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# Recent Progress in Neuroactive Marine Natural Products

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## 1 Introduction

Marine natural products are a rich source of potent, selective, and structurally novel compounds that alter mammalian neurological activity. Classical examples that include tetrodotoxins,[1] saxitoxins,[2–4] kainic and domoic acids,[5] cone snail venom peptides,[6] and sea anemone toxins[7–9] have received considerable attention from both chemical and neurobiological communities not just for their intriguing chemical structures and biological activities but also because of their potential as therapeutic agents.[2, 6, 8, 10–12] Many of these compounds now represent indispensable tools in physiological and related biological sciences. Despite the central importance of potent and selective neuroactive natural products, discovery-oriented research programs historically have been limited; most early research on neuroactive marine natural products was either opportunistic, based on fortuitous discovery of biological activities of interest, or was conducted in the context of food safety and public hygiene issues.[13–15] The past 15 years, however, has seen the emergence of new efforts geared towards discovery of new neuroactive molecules or re-evaluation of well-characterized molecules for neuronal activity. Excellent review articles or special issue collections have been published recently that discuss a number of these compounds (see sections below for references). In the present review, we will highlight new developments in the isolation and characterization of neuroactive marine natural products; these molecules illuminate the great chemical diversity to be found in marine organisms and accordingly could have significant potential as scaffolds for development of new therapeutics or research tools. Articles published between 1995 and the present were surveyed with a goal of collating information on defined compounds acting on neurologically relevant target receptors. We omit reference to reports in which either the active principle(s) or pharmacological target was unidentified; in most cases, we also focus less on those compounds (or group of related compounds) that have been exhaustively described in recent reviews.

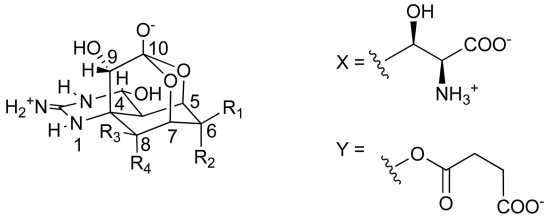
## 2 Molecules that target voltage gated ion channels

Voltage-gated ion channels are the molecular targets for a variety of marine toxins because of the essential nature of these proteins to many central neurological and motor functions. Conotoxin peptides of the δ, κ, μ, and ω families and sea anemone toxins act on these channels and have been the subject of extensive, ongoing research and recent comprehensive reviews.[6, 7] A synthetic form of the N-type voltage-gated calcium channel blocker ω-conotoxin MVIIA (ziconotide) recently was approved by the U.S. Federal Drug Administration for treatment of chronic pain and marketed with the trade name Prialt®, underscoring the potential of neuroactive marine natural products for therapeutic development. We focus here on some equally familiar neurotoxins that have yielded some surprising new insights, including the prototypical sodium channel blocker, tetrodotoxin, as well as less well-documented molecules that interact with voltage-gated ion channels -

particularly those with channel subtype selectivity and divergent mechanisms of channel modulation. Representative voltage-gated ion channel targets of marine-derived compounds are summarized in Scheme 1.

### 2.1 Guanidine neurotoxins

Tetrodotoxin (TTX, **1**) and its analogues, as well as the paralytic shellfish toxins (PST) that include saxitoxins (STX) and gonyautoxins (GTX), are collectively referred to as guanidine neurotoxins because both classes contain a guanidine substructure. TTX (**1**) is a prototypical small neurotoxin that has had an impact on our understanding of the biophysical basis of neurophysiological function that is difficult to overstate. Nonetheless, novel aspects of its chemistry and potential therapeutic use continue to be revealed. While primary source organisms, pufferfish and other members of the *Tetraodontidae* family, have been known to be toxic since antiquity, the first concerted research on the chemistry of TTX dates back to the late 1800's by Dr. Yoshizumi Tahara. Tahara improved the process of isolation and in 1910 named the purified molecule tetrodotoxin.[16] Not surprisingly, given the rich history associated with the investigation into TTX structure and pharmacological activities, there are an abundance of review articles focused on historical and more recent features of the molecule,[1, 17–22] its natural occurrence and biosynthesis,[3, 23, 24] potential ecological roles,[25–27] food safety,[28] analysis,[29, 30] chemical synthesis,[23, 31] pharmacology regarding interaction with voltage gated sodium channels (VGSC),[1, 3, 11, 32–36] and its possible use clinically.[11] The guanidine toxins nonetheless continue to intrigue, yielding surprises and enticing potential for therapeutic application.

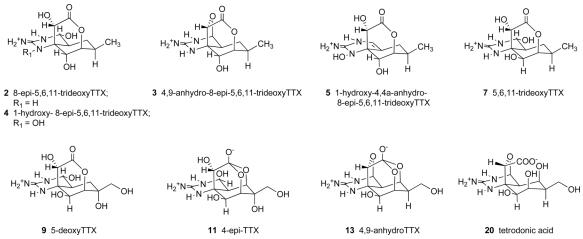



**1** tetrodotoxin (TTX); $R_1 = CH_2OH$, $R_2 = OH$, $R_3 = OH$, $R_4 = H$
**6** 6-epiTTX; $R_1 = OH$, $R_2 = CH_2OH$, $R_3 = OH$, $R_4 = H$
**8** 6,11-dideoxyTTX; $R_1 = CH_3$, $R_2 = H$, $R_3 = OH$, $R_4 = H$
**10** 11-deoxyTTX; $R_1 = CH_3$, $R_2 = OH$, $R_3 = OH$, $R_4 = H$
**12** chiriquitoxin; $R_1 = X$, $R_2 = OH$, $R_3 = OH$, $R_4 = H$
**14** 11-oxoTTX; $R_1 = CHO$, $R_2 = OH$, $R_3 = OH$, $R_4 = H$
**15** TTX-11-carboxylic acid; $R_1 = COOH$, $R_2 = OH$, $R_3 = OH$, $R_4 = H$
**16** 11-norTTX-6,6-diol; $R_1 = OH$, $R_2 = OH$, $R_3 = OH$, $R_4 = H$
**17** 11-norTTX-6-(*S*)-ol; $R_1 = OH$, $R_2 = H$, $R_3 = OH$, $R_4 = H$
**18** 11-norTTX-6-(*R*)-ol; $R_1 = H$, $R_2 = OH$, $R_3 = OH$, $R_4 = H$
**19** TTX-8-*O*-hemisccucinate; $R_1 = CH_2OH$, $R_2 = OH$, $R_3 = Y$, $R_4 = H$

The biosynthetic pathways that lead to TTX are amongst the most enduring mysteries associated with this toxin. TTXs are found from various marine organisms ranging from its most well-known source, *Fugu* (pufferfish), to bacteria, to numerous species of two terrestrial amphibians, the frog and newt.[26] Its wide distribution in marine species and the detection of TTX in marine bacterial cultures supports the conjecture that, in marine organisms, the toxin originates as a bacterial product that accumulates in higher animals via a food chain or symbiosis. It is less clear that analogous mechanisms account for TTX in amphibians, because TTX-producing bacteria have neither been found from microbes associated with newts or frogs nor resident in their habitats. Moreover, the gene(s) responsible for biosynthesis of TTX have not been identified despite the availability of toxin-producing, culturable microbes[23] and descriptions of plausible but thus-far speculative biogenic pathways.[37, 38]

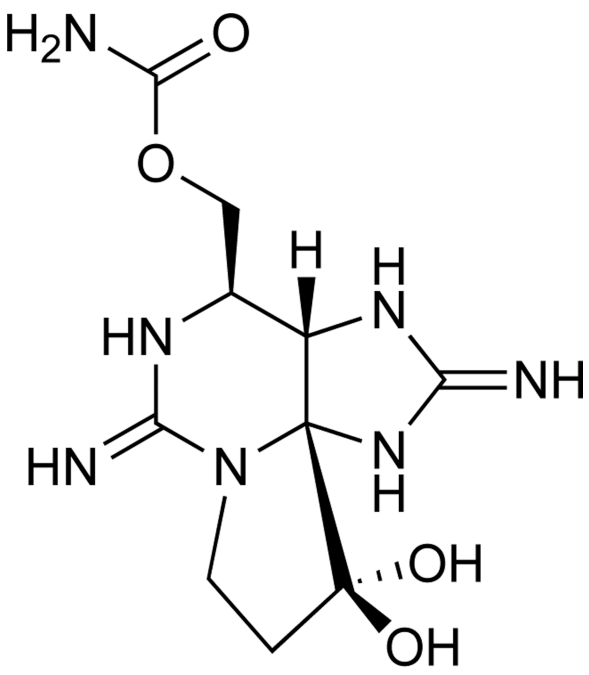
One means of making progress towards the goal of understanding the biosynthesis of TTX is identification of structural congeners of the toxin. Twenty such TTX analogues have been found as natural products, including recently reported four new 8-epi type analogs, 8-*epi*-5,6,11-trideoxyTTX (**2**), 4,9-anhydro-8-*epi*-5,6,11-trideoxyTTX (**3**), 1-hydroxy-8-*epi*-5,6,11-trideoxyTTX (**4**), and 1-hydroxy-4,4a-anhydro-8-*epi*-5,6,11-trideoxyTTX (**5**), all of which were derived from the newt *Cynops ensicauda popei*.[39] HPLC-MS analysis reveals that newts and pufferfish extracts have distinct distribution patterns of TTX congeners: i.e., 6-*epi*-TTX (**6**) and all 8-*epi*-deoxyTTX analogues (**2–5**) are newt-specific, whereas a series of deoxy derivatives, 5,6,11-trideoxyTTX (**7**), 6,11-dideoxyTTX (**8**), and 5-deoxyTTX (**9**) are largely present only in pufferfish (11-deoxyTTX (**10**) is present both in fish and newt). A trideoxy derivative (**7**) was hypothesized to be a bacterial precursor of TTX that undergoes sequential oxidizations to form **1**.[40] The discrete distribution of these TTX analogues suggest that the toxin is the product of distinct metabolic pathways in pufferfish and newts, but additional investigation will be required to support this hypothesis.

TTX is a potent VGSC blocker with discrete sensitivity for $Na_V1.5$, 1.8. and 1.9 (TTX-insensitive) over other subtypes ($Na_V1.1$–1.4, 1.6–1.7: TTX-sensitive)[32] that continues to be used extensively in neuroscience research even as novel structural analogs are explored for discrete channel selectivity profiles and neuroactivity. A structure-activity relationship of TTX and analogs with modification of hydroxyls that included natural 4-epiTTX (**11**), 6-epiTTX (**6**), chiriquitoxin (**12**), 11-deoxy TTX (**10**), 4,9-anhydro TTX (**13**), 5,6,11-trideoxy TTX (**7**), semi-synthetic 11-oxoTTX (**14**), TTX-11-carboxylic acid (**15**), 11-norTTX-6,6-diol (**16**), 11-norTTX-6(*S*)-ol (**17**), 11-norTTX-6(*R*)-ol (**18**), TTX-8-*O*-hemisuccinate (**19**), and tetrodonic acid (**20**), was performed by measuring displacement of radio-labeled STX from rat brain synaptic preparations.[41] These results established the importance of hydroxyl groups around C6 and C11 within the TTX framework. The derivatives with hydroxyl groups at C6 and C11 (**13, 14** (hydrated form) and **16**) showed comparable binding affinity as TTX for neuronal VGSCs. The newt-specific 6-*epi*-TTX **(6)**, 11-deoxy TTX **(10)**, and 11-nor derivatives **17** and **18** were 10–20 times less potent than TTX. Not unexpectedly, a puffer fish derived 5,6,11-trideoxy TTX (**7**) lost affinity for the channel. The C11 hydroxyl has been postulated to be important in interacting with the negatively charged Asp-1717 of domain IV of rat VGSC; a mutation (Asp1717Asn) results in reduction of TTX affinity by 19-fold. A significant loss of affinity with 11-carboxylic acid (**15**) supports the model in which an electric repulsion occurs between two negatively charged groups in the ligand and channel. The hydroxyls at C9 and C10 have been thought to be the most important of the six hydroxyls in TTX molecule, as (**13**) and (**20**) are weaker blockers or inactive at VGSCs. A large loss of affinity in 4-epiTTX (**11**, 38-fold from TTX) suggested that the weak activity of **13** (100-fold less than TTX) might result from an equal contribution to binding affinity from the C-4 and C-9 hydroxyl modifications. In addition, (**13**) was later reported as selective for the $Na_V1.6$ subtype of VGSCs;[42] this analog was 160–230-fold less effective than TTX at inhibiting currents from $Na_V$ 1.2, 1.3, 1.4., and 1.7 isoforms but only two-fold higher for $Na_V1.6$. The structural basis of this isoform specificity is not clear, however, because the three dimensional structure of outer vestibule of VGSC remains poorly defined.



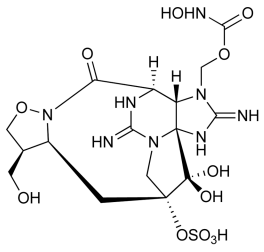
While pufferfish toxin was once used in Japan as an analgesic agent,[43] TTX is not used in this capacity in the modern clinic. A renewed interest in this potential therapeutic application has emerged recently.[11] Topical application of the toxin to rabbit cornea, for example, produces a long lasting anesthetic effect,[44, 45] and subcutaneous (s.c.) injection (0.3–6 μg/kg) suppressed a variety of pain behaviors in rodent models[46]. TTX reduced paclitaxel-induced neuropathic pain (1–6 μg/kg), in mice with mechanical and thermal stimuli, but even higher dose (3 and 6 μg/kg) TTX did not affect the same stimuli in control animals.[47] No serious adverse effects were observed in those studies. Recently, TTX was shown to be efficacious as an analgesic agent in a human clinical studies in which it was administered intramuscularly (7.5–30 μg per injection) two or three times a day to patients with severe cancer-related pain.[48, 49] In subsequent human trials[50] about 50% of cancer patients experienced amelioration of pain following TTX treatment[50]. Given that other, potentially lethal toxins such as botulinum toxin have found their place in the clinic, it remains possible that TTX or one of its analogs might yet be used therapeutically.

Other guanidine neurotoxins known as paralytic shellfish toxins (PSTs), as represented by saxitoxin (**21**), originate from both marine and fresh water organisms. PSTs are food contaminants in scallops, mussels and other various types of seafood. A long history of chemical and biological research into PSTs exists in large part because ingestion of contaminated food containing these toxins causes potentially lethal paralytic shellfish poisoning (PSP). Saxitoxin was identified as a causative agent of PSP in 1957, and to date 57 PSTs have been reported.[51] Comprehensive reviews[2, 3] as well as those focused on their natural occurrence, structures, biosyntheses, biological activities[17–21, 51–53] and food safety concerns[13] are readily available.

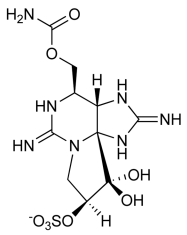


**21** saxitoxin (STX)

An unusual PST, zetekitoxin AB (**22**), was isolated recently from the Panamanian golden frog *Atelopus zeteki* and identified as an STX derivative.[54] Zetekitoxin AB (**22**) inhibited current from various VGSCs expressed in *Xenopus* oocytes at a significantly higher potency than STX (**21**). Like TTX derivatives, some degree of VGSC isoform specificity exists in the PST family of toxins. For example, STX and GTX-3 (**23**) exhibited markedly different potencies in blocking TTX-sensitive human $Na_V1.7$ compared to rat $Na_V1.4$ subtypes (whereas TTX itself did not show such selectivity). In this case, PST selectivity was predicted to arise from two amino acids of domain III in the outer pore region of the sodium channels that diverge between primates and non-primate orthologs.[55] This observation suggests the intriguing possibility of designing human $Na_V1.7$-selective blockers as potential therapeutic agents.

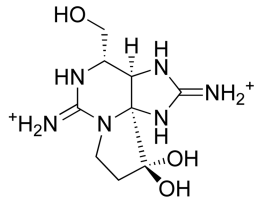


**22** zetekitoxin AB

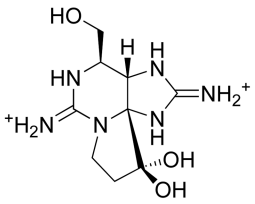


**23** gonyautoxin 3 (GTX 3)

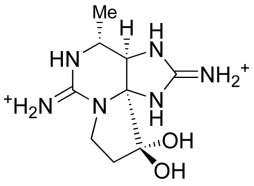
As with TTX, *de novo* and semi-syntheses of STX analogues have been pursued as tools to investigate VGSC structure-function. In addition to classical syntheses of STX,[56, 57] stereo-controlled syntheses of STX were reported recently by four different laboratories.[58–65] The Nagasawa group[61, 62, 64] synthesized (−)-decarbamoylSTX (**24**) (enantiomeric to the natural configuration), (+)-STX (natural configuration), (−) and (+)-decarbamyloxySTX (**25, 26**)[64], (+)-decarbamylSTX 27), and GTX-3 (**23**). They extended their strategy to synthesize STX derivatives that possess unnatural skeletal structures: (−)-FDdcSTX (**28**), (−)-FDSTX (**29**) and (−)-FDdoSTX (**30**).[66] Functional evaluation of these compounds found that inhibition of VGSCs by the active congeners **28** and **29** on rat $Na_V1.4$ and 1.5 was very weak (**28**: 18 and 182 μM for $Na_V1.4$ and 1.5, respectively; **29**: 3.8 and 118 μM); compound **28**, interestingly, exhibited an apparently irreversible inhibition of $Na_V1.5$. current.[66]



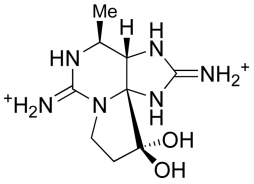
**24** (-)-decarbamoyl STX



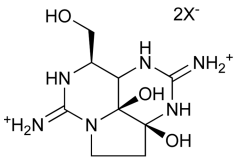
**27**(+)-decarbamoyl STX



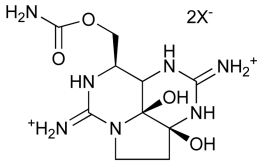
**25** (-)-decarbamoyloxy STX



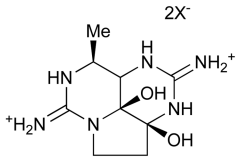
**26** (+)-decarbamoyloxy STX



**28** (-)-FD-dcSTX



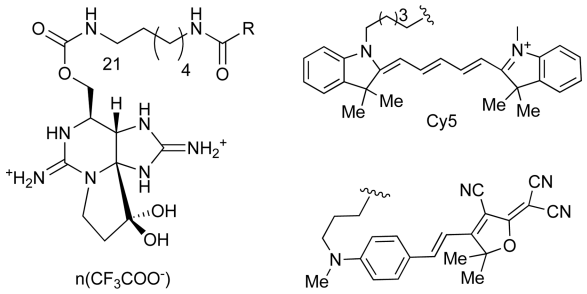
**29** (-)-FD-STX



**30** (-)-FD-doSTX

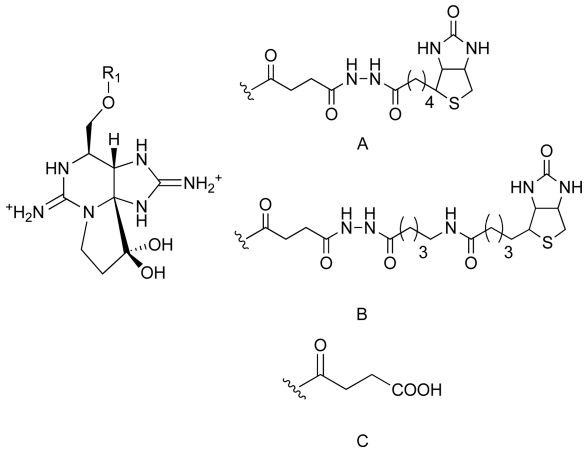
A clever and simplified total synthesis of STX was reported by the Du Bois group,[59, 60] which enabled preparation of STX analogues that were not easily accessible by other means including labeled STX for $Na_V$ structural studies.[67] Two fluorescently-labeled forms of STX, STX-Cy5 (**31**), and -DCDHF (**32**), were synthesized and retained high affinity for the

channel and reversible binding kinetics. Both of these compounds potently inhibited VGSCs.[67] Using these small molecular probes, single $Na_V$ channel proteins were tracked in live neurons at a resolution beyond the diffraction limit of light microscopy using super-resolution imaging techniques, revealing channel localization and dynamics at an unprecedented scale.[67]

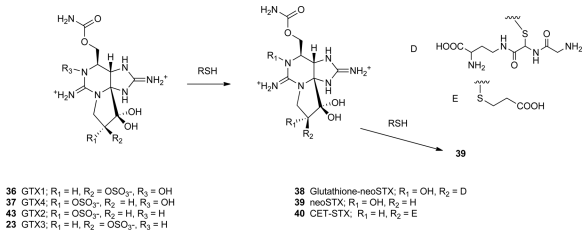



**31** STX-Cy5 : R=Cy5
**32** STX-DCDHF: R=DCDHF

Bifunctional, biotinylated forms of 4STX (**33**) and 11STX (**34**) were prepared from native STX. Those compounds exhibit comparable affinity as STX for binding to saxiphilin, an STX-binding protein,[68] and therefore also could be used to label neuronal VGSCs. A hemisuccinate, HS-dcSTX (**35**), was prepared with the aim of conjugating the STX core to a stationary substrate suitable for affinity chromatographic purification of STX-binding proteins. The sulfate group of GTX-1 (**36**) and -4 (**37**) was displaced by thiols such as glutathione to form an adduct (**38**), but further reduction by another thiol (mercaptoethanol) transformed **38** to neoSTX (**39**).[69] Utilizing this reaction, a C11 adduct, 3-mercaptopropanoate CET-STX (**40**) was also prepared for affinity chromatography.[70] Both **40** and **35** bound to VGSCs with reduced affinity (42- and 183-fold compared to STX, respectively), and saxiphilin from pufferfish plasma was purified successfully using **42** but not **41**. This study supports the utility of the C11 position as site for modification of the STX molecule for VGSC research.[70]

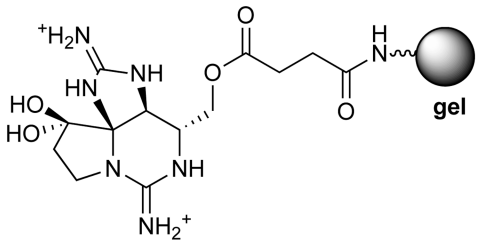



**33** Biotin-link4 STX; $R_1$ = A,
**34** Biotin-link11 STX; $R_1$ = B,
**35** HS-dcSTX; $R_1$ = C

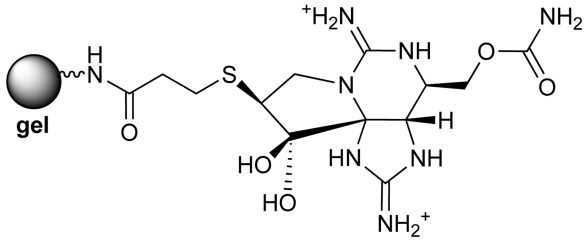



**36** GTX1; $R_1$ = H, $R_2$ = $OSO_3^-$, $R_3$ = OH
**37** GTX4; $R_1$ = $OSO_3^-$, $R_2$ = H, $R_3$ = OH
**43** GTX2; $R_1$ = $OSO_3^-$, $R_2$ = H, $R_3$ = H
**23** GTX3; $R_1$ = H, $R_2$ = $OSO_3^-$, $R_3$ = H

**38** Glutathione-neoSTX; $R_1$ = OH, $R_2$ = D
**39** neoSTX; $R_1$ = OH, $R_2$ = H
**40** CET-STX; $R_1$ = H, $R_2$ = E




**41**




**42**

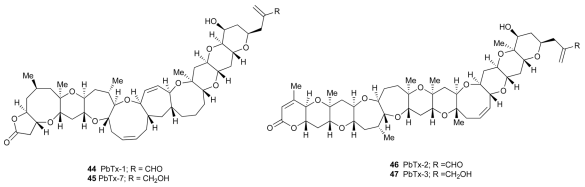
PSTs have been examined as local anesthetics.[71–73] For example, a small phase I clinical study with healthy volunteers demonstrated that subcutaneous injection of neoSTX (**39**) effectively blocked pain sensation without adverse effects.[71] Intrasphincter injections of a mixture of GTX-2 (**43**) and -3 (**23**) also were found to be very efficacious in healing anal fissures in patients.[51, 74, 75] Those pioneering applications of the toxins may lead to further development of TTXs and PSTs as safe and effective therapeutic agents.

## 2.2 Dinoflagellate polyethers

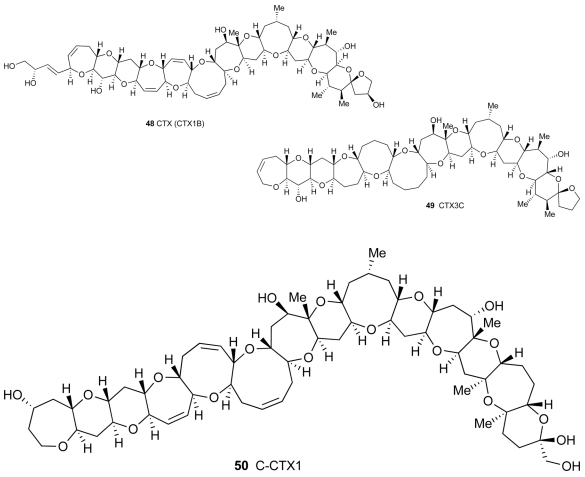
**2.2.1 Ladder-shaped polyethers—**The ladder-shaped polyether toxins originate from marine dinoflagellates, which are a diverse family of unicellular protists. LSPs are responsible for neurotoxic shellfish poisoning (NSP) and ciguatera fish poisonings (CFP) and for that reason have been the subject of a great deal of research into their occurrence and biological activity,[76, 77] public health impact,[78–80] and syntheses.[81, 82] Here we summarize aspects of their chemistry and interactions with ion channels relevant to neurological function.

Brevetoxins, one of the most widely studied LPSs, are produced by *Karenia brevis*, a dinoflagellate causative for NSP at high ingested doses and respiratory or other health problems after human exposure to red tide aerosol.[83] There are nine structures identified for naturally occurring brevetoxins, with two representative structural types: type 1 (brevetoxin A type) and type 2 (brevetoxin B type). The A-type compounds are PbTx-1 (**44**) PbTx-7

(**45**) and PbTx-10, and B-types are PbTx-2 (**46**), PbTx-3 (**47**) and PbTx-5~9. All brevetoxins bind to site 5 of VGSCs, between the pore forming domain III and voltage sensor VI, and have multiple effects on channel gating that together produce persistent activation at normal resting membrane potentials.[77, 84]



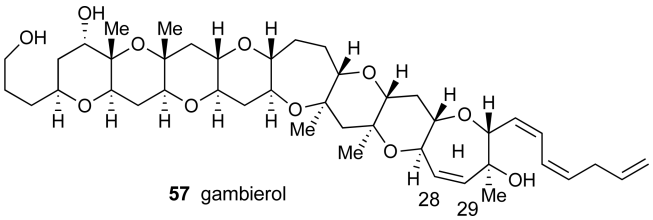

Ciguatoxins are a class of compounds comprised of the CFPs CTX1B (**48**), CTX3C (**49**), and a series of minor congeners isolated from viscera of Tahitian moray eel and dinoflagellate *Gambierdiscus toxicus*. Twenty-three structures fall into the CTX1B- and CTX3C-type on the basis of ring size arrangement.[85] These toxins are thought to cause the primarily neurological symptoms that are typically reported for CFP in the Pacific region and are therefore known as Pacific ciguatoxins.[86] Another group of ciguatoxins, as represented by C-CTX 1 (**50**), are responsible for CFP in the Caribbean Sea and produce predominantly gastro-intestinal symptoms.[86] Pacific CTXs share the same binding site, the α-subunit of VGSCs, and mechanism of action with brevetoxins, but CTXs bind to the channels with higher affinity.[87] Even though ladder-shaped polyethers exhibit various biological activities (*vide infra*), it has been postulated that common molecular target of this family of marine toxins is a transmembrane (TM) domain of ion channel or receptor subunits.[88–90]



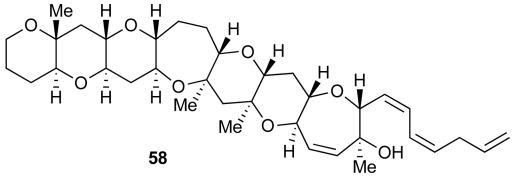

The importance of LSP length and hydrophobicity was explored systematically by measuring the affinity of synthetic toxins with tetra-, hepta- and deca-cyclic systems for either glycophorin A (GpA), a representative TM-containing protein, or a synthetic peptide corresponding to the isolated TM domain of GpA (GpA-TM).[91] The synthetic compounds with different in length and hydrophobicity (**51–56**, Scheme 2) showed various interactions with GpA or GpA-TM. ALP7B (**58**) had the highest affinity for GpA-TM among the tested molecules, whereas the shorter ALP4B (**52**) exhibited weaker affinity in surface plasmon resonance assays. (ALP10B was not tested because of poor solubility.) The artificial LSPs dissociated oligomeric GpA. The largest analog ALP10A (**55**) appeared to have a high affinity for the TM protein because it formed an insoluble complex with GpA but not the control protein. ALP7A (**53**), which lacks a hydrophobic benzyl group, and ALP10B (**60**) were inactive in the experiment. These results were explained by hydrophobic matching

between the LSP and membrane spanning protein; that is, high affinity is observed when the length of the hydrophobic region of the LSP matches well with the hydrophobic α-helical TM segments of integral channel proteins (Scheme 2). Further delineation of the molecular determinants of recognition between TM domains and LSPs will require focused libraries of toxins with various sizes and functional groups.[91]

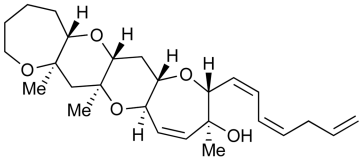
Gambierol (**57**) was isolated from *Gambierdiscus toxicus* as another causative compound of CFP and has potent lethal toxicity in mice. Recent synthetic efforts produced gambierol and analogues, facilitating the exploration of their neuronal activities.[92–98] In contrast to ciguatoxins,[99] gambierol inhibited currents from voltage-gated potassium channels ($K_V$s) (of mouse taste cells) rather than activating sodium channels.[100] Despite the lack of activity on native[100] or recombinant VGSCs,[101] gambierol was reported to act as a partial agonist action for VGSCs in human neuroblastoma cells[102] and as an antagonist in cerebellar neurons.[103] On the $K_V$3.1 potassium channel, gambierol exhibits state-dependent affinity in which the resting (or closed) channel is stabilized by the toxin such that the voltage dependence of activation is shifted out of the physiological range.[97] A structure-activity relationship with analogues of gambierol found a possible pharmacophore responsible for its mouse toxicity, the C28=C29 double bond in the H-ring and the triene of the side chain.[104] Guided by the SAR, truncated analogues of gambierol (**58** and **59**) were recently synthesized and had reduced toxicity but comparable potassium channel affinity as the parent toxin.[98]




**57** gambierol



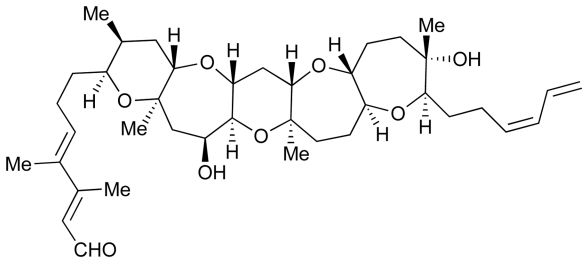

**58**




**59**

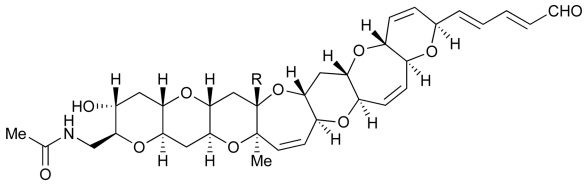
Gambierol analogues have been tested for toxicity and efficacy in neuronal models of disease, including cultured cerebellar granule cells and cortical neurons from 3xTg-AC mice, an Alzheimer's disease (AD) model animal. The heptacyclic **58** and tetracyclic **59** inhibited Kv currents from granule cells with potencies equivalent to that gambierol.[98] However, **58** and **59** were not cytotoxic for either granule cells or cortical neurons from 3xTg-AC mice, whereas **58** showed dose and time dependent toxicity.[92, 98] Sub-toxic concentrations of compounds **58–59** inhibited amyloid β (Aβ) accumulation and tau protein hyperphosphorylation in neurons from the AD model mouse,[92] suggesting therefore that simplified gambierol analogues might serve as tools for investigating AD pathogenesis modeled in the mutant mice.[92]

Brevenal (**60**) is a shorter LSP isolated from a culture of *K. brevis* that could in part underlie the observation that total LSP content in red tide blooms does not necessarily correlate with actual toxicity.[105] Brevenal, which is a nontoxic component of red tide-derived dinoflagellate cultures, showed antagonistic activity against the binding of brevetoxins to site 5 of neuronal VGSCs[105]; thus, varying concentrations of this "natural antagonist" to brevetoxin could underlie the varying toxicity of red tides.[105] The absolute stereochemistry of synthetic brevenal was determined and prompted revision of the originally proposed relative stereochemistry of **60**.[106, 107] Recently, four more syntheses for brevenal were published that likely will afford more convergent routes to prepare this potentially useful compound.[108–111]

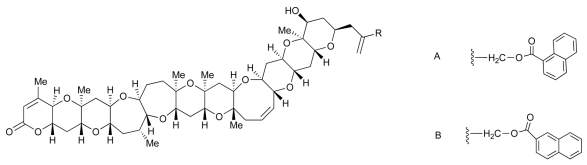


**60** brevenal

Newer LSPs known as tamulamides A (**61**) and B (**62**) were recently isolated from a culture of *K. brevis* and found to compete for the brevetoxins binding site on VGSCs. However, tamulamides lacked the fish and pulmonary toxicities characteristic of brevetoxins, suggesting that **61** and **62** are, like brevenal, antagonistic to brevetoxin. The semi-synthetic derivatives of brevetoxins α-naphthoyl Pb-Tx (**63**) and β-naphthoyl Pb-Tx (**64**) were also shown to antagonize the action of brevetoxins, but the modes of action appeared to differ between these molecules. That is, **63** only affected VGSC activation in the presence of the brevetoxin Pb-Tx, whereas **64** reduced opening even when VGSCs were not exposed to Pb-Tx.[112] These and other results suggest that the natural and synthetic brevetoxins antagonists could be of value not only to study mechanisms of VGSC modulation by LSPs but also to develop therapeutic agents for red tide-related airway symptoms[113] or mucociliary dysfunction including cystic fibrosis.[114, 115]



**61** tamulamide A; R = H
**62** tamulamide B; R = $CH_3$

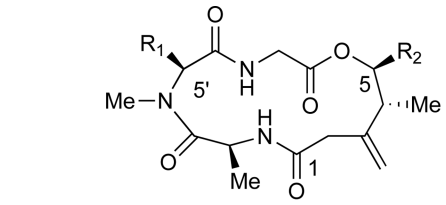


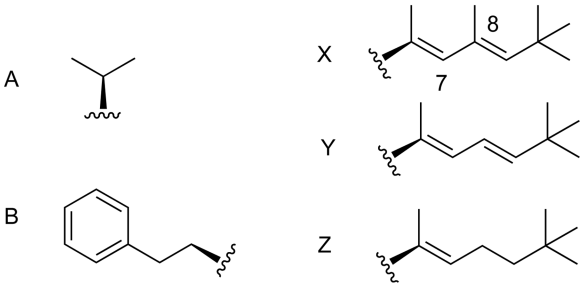
**63** α-naphthoyl Pb-Tx; R = A
**64** β-naphthoyl Pb-Tx; R = B

## 2.3 Cyanobacterial toxins

**2.3.1 Voltage gated sodium channel activators—**Several cyanobacterial non-ribosomal peptides and polyketides were found recently to act on neuronal sodium

channels.[53, 116] Antillatoxin A (**65**), a unique cyclic lipopeptide isolated from *Lyngbya majuscula* was first reported to be a potent ichthyotoxin,[117] and subsequently was shown to be cytotoxic for primary cultures of cerebellar granule neurons.[118] The toxicity of **65** was prevented by co-exposure with noncompetitive NMDA antagonists, MK801 and dextrorphan,[118] or TTX.[119] Antillatoxin activates VGSCs through interactions with site 4 of α subunits or additional undefined sites,[119, 120] and the toxin efficacy did not differ between heterologously expressed $Na_V1.2$, 1.4 and 1.5 channel isoforms.[120] Activation of VGSCs by **65**, like brevetoxin, induces depolarization-evoked $Na^+$ load and consequent glutamate release, activation of NMDA receptors, and $Ca^{2+}$ influx.[119]



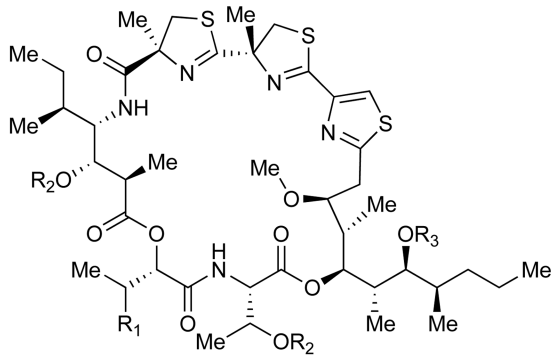

**65** antillatoxin A; $R_1$ = A, $R_2$ = X
**66** antillatoxin B; $R_1$ = B, $R_2$ = X
**67** analogue; $R_1$ = A, $R_2$ = Y
**68** analogue; $R_1$ = A, $R_2$ = Z

Natural and synthetic analogues of antillatoxin A have shed insight into the molecular determinants of activity on VGSCs. The natural product antillatoxin B (**66**) was shown to be 10-fold less active than antillatoxin A,[121] and stereoisomers of the cyclic depsipeptide backbone, (4*S*,5*R*), (4*S*,5*S*), and (4*R*,5*S*)-antillatoxin A, were 20–55 times less active than the natural (4*R*,5*R*) isomer.[122] Three synthetic analogues differing in the lipophilic side chain structure showed drastic changes in putative interactions with VGSCs (measured as cytotoxicity on Neuro-2a murine neuroblastoma cells).[118] Removal of the C8 methyl (**67**) reduced the cytotoxicity by ~250 fold. How that structural modification contributed to the substantial change in biological activity was assessed first by analyzing the conformations of **65** and **67** with NMR. The macrocyclic core for both compounds was identical, whereas the diene sidechain in **67** appeared planar in contrast to **65**, where it was in a twisted conformation (Scheme 3). Molecular dynamics calculations predicted a single lowest energy conformation in **61** in which the C7-C8=C9 dihedral angle was 180°, agreeing with the NMR data. In the case of **65**, however, two energy minima were predicted where the dihedral angles to be either 57° or 296°. These result suggested that the twisted conformation in the side chain of antillatoxins is a critical determinant for their ability to modulate VGSCs. This idea was tested by preparing compound **68**. The preferred dihedral angle in the energy minimized conformation **68** had predicted C7-C8=C9 dihedral angles of

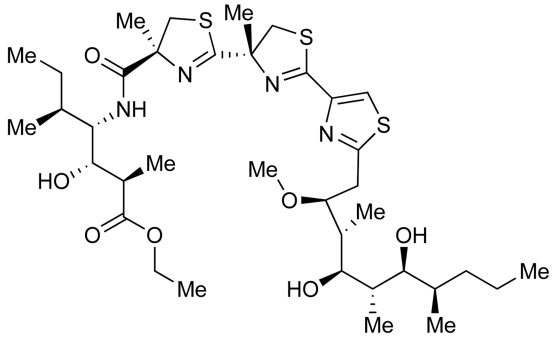
117° and 248° (Scheme 3), closer to those of **65**. The cytotoxicity of **68** for Neuro-2a cells showed a 10-fold higher potency than that of **67**, supporting the prediction.[123]

Recently, various analogues at C5 and C5' analogues of antillatoxin were prepared by incorporating diverse aryl or alkyl sidechains to common intermediates **69** or **70** using "click chemistry"; thus, the substituted triazoles were formed by copper catalyzed 1,3-dipolar coupling with acetylene terminal of **69** or **70** and azides (Scheme 4). Introduction of bulky groups at C5 resulted in a complete loss of Neuro-2a cytotoxicity with a single exception, whereas cytotoxicity was maintained (though significantly attenuated) upon analogous substitution of the C5' position.[124]

Hoiamide A (**71**), a cyclic depsipeptide, was isolated from the marine cyanobacteria *Lyngbya majuscula* and *Phormidium gracile*, which grow together as a inseparable mixture (referred to as environmental assemblage) in Papua New Guinea.[125] This structurally unusual toxin competes with batrachotoxin and veratridine for binding to site 2 on sodium channels but only exhibits ~40% efficacy for channel activation and therefore is characterized as a partial agonist. Site 5 binding toxins such as brevetoxin PbTx-3 enhanced activation of VGSC by hoiamide, consistent with allosteric interactions between sites 2 and 5 on VGSCs.[125, 126] Hoiamide B (**72**) was later found from a mixture of *Symploca* sp. and *Oscillatoria cf*. sp. collected in Papua New Guinea, and showed similar potency for stimulation of sodium influx as hoiamide A.[127] As well, the hoiamides suppressed spontaneous calcium oscillations in cultured mouse neocortical neurons, which likely occurs through mechanisms distinct from actions on VGSCs. A triacetate analogue (**73**) and the natural linear peptide hoiamide C (**74**) did not alter VGSC activity or calcium oscillations. A bromobenzoate hoiamide analogue (**75**) affected channel activities with a similar profile as hoiamide A and B.[127] Intriguing differences were observed in the cytotoxicity of natural and synthetic hoiamides.[127]

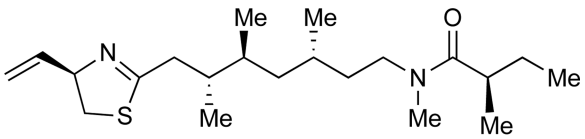


**71** hoiamide A; $R_1 = R_2 = R_3 = H$
**72** hoiamide B; $R_1 = Me$, $R_2 = R_3 = H$
**73** triacetate; $R_1 =$, $R_2 = R_3 = Ac$
**75** *p*-bromobenzoate; $R_1 = R_2 = H$, $R_3 = p$-bromobenzoyl

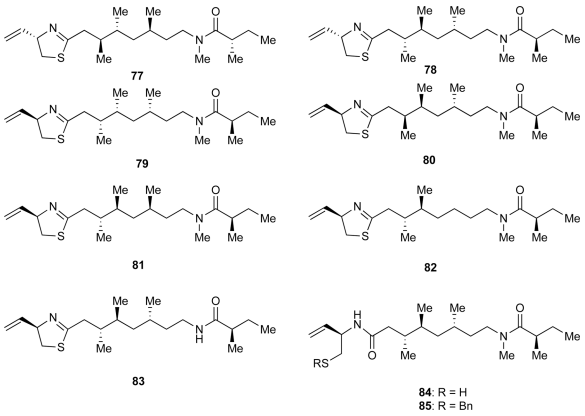


**74** hoiamide C

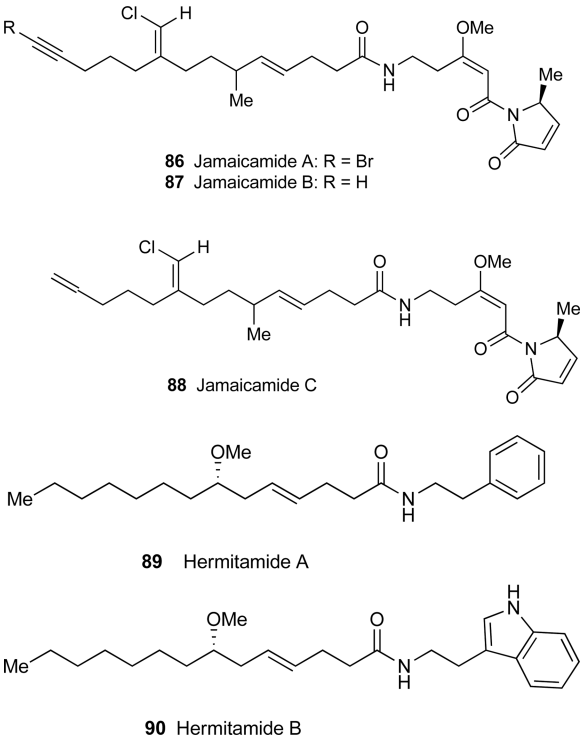
**2.3.2 Voltage gated sodium channel blockers—**A series of cyanobacterial lipophilic amides were found to be blockers of VGSCs. Kalkitoxin (**76**), a metabolite of *L. majuscula*, is a potent ichthyotoxin[118] that interacts with VGSCs at a site distinct from that batrachotoxin and blocks channel activation by veratridine.[128] Kalkitoxin has been synthesized and subjected to SAR studies.[129–132] An enantiomer, (−)-kalkitoxin (**77**), nor- and epi-kalkitoxins (**78–79**), and synthetic intermediates **84, 85**[132] all had lesser activity than the natural compound,[129] demonstrating that the methyl groups and their stereochemistry contribute as determinants of toxicity.[129]



**76** (+)-Kalikitoxin



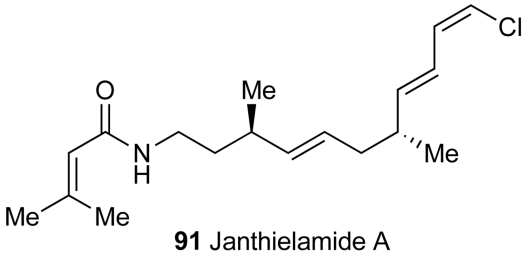

Jamaicamides A–C (**86–88**) were isolated from a Jamaican collection of *L. majuscula* as cytotoxic and ichthyotoxic compounds.[133] In H460 human lung cancer cells and Neuro-2a cells, **86–88** were cytotoxic with $LC_{50}$ values of ~15 μM, and their inhbition of sodium channels occurred in the low micromolar range.[134] Hermitamide A (**89**) and B (**90**) were isolated from *L. majuscula* collected in Papua New Guinea and reported to be cytotoxic for Neuro-2a cells at 5 and 18 μM.[135] The structural similarity these compounds share with jamaicamides and kalkitoxins facilitated development of possible pharmacophore models for the binding of the toxin to channels (Scheme 5).[136] The terminal π systems, 7-carbon linkages, and amide groups of jamaicamide C (**88**) and kalikitoxin (**76**) could overlap (Scheme 5, Mode 1). A second possible binding mode was conceived with **88** and hermitamide A (**89**) where the π-systems are separated by 2-carbon linkers, the amide groups, and the lipophilic chains overlap (Scheme 5, Mode 2).



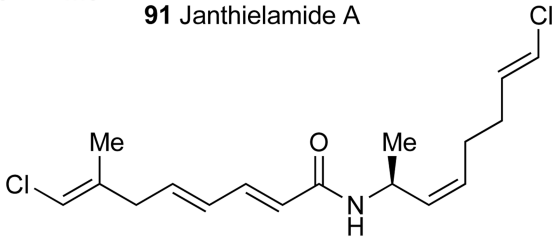

A synthetic study was conducted to test if hermitamides indeed block sodium channels as was predicted by Mode-2 of the pharmacophore (Scheme 5). Racemic and natural (*S*) and

enantiomer (*R*) forms of **89** and **90** both displaced [$^3$H]BTX from rat forebrain membrane at concentrations similar to that of phenytoin, a clinically used VGSC blocker anti-epileptic drug, regardless of the stereochemistry of the methoxy groups.[136] In electrophysiological experiments, **89** and **90** blocked activation of Nav1.2 channels expressed in HEK293 cells at much higher potency (70~88% block at 1 μM) than that of phenytoin (<10 % at 1 μM). These results suggest that **89** is a structurally simplified VGSC blocker, which could lead to large scale preparation and further structural modification.

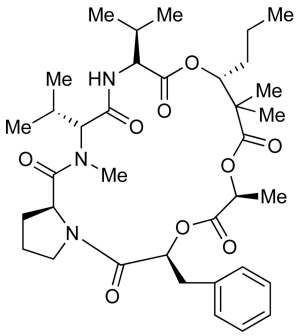
Janthielamide A (**91**) and kimbeamide A (**92**) are newer lipoamides with VGSC blocking activity. Compound **91** also antagonized veratridine-induced sodium influx in cerebrocortical neurons with an $IC_{50}$ of 5.2 μM.[137] The cyclic cyanobacterial metabolite palmyramide A (**93**), from a Palmyra Atoll collection of *L. majuscula*, also blocked VGSCs and exhibited modest cytotoxicity against H460 cells with micromolar potency.[138] Palmyrolide A (**94**) was isolated from a marine cyanobacterial mixture composed of *Leptolyngbya cf.* and *Oscillatoria* spp, also collected also from Palmyra Atoll, and blocked Neuro-2a VGSC currents and suppressed calcium oscillations in mouse cerebrocortical neurons but did not show cytotoxicity against H460 cells at concentrations as high as 20 μM.[139]



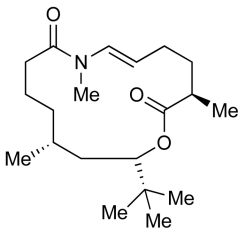

**91** Janthielamide A




**92** kinbeamide A




**93** Palmyramide A

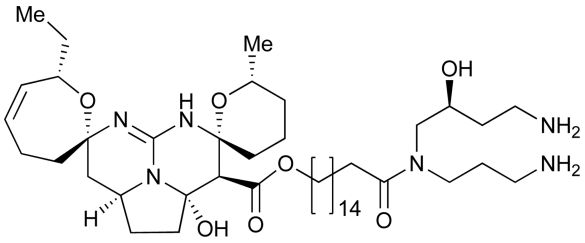



**94** Palmyrolide A

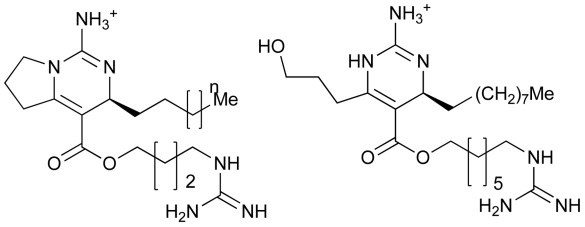
## 2.4 Sponge-derived alkaloids and bacterial glycine amide

Crambescidin 816 (**95**)[140] and crambescins[141] are metabolites isolated from the sponge *Crambe crambe*. Crambescidin 816 was reported to be a cytotoxic and antiviral compound but was later found to be a potent blocker of voltage-gated calcium channels in NG108-15

cells.[142] Recently, **95** was demonstrated to only partially block calcium current from high voltage-activated (HVA) calcium channels in cultured rat cortical neuron.[143] The main target of **95** was shown to be L-type ($Ca_V1$) but not N-type ($Ca_V2.2$) calcium channels. Compound **95** also inhibited VGSC currents but not potassium channel currents. In contrast, crambescin A2 (**96**), C1 (**97**), and norcrambescin A2 (**98**) weakly inhibited currents from $K_V$ channels. Halichlorine (**99**) is an isolate of the sponge *Halichondria okadai* that inhibited induction of vascular cell adhesion molecule-1.[144] Recently **99** also was shown to have a vasodilator effect in precontracted rat aorta;[145] this activity was ineffective in endothelial cells lacking L-type calcium channels and indeed voltage-dependent calcium channels currents were inhibited by halichlorine.[145] Finally, a lipophilic mycelial extract of marine bacterium, *Cytophaga* sp., inhibited binding of [$^{125}$I]-ω-conotoxin GVIA, a selective N-type calcium channel blocker, to guinea pig brain membranes,[146] and the *N*-(3-acyloxyacyl)glycines **100** and derivatives **101–102** were isolated as the active constituents. Thus, these small, marine-derived non-peptide molecules join the conotoxins as potentially clinical relevant antagonists for multiple types of voltage-gated calcium channels.

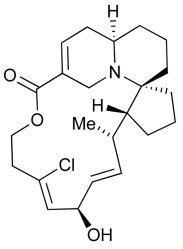


**95** crambescidin 816

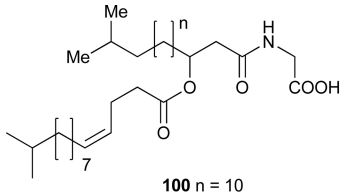


**96** crambescin A2, n = 9
**97** norcrambescin A2, n = 8

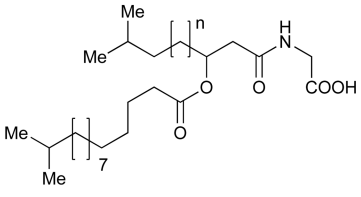
**98** crambescin C1



**99** halichlorine



**100** n = 10
**101** n = 9



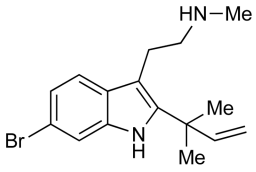
**102** n = 10

## 3 Molecules that target neurotransmitter receptors

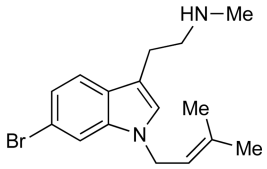
Chemical neurotransmission is transduced by families of integral membrane proteins that are either ligand-gated ion channels or G-protein coupled receptors (GPCRs, 7-transmembrane receptors). These proteins, as well as neuromodulator receptors, represent the molecular targets of a large number of neurotherapeutic drugs and neurotoxins. Marine natural products similarly interact with these diverse synaptic receptors with varying degrees of selectivity. Scheme 6 and 7 broadly summarize interactions between marine natural products and ligand-gated ion channels or GPCRs, resectively, and show some of the potential consequences and applications.

### 3.1 Acetylcholine receptors

**3.1.1 Indole alkaloids—**A bromotryptamine derivative, deformylflustrabromine (dFBr, **103**), isolated from the North Sea bryozoa *Flustra foliacea*, was shown to potentiate currents from recombinant human α4β2 nicotinic ACh receptors (nAChRs) through positive allosteric modulation of channel gating kinetics.[147, 148] A related series of bromotriptamines isolated from bryozoa failed to similarly modulate ACh currents, and **103** appeared to be selective for α4β2 nAChRs as ACh-evoked currents from α3β2, α3β4, α4β2, and α4β4 receptors expressed in *Xenopus* oocytes were unaffected when **103** was co-applied. On the other hand, homomeric α7 nAChRs were somewhat suppressed by dFBr.[149] More recently, α2β2 nAChRs also were shown to be potentiated by **103**.[150] Positive allosteric modulation by **103** reverses the inhibitory actions of amyloid peptide ($A\beta_{1-42}$) on both α2β2 and α4β2 nAChRs.[150] A synthetic salt of **103** produced a bell-shaped, concentration-dependent allosteric modulation of α4β2 nAChRs with a potentiating component $EC_{50}$ of 120 nM followed by an inhibiting component with an $IC_{50}$ of 150 μM. Inhibition of nAChR gating at higher concentrations was voltage-dependent and likely due to open channel block.[151, 152] A related natural compound, dFBr-B (**104**), only inhibited ACh-induced responses on both α7 and α4β2 nAChRs[151] The efficacy of **103** as a positive allosteric modulator of select isoforms of nAChRs is unprecedented and could be of value in both basic and therapeutic domains given the importance of cholinergic signaling in neurophysiological and neuropathological conditions (such as AD).

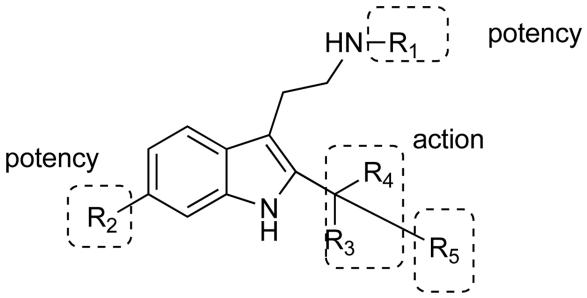



**103** dFBr



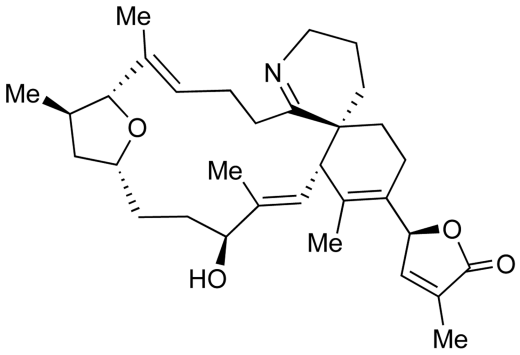

**104** dFBr-B

The structural determinants for action and potency of **103** were explored with eleven synthetic analogues of dFBr-B that fell into four groups **105–108**, which tested the efficacy of *N*-alkyl analogues (**105**), halogen substitution (**106**), methyl branching (**107**), and the terminal olefin (**108**). The study found that the lead structure **103** is optimum for potentiation of α4β2 nAChR currents, though reduction of the vinyl group enhanced selectivity for α4β2 receptors over α7 receptors. The geminal methyl groups and quaternary nature of the carbon bearing the methyl groups were necessary for potentiating activity. *N*-demethylation reduced potency by 50%, and the bromine atoms influenced potency but not functional activity.[153]

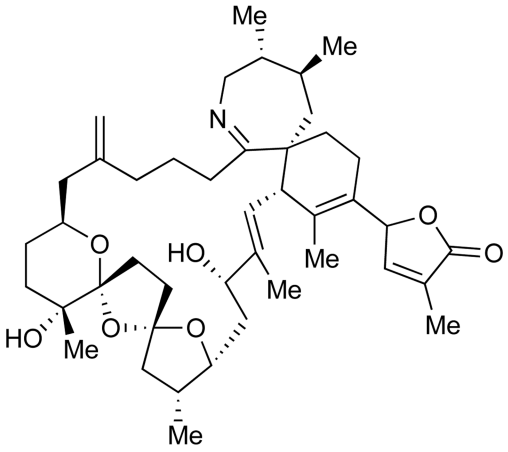



**105** $R_1 = CH_3$ or H
**106** $R_2$ = Br or H
**107** $R_3$ , $R_4 = CH_3$ or H
**108** $R_5$= H, $CH_3$, $CH_2CH_3$, or $CH{=}CH_2$

**3.1.2 Cyclic imines—**Dinoflagellate-derived cyclic imines (CIs) such as gymnodimine A (**109**) and 13-desmethylspirolide C (**110**) are nAChR antagonists. Because CIs are lethally toxic in mice[154] and accumulate in filter feeding marine bivalves such as shellfish, they represent a potential threat to human beings.[155] Five groups of CIs have been identified: gymnodimines, spirolides, pinnatoxins, pteriatoxin, prorocentrolide, and spiro-prorocentrimine.[155] Recent reviews describe their occurrence, isolation and structure elucidation,[155, 156] biological activity and mechanism of action,[154–156] and syntheses.[156, 157] The nature of continuing challenges to synthesize those structurally complex molecules also have been discussed recently.[158, 159] A detailed pharmacological study with **109** and **110** revealed that they are ligands for a wide range of nAChRs with high potency but limited selectivity among the receptor isoforms.[160, 161] Voltage clamp recording from muscle-type ($\alpha 1_2\beta\gamma\delta$) or neuronal ($\alpha 4\beta 2$) nAChRs revealed that **109** and **110** inhibit ACh-evoked currents with $IC_{50}$ values as low as 0.5 nM, making these compounds the most potent non-peptidyl nAChR antagonists.[160]




**109** gymnodimine A

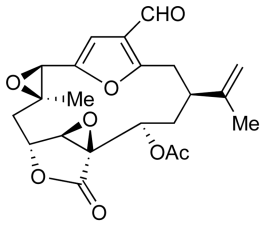



**110** 13-desmethylspirolide C

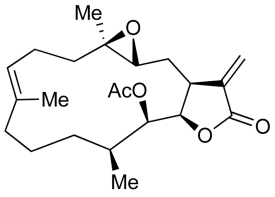
The molecular basis of high-affinity binding of CIs to AChRs was deduced from the X-ray crystal structure of acetylcholine binding protein (AChBP), a soluble structural homologue of the extracellular binding domain of nAchRs, in complex with **109** or **110**.[160] The imine moiety for **110** was positioned in the ACh binding pocket at the equivalent site occupied by the pyrrolidine nitrogen in nicotine. Other multiple binding loci were found throughout the interface between AChBP and the ligands that form a large surface area with the toxin, anchoring it deeply into the binding envelope, explaining the exceptionally high affinity of **110**.[160] Because of the central importance of cholinergic systems to Alzheimer's disease (AD), the long term effect of sub-toxic doses of **110** was assessed using the AD model 3xTg mice that overexpress both tau and Aβ proteins.[162] Long term incubation of 3xTg cortical neurons with **110** suppressed hyperphosphorylation of tau and accumulation of intracellular Aβ. These outcomes can be attributed to modification of the key kinases GSK-3 and ELK1/2 by **110**.[162] Compound **110** also protected the neuron from glutamate-induced cell death with an increase in cellular ACh level. Though the precise mechanism of regulation of enzymes related to AD pathology by **110** is unknown, these results demonstrate that CIs are potentially valuable tools for further elucidation of the complex AD pathology.

**3.1.3 Cembranoids—**Octocorals, a subclass of Anthozoan that includes soft corals, sea fans, and sea pens, are known to produce a variety of cembranoids, a group of diterpenes with a common 14-membered carbocyclic skeleton that can have activity on nAChRs.[163] The marine cembranoid lophotoxin (**111**) was the first of this group of compounds shown to act as a nAChR antagonist. A labeling experiment using a tritiated derivative of **111** showed

that electrophilic functional groups in **111** interacted with the receptor and resulted in formation of covalent complex with the conserved Tyr190 of the nAChR α subunit.[164, 165] It was proposed that a lactone oxygen and epoxide mimicked the acetate and quaternary ammonium, respectively, of ACh. The cembranoid eupalmerin acetate (EUAC, **112**) may have a more complex mode of action on muscle nAChRs in which **112** reversibly binds with varying affinities to multiple allosteric binding sites and functions as closed channel blocker. The positive or negative modulation depends on occupancy of each binding site by the ligand at a given concentration.[166] The neuroprotective activity of cembranoids resulting from nAChR block[167] or other mechanisms has been examined recently as well.[168] Given the structural diversity of marine and terrestrial cembranoids, additional research into the medicinal chemistry of this class of natural products for treatment of neurodegenerative diseases will be of particular interest.

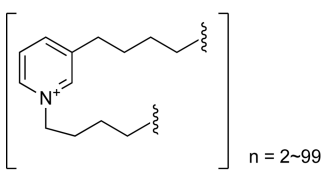



**111** lophotoxin




**112** eupalmerin acetate

**3.1.4 Alkylpyridine and alkylpyridinium derivatives—**Sponge-derived di- and polymeric alkylpyridines, as represented by **113**, are known to display a variety of biological activities[169] including inhibition of acetylcholinesterase[170] and membrane pore formation.[171] A number of biosynthetically related polycyclic amines have been isolated from marine sponges,[172] and the reduction products of haliclonacyclamines (e.g. haliclonacyclamine A, **115**) and a epimer (**116**) have been synthesized in racemic form.[173] In an ion channel and GPCR assay panel, racemic **115** inhibited radioligand binding to muscarinic M1 receptor, opioid κ receptors, and hERG potassium channels at 10 μM. Functional assays with the M1 muscarinic AChRs indicated that **115** was a full antagonist while **116** was a partial antagonist. Analysis of mAChRs with the abundant polycyclic amines that have been isolated from marine sources could lead to a new pharmacophore for ligands interacting with this important family of receptors.

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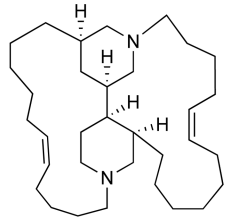
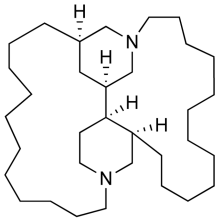


114 (-) haliclonacyclamine A



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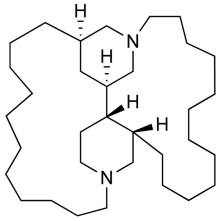


116

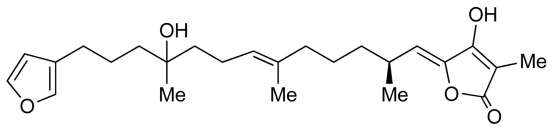
### 3.2 GABA and Glycine receptors

Ionotropic γ-aminobutyric acid receptors ($GABA_AR$) and glycine receptors (GlyR) are members of the Cys-loop superfamily of ligand-gated ion channels and are central mediators of inhibitory neurotransmission in the mammalian central and peripheral nervous systems. $GABA_A$ receptors are pentameric heteromers composed of numerous subtypes (nineteen in human) and represent a common target for a number of clinically used small molecule drugs acting as hypnotics, anticonvulsants, anaesthetic, and tranquillizers.[174] GlyRs are composed of five subtypes, α1–α4 and β; relatively few specific and subtype-selective small molecule ligands exist for GlyRs, in contrast to $GABA_A$ receptors.[175] Several marine natural products target inhibitory receptors, including the well-characterized sesquiterpene noncompetitive inhibitor picrotoxin, which while first derived from a terrestrial plant was also later discovered in a marine sponge.[176]

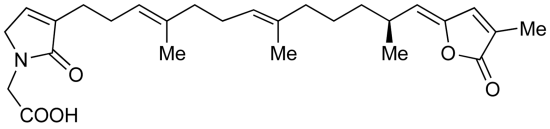
**3.2.1 Cembranoids—**EUAC (**112**), an allosteric modulator of nAChRs (see **3.1.3**) also potentiates $GABA_A$ receptors composed of the α1β2γ2L subunits.[177] Electrophysiological analysis suggested parallels between the biophysical activity and site of interaction of **112** and neurosteroids, which also allosterically modulate $GABA_A$ receptors. EUAC (**112**) also caused loss of righting and swimming reflexes in tadpole behavioral assays[177] and apoptosis in human malignant glioma cells,[178] effects consistent with actions on $GABA_A$ receptors. The data suggest that other cembranoids should be examined for activity on $GABA_A$ receptors, though the mode of action on these receptors will likely differ than that underlying nAChR modulation.

**3.2.2 Sponge sesterterpenes and alkaloids—**A search for subtype-selective allosteric modulators of glycine receptors from an Australia and Antarctic marine library of ~2500 extracts resulted in identification of three extracts from sponges of family Ircinidae.[179] Separation of the extracts afforded several sesterterpenes, **117–120**, which potentiated α1 GlyRs in the low- to sub-micromolar range. Compound **120** also weakly potentiated α3 GlyRs, whereas **117** potently antagonized α3 receptors. Compound **117** is therefore the first example of an α3-selective GlyR antagonist. Compounds **119** and **124** potentiated α1 over α3 GlyRs and thus could be considered prototype α1-selective potentiators that potentially lack the cross-reactivity with other receptors or channels

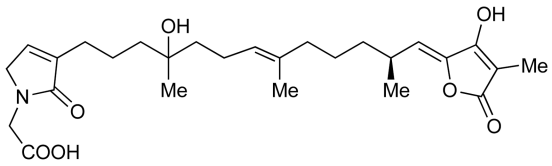
exhibited by GlyR modulators such as synthetic cannabinoids, a ginkolide B, dihydropyridine, and pregnenolone.[179, 180] Synthetic and structure-activity relationship studies for this class of compounds will facilitate development of useful tools to investigate GlyR physiology.



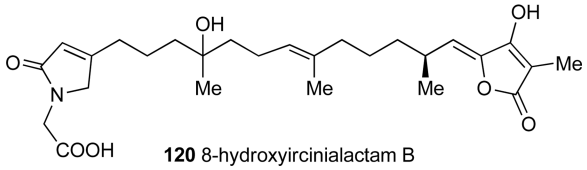

**117** (12*E*,20*Z*,18*S*)-8-hydroxyvariavilin




**118** ircinialactam A

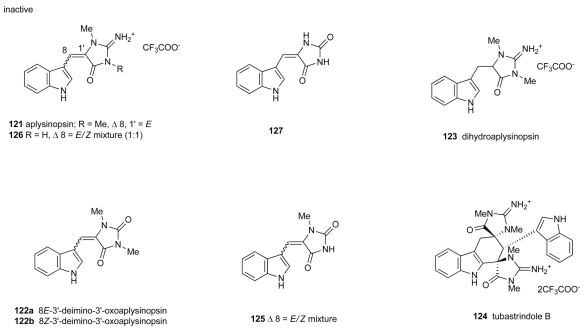



**119** 8-hydroxyircinialactam A




**120** 8-hydroxyircinialactam B

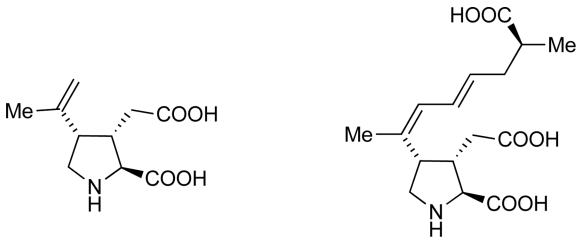
In the same screening panel, aplysinopsin derivatives from the extract of sponge *Ianthella* were identified as modulators of GlyRs.[181] Aplysinopsins were discovered initially in marine sponges and later in a wider range of marine benthic animals such as sea anemone and stony corals. They exhibit wide variety of biological activity in addition to neuroactivity, including cytotoxicity, inhibition of nitric oxide synthase and monoamine oxidase, antimicrobial and antiplasmodial actions, and, in the native ecosystem, mediation of symbiosis between sea anemones and anemone fish.[182] Compounds **121, 122ab** (a mixture of regioisomers), **123, 124** were identified as natural aplysinopsins and **125–126** (a mixture of Δ8 regioisomers) and **127** were prepared synthetically. Compound **122ab, 124, 125** exhibited moderate potency (μM) inhibition for α1 and α3 subtypes with some selectivity, in that, **122ab** preferred α3 receptors, while **124** was α1 receptor selective. Synthetic **126** inhibited both α1 and α3 receptors. Aplysinopsin (**121**), dyhydroaplysinopsin (**123**) and synthetic **127** did not show any activity, indicating that the *N*-methyl group and polar functional groups of the hydantoin ring, the double bond between the indole, and the hydantoin are determinants of GlyR activity.[181]




### 3.3 Glutamate receptors

Glutamate receptors (GluRs) mediate excitatory synaptic transmission in the mammalian CNS. Binding of the endogenous agonist, glutamate, activates both metabotropic and ionotropic GluRs. Metabotropic GluRs (mGluRs) belong to the GPCR family and initiate $G\alpha_{q/11}$-mediated signaling cascades. So far no marine-derived compound has been reported to interact with mGluRs, except for a weak agonist activity of dysiherbaine.[183] Ionotropic GluRs (iGluRs) belong to a family of glutamate gated cation channels comprised of a total of eighteen subtype proteins in mammals. Of those, sixteen are classified into three types based on their sensitivity to selective agonists and their structural identity: *N*-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate (KA) receptors. A functional iGluR is a homo- or hetero-tetrameric complex of subunits from within the same family of subunits. The function of each of these iGluR types differs in the CNS, and they are involved not only in central excitatory neurotransmission but also higher orders brain function such as memory formation and in some cases, neuronal disorders. A number of marine natural products have been identified as ligands for iGluRs.[5] Subtype-selective ligands for iGluRs are important tools in investigational research and potentially in clinical application.

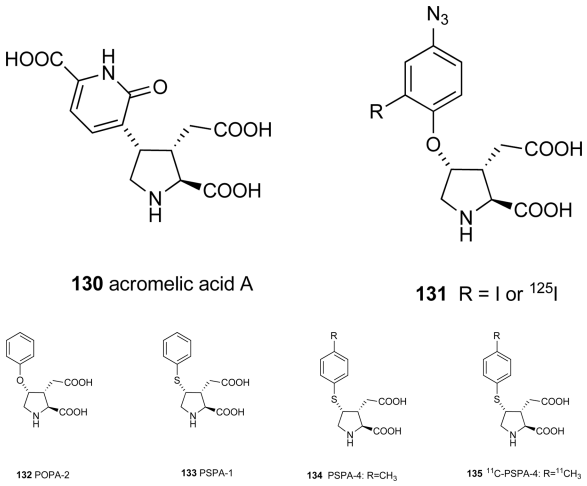
**3.3.1 Kainoids—**Kainic acid (**KA, 128**) and domoic acid (**129**) are classical excitatory amino acids and glutamate receptor agonists of marine origin. They are collectively referred to as kainoids on the basis of their shared 3-(carboxymethyl)pyrrolidine-2-carboxylic acid backbone. The occurrence, chemistry, and pharmacology of kainoids have been reviewed previously.[5] Kainic acid itself has been used as a standard reagent in neuropharmacology for some forty years. Recently, however, there has been renewed interest in KA, and to some extent domoic acid, as target compounds for synthetic chemists to test stereoselective and efficient synthetic methodology. More than thirty examples of KA syntheses were reviewed recently.[184]



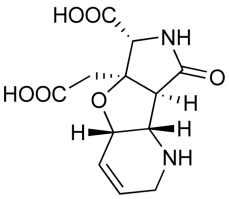

**128** (-)-kainic acid **129** (-)-domoic acid

Several novel synthetic compounds were introduced in the course of development of biologically active kainoids. For example, simplified analogues of a mushroom-derived kainoid, acromelic acid A (**130**), were synthesized as potential photoaffinity labeling

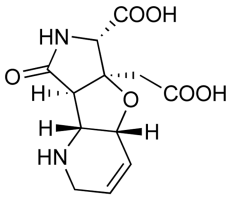
agents.[185] The biological activity of the azide **131** was evaluated in mouse pain models, because the parent kainoid caused allodynia in mice after intrathecal (i.t.) injection. Compound **131** was as active as **130** in this model, even though many other synthetic kainoids failed to show significant activity. The related compounds **132** and **133** were tested for their ability to induce allodynia in mice; whereas **136** was potent inducer of allodynia, **133** inhibited allodynia induced by **130** and by nerve injury.[186] Normal nociception and inflammatory pain were not affected by **133**. Further insights into the mechanism of **133** were assessed by preparing PSPA-4 (**134**) and its $^{11}$C-labeled analogue **135**.[187] Compound **134** both attenuated allodynia induced by **130** at lower doses and directly caused allodynia at higher doses. Allodynia induced by **134** was suppressed by GYKI53655, a non-competitive AMPA/kainate receptor antagonist, but not by the kainate antagonists NS102 and UPB296, suggesting that the mechanism of action of the kainoids likely involved AMPA receptors, one of the principle ionotropic glutamate receptors underlying excitatory synaptic transmission. Further studies are required to uncover mode of action of acromelic acid derivatives, but the data underscores the utility of kainoid-based probes as unique tools for investigating neuropathic pain transmission.[187]




A novel synthetic AMPA receptor antagonist IKM-159 (**136**) and related compounds (IKM compounds) with a kainoid-inspired structural motif were generated using tandem Ugi-Diels Alder reaction followed by domino metathesis with vinyl acetate that enabled efficient formation of the complex and diverse heterocyclic skeleton (Scheme 8).[188–191] Racemic IKM-159 (**136ab**) induced muscle relaxant activity in mice after intracerebroventricular (i.c.v.) injection[191]. Electrophysiological experiments characterized suppressive actions of **136ab** in recombinant AMPA receptors, cultured rat hippocampal neurons, and CA1 pyramidal neurons in hippocampal slice preparations. These data supported the interpretation that **136ab** is an antagonist for AMPA receptor,[191] which was confirmed subsequently upon resolution of the crystal structure of the ligand binding domain (LBD) of the AMPA receptor (GluA2) complexed with the 2*R* isomer of IKM-159. This result was consistent with the observation that only **136a**, prepared by enantioselective synthesis, was biologically active.[188] The binding affinity of racemic **136ab** to the GluA2 LBD and full length receptor was determined to be very low, with *K*i values of 0.21 and 0.59 mM, respectively. The development of an efficient, diversity-oriented route for synthesis of various IKM analogues incorporating different heteroatoms, ring sizes or double bonds in the C-ring (Scheme 8)[189, 190, 192] may facilitate discovery of new natural product-inspired synthetic molecules that exhibit selectivity for AMPA receptors.

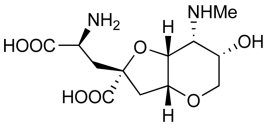


**136a** (2*R*)-IKM159

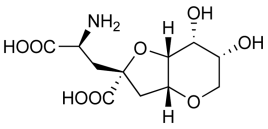


**136b** (2*S*)-IKM159

**3.3.2 Dysiherbaines—**Dysiherbaines are novel excitatory amino acids isolated from the Micronesian sponge *Lendenfeldia chondrodes*. Dysiherbaine (**137**)[193] and neodysiherbaine A (**138**)[194] are natural products; subsequently many analogues have been synthesized.[194–199] The sponge that contained **137** and **138** was originally identified to as *Dysidea herbacea*[193] but was corrected on the basis of ribosomal DNA sequence analysis.[200] Dysiherbaines are unique 4-substituted glutamates with a perhydro [3, 2*b*]furopyrane structure, and **137** is one of the most potent naturally occurring excitatory amino acid convulsants found to date.[201] The chemistry and pharmacology for dysiherbaines are well characterized[183, 202–208] and reviewed recently.[5, 201] Dysiherbaine activates both mGluR (albeit weakly) and iGluRs, but the most interesting characteristic of **137** is its particularly high affinity for the kainate receptor subunits GluK1 and GluK2 (*K*i = 0.74 and 1.2 nM, respectively), which gives rise to quite unusual gating behaviors from heteromeric kainate receptors.[208]

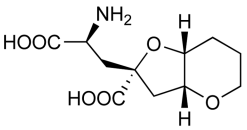


**137** dysiherbaine

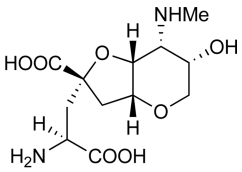


**138** neodysiherbaine-A

Characterization of synthetic dysiherbaine analogues revealed that varying the substituents at C8 and C9 produced discrete affinities and activities on kainate receptors and *in vivo* activity in mice.[201] For example, removal of both functional groups at C8 and C9 yielded MSVIII-19 (**139**), an analogue that elicited a coma-like sleeping state in mice,[199] apparent antagonist activity on GluK1-containing kainate receptors,[207] and analgesia in animal models of inflammatory and neuropathic pain.[202] A stereoisomer of neodysiherbaine A, 2,4-epi-neodysiherbaine (**140**), was also characterized to be an antagonist, while 4-epi-neodysiherbaine (**141**) was weak agonist for homomeric GluK1 and GluK2 receptors.[205] Thus, manipulation of the dysiherbaine template structure produced a wide range of pharmacological activity and kainate receptor specificity.[201]



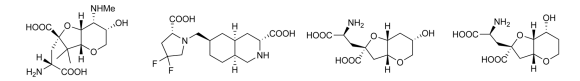
**139** MSVIII-19



**140** 4-*epi*-neodysiherbaine

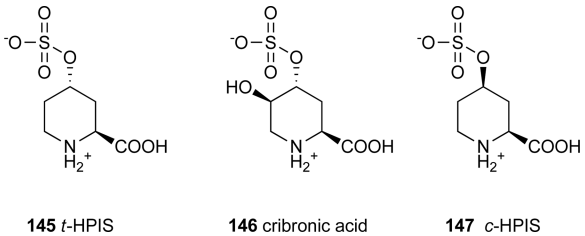
The molecular basis of the antagonist activities of **139** and **141** on kainate receptors was assessed by structure-function and computational studies. The resolved structures of the GluK1 LBD complexed with **139** or **137** were nearly identical and corresponded to a

"closed" conformation typically observed between full agonists and iGluR LBDs.[204] Further physiological characterization led to re-characterization of **137** as a very weak, fully desensitizing partial agonist rather than an antagonist.[204] Molecular dynamic simulations predicted a complex mechanism of antagonism by **139** or **140** on GluK1 kainate receptors in comparison with various iGluR ligands, including domoic acid, the antagonist LY466195 (**142**), glutamate and dysiherbaines. X-ray structures for other synthetic dysiherbaine analogues with diverse binding affinity and agonist efficacy, including 8-deoxyneodysiherbaine (**143**), 9-deoxyneodysiherbaine (**144**), and **137–139** complexed with human GluK1 and 2 LBDs were also solved recently.[209] Those data in combination with physiological and computational modeling studies could lead to insight into structural dynamics of GluK1 and 2 interactions with the molecules and predictions for development of more specific ligands.

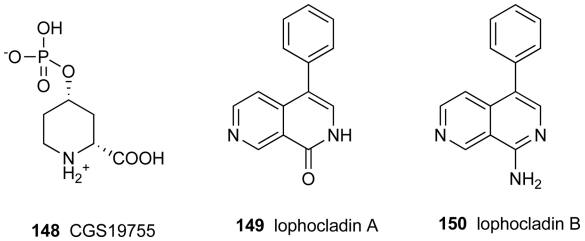


**141** 2,4-*epi*-neodysiherbaine **142** LY466195 **143** 8-deoxyneodysiherbaine **144** 9-deoxyneodysiherbaine

**3.3.3 Pipecolic acid derivatives and an algal naphthyridine alkaloid—**A number of pipecoline derivatives interact with NMDA receptors. The NMDA receptor agonist *trans*-hydroxypipecoline *O*-sulfate (*t*-HPIS, **145**), previously synthesized chemically, was isolated from Micronesian sponge *Axinella carteri* collected in Yap, and a related compound, cribronic acid (**146**), was found in the Palauan sponge *Cribrochalina olemda*.[210] Both **145** and **146** exhibited potent convulsant activity in mice i.c.v. injection and displaced radio-labeled ligand for the glutamate binding site from NMDA receptors in rat cortical membrane preparations. The stereoisomer synthetic *cis*-HPIS (**147**) was not active in mice.[210] Thus, **145** and **146** are competitive agonists for NMDA receptors; of note, the synthetic compound CGS19755 (**148**), an enantiomeric *cis*-HPIS with phosphate substitution is instead a competitive NMDA receptor antagonist. Lophocladines A (**149**) and B (**150**) were isolated from Fijian red alga *Lophocladia* sp. A high concentration of **149** was shown to displace radiolabeled MK-801, a non-competitive NMDA antagonist, and it also was shown to bind to the δ-opioid receptor (see 3.6.3). The related compound **150** did not show affinity for neuronal receptors, but instead was a tubulin depolymerizing agent.[211]



**145** *t*-HPIS **146** cribronic acid **147** *c*-HPIS



**148** CGS19755 **149** lophocladin A **150** lophocladin B

**3.3.4 Peptides and proteins—**Two groups of *Conus* peptides, conantokins and con-ikot-ikot (**151**), act on NMDA and AMPA type iGluRs, respectively. Recently, an

oligosaccharide-binding protein, the galectin CchG (**152**) from marine sponge *Cinachyrella*, was found to modify receptor kinetics of AMPA and kainate type iGluRs. Here we focus on aspects of structure and function of **151** and **152** because several reviews of conantokins and their activity were published recently.[5, 212–214] These proteins both allosterically modulate gating of iGluRs, with the most marked effect appearing as a slowing or reduction in agonist-dependent desensitization. The mechanisms of action of **151** and **152** are distinct despite the qualitatively similar pharmacological activity (positive allosteric modulation of iGluRs).

The unusual conopeptide, **151**, found in the fish-hunting snail *Conus striatus*, is composed of 86 amino acids, has a theoretical molecular weight of 9432, and contains 13 cysteine residues.[215] Con-ikot-ikot is named for the behavior of fish after injection of the toxin, as it means “spinning around” in Filipino. The active form of peptide was shown to be tetrameric (a dimer-of-dimers) in which dimers were covalently linked with disulfide bridges whereas the dimer-dimer interaction was non-covalent. Compound **151** strongly potentiated steady-state currents evoked by glutamate from either homomeric GluA1 AMPA receptors expressed in *Xenopus* oocytes or native AMPA receptors in rat CA1 pyramidal neurons. Con-ikot-ikot did not modulate kainate (GluK2), NMDA (GluN1/GluN2A) or $GABA_A$ receptors. Allosteric modulation of AMPA receptors by **151** was additive with that of the small-molecule PAM cyclothiazide, indicating that their binding sites on AMPA receptors were distinct. A peptide related to con-ikot-ikot, p21a (**153**), was isolated recently from the venom of *Conus purpurascens*.[216] The peptide has 32% sequence homology with **151**, and a similar but not identical organization of the cysteine residues (Figure 1). Two proline residues can be hydroxylated in **153** and the *N*-terminal is amidated. In contrast to **151**, p21a appears to be dimeric rather than tetrameric in SDS-PAGE and mass spectral analyses. The biological activity of p21a was not characterized because of a shortage of the toxin.[216]

A screening for molecules that modulate iGluR function yielded an extract of the ball sponge *Cinachyrella* sp.[217] that potently inhibited desensitization of recombinant kainate (GluK2a) and AMPA (GluA4) receptors. The active component was isolated, guided by the physiological and behavioral bioassays, and was identified as a galactose-binding lectin denoted CchG (**152**) (for *Cinachyrella* galectin). CchG is a biologically active mixture composed at least two proteins, CchGa and b. CchGs are 146 amino acid peptides that have weak sequence similarity to those of higher order prototype galectins. The X-ray crystal structure of **152** was solved and revealed that the protein forms a unusual dimer-of-dimer structure through non-covalent interactions, with each monomer folding in a evolutionarily conserved β-sandwich structure.[218] The toroid tetrameric structure formed by CchG assembly is unusual among galectins (Figure 1); as well, biological activity is retained even after heat denaturation and exposure to extreme pH ranges, suggests that the lectin is remarkably stable thermodynamically and can efficiently re-fold as a functional oligomeric assembly. Allosteric modulation of AMPA and kainate receptors was observed with both native and recombinant CchG, and this activity was completely abolished by application of lactose, indicating that the lectin induce their pharmacological actions through binding of complex *N*-glycans attached to receptor proteins. These observations and the conserved structural features between the sponge and animal orthologues suggest that the distantly related galectin family of molecules could have functional importance in modulation of iGluRs in the mammalian brain.

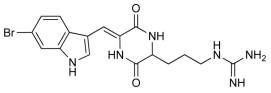
### 3.4 5-Hydroxytriptamine (5-HT) receptors

Receptors that transduce 5-HT, or serotonin, signaling are GPCRs with the exception of the 5-HT-3 ligand-gated ion channels, which are members of the Cys-loop superfamily of receptor proteins. 5-HT receptors are important drug targets for central disorders such as

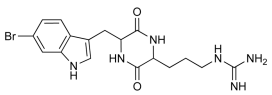
depression and migraine. Marine organisms are rich in indole alkaloids with a triptamine substructure, and thus could be a potential source of novel 5-HT receptor ligands.[219, 220] Few marine indoles have been characterized yet for their pharmacological actions on 5-HT receptors.

**3.4.1. Sponge-derived aromatic amines—**Aplysinopsins are known to possess a wide variety of biological activities including neuronal activity (see 3.2.2.),[182] and the brominated analogues, as well as *N*-ethyl-containing derivative were identified as ligands for 5-$HT_2$ receptors.[221] The aplysinopsin pharmacophore for 5-HT subtypes was further elaborated by synthesizing a series of analogues (Scheme 9),[222] which revealed that the $R_3$ alkyl group and type and number of halogen atoms influenced both potency and relative selectivity for 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors, and generally affinities for 5-$HT_{1A}$ receptors were weak. Additional SAR studies found that selectivity in affinity for 5-$HT_{2A}$ over 5-$HT_{2C}$ receptors was greater when the indole ring was non-halogenated (**154, 155**), or contained a 6-fluoro (**156–157**) substituent, while preference for 5-$HT_{2C}$ over 5-$HT_{2A}$ was evident for 6-chloro (**158, 159**) and 6-bromo (**160**) derivatives. Notably, the dichloro analogue **159** was a high-affinity and selective ligand for 5-$HT_{2C}$ receptors; it failed to bind to 5-$HT_{2A}$ receptors at even the highest concentration tested (100 μM).[222] Drugs that have this pharmacological selectivity have potential as anti-obesity drugs, with an example being the recently FDA-approved compound lorcasterin.[223]

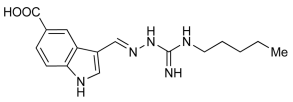
Other marine-derived compounds acting on 5-HT receptors include barettin (**161**) and 8,9-dihydrobarettin (**162**), which are structurally related to aplysinopsins and were isolated from the sponge *Geodia barrette*.[224] Those compounds also are chemically related to the 5-$HT_4$-selective drug, tegaserod (**163**), which was once used to manage constipation. Barettin (**161**) was approximately 10-fold selective for 5-$HT_{2C}$ over 5-$HT_{2A}$ and 5-$HT_4$ receptors, whereas the dihydro derivative **162** showed less affinity for 5-$HT_{2C}$. An acylated amino acid, bunodosine 391 (**164**), was found from venom of the Brazilian sea anemone *Bunodosoma cangicum*[225] and likely acts on 5-HT receptors. Bunodosine 391 was analgesic in animal models of pain, and this activity completely blocked by methysergide, a nonselective serotonin receptor antagonist, but not the opioid receptor antagonist naloxone.[225]



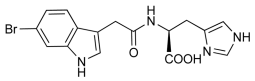

**161** barettin




**162** 8,9-dihydrobarettin

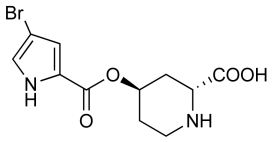



**163** tegaserod

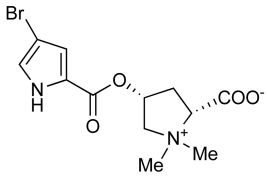



**164** bunodosine 391

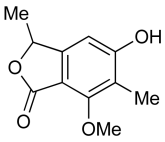
The novel bromopyrroles damipipecolin (**165**) and damituricin (**166**) were isolated from the Mediterranean sponge *Axinella damicornis* and shown to interact with 5-HT receptors in cultured rat primary cortical neurons.[226] Though further experiments are needed to characterize their mechanism of action, **165** and **166**, that inhibit 5-HT mediated $Ca^{2+}$ influx, could represent a new type of bromopyrrole 5-HT modulator.[226] Finally, a culture of the marine-derived fungus *Stachylidium* sp., isolated from Australian sponge *Callyspongia* sp., afforded the phthalide derivatives marilone A–D.[227] Of these, marilone B (**167**) exhibited selective antagonist activity for 5-$HT_{2B}$ receptors, with no interaction observed for most other defined receptor subtypes.[227].



**165** damipipecoline



**166** damituricin

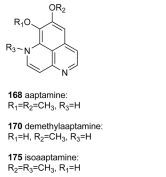


**167** marilone B

### 3.5 Other synaptic GPCRs and transporters

Marine compounds also interact with other neurotransmitter receptors and associated proteins important for the complex processes underlying chemical synaptic transmission in the mammalian CNS. Molecular targets such as adrenoceptors, histamine receptors, and monoamine transporters have long history of research and development in the pharmaceutical industry, resulting in numerous clinically used drugs. Natural products researchers therefore continue not just to pursue novel active molecules but also to develop novel pharmacophores for more potent and subtype selective agents based on natural ligands.

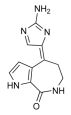
**3.5.1. Aromatic amines targeting adrenoceptors—**Sponge-derived adrenoceptor blockers such as aaptamine (**168**)[228] and hymenin (**169**)[229] were identified several decades ago. Aaptamine weakly inhibited the action of noradrenaline on α-adrenoceptors in vascular smooth muscles, while demethylaaptamine (**170**), demethyloxyaaptamine (**171**), dihydroaaptamine (**172**) and dihydrodemethylaaptamine (**173**) were inactive at the highest concentrations tested (10 – 100 μM).[228] Recently, aaptamine and 5,6-dibromo-*N*,*N*-dimethyltryptamine (**174**) were shown to exhibit antidepressant-like activity in the rodent forced swimming test model of depression.[230] In the tail suspension test, however, **168** was inactive, while **174** showed significant efficacy; neither demethylaaptamine nor isoaaptamine exhibited any antidepressant activity in these two tests.[230] Though the detailed mechanism of action of these compounds remains unknown, common sponge metabolites like **174** are reasonable candidates for further development in in-depth pharmacological characterization as well as SAR studies given their relatively simple chemical structures.



**168** aaptamine:
$R_1$=$R_2$=$CH_3$, $R_3$=H

**170** demethylaaptamine:
$R_1$=H, $R_2$=$CH_3$, $R_3$=H

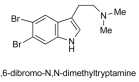
**175** isoaaptamine:
$R_2$=$R_3$=$CH_3$, $R_1$=H



**169** hymenin

**171** demethyloxyaaptamine

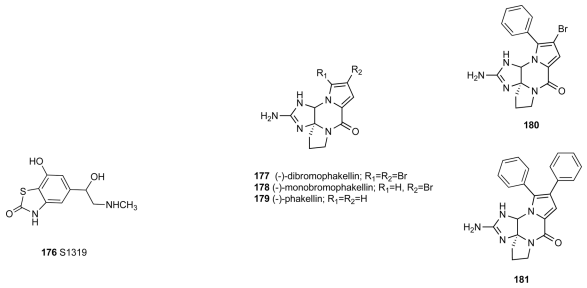
**172** dihydroaaptamine:
$R_1$=$R_2$=$CH_3$, $R_3$=H
**173** dihydrodemethylaaptamine:
$R_1$=H, $R_2$=$CH_3$, $R_3$=H



**174** 5,6-dibromo-N,N-dimethyltryptamine

S1319 (**176**) is a novel β-adrenergic-selective agonist isolated from the Okinawan sponge *Dysidea* sp.[231–233] S1319 was first characterized as novel adrenaline derivative with potent bronchodilator activity; the structure was determined on the basis of its spectroscopic data.[233] Synthesis has been achieved in racemic form[234] without disclosure of the absolute stereochemistry at the secondary alcohol. **176** binds to β1- and β2-adrenergic receptors and relaxes guinea-pig tracheal smooth muscle as potently as the clinically used anti-asthmatic β2 agonist formoterol, albeit with shorter duration.[235] Like other β2 agonists, S1319 inhibits IgE-mediated release of cytokines from human cultured mast cells and is therefore anti-inflammatory.[231] A distinct sponge metabolite, (−)-dibromophakelline (**177**), extracted from *Acanthella costata*, is related to the well-characterized family of bromopyrrols[236] and

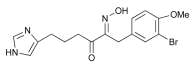
showed weak agonist activity for α2B-adrenergic receptor. The activity on other adrenergic receptors has not been reported. (−)-Dibromophakelline was chemically converted to derivatives **178–181**, but these compounds did not show analogous activity on adrenergic receptors.



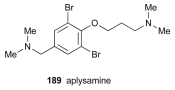

**3.5.3. Tyrosine and tryptophan metabolites targeting histamine and monoamine systems—**Histamine H1 and H2 receptor antagonists have been used widely for allergies and to control gastric acid production, respectively. Recently, H3 receptors also have gained significant attention as a target of antagonism for treating various CNS disorders.[237] Pharmacokinetically, non-imidazole compounds with H3 receptor activity could be favorable drug leads, because the imidazole group often inhibits P450 enzymes and thereby prevents clearance of co-administrated drugs, leading to potentially serious drug-drug interactions.[238] The monoamine transporters for norepinephrine (NET), dopamine (DAT), and serotonin (SERT) are also important target for drug development as many psychostimulant drugs target both monoamine systems.[239]

The brominated sponge metabolite dispyrin (**182**) interacts both with α-adrenergic and histamine receptors. Originally isolated from Caribbean sponge *Agelas dispar* as free amine, dispyrin was synthesized recently on the grams scale as a hydrochloride (**182**), enabling detailed pharmacological studies.[240] Screening of a large number of candidate molecular targets for synthetic **182** found that the compound possesses nanomolar affinity for $\alpha_{1D}$ and $\alpha_{2A}$ adrenergic receptors and low micromolar affinity for the H1 and H3 histamine receptors.[240] Because **182** conforms to a well-established pharmacophore for H3 antagonists (**183**), the structure was refined to generate more potent ligands for this receptor (Scheme 10).[241] The first generation syntheses generated 25 analogues from the core bromotyramine unit. The most potent compound, **184**, exhibited a 13-fold increase in affinity for H3 compared to dispyrin. In a second series of syntheses, incorporation of a functional group into the pyrrolidine ring lowered the affinity for H3 receptors, with the electron-withdrawing fluorine substitution have a particularly large effect. A truncated spacer chain also lowered the affinity, whereas altering the halogen atom from Br to Cl on the benzene ring (**185**, for example) had little effect. Finally, alteration of the amide group with a 5-oxazole (**186**) or 2-thiazole (**187**) produced analogues with approximately 33-fold higher affinity for and inhibition of H3 receptors compared to the natural product dispyrin.

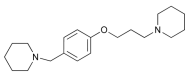
Several other marine natural products interact with histamine receptors. Early examples are verongamine (**188**)[242] and aplysamine-1 (**189**),[243] which are both metabolites from sponges of the *Verongidae* family acting as functional antagonists of the H3 histamine receptor. Recently an SAR study of **189** found that the compound binds H3 receptor selectively over H1, 2 and 4.[244] The SAR results agreed well with the pharmacophore model (Scheme 10), in which hydrophobic amines at both ends of the molecule have significant roles in conferring the receptor binding affinity. The aromatic bromine atom was instead an impediment to optimum binding, thus, derivatives (e.g. **190**) were shown to be potent non-imidazole H3 antagonists.[244]



188 verongamine

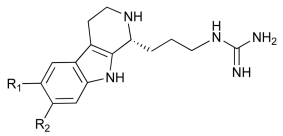


189 aplysamine

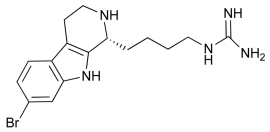


190

The trypargine derivatives (**191–192**) are bioactive β-carboline alkaloids found from an African frog,[245] venom of the Brazilian colonial spider,[246] a marine tunicate,[247] and a marine sponge.[248] The marine-derived **193** and its analogues were synthesized as β-carboline alkaloids are known to exhibit variety of biological activity, and the structure of **193** overlaps to some degree with the H3 pharmacophore (Scheme 10).[249] Screening of **193** against a panel of 68 GPCRs found the compound had micromolar binding and antagonist activity for H3 histamine receptors as well as the transporters NET and DAT.[249] These observations support further optimization of a novel pharmacophore for both the H3 receptor and monoamine transporters.



**191** trypargine; $R_1 = R_2 = H$
**192** 6-hydroxytrypargine; $R_1 = OH$, $R_2 = H$

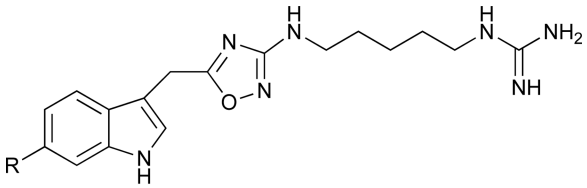


**193** 7-bromotrypargine; $R_1 = H$, $= Br$

## 3.6. Opioid receptors

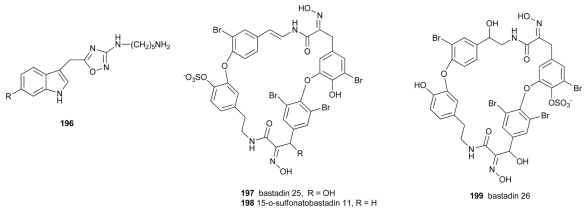
Opioid receptor agonists, like the potent analgesic morphine, are indispensable drugs for pain control, but narcotic activity and addiction are serious adverse effects that accompany use of these drugs. Three major opioid receptor subtypes, δ, κ and μ, are generally thought to be involved in analgesic mechanisms, while most adverse effects are mediated through the μ receptor. While subtype-selective compounds that could interact selectively with δ, or κ-opioid receptors could potentially be devoid of side effects, successful application of such compounds as analgesics is limited for varying reasons. For example, a δ receptor-selective drug was reported to be proconvulsant,[250] and the κ-agonist salvinorin A is hallucinogenic.[251] On the other hand, a κ receptor agonist was used as antipruritic drug.[252] As well, hetero-dimerization between μ and δ receptors could play a key role in antinociception activity; a compound interacting with μ/δ dimer was an effective analgesic with diminished drug tolerance relative to morphine.[253] Several marine-derived compounds with affinity for opioid receptors were characterized recently, raising the possibility of discovery of new drug leads for this important family of therapeutic targets.

**3.6.1. Molluscan guanidines—**The marine opisthobranch mollusk *Phidiana militaris* was the original source of cytotoxic 1,2,4-oxadiazole-containing alkaloid phidianidines A (**194**) and B (**195**), which also were synthesized recently.[254, 255] Despite fitting well within the H3 pharmacophore (Scheme 10), the phidianidines exhibited only weak activity on H3 histamine receptors; instead, they were found to be selective inhibitors of dopamine transporters (relative to NET and SERT) and weak partial agonists for μ-opioid receptors. Because the synthetic intermediate **196** retained activities on both DAT and μ-opioid receptors, the guanidine group was concluded to be nonessential for pharmacological activities. The selectivity that **194** and **195** exhibited for μ-opioid receptor as compared to δ- and κ-opioid receptors facilitated definition of a novel pharmacophore for μ-opioid ligands.



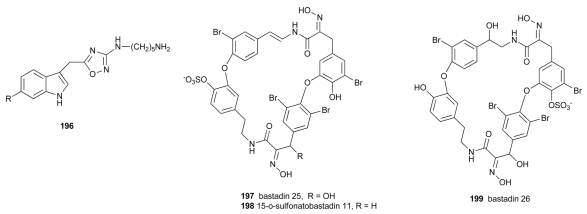
**194** phidanidine A; R = Br
**195** phidanidine B; R = H

**3.6.2. Bastadins as opioid receptor ligands—**The well-characterized sponge peptidyl metabolites known as bastadins were isolated from the Australian marine sponge *Ianthella flabelliformis* and identified as δ-opioid ligands.[256] Pharmacological analysis of three bastadins, bastadine 25 (**197**), 15-*O*-sulfonatobastadin 11 (**198**), and bastadin 26 (**199**), revealed that only **199** interacted with δ-opioid receptors. None of the three compounds showed affinity for μ- and κ-opioid receptors. The pharmacological activity of **199** has not yet been reported.



**196**
**197** bastadin 25, R = OH
**198** 15-o-sulfonatobastadin 11, R = H
**199** bastadin 26

**3.6.3. Other alkaloids—**The sponge-derived polycyclic amine purine 1,9-dimethyl-8-oxoisoguanine (**202**), isolated from the Palauan sponge *Cribrochalina olemda*, showed weak affinity for κ-and μ-opioid receptors.[257] This is the first example of simple purine derivative with opioid receptor activity. It remains to be determined if the compounds are agonists or antagonists. The algal NMDA receptor ligand lophocladines A (**149**) also displaces labeled enkephalin from expressed δ-opioid receptor weakly; because the compound did not show agonist activity at concentrations as high as 100 μM, it was proposed to be an antagonist.[211] Finally, the sponge cyclic imine derivative **115**, which interacts with mAChRs, also binds to the κ-opioid receptor.[173] These examples demonstrate that marine natural products afford an unexpectedly wide range of structural templates with affinity for opioid receptors. Future characterization of functional activity will be necessary to select promising lead compounds for further examination.

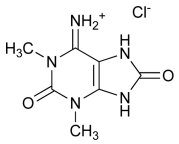


**196**
**197** bastadin 25, R = OH
**198** 15-o-sulfonatobastadin 11, R = H
**199** bastadin 26

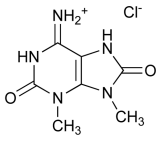
## 3.7. Purines with multiple GPCR targets

Marine invertebrates contain unusual purine derivatives. Caissarone (**200**)[258] and 1,3-dimethylisoguanine (**201**),[259] are products of sea anemones and sponges, respectively. Caissarone-induced twitch in electrically stimulated guinea pig ileum-myenteric plexus was attributed to antagonistic actions on adenosine receptors. Compound **201** showed a qualitatively similar but weaker activity as **200**. Recently, 8-oxoisoguanines of sponge origin were found to have diverse neuronal activities.[257] 1,9-dimethyl-8-oxoisoguanine (**202**)

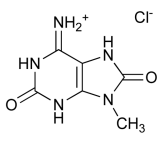
elicited potent convulsant behaviors in mice after i.c.v. injection, which likely arose from a reduction in inhibitory signaling in the CNS. Though **202** did not directly act on excitatory iGluRs or inhibitory $GABA_A$ receptors, it potently diminished the amplitude of postsynaptic inhibitory currents in the mammalian hippocampus. **202** exhibited sub-micromolar affinity for $\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1D}$ adrenoceptors, and weaker affinity for 5-$HT_{1E}$, nicotinic $\alpha 3\beta 2$, and κ- and μ-opioid receptors (see 3.6.3). The related compounds **203–205** also exhibited varying convulsant activities in mice, but the modes of actions have not yet been defined. These results suggest that small modified purines of the type often found in marine organisms can be modulators of neurotransmission through complex actions on multiple synaptic autoreceptors.



**203**



**204**

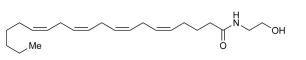


**205**

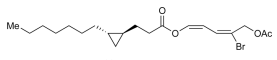
## 3.8 Cannabinoid receptors

Cannabinoid receptors ($CB_1$ and $CB_2$) are GPCR targets of $\Delta^9$-tetrahydrocannabinol (THC), a metabolite in *Cannabis* plants and the principle psychotropic agent in marijuana. THC and related compounds, as well as endogenous cannabinoids, are agonists with varying efficacy on cannabinoid receptors. $CB_1$ receptors are abundant in the brain and have a key role in regulation of neurotransmitter release. $CB_2$ receptors are located throughout many organs, including brain and retina, and in immune cells.[260]

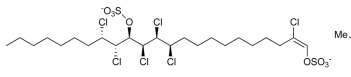
Drugs that interact with cannabinoid receptors have therapeutic potential in a variety of neurodegenerative diseases, including AD, and can be used to ameliorate chronic pain states.[261] The endocannabinoid anandamide (**206**) is an high-affinity partial agonist for $CB_1$ and $CB_2$[262] that is synthesized in part by fatty acid amid hydrolase (FAAH). The cyanobacterial metabolites grenadadiene (**207**) and malhamensilipin A (**208**) inhibit FAAH with relatively low affinity.[263] Grenadamide (**209**)[264] as well as semiplenamides A (**210**), B (**211**), and G (**212**)[265] showed a similar range of affinity (5~20 μM) for cannabinoid receptors rather than FAAH inhibition.[265] The anandamide membrane transporter (AMT) was inhibited by **210**.[265] Serinolamide A (**213**) was isolated from *L. majuscula* in Papua New Guinea and exhibited a moderate affinity for the $CB_1$ receptor but no binding to $CB_2$ receptors[266]. Semiplenamide B (**214**) and malingamide B (**215**) weakly displaced radioligands from $CB_1$ and $CB_2$ receptors, and both compounds reduced cAMP accumulation induced by the adenylyl cyclase activator forskolin, indicating that **214** and **215** are agonists for the $CB_1$ and $CB_2$ receptors.[267] These successes should stimulation additional discovery of marine products that target the clinically relevant cannabinoid signaling system.



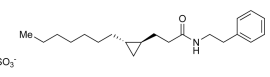
**206** anandamide



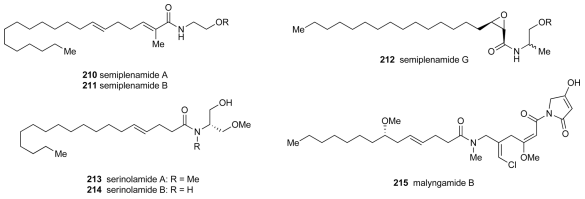
**207** gerandadiene



**208** malhamensilipin A



**209** gerandamide



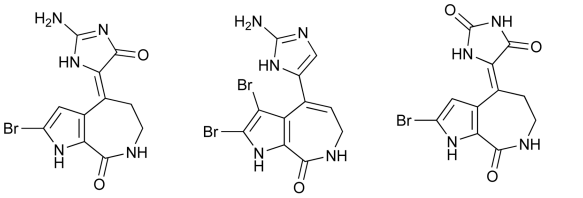

# 4 Enzyme modulators

## 4.1 Kinase modulators

Protein kinases play key roles in cellular signal transduction and regulation in the nervous system. More than 500 putative kinases are encoded in the human genome. Compounds that modulate specific kinases are of obvious importance as drug candidates, and a number of compounds (mostly anticancer drugs) are developed or under development. Kinases such as glycogen synthase kinase-3 GSK-3β, dual-specificity, tyrosine phosphorylation regulated kinases (DYRKs), cdc2-like kinases (CLKs) and cyclin dependent kinase-5 (CDK-5), are thought to have relevance in neurodegenerative diseases that include AD.[268] In AD pathology, GSK-3β or CDK-5 activation leads to hyperphosphorylation of tau proteins, which cause neurofibrillary tangles associated with amyloid deposition and neuronal death. It has been proposed that selective inhibitors could slow progression of the disease.[269, 270]

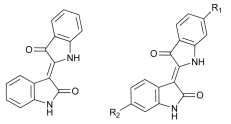
A number of marine natural products are known to inhibit mammalian kinase activity. A recent comprehensive review article discusses the occurrence, synthesis, medicinal chemistry and drug development of marine derived kinase inhibitors, a topic with a breadth reflected in the article's coverage of 354 compounds in a bibliography with 717 references.[271] Here we focus solely on compounds that possess inhibitory activity relevant to those kinases implicated in AD.

**4.1.1 Inhibitors—**In a screening study with sponge-derived brominated pyrrols, hymenialdisine (**216**), which is structurally related to aplysinopsin, was found to be an inhibitor of GSK-3, casein kinase 1 (CK1), and cyclin-dependent kinases (CDK 1 and 5) with nanomolar potency.[272] Consistent with its actions on these important kinases, hymenialdisine inhibited hyperphosphorylation of microtubule-associated protein (MAP)-1B and tau[272]. Hymenialdisine interacts with the ATP binding pocket of CDK2, similar to other inhibitors.[272] The structurally related compounds stivensine (**217**) and axinohydantoin (**218**) were not as effective as enzyme inhibitors.




Several indole alkaloids have also been identified as inhibitors of neuronally relevant kinases. Indirubin (**219**) inhibits kinases such as GSK-3, CDK1 and CDK5 and is an active ingredient in Chinese folk medicine used to treat leukemia.[273, 274] Brominated analogues (**220–222**) isolated from the Mediterranean purple dye-producing mollusk *Hexaplex trunculus* also inhibit GSK-3β.[275] The cytotoxic indole alkaloids meridianins (**223–224**), variolins (e.g. variolin A, **225**) and related compounds are also found to inhibit kinases at low micromolar concentrations. Though those compounds have been explored primarily as

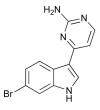
antitumor candidates because of their potent cytotoxicity, meridianins B (**223**) and E (**224**) inhibit GSK-3β.[276]



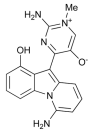
**219** indirubin



**220** $R_1$ = Br, $R_2$ = H
**221** $R_1$ = H, $R_2$ = Br
**222** $R_1$ = Br, $R_2$ = Br

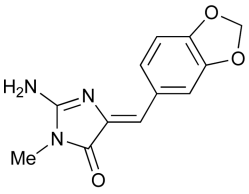


**223** meridianin B
**224** meridianin E

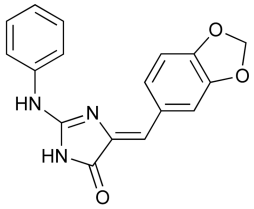


**225** variolin A

Leucettamine B (**226**), from the Palauan sponge *Leucetta microraphis*,[277, 278] is structurally related to hymenialdisine, aplysinopsins and other aminoimidazolone-containing marine alkaloids. Leucettamine B also inhibited DYRKs and CLKs, and for that reason an SAR study was carried out towards structural optimization.[279] The analogue L41 (**227**) exhibited improved potency and selectivity, and like other inhibitors completed with ATP for binding to the kinase. L41 reduced neuronal degradation in amyloid precursor protein (APP)-transfected brain slices through unknown mechanism(s).[280]



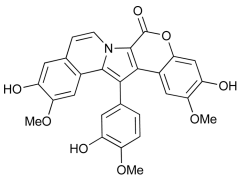
**226** leucettamine B



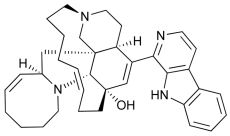
**227** leucettine L41

The lamellarins are polyaromatic pyrrole alkaloids from diverse marine organisms, including sponges and tunicates, and are known to be potent cytotoxic compounds.[281] Lamellarins are topoisomease I inhibitors and more recently were identified as potent inhibitors of kinases.[282] Among more than 30 analogs, lamellarin N (**228**) was shown to inhibit for GSK3α/β with nanomolar potency but also acted on a wide range of other kinases.[282] The mechanism of action of lamellarins is still unknown, as is their degree of specificity for particular enzymes.[282] Optimization of lamellarins selectivity will be necessary to establish their utility as kinase inhibitors.

Manzamines are marine alkaloids originally isolated from the Okinawan sponge *Haliclona* sp as cytotoxic compounds.[283, 284] Manzamine A (**229**) has antimalarial activity as well as other biological actions that include cytotoxicity and suppression of foam cell formation in macrophages, which can be an indication of atherosclerosis.[285, 286] Recently, **229** was shown to inhibit GSK-3β and CDK5, and accordingly reduced tau phosphorylation in human neuroblastoma cells.[287] A molecular docking study suggested that **229** inhibits GSK-3β via a site distinct from the ATP binding pocket.[287, 288]

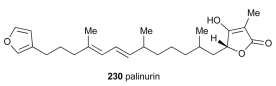


**228** lamellarin N

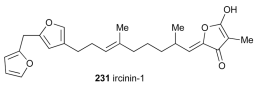


**229** manzamine A

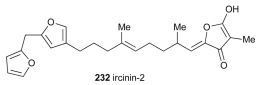
A sponge-derived sesterterpene, palinurin (**230**), inhibits both GSK-3α and β.[289] The related compounds ircinin-1 (**231**) and -2 (**232**) also inhibited GSK-3β. Inhibition of GSK-3β by **230** was selective over other related kinases, and docking analysis suggested that **230** binds to a site distinct from the ATP binding site but not that targeted by manzamines.[289] Carteriosulfonic acids A–C (**233–235**), isolated from a *Carteriospongia* sp. sponge collected in the Philippines, also inhibited GSK-3β, potentially through an allosteric mechanism.[290] These results suggest that optimization of marine-derived compounds as exemplified above could realize highly selective negative allosteric modulators of GSK-3β, particularly as compared to inhibitors competing with the highly conserved ATP binding site.



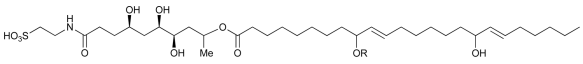
**230** palinurin



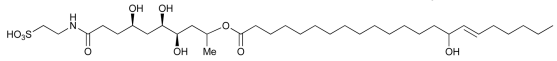
**231** ircinin-1



**232** ircinin-2

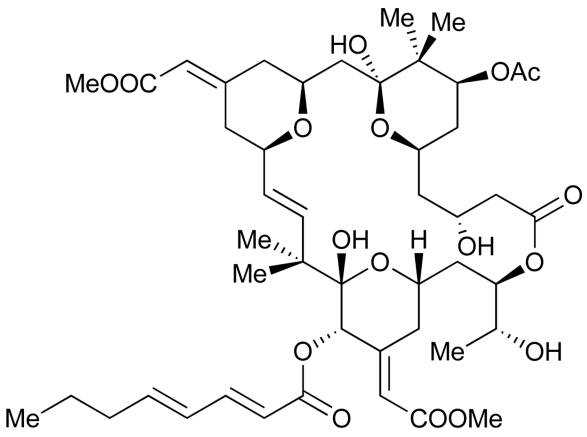


**233** Cateriosufonic acid A; R = H
**234** Cateriosufonic acid B; R = $COCH_3$



**235** Cateriosufonic acid C

**4.1.2 Activators—**Bryostatins are anticancer macrolides isolated from bryozoan *Bugula neritina*.[291] Bryostatin-1 (**236**) is one of the pioneering examples of a marine natural compound developed as antitumor drug, and thus a large body of research, including clinical trials, exists describing its properties and actions.[292] Bryostatins are nanomolar activator of protein kinase C (PKC). Generally, PKC activators like phorbol esters are potent tumor promoters, which precludes their clinical use; **236** however, lacks the tumor-promoting activity because it acts in a PKC isozyme-specific manner.[293] Isozyme-specific PKC activation is a candidate strategy for AD pathology because it indirectly lowers the production of Aβ peptide. Accordingly, bryostatin-1 reduced Aβ concentration in a transgenic AD mouse model and increased generation of a α-secretase-dependent breakdown product of APP in human cells lines from AD patients.[294] In rat behavioral assays, cognitive enhancement and antidepressant effects were observed upon administration of **236**.[295] These data lend support to the hypothesis that **236** could be a useful drug to treat AD therapeutically, particularly in view of the large body of existing clinical data for this compound.

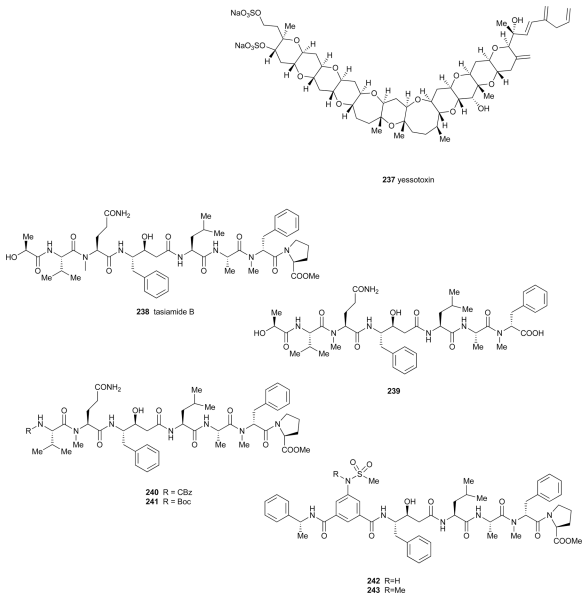



**236** bryostatin-1

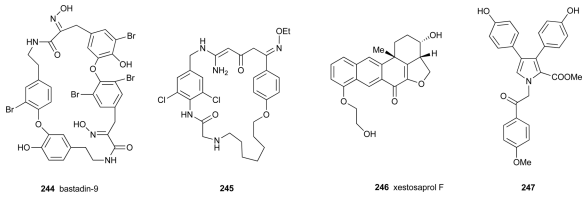
Yessotoxin (**237**, YTX) and its analogues are dinoflagellate LSPs first isolated from scallops likely contaminated with toxin-containing algae.[76] Several microalgae are known to produce YTX, and more than 40 YTX derivatives have been identified.[296] Unlike most other LSPs (e.g. brevetoxins, ciguatoxins, see section 2.2.1), the human toxicity of YTXs is not clearly defined, though they exhibit toxicity in cultured cells and mice.[296] YTXs are also known to induce apoptosis and exhibit immunoregulatory activity, which in the latter case was in related to PKC activation.[297] Recently, direct effects of YTX on cortical neurons were examined in the context of potential treatment of neurodegenerative diseases.[298] Subtoxic concentrations of YTX activated PKC and increased the inactive form of GSK-3β. Because YTX reduced production of Aβ and hyperphosphorylation of tau protein in 3xTgAD neurons, PKC activation by YTX could be another novel strategy for amelioration of AD pathology.[298]

### 4.2 BACE inhibitors

Inhibition of β-site amyloid precursor peptide (APP) cleaving enzyme type 1 (BACE1), or β-secretase, has been pursued as a strategy for treating AD, because this protease hydrolyzes APP to Aβ peptide. The cyanobacterial linear depsipeptide tasiamide B (**238**) inhibits aspartic proteases, including BACE1, with broad specificity.[299] Analogues of **238** designed to improve BACE1 selectivity yielded compounds **239–243**, which exhibited nanomolar inhibition of the protease. Those analogues containing an isophthalic acid moiety (**242, 243**) were selected for further evaluation because this structural feature was thought to enhance blood-brain barrier (BBB) penetrance and molecular stability as well as efficacy for reduction of Aβ *in vivo*. While **243** decreased Aβ levels significantly in rodents, **242** did not show efficacy, likely due to low BBB permeability.[299]




A screen for BACE1 inhibitors from marine extracts using sensitive high-throughput assays resulted in the isolation of several compounds, including bastadine-9 (**244**) which has structural similarity to a synthetic BACE1 inhibitor (**245**) from Bristol-Myers Squibb.[300] The xestosaprols F-M (**246**, for example) isolated from an Indonesian sponge *Xestospongia* sp. exhibited weak inhibitory activity against BACE1.[301] The Australian sponge *Ianthella* sp. contained a series of BACE1 inhibitory compounds with the most active being lamellarin O (**247**), which inhibited enzyme activity by 60% at 10 μM.[302]




## 5 Conclusions

The last decade has seen the discovery of increasing numbers of novel marine natural products that target neuronally relevant receptors and enzymes. In addition to new compounds, previously isolated compounds have been re-examined to reveal neuronal targets. Access to screening programs or commercially operated services provides new opportunities for natural products chemists to test compounds for neuroactivity. In many cases, interdisciplinary collaborations lead to further insight into mechanism of activity of bioactive compounds. The marine natural products reviewed here have varying selectivity and potency for their targets. Modern synthetic approaches and medicinal chemistry along with structural biological strategies will enable generation of pharmacophores and the preparation of optimized compounds for refinement of biological activity. The continued discovery and investigation of neuroactivity of marine compounds has the potential to realize new drugs for treatment of as yet unmet clinical treatment of neurological diseases.

## Acknowledgments

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A

**151*** SGPADCCRMKE**CC**TDRVN**EC**LQRYSGREDKFVSF**C**YQEATVT**C**GSFNEIVG**CC**YGYQM**C**MIRVVKPNSLSGAHEA**C**KTVS**C**GNPCA

**153** -FELLPSQDRS**CC**IQKTL**EC**LENYPGQASQRAHY**C**QQDATTN**C**PDT-YYFG**CC**PGYAT**C**MSINAG-NNVRSAFDK**C**INRL**C**FDPGH

*sequence for the mature peptide

B

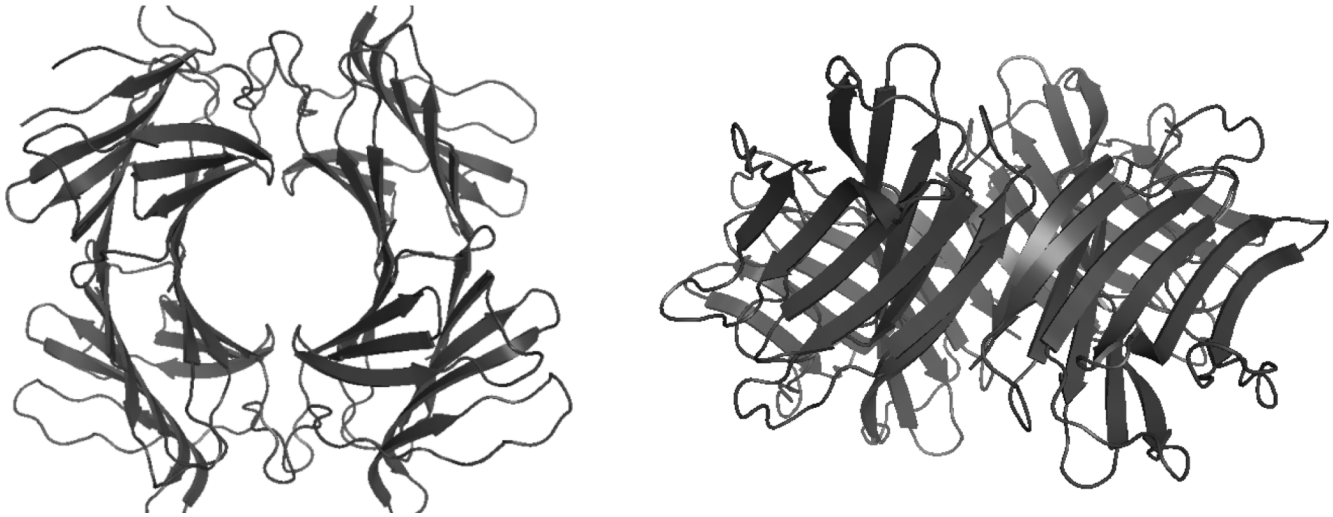
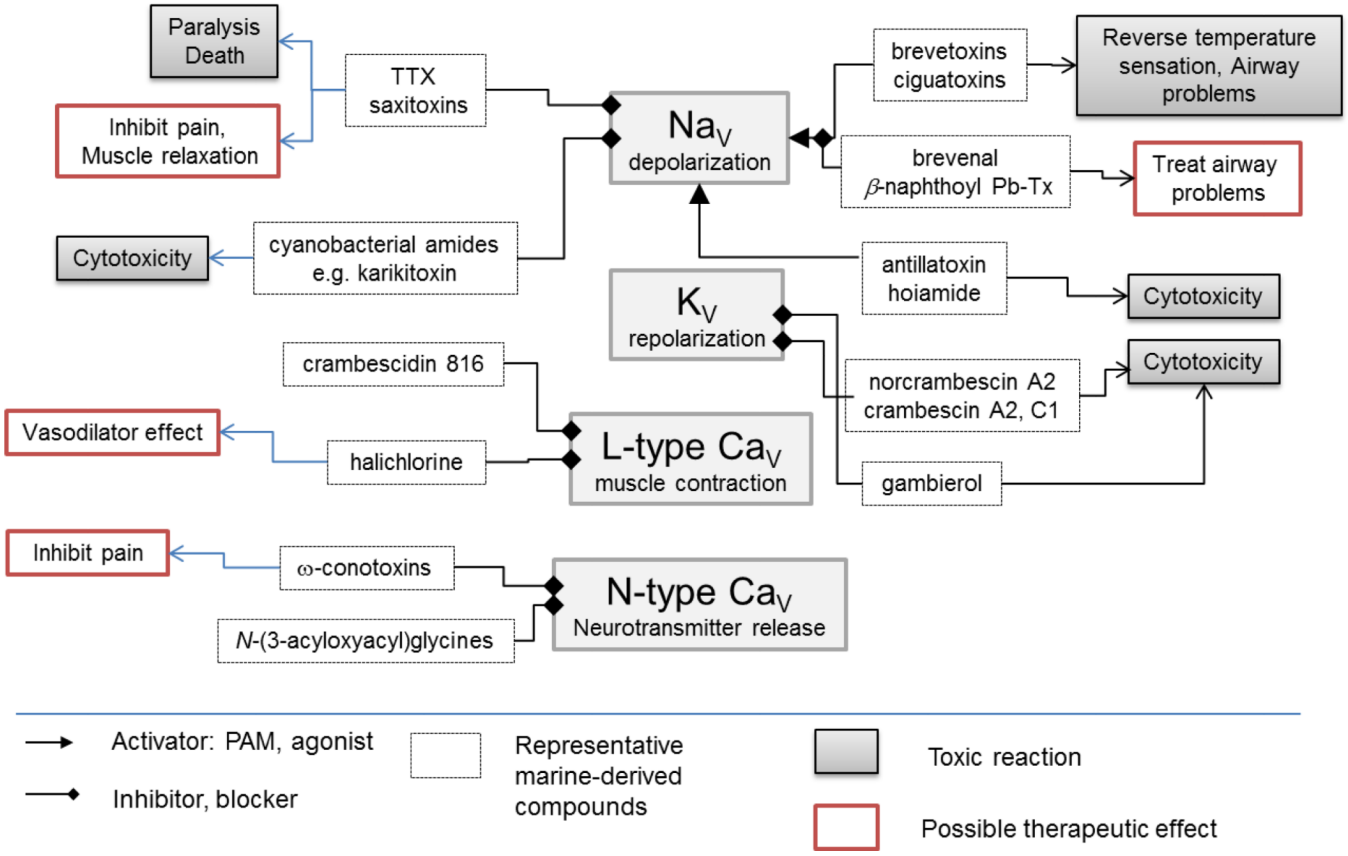
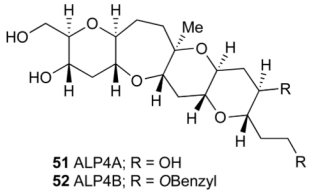


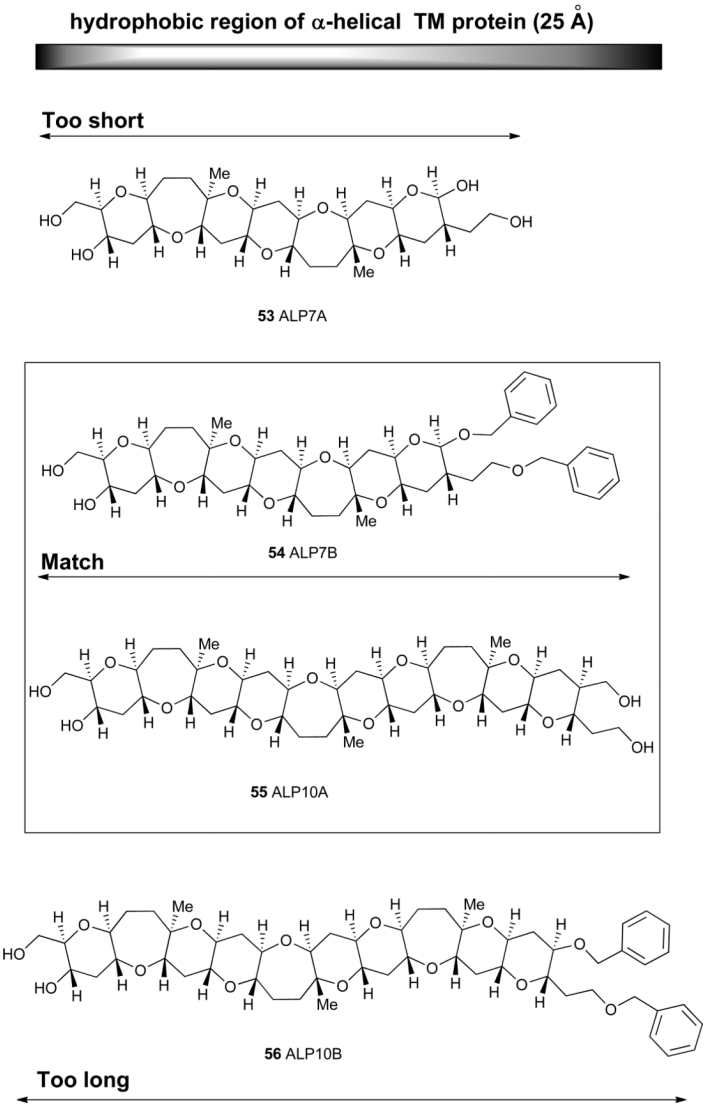
**Figure 1.**
Amino acid sequence of (A) con-ikot-ikot (**151**) and p21a (**153**), and (B) crystal structure of CchG (**152**)



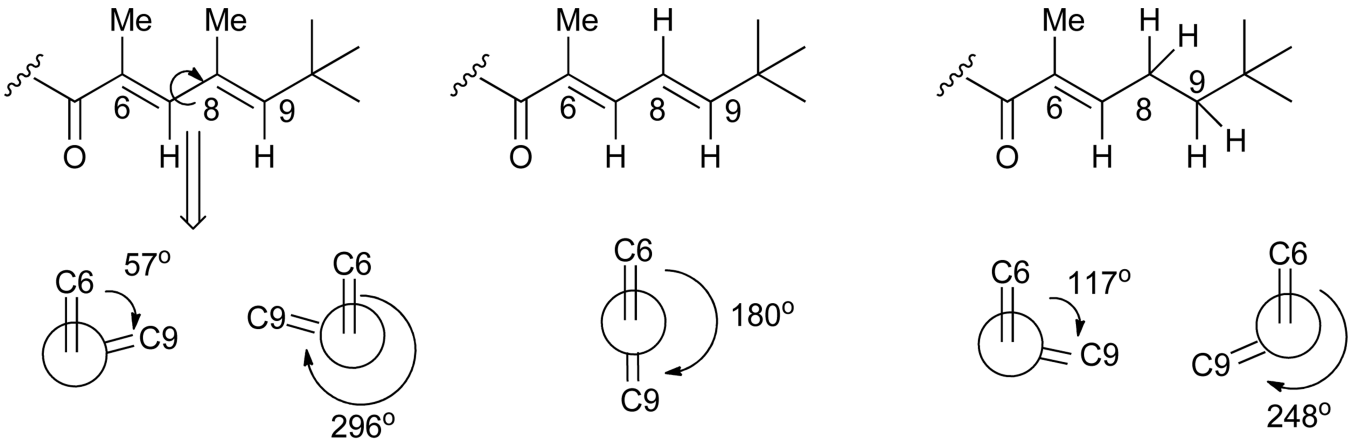

**Scheme 1.**
Marine-derived compounds that interact with voltage-gated ion channels



**51** ALP4A; R = OH
**52** ALP4B; R = *O*Benzyl

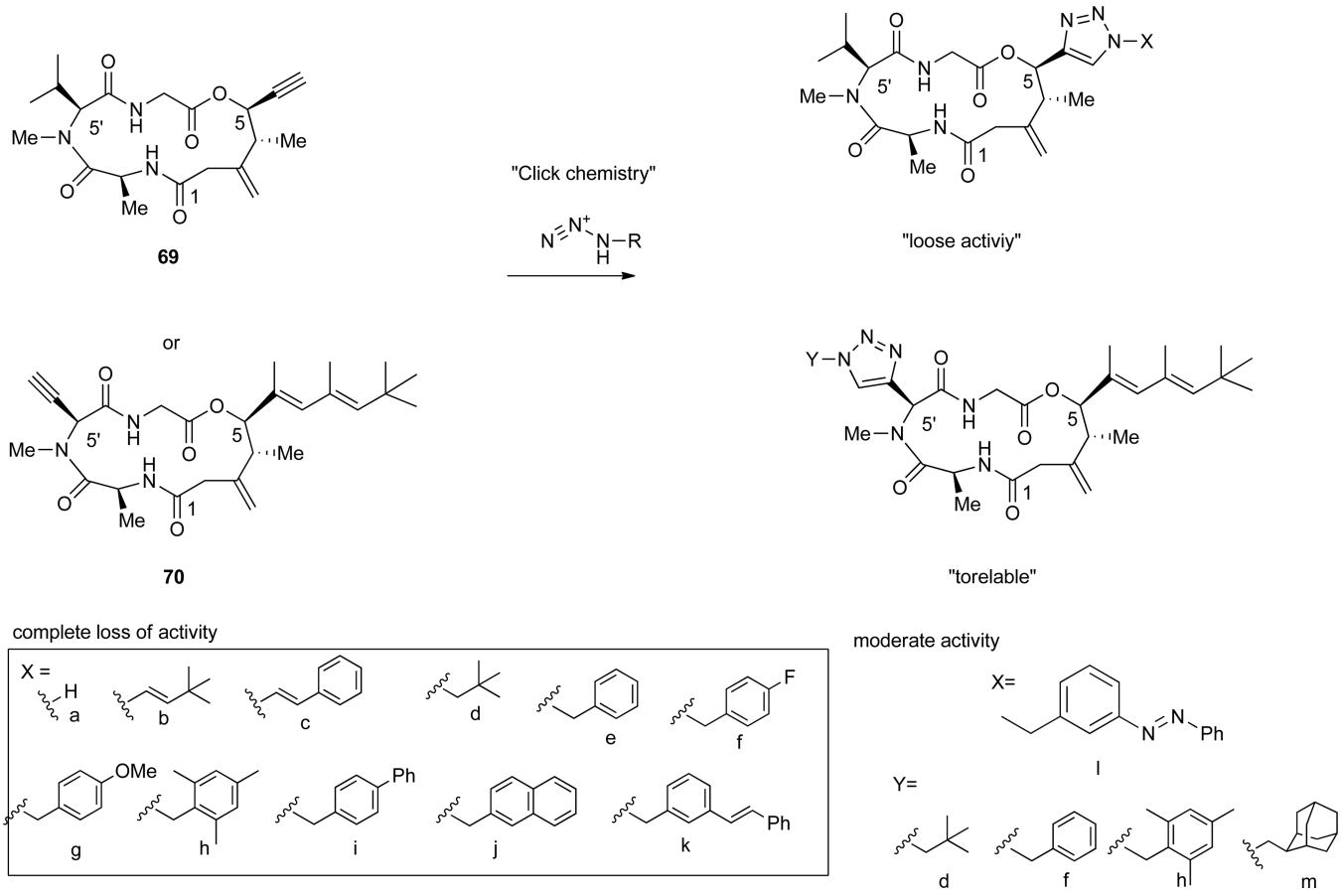



**Scheme 2.**

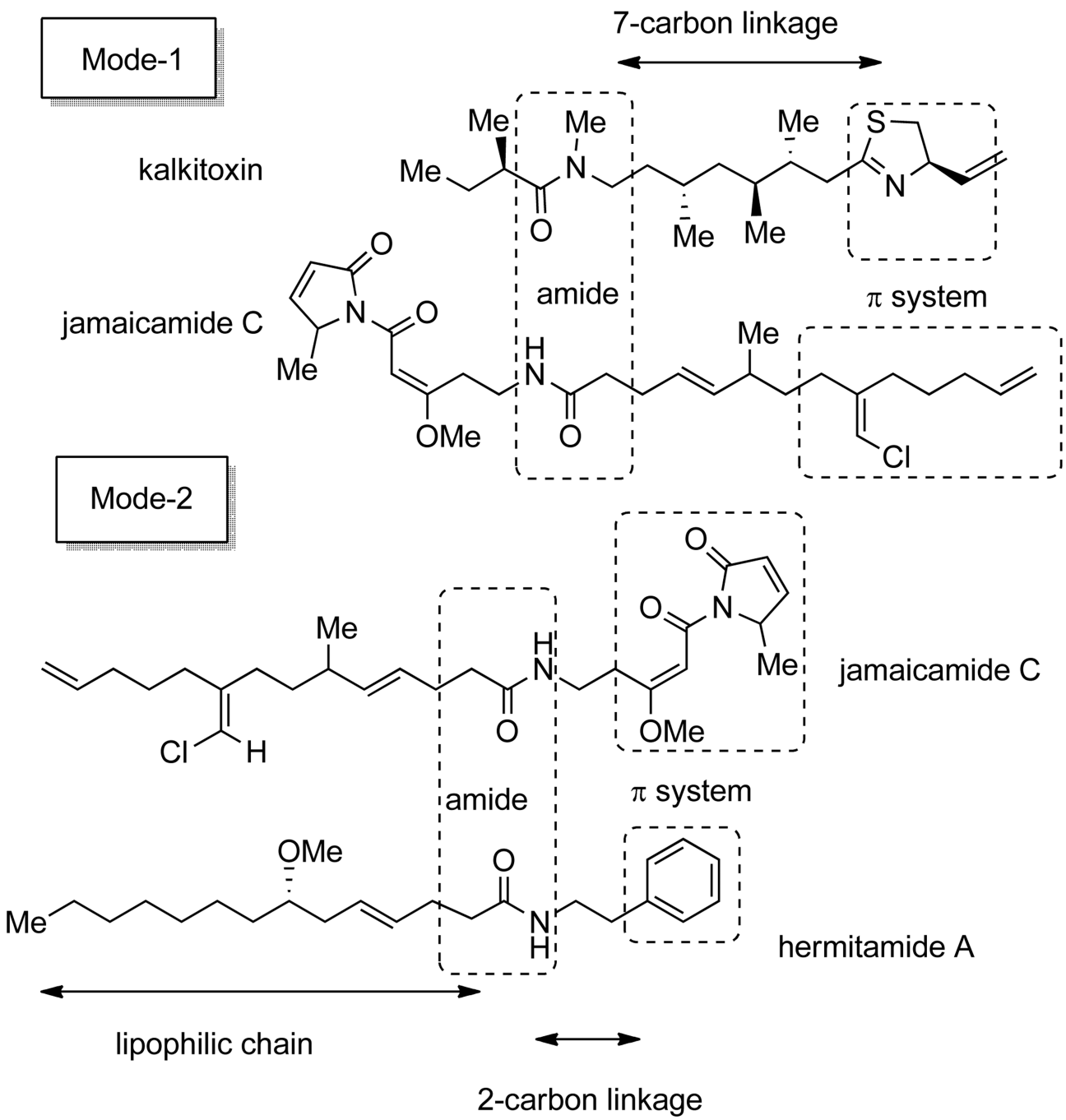



**65** **67** **68**

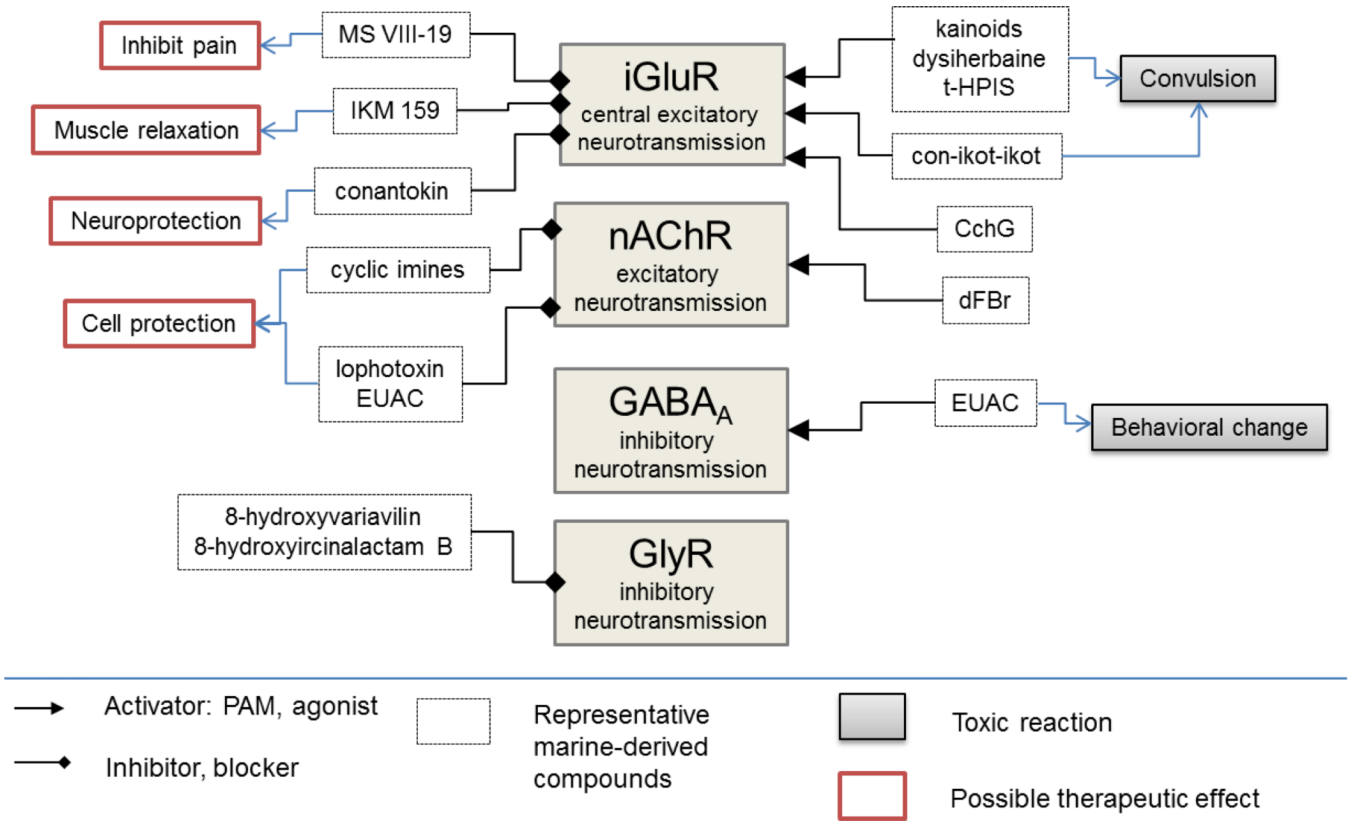
**Scheme 3.**



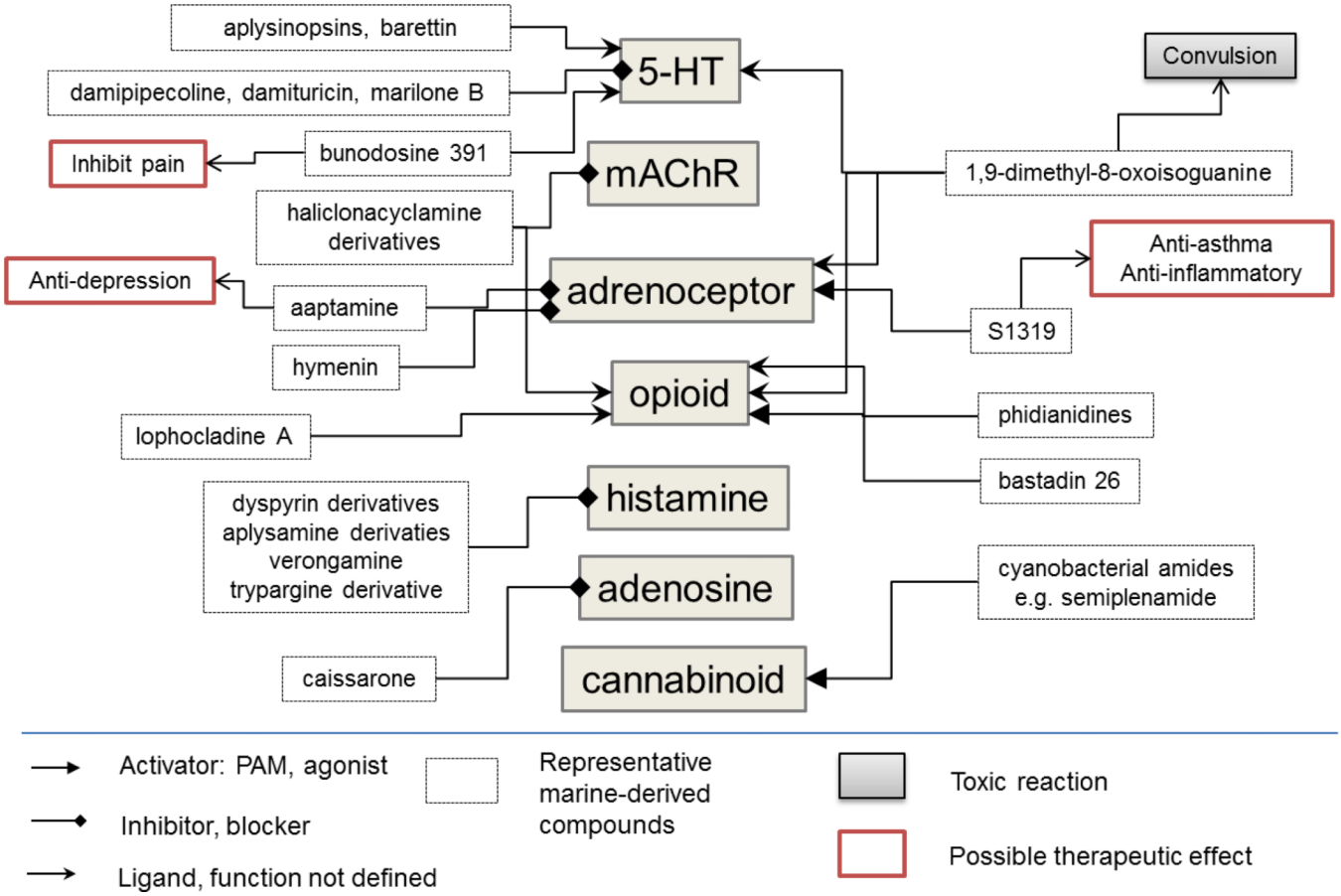

**Scheme 4.**



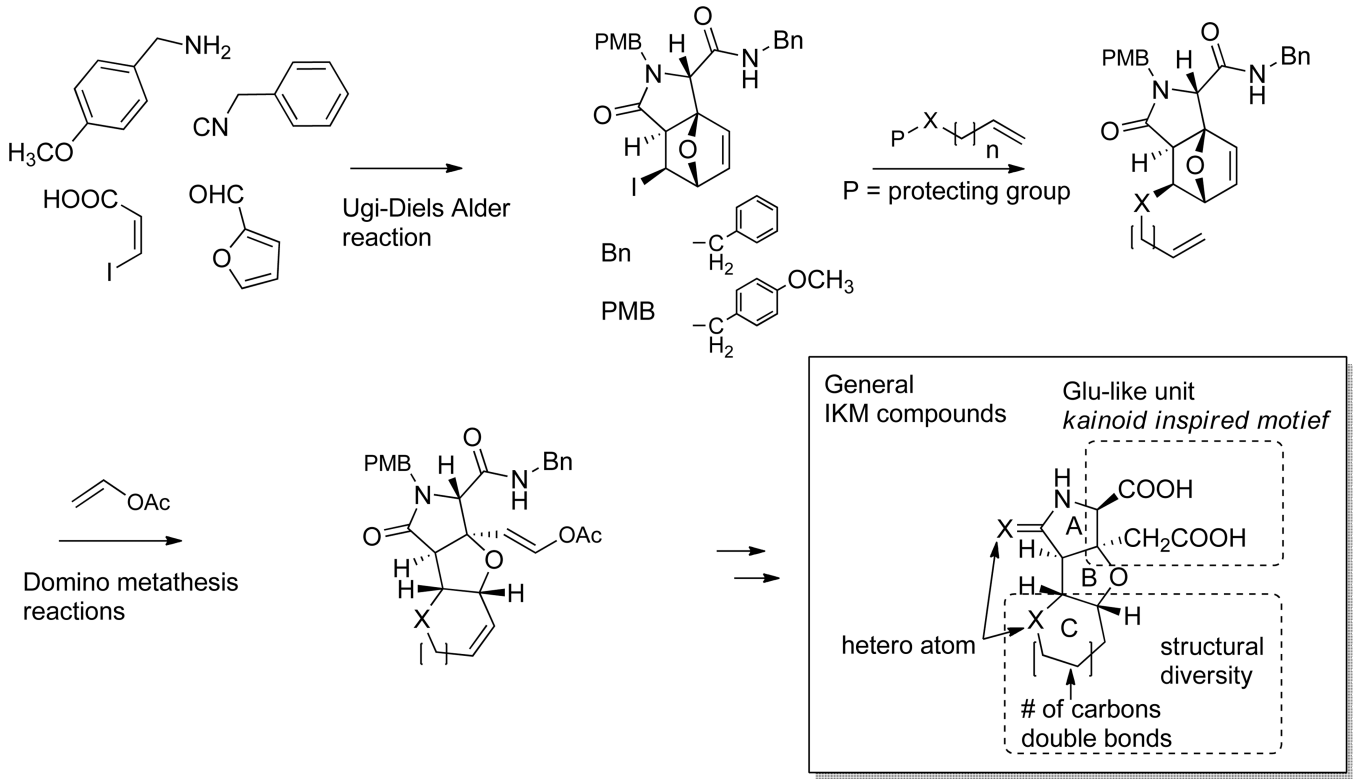

**Scheme 5.**



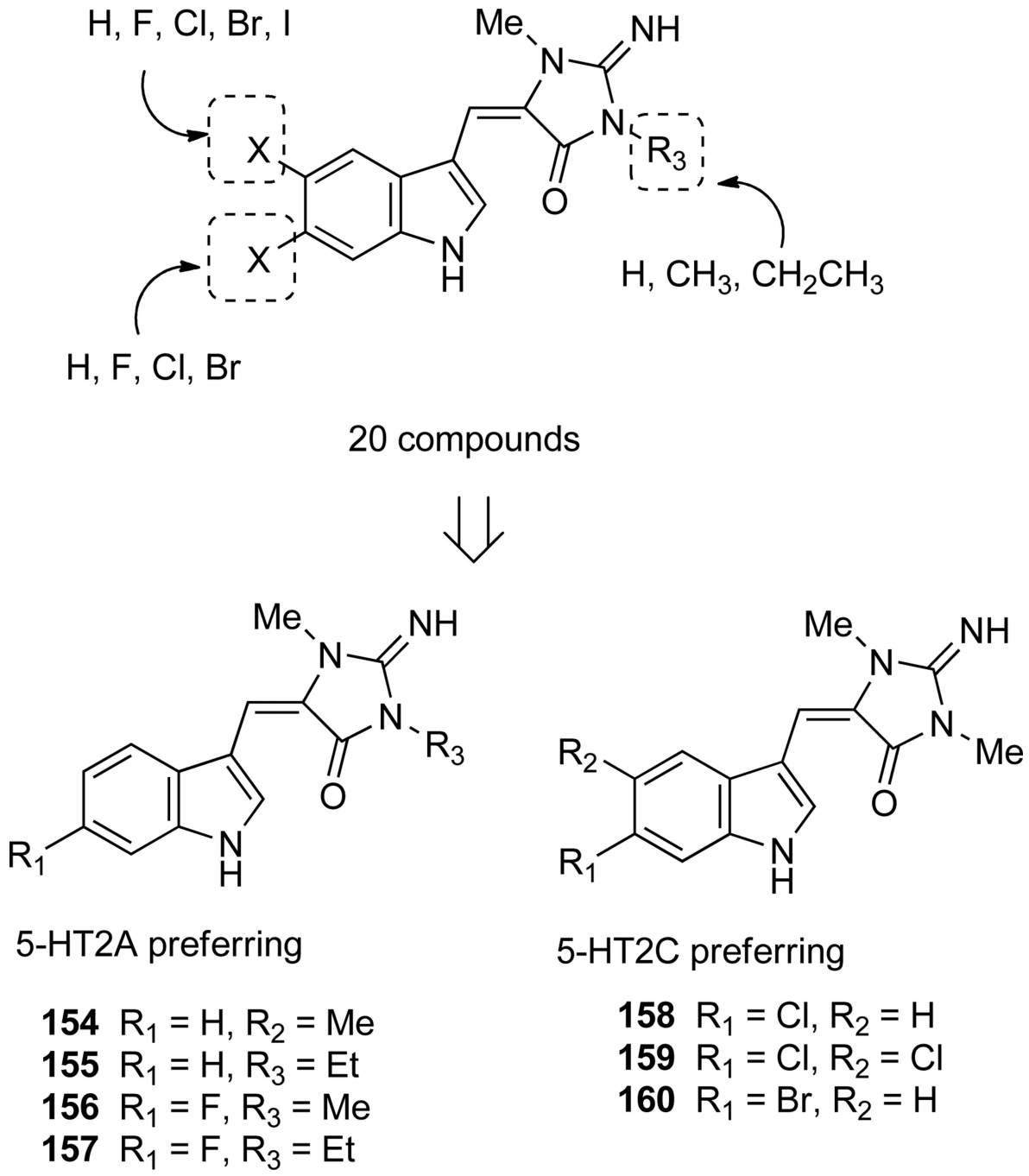

**Scheme 6.**
Marine-derived compounds and their target ligand-gated ion channels



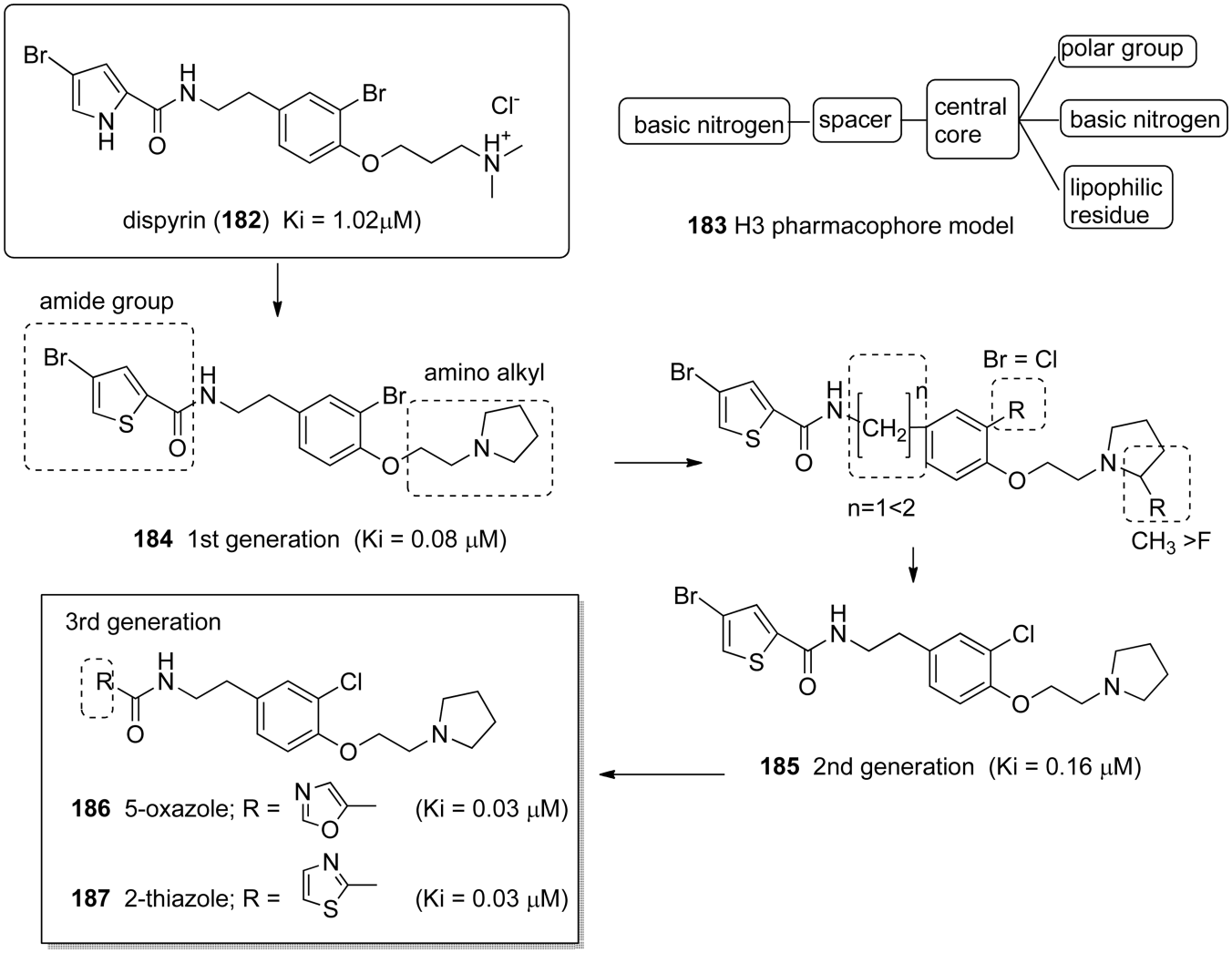

**Scheme 7.**
Marine-derived compounds and their target representative GPCRs




**Scheme 8.**




**Scheme 9.**




**Scheme 10.**