ANTIDEPRESSANT AND ANTIOXIDANT ACTIVITIES OF SOME 2-BENZOXAZOLINONE DERIVATIVES AS BUPROPION ANALOGUES

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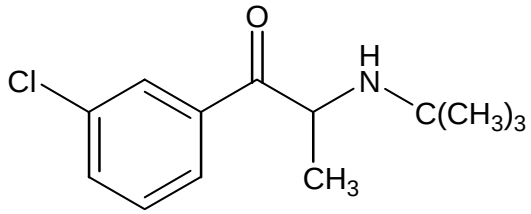
Summary

Recently we described the design and synthesis of four bupropion analogues, 3-Methyl-6-(substitutedamino) propionyl]-2-benzoxazolinone as antidepressant. Bupropion is a norepinephrine and dopamine reuptake inhibitor which is used as antidepressant. These compounds were studied for the antidepressant activity using forced swimming test in mice. All analogues were found to be effective in comparison to control at the doses 2.5-20 mg/kg. The activity of analogues was comparable to that of bupropion at the some doses. In addition, antioxidant activity of these derivatives was investigated, employing DPPH radical scavenging activity. IC_{50} was in the order: piperidino (107.6 ± 0.53) > diethylamino (142.1 ± 1.27) > tert-butylamino (370.8 ± 1.23) > morpholino (535.6 ± 3.04) mg ml^{-1}, respectively.

Key words: Antidepressant activity, Antioxidant activity, Benzoxazolinone, Bupropion, Forced swimming test.

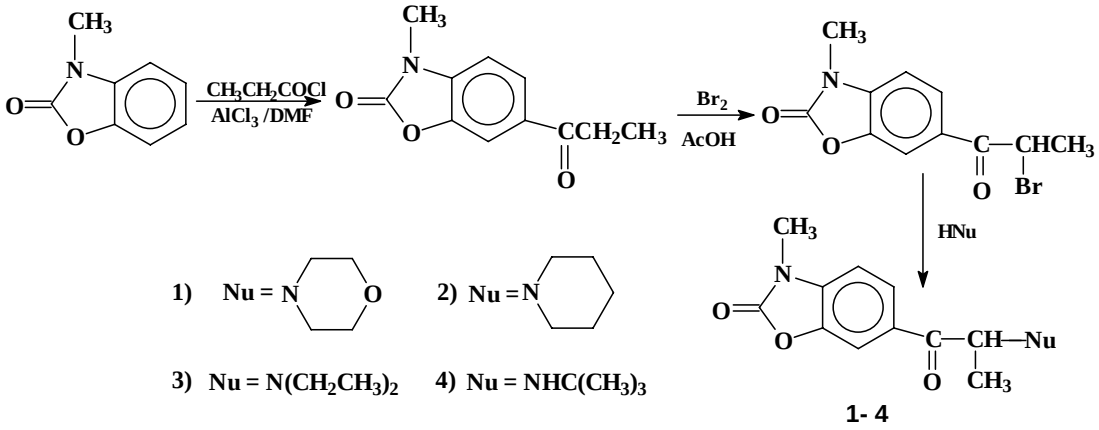
Introduction

Depression is a common, chronic and potentially debilitating illness that has tempered the human condition since the beginning of recorded history (1). It is a potentially life-threatening disorder that affects hundreds of millions 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 this disorder causes severe distress and disruption of life and, if left untreated, can be fatal (2). The area of pharmacotherapy of depression started in the 1950s, with landmark publications and discoveries that still govern the manner in which we treat depression. There are currently 22 medications have received FDA approval in USA for the treatment of antidepressants (1). They can be grouped into four categories: Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and miscellaneous. Bupropion is an antidepressant with a unique mechanism of action essentially lacking cardiovascular, anticholinergic and sexual dysfunction effects but incidence of seizures limited the use of bupropion as a first line agent (3). Bupropion is a trimethylated monocyclic phenylaminoketone that is an effective antidepressant in humans (4).



Bupropion

Its mechanism of action may be related to inhibition of norepinephrine and dopamine reuptake. Its usual dosage is 100 mg three times daily (1). Clinical trials comparing bupropion 300-750 mg/d with placebo show it to be superior to placebo in efficacy and as well tolerated. Bupropion, in controlled clinical trials, is as effective as amitriptyline or imipramine, with fewer side effects. Bupropion appears to be safe and effective in both adult and geriatric depressed patients. Although it appears to be safer and equally efficacious when compared with currently used antidepressants, it has not been tested by routine clinical use (5). In a our previous work we synthesized 2-Benzoxazolinone analogues 1-4 of bupropion (6,7) (scheme 1) and in this paper we report antidepressant and antioxidant effects of these analogues. 2-Benzoxazolinone could be prepared from 2-aminophenol and urea in fusion condition. Reaction with dimethyl sulfate in NaOH solution afforded our starting methylated materials. 3-methyl-6-propionyl-2-benzoxazolinone could be prepared either by reaction of propionic acid in PPA (in higher yield) or by Friedel Crafts reaction of propionyl chloride in DMF/$AlCl_3$ (in lower one). Bromination of this compound in glacial acetic acid afforded 2-bromopropionyl analog in good yield. Reaction of appropriate amine with the latter gave desired compounds 1-4 (6,7).



Scheme 1. Syntheses of 2-Benzoxazolinone derivative

Materials and methods

Animals: Male BALB/c mice, weighing 22-25 g, were kept in the animal house of Mashhad University of Medical Sciences, in colony rooms with 12/12 h light/dark cycle at 21±2° C. The animals had free access to food and water.

Preparation of samples: Test agents were dissolved in DMSO. The solution was injected intraperitoneally with a constant volume of 10 ml/kg. Doses used are shown in figure 1. Control animals were given DMSO of the same volume as the test agent. Six mice were used for each dose.

Forced Swimming Test: This test was performed essentially as previously described 26 groups of mice (n = 6/dose) were individually introduced into a cylinder (13 cm in diameter) containing water (13 cm deep, 25°C) and left there for 15 min (habituation). Mice were then dried and returned to their home cage. Twenty four hours later, mice were replaced in the cylinder containing water (17 cm deep, 25°C) and left there for 6 min; the total duration of immobility in each mouse was measured during the last 4 min (test). Mice were judged to be immobile when they ceased struggling and remained floating motionless in the water, making only those movements necessary to keep their heads above water. Test compounds were administered i.p. 23.5, 5 and 1 h before the test session. The effect of drug was expressed as the doses that produced a statistically significant reduction in the duration of immobility as compared with control (8).

DPPH radical-scavenging activity: The stable 1,1-diphenyl-2-picryl hydrazyl radical (DPPH) was used for determination of free radical-scavenging activity of compounds (9-13). Different concentrations of each compound were added, at an equal volume, to methanolic solution of DPPH (100 μM). After 15 min at room temperature, the absorbance was recorded at 517 nm. The experiment was repeated for three times. Vitamin C, BHA and quercetin were used as standard controls. IC_{50} values denote the concentration of sample, which is required to scavenge 50% of DPPH free radicals.

Statistical Analysis: The data were expressed as mean ± SEM and tested with analysis of variance followed by the multiple comparison test of Tukey-Kramer.

Results

DPPH radical-scavenging activity: It was found that the radical- scavenging activities of all the compounds increased with increasing concentration. IC_{50} for DPPH radical-scavenging activity was in the order: piperidino (107.6 ± 0.53) > diethylamino (142.1 ± 1.27) > tert-butylamino (370.8 ± 1.23) > morpholino (535.6 ± 3.04) mg ml^{-1}, respectively. The IC_{50} values for ascorbic acid, quercetin and BHA were 5.05 ± 0.12, 5.28 ± 0.43 and 53.96 ± 2.13 μg ml^{-1}, respectively.

Forced Swimming Test: The results are shown in figure 1. Bupropion was used as a standard antidepressant. Bupropion reduced the duration of immobility at 2.5, 5, 15 and 20 mg/kg i.p., and was inactive at dose 10 mg/kg i.p. According to previous reports bupropion in dose 30 mg/kg ip reduced immobility time in the FST (8). Analogue **1** was effective at doses 5, 10 mg/kg i.p. and had no significant effect at 2.5, 15 and 20 mg/kg i.p. Analogue **2** reduced immobility at 5, 10 and 15 mg/kg i.p. and was ineffective at 2.5 and 20 mg/kg i.p. Analogue 3 and 4 was found to be effective at all doses 2.5, 5, 10, 15 and 20 mg/kg i.p.

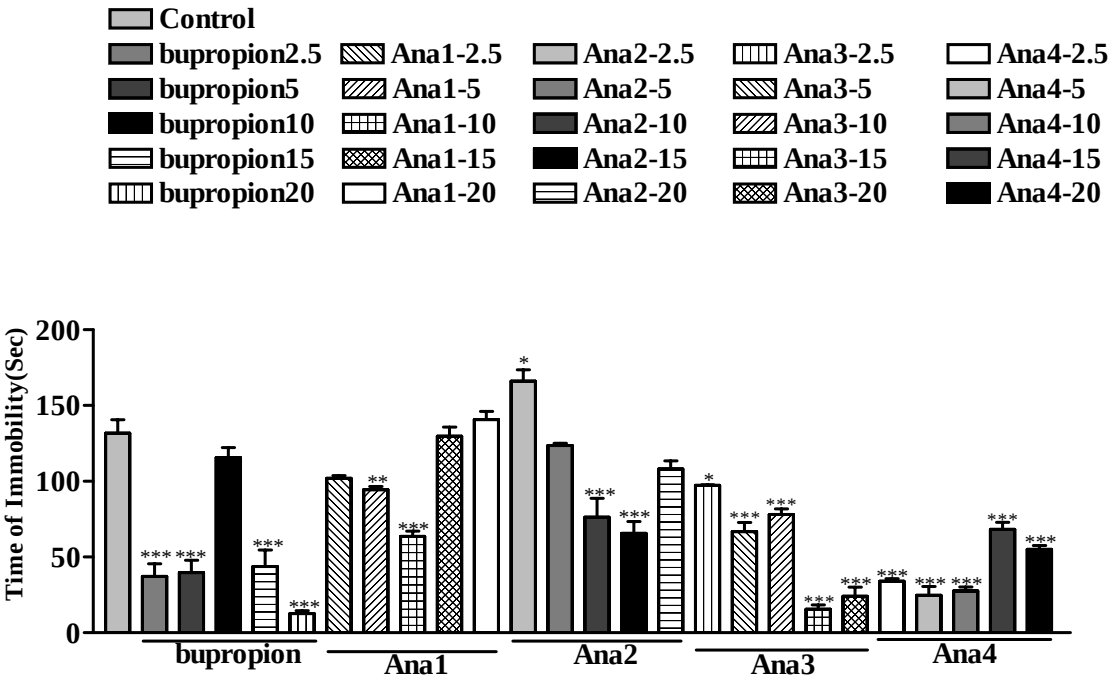


Figure 1: The effect of bupropion and its analogues (**1-4**) on immobility time in the forced swimming test. Agents were administered to mice intraperitoneally 23.5, 5 and 1h prior to test. Values are the mean ± S.E.M. for 6 mice, *P<0.05, **P< 0.01 and ***P<0.001, as compared to control, Tukey-Kramer.

Discussion

DPPH radical-scavenging activity: The model of scavenging the stable DPPH radical is a widely used method to evaluate the free radical scavenging ability of various samples (14). DPPH is a stable nitrogen-centered free radical the color of which changes from violet to yellow upon reduction by either the process of hydrogen- or electron- donation. Substances which are able to perform this reaction can be considered as antioxidants and therefore radical scavengers (15). It was found that the radical- scavenging activities of all the compounds increased with increasing concentration. All of them show weak antioxidant activity. Based on the IC_{50} results, it was also shown that piperidino 2 and its open ring analogue, diethylamino 3 had the higher DPPH-scavenging activity than others.

Pharmacology: The forced swim test (FST) was developed by Porsolt and colleagues (16) in the rat and subsequently, in the mouse. This test is the most widely used tool for assessing antidepressant activity preclinically (17). The compounds were tested by the porsolt swimming test method in order to identify potential antidepressant activity. Bupropion was used as a standard antidepressant. Analogue 3 and 4 was found to be effective at all doses 2.5, 5, 10, 15 and 20 mg/kg i.p. The present investigation demonstrated that some analogues were more potent than bupropion in forced swimming test model.

Acknowledgements

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

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