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Research Article

Design, synthesis and Anti-depressant activity of some novel derivatives of Benzothiazepine

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Abstract

Antidepressants are the drugs used to treat depression thereby elevates mood and modifies the behavior. The main aims in the development of new antidepressants were greater efficacy, absence of side effects, lack of toxicity in over dose and earlier onset of action. In this study, a series of novel substituted benzothiazepine was synthesized and evaluated for antidepressant-like activity by using or forced swim test (FST).

This study was designed to synthesized; identify and antidepressant-like activity of novel derivatives of benzothiazepine.

Our synthetic route started from substituted aromatic aldehyde which was reacted with 2-aminothiophenol and ethyl or methyl acetoacetate led to the formation of the title compounds. Total 22 benzothiazepine derivatives were synthesized. All compounds were tested for antidepressant activity by using or forced swim test (FST).

All the synthesized compounds were subjected to antidepressant-like activity study on Sprague-Dawley rats by despair swim test. Imipramine was used as standard control. The results showed that all the compounds showed antidepressant activity. Among them two Compounds (A_3, A_6, B_1 B_3, and B_6) showed significant antidepressant-like activity comparing with standard control imipramine.

We investigated the importance of functional group substitutions, in the structural framework of the compounds for their antidepressant-like activity. All compounds showed significant antidepressant-like activity at dose (30 mg/kg). Finally, the encouraging result of the antidepressant-like activity displayed by these compounds may be of interest for further structural modifications to the lead compound and next level studies in the hope of finding a new potent antidepressant prescription.

Keywords: Antidepressant, benzothiazepine, Sprague-Dawley Rats, forced swim test (FST).

1. Introduction

To the present knowledge, antidepressant drugs used in the treatment of major depressive disorders are believed to act on the central monoaminergic systems mainly serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline (NA) synaptic neurotransmissions. Selective serotonin reuptake inhibitors (SSRIs: paroxetine, fluoxetine, citalopram, escitalopram, fluvoxamine, sertraline) and noradrenaline reuptake inhibitors (NRIs: reboxetine, desipramine) are the most common prescribed antidepressant drugs[1]. They exert their therapeutic effects by increasing availability of 5HT and NA neurotransmitters in the synapses of different limbic areas including the frontal cortex. Although SSRIs and NRIs are effective in treating most depressive episodes, a significant proportion of depressed patients do not display signs of mood improvement until 2–3 weeks after the start of the treatment[2]. Furthermore, about one third of these patients show only partial or no response to the treatment[3]. In addition, some side effects are reported during the chronic treatment such as gain weight and sexual

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dysfunction. Thus, multiple strategies are in progress to improve the activity of these conventional antidepressant drugs.

Benzothiazepines are the class of compounds having benzodiazepine type nucleus. The only difference between them is of S (sulphar) in place of N (nitrogen) atom in the heterocyclic ring system. The versatile application of benzothiazepines in the treatment of ailments of cardiovascular system such as coronary vasodilation, hypertension etc. Benzothiazepines are the versatile pharmacophore having various biological activities like cardiovascular activity, antipsychotic activity, anti-HIV activity, analgesic activity, antimicrobial activity etc.

The behavioral despair test (BDT; also named the forced swim test) was developed using rats and then adapted to mice.[5]-[9] Since then it has become one of the most widely used tests for antidepressant screening. Despite its recognized predictive validity for antidepressants, the BDT has been criticized for relatively low sensitivity to antidepressants acting on serotonin and positive response to psychostimulants, with the latter considered to be devoid of real antidepressant activity.[10] The test is based on the observation that when placed in a cylinder containing water, rodents rapidly become immobile after unsuccessful attempts to escape. Antidepressants decrease the duration of immobility which is used as the main predictor of antidepressant-like activity. Other authors have analyzed active behaviors in the rat in addition to immobility but this method has not been widely used in the mouse.[11] Another parameter used to characterize antidepressant-like activity is the latency to immobility. Latency has been used to detect the efficacy of fluoxetine, antagonists of glutamate receptors and citidine in the rat BDT. Use of latency has also been described in the mouse to detect antidepressant-like activity, although much less often than in the rat.[12] Latency has also proved useful to study transgenic mice and antidepressant-like effects of calorie restriction.[13] The present study further evaluates the usefulness of latency to immobility in preclinical antidepressant screening to help improve sensitivity to antidepressant effects, distinguish selective serotonin reuptake inhibitors (SSRIs) from serotonin/norepinephrine reuptake inhibitors (SNRIs) and separate antidepressant and stimulant activities. In particular, we compared the duration of immobility with latency in mice treated with several classes of antidepressants, including tricyclics (imipramine and desipramine), selective SSRIs (fluoxetine and escitalopram) and SNRIs (duloxetine and venlafaxine) as well as psychostimulants (amphetamine and modafinil). Most experiments were performed in the NMRI strain of mice. In order to evaluate generalization of our findings, some experiments used C57Bl6/J mice since antidepressant effects can be strain-dependent.

Thus, the present study was aimed to evaluate the antidepressant-like effects of benzothiazepines derivatives using the forced swimming test (FST). This behavioural test is one of the most widely used preclinical paradigms for predicting antidepressant-like activity of drugs after their acute administration[14] alone or in combination.

2. Materials &Methods

2.1 Chemistry

Melting points were determined in open capillary method and are uncorrected. The ^{1}H-NMR spectra were recorded on sophisticated multinuclear FT-NMR Spec-trometer model Advance-II (Bruker) using dimethylsulfoxide-*d*6 as solvent and tetramethylsilane as internal standard. IR spectra were recorded on Jasco FT-IR-spectrophotometer using KBr disc method.

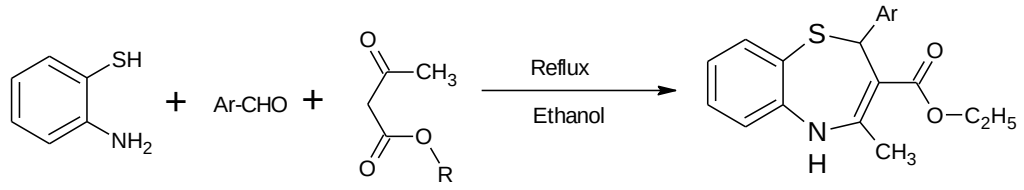
2.1.1 Procedure for synthesis of ethyl 4-methyl-2- substituted -2,5-dihydro-1,5- benzothiazepine-3 carboxylate

An equimolar mixture of 2-aminothiophenol, substituted benzaldehydes and ethyl acetoacetate, in 20 ml ethyl alcohol was refluxed for 50 min. Completion of the reaction was monitored by TLC [eluent ; ethyl acetate : pet. ether (3:7)]. After completion of the reaction, the reaction mixture was poured onto crushed ice; the solid crude product was washed with water. The crude product was purified by recrystallisation with hot ethanol. (A_1-A_{11})

2.1.2 Procedure for synthesis of methyl 4-methyl-2- substituted -2,5-dihydro-1,5-benzothiazepine-3 carboxylate

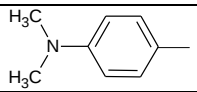
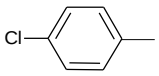
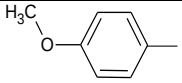
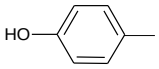
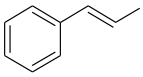
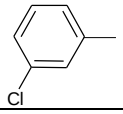
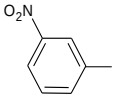
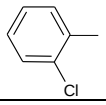
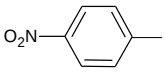
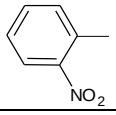
An equimolar mixture of 2-aminothiophenol, substituted benzaldehydes and methyl acetoacetate, in 20 ml ethyl alcohol was refluxed for 50 min at 70-90^{0} C. Completion of the reaction was monitored by TLC [eluent ; ethyl acetate : pet. ether (3:7)]. After completion of the reaction, the reaction mixture was poured onto crushed ice; the solid crude product was washed with water. The crude product was purified by recrystallisation with hot ethanol. (B_1-B_{11})

2.1.3 Scheme

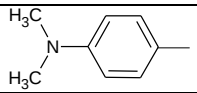
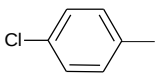
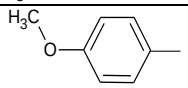
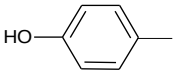
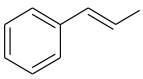
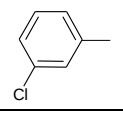
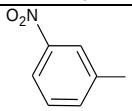
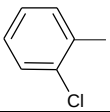
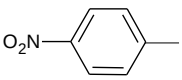
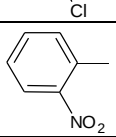


R = CH_3, C_2H_5

FOR COMPOUNDS A_1-A_{11}

Comp. Code	Ar	R	Comp. Code	Ar	R
A_1		CH_3	**A_7**		CH_3
A_2		CH_3	**A_8**		CH_3
A_3		CH_3	**A_9**		CH_3
A_4		CH_3	**A_{10}**		CH_3
A_5		CH_3	**A_{11}**		CH_3
A_6		CH_3			

FOR COMPOUNDS B_1-B_{11}

Comp. Code	Ar	R	Comp. Code	Ar	R
B_1		C_2H_5	**B_7**		C_2H_5
B_2		C_2H_5	**B_8**		C_2H_5
B_3		C_2H_5	**B_9**		C_2H_5
B_4		C_2H_5	**B_{10}**		C_2H_5
B_5		C_2H_5	**B_{11}**		C_2H_5
B_6		C_2H_5			

2.2 Pharmacology

Rat-Sprague Dawley (220-255 gm), 8-12 weeks old, was obtained from National Institute of Rat-Sprague Dawley (220-255 gm), 8-12 weeks old, was obtained from National Institute of Bioscience, Pune. They were housed in autoclaved polypropylene cages in groups of 2-3 rats per cage and kept in a room maintained at 19 to 25 ^{0}C and humidity 45 to 65 % with a 12-h light/dark cycle. They were allowed to acclimatize for four days before the experiments and were given free access to Standard sterilized extruded rodent diet was provided *ad libitum*, Reverse Osmosis water treated with UV light was provided *ad libitum* in autoclaved polypropylene bottles and Autoclaved corn cob was used as bedding material.

All procedures of the present study was in accordance with the standard operating procedures of the Prado Pvt. Ltd. guidelines provided by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) as published in The Gazette of India, December 15, 1998. Prior approval of the Institutional Animal Ethics Committee (IAEC) was obtained before initiation of the study (IAEC-13-003).

2.3 Acute oral toxicity study

In the present study acute oral toxicity of the synthesized compounds were performed by OECD guideline for testing of chemicals, No. 423, 'Acute Oral Toxicity – Acute Toxic Class Method'. In this method the toxicity of synthesized compounds were tested using a step wise procedure, each step using three rats of single sex (female). The rats were fasted prior to dosing (food but water should be with held) for three to four hours. Following the period of fasting the animal should be weighted and synthesized compounds were administered initially at a dose of 1000 mg/kg (b. w.) and 0.5 % Na CMC and were observed for 14 days for acute toxicity.[15][16]

2.4 Antidepressant Activity (Forced Swim Test in rat):

Behavioral despair or forced swim test (FST) was proposed as a model to test antidepressant activity by Porsolt *et al*[17][18]. It was suggested that mice or rats when forced to swim in restricted space from where they cannot escape are induced to a characteristic behavior of immobility. This behavior reflects a state of despair which can be reduced by several agents which are therapeutically effective in human depression. The behavioral despair test is employed to assess the antidepressant activity of synthesized derivatives. *Sprague-Dawley rats* of 200-270 gm in a group of two each were used and on the first day of the experiment (pretest session), rats were individually placed in a cylindrical recipient (Plexiglass cylinder) of dimensions (diameter, 10 cm; height, 25 cm) containing 10 cm of water 25°C. The animals were left to swim for 6 min before being removed, dried and returned to their cages. The procedure was repeated 24 h later, in 5 min swim session (test session). The synthesized compounds (30 mg kg-1), and imipramine, as a reference antidepressant drug (30 mg kg^{-1}) were suspended in a 0.5 % aqueous solution of Na CMC (Corboxy Methyl Cellulose). The drugs were given by gavage in a standard volume of 10ml/kg body weight, 1 h prior to the test. Each animal kept in individual cages after administration of test compounds. Control animals received 0.5 % aqueous solution of Na CMC (Corboxy Methyl Cellulose).

For individual animal video recording was made.Then, the rats were dropped individually into the Plexiglass cylinder and left in the water for 6 min. After the first 2 min of the initial vigorous struggling, the animals were immobile. An immobility time is the time spent by rat floating in water without struggling, making only those moment necessary to keep the head above the water. The total duration of immobility was recorded during the last 5 min of the 6 min test session.

2.4 Statistical analysis

Results are presented as Mean ± SEM. Data was analyzed using Graphpad Prism 6. Two way analysis of variance (ANOVA) was used for multiple group comparisons. $P<0.05$ was considered as statistically significant.

3. Result and Discussion

The structures, yields and melting points of the compounds have been given in the (Table 1). Melting points of the synthesized compounds were sharp indicating that the compounds were pure; the yield value of the compounds also suggested that the chemical methods were reliable for the synthesis of the compound.

Table 1: Analytical & Physicochemical data of the synthesized compounds (A_1-A_{11}) & (B_1-B_{11})

Comp. Code	Mol. Formula	Mol. Wt.	M.P. ° C	Yield %	Elemental analyses Calcd.(found)		
					C	H	N
A_1	$C_{20}H_{24}N_2O_2S$	354.47	195-200	72	67.77 (67.45)	6.26 (5.90)	7.90 (7.50)
A_2	$C_{19}H_{19}NO_3S$	341.17	235-238	75	66.84 (66.50)	5.61 (5.20)	4.10 (3.75)
A_3	$C_{20}H_{19}NO_2S$	337.11	205-207	67	71.19 (70.95)	5.68 (5.10)	4.15 (3.95)
A_4	$C_{18}H_{16}ClNO_2S$	345.06	230-232	71	62.51 (62.10)	4.46 (4.20)	4.05 (3.85)
A_5	$C_{18}H_{16}ClNO_2S$	345.06	202-205	78	62.51 (62.10)	4.46 (4.20)	4.05 (3.85)
A_6	$C_{18}H_{16}N_2O_4S$	356.40	265-267	69	60.66 (60.20)	4.53 (4.25)	7.86 (7.20)
A_7	$C_{18}H_{16}ClNO_2S$	345.06	230-233	72	62.51 (62.10)	4.46 (4.20)	4.05 (3.85)
A_8	$C_{18}H_{17}NO_3S$	327.09	234-238	65	66.03 (62.75)	5.23 (4.90)	4.28 (4.02)
A_9	$C_{18}H_{17}NO_3S$	327.09	210-215	65	66.03 (62.75)	5.23 (4.90)	4.28 (4.02)
A_{10}	$C_{18}H_{16}N_2O_4S$	356.40	185-190	71	60.66 (60.20)	4.53 (4.25)	7.86 (7.20)
A_{11}	$C_{18}H_{16}N_2O_4S$	356.40	240-242	62	60.66 (60.20)	4.53 (4.25)	7.86 (7.20)
B_1	$C_{21}H_{24}N_2O_2S$	368.18	200-205	75	68.45 (68.10)	6.56 (6.10)	7.60 (7.10)
B_2	$C_{20}H_{21}NO_3S$	355.12	235-238	75	67.58 (67.10)	5.95 (5.50)	3.94 (3.45)
B_3	$C_{21}H_{21}NO_2S$	351.13	215-220	68	71.76 (71.45)	6.02 (5.75)	3.94 (3.55)
B_4	$C_{19}H_{18}ClNO_2S$	359.87	230-232	65	63.41 (63.10)	5.04 (4.75)	3.89 (3.45)
B_5	$C_{19}H_{18}ClNO_2S$	359.87	240-245	78	63.41 (63.10)	5.04 (4.75)	3.89 (3.45)
B_6	$C_{19}H_{18}N_2O_4S$	370.10	265-267	68	61.61 (61.12)	4.90 (4.42)	7.56 (7.12)
B_7	$C_{19}H_{18}ClNO_2S$	359.87	232-235	72	63.41 (63.10)	5.04 (4.75)	3.89 (3.45)
B_8	$C_{19}H_{19}NO_3S$	341.11	234-238	65	66.84 (66.45)	5.61 (5.32)	4.10 (3.95)
B_9	$C_{19}H_{19}NO_3S$	341.11	220-225	65	66.84 (66.45)	5.61 (5.32)	4.10 (3.95)
B_{10}	$C_{19}H_{18}N_2O_4S$	370.10	214-220	75	61.61 (61.12)	4.90 (4.42)	7.56 (7.12)
B_{11}	$C_{19}H_{18}N_2O_4S$	370.10	242-245	62	61.61 (61.12)	4.90 (4.42)	7.56 (7.12)

All the compounds showed characteristic peak in IR and NMR spectroscopic studies. (Table 2)

Table 2: Spectral Data of the Synthesized Compounds (A_1-A_{11}) & (B_1-B_{11})

Comp. Code	FTIR (KBr, cm^{-1})	H^1 NMR ($CDCl_3$,ppm
A_1	3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
A_2	3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 3213.45 (-NH str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 1260.02 (-C-O str).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
A_3	3310.23 (-CH=CH str.), 3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str).	6.32-6.53 (-2H –CH=CH), 3.90 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
A_4	3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 940.23 (-C-Cl str.),	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
A_5	3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 930.21 (-C-Cl str.), 1260.02 (-C-O str).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
A_6	3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1260.02 (-C-O str), 1255.36 (-N-O str).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 3.82 (3H $–CH_3$, –C-O), 2.26 (3H CH_3).
A_7	3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 940.21 (C-Cl str.), 3600.12 (-OH str.).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 3.8 2.26 (3H CH_3).
A_8	3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1255.36 (-N-O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 3616.11 (-OH str.).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 9.43 (1H –OH), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
A_9	3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 3616.11 (-OH str.).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 9.43 (1H –OH), 6.8-7.2 (12H phenyl), 2.26 (3H CH_3).).
A_{10}	3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1255.36 (-N-O str.).	4.50 (1H thiazipine), 8.54 (1H –N=CH), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
A_{11}	3208.12 (-NH2 str.), 3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
B_1	3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str). 4	.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 3.66 (3H $–CH_3$, –C-N), 2.26 (3H-CH_3).
B_2	3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 3213.45 (-NH str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 1260.02 (-C-O str).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
B_3	3310.23 (-CH=CH str.), 3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str).	6.32-6.53 (-2H –CH=CH), 3.90 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
B_4	3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 940.23 (-C-Cl str.).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 8.54 (1H –NH sec. amide), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
B_5	3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 930.21 (-C-Cl str.), 1260.02 (-C-O str).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
B_6	3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1260.02 (-C-O str), 1255.36 (-N-O str).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 3.82 (3H $–CH_3$, –C-O), 2.26 (3H CH_3).
B_7	3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 940.21 (C-Cl str.).	4.50 (1H thiazipine), 8.54 (1H –N=CH), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), (3H CH_3).
B_8	3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1255.36 (-N-O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 3616.11 (-OH str.).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 9.43 (1H –OH), 6.8-7.2 (12H phenyl), 2.26 (3H CH_3).
B_9	3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 3616.11 (-OH str.).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 9.43 (1H –OH), 6.8-7.2 (7H phenyl), 2.26 (3H CH_3).
B_{10}	3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1255.36 (-N-O str.),	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (7H phenyl), 2.26 (3H
B_{11}	3208.12 (-NH2 str.), 3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str).	4.50 (1H thiazipine), 9.61 (1H –NH sec. amine), 6.8-7.2 (12H phenyl), 2.26 (3H CH_3).

3.1 Acute Oral Toxicity Studies

No sign of toxicity observed at 2000 mg/kg b.w. in the experimental animals, the LD50 value of the title compounds (V1-V3) expected to exceed 2000 mg/kg b.w. and represented as class 5 (2000 mg/kg < LD50 < 2500 mg/kg). Thus, 30 mg/k.g. b.w. was considered as the dose for the further studies.

3.2 Antidepressant Activity

All the synthesized compounds were subjected to antidepressant activity study on Sprague-Dawley rats by despair swim test. Imipramine was used as standard control. The results showed that all the compounds showed antidepressant activity comparing with standard control imipramine (Table 03).

Table 3: Mean immobility time in Forced swim test (A_1-A_{11}) & (B_1-B_{11})

Compound code.	Immobility time mean (sec.) ± S.E.M.
A_1	165± 2.30
A_2	177.83±1.75
A_3	166.83±2.54
A_4	170.5±1.76
A_5	160.3±1.42
A_6	162±1.18
A_7	169.33±1.02
A_8	169±1.71
A_9	155.16±1.32
A_{10}	172.33±0.91
A_{11}	172.16±1.77
Control	182.83±4.26
Imipramine (std.)	147.5±3.52
B_1	169±1.71
B_2	155.16±1.32
B_3	172.33±0.91
B_4	172.16±1.77
B_5	160.3±1.42
B_6	162±1.18
B_7	169.33±1.02
B_8	165± 2.30
B_9	177.83±1.75
B_{10}	166.83±2.54
B_{11}	170.5±1.76
Control	182.83±4.26
Imipramine (std.)	147.5±3.52

Effect of synthesized compounds on immobility duration in FST. Results are expressed as Mean ± S.E.M. n(6), when compared with control.

Figure 1: Antidepressant activity of synthesized compounds by using forced swim method.

4. Conclusion

We investigated the importance of functional group substitutions, in the structural framework of the compounds for their antidepressant activity. All compounds showed significant antidepressant activity at dose (30 mg/kg). Finally, the encouraging result of the antidepressant activity displayed by these compounds may be of interest for further structural modifications to the lead compound and next level studies in the hope of finding a new potent antidepressant prescription.

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