Enzyme Inhibitors from Marine Invertebrates

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Reviews

Enzyme Inhibitors from Marine Invertebrates

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Marine invertebrates are rich sources of small molecules with unique chemical skeletons and potent bioactivities. Historically, such compounds were discovered mainly through the use of assays for phenotype-oriented activities, such as cytotoxicity or antimicrobial effects. More recently, target-oriented searches for bioactive substances, as exemplified by enzyme inhibitors, have become much more common, given a growing need for small-molecule inhibitors essential for studies of complex processes at the interface of chemistry and biology. In this review, selected enzyme inhibitors from marine invertebrates are presented.

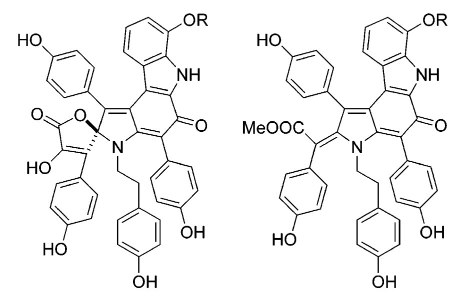
Enzymes are vital to living organisms, in mediating/regulating numerous biochemical events, including metabolism, catabolism, cellular signal transduction, cell cycling, and development. However, enzymes are often associated with human diseases, as evidenced by the molecular analysis of diseases. Various disorders in humans are caused by the dysfunction of enzymes as well as the overexpression or hyperactivation of enzymes.[1]

Umezawa's pioneering work on enzyme inhibitors resulted in the discovery of many valuable compounds from terrestrial microorganisms.[2] Thereafter, the search for small-molecule enzyme inhibitors has been pursued actively in both academia and the pharmaceutical industry. A considerable number of enzyme inhibitors have been developed as drugs, including such "blockbusters" as the statins. However, marine natural products chemists have embarked on the discovery of enzyme inhibitors comparatively recently; the first systematic investigation was done by our group in search of H,K-ATPase inhibitors.[3] Although a large number of enzyme inhibitors have been reported from marine organisms, those that were discovered by bioassay-guided isolation are quite few; most of them were found to inhibit enzymes by re-evaluation of their biological activity. This account describes structures and activities of selected enzyme inhibitors isolated from marine invertebrates. Inhibitors are listed according to the classification of target enzymes (EC number). For some inhibitors, their modes of actions are also discussed. However, we have excluded most of the bromotyrosines, polyacetylenes, and highly sulfated steroids that are often termed "nuisance compounds", because they show a variety of biological activities including inhibition of enzymes.

Oxidoreductases (EC 1)

Aldose Reductase (EC 1.1.1.21). Aldose reductase is known as an enzyme that catalyzes the reduction of glucose to sorbitol. Unusual accumulation of sorbitol in the eye lens or peripheral nerves is thought to cause cataracts or neuropathy. Three polycyclic bisindoles (**1**−**3**) from a marine sponge *Dictyodendrilla* sp. strongly inhibited bovine lens aldose reductase with IC_{50} values of 49, 125, and 112 nM, respectively. Interestingly, the sulfate group in **1** and **2** did not influence the activity (**4**: IC_{50} 102 nM), while the sulfate group in **3** potentiated the activity (**5**: IC_{50} 567 nM).[4]

Aldose Reductase Inhibitors



1 R = SO_3Na
2 R = SO_3H
4 R = H

3 R = SO_3H
5 R = H

Lipoxygenases (EC 1.13.11). Lipoxygenases (LO) mediate hydroperoxidation of polyunsaturated fatty acids (PUFAS), leading to formation of leukotrienes and lipoxins. Selective inhibitors of lipoxygenase isoforms could be useful as pharmacological agents, nutraceuticals, or molecular tools. Fucosides, originally isolated from the Caribbean gorgonian *Eunicea fusca*,[5] selectively and irreversibly inhibited leukotriene (LT) formation in murine models of inflammation. Further pharmacological study indicated that fucoside B (**6**) inhibits conversion of arachidonic acid (AA) to leukotriene B_4 (LTB_4) by inhibition of 5-LO with an IC_{50} of 18 μM.[5] Similarly, didemnilactones A (**7**) and B (**8**), isolated from the tunicate *Didemnum moseleyi*, showed inhibition against lipoxygenases of human polymorphonuclear leukocytes with IC_{50} values of 9.4 and 8.5 μM (**7** and **8**, respectively, against 5-LO) and 41 μM (**7** against 15-LO).[7]

Transferases (EC 2)

Glycosyltransferases (EC 2.4). α-1,3-Fucosyltransferases (Fuc Ts) catalyze the transfer of L-fucopyranoside residues from guanosine diphosphate fucose (GDP-fucose) to glycoconjugate acceptors and are known to be involved in the biosynthesis of sialyl Lewis X (SLe^X) present on the extracellular surfaces of leukocytes. The E-selectin−SLe^X interaction encourages leukocytes to move from the bloodstream into sites of injury or infection, thus causing inflammation, and indicating that inhibitors of α-1,3-fucosyltransferase are potential drugs for the treatment of inflammatory diseases.[8] The octa- and nonaprenylhydroquinone sulfates **9** and **10** isolated from an Australian sponge *Sarcotragus* sp. inhibited α-1,3-fucosyltransferase VII (Fuc TVII), with IC_{50} values of 3.9

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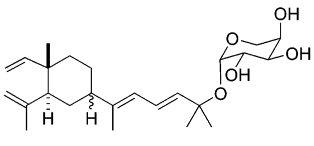
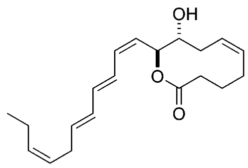
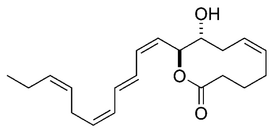
Lipoxygenase Inhibitors



fucoside B (**6**)



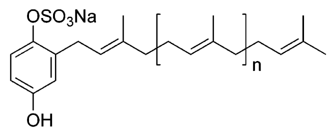
didemnilactone A (**7**)



didemnilactone B (**8**)

and 2.4 μg/mL, respectively, while they showed very weak activity against Fuc TVI.[9]

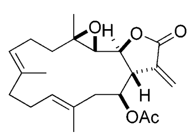
Glycosyltransferase Inhibitors



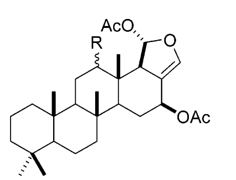
	n
octaprenylhydroquinone sulfate (**9**)	6
nonaprenylhydroquinone sulfate (**10**)	7

Farnesyl Protein Transferase (EC 2.5.1.58). The Ras family of guanine nucleotide-binding proteins plays important roles in signal transduction and the regulation of cell differentiation and proliferation. The Ras protein requires post-translational processing in order to associate with the plasma membrane and to function in signal transduction or cellular transformation. The first processing step is catalyzed by farnesyl protein transferase (FPT), which adds a farnesyl group to a cysteine residue near the carboxy terminus of the Ras protein. Inhibition of FPT is a potential therapeutic target for novel anticancer agents. Cembranolide diterpene **11**, isolated from the soft coral *Lobophytum cristagalli*, showed potent inhibitory activity against FPT with an IC_{50} value of 0.15 μM.[10] Bioassay-guided isolation of FPT inhibitors from the sponge *Hyrtios reticulate* yielded a known sesterterpene, heteronemin (**12**), as the active substance. Heteronemin (**12**) inhibited FPT with an IC_{50} value of 3 μM, while its 12-epimer (**13**) did not show any noticeable activity.[11] Solandelactones C (**14**), D (**15**), and G (**16**) are cyclopropyl oxylipins isolated from the hydroid *Solanderia secunda* and exhibited moderate inhibitory activity against FPT (69, 89, and 61% inhibition at 100 μg/mL, respectively).[12]

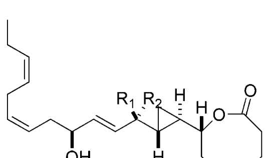
Farnesyl Protein Transferase Inhibitors



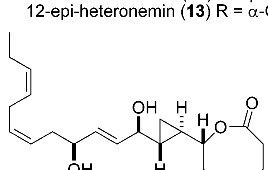
11



heteronemin (**12**) R = β-OH
12-epi-heteronemin (**13**) R = α-OH



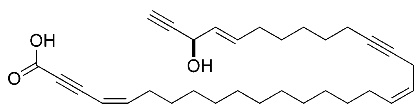
	R_1	R_2
solandelactone C (**14**)	OH	H
solandelactone D (**15**)	H	OH



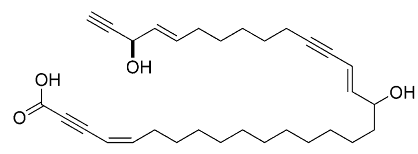
solandelactone G (**16**)

Geranylgeranyltransferase Type I (EC 2.5.1.59). Geranylgeranyltransferase type I (GGTase I) catalyzes the post-translational attachment of the geranylgeranyl unit on the carboxy terminal cysteine residues of proteins to promote membrane interaction and biological activities of these proteins.[13] Rho1p, a regulatory subunit of 1,3-β-D-glucan synthesis and the key player in cell wall biosynthesis,[14] is known as one of the targets of GGTase I and is essential for the viability of *Saccharomyces cerevisiae*. Since there is only a 30% sequence homology between human and pathogenic fungus *Candida albicans* GGTase I,[15] its inhibitors are expected to be selective antifungal agents. Corticatic acids are polyacetylenic GGTase I inhibitors isolated from the sponge *Petrosia corticata*. Corticatic acids A (**17**), D (**18**), and E (**19**) inhibited *C. albicans* GGTase I with IC_{50} values of 1.9, 3.3, and 7.3 μM, respectively, and corticatic acid A (**17**) also inhibited the growth of *C. albicans* with an MIC value of 54 μM.[16] Massadine (**20**), a highly oxygenated alkaloid, was isolated from the sponge *Stylissa* aff. *massa* as an inhibitor of GGTase I from *C. albicans*. Massadine (**20**) inhibited GGTase I with an IC_{50} value of 3.9 μM.[17]

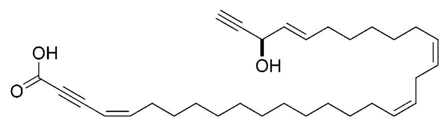
Geranylgeranyltransferase I (GGTase I) Inhibitors



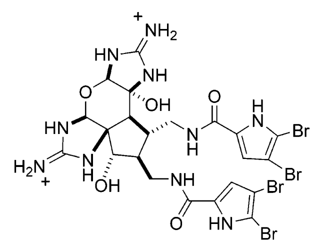
corticatic acid A (**17**)



corticatic acid D (**18**)

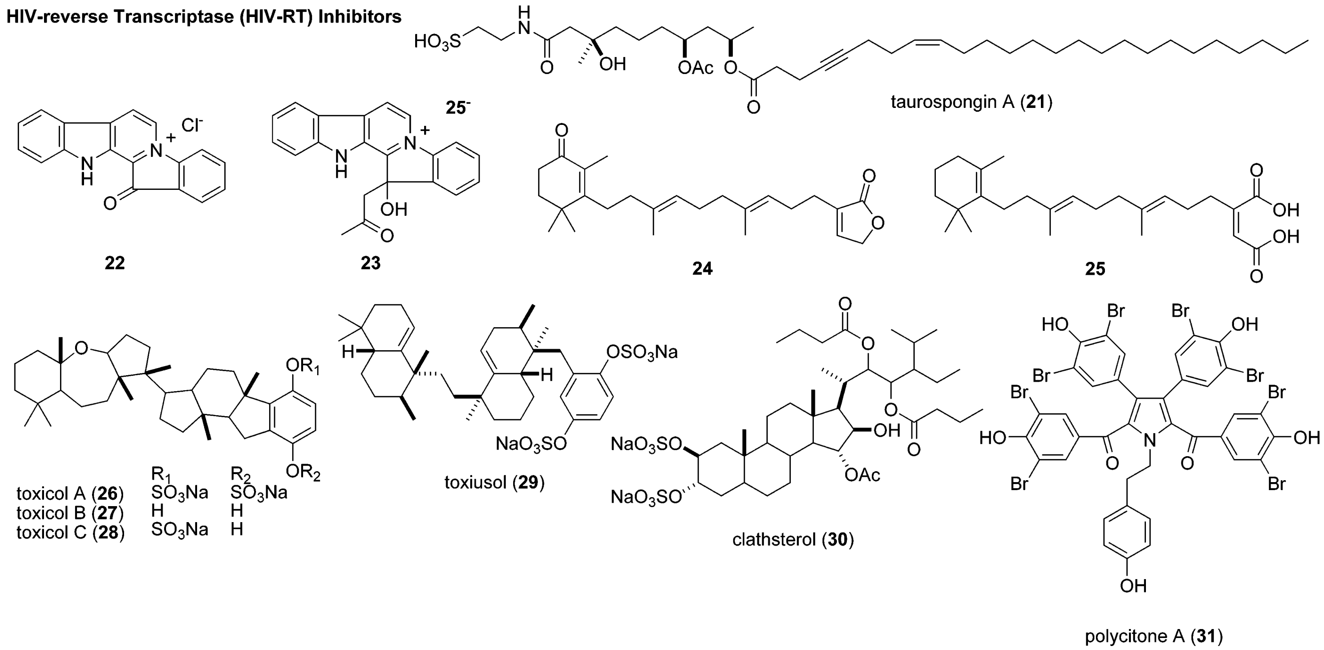


corticatic acid E (**19**)



massadine (**20**)

HIV Reverse Transcriptase (EC 2.7.7). Reverse transcriptase (RT) is the key enzyme in the life cycle of human immunodeficiency virus (HIV). RT is a multifunctional enzyme responsible for the transcription of viral RNA into double-stranded DNA and exhibits both RNA-dependent DNA polymerase (RDDP) and DNA-dependent DNA polymerase (DDDP) activities as well as an inherent ribonuclease H (RNase H) activity. All the catalytic functions of RT play a pivotal role in HIV replication. Taurospongin A (**21**), a metabolite of an Okinawan sponge *Hippospongia* sp., is an example of acetylenic compounds that possess HIV RT inhibitory activity (IC_{50} 6.5 μM, K_i 1.3 μM), along with inhibitory activity against DNA polymerase β (IC_{50} 7.0 μM, K_i 1.7 μM) and c-erbB-2 kinase (IC_{50} 28 μg/mL), but no cytotoxicity (IC_{50} >10 μg/mL) against L1210 and KB cells.[18] The tryptophan-derived pigments **22** and **23** and the accompanying sesterterpenes, **24** and **25**, isolated from the Fijian sponge *Fascaplysinopsis reticulate* showed weak inhibition against HIV RT.[19] Toxicols A−C (**26**−**28**) and toxiusol (**29**), triterpenes isolated from the Red Sea sponge *Toxiclona toxius*,



were reported to be inhibitory against HIV RT but without detailed bioactivities.[20] Clathsterol (**30**), isolated from a Red Sea sponge *Clathria* sp., showed anti-HIV-1 RT activity at 10 μM.[21] Polycitone A (**31**), a general inhibitor of retroviral reverse transcriptases and cellular DNA polymerases, was isolated from the ascidian *Polycitor* sp. It inhibited the RDDP and DDDP activities of HIV-1 RT with IC_{50} values of 245 and 470 nM, respectively, while it showed general inhibition against MuLV (murine leukemia virus) RT, MMTV (mouse mammary tumor virus) RT, calf-thymus pol α, human pol β, and KF (*E. coli* DNA polymerase I) with IC_{50} values ranging from 73 to 600 nM.[22]

HIV Integrase (EC 2.7.7). HIV integrase catalyzes the initial DNA breaking and joining reactions responsible for the attachment of HIV cDNA to host DNA. Since there are no similar proteins known to be important for normal function of cells, HIV integrase is a promising target for less toxic anti-HIV drugs. A series of ascidian alkaloids, the lamellarins (**32**−**37**), showed selective inhibition against HIV integrase with IC_{50} values of 16−73 μM for terminal cleavage and 14−51 μM for strand transfer activities, respectively. Lamellarin α 20-sulfate (**32**) demonstrated inhibition in the early steps of replication of HIV-1 in cell culture with an IC_{50} value of 8 μM.[23] Cyclodidemniserinol trisulfate (**38**), isolated from the Palauan ascidian *Didemnum guttatum*, exhibited inhibition against HIV integrase with an IC_{50} value of 60 μg/mL.[24] Haplosamates A (**39**) and B (**40**), isolated from two haplosclerid sponges (*Xestospongia* sp. and an unidentified sponge), inhibited HIV-1 integrase with IC_{50} values of 50 and 15 μg/mL, respectively.[25] Prenylhydroquinone sulfates **41** and **42** from the deep-water sponge *Ircinia* sp. also showed HIV-1 integrase inhibition (65% inhibition at 1 μg/mL and 45% inhibition at 5 μg/mL, respectively).[26]

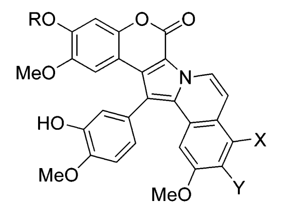
Telomerase (EC 2.7.7). Telomerase is a ribonucleoprotein enzyme that adds repeats of the DNA sequence TTAGGG, called telomeres, onto the 3″-ends of chromosomes.[27] Telomerase activity is found in about 90% of human tumors, but not in normal cells.[28] Thus, inhibitors of telomerase are considered to have potential as antitumor agents.[29] In fact, some synthetic inhibitors based on the function of telomerase have been successful in clinical trials.[30] From the sponge *Dictyodendrilla verongiformis* collected in southern Japan, five telomerase inhibitors, dictyodendrins A−E (**43**−**47**), were isolated along with the sodium salts of two known compounds (**2** and **3**), obtained as aldose reductase inhibitors from a marine sponge of the same genus.[4] All seven of these compounds showed 100% inhibition of telomerase activity at 50 μg/mL, while the desulfated analogue of dictyodendrin C (**45**) was not active at this concentration.[31] Recently, the total synthesis of dictyodendrins B (**44**), C (**45**), and E (**46**) was accomplished.[32] An unprecedented highly sulfated lipopolysaccharide, axinelloside A (**48**), isolated from the sponge *Axinella infundibula*, showed potent inhibition against human telomerase (IC_{50} 2.0 μg/mL).[33]

Epidermal Growth Factor Receptor Kinase (EC 2.7.10.1). Protein tyrosine kinases comprise a large family of enzymes that regulate cell growth and intracellular signaling pathways. Inhibitors of these enzymes may be potential anticancer drugs.[34] There are at least four members of the type 1 growth factor receptor gene family, including the epidermal growth factor receptors (EGFR), erbB-1, erbB-2, erbB-3, and erbB-4. Members of this tyrosine kinase receptor family have been implicated in the establishment or progression of human cancer, particularly breast cancer, and extensive efforts have been made to identify specific small-molecule inhibitors of EGFR tyrosine kinase.[35] Tauroacidins A (**49**) and B (**50**), bromopyrrole metabolites of an Okinawan sponge *Hymeniacidon* sp., exhibited inhibitory activity against c-erbB-2 kinase with an IC_{50} value of 20 μg/mL.[36] (+)-Aeroplysinin-1 (**51**), isolated from the sponge *Verongia aerophoba*, inhibited EGF receptor kinase completely at 0.5 μM.[37] Ma'edamine A (**52**), a cytotoxic bromotyrosine alkaloid isolated from a sponge *Suberea* sp., inhibited c-erbB-2 kinase with an IC_{50} value of 6.7 μg/mL.[38]

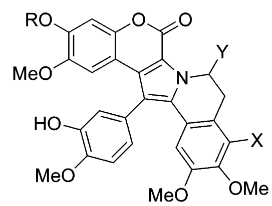
Tyrosine Kinase pp60^{V-SRC} (EC 2.7.10.2). A tyrosine kinase, pp60^{V-SRC}, is the oncogenic protein encoded by the Rous sarcoma virus. Halenaquinone (**53**), halenaquinol (**54**), halenaquinol sulfate (**55**), and xestoquinone (**56**) isolated from the Fijian sponge *Xestospongia* cf. *carbonaria* were found to inhibit the kinase activity of pp60^{V-SRC}, with IC_{50} values of 1.5, 60, 0.55, and 28 μM, respectively.[39] Halenaquinone (**53**) also inhibited phosphatidylinositol 3-kinase with an IC_{50} value of 3 μM.[40] Two more pp60^{V-SRC} inhibitors, 14-methoxyhalenaquinone (**57**) and xestoquinolide A (**58**), were isolated from the same sponge (IC_{50} values of 5 and 80 μM, respectively).[41] Melemeleone (**59**), a sesquiterpene quinone isolated from two *Dysidea* sponges, showed inhibitory activity against pp60^{V-SRC} with an IC_{50} of 28 μM.[42]

MSK1 (EC 2.7.11.1) and MAPKAPK-2. Mitogen- and stress-activated kinase (MSK1) and mitogen-activated protein kinase (MAPKAPK-2) are two serine protein kinases involved in signal transduction. Both of these enzymes are located in the nucleus and are involved in the late stage of the signal transduction pathway. Therefore, selective inhibitors of these enzymes are likely to exhibit highly specific cellular effects. Four cheilanthane sesterterpenoids, **60**−**63**, were isolated from the sponge *Ircinia* sp. as inhibitors of

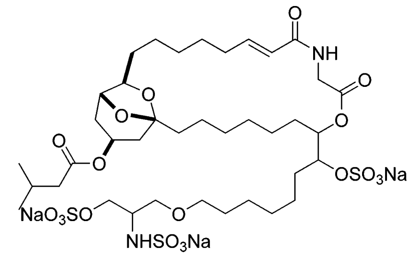
HIV Integrase Inhibitors



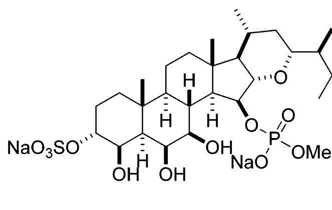
		R	X	Y
lamellarin α 20-sulfate	(**32**)	SO_3Na	H	OMe
lamellarin W	(**33**)	H	OMe	OMe
lamellarin N	(**34**)	H	H	OH



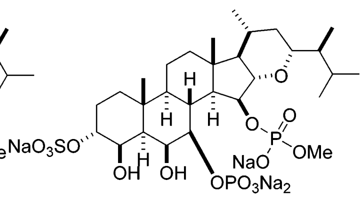
		R	X	Y
lamellarin U 20-sulfate	(**35**)	SO_3Na	H	H
lamellarin V 20-sulfate	(**36**)	SO_3Na	OMe	OH
lamellarin T	(**37**)	H	OMe	H



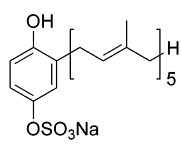
cyclodidemniserinol trisulfate (**38**)



haplosamate A (**39**)



haplosamate B (**40**)



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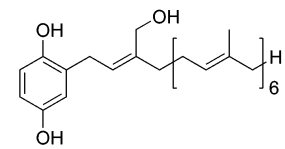


42

both MSK1 (IC_{50}'s: 4 μM for all compounds) and MAPKAPK-2 (IC_{50}'s: 90 μM for all compounds).[43]

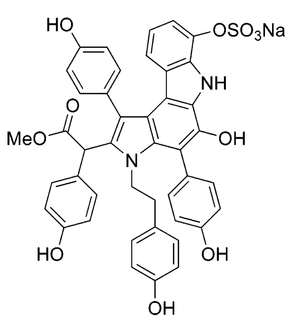
Tyrosine Protein Kinase. Four prenylhydroquinone sulfates, **41**/**42** and **64**/**65**, obtained from a deep-water sponge *Ircinia* sp. showed inhibition against tyrosine protein kinase (TPK) with IC_{50} values of 8, 4, 8, and 5.9 μg/mL, respectively. Compounds **41** and **42** were also reported to be HIV-1 integrase inhibitors.[26]

Raf/MEK-1/MAPK. The Ras-MAPK signaling cascade is found in all eukaryotic organisms and is involved in cellular signaling processes. Since the oncogenic form of Ras is associated with 30% of all cancers, Ras and the downstream kinases represent attractive targets for pharmacological intervention. The Raf/MEK-1/MAPK cascade inhibition assay-guided fractionation of the Philippine sponge *Stylissa massa* yielded eight known pyrrole alkaloids: aldisine (**66**), 2-bromoaldisine (**67**), 10*Z*-debromohymenialdisine (**68**), a 1:1 mixture of 10*E*- (**69**) and 10*Z*-hymenialdisines (**70**), hymenin (**71**), oroidin (**72**), and 4,5-dibromopyrrole-2-carbonamide (**73**), among which **67**−**71** were active, with IC_{50} values ranging from 3 to 1288 nM. The most active were **69** and **70** (IC_{50}'s 3 and 6 nM, respectively). In addition, all compounds showed essentially identical IC_{50} values in the MEK-1 to MAPK assay, while none of them showed activity in the Raf to MEK-1 assay.[44]

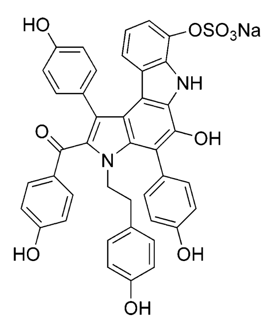
Checkpoint Kinases (EC 2.7.11.1). The synthetic 10*Z*-debromohymenialdisine (**68**) inhibited checkpoint kinases Chk1 and 2 with IC_{50} values of 3 and 3.5 μM.[45] Further investigation of inhibitory activity toward kinases by hymeniadisines led to the identification of 11 new targets for this class of alkaloids, including p90RSK, KDR, c-Kit, Fes, MAPK1, PAK2, PDK1, PKCθ PKD2, Rsk1, and SGK.[46]

Protein Kinase C (EC 2.7.11.13). Protein kinase C (PKC), a phospholipid-dependent protein phosphorylating enzyme, is a key player in cellular signal transduction and has been implicated in cancer, cardiovascular and renal disorders, immunosuppression, and autoimmune diseases such as rheumatoid arthritis. Therefore,

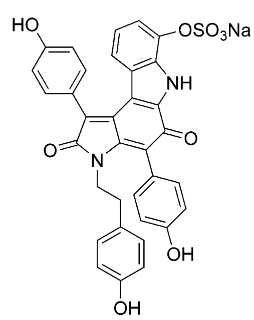
Telomerase Inhibitors



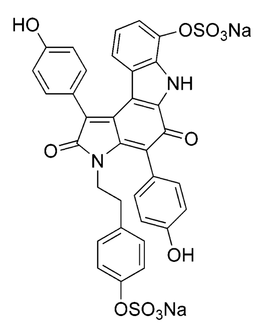
dictyodendrin A (**43**)



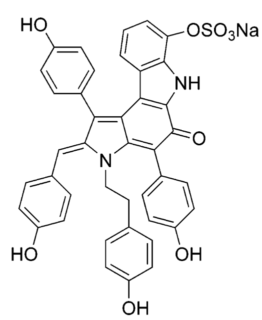
dictyodendrin B (**44**)



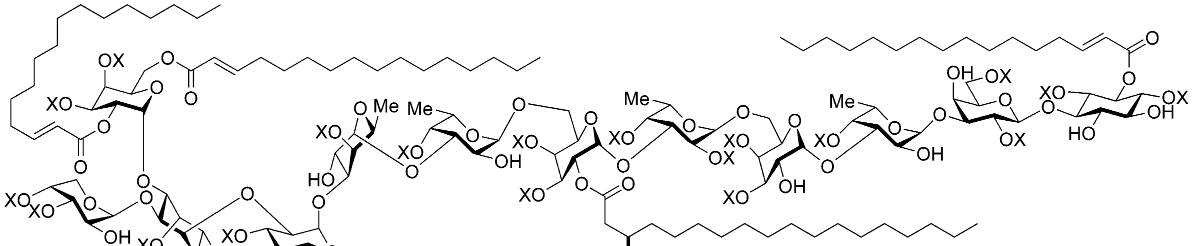
dictyodendrin C (**45**)



dictyodendrin D (**46**)



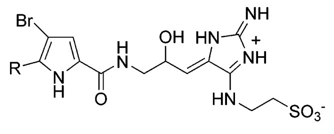
dictyodendrin E (**47**)



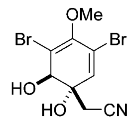
X = SO_3Na

axinelloside A (**48**)

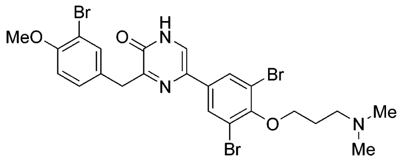
EGFR Kinase Inhibitors



	R
tauroacidin A (**49**)	Br
tauroacidin B (**50**)	H

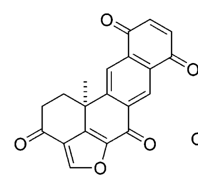


(+)-aeroplysinin-1 (**51**)

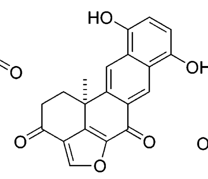


ma'edamine A (**52**)

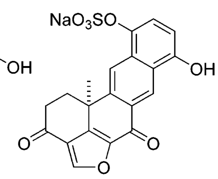
Tyrosine Kinase pp60$^{V\text{-}SRC}$ Inhibitors



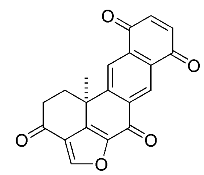
halenaquinone (**53**)



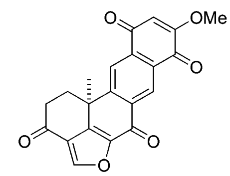
halenaquinol (**54**)



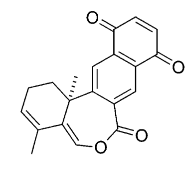
halenaquinol sulfate (**55**)



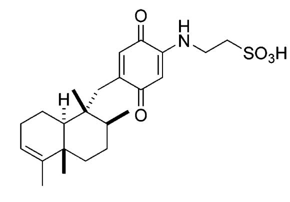
xestoquinone (**56**)



14-methoxyhalenaquinone (**57**)



xestoquinolide B (**58**)



melemeleone B (**59**)

inhibitors of protein kinase C (PKC) may be potential drug leads for the treatment of such diseases. Staurosporine (**74**), isolated from *Streptomyces staurosporeus*, is the most well-known natural product PKC inhibitor.[47] 11-Hydroxystaurosporine (**75**), isolated from a tunicate *Eudistoma* sp. collected in Pohnpei, inhibited PKC with an IC_{50} value of 2.2 nM, which is about 30% more potent than staurosporine (**74**) itself.[48] Staurosporine aglycon K252-c (**76**), isolated from another *Eudistoma* sp., inhibited eight cloned PKC isoenzymes, α, β I, β II, δ, ϵ, η, γ, and ζ, with IC_{50} values of 1.3, 0.6, 0.5, 1.2, 1.1, 0.8, 1.5, and >6.4 μM, respectively.[49] Xestocyclamine A (**77**), a bis-alkylpiperadine from a sponge *Xestospongia* sp., showed moderate inhibition of PKCϵ (IC_{50} 4 μg/mL).[50] Isoaaptamine (**78**), first reported from a suberitid sponge in 1988, was found to be a PKC inhibitor. However, recent evaluation of PKC inhibitory and antitumor activities for synthetic isoaaptamine and its derivatives revealed that none of them met the criteria for further evaluation after a primary screen in the NCI tumor cell line panel.[51] *Z*-Axinohydantoin (**79**) and debromo-*Z*-axinohydantoin (**80**), isolated from the sponge *Stylotella aurantium*, showed moderate inhibition of PKC (IC_{50} 9.0 and 22 μM, respectively).[52]

A mixture of corallidictyals A (**81**) and B (**82**), spirosesquiterpene aldehydes from the sponge *Aka* (*Siphonodictyon*) *coralliphagum*, inhibited PKC with an IC_{50} value of 28 μM. Interestingly, the corallidictyal mixture selectively inhibited PKCα with an IC_{50} value of 30 μM (for the ϵ, η, and ζ isoenzymes, IC_{50} values of 89, >300, and >300 μM, respectively). In addition, the corallidictyal mixture inhibited the growth of cultured Vero (African green monkey kidney) cells with an IC_{50} value of 1 μM after continuous exposure (72 h).[53] Nakijiquinones A−D (**83**−**86**), sesquiterpenes isolated from an Okinawan sponge of the family Spongiidae, showed inhibitory activity against PKC with IC_{50} values of 270, 200, 23, and 220 μM, respectively. They were also active against EGF receptor kinases and c-erbB-2 kinase with IC_{50} values of >400, 250, 170, and >400 μM and 30, 95, 26, and 29 μM, respectively.[54] Recently, the enantioselective total synthesis of the nakijiquinones and some closely related analogues was reported.[55] The evaluation of their biological activities disclosed that the C-2 epimer of nakijiquinone (**87**) was a potent and selective inhibitor of tyrosine kinase VEGFR2 (KDR), with an IC_{50} value of 21 μM. Since VEGFR2 is a receptor for the vascular endothelial growth factor (VEGF) family and is responsible for endothelial cell proliferation and blood vessel permeability, inhibitors of VEGFR2 may be potential antiangiogenic drugs.[55] Frondosines A−E (**88**−**92**), sesquiterpenoids from the sponge *Dysidea frondosa*, inhibited PKC with IC_{50} values of 1.8, 4.8, 20.9, 26, and 30.6 μM, respectively.[56]

Spongianolides A−E (**93**−**97**), cytotoxic sesterterpenes from a sponge *Spongia* sp., inhibited PKC with IC_{50} values of 20−30 μM.[57] Three secosterols, **98**−**100**, isolated from a gorgonian *Pseudopterogorgia* sp. inhibited human PKC α, βI, βII, γ, δ, ϵ, η, and ζ, with IC_{50} values in the range 12−50 μM. The semisynthetic derivatives **101**−**103** also showed similar activity.[35]

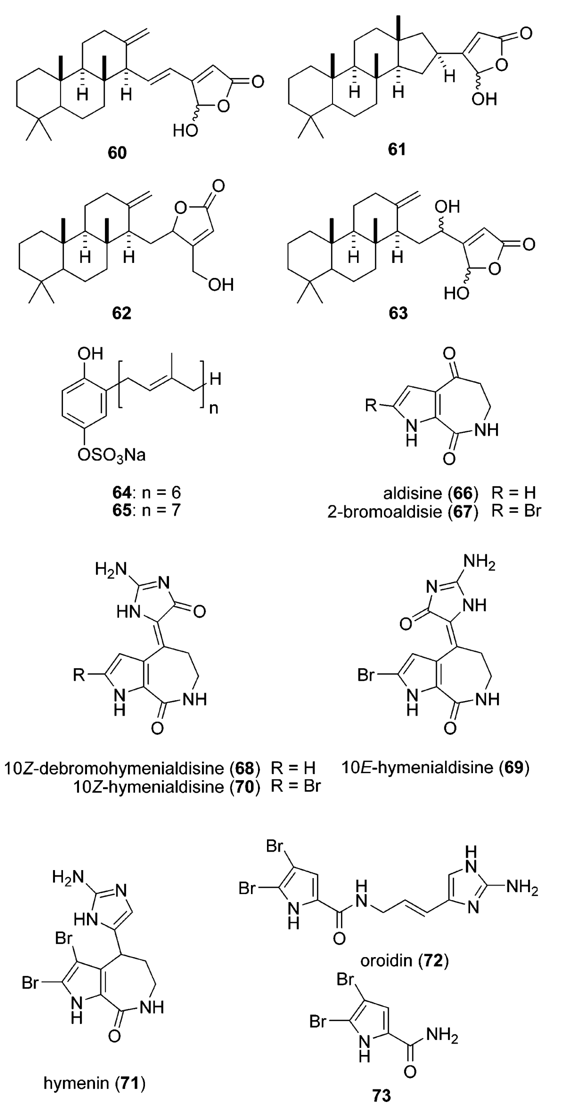
Penazetidine A (**104**), an azetidine isolated from the Indo-Pacific sponge *Penares sollasi*, inhibited PKC with an IC_{50} of 1 μM.[58] BRS1 (**105**), a C_{30} bis-amino, bis-hydroxy polyunsaturated lipid from an unidentified Australian sponge of the class Calcarea, inhibited not only PKC (EC_{50} 98 μM) but also radiolabeled phorbol ester binding to the enzyme (EC_{50} 9.2 μM).[59] Shimofuridin A (**106**), isolated from an Okinawan tunicate *Aplidium multiplicatum*, inhibited PKC with an IC_{50} value of 20.0 μg/mL.[60] Bryostatin-1 (**107**), which was isolated from the bryozoan *Bugula neritina* and is currently under phase I and II clinical trials as an anticancer agent,[61] is known to bind the C1 domain of PKC and to regulate its activity.[62]

Cyclin-Dependent Kinases (EC 2.7.11.22). Cyclin-dependent kinases (CDK) are also a family of protein tyrosine kinases, some of which are involved in cell cycling events, and their inhibitors may be expected to be potential anticancer drugs. Konbu'acidin A (**108**) is a bromopyrrole alkaloid possessing inhibitory activity against CDK4 (IC_{50} 20 μg/mL) and was isolated from a sponge *Hymeniacidon* sp.[63] Spongiacidins A (**109**) and B (**110**) also isolated from the same sponge inhibited c-erbB-2 kinase (IC_{50} 8.5 and 6.0 μg/mL, respectively) and cyclin-dependent kinase 4 (CDK4) (IC_{50} 32 and 12 μg/mL, respectively).[64] Ropaladins A−D, isolated from an Okinawan tunicate *Rhopalaea* sp., are the first examples of bis-indole alkaloids possessing an imidazolinone moiety as tunicate metabolites; rhopaladin B (**111**) inhibited CDK4 and c-erbB-2 kinase with IC_{50} values of 12.5 and 7.4 μg/mL, respectively.[65] Microxine (**112**) from an Australian sponge *Microxina* sp. inhibited CDK1 (cdc2) kinase with an IC_{50} value of 13 μM.[66]

Hydrolases (EC 3)

Phospholipase A_2 (EC 3.1.1.4). Phospholipase A_2 (PLA_2) cleaves the ester linkage of the β-position of phospholipids to release arachidonic acid, which is metabolized to prostaglandins, leukotrienes, and other mediators of inflammation. Prostaglandins are implicated in various forms of pain and inflammation. In the biogenesis of prostaglandins, arachidonic acid formation is the rate-determining step. Thus, PLA_2 inhibitors are expected to be potential antiinflammatory drugs. Manoalide (**113**), initially isolated as an antibacterial metabolite from the sponge *Luffariella variabilis*,[67] was found later to be a potent inhibitor of PLA_2 with IC_{50} 1.7 μM.[68]

Raf/MEK-1/MAPK and Checkpoint Kinases Inhibitors



Since manoalide is a potent PLA_2 inhibitor, more than 100 analogues were synthesized and evaluated for anti-inflammatory activity. However, manoalide proved ineffective during clinical trials and none of them were developed as drugs. Three congeners of manoalide were also obtained from the same sponge,[69] of which secomanoalide (**114**) is more potent against bovine pancreatic PLA_2.[70] Luffariellolide (**115**), from a Palauan *Luffariella* sp., also inhibited bee venom PLA_2 with an IC_{50} of 0.23 μM. The partially reversible and weaker inhibitory activity of **115** suggested that the γ-lactol group in **113** was responsible for the irreversible reaction of **113** with a Lys residue on PLA_2.[71] Luffariellins A (**116**) and B (**117**), isolated from *L. variabilis*, are very potent against bee venom PLA_2, with IC_{50} values of 56 and 62 nM, respectively.[72] These sesterterpenes are known to covalently and specifically modify PLA_2 by Schiff base formation between the Lys-56 residue of PLA_2 and the hemiacetal or aldehyde functionality of the terpenoids.[73] On the basis of this mechanism, Katsumura designed several PLA_2 inhibitors, of which one potently and selectively inhibited bovine pancreas PLA_2.[74]

Cacospongionolides (**118**−**120**), originally isolated as antitumor compounds from the Mediterannean sponge *Fasciospongia cavernosa*,[75] were found to selectively inhibit bee venom and human synovial PLA_2 among those of different origins. Cacospongionolide B (**119**) exhibited specific inhibition against human PLA_2,[76] while cacospongionolide E (**120**) was the most potent inhibitor toward human synovial PLA_2 (IC_{50} 1.4 μM), showing higher potency than manoalide.[77] A structure−activity relationship study on synthetic analogues suggested that **119** has an enantiospecific interaction with the enzyme that is independent of the γ-hydroxybutenolide moiety.[78] Furthermore, cacospongionolide B (**119**) was reported to suppress expression of inflammatory enzymes, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), as well as to reduce tumor necrosis factor-α (TNF-α).[79] Cavernolide (**121**), isolated from the sponge *Fasciospongia cavernosa*, selectively inhibited human PLA_2 with an IC_{50} value of 8.8 μM.[80]

Dysidiotronic acid (**122**), a sesquiterpenoid from a Vanuatu sponge *Dysidea* sp., inhibited human synovial PLA_2 with an IC_{50} value of 2.6 μM,[81] while bolinaquinone (**123**), dysidine (**124**), and a 1:1 mixture of dysideonones A (**125**) and B (**126**) significantly inhibited human synovial PLA_2. Compound **123** showed the most potent activity, with an IC_{50} value of 0.2 μM, but was not a selective inhibitor toward this enzyme. On the contrary, dysidine (**120**) showed selective inhibition against this enzyme with an IC_{50} value of 2.0 μM. In contrast, **123**−**126** did not inhibit cytosolic PLA_2 ($cPLA_2$).[82]

Petrosaspongiolides M−R (**127**−**131**), sesterterpenes from the New Caledonian sponge *Petrosaspongia nigra*, inhibited PLA_2. The most potent analogue (petrosaspongiolide M; **127**) inhibited human synovial and bee venom PLA_2 with IC_{50} values of 1.6 and 0.6 μM, respectively, while petrosaspongiolide P (**129**) inhibited human synovial PLA_2 (IC_{50} 3.8 μM) in a more selective manner than when evaluated against bee venom PLA_2 (IC_{50} >10 μM). Petrosaspongiolides N (**128**), Q (**130**), and R (**131**) showed only weak activity.[83] Petrosaspongiolide M was shown to form a covalent adduct with PLA_2 through the γ-hydroxybutenolide moiety, which is essential for the activity.[84] Ironically, a mild noncovalent PLA_2 inhibitor, 25-acetylpetrosaspongiolide M, was found to be hydrolyzed with PLA_2 to form the potent inhbitor petrosaspongiolide M (**127**).[85] The anti-inflammatory effects of petrosaspongiolide M (**127**) were suggested to be mediated by inhibition of the NF-κB signaling pathway.[86]

Aplyolide (**132**), a sesterterpene isolated from the sponge *Aplysinopsis elegans*, inhibited human PLA_2 with an IC_{50} 10.5 μM,[87] whereas the related terpenoid, luffolide (**133**) from a Palauan *Luffariella* sp., completely inhibited bee venom PLA_2 at a concentration of 3.5 μM.[88]

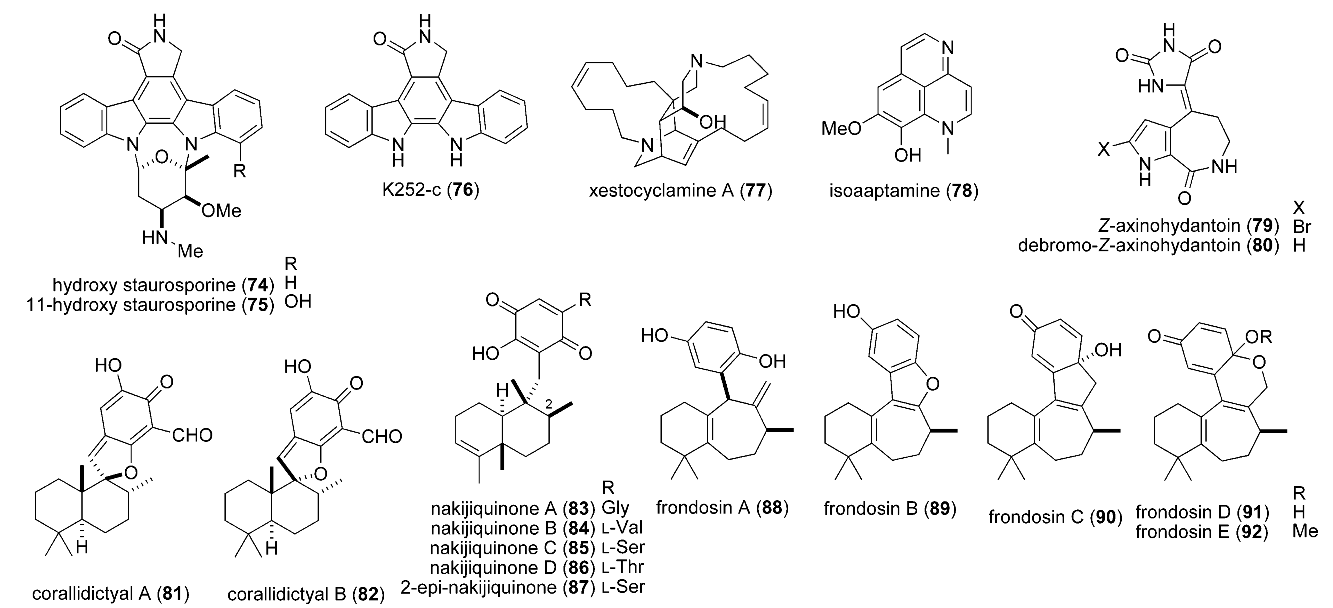
A homoscalarane sesterterpene, **134**, isolated from the sponge *Lendenfeldia frondosa*, showed moderate PLA_2 inhibition (35% inhibition at 8 μM).[89] A sesterterpene, 12-deacetyl-23-acetoxy-20-methyl-12-*epi*-scalaradial (**135**), from the Pacific nudibranchs *Glossodoris sedan* and *G. dalli* inhibited mammalian $cPLA_2$, with an IC_{50} value of 18.0 μM.[90] The parent compound, scalaradial (**136**), is more potent (IC_{50} 0.6 μM).[73a,91]

Halisulfate 1 (**137**), obtained from a halichondrid sponge, inhibited PLA_2 completely at 16 μg/mL, while a mixture of halisulfates 2−4 (**138**−**140**) inhibited PMA-induced inflammation in the mouse ear edema assay, as well as PLA_2 (data not shown).[92] Palinurin (**141**), originally isolated from the Mediterranean sponge *Ircinia variabilis*,[93] was inhibitory against PLA_2 with an IC_{50} value of 50 μM.[3] Two sesterterpenes, palauolol (**142**) and palauolide (**143**), isolated from a Palauan sponge *Fascaplysinopsis* sp. inhibited bee venom PLA_2 (85% and 82% inhibition at 0.8 μg/mL, respectively).[94]

Two polyhydroxy sterols, **144** and **145**, from the Korean gorgonian *Acabaria undulata* inhibited PLA_2 with IC_{50} values of 13.8 and 21.5 μM, respectively.[95] Valdivones A (**146**) and B (**147**), diterpenoids isolated from the South African soft coral *Alcyonium valdivae*, strongly inhibited chemically induced inflammation in the mouse ear assay (93% and 72% inhibition at 50 μg/ear, respectively), but their activity against bee venom PLA_2 was not potent (43% inhibition at 16 μg/mL for both).[96]

Acetylcholinesterase (EC 3.1.1.7). 3-Alkylpyridinium polymer **148** from the sponge *Reniera sarai* showed potent inhibitory activity

PKC Inhibitors 1



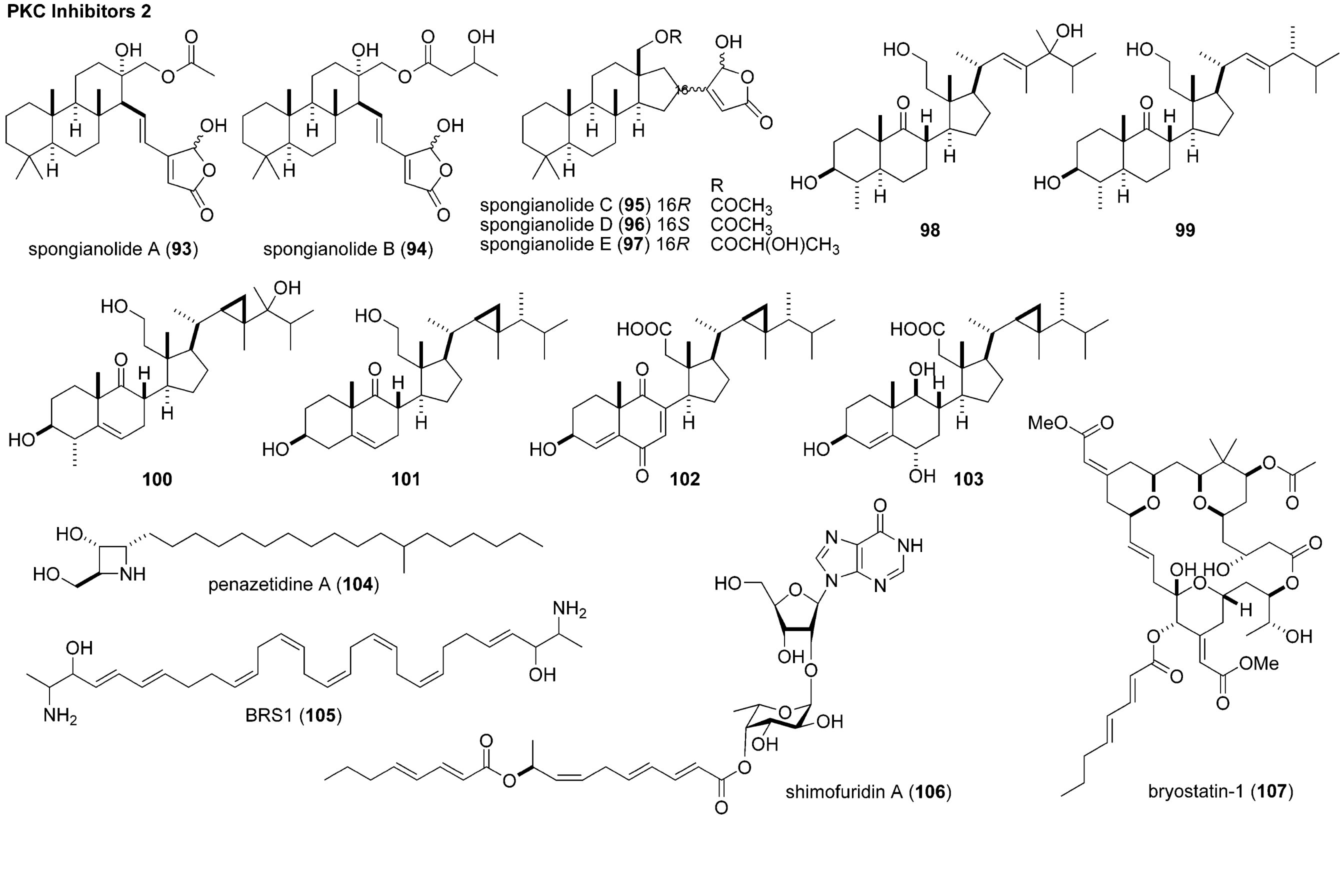
against electric eel acetylcholinesterase (AchE), human erythrocyte AchE, insect recombinant AchE, and horse serum butylcholinesterase (BuChE), with IC_{50} values of 0.06, 0.08, 0.57, and 0.14 μg/mL, respectively, while it did not inhibit trypsin or alkaline phosphatase.[97]

Protein Phosphatases (EC 3.1.3.16). Reversible protein serine/threonine phosphorylation regulates numerous cellular functions, including muscle contractions, neurotransmission, cell proliferation, carcinogenesis, and apoptosis. A large number of protein kinases have been well investigated for several decades, but it is only quite recently that our understanding of protein phosphatases (PPs), namely, PP1, PP2A, PP2B, and PP2C, has been considerably enhanced by the discovery of natural product inhibitors.

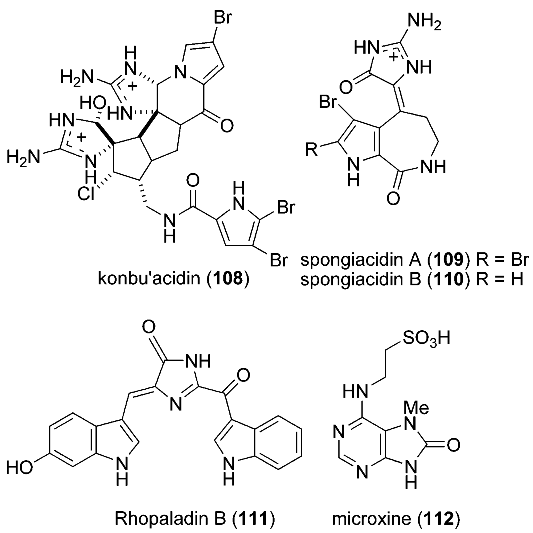
PP1 and PP2A. Okadaic acid (**149**), the first natural product inhibitor of PP1 and PP2A, is a polyether polyketide that was isolated as a cytotoxic substance from two sponges, Japanese *Halichondria okadai* and Caribbean *H. melanodocia*.[98] It was also identified as a causative agent of diarrhetic shellfish poisoning. Later, **149** was found to be a potent tumor promoter, which proved to show the potent inhibition of PP1 and PP2A, with IC_{50} values of 60−500 and 0.2−1 nM, respectively, whereas it showed only weak or no inhibition against PP2B or PP2C, respectively.[99] It has become a powerful tool for the study of biological processes mediated by protein phosphorylation. The crystal structure of PP1γ−okadaic acid complex was recently elucidated.[100]

Calyculin A (**150**) was originally isolated from the Japanese sponge *Discodermia calyx* as a potent cytotoxic compound.[101] It also turned out to be a potent inhibitor of protein phosphatases and, like okadaic acid, it showed tumor promotion activity. It inhibits PP1 and PP2A with IC_{50} values of 1.4 and 2.6 nM, respectively,

PKC Inhibitors 2



Cyclin-dependent Kinase Inhibitors



konbu'acidin (**108**); spongiacidin A (**109**) R = Br; spongiacidin B (**110**) R = H; Rhopaladin B (**111**); microxine (**112**)

while it showed little inhibition against PP2B.[102] Calyculins B−H (**151**−**157**), geometric isomers of **150**, or their 32-methyl derivatives, which were later isolated from the same sponge, showed similar inhibitory activity against PP2A (IC_{50} 1.0−6.0 nM).[103] Furthermore, calyculin J (**158**), calyculinamides A (**159**) and F (**160**), des-*N*-methylcalyculin A (**161**), and dephosphonocalyculin A (**162**) were isolated as PP2A inhibitors from *D. calyx*.[104] Quite recently, the isolation of hemicalyculin A (**163**) from *D. calyx* and a preliminary structure−activity relationship study were reported.[105] Hemicalyculin A (**163**) was found to be as potent as calyculin A (**150**) against PP1γ and PP2A, with IC_{50} values of 14 and 1.0 nM, respectively. Interestingly, however, **163** showed cytotoxicity over 2000 times less potent than that of **150**. More recently, the crystal structure of the calyculin A−PP1γ complex was solved by X-ray crystallography,[106] which showed that the hydrophobic tail and phosphate and OH-13 moieties are essential for binding to PP1γ. These features are similar to those of the PP1−microcystin LR[107] and PP1−okadaic acid complexes.[100] Clavosines A−C (**164**−**166**), glycosylated derivatives of C21-*epi*-calyculinamide C, were isolated from the sponge *Myriastra clavosa*. Clavosines A (**164**) and B (**166**) inhibited PP1cγ (IC_{50} 0.5 and 13 nM, respectively), native PP1c (IC_{50} 0.25 and 1.0 nM, respectively), and PP2Ac (IC_{50} 0.6 and 1.2 nM, respectively).[108]

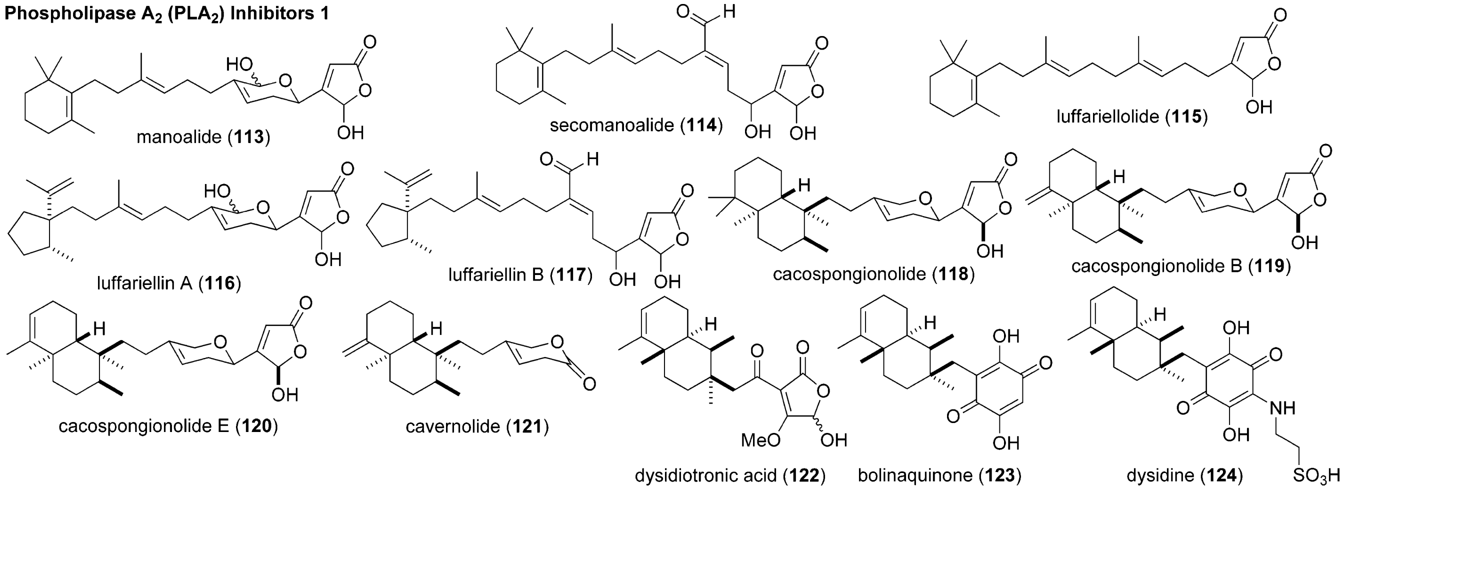
Motuporin A (**167**), one of the most potent PP1 inhibitors known, was isolated from the Papua New Guinea sponge *Theonella swinhoei* and inhibited PP1 at <1 nM.[109] Dragmacidins D (**168**) and E (**169**), purified from a southern Australian deep-water sponge *Spongosorites* sp., are potent serine-threonine protein phosphatase inhibitors. Compound **168** selectively inhibited PP1, while **169** inhibited both PP1 and PP2A in a preliminary assay (data not published). Dragmacidin E (**169**) seems to exist in tautomeric equilibrium between pyrazine and pyrazinone forms.[110] Spirastrellolide A (**170**) is a novel macrolide isolated from the sponge *Spirastrella coccinea* as an antimitotic agent.[111] Recently, its revised structure and selective inhibitory activity against PP2A (IC_{50} 1 nM) were reported.[112] Nagelamides are dimeric bromopyrrole alkaloids isolated from the sponge *Agelas* sp., among which nagelamides A−C (**171**−**173**), G (**174**), and H (**175**) were shown to inhibit PP2A (IC_{50} 13 to >50 μM).[113]

Calcineurin (PP2B). Calcineurin (CaN), a serine-threonine protein phosphatase (PP2B) involved in signal transduction, is recognized as one of the principal signaling molecules that regulates the immune response.[114] Immunosuppressants such as FK506 and cyclosporin A have been shown to exert their effects through inhibition of CaN following their association with binding proteins.[115] Thus, inhibitors of CaN may be useful as immunosuppressants. Secobatzellines A (**176**) and B (**177**), isolated from a Caribbean deep-water sponge *Batzella* sp., inhibited CaN with IC_{50} values of 0.55 and 2.21 μg/mL, respectively. Secobatzelline A (**176**) also inhibited peptidase activity of CPP32 (IC_{50} 0.02 μg/mL), a cysteine protease known as caspase-3, which plays a major role in the process of programmed cell death, which is also known as apoptosis.[116]

Protein Tyrosine Phosphatases (EC 3.1.3.48). Cdc25 is a dual-specificity protein tyrosine phosphatase that regulates activation of CDKs (cyclin-dependent kinases) through the dephosphorylation of both threonine and tyrosine residues of CDKs. As a result of their unique substrate selectivity and their essential functions in cell cycle control, cdc25 phosphatases represent attractive screening targets to identify new antimitotic compounds. Dysidiolide (**178**) is the first natural product inhibitor of cdc25A and was isolated from the Caribbean sponge *Dysidea etheria*. It inhibited the dephosphorylation of *p*-nitrophenol phosphate by cdc25A phosphatase with an IC_{50} of 9.4 μM.[117] Because of its unusual structure and interesting biological activity, a number of synthetic chemists undertook efforts directed toward the total synthesis of dysidiolide, from which some important structure−activity relationship information was obtained.[118] Coscinosulfate (**179**), a sesquiterpene sulfate isolated from the New Caledonian sponge *Coscinoderma matthewsi*, exhibited selective inhibition against cdc25A phosphatase with an IC_{50} value of 3 μM.[119]

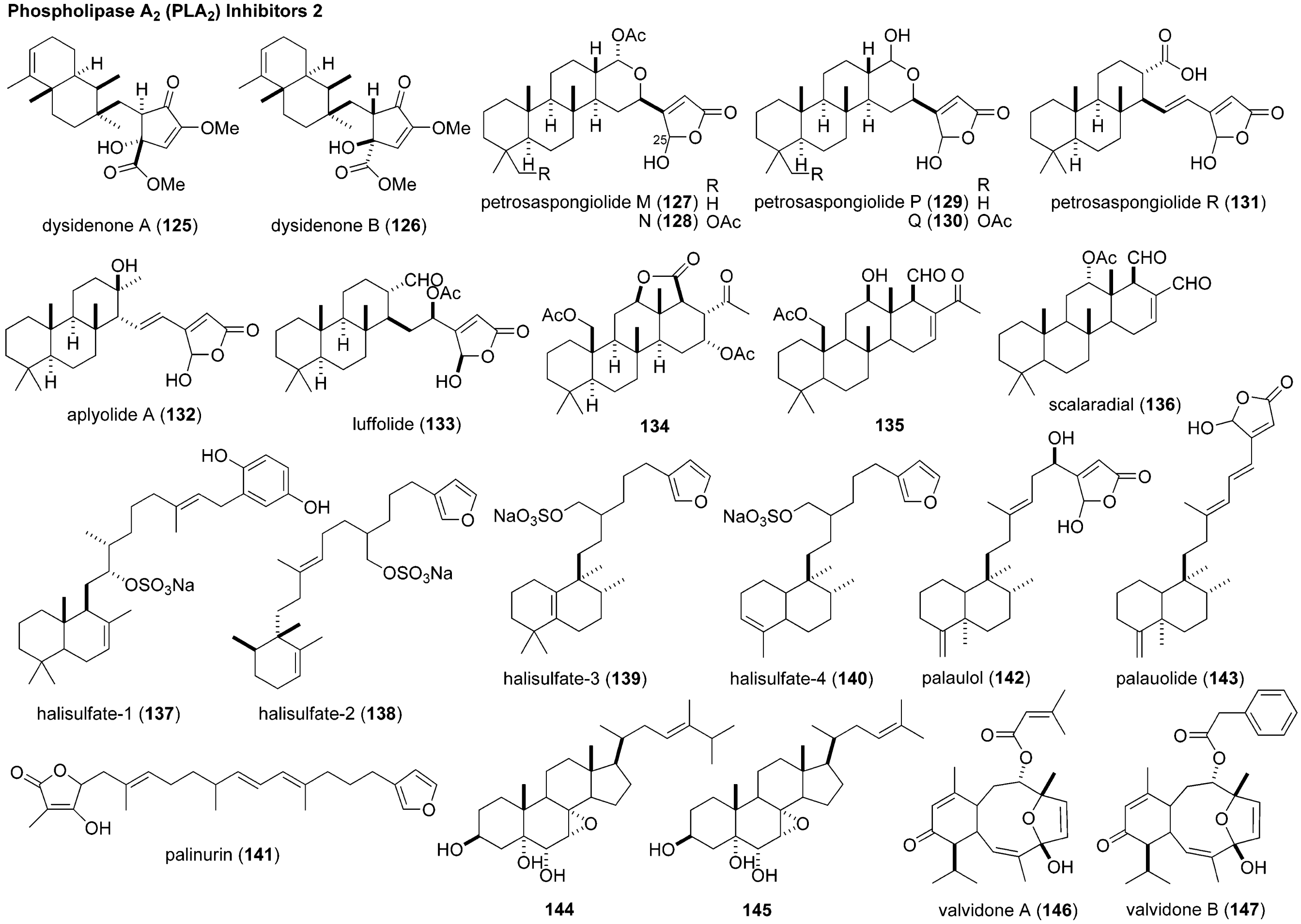
Phospholipase C (EC 3.1.4.3). Phosphatidylinositol-specific phospholipase C (PI-PLC) is the rate-limiting enzyme in phosphatidylinositol turnover. PI-PLC hydrolyzes the phosphate−glycerol linkage of phosphatidylinositol to produce two secondary messengers, inositol triphosphate and diacylglycerol, which play key roles in cellular signal transduction induced by growth factors

Phospholipase A_2 (PLA_2) Inhibitors 1



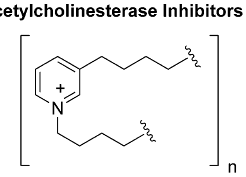
manoalide (**113**); secomanoalide (**114**); luffariellolide (**115**); luffariellin A (**116**); luffariellin B (**117**); cacospongionolide (**118**); cacospongionolide B (**119**); cacospongionolide E (**120**); cavernolide (**121**); dysidiotronic acid (**122**); bolinaquinone (**123**); dysidine (**124**)

Phospholipase A_2 (PLA_2) Inhibitors 2



and hormones.[120] Akaterpin (**180**), isolated from an Okinawan sponge *Callyspongia* sp., showed potent inhibition against PI-PLC (IC_{50} 0.5 μg/mL) as well as weak inhibition against neutral sphingomyelinase, with an IC_{50} value of 30 μg/mL.[121]

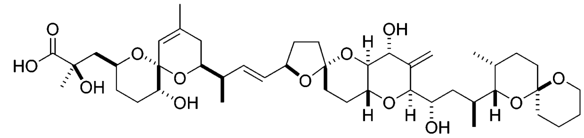
Acetylcholinesterase Inhibitors



MW 5520 & 18900
148

Phosphodiesterase (EC 3.1.4.). The Ca^{2+}−calmodulin system plays an important role in the control of cellular proliferation and tumor formation. A calmodulin antagonist, W-7, has been found to inhibit proliferation of Chinese hamster cells and the formation of mouse skin tumors. Eudistomidin A (**181**), a β-carboline alkaloid isolated from the Okinawan tunicate *Eudistoma glaucus*, inhibited calmodulin-activated brain phosphodiesterase with an IC_{50} value of 20 μM,[122] while eudistomidin C (**182**) exhibited calmodulin antagonistic activity (IC_{50} 30 μM).[123] Pseudodistomins A (**183**) and B (**184**), unusual alkylpiperazines from the Okinawan tunicate *Pseudodistoma kanoko*, inhibited calmodulin-activated brain phosphodiesterase with the same IC_{50} value of 30 μM and is about 3 times more potent than W-7.[124] Rigidin (**185**), purified from an Okinawan tunicate *Eudistoma* cf. *rigida*, inhibited calmodulin-activated brain phosphodiesterase with an IC_{50} value of 50 μM.[125] Stellettamide A (**186**), an unusual indolizidine alkaloid originally isolated from a sponge *Stelletta* sp. as an antifungal and cytotoxic compound,[126] was found to inhibit Ca^{2+}/calmodulin-dependent phosphodiesterase and (Ca^{2+}-Mg^{2+})-ATPase with IC_{50} values of 52 and 100 μM, respectively.[127] Three related alkaloids, stellettazole A (**187**)[128] and bistellettadines A (**188**) and B (**189**),[129] from the same sponge showed moderate inhibitory activity against Ca^{2+}/calmodulin-dependent phosphodiesterase (**187**: 45% inhibition at 100 μM, **188** and **189**: 40% inhibition at 100 μM).

PP1 and PP2A Inhibitors 1

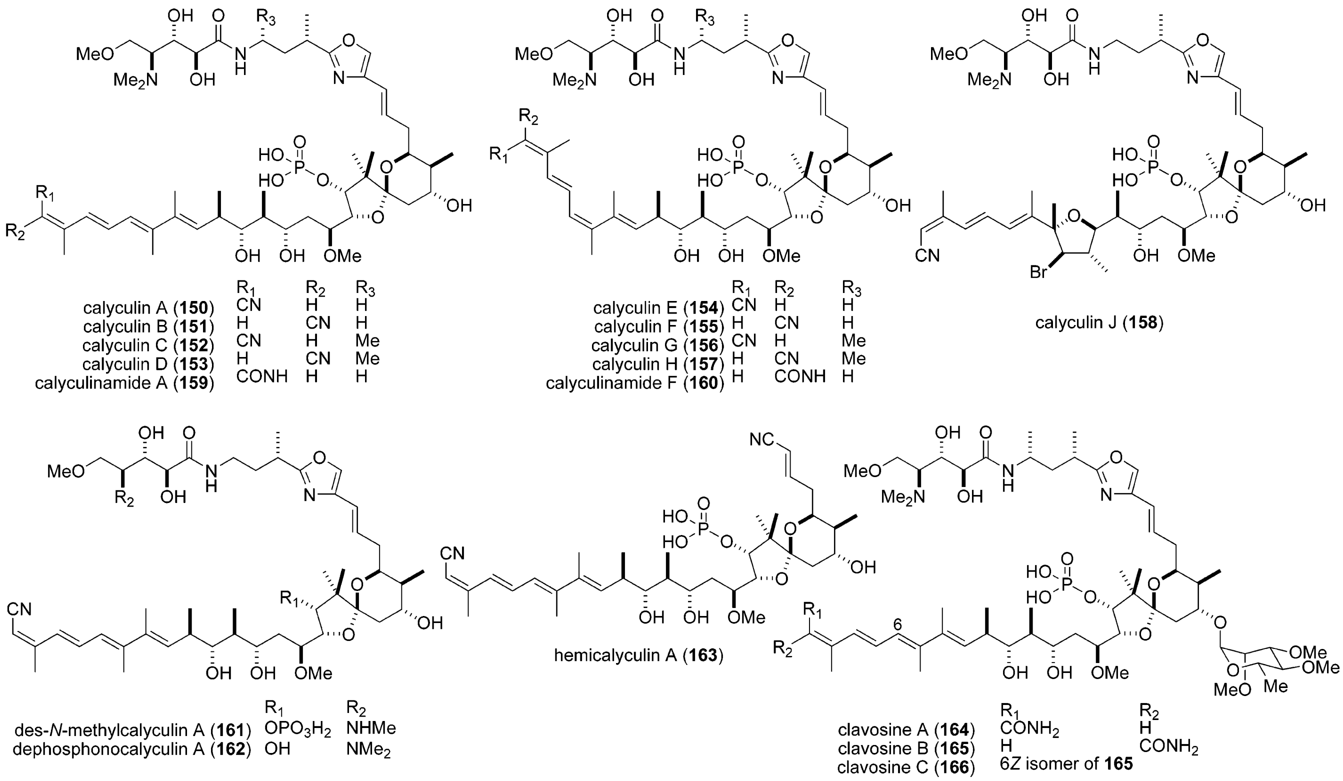


okadaic acid (**149**)

Glycosidases. Glycosidases are involved in various biological functions including the immune response, oncogenesis, tumor metastasis, viral and bacterial infections, and differentiation of neural cells. Specific inhibitors of glycosidases have potential for the treatment of a variety of diseases.

Sialidase (EC 3.2.1.18). Sialidase cleaves an α-linked terminal *N*-acetylneuraminic acid from glycoproteins, glycolipids, and oligosaccharides. In several viral and bacterial infections, sialidase plays important roles. For example, influenza virus employs this enzyme to detach itself from the infected cell in the budding stage, thus indicating a requirement of sialidase for replication of the virus. Therefore, selective inhibitors of sialidase are potential therapeutic agents against influenza. The α-glucosidase inhibitors schulzeines A−C (**190**−**192**) obtained from the sponge *Penares schulzei* were also inhibitory against viral sialidase, all having the same IC_{50} value of 60 μM. Calyceramides A−C (**193**−**195**), sulfated ceramides isolated from the sponge *Discodermia calyx*, inhibited sialidase from *Clostridium perfringens* with IC_{50} values of 0.4, 0.2, and 0.8 μg/mL, respectively.[130] Another example of a marine sialidase inhibitor is nobiloside (**196**), a triterpenoid saponin of the sponge *Erylus*

PP1 and PP2A Inhibitors 2



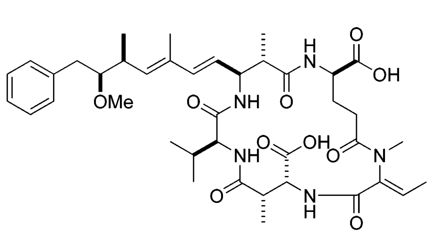
nobilis, which inhibited *Clostridium perfringens* sialidase with an IC_{50} value of 0.46 μg/mL.[131] Asteropine A (**197**) is the first cystine knot of sponge origin and was isolated from *Asteropus simplex*. Asteropine A showed potent and competitive inhibition against bacterial sialidases (from *Clostridium perfringens*, *Vibrio choleae*, and *Salmonella typhimurium*) with K_i values of 36.7, 340, and 350 nM, respectively.[132]

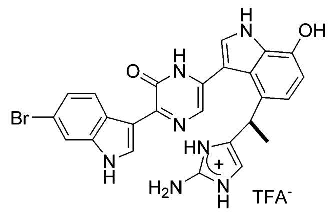
Chitinase (EC 3.2.1.14). Chitinase plays important roles in a wide variety of organisms ranging from nutrition to defense and control of ecdysis in arthropods, thus indicating the potential of chitinase inhibitors as antifungal and insecticidal agents. The styloguanidine analogues, **198**−**200**, isolated from the sponge *Stylotella aurantium* collected at Yap, showed inhibitory activity against chitinase from a bacterium *Schwanella* sp. at 2.5 μg/disk using a "squid chitin agar plate method".[133]

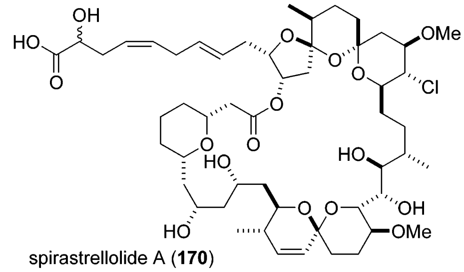
α-Glucosidases (EC 3.2.1.20). α-Glucosidases are involved in glycoprotein processing and glycogenolysis and, therefore, their inhibitors could be potentially useful in the treatment of diabetes, obesity, viral infections, or cancer. Penarolide sulfates A_1 (**201**) and A_2 (**202**), L-proline-containing macrolide trisulfates isolated from a sponge *Penares* sp., showed inhibition against α-glucosidase from yeast, with IC_{50} values of 1.2 and 1.5 μg/mL, respectively, while they showed little or no inhibition against β-glucosidase or β-galactosidase. The penarolide sulfates also inhibited thrombin with IC_{50} values of 3.7−4.2 μg/mL. The presence of the sulfate groups in **201** and **202** may be responsible for their activity.[134] A linear type congener, penasulfate A (**203**), in which L-proline was replaced by D-pipecolic acid, was isolated from the same sponge. Penasulfate A (**203**) showed about 10 times higher potency (IC_{50} 0.14 μg/mL) compared to the penarolide sulfates against the same enzyme, although the inhibitory activity against the enzyme obtained from different sources matched that of the latter congeners.[135] Callyspongynic acid (**204**), a polyacetylenic acid isolated from the Japanese sponge *Callyspongia truncata*, inhibited α-glucosidase with an IC_{50} value of 0.25 μg/mL, but was inactive against α-glucosidase, α-galactosidase, thrombin, and trypsin at 100 μg/mL. The presence of carboxylic acid and allylic alcohol moieties linked to the acetylene units is thought to be important for such activity.[136] From the sponge *Penares schulzei*, three new α-glucosidase inhibitors, schulzeines A−C (**190**−**192**), were isolated. Schulzeines A−C showed potent inhibitory activity against α-glucosidase with IC_{50} values in the range 48−170 nM. Desulfated schulzeines A and B still retained significant activity (IC_{50} 2.5 and 1.1 μM, respectively).[137]

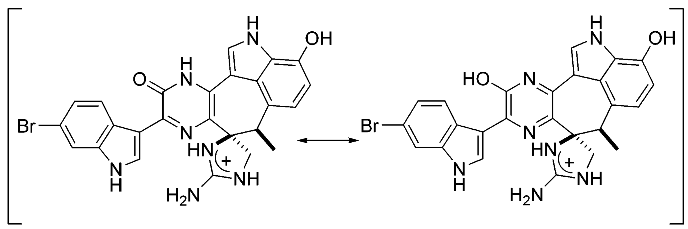
Serine Proteases (EC 3.4.21). Proteolytic enzymes are classfied into serine proteases, cysteine proteases, aspartic proteases, and metalloproteases on the basis of their catalytic centers. Trypsin-like enzymes, a group of serine proteases, are associated with many disease states. The hyperproteolytic activities of this homologous family of enzymes are attractive chemotherapeutic targets in pathways of blood coagulation, fibrinolysis, kinin formation, complement activation, digestion, reproduction, and phagocytosis. Thus, inhibitors of specific serine proteases can be potential drug leads for many disease states.[138] Cyclotheonamides A (**205**) and B (**206**) from a sponge *Theonella* sp. (now known to be *T. swinhoei*) inhibited thrombin, trypsin, and plasmin with IC_{50} values of 0.076, 0.2, and 0.3 μg/mL, respectively.[139] Further investigation of *T. swinhoei* yielded cyclotheonamides C (**207**) and D (**208**).[140] Cyclotheonamides E1−E5 (**210**−**214**) were not found from this sponge, but from another variant type of *T. swinhoei* with a white interior (E1−E3)[141] and from an Okinawan *Ircinia* sp. (E4, E5).[142] Cyclotheonamides C (**207**), D (**208**), and E1−E5 (**210**−**214**) showed potent inhibition against thrombin and trypsin with IC_{50} values of 2.9−68 and 7.4−55 nM, respectively. Cyclotheonamides E1 (**210**), E4 (**213**), and E5 (**214**) strongly inhibited both mouse and human tryptases (IC_{50}'s 6.9, 5.1, and 84.7 nM for human tryptase and 17.0, 6.5, and 54.1 nM for mouse tryptase, respectively).[142] Dihydrocyclotheonamide A (**209**), and pseudotheonamides A_1 (**215**), A_2 (**216**), B_2 (**217**), C (**218**), and D (**219**) from *T. swinhoei*, in which the α-ketohomoarginine (k-Arg) residues are modified, showed only moderate activity against these enzymes, with IC_{50}'s ranging from 0.19 to 3.0 μM (thrombin) and 3.8 to >10 μM (trypsin).[143] Complexes between cyclotheonamide A (**205**) and human α-thrombin, and between cyclotheonamide A (**205**) and trypsin, were crystallized successfully and their crystal structures were solved, disclosing that cyclotheonamide A binds to the

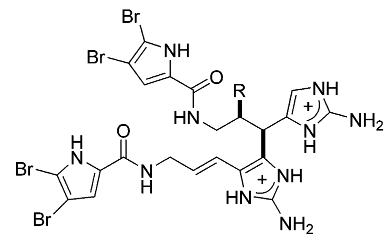
PP1 and PP2A Inhibitors 3

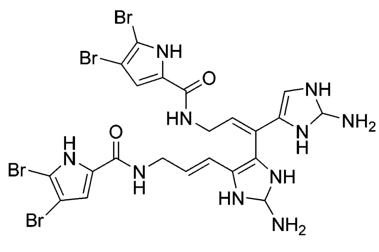

motuporin A (**167**)

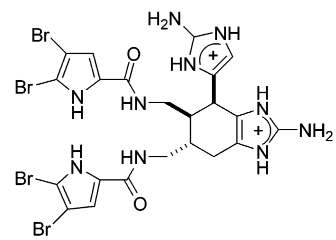

dragmacidin D (**168**)

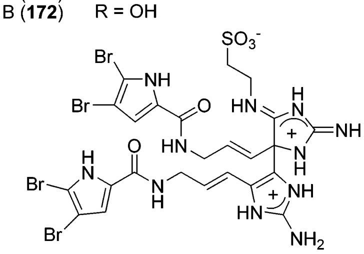

spirastrellolide A (**170**)


dragmacidin E (**169**)


nagelamide A (**171**) R = H
B (**172**) R = OH


nagelamide C (**173**)


nagelamide G (**174**)


nagelamide H (**175**)

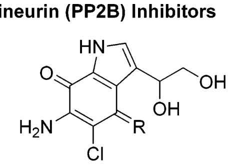
catalytic center of these enzymes. In particular, k-Arg forms a hemiacetal linkage with Ser195 as one of a catalytic triad and is important for the binding to the enzyme.[144] *T. swinhoei* also afforded a thrombin inhibitory linear peptide, nazumamide A (**220**), which inhibited thrombin at IC_{50} 2.8 μg/mL, but not trypsin at 100 μg/mL.[145] It was demonstrated by X-ray crystallography of the nazumamide A−thrombin complex that nazumamide A (**220**) binds to human thrombin in a "retro" fashion or opposite the typical peptide ligands.[146]

Toxadocials A−C (**221**−**223**) and toxadocic acid A (**224**), isolated from a sponge *Toxadocia* sp., are alkyl sulfate thrombin inhibitors with IC_{50} values of 6.5, 4.6, 3.2, and 2.7 μg/mL, respectively.[147]

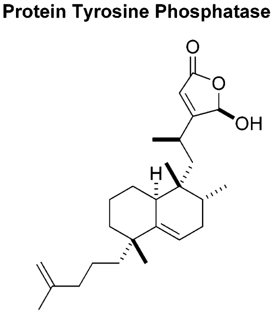
Dysinosins A−D (**225**−**228**) are inhibitors of factor VIIa and thrombin isolated from the Australian sponge *Lamellodysidea chlorea*. Dysinosins showed potent inhibitory activity against factor VIIa and thrombin with K_i values of 0.090 to 1.32 and 0.17 to >5.1 μM, respectively.[148] The structural similarity of the dysinosins to the aeruginosins (**229**), which were the serine protease inhibitors isolated from the cyanobactera *Microcystis aeruginosa*[149] and *Oscillatoria agardhii*,[150] implied that they may be biosynthesized by associated microbes.

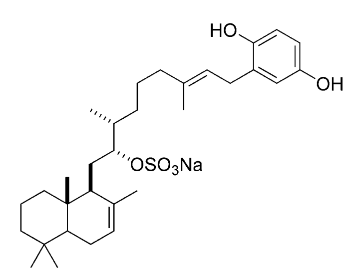
Cysteine Proteases (EC 3.4.22). Cysteine proteases having cysteine and histidine as the catalytic center are involved in cytosolic protein metabolism. Cathepsin B, a cysteine protease, is known to be involved in various disease states, such as inflammation, trauma, muscular dystrophy, and tumor development. In particular, its possible roles in cancer metastasis are of major concern in cancer chemotherapy. Two peptide inhibitors, tokaramide A (**230**)[151] and miraziridine A (**231**),[152] with IC_{50} values of 29 and 1400 ng/mL, were isolated from the sponge *Theonella* aff. *mirabilis*. Miraziridine A (**231**) contains three unusual amino acid residues, including particularly unusual vinylogous arginine and aziridine-2,3-dicarboxylic acid units. Secobatzelline A (**176**), isolated from a sponge *Batzella* sp., showed inhibition against the peptidase activity of CPP32, a member of the caspase family of cysteine proteases that play major roles in the apoptotic programmed cell death mechanism, with an IC_{50} value of 0.02 μg/mL.[116]

Calcineurin (PP2B) Inhibitors


secobatzelline A (**176**) R = NH
secobatzelline B (**177**) R = O

Protein Tyrosine Phosphatase Inhibitors

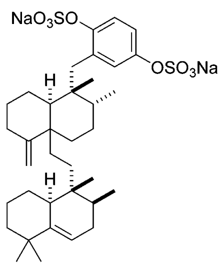

dysidiolide (**178**)


coscinosulfate (**179**)

Aspartic Proteases (EC 3.4.23)

HIV Protease (EC 3.4.23.47). Replication of HIV involves expression of several viral proteins that require the presence of a virus-specific protease for their maturation. Inhibition of this enzyme results in immature viral particles. Therefore, HIV-1 protease is considered as an excellent target in AIDS chemotherapeutics. Didemnaketals A (**232**) and B (**233**), isolated from a Palauan ascidian *Didemnum* sp., inhibited HIV-1 protease with IC_{50} values of 2 and 10 μM, respectively.[153] The unusual structures and potent activity of the didemnaketals makes them attractive synthetic targets.[154] Recently, simplified analogues lacking the spiroketal portion were synthesized, some of which are as potent as didemnaketal A (**232**). It has been also proposed that the didemnaketals inhibit dimerization of HIV-1 protease monomers.[155]

Phospholipase C (PLC) Inhibitors



akaterpin (**180**)

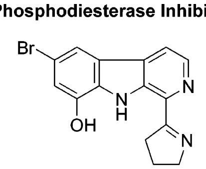
Metalloproteases (EC 3.4.24). Metalloproteases contain metal ions such as Zn^{2+}, Co^{2+}, and Mn^{2+} in their catalytic centers. The matrix metalloproteinases (MMPs), members of a large subfamily of proteases that contain a catalytic zinc-binding domain, play important roles in the remodeling and degradation of the extracellular matrix (ECM). They are linked to a range of physiological and pathological processes, including wound healing, bone remodeling, angiogenesis, inflammation, and tumor progression and metastasis. The membrane-type matrix metalloproteinases (MT-MMPs) are key enzymes in tumor metastasis. They activate progelatinase A to the fully matured form, which, in turn, degrades type IV collagen, the major component of the basal membrane that prevents tumor progression. Thus, inhibitors of MT-MMPs have potential as anticancer drugs. Ancorinosides B−D (**235**−**237**)[156] were isolated as MT1-MMP inhibitors from the sponge *Penares sollasi*, along with the known compound ancorinoside A (**234**),[157] which was originally isolated as an inhibitor of blastulation of starfish embryos from a sponge *Ancorina* sp. Ancorinosides A−D (**234**−**237**) inhibited MT1-MMP with IC_{50} values of 440, 500, 370, and 180 μg/mL, respectively. Ancorinoside B (**235**) also inhibited gelatinase A (MMP2) with an IC_{50} value of 22 μg/mL. Haplosamate A (**39**) and its congener **238** were isolated from a Japanese sponge *Cribrochalina* sp. as MT1-MMP inhibitors with IC_{50} values of 150 and 160 μg/mL, respectively;[158] compound **39** was originally isolated as an HIV integrase inhibitor from Philippine haplosclerid sponges.[25] Ageladine A (**239**) is a fluorescent alkaloid isolated from the sponge *Agelas nakamurai*. The IC_{50} values of **239** against MMPs 1, 2, 8, 9, 12, and 13 were 1.2, 2.0, 0.39, 0.79, 0.33, and 0.47 μg/mL, respectively, while its *N*-methylated derivatives did not inhibit MMP2. Unlike other MMP inhibitors, ageladine A (**239**) was not capable of chelating Zn^{2+} and is not a competitive inhibitor of MMP2.[159] Due to those interesting aspects of its mode of inhibition, as well as its antiangiogenic activity, ageladine A (**239**) became a target for total synthesis.[160]

Histone Deacetylases (EC 3.5.1). Histone acetylation and deacetylation are catalyzed by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively, and play important roles in transcriptional regulation.[161] Inhibitors of these enzymes are known to induce cell cycle arrest,[162] p53-independent induction of the cyclin-dependent kinase inhibitor p21,[163] tumor-selective apoptosis,[164] and differentiation of normal and malignant cells.[165] HDAC inhibitors have been demonstrated also to have antiangiogenic effects through the alteration of vascular endothelial growth factor (VEGF) signaling.[166] These direct and indirect effects on tumor growth and metastasis have indicated the HDAC inhibitors as potential anticancer agents. Six new psammaplins, E−J (**244**−**249**), were isolated from the sponge *Pseudoceratina purpurea*, collected in Papua New Guinea, along with the known compounds psammaplins A−D (**240**−**243**) and bisaprasin (**250**). These compounds showed potent inhibitory activity against HDAC (IC_{50}'s 2.1−327 nM) and cell-based p21 promoter activity (AC_{50} 0.7−15 μM), as well as inhibitory activity against DNA methyltransferase (DNMT).[167] NVP-LAQ824 (**251**), which was developed on the basis of the structures of HDAC inhibitors including the psammaplins,[168] entered phase I clinical trials in patients with solid tumors or leukemia.[169] Three new cyclostellettamines, cyclostellettamine G (**253**) and dehydrocyclostellettamines D (**254**) and E (**255**), were isolated together with the known compound cyclostellettamine A (**252**) from a sponge of the genus *Xestospongia*. These compounds inhibited HDAC with IC_{50} values between 17 and 80 μM.[170] Five new cyclic tetrapeptides, azumamides A−E (**256**−**260**), were isolated from the sponge *Mycale izuensis*. The azumamides showed inhibitory activity against human HDAC with IC_{50} values of 0.045−1.3 μM. In a cell-based assay using K562 cells, azumamide A (**256**) inhibited deacetylation of Ac-H3 (Lys9 and Lys 14) and Ac-H4 (Lys 8) in a dose-dependent manner (0.19−19 μM). Furthermore, azumamide A (**256**) inhibited angiogenesis in an in vitro vascular organization model using mouse ES cells.[171]

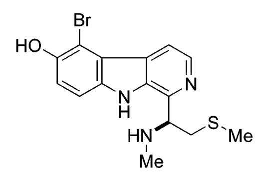
ATPases (EC 3.6.1.3)

H,K-ATPase. H,K-ATPase mediates acid secretion from gastric wall cells. Thus, excess activation of this enzyme leads to hyperacidity, causing gastric ulcers. In order to discover potential antiulcer leads, we screened a number of Japanese marine invertebrates for inhibition of porcine H,K-ATPase, which resulted in isolation of several inhibitors. *S*-(+)-Curcuphenol (**261**) and dehydrocurcuphenol (**262**), isolated from a Japanese sponge of the genus *Epipolasis*, inhibited porcine H,K-ATPase with IC_{50} values of 8.3 and 23 μM, respectively, while hydroxycurcuphenol was inactive.[172] *R*-(−)-Curcuphenol was reported from the Caribbean gorgonian *Pseudopterogorgia rigida* as an antimicrobial substance, but its enzyme-inhibiting activity was not tested.[173] Hexaprenylhydroquinone sulfate (**263**), obtained from a sponge of the genus *Dysidea*, inhibited H,K-ATPase with an IC_{50} of 4.6 μM.[174] Since compound **263** showed promising activity, we synthesized a number of analogues and evaluated them for inhibition of acid secretion and antiulcer activity, but no antiulcer activity in rats was observed at 300 mg/kg.[3] Sinulamide (**264**), derived from a soft coral *Sinularia* sp., inhibited the enzyme activity with an IC_{50} value of 5.5 μM.[3] The structure of **257** was recently refined using a synthetic approach.[175]

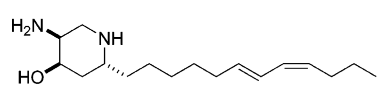
Phosphodiesterase Inhibitors 1



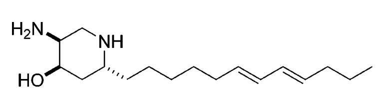
eudistomidin A (**181**)



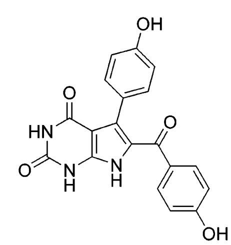
eudistomidin C (**182**)



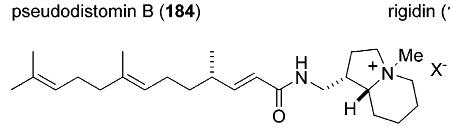
pseudodistomin A (**183**)



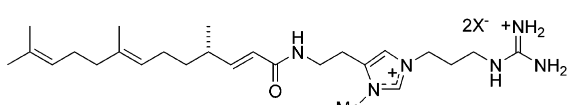
pseudodistomin B (**184**)



rigidin (**185**)

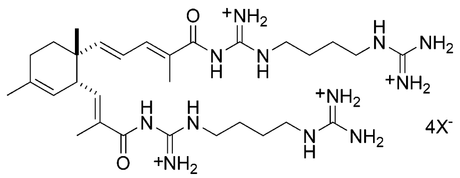


stellettamide A (**186**)

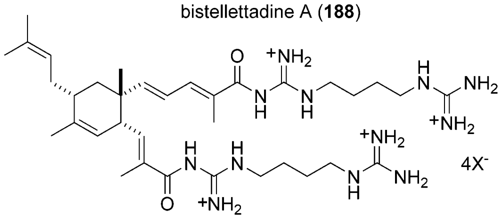


stellettazole A (**187**)

Phosphodiesterase Inhibitors 2



bistellettadine A (**188**)



bistellettadine B (**189**)

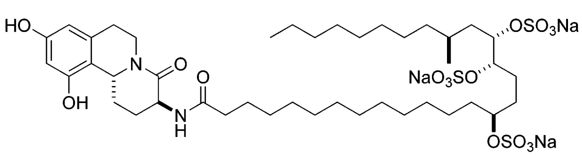
Na,K-ATPase. Na,K-ATPase regulates Na^+ transport through cell membranes and is directly related to contraction and relaxation of smooth muscles, thus indicating that inhibitors of this enzyme are potential drug leads for cardiovascular diseases. Agelasines A−F (**265**−**270**), 9-methyladenine derivatives of diterpenes that were purified from the Okinawan sponge *Agelas nakamurai*, were reported to inhibit Na,K-ATPase, although details of their activity are not available.[176] Two hypotaurocyamine derivatives of diterpene, agelasidines B (**271**) and C (**272**), from the same sponge, inhibited not only Na,K-ATPase, with IC_{50} values of 10−50 μM, but also the contraction of smooth muscle.[177]

Iantheran A (**273**), its diacetate, and α-hydroxy enone derivative, isolated from an Australian sponge *Ianthella* sp., showed moderate inhibitory activity against Na,K-ATPase, with IC_{50} values of 2.5, 5.0, and 10 μM, respectively.[178] This sponge also yielded ianthesins A−D (**274**−**277**), of which ianthesins B and C inhibited dog kidney Na,K-ATPase with IC_{50} values of 440, 50, and 280 μM, respectively.[179]

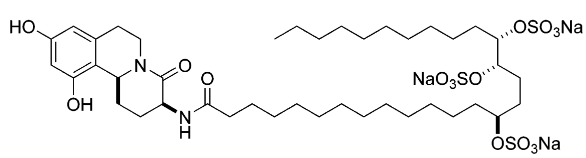
Xestoquinone (**56**), a polycyclic quinone, which was isolated together with the known antimicrobial substance halenaquinone (**53**)[180] from the Okinawan sponge *Xestospongia sapra*, was found to inhibit Na,K-ATPase. Xestoquinone is the first example of a marine natural product showing parallelism between an inotropic action and Na,K-ATPase inhibition. Halenaquinol (**54**),[181] a cardioactive pentacyclic hydroquinone from the sponge *Petrosia seriata*, was found to be a powerful inhibitor of rat brain stem and cortex Na,K-ATPases and rabbit muscle sarcoplasmic reticulum Ca^{2+}-ATPase, with IC_{50} values of 0.70, 1.3, and 2.5 μM, respectively.[182] Sarcochromenol sulfate A (**278**) and sarcohydroquinone sulfates A−C (**281**−**283**), isolated from the New Zealand sponge *Sarcotragus spinulosus*, inhibited rat brain Na,K-ATPase with IC_{50} values of 1.6, 1.6, 1.4, and 1.3 μM, respectively, while sarcochromenol sulfates B (**279**) and C (**280**) were inactive.[183]

Vacuolar ATPases. Vacuolar H^+-ATPases, a class of proton pumps present in all eukaryotic cells, are responsible for proton transport in bone-derived membrane vesicles, and the process of osteoclast-mediated bone resorption is directly dependent on H^+-translocating ATPases. Inhibition of osteoclast vascular H^+-ATPase may be effective for reducing the rate of bone resorption in pathological conditions such as osteoporosis. Adociasulfate 1 (**284**), a sesterterpenoid isolated from an Australian sponge of the genus *Adocia*, reduced proton pump activity in hen bone-derived membrane vesicles with an IC_{50} value of 3.6 μM and proton pumping in brain-derived vesicles with an IC_{50} value of 4.7 μM, while adociasulfates 7 (**285**) and 8 (**286**) were less active (IC_{50} 30 μM and 55% inhibition at 100 μM, respectively).[184] Recently, the antitumor polyketides salicylihalamides A (**287**) and B (**288**), isolated from a sponge *Haliclona* sp.,[185] and lobotamides

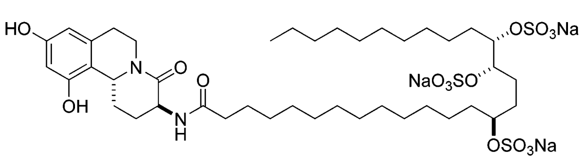
Sialidase Inhibitors



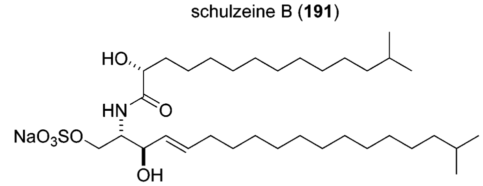
schulzeine A (**190**)



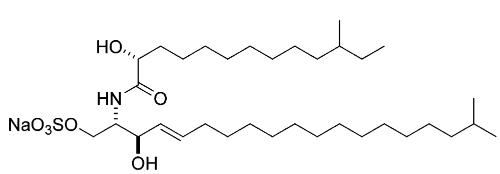
schulzeine B (**191**)



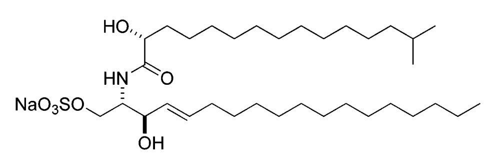
schulzeine C (**192**)



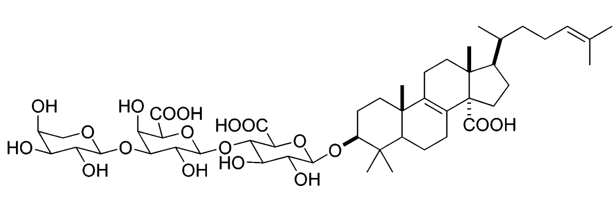
calyceramide A (**193**)



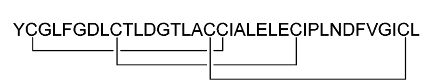
calyceramide B (**194**)



calyceramide C (**195**)

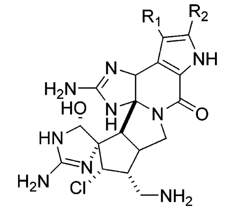


nobiloside (**196**)



asteropine A (**197**)

Chitinase Inhibitors



	R_1	R_2
styloguanidine (**198**)	H	H
3-bromostyloguanidine (**199**)	Br	H
2,3-dibromostyloguanidine (**200**)	Br	Br

A−F (**289**−**294**), from the tunicate *Aplidium lobatum*,[186] all of which share the same core structure with YM-75518 (**295**), an antifungal metabolite of *Pseudomonas* sp. Q38009,[187] were found to be potent and selective inhibitors of mammalian V-ATPases (IC_{50} 0.40−14.0 nM).[188]

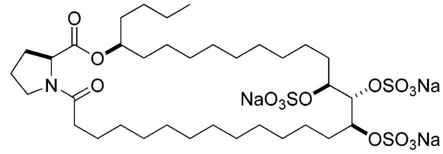
Lyases (EC 4)

ATP Citrate Lyase (EC 4.1.3.8). Since the very-low-density lipoproteins (VLDL) are metabolic precursors of the low-density lipoproteins (LDL) that play a key role in hyperchoresterolemia, intervention in VLDL synthesis has provided a strategic target for hypercholesterolemia therapy. Inhibitors of ATP-citrate lyase (ACL) are anticipated to reduce the production of acetyl CoA and can affect both lipogenesis and cholesterogenesis and, as a result, may be expected to reduce VLDL synthesis. Purpurone (**296**), a polycatecholic pyrrole isolated from a sponge of the genus *Iotrochota*, inhibited ATP-citrate lyase in a dose-dependent manner with an IC_{50} value of 7 μM.[189]

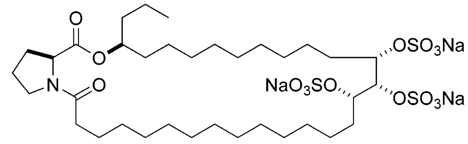
Isomerases (EC 5)

Topoisomerase. DNA topoisomerases are nuclear enzymes that catalyze DNA strand breaking and unwinding during cellular

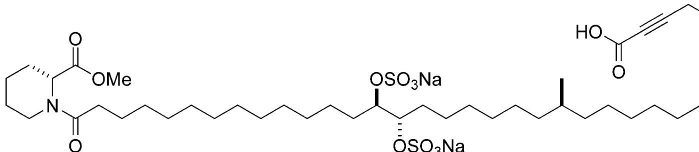
α-Glucosidase Inhibitors



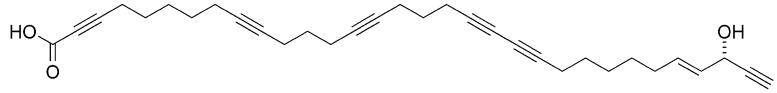
penarolide sulfate A_1 (**201**)



penarolide sulfate A_2 (**202**)

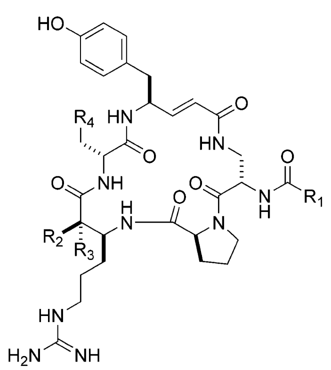


penasulfate A (**203**)

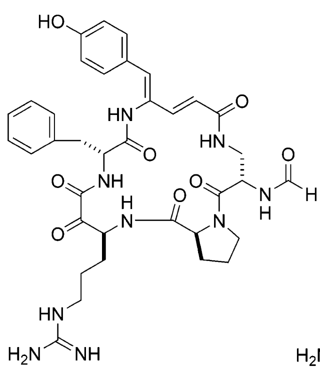


callyspongynic acid (**204**)

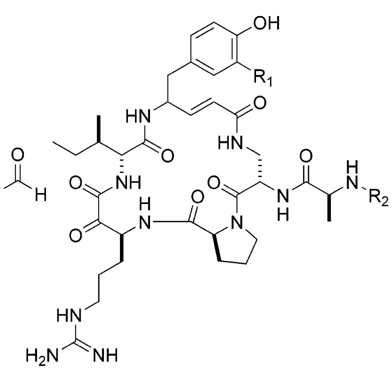
Serine Protease inhibitors 1



	R_1	R_2	R_3	R_4
cyclotheonamide A (**205**)	H	O	O	Ph
cyclotheonamide B (**206**)	Me	O	O	Ph
cyclotheonamide D (**208**)	H	O	O	i-propyl
dihydrocyclotheonamide A (**209**)	H	OH	H	Pf

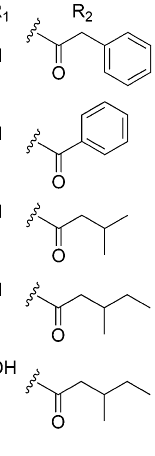


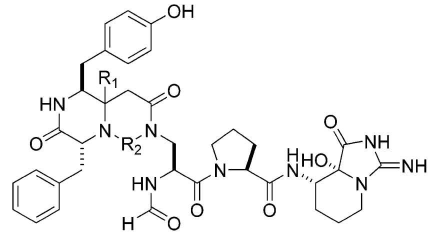
cyclotheonamide C (**207**)



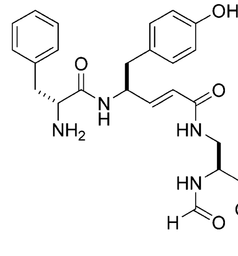
cyclotheonamide E's

	R_1	R_2
E1 (**210**)	H	
E2 (**211**)	H	
E3 (**212**)	H	
E4 (**213**)	H	
E5 (**214**)	OH	



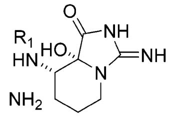


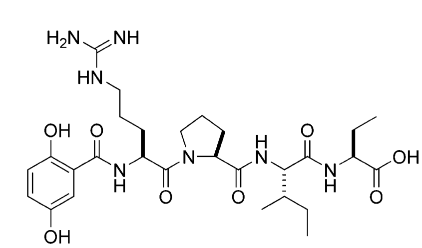
	R_1	R_2
pseudotheonamide A_1 (**215**)	βH	H, H
pseudotheonamide A_2 (**216**)	αH	H, H
pseudotheonamide B_2 (**217**)	αH	CH_2



pseudotheonamide C (**218**)

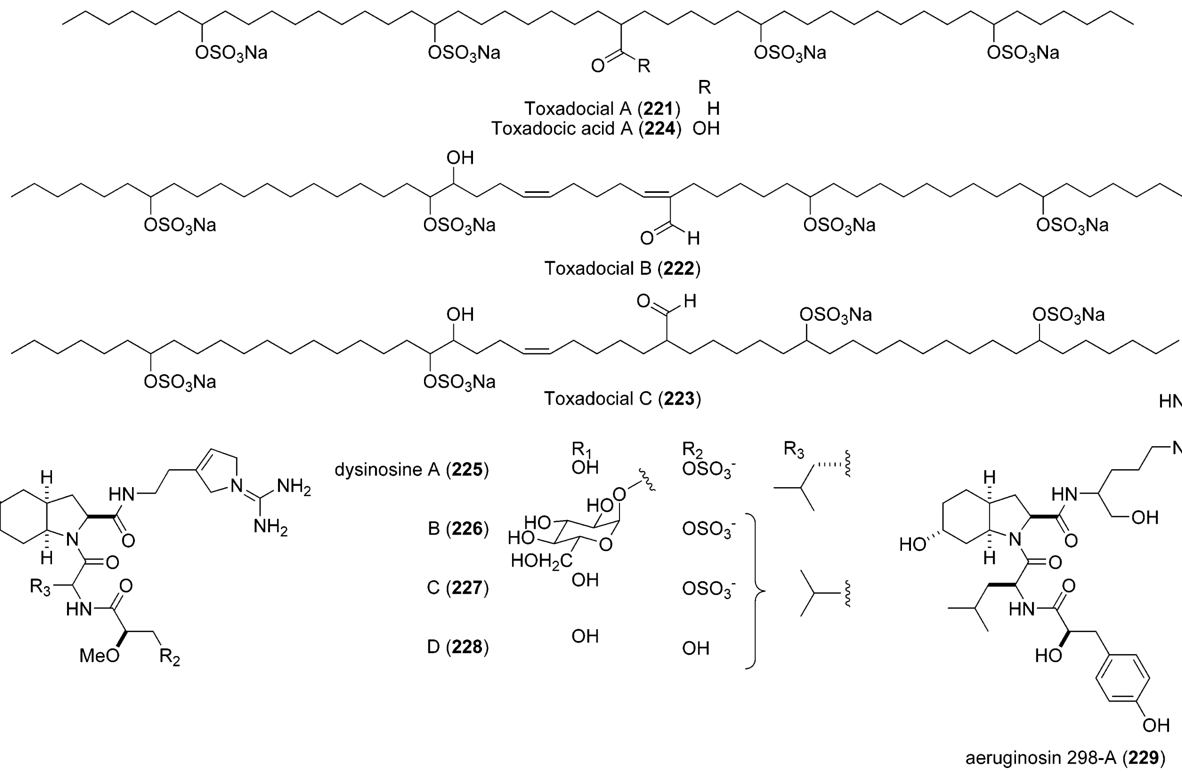
pseudotheonamide D (**219**) NH_2





nazumamide A (**220**)

Serine Protease Inhibitors 2

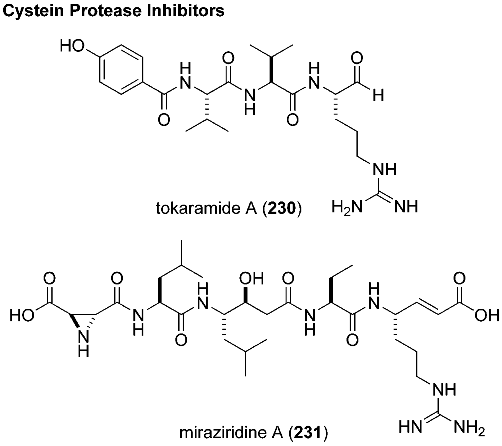


replication and RNA transcription. In eukaryotic cells, DNA topoisomerases I (topo I) and II (topo II) play distinct roles in DNA unwinding. Topo I catalyzes single-strand "nicking" to allow supercoiled DNA to unwind, whereas topo II facilitates chromosomal duplication by relaxing and unwinding the DNA duplex. Thus, new inhibitors of topo I and topo II are potentially important for cancer chemotherapy.

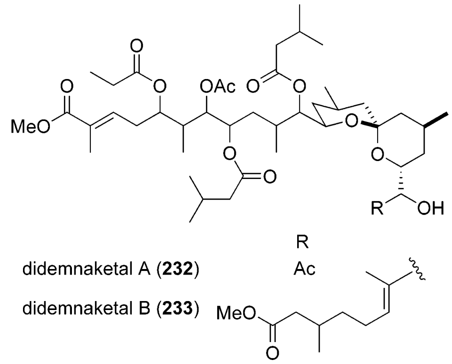
Topoisomerase I (EC 5.99.1.2). Xestoquinol sulfate (**297**) and xestosaprols A (**298**) and B (**299**), as well as a known compound **300** and halenaquinol sulfate (**55**), were isolated as topo I inhibitors from the Okinawan sponge *Xestospongia sapra*. Compounds **297**−**299** inhibited DNA topo I with MICs of 10, 12.5, and 12.5 μg/mL, respectively, while **300**, xestoquinone (**56**), and halenaquinone (**53**) were more potent, with MICs of 2.5, 2, and 0.4 μg/mL, respectively.[190] Interestingly, halenaquinol sulfate (**55**) was not active in this assay. Makaluvamine G (**301**), a cytotoxic pigment isolated from an Indonesian sponge *Histodermella* sp., inhibited topo I with an IC_{50} value of 3.0 μM.[191] Two ceramide 1-sulfates, **302** and **303**, from the Japanese bryozoan *Watersipora cucullata* inhibited human topo I with IC_{50} values of 0.4 and 0.2 μM, respectively.[192] Similarly, amphimic acid A (**304**), and related long-chain fatty acids from an Australian sponge of the genus *Amphimedon*, showed topo I inhibition with IC_{50} values ranging from 0.47 to 6.7 μM.[193]

Topoisomerase II (EC 5.99.1.3). Wakayin (**305**), a cytotoxic pyrroloiminoquinone alkaloid isolated from an ascidian *Clavelina* sp., inhibited topo II at 250 μM.[194] Another group of pyrroloiminoquinones, makaluvamines A−F (**306**−**311**), which were isolated from Fijian sponges of the genus *Zyzzya*, showed topo II inhibition with IC_{90} values of 41, >500, 420, 320, 310, and 25 μM, respectively, while the structurally related makaluvone and damirone B were not active. The makaluvamines showed differential toxicity toward the topo II-sensitive CHO cell line xrs-6. Makaluvamines A (**306**) and C (**308**) exhibited in vivo antitumor activity against the human ovarian carcinoma Ovcar3 implanted in athymic mice.[195] Similarly, makaluvamine N (**312**), isolated from the Philippine sponge *Zyzzya fuliginosa*,

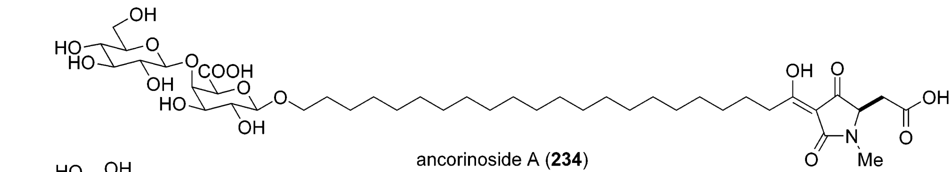
Cystein Protease Inhibitors



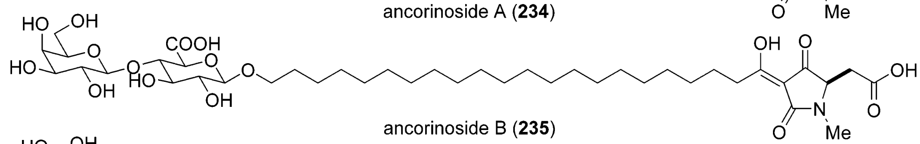
HIV Protease Inhibitors



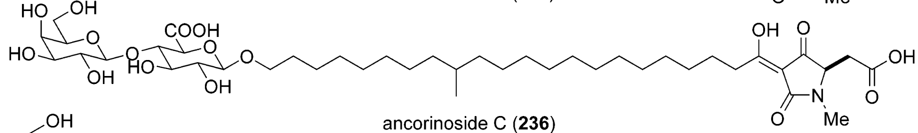
MMP Inhibitors



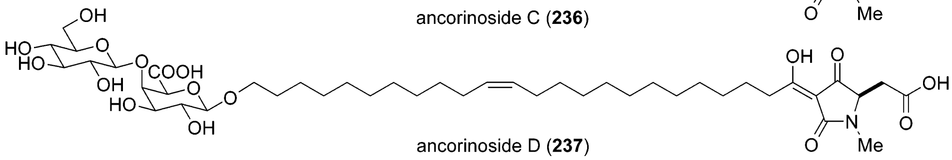
ancorinoside A (**234**)



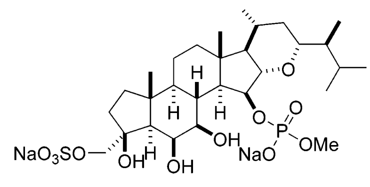
ancorinoside B (**235**)



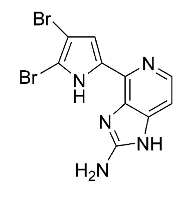
ancorinoside C (**236**)



ancorinoside D (**237**)



238



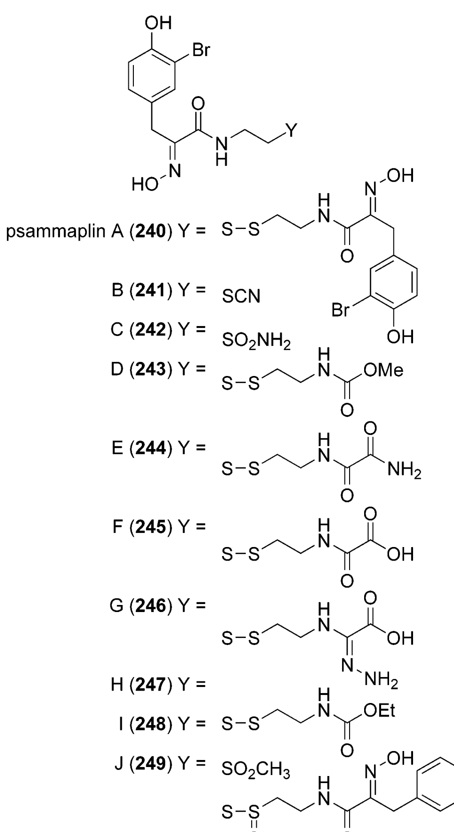
ageladine A (**239**)

exhibited greater than 90% inhibition of topo II at 5 μg/mL.[196] The other makaluvamines, G and H, did not show inhibitory activity against topo II,[197] whereas only makaluvamine G showed moderate inhibition against topo I.[190] Bengacarboline (**313**), a β-carboline alkaloid isolated from an ascidian *Didemnum* sp., inhibited topo II at 32 μM.[198]

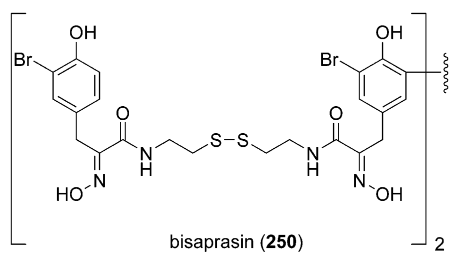
Two aromatic alkaloids, shermilamine B (**314**)[199] and ascididemin (**315**),[200] isolated originally from tunicates of the genera *Trididemnum* and *Didemnum*, respectively, were reported to inhibit topo II at 30 and 75 μM, respectively.[201] Similarly, dehydrokuanoiamine B (**316**), shermilamine C (**317**), cystodytin (**318**), kuanoniamine D (**319**), and diplamine (**320**), from an ascidian of the genus *Diplosoma*, inhibited topo II with IC_{90} values of 115, 138, 8.4, 127, and 9.2 μM, respectively.[202]

Popolohuanone E (**321**), an oxidatively dimerized arenarol derivative isolated from a Pohnpei sponge of the genus *Dysidea*, was reported to be inhibitory against topo II with an IC_{50} value of 400 nM and selectively cytotoxic against the A549 non-small-cell human lung cancer cell line (IC_{50} 2.5 μg/mL).[203] Puupehenone (**322**) and 21-chloropuupehenone (**323**), sesquiterpene hydroquinones isolated from a Verongid sponge, were tested for a wide variety of biological activities including inhibitory activity against topo II, adenosine deaminase (ADA), glutathione reductase (GR), dihydrofolate reductase (DHFR), and thymidylate synthetase

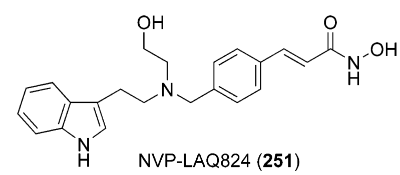
HDAC Inhibitors



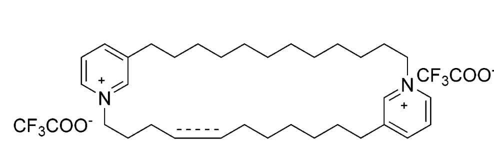
psammaplin A (**240**) Y =
B (**241**) Y = SCN
C (**242**) Y = SO_2NH_2
D (**243**) Y =
E (**244**) Y =
F (**245**) Y =
G (**246**) Y =
H (**247**) Y =
I (**248**) Y =
J (**249**) Y = SO_2CH_3



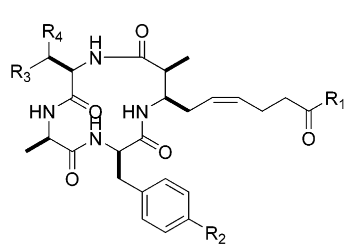
bisaprasin (**250**)



NVP-LAQ824 (**251**)

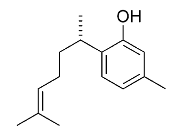


cyclostellettamine A (**252**): m = 1, n = 2
G (**253**): m = 1, n = 1
dehydrocyclostellettamine D (**254**): m = 1, n = 4, Δ^{13}
E (**255**): m = 2, n = 4, Δ^{13}

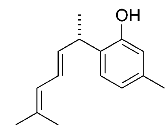


	R_1	R_2	$R_3 = R_4$
azumamide A (**256**)	NH_2	H	Me
B (**257**)	NH_2	OH	Me
C (**258**)	OH	OH	Me
D (**259**)	NH_2	H	H
E (**260**)	OH	H	Me

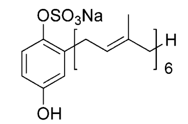
H,K-ATPase Inhibitors



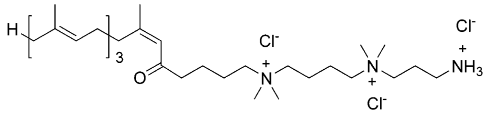
S-(+)-curcuphenol (**261**)



dehydrocurcuphenol (**262**)

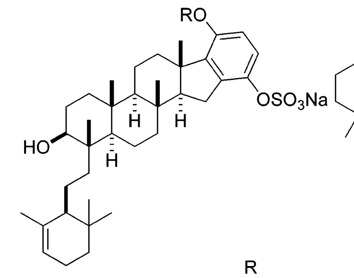


hexaprenylhydroquinone sulafte (**263**)

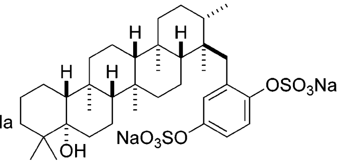


sinulamide (**264**)

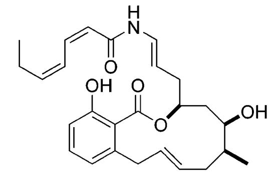
Vacuolar H$^+$-ATPase Inhibitors



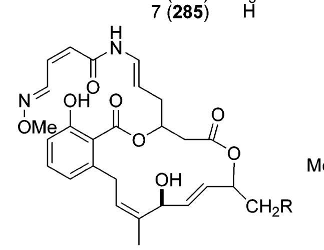
adociasulfate 1 (**284**) R = SO_3Na
7 (**285**) R = H



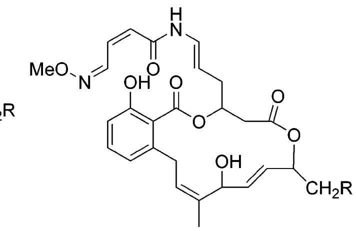
adociasulfate 8 (**286**)



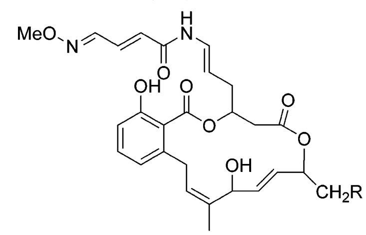
salicylihalamide A (**287**) Δ^{17} *trans*
salicylihalamide B (**288**) Δ^{17} *cis*



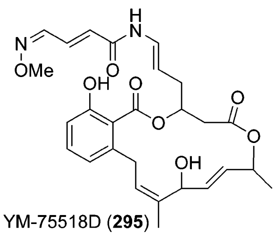
lobotamide A (**289**) R = H
(= YM-75518A)
lobotamide D (**292**) R = OH



lobotamide B (**291**) R = H
(= YM-75518B)
lobotamide E (**293**) R = OH



lobotamide C (**291**) R = H
(= YM-75518C)
lobotamide F (**294**) R = OH

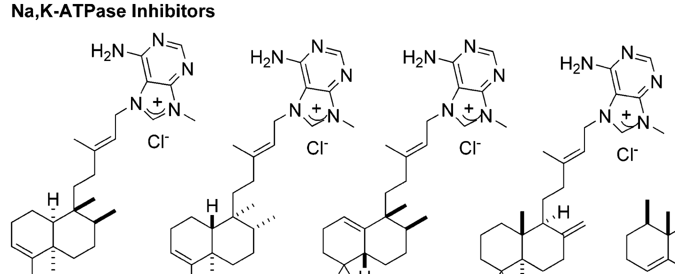


YM-75518D (**295**)

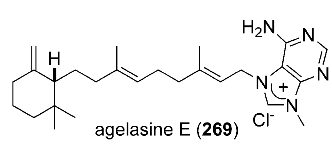
(TS) and revealed that **323** inhibited topo II with an IC_{50} value of 1 μg/mL. In addition, compounds **322** and **323** inhibited ADA with IC_{50} values of >25 μg/mL. In turn, GR was inhibited with an IC_{50} of 6 μg/mL by **323**; DHFR, by **322** and **323** with IC_{50} values of 5 μg/mL; and TS, with IC_{50} values of 8 and 3 μg/mL, respectively.[204]

Elenic acid (**324**), an unusual metabolite of an Indonesian sponge *Plakinastrella* sp., inhibited topo II with an IC_{50} of 0.1 μg/mL,[205] while 3-tetraprenyl-4-hydroxybenzylic acid (**325**), isolated from the marine sponge *Ircinia muscarum*, had an IC_{50} value of 0.5 μg/mL.[206] Bastadin 14 (**326**), from the sponge *Psammaplysilla purpurea*, showed inhibitory activity against topo II and DHFR with IC_{50} values of 2.0 and 2.5 μg/mL, respectively.[207] Virenamide A (**327**), a cytotoxic linear peptide from the Australian ascidian *Diplosoma virens*, exhibited topo II inhibitory activity with an IC_{50} value of 2.5 μg/mL.[208]

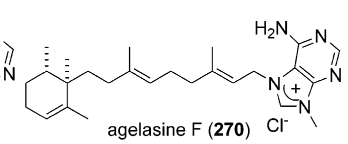
Na,K-ATPase Inhibitors



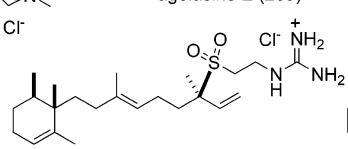
agelasine A (**265**) agelasine B (**266**) agelasine C (**267**) agelasine D (**268**)



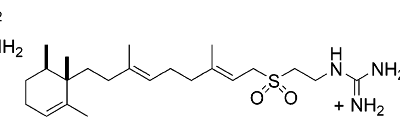
agelasine E (**269**)



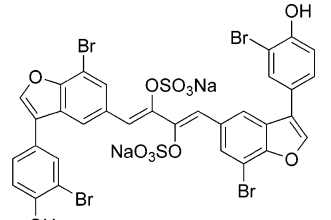
agelasine F (**270**)



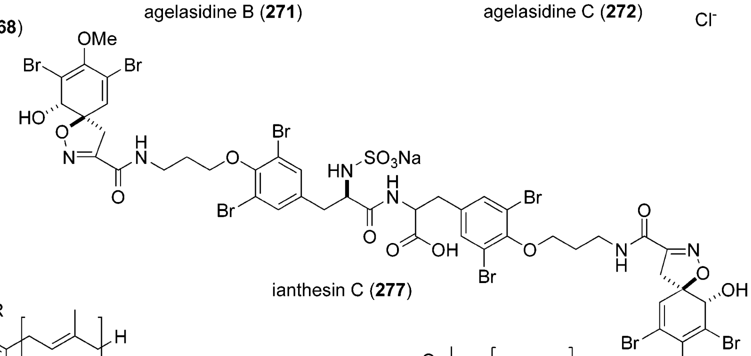
agelasidine B (**271**)



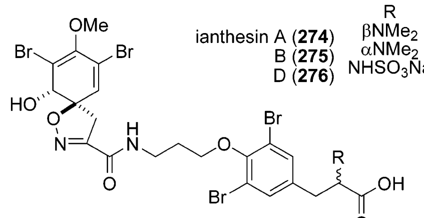
agelasidine C (**272**)



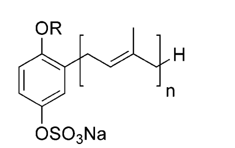
iantheran A (**273**)



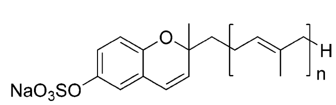
ianthesin C (**277**)



ianthesin A (**274**) R = βNMe$_2$
B (**275**) R = αNMe$_2$
D (**276**) R = NHSO$_3$Na

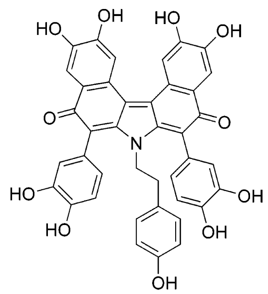


	R	n
sarcohydroquinone sulfate A (**281**)	H	6
sarcohydroquinone sulfate B (**282**)	SO_3Na	7
sarcohydroquinone sulfate C (**283**)	H	8



sarcochromenol sulfate A (**278**) n = 5
sarcochromenol sulfate B (**279**) n = 6
sarcochromenol sulfate C (**280**) n = 7

ATP-citrate Lyase Inhibitor

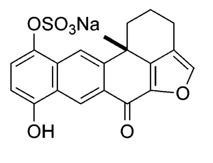


purpurone (**296**)

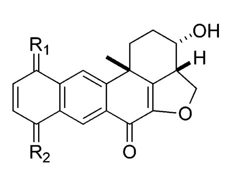
Conclusion

Over 300 metabolites isolated from marine invertebrates have been reported to inhibit an extensive array of enzymes. These compounds represent a wide variety of structural classes, ranging from simple terpenoids or polyketides to complex polyketides and oligopeptides. A significant number of structurally unique compounds, such as okadaic acid, calyculins, and cyclotheonamides, have been isolated as important enzyme inhibitors. It is quite likely that additional inhibitors with unprecedented structures and potent enzyme inhibitory activities will be discovered from marine invertebrates. It is hoped that other marine natural products chemists will embark on the search for enzyme inhibitors, which should result in the elucidation of inhibiting substances with drug potential.

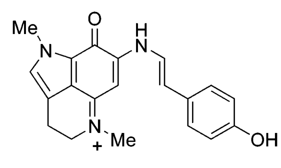
Topoisomerase I (topo I) Inhibitors



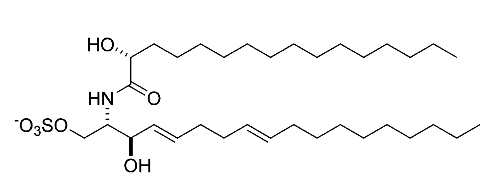
xestoquinol sulfate (**297**)



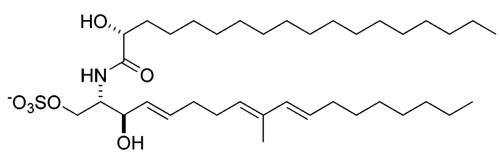
xestosaprol A (**298**) R_1 = H, OH; R_2 = O
xestosaprol B (**299**) R_1 = R_2 = H, OH
(**300**) R_1 = O; R_2 = H, OH



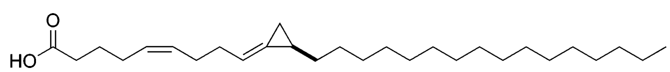
makaluvamine G (**301**)



302

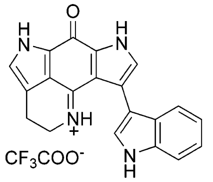


303

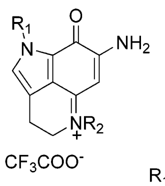


amphimic acid A (**304**)

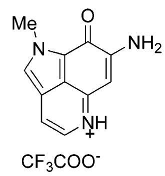
Topoisomerase II (topo II) Inhibitors



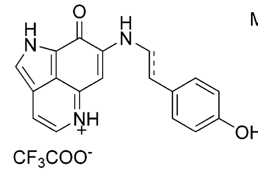
wakayin (**305**)



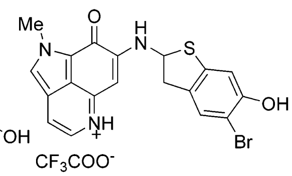
	R_1	R_2
makaluvamine A (**306**)	Me	H
makaluvamine C (**308**)	H	Me



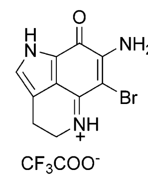
makaluvamine B (**307**)



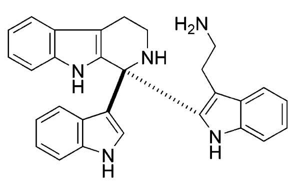
makaluvamine D (**309**)
makaluvamine E Δ (**310**)



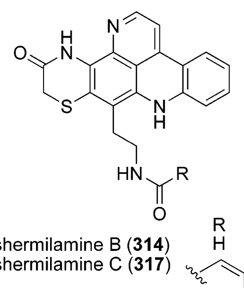
makaluvamine F (**311**)



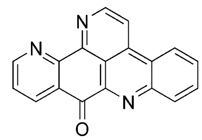
makaluvamine N (**312**)



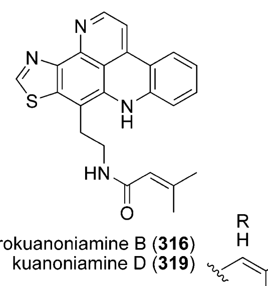
bengacarboline (**313**)



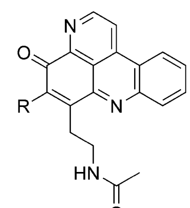
shermilamine B (**314**) R = H
shermilamine C (**317**)



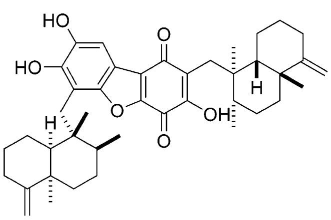
ascididemin (**315**)



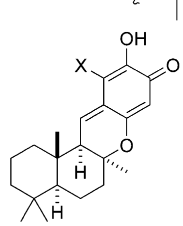
dehydrokuanoniamine B (**316**) R = H
kuanoniamine D (**319**)



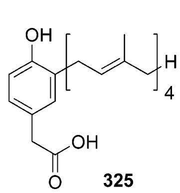
cystodytin J (**318**) R = H
diplamine (**320**) R = MeS



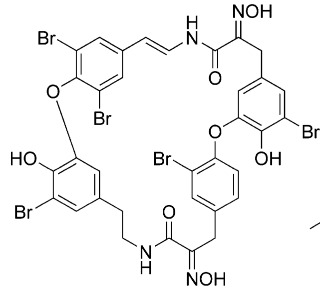
popolohuanone E (**321**)



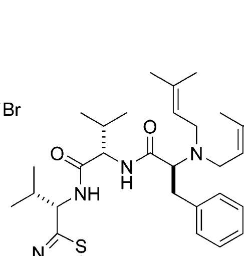
puupehenone (**322**): X = H
21-chloro-puupehenone (**323**): X = Cl



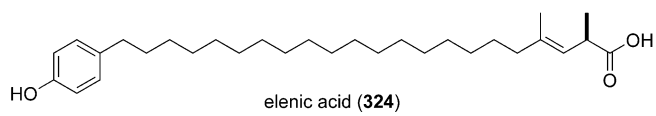
325



bastadin 14 (**326**)



virenamide A (**327**)



elenic acid (**324**)

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