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Short communication

New arylhexahydropyrimidinediones: synthesis, benzodiazepine receptor affinity and anticonvulsant activity

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Summary — Synthesis of new 3-alkyl-6-arylhexahydropyrimidine-2,4-dione derivatives was achieved starting from various benzaldehydes. Their affinity towards the benzodiazepine receptor and their anticonvulsant effect were evaluated.

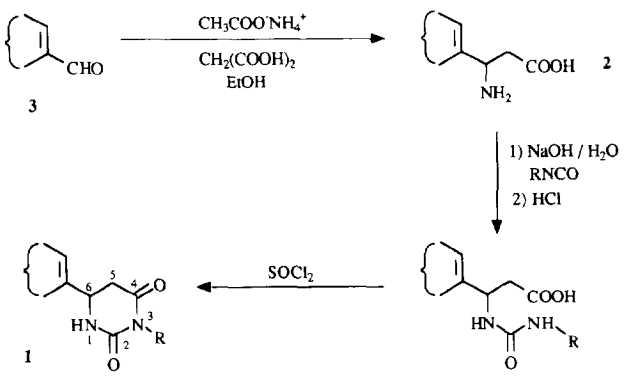
3-alkyl-6-arylhexahydropyrimidine-2,4-dione derivative / anticonvulsant activity / benzodiazepine receptor

Introduction

Benzodiazepine receptor (BZR) ligands do not only belong to the benzodiazepine series. A wide variety of various structural classes of agonists or inverse agonists has been described [1] and not all the molecular features responsible for receptor binding have been hitherto completely well established. In this context, we have recently undertaken the systematic biological evaluation of BZR ligands and related pharmacological studies of various new compounds synthesized in our laboratory. As part of this programme, we wish to describe herein the synthesis, BZR affinity and anticonvulsant activity of new arylhexahydropyrimidinediones.

Chemistry

During the course of our work concerning the synthesis of new heterocyclic compounds of potential therapeutic interest, we recently described the access to numerous 3-amino-3-aryl-propionic acids **2** starting from arylaldehydes **3** [2, 3]. The synthetic pathway involved the Rodionov–Johnson [4, 5] reaction using malonic acid and ammonium acetate in an ethanolic solution of starting material. Compounds **2** were treated with an equivalent amount of various isocyanates (2-chloroethyl and propylisocyanate) in the presence of an aqueous sodium hydroxide solution at room temperature to yield the sodium salts of the corresponding ureido acids, which remained in solution; upon addition of a mineral acid, the ureido acids **4a–h** were precipitated. The latter were refluxed in thionyl chloride to give, after removal of the solvent, the attempted 6-arylhexahydropyrimidine-2,4-diones **1a–h** (scheme 1, table I).



Scheme 1. Synthesis of compounds **1a–h**.

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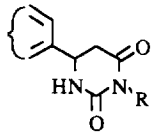
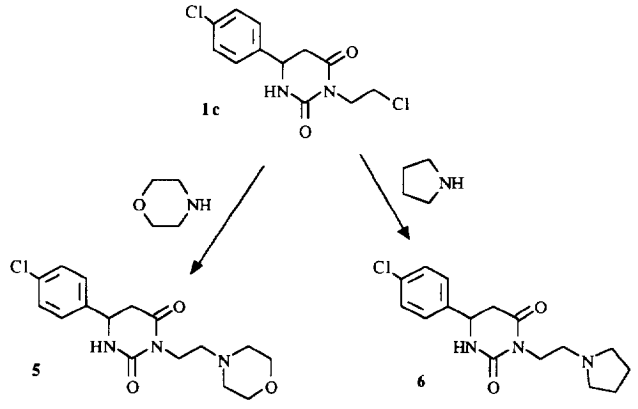
Table I. Structures of compounds **1a–h**, **5**, **6** and **7**.



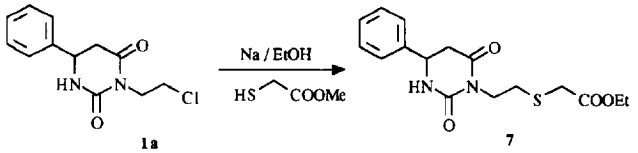
1a-h, 5, 6, 7

Compound		*R*
1a		Cl
1b	Cl	Cl
1c	Cl	Cl
1d	CH_3	Cl
1e		CH_3
1f	Cl	CH_3
1g	Cl	CH_3
1h	CH_3	CH_3
5	Cl	N O
6	Cl	N
7		S O OEt

The chloroethyl derivative **1c** was furthermore treated with secondary amines such as morpholine and pyrrolidine to give the corresponding tertiaryamines **5** and **6** (scheme 2, table I). Otherwise, reaction of 3-(2-chloroethyl)-6-phenylhexahydropyrimidine-2,4-dione **1a** with methylthioglycolate gave the sulfide **7** after a *trans*-esterification mechanism involving the solvent of the reaction (scheme 3, table I).



Scheme 2. Synthesis of compounds **5** and **6**.



Scheme 3. Synthesis of compound **7**.

Pharmacological results

Compounds **1a–h** and **5–7** were primarily tested for their ability to displace ^{3}H-flunitrazepam (FLU) (at 1 nM, K_d = 2 nM) from its specific binding in rat brain membranes. The percentage of inhibition (I%) was first determined at 10 μM and then the K_i values of the more active ones were evaluated (see *Experimental protocols*). Then, the latter compounds **1a–h** and **5–7** were screened for anticonvulsant activity after a preliminary evaluation of their gross behavioral effects and acute toxicity.

The results of the pharmacological evaluations are listed in table II. Among this series, four compounds **1a**, **1c**, **5** and **6** exhibited a good affinity to BZR. K_i values ranged from 0.82 to 4.75 μM. Concerning anticonvulsant activity, seven compounds **1a–c**, **1e–f**, **5** and **7** showed a clear-cut anticonvulsant effect evaluated in terms of protection against pentylenetetrazole-induced lethal convulsions [6]. The ED_{50} values of these dihydrouracyl derivatives ranged from 65 to 1023 mg/kg. The most active compounds were, in order of activity, **1a**, **1e**, **1b** and **5**, which moreover exhibited LD_{50}/ED_{50} ratios greater than 8. Concerning the behavioral effects evaluated in mice by the Irwin–Morpugo screening procedure, subtoxic doses of compounds **1a**, **1e** and **5** produced slight and incon-

Table II. Pharmacological data for the tested compounds.

Compound	*I%*[a]	*K_i (μM)*[b]	*Approximate IP LD_{50} in mice (mg/kg)*	*Anticonvulsant activity in mice*[c] *IP ED_{50} and 95% confidence interval (mg/kg)*
1a		0.82 ± 0.0054	> 700	65 (50–83)
1b		> 5	> 1500	85 (60–120)
1c		4.75 ± 0.14	> 1500	186 (120–288)
1d	10		ND	ND
1e		> 5	> 650	81 (69–96)
1f		> 5	> 1000	389 (346–437)
1g	24.5		ND	ND
1h	11.3		ND	ND
5		0.98 ± 0.09	> 750	86 (76–98)
6		1.24 ± 0.24	ND	ND
7	30	> 5	> 2000	1023 (840–1247)
Diazepam			75	0.55 (0.49–0.62)

[a]Percentage of inhibition (I%) of ^{3}H-FLU binding at 10 μM concentration; [b]K_i values are means ± SEM of four experiments; [c]protection against pentylenetetrazole-induced lethal convulsions (see *Experimental protocols*); ND not determined.

sistent signs of central nervous system depression such as sedation, passivity and decrease of spontaneous motor activity. No significant gross behavioral alterations were observed with the highest doses tested of the other compounds.

The derivative **1a** which exhibited the best affinity for BZR (K_i = 0.82 μM), was also the most active in terms of protective effect against pentylenetetrazole-induced lethal convulsions (ED_{50} = 65 mg/kg). This seemed to indicate a good correlation between anticonvulsant activity and displacing potency in the [^{3}H]-flunitrazepam binding of this compound. However, the mechanism of anticonvulsant action of this series could not be simply related via BZR interaction, because compound **1e**, with good anticonvulsant properties (ED_{50} = 81 mg/kg) had little affinity to BZR (K_i > 5 μM). So, additional investigations concerning the action mechanism of these new compounds must be conducted.

Experimental protocols

Chemistry

Melting points were determinated on a Kofler block and are uncorrected. IR spectra were recorded on a Philips PU-9716 spectrophotometer. ^{1}H-NMR spectra were recorded at 200 MHz with tetramethylsilane as an internal standard using a Jeol JMN-FX 200 spectrometer. Splitting patterns have been designated as follows: s = singlet; bs = broad singlet; d = doublet; t = triplet; q = quartet; and m = multiplet. Analyses indicated by the symbols of the element were within ±0.4% of the theoretical values.

General procedure for the preparation of 3-[3N'-(2-alkyl)ureido]-3-phenylpropionic acids ***4***

Amino acid **2** (0.1 mol) was dissolved in an aqueous solution of sodium hydroxide (1 N, 120 mL) and then alkylisocyanate (0.1 mol) was added to the reaction mixture which was stirred at room temperature for 1 h. The solution was filtered and acidified to pH = 1 with dilute hydrochloric acid The precipitate was filtered, washed with water and dried.

3-[3N'-(2-Chloroethyl)ureido]-3-phenylpropionic acid ***4a***. White crystals (92%): mp 130 °C; IR (KBr) 3330, 3250 (NH), 1690 (CO); ^{1}H-NMR (DMSO-d_6) δ: 12.20 (bs, 1H, OH), 7.29 (m, 5H, H arom), 6.76 (d, 1H, $J_{NH\ H\text{-}3}$ = 8.3 Hz, NH), 6.31 (t, 1H, $J_{NH\ CH_2}$ = 5.6 Hz, NH), 5.05 (m, 1H, H-3), 3.54 (t, 2H, CH_2), 3.31 (m, 2H, CH_2), 2.66 (d, 2H, $J_{H\text{-}2\ H\text{-}3}$ = 6.8 Hz, H-2). Anal calc for $C_{12}H_{15}N_2O_3Cl$: C, 53.24; H, 5.58; N, 10.95. Found: C, 53.22; H, 5.47; N, 10.80.

3-[3N'-(2-Chloroethyl)ureido]-3-(3-chlorophenyl)propionic acid ***4b***. White crystals (54%): mp 138 °C; IR (KBr) 3310 (NH), 1700 (CO); ^{1}H-NMR (DMSO-d_6) δ: 12.28 (bs, 1H, OH), 7.31 (m, 4H, H arom), 6.78 (d, 1H, $J_{NH\ H\text{-}3}$ = 8.3 Hz, NH), 6.32 (t, 1H, $J_{NH\ CH_2}$ = 5.6 Hz, NH), 5.04 (m, 1H, H-3), 3.52 (t, 2H, CH_2), 3.20 (m, 2H, CH_2), 2.65 (d, 2H, $J_{H\text{-}2\ H\text{-}3}$ = 6.8 Hz, H-2). Anal calc for $C_{12}H_{14}N_2O_3Cl_2$: C, 47.23; H, 4.62; N, 9.18. Found: C, 47.22; H, 4.63; N, 8.99.

3-[3N'-(2-Chloroethyl)ureido]-3-(4-chlorophenyl)propionic acid ***4c***. White crystals (70%): mp 152 °C; IR (KBr) 3320, 3260 (NH), 1695 (CO); ^{1}H-NMR (DMSO-d_6) δ: 12.32 (bs, 1H, OH), 7.49 (m, 4H, H arom), 6.80 (d, 1H, $J_{NH\ H\text{-}3}$ = 8.3 Hz, NH), 6.38 (t, 1H, $J_{NH\ CH_2}$ = 5.6 Hz, NH), 5.05 (m, 1H, H-3), 3.53 (t, 2H, CH_2), 3.30 (m, 2H, CH_2), 2.60 (d, 2H, $J_{H\text{-}2\ H\text{-}3}$ = 6.8 Hz, H-2). Anal calc for $C_{12}H_{14}N_2O_3Cl_2$: C, 47.23; H, 4.62; N, 9.18. Found: C, 47.32; H, 4.56; N, 9.03.

3-[3N'-(2-Chloroethyl)ureido]-3-(4-methylphenyl)propionic acid ***4d***. White crystals (75%): mp 150 °C; IR (KBr) 3350,

3280 (NH), 1705 (CO); ^{1}H-NMR (DMSO-d_6) δ: 12.22 (bs, 1H, OH), 7.15 (m, 4H, H arom), 6.64 (d, 1H, $J_{NH\ H\text{-}3}$ = 8.3 Hz, NH), 6.25 (t, 1H, $J_{NH\ CH_2}$ = 5.6 Hz, NH), 4.99 (m, 1H, H-3), 3.55 (t, 2H, CH_2), 3.30 (m, 2H, CH_2), 2.61 (d, 2H, $J_{H\text{-}2\ H\text{-}3}$ = 6.8 Hz, H-2), 2.27 (s, 3H, CH_3). Anal calc for $C_{13}H_{17}N_2O_3Cl$: C, 54.84; H, 6.02; N, 9.84. Found: C, 54.75; H, 5.93; N, 9.69.

3-[3N'-Propylureido]-3-phenylpropionic acid ***4e***. White crystals (72%): mp 126 °C; IR (KBr) 3410, 3390 (NH), 1690, 1625 (CO); ^{1}H-NMR (DMSO-d_6) δ: 12.20 (bs, 1H, OH), 7.29 (m, 5H, H arom), 6.42 (d, 1H, $J_{NH\ H\text{-}3}$ = 8.3 Hz, NH), 5.97 (t, 1H, $J_{NH\ CH_2}$ = 5.6 Hz, NH), 5.04 (m, 1H, H-3), 2.91 (m, 2H, CH_2), 2.65 (d, 2H, $J_{H\text{-}2\ H\text{-}3}$ = 6.8 Hz, H-2), 1.33 (m, 2H, CH_2), 0.81 (t, 3H, CH_3). Anal calc for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.23; H, 7.40; N, 11.21.

3-[3N'-Propylureido]-3-(3-chlorophenyl)propionic acid ***4f***. White crystals (50%): mp 108 °C; IR (KBr) 3370, 3270 (NH), 1690, 1630 (CO); ^{1}H-NMR (DMSO-d_6) δ: 12.15 (bs, 1H, OH), 7.27 (m, 4H, H arom), 6.50 (d, 1H, $J_{NH\ H\text{-}3}$ = 8.3 Hz, NH), 6.03 (t, 1H, $J_{NH\ CH_2}$ = 5.6 Hz, NH), 5.01 (m, 1H, H-3), 2.91 (m, 2H, CH_2), 2.66 (d, 2H, $J_{H\text{-}2\ H\text{-}3}$ = 6.8 Hz, H-2), 1.35 (m, 2H, CH_2), 0.81 (t, 3H, CH_3). Anal calc for $C_{13}H_{17}N_2O_3Cl$: C, 54.84; H, 6.02; N, 9.84. Found: C, 54.62; H, 6.08; N, 9.83.

3-[3N'-Propylureido]-3-(4-chlorophenyl)propionic acid ***4g***. White crystals (72%): mp 160 °C; IR (KBr) 3370, 3280 (NH), 1700, 1640 (CO); ^{1}H-NMR (DMSO-d_6) δ: 12.20 (bs, 1H, OH), 7.31 (m, 4H, H arom), 6.41 (d, 1H, $J_{NH\ H\text{-}3}$ = 8.3 Hz, NH), 5.96 (t, 1H, $J_{NH\ CH_2}$ = 5.6 Hz, NH), 4.96 (m, 1H, H-3), 2.87 (m, 2H, CH_2), 2.61 (d, 2H, $J_{H\text{-}2\ H\text{-}3}$ = 6.8 Hz, H-2), 1.31 (m, 2H, CH_2), 0.79 (t, 3H, CH_3). Anal calc for $C_{13}H_{17}N_2O_3Cl$: C, 54.84; H, 6.02; N, 9.84. Found: C. 54.96: H. 5.96: N. 9.69.

3-[3N'-Propylureido]-3-(4-methylphenyl)propionic acid ***4h***. White crystals (70%): mp 158 °C; IR (KBr) 3320 (NH), 1710, 1650 (CO); ^{1}H-NMR (DMSO-d_6) δ: 12.10 (bs, 1H, OH), 7.07 (m, 4H, H arom), 6.32 (d, 1H, $J_{NH\ H\text{-}3}$ = 8.3 Hz, NH), 5.88 (t, 1H, $J_{NH\ CH2}$ = 5.6 Hz, NH), 4.93 (m, 1H, H-3), 2.85 (m, 2H, CH_2), 2.55 (d, 2H, $J_{H\text{-}2\ H\text{-}3}$ = 6.8 Hz, H-2), 2.21 (s, 3H, CH_3), 1.29 (m, 2H, CH_2), 0.76 (t, 3H, CH_3). Anal calc for $C_{14}H_{20}N_2O_3$: C, 62.62; H, 7.63; N, 10.60. Found: C, 62.56; H, 17.50; N, 10.41.

General procedure for the preparation of 3-alkyl-6-arylhexahydropyrimidine-2,4-dione ***1a–h***

A solution of 3-[3*N*'-alkylureido]-3-phenylpropionic acids **4** (0.009 mol) in thionyl chloride (100 mL) was refluxed for 30 min and evaporated to dryness. The solid residue was then washed with water, filtered and dried.

3-(2-Chloroethyl)-6-phenylhexahydropyrimidine-2,4-dione ***1a***. White crystals (75%): mp 110 °C; IR (KBr) 3220 (NH), 1720, 1670 (CO); ^{1}H-NMR (DMSO-d_6) δ: 8.40 (s, 1H, NH), 7.35 (m, 5H, H arom), 4.68 (dd, 1H, $J_{H\text{-}6\ H\text{-}5b}$ = 6.84 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 5.86 Hz, H-6), 3.98 (t, 2H, CH_2), 3.65 (t, 2H, CH_2), 3.00 (dd, 1H, $J_{H\text{-}5a\ H\text{-}5b}$ = 16.12 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 5.86 Hz, H-5a), 2.78 (dd, 1H, $J_{H\text{-}5b\ H\text{-}5a}$ = 16.12 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 6.84 Hz, H-5b). Anal calc for $C_{12}H_{13}N_2O_2Cl$: C, 57.04; H, 5.19; N, 11.09. Found: C, 57.21; H, 4.99; N, 10.96.

3-(2-Chloroethyl)-6-(3-chlorophenyl)hexahydropyrimidine-2,4-dione ***1b***. White crystals (62%): mp 120 °C; IR (KBr) 3200 (NH), 1710, 1660 (CO); ^{1}H-NMR (DMSO-d_6) δ: 8.44 (s, 1H, NH), 7.38 (m, 4H, H arom), 4.72 (dd, 1H, $J_{H\text{-}6\ H\text{-}5b}$ = 6.84 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 5.86 Hz, H-6), 3.97 (t, 2H, CH_2), 3.64 (t, 2H, CH_2), 3.01 (dd, 1H, $J_{H\text{-}5a\ H\text{-}5b}$ = 16.12 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 5.86 Hz, H-5a), 2.85 (dd, 1H, $J_{H\text{-}5b\ H\text{-}5a}$ = 16.12 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 6.84 Hz, H-5b). Anal calc for $C_{12}H_{12}N_2O_2Cl_2$: C, 50.13; H, 4.21; N, 9.76. Found: C, 50.09; H, 4.36; N, 9.54.

3-(2-Chloroethyl)-6-(4-chlorophenyl)hexahydropyrimidine-2,4-dione ***1c***. White crystals (90%): mp 146 °C; IR (KBr) 3200 (NH), 1710, 1680 (CO); ^{1}H-NMR (DMSO-d_6) δ: 8.35 (s, 1H, NH), 7.36 (m, 4H, H arom), 4.68 (dd, 1H, $J_{H\text{-}6\ H\text{-}5b}$ = 6.84 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 5.86 Hz, H-6), 3.89 (t, 2H, CH_2), 3.62 (t, 2H, CH_2), 2.95 (dd, 1H, $J_{H\text{-}5a\ H\text{-}5b}$ = 16.12 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 5.86 Hz, H-5a), 2.81 (dd, 1H, $J_{H\text{-}5b\ H\text{-}5a}$ = 16.12 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 6.84 Hz, H-5b). Anal calc for $C_{12}H_{12}N_2O_2Cl_2$: C, 50.13; H, 4.21; N, 9.76. Found: C, 50.01; H, 4.21; N, 9.84.

3-(2-Chloroethyl)-6-(4-methylphenyl)hexahydropyrimidine-2,4-dione ***1d***. White crystals (82%): mp 120 °C; IR (KBr) 3210 (NH), 1720, 1675 (CO); ^{1}H-NMR (DMSO-d_6) δ: 8.35 (s, 1H, NH), 7.18 (m, 4H, H arom), 4.62 (dd, 1H, $J_{H\text{-}6\ H\text{-}5b}$ = 6.84 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 5.86 Hz, H-6), 3.95 (t, 2H, CH_2), 3.63 (t, 2H, CH_2), 2.96 (dd, 1H, $J_{H\text{-}5a\ H\text{-}5b}$ = 16.12 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 5.86 Hz, H-5a), 2.75 (dd, 1H, $J_{H\text{-}5b\ H\text{-}5a}$ = 16.12 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 6.84 Hz, H-5b), 2.28 (s, 3H, CH_3). Anal calc for $C_{13}H_{15}N_2O_2Cl$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.71; H, 5.46; N, 10.41.

6-Phenyl-3-propylhexahydropyrimidine-2,4-dione ***1e***. White crystals (87%): mp 118 °C; IR (KBr) 3310 (NH), 1715, 1665 (CO); ^{1}H-NMR (DMSO-d_6) δ: 8.24 (s, 1H, NH), 7.33 (m, 5H, H arom), 4.65 (dd, 1H, $J_{H\text{-}6\ H\text{-}5b}$ = 6.84 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 5.86 Hz, H-6), 3.58 (t, 2H, CH_2), 2.99 (dd, 1H, $J_{H\text{-}5a\ H\text{-}5b}$ = 16.12 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 5.86 Hz, H-5a), 2.76 (dd, 1H, $J_{H\text{-}5b\ H\text{-}5a}$ = 16.12 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 6.84 Hz, H-5b), 1.44 (m, 2H, CH_2) 0.77 (t, 3H, CH_3). Anal calc for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.32; H, 7.04; N, 12.27.

6-(3-Chlorophenyl)-3-propylhexahydropyrimidine-2,4-dione ***1f***. White crystals (80%): mp 132 °C; IR (KBr) 3200 (NH), 1710, 1660 (CO); ^{1}H-NMR (DMSO-d_6) δ: 8.31 (s, 1H, NH), 7.35 (m, 4H, H arom), 4.72 (dd, 1H, $J_{H\text{-}6\ H\text{-}5b}$ = 6.84 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 5.86 Hz, H-6), 3.60 (t, 2H, CH_2) 3.00 (dd, 1H, $J_{H\text{-}5a\ H\text{-}5b}$ = 16.12 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 5.86 Hz, H-5a), 2.80 (dd, 1H, $J_{H\text{-}5b\ H\text{-}5a}$ = 16.12 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 6.84 Hz, H-5b), 1.45 (m, 2H, CH_2), 0.77 (t, 3H, CH_3). Anal calc for $C_{13}H_{15}N_2O_2Cl$: C, 58.54; H, 5.67; N, 10.05. Found: C, 58.55; H, 5.89; N, 10.19.

6-(4-Chlorophenyl)-3-propylhexahydropyrimidine-2,4-dione ***1g***. White crystals (60%): mp 130 °C; IR (KBr) 3200 (NH), 1710, 1665 (CO); ^{1}H-NMR (DMSO-d_6) δ: 8.26 (s, 1H, NH), 7.50 (d, 2H, H arom), 7.39 (d, 2H, H arom), 4.77 (dd, 1H, $J_{H\text{-}6\ H\text{-}5b}$ = 6.84 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 5.86 Hz, H-6), 3.65 (t, 2H, CH_2), 3.12 (dd, 1H, $J_{H\text{-}5a\ H\text{-}5b}$ = 16.12 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 5.86 Hz, H-5a), 2.87 (dd, 1H, $J_{H\text{-}5b\ H\text{-}5a}$ = 16.12 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 6.84 Hz, H-5b), 1.49 (m, 2H, CH_2), 0.81 (t, 3H, CH_3). Anal calc for $C_{13}H_{15}N_2O_2Cl$: C, 58.54; H, 5.67; N, 10.05. Found: C. 58.61: H, 5.73: N, 10.10.

6-(4-Methylphenyl)-3-propylhexahydropyrimidine-2,4-dione ***1h***. White crystals (61%): mp 126 °C; IR (KBr) 3210 (NH), 1710, 1665 (CO); ^{1}H-NMR (DMSO-d_6) δ: 8.17 (s, 1H, NH), 7.16 (m, 4H, H arom), 4.58 (dd, 1H, $J_{H\text{-}6\ H\text{-}5b}$ = 6.84 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 5.86 Hz, H-6), 3.56 (t, 2H, CH_2), 2.85 (dd, 1H, $J_{H\text{-}5a\ H\text{-}5b}$ = 16.12 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 5.86 Hz, H-5a), 2.62 (dd, 1H, $J_{H\text{-}5b\ H\text{-}5a}$ = 16.12 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 6.84 Hz, H-5b), 2.28 (s, 3H, CH_3), 1.43 (m, 2H, CH_2), 0.78 (t, 3H, CH_3). Anal calc for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.18; H, 7.33; N, 11.22.

*General procedure for the preparation of 6-(4-chlorophenyl)-3-(2-morpholinoethyl)hexahydropyrimidine-2,4-dione **5** and 6-(4-chlorophenyl)-3-(2-pyrrolidinoethylhexahydropyrimidine-2,4-dione **6***

A solution 3*N*-(2-chloroethyl)-6-(4-chlorophenyl)-hexahydropyrimidine-2,4-dione **1** (8.61 g, 0.03 mol) in morpholine or pyrrolidine (100 mL) was refluxed for 2 h. The excess of solvent was evaporated to dryness, the residual oil was triturated in water to give crystals which were filtered, washed with water, dried and recrystallized from ether.

*6-(4-Chlorophenyl)-3-(2-morpholinoethyl)hexahydropyrimidine-2,4-dione **5**.* Beige crystals (40%): mp 162 °C; IR (KBr) 3210 (NH), 1720, 1660 (CO); ^{1}H-NMR (DMSO-d_6) δ: 8.30 (s, 1H, NH), 7.38 (m, 4H, H arom), 4.67 (dd, 1H, $J_{H\text{-}6\ H\text{-}5b}$ = 6.84 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 5.86 Hz, H-6), 3.77 (m, 2H, CH_2), 3.50 (t, 4H, CH_2), 3.03 (dd, 1H, $J_{H\text{-}5a\ H\text{-}5b}$ = 16.12 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 5.86 Hz, H-5a), 2.69 (dd, 1H, $J_{H\text{-}5b\ H\text{-}5a}$ = 16.12 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 6.84 Hz, H-5b), 2.37 (m, 4H, CH_2). Anal calc for $C_{16}H_{20}N_3O_3Cl$: C, 59.89; H, 5.97; N, 12.44. Found: C, 59.63; H, 5.85; N, 12.37.

*6-(4-Chlorophenyl)-3-(2-pyrrolidinoethyl)hexahydropyrimidine-2,4-dione **6**.* Beige crystals (63%): mp 150 °C; IR (KBr) 3420 (NH), 1720, 1660 (CO); ^{1}H-NMR (DMSO-d_6) δ: 8.28 (s, 1H, NH), 7.39 (m, 4H, H arom), 4.64 (dd, 1H, $J_{H\text{-}6\ H\text{-}5b}$ = 6.84 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 5.86 Hz, H-6), 3.75 (m, 2H, CH_2), 3.33 (t, 4H, CH_2), 3.01 (dd, 1H, $J_{H\text{-}5a\ H\text{-}5b}$ = 16.12 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 5.86 Hz, H-5a), 2.70 (dd, 1H, $J_{H\text{-}5b\ H\text{-}5a}$ = 16.12 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 6.84 Hz, H-5b), 2.42 (t, 4H, CH_2), 1.64 (m, 4H, CH_2). Anal calc for $C_{16}H_{20}N_3O_2Cl$: C, 59.72; H, 6.26; N, 13.06. Found: C, 59.50; H, 6.39; N, 12.97.

*Procedure for the preparation of ethyl-6-phenylhexahydropyrimidine-2,4-dioxo-3-(2-ethyl)mercaptoacetate **7***

Sodium (0.23 g, 0.01 mol) was dissolved in ethanol (50 mL). Methylthioglycolate (1.06 g, 0.01 mol) was added to the reaction mixture which was then stirred at room temperature for 1 h. 3*N*-(2-chloroethyl)-6-phenylhexahydropyrimidine-2,4-dione **1** (2.52 g, 0.01 mol) was added to the mixture which was refluxed for 2 h. The solution was filtered and evaporated to dryness under reduced pressure. The residual oil was triturated in water to give crystals that were filtered, washed with water, dried and recrystallized from ether.

White crystals (77%): mp 85 °C; IR (KBr) 3200 (NH), 1710, 1675 (CO); ^{1}H-NMR (DMSO-d_6) δ: 8.31 (s, 1H, NH), 7.35 (m, 5H, H arom), 4.69 (dd, 1H, $J_{H\text{-}6\ H\text{-}5b}$ = 6.84 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 5.86 Hz, H-6), 4.10 (q, 2H, CH_2), 3.84 (t, 2H, CH_2), 3.36 (s, 2H, CH_2), 3.06 (dd, 1H, $J_{H\text{-}5a\ H\text{-}5b}$ = 16.12 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 5.86 Hz, H-5a), 2.76 (dd, 1H, $J_{H\text{-}5b\ H\text{-}5a}$ = 16.12 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 6.84 Hz, H-5b), 2.70 (t, 2H, CH_2), 1.20 (t, 3H, CH_3). Anal calc for $C_{16}H_{20}N_2O_4$: C, 57.13; H, 5.99: N, 8.43. Found: C, 57.16: H, 5.85; N, 8.56.

Pharmacology

Benzodiazepine receptor-binding assays [7, 8]

Male Wistar rats (220–225 g) whole brains were homogenized in 100 volumes of Tris-citrate buffer (50 mM, pH = 7.4), using a Brinkman Polytron (setting 6, for 15 s). Homogenates were centrifuged at 20 000 *g* for 20 min at 4 °C. Tissues were resuspended and washed five more times before final resuspension in 100 volumes of buffer. The incubation mixture consisted of 0.5–0.6 mg of protein, 0.1 mL of [^{3}H]FLU (final concentration 1 nM), and varying amounts of the test compounds and buffer to a final volume of 1 mL. The mixture was incubated at 0 °C for 60 min, and the incubations were terminated by rapid filtration through Whatmann GF/B fiber filters. The filters were washed three times with 5 mL of the buffer and placed in minivials containing 5 mL of optiphase Highsafe 2 (Wallac). After 12 h, the radioactivity was counted with an liquid scintillation counter. Non-specific binding (using 10 μM FLU) was consistently < 10% of total binding. Protein content was determinated by the method of Lowry [9], using bovine serum albumin as standard. Each value was determinated in duplicate, and IC_{50} values were estimated from semilogarithmic plots. K_i values were calculated from the following equation: $K_i = IC_{50}/(1 + L/K_d)$, where L is the ligand concentration (1 nM) and K_d is the dissociation constant for [^{3}H]FLU, determinated by parallel experiments. The data shown are the means of at least four individual experiments.

Pharmacological evaluation

Female OF-1 mice (France, Iffa Credo) weighing 18–22 g were used for pharmacological studies. The animals were allowed free access to food and water and were housed at room temperature (20–22 °C). All the test compounds were administered via intraperitoneal injection (ip) in a 1% carboxymethylcellulose suspension.

Gross behavioral effects and acute toxicity in mice

Morpugo's modification [6] of Irwin's multidimensional screening procedure was used on groups of four mice to evaluate drug-induced behavioral alterations. The test compounds were administered in log-spaced doses, and detailed observations of the mice were made 1, 3 and 24 h after treatment. Perphenazine (50 mg/kg ip) and methylphenidate (50 mg/kg) were used for comparison. The approximate LD_{50} was obtained from the mortality observed during a 48 h period.

Anticonvulsant activity

Test compounds were given to groups of five mice, 30 min before the ip injection of 150 mg/kg pentylenetetrazole [6]. The protection against pentylenetetrazole-induced lethal convulsions was evaluated for a 15 min observation period. For the test compound, the initial dose was 1/4 LD_{50}. If such a dose was found to have an active effect, successive log-spaced doses were tested, the ED_{50} and 95% confidence intervals were estimated by the method of Spearman and Karber [10]. Diazepam was used as reference drug.

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