BROMOTYROSINE DERIVATIVES FROM THE MARINE SPONGE *SUBEREA* AFF. *PRAETENSA*

ANAKE KIJJOA*, RAWIWAN WATANADILOK**, PICHAI SONCHAENG**, SUMAITT PUCHAKARN**, PICHAN SAWANGWONG*** & WERNER HERZ****

*Instituto de Ciências Biomédicas de Abel Salazar- CIIMAR and Centro de Estudos de Química Orgânica, Fitoquímica e Farmacologia de Universidade do Porto, Rua Aníbal, 4050-047 Porto, Portugal
**Bangsaen Institute of Marine Science (BIMS), Burapha University, Bangsaen, 21031 Chonburi, Thailand
***Department of Aquatic Science, Faculty of Science, Burapha University, Bangsaen, 21031 Chonburi, Thailand
****Department of Chemistry, The Florida State University, Tallahassee, FL 32306-4390, USA
E-mail: ankijjoa@icbas.up.pt

ABSTRACT

Ethyl acetate extracts of the samples of *Suberea* aff. *praetensa*, collected in different dates but at the same locality in the Gulf of Thailand, furnished, besides clionasterol, fourteen tyrosine derived metabolites: fistularin-3; agelorins A and B; cavernicolin 1; cavernicolin 2; 5-chlorocavernicolin; 5-bromocavernicolin; 3,5-dibromo-1-hydroxy-4-oxo-2,5-cyclohexadiene-1-acetamide; 3,5-dibromo-4-hydroxyphenylacetamide; *bis*-oxazolidone derivative as well as the new compounds 11,17-dideoxyagelorins A and B and subereatensin.

KEY WORDS

Suberea aff. *praetensa,* bromotyrosine derivatives, biosynthesis.

INTRODUCTION

Marine sponges in the order Verongida are distinct both chemically and biologically from those in other orders of the Porifera (BERGQUIST & WELLS, 1980). All genera of the Verongida have so far been examined chemically contain secondary metabolites that are derived from bromotyrosine or from chlorotyrosine in which the side chain has been converted into a variety of nitrogenous groups while the aromatic ring has either been retained or has undergone rearrangement or partial reduction (KERNAN *et al.,* 1990). Typical constituents vary from the simple aeroplysinin to the relatively complex aerothionin or the fistularins (GOPICHAND & SCHMITZ, 1979) in which one or two modified tyrosine moieties are attached to a chain consisting of variously modified 3,5-dibromo-4-(γ-aminopropoxy)-phenylethylamines (CIMINO *et al.,* 1983; KERNAN *et al.,* 1990; GUNASEKERA & CROSS, 1992; CIMINIELLO *et al.,* 1997; COMPAGNONE *et al.,* 1999). The first and so far only bromotyrosine derivatives isolated from a non Verongid sponge were the agelorins A and B (KÖNIG & WRIGHT, 1993) isolated from *Agelas oroides* (Demospongiae, subclass Tetractinomorpha, order Axinellida, family Agelasidae).

MATERIAL AND METHODS

Suberea aff. *praetensa* (Row) was collected from a trawl net on the sea shore of Ban Phae Village at the Gulf of Thailand, Rayong Province, Thailand in March 1998 (first collection), November 1999 (second collection) and February 2001 (third collection). The sponge was identified by Dr. Rob W. M. van Soest, Institute for Biodiversity and Ecosystem Dynamics, Zoological Museum, University of Amsterdam and was registered as ZMA POR. 16715. The voucher of the specimen (BIMS-1954) was deposited at the Reference Collection Museum of Bangsaen Institute of Marine Science (BIMS), Burapha University, Chonburi 20131, Thailand.

Isolation and structure elucidation of the compounds from the three collections of *Suberea* aff. *praetensa* (Row) were described earlier (KIJJOA *et al.,* 2001; KIJJOA *et al*., 2002).

RESULTS

We now report the results of our study of three collections of *Suberea* aff. *praetensa* (Demospongiae, Ceractinomorpha, Verongida, family Aplysinellidae) from the same locality in the Gulf of Thailand. A collection of March 1998 (Fig. 1) furnished clionasterol, fistularin-3 (**1**) (GOPICHAND & SCHMITZ, 1979), agelorins A (**2a**) and B (**3a**) (KÖNIG & WRIGHT, 1993) and the new compounds 11,17-dideoxyagelorins A (**2b**) and B (**3b**). A second collection of November 1999 (Figs 1, 2) furnished again clionasterol and fistularin-3 (**1**) as well as 5-chloro- (**4**) and 5-bromocavernicolin (**5**) previously isolated from *Aplysina* (*Verongia*) *cavernicola* (D'AMBROSIO *et al.,* 1984; GUERRIERO *et al.,* 1984). A third collection undertaken in February 2001 (Figs 1, 2) gave clionasterol, fistularin-3 (**1**), agelorins A (**2a**) and B (**3a**), 3,5-dibromo-4-hydroxyphenylacetamide (**9**) and 3,5-dibromo-1-hydroxy-4-oxo-2,5-cyclohexadiene-1-acetamide (**10**), previously isolated from *Aplysina fistularis* (TYMIAK & RINEHART, 1981), the epimeric dibromolactams cavernicolin 1 (**6**) and cavernicolin 2 (**7**) earlier isolated from *Aplysina cavernicola* (D'AMBROSIO *et al.,* 1982), the bis-oxazolidone derivative (**11**), previously reported from *Verongia lacunosa* (BORDERS *et al.,* 1974) and *Aplysina fulva* (GOPICHAND & SCHMITZ, 1979) as well as the new unusual constituent subereatensin (**8**).

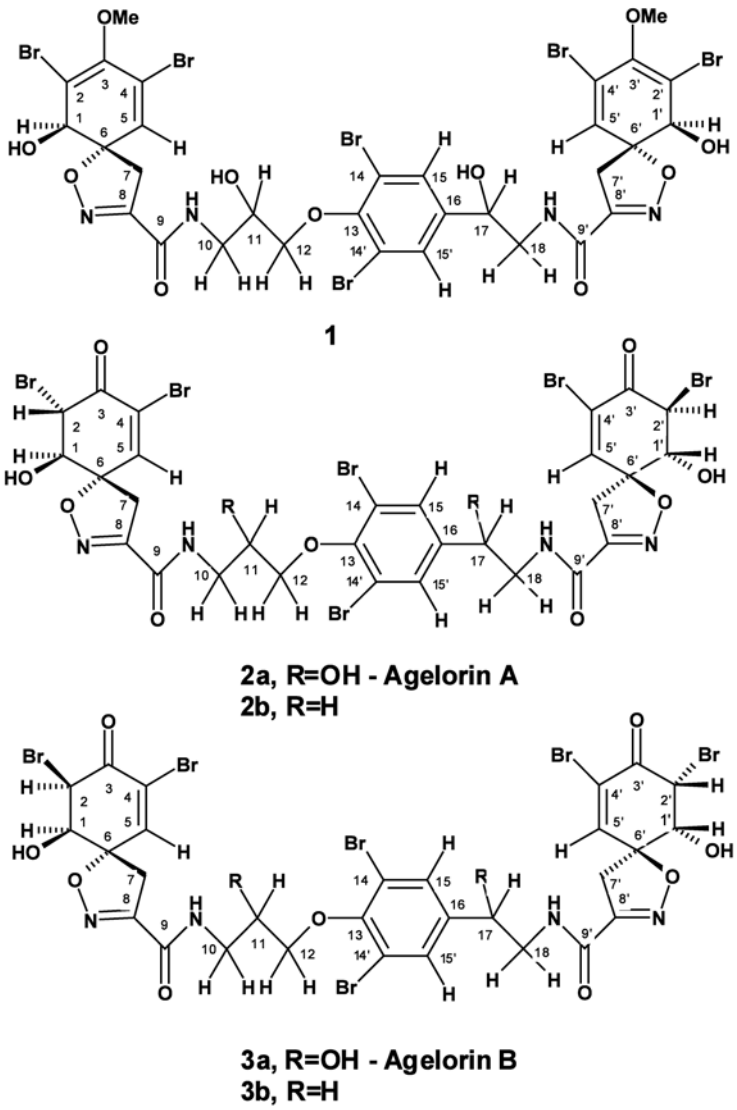

Fig. 1. Structures of the compounds from the first collection of *Suberea* aff. *praetensa*.

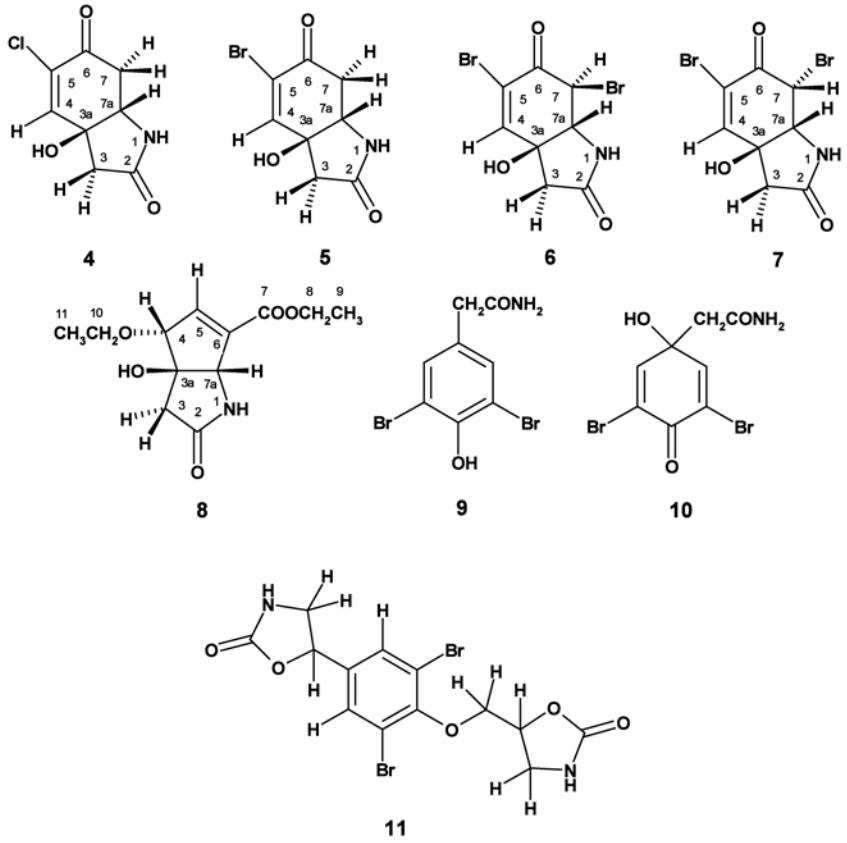

Fig. 2. Structures of the compounds from the second and third collections of *Suberea* aff. *praetensa*.

DISCUSSION AND CONCLUSIONS

Metabolites derived from brominated or chlorinated tyrosine are distinct markers for marine sponges belonging to the order Verongida. However, the references on biosynthesis of the compounds of this group are very scarce. In 1981, TYMIAK & RINEHART have investigated the biosynthesis of brominated phenols and bromoquinones in *Aplysina fistularis* and have demonstrated the conversion of phenylalanine and tyrosine to the dienone as well as the rearranged product dibromogentisamide (TYMIAK & RINEHART, 1981). The biosynthetic pathway proposed by Tymiak and Rinehart was consistent with their labelling studies as well as the known occurrence of bromophenol nitriles and oximes in *Verongia* species (MINALE, 1976). ROTEM *et al.* (1983) have proposed the biosynthesis of psammaplysin A and B, bromotyrosine derivatives isolated from *Psammaplysilla purpurea*.

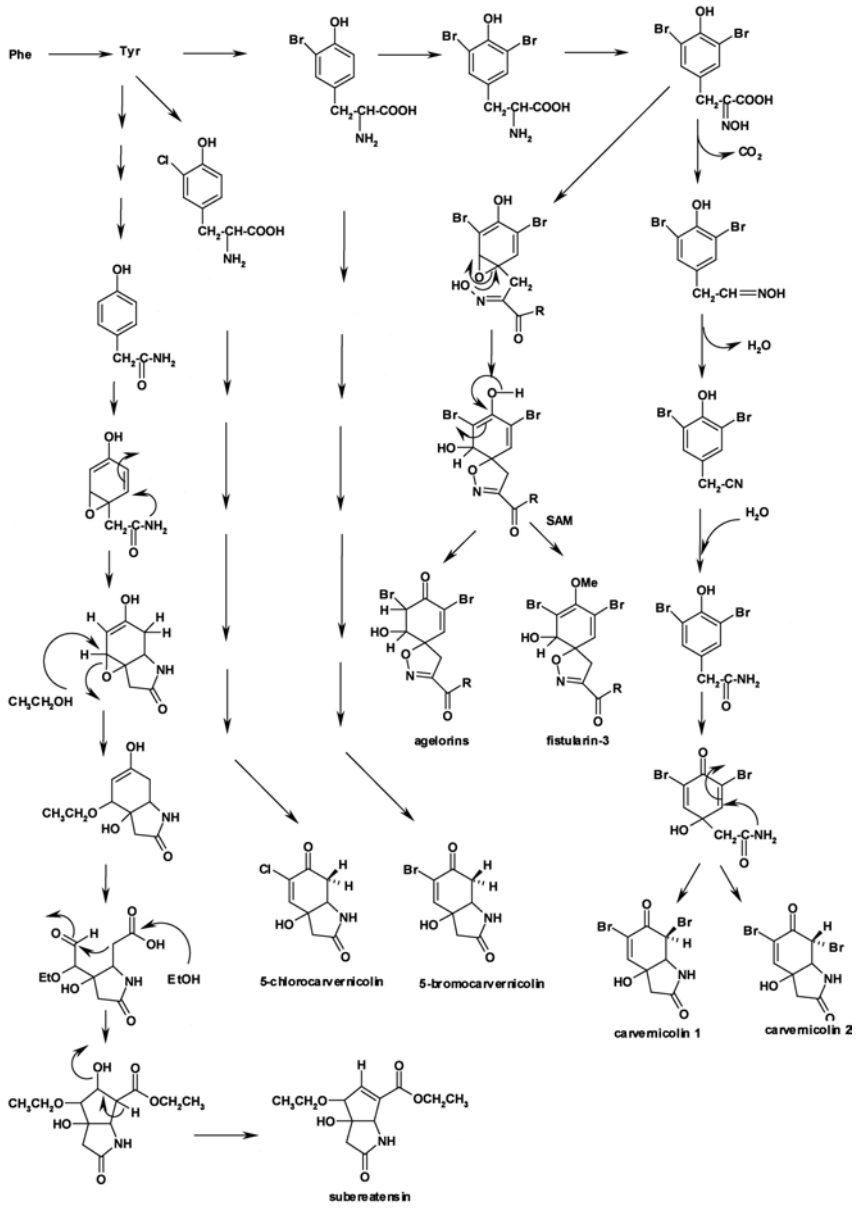

Fig. 3. Proposed biosynthetic pathway of the secondary metabolites from *Suberea* aff. *praetensa*.

From the structural point of view, the secondary metabolites isolated from the Thai collections of *Suberea* aff. *praetensa* are derived from tyrosine. However, these compounds differ from each other in the degree of halogenation and the mode of posterior cyclization. While cavernicolin 1 (**6**), cavernicolin 2 (**7**), fistularin-3 (**1**), agelorin A (**2a**) and B (**3a**), and 11,17-dideoxyagelorin A (**2b**) and B (**3b**) possess two bromine atoms in each tyrosine unit, 5-chlorocavernicolin (**4**) and 5-bromocavernicolin (**5**) have only one halogen atom. The isolation of the new compound subereatensin (**8**) from *Suberea* aff. *praetensa*, whose structure could be considered as a rearranged tyrosine skeleton leads to the assumption that the biosynthetic route of this metabolite must deviate from the pathway proposed by Tymiak and Rinehart just prior to the formation of halotyrosine by haloperoxidase. The occurrence of 5-chlorocavernicolin (**4**) suggested an interplay of the haloperoxidase enzymes in this organism. The co-occurrence of 5-bromocavernicolin (**5**), cavernicolin 1 (**6**) and cavernicolin 2 (**7**) indicated a stepwise bromination of tyrosine precursor by bromoperoxidase enzyme. Fig. 3 shows the proposed biosythetic pathway for the compounds isolated from *Suberea* aff. *praetensa.*

Contrary to the rest of the compounds isolated from *Suberea* aff. *praetensa*, the route to subereatensin (**8**) does not involve haloperoxidase enzyme(s). The biosynthesis of this metabolite must proceed via the route parallel to that of cavernicolins. However, the arene oxide should be formed as an intermediate, instead of the hydroxycyclohexadienone, prior to the formation of γ-lactam ring. Oxidative cleavage of the double bond of the six member ring intermediate followed by cyclization by aldol condensation resulted in formation of the cyclopentadiene moiety in subereatensin (**8**).

ACKNOWLEDGEMENT

Work in Portugal was supported by FCT (I&D) 22/94) POCTI (QCA III) and FEDER. We thank Dr. Rob W.M. van Soest, Institute for Biodiversity and Ecosystem Dynamics, Zoological Museum Zoological Museum, University of Amsterdam for sponge identification.

REFERENCES

BERGQUIST P., WELLS R., 1980 - Chemotaxonomy of the Porifera: the development and current status of the field. In P.J. Scheuer (ed.), *Marine Natural Products, Chemical and Biological Perspectives*. Vol. **5**, Academic Press, New York and London: 1-50.

BORDERS D., MORTON G., WETZEL E., 1974 - Structure of a novel bromine compound isolated from a sponge. *Tetrahedron Lett.,*: 2704-2712.

CIMINIELLO P., FATTORUSSO E., FORINO M., MAGNO S., PANSINI M., 1997 - Chemistry of Verongida sponge VIII. Bromocompounds from the Mediterranean sponges *Aplysina aerophoba* and *Aplysina cavernicola. Tetrahedron,* **53**: 6565-6572.

CIMINO G., DE ROSA S., DE STEPHANO S., SODANO G., 1983 - The Bromo-compounds of the true sponge *Verongia aerophoba. Tetrahedron Lett.,* **24**: 3029-3032.

COMPAGNONE R., AVILA R., SUÁREZ A., ABRAMS O., RANGEL H., ARVELA F., PINÃ I., MORENTO E., 1999 - 11-Deoxyfistularin-3, a new cytotoxic metabolite from the Caribbean Sponge *Aplysina fistularis insularis. J. Nat. Prod.,* **62**: 1443-1444.

D'AMBROSIO M, GUERRIERO A., PIETRA F., 1984 - Novel, racemic or nearly racemic antibacterial bromo and choroquinols and γ-lactams of the verongiaquinol and the

cavernicolin type from the marine sponge *Aplysina* (=*Verongia*) *cavernicola*. *Helv. Chim. Acta,* **67**: 4403-4406.

D'AMBROSIO M, GUERRIERO A., TRALDI P., PIETRA F., 1982 – Cavernicolin-1 and cavernicolin-2, two epimeric dibromolactones from the Mediterranean sponge *Aplysina* (=*Verongia*) *cavernicola*. *Tetrahedron Lett.,* **23**: 4403-4406.

GUERRIERO A., D'AMBROSIO M., TRALDI P., PIETRA F., 1984 - On the first marine natural product having low enantimeric purity. *Naturwissenschaften,* **71**: 425-426.

GOPICHAND Y., SCHMITZ F., 1979 - Marine natural products: fistularin-1, -2 and –3 from the sponge *Aplysina fistularis* forma *fulva*. *Tetrahedron Lett.,*:3921-3924.

GUNASEKERA S., CROSS S., 1992 - Fistularin-3 and 11- keto-fistularin-3, feline leukemia virus active bromotyrosine metabolites from the marine sponge *Aplysina archeri*. *J. Nat. Prod.,* **55**: 509-512.

KERNAN M., CAMBIE R., BERGQUIST P., 1990 - Chemistry of sponges. VII. 11,19-dideoxyfistularin-3 and 11-hydroxyaerothionin, bromotyrosine derivatives from *Pseudoceratina durissima*. *J. Nat. Prod.,* **53**: 615-622.

KIJJOA A., WATANADILOK R., SONCHAENG P., SILVA A, EATON G., HERZ W., 2001 - 11,17-Dideoxyagelorins A and B, new bromotyrosine derivatives and analogs from the marine sponge *Suberea* aff. *praetensa*. *Z. Naturforsch.,* **56c**: 1116-1120.

KIJJOA A., WATANADILOK R., SONCHAENG P., SAWANGWONG P., PEDRO M., NASCIMENTO M., SILVA A., EATON G., HERZ W., 2002 - Further halotyrosine derivatives from the marine sponge *Suberea* aff. *praetensa*. *Z. Naturforsch.,* **57c**: 732-738.

KÖNIG G, WRIGHT A., 1993 - Agelorins A and B, and 11-*epi*- fistularin-3, three new antibacterial fistularin-3 derivatives from the tropical marine sponge *Agelas oroides*. *Heterocycles,* **36**: 1351-1358.

MINALE L., 1976 - Natural product chemistry of the marine sponges. *Pure Appl. Chem.,* **48**: 7-23.

ROTEM M., CARMELY S., KASHMAN Y., 1983 - Two new antibiotics from the Red Sea sponge *Psammaplysilla purpurea*. *Tetrahedron,* **39**: 667-676.

TYMIAK A., RINEHART K., 1981 - Biosynthesis of dibromotyrosine derived antimicrobial compounds from the marine sponge *Aplysina fistularis* (*Verongia aurea*). *J. Am. Chem. Soc.,* **103**: 6763-6765.