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New iodotyramine derivatives from *Didemnum rubeum*

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ABSTRACT

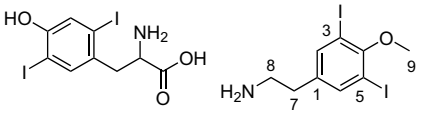
The study of an aqueous extract from the ascidian *Didemnum rubeum* permitted the isolation of a previously reported derivative diiodo-tyramine derivative together with six new iodo-tyramine derivatives. Their structures were elucidated by NMR and MS analysis.

1. Introduction

A vast diversity of organisms is able to biosynthesize halogen-containing metabolites with a great variety of structural arrangements and biological activities. Some, like the chlorine containing antibiotic vancomycin, are of commercial value.[1–3]

In nature, chlorinated and brominated derivatives are the most abundant metabolites, while iodinated and fluorinated compounds are less common.[1] In terrestrial environments *Streptomyces*, fungi and lichens are responsible for the production of most halogenated compounds, however, there are also reports from plants and animals, including humans.[2–5] The marine environment contains high concentrations of halogenated meta-bolites with the most prolific producers being algae and sponges. Novel halogenated metabolites are also produced by corals, nudibranchs, ascidians, bryozoans and acorn worms.[2,3,6] Many of these groups of organisms have not been studied extensively and so represent a rich source of possible new halogenated metabolites.[2,3]

The function of these halogenated metabolites produced by living organisms range from hormones to defensive compounds.[3] The first reported halometabolite was 2,5-diiodotyrosine (**1**) from the coral *Gorgonia cavolii* in the late nineteenth century.[1] Similar tyrosine derived halometabolites have been frequently isolated from other marine organisms such as the bromotyrosine compounds of the sponge *Aiolochroia crassa*,[7] iodotyrosine alkaloids from *Aplidium* sp.,[8] brominated and iodinated derivatives from the sponge *Iotrochota birotulata*,[9] and turbotoxins from the gastropod *Turbo marmorata*.[10,11]



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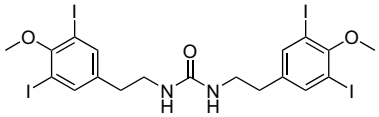

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The 2-(3,5-diiodo-4-methoxyphenyl)ethanamine (**2**) is a iodinated tyramine derivative which constitutes one of the main components isolated in several samples of tunicates of the genus *Didemnum*.[12,13] Apparently, **2** and the urea derivative **3** are produced by the association of the tunicate with prokaryotic algal symbionts due to their ability to fix nitrogen.[14] Presented here is the isolation and structure elucidation of compound **2**, its protonated ammonium form, and six additional iodinated compounds derived from **2** from a sample of the tunicate *Didemnum rubeum*.

2. Results and discussion

The *D. rubeum* crude aqueous extract was previously evaluated for anticancer activity and shown to be cytotoxic. The crude aqueous extract was desalted using Diaion HP20SS and fractions washed from the resin using a step gradient of methanol (MeOH) 50%, MeOH 100% and dichloromethane (DCM) 100%. The 50% MeOH fraction was chromatographed on Sephadex LH20 with MeOH:acetonitrile (ACN) (1:1) followed by C18 reverse phase HPLC

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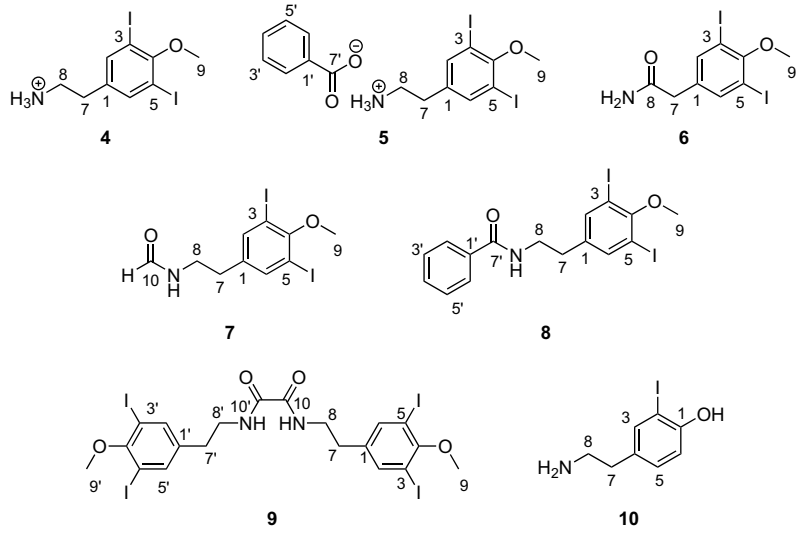
and afforded the protonated (**4**) and free base (**2**) tyramine derivatives, as well as the benzoate salt (**5**) as major compounds in the extract. The 100% MeOH fraction was also chromatographed on Sephadex LH20 followed successive C18 RP-HPLC using a water: MeOH gradient to afford the compounds **6** to **9**. Finally, all minor fractions from the 50% and 100% MeOH and 100% CH_2Cl_2 fractions, this compound was the amine **2**. Since the original extract was an aqueous extract it might be expected to contain **4** because it is the most water soluble form of **2**. The presence of **2** is most likely due to the acid-base equilibrium of the ammonium salt during the separation of the extract using the aqueous solvent systems used for HPLC.



4 **5** **6**

7 **8**

9 **10**

and organic solvent solubles from the aqueous washings were pooled, defatted with hexane and five fractions obtained by step gradient separation on solid phase extraction. Purification by C18 RP-HPLC gave the additional compound **10** together with more **4** and **7**. A literature and database search showed that the compounds **5** to **10** have not been previously reported from natural sources.

The positive ESIMS spectrum of compound **4** showed a $[M+H]^+$ at 403.78 *m*/*z* and HRESIMS measurements gave the molecular formula $C_9H_{12}NOI_2$. The ^1H NMR spectrum in CD_3OD (Table 1) showed signals for two degenerate aromatic protons at 7.77 (s, 2H), a methoxy group at 3.81 (s, 3H), and an A_2B_2 spin system at 3.13 (t, 2H, *J*=7.6 Hz) and 2.86 (t, 2H, *J*=7.6 Hz), while the ^{13}C NMR (Table 2) contained resonances for six sp^2 carbons at δ 159.9 (s), 141.6 (2C), 138.4 (s), 91.6 (2C); a methoxy at 61.3; and two methylene carbons at 41.8 and 33.0. All these signals were consistent with the reported structure of the tyramine derivative 2-(3,5-diiodo-4-methoxyphenyl) ethanaminium[8] and were corroborated by 2D spectra (Fig. 1). The second compound eluted as a shoulder of the C18 RP-HLPC peak for **4**. The ESIMS molecular ion and ^1H NMR signals in DMSO-d_6 (Table 1) were identical to those of **4**, except for a broad singlet at δ 7.46 integrating for two protons in the nitrogen, which was comparable to the broad signal integrating for three protons at δ 7.75 in **4**; evidence that

Positive ESIMS spectrum of compound **5** showed a $[M+H]^+$ at 403.79 *m*/*z* and HRESIMS measurements gave the molecular formula $C_9H_{12}NOI_2$, while the negative ESIMS showed a $[M-H]^-$ at 120.92

Table 2
^{13}C NMR Data for compounds **4**–**8**[a]

Position	**4**[b]	**5**[c,b]		**6**[d]	**7**[e]	**8**[d]
1	138.4	139.1	138.6[f]	134.1	138.7	138.9
2/6	141.6	139.8	141.6	140.4	140.2	140.2
3/5	91.6	91.3	91.6	90.6	90.9	90.6
4	159.9	156.9	159.8	158.2	157.9	157.7
7	33.0	33.3	33.3	40.9	34.0	34.0
8	41.8	40.7	41.8	171.9	39.3	41.0
9	61.3	60.2	61.3	60.6	60.9	60.7
10	—	—	—	—	161.3	—
1′	—	136.2	138.6[f]	—	—	134.6
2′/6′	—	129.0	130.4	—	—	126.9
3′/5′	—	127.7	128.9	—	—	128.7
4′	—	130.4	131.6	—	—	131.8
7′	—	168.7	175.5[f]	—	—	167.7

[a] Assignments based on COSY, HSQC and HMBC.
[b] Acquired in CD_3OD at 101 MHz.
[c] Acquired in DMSO-d_6 at 101 MHz.
[d] Deduced from HSQC and HMBC, acquired in $CDCl_3$ at 600 MHz.
[e] Acquired in $CDCl_3$ at 101 MHz.
[f] Deduced from HSQC and HMBC.

Table 1
^1H NMR Data for compounds **2**, **4**–**8**[a]

Position	**2**[b]	**4**[b,c]		**5**[b,c]		**6**[d]	**7**[e]	**8**[d]
2/6	7.75, s	7.75, s	7.77, s	7.72, s	7.75, s	7.71, s	7.61, s	7.63, s
7	2.75, t (7.4)	2.78, br s	2.86, t (7.6)	2.69, br m	2.86, t (7.6)	3.47, s	2.74, t (7.0)	2.81, t (7.0)
8	3.03, t (7.4)	3.01, t (7.3)	3.13, t (7.6)	2.91,br m	3.11, br m	—	3.52, dd (6.8, 6.8)	3.63, dd (6.8, 13.1)
9	3.73, s	3.73, s	3.81, s	3.72, s	3.80, s	3.87, s	3.84, s	3.83, s
10	—	—	—	—	—	—	8.18, s	
2′/6′	—	—	—	7.90, m	7.94, m	—	—	7.69, m
3′/5′	—	—	—	7.38, m	7.35, m	—	—	7.42, m
4′	—	—	—	7.45, m	7.41, m	—	—	7.49, m
NH	7.46, br s (2H)	7.75, br s (3H)	—	—	—	5.48, br d (2H)	5.57, br s (1H)	6.11, br s

[a] Coupling constants are in parentheses and given in hertz. ^1H and ^{13}C assignments aided by COSY, HSQC and HMBC experiments.
[b] Acquired in DMSO-d_6 at 400 MHz.
[c] Acquired in CD_3OD at 400 MHz.
[d] Acquired in $CDCl_3$ at 600 MHz.
[e] Acquired in $CDCl_3$ at 400 MHz.

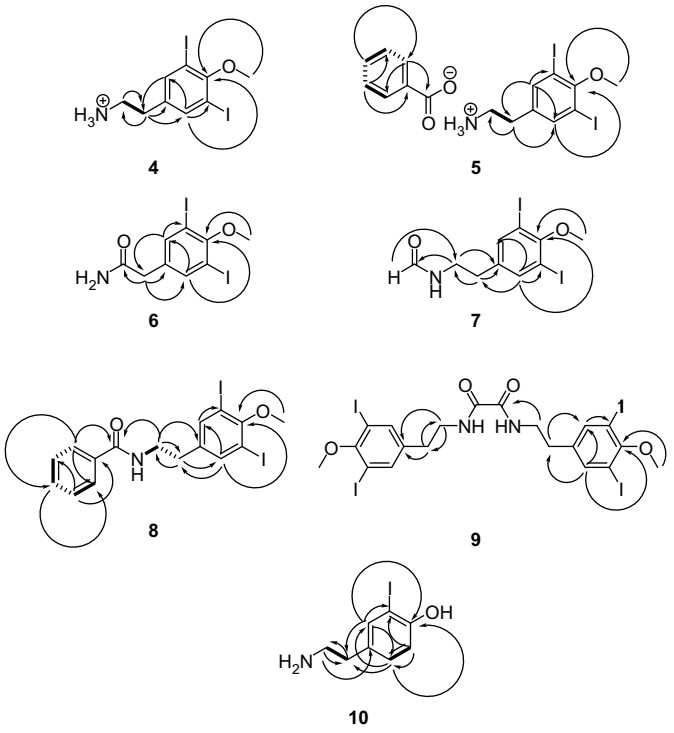


Figure 1. COSY (, ——) and HMBC ( ) correlations for compounds isolated in this work.

and HRESIMS measurements gave the molecular formula $C_7H_5O_2$. Both ^{1}H NMR (Table 1) and ^{13}C NMR (Table 2) spectra in CD_3OD and DMSO-d_6 presented similar signals to **4**; however, there were three additional sp^2 proton signals at δ_H (CD_3OD) 7.94 (m, 2H), 7.41 (m, 1H), 7.35 (m, 2H) and four carbon signals at δ_C (CD_3OD) 136.2 (s), 129.0 (2C), 127.7 (2C), 130.4 (s) that were consistent with a mono-substituted phenyl ring as corroborated by the COSY and HMBC correlations (Fig. 1); also, there was a further signal at δ 175.5 consistent with a carbonyl group. This information indicated that **4** was part of the molecule and that it was accompanied by a benzoyl group. The 2D NMR analysis (Fig. 1) showed that the two parts were not bound by an amide bond and as inferred from the negative MS results it was in fact the benzoate derivative of **4**. Benzoates salts such as the insecticide emamectin benzoate[15] and denatonium benzoate (Bitrex®), the bitterest known substance used in taste studies and as ingredient in household products to avoid intoxication,[16] are usually stable at room conditions; whether **5** is present in the tunicate was not determined in this study but **5** showed to be stable even during isolation and purifiction conditions. Natural benzoates are produced by plants and microbes through the shikimate pathway;[17–20] this information supports the idea that these metabolites are produced by a symbiont in the tunicate.

Compound **6** presented a positive ESIMS spectrum with a $[M+Na]^+$ at 439.86 m/z and HRESIMS measurements gave the molecular formula $C_9H_9NO_2I_2Na$. After analysing the ^{1}H NMR (Table 1), ^{13}C NMR (Table 2) and 2D NMR data (Fig. 1), it was evident that the compound contained a phenyl ring similar to **4**; however, the corresponding signal for protons in C8 was not present and C7 appeared as a singlet at δ 3.47, this together with the carbonyl signal at δ_C 171.9 and the presence of two protons in the nitrogen at δ 5.48 suggested the acetamide compound **6**. A database search showed that acetamide brominated derivatives similar to **6** have been isolated from sponges,[21] indicating this compound is produced naturally, possibly a biosynthetic intermediate, and was not an artifact.

Compound **7** had a $[M+Na]^+$ at 453.67 m/z in positive ESIMS spectrum which corresponded to a molecular formula $C_{10}H_{11}NO_2I_2Na$ by HRESIMS. Once again this compound presented all ^{1}H and ^{13}C NMR spectral characteristics (Tables 1 and 2) of the diiodo tyramine derivative **4**; the ^{1}H NMR contained an additional singlet at δ 8.18 (1H) and a broad singlet at δ 5.57 (1H). The ^{13}C NMR spectrum presented an additional carbonyl signal at δ_C 161.3; the 2D correlations (Fig. 1) confirmed this compound as the formamide derivative of **2**. This compound is very similar to antifouling ceratinamide A which was isolated previously from the sponge *Pseudoceratina purpurea*.[22] A database search shows that many formamide compounds are produced by microbes, which provides further evidence that the compounds derived from **2** are produced by a symbiont.

Compound **8** presented a positive ESIMS spectrum with a $[M+Na]^+$ at 529.91 m/z and a molecular formula $C_{10}H_{11}NO_2I_2Na$ by HRESIMS. The ^{1}H and ^{13}C NMR spectral data and 2D NMR COSY and HMBC correlations were similar to those of **5**; the main differences were found in the COSY correlation of NH proton with H8 and HMBC correlation of H8 with C7′ (carbonyl carbon), clearly indicating the compound was the benzamide derivative of **2**.

The positive ESIMS spectrum of compound **9** presented a $[M+Na]^+$ at 882.74 m/z and a molecular formula $C_{20}H_{20}N_2O_4I_4Na$ by HRESIMS. The ^{1}H NMR spectrum fully resembled that of **4** (Table 3) and ^{13}C NMR spectral data (Table 3) deduced from 2D correlations was similar; however, the compound presented an additional carbon at δ 159.8 for C10 (carbonyl carbon). The number of carbons was indicative of a symmetrical compound that initially was believed to be **3**; however, the MS results proved it to be a dimer of $C_{10}H_{10}NO_2I_2$, which was consistent with an oxalate diamide derivative of **2**. Similar oxalamide derivatives have also been isolated from sponges such *Ianthella basta*[23] and *P. purpurea*.[24] It is likely that the diamide was formed due to the high production of **2** by a symbiont which later formed the diamide with oxalate.

Table 3
^{1}H and ^{13}C NMR data for compound **9**

Position[a]	δ_H (J in Hz)[b]	δ_C[c]
1, 1′	—	138.1
2/6, 2′/6′	7.59, s	139.9
3/5, 3′/5′	—	90.8
4, 4′	—	158.0
7, 7′	2.73, t (7.3)	33.5
8, 8′	3.51, dd (6.8, 14.2)	41.0
9, 9′	3.82, s	60.6
10, 10′	—	159.8

[a] Assignments based on HSQC and HMBC.
[b] Acquired in $CDCl_3$ at 600 MHz.
[c] Deduced from HSQC and HMBC.

Compound **10** ^{1}H NMR spectral data (Table 4) showed three aromatic protons for a tri-substituted aromatic ring at δ 7.61 (d, 1H, J=2.1 Hz), 7.09 (dd, 1H, J=2.2 and 8.2 Hz) and 6.80 (d, 1H, J=8.2 Hz) and a A_2B_2 spin system similar to **4** with methylenes at δ 2.79 (pseudo triplet, 2H, J=7.9 and 7.3 Hz) and 3.06 (t, 2H, J=7.5 Hz). The

Table 4
^{1}H and ^{13}C NMR data for compound **10**

Position[a]	δ_H (J in Hz)[b]	δ_C[c]
1		157.2[d]
2		84.7[d]
3	7.61, d (2.1)	140.6
4		131.0
5	7.09, dd (2.2, 8.2)	131.0
6	6.80, d (8.2)	116.2
7	2.79, m	34.1
8	3.06, t (7.5)	42.5

[a] Assignments based on COSY, HSQC and HMBC.
[b] Acquired in CD_3OD at 400 MHz.
[c] Acquired in CD_3OD at 101 MHz.
[d] Deduced from HMBC.

^{13}C NMR spectral data (Table 4) presented six aromatic carbons δ_C 157.2, 140.6, 131.0, 131.0, 116.2, 84.7; the carbon at 157.2 was consistent with a phenolic substitution, while 84.7 was consistent with an aromatic iodinated carbon; on the other hand, the two methylenenic carbons at δ_C 42.5 and 34.1 were similar to those of **4** which suggested the tyramine derivative 4-(2-aminoethyl)-2-iodophenol, **10**. The structure was confirm by 2D NMR COSY and HMBC correlations and by the low resolution ESIMS which presented a $[M+H]^+$ at 263.9 consistent with the proposed structure, HRESIMS futher confirmed the molecular formula $C_8H_{11}NOI$.

Here we have described one known compound together with first reports of six iodo derivatives of tyramine which enrich our knowledge of naturally produced iodinated compounds. To establish the true role of these compounds in the tunicate will require further studies. However, it is clear that in this particular case some of the compounds are most likely to be produced by a putative symbiont present in the tunicate, since metabolic pathways exclusively used by plants and microbes are involved. Future studies regarding the biogenetic origin of the iodinated metabolites in *D. rubeum* are required, as it is highly unlikely that these structurally closely related natural products are derived from more than one producer.

3. Experimental

3.1. General experimental procedures

400 MHz ^1H and ^{13}C NMR spectra were recorded in CD_3OD, DMSO-d_6 or $CDCl_3$ NMR solvents, using the solvent line as reference (CD_3OD: δ_H=3.31, δ_C=49.15; DMSO-d_6: δ_H=2.50, δ_C=39.51; $CDCl_3$: δ_H=7.24, δ_C=77.23); the systems used were either a Varian Unity INOVA 400 MHz NMR spectrometer (Varian Inc.) with pulsed field gradients and waveform generator using a 1D probe (University of Aberdeen) or a Varian Mercury BB spectrometer (NMR spectrometry unit, University of Costa Rica) (Varian, Inc). 600 MHz ^1H and ^{13}C NMR spectra were collected in $CDCl_3$ on a Bruker Avance 600 MHz NMR spectrometer (Australian Institute of Marine Science) complete with cryoprobe operating at 600 MHz for ^1H and 125 MHz for ^{13}C.

Low resolution MS spectra for compounds **2**, **4** and **5** were recorded at the Chemistry Department of the University of Aberdeen on a Waters-Micromass Quattro Premier and HRESIMS for compounds **4** and **5** were determined on the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea. Low and High ESIMS for compounds **6** to **9** were were determined on a Bruker BioApex 4.7 Tesla FT mass spectrometer (Australian Institute of Marine Science) with an electrospray (ESI) Analytica of Branford source. Direct infusion of the sample (0.02 mg mL^{-1}) was carried out at a flow rate of 100 μl h^{-1} and ions detected in positive mode within a mass range of *m/z* 50–2000.[25] Low resolution ESIMS spectrum for compound **10** was recorded directly injecting 10 to 20 μL of sample on an ES-MS Agilent (MSD XCT, Agilent, USA), using flow injection mode with a solvent system of 0.1% formic acid in MeOH at a flow rate of 0.4 mL/min and a positive mode set at 4500 V capillary voltage for a mass range from 100–1000 *m/z*. The instrument was optimized using standard procedure from Agilent. High resolution ESIMS for compound **10** was recorded in a Thermo Orbitrap Discovery Mass spectrometer (Thermo Scientific, UK).

HPLC separation and purification was performed using either an Agilent 1100 Series quaternary gradient pump chromatographer (Agilent Technologies, UK) with a PDA detector, or a Waters 600 quaternary gradient pump chromatographer with a PDA detector (Waters Corporation, USA); gradients of Water:MeOH were used as solvent systems (flows ranging form 1 to 2 mL/min depending of the sample) on a Phenomenex Luna C18 column (5 μm, 100 Å, 150×10 mm) (Phenomenex, UK).

3.2. Tunicate material

D. rubeum crude aqueous extract code C011576 0CDN1627, was obtained from the US National Cancer Institute Natural Products Branch Open Repository from a sample that was collected by Coral Reef Research Foundation on August 24th 1993, at 10 m depth in Chuuk Atoll.

3.3. Extraction and isolation

Aqueous crude extract was desalted with DIAION HP20SS resin (Supelco, Sigma–Aldrich, UK), the resin was washed with water (PW, 1 L), then with MeOH/water (PM50, 1:1, 1 L), MeOH 100% (PM, 1 L) and finally with dichloromethane/MeOH (PD, 1:1. 500 mL); each fraction was evaluated by NMR and HPLC. PM50 and PM were chromatographed on Sephadex LH20 (Sigma–Aldrich) using MeOH/ACN (1:1) with fractions collected every 7 mL; these fractions were pooled based on their TLC (Silica gel 60, 20×20 cm, Riedel-de Haën, Sigma–Aldrich) profiles (PM50: three fractions; PM: five fractions); the pooled fractions were evaluated by NMR and HPLC. Interesting compounds were isolated by repeated C18 RP-HPLC, pooling similar peaks in fractions with the same composition. Minor fractions of PM and PM50 were pooled with PD fraction and the $CHCl_3$/EtOAc/*n*-BuOH solubles of PW. The combined fraction was dissolved in EtOH 80% (10 mL), defatted with hexane (4×20 mL) and separated on a C18-SPE cartridge (6 mL, Waters, USA). The compounds in each fraction were purified by HPLC.

3.4. Characteristic data for each compound

*3.4.1. 2-(3,5-Diiodo-4-methoxyphenyl)ethanamine (**2**)*

White amorphous solid (9.0 mg, 0.45% of crude extract); ^1H NMR and ^{13}C NMR see Tables 1 and 2 respectively; (+)-HRESIMS *m/z* 403.9004 (calculated for $C_9H_{12}NOI_2$, 403.9003±0.2 ppm).

*3.4.2. 2-(3,5-Diiodo-4-methoxyphenyl)ethanaminium (**4**)*

White amorphous solid (12.0 mg, 0.6% of crude extract); ^1H NMR and ^{13}C NMR see Tables 1 and 2 respectively; (+)-HRESIMS *m/z* 403.9004 (calculated for $C_9H_{12}NOI_2$, 403.9003±0.2 ppm).

*3.4.3. 2-(3,5-Diiodo-4-methoxyphenyl)ethanaminium benzoate (**5**)*

White amorphous solid (20.0 mg, 1% of crude extract); ^1H NMR and ^{13}C NMR see Tables 1 and 2 respectively; (+)-HRESIMS *m/z* 403.9003 (calculated for $C_9H_{12}NOI_2$, 403.9003±0.1 ppm), (−)-HRESIMS *m/z* 121.0295 (calculated for $C_7H_5O_2$, 121.0295±0.1 ppm).

*3.4.4. 2-(3,5-Diiodo-4-methoxyphenyl)acetamide (**6**)*

White amorphous solid (0.6 mg, 0.03% of crude extract); ^1H NMR and ^{13}C NMR see Tables 1 and 2 respectively; (+)-HRESIMS *m/z* 439.8613 (calculated for $C_9H_9NO_2I_2Na$, 439.8615±0.5 ppm).

*3.4.5. N-[2-(3,5-Diiodo-4-methoxyphenyl)ethyl] formamide (**7**)*

White amorphous solid (5.4 mg, 0.27% of crude extract); ^1H NMR and ^{13}C NMR see Tables 1 and 2 respectively; (+)-HRESIMS *m/z* 453.8743 (calculated for $C_{10}H_{11}NO_2I_2Na$, 453.8771±6 ppm).

*3.4.6. N-[2-(3,5-Diiodo-4-methoxyphenyl)ethyl] benzamide (**8**)*

White amorphous solid (1.0 mg, 0.05% of crude extract); ^1H NMR and ^{13}C NMR see Tables 1 and 2 respectively; (+)-HRESIMS *m/z* 529.9081 (calculated for $C_{16}H_{15}NO_2I_2Na$, 529.9084±0.6 ppm).

*3.4.7. N,N′-Bis[2-(3,5-diiodo-4-methoxyphenyl)ethyl] ethanediamide (**9**)*

White amorphous solid (0.7 mg, 0.035% of crude extract); ^1H NMR and ^{13}C NMR see Table 3; (+)-HRESIMS *m/z* 882.7492 (calculated for $C_{20}H_{20}N_2O_4I_4Na$, 882.7494±0.2 ppm).

*3.4.8. 4-(2-Aminoethyl)-2-iodophenol (**10**)*

White amorphous solid (3.4 mg, 0.17% of crude extract); LRESIMS *m*/*z* 263.9; ^{1}H NMR and ^{13}C NMR see Table 4; (+)-HRESIMS *m*/*z* 263.9879 (calculated for $C_8H_{11}NOI$, 263.9880±0.4 ppm).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.002.

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