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Diastereomeric separation of 1,5-benzodiazepines due to the presence of a chiral centre on the N-5 alkylic chain

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Abstract

The presence of a chain bearing a stereogenic centre at the N-5 position of 1-(1-adamantylmethyl)-3-arylureido-2,4-dioxo-1,5-benzodiazepines induces optical resolution. The synthesis of these compounds and their potency as potential CCK-B receptor antagonists is discussed briefly here. © 1998 Elsevier Science S.A.

Keywords: Cholecystokinin (CCK); 1,5-Benzodiazepines; Optical resolution

1. Introduction

The peptide Cholecystokinin (CCK) is present both in the central nervous system and in the gastrointestinal tract. The peripheral effects are mediated mainly through the A receptor subtype, while the central effects mainly by the B subtype. Amongst others, it has been demonstrated that CCK-B antagonists display anxiolytic activity [1–8].

During our search for a new CCK-B antagonist, a number of 1-alkyl-5-aryl-3-ureido-1,5-benzodiazepines derivatives of general formula **1** (Fig. 1) were synthesised [9–12]. It was noticed that the substituent at the N-1 position played an important role in achieving good selectivity for the type B receptors. In particular, the compound GV150013 bearing a bulky and lipophilic group such as 1-adamantylmethyl at N-1 was found to have a very good pharmacological profile (pK_i CCK-B = 9.02, selectivity B/A = 1175) and was recommended for exploratory development for the treatment of CNS disorders (Fig. 2) [10,11].

Further studies were directed to the synthesis of more hydrophilic compounds, which retained the binding and selectivity properties of GV150013. With this aim, we focused our work on the replacement of the N-5 aromatic ring [13,14] with a variety of alkyls bearing basic groups [15,16].

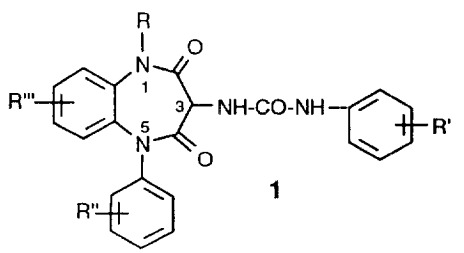

Fig. 1. 1-Alkyl-5-aryl-3-ureido-1,5-benzodiazepines.

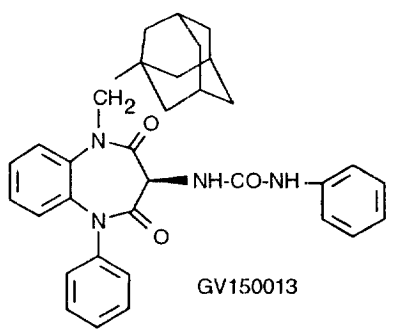

Fig. 2. Lead compound in the 1-alkyl-5-aryl series.

Considering that in the 5-aryl substituted series, the resolution at the C-3 position was crucial for both activity and selectivity [9,10], we considered the separation of new compounds into enantiomers also in this series. The introduction of a basic group in the alkyl chain would improve water solubility although the basic group would probably lead to a more difficult resolution with optically active acids (e.g. camphorsulfonic acid) [16]. On the other hand, optical resolution

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of benzodiazepines via formation of diastereomers is obtained by reaction of the 3-amino benzodiazepine with a chiral auxiliary [16,17].

However, during our search, amongst all the possible aminosubstituted alkyl chains to introduce at the N-5 position [15], the chiral 2-(*R*)-amino-3-hydroxypropyl group was also considered (Fig. 3).

In our mind, in fact, both the aminic and alcoholic functionalities could confer the desired improved hydrophilic characteristics while the stereogenic centre would induce separation of the diastereomers.

The synthesis of the diastereomers bearing a stereogenic centre on the N-5 substituent and the binding data showing their selective CCK-B receptor ligands properties are briefly reported here.

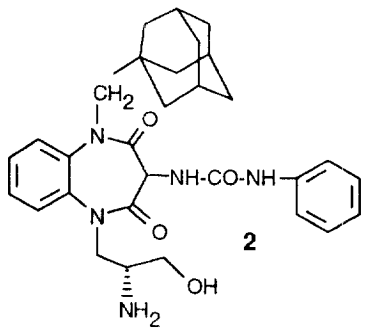
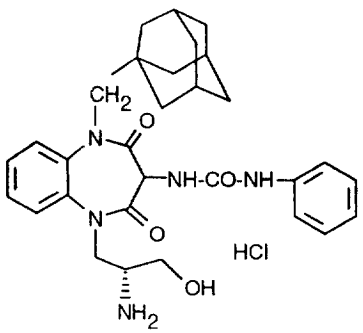


Fig. 3. N-5-[2-(*R*)-Amino-3-hydroxypropyl] derivatives.

Table 1
Potency of CCK ligands **2**, **2a** and **2b**, in inhibiting [^{3}H]CCK$_{8s}$ specific binding



Compound	Isomer	pK_i		Selectivity
		CCK-A	CCK-B	B/A
2	racemate	5.04 ± 0.05	8.18 ± 0.05	1380
2a	diastereomer 1	4.81 ± 0.10	8.49 ± 0.07	4786
2b	diastereomer 2	5.26 ± 0.11	7.34 ± 0.04	120

2. Chemistry

As outlined in Scheme 1, condensation of 2-nitroaniline (**3**) with adamantylcarbonyl chloride in the presence of triethylamine gave the nitro intermediate **4**, which was submitted to two subsequent reductions to obtain the aniline **6**. The hydroxyaminopropyl substituent at the 5 position was introduced via reductive amination using a chiral Boc-oxazolidine derivative [18] to give intermediate **7**, which was then converted to **8** by reaction with phenylhydrazonomalonyl dichloride [19].

Next catalytic hydrogenation led to the amine **9**. In order to separate the isomers, the latter was treated first with trifluoroacetic acid, following a known methodology [20], then with phenyl isocyanate to give the two ureido derivatives **10a** and **10b**. These were separated by flash chromatography, although some mixed fractions (**10**) were also obtained. Treatment of the mixture **10** and of both single diastereomers with gaseous hydrochloric acid in methanol led to final derivatives **2**, **2a** and **2b**, respectively.

The same synthetic sequence was applied to the (*S*) series of oxazolidine derivatives, although in this case no separation of the final diastereomers was obtained.

3. Results and discussion

All the compounds synthesised were tested in vitro in order to evaluate their CCK-A [21] and CCK-B [22] receptor affinity and thus their B/A selectivity (Table 1).

As for the 5-aryl series, different receptor affinity for the stereoisomers has been observed. In fact, after diastereomeric separation, the (−) diastereomer (**2a**) showed an increased affinity toward the CCK-B receptor coupled with a decrease of affinity for the CCK-A one.

The diastereomer with the (*S*) chain at the N-5 position did not show any interesting values with respect to the (*R*) one (pK_i CCK-A = 5.39, pK_i CCK-B = 7.52, selectivity B/A = 135) and therefore no more attempts for diastereomeric separation were done.

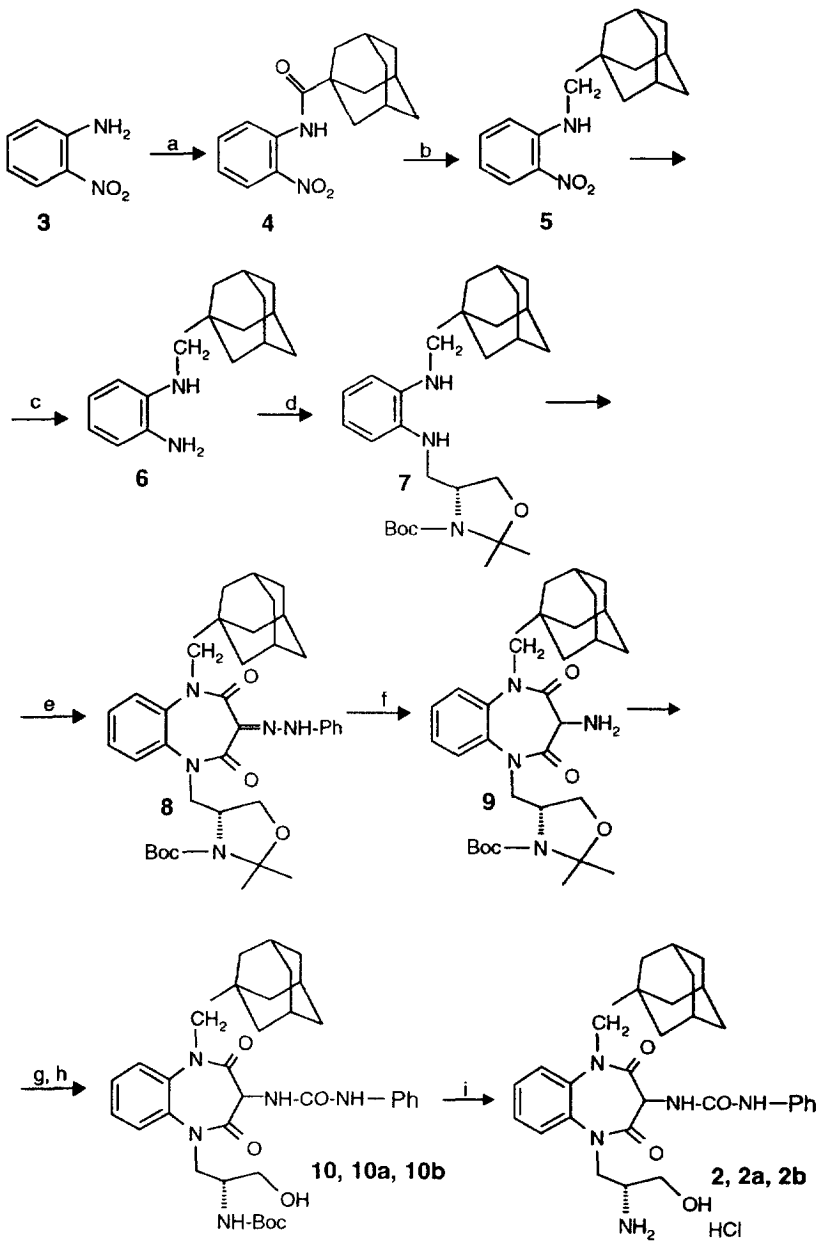
4. Conclusions

In conclusion, the initial intuition that separation at the C-3 position of the 1,5-benzodiazepine ring could be induced by an appropriate substituent at the N-5 position was validated by using a 2-(*R*)-amino-3-hydroxypropyl group. Furthermore, also in this case a strong selectivity toward the CCK-B receptor depending on the chirality at the C-3 position was demonstrated.

5. Experimental

5.1. Chemistry

Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected.



Scheme 1. (a) 1-Adamantylchloroformate, TEA, acetone; (b) BH_3 Me_2S, toluene; (c) $Na_2S_2O_4$, K_2CO_3, EtOH–H_2O; (d) 1,1-dimethylethyl (*R*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate, $NaBH_3CN$, MeOH, AcOH; (e) $PhNHN{=}C(COCl)_2$, THF; (f) Pd/C, *p*-TsOH, MeOH; (g) TFA, CH_2Cl_2; (h) PhNCO; (i) HCl_g, MeOH.

Proton magnetic resonance (^{1}H NMR) was recorded on a Varian 300 MHz spectrometer and chemical shifts are reported in ppm downfield from tetramethylsilane. IR spectra were recorded on an FT-IR instrument. FAB positive mass spectra were taken on a VG Quattro mass spectrometer.

Optical rotations were determined at 20°C with a Jasco DIP 360 instrument (l = 10 cm, cell volume = 1 ml, λ = 589 nm).

Flash silica gel chromatography employed Kieselgel 60, 230–400 mesh, supplied by Merck AG Darmstadt, Germany. TLC analysis were performed on silica gel 60 F-254 plates and visualised by charring with 4% phosphomolybdic acid in ethanol.

All solutions were dried over anhydrous sodium sulfate.

Methylene chloride was redistilled over calcium hydride; tetrahydrofuran was redistilled over sodium and ethyl acetate was dried over activated molecular sieves.

The following abbreviations are used in the text: AcOEt = ethyl acetate, THF = tetrahydrofuran, MeOH = methanol, DMF = *N*,*N*-dimethylformamide.

5.1.1. 1-(1-Adamantyl)carbonylamino-2-nitrobenzene (4)

A solution of 1-adamantanecarbonyl chloride (17.95 g, 0.0903 mol) in acetone (60 ml) was dropped into a solution of 2-nitroaniline (**3**) (10.4 g, 0.0753 mol) and triethylamine (12.6 ml, 0.0903 mol) in acetone (50 ml), at 23°C under a

nitrogen atmosphere. The mixture was stirred at 23°C for 22 h, then further acetone (50 ml) was added and the mixture was heated at 70°C for 3 h. The mixture was allowed to cool to r.t., then filtered. The brown solid obtained was crystallised from acetone to give **4** as a yellow solid (17.3 g).

Yield = 77%. TLC cyclohexane–AcOEt 10:2, R_f 0.67. M.p. 105–110°C. IR (nujol): 3342 (NH), 1697 (C=O), 1585 and 1337 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$): 10.68 (s, 1H), 8.85 (d, 1H), 8.22 (d, 1H), 7.64 (t, 1H), 7.15 (t, 1H), 2.13 (m, 2H), 2.6–1.5 (m, 15H). Mass spectrum: *m/z* 301 $[M+H]^+$.

5.1.2. 1-(1-Adamantyl)methylamino-2-nitrobenzene (5)

Borane dimethylsulfide complex (10 M solution, 6.0 ml) was dropped into a solution of intermediate **4** (13.5 g, 0.045 mol) in dry toluene (160 ml) previously cooled to 10°C under a nitrogen atmosphere. The solution was stirred at 10°C for 15 min, then heated at 110°C for 1 h. The solution was allowed to cool to r.t., then a 10% potassium carbonate solution (50 ml) was cautiously added and the mixture was stirred at 23° for 40 min. The layers were separated; the organic extract was washed with brine (50 ml), dried and concentrated in vacuo to a slurry solid, which was purified by flash chromatography (eluting with cyclohexane–AcOEt 10:1) to give **5** as an orange solid (7.0 g).

Yield = 54%. TLC cyclohexane–AcOEt 10:1, R_f 0.68. M.p. 106–109°C. IR (nujol): 3371 (NH), 1620 (C=C), 1574 and 1377 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$): 8.29 (s, 1H), 8.16 (d, 1H), 7.40 (m, 1H), 6.88 (d, 1H), 6.59 (m, 1H), 2.98 (d, 2H), 2.03 (m, 3H), 1.80–1.6 (m, 12H). Mass spectrum: *m/z* 286 $[M]^+$.

5.1.3. 2-(1-Adamantylmethyl)amino-aniline (6)

A solution of potassium carbonate (23.2 g, 0.168 mol) and sodium hydrosulfite (20.9 g, 0.12 mol) in water (150 ml) was added to a mixture of intermediate **5** (6.9 g, 0.024 mol) in ethanol (50 ml) and water (150 ml). The mixture was stirred at 23°C for 30 min, then acidified with conc. hydrochloric acid until pH = 3 and concentrated to half volume. The mixture was then basified with a 10% sodium hydroxide solution until pH = 10 and extracted with ethyl acetate (2×300 ml); the combined extracts were washed with brine (150 ml), dried and concentrated in vacuo to give **6** as a grey solid (5.0 g).

Yield = 81%. TLC cyclohexane–AcOEt 10:2, R_f 0.36. M.p. 101–104°C. IR (nujol): 3395 and 3342 (NH), 1616 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): 6.82 (m, 1H), 6.72 (m, 1H), 6.67 (m, 1H), 6.64 (m, 1H), 3.33 (s, 3H), 2.77 (s, 2H), 2.02 (m, 3H), 1.80–1.52 (m, 12H). Mass spectrum: *m/z* 256 $[M]^+$.

5.1.4. N-(1-Adamantylmethyl)-N'-[3-(1,1-dimethyl-ethoxycarbonyl)-2,2-dimethyl-4-methylen-oxazolidine]-1,2-phenylenediamine (7)

Acetic acid (1.6 ml, 0.0276 mol) and sodium cyanoborohydride (2.9 g, 0.046 mol) were added to a solution of intermediate **6** (6.0 g, 0.023 mol) and 1,1-dimethyl-(*R*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (7.4 g, 0.032 mol) in methanol (300 ml). The solution was stirred at 23°C for 1 h, then saturated sodium hydrogen carbonate (150 ml) was added and the reaction mixture extracted with ethyl acetate (2×250 ml). The organic extracts were washed with brine (300 ml), dried and concentrated in vacuo to an oil which was purified by flash chromatography (cyclohexane/AcOEt 9:1) to give **7** as a foam (5.86 g).

Yield = 54%. TLC cyclohexane–AcOEt 5:25, R_f 0.4. M.p. = 120°C. IR (nujol): 3400 (NH), 1684 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): 6.90–6.62 (m, 4H), 4.40–3.90 (m, 3H), 3.42–3.14 (m, 3H), 2.75 (m, 2H), 2.02 (m, 3H), 1.80–1.46 (m, 27H). Mass spectrum: *m/z* 469 $[M]^+$, 470 $[M+H]^+$.

5.1.5. 1-(1-Adamantylmethyl)-2,4-dioxo-5-[3-(1,1-dimethylethyloxycarbonyl)-2,2-dimethyl-4-methylen-oxazolidine]-3-phenylhydrazono-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (8)

A solution of **7** (5.8 g, 0.0123 mol) in THF (50 ml) and a solution of phenylhydrazonomalonyl dichloride (4.5 g, 0.018 mol) in THF (50 ml) were dropped simultaneously into a suspension of potassium carbonate (3.8 g, 0.0275 mol) in THF (20 ml) at 23°C under a nitrogen atmosphere. After complete addition, the solution was heated to 80°C for 2 h. The solution was cooled to r.t., diluted with ethyl acetate (300 ml) and washed with a saturated ammonium chloride solution (200 ml) and brine (2×200 ml). The organic layer was dried, concentrated in vacuo and the residue was purified by flash chromatography (cyclohexane/AcOEt 8:2) to give **8** as a foam (4.9 g).

Yield = 62%. TLC cyclohexane–AcOEt 2:1, R_f 0.8. M.p. = 94–95°C. IR (nujol): 1701 and 1672 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): 11.4–10.2 (m, 1H), 7.12–6.88 (m, 9H), 5.40 (m, 1H), 4.80–4.40 (m, 1H), 4.30–3.60 (m, 4H), 3.45–3.12 (m, 1H), 1.90 (m) and 1.75–1.30 (m + many s, 27H). Mass spectrum: *m/z* 642 $[M]^+$.

5.1.6. 1-(1-Adamantylmethyl)-3-amino-2,4-dioxo-5-[3-(1,1-dimethylethyloxycarbonyl)-2,2-dimethyl-4-methylen-oxazolidine]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (9)

p-Toluenesulfonic acid (1.4 g, 0.00788 mol) and 10%Pd/C (1.53 g) were added to a solution of **8** (4.6 g, 0.00717 mol) in methanol (100 ml). The mixture was hydrogenated at 23°C and 4 atm. for 1 h, then filtered on celite and concentrated in vacuo to give **9** as a white foam (3.7 g).

Yield = 85%. TLC AcOEt/MeOH 26:4, R_f 0.4. IR (nujol): 1697 (C=C) cm^{-1}. ^1H NMR (d_6-DMSO spectrum recorded at 80°C): 7.66 (m, 2H), 7.36 (m, 2H), 4.49 (m, 1H), 4.24 (dd, 1H), 4.24–3.86 (m, 3H), 3.99 and 3.92 (dd, 1H), 3.76–3.56 (m, 1H), 3.48 and 3.37 (dd, 1H), 1.94–1.74 (m, 3H), 1.66–1.54 (m, 8H), 1.50–1.10 (m, 21H). Mass spectrum: *m/z* 553 $[M+H]^+$.

*5.1.7. 1-(1-Adamantylmethyl)-2,4-dioxo-5-[3-hydroxy-2-(R)-(1,1-dimethylethyloxycarbonyl)amino-1-propyl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea (**10**, **10a**, **10b**)*

A 0.5 M solution of trifluoroacetic acid in dichloromethane (50 ml) was added to compound **9** (3.3 g, 0.006 mol). The resulting solution was stirred at 23°C for 1 h, then a 5% sodium hydrogen carbonate solution (100 ml) was added. The layers were separated and the organic phase was washed with brine (100 ml), dried and concentrated in vacuo. The residue was dissolved in acetonitrile (50 ml), then phenylisocyanate (0.072 ml) was added. The reaction mixture was stirred at 23°C for 15 h, then concentrated in vacuo to give a mixture of the two isomers.The residue was purified by flash chromatography eluting with cyclohexane/AcOEt 9:1 to give:

(i) isomer 1: (0.6 g) as a white solid (TLC cyclohexane–AcOEt 1:1, $R_f = 0.6$);

(ii) mixture of the two isomers in 1:1 ratio (0.34 g);

(iii) isomer 2: (0.9 g) as a white solid (TLC cyclohexane–AcOEt 1:1, R_f 0.58).

Overall yield = 48%. All diastereomers have m.p. = 180°C.

10a: IR ($CDCl_3$): 3431 (NH, OH), 1699 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): 7.66 (m, 1H), 7.46–7.24 (m, 7H), 7.05–6.99 (m, 2H), 6.34 (d, 1H), 5.42 (d, 1H), 5.16 (d, 1H), 4.39 (d, 1H), 4.30–4.18 (m, 2H), 3.96–3.80 (m, 2H), 3.66 (t, 1H), 3.49 (dd, 1H), 3.19 (d, 1H), 1.83 (m, 3H), 1.66–1.10 (m, 12H), 1.44 (s, 9H). Mass spectrum: *m/z* 632 $[M+H]^+$. $[\alpha]_D = -20.5$ ($c = 0.88$ in $CHCl_3$).

10b: IR (nujol): 3364 (NH, OH), 1697 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): 7.70–7.10 (m, 8H), 6.92 (m, 2H), 6.69 (d, 1H), 5.37 (d, 1H), 5.16 (d, 1H), 4.38 (d, 1H), 4.24–4.00 (m, 2H), 3.96–3.68 (m, 2H), 3.70–3.44 (m, 2H), 3.35 (d, 1H), 1.85 (m, 3H), 1.68–1.20 (m, 12H), 1.41 (s, 9H). Mass spectrum: *m/z* 632 $[M+H]^+$. $[\alpha]_D$42.9 ($c = 0.905$ in $CHCl_3$).

*5.1.8. 1-(1-Adamantylmethyl)-2,4-dioxo-5-[3-hydroxy-2-(R)-amino-1-propyl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea hydrochloride (**2**, **2a**, **2b**)*

Diastereomeric mixture **10** (0.34 g, 0.000538 mol) was dissolved in methanol (50 ml) previously saturated with gaseous HCl and the solution was stirred at 23°C for 4 h. Concentration in vacuo and crystallisation from methanol/diethyl ether led to the desired salt **2** (0.175 g). Yield = 60%.

The same procedure was used for the two separated diastereomers.

M.p. > 250°C for all diastereomers.

2: IR (nujol): 3440–2500 (NH_3^+, NH, OH), 1697–1684 and 1670 (C=O) cm^{-1}. ^1H NMR (d_6-DMSO): 9.20 (s, 1H), 8.36 (s, 1H), 8.09 (s, 2H), 7.74 (m, 2H), 7.46 (m, 2H), 7.33 (m, 2H), 7.21 (m, 2H), 6.90 (m, 2H), 5.69 (t, 1H), 5.41 (t, 1H), 4.92 (dd, 1H), 4.21 (m, 2H), 4.04–3.82 (m, 2H), 3.82–3.56 (m, 2H), 3.40 (m, 1H), 1.79 (m, 3H), 1.64–1.08 (m, 12H). Mass spectrum: *m/z* 532 $[M+H]^+$. *Anal.* Calc. for $C_{30}H_{39}ClN_5O_4$: C, 63.3; H,6.9; N,12.3; Cl, 6.06. Found C, 63.26; H6.9; N, 12.09; Cl, 6.06%.

2a: IR (nujol): 3373–3254 (NH), 3200–2500 (NH_3^+), 1699 and 1661 (C=O) cm^{-1}. ^1H NMR (d_6-DMSO): 9.19 (s, 1H), 8.31 (s, 3H), 7.80–7.64 (m, 2H), 7.46 (m, 2H), 7.33 (d, 2H), 7.21 (t, 2H), 6.90 (t, 1H), 6.88 (d, 1H), 5.40 (t, 1H), 4.91 (d, 1H), 4.22 (dd, 2H), 4.10 (m, 1H), 3.97 (m, 1H), 3.80–3.56 (m, 2H), 3.41 (d, 1H), 1.79 (m, 3H), 1.64–1.15 (m, 12H). Mass spectrum: *m/z* 532 $[M+H]^+$. $[\alpha]_D = -40.7$ ($c = 0.745$ in MeOH).

2b: IR (nujol): 3300–2500 (NH, NH_3^+), 1695 and 1663 (C=O) cm^{-1}. ^1H NMR (d_6-DMSO): 9.20 (s, 1H), 8.09 (s, 3H), 7.76 (m, 2H), 7.46 (m, 2H), 7.33 (d, 2H), 7.21 (t, 2H), 6.89 (m, 2H), 5.70 (s, 1H), 4.92 (d, 1H), 4.22 (dd, 2H), 3.89–3.75 (m, 3H), 3.50–3.30 (m, 1H), 1.80 (m, 3H), 1.64–1.40 and 1.26–1.10 (m and m, 12H). Mass spectrum: *m/z* 532 $[M+H]^+$. $[\alpha]_D$39.8 ($c = 0.94$ in MeOH).

5.2. Biochemistry

Inhibition constants (K_i) were determined for all compounds in guinea pig brain (CCK-B) and rat pancreas (CCK-A) membranes using [^{3}H]-CCK_{8s} at a concentration of 0.2 nM as the radiolabel. 250 μg (CCK-B) or 70 μg (CCK-A) of membranes were incubated in a total volume of 1 ml at 25 and 37°C, respectively. Receptor density (B_{max}) and the K_D for the radiolabel were determined in separate saturation binding isotherms. Non-specific binding was determined in the presence of 1 μM L-365-260 for CCK-B and of 0.1 μM L-364-718 for CCK-A receptors. Bound was separated from free ligand by rapid filtration over Whatman GF/C filters with a Brandel M-48 cell harvester. Filters were rinsed and analysed by liquid scintillation counting on a Packard TriCarb 1900CA.

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