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REVIEW OF NATURAL PRODUCTS FROM MARINE ORGANISMS IN THE RED SEA

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ABSTRACT: The marine environment is a rich source of both biological and chemical diversity. This diversity has been the source of unique chemical compounds with potential for drug development. In recent years, a significant number of novel metabolites with potent pharmacological properties have been discovered from the marine organisms. Specifically, the Red Sea is a natural source of these bioactive compounds. The Red Sea is a rich source of marine organisms that contain bioactive substances with intriguing and unique structural features. Examples of marine organisms commonly found in the Red Sea are sponges, soft corals, and algae. Secondary metabolites obtained from Red Sea marine organisms have been reported to show various biological activities such as: cytotoxic, antiproliferative, antiviral and anti-inflammatory activities. This review emphasizes the bioactivity of marine natural products specifically those isolated from the Red Sea. The present article highlights the latest progress in both chemistry and biological activities of metabolites isolated from Red Sea organisms till year 2014, also it provides a perspective on future areas of research interest. This review contains 435 structures and 138 references.

INTRODUCTION: The marine environment is a rich source of both biological and chemical diversity. This diversity is immense and therefore is an extraordinary resource for the discovery and development of various novel drug leads. Because of the different physical and chemical conditions found in the marine environment, almost every class of marine organism affords a variety of molecules with unique structural features. Research into the biological as well as pharmacological properties of marine natural products has led to the discovery of many potently active agents considered worthy of clinical application.

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The marine environment is an exceptional reservoir of bioactive natural products, many of which exhibit structural/chemical features not found in terrestrial natural products. [1] The intense concentration of species coexisting in the marine habitats necessarily makes them highly competitive and complex. Sessile macroscopic organisms such as algae, corals, sponges, and a variety of other marine invertebrates are in constant battle for suitable attachment space. Nutrients, light, water current, and temperature represent additional growth limiting components, further increasing competition. As a result of this intense competition, marine organisms have evolved various chemical means of defence against predators. [2] These chemical adaptations generally take the form of production of ‘‘secondary metabolites,’’ which involve well known chemical classes such as terpenoids, alkaloids, sterols, steroids, and other metabolites. [3]

The Red Sea is an important natural source of bioactive compounds. Distinctive features that have intrigued natural products chemists to investigate marine organisms in the Red Sea include its great seasonal fluctuations of air and water temperatures and its great marine biodiversity. Indeed, of the 180 soft corals species identified world-wide, approximately 40% are native to the Red Sea. [4]

Herein, there is an emphasis on various secondary metabolites that have been isolated from the Red Sea till year 2014, including their source organisms, chemical structures, biological activities, and potential for further development. Chemical constituents isolated from Red Sea marine organisms may be broadly classified to the following classes:

1. Terpenes
2. Alkaloids
3. Sterols & Steroidal glycosides
4. Other metabolites

1. Terpenes:

1.1 Sesquiterpenes: The first two sesquiterpene hydroquinones isolated from the Red Sea were peyssonol A **(1)** and peyssonol B **(2)**, which were isolated from Red Sea algae *Peyssonelia* sp. Both compounds have been shown to be potent inhibitors of the RNA-directed DNA synthesis of the reverse transcriptases (RTs) of human immunodeficiency virus (HIV)-1 and HIV-2. The authors proposed an explanation for the mechanism of the enzyme inhibition.[5] The study of *Sinularia gardineri* (Pratt) (Alcyoniidae), collected from the Red Sea, revealed a known sesquiterpene, guaianediol **(3)**, which showed cytotoxicity to murine leukemia (P-388), human lung carcinoma (A-549), human colon carcinoma (HT-29), and human melanoma cells (MEL-28).[6] Another sesquiterpene tetronic acid derivative, named smenotronic acid **(4)** was isolated from the Red Sea marine sponge *Smenospongia* sp.[7] Chemical investigation of the lipophilic extract of the Red Sea sponge *Diacarnus erythraenus* revealed one new sesquiterpene, O-Me guaianediol **(5)**. The cytotoxic activities for this compound had been reported against three types of cancer cells including murine leukemia, lung carcinoma and human colon carcinoma cells.[8] Three years later the two sesquiterpene γ - methoxybutenolides, hyrtiosenolides A **(6)** and B **(7)**, were isolated from a Red Sea sponge, *Hyrtios* species. Both compounds showed weak antibacterial activity against *Escherichia coli*.[9] Dioxosarcoguaiacol **(8)**, a 1,2-dioxolane sesquiterpene alcohol, along with (+)- alloaromadendrene **(9)** were isolated from the Red Sea soft coral *Sarcophyton glaucum*. (+)-Alloaromadendrene showed potent inhibition of the proliferation of the highly malignant +SA mammary epithelial cells at a dose of 20 mM.[10]

In 2012**,** three laurene-type sesquiterpenes, 12-hydroxy isolaurene **(10)**, 8,11-dihydro-12-hydroxy isolaurene **(11)** and isolauraldehyde **(12)** were isolated from the organic extract of the Red Sea red alga *Laurencia obtusa*. The isolated compounds were tested for their antimicrobial and antitumor activities. They exhibited potent activity against the gram positive *Bacillus subtilis* and *Staphylococcus aureus*, where isolauraldehyde proved to be active showing MIC 35 and 27mg/ml, respectively. Moreover, it exhibited a promising activity against *Candida albicans* (MIC of 70 mg/ml) and revealed to have remarkable activity in an *in vitro* model of Ehrlich ascites Carcinoma.[11]

1.2 Diterpenes: Cembranes are the most frequent secondary metabolites isolated from various Red Sea marine organisms. Cyclization of a geranylgeraniol-derived precursor between carbon 1 and 14 generates a 14-membered diterpenoid, named cembrane or thumbergane. These structures are characterized by an isopropyl-and three methyl-substituted 14-membered rings, with structural changes in the position of double bonds, epoxidation, allylic and isopropyl oxidation, and carbon cyclization.[12] In 1974, the first cembranoid diterpene that was isolated from the soft coral *Sarcophyton glaucum* present in the Red Sea was sarcophine **(13),** a crystalline compound, which is believed to be one of the repellants protecting the coral against predators. The whole molecular structure of sarcophine was determined by a single-crystal-3-dimensional X-ray diffraction study methods.[13] Later in 1977, known cembrane derivatives from alcyonarians of the Gulf of Eilat (Red Sea) were isolated, including nephtenol **(14)**, and 16-deoxysarcophine **(15)**. Also, the structure of a sinulariolide derivative, 11-episinulariolide

acetate **(16)**, isolated together with 11-dehydrosinulariolide **(17)**, from two of seven *Sinularia* sp. was illustrated.[14] Three cembranoids **(18-20)** were isolated from the Red Sea soft coral *Alcyonium flaccidum* namely, cembrene C **(18)**, sarcophytol B **(19)**, and 11,12-epoxy-13-hydroxy-14-acetoxycembrene C**,** named flaccidoxide **(20)**. Also, two 13-hydroxylobolides **(21,22)** in addition to lobolide **(23)** were isolated from *Lobophytum crassum*, another Red Sea soft coral whose chemical content changed markedly with the place of collection.[15] Several diterpenoids were further reported from the soft corals, *Alcyonium utinomii*, *Lobophytum pauciflorum*, and *Lobophytum crassum*.

These compounds were 1,3,7,10-cembratetraen-12-ol **(24)**, 1,3,6,11-cembratetraen-8-ol **(25)**, 1,3,7,12(20)-cembratetraen-11-ol **(26)**, 2,7,11-cembratrien-4,15-diol **(27)**, 3,7,10-cembratrien-12,15-diol **(28)**, deacetyldeepoxylobolide **(29)**, deepoxylobolide **(30)**, and deacetyl-13-hydroxylobolide **(31)**. They were identified by detailed spectral data and chemical studies (mainly ozonolysis).[16] Investigation of the terpenoid content of the Red Sea soft corals *Xenia macrospiculata*, *Xenia obscuronata*, and *Xenia lilielae* resulted in the isolation of eight diterpenes. Two of them belonged to the xeniolides, xenialactol-D **(32)** and xeniolide-E **(33)**, while the other six belonged to the xeniaphylanes (prenylated caryophyllanes), namely 4,14-diepoxyxeniaphyllene **(34)**, 4,5-epoxyxeniaphyllan-14,15-diol **(35)**, 4,14 diepoxyxeniaphyllenol-A **(36)**, xeniaphyllenol-B **(37)**, xeniaphyllenol-C **(38)**, and xeniaphyllantriol **(39)**. The structure determination of the various compounds was assigned based on the chemical transformations as well as on the ^{1}H and ^{13}C NMR spectra.[17] Rearranged spongian-type diterpenes including compounds (**40-43)** were isolated from two Red Sea Dysidea sponges. All the isolated compounds showed either a perhydroazulene or a Δ5(10)-octalin system as the carbobicyclic portion and contained one of four heterocycles, i.e., a disubstituted dihydrofuran, a trisubstituted γ-lactol, a trisubstituted δ-lactone, or a 2,7-dioxabi cyclo[3.2.1]octane.[18]

Juncins A-F **(44-49)**, six diterpenes, possessing the known briarane skeleton, were isolated from the gorgonian *Junceella juncea* collected from the Red Sea.[19] Three spongian-type diterpenes **(50-52)** were isolated from a Red Sea *Dysidea* sp. All three compounds embodied the substituted hydrindane portion but differed in the hydrophilic part of the molecule. Norrlandin **(50)** possessed the 2,7-dioxa-bicyclo[3.2.1]octane system, while seconorrisolide B **(51)** and seconorrisolide C **(52)** had different substituted γ-lactone rings. [20]

Three diterpenoids, chelodane **(53)**, barekoxide **(54)**, and zaatirin **(55)**, were isolated from the marine sponge, *Chelonaplysilla erecta*, collected from the Red Sea.[21] Chelodane and zaatirin were also isolated from another Red Sea sponge *Raspailia* sp. collected in the Dahlak archipelago, Eritrea.[22]

In 1996, a study of *Sinularia gardineri* (Pratt) (Alcyoniidae), collected in the Red Sea, revealed the isolation of known cembranolides 5-*epi*-sinuleptolide **(56)** and sinuleptolide **(57)**.[6] (El Sayed & Hamann 1996) In 1997, a lactone cembrane diterpene, sarcophytolide **(58)**, was obtained by bioactivity-guided fractionation of the alcoholic extract of the soft coral *Sarcophyton* sp. collected from the coral reefs near Hurghada, Egypt. Sarcophytolide was found to exhibit antimicrobial activity towards *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Saccharomyces cerevisia.*[23] Sarcophytol A **(59)**, sarcophytol B, and sarcophine were isolated from the Red Sea soft coral *Sarcophyton glaucum*. Sarcophine was found to serve as an effective inhibitor of JB6 cell transformation. It was subjected to preparative-scale fermentation with *Absidia glauca* ATCC 22752, *Rhizopus arrhizus* ATCC 11145, and *Rhizopus stolonifer* ATCC 24795, resulting in the production of the known compound (+)-7*α*,8*β*-dihydroxydeepoxysarcophine **(60)**. When evaluated for potential to inhibit TPA-induced JB6 cell transformation, several of the obtained metabolites had a good response, which was comparable to 13-*cis*-retinoic acid. These studies provided a basis for further development of novel furanocembranoids as anticancer agents.[24]

Two hydroazulenoid (prenyl guaiane) diterpenes, dictyone acetate **(61)** and 3,4-epoxy 13-hydroxy pachydictyol A **(62)** were isolated from the

petroleum ether fraction of the alcoholic extract of the brown alga, *Dictyota dichotoma* (Hudson)Lamouroux, which was collected from the Red Sea coasts at Hurgada, together with three known ones, pachydictyol A **(63)**, dictyone **(64)** and 11 hydroxypachydictyol A (dictyol E) **(65)**. The structures of the isolated compounds were determined on the basis of spectroscopic evidences as well as physical and chemical correlation with known compounds. Compounds **(61, 63-65)** showed moderate cytotoxic activity against two proliferating mouse cell lines, a normal fibroblast line NIH3T3 and virally transformed form of cells, KA3IT. [25] Dictyone was also isolated from the red sea brown alga *Sargassum asperifolium*. The identification of the isolated metabolite was established mainly by spectral methods and the chemical transformation its acetate.[26] 18,19-epoxyxenic-19-methoxy-18-hydroxy-4-acetoxy-6,9,13-triene **(66)** and 18,19-epoxyxenic-18,19-dimethoxy-4-hydroxy-6,9,13-triene **(67)** were obtained by column chromatography of the hexane fraction of the methanol extract of *Padina pavonia* (L.) Gaill. collected from the Red Sea at Hurghada. It was found that the isolated compounds exhibited various antitumor activities against lung carcinoma (H460) and liver carcinoma (HepG2) human cell lines (*in vitro*).[27]

In 2009, antimicrobial assays were performed with extracts of twenty-three Red Sea corals and sponges against bacteria isolated from their natural environment, the results revealed considerable variability in antimicrobial activity. Soft corals exhibited promising activity, sponges showed variability, and stony corals had little or no activity. Among the soft corals, *Xenia macrospiculata* exhibited the highest activity. Bioassay-directed fractionation of the extract indicated that the activity was due to a range of compounds, one of which was isolated and identified as the diterpene desoxyhavannahine **(68)**.[28]

In 2010, Pachycladins A-E (**69-73**), five eunicellin diterpenes, were isolated from the Red Sea soft coral *Cladiella pachyclados*. The known sclerophytin A, cladiellisin, 3-acetylcladiellisin, 3,6-diacetylcladiellisin, (+)-polyanthelin A, klysimplexin G, klysimplexin E, sclerophytin F Me ether, (6*Z*)- cladiellin (cladiella-6*Z*,11(17)-dien-3-ol), sclerophytin B, and patagonicol were also identified. These compounds were evaluated for their ability to inhibit growth, proliferation, invasion, and migration of the prostate cancer cells PC-3. Some of the isolated metabolites exhibited significant anti-invasive activity.[29]

In the same year, the following diterpenes, amijiol acetate (**74**), dolabellane, dolabellatrienol (**75**), dolastane and amijiol-7,10-diacetate (**76)** were isolated together with the previously known pachydictyol A, isopachydictyol A (**77**), 8*β*-hydroxypachydictyol A (**78**), amijiol (**79**), isodictyohemiacetal (**80**) and dictyol C (**81**) from the Red Sea brown alga *Dictyota dichotoma* var. implexa. Amijiol-7,10-diacetate and amijiol were found to have potent cytotoxic activity against WI-38, HepG2, and MCF-7 cell lines, as well as antioxidant activity using ABTS and erythrocytes hemolysis.[30]

Other cembrane diterpenes, 2*R*,7*R*,8*R*-dihydroxydeepoxysarcophine **(82)**, and 7*β*-acetoxy-8*α*-hydroxydeepoxysarcophine **(83)**, together with the two known compounds, 7*α*,8*β*-dihydroxydeepoxysarcophine, and sarcophine, were isolated from the Red Sea soft coral *Sarcophyton glaucum*. 7*β*-acetoxy-8*α*-hydroxy deepoxysarcophine was found to exhibit cytotoxic activity against HepG2, HCT-116, and HeLa cells with IC_{50} values of 3.6, 2.3, and 6.7 mg/ml, respectively.[31] The chemical investigation of the ethyl acetate extract of the Red Sea soft coral *Sarcophyton glaucum* had led to the isolation of two peroxide diterpenes, 11(*S*) hydroperoxyl sarcoph-12(20)-ene **(84)**, and 12(*S*)-hydroperoxyl sarcoph-10-ene **(85)**, as well as 8-*epi*-sarcophinone **(86)**. In addition to these three compounds, two other structures were identified including: *ent*-sarcophine **(87)** and sarcophine. Structures were elucidated by spectroscopic analysis, also the relative configuration of the first two structures was confirmed by x-ray diffraction. Isolated compounds were found to be inhibitors of cytochrome P450-1A activity as well as inducers of glutathione S-transferases (GST), quinone reductase (QR), and epoxide hydrolase (mEH) establishing chemo-preventive and tumor anti-initiating activity for these characterized metabolites.[32]

In 2013, the chemical investigation of the same Red Sea soft coral *Sarcophyton glaucum* led to the isolation of the cembranoid diterpene, namely (1*S*,2*E*,4*R*,6*E*,8*S*,11*R*,12*S*)-8,11-epoxy-4,12-epoxy-2,6-cembradiene **(88)**, two cembranoid diterpenes isolated for the first time, (1*S*,2*E*,4*R*,6*E*,8*R*, 11*S*,12*R*)-8,12-epoxy-2,6-cembradiene-4, 11-diol **(89)** and (1*S*,4*R*,13*S*)-cembra-2*E*,7*E*,11*E*-trien-4,13-diol **(90)** as well as three known previously mentioned compounds, sarcophine, (+)-7*α*,8*β*-dihydroxydeepoxysarcophine and sarcophytolide. The cytotoxic activities of the six isolated compounds were evaluated against mouse melanoma $B_{16}F_{10}$ cells at the concentration of 500 µm. (1*S*,2*E*,4*R*,6*E*,8*S*,11*R*,12*S*)-8,11-epoxy-4,12-epoxy-2,6-cembradiene, sarcophytolide, and (1*S*, 4*R*,13*S*)-cembra-2*E*,7*E*,11*E*-trien-4,13-diol showed promising cytotoxic activity. Sarcophine showed moderate antifungal activity against *Cryptococcus neoformans* with an IC_{50} value of 20µg/ml. [33]

Chemical examination of the soft coral *Sarcophyton trocheliophorum* yielded six cembranoids, trochelioid A **(91)**, trochelioid B **(92)**, and 16-oxosarcophytonin E **(93)**. In addition to the previously isolated cembranoids 8-*epi*-sarcophinone, sarcophine and *ent*-sarcophine. [34] Recently, three new cembranoids, sarcophytolol **(94)**, sarcophytolide B **(95)**, and sarcophytolide C **(96)**, along with the known metabolites: deoxosarcophine, and sarcophine were obtained from *Sarcophyton glaucum*. Sarcophytolol and sarcophytolide C had similar significant cytotoxic effects towards HepG2 (Human hepatocellular liver carcinoma; IC_{50}= 20 mM). Sarcophytolide B and C showed activity against MCF-7 (Human breast adenocarcinoma; IC_{50} 25 ± 0.0164 and 29 ± 0.030 mM, respectively).[35]

1.3 Sesterterpenes: In 1979, an isoprenoid, Muqubilin **(1)** was isolated from the Red Sea sponge of *Prianos* sp.[36] Hurghaperoxide A **(98),** norsesterterpene cyclic peroxide, was isolated from an undescribed Red Sea sponge.[37] In 1999, (-)-Wistarin **(99),** an enantiomeric sesterterpene, was isolated from the Red Sea sponge of *Ircinia* sp. This metabolite is the enantiomer of (+)- wistarin, a tetracyclic metabolite previously isolated from the sponge *Ircinia wistarii*. The enantiomeric relationship was proved by comparison of the CD spectrum of (-)- wistarin with that of a synthetic sample of the (+)- isomer.[38]

Bilosespens A **(100)** and B **(101)**, two sesterterpenes that were isolated from the Red Sea sponge *Dysidea cinerea* collected in the Dahlak archipelago, Eritrea. The mixture of bilosespens A and B was found to be cytotoxic to a few human cancer cells.[39] Later in 2001, the investigation of the lipophilic extract of the Red Sea sponge *Diacarnus erythraenus* revealed one norsesterterpene cyclic peroxide, aikupikoxide A **(102)**. The isolated compound was tested against the inhibition of proliferation of highly malignant +SA mammary epithelial cells.[8] A norsesterterpene acid, named muqubilone **(103)**, along with the known sigmosceptrellin-B **(104)** and muqubilin were isolated from the Red Sea sponge *Diacarnus erythraeanus*.

Sigmosceptrellin-B exhibited significant *in vitro* antimalarial activity against *Plasmodium falciparum* (D6 and W2 clones) with IC_{50} values of 1200 and 3400 ng/ml, respectively. Muqubilone and muqubilin showed *in vitro* antiviral activity against *herpes simplex* type 1 (HSV-1) with ED_{50} values of 7500 and 30,000 µg/ml, respectively. Sigmosceptrellin-B and muqubilin displayed potent *in vitro* activity against *Toxoplasma gondii* at a concentration of 0.1 mM without significant toxicity.[40] In 2002, the lipophilic partition of a methanol extract of the Red Sea sponge *Hyrtios erecta* yielded a novel pentacyclic sesterterpene ester salmahyrtisol A **(105)**, three scalarane-type sesterterpenes, 3-acetyl sesterstatin 1 **(106)**, 19-acetyl sesterstatin 3 **(107)**, and salmahyrtisol B **(108)**, together with the previously reported sesterterpenes hyrtiosal **(109)**, scalarolide **(110)**, and salmahyrtisol C **(111)**. The compounds isolated showed significant cytotoxicity to murine leukemia (P-388), human lung carcinoma (A-549), and human colon carcinoma (HT29). [41] Tasnemoxides A-C **(112-114)**, three cytotoxic cyclic norsestertepene peroxides, were isolated from the Red Sea sponge *Diacarnus erythraenus*, together with the known compound sigmosceptrellin B. Tasnemoxides A-C showed moderate cytotoxicity against three cancer cell lines including murine leukemia, human lung carcinoma and human colon carcinoma cells.[42]

Sesterstatin 7 **(115)**, a scalarane-type pentacyclic sesterterpene, was isolated from the Red Sea sponge *Hyrtios erecta*, together with 16-*epi*-scalarolbutenolide **(116)**, 25-dehydroxy-12-*epi*-deacetylscalarin **(117)**, 3 acetyl sesterstatin 1, and 21-acetoxydeoxyscalarin **(118)**.

Sesterstatin 7 showed 63% inhibition of *Mycobacterium tuberculosis* (H37Rv) at a concentration of 6.25mg/ml. 16-*epi*-scalarol butenolide displayed moderate inhibitory activity, while compounds 25-dehydroxy-12-*epi*-deacetylscalarin and 3-acetylsesterstatin 1 were weakly active against the same biological target. [43] In 2007, the sponge *Hyrtios erectus* collected from the Red Sea, Egypt, was chemically investigated. Three scalarane sesterterpenes: 16-hydroxyscalarolide (**119**), scalarolide, and 12-O-deacetyl-12-*epi*-scalarine (**120**) were isolated. The isolated compounds were tested for their cytotoxic and antimicrobial activities. 16-hydroxyscalarolide showed growth inhibition activity against the L5178Y cell line. Also, it showed mild antimicrobial activities against *Bacillus subtilis* and *Saccharomyces cerevisiae*.[44]

1.4 Triterpenes: The first squalene-derived triterpene isolated from the Red Sea was sipholenol (**121).** Sipholenol and its 4-keto derivative sipholenone **(123)** were isolated from the Red Sea sponge *Siphonochalina siphonella*. The structure of sipholenol was determined by spectral analysis and by x-ray analysis of its monoacetate **(122)**.[45]

Later in 1983, Siphonellinol **(124)** was isolated from the Red Sea sponge *Siphonochalina siphonella*, its structure was determined on the basis of NMR and mass spectra as well as biochemical correlations.[46] In the same year, eight squalene-derived triterpenes **(125-132)** were isolated from the same Red Sea sponge. The novel skeleton, designated sipholane, consists of a cis-octahydroazulene linked via an ethylene bridge to a trans-decahydro benzoxepine. The structure of the sipholane skeleton was established by an x-ray diffraction analysis of Sipholenol A **(125)**. [47] Later, sipholenol A isolated from the Red Sea sponge *Callyspongia siphonella*, proved to have the ability to reverse multidrug resistance in cancer cells that overexpress P-glycoprotein (P-gp). In this study, the antimigratory activity of sipholenol A and analogues was reported against the highly metastatic human breast cancer cell line MDA-MB-231 in a wound-healing assay. [48]

Neviotine-A **(133)** possessing a unique tetracyclic skeleton related to the sipholanes and siphonellanes, was isolated from the Red Sea sponge *Siphonochalina siphonella*. Its structure was elucidated mainly on the basis of NMR experiments and by chemical transformations and.[49] In 2001, a comparative study was done between the chemical content of the Red Sea sponge *Siphonochalina siphonella* in the northern Gulf of Eilat, and that present in the southern-central Dahlak archipelago. Clear differences were found, as the Dahlak sponge was found to be richer in the more polar triterpenes. Nine compounds were isolated and identified, among them two sipholane glycosides, sipholenoside A and B **(134,135)**, and one compound, dahabinone A **(136)**, possessing a different skeleton.[50]

In 2007, a study was made on the same Red Sea sponge *Callyspongia* (=*Siphonochalina*) *siphonella*, this study described the isolation of two triterpenoids, siphonellinol C **(137)** and sipholenol I **(138)**, along with several known sipholane triterpenoids. Allylic oxidation of the major sipholane triterpenoids, sipholenol A and sipholenone A, by selenium dioxide afforded four C-28-oxidized derivatives. Sipholane triterpenoids along with their semisynthetic derivatives were evaluated for their cytotoxicity and effect on reversing P-glycoprotein-mediated MDR to colchicine. Sipholenol A was found to be the most potent, and it increased the sensitivity of resistant KB-C2 cells by 16 times toward colchicine. This was the first report related to reversal of cancer chemotherapy resistance using these triterpenoids. [51] As mentioned before, the Red Sea sponge *Callyspongia* (= *Siphonochalina*) *siphonella* was found to be a rich source of sipholane triterpenoids. So, the biocatalysis of the major sipholanes, sipholenol A and sipholenone A by *Mucor ramannianus* ATCC 9628 and *Cunninghamella elegans* ATCC 7929 afforded four metabolites **(139-142)** along with sipholenol G **(143)** and 28-hydroxysipholenol A **(144)**.

Major sipholanes along with their biocatalytic products were investigated for their antiproliferative activity against the highly malignant +SA mouse mammary epithelial cell line. Sipholenone A was the most active sipholane inhibiting +SA cell proliferation with an IC_{50} value of 20-30 μM. Sipholenone A, also, showed cytotoxicity against MCF-7 at a dose of 0.9 μM and antiangiogenic activity in the CAM (chorio-allantoic membrane) assay.[52]

In 2014, Neviotane-C **(145)** and sipholenol L **(146)**, together with known triterpenes neviotine A, Sipholenol A and Sipholenone A, were isolated from *Siphonochalina siphonella*, collected from Saudi water. All compounds, except sipholenol L, were tested against PC-3, A549 and MCF-7. The isolated compounds showed considerable anti-proliferative activity selectively against PC-3 and A549 cell lines. Sipholenol A showed potent anticancer activity towards PC-3 and A549 with IC_{50} = 7.9 ± 0.120 and 8.9 ± 0.010 μm, respectively.[53]

1.5. Tetraterpenes: The study of *Sinularia gardineri* (Pratt) (Alcyoniidae), collected in the Red Sea, revealed a new heptacyclic norcembranoid dimer singardin **(147)**. Singardin showed cytotoxicity to murine leukemia (P-388), human lung carcinoma (A-549), human colon carcinoma (HT-29), and human melanoma cells (MEL-28). [6]

1.6. Norterpenes: Investigation of the lipophilic extract of the Red Sea sponge *Diacarnus erythraenus* revealed one norsesterterpene cyclic peroxide, aikupikoxide A **(148)**, three norditerpene cyclic peroxides, aikupikoxide B-D **(149-151)**,and the known norterpene peroxides muqubilin and nuapapuin A methyl ester **(152)**. The cytotoxic activities for the isolated compounds were reported against three types of cancer cells including murine leukemia, lung carcinoma and human colon carcinoma cells.[8]

2. Alkaloids: In screening for biologically active metabolites from marine sponges, the crude extract (Chloroform-Methanol, 9:1) of the Red Sea sponge *Hemimycale* species showed a remarkable activity. This extract was separated by chromatography to afford the antitumor, antiviral, and antifungal guanidine alkaloid, ptilomycalin A **(153)**. It had a new carbon skeleton possessing a polycyclic guanidine moiety, which was quite different from those of known guanidine compounds such as tetrodotoxins and saxitoxins.[54]

In 1988, eilatin **(154)** was first isolated from Red Sea tunicate *Eudistoma* sp.[55] Eilatin had an antileukemic effect against *in vitro* Ph+ cells.[56] Later, in 1989, five alkaloids **(155-159)**, segoline A **(155)**, segoline B **(156)**, isosegoline A **(157)**, norsegoline **(158)**, debromoshermilamine A **(159)**, altogether with the previously mentioned compound, eilatin, had been isolated from the Red Sea tunicate *Eudistoma*. The isolated compounds possessed the benzo-1,6-diazaphenanthroline ring system. Isosegoline A was unusual in having a symmetrical heptacyclic structure. The structures of all compounds were elucidated on the basis of spectroscopic data, and in the cases segoline A and B, the structures were also speculated by the aid of chemical transformations.[57] The effects of Eilatin and Norsegoline were evaluated on *in vitro* proliferation and differentiation of leukemic cell lines and blast cells of three AML patients. The results indicated that Eilatin and Norsegoline significantly inhibited self-renewal capacity of leukemic progenitors and provided a useful new tool for the treatment of AML patients.[58] In the same year, nine 2-amino imidazole alkaloids naamidines A-D **(160-163)**, isonaamidines A and B **(164,165)** naamines A and B **(166,167)** and isonaamine A **(168)** belonging to four different groups were isolated from the Red Sea sponge *Leucetta chagosensis.*[59]

Later, two cytotoxic tripyridine alkaloids, niphatoxin A **(169)** and B **(170)**, were isolated from the Red Sea sponge *Niphates*.[60] Aaptosine **(171),** a heteroaromatic substance, was isolated from the Red Sea sponge *Aaptos aaptos*, its structure had been determined on the basis of spectral data and chemical transformation to the two N-Me derivatives.[61] Hyrtiomanzamine **(172)**, a *β*-carboline alkaloid, was isolated from the marine sponge *Hyrtios erecta* collected in the Red Sea. Hyrtiomanzamine was the first 6-OH-*β*-carboline ring associated to a betaine unit isolated from the marine sponge *Hyrtios erecta*.

It showed immunosuppressive activity in the B lymphocytes reaction assay.[62]

In 1997, the C9 alkaloid hanishin **(173)**, isolated from a collection in the Hanish Islands (Red Sea) of the highly polymorphic sponge *Acanthella carteri*, had low enantiomeric purity and was viewed as a shunt metabolite from co-occurring oroidin.[63] Asmarines A-F **(174-179)**, three pairs of nitrogen-containing metabolites, were isolated from the Red Sea sponge *Raspailia* sp., collected in the Dahlak Archipelago, Eritrea. The absolute configuration of asmarine A was determined on the basis of CD measurements of its unstable 18-oxo derivative and mainly the Cotton effect of the dicarbonyl derivative.[64] Antifungal imidazole alkaloids were isolated from the Egyptian Red Sea sponge *Leucetta cf chagosensis* using HPLC. These compounds were the previously reported naamidine A, B, D, naamidine G **(180)** and the unreported symmetric imidazole alkaloid naamine D **(181)**.

Naamine D possessed moderate antifungal and NOS inhibitory activity.[65] Halichondramine **(182)**, a tetracyclic alkylbipiperidine alkaloid, was isolated from the marine sponge *Halichondria* sp., collected in the Dahlak archipelago (the Red Sea), Eritrea.[66]

Bioactive bis-1-oxaquinolizidine N-oxide alkaloids were isolated from the Red Sea specimens of *Xestospongia exigua*, (+)- araguspongine K **(183)**, (+)- araguspongine L **(184)**, (+)- araguspongine A **(185)**, (+)- araguspongine C **(186)**, (+)- araguspongine D **(187)**, (-)- araguspongine E **(188)**, and (+)- xestospongin B **(189)**. The promising *in vitro* antimalarial and antituberculosis activities of araguspongine C were reported.[67] Hyrtioerectines A-C **(190-192)** were isolated from a Red Sea specimen of the marine sponge *Hyrtios erectus*. Hyrtioerectine A contained the carbon bond-linked moieties 6-hydroxy-*β*-carboline and 6-hydroxyindole. Hyrtioerectines A-C were found to be moderately cytotoxic.[68] In 2006, 3-carboxy-1-methyl pyridinium (trigonelline) **(193)** was isolated from the crude extracts of *Sarcophyton glaucum* and *Lobophyton crassum*. The results showed that these soft corals contain natural products including 3-carboxy-1-methyl pyridinium that increased the excitability of DRG neurons, thus inhibiting voltage-activated K^+ currents and therefore contributing to chemical defenses.[69] Hyrtiazepine **(194)**, an azepino-indole-type alkaloid, was isolated from the methanolic crude extract of the Red Sea marine sponge *Hyrtios erectus*.[70]

In 2007, the sponge *Hyrtios erectus* collected from the Red Sea, Egypt was chemically investigated, thus a series of indole alkaloids were isolated, deoxyhyrtiosine A (**195**), and indole-3-carbaldehyde (**196**), in addition to the known indoles, 5-hydroxy-1H-indole-3-carboxylic acid methyl ester (**197**), 5-hydroxy-1H-indole-3-carbaldehyde (**198**) and hyrtiosine A (**199**). The isolated compounds were tested for their cytotoxic and antimicrobial activities. 5-Hydroxy-1H-indole-3-carboxylic acid methyl ester, and indole-3-carbaldehyde showed growth inhibition activity against the L5178Y cell line. Also, deoxyhyrtiosine A, and 5-hydroxy indole-3-carbaldehyde showed mild antimicrobial activities against *Bacillus subtilis* and *Saccharomyces cerevisiae*.[44]

Later, the investigation of the Red Sea sponge *Suberea mollis* afforded two bromotyrosine-derived alkaloids, subereamollines A **(200)** and B **(201)** as well as the known compounds aerothionin **(202)** and homoaerothionin **(203)**. The antimicrobial and antioxidant activities of the isolated compounds were reported.[71]

A comparison of the antimicrobial activity of different extracts of several stony and soft corals from the Red Sea was performed. The data revealed considerable variations between different species. Bioassay-directed fractionation of the active butanol fraction of *Amphimedon chloros* resulted in the isolation of the pyridinium alkaloid antibiotics, the halitoxins and amphitoxins **(204, 205)**. These compounds showed selective activity against specific bacteria, rather than being broad-spectrum. They were highly active against seawater bacteria, whereas bacteria associated with the sponge were resistant.[28]

Investigation of another collection of the Red Sea sponge *Suberea mollis* afforded two brominated arginine-derived alkaloids, subereamines A **(206)** and B **(207)**. The absolute configurations of both compounds were determined by acid hydrolysis

followed by chiral-phase LC-MS. The antimicrobial activities of the isolated compounds were evaluated. Both compounds were inactive against all tested organisms, *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans*.[72]

In 2012, the investigation of a collection of several Red Sea sponges led to the discovery of potential breast cancer migration inhibitors. Extracts of the Verongid sponges *Pseudoceratina arabica* and *Suberea mollis* were selected. Bioassay-directed fractionation of both sponges resulted into the isolation of several brominated alkaloids. Active fractions of the sponge *Pseudoceratina arabica* afforded five alkaloids, ceratinines A-E **(208-212)**, together with the known alkaloids moloka'iamine **(213)**, hydroxymoloka'iamine **(214)** and moloka' iakitamide **(215)**.

The active fraction of the sponge *Suberea mollis* afforded the three known alkaloids subereamolline A, aerothionin and homoaerothionin. Ceratinine B possessed an unprecedented 5,7-dibrominated dihydroindole moiety with an epoxy ring on the side chain of a fully substituted aromatic moiety. Ceratinines D and E possessed a terminal formamide moiety at the ethylamine side chain. Subereamolline A potently inhibited the migration and invasion of the highly metastatic human breast cancer cells MDA-MB-231. Subereamolline A and related brominated alkaloids could be considered as scaffolds appropriate for extensive future use for the control of metastatic breast cancer.[73]

3. Sterols & Steroidal glycosides: In 1979, the steroidal components of *Biemna fortis* were fractionated through reversed phase high-pressure liquid chromatography, analyzed by a combination of physical methods, including high resolution gas chromatography mass spectrometry and 360 MHz ^{1}H-NMR. The sponge contained five conventional D_5-sterols, which comprised ~25% of the mixture, and 2.5% of gorgosterol **(216)**, a sterol never found before in Porifera. Three D_5,7,22-sterols were also present as major components in the mixture (~70%): cholesta-5,7,22-trien-3*β*-ol **(217)** , ergosta-5,7,22-trien-3*β*-ol, **(218)** and (24*R*)-ethylcholesta-5,7,22-trien-3*β*-ol **(219)**, whereas two tetraunsaturated sterols were identified in minor amounts (2%): ergosta-5,7,9(11),22-tetraen-3*β*-ol **(220)** and 24ξ-ethylcholesta- 5,7,9(11),22-tetraen-3*β*-ol **(221)**. [74] Later, conicasterol **(222)** and theonellasterol **(223)** were isolated as the principal sterol constituents from the Red Sea sponges *Theonella conica* and *Theonella swinhoei*, respectively.

The structures were determined by chemical and spectral analyses as well as comparison to the spectral data of the synthesized 4 methylenecholestan-3*β*-ol.[75] The structures of lobophytosterol **(224)**, depresosterol **(225)**, and other three polyoxygenated sterols **(226-228**), isolated from *Lobophytum depressum*, were determined by NMR and mass spectral data, as well as chemical transformation. This was the first example of marine sterol possessing the C-28 atom in various oxidative states. [76] Eryloside A **(229)**, (R=*β*-D-Gal), was isolated from the Red Sea sponge, *Erylus lendenfeldi*.[77]

Three highly oxygenated sterols **(230-232)** were isolated from the Red Sea sponge *Dysidea herbacea*, along with the previously known compound 24-methylene-5*α*-cholest-7-ene-3*β*,5,6*β*-triol **(233)**.[78]

In 2001, as part of a search for novel inhibitors of human deficiency virus type 1 (HIV-1) reverse transcriptase (RT), the methanol ethyl acetate extract of a Red Sea sponge, *Clathria* sp., was shown to be active. Bioassay-guided fractionation of the extract yielded a sterol sulfate, clathsterol **(234)**, which was responsible for the activity and was found to be active at a concentration of 10 mM. Its structure was established mainly by interpretation of spectral data and by chemical transformations.[79] Later, the investigation of the natural products chemistry of the brown alga *Sargassum asperifolium* from the red sea yielded two steroidal metabolite, 24-vinyl cholest-4-ene-24-ol-3-one, saringosterone **(235)**, and 24-vinyl cholest-5-ene-3*β*,24-diol, saringosterol **(236)**. [26]

The steroidal compound, stigmasta-5,(*E*)-24(28)-dien-3-*β*-ol, fucosterol **(237)** was isolated from the petroleum ether fraction of the alcoholic extract of the brown alga, *Dictyota dichotoma* (Hudson) Lamouroux, which was collected from the Red Sea coasts at Hurgada. [25]

Fucosterol was also obtained from the brown alga *Sargassum* sp.[80] Hyrtiosterol **(238)**, a 4*α*-Me polyoxygenated steroid, was isolated from a Red Sea sponge, *Hyrtios* species.[9]

Further search for biologically active marine natural products had led to the isolation of two steroidal saponins, eryloside K **(239)** and eryloside L **(240)**, (R=*β*-D-Gal(1 2)-*β*-D-Gal), together with the known antitumor and antifungal glycoside eryloside A from the organic extract of the sponge *Erylus lendenfeldi* (Geodiidae). Eryloside K is the 24,25-didehydro congener of eryloside A, while eryloside L possessed an unusual 8*α*, 9*α* –epoxy - 4*α* – methyl - 8,9-secocholesta-7,9(11),14-triene skeleton. Eryloside A exhibited antibacterial activity against *Bacillus subtilis* and *Escherichia coli* as well as antifungal activity against *Candida albicans*.[81] Chemical investigation of the dichloromethane extract of the Red Sea marine sponge *Lamellodysidea herbacea* yielded four polyhydroxysteroids, cholesta-8-en-3*β*,5*α*,6*α*,25-tetrol **(241)**, cholesta-8(14)-en-3*β*,5*α*,6*α*-25-tetrol **(242)**, cholesta-8,24-dien-3*β*,5*α*,6*α*-triol **(243)**, and cholesta-8(14),24-dien-3*β*,5*α*,6*α*-triol **(244)**. Compounds **(243,244)** revealed antifungal activity against *Candida tropicalis*, with an inhibition diameter of 13 and 11 mm at 10 mg/disk, respectively.[82]

Other previously reported compounds including 24-methylene cholesterol **(245)**, and cholesterol **(246)** were isolated for the first time from the Red Sea sponge *Negombata corticata*. 24-methylene cholesterol showed anti-inflammatory activity.[83] In 2007, 5*α*,8*α*-epidioxy-cholesta-6-en-3*β*-ol (**247)** was isolated from the Red Sea sponge *Hyrtios erectus*.[44]

Bioassay-guided fractionation of the chloroform fractions of the methanol extracts obtained from the Red Sea sponges *Scalarispongia aqabaensis* and *Callyspongia siphonella* yielded two sterols namely, scalaristerol (5*α*,8*α*-dihydroxycholest-6-en-3*β*-ol) **(248)** from *Scalarispongia aqabaensis*, and callysterol (ergosta-5,11-dien-3*β*-ol) **(249)** from *Callyspongia siphonella*. Assessment of the anti-inflammatory activity of scalaristerol and callysterol using the rat-hind paw edema method was performed. The results indicated that callysterol had strong anti-inflammatory activity, while scalaristerol exhibited moderate anti-inflammatory activity.[84]

7-oxo-cholest-5(6)-en-3-ol **(250)** and cholesterol were isolated from the dichloromethane fraction of *Jania rubens*. The antitumor and antioxidant activities of extracts from the Red Sea seaweeds *Jania rubens*, *Sargassum subrepandum*, and *Ulva lactuca* were tested. Different parameters were measured to prove the anticancer and antioxidant nature of the algal extracts such as tumor marker levels, liver biochemical parameters, and hepatic oxidant/antioxidant status.[85] Chemical investigation of the extract of *Dendronephthya hemprichi*, collected from the Red Sea, Egypt, afforded dendrophen **(251)** and dendrotriol **(252)**. Dendrophen was considered to be the first 3*β*-acetoxy-glycyrrhetyl amino acid conjugate isolated from nature.[86]

The secondary metabolites of the Red Sea soft coral *Heteroxenia fuscescens* were studied. The soft coral's examination had led to the isolation of gorgosten-5(*E*)-3*β*-ol (**253**) and sarcoaldosterol A (**254**). The isolated compounds were identified for the first time from this soft coral. It was proved that the alcoholic extract possessed anti-inflammatory, antipyretic, analgesic and antioxidant activities. The antimicrobial activity of the total alcoholic extract and the isolated compounds were investigated against the following microorganisms: *Bacillus subtilis*, *Staphylococcu aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Syncephalastrum racemosum*, *Aspergillus fumigatus* and *Penicillium italicum*.

It was found that the total alcoholic extract of *Heteroxenia fuscescens* had a marked effect against all tested bacterial strains either gram positive or gram negative bacteria as well as all tested fungus strains, also the results revealed that the activity on gram negative bacteria was higher than gram positive bacteria. The extract showed the highest activity against *Escherichia coli* with inhibition zone diameter 20 mm. The isolated compounds exhibited antimicrobial activity against all tested bacteria except *Pseudomonas aeruginosa* and fungus strains.[87]

Gorgostan-3*β*,5*α*,6*β*-triol - 11 *α* - acetate **(255)**, together with two previously isolated gorgostane derivatives, gorgosten-5(*E*)-3*β*-ol and gorgostan-3*β*,5*α*,6*β*,11*α*-tetraol (sarcoaldosterol A) were obtained from the chloroform extract of the Egyptian Red Sea soft coral, *Heteroxenia ghardaquensis* (family Xeniidae). Gorgostan-3*β*,5*α*,6*β*-triol-11*α*-acetate was reported for the first time. Gorgosten-5(*E*)-3*β*-ol exhibited moderate activity as growth inhibitor of human colon tumor cell lines.[88]

Recently, the chloroform and ethyl acetate fractions of the methanolic extract of the Red Sea sponge *Dragmacidon coccinea* were investigated, which led to the isolation of clionasterol **(256)**, stigmasterol **(257)**, campesterol **(258)**, and brassicasterol **(259)**. [89]

4. Other metabolites: In 1983, two tetrabromo metabolites, psammaplysins A and B (**260, 261)** possessing the hitherto unknown spirocyclohexadienyloxazoline moiety were isolated from *Psammaplysilla purpurea*. Their structures were elucidated by using spectroscopic methods and chemical degradations.[90]

In 1985, Latrunculin A-D **(262-265)**, were isolated from the Red Sea sponge *Latrunculia magnifica*. The absolute configuration of latrunculin-A was determined by X-ray analysis, and chemical degradation.[91] In the same year, Swinholide-A **(266),** a 22-membered macrolide, was isolated from the Red Sea sponge *Theonella swinhoei*.[92] Six brominated unsaturated polyenynic C9-, C16-, and C18-acids **(267-272)** were isolated from the marine sponge *Xestospongia*, collected from the Gulf of Eilat, Red Sea.[93] In 1988, a hexachloro-metabolite, dysidamide **(273)** was isolated from a Red Sea sponge *Dysidea* sp.[94] Etzionin **(274)**, a diketopiperazine hydroxamate derivative, was isolated from a Red Sea tunicate.[95]

The structure of several ceramides and cerebrosides, ptiloceramides **(275)**, halicerebroside A **(276)**, and amphicerebrosides B-F**(277-281)**, were obtained from three marine sponges *Ptilocaulis spiculifer*, *Haliclona*, and *Amphimedon viridis* as well as the soft coral *Heteroxenia gardaquensis* collected in the Red Sea.[96]

Six avarol and avarone derivatives, 3'-hydroxyavarone **(282)**, 3',6'-dihydroxyavarone **(283)**, 6'-hydroxyavarol **(284)**, 6'-acetoxyavarol **(285)**, 6'-acetoxyavarone **(286)**, and 6'-hydroxy-4' methoxyavarone **(287)** were reported from the Red Sea sponge *Dysidea cinerea*. Cytotoxic, antimicrobial, and anti-HIV-1 reverse transcriptase activities were tested for some of the isolated compounds, where 6'-hydroxy-4'-methoxyavarone was found to be the most active.[97] Dysidamides B **(288)**, dysidamide C **(289)**, and a 1,4-dideoxyhexose **(290)** were isolated from the Red Sea sponge *Dysidea herbacea*, along with the previously known furodysinin lactone **(291)**, and *α*-D-xylopyranose **(292)**.[78]

Two hexapreynylhydroquinone-derived disulfates, shaagrockol B **(293)** and C **(294)** were obtained from the Red Sea sponge *Toxiclona toxius*.[98] Four hexaprenoid hydroquinone sulfates, toxicols A-C **(295-297)** and toxiusol A **(298)** were isolated from the Red Sea sponge *Toxiclona toxius*. Several of these compounds were found to possess antifungal activity against *Candida albicans*, and to inhibit HIV reverse transcriptase.[99] Specifically, toxiusol A had been shown to be a potent inhibitor of various viral reverse transcriptases.[100] Petrosynol and petrosolic acid **(299,300)**, two polyacetylenes, were reported from the Red Sea sponge *Petrosia* sp. Both inhibited the DNA polymerase activities of the reverse transcriptase of human immunodeficiency virus.[101]

Colpol **(301)**, a dibromo C6-C4-C6 metabolite, was isolated from the Red Sea alga *Colpomenia sinuosa*.[102] A hydroxy phenyl heptadienoic acid, 3-hydroxy-7-phenyl-4*E*,6*E*-heptadienoic acid **(302)**, had been obtained from the ascidian *Didemnum granulatum* collected from the Gulf of Eilat in the Red Sea.[103] In 1994, 3,5,8-trihydroxy-4-quinolone **(303)** was obtained from the Red Sea sponge *Verongia* sp.

It was found to inhibit HIV-1 and HIV-2 RNA-directed DNA synthesis of the reverse transcriptase (RTs). This compound was proved also to inhibit the catalytic activities of the RT of murine leukemia virus.[104] Erylusamine TA **(304)(** R_1=Ac, R_2=$CH_2CH_2CH_2CH_2CH_2NMe_2$, R_3=H, n=8, m=2), erylusine **(305) (**R_1=Ac, R_2=$CH_2CH_2CH_2NMe$ CH_2

$CH_2CH_2CH_2NMe_2$, R3=H, n=8, m=2) and erylusidine **(306)** (R_1=H, R_2=$CH_2CH_2CH_2CH_2$ NHC=NH(NH_2), R_3=$COCH_2CH(CH_3)_2$, n=8, m=3), three cytotoxic glycolipids, had been isolated from the Red Sea sponge *Erylus cf. lendenfeldi*.[105]

In 1997, hurghamides A-D **(307-310)**, four N-acyl-2-methylene-*β*-Ala Me esters, were reported from a Red Sea sponge *Hippospongia*.[106] Hanishenol B **(311)**, branched glycerol enol ether, and the unbranched analog, hanishenol A **(312)**, were isolated from the axinellid sponge *Acanthella carteri Dendy*, (= *Acanthella aurantiaca Keller*, 1889) from the Hanish Islands, Southern Red Sea, by ethanol extraction followed by flash chromatography and HPLC purification.[107] 2-hexaprenylhydroquinone (HPH) **(313)**, reported from the Red Sea sponge *Ircinia* sp. It had been shown to be a general inhibitor of retroviral reverse transcriptases (from HIV-1, HIV-2 and murine leukemia virus), also it inhibited cellular DNA polymerases (*Escherichia coli* DNA polymerase I, and DNA polymerases A and B).[108]

The Red Sea marine sponge *Acarnus cf. bergquistae* afforded two cyclic peroxide-containing polyketide C22 Me esters, which were identified as peroxyacarnoic acid methyl esters A and B **(314, 315)**. Both compounds contained a single 1,2-dioxane ring, an eneyne functionality, and a terminal double bond or triple bond, respectively. [109] Hurghadin **(316)**, a pigment, was isolated from the Red Sea nudibranch *Hexabranchus sanguineus*.[110] Me 3-oxo-cholan-24-oate **(317)** was obtained from the Red Sea sponge *Raspailia* sp., collected in the Dahlak Archipelago, Eritrea. [64] Three N-acyl-2-methylene-*β*-alanine methyl esters, hurghamides E-G **(318, 319(m+n=6), 320(m+n=8))** were isolated from a Red Sea sponge *Hippospongia* sp.[111] Six polyacetylenic compounds, aikupikanynes A-F **(321-326)** and octahydrosiphonochalyne **(327)**, were isolated and identified from the methanolic extract of the Red Sea sponge *Callyspongia* sp. [112] 16-*epi*-latrunculin B **(328)**, epimer of latrunculin B, was reported from the sponge *Negombata magnifica* collected from the Red Sea near Hurghada, Egypt. The cytotoxicity (murine tumor and normal cell lines) and antiviral (HSV-1) properties of both compounds were determined.[113]

The investigation of the Red Sea invertebrates *Dendrophyllia* sp., *Dendronephthya* sp. (red variety), *Dendronephthya* sp. (yellow variety), and *Tubipora musica* led to the isolation of eight brominated oxylipins **(329-336)**. The compounds gave positive results in the brine shrimp toxicity assay, the sea urchin eggs test (*Paracentrotus lividus*), and the crown gall tumor on potato disks test (*Agrobacterium tumefaciens*).[114]

In 2003, chagosensine **(337)**, a sixteen-membered chlorinated macrolide, was isolated from the Red Sea calcareous sponge *Leucetta chagosensis*.[115] Callyspongamide A **(338)**, a cytotoxic polyacetylenic amide, was isolated from the marine sponge *Callyspongia fistularis* collected in the Red Sea. Callyspongamide A is an amide derivative of a C17-polyacetylenic acid and phenethylamine.[116] The chemical investigation of the organic extract of the same Red Sea sponge, *Callyspongia* sp., resulted in the isolation and identification of three C22-polyacetylenic alcohols, callyspongenols A-C **(339-341)** together with dehydroisophonochalynol. All of the above compounds exhibited moderate cytotoxicity against P388 and HeLa cells.[117]

Latrunculinosides A and B **(342, 343)**, two glycosides containing unusual saccharides such as *β*-D-olivose, *β*-L-digitoxose, *α*-L-amicetose, and *β*-D-oliose, were reported from *Latrunculia corticata* collected in the Gulf of Aqaba, Israel. Both compounds gave positive results in antifeeding activity assays.[118] Lytophilippines A-C **(344-346)**, chloro-containing macrolactones, were isolated from the Red Sea hydroid *Lytocarpus philippinus*. The compounds gave positive results in the crown gall tumor inhibition test and brine shrimp toxicity assay.[119]

Latrunculeic acid **(347)**, an analog of latrunculin B, was isolated together with several known compounds including latrunculin B, 15-methoxylatrunculin B **(348)**, 16-*epi*-latrunculin B, and latrunculin C, from the Red Sea sponge *Negombata magnifica*.[120]

Seven polychlorinated derivatives **(349-355)** were obtained from the dichloromethane extract of the Red Sea marine sponge *Lamellodysidea herbacea*, in addition to the known compounds, dysidamide,

dysidamide B and dysidamide C. Dysidamide showed neurotoxic effects towards both mesencephalic and cortical murine neurons at 0.8 mg/ml.[121] The ethyl acetate extract of a *Cladosporium* sp., isolated from the Red Sea sponge *Niphates rowi*, was fractionated to yield a hexaketide, pandangolide 1a **(356)**, together with its known diastereomer pandangolide 1 **(357)** and the known iso-cladospolide B **(358)**. The absolute configurations of the stereocenters in these compounds were determined by Riguera's method and CD.[122]

The chemical examination of the Red Sea sponge *Negombata magnifica* afforded another latrunculin named latrunculin T **(359)**. Latrunculins showed potent antimicrobial activity against *Candida albicans*, *Saccharomyces cerevisiae*, *Staphylococcus aureus*, and *Bacillus cereus.* Latrunculins could be considered as potential leads that can be developed as anticancer and antimicrobial agents.[123] A diglyceride ester, corticaglyceride **(360)** and a sphingolipid, corticaceramide **(361)** were characterized from the Red Sea sponge *Negombata corticata*. Other previously reported compounds including nervonic acid **(362)** was also isolated for the first time from this genus. Compounds **(360** and **361)** showed mild anti-oxidant properties.[83]

Two macrolides, swinholide I **(363)** and hurghadolide A **(364)**, together with the previously isolated swinholide A, were isolated from the sponge *Theonella swinhoei*. Swinholide I is the first derivative of swinholide A with hydroxylation at the sidechain. Hurghadolide A possessed an unprecedented asymmetric 42-membered dilactone moiety, thus presenting a novel skeleton of macrolides. Swinholide I and hurghadolide A exhibited *in vitro* cytotoxicity against human colon adenocarcinoma (HCT-116) with IC_{50} values of 5.6 and 365 nM, respectively. Furthermore, both compounds were biologically active against *Candida albicans*.[124]

Thymidine **(365)**, a nucleoside, and two glycosides (methyl-*β*-D-xylopyranoside **(366)** and glycerol-2-*α*-D-glucopyranoside **(367)** were reported from the chloroform soluble fraction of the red alga *Liagora farinosa*, collected from the Red Sea, Egypt. The isolated compounds were tested for their antioxidant activity and showed variable activity.[125] Oxalatrunculin B (I) **(368)**, a latrunculin that was isolated from Red Sea sponge *Negombata corticata*. It exhibited significant antifungal activity against *Saccharomyces cerevisiae*, also its cytotoxic activity was evaluated against several cell lines including Hep G2, HCT-116 and 1301.[126]

Two brominated phenolic compounds, subereaphenols B **(369)** and C **(370)**, along with the known compounds 11,19-dideoxyfistularin-3 **(371)**, aeroplysinin-1 **(372)** and aeroplysinin-2 **(373)** were obtained from the Red Sea sponge *Suberea mollis*. The antimicrobial and antioxidant activities of the isolated compounds had been evaluated. Aeroplysinin-1 displayed significant antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Only subereaphenols B and C displayed a significant antioxidant activity.[71] In 2008, an antiepileptic ceramide mixture **(374)** (a: n_1=13, n_2=9 and b: n_1=11, n_2=11) was isolated from the Red Sea sponge *Negombata corticata*. Its anticonvulsant activity was measured *in vivo* using the pentylenetetrazole-induced seizure model.[127]

The Red Sea sponge *Pseudoceratina arabica* was chemically investigated to give a brominated phenolic compound, ceratinophenol A **(375)**, together with the known compounds ceratinamine **(376)**, 5-bromo - 2,3 - dihydroxy-6-methoxy benzaldehyde **(377)**, and psammaplysin-A **(378)**. Biological evaluation indicated that these compounds exhibited weak antibacterial and antifungal activities.[128] A cytotoxic and antimicrobial dibrominated phenol, subereaphenol A **(379)**, together with, 2-(3',5'-dibromo- 2'-hydroxy-4'-methoxyphenyl) acetamide **(380)**, dibromoverongia quinol **(381)**, bromo chloroverongiaquinol **(382)**, and 2-(3',5'-dibromo-4'-ethoxy-1' - hydroxy - 4'- methoxy -2', 5' - cyclo hexadien-1-yl) acetamide **(383)** were reported from the sponge *Suberea mollis* collected at the Egyptian Red Sea coast. The cytotoxic and the antimicrobial activities of the compounds were tested. Compound **(379)** showed moderate cytotoxicity against P-388 leukemia cells, while compound **(382)** was cytotoxic to HeLa cells with IC_{50}= 5 μg/ml.

The results of the antimicrobial activity proved that 1,4 quinol skeleton was required for maximum antimicrobial activity such as in compounds **(381,382)**.

Absence of the ketone functionality blocked the antimicrobial activity as in compound **(383)**. Moreover, the dibromo-substitution of the 1,4 quinol skeleton, as in compound **(381)**, exhibited higher activity than that of the chloro-bromo substitution as present in compound **(382)**. Also, the phenolic hydroxylation at C-4 of the aromatic skeleton was essential for the antimicrobial activity as in compound **(379)**, while the OH-methylation completely blocked the antimicrobial activity as in compound **(380)**.[129] 7-methyl-9-oxo-dec-7-eneoic acid **(384)**, a ketone, characterized and identified from the Red Sea sponge *Ircinia* sp.[130] Four γ-naphthopyrones **(385-388)**, 6-methoxycomaparvin 5-Me ether 8-O-sodiosulfate **(385)**, 6-methoxycomaparvin 8-O-sodiosulfate **(386)**, 6-methoxycomaparvin 5-Me ether **(387)**, and 6-methoxycomaparvin **(388)**, were isolated and identified from the crinoids *Oligometra serripinna* of the Red Sea. X-ray analysis was performed for 6-methoxycomaparvin 5-Me ether.

Compounds **(386-388)** were found to exhibit DPPH scavenging activities with EC_{50} values 46.5 mg/ml, 25.0 mg/ml and 22.5 mg/ml, respectively, thus illustrating antioxidant activity.[131] In a screening of marine bacteria, a Vibrio species isolated from the surface of the soft coral *Sinularia polydactyla* collected in the Red Sea was found to be a prolific producer of secondary metabolites with antibacterial and cytotoxic activities. Seven maleimide derivatives named aqabamycins A-G **(389-395)**, were isolated together with the known metabolites 3-nitro-1H-indazole **(396)**, indazole-3-carbaldehyde **(397)**, phenyl-2-bis-indolylmethane **(398)**, turbomycin B **(399)**, vibrindole A **(400)**, 1,4-dithiane **(401)**, 3-(3-nitro-4-hydroxyphenyl)-2-propenoic acid **(402)**, 3-nitro-4-hydroxybenzaldehyde **(403)**, phenylacetic acid **(404)**, benzoic acid **(405)**, 3-hydroxybenzoic acid **(406)** and 4-hydroxycinnamic acid **(407)**, from a Vibrio species isolated from the surface of the soft coral *Sinularia polydactyla* collected in the Red Sea. The aqabamycins, except aqabamycin A, beared a nitro group. Compounds **(396, 397, 401)** were described for the first time from a natural source, and vibrindole A was found to possess cytotoxic activity against Colo-320, MCF-7 and MDA-MB 321 cell lines.[132, 133]

In 2010, the chemical investigation of the ethanol extract of the marine-derived fungal strain MF 003 (Deuteromycete) obtained from Red Sea mangrove drift wood, led to the isolation of two benzofuranoids, deuteromycol A **(408)** and deuteromycol B **(409)**. Deuteromycols A and B contain a catecholic nucleus that is unusual in association with marine fungi secondary metabolites. The extracts exhibited *in vitro* antibacterial activity. [134] Furthermore, the investigation of a collection of the Red Sea sponge *Suberea mollis* afforded a brominated phenolic compound, subereaphenol D **(410)**, and the known compounds dichloroverongiaquinol **(411)**, and purealdin L **(412)**. Dichloroverongiaquinol and subereaphenol D exhibited promising antimicrobial activity. Subereaphenol D showed a significant antioxidant effect.[72] 4-oxo-pentanoic acid **(413)**, 2-methyl-acrylic acid 2-diethylaminoethyl ester **(414)**, juniper camphor **(415)**, hexitol **(416)** and 2-octadecanone **(417)** were isolated by chromatographic separation from the low-polarity components of the *Dendronephthya hemprichi* extract, collected from the Red Sea, Egypt.[86]

Fucoxanthin **(418)** was obtained from Red Sea macroalgae *Sargassum* sp., it was found that fucoxanthin had strong antioxidant and cytotoxicity against breast cancer (MCF-7) with IC_{50} = 11.5 mg/ml. Fucoxanthin could be used as safe antioxidant and as an antitumor compound.[80] Two grassypeptolides **(419,420)** and a lyngbyastatin analog (Ibuepidemethoxylyngbyastatin 3) **(421)**, together with the known dolastatin 12 (**422)**, had been isolated from field collections and laboratory cultures of the marine cyanobacterium *Leptolyngbya* sp. collected from the Red Sea.

Grassypeptolides D and E showed significant cytotoxicity to HeLa (IC_{50} = 335 and 192 nM, respectively) and mouse neuro-2α blastoma cells (IC_{50} = 599 and 407 nM, respectively), in contrast to Ibu-epidemethoxylyngbyastatin 3 (neuro-2α cells, IC_{50} > 10 mM) and dolastatin 12 (neuro-2α cells, IC_{50} > 1 mM).[135]

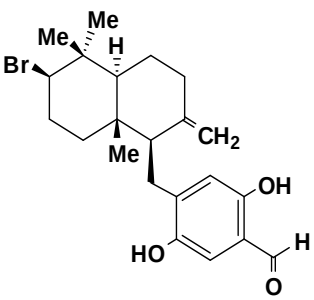
Miraziridine A **(423)**, a potent cathepsin B inhibitor, was isolated from the Red Sea sponge *Theonella swinhoei*.[136] The chemical analysis of the Red Sea soft coral *Heteroxenia fuscescens* concerning its secondary metabolites led to the isolation of 6-hydroxy-*α*-muurolene **(424)**, 1-nonadecyloxy - 2, 3 - propanediol **(425)** and (2*S*,3*R*,4*E*,8*E*)-*N* - hexadecanoyl - 2-amino 4,8-octadecadiene - 1, 3 - diol **(426)**.

The isolated compounds were reported for the first time from the soft coral *Heteroxenia fuscescens.* The isolated compounds were tested against *Bacillus subtilis*, *Staphylococcu aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Syncephalastrum racemosum*, *Aspergillus fumigates*, and *Penicillium italicum*. The isolated compounds showed antimicrobial activity against all tested bacteria except *Pseudomonas aeruginosa* and fungus strains except compound **(426)**, which didn`t show any antimicrobial activity.

While, compound **(424)** showed the highest antimicrobial activity against all tested organisms except *Pseudomonas aeruginosa* and showed highest activity against gram positive bacteria (*Staphylococcus aureus*), with inhibition zone diameter 24.4 mm.[87] In 2012, a new diglyceride ester **(427)** along with asebotin **(428)** were reported for the first time from the Red Sea grass *Thallasodendron ciliatum*. The results of the bioactivity guided fractionation indicated that the extracts of Red Sea grass *Thallasodendron ciliatum* possessed potent antiviral activity against the highly pathogenic avian influenza strain H_5N_1virus (100% inhibition at the concentration of 1 mg/ml). The two isolates showed reduction of virus titer by 67.26% and 53.81% inhibition at concentration of 1 ng/ml, respectively. [137]

In 2014, a new nucleoside, dragmacidoside **(429)**, along with known compounds, adenosine **(430)**, inosine **(431)**, deoxycytidine **(432)**, methyl-*α*-D-glucopyranoside **(433)** were obtained from the chloroform and ethyl acetate fractions of the methanolic extract the Red Sea sponge *Dragmacidon coccinea*. Biological testing revealed that the chloroform fraction showed significant anti-inflammatory activity using the carrageenan method.[89]

Recently, two new polyacetylenes, callyspongenol-D **(434)** and callyspongendiol **(435)** were isolated from the Red Sea sponge *Siphonochalina siphonella.* The cytotoxicity of the isolated compounds towards the human mammary carcinoma cell line MCF-7 was tested, where callyspongenol-D was found to be toxic with IC_{50} value of 11.7μM.[138]



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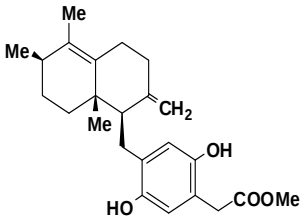

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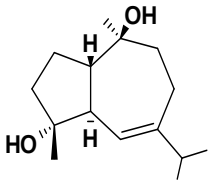

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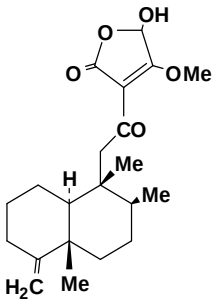

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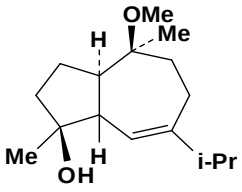

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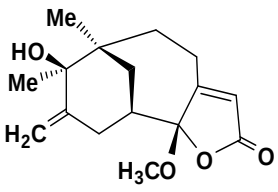

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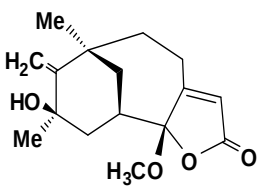

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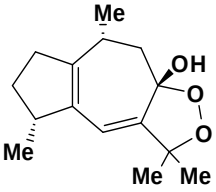

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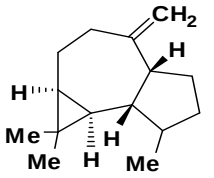

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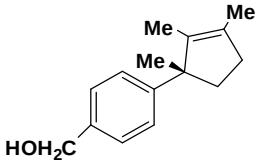

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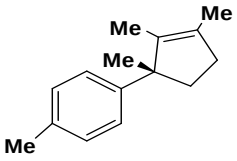

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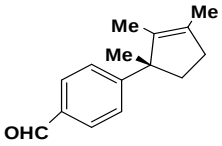

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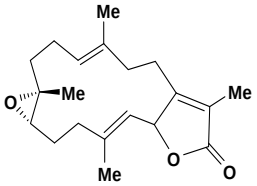
FIG. 1: SESQUITERPENES 1-12



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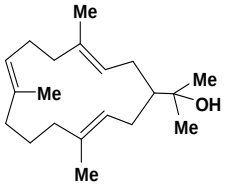

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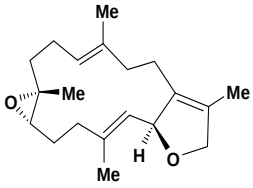

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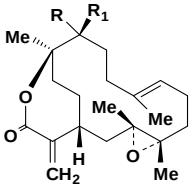
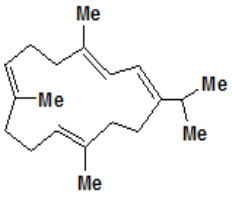


16, R=OAc, R_1=H
17 RR_1=O



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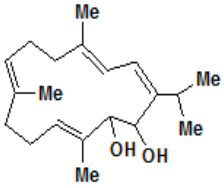

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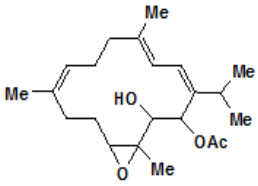

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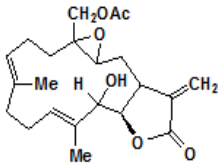

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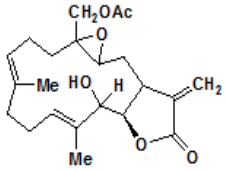

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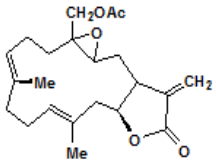

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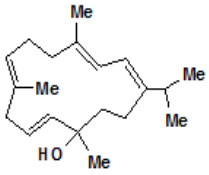

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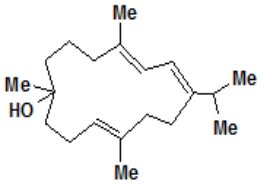

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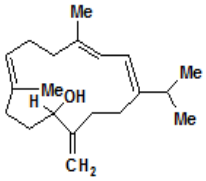

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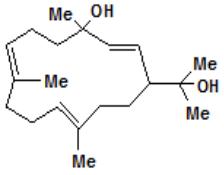

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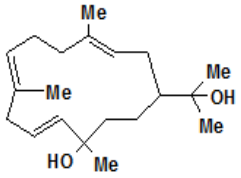

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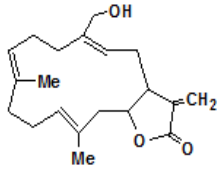

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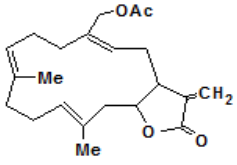

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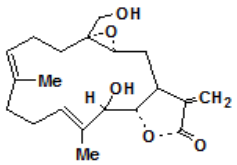

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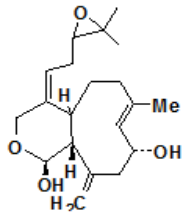

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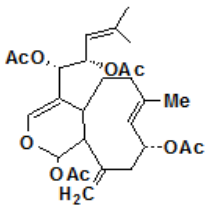

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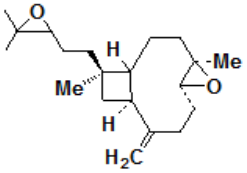

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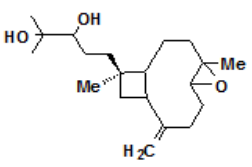

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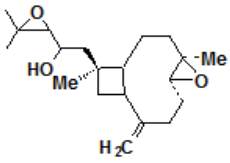

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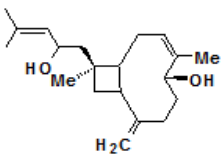

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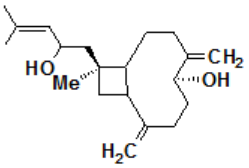

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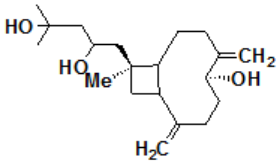

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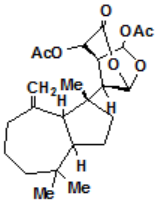

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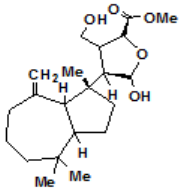

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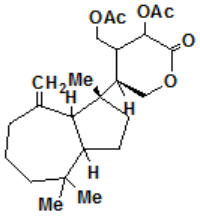

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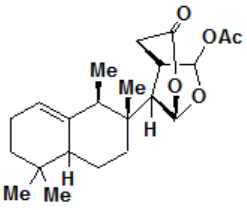

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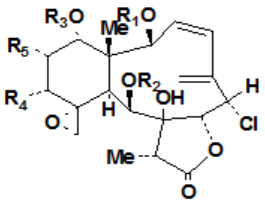

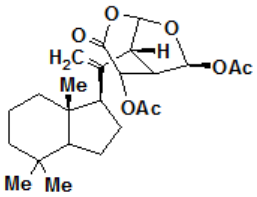

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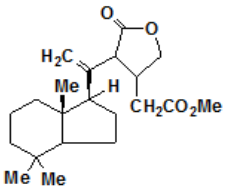
44, $R_1=R_2=R_3=Ac$, $R_4=R_5=H$
45, $R_1=R_2=R_3=Ac$, $R_4=R_5=H$, 11, 20 deoxy
46, $R_2=Ac$, R_1, R_3, OR_4=2 Ac + isovalerate, $R_5=H$
47, $R_1=R_2=R_3=Ac$, $R_4=OAc$, $R_5=H$
48, $R_1=R_2=R_3=Ac$, $R_4=R_5=OAc$
49, 49, 3, 4 dihydro, R_1, R_2, R_3, OR_4=3 Ac+isobutyrate, R5=H



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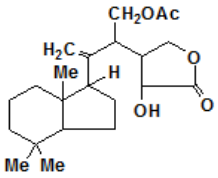

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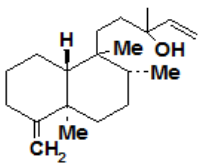

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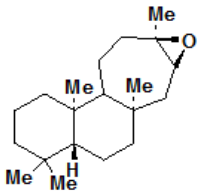

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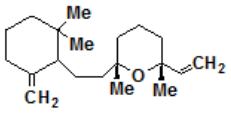

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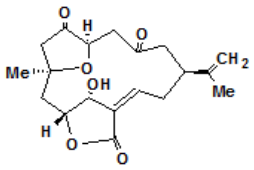

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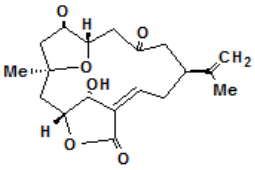

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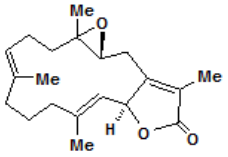
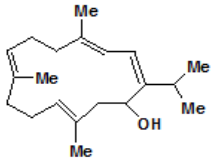


58



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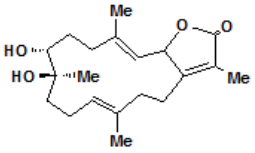

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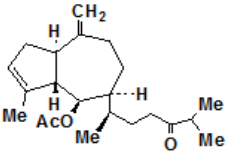

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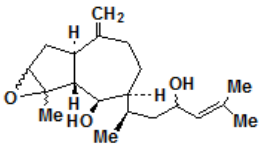

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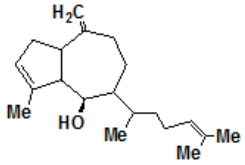

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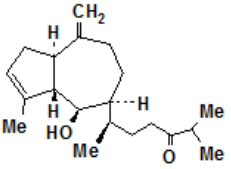
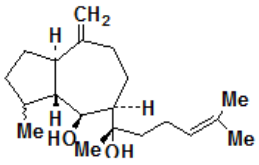


64



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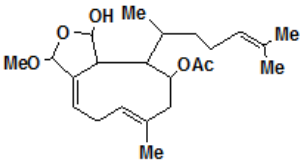

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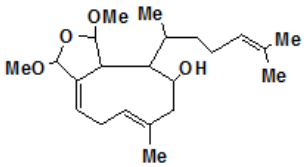
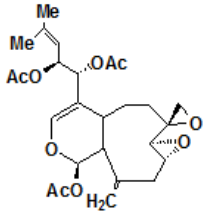
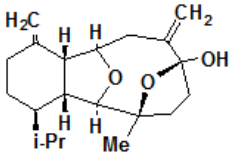


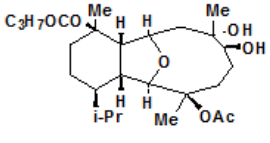
67



68



69



70

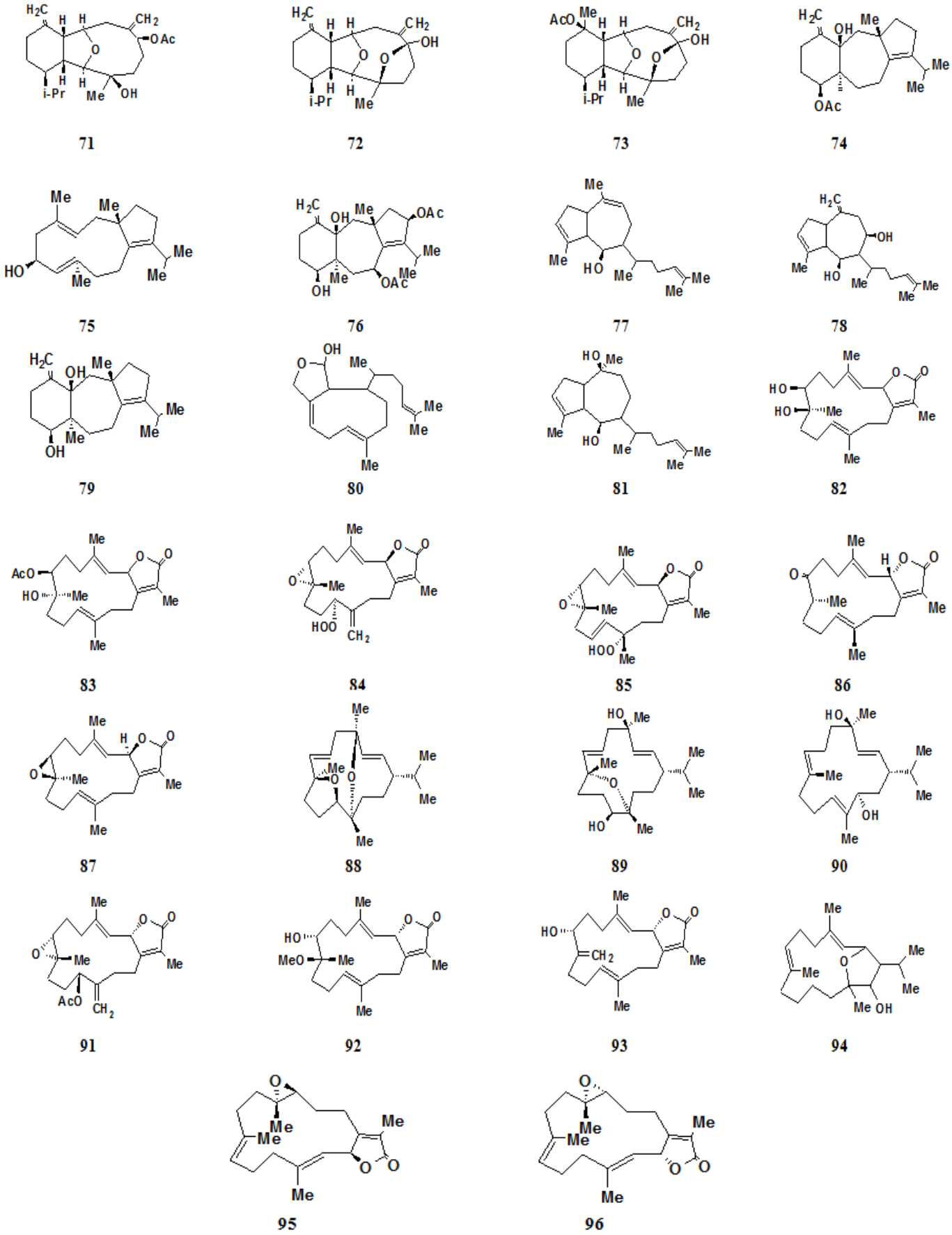


FIG. 2: DITERPENES 13-96

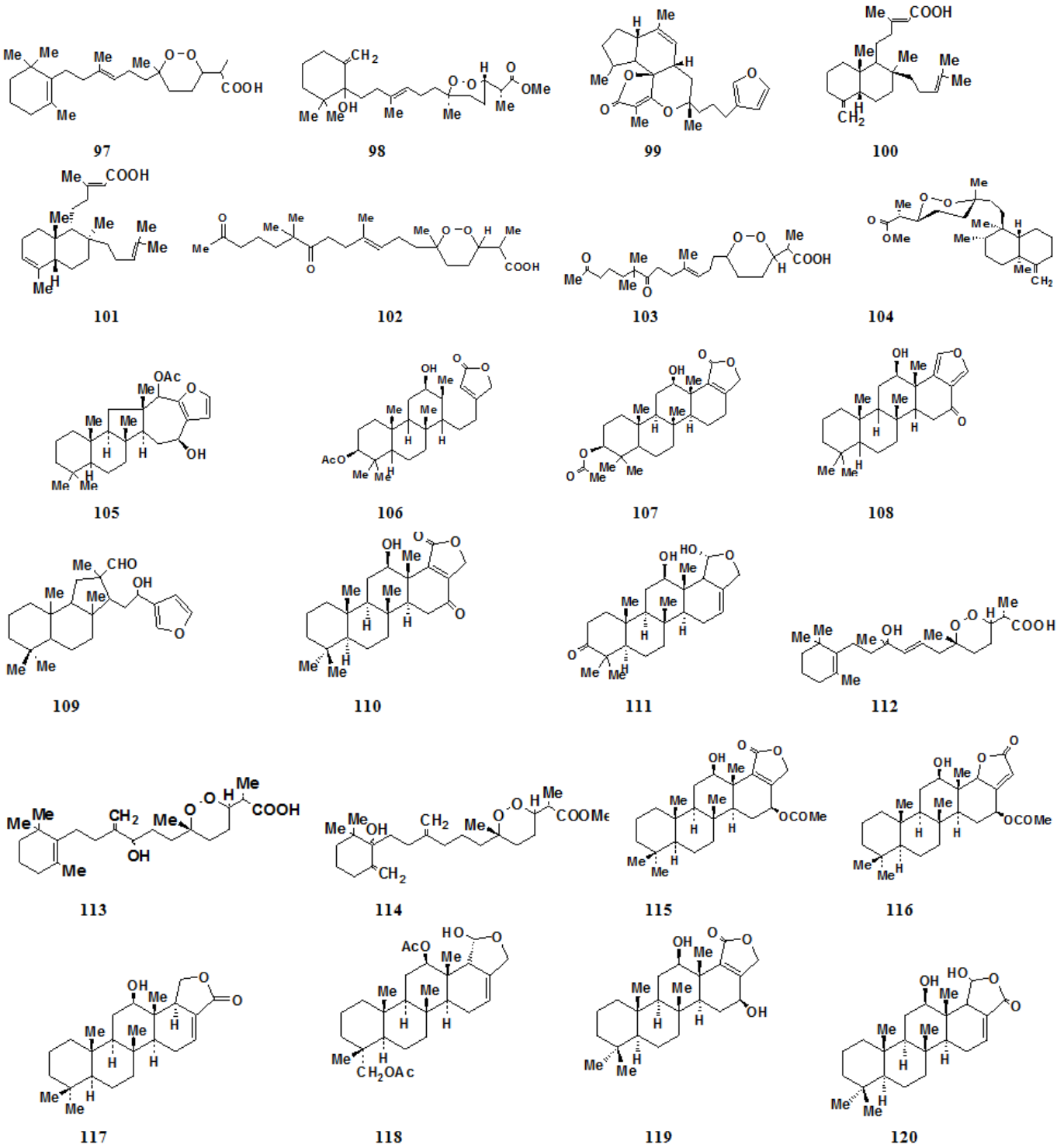
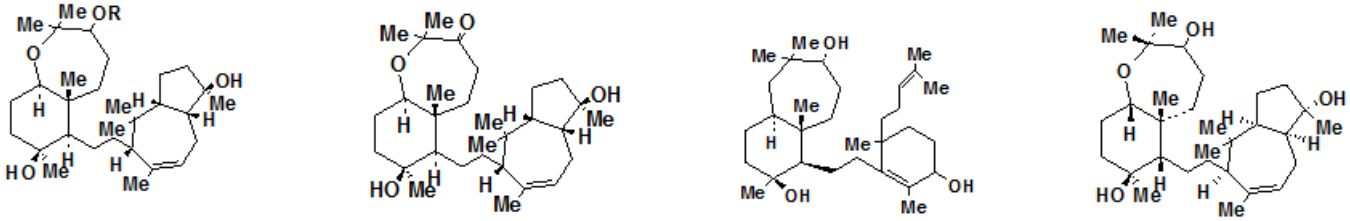


FIG. 3: SESTERTERPENES 97-120



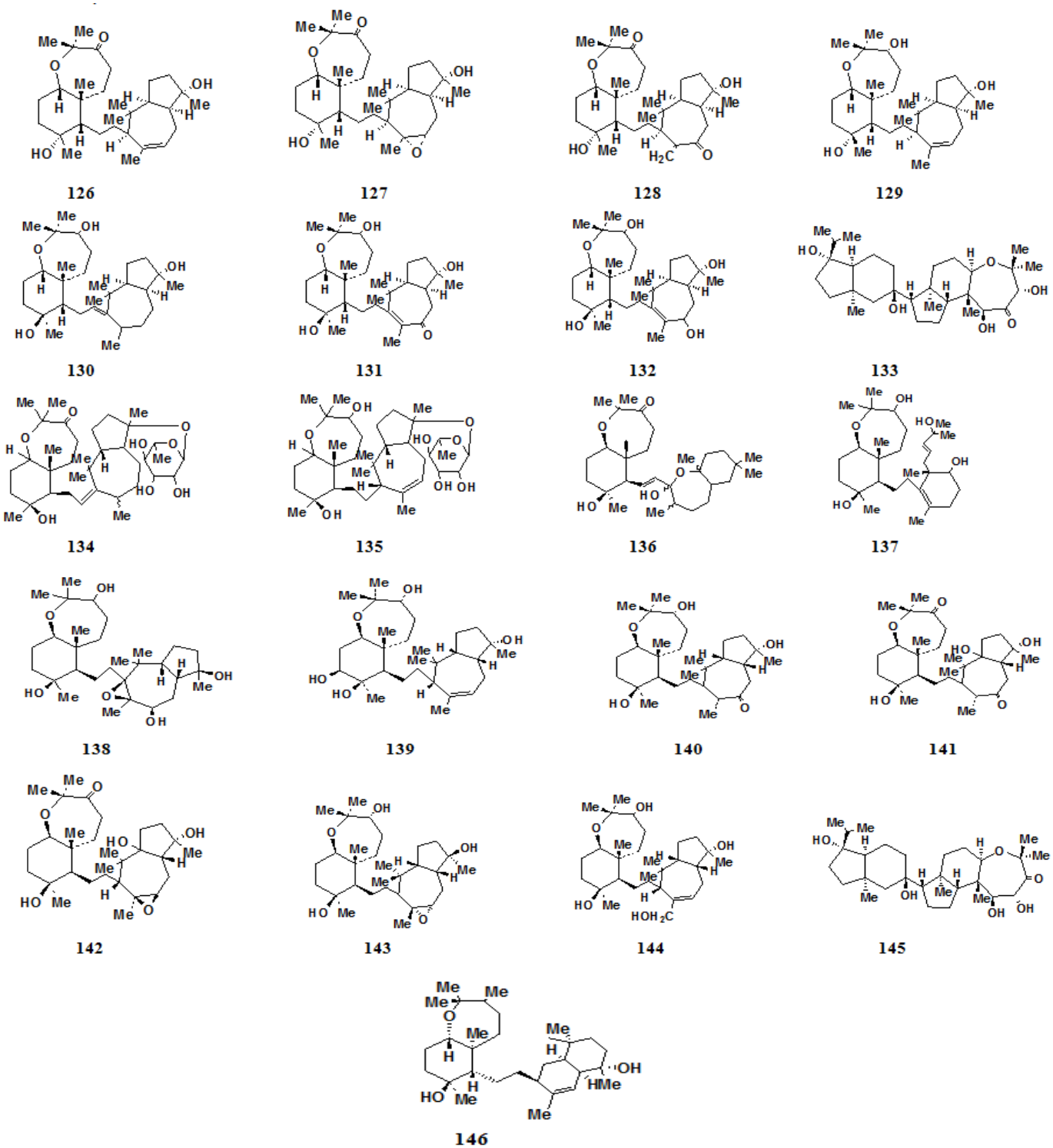


FIG. 4: TRITERPENES 121-146

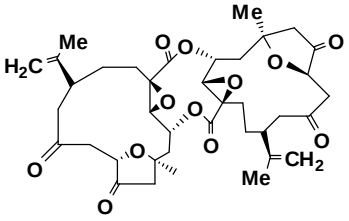
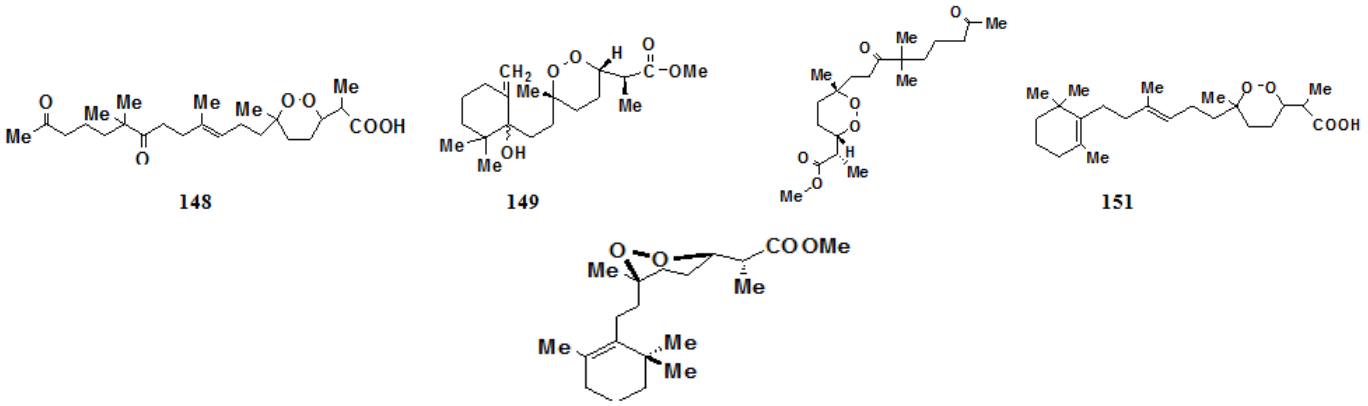
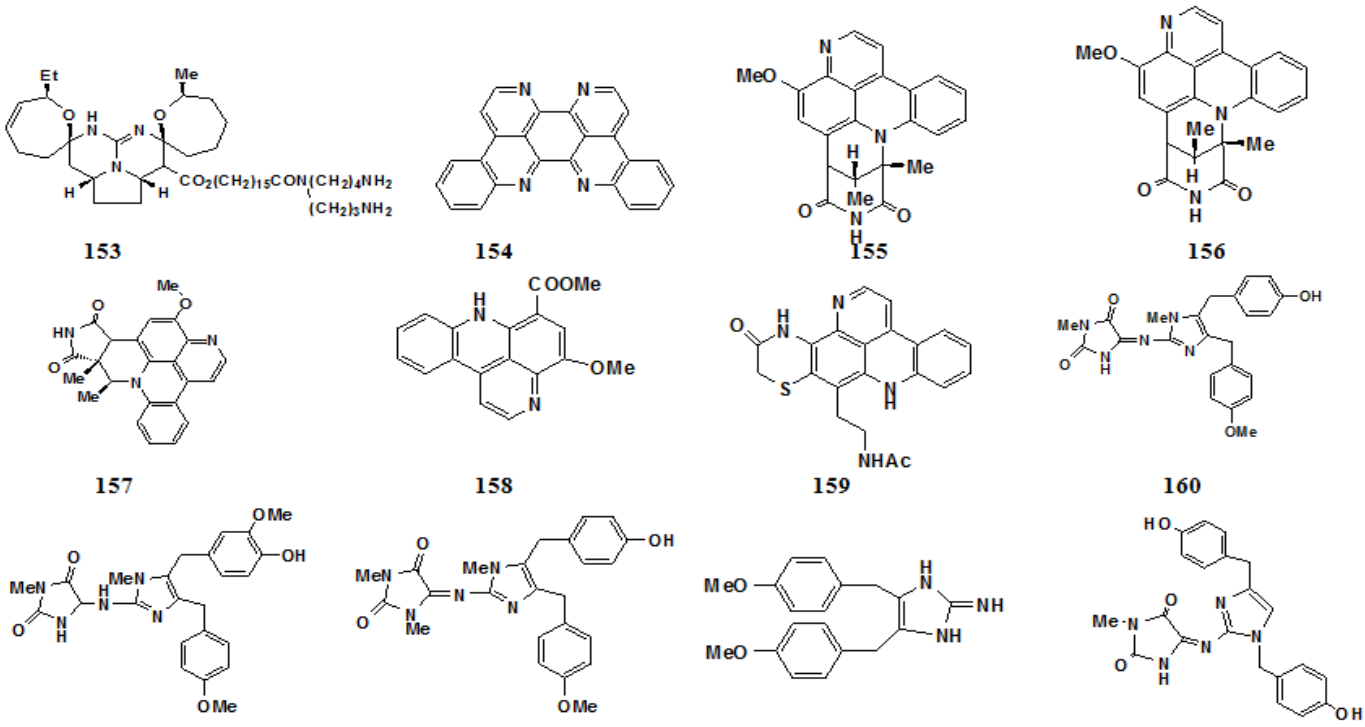


FIG. 5: TETRATERPENE 147



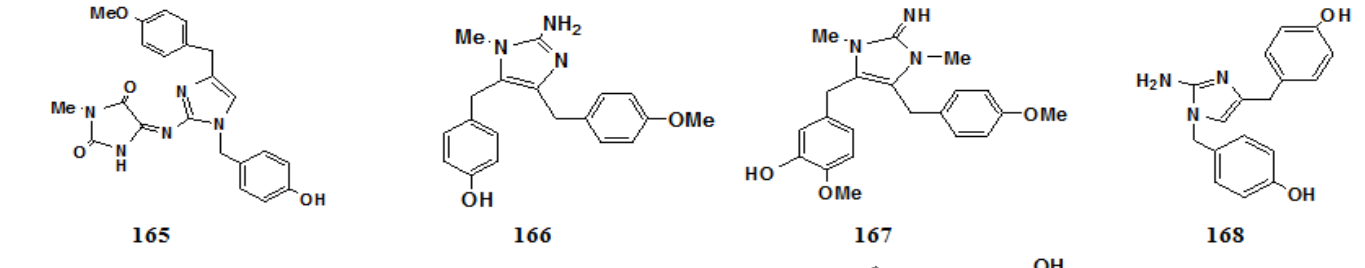
148 149 151 152

FIG. 6: NORTERPENES 148-152

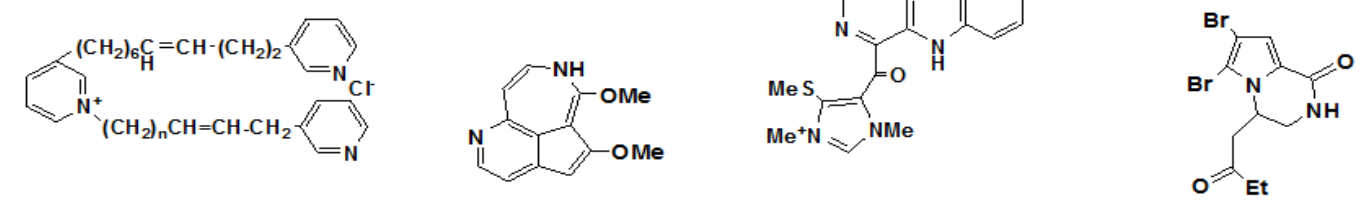


153 154 155 156 157 158 159 160

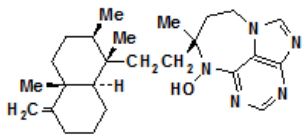
161 162 163 164



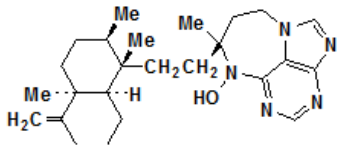
165 166 167 168



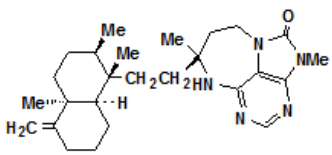
169, n=7
170, n=8 171 172 173



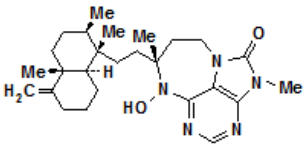
174



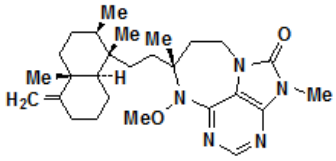
175



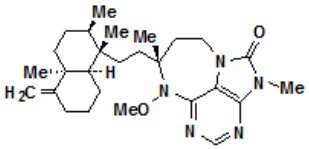
176



177



178



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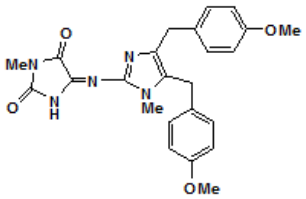

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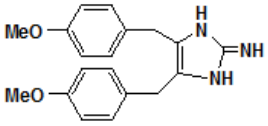

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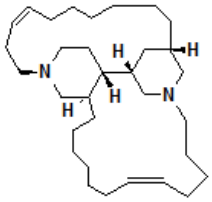
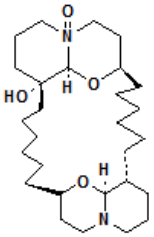
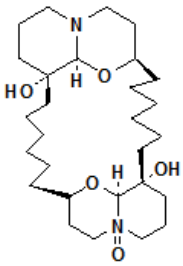


182



183



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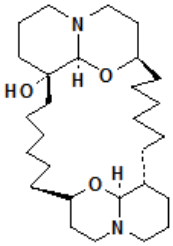

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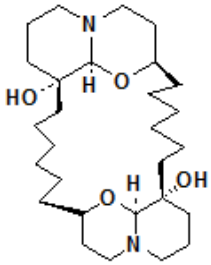

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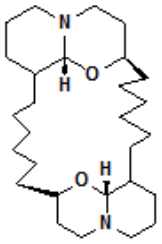

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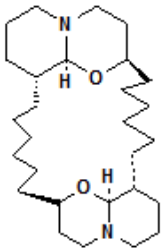

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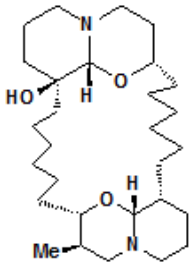
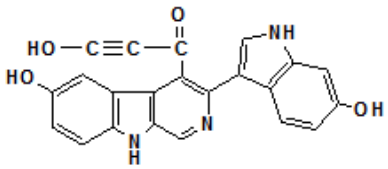


189



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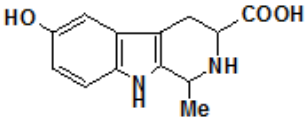

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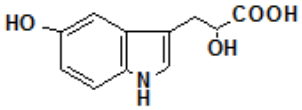
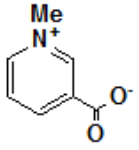
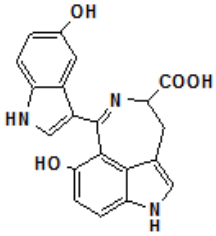


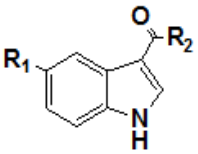
192



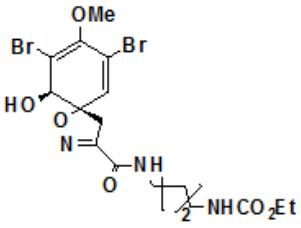
193



194



195, R_1=H, R_2=CH_2OH
196, R_1=H, R_2=H
197, R_1=OH, R_2=OCH_3
198, R_1=OH, R_2=H
199, R_1=OH, R_2=CH_2OH



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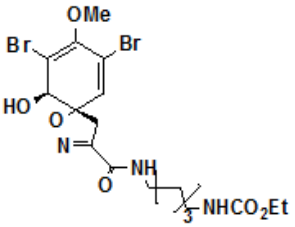


201

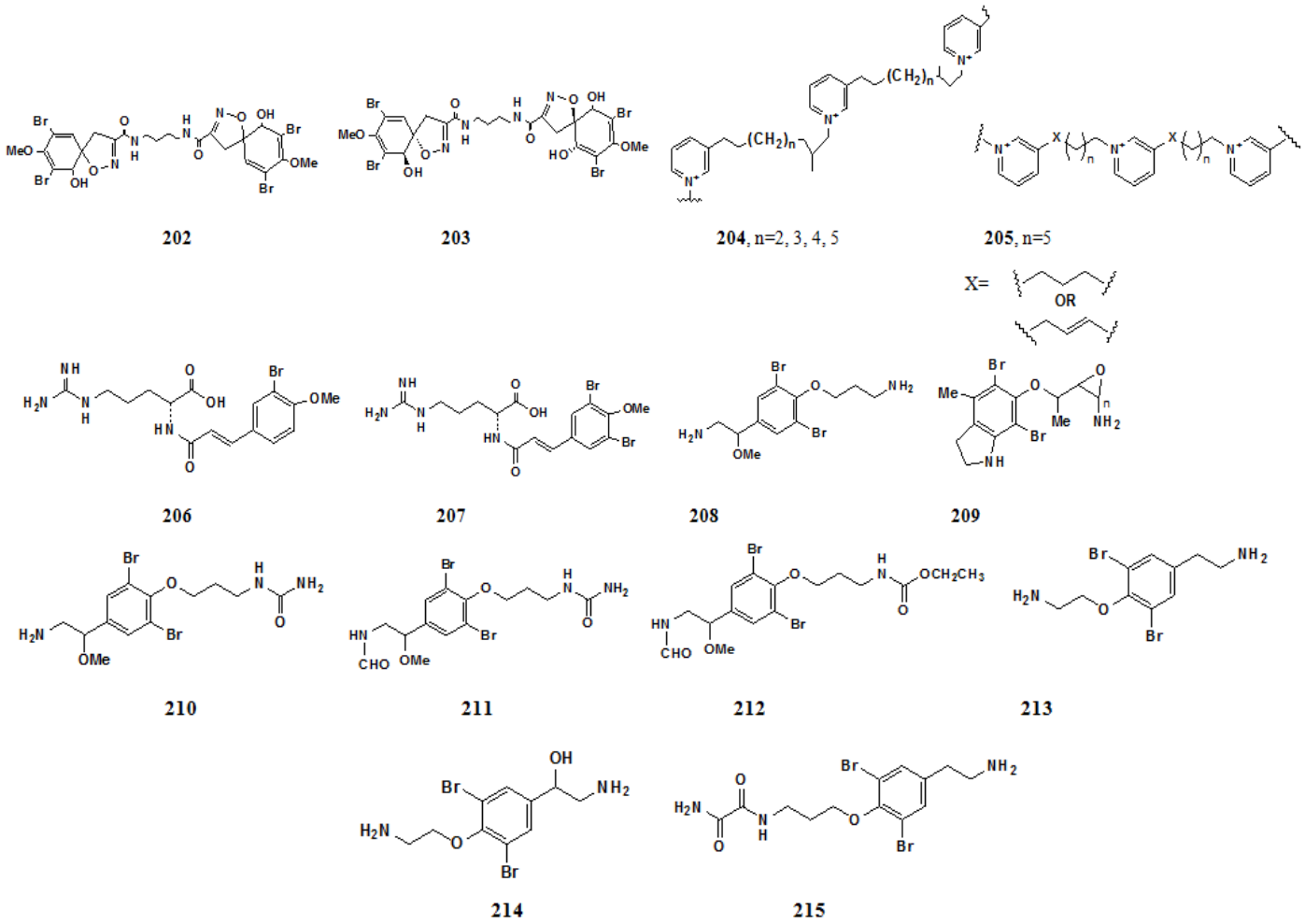
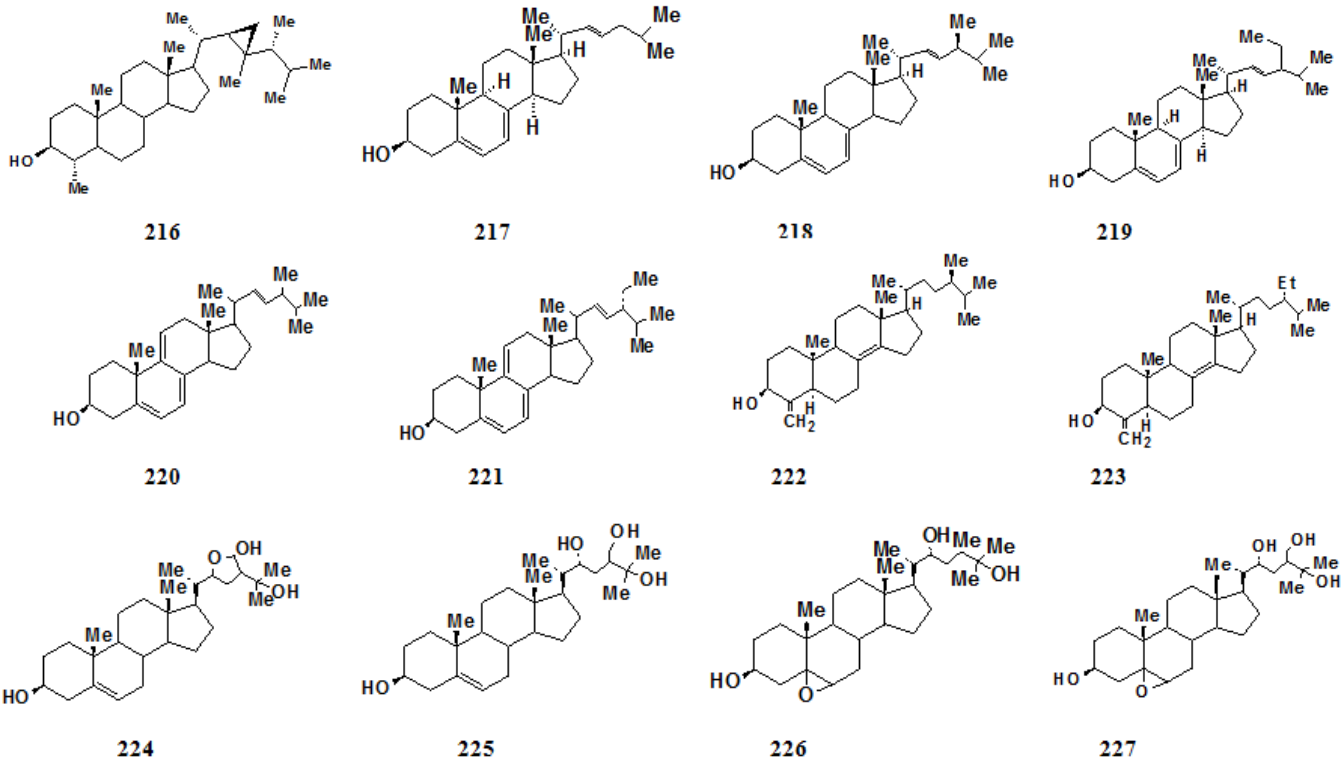
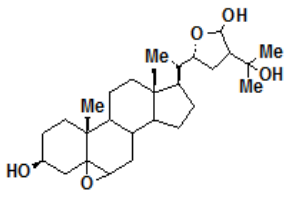
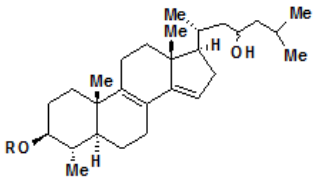


FIG. 7: ALKALOIDS 153-215





228



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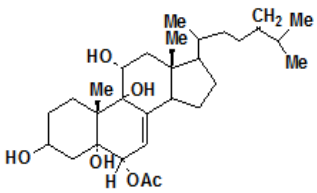

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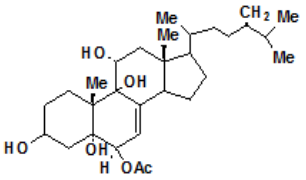

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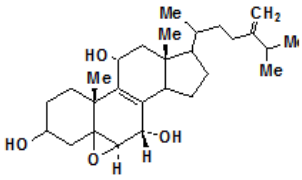

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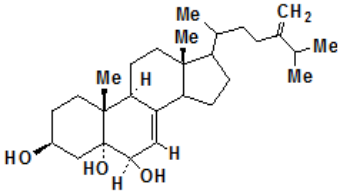

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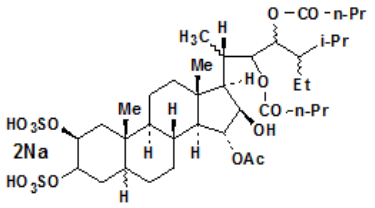

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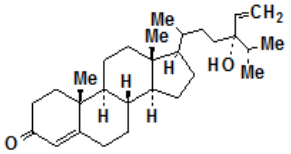

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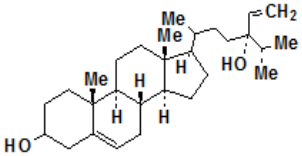

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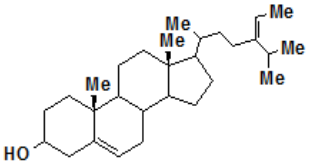

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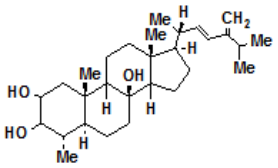

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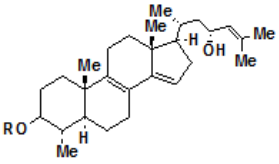

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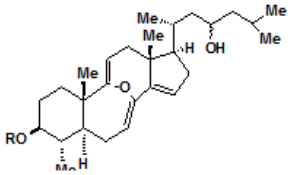

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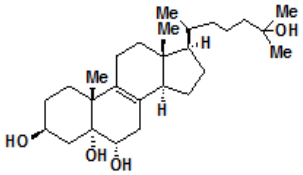

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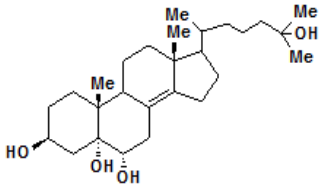

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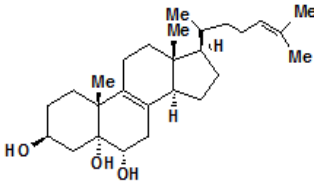

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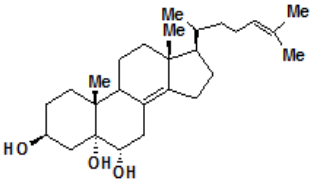

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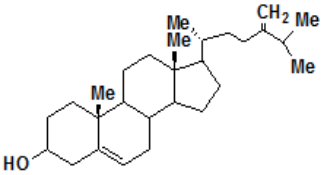
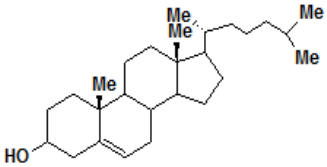
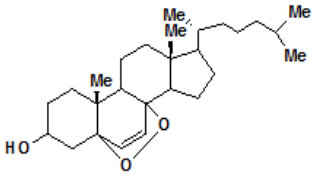


245



246



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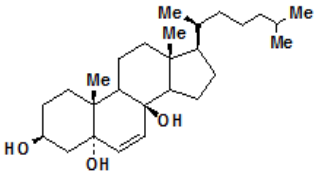

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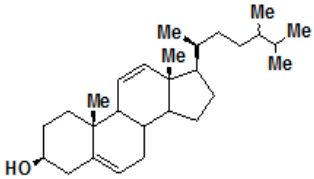

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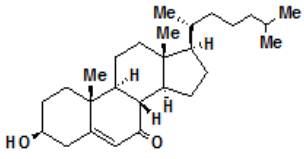

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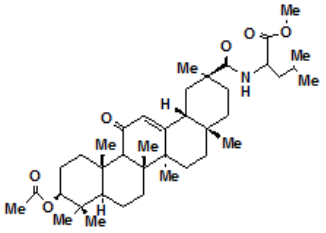
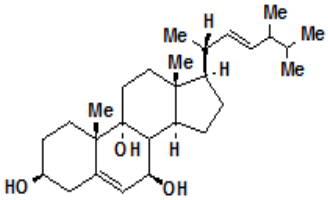
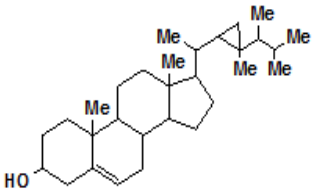


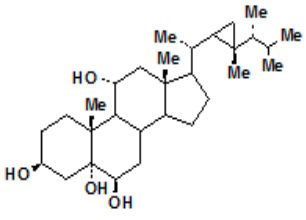
251



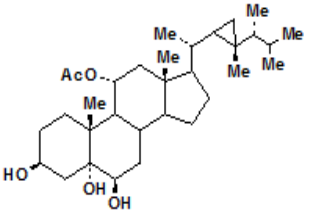
252



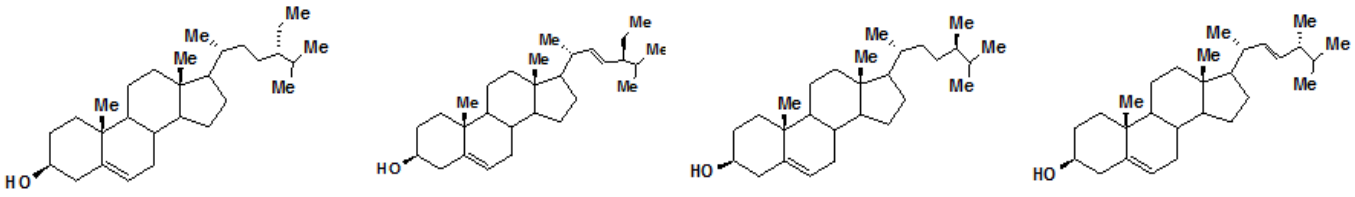
253



254

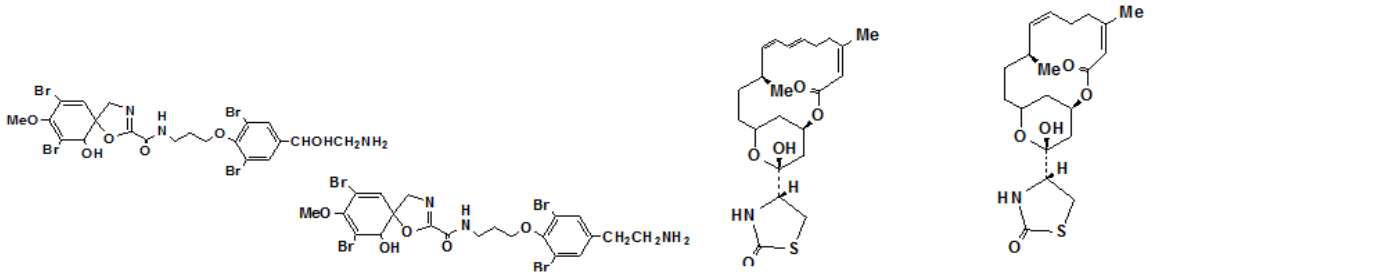


255

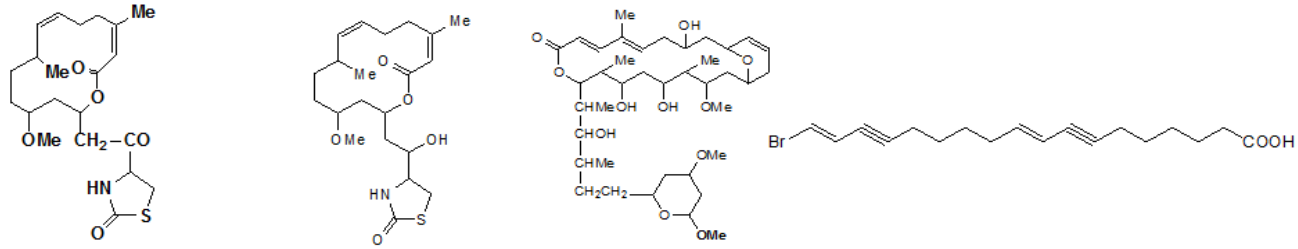


256 **257** **258** **259**

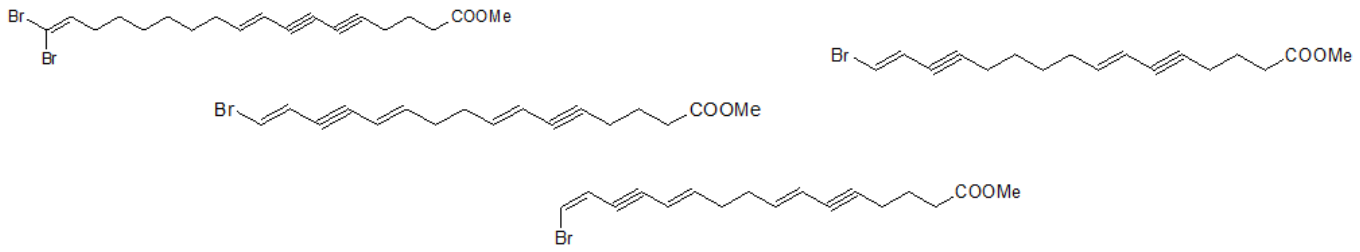
FIG. 8: STEROLS AND STEROIDAL GLYCOSIDES 216-259



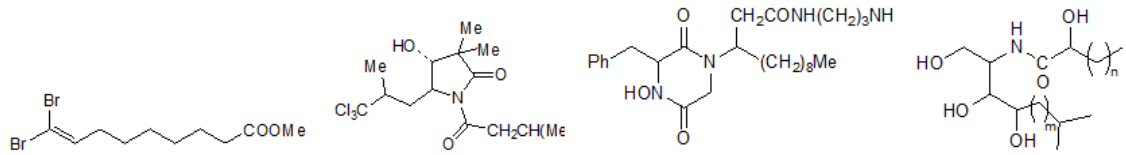
260 **261** **262** **263**



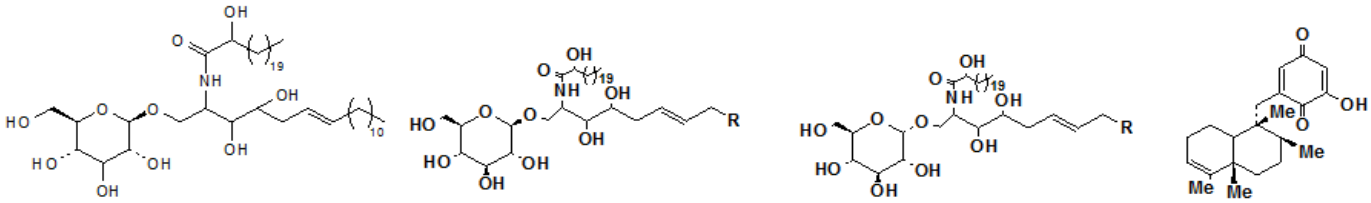
264 **265** **266** **267**



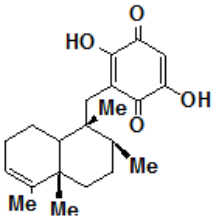
268 **269** **270** **271**



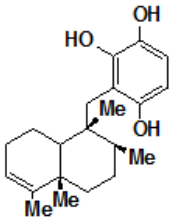
272 **273** **274** **275**, n=20, 21, 22
m=10, 11, 12



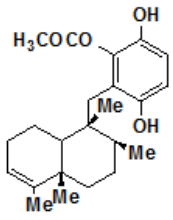
276 **277**, R=$CH_2CH=CH(CH_2)_{10}CHCH_3$
278, R=$CH=CH(CH_2)_{11}CH(CH_3)_2$
279, R=$C_{12}H_{24}CH(CH_3)_2$
280, R=$CH_2CH=CH(CH_2)_{10}CH(CH_3)_2$
281, R=$CH=CH(CH2)_{11}CH(CH_3)_2$
282



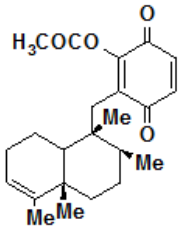
283



284



285



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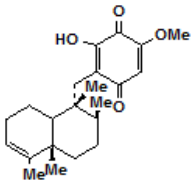
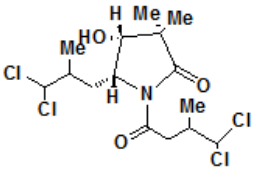
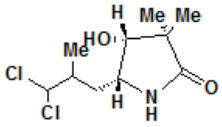


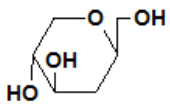
287



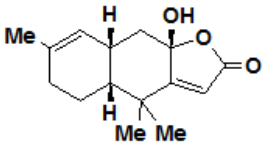
288



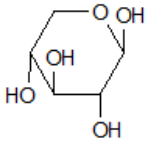
289



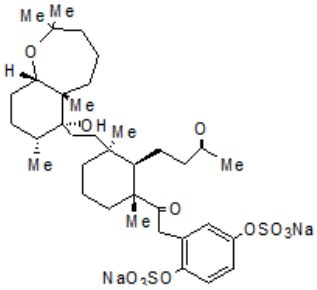
290



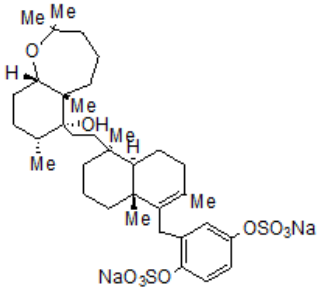
291



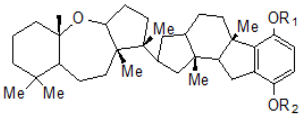
292



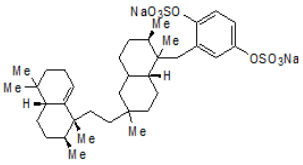
293



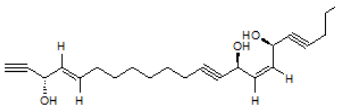
294



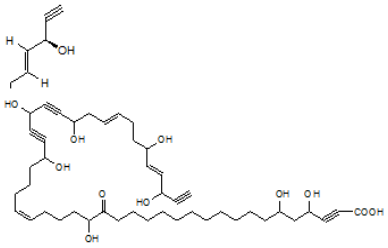
295, R_1=R_2=H
296, R_1=R_2=Ac
297, R_1=R_2=OSO_3Na



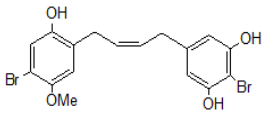
298



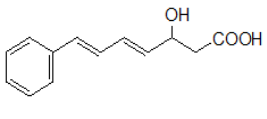
299



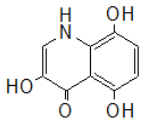
300



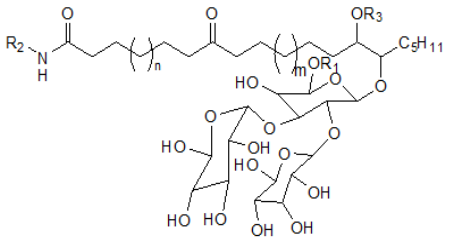
301



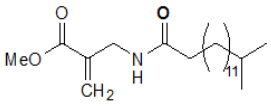
302



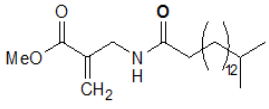
303



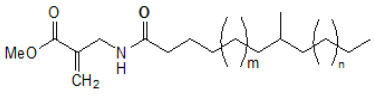
304-306



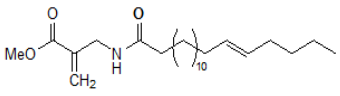
307



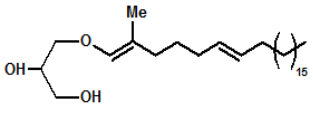
308



309, m+n=6



310



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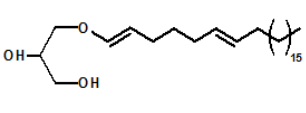

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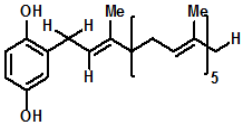

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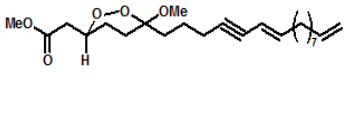

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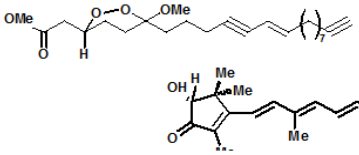

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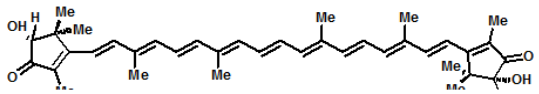

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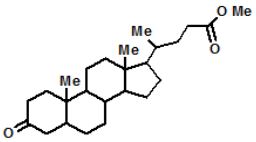

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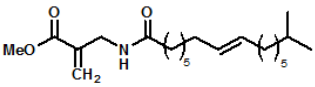

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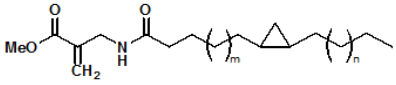

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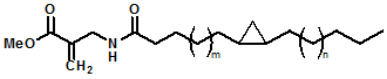

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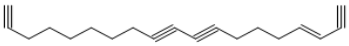

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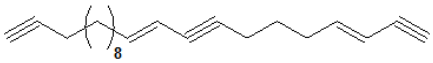

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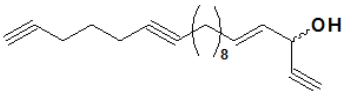

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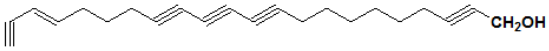

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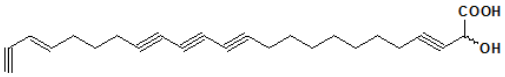

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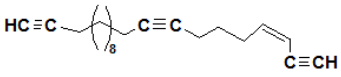

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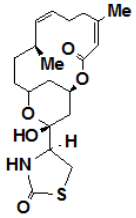

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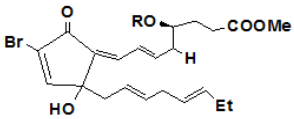
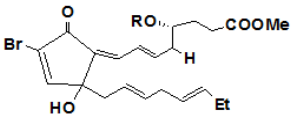


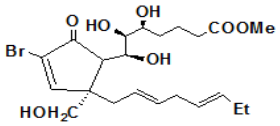
329, R=H

330, R=*α*-D-glucopyranosyl



331, R=H

332, R=*β*-D-glucopyranosyl



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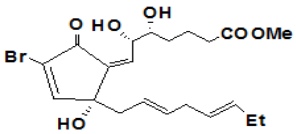

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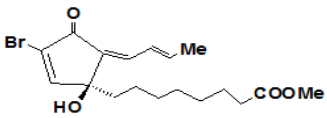

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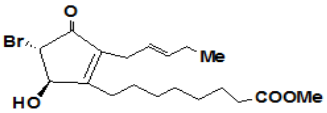

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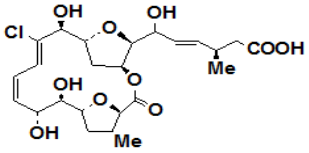

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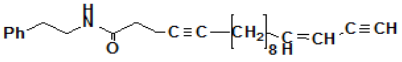

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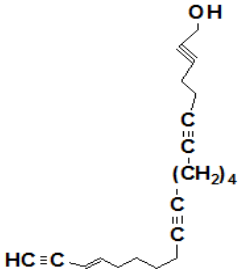

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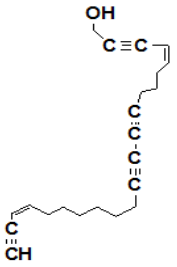

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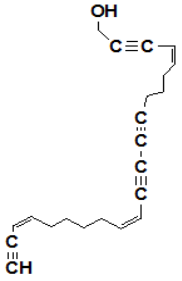

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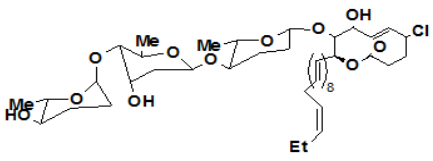

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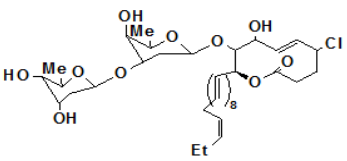

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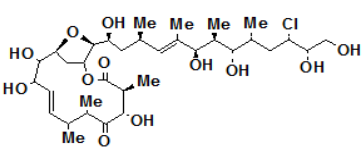

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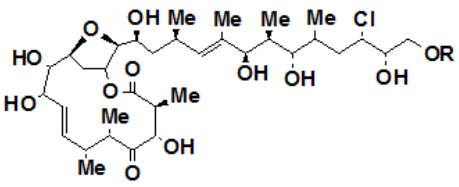
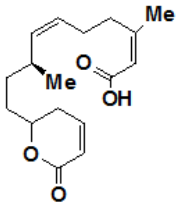


345, R=$OC(CH_2)_{14}CH_3$
346, R=$OC(CH_2)_7CH{=}CH(CH_2)_7CH_3$



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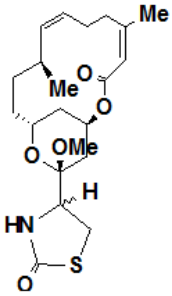

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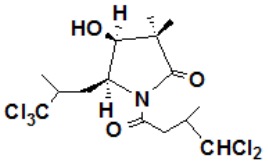

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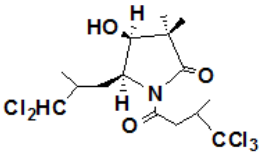

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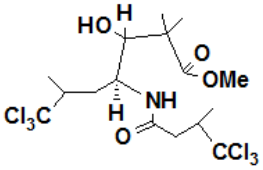

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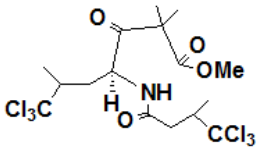

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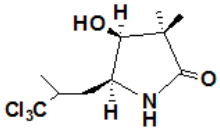

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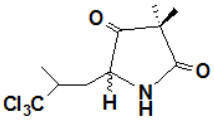
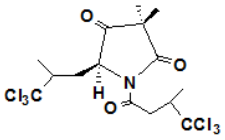
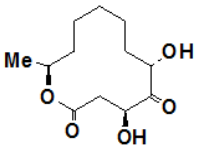


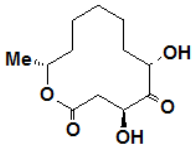
354



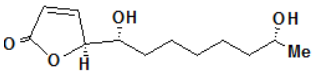
355



356



357



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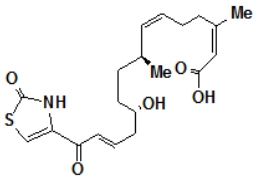

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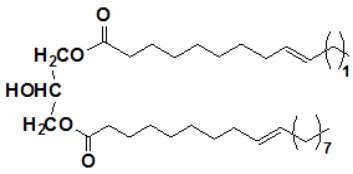

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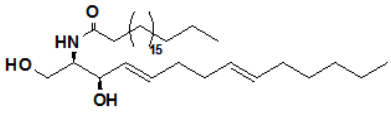
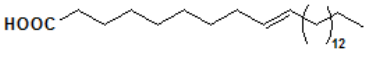


361



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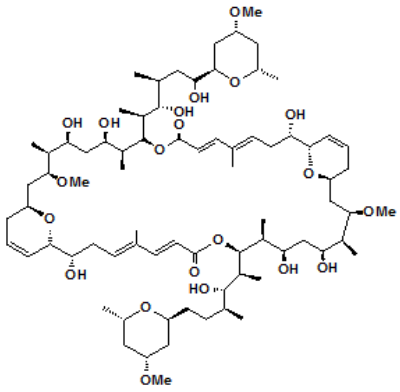

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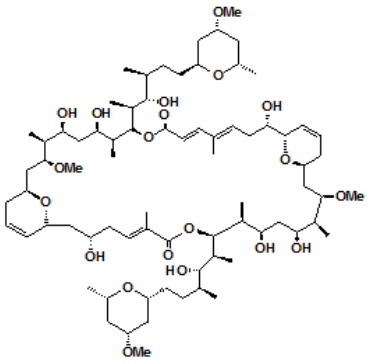

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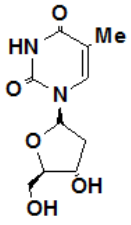
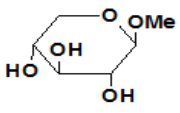


365



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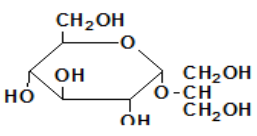

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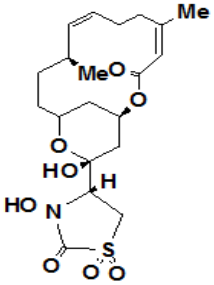

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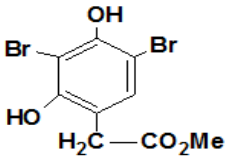

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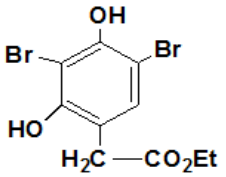

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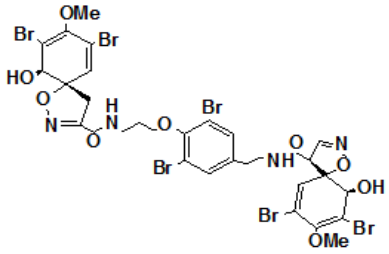

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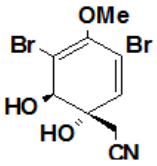

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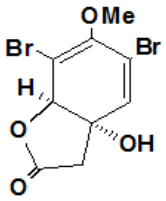

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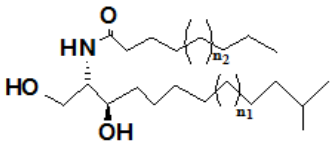

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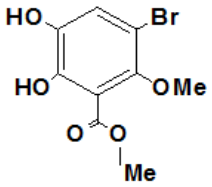

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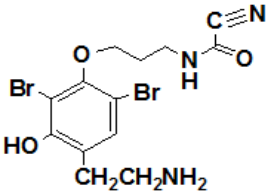

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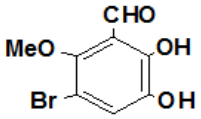

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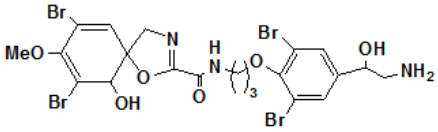

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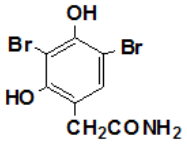

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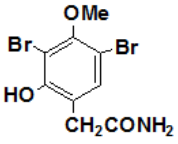

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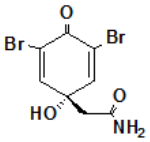

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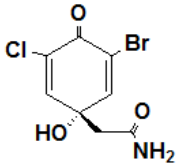

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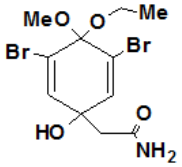

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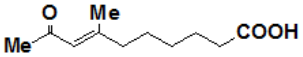

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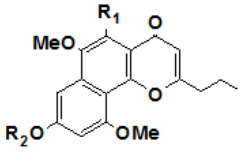
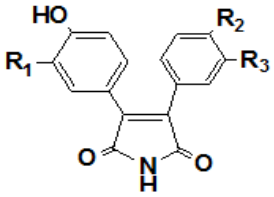
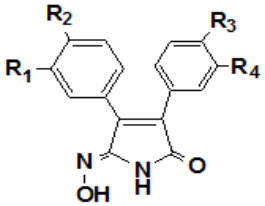


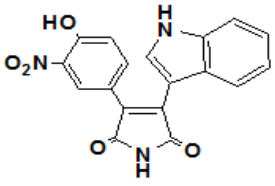
	R_1	R_2
385	OMe	OSO_3Na
386	OH	OSO_3Na
387	OMe	H
388	OH	H



389, R_1=R_2=R_3=H
390, R_1=H, R_2=OH, R_3=NO_2
391, R_1=NO_2, R_2=R_3=H
392, R_1=R_3=NO_2, R_2=OH



393, R_1= NO_2, R_2=OH, R_3=R_4=H
394, R_1= R_4= NO_2, R_2=R_3=OH



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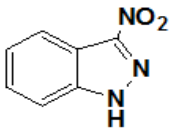

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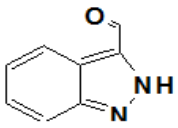

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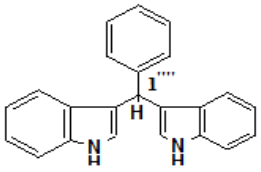
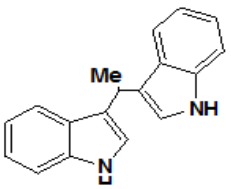


398
399, C+ instead of CH-1'''



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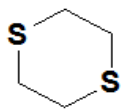

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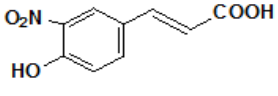

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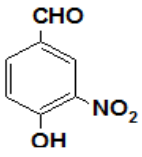

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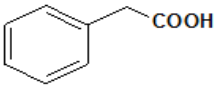

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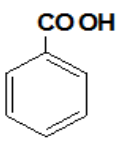

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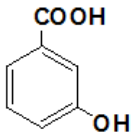

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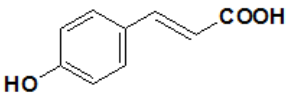

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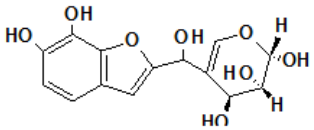

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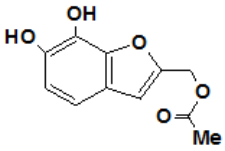

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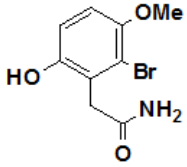

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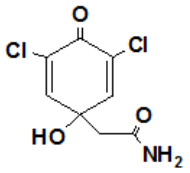

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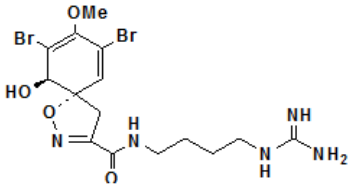

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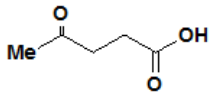

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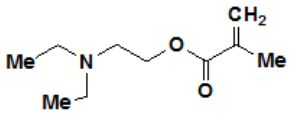

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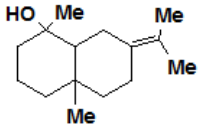

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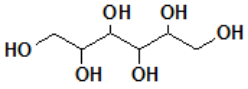

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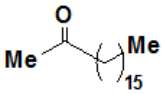

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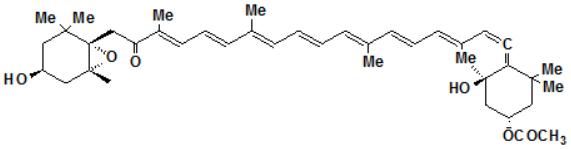

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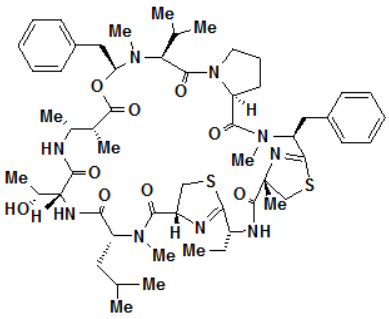

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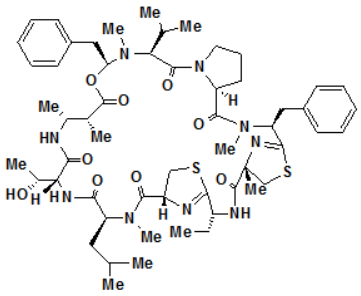

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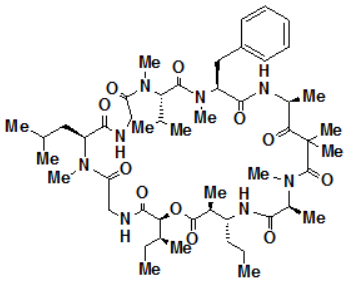

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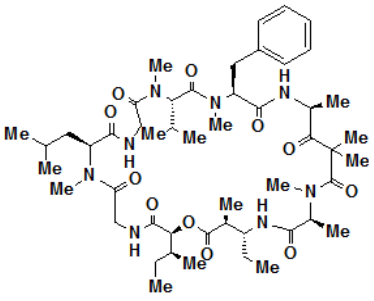

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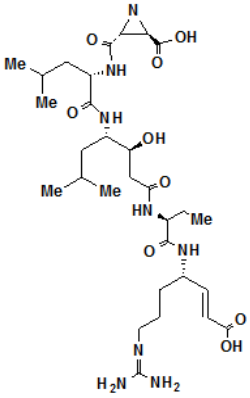

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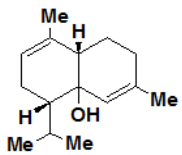

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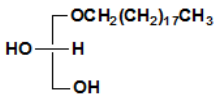

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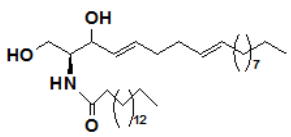

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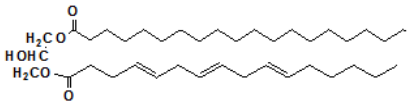

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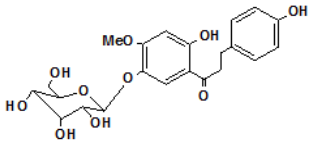

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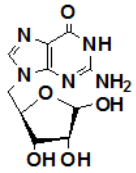

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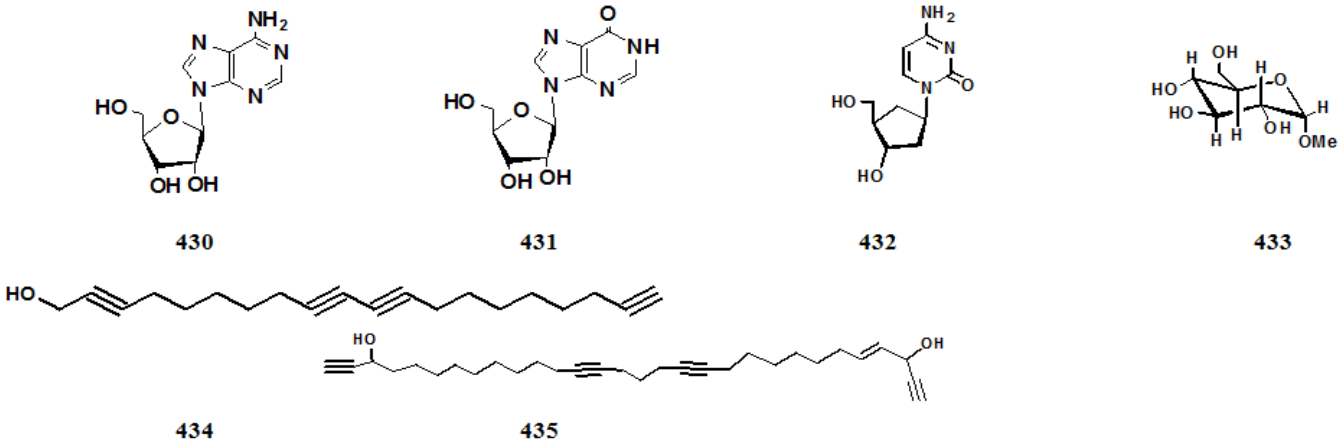

FIG. 9: OTHER METABOLITES 259-435

CONCLUSION: The Red Sea was found to be an exceptional reservoir rich of bioactive natural compounds. Most rich areas of Red Sea that were investigated include Red Sea coasts at Hurghada, Egypt and the Gulf of Eilat, Israel. Red Sea marine organisms that afforded secondary metabolites belong to one of the following classes: Sponges, soft corals, or algae. Cnidaria and Porifera were the two dominant phyla that provided sources of secondary metabolites in the Red Sea. The biological and pharmacological properties associated with marine products have recently been investigated, they are shown to be highly promising, thus require further investigations. Secondary metabolites obtained from the Red Sea marine organisms exhibited various biological activities such as: antiproliferative, cytotoxic, anti-inflammatory and antiviral activities.

These secondary metabolites provided not only a rich variety of novel core structures, but also impressive biological and pharmacological properties. Future studies investigating the differential activity of these secondary metabolites as well as their mechanism of action will be extremely valuable. The conversion of natural products into medicinal lead compounds requires the cooperation of several groups and technologies: collaboration with biologists and organic chemists in the synthesis, semi-synthesis, and structure–activity studies on active target compounds. With the advancement and application of these technologies, it can be expected that extensive structure–activity relationship studies on marine secondary metabolites can provide a direction for innovative medicinal lead compounds.

So, marine natural products chemistry will continue to have a major impact on drug development and discovery, thus inspiring the chemistry of the future.

CONFLICT OF INTEREST: The authors report no conflict of interest.

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