Oxindole as starting material in organic synthesis

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Abstract

This review highlights the advances in the use of oxindole as starting material in the synthesis of various organic compounds and drugs. The reactions can be performed on different reactive sites of oxindole which are the carbonyl group, C-3 site, nitrogen atom, and aromatic ring. In addition, the roles of oxindole in one-pot and domino reactions are discussed.

Keywords: Oxindole, cat's claw, one-pot reactions, domino reactions, Vilsmeier reactions

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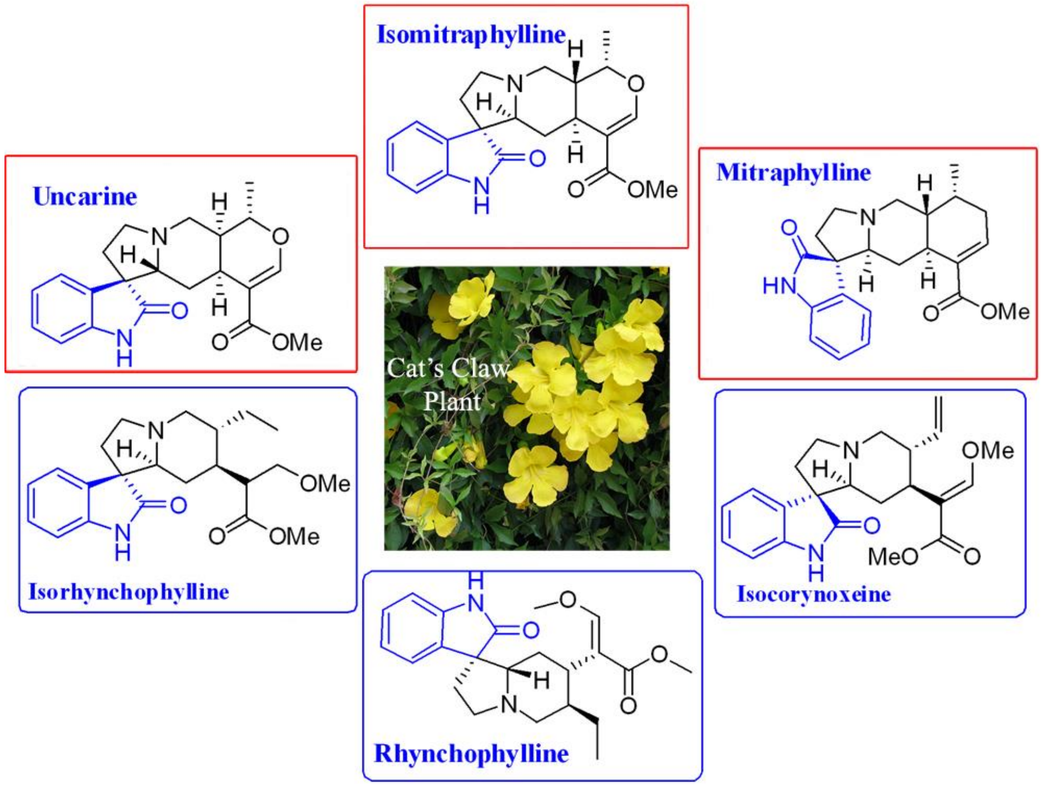
1. Introduction

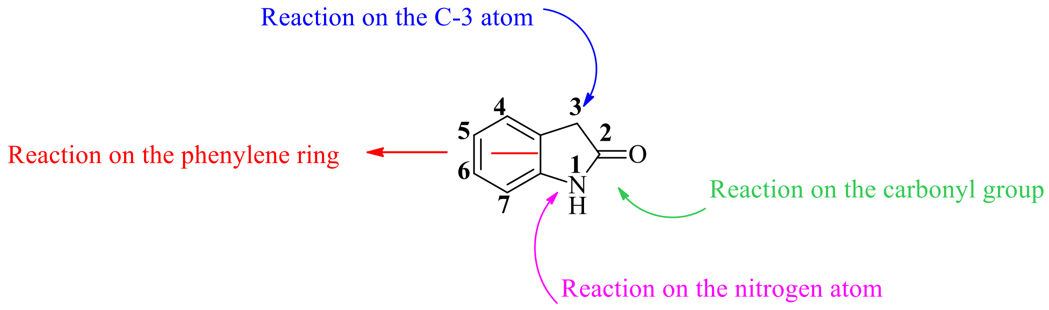
Oxindole is the core structure in a variety of natural products and drugs. For example there are two groups of oxindole alkaloids in the cat’s claw plant *Uncaria tomentosa* (Rubiaceae): pentacyclic oxindole alkaloids (POAs) and tetracyclic oxindole alkaloids (TOAs). POAs include pteropodine, isopteropodine, speciophylline, uncarine F, mitraphylline, and isomitraphylline, and TOAs include rhynchophylline, isorhynchophylline, corynoxeine, and isocorynoxeine (Scheme 1). Cat’s claw is a woody, tropical vine indigenous to the Amazon rainforest and other tropical areas of South and Central America. It is used for the treatment of infection, cancer, gastric ulcers, arthritis and other inflammatory processes.[1-5]

Oxindole derivatives[6] have demonstrated significant potential for use in a wide range of biological applications such as NMDA antagonist[7] and calcium channel blockers[8] as well as anti-angiogenic,[9] anti-cancer,[10] and analgesic effects.[11]



Scheme 1

As shown in Scheme 2, oxindole is reactive at four different positions, specifically the nitrogen atom 1, carbonyl group 2, carbon atom 3, and the aromatic ring.



Scheme 2. Four positions of oxindole reactivity.

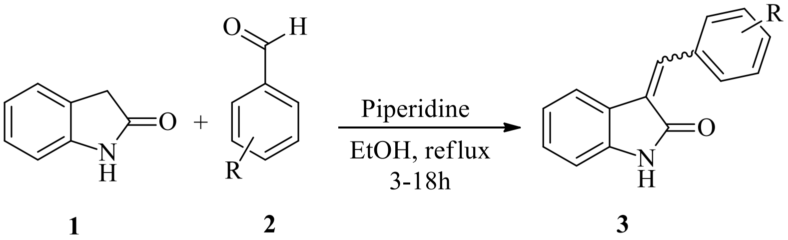
Oxindole and its derivatives are also versatile substrates in one-pot and domino reactions. In this review the focus is on the applications of oxindole in various organic reactions.

2. Reactions on the C-3 site

In oxindole, C-3 has two acidic hydrogen atoms that can be reacted separately or together. These reactions can be divided into condensation reactions, Michael addition reactions, as well as reactions with nitriles, alcohols, and halogenated compounds.

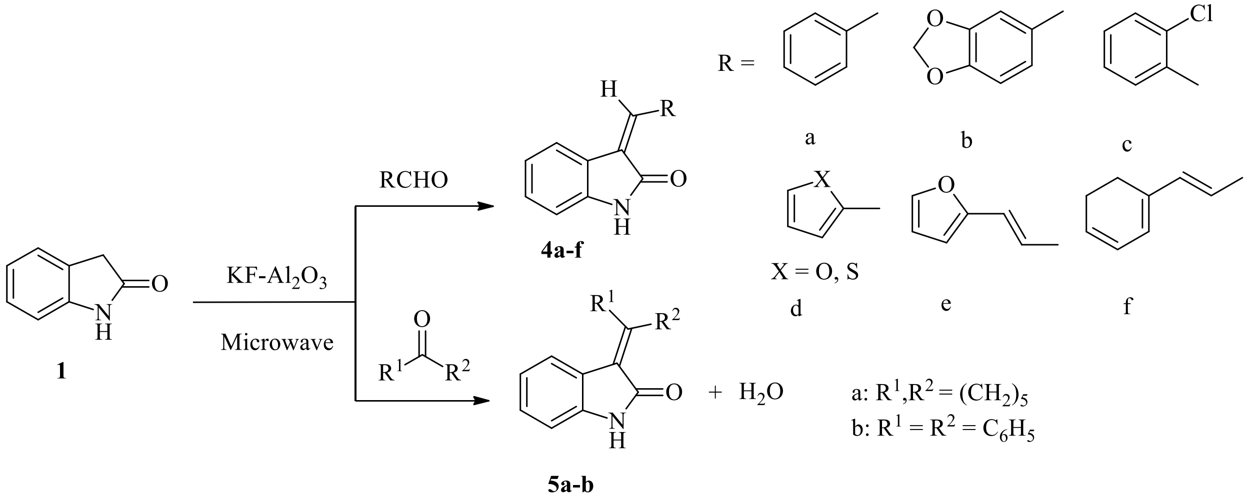
2.1. Condensation reactions

2.1.1. Knoevenagel condensations. Condensation reactions of oxindole **1** and benzaldehyde derivatives **2** in the presence of piperidine were reported by Wahl and Bagard in 1909 (Scheme 3).[12-14] This reaction was also examined under reflux conditions in EtOH in the presence and absence of piperidine.[15-17]



Scheme 3

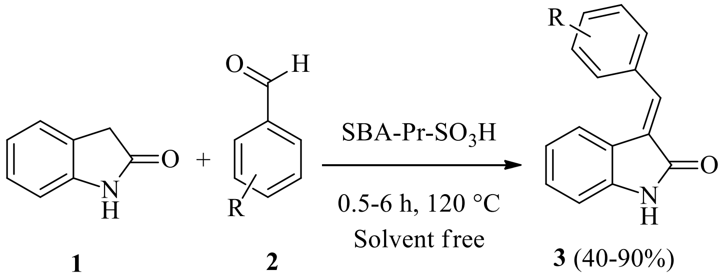
Many years later, in 1998, aldehydes and ketones were condensed with oxindole **1** in the presence of KF-Al_2O_3 and under microwave irradiation, forming good yields of products (81-94%) (Scheme 4). These condensation products **4** and **5** are useful for their biological properties and they can be used as synthons in organic synthesis.[18]



Scheme 4

In 2012, Mohammadi Ziarani and coworkers performed condensation reaction of oxindole **1** with benzaldehyde derivatives **2** in the presence of sulfonic acid functionalized nanoporous silica (SBA-Pr-SO_3H) under solvent-free condition to generate *E*-isomer of compound **3** (Scheme 5).[19]

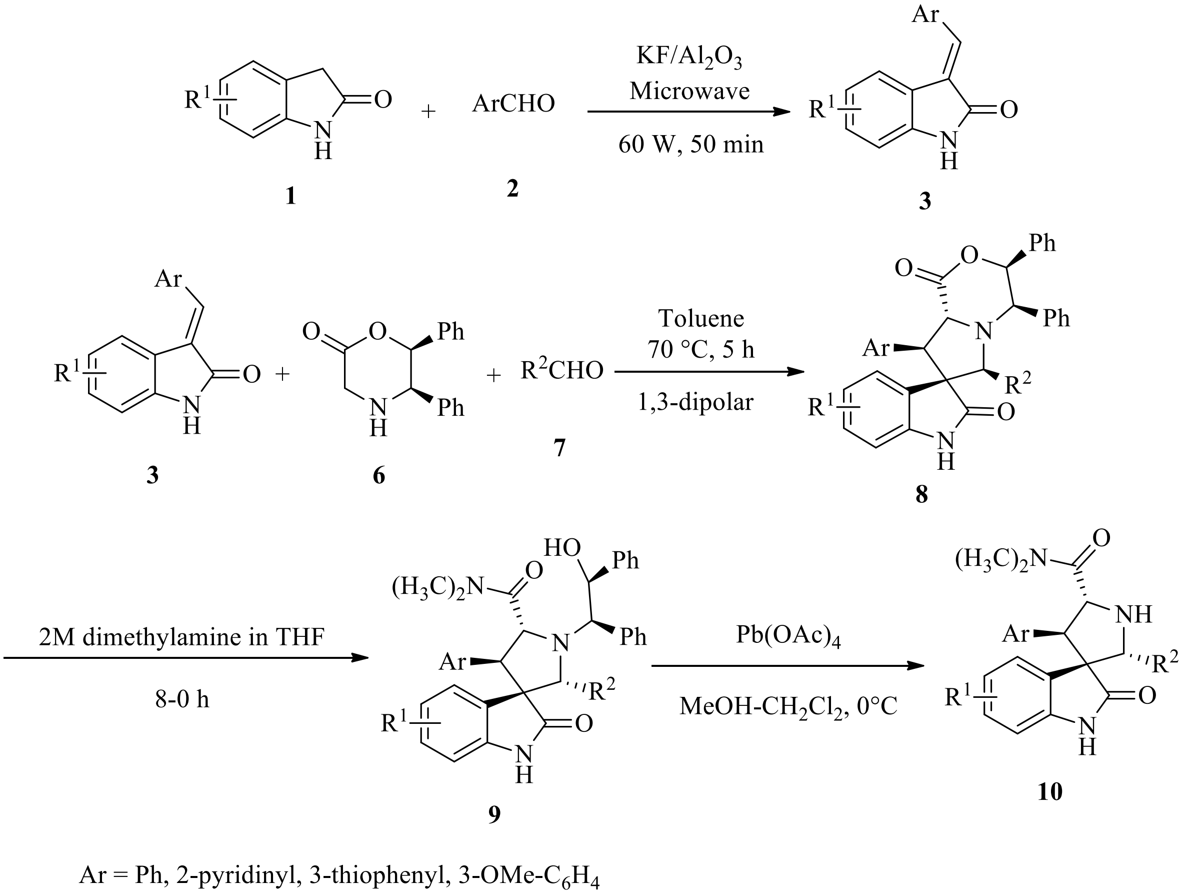
In a related study, compounds **3** were synthesized by condensation of oxindole **1** with several aromatic aldehydes **2**. Subsequent asymmetric 1,3-dipolar cycloaddition reaction was carried out by



R = H, 2-OMe, 3-OMe, 4-OMe, 2,3-(OMe)$_2$, 4-OH,
4-NMe$_2$, 4-Cl, 2,3-Cl$_2$, 3-NO$_2$

Scheme 5

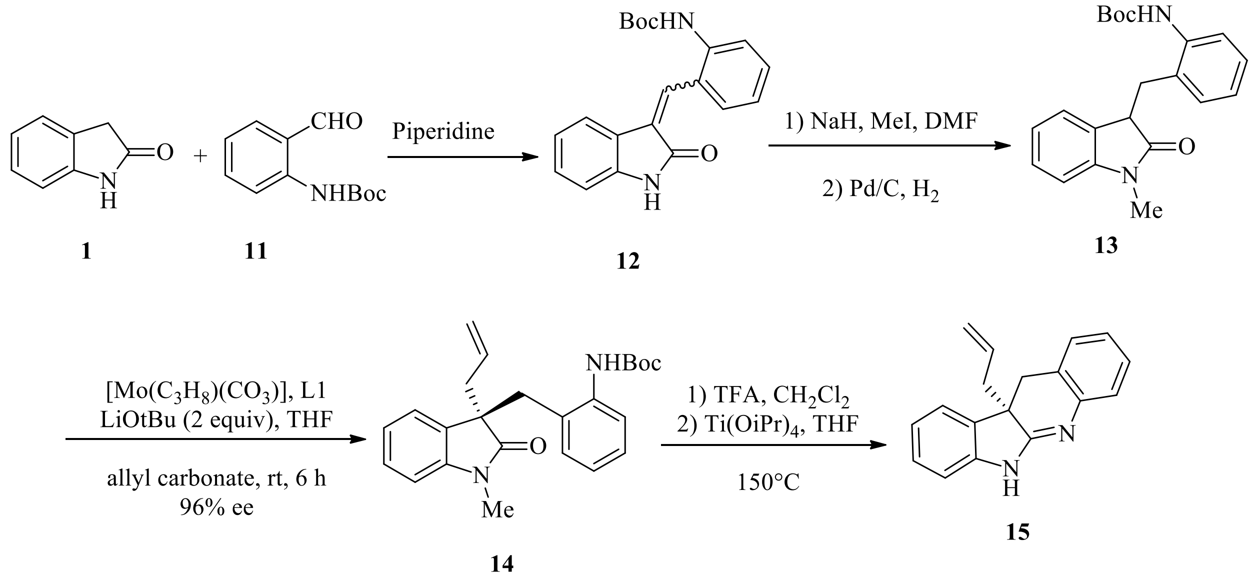
heating the adduct product **3** with alkyl aldehydes **7** and (5*R*,6*S*)-5,6-diphenylmorpholin-2-one **6** in the presence of a dehydrating agent. Compounds **8**, the major products of this reaction, were then treated with dimethylamine to afford amides **9** in good overall yields developed for the synthesis of final compounds **10**. These compounds are potential inhibitors of the p53-MDM2 interaction[20] (Scheme 6).



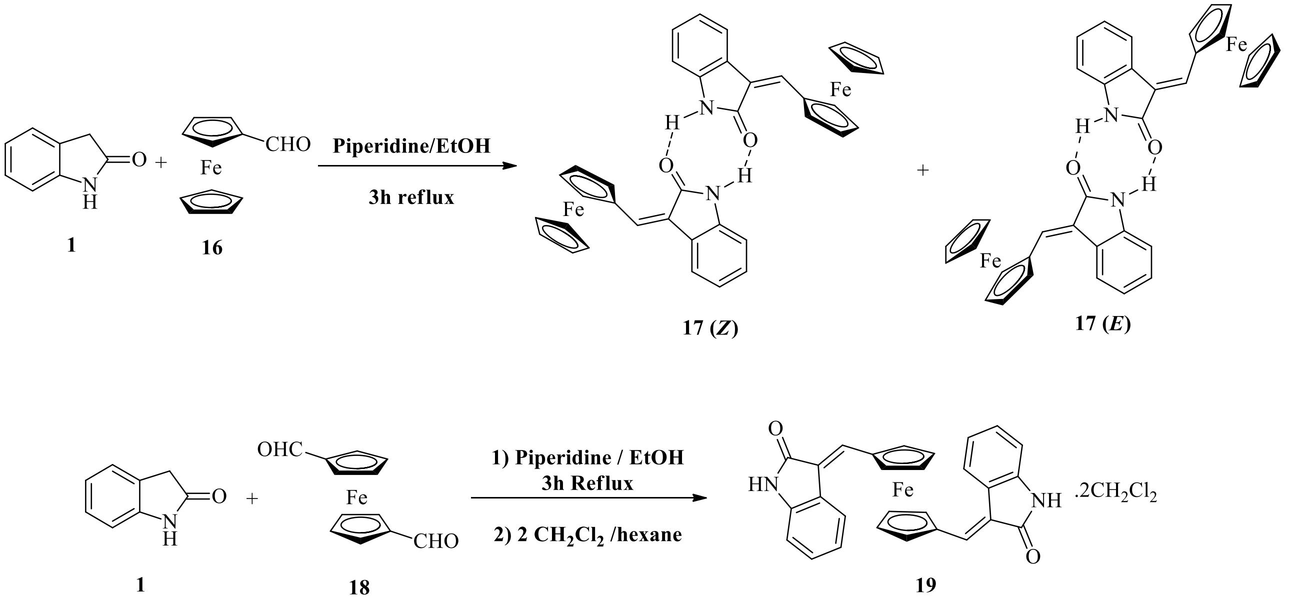
Ar = Ph, 2-pyridinyl, 3-thiophenyl, 3-OMe-C$_6$H$_4$
R^1 = H, 6-Cl, 6-Br, 6-F, 6-CF$_3$
R^2 = i-butyl, 2,2-dimethyl-propyl, 2,2-dimethyl-butyl, n-propyl

Scheme 6

Compound **12**, resulted from the condensation of oxindole **1** with aldehyde **11** under microwave heating, was subjected to *N*-methylation and hydrogenation reaction to afford compound **13** in 95% yield. The following Mo-catalyzed asymmetric allylic alkylation reactions (AAA reactions) proceeded well and the allylated product **14** was isolated in 96% yield and 95% ee. Deprotection of the Boc group with trifluoroacetic acid (TFA) and dehydrative cyclization with titanium tetraisopropoxide then provided the dihydro-indolinoquinoline **15** as the final product (Scheme 7).[21]



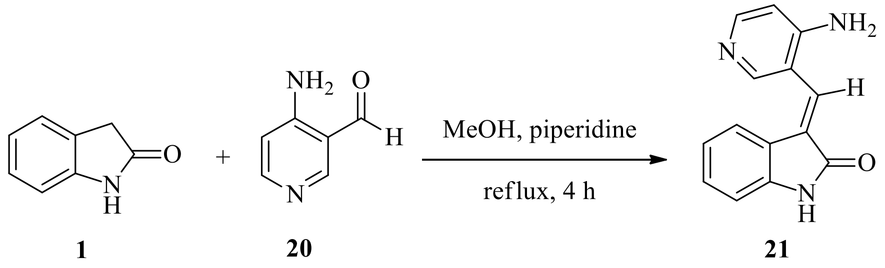
Scheme 7



Scheme 8

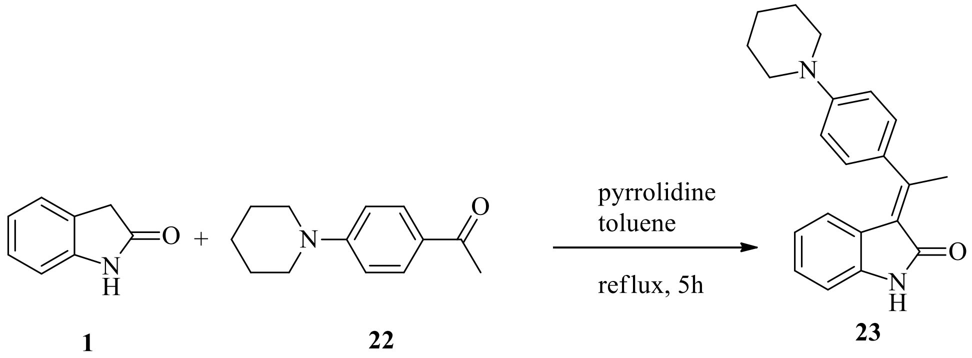
Male and coworkers reported their finding in the synthesis of the isomeric ferrocenyl oxindoles, (*E*)- and (*Z*)-3-(ferrocenylmethylidene)indolin-2-one **17**, which are readily separated and have excellent anti-cancer properties. Oxindole **1** also undergoes a Knoevenagel condensation with ferrocene-1,1′-dicarbaldehyde **18** to afford the complex 3,3′-[(*E*,*E*)-ferrocene-1,1′-diyldimethylidyne]diindolin-2-one **19** (as bisdichloromethane solvate) (Scheme 8).[22]

Compound **21**, with antiamnesic effects, has been synthesized by the condensing of oxindole **1** and 4-aminonicotinaldehyde **20** in methanol in the presence of piperidine as catalyst (Scheme 9).[23]



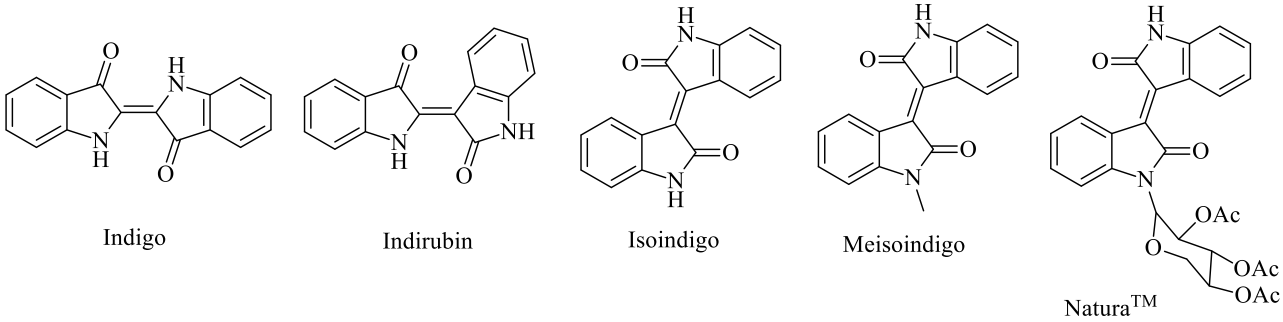
Scheme 9

Treatment of oxindole **1** with 4-(piperidin-1-yl)phenylacetone **22** in refluxing toluene in the presence of pyrrolidine provided the desired (*E*)-3-[1-[4-(Piperidin-1-yl)phenyl]ethylidenyl]indolin-2-one **23** (Scheme 10).[24]



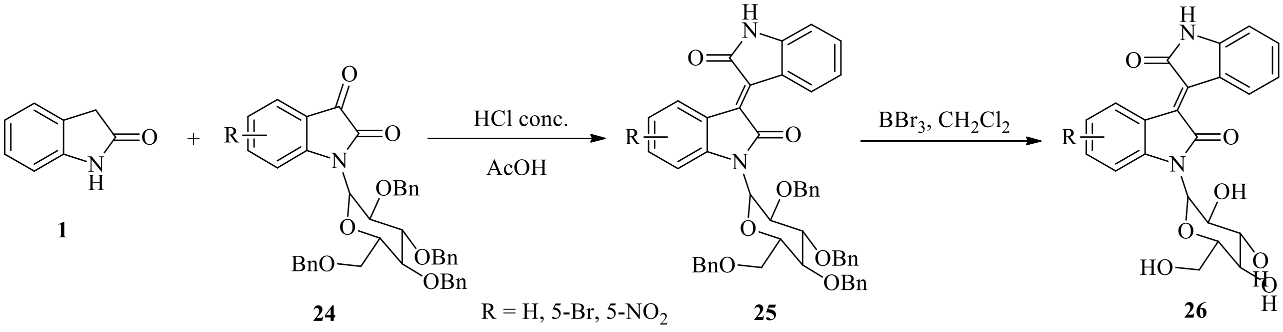
Scheme 10

2.1.2. Condensation reactions of oxindole with isatin derivatives. *Danguuei Longhui Wan* is a traditional Chinese recipe with a mixture of 11 herbal medicines for treatment of chronic myelocytic leukemia (CML). This powder contains a high level of the dark blue dye indigo, but its antileukaemic activity is attributed to the red-coloured isomer of indigo, indirubin.[25] Indirubin, indigo and isoindigo are isomers; meisoindigo (1-methylisoindigo) and Natura^{TM} (1-β-D-triacetylxylopyranosylisoindigo) are isoindigo derivatives of which meisoindigo is a therapeutic agent used for the treatment of CML in China, while the anti-cancer agent activity of Natura^{TM} is attributed to inhibition of several cyclin dependent kinases (CDKs) (Scheme 11).[26]

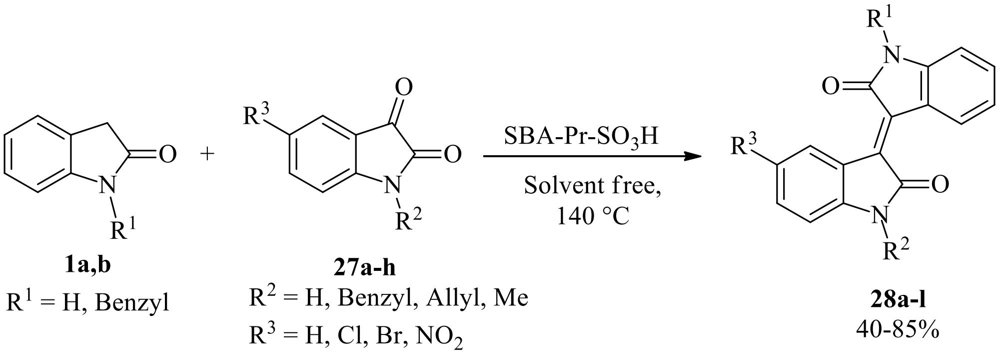


Scheme 11

The reaction of glycosyl-isatin derivatives **24** with oxindole **1** in an acidic medium has been reported by Moreau and coworkers.[27] Deprotection of the hydroxyl groups of the glycosyl moiety was performed by reaction with boron tribromide to give compounds **26** (Scheme 12). In another study, Mohammadi Ziarani and coworkers investigated the synthesis of isoindigo derivatives through the condensation of oxindole with isatin derivatives using SBA-Pr-SO$_3$H with pore size of 6 nm as a heterogeneous acid catalyst under solvent-free conditions (Scheme 13).[28] The synthesized compounds were screened for their antimicrobial activities.

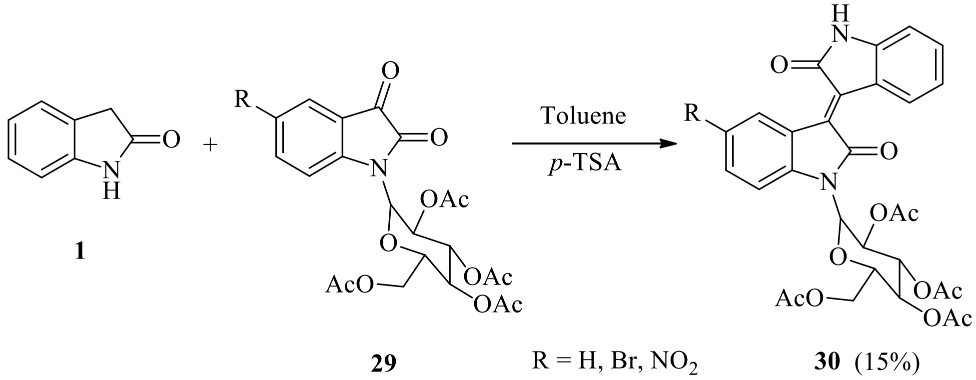


Scheme 12

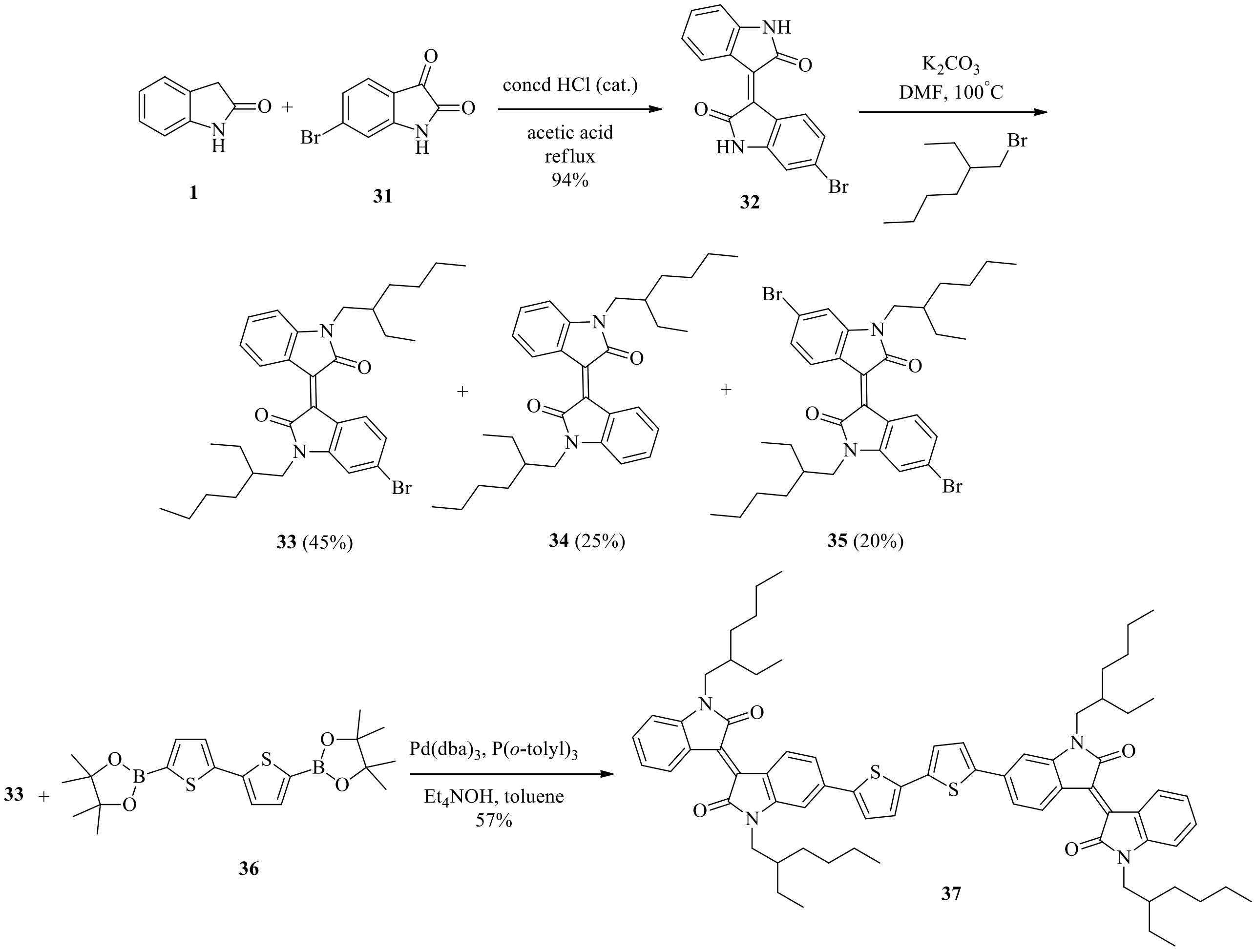


Scheme 13

In a similar approach, synthesis of acetylated glycosyl-isoindigo derivatives **30** by condensation of acetylated glycosyl-isatins **29** with oxindole **1** in the presence of *p*-toluenesulfonic acid (*p*-TSA) has been reported (Scheme 14).[29]



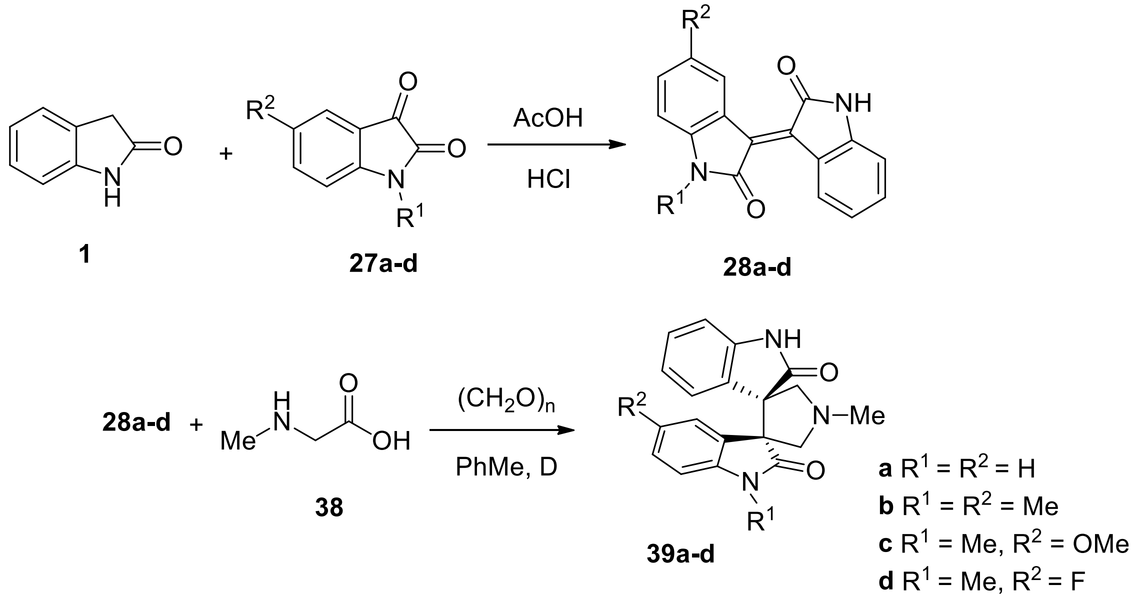
Scheme 14



Scheme 15

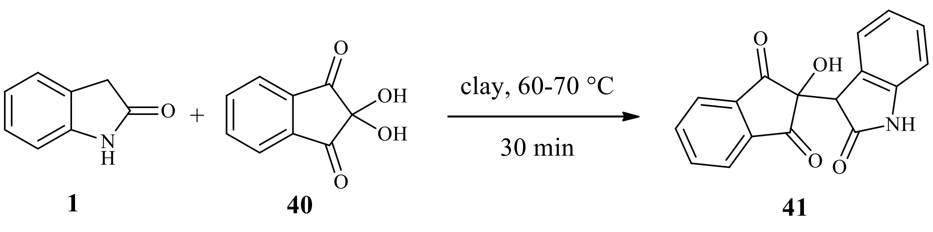
Acid-catalyzed condensation and dehydration of oxindole **1** and 6-bromoisatin **31** to afford 6-bromoisoindigo **32** has been reported. Interestingly, subsequent *N*-alkylation of compound **32** using branched alkyl bromide resulted in the formation of three products **33**, **34**, and **35**. With **33** in hand, isoindigo-based acceptor-donor-acceptor (ADA) oligothiophene **37** was successfully obtained by incorporating electron rich bithiophene units **36** via Suzuki coupling reaction (Scheme 15).[30] In this communication, the isoindigo unit was used as an electron acceptor to form ADA isoindigo-based oligothiophenes in conjunction with bithiophene as an electron donor.

The [3+2]-cycloaddition reaction of isoindigo derivatives **28**, obtained from oxindole **1** and isatin derivatives **27,** with azomethine ylides generated *in situ* from sarcosine **38** and paraformaldehyde, afforded products **39** in high yields and in a diastereoselective manner (Scheme 16).[31]



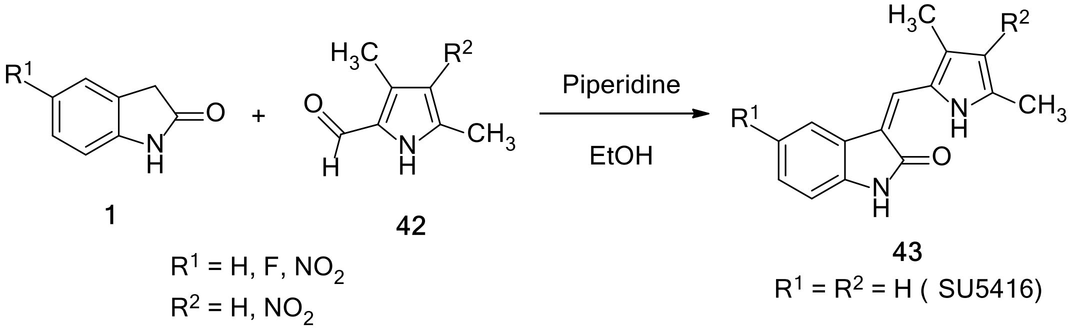
Scheme 16

2.1.3. Condensation reactions with ninhydrin. It was reported that the Knoevenagel condensation reaction of ninhydrin **40** with oxindole **1** in the presence of montmorillonite K10 clay afforded the adduct product **41** after 30 minutes (Scheme 17).[32]



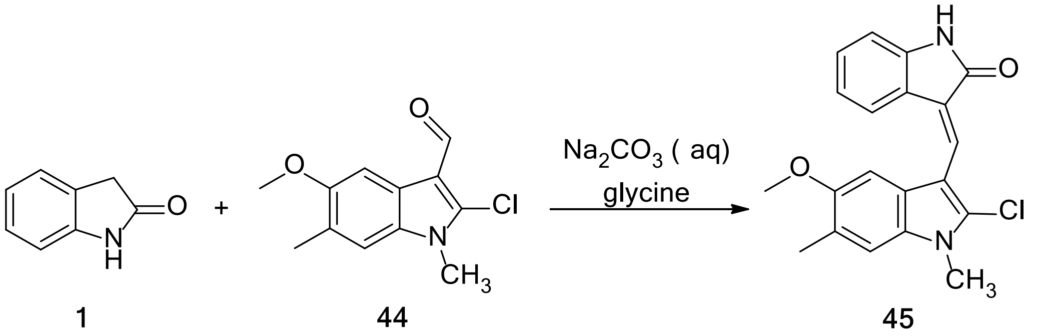
Scheme 17

2.1.4. Condensation reactions with carbaldehydes. The reaction of various substituted oxindoles **1** with 3,5-dimethylpyrrol-2-carbaldehyde derivatives **42** under Knoevenagel condensations afforded an array of nitro-substituted derivatives of Semaxinib **43** (SU5416) in good yields (Scheme 18).[33] Semaxinib is a potent inhibitor of signaling activity of the Receptor Tyrosine Kinases (RTKs) for the vascular endothelial growth factor (VEGF).



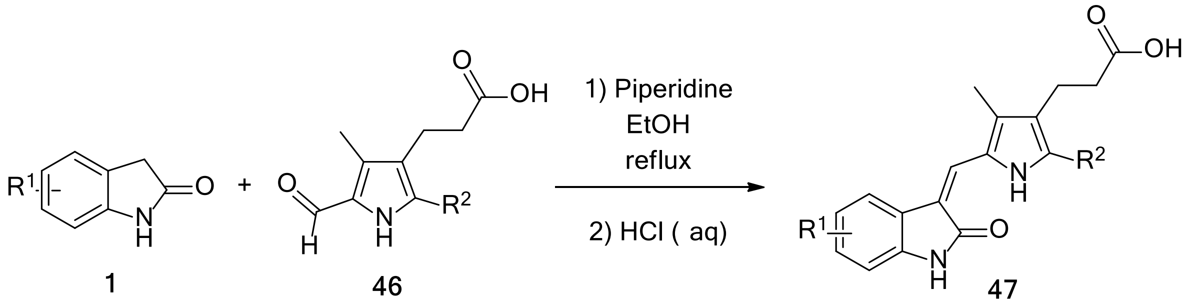
Scheme 18

The synthesis and anti-tumor activity of new (*E*)-3-(2-chloro-3-indolylmethylene)-1,3-dihydroindol-2-ones **45** via condensation of 2-chloro-5-methoxy-1,6-dimethylindole-3-carbaldehyde **44** with oxindole derivatives **1** have been reported (Scheme 19).[34] All the compounds were potent growth inhibitors.



Scheme 19

A series of 3-substituted oxindoles **47** containing propionic acid functionality attached to the pyrrole ring at the C-3 position of the core has been synthesized by the reaction of oxindoles **1** with 4-carboxyethyl-3-methylpyrrol-2-carboxaldehyde derivatives **46** (Scheme 20). The products have been identified as catalytic inhibitors of the vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) RTKs. Since these RTKs have crucial roles in many disease processes, they can be used for the treatment of human diseases including cancers, inflammatory diseases, cardiovascular diseases and fibrotic diseases of the lung, liver, and kidney.[35]

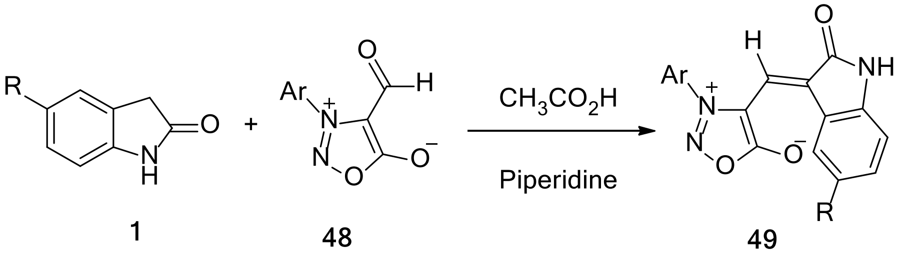


R^1 = H, 5-CO_2H, 5-SO_2NH_2, 6-OMe, 6-Ph,
6-(3-$MeOC_6H_4$), 6-(2-$MeOC_6H_4$), 6-(4-$MeOC_6H_4$)
R^2 = H, Me

R^2 = H (4h)
R^2 = Me (overnight)

Scheme 20

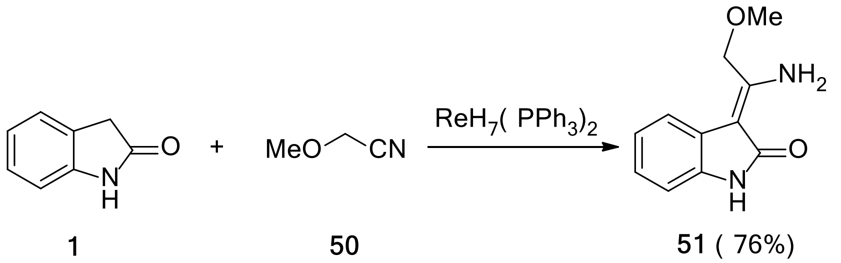
Shih and Yeh reported the syntheses of sydnonyl-substituted oxindole derivatives **49** by the modified Knoevenagel condensation of 3-aryl-4-formyl-sydnones **48** with oxindole and 5-chlorooxindole (Scheme 21).[36]



Ar = C_6H_5, p-MeC_6H_4, p-$MeOC_6H_4$, p-$EtOC_6H_4$
R = H, Cl

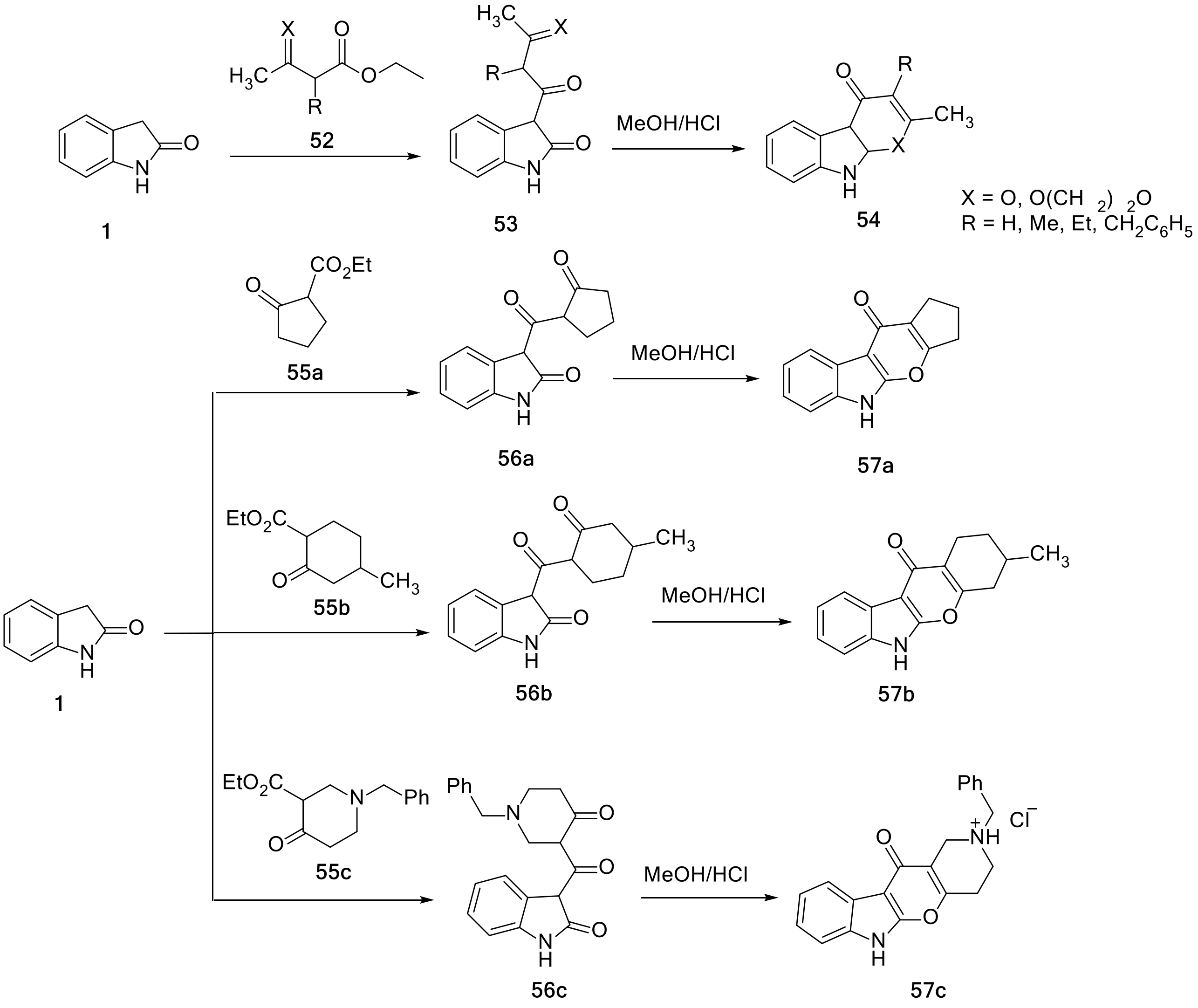
Scheme 21

2.1.5. Condensation reactions with esters and nitriles. Oxindole as a carbonyl compound in reaction with methoxyacetonitrile **50** in the presence of rhenium heptahydride complex as an excellent catalyst, leads to selective formation of the *Z* isomer of 3-(1'-amino-2'-methoxy)ethylindene indole-2-one **51** in 76% yield (Scheme 22).[37]



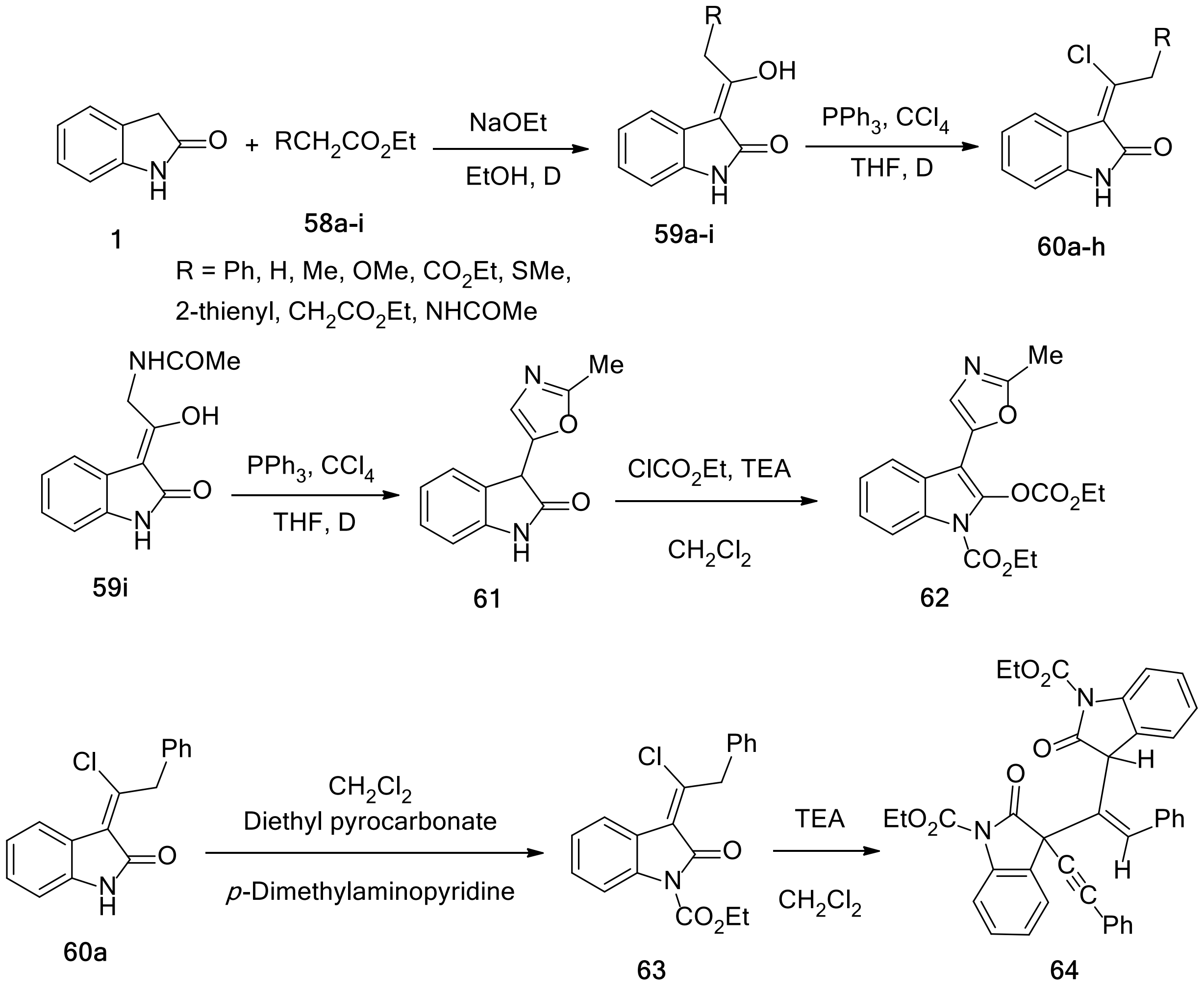
Scheme 22

The condensation of oxindole **1** with acetal esters **52** and cyclic β-ketoesters **55a-c** yielded the 3-acyloxindoles **53** and **56a-c**, respectively. Subsequent cyclization of these compounds to the 2- and 3-substituted pyrano[2,3-*b*]indolones **54** and **57a-c** has been developed (Scheme 23).[38] Later, Engqvist and Bergman indicated that when oxindole is condensed with methyl anthranilate under basic conditions angular products are obtained after a nucleophilic attack of oxindole followed by recyclization.[39]



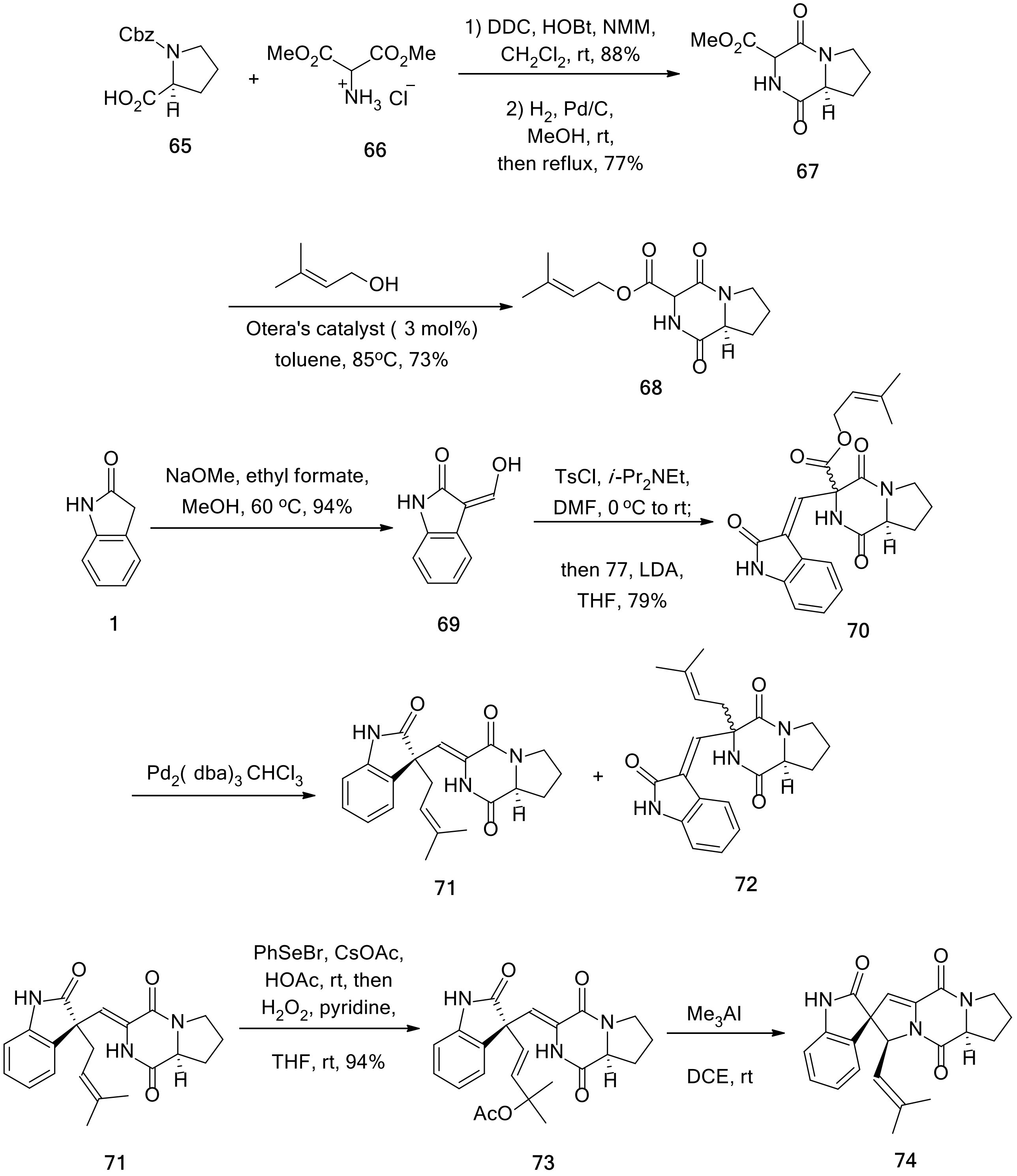
Scheme 23

In another study, oxindole **1** was condensed with ethyl esters **58a-i** to give the 3-[(1-hydroxy-2-substituted)ethylidene]indol-2(3*H*)-ones **59a-i**. The corresponding chloro-derivatives **60** were prepared by reaction with Ph_3P/CCl_4 in anhydrous THF. It was observed that compound **59i** did not afford the corresponding chloro-derivative, instead, the 3-oxazolylindol-2(3*H*)-one **61** was obtained, whose structure was confirmed by reaction with ethyl chloroformate and triethylamine (TEA), to give 1-ethoxycarbonyl-2-ethoxycarbonyloxy derivative **62**. On the assumption that the acylation of the indolic nitrogen does not alter the reactivity of the chloro-compounds **60** with the TEA, compound **63** was prepared from **60a**. The treatment of a dichloromethane solution of **63** with TEA afforded a reaction mixture from which a dimeric crystalline compound **64** was isolated (Scheme 24).[40,41]



Scheme 24

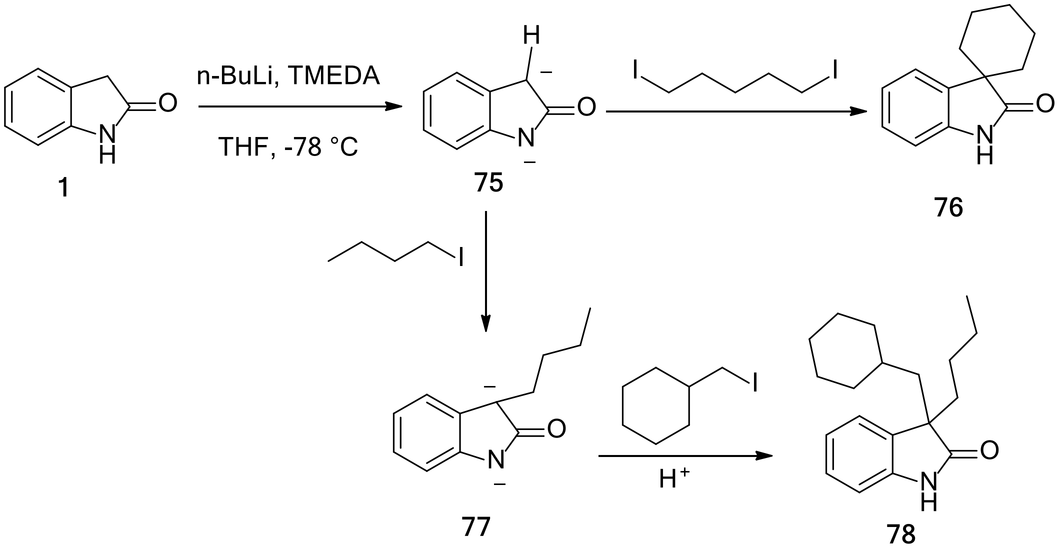
Spirotryprostatin B **74**, which has recently served as the blueprint for a library of cellular probes, has been synthesized in eight steps. The synthetic route starting from Cbz-proline **65** and dimethyl aminomalonate hydrochloride **66** resulted in the formation of known diketopiperazine **67** which was transesterified to prenyl ester **68** by Otera's catalyst. In a one-pot reaction, oxindole **69** was activated as its vinyl tosylate and reacted with the lithium salt of **68**. With the key substrate in hand, compound **70** was subjected to palladium catalyst and converted to compounds **71** and **72**. To functionalize the phenyl chain, **71** was first treated with PhSeOAc (prepared *in situ*) and then the selenide was oxidized and eliminated with H_2O_2, giving the allylic acetate **73**. For the final cyclization, the use of aluminium amide, generated *in situ* by the treatment of **73** with trimethylaluminium, does succeed to give spirotryprostatin B **74** (Scheme 25).[42]



Scheme 25

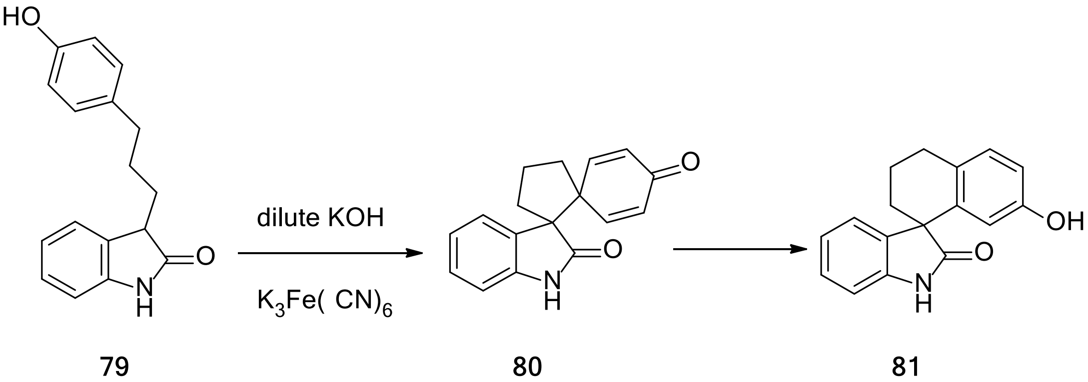
2.2. Reaction with halogenated compounds

Kende and Hodges converted oxindole **1** to its dianion **75** by treatment with *n*-BuLi and tetramethylethylenediamine (TMEDA). Using the enhanced and regiospecific reactivity of the oxindole dianion, alkylations with a number of common electrophiles such as *n*-alkyl iodides resulted in useful transformations leading to compounds **76** and 3,3-disubstituted oxindoles **78** (Scheme 26).[43] It is noteworthy that under these conditions no *N*-alkylation or *O*-alkylation was observed.



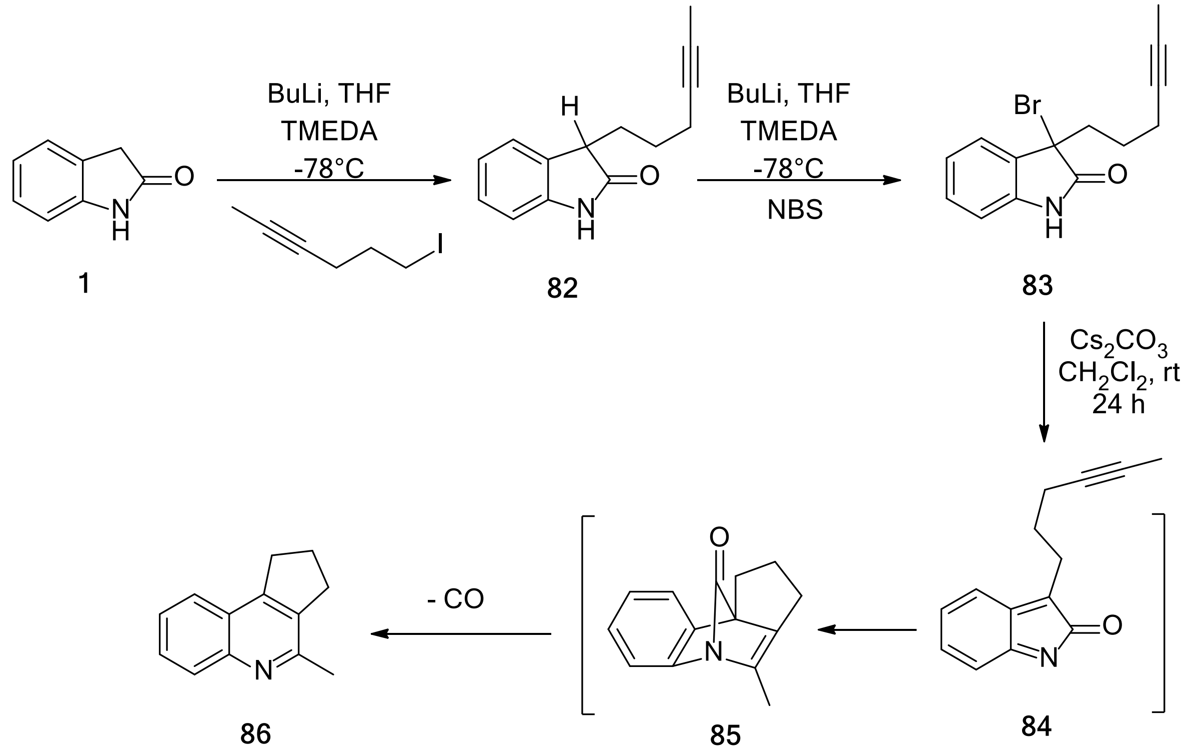
Scheme 26

Alkylation of the dianion of oxindole **75** with 3-(4-methoxyphenyl)propyl iodide following the previous procedure[43] gave 41% yield of the C-3 monoalkylation product **79** which was converted to compound **80** using $K_3Fe(CN)_6$ in dilute KOH. Compound **80** then rearranged to afford the crystalline phenol **81** in 91% yield (Scheme 27).[44]



Scheme 27

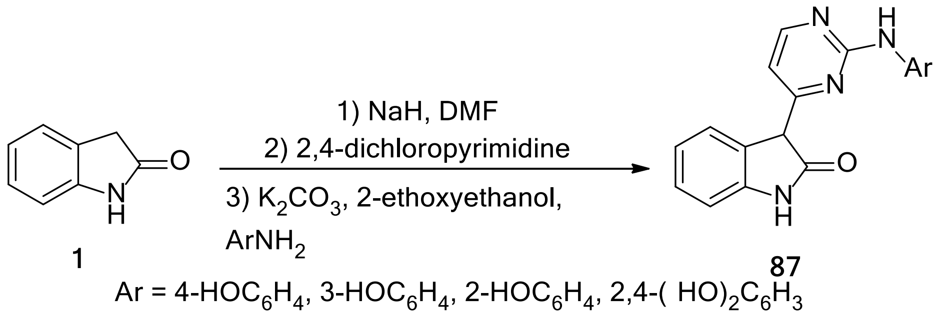
In another study, the dianion of oxindole was alkylated with the 6-iodo-2-hexyne according to the procedure of Kende.[43] Subsequent formation of the dianion of the alkylated oxindole **82** and treatment with *N*-Bromosuccinimide NBS at low temperature led to the formation of the 3-alkyl-3-bromoindolin-2-one **83**. Treatment of the alkyne **83** with cesium carbonate resulted in the formation of quinoline **86** in good yield (Scheme 28).[45] This transformation presumably occurs via cycloaddition of the tethered alkyne with the intermediate oxindole **84** to provide a strained bridged bicyclic lactam **85**. The lactam then undergoes a retrocheletropic reaction *in situ* to afford the final product **86**.



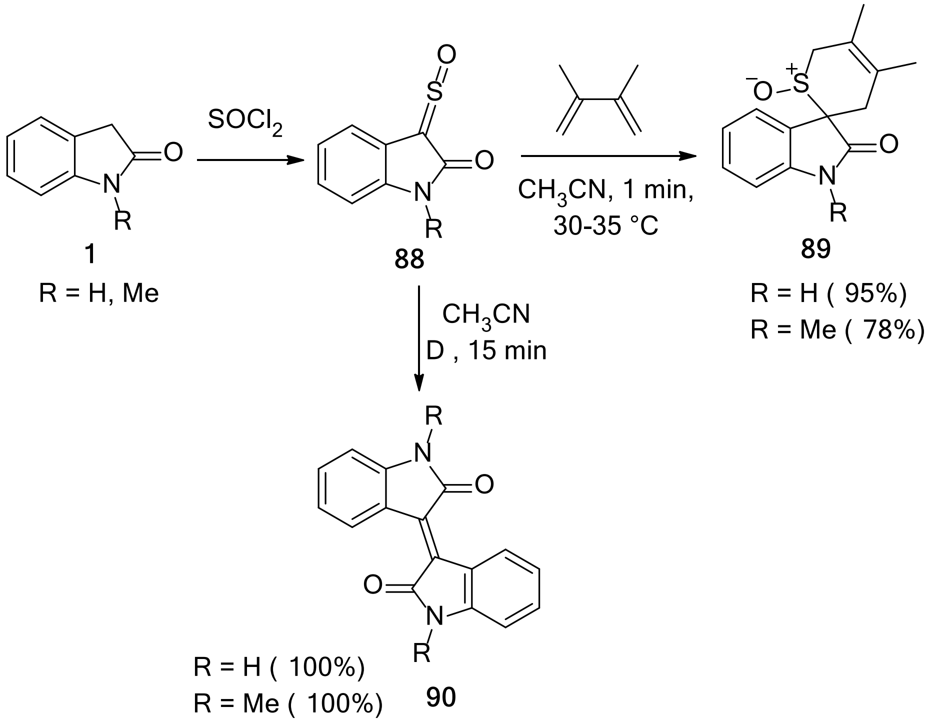
Scheme 28

Deprotonation of oxindole **1** with NaH followed by addition of 2,4-dichloropyrimidine and subsequent amination with various anilines led to the formation of compounds **87** which were screened for their inhibitory activity against transforming growth factor-β-activating kinase 1 (TAK1) (Scheme 29).[46]

Bergman and Romero published a study on the reactions of oxindoles **1** with thionyl chloride to give the isolable 3-sulfinatooxindoles **88**. Refluxing **88** in acetonitrile resulted in the formation of isoindigo **90** while in reaction with 2,3-dimethylbutadiene a colorless cycloadduct **89** was synthesized (Scheme 30).[47]

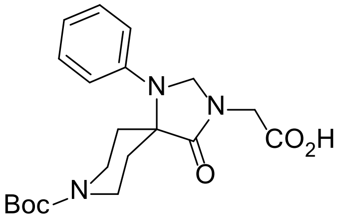


Scheme 29

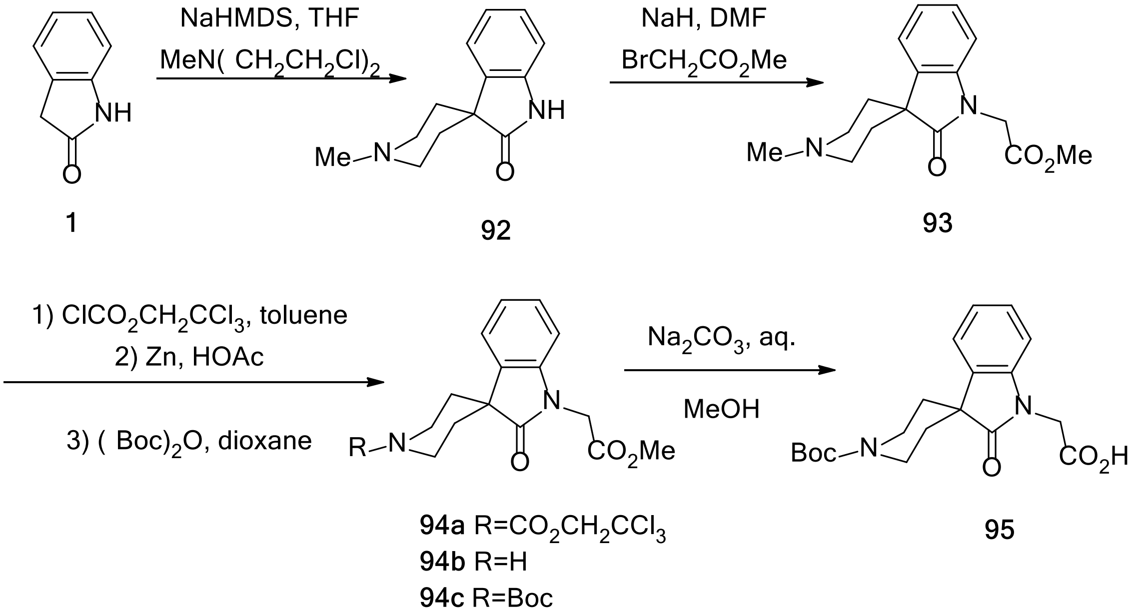


Scheme 30

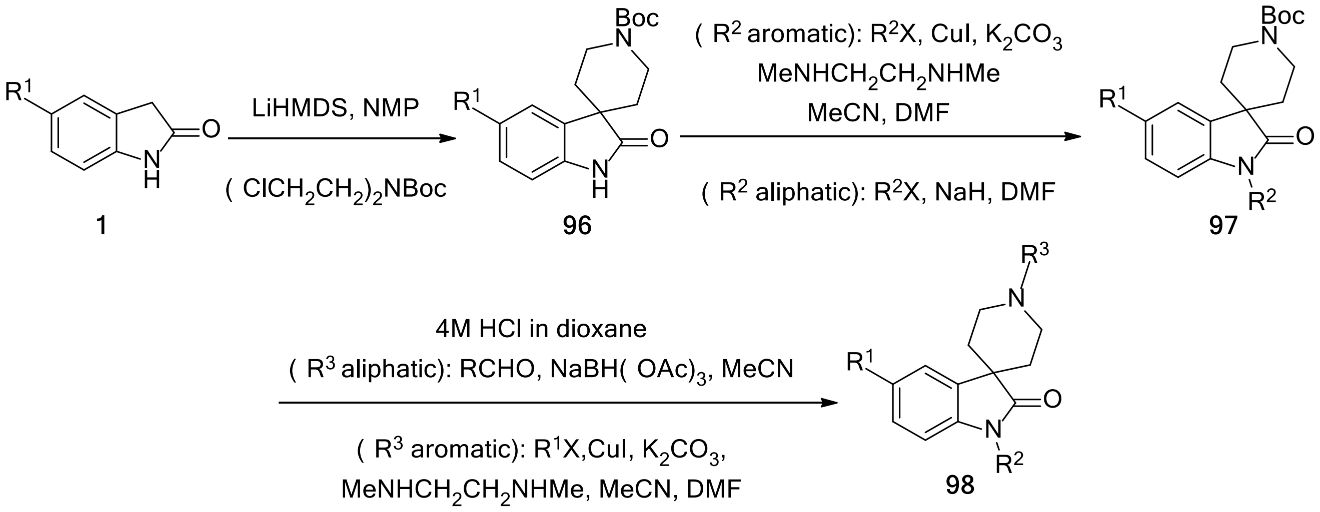
In a six-step synthetic route, compound **95**, a rotationally constrained analogue of **91**, was prepared. Starting from the reaction of oxindole **1** with sodium hexamethyldisilazide (NaHMDS) in THF, and following alkylation with *N*-methylbis-(2-chloroethyl)amine, the spirocyclic oxindole **92** was obtained. Deprotonation with sodium hydride in DMF followed by alkylation with methyl bromoacetate inserted the acetic acid side chain in compound **93**. Then, the *N*-methyl group in **93** could be replaced with a Boc group via a three step procedure, and finally saponification of the methyl ester resulted in a 74% yield of the desired Boc protected amino acid **95** (Scheme 31).[48]



91



Scheme 31

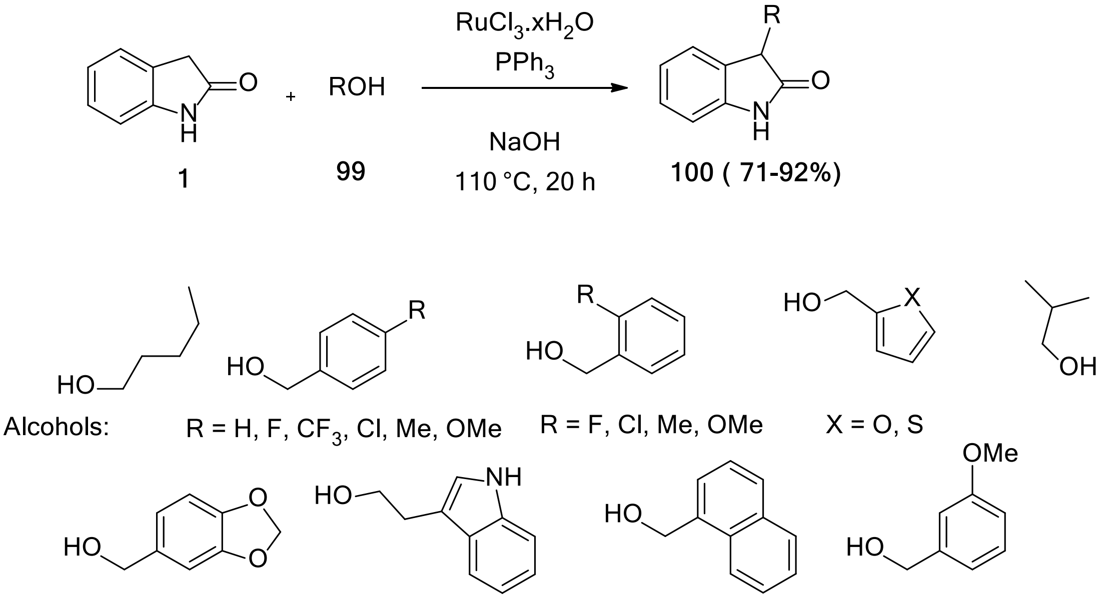


Scheme 32

Vachal and coworkers published a study on spirooxindoles that were optimized for prolyl hydroxylase (PHD2) inhibition. In this work, 1,3,8-triazaspiro[4.5]decane-2,4-diones **98** (spiro-hydantoins) were optimized as an advanced lead class derived from the original spiroindole hits **96** (Scheme 32).[49] These compounds have been investigated as a structural class of pan-inhibitors of the PHD family of enzymes for anemia treatment.

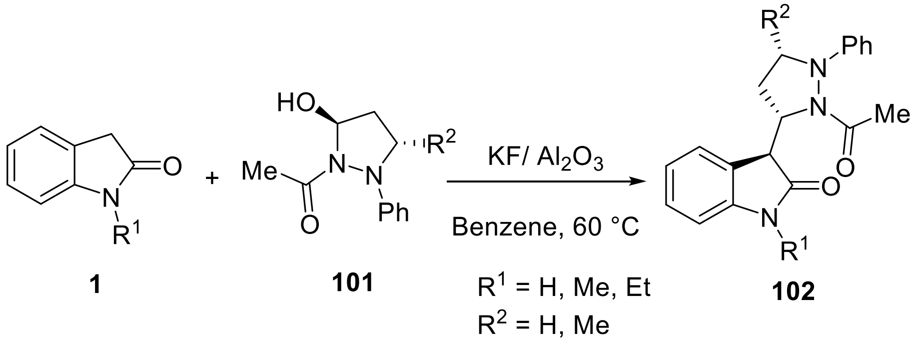
2.3. Reactions with alcohols

Mono-3-alkylation of oxindole **1** with alcohols **99** was mediated by the in situ generated catalyst from $RuCl_3.xH_2O$ and PPh_3 in the presence of sodium hydroxide (Scheme 33).[50] A wide range of aromatic, heteroaromatic, and aliphatic alcohols were used successfully in this reaction. This reaction was also carried out using iridium chloro-bridged compound $[Cp^*IrCl_2]_2$ as an effective catalyst under solvent-free thermal or microwave conditions[51] and also using an indene-functionalized mesoporous iridium catalyst.[52]



Scheme 33

The reaction of oxindoles **1** with 5-hydroxypyrazolidines **101** on the surface of potassium fluoride-modified alumina to give 3-(5-pyrazolidinyl)oxindoles **102** has been studied by Dlinnykh and coworkers (Scheme 34).[53] The use of potassium fluoride-modified alumina in benzene has been proved optimal for the all substrate pairs and the reactions were completed at 60 °C after 30-60 minutes.

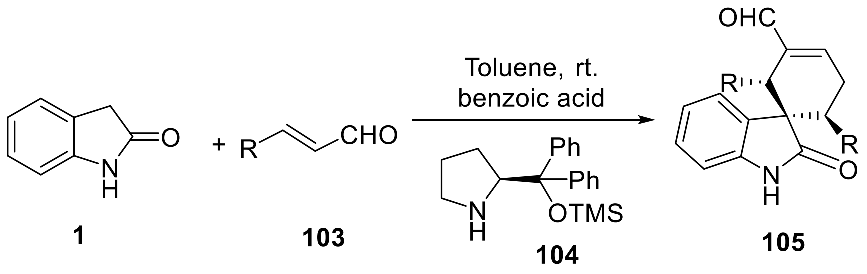


R^1 = H, Me, Et
R^2 = H, Me

Scheme 34

2.4. Michael additions

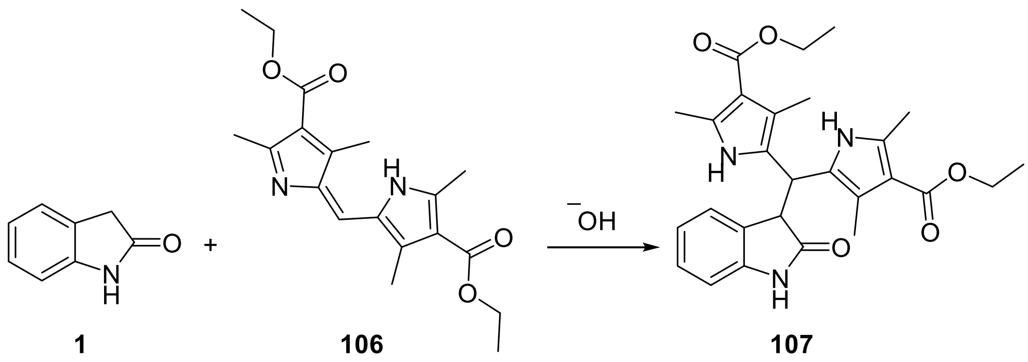
Oxindoles **1** could react with unsaturated aldehydes **103** via a Michael-Michael-aldol reaction to furnish the desired spirocyclic compounds **105** (Scheme 35).[54] Application of catalyst **104** as an organocatalyst in this method follows the rules of green and sustainable chemistry.



R = Ph, Me, CO_2Et, p-$O_2NC_6H_4$, p-NCC_6H_4, o-BrC_6H_4

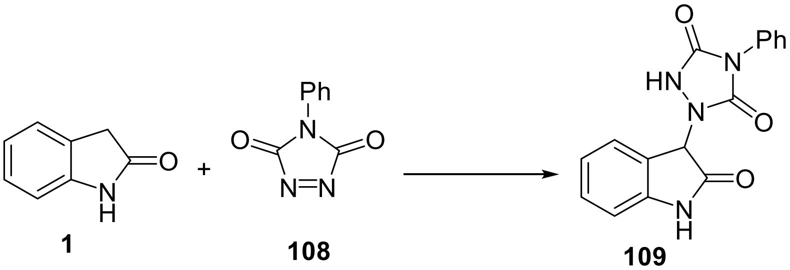
Scheme 35

Bis-(2,4-dimethyl-3-ethoxycarbonylpyrrolyl)methene (**106**), with high reactivity under basic conditions, acts as useful electrophilic reagent in treatment with oxindole **1** to form compound **107** which has been discovered as a new histone deacetylase (HDAC) inhibitor (Scheme 36).[55]



Scheme 36

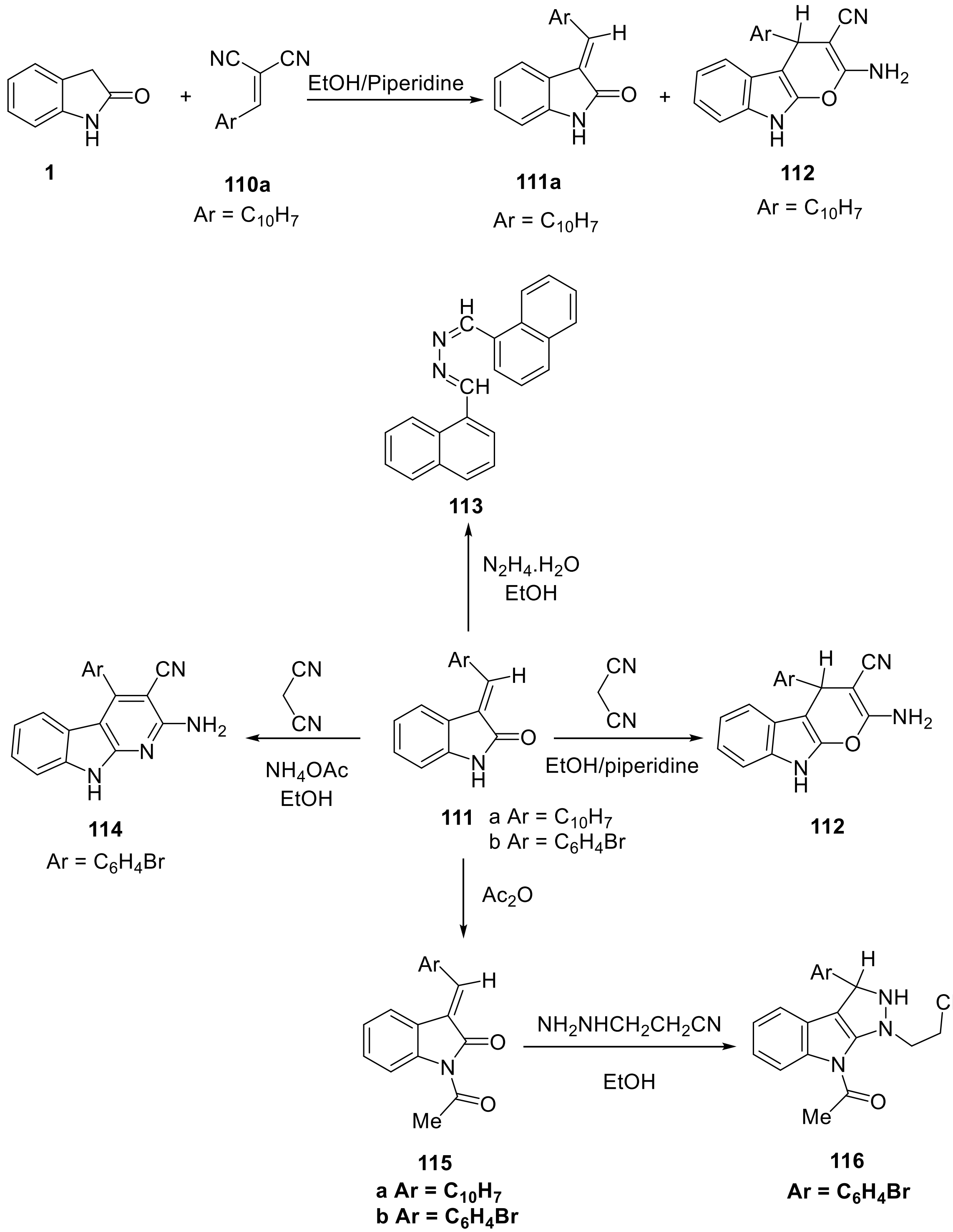
4-Phenyl-1,2,4-triazolinedione (PTAD, **108**) reacts with oxindole **1** to give the urazolyl compound **109** in the absence of a catalyst (Scheme 37).[56] However, with simpler carbonyl systems the reaction is greatly accelerated by an acid catalyst such as trifluoroacetic acid.



Scheme 37

2.5. Reactions with nitriles

Activated nitriles were used as starting materials to afford biologically activate fused heterocyclic compounds. Mahmoud and coworkers performed a condensation reaction between oxindole **1** and compound **110** upon treatment with piperidine to afford 3-arylidene oxindole **111** and pyrano[2,3-*b*]indole **112** (Scheme 39). Compound **112** also could be obtained from the reaction of **111** with malononitrile in refluxing EtOH in the presence of piperidine, while subsequent reaction of **111a** with hydrazine hydrate afforded the azine compound **113**. Similarly, the reaction of 2-bromobenzaldehyde with oxindole under the same conditions yielded the 3-(2-bromobenzylidene)oxindole **111b** that when fused with malononitrile afforded pyrido[2,3-*b*]indole **114**. Treatment of compounds **111a,b** with acetic anhydride yielded the N-acyl derivative **115a,b** which the reaction of **115b** with β-cyanoethylhydrazine in ethanol yielded pyrazolo[3,4-*b*]indole **116** (Scheme 38).[57] Compounds **114**, **115** and **116** proved to possess marked activity against *E. coli*, *S. aureus*, and *C. albicans*.

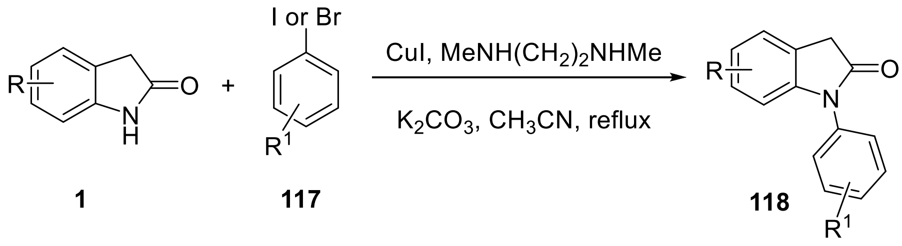

1
110a
Ar = C10H7
EtOH/Piperidine
111a
Ar = C10H7
112
Ar = C10H7
113
N2H4.H2O
EtOH
NH4OAc
EtOH
EtOH/piperidine
114
Ar = C6H4Br
111 a Ar = C10H7
b Ar = C6H4Br
112
Ac2O
NH2NHCH2CH2CN
EtOH
115
a Ar = C10H7
b Ar = C6H4Br
116
Ar = C6H4Br

Scheme 38

3. Reactions on the Nitrogen Atom

3.1. Reactions with halogen compounds

The coupling of aryl bromides or iodides **117** with oxindole **1** in the presence of a copper iodide-*N,N′*-dimethylethylenediamine (DMEDA) catalytic system was reported (Scheme 39).[58] Aryl iodides tend to give higher yields and shorter reaction times than the corresponding bromides.



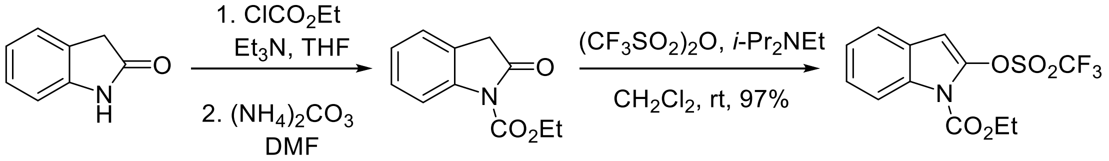
1 **117** **118**

aryl bromides R = H, 5-Cl, 6-Ph, 5-Me
R^1 = H, 3-CO_2Me, 4-CF_3, 3,4-Cl_2, 4-Pr, (2-F, 4-Me), 3,4-Me_2, 4/5=OCH_2O

aryl iodides R = H, 5-F, 6-Cl, 6-CF_3, 6-CO_2Me, 6-Br
R^1 = 3,5-Me_2, 3,4-Me_2, 3-CO_2Me

Scheme 39

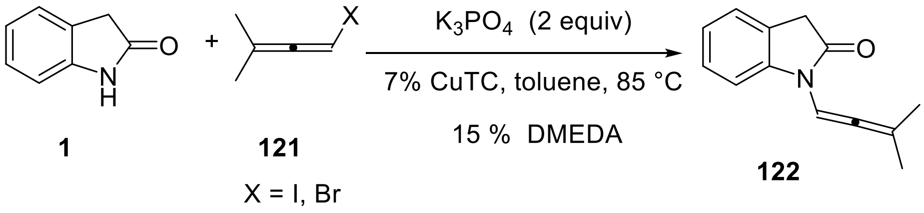
Ethyl 2-oxo-2,3-dihydroindole-1-carboxylate (**119**) obtained in 80% yield from oxindole **1**, could represent a useful building block for the synthesis of the corresponding triflate. Thus, 2-trifluoromethanesulfonyloxyindole-1-carboxylic acid ethyl ester **120** has been prepared by the treatment of **119** with triflic anhydride $(CF_3SO_2)_2O$ at room temperature in the presence of diisopropylethylamine (Scheme 40).[59]



1 **119** **120**

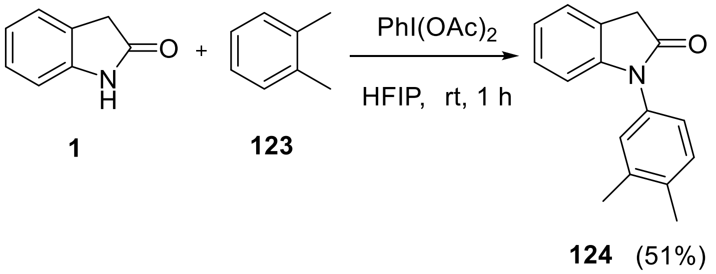
Scheme 40

Trost and Stiles have synthesized the *N*-substituted oxindole **122** by the copper-catalyzed coupling reaction between oxindole **1** and allenyl halide **121** (Scheme 41).[60] Copper thiophene-2-carboxylate (CuTC) was selected as a source of copper (I) because of its shelf-stability. This reaction was also carried out with chiral allenyl iodides using catalytic copper (I) salt and *N,N′*-dimethylethylenediamine.[61]



Scheme 41

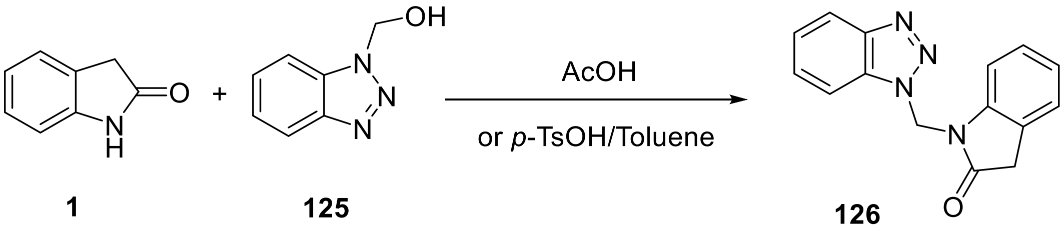
The cross-amination of oxindole **1** with *ortho*-xylene **123** in the presence of (diacetoxy)iodobenzene and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) has been described which resulted in the formation of desired product, *N*-aryl-2-oxindole **124**, as a single regioisomer (Scheme 42).[62]



Scheme 42

3.2. Reactions with alcohols

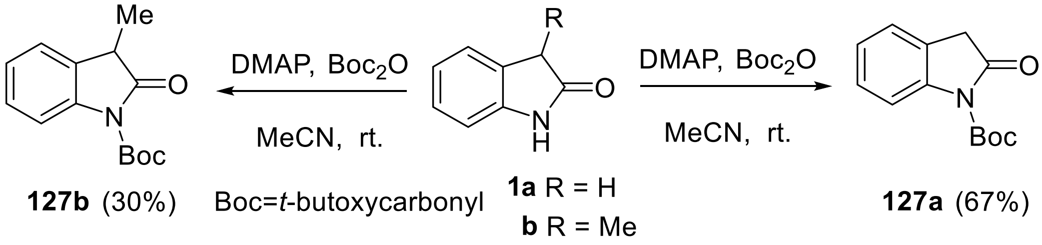
The reaction of oxindole **1** with 1-(hydroxymethyl)benzotriazole **125** in acetic acid or in refluxing toluene in the presence of *p*-toluenesulfonic acid afforded compound **126** in good yield (Scheme 43).[63]



Scheme 43

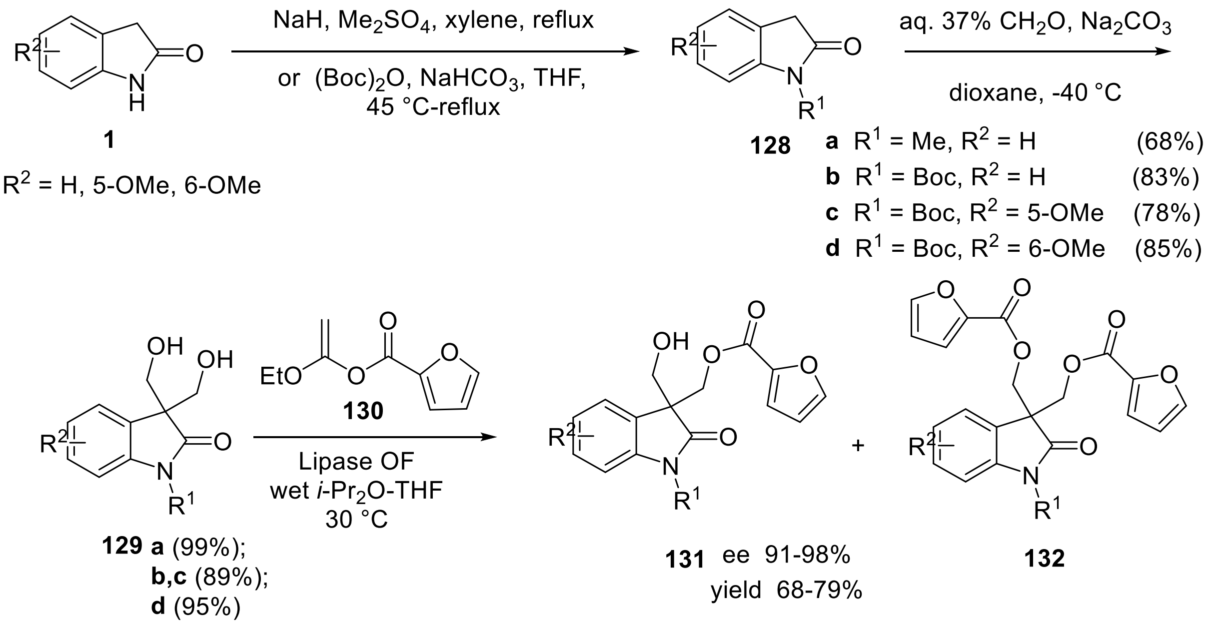
3.3. Reactions with anhydrides

4-Dimethylaminopyridine (DMAP) is a general catalyst well-known to catalyze acylation reactions involving a variety of functional groups.[64,65] Protection of oxindoles was carried out using Boc-anhydride and DMAP in acetonitrile. Application of this procedure to oxindole **1a** yielded *N*-Boc-oxindole **127a** in 67% yield. But, treatment of 3-methyloxindole **1b** with Boc_2O and DMAP under the same condition, yielded a complex mixture of mono and diacylated derivatives from which *N*-Boc-3-methyloxindole **127b** was isolated in 30% yield (Scheme 44).[66]



Scheme 44

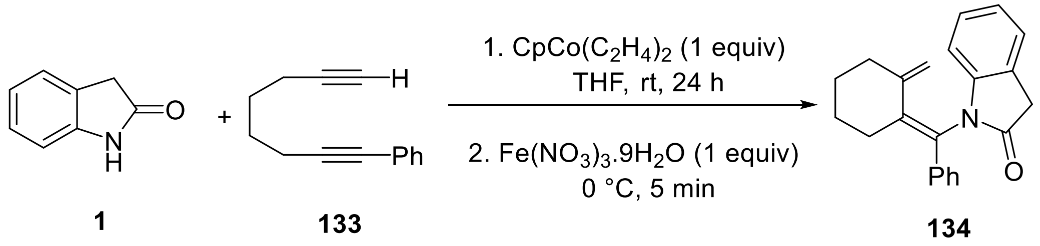
Oxindoles **131** having a chiral quaternary carbon center at the C-3 position, were synthesized via an enantioselective desymmetrization of prochiral 1,3-diols **129**. Using a *Candida rugosa* lipase (Meito OF) and a prominent acyl donor, 1-ethoxyvinyl 2-furoate **130**, is the key step of this reaction (Scheme 45).[67]



Scheme 45

3.4. Reactions with alkynes

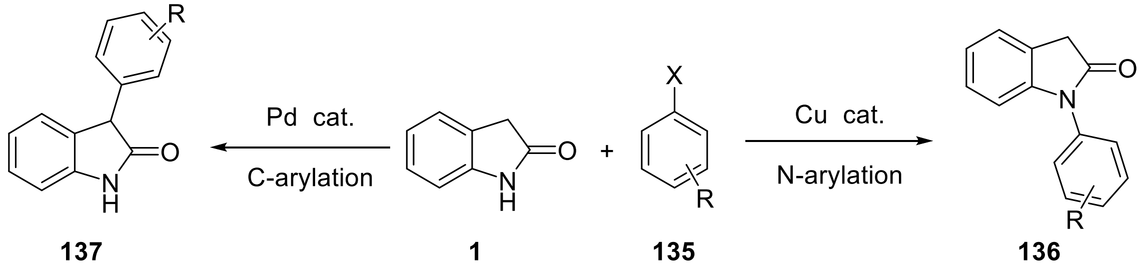
Oxindole **1** in the presence of a cobaltocyclopentadiene complex CpCo(C_2H_4)$_2$ reacts with α,ω-diynes **133** to give new dienamides **134** with control of regio- and stereochemistry (Scheme 46).[68] Dienamides are starting materials for the preparation of polycyclic systems.



Scheme 46

3.5. Competition between C-3 and nitrogen alkylation

In the cross-coupling reactions of unprotected oxindoles **1** with aryl halides, Pd- and Cu-based catalyst systems displayed orthogonal chemoselectivity. A Pd-dialkylbiarylphosphine-based catalyst chemoselectively arylated oxindole at the C-3 position **137**, while arylation occurred exclusively at the nitrogen atom **136** using a Cu-diamine-based catalyst system (Scheme 47).[69]



X = Br, Cl, OTs, OTf
R = 4-Me, 4-OMe, 3-CF_3, 4-OH, 4-F, 4-CN, 4-*t*-Bu, 3-OMe, 3-NMe_2, 3-CO_2Me

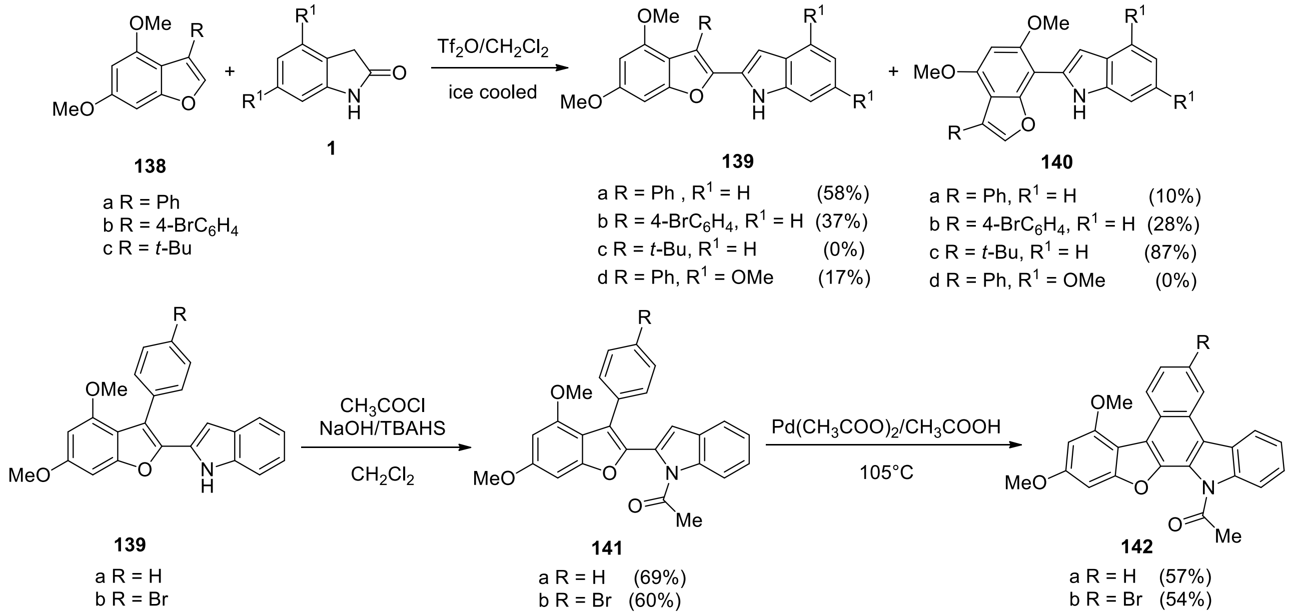
X = I, Br
R = 4-OMe, 4-CF_3, 3-NO_2, 4-Br, 4-F, 4-Cl, 4-CN, 3-OMe, 4-NMe_2, 3-CO_2Et, 3,5-Me_2

Scheme 47

4. Reactions on the Carbonyl Site

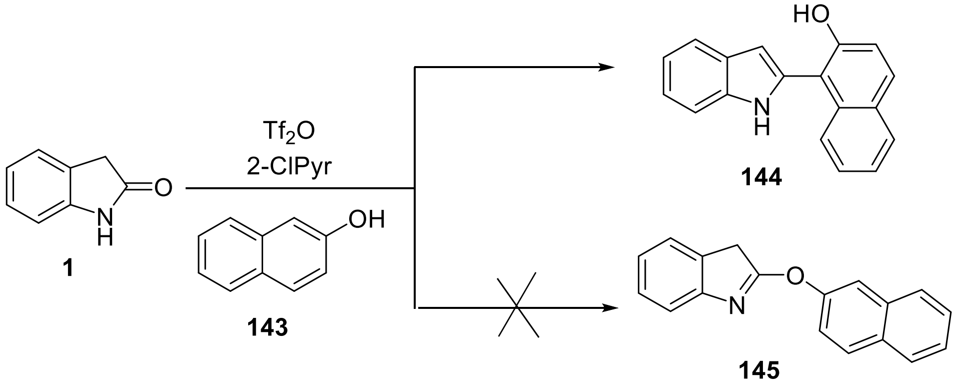
4.1. Reactions at the carbonyl carbon

Regioselective reactions of 3-substituted 4,6-dimethoxybenzofurans **138** with oxindole **1** and triflic anhydride afforded 7- and/or 2-substituted benzofuranylindoles **139** and **140**. Cyclization of compound **139** to benzofuran-fused benzocarbazoles **142** has been reported using palladium (II) acetate in acetic acid at 105 °C (Scheme 48).[70]



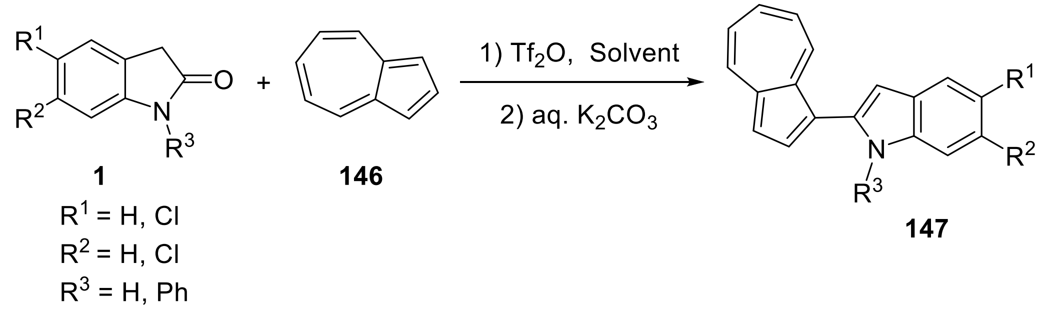
Scheme 48

The direct transformation of various secondary amides into *N*-arylimidates via mild electrophilic amide activation with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of 2-chloropyridine (2-ClPyr) has been described. While low-temperature amide activation followed by C–O bond formation with 2-naphthol **143** provided the desired *N*-arylimidates, in contrast, reaction with oxindole **1** proceeded via formation of a C–C bond to give 1-(1*H*-indol-2-yl)naphthalen-2-ol **144** (Scheme 49).[71] It is believed that the different behavior of oxindole in comparison to other amides relies on the different intermediates reacting with 2-naphthol.



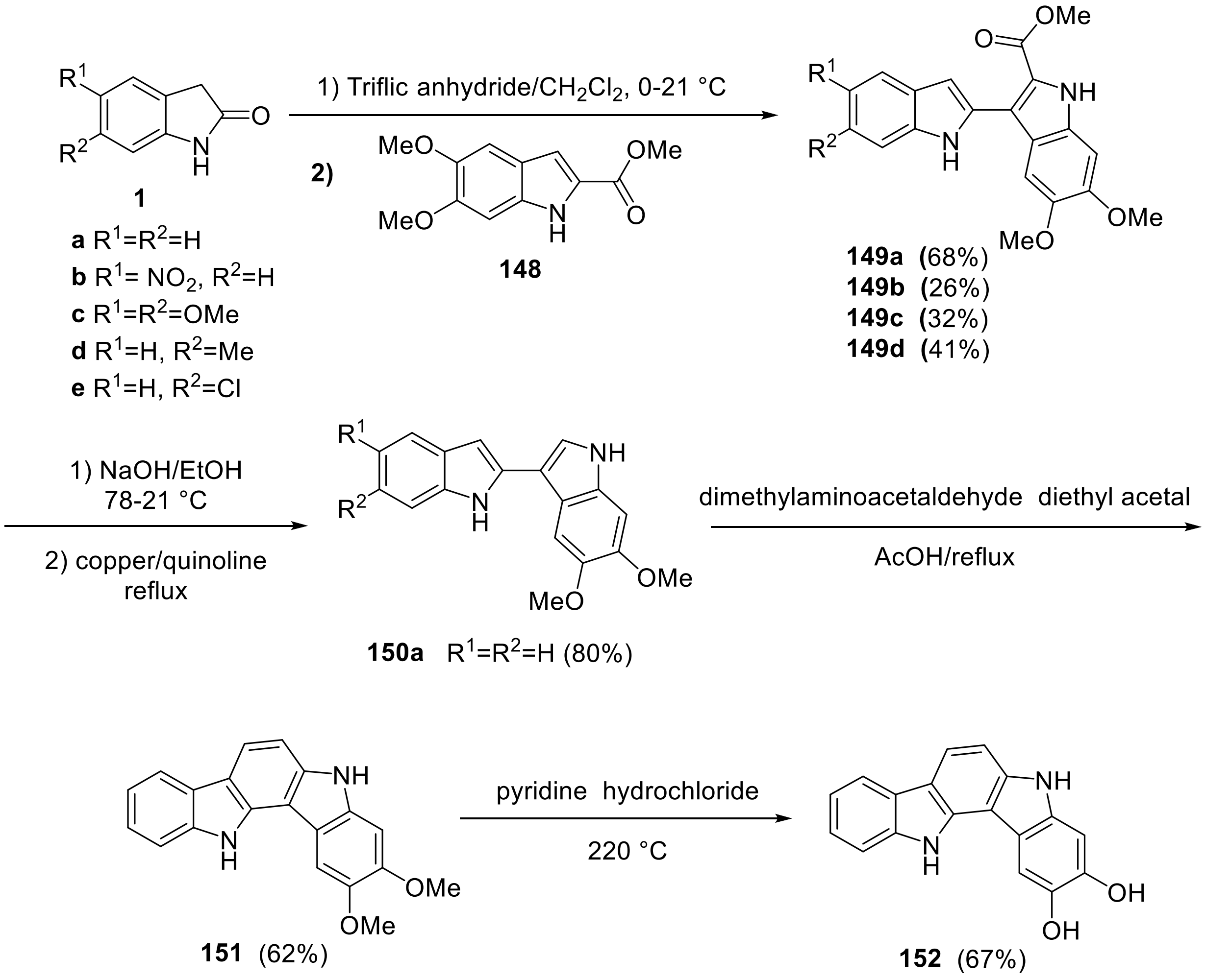
Scheme 49

Reaction of azulene derivatives **146** with oxinoles **1** in the presence of Tf_2O and following hydrolysis with aq. K_2CO_3 afforded 2-(azulen-1-yl)indoles **147** in good yields (Scheme 50).[72] This methodology is the first synthesis of such indole-substituted azulenes.



Scheme 50

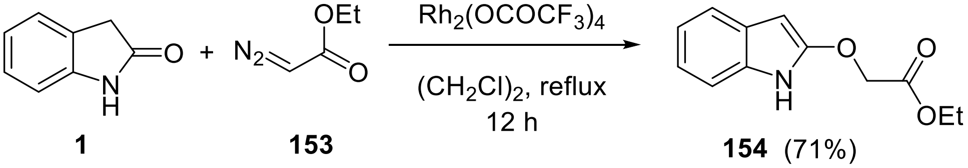
Several mono- and bis-indoles with therapeutic properties, have been isolated from a marine sponge of the Ancorina species.[73] Some activated 2,3′-biindolyls were prepared via modified Vilsmeier reactions. Reaction between oxindole **1** and methyl 5,6-dimethoxyindole-2-carboxylate **148** in triflic acid and following hydrolysis of the product afforded 2,3′-biindolyl **150** which was then transformed to the indolocarbazole **152** (Scheme 51).[74]



Scheme 51

4.2. Reactions on the carbonyl oxygen

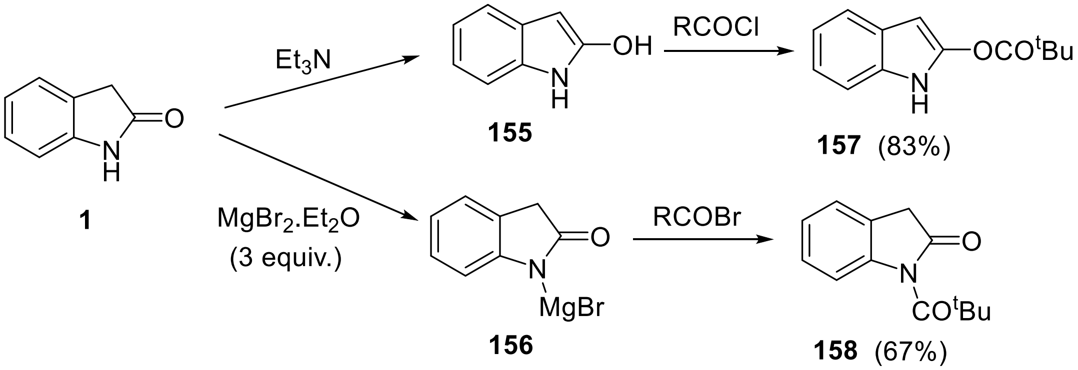
The Rh(II)-catalyzed reaction of diazoacetic esters **153** with the carbonyl group of oxindole **1** is an effective method for the synthesis of the indolyloxyacetate ester **154** derived from the corresponding enolic form (Scheme 52).[75]



Scheme 52

4.3. Competition between acylation at nitrogen and the carbonyl group

Acylation of oxindole with pivaloyl chloride in the presence of Et_3N resulted in the formation of the *O*-acyl compound **157** while acylation in the presence of $MgBr_2.Et_2O$ afforded *N*-acyl oxindole **158** (Scheme 53).[76]

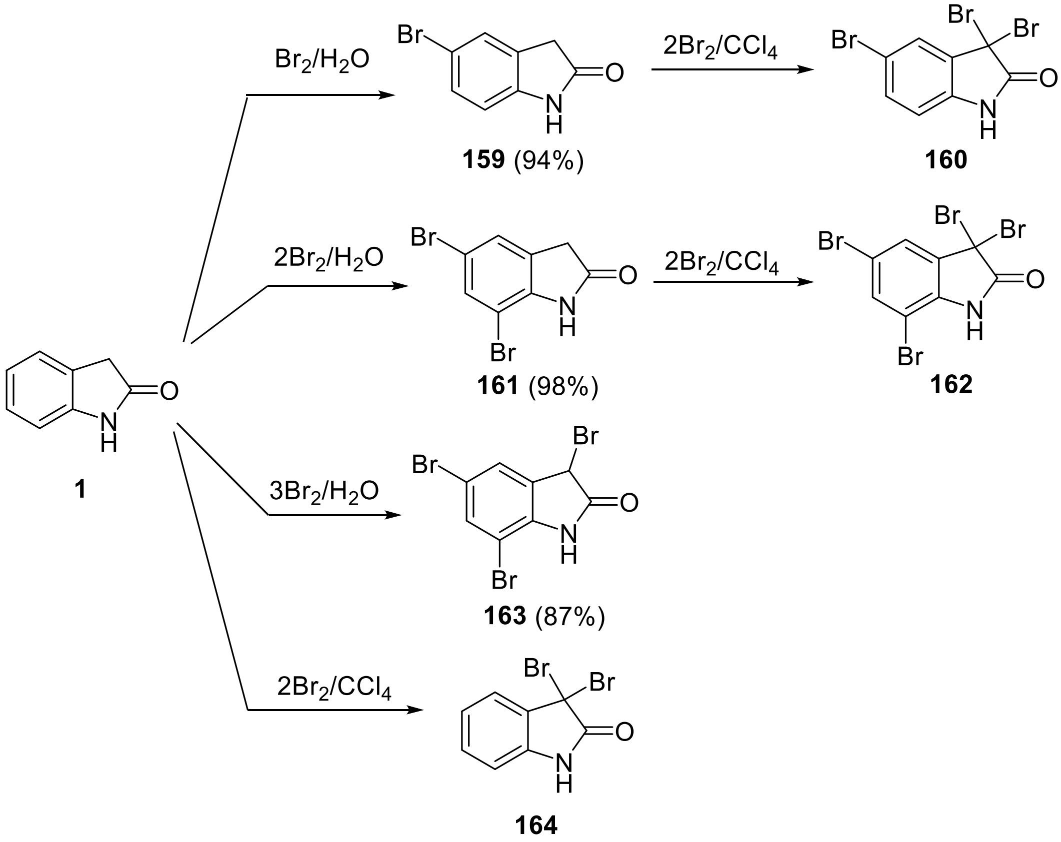


Scheme 53

5. Reactions on the Aromatic Ring

5.1. Bromination of oxindole

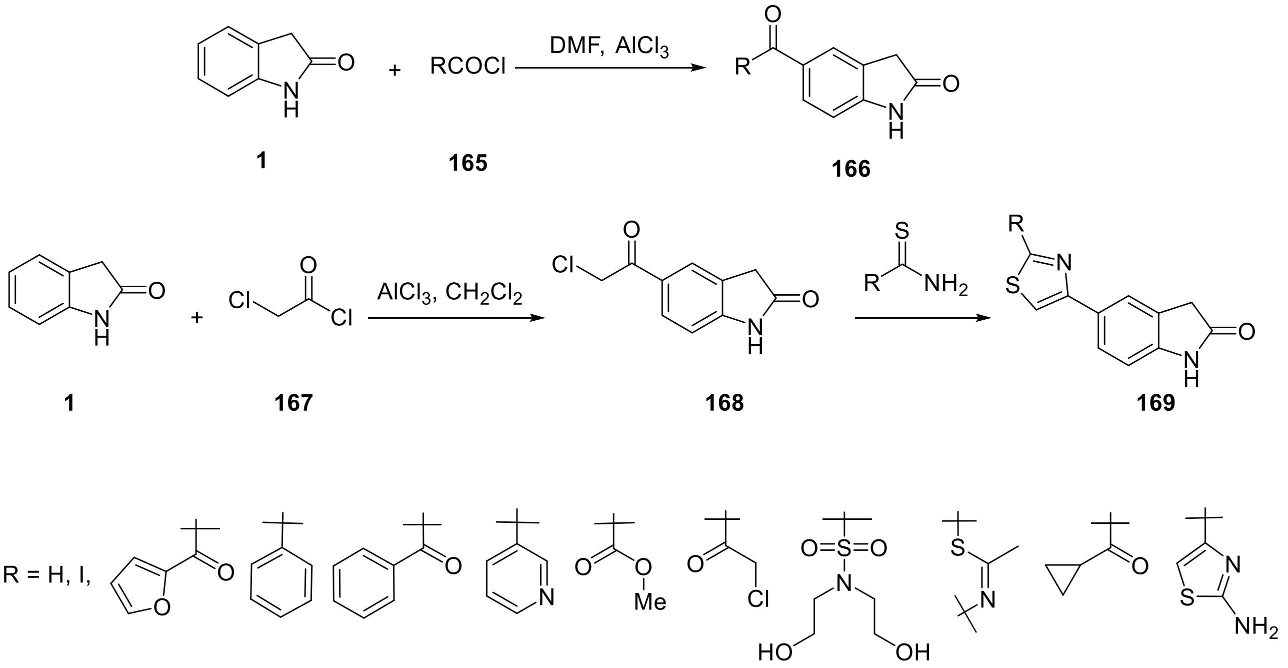
Bromination of oxindole **1** in aqueous solution in the presence of one, two and three equivalents of bromine yielded respectively 5-bromooxindole **159**, 5,7-dibromooxindole **161** and 3,5,7-tribromooxindole **163**. In addition, bromination of oxindole **1** and the substituted oxindole derivatives **159** and **161** in anhydrous CCl_4 afforded the corresponding 3,3-dibromooxindole derivatives **164**, **160** and **162**, respectively (Scheme 54).[77]



Scheme 54

5.2. Acylation of oxindole

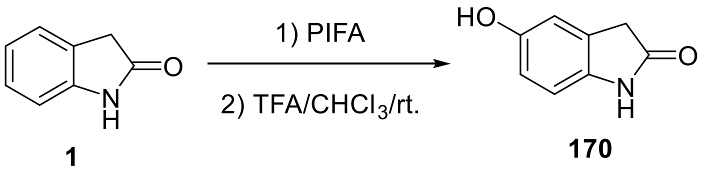
Selective acylation of oxindole utilizing a variety of acyl chlorides was achieved using aluminium chloride in DMF. Acylation of oxindole with chloroacetyl chloride readily afforded the 5-chloromethyl ketone derivatives **168** which were treated with thioureas and thioamides to give functionalized 5-thiazole oxindoles **169** (Scheme 55).[78]



Scheme 55

5.3. Hydroxylation of oxindole

Treatment of oxindole **1** with phenyliodine(III) bis(trifluoroacetate) (PIFA) in trifluoroacetic acid introduced a hydroxyl group at the aromatic ring of oxindole **170** (Scheme 56).[79]

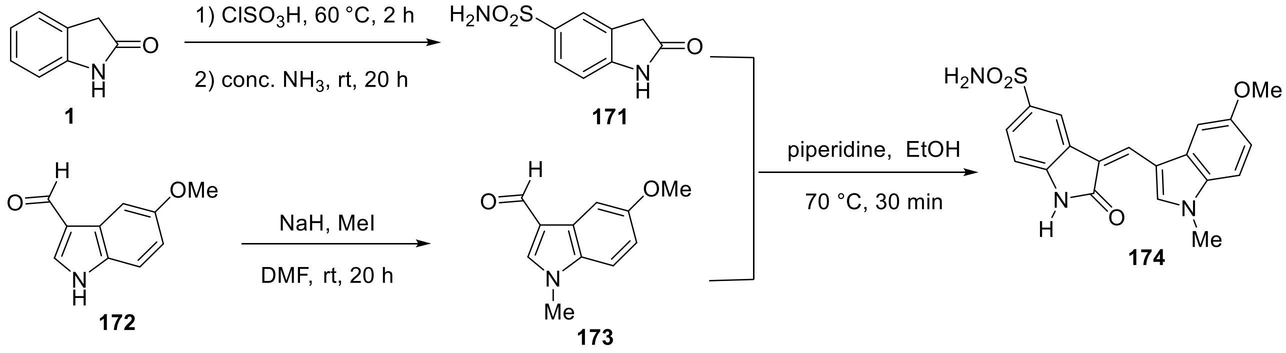


Scheme 56

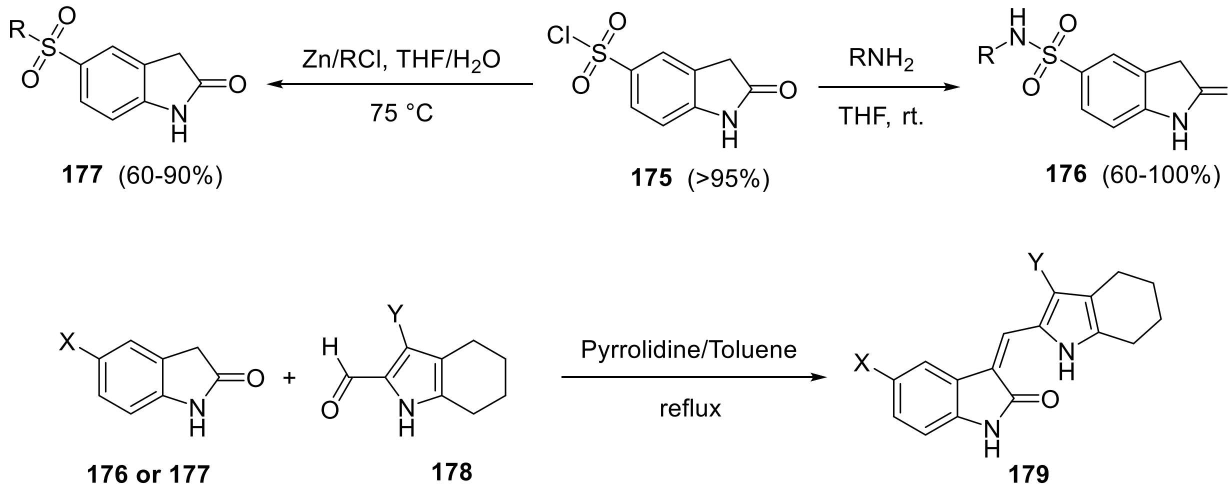
5.4. Oxindole sulfones and sulfonamides

Lai and coworkers prepared the oxindole sulfonamide **171** by the reaction of oxindole with chlorosulfonic acid and NH_3. The sulfonamide was then condensed with the indole aldehyde **173** in the presence of catalytic amount of piperidine to give the final product **174** (Scheme 57).[80]

A series of tetrahydroindole based indolinones **179** as tyrosine kinase inhibitors were synthesized through three steps reactions: (1) preparation of substituted oxindole cores **176** and **177** (2) preparation of functionalized pyrrole aldehydes **178** and (3) aldol condensation of the two moieties under basic condition. Oxindole sulfonamides **176** and sulfones **177** were prepared by chlorosulfonylation of oxindole to **175** followed by amidation or alkylation of the sulfonyl chloride group, respectively (Scheme 58).[4]



Scheme 57



X = SO_2NHCH_3, SO_2NH_2, $SO_2NHCH_2CH_2OH$, $SO_2NHCH_2(4\text{-}F\text{-}C_6H_4)$,
$SO_2NH(2\text{-}Cl\text{-}C_6H_4)$, $SO_2\text{-}NMe_2$, SO_2Me, SO_2Et, $SO_2CH(CH_3)_2$

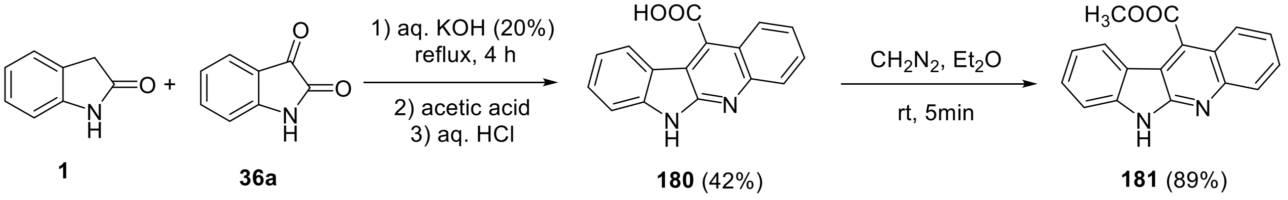
Y = H, CH_2COOH, $(CH_2)_3NH(CH_2CH_2)_2NCO_2Et$, $(CH_2)_3N(CH_2CH_2)_2NCOCH_2OH$,
$(CH_2)_3N(CH_2CH_2)_2NCH_2CO_2Et$,
$(CH_2)_3N(CH_2CH_2)_2CHOH$, $(CH_2)_3N(CH_2CH_2)_2NCH_2CH_2OH$, $(CH_2)_3N(CH_2CH_2)_2NMe$,
$(CH_2)_3N(CH_2CH_2)_2NH$,
$(CH_2)_2CON(CH_2CH_2)_2NMe$, $CH_2N(CH_2CH_2)_2O$

Scheme 58

6. Simultaneous Participation of More than One Site in Reactions

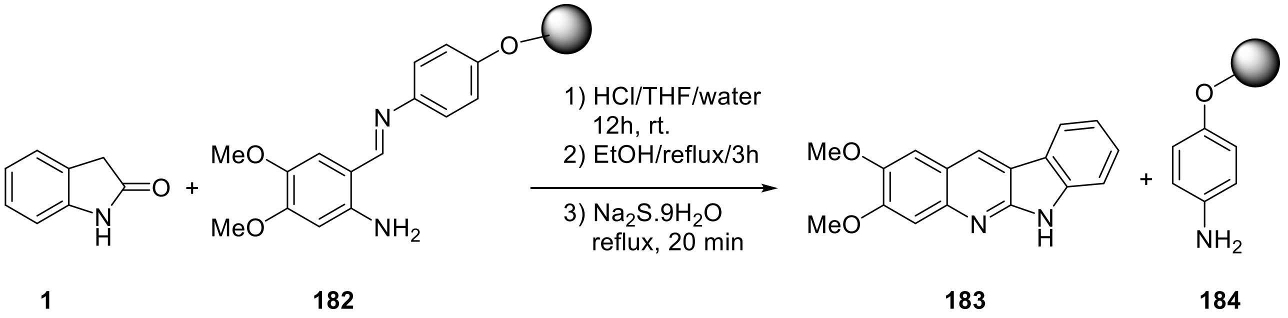
6.1. C-3 and carbonyl group

Condensation of oxindole with isatin **36a** under alkaline conditions afforded the acid **180** which in treatment with diazomethane was converted into the corresponding methyl ester **181** (Scheme 59).[81]



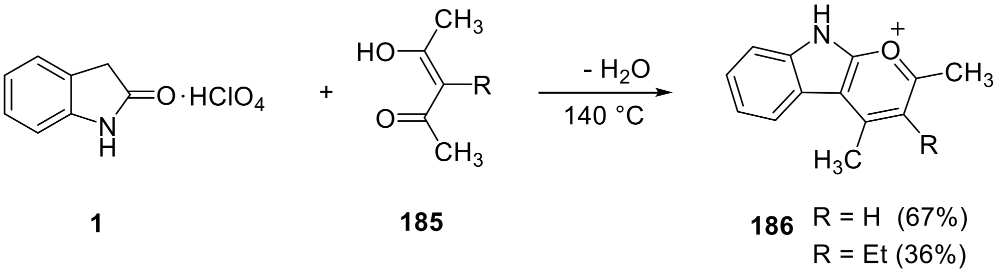
Scheme 59

In another study, a solid-phase synthesis of quinoline **183** was accomplished through the reaction of oxindole and the resin-bound azomethine **182**[82] based on Friedländer-type reaction (Scheme 60).[83,84]



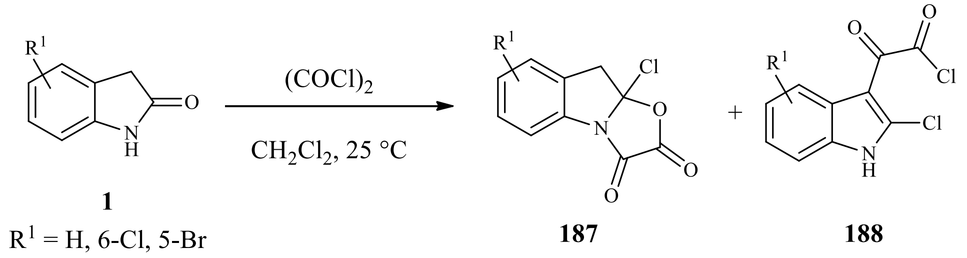
Scheme 60

Chuiguk found that oxindole perchlorate can react with β-diketones in alcoholic HCl to produce pyrano[2,3-*b*]indolium derivatives **186** (Scheme 61).[85] Heating of **186** with *p*-dimethylamino benzaldehyde in acetic anhydride results in the formation of polymethine dyes.



Scheme 61

Repeating the literature examples, Magnus and coworkers found that treatment of oxindole with oxalyl chloride gave a precipitate of **188** (46%) and the filtrate contained the compound **187** (42%) (Scheme 62).[86]

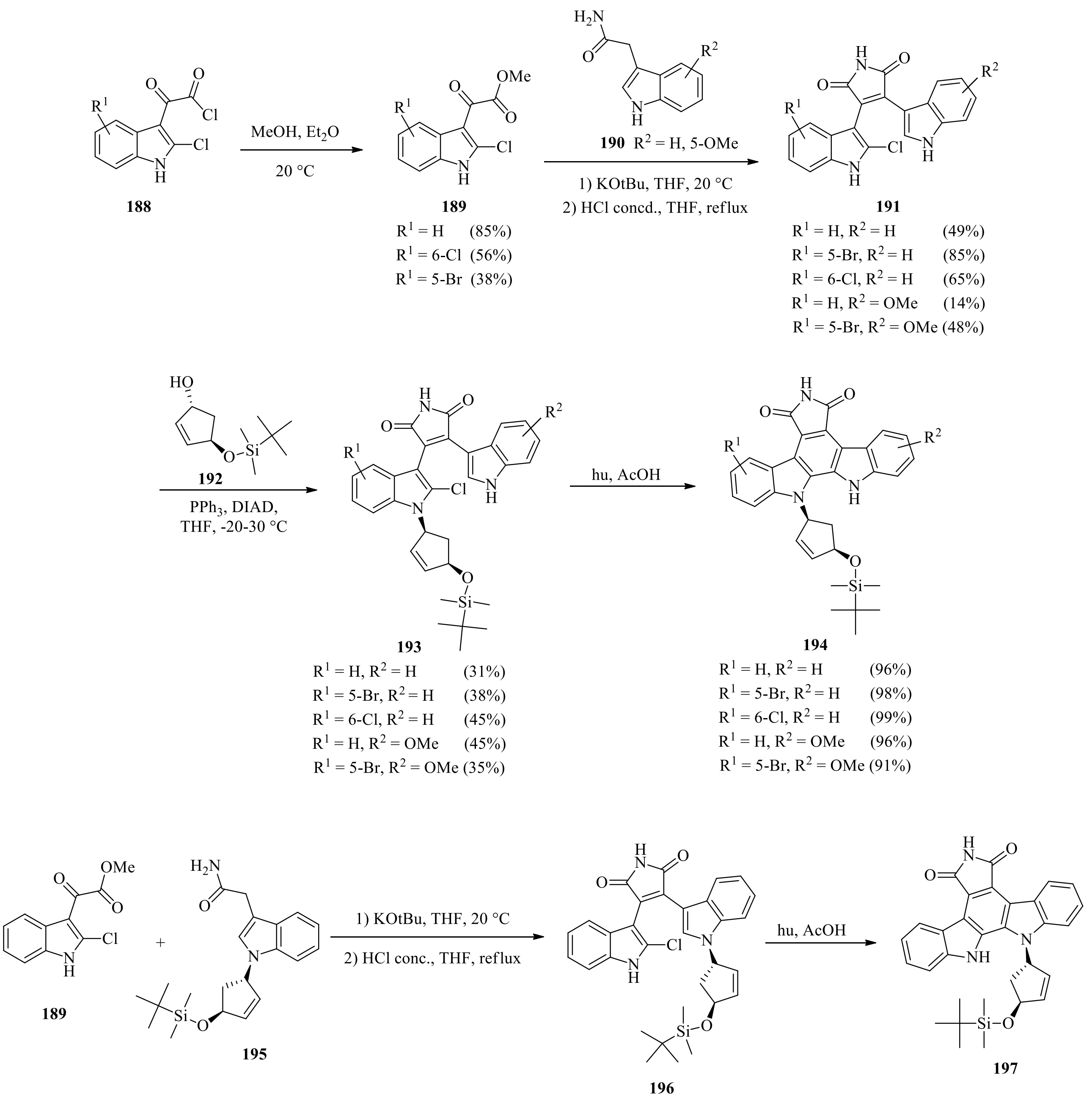


Scheme 62

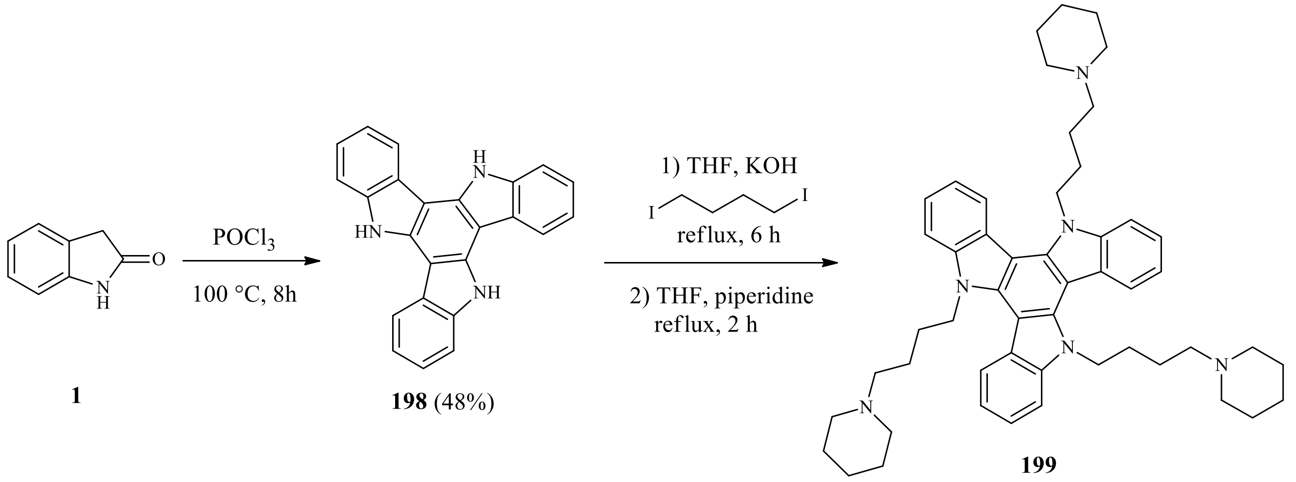
In another study, Sahugan and coworkers combined indole-derived building blocks with indolylacetamides to allow the direct region-controlled synthesis of *N*-indole-monosubstituted indolopyrrolocarbazoles (IPCs).

Intermolecular Perkin-type condensation of **189** with indole-3-acetamides **190** in the presence of KOtBu provided unsymmetrical bisindolylmaleimides **191**. Reaction of **191** with an allylic cyclopentenol under classical Mitsunobu conditions afforded the corresponding bisindolylmaleimides **193**. Finally, subsequent cyclization of **193** to IPCs **194** was performed by simple irradiation with a strong light source. A second strategy was elaborated for the synthesis of the opposite regioisomers **197**. Condensation of compound **195** with methyl 2-chloroindole-3-glyoxylates **189** provided the corresponding functionalized bisindolyl-maleimides **196** which cyclization to the complementary IPCs **197** was achieved as described before (Scheme 63).[87]

The reaction of oxindole with phosphoryl chloride to give the corresponding triazatruxene **198** has been described. The *N*-alkylation with an excess of diiodobutane in basic condition followed by substitution of the iodide with piperidine resulted in the formation of Azatrux **199**. The new compound Azatrux is a water-soluble triazatruxene derivative that selectively binds to G-quadruplex DNA (Scheme 64).[88]

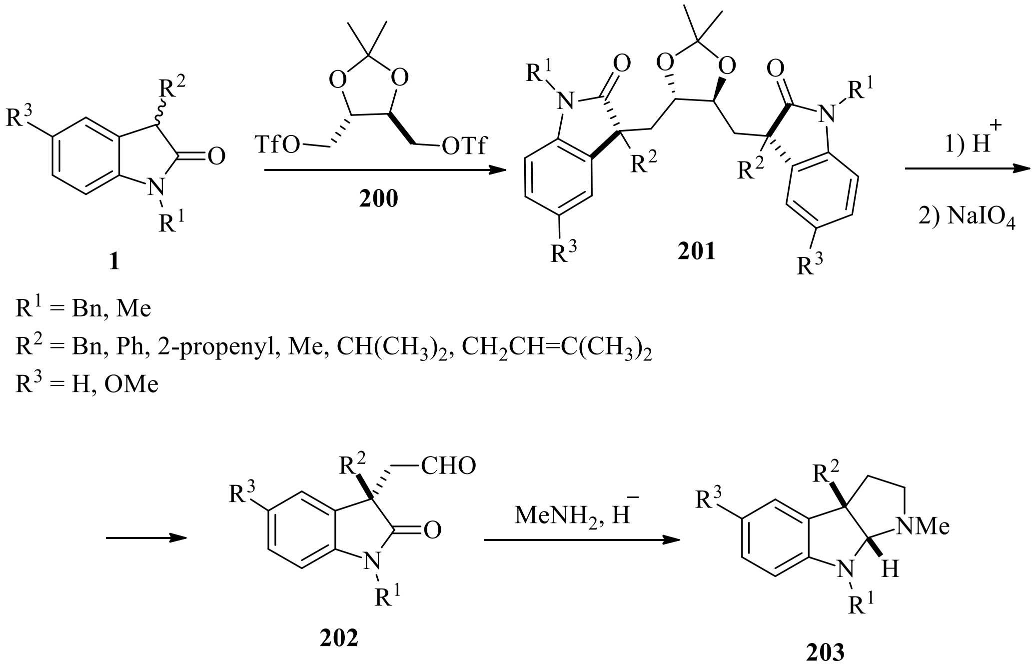

188
MeOH, Et$_2$O
20 °C
189
R^1 = H (85%)
R^1 = 6-Cl (56%)
R^1 = 5-Br (38%)
190 R^2 = H, 5-OMe
1) KOtBu, THF, 20 °C
2) HCl concd., THF, reflux
191
R^1 = H, R^2 = H (49%)
R^1 = 5-Br, R^2 = H (85%)
R^1 = 6-Cl, R^2 = H (65%)
R^1 = H, R^2 = OMe (14%)
R^1 = 5-Br, R^2 = OMe (48%)
192
PPh$_3$, DIAD,
THF, -20-30 °C
193
R^1 = H, R^2 = H (31%)
R^1 = 5-Br, R^2 = H (38%)
R^1 = 6-Cl, R^2 = H (45%)
R^1 = H, R^2 = OMe (45%)
R^1 = 5-Br, R^2 = OMe (35%)
hu, AcOH
194
R^1 = H, R^2 = H (96%)
R^1 = 5-Br, R^2 = H (98%)
R^1 = 6-Cl, R^2 = H (99%)
R^1 = H, R^2 = OMe (96%)
R^1 = 5-Br, R^2 = OMe (91%)
189
195
1) KOtBu, THF, 20 °C
2) HCl conc., THF, reflux
196
hu, AcOH
197

Scheme 63



Scheme 64

An asymmetric synthesis of hexahydropyrroloindoles **203** in high enantiopurity was achieved through the dialkylation of enantiopure ditriflate **200** with 2 equiv of oxindole enolates as the central step. As dialkylation product **201** encodes 2 equiv of oxindole aldehyde **202**, an attractive route to pyrrolidinoindolines **203** appeared possible (Scheme 65).[89]



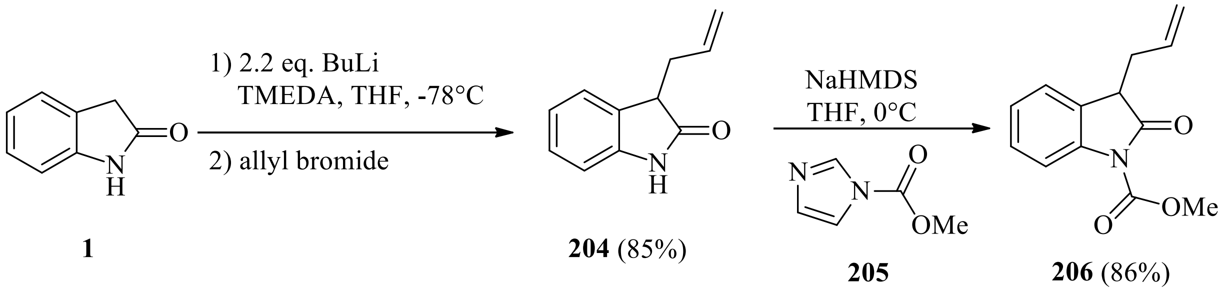
R^1 = Bn, Me
R^2 = Bn, Ph, 2-propenyl, Me, $CH(CH_3)_2$, $CH_2CH{=}C(CH_3)_2$
R^3 = H, OMe

Scheme 65

6.2. C-3 and nitrogen atom

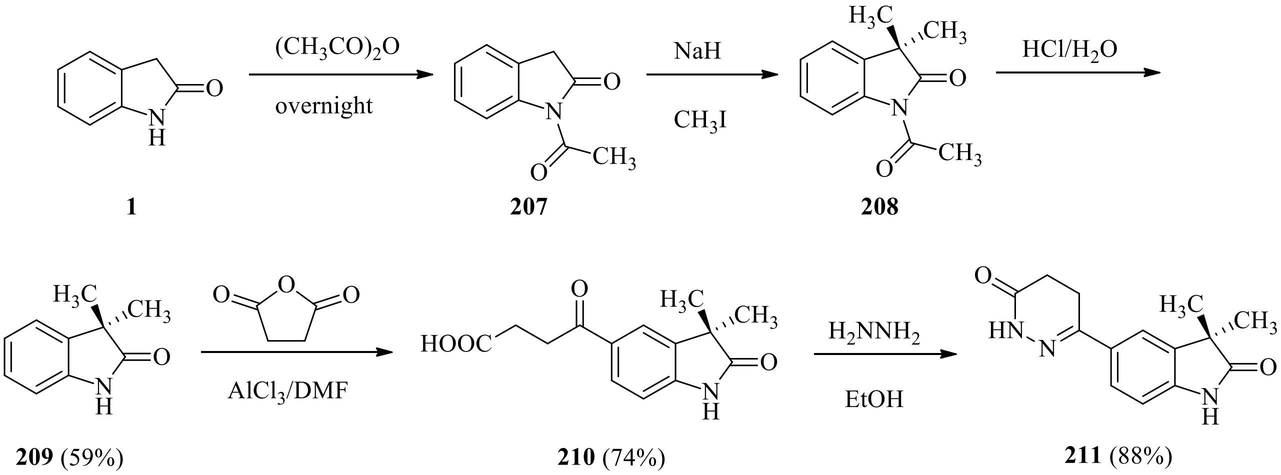
Reaction of oxindole with the excess of BuLi in the presence of TMEDA afforded the dianion of oxindole which can be quenched with allyl bromide to afford the monoallylated oxindole **204**.

Subjecting the Na salt of oxindole **204** to imidazole carboxylate **205** resulted in the mono-*N*-carbamoylated product **206** with high regioselectivity (Scheme 66).[90]



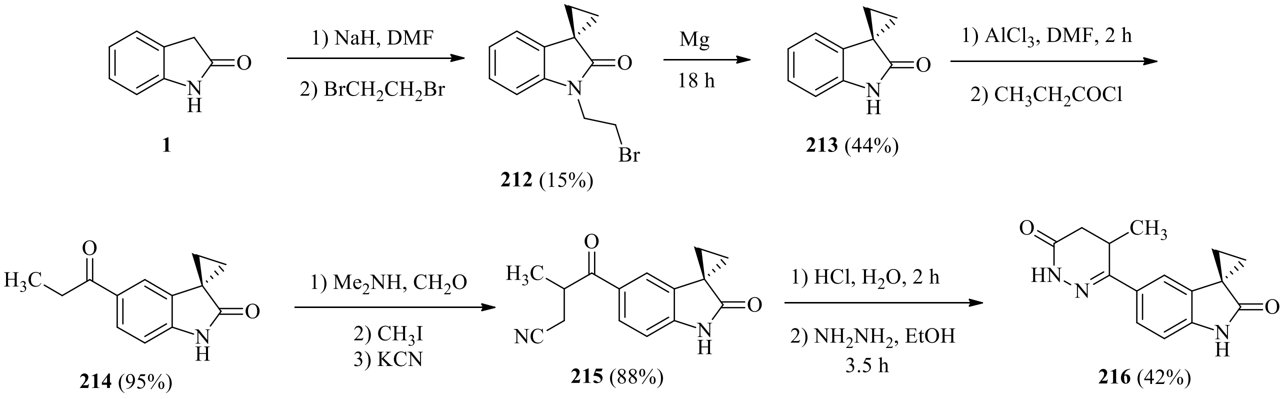
Scheme 66

Starting from oxindole and acetic anhydride, 1-acetyl-1,3-dihydro-2*H*-indol-2-one **207** was prepared. Exhaustive methylation of **207**, followed by removal of the protecting group, afforded 1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one **209**. Subsequent Friedel-Crafts acylation of compound **209** with succinic anhydride provided the 4-oxobutanoic acid **210** which its cyclization with hydrazine hydrate resulted in the formation of final product **211** (Scheme 67).[91] It was shown that compound **211** is a potent positive inotrope in dogs.



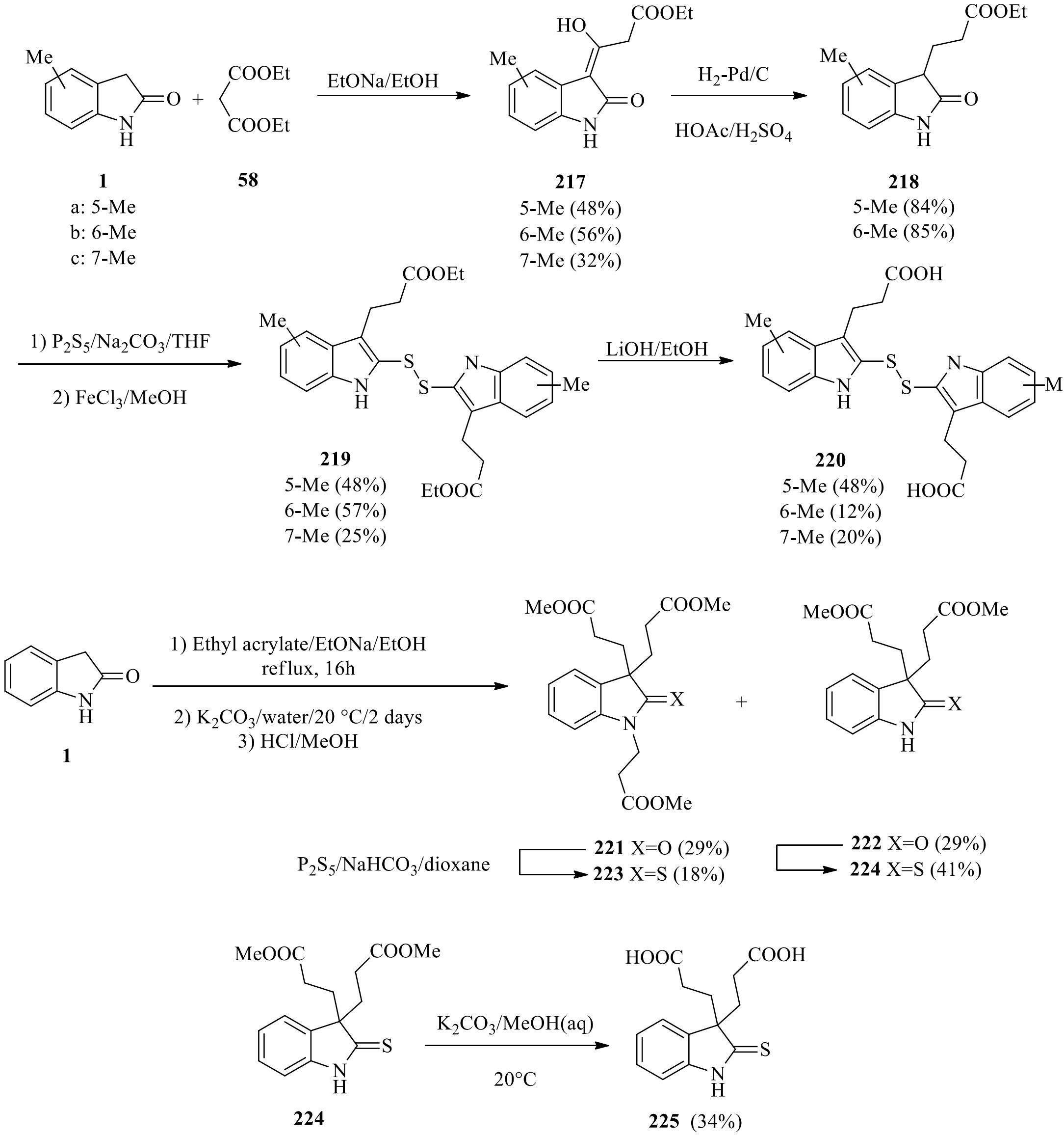
Scheme 67

In another study, oxindole was reacted with an excess of sodium hydride and 1,2-dibromoethane, followed by magnesium-induced debromoethylation to afford compound **213**. Friedel-Crafts acylation of compound **213** with propionyl chloride yielded **214**. Formation of the Mannich base, quaternarization with iodomethane, followed by reaction with potassium cyanide, produced γ-keto nitrile **215**. Sequential acid-catalyzed hydrolysis and hydrazine cyclization completed the synthesis of the final product **216** (Scheme 68).[92] Compound **216** is one of the most potent noncatecholamine, nonglycoside positive inotropes which has been examined.



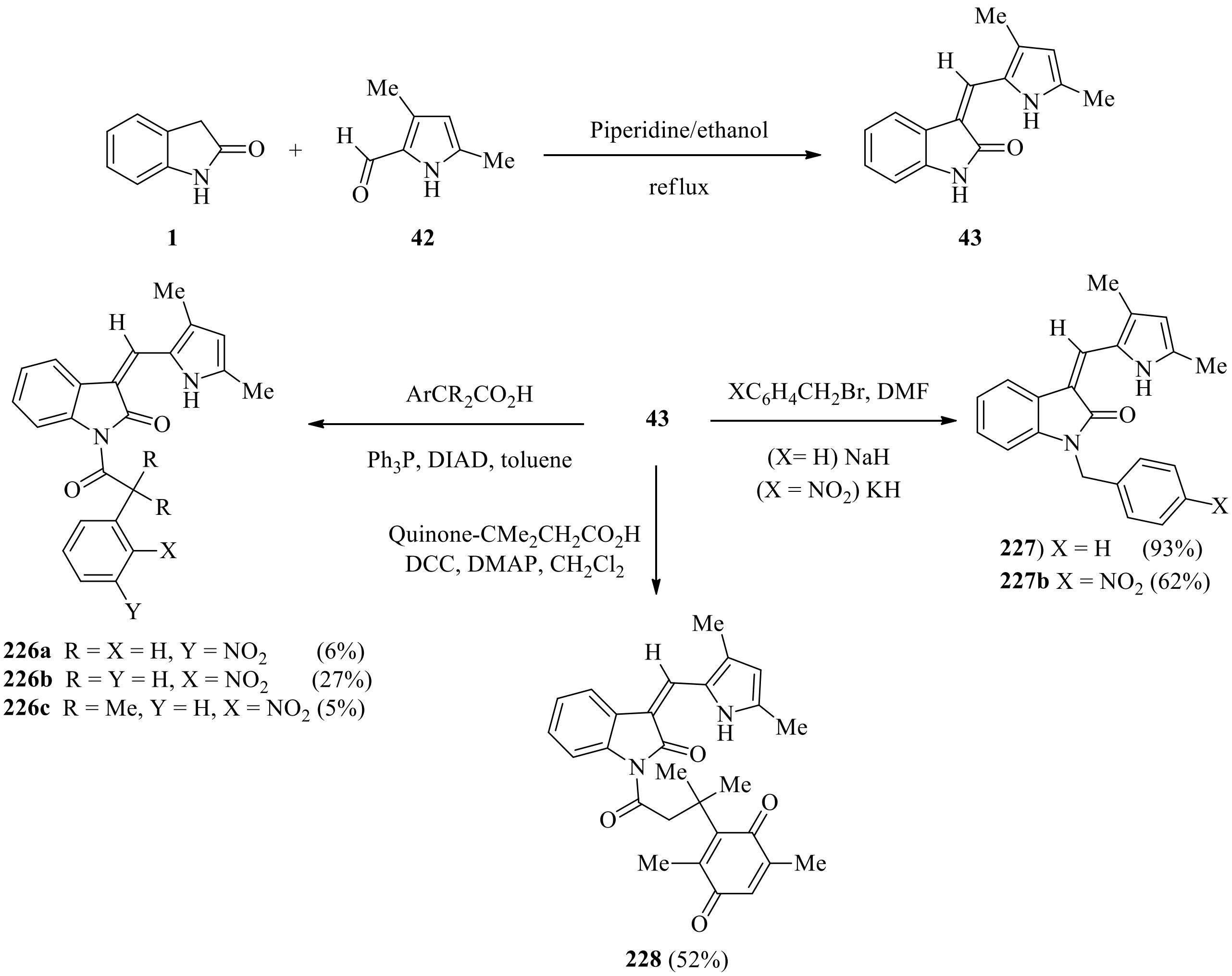
Scheme 68

The 5-, 6-, and 7-methyl derivatives of ethyl 2,3-dihydro-2-oxo-1*H*-indole-3-propanoate **217** were prepared by the condensation of methyl-substituted oxindoles **1** with diethyl malonate **58**. Compounds **217** undergo catalytic hydrogenation over palladium-on-carbon catalyst to the desired products **218**. Thiation with P_2S_5/Na_2CO_3, followed by oxidation with $FeCl_3$ then afforded 2,2′-dithiobis-1*H*-indole-3-propanoates **219**. Final hydrolysis of **219** with LiOH in aqueous EtOH resulted in 2,2′-dithiobis-1*H*-indole-3-propanoic acids **220**. In another reaction, the condensation of oxindole with ethyl acrylate followed by hydrolysis and methylation, resulted in a mixture of di- and trimethyl oxindolepropanoates (**222** and **221**). These compounds were separated by chromatography and were thiated with P_2S_5 (**224** and **223**) and hydrolyzed to give the diacid **225** (Scheme 69).[93]



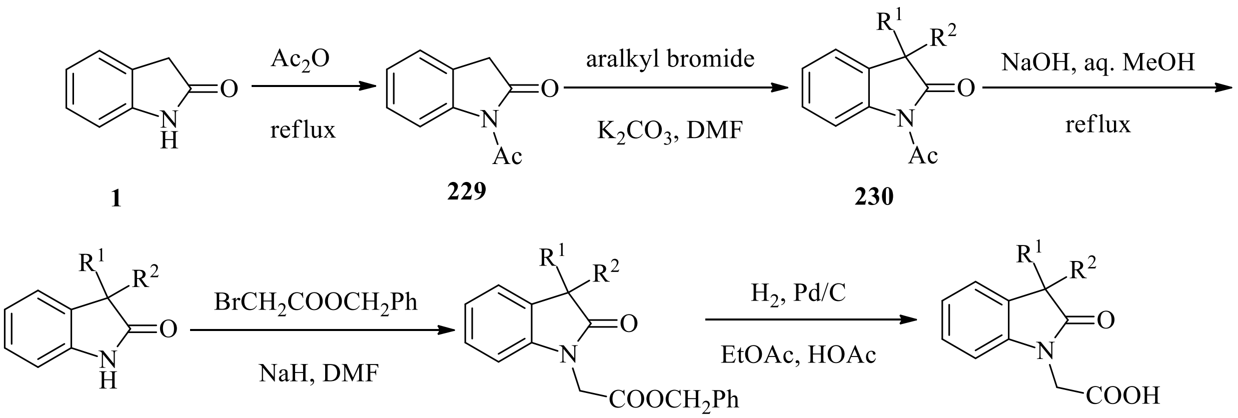
Scheme 69

Semaxinib **43** has been synthesized by the reaction between oxindole and 3,5-dimethylpyrrole-2-carboxaldehyde **42**,[94] as described before.[33] An analogous set of compounds **226**, **227** and **228** was prepared from Semaxanib as outlined in Scheme 70. Diisopropyl azodicarboxylate (DIAD), phenylacetic acid derivatives, and triphenylphosphine were reacted with Semaxanib to give compounds **226a-c** while compounds **227a-b** were prepared by benzylation of Semaxanib. Finally, Semaxanib, dicyclohexylcarbodiimide (DCC) and DMAP were added to 3-methyl-3-(3,6-dimethyl-2,5-dioxobenzen-2-yl)butanoic acid (quinone-$CMe_2CH_2CO_2H$) to generate compound **228**.[95] These compounds were screened for their anti-angiogenic activities.



Scheme 70

The preparation of the oxindole acetic acids was accomplished *via* two general processes. The 3,3-bis-substituted oxindole derivatives **233** and related spiro analogues were prepared by alkylation of an *N*-acetyl oxindole **229**, deacetylation of **230** to **231**, *N*-alkylation with benzyl bromoacetate, and final hydrogenation (Scheme 71).[96]



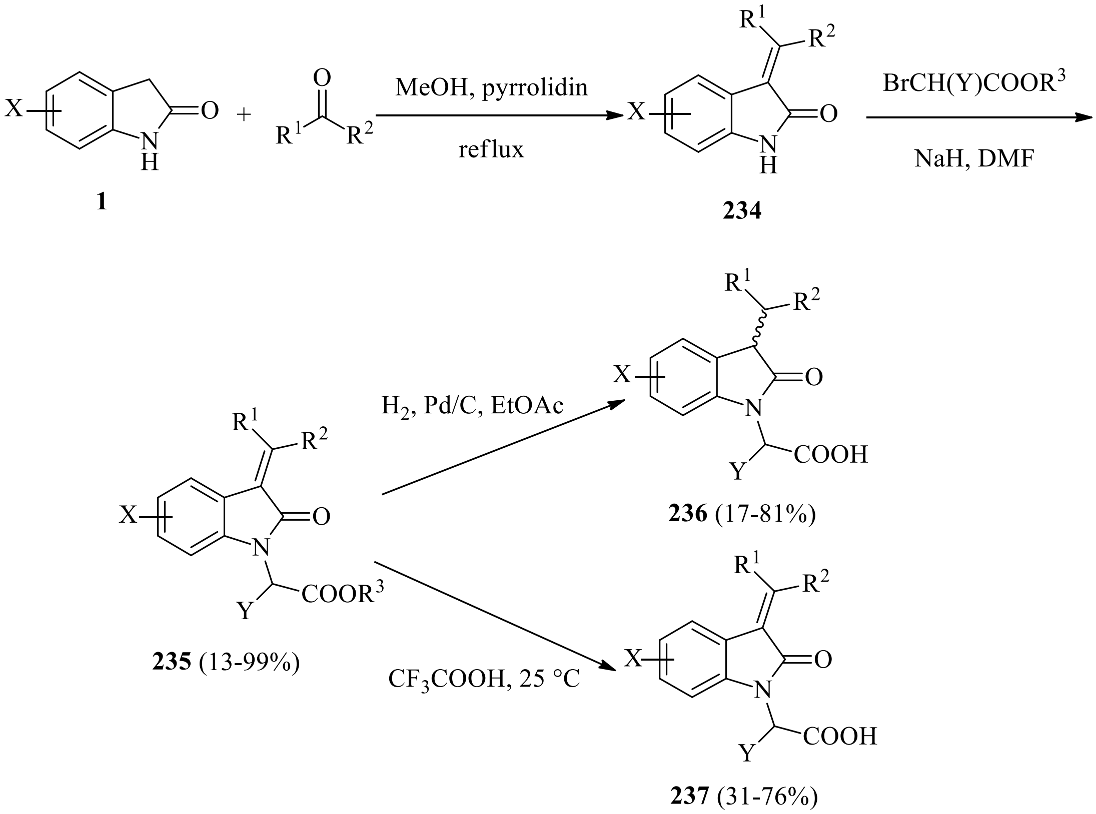
1 **229** **230** **231** **232** **233**

232		233	
$R^1,R^2 = 3,4\text{-}Cl_2C_6H_3CH_2$	(48%)	$R^1,R^2 = 3,4\text{-}Cl_2C_6H_3CH_2$	(65%)
$R^1 = H, R^2 = 1,2\text{-}(CH_2C_6H_4CH_2)$	(93%)	$R^1 = H, R^2 = 1,2\text{-}(CH_2C_6H_4CH_2)$	(13%)
$R^1 = H, R^2 = 4\text{-}Cl\text{-}1,2\text{-}(CH_2C_6H_4CH_2)$	(48%)	$R^1 = H, R^2 = 4\text{-}Cl\text{-}1,2\text{-}(CH_2C_6H_4CH_2)$	(89%)
$R^1 = H, R^2 = 3,4\text{-}Cl_2C_6H_3CH_2$	(79%)	$R^1 = H, R^2 = 3,4\text{-}Cl_2C_6H_3CH_2$	(72%)

Scheme 71

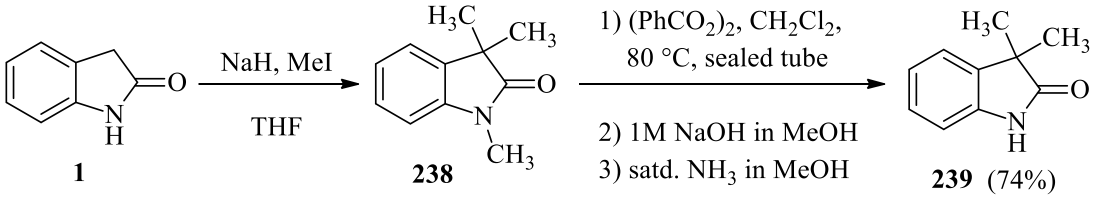
Similarly, the 3-monoalkylated oxindole acids **236** were prepared as shown in Scheme 72. Condensation of oxindole with aldehydes followed by alkylation of the intermediate alkylidenes **234** and hydrogenation of the esters **235** generated the desired acids. Alternatively, the sodium salt of compound **234** was treated with *tert*-butyl bromoacetate and the product **235** was hydrolyzed with trifluoroacetic acid to give the final acid **237**, retaining the double bond. Oxindole derivatives **233**, **236**, and **237** are *in vitro* inhibitors of aldose reductase[96] which is a key component of the procedure[97,98] in which an increase in the flux of glucose through the polyol pathway is implicated in the development of chronic complications in diabetes.[99]

In another study, compound **238** was synthesized *via* exhaustive methylation of oxindole. Treatment of **238** with dibenzoyl peroxide followed by NaOH and NH$_3$ in methanol, provided the desired product **239** in a remarkable yield (Scheme 73).[100]



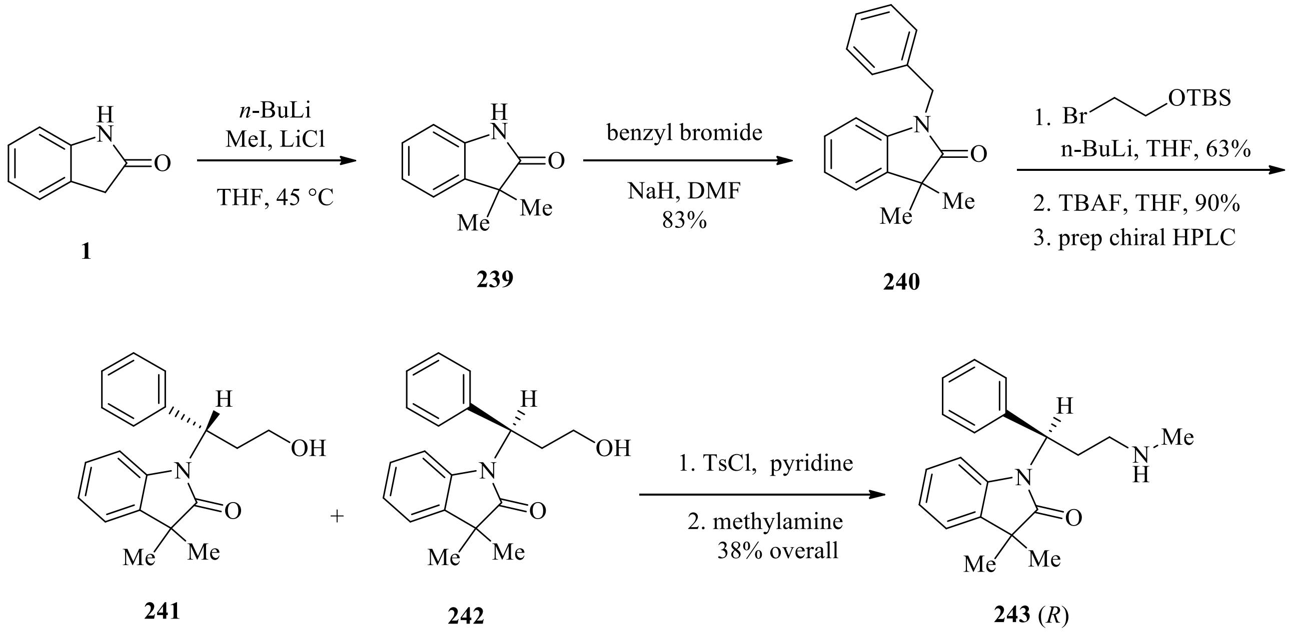
X = H, 5-Cl, 6-F, 5,6-F_2, 5-OMe, 5,6-$(OMe)_2$
$R^1 = R^2 =$ *cis*-3,4-$Cl_2C_6H_3CH$=, *trans*-3,4-$Cl_2C_6H_3CH$=, 3,4-$Cl_2C_6H_3CH$=, 3,4-$Cl_2C_6H_3CMe$=, 2-benzothiazolyl
Y = H, Me

Scheme 72



Scheme 73

A racemic synthesis of 1-(3-amino-1-phenylpropyl)indolin-2-ones **243** was developed by McComas and coworkers. Alkylation of oxindole at the 3-position provided **239** followed by *N*-alkylation with benzyl bromide to generate compound **240**. Installation of an ethanol side chain was accomplished by treatment with n-BuLi and (2-bromo-ethoxy)-*t*-butyl-dimethyl-silane followed by removal of the silyl group with tetra-n-butylammonium fluoride (TBAF). At this stage the racemic mixture of alcohols was resolved by preparative chiral HPLC to give enantiomers **241** and **242**. Alcohol **242** was then converted to the tosylate which was displaced with methylamine to give (*R*)-(3-amino-1-phenylpropyl)indolin-2-one **243** (Scheme 74).[101]

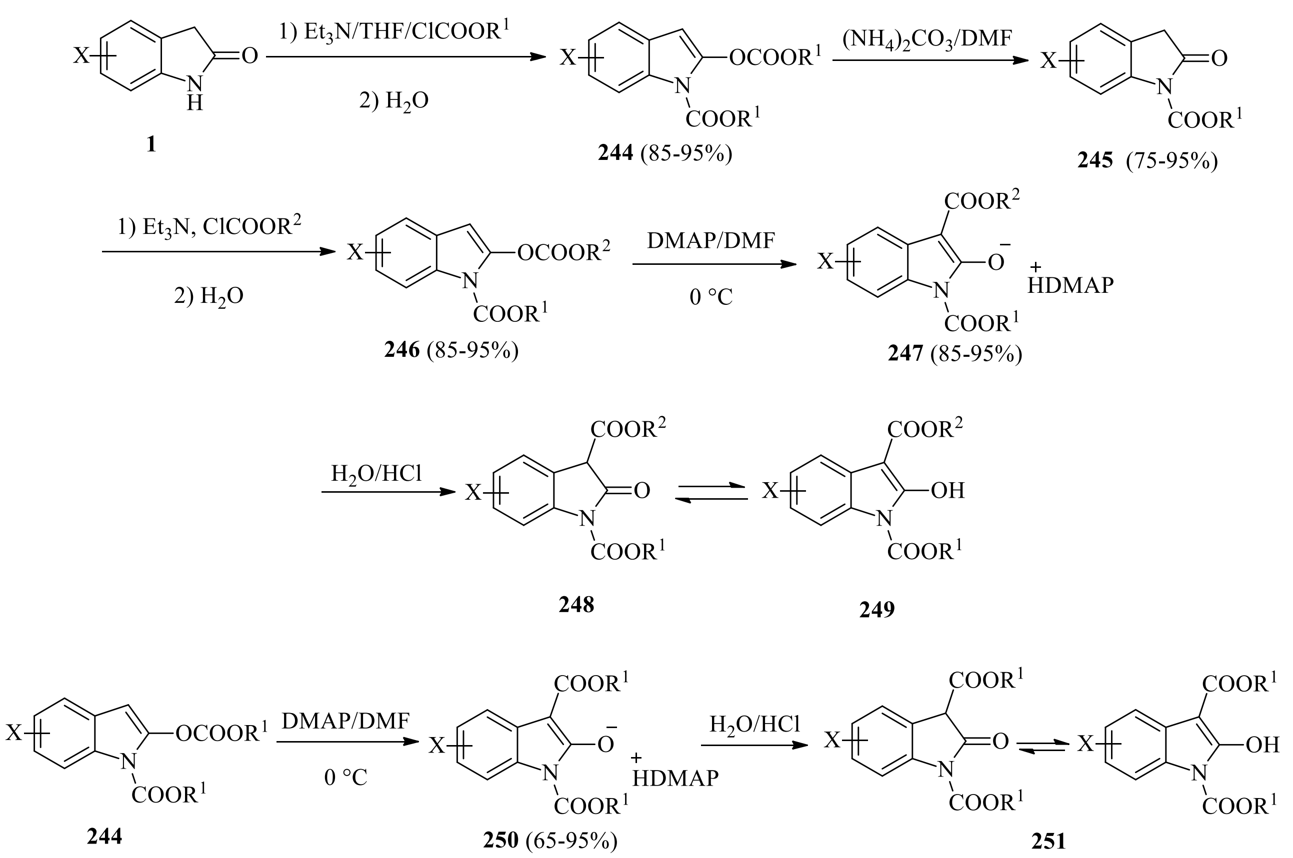


Scheme 74

6.3. Carbonyl group and nitrogen atom

Simig and coworkers synthesized 1,3-di[alkoxy(aryloxy)carbonyl]-2-oxo-2,3-dihydroindoles **248**, **249** and **251** which are very important compounds as starting materials in medicinal chemistry. Different oxindoles were treated with chloroformic acid esters and triethylamine affording *N,O*-diacylated derivatives **244**. The *O*-acyl moiety was removed by reaction with ammonium carbonate to give *N*-[alkoxy(or aryloxy)carbonyl]oxindoles **245** in good yields. The reaction of the *N*-acylated derivatives with chloroformic acid esters and triethylamine in THF afforded mixed *N,O*-diacylated derivatives **246**. Treatment of **246** and **244** with one equivalent of DMAP in DMF followed by addition of water gave the *N,C*(3)-diacylated dimethylaminopyridinium enolate **247** and **250**. Finally, the acidic treatment of these enolates resulted in the conjugated acids **248**, **249** and **251** (Scheme 75).[102]

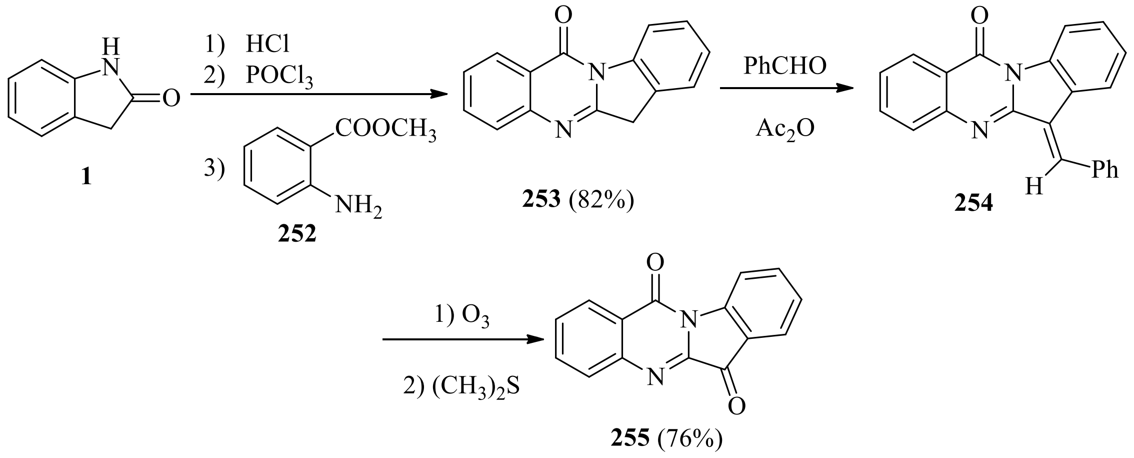
An efficient procedure for the preparation of tryptanthrine antibiotic **255** has been studied. The reaction of oxindole-HCl salt with $POCl_3$ followed by cyclization with methyl anthranilate **252** afforded the corresponding quinazolinone **253**. Subsequent two-step conversion of **253** prepared tryptanthrine **255** in 76% yield (Scheme 76).[103]



X = H, 5-Cl, 6-Cl, 5-NO_2 ; R^1 = Me, Et, Ph, CH_2Ph

R^1/R^2 = Ph/Me, Ph/Et, Ph/CH_2Ph, Me/Ph, Et/Ph, CH_2Ph/Ph, Et/CH_2Ph, CH_2Ph/Et

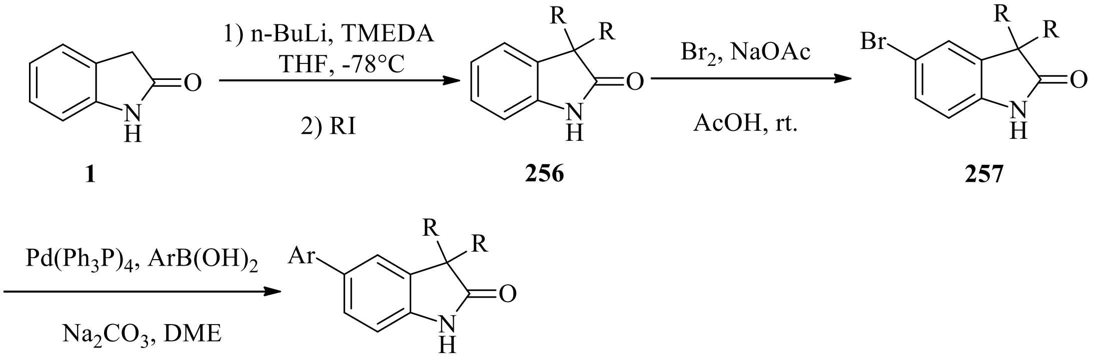
Scheme 75



Scheme 76

6.4. C-3 atom and aromatic ring

A series of 3,3-disubstituted-5-aryloxindoles **258** has been synthesized and evaluated for progesterone receptor (PR) antagonist activity. Treatment of oxindole with n-BuLi in the presence of TMEDA, followed by quenching the resulting anion with the corresponding alkyl iodide afforded the substituted oxindoles **256**. Reaction of **256** with bromine and sodium acetate in acetic acid yielded the bromide derivatives **257**. Finally, a Suzuki coupling between the compound **257** and a phenylboronic acid prepared the desired products **258** (Scheme 77).[104]

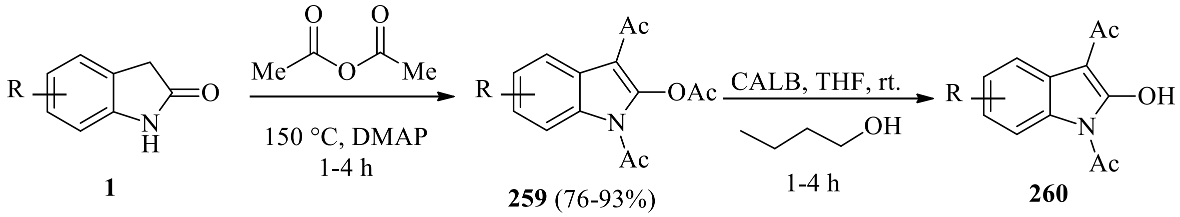


258 R = H, Me, Et, $-CH_2CH_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, CH_2Ph
Ar = $3-NO_2C_6H_4$, $3-ClC_6H_4$, $3-MeOC_6H_4$

Scheme 77

6.5. Participation of three sites in reaction

One-pot multiple acylation of oxindole was performed using acyl anhydride and catalytic amount of DMAP that resulted in the formation of triacetylated product **259**. Subsequently, an enzyme-assisted deacetylation resulted in the chemoselective deprotection of the acetoxy group to produce 1,3-diacetyl-2-hydroxyindoles **260** (Scheme 78).[105,106]

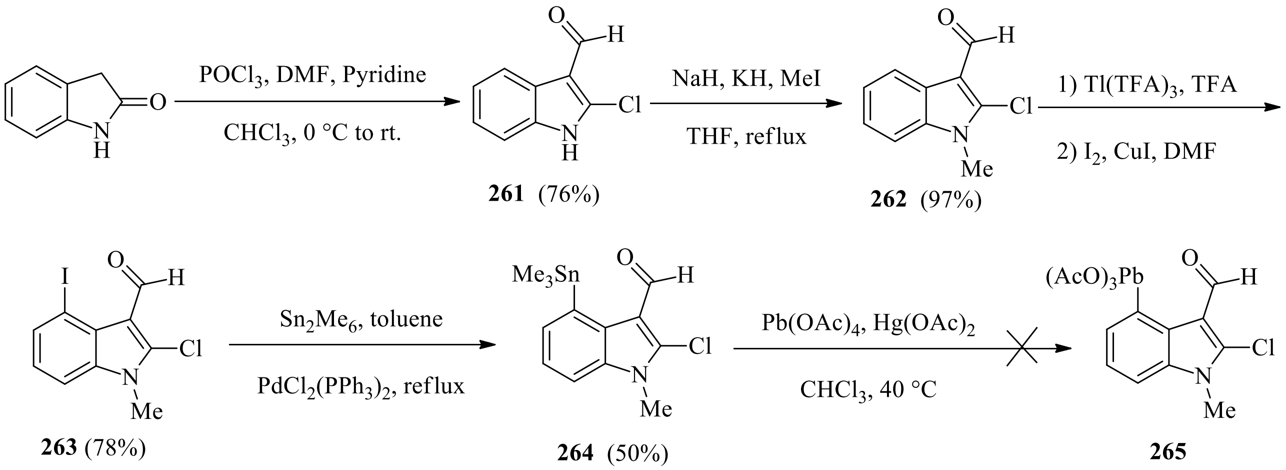


R = 5-NO$_2$, 5-F, 5-Br, 5-Me, 5-Cl, 6-Cl, 7-Cl

Scheme 78

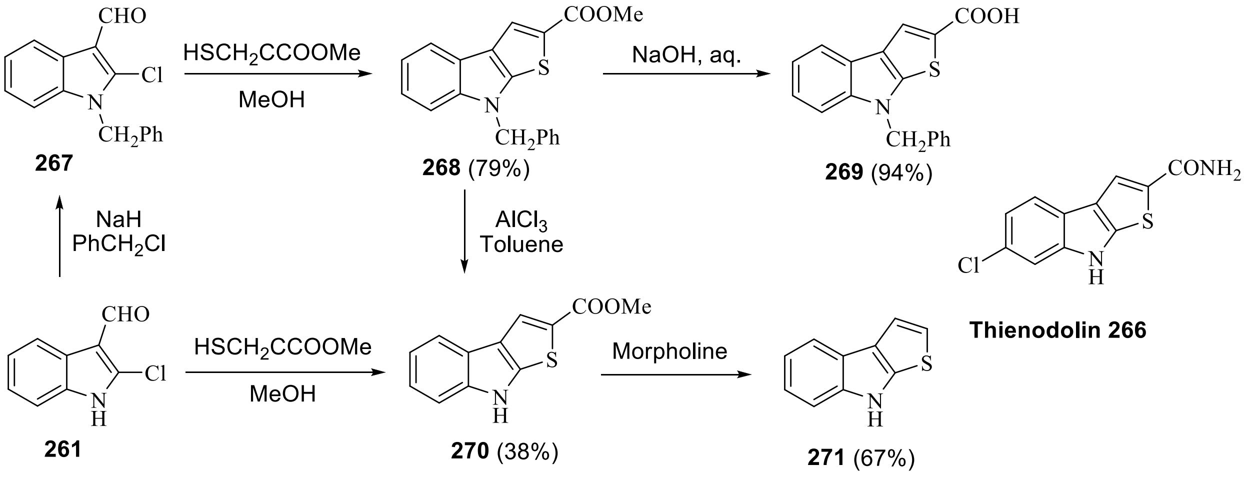
6.6. Vilsmeier reactions of oxindole

Vilsmeier chloroformylation of oxindole with $POCl_3$, DMF, and pyridine provided 2-chloro-3-formylindole **261**, methylation of which resulted in compound **262**. Treatment of **262** with thallium(III) trifluoroacetate in trifluoroacetic acid (TFA) and iodination with iodine and copper iodide yielded *N*-methyl-3-formyl-2-chloro-4-iodoindole **263**. Refluxing **263** with hexamethylditin in the presence of $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ as catalyst, iodine-tin exchange was achieved to give compound **264**. The final step to the desired indole-lead (IV) reagent was the transformation of **264** to **265** by tin-lead exchange. Compound **264** was reacted with lead tetraacetate and catalytic mercury (II) but none of the desired indolelead triacetate was formed (Scheme 79).[107]



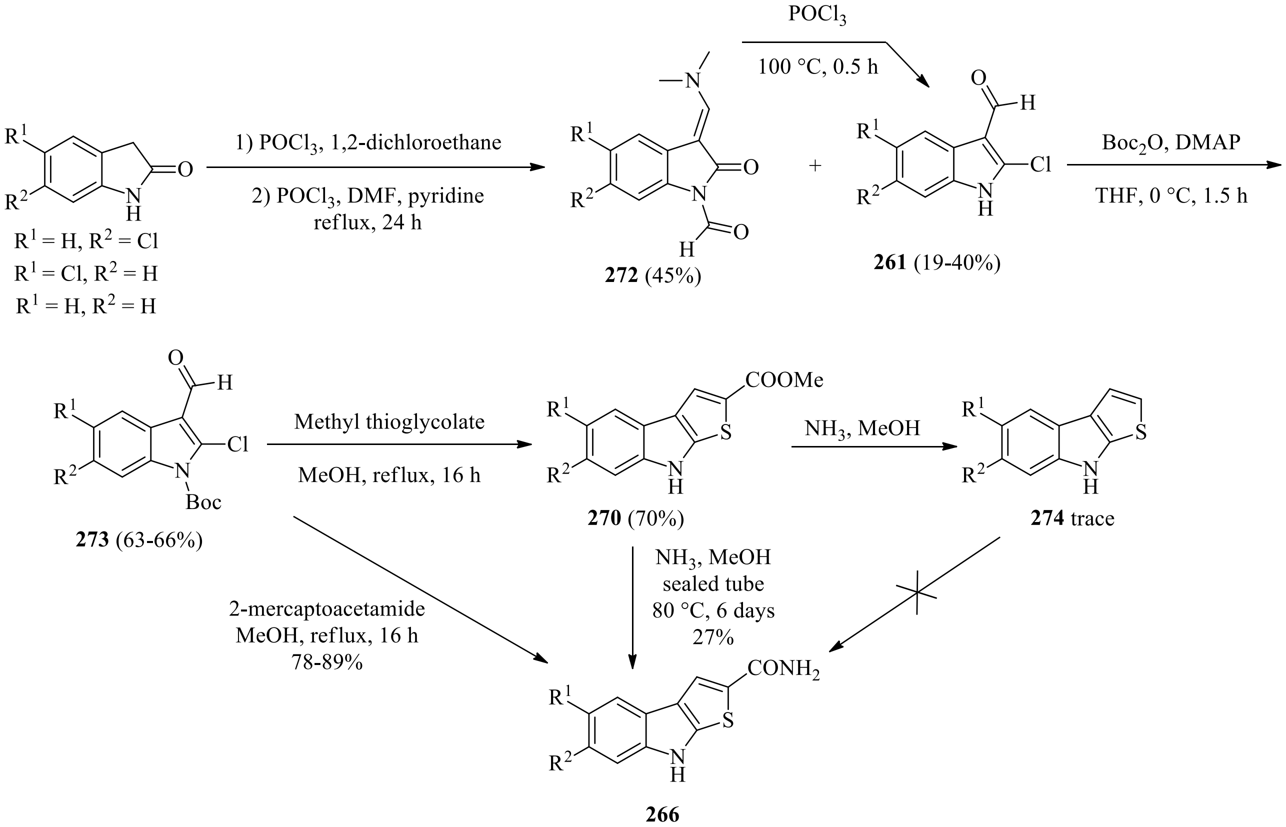
Scheme 79

Thienodolin **266** was shown to have both growth promoting and inhibiting activities in rice seedling.[108] Olesen *et al.* have synthesized methyl thieno[2,3-*b*]indolecarboxylaye **270** form it´s *N*-benzyl derivative **268** by debenzylation with aluminium trichloride in toluene, and then compound **270** was saponified and decarboxylated by heating in morpholine to give thieno[2,3-*b*]indole **271**.[109]



Scheme 80

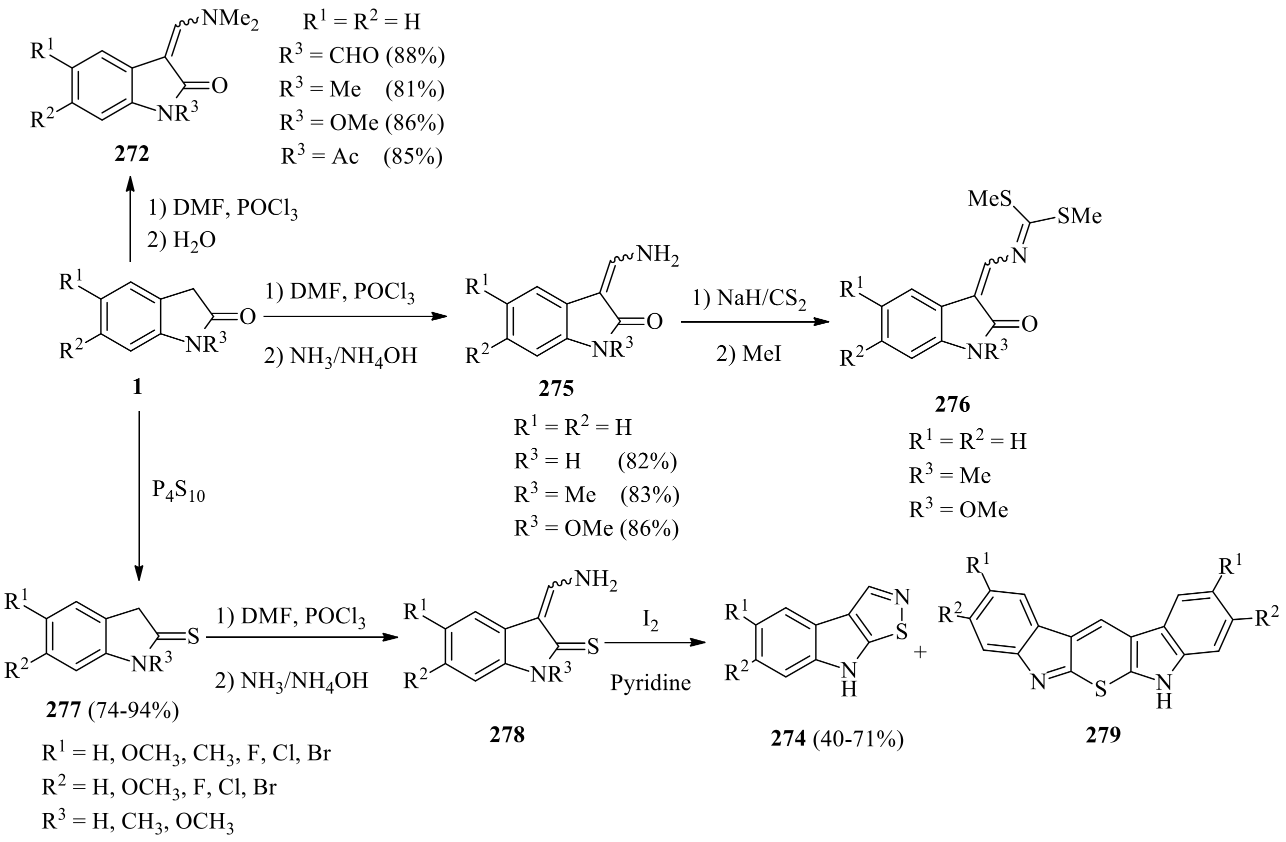
Engqvist *et al.* reported a total synthesis of the alkaloid thienodolin **266** and its derivatives in three steps from the corresponding oxindoles. They were achieved through an initial Vilsmeier reaction followed by protection at the indole nitrogen to give **273**, creation of the fused thiophene ring by nucleophilic substitution at the 2-position and an intramolecular cyclization using mercaptoacetamide (Scheme 81).[110]



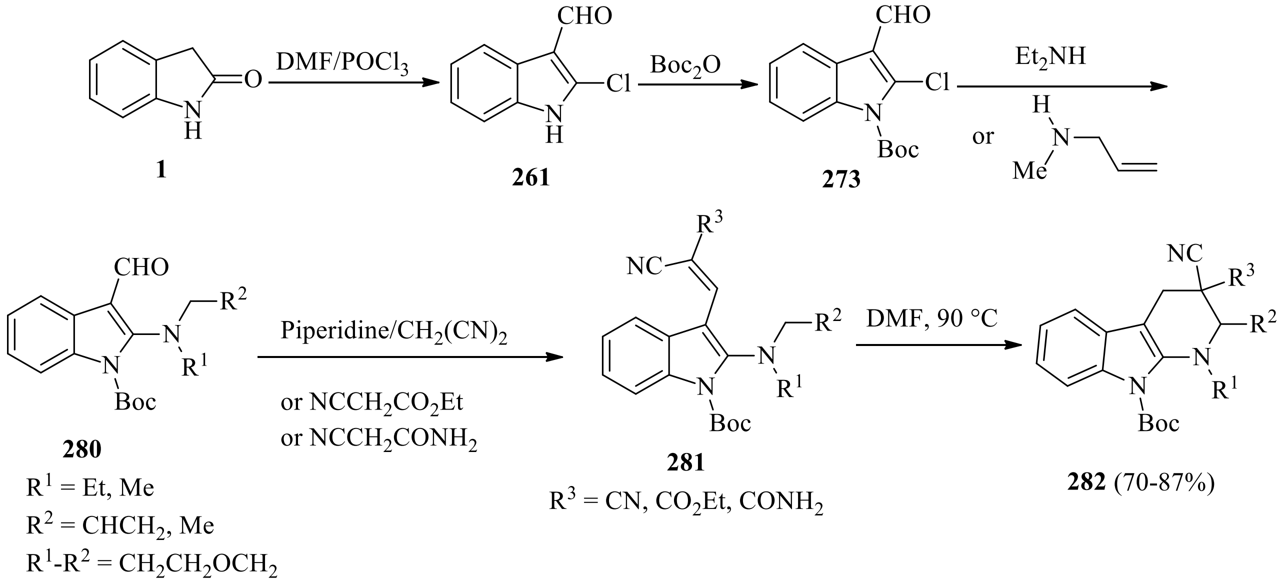
Scheme 81

Pedras and Jha synthesized the phytoalexin wasalexins **276** using the formylation and amination of oxindole. Oxindole has also been formylated via Vilsmeier reagent to afford brassilexin analogues **274**. Aqueous ammonia work-up procedure was shown to afford the desired products in reasonable yields (Scheme 82).[111] Phytoalexins are secondary metabolites biosynthesized *de novo* by plants in response to various forms of stress including pathogen attack.[112,113]

Oxindole on treatment with Vilsmeier reagent afforded the key β-haloaldehyde intermediate **261**. The Boc-protected indole **273** underwent nucleophilic substitution at C-2 by diethylamine to give **280**. Treatment of the tertiary amine **280** with nitrile afforded the indole derivative **281** with an olefinic bond at the β-position of the tertiary amine group, which is the requirement for the key reaction step. The final α-cyclization of the tertiary amine **281** was carried out at 90 °C using DMF as solvent, which afforded the α-carboline **281**. (Scheme 83).[114] α-Carbolines have diverse biological activities such as antitumor,[115] anti-HIV,[116,117] antiviral, anxiolytic, anti-inflammatory and CNS-stimulating activities.[118]

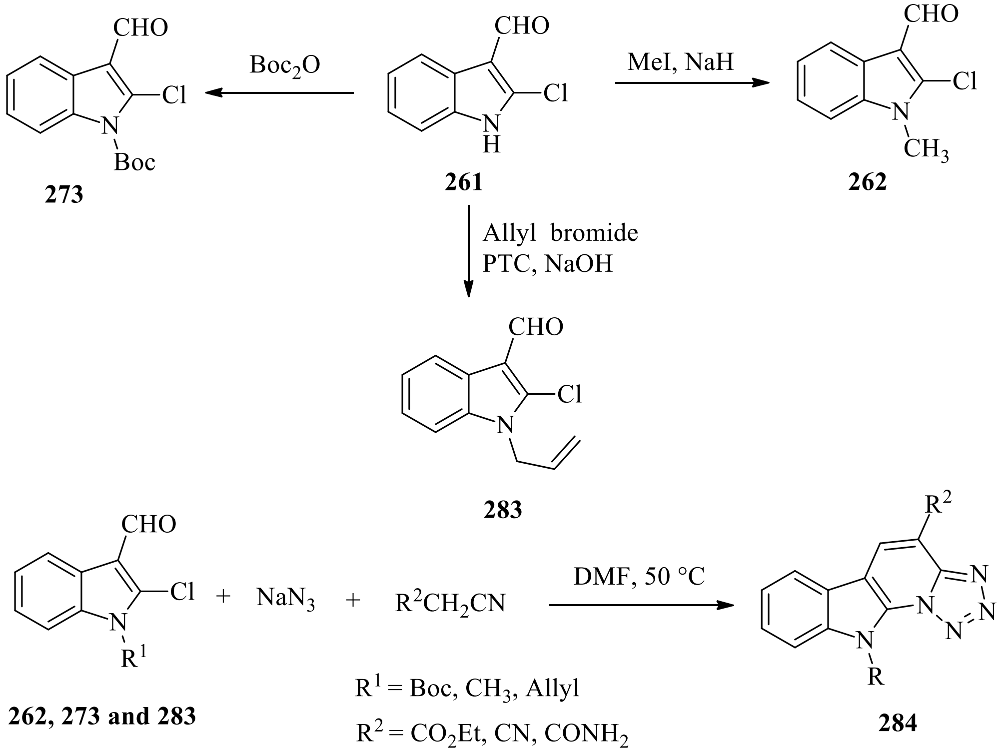


Scheme 82



Scheme 83

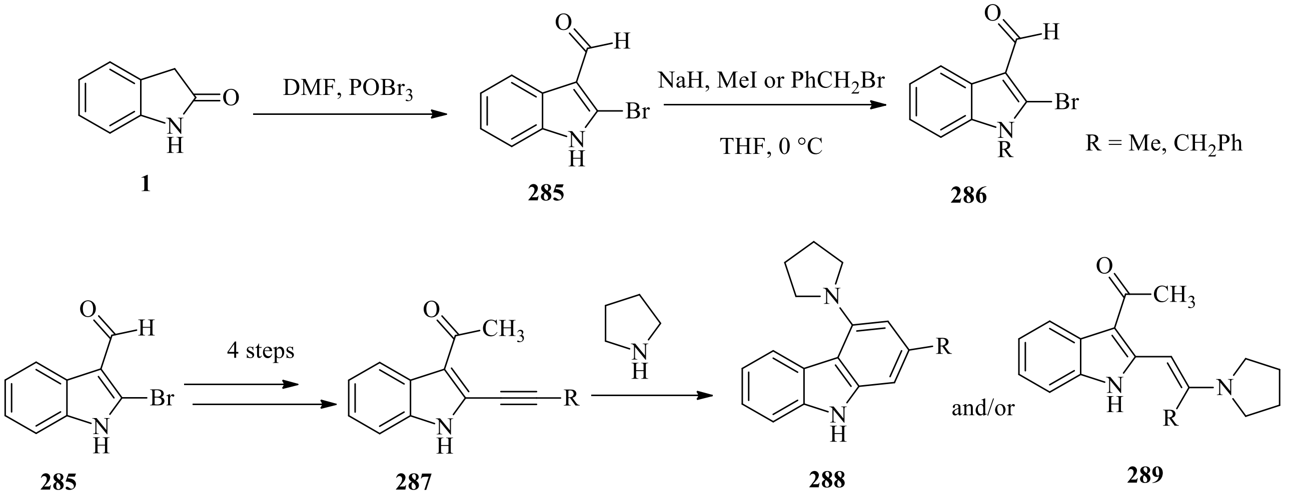
Annelated α-carbolines **284** have been synthesized from oxindole using a one-pot three-component reaction involving an intra molecular [3+2]-dipolar cycloaddition reaction of azides to nitriles (Scheme 84).[119]



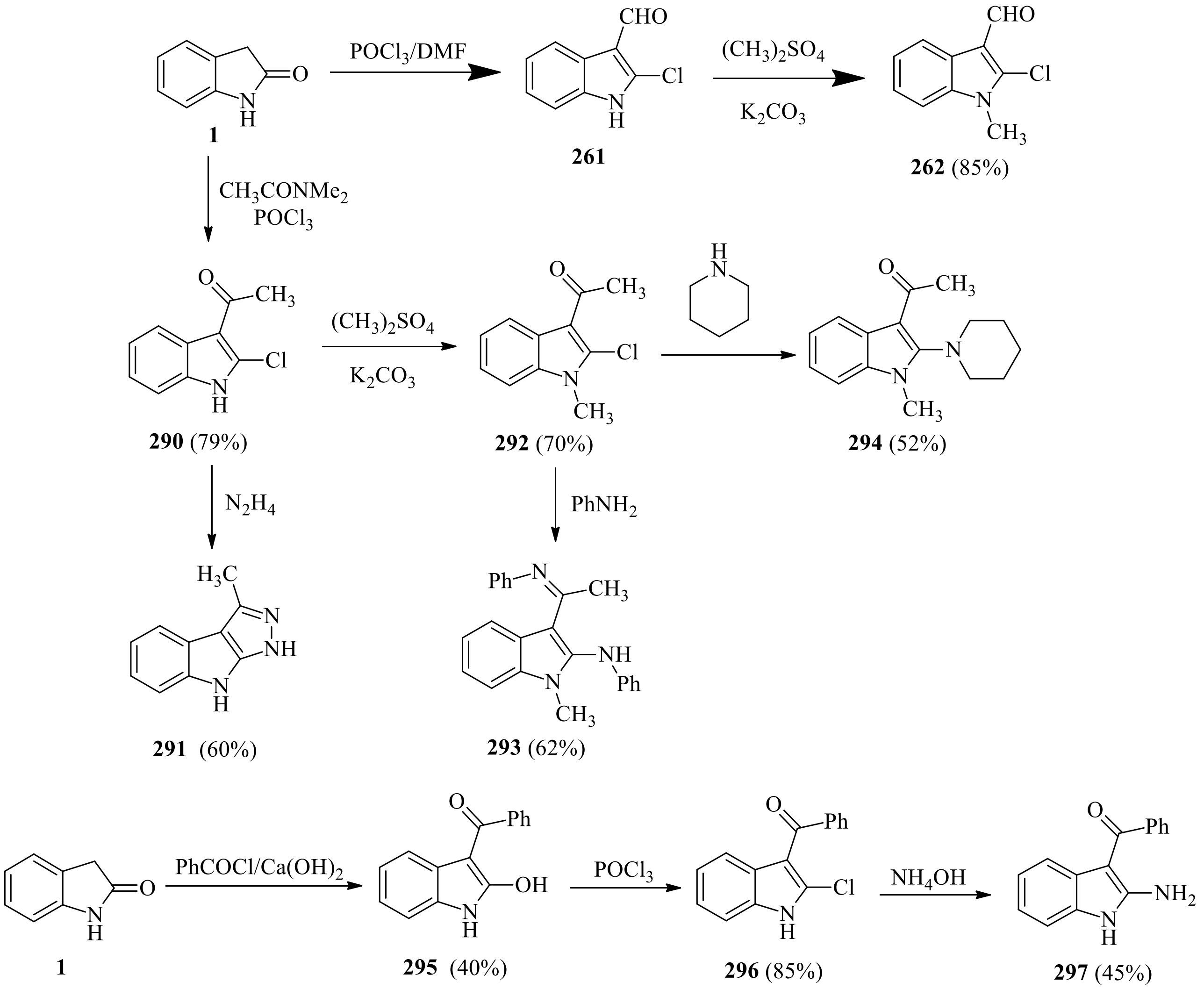
Scheme 84

A powerful aminobenzannulation reaction has been exploited for the synthesis of amino-substituted carbazoles **288**. The precursors are heterocycles bearing a methyl ketone group *ortho* to an internal alkyne **287** that can be obtained in three or four classical reactions. These reactions include Vilsmeier-Haack, Sonogashira, and Grignard reactions, and Ley's oxidation. Upon aminobenzannulation, an interesting range of carbazoles are obtained along with enamine formation in some cases. The reaction is useful since *meta*-substituted heterocycles **288** are produced and it also differs from classical heterocyclic methods which go through closure at the heteroatom containing ring instead of benzene ring formation (Scheme 85).[120]

According to Monge's studies, a series of aminoindoles **291**, **293**, **294**, and **295** were obtained from oxindole (Scheme 86) that were studied as anti-hypertensive agents and inhibitors of platelet aggregation.[121]



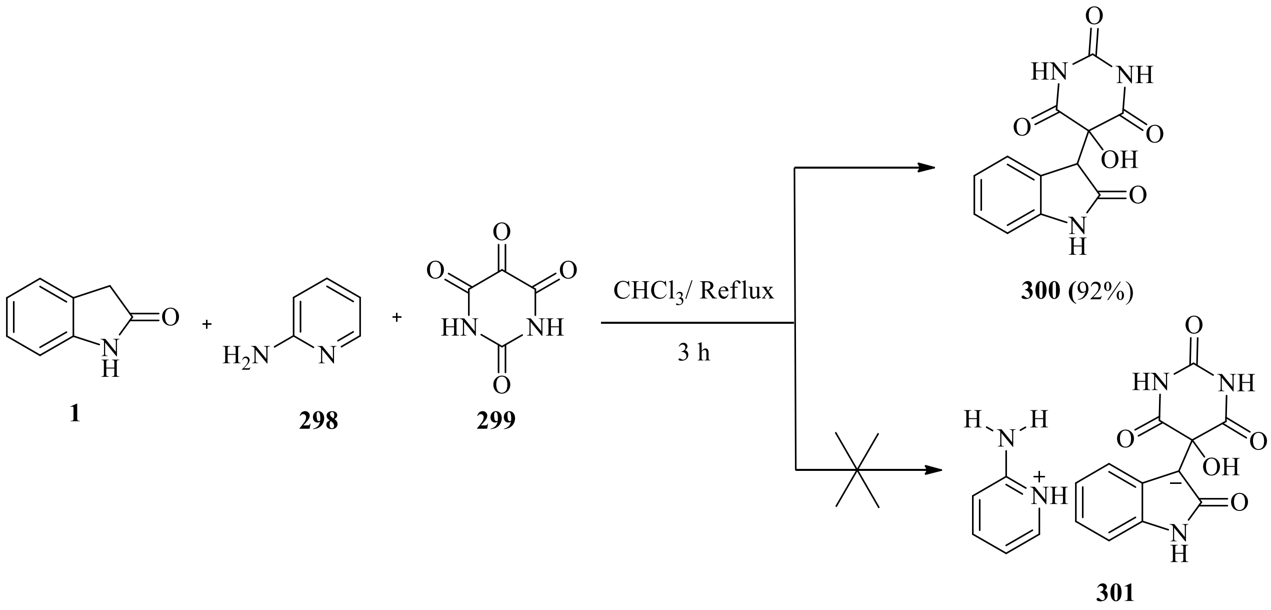
Scheme 85



Scheme 86

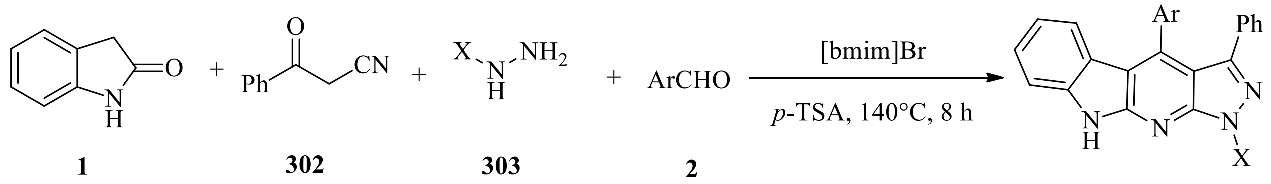
7. One-Pot Reactions

Bazgir and coworkers investigated the synthesis of new barbiturate salts containing a 2-amino-pyridinium moiety by an uncatalyzed three-component condensation of different C-H acids, 2-aminopyridines **298**, and pyrimidine-tetraones **299** in refluxing chloroform. Unlike with 1,3-dicarbonyl compounds, it was found that when oxindole **1** was used as a C-H acid, the desired barbituric salt **301** was not obtained and 5-hydroxy-5-(2-oxoindolin-3-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **300** resulted in 92% yield (Scheme 87).[122]



Scheme 87

A one-pot method for the synthesis of compound **304** was performed via a four-component condensation reaction of oxindole **1**, 3-oxo-3-phenylpropanenitrile **302**, various hydrazines **303**, and aldehydes in the ionic liquid [bmim]Br (Scheme 88).[123]

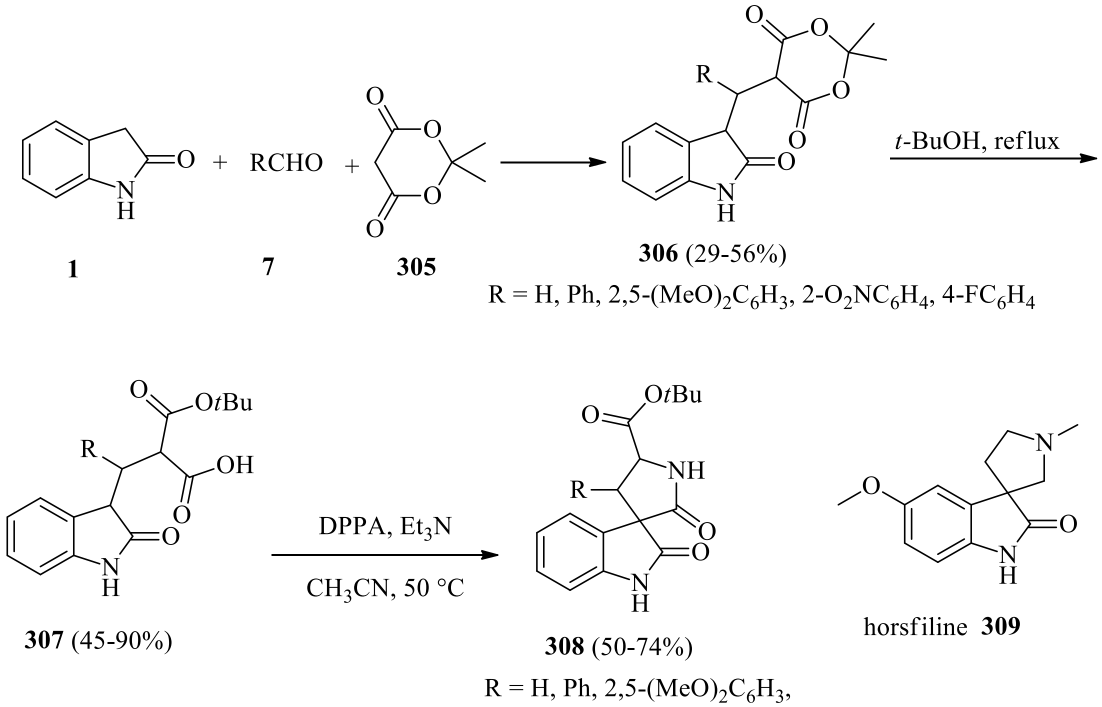


304 (61-92%)

X = C_6H_5 , 4-$O_2NC_6H_4$, H
Ar = C_6H_5, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, 4-BrC_6H_4, 3-BrC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 4-MeC_6H_4, 4-HOC_6H_4

Scheme 88

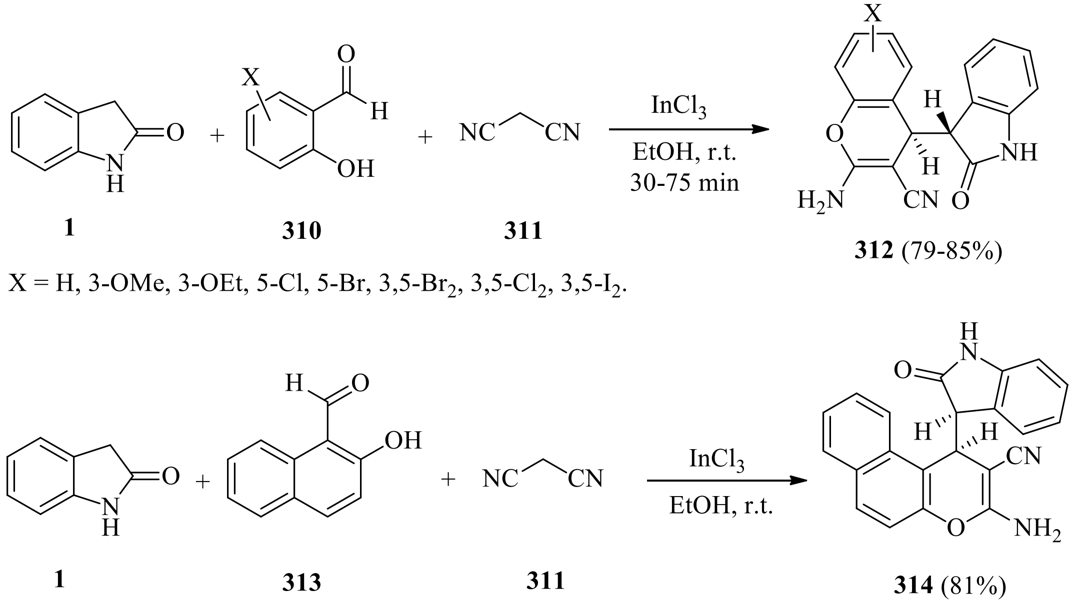
The one-pot reaction between oxindole, aldehydes, and Meldrum's acid **305** afforded the useful intermediates **306** for the synthesis of spiro[pyrrolidino-3,3′-oxindoles] **308** related to the natural product horsfiline **309** (Scheme 89).[124]



Scheme 89

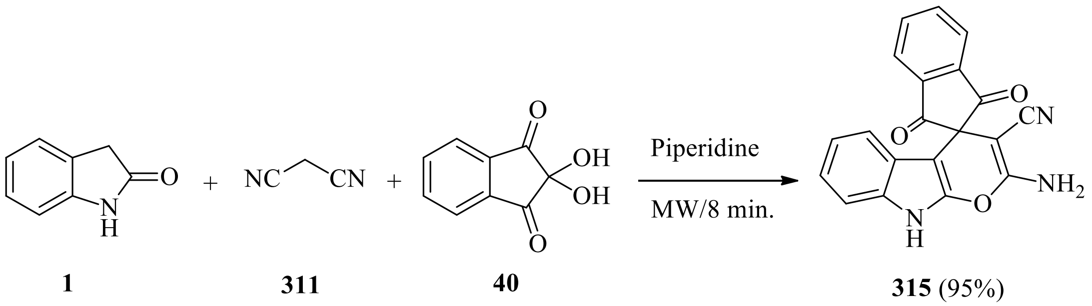
A facile one-pot synthesis of 4-substituted 2-amino-4H-chromenes **312** and **314** has been carried out using oxindole **1**, malononitrile **311**, and different substituted salicylaldehydes **310** or 2-hydroxynaphthalene-1-carbaldehyde **313** in the presence of indium trichloride as a catalyst (Scheme 90).[125]

Shaker and coworkers reported their findings in the three-component reaction of oxindole **1**, ninhydrin **40** and malononitrile **311** in the presence of piperidine under microwave irradiation to give the desired product **315** in high yield (Scheme 91).[126]



X = H, 3-OMe, 3-OEt, 5-Cl, 5-Br, 3,5-Br_2, 3,5-Cl_2, 3,5-I_2.

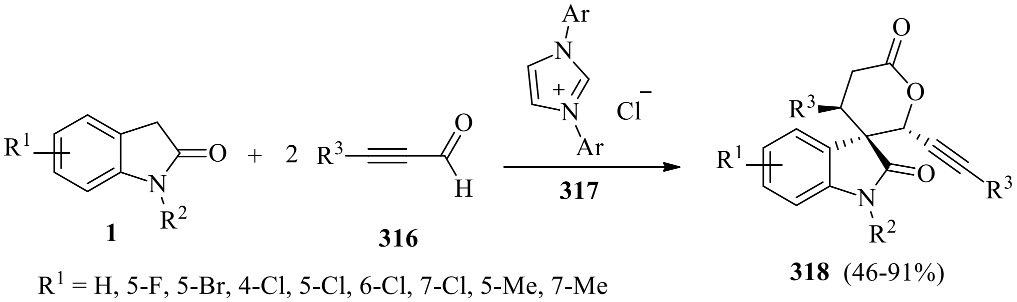
Scheme 90



Scheme 91

8. Domino Reactions

The stereoselective synthesis of spirooxindole-4*H*-pyran-2-one derivatives **318** was performed *via* an NHC-catalyzed (N-heterocyclic carbenes **317**) three-component domino reaction of alkynyl aldehydes **316** with oxindole **1** (Scheme 92).[127] The reaction proceeded smoothly in good yields with good to high diastereoselectivities.



R^1 = H, 5-F, 5-Br, 4-Cl, 5-Cl, 6-Cl, 7-Cl, 5-Me, 7-Me
R^2 = H, Me, CH_2Ph, allyl, acyl
R^3 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 3-C-C_6H_4, 4-Me,
3-Me, 4-OMe, 2,3-$(OMe)_2$, 2-furyl.

Scheme 92

9. Conclusions

The biological activities of oxindole derivatives make these compounds versatile synthetic targets as well as important structural units in medicinal and synthetic organic chemistry. In this review, we classified oxindole reactions in five classes including reactions on the C-3 atom, nitrogen atom, phenylene ring, carbonyl site, and composition of these reactions. Oxindole as a unique substrate is also a versatile starting material in one-pot and domino reactions.

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References

1. Dreifuss, A. A.; Bastos-Pereira, A. L.; Ávila, T. V.; Soley, B. de S.; Rivero, A. J.; Aguilar, J. L.; Acco, A. *J. Ethnopharmacol.* **2010**, *130*, 127-133.
1. http://dx.doi.org/10.1016/j.jep.2010.04.029
PMid:20435132
2. García Giménez, D.; García Prado, E.; Sáenz Rodríguez, T.; Fernández Arche, A.; De La Puerta, R. *Planta Med.* **2010**, *76*, 133-136.
http://dx.doi.org/10.1055/s-0029-1186048
PMid:19724995
3. Bishop, J. M. *Science* **1987**, *335*, 305-311.
http://dx.doi.org/10.1126/science.3541204

4. Guan, H.; Laird, A. D.; Blake, R. A.; Tang, C.; Liang, C. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 187-190.
http://dx.doi.org/10.1016/j.bmcl.2003.09.069
5. Plowman, G. D.; Ullrich, A.; Shawver, L. K. *Drug News Perspect.* **1994**, *7*, 334-339.
6. Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, 6821-6841.
7. Kang, T. H.; Murakami, Y.; Matsumoto, K.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **2002**, *455*, 27-34.
http://dx.doi.org/10.1016/S0014-2999(02)02581-5
8. Swensen, A. M.; Herrington, J.; Bugianesi, R. M.; Dai, G.; Haedo, R. J.; Ratliff, K. S.; Smith, M. M.; Warren, V. A.; Arneric, S. P.; Eduljee, C.; Parker, D.; Snutch, T. P.; Hoyt, S. B.; London, C.; Duffy, J. L.; Kaczorowski, G. J.; McManus, O. B. *Mol. Pharmacol*. **2012**, *81*, 488-497.
http://dx.doi.org/10.1124/mol.111.075226
PMid:22188924
9. Whatmore, J. L.; Swann, E.; Barraja, P.; Newsome, J. J.; Bunderson, M.; Beall, H. D.; Tooke, J. E.; Moody, C. J. *Angiogenesis* **2002**, *5*, 45-51.
http://dx.doi.org/10.1023/A:1021528628524
10. Peddibhotla, S. *Curr. Bioactive Compd*. **2009**, *5*, 20-38.
http://dx.doi.org/10.2174/157340709787580900
11. Abbadie, C.; McManus, O. B.; Sun, S. Y.; Bugianesi, R. M.; Dai, G.; Haedo, R. J.; Herrington, J. B.; Kaczorowski, G. J.; Smith, M. M.; Swensen, A. M.; Warren, V. A.; Williams, B.; Arneric, S. P.; Eduljee, C.; Snutch, T. P.; Tringham, E. W.; Jochnowitz, N.; Liang, A.; Euan MacIntyre, D.; McGowan, E.; Mistry, S.; White, V. V.; Hoyt, S. B.; London, C.; Lyons, K. A.; Bunting, P. B.; Volksdorf, S.; Duffy, J. L. *J. Pharmacol. Exp. Ther.* **2010**, *334*, 545-55.
http://dx.doi.org/10.1124/jpet.110.166363
PMid:20439438
12. Wahl, A.; Bagard, P. *Bull. Soc. Chim.* **1909**, *5*, 1033.
13. Wahl, A.; Bagard, P. *Compt. rend.* **1909**, *148*, 716.
14. Wahl, A.; Bagard, P. *Compt. rend.* **1910**, *149*, 132.
15. Ölgen, S.; Akaho, E.; Nebioglu, D. *Farmaco* **2005**, *60*, 497-506.
http://dx.doi.org/10.1016/j.farmac.2005.01.015
PMid:15927182
16. Kniess, T.; Bergmann, R.; Kuchar, M.; Steinbach, J.; Wuest, F. *Bioorg. Med. Chem*. **2009**, *17*, 7732-7742.
http://dx.doi.org/10.1016/j.bmc.2009.09.038
PMid:19822433
17. Zhang, W.; Go, M.-L. *Bioorg. Med. Chem*. **2009**, *17*, 2077-2090.
http://dx.doi.org/10.1016/j.bmc.2008.12.052
PMid:19200740
18. Villemin, D.; Martin, B. *Synth. Commun*. **1998**, *28*, 3201-3208.
http://dx.doi.org/10.1080/00397919808004422

19. Gholamzadeh, P.; Ziarani, G. M.; Badiei, A.; Bahrami, Z. *Eur. J. Chem.* **2012**, *3*, 279-282.
    http://dx.doi.org/10.5155/eurjchem.3.3.279-282.630
20. Ding, K.; Wang, G.; Deschamps, J. R.; Parrish, D. A.; Wang, S. *Tetrahedron Lett.* **2005**, *46*, 5949-5951.
    http://dx.doi.org/10.1016/j.tetlet.2005.06.114
21. Trost, B. M.; Zhang, Y. *Chem. Eur. J.* **2011**, *17*, 2916-2922.
    http://dx.doi.org/10.1002/chem.201002569
    PMid:21290436
22. Spencer, J.; Nielsen, B. V.; Thomas, M. J. K.; Male, L.; Coles, S. J. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2011**, *67*, m245-m248.
    http://dx.doi.org/10.1107/S0108270111021536
    PMid:21727623
23. Andreani, A.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Pietra, C.; Villetti, G. *Eur. J. Med. Chem.* **2000**, *35*, 77-82.
    http://dx.doi.org/10.1016/S0223-5234(00)00103-3
24. Sun, L.; Tran, N.; Tang, F.; App, H.; Hirth, P.; McMahon, G.; Tang, C. *J. Med. Chem.* **1998**, *41*, 2588-2603.
    http://dx.doi.org/10.1021/jm980123i
    PMid:9651163
25. Hoessel, R.; Leclerc, S.; Endicott, J. A.; Nobel, M. E. M.; Lawrie, A.; Tunnah, P.; Leost, M.; Damiens, E.; Marie, D.; Marko, D.; Niederberger, E.; Tang, W.; Eisenbrand, G.; Meijer, L. *Nat. Cell. Biol*. **1999**, *1*, 60-67.
    http://dx.doi.org/10.1038/9035
    PMid:10559866
26. Wee, X. K.; Yeo, W. K.; Zhang, B.; Tan, V. B. C.; Lim, K. M.; Tay, T. E.; Go, M.-L. *Bioorg. Med. Chem.* **2009**, *17*, 7562-7571.
    http://dx.doi.org/10.1016/j.bmc.2009.09.008
    PMid:19783149
27. Sassatelli, M.; Saab, E.; Anizon, F.; Prudhomme, M.; Moreau, P. *Tetrahedron Lett.* **2004**, *45*, 4827-4830.
    http://dx.doi.org/10.1016/j.tetlet.2004.04.167
28. Gholamzadeh, P.; Ziarani, G. M.; Badiei, A.; Soorki, A. A.; Lashgari, N. *Res. Chem. Intermed.* **2012**, In Press, Doi: 10.1007/s11164-012-0909-y.
    http://dx.doi.org/10.1007/s11164-012-0909-y
29. Sassatelli, M.; Bouchikhi, F.; Messaoudi, S.; Anizon, F.; Debiton, E.; Barthomeuf, C.; Prudhomme, M.; Moreau, P. *Eur. J. Med. Chem.* **2006**, *41*, 88-100.
    http://dx.doi.org/10.1016/j.ejmech.2005.10.004
    PMid:16330129
30. Mei, J.; Graham, K. R.; Stalder, R.; Reynolds, J. R. *Org. Lett.* **2010**, *12*, 660-663.
    http://dx.doi.org/10.1021/ol902512x
    PMid:20099892

31. Shvets, A.; Kurbatov, S. *Chem. Heterocycl. Compd.* **2009**, *45*, 866-867.
    http://dx.doi.org/10.1007/s10593-009-0344-1
32. Chakrabarty, M.; Mukherji, A.; Arima, S.; Harigaya, Y.; Pilet, G. *Monatsh. Chem*. **2009**, *140*, 189-197.
    http://dx.doi.org/10.1007/s00706-008-0066-6
33. Kniess, T.; Kuchar, M.; Wuest, F. *Synth. Commun*. **2008**, *38*, 3017-3022.
    http://dx.doi.org/10.1080/00397910802044256
34. Andreani, A.; Burnelli, S.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Calonghi, N.; Cappadone, C.; Farruggia, G.; Zini, M.; Stefanelli, C.; Masotti, L. *J. Med. Chem*. **2007**, *50*, 3167-3172.
    http://dx.doi.org/10.1021/jm070235m
    PMid:17559205
35. Sun, L.; Tran, N.; Liang, C.; Tang, F.; Rice, A.; Schreck, R.; Waltz, K.; Shawver, L. K.; McMahon, G.; Tang, C. *J. Med. Chem*. **1999**, *42*, 5120-5130.
    http://dx.doi.org/10.1021/jm9904295
36. Shih, M.-H.; Yeh, M.-Y. *Tetrahedron* **2003**, *59*, 4103-4111.
    http://dx.doi.org/10.1016/S0040-4020(03)00574-X
37. Takaya, H.; Ito, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2009**, *131*, 10824-10825.
    http://dx.doi.org/10.1021/ja9036669
    PMid:19606857
38. Bartsch, H.; Eiden, F.; Buchborn, H. *Arch. Pharm.* **1982**, *315*, 481-490.
    http://dx.doi.org/10.1002/ardp.19823150602
39. Engqvist, R.; Bergman, J. *Tetrahedron* **2003**, *59*, 9649-9653.
    http://dx.doi.org/10.1016/j.tet.2003.09.084
40. Beccalli, E. M.; Marchesini, A. *Synth. Commun.* **1993**, *23*, 2945-2955.
    http://dx.doi.org/10.1080/00397919308011136
41. M. Beccalli, E.; Marchesini, A.; Pilati, T. *Tetrahedron* **1994**, *50*, 12697-12712.
42. Trost, B. M.; Stiles, D. T. *Org. Lett.* **2007**, *9*, 2763-2766.
    http://dx.doi.org/10.1021/ol070971k
    PMid:17592853
43. Kende, A.; Hodges, J. *Synth. Commun.* **1982**, *12*, 1-10.
    http://dx.doi.org/10.1080/00397918208080058
44. Kende, A. S.; Koch, K.; Smith, C. A. *J. Am. Chem. Soc*. **1988**, *110*, 2210-2218.
    http://dx.doi.org/10.1021/ja00215a034
45. Fuchs, J. R.; Funk, R. L. *Org. Lett*. **2005**, *7*, 677-680.
    http://dx.doi.org/10.1021/ol047532v
    PMid:15704923
46. Lockman, J. W.; Reeder, M. D.; Robinson, R.; Ormonde, P. A.; Cimbora, D. M.; Williams, B. L.; Willardsen, J. A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1724-1727.
    http://dx.doi.org/10.1016/j.bmcl.2011.01.077
    PMid:21316225

47. Bergman, J.; Romero, I. *J. Heterocycl. Chem.* **2010**, *47*, 1215-1220.
http://dx.doi.org/10.1002/jhet.453
48. Goehring, R. R. *Org. Prep. Proced. Int.* **1995**, *27*, 691-694.
http://dx.doi.org/10.1080/00304949509458534
49. Vachal, P.; Miao, S.; Pierce, J. M.; Guiadeen, D.; Colandrea, V. J.; Wyvratt, M. J.; Salowe, S. P.; Sonatore, L. M.; Milligan, J. A.; Hajdu, R.; Gollapudi, A.; Keohane, C. A.; Lingham, R. B.; Mandala, S. M.; DeMartino, J. A.; Tong, X.; Wolff, M.; Steinhuebel, D.; Kieczykowski, G. R.; Fleitz, F. J.; Chapman, K.; Athanasopoulos, J.; Adam, G.; Akyuz, C. D.; Jena, D. K.; Lusen, J. W.; Meng, J.; Stein, B. D.; Xia, L.; Sherer, E. C.; Hale, J. J. *J. Med. Chem.* **2012**, *55*, 2945-2959.
http://dx.doi.org/10.1021/jm201542d
PMid:22364528
50. Jensen, T.; Madsen, R. *J. Org. Chem.* **2009**, *74*, 3990-3992.
http://dx.doi.org/10.1021/jo900341w
PMid:19371090
51. Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 4375-4383.
http://dx.doi.org/10.1016/j.tet.2009.03.065
52. Liu, G.; Huang, T.; Zhang, Y.; Liang, X.; Li, Y.; Li, H. *Catal. Commun.* **2011**, *12*, 655-659.
http://dx.doi.org/10.1016/j.catcom.2010.12.021
53. Dlinnykh, I. V.; Golubeva, G. A.; Leshcheva, I. F.; Nesterov, V. V.; Antipin, M. Y.; Sviridova, L. A. *Chem. Heterocycl. Compd.* **2004**, *40*, 1142-1149.
http://dx.doi.org/10.1023/B:COHC.0000048286.22570.9f
54. Companyo, X.; Zea, A.; Alba, A.-N. R.; Mazzanti, A.; Moyano, A.; Rios, R. *Chem. Commun.* **2010**, *46*, 6953-6955.
http://dx.doi.org/10.1039/c0cc01522a
PMid:20730196
55. Wang, H.; Chen, M.; Wang, L. *Chem. Pharm. Bull.* **2007**, *55*, 1439-1441.
http://dx.doi.org/10.1248/cpb.55.1439
56. Wilson, R. M.; Hengge, A. C.; Ataei, A.; Chantarasiri, N. *J. Org. Chem.* **1990**, *55*, 193-197.
http://dx.doi.org/10.1021/jo00288a032
57. Mahmoud, M. R.; El-Bordany, E. A. A.; Hassan, N. F.; El-Azm, F. S. M. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 2507-2521.
http://dx.doi.org/10.1080/10426500701506465
58. Phillips, D. P.; Hudson, A. R.; Nguyen, B.; Lau, T. L.; McNeill, M. H.; Dalgard, J. E.; Chen, J.-H.; Penuliar, R. J.; Miller, T. A.; Zhi, L. *Tetrahedron Lett.* **2006**, *47*, 7137-7138.
http://dx.doi.org/10.1016/j.tetlet.2006.08.004
59. Rossi, E.; Abbiati, G.; Canevari, V.; Celentano, G.; Magri, E. *Synthesis* **2006**, 299-304.
http://dx.doi.org/10.1055/s-2005-918509
60. Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117-2120.
http://dx.doi.org/10.1021/ol050395x
PMid:15901148

61. Shen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, 7, 3081-3084.
http://dx.doi.org/10.1021/ol051094q
PMid:15987210
62. Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem. Int. Ed*. **2011**, *50*, 8605-8608.
http://dx.doi.org/10.1002/anie.201102984
PMid:21793137
63. Katritzky, A. R.; Yao, G.; Lan, X.; Zhao, X. *J. Org. Chem.* **1993**, *58*, 2086-2093.
http://dx.doi.org/10.1021/jo00060a025
64. Sakakura, A.; Kawajiri, K.; Ohkubo, T.; Kosugi, Y.; Ishihara, K. *J. Am. Chem. Soc.* **2007**, *129*, 14775-14779.
http://dx.doi.org/10.1021/ja075824w
PMid:17983230
65. Berry, D. J.; DiGiovanna, C. V.; Metrick, S. S.; Murugan, R. *Arkivoc* **2001**, (i), 201-226.
66. Rajeswaran, W. G.; Cohen, L. A. *Tetrahedron* **1998**, *54*, 11375-11380.
http://dx.doi.org/10.1016/S0040-4020(98)00679-6
67. Akai, S.; Tsujino, T.; Naka, T.; Tanimoto, K.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 7315-7317.
http://dx.doi.org/10.1016/S0040-4039(01)01547-7
68. Gandon, V.; Aubert, C.; Malacriab, M.; Vollhardt, K. P. C. *Chem. Commun*. **2008**, 1599-1601.
http://dx.doi.org/10.1039/b716841a
PMid:18354812
69. Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2008**, *130*, 9613–9620.
http://dx.doi.org/10.1021/ja803179s
PMid:18588302 PMCid:2587375
70. Black, D. St.C.; Rezaie, R. *Tetrahedron Lett*. **1999**, *40*, 4251-4254.
http://dx.doi.org/10.1016/S0040-4039(99)00699-1
71. Ghandi, M.; Salahi, S.; Hasani, M. *Tetrahedron Lett.* **2011**, *52*, 270-273.
http://dx.doi.org/10.1016/j.tetlet.2010.11.019
72. Shoji, T.; Inoue, Y.; Ito, S. *Tetrahedron Lett*. **2012**, *53*, 1493-1496.
http://dx.doi.org/10.1016/j.tetlet.2012.01.044
73. Meragelman, K. M.; West, L. M.; Northcote, P. T.; Pannell, L. K.; McKee, T. C.; Boyd, M. R. *J. Org. Chem*. **2002**, *67*, 6671-6678.
http://dx.doi.org/10.1021/jo020120k
74. Wahlström, N.; Bergman, J. *Tetrahedron Lett.* **2004**, *45*, 7273-7275.
http://dx.doi.org/10.1016/j.tetlet.2004.08.024
75. Busch-Petersen, J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1641-1643.
http://dx.doi.org/10.1021/ol005964+
PMid:10841499
76. Yamada, S.; Yaguchi, S.; Matsuda, K. *Tetrahedron Lett.* **2002**, *43*, 647-651.
http://dx.doi.org/10.1016/S0040-4039(01)02208-0

77. Sumpter, W. C.; Miller, M.; Hendrick, L. N. *J. Am. Chem. Soc*. **1945**, *67*, 1656-1658.
http://dx.doi.org/10.1021/ja01226a011
78. Lackey, K.; Cory, M.; Davis, R.; Frye, S. V.; Harris, P. A.; Hunter, R. N.; Jung, D. K.; McDonald, O. B.; McNutt, R. W.; Peel, M. R.; Rutkowske, R. D.; Veal, J. M.; Wood, E. R. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 223-226.
http://dx.doi.org/10.1016/S0960-894X(99)00668-X
79. Itoh, N.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *J. Org. Chem.* **2002**, *67*, 7424-7428.
http://dx.doi.org/10.1021/jo0260847
80. Lai, J. Y. Q.; Cox, P. J.; Patel, R.; Sadiq, S.; Aldous, D. J.; Thurairatnam, S.; Smith, K.; Wheeler, D.; Jagpal, S.; Sofia Parveen; Fenton, G.; Harrison, T. K. P.; McCarthy, C.; Bamborough, P. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3111-3114.
http://dx.doi.org/10.1016/S0960-894X(03)00658-9
81. Bergman, J.; Engqvist, R.; Stålhandske, C.; Wallberg, H. *Tetrahedron* **2003**, *59*, 1033-1048.
http://dx.doi.org/10.1016/S0040-4020(02)01647-2
82. Patteux, C.; Levacher, V.; Dupas, G. *Org. Lett.* **2003**, *5*, 3061-3063.
http://dx.doi.org/10.1021/ol035049z
PMid:12916981
83. Friedländer, P. *Chem. Ber*. **1882**, *15*, 2572-2575.
http://dx.doi.org/10.1002/cber.188201502219
84. McGeachin, S. G. *Can. J. Chem*. **1966**, *44*, 2323-2328.
http://dx.doi.org/10.1139/v66-348
85. Chuiguk, V. *Chem. Heterocycl. Compd*. **1973**, *9*, 656-656.
http://dx.doi.org/10.1007/BF00480587
86. Chan, F.; Magnus, P.; McIver, E. G. *Tetrahedron Lett*. **2000**, *41*, 835-838.
http://dx.doi.org/10.1016/S0040-4039(99)02204-2
87. Fröhner, W.; Monse, B.; Braxmeier, T. M.; Casiraghi, L.; Sahagún, H.; Seneci, P. *Org. Lett*. **2005**, *7*, 4573-4576.
http://dx.doi.org/10.1021/ol051550a
PMid:16209482
88. Ginnari-Satriani, L.; Casagrande, V.; Bianco, A.; Ortaggi, G.; Franceschin, M. *Org. Biomol. Chem*. **2009**, *7*, 2513-2516.
http://dx.doi.org/10.1039/b904723a
PMid:19503922
89. Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc*. **2004**, *126*, 14043-14053.
http://dx.doi.org/10.1021/ja046690e
PMid:15506768
90. Trost, B. M.; Zhang, Y.; Zhang, T. *J. Org. Chem***.** **2009**, *74*, 5115-5117.
http://dx.doi.org/10.1021/jo900760r
PMid:19588998

91. Robertson, D. W.; Krushinski, J. H.; Beedle, E. E.; Wyss, V.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem.* **1986**, *29*, 1832-1840.
    http://dx.doi.org/10.1021/jm00160a006
92. Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem*. **1987**, *30*, 824-829.
    http://dx.doi.org/10.1021/jm00388a014
93. Thompson, A. M.; Rewcastle, G. W.; Tercel, M.; Dobrusin, E. M.; Fry, D. W.; Kraker, A. J.; Denny, W. A. *J. Med. Chem.* **1993**, *36*, 2459-2469.
    http://dx.doi.org/10.1021/jm00069a003
94. Corwin, A. H.; Krieble, R. H. *J. Am. Chem. Soc.* **1941**, *63*, 1829-1834.
    http://dx.doi.org/10.1021/ja01852a010
95. Blanche, E. A.; Maskell, L.; Colucci, M. A.; Whatmore, J. L.; Moody, C. J. *Tetrahedron* **2009**, *65*, 4894–4903.
    http://dx.doi.org/10.1016/j.tet.2009.04.014
96. Howard, H. R.; Sarges, R.; Siegel, T. W.; Beyer, T. A. *Eur. J. Org. Chem*. **1992**, *27*, 779-789.
97. Beyer, T. A.; Hutson, N. J. *Metab., Clin. Exp.* **1986**, *35*, 1-3.
98. Cheng, H.-M.; González, R. G.; Barnett, P. A.; Aguayo, J. B.; Wolfe, J.; Chylack, L. T. *Exp. Eye Res*. **1985**, *40*, 223-229.
    http://dx.doi.org/10.1016/0014-4835(85)90007-7
99. Niakan, E.; Harati, Y.; Comstock, J. P. *Metabolism* **1986**, *35*, 224-234.
    http://dx.doi.org/10.1016/0026-0495(86)90205-2
100. Beyersbergen van Henegouwen, W. G.; Fieseler, R. M.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Org. Chem*. **2000**, *65*, 8317-8325.
    http://dx.doi.org/10.1021/jo001119t
101. McComas, C. C.; Vu, A. T.; Mahaney, P. E.; Cohn, S. T.; Fensome, A.; Marella, M. A.; Nogle, L.; Trybulski, E. J.; Ye, F.; Zhang, P.; Alfinito, P.; Bray, J.; Johnston, G.; Koury, E.; Deecher, D. C. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 4929-4931.
    http://dx.doi.org/10.1016/j.bmcl.2008.08.060
    PMid:18771916
102. Porcs-Makkay, M.; Volk, B.; Kapiller-Dezsofi, R.; Mezei, T.; Simig, G. *Monatsh. Chem.* **2004**, *135*, 697-711.
    http://dx.doi.org/10.1007/s00706-003-0127-9
103. Lee, E. S.; Park, J.-G.; Jahng, Y. *Tetrahedron Lett*. **2003**, *44*, 1883-1886.
    http://dx.doi.org/10.1016/S0040-4039(03)00080-7
104. Fensome, A.; Bender, R.; Cohen, J.; Collins, M. A.; Mackner, V. A.; Miller, L. L.; Ullrich, J. W.; Winneker, R.; Wrobel, J.; Zhang, P.; Zhangb, Z.; Zhu, Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3487-3490.
    http://dx.doi.org/10.1016/S0960-894X(02)00746-1
105. Jha, M.; Blunt, B. *Tetrahedron Lett.* **2009**, *50*, 6044-6047.
    http://dx.doi.org/10.1016/j.tetlet.2009.08.057

106. Jha, M.; Chou, T.-Y.; Blunt, B. *Tetrahedron* **2011**, *67*, 982-989.
http://dx.doi.org/10.1016/j.tet.2010.11.105
107. Deng, H.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001-3004.
http://dx.doi.org/10.1021/ol016379r
PMid:11554828
108. Kanbe, K.; Naganawa, H.; Nakamura, K. T.; Okami, Y.; Takeuchi, T. *Biosci. Biotech. Biochem*. **1993**, *57*, 636-637.
http://dx.doi.org/10.1271/bbb.57.636
109. Olesen, P. H.; Hansen, J. B.; Engelstoft, M. *J. Heterocyclic Chem.* **1995**, *32*, 1641-1642.
http://dx.doi.org/10.1002/jhet.5570320540
110. Engqvist, R.; Javaid, A.; Bergman, J. *Eur. J. Org. Chem.* **2004**, 2589-2592.
111. Pedras, M. S. C.; Jha, M. *J. Org. Chem.* **2005**, *70*, 1828-1834.
http://dx.doi.org/10.1021/jo0479866
PMid:15730307
112. Pedras, M. S. C.; Hossain, M.; Sarwar, M. G.; Montaut, S. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 5469-5471.
http://dx.doi.org/10.1016/j.bmcl.2004.09.014
PMid:15482905
113. Soledade, M.; Pedras, C.; Smith, K. C. *Phytochemistry* **1997**, 46, 833-837.
http://dx.doi.org/10.1016/S0031-9422(97)00362-2
114. Majumder, S.; Bhuyan, P. *Synlett* **2011**, 173-176.
115. Burstein, H.; Overmoyer, B.; Gelman, R.; Silverman, P.; Savoie, J.; Clarke, K.; Dumadag, L.; Younger, J.; Ivy, P.; Winer, E. *Invest. New Drugs* **2007**, *25*, 161-164.
http://dx.doi.org/10.1007/s10637-006-9007-6
PMid:16969707
116. Li, X.; Vince, R. *Bioorg. Med. Chem.* **2006**, *14*, 2942-2955.
http://dx.doi.org/10.1016/j.bmc.2005.12.013
PMid:16386908
117. Zhao, G.; Wang, C.; Liu, C.; Lou, H. *Mini-Rev. Med. Chem*. **2007**, *7*, 707-725.
http://dx.doi.org/10.2174/138955707781024535
PMid:17627583
118. Paolini, L. *Sci. Rep. Ist. Super. Sanita* **1961**, *1*, 86.
119. Bhuyan, P.; Majumder, S. *Synlett* **2011**, 1547-1550.
120. Tiano, M.; Belmont, P. *J. Org. Chem.* **2008**, *73*, 4101-4109.
http://dx.doi.org/10.1021/jo800249f
PMid:18459813
121. Monge, A.; Palop, J.; Ramirez, C.; Font, M.; Fernandez-Alvarez, E. *Eur. J. Med. Chem*. **1991**, *26*, 179-188.
http://dx.doi.org/10.1016/0223-5234(91)90027-K
122. Ahadi, S.; Abaszadeh, M.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2012**, *68*, 2906-2916.
http://dx.doi.org/10.1016/j.tet.2012.01.069

123. Ghahremanzadeh, R.; Ahadi, S.; Bazgir, A. *Tetrahedron Lett.* **2009**, *50*, 7379-7381.
http://dx.doi.org/10.1016/j.tetlet.2009.10.077
124. Cochard, F.; Laronze, M.; Prost, É.; Nuzillard, J.-M.; Augé, F.; Petermann, C.; Sigaut, P.; Sapi, J.; Laronze, J.-Y. *Eur. J. Org. Chem.* **2002**, 3481-3490.
http://dx.doi.org/10.1002/1099-0690(200210)2002:20<3481::AID-EJOC3481>3.0.CO;2-C
125. Perumal, P.; Lakshmi, N.; Kiruthika, S. E. *Synlett* **2011**, 1389-1394.
http://dx.doi.org/10.1055/s-0030-1260563
126. Shaker, R. M.; Mahmoud, A. F.; Abdel-Latif, F. F. *J. Chin. Chem. Soc.* **2005**, *52*, 563-567.
127. Du, D.; Hu, Z.; Jin, J.; Lu, Y.; Tang, W.; Wang, B.; Lu, T. *Org. Lett.* **2012**, *14*, 1274-1277.
http://dx.doi.org/10.1021/ol300148f
PMid:22352352

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