Structure Activity Relationship of Organic Alcohol and Esters for Antidepressant-Like Activity

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Abstract: The synthesized compounds **1-7** were evaluated for their antidepressant activity, among which 2-phenylethyl alcohol **1** and isoamyl phenylacetate **3** showed 43 % and 37 % reduction in immobility time in mice using forced swim test, thereby, displaying antidepressant-like activity. Compound **1** and **3** were equipotent and both these compounds were 2x effective than the standard drug phenelzine. Considering other esters it appears that a decrease in alkyl chain length or addition of either NO_2 or OH groups to the phenyl ring caused a marked decline in the antidepressant-like activity.

Keywords: Alcohol, Esters, Antidepressant, Forced Swim Test.

1. INTRODUCTION

Antidepressants are commonly prescribed by psychiatrists and general practitioners to alleviate clinical depression or dysthymia (mild depression). It includes several groups of drugs such as monoamine oxidase inhibitors (MAOIs), dibenzocycloheptenes, tri- and tetracyclics [1-8]. In 2005, the most commonly prescribed antidepressants in the US were escitalopram, fluoxetine, sertraline and venlafaxine. Sertraline and escitalopram are found best of 12 in new generation antidepressants [9]. These SSRIs (Selective Serotonin Reuptake Inhibitors) antidepressants though popular, caused serotonin syndrome resulting from the over-stimulation of serotonin receptors and also induced suicidal tendencies in the adolescents [10]. Furthermore, somatic and psychological withdrawal symptoms were evident upon sudden discontinuation of the medication [11]. Antidepressants are often used in the treatment of other conditions including anxiety [12], bipolar [13] and eating disorders [14] as well as chronic pain [12].

Since esters have a characteristic pleasant, fruity odor, they are extensively used in the fragrance and flavor industry. The important ingredient of perfume industry, 2-phenylethyl alcohol **1**, is a colorless volatile constituent of roses, which contributes to its aroma and of many other flowers [15, 16]. It has also been reported to possess local anesthetic property [17]. In aromatherapy lavender and rosemary have been reported to lower the levels of stress hormone cortisol in the human saliva [18], supporting the importance of aromatherapy in the depressed state.

Esters are commonly prepared by Fischer esterification in the presence of an acid catalyst, sulfuric or Lewis acids with scandium (III) triflate [19, 20]. Alternative methods are Steglich esterification [21-27], reaction of acid chlorides or anhydrides with alcohols. It can also be prepared by oxidation, reduction and oxidative esterification.

Considering the harmful side effects of the available antidepressants and an association between aromatic compounds and their anti-stress potential prompted to prepare a series of aromatic esters and to evaluate them for anti-depressant activity in the animals.

2. RESULTS AND DISCUSSIONS

Chemistry and Biology

Phenethyl alcohol **1** [28] and series of esters **2-7** of different organic acids were synthesized as described below. All these compounds were evaluated for antidepressant activity in mice using forced swim test by monitoring their immobility time. The results indicate that compound **1** and isoamyl phenylacetate **3**, an ester, elicited 43 % and 37 % inhibition of immobility time in the mice which was significantly different from the control animals, better than all the other compounds tested and about 2x better than the standard antidepressant phenelzine (Table **1**). These results indicate that the aromatic alcohol **1** and ester **3** with **5** carbon branched alkyl group are behaving in similar manner. The other esters having short chain alkyl group that is ethyl phenylacetate **2** [29] and *n*-butyl phenylacetate **4** displayed 10 % and 17 % reduction in immobility time, but this decline is non-significantly different from the control (Table **1**). This further strengthens that the presence of long chain alkyl group in an ester is responsible for an enhancement in the antidepressant-like activity. Moreover, introduction of nitro group (one or two) to the phenyl ring though caused a decline in the antidepressant-like activity as reflected by ethyl-3, 5-dinitro benzoate **5** and ethyl-4-nitro benzoate **6**, which was non-significantly different from the control, indicate that the nitro group is causing a loss in the antidepressant-like activity in these esters. The addition of OH group at *ortho* position failed to elicit the reduction in the immobility time; on the contrary, the immobility was enhanced by 7 % thus inducing depression in the mice.

3. GENERAL EXPERIMENT

Ethanol, *n*-butanol and isoamyl alcohol, were dried by using standard methods. Phenylacetic, 3,5-dinitrobenzoic, 4-nitrobenzoic acid and salicylic acid, were of reagent grade and used directly without purification. ^{1}H-NMR spectroscopy was performed on a Bruker AC 400 (400 MHz) Spectrophotometer and the values are reported in δ (ppm). TMS was taken as internal standard. EIMS spectrometry was conducted on a Finnigan-MAT-311-A apparatus and the values are reported in *m/z.*

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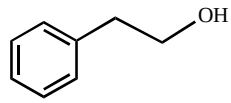
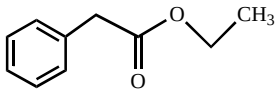
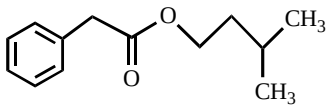
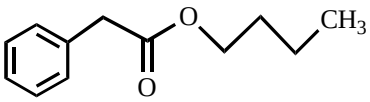
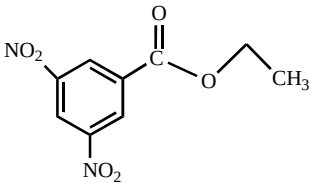
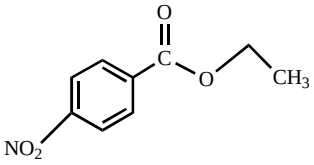
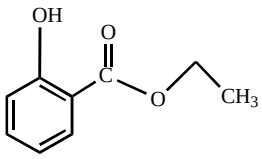
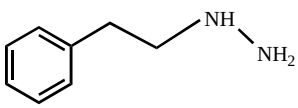
Table-1. Antidepressant-Like Activity of 2-phenylethyl Alcohol and Esters

Sr. No.	Name	Structure	% Change Immobility Time
1.	2-Phenylethyl alcohol		43 %↓*
2.	Ethyl phenylacetate		10 %↓
3.	Isoamyl phenylacetate		37 %↓*
4.	*n*-Butyl phenylacetate		17 %↓
5.	Ethyl-3,5-dinitrobenzoate		7.3 %↓
6.	Ethyl-4-nitrobenzoate		0.2 %↓
7.	Ethyl salicylate		7.04 %↑
Phenelzine (Standard)			21 %↓*

*p<0.05 as compared to control, ↓ = % Decrease in immobility time and ↑ = % Increase in immobility time of mice. Control: Immobility time = 98. 25 ± 7.06 s during 5 mins. session.

3.1. Animals

Male NMRI mice from Animal house International Center for Chemical and Biological Sciences, University of Karachi, Karachi, weighing 23-27 g were used in this study. Animals were housed in the plastic cages and maintained under standard conditions with a 12 hrs light/dark cycle under regulated temperature condition (25 ± 2°C). Food and water were available *ad libitum*. Experiments were carried out between 10:00 a.m. to 1:00 p.m. All the experiments in this study were performed in accordance with the guidelines of the Ethics Committee of the Institute for animal handling.

3.2. Drugs and Treatment

Phenelzine (standard antidepressant agent, Sigma Chemical Co., USA) and compounds at 10 mg/kg were dissolved in DMSO

(10 %) and administered intraperitoneally (*i.p.*, 10ml/kg). Control animals received appropriate vehicle.

3.3. Antidepressant Test in Mice (Forced Swim Test)

FST was performed as described by Porsolt *et al.*, 1978 [30] and Dar *et al.* 1997 [31]. The pre-test session was performed by placing them in FST tank (glass tank; height = 25cm, diameter = 15cm filled with 10cm water at 25^0C) for 15min. Movement of animals were noted carefully. Injured or ill animals e.g., those showing symptoms of nose bleeding were discarded. After 24hrs, mice received respective treatment and after 1 hr the animals were placed in FST tank and immobility time was recorded in seconds for 5 minutes. Mouse was considered immobile if it remained floating with all four limbs motionless keeping its nose above the water. Percent reduction in immobility time of the treated animals was calculated as follows:

Percent reduction in immobility time = (Mean Immobility time of test mice / Mean Immobility time of control x 100) – 100.

3.4. Preparation of esters 2-4

0.09 mole (12.24 g) of phenylacetic acid in different alcohols (ethanol, isoamyl alcohol and *n*-butanol) containing sulfuric acid (1ml) with activated Linde 4A molecular sieves (9.79 g). The reaction was refluxed for 24 hrs and monitored by TLC. After completion of reaction, the reaction mixture was cooled and dried by the addition of anhydrous sodium sulfate to absorb excess of sulfuric acid and water that was formed during the reaction. The excess of alcohol was removed by evaporation under reduced pressure and affording esters of phenylacetic acid.

3.4.1. Preparation of ethyl-3, 5-dinitrobenzoate (5), ethyl-4-nitrobenzoate (6) and ethyl salicylate (7)

Ethyl-3,5-dinitrobenzoate, ethyl-4-nitrobenzoate and ethyl salicylate were prepared using 3, 5-dinitrobenzoic, 4-nitrobenzoic and salicylic acid respectively by the method mentioned above.

3.4.2. Preparation of 2-Phenylethyl Alcohol (1)

Ethyl phenylacetate **2** (13.28 g) was dissolved in ethanol. Sodium metal (0.021 g) was added by continuous stirring. After one hr the reaction was completed (TLC analysis). Excess of ethanol was removed under reduced pressure and then by vacuum distillation. Yield 8.83 g (90 %); R_f = 0.70 (chloroform/methanol, 9:1); ^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.10 (m, 5H), 3.52 (2H, t, *J* = 6.3 Hz, CH_2), 2.61 (2H, t, *J* = 6.3 Hz, CH_2); HREIMS, *m/z*: 122.1640 [M^+, $C_8H_{10}O$ requires 122.1664].

3.4.3. Ethyl Phenylacetate (2)

Yield 13.28 g (90 %); R_f = 0.75 (chloroform/methanol, 9:1); ^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.05 (m, 5H), 4.08 (2H, q, *J* = 6.9 Hz, CH_2), 3.31 (2H, br s, CH_2), 1.24 (3H, t, *J* = 6.9 Hz, CH_3); HREIMS, *m/z*: 164.1256 [M^+, $C_{10}H_{12}O_2$ requires 164.1043].

3.4.4. Isoamyl Phenylacetate (3)

Yield 16.1 g (87 %); ^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.09-7.28 (m, 5H), 3.25 (2H, br s, CH_2), 4.06 (2H, t, *J* = 6.1 Hz, CH_2), 1.54 (2H, m, CH_2), 1.88 (1H, m, CH), 0.89 (6H, d, *J* = 6.6 Hz, $2CH_3$); HREIMS, *m/z*: 206.4167 [M^+, $C_{13}H_{18}O_2$ requires 206.2839].

3.4.5. n-Butyl Phenylacetate (4)

Yield 1.8 g (94 %); R_f = 0.7 (chloroform/methanol, 9:1); ^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.08–7.30 (m, 5H), 4.12 (2H, t, *J* = 6.3 Hz, CH_2), 3.23 (2H, s, CH_2), 1.31-1.52 (4H, m, $2CH_2$), 0.90 (3H, t, *J* = 6.4 Hz, CH_3); HREIMS, *m/z*: 192.2681 [M^+, $C_{12}H_{16}O_2$ requires 192.2570].

3.4.6. Ethyl-3, 5-dinitrobenzoate (5)

Yield 1.6 g (94 %); R_f = 0.6 (hexane/chloroform, 6:4); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.21 (1H, d, *J* = 2.1 Hz, H-4), 8.02 (2H, d, *J* = 2.1 Hz, H-2, 6), 4.32 (2H, q, *J* = 6.9 Hz, CH_2), 1.35 (3H, t, *J* = 6.9 Hz, CH_3); HREIMS, *m/z*: 240.0911 [M^+, $C_9H_8O_6N_2$ requires 240.1705].

3.4.7. Ethyl-4-nitrobenzoate (6)

Yield 1.82 g (93 %); R_f = 0.62 (hexane/chloroform, 4:6); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.27 (2H, d, *J* = 7.5 Hz, H-3, 5), 7.25 (2H, d, *J* = 7.5 Hz, H-2, 6), 4.05 (2H, q, *J* = 6.8 Hz, CH_2), 1.23 (3H, t, *J* = 6.8 Hz, CH_3); HREIMS, *m/z*: 195.1502 [M^+, $C_9H_9O_4N$ requires 195.1735].

3.4.8. Ethyl Salicylate (7)

Yield 12.5 g (84 %); ^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.77 (1H, dd, *J* = 8.1, 1.8 Hz, CH), 7.69 (1H, d, *J* = 8.0 Hz, CH), 7.46 (1H, dd, *J* = 8.0, 7.8 Hz, CH), 6.89 (1H, dd, *J* = 8.1, 7.8 Hz, CH), 4.36 (2H, q, *J* = 6.9 Hz, CH_2), 1.37 (3H, t, *J* = 6.9 Hz, CH_3); HREIMS, *m/z*: 166.1208 [M^+, $C_9H_{10}O_3$ requires 166.1754].

4. CONCLUSION

The result indicates that alcohol **1** and ester **3** having five carbon side chains demonstrate maximum antidepressant-like activity whereas, esters with short alkyl side chain **2** and **4** causes a dramatic decline in it. Similarly, addition of nitro group (electron withdrawing group) to the phenyl ring also has adverse effect on the antidepressant-like activity. Addition of hydroxyl group at *ortho* position of phenyl **7** elicit a complete loss of activity but displayed depressant activity that may be related to its electron donating nature which possibly activates the ring at 1, 4 and 6 positions.

Thus research towards ester with long chain alkyl group appears important and may lead to the new antidepressants.

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