Review

Current Scenario of Indole Marine-Derivatives: Synthetic Approaches and Therapeutic Applications

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Review

Current Scenario of Indole Marine-Derivatives: Synthetic Approaches and Therapeutic Applications

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Abstract: Indole is a versatile pharmacophore widely distributed in bioactive natural products. This privileged scaffold has been found in a variety of molecules isolated from marine organisms such as algae and sponges. Among these, indole alkaloids represent one of the biggest, most promising family of compounds, having shown a wide range of pharmacological properties, including anti-inflammatory, antiviral and anticancer activities. The aim of this review is to show the current scenario of marine indole alkaloid derivatives, covering not only the most common chemical structures, but also new synthetic routes developed during the last years as well as promising therapeutic applications.

Keywords: indole alkaloids; marine resources; biological activity; therapeutic application; synthetic strategies

1. Introduction

Marine organisms constitute an important source of natural products with tremendous biological and chemical diversity. Sponges, algae, corals, marine bacteria and fungi have shown to produce new secondary metabolites that may be the key to the production of new drugs to treat various diseases [1,2]. In this regard, marine natural products have important advantages over those of terrestrial origin: chemical novelty, new mechanisms of action, greater biological activity and better tolerance in general by patients. These valuable pharmacological properties can be explained due to the fact that many marine compounds have evolved to fight for their organism survival, becoming very powerful inhibitors against biological processes in competitors [3]. The potent analgesic Ziconotide (Prialt®) and the anticancer drugs Trabectedin (Yondelis®; Figure 1) and Eribulin mesylate (Halaven®; Figure 1) are examples of marine drugs accepted by the FDA that proceed by a novel mechanism of action [4,5]. On the other hand, the cyclic depsipeptide Largazole, isolated from a cyanobacterium, is one of the most potent class I histone deacetylase inhibitors, and the first cyanobacterial secondary metabolite containing a thioester (Figure 1) [6,7].

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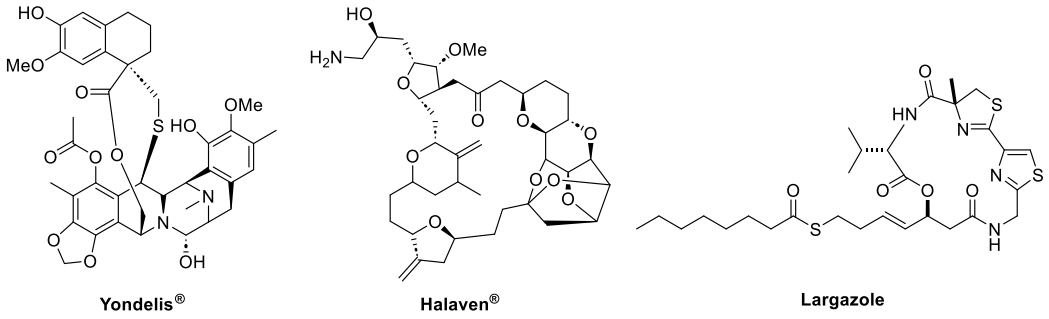

Figure 1. Example of marine drugs accepted by the FDA.

As stated before, marine organisms have proven to be an outstanding source of active molecules, being indole derivatives one of the most promising [8]. Chemically, indole (2,3-benzopyrrole) consists of benzene and pyrrole rings fused together. Indole is an important industrial product widely used in the production of fragrances [9], medicines [10], exogenous auxins [11] and colorants like indigo. The indolyl group is an important fragment present in a wide variety of natural products, such as the amino acid Tryptophan (Trp), involved in the synthesis and release of the neurotransmitter serotonin (related to mood), the hormone melatonin (which regulates sleep), indole-alkaloids, and the plant hormone auxin. Therefore, this moiety has also received much attention in the fields of synthetic organic chemistry and medicinal chemistry [8]. Importantly, recent research has shown clear evidence of the relationship between the chemical structure of the indole bicyclic skeleton and the biological activity it presents. In this sense, anticancer [12–14], anti-coronavirus [15,16], anti-diabetic [17–20] activities are observed when there are amide or chalcone group at C2 and/or C3 position of the indolyl group; anti-Alzeimer's disease activity [21]when seven membered nitrogen-containing heterocycles are present at C2 and/or C3 positions; anti-inflammatory [22,23] and antifungal activities [24,25] when different functional groups are placed in N1 position; and inhibition against osteoporosis [26] when a thiophene group is installed at C4 position (Figure 2).

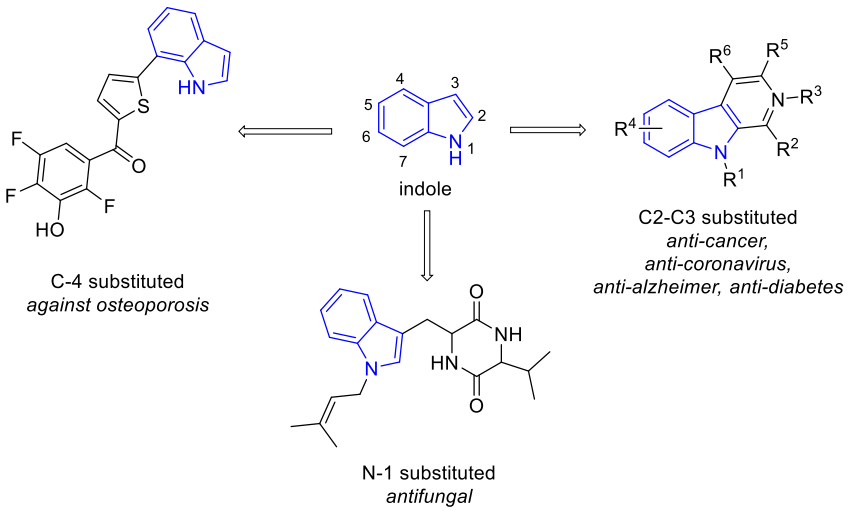

Figure 2. Structure/activity relationships of indole derivatives.

Recently Martinez et al. described several marine natural products as Breast Cancer Resistance Protein (BCRP) inhibitors [27]. Among them, three examples stand out: Fumitremorgin C (FTC), a prenylated indole alkaloid derived from the amino acids L-tryptophan and L-proline; Tryprostatin A, a natural analog of FTC formed by condensation of a proline unit and an isoprenyl tryptophan residue into a diketopiperazine unit; and the β-carboline alkaloid Harmina (Figure 3). Noteworthy, all these compounds are índole alkaloids.

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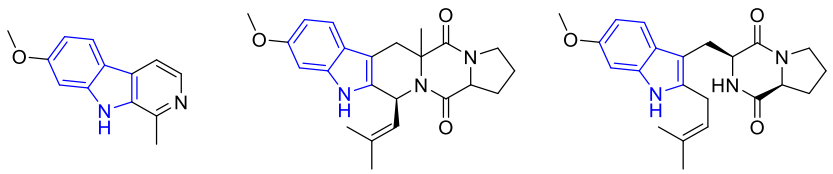

Figure 3. Structure of some marine indole alkaloids with anticancer activity.

Undoubtedly, many compounds derived from marine sources have marked milestones in the treatment of diseases. In particular, indole-containing alkaloids, one of the largest, most abundant and most chemically diverse family of natural compounds, have been shown outstanding potential in the development of new drug leads. However, there are still many obstacles to overcome, in particular the devastating side effects and the fact that many cancers develop resistance to several important pharmaceuticals. For these reasons, it is necessary to continue searching for new, safer and more efficient drugs. Within this context, the structural and functional versatility indole alkaloid derivatives spot them as privileged scaffolds that could streamline the discovery of chemical analogues with potential applications in drug discovery. Therefore, the purpose of this review is to exclusively cover indole alkaloid derivatives from marine sources with a therapeutic interest as well as the novel synthetic routes described to obtain these versatile compounds. The relationship between chemical structure and bioactivity is also addressed in those cases that are described in the literature.

2. Marine Indole Alkaloids

Marine Indole alkaloids (MIAs) present many different structural features and exhibit a wide biological activity such as anti-inflammatory, anti-cancer, anti-HIV, antibacterial, antifungal, antidiabetes, among many others. Both aspects require being organized and ordered. In this section origin and therapeutic applications of MIAs have been presented. Furthermore, synthetic routes from a large number of MIA families have also been included. Based on chemical structures, indole alkaloids can be classified into three groups: simple indole alkaloids, prenylated indoles and annelated indoles.

2.1. Simple indole alkaloids, (SIAs)

Simple indole alkaloids consisting of an indole nucleus with distinct substitution patterns at the N1, C3, C4, C5, C6, C7, and C8 positions [28,29]. In this section, the compounds of this group are ordered according to the complexity of the substituents of the indole moiety, starting from acyclic to cyclic ones.

2.1.1. C-3- acyclic subtituted simple indole alkaloids

The most common substitution in simple indole alkaloids occurs at the C3 position, a characteristic observed in many families of simple alkaloids [8,30]. Various examples showcase the biological activities of these compounds (Figure 4). For instance, 2-(1*H*-indol-3-yl)ethyl 2-hydroxypropanoate (**1**), isolated from the yeast strain (USF-HO25) of a marine sponge identified as *Pichia membranifaciens*, exhibits a mild response as a radical scavenger of 2,2-diphenyl-1-picrylhydrazyl (DPPH) [31]. Another example is methyl 1*H*-indole-3-carboxylate (**2**), obtained from *Spongosorites* sp., a marine sponge, demonstrating cytotoxic attributes against several human cancer cell lines [32]. Additionally, Hainanerectamine B (**3**), isolated from *Hyrtios erecta*, a marine sponge from Hainan, has shown the ability to inhibit Aurora A, a serine/threonine kinase involved in the regulation of cell division [33]. Finally, Tryptamine (**4**), was obtained from *Fascaplysinopsis reticulata* an lyophilized sponge, has demonstrated antibacterial growth inhibition activity confront *Vibriocarchariae* (MIC = 1 μM) [34].

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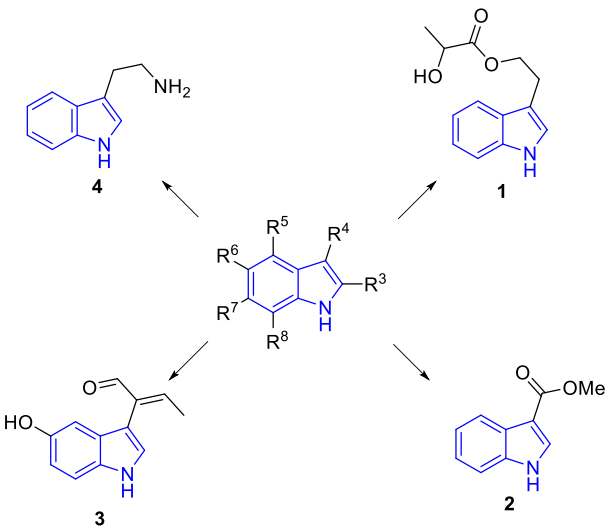

Figure 4. Structures of C3-acyclic substituted SIAs **1-4.**

The presence of carbonyl or carboxyl groups in the indole ring has demonstrated different and interesting biological activities [28,35,36]. Compound **5**, an indole carbaldehyde obtained from *E. chevaleri* KUFA 0006, a culture of an endophytic fungus, exhibited inhibitory activity against *S. aureus* ATCC 2592 biofilm settlement [37]. Hytiodoline (**6**) an indole aminoacid obtained from *Hyrtios* sponge, demonstrated potent anti-trypanosomal activity [38]. Becillamide A (**7**), a thiazole indole derivative obtained from *Bacillus sp.* marine bacterium, showed antibiotic activity against *Archangium gephyra*, immunosuppressing that myxobacterium [39]. Anthranoside (**8**) containing a carboxylated aniline was obtained from the sponge-originated actinomycete *Streptomyces sp.* CMN-62, and it exhibited anti-influenza activity against H1N1 virus and inhibited the reaction to NFκB [40]. Hermanine D (**9**), isolated from ascidian *Herdmania momus*, could inhibit mRNA expression of iNOS, consequently provoking an anti-inflammatory effect [36] (Figure 5).

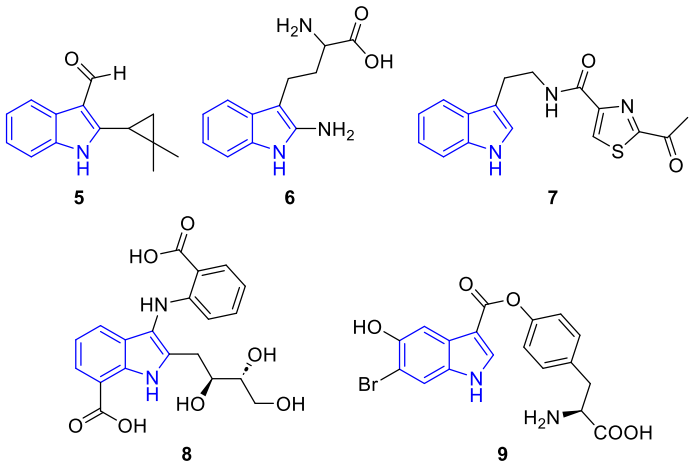

Figure 5. Structures of C3-carbaldehyde/carboxy-substituted SIAs **5-9**.

Quia Che and coworkers developed a biogenetic route to obtain Anthranoside C (**10**), starting with anthranilic acid (**11**) and D-glucose (**12**). The process involves linking two **11** molecules to a **12** molecule, which are then condensed to form an indole ring and in one step more the Anthranoside C (**10**) [40] (Figure 6).

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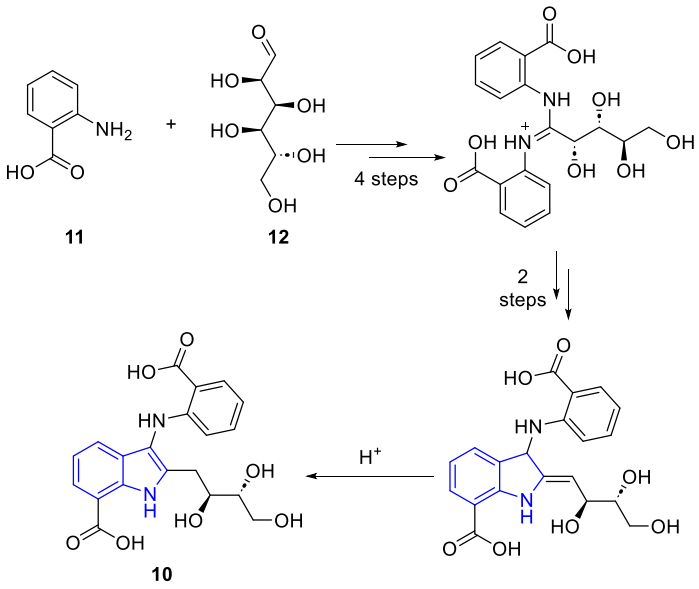

Figure 6. Biogenetic route to obtain Anthranoside C (**10**).

The prenylated simple indoles have also demonstrated diverse and fascinating biological activities [28,35,36]. In this sense, the prenylated indole carbaldehyde (**13**), obtained from *E. chevaleri* KUFA 0006, exhibited inhibitory activity against *S. aureus* ATCC 2592 biofilm settlement [37]. Eurotiumin (**14**), an amide indole derived from *Eurotium sp*. SCSIO F452, a sediment-derived fungus from the South China Sea [41], showed antioxidant properties in in DPPH assay [42]. Misszrtine A (**15**), an unusual *N*-substituted prenylated indole obtained from *Aspergillus* sp. SCSIO XWS03F03 sponge-derived fungus, exhibited strong activity against HL60 and LNCaP cell lines [43]. Terpetin (**16**), a polyamide indole obtained from *Aspergillus* sp. SpD081030G1f1, acted as a protector against L-glutamate toxicity in cells [44] (Figure 7).

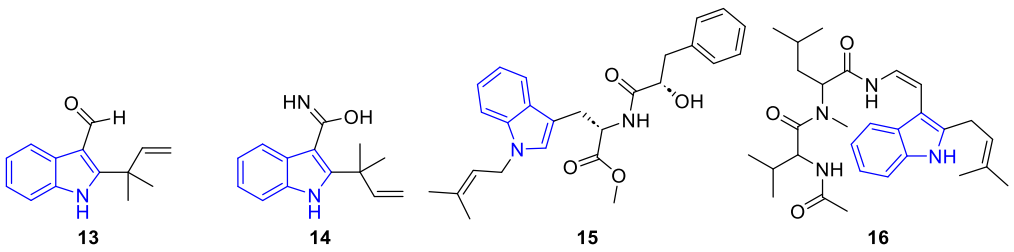

Figure 7. Structures of prenylated SIAs **13-16**.

May Zin et al. developed a biogenesis of isomers compounds **17** and **18**, starting with L-tryptophan (**19**). Isomer **16** was obtained in five steps, and isomer **18** required one additional isomerization step (Figure 8) [37].

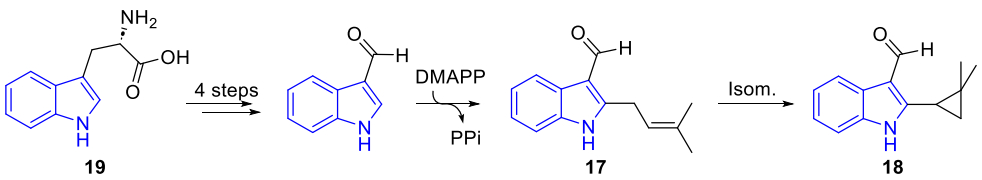

Figure 8. Biogenesis of isomers **17** and **18**.

The compounds described above have underscored the potential of indole alkaloids in both organic and medicinal chemistry, emphasizing the importance of exploring synthetic pathways to

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obtain simple indole alkaloids. Some straightforward methods for obtaining functionalized simple indole alkaloids include the Bartoli reaction, which involves nitrobenzene (**20**) and vinylmagnesium bromides (**21**) [45]. Another reaction involves intramolecular Rh-catalyzed decomposition of *ortho*-azydostyrenes (**22**), followed by C-H activation [46]. Additionally, two novel high-yielding, Au(I)-catalyzed reactions have been reported: one involving the intramolecular cyclization reaction of *ortho*-alkynylanilines (**23**) [47]; and the other involving the reaction between alkynyl-hydroxycyclohexadienones (**24**) and primary amines [48] (Figure 9).

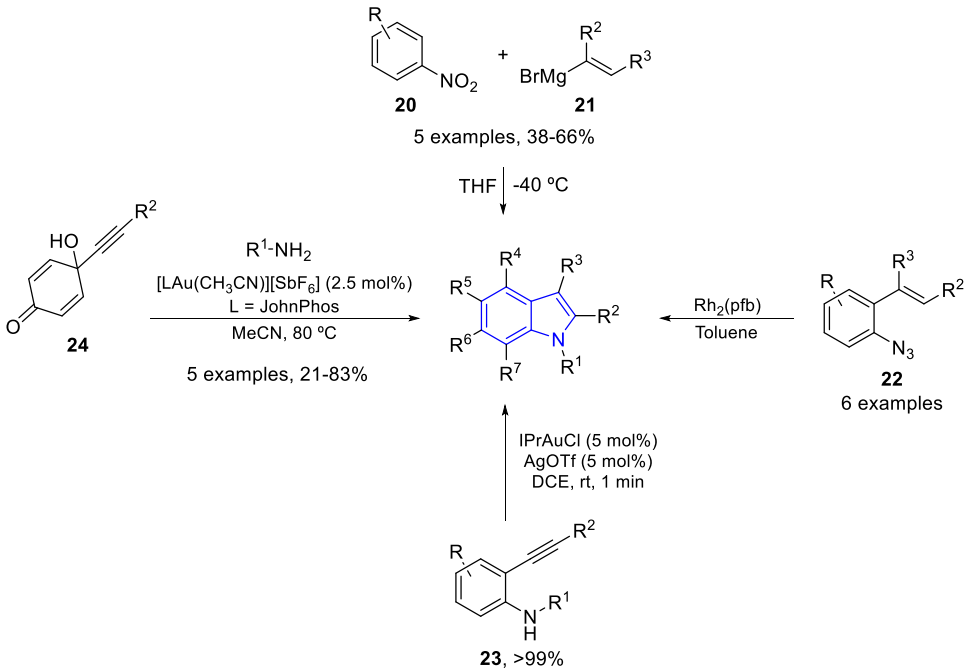

Figure 9. Synthetic approaches in the preparation of functionalized SIAs.

2.1.2. C3-(Iminoimidazolidin- and Pirazin-)-subtituted simple indole alkaloids

Usually, simple indole alkaloids are categorized into families based on similar structures, activities, or origins [35]. One example of this classification includes Trachycladindoles and Aplysinopsin, both of which feature an iminoimidazolidine ring in the above position. Trachycladindoles A (**25**), C (**26**), G (**27**), B (**28**), D (**29**), E (**30**) and F (**31**), isolated from a marine sponge *Trachycladus laevispirulifer*, have demonstrated cytotoxicity against human cancer cells (HT-29, A549, and MDA-MB-231) [49]. Additionally, Aplysinopsin (**32**) and its derivatives **33-39** were obtained from Thorectidae sponges (*Thorectandra* and *Smenospongia*) [50]. They have demonstrated activity against *Staphylococcus epidermidis*, with derivative **37** exhibiting the highest antimicrobial activity (MIC = 33 μM). Following this, derivatives **35** (MIC = 36.5 μM), **34** (MIC = 74.6 μM), **33** (MIC = 98.3 μM), and **36** (MIC = 273.8 μM) show decreasing levels of antimicrobial activity [35]. Derivative **33** was discovered in a Jamaican sponge *Smenospongia aurea*, and it exhibited a high affinity for two receptors, 5-HT2A and 5-HT2C [51]. The latest derivatives, **38-39**, were discovered in the marine sponge *Fascaplysinopsis reticulata*. They exhibited remarkable activity against the bacterium *Vibrio natrigens*, derivative **38** demonstrated potent activity with a MIC of 0.3 μM, while **39** exhibited significant activity (MIC = 2.4 μM) [34].

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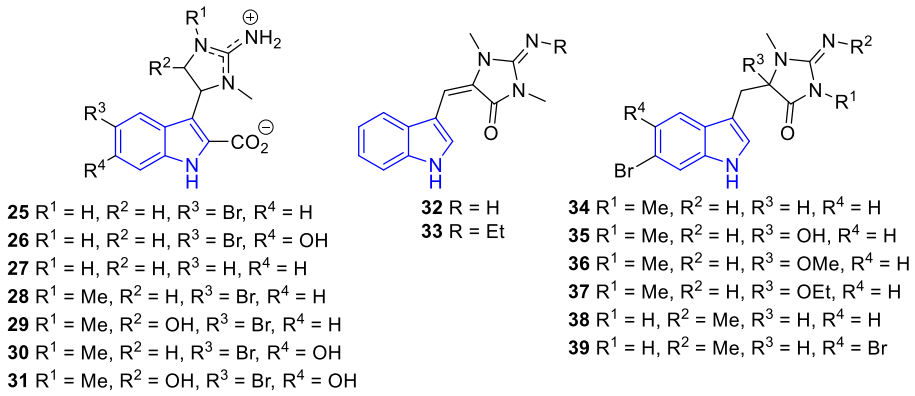

Figure 10. Trachycladindole A-G (**25-31**), aplysinopsins (**32**) and their derivatives (**33-39**).

A hypothetical method for the biosynthesis of trachycladindoles has been described by A. Hentz. The route starts with tryptophan (**19**), and trachycladindole A-G (**25-31**) are obtained in 5 steps [52] (Figure 11).

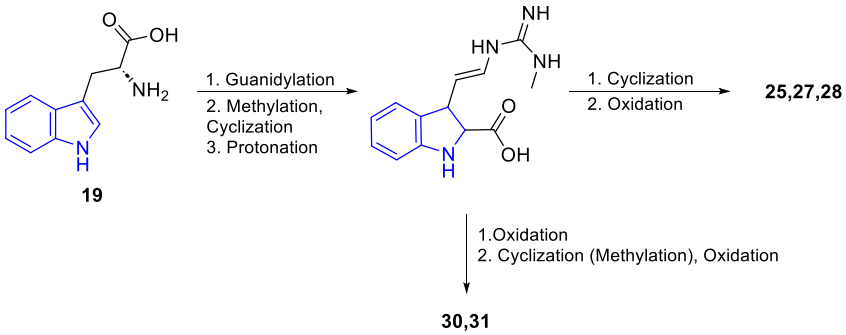

Figure 11. Trachycladindole hypothetical biosynthesis by A. Hentz.

The synthesis of Aplysinopsins derivate **38** is shown in Figure 12 as was described by Stanovnik and Svete [53]. The key step for the formation of the iminoimidazolinone core was achieved by addition of methylamine to a carbodiimide intermediate followed by intramolecular amidation reaction.

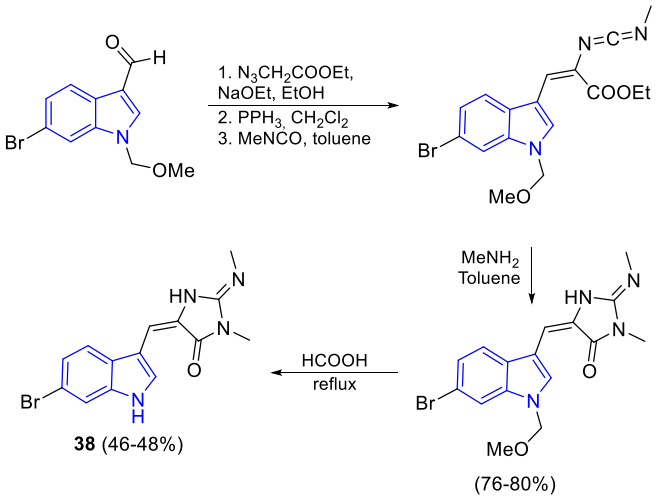

Figure 12. Stanovnik and Steve' synthesis of Aplysinopsin derivate **38**.

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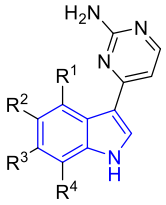
Meridianins A-G (**40-46**) are a family of SIAs characterized by having pyrazine rings at the C3 position (Figure 7). Meridianins were obtained from several sources, but mainly tunicates. Thus, the first was *Aplidium meridianum*, from which Meridianins A-E were isolated, [54] but other examples include *Aplidium falklandicum* and *Synoicum sp*. [55].



40 R^1 = OH, R^2 = H, R^3 = H, R^4 = H
41 R^1 = OH, R^2 = H, R^3 = Br, R^4 = H
42 R^1 = H, R^2 = Br, R^3 = H, R^4 = H
43 R^1 = H, R^2 = H, R^3 = Br, R^4 = H
44 R^1 = OH, R^2 = H, R^3 = H, R^4 = Br
45 R^1 = H, R^2 = Br, R^3 = Br, R^4 = H
46 R^1 = H, R^2 = H, R^3 = H, R^4 = H

Figure 13. Structure of Meridianins A-G (**40-46**).

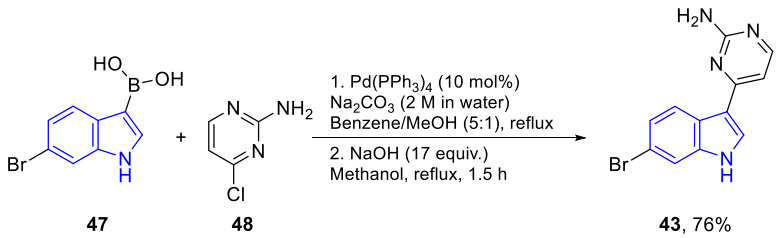
Meridianins B-E (**41-44**) are notable for their demonstrated cytotoxic effects against adenocarcinoma and murine mammary tumour cell lines (IC_{50} = 11.4, 9.3, 33.9, 11.1 μM, respectively) [54]. Moreover, **43** has exhibited antibiofilm potential against methicillin-resistant Staphylococcus aureus (MRSA) [35]. In general, Meridianin family has demonstrated a wide biological activity summarized in the Table 1 [55,56].

Table 1. Bioactivity of Meridianins A-G (**40-46**).

Meridianin	Anticancer effects	Prevention of Alzheimer's Disease	Antimalarian effects	Antitubercular effects
A (**40**)	Hela		*P. falciparum*	nd [1]
B (**41**)	PTP, Hep2, U937, LMM3		nd	nd
C (**42**)	PTP, Hep2, HT29, RD, U937, LMM3, Hela, MDA-MB-231, A549	GSK-3β, CK1δ, Dyrk1A and CLK1 [2]	*P. falciparum*	*M. tuberculosis*
D (**43**)	PTP, Hep2, HT29, RD, U937, LMM3, Hela, A549		nd	*M. smegatis* [3]
E (**44**)	PTP, Hep2, U937, LMM3	nd	nd	nd
F (**45**)	Hep2, U937, LMM3	nd	nd	nd
G (**46**)	Hela	Dyrk1A	*P. falciparum*	*M. tuberculosis*

[1]nd: not determited, [2]Inhived kinases, [3]Antibiofilm activity.

Meridianins can be accessed through several synthetic routes; being the first one developed by Jiang and Yang, from a 7-bromoindolylboronic acid (**47**) and a 4-chloro-pyrimidini-2-amine (**48**). In only two steps, **43** was obtained in high yield [57] (Figure 14).



47 **48** **43**, 76%

Figure 14. Jing and Yang synthesis of meridianin D (**43**).

However, Fresneda and Molina' methodology to obtain Meridianins **42** and **43** is the most used route up to date. Starting from the corresponding brominated indoles, this four-steps route presents high yields in all reactions [58] (Figure 15).

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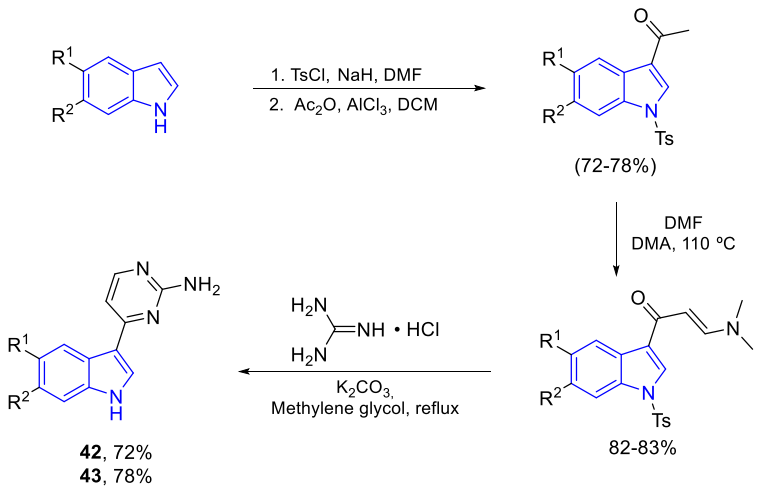

Figure 15. Fresneda and Molina' synthesis of Meridianins C (**42**) and D (**43**).

Noteworthy, most methodologies focus on the synthesis of **42** and **43**.[57] For example, Karpov *et al.* improved a three-component palladium-catalyzed carbonylated alkylation [59], while Müller and coworkers achieved it in a one-pot procedure based on Suzuki coupling following a Masuda borylation with a palladium catalyst [60]. Zhou and Chen developed a route to **42** and its derivatives [56], and Penoni employed indolization of nitrosoarenes to obtain **42** derivatives with the indole moiety functionalized [61]. Remarkably, Stanovnik and Svete described the synthesis of all Meridianinds **40-46** and Aplysinopsins derivatives **32-39** [53].

2.1.3. Bis-/tri-indole alkaloids.

Bis- and tris-indole alkaloids are characterized by the linkage of the indole moieties through (hetero)carbonated chains, typically between the C3 positions [35]. Usually, when indole alkaloids are bridged by an imidazole ring, they exhibit interesting biological activity. Examples such case are bis-indoles Dihydrospongotine C (**49**) and Spongotine C (**51**) and the tris-indole Tulongicin (**53**), isolated from the sponge *Topsentia*. They have demonstrated antiviral activity against HIV, HxB2 and YU2, with IC_{50} values ranging from 2.7 to 12 μM and 3.5 to 9.5 μM (respectively); as well as antimicrobial and antibacterial properties, particularly against *S. aureus* (MIC = 1.8 to 7.6 μM) [62] (Figure 7). Furthermore, Rhopaladin C (**52**), isolated from a marine tunicate, demonstrated antimicrobial efficacy against *Sarcina lutea* and *Corynebacterium xerosis* (IC_{50} = 36.9 μM) [63]. Lastly, Spongotine A (**50**) was isolated from *Topsentia pachastrelloides* sponge and showed antibacterial effects to both susceptible and methicillin-resistant strains of *S. aureus* [64] (Figure 16).

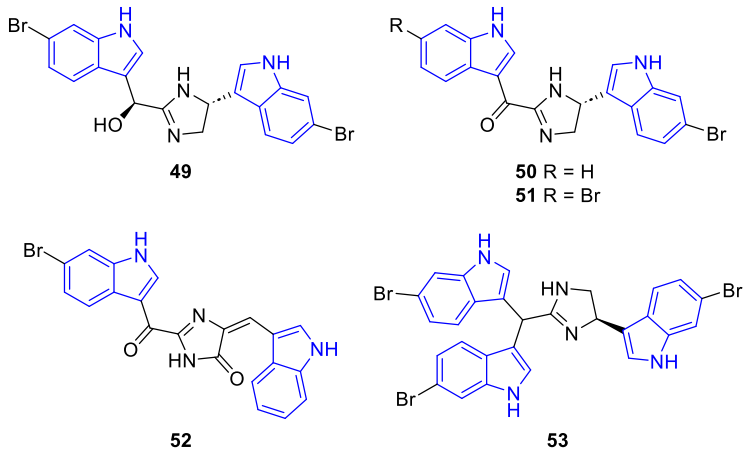

Figure 16. Structure of bis-indoles **49-52** and tris-indole **53**.

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Bromodeoxytopsentin (**54**) and dibromodeoxytopsentin (**55**) feature an unsaturated imidazole bridging the indole moiety. **54**, isolated from *Topsentia pachastrelloides* sponge, demonstrated antibacterial effects against both susceptible and methicillin-resistant strains of *S. aureus* [64]. **55**, obtained from a genus of the marine sponge *Topsentia*, also exhibited antibacterial properties against *S. aureus* (MIC = 22.7 μM) and shows additional potential as antiviral agent against HIV (YU2, IC_{50} = 57 μM) [62].

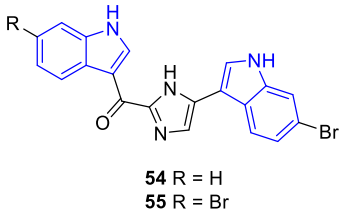

Figure 17. Structure of bromodeoxytopsentin (**54**) and dibromodeoxytopsentin (**55**).

Eusynstelamides A-B (**56-57**) and D-F (**58-60**) are brominated bis-indole bridged by a γ-lactam ring obtained from ascidians [65] and bryozoans [66]. **56** and **57** displayed only weak effectiveness against *S. aureus* [65]. However, compounds **58-60** proved stronger antibacterial properties, showing activity against *S. aureus* and *Corynebacterium glutamicum* (MIC = 7.8-17.4 μM), as well as *E. coli* and *P. aeruginosa* (MIC = 16.4-34.7 μM) [66].

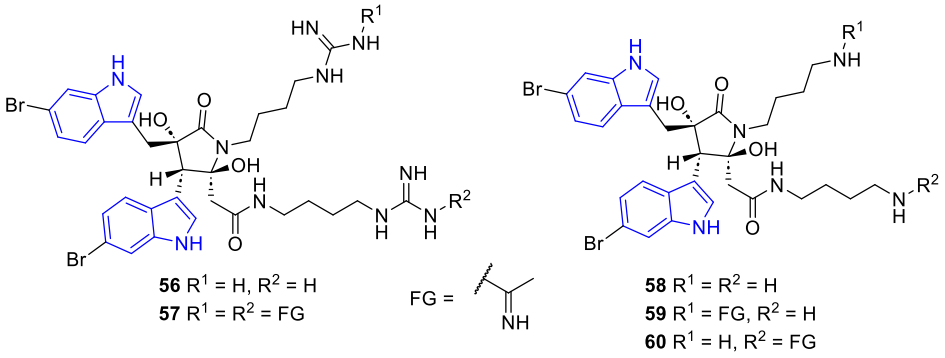

Figure 18. Structure of eusynstyelamide A-B and D-F (**56-60**).

Hamacanthins A-B (**61-62**) are bis-indole isomers linked by a pyrazinone ring, isolated from a marine sponge belonging to the genus *Hamacantha*. Both exhibited antimicrobial properties efficacy against *B. Subtilis* (MIC = 6.4 and 3.3 μM respectively) [67].

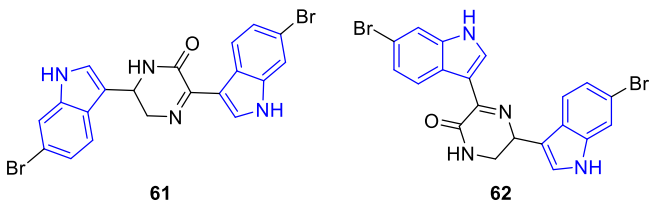

Figure 19. Structure of hamacanthin A-B (**61-62**).

Regarding the synthesis of bis- and tris-indole species, an illustrative example could be the synthesis of Rhopaladin C (**55**) developed by Janosik *et al.* [63]. Starting from 1*H*-indole-3-carbonyl cyanide, the desired product could be obtained by condensation of the nitrile group with the amino group from L-Tryptophan methyl ester to generate the imidazolone core. This transformation yields **55** in two steps with moderate yield (Figure 20).

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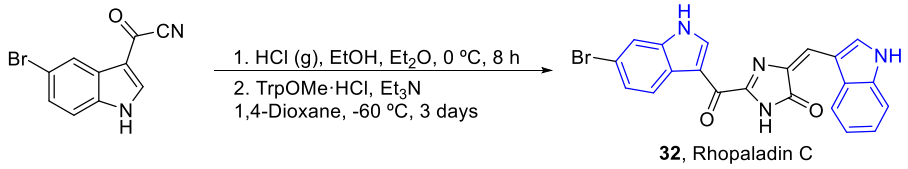

Figure 20. Janosik et al. synthesis of Rhopaladin C (**32**).

2.2. Prenylated Indole Alcaloids (PIA)

Prenylated indoles include several different families of compounds. For a better insight for the readers, the PIA are arranged in ascending order of complexity, ranging from indole core with a cyclic prenyl substituent to indole moiety fused with a variable number of prenyl-derived ring system. PIA containing the indole core with acyclic prenyl sustituents have been included in 2.1. Section.

2.2.1. Diketopiperazinas (DKPs) indole alkaloids

2.2.1.1. Simple diketopiperazines

Simple 2,5-Diketopiperazines (2,5-DKPs) are cyclodipeptides formed through the condensation of two α-amino acids, establishing two amide linkages to constitute the six membered ring [68,69]. This kind of compounds demonstrated a good catalytic performance in asymmetric synthesis of Reformatsky reaction [70]. Furthermore, they have been used as structural fragments in the desing of novel drugs [52].

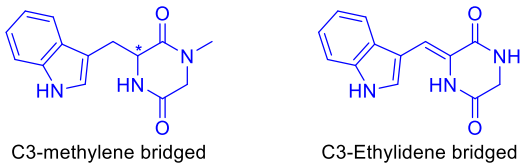

Figure 21. Basic structures of Simple Diketopiperizines.

Based on their chemical structure, simple indole diketopiperazines includes a wide variety of families of compounds [70]. Then, DKPs which have been found to present biological activity, have been orderer of increasing structural complexity into two main groups: monoindole and bisindole DKPs. Also, monoindole DKPs differ in how the indole is attached to the diketopiperazone, being ultimately divided in attached at C-3 with a methylene or ethylidene bridge.

Attached at C-3 with a methylene bridge

In this classification, it has been organized the monoindole diketopiperazines containing diketopiperazine ring attached at C3 indol core with an methylen bridge (Figures 22 and 23). This indole DKPs are commonly isolated from fungi, such as *Aspergillus*, *Penicillium*, among others [71]. An example of marine bioactive indole diketopiperazines alkaloids is Brevianamides, which are originated from tryptophan and proline.

The simplest member of this family of compounds is the (*S*)-Brevianamide F (**63**), derived from the hexahydropyrrolopyrazine and precursor of a variety of more complex prenylated alkaloids. Compound **63**, isolated from marine derived *Penicillium vinaceum*, has shown antibacterial activities against *Bacille Calmette-Guérin* (BCGs) (IC_{50} = 44.1 μM) and *S. aureus*; and antifungal activity against *C. albicans* [72,73]. (*R*)-Cyclo(D-Trp–L-Pro) (**64**), the enantiomer of Brevianamide F (**63**), has been isolated from the fungi and has shown antimicrobial activities [74]. Compound **65**, derived from fungus *Aspergillus fumigatus*, bears an *N-tert*-butoxycarbonyl protecting group which increase its antimicrobial activity against S. *aureus* and B. *subtilis* (IC_{50} = 2.1–3.3 μg/mL) [75].

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Other two examples whose estructure derived from the hexahydropyrrolopyrazine are 18-Oxotryprostatin A (**66**) and compound **67**, both isolated from the marine-derived fungus *Aspergillus sydowi*. 18-Oxotryprostatin A (**66**) exhibited weak cytotoxic activity against A-549 cells (IC_{50} =1.28 μM) [76]. Compound **67** showcased antimicrobial activity against S. *aureus* and B. *subtilis* (IC_{50} = 2.1–3.3 μg/mL), being this activity strongly enhanced due to the C2-isoprene and *N-tert*-butoxycarbonyl units [75].

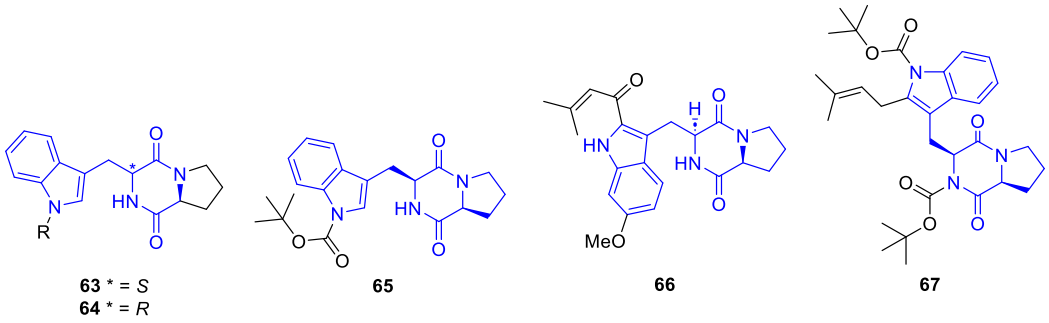

Figure 22. Chemical structures of simple DKPs **63-67** with C3-methylene bridge.

8,9-Dihydrobarettin (**68**), a brominated cyclodipeptide found in the boreal sponge *Geodia barretti*, exerted inhibitory activity against AChE and BChE, potent antifouling, antioxidant, and anti-inflammatory activities, making it a potential lead compound in prevention of chronic inflammatory diseases [77,78]. Also, it displayed a high affinity for the 5-HT receptor [78,79].

Cyclo(L-Trp–L-Ala) (**69**), Rubrumlines F (**70**), G (**71**), J (**72**), M (**73**), N (**74**) and O (**75**), 5-Piperazinedione **76**, 2,5-piperazinedione **77** and Preechinulin (**79**), found in marine-derived fungus *Eurotium rubrum*, present an effect against the influenza virus strain A/WSN/33 (H_1N_1) [80]. Echinulin (**80**), extracted from the marine derived fungus *Eurotium rubrum* MPUC136, presents two isoprene unit in the indole core, and has shown inhibitory activity against B16 melanoma cells [80,81].

The diketopiperazine **78**, ontained from the M-3 strain belonging to the *Ascomycota phylum*, exhibited a strong and selective antifungal activity against *Pyricularia oryzae*.

14-Hydroxyterezine D (**81**) was derived from *Aspergillus sydowi* PFW1-13 and has shown weak cytotoxic activity towards A549 (IC_{50} = 7.31 μM). Also, it was active against HL-60 cells (IC_{50} = 9.71 μM) [76]. Didehydroechinulin (**82**) was isolated from *Eurotium cristatum* EN-220 and has shown potent lethal activity against brine shrimp and weak nematicidal effect against *Panagrellus redivivus* (IC_{50} = 27.1 μg/mL) [82]. Both have one and two isoprene units in the indole core respectively.

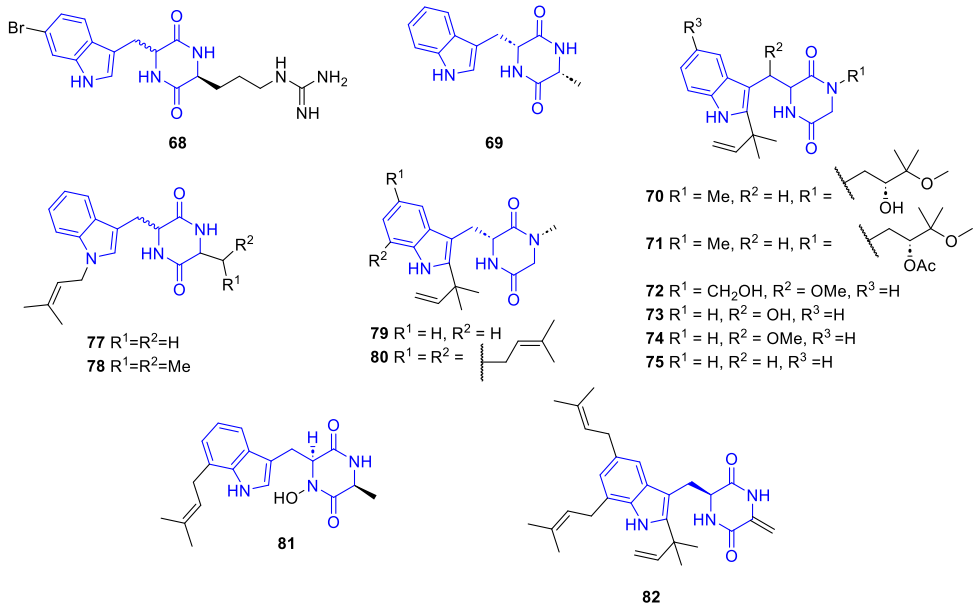

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Figure 23. Chemical structures of simple DKPs **68-82** with C3-methylene bridge.

Attached at C3 with an ethylidene bridge

Isoechinulin B (**83**), Cryptoechinuline G (**84**) and alkaloid E-7 (**85**) have been isolated from the marine derived fungus *Eurotium rubrum* MPUC136 and feature several isoprene units in the indole core. They exhibited inhibitory activity against melanin synthesis using B16 melanoma cells [80,81]. Demethyl-12-oxo-eurotechinulin B (**86**), obtained from the same fungal strain, has shown cytotoxic activity against SMMC-7721 line (IC_{50} = 30 μg/mL) [83].

Cristatumin A (**87**), isolated from *Eurotium cristatum* EN-220, has shown antibacterial activity against *S. aureus* and *E. Coli* (IC_{50} = 64 and 8 μg/mL). As far as we can ascertain, its synthesis has not been reported yet [84]. Aspechinulins C (**88**), isolated from the fungus *Aspergillus sp.* FS445, has exhibited the most potent inhibitory activities against nitric oxide (NO) production in comparison to other Aspechinulins (IC_{50} = 20-90 mM) [85].

Barettin (**89**), a brominated cyclodipeptide which isolated from the boreal sponge *Geodia barretti*. Like its reduced analogue 8,9-dihydrobarettin (**68**), it exhibited inhibitory activity; potent antifouling, antioxidant, and anti-inflammatory activities; and reduced DC secretion of IL-12p40 and IL-10 (IC_{50} = 21.0 and 11.8 μM, respectively) [77–79].

Neoechinulin A (**90**), isolated from the marine-derived fungus *Aspergillus sp.*, and Variecolorin O (**91**), extracted and characterized from *Eurotium sp.* SCSIO F452 fungus, exhibited a significant radical scavenging activity against DPPH [41], and **90** has also shown UV-A protecting activity (IC_{50} = 24 μM) [86]. Isoechinulin A (**92**) has been isolated *Eurotium rubrum* MPUC136 fungus, and has shown inhibitory activity against influenza A/WSN/33 virus (IC_{50} = 42.7 μM) [80,81].

Compound **93** was isolated from *Eurotium cristatum* EN-220 and has shown potent lethal activity against brine shrimp and weak nematicidal effect against *Panagrellus redivivus* (LD_{50} = 110.3 μg/mL) [82].

Neoechinulin B (**94**), Neoechinulin C (**95**), Rubrumline D (**96**) and Rubrumline E (**97**), obtained from *Eurotium rubrum* fungus, presented weak antiviral effect against the influenza virus strain A/WSN/33 (H_1N_1) that was propagated in MDCK cells [80].

Eurotiumin C (**98**), isolated and characterized from *Eurotium* sp. SCSIO F452 fungus, and has showed significant radical scavenging activities against DPPH (IC_{50} = 13 μM) [41].

Photopiperazines A–D (**99-102**), unsaturated diketopiperazine derivatives, were isolated from *Actinomycete bacterium* strain AJS-327 and exhibited selective toxicity toward U87 and SKOV3 lines (IC_{50} = 4.1×10^{-4} μM and 7.5×10^{-4} μM) [87].

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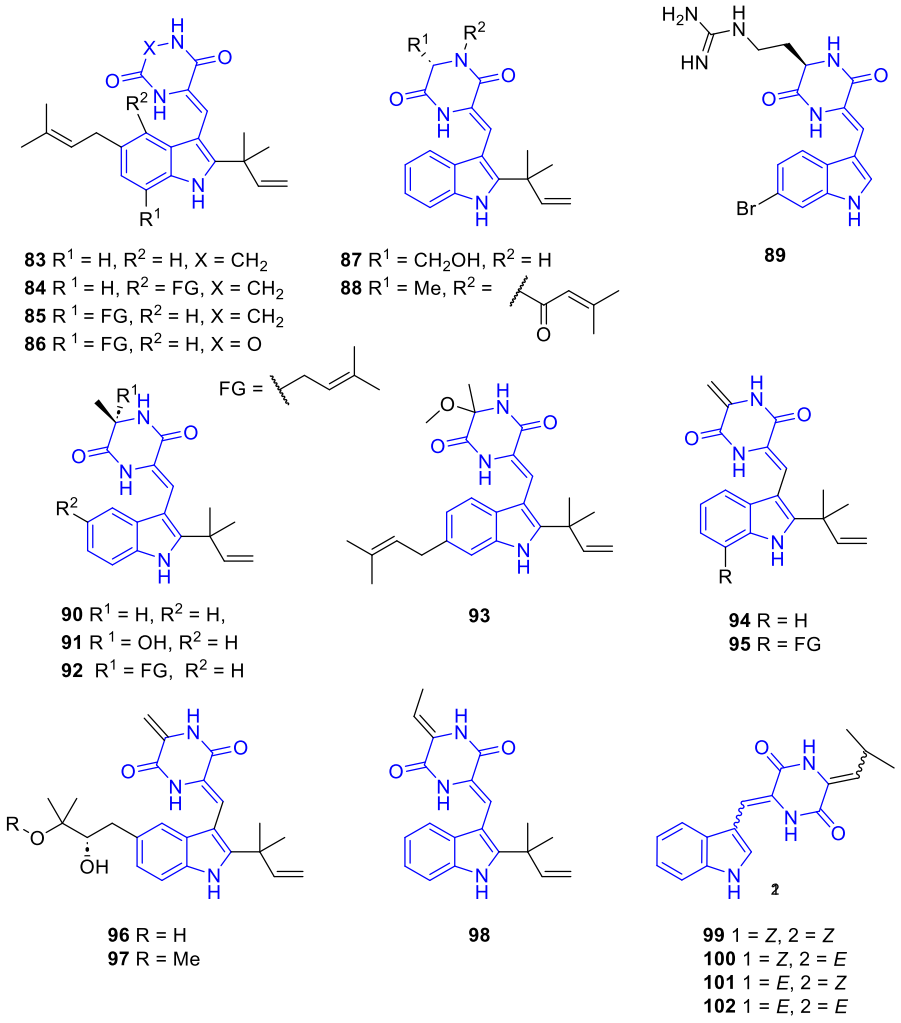

Figure 24. Chemical structures of simple DKPs **99-102** with C3-ethylidene bridge.

Bis-indole diketopiperazine

In this subsection, naturally occurring DKPs with biological activity containing two indole units have been summarized (Figure 25) [88]. Aspergilazine A (**103**), isolated from the marine derived fungus *Aspergillus taichungensis* ZHN-7-07, presents a rare N1 to C6 linkage between two DKP. Compound **103** has a weak activity against influenza A (H_1N_1) virus with the inhibition of 34.1% at a concentration of 50 μg/mL [89,90].

Brevianamide S (**104**), extracted from marine-derived fungus *Aspergillus versicolor*, has shown antibacterial activity against BCGs (IC_{50} = 9.0 μM) [72,73].

Dinotoamide J (**105**), obtained from a marine-derived fungus called *Aspergillus austroafricanus* Y32-2, demonstrated angiogenesis promoting activity and exhibited proangiogenic activity in a PTK787-induced vascular injury zebrafish model [91].

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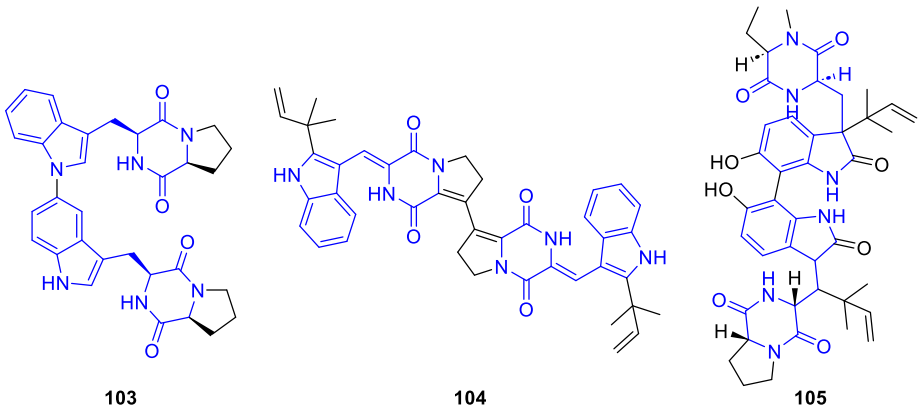

Figure 25. Chemical structures of bis-indol DKPs **103-105**.

Synthetic routes

To obtain indole DKP derivatives, there are two key steps in every synthetic route: the synthesis of the DKP core, and the coupling of the DKP and the indole unit. Regarding the construction of DKP ring, three immediate disconnections of a 2,5-diketopiperazine ring can be envisioned: the amide bond N1-C2 (**A**), the N1-C6 bond (**B**), and the C5−C6 bond (**C**). Additionally, other two possible disconnections involving two bonds can be devised: tandem cyclization via N1−C2/C3−N4 (**D**) and via C2−N1− C6 (**E**) (Figure 26).

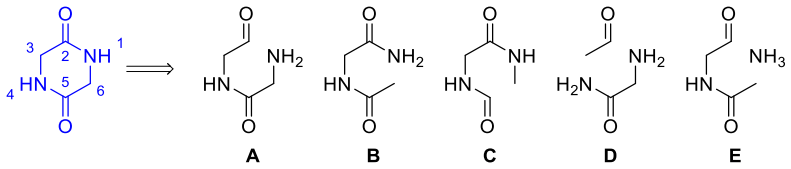

Figure 26. Possible disconnections of a 2,5-diketopiperazine ring.

The amide bond formation synthesis (A) can be carried out through four different methods: dipeptide formation followed by cyclization, Ugi chemistry, amino acid condensation and Aza-Witting cyclization. The *N*-alkylation synthesis (B) can be approached from three different ways: using α-haloacyl derivatives of amino acids, Aza-Michael addition, and Diels−Alder reaction. The approach C can occur via C-C cyclization radical-mediated or enolate acylation [70]. The tandem cyclization synthesis (D and E) can be regarded as extensions of A-C, and they share some common processes in tandem fashion.

Given the straightforward character of the procedure, and the huge chiral pool of commercially available α-amino acid, there are several synthetic examples of the dipeptide route using different coupling reagents.

A representative case of an intramolecular Aza-Witting reaction forming the 2,5-DKP ring is provided in Figure 27. The acylation between amino acids esters (**106**) and chloroacetyl chloride followed treatment with sodium azide (NaN_3) and Ph_3P affords 2,5-diketopiperazines **107** via iminophosphorane intermediates [92].

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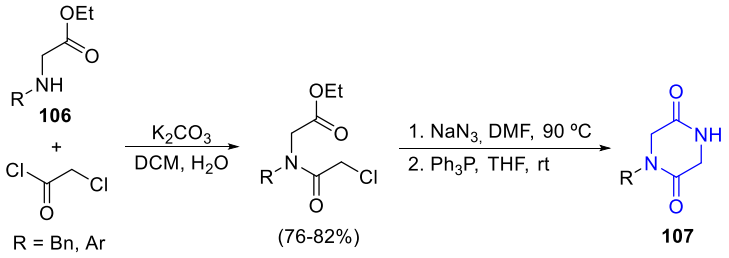

Figure 27. Scheme of Aza-Witting cyclization to synthesize DKPs **107**.

Considering the obtention of indole DKPs, many syntheses and biosynthesis have been described over decades, but surprisingly very few of them were employed to access biologically active compounds. As illustrative examples, a reported synthesis and a biosynthesis Brevianamide F (**63**) are depicted in Figure 28. Nicolás *et al.* carried out a solid phase methodology following Ashnagar synthesis, which furnished **63** in very good yields but required installation-removal of protecting groups (Figure 28a) [93,94]. On the contrary, the biosynthesis approach of **63** uses directly unprotected L-Trp (**19**) and L-Pro (**108**) as precursors. This way, using FtmPS (a nonribosomal peptide synthetase) from *Aspergillus fumigatus* as a catalyst, Bravianamide F (**63**) can be obtained (Figure 28b) [68].

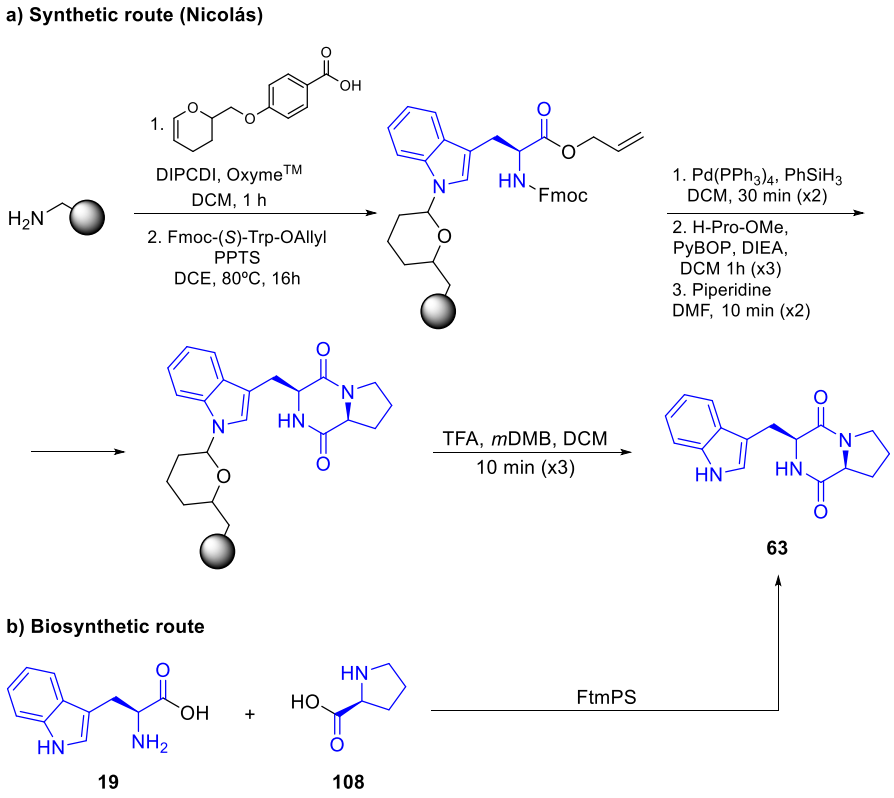

Figure 28. Scheme of synthesis and biosynthesis of Brevianamide F (**63**).

The synthesis of Neochenulin A (**94**) is an example of diketopiperazine attached at C-3 with an ethylidene bridge. The reaction of the aldehyde **109** and diketopiperazine **110** promoted *t*-BuOK in DMF affords the C3-ethylidene-bridged indole DKP core in one step. Subsequent deacetylation and elimination of methoxymethyl group (MOM) provide target compound **91** (Figure 29) [95].

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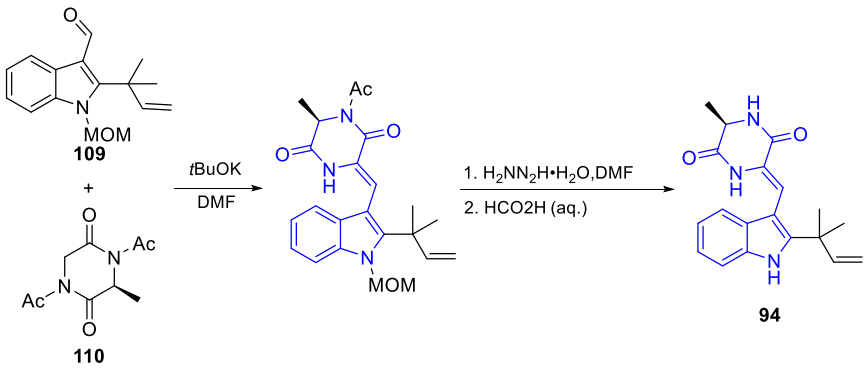

Figure 29. Scheme of the synthesis of Neochenulin A (**94**).

An example of a synthesis of a dimer of the natural product brevianamide F (**63**), aspergilazine A, it involves a selective palladium-catalyzed indole N-arylation with brevianamide F (**63**) and *N*-Boc bromo derivative **111** that gave an excellent yield of the product **112**, which upon facile deprotection gave aspergilazine A (**103**) (Figure 30) [74].

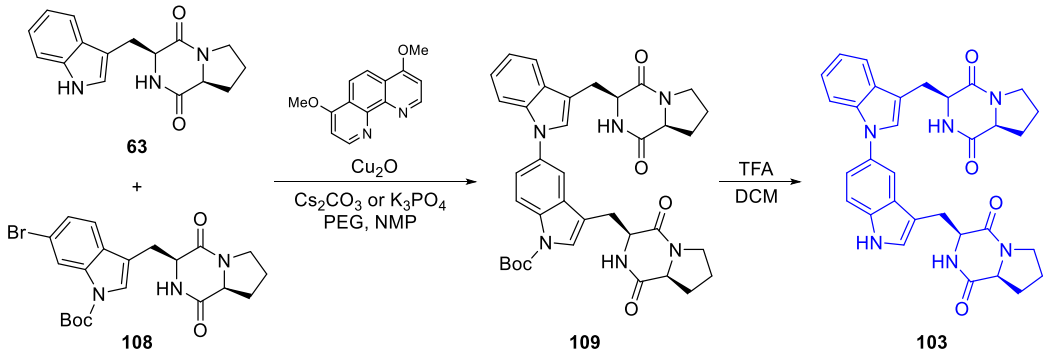

Figure 30. Scheme of the synthesis of Aspergilazine A (**103**).

2.2.1.2. DKPs featuring dimethylpyranoindole

Firstly, DKPs containing a hydropiran[3,2-*f*]indole nucleus were described. In this sense, Asperversamides (**113-116**) (Figure 31) have been extracted from the filamentous fungus *Aspergillus versicolor* collected from the mud in the South China Sea [96]. All of them containing a rare linearly fused dimethylpiranoindole. All these DKPs alkaloids exhibited potential iNOS inhibitory activities (related with anti-inflammatory activity). The best IC_{50} value was for compound **114** (5.39 μM), whose planarity was found to be important for its binding capacity to form strong hydrogen bonds with the HEME [96]. Studies of structural elucidation showed that compound **113** is a C17 epimer of Dihydrocarneamide A (**117**). This carneamide derivative and Iso-notoamide B (**118**) came from the marine derived endophytic fungus Paecilomyces variotii EN-291 and exhibited weak cytotoxic activity against NCI-H460 (IC_{50} = 69.3 and 55.9 μM, respectively) [97].

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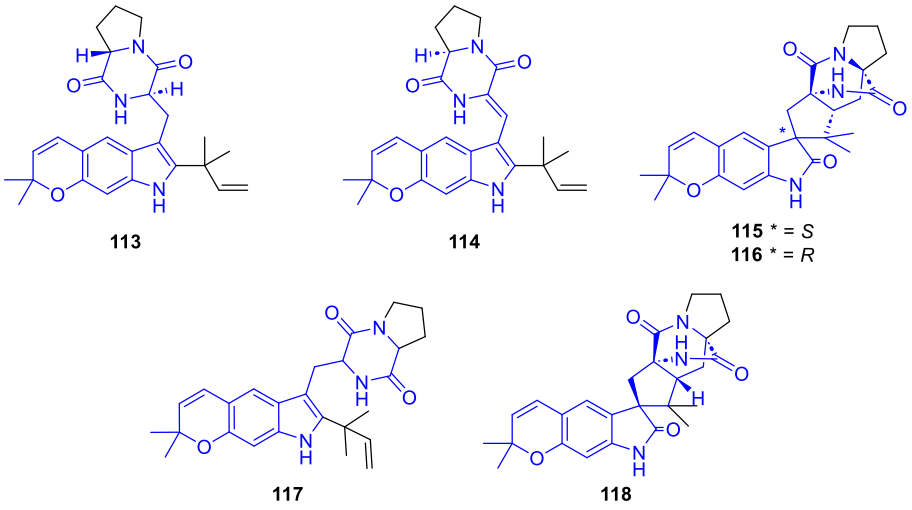

Figure 30. Structures of compounds **113-118**.

Notoamides are a wide family containing an hydropiran[3,2-*e*]indole, isolated from fungi *Aspergillus* species. Biosinthetically are related to breviamides, paraherquamides, marcfortines, sclerotiamides, asperalines, avrainvillamide and stephacidins [98,99]. The presence of a bicyclo[2.2.2]diazaoctane (Figure 32) in their structures causes that many of these alkaloids display a variety of biological activity [100]. Thus, Notoamides (**119-122**) showed moderate cytotoxicity against HeLa and L1210 cell lines (IC_{50} = 22-52 μM). Furthermore, Notoamide C (**121**) and 5-Chlorosclerotiamide (**123**) presented potent anti-fouling and antilarval settlement activity against *Bugula Neritina* [101]. Likewise, 17-O-ethylnotoamide M **(124)** did not display cytotoxicity to non-malignant HEK 293 T9 and MRC-9 cell lines, and inhibited the colony formation of 22Rv1 cells, related to resistance to hormone therapy against prostate cancer [102].

6-*epi*-Avrainvillamide (**125**) and 6-*epi*-Stephacidin A (**126**) were isolated from *Aspergillus taichungensis* and exhibited significant activities against HL-60 (IC_{50} = 4.45 and 1.88) and A549 (3.02 and 1.92) cell lines [103]. Asperthins A,F (**127, 128**), extracted of a culture of *Aspergillus sp*. YJ191021, displayed moderate anti-inflammatory activity by measuring the secretion of inflamtory factor 1L-1β by THP-1 cells [104]. Versicamide H (**129**), containing an eight-membered hexahydroazocine ring, was obtained from *A. Versicolor* HDN08-60 and showed moderate activity against HeLa, HCT-116, HL-60, K-562 cell lines and PTK inhibitory activities [105].

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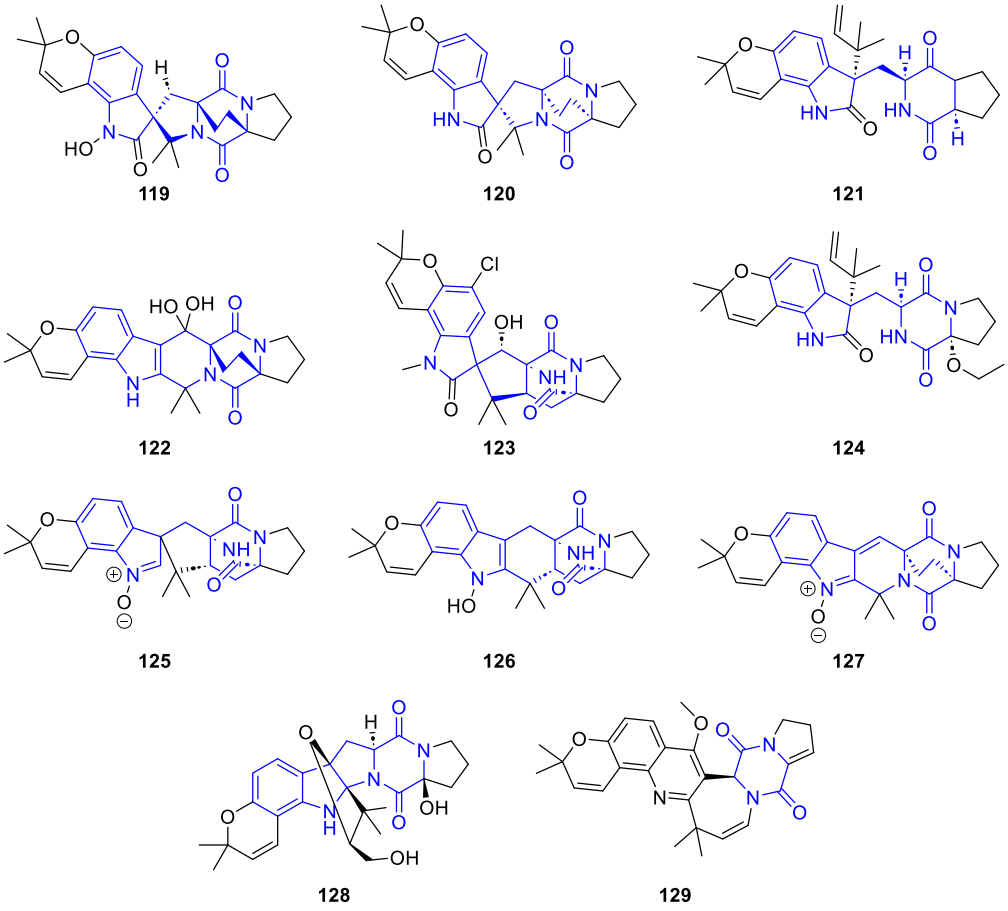

Figure 32. Structures of compounds **119-129.**

Synthesis of Brevianamides Byciclo[2.2.2]diazaoctano alkaloids

The synthetic approach to brevianamides from 1998 to 2017 has been reviewed by Lawrence *et al.* [106]. Recently these authors have developed a unified biomimetic synthetic strategy for prepare many of the known bicyclo[2.2.2]diazaoctane brevianamides (Figure 33).

The synthesis starts preparing (+)-Dehydro-deoxybreviamide E (**130**) from L-triptophan (**19**), in a five-steps gram-scale procedure. Subsequent treatment with *m*CPBA followed of exposure of the obtained dehydrobrevianamides E (**131**) to LiOH/(H_2O in water at room temperature gave the natural (+) enantiomers of Breviamide A (**132**) and B (**133**). The same procedure treating **130** with NCS and then LiOH/H_2O provide Brevianamide X (**134**) and Z (**135**).

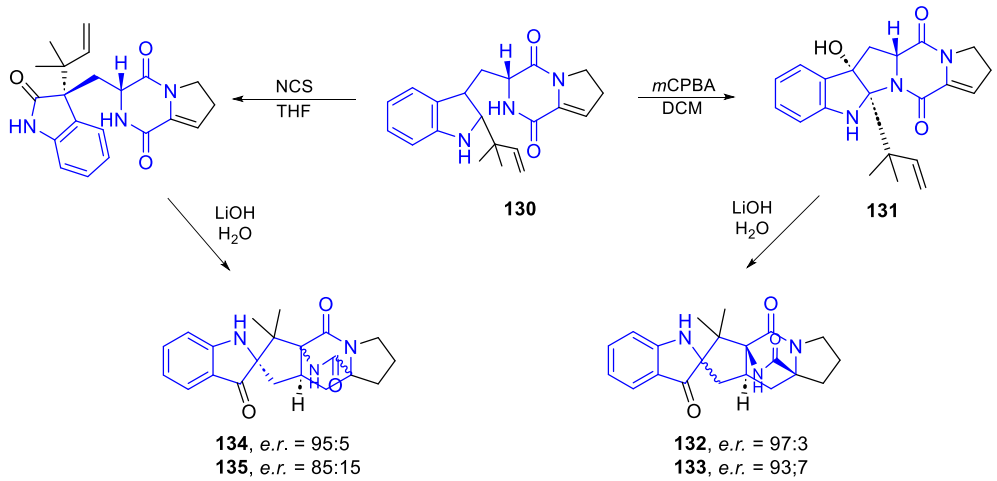

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Figure 33. Example of synthesis of breviamides **132-135.**

Synthesis general of hydropyranoindole alkaloids

The synthesis of natural products bearing a pyranoindole nucleus has been reviewed by Catalano *et al.* [107]. As seen, some marine indole alkaloids can be presented hydropyrano ring fused to the pyrrole in a linear or angular manner. In Figure 34, last step of both synthetic procedures is shown [108,109].

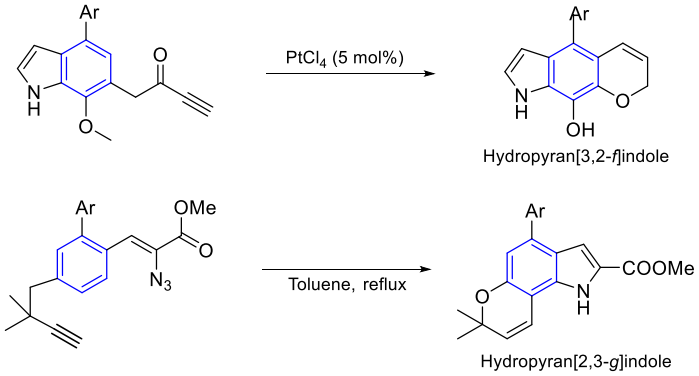

Figure 34. Synthesis of dimethyhydropiranoindole nucleus.

2.2.1.3. Spirocyclic DKP alkaloids

These prenylated indoles containing a spirocycle in their structures linked at indole or at diketopiperazine rings (Figure 35).

Eurotinoids A–C (**136-138**) were characterized from the sediment derived fungus *Eurotium* dp. SCSIO F452. All the spirocyclic alkaloids have shown significant radical scavenging activities against DPPH (IC_{50} = 3.7 -24.9 μM) [110].

Spirotryprostatin E **(139)** was isolated from the holothurian-derived fungus *Aspergillus fumigatus* and showed cytotoxicity against MOLT-4, A549, HL-60 and BEL-7420 [111].

Dihydrocriptoechinulin D **(140)** was isolated from a mangrove-derivated fungus, *Aspergillus effuses* H1-1 and showed activity against P388 and HL-60 cells lines and inhibitory activity on topoisomerase I [112].

Variecolorins A-C (**141-143**) were characterized from the sediment-derived fungus *Eurotium* sp. SCSIO F452. (+)-**141** exhibited stronger antioxidative activity than (−)-**141** against DPPH (IC_{50} = 58.4 μM and 159.2 μM respectively); while (+)-**142** and (+)-**143** showed more potent cytotoxicity against SF-268 (IC_{50} = 12.5 and 30.1 μM), and HepG2 cell lines (IC_{50} = 15.0 and 37.3 Mm). (−)-**142** and (−)-**143** were inactive (IC_{50} = >100 μM), which indicated that different enantiomers might result in different biological activities.[113]

Variecolortides A-C **(144-146)** were obtained from a halotolerant fungus Aspergillus variocolor B17 and displayed weak cytotoxicity towards the K562 human leukemia cell line [19] and showed an interesting caspase-3 inhibitory activity (associated with apoptosis cellular) [114].

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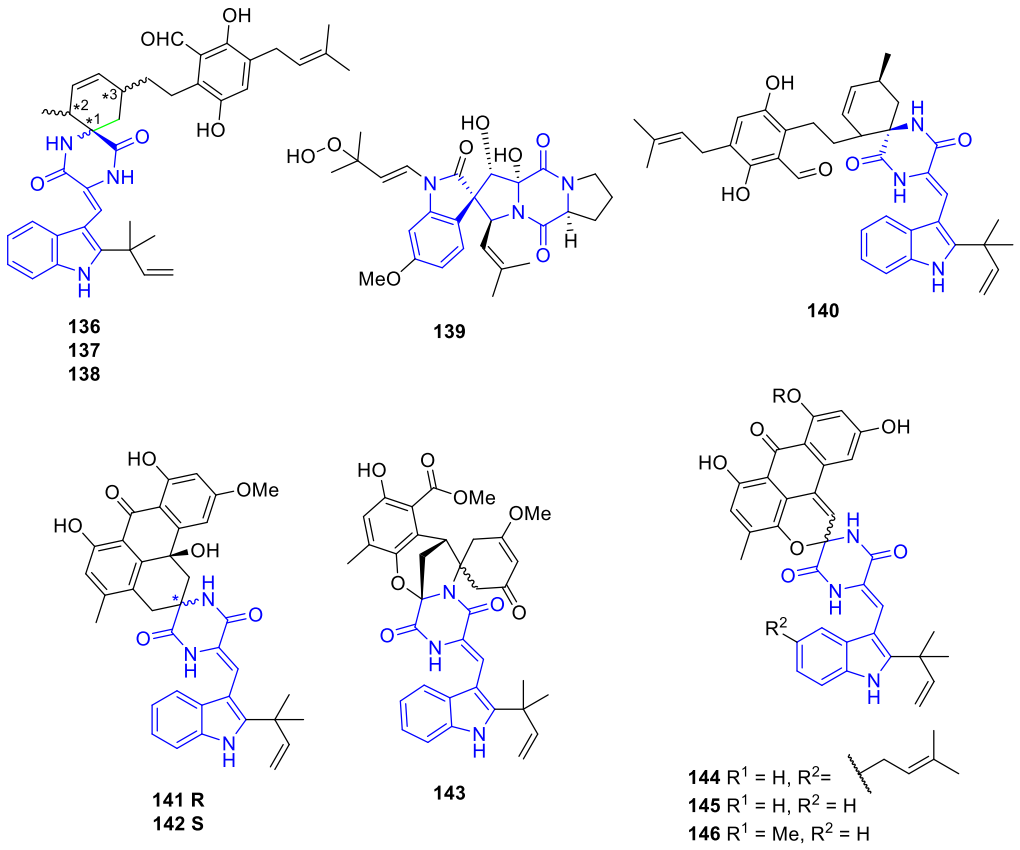

Figure 35. Structures of compounds **136-146**.

2.2.1.4. Other polycyclic DKP alkaloids

These prenylated indoles contain a variable number of cycles in their structures. They are presented below in increasing order of complexity (Figure 36).

Two Fumitremorgin B (**147,148**) derivatives were isolated from the holothurian-derived fungus *Aspergillus fumigatus* and showed similar bioactivity than Spirotryprostatin E, previously described [111]. A structural analogue, 13-*O*-Prenylverruculogen (**149**) containing a dioxazocane cycle exhibited a potent insecticidal activity against brine shrim (artemia salina) [115]. On the other hand, Prenylcycloprostratin (**150**) and 9-Hydroxifumitremorgin C (**151**) obtained from *A. fumigatus* YK-7 displayed activities towards U937 cell lines [116].

Drimentine G (**152**) isolated from marine-sediment actinomycete *Sterptomyces p.* CHQ-64, showed cytotoxic activities against HCT-8, Bel-7402, A549 and A2780 cell lines [117].

Brevicompanins (**153-158**) were isolated from the fungus *Penicilinum brevicompactum* and exhibitated anti-inflammatory activity associated with BV2 microglial cell lines [118]. Compound **153** also showed antiplasmodial activity. A structural analogue, Shornephine A (**159**) with a diketomorpholine ring was isolated from marine sediment-derived *Aspergillus sp.* (CMB-M081F), and was identified as a noncytotoxic inhibitor of P-glycoprotein associated with MDR cancer cells [119].

Okaramine S (**160**) was produced by *Aspergillus taichungensis* ZHN-7-07, isolated from the rhizosphere soil of the mangrove plant *Acrostichum aureum*. It has exhibited cytotoxic activity against HL-60 and K562 cell lines with IC_{50} values of 0.78 and 22.4 μM, respectively [120].

Deoxyisoaustamide derivatives (**161,162**), containing and eight-membered hexahydroazocine ring, were extracted of fungus *Penicillium dimorphosphorum* KMM 4689 from soft coral samples. These compounds showed neuroprotective activity against the acute toxicity of paraquat (PQ) murine neuroblastoma Neuro-2a cells [102], with no cytotoxicity towards these neuro-cells.

Raistrickindole A (**163**), containing oxindole ring was extrated from *Penicillium raistrickii* IMB17-034 and showed activity against the hepatitis C virus (HCV) with an EC_{50} value of 5.7 μM [121].

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Indotertine B (**164**) was isolated from the marine sediment-derived actinomycete *Streptomyces* sp. CHQ-64 and has exhibited cytotoxic activities against HCT-8, Bel-7402, A549, and A2780 cell lines with IC_{50} values of 2.81, 1.38, 1.01, and 2.54 μM, respectively [122].

Nocardioazine A (**165**) isolate from a marine sediment-derived bacterium, Nocardiopsis sp. (CMB-M0232) displayedd an effective and noncytotoxic inhibitor of the multidrug resistance factor P-glycoprotein, and is able to reverse resistance in SW620 Ad300 cells [124].

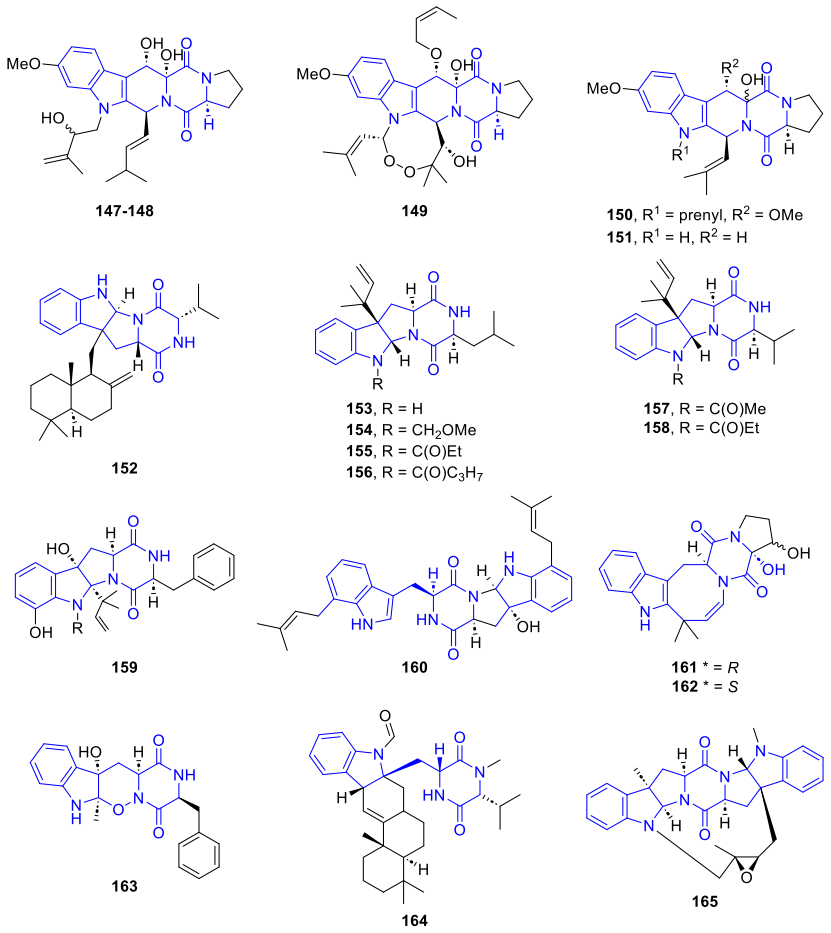

Figure 36. Structures of compounds **147-165**.

General Synthesis of indole DKP alkaloids

A general strategie for the synthesis of indole DKP alkaloids (Figure 37) has been described by *Jia et al.* [125]. Three kind of analogs of indole DKP alkaloids were synthetized: fused pentacyclic indole DKPs (**166**), trypostatin open-ring indole DKPs (**167**) and spiropentacyclic indol DKPs (**168** and **169**).

Pictet Spengler reaction of Methyl L-tryptophan hydrochloride **170** with several aldehydes lead to the corresponding chiral cyclic intermediate **171**. The subsequent reaction the **171** with F-moc-L-Pro-Cl provided **172**, which by treatment with morpholine provide the fused pentacyclic indole DKPs (**166**). When the compound **172** is treated with NBS undergoes a spiro rearreagement providing the corresponding spiro-pentacyclic indoles, which upon treatment with morpholine generates the DKPs derivatives, **166** (R = alkyl). When the substituents are aromatic, open-ring indoles (**167**) are formed. Another approach for the preparation of spiro-pentacyclic scaffold (**169**, R = aryl) explored a 1,3 dipolar cycloaddition of 2-oxoindolin-3-ylidenes with azomethine ylides, followed by the previously descrited procedure (treatment with F-moc-L-Pro-Cl and morpholine).

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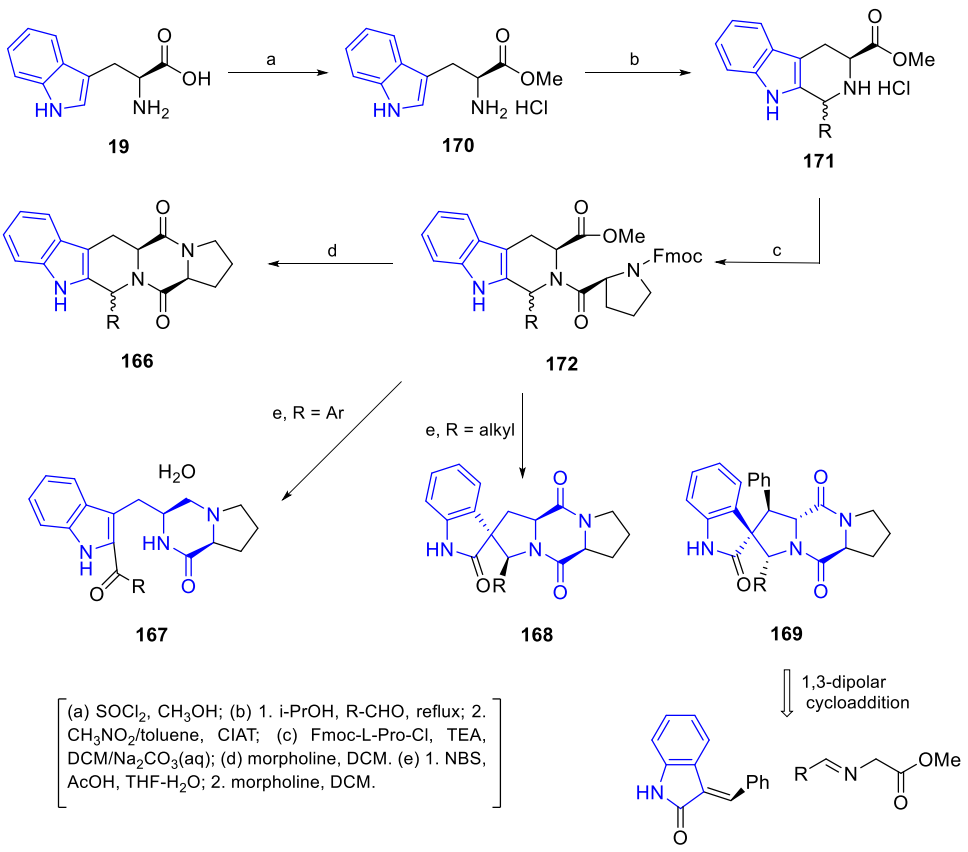

Figure 37. Synthesis of Indole diketopiperazine alkaloids.

2.2.2. HexahydroPyrrolo[2,3-b]indol (HPI) derivatives

In this kind of alkaloids, the indole group from tryptophan is fused with an additional pyrrole ring (Figure 38). Highlight a group of Flustramines isolated from the marine bryozoan Flustra foliacea [126]. The simple Flustramine C (**173**) showed activity to inhibit biofilm formation in *A. baumanniim*, a human pathogen associated with hospital acquired infections. A modification structural by adding a triazole amide moiety with a large hydrophobic chain at pyrrroloindole (**174**) increased antibiofilm activity, from IC_{50} values of 174 μM to 3.4 μM, respectively [116].

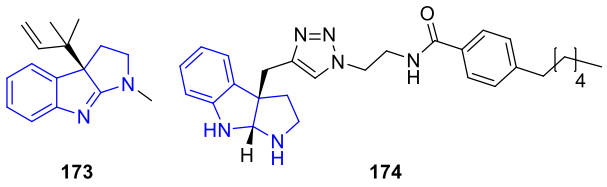

Figure 38. Structures of compounds **173** and **174**.

Synthesis of HexahydroPyrrolo[2,3-b]indol (HPI) derivatives

Several procedures have been described for the synthesis of pyrroloindole scalffold. Below, the focus is on the synthetic routes for the preparation of Flustramines (Figures 39 and 40) and on the known routes to build the HPI tricycle skeleton (Figure 41).

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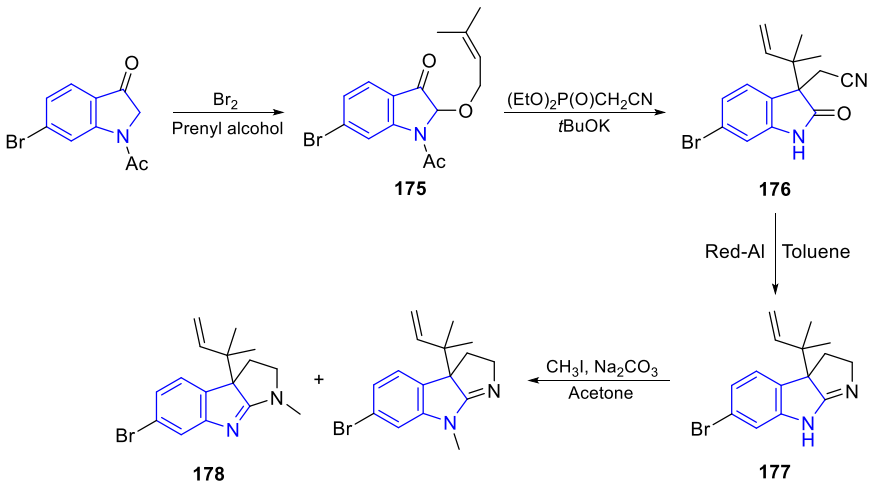

Figure 39. Classical synthesis of Flustramine C (**178**).

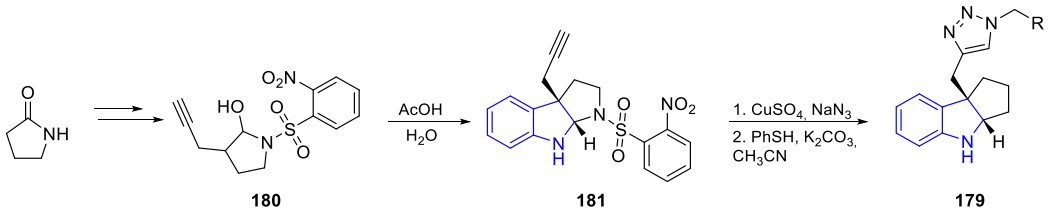

Figure 40. Synthesis of the flustramines analogues **179**.

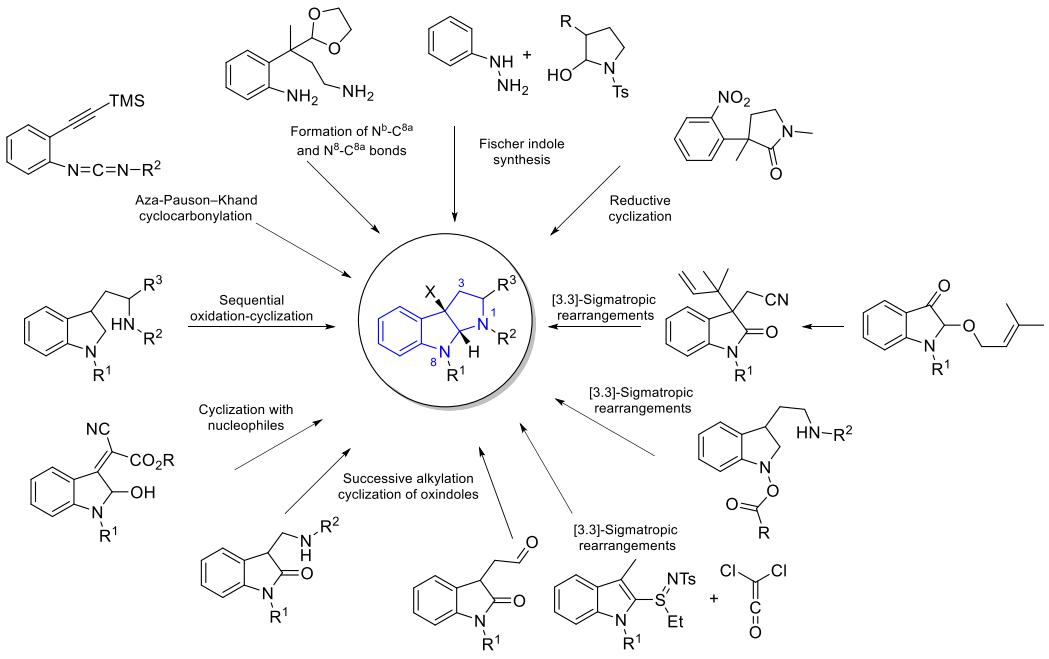

Figure 41. Synthetic routes of tricyclic HPI.

Synthesis of Flustramines

The general approach to Flustramines consists on tandem olefination, isomerization and Claisen rearrangement to provide intermediate **175**. Successive deacetylation, selective reduction of the nitrile

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group of compound **176** with subsequent cyclization leads to pyrroloindole **177**. A final methylation step furnishes Frustamine C (**178**) [34].

Bunders *et al.* [116] described and effective method to obtain Flustramine analogues **179** with a general scaffold. As indicated in Figure 40, a Fischer indolization reaction of hemiaminal **180** afforded the tricyclic core **181**. The corresponding functionalization of **181** and final deprotection provide the aforementioned product **179**.

Synthesis of HPI tricyclic skeleton

The synthesis of HPIs has been quite extensively reviewed by Albericio *et al.* [127]. Figure 41 shows the most significant synthetic routes to obtain a wide variety of HPI alkaloids derivatives, using functionalized indoles, oxidized indoles, and tryptamines as starting materials. The usually described procedures involve classic approaches by cyclization: acid-catalyzed, oxidative, reductive, alkylative and with nucleophiles. Other procedures take place by [3,3]-sigmatropic rearrangement and Fisher indolization. On the other hand, complex structures were obtained by modern procedures, including, Pd-catalyzed reactions as Larock heteroannulations or aza-Pauson-Khand cyclocarbonylation.

2.2.3. Indolactam alkaloids

Teleocidin analogues **182** and **183** were isolated from different *Streptomyces sp.*, obtained from marine sponges. The first compound **182** presented neurological activity via protein kinase C (PKC) pathway [36], while the second compound **183** exhibited cytotoxicity against HeLa and ACC-MESO-1 cell lines (Figure 42).

Pendolmycin analogues **184** and **185** were isolated from actinomycete *Marinactinospora thermotolerans* SCSIO 00652. They showed antiplasmodial activities against *Plasmodium falciparum strains* 3D7 and Dd2 [128].

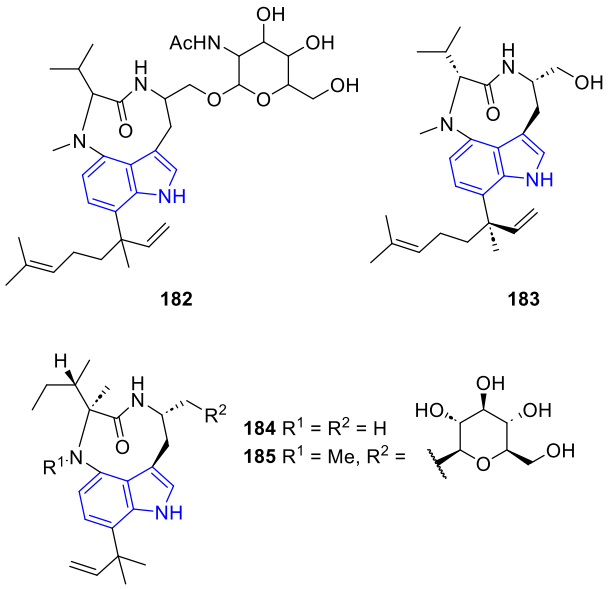

Figure 42. Structures of compounds **182-185**.

2.2.4. Other Polycyclic Indole alkaloids

Pentacyclic carbazole derivatives Xiamicyn A (**186**) and B (**187**) were isolated from different endophytic *Streptomyces sp.* Compound **187** was an anti-HIV agent [38], while compound **187** exhibited potent antibacterial properties (Figure 43) [121].

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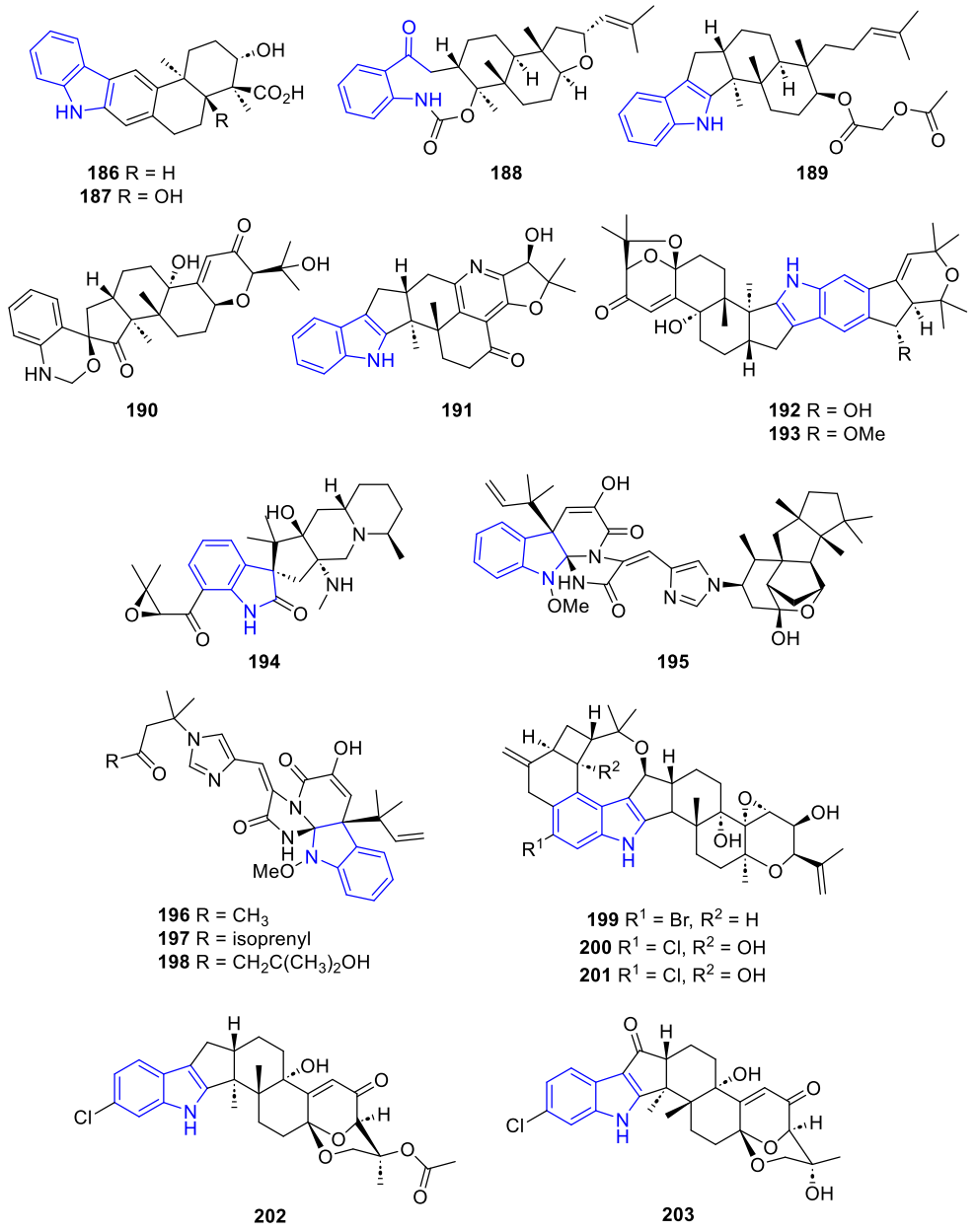

Figure 43. Structures of compounds **186-203**.

Fusaindoterpenes A (**188**) and B (**189**), extracted of a culture of *Fusarium sp.*, L1 showed an interesting antiviral activity against Zika virus with EC_{50} values of 12 and 7,5 μM, respectively. Structure-activity relationship study of these compounds revealed that the cyclopentane-pyrrole fused ring is essential for the higher antiviral activity [129].

Penerpenes A-B (**190,191**) are two indole diterpenoids obtained from *Penicillium sp.* KFD28, isolated from a bivalve mollusk. Both compounds displayed inhibitory activities against PTPs, becoming a promising target for drug discovery against diabetes [130,131].

Shearinines D and E (**192,193**) were isolated from the marine-derived strain of the fungus *Penicillium janthinellulm* Biourge [130]. Both compounds exhibited a varied bioactivity, such as induction of apoptosis in the human leukemia cell line HL-60 [130], as well as inhibition against *Candida albicans* biofilm formation [131].

Spirocyclic Citrinadin B (**194**) was extracted from *Penicillium citrinum*, obtained from a red alga, and showed cytotoxic activity against murine leukemia L1210 cells [132].

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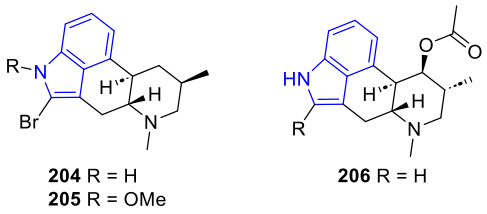
Triaza-spirocyclic Meleagrins B-E (**195-198**) were isolated from fungus *Penicillium sp.* and showed cytotoxicity against HL-60, MOLT-4, A549 and Bel-7402 cell lines. The bioactivity increases with the complexity of the Meleagrins, being lower for D,E than for B,C [133,134].

Penitrem derivatives (**199-201)** were isolated from marine-derived fungus *Penicillinum* commune and *Aspergillus nidulans* EN-330. Compound **199** showed significant anti-invasive and antiproliferative activity against MCF-7 and MDA-MB-231 tumor cell lines [135]. The other two Penitrems exhibited antimicrobial activity [136].

Asperindoles A (**202**) and Ascandinine D (**203**) are indolediterpenes with the same structural scaffold obtained from the culture of two different *Aspergillus sp.* Compound **202** exhibited toxicity against 22Rv1 (induction of cellular apoptosis), PC-3 and LnCaP prostate cancer cell lines [137]. While **203** was active against the HL-60 (promyelocytic leukemia) cell lines [138].

2.2.6. Ergot alkaloids

Pibocins A and B (**204-205**) and Fumigaclavine A (**206**) are examples of Ergot alkaloids with interesting bioactivity (Figure 44). Pibocins were isolated from ascidian *Eudistoma sp.* [139] and were found to present antimicrobial and cytotoxic effects against mouse Ehrlich carcinoma cells [139,140]. Compound **206** was extracted from fungus *Aspergillus fumigatus* [141] and induced apoptosis in MCF-7 breast cancer cells [142].



204 R = H
205 R = OMe

206 R = H

Figure 44. Structures of compounds **204-206**.

2.3. Annelated indole alkaloids

Within this subsection, alkaloids containing a single indole core fused with no prenyl derived (hetero)cyclic ring systems are disclosed (Figure 45).

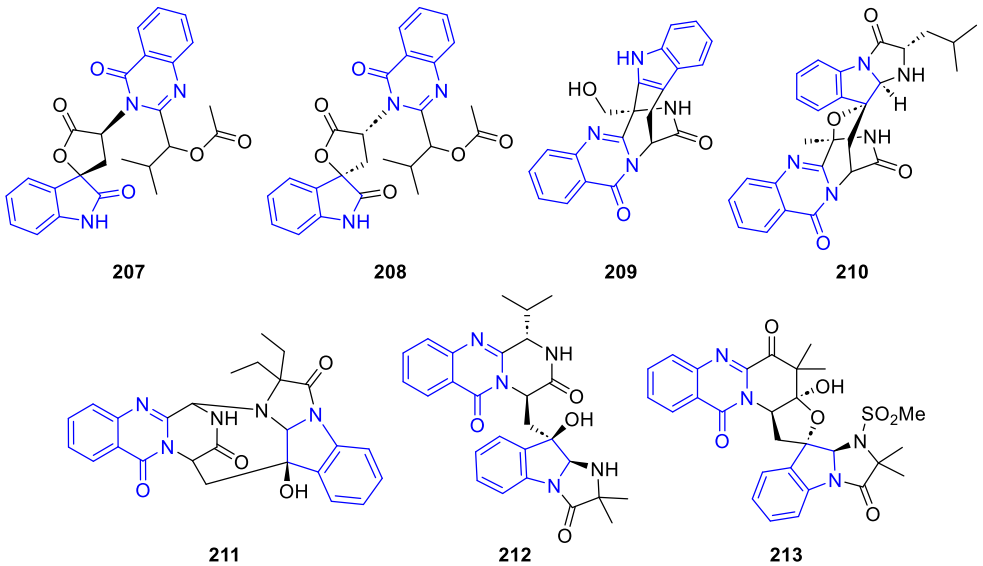


Figure 45. Structures of compounds **207-213**.

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2.3.1. Quinazoline(inone)-containing annelated indole

Aspertoryadins F and G (**207-208**) contain a 2-indolone moiety linked to a quinazolinone ring through five-membered spiro lactone. Both compounds were extracted of *Aspergillus sp*. from a bivalve mollusk. They exhibited quorum sensing (QS) inhibitory activity against *Chromobacterium violaceum* CV026, causing skin infections. These compounds prohibited bacterial pathogenicity [141].

Fumigatoside E (**209**) was obtained from *Aspergillus fumigatus* SCSIO 41012 and showed moderated to strong antibacterial and antifungal activity, with LC_{50} values of 6.25 μM against *A. baumannii* 15122 and *S. aureus* ATCC 16339, and 12.5 μM against *A. Baumannii* ATCC 19606 and *K. pneumoniae* ATCC 14578. Strong activity against *F. oxyosporum f. sp*. (LC_{50} = 1.56 μM) was also observed [143].

Fumiquinazoline J (**210**) was isolated from fungal strain *Aspergillus fumigatus* H1-04 and exhibited cytotoxicity against the cell lines ts FT210, P388, HL-60, A549 and Bel-7402 [142].

Cottoquinazoline D (**211**) obtained from marine-derived fungus *Aspergillus versicolor* was reported to show antifungal activity against *C. albicans* [144,145].

Scequinadoline A (**212**) and Scedapin C (**213**) contain an imidazoindolone ring and were isolated from extract of soft coral-associated fungus *S. apiospermum* F41-1. Both compounds displayed significant anti-HCV activity against the J8CC recombinant [146].

2.3.2. Imidazolone-containing pyrrolidinone

Securamines H and I (**214-216**) are hexacyclic annelated indole alkaloids isolated from the bryozoan *Securiflustra securifrons* that showed potent cytotoxicity against A2058, HT-29 and MCF-7 lines (Figure 46) [147].

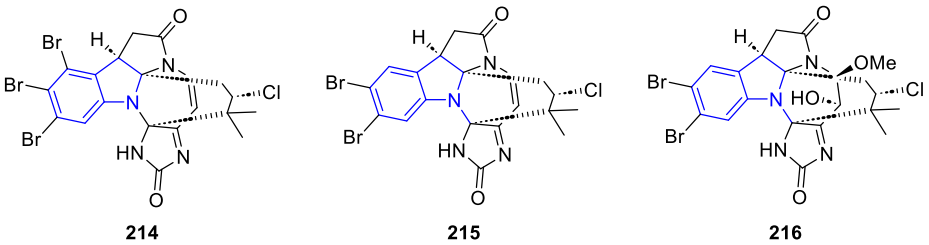

Figure 46. Structures of compounds **214-216**.

2.3.3. *β*-carbolines

β-Carboline alkaloids (*β*Cs) are a tryptophan-derived family of natural products whose basic structure derives from the tricyclic 9*H*-pyrido[3,4-*b*]indole (Figure 47). Although initially discovered in plants, a wide range of these compounds have been isolated over decades from marine sources, such as tunicates [148], sponges [149] and bryozoans [150]. *β*Cs display a wide range of outstanding biological activities and, to the best of our knowledge, several plant-isolated and synthetic representative examples, depicted in Figure 47, have been approved by the FDA and commercialized as drugs at some point: Taladafil [151] and Yohimbine [152], for treating erectile disfunction; Reserpine [153], Deserpidine [154] and Rescinnamine [155], as hypertension; Abecarnil [156], as anxiolytic; and Cipargamin [157], as antimalarial.

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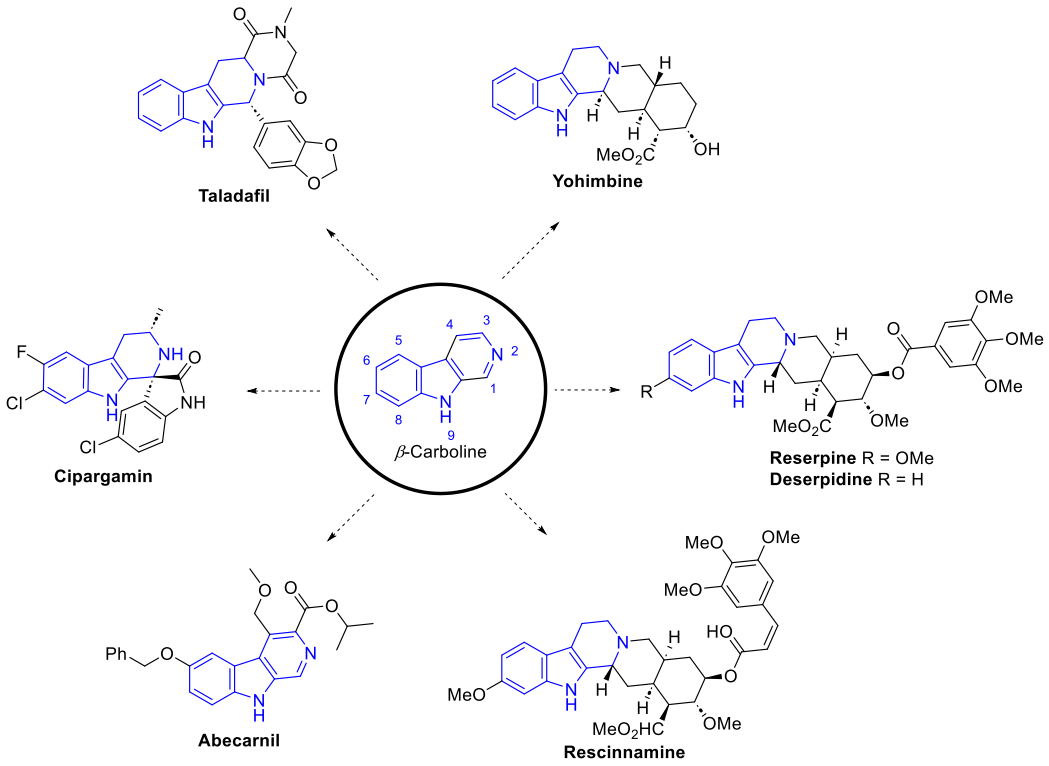

Figure 47. Representative commercialized *β*-carboline drugs.

However, no example marine-derived *β*Cs has been approved by the FDA to the best of our knowledge. This is quite surprising since, as will be showcased in the next subsections, they can exert a wide variety of biological activity, such as anticancer, antibiotic, antiplasmodial, antiinflamatory, antifungal, among others.

*β*Cs can be found in nature in monomeric or dimeric fashion [158], being the applications of the dimers closely related to their parent monomers. However, some of them do not contain the same monomer twice, but are hybrid structures with two different *β*C cores. Therefore, monomers and dimers will be disclosed in separate subsections and, attending to the absence or presence of extra fused rings in the basic *β*C skeleton, monomers will be subsequently grouped as 'simple'- and annelated-*β*Cs.

2.2.1.1. *β*-Carboline monomers

'Simple' β-Carbolines

Attending to the saturation of the indole-fused pyridine ring, these compounds can be classified as *β*-carbolines (*β*Cs), dihydro-*β*-carbolines (DH*β*Cs) and tetrahydro-*β*-carbolines (TH*β*Cs). It is worth mentioning that *N*-methyl quaternary salt of *β*-carboline alkaloids also occur in nature.

The simplest *β*-carboline, Norharmane (**217**), firstly isolated from a higher plant, can be found in different marine sponges. In 2007 Herraiz et al. showed that **217** presents possible applications against PD [159].

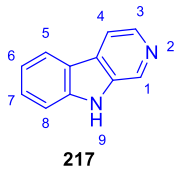

Figure 48. Structure of Norharmane **217**.

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The presence of substituents in the basic structure of βC and level of reduction of the ring lead to enhanced or new properties in comparison with **217**. The rest of the section has been structured according to the substituted position in the βC which is responsible for the therapeutic activity, trying to group them in their corresponding families and making a comparison with their reduced analogues when possible. Therefore, the following subsections will be presented: C1-subtituted-βCs, Manzamines, N2-substituted-βCs and C3-substituted-βCs. It is important to remark that although manzamines belong to C1-substituted-βCs, their specific structure and bioactivities require a separate discussion from their simpler analogues.

C1-substituted (DH/TH)-β-Carbolines:

βCs in which the C1-substitution is responsible for their therapeutic activity represent the largest family of these scaffolds. The variety of functional groups than can be found at C1 is pretty wide, ranging from simple alkyl chains or aryl groups to complex glycosides or polycycles.

Harmane (**218**) could be isolated from the culture of the marine-sponge associated fungus *Neosartorya tsunodae* KUFC 9213 [160]. Compound **218** exhibited stronger AChE and BuChE inhibition (Ic_{50} >10 μM) compared to **217** and a weak, in-vitro antileishmanial activity against *Leishmani infantum* [161]. 1-Ethyl-β-carboline (**219**), isolated from the marine bryozoan *Orthoscuticella ventricosa*, exhibited moderate antiplasmodial activity (IC_{50} = 18 μM) against *P. falciparum* K1 strain [150]. The addition of a C4-OMe to the pyridine ring (**220**) exerted detrimental effect on the activity [162]. Other βCs from the same bryozoan such as 1-Ethyl-4-methylsulfone-β-carboline (**222**), Orthoscuticelline C (**223**) and Orthoscuticelline D (**224**) had lower efficiency, indicating that the addition of C4-sulfone to the ring or hydroxy, amino or sulfonic acid groups to the alkyl chain were not beneficial [150,163].

However, Harmine (**221**), a C7-OMe analogue of **217** firstly isolated from plants but widely found in marine species, exhibited a wide range of bioactivity: antitumor, antibiotic, antifungal, antioxidant, antiplasmodial, antimutagenic, antigenotoxic, acts on gamma–aminobutyric acid type A and monoamine oxidase A or B receptor, improves insulin sensitivity, exerts vasorelaxant effect, suppress osteoclastogenesis, among others. These properties have been well documented by Patel and coworkers.[164]

Eudistalbin A (**225**), isolated from tunicate *Eudistoma album*, presented in vitro cytotoxicity (IC_{50} = 3.2 μg/mL) against KB cells.[148] Plakortamine A (**226**), isolated from the sponge *Plakortis nigra*, showed antitumor activity against HCT-116 line (IC_{50} = 3.2 μM) [149]. Both Eudistomidin C (**227**) and J (**228**), obtained from tunicate *Eudistoma glaucus*,[165] hold potent cytotoxicity against murine leukemia L1210 (IC_{50} = 0.36 and 0.047 μg/mL, respectively) [165,166], while only **228** is active also against P388 and KB cancer cells (IC_{50} = 0.043 and 0.063 μg/mL, respectively) [166]. 14-Methyleudistomidin C (**229**), from the ascidian *Eudistoma gilboverde*, demonstrated significant cytotoxicity against four different human tumor cell lines (IC_{50} < 1.0 μg/mL) [167]. Ingenine E (**230**), isolated from the sponge *Acanthostrongylophora ingens*, is strongly cytotoxic against MCF-7, HCT-116 and A549 lines [168]. It is worth to mention that although Orthoscuticelline C (**222**) is chemically similar to **215-228**, its anticancer biological activity has not been tested so far.

Opacalines A (**231**) and B (**232**), found in the ascidian *Pseudodistoma opacum*, exhibited antiplasmodial activity due to alkyl guanidine-substituted chains (IC_{50} = 2.5 and 4.5 μM, respectively) [169]. As observed, the N9-hydroxylation affects negatively to this activity. Other synthetic debromo- or THβCs derivatives of **231** and **232** were less active than the parent compounds, indicating that the Br atom plays an important role in the activity.

Eudistomins W (**233**) and X (**234**), isolated from tunicate *Eudistoma sp*., hold antifungal activity against *C. albicans* and *B. subtilis*, *S. aureus*, and *E. coli*, respectively; as well as some antibiotic properties [170].

Imidazolium-containing Gesashidine A (**235**), first isolated from a *Thorectidae* sponge, showed antibacterial activity against Micrococcus luteus but no cytotoxicity against cell line L5178Y [171]. Interestingly, the presence of a C3-carboxylate shuts down the antibacterial activity of

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Dragmacidonamine A (**236**), isolated from the same sponge, and its sulfoxide Hyrtimomine H (**237**), obtained from *Hyrtios* sponge. However, it enhances their cytotoxicity when compared to **235**.

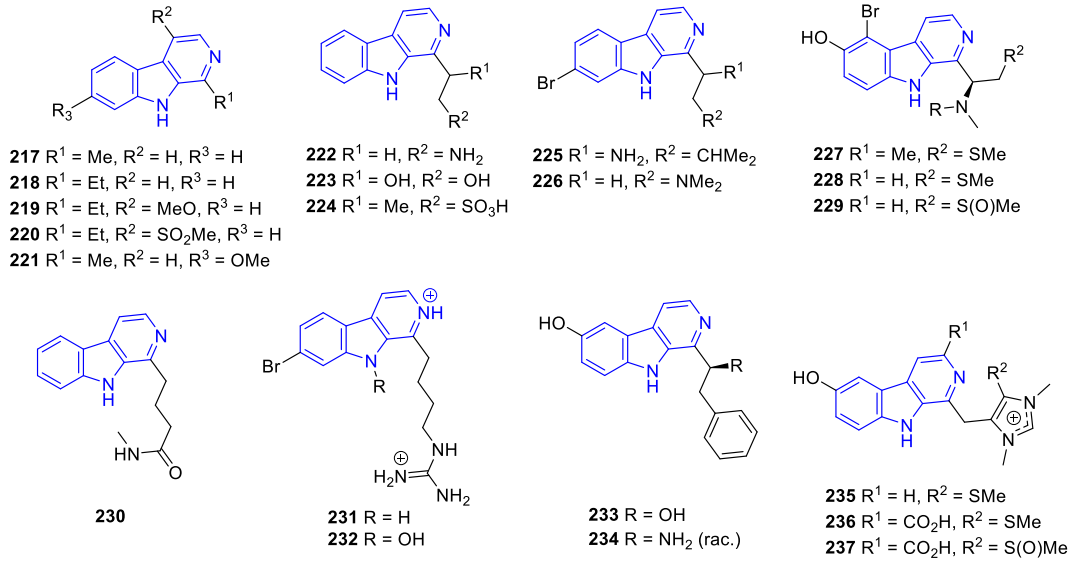

Figure 49. C1-substituted *β*C compounds **218-237**.

Reduced DH*β*C and TH*β*C analogues of compounds **218-237** (Figure 50) have similar therapeutic activity as their unsaturated counterparts. Eudistomidins B (**238**), G (**239**), H (**240**) and I (**241**), isolated from *Eudistoma glaucus*, exhibited cytotoxicity against L1210, L5178Y, P388 and KB cancer cells, although weaker than related compounds **223-237**. Ingenine F (**242**), obtained from *Acanthostrongylophora ingens*, showed similar levels of cytotoxic activity against MCF-7, HCT-116, and A549 lines as compound **230** [172]. (+)-7-Bromotrypargine (**243**), isolated from the marine sponge *Ancorina*, exerts antimalarial activity as **231**, but also weak cytotoxicity against HEK293 [173]. Haploscleridamine (**244**), isolated from *Haplisclerida* sponge, was identified as an inhibitor of cathepsin K [174]; while its C3-CO_2H analogue Hainanerectamine C (**245**), identified from *Hyrtios erecta* sponge, showed moderate anticancer activity as inhibitor of Aurora kinase A [33].

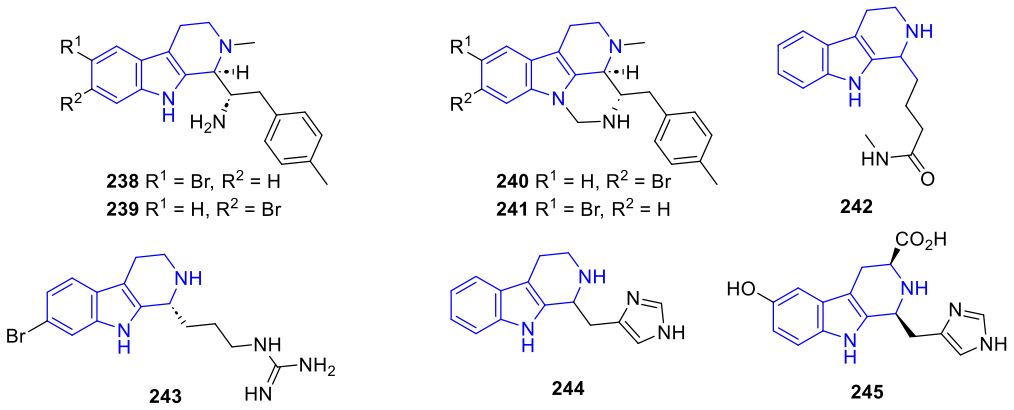

Figure 50. C1-substituted *β*C compounds **238-245**.

Hyrtimomine I (**246**) and **J** (**247**), hydroxyimidazolium *β*Cs found in *Hyrtios* sponge, exhibited antifungal activity against *A. niger* (IC_{50} = 8.0 μg/mL each) and *C. albicans* (IC_{50} = 2.0 μg/mL each), but only **246** against *C. neoform* (IC_{50} 4.0 μg/mL). However, Hyrtimomine H (**248**), from the same sponge, showed no activity, indicating that C3-CO_2H group is crucial [175]. It is worth noting that this kind of activity has not been reported so far for similar compounds **235-237**.

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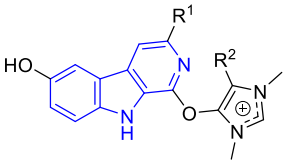
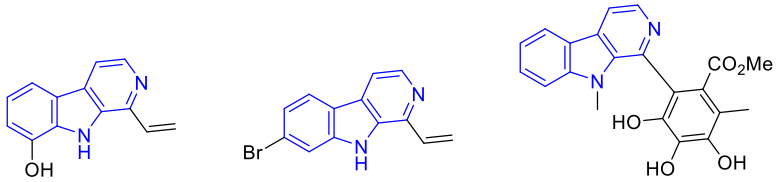


246 $R^1 = CO_2H$, $R^2 = H$
247 $R^1 = CO_2H$, $R^2 = S(O)Me$
248 $R^1 = H$, $R^2 = S(O)Me$

Figure 51. C1-substituted *β*C compounds **246-248**.

Blunt and Munro indicated that C1-vinyl groups might be beneficial for antitumor activity. 1-Vinyl-8-hydroxy-*β*-carboline (**249**), collected from bryozoan *Cribricellina cribaria* [176], and Plakortamine B (**250**), produced by the sponge *Plakortis nigra* [149], were found to be active against P388 (IC_{50} = 100 ng/mL) and HCT-116 line (IC_{50} = 3.2 μM) respectively. C1-aryl compound Chaetogline F (**251**), obtained from fish-derived fungus *Chaetomium globosum* 1C51 through biotransformation [177], represents a more promising structure for the design of anti-Alzheimer drugs [178], and presented antibiotic activity against *Veillonella parvula*, *Bacteroides vulgatus*, *Streptococcus sp.*, and *Pepto streptococcus sp.* [179]. Apart from antibiotic activities, other authors found that some synthetic C1-aryl derivatives exhibited activity against *Leishmania donovani* [180].



249 **250** **251**

Figure 52. C1-substituted *β*C compounds **249-251**.

C1-furyl-subtituted Flazin (**252**), obtained from the oyster *Crassostrea sikamea*,[181] is a promising candidate for the development of anti-HIV drugs [182]. An exhaustive SAR study carried out by Liu et al. identified the synthetic Flazinamide (**253**) as the most promising drug. Eudistomin I (**254**), isolated from *Eudistoma olivaceum* tunicate, contains a dihydropyrrole ring that confers its antibacterial effect [183–185]. Indole-substituted Eudistomin U (**255**) and Isoeudistomin U (**256**), isolated from *Lissoclinum fragile*, and their synthetic analogues, have been reported to have antibacterial, antimalarial, and anticancer properties, as extensively reviewed by Kolodina and Serdyuk [186]. Plakortamine D (**257**), a C1-isoxazolidine-substituted scaffold obtained from *Plakortis nigra* sponge, bestows antitumor activity against HCT-116 line (IC_{50} = 15 μM) [149]. Finally, Annomontine (**258**), Ingenine C (**259**) and Ingenine D (**260**), all of them bearing aminopyrimidine rings and isolated from the Indonesian sponge *Acanthostrongylophora ingens*, exhibited cytotoxic activities against MCF-7 and HCT-116 [168,187].

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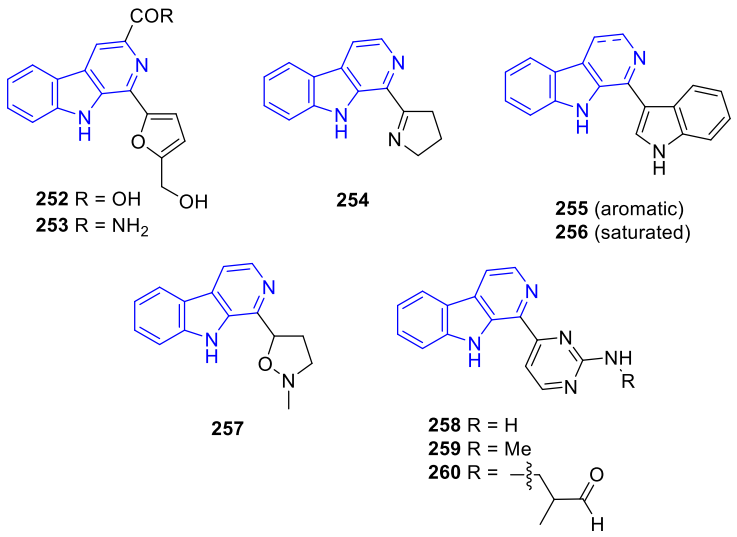

Figure 53. C1-substituted *β*C compounds **252-260**.

1-Acetyl-*β*-carboline (**261**), isolated from *Marinactinospora thermotolerans*, showed weak cytotoxicity against NCI-H460 cells (IC_{50} = 18.73 μg/mL)[188] and antibiotic properties against *S. Aureus* [189]. Eudistomidin K (**262**), from the tunicate *Eudistoma glaucus*, exhibited weak cytotoxicity against P388, L1210 and KB cells (IC_{50} > 10.0 μg/mL) [166]. Marinacarbolines A-D (**263-266**), obtained from *Marinactinospora thermotolerant*, and their synthetical derivatives, bear an additional C3-amido moiety with pendant aryl rings. Their cytotoxicity was firstly investigated in 2015 [190], but Hong and Lee have performed very recently and in-depth SAR study against ocetaxel-Resistant Triple-Negative Breast Cancer [191]. Compounds **263-266** also exhibit promising antimalarial activity [128]. Eudistalbin A (**267**), isolated from *Eudistoma album* tunicate, exerts cytotoxic activity in vitro against KB cells (IC_{50} = 3.2 μg/mL).[148] Eudistomin T (**268**), from the tunicate *Eudistoma olivaceum*, exhibited only weak phototoxicity, but also antibiotic properties [184].

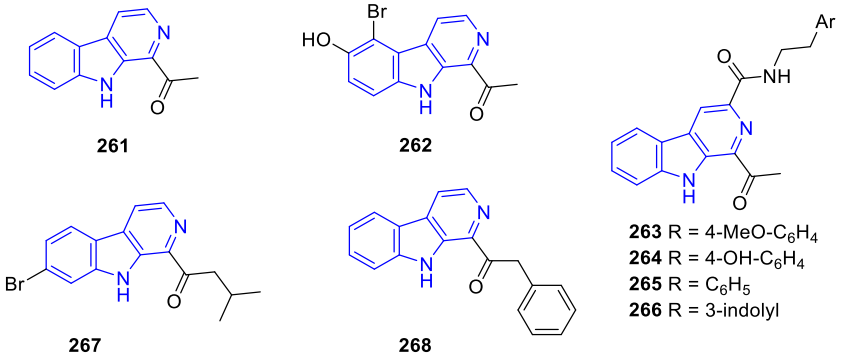

Figure 54. C1-substituted *β*C compounds **261-268**.

Eudistomin Y (**269**), isolated from *Eudistoma* tunicates, and its synthetic analogues, tend to exhibit antifungal [192] and antibiotic [192,193], but also significant cytotoxic and antiproliferative activity [192,194,195]. SAR analyses indicated that an increasing number of Br atoms in the aromatic rings increased their antibiotic effect. Reduction of the benzoyl moiety does not affect its properties, as found for Eudistomin Y_{11} (**270**).

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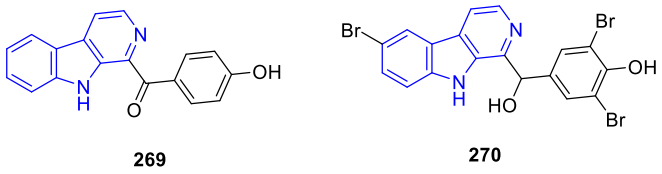
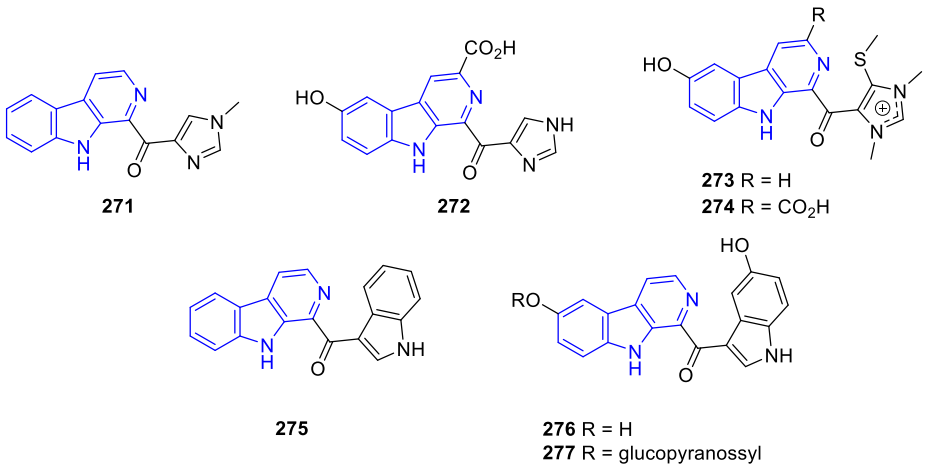


269 **270**

Figure 55. C1-substituted βC compounds **269-270**.

Xestomanzamine A (**271**), isolated from sponge *Acanthostrongylophora sp.*, presented moderate antibiotic, anti-HIV and antifungal activity, but no cytotoxicity against A594 and HCT-116 [196]. However, imidazol-containing Hyrtiocarboline (**272**), from *Hyrtios reticulatus* sponge, showed significant cytotoxicity against H522-T1, MDA-MB-435 and U937 lines (IC_{50} = 1.2, 3.0 and 1.5 μg/mL, respectively) [197]. Imidazolium-containing Hyrtiomanzamine (**273**), from *Hyrtios erecta* sponge, and Dragmacidonamine A (**274**), from *Dragmacidon* sponge, exhibited some cytotoxicity [171,197]. Also, **273** exhibited some immunosuppressive activity [198]. Indolyl-substituted Pityriacitrin (**275**), firstly isolated from a *Paracoccus* marine bacterium, exerts promising anticancer activity against MCF-7, MDA-231, and PC3 lines [199]. In-depth SAR analysis of Pityriacitrin analogues showed that C3 amide, hydrazide, hydrazones, 1,3,4-oxadiazole, 1,2,4-triazole, and pyrazole moieties are essential for potent anticancer activity [200].

Hyrtiosulawesine (**276**), found in the Indonesian sponge *Hyrtios erectus*, present a great variety of applications, such as antioxidant [201], antiphospholipase A2 [202], antidiabetic [203], anti-inflammatory [204], antimalarial [205], and cytotoxicity towards Hep-G2 line (IC_{50} = 19.3 μmol/L) [206]. 6-O-(β-glucopyranosyl)hyrtiosulawesine (**277**), from the same marine species, is only slightly cytotoxic on hepatic cells, and have antimalarial activity (IC_{50} = 5 μM).



271 **272** **273** R = H
274 R = CO_2H

275 **276** R = H
277 R = glucopyranossyl

Figure 56. C1-substituted βC compounds **271-277**.

Finally, Shishijimicin A-C (**278-280**) (Figure 57), isolated from sea squirt *Didemnum proliferum*, presents antitumor activity against P388 cells [207]. This property is attributed to the intricate conjugated en-diyne group, being **278** the most powerful enediyne-based antitumor antibiotic identified to date. Remarkably, the total synthesis of compound **278** was accomplished in 2015 by Nicolaou [208].

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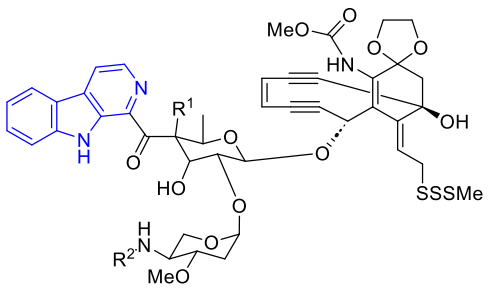

278 R^1 = SMe, R^2 = $CH(CH_3)_2$
279 R^1 = H, R^2 = $CH(CH_3)_2$
280 R^1 = SMe, R^2 = Et

Figure 57. Chemical structure of Shishijimicin A-C (**278-280**).

Manzamines:

Manzamines are a special family of C1-substituted βCs in which the C1-moiety generally consists of a characteristic complex penta- or tetracyclic system, or a monomacrocycle. Manzamine A (**281**) (also named Keramamine A) [209] was the first reported member of these compounds [210]. **281** showed a broad spectrum of biological effects: potent antileishmanial and antimycobacterial activity [211]; cytotoxicity against pancreatic cancer, P388, and human colorectal carcinoma [210,212,213]; and anti-Alzheimer activity [214]. It also exhibited antiviral effects against HSV-1, HSV-2 and HIV [211,215,216]. Compound **281** exhibited potent antitubercular activity against *M. tuberculosis* (H37Rv) [217]. 8-Hydroxymanzamine A (**282**) (also named manzamine G or manzamine K) exhibited moderate antitumor activity against KB and LoVo lines and anti-HSV-2 activity [216]. *ent*-8-Hydroxymanzamine A (**283**) is active against P388 (IC_{50} = 0.25 μg/mL) and exert in vitro antitrypanosomal effect [218]. Manzamine M (**284**) proved cytotoxicity against L1210 cells (IC_{50} = 0.3 μg/mL), and antibacterial activity against *Sarcina lutea* (MIC = 2.3 μg/mL) and *Corynebacterium xerosis* (MIC = 5.7 μg/mL) [219].

12,34-Oxamanzamine A (**285**), with a C12–C34 ether bridge, exhibited lower antimalarial and antituberculosis activity compared to the other manzamines [220]. 12,28-Oxamanzamine A (**286**) and 12,28-Oxa-8-hydroxymanzamine A (**287**), with C12-C28 or C12-C34 ether bridges, showed effective antifungal, anti-inflammatory and anti-HIV-1 activities [221].

3,4-Dihydro-6-hydroxymanzamine A (**288**) presented cytotoxicity against L1210 cells (IC_{50} = 1.4 μg/mL), and antibacterial activity against *Sarcina lutea* (MIC = 6.3μg/mL) and *Corynebacterium xerosis* (MIC = 3.1 μg/mL) [219]. *N*-Methyl-*epi*-manzamine D (**289**) and *epi*-Manzamine D (**290**) showed cytotoxicity against HeLa and B16-F10 cells [220]. 1,2,3,4-Tetrahydro-2-*N*-methyl-8-hydroxymanzamine A (**291**) (8-Hydroxy-2-*N*-methylmanzamine D) is cytotoxic toward P388 line (ED_{50} = 0.8 μg/mL) [222].

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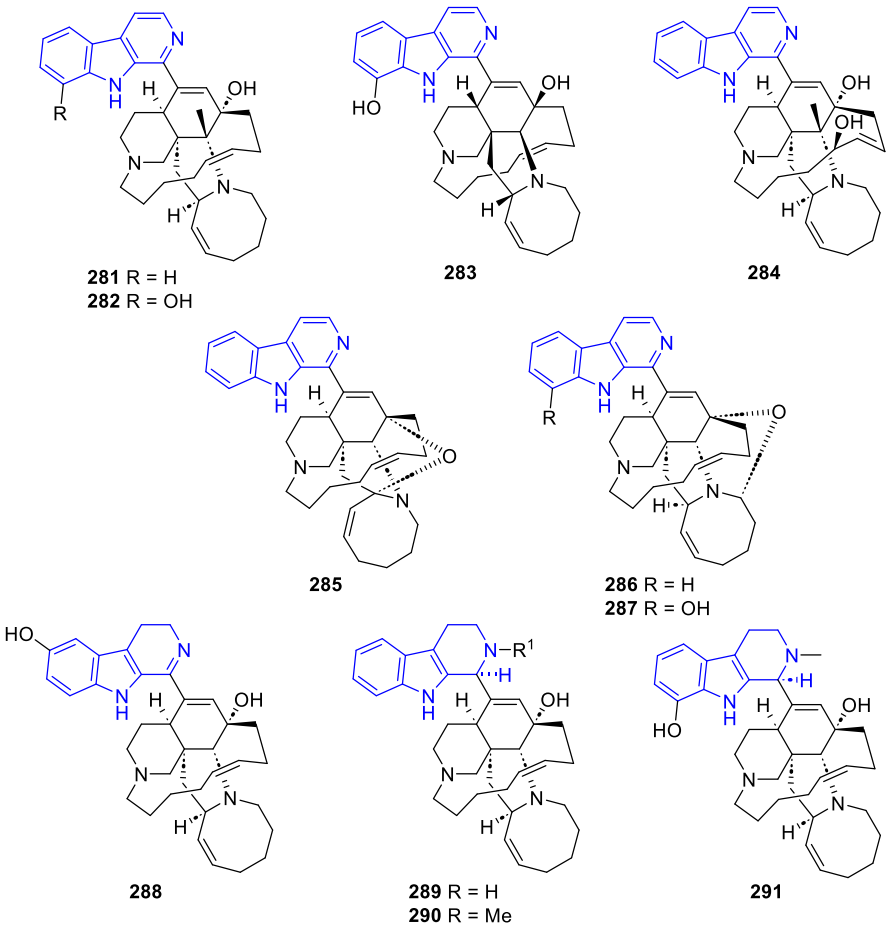

Figure 58. Chemical structures of Manzamines **281-291.**

Biologically active pentacyclic manzamines having a ketone or alcohol group in their eight-membered ring instead of a double bond have been also reported. Manzamine E (**292**) and Manzamine F (Keramamine B) (**293**) displayed cytotoxicity toward L5178Y and P388 cells [223]. *Ent*-manzanine F (**294**) inhibited H37Rv (IC_{50} < 12.5 μg/mL) [218]. *ent*-12,34-oxamanzamines E (**295**) and F (**296**) showed weak inhibitory activity against *M. tuberculosis* (IC_{50} value of 128 μg/mL) [220]. Pre-*neo*-kauluamine (**297**) exhibited proteasome inhibitory activity, potent antitrypanosomal effect and antimalarial activity [224,225].

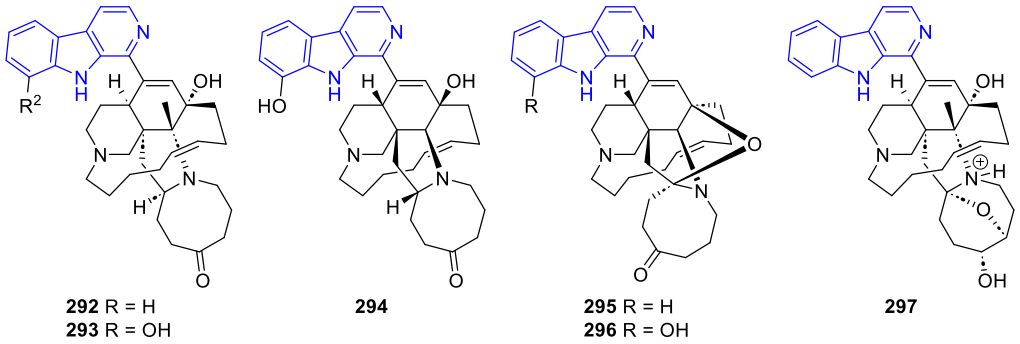

Figure 59. Chemical structures of Manzamines **292-297.**

Several biologically active manzamines containing a *β*C ring system with a C1-tetracyclic scaffold have been reported. Manzamine J (**298**) showed cytotoxic activity against KB cells (IC_{50} >10 μg/mL), while its *N*-oxide (**299**) against L1578Y (IC_{50} = 1.6 μg/mL). Additionally, **298** has anti-tubercular activity against H37Rv [217]. Manzamine B *N*-oxide (**300**) displayed weak activity against

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several Gram-positive and Gram-negative bacteria [226]. Acanthomanzamines D (**301**) and E (**302**), presented a strong proteasome inhibitory effect (IC_{50} = 0.63 and 1.5 μg/mL, respectively) [227].

Manzamines H (**303**) and L (**304**) hold cytotoxicity against KB cells (IC_{50} = 4.6 and 3.5, respectively). Compound **304** also possess weak activity antibiotic activity. [226] Ma'eganedin A (**305**), proved to be a potent antibiotic against *Sarcina lutea* and *B. subtilis* (MIC = 2.8 μg/mL each) [228].

Furthermore, 3,4-Dihydromanzamine J (**306**) and all the aforementioned manzamines **291,303-305** showed cytotoxic activity against L1210 line (IC_{50} = 5.0, 2.6, 1.3, 3.7 and 4.4 μg/mL, respectively) [217].

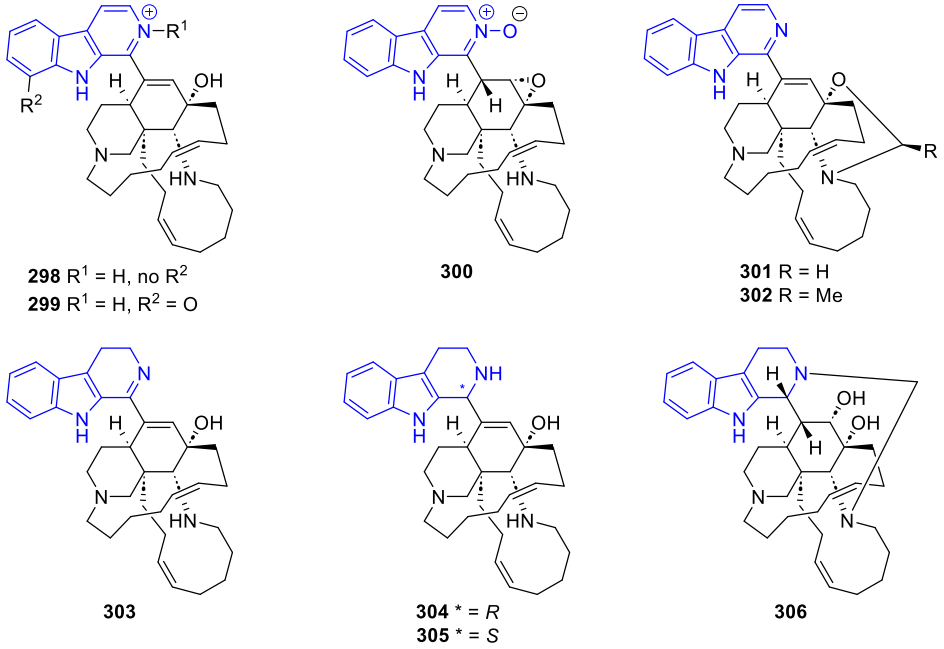

Figure 60. Chemical structures of Manzamines **298-306.**

Finally, other types of monomacrocyclic, and diverse hexa- and heptacyclic biologically active manzamines have been reported. Manzamine C (**307**) exhibited cytotoxicity against A549, HT-29 and P388 cells with (IC_{50} = 3.5, 1.5, and 2.6 μg/mL, respectively) [229]. Pyrrolizine-substituted Kepulauamine A (**308**) unveiled weak inhibition against K562 and A549 cells and is moderate antibiotic activity [226]. Manzamine X (**309**) exhibited cytotoxic activity against KB cells (IC_{50} = 7.9 μg/mL) [230], while 6-Deoxymanzamine X (**310**) against L5178 cells (ED_{50} = 1.8 μg/mL) [231]. Manadomanzamines A (**311**) and B (**312**) exhibited anti-tubercular effect (MIC = 1.9 and 1.5 μg/mL, respectively); antiviral activity against HIV-1 (EC_{50} = 7.0 and 16.5 μg/mL, respectively); cytotoxicity against A549 (IC_{50} = 2.5 μg/mL, only **311**) and HCT-116 cells (IC_{50} = 2.5 and 5.0 μg/mL, respectively); and antifungal effect against *C. albicans* (MIC = 20 μg/mL, only **312**) and *C. neoformans* (MIC = 3.5 μg/mL, only **311**) [196].

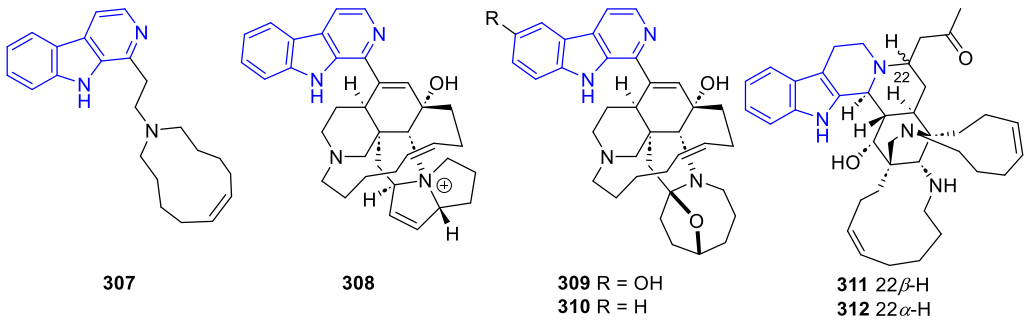

Figure 61. Chemical structures of Manzamines **307-312.**

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N2-substituted (DH/TH)β-Carbolines:

N2-methyl-*β*-carbolinium salts Irene-carbolines A (**313**) and B (**314**), isolated from ascidian *Cnemidocarpa irene*, exerted anti-Alzheimer activity [232]. Notably, other non-brominated derivatives identified in the same species didn't afford any activity.

N2-aryl-*β*-carbolinium species Reticulatol (**315**), Reticulatine (**316**) and Reticulatate (**317**) could be obtained from *Fascaplysinopsis reticulata* sponge. **316** and **317** presented modest antitumor activity, while **315** showed significant selectivity for leukemia [233].

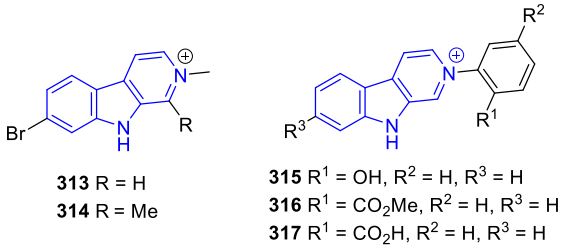

Figure 62. N2-substituted βC compounds **313-317.**

C3-substituted (DH/TH)*β*-Carbolines:

Variabines A (**318**) and B (**319**), with a C3-ester, were isolated from the sponge *Luffariealla variabilis*, have respectively little and significant effect in the inhibition of chymotrypsin-like activity of the proteasome and breast cancer metastasis [234]. Therefore, the inhibitory activities are lost by sulfonation of the 6-OH group. Stolonine C (**320**), from tunicate *Cnemidocarpa stolonifera*, induced apoptosis in PC3 line.[235] Tiruchanduramine (**321**), obtained from the ascidian *Synoicum macroglossum*, could be identified as a promising inhibitor of *α*-glucosidase due to the presence of a cyclic guanidine group [236].

C3-indole-subtituted *β*Cs have been also found in marine sources, such as the family of Hyrtioerectines isolated from the sponge *Hyrtios erectus*. Hyrtioerectine A (**322**) showed moderate cytotoxicity against HeLa cells (IC_{50} = 10 μg/mL) [237]. Hyrtioerectines D-F (**323–325**) exhibited antibacterial behavior against *C. albicans*, *S. Aureus* and *Pseudomonas aeruginosa*; antioxidant activity; and weak antitumor activity against MDA-MB-231, A549 and HT-29 lines, being **323** and **324** more active than compound **325**. Therefore, methylation of the phenol group hampers the antioxidant activity, while a C4-CO_2H moiety is more beneficial than an amido group for antitumor properties.

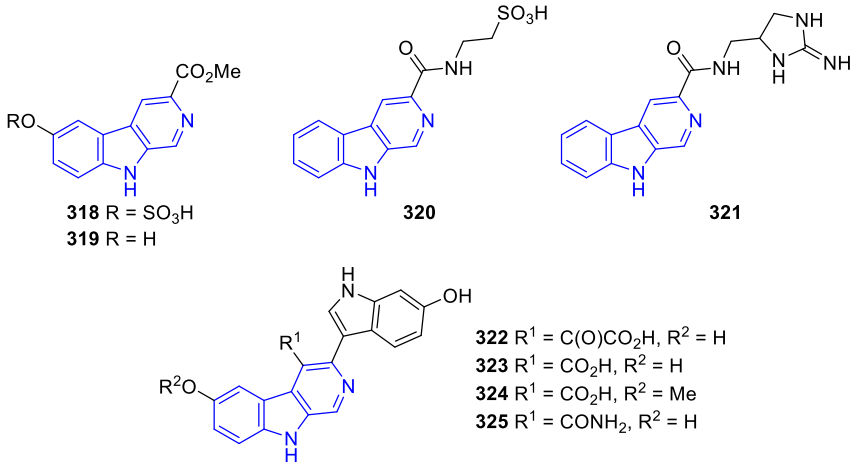

Figure 63. C3-substituted βC compounds **318-325.**

Regarding saturated carbolines, Hyrtioerectine B (**326**) prompted moderate cytotoxicity against HeLa cells (IC_{50} = 5.0 μg/mL).

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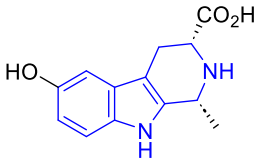


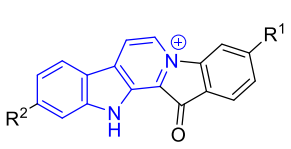
326

Figure 64. Chemical structures of Hyrtioerectine B (**326**).

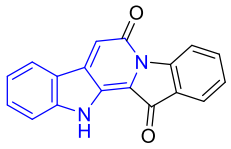
Annelated β-carbolines

Several βCs with different 5-, 6- or 7-membered fused rings in different positions have been isolated from marine sources over decades, and some of them exhibited promising activities. Fascaplysin (**327**), 3-Bromofascaplysin (**328**), 10-Bromofascaplysin (**329**), 3,10-Dibromofascaplysin (**330**), 6-Oxofascaplysin (**331**) and Homofascaplysate A (**332**) are pentacyclic compounds isolated from sponge *Fascaplysinopsis sp.* in which the βC core is fused to a 5-membered ring through C1 and N2. In general, Fascaplysin natural and synthetic derivatives represent excellent lead drugs since they exert multiple activities, namely anticancer, against Human Alveolar Rhabdomyosarcoma cells, leukemia, liver cancer cells, melanoma, small lung cancer cells, ovarian cancer cells, among others; analgesic; anti-thrombotic; anti-Alzheimer; and antimalarial [238]. Thorectandramine (**333**), from the marine sponge *Thorectandra sp*., presented weak cytotoxicity against MCF-7, OVCAR-3 and A549 cell lines (EC_{50} 27.0–55.0 μg/mL) [239].

Eudistomins C (**334**), E (**335**), K (**336**) and L (**337**), Eudistomin K sulfoxide (**338**) and Debromoeudistomin K (**339**), are tetracyclic THβC isolated from different marine ascidians, featuring a fused oxathiazepine ring between C1 and N2 responsible of their antiviral activity against HSV-1 and other DNA- or RNA-viruses [183]. Additionally, **336** presents potent antitumor activity against L1210, A549, HCT-8 and P388 lines [240].



327 R^1 = H, R^2 = H
328 R^1 = Br, R^2 = H
329 R^1 = H, R^2 = Br
330 R^1 = Br, R^2 = Br



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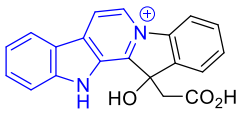

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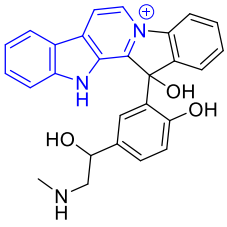

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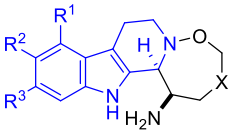

334 R^1 = H, R^2 = OH, R^3 = Br, X = S
335 R^1 = Br, R^2 = OH, R^3 = H, X = S
336 R^1 = H, R^2 = H, R^3 = Br, X = S
337 R^1 = H, R^2 = H, R^3 = Br, X = S(O)
338 R^1 = H, R^2 = H, R^3 = H, X = S
339 R^1 = H, R^2 = Br, R^3 = H, X = S

Figure 65. Annelated C1-N2 βC compounds **327-339.**

Hyrtimomines D (**340**) and E (**341**), which contain a fused D-ring between C1 and N9 forming a lactam unit, belonging to the canthin-6-ones family. Both present antifungal activity against *C. albicans* (IC_{50} = 4 and 8 μg/mL, respectively) and *C. neoformans* (IC_{50} = 4 and 8 μg/mL, respectively), but only **340** showed inhibitory activity against *T. mentagrophytes* (IC_{50} = 16 μg/mL) and *S. Aureus* (IC_{50} = 4 μg/mL). From their results, the authors inferred that the presence of a carboxylic acid is less beneficial for its antifungal properties [175].

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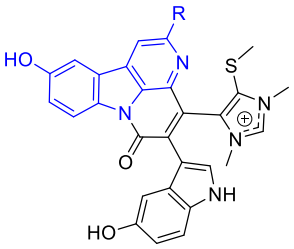

340 R = H
341 R = CO_2H

Figure 66. Annelated βC compounds **340-341.**

2.2.2.2. β-Carboline dimers

Some recent research has showcased a potential trend in which they tend to be more active than their corresponding monomer [158]. Therefore, several authors have turned to their attention to the synthesis and evaluation of these scaffolds. According to the linked positions of the βC monomers, they can be divided in 1,1-, 2,2-, 3,3-, 9,9-linked and 'hybrid' dimers, in which the two βC units are not equivalent.

However, these structures are not that commonly found in marine species compared to plants and, to the best of our knowledge, only a couple of marine-isolated or marine-inspired synthetic dimers with biological activity have been reported to date.

1,1-Linked dimers

As far as we can ascertain, only three examples of biologically active marine naturally occurring 1,1-dimers have been reported to date, varying the nature of the organic linker from simple alkyl chains to complex polycyclic structures. Orthoscuticellines A (**342**), a dimer derived from Plakortamine B (**250**) obtained from bryozoan *Orthoscuticella ventricosa*, present a 1,2-cyclobutane unit as linker. Although its *trans* dimer presented no activity, **342** demonstrated higher cytotoxicity than parent **250** and moderate antiplasmodial activity [150]. Plakortamine C (**343**), that can be regarded as Plakortamine A (**226**) dimer and was isolated from the same *Plakortis nigra* sponge, exhibited higher cytotoxic activity than **226** against HCT-116 line (IC_{50} = 2.15 mM) [149]. Finally, manzamine 1,1-dimer Neo-kauluamine (**344**), isolated from Indonesian *Acanthostrongylophora ingens* sponge, exhibited potent cytotoxic activity against H12999 (IC_{50} = 1.0 mM), proteasome inhibitory (IC_{50} = 0.13 mM) and accumulation of cholesterol esters inhibitory activities [224].

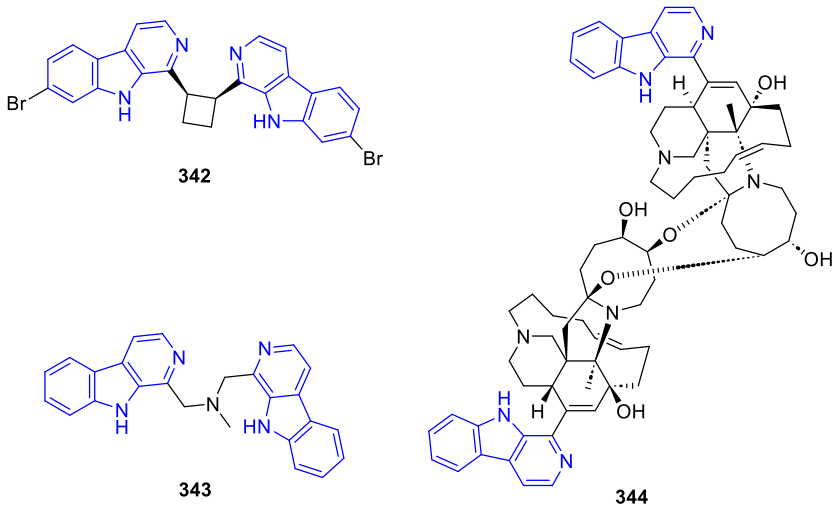

Figure 67. Naturally occurring marine βC 1,1-dimers **342-344.**

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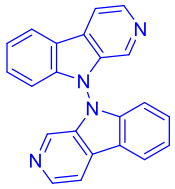
It is worth to mention that, inspired by these structures, Chatwichien et al. developed the synthesis of 1,1-dimers of simple Norharmane (**217**) linked by aminoalkylether chains [241]. Surprisingly, their biological activity against various cancer cell lines was as good as the one exerted by Neo-kualamine (**344**). Given the potential of these compounds, this area is still a hot topic of research with promising expectations.

9,9-Linked dimers

Interestingly, an N-N bonded 9,9-dimer (**345**) of Norharmane (**217**) was isolated from the *Didemnum sp.* ascidian. Although this species' antibiotic activity was diminished in comparison to **217**, other synthetic derivatives a wide application. In fact, the double N-methylated carbolinium salt was found to be more active for some strains such as *S. Aureus* [242].

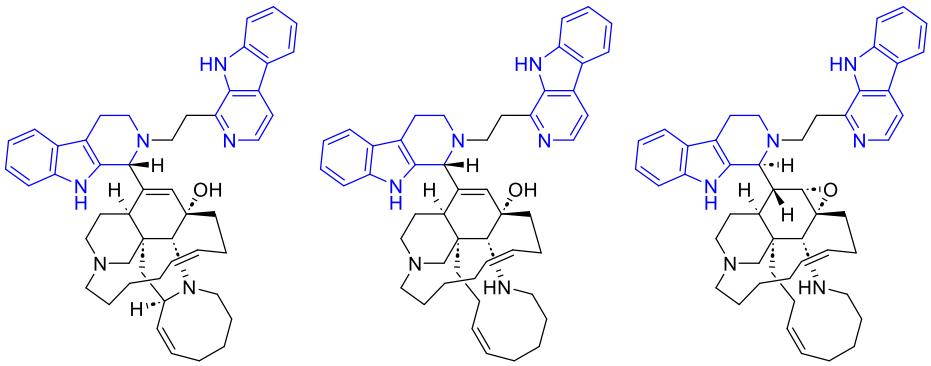


345

Figure 68. Structure of marine βC 9,9-dimer **345**.

'Hybrid' dimers

Some manzamine derivatives, in particular in the family of Zamamidines, were found to bear a second pendant βC unit, usually exhibiting N2-C1' linkage. Zamamidine C (**346**) demonstrated potent antitrypanosomal effect against *Trypanosoma brucei brucei* and antimalarial activity against *P. falciparum* [225]. Zamamidines A (**347**) and B (**348**) displayed cytotoxic activity against P388 cells (IC_{50} = 13.8 and 14.8 μg/mL, respectively) [217].



346 **347** **348**

Figure 69. Structure of manzamine hybrid-dimers **346-348**.

Finally, an interesting example of a 1,1'-hybrid manzamine dimer Kauluamine (**349**), isolated from the sponge *Prianos sp.*, revealed moderate immunosuppressive effect in a mixed lymphoma reaction [243].

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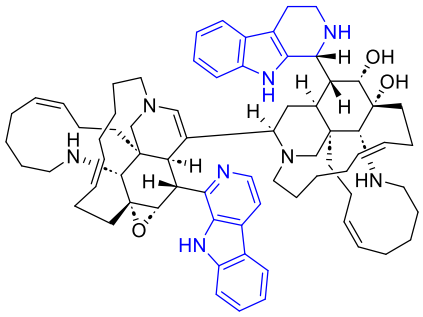

349

Figure 70. Structure of Kauluamine (**349**).

General syntheses of β-Carboline alkaloids

Within the last decade, the synthesis of *β*Cs has been quite extensively reviewed from diverse perspectives, focusing in the construction of the 9*H*-pyrido[3,4-*b*]indole [244]. Some of these authors distinguished between classical and current approaches, and a brief summary of each is provided below.

Classical routes, summarized in Figures 71 and 72, are mostly dominated by the use acid-/base-catalyzed or photochemical metal-free approaches. The most commonly exploited synthetic route for the formation of the βCs core, even nowadays, is the Pictet-Spengler reaction (Figure 71A) [245], starting from readily available trytophan derivatives and carbonyl compounds. Other variation of this method includes in situ reduction of nitriles (Figure 71B) [246]. A third variation of this methodology is the Bilschler-Napieralski reaction (Figure 71C) [247], in which amido-trypthophan derivatives are converted to electrophilic chlorimines using P_2O_5 or $POCl_3$. All this three routes yield tetrahydro-βC derivatives (THβCs), which require further oxidation steps to generate dihydro-βC (DHβC) or βCs. An important feature of Pictet-Spengler approach for the synthesis of saturated carbolines is the posibility of inducing chirality employing enantioselective aid catalysts [245].

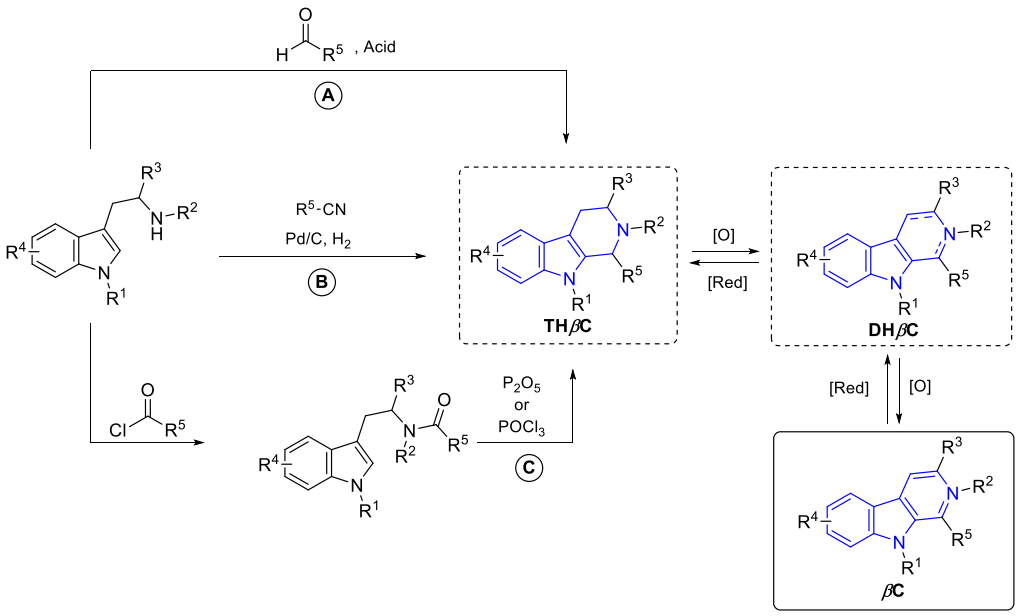

Figure 71. Most employed synthetic routes for synthesizing *β*Cs.

Other early works reported the synthesis of βCs from 3-vinylindoles (Figure 72A) [248], Diels-Alder reactions (Figure 72B) [249], Pd-catalyzed intramolecular arylation of anilinobromopyridines Figure 72C) [250], Graebe-Ullmann reactions (Figure 72D) [251], intramolecular nucleophilic

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substitutions of anilinofluoropyridines (Figure 72E) [252], and photocyclization of anilinopyridines (Figure 72F) [253]. However, some of these procedures lacked of functional group tolerance, accessing only simple βC structures.

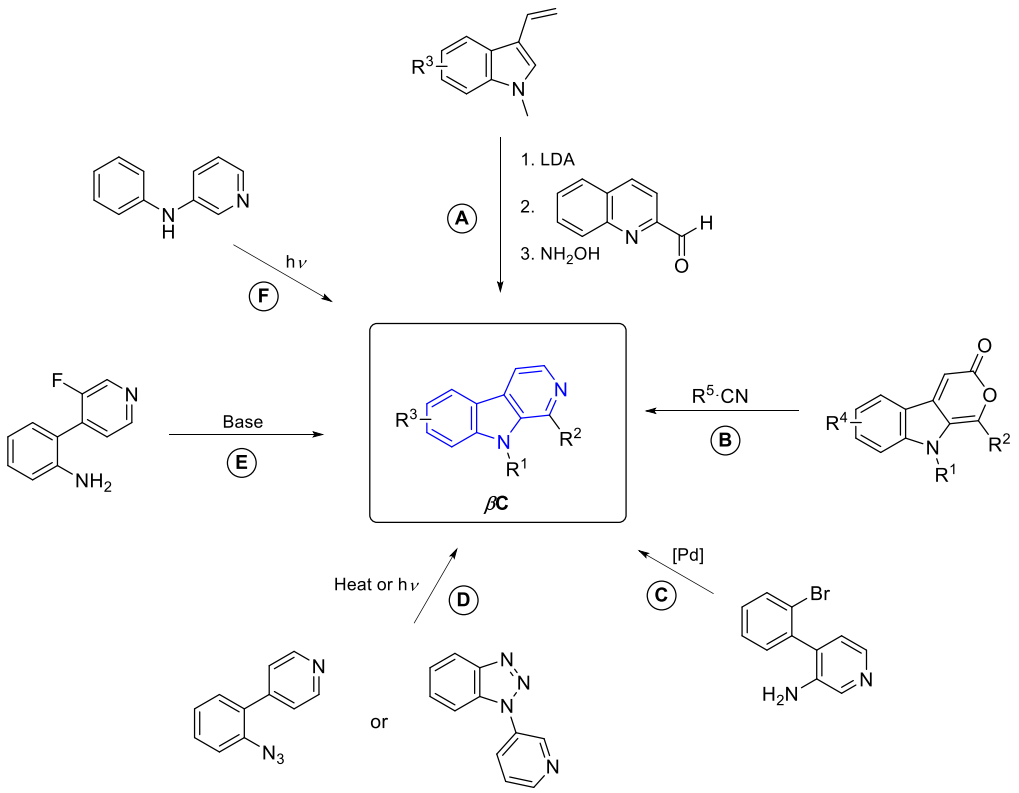

Figure 72. Other classical general synthetic routes towards the synthesis of *β*Cs.

Over the past two decades, the number or chemical tools for organic synthesis has grown exponentially and, given the promising application of βCs as drug, several new methodologies have been developed to build its azacarbazol skeleton. Mordi and Arshad performed an extensive review about these new methodologies [254], grouping them into the following cathegories: Larock heteroannulation (Figure 73A), C-H activation reactions (Figure 73B), Cycloaddition reactions (Figure 73C), 6π-Electrocyclizations (Figure 73D), Electrophilic cycloaromatization (not reported for βC so far), Cross-coupling reactions (Figure 73E), and Radical nucleophilic substitution (Scheme 3F). Summarizing all of these processes is a difficult quest, given the wide range of chemical structures that could be potential starting materials and transformations reported. Therefore, only one example of each it appears represented in Figure 73.

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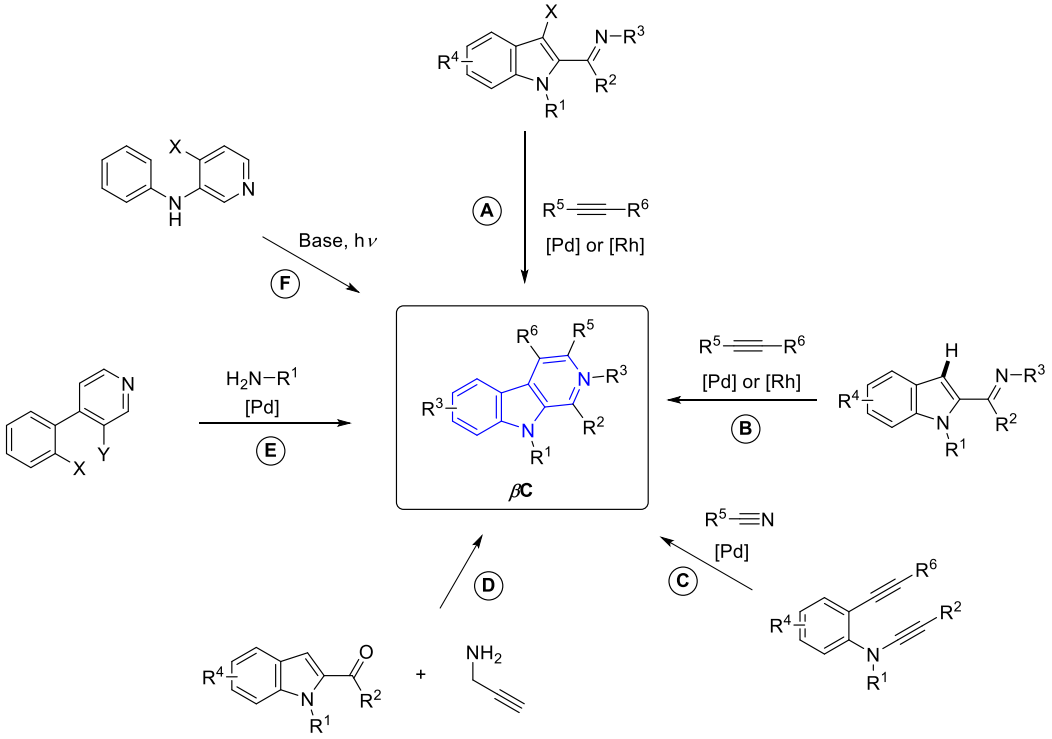


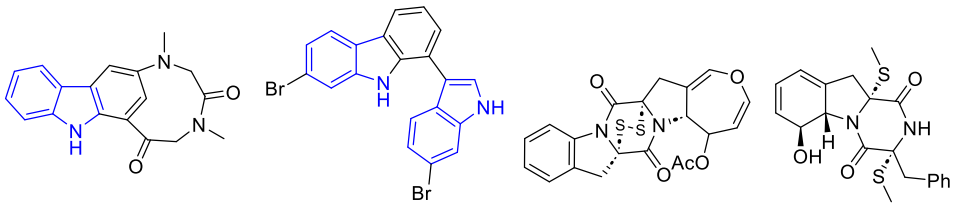
Figure 73. Representative modern approaches towards the synthesis of *β*Cs.

In this scenario, the elaboration of these scaffolds remains a hot area of research, although classical approaches are still preferred in most drug discovery programs. Notably, the development of valuable synthetic intermediates through these methodologies has allowed to also explored a great number of further derivatization processes [255].

2.3.4. Other annelated indole alkaloids

In this section some examples of annelated indole alkaloids (**350-353**) with varied structures have been included due to their cytotoxic activity against several human cancer cell lines (Table 2).

Table 2. Annelated indole alkaloids (**350-353**) and their cytotoxic activity.



350 **351** **352** **353**

Name annelated Indol	Structure	Cytotoxicity [Reference]
Antipathine A	**350**	SGC-791, Hep-G2 [256]
Indolyl-carbazole	**351**	HL-60, HeLa [257]
Deoxyapoaranotin	**352**	HCT-116 [1] [258]
Phomazine B	**353**	HL-60, HCT-116, K562, MGC-803, A549 [259] [1]

[1] Via apoptosis-inducing effects.

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3. Conclusions

Marine Indole Alkaloids comprise a wide variety of families of compounds. They originate from numerous marine organisms, such as fungi, sponges, corals and mollusk, among others. As they are compounds released in order to survive against pathogens/predators in their own natural environment, they present important biological and pharmacological properties, such as antibacterial (potentially interesting to combat resistance to hospital bacteria) and anti-cancer (to avoid the resistance that certain patients develop against certain therapies). Likewise, they have also been shown to be potentially useful for treating certain eating disorders and diabetes. The high number of marine indole alkaloids treated in this review highlights the enormous structural, chemical and biological versatility of this type of compounds, leaving an open horizon for new and interesting therapeutic applications.

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Abbreviations

Abbreviation	Meaning	Abbreviation	Meaning
5-HT	5-hydroxytryptamine receptors	HIV	Human Immunodeficiency Virus
5-HT2A	Hydroxytryptamine 2A	HL-60	Promyelocytic leukemia cell line
5-HT2C	5-Hydroxytryptamine 2C	HSV	Herpes Simplex Virus
A/WSN/33 (H1N1)	Influenza A Virus Subtype H1N1	HT-29	Human colon cancer cell line
A549	Adenocarcinomic human alveolar basal epithelial cell line	IC_{50}	Half-Maximum Inhibitory Concentration
AChE	Acetylcholinesterase	K562	Human myelogenous leukemia cell line
B16-F10	Melanoma cell line	KB	Human epithelial carcinoma cell line
βC	β-Carboline	L1210	Mouse lymphocytic leukemia cell line
BCG	Bacille Calmette-Guérin	L5178Y	Mouse lymphoma cell line
BChE	Butyrylcholinesterase	LMM3	Human Melanoma Cells
CK1◎	Casein Kinase 1 Delta	LoVo	Human colorectal cancer cell lines
CLK1	CDC-like Kinase 1	MCF-7	Human breast cancer cell line
DCE	1,2-Dicloroetane	MDA-MB-231	Human Metastatic Breast Carcinoma Cells
DCM	Dichloromethane	MDA-MB-435	Human Breast Carcinoma Cell line

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DHβC	Dihydro-*b*-Carboline	MDCK	Madin-Darby canine kidney
DKP	Diketopiperazine	MIC	Minimum Inhibitory Concentration
DMA	*N,N*-Dimethylacetamide	MRC-9	Human lung cancer cell line
DMAPP	Dimethylallyl pyrophosphate	MRSA	Methicillin-Resistant Staphylococcus aureus
DMF	*N,N*-Dimethylformamide	NCI-H460	Human non-small cell lung carcinoma cell line
DPPH	2,2-Diphenyl-1-picrylhydrazyl	NF◎B	Nuclear Factor κB
Dyrk1A	Dual-Specificity Tyrosine-Phosphorylation Regulated Kinase 1A	OVCAR-3	Human high-grade serous ovarian adenocarcinoma cell line
ED50	dose of a medication that produces the intended pharmacological effect in 50% of the patient population studied	P388	Leukemia cell line
FDA	Food and Drug Administration	PC3	Human prostatic adenocarcinoma cell line
GSK-3β	Glycogen Synthase Kinase 3 Beta	PD	Parkinson's Disease
H12999	Human non-small cell lung carcinoma cell line	PIA	Prenylated Indole Alkaloid
H37Rv	Mycobacterium tuberculosis strain	PPi	Pyrophosphate
H522-T1	human non-small cell lung cancer cell line	PTP	Protein Tyrosine Phosphatase
HCT-116	Human colon cancer cell line	RD	Human Rhabdomyosarcoma Cells
HCT-8	human colon carcinoma cell line	SIA	Simple Indole Alkaloid
HEK293	Human Embryonic Kidney cell line	THβC	Tetrahydro-*b*-Carboline
HEK293 T9	Non-malignant human kidney cell line	THF	Tetrahydrofuran
HeLa	Human Cervical Epidermoid Carcinoma Cells	U937	Human histiocytic lymphoma cell line
Hep2	Human Epithelial Carcinoma Cells	USF-HO25	University of South Florida - Human Osteosarcoma 25
Hep-G2	Human hepatocellular carcinoma cell line	UV	Ultraviolet

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