Synthesis and Antidepressant Activity of N-Substituted Imidazole-5-Carboxamides in Forced Swimming Test Model

Farzin Hadizadeh, Hossein Hosseinzadeh, Vahideh-Sadat Motamed-Shariaty, Mahmood Seifi and Shahab Kazemi

Abstract

Moclobemide is a selective and reversible monoamine oxidase-A inhibitor, which is used as an antidepressant. Three moclobemide analogues were synthesized by replacing moclobemide phenyl ring with substituted imidazoles. So, N-[4-(4-morpholinyl) ethyl]-1-benzyl-2-(alkylthio)-1H-imidazole-5-carboxamides (7a-c) were synthesized and studied for the antidepressant activity using forced swimming test in mice. Analogues 7a-c were found to be more potent than moclobemide. Minimum effective doses for moclobemide and analogues 7a-c were found to be 20, 2.5, 1.25 and 2.5 mg/kg i.p. respectively.

Keywords: Imidazolecarboxamides; MAOIs; Antidepressant; Forced swimming model.

Introduction

Depression is a potentially life-threatening disorder that affects should be typed connected of people all over the world. It can occur at any age from childhood to late life and is a tremendous cost to society as it causes severe distress and disruption of life and, if left untreated, it can be fatal (1).

The pharmacotherapy of depression started in the 1950s, with prominent publications and discoveries that still govern the manner in which we treat depression. There are currently 10 to 20 different drugs marketed as antidepressants, depending on the country. Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) were called first generation antidepressants, and selective serotonin reuptake inhibitors (SSRI) and reversible and selective inhibitors of monoamine oxidase A (RIMA) were called second generation antidepressants. Third-generation antidepressants include more recent drugs, such as mirtazapine, nefazodone, milnacipran, and reboxetine.

In the field of the antidepressant drugs, today efforts are focused towards the development of selective and reversible MAO-A inhibitors. The MAO-A inhibitors such as moclobemide are effective in the treatment of depression.

A few structure activity relationship studies have been previously reported regarding moclobemide (2, 3). In our previous work, we studied the effect of replacing morpholine ring with other heterocyclic rings (4). Recently, synthesis of the 4-arylpiperazine derivatives of moclobemide has also been reported (5). In another work, the pyrrole-2-carboxamides including moclobemide analogue, N-[2-(4-morpholinyl)ethyl] pyrrole-2-carboxamide, has been reported as as
monoamine oxidase inhibitor (6).

Our interest in the chemistry of nitrogen containing rings and specially imidazole, which provides more sites for binding to amino acids within the proteins and enzymes, motivated us to design similar structures to moclobemide by replacing moclobemide phenyl ring with substituted imidazoles. So, \(N\)-[2-(4-morpholinyl)ethyl]-1-benzyl-2-(alkylthio)-1H-imidazole-5-carboxamides (7a-c) were synthesized and tested as antidepressant by forced swimming test model in mice.

**Experimental**

**Chemistry**

Melting points were determined by using Capillary Electrothermal apparatus and were uncorrected. The IR spectra were obtained using a Unicam SP-1100 spectrophotometer, using samples prepared as KBr disks. \(^1\)H-NMR spectra were obtained using a Bruker Ac-80 spectrophotometer and chemical shifts (d) were reported as ppm relative to internal tetramethylsilane. Elemental microanalyses were carried out with a Perkin-Elmer instrument a temperature of 240 °C, and were within±0.4% of the theoretical values for C, H, and N. All solvents and reagents were purchased from the Fluka, Aldrich or Merck Chemical Company. Compounds 1-6 were synthesized as reported previously.

\(N\)-[2-(4-morpholinyl)ethyl]-1-benzyl-2-(methylthio)-1H-imidazole-5-carboxamide (7a)

To a stirred solution of 4-(2-aminoethyl)morpholine (260 mg, 2 mmol), in 25 ml of dry THF (tetrahydrofuran) at 0 °C, 2-methylthio-1-benzylimidazole-5-carbonyl chloride 6a (800 mg, 2 mmol) was successively added under nitrogen atmosphere. The system was then stirred for 24 h, after which the precipitate was filtered. The filtrate was dried and the crude material was purified by silica gel thin layer chromatography (CHCl\(_3\)/EtOH = 70:30) to obtain (7a) (420 mg, 55%) with melting point of 194-197°C. Calculated analyses for C\(_{18}\)H\(_{24}\)N\(_4\)O\(_2\)S were as follows: C, 59.97; H, 6.71; N, 15.54. and the found results were: C, 56.73; H, 6.55; N, 15.37%; IR \(\nu_{\text{max}}\): 3432 (N-H), 1648 (CONH).

\(^1\)H-NMR (CDCl\(_3\)) δ: 8.2 (s, 1H, H-C\(_4\)imidazole), 7.5-7.2 (m, 5H, arom), 7.0 (br, 1H, CONH), 5.7 (s, 2H, CH\(_2\)N), 5.5-5.0 (m, 6H, CH\(_2\)), 4.7-4.2 (m, 6H, CH\(_2\)), 2.8 (s, 3H, CH\(_3\)).

\(N\)-[2-(4-morpholinyl)ethyl]-1-benzyl-2-(ethylthio)-1H-imidazole-5-carboxamide (7b)

It was prepared from 6b, similar to 7a with a 60% yield and m.p of 177-179 °C; Calculated analyses for C\(_{19}\)H\(_{26}\)N\(_4\)O\(_2\)S were as follows: C, 50.10, H, 6.10, N, 15.00, S, 9.10.

\(N\)-[2-(4-morpholinyl)ethyl]-1-benzyl-2-(ethylthio)-1H-imidazole-5-carboxamide (7b)

It was prepared from 6b, similar to 7a with a 60% yield and m.p of 177-179 °C; Calculated analyses for C\(_{19}\)H\(_{26}\)N\(_4\)O\(_2\)S were as follows: C, 50.10, H, 6.10, N, 15.00, S, 9.10.
Synthesis and Antidepressant Activity of N-Substituted Imidazole-5-Carboxamides in

The forced swimming test (FST) was

Chemistry

Compounds 2-6 were synthesized as previously reported (7). Benzylamine hydrochloride (1) was stirred with 1, 3-dihydroxyacetone dimmer and potassium thiocyanate to give 5-hydroxymethyl-2-mercapto-1-benzylimidazole (2). Subsequent alkylation of compound 2 with alkyl halides resulted in 2-alkythio-1-benzyl-5-hydroxymethylimidazole (3). Oxidation of 3 with manganese dioxide gave 4, which was further oxidized by being boiled in alkaline solution of silver nitrate to give 2-alkythio-1-benzylimidazole-5-carboxylic acid (5). Compound 5 was converted to its acid halide (6). 2-Morpholinoethyamine was added dropwise to a solution of 6 in dry THF (tetrahydrofuran) to give N-[2-(4-morpholinyl)ethyl]-1-benzyl-2-(alkythio)-1H-imidazole-5-carboxamide (7a-c) (scheme 1).
developed by Porsolt and colleagues (8) in the rat and, subsequently, in the mouse. This test is the most widely used tool for assessing antidepressant activity preclinically (9).

The compounds were tested by the porsolt forced swimming test in order to identify potential antidepressant activity. Moclobemide was used as a standard antidepressant. The results are shown in Figure 1. Moclobemide reduced the duration of immobility at 20 mg/kg i.p., and was inactive at lower doses of 10 and 15 mg/kg i.p. According to previous reports moclobemide is inactive in this test at doses of lower than 30 mg/kg i.p. and is active at higher doses(10).

Analogue 7a was effective at doses of 2.5, 5, 10 and 15 mg/kg i.p. and had no significant effect at 20 mg/kg i.p. Analogue 7b reduced immobility at 1.25, 2.5 and 20 mg/kg i.p. and was ineffective at 5 mg/kg i.p. Analogue 7c was found to be effective at all doses, i.e. 2.5, 15 and 20 mg/kg i.p.

The present investigation demonstrated that analogues 7a-c were more potent than moclobemide in forced swimming test model.

**Acute toxicity**

LD$_{50}$ values of moclobemide and analogues 7a,b were 522.6 mg/kg, i.p. (447.1-610.7), 149.1 mg/kg, i.p. (134.5-165.3), and 196.0 mg/kg, i.p. (180.7-212.6), respectively. LD$_{50}$ for 7c was not determined. According to previous reports LD$_{50}$ of moclobemide is 730 mg/kg in mice. So, with respect to LD$_{50}$ values, analogues 7a, b were more toxic than moclobemide.

In conclusion, replacement of electron deficient 4-chlorophenyl in moclobemide with substituted electron-deficient ring imidazole in analogues 7a-c increased antidepressant potency and also toxicity.

**Acknowledgement**

This work was supported by a grant from Research Council of Mashhad University of Medical Sciences.

**References**


This article is available online at http://www.ijpr-online.com