Indenoindoles and Cyclopentacarbazoles as Bioactive Compounds: Synthesis and Biological Applications

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Graphical Abstract

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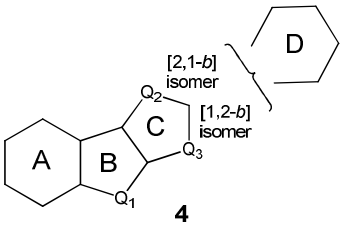

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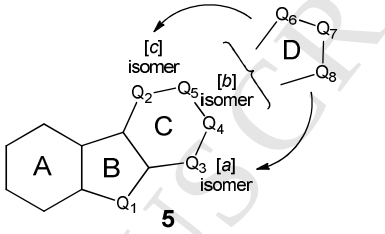
Indeno[x,y-*b*]indole regioisomers



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Cyclopenta[*n*]carbazole regioisomers, *n* = *a,b,c*

Review

Indenoindoles and cyclopentacarbazoles as bioactive compounds: synthesis and biological applications – A review

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ABSTRACT

Indenoindoles and their isomers cyclopentacarbazoles represent a wide class of synthetic and natural compounds. The great interest of these structures in (bio)organic chemistry is due to the use of various building blocks to get the elemental four ring structure. Depending on the synthetic route chosen, the chemists can achieve a large number of regioisomers. Each regioisomer can be considered as a template for specific functionalizations. Therefore, this mini-review aims (i) to present an overview on how to access this large family of heterocyclic compounds and (ii) to discuss their various biological applications and drug development in oncology (e.g. kinases), in CNS disorders (e.g. Alzheimer's disease), in endocrinology (e.g. hormone replacement therapy) and oxidative stress (e.g. organ preservation). Past and present works will be presented through the systems 6-5-5-6 and 6-5-6-5 (combination of 6-membered and 5-membered rings).

Keywords:

Indenoindoles

Cyclopentacarbazoles

Chemical syntheses

Biological applications

Cancer

Cardiovascular diseases

CNS disorders

Diabetes

Oxidative stress

1. Introduction

The indole nucleus is present in a large family of naturally occurring compounds. The indole scaffold and its role in medicinal chemistry and therapeutically active compounds have been frequently and recently reviewed [1,2]. Thus, there is a continued interest in the development of new analogues and efficient synthetic methods comprising the indole nucleus. The indenoindoles and cyclopentacarbazole structural moieties also occur in several natural products (Fig. 1). Tabersonine **1** was among twenty cytotoxic alkaloids, also called melodinines, isolated from the plant *Melodinus suaveolens*. Another cyclopentacarbazole, staurosporine **2**, isolated from the bacterium *Streptomyces staurosporeus* in 1977, was the first natural product isolated of over 50 alkaloids with the cyclopenta-carbazole moiety. Staurosporine was found to have a wide range of different biological activities such as anti-fungal and anti-hypertensive activity, but the main indication was kinase ATP-binding site activity [3]. (+)-Nodulisporic acid A (**3**) is a member of a family of indole-diterpenoids that are potent orally active antiflea agents derived from a fungus belonging to the genus *Nodulisporium*.

Insert Fig. 1.

Indenoindoles have also been used as metal complex polymerization catalysts in preparation of polypropylene production and as materials for organic electroluminescent devices [4,5].

This paper offers an exhaustive review of the main contributions on the access of indenoindoles and cyclopentacarbazoles (e.g. chemical strategies for functional indeno[1,2-*b*]indoles, access to cyclopenta[*b*]carbazolones) and also highlights the wide range of biological activities of these tetracyclic compounds. We put special emphasis on patents based on bioactive indenoindole-type compounds. Non-substituted indenoindoles and cyclopentacarbazoles with equal numbers of double bonds are constitutional isomers. Due to the vast number of permutations arising from various substitutions of the different regioisomers of these two classes of compounds, this article will be restricted to the definitions shown in Fig. 2, with general formulae **4** and **5**.

Insert Fig. 2.

The numbering of these tetracyclic compounds is important to be precise and two examples are shown in Fig. 3, with indeno[1,2-*b*]indole **6** and cyclopenta[*b*]carbazole **7**.

Insert Fig. 3.

2. Synthetic strategies and further structural considerations

2.1. Background

Condensed ring systems comprising the indole nucleus have been targeted in synthetic organic chemistry already in the 1920's by Perkins and Titley [6-8]. Different strategies for the preparation of indenoindoles by cyclisation of substituted indoles using the Fischer indole reaction or Diels Alder reactions were described in 1990 [9,10]. In the same period, the research group of Shertzer at the University of Cincinatti developed synthetic methods to prepare indenoindoles with promising antioxidative properties based on the classic Fischer, Bischler and Wender methods [11,12]. The Fisher method was also used for the preparation of indenoindoles by Martarello and co-workers [13]. Indanone and indole itself were used as starting materials for the preparation of keto-indenoindoles because of their role as molecular moieties in many biologically active natural products [14-16]. Regioisomeric keto-indenoindoles were also the target in the development of a preparative method from indane-1,2,3-trione monohydrate (ninhydrin) and 1,3-cyclohexanediones *via* the corresponding enaminones [17,18]. Microwave-assisted variations of Fischer-type reactions have shown to give selectively a variety of indenoindoles and tetrahydrocarbazoles, using phenylhydrazine with different regioisomers of indanone and tetrahydronaphtalen-ones [19,20].

2.2. Structural considerations

The indenoindole skeletons are found as ten isomers depending on the annulation on the indole ring: indeno[1,2-*b*]indole (**8**) and indeno[2,1-*b*]indole (**9**) mostly described in their dihydro forms [1,2-*b*] (5,10-dihydroindeno[1,2-*b*]indole **10**) and [2,1-*b*] (5,6-dihydroindeno[2,1-*b*]indole **11**) but also as [1,2-*g*] **12**, [1,2-*f*] **13**, [1,2-*e*] **14**, [2,1-*e*] **15**, [2,1-*f*] **16** and [2,1-*g*] **17** isomers (Fig. 4).

Insert Fig. 4.

The cyclopentacarbazole skeleton has basically three different isomers: cyclopenta[*a*], [*b*] and [*c*]carbazoles **18**, **19** and **20**, respectively (Fig. 5).

Insert Fig. 5.

2.3. Access to indenoindoles

2.3.1. Synthesis of indeno[1,2-*b*]indoles

The simplest synthesis of the indeno[1,2-*b*]indoles **23** is the Fischer indole synthesis applied to indanones **21** under suitable Lewis or protic acid conditions (Scheme 1) [12,21-26]. High yields (> 75%) were obtained with the halogen and alkoxy substituents.

Insert Scheme 1.

With phenylhydrazines bearing electron-rich substituents, the reaction failed. However this could be overcome by using *O*-tosylated analogs of the aryl hydrazines in presence of paratoluene sulfonic acid [12]. In a Wender synthesis of indoles, the *O*-lithiated N-trifluoroacetylaniline aza-anion **24** was condensed with α-bromoindanone **25a** to give the 2-methoxy-1,3-dimethyl-5,10-dihydroindeno[1,2-*b*]indole **26** (Scheme 2). However, reaction of **24** with α-chloroindanone **25b** gave the regioisomer 8-methoxy-7,9-dimethyl-5,6-dihydroindeno[2,1-*b*]indole (**27**) [21]. Both compounds **26** and **27** were isolated in poor yields.

Insert Scheme 2.

Other methods could be used to access indeno[1,2-*b*]indoles. Thermolysis of chromium aminocarbene complex gave a mixture containing benzo[*a*]carbazole and a substituted (in position 10) indeno[1,2-*b*]indole [27]. Flash vacuum pyrolysis of 2-phenylquinoline-3,4-dicarboxylic anhydride led to the indeno[1,2-*b*]indole which on reaction with carbanion afforded the 10-substituted 5,10-dihydro derivatives [28].

A new synthetically attractive method [29] was developed to get a new collection of 10-substituted indeno[1,2-*b*]indoles (Scheme 3). 2-(N-Boc-indol-2-yl)benzaldehyde (**28**) reacted with carbon or heteroatom nucleophiles (Nu) in a tandem ring-closing sequence, in the presence of a Pd-Sn heterobimetallic catalyst (e.g. C1: $PdCl(COD)SnCl_3$ with COD = cyclooctadiene) and one additive ($AgPF_6$). For example the compound **29** (Nu = 4-methylphenylamino) was obtained with an 80% yield.

Insert Scheme 3.

Concerning the preparation of the [1,2-*e*], [1,2-*f*] and [1,2-*g*] isomers, only the [1,2-*f*] isomer has been described and synthesized by a Fischer indole synthesis using the hydrazinofluorene which reacted with an

alkyl 2-oxopropanoate. Hydrolysis and decarboxylation of the corresponding indenoindole carboxylate led to the target isomer [30].

2.3.2. Synthesis of indeno[2,1-*b*]indoles

A method, known as the Bischler reaction (classically used to synthesize indole moieties), was used to obtain a mixture of isomeric indenoindoles **35** and **36** (Scheme 4). The α-amino ketone **32** obtained after the reaction of *p*-anisidine (**30**) with 2-bromoindan-1-one (**31**) was heated with *p*-anisidine at 180 °C. Then the reaction mixture was cooled and partitioned between hydrochloric acid and chloroform to initiate dehydratation and cyclization. At the end, after chromatography elution of the final residue, the two targeted tetracycles (**35**, **36**) were isolated with also two pentacycles (**37**, **38**). 2-Methoxy-5,6-dihydroindeno[2,1-*b*]indole **35** was isolated with a poor yield of 9%. The isomeric 5,10-dihydroindeno[1,2-*b*]indole **36** was collected with a yield of 5% [11].

Insert Scheme 4.

Alternative methods (e.g. Fisher and Wender reactions) are also described in a review [31] to access diverse indeno[2,1-*b*]indoles. The yields varied considerably (poor, medium, high) according to the starting materials.

2.4. Access to indenoindolones

Many publications and patents related to this type of compounds have been published, especially the [1,2-*b*] derivatives because of their biological properties. All other types of indenoindolones have been described less during the past years.

2.4.1. Synthesis of indeno[1,2-*b*]indol-10-ones

Ninhydrin (**39**) has been used for the synthesis of the ketone **42** (Scheme 5). Condensation of aniline **40** with ninhydrin (**28**) afforded the dihydroxy derivative **41** (R_1, R_2, R_3 = H [32]. Attempts to prepare the indenoindolone resulted in the formation of pyranoindoles [32] under acidic conditions. However, deoxygenation to the aromatic derivative **42** could be made with acetic acid in DMF [33] or in the presence of tetramethylsulfurous acid diamide (TMTA) [18]. Using this route and starting from diverse enaminones, quinone derivatives of indeno[1,2-*b*]indol-10-ones could be prepared by this multistep procedure, in good yields.

Insert Scheme 5.

A three-component domino reaction was successfully reported and optimized under microwave (MW) irradiation conditions (Scheme 6) [34]. This synthetic pathway using ninhydrine **39** and diverse enaminones **43** led to indeno[1,2-*b*]indole derivatives **44**, *via* a sequence (i) methyl migration, (ii) aromatization and (iii) esterification. The MW conditions were optimized with the enaminone **43a** (R = 4-fluorophenyl). This latter one was converted into the tetracyclic product in 85% yield at 120 °C for 25 min. Eighteen new compounds **44** (e.g. R = phenyl, 3-Me-Ph, 4-Me-Ph, 4-MeO-Ph) were synthesized and yields were superior to 60%.

Insert Scheme 6.

Reduction of 2-(2-nitrophenyl)indane-1,3-dione intermediates **46** have been used to prepare various indeno[1,2-*b*]indolones **48** [35]. 2-(2-Nitrophenylethynyl)benzoic acid esters **45**, obtained by Sonagashira coupling of *O*-bromobenzoates to 2-(2-nitrophenyl)acetylenes, were converted into indeno[1,2-*b*]indolones **48** by a three-step sequence, through the corresponding 2-(2-nitrophenyl)indane-1,3-dione **46**, the aminophenylindane-1,3-diones **47** and the final indeno[1,2-*b*]indol-10-ones **48** (Scheme 7). The reported yields of the last step were comprised between 25 and 50%.

Insert Scheme 7.

Another convenient route to indenoindolones **53** was monobromination of the lactone **49** followed by a Wittig reaction. The coupling of compound **50** with diverse *o*-nitrobenzaldehydes allowed the formation of derivatives **51**. Under basic conditions (e.g. NaOH 4M), rearrangement of the resulting benzylidene lactones **51** gave 2-(2-nitrophenyl)indane-1,3-diones **52** which are then catalytically reduced and cyclized to afford the targeted indenoindolones **53** (Scheme 8) [36,37].

Insert Scheme 8.

Various 3-aroylated indoles **54** have been used for the preparation of indenoindol-10-ones **55**. The tetracyclic template is obtained after an oxidative cyclization step. Many investigations have studied the combination between catalysts, ligands, bases, solvents and conditions to achieve this intramolecular cyclization [38-40]. For example, when R_1 = CH_3 and R_2, R_3 = OCH_3, the cyclization with $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), CsOAc (2 equiv) and DMA was found to be the best combination to get indeno[1,2-*b*]indol-10-ones **55** (Scheme 9) [40].

Insert Scheme 9.

A one-pot synthesis of indenoindolones was developed through the C3-H acylation of indoles **56** and subsequent intramolecular oxidative C-H/C-H coupling of indoles with arenes [41]. The first step, the coupling reaction of indoles **56** with corresponding benzonitrile derivatives **57**, was first optimized (palladium species, bidentate nitrogen ligand, additive, solvent, base) and extra addition of reagents ($Pd(OAc)_2$, $Cu(OAc)_2$, PivOH, K_2CO_3) allowed to achieve the reaction (Scheme 10). The highest yield on eight experiments was 62% (**58a**: R_1 = Br, R_2 = H).

Insert Scheme 10.

The 2-arylindole derivative **59** was protected as the corresponding Boc derivative **60** (yield = 89%), and this benzamide derivative was then cyclized in the presence of lithium tetramethylpiperidide (LiTMP) (Scheme 11) [42]. The corresponding indenoindole **61** was isolated with a 78% yield.

Insert Scheme 11.

2.4.2. Synthesis of indeno[1,2-*f*]indol-9-ones

The same pathway as used for preparing the corresponding indeno[1,2-*f*]indole **13** (Fig. 4), a Fischer indole synthesis performed on the corresponding hydrazinofluorenone gave access to the corresponding ketone [30].

2.4.3. Synthesis of indeno[2,1-*b*]indol-6-ones

A synthetic route using indanones **62** was used to access to indeno[2,1-*b*]indol-6-ones in three steps. The first step was the preparation of α-hydroxymethylidene ketones **63** using methyl formate and sodium methoxide in toluene. The Japp-Klingemann condensation of ketones **63** with diazonium salts led to the corresponding arylhydrazones **64**. Finally, Fischer synthesis under acidic conditions gave indenoindolones **65** in yields superior to 80% (Scheme 12) [13].

Insert Scheme 12.

2.5. Access to cyclopentacarbazoles

2.5.1. Synthesis of cyclopenta[*a*]carbazoles

Cyclopent[*a*]carbazoles have been prepared by different methods. The heating of 1-alkynylpyrano[3,4-*b*]indol-3-ones **66** resulted in an intramolecular Diels-Alder reaction with the extrusion of CO_2 to the desired compounds **67** (Scheme 13) [43,44].

Insert Scheme 13.

Starting from indane derivative **68** and a methyl 2-chloro-3-nitro-benzoate **69**, using a palladium coupling reaction (Suzuki coupling), an arylnitro compound **70** was formed which could be cyclized *via* nitrene formation to the cyclopenta[*a*]carbazole **71** (Scheme 14) [45].

Insert Scheme 14.

The N-methylindole-substituted cyclopropylketone **72** underwent cyclization under Lewis catalyzed conditions (e.g. $SnCl_4$, yield = 78%) to the cyclopenta[*a*]carbazole **73** (Scheme 15) [46].

Insert Scheme 15.

2.5.2. Synthesis of cyclopenta[*b*]carbazoles and cyclopenta[*b*]carbazolones

A cycloaddition study between a pyrano[3,4-*b*]indol-3-one **74** and diverse dienophiles allowed to synthesize (1,2-dihydro)carbazoles [47]. When the dienophile used was 2-cyclopentenone, two cyclopenta[*b*]carbazolone derivatives were isolated: the non-aromatic derivative **75** (yield: 46%) and the aromatic regioisomer **76** (yield: 32%) (Scheme 16). An explanation of the non-aromatizing process was attempted for compound **75**: an electron attracting group at position 1 could prevent the dehydrogenation.

Insert Scheme 16.

In order to achieve a regioselective synthesis of ellipticine, a cyclopenta[*b*]carbazole intermediate **81** was synthesized [48]. The synthesis of 1,2,3,5-tetrahydro-4,10-dimethylcyclopenta[*b*]carbazol-2-yl acetate (**81**) was achieved in a five-step synthetic pathway, using 4,7-dimethylindan-2-one **77** as starting material. The reaction sequence was as following: carbonyl reduction, iodination, esterification, Suzuki coupling and final cyclization (Scheme 17). All intermediates **78-81** were isolated with good to excellent yields (between 73 and 99%).

Insert Scheme 17.

The annulation of the 3-bromo-2-formylcarbazoles **82** with acetylenic derivatives under palladium catalysis led to cyclopenta[*b*]carbazoles **83** and **84** in one step (Scheme 18) [49].

Insert Scheme 18.

2.5.3. Synthesis of cyclopenta[*c*]carbazoles

A synthesis entitled "*in situ* vinylindole synthesis of tetrahydrocarbazoles" was used to access cyclopenta[*c*]carbazoles [50]. This one-pot three-component tandem reaction of indole (**85**) with excess cyclopentanone (**86**) and maleic acid (**87**) both as the catalyst for 3-vinylindole formation and as the dienophile for the Diels-Adler reaction succeeded to give the cyclopenta[*c*]carbazole-4-carboxylic acid intermediate **88** (Scheme 19). Esterification and aromatization steps completed this synthetic pathway to get the template of cyclopenta[*c*]carbazole **90**.

Insert Scheme 19.

Another synthetic investigation was done with N-methylcarbazole **91** and two isomeric cyclopentacarbazoles **92** and **93** were isolated and fully characterized [51]. The imminium salt complex initially prepared by acting N,N-dimethylacrylamide with trifluoromethanesulfonic anhydride was used as electrophile reagent on N-methylcarbazole. The initial attack occurred at the position 3 of the carbazole skeleton and the cyclization step took place at both positions 2 and 4. The lack of regioselectivity led to the formation of cyclopenta[*c*]carbazolone **92** and cyclopenta[*b*]carbazolone **93** derivatives in a 1:1 ratio (yields: 19% *versus* 16%) (Scheme 20).

Insert Scheme 20.

A series of aryl-2-(*N*-methyl/benzylindol-3-yl)cyclopropyl ketones **95** was obtained by cyclopropanation of indole intermediates **94** in the presence of dimethylsulfoxonium methylide generated *in situ* [52]. Next a domino carbocationic rearrangement of the cyclopropyl ketones **95** was observed when a solution of $SnCl_4$ in nitromethane was added dropwise (Scheme 21). Finally, the multi-step transformation of cyclopropyl ketones **95** [52] afforded a new series of 2,3-substitutedcyclopenta[*c*]carbazoles **96**.

Insert Scheme 21.

3. Biological activities

Indole- and indene-based scaffolds are precursors of many pharmaceuticals [1,53] and have fascinated organic and medicinal chemists worldwide. The combination of these bicyclic structures to indenoindoles offers an important number of biologically active compounds. Furthermore cyclopentacarbazoles also possess high potencies to design active substances. In the last thirty years, various biological activities were reported on indenoindoles and cyclopentacarbazoles. The most representative series and molecules are now presented.

3.1. Antioxidant activity

Diverse series of indeno[1,2-*b*]indole, indeno[1,2-*b*]indol-10-one and indeno[2,1-*b*]indol-6-one derivatives have been developed as active antioxidants [21,54]. Preparation [11,12,55] and structure-activity studies [56,57] identified derivatives with higher antioxidant potential than α-tocopherol and the synthetic antioxidant butylated hydroxytoluene (BHT). The inhibitory activity of 5,10-dihydroindeno[1,2-*b*]indole (**10**, DHII) on lipid peroxidation was due to the electron-deficient 10-carbon and the ability to stabilize free radicals **97** [56,58]. Two of the most active compounds were N-acetyl-5,10-dihydroindeno[1,2-*b*]indole (**98**) and a tetrahydro derivative H290/51 (**99**, cis-2-methoxy-4-methyl-5,5a,6,10b-tetrahydroindeno[2,1-*b*]indole, also called 9-methoxy-7-methyl-*iso*-THII) (Fig. 6). Inhibition of lipid peroxidation by H290/51 exerted protective effects on coronary endothelial function after long-term storage [59] and may represent a therapeutic alternative to preserve hearts used for transplantation [60]. Additionally H290/51 has a potential therapeutic value in the treatment of spinal cord injuries [61].

Insert Fig. 6.

Furthermore promising biological activity of indenoindoles *in vitro* and *in vivo* was found in models related to hepatotoxicity, diabetes and myocardial ischemia [58,62-65]. Indenoindole derivatives also were reported to affect the melatonine MT3 receptor on NRH-quinone oxidoreductase 2 enzyme, related to redox status of cells [66-67]. Compounds H290/51 and DHII were shown also to affect the activity of thyroid peroxidase and regulation of aromatic hydrocarbon gene battery enzymes, affecting the glutathione levels in mouse hepatoma cell lines, both related to redox processes *in vivo* [68-69]. In a sensitive and resistant mouse hepatocyte line, DHII also showed protection from menadione (vitamin K_3) toxicity [70-71]. Lipofuscin (LF) is finely granular yellow-brown pigment granules composed of lipid-containing residues of lysosomal digestion. In cultured rat myocardial cells, LF is considered to be an index of intra-lysosomal oxidative reactions as a consequence of Fenton reaction. DHII depressed LF formation in cultured neonatal rat myocardial cells [72].

More recently, a new series of functionalized 5,10-dihydroindeno[1,2-*b*]indoles **100** was developed as antioxidants [73]. These derivatives incorporating methoxy, hydroxyl, and halogen moieties on the indene fragment of the tetraheterocyclic system were evaluated by various *in vitro* assays and showed ferrous ion chelating, ferric ion reducing and radical scavenging activities (Fig. 7).

Insert Fig. 7.

3.2. Neuroprotective activity

Natural cyclopenta[*b*]carbazoles **101** belonging to claulansines (also called mafaicheenamines) were evaluated for neuroprotective effects on neuron-like PC12 cells (Fig. 8) [74].

Insert Fig. 8.

3.3. Targeting acetylcholinesterase

Acetylcholinesterase (AChE) inhibitors have been investigated for the treatment of Alzheimer's disease (AD). Tacrine **102** (Fig. 9), a reversible inhibitor of AChE, was launched in 1993 and was shown clinically to delay symptoms of the disease. However, adverse events consisting mainly in the elevated liver transaminase levels, promoted development of N-benzyl-piperidine-based AChE inhibitors like E-2020 (**103**) [75]. N-Benzyl-piperidine-based indenoindoles (e.g. compound **104**, Fig. 9) were shown to have lower activity but better selectivity in the same study. Presently E-2020 is now in clinical use under the name donepezil (Aricept®, Eisai) [76,77].

Insert Fig. 9.

3.4. Targeting carbonic anhydrase

The series of 5,10-dihydroindeno[1,2-*b*]indole derivatives, described in Fig. 7, were evaluated on human (h) and bovine carbonic anhydrase (CA) isoforms I, II, III, IV ad VI. Some compounds **100** demonstrated potencies to inhibit hCA I with more effective inhibitory activity compared to the reference compounds EMATE and AZA [78]. The hydroxyl group is important for the biological activity and the best CA inhibitor of the study was 5,10-dihydroindeno[1,2-*b*]indol-1-ol.

3.5. Targeting estrogen receptor

Selective Estrogen Receptor Modulators (SERMs) are very useful for treating or preventing many diseases including osteoporosis, breast cancer and uterine cancer. Some tetracyclic indoles like indeno[1,2-*b*]indoles **105** showed strong binding to the estrogen receptor (Fig. 10) [79]. For example compound **105a** has shown to possess mixed estrogen agonist/antagonist activity.

Insert Fig. 10.

3.6. Targeting DNA and topoisomerase-II

The indenoindole skeleton is relatively flat in many of the structural variations (Fig. 4 and 5), and as such they may be anticipated to have DNA intercalating abilities. Indeed, a series of substituted indenoindoles **106** (Fig. 11) were shown to intercalate into DNA with a preference for AT-rich sequences and strongly stimulate DNA cleavage by topoisomerase (topo)-II. One compound in this series **106a** (S36888, R = Me, Fig. 11) showed 100% complete colon tumour regression in mice at 25 mg/kg without significant body weight loss [36]. Rebeccamycin (RA, **107**, Fig. 11) is a bacterial metabolite isolated from *nocardia aerocoligenes* [80], and has been used as a scaffold for the development of new anticancer drugs. A recent study [81] allowed to identify a series of indolo(pyrrolo)carbazoles as very potent agents showing antiproliferative activity in three human cancer cell lines, A2780 (ovarian cancer), H460 (lung cancer), and GLC4. The RA analogue **108** showed dual simultaneous topo-I and -II inhibition in a phase II clinical study. However, the toxicities of RA, predominately myelosuppression, as also observed in the phase I study [82] rendered no clinical advantages of this drug over other agents on the market [83].

Insert Fig. 11.

Indeno[1,2-*b*]indolone derivatives were recently developed as potential topo-II inhibiting anticancer agents [84]. Diverse structural modifications were made on carbonyl moiety to enhance potency in inhibition of topo-II (Fig. 12). Hydrazones **109**, (thio)semicarbazones **110**, oximes **111** of indenoindolones and indenoindolols **112** were systematically studied and five compounds showed potent specific inhibition of human DNA topo-IIα, without any inhibitory activity on topo-I and DNA intercalation.

Insert Fig. 12.

3.7. Antiproliferative activity

A series of indeno[1,2-*b*]indoles was designed and synthesized *via* the Fisher indole synthesis. Thirteen compounds **113** (X = H, OMe; Y = Br, Cl, F, OMe, Fig. 13) were screened for *in vitro* cytotoxic activity

against human nasopharyngeal carcinoma (HONE-1) and gastric adenocarcinoma (NUGC-3) [85]. The lead compound **113a** (X = 6-OMe, Y = 2-F) exhibited significant percent growth inhibition at 20 μg/mL.

Insert Fig. 13.

A large series of cyclopenta[*c*]carbazoles **114** was developed as p53 activators and their use in the treatment of diseases including cancers (e.g. breast, colon, kidney, liver, pancreas) [86]. The p53 activation assay was performed with two reporter cell lines HT1080-L and RCC45ConALuc (Fig. 14). For example, using the described screening [86], the EC_{50} value of compound **114a** was 0.08 μM.

Insert Fig. 14.

3.8. Targeting TrkA kinase

The Trk family consists of three receptor kinases - TrkA, TrkB and TrkC. Trks can be activated by various neurotrophine proteins such as nerve growth factor (NGF). The abnormal stimulation of TrkA signal transduction pathway by NGF contributes to survival and proliferation of human cancers (e.g. neuroblastoma, medulloblastoma) [87]. Small molecule-based inhibitors of TrkA are developed to disrupt TrkA signalling pathway. Among actual known TrkA inhibitors, a large series of staurosporine analogues contributed to get a new library of TrkA inhibitors [88]. Structural requirements for selective inhibitors were determined by successive modifications using staurosporine aglycone (K-252c) **115** as starting point (Fig. 15).

Insert Fig. 15.

The most powerful pharmacomodulation of K-252c was to replace one of the indole moiety by an indene one and to introduce a carbamate side chain. A structure-activity relationship (SAR) of these indenopyrrolocarbazoles **116** led to the finding of a lead compound (R = Et) and was selected as a proof of concept molecule for *in vitro* and *in vivo* evaluation.

3.9. Targeting protein kinase CK2

Human protein kinase CK2 is a pleiotropic Ser/Thr kinase which appears to be involved in many disease patterns and metabolic disorders, including cancer, neurodegenerative disorders but also diabetes type II [89]. The planar character and the molecular dimensions of indeno[1,2-*b*]indoles makes them promising candidates to target the ATP binding site of therapeutic targets, in particular protein kinases.

Within a series of 19 phenolic and cyclohexenon derivatives of indeno[1,2-*b*]indoles [18,33] tested on *in vitro* inhibition of human CK2, 5-isopropyl-7,8-dihydroindeno[1,2-*b*]indole-9,10(5*H*,6*H*)-dione **117** (Fig. 16) was identified to be the most potent compound with an IC_{50} value of 110 nM [17]. ATP competitivity could be demonstrated obtaining a Ki value of 60 nM, and the compound appeared to be selective for CK2, as a panel of 22 kinases representing different branches of the humane kinome was not or only weakly inhibited. The N-isopropyl derivative **117**, however, showed only restricted inhibition of cell growth in different cancer cell lines. This was not due to a limited cell permeability of the compound (ClogP = 3.13), but appeared to be rather due to a rapid metabolic inactivation or transporter guided efflux.

Insert Fig. 16.

The cyclohexenon derivatives were used as the starting point for the synthesis of series of indeno[1,2-*b*]indoloquinones [90]. An N-isopropyl substituted derivative inhibited human CK2 with an IC_{50} of 5.05 µM (5-isopropyl-5*H*-indeno[1,2-*b*]indole-6,9,10-trione (**118**), Fig. 16) and a N-benzyl derivative **119** (5-benzyl-5*H*-indeno[1,2-*b*]indole-6,9,10-trione) with an IC_{50} of 1.49 µM. The N-isopropyl derivative **118** inhibited the growth of a series of different tumour cell lines (5637, SISO, KYSE-70, MCF-7, LCLC, A427) with GI values in the low micromolar range (1.3-1.7 µM), whereas carcinoma lines DAN-G and RT-4 remained unaffected. Beside human CK2, the N-isopropyl derivative **118** also inhibited human ARK5 with an IC_{50} of 0.57 µM and FLT-3 with an IC_{50} of 0.18 µM. This is to indicate that indeno[1,2-*b*]indoles are promising leads for the synthesis of potent kinase inhibitors, in particular of human protein kinase CK2 and/or the AMP activated Ser/Thr kinase ARK5. This scaffold deserves a more systematic approach to identify beneficial substitutions in the different ring systems, as the N-isopropyl substitution appears to be. At this point, it is worth mentioning that the mere indeno[1,2-*b*]indole scaffold without any substitutions (compound **120**, Fig. 16) was recently reported to inhibit cell growth of human kidney cancer cell line (HEK293) with higher potencies than cytotoxic agents in therapeutic use (e.g. etoposide and 5-fluorouracil) [91].

3.10. Targeting BK (big potassium) channels

Large-conductance voltage- and Ca^{2+}-activated K^+ channels (BK channels) play different specific physiological roles in most species. Impaired BK channels have been associated with hypertension, urinary incontinence, erectile dysfunction, and epilepsy [92]. Modulation of potassium channel openers may reduce excitability and relax smooth muscle cells. It has been shown that bladder smooth muscle contains several types of potassium channels and their activation may induce muscle relaxation. A series of benzofuroindoles and indenoindoles related to prototype compound **121** (8-bromo-10*H*-benzo[4,5]furo[3,2-*b*]indole-1-carboxylic acid, Fig. 17) was designed and the compounds were evaluated for their smooth muscle relaxant

properties [22,93]. Recently, paxilline (**122**, Fig. 17), an indole diterpene from fungi which potently and reversibly inhibits BK channels, protected neuronal cells against glutamate-induced cell death [94]. Indeno[1,2-*b*]indole scaffold seems to be important for promoting the biological activity related to BK channels.

Insert Fig. 17.

3.11. Targeting 17β-hydroxysteroid dehydrogenase type 1

We can illustrate the structural interest of indenoindoles and cyclopentacarbazoles by new pharmacomodulation works consisting in the combination of 6-membered and 5-membered rings with modifications of the nature and the position of heteroatom. For example, the system 6-5-6-5 allowed to access potent 17β-HSD1 inhibitors.

Development of breast cancer is frequently hormone-dependent. 17β-Hydroxysteroid dehydrogenase type 1 (17β-HSD1) is a key enzyme in the biosynthesis of female sex hormones like the estrogen derivatives (Fig. 18). Estradiol (E2, **124**) has a crucial role in the growth and development of tumours and is formed by 17β-HSD1 from estrone (**123**). Several thieno[2,3-d]pyrimidin-4(3*H*)-one based compounds like **125** and **126** were found to be potent 17β-HSD1 inhibitors [95]. The azepine-3-carboxaldehyde **126** was one of the most potent nonsteroidal 17β-HSD1 inhibitors reported to date. Furthermore, the majority of these compounds exhibited excellent selectivity over the oxidative isoform 17β-HSD2 and lacked estrogenic effects in an estrogen receptor (ER) binding assay [95].

Insert Fig. 18.

4. Conclusions

The great interest of indenoindoles and their isomers cyclopentacarbazoles is related to their wide occurrence in many biologically active natural compounds and the feasibility of the preparation of desired regioisomeric structural variations using a variety of organic reactions. This structural class represents a wide class of synthetic and natural compounds. Each regioisomer can be considered as a template for specific functionalizations, depending on the desired aim of the synthetic program. These tetracyclic compounds exhibit a broad spectrum of properties; they are also useful as industrial metal complex polymerization catalysts. Further, they may be used as scaffolds for the development of biologically active compounds and drugs, such as antioxidants, 17β-HSD1 inhibitors, kinase inhibitors and bioactive molecules in CNS disorders. The class of indenoindoles and cyclopentacarbazoles are also frequently occurring in

patents and patent applications, indicating that their academic and industrial use in both chemistry and pharmaceutical processes will continue to grow in the future.

Related indenoindoles and cyclopentacarbazoles such as indenobenzothiophens, indenobenzofurans and oxazinocarbazoles will be the subject of later publications.

5. Conflicts of interests

The authors declare no conflict of interest.

6. Acknowledgements

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List of Figures and Schemes

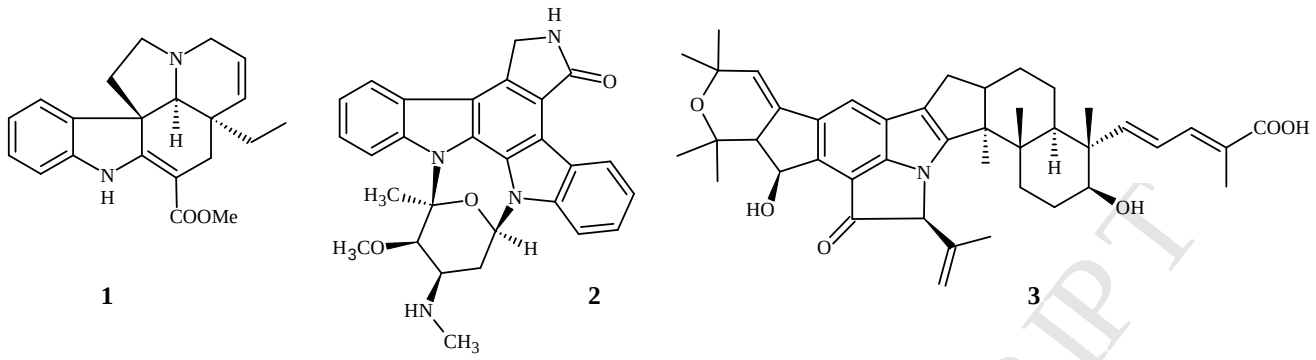


Fig. 1. Chemical structures of three naturally occurring compounds comprising the indenoindole or cyclopentacarbazole structural moieties.

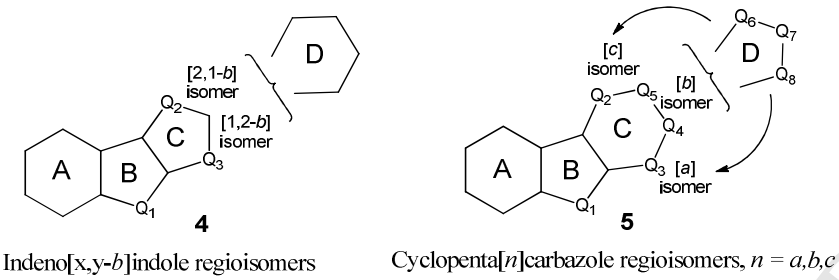


Fig. 2. General structures of regioisomers: indeno[x,y-*b*]indoles **4** and cyclopenta[*n*]carbazoles **5**.

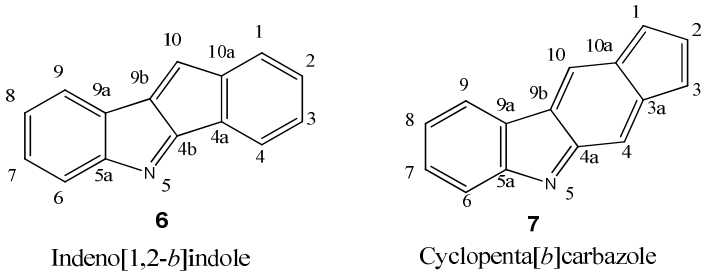
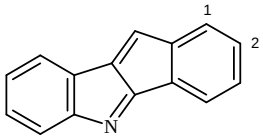


Fig. 3. Ring numbering of indeno[1,2-*b*]indole **6** and cyclopenta[*b*]carbazole **7**.



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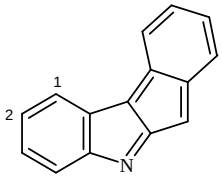

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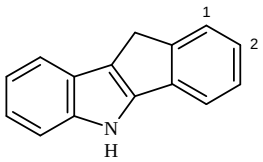
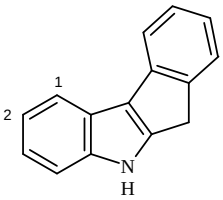
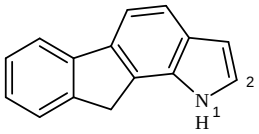


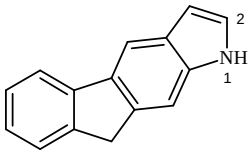
5,10-dihydroindeno[1,2-*b*]indole **10**



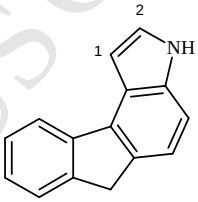
5,6-dihydroindeno[2,1-*b*]indole **11**



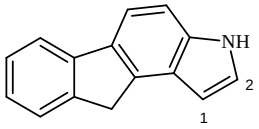
1,10-dihydroindeno[1,2-*g*]indole **12**



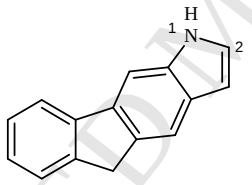
1,9-dihydroindeno[1,2-*f*]indole **13**



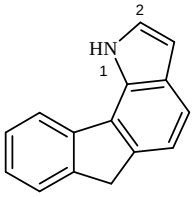
3,6-dihydroindeno[1,2-*e*]indole **14**



3,10-dihydroindeno[2,1-*e*]indole **15**



1,5-dihydroindeno[2,1-*f*]indole **16**



1,6-dihydroindeno[2,1-*g*]indole **17**

Fig. 4. Isomers of the indenoindole skeleton.

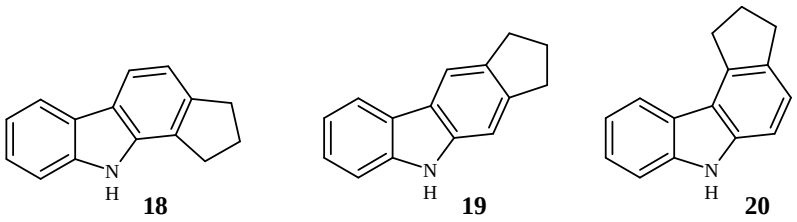
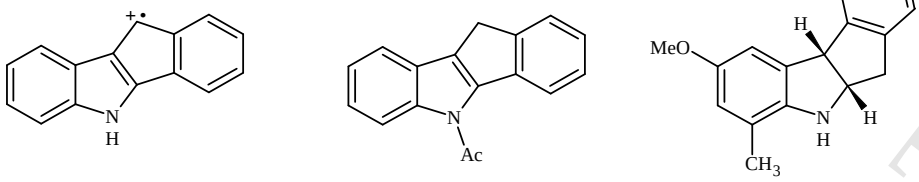


Fig. 5. Isomers of the cyclopentacarbazole skeleton.

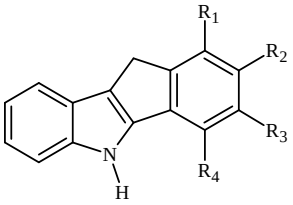


radical cation of 5,10-dihydro-indeno[1,2-*b*]indole **97**

N-acetyl-5,10-dihydro-indeno[1,2-*b*]indole **98**

H290/51 **99**

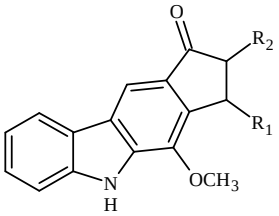
Fig. 6. Structures of the radical cation of DHII, a DHII-derivative and H290/51.



100

R_1 = H, OH, OCH_3
R_2 = H, OH, OCH_3, Br, Cl, F
R_2-R_3 = O-CH_2-O
R_3 = H, OH, OCH_3
R_4 = H, OH, OCH_3

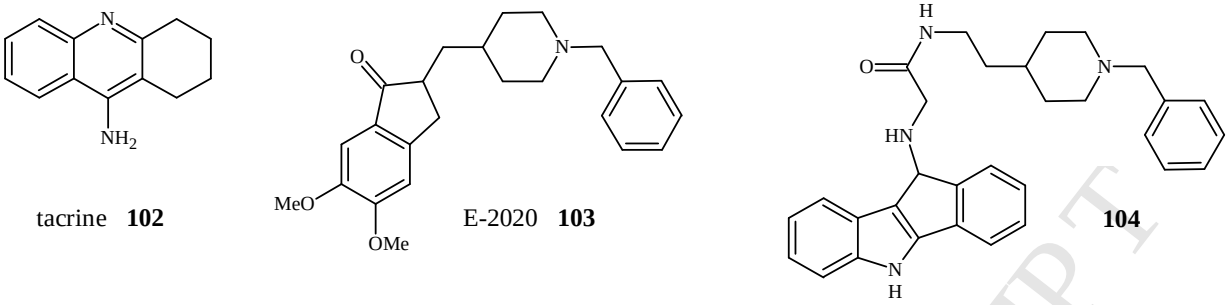
Fig. 7. Structure of some indenoindoles as antioxidants.



R_1 = H, OH
R_2 = H, =C(CH_3)$_2$

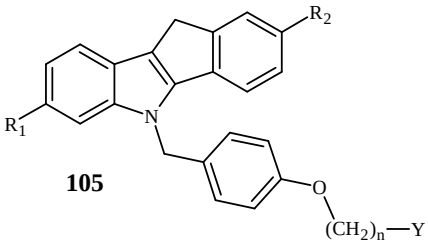
claulansines **101**

Fig. 8. Structure of cyclopenta[*b*]carbazoles from the stems of *Clausena lansium*.

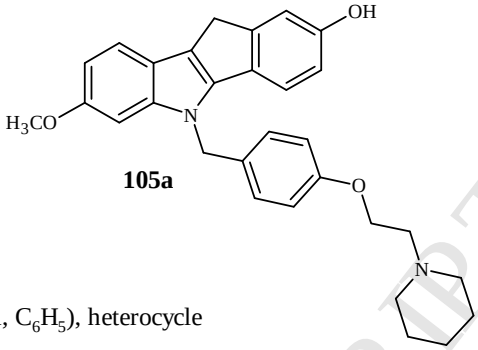


tacrine **102** E-2020 **103** **104**

Fig. 9. Structures of AchE inhibitors.



105

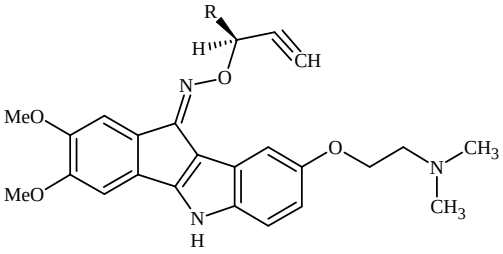


105a

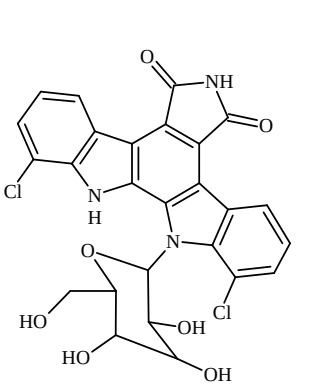
R_1, R_2 = H, OH, alkyl ethers

Y = NR_3R_4 (with R_3 and R_4 = H, C_1-C_6 alkyl, C_6H_5), heterocycle

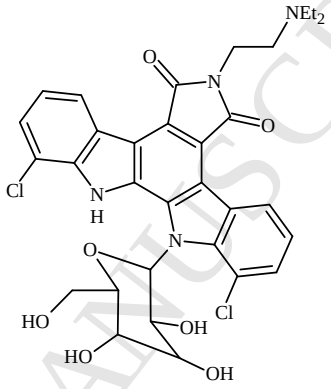
Fig. 10. Structure of indenoindole-type SERMs.



106: R = CH_3, furyl, C_6H_5
106a (S36888, R = CH_3)



RA **107**



108

Fig. 11. Structures of substituted indenoindoles and related.

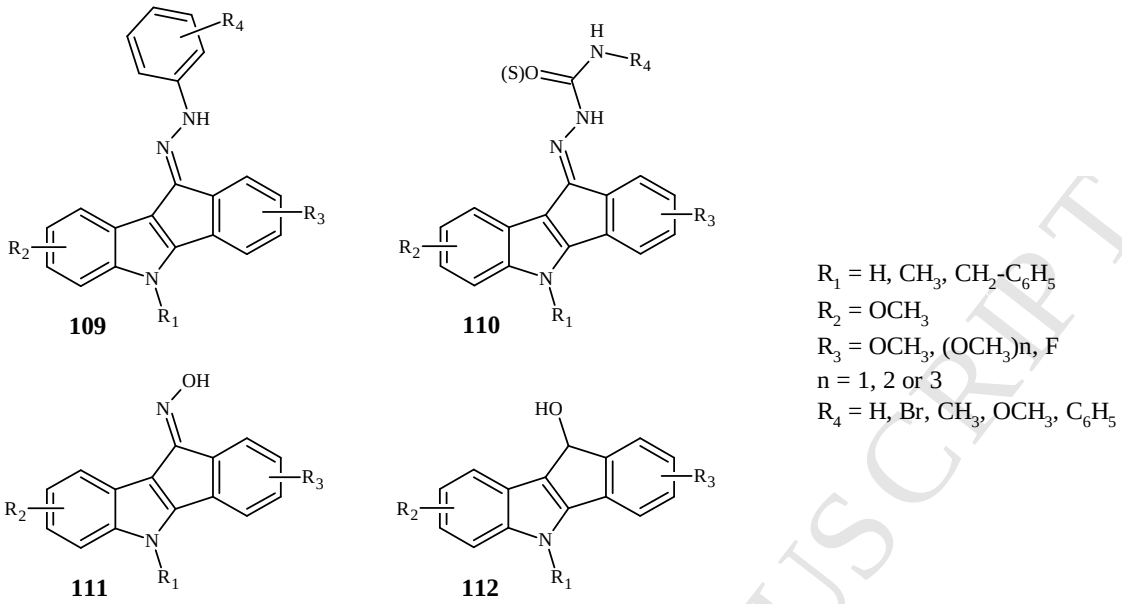
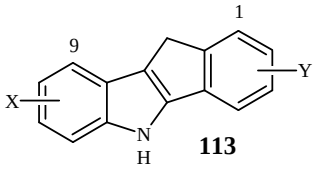
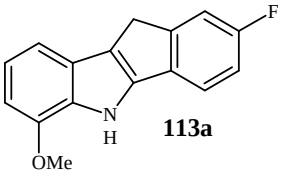


Fig. 12. Indenoindolone derivatives as topo-II inhibiting anticancer agents.



113



113a

X = H, 6-OCH_3, 8-OCH_3, 9-OCH_3

Y = 2-Br, 2-Cl, 2-F, 2,3-di-OCH_3

Fig. 13. Series of indeno[1,2-*b*]indoles screened for cytotoxic activity.

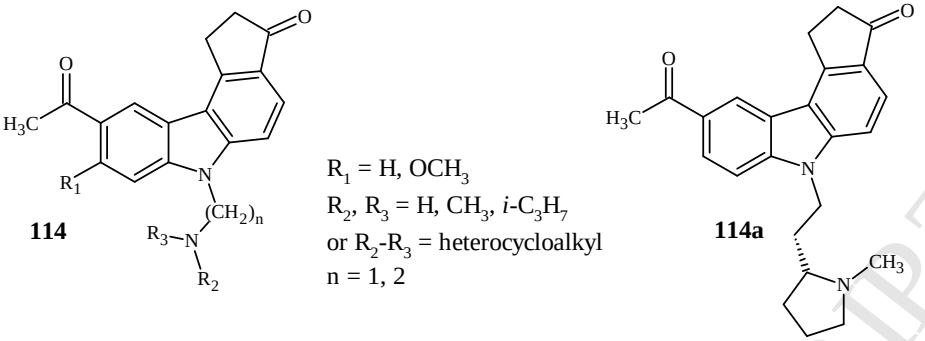
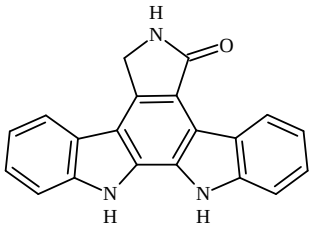
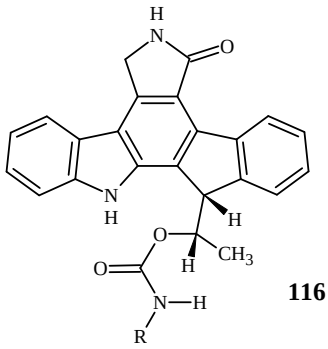


Fig. 14. Cyclopenta[*c*]carbazoles as p53 activators.



staurosporine aglycone
or K-252c **115**



116

R = C_2H_5, CH_2-CH=CH_2, C_6H_5, CH_2-C_6H_5

Fig. 15. Structure of staurosporine aglycone and indenopyrrolocarbazole derivatives.

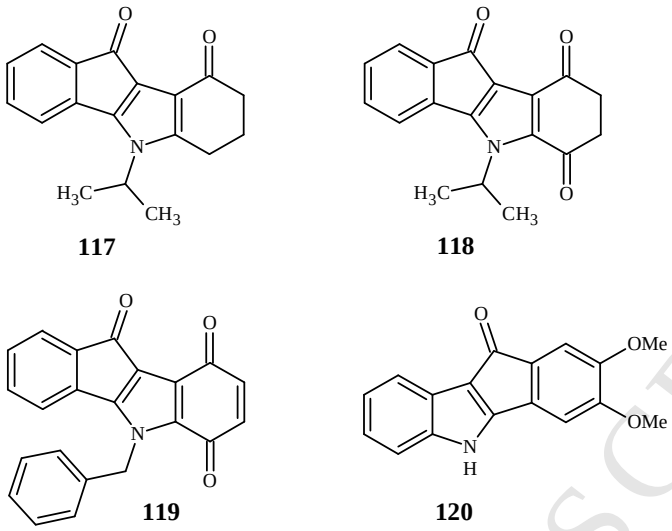


Fig. 16. Potent inhibitors of human protein kinase CK2 and tumor cell growth.

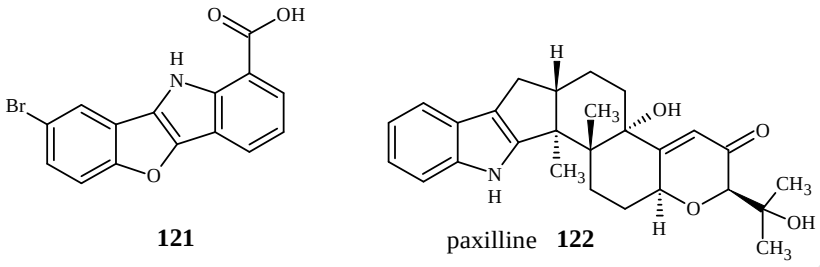


Fig. 17. Structures of 8-bromo-10*H*-benzo[4,5]furo[3,2-*b*]indole-1-carboxylic acid and paxilline.

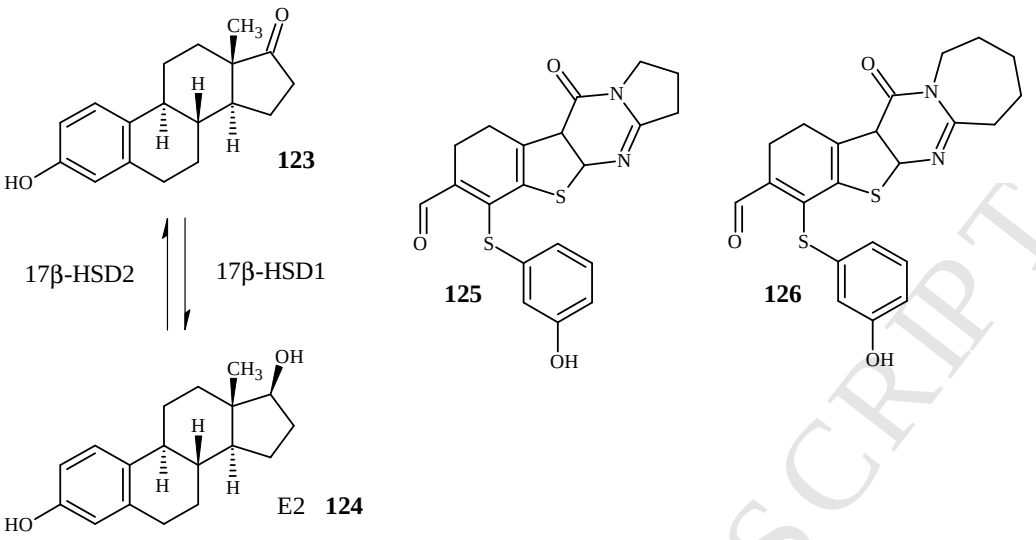
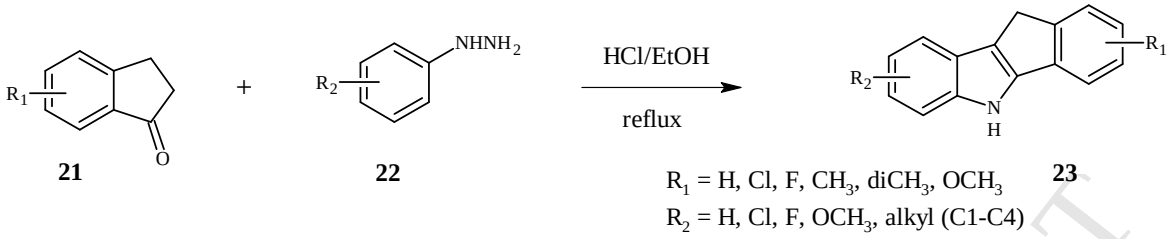
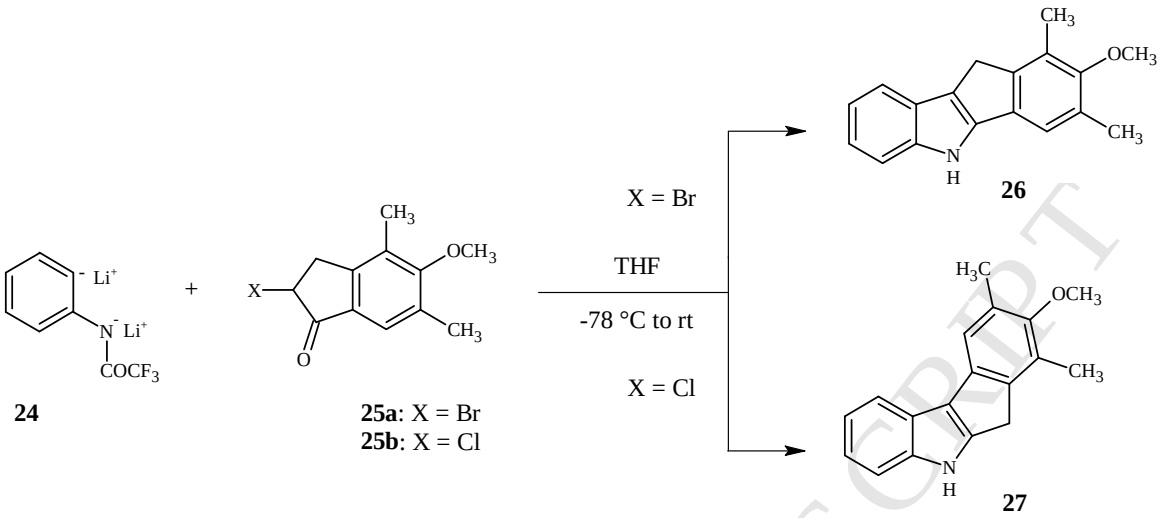


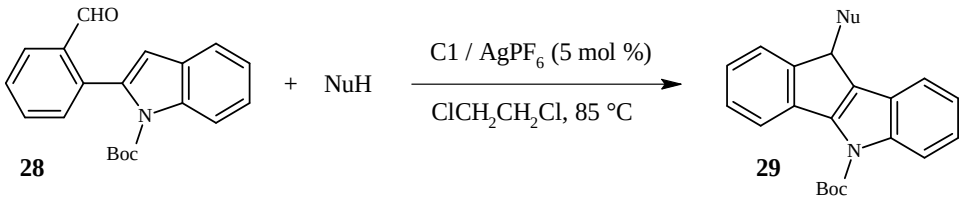
Fig. 18. The interconversion of estradiol/estrone and the structures of two thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives.



Scheme 1. The Fischer indole synthesis applied to indanones.

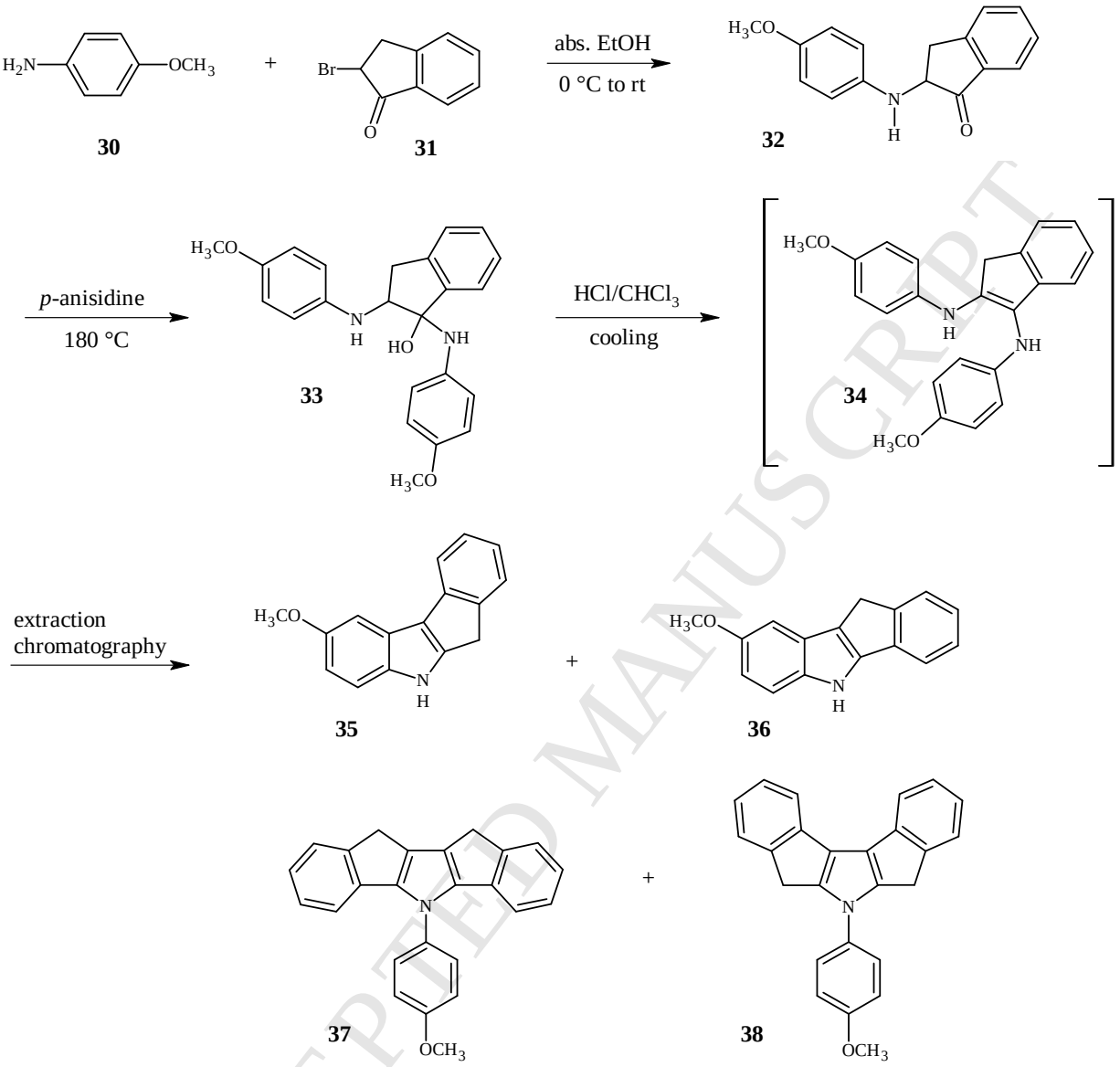


Scheme 2. Synthesis of 5,10-dihydroindeno[1,2-*b*]indole and 5,6-dihydroindeno[2,1-*b*]indole.

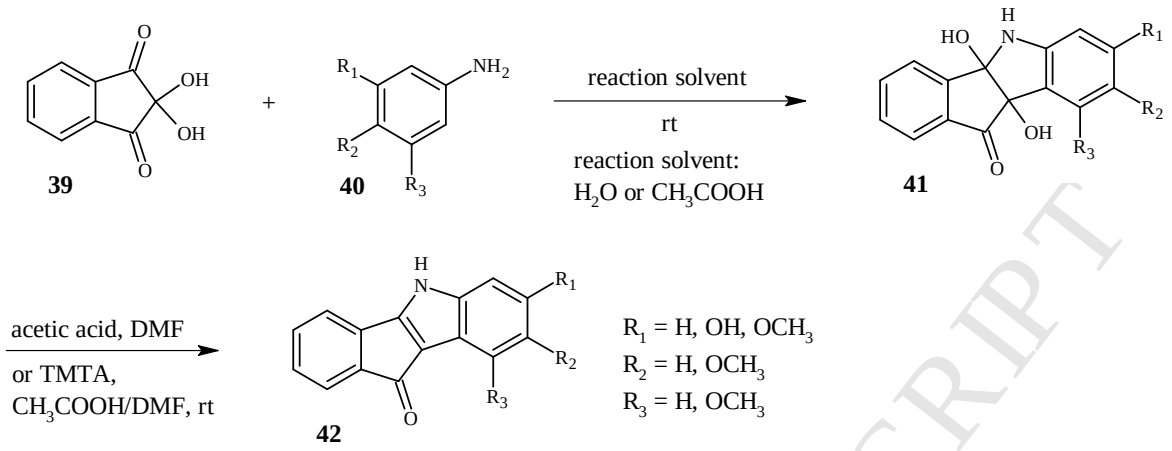


Nu = propylthio, phenylthio, 5-bromoindol-3-yl,
2,4,6-trimethoxyphenyl, 4-methylphenylamino

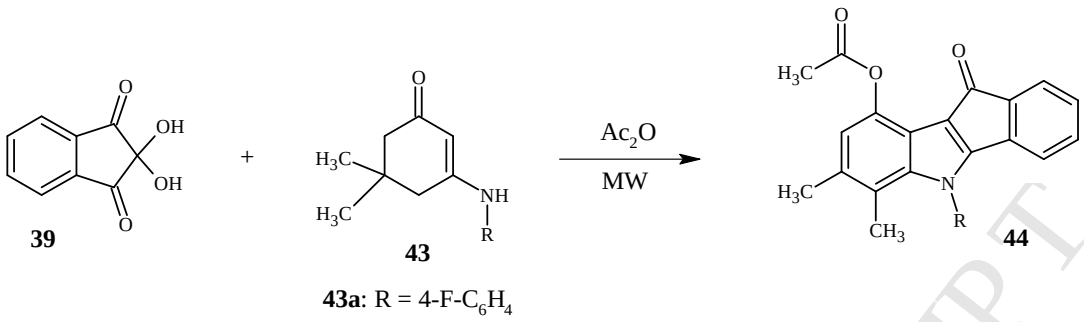
Scheme 3. Synthesis of 10-substituted indeno[1,2-*b*]indoles.



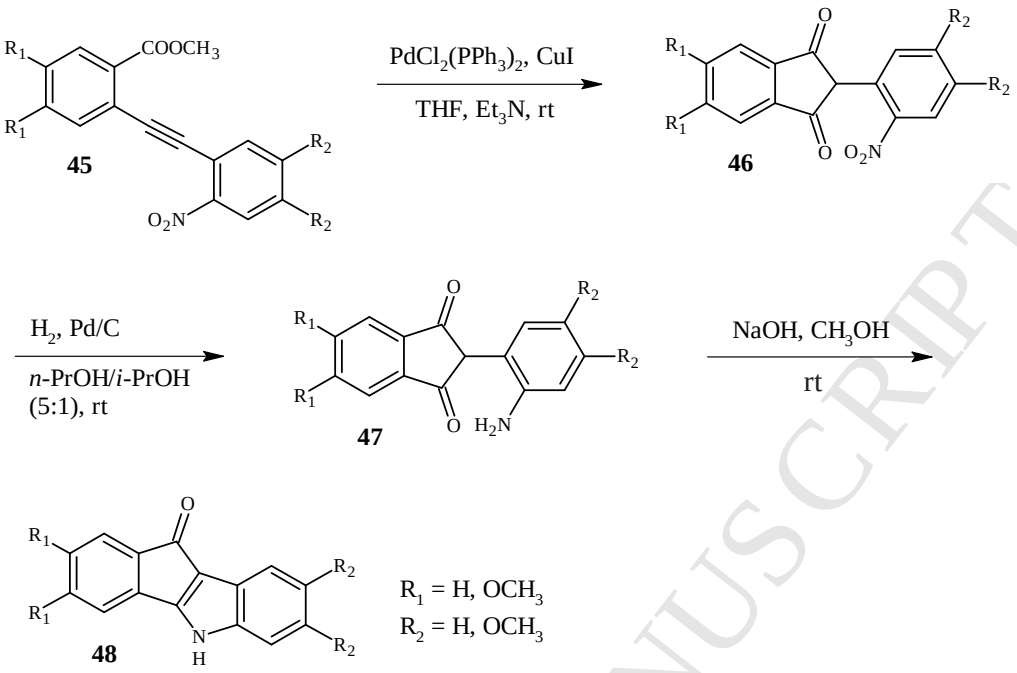
Scheme 4. Cyclization of α-amino ketone leading to 5,6-dihydroindeno[2,1-*b*]indole scaffold.



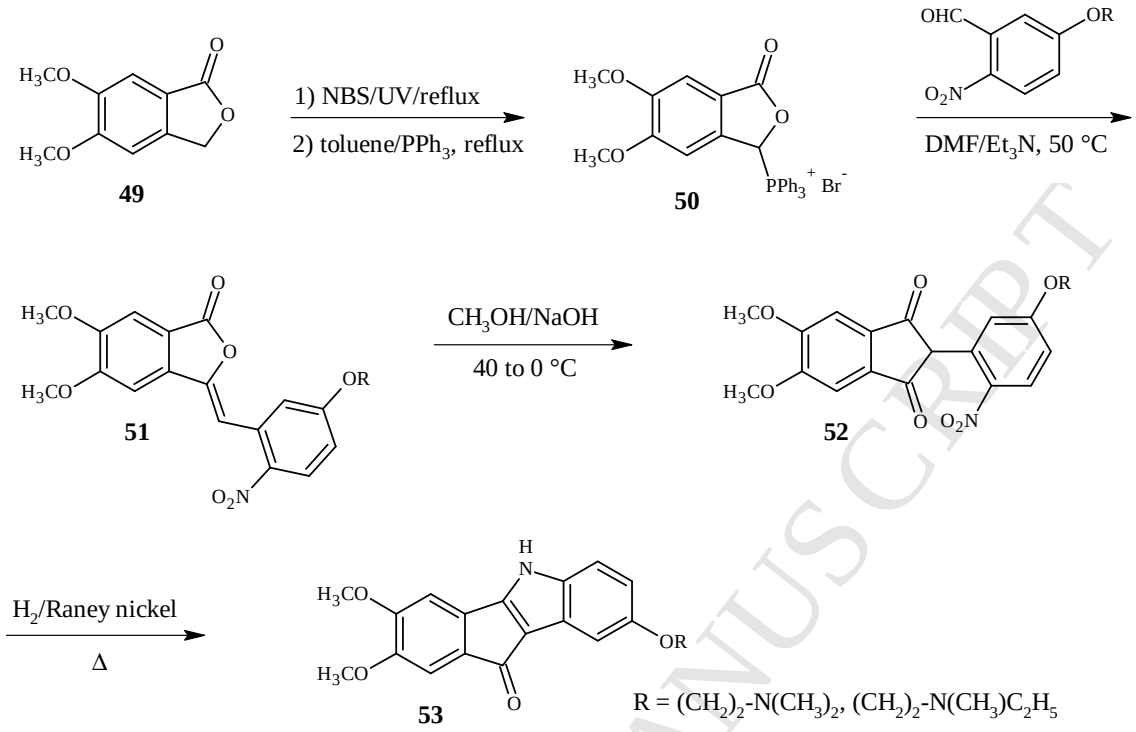
Scheme 5. Preparation of 5*H*-indeno[1,2-*b*]indol-10-ones.



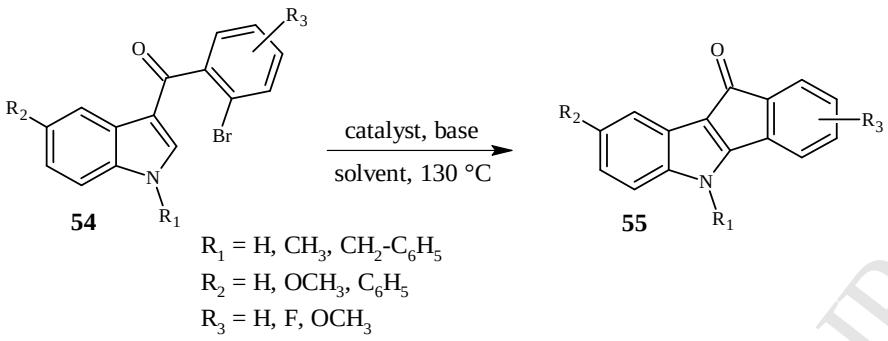
Scheme 6. Three-component reaction for the synthesis of multifunctionalized indeno[1,2-*b*]indoles.



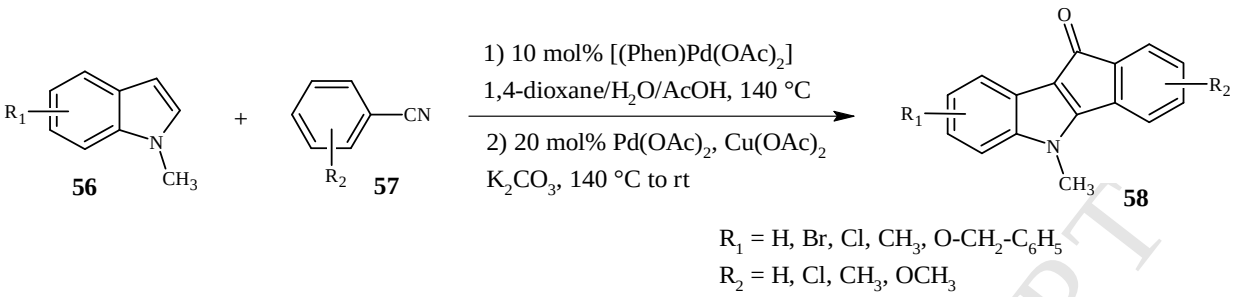
Scheme 7. Preparation of indeno[1,2-*b*]indol-10-ones.



Scheme 8. Preparation of indeno[1,2-*b*]indol-10-ones.

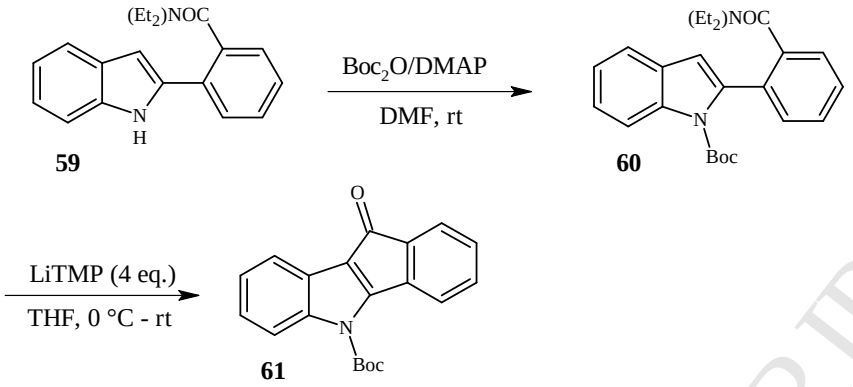


Scheme 9. Preparation of indeno[1,2-*b*]indol-10-ones.

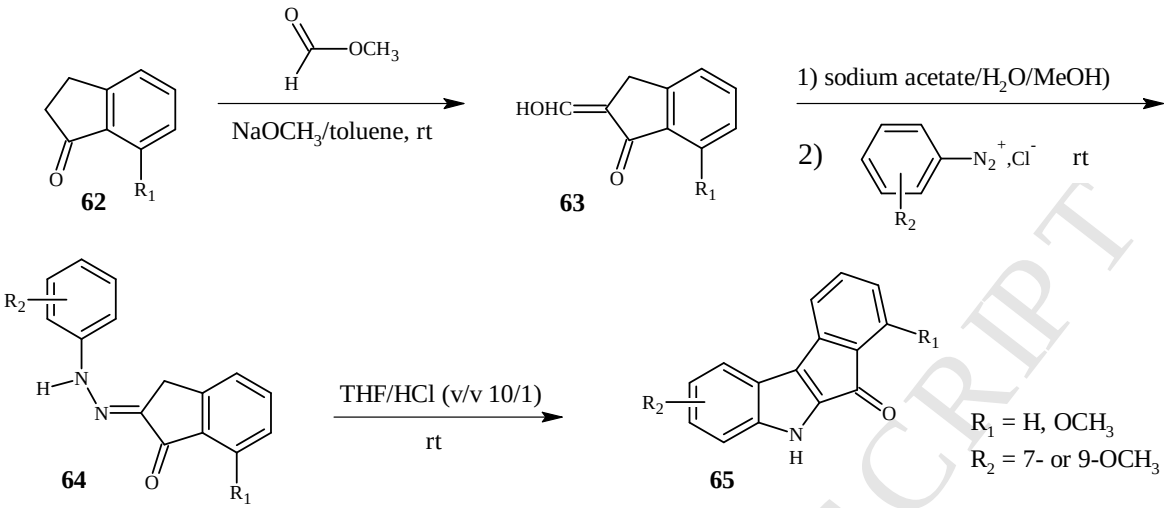


R_1 = H, Br, Cl, CH_3, O-CH_2-C_6H_5
R_2 = H, Cl, CH_3, OCH_3

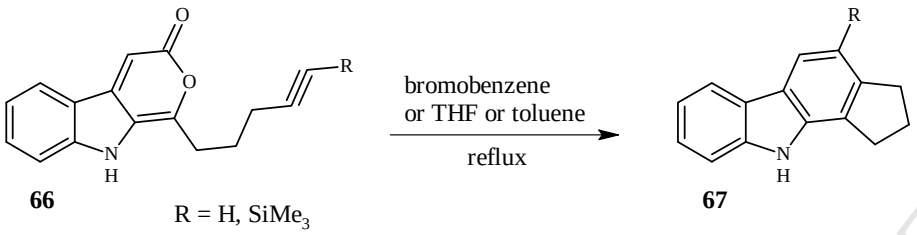
Scheme 10. One-pot synthesis of indenoindolones.



Scheme 11. Preparation of 5-Boc-indeno[1,2-*b*]indol-10-one.

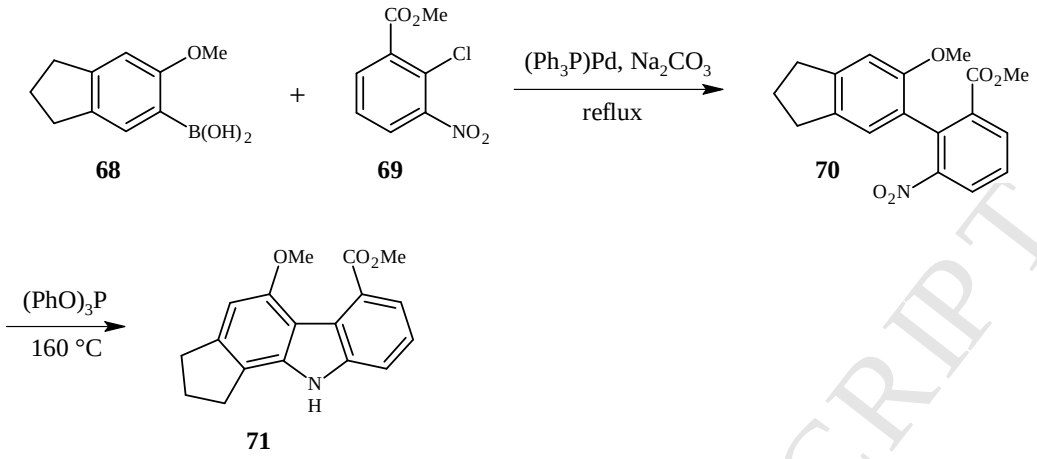


Scheme 12. Preparation of indeno[2,1-*b*]indol-6-ones.

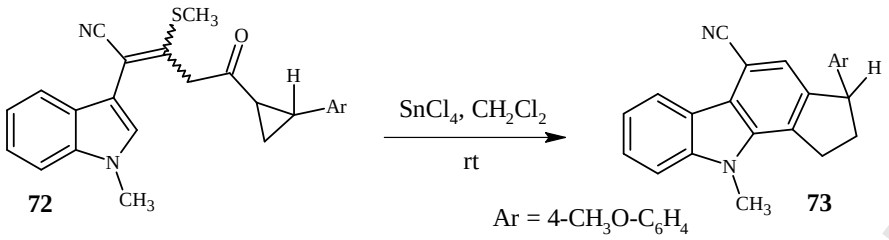


66 R = H, $SiMe_3$ **67**

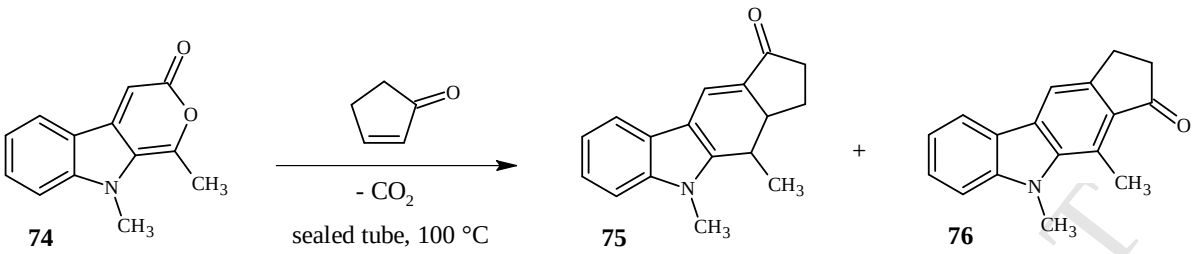
Scheme 13. Preparation of cyclopenta[*a*]carbazoles.



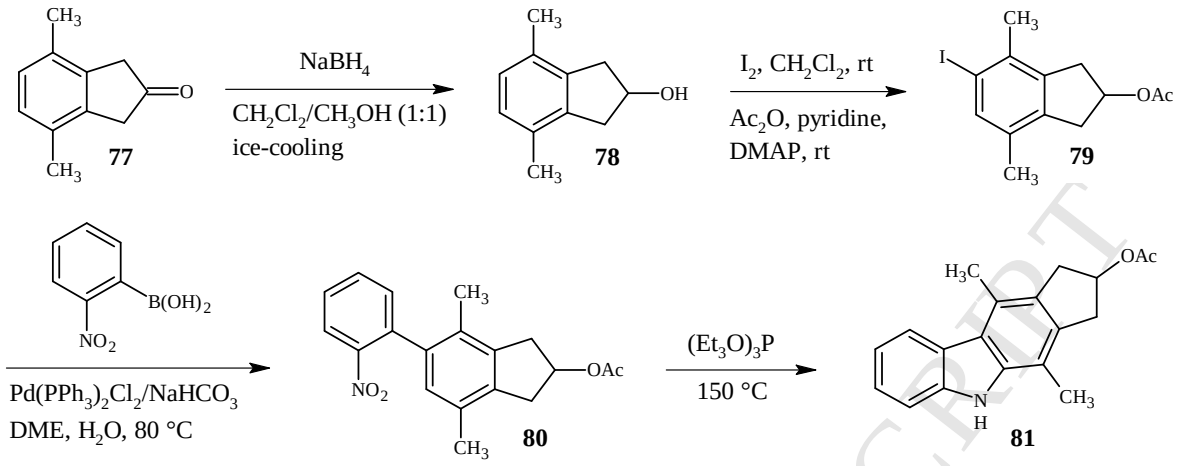
Scheme 14. Preparation of a cyclopenta[*a*]carbazole derivative.



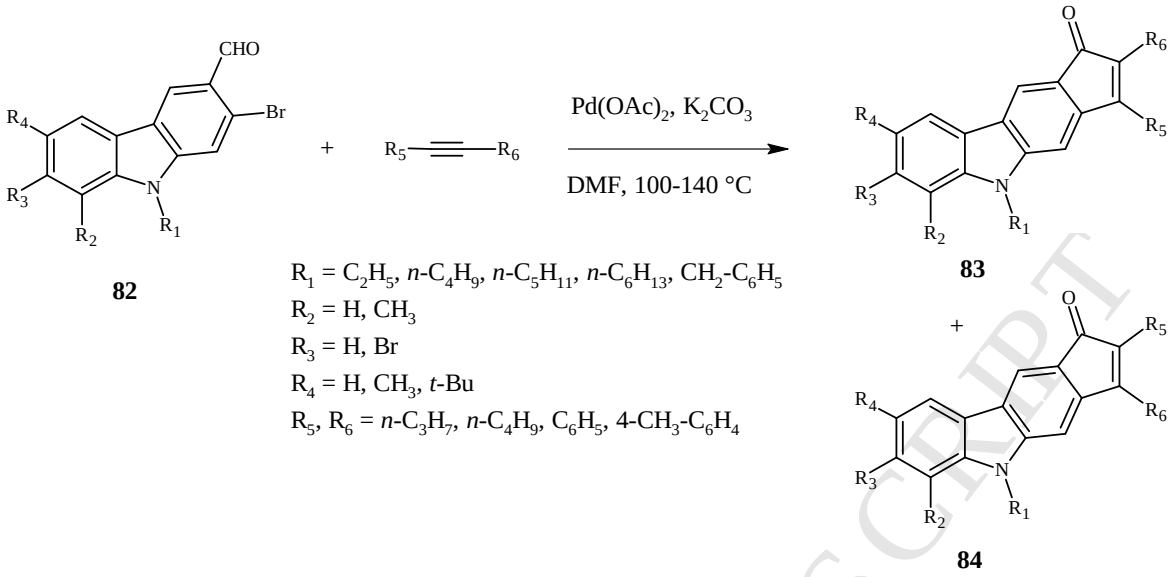
Scheme 15. Preparation of a cyclopenta[*a*]carbazole derivative.



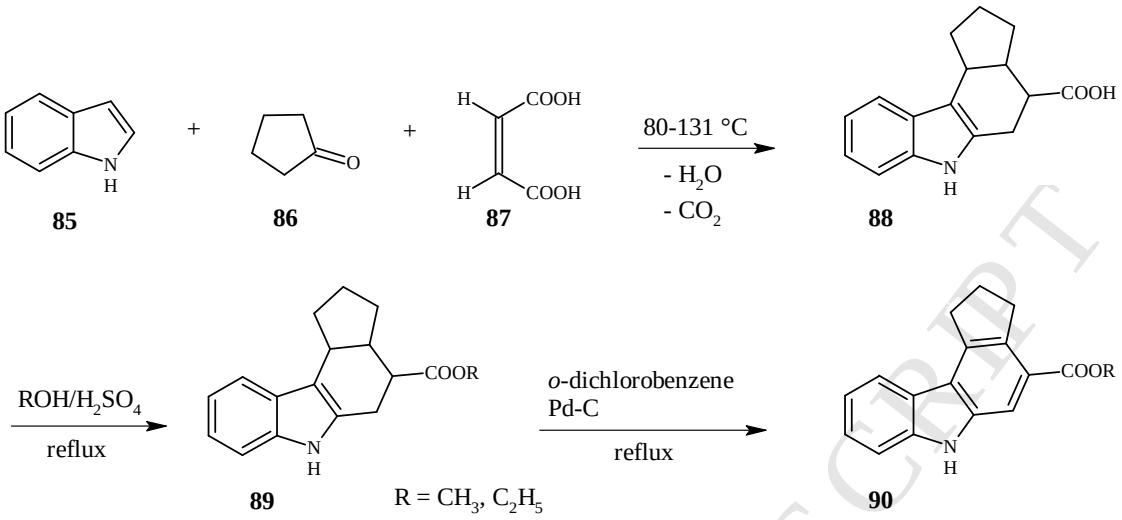
Scheme 16. Synthesis of cyclopenta[*b*]carbazolones.



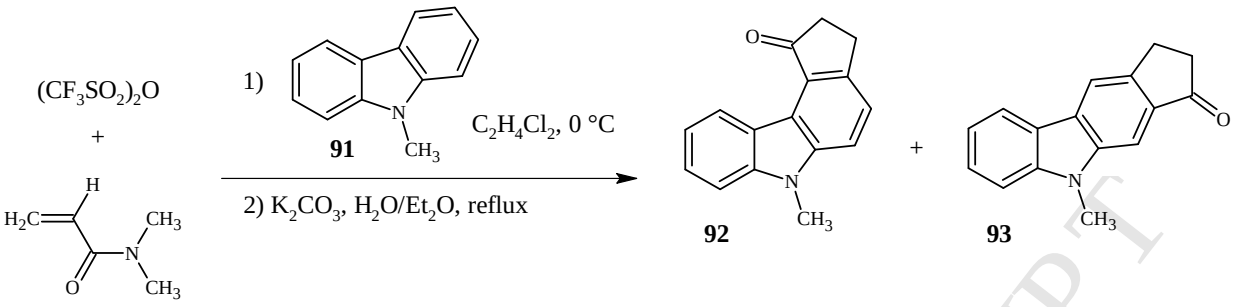
Scheme 17. Synthesis of a key cyclopenta[*b*]carbazole intermediate to access to ellipticine.



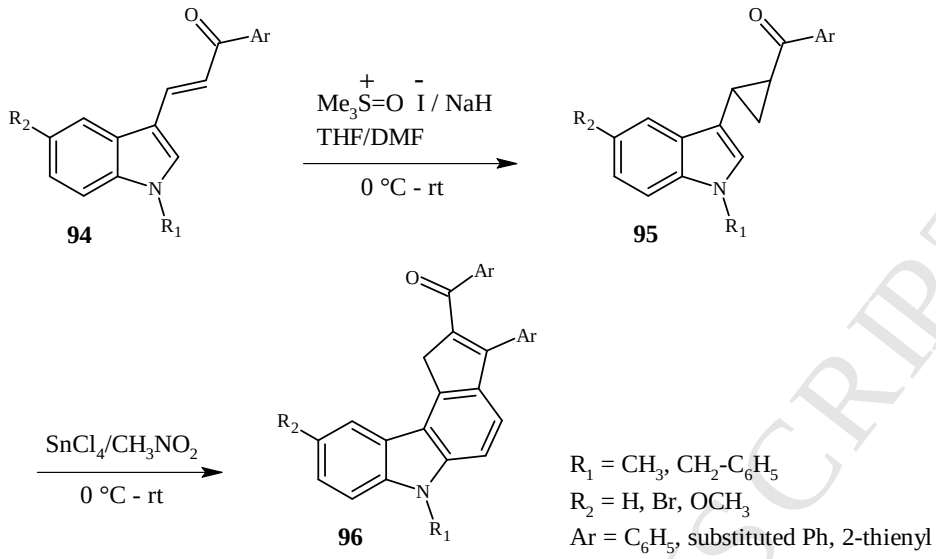
Scheme 18. Preparation of polysubstituted cyclopenta[*b*]carbazolones.



Scheme 19. Indole as starting material for the preparation of cyclopenta[*c*]carbazoles.



Scheme 20. One method for two isomeric cyclopentacarbazolones.



Scheme 21. A serendipitous route to cyclopenta[*c*]carbazole framework.

Highlights

Indenoindoles and cyclopentacarbazoles as bioactive compounds: synthesis and biological applications – A review

Pal Rongved, Gilbert Kirsch, Zouhair Bouaziz, Joachim Jose, Marc Le Borgne

- We report chemical syntheses to access to indeno[1,2-*b*]indoles and isomers [1,2-*n*].
- We report chemical syntheses to access to indeno[2,1-*b*]indoles and isomers [2,1-*n*].
- We report chemical syntheses to access to cyclopenta[*n*]carbazoles.
- Molecular diversity of biologically active indenoindole- and cyclopentacarbazole-derived compounds.