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 $LiAlH(OEt)_3$ to synthesise further analogues.

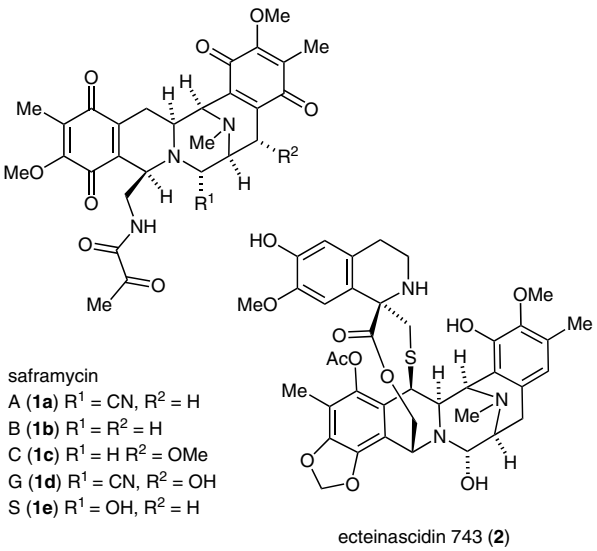
Key words: saframycins, piperazinones, diketopiperazines, cyclisation, tetrahydroisoquinolines

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 activity[4] (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 before[6] 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 methodlogy 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[9]) but complete conversion was obtained upon reaction with KOH in H_2O–CH_2Cl_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



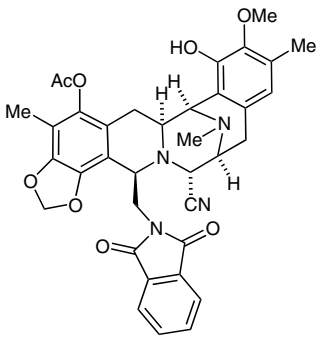


Figure 1 Examples of saframycins **1**, trabectedin (ecteinascidin 743, **2**), and the structurally related phthalascidin (**3**)

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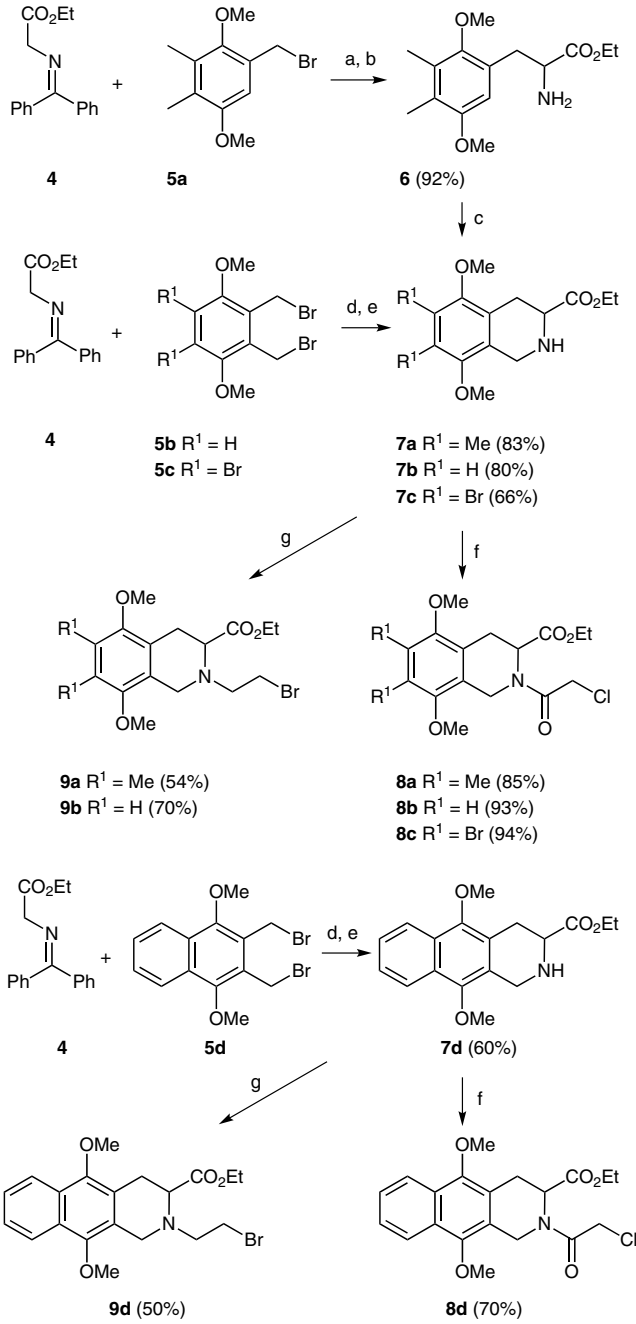
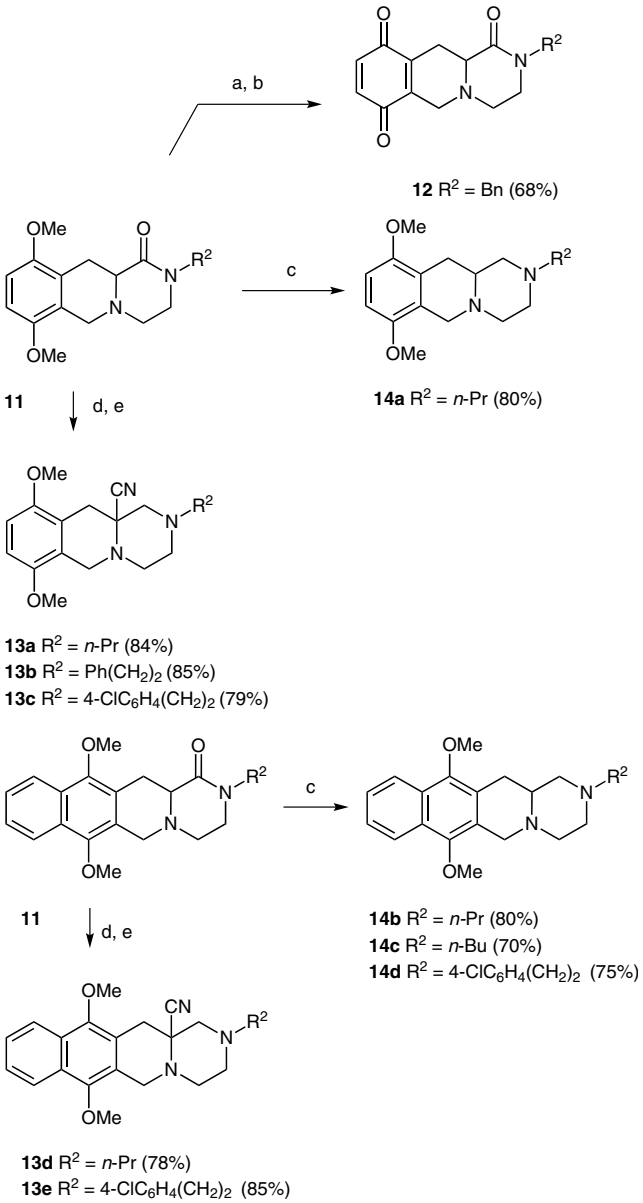
60–80% yields.[11] Next, the nitrogen atom was acylated with chloroacetyl chloride to afford *N*-chloroacetyl tetrahydroisoquinolines **8** in 50–70% yield[12] or alkylated with 1,2-dibromoethane to yield *N*-(2-bromoethyl)tetrahydroisoquinolines **9** in 70–94% yield[13] (Scheme 1). Finally, *N*-chloroacetyl 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, Bu_4NHSO_4 (1 equiv), CH_2Cl_2, r.t., 12 h; b) HCl (2 M) THF, r.t., 15 h; c) 37% HCHO in H_2O (2 equiv), TFA (2 equiv), CH_2Cl_2, Δ, 2 h; d) 30% aq KOH, Bu_4NHSO_4 (1 equiv), CH_2Cl_2, r.t., 30 min; e) HCl (2 M) THF, r.t., 30 min; f) $ClCH_2COCl$ (1.5 equiv), Et_3N (1.5 equiv), CH_2Cl_2, r.t., 2 h; g) $BrCH_2CH_2Br$ (20 equiv), K_2CO_3 (1 equiv), neat, 80 °C, 24 h.

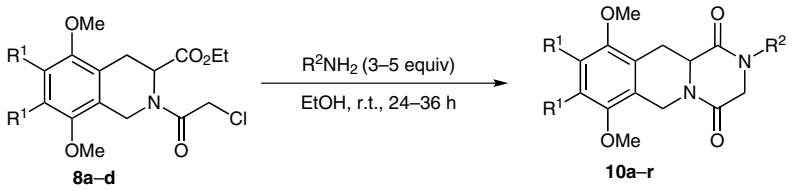
Starting from *N*-(2-bromoethyl)tetrahydroisoquinolines **9**, a range of piperazinones **11** was synthesised in high, albeit somewhat lower yields than diketopiperazines **10** (Table 2).[15]

The lactam function of piperazinones **11** was further reduced to create additional saframycin analogues. Reaction with $LiAlH_4$ 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 HNO_3 to yield quinone **12** (Scheme 2).[18]



Scheme 2 *Reagents and conditions*: a) BBr_3 (2.1 equiv), –78 °C, 1 h, then 0 °C, 45 min; b) HNO_3 (10 M), r.t., 45 min; c) $LiAlH_4$ (4 equiv), Et_2O, r.t., 4 h; d) $LiAlH(OEt)_3$ (10 equiv), THF, 0 °C, 30 min; e) AcOH (40 equiv), KCN (6 equiv), H_2O, r.t., 3 h.

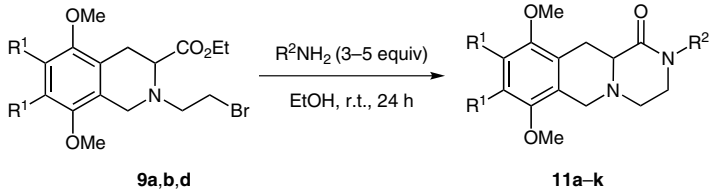
Table 1 Synthesis of Diketopiperazines **10**



Compd	R^1, R^1	R^2	Time (h)	Yield (%)
10a	Me, Me	*n*-Pr	24	87
10b	Me, Me	*n*-Bu	24	92
10c	Me, Me	Bn	24	73
10d	Me, Me	4-$ClC_6H_4CH_2$	24	78
10e	Me, Me	$Ph(CH_2)_2$	24	86
10f	H, H	*n*-Pr	24	86
10g	H, H	*n*-Bu	24	82
10h	H, H	Bn	24	85
10i	H, H	4-$ClC_6H_4CH_2$	24	77
10j	H, H	$Ph(CH_2)_2$	24	72
10k	Br, Br	*n*-Pr	36	98
10l	Br, Br	*n*-Bu	36	82
10m	Br, Br	Bn	36	86
10n	Br, Br	4-$ClC_6H_4CH_2$	36	78
10o	Br, Br	$Ph(CH_2)_2$	36	79
10p	–HC=CH–CH=CH–	*n*-Pr	24	85
10q	–HC=CH–CH=CH–	Bn	24	81
10r	–HC=CH–CH=CH–	4-$ClC_6H_4CH_2$	24	75

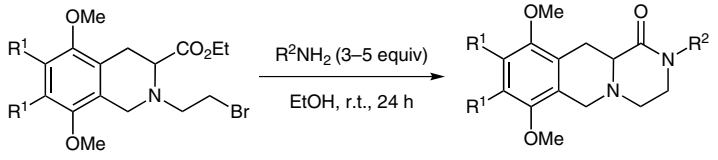
In summary, a library of hexahydropyrazino[1,2-*b*]isoquinolines has been synthesised as representative simplified saframycin analogues. Both piperazinones and diketopiperazines were synthesised. The piperazinones were further reacted with $LiAlH_4$ to obtain piperazines or $LiAlH(OEt)_3$ and KCN to insert an α-aminonitrile function.

Table 2 Synthesis of Piperazinones **11**



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

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



9a,**b**,**d** **11a–k**

Compd	R^1, R^1	R^2	Yield (%)
11e	H, H	4-$ClC_6H_4CH_2$	65
11f	H, H	$Ph(CH_2)_2$	75
11g	H, H	4-$ClC_6H_4(CH_2)_2$	63
11h	H, H	2,5-$(MeO)_2C_6H_3(CH_2)_2$	74
11i	–HC=CH–CH=CH–	*n*-Pr	72
11j	–HC=CH–CH=CH–	*n*-Bu	70
11k	–HC=CH–CH=CH–	4-$ClC_6H_4CH_2$	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-bisbromomethyl-1,4-dimethoxybenzene (**5b**, 972 mg, 3 mmol), and Bu_4NHSO_4 (1017 mg, 3 mmol) in CH_2Cl_2 (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 H_2O and exhaustively extracted with CH_2Cl_2. The combined organic phases were washed with sat. aq $NaHCO_3$, dried ($MgSO_4$), 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 Na_2CO_3 (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 $NaHCO_3$, dried ($MgSO_4$), 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. ^{1}H NMR (270 MHz, $CDCl_3$): 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, OCH_2), 6.60 (1 H, d, *J* = 8.9 Hz, H-6) 6.64 (1 H, d, *J* = 8.9 Hz, H-7). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 14.2 (Me), 26.3 (C-4), 42.9 (C-1), 55.3 (C-3), 55.4 (OMe), 55.6 (OMe), 60.9 (OCH_2), 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): ν = 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 $[C_{16}H_{22}NO_4]^+$: 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 Et_3N (222 mg, 2.2 mmol) in anhydrous CH_2Cl_2 (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 H_2O and exhaustively extracted with CH_2Cl_2. The combined organic phases were washed with sat. $NaHCO_3$, dried ($MgSO_4$), 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

^{1}H NMR (300 MHz, $CDCl_3$): δ = 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, OCH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.51 (Me), 12.54 (Me), 14.0 (OCH_2Me), 24.8 (C-4), 41.2 (C-2′), 41.4 (C-1), 51.3 (C-3), 60.4 (2 × OMe), 61.4 (OCH_2), 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): ν = 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 $[C_{18}H_{25}{}^{35}ClNO_5]^+$: 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 K_2CO_3 (417 mg, 3.02 mmol) was stirred at reflux for 24 h. Then, the mixture was poured onto H_2O and exhaustively extracted with EtOAc. The combined organic phases were washed with sat. $NaHCO_3$, dried ($MgSO_4$), 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

^{1}H NMR (300 MHz, $CDCl_3$): δ = 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, CH_2-1′), 3.20 (1 H, dd, *J* = 6.1, 17.3 Hz, H-4b), 3.50 (2 H, t, *J* = 7.2 Hz, CH_2-2′), 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, OCH_2), 6.60 (1 H, d, *J* = 9.1 Hz, H-6), 6.62 (1 H, d, *J* = 9.1 Hz, H-7). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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 (OCH_2), 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): ν = 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 $[C_{20}H_{14}NO_2]^+$: 300.1025; found: 300.1027.

(14) **7,10-Dimethoxy-8,9-dimethyl-2-propyl-2,3,11,11a-tetrahydro-6*H*-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 H_2O and exhaustively extracted with EtOAc. The combined organic phases were washed, dried ($MgSO_4$), 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-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**10a**, 150 mg, 87%).

Analytical Data

White powder, mp 169–169.5 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 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). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 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): ν = 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 $[C_{19}H_{27}N_2O_4]^+$: 347.1971; found: 347.1981.

(15) **7,10-Dimethoxy-2-propyl-3,4,11,11a-tetrahydro-2*H*,6*H*-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 H_2O and exhaustively extracted with EtOAc. The combined organic phases were washed, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by chromatography on silica (hexane–EtOAc) gave pure 7,10-dimethoxy-2-propyl-3,4,11,11a-tetrahydro-2*H*,6*H*-pyrazino[1,2-*b*]isoquinolin-1-one (**11b**, 120 mg, 79%).

Analytical Data

^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.91 (3 H, t, *J* = 7.3 Hz, Me), 1.55–1.64 (2 H, m, CH_2-2′), 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). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 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): ν = 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 $[C_{17}H_{25}N_2O_3]^+$: 305.1865; found: 305.1871.

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

To a solution of 7,10-dimethoxy-2-propyl-3,4,11,11a-tetrahydro-2*H*,6*H*-pyrazino[1,2-*b*]isoquinolin-1-one (**11b**, 100 mg, 0.33 mmol) in anhydrous Et_2O (5 mL) under a nitrogen atmosphere at 0 °C, was added $LiAlH_4$ (53 mg, 1.32 mmol) portionwise. The reaction mixture was stirred for 12 h at r.t. Afterwards, the mixture was poured onto H_2O and exhaustively extracted with Et_2O. The combined organic phases were washed, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by chromatography on silica (hexane–EtOAc) gave pure 7,10-dimethoxy-2-propyl-1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline (**14a**, 76 mg, 80%).

Analytical Data

Pale white solid; mp 105 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.92 (3 H, t, *J* = 7.3 Hz, CH_3), 1.50–1.59 (2 H, m, CH_2-2′), 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). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 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): ν = 2925, 1654, 1482, 1438, 1258, 1086, 1060, 810, 714 cm^{-1}. MS: *m/z* (%) = 291 (100) [M + H^+]. HRMS (ES^+): *m/z* calcd for $[C_{17}H_{27}N_2O_2]^+$: 291.2073; found: 291.2065.

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

To a mixture of fresh $LiAlH_4$ (40 mg, 1.0 mmol) in anhydrous Et_2O (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 H_2O was added dropwise (**CAUTION:** HCN formation!). The reaction mixture was stirred for 5 h at r.t., then the mixture was poured onto H_2O, neutralised with sat. aq $NaHCO_3$ solution and exhaustively extracted with EtOAc. The combined organic phases were washed, dried ($MgSO_4$), 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. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (3 H, t, *J* = 7.3 Hz, CH_3-3), 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). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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): ν = 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 $[C_{18}H_{26}N_3O_2]^+$: 316.2025; found: 316.2025.

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

To a solution of 7,10-dimethoxy-2-benzyl-3,4,11,11a-tetrahydro-2*H*,6*H*-pyrazino[1,2-b]isoquinolin-1-one (**11d**, 176 mg, 0.5 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise BBr_3 (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, HNO_3 (10 M, 10 mL) was added to the reaction mixture and stirring was continued for 45 min. Next, the mixture was poured onto H_2O, neutralised with a sat. aq $NaHCO_3$ solution and exhaustively extracted with CH_2Cl_2. The combined organic phases were washed, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by chromatography on silica (hexane–EtOAc) gave pure 2-benzyl-3,4,11,11a-tetrahydro-2*H*,6*H*-pyrazino[1,2-*b*]isoquinoline-1,7,10-trione (**12**, 110 mg, 68%).

Analytical Data

^{1}H NMR (270 MHz, $CDCl_3$): δ = 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). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 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): ν = 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).

