

Synthesis of Hexahydropyrazino[1,2-*b*]isoquinolines as Simplified Saframycin Analogues

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Abstract: Various hexahydropyrazino[1,2-*b*]isoquinolines were synthesised as simplified saframycin analogues. Construction of this core proceeded through a tetrahydroisoquinoline synthesis followed by acylation/alkylation of the tetrahydroisoquinoline nitrogen and subsequent ring closure using various aliphatic and aromatic amines. The resulting piperazinones were reacted with LiAlH_4 or $\text{LiAlH}(\text{OEt})_3$ to synthesise further analogues.

Key words: saframycins, piperazinones, diketopiperazines, cyclisation, tetrahydroisoquinolines

Saframycins **1**, isolated from *Streptomyces lavendulae*, belong to a family of microbial fermentation products with a remarkable antiproliferative activity. The most active derivative is saframycin A (**1a**), a bisquinone alkaloid bearing an α -aminonitrile function.² The mode of activity is connected to the iminium ions generated from this α -aminonitrile unit thus covalently modifying DNA. Quinoid alkaloids with antiproliferative activity such as the ecteinascidines,³ isolated from the marine tunicate *Ecteinascidia turbinata*, have raised new interest towards the synthesis of saframycin analogues.

Trabectedin (**2**; also known as ecteinascidin 743 or ET-743) is an antitumor drug approved for the treatment of advanced soft-tissue sarcoma. It is sold by Zeltia and Johnson & Johnson under the brand name Yondelis for the treatment of advanced soft-tissue sarcoma. Currently, simplified analogues such as phthalascidin (**3**) are known, bearing a similar activity⁴ (Figure 1).

All these compounds can be considered as dimers of structurally less complex tetrahydroisoquinoline subunits. Synthesis of this kind of simplified analogues has received little attention as most work focusses on total synthesis.⁵ Nevertheless, related piperazinones and diketopiperazines have been prepared before⁶ and pyrazino[1,2-*b*]isoquinolines have been examined for cytotoxicity.⁷ Therefore, the synthesis of quinone-type derivatives under their hydroquinone methyl ether form was envisaged.

We recently reported the synthesis of functionalised diketopiperazines as cyclotryprostatin and tryprostatin analogues.⁸ It was subsequently envisaged to apply this methodology to the synthesis of simplified saframycin

analogues. In initial studies, ethyl *N*-(diphenylmethylene)glycinate (**4**) failed to react with bromomethyl derivatives **5** (Na or KHMDS, -78°C or 0°C) but complete conversion was obtained upon reaction with KOH in $\text{H}_2\text{O}-\text{CH}_2\text{Cl}_2$ using Bu_4NHSO_4 as a phase-transfer catalyst. Tetrahydroisoquinoline **7a** was synthesised by means of a Pictet–Spengler reaction starting from 1-bromomethyl-2,5-dimethoxy-3,4-dimethylbenzene (**5a**)^{10a} via intermediate amine **6** in a yield of 76% over two steps. Tetrahydroisoquinolines **7b–d** were synthesised by reaction of bis(bromomethyl)benzene derivatives **5b–d**^{10b–e} with ethyl *N*-(diphenylmethylene)glycinate (**4**) under basic conditions followed by acid-induced ring closure in

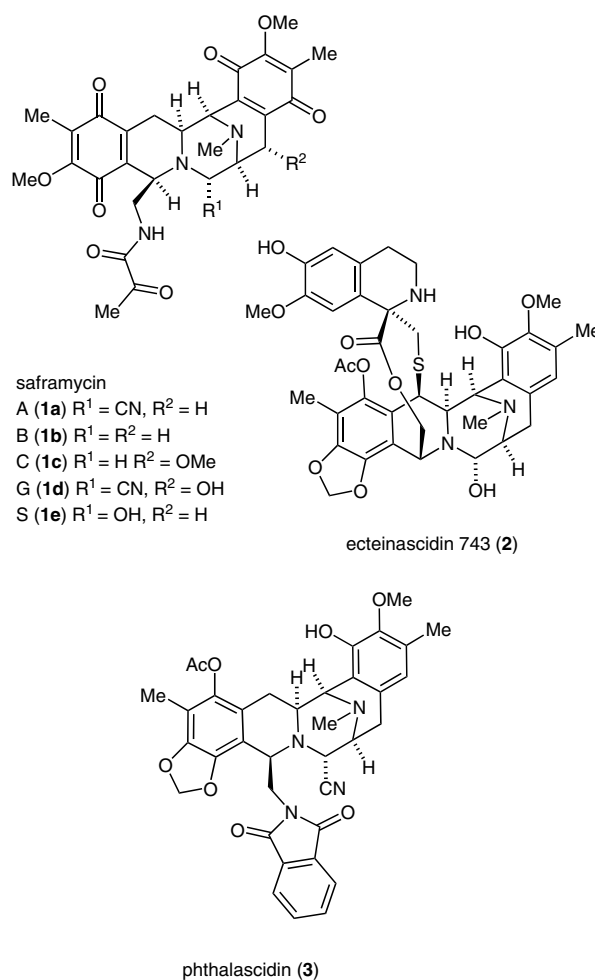
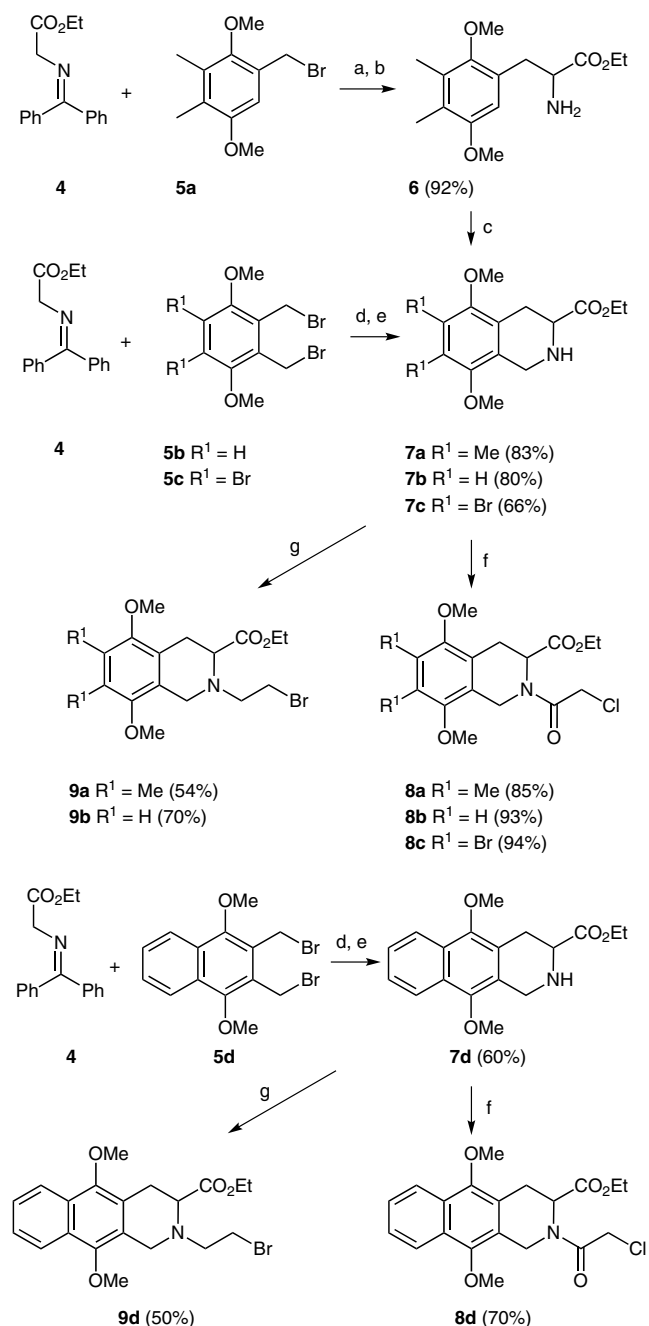


Figure 1 Examples of saframycins **1**, trabectedin (ecteinascidin 743, **2**), and the structurally related phthalascidin (**3**)

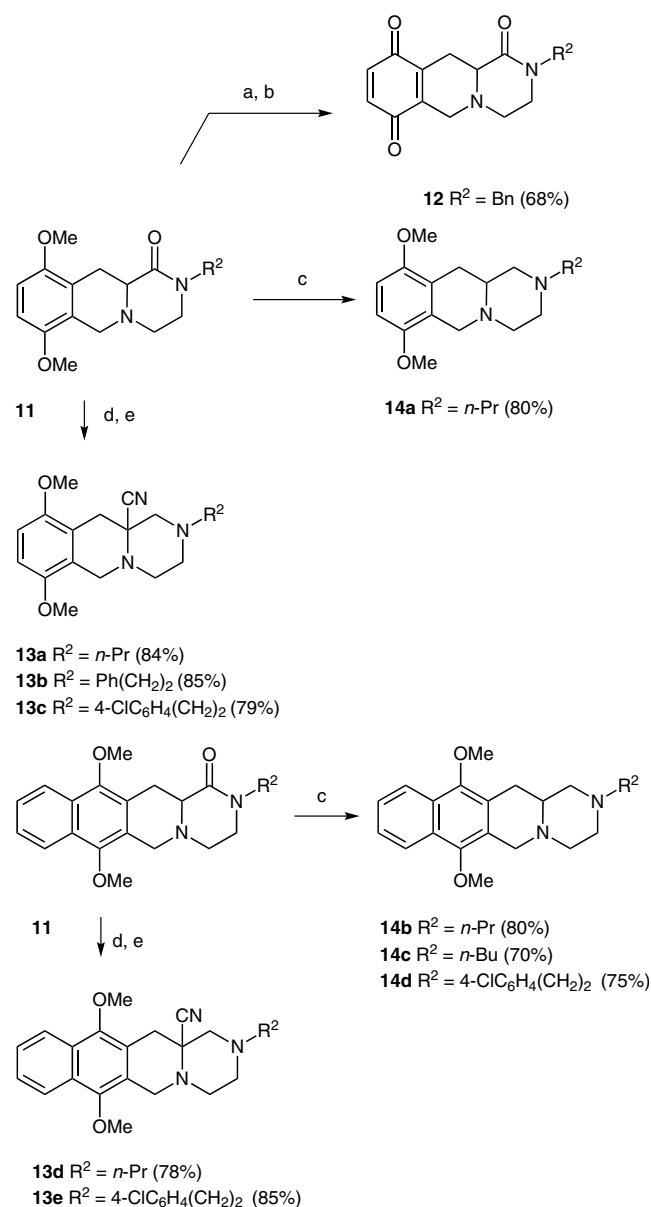
60–80% yields.¹¹ Next, the nitrogen atom was acylated with chloroacetyl chloride to afford *N*-chloroacetyl tetrahydroisoquinolines **8** in 50–70% yield¹² or alkylated with 1,2-dibromoethane to yield *N*-(2-bromoethyl)tetrahydroisoquinolines **9** in 70–94% yield¹³ (Scheme 1). Finally, *N*-chloroacetyl tetrahydroisoquinolines **8** were reacted with various primary amines in EtOH towards diketopiperazines **10** in good to excellent yields (Table 1).¹⁴



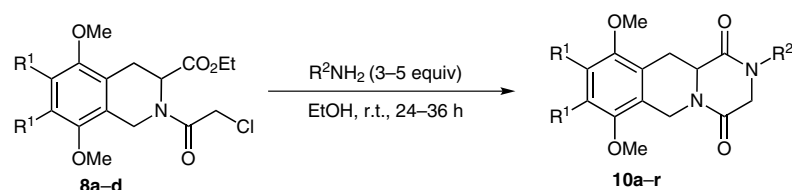
Scheme 1 Reagents and conditions: a) 30% aq KOH, Bu₄NHSO₄ (1 equiv), CH₂Cl₂, r.t., 12 h; b) HCl (2 M) THF, r.t., 15 h; c) 37% HCHO in H₂O (2 equiv), TFA (2 equiv), CH₂Cl₂, Δ, 2 h; d) 30% aq KOH, Bu₄NHSO₄ (1 equiv), CH₂Cl₂, r.t., 30 min; e) HCl (2 M) THF, r.t., 30 min; f) ClCH₂COCl (1.5 equiv), Et₃N (1.5 equiv), CH₂Cl₂, r.t., 2 h; g) BrCH₂CH₂Br (20 equiv), K₂CO₃ (1 equiv), neat, 80 °C, 24 h.

Starting from *N*-(2-bromoethyl)tetrahydroisoquinolines **9**, a range of piperazinones **11** was synthesised in high, albeit somewhat lower yields than diketopiperazines **10** (Table 2).¹⁵

The lactam function of piperazinones **11** was further reduced to create additional saframycin analogues. Reaction with LiAlH₄ resulted in complete reduction of the lactam moiety leading to piperazines **14** in 70–80% yield.¹⁶ Reaction with the less reactive LiAlH(OEt)₃ gave the hemiaminals, which were further converted into aminonitriles **13** with potassium cyanide and acetic acid.¹⁷ One piperazinone was demethylated with boron(III) bromide followed by oxidation with HNO₃ to yield quinone **12** (Scheme 2).¹⁸



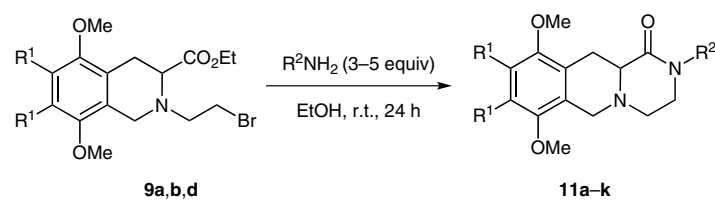
Scheme 2 Reagents and conditions: a) BBr₃ (2.1 equiv), –78 °C, 1 h, then 0 °C, 45 min; b) HNO₃ (10 M), r.t., 45 min; c) LiAlH₄ (4 equiv), Et₂O, r.t., 4 h; d) LiAlH(OEt)₃ (10 equiv), THF, 0 °C, 30 min; e) AcOH (40 equiv), KCN (6 equiv), H₂O, r.t., 3 h.

Table 1 Synthesis of Diketopiperazines **10**

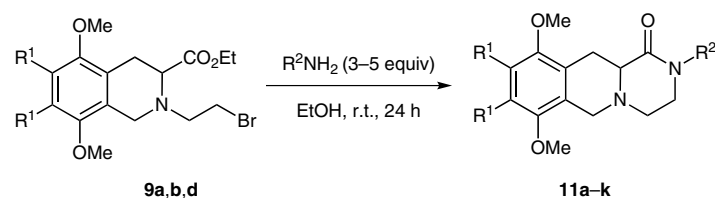
Compd	R ¹ , R ¹	R ²	Time (h)	Yield (%)
10a	Me, Me	<i>n</i> -Pr	24	87
10b	Me, Me	<i>n</i> -Bu	24	92
10c	Me, Me	Bn	24	73
10d	Me, Me	4-ClC ₆ H ₄ CH ₂	24	78
10e	Me, Me	Ph(CH ₂) ₂	24	86
10f	H, H	<i>n</i> -Pr	24	86
10g	H, H	<i>n</i> -Bu	24	82
10h	H, H	Bn	24	85
10i	H, H	4-ClC ₆ H ₄ CH ₂	24	77
10j	H, H	Ph(CH ₂) ₂	24	72
10k	Br, Br	<i>n</i> -Pr	36	98
10l	Br, Br	<i>n</i> -Bu	36	82
10m	Br, Br	Bn	36	86
10n	Br, Br	4-ClC ₆ H ₄ CH ₂	36	78
10o	Br, Br	Ph(CH ₂) ₂	36	79
10p	–HC=CH–CH=CH–	<i>n</i> -Pr	24	85
10q	–HC=CH–CH=CH–	Bn	24	81
10r	–HC=CH–CH=CH–	4-ClC ₆ H ₄ CH ₂	24	75

In summary, a library of hexahydropyrazino[1,2-*b*]isoquinolines has been synthesised as representative simplified saframycin analogues. Both piperazinones and diketopiperazines were synthesised. The piperazinones

were further reacted with LiAlH₄ to obtain piperazines or LiAlH(OEt)₃ and KCN to insert an α-aminonitrile function.

Table 2 Synthesis of Piperazinones **11**

Compd	R ¹ , R ¹	R ²	Yield (%)
11a	Me, Me	<i>n</i> -Pr	75
11b	H, H	<i>n</i> -Pr	79
11c	H, H	<i>n</i> -Bu	70
11d	H, H	Bn	59

Table 2 Synthesis of Piperazinones **11** (continued)

Compd	R ¹ , R ¹	R ²	Yield (%)
11e	H, H	4-ClC ₆ H ₄ CH ₂	65
11f	H, H	Ph(CH ₂) ₂	75
11g	H, H	4-ClC ₆ H ₄ (CH ₂) ₂	63
11h	H, H	2,5-(MeO) ₂ C ₆ H ₃ (CH ₂) ₂	74
11i	–HC=CH–CH=CH–	<i>n</i> -Pr	72
11j	–HC=CH–CH=CH–	<i>n</i> -Bu	70
11k	–HC=CH–CH=CH–	4-ClC ₆ H ₄ CH ₂	75

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- (11) **Ethyl 5,8-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7b)**
To a solution of ethyl *N*-(diphenylmethylene)glycinate (**4**, 801 mg, 3 mmol), freshly recrystallized 2,3-bis(bromomethyl)-1,4-dimethoxybenzene (**5b**, 972 mg, 3 mmol), and Bu₄NHSO₄ (1017 mg, 3 mmol) in CH₂Cl₂ (10 mL) was added an aq solution of KOH (30%, 5 mL). The reaction mixture was stirred at r.t. for 30 min. Next, the mixture was poured onto H₂O and exhaustively extracted with CH₂Cl₂. The combined organic phases were washed with sat. aq NaHCO₃, dried (MgSO₄), filtered, and evaporated in vacuo. To this crude residue was added THF (20 mL) and HCl (2 M, 20 mL). The reaction mixture was stirred at r.t. for 30 min and subsequently neutralized by treatment with a solution of aq Na₂CO₃ (2 M). Next, the solvent was evaporated in vacuo, and the residue was exhaustively extracted with EtOAc. The combined organic phases were washed with sat. aq NaHCO₃, dried (MgSO₄), filtered, and evaporated in vacuo. This crude mixture was purified column chromatography on silica (hexane–EtOAc) to obtain ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**7b**, 637 mg, 80%).
Note: In order to obtain a good yield, it is of utmost importance to use freshly recrystallized starting materials **4** and **5**.
Analytical Data
Colourless crystals; mp 90.5–91 °C. ¹H NMR (270 MHz, CDCl₃): δ = 1.31 (3 H, t, *J* = 7.0 Hz, Me), 1.63 (1 H, br s,

NH), 2.64 (1 H, dd, $J = 9.9$, 16.5 Hz, H-4a), 3.09 (1 H, dd, $J = 16.5$, 4.6 Hz, H-4b), 3.59 (1 H, dd, $J = 4.6$, 9.9 Hz, H-3), 3.76 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.80 (1 H, d, $J = 15.8$ Hz, H-1a), 3.84 (1 H, d, $J = 15.8$ Hz, H-1b), 4.19–4.27 (2 H, m, OCH₂), 6.60 (1 H, d, $J = 8.9$ Hz, H-6) 6.64 (1 H, d, $J = 8.9$ Hz, H-7). ¹³C NMR (68 MHz, CDCl₃): $\delta = 14.2$ (Me), 26.3 (C-4), 42.9 (C-1), 55.3 (C-3), 55.4 (OMe), 55.6 (OMe), 60.9 (OCH₂), 106.9 and 107.2 (C-6, C-7), 123.7 and 125.1 (C-5a, C-8a), 149.9 (=COMe), 151.2 (=COMe), 173.3 (C=O). IR (KBr): $\nu = 3250$ (NH), 2971, 2954, 2829, 1724 (C=O), 1605, 1484, 1464, 1438, 1260, 1225, 1182, 1091 cm⁻¹. MS: m/z (%) = 266 (100) [M + H⁺], 262 (20), 261 (20), 192 (20). HRMS (ES⁺): m/z calcd for [C₁₆H₂₂NO₄]⁺: 266.1392; found: 266.1396. Spectroscopic data are in accordance with literature data: Al-Horani, R. A.; Desai, U. R. *Tetrahedron* **2012**, *68*, 2027.

- (12) **Ethyl 2-(2-Chloroacetyl)-5,8-dimethoxy-6,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (8a)**
A mixture of ethyl 5,8-dimethoxy-6,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**7a**, 586 mg, 2 mmol) and Et₃N (222 mg, 2.2 mmol) in anhydrous CH₂Cl₂ (10 mL) was cooled to 0 °C and chloroacetyl chloride (264 mg, 2.2 mmol) was added dropwise. The reaction mixture was stirred at r.t. for 2 h. Then the mixture was poured onto H₂O and exhaustively extracted with CH₂Cl₂. The combined organic phases were washed with sat. NaHCO₃, dried (MgSO₄), filtered, and evaporated in vacuo. Purification by column chromatography on silica (hexane–EtOAc) gave pure ethyl 2-(2-chloroacetyl)-5,8-dimethoxy-6,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**8a**, 688 mg, 93%).

Analytical Data

¹H NMR (300 MHz, CDCl₃): $\delta = 1.15$ (3 H, t, $J = 6.9$ Hz, Me), 2.17 (6 H, s, 2 × Me), 2.90 (1 H, dd, $J = 5.9$, 16.5 Hz, H-4a), 3.47 (1 H, dd, $J = 3.0$, 16.5 Hz, H-4b), 3.65 (3 H, s, OMe), 3.68 (3 H, s, OMe), 4.00–4.17 (2 H, m, OCH₂), 4.24 (1 H, d, $J = 12.5$ Hz, H-1a), 4.29 (1 H, d, $J = 12.5$ Hz, H-1b), 4.73 (2 H, br s, 2 × H-2'), 5.46 (1 H, dd, $J = 3.0$, 5.9 Hz, H-3). ¹³C NMR (75 MHz, CDCl₃): $\delta = 12.51$ (Me), 12.54 (Me), 14.0 (OCH₂Me), 24.8 (C-4), 41.2 (C-2'), 41.4 (C-1), 51.3 (C-3), 60.4 (2 × OMe), 61.4 (OCH₂), 122.6 and 123.2 (C-5a, C-8a), 129.2 and 129.8 (C-6, C-7), 150.6 (=COMe), 152.0 (=COMe), 166.6 and 170.3 (2 × C=O). IR (NaCl): $\nu = 2942$, 2838, 1738 (C=O), 1732 (C=O), 1660, 1652, 1606, 1486, 1483, 1260, 1203, 1096 cm⁻¹. MS: m/z (%) = 370/372 (100) [M + H⁺], 324 (20), 296 (55), 294 (80), 266 (30), 220 (10). HRMS (ES⁺): m/z calcd for [C₁₈H₂₅³⁵ClNO₅]⁺: 372.1392; found: 372.1401.

- (13) **Ethyl 2-(2-Bromoethyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (9b)**
A mixture of tetrahydroisoquinoline **7b** (800 mg, 3.02 mmol), 1,2-dibromoethane (11.35 g, 60.4 mmol), and K₂CO₃ (417 mg, 3.02 mmol) was stirred at reflux for 24 h. Then, the mixture was poured onto H₂O and exhaustively extracted with EtOAc. The combined organic phases were washed with sat. NaHCO₃, dried (MgSO₄), filtered, and evaporated in vacuo. Purification chromatography on silica (hexane–EtOAc) gave pure ethyl 2-(2-bromoethyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**9b**, 786 mg, 70%).

Analytical Data

¹H NMR (300 MHz, CDCl₃): $\delta = 1.23$ (3 H, t, $J = 7.0$ Hz, Me), 2.95 (1 H, dd, $J = 6.3$, 17.3 Hz, H-4a), 3.08–3.18 (2 H, m, CH₂-1'), 3.20 (1 H, dd, $J = 6.1$, 17.3 Hz, H-4b), 3.50 (2 H, t, $J = 7.2$ Hz, CH₂-2'), 3.75 (3 H, s, OMe), 3.76 (3 H, s, OMe), 3.76 (1 H, dd, overlap, H-3), 3.85 (1 H, d, $J = 16.8$ Hz, H-1a), 3.96 (1 H, d, $J = 16.8$ Hz, H-1b), 4.07–4.18 (2 H,

m, OCH₂), 6.60 (1 H, d, $J = 9.1$ Hz, H-6), 6.62 (1 H, d, $J = 9.1$ Hz, H-7). ¹³C NMR (75 MHz, CDCl₃): $\delta = 14.4$ (Me), 25.8 (C-4), 30.3 (C-1'), 46.9 (C-1), 55.5 (OMe), 55.8 (OMe), 57.1 (CBr), 59.7 (C-3), 60.7 (OCH₂), 107.0 and 107.4 (C-6, C-7), 122.6 and 123.8 (C-5a, C-8a), 150.1 (=COMe), 151.2 (=COMe), 172.5 (C=O). IR (NaCl): $\nu = 2930$, 1731 (C=O), 1650, 1483, 1464, 1438, 1257, 1181, 1082 cm⁻¹. MS m/z (%) 372/374 (M+H⁺, 10), 310 (7), 393 (15), 392 (100). HRMS (ES⁺): m/z calcd for [C₂₀H₁₄NO₂]⁺: 300.1025; found: 300.1027.

- (14) **7,10-Dimethoxy-8,9-dimethyl-2-propyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-*b*]isoquinoline-1,4-dione (10a)**

A mixture of ethyl 2-(2-chloroacetyl)-5,8-dimethoxy-6,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**8a**, 184.5 mg, 0.5 mmol) and *n*-propylamine (132.5 mg, 2.5 mmol) in anhydrous EtOH (10 mL) was stirred for 24 h at r.t. Then, the mixture was poured onto H₂O and exhaustively extracted with EtOAc. The combined organic phases were washed, dried (MgSO₄), filtered, and evaporated in vacuo. Purification by chromatography on silica (hexane–EtOAc) gave pure 7,10-dimethoxy-8,9-dimethyl-2-propyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**10a**, 150 mg, 87%).

Analytical Data

White powder, mp 169–169.5 °C. ¹H NMR (270 MHz, CDCl₃): $\delta = 0.96$ (3 H, t, $J = 7.3$ Hz, H-3), 1.57–1.68 (2 H, m, 2 × H-2'), 2.18 (6 H, s, 2 × Me), 2.74 (1 H, dd, $J = 12.2$, 16.4 Hz, H-11a), 3.28–3.47 (2 H, m, H-1'a, H-1'b), 3.59 (1 H, dd, $J = 3.4$, 16.4 Hz, H-11b), 3.66 (3 H, s, OMe), 3.71 (3 H, s, OMe), 4.04 (2 H, s, H-3a, H-3b), 4.10 (1 H, d, $J = 17.5$ Hz, H-6a), 4.17 (1 H, dd, $J = 12.2$, 3.6 Hz, H-12), 5.40 (1 H, d, $J = 17.5$ Hz, H-6b). ¹³C NMR (68 MHz, CDCl₃): $\delta = 11.1$ (C-3'), 12.45 (Me), 12.54 (Me), 19.8 (C-2'), 28.5 (C-11), 40.1 (C-6), 47.6 (C-1'), 49.4 (C-3), 55.6 (C-12), 60.3 (2 × OMe), 122.9 and 123.9 (C-7a, C-10a), 129.3 and 129.5 (C-8, C-9), 151.0 (=COMe), 152.1 (=COMe), 162.3 (C=O), 165.0 (C=O). IR (KBr): $\nu = 2958$, 2834, 1661 (C=O), 1658 (C=O), 1479, 1465, 1334, 1260, 1274, 1086, 1061 cm⁻¹. MS: m/z (%) = 347 (30) [M + H], 345 (70), 314 (15), 218 (35), 191 (100), 176 (70), 124 (50), 83 (70). HRMS (ES⁺): m/z calcd for [C₁₉H₂₇N₂O₄]⁺: 347.1971; found: 347.1981.

- (15) **7,10-Dimethoxy-2-propyl-3,4,11,11a-tetrahydro-2H,6H-pyrazino[1,2-*b*]isoquinolin-1-one (11b)**

A mixture of ethyl 2-(2-bromoethyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**9b**) (186 mg, 0.5 mmol) and *n*-propylamine (132.5 mg, 2.5 mmol) in anhydrous EtOH (10 mL) was stirred for 24 h at r.t. Then, the mixture was poured onto H₂O and exhaustively extracted with EtOAc. The combined organic phases were washed, dried (MgSO₄), filtered, and evaporated in vacuo. Purification by chromatography on silica (hexane–EtOAc) gave pure 7,10-dimethoxy-2-propyl-3,4,11,11a-tetrahydro-2H,6H-pyrazino[1,2-*b*]isoquinolin-1-one (**11b**, 120 mg, 79%).

Analytical Data

¹H NMR (270 MHz, CDCl₃): $\delta = 0.91$ (3 H, t, $J = 7.3$ Hz, Me), 1.55–1.64 (2 H, m, CH₂-2'), 2.59–2.69 (2 H, m, H-11a, H-3a), 2.96 (1 H, dd, $J = 3.9$, 11.5 Hz, H-12), 3.09–3.29 (4 H, m, H-3b, H-4a, H-6a, H-1'a), 3.41–3.70 (3 H, m, H-4b, H-1'b, H-11b), 3.74 (3 H, s, OMe), 3.76 (3 H, s, OMe), 4.10 (1 H, d, $J = 15.5$ Hz, H-6b), 6.61 (1 H, d, $J = 8.1$ Hz, H-8), 6.63 (1 H, d, $J = 8.1$ Hz, H-9). ¹³C NMR (68 MHz, CDCl₃): $\delta = 11.2$ (Me), 20.2 (C-2'), 27.6 (C-11), 46.1 (C-4), 48.4 (C-1'), 50.4 (C-3), 53.2 (C-6), 55.6 (OMe), 55.7 (OMe), 61.5 (C-12), 107.1 and 107.7 (C-8, C-9), 123.4 and 124.7 (C-7a, C-10a), 149.7 (=COMe), 151.5 (=COMe), 168.6 (C=O). IR

(NaCl): $\nu = 2931, 1654$ (C=O), 1645, 1485, 1463, 1438, 1259, 1181, 1097 cm^{-1} . MS: m/z (%) = 305 (100) [M + H⁺], 301 (10), 227 (20). HRMS (ES⁺): m/z calcd for [C₁₇H₂₅N₂O₃]⁺: 305.1865; found: 305.1871.

(16) **7,10-Dimethoxy-2-propyl-1,3,4,6,11,11a-hexahydro-2H-pyrazino[1,2-*b*]isoquinoline (14a)**

To a solution of 7,10-dimethoxy-2-propyl-3,4,11,11a-tetrahydro-2H,6H-pyrazino[1,2-*b*]isoquinolin-1-one (**11b**, 100 mg, 0.33 mmol) in anhydrous Et₂O (5 mL) under a nitrogen atmosphere at 0 °C, was added LiAlH₄ (53 mg, 1.32 mmol) portionwise. The reaction mixture was stirred for 12 h at r.t. Afterwards, the mixture was poured onto H₂O and exhaustively extracted with Et₂O. The combined organic phases were washed, dried (MgSO₄), filtered, and evaporated in vacuo. Purification by chromatography on silica (hexane–EtOAc) gave pure 7,10-dimethoxy-2-propyl-1,3,4,6,11,11a-hexahydro-2H-pyrazino[1,2-*b*]isoquinoline (**14a**, 76 mg, 80%).

Analytical Data

Pale white solid; mp 105 °C. ¹H NMR (270 MHz, CDCl₃): $\delta = 0.92$ (3 H, t, $J = 7.3$ Hz, CH₃), 1.50–1.59 (2 H, m, CH₂-2'), 1.93 (1 H, dd, $J = 9.7, 11.0$ Hz, H-1a), 2.21–2.36 (3 H, m, overlap, H-3a, H-1'a, H-1'b), 2.41–2.53 (2 H, m, overlap, H-11a, H-4a), 2.79 (1 H, d, $J = 14.2$ Hz, H-11b), 2.95 (1 H, dd, $J = 2.3, 11$ Hz, H-1b), 3.01–3.09 (2 H, m, H-3b, H-4b), 3.13 (1 H, d, $J = 16.0$ Hz, H-6a), 3.77 (6 H, s, 2 × OMe), 4.06 (1 H, d, $J = 16.0$ Hz, H-6b), 6.62 (2 H, s, H-9, H-8). ¹³C NMR (68 MHz, CDCl₃): $\delta = 12.0$ (Me), 20.0 (C-2'), 28.2 (C-11), 52.1 (C-6), 53.2 (C-4), 54.6 (C-3), 55.6 (2 × OMe), 60.1 (C-1'), 60.7 (C-1), 76.6 (C-11a), 107.0 and 107.2 (C-8, C-9), 123.6 and 124.2 (C7a, C-10a), 149.8 (=COMe), 150.9 (=COMe). IR (ATR): $\nu = 2925, 1654, 1482, 1438, 1258, 1086, 1060, 810, 714$ cm^{-1} . MS: m/z (%) = 291 (100) [M + H⁺]. HRMS (ES⁺): m/z calcd for [C₁₇H₂₇N₂O₂]⁺: 291.2073; found: 291.2065.

(17) **7,10-Dimethoxy-2-propyl-1,2,3,4,6,11-hexahydro-pyrazino[1,2-*b*]isoquinoline-11a-carbonitrile (13a)**

To a mixture of fresh LiAlH₄ (40 mg, 1.0 mmol) in anhydrous Et₂O (5 mL) was added anhydrous EtOH (0.175 mL, 3.0 mmol) under a nitrogen atmosphere at 0 °C. After 90 min, a solution of **11a** (30 mg, 0.1 mmol) in anhydrous THF (5 mL) was added, and the reaction mixture was stirred at 0 °C for 30–50 min. Next, AcOH (0.226 mL, 4 mmol) was added. After 5 min, KCN (40 mg, 0.61 mmol) in H₂O was added dropwise (**CAUTION**: HCN formation!). The reaction mixture was stirred for 5 h at r.t., then the mixture was poured onto H₂O, neutralised with sat. aq NaHCO₃ solution and exhaustively extracted with EtOAc. The combined organic phases were washed, dried (MgSO₄), filtered, and evaporated in vacuo. Purification by chromatography on silica (hexane–EtOAc) gave pure 7,10-

dimethoxy-2-propyl-1,2,3,4,6,11-hexahydropyrazino[1,2-*b*]isoquinoline-11a-carbonitrile (**13a**, 26 mg, 84%).

Analytical Data

White powder; mp 128.5–129.3 °C. ¹H NMR (300 MHz, CDCl₃): $\delta = 0.94$ (3 H, t, $J = 7.3$ Hz, CH₃-3), 1.52–1.57 (2 H, m, 2 × H-2'), 2.11 (1 H, d, $J = 11.3$ Hz, H-1a), 2.27–2.38 (3 H, m, overlap, H-3a, H-1'a, H-1'b), 2.63–2.71 (2 H, m, overlap, H-11a, H-4a), 2.84–2.91 (2 H, m, overlap, H-3b, H-4b), 3.12 (1 H, d, $J = 17.0$ Hz, H-11b), 3.21 (1 H, d, $J = 11.3$ Hz, H-1b), 3.28 (1 H, d, $J = 16.8$ Hz, H-6a), 3.76 (3 H, s, OMe), 3.78 (3 H, s, OMe), 4.00 (1 H, $J = 16.8$ Hz, H-6b), 6.63 (2 H, s, H-9, H-8). ¹³C NMR (75 MHz, CDCl₃): $\delta = 11.7$ (Me), 19.8 (C-2'), 32.3 (C-11), 49.1 (C-6), 51.5 (C-4), 52.7 (C-3), 55.5 (2 × OMe), 56.7 (C-11a), 59.5 (C-1'), 61.7 (C-1), 107.5 and 107.6 (C-7, C-8), 117.5 (CN), 119.9 and 122.7 (C7a, C-10a), 149.6 (=COMe), 150.7 (=COMe). IR (KBr): $\nu = 2931, 2835, 2183$ (CN), 1652, 1607, 1486, 1463, 1456, 1259, 1172, 1080 cm^{-1} . MS: m/z (%) = 316 (15) [M + H⁺], 301 (15), 290 (25), 289 (100). HRMS (ES⁺): m/z calcd for [C₁₈H₂₆N₃O₂]⁺: 316.2025; found: 316.2025.

(18) **2-Benzyl-3,4,11,11a-tetrahydro-2H,6H-pyrazino[1,2-*b*]isoquinoline-1,7,10-trione (12)**

To a solution of 7,10-dimethoxy-2-benzyl-3,4,11,11a-tetrahydro-2H,6H-pyrazino[1,2-*b*]isoquinolin-1-one (**11d**, 176 mg, 0.5 mmol) in anhydrous CH₂Cl₂ (20 mL) was added dropwise BBr₃ (1035 mg, 1.05 mmol) under a nitrogen atmosphere at –78 °C. After 1 h, the reaction mixture was warmed to 0 °C and left for 30 min. Then, HNO₃ (10 M, 10 mL) was added to the reaction mixture and stirring was continued for 45 min. Next, the mixture was poured onto H₂O, neutralised with a sat. aq NaHCO₃ solution and exhaustively extracted with CH₂Cl₂. The combined organic phases were washed, dried (MgSO₄), filtered, and evaporated in vacuo. Purification by chromatography on silica (hexane–EtOAc) gave pure 2-benzyl-3,4,11,11a-tetrahydro-2H,6H-pyrazino[1,2-*b*]isoquinoline-1,7,10-trione (**12**, 110 mg, 68%).

Analytical Data

¹H NMR (270 MHz, CDCl₃): $\delta = 2.47$ –2.60 (1 H, m, H-11a), 2.64 (1 H, dt, $J = 3.6, 12.3$ Hz, H-3a), 3.02 (1 H, dd, $J = 4.1, 10.6$ Hz, H-12), 3.06–3.19 (3 H, m, overlap, H-4a, H-3b, H-6a), 3.33 (1 H, td, $J = 3.6, 19.8$ Hz, H-4b), 3.49 (1 H, dt, $J = 4.1, 11.2$ Hz, H-11b), 3.90 (1 H, dd, $J = 1.3, 19.8$ Hz, H-6b), 4.53 (1 H, d, $J = 14.5$ Hz, H-1'a), 4.73 (1 H, d, $J = 14.5$ Hz, H-1'b), 6.71 (1 H, d, $J = 10.2$ Hz, H-8), 6.76 (1 H, d, $J = 10.2$ Hz, H-9), 7.26–7.37 (5 H, m, 5 × =CH). ¹³C NMR (68 MHz, CDCl₃): $\delta = 26.4$ (C-11), 45.2 (C-4), 49.8 (C-3), 49.9 (C-1'), 51.5 (C-6), 60.4 (C-12), 127.7 (=CH), 128.1 (2 × =CH), 128.7 (2 × =CH), 136.0 (C-8), 136.3 (C_{quat}), 136.5 (C-9), 138.6 (C_{quat}), 140.4 (C_{quat}), 167.4 (C=O), 185.7 (C=O), 185.9 (C=O). IR (NaCl): $\nu = 2924, 1660$ (C=O), 1641 (C=O), 1496, 1453, 1352, 1311, 1250 cm^{-1} . MS: m/z (%) = 323 (5) [M + H⁺], 322 (20), 321 (100), 178 (7).

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