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Recent heterocyclic compounds from marine invertebrates: Structure and synthesis*

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Abstract: A large variety of unique heterocyclic natural marine products, without terrestrial counterparts, have been isolated from marine invertebrates, mainly sponges, ascidians, and soft corals. Many of these compounds display interesting biological activity. In this review, we report our recent studies on nitrogen-containing heterocyclic compounds ("alkaloids"), as well as some containing sulfur and oxygen, which have been isolated from Red Sea and Indo-Pacific organisms, and discuss progress on the synthesis of these natural products and structural analogs.

Keywords: marine natural compounds; heterocycles; NMR; structures; synthesis.

INTRODUCTION

Marine invertebrates are the source of many novel, natural products [1,2], some without terrestrial counterparts or analogy. More than 18 000 compounds appear in the 2006 Marinlit database [3]. While in the 1960s and 1970s, because of the applied extraction techniques, the majority of the isolated compounds were isoprenoids and polyketides, N-atom-containing compounds ("alkaloids"), isolated mainly from sponges and ascidians, only became more common in later years. The latter group includes many novel bioactive heterocycles with no terrestrial counterparts. Representative new heterocycles, isolated by us from Red Sea and Indo-Pacific sponges, tunicates, and a few soft corals, are shown in Fig. 1. All depicted new compounds exhibit unique structures, some of which display interesting bioactivity, for example, the antiviral activity of ptilomycalin A [4], the actin-binding activity of the latrunculins [5], and the cytotoxicity of the pyridoacridines, eilatin and norsegoline [6]. The interesting activity of the latter group has triggered the synthesis of several of these compounds and their analogs. In addition to N- and S-atom-containing compounds, there are also O-atom-containing ones. Structures of heterocycles, isolated by us in recent years, follow.

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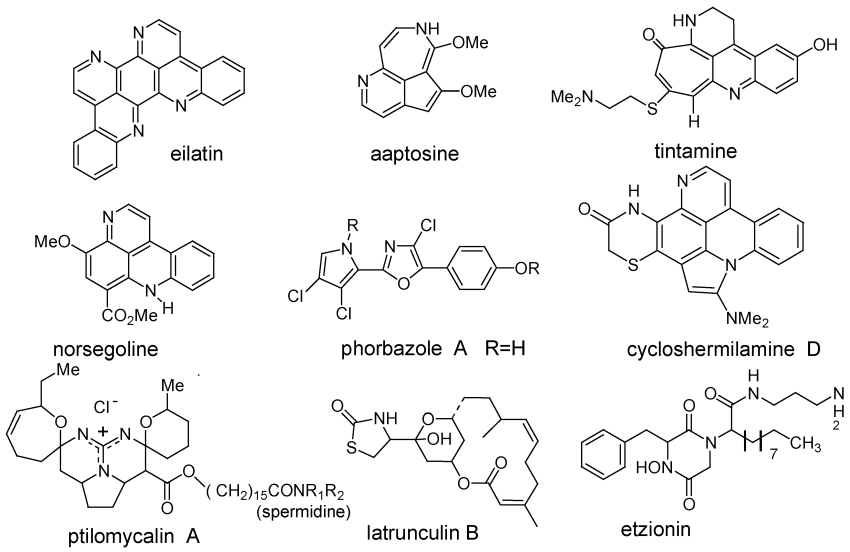

Fig. 1 A variety of unique heterocyclic systems.

RESULTS AND DISCUSSION

Rearranged spongian diterpenes are well-known secondary metabolites characterized by a carbobicyclic portion (the "left" part) and a second, highly oxygenated half (the "right" half of the molecule) [7]. The carbobicyclic part derives from rings AB of the spongian skeleton and shows up in different bicyclo[5.3.0], [4.4.0] or [4.3.0]decane or nonane ring systems, or even tricyclic ring systems (as in cheloviolin) [8]. The second, "right" half of the molecules, obtained from rings CD of the spongian skeleton, appears as a five- or six-membered lactone, a variety of dioxabicyclo[3.3.0] or [3.2.1]lactol-lactones or even dioxatricyclo[5.2.1.$0^{4.10}$] systems [7]. The parent compounds in this family are structurally related to the sponge-derived aplyroseols [9].

Omriolides, sinularectin, kitungolids, and likonids

New omriolide diterpenes (Fig. 2) were isolated from the Kenyan sponge *Dictyodendrilla off. retiara* collected at the Shimoni channel, Wasini Island [10]. Notable for the structure determination of the omriolides as well as other oxygenated diterpenes, are, in addition to the chemical shifts, the $J_{C(O)H}$ coupling constants. Characteristic one-bond coupling constants for a variety of oxymethine groups are depicted in Fig. 3 [11]. Thus, the $^1J_{CH}$ coupling constants of the various methinoxy groups of omriolide A were very helpful in its structure elucidation. The 125 Hz value for alkane-sp^3 carbon atoms increases with oxygen substitution and a decrease in the ring size. Characteristic values for alcoholic, lactone, methinoxy α- to carbonyl, anomeric, and epoxy methinoxy groups are around 135, 140, 155, 170, and 180 Hz, respectively. Values of 155, 141, 197, and 135 Hz were measured for omriolide A's C-5, C-10, C-11, and C-13, respectively. The epoxy 197 Hz ^1J-value, in agreement with the value measured for 2,3-epoxybutanolide (J = 202 and 198 Hz), is very large. The various increments affecting the ^1J-values are additive and strongly influenced by ring strain.

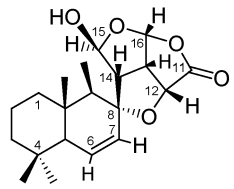

Fig. 2 Omriolide A.

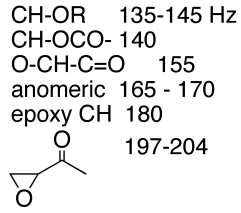

Fig. 3 One-bond C(O)H-coupling constants.

The all cis 2,5,9-trioxatricyclo[5.2.1.$0^{4,10}$]decan-3-one ring system of omriolide A forms a unique unprecedented "cap", only known as part of more complex polycyclic cage compounds [12]. The all cis stereochemistry of the "cap" became clear from H–H coupling constants and NOEs. The other omriolide A (the "left" part) was determined according to NMR data to be an 8,8-disubstituted-4,4,9,10-tetramethyl-6-octalin. This is the first reported Δ^6 octalin among the rearranged spongian diterpenes.

Another compound exemplifying the use of $^1J_{C(0)H}$ values for structure elucidation is sinularectin isolated from *Sinularia erecta* [11].

Kitungolides A–C, isolated from a Kenyan soft coral, are of a unique heterotricyclic skeleton consisting of an unprecedented hexahydrocoumarin system fused to a 3,4-dihydropyrane ring [13] that is characteristic of the *Xenia* xenicins [14] (Fig. 4). Similarity in the relative stereochemisty of part of the structure of the kitungolide xenicins and xeniolides suggest that the kitungolides are biogenetically related to the *Xenia* diterpenoids.

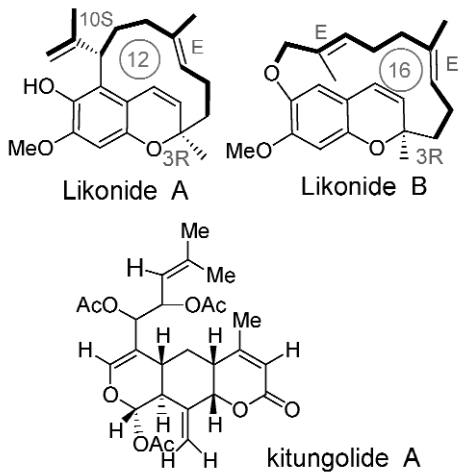

Fig. 4 Structure of kitungolide A and likonides A and B.

The likonides A and B, collected off Likoni in Kenya from a *Hyatella* sp. sponge, are another example of oxa-heterocycles belonging biogenetically to C_{15} + C_6 metabolites of mixed biogenesis (Fig. 4) [15]. C_{15} + C_6 Metabolides are well known from algae and especially from sponges [1–3]. More than 100 sesquiterpene quinones or quinols from marine sources have been reported [1–3]. Many of them exhibit a variety of promising biological activities such as cytotoxic, antiviral, antimicrobial, and immunomodulatory effects. Well-known examples are avarone, avarol [16], and ilimaquinone [17]. Likonides A and B (Fig. 4) are new ansa compounds. Likonide A can be considered a 1-oxa-[9]metacyclophane, [10]orthocyclophane, or 2,5-(4-methyl-7-isopropenyl-hept-3-enylene)-chromene, and likonide B can be looked upon as a 1-oxa-[13]metacyclophane, 1,12-dioxa-[12]paracyclophane, or 2,6-(2,6-dimethylnona-2,6-dienylene)-chromene [15].

From the biogenetic point of view, it was interesting to find sesquiterpene quinones, like avarone and other analogs, which appear in minute amounts, with the new ansa compounds in the same sponge. The latter's coexistence demonstrates different ways by which farnesyl and activated (to alkylation) hydroxylated benzenes can interact. Likonides A and B, although resembling the *Aplidium* tunicate longithorones and the like [1–3], are of different ring sizes and assembly being the first examples of these ansa compounds from sponges.

Barrenazines A and B

Two new cytotoxic alkaloids having an unprecedented 1,3,4,6,8,9-hexahydrodipyridino-[3,4-*b*:3',4'-e]pyrazine skeleton, barrenazines A and B, were isolated from an unidentified Madagascar tunicate [18] (Fig. 5). The tunicate, orange balls, was collected at Barren Island northwest of Madagascar (18°, 17', 260" south; 43°, 41', 200" east) at a depth of 18 m.

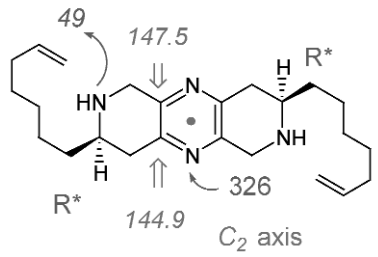

Fig. 5 Barrenazines A and B (saturated side chains).

Pyrazine ring systems are not widely distributed in marine metabolites and are mostly restricted to a few distinct types of structures. The most prevalent of these are the bis-steroidal pyrazines comprised of the anticancer cephalostatins isolated from the African marine worm *Cephalodiscus gilchristi* [19] and the cytotoxic ritterazines isolated from the tunicate *Ritterella tokioka* [20]. Other occurrences of the pyrazine ring include the antibiotic compounds, pelagionmicins, isolated from the marine bacteria *Pelagiobacte variabil*s [21], in which the pyrazine is part of a phenazine system; palythazin and isopalythazine which both consist of a hexahydrodipyranopyrazine, isolated from the zoanthid *Palythoa tuberculosa* [22]; as well as clavulazine, a trihydropyranopyrazine metabolite isolated from the soft coral *Clavulardia viridis* [23]. Other examples of compounds containing a pyrazine nucleus include botryllazines A and B that were isolated from the red ascidian *Botryllus leachi* [24].

The structures of the barrenazines were elucidated by interpretation of MS, COSY, HMQC, HMBC, NOESY, and ^{15}N HMBC data (Fig. 5). Two diastereomers, both chemically and magnetically symmetric, agreed with the C and H NMR data. ^{15}N HMBC correlations exhibiting a single class of both pyrazine and piperidine N-atoms, together with the observed optical activity of the barrenazines, established the R^*, R^* relative configuration of the molecules [18].

Violatinctamine

From the Kenyan tunicate, *Cystodytes cf. violatinctus* collected off Likoni at a depth of 16–17 m, we have isolated a new alkaloid designated violatinctamine possessing a unique heterocyclic skeleton, which combines a benzothiazole unit and a dihydroisoquinoline unit (Fig. 6) [25]. Violatinctamine was isolated from the tunicate along with four other known metabolites, styelsamine C [26], shermilamine D [27], 1,1-dimethyl-5,6-dihydroxyindolinium [28], and 3-(2-aminoethyl)phenol, which has not previously been reported from marine sources and is assumed to be a precursor of violatinctamin, vide infra.

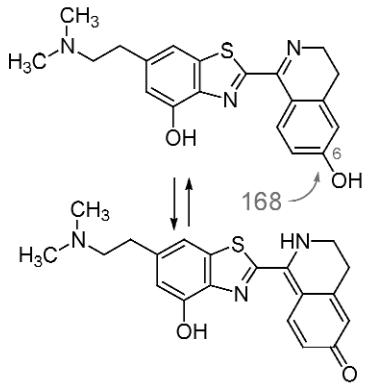

Fig. 6 Violatinctamine.

Tunicates are a rich source of diverse metabolites derived from amino acids. The amino acid DOPA [2-amino-3-(3',4'-dihydroxyphenyl)propionic acid] [29] appears to be especially important in the metabolism of these organisms and serves inter alia as a precursor of isoquinoline alkaloids like the well-known lamellarin metabolites. In contrast, benzothiazoles rarely occur as natural products.

The structure of violatinctamine, $C_{20}H_{21}O_2N_3S$, was established by comprehensive interpretation of the HR MS, 1D and 2D NMR data, as well as chemical transformation. Noteworthy is the chemical shift of C-6 at δ_c 167.6 ppm due to fast equilibrium between two tautomeric forms (Fig. 6). A biogenetic pathway for violatinctamine starting from 5-*S*-cysteinyl-DOPA was suggested [25].

Benzothiazoles rarely occur as marine natural products [3]. The first benzothiazoles from the marine biosphere were isolated from fermentation culture extracts of *Micrococcus* sp., a marine bacterium obtained from the tissues of the sponge *Tedania ignis* [30]. The latter compounds included 2-mercaptobenzothiazole, 2-methylbenzothiazole, 2-hydroxybenzothiazole, and 6-hydroxy-3-methyl-2-benzothiazolone. Another benzothiazole derivative designated S1319 was isolated from *Dysidea* sp. and exhibited bronchodilating activity [31].

Didemnum molle cyclic peptides

Ascidians have also been shown to be a rich source of cyclic peptides. Among the many interesting cyclic peptides from ascidians are the lissoclinamides [32] and prepatellamid A isolated from *Lissoclinum patella* [33] and the tamandarins A and B, which were isolated from an unidentified didemnid ascidian from Brazil [34].

Didemnum molle, a small, 1–5 cm in height, white–greenish, vase-like ascidian, is quite common in deep water of many reefs. This ascidian is green inside due to symbiotic prokaryotic unicellular algae, a symbiosis which might be responsible for the differences of secondary metabolites obtained from animals collected in divergent locations. Australian and Phillipine Indo-Pacific *D. molle* yielded

the cyclic peptides mollamide [35] and cyclodidemnamide [36]. From two localities in the Lagoon of Mayotte, Comore Islands, northwest of Madagascar, and two localities in the Lagoon of Tulear, Madagascar, we have isolated six cyclic hexapeptides; comoramides A and B, mayotamides A and B [36], and didmolamides A and B [35] (Fig 7). Cyclic peptides have been isolated from a number of marine taxa and many show remarkably high levels of cytotoxicity. The *D. molle* compounds exhibit mild cytotoxicity against several tumor cells. All six peptides incorporate in their structure five-membered heterocycles, namely, thiazole, thiazoline, and/or methyloxazoline rings, all in the L-configuration as determined by Marfey's method [37].

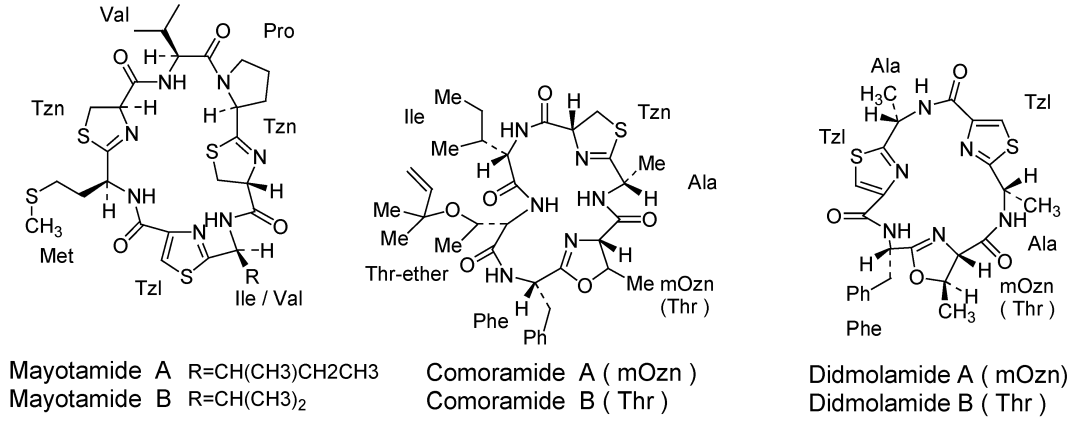

Fig. 7 Six cyclic peptides from *Didemnum molle*.

Aplyzanzine A and itampolins A and B

Bromotyrosine-derived compounds are well known from algae and Verongid sponges. Of these compounds, only a few still possess the carboxylic group of the dibromotyrosine precursor while the majority, more than 80, are decarboxylated [3]. The latter contain compounds incorporating one to three dibromotyramine moieties. Both aplyzanzine [38] and the itampolins [39] (Fig. 8) contain a combination of both the tyrosine and tyramine precursors.

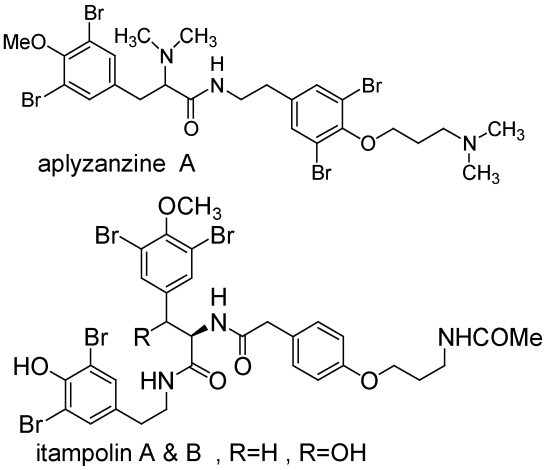

Fig. 8 Dibromotyrosine derivatives.

From *Aplysina* sp., (order Verongida, family Aplysinidae) collected near the coast of Zanzibar, west Indo-Pacific, we have isolated aplyzanzine A [38], while from the Madagascar *Iotrochota purpurea* (order Poecilosclerida) sponge, we have isolated itampolins A and B [39]. The structure of these brominated compounds was established by MS and NMR spectra (Fig. 8).

Polycitons, polycitrins, and prepolycitrins

Two ascidians, *Polycitor* sp. and *Polycitor africanos*, collected in Sodwana Bay, South Africa [40] and in the Lagoon of Tulear, Madagascar (or Lagoon of Mayotte, Comoro Islands), respectively, afforded five correlated highly brominated phenolic compounds, namely, polycitones A and B, polycitrins A and B, and prepolycitrin A (Fig. 9). The structures of the five were elucidated by MS and NMR data and for polycitrin A also confirmed by X-ray diffraction analysis. The latter compounds represent novel marine alkaloids with unprecedented skeleta. Close in structure are the lamellarins [42] and lukianol [43]. A possible common biogenetic relationship can be suggested. Interestingly, prepolycitrin A [41], assumed to be the natural precursor of polycitrin A, was also an intermediate in its synthesis [44]. Polyciton A exhibits potent inhibitory capacity of both RNA- and DNA-directed polymerases, and the mode and mechanism of inhibition of the DNA-polymerase activity associated with HIV-1 reverse transcriptase was studied [45].

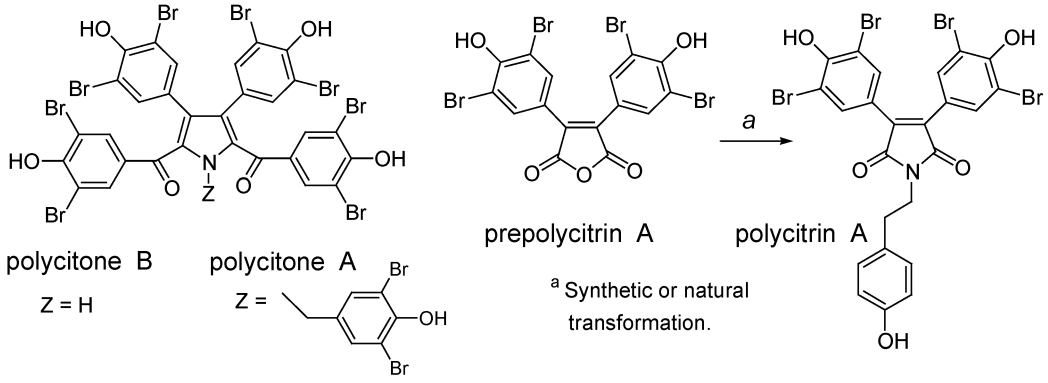

Fig. 9 Polybrominated alkaloids from *Polycitor* spp.

Haliclorensin and halitulin

An extract of the Indo-Pacific *Haliclona tulearensis* sponge (family Chalinidae, genus *Haliclona*) collected in Sodwana Bay, Durban, South Africa was found to be cytotoxic against P-388 mouse leukemia cells (IC50 = 0.1 mg/ml). Many interesting and bioactive N-containing metabolites were isolated from the genus *Haliclona*. Intensive chromatographic work resulted in two novel alkaloids, haliclorensin and halitulin (Fig. 10) [46,47]. The latter was responsible for the cytotoxicity. Comprehensive MS and mainly NMR work suggested for haliclorensin the *N*-(γ-propylamino)azacyclodecane structure. A structure that was eventually revised to methyl-1,5-diazacyclotetradecane following synthetic work, during which the suggested and revised structures were prepared (Fig. 10) [48]. The strong N–HN hydrogen bond most likely led to the wrong interpretation of the NMR data, suggesting the aza 10-membered rather than diaza 14-membered ring. Misleading also was the existence of the latter azecine ring in halitulin.

Coexistence of 10- and 14-membered rings in the sponge suggested a common 3-methyl-1,11-diazabicyclo[8,4,0]tetradecane precursor that was also synthesized. Indeed, high-performance liquid chromatography (HPLC) suggested the latter bicyclic compound existed in the extract.

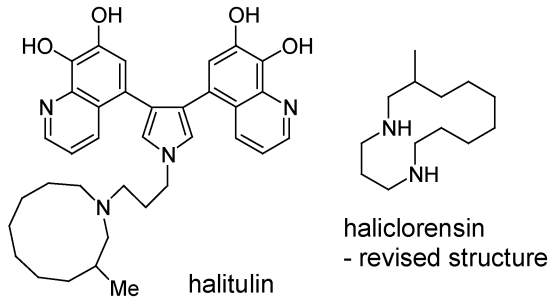

Fig. 10 Halitulin and haliclorensin.

The structure of halitulin, as far as the aromatic part is concerned, resembles the polycitone and the lamellarins. However, the two phenyl-C_3 units of the latter's biogenic precursors, are suggested in this case, to be replaced by two 5-substituted quinoline-C_3 compounds which will subsequently undergo decarboxylation. There does not appear to be a simple way to suggest a biogenesis for the latter C_9N–C_3 unit. The haliclorensin biogenesis, as suggested earlier for the above compounds, seems to be similar to the one suggested for manzamine C [49].

Halitulin was found to have cytotoxic activity. The activity, IC_{50} values, against cell cultures of P-388 murine leukemia, A-549 human lung carcinoma, HT-29 human colon carcinoma, and MEL-28 human melanoma is 0.025, 0.012, 0.012, and 0.025 μg/ml, respectively. The cytotoxicity of halitulin triggered its synthesis, a synthesis that confirmed its structure, with the azacyclodecane ring [50].

Netamines

The first report of a complex sponge-derived polycyclic guanidine alkaloid was on the pentacyclic ptilomycalin A (Fig. 1) [4], which we isolated from both a Caribbean sample of *Ptilocaulis spiculifer* and a Red Sea collection of *Hemimycale* sp. [4]. Shortly thereafter, the structure of hydroxylated ptilomycalins designated crambescidins 800, 816, 830, and 844, isolated from the Mediterranean sponge *Crambe crambe* and other sponges, were reported [51]. Pentacyclic guanidine alkaloids have also been reported from Brazilian specimens of *Monanchora unguiculata* [51] and Caribbean collection of *Batzella* sp. [52]. Tricyclic guanidine alkaloids bearing the (5,6,8b)-triazaperhydroacenaphthylene skeleton (ptilocaulin derivatives and mirabilins) were reported from *Batzella* spp. [52,53], *P. spiculifer*, and, curiously, from two New Caledonian starfish (probably due to sequestration of these alkaloids from prey sponges) [54]. Due to similar morphological characters and secondary metabolites, it is suggested that the above-mentioned sponges should eventually be united in one sponge genus which, for priority reasons, has to be *Crambe*.

Many of the cyclic guanidine derivatives show noteworthy biological activities (e.g., HIV gp120-human CD4-binding inhibition, $p56^{lck}$-CD4 dissociation induction, Ca^{2+} channel blocker activities, cytotoxicity and antifungal and antimicrobial activities) [54].

From three collections of the Madagascar sponge, *Biemna laboutei*, we have isolated seven new tricyclic guanidine alkaloids designated netamines A–G (Fig. 11), all seven possess the (5,6,8*b*)triazaperhydroacenaphthylene, ptilocaulin or mirabilin like, skeleton [55]. The structures of the netamines were elucidated mainly by 2D NMR including ^{15}NH HMBC spectra. The netamines are presumably derived via intramolecular cyclization of guanidine-substituted polyketides (C_{12} to C_{18}). Several of the compounds are mildly cytotoxic against three human tumor cells.

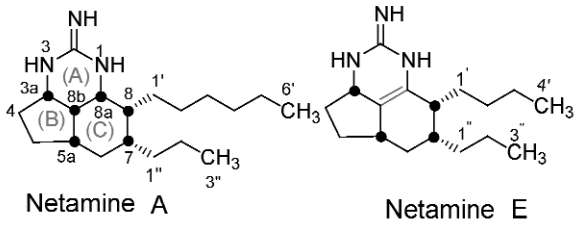

Fig. 11 Netamines A and E: Tricyclic guanidine alkaloids.

Asmarines

Specimens of the *Raspailia* sp. sponge collected from the Red Sea, Dahalk archipelago, and from the Indo-Pacific, Kenya, Shimoni Channel, and Madagascar, Nosy Be, were found to contain combined adenine-diterpene secondary metabolites designated asmarines as well as four diterpenes (Fig. 12) [56,57]. One of the diterpenes, chelodane, is a precursor of several asmarines [58]. Thus far, 11 asmarines, A–K, were identified with differing levels of cytotoxicity.

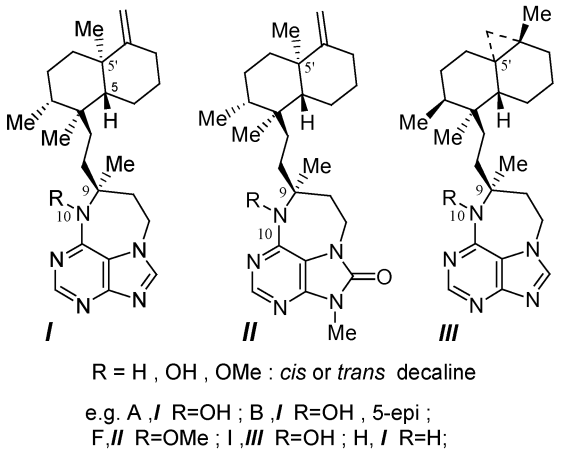

Fig. 12 Eleven asmarines from sponge *Raspailia* sp.

The content of the various asmarines varies in the different collections. While in the Red Sea sponge, the major asmarine was A [56], in the Kenya sponge, the major compound was asmarine F [57]. The asmarines possess an unprecedented tricyclic diazepinopurine ring system carrying in most asmarines a hydroxylamine functionality that is essential for the bioactivity. The unique structure of asmarines A and B, and their selective cytotoxicity, encouraged us to develop a synthetic mode for the preparation of asmarine analogs. The asmarines are structurally unusual compounds of mixed, adenine-diterpenoid, biogenesis. All embody a hydroxylaminopurine moiety attached to the diterpene skeleton of chelodane (or closely related diterpenes), together comprising the 9,9-disubstituted 10-hydroxy-tetrahydrodiazepinopurine (10-hydroxy-THDAP) system.

The selective cytotoxicity among the asmarines, asmarine B being the most active, indicates the importance of the lipophilic decalin portion for the activity. The bioactivity of the asmarines triggered the synthesis of asmarine analogs with a variety of substituents on C-9. It was also found that the *N*-OH group is essential for activity; i.e., asmarine H (Fig. 12, R = H) is devoid of activity.

A methodology for the preparation of asmarine analogs, with the unique tetrahydro[1,4]diazepino[1,2,3-*g,h*]purine (THDAP) ring system, has been developed [59–61]. Three cyclization methods were applied for the preparation of the 9,9-disubstituted 10-hydroxy-THDAP system, namely,

aminomercurization, iodocyclization, and acid-catalyzed cyclization. The DMPM group of the NOH functionality and cyanoethyl group of the N-9 atom were found to be the most suitable protecting groups [59–61]. The structure of all compounds was determined mainly from NMR measurements including ^{15}N chemical shifts obtained from ^{15}NH HMBC spectra [61]. The end products are at least one order of magnitude less active than the natural product asmarine B.

Comprehensive NMR interpretation (chemical shifts and mainly HSQC and HMBC experiments) enabled us to distinguish between alternative synthetic modes of cyclizations and derivatizations of the purine system. Assembled δ ^{15}N values from the synthesized molecules give a good database for structural characterization within the THDAP system, namely, differing between sp^2 and sp^3 N-atoms, tautomeric forms, and influences of substituents [60,61].

Following developing the methodology of the synthesis of 9,9-disubstituted THDAPs, we have synthesized the 9-methyl-9-adamantyl analog of asmarine A (Fig. 13).

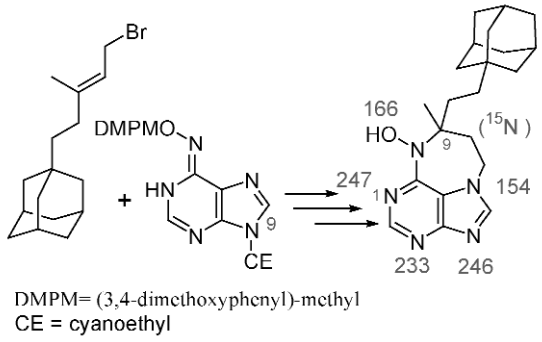

Fig. 13 Synthesis of adamantyl asmarine. DMPM = (3,4-dimethoxyphenyl)-methyl; CE = cyanoethyl.

Callyspongin A, cyclic endiamino and thioenamine peptides

From the southern Kenya (Shimoni Reef) sponge *Callyspongia abnormis*, we isolated a new cyclic peptide callynormine A of molecular weight 1187 ($C_{61}H_{93}N_{11}O_{13}$).

Nonribosomal cyclic peptides and depsipeptides are a large group of compounds known from microorganisms (first reported from *Fusarium streptomyces*) as well as marine organisms [62]. In fact, it is suggested that marine peptides also originate from symbiotic microorganisms living within the marine invertebrates. These nonribosomal peptides are a large family of natural products, with a considerable variety of unusual amino acids and other building blocks that include many medicinally important compounds. A recent review by Matsunaga and Fusetani [62] arranged these 190 (at 2003) marine peptides according to structural classes based on the IUPAC-IUB (biochemical nomenclature). Accordingly, callynormine A belongs to the heterodectic cyclic peptides.

Intensive NMR work on callynormine A pointed to a cyclic peptide comprised of 11 amino acids, and X-ray diffraction analysis established the complete structure of callynormine A, which turned out to be of a new type designated endiamino peptides possessing an α-amido-β-aminoacrylamide cyclization functionality, instead of the lactone group in depsipeptides (Fig. 14) [63].

Callynormine A comprises a cyclic peptide [Ile(1) to FGly (8)] with a linear tripeptide side chain [Pro(9)-Phe-LeuOH(11)] joined together by the naturally unprecedented α-amido-β-aminoacrylamide functional group. Evidently, the latter functionality is formed by condensation of the aldehyde of FG1y, obtained from oxidation of Ser or Cys, and the N-terminal amino acid amino group [Ile(1)], to give the conjugated acrylamide functionality, via a carbinol amine, directly or through isomerization of the Schiff base (Fig. 14) [63]. α-Formyl glycine (FGly) has recently been reported for both eukaryotic and prokaryotic sulfatases located within the catalytic site of the enzyme. It was shown that the FGly is gen-

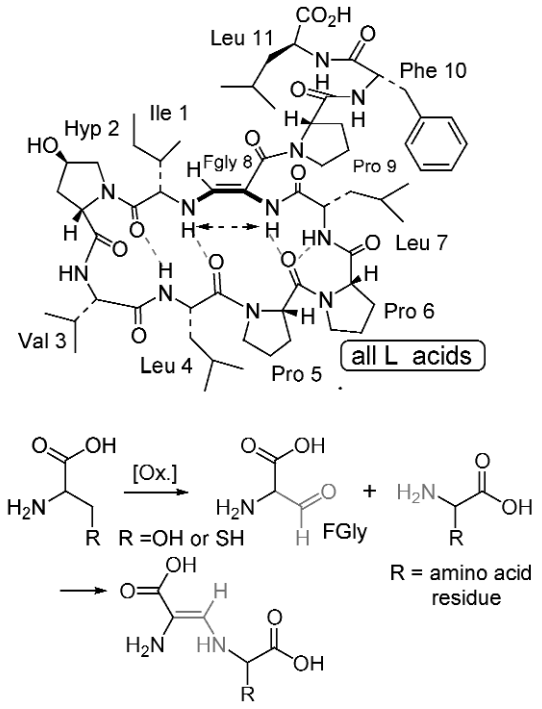

Fig. 14 Callynormine A and suggested biogenesis.

erated by oxidation of cysteine or serine and furthermore that the FGly hydrate is covalently sulfated or covalently phosphorylated during catalysis [63].

To the best of our knowledge, there are no reports of the highly likely internal (in the catalytic site of closing loops of the enzyme or peptide) or external bonds of the active FGly aldehyde group to amines (e.g., of Lys or Orn) to afford imines or the acrylamide moiety as in callynormine A (Fig. 15).

The endiamino group is of special interest for the synthesis of biomimetic cyclic peptides, as it is expected to introduce additional rigidity into their structure.

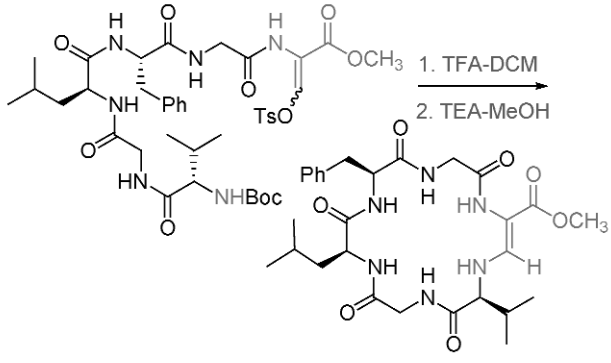

Fig. 15 Synthesis of cyclic endiamino peptides.

We recently [64] achieved the first synthesis of several cyclic endiamino peptides, including 2-(1*H*)-pyrazinone, which formally is the smallest member of this new group. We also demonstrated the preparation of endiamino-containing building blocks for biomimetic peptides. FGly is very unstable,

however, its enol-tosylate derivative [65] prepared from serine, is stable and acts with amino groups as an aldehyde to produce the α-amino-β-aminoacrylamide functionality.

Cyclic peptides and depsipeptides have been characterized in many organisms and show a wide spectrum of biological activities. Hence, the cyclic peptides are promising lead compounds for potential drugs. The special quality of these cyclic peptides stems, inter alia, from the reduction in conformational freedom brought about by the cyclization, which is expected to result in higher receptor binding affinities. Replacing an amide bond, or the ester group of depsipeptides, with the endiamino functionality is anticipated to introduce additional rigidity in the cyclic endiamino peptides.

The macrocyclization step, which is known to be the yield-determining step for cyclic peptides, can, in the case of the cyclic endiamino peptides, be achieved by the formation of either an amide or the endiamino functionality. Both routes were achieved [64]. It could also be expected that the tendency to cyclize will change with the size of the ring, as is known for cyclic peptides.

As FGly, by itself, is very unstable, we chose, for cyclizations, the masked enol-tosylate derivative of FGly [65] methyl ester that reacts with amino groups. Thus, for example, a hexapeptide could be cyclized to the desired cyclic endiamino hexapeptide (Fig. 15).

The endiamino group introduces a β-turn in the molecule (Figs. 15–17). The β-turn is one of the important secondary structure elements in proteins. There is a great deal of interest in the synthesis of small molecules that mimic a β-turn structure, for example mimicking or interfering with protein–protein interactions or binding with biological targets.

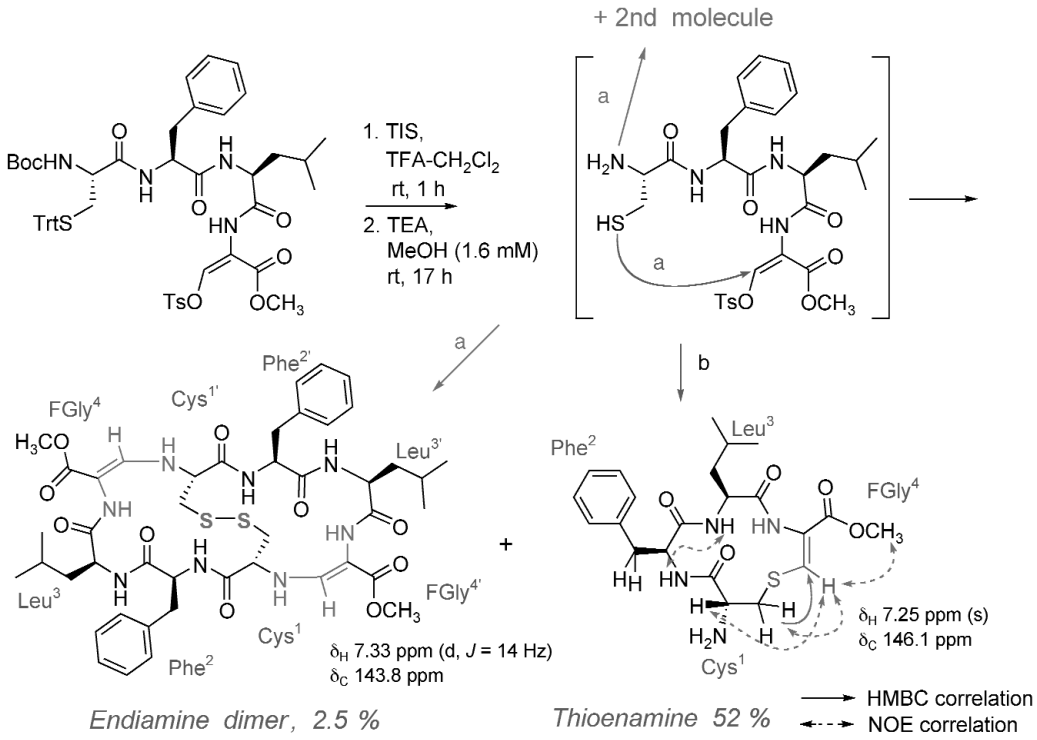

Fig. 16 Synthesis of cyclic endiamino and thioamino peptides.

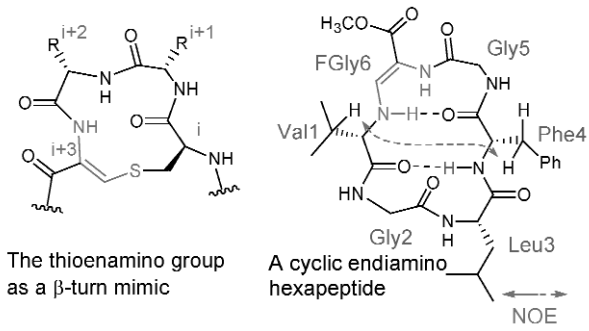

Fig. 17 β-turn mimics.

The α-amino-β-aminoacrylamide functionality, the endiamino group, represents a new class of β-turn mimic, as seen in the cyclic endiamino hexapeptide (Fig. 15). The β-turn, in the latter compound, as depicted in Fig. 17, was confirmed by the temperature coefficients of the NH groups, i.e., small coefficients were measured for the Val and Phe NH-protons and further supported by a NOESY cross-peak between Val Hβ and Phe Hβ.

Triggered by the above synthesis of cyclic endiamino peptides, we synthesized another class of cyclic peptides, possessing the α-amino-β-thioacrylamide functionality, designated cyclic thioenamino peptides [66], expected to reverse the direction of the peptide chain, i.e., become a β-turn (Fig. 17). The latter new class of cyclic peptides was prepared by cyclization of an appropriate peptide via the nucleophilic attack of a Cys-SH group on the enoltosylate of FGly, a reaction first tested by the reaction of Boc-FGly(OTs)-OMe (prepared from protected serine) with Boc-L-Cys-OEt. Indeed, this reaction yielded the expected dipeptide linked by the thioenamine group. Not only did the thiol substitute the OTs group, but this substitution even exceeded the reaction with primary amino groups [66].

After verifying the reaction of the enol-tosylate of FGly with the thiol group, L-Cys-L-Phe-L-Leu-FGly(OTs)-OMe was prepared to afford the desired thioenamino peptide in 52 % yield accompanied by a minute (2.5 %) amount of the dimeric cyclic endiamino peptide (Fig. 16). This reaction again confirmed the superiority of the SH group over the NH_2 group in the reaction with the enol-tosylate group.

The thioenamino group, supported by the low-temperature coefficients of NH groups, ca. 1 ppb/K, is indeed another β-turn mimic.

All the above-mentioned heterocyclic compounds clearly show the great potential of marine natural heterocycles as possible drugs and drug leads. The novel unique structures triggered the synthesis of quite a few of these compounds.

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