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Synthesis of Phidianidines A and B

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Abstract

Reaction of a substituted indole-3-acetyl chloride with *N*-5-azidopentyl-*N*′-hydroxyguanidine generated a substituted 3-(5-azidopentylamino)-5-((indol-3-yl)-methyl)-1,2,4-oxadiazole. Reduction of the azide with zinc and ammonium formate afforded the amine, which was elaborated to the guanidine, completing short and efficient syntheses of the cytotoxic natural products phidianidines A and B in 19% overall yield by a convergent route that will make analogues readily available for biological evaluation. Initial screening in the NCI 60 cell line at 10^{-5} M indicated that the bromine on the indole is necessary for activity and that the amine precursor to phidianidine A is more potent than phidianidine A.

Guo, Gavagnin, and co-workers recently reported the isolation of the guanidine-containing natural products phidianidines A (**1a**) and B (**1b**) as the trifluoroacetate salts from the shell-less marine opisthobranch mollusk *Phidiana militaris* (see Scheme 1).[1] Despite their relatively simple structure, the phidianidines are of interest because they appear to be the first natural products that contain an 1,2,4-oxadiazole ring.[2] Furthermore, they show significant cytotoxicity at 0.14 to 5.42 μM concentrations against the highly proliferating C6 rat glioma and HeLa epithelial cervical cancer cell lines and the embryonic 3T3-L1 murine embryonic fibroblast and H9c2 rat embryonic cardiac myoblast cell lines and are less toxic to the less rapidly proliferating CaCo-2 epithelial colorectal adenocarcinoma cell line (35 to 100 μM).[1] The mode of action is not known, but the closely related dodecylguanidinium acetate (**4**, dodine) has been in widespread use since 1956 as a fungicide and may act by membrane disruption.[3] As part of an ongoing program in the synthesis of structurally novel guanidine-containing natural products,[4] we planned to prepare phidianidines A (**1a**) and B (**1b**) by coupling of the appropriate ethyl indole-3-acetate (**2a** or **2b**) with hydroxyguanidine **3** containing a suitably protected nitrogen on the other end of the five carbon side chain. There is limited precedent for the synthesis of 3-amino-1,2,4-oxadiazoles by coupling of esters with hydroxyguanidines[5] and nature may use a related route for the biosynthesis of the phidianidines.

We chose to use hydroxyguanidine **8** with an azidopentyl side chain because the azide group can be easily elaborated into the guanidine of the phidianidines and a wide variety of analogues (see Scheme 2). Furthermore, 5-azido-1-pentanamine (**6**) is readily available in quantity in 85% yield by selective reduction of diazide **5** by Kim's procedure with triphenyl-phosphine in a two-phase system.[6a] After mono-reduction of the diazide in Et_2O/EtOAc, the azido amine is protonated and partitions into the 5% HCl solution, thereby preventing

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Supporting Information Available: Results from the NCI 60 cell screens of phidianidine A (**1a**), phidianidine B (**1b**), amine **12a**, and amine **12b**, tables of spectral data, and copies of ^{1}H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

reduction of the second azide. Reaction of amine **6** with cyanogen bromide[7] in CH_2Cl_2 and aqueous $NaHCO_3$ solution afforded somewhat unstable cyanamide **7**, which was treated with hydroxylamine hydrochloride[8] and K_2CO_3 in EtOH to give the unstable[8d] hydroxyguanidine **8**, which was used immediately for the next step.

Our initial attempt at 3-amino-1,2,4-oxadiazole synthesis using models *N*-butyl-*N*′-hydroxyguanidine and ethyl phenylacetate (3 equiv) with NaOEt (2–3 equiv) in EtOH at reflux for 5 h proceeded in 50–70% yield based on the hydroxyguanidine. However, the yield dropped to 0–15% without both excess ester and NaOEt and the reaction proceeded in only 30% yield with ethyl indole-3-acetate (3 equiv) and NaOEt (3 equiv). These initial results indicated that an ester is not sufficiently reactive to couple with a hydroxyguanidine unless it is used in large excess. We therefore chose use an acid chloride rather than an ester to form the 3-amino-1,2,4-oxadiazole, a protocol that has been reported in the recent patent literature.[9]

Indole-3-acetic acid (**9b**) was reacted with oxalyl chloride and catalytic DMF in CH_2Cl_2 to give acid chloride **10b**, which was treated with 1.5 equiv of freshly prepared **8** and Et_3N in CH_2Cl_2 for 2 h at 25 °C. The solution was concentrated, and a solution of the residue containing the initial coupling product in 1,2-dichloroethane was heated at 80 °C for 2 h to form the 3-amino-1,2,4-oxadiazole giving **11b** in 63% yield from **9b** and 40% yield from **6**. The change of solvents after the initial coupling was necessitated by the high temperature needed for ring closure to form the 1,2,4-oxadiazole and the poor solubility of **8** and **10b** in $ClCH_2CH_2Cl$.

Reduction of the azide group of **11b** was complicated by the sensitivity of the 1,2,4-oxadiazole.[2] Attempted hydrogenation over Pd destroyed the 1,2,4-oxadiazole ring. Reduction with Ph_3P was successful, but removal of the phosphine oxide byproduct was difficult. Eventually we found that reduction of the azide with activated zinc[10] and ammonium formate in MeOH for 7 h at 25 °C proceeded cleanly to give polar amine **12b** that was used without purification.[11a] Coupling of **12b** with Boc-protected *S*-methylisothiourea **13** using Et_3N and $AgNO_3$[4b, 12] in DMF for 2 h at 0 °C and 5 h at 25 °C afforded protected guanidine **14b** in 60% yield from **11b**. Deprotection of **14b** by stirring in 10:1 CH_2Cl_2/TFA for 8 h at 25 °C removed the Boc protecting groups providing phidianidine B (**1b**) in 92% yield. The ^1H and ^{13}C NMR spectral data of phidianidine B in both CD_3OD and DMSO-d_6 are identical to those reported for the natural product[1] confirming the presence of the 1,2,4-oxadiazole ring.

Phidianidine A (**1a**) was prepared by an analogous sequence of steps from 6-bromoindole-3-acetic acid (**9a**).[13] Acid chloride **10b** was coupled with hydroxyguanidine **8** to give **11a** in 61% yield from **9a** and 39% yield from **6**. Reduction of the azide of **11a** with zinc and ammonium formate afforded amine **12a** which was coupled with **13** using Et_3N and $AgNO_3$ in DMF to give protected guanidine **14a** in 61% yield from **11a**. Deprotection of **14a** in 10:1 CH_2Cl_2/TFA provided phidianidine A (**1a**) in 93% yield with ^1H and ^{13}C NMR spectral data in both CD_3OD and DMSO-d_6 identical to those reported for the natural product.[1]

Initial screening in the NCI 60 cell line screen at 10^{-5} M showed an average of 33% inhibition of cell growth with phidianidine A (**1a**). The amine precursor **12a** was more potent with an average of 81% inhibition of the 60 cell lines. Phidianidine B (**1b**) and amine **12b** were both much less effective with an average of 5% inhibition of cell growth. These results indicate that the bromine substituent on the indole is important for activity and that the amine of **12a** is more effective than the guanidine of **1a**. Full details for these four compounds with all 60 cell lines are provided in the Supporting Information.

In conclusion, *N*-5-azido-1-pentanamine (**6**) was elaborated to *N*-5-azidopentyl-*N*′-hydroxyguanidine (**8**) in two steps. Reaction of **8** with indole-3-acetyl chloride **10a** or **10b** afforded 3-(5-azidopentylamino)-5-((indol-3-yl)-methyl)-1,2,4-oxadiazoles **11a** and **11b** in 61–63% yield. Reduction of the azides with zinc and ammonium formate afforded amines **12a** and **12b**, which were elaborated to the guanidine, completing short and efficient syntheses of the cytotoxic natural products phidianidines A (**1a**) and B (**1b**) in 19% overall yield by a convergent route that will make analogues readily available for biological evaluation.

Experimental Section

General Experimental Methods

Reactions were conducted in flame- or oven-dried glassware under a nitrogen atmosphere and were stirred magnetically. The phrase "concentrated" refers to removal of solvents by means of a rotary-evaporator attached to a diaphragm pump (15–60 Torr) followed by removal of residual solvents at < 1 Torr with an vacuum pump. Flash chromatography was performed on silica gel 60 (230–400 mesh). Analytical thin layer chromatography (TLC) was performed using silica gel 60 F-254 pre-coated glass plates (0.25 mm). TLC Plates were analyzed by short wave UV illumination, or by dipping in CAM stain (40 g of ammonium molybdate, 1.6 g of ceric ammonium molybdate, 80 mL of concentrated sulfuric acid and 720 mL of water) and heating on a hot plate, or by spraying with permanganate solution (5 g $KMnO_4$ in 495 mL water). THF and ether were dried and purified by distillation from sodium/benzophenone. Et_3N, pyridine, acetonitrile and benzene were distilled from CaH_2. ^1H and ^{13}C NMR spectra were obtained on a 400 MHz spectrometer in $CDCl_3$ with tetramethylsilane as internal standard unless specifically indicated. Chemical shifts are reported in δ (ppm downfield from tetramethylsilane). Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and br (broad). IR spectra were acquired on an FT-IR spectrometer and are reported in wave numbers (cm^{-1}). High resolution mass spectra were obtained using electrospray ionization (ESI) analyzed by quadrupole time of flight (QTof).

5-Azido-1-pentanamine (5)[6]—To a solution of **5**[6,14] (1.1 g, 7.1 mmol) in 5 mL of Et_2O was added 5 mL of EtOAc and 9 mL of 5% HCl aqueous solution successively. To the resulting mixture at 0 °C was added PPh_3 (1.9 g, 7.2 mmol, 1.0 equiv) in small portions over 1 h. The mixture was stirred at room temperature for 30 h. 1 M HCl solution (10 mL) was added, the layers were separated, and the organic layer was discarded. The aqueous layer was washed with CH_2Cl_2 (20 mL × 2), which was discarded, and neutralized with 6 M NaOH until the pH reached 12. The basic aqueous layer was saturated with NaCl and extracted with CH_2Cl_2 (20 mL × 4). The combined organic layers were dried over Na_2SO_4 and concentrated to give 780 mg (85% from **5**) of **6** as a colorless oil: ^1H NMR 3.28 (t, 2, *J* = 6.8), 2.73 (t, 2, *J* = 6.8), 2.12 (br, 2, NH_2), 1.67-1.58 (m, 2), 1.55-1.45 (m, 2), 1.48-1.38 (m, 2); ^{13}C NMR 51.3, 41.7, 32.7, 28.6, 24.0; IR (neat) 3318 (br), 2933, 2862, 2089, 1558, 1469, 1390, 1300, 1259. The spectral data are identical to those previously reported.[6]

***N*-(5-Azidopentyl)-5-[(1*H*-indol-3-yl)methyl]-1,2,4-oxadiazol-3-amine (11b)—**To a suspension of **9b** (350 mg, 2.0 mmol) in 10 mL of CH_2Cl_2 at 0 °C was added DMF (2 drops) and oxalyl chloride (0.51 mL, 5.9 mmol, 3.0 equiv) successively. The mixture was stirred at 0 °C for 1.5 h and concentrated to give 450 mg of crude 1*H*-indole-3-acetyl chloride (**10b**), which was used for the synthesis of **11b** without further purification.

To a solution of **6** (400 mg, 3.1 mmol) in 6 mL of CH_2Cl_2 was added $NaHCO_3$ (1.6 g, 19 mmol, 6.0 equiv) and 7 mL of H_2O successively. To the resulting mixture was slowly added

a solution of BrCN (394 mg, 3.7 mmol, 1.2 equiv) in 2 mL of CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 0.5 h and at room temperature for 1 h. The reaction was quenched by addition of water (10 mL). The mixture was extracted with CH_2Cl_2 (15 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated to give 460 mg (96% from **6**) of > 90% pure **7** as a somewhat unstable pale yellow oil that can be stored for a few days at 0 °C: ^{1}H NMR 3.73 (br, 1, NH), 3.31 (t, 2, *J* = 6.8), 3.10 (dt, 2, *J* = 6.8, 6.8), 1.71-1.59 (m, 4), 1.52-1.42 (m, 2); ^{13}C NMR 116.0, 51.1, 46.0, 29.1, 28.3, 23.4; IR (neat) 3211 (br), 2937, 2865, 2215, 2090, 1454, 1351, 1246, 1159.

To a solution of crude **7** (460 mg, 3.0 mmol) in 10 mL of dry EtOH was added NH_2OH•HCl (252 mg, 3.6 mmol, 1.2 equiv) and K_2CO_3 (1.24 g, 9.0 mmol, 3.0 equiv) successively. The reaction mixture was stirred at room temperature for 5 h, diluted with EtOAc (20 mL) and filtered through Celite. The filtrate was dried over Na_2SO_4 and concentrated to give 502 mg of crude **8** as an unstable pale yellow sticky oil, which decomposed on storage at 0 °C overnight and should be used immediately in the next step: ^{1}H NMR (DMSO-d_6) 9.50 (br, 1, NH or OH), 7.49 (br, 1, NH or OH), 7.32 (br, 2, NH or OH), 3.33 (t, 2, *J* = 7.2), 3.14-3.06 (m, 2), 1.60-1.42 (m, 4), 1.38-1.26 (m, 2).

To a solution of freshly prepared crude **8** (502 mg, from 400 mg (3.1 mmol) of **6**) and NEt_3 (0.83 mL, 6.0 mmol) in 10 mL of CH_2Cl_2 at 0 °C was added a solution of crude **10b** (450 mg, from 350 mg (2.0 mmol) of **9b**) in 4 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 2 h and concentrated. To the residue was added 15 mL of $ClCH_2CH_2Cl$. The mixture was heated at 80 °C for 2 h and concentrated. To the residue was added 15 mL of saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (15 mL × 4). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (6:1 CH_2Cl_2/EtOAc) gave 410 mg (63% from **9b**, 40% from **6**) of **11b** as a beige solid: mp 58–59 °C; ^{1}H NMR 8.16 (br, 1, NH) 7.63 (br d, 1, *J* = 8.0), 7.37 (br d, 1, *J* = 8.0), 7.22 (br dd, 1, *J* = 8.0, 8.0), 7.20 (br s, 1), 7.15 (br dd, 1, *J* = 8.0, 8.0), 4.29 (br, 1, NH), 4.22 (s, 2), 3.25 (t, 2, *J* = 6.8), 3.23 (dt, 2, *J* = 6.8, 6.8), 1.68-1.56 (m, 4), 1.49-1.37 (m, 2); ^{13}C NMR 177.3, 168.6, 136.1, 126.7, 123.0, 122.5, 119.9, 118.7, 111.3, 108.1, 51.2, 43.1, 28.9, 28.5, 23.9, 23.4; IR (neat) 3306 (br), 2092, 1703, 1661, 1594, 1456, 1339, 1247, 740; HRMS (ESI) calcd for $C_{16}H_{20}N_7O$ (MH^+) 326.1729, found 326.1727.

***N*-(5-Azidopentyl)-5-[(6-bromo-1*H*-indol-3-yl)methyl]-1,2,4-oxadiazol-3-amine (11a)—**To a suspension of **9a** (254 mg, 1.0 mmol) in 10 mL of CH_2Cl_2 at 0 °C was added DMF (2 drops) and oxalyl chloride (0.26 mL, 3.0 mmol, 3.0 equiv) successively. The mixture was stirred at 0 °C for 1.5 h and concentrated to give 320 mg of crude **10a**, which was used for the synthesis of **11a** without further purification.

To a solution of freshly prepared crude **8** (see preparation of **11b** for procedure) (254 mg, from 200 mg (1.6 mmol) of **6**) and NEt_3 (0.42 mL, 3.0 mmol) in 5 mL of CH_2Cl_2 at 0 °C was added a solution of crude **10a** (320 mg, from 254 mg (1.0 mmol) of **9a**) in 2 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 2 h and concentrated. To the residue was added 8 mL of $ClCH_2CH_2Cl$. The mixture was heated at 80 °C for 2 h and concentrated. To the residue was added 15 mL of saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (15 mL × 4). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (6:1 CH_2Cl_2/EtOAc) gave 246 mg (61% from **9a**, 39% from **6**) of **11a** as a beige solid: mp 86–87 °C; ^{1}H NMR 8.21 (br, 1, NH) 7.51 (br s, 1), 7.47 (br d, 1, *J* = 8.4), 7.24 (br d, 1, *J* = 8.4), 7.16 (br s, 1), 4.29 (br, 1, NH), 4.18 (s, 2), 3.26 (t, 2, *J* = 6.8), 3.23 (dt, 2, *J* = 6.8, 6.8), 1.68-1.56 (m, 4), 1.49-1.37 (m, 2); ^{13}C NMR 177.0, 168.6, 136.9, 125.6, 123.7, 123.2, 120.0, 116.1, 114.2,

108.3, 51.2, 43.1, 28.9, 28.5, 23.9, 23.3; IR (neat) 3296 (br), 2092, 1594, 1453, 1330, 1236, 893, 803, 735; HRMS (ESI) calcd for $C_{16}H_{19}BrN_7O$ (MH^+) 404.0834, found 404.0833.

***N*-[5-[[Bis[[(1,1-dimethylethoxy)carbonyl]amino]methylene]amino]pentyl]-5-[(1*H*-indol-3-yl)methyl]-1,2,4-oxadiazol-3-amine (14b)—**To a solution of **11b** (410 mg, 1.26 mmol) in 8 mL of MeOH was added ammonium formate (397 mg, 6.30 mmol, 5.0 equiv) and activated zinc[10] (328 mg, 5.04 mmol, 4.0 equiv) successively. The mixture was stirred at room temperature for 7 h. The reaction was quenched by addition of 1 M NaOH (15 mL). The mixture was extracted with CH_2Cl_2 (15 mL × 4). The combined organic layers were dried over Na_2SO_4 and concentrated to give 390 mg of crude **12b**, which was used in the next step without purification: ^{1}H NMR 8.14 (br, 1, NH), 7.63 (br d, 1, *J* = 8.0), 7.38 (br d, 1, *J* = 8.0), 7.22 (br dd, 1, *J* = 8.0, 8.0), 7.22 (br s, 1), 7.15 (br dd, 1, *J* = 8.0, 8.0), 4.26 (br, 1, NH), 4.22 (s, 2), 3.23 (dt, 2, *J* = 6.8, 6.8), 2.68 (t, 2, *J* = 6.8), 1.68-1.54 (m, 2), 1.52-1.32 (m, 4).

To a solution of crude **12b** (390 mg) in 8 mL of DMF was added 1,3-bis(*tert*-butoxycarbonyl)-2-methylthiopseudourea (**13**) (561 mg, 1.89 mmol) and NEt_3 (1.40 mL, 10.1 mmol) successively. To the resulting mixture at 0 °C was added $AgNO_3$ (429 mg, 2.52 mmol) in small portions. The reaction was stirred at 0 °C for 2 h and at room temperature for 5 h. The reaction was quenched by addition of EtOAc (50 mL) and filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ (50 mL × 4), dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel (2:3 EtOAc/hexanes) gave 417 mg (61% from **11b**) of **14b** as a pale yellow sticky oil: ^{1}H NMR 11.49 (br s, 1, NH), 8.30 (br, 2, NH), 7.62 (br d, 1, *J* = 8.0), 7.37 (br d, 1, *J* = 8.0), 7.21 (br dd, 1, *J* = 8.0, 8.0), 7.20 (br s, 1), 7.14 (br dd, 1, *J* = 8.0, 8.0), 4.33 (br, 1, NH), 4.22 (s, 2), 3.37 (dt, 2, *J* = 6.8, 6.8), 3.20 (dt, 2, *J* = 6.8, 6.8), 1.64-1.54 (m, 4), 1.50 (s, 9), 1.49 (s, 9), 1.42-1.32 (m, 2); ^{13}C NMR 177.2, 168.7, 163.6, 156.1, 153.3, 136.1, 126.7, 123.0, 122.3, 119.8, 118.7, 111.3, 108.0, 83.1, 79.3, 43.1, 40.7, 29.0, 28.6, 28.3 (3 C), 28.0 (3 C), 24.0, 23.4; IR (neat) 3324 (br), 1719, 1597, 1414, 1366, 1325, 1129, 1053, 912, 731; HRMS (ESI) calcd for $C_{27}H_{40}N_7O_5$ (MH^+) 542.3091, found 542.3085.

***N*-[5-[[Bis[[(1,1-dimethylethoxy)carbonyl]amino]methylene]amino]pentyl]-5-[(6-bromo-1*H*-indol-3-yl)methyl]-1,2,4-oxadiazol-3-amine (14a)—**To a solution of **11a** (246 mg, 0.61 mmol) in 5 mL of MeOH was added ammonium formate (192 mg, 3.05 mmol, 5.0 equiv) and activated zinc[10] (159 mg, 2.44 mmol, 4.0 equiv) successively. The mixture was stirred at room temperature for 7 h. The reaction was quenched by addition of 1 M NaOH (15 mL). The mixture was extracted with CH_2Cl_2 (15 mL × 4). The combined organic layers were dried over Na_2SO_4 and concentrated to give 228 mg of crude **12a**, which was used in the next step without purification: ^{1}H NMR 8.15 (br, 1, NH) 7.53 (br s, 1), 7.48 (br d, 1, *J* = 8.4), 7.24 (br d, 1, *J* = 8.4), 7.19 (br s, 1), 4.29 (br, 1, NH), 4.18 (s, 2), 3.23 (dt, 2, *J* = 6.8, 6.8), 2.68 (t, 2, *J* = 6.8), 1.68-1.54 (m, 2), 1.52-1.32 (m, 4).

To a solution of crude **12a** (228 mg) in 4 mL of DMF was added 1,3-bis(*tert*-butoxycarbonyl)-2-methylthiopseudourea (**13**) (267 mg, 0.92 mmol) and NEt_3 (0.70 mL, 5.06 mmol) successively. To the resulting mixture at 0 °C was added $AgNO_3$ (207 mg, 1.22 mmol) in small portions. The reaction was stirred at 0 °C for 2 h and at room temperature for 5 h. The reaction was quenched by addition of EtOAc (30 mL) and filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ (30 mL × 4), dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel (2:3 EtOAc/hexanes) gave 226 mg (60% from **11a**) of **14a** as a pale yellow sticky oil: ^{1}H NMR 11.50 (br s, 1, NH), 8.70 (br, 1, NH), 8.31 (br, 1, NH), 7.52 (br s, 1), 7.47 (br d, 1, *J* = 8.0), 7.23 (br d, 1, *J* = 8.0), 7.16 (br s, 1), 4.47 (br, 1, NH), 4.18 (s, 2), 3.32 (dt, 2, *J* = 6.8, 6.8), 3.16 (dt, 2, *J* = 6.8, 6.8), 1.58-1.46 (m, 4), 1.49 (s, 18), 1.34-1.24 (m, 2); ^{13}C NMR 176.9, 168.7, 163.5, 156.1, 153.3,

136.9, 125.7, 123.7, 123.1, 120.0, 115.9, 114.3, 108.2, 83.1, 79.4, 43.1, 40.7, 29.0, 28.6, 28.3 (3 C), 28.0 (3 C), 24.0, 23.3; IR (neat) 3322 (br), 1718, 1598, 1413, 1366, 1330, 1131, 1052, 910, 803, 730; HRMS (ESI) calcd for $C_{27}H_{39}BrN_7O_5$ (MH^+) 620.2196, found 620.2187.

***N*-[5-[(Aminoiminomethyl)amino]pentyl]-5-[(1*H*-indol-3-yl)methyl]-1,2,4-oxadiazol-3-amine Trifluoroacetic Acid Salt (Phidianidine B, 1b)—14b** (417 mg, 0.77 mmol) was taken up in 20 mL of 1:10 TFA/CH_2Cl_2, and the resulting solution was stirred at room temperature for 8 h. The mixture was diluted with 25 mL MeOH and concentrated to give 326 mg (93%) of >95% pure **1b** as a pale yellow oil: ^{1}H NMR (CD_3OD) 7.52 (br d, 1, *J* = 8.0), 7.35 (br d, 1, *J* = 8.0), 7.21 (br s, 1), 7.11 (br dd, 1, *J* = 8.0, 8.0), 7.01 (br dd, 1, *J* = 8.0, 8.0), 4.22 (s, 2), 3.15 (t, 2, *J* = 6.8), 3.14 (t, 2, *J* = 6.8), 1.68-1.54 (m, 4), 1.46-1.36 (m, 2); (DMSO-d_6) 11.04 (br s, NH), 7.55 (br t, 1, *J* = 5.6, NH), 7.51 (br d, 1, *J* = 8.0), 7.37 (br d, 1, *J* = 8.0), 7.31 (br d, 1, *J* = 2.2), 7.09 (br dd, 1, *J* = 8.0, 8.0), 6.99 (br dd, 1, *J* = 8.0, 8.0), 6.72 (br t, 1, *J* = 5.6, NH), 4.20 (s, 2), 3.06 (dt, 2, *J* = 5.6, 5.6), 3.01 (dt, 2, *J* = 5.6, 5.6), 1.56-1.40 (m, 4), 1.35-1.25 (m, 2); ^{13}C NMR (CD_3OD, referenced to the residual solvent peaks centered at δ 49.15) 179.5, 170.2, 158.8, 138.2, 128.3, 124.8, 122.9, 120.2, 119.4, 112.5, 108.3, 43.9, 42.5, 29.9, 29.7, 25.0, 24.2; (DMSO-d_6, referenced to the residual solvent peaks centered at δ 39.51) 176.9, 168.5, 156.7, 136.2, 126.7, 124.2, 121.2, 118.7, 118.4, 111.5, 106.9, 42.3, 40.7, 28.1 (2 C), 23.4, 22.7; IR 3303 (br), 1671, 1599, 1201, 1137; HRMS (ESI) calcd for $C_{17}H_{24}N_7O$ (M^+) 342.2042, found 342.2047. In both solvents, the indole carbons near the nitrogen are doubled in various ratios due to the presence of both NH and ND forms of the indole.[15]

***N*-[5-[(Aminoiminomethyl)amino]pentyl]-5-[(6-bromo-1*H*-indol-3-yl)methyl]-1,2,4-oxadiazol-3-amine Trifluoroacetic Acid Salt (Phidianidine A, 1a)—14a** (100 mg, 0.16 mmol) was taken up in 5 mL of 1:10 TFA/CH_2Cl_2, and the resulting solution was stirred at room temperature for 8 h. The mixture was diluted with 5 mL MeOH and concentrated to give 79 mg (92%) of >95% pure **1a** as a pale yellow oil: ^{1}H NMR (CD_3OD) 7.52 (br d, 1, *J* = 1.7), 7.45 (br d, 1, *J* = 8.0), 7.23 (br s, 1), 7.13 (br dd, 1, *J* = 8.0, 1.7), 4.20 (s, 2), 3.15 (br t, 4, *J* = 7.2), 1.66-1.54 (m, 6), 1.46-1.36 (m, 2); (DMSO-d_6) 11.18 (br, s, NH), 7.56 (br d, 1, *J* = 1.7), 7.49 (br s, NH), 7.47 (br d, 1, *J* = 8.4), 7.35 (br d, 1, *J* = 2.5), 7.14 (br dd, 1, *J* = 8.4, 1.7), 6.73 (br t, 1, *J* = 6.0, NH), 4.20 (s, 2), 3.06 (dt, 2, *J* = 6.0, 6.0), 3.00 (dt, 2, *J* = 6.0, 6.0), 1.56-1.42 (m, 4), 1.34-1.22 (m, 2);^{13}C NMR (CD_3OD, referenced to the residual solvent peaks centered at δ 49.15) 179.1, 170.3, 158.8, 139.1, 127.3, 125.9, 123.4, 121.0, 116.3, 115.5, 108.8, 43.9, 42.5, 29.9, 29.7, 25.1, 24.1; (DMSO-d_6, referenced to the residual solvent peaks centered at δ 39.51) 176.7, 168.5, 156.7, 137.0, 125.8, 125.3, 121.6, 120.2, 114.2, 114.0, 107.4, 42.3, 40.7, 28.1 (2 C), 23.3, 22.5; IR 3280 (br), 1670, 1601, 1184, 1137; HRMS (ESI) calcd for $C_{17}H_{23}BrN_7O$ (M^+) 420.1147, found 420.1135. In both solvents, the indole carbons near the nitrogen are doubled in various ratios due to the presence of both NH and ND forms of the indole.[15]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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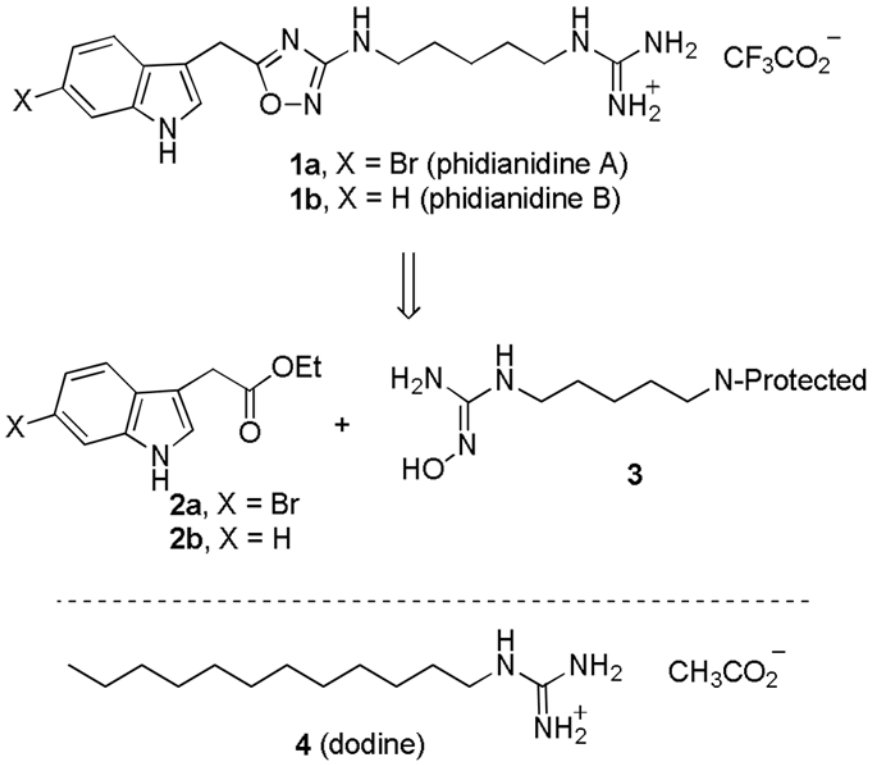
References and Notes

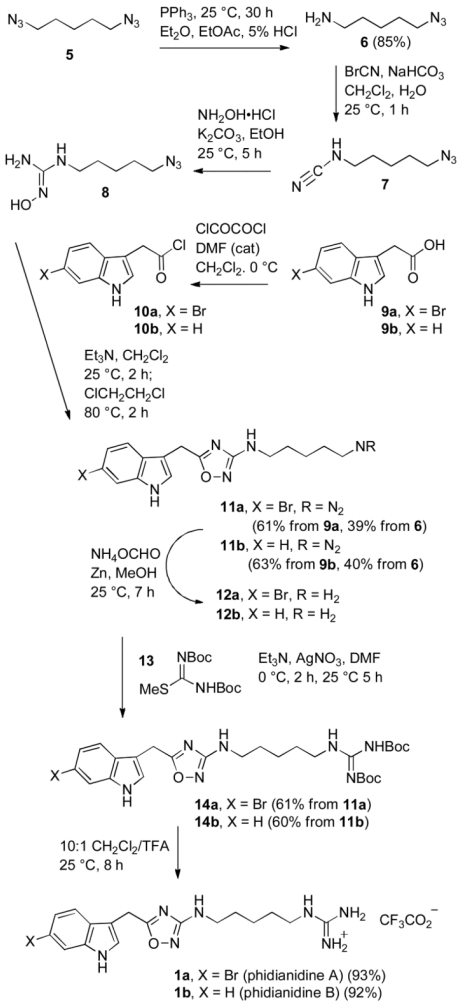
1. Carbone M, Li Y, Irace C, Mollo E, Castelluccio F, Di Pascale A, Cimino G, Santamaria R, Guo Y-W, Gavagnin M. Org Lett. 2011; 13:2516–2519. [PubMed: 21506595]
2. For reviews of 1,2,4-oxadiazoles, see: Hemming K. J Chem Res, Synop. 2001:209–216.Kayukova LA. Pharm Chem J. 2005; 39:539–547.Pace A, Pierro P. Org Biomol Chem. 2009; 7:4337–4348. [PubMed: 19830279]
3. (a) Byrde RJW, Clifford DR, Woodcock D. Ann Appl Biol. 1962; 50:291–298.(b) Srivastava SK, Smith TA. Phytochemistry. 1981; 21:997–1008.(c) Cabral JPS. Antimicrob Agents Chemother. 1991; 35:341–344. [PubMed: 1902648]
4. (a) Yu M, Pochapsky SS, Snider BB. J Org Chem. 2008; 73:9065–9074. [PubMed: 18928319] (b) Yu M, Snider BB. Org Lett. 2009; 11:1031–1032. [PubMed: 19166346] (c) Yu M, Pochapsky SS, Snider BB. Org Lett. 2010; 12:828–831. [PubMed: 20078082] (d) Barykina OV, Snider BB. Org Lett. 2010; 12:2664–2667. [PubMed: 20446668]
5. (a) Saunders J, MacLeod AM, Merchant K, Showell GA, Snow RJ, Street LJ, Baker R. J Chem Soc, Chem Commun. 1988:1618–1619.(b) Saunders J, Cassidy M, Freedman SB, Harley EA, Iversen LL, Kneen C, MacLeod AM, Merchant KJ, Snow RJ, Baker R. J Med Chem. 1990; 33:1128–1138. [PubMed: 2319559] (c) Street LJ, Baker R, Book T, Kneen CO, MacLeod AM, Merchant KJ, Showell GA, Saunders J, Herbert RH, Freedman SB, Harley EA. J Med Chem. 1990; 33:2690–2697. [PubMed: 2213823] (d) Showell GA, Gibbons TL, Kneen CO, MacLeod AM, Merchant K, Saunders J, Freedman SB, Patel S, Baker R. J Med Chem. 1991; 34:1086–1094. [PubMed: 2002451] (e) Chen, C-y; Senanayake, CH.; Bill, TJ.; Larsen, RD.; Verhoeven, TR.; Erider, PJ. J Org Chem. 1994; 59:3738–3741.(f) Ahmad S, Ngu K, Combs DW, Wu SC, Weinstein DS, Liu W, Chen B-C, Chandrasena G, Dorso CR, Kirby M, Atwal KS. Bioorg Med Chem Lett. 2004; 14:177–180. [PubMed: 14684323] (g) Vieira E, Huwyler J, Jolidon S, Knoflach F, Mutel V, Wichmann J. Bioorg Med Chem Lett. 2005; 15:4628–4631. [PubMed: 16099654]
6. (a) Lee JW, Jun SI, Kim K. Tetrahedron Lett. 2001; 42:2709–2711.(b) Srinivasan R, Tan LP, Wu H, Yang PY, Kalesh KA, Yao SQ. Org Biomol Chem. 2009; 7:1821–1828. [PubMed: 19590777]
7. (a) Snider BB, O'Hare SM. Tetrahedron Lett. 2001; 42:2455–2458.(b) Kumar V, Kaushik MP, Mazumdar A. Eur J Org Chem. 2008:1910–1916.(c) Sathe M, Karade HN, Kaushik MP. Synth Commun. 2008; 38:1375–1380.
8. (a) Pufahl RA, Nanjappan PG, Woodard RW, Marletta MA. Biochemistry. 1992; 31:6822–6828. [PubMed: 1379071] (b) Xian M, Fujiawara N, Wen Z, Cai T, Kazuma S, Janczuk AJ, Tang X, Telyatnikov VV, Zhang Y, Chen X, Miyamoto Y, Taniguchi N, Wang PG. Bioorg Med Lett. 2002; 10:3049–3055.(c) Cho JY, Dutton A, Miller T, Houk KN, Fukuto JM. Arch Biochem Biophys. 2003; 417:65–76. [PubMed: 12921781] (d) Schade D, Kotthaus J, Klein N, Kotthaus J, Clement B. Org Biomol Chem. 2011; 9:5249–5259. [PubMed: 21625725]
9. (a) Cai, SX.; Zhang, H-z; Kuemmerle, JD.; Zhang, H.; Kemnitzer, WE. PCT Int Appl. WO 2004058253 A1. 2004. Chem Abstr. 2004; 141:123632.(b) Fox, BM.; Iio, K.; Inaba, T.; Kayser, F.; Li, K.; Sagawa, S.; Tanaka, M.; Yoshida, A. PCT Int Appl. WO 2005013907 A2. 2005. Chem Abstr. 2005; 142:240441.(c) Kubota, H.; Nakamura, Y.; Higashijima, T.; Yamamoto, Y.; Oka, K.; Igarashi, S. US Pat Appl Publ. US 20070032485 A1. 2007. Chem Abstr. 2007; 146:229322.(d) Kubota, H.; Sugahara, M.; Furukawa, M.; Takano, M.; Motomura, D. US Pat Appl Publ. US 20070082896 A1. 2007. Chem Abstr. 2007; 146:421853.(e) Lachance, N.; Li, CS.; Leclerc, J-P.; Ramtohul, YK. PCT Int Appl. WO 2008064474 A1. 2008. Chem Abstr. 2008; 149:32315.(f) Bradbury, RH.; Hales, NJ.; Rabow, AA. PCT Int Appl. WO 2009081197 A1. 2009. Chem Abstr. 2009; 151:124013.(g) Li, X.; Liu, X.; Loren, J.; Molteni, V.; Nabakka, J.; Yeh, V.; Chianelli, D. PCT Int Appl. WO 2009105712 A1. 2009. Chem Abstr. 2009; 151:313557.(h) Bertram, LS.; Fyfe, MCT.; Gattrell, W.; Jeevaratnam, RP.; Keily, J.; Procter, M. J PCT Int Appl. WO 2010004348 A1. 2010. Chem Abstr. 2010; 152:144685.(i) Fox BM, Iio K, Li K, Choi R, Inaba T, Jackson S, Sagawa S, Shan B, Tanaka M, Yoshida A, Kayser F. Bioorg Med Chem Lett. 2010; 20:6030–6033. [PubMed: 20833038]
10. Hannick SM, Kishi Y. J Org Chem. 1983; 48:3833–3835.
11. (a) Srinivasa GR, Nalina L, Abiraj K, Gowda DC. J Chem Res, Synop. 2003:630–631.(b) Boruah A, Baruah M, Prajapati D, Sandhu JS. Synlett. 1997:1253–1253.(c) Lin W, Zhang X, He Z, Jin Y,

Gong L, Mi A. Synth Commun. 2002; 32:3279–3284.(d) Amantini D, Fringuelli F, Pizzo F, Vaccaro L. Org Prep Proced Int. 2002; 34:109–147.

12. (a) Ma D, Xia C, Jiang J, Zhang J. Org Lett. 2001; 3:2189–2191. [PubMed: 11440576] (b) Han S, Moore RA, Viola RE. Bioorg Chem. 2002; 30:81–94. [PubMed: 12020133] (c) DeMong DE, Williams RM. J Am Chem Soc. 2003; 125:8561–8565. [PubMed: 12848564]
13. (a) Rasmussen T, Jensen J, Anthoni U, Christophersen C, Nielsen PH. J Nat Prod. 1993; 56:1553–1558.(b) Baran PS, Shenvi RA. J Am Chem Soc. 2006; 128:14028–14029. [PubMed: 17061876]
14. Thomas JR, Liu X, Hergenrother PJ. J Am Chem Soc. 2005; 127:12434–12435. [PubMed: 16144359]
15. (a) Morales-Ríos MS, Del Río RE, Joseph-Nathan P. Magn Reson Chem. 1988; 26:552–558.(b) Joseph-Nathan P, Del Río RE, Morales-Ríos MS. Heterocycles. 1988; 27:377–383.



Scheme 1.
Retrosynthesis of Phidianidines A (1a) and B (1b)



Scheme 2.
Synthesis of Phidianidines A (1a) and B (1b)