

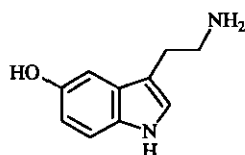
**SYNTHESIS AND SEROTONERGIC ACTIVITY OF 8-[4-(2,3-DIHYDRO-1,4-DIOXINO[2,3-*b*]PYRIDIN-2-YL-METHYLAMINO)BUTYL]-8-AZASPIRO[4.5]DECANE-7,9-DIONE**

**Abdelhakim Benarab and Gerald Guillaumet\***

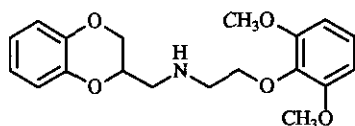
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**Abstract** - The synthesis of compound (**9**), a nitrogen-containing bioisostere of the 1,4-benzodioxane moiety of the MDL 72832, is detailed. This compound showed a moderate affinity for the 5-HT<sub>1A</sub> receptors.

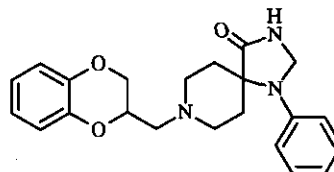
Serotonin (5-hydroxytryptamine, 5-HT) research has continued at a rapid pace. Never before has a single neurotransmitter been implicated in the ethiology or treatment of so many medical problems. These include anxiety, depression, obsessive-compulsive disorder, schizophrenia, hypertension, stroke, migraine, and nausea.<sup>1</sup> The ability to treat these distinctive disease states arises from differential drug interactions at multiple 5-HT receptor subtypes (5-HT<sub>1A-D</sub>, 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>).<sup>2</sup> Great strides are being made in the elucidation of the physiological components linked to these multiple receptor subtypes. Indeed, the forefront of 5-HT research today involves the search for agents that selectively interact with one receptor subtype. Of the 5-HT<sub>1</sub> receptors, only the 5-HT<sub>1A</sub> receptor has a selective and potent agonist: 8-OH-DPAT [8-hydroxy-2-(*N,N*-dipropylamino)tetralin]. The existence of this selective ligand for the 5-HT<sub>1A</sub> receptor has led to an understanding of its functions and potential role in anxiety and depression. This knowledge has given rise to the development of novel serotonergic anxiolytics, i.e., the buspirone and gepirone class of drugs, which are partial 5-HT<sub>1A</sub> receptor agonists.<sup>3</sup> Recently, it has been recognized that certain 1,4-benzodioxanes possess good affinity for the 5-HT<sub>1A</sub> receptor, for example, the  $\alpha_1$ -adrenergic agent WB 4101,<sup>4</sup> spiroxatrine,<sup>5</sup> MDL 72832<sup>6</sup> and its ethylene analogue MDL 73005.<sup>7</sup>



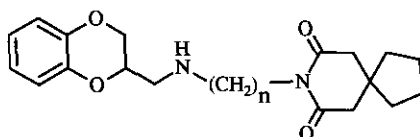
Serotonin (5-HT)



WB 4101



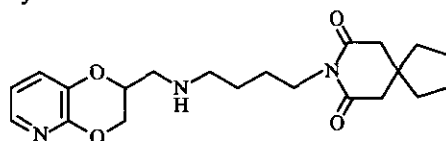
Spiroxatrine



n = 4 MDL 72832

n = 2 MDL 73005

In this work our attention has been focused on the synthesis of a nitrogen-containing 1,4-benzodioxane bioisostere to examine the consequences of the isosteric relationship between this compound and its 1,4-benzodioxane analogue MDL 72832. For this purpose, and in connection with our studies on polycondensed heterocycles with potential biological activity in the central nervous system,<sup>8,9</sup> and more precisely on 3-substituted 2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines,<sup>10</sup> 8-[*N*-(2,3-dihydro-1,4-dioxino[2,3-*b*]pyridin-2-yl)methylaminobutyl]-8-azaspiro[4.5]decane-7,9-dione (**9**) was synthesized, chemically characterized and evaluated for its serotonergic activity.

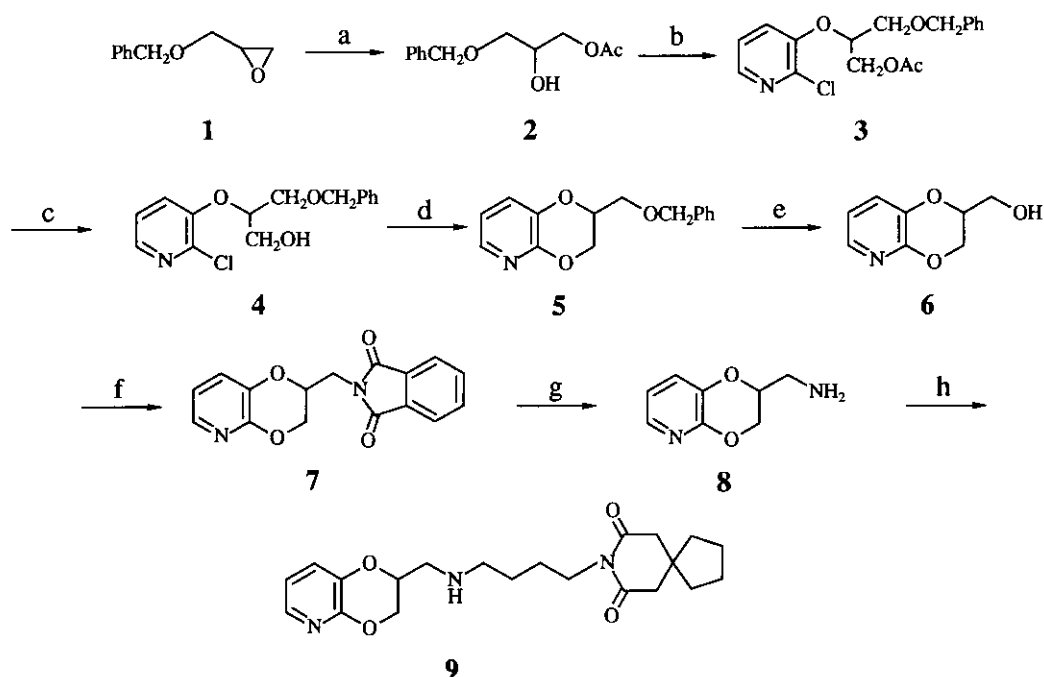


9

The synthesis of compound (**9**) begins with commercially available benzyl glycidyl ether and is outlined in Scheme I. Epoxide (**1**) was opened with sodium acetate in aqueous dioxane affording **2** in 65% yield. The intermediate alcohol (**2**) obtained was condensed with 2-chloro-3-pyridinol using Mitsunobu protocol.<sup>11</sup> Deacetylation of ether (**3**) followed by intramolecular cyclization<sup>10</sup> and *O*-debenzylation provided the desired alcohol (**6**). The latter was converted to phthalimide (**7**) by the Mitsunobu modification of the Gabriel

procedure.<sup>12</sup> Hydrazinolysis of phthalimide (**7**) afforded the amine (**8**) which was alkylated with 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione<sup>13</sup> to provide the final desired compound (**9**).

Scheme I



(a)  $\text{CH}_3\text{COO}^-\text{Na}^+$ , Dioxane /  $\text{H}_2\text{O}$ , reflux, 65%; (b) 2-Chloro-3-pyridinol, toluene, DEAD,  $\text{PPh}_3$ , room temperature, 89%; (c)  $\text{MeO}^-\text{Na}^+$ , MeOH, room temperature, 96%; (d) NaH, DME,  $82^\circ\text{C}$ , 64%; (e) Pd/C 10%, MeOH,  $\text{H}_2$ , 45 psi, room temperature, 90%; (f) Phthalimide, THF, DEAD,  $\text{PPh}_3$ , room temperature, 94%; (g)  $\text{H}_2\text{NNH}_2$ , EtOH, reflux, 79%; (h) R-Br, DMF,  $\text{Et}_3\text{N}$ , KI,  $60^\circ\text{C}$ , 50%.

The pharmacological characterization of **9** was carried out by measuring the ability of this compound to displace  $[^3\text{H}]$ -8-OH-DPAT and  $[^3\text{H}]$ -mesulepine from  $5\text{-HT}_{1\text{A}}$  and  $5\text{-HT}_{1\text{C}}$  receptor sites in cellular membranes of perfectly defined brain structures. The affinities (pKi) were determined and are shown in Table 1, including pKi values of MDL 72832 for comparison.

Table 1

Compd <sup>b</sup>	<i>pK<sub>i</sub></i> <sup>a</sup>	
	5-HT <sub>1A</sub>	5-HT <sub>1C</sub>
<b>9</b>	7.4	<5
<b>MDL 72832</b>	9.1	6.3

<sup>a</sup> The determination of 5-HT<sub>1A</sub> and 5-HT<sub>1C</sub> receptors binding affinities was based upon the methods of Peroutka *et al.* (ref. 14a) and Pazos *et al.* (ref. 14b). <sup>b</sup> Compounds (**9**) and MDL 72832 were tested as the fumarate and hydrochloride respectively.

The MDL 72832 analogue (**9**) binds with a little affinity at 5-HT<sub>1A</sub> receptors. Incorporation of a nitrogen at the 5-position (comparing **9** with MDL 72832) decreases the affinity. This comparison shows that the isosteric replacement, in the 1,4-benzodioxane moiety, of a carbon atom by a nitrogen atom can bring about very different results.

## EXPERIMENTAL

Melting points are uncorrected. <sup>1</sup>H Nmr (300 MHz) spectra were run on a Bruker AM 300 WB spectrometer. TMS served as internal standard. Ir spectra of liquid films or KBr pellets were recorded on a Perkin-Elmer 297 instrument. Mass spectra were registered on a Nermag R-10-10-C apparatus. Reaction products were purified by flash column chromatography using silica gel (Merck 230-400 mesh) according to Still *et al.*<sup>15</sup> Analytical tlc were performed on silica gel F<sub>254</sub> plates. All air- and moisture-sensitive reactions were conducted under a prepurified argon atmosphere in flame-dried glassware. Anhydrous solvents were transferred via syringe.

**1-Acetoxy-3-benzyloxy-2-propanol (2):** Epoxide **1** (1.72 g, 10.47 mmol) was dissolved in dioxane (46 ml) and treated with sodium acetate (4.3 g, 52.37 mmol) in H<sub>2</sub>O (12 ml). The mixture was heated at reflux for 12 h, cooled and the solvent removed *in vacuo*. The residue was partitioned between water and CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x30 ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo* to give crude **2**. This was purified by flash chromatography (1:1; petroleum ether/Et<sub>2</sub>O) to afford 1.55 g (65%) of **2** as an oil: Ir (neat) 3600-3200 (OH), 1720 (C=O) cm<sup>-1</sup>; <sup>1</sup>H nmr (300 MHz, CDCl<sub>3</sub> + D<sub>2</sub>O) δ 2.05 (s, 3H), 3.48 (dd, *J* = 6.0 and 9.5 Hz, 1H), 3.54 (dd, *J* = 4.4 and 9.5 Hz, 1H), 4.05 (m, 1H), 4.10 (dd, *J* = 5.5 and 11.8 Hz, 1H), 4.18 (dd, *J* = 4.3 and 11.8 Hz, 1H), 4.56 (s, 2H), 7.16-7.39 (m, 5H); ms *m/z*: 225 (M<sup>+</sup> + 1). *Anal.* Calcd for C<sub>12</sub>H<sub>16</sub>O<sub>4</sub>: C, 64.27; H, 7.19. Found: C, 64.33; H, 7.24.

**1-Acetoxy-2-(2-chloro-3-pyridinyloxy)-3-benzyloxypropane (3):** To a stirred solution of the alcohol **2** (1.07 g, 4.78 mmol) and triphenylphosphine (1.5 g, 5.73 mmol) in dry toluene (25 ml) was suspended the

2-chloro-3-pyridinol (742 mg, 5.73 mmol). Diethyl azodicarboxylate (DEAD) (0.9 ml, 5.73 mmol) was then added dropwise, and the reaction mixture was stirred at 0°C for 15 min and at room temperature for 2 h. The reaction mixture was concentrated and the residue was purified by flash chromatography (3:1 ; petroleum ether/Et<sub>2</sub>O) to give 1.43 g (89%) of **3** as an oil: Ir (neat) 1730 (C=O) cm<sup>-1</sup>; <sup>1</sup>H nmr (300 MHz, CDCl<sub>3</sub>) δ 2.03 (s, 3H), 3.75 (d, *J* = 5.2 Hz, 2H), 4.43 (dd, *J* = 5.0 and 11.8 Hz, 1H), 4.51 (dd, *J* = 5.7 and 8.3 Hz, 1H), 4.65 (s, 2H), 4.66-4.78 (m, 1H), 7.16 (dd, *J* = 4.7 and 8.3 Hz, 1H, H<sub>β</sub> pyridine), 7.25-7.38 (m, 5H), 7.40 (dd, *J* = 1.0 and 8.3 Hz, 1H, H<sub>γ</sub> pyridine), 8.02 (dd, *J* = 1.0 and 4.7 Hz, 1H, H<sub>α</sub> pyridine); ms *m/z*: 336 (M<sup>+</sup> + 1). *Anal.* Calcd for C<sub>17</sub>H<sub>18</sub>NO<sub>4</sub>Cl: C, 60.80; H, 5.40; N, 4.17. Found: C, 60.87; H, 5.42; N, 4.19.

**1-Benzyloxy-2-(2-chloro-3-pyridinyloxy)-3-propanol (4)**: A suspension of compound **3** (976 mg, 2.9 mmol) in absolute methanol (16 ml) was treated with a small amount of sodium methoxide 1M solution. The solution was stirred for 1 h at room temperature and concentrated. The residue was purified by flash chromatography (ether) to give 819 mg (96%) of **4** as an oil: Ir (neat) 3600-3100 (OH) cm<sup>-1</sup>; <sup>1</sup>H nmr (300 MHz, CDCl<sub>3</sub> + D<sub>2</sub>O) δ 3.75 (d, *J* = 5.7 Hz, 2H), 3.86 (dd, *J* = 5.4 and 12.0 Hz, 1H), 3.91 (dd, *J* = 4.1 and 12.0 Hz, 1H), 4.43-4.54 (m, 1H), 4.57 (s, 2H), 7.75 (dd, *J* = 4.3 and 8.2 Hz, 1H, H<sub>β</sub> pyridine), 7.25-7.38 (m, 5H), 7.43 (dd, *J* = 1.0 and 8.2 Hz, 1H, H<sub>γ</sub> pyridine), 8.02 (dd, *J* = 1.0 and 4.3 Hz, 1H, H<sub>α</sub> pyridine); ms *m/z*: 294 (M<sup>+</sup> + 1). *Anal.* Calcd for C<sub>15</sub>H<sub>16</sub>NO<sub>3</sub>Cl: C, 61.33; H, 5.49; N, 4.76. Found: C, 61.40; H, 5.52; N, 4.78.

**2,3-Dihydro-2-benzyloxymethyl-1,4-dioxino[2,3-*b*]pyridine (5)**: The alcohol **4** (734 mg, 2.5 mmol) dissolved in anhydrous DME (10 ml) was added to a magnetically stirred suspension of NaH (132 mg of 50% oil dispersion, 2.75 mmol) in DME (6 ml) under nitrogen. After stirring for 24 h at 82 °C, the reaction mixture was diluted with H<sub>2</sub>O (20 ml) and extracted into CH<sub>2</sub>Cl<sub>2</sub> (2x25 ml). The combined extracts were dried over MgSO<sub>4</sub> and concentrated to give a residue, which was purified by flash chromatography (2:1 ; petroleum ether/Et<sub>2</sub>O) to give 411 mg (64%) of **5** as an oil: Ir (neat) 1185 (C-O-C) cm<sup>-1</sup>; <sup>1</sup>H nmr (300 MHz, CDCl<sub>3</sub>) δ 3.67 (dd, *J* = 5.5 and 10.3 Hz, 1H), 3.74 (dd, *J* = 4.9 and 10.3 Hz, 1H), 4.26 (dd, *J* = 7.3 and 11.6 Hz, 1H), 4.32-2.39 (m, 1H), 4.47 (dd, *J* = 1.9 and 11.6 Hz, 1H), 4.60 (s, 2H), 6.86 (dd, *J* = 4.6 and 7.7 Hz, 1H, H<sub>β</sub> pyridine), 7.19 (dd, *J* = 1.0 and 7.7 Hz, 1H, H<sub>γ</sub> pyridine), 7.25-7.42 (m, 5H), 7.81 (dd, *J* = 1.0 and 4.6 Hz, 1H, H<sub>α</sub> pyridine); ms *m/z*: 258 (M<sup>+</sup> + 1). *Anal.* Calcd for C<sub>15</sub>H<sub>15</sub>NO<sub>3</sub>: C, 70.02; H, 5.87; N, 18.65. Found: C, 70.09; H, 5.90; N, 18.69.

**2,3-Dihydro-1,4-dioxino[2,3-*b*]pyridin-2-ylmethanol (6)**: A mixture of **5** (1.4 g, 5.44 mmol) and Pd/C (10%, 140 mg) in methanol (20 ml) was shaken in a Parr hydrogenator under 45 psi of hydrogen at room temperature for 24 h. The catalyst was filtered and the solvent was removed *in vacuo*. The residue was purified

by flash chromatography (ether) to give 818 mg (90%) of **6** as an oil: Ir (neat) 3600-3100 (OH)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (300 MHz,  $\text{CDCl}_3 + \text{D}_2\text{O}$ )  $\delta$  3.82-3.95 (m, 2H), 4.24-4.33 (m, 1H), 4.30 (dd,  $J = 7.5$  and 15.6 Hz, 1H), 4.49 (dd,  $J = 5.7$  and 15.6 Hz, 1H), 6.87 (dd,  $J = 4.6$  and 7.7 Hz, 1H,  $\text{H}_\beta$  pyridine), 7.20 (dd,  $J = 1.5$  and 7.7 Hz, 1H,  $\text{H}_\gamma$  pyridine), 7.80 (dd,  $J = 1.5$  and 4.6 Hz, 1H,  $\text{H}_\alpha$  pyridine); *ms m/z*: 168 ( $\text{M}^+ + 1$ ). *Anal.* Calcd for  $\text{C}_8\text{H}_9\text{NO}_3$ : C, 57.47; H, 5.42; N, 28.71. Found: C, 57.52; H, 5.44; N, 28.76.

**1,3-Dihydro-2-(2,3-dihydro-1,4-dioxino[2,3-*b*]pyridin-2-ylmethyl)-1,3-dioxo-2H-isoindole (7)**: To a stirred solution of alcohol (**6**) (668 mg, 4 mmol) and  $\text{PPh}_3$  (1.05 g, 4 mmol) in anhydrous THF (20 ml), was suspended phthalimide (588 mg, 4 mmol). Diethyl azodicarboxylate (0.63 ml, 4 mmol) was then added dropwise at 0 °C. Its decoloration indicates the evolution of the reaction. The reaction mixture was stirred during the night at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (1:1 ; ether/ $\text{CH}_2\text{Cl}_2$ ) to give 1.11 g (94%) of **7** as a white solid: mp 145-146 °C; Ir (KBr) 1760 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.90 (dd,  $J = 4.7$  and 14.2 Hz, 1H), 4.12 (dd,  $J = 7.1$  and 14.2 Hz, 1H), 4.24 (dd,  $J = 6.32$  and 11.8 Hz, 1H), 4.47-4.57 (m, 2H), 6.89 (dd,  $J = 4.6$  and 8.2 Hz, 1H,  $\text{H}_\beta$  pyridine), 7.18 (dd,  $J = 1.0$  and 8.2 Hz, 1H,  $\text{H}_\gamma$  pyridine), 7.77 (dd,  $J = 2.1$  and 6.2 Hz, 2H), 7.85 (dd,  $J = 1.0$  and 4.6 Hz, 1H,  $\text{H}_\alpha$  pyridine), 7.91 (dd,  $J = 2.1$  and 6.2 Hz, 2H); *ms m/z*: 297 ( $\text{M}^+ + 1$ ). *Anal.* Calcd for  $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_4$ : C, 64.85; H, 4.08; N, 9.45. Found: C, 64.90; H, 4.11; N, 9.50.

**2,3-Dihydro-1,4-dioxino[2,3-*b*]pyridin-2-yl-methanamine (8)** : To a stirred solution of phthalimide (**7**) (948 mg, 3.2 mmol) in EtOH (16 ml) was added dropwise 85% hydrazine monohydrate (942 mg, 16 mmol) in EtOH (2 ml). The mixture was heated to reflux for 3 h. After cooling to room temperature, the reaction mixture was diluted in  $\text{CH}_2\text{Cl}_2$  (30 ml). The resulting precipitates were removed by filtration, and the filtrate was washed with a small amount of water, dried over  $\text{MgSO}_4$  and concentrated to give a residue, which was purified by flash chromatography (9:1 ;  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) to afford 420 mg (79%) of **8** as an oil: Ir (neat) 3500-3100 (NH)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.68 (bs, 2H), 2.94 (d,  $J = 4.27$  Hz, 2H), 4.05-4.15 (m, 1H), 4.16 (d,  $J = 7.1$  Hz, 1H), 4.40 (d,  $J = 9.9$  Hz, 1H), 6.81 (dd,  $J = 4.6$  and 7.7 Hz, 1H,  $\text{H}_\beta$  pyridine), 7.14 (dd,  $J = 1.0$  and 7.7 Hz, 1H,  $\text{H}_\gamma$  pyridine), 7.75 (dd,  $J = 1.0$  and 4.6 Hz,  $\text{H}_\alpha$  pyridine); *ms m/z*: 167 ( $\text{M}^+ + 1$ ). *Anal.* Calcd for  $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$ : C, 57.81; H, 6.06; N, 16.86. Found: C, 57.86; H, 6.10; N, 16.91.

**8-[4-(2,3-Dihydro-1,4-dioxino[2,3-*b*]pyridin-2-yl-methylamino)butyl]-8-azaspiro[4.5]decane-7,9-dione (9)**: To a solution of amine (**7**) (400 mg, 2.4 mmol) and 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (872 mg, 2.8 mmol) in dry DMF (12 ml) was added triethylamine (1 ml, 12 mmol) and potassium iodide (80 mg, 0.48 mmol). The reaction was stirred at 60 °C for 24 h and the solvent was then removed under reduced

pressure. Water (15 ml) was added, and then the suspension was extracted to give crude **9**. This was purified by flash chromatography (95:5 ; CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to give 465 mg (50%) of **9** as an oil: Ir (neat) 3600-3200 (NH), 1715 and 1650 (C=O) cm<sup>-1</sup> ; <sup>1</sup>H nmr (300 MHz, CDCl<sub>3</sub> + D<sub>2</sub>O) δ 1.45-1.80 (m, 12H), 2.58 (s, 4H), 2.68 (t, J = 6.32 Hz, 2H), 2.86 (dd, J = 4.9 and 12.8 Hz, 1H), 2.92 (dd, J = 6.3 and 12.8 Hz, 1H), 3.78 (t, J = 7.11 Hz, 2H), 4.20 (dd, J = 7.9 and 11.4 Hz, 1H), 4.24-4.32 (m, 1H), 4.46 (dd, J = 1.6 and 11.4 Hz, 1H), 7.88 (dd, J = 4.6 and 8.2 Hz, 1H, H<sub>β</sub> pyridine), 7.16 (dd, J = 1.0 and 8.2 Hz, 1H, H<sub>γ</sub> pyridine), 7.84 (dd, J = 1.0 and 4.6 Hz, H<sub>α</sub> pyridine); ms m/z: 388 (M<sup>+</sup> + 1). Anal. Calcd for C<sub>21</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>: C, 65.09; H, 7.54; N, 10.84. Found: C, 65.13; H, 7.56; N, 10.88.

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