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REVIEW ARTICLE

A Comprehensive Review on Pyranoindole-containing Agents

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Abstract: A huge number of nitrogen-containing heterocyclic compounds are ubiquitous in natural products, pharmaceuticals, and bioactive molecules. Among these, the pyranoindole represents an important structural motif, as it constitutes the central subunit in both the biologically active natural products and therapeutic agents. Talathermophilins, notoamides, norgeamides, carneamides, and versicamides are examples of naturally occurring pyranoindoles, while the well-known etodolac and pemedolac are a tetrahydropyrano[3,4-*b*]indole deriving from synthetic procedures. Besides the well-known anti-inflammatory and fibrinolytic activity, molecules comprising the pyranoindole framework have been demonstrated to exhibit various biological activities, such as antiulcer, antidepressant, analgesic, and antiproliferative. Herein, we report the most common natural and synthetic products bearing a pyranoindole nucleus, their syntheses, and biological activities.

Keywords: Pyranoindole, etodolac, pemedolac, prenylated pyranoindole alkaloids, natural pyranoindoles, synthetic pyranoindoles.

1. INTRODUCTION

Heterocyclic compounds are present in various natural sources, such as plants, marine microbes, or other organisms, and many of them possess unique biological activity [1]. In addition to the nature-derived heterocyclic compounds, a large number of synthetic heterocycles are being used as key motifs in pharmaceutically active ingredients [2], organic synthesis [3, 4], and material sciences [5]. Over the last two centuries, new approaches to the synthesis of heterocycles had an enormous impact on both inorganic and organic chemistry. Organic and pharmaceutical chemists have been making extensive efforts to construct heterocyclic frameworks through developing versatile and efficient synthetic strategies. Approaches to the synthesis of heterocyclic compounds have been evolving constantly from classical condensation procedures to click reactions and new multicomponent procedures. However, recently, there has been an effort to use efficient catalytic methodologies aiming at high process performances by means of non-toxic/green and biodegradable chemicals [6]. Some of the recent advances in heterocycle preparation, employing more sustainable synthetic procedures, have been described [7]. In this context, molecules containing biologically interesting heterocycles fused scaffolds are of great value for both organic and medicinal chemists. The combination of two highly biologically active backbones may increase the activity of weak drugs and further improve drug activity. The indole ring (Fig. **1**) is considered a privileged structure in many biologically active natural products and pharmaceutical agents [8-10]. Consequently, great efforts have been devoted to the synthesis of numerous fused indoles with various heterocycles systems. Derivatives containing pyrano groups play an important role in the synthesis of biologically active compounds and in drug discovery (Fig. **1**) [11].

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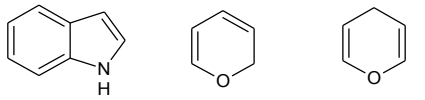


Fig. (1). Structure of indole and pyrans.

The presence of these two elements, linked together in one molecule, seems to be particularly interesting for medicinal chemists [12, 13]. It is noteworthy that the nucleus generally called pyranoindole is indeed a dihydropyranoindole one. An example is depicted in Fig. (**2**).

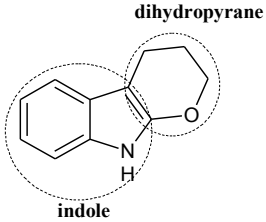


Fig. (2). Structure of a dihydropyranoindole.

In this review, we will call them "pyranoindoles" following what is generally reported in the literature. Several pyranoindoles exist (classes **1-8**, Fig. **3**), based on the position in which the pyrano and the indole groups may link each other.

Molecules comprising the pyranoindole framework are known to exhibit various biological activities, such as anti-inflammatory, antiulcer, antidepressant, and analgesic. Among the best-known compounds, the anti-inflammatory agent etodolac is a synthetic *pyranoindole* acetic acid derivative [14, 15], while several pyranoindole alkaloids, talathermophilins, norgeamides, carneamides, versicamides, and notoamides are natural compounds. Several studies on pyranoindole synthetic derivatives have been reported about the potential use of these drugs as antimycobacterial [16], antiulcer, antidepressant, antiviral, antiproliferative, analgesic, antioxidant, antinflammation, antinociceptive, and as a potential treatment for glaucoma, as detailed below. Our aim was to review natural and synthetic pyranoindoles along with their activities. Moreover, several common synthetic procedures to obtain pyranoindoles are mentioned.

2. PYRANOINDOLE ACTIVITIES AND DESCRIPTION

2.1. Natural Products

The secondary metabolites of *Talaromyces* include alkaloids, which are mainly nitrogen heterocyclic derivatives. Two yellow prenylated pyranoindole alkaloids, talathermophilins A and B (**5a** and **5b**, Fig. **4**), were isolated from a thermophilic fungus *T. thermophilus* strain YM1-3 [17, 18]. It has also been reported to be produced by *Dactylellina entomopaga* CBS 642.80 (syn. *Arthrobotrys entomopaga*) [19].

Talathermophilin C (**5c**, Fig. **5**) is a chiral pyranoindole alkaloid, which was isolated from the thermophilic fungus *T. thermophilus* strain YM3-4 [20, 21].

Several pyranoindole derivatives, norgeamides A, B, C, D (Fig. **6**), versicamides A, B, C, D, E, F (Fig. **7**), notoamides A, B, C, D, E, E2, E3, F, G, H, I, K, M, N, Q, R, P (Fig. **8**), and carneamides A, B, C (Fig. **9**), have been recently reviewed as fungal compounds, some of which endowed with activity on cancer cells [22].

Two prenylated pyranoindole alkaloids, dihydrocarneamide A and iso-notoamide B (Fig. **10**), were isolated from the marine-derived endophytic fungus *Paecilomyces variotii* EN-291 [23]. The structures of these metabolites were determined based on a comprehensive spectral analysis, together with the chiral HPLC analysis of the acidic hydrolysates. These compounds showed cytotoxic activities against the human lung carcinoma cell line NCI-H460.

Fontanesines A–C (**6a-c**, Fig. **11**) bear a pyrano[3,2-*e*]indole moiety fused with quinazolinone. They were isolated from the stem bark and leaf fractions of *Conchocarpus fontanesianus*, collected in Brazil by Queiroz and co-workers [24]. The antiproliferative effect of fontanesine B was evaluated on human colorectal cancer cells, DLD-1, by water-soluble tetrazolium salt (WST-1) assay and no inhibitory effects were recorded [25]. The total synthesis of fontanesine B has been recently reported [26].

Koniamborine is a pyrano[3,2-*b*]indole that was isolated from aerial parts of *Boronella koniambiensis,* a rutaceous tree endemic to New Caledonia (**7a**, Fig. **12**) [27]. The authors reported the koniamborine (**7a**) structure, for the first time, by means of NMR and mass studies, indicating that this novel type of alkaloid derives from the pyrano[3,2-*b*]indole basic skeleton. Koniamborine (**7a**), as well as its major metabolites, medicosmine, (+)-dehydroxycubebin, and *O*-geranylosthenol, possess anticancer activity against the L1210 cancer cell lines showing IC_{50} values of 38.2, 48.0, 72.1, and 15.7 μM, respectively.

2.2. Synthetic Pyranoindoles

The best known synthetic pyranoindoles with anti-inflammatory and analgesic activity bearing a tetrahydropyrano[3,4-*b*]indole skeleton are etodolac (1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]-indole-1-acetic

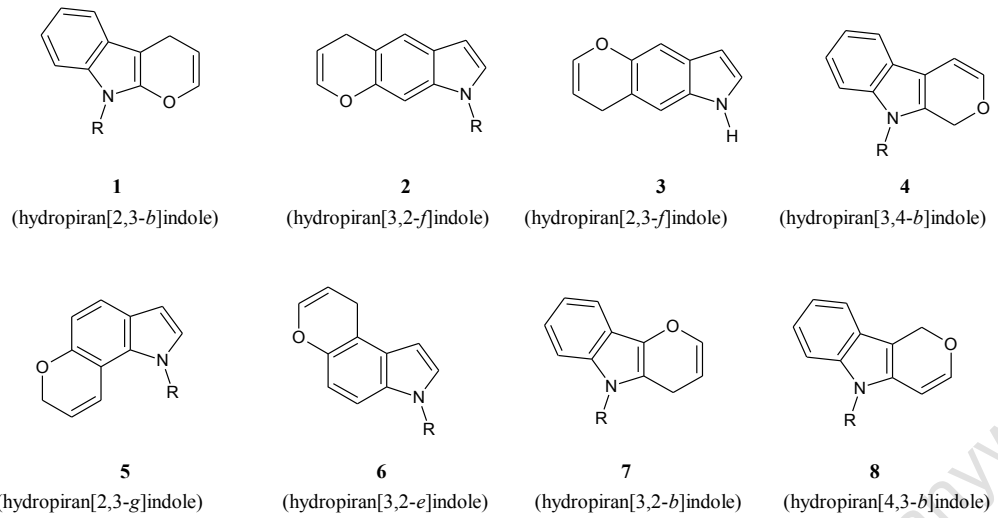


Fig. (3). Structures of common pyranoindoles.

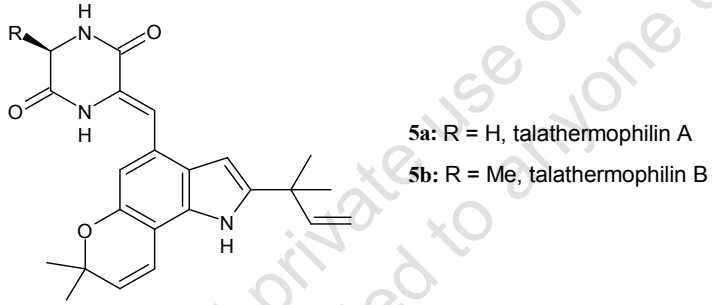


Fig. (4). Structures of talathermophilins A and B (**5a,b**).

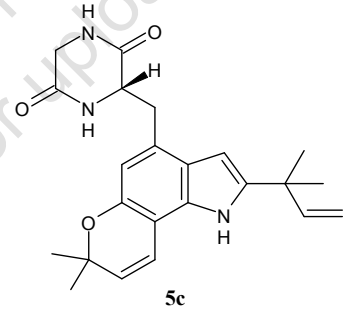


Fig. (5). Structure of talathermophilin C (**5c**).

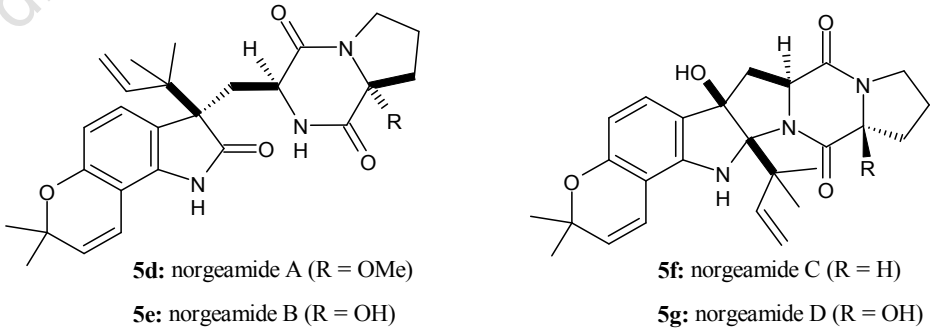


Fig. (6). Structure of norgeamides A-D (**5d-g**).

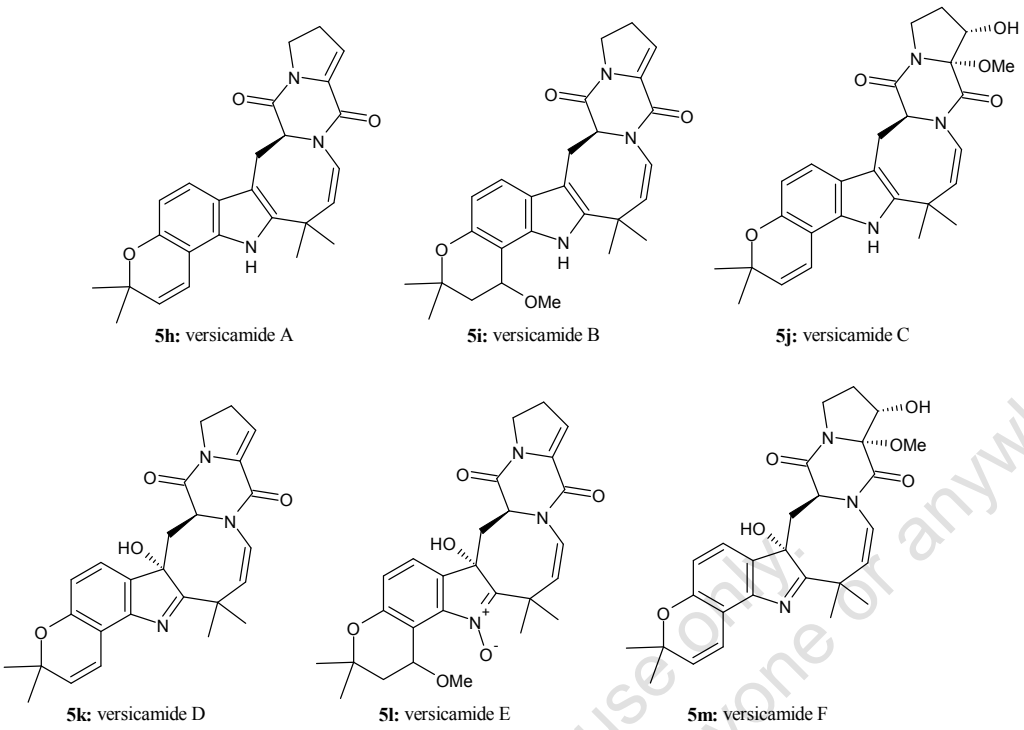


Fig. (7). Structure of versicamides A-F (**5h-m**).

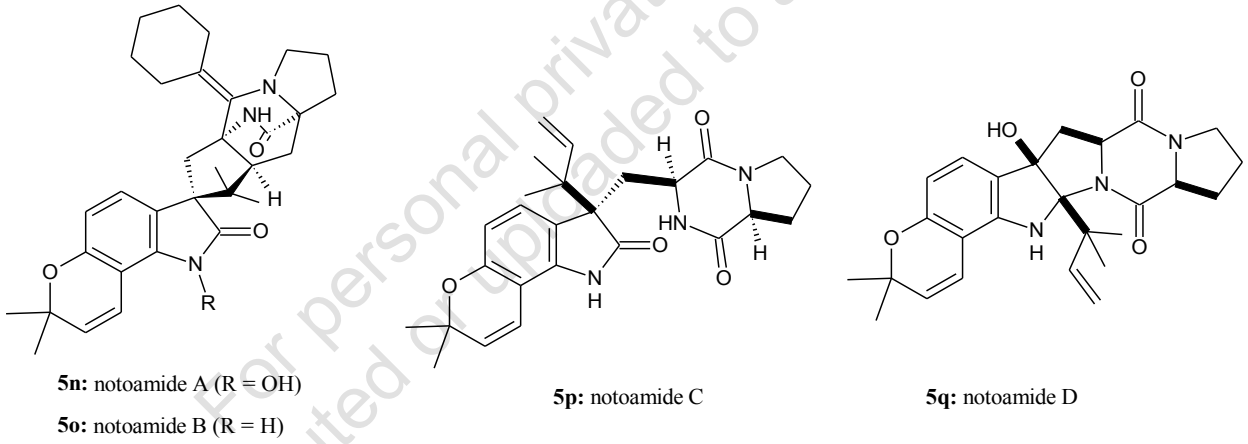


Fig. (8). Structure of notoamides A-D (**5n-q**).

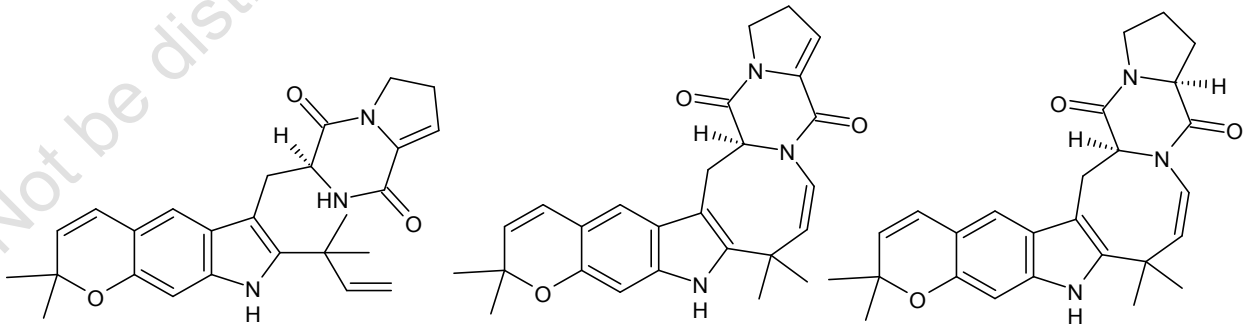
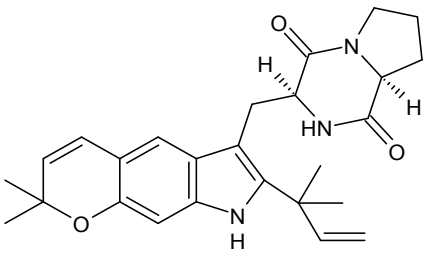
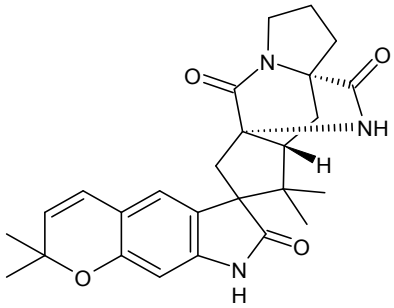


Fig. (9). Structure of carneamides A-C (**2a-c**).

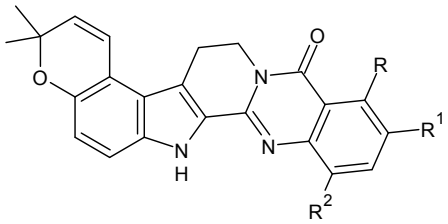


2d: dihydrocarneamide A



2e: iso-notoamide B

Fig. (10). Structure of dihydrocarneamide A (**2d**) and isonotoamide B (**2e**).



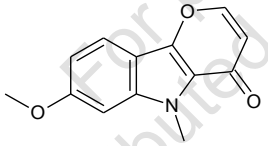
6a: fontanesine A (R = R^2 = H; R^1 = OH)

6b: fontanesine B (R = R^1 = R^2 = H)

6c: fontanesine C (R = R^1 = H; R^2 = OH)

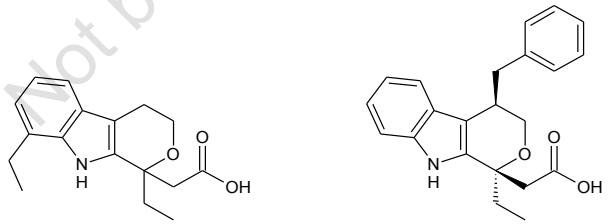
Fig. (11). Structure of Fontanesines A-C (**6a-c**).

acid) and pemedolac (*cis*-1-ethyl-1,3,4,9-tetrahydro-4-(phenyl-methyl)-pyrano[3,4-*b*]indole-1-acetic acid) (Fig. **13**) [28]. For simplicity, we will use the name of series **4** described above. Etodolac has been demonstrated to exert antitumor activity on many types of cancer, such as urogenital system cancers [29], Burkitt's lymphoma [30], multiple myeloma, chronic lymphocytic leukemia, and prostate cancer, too [31]. Nevertheless, a possible association between active use of etodolac and acute pancreatitis has been reported [32].



7a
(koniamborine)

Fig. (12). Structure of koniamborine.

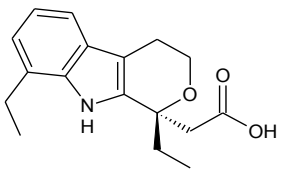


4a
(etodolac)

4b
(pemedolac)

Fig. (13). Structure of etodolac (**4a**) and pemedolac (**4b**).

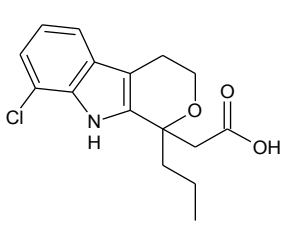
The *R*-isomer of etodolac (*R*-etodolac, **SDX-101**, Fig. **14**) is a pro-apoptotic agent with potential anti-tumor activity against B-cell chronic lymphocytic leukemia (B-CLL) [33]. It was shown to induce apoptosis in different cancer cells through the down-regulation of antiapoptotic proteins Bcl-2 and Mcl-1, activation of caspases, activation of PPARγ, suppression of cell adhesion molecules, β-catenin, and Wnt signaling. Both *R*-etodolac and its enantiomer individually showed an apoptotic activity against B-CLL cells comparable to that of the (*R,S*)-etodolac mixture.



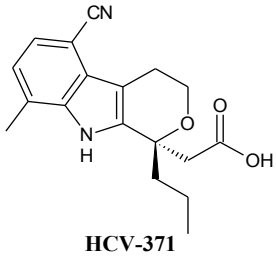
SDX-101

Fig. (14). Structure of SDX-101.

Pyranoindole was also described to be useful for the treatment of hepatitis C, the common and often progressive viral liver disease caused by infection of hepatitis C virus (HCV). The chiral pyranoindole **4c** (Fig. **15**) showed an HCV NS5B polymerase activity with an IC_{50} value of 3.0 μM [34]. It was found to be selective against human polymerase β (IC_{50} > 100 μM), calf thymus polymerase α (IC_{50} > 100 μM), helicase (IC_{50} > 75 μM), as well as human immunodeficiency virus (HIV) reverse transcriptase (IC_{50} > 100 μM). It was not cytotoxic in rapidly dividing and stationary Vero and

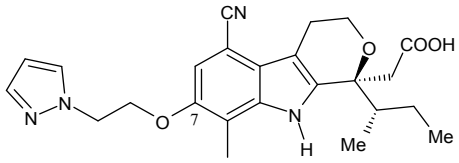


4c

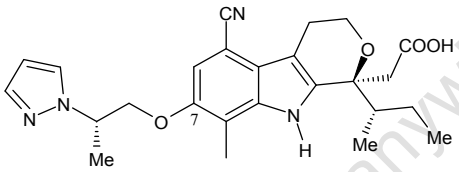


HCV-371

Fig. (15). Structure of **4c** and HCV-371**.**



4d



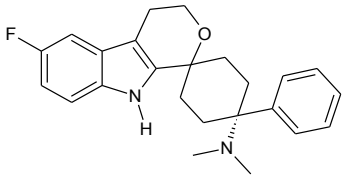
4e

Fig. (16). Structure of **4d** [37] and **4e** [42].

Huh7 cells, as measured by a standard MTS metabolic assay. The same group described the synthesis and biological evaluation of a series of tetrahydropyrano[3,4-*b*]indole-based allosteric inhibitors of HCV NS5B [35]. The most interesting of the series was (1*R*)-5-cyano-8-methyl-1-propyl-1,3,4,9-tetrahydropyano[3,4-*b*]indol-1-yl acetic acid (HCV-371), which is a very potent inhibitor of the NS5B enzyme and HCV replication. Moreover, it did not show cytotoxicity and had a large therapeutic window. Within the effective antiviral concentrations, there were no detectable toxicities in cellular metabolism and cell proliferation. In addition, long-term treatment of cells with HCV-371 did not result in adverse effects. Acceptable safety and tolerability of HCV-371 were observed in Phase I clinical trials, but unfortunately, it did not demonstrate significant antiviral activity in a Phase Ib efficacy study. Retrospective evaluation of this compound using the SCID/Alb-uPA mouse model also failed to afford a significant antiviral effect [36].

LaPorte *et al.* described the synthesis and *in vivo* evaluation of the analogue **4d** (Fig. **16**), an inhibitor of HCV NS5B polymerase belonging to a new class of pyranoindoles substituted at the C7 position of the heteroaromatic nucleus. It showed *in vivo* activity in a chimeric mouse model of HCV infection [37, 38]. It exhibited low nanomolar potency in both enzymatic and cell-based assays (IC_{50} = 0.003 μM, EC_{50} = 0.023 μM for NS5B polymerase genotype 1b, EC_{50} = 0.0045μM for NS5B polymerase genotype 1a). In an HCV-infected chimeric mouse experiment, it gave a considerable reduction in plasma HCV RNA levels during the first 3 days of dosing, but the viral load rebounded over the next 4−7 days, eventually leading to only an average −1.2 $\log_{10}$ IU/mL reduction in HCV RNA levels when compared to untreated mice on day 8. The second clinical candidate of the series, HCV-086 (structure not given, ViroPharma/Wyeth) [39], produced only a −0.32 $\log_{10}$ IU/mL decline in plasma HCV RNA levels in a 14-day phase 1 study; consequently, its development was discontinued [40, 41]. Structure–activity relationship of the C7-position of these compounds in the allosteric binding site was further explored, leading to compound **4e**, which showed activity similar to that of **4d** [42].

Cebranopadol (**4f**, Fig. **17**) is a spiro[cyclohexane-dihydropyrano[3,4-*b*]indole], which functions as an opioid analgesic of the benzenoid class [43].



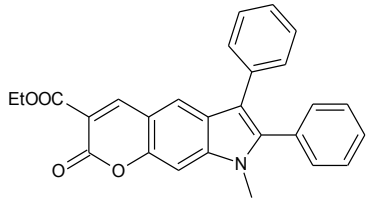
4f

Fig. (17). Structure of **4f** (Cebranopadol).

An anti-inflammatory activity was also reported for several synthetic pyranoindoles belonging to hydroxy-pyrano[3,2-*f*]indoles (series **2**) [44]. Compound **2f** (Fig. **18**) exerted a potent antiinflammatory effect compared to indomethacin in the inhibition of carageenin-induced paw oedema test [45].

Antiulcer activity was reported for several pyranoindole derivatives belonging to hydropyrano[4,3-

b]indoles (series **8**, Fig. **19**) [46]. Some compounds exhibit useful properties for the treatment and prevention of ulcers. Moreover, some of them seemed to exhibit significant antidepressant properties at dosages that do not elicit undesirable side effects. The antidepressant properties of compounds were demonstrated by their capacity to antagonize the depressant effects of reserpine.



2f

Fig. (18). Structure of compound **2f**.

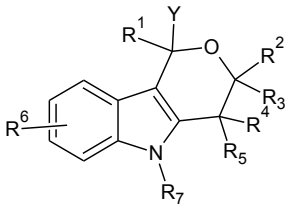


Fig. (19). Structure of pyranoindoles belonging to series **8** reported in ref [46].

Abe *et al.* (2019) [25] reported the antiproliferative activity studies of natural fontanesine B (**6b**, Fig. **11**) and its synthetic cyclic isomer **3a** (Fig. **20**). The latter strongly inhibited the growth of human colorectal cancer cells, DLD-1 at 100 μM (74.9 ± 1.7%, *vs.* control) in a dose dependent manner, as assessed by WST-1 assay.

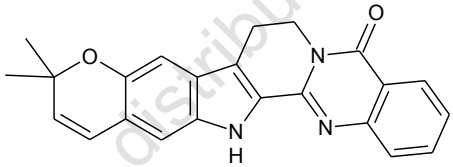
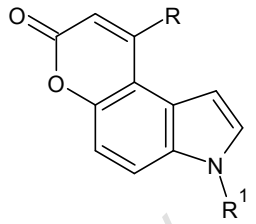


Fig. (20). Structure of **3a**.

Sinicropi *et al.* [47] studied two synthetic pyrano[3,2-*e*]indoles (**6a,b**, Fig. **21**) and evaluated their inhibition of NO production, antioxidant activity, and also their ability to inhibit *in vitro* the growth of four human tumor cell lines: large lung carcinoma (COR-L23), alveolar basal epithelial carcinoma (A549), amelanotic melanoma (C32) and melanoma (A375). These two compounds exhibited weak cytotoxicity with IC_{50} values > 50 μM on all cell lines. Compound **6a** showed activity similar to the reference drug indomethacin for inhibition of nitric oxide (NO) production in lipopolysaccharides (LPS)-induced murine monocytic macrophage cell line RAW 264.7. Recently, homologues of **6a,b** have been studied (**6c-e**, Fig. **21**) [48]. Among these, compound **6d** showed antioxidant properties with a DPPH inhibition percentage of 50% at the highest concentration.



6a: R = H; R^1 = H

6b: R = H; R^1 = Me

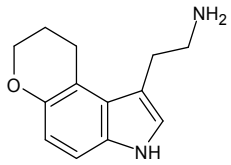
6c: R = H; R^1 = Et

6d: R = H; R^1 = *n*-Pr

6e: R = Me; R^1 = Et

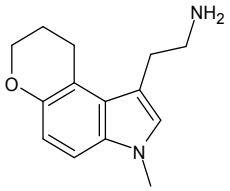
Fig. (21). Structure of compounds **6a-e**.

Some years ago, several pyrano[3,2-*e*]indol-3-ethylamines and the corresponding *N*,*N*-dimethylamino analogs were reported in conjunction with serotonin receptor binding profile studies. Two compounds (**6f,g**, Fig. **22**) were shown to possess a good affinity for the serotonin 5-HT receptors, though no utility has been associated with these compounds [49].



6f

(CP-123,484)



6g

Fig. (22). Structure of compounds **6f,g**.

Other compounds belonging to pyrano[3,2-*e*]indole (series **6)**, pyrano[3,2-*e*]indol-3-ethylamine, and pyrano[2,3-*g*]indol-1-ethylamine (Fig. **23**) were described as useful to lower and control elevated intraocular pressure (IOP) associated with normal-tension glaucoma, ocular hypertension, and glaucoma in warm blooded animals, including man. The compounds were formulated in pharmaceutical compositions suitable for topical delivery to the eye [50].

Recently, a series of chiral 4*H*-pyrano-[3,2-*b*]indole derivatives (Fig. **24**) with promising antibacterial activity against *S. aureus* and *S. epidermidis in vitro* have been described [51].

Pyrano[4,3-*b*]indol-1(5*H*)-ones were reported as tumor cell growth inhibitors against human cervix adenocarcinoma (HeLa) [52]. In particular, compound **8a**

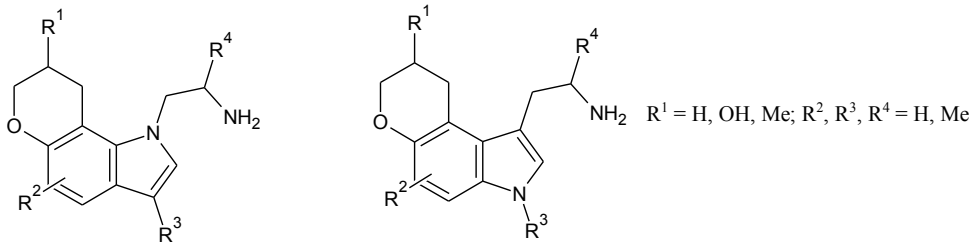


Fig. (23). Structure of compounds belonging to series **6** described by May and Chen [50].

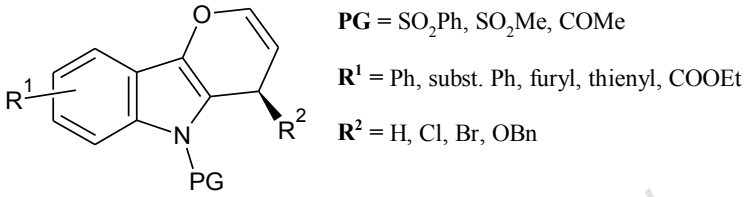


Fig. (24). Structure of compounds belonging to series **7** described by Zhou *et al.* [51].

(Fig. **25**) was the most active (IC_{50} = 0.69 μM) of the series, showing activity comparable to that of the standard *cis*-platin (IC_{50} = 0.08 μM).

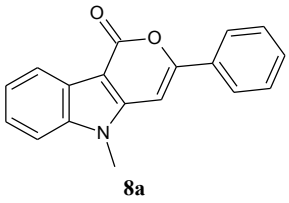


Fig. (25). Structure of compound **8a**.

Liu *et al.* assessed that, among the indol-fused heterocyclic compounds, pyrano[2,3-*b*]indoles and dihydropyrano[2,3-*b*]indoles (series **1**) were particularly interesting due to their potential application in biological and pharmacological activities [53]. However, these activities were not described.

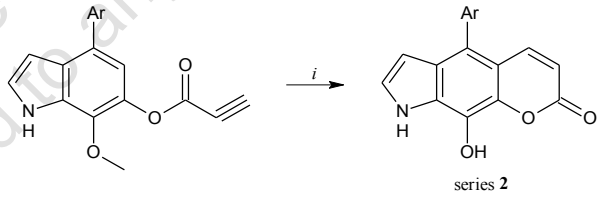
3. SYNTHESIS OF PYRANOINDOLES

3.1. Racemic Pyranoindoles

The synthesis of at least one compound for each series of pyranoindoles is described below.

The synthesis of hydroxypyrano[3,2-*f*]indoles (series **2**) was described by Wang *et al.* (Scheme **1**) [54]. Two different methods were used: in the former, esters were refluxed in dioxane-dichloroethane in the presence of $PtCl_4$; in the latter, tetrakis(triphenylphospine) palladium/trifluoroacetic acid were used as catalysts in dichloromethane.

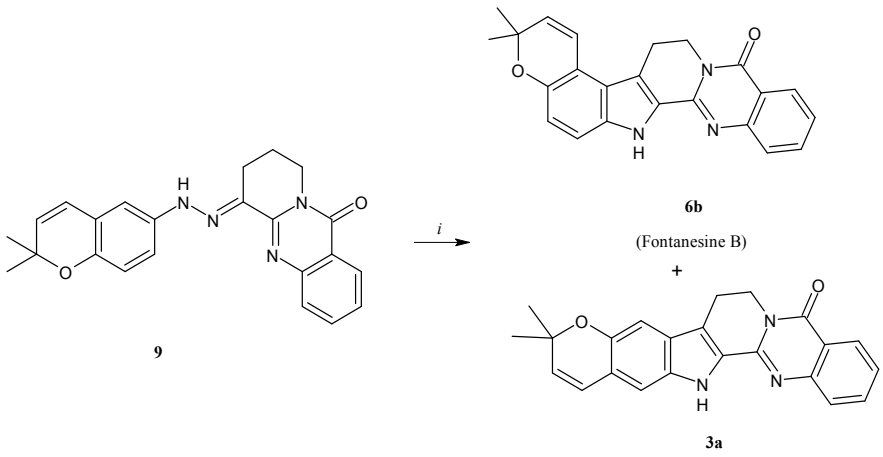
Compound **3a** (hydropyrano[2,3-*f*]indole, series **3**) was studied as an isomer of fontanesine B (pyrano[3,2-*e*]indole, series **6**). The synthesis was reported by Abe *et al.* [25] (Scheme **2**). When **9** was refluxed in AcOH, a mixture of **6b** and **3a** was obtained in 71% yield (**6b**/**3a** = 25:75).



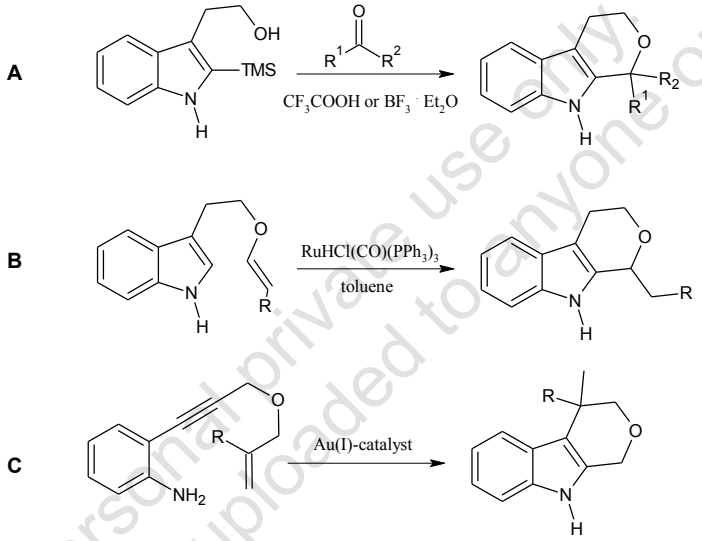
Scheme 1. Route for the synthesis of series **2** pyranoindoles. *Reagents and conditions:* (i) Method A: 5 mol% $PtCl_4$, 1,4-dioxane/1,2-dichloroethane = 1:1, N_2, 65 °C, 2 h. Method B: $Pd(PPh_3)_4$, trifluoroacetic acid, CH_2Cl_2, RT, 2 h.

For the synthesis of tetrahydropyrano[3,4-*b*]indoles (series **4**), Zhang *et al.* [55] reported a silicon-directed oxa-Pictet–Spengler cyclizations of 2-(2-trimethylsilanyl-1*H*-indol-3-yl)-ethanols with various aldehydes or ketones (**A**, Scheme **3**). Then, a ruthenium hydride/Brønsted acid-catalyzed tandem sequence towards the synthesis of pyranoindoles was described by Nielsen *et al.* (**B**, Scheme **3**) [56, 57]. Asensio *et al.* described an efficient synthesis of pyranoindoles *via* gold(I)-catalyzed intramolecular hydroaminative/arylative cascade (**C**, Scheme **3**) [58].

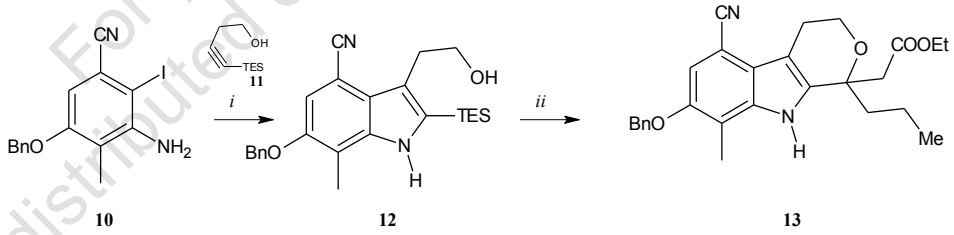
The synthesis of pyrano[3,4-*b*]indole-based allosteric inhibitors of HCV NS5B polymerase (tetrahydropyrano[3,4-*b*]indoles, series **4**) reported by Laporte *et al.* [37] is shown in Scheme **4**, where only the key steps to obtain cyclization are described. The reaction of *o*-iodoaniline **10** with the TES-protected alkyne **11**, under Larock conditions, provided the derivative **12** in a 72% yield with no detectable amount of the undesired



Scheme 2. Route for the synthesis of series **3** pyranoindoles. *Reagents and conditions:* (i) AcOH, reflux.



Scheme 3. Routes for the synthesis of series **4** pyranoindoles (Au(I)-catalysts are described in ref. 58).

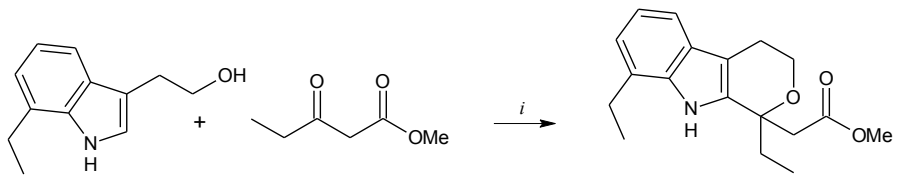


Scheme 4. Route for the synthesis of inhibitors of HCV NS5B polymerase (series **4**). *Reagents and conditions:* (i) $Pd(OAc)_2$, PPh_3, DIPEA, Bu_4NCl, DMF, 85 °C, 3.5 h, 72%; (ii) BF_3-etherate, CH_2Cl_2, RT, 1h then ethyl 3-oxohexanoate, RT, 3 h, 50%.

regioisomer. Compound **12** was pretreated with BF_3-etherate at 0 °C to affect initial desilylation; the subsequent addition of ethyl 3-oxohexanoate at RT then gave the cyclized derivative **13**.

Scheme **5** describes the synthesis of etodolac methyl ester (**16**) [59, 60]. It starts from 7-ethyltryptophol (**14**), which is reacted by Lewis acid-catalyzed oxa-Pictet-Spengler reaction with methyl 3-oxopentanoate (**15**) in an apolar solvent obtaining etodolac methyl ester (**16**). The hydrolysis of the ester gave etodolac.

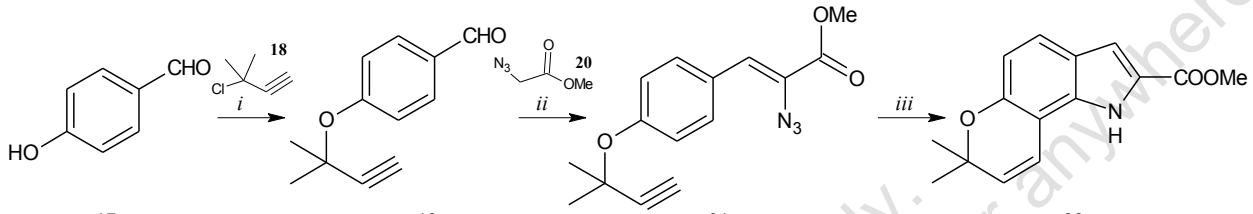
The method reported by Grubbs *et al.* [61] for the synthesis of dihydropyrano[2,3-*g*]indoles (series **5**) is depicted in Scheme **6**. 4-Hydroxybenzaldehyde (**17**) was alkylated with 3-chloro-3-methyl-1-butyne (**18**)



14 **15** **16**

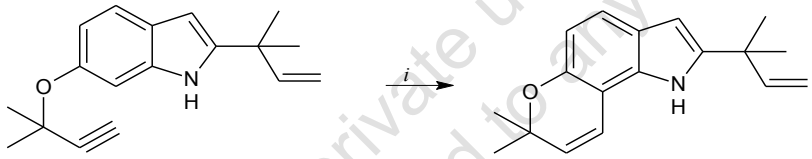
(etodolac methyl ester)

Scheme 5. Synthesis of **16** (etodolac methyl ester, series **4**). *Reagents and conditions:* (i) toluene, 0 °C.



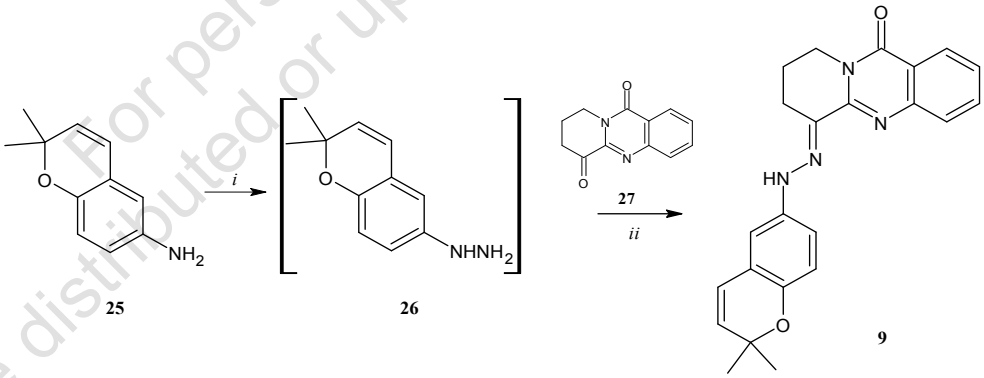
17 **19** **21** **22**

Scheme 6. Route for the synthesis of series **5** pyranoindoles. *Reagents and conditions:* (i) KI, K_2CO_3, acetone, reflux, 99%; (ii) NaOMe, MeOH, -15 °C to 5 °C, 82%; (iii) PhMe, reflux, 99%.



23 **24**

Scheme 7. Alternative route for the synthesis of series **5** pyranoindoles. *Reagents and conditions:* (i) 1,2-dichlorobenzene, reflux, 17 h, 92%.

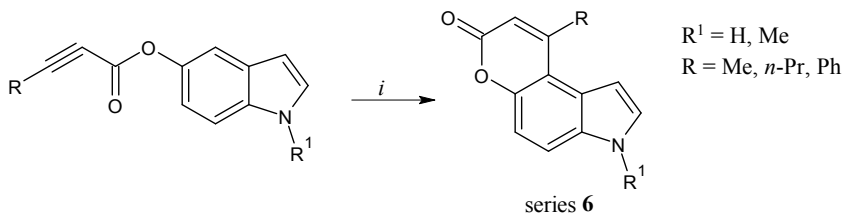


25 **26**

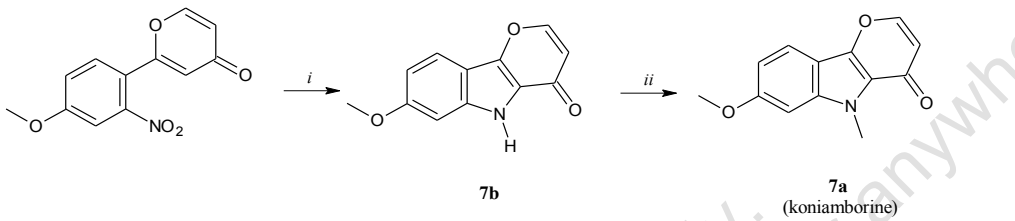
Scheme 8. Route for the synthesis of series **6** pyranoindoles. *Reagents and conditions:* (i) $NaNO_2$, aq. HCl, 0 °C, 0.5 h; $SnCl_2$, 5% HCl, 0 °C, 2 h; (ii) AcOH, EtOAc, reflux, 1 h; (iii) Fischer indolization.

using KI and K_2CO_3 in refluxing acetone affording the ether aldehyde (**19**) in excellent yield, which was submitted to condensation with methyl azidoacetate (**20**) to cleanly afford the conjugated azide **21** in good yield. Generation of nitrene from compound **21** in refluxing toluene facilitated the formation of the indole formation *via* CH insertion. Additionally, the pyran ring was formed under these conditions through a Claisen cyclization. Compound **22** was obtained in excellent yield as a single regioisomer. This procedure was used in the synthesis of notoamides [62].

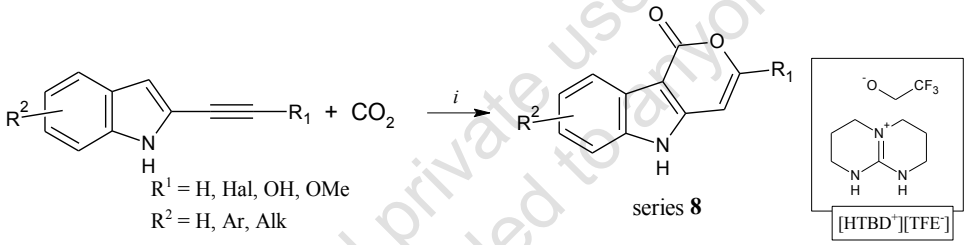
An alternative route for the synthesis of series **5** pyranoindoles may be used when the indole ring is already present. The dihydropyrano[2,3-*g*]indole group



Scheme 9. Alternative route for the synthesis of series **6** pyranoindoles *Reagents and conditions*: (i) $PtCl_4$, 1,4-dioxane/1,2-dicloroethane (1:1), reflux, 5 h.



Scheme 10. Route for the synthesis of series **7** pyranoindoles. Synthesis of koniamborine (**7a**). *Reagents and conditions:* (i) $Pd(dba)_2$, 1,10-phenanthroline, dppp, CO (6 atm), 120 °C, 75%; NaH, MeI, 92%.



Scheme 11. Synthesis of series **8** compounds described by Li *et al.* [69]. *Reagents and conditions:* (i) Protic ionic liquids ($[HTBD^+][TFE^-]$) in different ratios, CO_2 (balloon).

(compound **24**) is obtained by cyclization using 1,2-dichlorobenzene as solvent (Scheme **7**) [63].

The pyrano[3,2-*e*]indole nucleus (series **6**) that characterized fontanesines was obtained, as described by Abe *et al.* [25] (Scheme **8**). Treatment of hydrazine **26**, prepared from aniline **25**, with ketone **27** in the presence of AcOH resulted in a clean reaction affording hydrazone **9** in 50% yield for three steps as a single diastereoisomer. This compound was the starting material for the synthesis of fontanesine B, as described above in Scheme **2**.

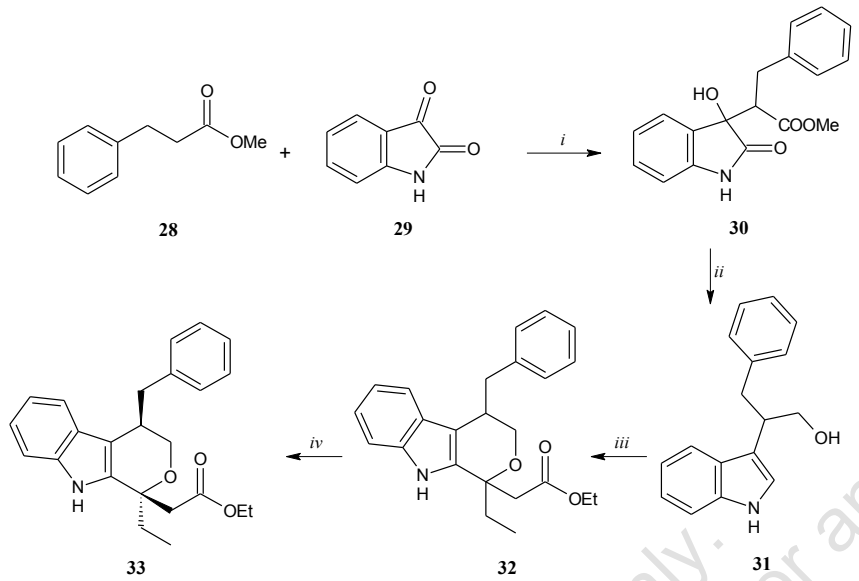
An alternative route to series **6** was reported by Sinicropi *et al.* (Scheme **9**) [47, 48]. Pyranoindoles were obtained by an intramolecular cyclization that occurred when heating esters under reflux in dioxane-dichloroethane in the presence of $PtCl_4$ as a catalyst (Scheme **9**).

The synthesis of koniamborine (series **7**) was reported by Clawson *et al.* [64]. Submitting γ-pyrone to the annulation conditions with bis (dibenzylidenacetone) palladium [$Pd(dba)_2$], 1,3-bis(diphenylphosphino) propane (dppp), and 1,10-phenanthroline in the presence of carbon monoxide, the expected pyrano[3,2-*b*]indole **7b** was obtained, then it was *N*-methylated using iodomethane to give koniamborine (Scheme **10**).

Typically, pyrano[4,3-*b*]indol-1(5*H*)-ones (series **8**) are synthesized *via* metal-catalyzed methods, using $AuCl_3$ [65], $[(Cp^*RhCl_2)_2]/Cu(OAc)_2$, [66], $Pd(OAc)_2/Ag_2O$ [67], and CuI [68]. However, these synthetic routes possess a negative environmental impact, thus an efficient synthesis of these compounds was recently obtained from CO_2 and alkynyl indoles promoted by a protic ionic liquid $[HTBD^+][TFE^-]$ as both the solvent and reaction promoter (Scheme **11**). [69].

3.2. Chiral hydropyrano[2,3-b]indoles and Hydropyrano[3,2-b]indoles

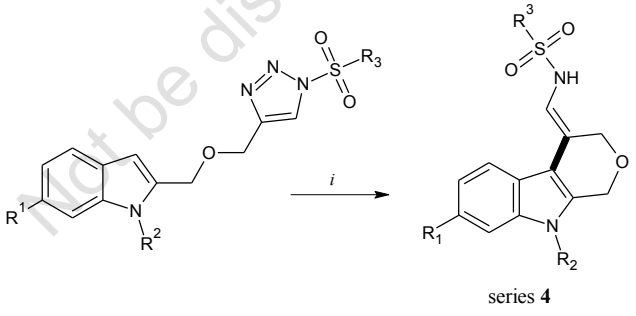
The synthesis of chiral hydropyrano[2,3-*b*]indoles (series **1**) was obtained *via* *N*-heterocyclic carbine (NHC) catalysis [70, 71], calcium phosphate catalysis [72], tertiary amine catalysis [73], or N,N'-dioxide/metal catalysis [74, 75]. The synthesis of pemedolac (series **4**) was achieved by Kats *et al.*



Scheme 12. Route for the synthesis of pemedolac (series **4**). *Reagents and conditions:* (i) LDA, –30 °C; (ii) $LiAlH_4$, THF; (iii) $Et(OMe)C{=}CHCO_2Me$, $BF_3 \cdot Et_2O$, CH_2Cl_2; (iv) separation of diasteroisomers.

(Scheme **12**) [76]. The enolate of methyl phenylpropionate (**28**) was trapped by isatine (**29**) to form the adduct **30** as a mixture of distereoisomers. The treatment with an excess of $LiAlH_4$ in THF afforded compound **31**, which was condensed with methyl propionyl acetate in dichlorometahane, in the presence of boron trifluoride etherate, gave a mixture of the diastereomeric esters **32**. The diastereoisomers were separated by flash chromatography or fractional crystallization. Hydrolysis of the ester **33** provided pemedolac (**4b**, Fig. **13**).

Gharpure and Prasath explored the oxa-Pictet-Spengler type reaction of vinylogous carbonates for the stereoselective synthesis of tetrahydropyrano[3,4-*b*]indoles (series **4**) [77]. Xie *et al.* reported the Rh(II)-catalyzed intramolecular annulation of *N*-sulfonyl-1,2,3-triazoles towards the highly stereoselective synthesis of series **4** pyranoindoles (Scheme **13**) [78].

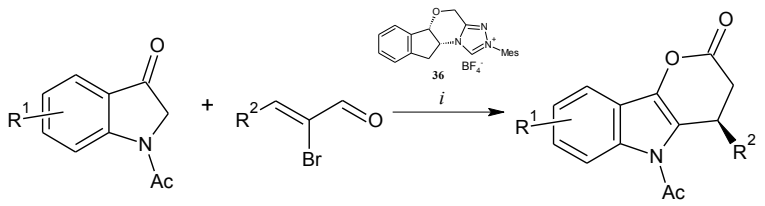


Scheme 13. Synthesis of series **4** compounds described by Xie *et al.* [78]. *Reagents and conditions:* (i) Rh_2L_4 catalyst, DCM or DCE or toluene, RT.

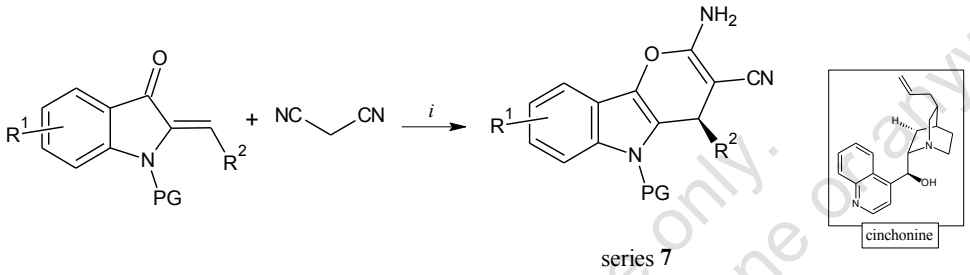
The stereoselective method for the synthesis of hydropyrano[3,2-*b*]indoles (series **7**) is more difficult. Ni *et al.* reported the NHC-catalyzed enantioselective[3+3]annulation of indolin-3-ones with 2-bromoenals to form chiral dihydropyrano[3,2-*b*]indol-2-ones in good yields and with good to excellent enantioselectivities [79]. 1-Acetylindolin-3-one (**34**), 2-bromocinnamaldehyde (**35**), and catalyst (**36**), in the presence of tetramethylethylenediamine, were stirred at room temperature in mesitylene to give the final compound belonging to series **7** (Scheme **14**).

More recently, Yang *et al.* reported a set of secondary amine-catalyzed inverse-electron-demand (IEA) oxa-Diels–Alder (oxa-DA) reactions of (*Z*)-2-ylideneoxindoles with aldehydes in the presence of a chiral secondary amine catalyst to give pyranoindoles belonging to series **7** in moderate to good yield with high stereoselectivity [80]. Chiral 4*H*-pyrano-[3,2-*b*]indole derivatives were recently obtained in moderate to excellent yield and enantioselectivity by a chiral tertiary amine-catalyzed[4+2]annulation of (*Z*)-2-arylmethylidenes with malononitrile (Scheme **15**) [51].

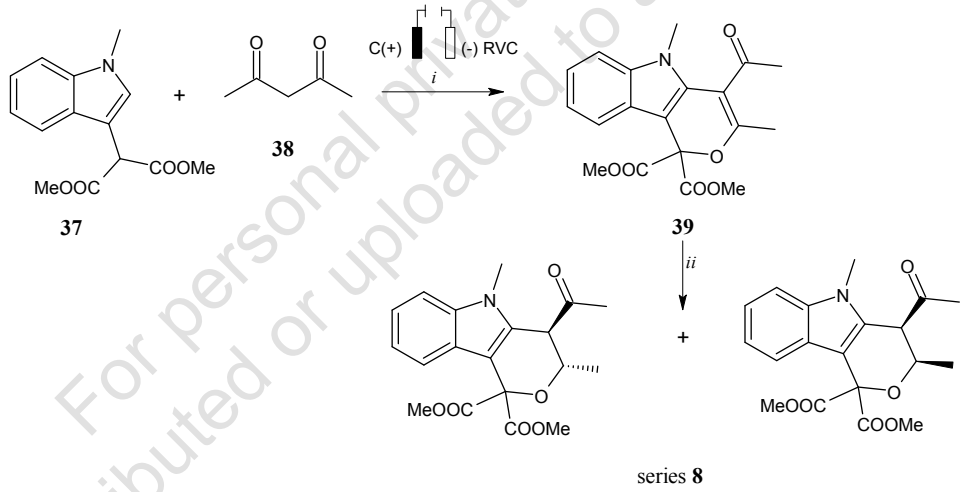
Recently, an electrochemical oxidative coupling of indoles with active methylene compounds, followed by tandem 6π-electrocyclization, has been used to obtain hydropyrano[4,3-*b*]indoles (series **8**) [81]. Electrolysis of **37** and **38** in the presence of NaI at a constant voltage of 3.0 V, with a graphite anode and a reticulated vitreous carbon (RVC) cathode in acetonitrile in an undivided cell, and using $NaBF_4$ as the electrolyte, at room temperature, provided the desired product in 77%



Scheme 14. Synthesis of series **7** compounds described by Ni *et al.* [79]. *Reagents and conditions:* (i) TMEDA, mesitylene, RT.



Scheme 15. Synthesis of series **7** compounds described by Zhou *et al.* [51]. *Reagents and conditions:* (i) cinchonine, toluene, 20 °C, 4Å MS.



Scheme 16. Synthesis of series **8** compounds described by Choi *et al.* [81]. *Reagents and conditions:* (i) NaI, $NaBF_4$, MeCN, 3 V, RT, air; (ii) Pd/C, H_2, EA, RT; DBU, MeCN, RT.

yield. Tetrahydropyrano[4,3-*b*]indoles were synthesized by hydrogenation and epimerization of **39**.

CONCLUSION

Indole fused six membered rings are an interesting structural motif found in biologically active compounds and natural products. Molecules comprising the pyranoindole framework are present in many biologically active natural products and pharmaceuticals and exhibit interesting biological activities, making them highly desirable targets in medicinal chemistry. This review focuses on the description of the most common pyranoindoles reported in the literature and their biological activities. Due to their interesting pharmacological properties, pyranoindoles have recently received considerable attention, which leads to the development of multiple synthetic routes to obtain this class of compounds. Moreover, a trend towards the employment of efficient catalytic methodologies coupled with a "green approach" has been recorded by means of non-toxic and biodegradable chemicals, which have enormous potential in medicinal chemistry with many advantages in terms of yield, safety, and environment.

LIST OF ABBREVIATIONS

A375	=	Melanoma Cell Lines
A549	=	Alveolar Basal Epithelial Carcinoma Cell Lines
Alk	=	Alkyl
Ar	=	Aryl
B-CLL	=	B-cell Chronic Lymphocytic Leukemia Cell Lines
C32	=	Amelanotic Melanoma Cell Lines
COR-L23	=	Large Lung Carcinoma Cell Lines
dppp	=	1,3-bis(diphenylphosphino)Propane
DCE	=	Dichloroethane
DCM	=	Dichloromethane
DLD-1	=	Human Colorectal Cancer Cell Lines
Hal	=	Halogen
HCV	=	Hepatitis C Virus
HIV	=	Human Immunodeficiency Virus
IEA	=	Inverse-electron-demand
LPS	=	Lipopolysaccharides
NCI-H460	=	Human Lung Cell Young Carcinoma Cell Lines
NHC	=	*N*-heterocyclic Carbine
NO	=	Nitric Oxide
oxa-DA	=	oxa-Diels–Alder
$Pd(dba)_2$	=	Bis(dibenzylidenacetone)Palladium
RAW 264.7	=	Murine Monocytic Macrophage Cell Lines
RVC	=	Reticulated Vitreous Carbon
THF	=	Tetrahydrofuran
TMEDA	=	Tetramethylethylenediamine
WST-1	=	Water-soluble Tetrazolium Salt

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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