Structure-Activity Relationship Studies of CNS Agents, Part 22[1]:

A Search for New Trazodone-Like Antidepressants: Synthesis and Preliminary Receptor Binding Studies

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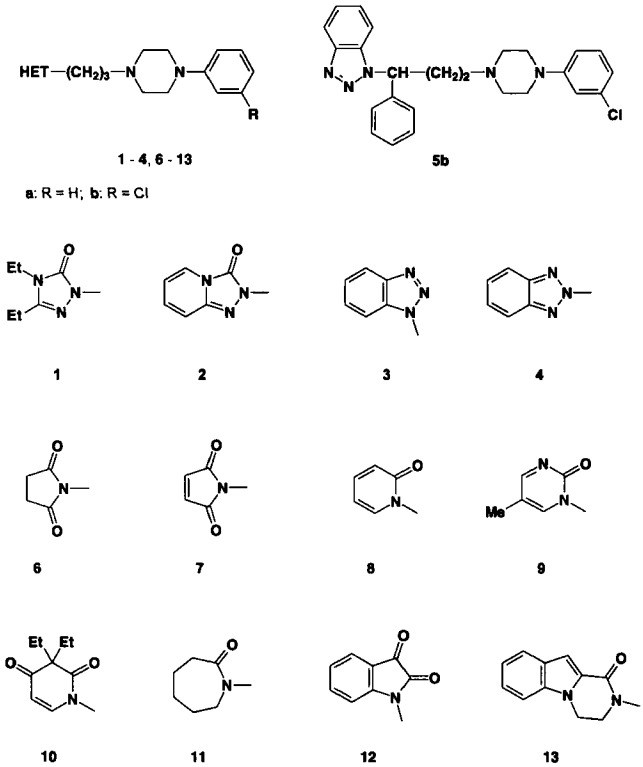
Summary

New 1-phenyl- and 1-(3-chlorophenyl)piperazines containing a 4-[3-(heterocyclic)propyl] fragment were synthesized. It was found that of all the investigated compounds **11b** (K_i = 13 ± 2 nM) and **8b** (K_i = 38 ± 2 nM) were the most active 5-HT$_{1A}$ and 5-HT$_{2A}$ ligands, respectively. Several derivatives (**3a**, **4a**, **8b**, **11b**, **12b**, **13a**, and **13b**) were selected as good candidates for new, potential antidepressants on the basis of their 5-HT$_{1A}$/5-HT$_{2A}$ receptor binding profiles.

Etoperidone (**1b**) and trazodone (**2b**) belong to the class of atypical antidepressants which are used in the therapy of depression and anxiety[2,3]. The basis for the antidepressant activity of these compounds has long been an object of interest[4–8]. It has been suggested that both the 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor affinities of **1b** and **2b** are sufficiently high to contribute to their overall pharmacological profile[6–8]. Indeed, it was reported that **1b** and **2b** may be classified as antagonists at both the 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors[5–8].

In order to search for new, non-selective 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor ligands, the present paper deals with the synthesis of a new set of 1-phenyl- and 1-(3-chlorophenyl)-piperazines **5b** and **6–13**, as well as with the 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor affinities of compounds **1–13**.



Scheme

Table: The 5-HT$_{1A}$ and 5-HT$_{2A}$ binding constants (K_i), and the 5-HT$_{1A}$/5-HT$_{2A}$ selectivity ratio of compounds **1–13.**

No.	K_i [nM] ± SEM [a]		Selectivity [b]
	5-HT$_{1A}$	5-HT$_{2A}$	$\frac{\text{5-HT}_{1A}}{\text{5-HT}_{2A}}$
8-OH-DPAT	1.4 ± 0.2	ND	
ritanserin	ND	1.1 ± 0.1	
1b [c]	201 ± 7	32 ± 3	6.3
2b [c]	244 ± 34	38 ± 9	6.4
3a	141 ± 12	75 ± 12	1.9
3b	42 ± 2	100 ± 5	0.42
4a	153 ± 34	39 ± 7	3.9
4b	80 ± 3	321 ± 62	0.25
5b	106 ± 9	219 ± 18	0.48
6a	812 ± 9	1270 ± 40	0.64
6b	317 ± 11	374 ± 5	0.85
7b	2710 ± 60	1540 ± 200	1.8
8a	136 ± 5	138 ± 13	0.99
8b	52 ± 3	38 ± 2	1.4
9a	689 ± 118	159 ± 10	4.3
10b	282 ± 6	437 ± 13	0.64
11a	41 ± 5	306 ± 8	0.13
11b	13 ± 2	67 ± 4	0.19
12a	71 ± 5	253 ± 10	0.28
12b	36 ± 2	80 ± 3	0.45
13a [d]	15 ± 2	40 ± 2	0.48
13b	31 ± 3	58 ± 5	0.53

[a] The mean value from at least three independent experiments run in triplicate. [b] Selectivity is expressed as a ratio of the K_i values.
[c] **1b** – Etoperidone, **2b** – trazodone. [d] Binding data taken from ref.[17].
ND – not determined.

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The investigated compounds showed a diversified affinity for both 5-HT_{1A} and 5-HT_{2A} receptors, which ranged from 10^{-8} to 3×10^{-6} M (Table). Furthermore, all of them may be classified as non-selective 5-HT_{1A}/5-HT_{2A} ligands, as the observed selectivity ratio did not exceed a factor of 8 (*cf.* selectivity ratios of 0.13 and 6.4 for **11a** and **2b**, respectively). At this stage of study, the role of a terminal heterocyclic moiety of long-chain 1-arylpiperazines in the formation and stabilization processes of bioactive complexes with 5-HT_{1A} or 5-HT_{2A} receptors is still hypothetical but such an additional anchoring group seems to be desired for the activity of this class of ligands[9–11]. On the other hand, terminal heterocyclic fragments of the investigated compounds may interact with the respective 5-HT_{1A} or 5-HT_{2A} receptor sites in several different ways. It is anticipated that the following interaction modes (between the terminal heterocyclic fragments and the receptor binding sites) may contribute to the observed 5-HT_{1A} and 5-HT_{2A} affinities: dipole-dipole and π-electron interactions, hydrogen bonds, or hydrophobic forces[9–15]. None of these effects, however, controls exclusively the affinity of the investigated compounds. Therefore only some general conclusions on the structure-affinity relationships may be drawn on the basis of the binding data presented in the Table. Introduction of the chlorine atom in the phenyl ring had a pronounced but typical effect on 5-HT_{1A} affinity (*cf.* series **b** *vs.* **a**, Table)[12,13]. The observed selectivity ratio did not differentiate between 1- and 2-benzotriazole isomers (*cf.* **3a** *vs.* **4a** and **3b** *vs.* **4b**). The extension of derivative **3b** with a phenyl group (**5b**) had no effect on the 5-HT_{1A}/5-HT_{2A} selectivity ratio, though the overall affinity of **5b** was twice as low as that of **3b**. The derivatives containing terminal fragments **6**, **7**, **9**, and **10** displayed considerably lower receptor affinities in comparison with etoperidone (**1b**) or trazodone (**2b**). By contrast, compounds **3a**, **4a**, **8b**, **11b**, **12b**, **13a**, and **13b** showed fairly high 5-HT_{1A} and 5-HT_{2A} affinities. The 5-HT_{2A} affinities of the latter compounds are comparable with those found for etoperidone (**1b**) and trazodone (**2b**). On the other hand, the 5-HT_{1A}/5-HT_{2A} selectivity factor differentiates the discussed derivatives. While **3a**, **4a**, and **8b** show the same direction of the selectivity as the lead compounds **1b** and **2b**, the other derivatives (**11b**, **12b**, **13a**, **13b**) show the inverse selectivity ratio (Table). Thus it is anticipated that at least the derivatives **3a**, **4a**, and **8b** may be regarded as candidates for new, potential antidepressants. Further behavioral studies on the functional activity of **3a**, **4a**, **8b**, **11b**, **12b**, **13a**, and **13b** at 5-HT_{1A} and 5-HT_{2A} receptors are presently in progress.

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Experimental Part

Melting points: Boetius apparatus (uncorrected).– Elemental analyses: Within ± 0.4% of calculated values. Perkin Elmer 240 analyser (Institute of Organic Chemistry, Warsaw).– ^{1}H NMR spectra ($CDCl_3$): Varian EM-360L (60 MHz) spectrometer, TMS int. standard.– MS spectra: LKB 2091 instrument (70 eV).– Materials: etoperidone (**1b**) and trazodone (**2b**) were obtained from the F. Angelini Research Institute, and compounds **3a,b** and **4a,b** were synthesized according to the published procedure[16].

*1-[3-(Benzotriazol-1-yl)-3-phenylpropyl]-4-(3-chlorophenyl)piperazine dihydrochloride (**5b**)*

A mixture of benzotriazole (0.95 g, 8 mmol) and cinnamaldehyde (0.53 g, 4 mmol) in Et_2O (30 ml, freshly distilled from Na/benzophenone) was stirred at room temp. for 6 h and left overnight. The reaction mixture was cooled in an ice-water bath and a solution of 1-(3-chlorophenyl)piperazine (0.67 g, 4 mmol) was added in one portion upon stirring. Then the mixture was allowed to reach room temp. and the stirring was continued for 20 h. Afterwards the solvent was evaporated, the residue was dissolved in dioxane (40 ml), treated with $NaBH_4$ (0.076 g, 2 mmol), refluxed for 4 h and left overnight at room temp. The reaction mixture was poured into 10% NaOH (40 ml) and extracted with Et_2O (3 × 30 ml). The combined organic layers were washed with water and dried over anhydrous $MgSO_4$. Then the solvent was evaporated, and the oily residue containing a mixture of **5b** and **5c** was separated by CC (SiO_2, AcOEt/*n*-hexane – 1/2). The products were converted into HCl salts according to a standard procedure[13]. **5b · 2 HCl:** yield 0.42 g (21%). Mp 144–146 °C (acetone).– ^{1}H NMR (base): δ = 2.3–2.8 (m, 8H, 4 CH_2), 3.0–3.35 (m, 4H, 2 CH_2), 5.9–6.3 (m, 1H, CH), 6.8–7.3 (m, 2H, aromatic H), 7.2–7.75 (m, 10H, aromatic H), 8.0–8.3 (m, 1H, benzotriazole H-7).– Anal. ($C_{25}H_{26}ClN_5 \cdot 2$ HCl). *1-(3-Chlorophenyl)-4-[(E)-3-phenyl-2-propenyl]piperazine dihydrochloride* (**5c**): yield 0.55 g (36%). Mp 168–170 °C (acetone).– ^{1}H NMR (base): δ = 2.4–2.75 (m, 4H, 2 CH_2), 3.05–3.45 (m, 6H, 3 CH_2), 6.35–6.65 (m, 2H, CH=CH), 6.65–7.0 (m, 3H, aromatic H), 7.2–7.65 (m, 6H, aromatic H).– Anal. ($C_{19}H_{21}ClN_2 \cdot 2$ HCl).

General procedure for preparing derivatives **6a** *and* **6b**

A mixture of succinimide (0.12 g, 1.21 mmol), an appropriate 4-(3-bromopropyl)-1-arylpiperazine (1.25 mmol) and K_2CO_3 (0.5 g, 3.6 mmol) in acetonitrile (20 ml) was refluxed for 4 h and cooled down. An inorganic precipitate was filtered off and the solvent was evaporated. The product was converted into a HCl salt according to a standard procedure[17].

*N-[3-(4-Phenyl-1-piperazinyl)propyl]succinimide dihydrochloride (**6a**)*

Yield 90%. Mp 232–234 °C (80% ethanol).– ^{1}H NMR (base): δ = 1.6–2.0 (m, 2H, CH_2), 2.2–2.6 (m, 6H, 3 CH_2), 2.5 (s, 4H, 2 CH_2), 3.0–3.3 (m, 4H, 2 CH_2), 3.57 (t, *J* = 7 Hz, 2H, CH_2), 6.7–7.3 (m, 5H, aromatic H).– Anal. ($C_{17}H_{23}N_3O_2 \cdot 2$ HCl · 0.5 H_2O).

*N-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]succinimide dihydrochloride (**6b**)*

Yield 86%. Mp 216–218 °C (ethanol/acetone – 1/1).– ^{1}H NMR (base): δ = 1.6–2.0 (m, 2H, CH_2), 2.2–2.8 (m, 10H, 5 CH_2), 3.0–3.3 (m, 4H, 2 CH_2), 3.6 (t, *J* = 7 Hz, 2H, CH_2), 6.7–7.5 (m, 4H, aromatic H).– Anal. ($C_{17}H_{22}ClN_3O_2 \cdot 2$ HCl).

General procedure for preparing derivatives **7–13**

A mixture of the heterocyclic amido-functionalized educt (2 mmol), an appropriate 4-(3-bromopropyl)-1-arylpiperazine (2.1 mmol), KF/Al_2O_3 catalyst (2 g) in acetonitrile (30 ml) was stirred for 2 h at room temp. (**7b**, **10b**), or was refluxed for 1 h (**8**, **9a**, **11–13**). An inorganic precipitate was filtered off and the solvent was evaporated. The residue was purified by CC (Al_2O_3, $CHCl_3$/*n*-hexane – 1/1 for **7b** and **10b**, or SiO_2, $CHCl_3$/methanol – 9/1 for all the others). Free bases were converted into HCl salts according to the standard procedure[17].

*N-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]maleimide dihydrochloride (**7b**)*

Yield 21%. Mp 215–217 °C (acetone).– ^{1}H NMR (base): δ = 1.8 (quint, *J* = 7 Hz, 2H, CH_2), 2.3–2.7 (m, 6H, 3 CH_2), 3.0–3.3 (m, 4H, 2 CH_2), 3.67 (t, *J* = 7 Hz, 2H, CH_2), 6.8 (s, 2H, CH=CH), 6.85–7.4 (m, 4H, aromatic H).– Anal. ($C_{17}H_{20}ClN_3O_2 \cdot 2$ HCl).

*N-[3-(4-Phenyl-1-piperazinyl)propyl]-2(1H)-pyridone dihydrochloride (**8a**)*

Yield 30%. Mp 64–65 °C (ether/*n*-hexane – 1/1, base), 230–232 °C (acetone, HCl salt).– MS (base); *m/z* (%): 297 (5) [M^+], 178 (12), 175 (10), 165 (100), 132 (22), 105 (11), 77 (15).– Anal. ($C_{18}H_{23}N_3O \cdot 2$ HCl).

N-{3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl}-2(1H)-pyridone dihydrochloride (**8b**)

Yield 25%. Mp 206–208 °C (acetone). ^{1}H NMR (salt, $CDCl_3$/[D_4]methanol): δ = 2.25–2.8 (m, 2H, CH_2), 3.25–3.8 (m, 10H, 5 CH_2), 4.45 (t, *J* = 7 Hz, 2H, CH_2), 6.9–7.35 (m, 6H, aromatic H), 7.95 (d, *J* = 7 Hz, 1H, 2(1H)-pyridone H-4), 8.35 (d, *J* = 6 Hz, 1H, 2(1*H*)-pyridone H-6).– Anal. ($C_{18}H_{22}ClN_3O \cdot 2$ HCl).

5-Methyl-2-oxo-1-[3-(4-phenyl-1-piperazinyl)propyl]-1,2-dihydropyrimidine dihydrochloride (**9a**)

Yield 19%. Mp 129–131 °C (acetone).– MS (base); *m/z* (%): 312 (100) [M^+], 180 (85), 173 (65), 132 (59), 105 (45), 77 (41).– Anal. ($C_{18}H_{24}N_4O \cdot 2$ HCl).

3,3-Diethyl-2,4-dioxo-N-{-[4-(3-chlorophenyl)-1-piperazinyl]propyl}-1,2,3,4-tetrahydropyridine dihydrochloride (**10b**)

Yield 80%. Mp 108–110 °C (acetone/ether – 9/1).– ^{1}H NMR (base): δ = 0.77 (t, *J* = 7 Hz, 6H, 2 CH_3), 1.67–2.2 (m, 6H, 3 CH_2), 2.23–2.8 (m, 6H, 3 CH_2), 3.0–3.3 (m, 4H, 2 CH_2), 3.87 (t, *J* = 6 Hz, 2H, CH_2), 5.53 (d, *J* = 8 Hz, 2H, CH=CH), 6.67–7.3 (m, 4H, aromatic H).– Anal. ($C_{22}H_{30}ClN_3O_2 \cdot 2$ HCl· 0.5 H_2O).

N-[3-(4-Phenyl-1-piperazinyl)propyl]caprolactam dihydrochloride (**11a**)

Yield 38%. Mp 200–203 °C (acetone).– MS (base); *m/z* (%): 315 (1) [M^+], 175 (100), 132 (18), 105 (20), 77 (13).– Anal. ($C_{19}H_{29}N_3O \cdot 2$ HCl · 2 H_2O).

N-{3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl}caprolactam dihydrochloride (**11b**)

Yield 27%. Mp 227–230 °C (acetone).– MS (base); *m/z* (%): 349 (5) [M^+], 351 (2) [M^+ +2], 266 (16), 211 (18), 209 (67), 183 (100), 154 (59).– Anal. ($C_{19}H_{28}ClN_3O \cdot 2$ HCl).

N-[3-(4-Phenyl-1-piperazinyl)propyl]-2,3-dioxoindoline dihydrochloride (**12a**)

Yield 71%. Mp 148–149 °C (acetone/ethanol – 3/1, base), 156–159 °C (acetone, HCl salt).– ^{1}H NMR (base): δ = 1.75–2.2 (m, 2H, CH_2), 2.35–2.7 (m, 6H, 3 CH_2), 3.05–3.3 (m, 4H, 2 CH_2), 3.85 (t, *J* = 7 Hz, 2H, CH_2), 6.8–7.35 (m, 7H, aromatic H), 7.4–7.75 (m, 2H, aromatic H).– Anal. ($C_{21}H_{23}N_3O_2 \cdot 2$ HCl).

N-{3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl}-2,3-dioxoindoline dihydrochloride (**12b**)

Yield 62%. Mp 153–155 °C (base, acetone/ethanol – 3/1), 182–184 °C (acetone/ether – 1/1).– ^{1}H NMR (base): δ = 1.7–2.2 (m, 2H, CH_2), 2.35–2.65 (m, 6H, 3 CH_2), 3.0–3.25 (m, 4H, 2 CH_2), 3.8 (t, *J* = 7 Hz, 2H, CH_2), 6.6–7.3 (m, 6H, aromatic H),7.4–7.7 (m, 2H, aromatic H).– Anal. ($C_{21}H_{22}ClN_3O_2 \cdot 2$ HCl).

N-{3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl}-4-oxo-1,2,3,4-tetrahydro[1,2-a]indole dihydrochloride (**13b**)

Yield 44%. Mp. 135–137 °C (benzene/*n*-hexane – 1/1, base), 129–133 °C (acetone, HCl salt).– ^{1}H NMR (base): δ = 1.7–2.2 (m, 2H, CH_2), 2.35–2.75 (m, 6H, 3 CH_2), 3.1–3.35 (m, 4H, 2 CH_2), 3.55–4.0 (m, 4H, 2 CH_2), 4.3 (t, *J* = 7 Hz, 2H, CH_2), 6.7–7.5 (m, 8H, aromatic H), 7.65–7.9 (m, 1H, aromatic H).– Anal. $C_{24}H_{27}ClN_4O \cdot 2$ HCl).

Binding experiments

Radioligand binding studies with 5-HT_{1A} and 5-HT_{2A} receptors were carried out in the rat brain (the hippocampus and cortex, respectively) according to a published procedure[18]. The radioligands used in the binding assays were [^{3}H]-8-OH-DPAT (190 Ci/mmol, Amersham) for 5-HT_{1A} receptors and [^{3}H]-ketanserin (60 Ci/mmol, NEN Chemicals) for 5-HT_{2A} ones. IC_{50} values were determined from a nonlinear single fit to data obtained from competition experiments in which 10–14 drug concentrations run in triplicate were used. The obtained data were analyzed by an F-test. The K_i values were calculated from the *Cheng-Prusoff* equation[19].

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