Synthesis of 4-Arylpiperazine Derivatives of Moclobemide: Potential Antidepressants with a Dual Mode of Action

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ABSTRACT

We report here the synthesis of substituted 4-chloro-*N*-[3-*oxo*-3-(4-aryl-1-piperazinyl)-propyl] benzamides (**5–9**), as potential new antidepressants, incorporating in a single molecule structural moieties related to a dual pharmacological profile: MAO-A inhibitor and 5-HT_{1A} receptor affinity.

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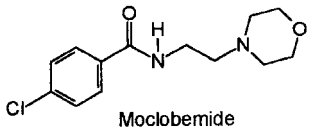
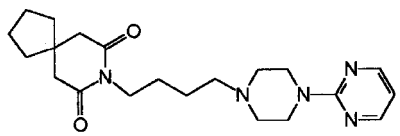
INTRODUCTION

Depression is one of the most frequent psychiatric disorders, affecting up to one third of all people at the same time. The causes of depression are multifactorial, although it is accepted that neurochemical disorders reflected by alterations in the levels of some central neurotransmitters are ultimately responsible for the appearance of the depressive symptoms.[1–3] The neurotransmitter serotonine (5-hydroxytryptamine, 5-HT) modulates the activity of central nervous system and peripheral tissues by interaction with seven classes of receptors (5-HT_{1-7}), containing 15 distinct subpopulations of receptors[4,5] where the 5-HT_{1A} subtype is the best studied due to its involvement in psychiatric disorders such as anxiety and depression.[6,7] A well-known class of 5-HT_{1A} receptor ligands are the "long chain" arylpiperazine derivatives. Among these Buspirone a partial agonist at 5-HT_{1A} receptors is an effective antianxiety and was the first arylpiperazine approved for clinical use. On the other hand Moclobemide, a reversible MAO-A inhibitor exerts its antidepressant therapeutic effect by preventing the degradation of neurotransmitters and xenobiotic amines (oxidative deamination), modulating the level of these biogenic amines.



Moclobemide
(MAO-A inhibitor)



Buspirone
(anxiolytic -antidepressant)

Although, a variety of method for the synthesis of Moclobemide and phenylpiperazine derivatives have been developed,[8–11] there is no report dealing with the obtention of 4-arylpiperazine, connected with the alkyl-*p*-chlorobenzamide framework of Moclobemide in a single chemical entity.

In this article, we describe the synthesis of a series of molecular templates of 4-chloro-*N*-[3-*oxo*-3-(4-aryl-1-piperazinyl)-propyl] benzamides, as potential antidepressants of dual action, based on coupling structural moieties related to reversible MAO-A inhibitor Moclobemide and typical 5-HT_{1A} ligands (Fig. 1).

The synthesis of the title benzamides started by reaction of *p*-chlorobenzoyl chloride with β-alanine hydrochloride, in the presence of anhydrous pyridine under inert atmosphere to give the ester (**2**) (93.2%), which was further hydrolyzed in basic medium to provide the carboxylic acid (**3**) (91.5%) (Sch. 1). The hydrolysis of the ester function of (**2**) had to be carried out with special care,

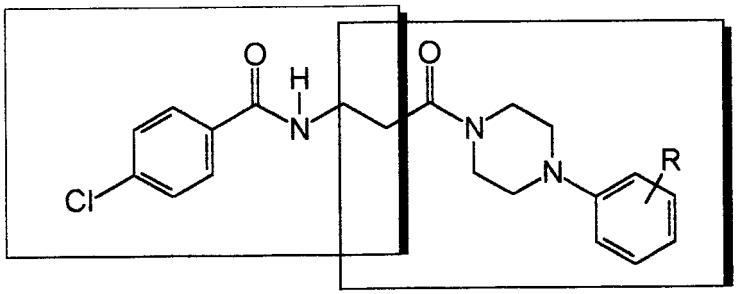
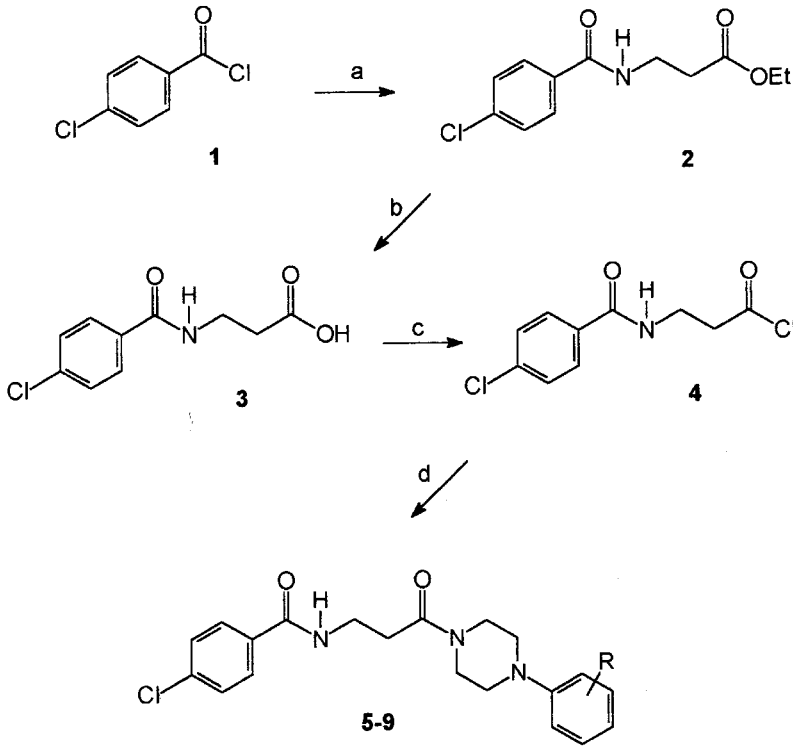


Figure 1.



Scheme 1. Reagents: (a) $NH_2(CH_2)_2$-COOEt hydrochloride/anhydrous THF, dry pyridine, N_2 atmosphere; (b) KOH–EtOH (30 min); (c) $SOCl_2$, 40°C (3 hr); (d) substituted 4-phenylpiperazines/anhydrous THF, dry pyridine, N_2 atmosphere.

Table 1. The synthesis of 4-arylpiperazine derivatives of Moclobemide (**5**–**9**) in excellent yields.

Compound	R	Yield (%)
5	Hydrogen	95.0
6	4-Nitro	96.2
7	2- Fluor	94.7
8	4-Fluor	93.6
9	2-Methoxy	98.3

in order to avoid competitive hydrolysis of the amide, which was detected as a side reaction.

Reaction of the carboxylic acid (**3**) with thionyl chloride under smooth conditions of heating gave the corresponding acid chloride (**4**), in near quantitative yield, which was rapidly identified by its IR spectrum (strong carbonylic band at 1798 cm^{-1}), and reacted under inert atmosphere with different 4-arylpiperazines to afford the expected 4-arylpiperazino benzamides (**5–9**) in high yields (Table 1).

In conclusion, we have described the synthesis of new 4-arylpiperazine derivatives of Moclobemide (**5–9**) in excellent yields, through a four step sequence, starting from commercially available reagents. The potential dual pharmacological profile of the synthesized products could lead to a new class of antidepressants. The corresponding biological assays of these compounds are in progress.

EXPERIMENTAL

All reagents were obtained commercially and used without further purification. Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded with a FT Bruker spectrophotometer for KBr. ^{1}H-NMR and ^{13}C-NMR spectra were obtained with a Bruker DRX-300 spectrophotometer. The chemical shifts are expressed in ppm (δ scale) downfield from TMS, J values are given in Hertz for solutions in $CDCl_3$ unless otherwise indicated. Microanalysis was determined on a Fisons EA 1108 analizer. Silica gel Merck 60 (70–230 mesh) and DC-alufolien 60 F_{254} were normally used for column and TLC chromatography, respectively.

Ethyl 3-[(4-chlorobenzoyl) amino] propanoate (2). To a stirred solution of 3-amino-propanoate ethyl ester hydrochloride (β-alanine) (500 mg,

3.25 mmo1), in dry THF (50 mL) containing anhydrous pyridine (381.3 mg, 4.88 mmol) at 0°C, was successively added 4-chloro benzoyl chloride (569.7 mg, 3.25 mmol) under nitrogen atmosphere, the whole was then stirred for 4 hr, upon this time the solution was poured into water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness. The crude was purified by silica gel column chromatography (CH_2Cl_2/AcOEt = 1 : 1) to afford (**2**) (775.8, 93.2%). M.p. 84–85°C white crystals (ethanol). Anal. Calcd. for $C_{12}H_{14}ClNO_3$: C, 56.46; H, 5.53; N, 5.49. Found: C, 56.22; H, 5.47; N, 5.32%; IR ν_{max}: 3338 (N-H), 1728 (COOEt), 1633 (CONH). ^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, 3H, $J = 7.1$, –CH2–CH_3), 2.64 (t, 2H, $J = 5.9$, –CH_2–COOEt), 3.72 (q, 2H, $J = 6.0$, NH–CH_2–CH_2), 4.17 (q, 2H, $J = 7.1$, COOCH_2CH_3), 6.97 (br. t, 1H, CONH–), 7.4 (d, 2H, $J = 8.4$, *p*-Cl–C_6H_4–, 3-H and 5-H), 7.71 (d, 2H, $J = 8.4$, *p*-Cl–C_6H_4–, 2-H and -6-H). ^{13}C-NMR ($CDCl_3$) δ: 14.2, 33.8, 35.4, 60.9, 128.4 (2C), 128.8 (2C), 132.7, 137.7, 166.3, 172.9.

3-[(4-Chlorobenzoyl) amino] propionic acid (3). A solution of the ester (**2**) (347 mg, 1.36 mmol) in 0.5 N KOH : EtOH (1 : 1 v/v), (50 mL) was stirred at room temperature for 30 min. The mixture was concentrated in vacuo and the aqueous residue was cooled at 10°C and acidified with 0.1 N HCl to pH 1, the resulting precipitate was filtered off to provide (**3**) (263 mg, 91.5%). Recrystallization from ethanol/petroleum ether (1 : 2) furnished pure carboxylic acid (**3**) a white needles.

M.p. 168–169°C (ethanol/petroleum ether, 1 : 2). Anal. Calcd. for $C_{10}H_{10}Cl\,NO_3$: C, 52.86; H, 4.44; N, 6.17. Found: C, 52.75; H, 4.28; N, 6.11%; IR ν_{max}: 3600–2870 (O-H), 3311 (N-H), 1702 (COOH), 1633 (NHC=O). ^{1}H-NMR (DMSO-d_6) δ: 2.31 (t, 2H, $J = 7.0$, –CH_2–COOH), 3.24 (q, 2H, $J = 6.2$, NH–CH_2–CH_2), 7.31 (d, 2H, $J = 8.6$, *p*-Cl–C_6H_4–, 3-H and 5-H), 7.65 (d, 2H, $J = 8.6$, *p*-Cl–C_6H_4-2-H and 6-H), 8.40 (br.t, 1H, ArCONH–), 12.2 (s, 1H, COOH). ^{13}C-NMR (DMSO-d_6) δ: 34.1, 36.0, 128.8 (2C), 129.6 (2C), 133.6, 136.4, 165.63, 173.3.

3-[(4-Chlorobenzoyl) amino] propanoyl chloride (4). A solution of carboxylic acid (**3**) (312 mg, 1.47 mmol) in thionyl chloride (40 mL) was smoothly refluxed in an oil silicone bath, at 40°C for 3 hr. The solvent was then removed in vacuo, to afford (357.7 mg, 98.6%) of propanoyl chloride (**4**) as a yellow pale oil, being immediately characterized by spectroscopic analysis and reacted. IR ν_{max}: 1797 (–COCl), 1664 (HO–C=N–). ^{1}H-NMR ($CDCl_3$) δ: 3.33 (t, 2H, $J = 6.2$, CH_2–CH_2–COCl), 3.97 (t, 2H, $J = 6.2$, C=N–CH_2–CH_2), 7.36 (d, 2H, $J = 8.6$, *p*-Cl–C_6H_4, 3-H and 5-H), 7.90 (d, 2H, $J = 8.6$, *p*-Cl–C_6H_4–, 2-H and 6-H). ^{13}C-NMR ($CDCl_3$) δ: 46.9, 49.2, 128.6 (2C), 130.2 (2C), 133.5, 138.2, 143.8, 172.2.

Preparation of 4-Chloro-*N*-[3-*oxo*-3-(4-aryl-1-piperazinyl)-propyl]-benzamide Derivatives (5–9). Typical Procedure. (5) As an Example

Propanoyl chloride (**4**) (292 mg, 1.19 mmol) in dry THF (10 mL) was slowly added to a stirred solution at 0°C of 4-phenyl-1-piperazine (193 mg, 1.19 mmol), pyridine (94 mg, 1.19 mmol) and dry THF (50 mL) in nitrogen atmosphere. The mixture was maintained with stirring for 6 hr at room temperature and then poured into a water solution (100 mL). The mixture was extracted with ethyl acetate (3 × 50 mL) and the organic layers dried over $MgSO_4$. Removal of the solvent afforded 4-chloro-*N*-[3-*oxo*-3-(4-phenyl-l-piperazinyl)-propyl]-benzamide (**5**) (420 mg, 95%), as a white powder which was purified by silica gel column chromatography (CH_2Cl_2/AcOEt = 1 : 1). m.p. 172–173°C (ethanol). Anal. Calcd for $C_{20}H_{22}ClN_3O_2$: C, 64.60; H, 5.96; N, 11.30. Found: C, 64.52; H, 5.94; N, 11.26%; IR ν_{max}: 3295 (N-H), 1639 (C–O), 1632 (C═O), 1542 (N–H). ^{1}H-NMR ($CDCl_3$) δ: 2.67 (t, 2H, $J = 5.5$, $-CH_2-$CO–Pip.), 3.14–3.18 (m, 4H, (2 × $-CH_2$), Pip.), 3.60 (m, 2H, CONH–CH_2-), 3.75–3.80 (m, 4H, (2 × $-CH_2$), Pip.), 6.89–6.93 (m, 3H, C_6H_5), 7.25–7.31 (m, 3H, C_6H_5 and –CONH–), 7.37 (d, 2H, $J = 8.6$, *p*-Cl–C_6H_4-, 3-H and 5-H), 7.40 (d, 2H, $J = 8.6$, *p*-Cl–C_6H_4 –2-H and 6-H). ^{13}C-NMR δ: 32.7, 35.6, 41.6, 45.3, 49.4, 49.6, 116.8 (2C), 121.0, 128.5 (2C), 128.8 (2C), 129.3 (2C), 132.8, 137.6, 150.8, 166.2, 170.3.

4-Chloro-*N*-[3-*oxo*-3-(4-(4-nitrophenyl)-1-piperazinyl)-propyl]-benzamide (6). Compound (**6**) (318 mg, 96.2%) yellow powder (column chromatographed, AcOEt/CH_2Cl_2 = 1 : 1). was prepared from (**4**) (195 mg, 0.793 mmol) and 4-nitrophenyl piperazine (164 mg, 0.793 mmol); m.p. 165–166°C (ethanol/petroleum ether = 3 : 1). Anal. Calcd for $C_{20}H_{21}Cl\ N_4O_4$: C, 57.63; H, 5.08; N, 13.44. Found: C, 57.36; H, 5.00; N, 13.24%; IR ν_{max}: 3300 (N-H), 1642 (CONH), 1635 (COPip.). ^{1}H-NMR ($CDCl_3$) δ: 2.70 (t, 2H, $J = 5.5$, $-CH_2-$CO–Pip.), 3.41–3.50 (m, 4H, (2 × CH_2)-Pip.), 3.64–3.68 (m, 2H, *p*-CI–CONH–CH_2-), 3.75–3.83 (m,4H, (2 × CH_2)-Pip.), 6.82 (d, 2H, $J = 9.4$, *p*-NO_2–C_6H_4-2′-H and 6′-H), 7.21 (br t, 1H, ArCONH–), 7.39 (d, 2H, $J = 8.6$, *p*-Cl–C_6H_4–3-H and 5-H), 7.73 (d, 2H, $J = 8.6$, *p*-Cl-C_6H_4–, 2-H and 6-H), 8.13 (d, 2H, $J = 9.4$, *p*-NO_2–C_6H_4–, 3′-H and 5′-H). ^{13}C-NMR δ: 32.8, 35.5, 40.9, 44.5, 46.7, 46.8, 113.0 (2C), 126.0 (2C), 128.5 (2C), 128.8 (2C), 132.7, 137.8, 139.1, 154.3, 166.3, 170.5.

4-Chloro-*N*-[3-*oxo*-3-(4-(2-fluorophenyl)-1-piperazinyl)-propyl]-benzamide (7). Compound (**7**) (795.3 mg, 94.7%) white powder (column chromatographed, AcOEt/CH_2Cl_2 = 1 : 1). was prepared from (**4**) (530 mg, 2.15 mmol) and 2-fluorophenyl piperazine (388 mg, 2.15 mmol); m.p. 184–185°C (ethanol–petroleum ether 1 : 1). Anal. Calcd for $C_{20}H_{21}ClFN_3O_2$: C,

61.68; H, 5.44; N, 10.80. Found: C, 61.46; H, 5.43; N, 10.82%; IR ν_{max}: 3308 (N–H), 1639 (C═O), 1635 (C═O), 1547 (N–H). ^{1}H-NMR (DMSO-d_6) δ: 2.65 (t, 2H, $J = 7.1$, $-CH_2-$CO–Pip.), 2.91–3.02 (m, 4H, (2 × CH_2)–Pip.), 3.46–3.54 (m, 2H, CONH–CH_2–), 3.59–3.65 (m, 4H, (2 × CH_2)–Pip.), 6.93–7.15 (m, 4H, *o*-F–C_6H_4–), 7.53 (d, 2H, $J = 8.6$, *p*-Cl–C_6H_4-, 3-H and 5-H), 7.86 (d, 2H, $J = 8.6$, *p*-Cl–C_6H_4–, 2-H and 6-H), 8.61 (br t, 1H, ArCONH–). ^{13}C-NMR (DMSO-d_6) δ: 32.7, 36.5, 41.5, 45.5, 50.6, 50.9, 116.5 (d, $^{2'}J_{C\text{-}F} = 21$ Hz), 120 (d, $^4J_{C-F} = 2.7$ Hz), 123.3 (d, $^{3'}J_{C-F} = 7.9$ Hz), 125.3 (d, $^2J_{C-F} = 3.5$ Hz), 128.9 (2C), 129.5 (2C), 133.6, 136.5, 140.0 (d, $^3J_{C-F} = 8.3$ Hz), 155.5 (d, $^1J_{C-F} = 244$ Hz), 165.6, 169.6.

4-Chloro-*N*-[3-*oxo*-3-(4-(4-fluorophenyl)-1-piperazinyl)-propyl]-benzamide (8). Compound (**8**) (365 mg, 93.6%) white crystals was prepared from (**4**) (246 mg, 1.0 mmol) and 4-fluorophenyl piperazine (180 mg, 1.0 mmol); m.p. 148–149°C (ethanol/petroleum ether 2 : 1). Anal. Calcd for $C_{20}H_{21}ClFN_3O_2$: C, 61.68; H, 5.44; N, 10.80. Found: C, 61.67; H, 5.35; N, 10.81%; IR ν_{max}: 3292 (N–H), 1638 (C–O), 1632 (C═O), 1538 (N–H). ^{1}H-NMR ($CDCl_3$) δ: 2.67 (t, 2H, $J = 5.5$, $-CH_2-$CO–Pip.), 3.04–3.10 (m, 4H, (2 × CH_2)–Pip.), 3.57–3.61 (m, 2H, NH–CH_2–), 3.74–3.80 (m, 4H, (2 × CH_2)-Pip.), 6.84–7.01 (m, 4H *o*-F-C_6H_4–), 7.24 (br t, 1H, ArCONH–), 7.38 (d, 2H, $J = 8.5$, *p*-Cl–C_6H_4–, 3-H and 5-H), 7.72 (d, 2H, $J = 8.5$, *p*-Cl–C_6H_4–, 2-H and 6-H). ^{13}C-NMR ($CDCl_3$) δ: 32.7, 35.4, 41.5, 45.3, 50.4, 50.7, 115.8 (d, 2C, $^2J_{C-F} = 22$ Hz), 118.7 (d, 2C, $^3J_{C-F} = 7.8$ Hz), 128.5 (2C), 128.8 (2C), 132.7, 137.7, 147.5 (d, $^4J_{C-F} = 2.3$ Hz), 157.7 (d, $^1J_{C-F} = 240$ Hz), 166.2, 170.3.

4-Chloro-N-[3-*oxo*-3-(4-(2-methoxy phenyl)-1-piperazinyl)-propyl] benzamide (9). Compound (**9**) (526 mg, 98.3%) was prepared from (**4**) (328 mg, 1.33 mmol) and 2-methoxyphenyl piperazine (256 mg, 1.33 mmol); m.p. 109–110°C white crystals (column chromatographed, AcOEt/CH_2Cl_2 = 2 : 1). Anal. Calcd for $C_{21}H_{24}ClN_3O_3$: C, 62.82; H, 6.03; N, 10.47. Found: C, 62.46; H, 6.15; N, 10.33%; IR ν_{max}: 3308 (N-H), 1656 (C═O), 1621 (C═O), 1538 (N-H). ^{1}H-NMR ($CDCl_3$) δ: 2.68 (t, 2H, $J = 5.5$, $-CH_2-$CO–Pip.), 3.01–3.06 (m, 4H, (2 × CH_2)–Pip.), 3.60–3.63 (m, 2H, NH-CH_2—), 3.72–3.81 (m, 4H, (2 × CH_2)–Pip.), 3.87 (s, 3H, *o*-OCH_3-C_6H_4–), 6.83–7.06 (m, 4H *o*-OCH_3-C_6H_4–), 7.38 (d, 3H, $J = 8.5$, *p*-Cl-C_6H_4 3-H, 5-H and *p*-Cl–C_6H_4CO*NH*–), 7.74 (d, 2H, $J = 8.5$, *p*-Cl-C_6H_4, 2-H, 6-H). ^{13}C-NMR ($CDCl_3$) δ: 32.7, 35.7, 41.9, 45.6, 50.5, 50.8, 55.4, 111.3, 118.4, 121.0, 123.7, 128.5 (2C), 128.7 (2C), 132.8, 137.6, 140.5, 152.2, 166.2, 170.3.

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