Reduction of 2,5-Bis(3'-indolyl)pyrazines to 2,5-Bis(3'-indolyl)piperazines: Synthesis of Bisindolylpiperazine Marine Alkaloids Dragmacidin A, B, and C

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Abstract: A concise total synthesis of the bisindole alkaloids dragmacidin A, B and C is described that centers on the preparation and reduction of 2,5-bis(3'-indolyl)pyrazines to 2,5-bis(3'-indolyl)piperazines.

Key words: total synthesis, indoles, reductions, pyrazines, piperazines

Bisindole alkaloids of marine origin are an emerging class of bioactive agents that exhibit a wide range of important biological activities including antitumor properties.¹ Isolated from the marine sponge Hexadella Sp., dragmacidin A (1) and dragmacidin B (2) demonstrated significant cytotoxicity in L1210 assays. The isolation and structure determination of 1 and 2 revealed a piperazine heterocycle linking two indole units in a head-to-tail fashion.² The relative stereochemistry of 1 and 2 was determined from ${}^{1}H$ NMR and NOE measurements. The indole and alkyl moieties are positioned in a chair-like all trans-diequatorial orientation about the piperazine ring. Subsequently, 2,5bis(6'-bromo-3'-indolyl)piperazine (3, dragmacidin C) was isolated from the marine tunicate Didemnum candidum (Figure 1). A cis or trans orientation of the bisindole moiety could not be definitively assigned at the time of isolation.³



Figure 1 Dragmacidin A, B and C

SYNTHESIS 2006, No. 1, pp 0049–0054 Advanced online publication: 25.10.2005 DOI: 10.1055/s-2005-918431; Art ID: M03505SS © Georg Thieme Verlag Stuttgart · New York The successful construction of the piperazine ring system in the dragmacidin family has been achieved by several groups,^{4–7} most commonly involving the reduction of piperazinone intermediates.

Early work on the reduction of pyrazinium salts and indoles has been known for many years. Lyle and Thomas studied the reduction of *N*-benzylpyrazinium salts using NaBH₄ which afforded a 9:1 mixture of *trans*- and *cis-N*benzylpiperazines, respectively (Equation 1).⁸ Gribble demonstrated that indoles can be transformed to indolines with and without concomitant N-alkylation by the action of borohydrides in acidic media (Equation 2).⁹



Equation 1



Equation 2

Based on the prior precedence of Lyle and Gribble, we felt that the direct reduction of pyrazines with sodium cyanoborohydride (NaBH₃CN) in a carboxylic acid medium would offer a convenient method for the preparation of piperazines.¹⁰ Herein, we describe the preparation of 2,5bis(3'-indolyl)pyrazines **9–11** and reduction with NaBH₃CN to afford 2,5-bis(3'-indolyl)piperazines in good yields. A short and efficient synthesis of the bis(indolyl)piperazine natural products, dragmacidin A–C is thus outlined.

From a strategic perspective, we felt that the most efficient manner to access the requisite pyrazines would be through the key oxotryptamine synthons **6–8** via cyclo-condensation and autooxidation chemistry that would afford the aromatic pyrazines. Starting from indole, indole-3-carbonyl nitrile (**5**) was prepared according to the procedure of Hogan and Sainsbury (Scheme 1).¹¹ Selective reduction of the nitrile functionality of acyl cyanide **5** as previously described produced oxotryptamine **6**.¹⁰ This sequence, which starts from indole, can be readily accom-

plished on a ten gram scale and has advantages over previous preparations involving Yonemitsu oxidation (DDQ) of N-protected tryptamines.¹² Bromination of **6** yielded a mixture of 5- and 6-bromooxotryptamines in 59 and 21% yields, respectively. The position of Br incorporation was determined from NOE measurements in which irradiation of the CH₂ hydrogens shows peak enhancements at δ = 8.38 (s) and 8.31 (d, *J* = 1.8 Hz) consistent with structure **7**.



Scheme 1 Preparation of oxotryptamines 6–8

Pyrazines 9-11 were conveniently prepared in good yields through a thermally assisted tandem cyclocondensation-autoxidation process involving oxotryptamines 6-8 (Scheme 2). The initial cyclocondensation must be carried out with the exclusion of air or else head-to-head topsentin type dimers are produced via a putative imi-



Scheme 2 Synthesis of 2,5-bis(3'-indolyl)pyrazines 9–11

noketone intermediate.¹³ Exposure of the reaction mixture to air leads to the spontaneous formation of the desired pyrazines.

With pyrazines **9–11** in hand, we next investigated their transformations into piperazines using sodium cyanoborohydride in carboxylic acids. Treatment of **9** with NaBH₃CN (30 equiv) in acetic acid produced *trans*-piperazine **12** in 67% yield as the major product. Careful analysis of the reaction products revealed the presence of five additional minor products **13–17**. Reduction of **9** in HCO₂H with excess NaBH₃CN gave *trans*- and *cis*-1,4-dimethylpiperazines **18** and **19** in an 8:1 ratio (Scheme 3).

For the *trans* products **12**, **13**, **14** and **18**, the magnitude of the methine H-2 and H-5 coupling constants (dd, J = 10.3, 2.7 Hz) is consistent with a chair conformation in which the two indole moieties as well as alkyl substituents occupy equatorial positions about the piperazine ring. The formation of these *trans* diastereomers as the major products is consistent with a stereoelectronically preferred axial



Scheme 3 NaBH₃CN reduction of 2,5-bis(3'-indolyl)pyrazine 9 and 10

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hydride delivery to a putative iminium ion intermediate in the reduction process.⁸ The *cis*-piperazines 15, 16, 17 and 19, which account for less than 5% each of the reaction products, are typically characterized by higher field ¹³C NMR chemical shifts for the piperazine ring carbons compared to their trans counterparts (Table 1). In addition, the ¹H NMR coupling constants for *trans* and *cis* substituted piperazines differ significantly. For example, the magnitude of the coupling constants observed for the methine H-2 and H-5 hydrogens in the piperazine ring of 14 (H-5: $\delta = 4.39 \text{ dd}, J = 10.3, 2.4 \text{ Hz and H-2:} \delta = 3.64 \text{ dd},$ J = 10.3, 3.1 Hz) suggests that the piperazine ring exists as a chair conformer with both indole substituents occupying equatorial positions. On the other hand, the smaller magnitude of the coupling constants of H-2 and H-5 in 17 (H-5: $\delta = 4.52 \text{ dd}, J = 5.4, 3.7 \text{ Hz}$ and H-2: $\delta = 3.98, \text{ dd},$ J = 6.5, 3.2 Hz) is more suggestive of a boat-like ring conformation rather than a chair. Likewise, reduction of 2,5bis(5'-bromo-3'-indolyl)pyrazine (10) produced piperazines 20 and 21 in which the trans product is favored over the *cis* in a ratio of 8:1.

Finally, transformation of 2,5-bis(6'-bromo-3'-indolyl)pyrazine (11) with NaBH₃CN in formic acid produced bisindole piperazine natural products dragmacidin A (1) and dragmacidin B (2) while reduction in acetic acid delivered *trans*-dragmacidin C (3a) and *cis*-dragmacidin C (3b) (Scheme 4). All spectral data for synthetic 1, 2 and 3b are consistent with data reported for the corresponding natural material.

While Faulkner and co-workers³ assigned a 'diequatorial' orientation to the bisindole group in the original structure of natural dragmacidin C, Kawasaki and co-workers^{6b} established the relative stereochemistry of the natural material as cis with the piperazine ring adopting a symmetrical boat-like conformation based on ¹H NMR data acquired in acetone- d_6 . This is a peculiarity since dragmacidin C appears to be the only naturally occurring 2,5-bisindolylpiperazine metabolite that has been isolated with a relative cis-bisindole configuration. Some confusion ensued, however, when Faulkner reported the piperazine CH₂ as a multiplet in DMSO- d_6 . Clearly these methylene signals appear as a distinct, two doublet of doublet set of signals in DMSO- d_6 for both synthetic *trans*- ($\delta = 3.13$ dd, J = 1.5, 2.4 Hz and $\delta = 2.86, dd, J = 11.5, 10.1$ Hz) and *cis*- (δ = 3.09 dd, *J* = 11.9, 5.7 Hz and δ = 3.03 dd, J = 11.9, 3.2 Hz) dragmacidin C although the magnitude



Scheme 4 Synthesis of dragmacidins A-C

of the coupling constants between these diastereomers differ. *cis*-Piperazines **15** (δ = 3.13 dd, *J* = 11.7, 5.6 Hz and δ = 3.03 dd, *J* = 11.7, 3.4 Hz) and **21** (δ = 3.10 dd, *J* = 12.0, 5.5 Hz and δ = 3.01 dd, *J* = 12.0, 3.4 Hz) also exhibit similar ¹H NMR splitting patterns in DMSO-*d*₆ consistent with a boat-like conformation.

In conclusion, we have described an investigation into the reduction of bisindolylpyrazines to bisindolylpiperazines using sodium cyanoborohydride in acidic media that results in a short synthesis of the bisindolylpiperazine marine alkaloids dragmacidins A, B and C. The methods described herein should be useful for the preparation of other bisindolylpiperazine-based analogues for biological evaluation.

Chemicals and reagents were obtained from common commerical vendors and generally used without further purification. All reactions were performed under an inert atmosphere unless otherwise specified.

| Assignment | 12 ^a | 13 | 14 | 15 | 16 | 17 | 18 ^a | 19 | 20 | 21 |
|------------|------------------------|--------|--------|--------|--------|--------|------------------------|--------|--------|--------|
| C-2 | 55.0 d | 60.9 d | 61.0 d | 52.1 d | 59.8 d | 58.3 d | 62.3 d | 58.5 d | 54.6 d | 52.0 d |
| C-3 | 54.2 t | 59.7 t | 54.9 t | 50.2 t | 56.8 t | 50.1 t | 63.8 t | 58.5 t | 54.1 t | 49.9 t |
| C-5 | 55.0 d | 60.9 d | 54.3 d | 52.1 d | 59.8 d | 51.4 d | 62.3 d | 58.5 d | 54.6 d | 52.0 d |
| C-6 | 54.2 t | 59.7 t | 59.8 t | 50.2 t | 56.8 t | 55.2 t | 63.8 t | 58.5 t | 54.1 t | 49.9 t |

 Table 1
 13 C NMR Chemical Shifts of the Piperazine Ring in *cis*- and *trans*-2,5-Bis(3'-indolyl)piperazines 12–21 in Acetone- d_6

^a Solvent = DMSO- d_6 .

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Oxotryptamine 6

A mixture of indole-3-carbonyl nitrile (5; 2.0 g, 11.8 mmol) and 10% Pd/C (0.6 g) in AcOH (100 mL) was stirred vigorously at 23 °C under a balloon of H₂ for 16 h. The mixture was filtered over a pad of Celite. After evaporation of the filtrate under reduced pressure, the resulting residue was treated with conc. 20% HCl-EtOH (v/v, 20 mL) and concentrated. EtOH was added to the resulting residue and concentrated in vacuo. This EtOH addition/evaporation sequence was repeated three times. The resulting residue was rinsed with Et₂O and decanted. Trituration with EtOH (10 mL) afforded 6·HCl (2 g, 81%) as a light tan solid. Flash chromatography of the filtrate over SiO₂ using a 9:1 solution of CH₂Cl₂-MeOH (sat. NH₃) as the eluent yielded 0.2 g (10%) of $\mathbf{6}$ as the free base.

Compound 6·HCl

IR (KBr): 3110, 1664, 1615, 1521, 1437 cm⁻¹.

¹H NMR (DMSO- d_6 , 300 MHz): δ = 12.48 (br s, 1 H), 8.51 (d, J = 3.2 Hz, 1 H), 8.38 (br s, 3 H), 8.15 (m, 1 H), 7.52 (m, 1 H), 7.23 (m, 2 H), 4.35 (br s, 2 H).

¹³C NMR (DMSO- d_6 , 100 MHz): δ = 187.5 (s), 137.4 (s), 136.0 (d), 126.0 (s), 124.1 (d), 123.2 (d), 121.8 (d), 114.0 (s), 113.4 (d), 44.7 (t)

HRFABMS: m/z calcd for $C_{10}H_{11}N_2O [M + H]^+$: 175.0871; found: 175.0869.

5-Bromooxotryptamine 7 and 6-Bromooxotryptamine 8

To a stirred solution of 6 (2.0 g, 11.5 mmol) in AcOH (60 mL)-HCO₂H (30 mL) was added Br₂ (0.6 mL, 11.5 mmol) at 23 °C. After 20 min, the mixture was concentrated under reduced pressure. Flash chromatography of the resulting residue over SiO₂ using a 19:1–9:1 gradient of CHCl₃–MeOH (NH₃) as the eluent gave 7 (1.7 g, 59%) and 8 (0.6 g, 21%).

Compound 7

IR (KBr): 3354, 1650, 1521, 1490, 1442 cm⁻¹.

¹H NMR (DMSO- d_6 , 300 MHz): $\delta = 8.38$ (s, 1 H), 8.31 (d, J = 1.8Hz, 1 H), 7.45 (d, J = 8.6 Hz, 1 H), 7.33 (dd, J = 8.6, 1.8 Hz, 1 H), 3.88 (s, 2 H).

¹³C NMR (DMSO- d_6 , 100 MHz): δ = 196.3 (s), 136.1 (s), 135.2 (d), 128.0 (s), 126.1 (d), 124.2 (d), 115.3 (s), 115.1 (d), 114.6 (s), 49.1 (t)

HRFABMS: m/z calcd for $C_{10}H_{10}^{79}BrN_2O [M + H]^+$: 252.9977; found: 252.9979.

Compound 8

IR (KBr): 3340, 1637, 1597, 1521, 1453 cm⁻¹.

¹H NMR (DMSO- d_6 , 300 MHz): $\delta = 8.35$ (s, 1 H), 8.10 (d, J = 8.4Hz, 1 H), 7.65 (d, J = 1.4 Hz, 1 H), 7.31 (dd, J = 8.4, 1.4 Hz, 1 H), 3.86 (s, 2 H).

¹³C NMR (DMSO- d_6 , 75 MHz): δ = 196.3 (s), 138.3 (s), 134.8 (d), 125.4 (d), 125.3 (s), 123.7 (d), 116.1 (s), 115.7 (d), 115.1 (s), 49.2 (t).

HRFABMS: m/z calcd for $C_{10}H_{10}^{79}BrN_2O [M + H]^+$: 252.9977; found: 252.9978.

2,5-Bis(3'-indolyl)pyrazine (9); Typical Procedure

A mixture of 6 (0.5 g, 2.87 mmol) in *p*-xylene (60 mL)-EtOH (12 mL) was heated in a sealed tube at 130 °C for 3 d under argon with the exclusion of air. After cooling to r.t., the mixture was exposed to air for 1 d, concentrated, and filtered to afford 9 (0.3 g, 67%) as a yellow solid.

IR (KBr): 3387, 1558, 1457, 1422, 1341 cm⁻¹.

HRFABMS: m/z calcd for $C_{20}H_{21}N_4$ [M + H]⁺: 317.1766; found: 317.1761.

trans-1,4-Diethyl-2,5-bis(3'-indolyl)piperazine (13)

¹H NMR (acetone- d_6 , 400 MHz): δ = 10.16 (br s, 2 H), 8.03 (d, *J* = 7.8 Hz, 2 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 2.3 Hz, 2 H),

¹³C NMR (DMSO- d_6 , 75 MHz): δ = 146.7 (s), 140.1 (d), 137.0 (s), 125.6 (d), 125.2 (s), 122.0 (d), 121.5 (d), 120.1 (d), 112.7 (s), 111.9 (d).

HRFABMS: m/z calcd for $C_{20}H_{15}N_4$ [M + H]⁺: 311.1297; found: 311.1300.

2,5-Bis(5'-bromo-3'-indolyl)pyrazine (10)

Following an analogous protocol for 9, pyrazine 10 was obtained from 7 in 60% yield.

IR (KBr): 3415, 1550, 1444, 1428, 1316 cm⁻¹.

¹H NMR (DMSO- d_6 , 400 MHz): $\delta = 11.87$ (d, J = 1.9 Hz, 2 H), 9.21 (s, 2 H), 8.69 (d, J = 1.9 Hz, 2 H), 8.34 (d, J = 2.8 Hz, 2 H), 7.48 (d, J = 2.8 Hz, 2 Hz, 2 H), 7.48 (d, J = 2.8 Hz, 2 Hz), 7.48 (d, J = 2.8 Hz, 2 Hz), 7J = 8.6 Hz, 2 H), 7.34 (dd, J = 8.6, 1.9 Hz, 2 H).

¹³C NMR (DMSO- d_6 , 100 MHz): δ = 147.2 (s), 141.0 (d), 136.5 (s), 127.9 (s), 127.8 (d), 125.4 (d), 124.6 (d), 114.8 (d), 113.7 (s), 113.1 (s).

HRFABMS: m/z calcd for $C_{20}H_{13}^{79}Br_2N_4$ [M + H]⁺: 466.9507; found: 466.9500.

2,5-Bis(6'-bromo-3'-indolyl)pyrazine (11)

Following an analogous protocol for 9, pyrazine 11 was obtained from 8 in 60% yield.

IR (KBr): 3393, 1549, 1447, 1417, 1172 cm⁻¹.

¹H NMR (DMSO- d_6 , 300 MHz): δ = 11.77 (d, J = 2.8 Hz, 2 H), 9.13 (s, 2 H), 8.39 (d, J = 8.6 Hz, 2 H), 8.27 (d, J = 2.8 Hz, 2 H), 7.66 (d, J = 1.7 Hz, 2 H), 7.28 (dd, J = 8.6, 1.7 Hz, 2 H).

¹³C NMR (DMSO- d_6 , 75 MHz): $\delta = 147.2$ (s), 141.0 (d), 138.7 (s), 127.4 (d), 125.1 (s), 124.1 (d), 123.9 (d), 115.6 (s), 115.3 (d), 113.7 (s).

HRFABMS: m/z calcd for $C_{20}H_{13}^{79}Br_2N_4$ [M + H]⁺: 465.9507; found: 466.9500.

NaBH₃CN Reduction of 9 in AcOH

To a stirred solution of 9 (0.1 g, 0.32 mmol) in AcOH at 0 °C (50 mL) under N2 was added NaBH3CN (0.6 g, 9.7 mmol). After 2 h, the mixture was concentrated in vacuo and the resulting residue was washed with Et₂O and triturated with a small amount of EtOH to yield trans-2,5-bis(3'-indolyl)piperazine (12; 67 mg, 67%) as a colorless solid. Flash chromatography of the combined Et₂O washings and filtrate using a 19:1 solution of CH₂Cl₂-MeOH (NH₃) as the eluent gave a residue that was subjected to further purification by PTLC using a 19:1-9:1 CH₂Cl₂-MeOH (NH₃) gradient to yield five additional minor products 13–17 ranging in yield from 2–4% each.

Compound 12

IR (KBr): 3146, 1629, 1501, 1456, 1386 cm⁻¹.

¹H NMR (DMSO- d_6 , 300 MHz): δ = 10.85 (br s, 2 H), 7.70 (d, J = 7.7 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 7.25 (d, J = 2.1 Hz, 2 H), 7.05 (t, J = 7.0 Hz, 2 H), 6.97 (t, J = 7.0 Hz, 2 H), 4.07 (dd, J = 10.1),2.3 Hz, 2 H), 3.18 (dd, J = 11.5, 2.3 Hz, 2 H), 2.87 (dd, J = 11.5, 10.1 Hz, 2 H).

¹³C NMR (DMSO- d_6 , 100 MHz): $\delta = 137.1$ (s), 127.0 (s), 122.6 (d), 121.7 (d), 120.1 (d), 119.0 (d), 117.8 (s), 112.3 (d), 55.0 (d), 54.2 (t).

7.14 (td, J = 8.1, 1.2 Hz, 2 H), 7.06 (td, J = 8.0, 1.1 Hz, 2 H), 3.87 (dd, J = 10.5, 3.0 Hz, 2 H), 3.12 (dd, J = 11.1, 3.0 Hz, 2 H), 2.74 (2 q, J = 7.4 Hz, 2 H), 2.62 (dd, J = 11.1, 10.5 Hz, 2 H), 2.02, (2 q, J = 6.9 Hz, 2 H), 0.88 (t, J = 7.2 Hz, 6 H).

¹³C NMR (acetone- d_6 , 100 MHz): δ = 137.5 (s), 127.3 (s), 123.4 (d), 121.7 (d), 120.7 (d), 118.9 (d), 116.6 (s), 111.7 (d), 60.9 (d), 59.7 (t), 48.2 (t), 11.5 (q).

HRFABMS: m/z calcd for $C_{24}H_{29}N_4$ [M + H]⁺: 373.2392; found: 373.2357.

trans-1-Ethyl-2,5-bis(3'-indolyl)piperazine (14)

¹H NMR (acetone- d_6 , 300 MHz): δ = 10.11 (br s, 2 H), 7.99 (d, J = 7.7 Hz, 1 H), 7.84 (d, J = 8.1 Hz, 1 H), 7.40 (dm, J = 7.9 Hz, 2 H), 7.34 (d, J = 1.8 Hz, 1 H), 7.31 (d, J = 2.4 Hz, 1 H), 7.13–7.00 (m, 4 H), 4.39 (dd, J = 10.3, 2.4 Hz, 1 H), 3.64 (dd, J = 10.3, 3.1 Hz, 1 H), 3.35 (dd, J = 10.8, 2.4 Hz, 1 H), 3.31 (dd, J = 11.7, 10.3 Hz, 1 H), 3.08 (dd, J = 11.7, 3.2 Hz, 1 H), 2.74 (2 q, J = 7.4 Hz, 1 H), 2.33, (dd, J = 10.8, 10.3 Hz, 1 H), 2.07 (2 q, J = 6.9 Hz, 1 H), 0.90 (t, J = 7.2 Hz, 3 H).

¹³C NMR (acetone- d_6 , 100 MHz): δ = 137.5 (s), 137.3 (s), 127.4 (s), 127.1 (s), 123.3 (d), 122.0 (d), 121.7 (d), 121.6 (d), 120.6 (d), 119.9 (d), 118.9 (d), 118.8 (d), 118.3 (s), 116.7 (s), 111.7 (2 d), 61.0 (d), 59.8 (t), 54.9 (t), 54.3 (d), 48.5 (t), 11.3 (q).

HRFABMS: m/z calcd for $C_{22}H_{25}N_4$ [M + H]⁺: 345.2079; found: 345.2072.

cis-2,5-Bis(3'-indolyl)piperazine (15)

¹H NMR (acetone- d_6 , 300 MHz): δ = 10.05 (br s, 2 H), 7.73 (d, J = 7.9 Hz, 2 H), 7.58 (d, J = 1.8 Hz, 2 H), 7.37 (d, J = 8.0 Hz, 2 H), 7.07 (t, J = 8.1 Hz, 2 H), 6.98 (t, J = 8.0 Hz, 2 H), 4.30 (dd, J = 5.9, 3.5 Hz, 2 H), 3.30 (dd, J = 11.6, 5.9 Hz, 2 H), 3.17 (dd, J = 11.6, 3.5 Hz, 2 H).

¹³C NMR (acetone- d_6 , 100 MHz): $\delta = 137.1$ (s), 127.6 (s), 123.3 (d), 121.4 (d), 119.6 (d), 118.8 (d), 117.9 (s), 111.5 (d), 52.1 (d), 50.2 (t).

HRFABMS: m/z calcd for $C_{20}H_{21}N_4$ [M + H]⁺: 317.1766; found: 317.1756.

cis-1,4-Diethyl-2,5-bis(3'-indolyl)piperazine (16)

¹H NMR (acetone- d_6 , 300 MHz): $\delta = 10.45$ (br s, 2 H), 7.97 (d, J = 7.9 Hz, 2 H), 7.57 (d, J = 1.7 Hz, 2 H), 7.49 (dm, J = 8.1 Hz, 2 H), 7.19 (td, J = 8.1, 1.2 Hz, 2 H), 7.11 (td, J = 8.0, 1.2 Hz, 2 H), 4.46 (br d, J = 8.4 Hz, 2 H), 3.51 (dd, J = 12.0, 2.3 Hz, 2 H), 3.22 (m, 2 H), 2.97 (m, 2 H), 2.52 (br s, 2 H), 1.03 (t, J = 7.2 Hz, 6 H).

¹³C NMR (acetone- d_6 , 100 MHz): δ = 137.3 (s), 126.9 (s), 125.0 (d), 122.5 (d), 119.9 (d), 119.7 (d), 112.3 (d), 111.3 (s), 59.8 (d), 56.8 (t), 48.2 (t), 10.3 (q).

HRFABMS: m/z calcd for $C_{24}H_{29}N_4$ [M + H]⁺: 373.2392; found: 373.2354.

cis-1-Ethyl-2,5-bis(3'-indolyl)piperazine (17)

¹H NMR (acetone- d_6 , 300 MHz): $\delta = 10.14$ (br s, 2 H), 7.81 (d, J = 8.0 Hz, 1 H), 7.75 (br s, 1 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.64 (br s, 1 H), 7.43–7.37 (m, 2 H), 7.12–6.95 (m, 4 H), 4.52 (dd, J = 5.4, 3.7 Hz, 1 H), 3.98 (dd, J = 6.5, 3.3 Hz, 1 H), 3.23 (dd, J = 11.4, 6.5 Hz, 1 H), 3.21 (dd, J = 11.2, 5.4 Hz, 1 H), 3.04 (dd, J = 11.4, 3.3 Hz, 1 H), 2.79 (dd, J = 11.2, 3.7 Hz, 1 H), 2.48 (m, 1 H), 2.27 (m, 1 H), 1.03 (t, J = 7.1 Hz, 3 H).

¹³C NMR (acetone- d_6 , 100 MHz): δ = 137.1 (s), 136.8 (s), 128.2 (s), 127.6 (s), 124.4 (d), 124.0 (d), 121.5 (d), 121.4 (d), 119.8 (d), 119.3 (d), 118.9 (2 d), 117.3 (s), 114.8 (s), 111.6 (2 d), 58.3 (d), 55.2 (t), 51.4 (d), 50.1 (t), 49.0 (t), 12.1 (q).

HRFABMS: m/z calcd for $C_{22}H_{25}N_4$ [M + H]⁺: 345.2079; found: 345.2099.

NaBH₃CN Reduction of 9 in HCO₂H

To a stirred solution of **9** (50 mg, 0.16 mmol) in formic acid at 0 °C (25 mL) under N₂ was added NaBH₃CN (0.6 g, 9.7 mmol). After 1 d, the mixture was concentrated in vacuo. Flash chromatography of the resulting residue using a 19:1 solution of CH₂Cl₂–MeOH (NH₃) as the eluent gave 30 mg (54%) of *trans*-1,4-dimethyl-2,5-bis(3'-indolyl)piperazine (**18**) and minor amounts of *cis*-1,4-dimethyl-2,5-bis(3'-indolyl)piperazine (**19**) (<5%).

Compound 18

IR (KBr): 3135, 1621, 1538, 1453, 1325 cm⁻¹.

¹H NMR (DMSO- d_6 , 300 MHz): δ = 10.92 (br s, 2 H), 7.84 (d, J = 7.7 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 2.0 Hz, 2 H), 7.07 (t, J = 7.4 Hz, 2 H), 6.98 (t, J = 7.3 Hz, 2 H), 3.53 (dd, J = 10.9, 2.2 Hz, 2 H), 2.87 (dd, J = 11.2, 2.2 Hz, 2 H), 2.57 (dd, J = 11.2, 10.9 Hz, 2 H), 1.97 (s, 6 H).

¹³C NMR (DMSO- d_6 , 75 MHz): δ = 137.3 (s), 127.1 (s), 124.2 (d), 121.8 (d), 120.6 (s), 119.2 (d), 115.6 (d), 112.3 (d), 63.8 (t), 62.3 (d), 43.8 (q).

HRFABMS: m/z calcd for $C_{22}H_{25}N_4$ [M + H]⁺: 345.2079; found: 345.2079.

Compound 19

¹H NMR (acetone- d_6 , 300 MHz): δ = 10.21 (br s, 2 H), 7.81 (d, J = 7.6 Hz, 2 H), 7.80 (br s, 2 H), 7.42 (d, J = 7.8 Hz, 2 H), 7.10 (t, J = 7.7 Hz, 2 H), 7.03 (t, J = 7.8 Hz, 2 H), 3.95 (br s, 2 H), 3.01 (dd, J = 11.1, 6.4 Hz, 2 H), 2.63 (dd, J = 11.1, 3.3 Hz, 2 H), 2.13 (s, 6 H).

¹³C NMR (acetone- d_6 , 100 MHz): δ = 136.7 (s), 128.5 (s), 125.1 (d), 121.5 (d), 119.4 (d), 119.2 (d), 113.4 (s), 111.8 (d), 58.5 (d and t), 43.1 (q).

HRFABMS: m/z calcd for $C_{22}H_{25}N_4$ [M + H]⁺: 345.2079; found: 345.2077.

NaBH₃CN Reduction of 10 in AcOH

To a stirred solution of **10** (66 mg, 0.14 mmol) in AcOH at 0 °C (25 mL) under N₂ was added NaBH₃CN (0.22 g, 3.5 mmol). After 2 h, the mixture was concentrated in vacuo. Flash chromatography of the resulting residue using a 19:1–9:1 gradient of CH₂Cl₂–MeOH (NH₃) as the eluent gave 40 mg (60%) of *trans*-2,5-bis(5'-bromo-3'-indolyl)piperazine (**20**) and minor amounts of *cis*-2,5-bis(5'-bromo-3'-indolyl)piperazine (**21**) (<5%).

Compound 20

IR (KBr): 3127, 1569, 1490, 1455, 1310 cm⁻¹.

¹H NMR (DMSO- d_6 , 300 MHz): δ = 11.10 (br s, 2 H), 7.93 (d, J = 1.5 Hz, 2 H), 7.32 (d, J = 8.6 Hz, 2 H), 7.32 (d, J = 2.0 Hz, 2 H), 7.17 (dd, J = 8.6, 1.4 Hz, 2 H), 4.03 (dd, J = 11.0, 2.6 Hz, 2 H), 3.13 (dd, J = 11.3, 2.6 Hz, 2 H), 1.89 (dd, J = 11.3, 11.0 Hz, 2 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ = 135.9 (s), 128.9 (s), 124.5 (d), 124.2 (d), 122.7 (d), 117.5 (s), 114.3 (d), 111.7 (s), 54.6 (d), 54.1 (t). HRFABMS: *m*/*z* calcd for $C_{20}H_{19}^{79}Br_2N_4$ [M + H]⁺: 472.9976; found: 472.9974.

Compound 21

¹H NMR (acetone- d_6 , 300 MHz): δ = 10.28 (br s, 2 H), 7.94 (d, J = 1.9 Hz, 2 H), 7.59 (br s, 2 H), 7.35 (d, J = 8.6 Hz, 2 H), 7.17 (dd, J = 8.6, 1.9 Hz, 2 H), 4.25 (dd, J = 5.9, 3.5 Hz, 2 H), 3.26 (dd, J = 11.9, 5.9 Hz, 2 H), 3.13 (dd, J = 11.9, 3.5 Hz, 2 H).

¹³C NMR (acetone- d_6 , 100 MHz): δ = 135.8 (s), 129.4 (s), 125.0 (d), 124.0 (d), 122.6 (d), 117.6 (s), 113.4 (d), 111.7 (s), 52.0 (d), 49.9 (t).

HRFABMS: m/z calcd for $C_{20}H_{19}^{79}Br_2N_4$ [M + H]⁺: 472.9976; found: 472.9969.

Dragmacidin A (1) and Dragmacidin B (2)

To a stirred solution of **11** (66 mg, 0.14 mmol) in formic acid at 0 °C (30 mL) under N₂ was added NaBH₃CN (0.45 g, 7.1 mmol). After 4 h, the mixture was concentrated in vacuo. Flash chromatography of the resulting residue using a 19:1 solution of CH₂Cl₂–MeOH (NH₃) as the eluent gave a residue that was subjected to further purification by PTLC using a 19:1–9:1 CH₂Cl₂–MeOH (NH₃) gradient to yield 10 mg of **1** (14%) and 40 mg of **2** (56%).

Compound 1

¹H NMR (acetone- d_6 , 400 MHz): δ = 10.33 (br s, 2 H), 7.94 (d, J = 8.5 Hz, 1 H), 7.84 (d, J = 8.4 Hz, 1 H), 7.64 (br s, 2 H), 7.41 (br s, 1 H), 7.38 (br s, 1 H), 7.20 (dm, J = 8.0 Hz, 2 H), 4.44 (dd, J = 10.4, 2.6 Hz, 1 H), 3.41 (dd, J = 10.5, 3.0 Hz, 1 H), 3.31 (dd, J = 11.0, 10.5 Hz, 1 H), 3.20 (dd, J = 11.0, 2.6 Hz, 1 H), 3.09 (dd, J = 11.0, 3.0 Hz, 1 H), 2.39 (dd, J = 11.0, 10.4 Hz, 1 H), 2.11 (s, 3 H).

¹³C NMR (acetone- d_6 , 100 MHz): δ = 138.7 (s), 138.5 (s), 126.5 (2 s), 124.9 (d), 123.7 (d), 122.6 (d), 122.4 (2 d), 122.1 (d), 118.6 (s), 117.1 (s), 115.3 (s), 115.2 (s), 115.04 (d), 114.99 (d), 64.4 (t), 63.2 (d), 54.6 (t), 54.3 (d), 44.2 (q).

HRFABMS: m/z calcd for $C_{21}H_{21}^{-79}Br_2N_4$ [M + H]⁺: 487.0133; found: 487.0131.

Compound 2

¹H NMR (acetone- d_6 , 300 MHz): δ = 10.29 (br s, 2 H), 7.92 (d, J = 8.5 Hz, 2 H), 7.61 (d, J = 1.8 Hz, 2 H), 7.37 (d, J = 1.4 Hz, 2 H), 7.17 (dd, J = 8.5, 1.8 Hz, 2 H), 3.58 (dd, J = 10.5, 2.9 Hz, 2 H), 2.92 (dd, J = 11.3, 2.9 Hz, 2 H), 2.62 (dd, J = 11.3, 10.5 Hz, 2 H), 2.04 (s, 6 H).

¹³C NMR (acetone- d_6 , 75 MHz): δ = 138.3 (s), 126.1 (s), 124.5 (d), 122.2 (d), 122.0 (d), 116.5 (s), 114.8 (s), 114.6 (d), 63.6 (t), 62.3 (d), 43.0 (q).

HRFABMS: m/z calcd for $C_{22}H_{23}^{79}Br_2N_4$ [M + H]⁺: 501.0289; found: 501.0297.

trans-Dragmacidin C (3a) and cis-Dragmacidin C (3b)

To a stirred solution of **11** (65 mg, 0.14 mmol) in AcOH at 0 °C (30 mL) under N₂ was added NaBH₃CN (0.22 g, 3.5 mmol). After 2 h, the mixture was concentrated in vacuo. Flash chromatography of the resulting residue using a 19:1–9:1 gradient of CH₂Cl₂–MeOH (NH₃) as the eluent gave 40 mg of **3a** (61%) and minor amounts of **3b** (<5%).

Compound 3a

IR (KBr): 3133, 1617, 1539, 1455, 1328 cm⁻¹.

¹H NMR (DMSO- d_6 , 300 MHz): $\delta = 11.03$ (br s, 2 H), 7.69 (d, J = 8.5 Hz, 2 H), 7.52 (d, J = 1.7 Hz, 2 H), 7.29 (d, J = 2.3 Hz, 2 H), 7.10 (dd, J = 8.5, 1.7 Hz, 2 H), 4.05 (dd, J = 10.1, 2.4 Hz, 2 H), 3.13 (dd, J = 11.5, 2.4 Hz, 2 H), 2.86 (dd, J = 11.5, 10.1 Hz, 2 H).

¹³C NMR (DMSO- d_6 , 75 MHz): δ = 138.0 (s), 126.0 (s), 123.9 (d), 121.98 (d), 121.95 (d), 117.9 (s), 114.8 (d), 114.5 (s), 54.6 (d), 53.9 (t).

HRFABMS: m/z calcd for $C_{20}H_{19}^{-79}Br_2N_4$ [M + H]⁺: 472.9976; found: 472.9968.

Compound 3b

¹H NMR (acetone- d_6 , 400 MHz): δ = 10.26 (br s, 2 H), 7.72 (d, J = 8.5 Hz, 2 H), 7.62 (br s, 2 H), 7.60 (d, J = 1.8 Hz, 2 H), 7.13 (dd, J = 8.5, 1.8 Hz, 2 H), 4.32 (dd, J = 5.4, 3.4 Hz, 2 H), 3.28 (dd, J = 11.8, 5.4 Hz, 2 H), 3.18 (dd, J = 11.8, 3.4 Hz, 2 H).

¹³C NMR (DMSO- d_6 , 75 MHz): δ = 137.8 (s), 126.5 (s), 125.1 (d), 121.8 (dx2), 117.1 (s), 114.7 (d), 114.3 (s), 51.5 (d), 49.9 (t).

HRFABMS: m/z calcd for $C_{20}H_{19}^{-79}Br_2N_4$ [M + H]⁺: 472.9976; found: 472.9968.

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