SYNTHESIS, REACTIVITY AND BIOLOGICAL PROPERTIES OF METHOXY-ACTIVATED INDOLES

DOI: http://dx.medra.org/10.17374/targets.2022.25.162

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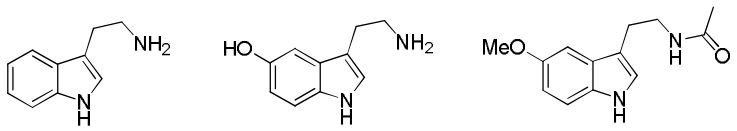
Abstract. *Indoles continue to play a central role in the development of new structures of chemical and biological interest. They are the source of numerous biologically active natural products by virtue of their derivation from tryptophan units which are essential to peptide, protein and enzyme structures. Although the indole unit is electron rich and displays a wide range of reactivity, many naturally-occurring indoles contain methoxy substituents, which enhance their reactivity. The synthesis of methoxyindoles has also become a strategy for diversifying the regiochemical behaviour of indoles. This review brings together a wide range of information relating to indoles incorporating one, two, or three methoxy groups. It deals with aspects of synthesis, reactivity, and biological activity as well as summarizing the scope of important natural products.*

Contents

1. Introduction

Indole is a bicyclic ring system in which benzene fused to C2 and C3 positions of pyrrole, is found extensively as subunits in complex biologically active compounds.[1] Indole heterocyclic systems are

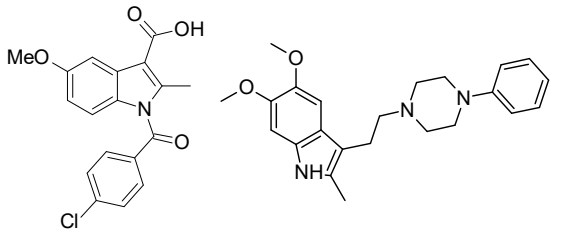
biologically important scaffolds that occur widely in many natural products such as those from plants, fungi and marine organisms.[2-4] Over the last fourteen decades, indole chemistry has been the subject of intense study and continues to be one of the most popular research areas of heterocyclic chemistry due to the interesting biological properties of indoles.[5] Therefore indole scaffolds are important target molecules for drug design studies.[5] The spectrum of activity possessed by indole based compounds includes antitubercular, antimicrobial, antifungal, anti-inflammatory, anticancer and antioxidant, properties.[6-11] Additionally, the natural indolic compounds and their synthetic analogues also show a wide range of biological activities. For example, the simple indole amino acid L-tryptophan **1** is necessary in the human diet and may also act in bacterial efflux pumps and inhibitors of CDK4, an anticancer drug.[12-13] The neurotransmitter serotonin (5-hydroxytryptamine) **2** is active in the central nervous system and regulates mood, appetite, sleep and self-control. Furthermore, melatonin (*N*-acetyl-5-methoxytryptamine) **3** is responsible for the control of circadian rhythm and blood pressure regulation (Figure 1).[14-15]



L-tryptophan **1** 5-hydroxytrptamine **2** Melatonin **3**

Figure 1

More specifically, the potent biological properties of indole derivatives containing electron donating methoxy groups on the benzene ring has led to research into their use as medicinal drugs. Indoles containing methoxy groups are frequently found in the literature and also display biological activities. Such clinically proven methoxy activated indole compounds include the anti-inflammatory agent indomethacine **4** for the gastrointestinal tract and the tranquilizer oxypertine **5** which is an anti-hypertensive drug (Figure 2).[16-17]



Indomethacine **4** Oxypertine **5**

Figure 2

From the synthetic point of view, the electron donating methoxy groups not only activate a benzenoid ring, but also enhance the general reactivity of the indoles, so that new reactions can be achieved. The extension of the reactivity of indole by methoxy groups provides an opportunity to synthesize new classes of natural and unnatural indoles.[18-19]

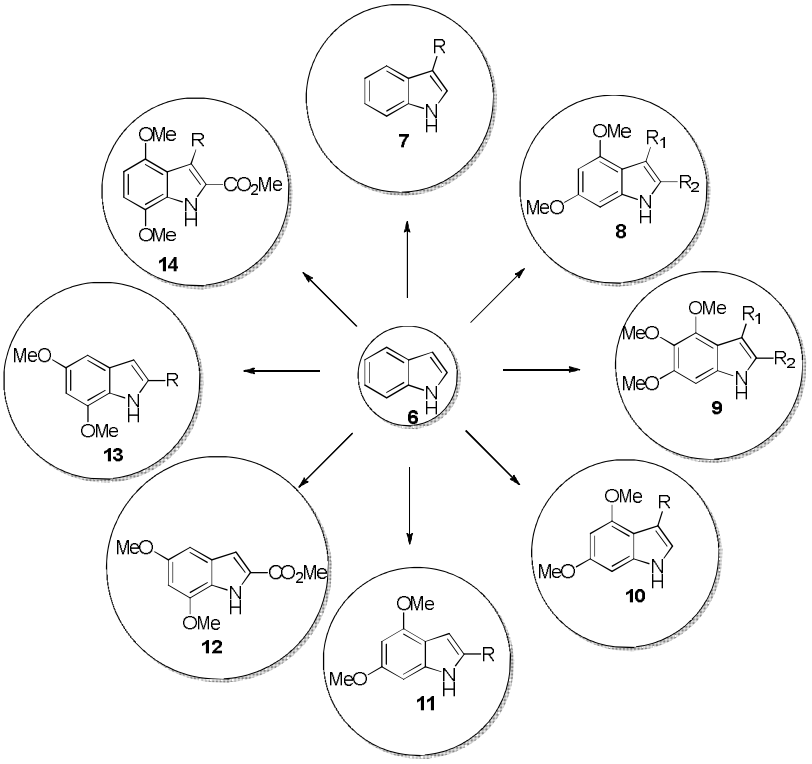
The synthesis, reactivity and biological activities of methoxy activated indole derivatives have been topics of research interest for well over a few decades. There have been various reports on methoxy-activated indole derivatives and their presence in pharmaceuticals, natural products and chemosensors.[20-25] The present chapter covers both the synthesis and the reactivity of the methoxy activated indole ring systems along with their biological activities.

2. The indole nucleus and its chemistry

The indole structure is classified as a π-excessive aromatic heterocycle which has 4 π-bonds and a single pair of electrons on the nitrogen atom that participate in the π system of the five-membered ring,

giving 10 π-electrons in total.[26-27] The indole -NH group is weakly acidic hence the deprotonation of indole requires strong bases.[26] It is well-established that the indole nucleus possesses a high electron density which is suited to electrophilic substitution by a wide variety of electrophiles. In terms of chemical reactivity, unsubstituted indole **6** generally undergoes electrophilic substitution and addition reactions preferentially at C3, followed by N1.[26-29] Many reactions onto the nitrogen are reversible, and therefore *N*-substitution is obtained only in certain cases where a nitrogen anion is the reactive intermediate. The C2 substitution of parent indole **6** is not favored due to disruption to the aromaticity of the benzene ring. Electrophilic substitution at C2 is observed, however, when the C3 position is blocked as in structure **7**.[30]

On the other hand, substitution is also possible on the benzenoid ring. The susceptibility of the indole nucleus towards electrophilic attack may be enhanced through the incorporation of appropriately placed electron donating methoxy groups on the benzene ring. The electron donating capacity of these groups enhances the susceptibility of the indole nucleus towards electrophilic attack at positions C4, C5, C6 and C7 on the indole ring.[31,32] For example, indoles **8** and **9** activated by the electron donating methoxy groups either at C4, C6 or C4, C5 and C6 are capable of undergoing reactions at the C7 position which do not occur in the case of simple indoles.[33,34] Notably, unsubstituted indole **6** shows no propensity to react at C7. While 3-substituted 4,6-dimethoxyindoles **10** undergo electrophilic substitution at both the C2 and C7 positions, 2-substituted 4,6-dimethoxyindoles **11** have been shown to undergo substitution reactions at C7 as well as C3 positions.[35-36] It was anticipated that methyl 5,7-dimethoxyindole-2-carboxylate **12** would undergo preferential electrophilic addition at C4 due to activation of this position *via* electron-donation methoxy groups on C5 and C7 positions.[32] 5,7-Dimethoxyindole **13** was also reported to give reaction at C3 and C4 positions.[32,37] In the case of methyl 4,7-dimethoxyindole-2-carboxylate **14**, the most preferable position for electrophilic substitution would probably be C6 because of delocalization of the lone pair of electrons on the indole nitrogen atom (Scheme 1).[32]



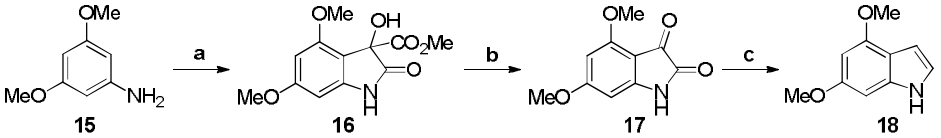
Scheme 1. Selected methoxy activated indole platforms.

This substitution pattern not only activates the benzene ring in particular, but it also enhances the general reactivity of the indoles, to initiate a range of reactions such as formylation, acylation, halogenation, nitration, oxidative dimerization, acid catalyzed addition of aldehydes and α-β-unsaturated ketones, imine and fused indole formation.[18,19]

3. Synthesis of methoxy-activated indoles

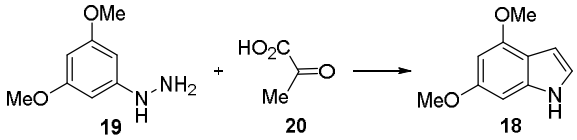
The methoxy-activated indole synthesis has been carried out employing numerous commercially available starting materials such as di- and trimethoxy aniline and benzaldehdye derivatives. It was revealed from the literature that a variety of synthetic methods for the construction of methoxy-activated indoles have been reported.[19] Among them, Fischer, Bischler and Hemetsberger indole synthesis methods are the most commonly used strategies for the preparation of methoxy-activated indoles.[32,33,38] Other synthetic pathways for building such systems have also been reported in the literature.

One of the oldest methods for the synthesis of 4,6-dimethoxyindole **18** was published by Brown, Skinner and McGraw in 1969. In their synthetic strategy, 3,5-dimethoxyaniline **15** was condensed with diethyl mesoxalate in acetic acid and the resulting hydroxy ester **16** was oxidized in 5% sodium hydroxide to afford 4,6-dimethoxyisatin **17**. In the final step the reduction of 4,6-dimethoxyisatin **17** with lithium aluminium hydride in dioxane produced 4,6-dimethoxyindole **18** (Scheme 2).[39]



Scheme 2. Reagents and conditions: a) $CO(CO_2Et)_2$, CH_3COOH, reflux, 2 h; b) NaOH, 100 °C; c) $LiAlH_4$, dioxane, 15 h.

Fischer indole synthesis, which remains the most versatile method for preparing indoles, has also been used to synthesise dimethoxy indoles. This method involves the acid-catalysed or thermal sigmatropic rearrangement of an *N*-aryl hydrazone to generate the indole skeleton after elimination of ammonia. The preparation of 4,6-dimethoxy indole by the Fischer method using microwave irradiation was examined by Bratulescu in 2008.[40] The microwave-assisted dimethoxy indole synthesis was carried out mixing phenylhydrazine **19**, pyruvic acid **20**, zinc chloride and phosphorus pentachloride in a Pyrex beaker. The reaction was then continued until a paste resulted. The paste was irradiated in a microwave oven for 5h to give the 4,6-dimethoxyindole **18** in 79% yield (Scheme 3).[40]

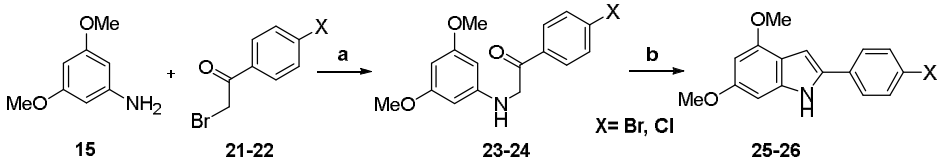


Scheme 3. Reagents and conditions: $ZnCl_2$, PCl_5, 5 h.

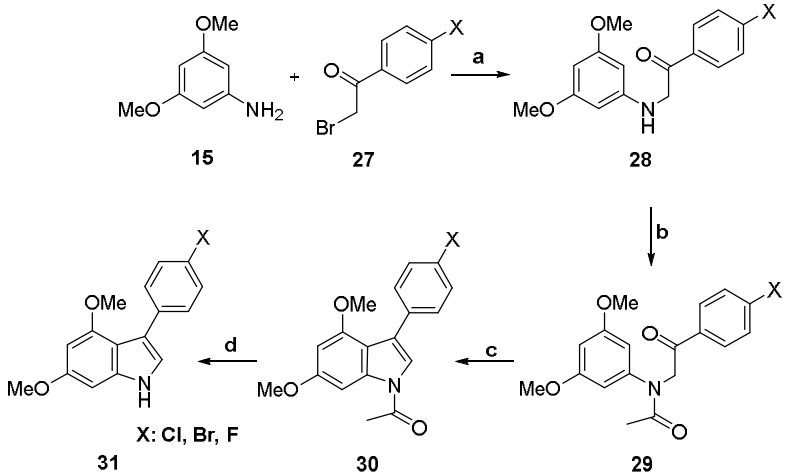
Over the last few decades, a large number of activated indoles bearing methoxy groups at the C4 and C6 positions have been investigated *via* Bischler rearrangement and modified Bischler indole synthesis methods. The Bischler rearrangement method involves the cyclisation of amino ketones **23-25** prepared from the reaction of 3,5-dimethoxyaniline **15** and phenacyl bromides **21-22** gave 2-substituted indoles **25-26**. The classical problem of Bischler technique is the rearrangement during the cyclization of secondary phenacylaniline, in the presence of a trace amount of aniline hydrobromide to give the 2-phenyl indole rather than 3-phenyl derivative (Scheme 4).[41]

By comparison, the modified Bischler method has been used to generate 3-substituted 4,6-dimethoxyindoles.[42] This approach involved treatment of 3,5-dimethoxyaniline **15** with halogenated ketones **27** in the presence of an inorganic base such as sodium bicarbonate to afford the intermediate

substituted phenacyl anilines **28**. The aniline ketones **28** subsequently undergo *N*-protection reaction with acetic anhydride to give the corresponding amides **29** followed by cyclisation in trifluoroacetic acid to generate *N*-acetyl indoles **30**. Deprotection *via* treatment with methanolic potassium hydroxide affords the desired 3-substituted 4,6-dimethoxyindoles **31** (Scheme 5).[42]

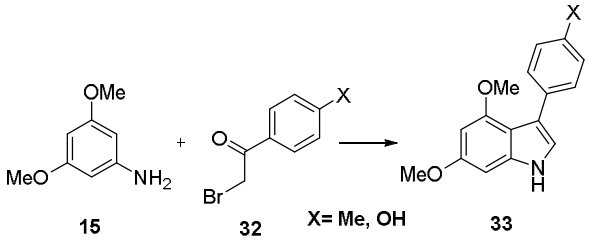


Scheme 4. Reagents and conditions: a) EtOH, $NaHCO_3$, reflux, 2 h; b) silicon oil, inert gas.



Scheme 5. Reagents and conditions: a) EtOH, $NaHCO_3$, reflux, 2 h; b) Ac_2O, r.t., overnight; c) TFA, 100 °C, Argon; d)MeOH, KOH, r.t.

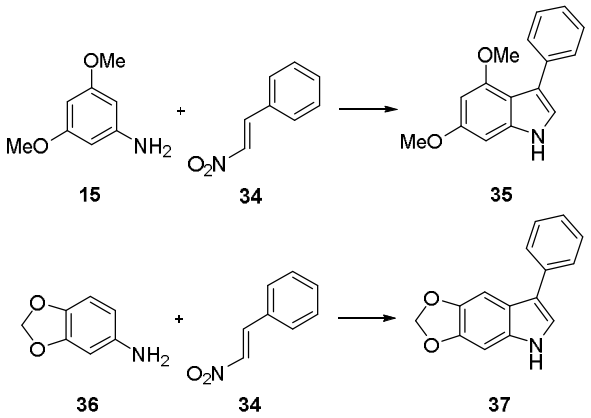
Synthesis of 3-substituted 4,6-dimethoxyindole **33** has also been achieved in a one-pot process by a direct cyclization of an arylaminoketone, in the presence of lithium bromide and sodium bicarbonate, under essentially neutral conditions. A mixture of 3,5-dimethoxyaniline **15**, 2-chloroacetophenone **32**, lithium bromide and sodium bicarbonate in 1-propanol was heated under reflux overnight to yield the indole **33** in 61% yield (Scheme 6).[43]



Scheme 6. Reagents and conditions: $NaHCO_3$, LiBr, 1-propanol, reflux.

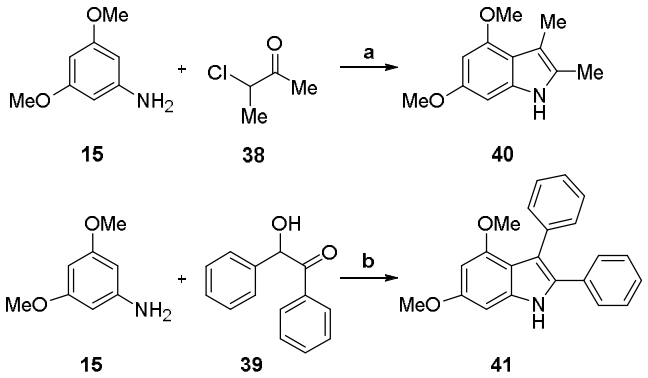
Recenlty, Gattu *et. al.* reported an alternative strategy for the modified Bischler indole synthesis method in order to generate methoxy activated 3-arylindoles. This method provided a simple and an efficient

way for the regioselective synthesis of 3-arylindole derivatives from the anilines having electron-donating groups such as 3,5-dimethoxy **15** and 3,4-methylenedioxy **36**. The treatment of methoxy anilines **15** and **36** with *trans*-β-nitrostyrene **34** in the presence of 10 mol% of bismuth(III) triflate as a catalyst in acetonitrile at 80 °C gave the corresponding 3-aryl indoles **35** and **37** in 80% and 68% yields, respectively (Scheme 7).[44]



Scheme 7. Reagents and conditions: 10 mol% $(BiOTf)_3$, CH_3CN, 80 °C.

Synthesis of both C2 and C3 substituted activated indoles was achieved thruogh a range of methods.[31] For example, a mixture of 3,5-dimethoxyaniline **15** and 3-chloro-2-butanone **38** was allowed to react in the presence of lithium bromide and sodium bicarbonate in absolute ethanol to produce directly the 2,3-dimethylindole **40** in a moderate yield. In the case of diphenyl indole, the reaction of 3,5-dimethoxyaniline **15** with benzoin **39** in the presence of aniline and acetic acid gave 4,6-dimethoxy-2,3-diphenylindole **41** in a single step in 63% yield (Scheme 8).[31]

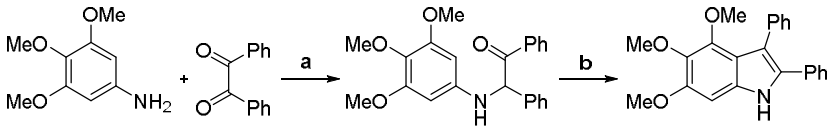


Scheme 8. Reagents and conditions: a) $NaHCO_3$, LiBr, 1-propanol, reflux; b) AcOH, reflux.

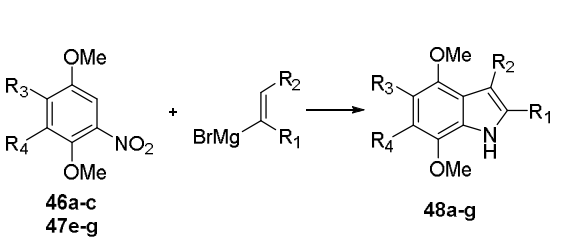
In a similar way, the synthesis of the 2,3-diphenyl-3,4,5-trimethoxyindole **45** was reported by Charrier.[45] The preparation of intermediate benzyl arylamine **44** was accomplished by the condensation of 3,4,5-trimethoxyaniline **42** with benzil **43** in the presence of acetic acid in ethanol at reflux. Indole **45** was subsequently synthesized upon reaction of benzyl arylamine with phosphorus pentasulfide in toluene (Scheme 9).[45]

On the other hand, the reaction of vinyl Grignard reagents with 1,4-dimethoxy-2,5-dinitrobenzenes **46a-c** and 2,5-dimethoxy-1,3-dinitrobenzenes **47f-g** yielded 4,7-dimethoxyindole derivatives **48a-g**. This

one-pot reaction pathway provides a very mild and efficient protocol for the preparation of 4,7-dimethoxyindoles along with electron-releasing nitro groups at C5 and C6 positons (Scheme 10).[46]



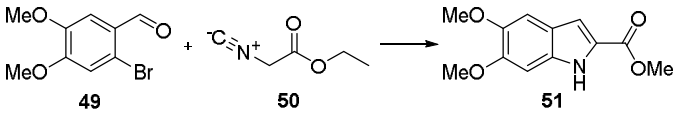
Scheme 9. Reagents and conditions: a) Etanol, AcOH reflux; b) Toluene, P_4S_{10}, reflux.



Compds.	R_1	R_2	R_3	R_4
a	H	H	NO_2	H
b	CH_3	H	NO_2	H
c	H	CH_3	NO_2	H
d	H	H	H	NO_2
e	CH_3	H	H	NO_2
f	H	CH_3	H	NO_2
g	H	CH_3	H	NO_2

Scheme 10. Reagents and conditions: THF, -78 °C, 2-3 h.

Another methoxy-activated indole derivative is 5,6-dimethoxyindole. A concise, efficient and simple synthetic route to 5,6-dimethoxyindole **51** involved the copper-catalyzed cyclization of 2-bromo-4,5-dimethox-benzaldehyde **49** with ethyl 2-isocyanoacetate **50** in DMSO (Scheme 11).[47]



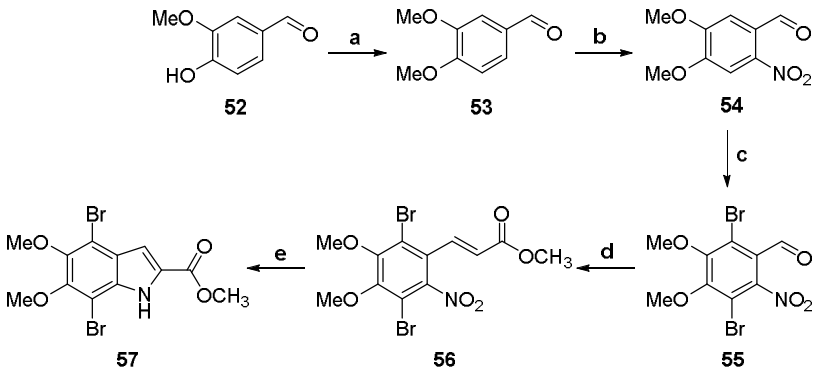
Scheme 11. Reagents and conditions: CuI, Cs_2CO_3, DMSO, 80 °C.

The synthesis of the methyl 4,7-dibromo-5,6-dimethoxy-1*H*-indole-2-carboxylate **57** from vanillin **52** was investigated as a new building block for organic semiconductors. Initially, vanillin **52** was methylated by methyl iodide and potassium carbonate to give dimethoxybenzaldehyde **53** in high yield. 2,3-Methoxybenzaldehyde **53** was then nitrated to give 4,5-dimethoxy-2-nitrobenzaldehyde **54**, which was brominated using *N*-bromosuccinimide to yield the compound **55**. In the next step, the olefin **56** was synthesized using methyl bromoacetate in aqueous sodium bicarbonate, followed by microwave-assisted Cadogan synthesis to afford the 5,6-dimethoxyindole **57** (Scheme 12).[48] The 5,6 dimethoxyindole possessing bromo groups at the 4 and 7 positions would allow for the further functionalization of the indole with alkynyl substituents using Sonogashira cross-coupling.

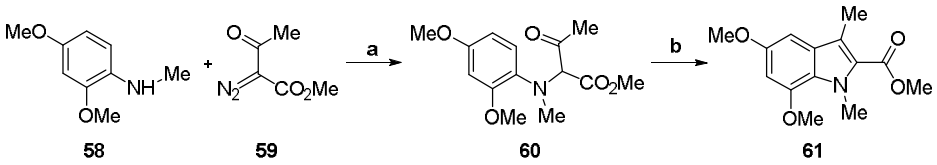
Methyl 5,7-dimethoxyindole-2-carboxylate, containing substituents at C3, has been prepared by Moody and Swann. Methyl *N*-methyl-5,7-dimethoxy-3-methylindole-2-carboxylate **61** was prepared *via* a modified Bischler synthesis involving a carbenoid N-H insertion reaction followed by an ion-exchange mediated cyclization.[49] *N*-Methylaniline **58** was condensed with an α-diazo-β-ketoester **59** in the presence of rhodium(II) acetate to give the α-(*N*-arylamino)ketone **60** which was subsequently cyclized *via* heating in the presence of Amberlyst® 15 to the indole **61** (Scheme 13).

5,7-Dimethoxyindole was also synthesized employing Reissert indole synthesis in five steps. The nitration of orcinol **62** was initially achieved using nitric acid in diethyl ether and gave the

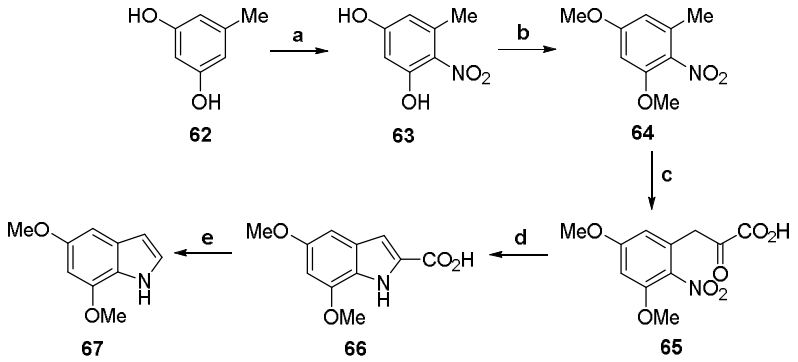
5-methyl-4-nitrobenzene-1,3-diol **63** which was methylated by dimethyl sulfate in acetone to yield the dimethoxy derivative **64**. The condensation of compound **64** was carried out with potassium ethoxide in ether and generated the nitrophenyl pyruvic acid **65**. This was reduced to the corresponding 5,7-dimethoxy-1*H*-indole-2-carboxylic **66** acid using ferrous sulphate and ammonium hydroxide. In the final step the decarboxylation of the compound **66** gave the 5,7-dimethoxyindole **67** (Scheme 14).[50]



Scheme 12. Reagents and conditions: a) CH_3I, K_2CO_3, 18-crown-6; b) HNO_3; c) NBS, H_2SO_4; d) PPH_3, $NaHCO_3$, methyl-2-bromoacetate; e)PPH_3, THF, $MoO_2Cl_2(DMF)_2$, MW.



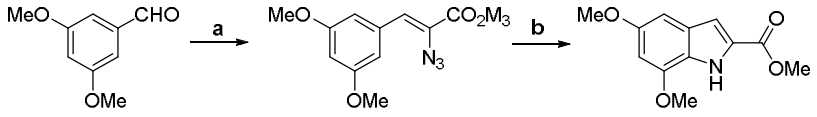
Scheme 13. Reagents and conditions: a) cat. $Rh_2(OAc)_4$, PhMe or $CHCl_3$; b) Amberlest 15, toluene.



Scheme 14. Reagents and conditions: a) HNO_3, diethyl ether; b) Me_2SO_4, K_2CO_3; c) Diethyl oxalate, KOEt, Ether; d) $FeSO_4$, NH_4OH; e) Copper chromite, quinoline.

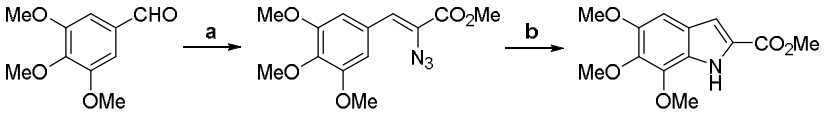
Alternatively, methyl 5,7-dimethoxyindole-2-carboxylate **70** was prepared *via* Hemetsberger indole synthesis, starting from 3,5-dimethoxybenzaldehyde **68** and proceeding *via* the vinyl azide **69** (Scheme 15).[51]

Similarly, Boger and co-workers synthesized methyl 5,6,7-trimethoxyindole-2-carboxylate **73** from 3,4,5-trimethoxybenzaldehyde **71** by an intramolecular cyclization of the intermediate azide **72** (Scheme 16).[52]



68 **69** **70**

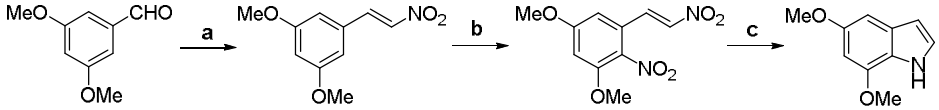
Scheme 15. Reagents and conditions: a) $N_3CH_2CO_2Me$, NaOMe, MeOH; b) 1,2-dichlorobenzene, reflux.



71 **72** **73**

Scheme 16. Reagents and conditions: a) $N_3CH_2CO_2Me$, NaOMe, MeOH, 0 ^oC; b) xylene, 140 ^oC.

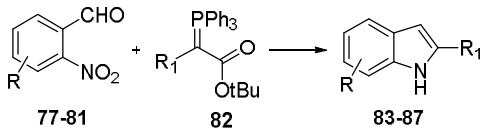
In another strategy, the 5,7-dimethoxy analog **67** was synthesized by reacting 3,5-dimethoxybenzaldehyde **74** with nitromethane to give the 2-β-nitrostyrene **75** which was nitrated using copper (II) nitrate to give the 2-β-dinitrostyrene **76**. Reduction and cyclization was then carried out with iron powder in 80% aqueous acetic acid to afford the indole **67** in 50% overall yield (Scheme 17).[53]



74 **75** **76** **67**

Scheme 17. Reagents and conditions: a) $MeNO_2$; b) $Cu(NO_3)_2$, Ac_2; c) Fe, AcOH.

Volvoikar and Tilve investigated the synthesis of indole **83**-**85** and 2-methyl indole **86**-**87** in a one pot process which involves a Wittig reaction, reductive cyclisation, hydrolysis and decarboxylation. According to their methods the reaction of o-nitrobenzaldehydes **77**-**81** bearing methoxy groups with triphenyl phosphine **82** in diphenyl ether at reflux yielded the di- and tri-methoxy indoles **83**-**87** (Scheme 18).[54]



77-81 **82** **83-87**

Comp.	R	R_1	Yield%
83	4,5-OMe	H	52
84	4,5,6-OMe	H	62
85	4,5-OCH_2O	H	45
86	4,5-OMe	CH_3	47
87	4,5-OCH_2O	CH_3	36

Scheme 18. Reagents and conditions: PPh_3 Ph_2O.

4. Methoxy activated bis-indoles and bis-indolyl synthesis

Bis-indolyl alkaloids are compounds consisting of two indoles connected to each other, often *via* heterocyclic units.[55,56] Bis-indole alkaloids are also an important structural class due to their interesting biological properties.[57,58] There is an enormous range of bis-indole ring systems that exhibit biological activity.[57,58] Furthermore, bis-indole systems may be readily exploited for the development of novel macrocyclic systems.[59] Owing to the structural diversity of this class of compounds, numerous synthetic methods for the synthesis of bis-indoles are reported in the literature.[60,61] 2,2'-Diindolyl compounds possess N1, N1', C3, C3', C7 and C7' positions as active sites (Figure 3).

3,3'-Diindolyl derivatives based on methoxy activated indoles on the other hand would be susceptible to electrophilic substitution reactions at N1, N1', C2, C2', C7 and C7' positions (Figure 4).

The synthetic strategies towards 3-substituted bis-indoles can be based upon the use of either substituted indoles or substituted heterocycles as the starting material. For example, the Suzuki-Miyaura coupling reaction was utilized as the first strategy for the preparation of the 3-substituted bis-indole system

89.[62] The 3-(4-bromophenyl)-4,6-dimethoxyindole **88** underwent one-pot Suzuki coupling with bis-(pinacolato)-diboron in the presence of $PdCl_2$ (dppf) and potassium acetate in dry DMF. This was followed by the addition of another equivalent of indole **88**, $Pd(PPh_3)_4$ and NaOH solution to generate 3,3'-diphenyl linked bis-indole **89** in 37% yield (Scheme19).[62]

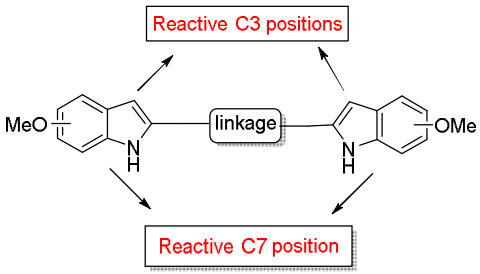


Figure 3. Active sites of 2,2'-diindolyl compounds.

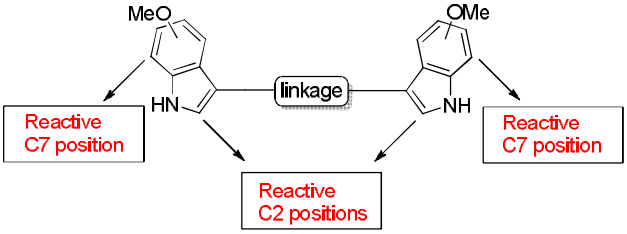
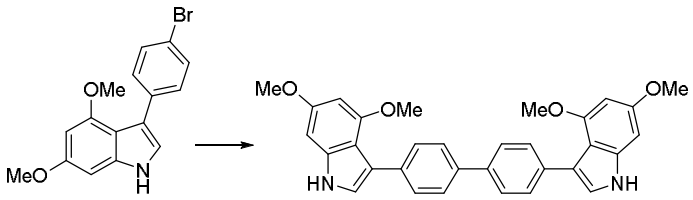


Figure 4. Active sites of 3,3'-diindolyl compounds.

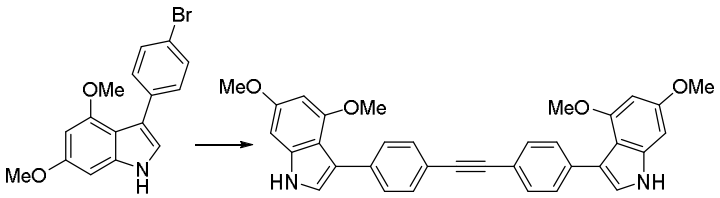


88 **89**

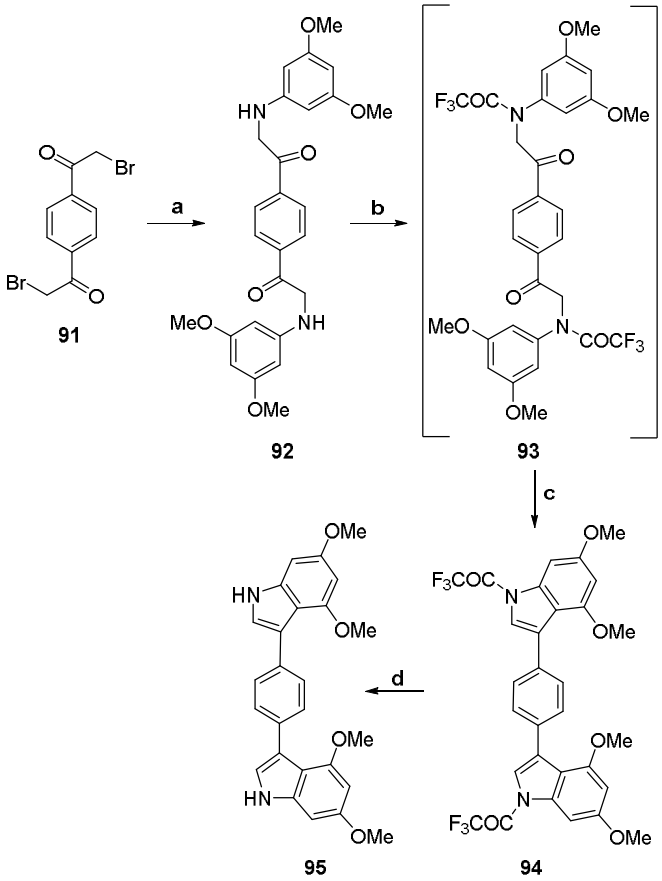
Scheme 19. Reagents and conditions: $Pd(PPh_3)_4$, NaOH, bis-(pinacolato)-diboron, $PdCl_2$, CH_3CO_2K, DMF.

The Sonogashira coupling reaction can be alternatively employed for the construction of bis-indoles. When a one-pot Sonogashira coupling reaction strategy was applied to 3-(4-bromophenyl)-4,6-dimethoxyindole **88**, the resulting bis-indole **90** was obtained in 56% yield (Scheme 20).[63]

The second strategy was represented by the adoption of the Nordlander indole synthesis for the preparation of bis-indolyl benzene **95**.[64] Treatment of 3,5-dimethoxyaniline with α,α'-dibromo-1,4-diacetylbenzene **91** afforded the phenacylaniline **92** in 80% yield. This compound was then allowed to react with trifluoroacetic anhydride to give the *N*-protected intermediate **93**, which was not isolated, but rather underwent cyclisation to the *N*-protected bis-indole **94** in 80% yield upon continued stirring in trifluoroacetic acid at room temperature for another three days under an inert atmosphere. The final step involved the use of methanolic potassium hydroxide solution to give the desired benzenoid-indole **95** in 95% yield (Scheme 21).[64]



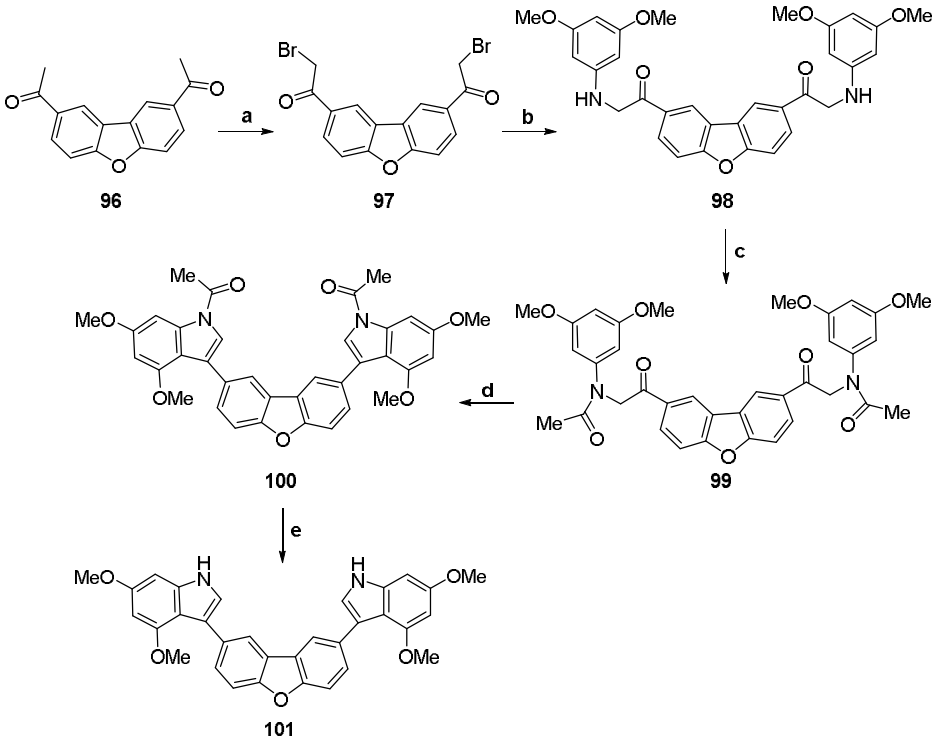
Scheme 20. Reagents and conditions: Et_3N, DMF, $PdCl_2(PPh_3)_2$, ethynytrimethylsilane, CuI, DBU.



Scheme 21. Reagents and conditions: a) 3,5-dimethoxyaniline, EtOH, $NaHCO_3$, reflux, 6 h; b)TFAA, N_2; c) TFA; d) MeOH, KOH.

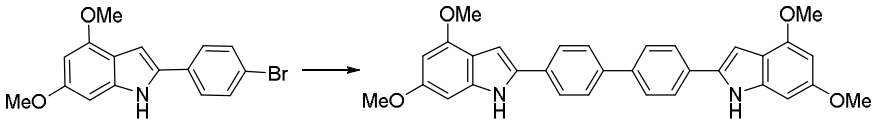
A modified Bischler indole synthetic strategy was also employed for the preparation of 3,6-bis-(3-indolyl)dibenzofuran **101** starting from 3,6-diacetyldibenzofuran. Bromination of 3,6-diacetyldibenzofuran **96** with two equivalents of bromine in glacial acetic acid gave 3,6-di(bromoacetyl)benzofuran **97** in 54% yield. Condensation of bromoketone **97** with two equivalents of 3,5-dimethoxyaniline in the presence of sodium bicarbonate afforded the corresponding phenacyl aniline **98** as a yellow solid in 90% yield. Phenacyl aniline **98** was subsequently treated with acetic anhydride at room temperature for 12 h, giving rise to the protected anilino-ketone **99** in 83% yield. Formation of the indole

ring systems was then achieved by cyclisation of the *N*-protected anilino-ketone **99** in the presence of trifluoroacetic acid at 100 °C for 3 h under an argon atmosphere. Finally, deprotection of bisindole **100** was carried out using potassium hydroxide in methanol, generating the targeted 3,6-bis-(3-indolyl)-dibenzofuran **101** as a white solid in 69% yield (Scheme 22).[64]



Scheme 22. Reagents and conditions: a) Br_2, AcOH; b) 3,5-dimethoxyaniline, EtOH, $NaHCO_3$, reflux, 6 h; c) Ac_2O; d) TFA; e) MeOH, KOH.

As with the 3-substituted bis-indoles, when 2-(4-bromophenyl)-4,6-dimethoxy-1H-indole **25** was subjected to the one-pot Suzuki-Miyaura coupling reaction, the targeted 2,2'-linked bis-indole **102** was obtained in 36% yield (Scheme 23).[62]



Scheme 23. Reagents and conditions: $Pd(PPh_3)_4$, NaOH, bis-pinacolato-diboron, $PdCl_2$, CH_3CO_2K, DMF.

On the other hand, for the construction of 3-substituted 7,7'-linked systems, various linkers such as amide, imine, amine, hydrazide, and related cyclic systems *e.g.* oxadiazole or oxazole have been utilized. The 3-substituted 7,7'-bis-indoles have a nucleophilic C2 and C2' position for further substitutions (Figure 5).

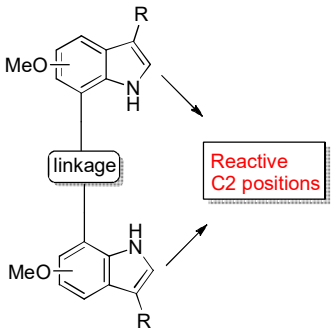
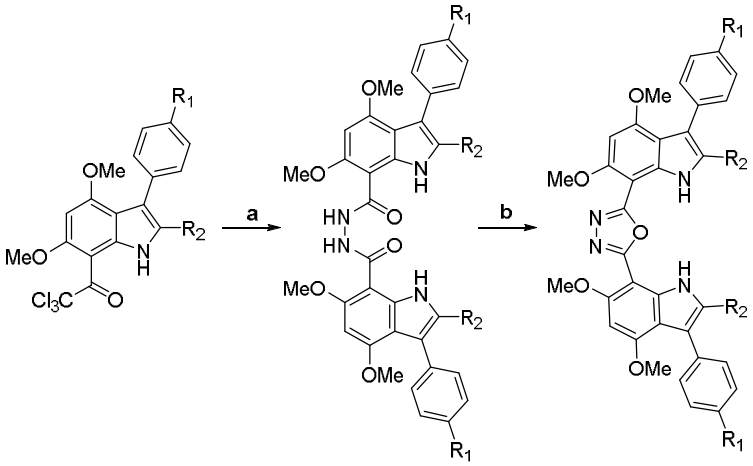


Figure 5. Active sites of 3-indoly compounds.

The synthesis of 1,3,4-oxadiazole linked 7,7′-bis-indoles **109-111** was achieved in a two-step protocol starting from a range of 7-trichloroacetyl-4,6-dimethoxyindoles **103-105**. In the first step, the treatment of two equivalents of **103-105** with one equivalent of hydrazine hydrate in acetonitrile in the presence of triethylamine gave the corresponding 7,7′-bis-indole carbohydrazides **106-108** in 49-81% yields. The final step was cyclodehydration of carbazohydrazides with dehydrating reagents. The treatment of bis-indoles **106-108** with excess phosphoryl chloride at reflux in ethyl acetate for two hours afforded the desired bis-indolyl-1,3,4-oxadiazoles **109-111** in 61, 71 and 82% yields, respectively (Scheme 24).[34]



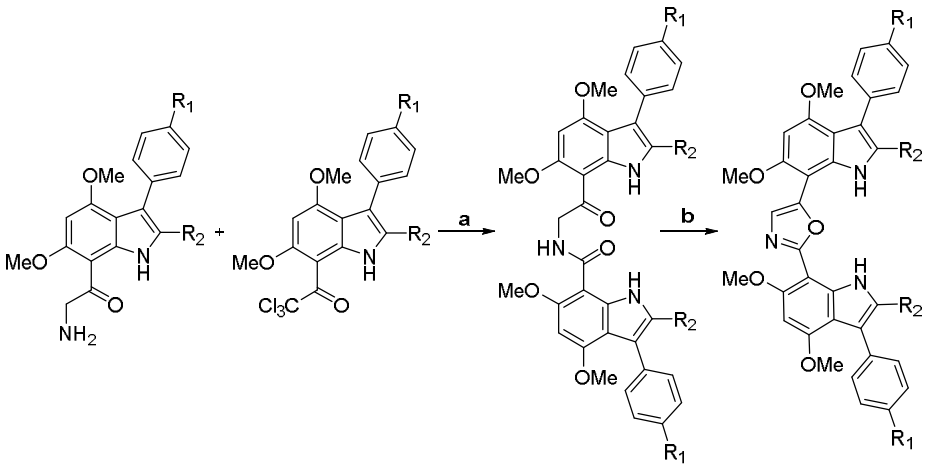
103 R_1 = Cl, R_2 = H
104 R_1 = Br, R_2 = H
105 R_1 = H, R_2 = Ph

106 R_1 = Cl, R_2 = H
107 R_1 = Br, R_2 = H
108 R_1 = H, R_2 = Ph

109 R_1 = Cl, R_2 = H
110 R_1 = Br, R_2 = H
111 R_1 = H, R_2 = Ph

Scheme 24. Reagents and conditions: a) hydrazine hydrate, Et_3N, CH_3CN; b) $POCl_3$, ethyl acetate.

Similarly, the successful preparation of 7,7′-bis-oxazoles **118** and **119** was achieved with a convenient two-step process. The first step involved heating 7-oxotryptamines **112** and **113** with 7-trichloroacetylindoles **114** and **115** at reflux overnight in the presence of triethylamine in acetonitrile to afford the unsymmetrical 7,7′-amide linked bis-indoles **116** and **117** in 61% and 55% yield respectively. In the next step, cyclodehydration was carried out by the treatment of bis-indoles **116** and **117** with excess phosphoryl chloride at reflux in ethyl acetate for two hours. The process afforded the desired bis-indolyl-oxazoles **118** and **119** in 63% and 61% yield respectively (Scheme 25).[65]

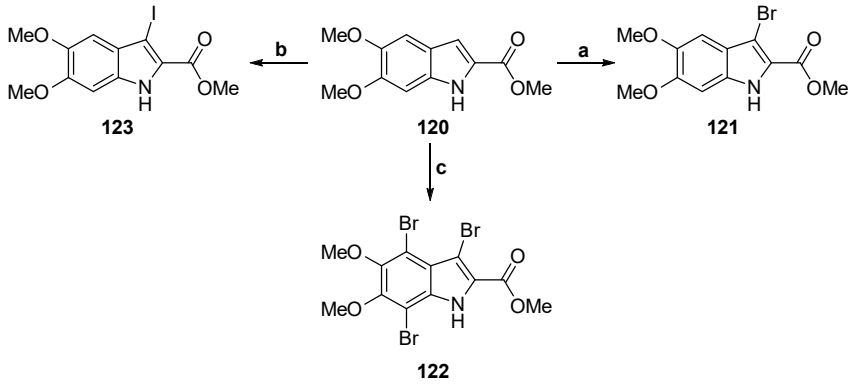


Scheme 25. Reagents and conditions: a) Et_3N, CH_3CN, reflux; b) $POCl_3$, ethyl acetate, reflux.

5. Functionalization of methoxy-activated indoles

5.1. Halogenation

It is well-known that indole itself undergoes bromination under a variety of conditions to yield 3- bromoindole. Methyl 5,6-dimethoxy-1H-indole-2-carboxylate **120** was regioselectively brominated at the 3-position. The reaction of 5,6-dimethoxyindole **120** with a single equivalent of NBS in acetonitrile produced the compound **121** in 87% yield. On the other hand, using excess NBS generated 3,4,7-tribromo-dimethoxyindole **122**. In the case of iodination, the reactivity of the 3-position also creates an opportunity for selective iodination with iodine under basic conditions to give 3-iodo-dimethoxyindole **123** in 84% yield (Scheme 26).[66]

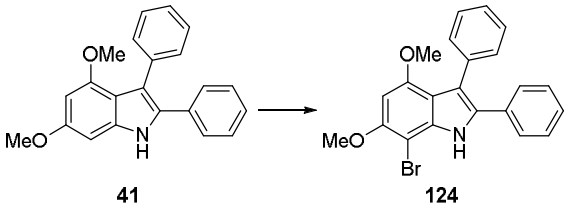


Scheme 26. Reagents and conditions: a) NBS, MeCN; b) I_2, KOH, DMF; c) excess NBS, MeCN.

4,6-Dimethoxy-2,3-diphenylindole **41** was brominated to give the stable 7-bromo-derivative **124** in high yield using bromine in dimethylformamide or trimethylammonium bromide in tetrahydrofuran (Scheme 27).[67]

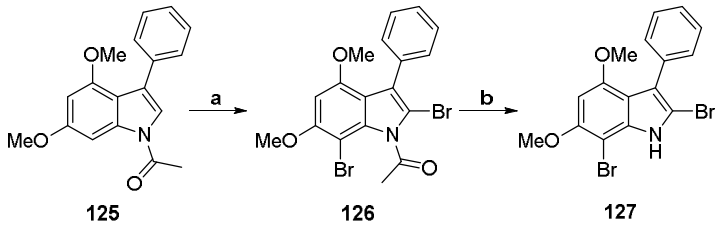
It was found that 3-substituted-4,6-dimethoxyindoles undergo C2-bromination with NBS in the presence of a bulky, deactivating *N*-substituent. Deactivation of the 4,6-dimethoxyindoles was achieved by the attachment of acetyl and phenylsulfonyl groups at N1. Reaction of

N-acetyl-4,6-dimethoxy-3-phenylindole **125** with NBS and silica gave only the 2,7-dibromo-*N*-acetylindole **126** in 60% yield. Removal of the acetyl group was readily achieved using methanolic potassium hydroxide to give the 2,7-dibromoindole **127** in 80% yield (Scheme 28).[67]



41 **124**

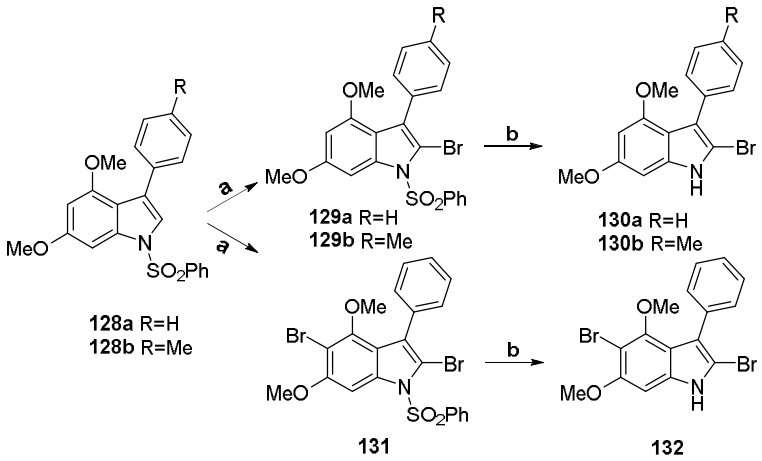
Scheme 27. Reagents and conditions: Br_2, DMF, THF.



125 **126** **127**

Scheme 28. Reagents and conditions: a) NBS/Silica (1 or 2 equiv), CH_2Cl_2; b) KOH, MeOH.

The phenylsulfonyl compounds **128a-b** were treated with one equivalent of NBS and silica to give the 2-bromo-*N*-sulfonylindoles **129a-b** in 80 and 67% yields, respectively. Treatment of indole **128a** with two equivalents gave the 2,5-dibromo-*N*-sulfonylindole **131** in 71% yield. Notably the phenylsulfonyl group protected C7 from bromination. The removal of the phenylsulfonyl group using methanolic potassium hydroxide afforded the 2-bromoindoles **130a-b** and the 2,5-dibromoindole **132** in 92, 66 and 98% yields, respectively (Scheme 29).[67] The larger deactivating group, such as phenylsulfonyl offered some added regioselectivity to the bromination reaction. Halogenation of methoxy activated indoles provides considerable opportunities for further synthesis, especially involving coupling reactions.



128a R=H
128b R=Me

129a R=H
129b R=Me

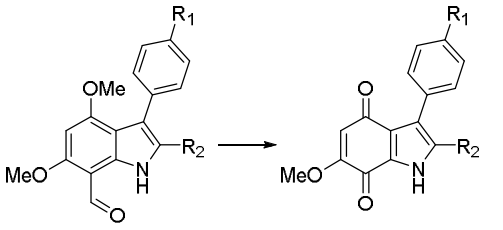
130a R=H
130b R=Me

131 **132**

Scheme 29. Reagents and conditions: a) NBS/Silica (1 or 2 equiv), CH_2Cl_2; b) KOH, MeOH.

5.2. Dakin oxidation

Dakin oxidation allows the preparation of phenols from aryl aldehydes *via* oxidation with hydrogen peroxide. Indoloquinones are an interesting and important class of bioreductive alkylating agents because they and their derivatives play a vital role in some biosynthetic processes. The reaction of 4,6-dimethoxyindole-7-carbaldehydes **133-141** with hydrochloric acid and hydrogen peroxide in a solution of methanol and tetrahydrofuran in two hours respectively gave the 6-methoxy-4,7-indoloquinones **142-150** in moderate to good yields after recrystallization from ethanol (Scheme 30).[68]

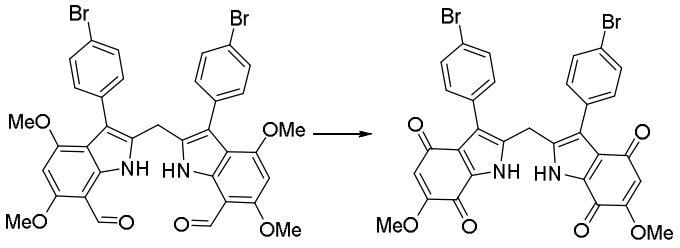


133-141 **142-150**

	R_1	R_2		R_1	R_2
133	Ph	Ph	**142**	Ph	Ph
134	Ph	Me	**143**	Ph	Me
135	Ph	H	**144**	Ph	H
136	4-ClC_6H_4	H	**145**	4-ClC_6H_4	H
137	4-BrC_6H_4	H	**146**	4-BrC_6H_4	H
138	4-$MeOC_6H_4$	H	**147**	4-$MeOC_6H_4$	H
139	4-PhC_6H_4	H	**148**	4-PhC_6H_4	H
140	Me	Me	**149**	Me	Me
141	Me	H	**150**	Me	H

Scheme 30. Reagents and conditions: H_2O_2, HCl, MeOH, THF.

Similarly, the 7,7'-dicarbaldehyde-2,2'-bisindolyl **151** was also oxidized employing hydrogen peroxide in a solution of methanol and tetrahydrofuran to give the bisindoloquinone **152** (Scheme 31). However, in this case a longer time (four hours) is required compared to the monomeric indoles for the completion of the reaction.[68]

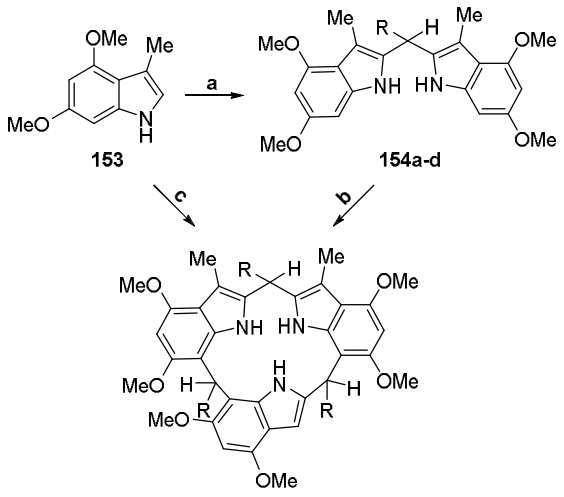


151 **152**

Scheme 31. Reagents and conditions: H_2O_2, HCl, MeOH, THF.

5.3. Cyclisation

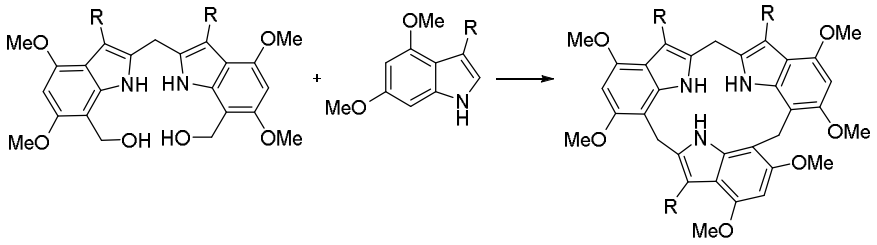
Activated 3-substituted indoles **153** have been found to undergo condensation with aromatic aldehydes in the presence of HCl to give 2,2'-di-indolylmethanes **154a-d**.[69] In contrast, condensation with the same aryl aldehydes in the presence of phosphoryl chloride afforded the macrocyclic calix[3]indoles **155a-d**. These compounds **155a-d** were also prepared from the related condensation of di-indolylmethanes **154a-d** with indole **153** and phosphoryl chloride in chloroform (Scheme 32).[69]



R	
154, 155a	Ph
154, 155b	4-ClC_6H_4
154, 155c	2-ClC_6H_4
154, 155d	4-BrC_6H_4

Scheme 32. Reagents and conditions: a) HCl, MeOH,r.t.; b) $POCl_3$, $CHCl_3$, reflux; c) aromatic aldehyde, $POCl_3$, $CHCl_3$, reflux.

In another approach, the reaction of dialcohols **156** with a 3-substituted 4,6-dimethoxyindole **157** in acetic acid has been reported to give the unsymmetrically linked calix[3]indoles **158** (Scheme 33).[70]

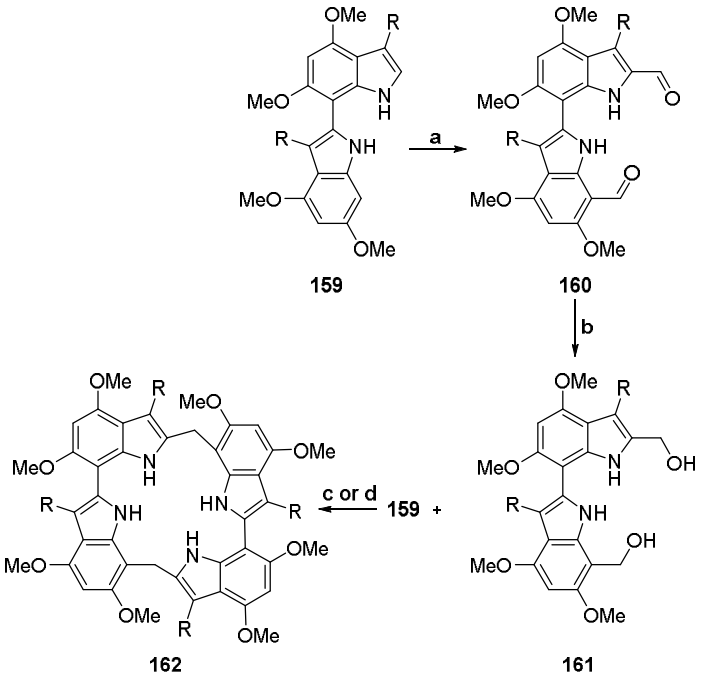


156 **157** **158**

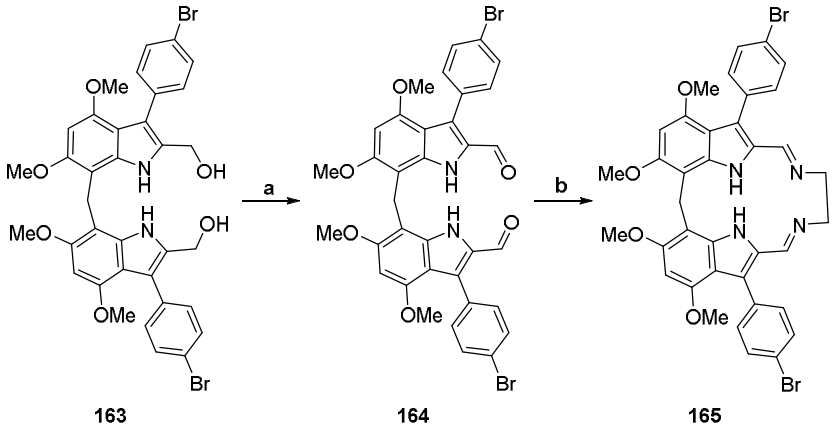
Scheme 33. Reagents and conditions: HOAc, r.t.

The synthesis of semi-calix[4]indole **162** from 2,7'-biindolyl **159** *via* acid catalysed condensation of 2,7'-biindolyl **159** with the bis(hydroxymethyl) derivative **161** derived from 2,7'-diformyl biindolyl **160** was also achieved**.** In the synthesis of semi-calix[4]indoles **162**, the acid catalysed condensation between hydroxymethyl groups and activated sites of the indoles was reported as an efficient strategy for cyclization (Scheme 34).[71]

In the case of imine bridged indole macrocycles, the bis-indole dimethanol **163** was converted in high yield to the corresponding dialdehyde **164** employing manganese dioxide in dichloromethane. The aldehyde was then heated overnight with 1,2-diaminoethane in isopropanol to afford the 15-membered imine macrocycle **165** in moderate yield (Scheme 35).[72]



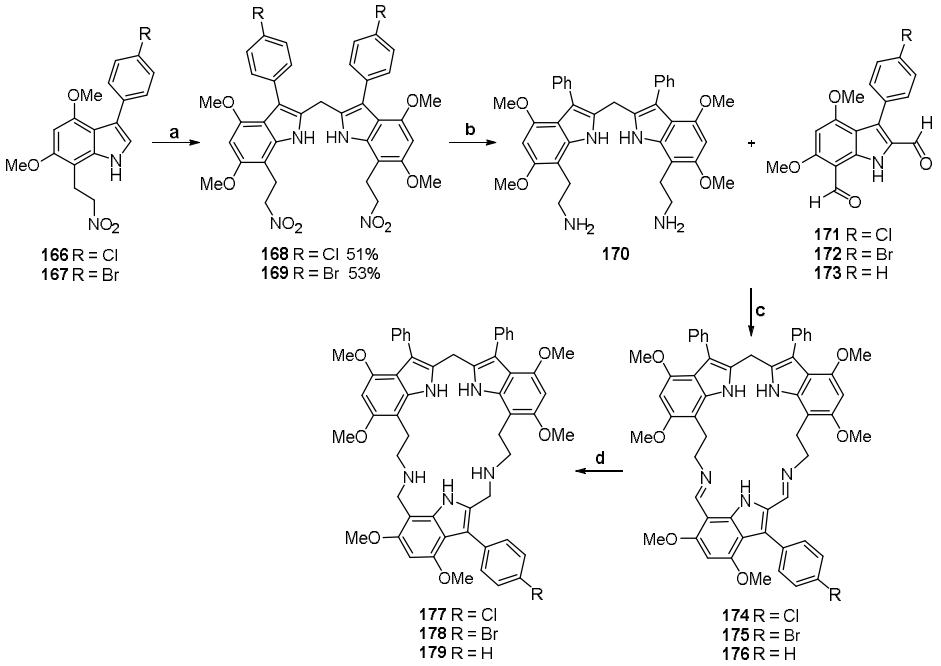
Scheme 34. Reagents and conditions: a) $POCl_3$, DMF, r.t., 8 h;. b) $NaBH_4$, THF, EtOH, r.t., 8 h.; c) conc. HCl (one drop), isopropanol; d) TFA, MeCN.



Scheme 35. Reagents and conditions: a) MeCN, diamines, r.t., 1 h.; b) conc. HCl, HCHO, MeOH.

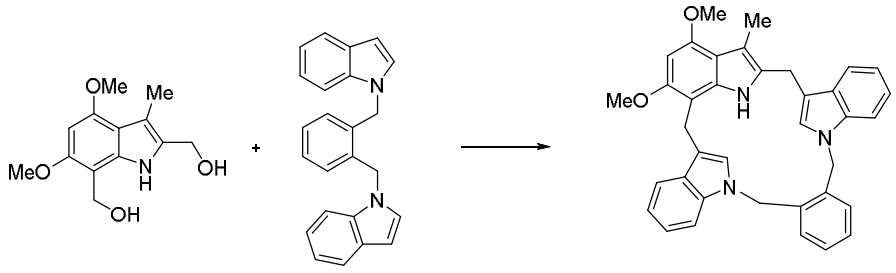
An alternative strategy was therefore devised in which the methylene bridge was introduced prior to attempted macrocyclisation *via* the formation of imine bonds. The condensation of intermediate 7-nitroethylindoles **166** and **167** with an excess of formaldehyde in the presence of hydrochloric acid in glacial acetic acid gave **168** and **169**. Reduction of compounds **168** and **169** with hydrazine hydrate and 10% Pd/C was carried out in a mixture of ethanol and tetrahydrofuran. It was revealed that the reduction of both compounds **168** and **169** gave the same bis-indole diamine **170**, due to the halogens on the aromatic rings also being replaced by hydrogen atoms. Synthesis of unsymmetrical macrocycles **174-176** was then achieved

by the tandem condensation of diamine **170** with 2,7-dialdehydes **171-173** in absolute ethanol. Products **174-176** precipitated from the reaction mixture and were collected by filtration in 58-71% yields. The imine linked macrocyclic compounds **174-176** were reduced to the corresponding amine linked macrocyclic compounds **177-179** with sodium borohydride in a mixture of hot ethanol and tetrahydrofuran (Scheme 36).[73]



Scheme 36. Reagents and conditions: a) HCHO, HCl, MeOH, reflux; b) hydrazine hydrate, Pd/C, EtOH, THF, reflux; c) EtOH, THF, reflux; d)EtOH, $NaBH_4$, reflux.

The acid-catalysed cyclisation of dimethanols is a versatile method for the preparation of novel macrocyclic systems. The generation of 16-membered ring macrocycle **182** was achieved *via* acid-catalysed condensation reaction of hydroxymethylindole **180** with diindolyl compound **181** in isopropanol in the presence of *p*-toluenesulfonic acid (Scheme 37).[74]

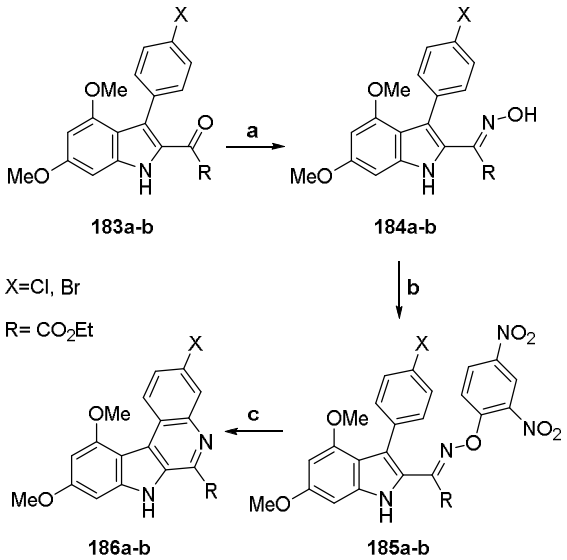


Scheme 37. Reagents and conditions: *p*-TsOH, i-PrOH, r.t., 1 h.

6. Indole fused-ring systems

There is enormous interest in developing new cyclisation reactions leading to novel molecular structures from activated indoles. The polycyclic structures based on indoles have received considerable attention due to their interesting biological properties such as antitumor, fungicidal, analgesic, anti-inflammatory, anthelmintic and antibacterial activities. The methoxy activated indole backbones have been utilized to produce a variety of five- and six-membered fused ring systems including isoxazolopyrroloquinolines, oxopyrroloquinolines, pyrroloquinolines and pyrroloindoles.

While the treatment of 2'-glyoxylic ester **183a** with hydroxylamine hydrochloride in absolute ethanol containing sodium acetate gave the corresponding indole oxime **184a**, the related indole oxime **184b** was obtained when the reaction was carried out in ethanol in the presence of pyridine under reflux overnight. Treatment of indole oximes **184a-b** with fluoro-2,4-dinitrobenzene in the presence of sodium ethoxide at 0°C for two hours yielded the expected indole oxime-ethers **185a-b** in high yields. Lastly, the cyclized product **186a-b** was obtained in good yields by treatment of the intermediate ethers **185a-b** with trimethylamine in tetrahydrofuran (Scheme 38).[75-76]

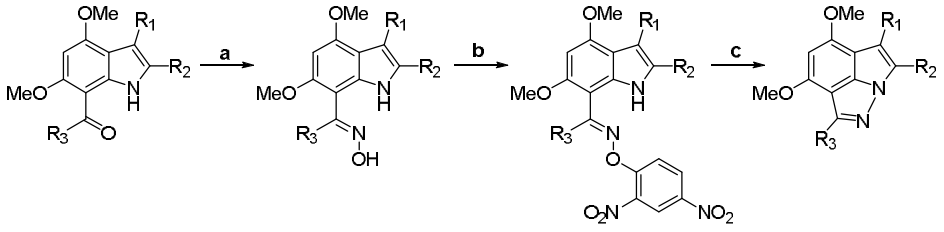


Scheme 38. Reagents and conditions: a) NH_2OH, HCl, EtOH; b) Na, EtOH, fluoro-2,4-dinitrobenzene; c) NEt_3, THF.

Treatment of 7-acyl-, 7-aroyl- and 7-glyoxyloyl-indoles **187a-f** with hydroxylamine hydrochloride and sodium hydroxide gave the indole-7-oximes **188a-f** which then were reacted with fluoro-2,4-dinitrobenzene to produce the indole oxime ethers **189a-f** in high yields. The cyclisation reaction of indole oxime ethers **189a-f** under basic conditions generated pyrroloindazoles **190a-f** (Scheme 39).[77-78]

Modified forms of the 4-oxopyrroloquinoline ring system have been found in alkaloids isolated from the Amaryllidaceae family and have received considerable attention. One pot synthesis of 4-oxo-4H-pyrrolo[3,2,1-ij]-quinolines **192** was achieved, while investigation of the Claisen-Schmidt condensation of indole-7-aldehydes **191** with carbonyl compounds gave α,β-unsaturated carbonyl compounds. The 7-formylindoles **191** have been reacted with ethyl acetate in the presence of sodium ethoxide to give 4-oxopyrroloquinolines **192** directly in high yields (Scheme 40).[79]

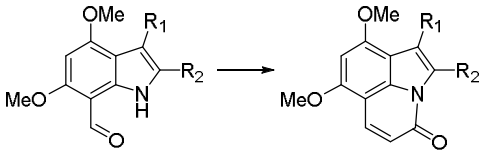
The 6-oxo analog **195** can be obtained by a simple route involving reaction of the 7-acetylindole **193** with diethyl oxalate and sodamide, followed by acid-catalyzed cyclisation of the intermediate glyoxylic ester **194** (Scheme 41).[19]



187a-f 188a-f 189a-f 190a-f

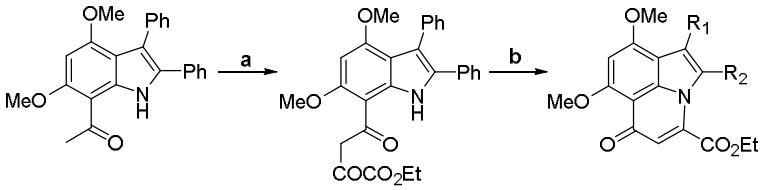
	R_1	R_2	R_3
a	4-BrC_6H_4	Me	Me
b	4-BrC_6H_4	H	Me
c	Ph	Me	4-ClC_6H_4
d	4-BrC_6H_4	Me	CF_3
e	4-BrC_6H_4	Me	CO_2Et
f	4-BrC_6H_4	Me	$CONMe_2$

Scheme 39. Reagents and conditions: a) NH_2OH. HCl, NaOH 10%; b) NaOEt, fluoro-2,4-dinitrobenzene; c) NEt_3 or NaH.



191 **192**

Scheme 40. Reagents and conditions: Ethyl acetate, NaOEt.



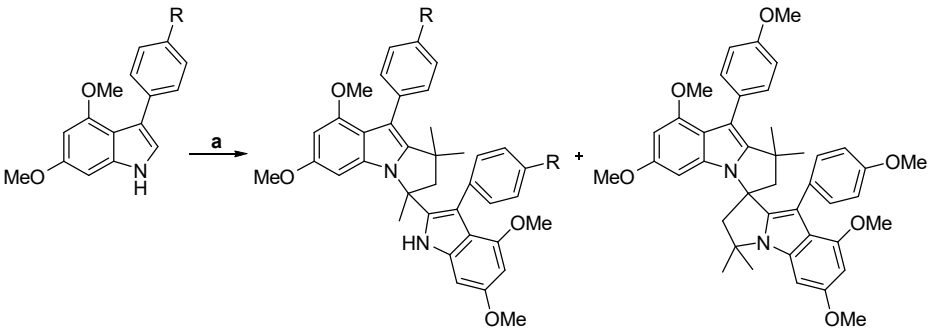
193 **194** **195**

Scheme 41. Reagents and conditions: a) Diethyl oxalate, $NaNH_2$; b) HCl, EtOH.

Yepuri *et al.* have recently reported that treatment of indoles **35** and **196** with acetone in the presence of sodium hydride and triflic anhydride produces pyrroloindoles **197** and **198** respectively. The more active indole **196** was also found to produce a 20% yield of the spiropyrroloindole **199** (Scheme 42).[80]

It has been reported that the reaction of activated indoles with aryl α,β-unsaturated ketones gave pyrroloindole systems. Heating methylindole **153** at reflux in isopropanol with chalcones **200a-d** and hydrochloric acid for two hours produced 9*H*-pyrrolo[1,2-*a*]indole **201a-d** (Scheme 43).[81]

Treatment of indole-7-carbaldehydes **202a-d** at room temperature with allyl bromide and potassium hydroxide in dimethylsulfoxide for 1 h afforded *N*-allyl derivatives **203a-d** in high yields. The indoles **203a-d** were heated under reflux in isopropanol with nitromethane and ammonium acetate for three hours to afford the corresponding-nitrostyrenes **204a-d** in 65-92% yield as red solids. The next step was the addition of the second alkene units in the preparation for the ring closing metathesis. Michael addition of allylmagnesium bromide to compounds **204a-d** under inert conditions in dry tetrahydrofuran yielded the compounds **205a-d**. The corresponding nine-membered ring precursors **206a-d** were produced upon treatment of indoles **204a-d** with butenylmagnesium bromide in dry THF (Scheme 44).[82]

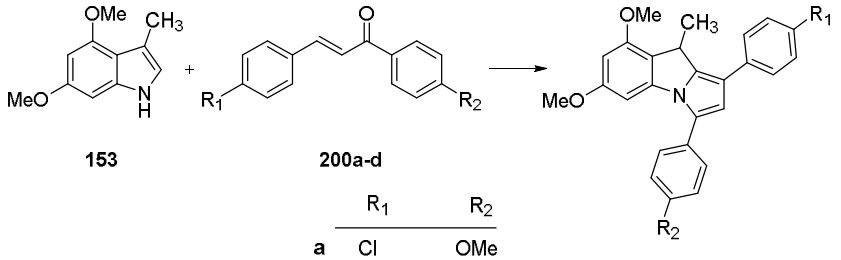


35 R= H
196 R=OMe

197 R=H
198 R=OMe

199

Scheme 42. Reagents and conditions: NaOH, acetone, triflic anhydride, reflux.



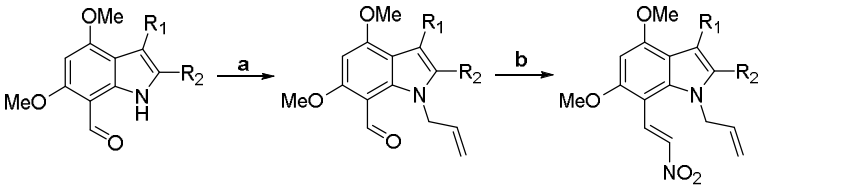
153

200a-d

	R_1	R_2
a	Cl	OMe
b	Cl	Me
c	OMe	Cl
d	Cl	Cl

201a-d

Scheme 43. Reagents and conditions: a) HCl reflux.

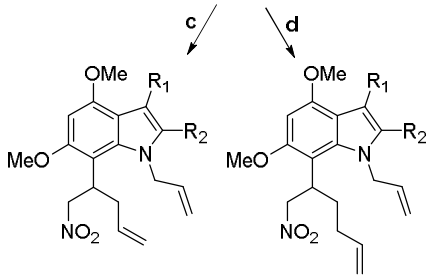


202a-d

203a-d

204a-d

	R_1	R_2
a	Ph	Ph
b	4-BrC_6H_4	H
c	4-ClC_6H_4	H
d	4-MeC_6H_4	H

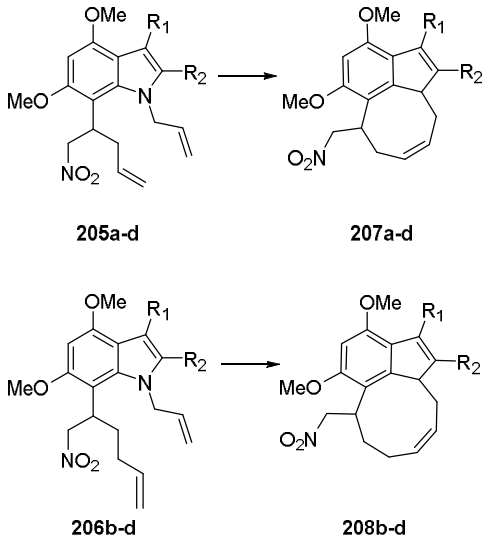


205a-d

206a-d

Scheme 44. Reagents and conditions: a) Allybromide, KOH, DMSO; b) CH_3NO_2, NH_4OAc; c) Allylmagnesium bromide, THF; d) Butenylmagnesium bromide, THF.

Ring closing metathesis of the Michael adducts **205a-d** and **206a-d** was performed by heating at reflux in dry, degassed toluene in the presence of 5-10 mol% of second-generation Grubbs catalyst. The reactions proceeded to completion within four hours and upon workup afforded the indole fused eight- and nine-membered ring compounds **207a-d** and **208a-d**, respectively (Scheme 45).[82]

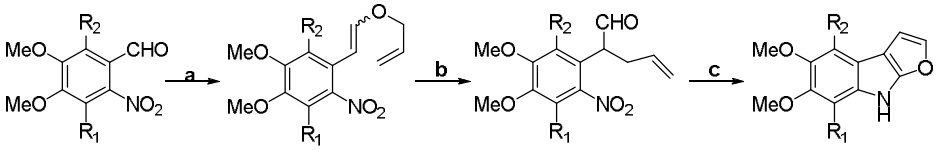


205a-d **207a-d**

206b-d **208b-d**

Scheme 45. Reagents and conditions: Grubbs catalyst.

Kulkarni *et al*. reported the successful application of a Wittig olefination–Claisen rearrangement protocol to synthesize methoxy-activated furano[2,3-*b*]indoles in four steps **212e**. The allyl vinyl ethers **210a-e** were generated by the reaction of *o*-nitrobenzaldehydes **209a-e** with allyloxy methylene triphenylphosphorane under basic conditions. Claisen rearrangement to the corresponding 4-pentenals **211a-e** was then achieved by heating at reflux in anhydrous xylene. The direct reduction of the nitro group under basic conditions yielded the desired furo[2,3-*b*]indoles **212a-e** (Scheme 46).[83]



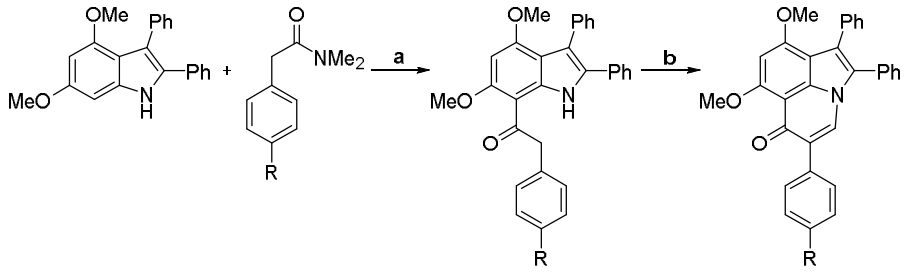
209a-e **210a-e** **211a-e** **212a-e**

Scheme 46. Reagents and conditions: a) *t*-BuONa, dry THF, $Ph_3PCH_2OCH_2CH{=}CHCl$; b) Dry xylene; c) MeOH, Na_2S, $NaHCO_3$.

The pyrroloquinolin-6-ones **217-218** were synthesised through electrophilic substitution of 2,3-diphenyl-4,6-dimethoxyindole **41** at C7 under acylation conditions. 2,3-Diphenyl-4,6-dimethoxyindole **41** was reacted with *N,N*-dimethylarylacetamides **213-214** in freshly distilled phosphoryl chloride at 70 °C for an hour to give 7-indolyldeoxybenzoins **215-216**, followed by cyclization with *N,N*-dimethylformamide dimethyl acetal in anhydrous THF at 160 °C for one day in a pressure tube to give the corresponding pyrroloquinolin-6-ones **217-218** (Scheme 47).[84]

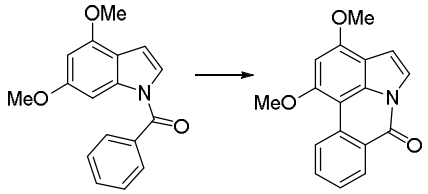
Since the C4 and C6 methoxy groups activate the C7 position, it was envisaged that the biaryl coupling reactions could be directed at C7 in preference to C2. Using this idea, a wide range of

N-benzoyl-4,6-dimethoxyindoles **219** could be converted directly into the corresponding pyrrolophenanthridones **220** in good yields (Scheme 48).[85]



41 **213** R=H, **214** R=OMe → **215** R=H, **216** R=OMe → **217** R=H, **218** R=OMe

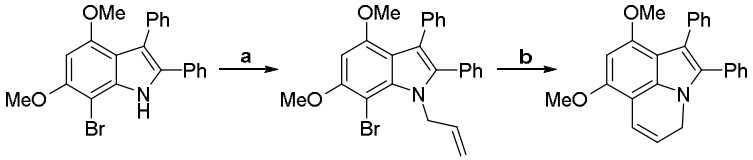
Scheme 47. Reagents and conditions: a) $POCl_3$, $CHCl_3$ b) *N,N*-Dimethylformamide, dimethyl acetal, THF, pressure tube.



219 **220**

Scheme 48. Reagents and conditions: $Pd(OAc)_2$, HOAc.

The reaction of 7-bromoindole **124** with allyl bromide in the presence of potassium hydroxide gave an intermediate **221.** This intermediate was then cyclized using Pd(II)acetate and tri-*o*-tolylphosphine to give pyrroloquinoline **222** (Scheme 49).[86]



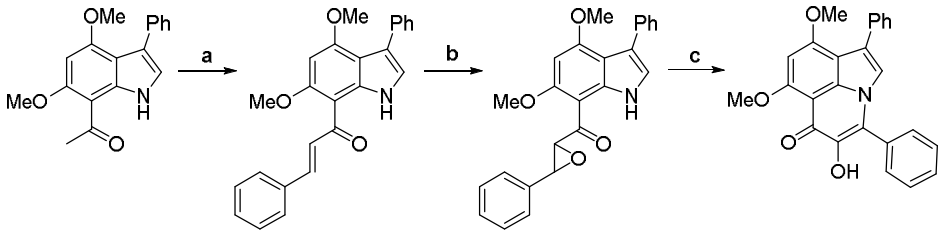
124 **221** **222**

Scheme 49. Reagents and conditions: a) Allybromide, KOH, DMSO; b) $Pd(AcO)_2$, tri-*o*-tolylphosphine.

In another study, the synthesis of pyrroloquinoline **226** as an indole analogue of flavonol was reported. 7-Acetyl-4,6-dimethoxy-3-phenylindole **223** was converted into 7-indolyl chalcone **224** by reaction with benzaldehyde under basic conditions. Oxidation of the chalcone **224** with alkaline hydrogen peroxide gave the epoxide **225**, which was cyclised to pyrroloquinoline **226** in the presence of potassium hydroxide (Scheme 50).[87]

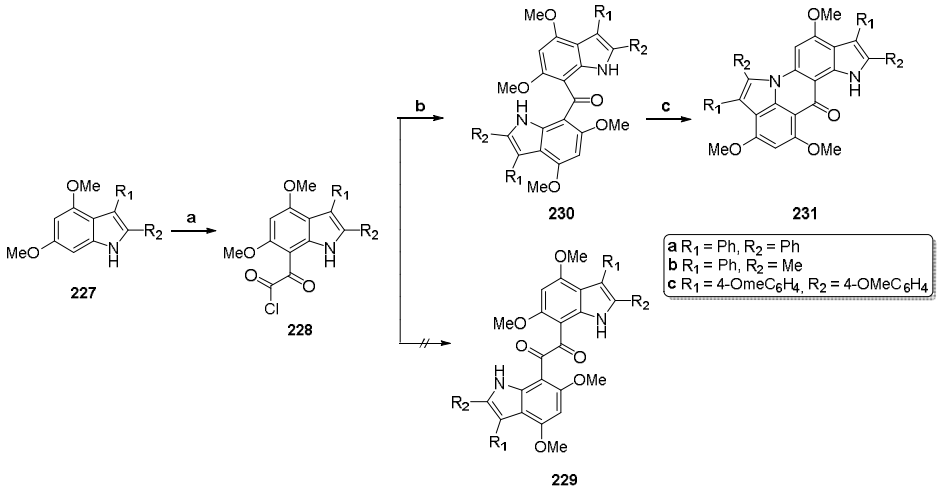
There are numerous examples where cyclisation between C7 and N1 leads to a new ring fused to the indole. However, an example of cyclisation from C7 to C6 is very rare. The indole **227** can be easily reacted with oxalyl chloride in dry tetrahydrofuran to give the 7-indolylglyoxylic acid chloride **228.** Consequently, the acylation of the indole **227** with the related glyoxylic acid chloride **228** resulted in formation of the symmetrical 7,7'-diindolylketone **230** in 52% yield, rather than the related diketone **229**. When the

diindolylketone **230** was heated under reflux in acetone with benzyltrimethylammonium hydroxide, the new dipyrrolo-acridone **231** was formed in 75% yield. The cyclisation reaction of the diindolylketones to form the acridinones presumably proceeds by formation of an indolyl anion, followed by its Michael-type addition to what is effectively an unsaturated ketone to generate a cyclic intermediate which loses methanol so as to restore the aromaticity of the structure (Scheme 51).[88]



223 **224** **225** **226**

Scheme 50. Reagents and conditions: a) Benzaldehyde, $NaNH_2$; b) H_2O_2; c) KOH.



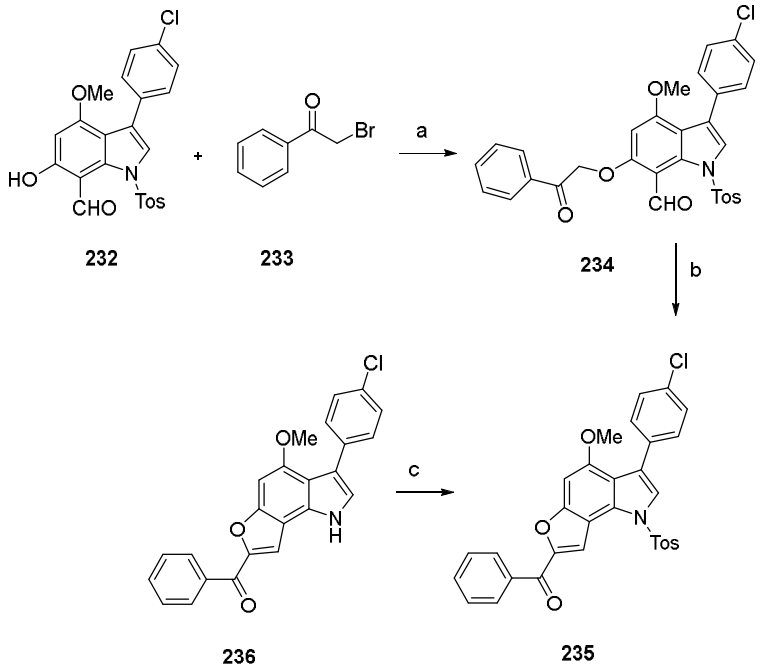
227 **228** **230** **231** **229**

Scheme 51. Reagents and conditions: a) ClCOCOCl, benzene; b) Graphite powder, 1,2-dichloroethane, reflux; c) Benzeyltrimethylammonium hydroxide, acetone, reflux.

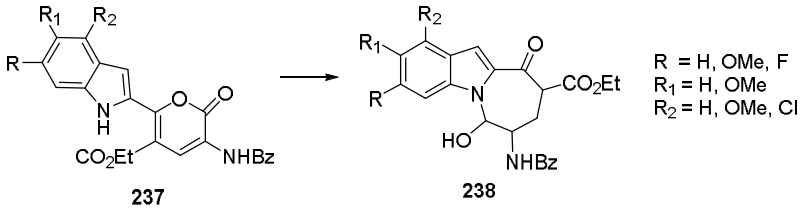
Additionally, the cyclisation between C7 and C6 leads to formation of furano[2,3-g]indoles. Treatment of tosyl protected indole **232** with α-bromoacetophenone **233** in acetone and potassium carbonate generated the corresponding indole **234** which then cyclised in trifluoroacetic acid to form the tosyl protected furoindole **235**. Finally, the tosyl group was easily removed by treating the tosyl derivative **235** with crushed potassium hydroxide in refluxing methanol, yielding the furoindole **23**6 (Scheme 52).[89]

Gelmi *et al*. reported the intramolecular condensation of 3-benzoylamino-6-(indolyl)-pyran-2-ones **237** upon treatment with potassium carbonate in refluxing acetonitrile to afford the corresponding azepino[1,2-a]indole-6-ones **238** (Scheme 53).[90]

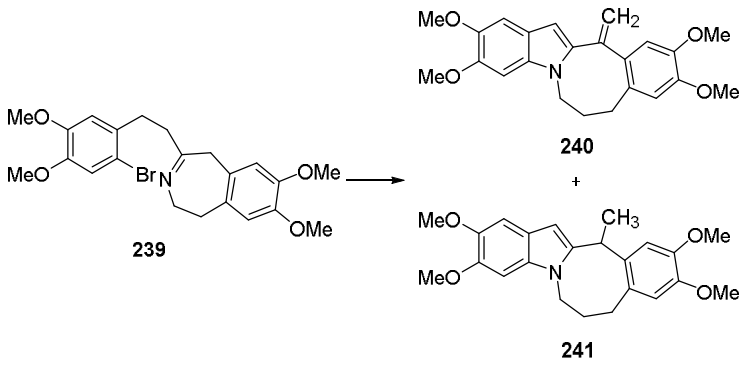
A quite different alternative approach to indole fused ring systems is *via* formation of the indole ring itself. This is illustrated by the synthesis of the indolo[1,2-a][3]benzazocines **240** and **241** in 43 and 8% yields, respectively, by the treatment of the benzazepine **239** with dimsylsodium in DMSO. The mechanism involves the attack by the $MeSOCH_2$ anaion at C1, followed by a ring closure-ring cleavage process (Scheme 54).[91]



Scheme 52. Reagents and conditions: a) K_2CO_3, acetone, reflux, overnight; b) TFA, reflux, 5 h; c) KOH, MeOH, reflux, 3 h.

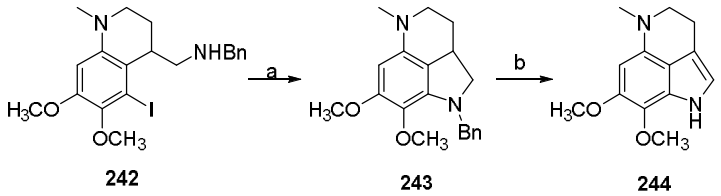


Scheme 53. Reagents and conditions: K_2CO_3, CH_3CN.



Scheme 54. Reagents and conditions: $MeSOCH_2$, DMSO.

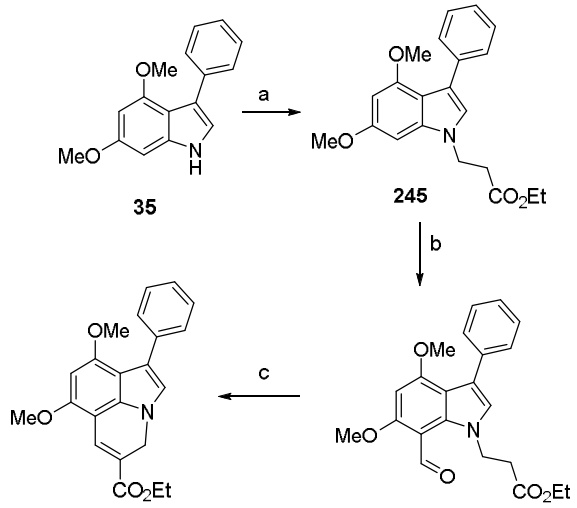
The synthesis of tetrahydropyrroloquinoline ring systems was reported by Buchwald and Peat in 1996. Reaction of **242** with $Pd_2(dba)_3$, P(o-tolyl)$_3$, and NaO*t*Bu at 80°C cleanly afforded the tricyclic heterocycle **243**, which was treated with 10 mol% Pd/C in the presence of ammonium formate to give **244**. The latter was then used as intermediate for the total synthesis of makaluvamine C and of damirones A and B (Scheme 55).[92]



242 **243** **244**

Scheme 55. Reagents and conditions: a) 2,5 mol% $Pd(dba)_3$, P(o-tolyl)$_3$, NaOtBu; b)10 mol% Pd/C, HCO_2NH_4, MeOH, reflux.

The method for the synthesis of pyrroloquinolines was also developed by Jumina *et al*. employing 4,6-dimethoxyindole scaffolds. Treatment of indole **35** with 2.5 equivalents of potassium hydroxide in dimethyl sulfoxide in the presence of potassium iodide, followed by the addition of 2.5 equivalents of ethyl 3-bromopropanoate gave alkylindole **245** in 46% yield. The compound **245** was then subjected to Vilsmeier-Haack formylation to afford formylindole **246** in 53% yield. Finally, formylindole **246** underwent an intramolecular aldol condensation under the influence of DBU in refluxing acetonitrile to form pyrroloquinoline **247** in 69% yield (Scheme 56).[93]



35 **245** **247** **246**

Scheme 56. Reagents and conditions: a) $BrCH_2CH_2CO_2Et$, KOH, DMSO, KI b)$POCl_3$, DMF c) DBU. MeCN.

7. Biological applications of methoxyindoles

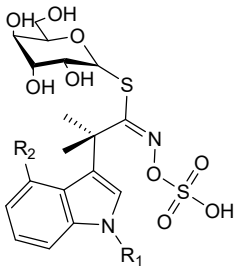
Indole heterocyclic systems with the methoxy substitutions on different locations are biologically valuable scaffolds that occur in many natural alkaloids and considerable effort has been devoted to the synthesis of complex and pharmacologically active indole alkaloids. Such compounds have been reported

for various biological activities such as antimicrobial, anticancer, anti-inflammatory, antidepressant, anti-tubercular, antioxidant, and anti-cholinesterase activities. We discuss the biological applications of methoxyindoles in this section.

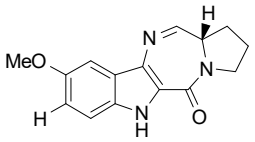
7.1. Anticancer activity

The indole-3-ylmethylglucosinates (IMG) **248** have been isolated from cruciferous plants as secondary metabolites. The IMG and their breakdown products that occur through the enzymatic reactions induced by the synthesis of phase-1 detoxifying enzymes, may in some cases prevent carcinogenesis. Epidemiological studies have reported the positive anticarcinogenic effects of a diet rich in cruciferous vegetables on the colon, rectum and lung cancer risk.[94-96]

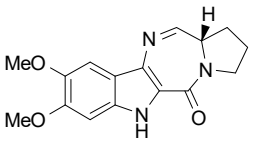
The design and synthesis of compounds that are structurally related to naturally occurring indoles has allowed the investigation of several new indole systems as potential drug targets. Specifically, the two cytotoxic analogues **249** and **250** of the novel pyrrolo[1',2':1,2][1,4]diazepin[7,6-*b*]indol-5(6*H*)-one nucleus, similar to the natural product anthramycin, have been prepared by Tsonitis and co-workers and shown micromolar potency in the human leukemic K_{562} cell line.[97]



248



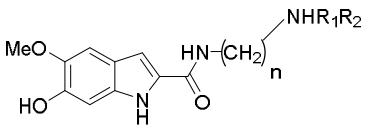
249



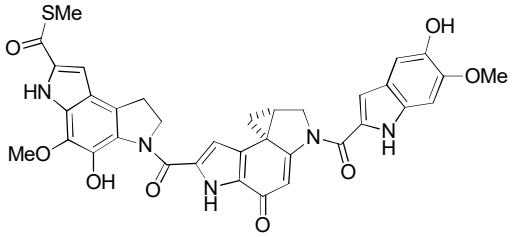
250

Tsotinis *et al*. reported the synthesis and cytotoxic evaluation of mono methoxyindole derivatives **251** against the NSCLC-N16-L16 human non-small cell lung cancer cell line. Some of the analogues showed promising cytotoxic activity, with the most effective compound having an IC_{50}value of 13.9 μM.[98]

Yatakemycin is a member of the duocarmycin family of natural products and is an extremely important compound containing a dimethoxyindole fragment with a range of pharmacological activities. The compound was reported as an extraordinarily toxic DNA alkylating agent with potent antimicrobial and antitumor properties. It was thought that the nucleotide-excision repair (NER) pathway is the mechanism of action for the removal of bulky DNA lesions from the genome.[99] Yatakemycin was also found to be a potent inhibitor for the growth of pathogenic fungi such as *Aspergillus fumigatus* and *Candida albicans* with the MIC values of 0.01-0.03 microg/ml being more potent than amphotericin B (MIC: 0.1-0.5 microg/ml) or itraconazole (MIC: 0.03-0.2 μg/mL).[100]

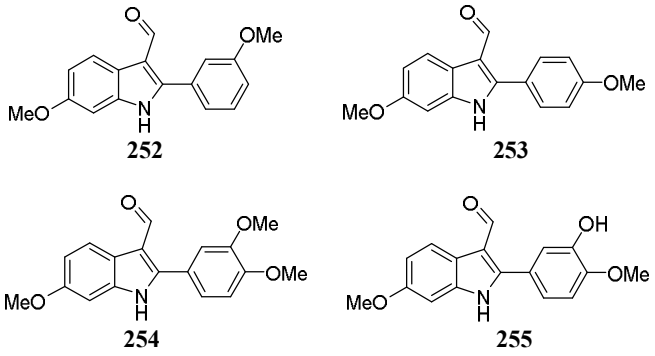


251



(+)-Yatakemycin

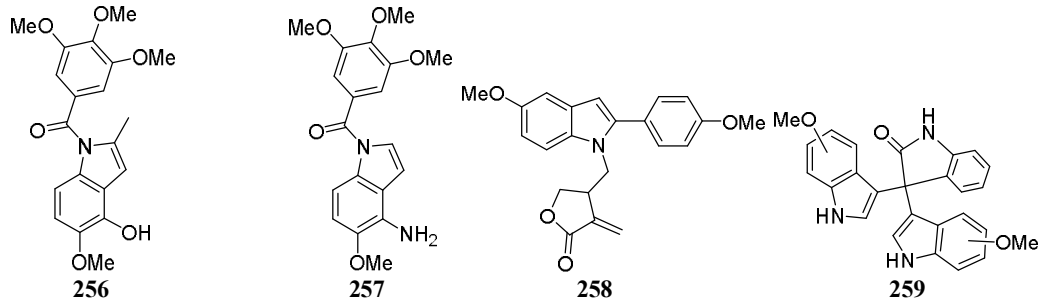
The antimitotic activities of 2-phenylindole-3-carbaldehydes **252-255** towards human breast cancer cells (Figure 31) have been evaluated by Kaufmann *et al*.[101] Two breast cancer cell lines, MDA-MB-231 and MCF 7, were used for the detection of anti-proliferative activity of 2-phenylindole-3-carbaldehydes. The designated compounds were also reported for the inhibition of tubulin polymerization with the interactions of the colchicine binding site. These properties caused the apoptotic death of cells due to cell cycle arrest in the G2/M phase.



Liou *et al.* have synthesised the 1-aroyl-7-methoxyindole systems and evaluated their properties as cytotoxic and antitubulin agents.[102] The antitubulin potencies of 4-hydroxy and 4-amino-1-aroylindoles **256** and **257** were found to be as potent as the standards colchicine and combretastatin A-4 with IC_{50} values of 0.9 and 0.6 μM, respectively. The antiproliferative activities of designated compounds were tested against a panel of human cancer cells and the values were found to be in the ranges of 1.2-5.4, and 0.3-0.6 nM, respectively.

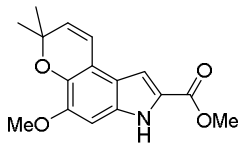
The novel indole α-methylene-γ-lactones **258** have been reported as potent inhibitors for AKT-m TOR signaling pathway kinases by Ding *et al*.[103] The inhibition activity is implicated by the unsubstituted γ-position of the lactone and a methoxy substituent on the phenyl ring.

Recently, Kamal *et al*. reported the synthesis of 3,3-diindolyl oxyindoles with ferric chloride catalysis and their *in vitro* evaluation towards five human cancer lines for the detection of cytotoxic efficiencies.[104] The compounds **259** with the methoxy substitutions on different locations (C4, C5 and C6) of the indole moiety were found to be selectively potent against the prostate cancer DU-145 cell lines with IC_{50} values of 5, 2.2, 1.2 μM.



Bingul *et al*. have developed a suitable methodology for the preparation of novel methoxy substituted dihydropyranoindoles *via* the Hemetsberger indole synthesis using azido-phenylacrylates, derived from the reaction of corresponding alkynyl-benzaldehydes with methyl azidoacetate, followed by thermal cyclization in high boiling solvents.[105] Anti-cancer activity of all the newly synthesized compounds was evaluated against the SH-SY5Y and Kelly neuroblastoma cells as well as the MDA-MB-231 and MCF-7 breast

adenocarcinoma cell lines. The SAR analysis revealed that location of the dihydropyran ring on the benzene ring was important for the cytotoxic efficiency of tricyclic dihydropyranoindoles. The compounds **260**, an example of the dihydropyrano[3,2-e]indole system, was found to be more potent against both neuroblastoma cells (Kelly and SH-SY5Y) than the dihydropyranoindole **261** which is a member of the dihydropyrano[2,3-g]indole scaffold.



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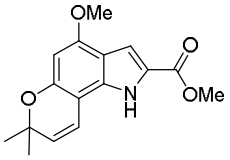
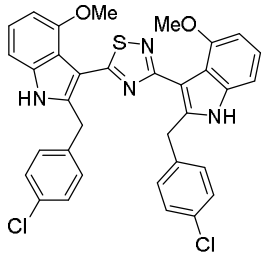


261

A range of human cancer cell lines has been used for the detection of anticancer potency of the compound 1-(4-chlorobenzyl)-3-(5-(1-(4-chlorobenzyl)-4-methoxy-1*H*-indol-3-yl)-1,2,4-thiadiazol-3-yl)-4-methoxy-1*H*-indole **262** reported by Kumar *et al*. The potential of the designated compound was found to be as potent as the standards.[106]

The cytotoxicity potency of methoxy substituted indolopyrrolemaleimides has been evaluated against several human cancer cell lines by Xu *et. al*.[107] The compound **263** demonstrated a moderate anticancer activity.



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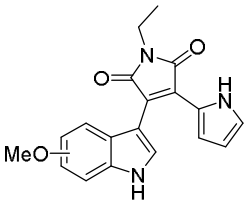
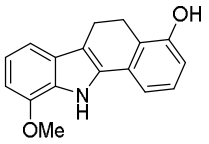


263

Hong *et al*. have synthesised a range of tricyclic and tetracyclic indoles and evaluated their anticancer activity.[108] The highest in vitro activities against human nasopharyngeal carcinoma (HONE-1) and gastric adenocarcinoma (NUGC-3) cell lines have been demonstrated by the compounds **264** and **265**.



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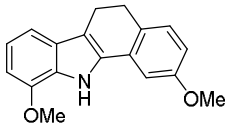
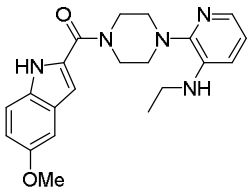


265

7.2. Anti-HIV activity

Ateviridine **266** is a marketed drug containing an indole nucleus and the therapeutic uses have been reported as a non-nucleoside reverse transcriptase inhibitor for the treatment of HIV.[109]

The compounds, (*E*)-4-(1-(3-chloro-5-fluorobenzyl)-4-methoxy1H-indol-3-yl)-2-hydroxy-4-oxobut-2-enoic acid **267**, (*E*)-4-(1-(4-chlorobenzyl)-4-methoxy-1*H*-indol-3-yl)-2-hydroxy-4-oxobut-2-enoic acid **268**, and (*E*)-4-(1-(4-chloro-3-fluorobenzyl)-4-methoxy-1*H*-indol-3-yl)-2-hydroxy-4-oxobut-2-enoic acid **269** have been determined as new HIV inhibitors (integrase strand-transfer inhibitors) towards Elvitegravir by molecular docking as well as biological studies.[110]



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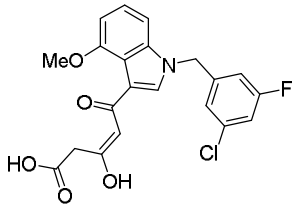

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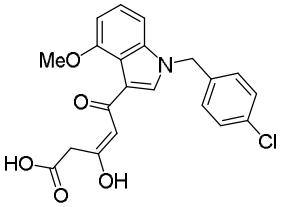

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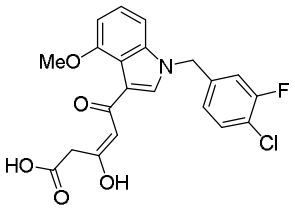

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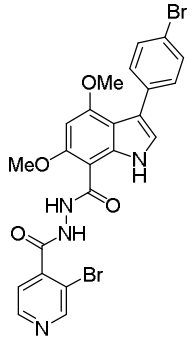
7.3. Antibacterial activity

The methoxy substituted indoles have been been used for the inhibition of transcription initiation in bacteria. A range of *N*,*N*'-disubstituted hydrazines **270**, **271** and imine-carbohydrazides incorporating dimethoxyindole systems **272-274** have been prepared and evaluated for the capability of inhibiting the *β*′-CH region-σ^{70}/σ^{A} interaction in ELISA at 15 μM.[111]



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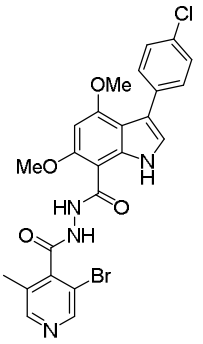

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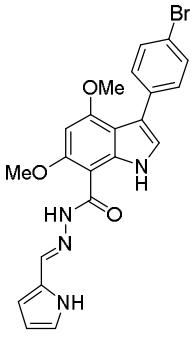

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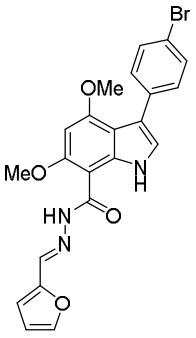

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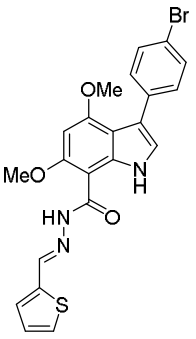

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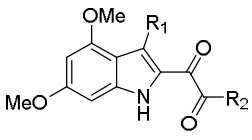
The determination of growth inhibition of *B. subtilis* and *E. coli* in culture at 200 μM has also been examined. The compounds with the hydrazine functionality and the pyridine substitution at the C7 position were found to be the most active inhibitors for *B. subtilis* and *E. coli* growth. In addition, the dimethoxyindoles with the imine carbohydrazide functionality demonstrated better inhibition potency against *E. coli* than *B. Subtilis.*

Mielczarek *et al*. have also carried out similiar research to target transcription initiation in bacteria and several dimethoxy substituted indole systems **275** and **276** have been prepared by the reaction of indole-2-, and indole-7-glyoxyloyl chlorides with amines and hydrazines to afford the targeted corresponding glyoxyloylamides and glyoxyloylhydrazides.[112] The capability of inhibiting the *β*′-CH region-σ^{70}/σ^{A} interaction of the synthesised compounds was determined by ELISA and reported the growth inhibition of both Gram-positive and Gram-negative bacteria in culture.



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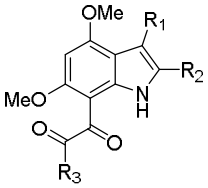
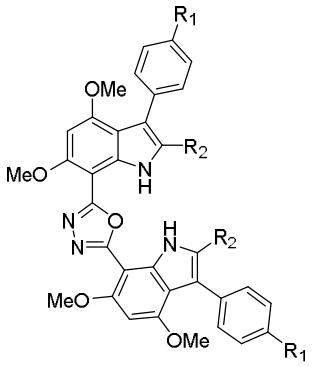


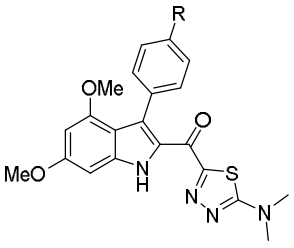
276

In another work, indole-7-glyoxyloylchlorides and 7-trichloroacetylindoles were used for the cyclodehydration reaction with phosphoryl chloride in ethyl acetate to produce 2,5-di(7-indolyl)-1,3,4-oxadiazoles **109-111** and a 2,2'-bi-1,3,4-oxadiazolyl. In addition, the synthesis of 2- and 7-indolyl 2-(1,3,4-thiadiazolyl)ketones **277** from related indolyl-hydrazine carbothioamides was also achieved by the same protocol. The biological aspects of the synthesised compounds were exhibited by the evaluation of their antimicrobial and antibacterial potencies. The inhibition of RNA polymerase enzyme as well as the Gram positive *Bacillus subtilis* and Gram negative *Escherichia coli* bacteria were chosen as the biological target for this study.[34]

The synthesis of 7,7'-, 2,2'-, 2,7'-linked bis-indole derivatives **278-280** with –CO–NH–NH–CO– and –CO–CO–NH–NH–CO– linkers was determined as another target to design new inhibitors of bacterial transcription initiation complex formation by the exhibition of essential interaction between bacterial RNA polymerase and σ^{70}/σ^{A}. The targeted molecules have been evaluated for activity against the *β*′-CH-σ^{70}/σ^{A} interaction in ELISA assays and inhibition potency for both Gram-positive and Gram-negative bacteria growth.[113]



109-111



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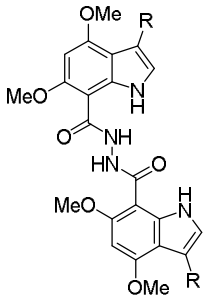

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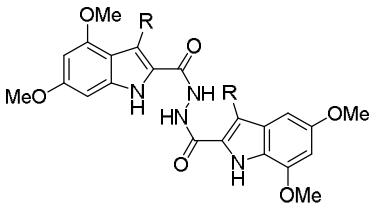

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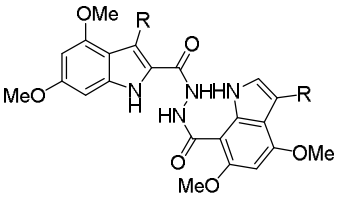
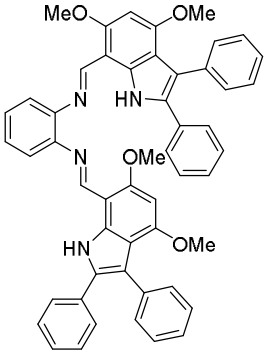


280

7.4. Anticholinesterase activity

The 4,6-dimethoxy-2,3-diphenylindole carbaldehyde system was used for the synthesis of bis-indolyl imine helical structures, *e.g.* **281**, by the Schiff base reaction with different *o*-phenyl diamines as bridges. The anticholinesterase potency was evaluated as the biological aspect of the synthesized compounds against the acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes. The highest inhibition was determined for compound **281** with the values of 89.21 and 96.06, better than standard galanthamine, for AChE and BChE, respectively.[114]

Also, the hydrazide-hydrazone (–(C=O)NHN=CH) functionality was located at two different positions on the 4,6-dimethoxyindole moiety to generate the novel 4,6-dimethoxyindole hydrazide hydrazones **282** and **283**.



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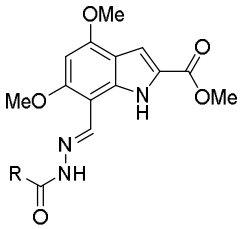

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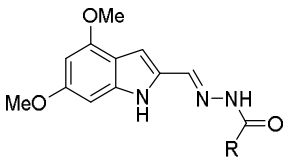

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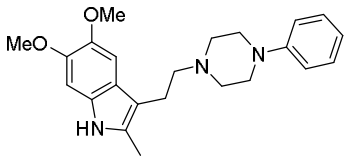
The condensation reactions of indole hydrazones, derived from the corresponding indole carbaldehydes and carboxylic acids in the presence of amide coupling reagent (EDC) was employed to produce the target compounds.[115] The anticholinesterase potency was investigated towards the acetyl- and butyrylcholinesterase enzymes (AChE and BChE) and molecular modelling studies were carried out to exhibit a complementary determination of biological potency. The biological study was found to be compatible with the molecular modeling study and the highest inhibition was determined in the presence of phenyl substitution with values of 83.31 and 73.55 for AChE and BChE, respectively.

7.5. Antidepressant activity

Oxypertine **5** is another marketed drug and hybrid molecule of the dimethoxyindole system and phenylpiperazine class and is used as an antipsychotic and antidepressant agent for the treatment of schizophrenia.[116]

The antidepressant activity of the methoxyindole aminoketoxime **284** has been evaluated by Abele *et al*. and found to be highly effective.[117]



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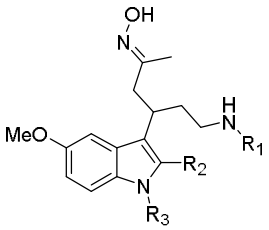
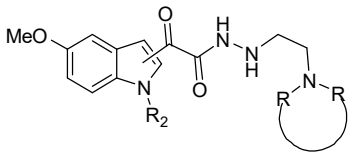


284

7.6. Antihistaminic activity

The antihistaminic activity of some methoxyindole-amide derivatives **285** has been examined by Battaglia *et al.* and their ability to antagonize histamine induced cutaneous vascular permeability in rats has been reported.[118]



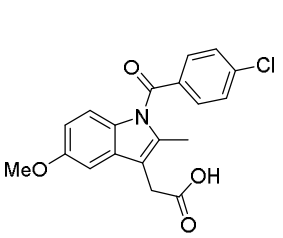
285

7.7. Anti-inflammatory activity

Indometacin or indomethacin **4** is a non-steroidal anti-inflammatory drug (NSAID) and prescribed for the reduction of fever, pain, stiffness, and swelling. The mechanism of action is known as the inhibition of prostaglandin production.[119,120]

Özdemir *et al.* have synthesised a range of indole-based chalcone derivatives such as **286** and evaluated COX-1 and COX-2 inhibition potency. The best candidate has been reported as the compound 3-(5-methoxy-1*H*-indol-3-yl)-1-(4-(methylsulfonyl)phenyl)prop-2-en-1-one **286**.[121]

The compound 5-methoxy-3-(3-phenylacryloyl)-1*H*-indole-2-carboxylic acid **287** has been generated by Prajapati *et al*. and investigated for anti-inflammatory activity.[122] The maximum inhibition efficiency has been determined with the value of 64.2% at 50 mg/kg.



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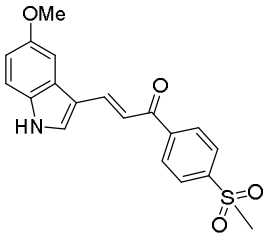

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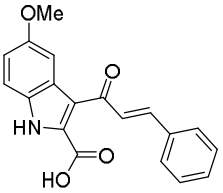
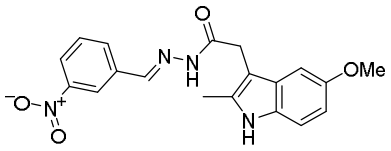


287

Bhat *et al.* have synthesised the compound (*E*)-*N*'-(3-nitrobenzylidene)-2-(5-methoxy-2-methyl-1-indol-3-yl) acetohydrazide **288** and investigated it for cyclooxygenase expression, lipid peroxidation, ulcerogenic, analgesic, and anti-inflammatory activities. The compound has been found to be a good candidate for analgesic and anti-inflammatory activity.[123]

The compound 1,2-disubstituted-5-methoxyindole/benz(g)indole-3-acetic acid **289** has been prepared by Kalaskar *et al*. and reported to show potent anti-inflammatory activity.[124]

The methoxy substituted indole oxime derivative **290** has been prepared by Abele *et al*. and reported as a potential agent for analgesic and anti-inflammatory activity.[125]



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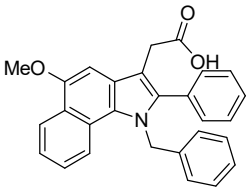

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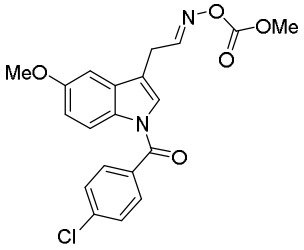
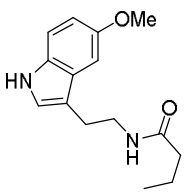


290

7.8. Antimalarıal activity

The antimalarial activities of *N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)butyramide **291**, *N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)hexanamide **292**, and *N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-2-phenylacetamide **293** have been evaluated against *Plasmodium falciparum* and these compounds have been found to be very active at low concentration by Schuck *et al*.[126]



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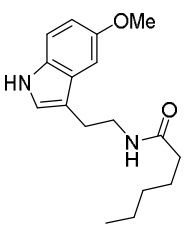

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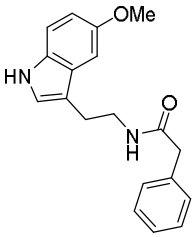
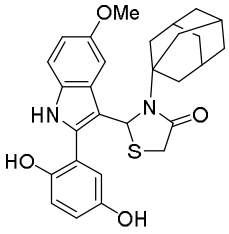


293

7.9. Anti-Parkinson activity

The compound 3-adamantyl-2-(2-(2,5-dihydroxyphenyl)-5-methoxy-1*H*-indol-3-yl)thiazolidin-4-one **294** has been synthesised and evaluated for anti-Parkinsonian activity by Kumar *et al.*[127] The compound demonstrated a potent inhibition as a Parkinsonian agent.



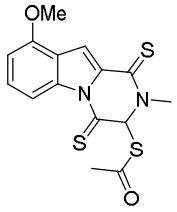
294

7.10. Antimicrobial activity

Gliotoxin **295**, a methoxy substituted analogue of pyrazino[1,2-*a*]indole-1,4-diones, was reported as a selective inhibitor of geranyltransferase I. The desigated compound is also known as an epidithiodiketopiperazine mycotoxin with immunosuppressive and antimicrobial activity.[128-130]

The synthesis of a range of methoxy substituted 2- and 3-arylindoles **296** and **297** was achieved by Leboho *et al.* and investigated for antibacterial and antifungal potencies.[131] The evaluation for antimicrobial activity was carried out by using the minimum inhibitory concentration (MIC) assay and the test organisms were chosen as Gram-positive (Staphylococcus aureus ATCC 6538 and Bacillus cereus ATCC 11778), Gram-negative (Escherichia coli ATCC 8739 and Klebsiella pneumoniae ATCC 8739) and yeasts (Candida

albicans ATCC 10231 and Cryptococcus neoformans ATCC 90112). The results indicated that the 5-methoxyindoles with the phenyl substitution on the C2 and C3 positions were the most potent compounds against the Gram-positive pathogens (S. aureus and B. cereus).



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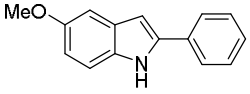

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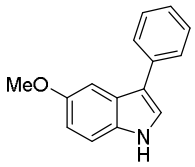
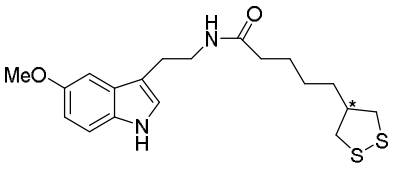


297

7.11. Antioxidant activity

Buyukbingol *et al*. reported the synthesis of indole-lipoic acid derivatives **298** and **299**, which posses significant antioxidant properties.[132] The antioxidant properties of target compounds were investigated measuring rat liver microsomal, NADPH dependent lipid peroxidation inhibition. The analog with the amide linker at position 3 of the indole ring has been found to be highly effective in inhibiting lipid peroxidation as compared to α-lipoic acid.



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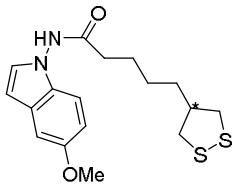
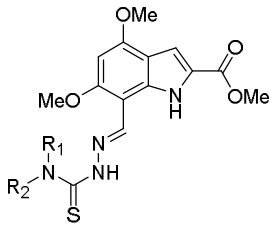


299

Two sets of novel dimethoxyindole-based thiosemicarbazone systems **300** and **301** have been prepared by the Schiff base condensation reaction of indole carbaldehydes with a range of thiosemicarbazides.[133] The antioxidant properties of the synthesised compounds have been determined by employing three different assays, namely 2,2-diphenyl-1-picrylhydrazyl hydrate–free radical scavenging, ABTS [2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)] cationic radical decolarization and cupric ion reducing antioxidant capacity. Moreover, the anticholinesterase properties of the products have also been investigated by acetylcholinesterase and butyrylcholinesterase enzyme inhibition assays.



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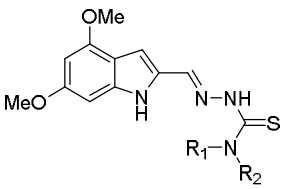
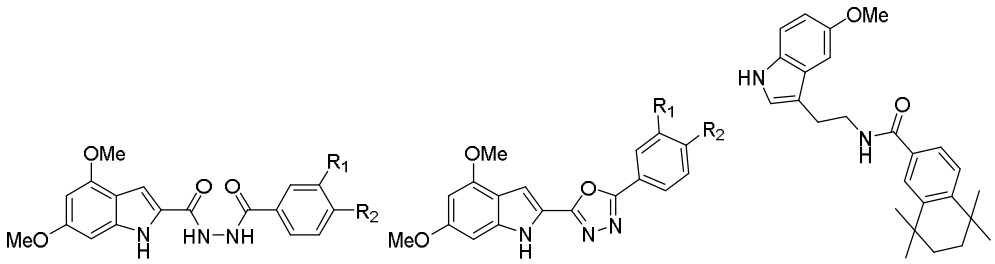


301

In another work, methyl 4,6-dimethoxy-1*H*-indole-2-carboxylate has been used for the synthesis of novel 4,6-dimethoxy-1*H*-indole-2-carbohydrazides **302** which underwent cyclodehydration to generate the corresponding 2-(indol-2-yl)-1,3,4-oxadiazole scaffold **303**. Biological aspects of all the novel compounds have been exhibited by the evaluation of antioxidant properties with three diferent assays. The anticholinesterase properties have also been evaluated by the acetylcholinesterase and butyrylcholinesterase

enzyme inhibition assays. In general, the indole compounds possessing carbohydrazide functionality were found to be more promising antioxidants than the 2-(indol-2-yl)-1,3,4-oxadiazole systems. However, important activity was obtained in the anticholinesterase enzyme inhibition assays in the case of 2-(indol-2-yl)-1,3,4-oxadiazole derivatives **303**.[134]

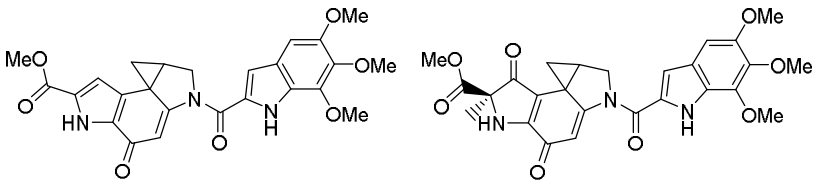
The melatonin retinamide systems derived from the hybridization of melatonin and tetrahydrotetramethylnaphthalene carboxylic acid have been reported by Ates-Alagoz *et al*. and evaluated for the antioxidant activity. The compound *N*-(2- (5-methoxy-1H-indol-3-yl)ethyl)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-2-carboxamide **304** has been shown as a weaker DPPH inhibitor but strong lipid peroxidation inhibitior.[135]



302 **303** **304**

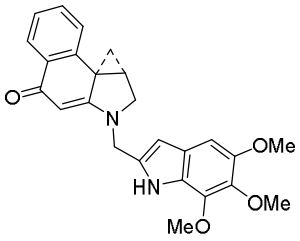
7.12. Antitumor activity

The duocarmycins **305** and **306** have been determined as potent antitumor antibiotics due to the sequence selective alkylation properties on the duplex DNA biomolecules. The preparation and evaluation of the 2-hydroxymethyl-5,6,7-trimethoxyindole fragment **307** have been reported by Boger *et al*. with the replacement of a methylene group for the amide linking of the duocarmycins. The selective alkylation capability of the synthesised compound on duplex DNA biomolecules has been found to be less than that for the molecules with the amide linkage functionalities and highlighted a fundamental role of this fragment in DNA alkylation catalysis.[20]



(+) duocarmycin SA
305

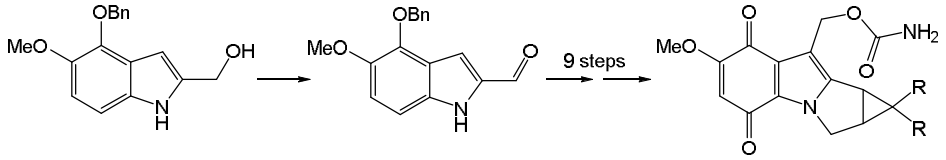
(+) duocarmycin A
306



307

The cyclopropamitosene **310** (7-methoxy-1,2-cyclopropapyrrolo[1,2-a]indoles), which is structurally similar to mitomycin C146, a compound with clinically important antitumor activity, was prepared by the

oxidation of 2-hydroxymethylindole **308** to form 4-benzyloxy-5-methoxyindole-2-carbaldehyde **309**. The biological investigations proved the potential efficiency of the designated compound for the cytotoxic activity (Scheme 57).[136]

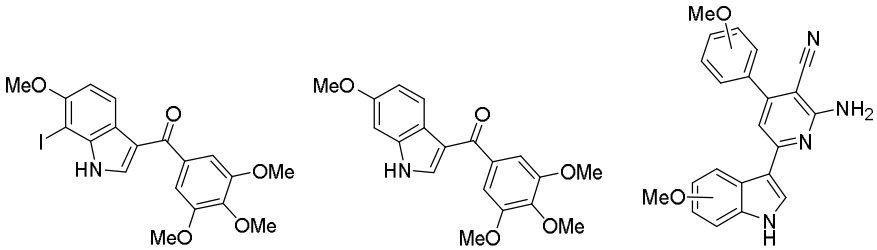


308 **309** **310**

Scheme 57. Reagents and conditions: MnO_2, CH_2Cl_2.

The cytotoxic potency evaluation of hydroxylated and *O*-demethylated phase I metabolites of antitumor agent 6-methoxy-3-(3′,4′,5′-trimethoxy-benzoyl)-1*H*-indole was carried out by Wu *et al*. The 6-methoxy substituted derivatives **311** and **312** demonstrated the cytotoxic efficiency at the level of nanomolar concentration while the iodo derivative was found to be more active against the KB, H460, and HT-29 cell lines with the IC_{50} reaching picomolar potency.[137]

The anti-tumor activity of some 2-amino-3-cyano-6-(1*H*-indol-3-yl)-4-phenylpyridine derivatives has been examined by Zhang *et al*. and the compound **313** with the methoxy substitution on the indole ring was found to be active againt various cell lines.[138]



311 **312** **313**

7.13. Receptor inhibitors

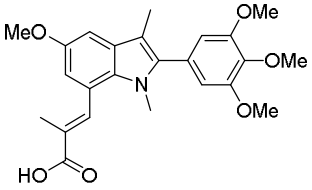
A series of substituted indole derivatives has been synthesized and evaluated as IL-1 generation inhibitors by Tanaka *et al*. The methoxy substituted indole **314** has been found to be a potent inhibitor of IL-1 generation.[139]

Endothelin has been found to be responsible for diseases such as renal failure, pulmonary hypertension, cerebral ischemia and vasospasm, endotoxic shock, and congestive heart failure.[140] The major portion of vasoconstrictor activity for endothelin in human vessels is mediated by the Endothelin A receptor. Biologically active scaffolds such as 1,3-diarylindole-2-carboxylic acids **315** are potent non-peptide endothelin antagonists and act as vasoconstrictors for many human diseases.[141]

7.14. Tubulin inhibitors

The methoxy substituted indole systems have been determined as potent tubulin polymerization inhibitors. The 2-aroylindoles **316** and **317** were prepared and found to be highly effective anti-tumor agents against paclitaxel-resistant cells.[142] Von Angerer *et al*. synthesised 2-phenylindole derivatives and the compound **318** was found to be very potent for the microtubule assembly blockage.[143]

The heterocombretastatin **319**, and 2,3-diarylindoles which are structurally related to the natural product combretastatin, were described by Medarde.[144] The tubulin polymerization inhibitory activity of 2,3-diarylindole **320** and 2-aryl-3-arylcarbonylindole **321** were reported by Flynn *et al.*[145]



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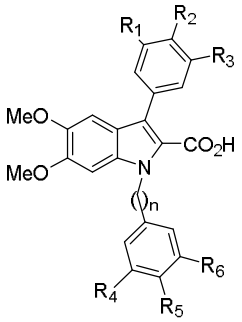

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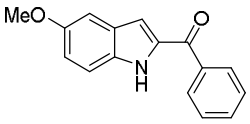

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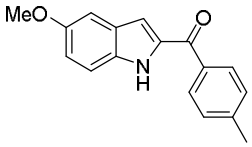

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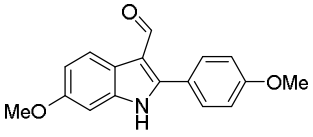

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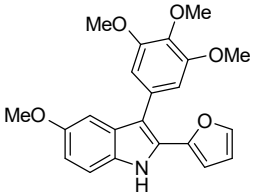

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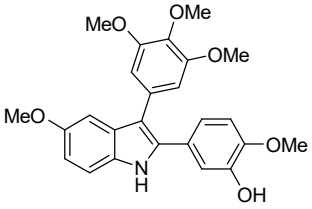

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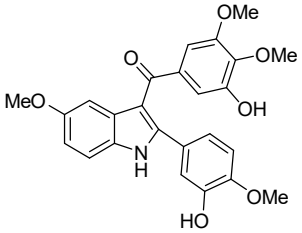
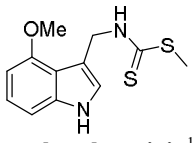


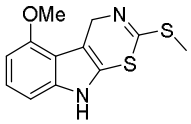
321

8. Methoxyindole containing natural products

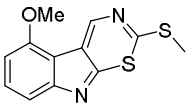
Phytoalexins are members of natural products containing an indole heterocyclic moiety and derived from (*S*)-tryptophan by the biochemical processes in plants. They have a crucial role for plant defence during a microbial attack by pathogens. In addition to their antimıcrobial behaviour, a range of cytotoxic activity has been reported for these structures.[146] The methoxy substituted indole examples of Phytoalexins are shown in this section.



4-methoxybrassinin[147]



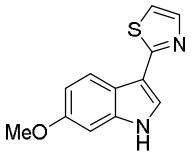
4-methoxycyclobrassinin[148]



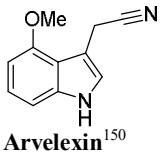
4-methoxydehydrocyclobrassinin[148]

The 135 species of *Rauwolfia*, a genus of the Apocynaceae family, show traditional usage as emetics, cathartics and expectorants for treating dropsy.[153-157] The *Rauwolfia* species have also been used to treat cardiovascular diseases, cancer, hypertension, various psychiatric diseases and snakebites and these indications have been associated with the monoterpene indole alkaloids.[156-158] Reserpine is one of the most important methoxy substituted indole containing natural products and is known as a powerful

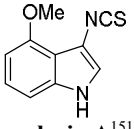
antihypertensive and tranquilizing agent for the treatment of hypertension, schizophrenia, paranoia, breast cancer and Parkinson's disease.[159-161] In this section, the natural products containing methoxyindole heterocyclic systems derived from *Rauwolfia* species are reported.



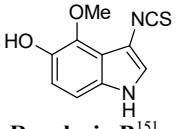
6-Methoxycamalexin[149]



Arvelexin[150]

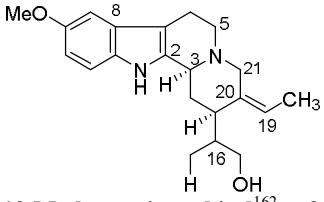


Rapalexin A[151]

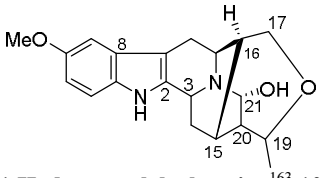


Rapalexin B[151]

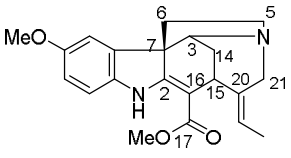
Isalexin[152]



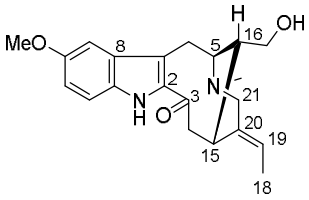
10-Methoxygeissoschizol[162]



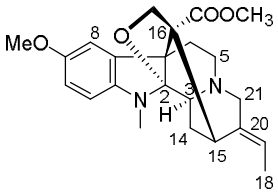
21-Hydroxycyclolochnerine[163]



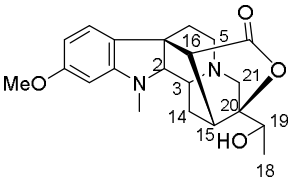
10-Methoxyakuammicine (Sewerine)[164,165]



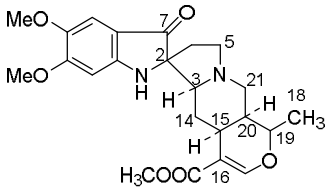
Pelirine (10-Methoxyepiaffinine)[166]



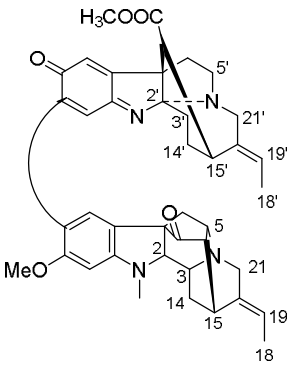
10-Methoxyakuammine[165]



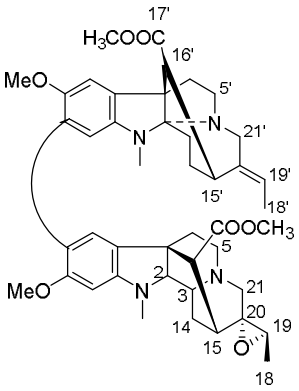
Caberoline[167]



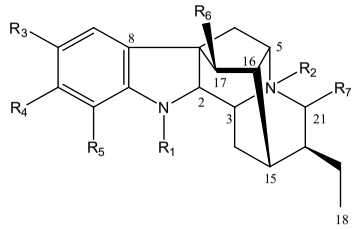
Isoreserpiline-φ-indoxyl[162,164]



Flexicorine[167]

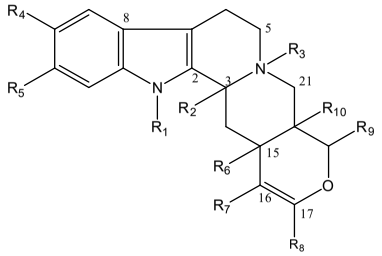


Cabufiline[167]



322a-g

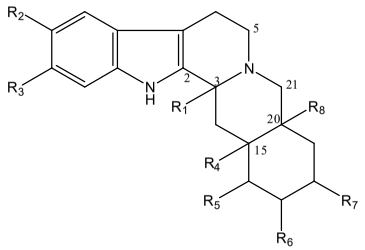
R_1	R_2	R_3	R_4	R_5	R_6	R_7	Compound number	Compound name	Reference
CH_3	-	H	H	OCH_3	OH	····· OH	322a	C_{19}-C_{21} (=) Seredamine	162, 168
H	-	H	H	OCH_3	OH	····· OH,	322b	C_{19}-C_{21} (=) Norseredamine	162, 168
CH_3	-	H	H	OCH_3	=O	H	322c	C_{19}-C_{21} (=) Purpeline	162, 168, 169
H	-	H	H	OCH_3	=O	H	322d	C_{19}-C_{21} (=) Norpurpeline	162, 168, 169
H	-	OCH_3	H	H	=O	H	322e	C_{19}-C_{21} (=) Endolobine	169
CH_3	-	H	H	OCH_3	=O	····· OH	322f	Vomalidine	162, 169
CH_3	-	OCH_3	H	H	OH	H	322g	C_{19}-C_{21} (=) 10-Methoxytetraphyllicine	162



323a-l

R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	Compound number	Compound name	Reference
H	····· H	-	H	OCH_3	····· H	$COOCH_3$	H	····· CH_3	▬ H	323a	Reserpinine (11-methoxytetrahydroalstonine)	170, 171, 162, 172
H	▬ H	-	H	OCH_3	····· H	$COOCH_3$	H	····· CH_3	····· H	323b	Isoreserpinine	170

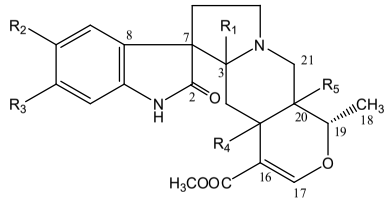
H	▬ H	-	OCH_3	OCH_3	····· H	$COOCH_3$	H	····· CH_3	····· H	323c	**Reserpiline**	163, 164, 170, 162, 172-176
H	····· H	-	OCH_3	OCH_3	····· H	$COOCH_3$	H	····· CH_3	····· H	323d	**Isoreserpiline**	164, 170, 162, 173, 174, 180, 172, 175, 176
H	▬ H	-	H	OCH_3	····· H	$COOCH_3$	H	····· CH_3	····· H	323e	**10-Demethoxy reserpiline**	175
H	▬ H	-	OCH_3	H	····· H	$COOCH_3$	H	····· CH_3	····· H	323f	**11-Demethoxyreserpiline**	175
H	▬ H	-	OCH_3	OCH_3	····· H	$COOCH_3$	H	····· CH_3	····· H	323g	**(C19=C20) 19,20-Dehydroreserpiline**	162
H	····· H	-	OCH_3	H	····· H	$COOCH_3$	H	····· CH_3	····· H	323h	**10-Methoxy tetrahydroalstonine (Aricine)**	175, 176
H	····· H	CH_3	OCH_3	H	····· H	····· $COOCH_3$	▬ OH	····· CH_3	▬ H	323i	**(C16-C17), Cabucinine**	177
H	····· H	CH_3	OCH_3	H	····· H	····· $COOCH_3$	····· OH	····· CH_3	····· H	323j	**(C16-C17), Rauvolcinine (17,20-epicabucinine)**	164
H	····· H	-	OCH_3	OCH_3	····· H	$COOCH_3$	H	▬ CH_3	▬ H	323k	**Rauvanine**	162
H	····· H	-	OCH_3	H	····· H	$COOCH_3$	H	▬ CH_3	····· H	323l	**Raumitorine**	162



324a-h

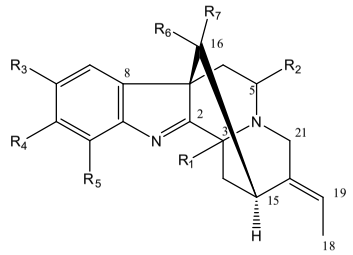
R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Compound number	Compound name	Reference
▬ H	H	OCH_3	····· H	▬ $COOCH_3$	····· OCH_3	▬ OTMB	····· H	324a	**Reserpine**	164, 178, 170, 171, 169, 162, 179, 180, 166, 181
▬ H	H	OCH_3	····· H	▬ $COOCH_3$	····· OH	▬ OTMB	····· H	324b	**Pseudoreserpine (Neonorreserpine)**	182

····· H	H	OCH_3	····· H	▬ $COOCH_3$	····· OCH_3	▬ OH	····· H	324c	Methylreserpate	171, 162
▬ H	H	OCH_3	····· H	▬ $COOCH_3$	····· OCH_3	▬ OTMC	····· H	324d	Rescinnamine	164, 178, 169, 162, 174
▬ H	H	OCH_3	····· H	▬ COOH	····· OCH_3	▬ OH	····· H	324e	Reserpic acid	183
····· H	H	OCH_3	····· H	····· $COOCH_3$	····· OH	H	▬ H	324f	11-Methoxyyohimbine	170, 162
····· H	OCH_3	OCH_3	····· H	▬ $COOCH_3$	····· OH	H	····· H	324g	Seredine	162
▬ H	H	OCH_3	····· H	▬ $COOCH_3$	····· OCH_3	▬ OTMB	····· H	324h	Renoxidine	162



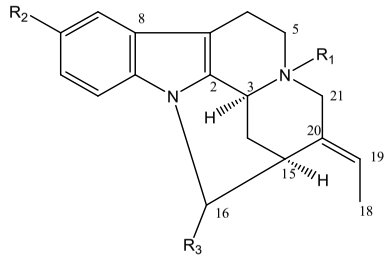
325a-f

R_1	R_2	R_3	R_4	R_5	Compound number	Compound name	Reference
····· H	H	OCH_3	····· H	····· H	325a	(C2 ····· C7, C7 ▬ C8), Reserpinine oxindole	173
····· H	OCH_3	OCH_3	····· H	····· H	325b	(C2 ▬ C7, C7 ····· C8), Carapanaubine	164, 162, 173
····· H	OCH_3	OCH_3	····· H	····· H	325c	(C2 ····· C7, C7 ▬ C8), Isocarapanaubine	162, 173
▬ H	OCH_3	OCH_3	····· H	····· H	325d	(C2 ····· C7, C7 ▬ C8), Rauvoxinine	173
▬ H	OCH_3	OCH_3	····· H	····· H	325e	(C2 ▬ C7, C7 ····· C8), Rauvoxine	162, 173
····· H	OCH_3	OCH_3	····· H	····· H	325f	(C2 ▬ C7, C7 ····· C8, N_b ⟶ O), Carapanaubine-N_b-oxide	173



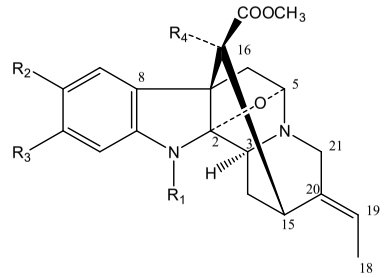
326a-b

R_1	R_2	R_3	R_4	R_5	R_6	R_7	Compound number	Compound name	Reference
····· H	H	H	OCH_3	H	····· H	▬ $COOCH_3$	326a	11-Methoxystrictamine	167
····· H	H	OCH_3	H	OCH_3	····· H	▬ $COOCH_3$	326b	10,12-Dimethoxystrictamine	184



327a-c

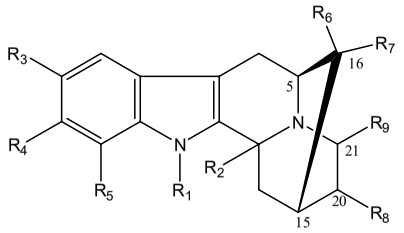
R_1	R_2	R_3	Compound number	Compound name	Reference
H	OCH_3	$COOCH_3$	327a	10-Methoxypleiocarpamine	164, 165
H	OCH_3	$COOCH_3$	327b	10-Methoxypleiocarpamine-2,7-dihydro (C2-C7)	164
H	OCH_3	$COOCH_3$	327c	(Nb ⇢ O) 10-Methoxypleiocarpamine-N_b-oxide	164



328a-c

R_1	R_2	R_3	R_4	Compound number	Compound name	Reference
CH_3	OCH_3	OCH_3	H	328a	10,11-Dimethoxy-Na-methylpicrinine	164, 162, 165

H	**OCH_3**	**OCH_3**	**H**	**328b**	**10,11-Dimethoxypicrinine**	164, 165
H	**OCH_3**	**H**	**H**	**328c**	**12-Demethoxytabemulosine**	185



329a-h

R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	Compound number	Compound name	Reference
H	**H**	**OCH_3**	**H**	**H**	**H**	**CH_2OH**	**$=CHCH_3$**	**H**	**329a**	**Lochnerine**	163, 170, 168, 174, 180
H	**H**	**OCH_3**	**H**	**H**	**H**	**CH_2OH**	**$=CHCH_2OH$**	**H**	**329b**	**18-Hydroxy lochnerine**	163, 174
H	**H**	**OCH_3**	**H**	**H**	**H**	**CH_2OH**	**$=CHCH_3$**	**H**	**329c**	**(N_b-CH_3) Lochneram**	186, 174
H	**H**	**OCH_3**	**H**	**H**	**CH_2OH**	**H**	**$=CHCH_3$**	**H**	**329d**	**Lochvinerine**	163
H	**H**	**H**	**H**	**OCH_3**	**H**	**CHO**	**$=CHCH_3$**	**H**	**329e**	**12-Methoxyvellosimine**	168
CH_3	**H**	**H**	**H**	**OCH_3**	**H**	**CHO**	**$=CHCH_3$**	**H**	**329f**	**12-Methoxy-Na-methylvellosimine**	168
H	**H**	**OCH_3**	**H**	**H**	**H**	**COOH**	**$=CHCH_3$**	**H**	**329g**	**(N_b CH_3) 10-Methoxypanarine**	186
CH_3	**H**	**H**	**H**	**OCH_3**	**H**	**CH_2OH**	**$=CHCH_3$**	**H**	**329h**	**(N_b H) 12-Methoxyaffinisine**	168

9. Conclusions

This review highlights the diverse range of methoxy-substituted indoles that have either been isolated from natural sources or synthesised for specific purposes. The chemistry of indoles is driven by the many important natural products containing indole rings, and from the broad scope of their resulting biological activity. The presence of methoxy groups has led to increased activation, resulting in diverse and in some cases unusual reactivity, which has further enhanced interest in the chemistry of indoles. There is clearly scope for further development of activated indoles, and by drawing attention to the current state of the literature on methoxyindoles, the review provides an example that could stimulate this activity involving other forms of activation.

Acknowledgements

We thank the University of New South Wales and the Turkish Government for financial support.

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