marine drugs

MDPI

Review

An Overview of Aplysinopsins: Synthesis and Biological Activities

Eslam R. El-Sawy [1,*] and Gilbert Kirsch [2,*]

[1] Chemistry of Natural Compounds Department, National Research Centre, Giza 12622, Egypt
[2] Laboratoire Lorrain de Chimie Moléculaire (L.2.C.M.), Université de Lorraine, 57050 Metz, France
* Correspondence: eslamelsawy@gmail.com (E.R.E.-S.); gilbert.kirsch@univ-lorraine.fr (G.K.); Tel.: +33-03-72-74-92-00 (G.K.); Fax: +33372749105 (G.K.)

Abstract: Marine products are among the most promising sources of biologically active molecules. Aplysinopsins, tryptophan-derived marine natural products, were isolated from different natural marine sources including sponges, stony corals (hard corals) especially genus scleractinian, as well as sea anemone, in addition to one nudibranch. Aplysinopsins were reported to be isolated from different marine organisms related to various geographic areas such as Pacific, Indonesia, Caribbean, and Mediterranean regions. This review gives an up-to-date overview of marine alkaloid aplysinopsins: their various sources, their synthesis, and the fact that many aplysinopsin derivatives are biologically active compounds.

Keywords: aplysinopsin; sources; synthesis; analogs; bioactivity

Citation: El-Sawy, E.R.; Kirsch, G. An Overview of Aplysinopsins: Synthesis and Biological Activities. *Mar. Drugs* **2023**, *21*, 268. https://doi.org/10.3390/md21050268

Academic Editors: Francisco Sarabia and Ivan Cheng-Sanchez

Received: 4 April 2023
Revised: 19 April 2023
Accepted: 24 April 2023
Published: 26 April 2023

1. Introduction

Marine organisms produce thousands of organic compounds, many of which have an exceptionally high biological activity [1]. Aplysinopsins are tryptophan-derived marine natural products [2], whose name derives from the marine sponge *Thorecta aplysinopsis*. Aplysinopsin (**1**) was firstly isolated and chemically elucidated by Kazlauskas et al. [3]. Aplysinopsins have also been purified from other sponges, including *Verongia spengelii* [4], *Dercitus* sp. [5], *Hyrtios erecta* [6], *Smenospongia aurea* [7], *Thorectandra*, *Smenospongia*, and *Verongula rigida* [8,9]. Additionally, aplysinopsins were previously isolated from mollusk, *Phestilla melanobrachia* mollusk [10], and corals such as *Tubastrea coccinea* [10], *Tubastraea aurea* [11], *Dendrophyllia* sp. [12], *Tubastraea faulkneri* [13], and *Thorectandra* sp. [14].

Aplysinopsins possess an array of biological activities, such as, antimalarial [15,16], antimicrobial [16,17], monoamine oxidase (MAO) inhibitor [18], anti-depressant [19], and antiviral [20]. Recently, it has been shown that aplysinopsins act as a blood–brain barrier permeable scaffold for anti-cholinesterase and anti-BACE-1 activity (beta-site amyloid-precursor protein-cleaving enzyme 1) [21]. Additionally, aplysinopsin and its derivatives were found to possess significant anticancer activity against several cancer cell lines, including multidrug resistance (MDR) cell lines, leukemia, and breast, colon, and uterine cancer cell lines [22,23]. This review gives an up-to-date overview of marine alkaloid aplysinopsins: their origin, isolation sources, synthesis, analogs, and bioactivity.

2. Different Sources and Chemical Structures of Aplysinopsins

The chemical backbone of the natural aplysinopsins include a simple configuration of monomeric aplysinopsin-type structures and their brominated derivatives at the A ring, variation in the structure of the C ring, the presence and configuration of the C-8-C-1′ double bond, the oxidation state of the 2-aminoimidazoline fragment and *N*-alkylated at the B ring (Figure 1), in addition to the aplysinopsin dimers form.

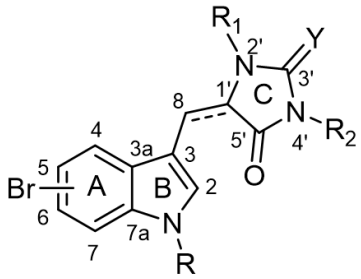
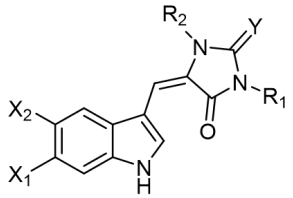


Figure 1. The chemical configuration of monomeric aplysinopsin-type structures shows detailed segmentation of the rings, carbon numbering, and type of bonds.

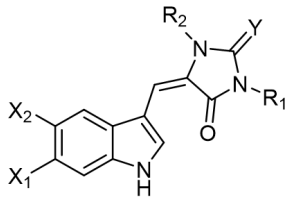
Aplysinopsin, (*E*)-5-((1*H*-indol-3-yl)methylene)-2-imino-1,3-dimethylimidazo-li-din-4-one (**1**), was first isolated from the sponge genus *Thorecta* of the Australian Great Barrier Reef by Kazlauskas et al. [3]. Sequentially, aplysinopsin and its derivatives have been reported in many other marine organisms from various geographic areas (Tables 1–4) [2].

Table 1. Monomeric aplysinopsin-type structures and their brominated derivatives.



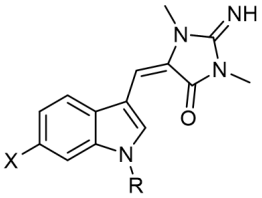
Aplysinopsin Derivatives	X_1	X_2	R_1	R_2	Y	Source [Ref.]
Aplysinopsin (**1**)	H	H	Me	Me	NH	*Thorecta sp.* sponge Great Barrier Reef Australia [3], *Verongia spengelli* sponge Florida Keys [4], *Dercitus* sp. sponge Caribbean [5], *Smenospongia aurea* sponge Caribbean [24], *Astroides calycularis* anthozoan Mediterranean [25], *Tubastraea aurea* Japan scleractinian coral [11], *Tubastraea* sp. scleractinian coral Philippines [12], *Radianthus kuekenthali* sea anemone Japan [26], *Aplysina* sp. sponge Japan [27], *Tubastraea faulkneri* scleractinian coral Australia [13], *Tubastraea* sp. scleractinian Japane [14], *Smenospongia* sp. sponge Indo-Pacific reefs [8], and *Verongula rigida* sponge Florida Keys [9].
Isoaplysinopsin (**2**)	H	H	H	Me	NMe	*Aplysina* sp. sponge Japan [27] and *Smenospongia aurea* sponge Jamaica [7].
2′-de-*N*-methylaplysinopsin (**3**)	H	H	H	Me	H	*Dercitus* sp. sponge Caribbean [5], *Tubastrea coccinea* coral Hawaii [10], *Phestilla melanobrachia* mollusk [10], *Dendrophyllia* sp. scleractinian coral Philippines [12], *Smenospongia aurea* sponge Jamaica [7], *Verongula rigida* sponge Florida Keys [9].
Methylaplysinopsin (**4**)	H	H	Me	Me	NMe	*Aplysinopsis reticulata* sponge Australia [2] and *Smenospongia aurea* sponge Jamaica [7].
4′-Demethyl-3′-N-methylaplysinopsin (**5**)	H	H	Me	H	NMe	*Dendrophyllia* sp. scleractinian coral Philippines [12] and *Smenospongia aurea* sponge Jamaica [7].
N-3′-ethyl-aplysinopsin (**6**)	H	H	Me	Et	NMe	*Smenospongia aurea* sponge Jamaica [7].
3′-Deimino-2′,4′-bis(demethyl)-3′-oxo-aplysinopsin (**7**)	H	H	H	H	O	*Leptopsammia pruvoti* scleractinian coral France [12].

Table 1. *Cont.*



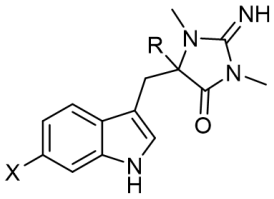
Aplysinopsin Derivatives	X_1	X_2	R_1	R_2	Y	Source [Ref.]
3′-Deimino-3′oxoaplysinopsin (**8**)	H	H	Me	Me	O	*Thorecta* sp. sponge Great Barrier Reef Australia [3] and *Tubastraea* sp. scleractinian coral Philippines [12].
6-Bromo-2′-de-*N*-methylaplysinopsin (**9**)	Br	H	Me	H	NH	*Dercitus* sp. sponge Caribbean [5], *Tubastrea coccinea* coral Hawaii [10], *Phestilla melanobrachia* mollusk [10], *Dendrophyllia* sp. scleractinian coral Philippines [12], *Tubastraea faulkneri* scleractinian coral Australia [13], *Smenospongia aurea* sponge Jamaica [7], *Hyrtios erecta* sponge Japan [6].
6-Bromoaplysinopsin (**10**)	Br	H	Me	Me	NH	*Tubastrea coccinea* coral Hawaii [10], *Smenospongia aurea* sponge Caribbean [24], *Astroides calycularis* anthozoan Mediterranean [25], *Radianthus kuekenthali* sea anemone Japan [26], *Tubastraea faulkneri* scleractinian coral Australia [13], *Smenospongia aurea* sponge Jamaica [7], *Smenospongia aurea* sponge Florida Keys [9].
6-Bromo-4′-de-*N*-methylaplysinopsin (**11**)	Br	H	H	Me	NH	*Smenospongia aurea* sponge Caribbean [24].
6-Bromo-4′-demethyl-3′-*N*-methyl-aplysinopsin (**12**)	Br	H	H	Me	NMe	*Dendrophyllia* sp. scleractinian coral Philippines [12].
5,6-Dibromo-2′-demethylaplysinopsin (**13**)	Br	Br	Me	H	NH	*Hyrtios erecta* sponge Japan [6].
6-Bromo-3′-deimino-2′,4′-bis(demethyl)-3′-Oxoaplysinopsin (**14**)	Br	H	H	H	O	*Smenospongia aurea* sponge Caribbean [28] and *Leptopsammia pruvoti* scleractinian coral France [12].
6-Bromo-3′-deimino-3′-oxoaplysinopsin (**15**)	Br	H	Me	Me	O	*Astroides calycularis* anthozoan Mediterranean [25] and *Tubastraea* sp. scleractinian coral Philippines [12].

Table 2. Aplysinopsins substituted at the nitrogen atom.



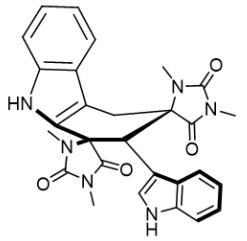
Aplysinopsin Derivatives	X	R	Sources [Ref.]
N-propionylaplysinopsin (**16**)	H	$OCCH_2CH_3$	*Astroides calycularis* anthozoan Mediterranean [25].
6-Bromo-*N*-propionylaplysinopsin (**17**)	Br	$OCCH_2CH_3$	
N-methylaplysinopsin (**18**)	H	CH_3	*Aplysina* sp. sponge Japan [27].

Table 3. Aplysinopsins with a single C-8-C-1′ bond.

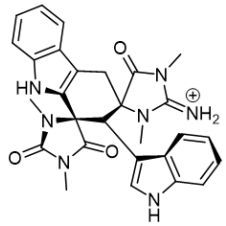


Aplysinopsin Derivatives	R	X	Sources [Ref.]
1′,8-Dihydroaplysinopsin (**19**)	H	H	*Tubastrea coccinea* coral Hawaii [10], *Radianthus kuekenthali* sea anemone Japan [26], and *Thorectandra* sp. sponge Indo-Pacific reefs [8].
6-Bromo-1′,8-dihydroaplysinopsin (**20**)	Br	H	
6-Bromo-1-hydroxy-1′,8-dihydroaplysinopsin (**21**)	Br	OH	*Thorectandra* sp. sponge Indo-Pacific reefs [8].
6-Bromo-1-methoxy-1′,8-dihydroaplysinopsin (**22**)	Br	OCH_3	
6-Bromo-1-ethoxy-1′,8-dihydroaplysinopsin (**23**)	Br	OCH_2CH_3	

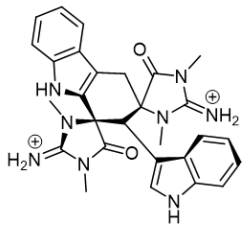
Table 4. Aplysinopsin dimers.



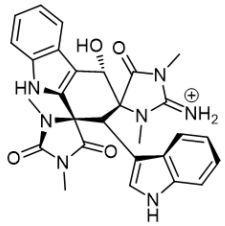
Cycloaplysinopsin A (**24**)



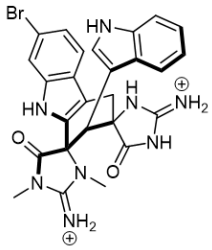
Tubastrindole C (**25**)



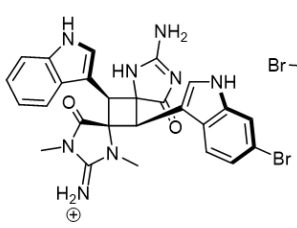
Tubastrindole B (**26**)



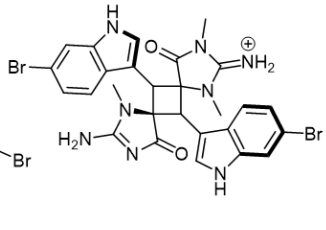
Tubastrindole E (**27**)



Dictazolines C (**28**)



dictazole A (**29a**)



dictazole B (**29b**)

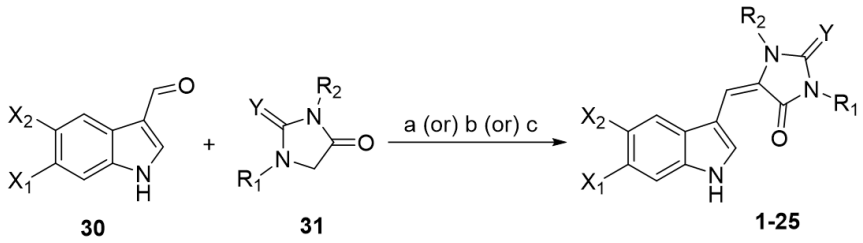
Aplysinopsin Dimers	Sources [Ref.]
Cycloaplysinopsin (**24**)	Scleractinian corals of the family Dendrophylliidae from Comoro islands and hard coral *Tubastraea* sp., from the Great Hanish in the Archipelago of the Hanish Islands, Yemen, tropical Indo-Pacific (Comoros, Philippines) scleractinian corals of the family Dendrophylliidae [29,30].
Tubastrindoles A–C (**25**)	Stony Coral, *Tubastraea* sp. scleractinian Japane [14].
Tubastrindole B (**26**)	Australian Marine Sponge, a specimen of the sponge *Ianthella* cf. *flabelliformis* [31].
Tubastrindoles D–H (**27**)	Stony Coral, *Tubastraea aurea* Odomari area, Kagoshima Prefecture, Japan [32].
Dictazolines A and B	Marine Sponge *Smenospongia cerebriformis*, Hospital Point on Solarte Isle, Boca del Toro, on the northwest coast of Panama [33].
Dictazolines C–E (**28**) and Dictazoles A and B (**29**)	Marine Sponge *Smenospongia cerebriformis*, Panamanian sponge [34].

3. Synthesis

The simple chemical structures of aplysinopsin motivated many researchers to prepare aplysinopsin-type structures in order to enrich various analogs and to study their activity besides the mode of action via their structure–activity relationships. Several synthetic approaches towards aplysinopsin-type structures have been reported.

The synthetic approaches toward the preparation of monomeric aplysinopsin-type structures involve the condensation reaction of the appropriate 3-formylindole **30** with a

five-membered ring **31**, an imidazolidinone, by fusion [5,25] or boiling in acetic acid in the presence of sodium acetate [24] or boiling in piperidine [35] (Scheme 1).



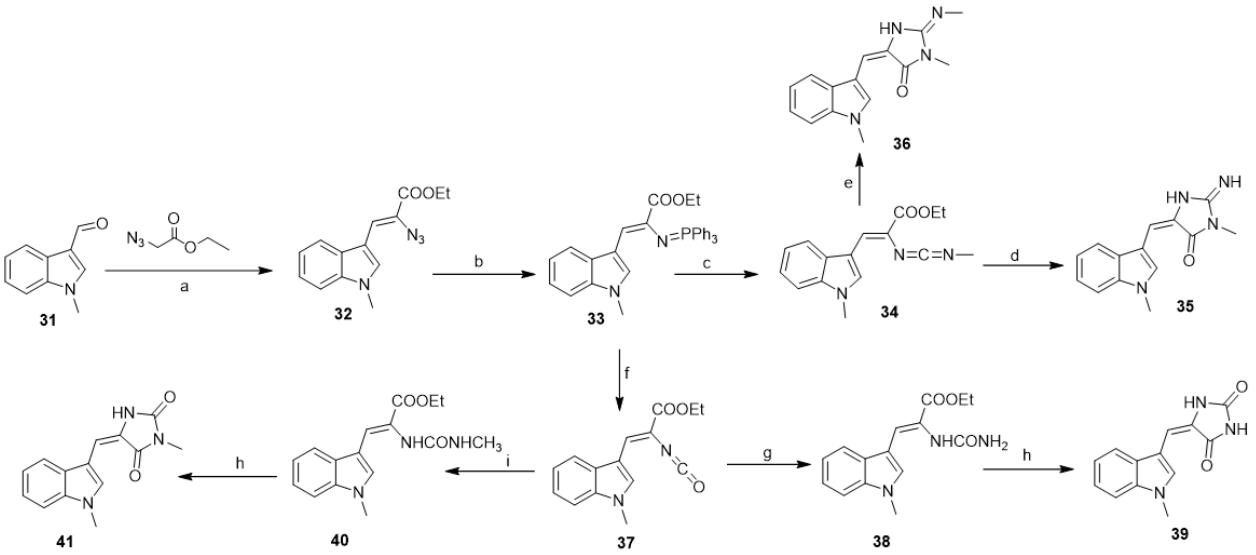
Scheme 1. General procedure for the preparation of monomeric aplysinopsin-type structures. Reagents and conditions: (a) fusion; (b) AcOH, sodium acetate, boiling; (**c**) piperidine, boiling.

Molina et al. developed a simple and general entry to aplysinopsin alkaloids by tandem aza-Wittig/heterocumulene-mediated annelation [36]. Thus, ethyl 2-azido-3-(1-methylindol-3-yl)prop-2-enoate (**32**), available from 3-formyl-1-methyl indole (**31**) and ethyl azidoacetate, reacts with triphenylphosphine in dry dichloromethane to give the iminophosphorane (**33**). Compound (**33**), on the reaction with methyl isocyanate at room temperature, gave the carbodiimide (**34**). The reaction of (**34**) with ammonium acetate in acetonitrile afforded (**35**) in a 40% yield, while the reaction of (**34**) with methylamine in toluene at 45 °C afforded 2′-demethyl-3′-methylaplysinopsin (**36**) (Scheme 2). On the other hand, the reaction of (**33**) with carbon dioxide in dry toluene at 90 °C afforded the isocyanate (**37**) in a 80% yield. The reaction of the isocyanate (**37**) with ammonium acetate in acetonitrile at room temperature afforded the urea derivative (**38**) (78%), which undergoes cyclization using acetic anhydride and provided the 3′-deimino-2′,4′-bis(demethyl)-3′-oxo aplysinopsin (**39**) in a 50% yield. Similarly, compound (**37**), by the reaction with methylamine and further cyclization by the action of acetic anhydride, led to the formation of (**41**) in a 50% overall yield (Scheme 2).

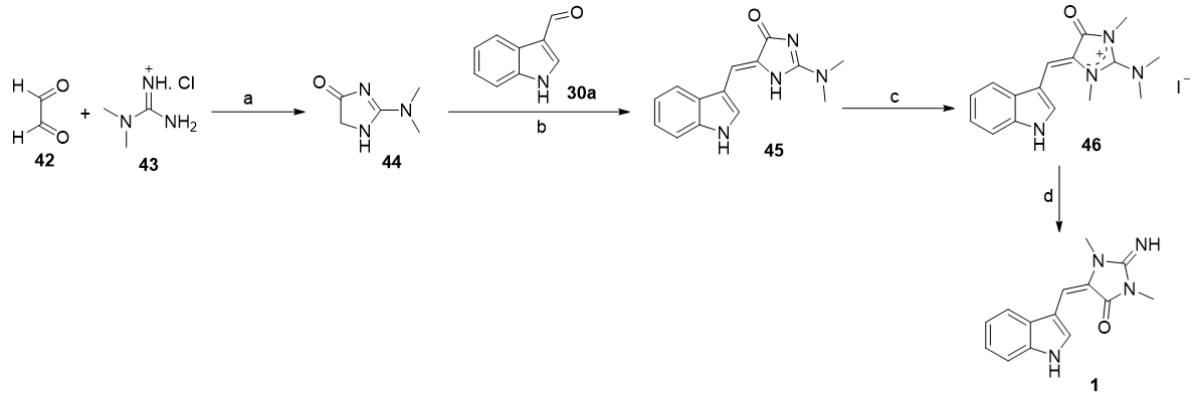
Poisson et al. reported an alternative method to prepare aplysinopsin (**1**) (Scheme 3) [37]. In detail, the reaction of dimethyl guanidine hydrochloride (**43**) with glyoxal (**42**) afforded the corresponding 2-(dimethylamino)-1,5-dihydro-4*H*-imidazol-4-one (**44**). The base catalyzed reaction of (**44**) with indole-3-carboxaldehyde (**30a**) yielded (*Z*)-5-((1*H*-indol-3-yl)methylene)-2-(dimethylamino)-1,5-dihydro-4*H*-imidazol-4-one (**45**). The methylation of (**45**) with methyl iodide, followed by basic hydrolysis using KOH (1N), provided aplysinopsin (**1**) (Scheme 3) [37].

Skiredj et al. reported the synthesis of dictazole B (**29b**), an example of aplysinopsin dimers, as shown in Scheme 4 [38]. After several trials and reaction optimization, Skiredj et al. reached the best route to obtain dictazole B via irradiation with artificial sunlight of the three monomers **1**, **10**, and **47**, in the presence of bismuth(III) triflate ($Bi(OTf)_3$) (Scheme 4).

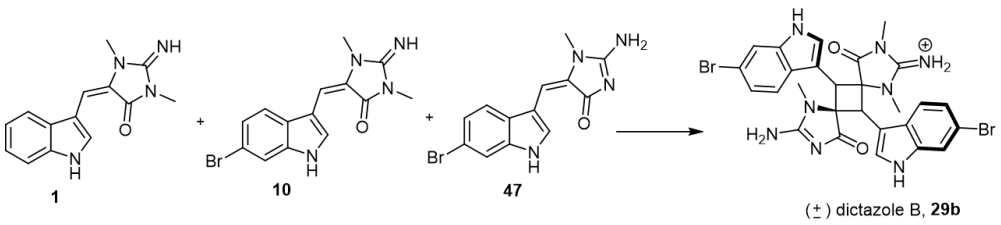
Additionally, in 2014 and 2015, Skiredj et al. reported the total synthesis of the cycloaplysinopsin-type, tubastrindole B (**26**) (Scheme 5), via a ring-expansion cascade of a dictazole-type precursor [39,40]. In detail, the cyclobutane (**48**) was produced by photochemical [2 + 2] homodimerization of aplysinopsin (**1**). Two minor compounds, **49** and **50**, have been isolated in addition to compound **48**. Compound (**48**) has been isolated by HPLC with a 16% yield to be involved in the next step. The ring-expansion of compound (**48**) in water with TFA under heating for 85 s and under microwave irradiation gave tubastrindole B (**26**) with a 40% yield (Scheme 5).



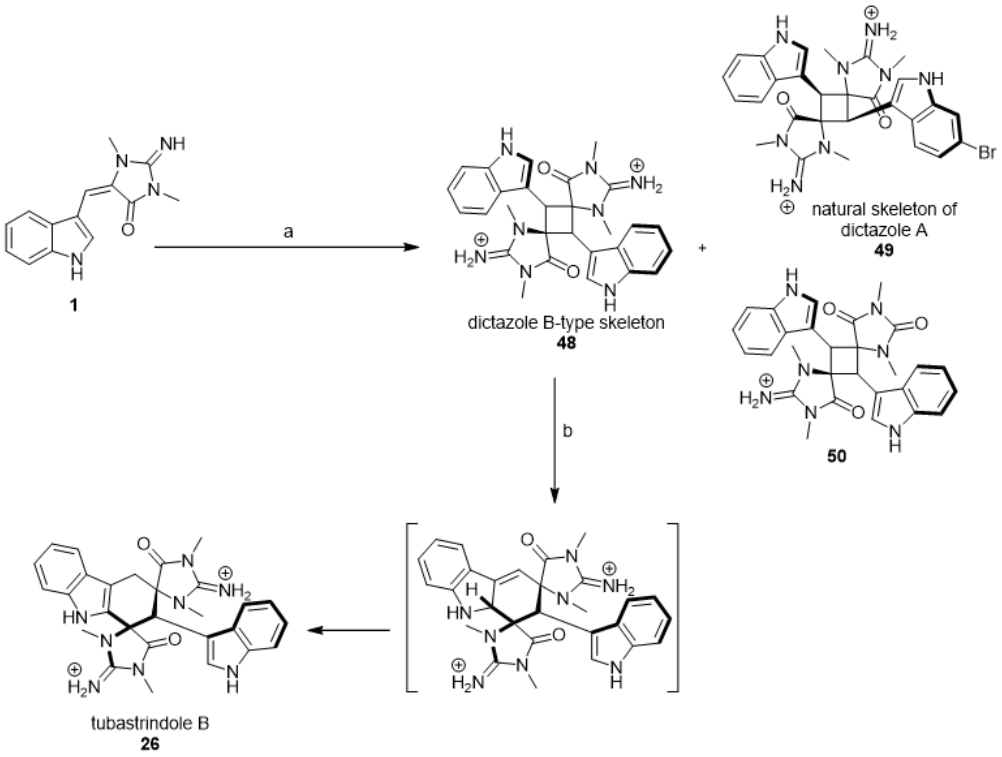
Scheme 2. Aplysinopsin-type alkaloids by tandem aza-Wittig/heterocumulene-mediated annelation. Reagents and conditions: (a) ethanol, piperidine, reflux; (b) Ph_3P, CH_2C1_2, 0 °C; (c) methylisocyanate, toluene, N_2, rt, 35 h; (d) CH_3COONH_4, CH_3CN, 45 °C, 14 h; (e) methylamine, toluene, 45 °C, 14 h; (f) CO_2, dry toluene, 90 °C; (g) CH_3COONH_4, CH_3CN, room temperature (rt); (h) Ac_2O, reflux; (i) methylamine, CH_3CN, rt.



Scheme 3. Synthesis of aplysinopsin (**1**) from dimethyl guanidine hydrochloride. Reagents and conditions: (a) H_2O, reflux, 8 h; (b) piperidine, reflux, 2 h; (c) MeI, DMF, rt, 48 h; (d) KOH (1N), EtOH, reflux, 2 h.

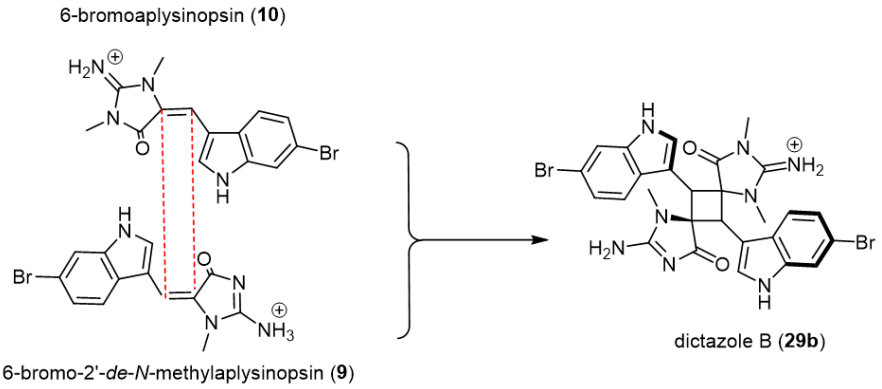


Scheme 4. Synthesis of dictazole B (**29b**). Reagents and conditions: DMF, *hν*, 10 (1 equiv.), 47 (1 equiv.), $Bi(OTf)_3$ (1 equiv.), 14 h, 14% yield.



Scheme 5. Synthesis of (±)-tubastrindole B (**26**) via biosynthetically relevant precursors. Reagent and conditions: (a) light 14 h, 0.5 equiv., CuOTf-toluene complex, DMF; (b) MW, 110 °C, 85 s, TFA, H_2O.

In advanced research for the same research team, Skiredj and his group [41] have developed an unprecedented DNA-templated [2 + 2] photodimerization process for synthesizing spiro-fused cyclobutane-containing compounds including the natural heterodimer dictazole B (**29b**) (Scheme 6).

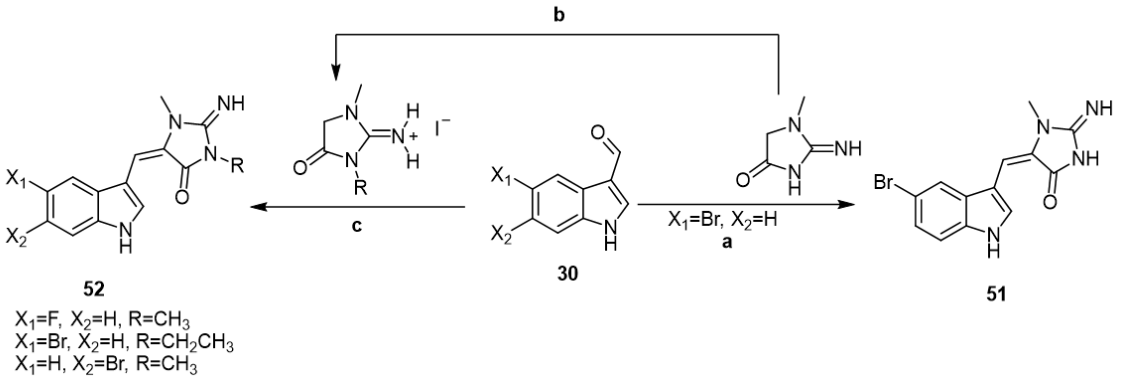


Scheme 6. DNA-templated [2 + 2] photodimerization process for synthesizing dictazole B (**28**). Reagents and conditions: *hν* (λ = 280–315 nm), st-DNA, MOPS buffer/DMSO (3:1), pH 6.5.

The method was developed based on the dimerization of (*E*)-aplysinopsin (**1**), which was previously shown to be unproductive in solution [39]. Upon this developed technique, exposure of 6-bromo-2′-*de*-*N*-methylaplysinopsin (**9**) and 6-bromoaplysinopsin (**10**), tryptophan-derived olefin, to light in the presence of salmon testes DNA (st-DNA) reproducibly afforded the corresponding homo-dimerized spiro-fused cyclobutane, Dictazole B (**29b**), with an excellent yield of 16% (Scheme 6). Through this, compartmentalization properties offered by DNA could facilitate bypassing the inability of the monomers to self-organize in solution and ultimately promote the target cycloaddition.

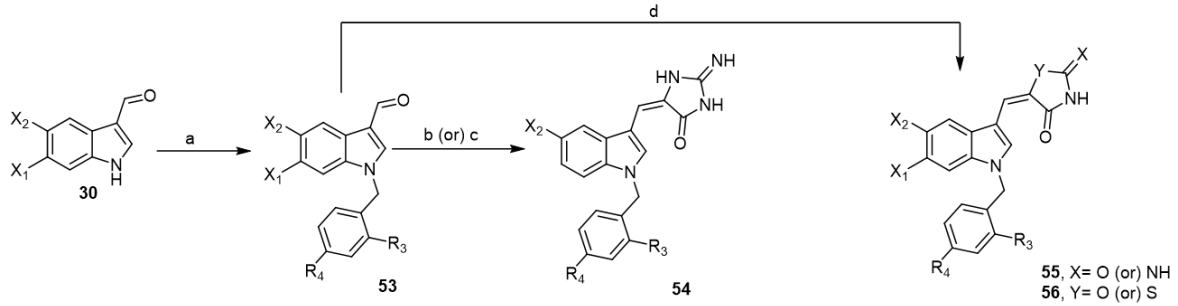
4. Aplysinopsins Analogs

In 2009, various aplysinopsin analogs **51** and **52** were synthesized by the reaction of indole-3-carboxaldehyds **30**, namely, 5-bromo, 5-fluoro, and 6-brom-1*H*-indole-3-carboxaldehydes, with either creatinine or 2-imino-1,3-dimethyl-imidazolidin-4-one or 2-imino-1-methyl-3-ethylimidazolidin-4-one (Scheme 7) [42].



Scheme 7. Reagents and conditions: (a) Bunsen burner, heat, 153 °C, 10 min; (b) alkyl iodide, EtOH, reflux, 7 days; (c) Bunsen burner, heat, 153 °C, 10 min.

The preparation of an *N*-benzyl-1*H*-indoles to be *N*-benzyl aplysinopsin analogs was of interest to a group of researchers as potential anticancer agents. In 2010, they reported a series of substituted (*Z*)-5-(*N*-benzylindol-3-ylmethylene)imidazolidine-2,4-dione analogs **54** using microwave irradiation and conventional heating methods (Scheme 8) [23].

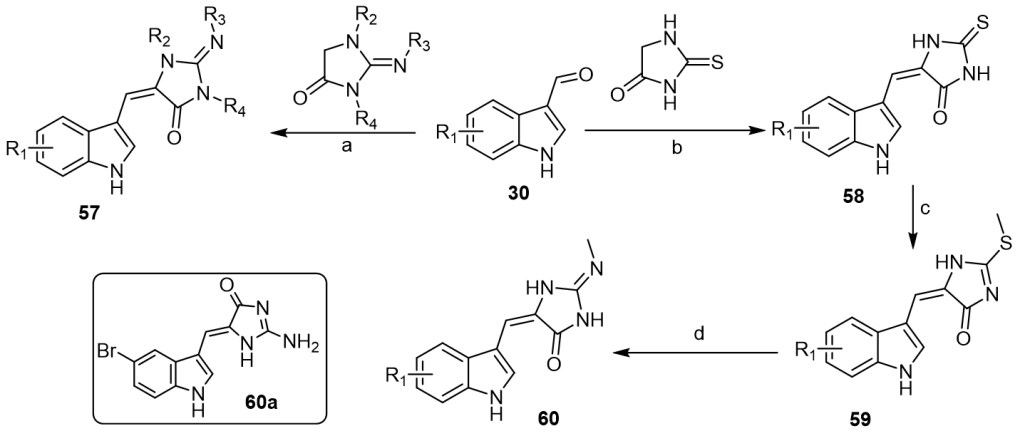


Scheme 8. Synthesis of *N*-benzyl aplysinopsin analogs. Reagents and conditions: (a) appropriate benzyl halide, aq. NaOH solution (50%), triethylbenzylammonium chloride (TEBA), DCM, rt, 2 h; (b) hydantoin, ammonium acetate, acetic acid, microwave irradiation, 40–60 s; (c) hydantoin, ammonium acetate, acetic acid, 115–116 °C, 8–12 h; (d) hydantoin or 2-iminothiazolidin-4-one, ammonium acetate, acetic acid, microwave irradiation, 30–60 s.

In 2011, they developed a series of substituted (*Z*)-5-((1-benzyl-1*H*-indol-3-yl)methylene) imidazolidin-2,4-diones **55** and (*Z*)-5-((1-benzyl-1*H*-indol-3-yl) methyl-ene)-2-iminothiazolidin-4-ones **56** utilizing microwave irradiation method (Scheme 8) [22]. These analogs were evaluated for in vitro cytotoxicity against a panel of human tumor cell lines. Several of these analogs showed potent growth inhibition against melanoma UACC-257, OVCAR-8 ovarian, and MCF-7 breast cancer cells besides significant cytotoxicity. Therefore, these analogs could be regarded as useful lead compounds for further structural optimization as antitumor agents [22,23].

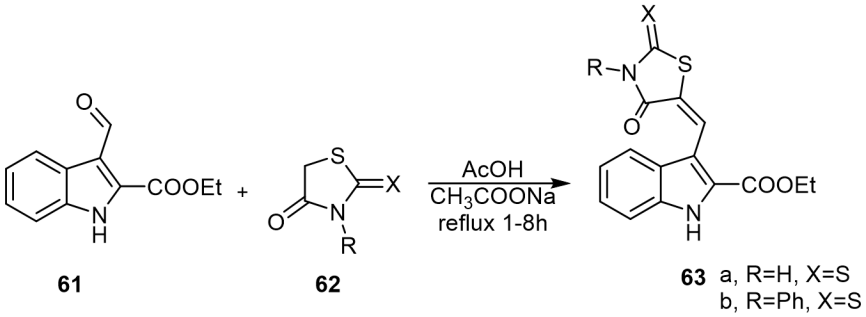
On the other hand, Cummings et al. reported low-molecular weight aplysinopsin analogs that served as a chemical scaffold for synthesizing compounds capable of differentiating between cloned human 5-HT_{2C} and 5-HT_{2A} receptor subtypes [43]. First, indole aldehydes **30** were reacted with the appropriate imidazolidinones to afford the corresponding aplysinopsin analogs **57** (Scheme 9). Additionally, aplysinopsin analogs **58** were

obtained via condensation of indole aldehydes **30** with thiohydantoin followed by methylation of intermediate thiones **58** to afford the corresponding thioethers **59**. Thioethers were allowed to react with methylamine to yield the corresponding *N*-methylamine aplysinopsin analogs **60** (Scheme 9). The prepared analogs have been evaluated in the chick anxiety–depression model. In vitro receptor binding assays showed that analogs revealed high affinity with selectivity for 5-HT_{2B} over 5-HT_{2A} and 5-HT_{2C}. Regarding the in vivo studies of aplysinopsins using different depression models, aplysinopsins were unable to reproduce the in vitro efficacy in an animal model. However, one compound, (*Z*)-2-amino-5-((5-bromo-1*H*-indol-3-yl) methylene)-1*H*-imidazol-4(5*H*)-one (**60a**), showed a modest antidepressant effect in the later stages of the evaluation period.



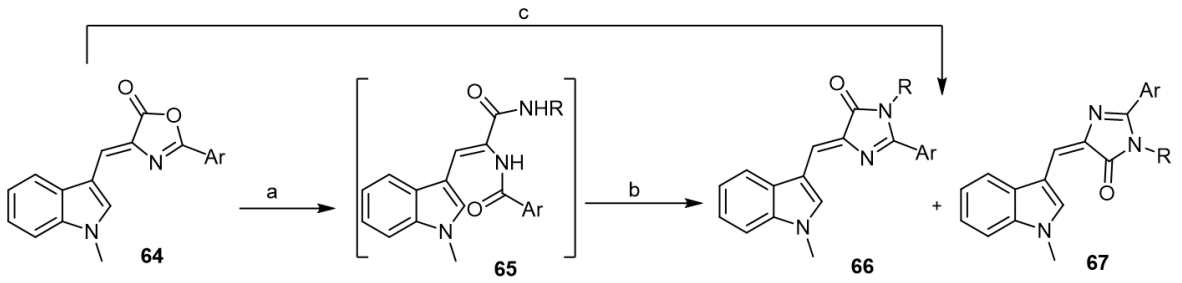
Scheme 9. Synthesis of low-molecular weight aplysinopsin analogs. Reagents and conditions: (a) piperidine, reflux, 2 h; (b) ETA, EtOH, reflux, 1 h; (c) CH_3I, NaOH, MeOH, rt, 18 h; (d) CH_3NH_2, EtOH, sealed vessel, 70 °C, 24 h.

JakŠe et al. reported various aplysinopsin-thiohydantoin analogs via the reaction of ethyl 3-formyl-1*H*-indole-2-carboxylate (**61**) with the active methylene group of 2-thiohydantoin (**62**) in a mixture of acetic acid and sodium acetate (Scheme 10) [44].



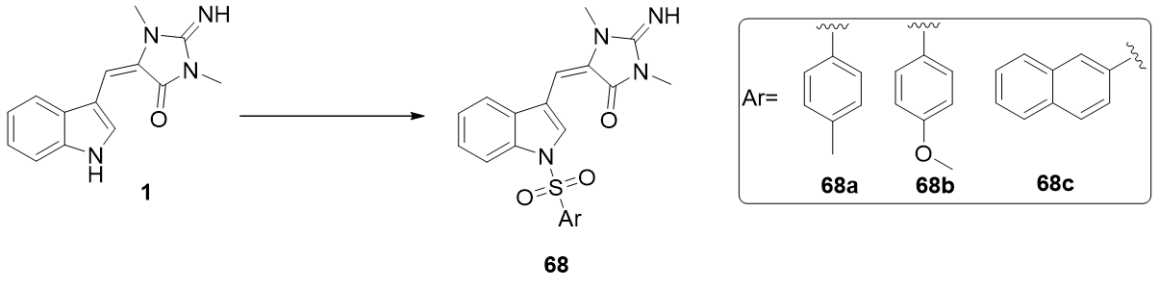
Scheme 10. Synthesis of aplysinopsin-thiohydantoin analogs. Reagents and conditions: AcOH, CH_3COONa, reflux 1–8 h.

In 2016, Suzdalev and Babakova developed an efficient approach toward the synthesis of aplysinopsin analogs from 4-[(1*H*-indol-3-yl)-methylene]-1,3-oxazol-5(4*H*)-ones (**64**) [45]. The reaction of *Z*-isomers of oxazolones **64** with primary amines under reflux in dimethylformamide or ethylene glycol led to the formation of imidazolone derivatives **66** and **67** (Scheme 11).



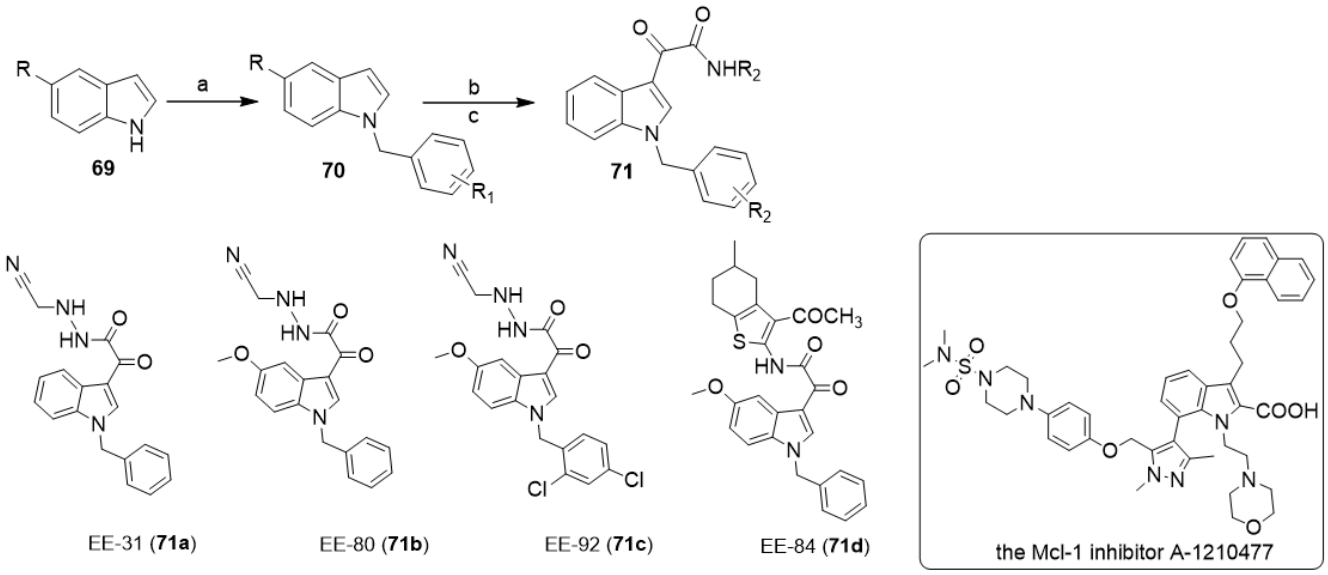
Scheme 11. Synthesis of aplysinopsin analogs starting from 1,3-oxazol-5(4*H*)-ones. Reagents and conditions: (a) RNH_2, reflux, acetonitrile, 1 h; (b) heat, dimethylformamide, 10 h (or) ethylene glycol, 30 min; (c) RNH_2, reflux, dimethylformamide, 10 h (or) ethylene glycol, 30 min.

In 2021, Nuthakki et al. reported the insertion of sulphonamide moieties on the indole ring of aplysinopsin (**1**) and studied the effect of the obtained analogs on cholinesterases and beta-site amyloid-precursor protein-cleaving enzyme 1 (BACE-1) [21]. Aplysinopsin (**1**) inhibits electric eel acetylcholinesterase (AChE), equine serum butyrylcholinesterase (BChE), and human BACE-1 with IC_{50} values of 33.9, 30.3, and 33.7 µM, respectively, and it also showed excellent BBB permeability (8.92×10^{-6}). The *N*-sulphonamide derivative **68b** displayed better cholinesterase inhibition and was found to effectively permeate the BBB ($Pe > 5 \times 10^{-6}$ cm/s). The sulphonamide derivatives were prepared by the reaction of aplysinopsin (**1**) with different substituted sulphonyl chlorides in the presence of 4-dimethyl-aminopyridine (DMAP) and *N*,*N*-diisopropylethylamine (DIPEA) (Scheme 12) [21].



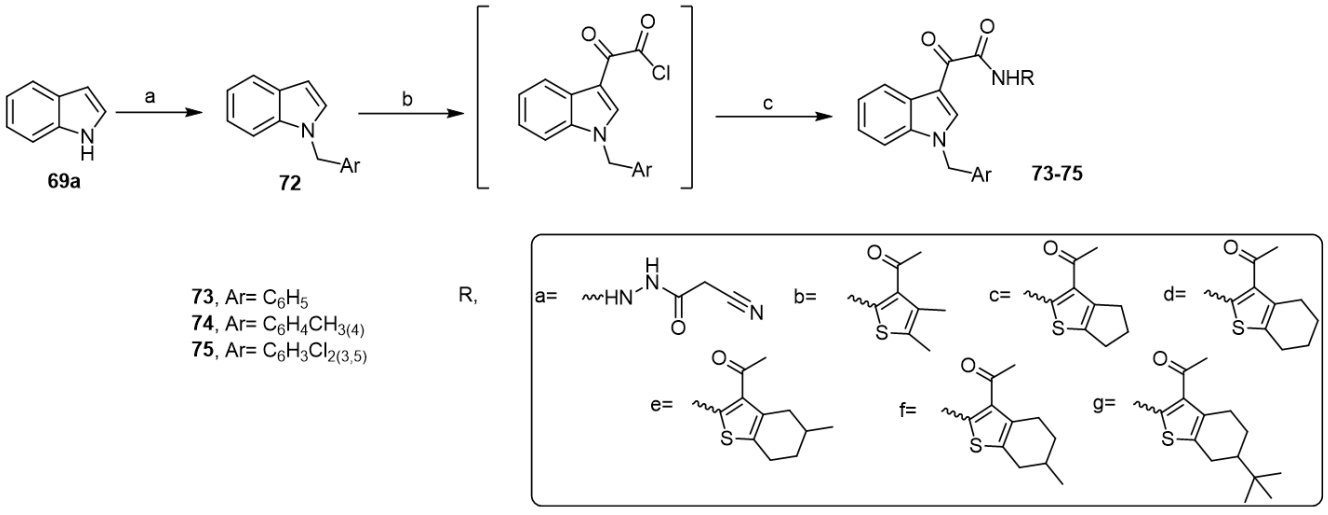
Scheme 12. Synthesis of sulphonyl aplysinopsin analogs. Reagents and conditions: $ArSO_2Cl$ (1.1 equiv.), DMAP (0.05 equiv.), DIPEA (1.5 equiv.), methylene chloride, rt, 20 h.

In 2021, Diederich and co-workers synthesized a series of aplysinopsin analogs EE (**71**) via the reaction of indole derivatives **69** with oxalyl chloride followed by the reaction with alkyl or arylamines (Scheme 13) [35]. Through the in vitro and in vivo proliferation and viability screening of the newly synthesized aplysinopsin analogs on myelogenous leukemia cell lines and zebrafish toxicity tests, as well as the analysis of differential toxicity in noncancerous RPMI 1788 cells and PBMCs, they identified EE-84 (**71d**) as a promising novel drug candidate against chronic myeloid leukemia. Furthermore, they proved that EE-84 induced a senescent-like phenotype in K562 cells in line with its cytostatic effect. Finally, they demonstrated the synergistic cytotoxic effect of EE-84 with a BH3 mimetic, the Mcl-1 inhibitor A-1210477, against imatinib-sensitive and -resistant K562 cells, highlighting the inhibition of antiapoptotic BCL2 proteins as a promising novel senolytic approach against chronic myeloid leukemia [35].



Scheme 13. Chemical structures of aplysinopsin analogs (EE-31, EE-80, EE-84, EE-92), and the Mcl-1 inhibitor A-1210477. Reagents and conditions: (a) benzyl chlorides, NaH, DMF; (b) oxalyl chloride, dry ethyl ether, 40 °C; (c) alkyl or arylamines, dry THF, TEA, stirring, 3 h.

Recently, El-Sawy et al. synthesized a new series of aplysinopsin analogs under the previous reaction conditions (Scheme 14) and investigated their cytotoxic activity against prostate cancer [46]. Five analogs showed high antitumor activity via suppressing the expression of the anti-apoptotic gene Bcl2, simultaneously increasing the expression of the pro-apoptotic genes p53, Bax, and Caspase 3. The inhibition of BCL2 led to the activation of BAX, which in turn activated Caspase 3, leading to apoptosis. This dual mechanism of action via apoptosis and cell cycle arrest induction was responsible for the antitumor activity of the aplysinopsin analogs.



Scheme 14. Synthesis of aplysinopsin analogs. Reagents and conditions: (a) benzyl chlorides, NaH, DMF; (b) oxalyl chloride, dry ethyl ether, 40 °C; (c) alkyl or arylamines (a–g), dry THF, TEA, stirring, 3 h.

5. Biological Activity

Aplysinopsins possess an array of biological activities (Table 5).

Table 5. Biological activities of aplysinopsins.

Aplysinopsin Derivatives	Activity [Ref.]
Aplysinopsin (**1**)	- CNS permeable scaffold for dual inhibition of cholinesterase and BACE-1 inhibition [21,47]. - Possess monoamine oxidase (MAO) inhibitory activity (IC_{50} of 5.6 nM) [19]. - Antiplasmodial activity (IC_{50}: 0.43 µg/mL) [48]. - Antineoplastic activity (IC_{50} values against L-1210 and KB cells, respectively, 2.3 and 6.4 µg/mL [4,27]. - Inhibit the growth of *Staphylococcus epidermidis* [8]. - An inhibitor of development of fertilized sea urchin eggs at 2.5 µg/mL [11]. - Induce symbiosis between sea anemone and anemonefish [26].
Isoaplysinopsin (**2**)	- Showed cytotoxic against murine lymphoma L-1210 (IC_{50} 11.5 µg/mL) and human epidermoid carcinoma KJ3 (31% inhibition at 20 µg/mL) cells [27].
Methylaplysinopsin (**4**)	- Antidepressant activity by enhancing serotonin activity in the central nervous system [49,50]. - Inhibition of monoamine oxidase (MAO) [50]. - Showed cytotoxicity (IC_{50} values against L-1210 and KB cells of 3.5 and 6.7 µg/mL, respectively) [27].
N-3′-ethyl-aplysinopsin (**6**)	- Serotonin receptors modulator with Ki value 1.7 µM to the 5-HT_{2A} and 3.5 µM to 5-HT_{2C} serotonin subtypes [7].
6-Bromo-2′-de-*N*-methylaplysinopsin (**9**)	- Serotonin receptors modulator (showed significant selectivity to the 5-HT_{2C} serotonin subtype over the 5-HT_{2A} subtype) [7]. - Antiplasmodial. - Inhibitor of nitric oxide synthase (nNOS).
6-Bromoaplysinopsin (**10**)	- Serotonin receptors modulator (showed highest affinity to 5-HT_{2C} with a Ki value similar to that of serotonin 0.33 µM) [7].
5,6-Dibromo-2′-demethylaplysinopsin (**13**)	- Inhibitor of nitric oxide synthase (nNOS) [6].
6-Bromo-3′-deimino-3′-oxoaply-sinopsin (**15**)	- Antiplasmodial activity [30].
1′,8-Dihydroaplysinopsin (**19**)	- Induce symbiosis between sea anemone and anemonefish [26].
6-Bromo-1′,8-dihydroaplysinopsin (**20**) 6-Bromo-1-hydroxy-1′,8-dihydroaplysinopsin (**21**) 6-Bromo-1-methoxy-1′,8-dihydroaplysinopsin (**22**) 6-Bromo-1-ethoxy-1′,8-dihydroaplysinopsin (**23**)	- Inhibit the growth of *Staphylococcus epidermidis* [8].

6. Conclusions

Aplysinopsins are one of the most celebrated bicyclic arenas in the scientific literature, and they are tryptophan-derived marine natural products. Aplysinopsins represented the skeleton of indole and imidazolidin-4-ones cores that have been obtained from various sources of marine organisms. This survey touched upon the various sources of aplysinopsins, their synthesis, and the fact that many aplysinopsin derivatives are biologically active molecules. Aplysinopsins have been listed as anti-cancer, antimicrobial, inhibitors of monoamine oxidase (MAO), antidepressant, and serotonin receptors modulator. These facts open the field for scientific researchers to synthesize new aplysinopsin analogs to enrich their activity. An interesting observation is that the indole ring of aplysinopsin is considered an essential core of their structures. Therefore, future work should be focused on the optimization of the targeted imidazolidinone core.

Author Contributions: Resources, writing—original draft preparation, E.R.E.-S.; writing—review and editing, E.R.E.-S. and G.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: E.R.E.-S. appreciates the support she received from the National Research Center (Egypt) and the support provided by the University of Lorraine (France).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Karthikeyan, A.; Joseph, A.; Nair, B.G. Promising bioactive compounds from the marine environment and their potential effects on various diseases. *J. Genet. Eng. Biotechnol.* **2022**, *20*, 14. [CrossRef] [PubMed]
2. Bialonska, D.; Zjawiony, J.K. Aplysinopsins—Marine Indole Alkaloids: Chemistry, Bioactivity and Ecological Significance. *Mar. Drugs* **2009**, *7*, 166. [CrossRef] [PubMed]
3. Kazlauskas, R.; Murphy, P.T.; Quinn, R.J.; Wells, R.J. Aplysinopsin, a new tryptophan derivative from a sponge. *Tetrahedron Lett.* **1977**, *18*, 61–64. [CrossRef]
4. Kh, H.; Fj, S. Aplysinopsin: Antineoplastic Tryptophan Derivative from the Marine Sponge *Verongia Spengelii*. *Lloydia* **1977**, *40*, 479–481.
5. Djura, P.; Faulkner, D.J. Metabolites of the marine sponge Dercitus species. *J. Org. Chem.* **1980**, *45*, 735–737. [CrossRef]
6. Aoki, S.; Ye, Y.; Higuchi, K.; Takashima, A.; Tanaka, Y.; Kitagawa, I.; Kobayashi, M. Novel Neuronal Nitric Oxide Synthase (nNOS) Selective Inhibitor, Aplysinopsin-Type Indole Alkaloid, from Marine Sponge *Hyrtios erecta*. *Chem. Pharm. Bull.* **2001**, *49*, 1372–1374. [CrossRef] [PubMed]
7. Hu, J.-F.; Schetz, J.A.; Kelly, M.; Peng, J.-N.; Ang, K.K.H.; Flotow, H.; Leong, C.Y.; Ng, S.B.; Buss, A.D.; Wilkins, S.P.; et al. New Antiinfective and Human 5-HT2 Receptor Binding Natural and Semisynthetic Compounds from the Jamaican Sponge *Smenospongia aurea*. *J. Nat. Prod.* **2002**, *65*, 476–480. [CrossRef]
8. Segraves, N.L.; Crews, P. Investigation of Brominated Tryptophan Alkaloids from Two Thorectidae Sponges: *Thorectandra* and *Smenospongia*. *J. Nat. Prod.* **2005**, *68*, 1484–1488. [CrossRef]
9. Kochanowska, A.J.; Rao, K.V.; Childress, S.; El-Alfy, A.; Matsumoto, R.R.; Kelly, M.; Stewart, G.S.; Sufka, K.J.; Hamann, M.T. Secondary Metabolites from Three Florida Sponges with Antidepressant Activity. *J. Nat. Prod.* **2008**, *71*, 186–189. [CrossRef]
10. Okuda, R.K.; Klein, D.; Kinnel, R.B.; Li, M.; Scheuer, P.J. Marine natural products: The past twenty years and beyond. *Pure Appl. Chem.* **1982**, *54*, 1907–1914. [CrossRef]
11. Fusetani, N.; Asano, M.; Matsunaga, S.; Hashimoto, K. Bioactive marine metabolites—XV. Isolation of aplysinopsin from the *Scleractinian* coral *Tubastrea aurea* as an inhibitor of development of fertilized sea urchin eggs. *Comp. Biochem. Physiol. Part B Comp. Biochem.* **1986**, *85*, 845–846. [CrossRef]
12. Guella, G.; Mancini, I.; Zibrowius, H.; Pietra, F. Novel Aplysinopsin-Type Alkaloids from *Scleractinian* Corals of the Family Dendrophylliidae of the Mediterranean and the Philippines. Configurational-assignment criteria, stereospecific synthesis, and photoisomerization. *Helvetica Chim. Acta* **1988**, *71*, 773–782. [CrossRef]
13. Koh, E.G.; Sweatman, H. Chemical warfare among scleractinians: Bioactive natural products from *Tubastraea faulkneri* Wells kill larvae of potential competitors. *J. Exp. Mar. Biol. Ecol.* **2000**, *251*, 141–160. [CrossRef] [PubMed]
14. Iwagawa, T.; Miyazaki, M.; Okamura, H.; Nakatani, M.; Doe, M.; Takemura, K. Three novel bis(indole) alkaloids from a stony coral, *Tubastraea* sp. *Tetrahedron Lett.* **2003**, *44*, 2533–2535. [CrossRef]
15. Jaromin, A.; Czopek, A.; Parapini, S.; Basilico, N.; Misiak, E.; Gubernator, J.; Zagórska, A. Synthesis and Antiplasmodial Activity of Novel Bioinspired Imidazolidinedione Derivatives. *Biomolecules* **2021**, *11*, 33. [CrossRef] [PubMed]
16. Campos, P.-E.; Pichon, E.; Moriou, C.; Clerc, P.; Trépos, R.; Frederich, M.; De Voogd, N.; Hellio, C.; Gauvin-Bialecki, A.; Al-Mourabit, A. New Antimalarial and Antimicrobial Tryptamine Derivatives from the Marine Sponge Fascaplysinopsis reticulata. *Mar. Drugs* **2019**, *17*, 167. [CrossRef] [PubMed]
17. Almeida, M.C.; Resende, D.I.S.P.; da Costa, P.M.; Pinto, M.M.M.; Sousa, E. Tryptophan derived natural marine alkaloids and synthetic derivatives as promising antimicrobial agents. *Eur. J. Med. Chem.* **2020**, *209*, 112945. [CrossRef]
18. Hong, A.; Tu, L.C.; Yang, I.; Lim, K.-M.; Nam, S.-J. Marine natural products with monoamine oxidase (MAO) inhibitory activity. *Pharm. Biol.* **2020**, *58*, 716–720. [CrossRef]
19. Lewellyn, K.; Bialonska, D.; Loria, M.J.; White, S.W.; Sufka, K.J.; Zjawiony, J.K. In vitro structure–activity relationships of aplysinopsin analogs and their in vivo evaluation in the chick anxiety–depression model. *Bioorganic Med. Chem.* **2013**, *21*, 7083–7090. [CrossRef]
20. Serkedjieva, J.; Konaklieva, M.; Dimitrova-Konaklieva, S.; Ivanova, V.; Stefanov, K.; Popov, S. Antiinfluenza Virus Effect of Extracts from Marine Algae and Invertebrates. *Z. Naturforschung. C J. Biosci.* **2000**, *55*, 87–93. [CrossRef]
21. Nuthakki, V.K.; Yadav Bheemanaboina, R.R.; Bharate, S.B. Identification of aplysinopsin as a blood-brain barrier permeable scaffold for anti-cholinesterase and anti-BACE-1 activity. *Bioorganic Chem.* **2021**, *107*, 104568. [CrossRef] [PubMed]
22. Penthala, N.R.; Yerramreddy, T.R.; Crooks, P.A. Synthesis and in vitro screening of novel N-benzyl aplysinopsin analogs as potential anticancer agents. *Bioorganic Med. Chem. Lett.* **2011**, *21*, 1411–1413. [CrossRef]
23. Thirupathi Reddy, Y.; Narsimha Reddy, P.; Koduru, S.; Damodaran, C.; Crooks, P.A. Aplysinopsin analogs: Synthesis and anti-proliferative activity of substituted (Z)-5-(N-benzylindol-3-ylmethylene)imidazolidine-2,4-diones. *Bioorganic Med. Chem.* **2010**, *18*, 3570–3574. [CrossRef] [PubMed]

24. Tymiak, A.A.; Rinehart, K.L.; Bakus, G.J. Constituents of morphologically similar sponges: *Aplysina* and *Smenospongia* Species. *Tetrahedron* **1985**, *41*, 1039–1047. [CrossRef]
25. Fattorusso, E.; Lanzotti, V.; Magno, S.; Novellino, E. Tryptophan Derivatives from a Mediterranean Anthozoan, *Astroides calycularis*. *J. Nat. Prod.* **1985**, *48*, 924–927. [CrossRef]
26. Murata, M.; Miyagawa-Kohshima, K.; Nakanishi, K.; Naya, Y. Characterization of Compounds That Induce Symbiosis Between Sea Anemone and Anemone Fish. *Science* **1986**, *234*, 585–587. [CrossRef] [PubMed]
27. Kondo, K.; Nishi, J.; Ishibashi, M.; Kobayashi, J. Two New Tryptophan-Derived Alkaloids from the Okinawan Marine Sponge *Aplysina* sp. *J. Nat. Prod.* **1994**, *57*, 1008–1011. [CrossRef] [PubMed]
28. Djura, P.; Stierle, D.B.; Sullivan, B.; Faulkner, D.J.; Arnold, E.V.; Clardy, J. Some metabolites of the marine sponges *Smenospongia aurea* and *Smenospongia* (Ident.Polyfibrospongia) echina. *J. Org. Chem.* **1980**, *45*, 1435–1441. [CrossRef]
29. Mancini, I.; Guella, G.; Zibrowius, H.; Pietra, F. On the origin of quasi-racemic aplysinopsin cycloadducts, (bis)indole alkaloids isolated from scleractinian corals of the family Dendrophylliidae. Involvement of enantiodefective Diels–Alderases or asymmetric induction in artifact processes involving adventitious catalysts? *Tetrahedron* **2003**, *59*, 8757–8762. [CrossRef]
30. Meyer, M.; Delberghe, F.; Liron, F.; Guillaume, M.; Valentin, A.; Guyot, M. An antiplasmodial new (*bis*)indole alkaloid from the hard coral *Tubastraea* sp. *Nat. Prod. Res.* **2009**, *23*, 178–182. [CrossRef]
31. Balansa, W.; Islam, R.; Gilbert, D.F.; Fontaine, F.; Xiao, X.; Zhang, H.; Piggott, A.M.; Lynch, J.W.; Capon, R.J. Australian marine sponge alkaloids as a new class of glycine-gated chloride channel receptor modulator. *Bioorganic Med. Chem.* **2013**, *21*, 4420–4425. [CrossRef] [PubMed]
32. Iwagawa, T.; Miyazaki, M.; Yokogawa, Y.; Okamura, H.; Nakatani, M.; Doe, M.; Morimoto, Y.; Takemura, K. Aplysinopsin Dimers from a Stony Coral. *Tubastraea aurea*. *Heterocycles* **2008**, *75*, 2023. [CrossRef]
33. Dai, J.; Jiménez, J.I.; Kelly, M.; Barnes, S.; Lorenzo, P.; Williams, P. Dictazolines A and B, Bisspiroimidazolidinones from the Marine Sponge *Smenospongia cerebriformis*. *J. Nat. Prod.* **2008**, *71*, 1287–1290. [CrossRef]
34. Dai, J.; Jiménez, J.I.; Kelly, M.; Williams, P.G. Dictazoles: Potential Vinyl Cyclobutane Biosynthetic Precursors to the Dictazolines. *J. Org. Chem.* **2010**, *75*, 2399–2402. [CrossRef] [PubMed]
35. Song, S.; Kim, S.; El-Sawy, E.R.; Cerella, C.; Orlikova-Boyer, B.; Kirsch, G.; Christov, C.; Dicato, M.; Diederich, M. Anti-Leukemic Properties of Aplysinopsin Derivative EE-84 Alone and Combined to BH3 Mimetic A-1210477. *Mar. Drugs* **2021**, *19*, 285. [CrossRef]
36. Molina, P.; Fresneda, P.M.; Almendros, P. A simple and general entry to Aplysinopsine-type alkaloids by tandem Aza-Wittig/heterocumulene-mediated annelation. *Tetrahedron Lett.* **1992**, *33*, 4491–4494. [CrossRef]
37. Dalkafouki, A.; Ardisson, J.; Kunesch, N.; Lacombe, L.; Poisson, J.E. Synthesis of 2-dimethylaminoimidazole derivatives: A new access to indolyl-imidazole alkaloids of marine origin. *Tetrahedron Lett.* **1991**, *32*, 5325–5328. [CrossRef]
38. Skiredj, A.; Beniddir, M.A.; Joseph, D.; Leblanc, K.; Bernadat, G.; Evanno, L.; Poupon, E. Spontaneous Biomimetic Formation of (±)-Dictazole B under Irradiation with Artificial Sunlight. *Angew. Chem. Int. Ed.* **2014**, *53*, 6419–6424. [CrossRef]
39. Skiredj, A.; Beniddir, M.; Joseph, D.; Leblanc, K.; Bernadat, G.; Evanno, L.; Poupon, E. A Unified Bioinspired "Aplysinopsin Cascade": Total Synthesis of (±)-Tubastrindole B and Related Biosynthetic Congeners. *Org. Lett.* **2014**, *16*, 4980–4983. [CrossRef]
40. Skiredj, A.; Beniddir, M.A.; Joseph, D.; Bernadat, G.; Evanno, L.; Poupon, E. Harnessing the Intrinsic Reactivity within the Aplysinopsin Series for the Synthesis of Intricate Dimers: Natural from Start to Finish. *Synthesis* **2015**, *47*, 2367–2376. [CrossRef]
41. Duchemin, N.; Skiredj, A.; Mansot, J.; Leblanc, K.; Vasseur, J.-J.; Beniddir, M.A.; Evanno, L.; Poupon, E.; Smietana, M.; Arseniyadis, S. DNA-Templated [2 + 2] Photocycloaddition: A Straightforward Entry into the Aplysinopsin Family of Natural Products. *Angew. Chem.* **2018**, *130*, 11960–11965. [CrossRef]
42. Johnson, J.E.; Canseco, D.C.; Dolliver, D.D.; Schetz, J.A.; Fronczek, F.R. Synthesis and Characterization of Aplysinopsin Analogs. *J. Chem. Crystallogr.* **2009**, *39*, 329–336. [CrossRef]
43. Cummings, D.F.; Canseco, D.C.; Sheth, P.; Johnson, J.E.; Schetz, J.A. Synthesis and structure–affinity relationships of novel small molecule natural product derivatives capable of discriminating between serotonin 5-HT1A, 5-HT2A, 5-HT2C receptor subtypes. *Bioorganic Med. Chem.* **2010**, *18*, 4783–4792. [CrossRef] [PubMed]
44. Jakše, R.; Bevk, D.; Golobič, A.; Svete, J.; Stanovnik, B. Synthesis and Transformations of Ethyl 3-Formyl-1H-indole-2-carboxylate. Preparation of Aplysinopsin and β-Carboline Thiohydantoin Analogues. *Z. Nat. B* **2006**, *61*, 413–419. [CrossRef]
45. Suzdalev, K.F.; Babakova, M.N. Synthesis of Analogues of Indole Alkaloids from Sea Sponges—Aplysinopsins by the Reaction of Amines with (4*Z*)-4-[(1*H*-indol-3-yl)-methylene]-1,3-oxazol-5(4*H*)-ones. *J. Heterocycl. Chem.* **2016**, *53*, 1200–1206. [CrossRef]
46. El-Sawy, E.R.; El-Shahid, Z.A.; Soliman, A.A.F.; Nassrallah, A.; Abdelwahab, A.B.; Kirsch, G.; Abdelmegeed, H. Synthetic Analogs of Marine Alkaloid Aplysinopsin Suppress Anti-Apoptotic Protein BCL2 in Prostate Cancer. *Molecules* **2023**, *28*, 109. [CrossRef]
47. Nuthakki, V.K.; Sharma, A.; Kumar, A.; Bharate, S.B. Identification of embelin, a 3-undecyl-1,4-benzoquinone from *Embelia ribes* as a multitargeted anti-Alzheimer agent. *Drug Dev. Res.* **2019**, *80*, 655–665. [CrossRef]
48. Passemar, C.; Saléry, M.; Soh, P.N.; Linas, M.-D.; Ahond, A.; Poupat, C.; Benoit-Vical, F. Indole and aminoimidazole moieties appear as key structural units in antiplasmodial molecules. *Phytomedicine* **2011**, *18*, 1118–1125. [CrossRef]

49. Wells, R.J.; Murphy, P.T. 5-(Indol-3-Ylmethylene)-1,3-Dimethyl-2-Methylamino-4-Imidazolidinone. U.S. Patent US4195179A, 25 March 1980.
50. Baird-Lambert, J.; Davis, P.A.; Taylor, K.M. Methylaplysinopsin: A natural product of marine origin with effects on serotonergic neurotransmission. *Clin. Exp. Pharmacol. Physiol.* **1982**, *9*, 203–212. [CrossRef]