

# 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<sub>4</sub> or LiAlH(OEt)<sub>3</sub> to synthesise further analogues.

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

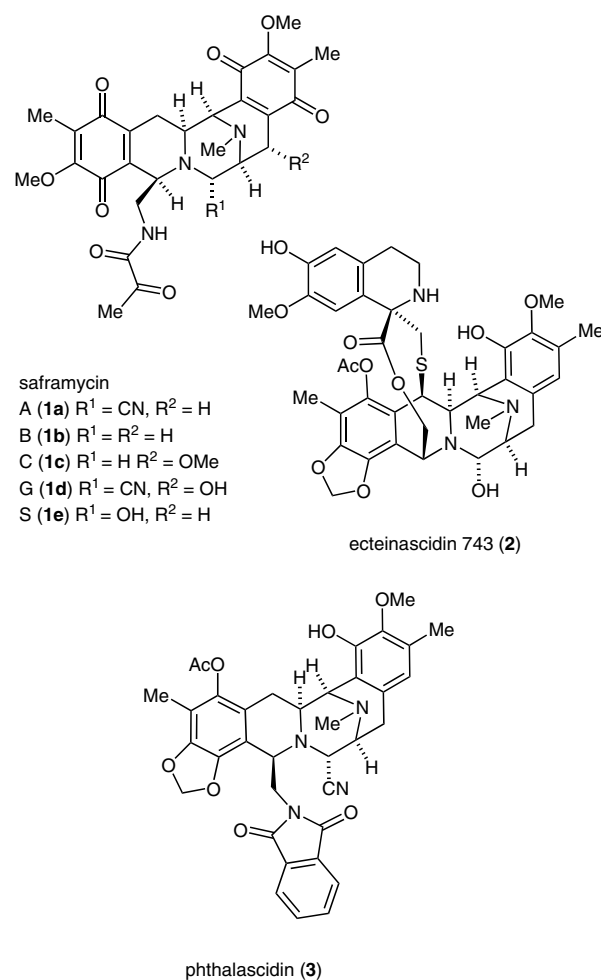
Saframycins **1**, isolated from *Streptomyces lavendulae*, belong to a family of microbial fermentation products with a remarkable antiproliferative activity. The most active derivative is saframycin A (**1a**), a bisquinone alkaloid bearing an  $\alpha$ -aminonitrile function.<sup>2</sup> The mode of activity is connected to the iminium ions generated from this  $\alpha$ -aminonitrile unit thus covalently modifying DNA. Quinoid alkaloids with antiproliferative activity such as the ecteinascidines,<sup>3</sup> 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<sup>4</sup> (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.<sup>5</sup> Nevertheless, related piperazinones and diketopiperazines have been prepared before<sup>6</sup> and pyrazino[1,2-*b*]isoquinolines have been examined for cytotoxicity.<sup>7</sup> 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.<sup>8</sup> 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<sup>9</sup>) but complete conversion was obtained upon reaction with KOH in H<sub>2</sub>O–CH<sub>2</sub>Cl<sub>2</sub> using Bu<sub>4</sub>NHSO<sub>4</sub> 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**)<sup>10a</sup> 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**<sup>10b–e</sup> 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**)

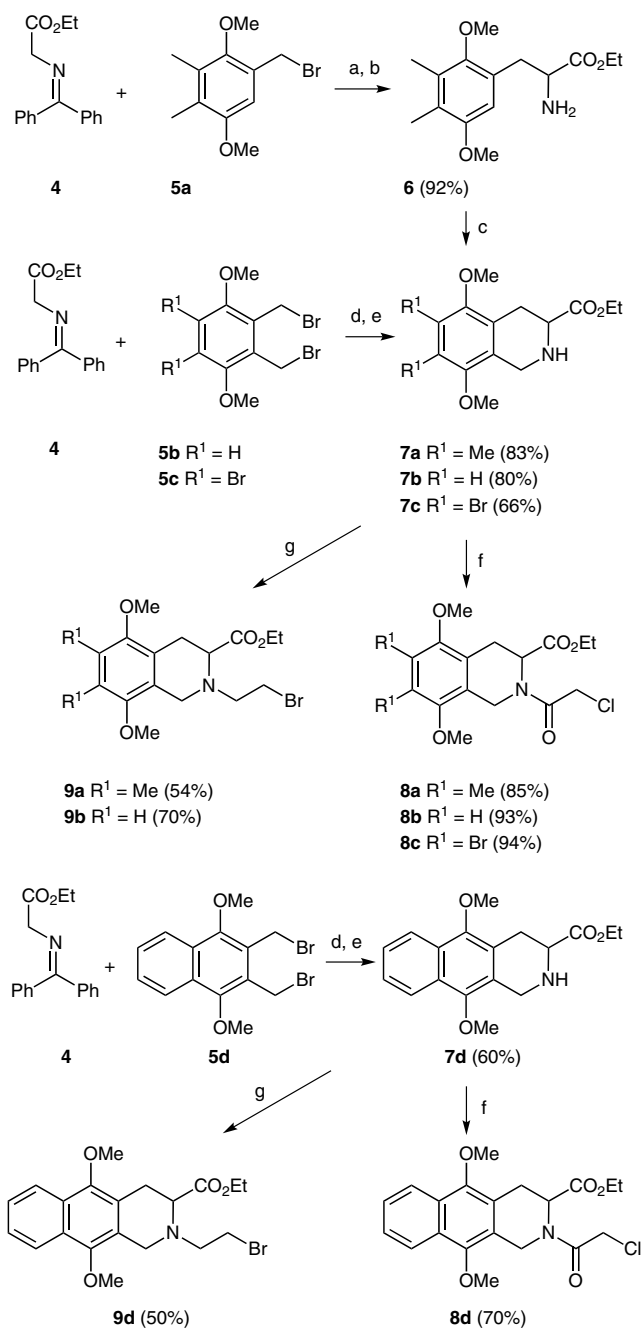
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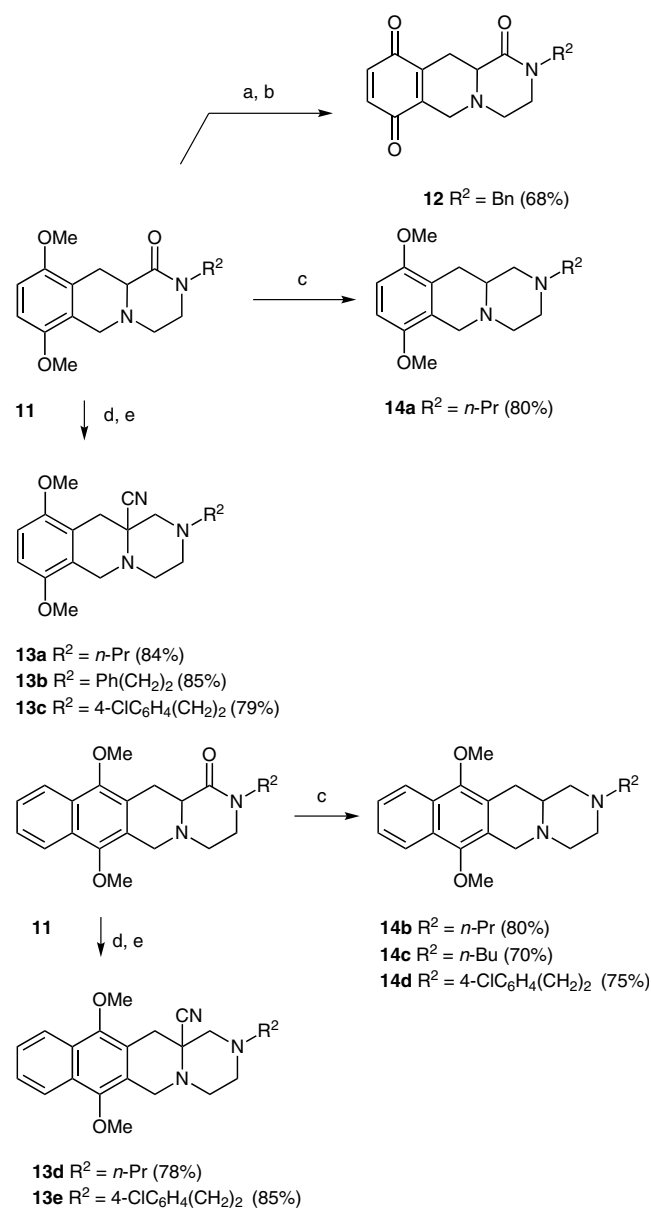
60–80% yields.<sup>11</sup> Next, the nitrogen atom was acylated with chloroacetyl chloride to afford *N*-chloroacetyl tetrahydroisoquinolines **8** in 50–70% yield<sup>12</sup> or alkylated with 1,2-dibromoethane to yield *N*-(2-bromoethyl)tetrahydroisoquinolines **9** in 70–94% yield<sup>13</sup> (Scheme 1). Finally, *N*-chloroacetyl tetrahydroisoquinolines **8** were reacted with various primary amines in EtOH towards diketopiperazines **10** in good to excellent yields (Table 1).<sup>14</sup>



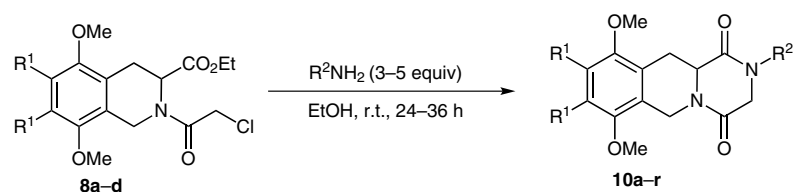
**Scheme 1** Reagents and conditions: a) 30% aq KOH,  $\text{Bu}_4\text{NHSO}_4$  (1 equiv),  $\text{CH}_2\text{Cl}_2$ , r.t., 12 h; b) HCl (2 M) THF, r.t., 15 h; c) 37% HCHO in  $\text{H}_2\text{O}$  (2 equiv), TFA (2 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $\Delta$ , 2 h; d) 30% aq KOH,  $\text{Bu}_4\text{NHSO}_4$  (1 equiv),  $\text{CH}_2\text{Cl}_2$ , r.t., 30 min; e) HCl (2 M) THF, r.t., 30 min; f)  $\text{ClCH}_2\text{COCl}$  (1.5 equiv),  $\text{Et}_3\text{N}$  (1.5 equiv),  $\text{CH}_2\text{Cl}_2$ , r.t., 2 h; g)  $\text{BrCH}_2\text{CH}_2\text{Br}$  (20 equiv),  $\text{K}_2\text{CO}_3$  (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).<sup>15</sup>

The lactam function of piperazinones **11** was further reduced to create additional saframycin analogues. Reaction with  $\text{LiAlH}_4$  resulted in complete reduction of the lactam moiety leading to piperazines **14** in 70–80% yield.<sup>16</sup> Reaction with the less reactive  $\text{LiAlH}(\text{OEt})_3$  gave the hemiaminals, which were further converted into aminonitriles **13** with potassium cyanide and acetic acid.<sup>17</sup> One piperazinone was demethylated with boron(III) bromide followed by oxidation with  $\text{HNO}_3$  to yield quinone **12** (Scheme 2).<sup>18</sup>



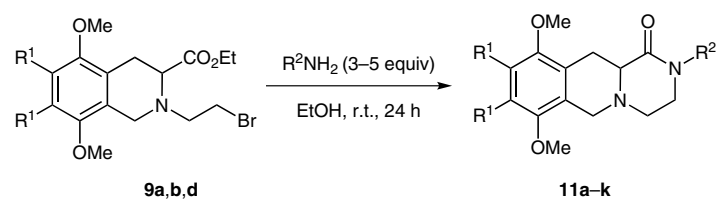
**Scheme 2** Reagents and conditions: a)  $\text{BBr}_3$  (2.1 equiv),  $-78^\circ\text{C}$ , 1 h, then  $0^\circ\text{C}$ , 45 min; b)  $\text{HNO}_3$  (10 M), r.t., 45 min; c)  $\text{LiAlH}_4$  (4 equiv),  $\text{Et}_2\text{O}$ , r.t., 4 h; d)  $\text{LiAlH}(\text{OEt})_3$  (10 equiv), THF,  $0^\circ\text{C}$ , 30 min; e)  $\text{AcOH}$  (40 equiv), KCN (6 equiv),  $\text{H}_2\text{O}$ , r.t., 3 h.

**Table 1** Synthesis of Diketopiperazines **10**

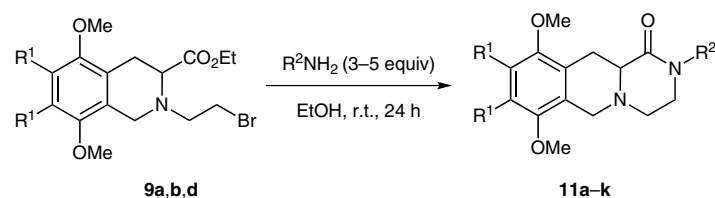
Compd	R <sup>1</sup> , R <sup>1</sup>	R <sup>2</sup>	Time (h)	Yield (%)
<b>10a</b>	Me, Me	<i>n</i> -Pr	24	87
<b>10b</b>	Me, Me	<i>n</i> -Bu	24	92
<b>10c</b>	Me, Me	Bn	24	73
<b>10d</b>	Me, Me	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	24	78
<b>10e</b>	Me, Me	Ph(CH <sub>2</sub> ) <sub>2</sub>	24	86
<b>10f</b>	H, H	<i>n</i> -Pr	24	86
<b>10g</b>	H, H	<i>n</i> -Bu	24	82
<b>10h</b>	H, H	Bn	24	85
<b>10i</b>	H, H	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	24	77
<b>10j</b>	H, H	Ph(CH <sub>2</sub> ) <sub>2</sub>	24	72
<b>10k</b>	Br, Br	<i>n</i> -Pr	36	98
<b>10l</b>	Br, Br	<i>n</i> -Bu	36	82
<b>10m</b>	Br, Br	Bn	36	86
<b>10n</b>	Br, Br	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	36	78
<b>10o</b>	Br, Br	Ph(CH <sub>2</sub> ) <sub>2</sub>	36	79
<b>10p</b>	–HC=CH–CH=CH–	<i>n</i> -Pr	24	85
<b>10q</b>	–HC=CH–CH=CH–	Bn	24	81
<b>10r</b>	–HC=CH–CH=CH–	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	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<sub>4</sub> to obtain piperazines or LiAlH(OEt)<sub>3</sub> and KCN to insert an α-aminonitrile function.

**Table 2** Synthesis of Piperazinones **11**

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

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

Compd	R <sup>1</sup> , R <sup>1</sup>	R <sup>2</sup>	Yield (%)
<b>11e</b>	H, H	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	65
<b>11f</b>	H, H	Ph(CH <sub>2</sub> ) <sub>2</sub>	75
<b>11g</b>	H, H	4-ClC <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub>	63
<b>11h</b>	H, H	2,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub>	74
<b>11i</b>	–HC=CH–CH=CH–	<i>n</i> -Pr	72
<b>11j</b>	–HC=CH–CH=CH–	<i>n</i> -Bu	70
<b>11k</b>	–HC=CH–CH=CH–	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	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-bisbromo-methyl-1,4-dimethoxybenzene (**5b**, 972 mg, 3 mmol), and Bu<sub>4</sub>NHSO<sub>4</sub> (1017 mg, 3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>O and exhaustively extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with sat. aq NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>), 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<sub>2</sub>CO<sub>3</sub> (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<sub>3</sub>, dried (MgSO<sub>4</sub>), 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. <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 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<sub>2</sub>), 6.60 (1 H, d,  $J = 8.9$  Hz, H-6) 6.64 (1 H, d,  $J = 8.9$  Hz, H-7). <sup>13</sup>C NMR (68 MHz, CDCl<sub>3</sub>):  $\delta = 14.2$  (Me), 26.3 (C-4), 42.9 (C-1), 55.3 (C-3), 55.4 (OMe), 55.6 (OMe), 60.9 (OCH<sub>2</sub>), 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<sup>-1</sup>. MS:  $m/z$  (%) = 266 (100) [M + H<sup>+</sup>], 262 (20), 261 (20), 192 (20). HRMS (ES<sup>+</sup>):  $m/z$  calcd for [C<sub>16</sub>H<sub>22</sub>NO<sub>4</sub>]<sup>+</sup>: 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<sub>3</sub>N (222 mg, 2.2 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>O and exhaustively extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with sat. NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>), 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**

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.15$  (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, OCH<sub>2</sub>), 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). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 12.51$  (Me), 12.54 (Me), 14.0 (OCH<sub>2</sub>Me), 24.8 (C-4), 41.2 (C-2'), 41.4 (C-1), 51.3 (C-3), 60.4 (2 × OMe), 61.4 (OCH<sub>2</sub>), 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<sup>-1</sup>. MS:  $m/z$  (%) = 370/372 (100) [M + H<sup>+</sup>], 324 (20), 296 (55), 294 (80), 266 (30), 220 (10). HRMS (ES<sup>+</sup>):  $m/z$  calcd for [C<sub>18</sub>H<sub>25</sub><sup>35</sup>ClNO<sub>5</sub>]<sup>+</sup>: 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<sub>2</sub>CO<sub>3</sub> (417 mg, 3.02 mmol) was stirred at reflux for 24 h. Then, the mixture was poured onto H<sub>2</sub>O and exhaustively extracted with EtOAc. The combined organic phases were washed with sat. NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>), 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**

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.23$  (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, CH<sub>2</sub>-1'), 3.20 (1 H, dd,  $J = 6.1$ , 17.3 Hz, H-4b), 3.50 (2 H, t,  $J = 7.2$  Hz, CH<sub>2</sub>-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<sub>2</sub>), 6.60 (1 H, d,  $J = 9.1$  Hz, H-6), 6.62 (1 H, d,  $J = 9.1$  Hz, H-7). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 14.4$  (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 (OCH<sub>2</sub>), 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<sup>-1</sup>. MS  $m/z$  (%) 372/374 (M+H<sup>+</sup>, 10), 310 (7), 393 (15), 392 (100). HRMS (ES<sup>+</sup>):  $m/z$  calcd for [C<sub>20</sub>H<sub>14</sub>NO<sub>2</sub>]<sup>+</sup>: 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 H<sub>2</sub>O and exhaustively extracted with EtOAc. The combined organic phases were washed, dried (MgSO<sub>4</sub>), 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. <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta = 0.96$  (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). <sup>13</sup>C NMR (68 MHz, CDCl<sub>3</sub>):  $\delta = 11.1$  (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<sup>-1</sup>. MS:  $m/z$  (%) = 347 (30) [M + H], 345 (70), 314 (15), 218 (35), 191 (100), 176 (70), 124 (50), 83 (70). HRMS (ES<sup>+</sup>):  $m/z$  calcd for [C<sub>19</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>]<sup>+</sup>: 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 H<sub>2</sub>O and exhaustively extracted with EtOAc. The combined organic phases were washed, dried (MgSO<sub>4</sub>), 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**

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta = 0.91$  (3 H, t,  $J = 7.3$  Hz, Me), 1.55–1.64 (2 H, m, CH<sub>2</sub>-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). <sup>13</sup>C NMR (68 MHz, CDCl<sub>3</sub>):  $\delta = 11.2$  (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  $\text{cm}^{-1}$ . MS:  $m/z$  (%) = 305 (100) [M + H<sup>+</sup>], 301 (10), 227 (20). HRMS (ES<sup>+</sup>):  $m/z$  calcd for [C<sub>17</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub>]<sup>+</sup>: 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 Et<sub>2</sub>O (5 mL) under a nitrogen atmosphere at 0 °C, was added LiAlH<sub>4</sub> (53 mg, 1.32 mmol) portionwise. The reaction mixture was stirred for 12 h at r.t. Afterwards, the mixture was poured onto H<sub>2</sub>O and exhaustively extracted with Et<sub>2</sub>O. The combined organic phases were washed, dried (MgSO<sub>4</sub>), 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. <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta = 0.92$  (3 H, t,  $J = 7.3$  Hz, CH<sub>3</sub>), 1.50–1.59 (2 H, m, CH<sub>2</sub>-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). <sup>13</sup>C NMR (68 MHz, CDCl<sub>3</sub>):  $\delta = 12.0$  (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):  $\nu = 2925, 1654, 1482, 1438, 1258, 1086, 1060, 810, 714$   $\text{cm}^{-1}$ . MS:  $m/z$  (%) = 291 (100) [M + H<sup>+</sup>]. HRMS (ES<sup>+</sup>):  $m/z$  calcd for [C<sub>17</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>]<sup>+</sup>: 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 LiAlH<sub>4</sub> (40 mg, 1.0 mmol) in anhydrous Et<sub>2</sub>O (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<sub>2</sub>O was added dropwise (**CAUTION**: HCN formation!). The reaction mixture was stirred for 5 h at r.t., then the mixture was poured onto H<sub>2</sub>O, neutralised with sat. aq NaHCO<sub>3</sub> solution and exhaustively extracted with EtOAc. The combined organic phases were washed, dried (MgSO<sub>4</sub>), 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. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 0.94$  (3 H, t,  $J = 7.3$  Hz, CH<sub>3</sub>-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). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 11.7$  (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  $\text{cm}^{-1}$ . MS:  $m/z$  (%) = 316 (15) [M + H<sup>+</sup>], 301 (15), 290 (25), 289 (100). HRMS (ES<sup>+</sup>):  $m/z$  calcd for [C<sub>18</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub>]<sup>+</sup>: 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 CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added dropwise BBr<sub>3</sub> (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<sub>3</sub> (10 M, 10 mL) was added to the reaction mixture and stirring was continued for 45 min. Next, the mixture was poured onto H<sub>2</sub>O, neutralised with a sat. aq NaHCO<sub>3</sub> solution and exhaustively extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed, dried (MgSO<sub>4</sub>), 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**

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta = 2.47$ –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). <sup>13</sup>C NMR (68 MHz, CDCl<sub>3</sub>):  $\delta = 26.4$  (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<sub>quat</sub>), 136.5 (C-9), 138.6 (C<sub>quat</sub>), 140.4 (C<sub>quat</sub>), 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  $\text{cm}^{-1}$ . MS:  $m/z$  (%) = 323 (5) [M + H<sup>+</sup>], 322 (20), 321 (100), 178 (7).