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Synthesis, conformational analysis and antidepressant activity of moclobemide new analogues [1]

Alireza Ghanbarpour [a], Farzin Hadizadeh [a], Faride Piri [b], Parviz Rashidi-Ranjbar [b,*]

[a] *Department of Organic Chemistry, Faculty of Pharmacy, Medical Science, University of Tehran, Tehran, Iran*
[b] *Department of Chemistry, Faculty of Science, University of Tehran, Tehran, Iran*

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Abstract

Three new analogues of moclobemide are synthesized. Antidepressant activity of compounds assayed by the Porsolt method reveals that the morpholine ring in moclobemide is one of the key structural parts necessary for antidepressant activity. Superimposition of norepinephrine and gauche forms of serotonin and moclobemide suggest that the phenyl ring, electronegative group attached to the aromatic ring and the amine terminal group may serve as the recognition elements for binding to monoamine oxidase-A (MAO-A).

Keywords: Monoamine oxidase inhibitors; Moclobemide analogues; Antidepressant activity; Conformational analysis

1. Introduction

Moclobemide (4-chloro-N-[2-(4-morpholinyl)ethyl] benzamide is reported as a well tolerated and effective antidepressant with a rapid onset of action (Casacchia et al., 1984; Larsen et al., 1984; Postma and Vranesic, 1985). A large body of chemical evidence shows that the risks of hypertensive reactions and of interactions with other drugs are much less pronounced with moclobemide, a reversible type A, MAOIs (Da Prada et al., 1984a,b, 1989; Tiller et al., 1987; Korn et al., 1988a,b). Several biochemical aspects of the action of moclobemide are also reported (Da Prada et al., 1984a,b, 1989; Burkard et al., 1989; Kan et al., 1987). To address questions about the structure–activity relationship and the key structural component responsible for binding to MAO-A; the synthesis, conformational analysis and pharmacological activity of moclobemide and its three new analogues are investigated.

2. Experimental

2.1. Chemistry

Melting points were taken on a Kofler hot stage microscope and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 267 spectrophotometer. NMR spectra were run on a Varian 400 MHz Unity Plus or Bruker 80 MHz spectrometers. Tetra methyl silane was used as an internal standard. Mass spectra were recorded by a Varian TSQ-70 spectrometer.

2.1.1. N-(2-chloroethyl) benzamide (1)

To 4.176 g (36.0 mmol) of 2-chloroethylamine hydrochloride in 20 ml of dichloromethane, 30 ml of saturated solution of sodium carbonate in water was added and the mixture stirred for 30 min. A solution of 6.3 g (36.0 mmol) of 4-chlorobenzoyl chloride in 10 ml of dichloromethane was added to the mixture while kept in an ice bath, the mixture was stirred at room temperature overnight. Precipitated material was filtered off and washed with chloroform. The solution was extracted with chloroform and the combined organic layers evaporated. The residue was crys-

* Corresponding author.

[1] This paper is dedicated to Professor Alireza Ghanbarpour who died during the progress of this work.

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tallised in ethyl acetate to give 5.5 g of **1**, yield 65%, mp 105°C.

^{1}H-NMR: ppm ($CDCl_3$, 80 MHz) 3.72(4H, m), 6.78(1H, b), 7.42(2H, d), 7.71(2H, d).

^{13}C-NMR: ppm ($CDCl_3$, 400 MHz), 41.65, 43.71, 128.13, 132.24, 137.87, 166.65.

Mass: m/z 221($M^+ + 4$, 10.2), 219($M^+ + 2$, 16.4), 217(M^+, 26.4), 182(21.8), 151(10.9), 139(100), 111(11.8), 75(6.3).

2.1.2. 4-chloro-N-[2-(4-morpholinyl)ethyl] benzamide (2)

To 0.78 g (6 mmol) N-(2-aminoethyl) morpholine in 20 ml pyridine, 1 g (6 mmol) 5-chlorobenzoyl chloride was added dropwise at 0–5°C (Burkard and Wyss, 1987). The mixture was stirred overnight, the solvent was evaporated to dryness and made basic (10% ammonia solution). The aqueous solution was extracted by dichloromethane. The organic layer was dried (sodium sulfate) and the solvent was evaporated to dryness. The residue was crystallised in isopropanol. 1.41 g of **2**, yield 71%, mp 135–137°C was obtained.

^{1}H-NMR: ppm ($CDCl_3$, 400 MHz), 2.5(4H, m), 2.60(2H, t), 3.45(2H, d of d), 3.73(4H, t), 6.78(1H, b), 7.42(2H, d), 7.71(2H, d).

^{13}C-NMR: ppm ($CDCl_3$, 400 MHz), 35.95, 53.18, 56.65, 66.85, 128.22, 128.67, 132.79, 137.46, 166.17.

Mass: m/z 268(M^+, 4.1), 139(9.1), 113(12.7), 100(100), 70(3.6), 56(5.4).

2.1.3. 4-chloro-N-[2-(1-pyrrolidinyl)ethyl] benzamide (3)

To a solution of 1.75 g (10.0 mmol) of 4-chlorobenzoyl chloride in 20 ml dry THF, 1.14 g (100 mmol) of N-(2-aminoethyl) pyrrolidine was added dropwise over 10–12 min in an ice bath. The mixture was stirred at room temperature for another 24 h. The solvent was evaporated and to the residue, 20 ml of water was added. The solution was made basic by sodium bicarbonate, dichloromethane was added and the organic layer was separated, dried (sodium sulfate) and evaporated. The residue was crystallised in ethanol. 2.0 g of **3**, yield 80% was obtained, mp 115°C.

^{1}H-NMR: ppm ($CDCl_3$, 400 MHz) 1.79(4H, b), 2.55(4H, b), 2.69(2H, t), 3.53(2H, d of d), 6.85(1H, b), 7.41(2H, d), 7.73(2H, d).

^{13}C-NMR: ppm ($CDCl_3$, 400 MHz), 23.37, 38.47, 53.75, 54.31, 128.35, 128.53, 132.91, 137.28, 166.28.

Mass: m/z 252(M^+, 3.5), 182(3.0), 149(7.5), 139(15.5), 111(13.5), 84(100), 97(39), 55(9.5), 42(12.5).

2.1.4. 4-chloro-N-[2-(1-piperidinyl) ethyl] benzamide (4)

Piperidine in excess was added to 0.5 g (2.13 mmol) of N-(2-chloroethyl) benzamide. The mixture was stirred at 90°C for 24 h. After cooling, piperidine was removed by distillation in vacuum. The resultant salt was dissolved in water and neutralised with sodium bicarbonate. The water was removed by distillation in vacuum and the residue was crystallised in absolute ethanol. 0.2 g of **4**, yield 35% was obtained, mp 103–105°C.

^{1}H-NMR: ppm ($CDCl_3$, 400 MHz), 1.47(2H, m), 1.59(4H, m), 2.43(4H, b), 2.51(2H, t), 3.51(2H, d of d), 7.1(1H, b), 7.4(2H, d), 7.58(2H, d).

^{13}C-NMR: ppm ($CDCl_3$, 400 MHz), 24.11, 25.78, 36.27, 54.12, 57.00, 128.34, 132.83, 137.30, 166.16.

Mass: m/z 266(M^+, 11.5), 139(10.0), 111(10.5), 98(100), 70(3.0), 42(3.0).

2.1.5. 4-chloro-N-[2-(4-methyl-1-piperazinyl) ethyl] benzamide (5)

1-Methylpiperazine was added to 0.5 g (2.13 mmol) of N-(2-chloroethyl) benzamide as described for **3**, 0.18 g (0.64 mmol) of **5**, yield 30%, mp 120°C was obtained.

^{1}H-NMR: ppm ($CDCl_3$, 400 MHz), 1.814(4H, b), 2.30(3H, s), 2.46(2H, d), 2.54(2H, b), 2.6(2H, t), 3.53(2H, d of d), 6.85(1H, b), 7.4(2H, d), 7.7(2H, d).

^{13}C-NMR: ppm ($CDCl_3$, 400 MHz), 36.23, 45.81, 52.58, 54.85, 56.22, 128.30, 128.56, 132.74, 137.35, 166.21.

Mass: m/z 281(M^+, 4.8), 225(3.0), 182(5.2), 130(30.5), 113(100), 98(10.0), 70(69.5), 42(11.4).

2.2. Pharmacology

Test agents were dissolved in double distilled water, if not dissolved a few drops of acetic acid was added. The solutions were injected intraperitoneally with a constant volume of 10 ml/kg. Doses used are shown in Table 1. Control animals were given 0.9% NaCl solution of the same volume as the test agent. Six mice were used for each dose.

2.3. Calculation

Conformational analysis of serotonin, norepinephrine and moclobemide were preliminary performed by a MMX force field implemented in PC-MODEL software (PCMODEL). The conformers were optimized further by PM3 method using MOPAC 6.0 (QCPE). Moclobemide shows one global and three local forms. The difference between conformers due to morpholine orientation was not considered. Only the gauche forms of serotonin and moclobemide could be superimposed, which in gauche forms are superimposable on the extended form of norepinephrine.

3. Results and discussion

3.1. Chemistry

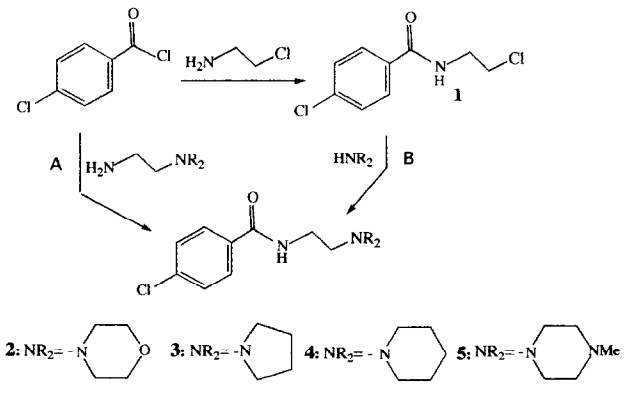
Moclobemide and analogues were synthesised according to general methods A and B as shown in Scheme 1 (Zagorezskii et al., 1989).

3.2. Pharmacology

The compounds were tested by the Porsolt swimming test method (Porsolt et al., 1978) in order to identify potential antidepressant activity. Imipramine was used as standard antidepressant. The results are shown in Table 1. Only moclobemide and imipramine had a significant effect on immobility time. It seems that the morpholine ring in moclobemide has an essential role in the antidepressant activity of this compound. Other compounds probably will not bind the MAO-A in vivo to show any antidepressant activity. Binding analysis of moclobemide new analogues to MAO-A in vitro is desirable, which is in progress.

3.3. Calculations

The pK_a of moclobemide has been reported to be 6.31; at plasma it may act as an unprotonated form and inhibit the MAO-A, (Zagorezskii et al., 1989) therefore conformational analysis was done on moclobemide as a free base. As the serotonin and norepinephrine are the selective MAO-A substrates and moclobemide is a competitive substrate of both, it is likely that the binding site for all should be similar. It is therefore desirable to find out the common structural elements, the so called 'pharmacophore'. The best superimposition between energy minima conformers of serotonin (gauche form, **I**) and norepinephrine (extended form, **II**) suggest that the phenyl ring, electronegative phenolic hydroxy group and the amino nitrogen could be considered as common structural elements (Fig. 1). The



Scheme 1.

Table 1
The effect of moclobemide, its three new analogues and imipramine on immobilization time in the Porsolt forced swimming test. Each dose is injected into six mice

Compound No.	Dose i.p. (mg/kg)	Immobilization time mean ± SEM (s)	% control
2	1.0	171.8 ± 19.2	70.0
	5.0	122.7 ± 35.0	50.0
	10.0	74.1 ± 32.6	30.2
3	5.0	230.6 ± 22.7	94.1
	10.0	282.2 ± 21.1	115.0
	30.0	257.8 ± 16.4	105.0
4	5.0	287.1 ± 12.5	116.9
	10.0	223.3 ± 19.4	91.0
	30.0	262.3 ± 24.7	106.8
5	5.0	227.6 ± 17.1	92.7
	10.0	213.5 ± 25.6	87.0
	30.0	255.2 ± 11.2	103.9
Imipramine	7.5	232.4 ± 20.3	94.7
	15.0	127.6 ± 28.9	52.0
	30.0	66.3 ± 12.3	27.0

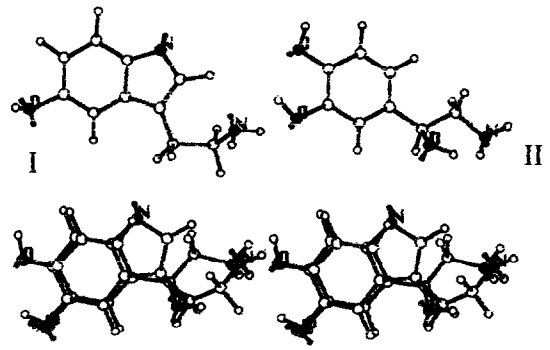


Fig. 1. Stereoview of the superimposition of the gauche form of serotonin (**I**) and the extended form of norepinephrine (**II**).

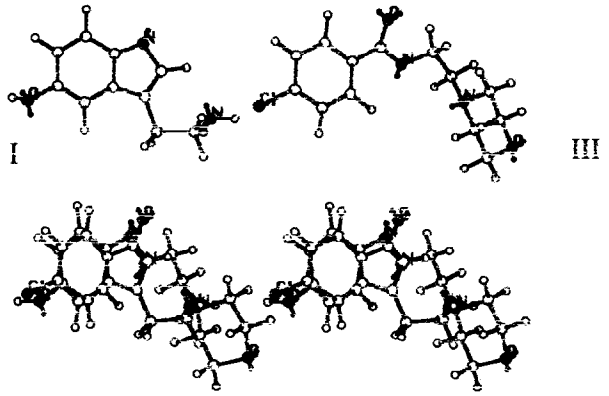


Fig. 2. Stereoview of the superimposition of two gauche forms of serotonin (**I**) and moclobemide (**III**).

gauche form of serotonin is also superimposable on one of the moclobemide gauche conformers (**III**), in this case chlorine is considered as the electronegative group (Fig. 2).

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