Full Paper

Synthesis and Antidepressant-Like Profile of Novel 1-Aryl-3-[(4-benzyl)piperidine-1-yl]propane Derivatives

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This study describes the chemical synthesis and pharmacological evaluation of some new 1-aryl-3-[(4-benzyl)piperidine-1-yl]propane derivatives as antidepressants. The structures attributed to the compounds were elucidated using IR and ^{1}H-NMR spectroscopic techniques besides elemental analysis. The antidepressant-like effect of these compounds was assessed by using the forced swimming test (FST), a validated experimental model of depression in mice. A clear antidepressant-like effect was shown for compounds **1, 2** and **4** by a significant decrease in immobility behaviour.

Keywords: Antidepressant-like effect / Aryl propane derivatives / Forced swimming test / SSRI (selective serotonine reuptake inhibitors) / Substituted piperidine

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Introduction

Depression is one of the most common psychological problems, affecting people independent of gender, age and background. In the early 1970s, evidence of the role of serotonin (5-hydroxytryptamine; 5-HT) in depression began to emerge and the hypothesis that enhancing 5-HT neurotransmission would be an available mechanism for antidepressant response was put forward. On the basis of this hypothesis, efforts to develop agents inhibiting the uptake of 5-HT have lead to the discovery and development of selective serotonin inhibitors [1].

Although many antidepressant drugs have been used for the treatment of depression, the selective serotonine reuptake inhibitors (SSRIs) have played an important role in pharmacotherapeutic treatment of depression because they are well tolerated and have less severe side effects than first-generation drugs, tricyclic antidepressants and nonselective monoamine oxidase inhibitors [2, 3]. Fluoxetine (Prozac®; a γ-phenoxypropylamine derivative) is a potent antidepressant drug which exerts its therapeutic action by selectively inhibiting 5-HT reuptake [4]. There are also many other SSRIs that share this γ-phenoxypropylamine structural feature and also inhibit the 5-HT transporter with high selectively as shown in Fig. 1.

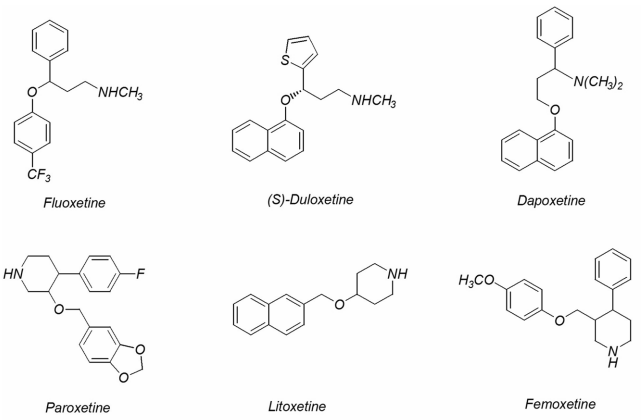

Figure 1. Different SSRIs with γ-phenoxypropylamine structural feature.

Although SSRIs are currently the first-line therapy for depression, a major problem associated with them is long-term treatment requirement for clinical efficacy. Furthermore, some of the undesired effects such as sex-

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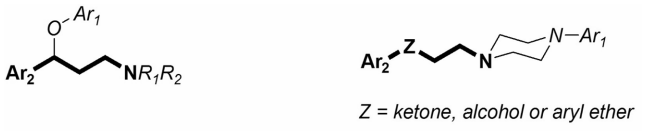


Figure 2. General structure pattern of the presented dual activity compounds.

ual dysfunction, gastrointestinal intolerance and activating effects such as nervousness, anxiety and insomnia were demonstrated for all available SSRIs [5, 6]. Therefore, one of the still therapeutic needs is the availability of antidepressants with a more rapid onset of action and less side effects.

In antidepressant drug development, recent studies have focused on a dual mode of action: serotonin reuptake inhibition and 5-HT_{1A} receptor antagonism. It has been proposed that addition of a 5-HT_{1A} antagonist component to the action of an SSRI can limit the negative feedback through blockage of the autoreceptor, allowing an intermediate increase in the synaptic 5-HT. In support of this hypothesis, clinical trials performed and showed that incorporating both 5-HT_{1A} antagonism and 5-HT reuptake inhibition within a single molecule should provide an immediate increase in 5-HT in the frontal cortex, resulting in a rapid-onset antidepressant. This dual-action feature would thus form the basis of the next generation of antidepressant therapy [4, 6–13].

Martinez and coworkers have dealt with this strategy of combining two chemically different structures associated with the dual mode of action: the nitrogen of the γ-phenoxypropylamine moiety of related SSRIs has been combined with an arylpiperazine ring and they could show that these compounds without an aromatic ring Ar_1 were endowed with the dual activity as potent 5-HT ligands [4, 14, 15] (Fig. 2).

In a series of studies, Takeuchi *et al*. have identified fused aryl-substituted piperidines as an essential pharmacophore for 5-HT reuptake inhibition and described a structure-activity relationship (SAR) study focused on the piperidine ring of 1-(1-*H*-indol-4-yloxy)-3-(4-benzo[*b*]thiophen-2-ylpiperidinylpropan-2-ols in order to optimize the activity in the development of more effective antidepressants [7–10]. In view of these literature results, we aimed at modifications on the general SSRI structure by exchanging the amine group with a benzylpiperidine group to obtain new antidepressant compounds with a better efficacy and less side-effects. The antidepressant-like effect of these synthesized compounds was studied in comparison with other antidepressants (fluoxetine, sertraline, imipramine) in the forced swimming test (FST).

Table 1. Structure and chemical data of the compounds **1–6**.

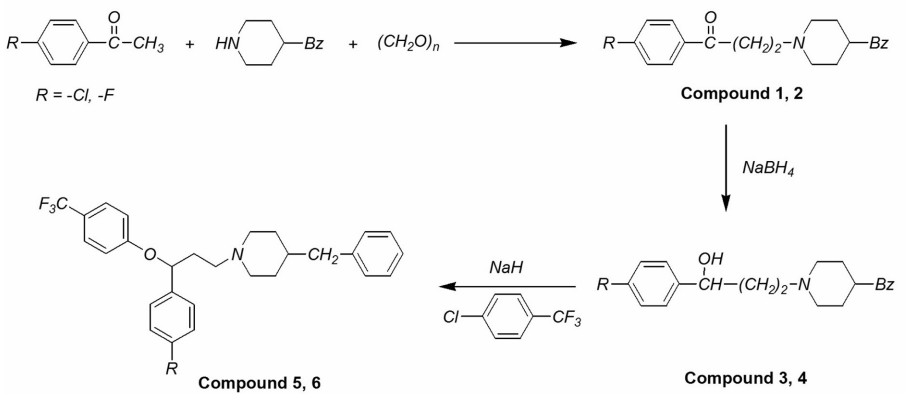
Compound	R	Formula[a)]	Melting point (°C)	Yield (%)
1	–Cl	$C_{21}H_{24}ClNO$	94	40
2	–F	$C_{21}H_{24}FNO$	97	32
3	–Cl	$C_{21}H_{26}ClNO$	110	61
4	–F	$C_{21}H_{26}FNO$	Decomp.	78
5	–Cl	$C_{28}H_{29}ClF_3NO$	105	34
6	–F	$C_{28}H_{29}F_4NO$	126	26

[a)] Elemental analyses for C, H and N are within ± 0.4% of the theoretical values.

Results and discussion

Chemistry

The 1-aryl-3-[(4-benzyl)piperidine-1-yl]propane derivatives presented in this study were prepared according to reported methods as shown in Scheme 1. Ketone derivatives were prepared by Mannich reaction of the corresponding acetophenones with benzylpiperidine, paraformaldehyde in ethanol. The reduction of ketones with sodium borohydride in methanol afforded the corre-



Scheme 1. Synthesis of presented 1-aryl-3-[(4-benzyl)piperidine-1-yl]propane derivatives.

Table 2. Spectral data of compounds **1 – 6**.

Compound	IR (KBr) ν (cm^{-1})	^{1}H-NMR δ (ppm)
1	3082, 2843 (C – H); 1678 (C=O); 1453 (C=C); 827, 748, 702 (subst. benzene)	($CDCl_3$)1.23 – 1.30 (m, 1H, piperidine C**H**), 1.51 – 1.65 (m, 4H, piperidine N – CH_2**CH_2** –), 1.82 – 1.89 (m, 4H, piperidine N – C**H_2**CH_2 –), 2.53 – 2.58 (t, 2H, CH_2**CH_2** – N), 2.84 – 2.88 (d, 2H, – C**H_2** – C_6H_5), 2.92 – 2.99 (t, 2H, CO – C**H_2** –), 7.13 – 7.31 (m, 9H, aromatic)
2	3102, 2988 (C – H); 1681(C=O); 1470 (C=C); 827, 749, 734 (subst. benzene)	($CDCl_3$) 1.24 – 1.31 (m, 1H, piperidine C**H**), 1.60 – 1.64 (m, 4H, piperidine N – CH_2**CH_2** –), 1.84 – 1.90 (m, 4H, piperidine N – C**H_2**CH_2 –), 2.53 – 2.56 (t, 2H, CH_2**CH_2** – N), 2.86(d, 2H, – C**H_2** – C_6H_5), 2.93 – 2.96 (dd, 2H, CO – C**H_2** –), 7.14 – 7.31 (m, 9H, aromatic)
3	3413 (O – H); 1468 (C=C); 1256 (C – O); 831, 745, 699 (subst. benzene)	(DMSO) 0.99 – 1.01 (m, 1H, piperidine C**H**), 1.39 – 1.50 (m, 4H, piperidine N – CH_2**CH_2** –), 1.70 – 1.76 (m, 2H, – CHC**H_2**CH_2 –), 2.13 – 2.50 (m, 6H, – C**H_2** – N – (C**H_2**)$_2$), 2.84 – 2.87 (d, 2H, – C**H_2** – C_6H_5), 4.30 (t, 1H, – C**H** –), 6.30 (s, 1H, OH), 7.14 – 7.28 (m, 9H, aromatic)
4	3362 (O – H); 1480 (C=C); 1252 (C – O); 827, 749, 700 (subst. benzene)	(DMSO) 1.13 – 1.16 (m, 1H, piperidine C**H**), 1.43 – 1.52 (m, 4H, piperidine N – CH_2**CH_2** –), 1.65 – 1.78 (m, 2H, – CHC**H_2**CH_2 –), 2.37 – 2.76 (m, 6H, – C**H_2** – N – (C**H_2**)$_2$), 2.84 – 2.93 (d, 2H, – C**H_2** – C_6H_5), 4.68 (t, 1H, – C**H** –), 6.24 (s, 1H, OH), 7.10 – 7.31 (m, 9H, aromatic)
5	2928 (C – H); 1653 (C=C); 1256 (C – O)	(DMSO) 1.23 – 1.27 (m, 1H, piperidine C**H**), 1.55 – 1.59 (m, 4H, piperidine N – CH_2**CH_2** –), 2.07 – 2.18 (m, 2H, – CHC**H_2**CH_2 –), 2.35 – 2.50 (m, 6H, – C**H_2** – N – (C**H_2**)$_2$), 2.54 – 2.77 (d, 2H, – C**H_2** – C_6H_5), 5.0 (dd, 1H, – C**H** –), 6.75 – 7.16 (m, 9H, aromatic), 7.26 – 7.34 (m, 4H, p-$CF_3C_6H_4$)
6	3023 (C – H); 1601 (C=C); 1511 (C=C); 1252 (C – O)	(DMSO) 1.22 – 1.28 (m, 1H, piperidine C**H**), 1.30 – 1.37 (m, 4H, piperidine N – CH_2**CH_2** –), 1.55 – 1.59 (m, 2H, – CHC**H_2**CH_2 –), 2.11 – 2.27 (m, 6H, – C**H_2** – N – (C**H_2**)$_2$), 2.53 – 2.65 (d, 2H, – C**H_2** – C_6H_5), 4.76 (dd, 1H, – C**H** –), 7.01 – 7.22 (m, 9H, aromatic), 7.26 – 7.31 (m, 4H, p-$CF_3C_6H_4$)

sponding alcohol. Treatment of alcohols with sodium hydride and 4-chloro-1-trifluoromethylbenzen led to phenolic ether. Yields, the physical and spectroscopic properties of the compounds are reported in Tables 1 and 2.

The IR spectrum of the compounds displayed strong absorption bands for characteristics of the functional groups ketone, alcohol and ether for compounds **1, 2**, **3, 4** and **5, 6** in 1681 – 1678 cm^{-1}, 3413 – 3362 cm^{-1}, 1256 – 1252 cm^{-1}, respectively. ^{1}H-NMR spectrums showed the expected chemical shifts of protons as explained in details in Table 2.

Pharmacology

The antidepressant activity of the synthesised compounds was evaluated by forced swimming test (FST). Results of the immobility time and locomotor activity are given in Table 3.

The compounds 3-(4-benzylpiperidine-1-yl)-1-(4-chloro/fluorophenyl)propane-1-one **1**, **2** and 3-(4-benzylpiperidine-1-yl)-1-(4-fluorophenyl)propane-1-ol **4** clearly present antidepressant-like profiles of action as shown by the significant reduction in the immobility time recorded in FST with meaningful statistical results. A reduction in the immobility time in FST is exhibited by therapeutically useful antidepressant drugs and is very well accepted as a reliable indicator of this kind of pharmacological activity [16, 17]. Due to the fact that the FST is based on a motor response of animals, it could be affected by changes in their motor activity and/or performance. For this reason, animals were also evaluated by locomotor activity tests. The locomotor activity test is commonly used as a complement of the FST to discard unspecific actions of antidepressant treatments. In this test, it is considered as a false positive, when a compound increases general activity as well as active behaviors in the FST. By contrast, a compound that decreases general activity in locomotor activity test and still increases active behaviors in the FST is considered to possess antidepressant-like actions, in spite of its effects on general activity. It is common for antidepressants to decrease locomotor activity in locomotor activity test and still promote a reduction of immobility in the FST [18, 19]. Intraperitoneal administration of compounds at effective doses generally did not alter the behavioural performance of the animals which essentially depends on their motor function. Only compound **1**, at dose of 30 mg/kg, *ip*, decreased the locomotor activity drastically but not statisticaly when compared to the control and standard

Table 3. Antidepressant activity of compounds **1 – 6.**

Treatment	Dose (mg/kg)	Immobility time (s)	Locomotor activity (count/5 min)
Control 1[a]	1 ml/kg	162.22 ± 18.9	384.3 ± 33.2
Control 2[a]	1 ml/kg	193.12 ± 13.24	365.8 ± 28.9
Fluoxetine	30	84.1 ± 8.2[b]	310.5 ± 30.6
Sertraline	20	86.2 ± 9.2[b]	303.4 ± 21.5
Imipramine	20	71.2 ± 7.4[b]	356.5 ± 25.5
Compound 1	0.1	267 ± 12.8	300.5 ± 19.6
	1	229 ± 9.6	297.6 ± 22.3
	10	157.5 ± 18.8	287. 8 ± 24.4
	30	44.8 ± 8.9[c]	260.4 ± 21.5
Compound 2	0.1	263.57 ± 15.2	365.6 ± 26.7
	1	222.8 ± 18.3	390.6 ± 31.1
	10	110.71 ± 21.1[c]	386.5 ± 22.8
	30	94.0 ± 12.3[c]	340.1 ± 25.4
Compound 3	0.1	238 ± 22.6	280.5 ± 25.4
	1	235 ± 12.8	320.6 ± 32.4
	10	171 ± 15.6	298.8 ± 25.6
	30	137.2 ± 12.1	302.3 ± 31.5
Compound 4	0.1	210.7 ± 17.9	332.5 ± 22.4
	1	203.2 ± 10.3	350.4 ± 30.5
	10	140 ± 26.8	321.0 ± 25.4
	30	82.2 ± 15.7[b]	358.5 ± 26.3
Compound 5	0.1	180.2 ± 16.8	303.6 ± 31.5
	1	178.5 ± 12.2	290.5 ± 21.4
	10	165.5 ± 19.5	325.6 ± 28.3
	30	156.7 ± 16.4	346.6 ± 22.4
Compound 6	0.1	236.42 ± 17.1	389.6 ± 15.5
	1	220.71 ± 22.18	398.4 ± 23.4
	10	214.16 ± 18.1	400.5 ± 21.5
	30	215.28 ± 13.6	380.6 ± 31.0

[a] Control 1 and 2 received distilled water and DMSO, respectively. Values are expressed as means ± S.E.M. of 8 – 10 mice. Compounds were administered ip 30 min before the test.

[b] $p < 0.05$, compared to control group 1.

[c] $p < 0.05$, compared to control group 2.

antidepressant drugs. These observations strongly indicate that the reduction in the immobility time is due to a selective antidepressant-like effect of these compounds, and not merely the results of a general stimulation of the animals' motor activity.

Although compounds **5** and **6** comply with the pharmacophore groups of well-known SSRIs such as fluoxetine and duloxetine, the incorporation of the third ring provoked a loss of antidepressant activity, probably caused by the associated increase in volume to these esters. These results are in accordance with literature data given before [4, 14].

Conclusion

In conclusion, the present results show a clear antidepressant-like effect for compounds **1, 2** and **4** compared to a control group and also better reduction in immobility time in FST than standards for compounds **1** and **4**. Due to these experimental results and taking the chemical structures of the active compounds into consideration, we agree to the hypothesis of Martinez *et al*. that compounds without the second aryl on the alcohol group of propyl moiety show potent antidepressant activity [15]. Further pharmacological studies characterised by radioligand-binding studies at both the 5-HT_{1A} receptor and the 5-HT transporter for the active compounds will clarify the mechanism of action to support this antidepressant-like activity. Therefore, these active compounds deserve to be studied further, since the present results shown here are highly significant because they reveal new potential tools for the treatment of depression one the most prevalent psychopathologies in the world and still in need of new and perhaps better therapeutic approaches.

Experimental

Chemistry

Melting points (°C) were determined by using a Mettler Toledo FP62 capillary melting point apparatus (Mettler-Toledo, Greifensee, Switzerland) and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrum (Perkin Elmer, Norwalk, CT, USA). One series FTIR apparatus (Version 5.0.1), using potassium bromide pellets, the frequencies are expressed in cm^{-1}. The ^{1}H-NMR spectra were obtained with a Varian Mercury 400 MHz FT-NMR spectrometer (Varian Inc., Palo Alto, CA, USA), using tetramethylsilane as the internal reference, with chloroform-$CDCl_3$ or dimethylsulphoxide-DMSO-d_6 as solvents, the chemical shifts are reported in parts per million (ppm). Elemental analyses were performed on a Leco CHNS 932 analyzer (Leco, Philadephia, PA, USA) at the Scientific and Technical Research Council of Turkey, Instrumental Analysis Laboratory in Ankara.

Synthesis

3-(4-Benzylpiperidine-1-yl)-1-(4-substitutedphenyl)propane-1-one ***1, 2***

The mixture of the appropriated substituted acetophenones (30 mmol), 4-benzylpiperidine (30 mmol) in ethanol (40 mL) was refluxed. Paraformaldehyde (90 mmol) was added in four equal portions over a period of 40 min. The reaction mixture was refluxed for another 8 h, cooled and poured onto crushed ice. The separated solid was filtered and recrystallized from isopropanol.

3-(4-Benzylpiperidine-1-yl)-1-(4-substitutedphenyl)propane-1-ol ***3, 4***

An excess of sodium borohydride was added to a well-stirred solution or suspension of the corresponding 3-(4-benzylpiperidine-1-yl)-1-(4-substituted phenyl)propane-1-one (3 mmol) in methanol, over a period of 15 min at 00C. The stirring was continued for another 8 – 12 h. The solvent was removed under reduced

pressure; the residue was triturated with *n*-hexane and allowed to sit with the solvent in refrigerator over the night. The precipitated product was filtered and dried.

3-[4-Benzylpiperidine-1-yl]-1-(4-substitutedphenyl)-1-(4-trifluoromethylphenoxy)-propane ***5, 6***

3-(4-Benzylpiperidine-1-yl)-1-(4-substituted phenyl)propane-1-ol (2.5 mmol) was dissolved in *N*,*N*-dimethylacetamide or DMSO (25 mL) and heated to 75°C. Sodium hydride (2.5 mmol) was added and the reaction mixture was maintained at 75°C for 2 h to allow the formation of salt. After this period of time, 4-chloro-1-trifluoromethylbenzen (2.5 mmol) was added and the resulting mixture was poured onto crushed ice. It was then extracted with diethyl ether (4 × 10 mL), washed with brine (3 × 10 mL) and dried with anhydrous sodium sulphate. The solvent was removed under reduced pressure and recrystallized from a suitable solvent.

Pharmacology

Animals

Male Balb/c mice weighing 25 – 35 g were housed collectively in groups of ten in polycarbonate cages. They were maintained on a 12 h light/dark cycle (lights on 08:00/20:00 h) in a temperature controlled (20 ± 2°C) laboratory. Food and water were available *ad libitum*. These conditions were maintained constant throughout the experiments. All procedures in this study are in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the National Institutes of Health.

Forced swimming test

FST consisted of placing mice into individual plexiglass cylinders (16 cm diameter) containing 23 – 25°C water, 11 cm deep; mice could not support themselves by touching the bottom with their paws. Two swimming sessions were conducted: an initial 15-min pretest followed 24 h later by a 6-min test. After an initial 2-min period of vigorous activity, each animal assumed an immobile posture. The total duration of immobility was recorded during last 4 min of the 6-min testing period. Following each swimming session, the mice were removed from the cylinders, dried with paper towels, placed in heated cages for 30 min and then returned to their home cages. Test sessions were videotaped for later scoring. A single observer, who was blind to the treatment conditions, did all the behavioural scoring.

Locomotor activity test

Spontaneous locomotor activity was measured in an activity cage (Ugo Basile, Varese, Italy) having dimensions of 39 × 28 × 26 cm. The values indicate pulses recorded by the apparatus as the stainless steel bars tilt in response to animal movements. The activity of each mouse was automatically recorded for 5 min.

Evaluation

Evaluation of the antidepressant-like effect

The compounds were administered intraperitoneally (ip) at doses of 0.1 – 30 mg/kg 30 min. before the forced swimming test. Sertraline (20 mg/kg, ip), fluoxetine (30 mg/kg, ip) and imipramine (20 mg/kg, ip) were employed as the standard antidepressant drugs. The control groups received sterile distilled water and DMSO (1 mL/kg, ip)

Evaluation of the locomotor activity

The compounds were administered intraperitoneally (ip) at doses of 0.1 – 30 mg/kg 30 min. before the locomotor activity test (5 min.). Sertraline (20 mg/kg, ip) fluoxetine (30 mg/kg, ip) and imipramine (20 mg/kg, ip) were employed as the standard antidepressant drug. The control groups received distilled water and DMSO (1 mL/kg, ip)

Statistical analysis

All results are expressed as the mean ± S.E.M. The data were analysed by student-t test. The level of significance was defined as $p < 0.05$.

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