Nat. Prod. Rep., 2005, **22**, 15-61

Marine natural products

John W. Blunt,[*a] **Brent R. Copp**,[b] **Murray H. G. Munro**,[a] **Peter T. Northcote**[c] **and Michèle R. Prinsep**[d]

[a] *Department of Chemistry, University of Canterbury, Christchurch, New Zealand. E-mail: john.blunt@canterbury.ac.nz*

[b] *Department of Chemistry, University of Auckland, Auckland, New Zealand*

[c] *School of Chemical and Physical Sciences, Victoria University of Wellington, Wellington, New Zealand*

[d] *Department of Chemistry, University of Waikato, Hamilton, New Zealand*

Received (in Cambridge, UK) 10th November 2004

First published as an Advance Article on the web 19th January 2005

This review covers the literature published in 2003 for marine natural products, with 619 citations (413 for the period January to December 2003) referring to compounds isolated from marine microorganisms and phytoplankton, green algae, brown algae, red algae, sponges, coelenterates, bryozoans, molluscs, tunicates and echinoderms. The emphasis is on new compounds (656 for 2003), together with their relevant biological activities, source organisms and country of origin. Biosynthetic studies or syntheses that lead to the revision of structures or stereochemistries have been included (78), including any first total syntheses of a marine natural product.

Covering: 2003. Previous review: *Nat. Prod. Rep.*, 2004, **21**, 1.

1 Introduction

This review is of the literature for 2003 and describes 656 new compounds from 243 articles. These numbers are comparable to those of the past few years. We show structures only for new compounds, or for previously reported compounds where there has been a structural revision or a newly established stereochemistry. Previously reported compounds for which first syntheses or new bioactivities are described, are referenced, but separate structures are generally not shown.

2 Reviews

A number of reviews have dealt with classes of compounds: "Sterols in microorganisms",[1] "Bioactive macrolides and polyketides from marine dinoflagellates",[2] "Chemistry and biology of new marine alkaloids from the indole and annelated indole series",[3] "Brominated diterpenes of marine origin",[4] "Sulfur-containing natural products from marine invertebrates",[5] "The cerebrosides",[6] "Nonribosomal peptides from marine sponges",[7] "Bioactive polyhydroxysterols and their sapogenins from marine organisms",[8] "Sphingolipids from marine organisms",[9] "A review of research on the cyanotoxin cylindrospermopsin",[10] and "The manzamine alkaloids".[11]

Reviews that focus on bioactivity and development as drug candidates include: "Natural products as sources of new drugs over the period 1981-2002",[12] "Marine natural products as prototype agrochemical agents",[13] "Detection of pharmacologically active natural products using ecology",[14] "Marine pharmacology in 2000: antitumour and cytotoxic compounds",[15] "Bioactive natural products from marine invertebrates and associated fungi",[16] "Marine pyridoacridine alkaloids and synthetic analogues as antitumour agents",[17] "Drugs from the deep: marine natural products as drug candidates",[18] "Marine-derived anticancer agents in clinical trials",[19] "Marine natural products as lead anti-HIV agents",[20] "Natural products with anti-HIV activity from marine organisms",[21] "Algae, a possible source for new drugs in the treatment of HIV and other viral diseases",[22] and "Antimycobacterial natural products".[23]

Chemical synthesis is the theme of a number of reviews covering specific types of compounds through to more generally applicable methodology: "Total synthesis of (+)-macrosphelides A, C, E, F and G based on enzymatic function",[24] "The total syntheses of phorboxazoles-new classes in natural product synthesis",[25] "The development of a practical total synthesis of discodermolide",[26] "Synthesis of the pyrrole-imidazole alkaloids",[27] "Chemistry of bis-spiroacetal systems: natural products, synthesis and stereochemistry",[28] "Approaches towards the

synthesis of cephalostatins, ritterazines and saponins from *Ornithogalum saundersiae*",[29] "New and old challenges in total synthesis. From concept to practise"[30] and "Microtubule-stabilizing marine metabolite laulimalide and its derivatives: synthetic approaches and antitumour activity".[31]

Other more general reviews include: "Molecular biodiversity. Case study: Porifera (sponges)",[32] "Microalgal metabolites",[33] "Enhancing marine natural product structural diversity and bioactivity through semisynthesis and biocatalysis",[34] and "Marine natural products".[35] References to other reviews are more appropriately placed in the following sections. The Marinlit database[36] continues to be updated and has again been used as the basis for the preparation of this present review.

3 Marine micoorganisms and phytoplankton

Probably the most important paper on marine microorganisms in 2003 was the first report on chemistry from the new obligate marine actinomycete taxon *Salinospora*.[37] In excess of 2,500 strains from this taxon have now been isolated and the potent proteasome inhibitor salinosporamide A **1** was isolated from a culture of a *Salinospora* sp. originating from a heat-treated marine sediment sample from the Bahamas. The structure of salinosporamide A, including the absolute stereochemistry, was deduced through spectral and X-ray analyses. Salinosporamide A displayed potent and selective *in vitro* cytotoxicity against cell lines in the NCI panel. Salinosporamide A also exhibited highly potent inhibition of the proteasomal chymotrypsin-like proteolytic activity of purified 20S proteasome. The unique functionalisation of the core-fused γ-lactam-β-lactone bicyclic ring structure of salinosporamide A **1** appears to contribute to its potency. The thiazolyl peptide antibiotics, nocathiacins I–III **2**–**4**, have been isolated from the culture broth of *Nocardia* sp. (source not given).[38] The nocathiacins exhibit potent *in vitro* activity against a wide range of bacteria, including several multiple-drug resistant pathogens and also exhibit excellent *in vivo* efficacy in a systemic *Staphylococcus aureus* infection mouse model.[39] However, nocathiacin I **2** was found to

be identical to an antibiotic isolated from *Amycolatopsis* sp.[40] but spectral data and stereochemical details had not been originally reported for this compound. Two cyclic thiopeptides **5** and **6**, obtained from a culture of *Bacillus cereus* isolated from the marine sponge *Halichondria japonica*,[41] exhibited potent antibacterial activities against *Staphylococci* and *Enterococci* sp., and were active against multiple-drug resistant strains.[42] (*6Z*)-Geometry for these compounds was implied by ROESY correlations. ^{1}H-^{15}N HMBC analysis was used in determining the structure of bacillamide **7**, a peptidic metabolite of an algicidal marine *Bacillus* sp. isolated during the termination of a bloom of *Cochlodinium polykrikoides* in Masan Bay, Korea.[43] Bacillamide was shown to be active against a wide range of dinoflagellates and raphidophytes.[44] Culture of an exocellular extract of a *Pseudomonas* sp. associated with *Ircinia muscarum* from the Bay of Naples, Italy gave the cyclotetrapeptide **8**.[45] The amino acid stereochemistry was established by standard methods (for example, chiral HPLC analysis of the acid hydrolysate, Marfey's method etc). Four *Streptomyces* sp. of diverse origin yielded a range of metabolites. Firstly, culture of a *Streptomyces* sp. from a sediment sample from Oahu, Hawaii, yielded the antibacterial and antifungal metabolite bonactin **9**.[46] Parimycin **10**, a new 1,4-anthraquinone, was isolated from a *Streptomycete* sediment sample from Laguna de Terminos, Gulf of Mexico. Parimycin had moderate activity against *B. subtilis*, *Streptomyces viridochromogenes*, *S. aureus* and *E. coli*, in addition to activity against a number of human tumour cell lines.[47] A *Streptomyces* sp. cultured from an unidentified Mexican marine invertebrate yielded the cytotoxic indoles **11–13** which had moderate activity against a panel of 14 tumour cell lines.[48] Finally, the anthracycline komodoquinone A **14** and the aglycone komodoquinone B **15** were isolated from a culture of a *Streptomyces* sp. isolated from marine sediment off Komodo Island, Indonesia. Komodoquinone A displayed dose-dependent neuritogenic activity against the neuroblastoma cell line Neuro 2A.[49] A culture broth of an ATCC strain of the marine gliding bacterium *Saprospira grandis* yielded four neoverrucosane diterpenoids, **16–19**. The relative and absolute stereochemistries of **16** were determined by standard methods[50] (for example, X-ray analysis, NOESY and ROESY NMR experiments, the modified Mosher method, chiral

HPLC, comparison of circular dichroism (CD) or other optical data against standards or model compounds etc). The marine myxobacterium *Haliangium ochraceum*,[51] originally *H. luteum,* yielded several new isomers of the polyene antifungal antibiotic haliangicin.[52,53] These are *cis*-haliangicin **20** and haliangicins B–D **21**–**23**, geometrical isomers of the polyene and epoxide moieties. The stereochemistry of the epoxide in the known haliangicin **24**[53] has been determined as *trans*. All of the haliangicins were active against the phytopathogenic fungus *Phytophthora capsici*.[54] Two siderophores, pseudoalterobactins A **25** and B **26**, were isolated from a culture of the bacterium *Pseudoalteromonas* sp. isolated from the marine sponge *Cinachyrella australiensis* collected in Palau. Both compounds displayed strong binding affinity for the ferric ion in the chrome azurol S (CAS) assay.[55] The bactericidal compound **27**, obtained from a culture of a new marine species *Pseudoalteromonas phenolica* sp. nov., isolated from seawater collected off Ogasawara Island Japan,[56] had potent activity against methicillin-resistant *S. aureus* (MRSA) and was also strongly active against *Enterococcus serolicida*, *E. faecium* and *E. faecalis*.[57] This compound is available commercially, but this is the first reported isolation as a natural product. Cultures of two marine bacterial strains isolated from cultures of *Pecten maximus* larvae in Galicia, Spain, led to the first reported isolation, as natural products, of a series of DD-diketopiperazines **28**–**31** and established them as potent inhibitors of the pathogenic marine bacterium *Vibrio anguillarum*. The structures were confirmed by synthesis.[58] A cytotoxic polycyclic xanthone **32** has been isolated from the culture broth of the actinomycete *Actinomadura* sp.[59] The phenoxazin-3-one antibiotics, chandrananimycins A–C **33**–**35**, were also isolated from a culture of *Actinomadura* sp. derived from sediment from Jiaozhou Bay, China. Chandrananimycins A–C were active against human tumour cell lines while **35** exhibited potent activity against the fungus *Mucor meihei* and the bacteria *B. subtilis* and *E. coli*, and antialgal activity against the microalgae, *Chlorella vulgaris*, *C. sorokiniana* and *Scenedesmus suspicatus*.[60] The fungus *Aspergillus tamarii* was isolated from driftwood collected in Okinawa and cultured to yield a pentacyclic oxindole alkaloid, speradine A **36**. The structure and relative stereochemistry of **36** were confirmed by X-ray analysis. Speradine A

exhibited inhibitory activity against histone deacetylase and antibacterial activity against *Micrococcus luteus*.[61] A culture of the fungus *Aspergillus ostianus,* isolated from an unidentified marine sponge from Pohnpei, was the source of three chlorinated antibiotics, the asperlactone derivatives **37** and **38** and the aspyrone derivative **39**. Compound **37** was the most potent, inhibiting the growth of the marine bacterium *Ruegeria atlantica* and that of *E. coli* and *S. aureus* to a lesser extent.[62] Five novel depsipeptides, aspergillicins A–E **40**–**44**, were obtained from a culture of *Aspergillus carneus* collected from estuarine sediment in Tasmania, Australia. The amino acid sequences were assigned by MS^n ion-trap ESI mass spectrometry and stereochemistry was assigned by standard methodology. The aspergillicins exhibited modest cytotoxicity against *Haemonchus contortus*.[63] A chiral dipyrrolobenzoquinone derivative, terreusinone **45**, has been obtained from a cultured strain of the marine algicolous fungus *Aspergillus terreus* isolated from the surface of the marine red alga *Halymenia acuminata* collected from Bijin Island, South Korea. The absolute stereochemistry was determined by a combination of Horeau's method and quantum chemistry calculations. Terreusinone has intense UV-A absorbtivity.[64] A culture of *Penicillium brocae* from the tissue of the Fijian sponge *Zyzzya* sp. was the source of three novel cytotoxic polyketides, brocaenols A–C **46**–**48**. These contain the unusual enolised oxepine lactone ring system. Structure determination included an INADEQUATE experiment on brocaenol A. The absolute stereochemistry of **46** was established by a standard method and extended to **47** and **48** by comparison of CD and optical rotation data.[65] Brocaenols A–C displayed moderate activity against the HCT-116 cell line. Structures for brocaenols B and C were reversed in the original paper, but a correction has since been published.[66] The steroids isocyclocitrinol A **49** and 22-acetylisocyclocitrinol A **50** were extracted from a salt water culture of *Penicillium citrinum* isolated from *Axinella* sp. collected in Papua New Guinea.[67] The absolute stereochemistry of **50** was established by standard methods, extended to **49**, leading to the structural revision of cyclocitrinol, previously isolated from a terrestrial *P. citrinum*,[68] to **51**. Compounds **49** and **50** displayed weak antibacterial activity against *Staphylococcus epidermidis* and *Enterococcus durans*. The halovirs A–

E **52**–**56**, lipophilic linear peptides, are potent *in vitro* inhibitors of *Herpes simplex* viruses 1 and 2 and were isolated from a *Scytalidium sp.* sourced from the Caribbean seagrass *Halodule wrightii*.[69] Two cyclic heptapeptides, scytalidamides A **57** and B **58**, have been isolated from the culture broth of another *Scytalidium* sp. derived from the surface of the green alga *Halimeda* sp. collected off the Bahamas. The absolute configurations were confirmed by standard methods including CD measurements. Both scytalidamides displayed moderate cytotoxicity to the HCT-116 cell line *in vitro*.[70] Trichodermamides A **59** and B **60**, modified dipeptides, were isolated from cultures of *Trichoderma virens* isolated from the ascidian *Didemnum molle* and from the surface of a green alga of the genus *Halimeda*, both collected in Papua New Guinea. The ascidian-derived culture contained trichodermamide A with traces of trichodermamide B while a greater quantity of trichodermamide B was isolated from the algal-derived strain. The structure of **59** was assigned by X-ray diffraction while the absolute stereochemistry was determined using the modified Mosher method. Trichodermamide B displayed significant *in vitro* cytotoxicity against HCT-116 and moderate antimicrobial activity against amphoterocin-resistant *C. albicans*, MRSA and vancomycin-resistant *E. faecium*.[71] Trichodermamide A is closely related to penicillazine, reported from a marine-derived *Penicillium* sp.[72] The reported structures differ only in the translocation of ester and amide bonds, but spectral data comparison suggests that these compounds may be identical. Two macrolides, modiolides A **61** and B **62**, and a linear pentaketide modiolin **63** have been isolated from the culture of *Paraphaeosphaeria* sp. separated from the marine horse mussel *Modiolus auriculatus*, collected in Okinawa. The absolute stereochemistry of **61** was determined by the exciton chirality method[73] using a *p*-methoxycinnamoyl ester, while the absolute stereochemistry of **63** was defined by the modified Mosher method. Modiolides A and B exhibited modest antibacterial activity against *Micrococcus luteus* and *Neurospora crassa*.[74] A culture of the marine fungus *Wardomyces anomalus*, isolated from the green alga *Enteromorpha* sp. collected in the Baltic Sea, yielded two xanthone derivatives, anomalin A **64** and B **65**.[75] The anomalins were only weakly antimicrobial, but anomalin A possessed significant tyrosine kinase p56^{lck} enzyme

inhibitor activity and antioxidative properties. Remisporine A **66**, a novel cyclopentachromenone, isolated from a culture of the marine fungus *Remispora maritima* from an unspecified wood source, is unstable under normal conditions and autocatalytically dimerises stereospecifically, via a Diels-Alder reaction, to remosporine B.[76] A new anthraquinone, evariquinone **67**, and the new prenylxanthone isoemericellin **68** were isolated from a culture of the fungus *Emericella variecolor* derived from the marine sponge *Haliclona valliculata* collected at Elba, Italy. The known C-glycosidic depside stromemycin **69**[77] was also isolated, and the previously undescribed double bond configurations established. Evariquinone **67** showed antiproliferative activity towards KB and NCI-H460 cells.[78] A culture of a marine strain of the fungus *Epicoccum purpurascens*, isolated from inner tissue of the jellyfish *Aurelia aurita* collected from the North Sea, Germany, yielded the tetramic acid derivative epicoccamide **70**. Attempts to resolve the stereochemistry at C-4 and C-8 by comparision of CD spectra with those of similar compounds were ambiguous.[79] Two highly oxygenated polyketides, phomoxin **71** and phomoxide **72**, are metabolites from a *Phoma* sp. isolated from a microbial mat collected from a Bahaman hypersaline pond, along with eupenoxide **73**, a previously synthesised, but unpublished fungal metabolite.[80] An actinomycete, *Pseudonocardia* sp., isolated from littoral sediment from Mauritius, Indian Ocean, was the source of a new phenazine derivative, phenazostatin D **74** which is the *meso*- form of the known antibiotic phenazostatin B.[81,82] Investigations of a collection of *Lyngbya majuscula* from Puerto Rico resulted in the isolation of three new metabolites, a quinoline alkaloid, **75**, malyngamide T **76** and a tryptophan derivative **77**.[83] Geometries for the vinyl chloride functionalities of **75** and **76** were established as (*E*) by ^{1}H-^{13}C coupling constant measurement from HSQMBC NMR experiments.[84] Six cyclic depsipeptides, guineamides A–F **78**–**83**, were isolated from a collection of *Lyngbya majuscula* collected from Papua New Guinea. Absolute stereochemistries for most of the amino acids were determined by standard methods. Guineamides B and C were moderately cytotoxic to a mouse neuroblastoma cell line.[85] *L. majuscula* from Papua New Guinea was the source of the novel cyclic dodecapeptide wewakazole **84** which contains an unprecedented number of five-membered

heterocyclic rings (six). Due to extensive signal overlap the structural assignment required multiple NMR and MS/MS experiments. The absolute stereochemistry was determined by standard methods.[86] *L. majuscula* from the southern Kenyan Coast was the source of the cyclic depsipeptide homodolastatin 16 **85**. The absolute stereochemistries of most of the amino acids in homodolastatin 16 were determined by standard methods. Homodolastatin 16 **85** displayed moderate activity against oesophageal and cervical cancer cell lines.[87] The cyclic peptide lyngbyastatin 3 **86**, isolated from *L. majuscula* collected from Guam, contains two unusual amino acid units, including 4-amino-2,2-dimethyl-3-oxopentanoic acid (Ibu). The configuration of the Ibu unit was established by acid hydrolysis and comparison with synthetic standards, while the absolute stereochemistries of the remaining residues were determined by standard methods. Lyngbyastatin 3, along with the previously isolated lyngbyastatin 1 and dolastatin 12,[88] are in fact diastereotopic mixtures of both Ibu epimers. Lyngbyastatin 3 **86** exhibited activity against KB and LoVo cell lines *in vitro*, but was poorly tolerated *in vivo* with little antitumour activity.[89] Three new malyngamides, U–W **87**–**89**, have been isolated from *L. majuscula* collected in Papua New Guinea. Partial relative stereochemistries only were determined.[90] A collection of *Lyngbya* sp. from Palau yielded ulongapeptin **90**, a cytotoxic cyclic depsipeptide,[91] while a *Lyngbya* sp. from Guam yielded two new compounds, 15-norlyngbyapeptin A **91** and lyngbyabellin D **92**.[92] The absolute stereochemistries in each case were determined through degradative studies and/or comparison with commercially available and synthetic standards. Ulongapeptin was moderately cytotoxic against KB cells *in vitro*[91] and lyngbyabellin D displayed activity against the KB cell line.[92] Bioassay-guided fractionation of an extract from a *Lyngbya* sp. collected in Palau led to the isolation of palau'amide **93**. Effective use was made of a band-selective HMBC experiment to unambiguously assign ^{13}C NMR signals that were separated by only 0.1 ppm.[93] Except for C-37, relative and absolute configurations were determined by standard methods. By modelling, and from NOE data, C-37 was assigned as having the (*S*) configuration. Palau'amide **93** exhibited potent cytotoxicity against KB cells.[94] Semiplenamides A–G **94**–**100**, anandamide-like fatty acid amides, were isolated from a

collection of *Lyngbya semiplena* collected in Papua New Guinea. The absolute stereochemistries of the amino alcohols in semiplenamides C–E **96**–**98** were elucidated as all L by chemical derivatisation and chiral GCMS methods. All of the semiplenamides displayed toxicity in the brine shrimp assay, while semiplenamides A, B and G exhibited weak affinity for the rat cannabinoid CB1 receptor. Semiplenamide A was also a moderate inhibitor of the anandamide membrane transporter (AMT).[95] Samples of the marine cyanobacterium *Symploca* sp. collected in Palau were the source of the depsipeptides tasipeptins A **101** and B **102**,[96] and a cytotoxic peptide, tasiamide B **103**.[97] The relative and absolute configurations of the tasipeptins and tasiamide B were determined by standard methods except for the configuration of C-28 in tasiamide B. This was tentatively suggested as (*S*) from NMR data analysis.[97] Both tasipeptins exhibited moderate cytotoxicity towards KB cells *in vitro*. Also collected in Palau was an assemblage of a *Symploca* sp. cyanobacterium and an unidentified red alga. From this was isolated the iodinated diterpenes, tasihalides A **104** and B **105**. These compounds possess a novel cage structure with both an oxabicyclic ring system and a *cis*-decalin system. These are the only examples of iodinated diterpenes in nature. Since terpenoids are almost never reported from marine cyanobacteria, but halogenated terpenes are ubiquitous in red algae, the authors speculate that the more likely source of the tasihalides is the alga and not the cyanobacterium.[98] Two polyunsaturated monocyclic triterpenes **106** and **107** have been isolated from a culture of the common marine diatom *Rhizosolenia setigera*. The structure of a related monocyclic sesterterpene **108** was also proposed on the basis of mass spectral comparisons with compounds **106** and **107**.[99] Amphidinolide X **109**[100] and amphidinolide Y **110**[101] are cytotoxic 16- and 17-membered macrodiolides isolated from cultures of the marine dinoflagellate *Amphidinium* sp., originally separated from the inside cells of the marine acoel flatworm *Amphiscolops* sp. collected from Okinawa. Amphidinolide Y exists as a 9:1 equilibrium mixture of the 6-keto- **110** and 6(9)-hemiacetal **111** forms. Both amphidinolides X and Y were moderately cytotoxic against murine lymphoma L1210 and human epidermoid carcinoma KB cells *in vitro*. Feeding experiments with ^{13}C-labelled acetates suggested that

amphidinolide Y might be a precursor of amphidinolide X.[101] A culture of the dinoflagellate *Symbiodinium* sp., a symbiont of the soft coral *Clavularia viridis* collected from Okinawa, yielded two diastereoisomeric norcarotenoids **112** and **113**. Both compounds exhibited moderate growth-inhibitory activity *in vitro* against a range of human cancer cell lines.[102] A culture of the free-living marine dinoflagellate *Symbiodinium* sp. isolated from a tide pool, Coconut Island, Hawaii,[103] yielded the polyhydroxy compound zooxanthellamide A **114**.[104] Cultures of a strain of the dinoflagellate *Prorocentrum lima*[105] afforded okadaic acid methyl ester **115**, norokadanone **116** and an okadaic acid diol ester **117**.[106] Three hydroxybenzoate saxitoxin analogues, GC1–GC3 **118**–**120**, have been isolated from the cultured dinoflagellate *Gymnodinium catenatum* originally isolated from a planktonic bloom in Tasmania. GC1 and GC2 are the epimeric 11-hydroxysulfate derivatives of GC3, the 4-hydroxybenzoate ester derivative of decarbamoylsaxitoxin. Preliminary investigations indicate that the compounds bind to rat brain sodium channels, in keeping with known PSP toxins.[107] Biosynthetic investigations using ^{13}C-labelled precursors of the meroterpenoid neomarinone, originally isolated from culture of an unidentified marine actinomycete from sediment from Batiquitos Lagoon, California,[108] led to the structural revision of neomarinone to **121**.[109] A correction to the text of the article describing the structure and absolute stereochemistry of phormidolide from the marine cyanobacterium *Phormidium* sp.[110] has been published, amending two descriptors [(17*R*,26*R*) to (17*S*,26*S*)].[111] The absolute configuration of the fungal metabolite phomopsidin **122**, derived from a cultured strain of *Phomopsis* sp.,[112] has been determined by the exciton chirality method. Phomopsidin exhibited potent anti-microtubule activity in a microtubule assembly assay utilising purified porcine brain microtubule proteins.[113] A total synthesis of petrobactin, a siderophore isolated from the marine bacterium *Marinobacter hydrocarbonoclasticus* has been completed. Comparison of the ^{1}H NMR spectrum of the synthetic product with literature data for the natural product[114] resulted in a structural revision of petrobactin from 2,3-dihydroxybenzoyl- to 3,4-dihydroxybenzoyl-moieties. This 3,4-dihydroxybenzoyl analogue **123** was also synthesised, giving ^{1}H and ^{13}C NMR spectra that were consistent with those

of the natural product.[115] The first total synthesis of yanucamide A **124**, which was isolated from an assemblage of *L. majuscula* and a *Schizothrix* species,[116] has been achieved via amide and ester coupling methods. The synthesis established the configuration at C-3, originally unassigned due to ambiguity, and revised the configuration at C-22.[117] In synthetic studies towards congeners of phomactin A, total syntheses of structures isomeric to that proposed for the phomactin known as Sch 49028, also isolated from the marine fungus *Phoma* sp.,[118] are described. None of the isomers showed spectral data consistent with those of the natural product so it is proposed that Sch 49028 does not exist and that the NMR spectral data should have been assigned as phomactin A.[119] Other first total syntheses reported include that of (±)-spiroxin C, originally isolated from culture of an unidentified fungal strain from a soft coral from Vancouver Island, Canada.[120] This involved a Suzuki-Miyaura cross-coupling reaction.[121] Apratoxin A, a cyclodepsipeptide from *Lyngbya* sp. collected in both Guam[122] and Palau,[123] has been synthesised.[124] The relative and absolute stereochemistries of amphidinoketide I **125**, originally isolated from the dinoflagellate *Amphidinium* sp. collected in the Virgin Islands,[125] have been determined by total synthesis of all four diastereoisomers. Molecular modelling was used to infer that the natural product is not the thermodynamically preferred diastereoisomer.[126] Two syntheses of the 19-membered macrolide (+)-amphidinolide T1[127,128] have been achieved,[129,130] along with the synthesis[130] of amphidinolides T3[131] and T5.[128] Synthesis of the structurally complex gymnocin-A, a polyether toxin with 14 contiguous rings, from the red tide dinoflagellate *Karenia mikimotoi,*[132] has been accomplished through the use of *B*-alkyl Suzuki-Miyaura coupling-based methodology.[133] Following the first total synthesis of gambierol, a marine polycyclic ether toxin originally isolated from the marine dinoflagellate *Gambierdiscus toxicus*,[134] preliminary structure-activity relationship studies suggest that functionalities in the H ring and unsaturated sidechain are essential for potent murine toxicity.[135] A competitive inhibition assay using the isotopically labelled brevetoxin dihydro BTX-B ([^{3}H]PbTx-3), demonstrated that gambierol[134,136] and gambieric acid-A[137,138] from the dinoflagellate *Gambierdiscus toxicus* inhibit the binding of brevetoxins to site 5 of the voltage-gated sodium

channel of excitable membranes,[139] while effects of brevetoxins produced by the dinoflagellate *Karenia brevis* (formerly *Ptychodiscus breve* and *Gymnodinium breve*)[140] on the murine myeloma cell line SP2/O, a possible model for *in vitro* studies for immune cells, suggest that the brevetoxins have an aberrant effect on cell division.[141]

4 Green algae

As in 2002, very few new compounds have been reported from green algae. The cyclic depsipeptide kahalalide F **126**, originally isolated from both the mollusc *Elysia rufescens* and from the dietary source, the green alga *Bryopsis* sp.,[142] was introduced into Phase I trials by Pharma Mar SA as a lead compound against prostate cancer. The structure of kahalalide F has been corrected based on a series of degradation reactions. The planar structure only was originally defined and the stereochemistry subsequently assigned.[143] The degradation results indicate that the correct structure is a stereoisomer **126**, in which the original assignments for Val-3 and Val-4 have been reversed. This stereochemistry is crucial for the observed bioactivity.[144] Twelve new terpene esters, **127**–**138** have been isolated from the green alga *Caulerpa prolifera* collected from Saronicos Gulf, Greece. The *C. prolifera* extract exhibited moderate to significant activity against three unidentified strains of marine bacteria, in addition to strong growth inhibitory effects on the fouling microalga *Phaeodactylum tricornutum*.[145] The first total synthesis of (±)-dihydrorhipocephalin, a bioactive sesquiterpene isolated from Caribbean marine green algae of the genera *Penicillus* and *Udotea*,[146] has been reported.[147]

5 Brown algae

A wider range of compounds has been reported from brown algae in 2003 than in 2002, when terpenes and steroids were the predominantly reported compound classes. Six tetraprenyltoluquinols

139–**144**, two triprenyltoluquinols **145** and **146** and two tetraprenyltoluquinones **147** and **148** were isolated from the brown alga *Cystoseira crinita* collected from the south coast of Sardinia. All compounds were tested for antioxidative properties in the α,α-diphenyl-β-picrylhydrazyl radical (DPPH) and thiobarbituric acid reactive substances (TBARS) assay systems. Compounds **139**–**146** exhibited potent radical-scavenging effects while **147** and **148** were significantly less active, but still comparable to that of butylated hydroxytoluene (BHT). The radical scavenging activity of compounds **142**, **144** and **148** was further assessed using the Trolox equivalent antioxidant capacity (TEAC) and photochemiluminescence (PCL) assays that confirmed the potent radical scavenging ability. Compounds **139** and **140** were moderately cytotoxic against several carcinoma cell lines.[148] Four hydroazulene diterpenes, dictyone acetate **149**, dictyol F monoacetate **150**, isodictytriol monoacetate **151** and cystoseirol monoacetate **152**, were isolated from the brown alga *Cystoseira myrica* collected in the Gulf of Suez. All four compounds exhibited moderate cytotoxicity against the murine cancer cell line KA3IT, but reduced cytotoxicity against normal NIH3T3 cells.[149] Dictyone acetate along with a pachydictyol A derivative **153** (incorrect structures shown in original reference) were also isolated from the brown alga *Dictyota dichotoma* collected from the Red Sea.[150] *D. dichotoma* from the Arabian Sea was the source of two seco-dolastanes dichotone **154** and dichotodione **155**,[151] two dolastane diterpenoids, dichototetraol **156** and dichopentaol **157**,[152] and the related dichotenones A **158** and B **159**, two enone dolastane diterpenoids.[153] The configurations of **154** and **155** were determined by comparison of spectral data against those of known compounds. The new diterpene dictyocrenulol **160** was isolated from the brown alga *Dictyota crenulata* collected from Easter Island.[154] *Eisenia bicyclis* collected at Johgashima Island, Japan, was the source of nine novel oxylipin compounds **161**–**169**.[155] Five of these, eiseniachlorides A–C **161**–**163** and eiseniaiodides A **164** and B **165**, are ecklonialactone derivatives and two more, **166** and **167**, are cymathere type oxylipins. Stereochemistries of compounds **161**–**165** and **169** were elucidated by NMR analyses, but the relative stereochemistry at C-9 in **168** could not be determined unambiguously. Olefin geometry in **166** was ambiguous, but considered to be (*Z*) on biosynthetic

grounds, and at least one olefin in compound **167** was (*Z*). A 22-membered cyclic lactone, lobophorolide **170**, was isolated from the common brown alga *Lobophora variegata*, collected at several reef locations in the Bahamas and from the Red Sea. The structure was elucidated by spectral data analysis and comparison against data published for tolytoxin[156] and swinholide A.[157,158] It is proposed that lobophorolide and tolytoxin share the same relative configuration at all stereogenic centres in the macrolide portion of the molecule, while a (6*R*) configuration is suggested for both compounds rather than the (6*S*) configuration proposed previously for tolytoxin.[156] The absolute configuration of lobophorolide is proposed to be the same as that of tolytoxin based on optical rotation. Lobophorolide **170** displayed potent and highly specific activity against the marine filamentous fungi *Dendryphiella salina* and *Lindra thalassiae* in addition to potent activity against *C. albicans* and antineoplastic activity against the HCT-116 cell line.[159] The brown alga *Sargassum asperfolium*, collected in the Suez Gulf, was the source of the steroidal metabolite saringosterone **171**,[160] while a novel steroid **172** has been isolated from the brown alga *S. carpophyllum* from the South China Sea.[161] *Ecklonia stolonifera* collected from S. Korea yielded a new phlorotannin, eckstolonol **173**, which possessed potent DPPH radical scavenging activity.[162] Dolabellane 1, originally isolated from the opistobranch mollusc *Dolabella californica*,[163] has been characterised as the major secondary metabolite and active chemical defense agent against herbivores (sea urchins and fish) in the brown alga *Dictyota pfaffi*.[164] (±)-Hedaol B, a bisnorditerpene isolated from the Japanese brown alga *Sargassum* sp.,[165] has been synthesised with geranyl acetone as a starting material and alkylation of silyl cyanide as the key step in the synthesis.[166]

6 Red algae

The genus *Laurencia* continues to be a prolific source of new metabolites. A brominated bisabolene derivative, aldingenin A **174**, was isolated from *Laurencia aldingensis* collected from Brazil.

Biogenetic considerations were of value in the structural assignment.[167] From *L. microcladia* from Elba Island, a calenzanane sesquiterpene, debromoisocalenzanol **175** and an indene-type sesquiterpene **176** were isolated,[168] while four new sesquiterpenes, **177**–**180** including the snyderol derivatives **179** and **180**, have been isolated from *L. obtusa* collected from Bademli, Turkey. Compound **179** was active against D6 and W2 clones of the malaria parasite *Plasmodium falciparum*.[169] *Laurencia perforata,* collected from the Great Barrier Reef, Australia, was the source of the sesquiterpenes 4-hydroxy-1,8-*epi*-isotenerone **181** and two 3-*epi*-perforenone A derivatives, **182** and **183**.[170] A collection of *L. obtusa* from Greece yielded four new brominated diterpenes,[171] prevezols C–E **184**–**186**, and neorogioldiol B **187**, together with the known prevezol B **188**, whose structure has been revised from that reported originally.[172] Prevezol B and neorogioldiol displayed significant cytotoxicity against the human tumour cell lines MCF7, PC3, HeLa, A431 and K562 while prevezol C only exhibited significant cytotoxicity against HeLa and A431 cell lines. Prevezol D was moderately active against all cell lines.[171] Two labdane type brominated diterpenes **189** and **190** have been isolated from *L. obtusa* from Greece. These structures contain unprecedented eight- and seven-membered ether rings respectively.[173] Six new bromophenols, **191**–**196** were isolated from *Rhodomela confervoides* collected from the coast of Qingdao, China.[174] Compounds **193** and **195** may be artifacts of the extraction and isolation processes.[174] Compounds **194** and **195** were also reported in another paper by the same authors, along with the isolation of the known 3-bromo-4,5-dihydroxybenzoic acid methyl ester (but new as a natural product) from the same source (*R. confervoides*).[175] This benzoyl ester has previously been synthesised[176] but the spectral data were not reported. *R. confervoides* from Qingdao was also the source of bromophenols, **197** and **198**. The phenol **198**, which might also be derived from **197** during isolation,[177] exhibited moderate activity against five strains of bacteria.[178] Five monoterpenes **199**–**203** of the ochtodane class have been isolated from the red alga *Portieria hornemanni* (source not given).[179] The marine polyether triterpenoid dehydrothyrsiferol, originally isolated from the red alga *Laurencia pinnatifida*,[180] was shown to induce apoptosis in estrogen-dependent and independent breast cancer cells.[181] Elatol, a

halogenated sesquiterpene alcohol from the red alga *L. elata*[182] inhibited six species of human pathogenic bacteria, with significant antibacterial activities against *Staphylococcus epidermis*, *Klebsiella pneumonia* and *Salmonella* sp.[183] Iso-obtusol from the red alga *Laurencia obtusa*[184,185] exhibited antibacterial activity against four bacterial species with significant activity against *K. pneumonia* and *Salmonella* sp. Further tests indicated that both compounds were bacteriostatic rather than bacteriocidal against the bacteria tested.[183] Glutathione transferase specific activity in *Katharina tunicata* (black chiton) was shown to be affected by the brominated phenol lanosol,[186] which is prevalent among filamentous red algae of the Rhodomelaceae, and frequently consumed by *K. tunicata*.[187] The first asymmetric total syntheses of (+)-3-(*E*)- and (+)-3-(*Z*)-pinnatifidenyne, originally isolated from *Laurencia pinnatifida*,[188,189] have been reported and utilise an "olefin geometry-dependent" internal alkylation to give excellent stereoselectivity.[190] The seven-membered ring ether (+)-neoisoprelaurefucin **204**, originally isolated from *L. nipponica*,[191] has also been synthesised, allowing the assignment of the absolute stereochemistry of the natural product.[192] A nickel-catalysed coupling reaction of an alkynyl enone and an alkenylzirconium were the key steps in the synthesis of isodomoic acid G **205**, originally isolated from the red alga *Chondria armata* from Kyushu Island.[193] The sidechain stereochemistry was established as (5'*R*) by comparison of CD spectra of the natural and synthetic products.[194]

7 Sponges

Sponges continue to be an important source of novel secondary metabolites and a notable growing trend is the characterisation of compounds from bacteria and fungi that have been isolated from sponges. Such compounds have been included in Section 3 of this review. There has also been increased interest in fatty-acid derivatives, many of which have biological activities. An unusual galactofuranosylceramide, ectyoceramide **206**, was isolated from the Bahaman sponge *Ectyoplasia ferox*,[195] while a *Jaspis* species collected in Vanuatu was found to contain the cytotoxic sphingosine

derivatives jaspines A **207** and B **208**.[196] The Korean sponge *Erylus nobilus* was the source of the taurine derivative **209**.[197] Another Korean sponge, a *Stelletta* species, has yielded two cytotoxic compounds, glycerol ether **210**[198] and cyclitol derivative norsarcotride A **211**.[199] Plakevulin A **212**, found to inhibit DNA polymerases α and γ, was isolated from the Okinawan sponge *Plakortis* sp.[200] *Latrunculia corticata*, collected in the Gulf of Aqaba, Israel, was found to contain decalactone glycosides latrunculinoside A **213** and B **214**, which have anti-feedant activity against goldfish.[201] An inhibitor of membrane type 1 matrix metalloproteinase (MT1-MMP), callysponginol sulfate A **215**, was isolated from *Callyspongia truncata* collected in Japan.[202] An undescribed Korean species of *Stelletta* was found to contain cytotoxic acetylenic acids: stellettic acid A **216**, (*Z*)- and (*E*)-stellettic acid B **217** and **218**, and stellettic acid C **219** that exhibited marginal to moderate toxicity to five human tumour cell lines.[203] Interestingly, the same sponge also yielded the glycerol derivatives of **217**, the mildly cytotoxic **220** and **221** (inactive), along with other lysophosphatidylcholines and monoglycerides **222**–**225**.[204] From a seemingly identical *Stelletta* species, collected at a different Korean location, a similar series of acetylenic acids was isolated including **216**, a dimeric anhydride **226** and a desmethoxy analogue **227**; all were mildly cytotoxic to human leukemia cells.[205] The Indonesian sponge *Callyspongia pseudoreticulata* yielded the diyne **228**, which was found to be toxic in the brine shrimp assay.[206] A *Diplastrella* species, collected in the Philippines, yielded a series of polyacetylenic diols, the diplynes A–E **229**–**233** and corresponding sulfates **234**–**236**.[207] Three new chlorinated polyacetylenes **237**–**239** were isolated from the Californian sponge *Haliclona lunisimilis*[208] along with known compounds originally isolated from the *Haliclona*'s nudibranch predator, *Diaulula sandiegensis*.[209] The moderately cytotoxic polyacetylenic amide, callyspongamide A **240**, was obtained from *Callyspongia fistularis* collected in the Red Sea.[210] Three new amides, **241**–**243**, along with the previously reported clathrynamide A **244**,[211] were isolated from an Okinawan *Psammoclemma* species.[212] The stereochemistry of **244** was determined (Mosher method). All four compounds were found to be antifungal. The absolute stereochemistry of the amino alcohol xestoaminol C, originally isolated

from a Fijian *Xestospongia* species,[213] has been established as (2*S*,3*R*) by the synthesis of the *N,O*-diacetyl derivative from (*S*)-alanine.[214] A racemic synthesis of 2-methoxy-13-methyltetradecanoic acid, isolated from a Puerto Rican specimen of *Amphimedon complanata*,[215] has been reported.[216] (*R*)-Strongylodiol B, originally isolated from a *Strongylophora* species,[217] was synthesised enantioselectively using a Zn(II) acetylide addition to an aldehyde.[218] Callyberynes A and B, also known as callypentaynes, obtained from Japanese specimens of *Callyspongia truncata*[219] and *Callyspongia* sp.,[220] were synthesised using sequential Cadiot-Chodkiewicz cross-coupling reactions.[221] *Erylus trisphaerus,* collected in Dominica, was found to contain the mildly cytotoxic polyketide lactone, trisphaerolide A **245**.[222] A Madagascar specimen of *Plakortis aff. simplex* yielded three cyclic peroxides, the plakortolides H **246** and I **247** and andavadoic acid **248**, all of which were cytotoxic against a range of human tumour cell lines.[223] The antimicrobial tetramic acid, melophlin C **249**, from an Indonesian specimen of *Melophlus sarassinorum*, was isolated as an inseparable mixture of four stereoisomers arising from the stereogenic centres at C-5 and C-10 (as evidenced by NMR and modified Marfey's method). A further twelve, less active tetramic acids, melophlins D–O **250**–**261**, were also isolated from the same sponge.[224] Both plakortides M **262** and N **263**, isolated from a collection of *Plakortis halichondrioides* from Puerto Rico, exhibited potent cytotoxicity to an array of human tumour cell lines.[225] A Japanese specimen of *Monotria japonica* yielded the monotriajaponides A–D **264**–**267** which can lyse starfish oocytes without disruption of nuclear structure.[226] Interestingly, the absolute stereochemistries of **265**–**267**, as determined by reduction and a modified Mosher method, were opposite to those determined for the plakortides **262** and **263**. The asymmetric synthesis of (+)-rottnestol, originally isolated from a *Haliclona* species,[227] using a Stille coupling firmly established the absolute stereochemistry as (12*R*). Similarly, syntheses of (+)-raspailol A and (+)-raspailol B, originally obtained from a *Raspailia* species,[228] have established a (12*R*) configuration for these two metabolites also.[229] An unusual bis-dimedone thioether with strong UV A and B absorption, benzylthiocrellidone **268**, was isolated from a Great Barrier Reef collection of *Crella spinulata*; the structure was reported in

2002,[230] but was omitted from the 2002 review.[231] Okadaic acid, originally isolated from *Halichondria okadai*,[232] and subsequently found to be a dinoflagelate and shellfish toxin,[233,234] has been investigated for potential as a defense molecule for the Adriatic sponge *Suberites domuncula*. Use of an ELISA assay established that okadaic acid was localised in the epithelium of the lacunae and water channels of the sponge, as well as in bacteria located in the sponge tissue. It was postulated that okadaic acid acts as a stimulant of the sponge immune system to the presence of bacteria, but in higher concentrations causes apoptosis.[235] Two analogues of okadaic acid, 27-*O*-acetylokadaic acid **269** and 27-*O*-acetyldinophysistoxin 1 **270**, were isolated from a British Columbian sponge *Merrianum oxeato* and found to be potent G2 checkpoint inhibitors and highly cytotoxic.[236] A Papua New Guinean sponge, *Cymbastela* sp., was found to contain the cytotoxic peptide milnamide D **271** along with the related peptides hemiasterlin[237] and milnamide A.[238] All three compounds were inhibitors of tubulin polymerisation.[239] Three unusual new cyclic peptides, the kapakahines E–G **272**–**274**, have been isolated from a Micronesian collection of *Cribrochalina olemda* and reported as cytotoxic to P388 murine leukemia cells.[240] The previously described sulfoxide, waiakeamide **275**, and a new sulfone analogue **276** were isolated from a *Haliclona* sp. collected in Palau. The sulfone **276** was found to inhibit the settlement of larvae of the blue mussel (*Mytilus edulis galloprovincialis*).[241] The myriastramides A–C **277**–**279** were isolated from the same Philippine collection of *Myriastra clavosa* that had previously yielded the clavoside macrolides.[242,243] Leucamide A, originally isolated from the Australian sponge *Leucetta microraphis*,[244] has been synthesised.[245] Due to differences in biological activity, the *cis,cis*- **280** and reputed *trans,trans*- **281** isomers of ceratospongamide, originally isolated from the Indonesian symbiotic pairing of the red alga *Ceratodictyon spongiosum* and the sponge *Sigmadocia symbiotica*,[246] continue to attract considerable attention from synthetic chemists. Although both rotamers had been synthesised previously,[247] slight differences in the NMR spectra of the synthetic *trans,trans* isomer **281** and the isolated natural product were noted. Suspecting a possible epimerisation the *trans,trans*-[D-*allo*-Ile] isomer, **282** was synthesised, by two separate routes, to

produce a compound that is identical in all respects to the natural isomerisation product.[248] Phakellistatins 1[249] and 10,[250] have been synthesised.[251] Phakellistatin 1 was found to exist as the all-*cis* rotamer at the proline residues, while phakellistatin 10 was determined to be all-*trans*. Interestingly, both synthetic products were more than 100-fold less cytotoxic than the natural product.[251] A large (500 Kg) collection of a *Phakellia* species from Chuuk, Micronesia, yielded the growth inhibitory phakellistatin 12 **283**,[252] while a Chinese collection of *Phakellia fusca* yielded the very cytotoxic phakellistatin 13 **284**.[253] The macrolide spirastrellolide A was isolated as its methyl ester **285** from the Caribbean sponge *Spirastrella coccinea*. Unlike many other sponge-derived antimitotic macrolides, **285** does not effect tubulin polymerisation.[254] An asymmetric synthesis of (–)-peloruside A, the antipode of the natural product **286** originally isolated from the New Zealand sponge *Mycale hentscheli*,[255] has been achieved via a Mitsunobu-type lactonisation.[256] The synthetic antipode proved to be biologically inactive in cytotoxicity assays, but established the absolute stereochemistry of the natural (+)-enantiomer **286** as drawn. The relative and absolute stereochemistries of the C23-C35 portion of reidispongiolide A **287**, isolated from the New Calidonean sponge *Reidispongia coerulea*,[257] have been established by synthesis of an ozonolysis fragment of the natural product.[258] The total synthesis of (+)-13-deoxytedanolide, originally isolated from the Japanese sponge *Mycale adherens*,[259] has been accomplished.[260] The natural enantiomer of lasonolide A, isolated from a Caribbean *Forcepia* species,[261] has also been synthesised and found to be bioactive.[262] The hexabromobiphenylether from *Dysidea herbacea*[263] has been synthesised and found to be a potent aldose reductase (ALR2) inhibitor.[264] The Micronesian sponge *Cribrochalina olemda* was found to contain a new *N*-methyl-D-aspartate (NMDA) receptor ligand, cribronic acid **288**, which has potent convulsant activity in mice.[265] The known antioxidant amino acid L-5-hydroxytryptophan was found to be a major constituent of the NW Atlantic intertidal sponge *Hymeniacidon heliophila* and was observed to suppress apoptosis in human lymphocytes at concentrations similar to those found in the sponge tissue. Since UV light induces apoptosis, it is proposed that the high concentrations of L-5-hydroxytryptophan act to

protect this sponge species from sunlight UV damage.[266] The pyridinium alkaloid simplakidine A **289** was isolated from the Caribbean sponge *Plakortis simplex*.[267] The rather remarkable tris-pyridinium alkaloid viscosamine **290** has been isolated from the Arctic sponge *Haliclona viscose*. The trimeric nature of this alkaloid was deduced from a series of ions in the mass spectrum.[268] Halitulin **291**, isolated from a South African collection of *Haliclona tulearensis*,[269] has been synthesised, establishing C-15 as (*S*).[270] Clathryimine, originally isolated from *Clathria basilana*,[271] has been synthesised using palladium-catalyzed cross-coupling reactions.[272] Hachijodines F and G, isolated originally from *Xestospongia* and *Amphimedon* species,[273] have been synthesised. The *N*-oxide moieties were introduced using modified Mukiyama conditions.[274] Pyrinodemin A **292**, isolated from a Okinawan collection of an *Amphimedon* species,[275] continues to attract considerable attention from synthetic organic chemists.[231] The position of the *cis* double bond has been contentious, with the originally published structure **292** being modified to **293**[276] and **294**[277] respectively. The structure **294** has now been synthesised asymmetrically by two independent groups establishing the absolute stereochemistry of the bicyclic core.[278,279] One group was also able to compare the spectral data to the original spectra of the natural product and confirm the structure as **294**.[278] Petrosin and petrosin A, originally isolated from *Petrosia seriata*,[280,281] were found to inhibit HIV-1 replication and HIV-1 reverse transcriptase.[282] The total synthesis of the (+)-antipode of nakadomarin A **295**, originally isolated from an *Amphimedon* species,[283] has established the absolute stereochemistry of the (–)-natural enantiomer as (*RRRR*).[284] Three new manzamine alkaloids **296**–**298**, the related harman-1-one **299**, and des-*N*-methylxestomanzamine A **300** were isolated from an Indonesian sponge.[285] Three β-carbolines, 3-bromofascaplysin **301**, 14-bromoreticulatine **302** and 14-bromoreticulatate **303**, have been reported as metabolites of *Fascaplysinopsis reticulata* from Indonesia and Fiji. 3-Bromofascaplysin was also reported as a metabolite of the tunicate *Didemnum* sp.[286] Three iodine-containing indole alkaloids, plakohypaphorines A–C **304**–**306**, were also obtained from the same Caribbean *Plakortis simplex* collection that yielded simplakidine (*vide supra*). This is the first report of naturally occurring

iodoindole alkaloids.[287] Damirones A and B[288] have been prepared from the corresponding makaluvamines by alkaline hydrolysis, suggesting that the damirones may be artifacts of isolation and not naturally-occurring compounds.[289] The Indonesian sponge *Biemna fortis* yielded the pyridoacridine alkaloid labuanine **307**, which along with two related synthetic pyridoacridine alkaloids and the previously isolated biemnadin,[290] were found to be inducers of neuronal differentiation.[291] Several new antimicrobial aaptamine type alkaloids **308**–**312** were isolated from an Indonesian *Xestospongia* species,[292] while from a Japanese *Neopetrosia* sp. a further tetrahydroisoquinoline alkaloid, renieramycin J **313**, was reported.[293] The dark blue, cytostatic and antimicrobial metabolite, cribrostatin 6 **314**, was isolated from a species of *Cribrochalina* from the Maldives.[294] The dictyodendrins A–E **315**–**319**, isolated from the Japanese sponge *Dictyodendrilla verongiformis* were found to inhibit telomerase activity.[295] Phloeodictine A1, originally isolated from a New Caledonian sponge of the genus *Phloeodictyon*,[296] has been synthesised.[297] *N,N*-Dimethyl naamine D **320** and leucettamine C **321** are reported as new, mildly antimicrobial metabolites of two Fijian *Leucetta* species.[298] The same research group has also isolated three further imidazole-containing alkaloids, calcaridine A **322** spirocalcaridine A **323** and spirocalcaridine C **324**, from one of the two *Leucetta* collections.[299] Isonaamidines A and C, originally isolated from an Indo-Pacific *Leucetta* species,[300] have been synthesised.[301] Sventrin, isolated from *Agelas sventes*,[302] has been synthesised by a Red-Al reduction of an alkyne.[303] An MT1-MMP inhibitor, ageladine A **325**, was isolated from a Japanese *Agelas nakamuri* collection.[304] Oroidin-type alkaloids with novel skeletons, the latonduines A **326** and B **327**, were obtained from an Indonesian *Stylissa carteri* collection.[305] A *Stylissa aff. massa*, obtained from Japanese waters, was found to contain a geranylgeranyltranferase type I inhibitor, massadine **328**.[306] Crambescidin 826 **329**, isolated from a *Monanchora* sp. collected in Palau, was found to be a potent inhibitor of HIV-1 envelope-mediated fusion, along with the known compounds crambescidin 800[307] and fromiamycalin,[308] while dehydrocrambine A **330**, also isolated from this sponge, was found to be a weak inhibitor only.[309] A related antibacterial guanidine alkaloid, Sch

575948 **331**, was isolated from a *Ptilocaulis spiculifer* (*Crambe crambe*) specimen.[310] Two antimitotic guanidine/bromotyrosine alkaloids, ceratamines A **332** and B **333**, were isolated from a Papua New Guinean *Pseudoceratina* sp.[311] An Indian collection of *Psammaplysilla purpurea* was found to contain the antibacterial bromotyrosine-derived alkaloids purpuramine K **334** and L **335**.[312] Aerothionin, originally isolated from *Verongia aerophoba*,[313] has been found to be active against drug-resistant strains of *Mycobacterium tuberculosis* and several other *Mycobacterium* sp.[314] A Chinese collection of the sponge *Phakellia fusca* yielded a remarkable series of fluorinated uracil derivatives **336**–**340**. The presence of fluorine was confirmed by X-ray diffraction and ^{19}F NMR studies. This is the first report of fluorine-containing marine natural products.[315] Sponge-derived merosequiterpenoids continue to be a fruitful area of research for both natural product and synthetic chemists. Isoarenarol **341**, isolated from a Papua New Guinean collection of *Dysidea arenaria*, was found to be a potent protein kinase inhibitor.[316] Spongiaquinone, isolated from *Stelospongia conulata*,[317] has been prepared in an asymmetric synthesis. The absolute stereochemistry was assigned based on comparison of the optical rotation of the synthetic methyl ether with that of the natural compound.[318] A Micronesian *Aka* species has yielded three new sesquiterpenoid quinols, akaol A **342**, **343**, and the tentatively assigned siphonodictyol I **344**.[319] Also isolated was siphonodictyal C **345**, originally isolated from *Siphonodictyon coralliphagum*[320] and previously described as a free phenol. However the sample isolated from the *Aka* sp. had identical NMR spectra and clearly shows the presence of SO_3Na by ESIMS.[319] The sulfate group is lost in EIMS, the technique used for characterisation in the original isolation procedure.[320] Siphonodictyal C was a modest inhibitor of complexation in the CDK4/cyclin D1 assay.[320] The moderately cytotoxic neodactyloquinone **346** and the dactylolactones A–D **347**–**350** were obtained from an Okinawan collection of *Dactylospongia elegans*.[321] A Great Barrier Reef species of *Spongia* yielded the sesquiterpenoid aminoquinone cyclosmenospongine **351**, which was found to be moderately cytotoxic to murine Ehrlich carcinoma cells.[322] Methanolic extracts of an Indonesian sponge of the genus *Hyrtios* yielded three new puupehenone derivatives **352**–**354**, but which are

650 proposed to be artifacts of isolation from puupehenone.[323] The biosynthesis of the sesquiterpenoid dichloroimines, stylotellanes A and B,[324] was investigated. Incorporation of labelled farnesyl isocyanide and farnesyl isothiocyanate demonstrated the role of these compounds as intermediates in the formation of the stylotellanes.[325] 10-Formamido-4-cadinene **355**, isolated from the Japanese sponge *Acanthella cavernosa*, was found to inhibit the settling of the cyprid (barnacle) larvae 655 *Balanus ainphitrite*.[326] The Indonesian sponge *Axinyssa aculeata* and its nudibranch predator *Phyllidia varicosa* were both found to contain the moderately antifungal 9-thiocyanatopupukeanane sesquiterpenoids **356** and **357**.[327] 2-Thiocyanatoneopupukeanane **358**, originally isolated from the sponge *Phycopsis terpnis*,[328] was subsequently revised to the *endo* stereochemistry on the basis of long-range ^{1}H-^{1}H coupling and NOE correlations.[329] Both enantiomers have been synthesised from 660 (*R*)-carvone via the corresponding alcohols[330] and the stereochemistry of **358** has now been fully established via an X-ray structure of the nitrobenzoate derivative of the corresponding alcohol.[331] A Japanese *Axynissa* species yielded the mildly cytotoxic diterpene, axinyssene **359**.[332] An enantioselective synthesis of (–)-nakamurol, originally isolated from the Okinawan sponge *Ageles nakamuri*,[333] established the relative and absolute stereochemistries of the naturally-occurring **360** 665 enantiomer.[334] Synthesis of the proposed structure of aplyroseol-14 **361**, originally isolated from the New Zealand sponge *Aplysilla rosea*,[335] did not yield spectra similar to those of the natural product. The revised structure, **362**, was synthesised and found to be spectrally identical with aplyroseol-14.[336] Six cycloamphilectenes isolated from an *Axinella* species collected in Vanuatu were found to be potent inhibitors of nitric oxide production by murine macrophages.[337] Only one 670 (*N*-formyl-7-amino-11-cyclocamphilectene) of the six compounds in this study has had a structure determination published.[338] The C-25 sesterterpenoids and related nor-compounds are characteristic of sponges, especially those of Dictyoceratid origin. A cytotoxic norsesterterpenoid, mycaleperoxide **363**, was isolated from a *Mycale* species collected in Thailand. The relative and absolute stereochemistries were established by standard methodology, including chemical 675 interconversions.[339] Two moderately cytotoxic norsesterterpenoids, sarcotins N **364** and O **365**,

along with a sesterterpenoid **366**, four pyrrolosesterterpenoids **367**–**370** and *ent*-kurospongin **371** were isolated from two Korean *Sarcotragus* species.[340] The previously reported sarcotin I **372**[341] was found to have the (21*R*) configuration.[340] Three norsesterterpenoids **373**–**375** and two sesterterpenoids **376** and **377**, isolated from an Okinawan *Ircinia* species, were found to be moderately cytotoxic.[342] *Darwinella australensis* collected from NW Australia contained sesterterpenoid sulfates **378**–**380** that inhibited the cell division of sea urchin eggs, but were not cytotoxic to human leukemia cells.[343] An *Ircinia* species collected at -70 m by dredging in the Gulf of Mexico contained a tricyclic sesterterpenoid, Sch 599473 **381**,[344] while the Antarctic sponge, *Suberites caminatus* yielded the rearranged sesterterpenoid aldehyde caminatal **382**.[345] An asymmetric synthesis of (–)-cacospongionolide F, isolated from *Fasciospongia cavernosa*,[346] confirmed the original stereochemical assignments.[347] The bicyclic lactone astakolactin **383** and the pentacyclic diacetate 16-acetoxy-dihydrodeoxoscalarin **384** were obtained from specimens of *Cacospongia scalaris* collected in Greece.[348] A *Spongia* species collected in Japan yielded three cytotoxic pentacyclic sesterterpenoids **385**–**387**.[349] Seven new polyhydroxy sterols **388**–**394** were isolated from a Japanese *Acanthodendrilla* species along with three known agosterols. These were found to be proteasome inhibitors.[350] Clathriol B **395**, isolated from the New Zealand sponge *Clathria lissosclera*, was found to inhibit the production of superoxide from human neutrophils.[351] A sterol sulfate, Sch 572423 **396**, along with the previously described halistanol sulfate,[352] isolated from a *Topsentia* species collected in the Bahamas, were found to bind to $P2Y_{12}$ receptors.[353] Another deep-water Bahaman sponge, belonging to the family Astroscleridae, yielded the trisulfated sterol Sch 575867 **397**,[354] while a series of steroidal oligoglycosides, the mycalosides B–I **398**–**405**, have been isolated from the Cuban sponge *Mycale laxissima*. The mycalosides are inhibitors of the fertilisation of sea urchin eggs.[355] Four significantly cytotoxic steroidal alkaloids, plakinamines I–K **406**–**408** and dihydroplakinamine K **409**, were isolated from a Philippine sponge *Corticium niger*.[356] The halogenated and rearranged norsteroid, nakiterpiosin **410**, isolated from the Okinawan *Terpios hoshinota*, was found to be cytotoxic to murine P388 leukemia cells.[357]

Hippospongic acid A, originally isolated from a Japanese *Hippospongia* species,[358] inhibits all classes of vertebrate DNA polymerases and human topoisomerases I and II, but is inactive towards DNA polymerases from plants, insects and prokaryotes.[359] Two mildly cytotoxic polyoxygenated triterpenes, yardenones A **411** and B **412** were isolated from a Yemenese collection of *Axinella cf. bidderi*.[360]

8 Coelenterates

The number of new metabolites reported annually from coelenterates has remained relatively constant over the 2002-2003 period. A new sphingosine derivative **413** was reported from a soft coral *Nephthea* sp. collected at the Andaman and Nicobar Islands, Indian Ocean,[361] while investigations of *Sinularia grandilobata* and *Sinularia* sp. specimens from the same location afforded **414**–**416** as antimicrobial metabolites.[362] The absolute stereochemistry of the *N*-palmitate **417**, isolated from a Bay of Bengal collection of *Nephthea* sp., was deduced by analysis of ^{1}H-^{1}H coupling constants of the acetonide derivative and comparison of optical properties with known compounds.[363] Acylspermidines **418**–**420**, isolated from an Okinawan collection of *Sinularia* sp. soft coral,[364] were all potently cytotoxic towards A431 cells. In a separate study **419** and **420** were found to be potent inhibitors of plant vacuolar H^{+}-pyrophosphatase.[365] The phenol **421** was isolated from a Taiwanese collection of *Isis hippuris*,[366] while investigation of a Japanese collection of the stony coral *Tubastraea* sp. afforded bisindole alkaloids **422**–**424**.[367] From Israel, eight new oxylipin derivatives were reported from Gulf of Aqaba collections of *Dendronephthya* sp. (**425**–**428**), *Tubipora musica* (**429** and **430**) and *Dendrophyllia* sp. (**431** and **432**) coelenterates.[368] Stereochemical configurations were secured by standard methods. All eight metabolites exhibited biological activity towards bacteria, brine shrimp, sea urchin egg development and crown gall potato tumours. Fifteen new members of the clavulone family of prostanoids **433**–**447** were reported from an Okinawan collection of *Clavularia viridis*.[369] The absolute configurations of **433**–

443, **445** and **446** were secured by analysis of CD data while those of **444** and **447** were proposed based upon biogenetic considerations. Prostanoids **448**–**450**, possible biosynthetic precursors to the clavulones, were also isolated from an Okinawan collection of *C. viridis*.[370] By utilising protease and detergent fractionation methodology, clavulones and arachidonic acid have been located in host *C. viridis* membranes, as opposed to the closely associated symbiont *Symbiodinium* sp.[371] Sesquiterpenes ainigmaptilones A **451** and B **452** were isolated from a Weddell Sea, Antarctica, collection of *Ainigmaptilon antarcticus*.[372] Ainigmaptilone A demonstrated activity in a number of ecologically-relevant assays, including antibiotic and feeding deterrence properties. Furanosesquiterpene **453**, reported from the Antarctic gorgonian *Dasystenella acanthina*, bears a *trans*-ring junction as determined by NOESY NMR experiments and comparison with related *cis*-fused isomers.[373] Asymmetric synthesis of both enantiomers of acetoxytubipofuran **454**, originally isolated from a Japanese collection of *Tubipora musica*,[374] defined the absolute stereochemistry as shown,[375] while the structure of echinofuran[376] has been confirmed by racemic synthesis.[377] Confertol **455** and nephalbidol **456** were isolated from the soft corals *Sinularia conferta* and *Nephthea albida* respectively,[378] while cladioxazole **457** was isolated from an Andaman Island, Indian Ocean, collection of *Cladiella* sp.[379] A full account of the synthesis of the dolabellane diterpene claenone, previously reported from *Clavularia* sp.,[380] the first synthesis of palominol, from *Eunicea laciniata*,[381] and a new route to dolabellatrienone, also from *E. laciniata*,[381,382] have also been reported.[383] Stereoselective synthesis of (+)-4,5-deoxyneodolabelline, a metabolite of an Australian collection of *Cespitularia* sp.,[384] has been reported.[385] The structure of kallosin A **458**, a rearranged pseudopterane diterpenoid isolated from a Caribbean collection of *Pseudopterogorgia kallos*, was secured by spectroscopic and X-ray analyses.[386] Elisabethin A, isolated from *P. elisabethae*,[387] has been synthesised utilising intramolecular [4+2] cyclisation under biomimetic conditions.[388] The first synthesis of the related diterpene elisapterosin B and a new route to colombiasin A, also isolated from *P. elisabethae*,[389,390] have been achieved based on [5+2] and [4+2] intramolecular cyclisations of a common diene intermediate.[391] New members of the

elisapterosin family, D **459** and E **460**, were reported from a Caribbean collection of the same organism.[392] *P. elisabethae* is also a well recognised source of anti-inflammatory diterpenes, new examples of which include elisabethadione **461**, elisabethol **462**, pseudopterosins M–O **463**–**465** and seco-pseudopterosins E–G **466**–**468**.[393] Of the eight diterpenes, **461**, **464** and **466** were the most potent in the mouse ear edema assay. The chemical steps involved in the biosynthesis of the pseudopterosins in *P. elisabethae* have been studied using ^{3}H-labelled precursors,[394] with a subsequent study showing that diterpene production is occurring within the dinoflagellate symbiont *Symbiodinium* sp.[395] Preparation of all four C-1 and C-7 stereoisomers of pseudopteroxazole **469**, a mildly antimycobacterial diterpene isolated from *P. elisabethae*,[396] required a revision of assigned stereochemistry to that shown,[397] while a new bioactive congener, homopseudopteroxazole **470**, has been reported from the same organism collected near San Andrés Island, Colombia.[398] The structures of the *P. elisabethae* metabolites, elisabatins B[399] and C,[400] have been confirmed by X-ray studies.[401] Investigation of a Great Barrier Reef collection of *Sarcophyton cherbonnieri* yielded furano-cembranoids **471**–**473**, while the same study[402] also reported new seco-cembranoids **474** and **475** from a Fijian collection of *Nephthea* sp. in addition to the known cembrane decaryiol.[403] Modest cytotoxicity towards a panel of tumour cell lines was exhibited by **471**, **473** and decaryiol while the latter was shown to arrest the cell cycle at G2/M. Structures of sarcocrassolide B **476**[404] and sarcophyocrassolide A **477**,[405] cytotoxic cembrane diterpenes isolated from a Chinese collection of *Sarcophyton crassocaule*, were secured by X-ray studies,[406] as was that of 11-*epi*-sinulariolide acetate **478**,[407] previously reported from gorgonians collected from the Gulf of Elat. 11-*epi*-Sinulariolide acetate was found to exhibit moderate cytotoxicity towards a range of tumour cell lines. In addition to a number of known metabolites, new nor-cembrane diterpenes leptocladolides A **479**, B **480** and C **481** were isolated from a Taiwanese collection of *Sinularia leptoclados*, while **479** and related compounds 1-*epi*-leptocladolide A **482** and (7*E*)-leptocladolide A **483** were isolated from an ethanolic extract of *S. parva*.[408] Both **479** and **483** exhibited modest cytotoxicity towards two tumour cell lines, but **482** was less active. Two known diterpenes, sinuleptolide **484**[409] and

norcembrenolide **485**,[410] inhibit LPS-induced TNF-α production by murine macrophage-like cells in a dose-dependent manner.[411] Note that while the characterisation data for the two diterpenes reported in the reference agree with original and recent reports,[408] the structures are represented with incorrect relative stereochemistry at C-11. Cembranes **486**–**489** were isolated from an eastern Caribbean collection of *Eunicea tourniforti*.[409] The structure and relative stereochemistry of the highly oxygenated diterpene providencin **490**, purified from Caribbean collections of *Pseudopterogorgia kallos*, was secured by X-ray analysis.[410] Mild cytotoxicity towards human tumour cell lines was observed for **490**. In addition to the known metabolites stolonidiol **491** and stolonidiol monoacetate **492**, two new dolabellane diterpenes, clavinflols A **493** and B **494**, were isolated from a Taiwanese collection of *Clavularia inflata*.[411] While **491**, **492** and **494** exhibited selective cytotoxicity towards the KB cell line, **493** was selective towards the Hepa cell line. In contrast, the acetoxy derivatives **495** and **496** were essentially inactive in the same assays. Pachyclavulariolides M–R **497**–**502** were isolated from a Taiwanese collection of *Pachyclavularia violacea*.[412] P388 cell line growth inhibition was observed for **497**. (*Z*)-Sarcodictyin A **503** is a potently cytotoxic diterpenoid isolated from a Japanese collection of *Bellonella albiflora*.[413] The absolute stereochemistry of **503** was related to sarcodictyin A **504** by transesterification and comparison of CD spectra. Spectroscopic discrepancies observed for the enantioselectively synthesised structure originally proposed for alcyonin **505**, isolated from the Okinawan soft coral *Sinularia flexibilis*,[414] has led to the proposal that the correct structure of the natural product is the allylic peroxide **506**.[415] The structures of briarellins E **507** and F **508**, isolated from a Puerto Rican collection of *Briareum asbestinum*,[416] were confirmed by enantioselective total synthesis, which also established the absolute configuration of the diterpenes.[417] In addition to a number of known compounds, new briarellins J–P **509**–**515**, two unnamed congeners **516** and **517** and polyanthellin A **518** were reported from a Puerto Rican collection of *Briareum polyanthes*.[418] Spectroscopic evidence was also presented for revision of the structure of briarellin A from **519**[419] to peroxide **520**, and reformulation of the structures of **521** and **522**, isolated from an Australian collection of

Briareum sp. in 1989,[420] to the enantiomers of **518** and **523** respectively. Antimalarial testing against *Plasmodium falciparum* indicated **511**, **516** and **517** to be the most active. Two investigations of the chemistry of *Junceella juncea*, one using specimens collected from the Tuticorin coast of the Indian Ocean, yielded juncins I–M **524**–**528**,[421] while a Taiwanese collection of the same organism afforded juncin N **529**.[422] Additional studies of *J. juncea* from Taiwan afforded juncenolides B-D **530**-**532**[423] and juncenolide E **533**,[424] of which **531** exhibited mild cytotoxicity towards Hepa and KB cell lines.[423] A different diterpene structure **534**, isolated from an Indian Ocean collection of *J. juncea*, was also given the trivial name juncenolide B.[425] A Taiwanese collection of *Junceella fragilis* yielded 9-*O*-deacetylumbraculolide A **535**.[426] The structurally related epoxides briaexcavatolides S–V **536**–**539** were isolated from Taiwanese specimens of *Briareum excavatum*,[427] while a Taiwanese collection of *J. fragilis* was the source of junceellolide H **540**.[428] Briarlides A–H **541**–**548**, obtained from Amami Oshima, Kagoshima Prefecture collections of *Briareum* sp., were evaluated for cytotoxicity towards Vero and MDCK cell lines where modest activity was observed for **541**, **544**–**546**, weak activity for **542**, **543** and **547** while **548** was inactive.[429] In addition to a number of known metabolites, seven new briaranes, erythrolides R–U **549**–**552**, an erythrane, erythrolide V **553**, and two aquariane-skeletoned diterpenes, aquariolides B **554** and C **555**, were reported from a Caribbean collection of *Erythropodium caribaeorum*.[430] Aquariolide A **556**, previously isolated from aquarium-grown specimens of *E. caribaeorum*,[431] was also identified from the organism collected in the wild. The relative stereochemistries of **549**–**555** were determined either by conversion to known related derivatives, or by interpretation of ROESY NMR data, while for erythrolide S **550**, Mosher methodology established the absolute configuration of the 3-hydroxybutanoyl side chain as (3'*S*). The biosynthetic relationships between a number of erythrolide diterpenes, involving possible enzymatic-mediated di-π-methane and vinyl-propane rearrangements was discussed. The study also reported that the known metabolites erythrolides P[432] and J[433] exhibited modest cytotoxicity towards the MCF7 tumour cell line. An Okinawan collection of *Xenia* sp. yielded the known metabolite

xeniolide A[434] as well as new xenicane diterpenes dihydroxeniolide A **557** and isoxeniatriacetate **558**.[435] The absolute configuration of **557** was established (Mosher method), while the absolute configuration of **558** was determined by synthesis from the stereochemically-defined xeniolide A.[436]

13-*Epi*-9-deacetoxyxenicin **559** was isolated as a cytotoxic component of *Asterospicularia laurae* collected on the Great Barrier Reef, Australia.[437] Good activity was observed for **559** against P388D1 cells, while the known metabolite 13-*epi*-9-deacetylxenicin **560**[438] was less active. DCM or ether solutions of **559** readily underwent autoxidation to afford the hydroperoxide **561**, while **560** was found to be resistant to further reaction. The stereochemistries of sesterterpenes cladocorans A **562** and B **563**, isolated from Mediterranean collections of *Cladocora cespitosa*,[439] have been revised by total synthesis,[440] while preparation and testing of related stereoisomers indicated the series exhibits cytotoxicity towards a panel of human tumour cell lines.[441] Pregnane acetal **564** was isolated from an ethanol extract of *Subergorgia suberosa*, collected off the Mandapam coast, Indian Ocean,[442] while a Taiwanese collection of *Isis hippuris* afforded the polyoxygenated steroids hippuristerones E–I **565**–**569**.[443] New gorgosterol and ergosterol derivatives **570**–**574** were isolated from a Great Barrier Reef collection of *Capnella lacertiliensis*.[444] All compounds exhibited weak antifungal activity while **573** and **574** also weakly inhibited tyrosine kinase p56^{lck}. The spiroketal steroid **575** was isolated from a Tuticorin coast, Indian Ocean collection of *Gorgonella umbraculum*,[445] while the mildly cytotoxic gibberoketosterol **576** was isolated from a Taiwanese collection of *Sinularia gibberosa*.[446] A South China Sea collection of *Nephthea chabroli* afforded the weakly cytotoxic sterols **577** and **578**,[447] and the arabinopyranosylsterol **579** was isolated from *Cladiella krempfi*, also collected in Chinese waters.[448] APETx1, a 4,552 Da 42-amino acid peptide cross-linked by three disulfide bonds, was isolated from the sea anemone *Anthopleura elegantissima*.[449] The toxin inhibits HERG voltage-dependent K^+ channels via gating modification rather than channel pore occlusion. Pore formation by equinatoxin II, a protein toxin isolated from the Mediterranean sea anemone *Actinia equina*,[450] has been examined using combinations of ^{31}P NMR, ^{31}P MAS NMR, electron microscopy,[451] FTIR[452] and toxin mutagenesis.[453] The ability of

surface plasmon resonance to study membrane binding processes of pore forming toxins has been reviewed.[454]

9 Bryozoans

Once again, few new compounds have been reported from bryozoans. The structural determination of the alkaloids pterocellins A **580** and B **581**, isolated from the marine bryozoan *Pterocella vesiculosa* collected in New Zealand, relied in part on an X-ray diffraction study of pterocellin A **580**. Both pterocellins A and B exhibit potent antimicrobial and antitumour activity *in vitro,* but only displayed modest activity in an *in vivo* hollow fibre assay.[455] The β-carboline alkaloid 8-hydroxyharman **582** was isolated from a sample of the New Zealand marine bryozoan *Cribricellina cribraria*.[456] A number of brominated alkaloids and a diterpene from the North Sea bryozoan *Flustra foliacea*[457,458,459,460,461] were tested against bacteria derived from marine and terrestrial environments. These compounds exhibited significant activities against one or more marine bacterial strains originally isolated from *F. foliacea*, but only weak activities against the terrestrial bacteria. Dihydroflustramine C[462] and flustramine D[461] exhibited *N*-acyl-homoserine lactone (AHL)-antagonistic activity as determined by using the biosensors *Pseudomonas putida* (pKR-C12), *P. putida* (pAS-C8) and *E. coli* (pSB403).[458] A synthesis of the cytotoxic isoquinoline alkaloid perfragilin A, originally isolated from the bryozoan *Membranipora fragilis*,[463] has been reported.[464]

10 Molluscs

There was a slight increase in new chemistry identified from molluscs in 2003 over that reported for the time frame of the previous review. Irregular polypropionates placidenes C–F **583**–**586** and hydroperoxide **587** were isolated from a Mediterranean collection of *Placida dendritica*.[465] It is

likely that **587** is derived from the known metabolite placidene A **588**,[466] but whether the hydroperoxide is an artifact of isolation, or a true natural product is unclear. The first synthesis (racemic) of the unsaturated polypropionate photodeoxytridachione, isolated from *Placobranchus ocellatus*[467] and other molluscs,[468] has been reported.[469] Five new azaspiracid analogues **589**–**593**, identified using tandem mass spectrometric techniques, were isolated from *Mytilus edulis* collected off the west coast of Ireland.[470] The stereochemistries of the new azaspiracid analogues are arbitrarily shown as matching that of azaspiracid-1 **594**,[471] the structure and stereochemistry of which has been called in to question by stereoselective synthetic studies.[472,473] The isolation of *N*-methyl-D-glutamic acid **595** from the Japanese mollusc *Scapharca broughtonii* is the first report of this amino acid derivative as a natural product.[474] Monterey Bay, California, collections of *Calliostoma canaliculatum* afforded the disulfide-linked dimer of 6-bromo-2-mercaptotryptamine **596** as a channel-gating antagonist of voltage-gated potassium channels.[475] 6-Bromoindirubin **597**, isolated from the Mediterranean mollusc *Hexaplex trunculus*, and the synthetic oxime **598** were found to be potent inhibitors of glycogen synthase kinase-3 (GSK-3).[476] The molecular geometry of GSK-3β inhibition by **598** was determined by a co-crystallisation X-ray study. Radio- and stable isotope incorporation studies have identified nicotinic acid and acetate as biosynthetic precursors of haminol-2,[477] a *de novo* biosynthesised metabolite of the Mediterranean mollusc *Haminoea orbignyana*.[478] The ability of the fungal alkaloid gliotoxin to act as a bioaccumulated toxin of shellfish has been examined using *Mytilus edulis*.[479] Lamellarin D, a polycyclic alkaloid first isolated from molluscs of the genus *Lamellaria*,[480] has been found to be a potent inhibitor of the DNA-processing enzyme topoisomerase I.[481] Japanese and US collections of *Aplysia kurodai* and *A. californica* were sources of the gut and vasculature contraction inhibitory pentapeptide Pro-Arg-Gln-Phe-Val-amide (PRQFVa).[482] Precursoral peptide cDNA was successfully cloned while PRQFVa-positive neuron distribution in CNS and peripheral tissue was mapped using *in situ* hybridisation and immunocytochemistry. Five excitatory peptides, r11a–e **599**–**603** were isolated from the venom of the fish-hunting cone snail *Conus radiatus* collected in the Philippines.[483]

Further molecular analysis of cDNA clones defined the isolated peptides as belonging to a new class, the I-superfamily, of conotoxins, which contain a scaffold with four disulfide bonds (linkages not defined). The solution conformation of αA-conotoxin EIVA **604**, originally isolated from the Atlantic cone shell *C. ermineus*,[484] was determined by NMR experiments and restrained molecular dynamics calculations.[485] A South China Sea collection of *Conus betulinus* yielded κ-conotoxin BtX **605**, a 31 residue four disulfide bond-containing K^+ channel up-modulator.[486] As noted in Section 4, the revised structure[487] of kahalalide F **126**, a potently cytotoxic[488] depsipeptide isolated from the mollusc *Elysia rufescens* and the algal dietary source *Bryopsis* sp.,[142] has been confirmed by careful analysis of degradation products and chiral derivatisation.[144] The mechanism of biological action of dolastatin 11, a cytotoxic depsipeptide isolated from the sea hare *Dolabella auricularia*,[489] involves stabilisation of F-actin, which has been studied using X-ray fibre diffraction of oriented filament sols.[490] Also isolated from a Japanese collection of the sea hare *D. auricularia*, dolabellanin B2, a 33 amino acid residue peptide, exhibits a broad spectrum of antimicrobial activity.[491] The solution structure of attractin, a 58-residue water-borne protein pheromone isolated from *Aplysia californica* has been determined by NMR methods.[492] Austrodoral **606** and austrodoric acid **607** are new nor-sesquiterpenes isolated from the Antarctic nudibranch *Austrodoris kerguelenensis,* but with **607** most likely being an artifact of isolation.[493] As noted in Section 7, the thiocyanatopupukeanane sesquiterpenes **356** and **357** were isolated as an epimeric mixture from the nudibranch *Phyllidia varicosa* and the nudibranch's dietary sponge *Axinyssa aculeata*.[327] While both compounds were isolated from the digestive gland of the nudibranch, epimer **357** was found to accumulate in the mantle, suggestive of a role in chemical defense. Both compounds exhibited mild toxicity towards brine shrimp and antimicrobial activity with **357** being more potent. *De novo* biosynthesis, via mevalonic acid, of fatty acid ester derivatives of drimane **608** and sesquiterpene **609**[494] in the nudibranch *Doriopsilla areolata* has been determined by feeding studies utilising [1-^{13}C]glucose, [1,2-$^{13}C_2$]glucose and [1,2-$^{13}C_2$]acetate.[495] Investigation of the diterpenoid acylglycerol fraction of an extract of the mantle of the Antarctic nudibranch *Austrodoris kerguelenensis* afforded

the acylglycerols **610** and **611**.[496] Also isolated were two known 1,2-diacylglyceryl esters, previously reported from the same organism,[497,498] the structures of which were corrected to **612** and **613** based upon interpretation of HMBC NMR correlations. The *de novo* biosynthesis of the structurally related diterpenoid glyceride verrucosin A[499,500] by the Mediterranean nudibranch *Doris verrucosa* has been investigated using both ^{13}C- and ^{14}C-labelled precursors.[501] Four new labdane diterpenes **614**–**617** were isolated from the pulmonate *Trimusculus peruvianus*, collected near the Antofagasta Coast of Chile.[502] Absolute stereochemistry was secured by standard methods. Compounds **616** and **617** exhibited mild cytotoxicity towards human tumour cell lines *in vitro*. The structure of aplysiallene **618**, deduced for a metabolite isolated from a Japanese collection of the sea hare *Aplysia kurodai*,[503] has been retracted[504] and corrected to the known bromoallene algal metabolite **619**.[505] The first diastereoselective synthesis of (–)-spongian-16-oxo-17-al, originally isolated from the nudibranch *Ceratosoma brevicaudatum*,[506] has confirmed the absolute stereochemistry of the metabolite, while synthesis of the related compound (–)-acetyldendrillol-1 **620**, isolated from the nudibranch *Cadlina luteomarginata*,[507] has led to correction of stereochemistry at C-17.[336] A further collection of *Trimusculus peruvianus*, again from the Antofagasta Coast of Chile, yielded two mildly cytotoxic polyhydroxylated steroids **621** and **622**.[508] The stereochemistries of **621** and **622** were determined by interpretation of NOESY NMR data and comparison of chemical shifts with stereochemically-defined related compounds.

11 Tunicates (ascidians)

The number of new secondary metabolites reported from ascidians has remained essentially static for each of 2002 and 2003. Three new glycosphingolipid molecular species, the major component of each being represented by **623**–**625**, were isolated from a Mediterranean collection of *Microcosmus sulcatus*.[509] A full account of the synthesis of lobatamide C, a cytotoxic macrolide isolated from *Aplidium lobatum* collected off the southwestern coast of Australia,[510] has been

reported.[511] In addition, preliminary V-ATPase inhibition structure-activity data was reported indicating the importance of the salicylate ring and enamide moieties for activity. The absolute configuration of iejimalide B **626**, a cytotoxic 24-membered macrolide isolated from a Japanese collection of *Eudistoma* cf. *rigida*,[512] has been defined by analysis of ^{1}H-^{1}H and ^{1}H-^{13}C coupling constants, distance geometry calculations and analysis of oxidative degradation products.[513] During the study the gross structure was also corrected to that shown (13*Z*). Floresolides A **627**, B **628** and C **629** are moderately cytotoxic cyclofarnesylated hydroquinones isolated from an *Aplidium* sp. ascidian collected at Flores Island.[514] The structures and absolute configurations of all three metabolites were secured by X-ray analysis of **629**. The structures of the 3-aza-[7]-paracyclophane-containing alkaloids haouamines A **630** and B **631**, isolated from *Aplidium haouarianum* collected off Tarifa Island, Cádiz, were also secured by X-ray analysis.[515] Both haouamines exhibited two sets of NMR signals, attributed to the presence of isomers resulting from either atropisomerism or slow pyramidal inversion of the bridgehead amine. Of the two compounds, haouamine A was the more potent antitumour agent. Ascidians are a well-established source of cyclic peptides, many of which exhibit cytotoxicity. Didmolamides A **632** and B **633** are cyclic hexapeptides containing all (*S*)-configuration amino acids isolated from *Didemnum molle* collected in Madagascar.[516] Both compounds exhibited modest cytotoxicity towards a panel of tumour cell lines. Six new congeners of the bistratamide family of cyclic hexapeptides, E–J **634**–**639**, were reported from a Tablas Island, Philippines collection of *Lissoclinum bistratum*.[517] All six compounds showed weak to moderate activity towards the HCT-116 tumour cell line. A full account of the synthesis of mollamide, a cytotoxic cycloheptapeptide isolated from an Australian collection of *Didemnum molle*,[518] has been reported.[519] The solution structure of the cytotoxic cycloheptapeptide trunkamide A **640**[520,521] has been determined using 2D-NMR data and simulated annealing methods.[522] Fluorescent analogues of ascidian-derived depsipeptides didemnin B and tamandarin A have been used to study short-term predator-prey relationships between fish and marine invertebrate larvae.[523] Plicatamide, a modified octapeptide isolated from the blood of a San Diego Bay specimen of *Styela plicata*,[524] and several

synthetic analogues have been found to exhibit potent antimicrobial activity, to cause K^+ efflux in *Staphylococcus aureus*, were potently hemolytic for human red blood cells, and formed cation-selective channels in model lipid bilayers.[525] Structure-activity studies of halocidin, an antimicrobial peptide (3443 Da) isolated from hemocytes of the solitary ascidian *Halocynthia aurantium*,[526] identified one congener with potent antimicrobial activity, but reduced hemolytic activity.[527] Further biological investigation of the cytotoxic depsipeptide aplidine, isolated from *Aplidium albicans*,[528] indicates that the compound inhibits the growth and induces apoptosis in MOLT-4 cells through inhibition of vascular endothelial growth factor (VEGF) secretion which blocks the VEGF-VEGFR-1 autocrine loop necessary for growth of these cells.[529] In addition, aplidine prevents the *in vitro* aggregation of the prion peptide PrP 106-126.[530] EPR studies of vanadium-binding proteins, isolated from the vanadocytes of the ascidian *Ascidia sydneiensis samea*, indicate that up to 24 vanadium ions bind per protein molecule in a mononuclear state and that coordination is through amine nitrogens.[531] The absolute configuration of etzionin **641**, an antifungal diketopiperazine hydroxamate originally isolated from an unidentified Red Sea ascidian,[532] has been secured by synthesis of all four stereoisomers of derivative **642**, and direct comparison of optical rotation values with the same natural derivative.[533] An initial attempt at expanding the structure-activity relationship of the cytotoxic quinolizidine alkaloid clavepictine B isolated from the Bermudian ascidian *Clavelina picta*,[534] has indicated the importance of sidechain unsaturation, and that relative stereochemistry about the ring system does not seem to be important for cytotoxicity.[535] Two full accounts of the stereoselective synthesis of lepadiformine, a biologically active alkaloid isolated from the ascidians *Clavelina lepadiformis* and *C. moluccensis*,[536,537] have been reported.[538,539] The structurally related ascidian alkaloids (+)-cylindricines C–E, isolated from an Australian collection of *Clavelina cylindrica*,[540] were prepared using ruthenium-catalysed hydrative diyne cyclisation methodology.[541] The quaternised indole-enamine conicamin **643** was isolated as a histamine antagonist from a Mediterranean collection of *Aplidium conicum*.[542] Cynthichlorine **644**, previously known as a synthetic product from the chlorination of methylindolyl methylester,[543] was isolated

from a Moroccan collection of *Cynthia savignyi*.[544] The alkaloid exhibited antifungal activity towards two tomato pathogenic fungi and bacteria and was also cytotoxic in the brine shrimp lethality assay. Studies of an unidentified ascidian collected in Madagascar have afforded the mildly cytotoxic alkaloids barrenazine A **645** and B **646**.[545] The structures of the barrenazines were secured by use of ^{1}H-^{15}N HMBC NMR experiments, while the observance of optical rotatory properties for **645** suggested the (*R**,*R**) configuration. Further investigation of the Mediterranean collection of *Aplidium conicum* yielded conicaquinones A **647** and B **648**, both of which exhibited cytotoxicity towards a rat glioma cell line.[546] Kottamide E **649**, the first example of a natural product bearing the amino acid 4-amino-1,2-dithiolane-4-carboxylic acid (Adt), was isolated from the New Zealand ascidian *Pycnoclavella kottae*.[547] Benzotrithioles related to the cytotoxic pentathiepin ascidian alkaloids varacin[548] and lissonclinotoxin A[549,550] have been prepared and optical rotatory properties and crystal structures investigated.[551] Lissoclinotoxins E **650** and F **651** were isolated as mildly cytotoxic components of a Philippine didemnid ascidian.[552] The relative orientation of the aromatic rings of **650** and **651** were deduced, as shown, based upon molecular modeling studies. New members of the rigidin family of pyrrolopyrimidine alkaloids, rigidins B–D **652**–**654**, were isolated from an Okinawan collection of *Cystodytes* sp.,[553] while rigidin E **655** was isolated from a Papua New Guinea collection of a *Eudistoma* species.[554] Rigidins B–D were mildly cytotoxic towards the L1210 murine leukemia cell line[553] while rigidin **656**[555] and rigidin E were not cytotoxic towards A431 and wild-type and p53 deficient HCT-116 human tumour cell lines.[554] Two β-carboline alkaloids, eudistomins W **657** and X **658**, were isolated from Chuuk Atoll, Micronesia collections of a *Eudistoma* species.[556] The absolute stereochemistry of **657** was ascertained (Mosher method), and **658** was found to be more potent in antimicrobial assays. Shishijimicins A–C **659**–**661** are extraordinarily potent cytotoxic enediyne antibiotics isolated from a South Japan collection of *Didemnum proliferum*.[557] Relative and absolute stereochemistries were determined by standard methods and by comparison of CD data with that reported for the calicheamicins, terrestrial microbe-derived enediyne antibiotics. Distomadines A **662** and B **663** are new 6-hydroxyquinoline

alkaloids from the New Zealand ascidian *Pseudodistoma aureum*.[558] The structure of styelsamine C, an hydroxylpyridoacridine alkaloid isolated from the Indonesian ascidian *Eusynstyela latericius*,[559] has been confirmed by synthesis.[560] As noted in Section 7, 3-bromofascaplysin **301** was isolated from extracts of a *Didemnum* species ascidian collected at Chuuk Atoll, Micronesia, as well as from Fijian collections of *Fascaplysinopsis* sponges.[286] The structure of sebastianine A, a pentacyclic alkaloid isolated from a Brazilian collection of *Cystodytes dellechiajei*,[561] has been confirmed by total synthesis.[562] Continued study of ascididemin, isolated from a Japanese collection of a *Didemnum* sp.,[563] indicates that derivatives are also active in antiparasitic assays,[564] that the antitumour activity can be varied somewhat predictably,[565,566] and that a mechanism of reductive activation to form reactive oxygen species also contributes to the cytotoxicity of the parent alkaloid.[567] The structure of bengacarboline, a cytotoxic alkaloid isolated from a Fijian collection of a *Didemnum* sp.,[568] has been confirmed by total racemic synthesis.[569] A convenient solid-phase synthesis of the ascidian metabolites lamellarin L[570] and U[571] has been reported.[572] New improved syntheses of (–)-diazonamide A **664** have been reported,[573,574] and investigation of the mechanism of action of **664** and analogue **665** indicate that the alkaloids are potent inhibitors of microtubule assembly, possibly at a unique site.[575] Efficient syntheses of the naturally occurring cytotoxic ecteinascidins ET-729, -745, -759B, -736, -637 and -594[576,577,578,579,580] from the fermentation product cyanosafracin B have been reported.[581] The parent compound, ET-743, continues to progress through clinical trials.[582,583,584] Ritterazine B, a dimeric steroidal alkaloid isolated from *Ritterella tokioka*,[585] induces apoptosis in HL-60 cells and causes cell cycle accumulation at G2/M, but has no caspase activation effect nor does it alter phosphorylation of bcl-2.[586] Aplidiasterols A **666** and B **667** are new cytotoxic secosterols isolated from a Mediterranean collection of *Aplidium conicum*.[587] The structure and absolute stereochemistry of a steroidal sperm-activating and attracting factor **668** isolated from the ascidian *Ciona intestinalis*[588] has been unambiguously determined by total synthesis.[589]

12 Echinoderms

A similar number of new compounds were reported from echinoderms in 2003 compared with 2002. This field continues to be dominated by glycosylated ceramides and saponins. Taurine derivative **669** was isolated from a Gomun Island, Korea, collection of the starfish *Certonardoa semiregularis*.[197] Investigation of the Patagonian starfish *Anasterias minuta* afforded a range of metabolites including the new glucosylceramide anasterocerebroside A **670**.[590] The known ceramide **671**[591,592] was also characterised for the first time. A Japanese collection of the starfish *Luidia maculata* yielded four ceramide lactosides, luidialactosides A–D **672**–**675**.[593] The position of the olefin in the long chain base of **674** was deduced by FABMS analysis of a dimethyl disulfide derivative. Three ganglioside molecular species, SCG-1–3, the major species of which are represented by **676**–**678**, were isolated from the Japanese sea cucumber *Stichopus chloronotus*.[594] All three species displayed neuritogenic activity against PC12 cells in the presence of nerve growth factor. A structurally more complex ganglioside molecular species SJG-2 **679**, isolated from a Japanese collection of *Stichopus japonicus*, also exhibited neuritogenic activity.[595] Brine shrimp lethality assay-directed fractionation of the starfish *Certonardoa semiregularis*, collected off Komun Island, Korea, afforded thirteen new polyhydroxysterols. These were certonardosterols A–M **680**–**692**,[596] as well as the known **693**.[597] Side chain configurations at C-24 (for **686** and **693**), C-25 (for **680**) and both C-24 and C-25 (for **688**) were determined (Mosher method). All of the sterols, with the exception of **692**, exhibited modest *in vitro* cytotoxicity towards a panel of human tumour cell lines. A range of hemolytic steroid disulfates, including new examples **694** and **695**, were reported from the starfish *Pteraster pulvillus* collected by trawling in the Sea of Okhotsk in the Far East.[598] Unusual alkaloid cation and steroidal anion compounds **696**–**698** were isolated from the starfish *Lethasterias nanimensis chelifera* collected by trawling near the Kuril Islands in the Far East.[599] Comparison of optical rotation values identified the cation as being the (*R*)-isomer of salsolinol. Steroid glycosides (saponins), commonly isolated from echinoderms, present challenges

in structural elucidation and exhibit a diverse range of biological activities, both aspects of which have been reviewed.[600,601] Four new saponins, certonardosides K–N **699**–**702**, isolated from the starfish *Certonardoa semiregularis* collected off Komun Island, Korea, exhibited varied biological activity towards a range of tumour cell lines and bacteria.[602] Configuration at C-24 in **699**, **701** and **702** was secured by methanolysis and analysis of MTPA ester derivatives. The polyhydroxylated steroid ketone **703** and monoglycosylated steroid **704** were reported from collections of the Far Eastern starfish *Henricia sanguinolenta* and *H. leviuscula leviuscula*.[603] Both compounds mildly inhibited division of fertilised sea urchin eggs. A South China Sea collection of the sea cucumber *Mensamaria intercedens* yielded intercedensides A–C **705**–**707**, novel triterpene glycosides that exhibited *in vitro* cytotoxicity towards a panel of human tumour cell lines.[604] Intercedenside A also exhibited *in vivo* activity towards Lewis lung and mouse S180 sarcoma tumour models. A Sea of Japan collection of the sea cucumber *Cucumaria conicospermium* also afforded triterpene glycosides, cucumariosides A_2-5 **708**, A_3-2 **709**, A_3-3 **710** and isokoreoside A **711**, all of which contain the same pentasaccharide moiety, but differ in the number and position of the sulfate groups and the aglycone.[605] Limited quantities of two new saponins ruberoside E **712** and F **713** were isolated from specimens of the starfish *Asterias rubens* collected in the Baltic Sea.[606] The structures of both compounds were secured using a cryogenic NMR probe in an LC-NMR-MS configuration. Two mildly cytotoxic saponins, luidiaquinoside **714** and psilasteroside **715**, were reported from collections of the starfish *Luidia quinaria* collected at Sendai (Japan) and *Psilaster cassiope* collected in the northern Gulf of Mexico respectively.[607] The pathological effects of sea urchin toxins has been reviewed.[608]

13 Miscellaneous

Three alkylpyrrole sulfamates **716**–**718** were isolated as fish-feeding deterrent metabolites from the annelid *Cirriformia tentaculata*, collected in Florida.[609] Close to forty years after the structure of

tetrodotoxin was elucidated,[610,611,612] the first asymmetric syntheses of the alkaloid have been reported.[613,614]

14 Conclusion

In the early years of marine natural products research there was less emphasis on biological testing, but increasingly there has been a focus on the biological properties of these compounds. In the first of the Faulkner reviews (1977),[615] mention was made of the antibiotic properties of only a handful of compounds and reference made to the P388 activity of some *Dolabella auricularia* metabolites. In this review of the literature for 2003, over 720 compounds are included with biological activities being reported for 354 of these. The distribution of biological activities and source phyla for these compounds in 2003 is shown graphically in Figures 1 and 2. The sponges and coelenterates continue to dominate as source phyla of new compounds, with microorganisms being the other major source. The relative incidence of bioactivity detected was greatest from the green alga followed by tunicates, echinoderms and sponges, but in absolute numbers the sponges dominated. The reported biological testing has been grouped into five categories, but is dominated by various tests for anticancer and antimicrobial/antiinfective properties. Tunicates, echinoderms and sponges were prime sources for the detection of potential anti-cancer properties. This combination of source and biological activity is very much in keeping with the data presented in the timely review on marine natural products and related compounds in clinical and advanced clinical trials.[616] A graphical representation of the tabular data presented in that review is shown in Figure 3. Progress towards marine anticancer drugs dominates with the prime source phyla being sponges followed by microorganisms, tunicates and molluscs. The other categories where marine natural products are progressing are in drugs for pain and asthmatic conditions where the interest is centered on *Conus* toxins and analogues of sponge sterols respectively.[616]

Since the discovery of the arabinose-based nucleosides by Bergman over 50 years ago,[617-619] the explosion of interest in alternative nucleoside compositions and the subsequent development of Ara-C and Ara-A as drugs with obvious linkages to later antiviral drugs such as acyclovir and AZT, there has been a tacit assumption that marine-based drugs would soon be forthcoming. That has not yet happened, but the first truly marine drugs should be licensed within the next two years.[616] Yondelis, better known as ecteinascidin 743, is in Phase II and III trials in Europe and the USA against soft tissue sarcoma, while the *Conus* toxin known as Ziconotide or Prialt is in Phase III clinical trials for intractable pain with plans for launching as a new drug in 2005. Despite problems in 2003 with the European Agency for the Evaluation of Medicinal Products, Yondelis will probably also be launched in 2005.[616]

15 Acknowledgement

We thank Ekkehard Unger for the collection of data for this review.

16 References

1 J. K. Volkman, *Appl. Microbiol. Biotechnol*., 2003, 60, 495.

2 J. Kobayashi, K. Shimbo, T. Kubota and M. Tsuda, *Pure Appl. Chem.*, 2003, **75**, 337.

3 A. Aygün and U. Pindur, *Curr. Med. Chem.*, 2003, **10**, 1113.

4 J.-M. Kornprobst and H.-S. Al-Easa, *Curr. Org. Chem.*, 2003, **7**, 1181.

5 M. R. Prinsep, *Stud. Nat. Prod. Chem.*, 2003, **28**, 617.

6 R. X. Tan and J. H. Chen, *Nat. Prod. Rep.*, 2003, **20**, 509.

7 S. Matsunaga and N. Fusetani, *Curr. Org. Chem.*, 2003, **7**, 945.

8 L. D. Han, J. G. Cui and C. S. Huang, *Chin. J. Org. Chem.*, 2003, **23**, 305.

9 P. Muralidhar, P. Radhika, N. Krishna, D. V. Rao and Ch. B. Rao, *Nat. Prod. Sci.*, 2003, **9**, 117.

10 D. J. Griffiths and M. L. Saker, *Environ. Toxicol.*, 2003, **18**, 78.

11 J.-F. Hu, M. T. Hamann, R. Hill and M. Kelly, *Alkaloids*, 2003, **60**, 207.

12 D. J. Newman, G. M. Cragg and K. M. Snader, *J. Nat. Prod.*, 2003, **66**, 1022.

13 J. Peng, X. Shen, K. A. El Sayed, D. C. Dunbar, T. L. Perry, S. P. Wilkins, M. T. Hamann, S. Bobzin, J. Huesing, R. Camp, M. Prinsen, D. Krupa and M. A. Wideman, *J. Agric. Food Chem.*, 2003, **51**, 2246.

14 P. Proksch, R. Ebel, R. A. Edrada, P. Schupp, W. H. Lin, Sudarsono, V. Wray and K. Steube, *Pure Appl. Chem.*, 2003, **75**, 343.

15 A. M. S. Mayer and K. R. Gustafson, *Int. J. Cancer*, 2003, **105**, 291.

16 P. Proksch, R. Ebel, R. A. Edrada, V. Wray and K. Steube, *Sponges*, 2003, 117.

17 E. Delfourne and J. Bastide, *Med. Res. Rev.*, 2003, **23**, 234.

18 B. Haefner, *Drug Discovery Today*, 2003, **8**, 536.

19 G. Schwartsmann, A. Brondani da Rocha, J. Mattei and R. M. Lopes, *Expert Opinion on Investigational Drugs*, 2003, **12**, 1367.

20 D. J. Gochfeld, K. A. El Sayed, M. Yousaf, J. F. Hu, P. Bartyzel, D. C. Dunbar, S. P. Wilkins, J. K. Zjawiony, R. F. Schinazi, S. S. Wirtz, P. M. Tharnish and M. T. Hamann, *Mini Reviews in Med. Chem.*, 2003, **3**, 401.

21 L.-A. Tziveleka, C. Vagias and V. Roussis, *Curr. Topics in Medicinal Chemistry*, 2003, **3**, 1512.

22 M. Luescher-Mattli, *Curr. Med. Chem. - Anti-Infective Agents*, 2003, **2**, 219.

23 B. R. Copp, *Nat. Prod. Rep.*, 2003, **20**, 535.

24 H. Akita, H. Nakamura and M. Ono, *Chirality*, 2003, **15**, 352.

25 L. O. Haustedt, I. V. Hartung and H. M. R. Hoffmann, *Angew. Chem. Int. Ed. Eng.*, 2003, **42**, 2711.

26 I. Paterson and G. J. Florence, *Eur. J. Org. Chem.*, 2003, 2193.

27 H. Hoffmann and T. Lindel, *Synthesis*, 2003, **12**, 1753.

28 M. A. Brimble and D. P. Furkert, *Curr. Org. Chem.*, 2003, **7**, 1461.

29 A. Gryszkiewicz-Wojtkielewicz, I. Jastrzebska, J. W. Morzycki and D. B. Romanowska, *Curr. Org. Chem.*, 2003, **7**, 1257.

30 S. Hanessian, R. Margarita, A. Hall, S. Johnstone, M. Tremblay and L. Parlanti, *Pure Appl. Chem*., 2003, **75**, 209.

31 J. Mulzer and E. Öhler, *Chem. Rev.*, 2003, **103**, 3753.

32 W. E. G. Müller, F. Brümmer, R. Batel, I. M. Müller and H. C. Schröder, *Naturwissenschaften*, 2003, **90**, 103.

33 Y. Shimizu, *Curr. Opin. Microbiol.*, 2003, **6**, 236.

34 M. T. Hamann, *Curr. Pharm. Des.*, 2003, **9**, 879.

35 R. A. Hill, *Annu. Rep. Prog. Chem., Sect. B*, 2003, **99**, 183.

36 MarinLit database, Department of Chemistry, University of Canterbury: http://www.chem.canterbury.ac.nz/ marinlit/marinlit.shtml

37 R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen and W. Fenical, *Angew. Chem. Int. Ed. Eng*., 2003, **42**, 355.

38 J. E. Leet, W. Li, H. A. Ax, J. A. Matson, S. Huang, R. Huang, J. L. Cantone, D. Drexler, R. A. Dalterio and K. S. Lam, *J. Antibiot.*, 2003, **56**, 232.

39 W. Li, J. E. Leet, H. A. Ax, D. R. Gustavson, D. M. Brown, L. Turner, K. Brown, J. Clark, H. Yang, J. Fung-Tomc and K. S. Lam, *J. Antibiot.*, 2003, **56**, 226.

40 T. Sasaki, T. Ohtani, H. Matsumoto, N. Unemi, M. Hamada, T. Takeuchi and M. Hori, *J. Antibiot.*, 1998, **51**, 715.

41 K. Nagai, K. Kamigiri, N. Arao, K.-I. Suzumura, Y. Kawano, M. Yamaoka, H. Zhang, M. Watanabe and K. Suzuki, *J. Antibiot.*, 2003, **56**, 123.

42 K.-I. Suzumura, T. Yokoi, M. Funatsu, K. Nagai, K. Tanaka, H. Zhang and K. Suzuki, *J. Antibiot.*, 2003, **56**, 129.

43 Y. T. Park, J. B. Park, S. Y. Jeong, B. C. Song, W. A. Lim, C. H. Kim and W. J. Lee, *J. Kor. Fish. Soc*., 1998, **31**, 767.

44 S.-Y. Jeong, K. Ishida, Y. Ito, S. Okada and M. Murakami, *Tetrahedron Lett*., 2003, **44**, 8005.

45 M. Mitova, G. Tommonaro and S. De Rosa, *Z. Naturforsch. C Biosci*., 2003, **58**, 740.

46 R. W. Schumacher, S. C. Talmage, S. A. Miller, K. E. Sarris, B. S. Davidson and A. Goldberg, *J. Nat. Prod*., 2003, **66**, 1291.

47 R. P. Maskey, E. Helmke, H.-H. Fiebig and H. Laatsch, *J. Antibiot.*, 2003, **55**, 1031.

48 J. M. Sánchez López, M. Martinez Insua, J. Pérez Baz, J. L. Fernández Puentes and L. M. Cañedo Hernández, *J. Nat. Prod*., 2003, **66**, 863.

49 T. Itoh, M. Kinoshita, S. Aoki and M. Kobayashi, *J. Nat. Prod*., 2003, **66**, 1373.

50 A. Spyere, D. C. Rowley, P. R. Jensen and W. Fenical, *J. Nat. Prod*., 2003, **66**, 818.

51 R. Fudou, Y. Jojima, T. Iizuka and S. Yamanaka, *J. Gen. Appl. Microbiol*., 2002, **48**, 109.

52 R. Fudou, T. Iizuka and S. Yamanaka, *J. Antibiot.*, 2001, **54**, 149.

53 R. Fudou, T. Iizuka, S. Sato, T. Ando, N. Shimba and S. Yamanaka, *J. Antibiot.*, 2001, **54**, 153.

54 B. A. Kundim, Y. Itou, Y. Sakagami, R. Fudou, T. Iizuka, S. Yamanaka and M. Ojika, *J. Antibiot.*, 2003, **56**, 630.

55 K. Kanoh, K. Kamino, G. Leleo, K. Adachi and Y. Shizuri, *J. Antibiot.*, 2003, **56**, 871.

56 A. Isnansetyo and Y. Kamei, *Int. J. Syst. Evol. Microbiol*., 2003, **53**, 583.

57 A. Isnansetyo and Y. Kamei, *Antimicrob. Agents Chemother*., 2003, **47**, 480.

58 F. Fdhila, V. Vázquez, J. L. Sánchez and R. Riguera, *J. Nat. Prod*., 2003, **66**, 1299.

59 J. C. Rodriguez, J. L. Fernández Puentes, J. Pérez Baz and L. M. Cañedo, *J. Antibiot.*, 2003, **56**, 318.

60 R. P. Maskey, F. C. Li, S. Qin, H. H. Fiebig and H. Laatsch, *J. Antibiot.*, 2003, **56**, 622.

61 M. Tsuda, T. Mugishima, K. Komatsu, T. Sone, M. Tanaka, Y. Mikami, M. Shiro, M. Hirai, Y. Ohizumi and J. Kobayashi, *Tetrahedron*, 2003, **59**, 3227.

62 M. Namikoshi, R. Negishi, H. Nagai, A. Dmitrenok and H. Kobayashi, *J. Antibiot.*, 2003, **56**, 755.

63 R. J. Capon, C. Skene, M. Stewart, J. Ford, R. A. J. O'Hair, L. Williams, E. Lacey, J. H. Gill, K. Heiland and T. Friedel, *Org. Biomol. Chem*., 2003, **1**, 1856.

64 S. M. Lee, X. F. Li, H. Jiang, J. G. Cheng, S. Seong, H. D. Choi and B. W. Son, *Tetrahedron Lett*., 2003, **44**, 7707.

65 T. S. Bugni, V. S. Bernan, M. Greenstein, J. E. Janso, W. M. Maiese, C. L. Mayne and C. M. Ireland, *J. Org. Chem*., 2003, **68**, 2014.

66 T. S. Bugni, V. S. Bernan, M. Greenstein, J. E. Janso, W. M. Maiese, C. L. Mayne and C. M. Ireland, *J. Org. Chem*., 2003, **68**, 6846.

67 T. Amagata, A. Amagata, K. Tenney, F. A. Valeriote, E. Lobkovsky, J. Clardy and P. Crews, *Org. Lett*., 2003, **5**, 4393.

68 A. G. Kozlovsky, V. P. Zhelifonova, S. M. Ozerskaya, N. G. Vinokurova, V. M. Adanin and U. Grafe, *Die Pharmazie*, 2000, **55**, 470.

69 D. C. Rowley, S. Kelly, C. A. Kauffman, P. R. Jensen and W. Fenical, *Bioorg. Med. Chem*., **11**, 4263.

70 L. T. Tan, X. C. Cheng, P. R. Jensen and W. Fenical, *J. Org. Chem*., 2003, **68**, 8767.

71 E. Garo, C. M. Starks, P. R. Jensen, W. Fenical, E. Lobkovsky and J. Clardy, *J. Nat. Prod*., 2003, **66**, 423.

72 Y. Lin, Z. Shao, G. Jiang, S. Zhou, J. Cai, L. L. P. Vrijmoed and E. B. G. Jones, *Tetrahedron*, 2000, **56**, 9607.

73 N. Harada, K. Nakanishi, *Circular Dichroic Spectrometry-Exciton Coupling in Organic Stereochemistry*, University Science Books: Milly Valley, California, 1983.

74 M. Tsuda, T. Mugishima, K. Komatsu, T. Sone, M. Tanaka, Y. Mikami and J. Kobayashi, *J. Nat. Prod*., 2003, **66**, 412.

75 A. Abdel-Lateff, C. Klemke, G. M. König and A. D. Wright, *J. Nat. Prod*., 2003, **66**, 706.

76 F. Kong and G. T. Carter, *Tetrahedron Lett*., 2003, **44**, 3119.

77 C. Hopmann, M. A. Knauf, K. Weithmann and J. Wink, *PCT Int. Appl*., WO 01/44264 A2.

78 G. Bringmann, G. Lang, S. Steffens, E. Günther and K. Schaumann, *Phytochemistry*, 2003, **63**, 437.

79 A. D. Wright, C. Osterhage and G. M. König, *Org. Biomol. Chem*., 2003, **1**, 507.

80 Z. Liu, P. R. Jensen and W. Fenical, *Phytochemistry*, 2003, **64**, 571.

81 R. P. Maskey, I. Kock, E. Helmke and H. Laatsch, *Z. Naturforsch. B Chem. Sci*., 2003, **58**, 692.

82 B.-S. Yun, I.-J. Ryoo, W.-G. Kim, J.-P. Kim, H. Koshino, H. Seto and I.-D. Yoo, *Tetrahedron Lett*., 1996, **37**, 8529.

83 L. M. Nogle and W. H. Gerwick, *J. Nat. Prod*., 2003, **66**, 217.

84 R. T. Williamson, B. L. Marquez, W. H. Gerwick and K. E. Kover, *Magn. Reson. Chem*., 2000, **38**, 265.

85 L. T. Tan, N. Sitachitta and W. H. Gerwick, *J. Nat. Prod*., 2003, **66**, 764.

86 L. M. Nogle, B. L. Marquez and W. H. Gerwick, *Org. Lett*., 2003, **5**, 3.

87 M. T. Davies-Coleman, T. M. Dzeha, C. A. Gray, S. Hess, L. K. Pannell, D. T. Hendricks and C. E. Arendse, *J. Nat. Prod*., 2003, **66**, 712.

88 G. G. Harrigan, W. Y. Yoshida, R. E. Moore, D. G. Nagle, P. U. Park, J. Biggs, V. J. Paul, S. L. Mooberry, T. H. Corbett and F. A. Valeriote, *J. Nat. Prod*., 1998, **61**, 1221.

89 P. G. Williams, R. E. Moore and V. J. Paul, *J. Nat. Prod*., 2003, **66**, 1356.

90 K. L. McPhail and W. H. Gerwick, *J. Nat. Prod*., 2003, **66**, 132.

91 P. G. Williams, W. Y. Yoshida, M. K. Quon, R. E. Moore and V. J. Paul, *J. Nat. Prod*., 2003, **66**, 651.

92 P. G. Williams, H. Luesch, W. Y. Yoshida, R. E. Moore and V. J. Paul, *J. Nat. Prod*., 2003, **66**, 595.

93 C. Gaillet, C. Lequart, P. Debeire and J. Nuzillard, *J. Magn. Reson*., 1999, **139**, 454.

94 P. G. Williams, W. Y. Yoshida, M. K. Quon, R. E. Moore and V. J. Paul, *J. Nat. Prod*., 2003, **66**, 1545.

95 B. Han, K. L. McPhail, A. Ligresti, V. Di Marzo and W. H. Gerwick, *J. Nat. Prod*., 2003, **66**, 1364.

96 P. G. Williams, W. Y. Yoshida, R. E. Moore and V. J. Paul, *J. Nat. Prod*., 2003, **66**, 620.

97 P. G. Williams, W. Y. Yoshida, R. E. Moore and V. J. Paul, *J. Nat. Prod*., 2003, **66**, 1006.

98 P. G. Williams, W. Y. Yoshida, R. E. Moore and V. J. Paul, *Org. Lett*., 2003, **5**, 4167.

99 S. T. Belt, G. Massé, W. G. Allard, J.-M. Robert and S. J. Rowland, *Tetrahedron Lett*., 2003, **44**, 9103.

100 M. Tsuda, N. Izui, K. Shimbo, M. Sato, E. Fukushi, J. Kawabata, K. Katsumata, T. Horiguchi and J. Kobayashi, *J. Org. Chem*., 2003, **68**, 5339.

101 M. Tsuda, N. Izui, K. Shimbo, M. Sato, E. Fukushi, J. Kawabata and J. Kobayashi, *J. Org. Chem*., 2003, **68**, 9109.

102 M. Suzuki, K. Watanabe, S. Fujiwara, T. Kurasawa, T. Wakabayashi, M. Tsuzuki, K. Iguchi and T. Yamori, *Chem. Pharm. Bull*., 2003, **51**, 724.

103 A. A. Carlos, B. K. Baillie, M. Kawachi and T. Maruyama, *J. Phycol*., 1999, **35**, 1054.

104 K. Onodera, H. Nakamura, Y. Oba and M. Ojika, *Tetrahedron*, 2003, **59**, 1067.

105 B. Suárez-Gómez, M. L. Souto, M. Norte and J. J. Fernández, *J. Nat. Prod*., 2001, **64**, 1363.

106 J. J. Fernández, B. Suárez-Gómez, M. L. Souto and M. Norte, *J. Nat. Prod*., 2003, **66**, 1294.

107 A. Negri, D. Stirling, M. Quilliam, S. Blackburn, C. Bolch, I. Burton, G. Eaglesham, K. Thomas, J. Walter and R. Willis, *Chem. Res. Toxicol*., 2003, **16**, 1029.

108 I. H. Hardt, P. R. Jensen and W. Fenical, *Tetrahedron Lett*., 2000, **41**, 2073.

109 J. A. Kalaitzis, Y. Hamano, G. Nilsen and B. S. Moore, *Org. Lett*., 2003, **5**, 4449.

110 R. T. Williamson, A. Boulanger, A. Vulpanovici, M. A. Roberts and W. H. Gerwick, *J. Org. Chem*., 2002, **67**, 7927.

111 R. T. Williamson, A. Boulanger, A. Vulpanovici, M. A. Roberts and W. H. Gerwick, *J. Org. Chem*., 2003, **68**, 2060.

112 M. Namikoshi, H. Kobayashi, T. Yoshimoto and T. Hosoya, *J. Antibiot.*, 1997, **50**, 890.

113 H. Kobayashi, S. Meguro, T. Yoshimoto and M. Namikoshi, *Tetrahedron*, 2003, **59**, 455.

114 K. Barbeau, G. Zhang, D. H. Live and A. Butler, *J. Am. Chem. Soc*., 2002, **124**, 378.

115 R. J. Bergeron, G. Huang, R. E. Smith, N. Bharti, J. S. McManis and A. Butler, *Tetrahedron*, 2003, **59**, 2007.

116 N. Sitachitta, R. T. Williamson and W. H. Gerwick, *J. Nat. Prod*., 2000, **63**, 197.

117 Z. Xu, Y. Peng and T. Ye, *Org. Lett*., 2003, **5**, 2821.

118 M. Chu, I. Truumees, I. Gunnarsson, W. R. Bishop, W. Kreutner, A. C. Horan, M. G. Patel, V. P. Gullo and M. S. Puar, *J. Antibiot.*, 1993, **46**, 554.

119 J. W. C. Cheing, W. P. D. Goldring and G. Pattenden, *Chem. Commun*., 2003, 2788.

120 L. A. McDonald, D. R. Abbanat, L. R. Barbieri, V. S. Bernan, C. M. Discafani, M. Greenstein, K. Janota, J. D. Korshalla, P. Lassota, M. Tischler and G. T. Carter, *Tetrahedron Lett*., 1999, **40**, 2489.

121 K. Miyashita, T. Sakai and T. Imanishi, *Org. Lett*., 2003, **5**, 2683.

122 H. Luesch, W. Y. Yoshida, R. E. Moore, V. J. Paul and T. H. Corbett, *J. Am. Chem. Soc*., 2001, **123**, 5418.

123 H. Luesch, W. Y. Yoshida, R. E. Moore, V. J. Paul and T. H. Corbett, *Bioorg. Med. Chem*., 2002, **10**, 1973.

124 J. Chen and C. J. Forsyth, *J. Am. Chem. Soc*., 2003, **125**, 8734.

125 I. Bauer, L. Maranda, K. A. Young, Y. Shimizu and S. Huang, *Tetrahedron Lett*., 1995, **36**, 991.

126 L. M. Walsh and J. M. Goodman, *Chem. Commun*., 2003, 2616.

127 J. Kobayashi, T. Kubota, M. Tsuda and T. Endo, *J. Org. Chem*., 2000, **65**, 1349.

128 T. Kubota, T. Endo, M. Tsuda, M. Shiro and J. Kobayashi, *Tetrahedron*, 2001, **57**, 6175.

129 A. K. Gosh and C. Liu, *J. Am. Chem. Soc*., 2003, **125**, 2374.

130 C. Aïssa, R. Riveiros, J. Ragot and A. Fürstner, *J. Am. Chem. Soc*., 2003, **125**, 15512.

131 J. Kobayashi, T. Kubota, T. Endo and M. Tsuda, *J. Org. Chem*., 2001, **66**, 134.

132 M. Satake, M. Shoji, Y. Oshima, H. Naoki, T. Fujita and T. Yasumoto, *Tetrahedron Lett*., 2002, **43**, 5829.

133 C. Tsukano and M. Sasaki, *J. Am. Chem. Soc*., 2003, **125**, 14294.

134 Satake, M. Murata and T. Yasumoto, *J. Am. Chem. Soc*., 1993, **115**, 361.

135 H. Fuwa and M. Sasaki, *J. Synth. Org. Chem. Japan*, 2003, **61**, 742.

136 A. Morohashi, M. Satake and T. Yasumoto, *Tetrahedron Lett*., 1999, **40**, 97.

137 H. Nagai, M. Murata, K. Torigoe, M. Satake and T. Yasumoto, *J. Org. Chem*., 1992, **57**, 5448.

138 A. Morohashi, M. Satake, H. Nagai, Y. Oshima and T. Yasumoto, *Tetrahedron*, 2000, **56**, 8995.

139 M. Inoue, M. Hirama, M. Satake, K. Sugiyama and T. Yasumoto, *Toxicon*, 2003, **41**, 469.

140 Y.-Y. Lin, M. Risk, S. M. Ray, D. Van Engen, J. Clardy, J. Golik, J. C. James and K. Nakanishi, *J. Am. Chem. Soc*., 1981, **103**, 6773.

141 T. K. Han, M. Derby, D. F. Martin, S. D. Wright and M. L. Dao, *Int. J. Toxicol*., 2003, **22**, 73.

142 M. T. Hamann and P. J. Scheuer, *J. Am. Chem. Soc*., 1993, **115**, 5825.

143 G. Goetz, W. Y. Yoshida and P. J. Scheuer, *Tetrahedron*, 1999, **55**, 7739.

144 I. Bonnard, I. Manzanares and K. L. Rinehart, *J. Nat. Prod*., 2003, **66**, 1466.

145 V. Smyrniotopoulos, D. Abatis, L.-A. Tziveleka, C. Tsitsimpikou, V. Roussis, A. Loukis and C. Vagias, *J. Nat. Prod*., 2003, **66**, 21.

146 V. J. Paul and W. Fenical, *Mar. Ecol. Prog. Ser.*, 1986, **34**, 157.

147 L. Commeiras, R. Valls, M. Santelli and J.-L. Parrain, *Synlett*., 2003, 1716.

148 K. M. Fisch, V. Böhm, A. D. Wright and G. M. König, *J. Nat. Prod*., 2003, **66**, 968.

149 S.-E. N. Ayyad, O. B. Abdel-Halim, W. T. Shier and T. R. Hoye, *Z. Naturforsch. C Biosci*., 2003, **58**, 33.

150 S. R. Gedara, O. B. Abdel-Halim, S. H. El-Sharkawy, O. M. Salama, T. W. Shier and A. F. Halim, *Z. Naturforsch. C Biosci*., 2003, **58**, 17.

151 M. S. Ali and M. K. Pervez, *Z. Naturforsch. B Chem. Sci*., 2003, **58**, 438.

152 M. S. Ali and M. K. Pervez, *Nat. Prod. Res*., 2003, **17**, 281.

153 M. S. Ali, M. K. Pervez, M. Saleem and F. Ahmed, *Nat. Prod. Res*., 2003, **17**, 301.

154 H. Soto, J. Rovirosa and A. San-Martín, *Z. Naturforsch. B Chem. Sci*., 2003, **58**, 795.

155 K. Kousaka, N. Ogi, Y. Akazawa, M. Fujieda, Y. Yamamoto, Y. Takada and J. Kimura, *J. Nat. Prod*., 2003, **66**, 1318.

156 S. Carmeli, R. E. Moore and G. M. L. Patterson, *J. Nat. Prod*., 1990, **53**, 1533.

157 S. Carmely, M. Rotem and Y. Kashman, *Magn. Reson. Chem*., 1986, **24**, 343.

158 I. Kitagawa, M. Kobayashi, T. Katori, M. Yamashita, J. Tanaka, M. Doi and T. Ishida, *J. Am. Chem. Soc*., 1990, **112**, 3710.

159 J. Kubanek, P. R. Jensen, P. A. Keifer, M. C. Sullards, D. O. Collins and W. Fenical, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 6916.

160 S.-E. N. Ayyad, S. Z. A. Sowellim, M. S. El-Hosini and A. Abo-Atia, *Z. Naturforsch. C Biosci*., 2003, **58**, 333.

161 H. Tang, Y. Yi, X. Yao, Q. Xu, S. Zhang and H. Lin, *Zhongguo Haiyang Yaowu*, 2003, **22**, 28.

162 H. S. Kang, H. Y. Chung, J. H. Jung, B. W. Son and J. S. Choi, *Chem. Pharm. Bull*., 2003, **51**, 1012.

163 C. Ireland and D. J. Faulkner, *J. Org. Chem*., 1977, **42**, 3157.

164 J. P. Barbosa, V. L. Teixeira, R. Villaça, R. C. Pereira, J. L. Abrantes and I. C. P. da Paixão Frugulhetti, *Biochem. Syst. Ecol*., 2003, **31**, 1451.

165 N. Takada, R. Watanabe, K. Suenaga, K. Yamada and D. Uemura, *J. Nat. Prod*., 2001, **64**, 653.

166 Y. Li, B. Lu, C. Li and Y. Li, *Synth. Commun*., 2003, **33**, 1417.

167 L. R. de Carvalho, M. T. Fujii, N. F. Roque, M. J. Kato and J. H. G. Lago, *Tetrahedron Lett*., 2003, **44**, 2637.

168 G. Guella, D. Skropeta, I. Mancini and F. Pietra, *Chem. Eur. J*., 2003, **9**, 5770.

169 G. Topcu, Z. Aydogmus, S. Imre, A. C. Gören, J. M. Pezzuto, J. A. Clement and D. G. I. Kingston, *J. Nat. Prod*., 2003, **66**, 1505.

170 A. D. Wright, E. Goclik and G. M. König, *J. Nat. Prod*., 2003, **66**, 435.

171 D. Iliopoulou, N. Mihopoulos, C. Vagias, P. Papazafiri and V. Roussis, *J. Org. Chem*., 2003, **68**, 7667.

172 N. Mihopoulos, C, Vagias, E. Mikros, M. Scoullos and V. Roussis, *Tetrahedron Lett*., 2001, **42**, 3749.

173 D. Iliopoulou, N. Mihopoulos, V. Roussis and C. Vagias, *J. Nat. Prod*., 2003, **66**, 1225.

174 X. Fan, N.-J. Xu and J.-G. Shi, *J. Nat. Prod*., 2003, **66**, 455.

175 X. Fan, N. J. Xu and J. G. Shi, *Chinese Chemical Letters*, 2003, **14**, 1045.

176 J. A. Shepherd, W. W. Poon, D. C. Myles and C. F. Clarke, *Tetrahedron Lett*., 1996, **37**, 2395.

177 X. Fan, N. J. Xu and J. G. Shi, *Chinese Chemical Letters*, 2003, **14**, 939.

178 N. Xu, X. Fan, X. Yan, X. Li, R. Niu and C. K. Tseng, *Phytochemistry*, 2003, **62**, 1221.

179 M. Kuniyoshi, N. Oshiro, T. Miono and T. Higa, *J. Chin. Chem. Soc.*, 2003, **50**, 167.

180 M. Norte, J. J. Fernández, M. L. Souto, J. A. Gavín and M. D. Garcia-Grávalos, *Tetrahedron*, 1997, **53**, 3173.

181 M. K. Pec, A. Aguirre, K. Moser-Thier, J. J. Fernandez, M. L. Souto, J. Dorta, F. Diaz-Gonzalez and J. Villar, *Biochem. Pharmacol*., 2003, **65**, 1451.

182 J. J. Sims, G. H. Y. Lin and R. M. Wing, *Tetrahedron Lett*., 1974, **39**, 3487.

183 C. S. Vairappan, *Biomol. Eng*., 2003, **20**, 255.

184 A. G. González, J. Darias, A. Díaz, J. D. Fourneron, J. D. Martín and C. Pérez, *Tetrahedron Lett*., 1976, **35**, 3051.

185 A. G. González, M. J. Delgado, V. S. Martín, M. Martínez-Ripoll and J. Fayos, *Tetrahedron Lett*., 1979, **29**, 2717.

186 M. Pedersen, P. Saenger and L. Fries, *Phytochemistry*, 1974, **13**, 2273.

187 J. M. Kuhajek and D. Schlenk, *Comp. Biochem. Physiol*., 2003, **134C**, 473.

188 A. G. González, J. D. Martín, V. S. Martín, M. Norte, R. Pérez and J. Ruano, *Tetrahedron*, 1982, **38**, 1009.

189 M. Norte, A. G. González, F. Cataldo, M. L. Rodriguez and I. Brito, *Tetrahedron*, 1991, **47**, 9411.

190 H. Kim, W. J. Choi, J. Jung, S. Kim and D. Kim, *J. Am. Chem. Soc*., 2003, **125**, 10238.

191 M. Suzuki, Y. Misano, Y. Matsuo and M. Masuda, *Phytochemistry*, 1996, **43**, 121.

192 H. Lee, H. Kim, S. Baek, S. Kim and D. Kim, *Tetrahedron Lett*., 2003, **44**, 6609.

193 L. Zaman, O. Arakawa, A. Shimosu, Y. Onoue, S. Nishio, Y. Shida and T. Noguchi, *Toxicon*, 1997, **35**, 205.

194 Y. Ni, K. K. D. Amarasinghe, B. Ksebati and J. Montgomery, *Org. Lett*., 2003, **5**, 3771.

195 V. Costantino, E. Fattorusso, C. Imperatore and A. Mangoni, *Eur. J. Org. Chem.,* 2003, 1433.

196 V. Ledroit, C. Debitus, C. Lavaud and G. Massiot, *Tetrahedron Lett.,* 2003, **44**, 225.

197 W. Wang, Y. M. Lee, J. Hong, C.-O. Lee, J. H. Park and J. H. Jung, *Nat. Prod. Sci.*, 2003, **9**, 241.

198 S.-Y. Lee, Q. Zhao, K. Choi, J. Hong, D. S. Lee, C.-O. Lee and J. H. Jung, *Nat. Prod. Sci.*, 2003, **9**, 232.

199 Q. Zhao, Y. Liu, J. Hong, C.-O. Lee, J. H. Park, D. S. Lee and J. H. Jung, *Nat. Prod. Sci.,* 2003, **9**, 18.

200 M. Tsuda, T. Endo, M. Perpelescu, S. Yoshida, K. Watanabe, J. Fromont, Y. Mikami and J. Kobayashi, *Tetrahedron*, 2003, **59**, 1137.

201 T. Rezanka and V. M. Dembitsky, *Eur. J. Org. Chem.,* 2003, 2144.

202 M. Fujita, Y. Nakao, S. Matsunaga, R. W. M. van Soest, Y. Itoh, M. Seiki and N. Fusetani, *J. Nat. Prod.,* 2003, **66**, 569.

203 Q. Zhao, S.-Y. Lee, J. Hong, C.-O. Lee, K. S. Im, C. J. Sim, D. S. Lee and J. H. Jung, *J. Nat. Prod.,* 2003, **66**, 408.

204 Q. Zhao, T. A. Mansoor, J. Hong, C.-O. Lee, K. S. Im, D. S. Lee and J. H. Jung, *J. Nat. Prod.,* 2003, **66**, 725.

205 H.-S. Lee, J.-R. Rho, C. J. Sim and J. Shin, *J. Nat. Prod.,* 2003, **66**, 566.

206 J. C. Braekman, D. Daloze, C. Devijver, D. Dubut and R. W. M. van Soest, *J. Nat. Prod.,* 2003, **66**, 871.

207 M. L. Lerch, M. K. Harper and D. J. Faulkner, *J. Nat. Prod.,* 2003, **66**, 667.

208 R. P. de Jesus and D. J. Faulkner, *J. Nat. Prod.,* 2003, **66**, 671.

209 R. P. Walker and D. J. Faulkner, *J. Org. Chem.*, 1981, **46**, 1475.

210 D. T. A. Youssef, R. W. M. van Soest and N. Fusetani, *J. Nat. Prod.,* 2003, **66**, 861.

211 S. Ohta, H. Okada, H. Kobayashi, J. M. Oclarit and S. Ikegami, *Tetrahedron Lett.*, 1993, **34**, 5935.

212 M. Ojika, Y. Itou and Y. Sakagami, *Biosci. Biotechnol. Biochem.,* 2003, **67**, 1568.

213 C. Jiménez and P. Crews, *J. Nat. Prod.*, 1990, **53**, 978.

214 M. Ichihashi and K. Mori, *Biosci. Biotechnol. Biochem.,* 2003, **67**, 329.

215 N. M. Carballeria and J. Alicea, *Lipids*, 2001, **36**, 83.

216 N. M. Carballeira, H. Cruz, E. A. Orellano and F. A. González, *Chem. Phys. Lipids*, 2003, **126**, 149.

217 K. Watanabe, Y. Tsuda, Y. Yamane, H. Takahashi, K. Higuchi, H. Naoki, T. Fujita and R. M. W. van Soest, *Tetrahedron Lett.*, 2000, **41**, 9271.

218 S. Reber, T. F. Knöpfel and E. M. Carreira, *Tetrahedron*, 2003, **59**, 6813.

219 S. Tsukamoto, H. Kato, H. Hirota and N. Fusetani, *J. Nat. Prod.*, 1997, **60**, 126.

220 A. Umeyama, C. Nagano and S. Arihara, *J. Nat. Prod.*, 1997, **60**, 131.

221 S. López, F. Fernández-Trillo, L. Castedo and C. Saá, *Org. Lett.,* 2003, **5**, 3725.

222 I. van Altena, R. van Soest, M. Roberge and R. J. Andersen, *J. Nat. Prod.,* 2003, **66**, 561.

223 A. Rudi, R. Afanii, L. G. Gravalos, M. Aknin, E. Gaydou, J. Vacelet and Y. Kashman, *J. Nat. Prod.,* 2003, **66**, 682.

224 C.-Y. Wang, B.-G. Wang, S. Wiryowidagdo, V. Wray, R. van Soest, K. G. Steube, H.-S. Guan, P. Proksch and R. Ebel, *J. Nat. Prod.,* 2003, **66**, 51.

225 M. del-S. Jiménez, S. P. Garzón and A. D. Rodríguez, *J. Nat. Prod.,* 2003, **66**, 655.

226 M. Yanai, S. Ohta, E. Ohta, T. Hirata and S. Ikegami, *Bioorg. Med. Chem.,* 2003, **11**, 1715.

227 K. L. Erikson, J. A. Beutler, J. H. Cardellina and M. R. Boyd, *Tetrahedron*, 1995, **51**, 11953.

228 C. M. Cerda-García-Rojas and D. J. Faulkner, *Tetrahedron*, 1995, **51**, 1087.

229 I. R. Czuba, S. Zammit and M. A. Rizzacasa, *Org. Biomol. Chem.,* 2003, **1**, 2044.

230 W. M. Bandaranayake, G. Pattenden and W. A. Wickramasinghe, *Trends Comp. Biochem. Physiol.*, 2002, **9**, 205.

231 J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote and M. R. Prinsep, *Nat. Prod. Rep.*, 2004, **21**, 1.

232 K. Tachibana, P. J. Scheuer, Y. Tsukitani, H. Kikuchi, D. van Engen, J. Clardy, Y. Gopichand and F. J. Schmitz, *J. Am. Chem. Soc.*, 1981, **103**, 2469.

233 T. Yasumoto, M. Murata, Y. Oshima, M. Sano, G. K. Matsumoto and J. Clardy, *Tetrahedron*, 1985, **41**, 1019.

234 Y. Murakami, Y. Oshima and T. Yasumoto, *Bull. Jap. Soc. Sci. Fish.*, 1982, **48**, 69.

235 M. Wiens, B. Luckas, F. Brümmer, M. Shokry, A. Ammar, R. Steffen, R. Batel, B. Diehl-Seifert, H. C. Schröder and W. E. G. Müller, *Mar. Biol.*, 2003, **142**, 213.

236 R. Britton, M. Roberge, C. Brown, R. van Soest and R. J. Andersen, *J. Nat. Prod.,* 2003, **66**, 838.

237 R. Talpir, Y. Benayahu, Y. Kashman, L. Pannell and M. Schleyer, *Tetrahedron Lett.*, 1994, **35**, 4453.

238 P. Crews, J. J. Farias, R. Emrich and P. A. Keifer, *J. Org. Chem*., 1994, **59**, 2932.

239 C. Chevallier, A. D. Richardson, M. C. Edler, E. Hamel, M. K. Harper and C. M. Ireland, *Org. Lett.,* 2003, **5**, 3737.

240 Y. Nakao, J. Kuo, W. Y. Yoshida, M. Kelly and P. J. Scheuer, *Org. Lett.,* 2003, **5**, 1387.

241 Y. Sera, K. Adachi, K. Fujii and Y. Shizuri, *J. Nat. Prod.,* 2003, **66**, 719.

242 K. L. Erickson, K. R. Gustafson, D. J. Milanowski, L. K. Pannell, J. R. Klose and M. R. Boyd, *Tetrahedron*, 2003, **59**, 10231.

243 K. L. Erickson, K. R. Gustafson, L. K. Pannell, J. A. Beutler and M. R. Boyd, *J. Nat. Prod.*, 2002, **65**, 1303.

244 S. Kehraus, G. M. König, A. D. Wright and G. Woerheide, *J. Org. Chem.*, 2002, **67**, 4989.

245 W. Wang and F. Nan, *J. Org. Chem.,* 2003, **68**, 1636.

246 L. T. Tan, R.T. Williamson, W. H. Gerwick, K. S. Watts, K. McGough and R. Jacobs, *J. Org. Chem.*, 2000, **65**, 419.

247 S. Deng and J. Taunton, *J. Am. Chem. Soc.*, 2002, **124**, 916.

248 F. Yokokawa, T. Shiori, Y. In, K. Minoura and T. Ishida, *Pept. Sci.*, 2002, **39**, 41.

249 G. R. Pettit, Z. Cichacz, J. Barkoczy, A. C. Dorsaz, D. L. Herald, M. D. Williams, D. L. Doubek, J. M. Schmidt, L. P. Tackett, D. C. Brune, R. L. Cerny, J. N. A. Hooper and G. J. Bakus, *J. Nat. Prod*., 1993, **56**, 260.

250 G. R. Pettit, R. Tan, Y. Ichihara, M. D. Williams, D. L. Doubek, L. P. Tackett, J. M. Schmidt, R. L. Cerny, M. R. Boyd and J. N. A. Hooper, *J. Nat. Prod*., 1995, **58**, 961.

251 A. Napolitano, M. Rodriquez, I. Bruno, S. Marzocco, G. Autore, R. Riccio and L. Gomez-Paloma, *Tetrahedron*, 2003, **59**, 10203.

252 G. R. Pettit and R. Tan, *Bioorg. Med. Chem. Lett.,* 2003, **13**, 685.

253 W.-L. Li, Y.-H. Yi, H.-M. Wu, Q.-Z. Xu, H.-F. Tang, D.-Z. Zhou, H.-W. Lin and Z.-H. Wang, *J. Nat. Prod.,* 2003, **66**, 146.

254 D. E. Williams, M. Roberge, R. van Soest and R. J. Andersen, *J. Am. Chem. Soc.*, 2003, **125**, 5296.

255 L. M. West, P. T. Northcote and C. N. Battershill, *J. Org. Chem*., 2000, **65**, 445.

256 X. Liao, Y. Wu and J. K. de Brabander, *Angew. Chem. Int. Ed. Eng.*, 2003, **42**, 1648.

257 M. V. D'Auria, L. Gomez-Paloma, L. Minale, A. Zampella, J. F. Verbist, C. Roussakis, C. Debitus and J. Patissou, *Tetrahedron*, 1994, **50**, 4829.

258 A. Zampella, V. Sepe, R. D'Orsi, G. Bifulco, C. Bassarello and M. V. D'Auria, *Tetrahedron: Asymmetry*, 2003, **14**, 1787.

259 N. Fusetani, T. Sugawara, S. Matsunaga and H. Hirota, *J. Org. Chem.*, 1991, **56**, 4971.

260 A. B. Smith III, C. M. Adams, S. A. Barbosa and A. P. Degnan, *J. Am. Chem. Soc.*, 2003, **125**, 350.

261 P. A. Horton, F. E. Koehn, R. E. Longley and O. J. McConnell, *J. Am. Chem. Soc.*, 1994, **116**, 6015.

262 H. Y. Song, J. M. Joo, J. W. Kang, D.-S. Kim, C.-K. Jung, H. S. Kwak, J. H. Park, E. Lee, C. Y. Hong, S. Jeong, K. Jeon and J. H. Park, *J. Org. Chem.,* 2003, **68**, 8080.

263 R. S. Norton, K. D. Croft and R. J. Wells, *Tetrahedron*, 1981, **37**, 2341.

264 J. Á. de la Fuente, S. Manzanaro, M. J. Martín, T. G. de Quesada, I. Reymundo, S. M. Luengo and F. Gago, *J. Med. Chem.*, 2003, **46**, 5208.

265 R. Sakai, H. Matsubara, K. Shimamoto, M. Jimbo, H. Kamiya and M. Namikoshi, *J. Nat. Prod.,* 2003, **66**, 784.

266 N. Lysek, R. Kinscherf, R. Claus and T. Lindel, *Z. Naturforsch. C BioSci.,* 2003, **58**, 568.

267 C. Campagnuolo, C. Fattorusso, E. Fattorusso, A. Ianaro, B. Pisano and O. Taglialatela-Scafati, *Org. Lett.,* 2003, **5**, 673.

268 C. A. Volk and M. Köck, *Org. Lett.,* 2003, **5**, 3567.

269 Y. Kashman, G. Koren-Goldshlager, M. D. Garcia Gravalos and M. Schleyer, *Tetrahedron Lett.*, 1999, **40**, 997.

270 M. R. Heinrich, W. Steglich, M. G. Banwell and Y. Kashman, *Tetrahedron*, 2003, **59**, 9239.

271 S. Sperry and P. Crews, *Tetrahedron Lett.*, 1996, **37**, 2389.

272 J. C. Daab and F. Bracher, *Monatsh. Chem.,* 2003, **134**, 573.

273 S. Tsukamoto, M. Takahashi, S. Matsunaga, N. Fusetani and R. W. M. van Soest, *J. Nat. Prod.*, 2000, **63**, 682.

274 W. R. F. Goundry, J. E. Baldwin and V. Lee, *Tetrahedron*, 2003, **59**, 1719.

275 M. Tsuda, K. Hirano, T. Kubota and J. Kobayashi, *Tetrahedron Lett.*, 1999, **40**, 4819.

276 B. B. Snider and B. Shi, *Tetrahedron Lett.*, 2001, **42**, 1639.

277 S. P. Romeril, V. Lee, T. D. W. Claridge and J. E. Baldwin, *Tetrahedron Lett.*, 2002, **43**, 327.

278 Y. Morimoto, S. Kitao, T. Okita and T. Shoji, *Org. Lett.,* 2003, **5**, 2611.

279 S. P. Romeril, V. Lee, J. E. Baldwin, T. D. W. Claridge and B. Odell, *Tetrahedron Lett.,* 2003, **44**, 7757.

280 J. C. Braekman, D. Daloze, P. Macedo de Abreu, C. Piccinni-Leopardi, G. Germain and M. van Meerssche, *Tetrahedron Lett.*, 1982, **23**, 4277.

281 J. C. Braekman, D. Daloze, N. Defay and D. Zimmermann, *Bull. Soc. Chim. Belg.*, 1984, **93**, 941.

282 T. V. Goud, N. S. Reddy, N. R. Swamy, T. S. Ram and Y. Venkateswarlu, *Biol. Pharm. Bull.*, 2003, **26**, 1498.

283 J. Kobayashi, D. Watanabe, N. Kawasaki and M. Tsuda, *J. Org. Chem.*, 1997, **62**, 9236.

284 T. Nagata, M. Nakagawa and A. Nishida, *J. Am. Chem. Soc.*, 2003, **125**, 7484.

285 K. V. Rao, B. D. Santarsiero, A. D. Mesecar, R. F. Schinazi, B. L. Tekwani and M. T. Hamann, *J. Nat. Prod.,* 2003, **66**, 823.

286 N. L. Segraves, S. Lopez, T. A. Johnson, S. A. Said, X. Fu, F. J. Schmitz, H. Pietraszkiewicz, F. A. Valeriote and P. Crews, *Tetrahedron Lett.,* 2003, **44**, 3471.

287 C. Campagnuolo, E. Fattorusso and O. Taglialatela-Scafati, *Eur. J. Org. Chem.,* 2003, 284.

288 D. B. Stierle and D. J. Faulkner, *J. Nat. Prod*., 1991, **54**, 1131.

289 N. K. Utkina, A. V. Gerasimenko and D. Y. Popov, *Russ. Chem. Bull.*, 2003, **52**, 258.

290 C. M. Zeng, M. Ishibashi, K. Matsumoto, S. Nakaike and J. Kobayashi, *Tetrahedron*, 1993, **49**, 8337.

291 S. Aoki, H. Wei, K. Matsui, R. Rachmat and M. Kobayashi, *Bioorg. Med. Chem.,* 2003, **11**, 1969.

292 L. Calcul, A. Longeon, A. Al-Mourabit, M. Guyot and M. Bourguet-Kondracki, *Tetrahedron*, 2003, **59**, 6539.

293 N. Oku, S. Matsunaga, R. W. M. van Soest and N. Fusetani, *J. Nat. Prod.,* 2003, **66**, 1136.

294 G. R. Pettit, J. C. Collins, J. C. Knight, D. L. Herald, R. A. Nieman, M. D. Williams and R. K. Pettit, *J. Nat. Prod.,* 2003, **66**, 544.

295 K. Warabi, S. Matsunaga, R. W. M van Soest and N. Fusetani, *J. Org. Chem.,* 2003, **68**, 2765.

296 E. Kourany-Lefoll, O. Laprévote, T. Sévenet, A. Montagnac, M. Païs and C. Debitus, *Tetrahedron*, 1994, **50**, 3415.

297 B. J. Neubert and B. B. Snider, *Org. Lett.,* 2003, **5**, 765.

298 P. Crews, D. P. Clark and K. Tenney, *J. Nat. Prod.,* 2003, **66**, 177.

299 R. A. Edrada, C. C. Stessman and P. Crews, *J. Nat. Prod.,* 2003, **66**, 939.

300 K. A. Alvi, B. M. Peters, L. M. Hunter and P. Crews, *Tetrahedron*, 1993, **49**, 329.

301 S. Nakamura, I. Kawasaki, M. Yamashita and S. Ohta, *Heterocycles*, 2003, **60**, 583.

302 M. Assmann, S. Zea and M. Köck, *J. Nat. Prod*., 2001, **64**, 1593.

303 G. Breckle, K. Polborn and T. Lindel, *Z. Naturforsch. B Chem. Sci.,* 2003, **58**, 451.

304 M. Fujita, Y. Nakao, S. Matsunaga, M. Seiki, Y. Itoh, J. Yamashita, R. W. M. van Soest and N. Fusetani, *J. Am. Chem. Soc.,* 2003, **125**, 15700.

305 R. G. Linington, D. E. Williams, A. Tahir, R. van Soest and R. J. Andersen, *Org. Lett.,* 2003, **5**, 2735.

306 S. Nishimura, S. Matsunaga, M. Shibazaki, K. Suzuki, K. Furihata, R. W. M. van Soest and N. Fusetani, *Org. Lett.,* 2003, **5**, 2255.

307 E. A. Jares-Erijman, R. Sakai and K. L. Rinehart, *J. Org. Chem*., 1991, **56**, 5712.

308 E. Palagiano, S. De Marino, L. Minale, R. Riccio, F. Zollo, M. Iorizzi, J. B. Carré, C. Debitus, L. Lucarain and J. Provost, *Tetrahedron*, 1995, **51**, 3675.

309 L. Chang, N. F. Whittaker and C. A. Bewley, *J. Nat. Prod.,* 2003, **66**, 1490.

310 S.-W. Yang, T.-M. Chang, S. A. Pomponi, G. Chen, A. E. Wright, M. Patel, V. Gullo, B. Pramanik and M. Chu, *J. Antibiot.*, 2003, **56**, 970.

311 E. Manzo, R. van Soest, L. Matainaho, M. Roberge and R. J. Andersen, *Org. Lett.,* 2003, **5**, 4591.

312 T. V. Goud, M. Srinivasulu, V. L. N. Reddy, A. V. Reddy, T. P. Rao, D. S. Kumar, U. S. Murty, and Y. Venkateswarlu, *Chem. Pharm. Bull.*, 2003, **51**, 990.

313 K. Moody, R. H. Thomson, E. Fattorusso, L. Minale and G. Sodano, *J. Chem. Soc. Perkins Trans. 1*, 1972, 18.

314 R. Encarnación-Dimayuga, M. R. Ramírez and J. Luna-Herrera, *Pharm. Biology*, 2003, **41**, 384.

315 X.-H. Xu, G.-M. Yao, Y.-M. Li, J.-H. Lu, C. Lin, X. Wang and C.-H. Kong, *J. Nat. Prod.,* 2003, **66**, 285.

316 H.-D. Yoo, D. Leung, J. Sanghara, D. Daley, R. van Soest and R. J. Andersen, *Pharm. Biology*, 2003, **41**, 223.

317 R. Kazlauskas, P. T. Murphy, R. G. Warren, R. J. Wells and J. F. Blount, *Aust. J. Chem.*, 1978, **31**, 2685.

318 A. Bernet, J. Schröder and K. Seifert, *Helv. Chim. Acta*, 2003, **86**, 2009.

319 V. J. R. V. Mukku, R. A. Edrada, F. J. Schmitz, M. K. Shanks, B. Chaudhuri and D. Fabbro, *J. Nat. Prod.,* 2003, **66**, 686.

320 B. Sullivan, P. Djura, D. E. McIntyre and D. J. Faulkner, *Tetrahedron*, 1981, **37**, 979.

321 H. Mitome, T. Nagasawa, H. Miyaoka, Y. Yamada and R. W. M. van Soest, *J. Nat. Prod.,* 2003, **66**, 46.

322 N. K. Utkina, V. A. Denisenko, O. V. Scholokova, M. V. Virovaya and N. G. Prokof'eva, *Tetrahedron Lett.,* 2003, **44**, 101.

323 I. C. Piña, M. L. Sanders and P. Crews, *J. Nat. Prod.,* 2003, **66**, 2.

324 J. S. Simpson, P. Raniga and M. J. Garson, *Tetrahedron Lett*., 1997, **38**, 7947.

325 A. Brust and M. J. Garson, *Tetrahedron Lett.*, 2003, **44**, 327.

326 Y. Nogata, E. Yoshimura, K. Shinshima, Y. Kitano and I. Sakaguchi, *Biofouling*, 2003, **19**, 193.

327 Yasman, R. A. Edrada, V. Wray and P. Proksch, *J. Nat. Prod*., 2003, **66**, 1512.

328 A. T. Pham, T. Ichiba, W. Y. Yoshida, P. J. Scheuer, T. Uchida, J.-I. Tanaka and T. Higa, *Tetrahedron Lett.*, 1991, **32**, 4843.

329 H.-Y. He, J. Salva, R. F. Catalos and D. J. Faulkner, *J. Org. Chem.*, 1992, **57**, 3191.

330 A. Srikishna and S. Gharpure, *J. Chem. Soc. Perkin Trans. 1*, 2000, 3191.

331 A. Srikrishna, S. J. Gharpure and P. Venugopalan, *Indian J. Chem. Sect. B*, 2003, **42**, 129.

332 K. Kodama, R. Higuchi, T. Miyamoto and R. W. M. van Soest, *Org. Lett.,* 2003, **5**, 169.

333 N. Soji, A. Umeyama, M. Teranaka and S. Arihara, *J. Nat. Prod.*, 1996, **59**, 448.

334 S. Díaz, J. Cuesta, A. González and J. Bonjoch, *J. Org. Chem.,* 2003, **68**, 7400.

335 W. C. Taylor and S. Toth, *Aust. J. Chem.*, 1997, **50**, 895.

336 M. Arnó, M. A. González and R. J. Zaragozá, *J. Org. Chem.,* 2003, **68**, 1242.

337 R. Lucas, A. Casapullo, L. Ciasullo, L. Gomez-Paloma and M. Payá, *Life Sci.,* 2003, **72**, 2543.

338 L. Ciasullo, A. Cutignano, A. Casapullo, R. Puliti, C. A. Mattia, C. Debitus, R. Riccio and L. Gomez-Paloma, *J. Nat. Prod*., 2002, **65**, 1210.

339 P. Phuwapraisirisan, S. Matsunaga, N. Fusetani, N. Chaitanawisuti, S. Kritsanapuntu and P. Menasveta, *J. Nat. Prod.,* 2003, **66**, 289.

340 Y. Liu, T. A. Mansoor, J. Hong, C.-O. Lee, C. J. Sim, K. S. Im, N. D. Kim and J. H. Jung, *J. Nat. Prod.,* 2003, **66**, 1451.

341 Y. Liu, J. Hong, C.-O. Lee, K. S. Im, N. D. Kim, J. S. Choi and J. H. Jung, *J. Nat. Prod*., 2002, **65**, 1307.

342 H. H. Issa, J. Tanaka and T. Higa, *J. Nat. Prod.,* 2003, **66**, 251.

343 T. N. Makarieva, J.-R. Rho, H.-S. Lee, E. A. Santalova, V. Stonik and J. Shin, *J. Nat. Prod.,* 2003, **66**, 1010.

344 S.-W. Yang, T.-M. Chan, S. A. Pomponi, W. Gonsiorek, G. Chen, A. E. Wright, W. Hipkin, M. Patel, V. Gullo, B. Pramanik, P. Zavodny and M. Chu, *J. Antibiot*., 2003, **56**, 783.

345 A. R. Díaz-Marrero, I. Brito, E. Dorta, M. Cueto, A. San-Martín and J. Darias, *Tetrahedron Lett.,* 2003, **44**, 5939.

346 S. De Rosa, A. Crispino, A. De Giulio, C. Iodice, P. Amodeo and T. Tancredi, *J. Nat. Prod.*, 1999, **62**, 1316.

347 D. Demeke and C. J. Forsyth, *Org. Lett.,* 2003, **5**, 991.

348 M. Tsoukatou, H. Siapi, C. Vagias and V. Roussis, *J. Nat. Prod.,* 2003, **66**, 444.

349 S. Tsukamoto, S. Miura, R. W. M. van Soest and T. Ohta, *J. Nat. Prod.,* 2003, **66**, 438.

350 S. Tsukamoto, M. Tatsuno, R. W. M. van Soest, H. Yokosawa and T. Ohta, *J. Nat. Prod.,* 2003, **66**, 1181.

351 R. A. Keyzers, P. T. Northcote and M. V. Berridge, *Aust. J. Chem.,* 2003, **56**, 279.

352 N. Fusetani, S. Matsunaga and S. Konosu, *Tetrahedron Lett.*, 1981, **22**, 1985.

353 S.-W. Yang, A. Buivich, T.-M. Chan, M. Smith, J. Lachowicz, S. A. Pomponi, A. E. Wright, R. Mierzwa, M. Patel, V. Gullo and M. Chu, *Bioorg. Med. Chem. Lett.,* 2003, **13**, 1791.

354 S.-W. Yang, T.-M. Chan, S. A. Pomponi, G. Chen, D. Loebenberg, A. Wright, M. Patel, V. Gullo, B. Pramanik and M. Chu, *J. Antibiot*., 2003, **56**, 186.

355 A. S. Antonov, S. S. Afiyatullov, A. I. Kalinovsky, L. P. Ponomarenko, P. S. Dmitrenok, D. L. Aminin, I. G. Agafonova and V. A. Stonik, *J. Nat. Prod.,* 2003, **66**, 1082.

356 C. P. Ridley and D. J. Faulkner, *J. Nat. Prod.,* 2003, **66**, 1536.

357 T. Teruya, S. Nakagawa, T. Koyama, K. Suenaga, M. Kita and D. Uemura, *Tetrahedron Lett.,* 2003, **44**, 5171.

358 S. Ohta, M. Uno, M. Tokumasu, Y. Hiraga and S. Ikegami, *Tetrahedron Lett.*, 1996, **37**, 7765.

359 Y. Mizushina, C. Murakami, H. Takikawa, N. Kasai, X. Xu, K. Mori, M. Oshige, T. Yamaguchi, M. Saneyoshi, N. Shimazaki, O. Koiwai, H. Yoshida, F. Sugawara and K. Sakaguchi, *J. Biochem.*, 2003, **133**, 541.

360 I. Carletti, C. Long, C. Funel and P. Amade, *J. Nat. Prod.,* 2003, **66**, 25.

361 C. B. Rao, V. C. Sekhar, D. V. Rao, B. Sarvani and D. K. M. Lakshmi, *Asian J. Chem.*, 2003, **15**, 1161.

362 A. S. Dmitrenok, P. Radhika, V. Anjaneyulu, S. Subrahmanyam, P. V. Subba Rao, P. S. Dmitrenok and V. M. Boguslavsky, *Russ. Chem. Bull.*, 2003, **52**, 1868.

363 A. Patra and A. Majumdar, *ARKIVOC*, 2003, 133.

364 M. Ojika, M. K. Islam, T. Shintani, Y. Zhang, T. Okamoto and Y. Sakagami, *Biosci. Biotechnol. Biochem.*, 2003, **67**, 1410.

365 M. Hirono, M. Ojika, H. Mimura, Y. Nakanishi and M. Maeshima, *J. Biochem.*, 2003, **133**, 811.

366 Y. T. Chang, C. L. Lin, A. T. Khalil and Y. C. Shen, *Chin. Pharm. J.*, 2003, **55**, 129.

367 T. Iwagawa, M. Miyazaki, H. Okamura, M. Nakatani, M. Doe and K. Takemura, *Tetrahedron Lett.*, 2003, **44**, 2533.

368 T. Rezanka and V. M. Dembitsky, *Eur. J. Org. Chem.*, 2003, 309.

369 K. Watanabe, M. Sekine and K. Iguchi, *J. Nat. Prod.*, 2003, **66**, 1434.

370 K. Watanabe, M. Sekine and K. Iguchi, *Chem. Pharm. Bull.*, 2003, **51**, 909.

371 N. Hashimoto, S. Fujiwara, K. Watanabe, K. Iguchi and M. Tsuzuki, *Lipids*, 2003, **38**, 991.

372 K. B. Iken and B. J. Baker, *J. Nat. Prod.*, 2003, **66**, 888.

373 M. Gavagnin, E. Mollo, F. Castelluccio, A. Crispino and G. Cimino, *J. Nat. Prod.*, 2003, **66**, 1517.

374 K. Iguchi, K. Mori, M. Suzuki, H. Takahashi and Y. Yamada, *Chem. Lett.*, 1986, 1789.

375 E. P. Kündig, R. Cannas, M. Laxmisha, L. Ronggang and S. Tchertchian, *J. Am. Chem. Soc.*, 2003, **125**, 5642.

376 J. Tanaka, H. Miki and T. Higa, *J. Nat. Prod.*, 1992, **55**, 1522.

377 H. K. Yim, Y. Liao and H. N. C. Wong, *Tetrahedron*, 2003, **59**, 1877.

378 J. Y. Su, Y. Y. Kuang and L. M. Zeng, *Huaxue Xuebao*, 2003, **61**, 1097.

379 A. Ata, J. Ackerman and P. Radhika, *Tetrahedron Lett.*, 2003, **44**, 6951.

380 K. Mori, K. Iguchi, N. Yamada, Y. Yamada and Y. Inouye, *Chem. Pharm. Bull.*, 1988, **36**, 2840.

381 J. Shin and W. Fenical, *J. Org. Chem.*, 1991, **56**, 3392.

382 S. A. Look and W. Fenical, *J. Org. Chem.*, 1982, **47**, 4129.

383 H. Miyaoka, Y. Isaji, H. Mitome and Y. Yamada, *Tetrahedron*, 2003, **59**, 61.

384 B. F. Bowden, J. C. Coll, J. M. Gulbis, M. F. Mackay and R. H. Willis, *Aust. J. Chem.*, 1986, **39**, 803.

385 D. R. Williams and R. W. Heidebrecht, *J. Am. Chem. Soc.*, 2003, **125**, 1843.

386 J. Marrero, A. D. Rodríguez, P. Baran and R. G. Raptis, *J. Org. Chem.*, 2003, **68**, 4977.

387 A. D. Rodríguez, E. González and S. D. Huang, *J. Org. Chem.*, 1998, **63**, 7083.

388 T. J. Heckrodt and J. Mulzer, *J. Am. Chem. Soc.*, 2003, **125**, 4680.

389 A. D. Rodríguez, C. Ramirez, I. I. Rodríguez and C. L. Barnes, *J. Org. Chem.*, 2000, **65**, 1390.

390 A. D. Rodríguez and C. Ramirez, *Org. Lett.*, 2000, **2**, 507.

391 A. I. Kim and S. D. Rychnovsky, *Angew. Chem. Int. Ed. Eng.*, 2003, **42**, 1267.

392 Y. P. Shi, I. I. Rodríguez and A. D. Rodríguez, *Tetrahedron Lett.*, 2003, **44**, 3249.

393 A. Ata, R. G. Kerr, C. E. Moya and R. S. Jacobs, *Tetrahedron*, 2003, **59**, 4215.

394 A. C. Kohl, A. Ata and R. G. Kerr, *J. Ind. Microbiol. Biotechnol.*, 2003, **30**, 495.

395 L. D. Mydlarz, R. S. Jacobs, J. Boehnlein and R. G. Kerr, *Chem. Biol.*, 2003, **10**, 1051.

396 A. D. Rodríguez, C. Ramirez, I. I. Rodríguez and E. González, *Org. Lett.*, 1999, **1**, 527.

397 J. P. Davidson and E. J. Corey, *J. Am. Chem. Soc.*, 2003, **125**, 13486.

398 I. I. Rodríguez and A. D. Rodríguez, *J. Nat. Prod.*, 2003, **66**, 855.

399 A. D. Rodríguez, C. Ramirez and I. I. Rodríguez, *J. Nat. Prod.*, 1999, **62**, 997.

400 A. D. Rodríguez and Y. P. Shi, *Tetrahedron*, 2000, **56**, 9015.

401 P. Baran, R. G. Raptis, A. D. Rodríguez, I. I. Rodríguez and Y. P. Shi, *J. Chem. Crystallogr.*, 2003, **33**, 711.

402 H. Gross, S. Kehraus, M. Nett, G. M. König, W. Beil and A. D. Wright, *Org. Biomol. Chem.*, 2003, **1**, 944.

403 S. Carmely, A. Groweiss and Y. Kashman, *J. Org. Chem.*, 1981, **46**, 4279.

404 X. H. Xu, C. H. Kong, C. J. Lin, X. Wang and J. H. Lu, *Gaodeng Xuexiao Huaxue Xuebao*, 2003, **24**, 1023.

405 X. H. Xu, C. H. Kong, C. J. Lin, X. Wang, Y. D. Zhu and H. S. Yang, *Chin. J. Chem.*, 2003, **21**, 1506.

406 P. W. Hsieh, F. R. Chang, A. T. McPhail, K. H. Lee and Y. C. Wu, *Nat. Prod. Res.*, 2003, **17**, 409.

407 Y. Kashman, M. Bodner, Y. Loya and Y. Benayahu, *Isr. J. Chem.*, 1977, **16**, 1.

408 A. F. Ahmed, R. T. Shiue, G. H. Wang, C. F. Dai, Y. H. Kuo and J. H. Sheu, *Tetrahedron*, 2003, **59**, 7337.

409 K. I. Marville, S. McLean, W. F. Reynolds and W. F. Tinto, *J. Nat. Prod.*, 2003, **66**, 1284.

410 J. Marrero, A. D. Rodríguez, P. Baran and R. G. Raptis, *Org. Lett.*, 2003, **5**, 2551.

411 Y. C. Shen, Y. L. Pan, C. L. Ko, Y. H. Kuo and C. Y. Chen, *J. Chin. Chem. Soc.*, 2003, **50**, 471.

412 J. H. Sheu, G. H. Wang, C. Y. Duh and K. Soong, *J. Nat. Prod.*, 2003, **66**, 662.

413 Y. Nakao, S. Yoshida, S. Matsunaga and N. Fusetani, *J. Nat. Prod.*, 2003, **66**, 524.

414 T. Kusumi, H. Uchida, M. O. Ishitsuka, H. Yamamoto and H. Kakisawa, *Chem. Lett.*, 1988, 1077.

415 O. Corminboeuf, L. E. Overman and L. D. Pennington, *Org. Lett.*, 2003, **5**, 1543.

416 A. D. Rodríguez and O. M. Cóbar, *Chem. Pharm. Bull.*, 1995, **43**, 1853.

417 O. Corminboeuf, L. E. Overman and L. D. Pennington, *J. Am. Chem. Soc.*, 2003, **125**, 6650.

418 C. A. Ospina, A. D. Rodríguez, E. Ortega-Barria and T. L. Capson, *J. Nat. Prod.*, 2003, **66**, 357.

419 A. D. Rodríguez and O. M. Cóbar, *Tetrahedron*, 1995, **51**, 6869.

420 B. F. Bowden, J. C. Coll and I. M. Vasilescu, *Aust. J. Chem.*, 1989, **42**, 1705.

421 A. S. R. Anjaneyulu, V. L. Rao, V. G. Sastry, M. J. R. V. Venugopal and F. J. Schmitz, *J. Nat. Prod.*, 2003, **66**, 507.

422 P. J. Sung, T. Y. Fan, L. S. Fang, J. H. Sheu, S. L. Wu, G. H. Wang and M. R. Lin, *Heterocycles*, 2003, **61**, 587.

423 Y. C. Shen, Y. C. Lin, C. L. Ko and L. T. Wang, *J. Nat. Prod.*, 2003, **66**, 302.

424 Y. C. Shen, Y. C. Lin and Y. L. Huang, *J. Chin. Chem. Soc.*, 2003, **50**, 1267.

425 N. Krishna, P. Muralidhar, M. M. K. Kumar, D. V. Rao and C. B. Rao, *Asian J. Chem.*, 2003, **15**, 344.

426 P. J. Sung and T. Y. Fan, *Heterocycles*, 2003, **60**, 1199.

427 S. L. Wu, P. J. Sung, J. H. Su and J. H. Sheu, *J. Nat. Prod.*, 2003, **66**, 1252.

428 P. J. Sung, T. Y. Fan, L. S. Fang, S. L. Wu, J. J. Li, M. C. Chen, Y. M. Cheng and G. H. Wang, *Chem. Pharm. Bull.*, 2003, **51**, 1429.

429 T. Iwagawa, N. Nishitani, S. Kurosaki, H. Okamura, M. Nakatani, M. Doe and K. Takemura, *J. Nat. Prod.*, 2003, **66**, 1412.

430 O. Taglialatela-Scafati, K. S. Craig, D. Rebérioux, M. Roberge and R. J. Andersen, *Eur. J. Org. Chem.*, 2003, 3515.

431 O. Taglialatela-Scafati, U. Deo-Jangra, M. Campbell, M. Roberge and R. J. Andersen, *Org. Lett.*, 2002, **4**, 4085.

432 D. Banjoo, B. S. Mootoo, R. S. Ramsewak, R. Sharma, A. J. Lough, S. McLean and W. F. Reynolds, *J. Nat. Prod.*, 2002, **65**, 314.

433 R. Dookran, D. Maharaj, B. S. Mootoo, R. Ramsewak, S. McLean, W. F. Reynolds and W. F. Tinto, *J. Nat. Prod.*, 1993, **56**, 1051.

434 Y. Kashman and A. Groweiss, *Tetrahedron Lett.*, 1978, 4833.

435 H. Miyaoka, M. Nakano, K. Iguchi and Y. Yamada, *Heterocycles*, 2003, **61**, 189.

436 H. Miyaoka, H. Mitome, H. M. Nakano and Y. Yamada, *Tetrahedron*, 2000, **56**, 7737.

437 B. F. Bowden, B. J. Cusack and A. Dangel, *Marine Drugs*, 2003, 18.

438 J. C. Braekman, D. Daloze, B. Tursch, J. P. Declercq, G. Germain and M. van Meerssche, *Bull. Soc. Chim. Belg.*, 1979, **88**, 71.

439 A. Fontana, M. L. Ciavatta and G. Cimino, *J. Org. Chem.*, 1998, **63**, 2845.

440 H. Miyaoka, M. Yamanishi, Y. Kajiwara and Y. Yamada, *J. Org. Chem.*, 2003, **68**, 3476.

441 I. S. Marcos, A. B. Pedrero, M. J. Sexmero, D. Diez, P. Basabe, N. García, R. F. Moro, H. B. Broughton, F. Mollinedo and J. G. Urones, *J. Org. Chem.*, 2003, **68**, 7496.

442 C. Subrahmanyam, S. R. Kumar and G. D. Reddy, *Indian J. Chem. Sect. B*, 2003, **42**, 219.

443 J. H. Sheu, L. F. Huang, S. P. Chen, Y. L. Yang, P. J. Sung, G. H. Wang, J. H. Su, C. H. Chao, W. P. Hu and J. J. Wang, *J. Nat. Prod.*, 2003, **66**, 917.

444 A. D. Wright, E. Goclik and G. M. König, *J. Nat. Prod.*, 2003, **66**, 157.

445 A. S. R. Anjaneyulu, V. L. Rao and V. G. Sastry, *Nat. Prod. Res.*, 2003, **17**, 149.

446 A. F. Ahmed, C. F. Dai, Y. H. Kuo and J. H. Sheu, *Steroids*, 2003, **68**, 377.

447 W. H. Zhang, W. K. Liu and C. T. Che, *Chem. Pharm. Bull.*, 2003, **51**, 1009.

448 W. J. Lan, C. W. Lin, J. Y. Su and L. M. Zeng, *Gaodeng Xuexiao Huaxue Xuebao*, 2003, **24**, 2019.

449 S. Diochot, E. Loret, T. Bruhn, L. Béress and M. Lazdunski, *Mol. Pharmacol.*, 2003, **64**, 59.

450 P. Macek and D. Lebez, *Toxicon*, 1988, **26**, 441.

451 B. B. Bonev, Y. H. Lam, G. Anderluh, A. Watts, R. S. Norton and F. Separovic, *Biophys. J.*, 2003, **84**, 2382.

452 G. Anderluh, M. D. Serra, G. Viero, G. Guella, P. Macek and G. Menestrina, *J. Biol. Chem.*, 2003, **278**, 45216.

453 P. Malovrh, G. Viero, M. D. Serra, Z. Podlesek, J. H. Lakey, P. Macek, G. Menestrina and G. Anderluh, *J. Biol. Chem.*, 2003, **278**, 22678.

454 G. Anderluh, P. Macek and J. H. Lakey, *Toxicon*, 2003, **42**, 225.

455 B. Yao, M. R. Prinsep, B. K. Nicholson and D. P. Gordon, *J. Nat. Prod*., 2003, **66**, 1074.

456 D. T. Harwood, S. Urban, J. W. Blunt and M. H. G. Munro, *Nat. Prod. Res*., 2003, **17**, 15.

457 L. Peters, G. M. König, H. Terlau and A. D. Wright*, J. Nat. Prod*., 2002, **65**, 1633.

458 L. Peters, G. M. König, A. D. Wright, R. Pukall, E. Stackebrandt, L. Eberl and K. Riedel, *Appl. Environ. Microbiol*., 2003, **69**, 3469.

459 P. Wulff, J. S. Carle and C. Christophersen, *J. Chem. Soc. Perkin Trans. 1*, 1981, 2895.

460 J. S. Carle and C. Christophersen, *J. Org. Chem*., 1981, **46**, 3440.

461 M. V. Laycock, J. L. C. Wright, J. A. Findlay and A. D. Patil, *Can. J. Chem*., 1986, **64**, 1312.

462 J. L. C. Wright, *J. Nat. Prod*., 1984, **47**, 893.

463 Y. H. Choi, A. Park, F. J. Schmitz and I. van Altena, *J. Nat. Prod*., 1993, **56**, 1431.

464 V. F. Ferreira, A. Park, F. J. Schmitz and F. A. Valeriote, *Tetrahedron*, 2003, **59**, 1349.

465 A. Cutignano, A. Fontana, L. Renzulli and G. Cimino, *J. Nat. Prod.*, 2003, **66**, 1399.

466 R. R. Vardaro, V. Di Marzo and G. Cimino, *Tetrahedron Lett.*, 1992, **33**, 2875.

467 C. Ireland and P. J. Scheuer, *Science*, 1979, **205**, 922.

468 M. Gavagnin, A. Spinella, F. Castelluccio, G. Cimino and A. Marin, *J. Nat. Prod.*, 1994, **57**, 298.

469 A. K. Miller and D. Trauner, *Angew. Chem. Int. Ed. Eng.*, 2003, **42**, 549.

470 K. J. James, M. D. Sierra, M. Lehane, A. B. Magdalena and A. Furey, *Toxicon*, 2003, **41**, 277.

471 M. Satake, K. Ofuji, H. Naoki, K. J. James, A. Furey, T. McMahon, J. Silke and T. Yasumoto, *J. Am. Chem. Soc.*, 1998, **120**, 9967.

472 K. C. Nicolaou, Y. Li, N. Uesaka, T. V. Koftis, S. Vyskocil, T. Ling, M. Govindasamy, W. Qian, F. Bernal and D. Y. K. Chen, *Angew. Chem. Int. Ed. Eng.*, 2003, **42**, 3643.

473 K. C. Nicolaou, D. Y. K. Chen, Y. Li, W. Qian, T. Ling, S. Vyskocil, T. V. Koftis, M. Govindasamy and N. Uesaka, *Angew. Chem. Int. Ed. Eng.*, 2003, **42**, 3649.

474 A. Tarui, K. Shibata, S. Takahashi, Y. Kera, T. Munegumi and R. H. Yamada, *Comp. Biochem. Physiol.*, 2003, **134B**, 79.

475 W. P. Kelley, A. M. Wolters, J. T. Sack, R. A. Jockusch, J. C. Jurchen, E. R. Williams, J. V. Sweedler and W. F. Gilly, *J. Biol. Chem.*, 2003, **278**, 34934.

476 L. Meijer, A. L. Skaltsounis, P. Magiatis, P. Polychronopoulos, M. Knockaert, M. Leost, X. P. Ryan, C. A. Vonica, A. Brivanlou, R. Dajani, C. Crovace, C. Tarricone, A. Musacchio, S. M. Roe, L. Pearl and P. Greengard, *Chem. Biol.*, 2003, **10**, 1255.

477 A. Cutignano, A. Tramice, S. De Caro, G. Villani, G. Cimino and A. Fontana, *Angew. Chem. Int. Ed. Eng.*, 2003, **42**, 2633.

478 A. Spinella, L. A. Alvarez, A. Passeggio and G. Cimino, *Tetrahedron*, 1993, **49**, 1307.

479 O. Grovel, Y. F. Pouchus and J. F. Verbist, *Toxicon*, 2003, **42**, 297.

480 R. J. Andersen, D. J. Faulkner, H. C. Heng, G. D. van Duyne and J. Clardy, *J. Am. Chem. Soc.*, 1985, **107**, 5492.

481 M. Facompré, C. Tardy, C. Bal-Mahieu, P. Colson, C. Perez, I. Manzanares, C. Cuevas and C. Bailly, *Cancer Res.*, 2003, **63**, 7392.

482 Y. Furukawa, K. Nakamaru, K. Sasaki, Y. Fujisawa, H. Minakata, S. Ohta, F. Morishita, O. Matsushima, L. Li, V. Alexeeva, T. A. Ellis, N. C. Dembrow, J. Jing, J. V. Sweedler, K. R. Weiss and F. S. Vilim, *J. Neurophysiology*, 2003, **89**, 3114.

483 E. C. Jimenez, R. P. Shetty, M. Lirazan, J. Rivier, C. Walker, F. C. Abogadie, D. Yoshikami, L. J. Cruz and B. M. Olivera, *J. Neurochem.*, 2003, **85**, 610.

484 R. Jacobsen, D. Yoshikami, M. Ellison, J. Martinez, W. R. Gray, G. E. Cartier, K. J. Shon, D. R. Groebe, S. N. Abramson, B. M. Olivera and J. M. McIntosh, *J. Biol. Chem.*, 1997, **272**, 22531.

485 S. W. Chi, K. H. Park, J. E. Suk, B. M. Olivera, J. M. McIntosh and K. H. Han, *J. Biol. Chem.*, 2003, **278**, 42208.

486 C. X. Fan, X. K. Chen, C. Zhang, L. X. Wang, K. L. Duan, L. L. He, Y. Cao, S. Y. Liu, M. N. Zhong, C. Ulens, J. Tytgat, J. S. Chen, C. W. Chi and Z. Zhou, *J. Biol. Chem.*, 2003, **278**, 12624.

487 A. López-Macià, J. C. Jiménez, M. Royo, E. Giralt and F. Albericio, *J. Am. Chem. Soc.*, 2001, **123**, 11398.

488 Y. Suarez, L. Gonzalez, A. Cuadrado, M. Berciano, M. Lafarga and A. Munoz, *Molecular Cancer Therapeutics*, 2003, **2**, 863.

489 G. R. Pettit, Y. Kamano, H. Kizu, C. Dufresne, C. L. Herald, R. J. Bontems, J. M. Schmidt, F. E. Boettner and R. A. Nieman, *Heterocycles*, 1989, **28**, 553.

490 T. Oda, Z. D. Crane, C. W. Dicus, B. A. Sufi and R. B. Bates, *J. Mol. Biol.*, 2003, **328**, 319.

491 R. Iijima, J. Kisugi and M. Yamazaki, *Dev. Comp. Immunol.*, 2003, **27**, 305.

492 R. Garimella, Y. Xu, C. H. Schein, K. Rajarathnam, G. T. Nagle, S. D. Painter and W. Braun, *Biochemistry*, 2003, **42**, 9970.

493 M. Gavagnin, M. Carbone, E. Mollo and G. Cimino, *Tetrahedron Lett.*, 2003, **44**, 1495.

494 A. Spinella, L. A. Alvarez, C. Avila and G. Cimino, *Tetrahedron Lett.*, 1994, **35**, 8665.

495 A. Fontana, A. Tramice, A. Cutignano, G. d'Ippolito, M. Gavagnin and G. Cimino, *J. Org. Chem.*, 2003, **68**, 2405.

496 M. Gavagnin, M. Carbone, E. Mollo and G. Cimino, *Tetrahedron*, 2003, **59**, 5579.

497 M. T. Davies-Coleman and D. J. Faulkner, *Tetrahedron*, 1991, **47**, 9743.

498 M. Gavagnin, A. de Napoli, G. Cimino, K. Iken, C. Avila and F. J. Garcia, *Tetrahedron: Asymmetry*, 1999, **10**, 2647.

499 G. Cimino, M. Gavagnin, G. Sodano, R. Puliti, C. A. Mattia and L. Mazzarella, *Tetrahedron*, 1988, **44**, 2301.

500 M. Gavagnin, A. Spinella, G. Cimino and G. Sodano, *Tetrahedron Lett.*, 1990, **31**, 6093.

501 A. Fontana, A. Tramice, A. Cutignano, G. d'Ippolito, L. Renzulli and G. Cimino, *Eur. J. Org. Chem.*, 2003, 3104.

502 A. R. Díaz-Marrero, E. Dorta, M. Cueto, J. Rovirosa, A. San-Martín, A. Loyola and J. Darias, *Tetrahedron*, 2003, **59**, 4805.

503 Y. Okamoto, N. Nitanda, M. Ojika and Y. Sakagami, *Biosci. Biotechnol. Biochem.*, 2001, **65**, 474.

504 Y. Okamoto, N. Nitanda, M. Ojika and Y. Sakagami, *Biosci. Biotechnol. Biochem.*, 2003, **67**, 460.

505 M. Suzuki and E. Kurosawa, *Phytochemistry*, 1985, **24**, 1999.

506 M. B. Ksebati and F. J. Schmitz, *J. Org. Chem.*, 1987, **52**, 3766.

507 E. J. Dumdei, J. Kubanek, J. E. Coleman, J. Pika, R. J. Andersen, J. R. Steiner and J. Clardy, *Can. J. Chem.*, 1997, **75**, 773.

508 A. R. Díaz-Marrero, E. Dorta, M. Cueto, J. Rovirosa, A. San-Martín, A. Loyola and J. Darias, *ARKIVOC*, 2003, 107.

509 A. Aiello, E. Fattorusso, A. Mangoni and M. Menna, *Eur. J. Org. Chem.*, 2003, 734.

510 T. C. McKee, D. L. Galinis, L. K. Pannell, J. H. Cardellina, J. Laakso, C. M. Ireland, L. Murray, R. J. Capon and M. R. Boyd, *J. Org. Chem.*, 1998, **63**, 7805.

511 R. Shen, C. T. Lin, E. J. Bowman, B. J. Bowman and J. A. Porco, *J. Am. Chem. Soc.*, 2003, **125**, 7889.

512 J. Kobayashi, J. F. Cheng, T. Ohta, H. Nakamura, S. Nozoe, Y. Hirata, Y. Ohizumi and T. Sasaki, *J. Org. Chem.*, 1988, **53**, 6147.

513 M. Tsuda, K. Nozawa, K. Shimbo, H. Ishiyama, E. Fukushi, J. Kawabata and J. Kobayashi, *Tetrahedron Lett.*, 2003, **44**, 1395.

514 H. H. Issa, J. Tanaka, R. Rachmat and T. Higa, *Tetrahedron Lett.*, 2003, **44**, 1243.

515 L. Garrido, E. Zubía, M. J. Ortega and J. Salvá, *J. Org. Chem.*, 2003, **68**, 293.

516 A. Rudi, L. Chill, M. Aknin and Y. Kashman, *J. Nat. Prod.*, 2003, **66**, 575.

517 L. J. Perez and D. J. Faulkner, *J. Nat. Prod.*, 2003, **66**, 247.

518 A. R. Carroll, B. F. Bowden, J. C. Coll, D. C. R. Hockless, B. W. Skelton and A. H. White, *Aust. J. Chem.*, 1994, **47**, 61.

519 B. McKeever and G. Pattenden, *Tetrahedron*, 2003, **59**, 2701.

520 A. R. Carroll, J. C. Coll, D. J. Bourne, J. K. MacLeod, M. T. Zabriskie, C. M. Ireland and B. F. Bowden, *Aust. J. Chem.*, 1996, **49**, 659.

521 P. Wipf and Y. Uto, *J. Org. Chem.*, 2000, **65**, 1037.

522 X. Salvatella, J. M. Caba, F. Albericio and E. Giralt, *J. Org. Chem.*, 2003, **68**, 211.

523 M. M. Joullié, M. S. Leonard, P. Portonovo, B. Liang, X. Ding and J. J. La Clair, *Bioconjugate Chem.*, 2003, **14**, 30.

524 J. A. Tincu, A. G. Craig and S. W. Taylor, *Biochem. Biophys. Res. Commun.*, 2000, **270**, 421.

525 J. A. Tincu, L. P. Menzel, R. Azimov, J. Sands, T. Hong, A. J. Waring, S. W. Taylor and R. I. Lehrer, *J. Biol. Chem.*, 2003, **278**, 13546.

526 W. S. Jang, K. N. Kim, Y. S. Lee, M. H. Nam and I. H. Lee, *FEBS Lett.*, 2002, **521**, 81.

527 W. S. Jang, C. H. Kim, K. N. Kim, S. Y. Park, J. H. Lee, S. M. Son and I. H. Lee, *Antimicrob. Agents Chemother.*, 2003, **47**, 2481.

528 J. L. Urdiales, P. Morata, I. Nunez de Castro and F. Sanchez-Jimenez, *Cancer Letters*, 1996, **102**, 31.

529 M. Broggini, S. V. Marchini, E. Galliera, P. Borsotti, G. Taraboletti, E. Erba, M. Sironi, J. Jimeno, G. T. Faircloth, R. Giavazzi and M. D'Incalci, *Leukemia*, 2003, **17**, 52.

530 M. Pérez, M. Sadqi, V. Muñoz and J. Ávila, *Biochim. Biophys. Acta*, 2003, **1639**, 133.

531 K. Fukui, T. Ueki, H. Ohya and H. Michibata, *J. Am. Chem. Soc.*, 2003, **125**, 6352.

532 S. Hirsch, A. Miroz, P. McCarthy and Y. Kashman, *Tetrahedron Lett.*, 1989, **30**, 4291.

533 E. Vaz, M. Fernandez-Suarez and L. Muñoz, *Tetrahedron: Asymmetry*, 2003, **14**, 1935.

534 M. F. Raub, J. H. Cardellina, M. I. Choudhary, C. Z. Ni, J. Clardy and M. C. Alley, *J. Am. Chem. Soc.*, 1991, **113**, 3178.

535 C. Agami, F. Couty, G. Evano, F. Darro and R. Kiss, *Eur. J. Org. Chem.*, 2003, 2062.

536 J. F. Biard, S. Guyot, C. Roussakis, J. F. Verbist, J. Vercauteren, J. F. Weber and K. Boukef, *Tetrahedron Lett.*, 1994, **35**, 2691.

537 M. Jugé, N. Grimaud, J. F. Biard, M. P. Sauviat, M. Nabil, J. F. Verbist and J. Y. Petit, *Toxicon*, 2001, **39**, 1231.

538 S. M. Weinreb, *Acc. Chem. Res.*, 2003, **36**, 59.

539 C. Kibayashi, S. Aoyagi and H. Abe, *Bull. Chem. Soc. Japan*, 2003, **76**, 2059.

540 C. Li and A. J. Blackman, *Aust. J. Chem.*, 1994, **47**, 1355.

541 B. M. Trost and M. T. Rudd, *Org. Lett.*, 2003, **5**, 4599.

542 A. Aiello, F. Borrelli, R. Capasso, E. Fattorusso, P. Luciano and M. Menna, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 4481.

543 J. Bergman, *Acta Chem. Scand.*, 1971, **25**, 2865.

544 A. Abourriche, Y. Abboud, S. Maoufoud, H. Mohou, T. Seffaj, M. Charrouf, N. Chaib, A. Bennamara, N. Bontemps and C. Francisco, *Il Farmaco*, 2003, **58**, 1351.

545 L. Chill, M. Aknin and Y. Kashman, *Org. Lett.*, 2003, **5**, 2433.

546 A. Aiello, E. Fattorusso, P. Luciano, M. Menna, G. Esposito, T. Iuvone and D. Pala, *Eur. J. Org. Chem.*, 2003, 898.

547 D. R. Appleton and B. R. Copp, *Tetrahedron Lett.*, 2003, **44**, 8963.

548 B. S. Davidson, T. F. Molinski, L. R. Barrows and C. M. Ireland, *J. Am. Chem. Soc.*, 1991, **113**, 4709.

549 M. Litaudon and M. Guyot, *Tetrahedron Lett.*, 1991, **32**, 911.

550 M. Litaudon, F. Trigalo, M. T. Martin, F. Frappier and M. Guyot, *Tetrahedron*, 1994, **50**, 5323.

551 T. Kimura, M. Hanzawa, S. Ogawa, R. Sato, T. Fujii and Y. Kawai, *Heteroatom Chemistry*, 2003, **14**, 88.

552 R. A. Davis, I. T. Sandoval, G. P. Concepcion, R. M. da Rocha and C. M. Ireland, *Tetrahedron*, 2003, **59**, 2855.

553 M. Tsuda, K. Nozawa, K. Shimbo and J. Kobayashi, *J. Nat. Prod.*, 2003, **66**, 292.

554 R. A. Davis, L. V. Christensen, A. D. Richardson, R. M. da Rocha and C. M. Ireland, *Marine Drugs*, 2003, 27.

555 J. Kobayashi, J. F. Cheng, Y. Kikuchi, M. Ishibashi, S. Yamamura, Y. Ohizumi, T. Ohta and S. Nozoe, *Tetrahedron Lett.*, 1990, **31**, 4617.

556 P. Schupp, T. Poehner, R. A. Edrada, R. Ebel, A. Berg, V. Wray and P. Proksch, *J. Nat. Prod.*, 2003, **66**, 272.

1990 557 N. Oku, S. Matsunaga and N. Fusetani, *J. Am. Chem. Soc.*, 2003, **125**, 2044.

558 A. N. Pearce, D. R. Appleton, R. C. Babcock and B. R. Copp, *Tetrahedron Lett.*, 2003, **44**, 3897.

559 B. R. Copp, J. Jompa, A. Tahir and C. M. Ireland, *J. Org. Chem.*, 1998, **63**, 8024.

560 S. Nakahara and A. Kubo, *Heterocycles*, 2003, **60**, 2017.

1995 561 Y. R. Torres, T. S. Bugni, R. G. S. Berlinck, C. M. Ireland, A. Magalhães, A. G. Ferreira and R. M. da Rocha, *J. Org. Chem.*, 2002, **67**, 5429.

562 L. Legentil, J. Bastide and E. Delfourne, *Tetrahedron Lett.*, 2003, **44**, 2473.

563 J. Kobayashi, J. F. Cheng, H. Nakamura, Y. Ohizumi, Y. Hirata, T. Sasaki, T. Ohta and S. Nozoe, *Tetrahedron Lett.*, 1988, **29**, 1177.

2000 564 B. R. Copp, O. Kayser, R. Brun and A. F. Kiderlen, *Planta Med.*, 2003, **69**, 527.

565 B. Debnath, S. Gayen, S. Bhattacharya, S. Samanta and T. Jha, *Bioorg. Med. Chem.*, 2003, **11**, 5493.

566 E. Delfourne, F. Darro, P. Portefaix, C. Galaup, S. Bayssade, A. Bouteillé, L. Le Corre, J. Bastide, F. Collignon, B. Lesur, A. Frydman and R. Kiss, *J. Med. Chem.*, 2002, **45**, 3765.

2005 567 S. S. Matsumoto, J. Biggs, B. R. Copp, J. A. Holden and L. R. Barrows, *Chem. Res. Toxicol.*, 2003, **16**, 113.

568 T. A. Foderaro, L. R. Barrows, P. Lassota and C. M. Ireland, *J. Org. Chem.*, 1997, **62**, 6064.

569 A. Pouilhès, Y. Langlois and A. Chiaroni, *Synlett*, 2003, **10**, 1488.

570 A. R. Carroll, B. F. Bowden and J. C. Coll, *Aust. J. Chem.*, 1993, **46**, 489.

2010 571 M. V. R. Reddy and D. J. Faulkner, *Tetrahedron*, 1997, **53**, 3457.

572 P. Cironi, I. Manzanares, F. Albericio and M. Álvarez, *Org. Lett.*, 2003, **5**, 2959.

573 K. C. Nicolaou, P. B. Rao, J. Hao, M. V. Reddy, G. Rassias, X. Huang, D. Y. K. Chen and S. A. Snyder, *Angew. Chem. Int. Ed.*, 2003, **42**, 1753.

574 A. W. G. Burgett, Q. Li, Q. Wei and P. G. Harran, *Angew. Chem. Int. Ed.*, 2003, **42**, 4961.

575 Z. Cruz-Monserrate, H. C. Vervoort, R. Bai, D. J. Newman, S. B. Howell, G. Los, J. T. Mullaney, M. D. Williams, G. R. Pettit, W. Fenical and E. Hamel, *Mol. Pharmacol.*, 2003, **63**, 1273.

576 K. L. Rinehart, T. G. Holt, N. L. Fregeau, J. G. Stroh, P. A. Keifer, F. Sun, L. H. Li and D. G. Martin, *J. Org. Chem.*, 1990, **55**, 4512.

577 A. E. Wright, D. A. Forleo, G. P. Gunawardana, S. P. Gunasekera, F. E. Koehn and O. J. McConnell, *J. Org. Chem.*, 1990, **55**, 4508.

578 K. L. Rinehart, T. G. Holt, N. L. Fregeau, J. G. Stroh, P. A. Keifer, F. Sun, L. H. Li and D. G. Martin, *J. Org. Chem.*, 1991, **56**, 1676.

579 R. Sakai, K. L. Rinehart, Y. Guan and A. H. J. Wang, *Proc. Natl. Acad. Sci. U. S. A.*, 1992, **89**, 11456.

580 R. Sakai, E. A. Jares-Erijman, I. Manzanares, M. V. S. Elipe and K. L. Rinehart, *J. Am. Chem. Soc.*, 1996, **118**, 9017.

581 R. Menchaca, V. Martínez, A. Rodríguez, N. Rodríguez, M. Flores, P. Gallego, I. Manzanares and C. Cuevas, *J. Org. Chem.*, 2003, **68**, 8859.

582 M. D'Incalci and J. Jimeno, *Expert opinion on investigational drugs*, 2003, **12**, 1843.

583 C. Laverdiere, E. A. Kolb, J. G. Supko, R. Gorlick, P. A. Meyers, R. G. Maki, L. Wexler, G. D. Demetri, J. H. Healey, A. G. Huvos, A. M. Goorin, R. Bagatell, A. Ruiz-Casado, C. Guzman, J. Jimeno and D. Harmon, *Cancer*, 2003, **98**, 832.

584 Ch. Van Kesteren, M. M. M. de Vooght, L. López-Lázaro, R. A. A. Mathôt, J. H. M. Schellens, J. M. Jimeno and J. H. Beijnen, *Anti-Cancer Drugs*, 2003, **14**, 487.

585 S. Fukuzawa, S. Matsunaga and N. Fusetani, *J. Org. Chem.*, 1995, **60**, 608.

586 T. Komiya, N. Fusetani, S. Matsunaga, A. Kubo, F. J. Kaye, M. J. Kelley, K. Tamura, M. Yoshida, M. Fukuoka and K. Nakagawa, *Cancer Chemother. Pharmacol.*, 2003, **51**, 202.

587 A. Aiello, G. Esposito, E. Fattorusso, T. Iuvone, P. Luciano and M. Menna, *Steroids*, 2003, **68**, 719.

588 M. Yoshida, M. Murata, K. Inaba and M. Morisawa, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 14831.

589 T. Oishi, H. Tsuchikawa, M. Murata, M. Yoshida and M. Morisawa, *Tetrahedron Lett.*, 2003, **44**, 6387.

590 H. D. Chludil, A. M. Seldes and M. S. Maier, *Z. Naturforsch. C Biosci.*, 2003, **58**, 433.

591 M. E. Díaz de Vivar, A. M. Seldes and M. S. Maier, *Lipids*, 2002, **37**, 597.

592 M. S. Maier, A. Kuriss and A. M. Seldes, *Lipids*, 1998, **33**, 825.

593 M. Inagaki, K. Nakamura, S. Kawatake and R. Higuchi, *Eur. J. Org. Chem.*, 2003, 325.

594 K. Yamada, A. Hamada, F. Kisa, T. Miyamoto and R. Higuchi, *Chem. Pharm. Bull.*, 2003, **51**, 46.

595 M. Kaneko, F. Kisa, K. Yamada, T. Miyamoto and R. Higuchi, *Eur. J. Org. Chem.*, 2003, 1004.

596 W. Wang, F. Li, Y. Park, J. Hong, C. O. Lee, J. Y. Kong, S. Shin, K. S. Im and J. H. Jung, *J. Nat. Prod.*, 2003, **66**, 384.

597 R. Riccio, M. V. D'Auria, M. Iorizzi, L. Minale, D. Laurent and D. Duhet, *Gazz. Chim. Ital.*, 1985, **115**, 405.

598 N. V. Ivanchina, A. A. Kicha, A. I. Kalinovsky, P. S. Dmitrenok and V. A. Stonik, *J. Nat. Prod.*, 2003, **66**, 298.

599 A. A. Kicha, N. V. Ivanchina, A. I. Kalinovsky, P. S. Dmitrenok and V. A. Stonik, *Tetrahedron Lett.*, 2003, **44**, 1935.

600 H. D. Chludil, A. P. Murray, A. M. Seldes and M. S. Maier, *Stud. Nat. Prod. Chem.*, 2003, **28**, 587.

601 N. G. Prokof'eva, E. L. Chaikina, A. A. Kicha and N. V. Ivanchina, *Comp. Biochem. Physiol. B Comp. Biochem.*, 2003, **134**, 695.

602 W. H. Wang, F. M. Li, J. K. Hong, C. O. Lee, H. Y. Cho, K. S. Im and J. H. Jung, *Chem. Pharm. Bull.*, 2003, **51**, 435.

603 E. V. Levina, A. I. Kalinovskii, V. A. Stonik and P. S. Dmitrenok, *Russ. Chem. Bull.*, 2003, **52**, 1623.

604 Z. R. Zou, Y. H. Yi, H. M. Wu, J. H. Wu, C. C. Liaw and K. H. Lee, *J. Nat. Prod.*, 2003, **66**, 1055.

605 S. A. Avilov, A. S. Antonov, A. S. Silchenko, V. I. Kalinin, A. I. Kalinovsky, P. S. Dmitrenok, V. A. Stonik, R. Riguera and C. Jimenez, *J. Nat. Prod.*, 2003, **66**, 910.

606 M. Sandvoss, A. Preiss, K. Levsen, R. Weisemann and M. Spraul, *Magn. Reson. Chem.*, 2003, **41**, 949.

607 S. de Marino, N. Borbone, M. Iorizzi, G. Esposito, J. B. McClintock and F. Zollo, *J. Nat. Prod.*, 2003, **66**, 515.

608 H. Nakagawa, T. Tanigawa, K. Tomita, Y. Tomihara, Y. Araki and E. Tachikawa, *J. Toxicol. Toxin Rev.*, 2003, **22**, 633.

609 T. Barsby, C. E. Kicklighter, M. E. Hay, M. C. Sullards and J. Kubanek, *J. Nat. Prod.*, 2003, **66**, 1110.

610 T. Goto, Y. Kishi, S. Takahashi and Y. Hirata, *Tetrahedron*, 1965, **21**, 2059.

611 K. Tsuda, S. Ikuma, M. Kawamura, R. Tachikawa, K. Sakai, C. Tamura and O. Amakasu, *Chem. Pharm. Bull.*, 1964, **12**, 1357.

612 R. B. Woodward, *Pure Appl. Chem.*, 1964, **9**, 49.

613 N. Ohyabu, T. Nishikawa and M. Isobe, *J. Am. Chem. Soc.*, 2003, **125**, 8798.

614 A. Hinman and J. Du Bois, *J. Am. Chem. Soc.*, 2003, **125**, 11510.

615 D. J. Faulkner, *Tetrahedron*, 1977, **33**, 1421.

616 D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2004, **67**, 11216.

617 W. Bergmann and R. J. Feeney, *J. Am. Chem. Soc.*, 1950, **72**, 2809.

618 W. Bergmann and R. J. Feeney, *J. Org. Chem.*, 1951, **16**, 981.

619 W. Bergmann and R. J. Feeney, *J. Org. Chem.*, 1955, **20**, 1501.

Captions for Figures 1–3

Fig. 1 Distribution of biologically-active and non-active marine natural products by phylum, 2003.

(**Non-active** – compounds for which no biological activity has been reported; **Active** – compounds that are active in at least one bioassay)

Fig. 2 Distribution of biological activity by phylum.

(**AC** – cancer related assays including cytotoxicity, antimitotic, histone deacetylase, proteasome, TNF, a range of kinases, DNA binding and matrix metalloproteinase; **AM** – antimicrobial, antiinfective, antiTb, antimalarial assays; **AO** – antioxidant assays; **IV** – *in vivo* assays such as brine shrimp and sea urchin eggs; **Other** – includes antiviral assays, assays based on central nervous system responses, feeding deterrent assays, ion channel assays, antifouling assays and assays for Fe siderophores, neuronal differentiation, oocyte lysis, sperm attractant and UV-A activity)

Fig. 3 Numbers and distribution of marine and marine-derived compounds in clinical and pre-clinical trials.

(Data extracted from Table 1 in reference 616)
(**C** – anticancer drugs; **AI** – antiinflammatory drugs; **P** – drugs for intractable pain; **A** – Alzheimers)