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Serotonin and dopamine derivatives from the Papua New Guinea zoantharian *Zoanthus* cf. *sansibaricus*

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ABSTRACT

In our continuous search for bioactive natural products from marine zoantharians, three serotonin derivatives **1**-**3** and one dopamine analogue **4** together with the known ecdysteroids ajugasterone C (**5**) and turkesterone (**6**) and zoanthoxanthin derivative 3-norpseudozoanthoxanthin (**7**) were isolated from *Zoanthus* cf. *sansibaricus* collected off the coast of Papua New Guinea. The structures of these alkaloids were elucidated through spectroscopic analyses including 1D and 2D NMR experiments and HRESIMS data. This is the first report of serotonin and dopamine derived alkaloids from species of the genus *Zoanthus*. Compounds **1**-**3** demonstrated moderate bactericidal activity against *S. aureus* NCTC 7447 with an IC_{50} value of 83.3, 41.9 and 37.4 μM.

1. Introduction

Zoantharians (Cnidaria: Hexacorallia: Zoantharia) are sessile marine invertebrates widely distributed from shallow to deep sea environments in tropical and sub-tropical areas. They represent a prolific source of structurally unique metabolites with significant biological activities. Recently, the chemical diversity of zoantharians was reviewed (Guillen et al., 2019a) and the main families of natural products reported includes palytoxin derivatives (Ciminiello et al., 2009; Moore and Scheuer, 1971), ecdysteroids (Guerriero and Pietra, 1985; Suksamrarn et al., 2002), steroids (Bergmann et al., 1951; Gupta and Scheuer, 1969), and three families of alkaloids: zoanthamines (Chen et al., 2019; Rao et al., 1984), the fluorescent pigments zoanthoxanthins and few halogenated tyrosine derivatives (Cachet et al., 2009; Guillen et al., 2019b; Schwartz et al., 1978).

Despite the broad distribution of zoantharians, the biological and chemical studies on these invertebrates have been mainly overlooked in some coral reefs such as Papua New Guinea (PNG) (Reimer et al., 2014). The maritime areas of PNG along with Indonesia, Malaysia, the Philippines, Timor Leste and Solomon Islands compose the coral triangle well known as a major hotspot of marine biodiversity (Maclean and Mallery, 2014). Although most of the chemical studies from PNG marine biodiversity focused on sponges shaping the ecosystems, the bio and chemo diversity of zoantharians have been rarely considered. Some of the zoantharian species reported from PNG includes *Palythoa* cf. *heliodiscus*, *Palythoa tuberculosa, Epizoanthus illoricatus* and *Epizoanthus beriber* (Kise and Reimer, 2016; Reimer et al., 2014).

An inventory of marine invertebrates has been undertaken in the context of the *Tara* Pacific expedition around Kimbe Bay in PNG 2017. In our continued interest for the chemical diversity of zoantharians, a preliminary UHPLC-HRMS analysis of the aqueous/methanolic extract of *Zoanthus* cf. *sansibaricus* collected off the coast of PNG revealed the presence of unknown masses and characteristic isotopic patterns of monobrominated compounds. Herein, we report the isolation and structure elucidation of three serotonin derivatives **1–3** and one dopamine analogue **4** together with the known ecdysteroids ajugasterone C (**5**) (Suksamrarn et al., 2002); turkesterone (**6**) (Cheng et al., 2016); and 3-norpseudozoanthoxanthin (**7**) (Cariello et al., 1979) (Fig. 1). This is

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the first chemical study of *Z.* cf. *sansibaricus* and the first report of serotonin and dopamine analogues and zoanthoxanthin derivatives from a species of the genus *Zoanthus*.

2. Results and discussion

The zoantharian *Zoanthus* cf. *sansibaricus* was collected by SCUBA off the coast of Papua New Guinea. The freeze-dried sample (88 g) was extracted with CH_3OH/CH_2Cl_2 (1:1) under sonication and the crude extract (13 g) was then subjected to fractionation through (RP)-C18 Vacuum Liquid Chromatography (VLC) using a mixture of solvents of decreasing polarity. The aqueous methanolic fractions were analyzed by UPLC-DAD-ELSD and purified by semi-preparative RP-HPLC using a C18 column to yield three serotonin derivatives **1–3** and one dopamine analogue **4**, along with the known ecdysteroids ajugasterone C (**5**), turkesterone (**6**) and the zoanthoxanthin derivative 3-norpseudozoanthoxanthin (**7**).

Compound **1** was isolated as a brown amorphous powder and its (+)-HRESIMS analysis revealed an isotopic cluster of ions at *m/z* 269/271 $[M+H]^+$ in a 1:1 ratio characteristic of a monobrominated compound and consistent with the molecular formula $C_{11}H_{13}BrN_2O$. A first inspection of the ^{1}H NMR spectrum revealed the presence of three aromatic singlets at δ_H 7.17 (s, H-2), 7.16 (s, H-4) and 7.57 (s, H-7), characteristic of a 3, 5, 6-trisubstituted indole ring system (Table 1). Additionally, the ^{1}H NMR, COSY and HSQC spectra evidenced an A_2X_2 system with two signals at δ_H 3.23 (t, J =7.0 Hz, H_2-9) and 3.08 (t, J =7.0 Hz, H_2-8) and one deshielded methyl singlet at δ_H 3.90, characteristic of an aromatic methoxy group. Since the methoxy group could be located either at position C-5 or C-6 of the indole ring, the ^{13}C NMR chemical shifts of **1** were compared with those of analogues with a methoxy group substituted at positions C-5 or C-6, revealing similar chemical shifts with those having the methoxy group at C-5 position (Bifulco et al., 1995; Reyes et al., 2008; Yamagishi et al., 2008). This assignment was further confirmed by the deshielded chemical shift of the carbon at δ_C 151.2 (C-5) and key 5−OCH_3/C-5, and H-7/C-3a and C-6 HMBC correlations (Fig. 2). Even though this compound was previously synthesized by the group of Nakagawa as a Bischler-Napieralski precursor in the synthesis of eudistomin P (Hino et al., 1989), this is the first report of **1** as a natural product.

Compound **2** was isolated as a brown amorphous powder and the (+)-HRESIMS data revealed a major peak at *m/z* 205.1331 $[M+H]^+$ consistent with the molecular formula $C_{12}H_{17}N_2O$. The main differences in the MS and NMR spectra of **2** compared to **1** were: the lack of the bromine atom in the molecular formula; the presence of two aromatic spin coupled proton signals at δ_H 6.81 (dd, J = 8.5, 2.0 Hz, H-6) and 7.27 (d, J=8.5 Hz, H-7) in place of the aromatic singlet proton signal for H-7 in **1**; and a new methyl singlet at δ_H 2.71 (s, H_3-11) located on the primary amine. The ^{1}H NMR spectrum of **2** also revealed the presence of a singlet at δ_H 3.84 corresponding to an aromatic methoxy group. Like for **1**, similar chemical shifts were observed with those of *O*-methylserotonin derivatives (Moreira et al., 2015; Ríos and Nathan, 1987), suggesting the location of the methoxy group at position C-5. This assignment was further confirmed through key H-4 and H-7/C-5 HMBC correlation. Although, this deacetylated melatonin derivative was first isolated from the red canary grass *Phalaris arundinacea* (Wilkinson, 1958), this is the first report of **2** from marine sources.

Compound **3** was isolated as a brown amorphous powder and the molecular formula $C_{13}H_{19}N_2O$ was determined by (+)-HRESIMS with a molecular ion at *m/z* 219.1485 $[M+H]^+$ indicating that **3** is a homologue of **2**. The ^{1}H NMR spectrum of **3** revealed similar aromatic signals to those of **2** at δ_H 7.27 (d, J =9.0 Hz, H-7), 7.18 (s, H-2), 7.08 (d, J =2.0 Hz, H-4) and 6.81 (dd, J = 9.0, 2.0 Hz, H-6), and a methoxy singlet at δ_H 3.84 indicating the presence of a 3, 5 disubstituted indole ring system (Table 1). The only difference of the NMR data when compared with those of **2** was the presence of a methyl singlet integrated for six protons at δ_H 2.94 which was assigned to two methyls located on the primary amine. The presence of *N,N,O*-trimethylserotonin was initially described from the bark of the Brazilian tree *Dictyoloma incanescens* D.C (Pachter et al., 1959). However, this is the first time that compound **3** is isolated as a marine natural product.

Compound **4** was obtained as a yellow amorphous powder and its (+)-HRESIMS analysis revealed a major peak at *m/z* 208.1335 $[M+H]^+$ consistent with the molecular formula $C_{12}H_{18}NO_2$. The ^{1}H NMR spectrum of **4** revealed two aromatic singlets at δ_H 7.35 (s, H-3) and 7.06 (s, H-6), two deshielded methyl singlets at δ_H 3.90 (4−OCH_3) and 3.88 (5−OCH_3) corresponding to aromatic methoxy groups and two spin coupled methylene signals at δ_H 4.20 (t, J =7.0 Hz, H_2-8) and 3.35 (t, J =7.0 Hz, H_2-7). The singlet at δ_H 3.50 integrating for six protons was assigned to two equivalent *N*-methyl groups. The ^{13}C NMR spectrum of **4** revealed signals corresponding to four non-protonated and aromatic carbons at δ_C 153.1 (C-5), 151.7 (C-4), 140.1 (C-2) and 126.3 (C-1) and key H-3/C-5 and C-1, H-6/C-7, H_2-7/C-1 and $N(CH_3)_2$/C-8 and C-2 HMBC correlations were consistent with the closure of a second ring on the benzene ring through the nitrogen, leading to an indoline moiety (Fig. 2). The location of the two methoxy groups on the aromatic ring was inferred from key HMBC correlations between 4−OCH_3 (δ_H 3.90) to C-4 and 5−OCH_3 (δ_H 3.88) to C-5. Therefore, compound **4** was assigned as *N,N,O,O*-tetramethylcyclodopamine. Even though, compound **4** has been previously synthesized through a biomimetic oxidative cyclisation of dopamine derivatives (Clews et al., 2000), this is the first report of **4** isolated as a natural product.

Compounds **1–4** were evaluated for their antimicrobial activity against *Acinetobacter baumannii*NCTC 12,156, *Escherichia coli* NCTC 12,241, *P. aeruginosa* NCTC 10,332 and *Staphylococcus aureus* NCTC 7447. All compounds did not show activity against *Acinetobacter baumannii*NCTC 12,156 and *Escherichia coli* NCTC 12241. Compounds **1–3** displayed activity on *S. aureus* with MIC and MBC values of 32, 8, 8 and 64, 16 and 16 μg/mL respectively (Fig. S2). In the case of *P. aeruginosa,* compounds **1–3** showed an inhibitory activity (bacteriostatic), however a significant reduction in the population of *P. aeruginosa* was observed in the subcultured Nutrient Agar plates at 128 μg/mL of all the compounds tested (Fig. = S3). Compound **4** did not have any effect on the growth and proliferation of both pathogens. The IC_{50} and MIC values obtained for all compounds are shown in Table S1.

3. Experimental data

3.1. 6-bromo-O-methylserotonin (1)

Brown amorphous powder; UV (DAD, MeOH) λ_{max} 288, 224, 206 nm; ^{1}H NMR and ^{13}C NMR, see Table 1; HRESIMS *m/z* 269.0277 $[M]^+$ (calcd for $C_{11}H_{14}BrN_2O$, 269.0284, Δ -2.6 ppm).

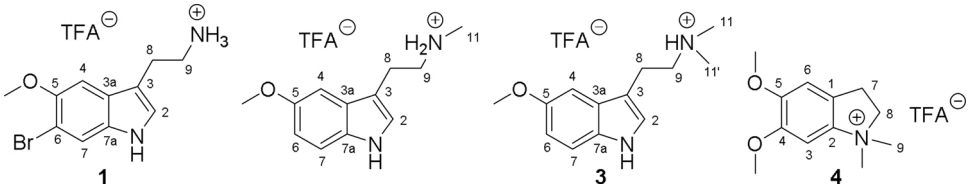

Fig. 1. Chemical structures of compounds **1-4** from *Zoanthus* cf. *sansibaricus*.

Table 1
NMR data for compounds **1-3** in CD_3OD (500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR data).

Position	1		2		3	
	δ_H, Mult. (*J* in Hz)	δ_C	δ_H, Mult. (*J* in Hz)	δ_C	δ_H, Mult. (*J* in Hz)	δ_C
2	7.17, s	125.6	7.15, s	125.0	7.18, s	125.0
3		110.3		109.5		109.1
3a		127.8		128.4		128.4
4	7.16, s	101.6	7.06, s	101.0	7.08, d (2.0)	101.0
5		151.2		155.3		155.3
6		108.2	6.81, dd (8.5, 2.0)	113.0	6.81, dd (9.0, 2.0)	113.0
7	7.57, s	116.9	7.27, d (8.5)	113.3	7.27, d (9.0)	113.3
7a		132.5		133.6		133.5
8a 8b	3.08, t (7.0)	24.3	3.12, t (7.0)	23.3	3.18, t (8.0)	21.9
9a 9b	3.23, t (7.0)	41.1	3.30[a]	50.7	3.44, t (8.0)	59.1
11			2.71, s	33.7	2.94, s	43.5
5-OCH_3	3.90, s	57.3	3.84, s	56.3	3.84, s	56.3

[a] Overlap with solvent signal.

3.2. N,O-dimethylserotonin (2)

Brown amorphous powder; UV (DAD, MeOH) λ_{max} 292, 278, 220, 202 nm; ^1H and ^{13}C NMR, see Table 1; HRESIMS *m/z* 205.1331 $[M+H]^+$ (calcd for $C_{12}H_{17}N_{2O}$, 205.1335, Δ -1.94 ppm).

3.3. N,N,O-trimethylserotonin (3)

Brown amorphous powder; UV (DAD, MeOH) λ_{max} 296, 276, 224, 196 nm; ^1H and ^{13}C NMR, see Table 1; HRESIMS *m/z* 219.1485 $[M+H]^+$ (calcd for $C_{13}H_{19}N_2O$, 219.1492, Δ -3.19 ppm).

3.4. N,N,O,O-tetramethylcyclodopamine (4)

Yellow amorphous powder; UV (DAD, MeOH) λ_{max} 200, 234, 290 nm; HRESIMS *m/z* 208.1335 $[M+H]^+$ (calcd for $C_{12}H_{18}NO_2$, 208.1332, Δ +1.44 ppm); ^1H NMR (CD_3OD, 500 MHz) δ_H 7.35 (1H, s, H-3), 7.06 (1H, s, H-6), 4.20 (2H, t, *J* =7.0 Hz, H_2-8), 3.90 (3H, s, 4−OCH_3), 3.88 (3H, s, 5−OCH_3), 3.50 (6H, s, $N(CH_3)_2$), 3.35 (2H, t, *J* =7.0 Hz, H_2-7); ^{13}C NMR (CD_3OD, 125 MHz) δ_C 151.7 (C-4), 153.1 (C-5), 140.1 (C-2), 126.3 (C-1), 109.2 (C-6), 101.4 (C-3), 70.0 (C-8), 57.0 (4−OCH_3), 56.8 (5−OCH_3), 55.2 ($N(CH_3)_2$), 27.8 (C-7).

4. Conclusions

Serotonin and dopamine analogues are neurotransmitters characterized by their capacity to modulate different biological and neurological processes in humans through the stimulation or inhibition of serotonin (5-HT) receptors (Pithadia and Jain, 2009). Interestingly, serotonin derivatives and different neurotoxic peptides with high-affinity for 5-HT receptors and pharmacological properties have been reported from cnidarians (Santhanam, 2020), and other marine organisms (Özogul and Hamed, 2018). In zoantharians, diverse neurotoxic peptides have been identified from *Palythoa caribaeorum* (Cuevas-Cruz et al., 2019; Liao et al., 2018a, b), *Protopalythoa variabilis* (Liao et al., 2019) and serotonin analogues have only been described from *Palythoa tuberculosa* (Chen et al., 2018). Although, *Zoanthus* species have been scarcely studied for their toxin content, the presence of the cyanotoxin microcystin-LR and structurally related peptides to those ω-conotoxin GVIA as modulators of voltage-gated Ca^{2+} channels in *Zoanthus sociatus* (Diaz-Garcia et al., 2012; Domínguez-Pérez et al., 2017) demonstrates the potential for the discovery of novel toxins with therapeutic applications. Different studies have shown that biogenic amines such as serotonin and dopamine can induce pain and enhance vasodilatation to promote the distribution of other venom components in the prey. For example, it was observed that serotonin present in marine snail venom produces vasodilatation in mollusks (Weisel-Eichler and Libersat, 2004). Therefore, the presence of these compounds in *Zoanthus* species suggests a role as predation or self-protection. This is the first report of serotonin and dopamine derivatives from a species of the genus *Zoanthus*, thus adding one more family of alkaloids present in these organisms. The biosynthetic pathways of these compounds should be similar to the pathways described for serotonin and dopamine in the terrestrial environment. Interestingly, methylation seems favored on the primary amine and halogenation can occur at the C-6 position in **1** as already found for marine natural products and the cyclisation of the dopamine derivative into **4** should derive from a radical oxidation of the enriched benzene ring. Additionally, zoanthoxanthin derivatives have been described from *Palythoa* (Cariello et al., 1979), *Epizoanthus* (Cariello et al., 1974), *Parazoanthus* and *Savalia* species (Cariello et al., 1973; Schwartz et al., 1979), but their presence in *Zoanthus sociatus*, *Z.* cfr. *Pacificus*, *Z.* cf. *sociatus* and *Z.* cf. *pulchellus* were only reported from MS fragmentation pattern (Cariello et al., 1979; Jaramillo et al., 2018). Finally, compounds **1-3** possesses moderated inhibitory activity on *P. aeruginosa* NCTC 10,332 and bactericidal activity on *S. aureus* NCTC 7447 human pathogens.

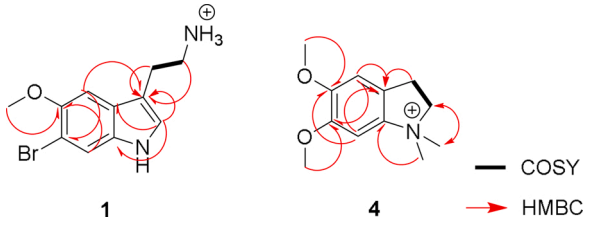

Fig. 2. COSY and key HMBC correlation for compounds **1** and **4**.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phytol.2020.09.001.

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