* as a brown solid (810 mg, 62%). M.p. 160-161 °C; UV (CH_3CN): λ_{max} 210 nm (ε 14,851 $cm^{-1}M^{-1}$), 257 (5,414), 352 (6,274); IR (KBr): ν_{max} 3273 (br), 1686, 1613, 1542, 1498, 1426, 1374, 1288, 1150, 1011, 949, 841, 775, 729, 696 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 5.45 (s, 1H, H3), 5.94 (s, 1H, H6), 6.03 (s, 1H, H8), 7.21 (m, 5H, ArH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 94.17 (ArCH), 94.21 (ArC), 98.20 (ArCH), 109.77 (ArCH), 128.48 (2 × ArCH), 128.65 (2 × ArCH), 128.79 (ArCH), 141.62 (ArC), 154.39 (ArC), 157.35 (ArC), 157.73 (ArC), 159.08 (ArC), 161.39 (C=O); HRMS *m/z*: Calcd. for $C_{15}H_{11}NO_3$ $[M + 1]^+$ 254.0739. Found 254.0810.

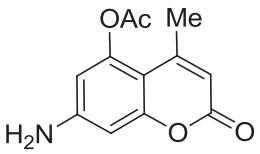
7-((Benzyloxy)carbonyl)amino)-4-methyl-2-oxo-chromen-5-yl acetate (209)



The acetyl coumarin **209** was prepared from benzyl (5-hydroxy-4-methyl-2-oxo-2H-chromen-7-yl) carbamate **197** (300 mg, 0.92 mmol), pyridine (5.0 mL) and acetic anhydride (2.0 mL) according to **GP-5**, to yield the *title compound* as yellow crystals (291 mg, 86%). M.p.180-182 °C; UV (MeOH) λ_{max} 212 nm (ε 22,533 $cm^{-1}M^{-1}$), 228 (10,753), 325

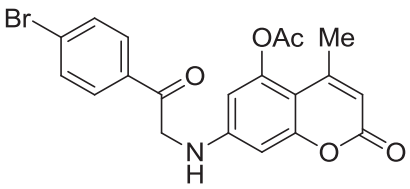
(8,477); IR (KBr) ν_{max} 3283, 1760, 1736, 1708, 1632, 1611, 1586, 1523, 1498, 1447, 1383, 1373, 1328, 1227, 1198, 1072, 1058, 1019, 1000, 899, 769, 733, 696 cm^{-1}; ^{1}H NMR (300 MHz, acetone-*d6*) δ 2.37 (s, 3H, $COCH_3$), 2.48 (s, 3H, CH_3), 5.19 (s, 2H, CH_2), 6.11 (s, 1H, H3), 7.33-7.45 (m, 7H, ArH), 9.27 (s, 1H, NH); ^{13}C NMR (75.6 MHz, acetone-*d6*): δ 20.32 ($CO\underline{C}H_3$), 21.56 (CH_3), 66.55 (CH_2), 102.91 (ArC), 102.97 (ArCH), 108.59 (ArC), 109.47 (ArCH), 114.13 (ArCH), 128.05 (2 x ArCH), 128.08 (ArCH), 128.34 (2 x ArCH), 136.35 (ArC), 142.09 (ArC), 148.66 (ArC), 150.92 (ArC), 153.01 (ArC), 155.46 (ArC), 158.83 (C=O), 168.70 ($O\underline{C}OCH_3$); HRMS *m/z*: Calcd. for $C_{20}H_{17}NO_6$ $[M + 1]^+$ 368.1056. Found 368.1129.

7-Amino-4-methyl-2-oxo-chromen-5-yl acetate (210)



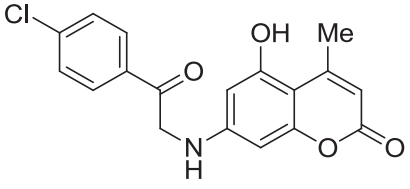
The aminocoumarin **210** was prepared from 7-((benzyloxy)carbonyl)amino)-4-methyl-2-oxo-2*H*-chromen-5-yl acetate **209** (250 mg, 0.68 mmol), 5% Pd/C (40 mg) in *N*,*N*-dimethylformamide (5.0 mL) according to **GP-8** to give the *title compound* as a brown solid (103 mg, 65%). M.p. 210-211 °C; UV (MeOH) λ_{max} 210 nm (ε 12,720 $cm^{-1}M^{-1}$), 271 (4,316), 355 (6,551); IR (KBr) ν_{max} 3448, 3346, 3219, 2927, 1782, 1701, 1686, 1635, 1612, 1595, 1544, 1507, 1458, 1388, 188, 1171, 1081, 1062, 1035, 1022, 1002, 887, 728, 485 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 6H, CH_3 and $COCH_3$), 5.85 (s, 1H, H3), 6.23 (d, *J* = 3.0 Hz, 1H, H6), 5.25 (bs, 2H, NH_2), 6.31 (d, *J* = 3.0 Hz, 1H, H8); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 21.52 ($CO\underline{C}H_3$), 22.26 (CH_3), 97.52 (ArCH), 102.86 (ArC), 106.28 (ArCH), 109.80 (ArCH), 149.07 (ArC), 152.29 (ArC), 152.58 (ArC), 156.56 (ArC), 160.12 (C=O), 160.90 ($O\underline{C}$=O); HRMS *m/z*: Calcd. for $C_{12}H_{11}NO_4$ $[M + 1]^+$ 234.0688. Found 234.0759.

7-((2-(4-Bromophenyl)-2-oxoethyl)amino)-4-methyl-2-oxo-chromen-5-yl acetate (211)



The anilinoketone **211** was prepared from the coumarin **210** (90 mg, 0.21 mmol), 4-bromophenacylbromide (58 mg, 0.21 mmol) and potassium carbonate (58 mg, 0.42 mmol) in acetone (100 mL) according to **GP-9** to give the *title compound* as a white solid (113 mg, 68%). M.p. 220-223°C (dec.); UV (MeOH): λ_{max} 209 nm (ε 38,738 $cm^{-1}M^{-1}$), 255 (24,238), 352 (16,473); IR (KBr): ν_{max} 3213, 1653, 1630, 1585, 1566, 1521, 1475, 1420, 1399, 1325, 1246, 1218, 1179, 1134, 1102, 1008, 964, 929, 884, 829, 835 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.28 (s, 3H, $COCH_3$), 2.44 (s, 3H, CH_3), 4.94 (s, 2H, N-CH_2), 5.57 (s, 1H, H3), 5.84 (d, *J* = 3.0, 1H, H6), 6.11 (d, *J* = 3.0 Hz, 1H, H8), 7.26-7.32 (m, 4H, ArH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 20.31 ($COCH_3$), 25.21 (CH_3), 72.17 (N-CH_2), 92.24 (ArCH), 93.81 (ArCH), 101.52 (ArC), 105.59 (ArCH), 127.35 (ArC), 131.23 (2 × ArCH), 131.34 (2 × ArCH), 132.61 (ArC), 152.24 (ArC), 154.00 (ArC), 156.29 (ArC), 156.81 (ArC), 160.52 (C=O), 192.43 ($CH_2\underline{CO}$); HRMS *m/z*: Calcd. for $C_{18}H_{16}BrNO_5$ $[M]^+$ 429.0212. Found 429.0218.

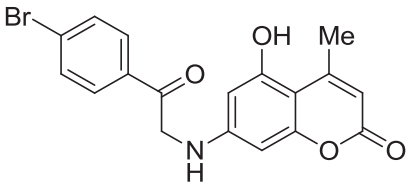
7-((2-(4-Chlorophenyl)-2-oxoethyl)amino)-5-hydroxy-4-methyl-chromen-2-one (213)



The anilinoketone **213** was prepared from the coumarin **207** (200 mg, 1.04 mmol), 4-chlorophenacylbromide (240 mg, 1.04 mmol) and potassium carbonate (145 mg, 1.04 mmol) in acetone (100 mL) according to **GP-9** to

give the *title compound* as a white solid (278 mg, 77%). M.p. 160-161°C; UV (MeOH): λ_{max} 208 nm (ε 24,764 $cm^{-1}M^{-1}$), 251 (15,092), 354 (8,986); IR (KBr): ν_{max} 3439, 3357, 3227, 2974, 2927, 1698, 1591, 1489, 1463, 1392, 1366, 1237, 1177, 1092, 1031, 1004, 971, 902, 824, 629, 528 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 2.56 (s, 3H, CH_3), 5.58 (s, 2H, N-CH_2), 5.71 (s, 1H, H3), 6.16 (d, *J* = 3.0 Hz, 1H, H6), 6.27 (d, *J* = 3.0, 1H, H8), 7.60 (d, *J* = 8.6 Hz, 2H, ArH), 8.06 (d, *J* = 8.6 Hz, 2H, ArH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 23.67 (CH_3), 70.52 (N-CH_2), 93.31 (ArCH), 94.84 (ArCH), 108.30 (ArCH), 127.26 (ArC), 127.17 (2 × ArCH), 127.43 (2 × ArCH), 130.56 (ArC), 140.19 (ArC), 153.81 (ArC), 157.36 (ArC), 157.45 (ArC), 160.41 (C=O), 163.97 (ArC), 192.20 (CH_2C=O); HRMS *m/z*: Calcd. for $C_{18}H_{14}ClNO_4$ $[M + 1]^+$ 344.0611 Found 344.0685.

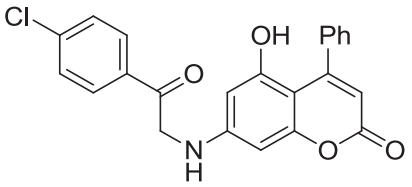
7-((2-(4-Bromophenyl)-2-oxoethyl)amino)-5-hydroxy-4-methyl-chromen-2-one (214)



The anilinoketone **214** was prepared from the coumarin **207** (200 mg, 1.04 mmol), 4-bromophenacylbromide (286 mg, 1.04 mmol) and potassium carbonate (145 mg, 1.04 mmol) in acetone (100 mL) according to **GP-9** to give the *title compound* as a white solid (298 mg, 73%). M.p. 230-231 °C; UV (CH_3CN): λ_{max} 227 nm (ε 34,713 $cm^{-1}M^{-1}$), 303 (13,080), 338 (10,681); IR (KBr): ν_{max} 3442, 3358, 3239, 3094, 2905, 2847, 2366, 1708, 1685, 1619, 1586, 1547, 1502, 1394, 1367, 1229, 1179, 1138, 1070, 1002, 1029, 913, 820, 700, 625, 578, 546, 493 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.43 (s, 3H, CH_3), 4.95 (s, 2H, N-CH_2), 5.58 (s, 1H, H3), 5.85 (d, *J* = 3.0, 1H, H6), 6.12 (d, *J* = 3.0 Hz, 1H, H8), 7.25-7.33 (m, 4H, ArH), ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 24.23 (CH_3),

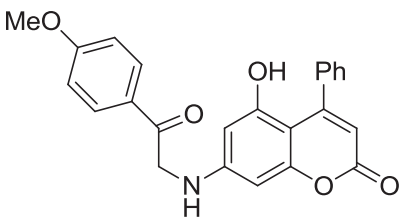
71.18 (N-CH_2), 93.23 (ArCH), 94.86 (ArCH), 100.53 (ArC), 107.53 (ArCH), 128.37 (ArC), 130.22 (2 × ArCH), 132.35 (2 × ArCH), 133.63 (ArC), 153.25 (ArC), 155.00 (ArC), 157.29 (ArC), 157.81 (ArC), 160.61 (C=O), 193.41 (CH_2<u>CO</u>); HRMS *m/z*: Calcd. for $C_{18}H_{14}BrNO_4Na$ $[M + Na]^+$ 410.0106. Found 410.0100.

7-((2-(4-Chlorophenyl)-2-oxoethyl)amino)-5-hydroxy-4-phenyl-chromen-2-one (215)



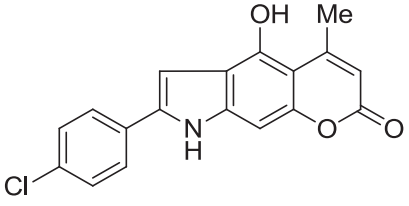
The anilinoketone **215** was prepared from the coumarin **208** (200 mg, 0.79 mmol), 4-chlorophenacylbromide (145 mg, 0.79 mmol) and potassium carbonate (109 mg, 0.79 mmol) in acetone (100 mL) according to **GP-9** to give the *title compound* as a white solid (221 mg, 69%). M.p. 234-235 °C; UV (MeOH): λ_{max} 209 nm (ε 26,446 $cm^{-1}M^{-1}$), 255 (16,564), 367 (8,586); IR (KBr): ν_{max} 3462, 3376, 3227, 3091, 1702, 1688, 1625, 1589, 1539, 1508, 1460, 1381, 1277, 1220, 1169, 1140, 1090, 1007, 960, 852, 814, 751, 732, 577, 561 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.00 (s, 2H, N-CH_2), 5.57 (s, 1H, ArH), 5.98 (d, *J* = 3.0 Hz, 1H, ArH), 76.14 (d, *J* = 3.0 Hz, 1H, ArH), 6.18 (bs, 1H, OH), 7.21-7.28 (m, 5H, ArH), 7.53 (d, *J* = 6.0 Hz, 2H, ArH), 7.75 (d, *J* = 6.0 Hz, 2H, ArH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 71.83 (CH_2), 95.92 (ArCH), 96.16 (ArCH), 116.63 (ArCH), 121.08 (ArC), 128.36 (2 × ArCH), 128.47 (2 × ArCH), 128.50 (ArCH), 129.62 (ArCH), 129.78 (2 × ArCH), 130.99 (ArCH), 131.43 (ArC), 132.90 (ArC), 136.86 (ArC), 144.69 (ArC), 151.03 (ArC), 152.65 (ArC), 155.79 (ArC), 159.53 (C=O), 195.01 (CH_2<u>CO</u>); HRMS *m/z*: Calcd. for $C_{23}H_{16}ClNO_4$ $[M + 1]^+$ 406.0768. Found 406.0846.

5-Hydroxy-7-((2-(4-methoxyphenyl)-2-oxoethyl)amino)-4-phenyl-chromen-2-one (216)



The anilinoketone **216** was prepared from the coumarin **208** (200 mg, 0.79 mmol), 4-methoxyphenacylbromide (180 mg, 0.79 mmol) and potassium carbonate (109 mg, 10.79 mmol) in acetone (100 mL) according to **GP-9** to give *title compound* as a white solid (245 mg, 77%). M.p. 130-132 °C; UV (MeOH): λ_{max} 210 nm (ε 24,902 $cm^{-1}M^{-1}$), 273 (17,162), 365 (8,581); IR (KBr): ν_{max} 3451, 3344, 2970, 2933, 2834, 1696, 1600, 1510, 1462, 1379, 1263, 1171, 1134, 1023, 962, 832, 774, 748, 699 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.82 (s, 3H, OCH_3), 4.95 (s, 2H, N-CH_2), 5.58 (s, 1H, H3), 5.85 (d, *J* = 3.0 Hz, 1H, H6), 6.12 (d, *J* = 3.0 Hz, 1H, H8), 6.18 (s, 1H, OH), 6.99 (d, *J* = 8.7 Hz, 2H, H2′, H6′), 7.25-7.33 (m, 5H, ArH), 7.74 (d, *J* = 8.7 Hz, 2H, H3′, H5′); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 56.00 (OCH_3), 70.56 (N-CH_2), 93.33 (ArCH), 94.85 (ArCH), 98.95 (ArC), 108.40 (ArCH), 114.33 (2 × ArCH), 127.16 (ArC), 127.47 (2 × ArCH), 127.53 (2 × ArCH), 128.02 (ArCH), 130.76 (2 × ArCH), 140.29 (ArC), 153.85 (ArC), 156.14 (ArC), 157.16 (ArC), 157.55 (ArC), 160.41 (C=O), 163.98 (ArC), 192.30 ($CH_2\underline{C}$=O); HRMS *m/z*: Calcd. for $C_{24}H_{19}NO_5$ $[M + 1]^+$ 402.1263. Found 402.1338.

6-(4-Chlorophenyl)-5-hydroxy-4-methylpyrano[3,2-*f*]indol-2-one (217)

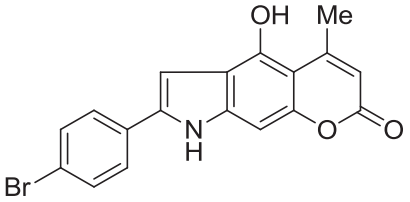


The pyranoindole **217** was prepared from 5-hydroxy-4-methyl-7-((2-oxo-2-phenylethyl)amino) chromone **213** (100 mg, 0.29 mmol) in

trifluoroacetic acid (10 mL) according to **GP-10** to give the *title compound* as a white solid (62 mg, 65%). M.p. 151-52 °C; UV (MeOH): λ_{max} 202 nm (ε 28,925 $cm^{-1}M^{-1}$), 226 (31,037), 300 (11,082), 345 (7,995); IR (KBr): ν_{max} 3493, 3375, 2964, 2929, 1742, 1712, 1627, 1603, 1575, 1525, 1487, 1441, 1365, 1328, 1213, 1171, 1118, 1090, 1056, 1016, 985, 889, 837, 731, 676, 650, 609, 557, 525 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 2.57 (s, 3H, CH_3), 6.27 (s, 1H, ArH), 6.97 (s, 1H, ArH), 7.02 (s, 1H, ArH), 7.25-7.47 (m, 4H, ArH); ^{13}C NMR (75.6 MHz, acetone-d_6): δ 20.90 (CH_3), 106.27 (ArC), 108.59 (ArCH), 114.67 (2 × ArCH), 115.23 (ArC), 128.52 (2 × ArCH), 128.84 (ArC), 130.93 (2 × ArCH), 133.90 (ArC), 141.21 (ArC), 143.91 (ArC), 151.20 (ArC), 155.01 (ArC), 160.14 (ArC), 160.53 (C=O); HRMS *m/z*: Calcd. for $C_{18}H_{12}ClNO_3Na$ $[M + Na]^+$ 348.0506. Found 348.0397.

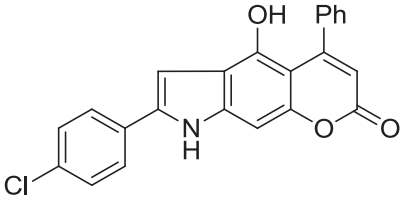
7-(4-Bromophenyl)-5-hydroxy-4-methylpyrano[3,2-*f*]indol-2-one (218)

The pyranoindole **218** was prepared from 5-hydroxy-4-methyl-7-((2-oxo-2-phenylethyl)amino)chromone **214** (200 mg, 0.51 mmol) in trifluoroacetic acid (10 mL) according to **GP-10** to give the *title compound* as a white solid (121 mg, 64%). M.p. 160-162 °C; UV (MeOH): λ_{max} 202 nm (ε 32,582 $cm^{-1}M^{-1}$), 227 (34,649), 306 (10,368), 347 (10,442); IR (KBr): ν_{max} 3482, 3340, 3217, 3084, 2926, 1705, 1630, 1572, 1525, 1481, 1444, 1293, 1170, 1133, 1071, 1012, 988, 913, 858, 828, 720, 646, 605, 556, 516 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H, CH_3), 6.24 (s, 1H, ArH), 6.71 (s, 1H, ArH), 6.73 (s, 1H, ArH), 7.23-7.46 (m, 4H, ArH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 21.74 (CH_3), 95.31 (ArCH), 98.18 (ArC), 106.82 (ArCH), 111.14 (ArCH), 118.91 (ArC), 131.29 (2 × ArCH), 131.34 (2 × ArCH),



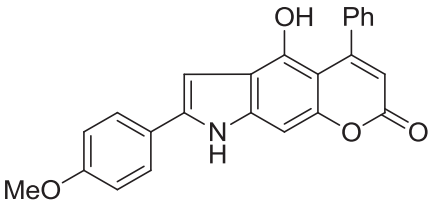
131.52 (ArC), 132.15 (ArC), 132.42 (ArC), 142.37 (ArC), 152.33 (ArC), 154.50 (ArC), 159.68 (ArC), 160.67 (C=O); HRMS *m/z*: Calcd. for $C_{18}H_{12}BrNO_3Na$ $[M + Na]^+$ 392.0001. Found 391.9892.

6-(4-Chlorophenyl)-5-hydroxy-4-phenylpyrano[3,2-*f*]indol-2-one (219)



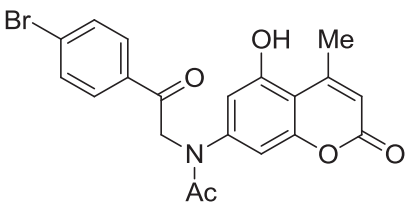
The pyranoindole **219** was prepared from 5-hydroxy-4-methyl-7-((2-oxo-2-phenylethyl)amino) chromone **215** (100 mg, 0.25 mmol) in trifluoroacetic acid (10 mL) according to **GP-10** to give the *title compound* as a white solid (59 mg, 62%). M.p. 259-261 °C; UV (MeOH): λ_{max} 202 nm (ε 26,122 $cm^{-1}M^{-1}$), 235 (22,678), 308 (7,391); IR (KBr): ν_{max} 3298, 2928, 2850, 1743, 1703, 1620, 1604, 1574, 1488, 1384, 1341, 1206, 1166, 1091, 1059, 871, 834, 704, 650 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 6.22 (s, 1H, H3), 7.38-7.62 (m, 11H, ArH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 105.55 (ArC), 111.37 (2 × ArCH), 116.61 (ArCH), 119.36 (ArC), 121.09 (ArC), 128.36 (2 × ArCH), 128.48 (2 × ArCH), 128.50 (2 × ArCH), 129.63 (ArC), 129.78 (ArCH), 131.00 (2 × ArCH), 132.90 (ArC), 136.87 (ArC), 144.69 (ArC), 151.03 (ArC), 152.05 (ArC), 152.65 (ArC), 159.53 (C=O); HRMS *m/z*: Calcd. for $C_{23}H_{14}ClNO_3Na$ $[M + Na]^+$.410.0662. Found 410.0553.

5-Hydroxy-7-(4-methoxyphenyl)-4-phenylpyrano[3,2-*f*]indol-2-one (220)



The pyranoindole **220** was prepared from 5-hydroxy-4-methyl-7-((2-oxo-2-phenylethyl)amino) chromone **216** (100 mg, 0.24 mmol) in trifluoroacetic acid (10 mL) according to **GP-10** to give the *title compound* as a white solid (61 mg, 64%). M.p. 160-161 °C (from CH_2Cl_2); UV (MeOH): λ_{max} 202 nm (ε 32,401 $cm^{-1}M^{-1}$), 223 (27,307), 366 (6,089); IR (KBr): ν_{max} 3445, 3372, 2926, 2844, 1741, 1710, 1622, 1581, 1510, 1464, 1444, 1382, 1254, 1176, 1119, 1031, 950, 855, 839, 702, 661 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.81 (s, 3H, OCH_3), 6.28 (s, 1H, H3), 6.98 (s, 1H, H6), 7.01 (s, 1H, H8), 7.26-7.48 (m, 9H, ArH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 56.46 (OCH_3), 104.10 (ArCH), 104.36 (ArCH), 114.54 (ArC), 115.09 (ArCH), 115.68 (ArCH), 119.75 (ArC), 121.10 (ArC), 127.96 (2 × ArCH), 128.11 (2 × ArCH), 129.40 (2 × ArCH), 130.75 (2 × ArCH), 131.93 (ArC), 136.60 (ArC), 142.25 (ArC), 150.44 (ArC), 152.75 (ArC), 153.09 (ArC), 160.14 (ArC), 160.53 (C=O); HRMS *m/z*: Calcd. for $C_{24}H_{17}NO_4$ $[M + 1]^+$ 384.1158. Found 384.1225.

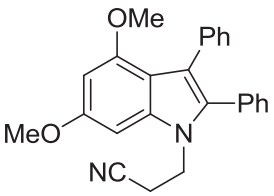
7-((2-(4-Bromophenyl)-2-oxoethyl)amino)-5-hydroxy-4-methyl-chromen-2-one (223)



The acetyl coumarin **233** was prepared from the coumarin **214** (150 mg, 0.38 mmol), pyridine (3.0 mL) and acetic anhydride (2.0 mL) according to **GP-5** to give the *title compound* as a pale yellow solid (103 mg, 62%). M.p. 224-225 °C; UV (MeOH): λ_{max} 228 nm (ε 33,713 $cm^{-1}M^{-1}$),

302 (14,080), 337 (11,681); IR (KBr): ν_{max} 3443, 3359, 3238, 3094, 2905, 2847, 2366, 1708, 1685, 1620, 1586, 1548, 1501, 1393, 1367, 1228, 1178, 1138, 1071, 1002, 1028, 913, 821, 702, 624, 575, 547, 494 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.04 (s, 3H, $COCH_3$), 2.42 (s, 3H, CH_3), 4.99 (s, 2H, N-CH_2), 5.59 (s, 1H, H3), 5.87 (d, *J* = 3.0 Hz, 1H, H6), 6.14 (d, *J* = 3.0 Hz, 1H, H8), 7.26-7.34 (m, 4H, ArH), ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 22.60 ($COCH_3$), 24.23 (CH_3), 52.02 (N-CH_2), 93.23 (ArCH), 94.86 (ArCH), 100.53 (ArC), 107.53 (ArCH), 128.37 (ArC), 130.22 (2 × ArCH), 132.35 (2 × ArCH), 133.63 (ArC), 151.07 (ArC), 153.25 (ArC), 155.00 (ArC), 157.29 (ArC), 157.81 (ArC), 167.62 (C=O), 191.04 ($CH_2\underline{CO}$); HRMS *m/z*: Calcd. for $C_{20}H_{16}BrNO_5$ $[M]^+$ 429.0212. Found 429.0224.

3-(4,6-Dimethoxy-2,3-diphenyl-indol-1-yl)propanenitrile (267)

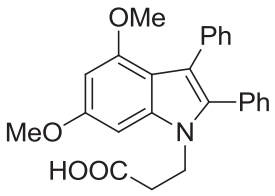


A mixture of 4,6-dimethoxy-2,3-diphenylindole **76** (300 mg, 0.91 mmol), acrylonitrile (0.2 mL, 3.6 mmol) and tetrabutylammonium hydroxide (2 drops) was stirred at room temperature for 5 min followed by heating under reflux for 10 min. Evaporation of excess acrylonitrile gave a yellow solid which was passed through a pad of SiO_2 eluting with 40-50% dichloromethane/hexane to give the *title compound* as a white solid (250 mg, 71%). M.p. 199-200 °C; UV (CH_3CN): λ_{max} 224 nm (ε 22,843 cm^{-1} M^{-1}), 243 (16,754), 303 (7,834); IR (KBr): ν_{max}: 2957, 2249, 1666, 1605, 1583, 1503, 1454, 1377, 1261, 1214, 1151, 1062, 1047, 979, 941, 810, 756, 704 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 2.79 (t, *J* = 6.0 Hz, 2H, CH_2), 3.68 (s, 3H, OMe), 3.88 (s, 3H, OMe), 4.41 (t, *J* = 6.0 Hz, 2H, CH_2), 6.29 (bs, 1H, H5), 6.85 (bs, 1H, H7), 7.06-7.37 (m, 10H, ArCH); ^{13}CNMR (75.6MHz, acetone-d_6): δ 17.24 (CH_2), 39.39 (CH_2), 54.36 (OMe),

54.96 (OMe), 85.98 (ArCH), 92.52 (ArCH), 117.34 ($CH_2\underline{C}N$), 125.12 (ArCH), 126.45 (2 × ArCH), 127.87 (ArCH), 128.16 (2 × ArCH), 131.26 (2 × ArCH), 131.55 (2 × ArCH), 131.71 (ArC), 134.95 (ArC), 135.77 (ArC), 137.81 (ArC), 139.01 (ArC), 154.93 (ArC), 157.90 (2 × ArC); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{25}H_{22}N_2O_2$ $[M + 1]^+$ 383.1681. Found 383.1613.

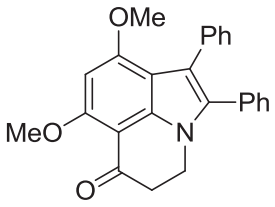
3-(4,6-Dimethoxy-2,3-diphenyl-indol-1-yl)propanoic acid (268)

3-(4,6-Dimethoxy-2,3-diphenyl-1H-indol-1-yl)propanenitrile **267** (200 mg, 0.52 mmol) was heated under reflux with 20% sodium hydroxide in ethanol (25 mL) for 2 h. Evaporation of ethanol and acidification of reaction mixture with 1 N HCl (25 mL) gave a white precipitate, which was filtered and washed with water till neutral. Recrystallization from ethanol gave the *title compound* as a white solid (160 mg, 76%).



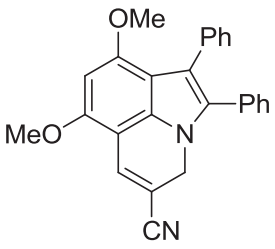
M.p. >300 °C; UV (MeOH): λ_{max} 203 nm (ε 32,240 cm^{-1} M^{-1}), 223 (28,190), 311 (8,573); IR (KBr): ν_{max}: 3469, 3062, 2924, 2841, 1714, 1604, 1585, 1501, 1456, 1401, 1370, 1332, 1260, 1150, 1062, 1048, 980, 939, 806, 760, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (t, *J* = 6.0 Hz, 2H, CH_2), 3.64 (s, 3H, OMe), 3.83 (s, 3H, OMe), 4.27 (t, *J* = 6.0 Hz, 2H, CH_2), 6.20 (d, *J* = 3.0 Hz, 1H, H5), 6.44 (d, *J* = 3.0 Hz, 1H, H7), 7.05-7.25 (m, 10H, ArCH); ^{13}CNMR (75.6MHz, acetone-d_6): δ 34.00 (CH_2), 39.73 (CH_2), 55.65 (OMe), 56.24 (OMe), 85.91 (ArCH), 92.85 (ArCH), 125.74 (ArCH), 127.17 (2 × ArCH), 128.31 (ArCH), 128.78 (2 × ArCH), 131.61 (ArC), 131.82 (2 × ArCH), 131.26 (2 × ArCH), 130.55 (2 × ArC), 130.71 (ArC), 133.95 (ArC), 135.77 (ArC), 136.81 (ArC), 154.93 (ArC), 163.40 (C=O); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{25}H_{23}NO_4Na$ $[M + Na]^+$ 424.1627. Found 424.1520.

7,9-Dimethoxy-1,2-diphenyl-4H-pyrrolo[3,2,1-*ij*]quinolin-6-one (269)



3-(4,6-Dimethoxy-2,3-diphenyl-1H-indol-1-yl)propanoic acid **268** (120 mg, 0.3 mmol) was heated under reflux with polyphosphoric acid for 1 h. After cooling the reaction mixture to room temperature, water (50 mL) was added and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, 10% Ethyl acetate/hexane) to give the *title compound* as a white solid (35 mg, 30%). M.p. 260-261 °C; UV (MeOH): λ_{max} 204 nm (ε 21,486 cm^{-1} M^{-1}), 260 (11,451), 331 (5,438); IR (KBr): ν_{max}: 3514, 3056, 2837, 1737, 1650, 1600, 1582, 1466, 1352, 1252, 1216, 1137, 1057, 974, 802, 761, 745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (t, *J* = 6.0 Hz, 2H, CH_2), 3.89 (s, 3H, OMe), 4.07 (s, 3H, OMe), 4.23 (t, *J* = 6.0 Hz, 2H, CH_2), 6.26 (s, 1H, H5), 7.19-7.30 (m, 10H, ArCH); ^{13}CNMR (75.6MHz, acetone-d_6): δ 39.30 (CH_2), 42.77 (CH_2), 55.82 (OMe), 57.01 (OMe), 88.50 (ArCH), 126.23 (ArCH), 127.17 (ArC), 127.60 (2 × ArCH), 128.34 (ArCH), 128.83 (2 × ArCH), 131.18 (2 × ArCH), 131.67 (2 × ArCH), 131.26 (ArC), 131.67 (ArC), 135.14 (ArC), 135.83 (ArC), 141.88 (ArC), 159.05 (2 × ArC), 160.69 (ArC), 190.03 (C=O); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{25}H_{21}NO_3Na$ $[M + Na]^+$ 406.1521. Found 406.1414.

7,9-Dimethoxy-5,6-diphenyl-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carbonitrile (279)

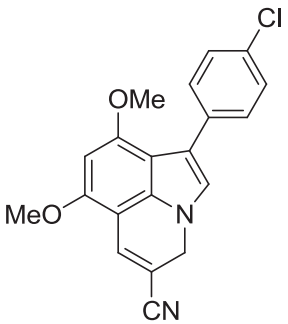


The pyrroloquinoline **279** was prepared from indole-7-carbaldehyde[32] **84** (100 mg, 0.28 mmol), acrylonitrile (0.31 mL, 5.6 mmol) and tetrabutylammonium hydroxide (2 drops)

according to **GP-11** to give the *title compound* as a yellow solid (90 mg, 82%). M.p. 171-173 °C; UV (CH_3CN): λ_{max} 249 nm (ε 27,910 cm^{-1} M^{-1}), 394 (16,072); IR (KBr): ν_{max}: 2917, 2847, 2204, 1590, 1516, 1468, 1435, 1363, 1270, 1213, 1063, 979, 804, 701, 530. cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H, OMe), 3.91 (s, 3H, OMe), 4.93 (s, 2H, CH_2), 6.06 (s, 1H, ArCH), 7.14-7.34 (m, 10H, ArCH), 7.53 (s, 1H, CH); ^{13}CNMR (75.6 MHz, $CDCl_3$): δ 45.45 (CH_2), 55.31 (OMe), 56.39 (OMe), 88.13 (ArCH), 96.76 (ArC), 109.44 (ArC), 116.69 (ArC), 118.90 (CN), 125.70 (ArCH), 127.09 (2 × ArCH), 127.38 (2 × ArCH), 128.02 (2 × ArCH), 128.24 (ArCH), 128.37 (ArCH), 128.46 (ArCH), 130.35 (ArC), 130.62 (ArC), 134.34 (ArC), 135.00 (ArC), 135.05 (ArC), 142.61 (CH), 154.08 (ArC), 158.73 (ArC); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{26}H_{20}N_2O_2$ $[M + 1]^+$ 393.1525. Found 393.1575.

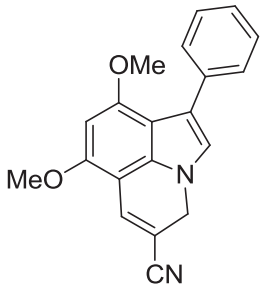
6-(4-Chlorophenyl)-7,9-dimethoxy-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carbonitrile (280)

The pyrroloquinoline **280** was prepared from indole-7-carbaldehyde[191] **174** (100 mg, 0.31 mmol), acrylonitrile (0.35 mL, 6.3 mmol) and tetrabutylammonium hydroxide (2 drops) according to **GP-11** to give the *title compound* as a yellow solid (92 mg, 82%). M.p. 120-122 °C; UV (CH_3CN): λ_{max} 234 nm (ε 25,865cm^{-1} M^{-1}), 264 (20,300), 390 (16,065); IR (KBr) ν_{max}: 935, 2844, 2201, 1637, 1595, 1535, 1492, 1463, 1363, 1267, 1206, 1067, 969, 834, 789, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H, OMe), 3.90 (s, 3H, OMe), 5.14 (s, 2H, CH_2), 6.05 (s, 1H, ArCH), 6.83 (s, 1H, ArCH), 7.30-7.34 (m, 2H, ArCH), 7.47-7.50 (m, 3H, ArCH and CH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 46.06 (CH_2), 55.28 (OMe),



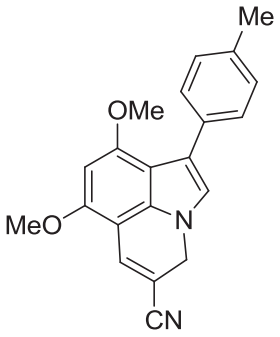
56.32 (OMe), 87.79 (ArCH), 96.33 (ArC), 98.34 (ArC), 107.94 (ArC), 118.70 (CN), 188.94 (ArC), 122.45 (ArC), 127.91 (2 × ArCH), 130.08 (2 × ArCH), 131.89 (ArC), 133.7 (ArC), 134.02 (ArCH), 142.35 (CH), 154.35 (ArC), 158.57 (ArC); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{20}H_{15}ClN_2O_2$ $[M + 1]^+$ 351.0822. Found 351.0763.

7,9-Dimethoxy-6-phenyl-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carbonitrile (281)



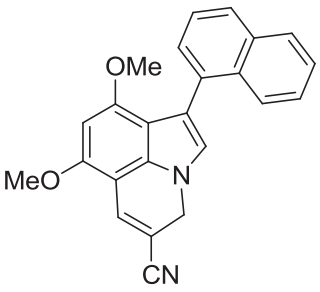
The pyrroloquinoline **281** was prepared from indole-7-carbaldehyde[192] **272** (100 mg, 0.35 mmol), acrylonitrile (0.4 mL, 0.7 mmol) and tetrabutylammonium hydroxide (2 drops) according to **GP-11** to give the *title compound* as a yellow solid (85 mg, 75%). M.p. 120-121 °C (from CH_2Cl_2); UV (MeOH): λ_{max} 265 nm (ε 19,212 cm^{-1} M^{-1}), 395 (14,662); IR (KBr) ν_{max}: 2936, 2846, 2200, 1637, 1596, 1515, 1264, 1205, 1066, 794, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 3H, OMe), 3.99 (s, 3H, OMe), 5.15 (s, 2H, CH_2), 6.05 (s, 1H, ArCH), 6.85 (s, 1H, ArCH), 7.26-7.49 (m, 6H, ArCH and CH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 46.06 (CH_2), 55.27 (OMe), 56.32 (OMe), 87.87 (ArCH), 118.81 (CN), 120.10 (ArC), 122.10 (ArC), 126.04 (ArC), 127.80 (2 × ArCH), 128.13 (ArC), 128.72 (ArCH), 128.90 (2 × ArCH), 134.10 (ArCH), 134.72 (ArC), 135 (ArC), 142.02 (CH), 146.13 (ArC), 157.04 (ArC); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{20}H_{16}N_2O_2$ $[M + 1]^+$ 317.1212. Found 317.1268.

7,9-Dimethoxy-6-p-tolyl-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carbonitrile (282)



The pyrroloquinoline **282** was prepared from indole-7-carbaldehyde[193] **270** (150 mg, 0.5 mmol), acrylonitrile (0.2 mL, 10 mmol) and tetrabutylammonium hydroxide (2 drops) according to **GP-11** to give the *title compound* as a yellow solid (135 mg, 83%). M.p. 145-146 °C; UV (CH_3CN): λ_{max} 252 nm (ε 28,373 cm^{-1} M^{-1}), 338 (18,467), 374 (12,655); IR (KBr) ν_{max}:936, 2844, 2203, 1636, 1593, 1518, 1469, 1360, 1288, 1203, 1060, 869, 824, 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 1H, CH_3), 3.80 (s, 3H, OMe), 3.83 (s, 3H, OMe), 5.06 (s, 2H, CH_2), 5.96 (s, 1H, ArCH), 6.74 (s, 1H, ArCH), 7.12 (d, *J* = 9.0 Hz, 2H, ArH), 7.41 (d, *J* = 9.0 Hz, 2H, ArH), 7.51 (s, 1H, CH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 21.55 (CH_3), 46.53 (CH_2), 55.76 (OMe), 56.80 (OMe), 88.29 (ArCH), 96.70 (ArC), 98.81 (ArC), 108.65 (ArC), 119.34 (CN), 120.51 (ArC), 122.65 (ArCH), 129.05 (2 × ArCH), 129.27 (2 × ArCH), 134.59 (ArCH), 136.01 (ArC), 136.17 (ArC), 142.06 (CH), 154.74 (ArC), 158.57 (ArC); MS (TOF-ESI) *m/z*: Calcd. for $C_{21}H_{18}N_2O_2$ $[M + 1]^+$ 331.13. Found 331.15; Anal. Calcd. for C, 76.34; H, 5.49; N, 8.48. Found. C, 76.41; H, 5.55; N, 8.22.

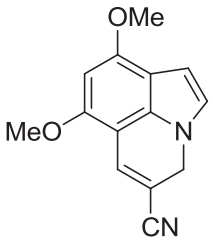
7,9-Dimethoxy-1-(naphthalen-1-yl)-4H-pyrrolo[3,2,1-*ij*]quinoline-5-carbonitrile (283)



The pyrroloquinoline[194] **283** was prepared from indole-7-carbaldehyde **271** (100 mg, 0.3 mmol), acrylonitrile (0.33 mL, 6.0 mmol) and tetrabutylammonium

hydroxide (2 drops) according to **GP-11** to give the *title compound* as a yellow solid (89 mg, 80%). M.p. 129-131 °C (from CH_2Cl_2); UV (MeOH) λ_{max} 254 nm (ε 12,736 cm^{-1} M^{-1}), 393 (9,699); IR (KBr):ν_{max}: 2921, 2148, 2201, 1594, 1515, 1463, 1364, 1264, 1215, 1065, 794, 779, 729 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.51 (s, 3H, OMe), 3.90 (s, 3H, OMe), 5.21 (s, 2H, CH_2), 5.99 (s, 1H, ArCH), 6.85 (s, 1H, ArCH), 7.33-7.55 (m, 5H, ArCH), 7.80-9.93 (m, 3H, ArCH and CH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 46.16 (CH_2), 55.14 (OMe), 56.35 (OMe), 88.02 (ArCH), 96.38 (ArC), 110.28 (ArC), 118.87 (CN), 123.53 (ArC), 124.97 (ArC), 125.09 (ArCH), 125.33 (ArCH), 126.75 (ArCH), 127.12 (2 × ArCH), 127.77 (2 × ArCH), 132.86 (ArC), 133.01 (ArC), 133.41 (ArC), 134.20 (ArCH), 135.06 (ArC), 142.06 (CH), 154.41 (ArC), 158.77 (ArC); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{24}H_{18}N_2O_2$ $[M]^+$ 366.1368. Found 366.1318.

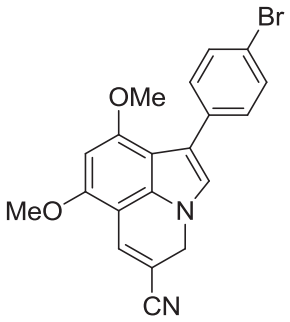
7,9-Dimethoxy-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carbonitrile (284)



The pyrroloquinoline **284** was prepared from indole-7-carbaldehyde[32] **276** (100 mg, 0.48 mol) and acrylonitrile (0.54 mL, 9.7 mmol) was added tetrabutylammonium hydroxide (2 drops) according to **GP-11** to give the *title compound* as a yellow solid (83 mg, 70%). M.p. 139-141 °C; UV (MeOH): λ_{max} 250 nm (ε 16,672 cm^{-1} M^{-1}), 389 (18,840); IR (KBr) ν_{max}: 2940, 2848, 2204, 1638, 1594, 1518, 1466, 1363, 1261, 1261, 1064, 957, 801, 711, 527 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H, OMe), 3.96 (s, 3H, OMe), 5.12 (s, 2H, CH_2), 6.01 (s, 1H, ArCH), 6.47 (s, 1H, ArCH), 7.46 (s, 1H, ArCH), 7.49 (s, 1H, CH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 46.16 (CH_2), 55.59 (OMe), 56.37 (OMe), 87.92 (ArCH), 96.38 (ArC), 98.38 (ArC), 100.82 (ArCH), 110.37 (ArC), 118.91 (CN), 123.71 (ArCH), 134.23 (ArC), 142.60 (CH), 154.20 (ArC),

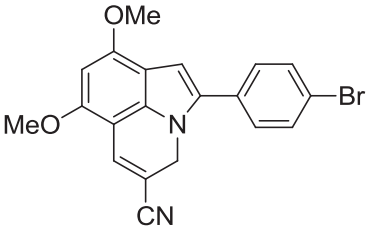
157.66 (ArC); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{14}H_{12}N_2O_2$ $[M]^+$ 240.899. Found 240.0848.

6-(4-Bromophenyl)-7,9-dimethoxy-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carbonitrile (285)



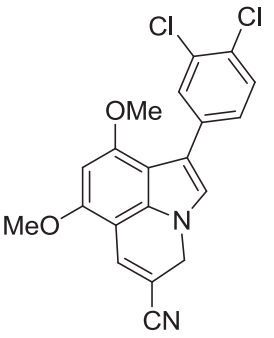
The pyrroloquinoline **285** was prepared from indole-7-carbaldehyde[122] **273** (100 mg, 0. 25 mmol), acrylonitrile (0.28 mL, 5 mmol) and tetrabutylammonium hydroxide (2 drops) according to **GP-11** to give the *title compound* as a bright yellow solid (92 mg, 84%). M.p. 190-192 °C; UV (MeOH): λ_{max} 265 nm (ε 23,600 cm^{-1} M^{-1}), 395 (19,069); IR (KBr): ν_{max} 2932, 2845, 2197, 1636, 1594, 1534, 1265, 1204, 1067, 967, 834, 789, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H, OMe), 3.90 (s, 3H, OMe), 5.15 (s, 2H, CH_2), 6.05 (s, 1H, ArCH), 6.85 (s, 1H, ArCH), 7.26 (s, 1H, ArCH), 7.44-7.48 (m, 4H, ArCH and CH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 46.07 (CH_2), 55.28 (OMe), 56.32 (OMe), 87.98 (ArCH), 96.33 (ArC), 98.34 (ArC), 117.30 (CN), 122.43 (ArC), 124.20 (ArC), 130.45 (2 × ArCH), 130.85 (2 × ArCH), 132.13 (ArC), 133.7 (ArCH), 134.04 (ArCH), 136.01 (ArC), 142.60 (CH), 154.53 (ArC), 158.57 (ArC); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{20}H_{15}BrN_2O_2[M + 1]^+$ 395.0317. Found 395.0249.

5-(4-Bromophenyl)-7,9-dimethoxy-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carbonitrile (286)



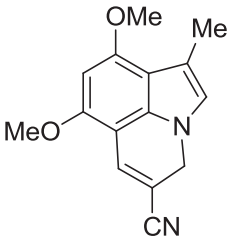
The pyrroloquinoline **286** was prepared from indole-7-carbaldehyde[32] **274** (100 mg, 0.25 mol) acrylonitrile (0.28 mL, 0.5 mol) and tetrabutylammonium hydroxide (2 drops) according to **GP-11** to give the *title compound* as a yellow solid (72 mg, 80%). M.p. 180-182 °C; UV (MeOH): λ_{max} 247 nm (ε 24,253 cm^{-1} M^{-1}), 323 (11,455), 387 (12,245); IR (KBr) ν_{max}: 2918, 2205, 1637, 1606, 1516, 1466, 1393, 1377, 1254, 1216, 1161, 1049, 975, 821, 776. cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H, OMe), 3.91 (s, 3H, OMe), 5.01 (s, 2H, CH_2), 5.98 (s, 1H, ArCH), 6.45 (s, 1H, ArCH), 7.23-7.26 (m, 2H, ArCH), 7.42 (m, 1H, ArCH), 7.49-7.52 (m, 2H, ArCH), 7.51 (s, 1H, CH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 44.87 (CH_2), 54.71 (OMe), 55.44 (OMe), 87.24 (ArCH), 95.78 (ArC), 97.90 (ArC), 99.71 (ArCH), 109.99 (ArC), 121.26 (CN), 128.60 (2 × ArCH), 129.58 (ArC), 131.01 (2 × ArCH), 133.19 (ArC), 135.25 (ArC), 136.14 (ArC), 142.02 (CH), 163.32 (ArC), 156.49 (ArC); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{20}H_{15}BrN_2O_2$ $[M + 1]^+$ 395.0317 Found 395.0229.

6-(3,4-Dichlorophenyl)-7,9-dimethoxy-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carbonitrile (287)



The pyrroloquinoline **287** was prepared from indole-7-carbaldehyde[194] **275** (100 mg, 0.28 mmol), acrylonitrile (0.32 mL, 5.6 mmol) and tetrabutylammonium hydroxide (2 drops) according to **GP-11** to give the *title compound* as a yellow solid (93 mg, 84%). M.p. 211-212 °C; UV (MeOH) λ_{max} 239 nm (ε 28,682 cm^{-1} M^{-1}), 391 (20,443); IR (KBr) ν_{max}: 2916, 2847, 2196, 1637, 1600, 1572, 1518, 1485, 1470, 1448, 1434, 1269, 1182, 1105, 1028, 977, 881, 791, 526 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 6H, 2 × OMe), 5.07 (s, 2H, CH_2), 5.99 (s, 1H, ArCH), 6.81 (s, 1H, ArCH), 7.32 (s, 2H, ArCH), 7.41-7.42 (m, 1H, ArCH), 7.50 (s, 1H, CH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 46.07 (CH_2), 55.31 (OMe), 56.33 (OMe), 88.10 (ArCH), 96.33 (ArC), 98.34 (ArC), 104.03 (ArC), 117.31 (CN), 122.74 (ArC), 127.74 (2 × ArCH), 129.61 (ArCH), 130.59 (ArC), 133.98 (ArCH), 134.91 (ArC), 135.12 (ArC), 136.05 (ArC), 142.63 (CH), 154.31 (ArC), 157.10 (ArC); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{20}H_{14}Cl_2N_2O_2$ $[M + 1]^+$ 385.0432. Found 385.0343.

7,9-Dimethoxy-6-methyl-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carbonitrile (288)

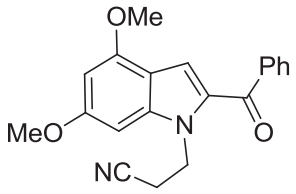


The pyrroloquinoline **288** was prepared from indole-7-carbaldehyde[32] **278** (100 mg, 0.3 mmol), acrylonitrile (0.91 mL, 9.1 mmol) and tetrabutylammonium hydroxide (2 drops) according to **GP-11** to give the *title compound* as a yellow solid (81 mg, 70%). M.p. 145-147 °C; UV (MeOH): λ_{max} 245 nm (ε 23,600 cm^{-1} M^{-1}),

334 (19,069); IR (KBr) ν_{max}: 2939, 2846, 2248, 2223, 1642, 1600, 1460, 1430, 1214, 1171, 1095, 993, 951cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3), 3.87 (s, 3H, OMe), 3.91 (s, 3H, OMe), 5.05 (s, 2H, CH_2), 5.93 (s, 1H, ArCH), 6.49 (s 1H, ArCH), 7.43 (s, 1H, CH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 11.50 (CH_3), 45.92 (CH_2), 55.24 (OMe), 56.35 (OMe), 86.90 (ArCH), 96.28 (ArC), 98.26 (ArC), 110.28 (ArC), 113.45 (ArC), 117.32 (CN), 121.25 (ArCH), 134.23 (ArC), 142.60 (CH), 154.15 (ArC), 159.30 (ArC); MS (TOF-ESI) *m/z:* Calcd. for $C_{15}H_{14}N_2O_2$ $[M + 1]^+$ 255.10. Found 255.12; Anal. Calcd. for C, 70.85; H, 5.55; N, 11.02. Found. C, 70.93; H, 5.65; N, 10.88.

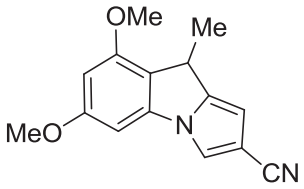
3-(2-Benzoyl-4,6-dimethoxy-1H-indol-1-yl)propanenitrile (290)

The cyanoethylindole **290** was prepared from indole[122] **289** (100 mg, 0.29 mol) acrylonitrile (0.28 mL, 0.5 mol) and tetrabutylammonium hydroxide (2 drops) according to **GP-11** to give the *title compound* as a white solid (83 mg, 70%). M.p. 230-232 °C; UV (CH_3CN): λ_{max} 222 nm (ε 24,843 cm^{-1} M^{-1}), 242 (15,751), 302 (7,734); IR (KBr): ν_{max}: 2958, 2248, 1676, 1615, 1583, 1403, 1444, 1387, 1271, 1214, 1141, 1062, 1037, 979, 931, 812, 754, 702 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 2.77 (t, J = 6.0 Hz, 2H, CH_2), 3.69 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.42 (t, J = 6.0 Hz, 2H, CH_2), 6.28 (bs, 1H, H5), 6.86 (bs, 1H, H7), 7.06-7.57 (m, 6H, ArCH); ^{13}CNMR (75.6MHz, acetone-d_6): δ 17.27 (CH_2), 39.42 (CH_2), 54.37 (OMe), 54.97 (OMe), 85.99 (ArCH), 92.54 (ArCH), 117.33 ($CH_2\underline{C}N$), 125.13 (ArCH), 126.87 (ArCH), 128.14 (2 × ArCH), 131.27 (2 × ArCH), 131.73 (ArC), 133.94 (ArC), 137.82 (ArC), 139.02 (ArC), 154.92 (ArC),



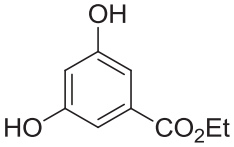
157.91 (ArC), 187.12 (CO); MS (TOF-ESI) *m/z* Calcd. for $C_{20}H_{18}N_2O_3$ $[M + Na]^+$ 357.1317. Found 357.1319.

6,8-Dimethoxy-9-methyl-3H-pyrrolo[1,2-*a*]indole-2-carbonitrile (291)



The pyrroloquinoline **291** was prepared from indole-7-carbaldehyde[32] **277** (100 mg, 0.45 mmol), acrylonitrile (0.51 mL, 9.1 mmol) and tetrabutylammonium hydroxide (2 drops) according to **GP-11** to give the *title compound* as a yellow solid (94 mg, 81%). M.p. 197-198 °C; UV(CH_3CN): λ_{max} 224 nm (ε 19,737 cm^{-1} M^{-1}), 263 (10,830), 271 (11,033), 287 (5,350), 297 (5,555); IR (KBr) ν_{max}: 2961, 2223, 1728, 1632, 1601, 1505, 1462, 1300, 1286, 1156, 1111, 1036, 822, 803 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (d, *J* = 6.0 Hz, 3H, CH_3), 3.86 (s, 6H, 2 × OMe), 3.99 (q, *J* = 6.0 Hz, 1H, CH), 6.31 (s, 2H, ArCH), 6.50 (d, *J* = 1.8 Hz, 1H, ArCH), 7.44 (s, 1H, ArCH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 17.70 (CH_3), 34.19 (CH), 46.07 (CH), 55.38 (OMe), 55.76 (OMe), 89.25 (ArCH), 95.36 (ArCH), 96.53 (ArC), 104.20 (CH), 116.41 (CH), 116.85 (CN), 119.35 (ArC), 140.18 (ArC), 143.48 (ArC), 157.46 (ArC), 161.59 (ArC), 172.75 (ArC); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{15}H_{14}N_2O_2$ $[M + Na]^+$ 277.1055. Found 277.0943.

Ethyl 3,5-dihydroxybenzoate (331)

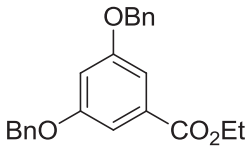


A solution of 3,5-dihydroxybenzoic acid **330** (10 g, 0.54 mol) in absolute ethanol (200 mL) containing Conc. sulfuric acid (5.0 mL) was heated under reflux overnight. After cooling the reaction mixture to room

temperature ethanol and sulfuric acid were evaporated off to yield a thick syrup. The syrup was cooled in ice untill it solidified. It was diluted with water, filtered and air dried. The solid obtained was further dried in a desiccator overnight under vacuum to give the *title compound* as a white solid (10.3 g, 97%). M.p. 129-129 °C, *lit*[195] 124-126 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.52 (t, *J* = 7.1 Hz, 3H, CH_3), 4.48 (q, *J* = 7.1 Hz, 2H, CH_2), 6.69 (t, *J* = 2.2 Hz, IH, ArH), 7.06 (d, *J* = 2.2 Hz, 2H, ArH), 9.89 (s, 2H, OH).

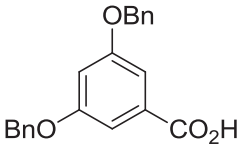
Ethyl 3,5-bis(benzyloxy)benzoate (332)

To dimethyl sulfoxide (150 mL) was added freshly powdered potassium hydroxide (3.6 g, 0.064 mol) after stirring for 5 min 3,5-dihydroxybenzoate **331** (5.0 g, 0.032 mol) was added.



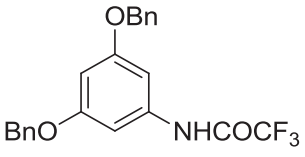
Further stirring was continued for 30 min. The colour of the reaction mixture changed from colourless to dark brown. Benzyl bromide (7.8 mL, 0.064 mol) was added dropwise and the reaction mixture was further stirred for 45 min. Water (300 mL) was added and the mixture was extracted with diethyl ether (3 × 300 mL). The diethyl ether layer was washed with water (3 × 200 mL), dried over sodium sulfate and concentrated under reduced pressure to yield the *title compound* as a white solid (7.2 g, 72%). M.p. 66-67 °C *lit*[196] 68-68.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.1 Hz, 3H, CH_3), 4.35 (q, *J* = 7.1 Hz, 2H, CH_2), 5.06 (s, 4H, O-CH_2Ph), 6.77 (t, *J* = 2.2 Hz, 1H, ArH), 7.31 (d, *J* = 2.3 Hz, 2H, ArH), 7.32 - 7.34 (m, 10H, ArH).

3,5-Dibenzyloxybenzoic acid (333)



Sodium hydroxide (20%, 25 mL) in ethanol was added to a solution of the ester **332** (5.0 g, 0.13 mol) in ethanol (200 mL). After being heated under reflux for 2 h, the reaction mixture was neutralized with concentrated hydrochloric acid with ice cooling, and the mixture was then evaporated under reduced pressure. The residue was extracted with diethyl ether and the diethyl ether solution was washed with water, dried over sodium sulfate and evaporated to dryness. The crystalline residue was recrystallised from ethyl acetate-light petroleum (1:1) to give the *title compound* as a white solid (3.70 g, 80%). M.p. 211-212 °C, *lit*[197] 210-211 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.11 (s, 4H, 2 × CH_2), 6.86 (t, *J* = 3.0 Hz, 1H, ArH), 7.12 (d, *J* = 3.0 Hz, 2H, ArH), 7.30-7.44 (m, 10H, ArH).

***N*-(3,5-Bis(benzyloxy)phenyl)-2,2,2-trifluoroacetamide (336)**



To a solution of 3,5-dibenzyloxybenzoic acid **333** (5.0 g, 0.04 mol) in dry dichloromethane (100 mL), thionyl chloride (10 mL) was added dropwise under nitrogen atmosphere. The resulting mixture was stirred overnight and the crude acid chloride was purified by distillation under reduced pressure (b.p. 81-83 °C, 30 mmHg) to give **334** as a colourless liquid, (4.0 g, 0.01 mol). This acid chloride was immediately used in the subsequent modified Curtius reaction.

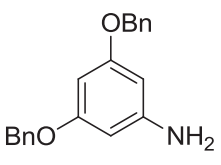
The acid chloride **334** thus obtained was dissolved in dry dichloromethane (100 mL) followed by the addition of tetrabutylammonium bromide (3.50 g, 0.01 mmol). The reaction mixture was cooled in an ice bath, and sodium azide (0.65 g, 0.01 mmol) in

water (25 mL) was added. The reaction mixture was stirred at 0 °C for 2 h and the organic layer was washed with water (2 × 50 mL). $MgSO_4$ (5.0 g) was added to the organic layer and the resulting mixture was heated for 20 h. The libration of bubbles due to decomposition of azide was observed at this stage. After cooling, the $MgSO_4$ was filtered off and trifluoroacetic acid (50 mL) was added dropwise with cooling. The mixture was heated under reflux for 6 h, and trifluoroacetic acid was removed under reduced pressure. The residue was extracted with CH_2Cl_2, and washed with water (2 × 100 mL) followed by drying over sodium sulphate. Concentration under reduced pressure gave the *title compound* as a white solid (0.5 g, 11%). M.p. 133-134 °C; UV (MeOH): λ_{max} 210 nm (ε 25,463 $cm^{-1}M^{-1}$), 252 (18,085) 305 (1,403); IR (KBr): ν_{max} 3087, 3068, 3031, 2891, 2359, 2336, 2266, 2188, 2148, 1685, 1594, 1496, 1470, 1442, 1378, 1343, 1295, 1250, 1081, 1064, 954, 903, 893, 852, 840, 795, 694, 669, 637, 582, 458, 465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.03 (s, 4H, 2 × O-CH_2), 6.51 (t, *J* = 3.0 Hz, 1H, ArH), 6.88 (d, *J* = 3.0 Hz, 2H, ArH), 7.26-7.43 (m, 10H, ArH), 7.92 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 70.14 (2 × O-CH_2), 99.85 (2 × ArCH), 100.19 (ArCH), 114.01 (CF_3), 117.5 (ArC), 127.44 (4 × ArCH), 128.07 (2 × ArCH), 128.56 (4 × ArCH), 136.29 (2 × ArC), 136.67 (ArC), 155.05 (C=O), 160.25 (ArC); HRMS *m/z*: Calcd. for $C_{22}H_{18}F_3NO_3$ $[M + 1]^+$ 402.1239. Found 402.1099.

3,5-Dibenzyloxyaniline (337)

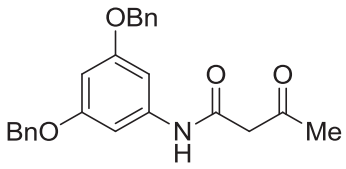
Method 1

A solution of trifluroacetamide **336** (5.0 g, 0.12 mol) in methanol (150 mL) and potassium carbonate (16.5 g, 0.12



mmol) in water (50 mL) was stirred at room temperature under nitrogen atmosphere for overnight. Methanol was removed under reduced pressure and the resulting solution was extracted with diethyl ether (3 × 100 mL). The combined organic phase was dried over sodium sulfate, and concentrated to give the *title compound* as a white solid (2.51 g, 66%). M.p. 193-193 °C *lit*[186] 191-193 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.94 (s, 4H, 2 × O-CH_2), 5.04 (s, 2H, NH_2), 5.82-5.83 (m, 3H, ArH), 7.28-7.32 (m, 10H, ArH).

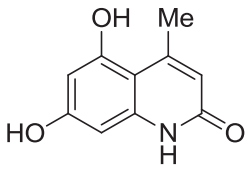
_N_-(3,5-Bis(benzyloxy)phenyl)-3-oxobutanamide (338)



A mixture of 3,5-dibenzyloxyaniline **337** (200 mg, 0.65 mmol) and ethyl acetoacetate (1.35 mL, 10.4 mmol) was heated at 145 ^{o}C for 30 min, then cooled to room temperature. Conc. sulfuric acid (1.0 mL) was added dropwise to the reaction mixture followed by heating at 145 ^{o}C for 30 min, which gave a precipitate upon addition of crushed ice (50 g). The resulting precipitate was filtered and washed with water (100 mL) to yield the *title compound* as a white solid (195 mg, 76%). M.p. 122-123 °C; UV (MeOH): λ_{max} 212 nm (ε 35,321cm^{-1} M^{-1}), 252 (8,985); IR (KBr): ν_{max} 3258, 3156, 3067, 3033, 3003, 2924, 2894, 2859, 1720, 1649, 1600, 1550, 1468, 1446, 1378, 1316, 1360, 1295, 1247, 1223, 1209, 1078, 1030, 990, 966, 837, 816, 732, 701, 675 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 3.56 (s, 2H, $COCH_2$), 5.02 (s, 4H, 2 × OCH_2), 6.40 (bs, 1H, ArCH), 6.90 (bs, 2H, ArCH), 7.31-7.43 (m, 10H, ArCH), 9.03 (bs, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 31.28 ($COCH_3$), 49.49 (CH_2), 70.01 (2 × OCH_2), 98.56 (ArCH), 99.41 (2 × ArCH), 127.47 (4 × ArCH), 127.91 (2 × ArCH), 128.48 (4 × ArCH), 130.81 (ArC), 136.63 (ArC), 139.05 (ArC), 160.07 (2 × ArC),

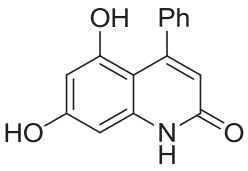
163.21 (C=O), 205.28 ($CH_2\underline{CO}CH_3$); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{24}H_{23}NO_4Na$ $[M + Na]^+$ 412.1627. Found 412.1618.

5,7-Dihydroxy-4-methylquinolin-2-one (305)



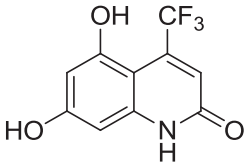
The quinolone **305** was prepared from 5-aminoresorcinol **105** (200 mg, 1.6 mmol), ethyl-3-oxobutanoate (1.0 mL, 6.4 mmol) and. Conc. sulfuric acid (1.0 mL) according to **GP-12** to give the *title compound* as a white solid (199 mg, 65%). M.p. 300-301 °C (dec.), *lit*[88] 300 °C (dec.) ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.49 (s, 3H, CH_3), 5.99 (bs, 1H, ArH), 6.20-6.23 (m, 2H, ArH), 10.00 (s, 1H, OH), 10.20 (s, 1H, OH).

5,7-Dihydroxy-4-phenylquinolin-2-one (308)



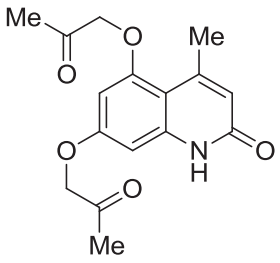
The quinolone **308** was prepared from 5-aminoresorcinol **105** (200 mg, 1.6 mmol), ethyl 3-oxo-3-phenylpropanoate (1.2 mL, 6.4 mmol) and Conc. sulfuric acid (1.0 mL) according to **GP-12** to give the *title compound* as brown solid (260 mg, 64%). M.p. 203-204 °C, *lit*[88] 204-205 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 5.74 (s, 1H, H3), 5.97 (d, *J* = 2.3 Hz, 1H, H6), 6.25 (d, *J* = 2.3 Hz, 1H, H8), 7.21-7.30 (m, 5H, ArH), 9.61 (s, 1H, OH), 9.88 (s, 1H, OH), 11.41 (bs, 1H, NH).

5,7-Dihydroxy-4-(trifluoromethyl)quinolin-2-one (309)



The quinolone **309** was prepared from 5-aminoresorcinol **105** (200 mg, 1.6 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate (1.2 mL, 6.4 mmol) and Conc. sulfuric acid (1.0 mL) according to **GP-12** to give the *title compound* as a yellow solid (253 mg, 64%). M.p. 220-221 °C (dec.); UV (MeOH): λ_{max} 214 nm (ε 22,491 $cm^{-1}M^{-1}$), 267 (9,922), 333 (6,933); IR (KBr): ν_{max} 3135, 1663, 1541, 1476, 1423, 1388, 1358, 1271, 1166, 1149, 1098, 984, 879, 850, 822, 768, 700 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): 5.99 (s, 1H, H3), 6.20-6.22 (m, 2H, ArH), 9.97 (bs, 1H, NH), 10.15 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 93.22 (ArCH), 98.01 (ArC), 98.45 (ArCH), 116.89 (ArCH), 116.88 (ArC), 122.91 (CF_3), 143.55 (ArC), 155.72 (ArC), 160.95 (ArC), 161.35 (C=O); HRMS *m/z:* Calcd. for $C_{10}H_6F_3NO_3$ $[M + 1]^+$ 246.0300. Found 246.0373.

4-Methyl-5,7-bis (2-oxopropoxy)quinolin-2-one (310)

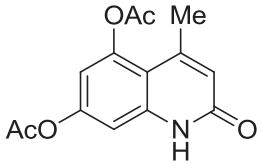


The quinolone ether **310** was prepared from 5,7-dihydroxy-4-methylquinolin-2-one **305** (200 mg, 1.04 mmol), chloroacetone (0.25 mL, 2.61 mmol), sodium acetate (215 mg, 2.61 mmol) in *N*,*N*-dimethylformamide (40 mL) according to **GP-13** to give the *title compound* as a white solid (280 mg, 88%). M.p. 213-214 °C; UV (MeOH): λ_{max} 215 nm (ε 29,164 cm^{-1} M^{-1}), 239 (17,783), 257 (12,014), 315 (9,224); IR (KBr): ν_{max} 3442, 2923, 1722, 1655, 1625, 1551, 1403, 1358, 1225, 1183, 1131, 1091, 1052, 963, 826, 767 cm^{-1};^{1}H NMR (300 MHz, DMSO-d_6): δ 2.15 (s, 6H, 2 × $COCH_3$), 2.48 (s, 3H, CH_3), 4.79 (s, 2H, OCH_2), 4.92 (s, 2H, OCH_2), 6.03 (s,

1H, ArCH), 6.24 (d, *J* = 2.2 Hz, 1H, ArCH), 6.32 (d, *J* = 2.2 Hz, 1H, ArCH), 11.31 (s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 24.70 (CH_3), 26.65 ($CO\underline{C}H_3$), 26.77 ($CO\underline{C}H_3$), 72.52 (OCH_2), 73.27 (OCH_2), 92.91 (ArCH), 94.83 (ArCH), 105.48 (ArC), 118.86 (ArCH), 142.45 (ArC), 149.02 (ArC), 157.78 (ArC), 159.88 (ArC), 161.81 (CO), 203.91 ($\underline{C}OCH_3$), 203.91 ($\underline{C}OCH_3$); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{16}H_{17}NO_5$ $[M + 1]^+$ 304.1107. Found 304.1180.

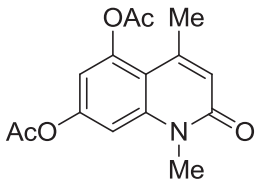
5,7-Diacetoxy-4-methylquinolin-2-ones (312)

The acetoxyquinolone **312** was prepared from 5,7-dihydroxy-4-methylquinolin-2-one **305** (200 mg, 1.04 mmol), pyridine (5 mL) and acetic anhydride (2.0 mL) according to **GP-5** to give the *title compound* as a white solid (243 mg, 84%). M.p. 180 °C (dec.); UV (MeOH): λ_{max} 276 nm (ε 8,772 cm^{-1} M^{-1}), 323 (9,075); IR (KBr): ν_{max} 3441, 2941, 2850, 1765, 1675, 1368, 1152, 1093, 1029, 906, 843, 506 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH_3), 2.32 (s, 3H, $COCH_3$), 2.42 (s, 3H, $COCH_3$), 6.33 (s, 1H, ArCH), 6.81 (d, *J* = 2.3, 1H, ArCH), 6.99 (d, *J* = 2.6, 1H, ArCH), 11.82 (bs, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 21.49 ($COCH_3$), 22.29 ($COCH_3$), 23.60 (CH_3), 103.97 (ArCH), 110.59 (ArCH), 114.49 (ArCH), 127.37 (ArC), 142.33 (ArC), 148.25 (ArC), 151.60 (ArC), 155.04 (ArC), 161.47 (C=O), 169.77 ($CH_3\underline{C}O$), 169.89 ($CH_3\underline{C}O$); HRMS (TOF-ESI) *m/z*: Calcd. for $C_{14}H_{13}NO_5$ $[M + 1]^+$ 276.0794. Found 276.0868.



1,4-Dimethyl-2-oxo-1,2-dihydroquinoline-5,7-diyl diacetate (313)

Method-1

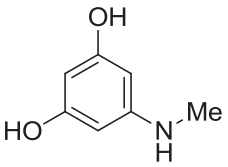


5,7-Diacetoxy-4-methylquinolin-2-one **312** (200 mg, 0.72 mmol) and potassium carbonate (200 mg, 1.45 mmol) were suspended in *N*,*N*-dimethylformamide, and the mixture was stirred at room temperature for 30 min. Iodomethane (0.15 mL, 1.45 mmol) was added dropwise and the mixture was stirred at room temperature for 24 h. Water (20 mL) was added and the resulting precipitate was filtered, washed with water (30 mL) and dried to yield the *title compound* as a white solid (170 mg, 85%).

Method-2

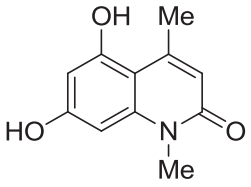
The acetoxyquinolone **313** was prepared from 5,7-dihydroxy-1,4-dimethylquinolin-2-one **314** (200 mg, 0.97 mmol), pyridine (5 mL) and acetic anhydride (2.0 mL) according to **GP-5** to give the *title compound* as a white needles (230 mg, 81%). M.p. 241-242 °C; UV (CH_3CN): λ_{max} 235 nm (ε 16,184 cm^{-1} M^{-1}), 275 (2,312); IR (KBr): ν_{max} 1763, 1654, 1624, 1545, 1419, 1205, 1126, 1075, 1028, 898, 848, 733, 542 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, $COCH_3$), 2.30 (s, 3H, $COCH_3$), 2.45 (s, 3H, CH_3), 3.58 (s, 3H, N-CH_3), 6.43 (s, 1H, ArCH), 6.72 (d, *J* = 2.2 Hz, 1H, ArCH), 6.99 (d, *J* = 2.2 Hz, 1H, ArCH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 21.56 ($COCH_3$), 21.86 ($COCH_3$), 23.74 (CH_3), 30.45 (N-CH_3), 106.15 (ArCH), 111.85 (ArCH), 133.32 (ArC), 123.32 (ArCH), 142.68 (ArC), 144.83 (ArC), 149.34 (ArC), 151.81 (ArC), 161.79 (C=O), 169.06 ($CH_3\underline{CO}$), 169.32 ($CH_3\underline{CO}$); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{15}H_{15}NO_5$ [M + 1]$^+$ 290.0950. Found 290.1021; Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.28; H, 5.22; N, 4.92.

5-Methylaminoresorcinol (315)



Aqueous methylamine (40%, 10 mL) was added dropwise at 25 °C to a solution of (10.0 g, 0.8 mol) of phloroglucinol **193** in *N*,*N*-dimethylformamide (150 mL) and of water (100 mL). The mixture was stirred for 20 h at room temperature and the solvent was distilled off at 70 °C under vacuum. The residue was triturated with diethyl ether, filtered and dried to give the *title compound* in the form of white needles (9.23 g, 83%). M.p.131-133 °C *lit*[190] 130 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.55 (d, *J* = 6.0 Hz, 3H, N-CH_3), 5.29 (q, *J* = 6.0 Hz, 1H, NH), 5.43-5.47 (m, 3H, ArH), 8.71 (s, 2H, OH).

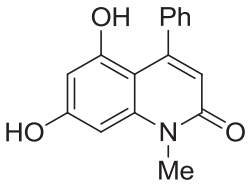
5,7-Dihydroxy-1,4-dimethylquinolin-2-one (314)



The quinolone **314** was prepared from 5-methylaminoresorcinol **315** (5.0 g, 0.35 mol), ethyl acetoacetate (45.5 mL, 0.35 mol) and Conc. sulfuric acid (4.0 mL) according to **GP-12** to give the *title compound* as an off white solid (5.5 g, 74%). M.p. 298-299 °C (dec.); UV (CH_3CN): λ_{max} 210 nm (ε 11,808 $cm^{-1}M^{-1}$), 241 (13,325), 260 (5,309), 305 (4,612); IR (KBr): ν_{max} 3336, 2929, 2359, 1630, 1550, 1458, 1433, 1380, 1289, 1248, 1149, 1070, 1024, 966, 823, 694, 650, 563, 543, 563, 477 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.49 (s, 3H, CH_3), 3.41 (s, 3H, N-CH_3), 5.99 (d, *J* = 3.0 Hz, 1H, ArH), 6.20-6.23 (m, 2H, ArH), 10.00 (s, 1H, OH), 10.20 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 24.15 (CH_3), 29.19 (N-CH_3), 92.46 (ArCH), 97.34 (ArCH), 103.80 (ArC), 115.43 (ArCH), 143.10 (ArC), 147.78 (ArC), 158.22 (ArC), 159.96 (ArC), 161.01 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{11}H_{11}NO_3$ $[M + 1]^+$ 206. 0739. Found 206.0719;

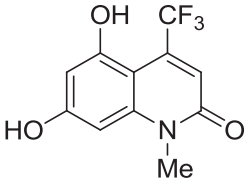
Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.54; H, 5.42; N, 6.73.

5,7-Dihydroxy-1-methyl-4-phenylquinolin-2-one (317)



The quinolone **317** was prepared from 5-methylaminoresorcinol **315** (5.0 g, 0.35 mol), ethyl 3-oxo-3-phenylpropanoate (67 mL, 0.35 mol) and Conc. sulfuric acid (4.0 mL) according to **GP-12** to give the *title compound* as brown solid (7.10 g, 73%). M.p. 240-241 °C (dec.); UV (MeOH): λ_{max} 209 nm (ε 11,587 $cm^{-1}M^{-1}$), 241 (7,783), 265 (8,357), 327 (4,512); IR (KBr): ν_{max} 3232, 2600, 1628, 1608, 1547, 1496, 1438, 1408, 1372, 1317, 1275, 1143, 1118, 1030, 925, 871, 843, 781, 729, 700, 659, 607, 586, 538 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.50 (s, 3H, N-CH_3), 5.58 (bs, 1H, H3), 6.10 (bs, 1H, H6), 6.32 (s, 1H, H8), 7.20-7.31 (m, 5H, ArH), 9.83 (bs, 1H OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 30.05 (N-CH_3), 92.90 (ArCH), 97.74 (ArCH), 102.54 (ArC), 116.76 (ArCH), 127.11 (ArCH), 127.42 (2 × ArCH), 127.76 (2 × ArC), 142.31 (ArC), 143.59 (ArC), 150.59 (ArC), 157.62 (ArC), 161.06 (ArC), 161.09 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{16}H_{13}NO_3$ $[M + 1]^+$ 268. 0895. Found 268.0904; Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.93; H, 4.74; N, 5.64.

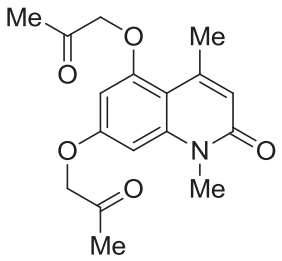
5,7-Dihydroxy-1-methyl-4-(trifluoromethyl)quinolin-2-one (318)



The quinolone **318** was prepared from 5-methylaminoresorcinol **315** (5.0 g, 0.35 mol), ethyl 4,4,4-trifluoro-3-oxobutanoate (64.5

mL, 0.35 mol) and Conc. sulfuric acid (4.0 mL) according to **GP-12** to give the *title compound* as a yellow solid (7.11 g, 76%). M.p. 235-236 °C (dec.); UV (MeOH): λ_{max} 216 nm (ε 6,307 $cm^{-1}M^{-1}$), 267 (4,981), 335 (3,792); IR (KBr): ν_{max} 3380, 3126, 1625, 1570, 1530, 1468, 1433, 1376, 1281, 1237, 1208, 1189, 1141, 1023, 941, 879, 827, 738, 691, 516 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.53 (s, 3H, N-CH_3), 6.34 (s, 1H, H3), 6.39 (s, 1H, H6), 6.69 (s, 1H, H8), 10.38 (s, 1H, OH), 10.66 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 30.32 (N-CH_3), 93.54 (ArCH), 98.39 (ArCH), 101.43 (ArC), 103.63 (ArC), 115.90 (ArCH), 122.09 (CF_3), 144.16 (ArC), 156.35 (ArC), 150.34 (ArC), 161.70 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{11}H_8F_3NO_3Na$ $[M + Na]^+$ 282.0413. Found 282.0391; Anal. Calcd. for $C_{11}H_8F_3NO_3$: C, 50.98; H, 3.11; N, 5.40. Found: C, 50.48; H, 3.17; N, 5.40.

1,1'-(1,4-Dimethyl-2-oxo-1,2-dihydroquinoline-5,7-diyl)bis(oxy)dipropan-2-one (319)

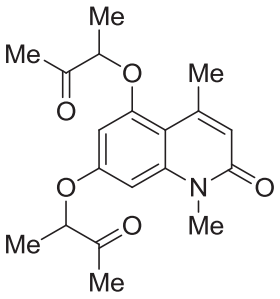


The quinolone ether **319** was prepared from 5,7-dihydroxy-1,4-dimethylquinolin-2-one **314** (200 mg, 0.97 mmol), chloroacetone (0.2 mL, 1.95 mmol), potassium carbonate (270 mg, 1.95 mmol) and acetone (100 mL) according to **GP-13** to give the *title compound* as a white solid (248 mg 80%). M.p. 180-181 °C; UV (CH_3CN): λ_{max} 216 nm (ε 19,423 cm^{-1} M^{-1}) 241 (19,734), 303 (7,314), 320 (6,037); IR (KBr): ν_{max} 3433, 2927, 1722, 1660, 1618, 1597, 1562, 1508, 1380, 1277, 1149, 1137, 1086, 1006, 876, 812, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, $COCH_3$), 2.29 (s, 3H, $COCH_3$), 2.65 (s, 3H, CH_3), 3.60 (s, 3H, N-CH_3), 4.62 (s, 2H, OCH_2), 4.67 (s, 2H, OCH_2), 6.13 (bs, 1H, ArCH), 6.34 (bs, 1H, ArCH), 6.37 (bs, 1H, ArCH); ^{13}C

NMR (75.6 MHz, $CDCl_3$): δ 25.60 (CH_3), 26.55 ($CO\underline{C}H_3$), 26.60 ($CO\underline{C}H_3$), 29.92 (N-CH_3), 72.77 (OCH_2), 73.29 (OCH_2), 92.71 (ArCH), 94.10 (ArCH), 107.39 (ArC), 119.23 (ArCH), 143.34 (ArC), 147.24 (ArC), 157.94 (ArC), 159.37 (ArC), 161.93 (C=O), 203.91 ($\underline{C}OCH_3$), 203.91 ($\underline{C}OCH_3$); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{17}H_{19}NO_5Na$ $[M + Na]^+$ 340.1283. Found 340.1180.

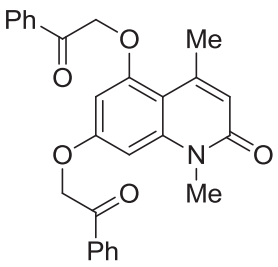
3,3'-(1,4-Dimethyl-2-oxo-1,2-dihydroquinoline-5,7-diyl)bis(oxy)dibutan-2-one (320)

The quinolone ether **320** was prepared from 5,7-dihydroxy-1,4-dimethylquinolin-2-one **314** (200 mg, 0.97 mmol), 3-chloro-2-butanone (0.2 mL, 1.95 mmol), potassium carbonate 270 mg, 1.92 mmol) and potassium iodide (80 mg, 0.48 mmol) in acetone (100 mL) according to **GP-13** to give the



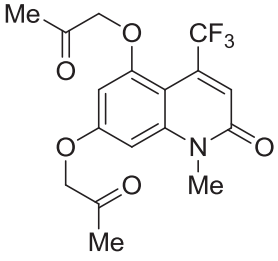
title compound as a white solid (265 mg, 78%). M.p.187-188 °C; UV (CH_3CN): λ_{max} 217 nm (ε 22,873 cm^{-1} M^{-1}), 242 (22,942), 303 (9,177), 321 (7,486); IR (KBr): ν_{max} cm^{-1} 2929, 2942, 1720, 1670, 1614, 1601, 1562, 1504, 1374, 1273, 1148, 1132, 1101, 1057, 941, 879, 814, 740, 693 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44-1.54 (m, 6H, 2 × CH_3), 2.06-2.12 (m, 6H, 2 × CH_3), 2.57 (s, 3H, CH_3), 3.49 (s, 3H, N-CH_3), 4.58-4.68 (m, 2H, CH), 5.89 (d, *J* = 2.1 Hz, 1H, ArCH), 6.24-6.28 (m, 2H ArCH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 17.32 ($CH\underline{C}H_3$), 17.38 ($CH\underline{C}H_3$), 17.46 (CH_3), 24.46 ($CO\underline{C}H_3$), 24.55 ($CO\underline{C}H_3$), 29.82 (N-CH_3), 79.23 (CH), 79.18 (CH), 93.21 (ArCH), 94.09 (ArCH), 119.25 (ArCH), 143.52 (ArC), 147.04 (ArC), 157.62 (ArC), 159.17 (ArC), 159.33 (ArC), 161.86 (C=O), 208.39 (2 × $CH_3\underline{C}O$); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{19}H_{23}NO_5Na$ $[M + Na]^+$ 368.1576. Found 368.1548.

2,2'-(1,4-Dimethyl-2-oxo-1,2-dihydroquinoline-5,7-diyl)bis(oxy)bis(1-phenylethanone) (321)



The quinolone ether **321** was prepared from 5,7-dihydroxy-1,4-dimethylquinolin-2-one **314** (200 mg, 0.97 mmol), phenacylbromide (386 mg, 1.95 mmol), potassium carbonate (270 mg, 1.95 mmol) in acetone (100 mL) according to **GP-13** to give the *title compound* as a white solid (298 mg, 69%). M.p. 200-201 °C; UV (CH_3CN): λ_{max} 241 nm (ε 22,536 cm^{-1} M^{-1}), 302 (5,114); IR (KBr): ν_{max} 3374, 2935, 2840, 1712, 1689, 1625, 1574, 1512, 1491, 1422, 1365, 1312, 1272, 1233, 1158, 1073, 1028, 988, 962, 833, 803, 693 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.64 (s, 3H, CH_3), 3.51 (s, 3H, N-CH_3), 5.71 (s, 4H, 2 × CH_2), 6.20 (s, 1H, ArCH), 6.64 (s, 2H, ArCH), 7.56-8.02 (m, 10H, ArCH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 25.23 (CH_3), 30.01 (N-CH_3), 70.67 (O-CH_2), 71.66 (O-CH_2), 93.38 (ArCH), 95.70 (ArCH), 118.11 (ArCH), 128.28 (4 × ArCH), 129.21 (4 × ArCH), 134.23 (2 × ArCH), 134.23 (2 × ArC), 134.69 (2 × ArC), 143.23 (ArC), 147.61 (ArC), 158.38 (ArC), 160.58 (C=O), 194.11 (CH_2<u>CO</u>Ph), 194.35 (CH_2<u>CO</u>Ph); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{27}H_{23}NO_5Na$ [M + Na]$^+$ 464.1576. Found 464.1501.

1,1'-(1-Methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydroquinoline-5,7-diyl)bis(oxy)dipropan-2-one (322)

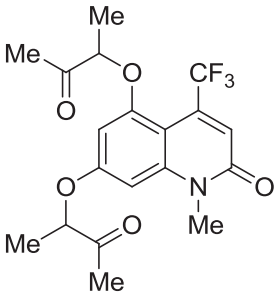


The quinolone ether **322** was prepared from 5,7-dihydroxy-1-methyl-4-(trifluoromethyl)quinolin-2-one **318** (200 mg, 0.77 mmol), chloroacetone (0.15 mL, 1.54 mmol), potassium

carbonate (212 mg, 1.54 mmol) and acetone (100 mL) according to **GP-13** to give the *title compound* as a yellow solid (220 mg, 76%). M.p. 180-181 °C (from Ethyl acetate); UV (CH_3CN): λ_{max} 219 nm (ε 35,727 cm^{-1} M^{-1}), 243 (22,816), 264 (10,944), 322 (11,649); IR (KBr): ν_{max} 3433, 2927, 1722, 1664, 1618, 1599, 1563, 1507, 1432, 1410, 1351, 1328, 1280, 1248, 1134, 1007, 971, 939, 880, 813, 742, 685 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 6H, 2 × $COCH_3$), 3.65 (s, 3H, N-CH_3), 4.94 (s, 2H, O-CH_2), 5.00 (s, 2H, O-CH_2), 6.42 (s, 1H, ArH), 6.68 (d, *J* = 3.0 Hz, 1H, H6), 6.86 (d, *J* = 3.0 Hz, 1H, H8); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 25.23 ($COCH_3$), 25.44 ($COCH_3$), 28.58 (N-CH_3), 72.36 (O-CH_2), 73.29 (O-CH_2), 93.40 (ArCH), 95.39 (ArCH), 114.14 (ArC), 118.64 (ArCH), 118.75 (ArC), 123.01 (CF_3), 144.14 (ArC), 156.20 (ArC), 159.88 (ArC), 161.35 (C=O), 202.20 (2 × $COCH_3$); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{17}H_{16}F_3NO_5$ $[M + 1]^+$ 372.0981. Found 372.1055.

3,3'-(1-Methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydroquinoline-5,7-diyl)bis(oxy)dibutan-2-one (323)

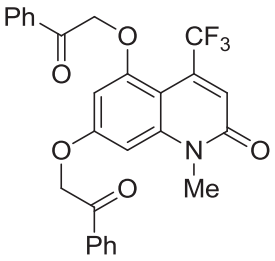
The quinolone ether **323** was prepared from 5,7-dihydroxy-1-methyl-4-(trifluoromethyl)quinolin-2-one **318** (200 mg, 0.74 mmol), 3-chloro-2-butanone (0.13 mL, 1.49 mmol), potassium carbonate (205 mg, 1.49 mmol) and potassium iodide (79 mg, 0.48 mmol) in acetone (100 mL) according to **GP-13** to give the



title compound as a yellow solid (230 mg, 74%). M.p. 100-101 °C; UV (CH_3CN): λ_{max} 219 nm (ε 35,727 cm^{-1} M^{-1}), 243 (22,816), 264 (10,944), 322 (11,760); IR (KBr): ν_{max} 2990, 2942, 1720, 1670, 1614, 1562, 1504, 1449, 1376, 1272, 1216, 1205, 1148, 1133, 1089, 1057, 985, 945, 883, 822, 814, 740, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ

1.52-1.59 (m, 6H, 2 × CH_3), 2.09-2.17 (m, 6H, 2 × CH_3), 3.61 (s, 3H, N-CH_3), 4.62-4.72 (m, 2H, 2 × -CHCH_3), 6.01 (s, 1H, H3), 6.39 (d, *J* = 3.0 Hz, 1H, H6), 7.03 (d, *J* = 3.0 Hz, 1H, H8); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 16.79 (CH_3), 17.22 (CH_3), 23.76 (CH_3), 24.35 (CH_3), 30.45 (N-CH_3), 79.30 (ArC), 80.26 (ArC), 93.35 (CH), 94.36 (ArCH), 101.52 (ArCH), 119.52 (ArCH), 125.03 (CF_3), 144.13 (2 × ArC), 155.54 (ArC), 160.33 (ArC), 160.82 (CO), 208.10 (COCH_3), 209.17 (COCH_3); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{19}H_{20}F_3NO_5Na$ $[M + Na]^+$ 422.1294. Found 422.1282.

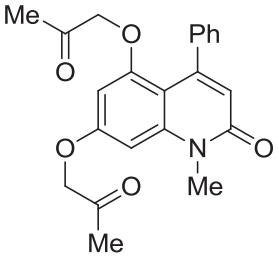
2'-(1-Methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydroquinoline-5,7-diyl)bis(oxy)bis (1-phenylethanone) (324)



The quinolone ether **324** was prepared from 5,7-dihydroxy-1-methyl-4-(trifluoromethyl)quinolin-2-one **318** (200 mg, 0.77 mmol), phenacyl bromide (295 mg, 1.49 mmol), potassium carbonate (200 mg, 1.49 mmol) and acetone (100 mL) according to **GP-13** to give the *title compound* as a yellow solid (268 mg, 70%). M.p. 200-201 °C; UV (CH_3CN): λ_{max} 243 nm (ε 40,590 cm^{-1} M^{-1}), 324 (9,999); IR (KBr): ν_{max} 3374, 2935, 2840, 1712, 1689, 1625, 1600, 1574, 1512, 1491, 1453, 1402, 1365, 1312, 1272, 1233, 1158, 1073, 1028, 988, 962, 885, 833, 803, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64 (s, 3H, N-CH_3), 5.78 (s, 2H, CH_2), 5.82 (s, 2H, CH_2), 6.64 (bs 1H, ArCH), 6.79 (bs, 1H, ArCH), 6.91 (s, 1H, ArCH), 7.55-7.74 (m, 6H, ArCH), 7.99-8.00 (m, 4H, ArCH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 31.06 (N-CH_3), 70.79 (O-CH_2), 71.58 (O-CH_2), 94.12 (ArCH), 96.48 (ArCH), 100.88 (ArCH), 104.04 (ArC), 120.01 (CF_3), 128.23 (3 × ArCH), 128.29 (2 × ArCH), 129.18 (3 × ArCH), 134.23 (2 × ArCH), 134.43 (ArC), 134.57 (ArC), 134.68 (ArC), 143.91 (ArC), 156.26 (2 × ArC), 161.17

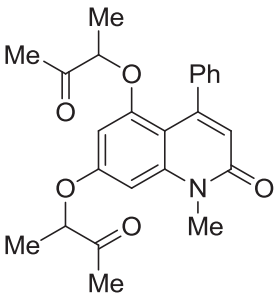
(C=O), 193.85 (COPh), 194.07 (COPh); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{27}H_{20}F_3NO_5Na$ $[M + Na]^+$ 518.1294. Found 518.1206.

1,1'-(1-Methyl-2-oxo-4-phenyl-1,2-dihydroquinoline-5,7-diyl)bis(oxy)dipropan-2-one (325)



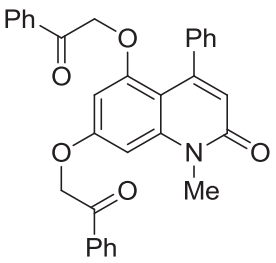
The quinolone ether **325** was prepared from 5,7-dihydroxy-1-methyl-4-phenylquinolin-2-one **317** (200 mg, 0.74 mmol), chloroacetone (0.15 mL, 1.49 mmol), potassium carbonate (200 mg, 1.49 mmol) and acetone (100 mL) according to **GP-13** to give the *title compound* as a white solid (201 mg, 71%). M.p.150-152 °C; UV (CH_3CN): λ_{max} 226 nm (ε 26,946 cm^{-1} M^{-1}), 243 (21,224), 314 (7,580); IR (KBr): ν_{max} 3411, 3058, 2918, 1716, 1639, 1607, 1585, 1500, 1444, 1419, 1370, 1358, 1202, 1142, 1059, 881, 840, 727, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 6H, 2 × $COCH_3$), 3.69 (s, 3H, N-CH_3), 4.14 (s, 2H, O-CH_2), 4.65 (s, 2H, O-CH_2), 6.14 (s, 1H, ArH), 6.38 (s, 1H, ArH), 6.48 (s, 1H, ArH), 7.26-7.34 (m, 5H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 25.84 (CO$\underline{CH_3}$), 26.55 (CO$\underline{CH_3}$), 30.10 (N-CH_3), 72.83 (O-CH_2), 73.65 (O-CH_2), 93.12 (ArCH), 94.87 (ArCH), 105.82 (ArC), 120.66 (ArCH), 127.34 (2 × ArCH), 127.38 (ArCH), 127.56 (2 × ArCH), 141.68 (ArC), 143.85 (ArC), 149.19 (ArC), 156.99 (ArC), 160.01 (ArC), 161.67 (C=O), 203.76 ($CH_3\underline{CO}$), 204.50 ($CH_3\underline{CO}$); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{22}H_{21}NO_5Na$ $[M + Na]^+$ 402.1420. Found 402.1347.

3,3'-(1-Methyl-2-oxo-4-phenyl-1,2-dihydroquinoline-5,7-diyl)bis(oxy)dibutan-2-one (326)



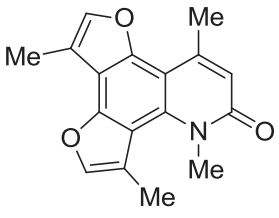
The quinolone ether **326** was prepared from 5,7-dihydroxy-1-methyl-4-phenylquinolin-2-one **317** (200 mg, 0.74 mmol), 3-chloro-2-butanone (0.16 mL, 1.49 mmol), potassium carbonate (200 mg, 1.49 mmol) and potassium iodide (80 mg, 0.48 mmol) in acetone (100 mL) according to **GP-13** to give the *title compound* as a white solid (256 mg, 84%). M.p. 135-136 °C; UV (CH_3CN): λ_{max} 209 nm (ε 29,141 cm^{-1} M^{-1}), 225 (29,344), 243 (24,827), 312 (10,297); IR (KBr): ν_{max} 3054, 2985, 2932, 2361, 2340, 1718, 1657, 1607, 1550, 1501, 1443, 1368, 1307, 1261, 1201, 1173, 1142, 1122, 1053, 1022, 869, 821, 779, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (m, 3H, -CH<u>CH$_3$</u>), 1.52 (m, 3H, -CH<u>CH$_3$</u>), 1.83 (s, 3H, $COCH_3$), 2.17 (s, 3H, $COCH_3$), 3.65 (s, 3H, N-CH_3), 4.28 (m, 1H, <u>CH</u>CH_3), 4.67 (m, 1H, <u>CH</u>CH_3), 5.89 (s, 1H, H3), 6.35 (bs, 1H, H6), 6.39 (m, 1H, H8), 7.21-7.33 (m, 5H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 16.21 (CH<u>CH$_3$</u>), 17.35 (CH<u>CH$_3$</u>), 23.97 ($COCH_3$), 24.34 ($COCH_3$), 30.03 (N-CH_3), 78.89 (<u>CH</u>CH_3), 79.24 (<u>CH</u>CH_3), 92.90 (ArCH), 94.01 (ArCH), 105.53 (ArC), 119.97 (ArCH), 120.03 (ArC), 126.95 (2 × ArCH), 127.15 (ArCH), 127.39 (2 × ArCH), 142.15 (ArC), 143.45 (ArC), 149.52 (ArC), 156.52 (ArC), 159.80 (ArC), 161.66 (ArC), 209.03 (<u>CO</u>CH_3); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{24}H_{25}NO_5Na$ $[M + Na]^+$ 430.1733. Found 430.1644.

2,2'-(1-Methyl-2-oxo-4-phenyl-1,2-dihydroquinoline-5,7-diyl)bis(oxy)bis(1-phenylethanone) (327)



The quinolone ether **327** was prepared from 5,7-dihydroxy-1-methyl-4-phenylquinolin-2-one **317** (200 mg, 0.74 mmol), phenacyl bromide (295 mg, 1.49 mmol), potassium carbonate (200 mg, 1.49 mmol) and acetone (100 mL according to **GP-13** to give the *title compound* as a white solid (260 mg, 69%). M.p. 200-201 °C; UV (CH_3CN): λ_{max} 242 nm (ε 39,787 cm^{-1} M^{-1}), 312 (8,752); IR (KBr): ν_{max} 3055, 2919, 1693, 1650, 1610, 1588, 1503, 1448, 1372, 1315, 1282, 1252, 1200, 1146, 1088, 1073, 1031, 1000, 1023, 865, 817, 777, 731, 672 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.59 (s, 3H, N-CH_3), 4.67 (s, 2H, CH_2), 5.26 (s, 2H, CH_2), 6.17 (s, 1H, ArCH), 6.28 (s, 1H, ArCH), 6.49 (s, 1H, ArCH), 7.15-7.19 (m, 2H, ArCH), 7.29-7.92 (m, 13H, ArCH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 30.55 (CH_3), 71.02 (CH_2), 71.78 (CH_2), 94.06 (ArCH), 95.76 (ArCH), 120.64 (ArCH), 127.43 (ArCH), 127.56 (2 × ArCH), 127.78 (2 × ArCH), 128.51 (2 × ArCH), 128.84 (2 × ArCH), 129.02 (2 × ArCH), 129.42 (2 × ArCH), 134.30 (ArCH), 134.40 (ArCH), 134.64 (ArC), 134.67 (ArC), 142.07 (2 × ArC), 143.71 (ArC), 150.09 (ArC), 156.01 (ArC), 161.20 (ArC), 162.28 (CO), 194.07 (2 × COPh); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{32}H_{25}NO_5Na$ $[M + Na]^+$ 526.1733. Found 526.1662.

3,6,7,10-Tetramethyldifuro[2,3-*f*:2',3'-*h*]quinolin-8-one (329)

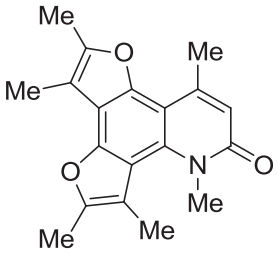


The furoquinolone **329** was prepared from quinolone ether **319** (200 mg, 0.71 mmol) and trifluoroacetic acid (10.0 mL) according to **GP-14** to give the *title compound* as a white solid

(110 mg, 62%). M.p. 148-149 °C; UV (CH_3CN): λ_{max} 233nm (ε 19,670 cm^{-1} M^{-1}), 302 (7,699), 342 (5,451); IR (KBr): ν_{max} 3380, 3346, 3106, 2927, 1724, 1629, 1591, 1610, 1532, 1511, 1389, 1331, 1179, 1164, 1114, 1052, 1004, 911, 851, 859, 824, 730, 660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 9H, 3 × CH_3), 2.78 (s, 3H, N-CH_3), 6.27 (s, 1H, ArCH), 7.69 (s, 1H, ArCH), 8.26 (s, 1H, ArCH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 6.59 (CH_3), 9.40 (CH_3), 19.02 (CH_3), 29.92 (N-CH_3), 107.39 (ArC), 116.02 (2 × ArC), 119.23 (ArCH), 141.04 (2 × ArCH), 143.34 (ArC), 147.24 (ArC), 148.14 (ArC), 149.12 (ArC), 157.94 (ArC), 159.37 (ArC), 161.93 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{17}H_{15}NO_3Na$ $[M + Na]^+$ 304.1052. Found 304.1052.

2,3,5,6,7,10-Hexamethyldifuro[2,3-*f*:2',3'-*h*]quinolin-8-one (330)

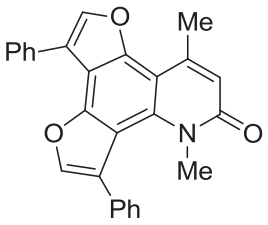
The furoquinolone **330** was prepared from quinolone ether



320 (200 mg, 0.64 mmol) and trifluoroacetic acid (10 mL) according to **GP-14** to give the *title compound* as a white solid (109 mg, 61%). M.p. 180-181 °C; UV (CH_3CN): λ_{max} 244 nm (ε 17,551 cm^{-1} M^{-1}), 276 (24,750); IR (KBr): ν_{max} 2917, 1660, 1624, 1580, 1594, 1465, 1421, 1388, 1349, 1308, 1273, 1134, 1097, 1040, 1017, 950, 928, 847, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 6.52 (s, 1H, ArCH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 8.37 (CH_3), 10.06 (CH_3), 12.61 (CH_3), 15.16 (CH_3), 22.19 (CH_3), 41.15 (N-CH_3), 106.24 (ArC), 109.46 (ArC), 112.03 (ArC), 113.98 (ArC), 117.03 (ArCH), 133.80 (ArC), 147.07 (ArC), 147.16 (ArC), 148.51 (ArC), 149.37 (ArC),

150.01 (ArC), 150.09 (ArC), 164.18 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{19}H_{19}NO_3Na$ $[M + Na]^+$ 332.1365. Found 332.1289.

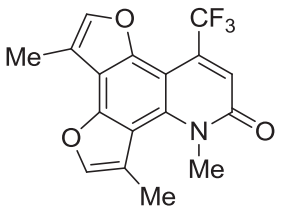
7,10-Dimethyl-3,6-diphenyldifuro[2,3-*f*:2',3'-*h*]quinolin-8-one (331)



The furoquinolone **331** was prepared from quinolone ether **321** (200 mg, 0.45 mmol) and trifluoroacetic acid (10.0 mL) according to **GP-14** to give the *title compound* as a white solid (107 mg, 58%). M.p. 190-191 °C; UV (CH_3CN): λ_{max} 274 nm (ε 29,038 cm^{-1} M^{-1}) 348 (2,713); IR (KBr): ν_{max} 3635, 3483, 2927, 2850, 1648, 1619, 1587, 1571, 1557, 1488, 1446, 1357, 1141, 1083, 1022, 851, 770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.87 (s, 3H, CH_3), 3.05 (s, 3H, N-CH_3), 6.60 (s, 1H, ArCH), 7.34-7.62 (m, 9H, ArCH), 7.83-7.87 (m, 3H, ArCH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 23.07 (CH_3), 39.93 (N-CH_3), 108.79 (ArC), 119.47 (ArCH), 127.89 (ArCH), 127.95 (ArCH), 128.09 (2 × ArCH), 128.26 (2 × ArCH), 128.75 (2 × ArCH), 129.18 (2 × ArCH), 139.44 (ArC), 139.81 (ArC), 142.13 (ArC), 142.53 (2 × ArCH), 146.56 (ArC), 146.65 (ArC), 150.77 (ArC), 150.88 (ArC), 152.07 (ArC), 152.18 (ArC), 160.38 (ArC), 161.16 (ArC), 163.89 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{27}H_{19}NO_3Na$ $[M + Na]^+$ 428.1365. Found 428.1269.

3,6,7-Trimethyl-10- (trifluoromethyl)difuro[2,3-*f*:2',3'-*h*]quinolin-8-one (332)

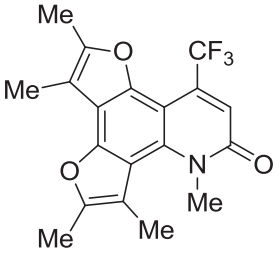
The furoquinolone **332** was prepared from quinolone ether



322 (100 mg, 0.26 mmol) and trifluoroacetic acid (10.0 mL) according to **GP-14** to give the *title compound* as a yellow solid (59 mg, 65%). M.p. 170-171 °C; UV (CH_3CN): λ_{max} 219 nm (ε 35,727 cm^{-1} M^{-1}); IR (KBr): ν_{max} 3457, 3027, 2858, 1603, 1584, 1552, 1596, 1430, 1380, 1323, 1254, 1209, 1170, 1091, 1026, 964, 819, 733, 695 cm^{-1}; 202 (23,919), 213 (25,125), 266 (24,123); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 6H, 2 × CH_3), 2.76 (s, 3H, N-CH_3), 6.25 (s, 1H, ArCH), 7.68 (s, 1H, ArCH), 8.25 (s, 1H, ArCH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 6.71 (CH_3), 9.60 (CH_3), 29.92 (N-CH_3), 107.39 (ArC), 119.23 (ArCH), 122.80 (CF_3), 129.05 (2 × ArC), 141.02 (2 ×ArCH). 143.34 (ArC), 147.24 (ArC), 149.23 (ArC), 157.94 (ArC), 159.37 (2 × ArC), 161.93 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{17}H_{12}F_3NO_3Na$ $[M + Na]^+$ 358.0769. Found 358.0753.

2,3,5,6,7-Pentamethyl-10-(trifluoromethyl)difuro[2,3-*f*:2',3'-*h*]quinolin-8-one (333)

The furoquinolone **333** was prepared from quinolone ether

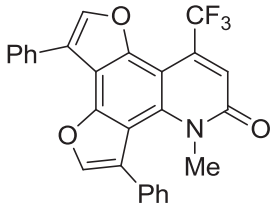


323 (100 mg, 0.25 mmol) and trifluoroacetic acid (10.0 mL) according to **GP-14** to give the *title compound* as a yellow solid (53 mg, 58%). M.p. 170-171 °C; UV (MeOH): λ_{max} 202 nm (ε 23,958 cm^{-1} M^{-1}), 240 (30,310), 184 (33,686), 336 (6,860); IR (KBr): ν_{max} 2965, 2925, 2859, 1666, 1620, 1575, 1466, 11452, 1428, 1396, 1374, 1356, 1315, 1267, 1232, 1215, 1035, 918, 877, 747; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 2.42 (s, 3H,

CH_3), 2.45 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.93 (s, 3H, N-CH_3), 7.29 (s, 1H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 8.98 (CH_3), 11.54 (CH_3), 12.13 (CH_3), 14.15 (CH_3), 41.19 (N-CH_3), 101.08 (ArC), 108.26 (ArC), 109.29 (ArC), 113.65 (ArC), 114.21 (ArC), 116.31 (ArCH), 120.43 (ArC), 124.07 (ArC), 134.07 (ArC), 144.98 (ArC), 150.42 (ArC), 151.11 (ArC), 151.36 (ArC), 163.22 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{19}H_{16}F_3NO_3Na$ $[M + Na]^+$ 386.1082. Found 386.1211.

7-Methyl-3,6-diphenyl-10-(trifluoromethyl)difuro[2,3-*f*:2',3'-*h*]quinolin-8-one (334)

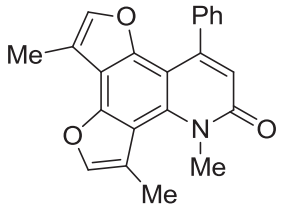
The furoquinolone **334** was prepared from quinolone ether



324 (100 mg, 0.2 mmol) and trifluoroacetic acid (10.0 mL) according to **GP-14** to give the *title compound* as a yellow solid (57 mg, 61%). M.p. 194-165 °C; UV (CH_3CN): λ_{max} 238 nm (ε 35,756 cm^{-1} M^{-1}), 362 (7,160); IR (KBr): ν_{max} 3038, 1696, 1657, 1589, 1519, 1375, 1279, 1188, 1153, 1130, 1114, 1072, 1030, 1000, 949, 809, 689, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H, N-CH_3), 6.68 (s, 1H, ArCH), 7.10 (s, 1H, ArCH), 7.25-7.87 (m, 11H, ArCH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 30.90 (N-CH_3), 93.45 (ArC), 107.04 (ArC), 118.57 (ArC), 120.70 (ArCH), 121.03 (2 × ArC), 122.90 (CF_3), 127.67 (ArC), 127.98 (2 × ArCH), 128.07 (2 × ArCH), 128.42 (2 × ArCH), 128.90 (2 × ArCH), 129.70 (2 × ArCH), 131.20 (2 × ArC), 134.29 (ArC), 141.51 (2 × ArCH), 151.02 (2 × ArC), 161.78 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{27}H_{16}F_3NO_3Na$ $[M + Na]^+$ 482.1082. Found 482.1095.

3,6,7-Trimethyl-10-phenyldifuro[2,3-*f*:2',3'-*h*]quinolin-8-one (335)

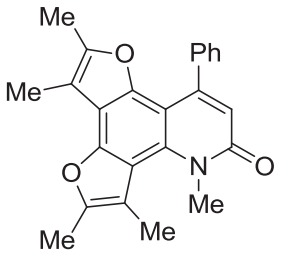
The furoquinolone **335** was prepared from quinolone ether



325 (100 mg, 0.26 mmol) and trifluoroacetic acid (10.0 mL) according to **GP-14** to give the *title compound* as a white solid (61 mg, 66%). M.p. 140-142 °C; UV (CH_3CN): λ_{max} 246 nm (ε 19,996 cm^{-1} M^{-1}), 264 (17,698); IR (KBr): ν_{max} 3448, 1814, 1716, 1642, 1610, 1444, 1371, 1203, 1169, 1142, 1074, 868, 775, 700; cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.97 (s, 3H, N-CH_3), 6.64 (s, 1H, ArCH), 7.07 (s, 1H, ArCH), 7.36-7.45 (m, 5H, ArCH), 7.56 (s, 1H, ArCH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 9.10 (CH_3), 14.64 (CH_3), 29.70 (N-CH_3), 105.02 (ArC), 108.03 (ArCH), 114.04 (ArC), 115.97 (ArC), 116.31 (2 × ArC), 127.75 (2 × ArCH), 128.11 (ArCH), 128.34 (2 × ArCH), 136.23 (ArC), 138.04 (ArC), 140.84 (ArC), 141.96 (2 × ArCH), 151.27 (ArC), 152.10 (ArC), 160.23 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{22}H_{17}NO_3Na$ $[M + Na]^+$ 366.1208. Found 366.1095.

2,3,5,6,7-Pentamethyl-10-phenyldifuro[2,3-*f*:2',3'-*h*]quinolin-8-one (336)

The furoquinolone **336** was prepared from quinolone ether

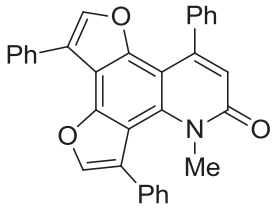


326 (100 mg, 0.24 mmol) and trifluoroacetic acid (10.0 mL) according to **GP-14** to give the *title compound* as a white solid (62 mg, 68%). M.p. 160-161 °C; UV (CH_3CN): λ_{max} 245 nm (ε 35,467 cm^{-1} M^{-1}), 280 (33,278); IR (KBr): ν_{max} 3055, 2982, 2918, 2851, 1804, 1653, 1621, 1576, 1456, 1442, 1418, 1384, 1350, 1230, 1218, 1150, 1120, 1081, 1074, 906,

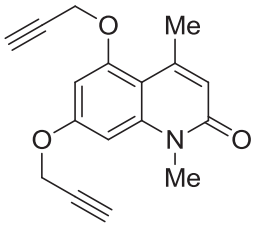
765, 704, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.99 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 6.59 (s, 1H, ArCH), 7.35-7.43 (m, 5H, ArCH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 9.09 (CH_3), 11.20 (CH_3), 12.24 (CH_3), 14.39 (CH_3), 40.32 (N-CH_3), 104.95 (ArC), 107.83 (ArCH), 109.52 (2 × ArC), 112.32 (ArC), 113.94 (ArC), 118.69 (ArC), 127.49 (2 × ArCH), 127.92 (ArCH), 128.38 (2 × ArCH), 134.84 (ArC), 139.84 (ArC), 147.52 (ArC), 149.64 (ArC), 149.77 (ArC), 149.79 (ArC), 150.11 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{24}H_{21}NO_3Na$ $[M + Na]^+$ 394.1521. Found 394.1412.

7-Methyl-3,6,10-triphenyldifuro[2,3-*f*:2',3'-*h*]quinolin-8-one (337)

The furoquinolone **337** was prepared from quinolone ether **327** (100 mg, 0.2 mmol) and trifluoroacetic acid (10.0 mL) according to **GP-14** to give the *title compound* as a white solid (55 mg, 59%). M.p. 125-127 °C; UV (CH_3CN): λ_{max} 246 nm (ε 29,421 cm^{-1} M^{-1}), 278 (28,346); IR (KBr): ν_{max} 3059, 2917, 1702, 1685, 1643, 1611, 1585, 1552, 1503, 1449, 1352, 1230, 1211, 1170, 1144, 1069, 1075, 1022, 1022, 1000, 972, 857, 820, 780, 757, 740, 664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.50 (s, 3H, N-CH_3), 6.58 (s, 1H, ArCH), 7.34-7.42 (m, 15H, ArCH), 8.12 (s, 2H ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 40.32 (N-CH_3), 104.95 (ArC), 107.83 (ArC), 109.52 (2 × ArC), 112.32 (ArC), 113.94 (ArC), 118.67 (ArCH), 127.46 (4 × ArCH), 127.90 (2 × ArCH), 128.36 (4 × ArCH), 129.03 (4 × ArCH), 131.21 (ArCH), 134.81 (ArC), 139.83 (2 × ArCH), 147.51 (ArC), 149.62 (ArC), 149.75 (ArC), 149.77 (2 × ArC), 160.11 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{32}H_{21}NO_3Na$ $[M + Na]^+$ 490.1521. Found 490.1432.

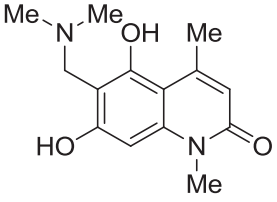


1,4-Dimethyl-5,7-bis(prop-2-yn-1-yloxy)quinolin-2-one (339)



The quinolone ether **339** was prepared from 5,7-dihydroxy-1-methyl-4-phenylquinolin-2-ones **314** (200 mg, 0.35 mmol), propargyl bromide (100 µL, 0.70 mmol), potassium carbonate (100 mg, 0.70 mmol) and acetone (100 mL) according to **GP-13** to give the *title compound* as brown solid (137 mg, 66%). M.p. 280-281 °C; UV (CH_3CN): λ_{max} 243 nm (ε 37,786 cm^{-1} M^{-1}), 311 (8,652); IR (KBr): ν_{max} 3056, 2917, 1694, 1653, 1611, 1587, 1504, 1447, 1375, 1313, 1281, 1253, 1201, 1145, 1087, 1072, 1032, 1001, 1022, 864, 815, 776, 730 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 1.54 (s, 2H, CH), 2.49-2.54 (m, 3H, CH_3), 3.58 (s, 3H, N-CH_3), 4.69 (s, 2H, CH_2), 4.73 (s, 2H, CH_2), 6.27 (s, 1H, ArCH), 6.41 (d, *J* = 3.0 Hz, 1H, ArCH), 6.51 (d, *J* = 3.0 Hz, 1H, ArCH); ^{13}C NMR (75.6 MHz, acetone-d_6): δ 19.31 (CH_3), 30.29 (N-CH_3), 56.90 (O-CH_2), 57.31 (O-CH_2), 76.04 (2 × C≡CH), 78.21 (2 × C≡CH), 91.20 (ArCH), 96.90 (ArCH), 104.60 (ArC), 134.02 (ArC), 137.12 (ArC), 148.80 (ArC), 158.81 (ArC), 161.01 (ArC), 162.03 (CO); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{17}H_{15}NO_3Na$ $[M + Na]^+$ 304.1052. Found 304.1056.

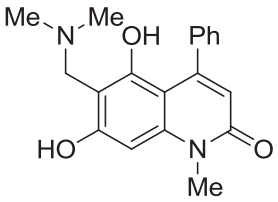
6-((Dimethylamino)methyl)-5,7-dihydroxy-1,4-dimethylquinolin-2-one (341)



Bis(dimethylamino)methane (437 µL, 2.13 mmol) was added with stirring to a solution of 5,7-dihydroxy-1,4-dimethylquinolin-2-one **314** (200 mg, 0.97 mmol) in absolute ethanol (5.0 mL) and the mixture was heated under reflux for 3 h. Evaporation of the solvent gave an orange solid, which was dissolved in a small volume of ethyl acetate and precipitated with light petroleum. The precipitate was

filtered to yield the *title compound* as a pale yellow solid (170 mg, 66%). M.p. 310-311 °C (dec.); UV (MeOH): λ_{max} 208 nm (ε 27,222 $cm^{-1}M^{-1}$), 221 (27,885), 242 (27,066), 262 (18,954), 321 (14,742); IR (KBr): ν_{max} 3385, 3101, 2980, 2951, 2856, 2790, 2677, 1616, 1552, 1428, 1361, 1298, 1273, 1103, 1160, 1045, 994, 840, 815, 730, 543, 448 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 2.34 (s, 6H, 2 × N-CH_3), 2.58 (s, 3H, CH_3), 3.44 (s, 3H, N-CH_3), 3.79 (s, 2H, CH_3); 6.02 (s, 1H, H3), 6.37 (s, 1H, H8); ^{13}C NMR (75.6 MHz, acetone-d_6): δ 15.50 (CH_3), 23.75 (N-CH_3), 43.31 (2 × N-CH_3), 54.80 (N-CH_2), 91.38 (ArCH), 102.12 (ArC), 106.21 (ArC), 116.35 (ArCH), 136.13 (ArC), 149.33 (ArC), 158.31 (ArC), 160.01 (ArC), 161.77 (C=O); HRMS *m/z* Calcd. for $C_{14}H_{18}N_2O_3$ $[M + 1]^+$ 263.1317. Found 263.1392.

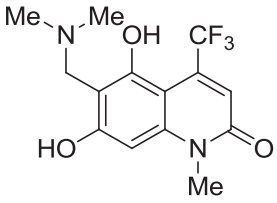
6-((Dimethylamino)methyl)-5,7-dihydroxy-1-methyl-4-phenylquinolin-2-one (342)



Bis(dimethylamino)methane (434 µL, 1.62 mmol) was added with stirring to a solution of 5,7-dihydroxy-1-methyl-4-phenylquinolin-2-one **317** (200 mg, 0.74 mmol) in absolute ethanol (5.0 mL) and the mixture was heated under reflux for 3 h. Evaporation of the solvent gave an orange solid, which was dissolved in a small volume of ethyl acetate and precipitated with light petroleum. The precipitate was filtered to yield the *title compound* as an orange solid (178 mg, 68%). M.p. 300-301 °C (dec.); UV (MeOH): λ_{max} 204 nm (ε 17,658 $cm^{-1}M^{-1}$), 225 (18,824), 265 (9,104), 322 (6,440); IR (KBr): ν_{max} 3443, 3056, 1618, 1592, 1550, 1443, 1427, 1296, 1271, 1159, 1035, 1014, 989, 855, 770, 700, 554, 515, 440 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 6H, 2 × N-CH_3), 3.67 (s, 3H, CH_3), 3.69 (s, 2H, N-CH_2), 6.22 (s, 1H, H3), 6.50 (s, 1H, H8), 7.39-7.52 (m, 5H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 30.10 (N-CH_3), 43.34 (2 × N-CH_3), 55.36 (N-CH_2), 94.20 (ArCH), 102.24

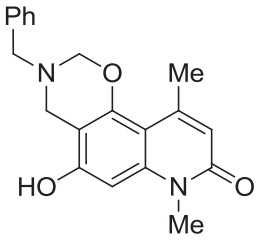
(ArC), 103.50 (ArC), 106.13 (ArC), 118.00 (ArCH), 128.07 (2 × ArCH), 129.16 (2 × ArCH), 129.19 (ArCH), 136.03 (ArC), 142.20 (ArC), 156.21 (ArC), 159.31 (ArC), 161.77 (C=O); HRMS *m/z:* Calcd. for $C_{19}H_{20}N_2O$ $[M + 1]^+$ 325.1474. Found 325.1542.

6-((Dimethylamino)methyl)-5,7-dihydroxy-1-methyl-4-(trifluoromethyl)quinolin-2(1H)-one (343)



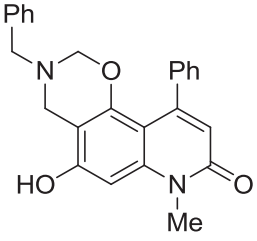
Bis(dimethylamino)methane (438 µL, 1.69 mmol) was added with stirring to a solution of 5,7-dihydroxy-1-methyl-4-(trifluoromethyl)quinolin-2-one **318** (200 mg, 0.77 mmol) in absolute ethanol (5.0 mL) and the mixture was heated under reflux for 3 h. Evaporation of the solvent gave an orange solid, which was dissolved in a small volume of ethyl acetate and precipitated with light petroleum. The precipitate was filtered to yield the *title compound* as a pale yellow solid (160 mg, 65%). M.p. 230-231 °C, (dec.); UV (MeOH): λ_{max} 202 nm (ε 25,280 $cm^{-1}M^{-1}$), 220 (27,808), 269 (13,366), 287 (10,554), 342 (12,112); IR (KBr): ν_{max} 3443, 3056, 1618, 1592, 1550, 1443, 1427, 1296, 1271, 1159, 1035, 1014, 989, 855, 770, 700, 554, 515, 440 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.34 (s, 6H, 2 × N-CH_3), 3.47 (s, 3H, CH_3), 3.78 (s, 2H, N-CH_2), 6.31 (s, 1H, H3), 6.59 (s, 1H, H8); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 30.02 (N-CH_3), 43.38 (2 × N-CH_3), 55.01 (N-CH_2), 91.28 (ArCH), 99.30 (ArC), 102.36 (ArC), 106.03 (ArC), 115.03 (ArCH), 122.09 (CF_3), 142.83 (ArC), 159.39 (ArC), 159.89 (ArC), 160.38 (C=O); HRMS *m/z:* Calcd. for $C_{14}H_{15}F_3N_2O$ $[M + 1]^+$ 317.1035. Found 317.1111.

3-Benzyl-5-hydroxy-7,10-dimethyl-3,4-dihydro-2H-[1,3]oxazino[6,5-*f*]quinolin-8(7H)-one (344)



The benzoxazinoquinolone **344** was prepared from quinolone **314** (250 mg, 1.21 mmol), benzylamine (260 µL, 2.42 mmol) and formaldehyde (0.4 mL, 37%, 12.1 mmol) in absolute ethanol (5.0 mL) according to **GP-15** to give the *title compound* as a yellow solid (300 mg, 73%). M.p. 280-281 °C (dec.); UV (MeOH): λ_{max} 209 nm (ε 28,022 $cm^{-1}M^{-1}$), 241 (23,049), 260 (12,801), 320 (11,121) IR (KBr): ν_{max} 3311, 3025, 2930, 2853, 1598, 1507, 1494, 1451, 1357, 1270, 1197, 1113, 1073, 1057, 1027, 1013, 967, 738,697 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 3.65 (s, 3H, CH_3), 3.48 (s, 3H, N-CH_3), 3.92 (s, 4H, 2 × N-CH_2), 4.98 (s, 2H, O-CH_2), 6.09 (s, 1H, ArH), 6.50 (s, 1H, ArH), 7.24-7.42 (m, 5H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 24.71 (CH_3), 29.61 (N-CH_3), 45.70 (N-CH_2), 55.79 (N-CH_2), 81.84 (O-CH_2), 93.07 (ArCH), 102.66 (ArC), 105.47 (ArC), 116.14 (ArCH), 127.34 (ArCH), 128.38 (2 × ArCH), 128.92 (2 × ArCH), 129.24 (ArC), 137.82 (ArC), 140.77 (ArC), 149.20 (ArC), 154.39 (ArC), 158.08 (ArC), 162.66 (C=O); HRMS (ESI) *m/z*: Calcd. for $C_{20}H_{20}N_2O_3$ $[M]^+$ 336.1474. Found 336.1737.

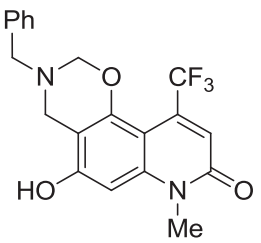
3-Benzyl-5-hydroxy-7-methyl-10-phenyl-3,4-dihydro-2H-[1,3]oxazino[6,5-*f*]quinolin-8(7H)-one (345)



The benzoxazinoquinolone **345** was prepared from quinolone **317** (200 mg, 0.93 mmol), benzylamine (200 µL, 1.8 mmol) and formaldehyde (0.3 mL, 37%, 9.3 mmol) in absolute ethanol (5.0 mL) according to **GP-15** to give the *title compound* as a white solid (269 mg, 69%). M.p. 281-283 °C (dec.); UV (MeOH): λ_{max} 206 nm (ε 18,156 cm^{-1}

$^{1}M^{-1}$), 241 (16,245), 283 (5,098), 368 (8,918) IR (KBr): ν_{max} 3488, 3059, 3030, 2373, 1607, 1560, 1356, 1248, 1203, 1169, 1115, 1074, 967, 697 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.52 (s, 3H, N-CH_3), 3.69 (s, 2H, N-CH_2), 3.75 (s, 2H, N-CH_2), 4.32 (s, 2H, O-CH_2), 5.98 (s, 1H, ArH), 6.50 (s, 1H, ArH), 7.24-7.33 (m, 10H ArH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 29.60 (N-CH_3), 45.19 (N-CH_2), 55.13 (N-CH_2), 81.39 (O-CH_2), 92.94 (ArCH), 101.97 (ArC), 102.34 (ArC), 117.62 (ArCH), 127.32 (ArCH), 127.45 (2 × ArCH), 127.55 (2 × ArCH), 127.60 (ArCH), 128.62 (2 × ArCH), 129.22 (2 × ArCH), 138.25 (ArC), 141.34 (ArC), 141.96 (ArC), 149.67 (ArC), 153.10 (ArC), 158.38 (ArC), 160.86 (C=O); HRMS (ESI) *m/z:* Calcd. for $C_{25}H_{22}N_2O_3$ $[M + 1]^+$ 399.1630. Found 399.1602.

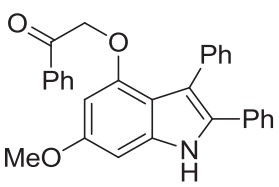
3-Benzyl-5-hydroxy-7-methyl-10-(trifluoromethyl)-3,4-dihydro-2H-[1,3]oxazino[6,5-*f*]quinolin-8(7H)-one (346)



The benzoxazinoquinolone **346** was prepared from quinolone **318** (200 mg, 0.77 mmol), benzylamine (165 µL, 1.54 mmol) and formaldehyde (0.3 mL, 37%, 7.7 mmol) in absolute ethanol (5.0 mL) according to **GP-15** to give the *title compound* as a pale cream solid (191 mg, 63%). M.p. 200-201 °C (dec.); UV (MeOH): λ_{max} 244 nm (ε 36,777 $cm^{-1}M^{-1}$), 266 (23,709), 355 (22,464); IR (KBr): ν_{max} 3127, 1653, 1611, 1568, 1459, 1428, 1373, 1356, 1277, 1145, 1139, 1089, 1017, 879, 812, 755 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 3.45 (N-CH_3), 3.81 and 3.85 each (s, 4H, 2 × N-CH_2), 4.87 (s, 2H, O-CH_2), 6.50 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.24-7.26 (m, 5H, ArH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 30.16 (N-CH_3), 44.72 (N-CH_2), 55.28 (N-CH_2), 82.63 (O-CH_2), 93.56 (ArCH), 98.45 (ArC), 102.69 (ArC), 116.81 (ArCH), 116.91 (CF_3), 127.76

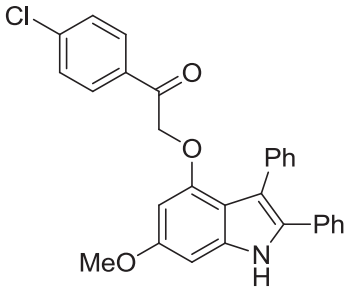
(ArCH), 128.75 (2 × ArCH), 129.04 (2 × ArCH), 134.65 (ArC), 138.29 (ArC), 141.89 (ArC), 151.94 (ArC), 159.10 (ArC), 160.62 (C=O); HRMS (ESI) *m/z*: Calcd. for $C_{20}H_{17}F_3N_2O_3$ $[M + 1]^+$ 391.1191. Found 391.1269.

2-((6-Methoxy-2,3-diphenyl-1H-indol-4-yl)oxy)-1-phenylethanone (378)



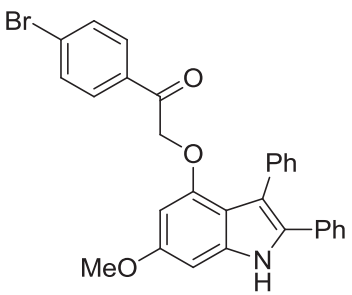
The acyl indole **378** was prepared from indole **378** (150 mg, 0.47 mmol), phenacylbromide (93 mg, 0.47 mmol) and potassium carbonate (65 mg, 0.47 mmol) in acetone (50 mL) according to **GP-16** to give the *title compound* as a white solid (171 mg, 83%). M.p. 140-141 °C; UV (MeOH): λ_{max} 203 nm (ε 26,716 $cm^{-1}M^{-1}$), 244 (15,284), 322 (7,750); IR (KBr): ν_{max} 3397, 3056, 2926, 1700, 1684, 1598, 1501, 1448, 1374, 1287, 1261, 1225, 1197, 1153, 1070, 1000, 965, 912, 805, 765, 728, 697, 655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 4.96 (s, 2H, O-CH_2), 6.22 (d, *J* = 3.0 Hz, 1H, H5), 6.54 (d, *J* = 3.0 Hz, 1H, H7), 7.10-7.72 (m, 15H, ArH), 8.20 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.61 (OCH_3), 71.57 (O-CH_2), 87.74 (ArCH), 94.18 (ArCH), 113.38 (ArC), 114.84 (ArC), 125.95 (ArCH), 126.91 (ArCH), 127.24 (2 × ArCH), 127.64 (2 × ArCH), 128.39 (2 × ArCH), 128.41 (2 × ArCH), 128.46 (2 × ArCH), 131.35 (2 × ArCH), 132.02 (ArC), 132.68 (ArC), 133.35 (ArCH), 134.50 (ArC), 135.59 (ArC), 137.58 (ArC), 153.11 (ArC), 157.36 (ArC) 195.11 (C=O); HRMS *m/z*: Calcd. for $C_{29}H_{23}NO_3$ $[M + 1]^+$ 434.1678. Found 434.1759.

1-(4-Chlorophenyl)-2-((6-methoxy-2,3-diphenyl-indol-4-yl)oxy)ethanone (379)



The acyl indole **379** was prepared from indole **164** (150 mg, 0.47 mmol), 4-chlorophenacylbromide (151 mg, 0.47 mmol) and potassium carbonate (65 mg, 0.47 mmol) in acetone (50 mL) according to **GP-16** to give the *title compound* as a white solid (161 mg, 72%). M.p. 128-129 °C; UV (MeOH): λ_{max} 207 nm (ε 34,698 $cm^{-1}M^{-1}$), 254 (25,918), 321 (10,927); IR (KBr): ν_{max} 3426, 2918, 2283, 1688, 1628, 1510, 1453, 1196, 1153, 1094, 761, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 4.90 (s, 2H, O-CH_2), 6.21 (s, 1H, H5), 6.55 (s, 1H, H7), 7.09-7.64 (m, 14H, ArH), 8.26 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.61 (OCH_3), 71.62 (O-CH_2), 87.81 (ArCH), 93.87 (ArCH), 113.20 (ArC), 114.66 (ArC), 126.01 (ArCH), 126.96 (ArCH), 127.21 (2 × ArCH), 127.66 (2 × ArCH), 128.42 (2 × ArCH), 128.67 (2 × ArCH), 130.08 (2 × ArCH), 131.34 (2 × ArCH), 132.13 (ArC), 132.57 (ArC), 132.72 (ArC), 135.59 (ArC), 137.58 (ArC), 139.72 (ArC), 152.78 (ArC), 157.32 (ArC) 194.48 (C=O); HRMS *m/z:* Calcd. for $C_{29}H_{22}ClNO_3$ $[M + 1]^+$ 468.1288. Found 468.1362.

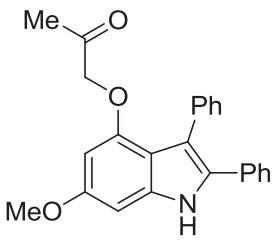
2-((6-Methoxy-2,3-diphenyl-1H-indol-4-yl)oxy)-1-phenylethanone (380)



The acyl indole **380** was prepared from indole **164** (150 mg, 0.47 mmol), 4-bromophenacylbromide (129 mg, 0.47 mmol) and potassium carbonate (65 mg, 0.47 mmol) in acetone (50 mL) according to **GP-16** to give the *title compound* as a white solid (189 mg, 77%). M.p. 156-158 °C; UV (MeOH): λ_{max} 203 nm (ε 44,559 $cm^{-1}M^{-1}$), 257 (30,200), 321 (13,797); IR

(KBr): ν_{max} 3347, 3057, 2364, 1689, 1627, 1599, 1548, 1513, 1498, 1442, 1392, 1289, 1265, 1196, 1153, 1123, 1077, 1053, 1006, 965, 915, 826, 974, 764, 769 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 4.89 (s, 2H, O-CH_2), 6.21 (d, *J* = 3.0 Hz, 1H, H5), 6.53 (d, *J* = 3.0 Hz, 1H, H7), 7.11-7.56 (m, 14H, ArH), 8.24 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.60 (OCH_3), 71.60 (O-CH_2), 87.83 (ArCH), 93.88 (ArCH), 94.90 (ArC), 113.20 (ArC), 114.01 (ArC), 126.04 (ArCH), 126.97 (ArCH), 127.22 (2 × ArCH), 127.66 (2 × ArCH), 128.42 (2 × ArCH), 130.60 (2 × ArCH), 131.34 (2 × ArCH), 131.65 (2 × ArCH), 132.14 (ArC), 132.56 (ArC), 133.11 (ArC), 135.58 (ArC), 137.58 (ArC), 152.77 (ArC), 157.21 (ArC), 194.70 (C=O); HRMS *m/z:* Calcd. for $C_{29}H_{22}BrNO_3$ $[M + 1]^+$ 512.0783. Found 512.0856.

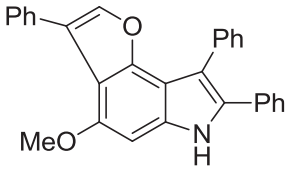
1-((6-Methoxy-2,3-diphenyl-1H-indol-4-yl)oxy)propan-2-one (381)



The acyl indole **381** was prepared from indole **164** (150 mg, 0.47 mmol), chloroacetone (50 µL, 0.47 mmol) and potassium carbonate (65 mg, 0.47 mmol) in acetone (50 mL) according to **GP-16** to give the *title compound* as a white solid (130 mg, 73%). M.p. 190-192 °C; UV (CH_2Cl_2): λ_{max} 227 nm (ε 21,109 $cm^{-1}M^{-1}$), 263 (24,300), 341 (11,352); IR (KBr): ν_{max} 3391, 2920, 2841, 1713, 1632, 1601, 1586, 1508, 1434, 1413, 1360, 1326, 1201, 1164, 1132, 1047, 1028, 971, 953, 830, 766, 777, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (s, 3H, $COCH_3$), 3.84 (s, 3H, OCH_3), 4.30 (s, 2H, O-CH_2), 6.11 (d, *J* = 3.0 Hz, 1H, H5), 6.57 (d, *J* = 3.0 Hz, 1H, H7), 7.19-7.43 (m, 10H, ArH), 8.37 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 25.44 ($CH_2CO\underline{CH_3}$), 54.77 (OCH_3), 72.85 (O-CH_2), 87.42 (ArCH), 92.87 (ArCH), 94.90 (ArC), 114.01 (ArC), 125.90 (ArCH), 126.54 (ArCH), 127.47 (2 × ArCH), 127.54 (2 × ArCH), 128.12 (2 ×

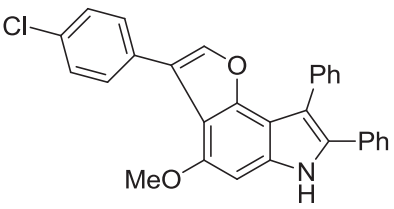
ArCH), 131.35 (2 × ArCH), 132.13 (ArC), 132.54 (ArC), 136.38 (ArC), 137.51 (ArC), 152.72 (ArC), 157.40 (ArC), 207.09 (C=O); HRMS *m/z:* Calcd. for $C_{24}H_{21}NO_3$ $[M + 1]^+$ 372.1521. Found 372.1592.

4-Methoxy-3,7,8-triphenyl-6H-furo[2,3-*e*]indole (383)



The furoindole **383** was prepared from indole **378** (100 mg, 0.23 mmol) in trifluoroacetic acid (10 mL) according to **GP-17** to give the *title compound* as a white solid (62 mg, 65%). M.p. 152-153 °C; UV (MeOH): λ_{max} 202 nm (ε 15,272 $cm^{-1}M^{-1}$), 229 (10,582), 274 (7,885), 327 (4,897); IR (KBr): ν_{max} 3348, 2923, 2852, 1741, 1635, 1602, 1547, 1448, 1413, 1288, 1205, 1117, 1071, 1043, 923, 804, 764, 696, 613, 571 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H, OCH_3), 6.74 (s, 1H, H7), 7.25-7.65 (m, 16H, ArH), 8.28 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.52 (OCH_3), 88.34 (ArCH), 109.43 (ArC), 110.49 (ArC), 113.41 (ArC), 120.91 (ArC), 122.13 (ArC), 126.34 (ArCH), 127.23 (ArCH), 127.64 (2 × ArCH), 128.02 (2 × ArCH), 128.60 (2 × ArCH), 129.55 (2 × ArCH), 130.68 (2 × ArCH), 131.14 (2 × ArCH), 131.79 (ArCH), 132.02 (ArC), 132.83 (ArC), 134.95 (ArC), 134.97 (ArC), 139.11 (ArCH), 149.90 (ArC), 151.58 (ArC); HRMS *m/z:* Calcd. for $C_{29}H_{21}NO_2$ $[M + 1]^+$ 416.1572. Found 416.1645.

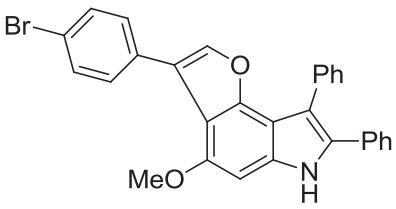
3-(4-Chlorophenyl)-4-methoxy-7,8-diphenyl-6H-furo[2,3-*e*]indole (384)



The furoindole **384** was prepared from indole **379** (100 mg, 0.21 mmol) in trifluoroacetic acid (10.0 mL)

according to **GP-17** to give the *title compound* as a white solid (61 mg, 63%). M.p. 289-290 °C; UV (MeOH): λ_{max} 202 nm (ε 44,720 $cm^{-1}M^{-1}$), 236 (34,932), 275 (21,058), 320 (16,702); IR (KBr): ν_{max} 3420, 2930, 1636, 1601, 1572, 1547, 1493, 1408, 1353, 1298, 1285, 1204, 1149, 1121, 1091, 1070, 1041, 1014, 962, 923, 832, 766, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 6.73 (s, 1H, H7), 7.26-7.59 (m, 15H, ArH), 8.29 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.46 (OCH_3), 88.36 (ArCH), 109.43 (ArC), 110.55 (ArC), 113.40 (ArC), 122.10 (ArC), 126.34 (ArCH), 127.23 (ArCH), 127.80 (2 × ArCH), 127.87 (2 × ArCH), 128.03 (2 × ArCH), 128.60 (2 × ArCH), 130.62 (2 × ArCH), 130.80 (2 × ArCH), 131.09 (ArC), 131.31 (ArCH), 132.02 (ArC), 132.73 (ArC), 134.99 (ArC), 139.10 (ArCH), 139.31 (ArC), 149.90 (ArC), 151.57 (ArC); HRMS *m/z:* Calcd. for $C_{29}H_{20}ClNO_2$ $[M + 1]^+$ 450.1183. Found 450.1256.

3-(4-Bromophenyl)-4-methoxy-7,8-diphenyl-6H-furo[2,3-*e*]indole (385)

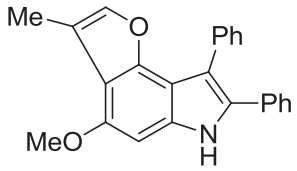


The furoindole **385** was prepared from indole **380** (100 mg, 0.19 mmol) in trifluoroacetic acid (10.0 mL) according to **GP-17** to give the *title compound* as a white solid (64 mg, 66%). M.p. 200-201 °C; UV (MeOH): λ_{max} 203 nm (ε 29,475 $cm^{-1}M^{-1}$), 237 (23,226), 277 (13,008), 320 (11,239); IR (KBr): ν_{max} 3403, 3059, 2935, 2361, 1635, 1600, 1570, 1550, 1491, 1481, 1440, 1409, 1389, 1351, 1313, 1298, 1286, 1273, 1204, 1147, 1100, 1070, 1011, 1040, 962, 923, 900, 834, 797, 767, 731, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H, OCH_3), 6.74 (s, 1H, H7), 7.26-7.61 (m, 15H, ArH), 8.29 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.47 (OCH_3), 88.34 (ArCH), 109.43 (ArC), 110.49 (ArC), 113.41 (ArC),

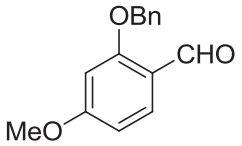
120.91 (ArC), 122.13 (ArC), 126.34 (ArCH), 127.23 (ArCH), 127.86 (2 × ArCH), 128.02 (2 × ArCH), 128.60 (2 × ArCH), 130.61 (2 × ArCH), 130.75 (2 × ArCH), 131.14 (2 × ArCH), 131.79 (ArCH), 132.02 (ArC), 132.68 (ArC), 134.95 (ArC), 134.97 (ArC), 139.09 (ArCH), 149.92 (ArC), 151.58 (ArC); HRMS *m/z:* Calcd. for $C_{29}H_{20}BrNO_2$ $[M + 1]^+$ 494.0677. Found 494.0749.

4-Methoxy-3-methyl-7,8-diphenyl-6*H*-furo[2,3-*e*]indole (386)

The furoindole **386** was prepared from indole **381** (100 mg, 0.26 mmol) in trifluoroacetic acid (10.0 mL) according to **GP-17** to give the *title compound* as a white solid (59 mg, 62%). M.p. 160-161 °C; UV (MeOH): λ_{max} 203 nm (ε 34,241 $cm^{-1}M^{-1}$), 293 (24,392), 267 (22,945), 326 (14,826); IR (KBr): ν_{max} 3398, 3057, 3027, 2995, 2927, 2950, 2358, 2344, 1636, 1601, 1548, 1474, 1295, 1277, 1203, 1106, 80, 764, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 6.66 (s, 1H, H7), 7.18-7.60 (m, 11H, ArH), 8.22 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 10.03 (CH_3), 55.48 (OCH_3), 87.34 (ArC), 109.40 (ArCH), 113.04 (ArC), 133.33 (ArC), 116.16 (ArCH), 126.16 (ArCH), 127.05 (ArCH), 127.87 (2 × ArCH), 127.93 (2 × ArCH), 128.55 (2 × ArCH), 130.59 (2 × ArCH), 132.93 (ArC), 134.77 (ArC), 135.14 (ArC), 138.12 (ArC), 141.01 (ArC),149.54 (ArC), 152.46 (ArC); HRMS *m/z:* Calcd. for $C_{24}H_{19}NO_2$ $[M]^+$ 353.1416. Found 353.1416.

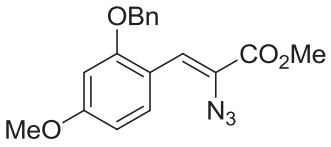


2-Benzyloxy-4-methoxybenzaldehyde (388)



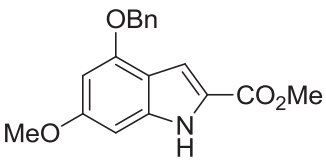
The benzyloxy aldehyde **388** was prepared from 2-hydroxy-4-methoxybenzaldehyde **387** (10.0 g, 0.08 mol), anhydrous potassium carbonate (11.0 g, 0.08 mol), benzyl bromide (9.8 mL, 0.08 mmol), in anhydrous *N*,*N*-dimethylformamide (100 mL) according to **GP-18** to give the *title compound* as a yellow solid (12.30 g, 77%). M.p. 64-66 °C, *lit*[198] 65-66 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H, O-CH_3), 5.16 (s, 2H, O-CH_2), 6.51 (s, 1H, ArH), 6.54-6-58 (m, 1H, ArH), 7.34-7.46 (m, 5H, ArH), 7.83 (bs, 1H, ArH), 10.38 (s, 1H, CHO).

***(Z)*-Methyl 2-azido-3-(2-(benzyloxy)-4-methoxyphenyl)acrylate (289)**



The azidocinnamate **289** was prepared from aldehyde **388** (3.0 g, 0.12 mol), sodium (19.0 g, 1.2 mol) and methyl azidoacetate (110 g, 0.96 mol) in anhydrous methanol (50 mL) according to **GP-19** to give the *title compound* as a pale yellow solid (3.20 g, 76%). M.p. 93-94 °C, *lit*[199] 91-93 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 3H, $COOCH_3$), 3.87 (s, 3H, OCH_3), 5.05 (s, 2H, O-CH_2), 6.44-6.51 (m, 1H, ArH), 7.20-7.39 (m, 7H, ArH), 7.78 (d, *J* = 9.0 Hz, CH).

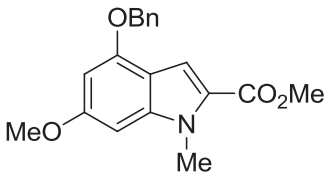
Methyl 4-(benzyloxy)-6-methoxy-indole-2-carboxylate (390)



The indole **390** was prepared from *(Z)*-methyl-2-azido-3-(2-(benzyloxy)-4-methoxyphenyl) acrylate **389** (3.0 g, 0.0075

mol) in 1,2-dichlorobenzene (50 mL) according to **GP-20** to give the *title compound* as a white granular solid (1.9 g, 69%). M.p. 186-188 °C, *lit*[199] 187-188 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H, O-CH_3), 3.90 (s, 3H, $COOCH_3$), 5.16 (s, 1H, O-CH_2), 6.26 (d, *J* = 3.0 Hz, 1H, H5), 6.44 (d, *J* = 3.0 Hz, 1H, H7), 7.25-7.50 (m, 6H, ArH), 8.76 (bs, 1H, NH).

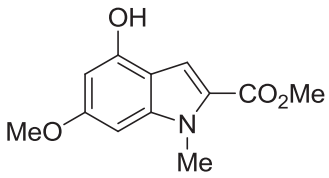
Methyl 4-(benzyloxy)-6-methoxy-1-methyl-indole-2-carboxylate (391)



Dimethyl sulfoxide (25 mL) was added to powdered potassium hydroxide (0.67 g, 0.012 mmol) and the mixture was stirred at room temperature for 10 min. indole **390** (2.0 g, 0.0061 mol) was then added and the mixture was stirred at room temperature for 1 h. The reaction mixture was cooled briefly on ice bath. Iodomethane (1.15 mL, 0.0122 mol) was addedto the reaction mixture and stirred at room temperature for a further 1 h. The reaction mixture was diluted with water and extracted with diethyl ether. The organic layer was washed with water, dried ($MgSO_4$), and concentrated to yield the *title compound* as a white solid (1.90 g, 95%). M.p. 120-121 °C; UV (CH_2Cl_2): λ_{max} 223 nm (ε 4,095 $cm^{-1}M^{-1}$), 256 (9,782); IR (KBr): ν_{max} 2948, 2901, 1711, 1623, 1590, 1499, 1462, 1448, 1433, 1382, 1349, 1305, 1252, 1236, 1212, 1187, 1165, 1140, 1087, 1066, 1046, 1030, 997, 948, 948, 818, 785, 762, 731, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (bs, 6H, O-CH_3 and $COOCH_3$), 3.98 (s, 3H, N-CH_3), 5.14 (s, 2H, O-CH_2), 6.25 (d, *J* = 3.0 Hz, 1H, H5), 6.33 (d, *J* = 3.0 Hz, 1H, H7), 7.33-7.49 (m, 6H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 31.74 (N-CH_3), 51.24 (COO$\underline{CH_3}$), 55.48 (O-CH_3), 69.75 (O-CH_2), 84.77 (ArCH), 93.69 (ArCH), 108.59 (ArCH), 112.28 (ArC), 125.05 (ArC), 127.28 (2 × ArCH), 127.84 (ArCH), 128.46 (2 × ArCH), 136.78 (ArC), 141.40 (ArC),

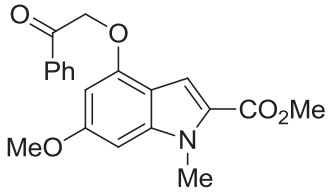
153.97 (ArC), 159.98 (ArC), 162.41 (C=O); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{19}H_{19}NO_4$ $[M]^+$ 325.1314. Found 325.1318; Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.09; H, 5.96; N, 4.74.

Methyl 4-hydroxy-6-methoxy-1-methyl-indole-2-carboxylate (392)



The hydroxyindole **392** was prepared from indole **391** (1.80 g 0.007 mol), 5% Pd/C catalyst (60 mg) in tetrahydrofuran (5.0 mL) according to **GP-8** to give the *title compound* as a brown solid (0.78 g, 69%). M.p. 187-189 °C; UV (MeOH): λ_{max} 207 nm (ε 18,377 $cm^{-1}M^{-1}$), 248 (20,163), 308 (15,345); IR (KBr): ν_{max} 3304, 2553, 2844, 2356, 1680, 1626, 1588, 1512, 1449, 1378, 1251, 1203, 1173, 1139, 1088, 1044, 817, 760, 559, 498 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 3.69 (s, 6H, O-CH_3 and $COOCH_3$), 3.84 (s, 3H, N-CH_3), 6.06 (d, *J* = 3.0 Hz, 1H, H5), 6.37 (d, *J* = 3.0 Hz, 1H, H7), 7.17 (s, 1H, H3); ^{13}C NMR (75.6 MHz, acetone-d_6): δ 31.74 (N-CH_3), 51.76 (COO$\underline{CH_3}$), 55.93 (O-CH_3), 69.75 (O-CH_2), 85.38 (ArCH), 96.79 (ArCH), 98.79 (ArC), 108.94 (ArCH), 112.65 (ArC), 143.31 (ArC), 153.48 (ArC), 163.03 (C=O); HRMS *m/z:* Calcd. for $C_{12}H_{13}NO_4$ $[M]^+$ 235.0845. Found 235.0855.

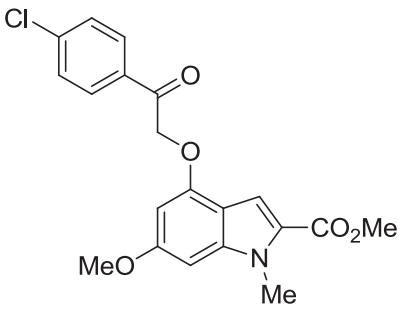
Methyl 6-methoxy-1-methyl-4-(2-oxo-2-phenylethoxy)-indole-2-carboxylate (387)



The acyl indole **387** was prepared from indole **392** (200 mg, 0.85 mmol), phenacylbromide (168 mg, 0.85 mmol) and potassium carbonate (117 mg, 0.85 mmol) in acetone (50 mL) according to **GP-16** to give the *title compound* as a white solid (219 mg, 73%).

M.p.154-155 °C; UV (MeOH): λ_{max} 244 nm (ε 30,852 $cm^{-1}M^{-1}$), 309 (17,332); IR (KBr): ν_{max} 3355, 3016, 2951, 2896, 2836, 1705, 1693, 1628, 1586, 1502, 1470, 1446, 1434, 1380, 1355, 1306, 1245, 1214, 122 82, 1190, 1165, 1144, 1103, 1088, 1057, 999, 952, 85504, 760, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H, O-CH_3), 3.79 (s, 3H, $COOCH_3$), 3.93 (s, 3H, N-CH_3), 5.26 (s, 1H, O-CH_2), 6.05 (d, *J* = 3.0 Hz, 1H, H5), 6.29 (d, *J* = 3.0 Hz, 1H, H7), 7.33 (s, 1H, H3), 7.39-7.54 (m, 3H, ArH), 7.93-7.96 (m, 2H, ArH); ^{13}C NMR (75.6 MHz, acetone-d_6): δ 32.29 (N-CH_3), 51.80 (COO$\underline{CH_3}$), 56.02 (O-CH_3), 71.33 (O-CH_2), 85.90 (ArCH), 94.25 (ArCH), 109.03 (ArCH), 112.60 (ArC), 125.86 (ArC), 128.65 (2 × ArCH), 129.22 (2 × ArCH), 134.26 (ArCH), 135.02 (ArC), 141.96 (ArC), 153.67 (ArC), 160.19 (ArC), 162.93 (C=O), 194.53 ($CH_2\underline{CO}$Ph); HRMS *m/z:* Calcd. for $C_{20}H_{19}NO_5$ $[M + 1]^+$ 354.1263. Found 354.1336.

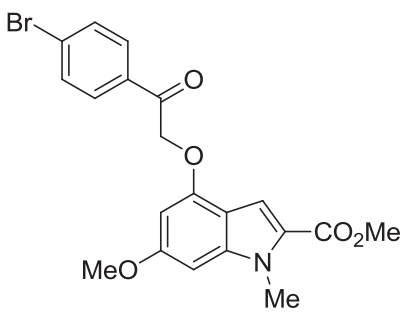
Methyl 4-(2-(4-chlorophenyl)-2-oxoethoxy)-6-methoxy-1-methyl-indole-2-carboxylate (388)



The acyl indole **388** was prepared from indole **392** (200 mg, 0.85 mmol), 4-chlorophenacylbromide (197 mg, 0.85 mmol) and potassium carbonate (117 mg, 0.85 mmol) in acetone (50 mL) according to **GP-16** to give the *title compound* as a white solid (249 mg, 75%). M.p. 148-149 °C; UV (MeOH): λ_{max} 207 nm (ε 35,874 $cm^{-1}M^{-1}$), 247 (31,076), 309 (20,240); IR (KBr): ν_{max} 3134, 3087, 3056, 2957, 2918, 2899, 2848, 1727, 1708, 1625, 1587, 1500, 1472, 1457, 1399, 1377, 1244, 1207, 1190, 1144, 1092, 1046, 1009, 979, 946, 820. 763 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H, O-CH_3), 3.80 (s, 3H, $COOCH_3$), 3.92 (s, 3H, N-CH_3), 5.19 (s, 2H, CH_2), 6.04 (d, *J* = 3.0 Hz, 1H, H5), 6.29

(d, *J* = 3.0 Hz, 1H, H7), 7.18 (s, 1H, H3), 7.37-7.40 (m, 2H, ArH), 7.89-7.91 (m, 2H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 32.30 (N-CH_3), 51.82 (COO$\underline{CH_3}$), 56.03 (O-CH_3), 71.45 (O-CH_2), 86.02 (ArCH), 94.23 (ArCH), 108.83 (ArCH), 112.49 (ArC), 125.94 (ArC), 129.54 (2 × ArCH), 130.21 (2 × ArCH), 133.33 (ArC), 140.74 (ArC), 141.94 (ArC), 153.45 (ArC), 160.17 (ArC), 162.86 (C=O), 193.15 ($CH_2\underline{CO}$-); HRMS *m/z:* Calcd. for $C_{20}H_{18}ClNO_5Na$ $[M + Na]^+$ 410.0874. Found 410.0764.

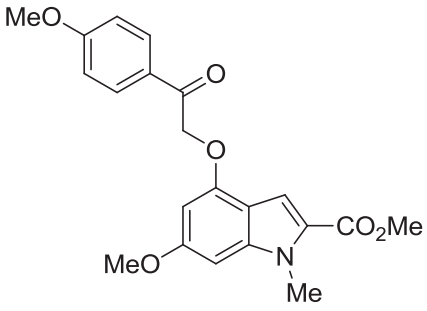
Methyl 4-(2-(4-bromophenyl)-2-oxoethoxy)-6-methoxy-1-methyl-indole-2-carboxylate (389)



The acyl indole **389** was prepared from indole **392** (200 mg, 0.85 mmol), 4-bromophenacylbromide (234 mg, 0.85 mmol) and potassium carbonate (117 mg, 0.85 mmol) in acetone (50 mL) according to **GP-16** to give the *title compound* as a brown solid (251 mg, 78%). M.p. 140-142 °C; UV (MeOH): λ_{max} 205 nm (ε 35,874 $cm^{-1}M^{-1}$), 248 (24,136), 309 (15,516); IR (KBr): ν_{max} 3139, 3086, 3053, 2951, 2924, 2897, 2847, 2359, 1727, 1709, 1624, 1585, 1500, 1485, 1426, 1398, 1376, 1303, 1241, 1207, 1189, 1163, 1091, 1070, 1045, 1006, 952, 945, 826, 817, 762 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 3H, O-CH_3), 3.80 (s, 3H, $COOCH_3$), 3.93 (s, 3H, N-CH_3), 5.19 (s, 2H, CH_2), 6.04 (d, *J* = 3.0 Hz, 1H, H5), 6.30 (d, *J* = 3.0 Hz, 1H, H7), 7.29 (s, 1H, H3), 7.54-7.57 (m, 2H, ArH), 7.82-7.85 (m, 2H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 32.31 (N-CH_3), 51.83 (COO$\underline{CH_3}$), 56.04 (O-CH_3), 71.46 (O-CH_2), 86.03 (ArCH), 94.23 (ArCH), 108.83 (ArCH), 112.49 (ArC), 125.95 (ArC), 130.29 (2 × ArCH), 132.54 (2 × ArCH), 133.73 (ArC), 140.75 (ArC), 141.95 (ArC), 153.44 (ArC), 160.17 (ArC), 162.87 (C=O), 193.14

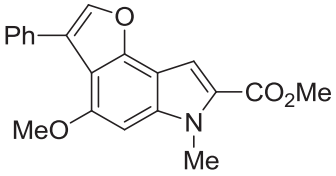
($CH_2\underline{CO}$-); HRMS *m/z:* Calcd. for $C_{20}H_{18}BrNO_5Na$ $[M + Na]^+$ 454.0368 Found 454.0265.

Methyl 6-methoxy-4-(2-(4-methoxyphenyl)-2-oxoethoxy)-1-methyl-indole-2-carboxylate (390)



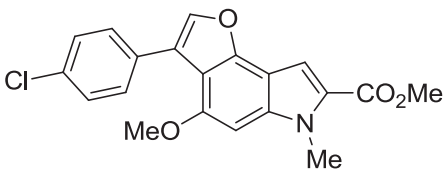
The acyl indole **390** was prepared from indole indole **392** (200 mg, 0.85 mmol), 4-methoxyphenacylbromide (168 mg, 0.85 mmol) and potassium carbonate (117 mg, 0.85 mmol) in acetone (50 mL) according to **GP-16** to give the *title compound* as a white solid (248 mg, 76%). M.p. 130-131 °C; UV (MeOH): λ_{max} 243 nm (ε 23,133 $cm^{-1}M^{-1}$), 310 (17,311); IR (KBr): ν_{max} 2949, 2839, 2360, 1707, 1690, 1629, 1599, 1571, 1498, 1460, 1433, 1374, 1314, 1233, 1204, 1161, 1141, 1089, 1048, 1029, 969, 837, 800, 762, 683, 607, 629, 572 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H, O-CH_3), 3.79 (s, 3H, O-CH_3), 3.80 (s, 3H, $COOCH_3$), 3.92 (s, 3H, N-CH_3), 5.71 (s, 2H, O-CH_2), 6.05 (d, *J* = 3.0 Hz, 1H, H5), 6.29 (d, *J* = 3.0 Hz, 1H, H7), 6.86 (bs, 1H, ArH), 7.53-7.56 (m, 2H, ArH), 7.83-7.87 (m, 2H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 32.28 (N-CH_3), 51.79 ($COO\underline{CH_3}$), 55.92 (O-CH_3), 56.02 (O-CH_3), 71.33 (O-CH_2), 85.86 (ArCH), 94.23 (ArCH), 109.06 (ArCH), 112.61 (ArC), 114.39 (2 × ArCH), 125.82 (ArC), 128.11 (ArCH), 131.08 (2 × ArCH), 141.96 (ArC), 153.75 (ArC), 160.23 (ArC), 162.94 (C=O), 164.42 (ArC), 193.15 ($CH_2\underline{CO}$-); HRMS *m/z:* Calcd. for $C_{21}H_{21}NO_6$ $[M + 1]^+$ 384.1369. Found 384.1446.

Methyl 4-methoxy-6-methyl-3-phenyl-6*H*-furo[2,3-*e*]indole-7-carboxylate (391)



The furoindole **391** was prepared from acyl indole **387** (100 mg, 0.28 mmol) in trifluoroacetic acid (10.0 mL) according to **GP-17** to give the *title compound* as a white solid (59 mg, 62%). M.p. 194-195 °C; UV (MeOH): λ_{max} 202 nm (ε 15,242 $cm^{-1}M^{-1}$), 240 (16,984), 308 (10,820); IR (KBr): ν_{max} 3138, 2999, 2948, 1700, 1650, 1602, 1571, 1507, 1471, 1436, 1456, 1413, 1360, 1315, 1304, 1229, 1181, 1164, 1133, 1093, 1057, 1025, 970, 953, 918, 811, 782, 818, 782, 748, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H, O-CH_3), 3.84 (s, 3H, $COOCH_3$), 4.04 (s, 3H, N-CH_3), 6.50 (s, 1H, ArH), 7.30-7.34 (m, 3H, ArH), 7.43 (s, 1H, ArH), 7.50 (s, 1H, ArH), 7.55 (bs, 2H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 31.18 (N-CH_3), 50.46 (COO$\underline{CH_3}$), 54.45 (O-CH_3), 85.37 (ArCH), 105.64 (ArCH), 106.63 (ArC), 109.98 (ArC), 122.78 (ArC), 124.57 (ArC), 126.04 (ArCH), 126.79 (2 × ArCH), 128.53 (2 × ArCH), 131.46 (ArC), 138.40 (ArCH), 138.58 (ArC), 149.31 (ArC), 153.30 (ArC), 161.45 (C=O); HRMS *m/z:* Calcd. for $C_{20}H_{17}NO_4$ $[M + 1]^+$ 336.1158. Found 336.1230.

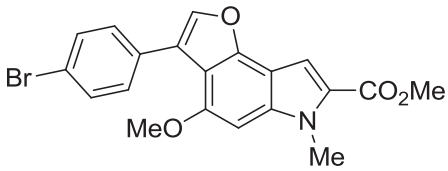
Methyl 3-(4-chlorophenyl)-4-methoxy-6-methyl-6*H*-furo[2,3-*e*]indole-7-carboxylate (392)



The furoindole **392** was prepared from acyl indole **388** (100 mg, 0.28 mmol) in trifluoroacetic acid (10.0 mL) according to **GP-17** to give the *title compound* as a white solid (52 mg, 60%). M.p. 180-181 °C; UV (MeOH): λ_{max} 223 nm (ε 34,722 $cm^{-1}M^{-1}$), 263 (27,748), 324 (17,084); IR (KBr): ν_{max} 2945, 2841, 1702, 1646, 1572, 1508, 1493, 1474, 1433, 1395, 1341,

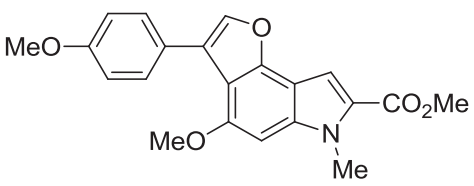
1303, 1233, 1179, 1130, 1090, 1051, 1018, 975, 835, 792, 777, 761, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H, O-CH_3), 3.83 (s, 3H, $COOCH_3$), 4.04 (s, 3H, N-CH_3), 6.50 (s, 1H, ArH), 7.18-7-49 (m, 6H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 31.19 (N-CH_3), 50.48 (COO$\underline{CH_3}$), 54.43 (O-CH_3), 85.37 (ArCH), 105.65 (ArCH), 106.63 (ArC), 109.98 (ArC), 110.12 (ArC), 125.04 (ArC), 126.95 (2 × ArCH), 129.79 (2 × ArCH), 132.00 (ArC), 138.39 (ArCH), 138.59 (ArC), 150.00 (ArC), 153.08 (ArC), 161.07 (C=O); HRMS *m/z* Calcd. for $C_{20}H_{16}ClNO_4$ $[M]^+$ 369.0768. Found 369.0752.

Methyl 3-(4-bromophenyl)-4-methoxy-6-methyl-6*H*-furo[2,3-*e*]indole-7-carboxylate (393)



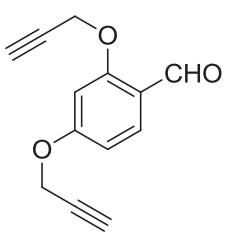
The furoindole **393** was prepared from acyl indole **389** (100 mg, 0.28 mmol) in trifluoroacetic acid (10.0 mL) according to **GP-17** to give the *title compound* as a white solid (62 mg, 65%). M.p. 163-164 °C; UV (MeOH): λ_{max} 202 nm (ε 30,170 $cm^{-1}M^{-1}$), 247 (32,756), 306 (21,119); IR (KBr): ν_{max} 2917, 2848, 1701, 1645, 1508, 1491, 1472, 1393, 1341, 1303, 1178, 1132, 1093, 1069, 1049, 1011, 974, 832, 792, 762 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H, O-CH_3), 3.84 (s, 3H, $COOCH_3$), 4.01 (s, 3H, N-CH_3), 6.51 (s, 1H, ArH), 7.40-7-50 (m, 6H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 31.98 (N-CH_3), 51.90 (COO$\underline{CH_3}$), 55.86 (O-CH_3), 86.91 (ArCH), 107.04 (ArCH), 111.09 (ArC), 109.97 (ArC), 110.13 (ArC), 124.04 (ArC), 126.14 (2 × ArCH), 129.78 (2 × ArCH), 131.32 (ArC), 131.55 (ArC), 139.78 (ArCH), 140.03 (ArC), 150.79 (ArC), 154.50 (ArC), 161.06 (C=O); HRMS *m/z* Calcd. for $C_{20}H_{16}BrNO_4$ $[M + 1]^+$ 414.0263. Found 414.0267.

Methyl 4-methoxy-3-(4-methoxyphenyl)-6-methyl-6*H*-furo[2,3-*e*]indole-7-carboxylate (394)



The furoindole **394** was prepared from acyl indole **390** (100 mg, 0.28 mmol) in trifluoroacetic acid (10.0 mL) according to **GP-17** to give the *title compound* as a white solid (64 mg, 67%). M.p. 190-192 °C; UV (MeOH): λ_{max} 204 nm (ε 26,864 $cm^{-1}M^{-1}$), 241 (34,127), 307 (17,994); IR (KBr): ν_{max} 3148, 2921, 2848, 1709, 1644, 1571, 1469, 1456, 1415, 1359, 1340, 1289, 1258, 1178, 1129, 1089, 1053, 1030, 969, 953, 916, 836, 808, 792, 763, 747, 717, 561 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 3H, O-CH_3), 3.82 (s, 3H, O-CH_3), 3.84 (s, 3H, $COOCH_3$), 4.04 (s, 3H, N-CH_3), 6.49 (s, 1H, H5), 6.47-6.90 (m, 2H, ArH), 7.42-7.48 (m, 4H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 31.18 (N-CH_3), 50.44 (COO$\underline{CH_3}$), 54.28 (O-CH_3), 54.48 (O-CH_3), 85.37 (ArCH), 105.65 (ArCH), 106.63 (ArC), 109.98 (ArC), 110.12 (ArC), 112.19 (2 × ArCH), 122.54 (ArC), 123.83 (ArC), 124.54 (ArC), 129.63 (2 × ArCH), 137.91 (ArCH), 138.55 (ArC), 153.36 (ArC), 157.85 (ArC), 171.53 (C=O); HRMS *m/z* Calcd. for $C_{21}H_{19}NO_5$ $[M + 1]^+$ 366.1263. Found 366.1337.

2,4-Bis(prop-2-yn-1-yloxy)benzaldehyde (415)

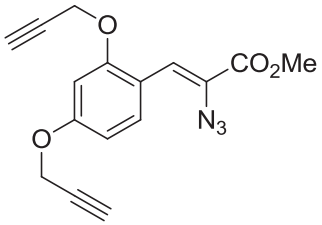


The propagyloxybenzaldehyde **415** was prepared from hydroxy-benzaldehyde **414** (500 mg, 3.62 mmol), potassium iodide (0.3 g, 1.8), potassium carbonate (0.9 g, 7.24) and propargyl bromide (0.9 mL, 7.24 mmol) in acetone according to **GP-21** to give the *title compound* as an orange solid (0.63 g, 81%). M.p. 109-111 °C *lit*[200] 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (bs, 2H, CH≡C), 4.65 (d, *J* = 3.0 Hz, 2H, O-CH_2), 4.74 (d, *J*

= 3.0 Hz, 2H, O-CH_2), 6.59-6.62 (m, 2H, ArH), 7.80 (d, *J* = 3.0 Hz, 1H, ArH), 10.25 (s, 1H, CHO).

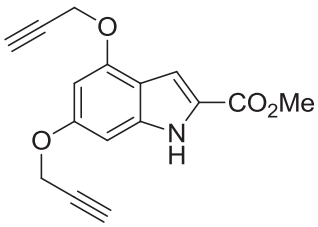
***(Z)*-Ethyl 2-azido-3-(2,4-bis(prop-2-yn-1-yloxy)phenyl)acrylate (416)**

The azidocinnamate **416** was prepared from aryl ether **415** (500 mg, × 2.33 mmol), methyl azidoacetate (2.7 mL, × 23.3 mmol) in MeOH (25 mL) and sodium (535 mg, 23.3 mmol) in MeOH (100 mL) according to **GP-19** to give the *title compound* as a white solid (720 mg, 75%). M.p. 149-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.32 (s, 2H, CH≡C), 3.78 (s, 3H, COOMe), 4.67 (s, 4H, 2 × O-CH_2), 6.42-6.51 (m, 2H, ArH), 8.02 (d, *J* = 9.0 Hz, 1H, ArH), 8.19 (d, *J* = 9.0 Hz, 1H, ArH).



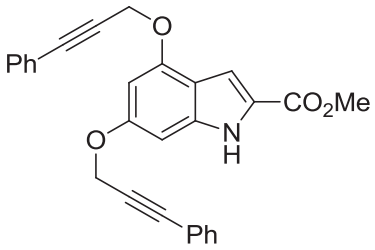
Methyl 4,6-bis(prop-2-yn-1-yloxy)-indole-2-carboxylate (417)

The indole **417** was prepared from azidocinnamate **416** (200 mg, 0.6 mmol) was dissolved in xylene (100 mL) according to **GP-20** to give the *title compound* as a white solid (150 mg, 82%). M.p. 150-151 °C; UV (MeOH): λ_{max} 206 nm (ε 16,245 $cm^{-1}M^{-1}$), 243 (20,729), 303 (13,625); IR (KBr): ν_{max} 3312, 3279, 3026, 2947, 2937, 2887, 2123, 1714, 1625, 1572, 1524, 1512, 1437, 1456, 1381, 1265, 1183, 1136, 1192, 1073, 998, 977, 963, 935, 872, 766, 736, 665, 641, 585 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (bs, 2H, 2 × CH≡C), 3.93 (s, 3H, $COOCH_3$), 4.73 (d, *J* = 3.0 Hz, 2H, OCH_2), 4.80 (d, *J* = 3.0 Hz, 2H, OCH_2), 6.38 (s, 1H, ArH), 6.60 (s, 1H, ArH), 7.27 (bs, 1H, ArH), 8.90 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 52.47 ($COOCH_3$), 56.77 (O-CH_2), 58.85 (O-CH_2), 76.99 (2 × C≡CH),



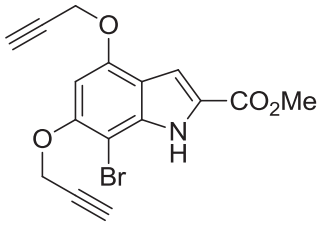
77.84 (2 × C≡CH), 87.22 (ArCH), 94.47 (ArCH), 108.02 (ArCH), 115.72 (ArC), 126.61 (ArC), 137.60 (ArC), 152.36 (2 × ArC), 162.13 ($\underline{CO}CH_3$); HRMS (ESI) *m/z:* Calcd. for $C_{16}H_{13}NO_4Na$ $[M + Na]^+$ 306.0845. Found 306.0841.

Methyl-4,6-bis((3-phenylprop-2-yn-1-yl)oxy)-indole-2-carboxylate (419)



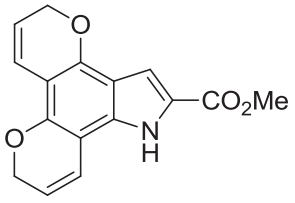
A mixture of iodobenzene (100 µL, 0.7 mmol), indole **417** (100 mg, 0.35 mmol), $PdCl_2(PPh_3)_2$ (11.0 mg, 0.025 mmol), CuI (6.0 mg, 0.029 mmol), triethylamine (2.0 mL) in dry toluene (10.0 mL) was stirred at 0 °C under an argon atmosphere for 2 h. The reaction mixture was quenched with water (5.0 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases was dried over sodium sulfate. Purification of the crude product by column chromatography (SiO_2, 30% Ethyl acetate/hexane) to give the *title compound* as a white solid (90 mg, 58%). M.p. 124-125 °C; UV (MeOH): λ_{max} 202 nm (ε 32,364 $cm^{-1}M^{-1}$), 247 (17,139), 295 (12,528); IR (KBr): ν_{max} 3437, 2950, 2915, 2850, 1701, 1684, 1653, 1540, 1507, 1491, 1261, 1149, 1114, 760, 700 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 3.72 (s, 3H, $COOCH_3$), 4.89 (s, 2H, O-CH_2), 5.02 (s, 2H, O-CH_2), 6.39 (s, 1H, ArH), 6.74 (s, 1H, ArH), 7.04 (s, 1H, ArH), 7.23-7.32 (m, 10H, ArH), 10.71 (s, 1H, NH); ^{13}C NMR (75.6 MHz, acetone-d_6): δ 52.03 ($COO\underline{C}H_3$), 57.53 (O-CH_2), 57.70 (O-CH_2), 85.37 (PhC≡$\underline{C}$), 85.59 (PhC≡C), 87.67 (CH≡$\underline{C}$Ph), 87.78 (CH≡$\underline{C}$Ph), 90.17 (ArCH), 95.41 (ArCH), 106.75 (ArCH), 115.19 (ArC), 123.43 (ArC), 126.43 (ArC), 126.57 (ArC), 129.62 (4 × ArCH), 129.88 (ArCH), 129.90 (ArCH), 132.65 (2 × ArCH), 132.70 (2 × ArCH), 140.25 (ArC), 153.99 (ArC), 159.00 (ArC), 162.62 (C=O); HRMS (ESI) *m/z:* Calcd. for $C_{28}H_{21}NO_4$ $[M]^+$ 435.1471. Found 435.1001.

Methyl 7-bromo-4,6-bis(prop-2-yn-1-yloxy)-indole-2-carboxylate (412)



To a solution of indole **417** (150 mg, 0.41 mmol) in CCl_4 (25 mL), phenyltrimethylammonium tribromide (154 mg, 0.41 mmol) was added. The reaction mixture was stirred at room temperature until no more starting material remained (~5 h). The reaction was concentrated under reduced pressure and water (25 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 25 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified using column chromatography (SiO_2, 20% Ethyl acetate/hexane) to give the *title compound* as a white solid (130 mg, 68%). M.p. 178-179 °C; UV (MeOH): λ_{max} 205 nm (ε 17,255 $cm^{-1}M^{-1}$), 242 (20,829), 302 (12,635); IR (KBr): ν_{max} 3311, 3278, 3027, 2948, 2936, 2888, 2124, 1712, 1626, 1573, 1525, 1510, 1438, 1455, 1380, 1266, 1182, 1137, 1191, 1074, 997, 978, 961, 937, 873, 767, 737, 667, 640, 586 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48-2.50 (m, 2H, C≡CH), 3.86 (s, 3H, $COOCH_3$), 4.75-4.79 (m, 4H, 2 × O-CH_2), 6.57 (s, 1H, H5), 7.28 (s, 1H, H3), 8.80 (bs, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 52.47 ($COOCH_3$), 56.77 (O-CH_2), 58.85 (O-CH_2), 76.99 (2 × C≡CH), 77.84 (2 × C≡CH), 87.22 (ArC), 94.47 (ArCH), 108.02 (ArCH), 115.72 (ArC), 126.61 (ArC), 137.60 (ArC), 152.36 (2 × ArC), 162.13 ($COCH_3$); HRMS (ESI) *m/z:* Calcd. for $C_{16}H_{12}BrNO_4Na$ $[M + Na]^+$ 383.9950. Found 383.9835.

Methyl 5,9-dihydro-1*H*-dipyrano[2,3-*e*:2',3'-*g*]indole-2-carboxylate (418)

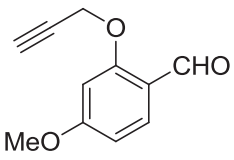


The dihydropyranoindole **418** was prepared from indole **417** (120 mg, 0.42 mmol) in chlorobenzene (100 mL) according to

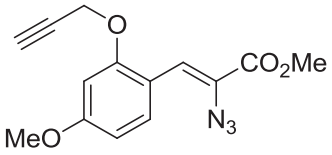
GP-22 to give the *title compound* as a white solid (91 mg, 75%). M.p. 220-221 °C; UV (CH_3CN): λ_{max} 229 nm (ε 12,624 $cm^{-1}M^{-1}$), 281 (7,414); IR (KBr): ν_{max} 3423, 3285, 2955, 2917, 2844, 2252, 2122, 1746, 1708, 1612, 1536, 1504, 1438, 1371, 1263, 1212, 1161, 1112, 1023, 802, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 3H, $COOCH_3$), 4.75 (bs, 2H, O-CH_2), 4.82 (bs, 2H, O-CH_2), 5.59 (m, 2H, CH), 6.61 (m, 2H, CH), 7.10 (bs, 1H, ArH), 8.75 (s, 1H NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 50.19 ($COOCH_3$), 64.68 (O-CH_2), 64.72 (O-CH_2), 98.93 (ArC), 103.84 (ArC), 106.01 (ArCH), 115.48 (CH), 115.84 (CH), 118.38 (CH), 118.83 (CH), 124.62 (ArC), 133.80 (ArC), 148.01 (2 × ArC), 161.25 (C=O); HRMS (ESI) *m/z:* Calcd. for $C_{16}H_{13}NO_4Na$ $[M + Na]^+$ 306.0845. Found 306.0737.

4-Methoxy-2-(prop-2-yn-1-yloxy) benzaldehyde (422)[201]

The propagyloxybenzaldehyde **422** was prepared from hydroxy-benzaldehyde **387** (1.0 g, 0.006 mol), potassium iodide (1.0 g, 0.006), potassium carbonate (0.8 g, 0.006 mol) and propargyl bromide (0.6 mL, 0.006 mol) according to **GP-21** to give the *title compound* as yellow oil (0.89 g, 69%). ^1H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 1H, CH≡C), 3.81 (s, 1H, OMe), 4.74 (s, 2H, O-CH_2), 6.52-6.55 (m, 2H, H3 and H5), 7.77 (d, *J* = 3.0 Hz, 1H, H6), 10.23 (s, 1H, CHO).

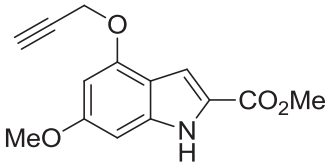


***(Z)*-Methyl 2-azido-3-(4-methoxy-2-(prop-2-yn-1-yloxy)phenyl)acrylate (423)**



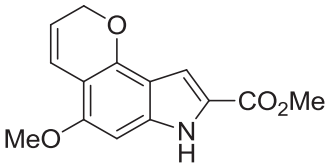
The azidocinnamate **423** was prepared from aryl ether **422** (250 mg, 0.87 mmol), methyl azidoacetate (1.0 mL, 8.7 mmol) in MeOH (10.0 mL) and sodium (200 mg, 8.7 mmol) according to **GP-19** to give the *title compound* as a white solid (291 mg, 76%). M.p. 157-155 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 1H, CH≡C), 3.77 (s, 3H, COOMe), 3.82 (s, 3H, OMe), 4.68 (s, 1H, O-CH_2), 6.50-6.52 (m, 2H, ArH), 7.26 (bs, 1H, ArH), 8.17 (d, *J* = 9.0 Hz, 1H, ArH).

Methyl 6-methoxy-4-(prop-2-yn-1-yloxy)-indole-2-carboxylate (424)



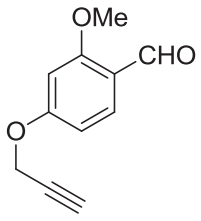
The indole **424** was prepared from azidocinnamate **423** (150 mg, 0.52 mmol) in xylene (50 mL). according to **GP-20** to give the *title compound* as a white solid (95 mg, 70%). M.p. 200-201 °C; UV (MeOH): λ_{max} 206 nm (ε 8,316 $cm^{-1}M^{-1}$), 243 (6,062), 306 (6,762); IR (KBr): ν_{max} 3315, 3264, 3026, 2937, 2118, 1690, 1630, 1584, 1518, 1460, 1460, 1437, 1385, 1350, 1278, 1255, 1200, 1149, 1045, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (bs, 1H, CH≡C), 3.55 (s, 3H, OCH_3), 3.90 (s, 3H, $COOCH_3$), 4.80 (d, *J* = 3.0 Hz, 2H, OCH_2), 6.32 (d, *J* = 3.0 Hz, 1H, H5), 6.47 (d, *J* = 3.0 Hz, 1H, H7), 7.28 (s, 1H, H3), 8.77 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 51.71 (COO$\underline{C}H_3$), 55.55 (O$\underline{C}H_3$), 55.84 (O-CH_2), 76.50 ($\underline{C}$H≡C), 76.92 (CH≡$\underline{C}$), 86.83 (ArCH), 94.04 (ArCH), 106.87 (ArCH), 113.82 (ArC), 124.67 (ArC), 138.52 (ArC), 152.75 (ArC), 159.90 (ArC), 162.19 (C=O); HRMS (ESI) *m/z:* Calcd. for $C_{14}H_{13}NO_4$ $[M]^+$ 259.2573. Found 259.0810.

Methyl 5-methoxy-2,7-dihydropyrano[2,3-*e*]indole-8-carboxylate (425)



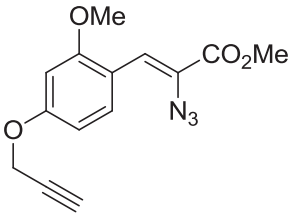
The dihydropyranoindole **425** was prepared from indole **424** (100 mg, 0.38 mmol) in chlorobenzene (50 mL) according to **GP-22** to give the *title compound* as a white solid (62 mg, 62%). M.p. 178-180 °C; UV (CH_3CN): λ_{max} 206 nm (ε 7,795 $cm^{-1}M^{-1}$), 279 (12,432), 289 (13,338); IR (KBr): ν_{max} 3337, 3053, 3002, 2948, 2814, 1685, 1638, 1615, 1579, 1540, 1495, 1466, 1356, 1223, 1196, 1112, 1042, 1020, 998, 981, 833, 774, 762, 724 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H, OCH_3), 3.91 (s, 3H, $COOCH_3$), 4.86 (d, *J* = 3.0 Hz, 2H, O-CH_2), 5.60 (m, 1H, CH), 6.37 (s, 1H, ArH), 6.77 (m, 1H, CH), 7.17-7.18 (m, 1H, ArH), 8.78 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 51.74 (COO<u>C</u>H_3), 55.64 (OCH_3), 65.39 (O<u>C</u>H_2), 85.61 (ArCH), 105.64 (ArC), 106.60 (ArCH), 112.59 (ArC), 115.79 (CH), 120.22 (ArC), 125.05 (CH), 138.34 (ArC), 149.15 (ArC), 155.47 (ArC), 162.19 (C=O); HRMS (ESI) *m/z:* Calcd. for $C_{14}H_{13}NO_4$ $[M + 1]^+$ 260.0845. Found 260.0912.

2-Methoxy-4-(prop-2-yn-1-yloxy)benzaldehyde (427)[202]



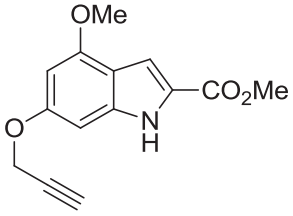
The propagyloxybenzaldehyde **427** was prepared from hydroxy-benzaldehyde, **426** (0.50 g, 0.003 mol), propargyl bromide (0.3 mL, 0.003 mol), potassium iodide (0.50 g, 0.003) and potassium carbonate (0.40 g, 0.003 mol) in acetone (50 mL) according to **GP-21** to give *title compound* as orange oil (0.40 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 1H, CH≡C), 3.83 (s, 1H, OMe), 4.72 (s, 1H, O-CH_2), 6.51-6.53 (m, 2H, ArH), 7.75 (d, *J* = 3.0 Hz, 1H, H6), 10.19 (s, 1H, CHO).

***(Z)*-Ethyl-2-azido-3-(2-methoxy-4-(prop-2-yn-1-yloxy)phenyl)acrylate (428)**



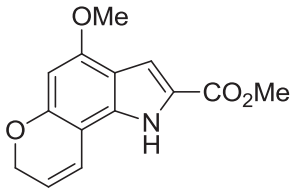
The azidocinnamate **428** was prepared from aryl ether **427** (250 mg, 1.31 mmol), methyl azidoacetate (1.5 mL, 13.1 mmol), sodium (3.01 g, 13.1 mmol) MeOH (40 mL) according to **GP-19** to give the *title compound* as a white solid (270 mg, 72%). M.p. 154-155 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.32 (s, 1H, CH≡C), 3.78 (s, 3H, COMe), 3.82 (s, 3H, COOMe), 4.67 (s, 2H, O-CH_2), 6.42-6.51 (m, 2H, ArH), 8.02 (d, *J* = 9.0 Hz, 1H, ArH), 8.19 (d, *J* = 9.0 Hz, 1H, ArH).

Methyl 4-methoxy-6-(prop-2-yn-1-yloxy)-indole-2-carboxylate (429)



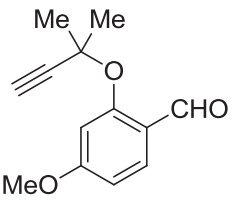
The indole **429** was prepared from azidocinnamate **428** (200 mg, 0.69 mmol) in xylene (100 mL) according to **GP-20** to give the *title compound* as a white solid (124 mg, 68%). M.p. 197-198 °C; UV (MeOH): λ_{max} 203 nm (ε 15,778 $cm^{-1}M^{-1}$), 244 (6,736), 307 (6,736); IR (KBr): ν_{max} 3315, 3264, 3026, 2937, 2118, 1690, 1630, 1584, 1518, 1460, 1437, 1385, 1350, 1278, 1255, 1212, 1200, 1184, 1149, 1129, 1090, 1045, 996, 984, 934, 914, 811, 772, 742, 706, 680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.33 (s, 1H, C≡CH), 3.83 (s, 3H, OMe), 3.87 (s, 3H, COOMe), 5.65 (s, 2H, O-CH_2), 6.71 (bs, 1H, ArH), 6.75 (d, *J* = 3.0 Hz, 1H, ArH), 7.22 (d, *J* = 3.0 Hz, 1H, ArH), 9.36 (bs, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 51.73 (COO$\underline{C}H_3$), 55.53 (O$\underline{C}H_3$), 55.81 (O-CH_2), 76.51 ($\underline{C}$H≡C), 76.93 (CH≡$\underline{C}$), 86.81 (ArCH), 94.01 (ArCH), 106.84 (ArCH), 113.80 (ArC), 124.61 (ArC), 138.53 (ArC), 152.74 (ArC), 159.91 (ArC), 161.19 (C=O); HRMS (ESI) *m/z* Calcd. for $C_{14}H_{13}NO_4Na$ $[M + Na]^+$ 282.0845. Found 282.0730.

Methyl 4-methoxy-1,7-dihydropyrano[2,3-*g*]indole-2-carboxylate (430)



The dihydropyranoindole **430** was prepared from aryl ether **429** (100 mg, 0.38 mmol) in chlorobenzene (50 mL) according to **GP-22** to give the *title compound* as a white solid (74 mg, 74%). M.p. 180-181 °C(dec.); UV (MeOH): λ_{max} 205 nm (ε 11,525 $cm^{-1}M^{-1}$), 279 (15,773), 289 (14,840); IR (KBr): ν_{max} 3337, 3053, 3006, 2949, 2814, 1686, 1638, 1615, 1580, 1495, 1466, 1435, 1419, 1392, 1357, 1284, 1225, 1198, 1148, 1113, 1043, 1021, 999, 982, 954, 933, 899, 834, 801, 775, 763, 725, 652 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 3H, O-CH_3), 3.91 (s, 3H, $COOCH_3$), 4.86 (m, 2H O-CH_2), 5.60 (m, 1H, H8), 6.76 (m, 1H, H9), 6.51 (s, 1H, H5), 7.17-7.19 (m, 1H, H3), 8.88 (bs, 1H NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 51.14 ($COOCH_3$), 55.63 (O-CH_3), 65.39 (O-CH_2), 85.64 (ArCH), 105.63 (ArC), 106.61 (ArCH), 112.58 (ArC), 115.78 (ArCH), 120.22 (ArCH), 125.04 (ArC), 138.40 (ArC), 149.14 (ArC), 155.46 (ArC), 162.25 (C=O); HRMS (ESI) *m/z*: Calcd. for $C_{14}H_{13}NO_4$ $[M + 1]^+$ 260.0845. Found 260.0920.

4-Methoxy-2-((2-methylbut-3-yn-2-yl)oxy) benzaldehyde (431)

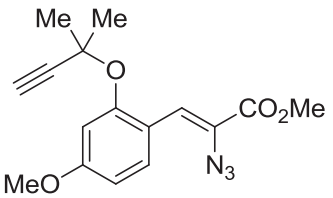


3-Chloro-3-methylbutyne (0.2 mL, 1.9 mmol) was added to a mixture of potassium iodide (132 mg, 0.8 mmol), potassium carbonate (220 mg, 1.6 mmol) and 2-hydroxy-4-methoxybenzaldehyde **387** (200 mg, 1.6 mmol) in acetone. The reaction mixture was heated under reflux with stirring until no more starting material remained by TLC (10% Et_2O/hexane ~30 h). The reaction mixture was cooled to room temperature and Et_2O (100 mL) was added. The ethereal solution was washed with NaOH (1N, 3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the *title*

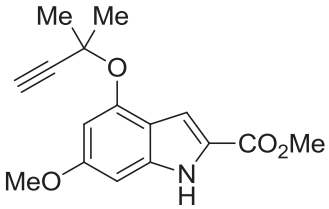
compound as orange oil (229 mg, 82%). UV (MeOH): λ_{max} 203 nm (ε 12,229 $cm^{-1}M^{-1}$), 230 (7,063), 274 (4,578), 315 (4,360); IR (KBr): ν_{max} 3460 (br), 2925, 1671, 1606, 1555, 1502, 1444, 1372, 1329, 1264, 1205, 1168, 1112, 1099, 1008, 822 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 1.62 (s, 6H, 2 × CH_3), 2.61 (s, 1H, C≡CH), 3.73 (s, 3H, O-CH_3), 6.52-6.56 (m, 1H, ArH), 7.01 (d, *J* = 3.0 Hz, 1H, ArH), 7.70 (d, *J* = 3.0 Hz, 1H, ArH), 10.15 (s, 1H, CHO); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 28.38 (2 × CH_3), 54.46 (O-CH_3), 72.57 (C≡CH), 74.48 (C≡CH), 84.07 (ArC), 104.43 (ArCH), 107.76 (ArCH), 121.21 (ArC), 128.59 (ArCH), 159.14 (ArC), 164.04 (ArC), 187.47 (CHO); HRMS (ESI) *m/z:* Calcd. for $C_{13}H_{14}O_3Na$ $[M + Na]^+$ 241.0943. Found 241.0833.

_(Z)_-Mthyl 2-azido-3-(4-methoxy-2-((2-methylbut-3-yn-2-yl)oxy)phenyl)acrylate (432)

The azidocinnamate **432** was prepared from aryl ether **431** (300 mg, 1.37 mmol), methyl azidoacetate (1.2 mL, 11.0 mmol), MeOH (40 mL) and sodium (315 according to **GP-19** to give the *title compound* as orange oil (309 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (s, 6H, 2 × CH_3), 3.52 (s, 1H, CH≡C), 3.77 (s, 3H, COOMe), 3.80 (s, 3H, OMe), 6.54 (s, 1H, ArH), 6.75 (d, *J* = 8.2 Hz, 1H, ArH), 7.20 (d, *J* = 8.2 Hz, 1H, ArH), 7.74 (d, *J* = 8.2 Hz, 1H, CH).

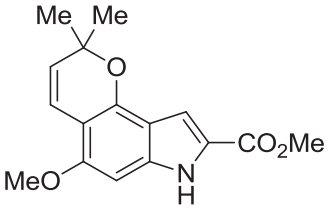


Methyl 6-methoxy-4-((2-methylbut-3-yn-2-yl)oxy)-indole-2-carboxylate (433)



The indole **433** was prepared from azidocinnamate **432** (200 mg, 0.63 mmol) in xylene (50 mL) according to **GP-20** to give the *title compound* as a white solid (124 mg, 68%). M.p. 202-203 °C; UV (CH_3CN): λ_{max} 206 nm (ε 4,563 $cm^{-1}M^{-1}$), 278 (7,978), 288 (9,155); IR (KBr): ν_{max} 3364, 3313, 2971, 2930, 2841, 1694, 1678, 1639, 1579, 1527, 1462, 1450, 1419, 1392, 1302, 1276, 1245, 1148, 1019, 995, 880, 775, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (s, 6H, 2 × CH_3), 2.52 (s, 1H, CH), 3.84 (s, 3H, OCH_3), 3.90 (s, 3H, $COOCH_3$), 6.35 (bs, 1H, ArH), 6.68 (bs, 1H, ArH), 7.24 (bs, 1H, ArH), 8.81 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 28.73 (2 × CH_3), 51.63 ($COO\underline{C}H_3$), 55.59 ($O\underline{C}H_3$), 85.02 (ArCH), 85.09 (ArC), 104.12 (ArC), 106.91 (ArCH), 113.27 (ArC), 117.35 (ArCH), 124.76 (ArC), 125.28 (ArC), 138.37 (ArC), 148.00 (ArC), 155.52 (ArC), 162.28 (C=O); HRMS (ESI) *m/z:* Calcd. for $C_{16}H_{17}NO_4$ $[M + 1]^+$ 288.1158. Found 288.1245.

Methyl 5-methoxy-2,2-dimethyl-2,7-dihydropyrano[2,3-*e*]indole-8-carboxylate (434)

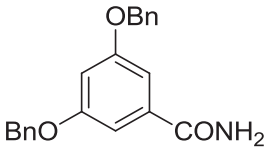


The dihydropyranoindole **434** was prepared from aryl ether **433** (100 mg, 0.34 mmol) in chlorobenzene (50 mL) according to **GP-22** to give the *title compound* as a white solid (63 mg, 63%). M.p. 194-195 °C; UV (CH_3CN): λ_{max} 206 nm (ε 14,350 $cm^{-1}M^{-1}$), 227 (9,758), 279 (21,639), 288 (24,509); IR (KBr): ν_{max} 3364, 3313, 2970, 2927, 2837, 1701, 1678, 1639, 1579, 1526, 1462, 1450, 1419, 1391, 1302, 1276, 1245, 1148, 1019,

995, 880, 775, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 6H, 2 × CH_3), 3.77 (s, 3H, OCH_3), 3.83 (s, 3H, $COOCH_3$), 5.37 (d, 9.0 Hz, 1H, CH), 6.27 (s, 1H, ArH), 6.60 (d, 9.0 Hz, 1H, CH), 7.18 (bs, 1H, ArH), 8.70 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 28.24 (2 × CH_3), 52.17 ($COO\underline{C}H_3$), 56.10 ($O\underline{C}H_3$), 85.52 (ArCH), 85.55 (ArC), 104.64 (ArC), 107.40 (ArCH), 113.78 (ArC), 117.87 (ArCH), 125.28 (ArC), 125.79 (ArCH), 138.86 (ArC), 148.52 (ArC), 156.04 (ArC), 162.75 (C=O); HRMS (ESI) *m/z:* Calcd. for $C_{16}H_{17}NO_4$ $[M + 1]^+$ 288.1158. Found 288.1245.

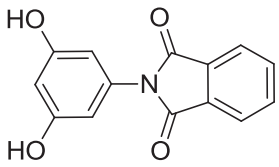
3,5-Dibenzyloxybenzamide (456)

To a solution of 3,5-dibenzyloxybenzoic acid **332** (2.0 g, 5.98 mmol) in dry dichloromethane (50 mL), thionyl chloride (15 mL) was added dropwise under nitrogen atmosphere. The resulting mixture was stirred overnight. After cooling toluene (10.0 mL) was added to the reaction mixture, and the crude product was purified by distillation under reduced pressure (b.p. 81-83 °C, 30 mmHg), as a colourless liquid (1.51 g, 71%). The acid chloride obtained thus was dissolved in dry tetrahydrofuran (25 mL), cooled in an ice bath to 0 °C. Ammonia gas was bubbled in the mixture for 30 min. The resulting solution was concentrated under reduced pressure, extracted with ethyl acetate (3 × 50 mL), dried over sodium sulfate, and concentrated under reduced pressure to yield the *title compound* as a white solid (398 mg, 80%). M.p. 190-192 °C; UV (MeOH): λ_{max} 210 nm (ε 12,103 $cm^{-1}M^{-1}$), 249 (2,606), 298 (1,529); IR (KBr): ν_{max} 3425, 3310, 3192, 3033, 2883, 2147, 1650, 1593, 1497, 1454, 1443, 1403, 1391, 1308, 1255, 1216, 1060, 1039, 855, 833, 754, 735, 703, 693, 634, 616, 592, 533, 489, 460 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.35 (s, 4H, 2 × O-CH_2), 8.05 (t, *J* = 3.0 Hz, 1H, ArH), 8.40 (d, *J* =



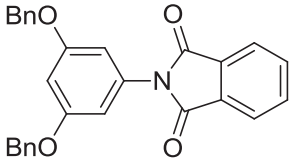
3.0 Hz, 2H, ArH), 8.55-8.69 (m, 10H, ArH), 9.26 (s, 2H, NH_2); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 71.09 (2 × O-CH_2), 106.35 (ArCH), 108.18 (2 × ArCH), 129.33 (4 × ArCH), 129.50 (2 × ArCH), 130.06 (4 × ArCH), 137.97 (ArC), 138.43 (2 × ArC), 160.93 (2 × ArC), 168.99 (CO); HRMS *m/z* Calcd. for $C_{21}H_{19}NO_3$ $[M + 1]^+$ 334.1365. Found 334.1440.

5-Phthalimidoresorcinol (457)



A mixture of 5-aminoresorcinol **105** (20 g, 0.12 mol), phthalic anhydride (12.76 g, 0.18 mol) and glacial acetic acid (250 mL) was stirred and heated under reflux for 1 h. The mixture was then poured, with stirring, into 500 mL hot water. This mixture was boiled for 5 min, and the solid was collected by filtration and washed with 250 mL of hot water to give the *title compound* as a pale tan solid (32.10 g, 78%). M.p. > 300 °C (dec), *lit*[186] >300 °C (dec); ^1H NMR (300 MHz, DMSO-d_6): δ 6.26 (s, 3H, ArH), 7.84-7.93 (m, 4H, ArH), 9.57 (s, 2H, OH).

5-Phthalimidoresorcinol dibenzyl ether (458)

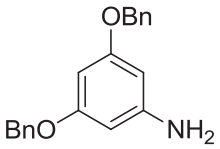


The dibenzyl ether **458** was prepared from 5-phthalimidoresorcinol **457** (10.0 g, 0.039 mol) potassium carbonate (107.0 g, 0.78 mol) and (85.5 mL, 0.78 mol) of benzyl bromide in *N*,*N*-dimethylformamide according to **GP-18** to give the *title compound* in the form of white crystals (14.10 g 82%). M.p. 136-137 °C, *lit*[186] 137-139 °C; ^1H NMR (300 MHz,

DMSO-d_6): δ 5.08 (s, 4H, O-CH_2), 6.73 (s, 3H, ArH), 7.30-7.45 (m, 10H, ArH), 7.87-7.93 (m, 4H, ArH).

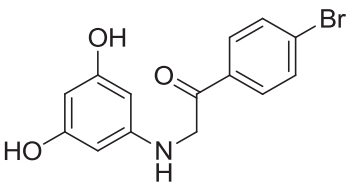
3,5-Dibenzyloxyaniline (337)

Method 2



To a stirred suspension of 5-phthalimidoresorcinol dibenzyl ether **458** (14.0 g, 0.032 mol) in 100 mL of ethanol was added (5.0 mL, 0.08 mol) of 85% aqueous solution of hydrazine hydrate. The reaction mixture was heated under reflux for 2 h (thickening of the reaction mixture required an additional 50 mL of ethanol during this period. Concentration under vacuum gave a white paste which was slurried with 100 mL of diethyl ether and the mixture was combined with 75 mL of 40% aqueous KOH. The layers were allowed to separate, and the aqueous layer was extracted diethyl ether (3 × 100 mL). The combined diethyl ether extract was dried over sodium sulfate, concentrated and the crude product was purified by column chromatography (SiO_2, 30% Ethyl acetate/hexane) to give the *title compound* as white crystals (8.6 g, 87%). M.p. 193-193 °C *lit* [xx] 191-193 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.94 (s, 4H, O-CH_2), 5.04 (s, 2H, NH_2), 5.82-5.83 (m, 3H, ArH), 7.28-7.32 (m, 10H, ArH).

1-(4-Bromophenyl)-2-((3,5-dihydroxyphenyl)amino)ethanone (459)

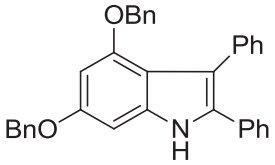


The anilinoketone **459** was prepared from 3,5-dihydroxyaniline **105** (5.0 g, 0.04 mol), 4-

bromophenacylbromide (11.0 g, 0.04 mmol) and sodium acetate (3.60 g, 044 mol) in Ethanol (200 mL) according to **GP-1** to give the *title compound* as a white solid (8.10 g, 63%). M.p. 230-232 °C; UV (CH_3CN): λ_{max} 206 nm (ε 8,281 $cm^{-1}M^{-1}$), 278 (12,326), 289 (13,353); IR (KBr): ν_{max} 3416, 1700, 1696, 1602, 1669, 1444, 1415, 1373, 1341, 1302, 1264, 1219, 1194, 1163, 1054, 1018, 1005, 972, 815, 751, 727, 697 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.48 (d, *J* = 3.0 Hz, 2H, N-CH_2), 5.47-5.52 (m, 3H, ArH), 5.58 (t, *J* = 6.0 Hz, 1H, NH), 7.74 (d, *J* = 6.0 Hz, 2H ArH), 7.95 (d, *J* = 6.0 Hz, 2H, ArH), 8.70 (s, 2H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 50.46 (N-CH_2), 91.85 (2 × ArCH), 92.50 (ArCH), 127.03 (ArC), 130.27 (2 × ArCH), 132.20 (2 × ArCH), 134.53 (ArC), 150.17 (ArC), 159.15 (2 × ArC), 196.92 ($CH_2\underline{CO}$); HRMS *m/z* Calcd. for $C_{14}H_{12}BrNO_3$ $[M]^+$ 321.0001. Found 321.0173.

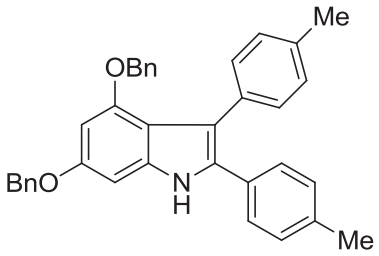
4,6-Dibenzyloxy-2,3-diphenylindole (461)

The indole **461** was prepared from 3,5-dibenzyloxyaniline **337** (1.0 g, 0.0032 mol), benzoin (0.7 g, 0.0032 mol) in silicone oil (30.0 mL), aniline (1.0 mL) and acetic acid (10.0 mL) according to **GP-2** to give the *title compound* as a white solid (1.17 g, 78%). M.p. 164-165 °C; UV (MeOH): λ_{max} 204 nm (ε 37,181 $cm^{-1}M^{-1}$), 256 (15,343), 320 (11,014); IR (KBr): ν_{max} 3419, 3059, 3027, 2859, 2146, 1954, 1625, 1601, 1587, 1554, 1500, 1447, 1380, 1346, 1263, 1192, 1152, 1125, 1095, 1070, 1035, 1026, 1001, 976, 919, 763, 729, 694, 661, 628, 581, 496, 479 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.99 (s, 2H, O-CH_2), 5.12 (s, 2H, O-CH_2), 6.44 (d, *J* = 3.0 Hz, 1H, H5), 6.60 (d, *J* = 3.0 Hz, 1H, H7), 6.90-7.52 (m, 20H, ArH), 8.12 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 69.55 (O-CH_2), 70.51 (O-CH_2), 88.22 (ArCH), 94.21 (ArCH), 113.77 (ArC), 115.17 (ArC), 125.96



(ArCH), 126.55 (2 × ArCH), 126.82 (ArCH), 127.07 (ArCH), 127.47 (2 × ArCH), 127.50 (2 × ArCH), 127.61 (2 × ArCH), 127.89 (ArCH), 127.99 (2 × ArCH), 128.43 (2 × ArCH), 128.56 (2 × ArCH), 131.44 (2 × ArCH), 131.87 (ArC), 132.76 (ArC), 136.27 (ArC), 136.80 (ArC), 137.23 (ArC), 137.24 (ArC), 154.04 (ArC), 156.67 (ArC); HRMS *m/z* Calcd. for $C_{34}H_{27}NO_2$ $[M]^+$ 481.2042. Found 481.2040.

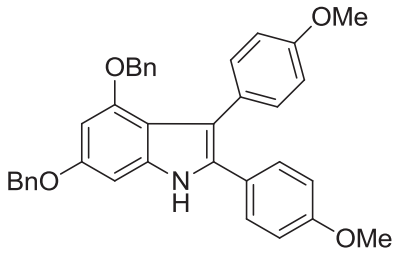
4,6-Dibenzyloxy-2,3-di-*p*-tolylindole (462)



The indole **462** was prepared from 3,5-dibenzyloxyaniline **337** (1.0 g, 0.0032 mol), 4-4′-dimethylbenzoin (0.76 g, 0.0032 mol) in silicone oil (30.0 mL), aniline (1.0 mL) and acetic acid (10.0 mL) according to **GP-2** to give the *title compound* as a white solid (1.11 g, 69%). M.p. 162-163 °C; UV (CH_3CN): λ_{max} 202 nm (ε 43,417 $cm^{-1}M^{-1}$), 251 (18,273), 320 (13,030); IR (KBr): ν_{max} 3413, 3062, 3029, 2856, 1627, 1585, 1508, 1452, 1378, 1346, 1321, 1285, 1259, 1211, 1158, 1027, 999, 906, 815, 784, 735, 696, 502, 480 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.98 (s, 2H, O-CH_2), 5.13 (s, 2H, O-CH_2), 6.42 (bs, 1H, H5), 6.61 (bs, 1H, H7), 6.91-7.52 (m, 18H, ArH), 8.11 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 21.58 (CH_3), 21.75 (CH_3), 70.04 (O-CH_2), 70.99 (O-CH_2), 88.69 (ArCH), 94.57 (ArCH), 114.44 (ArC), 115.09 (ArC), 127.09 (3 × ArCH), 127.46 (ArCH), 127.71 (ArCH), 127.94 (2 × ArCH), 128.31 (3 × ArCH), 128.78 (2 × ArCH), 129.01 (3 × ArCH), 129.61 (2 × ArCH), 130.46 (ArC), 131.68 (ArCH), 132.29 (ArC), 133.80 (ArC), 135.71 (ArC), 136.98 (ArC), 137.34 (ArC), 137.56 (ArC), 137.74 (ArC), 154.46 (ArC), 156.98 (ArC); HRMS (TOF-ESI) *m/z*

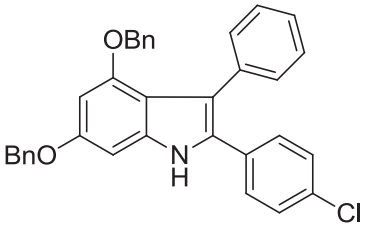
Calcd. for $C_{36}H_{31}NO_2$ $[M]^+$ 509.2355. Found 509.2371; Anal. Calcd. for $C_{36}H_{31}NO_2$: C, 84.84; H, 6.13; N, 2.75. Found: C, 84.85; H, 6.14; N, 2.71.

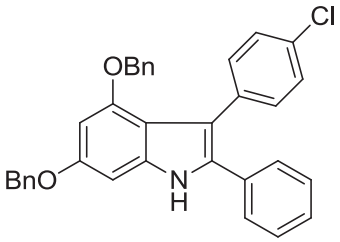
4,6-Dibenzyloxy-2,3-bis(4′-methoxyphenyl)-indole (463)



The indole **463** was prepared from 3,5-dibenzyloxyaniline **337** (1.0 g, 0.0032 mol), anisoin (0.8 g, 0.0032 mol) in silicone oil (30.0 mL), aniline (1.0 mL) and acetic acid (10.0 mL) according to **GP-2** to give the *title compound* as a white solid (1.10 g, 66%). M.p. 158-159 °C; UV (CH_3CN): λ_{max} 202 nm (ε 28,510 $cm^{-1}M^{-1}$), 265 (15,689), 303 (13,849); IR (KBr): ν_{max} 3386, 3061, 3029, 2903, 2835, 1627, 1593, 1555, 1576, 1509, 1452, 1245, 1237, 1152, 1135, 1034, 835, 794, 733, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.36 (s, 3H, O-CH_3), 3.40 (s, 3H, O-CH_3), 4.55 (s, 2H, O-CH_2), 4.69 (s, 2H, O-CH_2), 5.99 (d, *J* = 3.0 Hz, 1H, H5), 6.16 (d, *J* = 3.0 Hz, 1H, H7), 6.35-6.95 (m, 18H, ArH), 7.62 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 54.60 (O-CH_3), 54.70 (O-CH_3), 69.15 (O-CH_2), 70.07 (O-CH_2), 87.81 (ArCH), 93.61 (ArCH), 112.57 (ArC), 113.47 (ArC), 125.02 (ArC), 125.86 (ArC), 126.29 (3 × ArCH), 126.67 (ArCH), 127.03 (3 × ArCH), 127.40 (2 × ArCH), 127.45 (3 × ArCH), 128.09 (3 × ArCH), 128.19 (2 × ArCH), 131.28 (ArCH), 131.96 (ArC), 136.41 (2 × ArC), 136.55 (2 × ArC), 153.46 (ArC), 155.93 (ArC), 157.50 (ArC), 157.99 (ArC); HRMS (TOF-ESI) *m/z* Calcd. for $C_{36}H_{31}NO_4$ $[M]^+$ 541.2253. Found 541.2219; Anal. Calcd for $C_{36}H_{31}NO_4$: C, 79.83; H, 5.77; N, 2.59. Found: C, 79.85; H, 5.79; N, 2.50.

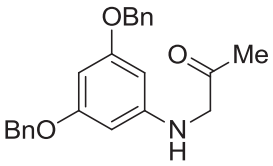
4,6-Dibenzyloxy-2-(4′-chlorophenyl)-3-phenylindole and 4,6-dibenzyloxy-3-(4′-chlorophenyl)-2-phenylindole (465) and **(466)**





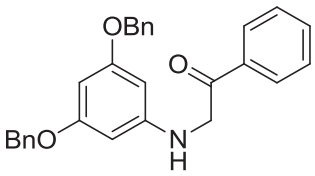
The indoles **465** and **466** were prepared from 3,5-dibenzyloxyaniline **337** (1.0 g, 0.0032 mol), 4-chloroanisoin **464** (0.78 g, 0.0032 mol) in silicone oil (30.0 mL), aniline (1.0 mL) and acetic acid (10.0 mL) according to **GP-2** to give *title compounds* as a mixture in the form of white crystals (1.23, 73%). M.p. 144-145 °C; UV (CH_3CN): λ_{max} 207 nm (ε 51,036 $cm^{-1}M^{-1}$), 252 (21,218), 325 (15,759); IR (KBr): ν_{max} 3388, 3059, 3030, 2860, 1625, 1583, 1499, 1451, 1320, 1307, 1259, 1150, 1126, 1099, 1037, 1026, 1015, 971, 955, 902, 874, 732, 692, 624, 609, 562, 514, 496 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.89 (s, 2H, O-CH_2), 5.06 (s, 2H, O-CH_2), 6.33 (bs, 1H, H5), 6.53 (bs, 1H, H7), 7.12-7.42 (m, 19H, ArH), 8.04 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 70.97 (O-CH_2), 70.99 (O-CH_2), 88.60 (ArCH), 94.56 (ArCH), 113.99 (ArC), 114.27 (ArC), 126.62 (ArCH), 126.97 (ArCH), 127.16 (ArCH), 127.53 (ArCH), 127.84 (2 × ArCH), 127.92 (2 × ArCH), 127.96 (ArCH), 128.18 (2 × ArCH), 128.37 (ArCH), 128.45 (ArCH), 128.51 (ArCH), 129.03 (3 × ArCH), 129.10 (ArCH),), 131.76 (ArCH), 132.32 (ArC), 132.47 (ArC), 133.22 (ArC), 137.61 (ArC), 137.65 (ArC), 137.79 (ArC), 154.41 (ArC), 154.53 (ArC), 157.35 (ArC); HRMS *m/z* Calcd. for $C_{34}H_{26}ClNO_2$ $[M + 1]^+$ 516.1652. Found 516.1721.

1-((3,5-Bis(benzyloxy)phenyl)amino)propan-2-one (469)



The anilinoketone **469** was prepared from 3,5-dibenzyloxyaniline **337** (500 mg, 1.6 mmol), chloroacetone (440 mg, 1.6 mmol) and sodium hydrogen carbonate (0.2 mL, 1.76 mmol) in Ethanol (200 mL) according to **GP-1** to give the *title compound* as a white solid (403 mg, 68%). M.p. 138-140 °C; UV (CH_2Cl_2): λ_{max} 228 nm (ε 23,465 $cm^{-1}M^{-1}$), 262 (7,581); IR (KBr): ν_{max} 2894, 1725, 1624, 1590, 1559, 1458, 1450, 1378, 1308, 1274, 1167, 1108, 1052, 1036, 1000, 972, 795, 747, 732, 696, 691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H, CH_3), 4.59 (s, 2H, N-CH_2), 5.08 (s, 2H, O-CH_2), 5.16 (s, 2H, O-CH_2), 6.29 (bs, 1H, ArH), 6.41 (bs, 1H, ArH), 6.59 (bs, 1H, ArH), 7.36-7.54 (m, 10H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 26.53 (CH_3), 55.98 (N-CH_2), 69.73 (O-CH_2), 70.56 (O-CH_2), 86.47 (ArCH), 93.10 (2 × ArCH), 127.10 (2 × ArCH), 127.62 (3 × ArCH), 127.89 (ArCH), 128.44 (2 × ArCH), 128.52 (2 × ArCH), 137.12 (ArC), 137.25 (ArC), 138.39 (ArC), 154.62 (ArC), 156.81 (ArC), 205.37 ($CH_2\underline{CO}$); HRMS *m/z* Calcd. for $C_{23}H_{23}NO_3Na$ $[M + Na]^+$ 384.1678. Found 384.1661; Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.43; H, 6.37; N, 3.48.

2-((3,5-Bis(benzyloxy)phenyl)amino)-1-phenylethanone (470)

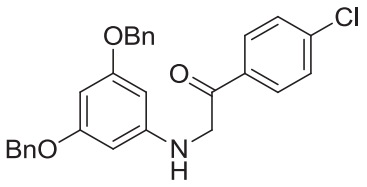


The anilinoketone **470** was prepared from 3,5-dibenzyloxyaniline **337** (200 mg, 0.65 mmol), phenacylbromide (129 mg, 0.65 mmol) and sodium hydrogen carbonate (55 mg, 0.65 mmol) in Ethanol (150 mL) according to **GP-1** to give the *title compound* as a white solid (219 mg, 79%). M.p.110-111 °C; UV (MeOH): λ_{max}

203 nm (ε 39,888 $cm^{-1}M^{-1}$), 245 (19,838); IR (KBr): ν_{max} 3448, 2917, 1697, 1670, 1602, 1588, 1498, 1445, 1416, 1382, 1342, 1303, 1267, 1219, 1194, 1069, 1054, 1018, 1004, 972, 839, 827, 816, 751, 727, 697, 632, 548, 504 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.58 (s, 2H, N-CH_2), 5.02 (s, 4H, 2 × O-CH_2), 6.00 (d, *J* = 3.0 Hz, 2H, ArH), 6.10 (t, *J* = 3.0 Hz, 1H, ArH), 7.29-7.65 (m, 13 H, ArH), 7.69 (d, *J* = 6.0 Hz, 2H ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 50.25 (N-CH_2), 69.91 (2 × O-CH_2), 91.61 (ArCH), 93.05 (2 × ArCH), 127.48 (4 × ArCH), 127.67 (2 × ArCH), 127.84 (2 × ArCH), 128.48 (4 × ArCH), 128.81 (2 × ArCH), 133.81 (ArCH), 134.76 (ArC), 137.01 (ArC), 148.86 (2 × ArC), 160.94 (2 × ArC), 194.73 ($CH_2\underline{CO}$); HRMS *m/z* Calcd. for $C_{28}H_{25}NO_3$ $[M + 1]^+$ 424.1834. Found 424.1909.

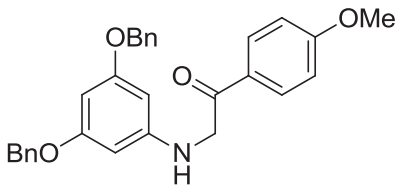
2-((3,5-Bis(benzyloxy)phenyl)amino)-1-(4′-chlorophenyl)ethanone (471)

The anilinoketone **471** was prepared from 3,5-dibenzyloxyaniline **337** (200 mg, 0.65 mmol), 4-chlorophenacylbromide (151 mg, 0.65 mmol) and sodium hydrogen carbonate (90 mg, 0.65 mmol) in Ethanol (150 mL) according to **GP-1** to give the *title compound* as a white solid (213 mg, 71%). M.p. 130-132 °C; UV (MeOH): λ_{max} 207 nm (ε 39,859 $cm^{-1}M^{-1}$), 254 (13,719); IR (KBr): ν_{max} 2917, 1701, 1697, 1601, 1668, 1443, 1414, 1374, 1342, 1301, 1263, 1218, 1193, 1164, 1053, 1017, 1004, 971, 814, 752, 725, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.52 (s, 2H, N-CH_2), 5.02 (s, 4H, 2 × O-CH_2), 5.96 (d, *J* = 3.0 Hz, 2H, ArH), 6.08 (t, *J* = 3.0 Hz, 1H, ArH), 7.33-7.46 (m, 10H, ArH), 7.66 (d, *J* = 6.0 Hz, 2H ArH), 7.86 (d, *J* = 6.0 Hz, 2H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 50.23 (N-CH_2), 69.93 (2 × O-CH_2), 91.73 (ArCH), 93.07 (2 × ArCH), 127.35 (ArC), 127.47 (4 ×



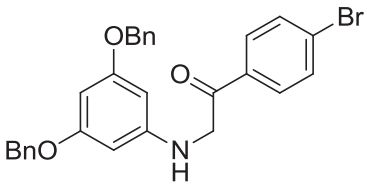
ArCH), 127.86 (2 × ArCH), 128.47 (4 × ArCH), 129.06 (ArC), 129.13 (2 × ArCH), 133.18 (2 × ArCH), 133.45 (ArC), 136.97 (ArC), 148.67 (ArC), 160.95 (2 × ArC), 193.85 ($CH_2\underline{CO}$); HRMS *m/z* Calcd. for $C_{28}H_{24}ClNO_3$ $[M + 1]^+$ 458.1445. Found 458.1441.

2-((3,5-Bis(benzyloxy)phenyl)amino)-1-(4′-methoxyphenyl)ethanone (472)



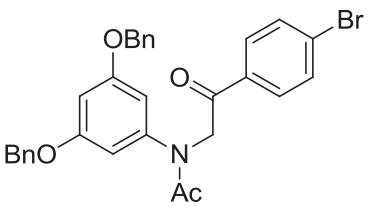
The anilinoketone **472** was prepared from 3,5-dibenzyloxyaniline **337** (200 mg, 0.65 mmol), 4-methoxyphenacylbromide (45 mg, 0.65 mmol) and sodium hydrogen carbonate (55 mg, 0.65 mmol) in Ethanol (150 mL) according to **GP-1** to give the *title compound* as a white solid (249 mg, 84%). M.p.114-115 °C; UV (MeOH): λ_{max} 209 nm (ε 40,905 $cm^{-1}M^{-1}$), 255 (25,594); IR (KBr): ν_{max} 3387, 3029, 2933, 2838, 2049, 1966, 1689, 1679, 1598, 1510, 1479, 1454, 1419, 1378, 1318, 1250, 1159, 1082, 1067, 1044, 988, 916, 831, 796, 731, 696, 673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H, O-CH_3), 4.50 (s, 2H, N-CH_2), 5.04 (s, 2H, O-CH_2), 5.05 (s, 2H, O-CH_2), 5.02 (d, *J* = 3.0 Hz, 2H, ArH), 6.12 (t, *J* = 3.0 Hz, 1H, ArH), 6.96 (d, *J* = 6.0 Hz, 2H, ArH), 7.10 (d, *J* = 6.0 Hz, 2H, ArH), 7.27-7.50 (m, 10H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 49.89 (N-CH_2), 55.47 (O-CH_3), 69.90 (2 × O-CH_2), 91.64 (ArCH), 93.13 (2 × ArCH), 113.99 (ArC), 127.55 (6 × ArCH), 127.87 (ArCH), 128.51 (6 × ArCH), 130.01 (ArCH), 137.01 (2 × ArC), 148.85 (ArC), 160.92 (2 × ArC), 164.01 (ArC), 193.17 (C=O); HRMS *m/z* Calcd. for $C_{29}H_{27}NO_4$ $[M + 1]^+$ 454.1940. Found 454.2015.

2-((3,5-Bis(benzyloxy)phenyl)amino)-1-(4′-bromophenyl)ethanone (473)



The anilinoketone **473** was prepared from 3,5-dibenzyloxyaniline **337** (500 mg, 1.6 mmol), 4-bromophenacylbromide (440 mg, 1.6 mmol) and sodium hydrogen carbonate (147 mg, 1.76 mmol) in Ethanol (150 mL) according to **GP-1** to give the *title compound* as a white solid (698 mg, 85%). M.p. 128-129 °C; UV (MeOH): λ_{max} 208 nm (ε 39,879 $cm^{-1}M^{-1}$), 255 (14,729); IR (KBr): ν_{max} 2916, 1700, 1696, 1602, 1669, 1444, 1415, 1373, 1341, 1302, 1264, 1219, 1194, 1163, 1054, 1018, 1005, 972, 815, 751, 727, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.53 (s, 2H, N-CH_2), 5.01 (s, 4H, 2 × O-CH_2), 5.97 (d, *J* = 3.0 Hz, 2H, ArH), 6.09 (t, *J* = 3.0 Hz, 1H, ArH), 7.32-7.44 (m, 10H, ArH), 7.65 (d, *J* = 6.0 Hz, 2H ArH), 7.85 (d, *J* = 6.0 Hz, 2H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 50.24 (N-CH_2), 69.92 (2 × O-CH_2), 91.71 (ArCH), 93.08 (2 × ArCH), 127.36 (ArC), 127.46 (4 × ArCH), 127.85 (2 × ArCH), 128.48 (4 × ArCH), 129.05 (ArC), 129.12 (2 × ArCH), 132.18 (2 × ArCH), 133.43 (ArC), 136.96 (ArC), 148.68 (ArC), 160.94 (2 × ArC), 193.84 ($CH_2\underline{CO}$); HRMS *m/z* Calcd. for $C_{28}H_{24}BrNO_3$ $[M + 1]^+$ 502.0940. Found 502.1013.

***N*-(3,5-Bis(benzyloxy)phenyl)-*N*-(2-(4′-bromophenyl)-2-oxoethyl) acetamide (476)**

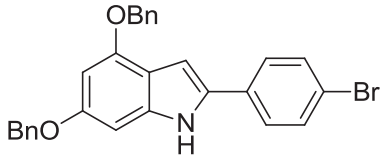


A soution of anilinoketone **473** (200 mg, 0.39 mmol) in acetic anhydride (25 mL) was heated under reflux for 3 h. The mixture was cooled to room temperature; water (50 mL) was added. The mixture was extracted with Ethyl acetate (50 mL), and washed with water (2 × 25 mL), saturated aqueous sodium

hydrogen carbonate (2 × 25 mL) and brine (2 × 25 mL). The organic layer was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Recrystallisation from Ethanol gave the *title compound* as a white solid (189 mg, 87%). M.p. 160-161 °C; UV (MeOH): λ_{max} 206 nm (ε 49,630 $cm^{-1}M^{-1}$), 256 (20,525); IR (KBr): ν_{max} 3092, 3062, 3034, 2916, 2862, 1697, 1670, 1602, 1584, 1455, 1445, 1416, 1382, 1373, 1342, 1302, 1267, 1163, 1069, 1054, 1018, 1004, 972, 839, 816, 751, 727, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (s, 3H, $COCH_3$), 4.98 (s, 2H, N-CH_2), 5.02 (s, 4H, 2 × O-CH_2), 6.60 (s, 3H, ArH), 7.31-7.42 (m, 10H, ArH), 7.60 (d, *J* = 6.0 Hz, 2H ArH), 7.78 (d, *J* = 6.0 Hz, 2H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 22.32 (CO<u>CH_3</u>), 56.33 (N-CH_2), 70.71 (2 × O-CH_2), 102.44 (ArCH), 107.79 (2 × ArCH), 127.97 (4 × ArCH), 128.59 (2 × ArCH), 129.06 (4 × ArCH), 129.90 (2 × ArCH), 132.45 (2 × ArCH), 133.45 (ArC), 136.68 (2 × ArC), 145.39 (2 × ArC), 160.81 (2 × ArC), 171.17 (<u>CO</u>CH_3), 193.16 (CH_2<u>CO</u>); HRMS *m/z* Calcd. for $C_{30}H_{26}BrNO_4$ $[M]^+$ 544.1045. Found 544.1117.

4,6-Dibenzyloxy-2-(4′-bromophenyl)-indole (474)

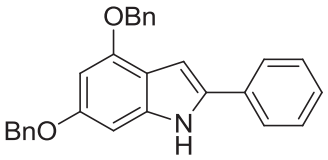
The indole **474** was prepared from 3,5-dibenzyloxyaniline **337** (200 mg, 0.65 mmol), 4-bromophenacylbromide (180 mg, 0.65 mmol), sodium hydrogen carbonate (54 mg, 0.65 mmol) and LiBr (56 mg, 0.65 mmol) in *N*,*N*-dimethylformamide (50 mL) according to **GP-23** to give a yellow solid. Purification using column chromatography (SiO_2, 20% CH_2Cl_2/hexane) to give the *title compound* as a white solid (234 mg, 74%). M.p. 151-152 °C; UV (CH_3CN): λ_{max} 205 nm (ε 35,017 $cm^{-1}M^{-1}$), 254 (15,794), 332 (18,933); IR (KBr): ν_{max} 3421, 3027, 2907, 1630, 1599, 1567, 1537, 1510, 1479, 1449, 1416, 1303, 1274, 1213, 1151, 1135, 1069, 1027, 898,



806, 783, 734, 694, 645, 627, 501, 463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.91 (s, 2H, O-CH_2), 5.05 (s, 2H, O-CH_2), 6.28 (d, *J* = 3.0 Hz, 1H, H5), 6.37 (s, *J* = 3.0 Hz, 1H, H7), 6.77 (bs, 1H, H3), 7.13-7.99 (m, 14H, ArH), 8.00 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 68.93 (O-CH_2), 69.52 (O-CH_2), 87.42 (ArCH), 92.97 (ArCH), 96.97 (ArCH), 113.94 (ArC), 119.52 (ArC), 124.83 (2 × ArCH), 126.43 (2 × ArCH), 126.54 (2 × ArCH), 126.87 (ArCH), 126.92 (ArCH), 127.50 (2 × ArCH), 127.54 (2 × ArCH), 130.29 (ArC), 130.92 (2 × ArCH), 133.01 (ArC), 136.01 (ArC), 136.07 (ArC), 137.18 (ArC), 151.80 (ArC), 155.98 (ArC); HRMS (TOF-ESI) *m/z* Calcd. for $C_{28}H_{22}BrNO_2$ $[M + 2]^+$ 485.0834. Found 485.0832; Anal. Calcd. for $C_{28}H_{22}BrNO_2$: C, 69.43; H, 4.58; N, 2.89. Found: 69.40; H, 4.58; N, 2.84.

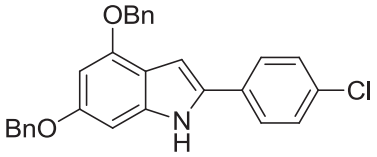
4,6-Dibenzyloxy-2-phenylindole (482)

The indole **482** was prepared from 3,5-dibenzyloxyaniline **337** (200 mg, 0.65 mmol), acetophenone (129 mg, 0.65 mmol), sodium hydrogen carbonate (54 mg, 0.65 mmol) and LiBr (56 mg, 0.65 mmol) in *N*,*N*-dimethylformamide (50 mL) according to **GP-23** to give the *title compound* as a yellow solid (192 mg, 72%). M.p. 100-101 °C; UV (CH_3CN): λ_{max} 206 nm (ε 22,558 $cm^{-1}M^{-1}$), 247 (11,056), 323 (8,140); IR (KBr): ν_{max} 3381, 3060, 3030, 2865, 1686, 1623, 1600, 1581, 1542, 1496, 1450, 1370, 1339, 1316, 1205, 1151, 1124, 1063, 1027, 968, 759, 732, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.97 (s, 2H, O-CH_2), 5.09 (s, 2H, O-CH_2), 6.31 (bs, 1H, H5), 6.47 (bs, 1H, H7), 6.82 (bs, 1H, H2), 7.15-7.50 (m, 15H, ArH), 8.11 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 70.41 (O-CH_2), 71.05 (O-CH_2), 88.95 (ArCH), 94.35 (ArCH), 97.91 (ArCH), 115.49 (ArC), 124.95 (2 × ArCH), 127.44 (ArCH), 127.89 (2 × ArCH), 128.01 (2 ×



ArCH), 128.30 (ArCH), 128.36 (ArCH), 128.97 (2 × ArCH), 129.03 (2 × ArCH), 129.39 (2 × ArCH), 132.94 (ArC), 135.69 (ArC), 137.65 (ArC), 137.71 (ArC), 138.53 (ArC), 158.23 (ArC), 160.01 (ArC); HRMS *m/z* Calcd. for $C_{28}H_{23}NO_2$ $[M]^+$ 405.1729. Found 405.1300; Anal. Calcd for $C_{28}H_{23}NO_2$: C, 82.94; H, 5.72; N, 3.45. Found: C, 82.71; H, 5.73; N, 3.32.

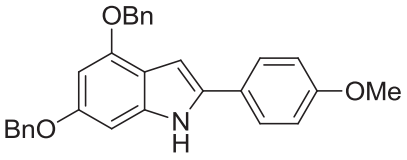
4,6-Dibenzyloxy-2-(4′-chlorophenyl)-indole (483)



The indole **483** was prepared from 3,5-dibenzyloxyaniline **337** (200 mg, 0.65 mmol), acetophenone (151 mg, 0.65 mmol), sodium hydrogen carbonate (54 mg, 0.65 mmol) and LiBr (56 mg, 0.65 mmol) in *N*,*N*-dimethylformamide (50 mL) according to **GP-23** to give the *title compound* as a white solid (209 mg, 73%). M.p. 150-151 °C; UV (CH_3CN): λ_{max} 211 nm (ε 30,730 $cm^{-1}M^{-1}$), 252 (15,628), 329 (18,701); IR (KBr): ν_{max} 3401, 3032, 2924, 2851, 1621, 1593, 1572, 1481, 1452, 1421, 1336, 1305, 1277, 1209, 1141, 1021, 1008, 961, 902, 826, 813, 789, 736, 694, 711, 652, 637, 505, 481, 458 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.91 (s, 2H, O-CH_2), 5.05 (s, 2H, O-CH_2), 6.29 (d, *J* = 3.0 Hz, 1H, H5), 6.38 (s, *J* = 3.0 Hz, 1H, H7), 6.76 (bs, 1H, H2), 7.19-7.40 (m, 14H, ArH), 8.00 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 70.43 (O-CH_2), 71.04 (O-CH_2), 88.96 (ArCH), 94.48 (ArCH), 98.39 (ArCH), 115.45 (ArC), 126.05 (2 × ArCH), 127.90 (2 × ArCH), 128.01 (2 × ArCH), 128.34 (ArCH), 138.38 (ArCH), 128.97 (2 × ArCH), 129.02 (2 × ArCH), 129.49 (2 × ArCH), 131.39 (ArC), 132.97 (ArC), 134.52 (ArC), 137.53 (ArC), 137.60 (ArC), 138.67 (ArC), 153.29 (ArC), 157.46 (ArC); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{28}H_{22}ClNO_2$ $[M]^+$ 439.1339. Found

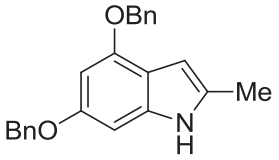
439.1331; Anal. Calcd for $C_{28}H_{22}ClNO_2$: C, 76.44; H, 5.04; N, 3.18. Found: C, 76.16; H, 5.15; N, 3.11.

4,6-Dibenzyloxy-2-(4′-methoxyphenyl)-indole (484)



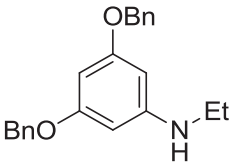
The indole **484** was prepared from 3,5-dibenzyloxyaniline **337** (200 mg, 0.65 mmol), acetophenone (149 mg, 0.65 mmol), sodium hydrogen carbonate (54 mg, 0.65 mmol) and LiBr (56 mg, 0.65 mmol) in *N*,*N*-dimethylformamide (50 mL) according to **GP-23** to give the *title compound* as off white solid (229 mg, 80%). M.p. 140-141 °C; UV (CH_3CN): λ_{max} 201 nm (ε 37,366 $cm^{-1}M^{-1}$), 256 (15,094), 303 (13,093); IR (KBr): ν_{max} 3440, 3012, 2910, 2858, 1626, 1600, 1579, 1549, 1510, 1451, 1428, 1370, 1308, 1281, 1247, 1212, 1149, 1134, 1110, 966, 913, 898, 826, 804, 790, 755, 730, 644, 625, 607, 523, 460, 448 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H, O-CH_3), 5.06 (s, 2H, O-CH_2), 5.19 (s, 2H, O-CH_2), 6.40 (d, *J* = 3.0 Hz, 1H, H5), 6.55 (d, *J* = 3.0 Hz, 1H, H7), 6.79 (d, *J* = 3.0 Hz, 1H, H2), 6.93 (d, *J* = 6.0 Hz, 2H, ArH), 7.33-7.53 (m, 14H, ArH), 8.15 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.27 (O-CH_3), 69.88 (O-CH_2), 70.55 (O-CH_2), 88.52 (ArCH), 93.75 (ArCH), 96.13 (ArCH), 114.33 (2 × ArCH), 125.80 (2 × ArCH), 127.36 (2 × ArCH), 127.42 (ArC), 127.49 (2 × ArCH), 127.75 (ArCH), 127.81 (ArCH), 128.44 (2 × ArCH), 128.49 (2 × ArCH), 135.28 (ArC), 137.21 (ArC), 137.25 (ArC), 137.81 (ArC), 152.54 (ArC), 156.42 (ArC), 158.77 (ArC), 160.83 (ArC); HRMS *m/z* Calcd. for $C_{29}H_{25}NO_3$ $[M + 1]^+$ 436.1834. Found 436.1907.

4,6-Dibenzyloxy-2-methylindole (485)



The indole **485** was prepared from3,5-dibenzyloxyaniline **337** (200 mg, 0.65 mmol), chloroacetone (0.1 mL, 1.3 mmol), sodium hydrogen carbonate (54 mg, 0.65 mmol) and LiBr (56 mg, 0.65 mmol) in *N*,*N*-dimethylformamide (50 mL) according to **GP-23** to give the *title compound* as a white solid (172 mg, 76%). M.p. 200-201 °C; UV (CH_3CN): λ_{max} 205 nm (ε 23,529 $cm^{-1}M^{-1}$), 227 (28,469), 276 (5,590); IR (KBr): ν_{max} 3067, 3031, 2872, 2639, 1691, 1595, 1498, 1473, 1422, 1378, 1346, 1301, 1273, 1216, 1165, 1058, 1029, 967, 933, 903, 880, 841, 768, 754, 738, 694, 676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 4.96 (s, 2H, O-CH_2), 5.05 (s, 2H, O-CH_2), 6.26 (d, *J* = 3.0 Hz, 1H, H5), 6.39 (d, *J* = 3.0 Hz, 1H, H7), 6.60 (d, *J* = 3.0 Hz, 1H, H2), 7.21-7.43 (m, 10H, ArH), 7.59 (bs, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 12.75 (CH_3), 70.13 (O-CH_2), 70.93 (O-CH_2), 88.86 (ArCH), 93.41 (ArCH), 112.65 (ArC), 113.49 (ArC), 119.45 (ArCH), 127.51 (2 × ArCH), 127.94 (2 × ArCH), 128.01 (ArCH), 128.25 (ArCH), 128.86 (2 × ArCH), 128.96 (2 × ArCH), 137.79 (ArC), 137.85 (ArC), 138.42 (ArC), 154.79 (ArC), 156.86 (ArC); HRMS (TOF-ESI) *m/z:* Calcd. for $C_{23}H_{21}NO_2$ $[M]^+$ 343.1572. Found 343.1576; Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08; O, 9.32. Found: C, 80.25; H, 6.30; N, 4.32.

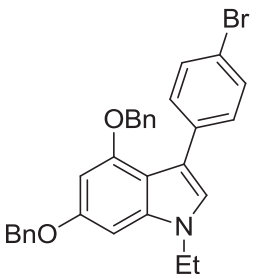
3,5-Dibenzyloxy-*N*-ethylaniline (486)



Potassium carbonate (0.8 g, 0.006 mol) was added to a solution of 3,5-dibenzyloxyaniline **337** (1.0 g, 0.003 mol) in acetonitrile (100 mL), and the mixture was stirred at room temperature for 10 min. The reaction mixture was cooled briefly in an ice bath followed by addition of

iodoethane (0.36 mL, 0.003 mol). The reaction mixture stirred at room temperature for overnight, and concentrated under reduced pressure. The residue was diluted with water (100 mL), and extracted with diethyl ether (3 × 100 mL). The combined organic layer was washed with water (2 × 100 mL), dried over $MgSO_4$ and concentrated to give the *title compound* as brown oil (0.63 g, 72%). UV (MeOH): λ_{max} 216 nm (ε 14,751 $cm^{-1}M^{-1}$), 254 (2,897); IR (KBr): ν_{max} 3408, 3030, 2926, 1616, 1595, 1512, 1498, 1453, 1375, 1300, 1264, 1189, 1151, 1057, 807, 735, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (t, *J* = 6.0 Hz, 3H, CH_3), 3.01 (q, *J* = 6.0 Hz, 2H, $C\underline{H_2}CH_3$), 4.89 (s, 4H, 2 × O-CH_2), 5.79 (d, *J* = 3.0 Hz, 2H, ArH), 5.95 (t, *J* = 3.0 Hz, 1H, ArH), 7.21-7.34 (m, 10H, ArH), 11.12 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 15.27 (CH_3), 38.89 ($C\underline{H_2}CH_3$), 70.37 (2 × O-CH_2), 91.72 (ArCH), 93.20 (2 × ArCH), 127.99 (6 × ArCH), 128.32 (2 × ArCH), 129.00 (2 × ArCH), 137.68 (2 × ArC), 150.79 (ArC), 161.39 (2 × ArC); IR (KBr): ν_{max} 3408, 3030, 2926, 1616, 1595, 1512, 1498, 1453, 1375, 1300, 1264, 1189, 1151, 1057, 807, 735, 697 cm^{-1}; HRMS *m/z:* Calcd. for $C_{22}H_{23}NO_2$ $[M + 1]^+$ 334.1729. Found 334.1805.

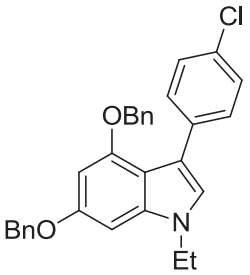
4,6-Dibenzyloxy-3-(4′-bromophenyl)-1-ethylindole (487)



The indole **487** was prepared from 3,5-dibenzyloxy-*N*-ethylaniline **337** (200 mg, 0.6 mmol), acetophenone (165 mg, 0.6 mmol), sodium hydrogen carbonate (50 mg, 0.6 mmol) and LiBr (52 mg, 0.6 mmol) in *N*,*N*-dimethylformamide (50 mL) according to **GP-23** to give the *title compound* as a white solid (249 mg, 81%). M.p. 149-150 °C; UV (MeOH): λ_{max} 203 nm (ε 47.165 $cm^{-1}M^{-1}$), 247 (21,768), 314 (16,965); IR (KBr): ν_{max} 3028, 2967, 2927, 2852, 1619, 1579, 1535, 1558, 1498, 1450, 1375,

1353, 1327, 1284, 1263, 1243, 1196, 1151, 1098, 1048, 1027, 1006, 985, 974, 905, 887, 833, 801, 789, 751, 733, 695, 676, 623, 540 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (t, *J* = 6.0 Hz, 3H, CH_3), 3.98 (q, *J* = 6.0 Hz, 2H, N-CH_2), 4.95 (s, 2H, O-CH_2), 5.03 (s, 2H, O-CH_2), 6.34 (d, *J* = 3.0 Hz, 1H, H5), 6.44 (d, *J* = 3.0 Hz, 1H, H7), 6.83 (s, 1H, H2), 7.02-7.41 (m, 14H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 15.63 (CH_3), 41.57 (N-$C\underline{H_2}CH_3$), 70.59 (O-CH_2), 71.15 (O-CH_2), 87.62 (ArCH), 94.16 (ArCH), 112.01 (ArC), 116.94 (ArC), 119.83 (ArCH), 124.00 (ArC), 127.71 (2 × ArCH), 128.07 (2 × ArCH), 128.40 (2 × ArCH), 128.65 (2 × ArCH), 129.03 (2 × ArCH), 130.93 (2 × ArCH), 131.84 (2 × ArCH), 135.49 (ArC), 137.07 (ArC), 137.68 (ArC), 138.48 (ArC), 154.42 (ArC), 156.90 (ArC); HRMS *m/z:* Calcd. for $C_{30}H_{26}BrNO_2$ $[M + 1]^+$ 512.1147. Found 512.1223.

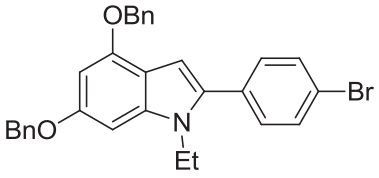
4,6-Dibenzyloxy-3-(4′-chlorophenyl)-1-ethylindole (488)



The indole **488** was prepared from 3,5-dibenzyloxy-*N*-ethylaniline **337** (200 mg, 0.6 mmol), acetophenone (165 mg, 0.6 mmol), sodium hydrogen carbonate (50 mg, 0.6 mmol) and LiBr (52 mg, 0.6 mmol) in *N*,*N*-dimethylformamide (50 mL) according to **GP-23** to give the *title compound* as a white solid (221 mg, 78%). M.p. 162-163 °C; UV (MeOH): λ_{max} 202 nm (ε 22,416 $cm^{-1}M^{-1}$), 228 (15, 270), 285 (6,538); IR (KBr): ν_{max} 3435, 3059, 3028, 2969, 2929, 2852, 1619, 1580, 1561, 1537, 1497, 1450, 1376, 1352, 1310, 1285, 1264, 1243, 1089, 1027, 985, 974, 801, 791734, 695, 682, 624, 541, 499, 468, 451 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (t, *J* = 3.0 Hz, 3H, CH_3), 4.12 (q, *J* = 3.0 Hz, 2H, N-CH_2), 5.09 (s, 2H, O-CH_2), 5.19 (s, 2H, O-CH_2), 6.46 (s, 1H, H5), 6.56 (s, 1H, H7), 6.97 (s, 1H, H2), 7.17-7.38 (m, 14H, ArH); ^{13}C NMR

(75.6 MHz, $CDCl_3$): δ 14.71 (CH_3), 40.65 (N-$C\underline{H_2}CH_3$), 69.67 (O-CH_2), 70.24 (O-CH_2), 86.68 (ArCH), 93.21 (ArCH), 110.81 (ArC), 116.00 (ArC), 123.13 (ArCH), 126.80 (2 × ArCH), 127.05 (2 × ArCH), 127.15 (2 × ArCH), 127.16 (ArC), 127.48 (ArCH), 127.71 (2 × ArCH), 128.11 (2 × ArCH), 130.52 (2 × ArCH), 130.78 (ArCH), 134.08 (ArC), 136.16 (ArC), 136.74 (ArC), 137.53 (ArC), 153.49 (ArC), 155.94 (ArC); HRMS *m/z:* Calcd. for $C_{30}H_{26}ClNO_2$ $[M + 1]^+$ 468.1652. Found 468.1729.

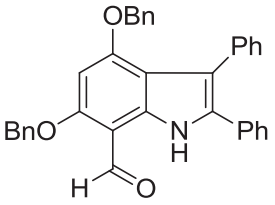
4,6-Bis(benzyloxy)-2-(4′-bromophenyl)-1-ethylindole (489)



Dimethyl sulfoxide (25 mL) was added to powdered potassium hydroxide (36 mg, 0.65 mmol) and the mixture was stirred at room temperature for 10 min followed by the addition of indole **474** (200 mg, 0.65 mmol). The mixture was stirred at room temperature for 1 h before cooling briefly on ice bath, iodoethane (0.1 mL, 0.65 mmol) was then added, and the reaction mixture stirred at room temperature for a further 1 h. After diluting with water (100 mL) the mixture was extracted with diethyl ether (3 × 100 mL). The organic layer was washed with water, dried ($MgSO_4$), and concentrated. Purification using column chromatography (SiO_2, 30% CH_2Cl_2/hexane) to give the *title compound* as a white solid (179 mg, 85%). M.p. 122-124 °C; UV (CH_3CN): λ_{max} 204 nm (ε 49,311 $cm^{-1}M^{-1}$), 229 (30,097), 286 (12,877); IR (KBr): ν_{max} 3447, 3027, 2928, 1630, 2359, 2359, 2343, 1623, 1589, 1560, 1496, 1452, 1375, 1278, 1183, 1161, 1127, 1069, 1026, 1008, 800, 735, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, *J* = 6.0 Hz, 3H, CH_3), 4.10 (q, *J* = 6.0 Hz, 2H, N-CH_2), 5.13 (s, 2H, O-CH_2), 5.19 (s, 2H, O-CH_2), 6.42 (d, *J* = 3.0 Hz, 1H, H5), 6.56 (d, *J* = 3.0 Hz, 1H, H7), 6.62 (s, 1H, H2), 7.26-7.58 (m, 14H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 15.09 (CH_3), 38.91

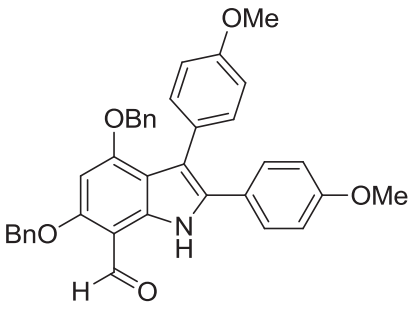
(N-C<u>H</u>$_2$CH$_3$), 69.87 (O-CH$_2$), 70.73 (O-CH$_2$), 87.86 (ArCH), 93.56 (ArCH), 99.88 (ArCH), 113.77 (ArC), 121.61 (ArC), 127.27 (2 × ArCH), 127.58 (2 × ArC), 127.72 (2 × ArCH), 127.86 (2 × ArCH), 128.42 (2 × ArCH), 128.50 (2 × ArCH), 130.52 (2 × ArCH), 131.57 (2 × ArCH), 132.14 (ArC), 137.18 (2 × ArC), 138.61 (ArC), 152.78 (ArC), 156.48 (2 × ArC); HRMS *m/z:* Calcd. for $C_{30}H_{26}BrNO_2$ $[M + 1]^+$ 512.1147. Found 512.1220.

4,6-Dibenzyloxy-2,3-diphenylindole-7-carbaldehyde (490)



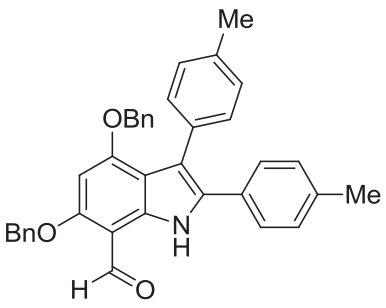
The formyl indole **490** was prepared from indole **461** (100 mg, 0.2 mmol) in dimethylformamide (3.0 mL) and phosphoryl chloride (0.1 mL, 0.3 mmol) according to **GP-24** to give the *title compound* as a white solid (89 mg, 75%). M.p. 180-181 °C; UV (MeOH): λ_{max} 203 nm (ε 38.429 cm^{-1}M^{-1}), 260 (15,168), 326 (9,772); IR (KBr): ν_{max} 3312, 3036, 2901, 2867, 1647, 1591, 1547, 1499, 1449, 1383, 1364, 1252, 1225, 1171, 1123, 1076, 1002, 955, 917, 906, 838, 788, 763, 735, 692, 678, 663, 620, 598, 468 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.03 (s, 2H, O-CH$_2$), 5.23 (s, 2H, O-CH$_2$), 6.29 (s, 1H, H5), 6.88-7.43 (m, 20H, ArH), 10.49 (s, 1H, NH), 10.61 (s, 1H, CHO); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 69.81 (O-CH$_2$), 71.42 (O-CH$_2$), 89.81 (ArCH), 104.86 (ArC), 113.52 (ArC), 114.61 (ArC), 126.24 (ArCH), 126.51 (2 × ArCH), 127.18 (ArCH), 127.29 (2 × ArCH), 127.55 (3 × ArCH), 128.69 (2 × ArCH), 128.23 (3 × ArCH), 128.41 (2 × ArCH), 128.69 (2 × ArCH), 131.26 (2 × ArCH), 132.02 (ArC), 133.27 (ArC), 135.59 (ArC), 135.63 (ArC), 136.22 (ArC), 136.59 (ArC), 160.10 (ArC), 161.67 (ArC), 188.43 (CHO); HRMS *m/z:* Calcd. for $C_{35}H_{27}NO_3$ $[M + 1]^+$ 510.1991. Found 510.2068.

4,6-Dibenzyloxy-2,3-bis(4′-methoxyphenyl)-indole-7-carbaldehyde (491)



The formyl indole **491** was prepared from indole **462** (100 mg, 0.19 mmol) in *N*,*N*-dimethylformamide (3.0 mL) and phosphoryl chloride (0.1 mL, 0.3 mmol) according to **GP-24** to give the *title compound* as a yellow solid (81 mg, 76%). M.p. 191-191 °C; UV (CH_2Cl_2): λ_{max} 232 nm (ε 28, 510 $cm^{-1}M^{-1}$), 277 (20,774), 358 (17,853); IR (KBr): ν_{max} 3324, 2934, 2924, 2865, 1648, 1589, 1573, 1553, 1518, 1496, 1518, 1507, 1451, 1402, 1377, 1363, 1292, 1260, 1246, 1234, 1197, 1177, 1101, 1033, 994, 837, 810, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H, O-CH_3), 3.81 (s, 3H, O-CH_3), 5.03 (s, 2H, O-CH_2), 5.23 (s, 2H, O-CH_2), 5.28 (s, 1H, H5), 6.75-7.46 (m, 18H, ArH), 10.48 (s, 1H, CHO), 10.52 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.01 (O-CH_3), 55.11 (O-CH_3), 69.81 (O-CH_2), 71.44 (O-CH_2), 89.69 (ArCH), 104.89 (ArC), 104.87 (ArC), 113.10 (ArC), 113.88 (ArC), 124.70 (ArC), 126.68 (3 × ArCH), 127.28 (3 × ArCH), 127.58 (ArCH), 128.01 (ArC), 128.12 (2 × ArCH), 128.20 (ArCH), 128.66 (2 × ArCH), 128.73 (3 × ArCH), 132.25 (3 × ArCH), 133.12 (ArC), 135.64 (ArC), 136.26 (ArC), 158.11 (ArC), 158.70 (ArC), 159.92 (ArC), 161.39 (ArC), 188.45 (CHO); HRMS *m/z:* Calcd. for $C_{37}H_{31}NO_5$ $[M + 1]^+$ 570.2202. Found 570.2272.

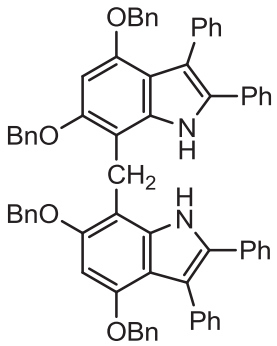
4,6-Dibenzyloxy-2,3-di-*p*-tolyl-indole-7-carbaldehyde (492)



The formyl indole **492** was prepared from indole **463** (100 mg, 0.18 mmol) in dimethylformamide (3.0 mL) and phosphoryl chloride (0.1 mL, 0.3 mmol) and

according to **GP-24** to give the *title compound* as a yellow solid (74 mg, 71%). M.p. 180-181 °C; UV (MeOH): λ_{max} 202 nm (ε 48,330 $cm^{-1}M^{-1}$), 264 (25,614), 304 (16,754), 327 (16,120); IR (KBr): ν_{max} 3420, 3319, 3026, 2917, 2858, 1639, 1593, 1570, 1507, 1496, 1453, 1405, 1380, 1360, 1346, 1320, 1229, 1168, 1109, 994, 974, 847, 823, 792, 732, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 5.03 (s, 2H, O-CH_2), 5.23 (s, 2H, O-CH_2), 6.28 (s, 1H, H5), 6.90-7.48 (m, 18H, ArH), 10.49 (s, 1H, CHO), 10.57 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 21.12 (CH_3), 21.25 (CH_3), 69.78 (O-CH_2), 71.42 (O-CH_2), 89.71 (ArCH), 104.86 (ArC), 113.71 (ArC), 114.06 (ArC), 126.60 (2 × ArCH), 127.29 (2 × ArCH), 127.35 (2 × ArCH), 127.48 (ArCH), 128.06 (2 × ArCH), 128.20 (ArCH), 128.40 (2 × ArCH), 128.66 (2 × ArCH), 129.12 (2 × ArCH), 129.23 (ArC), 131.05 (2 × ArCH), 132.68 (ArC), 133.25 (ArC), 135.56 (ArC), 135.65 (ArC), 136.26 (ArC), 136.46 (ArC), 136.93 (ArC), 160.04 (ArC), 161.51 (ArC), 188.42 (CHO); HRMS *m/z:* Calcd. for $C_{37}H_{31}NO_3$ $[M + 1]^+$ 538.2304. Found 538.2375.

4,6-Dibenzyloxy-2,3-diphenyl-indol-7-yl)methane (493)

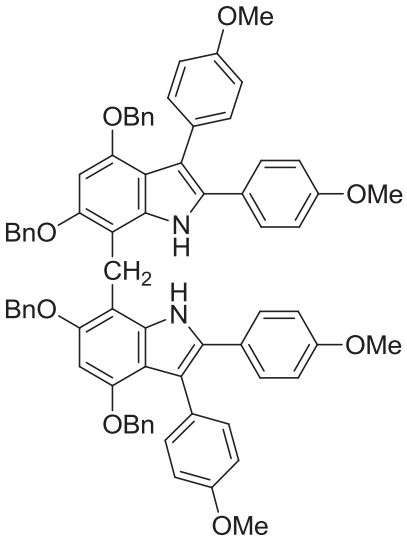


The indolylmethane **493** was prepared from indole **461** (100 mg, 0.24 mmol) in glacial acetic acid (5.0 mL) and formaldehyde (37%, 2.0 mL) according to **GP-25** to give the *title compound* as a white solid (88 mg, 87%). M.p. 220-221 °C; UV (CH_2Cl_2): λ_{max} 228 nm (ε 86,880 $cm^{-1}M^{-1}$), 263 (90,289), 341 (39,934); IR (KBr): ν_{max} 3330, 3060, 3028, 2926, 2866, 1816, 1600, 1516, 1502, 1452, 1438, 1378, 1341, 1308, 1287, 1265, 1155, 1100, 1028, 992, 910, 878, 801, 761, 734, 695, 666, 620, 587, 526 cm^{-1}; ^{1}H NMR (300

MHz, $CDCl_3$): δ 4.54 (s, 1H, CH_2), 4.88 (s, 2H, O-CH_2), 5.29 (s, 2H, O-CH_2), 6.46 (s, 1H, H5), 6.82-7.39 (m, 20H, ArH), 10.01 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 19.71 (CH_2), 69.94 (O-CH_2), 75.46 (O-CH_2), 94.15 (ArCH), 106.20 (ArC), 114.88 (ArC), 115.32 (ArC), 125.79 (ArCH), 126.42 (ArCH), 126.54 (2 × ArCH), 127.01 (2 × ArCH), 127.50 (2 × ArCH), 127.94 (2 × ArCH), 128.17 (2 × ArCH), 128.40 (2 × ArCH), 128.46 (2 × ArCH), 128.76 (2 × ArCH), 131.37 (2 × ArCH), 132.84 (ArC), 133.28 (ArC), 136.54 (ArC), 136.58 (ArC), 136.65 (ArC), 136.86 (ArC), 151.05 (ArC), 153.00 (ArC); HRMS *m/z:* Calcd. for $C_{69}H_{54}N_2O_4$ $[M + 1]^+$ 975.4084. Found 975.4247.

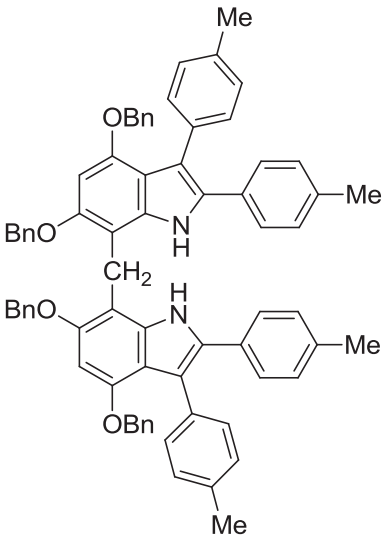
Bis(4,6-bis(benzyloxy)-2,3-bis(4′-methoxyphenyl)-indol-7-yl)methane (494)

The indolylmethane **494** was prepared from indole **462** (100 mg, 0.18 mmol) in glacial acetic acid (5.0 mL) and formaldehyde (37%, 2.0 mL) according to **GP-25** to give the *title compound* as a white solid (87 mg, 86%). M.p. 230-231 °C; UV (MeOH): λ_{max} 260 nm (ε 92,443 $cm^{-1}M^{-1}$), 311 (59,404); IR (KBr): ν_{max} 3320, 3062, 3030, 2932, 2831, 1617, 1576, 1515, 1495, 1453, 1379, 1341, 1297, 1263, 1177, 1097, 1031, 992, 833, 806, 793, 736, 696 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 3.77 (s, 6H, 2 × O-CH_3), 4.57 (s, 1H, CH_2), 4.97 (s, 2H, O-CH_2), 5.45 (s, 2H, O-CH_2), 6.65-7.76 (m, 19H, ArH), 10.07 (s, 1H, NH); ^{13}C NMR (75.6 MHz, acetone-d_6): δ 19.27 (CH_2), 54.35 (O-CH_3), 54.50 (O-CH_3), 69.28 (O-CH_2), 72.12 (O-CH_2), 93.96 (ArCH), 106.15 (ArC), 112.88 (2 × ArCH), 113.73 (2 × ArCH), 125.29 (ArC), 126.64 (2 × ArCH), 126.89 (2 × ArCH), 127.72 (2 × ArCH), 128.35 (2 × ArCH), 128.69 (2 × ArCH), 128.78 (2 ×



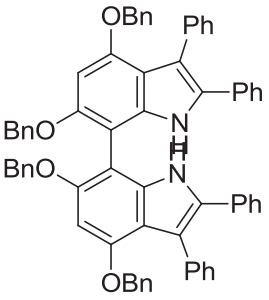
ArCH), 129.02 (ArC), 132.19 (2 × ArCH), 132.62 (ArC), 136.25 (2 × ArC), 137.16 (2 × ArC), 137.23 (ArC), 150.34 (ArC), 152.29 (ArC), 158.19 (ArC), 158.48 (ArC); HRMS *m/z:* Calcd. for $C_{73}H_{62}N_2O_8$ $[M + 1]^+$ 1095.4506. Found 1095.4570.

Bis(4,6-bis(benzyloxy)-2,3-di-*p*-tolyl-indol-7-yl)methane (495)



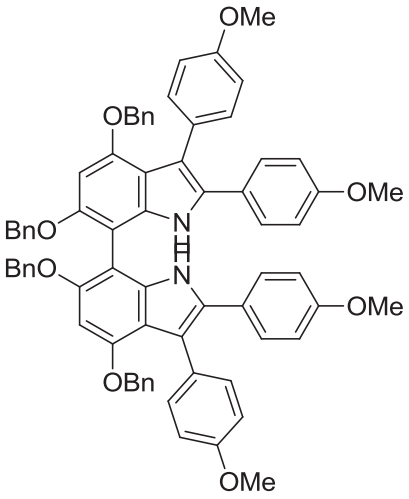
The indolylmethane **495** was prepared from indole **463** (100 mg, 0.19 mmol) in glacial acetic acid (10 mL) and formaldehyde (40%, 2.0 mL) according to **GP-25** to give the *title compound* as a white solid (75 mg, 74%). M.p. 228-230 °C; UV (CH_3CN): λ_{max} 202 nm (ε 38,831 $cm^{-1}M^{-1}$), 252 (16,583), 320 (11,124); IR (KBr): ν_{max} 3339, 3062, 3026, 2917, 2860, 1594, 1572, 1514, 1496, 1452, 1379, 1326, 1310, 1286, 1262, 1213, 1157, 1099, 1026, 992, 822, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.57 (s, 1H, CH_2), 4.92 (s, 2H, O-CH_2), 5.34 (s, 2H, O-CH_2), 6.49 (s, 1H, H5), 6.89-7.65 (m, 18H, ArH), 10.10 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 19.71 (CH_2), 21.17 (CH_3), 21.27 (CH_3), 70.06 (O-CH_2), 75.46 (O-CH_2), 94.19 (ArCH), 106.27 (ArC), 114.34 (ArC), 115.56 (ArC), 126.68 (2 × ArCH), 126.99 (ArCH), 127.38 (2 × ArCH), 127.83 (2 × ArCH), 128.26 (2 × ArCH), 128.43 (3 × ArCH), 128.75 (2 × ArCH), 128.94 (2 × ArCH), 130.15 (ArC), 131.21 (2 × ArCH), 133.27 (ArC), 133.67 (ArC), 135.08 (ArC), 136.04 (ArC), 136.50 (ArC), 136.78 (ArC), 136.99 (ArC), 150.45 (ArC), 152.42 (ArC); HRMS *m/z:* Calcd. for $C_{73}H_{62}N_2O_4$ $[M + 1]^+$ 1031.4710. Found 1031.4772.

4,4',6,6'-Tetrakis(benzyloxy)-2,2',3,3'-tetraphenyl-7,7'-biindole (496)



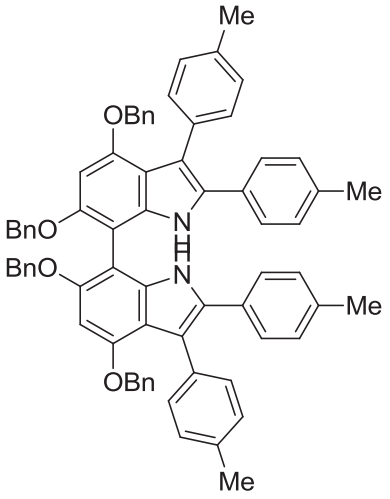
The biindolyl **496** was prepared from indole **461** (100 mg, 0.24 mmol) in tetrahydrofuran (4.0 mL) containing hydrochloric acid (2.0 ml) and 1,4-benzoquinone (30 mg) according to **GP-26** to give the *title compound* as a white solid (62 mg, 61%). M.p. 220-221 °C; UV (CH_3CN): λ_{max} 203 nm (ε 85,440 $cm^{-1}M^{-1}$), 259 (47,328), 311 (30,432); IR (KBr): ν_{max} 3449, 3025, 2928, 2844, 1600, 1555, 1500, 1452, 1426, 1331, 1257, 1231, 1133, 1096, 1064, 1028, 989, 911, 876, 760, 750, 741, 774, 662, 476 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 4.96 (s, 2H, O-CH_2), 5.02 (s, 2H, O-CH_2), 6.66 (s, 1H, H5), 6.86-7.25 (m, 20H, ArH), 10.00 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 68.79 (O-CH_2), 70.99 (O-CH_2), 92.32 (ArCH), 100.04 (ArC), 113.45 (ArC), 114.00 (ArC), 114.04 (ArC), 125.25 (ArCH), 125.96 (ArCH), 126.22 (2 × ArCH), 126.51 (ArCH), 126.64 (3 × ArCH), 127.06 (2 × ArCH), 127.34 (2 × ArCH), 127.47 (3 × ArCH), 127.74 (3 × ArCH), 131.11 (2 × ArCH), 132.49 (ArC), 132.63 (ArC), 136.88 (ArC), 136.92 (ArC), 137.72 (ArC), 152.66 (ArC), 153.24 (ArC); HRMS *m/z:* Calcd. for $C_{68}H_{52}N_2O_4$ $[M + 1]^+$ 961.3927. Found 961.3703.

4,4',6,6'-Tetrakis(benzyloxy)-2,2',3,3'-tetrakis(4′-methoxyphenyl)-7,7'-biindole (497)



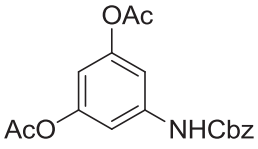
The biindolyl **497** was prepared from indole **462** (100 mg, 0.18 mmol) in tetrahydrofuran (4.0 mL) containing hydrochloric acid (2.0 ml) and 1,4-benzoquinone (30 mg) according to **GP-26** to give the *title compound* as a white solid (60 mg, 62%). M.p. 200-201 °C (dec.); UV (CH_2Cl_2): λ_{max} 228 nm (ε 107,784 $cm^{-1}M^{-1}$), 265 (82,080), 358 (57,780); IR (KBr): ν_{max} 3454, 2957, 2874, 1723, 1659, 1617, 1578, 1520, 1454, 1326, 1260, 1174, 1127, 1066, 1035, 957, 834, 793, 736, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 3H, O-CH_3), 3.83 (s, 3H, O-CH_3), 4.93 (s, 2H, O-CH_2), 5.02 (s, 2H, O-CH_2), 6.59 (s, 1H, H5), 6.70-7.35 (m, 18H, ArH), 8.22 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.03 (O-CH_3), 55.08 (O-CH_3), 69.39 (O-CH_2), 69.84 (O-CH_2), 94.66 (ArCH), 101.06 (ArC), 112.98 (ArC), 113.55 (ArC), 114.20 (ArC), 125.41 (ArC), 126.81 (3 × ArCH), 126.93 (ArCH), 127.19 (3 × ArCH), 127.35 (ArCH), 127.93 (3 × ArCH), 128.13 (3 × ArCH), 128.81 (ArC), 128.99 (2 × ArCH), 132.28 (ArC), 132.46 (2 × ArCH), 132.96 (ArC), 136.49 (ArC), 136.85 (ArC), 137.44 (ArC), 157.89 (ArC), 158.45 (ArC); HRMS *m/z:* Calcd. for $C_{72}H_{60}N_2O_4$ $[M + 1]^+$ 1081.4350. Found 1081.4408.

4,4',6,6'-Tetrakis(benzyloxy)-2,2',3,3'-tetra-*p*-tolyl-7,7'-biindole (498)



The biindolyl **498** was prepared from indole **463** (100 mg, 0.19 mmol) in tetrahydrofuran (4.0 mL) containing hydrochloric acid (2.0 mL) and 1,4-benzoquinone (30 mg) according to **GP-26** to give the *title compound* as a white solid (52 mg, 51%). M.p. 152-153 °C; UV (MeOH): λ_{max} 203 nm (ε 71,628 $cm^{-1}M^{-1}$), 257 (32,308), 317 (20,218); IR (KBr): ν_{max} 3459, 3065, 3028, 2917, 2886, 1704, 1602, 1585, 1552, 1504, 1453, 1431, 1380, 1283, 1256, 1225, 1130, 1090, 1046, 1026, 996, 819, 736, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.95 (s, 2H, O-CH_2), 5.04 (s, 2H, O-CH_2), 6.61 (s, 1H, H5), 6.96-7.36 (m, 18H, ArH), 8.23 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 21.09 (CH_3), 21.29 (CH_3), 69.84 (O-CH_2), 73.24 (O-CH_2), 94.17 (ArCH), 101.04 (ArC), 114.43 (ArC), 114.85 (ArC), 126.73 (2 × ArCH), 127.09 (ArCH), 127.37 (2 × ArCH), 127.49 (ArCH), 127.67 (2 × ArCH), 127.90 (2 × ArCH), 128.15 (2 × ArCH), 128.29 (2 × ArCH), 128.96 (2 × ArCH), 129.95 (ArC), 131.31 (2 × ArCH), 133.11 (ArC), 133.42 (ArC), 135.16 (ArC), 136.52 (ArC), 136.63 (ArC), 136.89 (ArC), 137.45 (ArC), 152.52 (ArC), 153.44 (ArC); HRMS *m/z:* Calcd. for $C_{72}H_{60}N_2O_4$ $[M + 1]^+$ 1017.4553. Found 1017.4627.

5-((Benzyloxy)carbonyl)amino)-1,3-phenylene diacetate (499)

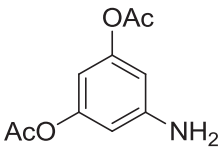


The diacetoxy resorcinol **499** was prepared from benzyl (3,5-dihydroxyphenyl) carbamate **196** (200 mg, 0.77 mmol), pyridine (5.0 mL) and acetic anhydride (3.0 mL) according to **GP-5** to give the *title compound* as

white solid (239 mg, 90%). M.p. 90-91 °C (from Ethanol); UV (MeOH): λ_{max} 203 nm (ε 39,888 $cm^{-1}M^{-1}$), 245 (19,838); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 6H, 2 × $COCH_3$), 5.14 (s, 2H, O-$\underline{CH_2}$-ph), 6.57 (t, *J* = 3.0 Hz, 1H, ArH), 7.08 (s, 2H, ArH), 7.32-7.36 (m, 5H, ArH), 7.49 (s, 1H NH); IR (KBr): ν_{max} 3269, 3154, 3115, 3093, 3033, 1769, 1723, 1613, 1554, 1496, 1476, 1454, 1301, 1246, 1208, 1121, 1079, 1029, 999, 969, 911, 842, 769, 753, 672 cm^{-1}; ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 20.88 (2 × CO$\underline{CH_3}$), 66.93 (O-$\underline{CH_2}$-ph), 109.13 (ArCH), 109.85 (2 × ArCH), 128.12 (2 × ArCH), 128.24 (ArCH), 128.49 (2 × ArCH), 135.89 (ArC), 139.67 (ArC), 151.16 (2 × ArC), 153.06 (ArC), 169.12 (2 × $COCH_3$); HRMS *m/z:* Calcd. for $C_{18}H_{17}NO_6$ $[M + 1]^+$ 344.1056. Found 344.1130.

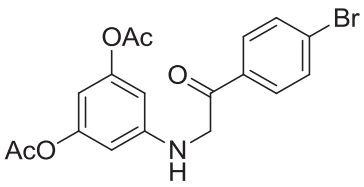
3,5-Diacetoxyaniline (500)

The 3,5-diacetoxyaniline **500** was prepared from 5-((benzyloxy) carbonyl)amino)-1,3-phenylene diacetate **499**



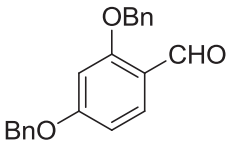
(200 mg, 0.58 mmol), 10% Pd/C catalyst (20 mg) in *N*,*N*-dimethylformamide (50 mL) according to **GP-8** to give the *title compound* as a white solid (87 mg, 71%). M.p. 128-129 °C; UV (MeOH): λ_{max} 206 nm (ε 19,019 $cm^{-1}M^{-1}$), 240 (9,572), 289 (2,110); IR (KBr): ν_{max} 3415, 3356, 3093, 3050, 1757, 1654, 1615, 1589, 1552, 1480, 1430, 1337, 1211, 1153, 1112, 1044, 979, 906, 855, 827, 732, 662, 587, 562, 587, 522 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 6H, 2 × $COCH_3$), 3.85 (bs, 2H, NH_2), 6.21-6.23 (m, 3H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 21.03 (2 × CO$\underline{CH_3}$), 104.61 (ArCH), 105.81 (2 × ArCH), 148.68 (ArC), 151.77 (2 × ArC), 169.24 (2 × $\underline{CO}CH_3$); HRMS *m/z:* Calcd. for $C_{10}H_{11}NO_4$ $[M + 1]^+$ 210.0688. Found 210.0760.

2-((3,5-Bis(benzyloxy)phenyl)amino)-1-(4′-bromophenyl)ethanone (501)



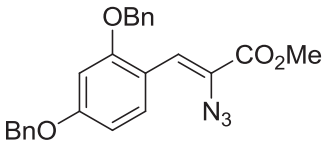
The diacetoxy anilinoketone **501** was prepared from 3,5-diacetoxyaniline **500** (100 mg, 0.47 mmol), 4-bromophenacylbromide (132 mg, 0.47 mmol) and sodium hydrogen carbonate (40 mg, 0.47 mmol) in Ethanol (100 mL) according to **GP-1** to give the *title compound* as a white solid (113 mg, 75%). M.p. 128-129 °C; UV (MeOH): λ_{max} 208 nm (ε 39,879 $cm^{-1}M^{-1}$), 255 (14,729); IR (KBr): ν_{max} 3374, 1757, 1700, 1686, 1624, 1608, 1522, 1476, 1419, 1369, 1295, 1212, 1120, 1186, 1175, 1071, 1029, 1009, 987, 892, 813 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 6H, 2 × $COCH_3$), 4.51 (d, *J* = 3.0 Hz, 2H, ArH), 5.11 (t, *J* = 3.0 Hz, 1H, NH), 6.28-6.31 (m, 3H, ArH), 7.65 (d, *J* = 6.0 Hz, 2H ArH), 7.86 (d, *J* = 6.0 Hz, 2H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 21.08 (2 x CO$\underline{CH_3}$), 49.86 (NH-CH_2), 103.58 (ArCH), 104.41 (2 × ArCH), 129.18 (2 × ArCH), 129.24 (ArC), 132.21 (2 × ArCH), 133.19 (ArC), 148.16 (ArC), 151.98 (2 × ArC), 169.00 (2 × $\underline{CO}CH_3$), 193.15 (C=O); HRMS *m/z:* Calcd. for $C_{18}H_{16}BrNO_5Na$ $[M + Na]^+$ 428.0212. Found 428.0104.

2,4-Dibenzyloxybenzaldehyde (38)



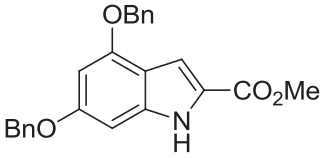
The aldehyde **38** was prepared from 2,4-dihydroxybenzaldehyde **414** (5.0 g, 0.03 mol), potassium carbonate (8.28 g, 0.06 mol) and benzyl bromide (7.3 mL, 0.06 mol) in *N*,*N*-dimethylformamide (100 mL) according to **GP-18** to give the *title compound* as a white solid (9.10 g, 78%). M.p. 86-87 °C, *lit*[203] 85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (s, 2H, O-CH_2), 5.13 (s, 2H, O-CH_2), 6.59 (d, *J* = 3.0 Hz, 1H, ArH), 6.63 (dd, *J* = 9.0 Hz, 2.0 Hz, 1H, ArH), 7.32-7.43 (m, 10H, ArH), 7.83 (d, *J* = 9.0 Hz, 1H), 10.38 (s, 1H, CHO).

***(Z)*-Methyl 2-azido-3-(2,4-bis(benzyloxy)phenyl)acrylate (39)**



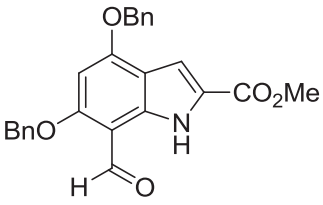
The azidocinnamate **39** was prepared from aldehyde **38** (5.0 g, 0.015 mol), methyl azidoacetate (17.3 mL, 0.15mol) in Methanol (25 mL) and sodium (3.45 g, 0.15 mol) in dry Methanol according to **GP-19** to give the *title compound* as a pale yellow soild (4.2 g, 64%). M.p. 93-94 °C, *lit*[189] 94-95 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H, $COOCH_3$), 5.05 (s, 2H, O-CH_2), 5.09 (s, 2H, O-CH_2), 6.54 (d, *J* = 3.0 Hz, 1H, ArH), 6.61 (d, *J* = 3.0 Hz, 1H, ArH), 7.30-7.45 (m, 11H, ArH), 8.24 (d, *J* = 9.0 Hz, 1H, CH=C).

Methyl 4,6-dibenzyloxy-indole-2-carboxylate (40)



The indole **40** was prepared from azidocinnamate **39** (4.0 g, 0.1 mol) in xylene (150 mL) according to **GP-20** to yield the *title compound* as a white solid (2.7 g, 72%). M.p. 175-176 °C, *lit*[189] 174 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (s, 3H, $COOCH_3$), 5.10 (s, 2H, O-CH_2), 5.19 (s, 2H, O-CH_2), 6.41 (d, *J* = 3.0 Hz, 1H, H5), 6.53 (d, *J* = 3.0 Hz, 1H, H7), 7.01-7.53 (m, 11H, ArH), 8.93 (s, 1H, NH).

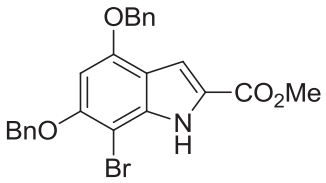
Methyl 4,6-dibenzyloxy-7-formyl-indole-2-carboxylate (503)



The formyl indole **503** was prepared from indole **40** (200 mg, 0.51 mmol) in anhydrous *N*,*N*-dimethylformamide (~5.0 mL) phosphoryl chloride (0.1 mL, 0.51 mmol) in anhydrous *N*,*N*-

dimethylformamide (~0.4 mL) according to **GP-24** to give the *title compound* as a yellow solid (159 mg, 74%). M.p. 166-167 °C; UV (CH_2Cl_2): λ_{max} 239 nm (ε 30.461 $cm^{-1}M^{-1}$), 326 (11,329); IR (KBr): ν_{max} 3422, 2949, 2850, 1696, 1640, 1597, 1525, 1512, 1453, 1412, 1383, 1254, 1186, 1167, 1129, 988, 960, 937, 919, 848, 796, 769, 756, 738, 714 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 3H, $COOCH_3$), 5.18 (s, 2H, O-CH_2), 5.23 (s, 2H, O-CH_2), 6.29 (s, 1H, H5), 7.31 (s, 1H, H3), 7.34-7.45 (m, 10H, ArH), 10.40 (s, 1H, CHO), 10.67 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 51.78 (COO$\underline{CH_3}$), 70.44 (O-CH_2), 71.39 (O-CH_2), 90.16 (ArCH), 105.11 (ArCH), 106.88 (ArC), 113.68 (ArC), 126.49 (ArC), 127.21 (2 × ArCH), 127.23 (2 × ArCH), 128.35 (2 × ArCH), 128.71 (2 × ArCH), 128.72 (2 × ArCH), 135.57 (ArC), 135.79 (ArC), 137.25 (ArC), 160.19 (ArC), 161.35 (ArC), 163.96 (ArC), 187.95 (CHO); HRMS *m/z:* Calcd. for $C_{25}H_{21}NO_5$ $[M + 1]^+$ 416.1420. Found 416.1492.

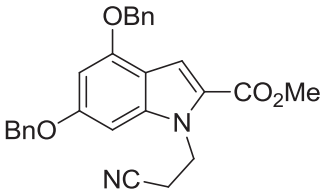
Methyl 4,6-dibenzyloxy-7-bromo-indole-2-carboxylate (504)



To a mixture of indole **40** (200 mg, 0.51 mmol) in carbon tetrachloride (10 mL), *N*-bromosuccinimide (90 mg, 0.51 mmol) was added slowly. The reaction mixture was was stirred at room temperature overnight. Ethyl acetate (15 mL) was added, and the resulting precipitate was filtered off. The organic phase washed with water (2 × 25 mL) and dried over sodium sulfate. The crude product was purified using column chromatography (SiO_2, 30% CH_2Cl_2/hexane) to give the *title compound* as a white solid (198 mg, 82%). M.p. 129-130 °C; UV (MeOH): λ_{max} 206 nm (ε 25,389 $cm^{-1}M^{-1}$), 245 (18,646), 305 (11,206); IR (KBr): ν_{max} 3324, 3162, 3088, 3025, 2952, 2860, 1772, 1708, 1628, 1573, 1517, 1454, 1438, 1377, 1348, 1268, 1193, 1091, 1027, 972, 934, 916, 901,

849, 790, 767, 736, 696, 645, 601 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H, $COOCH_3$), 5.14 (s, 2H, O-CH_2), 5.17 (s, 2H, O-CH_2), 6.68 (s, 1H, H5), 7.15 (s, 1H, H3), 7.17-7.43 (m, 10H, ArH), 10.29 (s, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 52.19 (COO$\underline{CH_3}$), 71.15 (O-CH_2), 72.80 (O-CH_2), 94.50 (ArCH), 108.19 (ArCH), 115.91 (ArC), 121.65 (ArC), 128.61 (4 × ArCH), 128.94 (ArCH), 129.01 (ArCH), 129.50 (2 × ArCH), 129.61 (2 × ArCH), 177.92 (ArC), 138.12 (ArC), 138.32 (ArC), 138.84 (ArC), 154.35 (ArC), 155.38 (ArC), 162.16 (ArC); HRMS *m/z:* Calcd. for $C_{24}H_{20}BrNO_4$ $[M + 1]^+$ 466.0576. Found 466.0635.

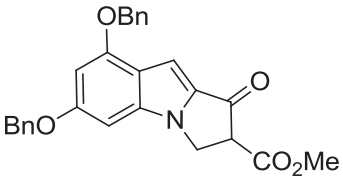
Methyl 4,6-dibenzyloxy-1-(2-cyanoethyl)-indole-2-carboxylate (505)



The cyanoethylindole **505** was prepared from indole (100 mg, 0.25 mmol), acrylonitrile (1.5 mL, 25 mmol) and tetrabutylammonium hydroxide (2 drops) according to **GP-11** to yield the *title compound* as a white solid (91 mg, 79%). M.p. 168-169 °C; UV (MeOH): λ_{max} 209 nm (ε 33,220 $cm^{-1}M^{-1}$), 244 (16,456), 308 (12,188); IR (KBr): ν_{max} 3047, 3010, 2993, 2935, 2842, 2361, 2250, 1617, 1583, 1570, 1553, 1503, 1465, 1433, 1418, 1379, 1291, 1272, 1259, 1175, 1124, 1062, 1046, 979, 941, 914, 811, 770, 745, 703, 632, 546 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.85 (t, *J* = 6.0 Hz, 2H, CH_2), 3.88 ($COOCH_3$), 4.74 (t, *J* = 6.0 Hz, 2H, CH_2), 5.12 (s, 2H, O-CH_2), 5.15 (s, 2H, O-CH_2), 6.39 (bs, 1H, H5), 6.51 (bs, 1H, H7), 7.34-7.39 (m, 11H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 18.67 (N-$CH_2\underline{CH_2}$CN), 40.65 (N-$\underline{CH_2}CH_2$CN), 51.54 (COO$\underline{CH_3}$), 69.91 (O-CH_2), 70.58 (O-CH_2), 85.96 (ArCH), 94.76 (ArCH), 110.26 (ArCH), 112.70 (ArC), 117.56 (ArC), 124.12 (ArC), 127.33 (2 × ArCH), 127.62 (2 × ArCH), 127.96 (2 × ArCH), 128.08 (2 × ArCH), 128.50 (2 × ArCH), 136.51 (ArC), 136.53 (ArC), 140.61

(ArC), 154.28 (ArC), 159.73 (ArC), 162.18 (C=O); HRMS *m/z:* Calcd. for $C_{27}H_{24}N_2O_4$ $[M + 1]^+$ 441.1736. Found 441.1710.

Methyl 6,8-bis(benzyloxy)-pyrrolo[1,2-*a*]indole-1-carboxylate (506)



Sodium hydride (60% dispersion in paraffin liquid) (120 mg, 10 mmol) was added slowly to an ice-cooled solution of indole **40** (200 mg, 0.5 mmol) in dry toluene (10 mL) followed by methyl acrylate (0.2 mL, 2 mmol). The reaction mixture was heated under reflux overnight. After cooling the reaction mixture to room temperature, was dropped on to the crushed ice (100 g), followed by the addition of water (50 mL). The resulting mixture was extracted in ethyl acetate, dried over sodium sulfate and concentrated under reduced pressure to yield a brown solid. The crude product was purified on column chromatography (SiO_2, 30% CH_2Cl_2/hexane) to give the *title compound* as a brown solid (139 mg, 61%). M.p. 154-155 °C; UV (MeOH): λ_{max} 210 nm (ε 32.810 $cm^{-1}M^{-1}$), 254 (17,066), 338 (11,466); IR (KBr): ν_{max} 3423, 3053, 2913, 1626, 1600, 1451, 1375, 1277, 1242, 1090, 1026, 821, 760, 697, 564 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 3H, $COOCH_3$), 4.21 (dd, *J* = 6.0 Hz, 9.0 Hz, 1H, CH), 4.50 (dd, *J* = 9.0 Hz, 12.0 Hz, 2H, CH_2), 4.74 (dd, *J* = 3.0 Hz, 12.0 Hz, 2H, CH_2), 5.11 (s, 2H, O-CH_2), 5.17 (s, 2H, O-CH_2), 6.37 (d, *J* = 3.0 Hz, 1H, ArH), 6.45 (s, 1H, ArH), 7.21 (s, 1H, ArH), 7.31-7.47 (m, 10H, ArH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 43.22 (N$\underline{CH_2}$CH), 53.27 ($COOCH_3$), 56.32 (CH), 69.89 (O-CH_2), 70.44 (O-CH_2), 85.51 (ArCH), 95.46 (ArCH), 100.04 (ArCH), 119.96 (ArC), 127.26 (2 × ArCH), 127.63 (2 × ArCH), 127.70 (ArCH), 128.14 (ArCH), 128.51 (2 × ArCH), 128.67 (2 × ArCH), 131.64 (ArC), 136.49 (ArC), 136.51

(ArC), 137.18 (ArC), 155.16 (ArC), 159.85 (ArC), 168.03 (<u>CO</u>OCH$_3$), 183.74 (C=O); HRMS *m/z:* Calcd. for $C_{27}H_{23}NO_4$ $[M + 1]^+$ 442.1576. Found 442.1653.

CHAPTER 9

Appendix: X-ray Crystallography data

9.1 Introduction

The X-ray crystallography data shown in the appendix were obtained by Mohan Bhadbade and Donald Craig and at the University of New South Wales, Sydney.

9.1.1 Structural determination

Reflection data were measured with an Enraf-Nonius CAD-4 diffractometer in $\theta/2\theta$ scan mode using nickel filtered copper radiation (λ 1.5418 Å). Reflections with $I>3\sigma(I)$ were considered observed. The structures were determined by direct phasing and Fourier methods. Hydrogens were included in calculated positions and were assigned thermal parameters equal to those of the atom to which they were bonded. Positional and anisotropic thermal parameters for the non-hydrogen atoms were refined using full matrix least squares. Reflection weights used were $1/\sigma^2(F_0)$, $\sigma(F_0)$ being derived from $\sigma(I_0) = [\sigma^2(I_0) + (0.04I_0)^2]^{1/2}$. The weighted residual is defined as $R_w = (\sum w\Delta^2/\sum wF_0^2)^{1/2}$. Atomic scattering factors and anomalous dispersion parameters were from International Tables of X-crystallography.[1] Structures solutions were performed SIR92[2] and refinements used RAELS.[3] ORTEP-II[4] running on a Macintosh was used for the structural diagrams.

1. Ibers, J. A. and Hamilton, W. C., (Eds) International Tables for X-ray crystallography Vol. 4, Kynoch Press, Birmingham, 1974.

2. Altomare, A., Burla, M. C., Camalli, M., Cascarano, G., Giacavazzo, C., Guagliardi, A., Polidori, G. *J. Appl. Cryst.* 1997, *27*,435.

3. Rae, A. D., RAELS. A comprehensive Constrained Least Squares Refinement Program. The University of New South Wales, 1989.

4. Johnson, C. K., ORTEP-II, Oak Ridge National Laboratory, Tennessee, U.S.A., 1976.

9.2 Crystallographic data for compound 176a

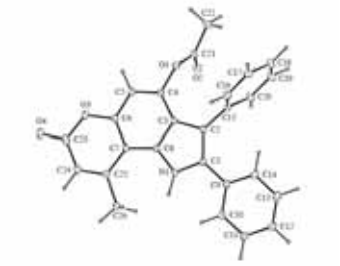


Table 9-1 Experimental details

	dnk92
Crystal data	
Chemical formula	$C_{26}H_{19}NO_4$
M_r	409.4
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	294
α, β, γ (Å)	8.245 (3), 10.136 (4), 13.205 (6)

□, □, □ (°)	106.13 (3), 98.68 (2), 104.79 (2)
V (Å^3)	995.3 (7)
Z	2
Radiation type	Mo K□
□ (mm^{-1})	0.09
Crystal size (mm)	0.30 × 0.25 × 0.05
Data collection	
Diffractometer	Nonius CAD-4 diffractometer
Absorption correction	–
No. of measured, independent and observed [I > 2□(I)] reflections	3650, 3484, 2349
R_{int}	0.012
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.046, 0.051, 1.33
No. of reflections	3484
No. of parameters	280
No. of restraints	-
H-atom treatment	H-atom parameters not refined
Δ⟩$_{max}$, Δ⟩$_{min}$ (e Å^{-3})	0.28, -0.31

Computer programs: CAD4 Version 5.0, (Schagen *et al.*, 1989), *SIR92* (Altomare *et al.*, 1994), RAELS, (Rae, 1996), *ORTEP*-II, (Johnson, 1976), Local programs.

Table 9- 2 Selected geometric parameters (Å, º)

O1—C4	1.403 (2)	C7—C25	1.444 (2)
O1—C21	1.367 (2)	C9—C10	1.393 (3)
O2—C21	1.198 (2)	C9—C14	1.386 (3)
O3—C6	1.382 (2)	C10—C11	1.384 (3)
O3—C23	1.377 (2)	C11—C12	1.374 (3)
O4—C23	1.208 (2)	C12—C13	1.366 (3)
N1—C1	1.390 (2)	C13—C14	1.392 (3)
N1—C8	1.377 (2)	C15—C16	1.385 (3)
C1—C2	1.382 (2)	C15—C20	1.379 (3)
C1—C9	1.473 (3)	C16—C17	1.383 (3)
C2—C3	1.438 (2)	C17—C18	1.376 (3)
C2—C15	1.489 (2)	C18—C19	1.371 (3)
C3—C4	1.407 (2)	C19—C20	1.380 (3)
C3—C8	1.407 (2)	C21—C22	1.478 (3)
C4—C5	1.362 (2)	C23—C24	1.439 (3)
C5—C6	1.394 (3)	C24—C25	1.356 (3)
C6—C7	1.395 (2)	C25—C26	1.501 (3)
C7—C8	1.414 (2)		
C4—O1—C21	117.7 (1)	C1—C9—C14	121.8 (2)

C6—O3—C23	122.0 (2)	C10—C9—C14	117.7 (2)
C1—N1—C8	110.0 (1)	C9—C10—C11	120.4 (2)
N1—C1—C2	108.8 (2)	C10—C11—C12	121.3 (2)
N1—C1—C9	118.7 (2)	C11—C12—C13	118.7 (2)
C2—C1—C9	132.3 (2)	C12—C13—C14	120.8 (2)
C1—C2—C3	106.1 (2)	C9—C14—C13	121.0 (2)
C1—C2—C15	129.1 (2)	C2—C15—C16	119.8 (2)
C3—C2—C15	124.8 (2)	C2—C15—C20	122.5 (2)
C2—C3—C4	134.2 (2)	C16—C15—C20	117.7 (2)
C2—C3—C8	108.5 (2)	C15—C16—C17	121.2 (2)
C4—C3—C8	117.3 (2)	C16—C17—C18	120.2 (2)
O1—C4—C3	119.4 (2)	C17—C18—C19	119.1 (2)
O1—C4—C5	119.0 (2)	C18—C19—C20	120.5 (2)
C3—C4—C5	121.5 (2)	C15—C20—C19	121.3 (2)
C4—C5—C6	118.9 (2)	O1—C21—O2	121.8 (2)
O3—C6—C5	114.5 (2)	O1—C21—C22	110.3 (2)
O3—C6—C7	121.2 (2)	O2—C21—C22	127.9 (2)
C5—C6—C7	124.2 (2)	O3—C23—O4	116.7 (2)
C6—C7—C8	114.4 (2)	O3—C23—C24	116.7 (2)
C6—C7—C25	118.3 (2)	O4—C23—C24	126.6 (2)
C8—C7—C25	127.4 (2)	C23—C24—C25	123.0 (2)
N1—C8—C3	106.5 (2)	C7—C25—C24	118.8 (2)
N1—C8—C7	129.8 (2)	C7—C25—C26	121.0 (2)
C3—C8—C7	123.6 (2)	C24—C25—C26	120.3 (2)

C1—C9—C10	120.4 (2)		
C21—O1—C4—C3	93.6 (2)	O1—C4—C5—C6	-174.7 (2)
C21—O1—C4—C5	-90.0 (2)	C3—C4—C5—C6	1.5 (3)
C4—O1—C21—O2	-4.2 (3)	C4—C5—C6—O3	177.3 (2)
C4—O1—C21—C22	176.4 (2)	C4—C5—C6—C7	-2.7 (3)
C23—O3—C6—C5	179.2 (2)	O3—C6—C7—C8	-178.6 (2)
C23—O3—C6—C7	-0.7 (3)	O3—C6—C7—C25	1.1 (3)
C6—O3—C23—O4	178.8 (2)	C5—C6—C7—C8	1.4 (3)
C6—O3—C23—C24	-0.5 (3)	C5—C6—C7—C25	-178.9 (2)
C8—N1—C1—C2	-0.4 (2)	C6—C7—C8—N1	-178.2 (2)
C8—N1—C1—C9	-177.1 (2)	C6—C7—C8—C3	1.0 (3)
C1—N1—C8—C3	1.1 (2)	C25—C7—C8—N1	2.2 (3)
C1—N1—C8—C7	-179.6 (2)	C25—C7—C8—C3	-178.7 (2)
N1—C1—C2—C3	-0.5 (2)	C6—C7—C25—C24	-0.1 (3)
N1—C1—C2—C15	176.4 (2)	C6—C7—C25—C26	-179.9 (2)
C9—C1—C2—C3	175.6 (2)	C8—C7—C25—C24	179.5 (2)
C9—C1—C2—C15	-7.5 (3)	C8—C7—C25—C26	-0.2 (3)
N1—C1—C9—C10	6.1 (3)	C1—C9—C10—C11	177.5 (2)
N1—C1—C9—C14	-176.6 (2)	C14—C9—C10—C11	0.0 (3)
C2—C1—C9—C10	-169.7 (2)	C1—C9—C14—C13	-177.2 (2)
C2—C1—C9—C14	7.6 (3)	C10—C9—C14—C13	0.2 (3)
C1—C2—C3—C4	-177.2 (2)	C9—C10—C11—C12	-0.4 (4)
C1—C2—C3—C8	1.2 (2)	C10—C11—C12—C13	0.5 (4)

C15—C2—C3—C4	5.7 (3)	C11—C12—C13—C14	-0.2 (4)
C15—C2—C3—C8	-175.8 (2)	C12—C13—C14—C9	-0.1 (4)
C1—C2—C15—C16	-89.9 (3)	C2—C15—C16—C17	-176.4 (2)
C1—C2—C15—C20	92.3 (3)	C20—C15—C16—C17	1.5 (3)
C3—C2—C15—C16	86.4 (2)	C2—C15—C20—C19	177.1 (2)
C3—C2—C15—C20	-91.4 (2)	C16—C15—C20—C19	-0.8 (3)
C2—C3—C4—O1	-4.7 (3)	C15—C16—C17—C18	-1.2 (3)
C2—C3—C4—C5	179.0 (2)	C16—C17—C18—C19	0.1 (4)
C8—C3—C4—O1	176.9 (2)	C17—C18—C19—C20	0.6 (4)
C8—C3—C4—C5	0.7 (3)	C18—C19—C20—C15	-0.3 (4)
C2—C3—C8—N1	-1.4 (2)	O3—C23—C24—C25	1.5 (3)
C2—C3—C8—C7	179.2 (2)	O4—C23—C24—C25	-177.7 (2)
C4—C3—C8—N1	177.3 (2)	C23—C24—C25—C7	-1.2 (3)
C4—C3—C8—C7	-2.0 (3)	C23—C24—C25—C26	178.6 (2)

9.3 Crystallographic data for compound 314a

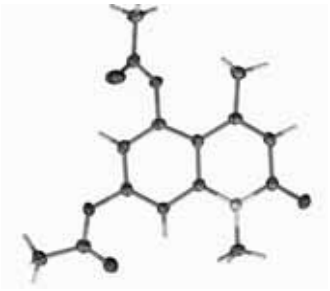


Table 9-3 Experimental details

	taj1p21byn
Crystal data	
Chemical formula	$C_{15}H_{15}NO_5$
M_r	289.28
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	150
α, β, γ (Å)	3.9632 (9), 20.527 (4), 16.279 (4)
□ (°)	95.719 (8)
V (Å^3)	1317.7 (5)

Z	4
Radiation type	Mo *K*□
□ (mm^{-1})	0.11
Crystal size (mm)	0.21 × 0.05 × 0.02
Data collection	
Diffractometer	Bruker kappa APEXII CCD Diffractometer
Absorption correction	Multi-scan *SADABS* (Bruker, 2001)
T_{min}, T_{max}	0.977, 0.998
No. of measured, independent and observed [$I > 2\square(I)$] reflections	17496, 2320, 1547
R_{int}	0.094
Refinement	
$R[F^2 > 2\square(F^2)]$, $wR(F^2)$, *S*	0.045, 0.106, 1.02

No. of reflections	2320
No. of parameters	195
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.27, -0.20

Computer programs: *APEX2* (Bruker, 2007), *SHELXS-97* (Sheldrick, 2008), *SHELXL-97* (Sheldrick, 2008), *SHELXTL-Plus* (Sheldrick, 2008).

Table 9-4 Selected geometric parameters (Å, º)

O1—C1	1.235 (3)	C6—H6	0.9500
O2—C12	1.369 (3)	C7—C8	1.369 (3)
O2—C5	1.401 (3)	C8—C9	1.401 (3)
O3—C12	1.200 (3)	C8—H8	0.9500
O4—C14	1.370 (3)	C10—H10A	0.9800
O4—C7	1.406 (3)	C10—H10B	0.9800
O5—C14	1.192 (3)	C10—H10C	0.9800
N1—C1	1.385 (3)	C11—H11A	0.9800
N1—C9	1.391 (3)	C11—H11B	0.9800

N1—C10	1.469 (3)	C11—H11C	0.9800
C1—C2	1.440 (3)	C12—C13	1.485 (3)
C2—C3	1.343 (3)	C13—H13A	0.9800
C2—H2	0.9500	C13—H13B	0.9800
C3—C4	1.452 (3)	C13—H13C	0.9800
C3—C11	1.510 (3)	C14—C15	1.489 (3)
C4—C5	1.406 (3)	C15—H15A	0.9800
C4—C9	1.424 (3)	C15—H15B	0.9800
C5—C6	1.365 (3)	C15—H15C	0.9800
C6—C7	1.384 (3)		
C12—O2—C5	117.91 (18)	C8—C9—C4	120.8 (2)
C14—O4—C7	122.64 (18)	N1—C10—H10A	109.5
C1—N1—C9	122.22 (19)	N1—C10—H10B	109.5
C1—N1—C10	117.97 (18)	H10A—C10—H10B	109.5
C9—N1—C10	119.80 (18)	N1—C10—H10C	109.5
O1—C1—N1	120.9 (2)	H10A—C10—H10C	109.5
O1—C1—C2	122.8 (2)	H10B—C10—H10C	109.5
N1—C1—C2	116.3 (2)	C3—C11—H11A	109.5
C3—C2—C1	124.6 (2)	C3—C11—H11B	109.5
C3—C2—H2	117.7	H11A—C11—H11B	109.5
C1—C2—H2	117.7	C3—C11—H11C	109.5
C2—C3—C4	118.1 (2)	H11A—C11—H11C	109.5
C2—C3—C11	117.8 (2)	H11B—C11—H11C	109.5

C4—C3—C11	124.1 (2)	O3—C12—O2	122.5 (2)
C5—C4—C9	116.0 (2)	O3—C12—C13	126.8 (2)
C5—C4—C3	125.5 (2)	O2—C12—C13	110.8 (2)
C9—C4—C3	118.5 (2)	C12—C13—H13A	109.5
C6—C5—O2	118.4 (2)	C12—C13—H13B	109.5
C6—C5—C4	123.6 (2)	H13A—C13—H13B	109.5
O2—C5—C4	117.94 (19)	C12—C13—H13C	109.5
C5—C6—C7	118.3 (2)	H13A—C13—H13C	109.5
C5—C6—H6	120.9	H13B—C13—H13C	109.5
C7—C6—H6	120.9	O5—C14—O4	124.1 (2)
C8—C7—C6	122.1 (2)	O5—C14—C15	126.6 (2)
C8—C7—O4	123.6 (2)	O4—C14—C15	109.3 (2)
C6—C7—O4	114.0 (2)	C14—C15—H15A	109.5
C7—C8—C9	119.2 (2)	C14—C15—H15B	109.5
C7—C8—H8	120.4	H15A—C15—H15B	109.5
C9—C8—H8	120.4	C14—C15—H15C	109.5
N1—C9—C8	118.95 (19)	H15A—C15—H15C	109.5
N1—C9—C4	120.22 (19)	H15B—C15—H15C	109.5
C9—N1—C1—O1	-177.6 (2)	C5—C6—C7—C8	1.0 (4)
C10—N1—C1—O1	3.3 (3)	C5—C6—C7—O4	-174.1 (2)
C9—N1—C1—C2	3.1 (3)	C14—O4—C7—C8	43.2 (3)
C10—N1—C1—C2	-176.0 (2)	C14—O4—C7—C6	-141.7 (2)
O1—C1—C2—C3	179.2 (2)	C6—C7—C8—C9	0.3 (4)

N1—C1—C2—C3	-1.5 (3)	O4—C7—C8—C9	175.0 (2)
C1—C2—C3—C4	-0.8 (3)	C1—N1—C9—C8	176.3 (2)
C1—C2—C3—C11	179.5 (2)	C10—N1—C9—C8	-4.7 (3)
C2—C3—C4—C5	-178.2 (2)	C1—N1—C9—C4	-2.5 (3)
C11—C3—C4—C5	1.5 (4)	C10—N1—C9—C4	176.6 (2)
C2—C3—C4—C9	1.5 (3)	C7—C8—C9—N1	179.9 (2)
C11—C3—C4—C9	-178.8 (2)	C7—C8—C9—C4	-1.3 (3)
C12—O2—C5—C6	-65.8 (3)	C5—C4—C9—N1	179.7 (2)
C12—O2—C5—C4	117.2 (2)	C3—C4—C9—N1	0.1 (3)
C9—C4—C5—C6	0.3 (3)	C5—C4—C9—C8	1.0 (3)
C3—C4—C5—C6	180.0 (2)	C3—C4—C9—C8	-178.7 (2)
C9—C4—C5—O2	177.11 (19)	C5—O2—C12—O3	1.4 (3)
C3—C4—C5—O2	-3.2 (3)	C5—O2—C12—C13	-177.3 (2)
O2—C5—C6—C7	-178.1 (2)	C7—O4—C14—O5	-3.7 (4)
C4—C5—C6—C7	-1.4 (4)	C7—O4—C14—C15	175.5 (2)

9.4 Crystallographic data for compound obtained from the reaction of 337 and 364

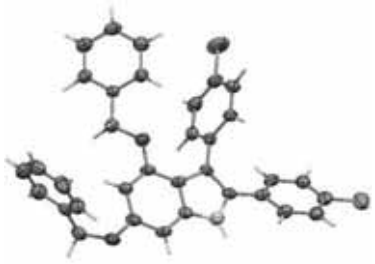


Table 9-5 Experimental details

	taj3p21byn
Crystal data	
Chemical formula	$C_{34}H_{25}ClNO_2$
M_r	515.00
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	150
α, β, γ (Å)	21.152 (2), 5.8456 (6), 21.774 (2)
□ (°)	105.126 (6)
V (Å^3)	2598.9 (5)
Z	4
Radiation type	Mo K□
□ (mm^{-1})	0.18
Crystal size (mm)	0.28 × 0.08 × 0.02
Data collection	
Diffractometer	Bruker kappa APEXII CCD Diffractometer
Absorption correction	Multi-scan *SADABS* (Bruker, 2001)
T_{min}, T_{max}	0.951, 0.996
No. of measured, independent and observed [$I > 2$□(I)] reflections	16764, 4487, 1722
R_{int}	0.141
Refinement	

$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.062, 0.162, 0.95
No. of reflections	4487
No. of parameters	353
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.26, -0.21

Table 9-6 Selected geometric parameters (Å, º)

C1—C2	1.367 (5)	C19—C20	1.393 (5)
C1—N1	1.377 (5)	C19—H19	0.9500
C1—C9	1.457 (6)	C20—H20	0.9500
C2—C3	1.440 (5)	C21—O1	1.435 (5)
C2—C15	1.486 (5)	C21—C22	1.512 (5)
C3—C4	1.401 (5)	C21—H21A	0.9900
C3—C8	1.409 (5)	C21—H21B	0.9900
C4—O1	1.364 (4)	C22—C27	1.372 (6)
C4—C5	1.375 (5)	C22—C23	1.380 (5)
C5—C6	1.411 (5)	C23—C24	1.388 (6)
C5—H5	0.9500	C23—H23	0.9500
C6—C7	1.376 (5)	C24—C25	1.379 (6)
C6—O2	1.385 (4)	C24—H24	0.9500
C7—C8	1.384 (5)	C25—C26	1.376 (6)

C7—H7	0.9500	C25—H25	0.9500
C8—N1	1.369 (5)	C26—C27	1.387 (6)
C9—C10	1.378 (5)	C26—H26	0.9500
C9—C14	1.410 (5)	C27—H27	0.9500
C10—C11	1.391 (6)	C28—O2	1.438 (5)
C10—H10	0.9500	C28—C29	1.499 (6)
C11—C12	1.382 (5)	C28—H28A	0.9900
C11—H11	0.9500	C28—H28B	0.9900
C12—C13	1.365 (6)	C29—C34	1.371 (6)
C12—Cl1A	1.647 (5)	C29—C30	1.384 (6)
C13—C14	1.381 (5)	C30—C31	1.394 (6)
C13—H13	0.9500	C30—H30	0.9500
C14—H14	0.9500	C31—C32	1.370 (6)
C15—C20	1.383 (5)	C31—H31	0.9500
C15—C16	1.387 (5)	C32—C33	1.355 (7)
C16—C17	1.385 (5)	C32—H32	0.9500
C16—H16	0.9500	C33—C34	1.393 (6)
C17—C18	1.368 (6)	C33—H33	0.9500
C17—H17	0.9500	C34—H34	0.9500
C18—C19	1.384 (6)	N1—H1	0.8800
C18—Cl1B	1.707 (5)		
C2—C1—N1	109.0 (4)	C15—C20—C19	120.7 (4)
C2—C1—C9	131.5 (4)	C15—C20—H20	119.7

N1—C1—C9	119.5 (4)	C19—C20—H20	119.7
C1—C2—C3	107.0 (4)	O1—C21—C22	107.8 (3)
C1—C2—C15	127.1 (4)	O1—C21—H21A	110.1
C3—C2—C15	125.9 (4)	C22—C21—H21A	110.1
C4—C3—C8	117.7 (4)	O1—C21—H21B	110.1
C4—C3—C2	135.4 (4)	C22—C21—H21B	110.1
C8—C3—C2	106.9 (4)	H21A—C21—H21B	108.5
O1—C4—C5	124.1 (4)	C27—C22—C23	119.9 (4)
O1—C4—C3	115.6 (4)	C27—C22—C21	118.6 (4)
C5—C4—C3	120.3 (4)	C23—C22—C21	121.5 (4)
C4—C5—C6	119.8 (4)	C22—C23—C24	119.6 (5)
C4—C5—H5	120.1	C22—C23—H23	120.2
C6—C5—H5	120.1	C24—C23—H23	120.2
C7—C6—O2	115.8 (4)	C25—C24—C23	120.4 (5)
C7—C6—C5	121.9 (4)	C25—C24—H24	119.8
O2—C6—C5	122.3 (4)	C23—C24—H24	119.8
C6—C7—C8	117.0 (4)	C26—C25—C24	119.9 (4)
C6—C7—H7	121.5	C26—C25—H25	120.0
C8—C7—H7	121.5	C24—C25—H25	120.0
N1—C8—C7	129.5 (4)	C25—C26—C27	119.6 (5)
N1—C8—C3	107.2 (4)	C25—C26—H26	120.2
C7—C8—C3	123.3 (4)	C27—C26—H26	120.2
C10—C9—C14	117.1 (4)	C22—C27—C26	120.6 (5)
C10—C9—C1	121.4 (4)	C22—C27—H27	119.7

C14—C9—C1	121.6 (4)	C26—C27—H27	119.7
C9—C10—C11	122.1 (4)	O2—C28—C29	113.9 (4)
C9—C10—H10	119.0	O2—C28—H28A	108.8
C11—C10—H10	119.0	C29—C28—H28A	108.8
C12—C11—C10	119.4 (5)	O2—C28—H28B	108.8
C12—C11—H11	120.3	C29—C28—H28B	108.8
C10—C11—H11	120.3	H28A—C28—H28B	107.7
C13—C12—C11	119.9 (5)	C34—C29—C30	118.5 (5)
C13—C12—Cl1A	118.7 (4)	C34—C29—C28	121.5 (5)
C11—C12—Cl1A	121.4 (4)	C30—C29—C28	120.0 (5)
C12—C13—C14	120.8 (4)	C29—C30—C31	120.5 (5)
C12—C13—H13	119.6	C29—C30—H30	119.7
C14—C13—H13	119.6	C31—C30—H30	119.7
C13—C14—C9	120.8 (4)	C32—C31—C30	119.8 (5)
C13—C14—H14	119.6	C32—C31—H31	120.1
C9—C14—H14	119.6	C30—C31—H31	120.1
C20—C15—C16	118.5 (4)	C33—C32—C31	120.2 (6)
C20—C15—C2	120.2 (4)	C33—C32—H32	119.9
C16—C15—C2	121.3 (4)	C31—C32—H32	119.9
C17—C16—C15	121.0 (4)	C32—C33—C34	120.2 (5)
C17—C16—H16	119.5	C32—C33—H33	119.9
C15—C16—H16	119.5	C34—C33—H33	119.9
C18—C17—C16	120.0 (5)	C29—C34—C33	120.8 (5)
C18—C17—H17	120.0	C29—C34—H34	119.6

C16—C17—H17	120.0	C33—C34—H34	119.6
C17—C18—C19	120.1 (4)	C8—N1—C1	110.0 (4)
C17—C18—Cl1B	120.6 (4)	C8—N1—H1	125.0
C19—C18—Cl1B	119.3 (4)	C1—N1—H1	125.0
C18—C19—C20	119.6 (5)	C4—O1—C21	118.6 (3)
C18—C19—H19	120.2	C6—O2—C28	117.2 (3)
C20—C19—H19	120.2		
N1—C1—C2—C3	-0.2 (5)	C3—C2—C15—C16	116.5 (5)
C9—C1—C2—C3	179.3 (4)	C20—C15—C16—C17	1.8 (6)
N1—C1—C2—C15	-178.0 (4)	C2—C15—C16—C17	-178.6 (4)
C9—C1—C2—C15	1.5 (8)	C15—C16—C17—C18	-2.1 (7)
C1—C2—C3—C4	-179.8 (5)	C16—C17—C18—C19	0.7 (7)
C15—C2—C3—C4	-2.0 (8)	C16—C17—C18—Cl1B	-179.5 (3)
C1—C2—C3—C8	-1.3 (5)	C17—C18—C19—C20	1.1 (7)
C15—C2—C3—C8	176.6 (4)	Cl1B—C18—C19—C20	-178.7 (3)
C8—C3—C4—O1	178.2 (4)	C16—C15—C20—C19	0.1 (6)
C2—C3—C4—O1	-3.4 (7)	C2—C15—C20—C19	-179.6 (4)
C8—C3—C4—C5	-1.0 (6)	C18—C19—C20—C15	-1.5 (6)
C2—C3—C4—C5	177.4 (5)	O1—C21—C22—C27	159.9 (4)
O1—C4—C5—C6	-179.5 (4)	O1—C21—C22—C23	-20.9 (6)
C3—C4—C5—C6	-0.3 (6)	C27—C22—C23—C24	-0.7 (7)
C4—C5—C6—C7	1.9 (7)	C21—C22—C23—C24	-179.8 (4)
C4—C5—C6—O2	179.1 (4)	C22—C23—C24—C25	1.1 (7)

O2—C6—C7—C8	-179.3 (4)	C23—C24—C25—C26	-0.8 (7)
C5—C6—C7—C8	-1.9 (6)	C24—C25—C26—C27	0.0 (7)
C6—C7—C8—N1	-179.7 (4)	C23—C22—C27—C26	0.0 (7)
C6—C7—C8—C3	0.5 (6)	C21—C22—C27—C26	179.1 (4)
C4—C3—C8—N1	-178.9 (4)	C25—C26—C27—C22	0.4 (7)
C2—C3—C8—N1	2.3 (5)	O2—C28—C29—C34	-28.9 (6)
C4—C3—C8—C7	0.9 (6)	O2—C28—C29—C30	153.4 (4)
C2—C3—C8—C7	-177.9 (4)	C34—C29—C30—C31	-1.7 (7)
C2—C1—C9—C10	149.3 (5)	C28—C29—C30—C31	176.2 (4)
N1—C1—C9—C10	-31.3 (6)	C29—C30—C31—C32	1.2 (7)
C2—C1—C9—C14	-32.4 (7)	C30—C31—C32—C33	-0.5 (8)
N1—C1—C9—C14	147.0 (4)	C31—C32—C33—C34	0.2 (8)
C14—C9—C10—C11	1.5 (6)	C30—C29—C34—C33	1.4 (7)
C1—C9—C10—C11	179.9 (4)	C28—C29—C34—C33	-176.4 (4)
C9—C10—C11—C12	-0.7 (7)	C32—C33—C34—C29	-0.8 (7)
C10—C11—C12—C13	-0.1 (6)	C7—C8—N1—C1	177.7 (4)
C10—C11—C12—Cl1A	-177.4 (4)	C3—C8—N1—C1	-2.5 (5)
C11—C12—C13—C14	0.0 (7)	C2—C1—N1—C8	1.7 (5)
Cl1A—C12—C13—C14	177.3 (3)	C9—C1—N1—C8	-177.9 (4)
C12—C13—C14—C9	0.9 (7)	C5—C4—O1—C21	1.9 (6)
C10—C9—C14—C13	-1.6 (6)	C3—C4—O1—C21	-177.3 (4)

C1—C9—C14—C13	-180.0 (4)	C22—C21—O1—C4	176.3 (4)
C1—C2—C15—C20	113.5 (5)	C7—C6—O2—C28	-158.5 (4)
C3—C2—C15—C20	-63.9 (6)	C5—C6—O2—C28	24.1 (6)
C1—C2—C15—C16	-66.1 (6)	C29—C28—O2—C6	-89.1 (4)

9.5 Crystallographic data for compound 474

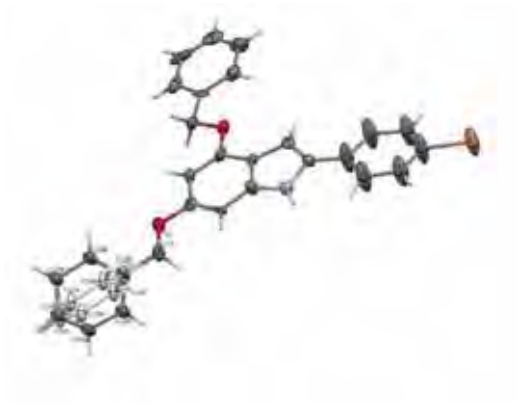


Table 9-7 Experimental details

	taj2pna21
Crystal data	
Chemical formula	$C_{28}H_{22}BrNO_2$
M_r	484.38
Crystal system, space	Orthorhombic, $Pna2_1$

group	
Temperature (K)	150
α, β, γ (Å)	17.604 (2), 4.9807 (6), 25.159 (2)
V (Å^3)	2205.9 (4)
Z	4
Radiation type	Mo $K\square$
$\square$ (mm^{-1})	1.89
Crystal size (mm)	0.22 × 0.09 × 0.04
Data collection	
Diffractometer	Bruker kappa APEXII CCD Diffractometer
Absorption correction	Multi-scan *SADABS* (Bruker, 2001)
T_{min}, T_{max}	0.686, 0.930
No. of measured, independent and observed [$I > 2\square(I)$] reflections	8032, 3337, 1627
R_{int}	0.087

Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.066, 0.159, 1.09
No. of reflections	3337
No. of parameters	332
No. of restraints	145
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.51, -0.49
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Flack parameter	0.00

Table 9-8 Selected geometric parameters (Å, º)

C23A—C24A	1.3900	C2—H2	0.9500
C23A—C28A	1.3900	C3—C4	1.389 (11)
C23A—C22	1.500 (12)	C3—C8	1.391 (11)
C24A—C25A	1.3900	C4—C5	1.366 (12)

C24A—H24A	0.9500	C5—C6	1.422 (12)
C25A—C26A	1.3900	C5—H5	0.9500
C25A—H25A	0.9500	C6—C7	1.350 (13)
C26A—C27A	1.3900	C7—C8	1.393 (12)
C26A—H26A	0.9500	C7—H7	0.9500
C27A—C28A	1.3900	C9—C10	1.277 (15)
C27A—H27A	0.9500	C9—C14	1.362 (15)
C28A—H28A	0.9500	C10—C11	1.413 (15)
C23B—C28B	1.33 (4)	C10—H10	0.9500
C23B—C24B	1.35 (3)	C11—C12	1.277 (15)
C23B—C22	1.52 (2)	C11—H11	0.9500
C24B—C25B	1.42 (3)	C12—C13	1.220 (15)
C24B—H24B	0.9500	C13—C14	1.412 (15)
C25B—C26B	1.22 (3)	C13—H13	0.9500
C25B—H25B	0.9500	C14—H14	0.9500
C26B—C27B	1.35 (3)	C15—C16	1.495 (12)

C26B—H26B	0.9500	C15—H15A	0.9900
C27B—C28B	1.44 (3)	C15—H15B	0.9900
C27B—H27B	0.9500	C16—C17	1.383 (12)
C28B—H28B	0.9500	C16—C21	1.386 (13)
Br1—C12	1.913 (11)	C17—C18	1.405 (13)
O1—C4	1.399 (10)	C17—H17	0.9500
O1—C15	1.430 (9)	C18—C19	1.374 (14)
O2—C6	1.372 (11)	C18—H18	0.9500
O2—C22	1.433 (11)	C19—C20	1.321 (14)
N1—C8	1.379 (11)	C19—H19	0.9500
N1—C1	1.432 (11)	C20—C21	1.376 (14)
N1—H1	0.8800	C20—H20	0.9500
C1—C2	1.358 (12)	C21—H21	0.9500
C1—C9	1.453 (14)	C22—H22A	0.9900
C2—C3	1.451 (10)	C22—H22B	0.9900
C24A—C23A—C28A	120.0	C6—C7—C8	116.7 (9)

C24A—C23A—C22	121.1 (9)	C6—C7—H7	121.6
C28A—C23A—C22	118.9 (9)	C8—C7—H7	121.6
C23A—C24A—C25A	120.0	N1—C8—C3	106.8 (7)
C23A—C24A—H24A	120.0	N1—C8—C7	129.6 (9)
C25A—C24A—H24A	120.0	C3—C8—C7	123.6 (8)
C26A—C25A—C24A	120.0	C10—C9—C14	112.6 (11)
C26A—C25A—H25A	120.0	C10—C9—C1	126.6 (12)
C24A—C25A—H25A	120.0	C14—C9—C1	120.8 (12)
C25A—C26A—C27A	120.0	C9—C10—C11	123.9 (13)
C25A—C26A—H26A	120.0	C9—C10—H10	118.0
C27A—C26A—H26A	120.0	C11—C10—H10	118.0
C28A—C27A—C26A	120.0	C12—C11—C10	120.8 (13)
C28A—C27A—H27A	120.0	C12—C11—H11	119.6
C26A—C27A—H27A	120.0	C10—C11—H11	119.6
C27A—C28A—C23A	120.0	C13—C12—C11	118.5 (12)
C27A—C28A—H28A	120.0	C13—C12—Br1	119.5 (10)

C23A—C28A—H28A	120.0	C11—C12—Br1	122.0 (11)
C28B—C23B—C24B	116 (2)	C12—C13—C14	122.6 (12)
C28B—C23B—C22	123 (2)	C12—C13—H13	118.7
C24B—C23B—C22	120 (3)	C14—C13—H13	118.7
C23B—C24B—C25B	118 (2)	C9—C14—C13	121.4 (12)
C23B—C24B—H24B	120.8	C9—C14—H14	119.3
C25B—C24B—H24B	120.8	C13—C14—H14	119.3
C26B—C25B—C24B	127 (2)	O1—C15—C16	109.3 (7)
C26B—C25B—H25B	116.5	O1—C15—H15A	109.8
C24B—C25B—H25B	116.5	C16—C15—H15A	109.8
C25B—C26B—C27B	117 (2)	O1—C15—H15B	109.8
C25B—C26B—H26B	121.4	C16—C15—H15B	109.8
C27B—C26B—H26B	121.4	H15A—C15—H15B	108.3
C26B—C27B—C28B	119 (2)	C17—C16—C21	118.0 (10)
C26B—C27B—H27B	120.7	C17—C16—C15	121.7 (9)
C28B—C27B—H27B	120.7	C21—C16—C15	120.2 (9)

C23B—C28B—C27B	123 (2)	C16—C17—C18	119.7 (10)
C23B—C28B—H28B	118.7	C16—C17—H17	120.1
C27B—C28B—H28B	118.7	C18—C17—H17	120.1
C4—O1—C15	116.4 (7)	C19—C18—C17	119.3 (11)
C6—O2—C22	114.9 (7)	C19—C18—H18	120.3
C8—N1—C1	109.4 (7)	C17—C18—H18	120.3
C8—N1—H1	125.3	C20—C19—C18	121.2 (12)
C1—N1—H1	125.3	C20—C19—H19	119.4
C2—C1—N1	108.2 (8)	C18—C19—H19	119.4
C2—C1—C9	132.3 (10)	C19—C20—C21	120.4 (13)
N1—C1—C9	119.4 (9)	C19—C20—H20	119.8
C1—C2—C3	106.7 (9)	C21—C20—H20	119.8
C1—C2—H2	126.6	C20—C21—C16	121.3 (11)
C3—C2—H2	126.6	C20—C21—H21	119.4
C4—C3—C8	117.7 (8)	C16—C21—H21	119.4
C4—C3—C2	133.2 (9)	O2—C22—C23A	110.6 (10)

C8—C3—C2	108.9 (8)	O2—C22—C23B	106.1 (17)
C5—C4—C3	120.5 (9)	C23A—C22—C23B	4.5 (19)
C5—C4—O1	125.0 (9)	O2—C22—H22A	109.5
C3—C4—O1	114.5 (8)	C23A—C22—H22A	109.5
C4—C5—C6	119.5 (9)	C23B—C22—H22A	112.2
C4—C5—H5	120.3	O2—C22—H22B	109.5
C6—C5—H5	120.3	C23A—C22—H22B	109.5
C7—C6—O2	124.5 (9)	C23B—C22—H22B	111.4
C7—C6—C5	122.0 (9)	H22A—C22—H22B	108.1
O2—C6—C5	113.5 (9)		

C28A—C23A—C24A—C25A	0.0	C4—C3—C8—C7	-2.0 (14)
C22—C23A—C24A—C25A	179.2 (18)	C2—C3—C8—C7	-178.6 (9)
C23A—C24A—C25A—C26A	0.0	C6—C7—C8—N1	-177.1 (9)

C24A—C25A—C26A—C27A	0.0	C6—C7—C8—C3	1.1 (14)
C25A—C26A—C27A—C28A	0.0	C2—C1—C9—C10	-178.2 (15)
C26A—C27A—C28A—C23A	0.0	N1—C1—C9—C10	-4 (2)
C24A—C23A—C28A—C27A	0.0	C2—C1—C9—C14	-1 (2)
C22—C23A—C28A—C27A	-179.2 (17)	N1—C1—C9—C14	173.5 (12)
C28B—C23B—C24B—C25B	-3 (5)	C14—C9—C10—C11	5 (3)
C22—C23B—C24B—C25B	169 (2)	C1—C9—C10—C11	-176.9 (15)
C23B—C24B—C25B—C26B	3 (5)	C9—C10—C11—C12	-6 (3)
C24B—C25B—C26B—C27B	0 (5)	C10—C11—C12—C13	2 (3)
C25B—C26B—C27B—C28B	-2 (5)	C10—C11—C12—Br1	-178.1 (13)

C24B—C23B—C28B—C27B	2 (5)	C11—C12—C13—C14	1 (3)
C22—C23B—C28B—C27B	-171 (3)	Br1—C12—C13—C14	-178.8 (12)
C26B—C27B—C28B—C23B	1 (5)	C10—C9—C14—C13	-2 (2)
C8—N1—C1—C2	-0.8 (10)	C1—C9—C14—C13	180.0 (13)
C8—N1—C1—C9	-176.3 (10)	C12—C13—C14—C9	-1 (3)
N1—C1—C2—C3	0.7 (11)	C4—O1—C15—C16	-178.0 (7)
C9—C1—C2—C3	175.4 (12)	O1—C15—C16—C17	-5.3 (12)
C1—C2—C3—C4	-176.3 (10)	O1—C15—C16—C21	178.1 (8)
C1—C2—C3—C8	-0.5 (11)	C21—C16—C17—C18	-1.2 (14)
C8—C3—C4—C5	2.3 (14)	C15—C16—C17—C18	-177.8 (9)
C2—C3—C4—C5	177.9 (10)	C16—C17—C18—C19	0.7 (15)
C8—C3—C4—O1	-177.3 (8)	C17—C18—C19—C20	0.7 (17)
C2—C3—C4—O1	-1.7 (16)	C18—C19—C20—C21	-1.6 (18)
C15—O1—C4—C5	-3.0 (13)	C19—C20—C21—C16	1.1 (17)

C15—O1—C4—C3	176.5 (8)	C17—C16—C21—C20	0.3 (14)
C3—C4—C5—C6	-1.8 (15)	C15—C16—C21—C20	177.0 (9)
O1—C4—C5—C6	177.7 (8)	C6—O2—C22—C23A	-173.8 (9)
C22—O2—C6—C7	1.7 (13)	C6—O2—C22—C23B	-173.3 (14)
C22—O2—C6—C5	-179.4 (8)	C24A—C23A—C22—O2	53.0 (14)
C4—C5—C6—C7	0.9 (14)	C28A—C23A—C22—O2	-127.8 (10)
C4—C5—C6—O2	-178.0 (8)	C24A—C23A—C22—C23B	47 (19)
O2—C6—C7—C8	178.2 (8)	C28A—C23A—C22—C23B	-134 (20)
C5—C6—C7—C8	-0.5 (14)	C28B—C23B—C22—O2	-50 (4)
C1—N1—C8—C3	0.5 (10)	C24B—C23B—C22—O2	138 (3)
C1—N1—C8—C7	178.9 (10)	C28B—C23B—C22—C23A	125 (21)
C4—C3—C8—N1	176.6 (8)	C24B—C23B—C22—C23A	-47 (19)
C2—C3—C8—N1	0.0 (10)		

CHAPTER 10

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