

## Synthesis of Phidianidine B, a highly cytotoxic 1,2,4-oxadiazole marine metabolite

Emiliano Manzo,\* Dario Pagano, Marianna Carbone, M. Letizia Ciavatta, and Margherita Gavagnin

Consiglio Nazionale delle Ricerche (CNR), Istituto di Chimica Biomolecolare (ICB), Via Campi Flegrei, 34, 80078 Pozzuoli (Na), Italy

E-mail address: [emanzo@icb.cnr.it](mailto:emanzo@icb.cnr.it)

DOI: <http://dx.doi.org/10.3998/ark.5550190.0013.919>

### Abstract

Phidianidine B (**1**), a natural 1,2,4-oxadiazole linking both an indole system and an aminoalkyl guanidine group that has been recently reported from a marine mollusk, has been synthesized in seven steps (14% total yield). The synthetic procedure, which is based on the coupling of 3-indolacetic acid methyl ester and the amino-alkyl hydroxy guanidine intermediate **2**, opportunely prepared, is of general application and allows the synthesis of analogues with either different alkyl chain length or substitution on the indole ring.

**Keywords:** 1,2,4-Oxadiazole, phidianidine, chemical synthesis

### Introduction

Phidianidine B (**1**) (Figure 1) is a natural product recently isolated in our laboratory along with the corresponding 6-bromo-derivative, phidianidine A, from the opisthobranch mollusk *Phidiana militaris*.<sup>1</sup> Phidianidines revealed to be highly cytotoxic against some tumor and non-tumor cell lines and exhibited specificity towards some cell types relative to others with IC<sub>50</sub> values within the nanomolar range.<sup>1</sup>

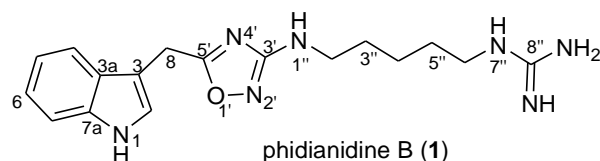
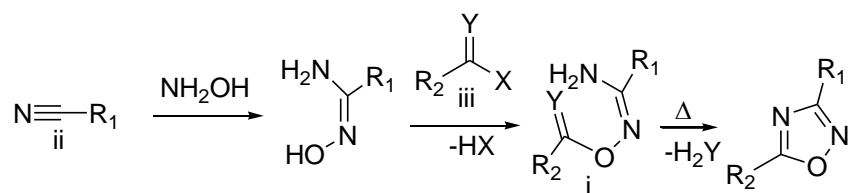


Figure 1

The structure of phidianidines is characterized by the presence of a 1,2,4-oxadiazole ring representing the first report of this scaffold in a marine natural product. Although 1,2,4-oxadiazole derivatives are extremely rare also in terrestrial sources, there is a wide interest in the chemistry community towards the synthesis of compounds containing this system.<sup>2-6</sup> In fact, 1,2,4-oxadiazole is extensively utilized in the design of compounds with improved physicochemical properties and bioavailability being a bioisostere of esters and amides and a dipeptide mimetic. For these reasons it can be found in a number of biologically important synthetic molecules, such as muscarinic agonists, serotonergic (5-HT<sub>3</sub>) antagonists, benzodiazepine receptor agonists, and dopamine ligands.<sup>7-9</sup>

Among the known synthetic strategies to obtain 1,2,4-oxadiazoles,<sup>2</sup> one of the most common routes utilizes the cyclization of a suitable amidoxime derivative (**i**), which can be easily prepared by reaction of a nitrile (**ii**) with hydroxylamine followed by reaction with an activated carboxylic substrate (**iii**) (Scheme 1).



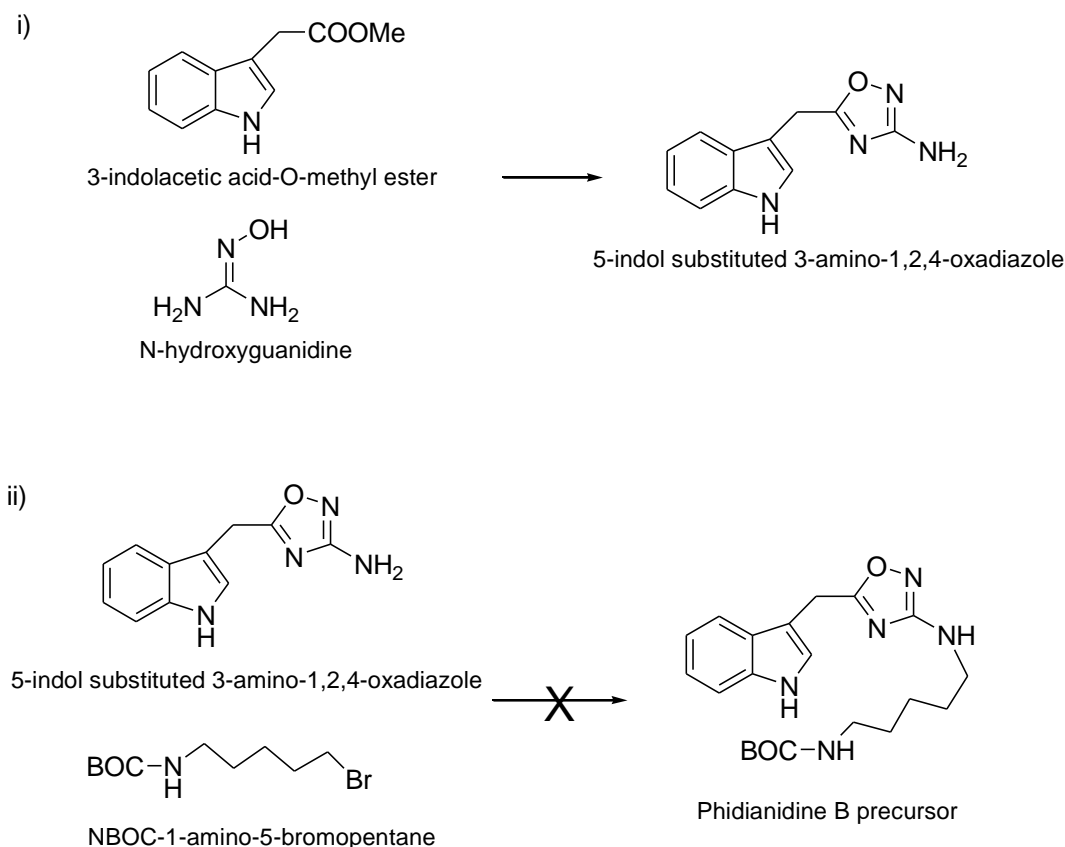
**Scheme 1.** Amidoxime cyclization route.

With the aim at confirming the proposed structures and getting phidianidines as well as their analogues in sufficient amounts for further investigating the promising biological activity, we have performed a synthesis of phidianidine B (**1**).<sup>10</sup> According to amidoxime cyclization strategy, our synthesis is based on the coupling of 3-indolacetic acid methyl ester and a suitable N-functionalized amino alkyl hydroxy-guanidine **2**.<sup>10</sup>

As we were preparing this manuscript, two papers by Snider *et al.*<sup>11</sup> and Lindsley *et al.*<sup>12</sup> reporting the synthesis of phidianidines appeared in the literature. Both synthetic approaches are similar to that we describe here but they present some critical aspects such as the use of very toxic reagents (i.e. cyanogen bromide)<sup>11,12</sup> and the formation of unstable intermediates.<sup>11</sup> Our synthetic scheme seems to be simpler and easier to run by avoiding these inconveniences.

## Results and Discussion

The synthesis (Scheme 2) was firstly planned by considering two subsequent steps: (i) the formation of a 5-indol substituted 3-amino-1,2,4-oxadiazole and (ii) the alkylation of the amino residue on the oxadiazole ring with a proper alkyl moiety linking a terminal protected amino group.

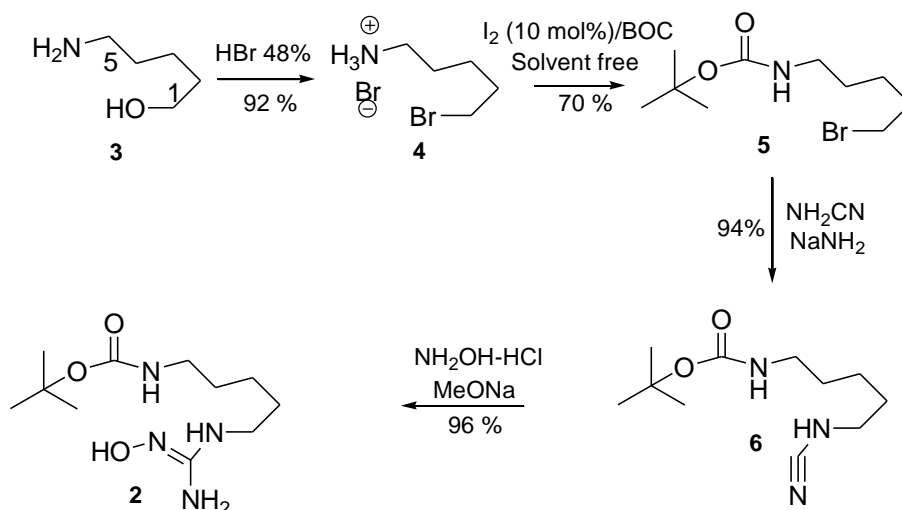


**Scheme 2.** Route 1: (i) preparation of 3-amino-1,2,4-oxadiazole moiety; (ii) failed step to phidianidine B precursor.

Although the first step was easily accomplished by coupling 3-indolacetic acid methyl ester with hydroxy guanidine, the subsequent alkylation of the amino residue on the oxadiazole was unsuccessful, even conducted under different experimental conditions. In fact, a complex inseparable mixture of N-mono- and poly-alkylated products was formed, probably due to the presence of different competing nitrogen atoms with comparable nucleophilic reactivity.

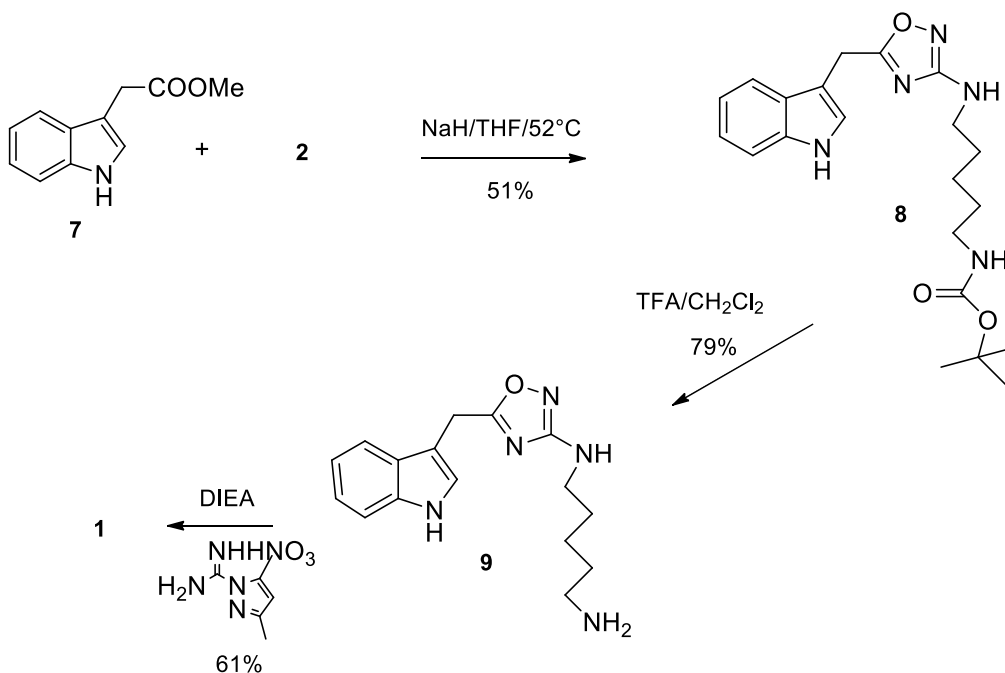
A different synthetic route was then planned (Schemes 3 and 4). The key intermediate of this strategy was an N-functionalized alkyl hydroxy guanidine (**2**) which was prepared starting from the commercial 5-amino-1-pentanol (**3**, Scheme 3).<sup>10</sup>

Compound **3** was treated with hydrogen bromide (48% HBr) to obtain the aminobromo derivative **4**.<sup>13</sup> The subsequent introduction of the *tert*-butoxycarbonyl (BOC) group on the amino function of **4** was achieved by using di-*tert*-butyl dicarbonate and 10 mol% of I<sub>2</sub> in a solvent free reaction, obtaining the protected derivative **5**.<sup>14</sup> The following addition of a *N,N*-dimethyl formamide solution of cyanamide and sodium amide to compound **5** gave the corresponding 1-cyanamino derivative **6**. This latter compound was treated with hydroxylamine hydrochloride and sodium methoxide in anhydrous methanol leading to the key intermediate **2**.



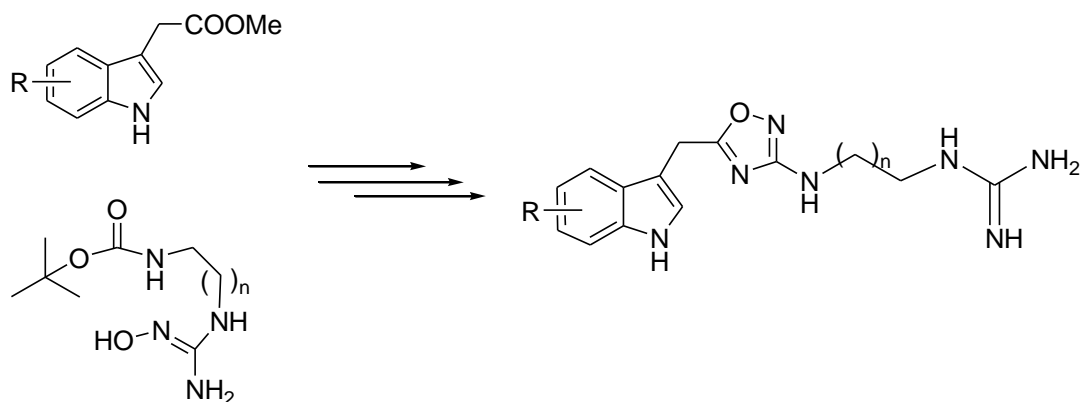
**Scheme 3.** Route 2: synthesis of key intermediate **2**.

Compound **2** was allowed to react under alkaline conditions (NaH/THF) with 3-indolacetic acid methyl ester (**7**), which was prepared by methylation of commercial 3-indolacetic acid (Scheme 4). The coupling product **8** containing the 1,2,4-oxadiazole nucleus was first deprotected by removing *t*-BOC group with trifluoroacetic acid, and then guanylated by 3,5-dimethyl-1-pyrazolylformaminidum nitrate.<sup>15</sup> The final product of these reactions resulted to be identical with natural phidianidine B (**1**) (see Experimental Section).<sup>1</sup>



**Scheme 4.** Route 2: 1,2,4-oxadiazole formation and functionalization steps.

Starting from the commercially available 6-bromo-3-indolacetic acid, the same synthetic strategy here described could be used for the preparation of phidianidine A, the bromo derivative of **1**. More generally, this methodology provides a general approach to the synthesis of phidianidine analogues differing in the alkyl chain length and/or in the indole substitution pattern (Scheme 5).<sup>10</sup>



**Scheme 5.** General scheme for phidianidines analogues preparation.

Considering the very promising biological activity showed by natural phidianidines,<sup>1,11,12</sup> the preparation of a library of phidianidine-based compounds could be of great interest for SAR studies aiming to deeply understand and optimize the mode of action of these unusual marine natural products.

## Experimental Section

**General.** 1D and 2D NMR spectra were recorded on a Bruker Avance-400 and on a Bruker DRX-600 equipped with TXI CryoProbe™ in CD<sub>3</sub>OD, CD<sub>2</sub>Cl<sub>2</sub>, CDCl<sub>3</sub>, and *d*<sub>6</sub>-DMSO ( $\delta_{\text{H}}$  values are referred to CH<sub>3</sub>OH, CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, and DMSO protons at 3.34, 5.32, 7.25, and 2.49 ppm, respectively). <sup>13</sup>C NMR spectra were recorded on a Bruker DPX-300 (75.0 MHz) and Bruker DRX-600 (150 MHz) ( $\delta_{\text{C}}$  values are referred to CD<sub>3</sub>OD, CD<sub>2</sub>Cl<sub>2</sub>, CDCl<sub>3</sub>, and DMSO carbons at 49.0, 53.8, 77.0, and 39.5 ppm, respectively). HRESIMS were carried out on a Micromass Q-TOF micro. TLC plates (KieselGel 60 F254) were from Merck (Darmstadt, Germany), silica gel powder (Kieselgel 60 0.063-0.200 mm) was from Merck (Darmstadt, Germany). All solvents and reagents were purchased by Sigma-Aldrich. For the synthetic compounds the protons linked to nitrogens can't be evidenced because they exchange with deuterium of the deuterated solvents

**3-Indoleacetic acid methyl ester.** 3-Indoleacetic acid (2.0 g, 0.0114 mol) was dissolved in 25 mL of anhydrous hydrochloric acid in methanol (0.5 M). After stirring for 2 h at room

temperature, the reaction mixture was evaporated and purified by silica gel chromatography using a gradient of  $\text{CHCl}_3/\text{CH}_3\text{OH}$  to give 3-indolacetic acid methyl ester (2.1 g, 0.0112 mol, 98%) as colorless oil,  $R_f$  ( $\text{CHCl}_3$ ) 0.32, IR (liquid film)  $\nu_{\text{max}}$  2970, 1714, 1530, 1220  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.62 (1H, bd,  $J$  7.4 Hz, H-7), 7.31 (1H, bd,  $J$  7.4 Hz, H-4), 7.20 (1H, bt,  $J$  7.4 Hz, H-6), 7.16 (1H, bt,  $J$  7.4 Hz, H-5), 6.9 (1H, s, H-2), 3.69 (2H, s, H-8), 3.46 (3H, s,  $\text{OCH}_3$ ).  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  173.9 (C), 136.7 (C), 127.4 (C), 124.0 (CH), 121.9 (CH), 118.6 (CH), 119.2 (CH), 111.7 (CH), 107.6 (C), 51.6 ( $\text{CH}_3$ ), 30.8 ( $\text{CH}_2$ ). HRESIMS:  $m/z$  calcd. for  $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{Na}$ : 212.0687  $[\text{M}+\text{Na}]^+$ ; found: 212.0682.

**1-amino-5-bromopentane-hydrobromide (4).** 5-Amino-1-pentanol (**3**) (2.0 g, 0.0194 mol) was dissolved in 20 mL of hydrobromic acid (48%). The reaction mixture was refluxed for 3 h and then evaporated to give a white crystalline solid (compound **4**, 4.37 g, 0.0178 mol, 92%) as pale yellow oil.  $^1\text{H}$ -NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  3.52 (2H, t,  $J$  6.6 Hz,  $\text{H}_2$ -1), 3.01 (2H, bt,  $J$  7.2 Hz,  $\text{H}_2$ -5), 1.95 (2H, m, methylene), 1.78 (2H, m, methylene), 1.60 (2H, m, methylene).  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  40.5 ( $\text{CH}_2$ ), 34.1 ( $\text{CH}_2$ ), 33.1 ( $\text{CH}_2$ ), 27.4 ( $\text{CH}_2$ ), 25.8 ( $\text{CH}_2$ ). HRESIMS  $m/z$  calcd. for  $\text{C}_5\text{H}_{13}\text{BrN}$ : 166.0226  $[\text{M}+\text{H}]^+$ ; found: 166.0228.

**N-BOC-1-amino-5-bromopentane (5).** Di-*ter*-butyl-dicarbonate (0.88 mL, 0.0041 mol) and iodine (53 mg, 0.00041 mol) were added to **4** (1.0 g, 0.0041 mol). After stirring for 4 h at room temperature, the reaction mixture was partitioned between saturated sodium carbonate aqueous solution and diethyl ether. The organic phase was purified by silica gel chromatography using a gradient of light petroleum ether and diethyl ether to afford compound **5** (0.76 g, 0.0029 mol, 70%) as yellow oil.  $^1\text{H}$ -NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  3.42 (2H, t,  $J$  6.6 Hz,  $\text{H}_2$ -1), 3.09 (2H, dt,  $J$  6.1, 5.9 Hz,  $\text{H}_2$ -5), 1.88 (2H, m, methylene), 1.52-1.40 (4H, m, 2 methylenes), 1.43-1.40 (9H, m, BOC-methyls).  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  156.3 (C), 79.1 (C), 40.7 ( $\text{CH}_2$ ), 34.3 ( $\text{CH}_2$ ), 32.9 ( $\text{CH}_2$ ), 28.5 (BOC-  $\text{CH}_3$ ), 27.6 ( $\text{CH}_2$ ), 25.8 ( $\text{CH}_2$ ). HRESIMS  $m/z$  calcd for  $\text{C}_{10}\text{H}_{21}\text{BrNO}_2$ : 266.0752  $[\text{M}+\text{H}]^+$ ; found: 266.0755.

**N-BOC-1-amino-5-cyanamide-pentane (6).** Cyanamide (80 mg, 0.0019 mol) was dissolved in 1 mL of anhydrous *N,N*-dimethyl formamide at 0 °C and sodium amide (75 mg, 0.0019 mol) was added. The reaction mixture was warmed at room temperature and stirred for 30 min. After, compound **5** (0.50 g, 0.0019 mol), dissolved in 1 mL of anhyd. *N,N*-dimethyl formamide, was added. The mixture was stirred overnight, then evaporated by nitrogen stream and purified by silica gel chromatography, using a gradient of light petroleum ether and diethyl ether, to give compound **6** (0.408 g, 0.0018 mol, 94%) as pale yellow oil.  $^1\text{H}$ -NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  3.07 (2H, m,  $\text{H}_2$ -5), 3.00 (2H, t,  $J$  7.4 Hz,  $\text{H}_2$ -1), 1.62 (2H, m,  $\text{H}_2$ -2), 1.48 (2H, m,  $\text{H}_2$ -4), 1.45-1.39 (9H, m, BOC- methyls), 1.33 (2H, m,  $\text{H}_2$ -3).  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  156.4 (C), 117.4 (C), 79.0 (C), 46.0 ( $\text{CH}_2$ ), 40.5 ( $\text{CH}_2$ ), 29.9 ( $\text{CH}_2$ ), 28.4 ( $\text{CH}_3$ ), 27.5 ( $\text{CH}_2$ ), 23.8 ( $\text{CH}_2$ ); HRESIMS  $m/z$  calcd for  $\text{C}_{11}\text{H}_{22}\text{N}_3\text{O}_2$ : 228.1712  $[\text{M}+\text{H}]^+$ ; found: 228.1710.

**N-BOC-1-amino-5-[(*E*)-2-hydroxyguanidino]-pentane (2).** Sodium methoxide (97 mg, 0.0018 mol) was added to an anhydrous methanol solution (2.1 mL) of hydroxylamine hydrochloride (124 mg, 0.0018 mol). The reaction mixture was stirred under argon and, after 1 h, compound **6** (0.408 g, 0.0018 mol), dissolved in anhydrous methanol (1 mL), was added. After stirring at

room temperature for 10 h, the mixture was warmed at 53 °C, stirred for additional 7 h and then filtered to give compound **2** (0.442 g, 0.00170 mol, 96%) as pale yellow oil. <sup>1</sup>H-NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ 3.24 (2H, bt, *J* 7.5 Hz, H<sub>2</sub>-5), 3.06 (2H, m, H<sub>2</sub>-1), 1.59 (2H, m, H<sub>2</sub>-4), 1.52-1.33 (4H, m, H<sub>2</sub>-2, H<sub>2</sub>-3), 1.42-1.36 (9H, m, BOC-methyls). <sup>13</sup>C-NMR (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ 158.7 (C), 157.6 (C), 79.3 (C), 41.8 (CH<sub>2</sub>), 40.5 (CH<sub>2</sub>), 29.8 (CH<sub>2</sub>), 28.6 (CH<sub>3</sub>), 27.1 (CH<sub>2</sub>), 24.0 (CH<sub>2</sub>); HRESIMS: *m/z* calcd for C<sub>11</sub>H<sub>25</sub>N<sub>4</sub>O<sub>3</sub>: 261.1927 [M+H]<sup>+</sup>; found: 261.1931.

***N*-(5-BOC-aminopentyl)-5-[(1*H*-indol-3-yl)methyl]-1,2,4-oxadiazol-3-amine (8).** Sodium hydride (50% in mineral oil, 645 mg, 0.013 mol) was dissolved in 3 mL of anhydrous tetrahydrofuran and compound **2** (2.9 g, 0.0112 mol), dissolved in anhydrous tetrahydrofuran (3mL), was added. The reaction mixture was warmed at 52 °C and 3-indolacetyl acid- OMe ester (1.05 g, 0.0056 mol) dissolved in tetrahydrofuran (3mL) was added, after 40 min under stirring. After 1.5 h at 52 °C, the mixture was partitioned between water and ethyl acetate. The organic phase was purified by silica gel chromatography using a gradient of CHCl<sub>3</sub>/CH<sub>3</sub>OH to give **8** (1.34 g, 0.0029 mol, 51%) as yellow oil. *R<sub>f</sub>* (CHCl<sub>3</sub>/CH<sub>3</sub>OH 9:1) = 0.90; IR (liquid film) *v*<sub>max</sub> 3324, 2890, 1721, 1529, 1414, 1240 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CD<sub>3</sub>OD): δ 7.57 (1H, bd, *J* 7.7 Hz, H-7), 7.39 (1H, bd, *J* 7.7 Hz, H-4), 7.26 (1H, s, H-2), 7.15 (1H, bt, *J* 7.7 Hz, H-6), 7.07 (1H, bt, *J* 7.7 Hz, H-5), 4.26 (2H, s, H<sub>2</sub>-8), 3.09 (2H, m, H<sub>2</sub>-2''), 3.08 (2H, m, H<sub>2</sub>-6''), 1.61 (2H, m, H<sub>2</sub>-3''), 1.51-1.40 (4H, m, H<sub>2</sub>-5'', H<sub>2</sub>-4''), 1.45-1.38 (9H, s, BOC-methyls). <sup>13</sup>C-NMR (75 MHz, CD<sub>3</sub>OD): δ 178.9 (C), 170.5 (C), 158.3 (C), 137.9 (C), 128.0 (C), 124.5 (CH), 122.4 (CH), 120.0 (CH), 119.4 (CH), 112.2 (CH), 108.1 (C), 79.8 (C), 41.1-40.6 (2 CH<sub>2</sub>), 30.7 (CH<sub>2</sub>), 28.8 (CH<sub>3</sub>), 28.3 (CH<sub>2</sub>), 24.9 (CH<sub>2</sub>); HRESIMS: *m/z* calcd. for C<sub>21</sub>H<sub>30</sub>N<sub>5</sub>O<sub>3</sub>: 400.2349 [M+H]<sup>+</sup>; found: 400.2343.

**5-Aminopentyl-5-[(1*H*-indol-3-yl)methyl]-1,2,4-oxadiazol-3-amine (9).** Compound **8** (1.34 g, 0.0029 mol) was dissolved in 12 mL of trifluoroacetic and dichloromethane solution (1/1). After stirring at room temperature for 3h, the mixture was evaporated by nitrogen stream and purified by silica gel chromatography using a gradient of CHCl<sub>3</sub>/CH<sub>3</sub>OH to give **9** (0.75 g, 0.00230 mol, 79%) as pale yellow oil. *R<sub>f</sub>* (CHCl<sub>3</sub>/CH<sub>3</sub>OH 8:2) = 0.25; IR (liquid film) *v*<sub>max</sub> 3328, 2920, 1718, 1530, 1416, 1225 cm<sup>-1</sup>. <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ 7.57 (1H, bd, *J* 7.7 Hz, H-7), 7.39 (1H, bd, *J* 7.7 Hz, H-4), 7.24 (1H, s, H-2), 7.15 (1H, bt, *J* 7 Hz, H-6), 7.05 (1H, bt, *J* 7.7 Hz, H-5), 4.26 (2H, s, H<sub>2</sub>-8), 3.16 (2H, bt, *J* 6.6 Hz, H<sub>2</sub>-2''), 2.94 (2H, bt, *J* 7.2 Hz, H<sub>2</sub>-6''), 1.73-1.62 (4H, m, H<sub>2</sub>-3'', H<sub>2</sub>-5''), 1.47 (2H, m, H<sub>2</sub>-4''). <sup>13</sup>C-NMR (75 MHz, CD<sub>3</sub>OD): δ 179.3 (C), 170.7 (C), 138.1 (C), 128.1 (C), 124.7 (CH), 122.7 (CH), 120.0 (CH), 119.3 (CH), 112.3 (CH), 108.3 (C), 40.6-40.2 (2 CH<sub>2</sub>), 30.7 (CH<sub>2</sub>), 28.3 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>). HRESIMS *m/z* calcd for C<sub>16</sub>H<sub>22</sub>N<sub>5</sub>O: 300.1824 [M+H]<sup>+</sup>; found: 300.1820.

**Phidianidine B (1).** 3,5-Dimethyl-1-pyrazolylformaminidinium nitrate (0.452 g, 0.00226 mol) and diisopropyl ethylamine (0.00226 mol) were added to a solution of **9** (0.57 g, 0.00174 mol) in 10 mL of anhydrous *N,N*-dimethyl formamide. After stirring overnight at room temperature, the mixture was evaporated by nitrogen stream and purified by silica gel chromatography using a gradient of CHCl<sub>3</sub>/CH<sub>3</sub>OH to give phidianidine B (**1**, 0.456 g, 0.00107 mol, 61%) as pale yellow oil, isolated as protonated form.<sup>1</sup> Synthetic **1**: *R<sub>f</sub>* (CHCl<sub>3</sub>/CH<sub>3</sub>OH 7:3)= 0.51; IR (liquid film) *v*<sub>max</sub>

3309, 2890, 1680, 1589, 1220, 1150  $\text{cm}^{-1}$   $^1\text{H}$ -NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.57 (1H, bd,  $J$  7.7 Hz, H-7), 7.39 (1H, bd,  $J$  7.7 Hz, H-4), 7.26 (1H, s, H-2), 7.15 (1H, bt,  $J$  7.7 Hz, H-6), 7.05 (1H, bt,  $J$  7.7 Hz, H-5), 4.24 (2H, s,  $\text{H}_2$ -8), 3.17 (4H, m,  $\text{H}_2$ -2",  $\text{H}_2$ -6"), 1.72-1.62 (4H, m,  $\text{H}_2$ -3",  $\text{H}_2$ -5"), 1.46 (2H, m,  $\text{H}_2$ -4").  $^1\text{H}$ -NMR (400 MHz,  $d_6$ -DMSO):  $\delta$  11.0 (1H, bs, NH-1), 7.51 (1H, d,  $J$  7.9 Hz, H-4), 7.44 (1H, m, NH-7"), 7.37 (1H, d,  $J$  7.9 Hz, H-7), 7.32 (1H, bs, H-2), 7.10 (1H, bt,  $J$  7.8 Hz, H-6), 7.00 (1H, bt,  $J$  7.8 Hz, H-5), 6.71 (1H, t,  $J$  5.1 Hz, NH-1"), 4.21 (2H, s,  $\text{H}_2$ -8), 3.06-3.01 (4H, m,  $\text{H}_2$ -2",  $\text{H}_2$ -6"), 1.57-1.36 (4H, m,  $\text{H}_2$ -3",  $\text{H}_2$ -5"), 1.29 (2H, m,  $\text{H}_2$ -4");  $^{13}\text{C}$ -NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  176.8 (C), 168.6 (C), 156.4 (C), 136.3 (C), 126.6 (C), 125.1 (CH), 120.3 (CH), 118.4 (CH), 118.2 (CH), 106.8 (C), 42.5 ( $\text{CH}_2$ ), 40.4 ( $\text{CH}_2$ ), 28.2-28.0 (2  $\text{CH}_2$ ), 23.4 ( $\text{CH}_2$ ), 22.8 ( $\text{CH}_2$ ). HRESIMS  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{24}\text{N}_7\text{O}$ : 342.2042  $[\text{M}+\text{H}]^+$ ; found: 342.2039.

## Acknowledgements

The authors thank Mrs. D. Melck and Mr. A. Esposito of ICB-NMR service, M. Zampa of "Servizio di Spettrometria di Massa" for HRESIMS, and C. Iodice for spectrophotometric measurements. This research work was financially supported by PRIN-MIUR 2009 Project "Prodotti naturali da molluschi opisthobranchi: identificazione di nuovi lead compounds per lo sviluppo di farmaci antitumorali".

## References

1. Carbone, M.; Yan, L.; Irace, C.; Mollo, E.; Castelluccio, F.; Di Pascale, A.; Cimino, G.; Santamaria, R.; Guo, Y.-W.; Gavagnin, M. *Org. Lett.* **2011**, *13* (10), 2516-2519.
2. Pace, A.; Pierro, P. *Org. Biomol. Chem.* **2009**, *7*, 4337-4348 and references cited herein.
3. Kumar, D.; Patel, G.; Chavers, A. K.; Chang, K.-H.; Shah, K. *Eur. J. Med. Chem.* **2011**, *46*, 3085-3092.
4. Coté, J.B.; Roughton, A.; Nasielski, J.; Wilson, J.; You, J. C.; Berman, J. M. *Tetrahedron Lett.* **2011**, *52*, 5750-5751.
5. Augustine, J. K.; Akabote, V.; Hegde, S.G.; Alagarsamy, P. *J. Org. Chem.* **2009**, *74*, 5640-5643.
6. Sanchit, S.; Pandeya, S. N. *IJRAP* **2011**, *2*, 459-468.
7. Diana, G. D.; Volkots, D. L.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Peveur, D. C.; Dutko, F. J. *J. Med. Chem.* **1994**, *37*, 2421-2436.
8. Andersen, K. E.; Jørgensen, A. S.; Braestrup, C. *Eur. J. Med. Chem.* **1994**, *29*, 393-399.
9. Andersen, K. E.; Lundt, B. F.; Jørgensen, A. S.; Braestrup, C. *Eur. J. Med. Chem.* **1996**, *31*, 417-425.
10. Manzo, E.; Pagano, D.; Ciavatta, M. L.; Carbone, M.; Gavagnin, M. Pending Italian patent application n. MI2012A000422 (filling date: 19-03-2012).
11. Lin, H-Y; Snider, B. B. *J. Org. Chem.* **2012**, *77*, 4832-4836.
12. Brogan, J. T.; Stoops, S. L.; Lindsley, C. *ACS. Chem. Neuroscience* **2012**, DOI: 10.1021/cn300064r.



13. Minin, P. L.; Walton, J. C. *J.Org. Chem.* **2003**, 68, 2960-2963.
14. Varala, R.; Nuvula, S.; Adapa, S. R. *J.Org. Chem.* **2006**, 71, 8283-8286.
15. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J.Org. Chem.* **1992**, 57, 2497-2502.