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Synthesis of various analog derivatives of ORG13514 as 5-HT_{1A} ligands

Corinne Comoy [a], Abdelhakim Benarab [a], Michel Leinot [b], André Monteil [b], Gérald Guillaumet [a,*]

[a] *Institut de Chimie Organique et Analytique, associé CNRS, Université d'Orléans, BP 6759, 45067 Orleans Cedex 2, France*
[b] *RL-CERM, Z.I. de la Varenne, Rue H. Goudier, 63203 Riom Cedex, France*

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Abstract

In connection with the development of new potential 5-HT_{1A} ligands, multistep synthesis of *N*-substituted-3-aminomethyl-2,3-dihydro-1,4-dioxinol[2,3-*b*]pyridine derivatives as ORG13514 analogs are described. Their biological activity as 5-HT_{1A} type ligands is reported and compared with ORG13514 affinity and selectivity for 5-HT_{1A} receptors. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: 2,3-Dihydro-1,4-dioxino[2,3-*b*]pyridine; 5-HT_{1A} receptor binding; Anti-depressant drug

1. Introduction

Serotonin (5-HT, 5-hydroxytryptamine) was discovered as a central neurotransmitter about 40 years ago and disorders of serotoninergic transmission were known to implicate modifications in physiological, and pathophysiological processes [1–5]. Serotonin receptors were classified in seven types (5-HT_{1-7}) and several classes have been further subdivided into different subtypes [6].

The 5-HT_{1A} receptor subtype is the best studied and it was shown to be involved in psychiatric disorders such as depression [7–9] and anxiety [10,11]. Long chain arylpiperazines with an amide or imide moiety represent one of the most important classes of 5-HT_{1A} receptor ligands, for instance buspirone, the first agent to be approved for clinical use [12–14], and gepirone. The 2,3-dihydro-1,4-benzodioxine family, substituted with an alkylimide group like MDL72832 and MDL73005, was also reported to exhibit high affinity for 5-HT_{1A} receptors (Fig. 1) [15,16].

In connection with our work concerning the preparation of products liable to affect the central nervous system [17–21] and particularly the 5-HT_{1A} receptor, we performed synthetic and pharmacological activity studies of ORG13514 [22] and ORG13653 [23], pyridine isosters of MDL72832 and MDL73005, respectively (Fig. 1).

We describe in the present paper the synthesis of 3-aminomethyl-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines (**1**), as ORG13514 analogs, with a *n*-propyl- or *n*-butylchain and amide or imide moiety (Fig. 2).

2. Chemistry

The general procedure for the preparation of the various 3-aminomethyl-2,3-dihydro-1,4-dioxino[2,3-*b*]-pyridines (**1a**–**f**) is reported in Scheme 1. The 3-(2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine)yl methanamine (**2**) was conveniently obtained in four steps. First, the reaction of 2-chloro-3-pyridinol and epichlorhydrin in the presence of sodium hydride in *N*,*N*-dimethylformamide afforded 2-chloro-3-(oxiranylmethoxy)pyridine as an intermediate. Then, ring opening of this epoxide using sodium azide followed by an intramolecular cyclisation and a reduction of the azide gave amine **2** [23]. The expected compounds **1a**–**f** were obtained from **2** by a *N*-alkylation using the appropriate bromoderivatives, triethylamine and a catalytic amount of potassium iodide in *N*,*N*-dimethylformamide. Bromobutylimide derivatives were commercially available or obtained by

* Corresponding author.
E-mail address: c.comoy@meseb.u-nancy.fr (C. Comoy)

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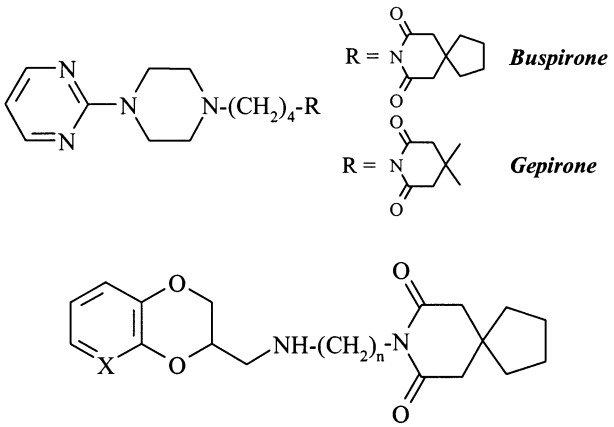


Fig. 1.

known procedures [18]. Bromobutylamide derivatives were prepared according to the procedure reported in Section 5.

The second part of our study concerned the elaboration of derivatives **1g**–**h**. To increase the overall yield, the procedure outlined in Scheme 2 was carried out. The ring opening of the 2-chloro-3-(oxiranylmethoxy)pyridine (**3**) [24] by the *N*-benzyl-*N*-[3-(benzyloxy)propyl]amine [25] in tetrahydrofuran yielded the expected amine **4** (97%). Treatment of **4** with sodium hydride in ethylene glycol dimethyl ether led to an intramolecular cyclization and gave the dioxinopyridine **5** in satisfactory yield (60%). The benzyl groups were removed by catalytic hydrogenolysis using palladium on carbon in methanol in the presence of hydrochloric acid to afford the derivative **6** in good yield (78%). Then, a Mitsunobu reaction [26,27] between the alcohol **6** and tetramethylene glutarimide or phthalimide, in the presence of equimolar quantity of triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran, afforded

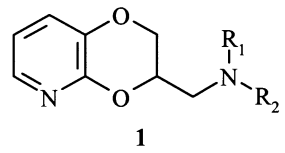


Fig. 2.

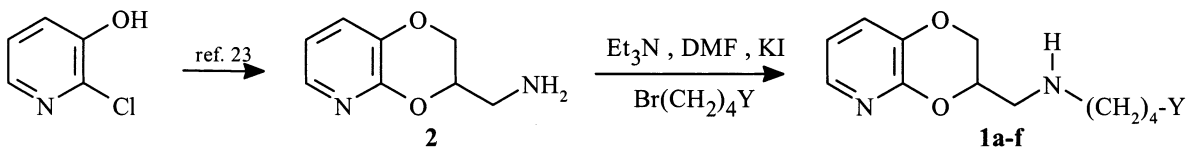
the expected derivatives **1g** and **1h** in 74 and 68% yield, respectively.

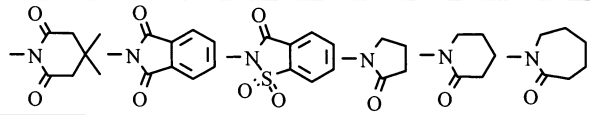
The third studied series deals with the *N*-methyl substituted class (Scheme 3). The ring opening of epoxide **3** with benzylmethylamine in tetrahydrofuran followed by an intramolecular cyclization of the obtained 1-(2-chloro-3-pyridinyl)alcohol in the presence of sodium hydride, in ethylene glycol dimethyl ether, gave the expected methylamine **7** in good yield. Debenzylation of **7** by the catalytic hydrogenolysis with palladium on carbon in methanol, in the presence of hydrochloric acid, led to the derivative **8** in 82% yield. Then, **8** was alkylated with appropriate imides in the presence of triethylamine and a catalytic amount of potassium iodide, in *N*,*N*-dimethylformamide, to afford the expected compounds **1i** and **1j** in 89 and 88% yield, respectively.

We had already described the synthesis and spectral data of imidoethyl-3-aminomethyl-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine derivatives ORG13653 and ORG13380 (Fig. 3) [23].

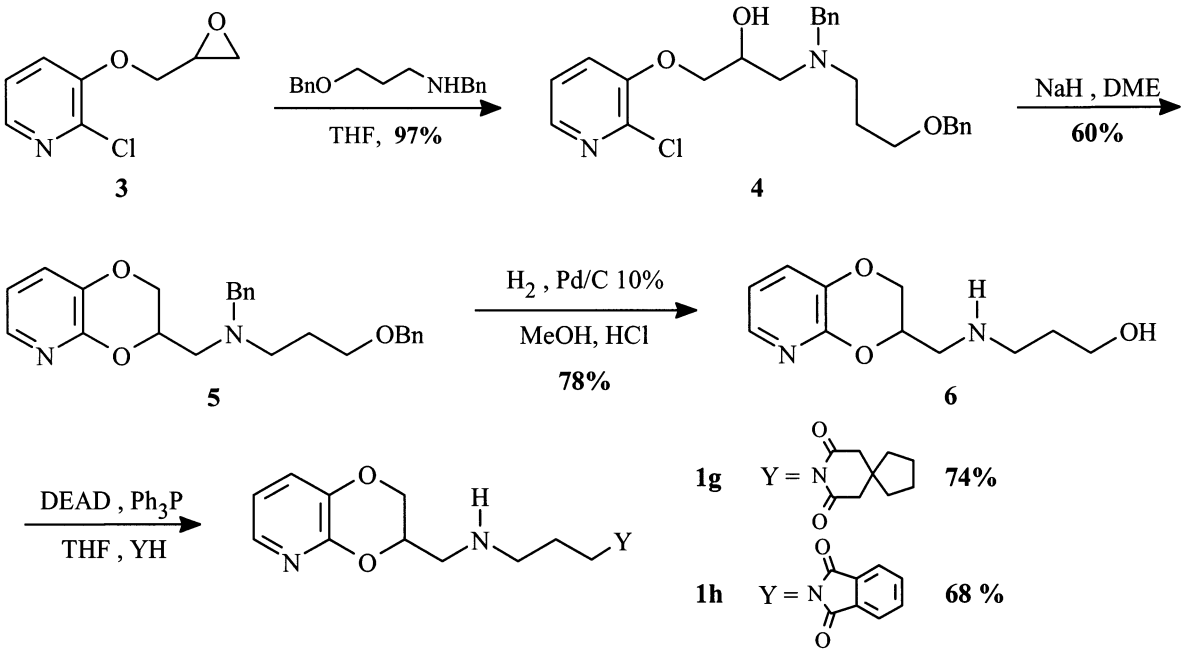
3. Biological results and discussion

The biological activity of **1a**–**j**, ORG13653 and ORG13380 was studied and the results were compared with the affinity and the selectivity of ORG13514 for the 5-HT_{1A} receptors. The binding affinities (pK_i) were determined on several 5-HT receptor subtypes, on α_1- and α_2-adrenergic, and on D_2-dopaminergic receptors using rat brain homogenates as described in Section 5 [28–33]. Also included are the pK_i values of the reference compounds ORG13514, MDL72832 and Buspirone.



Cpd	1a	1b	1c	1d	1e	1f
Y						
Yield %	54	52	56	64	50	47

Scheme 1.

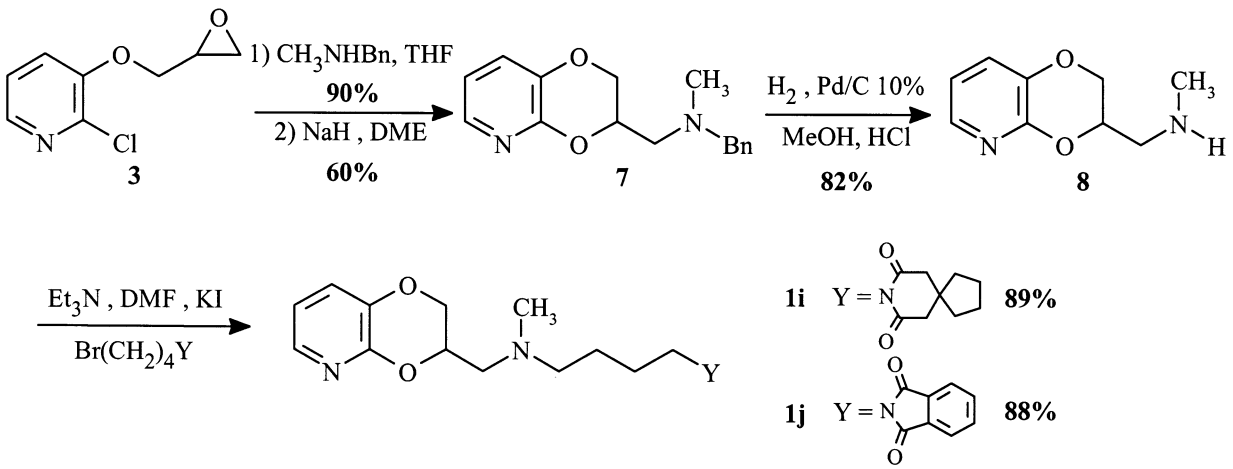


Scheme 2.

The derivatives ORG13514, **1a**, **1b**, **1c**, **1d**, **1e** and **1f** were reported to display a high or very high affinity for 5-HT_{1A} sites with pK_i values of 10.9, 8.9, 9.1, 9.8, 8.5, 9.1 and 8.7, respectively. The compounds **1g**, **1h**, **1i**, **1j**, ORG13653 and ORG13380 show much reduced affinity in so far as their pK_i values are lower than 8.0. Furthermore **1a** and ORG13514 exhibited a 100 or 10 000-fold selectivity for the 5-HT_{1A} receptors, respectively, compared to the 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, α_1, α_2 and D_2 receptors. Moreover, ORG13514 and **1a** are around 10–100-fold more selective than MDL72832 for the 5-HT_{1A} sites (Table 1).

Preliminary behavioural observations in rats confirm that amines ORG13514 and **1a** are very potent in the lower lip retraction LLR test [34] with ED_{50} values of 0.1 mg/kg sc and 1 mg/kg po for ORG13514 and of 0.8 mg/kg sc for **1a**. In comparison, buspirone had ED_{50} values of 1 mg/kg sc and 40 mg/kg po, 8-OH-DPAT 0.1 mg/kg sc and >10 mg/kg po, and MDL72832 0.1 mg/kg sc.

In addition studies of the effects in EEG-defined rat sleep-waking behaviour [35–38] show that amine ORG13514 causes a selective reduction of the total duration of REM-sleep at very low doses ($ED_{50} = 0.32$ mg/kg i.p.) compared to 2.2 mg/kg i.p. for buspirone. Moreover, this compound increases the latencies periods before REM and deep-sleep, which is characteristic of anti-depressant drugs. The duration of the effects is dose dependant and lasting from 4 to 8 h after administration.



Scheme 3.

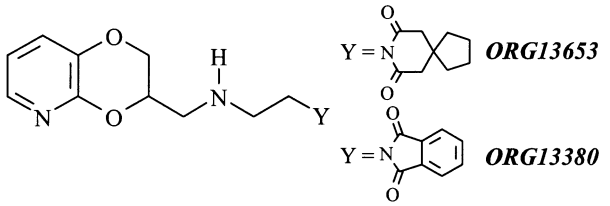


Fig. 3.

4. Conclusions

Many new dihydropyridine analogs (**1a**–**j**) of the *N*-substituted-3-aminomethyl-2,3-dihydro-1,4-dioxino-[2,3-*b*]pyridine ORG13514 have been prepared with good yields. Studies of biological activity revealed that, among these new derivatives, only one, the compounds **1a**, exhibits a 100-fold selectivity for the 5-HT_{1A} sites compared to the 5-$HT_{1B, 2A, 2C}$, $\alpha_{1\ or\ 2}$ and D_2 receptors. This aminopyridine **1a** shows around a tenfold selectivity greater than the MDL72832.

However, the ligand which shows the highest affinity and an excellent selectivity for the 5-HT_{1A} subtypes is the derivative ORG13514 [22].

5. Experimental

5.1. Chemistry

Organic solvents were purified when necessary by the methods described by Perrin, Armarego and Perrin [39]. All solutions were dried over anhydrous magnesium sulfate and evaporated on a Büchi rotatory evaporation. Column chromatography was performed on silica gel (Kieselgel–Merck, 70–230 mesh for gravity columns and 230–400 mesh for flash columns). Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, Merck $60F_{254}$) and spots were visualized with UV light. The column chromatography solvents employed were glass distilled and eluent mixtures are reported as volume to volume ratios. Melting points (uncorrected) were determined on a Köfler hotstage apparatus. Infrared spectra were recorded on a Perkin–Elmer 297 spectrometer. Mass spectra were recorded on a R-10-10-C Nermag spectrometer. ^{1}H NMR spectra were recorded on Bruker AM 300WB or Hitachi Perkin–Elmer R-24B 60WB spectrometers. The deuterated NMR solvents contained 99.8% deuterium with 1% v/v TMS and were obtained from Aldrich Chimie. The ^{1}H NMR coupling constants (J values) were listed in Hertz (Hz) and spin multiplicities were reported as singulets (s), doublets (d), triplets (t), multiplets (m) and broad signals (br s). Chemical shifts were reported in parts per millions (δ, ppm) downfield from tetramethylsilane (TMS) which was used as an internal standard. Analysis indicated by the symbols of the elements were within $\pm 0.4\%$ of the theoretical values.

5.2. 1-[4-[N-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridine-3-ylmethyl) amino]butyl]-4,4-dimethylpiperidine-2,6-dione (*1a*)

To a solution of the amine **2** [23] (1.660 g, 10.0 mmol) in dry *N*,*N*-dimethylformamide (DMF) (15 ml) were added dropwise 1-(4-bromobutyl)-4,4-dimethylpiperidin-2,6-dione (3.310 g, 12.0 mmol) in DMF (6 ml), triethylamine (4.2 ml, 30.0 mmol) and potassium iodide (0.332 g, 2.0 mmol). The mixture was heated at 60°C. After total consumption of **2**, the solution was hydrolyzed and the product was extracted with dichloromethane (CH_2Cl_2). The organic layer was washed with a saturated sodium hydrogen carbonate solution. After evaporation of solvent, column chromatography (eluent: 25:5 CH_2Cl_2–MeOH) afforded the expected product **1a** as a white solid (1.950 g) in 54% yield: m.p. 208–209°C. IR (KBr): ν 3500–3300 (NH), 1715 and 1660 (N–CO), 1190 (C–O–C) cm^{-1}. ^{1}H NMR ($CDC1_3$) δ 1.09 (s, 6H, **CH_3**), 1.46–1.60 (m, 4H, **CH_2**), 1.68 (br s, 1H, **NH**), 2.50 (s, 4H, **CH_2**CO), 2.60–2.76 (m, 2H, NH**CH_2**CH_2), 2.90 (dd, 1H, CH**CH_2**NH, $J=$ 4.6, $J=11.7$), 2.97 (dd, 1H, CH**CH_2**NH, $J=6.0$, $J=$ 11.7), 3.76 (t, 2H, **CH_2**NCO, $J=7.3$), 4.04 (dd, 1H, O**CH_2**CH, $J=7.8$, $J=11.8$), 4.25 (dd, 1H, O**CH_2**CH, $J=1.9$, $J=11.8$), 4.40–4.49 (m, 1H, **CH**), 6.85 (dd, 1H, **H_7**, $J=5.0$, $J=7.6$), 7.17 (dd, 1H, **H_8**, $J=1.3$, $J=7.6$), 7.80 (dd, 1H, **H_6**, $J=1.3$, $J=5.0$). MS (CI/NH_3): m/z 362 [$M+1$]. *Anal.* ($C_{19}H_{27}N_3O_4$) C, H, N.

Table 1
Binding of derivatives ORG13514, **1a**, MDL72832 and Buspirone (pK_i values)

Compounds	5-HT_{1A}	5-HT_{1B}	5HT_{2A}	5-HT_{2C}	α_1	α_2	D_2
ORG13514 [a]	10.9	< 5.0	6.3	< 5.3	7.5	7.0	6.5
1a [a]	8.9	6.0	5.3	< 5.3	7.0	6.6	6.3
MDL72832 [b]	9.1	6.2	6.2	6.3	7.8	6.3	6.8
Buspirone [b]	7.6	5.2	6.1	5.1	5.5	5.6	6.4

[a] Compounds ORG13514 and **1a** were tested as fumarate.
[b] MDL72832 and Buspirone were tested as hydrochloride.

5.3. 1,3-Dihydro-2-[4-[N-(2,3-dihydro-1,4-dioxino-[2,3-b]pyridine-3-ylmethyl)amino]butyl]-1,3-dioxo-2H-isoindole (**1b**)

The compound **1b** was prepared according to the method used for **1a** from the amine **2** (1.660 g, 10.0 mmol) and 2-(4-bromobutyl)-1,3-dioxo-2*H*-isoindole (3.385 g, 12.0 mmol). After a column chromatography (eluent: 47:47:6 Et_2O–CH_2Cl_2–MeOH), **1b** was obtained as an oil (1.910 g) in 52% yield. IR (film): *v* 3500–3300 (NH), 1760 and 1700 (N–CO), 1185 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.47–1.88 (m, 4H, $\mathbf{CH_2}$), 1.96 (br s, 1H, **NH**), 2.62–2.75 (m, 2H, NH$\mathbf{CH_2}CH_2$), 2.91 (dd, 1H, NH$\mathbf{CH_2}$CH, $J = 4.7$, $J = 11.8$), 2.97 (dd, 1H, NH$\mathbf{CH_2}$CH, $J = 6.0$, $J = 11.8$), 3.77 (t, 2H, $\mathbf{CH_2}$NCO, $J = 7.2$), 4.03 (dd, 1H, O$\mathbf{CH_2}$CH, $J = 7.9$, $J = 11.8$), 4.29 (dd, 1H, O$\mathbf{CH_2}$CH, $J = 1.9$, $J = 11.8$), 4.40–4.48 (m, 1H, **CH**), 6.84 (dd, 1H, $\mathbf{H_7}$, $J = 4.6$, $J = 7.7$), 7.16 (dd, 1H, $\mathbf{H_8}$, $J = 1.6$, $J = 7.7$), 7.67–7.73 (m, 2H, $\mathbf{H_{arom}}$), 7.78–7.85 (m, 3H, $\mathbf{H_6}$, $\mathbf{H_{arom}}$). MS (CI/NH_3): *m*/*z* 368 [*M* + 1]. *Anal*. Calc. ($C_{20}H_{21}N_3O_4$) C, H, N.

5.4. 2-[4-[N-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridine-3-ylmethyl) amino]butyl]-1,1-dioxo-1,2-benzisothiazol-3(2H)-one (**1c**)

This compound, prepared according to the method used for **1a** from **2** (1.660 g, 10.0 mmol) and 2-(4-bromobutyl) - 1,2 - benzisothiasol - 3(2*H*) - one - 1,1 - dioxide (3.815 g, 12.0 mmol), was obtained after column chromatography (eluent: 47:47:6 Et_2O–CH_2Cl_2–MeOH), as an oil (2.225 g) in 56% yield. IR (film) *v* 3500–3300 (NH), 1715 (N–CO), 1160 (C–O–C), 1180 (SO_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.55–2.00 (m, 5H, $\mathbf{CH_2}$, **NH**), 2.68–2.81 (m, 2H, NH$\mathbf{CH_2}$), 2.91 (dd, 1H, CH$\mathbf{CH_2}$NH, $J = 5.0$, $J = 12.4$), 2.98 (dd, 1H, CH$\mathbf{CH_2}$NH, $J = 5.9$, $J = 12.4$), 3.80 (t, 2H, $\mathbf{CH_2}$NCO, $J = 7.4$), 4.04 (dd, 1H, O$\mathbf{CH_2}$CH, $J = 7.9$, $J = 11.8$), 4.29 (dd, 1H, O$\mathbf{CH_2}$CH, $J = 2.0$, $J = 11.8$), 4.40–4.49 (m, 1H, **CH**), 6.84 (dd, 1H, $\mathbf{H_7}$, $J = 4.7$, $J = 7.9$), 7.17 (dd, 1H, $\mathbf{H_8}$, $J = 0.8$, $J = 7.9$), 7.78–7.94 (m, 4H, $\mathbf{H_{arom}}$), 8.05 (dd, 1H, $\mathbf{H_6}$, $J = 0.8$, $J = 4.7$). MS (CI/NH_3): *m*/*z* 404 [*M* + 1]. *Anal*. Calc. ($C_{19}H_{21}N_3O_5S$) C, H, N.

5.5. Procedure used to prepare bromobutylamide derivatives

The amide (15.0 mmol) dissolved in dry DMF (20 ml) was added dropwise to a suspension of sodium hydride (16.5 mmol, 60% dispersion in mineral oil). After stirring 15 min, 1,4-dibromobutane (30.0 mmol) in dry DMF (5 ml) was added. The mixture was heated at 80°C for 24 h then cooled to room temperature and hydrolyzed. The product was extracted with CH_2Cl_2 and purified by column chromatography (eluent: Et_2O).

5.5.1. 1-(4-Bromobutyl)-2-pyrrolidone

This compound was obtained from 2-pyrrolidone (1.275 g) as an oil (2.145 g) in 65% yield. IR (film): *v* 1650 (N–CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.62–1.71 (m, 2H, $\mathbf{CH_2}$), 1.79–1.90 (m, 2H, $\mathbf{CH_2}$), 1.97–2.08 (m, 2H, $\mathbf{CH_2}$), 2.32 (t, 2H, CO$\mathbf{CH_2}$, $J = 7.80$), 3.25–3.47 (m, 6H, Br$\mathbf{CH_2}$, $\mathbf{CH_2}$NCO); *Anal*. Calc. ($C_8H_{14}BrNO$) C, H, N.

5.5.2. 1-(4-Bromobutyl)-2-piperidone

This compound was obtained from 2-piperidone (1.485 g) as an oil (2.245 g) in 64% yield. IR (film): *v* 1645 (N–CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.60–1.88 (m, 8H, $\mathbf{CH_2}$), 2.32 (t, 2H, CO$\mathbf{CH_2}$, $J = 6.1$), 3.24 (t, 2H, $\mathbf{CH_2}$NCO, $J = 5.5$), 3.33–3.34 (m, 4H, Br$\mathbf{CH_2}$, $\mathbf{CH_2}$NCO); *Anal*. Calc. ($C_9H_{16}BrNO$) C, H, N.

5.5.3. 1-(4-Bromobutyl)-2-azepinone

This compound was obtained from 2-azepinone (1.695 g) as an oil (2.155 g) in 58% yield. IR (film): *v* 1645 (N–CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.60–1.94 (m, 10H, $\mathbf{CH_2}$), 2.50–2.54 (m, 2H, CO$\mathbf{CH_2}$), 3.31–3.47 (m, 6H, Br$\mathbf{CH_2}$, $\mathbf{CH_2}$NCO); *Anal*. Calc. ($C_{10}H_{18}BrNO$) C, H, N.

5.6. 1-[4-[N-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridine-3-ylmethyl) amino]butyl]pyrrolidin-2-one (**1d**)

This product was prepared according to the method used for **1a** from **2** (1.660 g, 10.0 mmol) and 1-(4-bromobutyl)-2-pyrrolidone (2.640 g, 12.0 mmol). Purification by a column chromatography (eluent: 47:47:6 Et_2O–CH_2Cl_2–MeOH) gave **1d** as an oil (1.950 g) in 64% yield. IR (film): *v* 3500–3200 (NH), 1610 (N–CO), 1185 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.44–1.64 (m, 4H, $\mathbf{CH_2}$), 1.68 (br s, 1H, **NH**), 2.01 (q, 2H, $\mathbf{CH_2}CH_2CO$, $J = 7.5$), 2.37 (t, 2H, $\mathbf{CH_2}$CO, $J = 7.5$), 2.61–2.75 (m, 2H, NH$\mathbf{CH_2}CH_2$), 2.91 (dd, 1H, CH$\mathbf{CH_2}$NH, $J = 5.0$, $J = 12.6$), 2.97 (dd, 1H, CH$\mathbf{CH_2}$NH, $J = 6.0$, $J = 12.6$), 3.28 (t, 2H, $\mathbf{CH_2}$NCO, $J = 7.5$), 3.37 (t, 2H, $\mathbf{CH_2}$NCO, $J = 7.5$), 4.03 (dd, 1H, O$\mathbf{CH_2}$CH, $J = 7.7$, $J = 11.6$), 4.28 (dd, 1H, O$\mathbf{CH_2}$CH, $J = 2.5$, $J = 11.6$), 4.41–4.50 (m, 1H, **CH**), 6.85 (dd, 1H, $\mathbf{H_7}$, $J = 4.6$, $J = 8.2$), 7.18 (dd, 1H, $\mathbf{H_8}$, $J = 1.0$, $J = 8.2$), 7.80 (dd, 1H, $\mathbf{H_6}$, $J = 1.0$, $J = 4.6$). MS (CI/NH_3): *m*/*z* 306 [*M* + 1]; *Anal*. Calc. ($C_{16}H_{23}N_3O_3$) C, H, N.

5.7. 1-[4-[N-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridine-3-ylmethyl) amino]butyl]piperidin-2-one (**1e**)

This compound was prepared according to the method used for derivative **1a** from **2** (1.660 g, 10.0

mmol) and 1-(4-bromobutyl)piperidin-2-one (2.810 g, 12.0 mmol). Column chromatography (eluent: 47:47:6, Et_2O–CH_2C1_2–MeOH) gave the desired product **1e** as an oil (1.595 g) in 50% yield. IR (film): ν 3500–3200 (NH), 1610 (N–CO), 1190 (C–O–C) cm^{-1}. ^1H NMR ($CDC1_3$): δ 1.42–1.85 (m, 9H, **CH_2**, **NH**), 2.36 (t, 2H, **CH_2**CO, $J = 6.5$), 2.62–2.76 (m, 2H, NH**CH_2**CH_2), 2.92 (dd, 1H, CH**CH_2**NH, $J = 4.7$, $J = 13.0$), 2.97 (dd, 1H, CH**CH_2**NH, $J = 5.9$, $J = 13.0$), 3.26 (t, 2H, **CH_2**NCO, $J = 7.1$), 3.36 (t, 2H, **CH_2**NCO, $J = 7.1$), 4.04 (dd, 1H, O**CH_2**, CH, $J = 7.9$, $J = 11.8$), 4.28 (dd, 1H, O**CH_2**CH, $J = 2.4$ $J = 11.8$), 4.43–4.51 (m, 1H, **CH**), 6.84 (dd, 1H, **H_7**, $J = 4.7$, $J = 7.9$), 7.18 (dd, 1H, **H_8**, $J = 1.2$, $J = 7.9$), 7.80 (dd, 1H, **H_6**, $J = 1.2$, $J = 4.7$). MS (CI/NH_3): m/z 320 [$M + 1$]; *Anal.* Calc. (C_{17} $H_{25}N_3O_3$) C, H, N.

*5.8. 1-[4-[N-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridine-3-ylmethyl) amino]butyl]hexahydro-2H-azepine-2-one (**1f**)*

This compound, prepared according to the method used for **1a** from **2** (1.660 g, 10.0 mmol) and 1-(4-bromobutyl)-2-azepinone (2.980 g, 12.0 mmol), was obtained after column chromatography (eluent: 47:47:6, Et_2O–CH_2C1_2–MeOH) as an oil (1.565 g) in 47% yield. IR (film): ν 3600–3200 (NH), 1630 (N–CO), 1160 (C–O–C) cm^{-1}. ^1H NMR ($CDC1_3$): δ 1.45–1.79 (m, 10H, **CH_2**), 2.41 (br s, 1H, **NH**), 2.46–2.53 (m, 2H, **CH_2**CO), 2.71–2.80 (m, 2H, NH**CH_2**CH_2), 2.92 (dd, 1H, CH**CH_2**NH, $J = 5.0$, $J = 13.1$), 2.97 (dd, 1H, CH**CH_2**NH, $J = 6.2$, $J = 13.1$), 3.28–3.41 (m, 4H, **CH_2**NCO), 4.04 (dd, 1H, O**CH_2**CH, $J = 7.1$, $J = 11.4$), 4.27 (dd, 1H, O**CH_2**CH, $J = 1.4$, $J = 11.4$), 4.51–4.61 (m, 1H, **CH**), 6.85 (dd, 1H, **H_7**, $J = 4.7$, $J = 7.6$), 7.18 (dd, 1H, **H_8**, $J = 0.9$, $J = 7.6$), 7.80 (dd, 1H, **H_6**, $J = 0.9$, $J = 4.7$). MS (CI/NH_3): m/z 334 [$M + 1$]; *Anal.* Calc. ($C_{18}H_{27}N_3O_3$) C, H, N.

*5.9. 1-(2-Chloro-3-pyridinyloxy)-3-[N-benzyl-N-[3-(benzyloxy) propyl]amino]propan-2-ol (**4**)*

To a solution of 2-chloro-3-(oxiranylmethoxy)-pyridine **3** [24] (0.925 g, 5.0 mmol) in dry tetrahydrofuran (THF) (30 ml) was added dropwise *N*-benzyl-*N*-[3-(benzyloxy)propyl]amine [25] (3.810 g, 14.9 mmol). The mixture was then heated to 60°C for 24 h. After total consumption of **3**, the solution was allowed to cool to room temperature and hydrolyzed with water (50 ml). The product was extracted with CH_2Cl_2. The organic layer was washed with a saturated sodium hydrogen carbonate solution. The solvents were removed under reduced pressure and the crude product was purified by column chromatography (eluent: 1:1, Et_2O–CH_2C1_2) to give the expected alcohol as an oil (2.135 g) in 97% yield. IR (film): ν 3600–3200 (OH), 1290 and 1210 (C–O–C) cm^{-1}. ^1H NMR ($CDC1_3$, D_2O): δ 1.80–1.91 (m, 2H, **CH_2**), 2.58–2.82 (m, 4H, **CH_2**N), 3.52 (t, 2H, **CH_2**O, $J = 6.0$), 3.56 (d, 1H, N**CH_2**Ph, $J = 13.3$), 3.79 (d, 1H, N**CH_2**Ph, $J = 13.3$), 3.98 (d, 2H, O**CH_2**CH, $J = 4.7$), 4.00–4.10 (m, 1H, **CH**), 4.45 (s, 2H, O**CH_2**Ph), 7.15–7.38 (m, 12H, **H_7**, **H_8**, **H_{arom}**), 7.98 (dd, 1H, **H_6**, $J = 1.9$, $J = 3.8$); *Anal.* Calc. ($C_{25}H_{29}N_2O_3C1$) C, H, N.

*5.10. 3-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridine)yl-N-benzyl-N-[3-(benzyloxy)propyl]methanamine (**5**)*

To a suspension of sodium hydride (0.048 g, 60% dispersion in mineral oil, 1.2 mmol) in ethylene glycol dimethyl ether (DME) (5 ml) was added dropwise the alcohol **4** (0.440 g, 1.0 mmol) in DME (7 ml). The mixture was heated to 80°C for 20 h. After hydrolysis, the product was extracted with CH_2C1_2 and the organic layer was washed with saturated sodium hydrogen carbonate solution, dried over magnesium sulfate and evaporated. A flash chromatography (eluent: 1:1, Et_2O–CH_2C1_2) gave the expected compound **5** as an oil (0.240 g) in 60% yield. IR (film): ν 1280 and 1220 (C–O–C) cm^{-1}. ^1H NMR ($CDC1_3$): δ 1.73–1.89 (m, 2H, **CH_2**), 2.62–2.75 (m, 2H, CH_2**CH_2**N), 2.71 (dd, 1H, CH**CH_2**N, $J = 5.9$, $J = 13.6$), 2.85 (dd, 1H, CH**CH_2**N, $J = 4.7$, $J = 13.6$), 3.53 (t, 2H, O**CH_2**CH_2, $J = 6.9$), 3.55 (d, 1H, N**CH_2**Ph, $J = 13.5$), 3.75 (d, 1H, N**CH_2**Ph, $J = 13.5$), 3.81 (dd, 1H, O**CH_2**CH, $J = 6.9$, $J = 10.4$), 4.25 (dd, 1H, O**CH_2**CH, $J = 1.4$, $J = 10.4$), 4.27–4.45 (m, 1H, **CH**), 4.46 (s, 2H, O**CH_2**Ph), 6.81 (dd, 1H, **H_7**, $J = 4.7$, $J = 8.3$), 7.12 (d, 1H, **H_8**, $J = 8.3$), 7.14–7.37 (m, 10H, **H_{arom}**), 7.79 (d, 1H, **H_6**, $J = 4.7$); *Anal.* Calc. ($C_{25}H_{28}N_2O_3$) C, H, N.

*5.11. 3-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridine)yl-N-(3-hydroxy propyl)methanamine (**6**)*

To a solution of **5** (0.405 g, 1.0 mmol) in MeOH (10 ml) were added a few concentrated hydrochloride acid drops and palladium on 10% carbon (0.040 g). The mixture was stirred at room temperature in a Parr apparatus under hydrogen pressure (45 psi). After 24 h, the palladium catalyst was filtered and washed with MeOH. The solution was neutralized with K_2CO_3 and **6** was obtained, after column chromatography (eluent: 9:1, CH_2C1_2–MeOH), as an oil (0.175 g) in 78% yield. IR (film): ν 3500–3100 (NH, OH) cm^{-1}. ^1H NMR ($CDC1_3$, D_2O): δ 1.71–1.83 (m, 2H, **CH_2**), 2.88–3.08 (m, 4H, **CH_2**N), 3.82 (t, 2H, **CH_2**OH, $J = 5.1$), 4.03 (dd, 1H, O**CH_2**CH, $J = 7.9$, $J = 11.4$), 4.29 (dd, 1H, O**CH_2**CH, $J = 2.0$, $J = 11.4$), 4.47–4.55 (m, 1H, **CH**), 6.88 (dd, 1H, **H_7**, $J = 4.6$, $J = 8.2$), 7.20 (dd,1H, **H_8**, $J = 1.0$, $J = 8.2$), 7.83 (dd,1H, **H_6**, $J = 1.0$, $J = 4.6$); *Anal.* Calc. ($C_{11}H_{16}N_2O_3$) C, H, N.

*5.12. 8-[3-[N-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridine-3-ylmethyl) amino]propyl]-8-azaspiro[4.5]decane-7,9-dione (**1g**)*

To a solution of alcohol **6** (0.460 g, 2.1 mmol) in dry THF (8 ml) were added triphenylphosphine (0.700 g, 2.7 mmol) and tetramethylene glutarimide (0.516 g, 3.1 mmol). The mixture was stirred for 15 min and cooled to 0°C. Diethyl azodicarboxylate (0.42 ml, 2.68 mmol) was added dropwise. After stirring for 2 h at room temperature, the solution was hydrolyzed and the product was extracted with CH_2C1_2. Column chromatography (eluent: 95:5, Et_2O–MeOH) gave the expected derivative **1g** as an oil (0.570g) in 74% yield. IR (film): *v* 3600–3300 (NH), 1710 and 1650 (N–CO), 1185 (C–O–C) cm^{-1}. ^1H NMR ($CDC1_3$): δ 1.48–1.58 (m, 2H, **CH_2**), 1.66–1.84 (m, 9H, **CH_2**, **NH**), 2.62 (s, 4H, **CH_2**CO), 2.63–2.75 (m, 2H, NH**CH_2**CH_2), 2.94 (dd, 1H, CH**CH_2**NH, $J = 4.7$, $J = 12.6$), 3.00 (dd, 1H, CH**CH_2**NH, $J = 5.5$, $J = 12.6$), 3.87 (t, 2H, **CH_2**NCO, $J = 7.1$), 4.08 (dd, 1H, O**CH_2**CH, $J = 7.9$, $J = 11.3$), 4.34 (dd, 1H, O**CH_2**CH, $J = 2.4$, $J = 11.3$), 4.42–4.52 (m, 1H, **CH**), 6.88 (dd, 1H, **H_7**, $J = 4.7$, $J = 7.9$), 7.21 (dd, 1H, **H_8**, $J = 1.2$, $J = 7.9$), 7.83 (dd, 1H, **H_6**, $J = 1.2$, $J = 4.7$). MS (CI/NH_3): *m*/*z* 374 [$M + 1$]; *Anal.* Calc. ($C_{20}H_{27}N_3O_4$) C, H, N.

*5.13. 1,3-Dihydro-2-[3-[N-(2,3-dihydro-1,4-dioxino-[2,3-b]pyridine-3-ylmethyl)amino]propyl]-1,3-dioxino-2H-isoindole (**1h**)*

The amine **1h** was prepared according to the method used for **1g** from **6** (0.500 g, 2.23 mmol) and phthalimide (0.491 g, 3.34 mmol). Column chromatography (eluent: 47:47:6 Et_2O–CH_2Cl_2–MeON) gave the expected product **1h** as a white solid (0.582 g) in 68% yield: m.p. 164–165°C. IR (KBr): *v* 3500–3200 (NH), 1760 and 1700 (N–CO), 1185 (C–O–C) cm^{-1}. ^1H NMR ($CDC1_3$): δ 1.50 (br s, 1H, **NH**), 1.82–1.92 (m, 2H, **CH_2**), 2.65–2.80 (m, 2H, NH**CH_2**), 2.89–3.00 (m, 2H, CH**CH_2**NH), 3.80 (m, 2H, **CH_2**NCO), 4.04 (m, 1H, O**CH_2**CH), 4.29 (m, 1H, O**CH_2**CH), 4.38–4.46 (m, 1H, **CH**), 6.85 (m, 1H, **H_7**), 7.16 (m, 1H, **H_8**), 7.68–7.70 (m, 2H, **H_{arom}**), 7.79–7.88 (m, 3H, **H_6**, **H_{arom}**). MS (CI/NH_3): *m*/*z* 354 [$M + 1$]; *Anal.* Calc. ($C_{19}H_{19}N_3O_4$) C, H, N.

*5.14. 3-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridine)yl-N-methyl-N-benzyl-methanamine (**7**)*

The compound **7** was obtained in two steps according to the method used for **5** from the epoxide **3** (1.250 g, 6.7 mmol) and *N*-methyl-*N*-benzylamine (1.621 g, 13.4 mmol). After distillation of the *N*-methyl-*N*-benzylamine in excess, the expected alcohol was purified by chromatography (eluent: 1:1, petroleum ether–Et_2O) and was obtained as an oil (1.860 g) in 90% yield. IR (film): *v* 3500–3200 (OH), 1285 and 1205 (C–O–C) cm^{-1}. ^1H NMR ($CDC1_3$): δ 2.30 (s, 3H, **CH_3**), 2.60 (dd, 1H, **CH_2**N, $J = 4.7$, $J = 12.4$), 2.72 (dd, 1H, **CH_2**N, $J = 8.9$, $J = 12.4$), 3.50 (d, 1H, **CH_2**Ph, $J = 13.1$), 3.72 (d, 1H, **CH_2**Ph, $J = 13.1$), 4.00–4.06 (m, 3H, O**CH_2**, **OH**), 4.08–4.17 (m, 1H, **CH**), 7.11–7.35 (m, 7H, **H_8**, **H_7**, **H_{arom}**), 7.97 (dd, 1H, **H_6**, $J = 1.4$, $J = 4.7$).

The alcohol described above (0.337 g, 1.1 mmol) was then treated in the presence of sodium hydride to give, after column chromatography (eluent: 1:1, petroleum ether–AcOEt), the expected amine **7** as an oil (0.178 g) in 60% yield. IR (film): *v* 1190 (C–O–C) cm^{-1}. ^1H NMR ($CDC1_3$): δ 2.35 (s, 3H, **CH_3**), 2.72 (dd, 1H, **CH_2**N, $J = 7.1$, $J = 13.3$), 2.79 (dd, 1H, **CH_2**N, $J = 5.0$, $J = 13.3$), 3.53 (d, 1H, **CH_2**Ph, $J = 12.8$), 3.65 (d, 1H, **CH_2**Ph, $J = 12.8$), 3.93 (dd, 1H, **CH_2**O, $J = 7.6$, $J = 11.4$), 4.33 (dd, 1H, **CH_2O**, $J = 2.4$, $J = 11.4$), 4.39–4.48 (m, 1H, **CH**), 6.83 (dd, 1H, **H_7**, $J = 4.7$, $J = 7.7$), 7.15 (dd, 1H, **H_8**, $J = 1.2$, $J = 7.7$), 7.24–7.32 (m, 5H, **H_{arom}**), 7.53 (dd, 1H, **H_6**, $J = 1.2$, $J = 4.7$); *Anal.* Calc. ($C_{16}H_{18}N_2O_2$) C, H, N.

*5.15. 3-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridine)yl-N-methylmethanamine (**8**)*

The compound **8** was obtained according to the method used for the preparation of **6** from the amine **7** (2.106 g, 7.8 mmol). After column chromatography (eluent: CH_2C1_2), **8** was obtained as an oil (1.380 g) in 82% yield. IR (film): *v* 3500–3150 (NH), 1185 (C–O–C) cm^{-1}. ^1H NMR ($CDC1_3$, D_2O): δ 2.50 (s, 3H, **CH_3**), 2.91 (dd, 1H, **CH_2**N, $J = 4.7$, $J = 12.8$), 2.97 (dd, 1H, **CH_2**N, $J = 6.4$, $J = 12.8$), 4.04 (dd, 1H, O**CH_2**, $J = 7.7$, $J = 11.6$), 4.29 (dd, 1H, O**CH_2**, $J = 2.2$, $J = 7.7$), 4.46–4.55 (m, 1H, **CH**), 6.86 (dd, 1H, **H_7**, $J = 4.6$, $J = 7.7$), 7.18 (dd, 1H, **H_8**, $J = 1.0$, $J = 7.7$), 7.82 (dd, 1H, **H_6**, $J = 1.0$, $J = 4.6$). MS (CI/NH_3): *m*/*z* 181 [$M + 1$]; *Anal.* Calc. ($C_9H_{12}N_2O_2$) C, H, N.

*5.16. 8-[4-[N-(2,3-Dihydro-1,4-dioxino[2.3-b]pyridine-3-ylmethyl)-N-methylamino]butyl]-8-azaspiro[4.5]-decane-7,9-dione (**1i**)*

The compound **1i** was prepared according to the method used for **1a** from **8** (1.800 g, 10.0 mmol) and 8 - (4 - bromobutyl) - 8 - azaspiro[4.5]decane - 7,9 - dione (3.625 g, 12.0 mmol). Column chromatography (eluent: Et_2O) gave the expected derivative **1i** (3.570 g) in 89% yield. IR (film): *v* 1705 and 1650 (N–CO), 1175 (C–O–C) cm^{-1}. ^1H NMR ($CDC1_3$): δ 1.31–1.51 (m, 8H, **CH_2**), 1.57–1.68 (m, 4H, **CH_2**), 2.23 (s, 4H, CO**CH_2**), 2.29–2.46 (m, 2H, N**CH_2**CH_2), 2.51 (s, 3H, N**CH_3**), 2.58 (dd, 1H, CH**CH_2**N, $J = 7.1$, $J = 13.8$), 2.65 (dd, 1H, CH**CH_2**N, $J = 4.7$, $J = 13.8$), 3.68 (t, 2H, **-mCH_2**NCO, $J = 7.1$), 3.92 (dd, 1H, O**CH_2**, $J = 7.1$, $J = 11.1$), 4.27 (dd, 1H, O**CH_2**,

$J = 2.4$, $J = 11.1$), 4.31–4.38 (m, 1H, **CH**), 6.76 (dd, 1H, $\mathbf{H_7}$, $J = 4.7$, $J = 7.9$), 7.09 (dd, 1H, $\mathbf{H_8}$, $J = 2.0$, $J = 7.9$), 7.72 (dd, 1H, $\mathbf{H_6}$, $J = 2.0$, $J = 4.7$). MS (CI/NH_3): m/z 402 [$M + 1$]; *Anal.* Calc. ($C_{22}H_{31}N_3O_4$) C, H, N.

*5.17. 1,3-Dihydro-2-[4-[N-(2,3-dihydro-1,4-dioxino-[2,3-b]pyridine-3-ylmethyl)-N-methylamino]butyl]-1,3-dioxo-2H-isoindole (**1j**)*

The compound **1j** was prepared according the method used for **1a** from **8** (1.800 g, 10.0 mmol). Column chromatography (eluent: Et_2O) afforded the expected product **1j** as an oil (3.350 g) in 88% yield. IR (film): ν 1760 and 1700 (N–CO), 1185 (C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.41–1.73 (m, 4H, $\mathbf{CH_2}$), 2.27 (s, 3H, $\mathbf{NCH_3}$), 2.36–2.52 (m, 2H, $\mathbf{NCH_2}CH_2$), 2.63 (dd, 1H, $CH\mathbf{CH_2}N$, $J = 4.9$, $J = 12.0$), 2.70 (dd, 1H, $CH\mathbf{CH_2}N$, $J = 6.1$, $J = 12.0$), 3.67 (t, 2H, $\mathbf{CH_2}NCO$, $J = 7.1$), 3.95 (dd, 1H, $\mathbf{OCH_2}$, $J = 7.9$, $J = 11.8$), 4.30 (dd, 1H, $\mathbf{OCH_2}$, $J = 1.9$, $J = 11.8$), 4.32–4.41 (m, 1H, **CH**), 6.79 (dd, 1H, $\mathbf{H_7}$, $J = 7.7$, $J = 4.6$), 7.10 (dd, 1H, $\mathbf{H_8}$, $J = 7.7$, $J = 1.6$), 7.64–7.71 (m, 2H, $\mathbf{H_{arom}}$), 7.73–7.80 (m, 3H, $\mathbf{H_6}$, $\mathbf{H_{arom}}$). MS (CI/NH_3): m/z 382 [$M + 1$]; *Anal.* Calc. ($C_{21}N_{23}N_3O_4$) C, H, N.

6. Pharmacology

6.1. Binding experiments [28–33]

Radioligand binding studies were carried out on several different brain membrane fractions as follows: in vitro test for inhibition of 8-OH-DPAT binding to 5-HT_{1A} receptor in rat brain hippocampal membrane homogenates; in vitro test for inhibition of 5-HT binding to 5-HT_{1B} receptor in rat brain striatal membrane homogenates; in vitro test for inhibition of 5-HT binding to 5-HT_{1D} receptor in pig brain striatal membrane homogenates; in vitro test for inhibition of ketanserin binding to 5-HT_{2A} receptor in rat brain frontal cortex membrane homogenates; in vivo test for inhibition of mesurlergine binding to 5-HT_{2C} receptor in pig brain choroïd plexus membrane homogenates; in vitro test for inhibition of prazosine binding to α_1-adrenoreceptor in rat brain cortex membrane homogenates; in vitro test for inhibition of ranwolsane binding to α_2-adrenergic receptors in rat brain cortex membrane homogenates and the in vitro test for the inhibition of spiperone binding to dopaminergic D_2 receptors in rat brain striatal membrane homogenates.

6.2. *Method of lower lip retraction test in rats (LLR) [34]*

On the day of the experiment the rats (male, 180–350 g, 10 animals per treatment) were transported to the experimental room in their home cages. They were weighed and the test or reference compound (buspirone, 8-OH-DPAT, MDL72832) was administered. Immediately following treatment the rats were placed individually into the observation cages and 15, 30 and 45 min later they are scored for lower lip retraction as follows:

0 = lower incisors hidden or hardly visible (not different from untreated rats);
0.5 = lower incisors partly visible;
1 = lower incisors completely visible.

After the last observation the rats are replaced in their home cages. They are used at most three times in similar experiments with periods of rest of at least five days between experiments. Hereafter they are sacrificed using CO_2-gas.

6.3. Method of test for modification of EEG-defined sleep-waking behaviour in rats [35–38]

The rats (male rats, 250–350 g at surgery, 400–650 g during the experiment) are weighed and the test compound given by ip, sc or po administration at 8.00–9.00 h or at 18.00–19.00 h (winter-time). Following administration, each rat is immediately connected to the recording cable and placed in the experimental cage after which recording is started. The point of time of administration and start of recording are recorded. The hypnograms for the different rats are synchronized with respect to the recording start time. Between the administration of the first and the last rat a time span of 20 to 30 min elapses. The rats are left in their cages for 8, 24 or 29 h and are inspected for external signs of toxicity before they are replaced in their housing cages. The recordings of EEG and EMG from rats which show an abnormal sleep-waking behaviour, are visually inspected. A wash-out period of at least two weeks is allowed before the rats are used again in another experiment. The rats are used at most for fifteen experiments after which they are sacrificed with CO_2-gas.

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