Simple Approach to Highly Functionalized Trisubstituted Tetrahydropyrimidine-2,4-diones from Perhydropyrazino[1,2-f]pyrimidine-3,6,8-trione Precursors

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Received 3 November 2006; revised 24 January 2007

Abstract: Unprecedented trisubstituted tetrahydropyrimidine-2,4-diones were easily synthesized in two steps involving Boc-amide protection and controlled ring opening, from perhydropyrazino[1,2-*f*]pyrimidine-3,6,8-triones. These bicyclic derivatives were prepared by reaction of 2-oxopiperazines derived from dipeptides with isocyanates, followed by cyclization. The monocyclic pyrimidinone derivatives were further elaborated to potential CCK ligands that have contributed to a better understanding of the structural requirements for efficient binding at the CCK_1 receptor.

Key words: heterocycles, peptides, bicyclic compounds, ring opening, medicinal chemistry

Monocyclic and fused dihydropyrimidinones and tetrahydropyrimidin-2-one derivatives have attracted much attention in medicinal chemistry programs due to the large range of biological activities displayed by these compounds.[1,2] In a similar way, the related tetrahydropyrimidin-2,4-dione is the common heterocycle nucleus in biologically active molecules, such as HIV-integrase inhibitors,[3] anti-epileptic agents,[4] ligands for somatostatin receptors,[5] and α-glucosidase inhibitors,[6] among others. Additionally, some tetrahydropyrimidinone derivatives have been used as proline mimetics,[7] and as temporary chiral scaffolds for asymmetric synthesis.[8]

The most common methods for the synthesis of tetrahydropyrimidin-2,4-diones involve the three-component condensation of primary amines, isocyanates and β-dielectrophiles,[9] the reduction and photochemical transformations of dihydropyrimidinone derivatives,[10] and the cyclization of β-amino ester derived ureas.[11]

In recent years, we have dedicated part of our efforts to the design, synthesis and pharmacological study of a family of highly selective CCK_1 receptor antagonists, having a 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine central scaffold (exemplified here by compound **1**, Figure 1).[12] Structure–activity relationship studies on these CCK_1 receptor antagonists showed the importance of the 2-substituent and the Boc-Trp moiety,[13] and suggested that the topography defined by the 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine scaffold is an essential requirement for potent and selective binding to CCK_1 receptors.[14] Thus, the corresponding pyrrolopyrimidine lower homologues (as compound **2**), incorporating a highly constrained five-membered ring instead of the perhydropyridine moiety of **1**, were completely devoid of affinity at CCK_1 receptors.[14] To further investigate this family of pyridopyrimidine CCK ligands, we were interested in derivatives with higher flexibility, but maintaining the essential pyrimidinedione ring. Starting from compound **1**, selected as a representative model, we designed monocyclic compounds of general formula **A** (Figure 1), to establish the significance of the pyrido part of the bicyclic skeleton upon CCK receptors binding. This contribution describes a convenient synthetic procedure for the preparation of suitable 1,3,6-trisubstituted tetrahydropyrimidin-2,4-diones and their application to the preparation of compounds **A**.

Our retrosynthetic planning for compounds **A** identified the perhydropyrazino[1,2-*f*]pyrimidine-3,6,8-triones **B** as key intermediates, and proposed the controlled opening of the pyrazino ring to generate the monocyclic pyrimidinone skeleton (Figure 1). Similar opening of lactams was described for other related heterocyclic systems.[15,16] The synthesis of bicyclic derivatives **B** could be envisaged by elaboration of oxopiperazines **C**, following synthetic protocols similar to that reported for the preparation of 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidines.[12] 2-Oxopiperazines **C** can be easily prepared in two steps from commercially available Z-Xaa-Gly dipeptide derivatives. [17]

The reaction of the 2-oxopiperazines **3**–**5**[17] with phenylisocyanate at 0 °C afforded the corresponding urea derivatives **6**–**8** in excellent yield (80–90%, Scheme 1). However, when the reaction of compound **3** was carried out at room temperature, the expected urea **6** (43%) was formed along with an important amount of the bisurea derivative **9** (34%). Compound **6** was obtained as a racemic mixture starting from racemic **3**, while compounds **7** and **8** were enantiopure, and have 3*S*,5*R* configuration as their immediate precursors **4** and **5**.[17]

SYNTHESIS 2007, No. 7, pp 1047–1053
Advanced online publication: 28.02.2007
DOI: 10.1055/s-2007-965962; Art ID: T16606SS

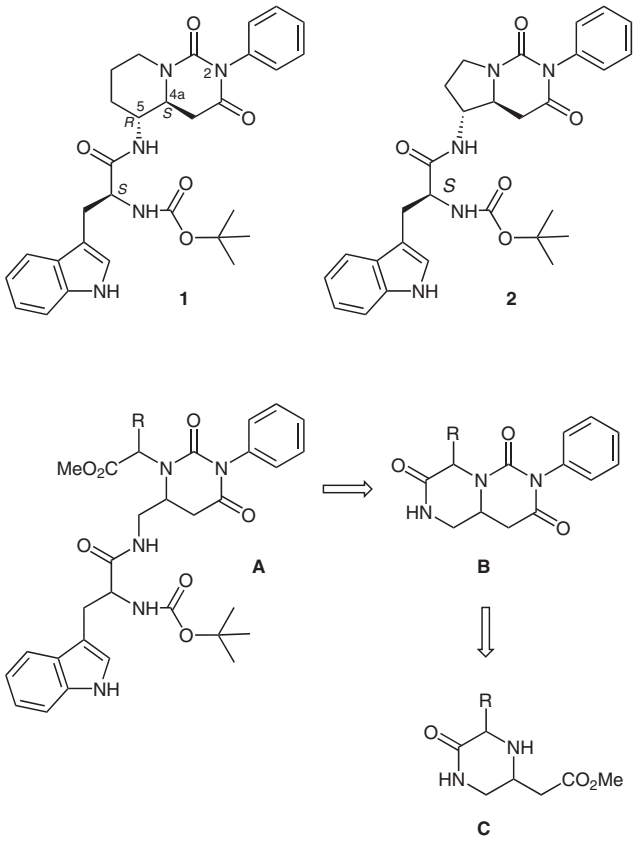
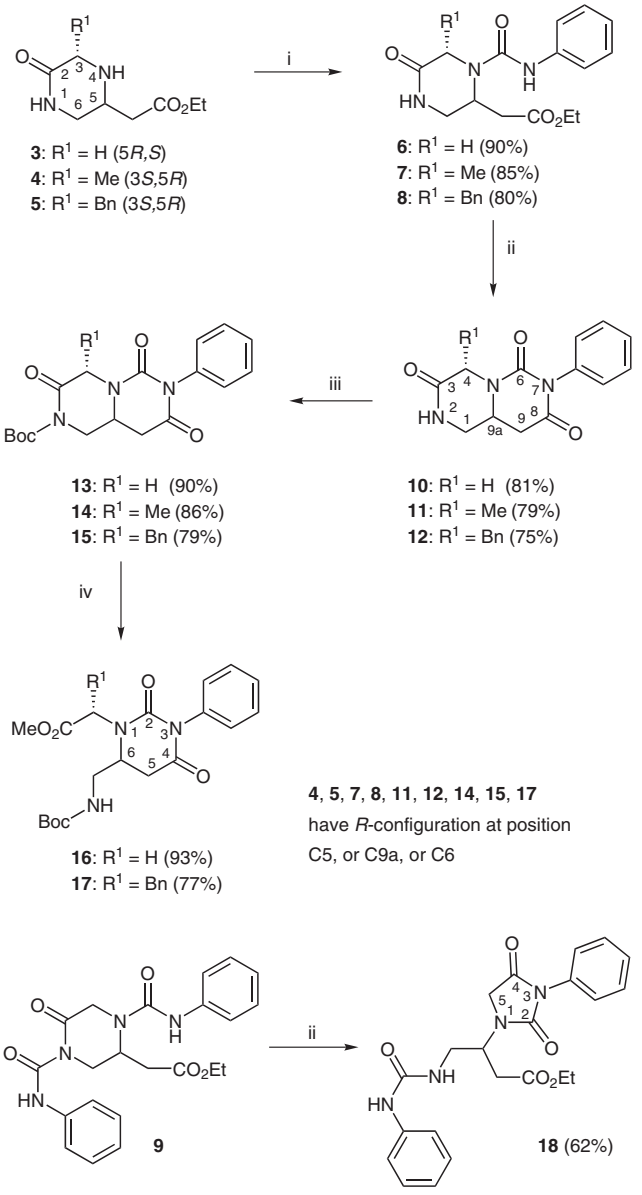


Figure 1 Model bicyclic CCK ligands and retrosynthetic pathway to the designed monocyclic analogues **A**

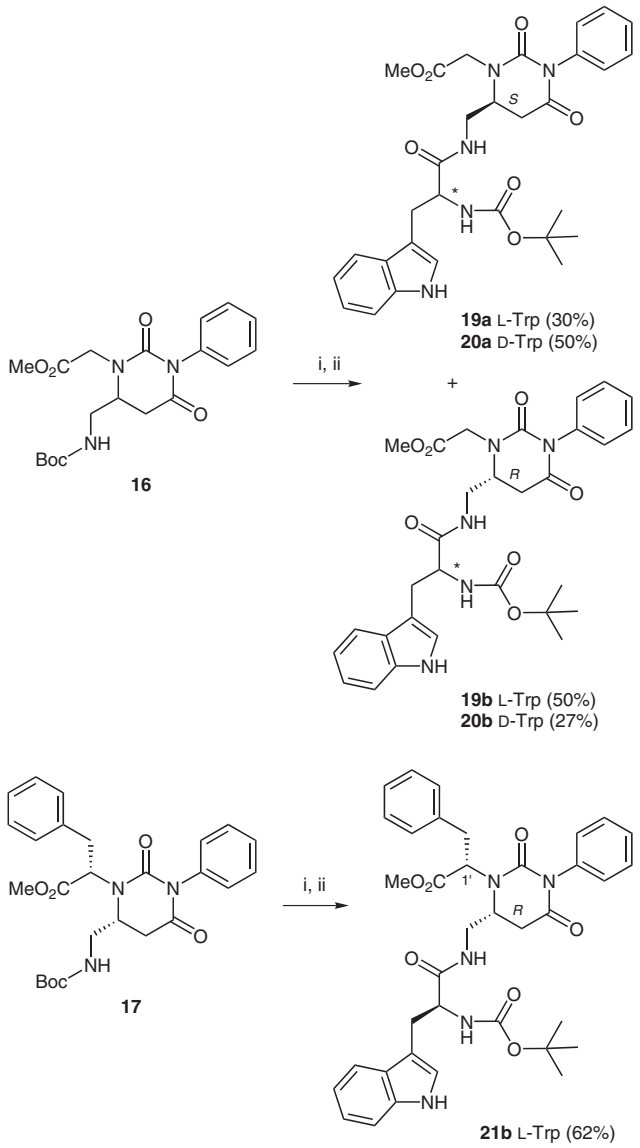


Scheme 1 *Reagents and conditions*: i) PhNCO, THF, 0 °C; ii) DBU, THF; iii) $(Boc)_2O$, Et_3N, DMAP; iv) NH_3, MeOH.

The DBU-promoted intramolecular cyclization of the urea intermediates **6**–**8** provided the pyrazino[1,2-*f*]pyrimidine-3,6,8-triones **10**–**12** in good yields (Scheme 1). Then, compounds **13**–**15** were prepared in 90, 86 and 79% yield, respectively, by treatment of **10**–**12** with di-*tert*-butyl dicarbonate. The *N*-urethane substituent in **13**–**15** has a double function, as an activating moiety facilitating the ring cleavage and, after the ring opening, as a protector of the resulting amino group.

Activated pyrazino[1,2-*f*]pyrimidines **13** and **15** underwent fast regioselective alcoholysis by treatment with NH_3/MeOH to give the targeted trisubstituted pyrimidine-2,4-diones **16** (93%) and **17** (77%), respectively. The pyrazino ring opening was also observed in the attempts to cyclize compound **9** to the corresponding bicyclic pyrazino[1,2-*f*]pyrimidine. In this case, the abstraction of the 4-urea proton in **9** proceeded with the attack at the 2-CO group, activated by means of the 1-carbamoyl substituent, with concomitant pyrazino ring opening to yield the hydantoin derivative **18**. Although, most probably, a concerted-like process occurs in the formation of **18**, a two-step procedure, involving ring opening followed by cyclization to the preferred five-membered cycle, cannot be discarded.

Compounds **16** and **17** were deprotected, by treatment with TFA, and coupled to Boc-L- or Boc-D-Trp-OH to afford final compounds **19**–**21** (Scheme 2). Compounds **19** and **20** were obtained as approximately 1:1.7 and 1.8:1 **a**:**b** distereoisomeric mixtures, respectively, which were resolved into their corresponding C6-epimers by preparative TLC.[18] Although a 1:1 mixture would be expected from the use of racemic **16**, the existence of some kinetic resolution in the coupling of **16** with the enantiopure Trp derivatives could explain the higher isomer ratio. A significant shielding of the H-5 protons was observed in the ^{1}H NMR spectra of compound **21b** compared to the same protons in the 1′-unsubstituted analogue **19b**, and in the starting pyrimidine intermediate **17**.[19] This seems to indicate that compound **21b** adopts a preferential conformation in solution in which the indole nucleus of the Trp residue folds over the pyrimidine ring. Since this shielding was not observed for compounds **19** and **20**, lacking the 1′-substituent, the observed behavior could be caused



Scheme 2 *Reagents and conditions*: i) TFA–CH_2Cl_2; ii) Boc-L- or Boc-D-Trp-OH, BOP, Et_3N, CH_2Cl_2.

by the need of suitable accommodation of the two appended hydrophobic residues, benzyl and indole, in compound **21b**.

When these compounds were assayed for their binding properties at CCK_1 receptors, derivatives **19a** and **19b** showed two-orders of magnitude lower affinities than the model compound **1** (Table 1). D-Trp-containing analogues **20a**,**b** and the 1′-benzyl substituted derivative **21a** were totally ineffective. These results provide further evidence for the significant role of the perhydropyridine ring in the bicyclic 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine skeleton. The importance of the perhydropyridine C6 and C7 methylene groups for the interaction with a hydrophobic cavity of the CCK_1 receptor had been anticipated by a three-dimensional model complex between the CCK_1 receptor and the pyridopyrimidine antagonists.[20]

Table 1 Inhibition of the [^{3}H]pCCK8-Specific Binding to Rat Pancreas (CCK_1) and Cerebral Cortex Membranes (CCK_2) by Pyrimidine Derivatives

Product	Config. Trp	Config. **6**	IC_{50} (nM)[a] CCK_1	CCK_2
19a	L	*S*	125.0 ± 13.8	>10000
19b	L	*R*	330.0 ± 40.5	>10000
20a	D	*S*	>1000	>10000
20b	D	*R*	>1000	>10000
21b	L	*R*	>1000	>10000
1	L	*S*[b]	1.18 ± 0.72[c]	>10000
2	L	*R*[b]	>1000[d]	>10000

[a] Values are the mean or mean ± SEM of at least three experiments, performed with seven concentrations of test compounds in triplicate.
[b] In this case the configuration of position 4a of the pyrido[1,2-*c*]pyrimidine or the pyrrolo[1,2-*c*]pyrimidine ring system is indicated.
[c] Values from reference 13b.
[d] Values from reference 14.

In summary, we have described a simple four-step procedure for the synthesis of highly functionalized 1,3,6-trisubstituted tetrahydropyrimidine-2,4-dione derivatives. Starting from dipeptide-derived piperazin-2-ones, the process implies acylation with isocyanates, cyclization to perhydropyrazino[1,2-*f*]pyrimidine-3,6,8-triones, activation with di-*tert*-butyl dicarbonate, and controlled aperture of the pyrazine ring from the bicyclic skeleton. Some of these tetrahydropyrimidine-2,4-diones, obtained after convenient modification, have been evaluated for their affinity at CCK receptors. Although low affinities were found in the best cases, these pyrimidinone derivatives served to clarify some structural features essential for the CCK_1 receptor recognition.

All reagents were of commercial quality. Solvents were dried and purified by standard methods. ^{1}H NMR spectra were recorded on a Varian Gemini 200 or a Varian Unity 300 spectrometer operating at 200 and 300 MHz, respectively, using TMS as internal standard. ^{13}C NMR spectra were recorded on a Varian Gemini 200 (50 MHz) or a Varian Unity 300 (75 MHz) spectrometer. COSY and HSQC two-dimensional experiments were used for ^{1}H and ^{13}C assignments, respectively. The H-assignments marked with a superscript 'i' in compounds **19a**,**b** and **21b** belong to the indole fragment of the molecule. Optical rotations were measured at 25 °C using a Perkin-Elmer 141 polarimeter. Elemental analyses were obtained on a CHN-O-RAPID instrument. Analytical TLC was performed on aluminum sheets coated with a 0.2 mm layer of silica gel 60 F254 (Merck). Silica gel 60 (230400 mesh, Merck) was used for column chromatography. Analytical HPLC was performed on a Waters Nova-pak C_{18} (3.9 × 150 mm, 4 μm) column, with a flow rate of 1 mL/min, using a tunable UV detector set at 214 nm. Mixtures of MeCN (solvent A) and 0.05% TFA in H_2O (solvent B) were used as mobile phase. Starting 2-oxopiperazine derivatives **3**–**5** were prepared as described.[17]

Abbreviations: BOP: benzotriazol-l-yloxytris(dimethylamino)phosphonium hexafluorophosphate; CCK: cholecystokinin.

Reaction of 2-Oxopiperazines 3–5 with Phenyl Isocyanate; General Procedure

A solution of the corresponding 2-oxopiperazine **3–5** (3.3 mmol) in anhyd THF (24 mL) at 0 °C, was treated with phenyl isocyanate (0.36 mL, 3.3 mmol) and stirred at the indicated temperature for 30 min. The white solid that formed was filtered and, after evaporation, the resulting residue was purified on a silica gel column, using CH_2Cl_2–MeOH (100:1) as eluent.

(5*RS*)-5-(1′-Ethoxycarbonyl)methyl-4-(*N*-phenyl)carbamoylpiperazin-2-one (6)

Yield: 90% (from **3**); white foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (s, 1 H, H-1), 7.41–7.01 (m, 5 H, C_6H_5), 6.86 (s, 1 H, 4-CONH), 4.80–4.78 (m, 1 H, H-5), 4.68 (d, *J* = 18.4 Hz, 1 H, H-3), 4.19 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 3.80 (d, *J* = 18.4 Hz, 1 H, H-3), 3.71 (dd, *J* = 18.4, 4.0 Hz, 1 H, H-6), 3.32–3.26 (m, 1 H, H-6), 2.91 (dd, *J* = 16.7, 8.8 Hz, 1 H, 5-CH_2), 2.63 (dd, *J* = 16.7, 4.9 Hz, 1 H, 5-CH_2), 1.27 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 167.9, 154.3 (C=O), 138.9, 128.7, 123.0, 119.8 (C_6H_5), 61.5 (CH_2CH_3), 46.0 (C-5), 44.5 (C-3), 44.0 (C-6), 35.3 (5-CH_2), 13.9 (CH_2CH_3).

Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found: C, 58.97; H, 6.29; N, 13.70.

(3*S*,5*R*)-5-(1′-Ethoxycarbonyl)methyl-3-methyl-4-(*N*-phenyl)carbamoylpiperazin-2-one (7)

Yield: 85% (from **4**); white foam; $[\alpha]_D$ –1.5 (*c* = 0.99, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–6.91 (m, 5 H, C_6H_5), 6.27 (s, 1 H, H-1), 5.89 (s, 1 H, 4-CONH), 4.63–4.58 (m, 1 H, H-3), 4.52–4.49 (m, 1 H, H-5), 4.14 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 3.93–3.87 (m, 1 H, H-6), 3.80–3.73 (m, 1 H, H-6), 3.08 (dd, *J* = 17.3, 3.6 Hz, 1 H, 5-CH_2), 2.61 (dd, *J* = 17.3, 7.6 Hz, 1 H, 5-CH_2), 1.50 (d, *J* = 7.3 Hz, 1 H, 3-CH_3), 1.25 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 169.0, 157.2 (C=O), 138.9, 128.7, 122.6, 119.2 (C_6H_5), 61.2 (CH_2CH_3), 51.3 (C-3), 46.7 (CH-5), 40.9 (C-6), 35.0 (5-CH_2), 20.0 (3-CH_3), 14.1 (CH_2CH_3).

Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.17; H, 6.63; N, 13.16. Found: C, 60.11; H, 6.39; N, 13.02.

(3*S*,5*R*)-3-Benzyl-5-(1′-ethoxycarbonyl)methyl-4-(*N*-phenyl)carbamoylpiperazin-2-one (8)

Yield: 80% (from **5**); white foam; $[\alpha]_D$ 70.2 (*c* = 0.70, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.48 (s, 1 H, H-1), 7.34–6.98 (m, 10 H, C_6H_5), 6.84 (br s, 1 H, 4-CONH), 5.03 (t, *J* = 5.0 Hz, 1 H, H-3), 4.60–4.53 (m, 1 H, H-5), 4.21–4.03 (m, 2 H, CH_2CH_3), 3.64 (dd, *J* = 12.8, 3.4 Hz, 1 H, H-6), 3.42 (dd, *J* = 13.7, 4.6 Hz, 1 H, 3-CH_2), 3.25 (dd, *J* = 13.7, 5.4 Hz, 1 H, 3-CH_2), 3.15 (ddd, *J* = 12.8, 5.4, 2.8 Hz, 1 H, H-6), 2.22 (dd, *J* = 18.1, 3.1 Hz, 1 H, 3-CH_2), 1.98 (dd, *J* = 18.1, 9.1 Hz, 1 H, 3-CH_2), 1.27 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 170.0, 155.7 (C=O), 139.3, 138.3, 130.5, 128.8, 128.4, 126.8, 119.1 (C_6H_5), 61.4 (CH_2CH_3), 57.5 (C-3), 48.4 (C-5), 45.8 (C-6), 37.1 (3-CH_2), 35.9 (5-CH_2), 13.9 (CH_2CH_3).

Anal. Calcd for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63. Found: C, 66.92; H, 6.36; N, 10.51.

(3*S*,5*R*)-5-(1′-Ethoxycarbonyl)methyl-1,4-bis(*N*-phenyl)carbamoylpiperazine-2-one (9)

Yield: 34% (from **3**, in a reaction performed at r.t.); white foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.12 (s, 1 H, NH), 8.56 (s, 1 H, NH), 7.53–7.03 (m, 10 H, C_6H_5), 4.76–4.70 (m, 2 H, H-3, H-5), 4.32 (dd, *J* = 14.0, 5.2 Hz, 1 H, H-6), 4.25 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 3.97 (d, *J* = 18.2 Hz, 1 H, H-3), 3.92 (dd, *J* = 14.0, 4.1 Hz, 1 H, H-6), 2.79 (dd, *J* = 17.6, 9.1 Hz, 1 H, 5-CH_2), 2.64 (dd, *J* = 17.6, 3.2 Hz, 1 H, 5-CH_2), 1.29 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 172.6, 170.7, 154.7, 150.4 (C=O), 138.8, 137.0, 128.9, 128.8, 124.5, 123.0, 120.4, 119.5 (C_6H_5), 62.0 (CH_2CH_3), 48.8 (C-5), 46.4 (C-3), 44.9 (C-6), 36.9 (5-CH_2), 13.9 (CH_2CH_3).

Anal. Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found: C, 61.99; H, 5.71; N, 13.13.

Pyrazino[1,2-*f*]pyrimidine-3,6,8-triones 10–12, 18; General Procedure

A stirred solution of the corresponding compound **6–9** (2.5 mmol) in anhyd THF (23 mL) was treated with DBU (0.95 mL, 6.3 mmol). Stirring was continued for 6 days at r.t. The solid that formed was filtered and the solvent was concentrated in vacuo. The resulting residue was chromatographed on a silica gel column eluting with CH_2Cl_2–MeOH (100:1).

(9a*RS*)-7-Phenyl-4-*H*-tetrahydropyrazino[1,2-*f*]pyrimidine-3,6,8-trione (10)

Yield: 81% (from **6**); white foam.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.24 (s, 1 H, H-2), 7.42–7.14 (m, 5 H, C_6H_5), 4.07 (d, *J* = 17.6 Hz, 1 H, H-4), 4.01–3.97 (m, 1 H, H-9a), 3.84 (d, *J* = 17.6 Hz, 1 H, H-4), 3.34–3.21 (m, 2 H, H-1), 2.93 (dd, *J* = 16.5, 5.0 Hz, 1 H, H-9), 2.80 (dd, *J* = 16.5 10.2 Hz, 1 H, H-9).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.6 (C-3), 166.3 (C-8), 152.1 (C-6), 135.9, 129.0, 128.2, 127.5 (C_6H_5), 46.6 (C-9a), 46.4 (C-4), 43.8 (C-1), 33.6 (C-9).

Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.07; H, 5.27; N, 16.24.

(4*S*,9a*R*)-4-Methyl-7-phenyl-4-*H*-tetrahydropyrazino[1,2-*f*]pyrimidine-3,6,8-trione (11)

Yield: 79% (from **7**); white foam; $[\alpha]_D$ 2.4 (*c* = 1.05, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–6.99 (m, 6 H, C_6H_5, H-2), 4.65 (q, *J* = 6.9 Hz, 1 H, H-4), 4.03–3.95 (m, 1 H, H-9a), 3.71 (dd, *J* = 14.0, 4.5 Hz, 1 H, H-1), 3.48–3.41 (m, 1 H, H-1), 2.87 (dd, *J* = 16.2, 3.5 Hz, 1 H, H-9), 2.72 (dd, *J* = 16.2, 13.2 Hz, 1 H, H-9), 1.58 (d, *J* = 7.0 Hz, 3 H, 4-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7 (C-3), 167.4 (C-8), 152.3 (C-6), 136.3, 129.1, 128.6 (C_6H_5), 53.6 (C-4), 48.2 (C-9a), 43.7 (C-1), 35.9 (C-9), 20.2 (4-CH_3).

Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.40; H, 5.31; N, 15.44.

(4*S*,9a*R*)-4-Benzyl-7-phenyl-4-*H*-tetrahydropyrazino[1,2-*f*]pyrimidine-3,6,8-trione (12)

Yield: 75% (from **8**); white foam; $[\alpha]_D$ 86.0 (c = 1.09, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.17 (m, 11 H, C_6H_5, H-2), 4.85 (dd, *J* = 5.8 Hz, 2.8, 1 H, H-4), 3.84–3.79 (m, 1 H, H-9a), 3.48 (dd, *J* = 13.7, 2.8 Hz, 1 H, 4-CH_2), 3.23 (dd, *J* = 13.7, 5.8 Hz, 1 H, 4-CH_2), 2.88–2.80 (m, 1 H, H-1), 2.58 (dd, *J* = 16.3, 3.2 Hz, 1 H, H-9), 2.31 (dd, *J* = 16.3, 13.4 Hz, 1 H, H-9), 1.60 (dd, *J* = 14.5, 11.4 Hz, 1 H, H-1).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.4 (C-3), 167.5 (C-8), 152.7 (C-6), 136.3, 134.8, 130.0, 129.2, 128.6, 128.4, 127.6 (C_6H_5), 59.2 (C-4), 46.9 (C-9a), 42.4 (C-1), 37.9 (4-CH_2), 35.5 (C-9).

Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.48; H, 5.53; N, 12.08.

(2′*RS*)-3-Phenyl-1-[3′-(phenylcarbamoyl)-1′-ethoxycarbonylprop-2′-yl]hydantoin (18)
Yield: 62% (from **9**); syrup.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.12 (s, 1 H, NH), 8.56 (s, 1 H, NH), 7.49–6.91 (m, 10 H, C_6H_5), 4.61–4.58 (m, 1 H, H-2′), 4.49 (d, *J* = 16.8 Hz, 1 H, H-5), 4.16 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 3.92 (d, *J* = 16.8 Hz, 1 H, H-5), 3.81–3.70 (m, 1 H, H-3′), 3.10–3.06 (m, 1 H, H-3′), 2.61 (d, *J* = 7.3 Hz, 2 H, H-1′), 1.25 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 157.1, 155.9 (C=O), 150.4 (C-2), 138.8, 131.5, 129.1, 129.0, 128.8, 128.3, 126.5 (Ar), 61.2 (CH_2CH_3), 51.3 (C-2′), 46.8 (C-5), 40.9 (C-3′), 35.0 (C-1′), 14.1 (CH_2CH_3).

Anal. Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found: C, 62.15; H, 5.61; N, 13.07.

Boc-Protected Pyrazino[1,2-*f*]pyrimidine-3,6,8-triones 13–15; General Procedure
To a solution of the pyrazino[1,2-*f*]pyridine-3,6,8-triones derivatives **10**–**12** (1.2 mmol) in anhyd THF (11 mL), were added Et_3N (0.17 mL, 1.22 mmol), DMAP (15 mg, 0.123 mmol) and di-*tert*-butyl dicarbonate (546 mg, 2.5 mmol). The mixture was stirred at r.t. for 15 min and then concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (EtOAc–hexane, 1:6).

(9a*RS*)-2-*tert*-Butoxycarbonyl-7-phenyl-4*H*-tetrahydropyrazino[1,2-*f*]pyrimidine-3,6,8-trione(13)
yield: 90% (from **10**); syrup.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.43–7.15 (m, 5 H, C_6H_5), 4.28 (d, *J* = 17.3 Hz, 1 H, H-4), 4.22–4.18 (m, 2 H, H-1, H-9a), 4.12 (d, *J* = 17.3 Hz, 1 H, H-4), 3.74 (dd, *J* = 13.4, 7.7 Hz, 1 H, H-1), 2.92–2.86 (m, 2 H, H-9), 1.48 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 168.3 (C-3), 165.9 (C-6), 151.8 (C-8), 150.8 (CO_2Boc), 136.1, 129.2, 128.5, 127.8 (C_6H_5), 82.9 [$C(CH_3)_3$], 46.8 (CH-9a), 45.6 (C-4), 37.9 (C-1), 33.8 (C-9), 27.3 [$C(CH_3)_3$] .

Anal. Calcd for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.04; H, 5.85; N, 11.70.

(4*S*,9a*R*)-2-*tert*-Butoxycarbonyl-4-methyl-7-phenyl-4*H*-tetrahydropyrazino[1,2-*f*]pyrimidine-3,6,8-trione (14)
Yield: 86% (from **11**); syrup; $[\alpha]_D$ 12.6 (*c* = 0.90, $CHCl_3$).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.4–7.14 (m, 5 H, C_6H_5), 4.84 (q, *J* = 7.1 Hz, 1 H, H-4), 4.48 (dd, *J* = 13.8, 3.1 Hz, 1 H, H-1), 4.08–4.02 (m, 1 H, H-9a), 3.42 (dd, *J* = 13.8, 11.1 Hz, 1 H, H-1), 2.93 (dd, *J* = 16.2, 3.4 Hz, 1 H, H-9), 2.74 (dd, *J* = 16.2, 3.3 Hz, 1 H, H-9), 1.58 (m, 12 H, 4-CH_3, *t*-C_4H_9).

Anal. Calcd for $C_{19}H_{23}N_3O_5$: C, 61.11; H, 6.21; N, 11.25. Found: C, 60.78; H, 6.00; N, 11.12.

(4*S*,9a*R*)-4-Benzyl-2-*tert*-butoxycarbonyl-7-phenyl-4*H*-tetrahydropyrazino[1,2-*f*]pyrimidine-3,6,8-trione (15)
Yield: 79% (from **12**); syrup.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.13 (m, 10 H, C_6H_5), 5.02 (dd, *J* = 5.6, 3.3 Hz, 1 H, H-4), 3.91–3.83 (m, 1 H, H-9a), 3.72 (dd, *J* = 13.6, 3.4 Hz, 1 H, H-1), 3.45 (dd, *J* = 13.8, 5.7 Hz, 1 H, 4-CH_2), 3.28 (dd, *J* = 13.8, 3.3 Hz, 1 H, 4-CH_2), 2.66 (dd, *J* = 16.4, 3.3 Hz, 1 H, H-9), 2.37 (dd, *J* = 16.4, 13.4 Hz, 1 H, H-9), 1.63 (dd, *J* = 13.6, 11.3 Hz, 1 H, H-1), 1.55 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2 (C-3), 167.0 (C-6), 152.2 (C-8), 150.5 (CO_2 Boc), 136.1, 134.6, 129.8, 129.2, 128.7, 128.6, 127.8 (C_6H_5), 84.6 [$C(CH_3)_3$], 61.0 (C-4), 47.2 (C-9a), 45.1 (C-1), 38.9 (4-CH_2), 35.3 (C-9), 27.8 [$C(CH_3)_3$].

Anal. Calcd for $C_{25}H_{27}N_3O_5$: C, 66.80; H, 6.05; N, 9.35. Found: C, 66.51; H, 5.87; N, 9.25.

Ring Opening of Boc-Protected Pyrazino[1,2-*f*]pyrimidine-3,6,8-triones 13,15; General Procedure
Sat. NH_3/MeOH (5 mL) was added to the corresponding 2-*tert*-butoxycarbonylpyrazino[1,2-*f*]pyrimidine-3,6,8-trione derivative **13**, **15**. After being stirred for 10 min at r.t., the solution was evaporated and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 100:1).

(6*RS*)-6-(*tert*-Butoxycarbonyl)aminomethyl-1-(methoxycarbonyl)methyl-3-phenyltetrahydropyrimidine-2,4-dione (16)
Yield: 93% (from **13**); white foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.19 (m, 5 H, C_6H_5), 5.36 (t, *J* = 6.1 Hz, 1 H, N*H*Boc), 4.27 (d, 1 H, *J* = 17.6 Hz, 1-CH_2), 4.13 (d, 1 H, *J* = 17.6 Hz, 1-CH_2), 3.78 (s, 3 H, OCH_3), 3.77–3.67 (m, 1 H, H-6), 3.64–3.55 (m, 1 H, 6-CH_2), 3.31–3.19 (m, 2 H, H-5, 6-CH_2), 2.91 (d, *J* = 16.7 Hz, 1 H, H-5), 1.44 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0 (CO_2CH_3), 167.9 (C-4), 155.8 (C-2), 153.1 (CO_2Boc), 135.2, 129.1, 128.9, 128.8, 128.3, 125.9 (C_6H_5), 80.2 [$C(CH_3)_3$], 53.7 (C-6), 52.4 (OCH_3), 49.5 (1-CH_2), 42.9 (6-CH_2), 34.8 (C-5), 28.3 [$C(CH_3)_3$].

Anal. Calcd for $C_{19}H_{25}N_3O_6$: C, 58.30; H, 6.44; N, 10.74. Found: C, 58.49; H, 6.67; N, 10.61.

(6*R*,1′*S*)-6-(*tert*-Butoxycarbonyl)aminomethyl-1-[1′-(methoxycarbonyl)-2′-phenyl]ethyl-3-phenyltetrahydropyrimidine-2,4-dione (17)
Yield: 77% (from **15**); white foam; $[\alpha]_D$ 2.8 (*c* = 0.68, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.16 (m, 10 H, C_6H_5), 5.59 (t, *J* = 6.4 Hz, 1 H, N*H*Boc), 3.93 (dd, *J* = 11.3, 4.9 Hz, 1 H, H-1′), 3.82 (s, 3 H, OCH_3), 3.54–3.43 (m, 2 H, H-2′, 6-CH_2), 3.36 (dd, *J* = 13.9, 4.9 Hz, 1 H, H-2′), 3.25–3.17 (m, 1 H, 6-CH_2), 2.87–2.82 (m, 1 H, H-6), 2.44 (d, *J* = 16.5 Hz, 1 H, H-5), 2.08 (dd, *J* = 16.5, 7.5 Hz, 1 H, H-5), 1.42 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7 (CO_2Me), 167.6 (C-2), 155.7 (C-4), 152.1 (CO_2Boc), 137.7, 134.8, 129.0, 128.9, 128.7, 128.4, 127.2 (C_6H_5), 80.0 [$C(CH_3)_3$], 65.4 (C-1), 56.1 (C-6), 52.9 (OCH_3), 42.8 (6-CH_2), 34.4 (C-5), 33.8 (C-1′), 33.8 (C-2′), 28.3 [$C(CH_3)_3$].

Anal. Calcd for $C_{26}H_{31}N_3O_6$: C, 64.85; H, 6.49; N, 8.73. Found: C, 64.63; H, 6.26; N, 8.77.

Coupling of 16 and 17 with Boc-L- or Boc-D-Trp-OH; General Procedure
TFA (3 mL) was added to a solution of the corresponding *N*-Boc-protected dihydropyrimidine-2,4-dione derivative **16** or **17** (0.4 mmol) in CH_2Cl_2 (6 mL). After 30 min at r.t., the solvents were evaporated to dryness and the residue was co-evaporated several times with CH_2Cl_2. The residue was dissolved in anhyd CH_2Cl_2 (5 mL) and Boc-L- or D-Trp-OH (162 mg, 0.5 mmol), BOP (235 mg, 0.5 mmol) and Et_3N (0.14 mL, 1 mmol) were added successively to the solution. After being stirred overnight at r.t., the solvent was evaporated. The residue was dissolved in EtOAc (25 mL) and washed successively with 10% citric acid (10 mL), aq 10% $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated. The resulting Boc-tryptophyl derivative was purified by preparative TLC ($CHCl_3$–MeOH, 100:1). Using this chromatographic procedure, compounds **19** and **20** were also resolved into diastereoisomers **a** (6*S*) and **b** (6*R*).

(6*S*)-6-[*N*-(*tert*-Butoxycarbonyl)-L-tryptophyl]aminomethyl-1-(methoxycarbonyl)methyl-3-phenyltetrahydropyrimidine-2,4-dione (19a)

Yield: 30% (from 16); white foam; HPLC: t_R = 69.60 min (25:75); $[\alpha]_D$ –17.9 (*c* = 1.45, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (s, 1 H, NH^i), 7.61 (d, *J* = 7.9 Hz, 1 H, H-4^i), 7.43–7.34 (m, 3 H, C_6H_5, H-7^i), 7.22 (t, *J* = 7.9 Hz, 1 H, H-6^i), 7.15–7.07 (m, 4 H, C_6H_5, H-5^i), 7.02 (d, *J* = 2.2 Hz, 1 H, H-2^i), 6.72 (br t, 1 H, α-NH), 5.06 (d, *J* = 7.0 Hz, 1 H, N*H*Boc), 4.38–4.34 (m, 1 H, α-CH), 3.83–3.78 (m, 2 H, H-1′), 3.69 (s, 3 H, OCH_3), 3.41–3.27 (m, 4 H, β-CH_2, H-6, 6-CH_2), 3.13 (dd, *J* = 14.3, 7.4 Hz, 1 H, β-CH_2), 2.89 (dd, *J* = 16.7, 5.8 Hz, 1 H, H-5), 2.40 (d, *J* = 16.7 Hz, 1 H, H-5), 1.44 (s, 9 H, *t*-C_4H_9).

Anal. Calcd for $C_{30}H_{35}N_5O_7$: C, 62.38; H, 6.11; N, 12.12. Found: C, 62.27; H, 5.93; N, 12.03.

(6*R*)-6-[*N*-(*tert*-Butoxycarbonyl)-L-tryptophyl]aminomethyl-1-(methoxycarbonyl)methyl-3-phenyltetrahydropyrimidine-2,4-dione (19b)

Yield: 50% (from **16**); white foam; HPLC: t_R = 73.97 min (25:75); $[\alpha]_D$ –17.3 (*c* = 0.12, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (s, 1 H, NH^i), 7.61 (d, *J* = 7.9 Hz, 1 H, H-4^i), 7.42–7.34 (m, 3 H, C_6H_5, H-7^i), 7.26 (t, *J* = 7.9 Hz, 1 H, H-6^i), 7.22–7.06 (m, 4 H, C_6H_5, H-5^i), 7.03 (d, *J* = 2.2 Hz, 1 H, H-2^i), 6.67 (br t, 1 H, NH), 5.01 (br s, 1 H, N*H*Boc), 4.40–4.35 (m, 1 H, α-CH), 3.91–3.79 (m, 2 H, H-1′), 3.72 (s, 3 H, OCH_3), 3.48–3.43 (m, 1 H, 6-CH_2), 3.36–3.29 (m, 2 H, β-CH_2, H-6), 3.24–3.21 (m, 1 H, 6-CH_2) 3.15 (dd, *J* = 14.5, 7.8 Hz, 1 H, β-CH_2), 2.89 (dd, *J* = 16.7, 5.6 Hz, 1 H, H-5), 2.41 (d, *J* = 16.7 Hz, 1 H, H-5), 1.44 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 170.0, 168.4 (C=O), 155.4 (*C*O_2Boc), 152.5 (C-2), 136.1, 134.8, 129.0, 128.4, 127.2, 123.1, 122.4, 119.7, 118.8, 111.3, 110.4 (Ar), 80.4 [*C*$(CH_3)_3$], 55.5 (α-CH), 52.6 (C-6), 52.5 (OCH_3), 49.4 (C-1′), 41.1 (6-CH_2), 34.2 (C-5), 29.6 (β-CH_2), 28.2 [C(*C*$H_3)_3$].

Anal. Calcd for $C_{30}H_{35}N_5O_7$: C, 62.38; H, 6.11; N, 12.12. Found: C, 62.10; H, 5.95; N, 12.00.

(6*R*)-6-[*N*-(*tert*-Butoxycarbonyl)-D-tryptophyl]aminomethyl-1-(methoxycarbonyl)methyl-3-phenyltetrahydropyrimidine-2,4-dione (20a)

Yield: 50% (from **16**); white foam; $[\alpha]_D$ = 16.4 (*c* = 0.65, $CHCl_3$).

This compound showed analytical and spectroscopic data identical to those of its enantiomer **19b**.

Anal. Calcd for $C_{30}H_{35}N_5O_7$: C, 62.38; H, 6.11; N, 12.12. Found: C, 62.43; H, 6.04; N, 12.15.

(6*S*)-6-[*N*-(*tert*-Butoxycarbonyl)-D-tryptophyl]aminomethyl-1-(methoxycarbonyl)methyl-3-phenyltetrahydropyrimidine-2,4-dione (20b)

Yield: 27% (from **16**); white foam.

This compound showed analytical and spectroscopic data identical to those of its enantiomer **19a**.

Anal. Calcd for $C_{30}H_{35}N_5O_7$: C, 62.38; H, 6.11; N, 12.12. Found: C, 62.29; H, 5.97; N, 12.21.

(6*R*)-6-[*N*-(*tert*-Butoxycarbonyl)-L-tryptophyl]aminomethyl-1-[1′-(methoxycarbonyl)-2′-phenyl]ethyl-3-phenyltetrahydropyrimidine-2,4-dione (21b)

Yield: 62% (from **17**); white foam; HPLC: t_R = 11.95 min (45:55); $[\alpha]_D$ –118.7 (*c* = 0.29, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (s, 1 H, NH^i), 7.63 (d, *J* = 7.8 Hz, 1 H, H-4^i), 7.52 (br s, 1 H, NH), 7.44–7.00 (s, 14 H, C_6H_5, H^i), 5.19 (d, *J* = 7.9 Hz, 1 H, N*H*Boc), 4.43–4.37 (m, 1 H, α-CH), 3.71 (s, 3 H, OCH_3), 3.55–3.46 (m, 1 H, 6-CH_2), 3.36–2.94 (m, 4 H, β-CH_2, H-1′, H-2′, 6-CH_2), 2.51–4.49 (m, 1 H, H-6), 2.05 (d, *J* = 19.3 Hz, 1 H, H-5), 1.45 (s, 9 H, *t*-C_4H_9), 1.33–1.19 (m, 1 H, H-5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 171.1, 168.0 (C=O), 155.2 (*C*O_2Boc), 151.2 (C-2), 136.0, 134.5, 129.1, 129.0, 128.9, 128.5, 127.4, 127.2, 123.2, 122.5, 119.8, 118.9, 111.2, 110.9 (Ar), 80.0 [*C*$(CH_3)_3$], 64.8 (C-1′), 55.9 (α-CH), 53.0 (OCH_3), 53.0 (C-6), 41.6 (6-CH_2), 33.8 (C-2′), 33.7 (C-5), 28.8 (β-CH_2), 28.3 [C(*C*$H_3)_3$].

Anal. Calcd for $C_{37}H_{41}N_5O_7$: C, 66.55; H, 6.19; N, 10.49. Found: C, 66.64; H, 6.21; N, 10.44.

Binding Assays

CCK_1 and CCK_2 receptor binding assays were performed using rat pancreas and cerebral cortex homogenates, respectively, according to the method previously described.[12b]

Acknowledgment

We thank the Plan Nacional de Biomedicina (SAF 2003-07207-C02) for financial support.

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