

# Natural Products Chemistry in Marine Ascidians of the Genus *Aplidium*

Eva Zubía, María J. Ortega and Javier Salvá\*

*Departamento de Química Orgánica, Facultad de Ciencias del Mar y Ambientales, Universidad de Cádiz, Apdo. 40, 11510 Puerto Real, Cádiz, Spain*

**Abstract:** Ascidians (tunicates) are widely recognized as one of the most prolific producers of bioactive natural products in the marine environment. In particular, ascidians of the genus *Aplidium* are renowned for the variability in the metabolites that they content. The non-nitrogenous compounds are dominated by the presence of meroterpenoids exemplified by the longithorones. Among the nitrogen containing group, nucleosides, cyclic peptides and a high variety of alkaloids can be mentioned. In this review the most interesting aspects of structure elucidation and bioactivity of the natural products from species of the genus *Aplidium* reported up to the end of 2004 will be presented.

**Keywords:** Natural products, marine metabolites, ascidians, tunicates, *Aplidium*.

## I. INTRODUCTION

Nowadays marine organisms are widely recognized not only as an immense source of chemodiversity but also as an emerging supply of compound-tools for biomedical and pharmacological research. Both macro- and microorganisms of marine origin have given rise to a high number of novel metabolites; among the former, the studied groups of marine organisms include algae and invertebrates such as sponges, corals, bryozoans, molluscs, echinoderms, and ascidians (tunicates). Over the last thirty years a vast number of papers have been published in the field. However, the literature in marine natural products is well structured due to the excellent reviews accomplished yearly by Prof. John Faulkner [1] and continuators [2]. In addition, other reviews cover more specific aspects centred either in the chemical structure of compounds, in certain biomedical aspects, or in the biological starting material [3].

Among the marine invertebrates that have focussed attention of organic chemists, the group of ascidians has been traditionally a source of metabolites both of chemical and biomedical interest [1,2]. Undoubtedly, to compile the hundreds of compounds ascribed to marine ascidians or even to one of the Families of the Class Ascidiacea would by far exceed the scope of this concise review. Therefore this paper will concern about the metabolites isolated from one of the most prolific groups of marine ascidians: the genus *Aplidium* of the Polyclinidae Family. In the present review the compounds isolated from organisms belonging to this genus up to December 2004 will be reported along with structural, biogenetic, pharmacological remarks, and, in certain instances the synthetic efforts accomplished, particularly when the syntheses have been decisive for structural confirmation.

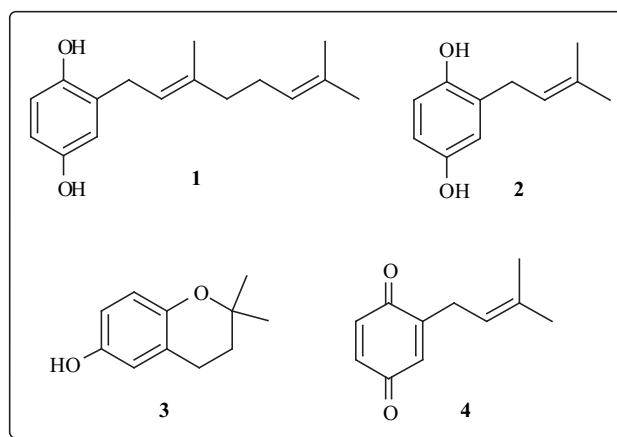
## II. NON-NITROGENOUS METABOLITES

The non-nitrogenous metabolites isolated from ascidians of the genus *Aplidium* are prenyl hydroquinones and prenyl

quinones either linear or cyclic. These metabolites of mixed biogenesis are generally known as meroterpenes.

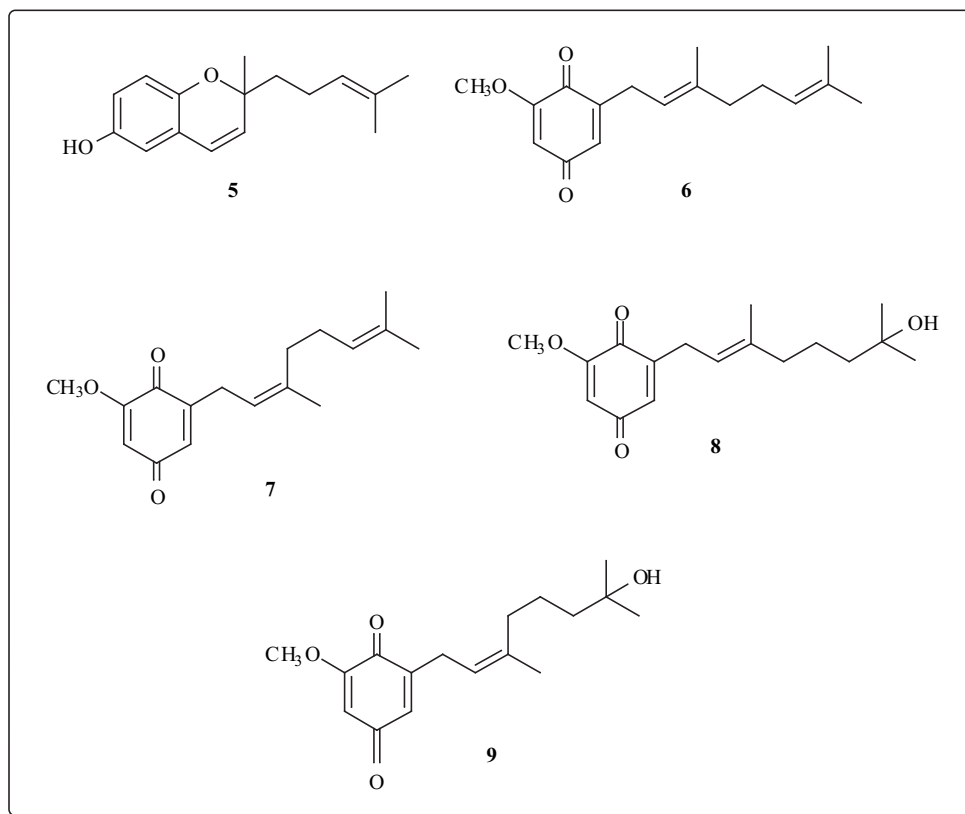
The first non-nitrogenous metabolite from this genus was reported by Fenical in 1974, from an unidentified *Aplidium* sp. from Puerto Vallarta, Mexico [4]. The compound was characterized as the geranyl hydroquinone **1** and exhibited protecting activity against leukaemia and tumour development *in vivo*.

A few years later, two additional prenyl hydroquinones **2**, **3** and the quinone **4** were described from *Aplidium californicum* [5]. The proposed structures were confirmed by synthesis. Compound **3** was described for the first time, while **2** and **4** had been reported as constituents of the plant *Phagnalon saxatile* [6]. A posterior study of *A. californicum* stated the antioxidant activity of its prenyl hydroquinone constituents [7]. Cordiachromene A (**5**) that was isolated from the tunicate *A. constellatum* [8] had been reported as a metabolite of the American tree *Cordia alliodora* [9]. Both cordiachromene A (**5**) and geranyl hydroquinone **1** were also described in a later study of the cytotoxic and antibacterial components of *A. antillense* [10].



An unidentified species of the genus *Aplidium* from the Atlantic French coast yielded four new prenyl quinones, the verapliquinones A-D (**6-9**), as inseparable 4:1 mixtures of verapliquinones A/B and C/D. Their structures were elucidated by spectroscopic methods and were confirmed

\*Address correspondence to this author at the Departamento de Química Orgánica, Facultad de Ciencias del Mar y Ambientales, Apdo. 40, 11510 Puerto Real, Cádiz, Spain; Tel.: 34 956 016022; Fax: 34 956 016797; E-mail: javier.salva@uca.es



upon transformation of the alcohols **8/9**, into **6/7**, respectively, and by reduction of these latter quinones into the corresponding hydroquinones [11].

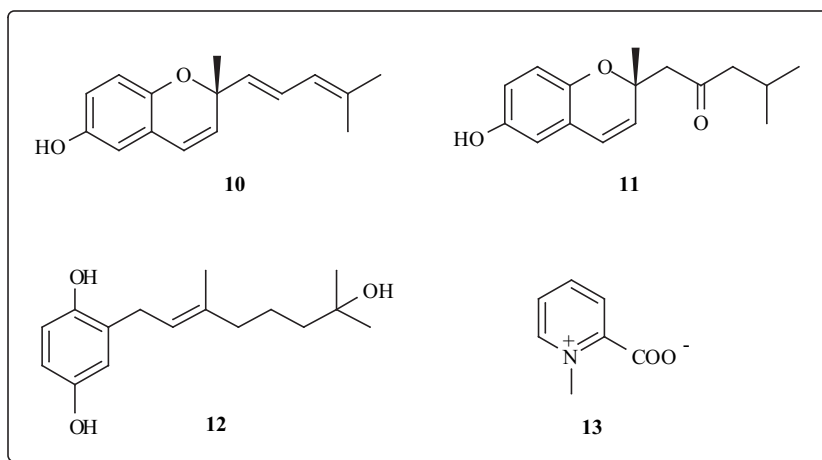
Two related chromenols **10** and **11** were obtained from a specimen of *A. solidum* collected off the south coast of Australia. The absolute stereochemistry *2R* of compound **10** was assigned as follows. Hydrogenation of **10** and further ozonolysis yielded a lactone which was identified as (4*R*)-4,8-dimethylnonan-4-olide ( $[\alpha]_D = +5^\circ$ ) upon comparison of its specific optical rotation with that reported for its enantiomer ( $[\alpha]_D = -4.9^\circ$ ). In the absence of an independent determination, the absolute stereochemistry of **11** was proposed as depicted (*2R*) on biogenetic grounds [12].

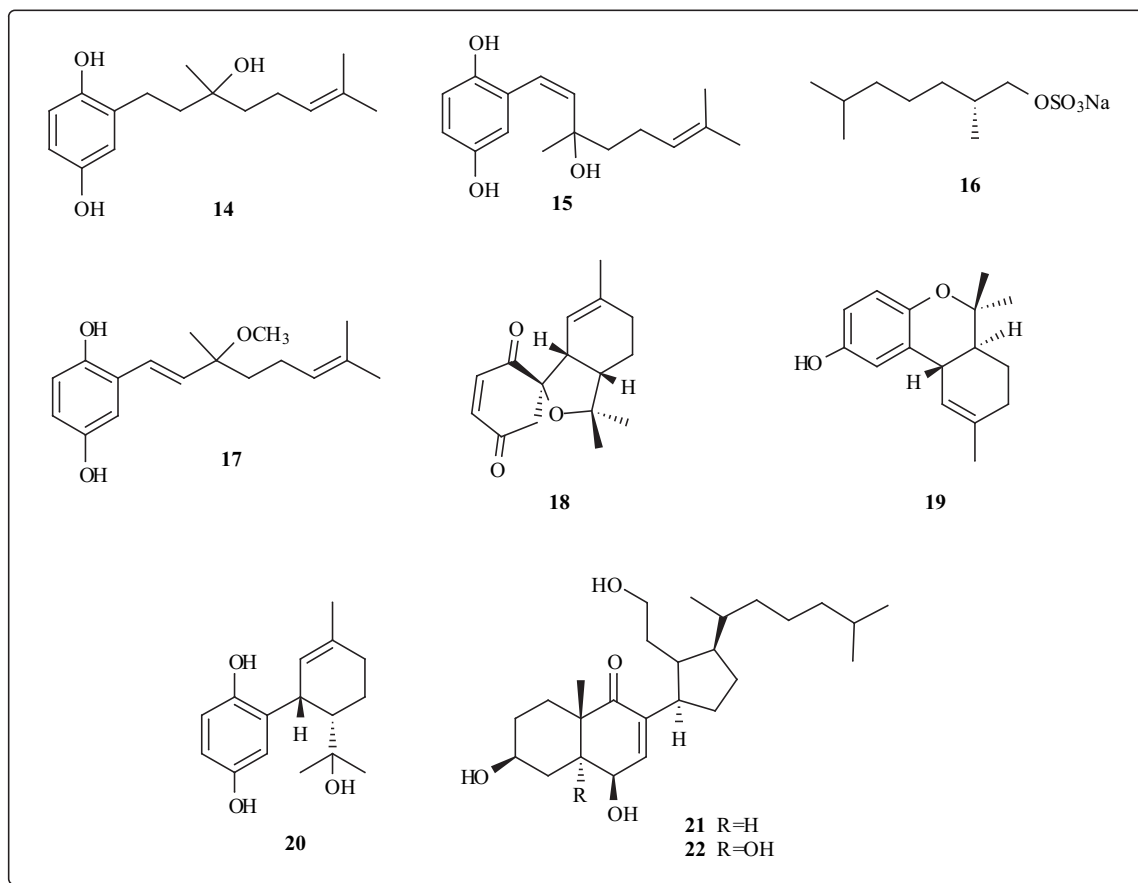
A Spanish *Aplidium* sp. from Almería yielded the new cytotoxic prenyl hydroquinone **12** together with the known

geranyl hydroquinone **1** [13]. Both compounds exhibited cytotoxicity against a collection of tumour cell lines with selectivity against P-388 mouse lymphoma suspension culture.

In a comparative study of the metabolites of tunicates from the Venice Lagoon [14], the ascidian *A. nordmani* gave rise to several known compounds including homarine (**13**), the prenylated derivatives **1** and **4**, and several common carotenoids, sterols and lipids.

The ascidian *A. savigni* from Comoro Island contained the known linear prenyl hydroquinones **1** and **14** together with the related new compound **15** [15]. Compound **14** had been previously isolated from the tunicate *Amarocium multiplicatum* [16]. Frequently, species of *Amarocium* have been later reclassified as belonging to the *Aplidium* genus.

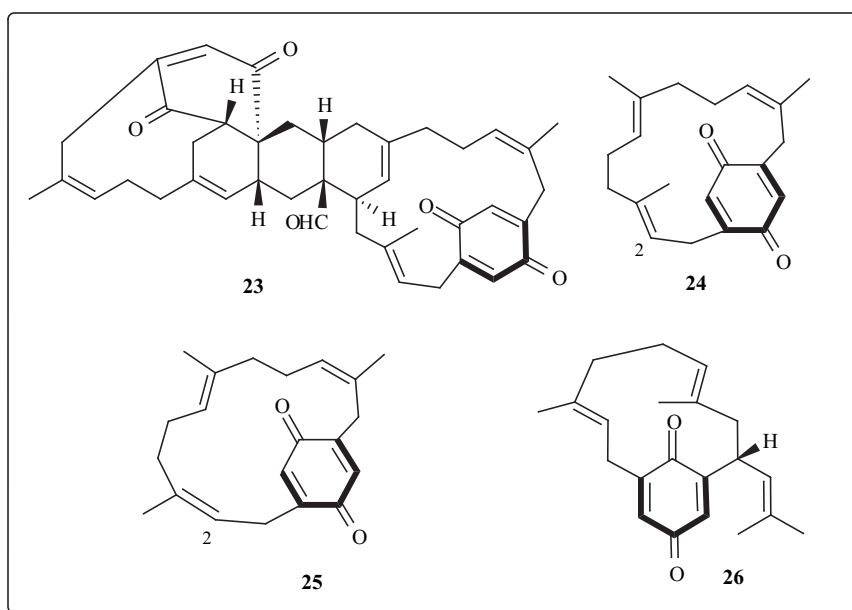




The tunicate *A. conicum* has been extensively studied. The sulphate normonoterpene **16** was initially reported as a major constituent of this ascidian [17]. Later, a specimen of *A. conicum* from Tarifa Island afforded the linear prenyl hydroquinone **17** together with three related meroterpenoids: conidione (**18**), conicol (**19**), and conitriol (**20**) in addition to several related known compounds [18]. An splitted study of *A. conicum* from the Mediterranean Sea gave rise to the isolation of aplidiasterols A (**21**) and B (**22**), together with

some nitrogenous metabolites which will be cited in the following section. The aplidiasterols **21** and **22** exhibited cytotoxicity against rat glioma (C6) and murine monocyte/macrophage (J774) tumour cells *in vitro* [19].

Among the cyclic prenyl metabolites from *Aplidium* species, the longithorones and the longithorols are the most renowned compounds. These natural products are structurally characterized by the presence of a paracyclophane and/or

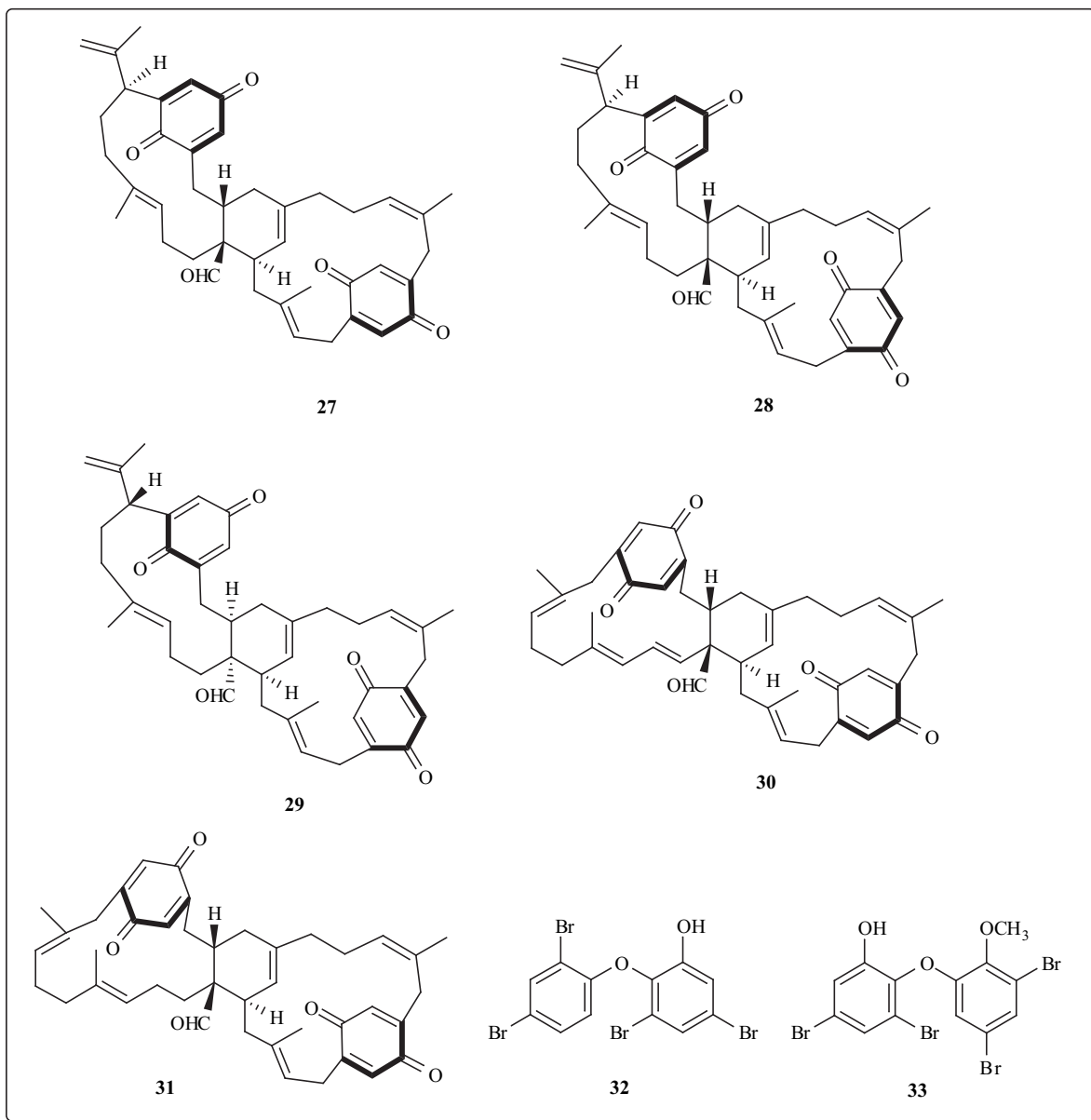


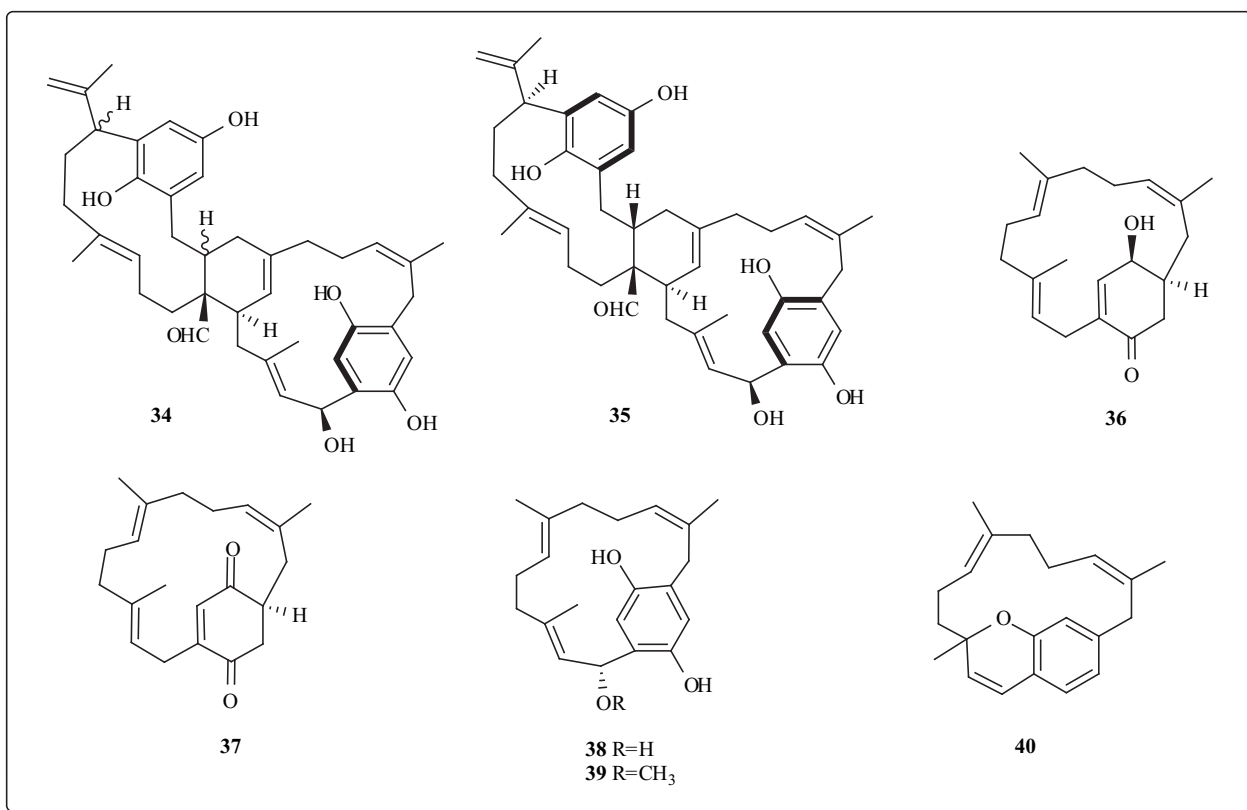
metacyclophane system built in a farnesyl quinone or hydroquinone. In 1994 Schmitz and co-workers isolated the first member of the longithorone series, longithorone A (**23**), from *A. longithorax* collected in Palau. Longithorone A (**23**) is a dimeric prenylated quinone whose highly strained structure was determined by X-ray analysis [20]. The authors proposed that **23** might biosynthetically derive by Diels-Alder cyclization of two appropriate cyclofarnesyl benzoquinones. The feasibility of this proposal was confirmed when (-)-longithorone A was enantioselectively synthesized using Diels-Alder reactions [21,22]. Longithorones B-D (**24-26**) which are closely related to the proposed monomer precursors of longithorone A, were isolated as minor components of *A. longithorax* together with the dimeric longithorones E-I (**27-31**). Longithorones B (**24**) and C (**25**) are optically active compounds that share an opposite geometry on C-2, C-3 double bond. On the other hand, the dimers longithorones E (**27**) and F (**28**) are atropisomers about the *para* disubstituted benzoquinone ring. The proposed relative stereochemistry of longithorones

F-I (**28-31**) displaying a *cis* ring fusion was in agreement with the intramolecular Diels-Alder reaction evoked to explain their biosynthesis. Finally, among the minor metabolites of *A. longithorax* isolated in this study the polybrominated diphenyl ethers **32** and **33** were included [23].

A further study of the more polar components of *A. longithorax* led to the isolation of the isomeric longithorols A (**34**) and B (**35**) as their corresponding penta-acetates. The longithorols are highly unstable hydroquinones structurally related to longithorone E (**27**) although the complete relative stereochemistry of **34** could not be fully defined [24].

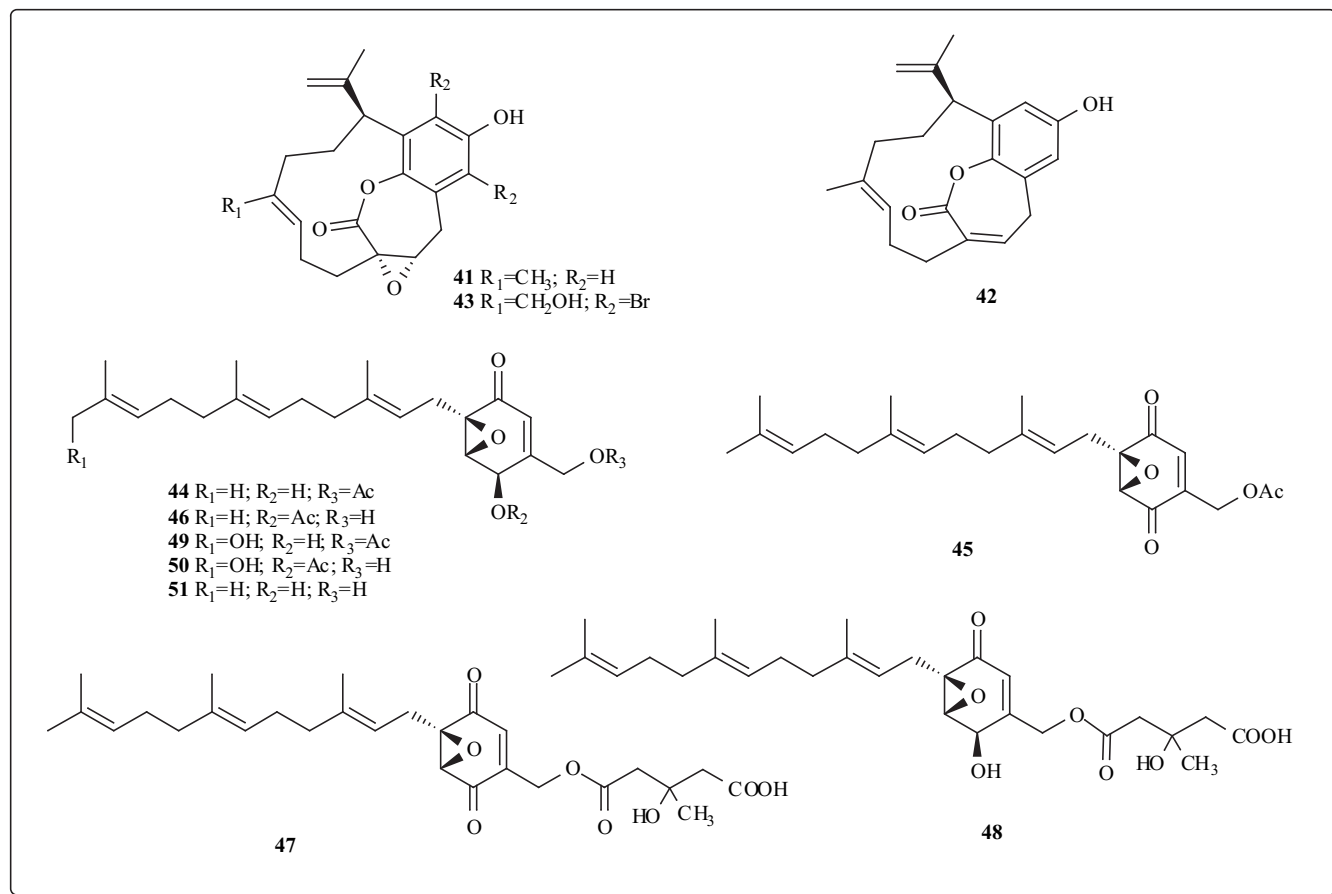
Another series of related compounds were obtained from specimens of *A. longithorax* from Australia. This study resulted in the description of the longithorones J (**36**) and K (**37**) [25] and the longithorols C-E (**38-40**) [26]. The absolute stereochemistry of longithorol C (**38**) was determined as *1R* by employing the Mosher's method, while the possibility that longithorol E (**40**) might be an artefact produced during the isolation process could not be ruled out.





An unidentified species of *Aplidium* from Flores Island, Indonesia, afforded three new metacyclophane hydroquinone

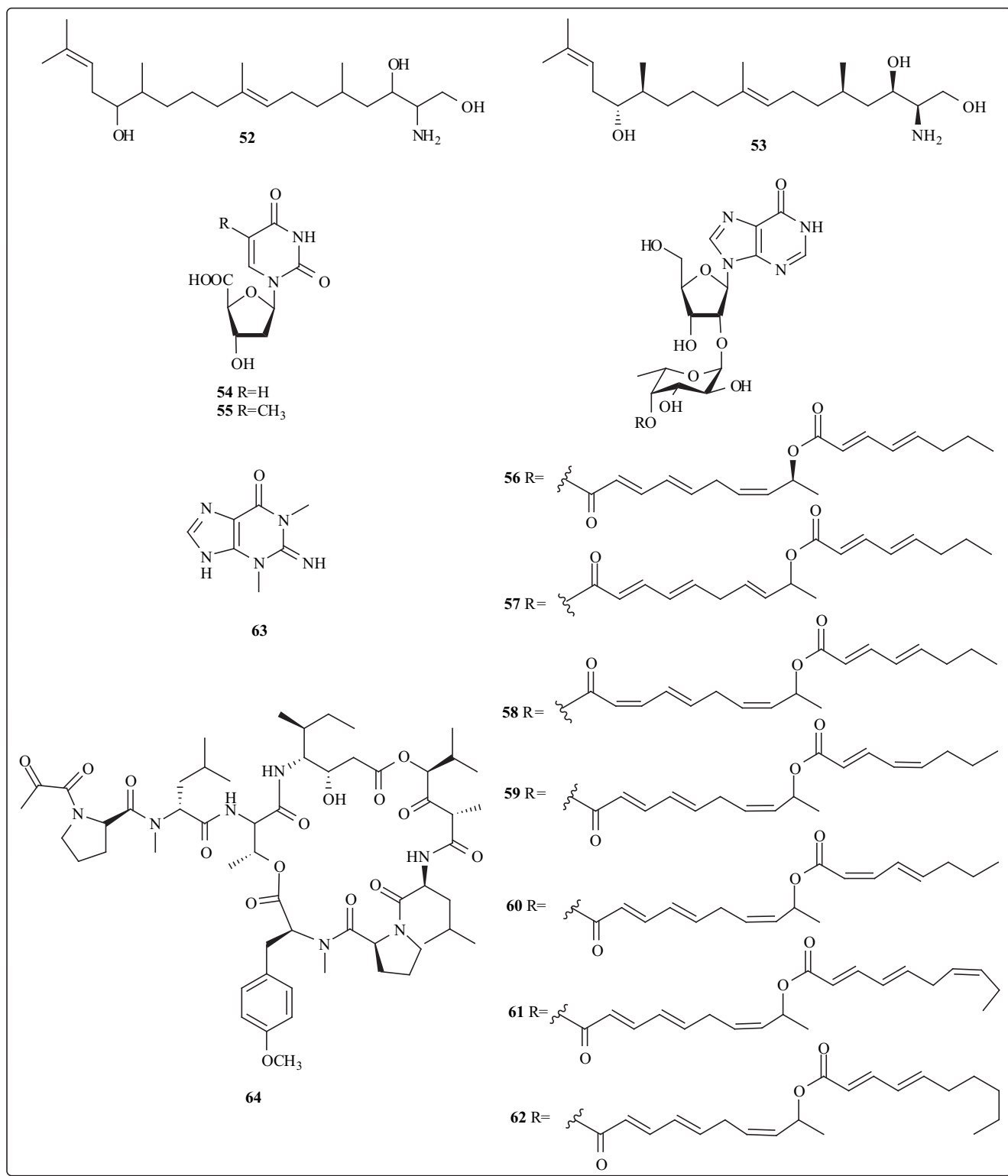
lactones, the floresolides A-C (**41-43**) which exhibited an  $\epsilon$ -lactone bridging the aromatic ring and a [10]metacyclophane.



The structures were elucidated by spectroscopic and X-ray diffraction analysis. The floresolides showed a moderate cytotoxicity against KB carcinoma cells [27].

Finally, a series of farnesylated epoxy cyclohexenones were isolated from the culture of the fungus *Aspergillus niger* obtained from tissue homogenates of an *Aplidium* sp.: the yaunthones A-E (**44-48**), 1-hydroxyyaunthone A (**49**), 1-hydroxyyaunthone C (**50**), and 22-deacetylyaunthone A (**51**)

[28]. The close structural relationship between the longithorones and the yaunthones led the authors to propose that the quinone subunit of the longithorones might have a fungic origin. Also a non-ascidian origin was attributed to the presence of structurally unrelated non-nitrogenous metabolites like two bryostatins in *A. californicum*. Their appearance in the study of the tunicate seemed to be the result of contamination of the sample by the bryozoan *Bugula neritina* [29].



### III. NITROGENOUS METABOLITES

Nitrogen containing metabolites represent by far the most characteristic group of compounds isolated from ascidians. In addition to the general reviews above mentioned, bioactive alkaloids [30] and natural peptides [31] have been compiled in specific reviews.

An unidentified species of *Aplidium* collected in the Gulf of California afforded the antimicrobial and fungicide compound aplidiasfingosine (**52**) [32]. The elucidation of the stereochemistry at the five stereogenic centres of **52** was accomplished by synthesis [33]. The synthetic stereoisomer **53** shares an identical relative stereochemistry with the natural metabolite as deduced by comparison of the spectroscopic data. However, since the specific optical rotation of this latter compound had not been reported, its absolute stereochemistry remains undefined.

Nucleosides and related compounds have been frequently encountered in *Aplidium* tunicates. Two uncommon 2'-deoxy-nucleoside uronic acids, thymidine-5'-carboxylic acid (**54**) and 2'-deoxyuridine-5'-carboxylic acid (**55**) were obtained from *A. fuscum* [34]. In 1994, Kobayashi reported the characterization of a new nucleoside derivative, shimofuridin A (**56**) from the tunicate *A. multiplicatum*. Shimofuridin A (**56**) exhibited cytotoxic, antibacterial, antifungal and kinase C inhibitory activities [35]. Further study of the minor components of *A. multiplicatum* led to the description of the related shimofuridins B-G (**57-62**) [36]. Due to the great similarity between shimofuridin A (**56**) and the minor shimofuridins B-E (**57-60**) the authors investigated their mutual interconversion. A solution of shimofuridin A (**56**) was stable for several days at room temperature; however the shimofuridins **57-60** were obtained upon irradiation of a solution of shimofuridin A (**56**) with UV light.

The base 1,3-dimethylguanaine (**63**) has been detected in an array of ascidians from New Zealand including *Aplidium scabellum* [37]. This broad distribution of **63** led the authors to propose that the presence of this metabolite might be crucial on the tunicate physiology.

Aplidine (**64**), also known as dehydrodidemnin B, is probably the most renowned metabolite obtained from ascidians of the genus *Aplidium*. This cyclic depsipeptide was described in 1989 by Rinehart from a Mediterranean collection of *A. albicans* [38]. Aplidine (**64**) was a blockbuster in marine natural product chemistry because it exhibited an improved antitumour activity in comparison with other members of the didemnins family but with a minor toxicity in preclinical trials [39]. Aplidine (**64**) is a cell-cycle inhibitor which is being developed for the potential treatment of a variety of cancers [40] and is currently undergoing clinical phase trials [41]. In addition, the mechanism of action of this agent is at present under intensive research [42].

The ascidians of the genus *Aplidium* have given rise to alkaloids of diverse structures. Thus, the study of *A. pliciferum* from the south coast of Australia led to the isolation of 2-vanilloyl thiazole (**65**) and its dihydroderivative **66**, together with the imidazole derivative **67**. Their structures were elucidated by spectroscopic methods and those of **65** and **66** were additionally confirmed by synthesis [43]. A year later, the cytotoxic and

antimicrobial 1,2,3-trithiane derivative **68** was isolated from a New Zealand species of *Aplidium*. Although compound **68** was stable in acidic CD<sub>3</sub>OD solution, on standing in neutral or slightly basic solutions at room temperature for one month gave the 2-vanilloyl imidazole **67**, suggesting that this latter compound might be an artefact [44].

Three new iodinated alkaloids (**69-71**) were obtained from two likely different but unidentified *Aplidium* species from Australia. Their structures were elucidated by means of 2D NMR studies and by the synthesis of compound **70** from L-diiodytyrosine. Compounds **69** and **71** were assumed to belong to the same enantiomeric series than compound **70** based on the similarities of their optical rotation values. The alkaloids **70** and **71** exhibited cytotoxicity against several cell lines and significant inhibition of glutathione reductase activity [45].

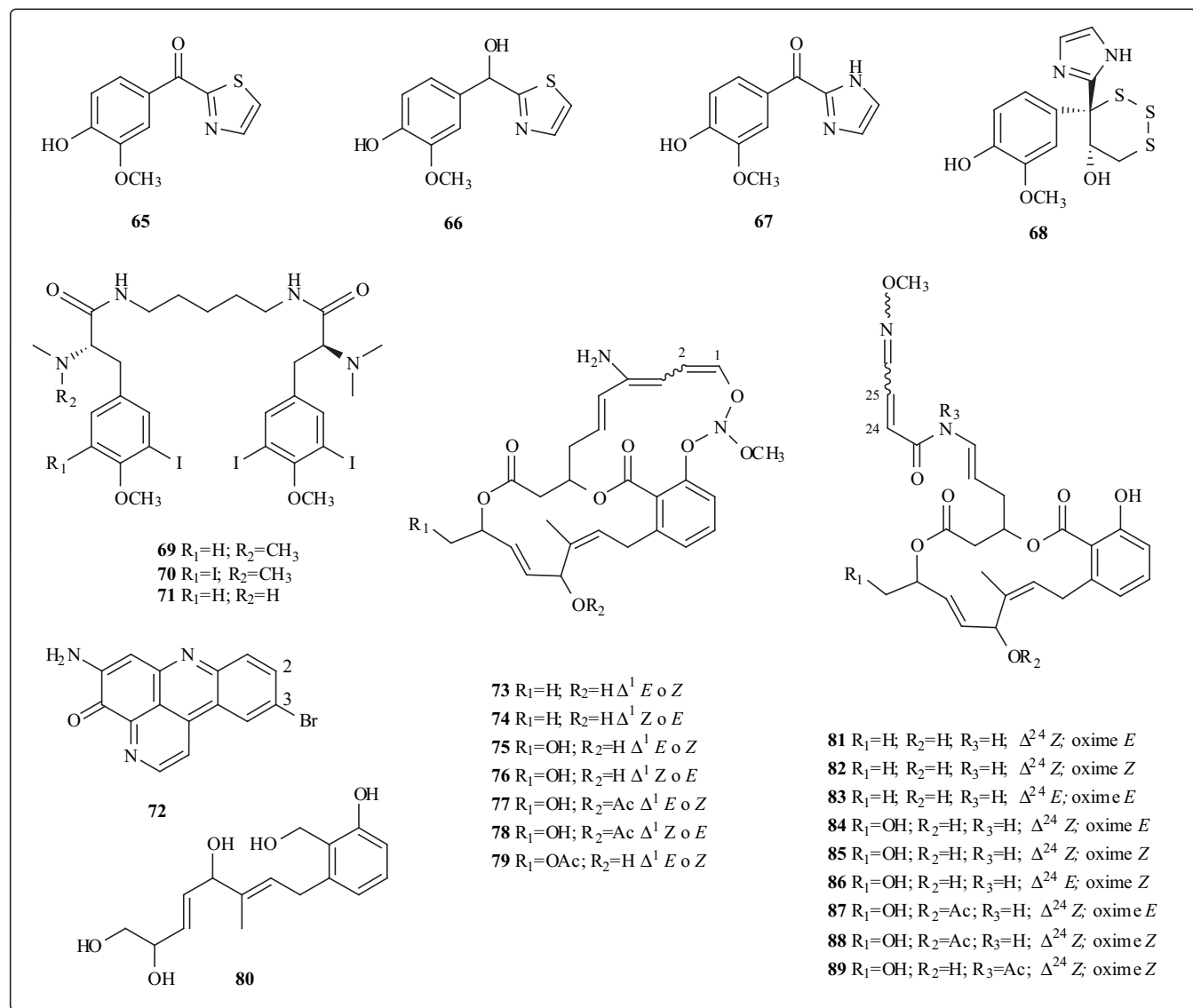
Pantherinine (**72**) is a mildly cytotoxic tetracyclic alkaloid that was isolated from the south Australian tunicate *A. pantherinum* [46]. The structure of **72** was unusual since it presents the bromine substituent at C-3 rather than at the more common C-2 position; however, the proposed structure was confirmed by synthesis starting from 5,8-dimethoxy-7-nitro-4-quinolone [47].

The chemical study of an unidentified species of *Aplidium* from Australia led to the isolation of seven metabolites which were initially characterized as macrocyclic alkaloids possessing a very uncommon orthonitrite function: the aplidites A-G (**73-79**) [48]. The geometry of the C-1,C-2 double bond could not be defined in the three pairs **73/74**, **75/76**, and **77/78**. A sample containing both aplidite C (**75**) and D (**76**) was treated with lithium aluminum hydride affording the reduction compound **80**, whose spectroscopic data were employed by the authors to confirm the presence of the questionable orthonitrite function in the aplidites. In fact, the structures of the aplidites were later revised in the terms detailed below.

Two years later, two cytotoxic macrolides, the lobatamides A (**81**) and B (**82**) were isolated from *A. lobatum* from Australia [49]. Their structures, which featured the presence of an *O*-methyl oxime conjugated to a *Z* double bond, were confirmed by exhaustive NMR and MS studies and differed on the geometry about the oxime functionality.

A reinvestigation of Australian specimens of *A. lobatum* led to the description of four new lobatamides, the lobatamides C-F (**83-86**) together with the known lobatamides A (**81**) and B (**82**). Since the lobatamides A (**81**), B (**82**), D (**84**), and E (**85**) presented identical physical and spectroscopic data to those reported for the aplidites A (**73**), B (**74**), C (**75**), and D (**76**), respectively, the authors proposed the revision of the structures of these latter aplidites to the structures **81**, **82**, **84**, and **85**, respectively. Similarly, the authors suggested that the structures of the aplidites E-G (**77-79**) should be revised to **87-89**, respectively, and therefore brought to an end the controversy about the presence of the orthonitrite moiety. This research also included the isolation of a mixture of lobatamides A and B (**81/82**) from specimens of an *Aplidium* sp. from the Philippines [50].

Simultaneously to the publication of the first lobatamide paper, the compound YM-75518 with an identical structure



to that of lobatamide A (**81**) was identified from a terrestrial bacteria of the genus *Pseudomonas* [51]. Since the same metabolite was obtained from two geographical distinct populations of *Aplidium* and, even more, from ascidians and bacteria, the authors suggested that the presence of these compounds might be due to a symbiotic association. It was also proposed that the tunicates might have acquired from other organisms the biosynthetic machinery needed to produce or to transform these natural products.

In general, the lobatamides have exhibited a significant antitumour activity in the standard NCI 60-cell panel [50]. The lobatamides are often grouped with the salicylihamides [52] and oximidines [53] as salicylate enamide macrolides and share with them essentially identical 60-cell tumour screening profiles. From this screening it has been suggested a common and novel mechanism of action since their activity profile differed from other compounds of known mechanisms of action [54]. Further research in this field has stated that these compounds inhibit mammalian vacuolar-type ( $H^+$ )-ATPases (V-ATPases) from human kidney, liver, and osteoclastic giant-cell tumour of bone but were inactive against some fungal ATPases [55,56].

The interesting bioactivity exhibited by the lobatamides has attracted attention of synthetic organic chemists. After initial approaches [57,58] the total syntheses of lobatamide C (**83**) and three additional stereoisomers have been reported and their V-ATPase inhibition activity evaluated [59,60]. In addition the synthesis and evaluation of simplified analogues have shown that the salicylate phenol, the enamide NH, and the *ortho*-substitution of the salicylate ester are important for the V-ATPase inhibitory activity [61]. More recently a stereocontrolled introduction of the enamide side chains of lobatamides A (**81**) and D (**84**) has been reported [62].

Specimens of the ascidian *A. meridianum* from the South Georgia Island led to obtain a new series of indole alkaloids, the meridianins (**90-94**). These compounds are indoles substituted at C-3 with a 2'-aminopyrimidine ring and exhibited a moderate cytotoxicity against LMM3 murine mammary adenocarcinoma cell line [63]. The syntheses of meridianins have been achieved either by a palladium catalysed cross-coupling reaction between indole and pyrimidine moieties [64,65] or by construction of the aminopyrimidine ring from an indole precursor [66,67].



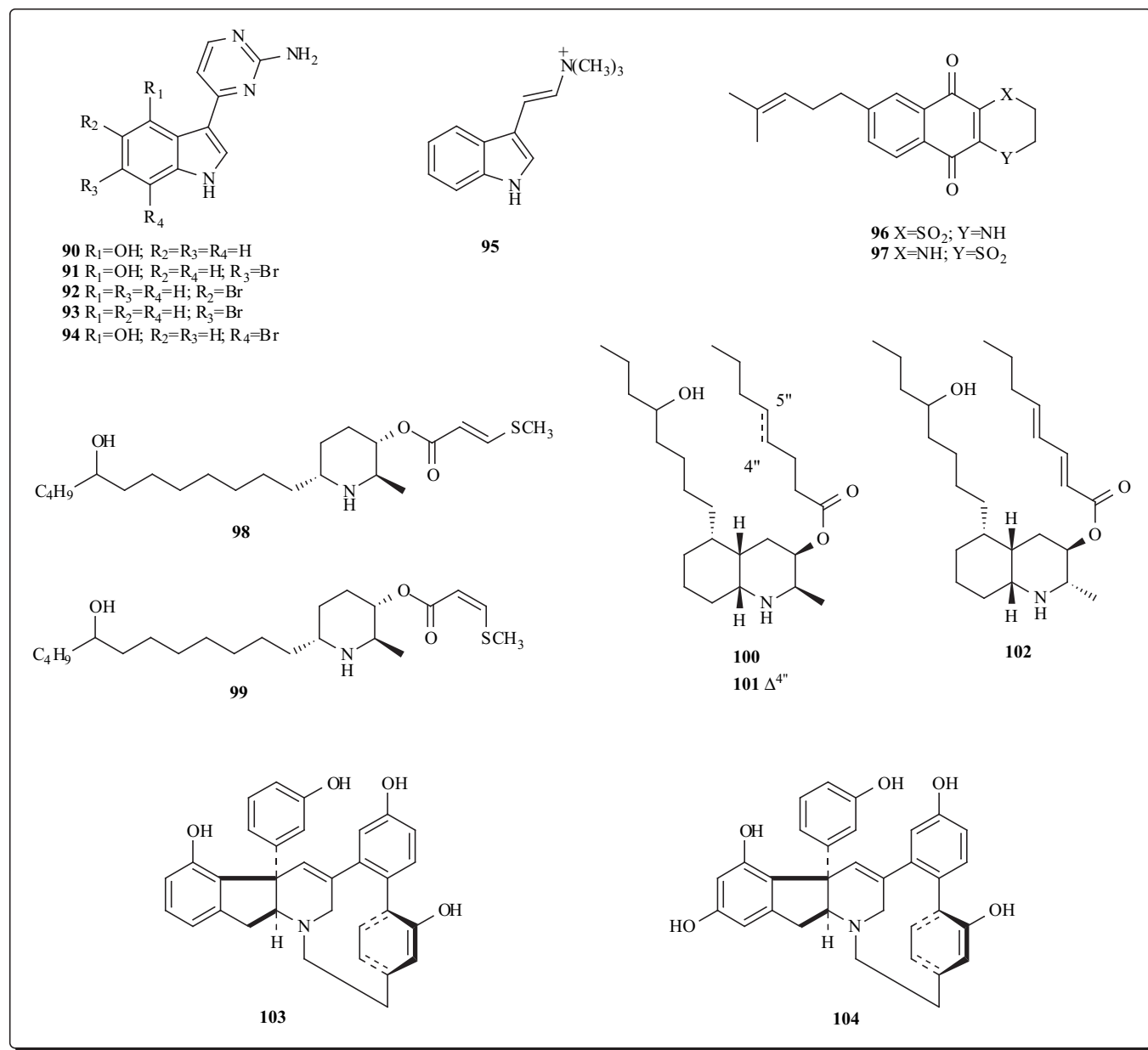
Recently, the protein kinase inhibition activity of meridianins has been stated suggesting that this family of compounds might constitute a new scaffold of protein kinase inhibitors [68].

The hydrophilic fractions of a methanolic extract of the ascidian *A. conicum* from the Mediterranean Sea, already mentioned on the previous section, led to the isolation of a new indole alkaloid, conicamin (**95**), which exhibited antagonist effect of a non-competitive type toward histamine receptors [69]. In addition, this ascidian also has afforded the nitrogenous metabolites conicaquinones A (**96**) and B (**97**), which are cytotoxic prenyl naphtoquinones possessing a 1,1-dioxo-1,4-thiazine ring. Both compounds (**96**, **97**) exhibited a strong cytotoxicity *in vitro* against rat glioma (C6) cells [70].

The piperidine nucleus was present in the metabolites described from the ascidian *A. uouo* from Maui. The uoamines A (**98**) and B (**99**) are alkylpiperidines that differed

only in the geometry of the double bond of a 3-thiomethylacrylate ester group. The conformational mobility exhibited by the compounds in the NMR time domain complicated the structural elucidation process [71].

Marine ascidians of the genus *Aplidium* have also been source of decahydroquinoline alkaloids. Thus, the investigation of *A. tabascum* from the Great Barrier Reef resulted in the isolation of three new *cis*-decahydroquinoline alkaloids, the lepadins F (**100**), G (**101**), and H (**102**) [72]. The lepadins are a family of compounds that were originally obtained from the flatworm *Prostheceraeus villatus* and its ascidian prey *Clavellina lepadiformis* [73]. NMR and molecular modelling studies indicated that compounds **100-102** adopt a chair-chair conformation with the nitrogen equatorially substituting the carbon ring, in contrast with the axial orientation found in previous members of this series [72]. Lepadin F (**100**) was also reported to be an antiplasmodial and antitrypanosomal agent from *Didemnum* sp. from the Great Barrier Reef [74].



Finally, two unprecedented alkaloids have been obtained from *A. haouarianum* from Tarifa Island [75]. The haouamines A (**103**) and B (**104**) belong to a novel class of alkaloids characterized by the presence of a 3-aza[7]paracyclophane moiety in their structures. The structure of the major component haouamine A (**103**) was established by a detailed analysis of its spectroscopic data and those of its *N*-methyl derivative. X-ray crystallographic analysis provided further confirmation to the novel structure of haouamine A (**103**). The minor component haouamine B (**104**) was identified by means of the spectroscopic data of its peracetyl derivative. The structure determination of the haouamines was a challenging task due to the duplicity of NMR signals. This fact led to propose that the haouamines exist in solution as an inseparable mixture of interconverting isomers, generated either by pyramidal inversion of the nitrogen or by atropisomerism of the 3-aza[7]paracyclophane system. Haouamine A (**103**) exhibited a selective cytotoxicity against the HT-29 human colon carcinoma cell line.

#### IV. CONCLUSIONS

The results presented in this review clearly state the potential of ascidians of the genus *Aplidium* as producers of new bioactive natural products. A great chemodiversity is devised from non-nitrogenous metabolites, mainly prenyl quinones or hydroquinones either linear or cyclic to a vast array of nitrogenous compounds. Among the former, longithorones and longithorols are the most representative examples. The capability of *Aplidium* tunicates to produce nitrogenous metabolites is currently beyond any question. Thus, nucleosides, like the shimofuridins; depsipeptides, like aplidine; macrolides, like the lobatamides; and alkaloids ranging from indoles, piperidins and decahydroquinolines to the novel haouamines, can be encountered. In the field of bioactivities, perhaps the hottest field relies on the anticancer applications of aplidine and on the protein kinase inhibition activity of meridianins. The results available at present by far justify the research efforts accomplished and encourage further study of other species of the genus *Aplidium* whose chemistry still remain unexplored.

#### ACKNOWLEDGEMENTS

Financial support from Ministerio de Ciencia y Tecnología (research projects PPQ2001-0020 and PPQ2003-02928) and from Junta de Andalucía (PAI, FQM285) is gratefully acknowledged. The authors wish to thank all the members of the research group over the last twelve years who assisted the authors in the review of Marine Natural Products Literature.

#### REFERENCES

- [1] Faulkner, D.J. *Nat. Prod. Rep.* **2002**, *19*, 1, and previous reviews of this series.
- [2] (a) Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. *Nat. Prod. Rep.* **2004**, *21*, 1; (b) *ibid.* **2003**, *20*, 1; (c) Hill, R.A. *Annu. Rep. Prog. Chem. Sect. B*, **2004**, *100*, 169-189; (d) *ibid.* **2003**, *99*, 183-207.
- [3] For recent reviews covering concrete aspects related to metabolites from marine ascidians see: (a) Bailly, C. *Curr. Med. Chem.: Anti-Cancer Agents* **2004**, *4*, 363; (b) Lehrer, R.I.; Tincu, J.A.; Delfourne, E.; Bastide, J. *Med. Res. Rev.* **2003**, *23*, 234; (c) Vera, M.D.; Joullié, M.M. *Med. Res. Rev.* **2002**, *22*, 102.
- [4] Fenical, W. Food-Drugs from the Sea, Proceedings, 4th, 1974, **1976**, 388.
- [5] Howard, B.M.; Clarkson, K.; Bernstein, R.L. *Tetrahedron Lett.* **1979**, *20*, 4449.
- [6] Bohlmann, F.; Kleine, K.M. *Chem. Ber.* **1965**, *99*, 885.
- [7] Cotellet, N.; Moreau, S.; Bernier, J.L.; Catteau, J.P.; Henichard, J.P. *Free Radical Biol. Med.* **1991**, *11*, 63.
- [8] Targett, N.M.; Keeran, W.S. *J. Nat. Prod.* **1984**, *47*, 556.
- [9] Manners, G.D.; Jurd, L. *J. Chem. Soc., Perkin I* **1977**, 405.
- [10] Benslimane, A.F.; Pouchus, Y.F.; Le Botterf, J.; Verbist, J.F. *J. Nat. Prod.* **1988**, *51*, 582.
- [11] Guella, G.; Mancini, I.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 621.
- [12] Rochfort, S.J.; Metzger, R.; Hobbs, L.; Capon, R.J. *Aust. J. Chem.* **1996**, *49*, 1217.
- [13] Rueda, A.; Zubía, E.; Ortega, M.J.; Salvá, J. *Nat. Prod. Lett.* **1998**, *11*, 127.
- [14] Aiello, A.; Fattorusso, E.; Menna, M. *Biochem. Syst. Ecol.* **1996**, *24*, 521.
- [15] Akin, M.; Dayan, T.L.; Rudi, A.; Kashman, Y.; Gaydou, E.M. *J. Agric. Food Chem.* **1999**, *47*, 4175.
- [16] Sato, A.; Shindo, T.; Kasanuki, N.; Hasegawa, K. *J. Nat. Prod.* **1989**, *52*, 975.
- [17] De Rosa, S.; Milone, A.; Crispino, A.; Jaklin, A.; De Giulio, A. *J. Nat. Prod.* **1997**, *60*, 462.
- [18] Garrido, L.; Zubía, E.; Ortega, M.J.; Salvá, J. *J. Nat. Prod.* **2002**, *65*, 1328.
- [19] Aiello, A.; Esposito, G.; Fattorusso, E.; Iuvone, T.; Luciano, P.; Menna, M. *Steroids* **2003**, *68*, 719.
- [20] Fu, X.; Hossain, M.B.; van der Helm, D.; Schmitz, F.J. *J. Am. Chem. Soc.* **1994**, *116*, 12125 [Erratum: *ibid.* **1995**, *117*, 9381].
- [21] Layton, M.E.; Morales, C.A.; Shair, M.D. *J. Am. Chem. Soc.* **2002**, *124*, 773.
- [22] Morales, C.A.; Layton, M.E.; Shair, M.D. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12036.
- [23] Fu, X.; Hossain, M.B.; Schmitz, F.J.; van der Helm, D. *J. Org. Chem.* **1997**, *62*, 3810.
- [24] Fu, X.; Ferreira, M.L.G.; Schmitz, F.J. *J. Nat. Prod.* **1999**, *62*, 1306.
- [25] Davis, R.A.; Carrol, A.R.; Quinn, R.J. *J. Nat. Prod.* **1999**, *62*, 158.
- [26] Davis, R.A.; Carrol, A.R.; Quinn, R.J. *J. Nat. Prod.* **1999**, *62*, 1405.
- [27] Issa, H.H.; Janaka, J.; Rachmat, R.; Higa, T. *Tetrahedron Lett.* **2003**, *44*, 1243.
- [28] Bugni, T.S.; Abbanat, D.; Bernan, V.S.; Maiese, W.M.; Greenstein, M.; Van Wagoner, R.M.; Ireland, C.M. *J. Org. Chem.* **2000**, *65*, 7195.
- [29] Pettit, G.R.; Leet, J.E.; Herald, C.L.; Kamano, Y.; Doubek, D.L. *J. Nat. Prod.* **1986**, *49*, 231.
- [30] Urban, S.; Hickford, S.J.H.; Blunt, J.W.; Munro, M.H.G. *Curr. Org. Chem.* **2000**, *4*, 765.
- [31] Lehrer, R.I.; Tincu, J.A.; Taylor, S.W.; Menzel, L.P.; Waring, A.J. *Int. Comp. Biol.* **2003**, *43*, 313.
- [32] Carter, G.T.; Rinehart, K.L., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 7441.
- [33] Mori, K.; Umemura, T. *Tetrahedron Lett.* **1982**, *23*, 3391.
- [34] Demattè, N.; Guerriero, A.; Lafargue, F.; Pietra, F. *Comp. Biochem. Physiol.* **1986**, *84B*, 11.
- [35] Kobayashi, J.; Doi, Y.; Ishibashi, M. *J. Org. Chem.* **1994**, *59*, 255.
- [36] Doi, Y.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1994**, *50*, 8651.
- [37] Lindsay, B.S.; Battershill, C.N.; Copp, B.R. *J. Nat. Prod.* **1999**, *62*, 638.
- [38] Rinehart, K.L. *British Patent Application* #8922026.3, Sept. 29, **1989**.
- [39] Rinehart, K.L. *Med. Res. Rev.* **2000**, *20*, 1.
- [40] Yao, L. *IDrugs* **2003**, *6*, 246.
- [41] Jimeno, J.; Faircloth, G.; Fernández Sousa-Faro, J.M.; Scheuer, P.; Rinehart, K. *Marine Drugs* **2004**, *2*, 14.
- [42] Taraboletti, G.; Poli, M.; Dossi, R.; Manenti, L.; Borsotti, P.; Faircloth, G.T.; Broggin, M.; D'Incali, M.; Ribatti, D.; Giavazzi, R. *Brit. J. Cancer* **2004**, *90*, 2418.
- [43] Arabshahi, L.; Schmitz, F.J. *Tetrahedron Lett.* **1988**, *29*, 1099.
- [44] Copp, B.R.; Blunt, J.W.; Munro, M.H.G.; Panell, L.K. *Tetrahedron Lett.* **1989**, *30*, 3703.
- [45] Carroll, A.R.; Bowden, B.F.; Coll, J.C. *Aust. J. Chem.* **1993**, *46*, 825.

- [46] Kim, J.; Pordesimo, E.O.; Toth, S.I.; Schmitz, F.J.; Van Altena, I. *J. Nat. Prod.* **1993**, *56*, 1813.
- [47] Nakahara, S.; Matsui, J.; Kubo, A. *Tetrahedron Lett.* **1998**, *39*, 5521.
- [48] Murray, L.; Lim, T.K.; Curri, G.; Capon, R.J. *Aust. J. Chem.* **1995**, *48*, 1253.
- [49] Galinis, D.L.; McKee, T.C.; Pannell, L.K.; Cardellina II, J.H.; Boyd, M.R. *J. Org. Chem.* **1997**, *62*, 8968.
- [50] McKee, T.C.; Galinis, D.L.; Pannell, L.K.; Cardellina II, J.H.; Laakso, J.; Ireland, C.M.; Murray, L.; Capon, R.J.; Boyd, M.R. *J. Org. Chem.* **1998**, *63*, 7805.
- [51] Suzumura, K.; Takahashi, I.; Matsumodo, H.; Nagai, K.; Setiawan, B.; Rantiatmodjo, R.M.; Suzuki, K.; Nagano, N. *Tetrahedron Lett.* **1997**, *38*, 7573.
- [52] Erickson, K.L.; Beutler, J.; Cardellina, J.H., II; Boyd, M.R. *J. Org. Chem.* **1997**, *62*, 8188.
- [53] Kim, J.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153.
- [54] Yet, L. *Chem. Rev.* **2003**, *103*, 4283.
- [55] Boyd, M.R.; Farina, C.; Belfiore, P.; Gagliardi, S.; Kim, J.W.; Hayakawa, Y.; Beutler, J.A.; McKee, T.C.; Bowman, B.J.; Bowman, E.J. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 114.
- [56] Beutler, J.A.; McKee, T.C. *Curr. Med. Chem.* **2003**, *10*, 787.
- [57] Shen, R.; Porco, J.A., Jr. *Org. Lett.* **2000**, *2*, 1333.
- [58] Raw, S.A.; Taylor, R.J.K. *Tetrahedron Lett.* **2000**, *41*, 10357.
- [59] Shen, R.; Lin, C.T.; Porco, J.A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650.
- [60] Shen, R.; Lin, C.T.; Bowman, E.J.; Bowman, B.J.; Porco, J.A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889.
- [61] Shen, R.; Lin, C.T.; Bowman, E.J.; Bowman, B.J.; Porco, J.A., Jr. *Org. Lett.* **2002**, *4*, 3103.
- [62] Coleman, R.S.; Lin, P.-H. *Org. Lett.* **2004**, *6*, 577.
- [63] Hernández Franco, L.; Joffe, E.B.K.; Puricelli, L.; Tatian, M.; Seldes, A.M.; Palermo, J.A. *J. Nat. Prod.* **1998**, *61*, 1130.
- [64] Jiang, B.; Yang, C.-G. *Heterocycles* **2000**, *53*, 1489.
- [65] Jiang, B.; Yang, C.-G.; Xiong, W.-N.; Wang, J. *Biorg. Med. Chem.* **2001**, *9*, 1149.
- [66] Fresneda, P.M.; Molina, P.; Delgado, S.; Bleda, J.A. *Tetrahedron Lett.* **2000**, *41*, 4777.
- [67] Fresneda, P.M.; Molina, P.; Bleda, J.A. *Tetrahedron* **2001**, *57*, 2355.
- [68] Gompel, M.; Leost, M.; Joffe, E.B.K.; Puricelli, L.; Franco, L.H.; Palermo, J.; Meijer, L. *Biorg. Med. Chem. Lett.* **2004**, *14*, 1703.
- [69] Aiello, A.; Borelli, F.; Capasso, R.; Fattorusso, E.; Luciano, P.; Menna, M. *Biorg. Med. Chem. Lett.* **2003**, *13*, 4481.
- [70] Aiello, A.; Fattorusso, E.; Luciano, P.; Menna, M.; Esposito, G.; Iuvone, T.; Pala, D. *Eur. J. Org. Chem.* **2003**, 898.
- [71] McCoy, M.C.; Faulkner, D.J. *J. Nat. Prod.* **2001**, *64*, 1087.
- [72] Davis, R.H.; Carroll, A.R.; Quinn, R.J. *J. Nat. Prod.* **2002**, *65*, 454.
- [73] Kubanek, J.; Williams, D.E.; Dilip de Silva, E.; Allen, T.; Andersen, R.J. *Tetrahedron Lett.* **1995**, *36*, 6189.
- [74] Wright, A.D.; Goclik, E.; Koenig, G.M.; Kaminsky, R. *J. Med. Chem.* **2002**, *45*, 3067.
- [75] Garrido, L.; Zubía, E.; Ortega, M.J.; Salvá, J. *J. Org. Chem.* **2003**, *68*, 293.

---

Received: February 25, 2005

Accepted: March 7, 2005

Copyright of Mini-Reviews in Organic Chemistry is the property of Bentham Science Publishers Ltd.. The copyright in an individual article may be maintained by the author in certain cases. Content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.