International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 8s, 2025
https://www.theaspd.com/ijes.php

Antidepressant Activity Of 1,3,4-Oxadiazole Scaffolds Incorporated Piperine Derivatives

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Abstract
In the present study, ten derivatives of Piperine were synthesized by incorporating 1, 3, 4-oxadiazole scaffolds via a four steps reaction synthetic scheme. First step involves synthesis of (2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienoic acid(1) from isolated Piperine in ethanol. In the second step an ester methyl (2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienoate(2), has been synthesized by esterification of (1) with ethyl alcohol and concentrated H2SO4. This is then converted into (2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienehydrazide(3) in third step by hydrogenolysis in the presence of hydrazine hydrate. In the fourth step, Piperine derivatives (4a-4j) were synthesized by treating the hydrazide (3) with various p-substituted aromatic acids such as benzoic acid/p-hydroxy benzoic acid/ p-nitro benzoic acid/ p-amino benzoic acid/ p-bromo benzoic acid/ p-chloro benzoic acid/ p-fluoro benzoic acid/ p-methyl benzoic acid/ p-methoxy benzoic acid/ p-ethoxy benzoic acid in ethanol and phosphorous oxychloride. The synthesized compounds were confirmed by melting point, TLC, IR and 1H NMR studies and are in good agreement with assigned structures. Antidepressant activity of 4a, 4b and 4c was carried out using forced swimming test model. Among three derivatives tested 4a and 4b were found to possess profound antidepressant activity.

Keywords: *Piperine; 1,3,4-oxadiazole; Antidepressant; Substituted benzoic acids; forced swimming test.*

INTRODUCTION

Depression is a prevalent mental illness that manifests as low energy, difficulty in concentration, loss of interest or pleasure, and a gloomy mood[1]. A melancholy mood may be a natural, transient response to life circumstances like losing loved ones. These issues can become severe or persistent, which can seriously impair a person's capacity to fulfil everyday obligations. Around 121 million individuals worldwide suffer from depression, which is getting more widespread [2]. In India, the prevalence rate for all mental illnesses is 65.4 per 1000 people. Of these, the estimated prevalence rate for depressive disorders is 31.2/1000 people. Major depression is thought to affect 2% of people over 65 in the general population[3].Teenage depression can be a significant risk factor for suicide[4]. Depressed people may have trouble recalling specifics, trouble making decisions or navigating relationships, which can potentially contribute to suicidal thoughts and self-harm.

Patients with clinical depression are typically treated with a variety of synthetic medications. These include sertraline, fluoxetine, escitalopram, imipramine, despiramine, citalopram, and fluoxetine etc.,[5]. Nausea, increased appetite and weight gain, sleepiness and exhaustion, insomnia, dry mouth, blurred vision, constipation, dizziness, agitation, irritability, anxiety etc., are the common side effects associated with the above mentioned drugs [6]. These facts striked the clinicians to use active constituents of plant as an alternative treatment for depression. Piperine is one such active constituents of Piper nigrum used in traditional medicine as antidepressant, anti-inflammatory, anti-microbial, anticonvulsant, and antioxidant properties etc., [7,8].

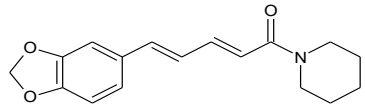
1,3,4-oxadiazole is an heterocyclic scaffold and its derivatives are having anti-inflammatory, analgesic, anti-ulcerogenic, antibacterial, antifungal, antitubercular, anticonvulsant, antitumor, antiviral, antihypertensive, and antidepressant activities [9,10] . There is a paucity of literature on antidepressant activity of piperine incorporated 1,3,4-oxadiazole derivatives. In view of these importance of piperine and 1,3,4 oxadiazoles and in continuation of the earlier work on piperine in our laboratories[11] , in the present study an attempt has

been made to synthesize and characterize the 1,3,4-oxadiazole derivatives (Scheme1) of piperine as possible anti-depressant agents.

MATERIALS AND METHODS

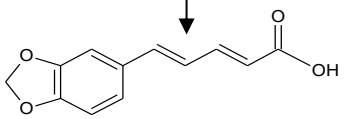
The Chemicals required for the present study were procured from (Qualigens, SD fine chemicals, Merck) and were used without further purification. Melting point of the synthesized compounds were determined in an open capillary tube and are uncorrected. IR spectras of the derivatives were recorded on Shimadzu (FTIR IR Affinity 1S spectrophotometer) and ^{1}H NMR spectra of these derivatives were taken from Bruker AV400 model with field strengths of 400MHz in solvent $CDCl_3$ and TMS as internal standard.

Scheme1: Synthesis of Piperine incorporated 1,3,4-oxadiazole derivatives (4a-4j)



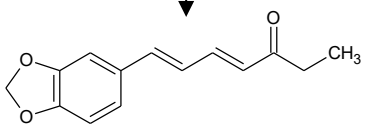
(2E,4E)-5-(1,3-benzodioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one

KOH, 95% ethanol



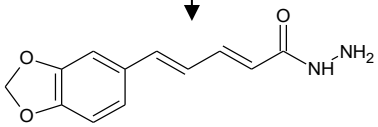
(2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienoic acid (1)

conc. H_2SO_4, Ethanol



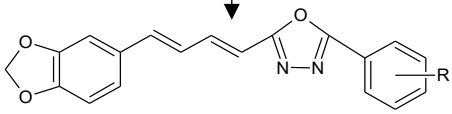
methyl (2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienoate (2)

$NHNH_2.H_2O$



(2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienehydrazide (3)

R-Ar COOH, $POCl_3$



2-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-5-phenyl-1,3,4-oxadiazole **(4a-4j)**

where R= H, OH, NO_2, NH_2, Br, Cl, F, CH_3, OCH_3, OC_2H_5

Step 1: Synthesis of (2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienoic acid

2g(0.001mol) of KOH was dissolved in 20ml ethanol using a magnetic stirrer. In a dry RBF 14g (0.03 mol) of Piperine was taken equipped with a magnetic stirrer and water cooled condenser. 20ml of ethanolic KOH solution was added dropwise to the above solution with stirring. This reaction was refluxed at 60^0C for 24 hours. The progress of the reaction was monitored by TLC. And the mixture was allowed to cool. Half the quantity of ethanol was removed using rota vapour. To the remaining mixture 100ml water was added and stirred well. The solution was filtered and the residue thus obtained was washed with hot water. To the filtrate conc.HCl was added till the product precipitated out. The product was filtered and dried.

Molecular formula: $C_{12}H_{10}O_4$; Molecular weight: 209g/mol; Percentage yield: 47.01%; m.p: 204^0C; R_f: 0.24; IR(cm-1): (C-O) 1253.73, C-H (Alkane) 2922.16, C=C (Aromatic) 1606.70, C=C (Alkenyl) 1680.00, C=O (Acid) 1743.65, O-H (Acid) 3161.33;

Step 2: Synthesis of methyl (2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienoate

(0.04mol) 10g Piperic acid was dissolved in 20ml of ethanol placed in a 2 necked RBF. 2ml of conc.H_2SO_4 was added dropwise with stirring. This was refluxed at 50^0C for 24 hours. Excess of ethanol was removed in rota vapour under vacuum. The liquid remained was subjected to TLC and IR analysis.

Molecular formula: $C_{14}H_{13}O_4$; Molecular weight: 248g/mol; Percentage yield: 64%;

m.p: 89^0C; R_f value: 0.83; IR(cm-1): C-O (1001.06), C-H (Alkane) 2978.09cm^{-1} , (-CH_2) 1477.47, (-CH_3) 1386.82, C=C (Aromatic) 1477.47, C=C (Alkenyl) 1649.14, C=O (Ester) 1734.01;

Step 3: Synthesis of (2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienehydrazide

(0.06mol) 15ml of methyl (2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienoate in ethanol was taken in RBF equipped with magnetic bead on a magnetic stirrer. This setup was completed by fixing a water condenser to the RBF. To the above solution triple the quantity of hydrazine hydrate (0.18 mol) 9ml was added slowly with stirring. This mixture was refluxed for about 18 hours. The resulting solution was cooled to room temperature. Extracted with chloroform in triplicate. The chloroform layer was evaporated at room temperature. The resulting semi solid was characterized by TLC and IR.

Molecular formula: $C_{12}H_{12}N_2O_3$ Molecular weight: 232g/mol Percentage yield: 78.01%; R_f value: 0.73; IR(cm-1): C-O 1010.70, C-H (Alkane) 2922.16, C-H (Aromatic) 3113.11, C=C (Aromatic) 1502.55, C=O (Amide) 1631.78, N-H (Stretch) 3332.99, N-H (Bend) 1539.20;

Step 4: Synthesis of 2-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-5-phenyl-1,3,4-oxadiazole

(0.05mol) 12g of (2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienehydrazide was dissolved in ethanol taken in a clean dry RBF. 0.05 mol of benzoic acid/substituted benzoic acid was dissolved in ethanol and introduced into RBF. (0.1mol) 15.33ml of $POCl_3$ was added slowly with stirring. This reaction mixture was refluxed for 18-20 hours at 90^0C. After cooling to room temperature the reaction mixture was slowly poured over crushed ice and kept overnight. The semi-solid product obtained was subjected to characterization.

4a: 2-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-5-phenyl-1,3,4-oxadiazole

Molecular formula: $C_{19}H_{14}N_2O_3$ Molecular weight: 318g/mol; Percentage yield: 65%; R_f value: 0.65; IR(cm-1): C-O 1068.56, C-H (Alkane) 2949.16, C-H (Aromatic) 3078.39, C=C (Aromatic) 1485.19, C=C (Alkenyl) 1604.77, C=N (Imines) 1651.07, C-O-C (stretch) 1197.79; ^{1}H NMR(delta ppm): Methylene attached to oxygen

atoms (Doublet) 3.6, Alkenic (Quadruplet), Aromatic (Triplet) 6.64-6.68, Aromatic attached to oxadiazole ring (Multiplet) 7.4-8.0.

4b: 4-{5-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-1,3,4-oxadiazol-2-yl}phenol

Molecular formula: $C_{19}H_{13}N_3O_4$; Molecular weight: 334 g/mol; Percentage yield: 74.3%; R_f value: 0.53 ; IR(cm-1): C-O 1080.14, C-H (Alkane) 2924.09, C-H (Aromatic) 3088.03, C=C (Aromatic) 1492.90, C=C (Alkenyl) 1625.99, C=N (Imines) 1660.71, C-O-C (stretch) 1246.02, C-OH (free) 3633.89; ^{1}H NMR(delta ppm): Methylene attached to oxygen atoms (Doublet) 3.5-3.6, Alkenic (Quadruplet) 4.2-5.8, Aromatic (Triplet) 6.5-6.6, Aromatic attached to oxadiazole ring (Multiplet) 4.07-4.12.

4c: 2-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-5-(4-nitrophenyl)-1,3,4-oxadiazole

Molecular formula: $C_{19}H_{13}N_3O_5$; Molecular weight: 363g/mol; Percentage yield: 52%; R_f value: 0.75; IR(cm-1): C-O 1043.49, C-H (Alkane) 2916.37, C-H (Aromatic) 3099.61, C=C (Aromatic) 1469.76, C=C (Alkenyl) 1610.56, C=N (Imines) 1656.85, C-O-C (stretch) 1276.88, C-N (Amines) 1232.51, N-O 1544.98; ^{1}H NMR(delta ppm): Methylene attached to oxygen atoms (Doublet) 3.6, Alkenic (Quadruplet) 4.3-4.8, Aromatic (Triplet) 8.2-8.3, Aromatic attached to oxadiazole ring (Multiplet) 6.60-6.69.

4d: 4-{5-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-1,3,4-oxadiazol-2-yl}aniline

Molecular formula: $C_{19}H_{15}N_3O_3$; Molecular weight: 333g/mol; Percentage yield: 37.5%; R_f value: 0.41; IR(cm-1): C-O 1097.50, C-H (Alkane) 2899.01, C-H (Aromatic) 3103.46, C=C (Aromatic) 1595.13, C=C (Alkenyl) 1651.07, C=N (Imines) 1683.86 C-O-C (stretch) 1235.10 C-N (Amines) 1062.78 N-H (Stretch) 3103.46 N-H (Bend) 1575.84; ^{1}H NMR(delta ppm): Methylene attached to oxygen atoms (Doublet) 3.5-3.6, Alkenic (Quadruplet) 4.008-4.107, Aromatic (Triplet) 6.45-6.50, Aromatic attached to oxadiazole ring (Multiplet) 6.58-6.69.

4e: 2-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-5-(4-bromophenyl)-1,3,4-oxadiazole

Molecular formula: $C_{19}H_{13}N_2O_3Br$; Molecular weight: 369.9g/mol; Percentage yield: 40.3%; R_f value: 0.85; IR(cm-1): C-O 1089.78, C-H (Alkane) 2966.52, C-H (Aromatic) 3022.45, C=C (Aromatic) 1471.69, C=C (Alkenyl) 1606.70, C=N (Imines) 1676.14, C-O-C (stretch) 1139.93, C-N (Amines) 1344.38, C-Br 644.22; ^{1}H NMR(delta ppm): Methylene attached to oxygen atoms (Doublet) 3.8, Alkenic (Quadruplet) 4.09-4.17, Aromatic (Triplet) 7.56-7.55, Aromatic attached to oxadiazole ring (Multiplet) 6.5-6.7.

4f: 2-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-5-(4-chlorophenyl)-1,3,4-oxadiazole

Molecular Formula: $C_{19}H_{13}ClN_2O_3$; Molecular Weight = 352.77112g/mol; Percentage yield: 30.3%; R_f value: 0.73; IR(cm-1): C-O 1125.30, C-H (Alkane) 2989.32, C-H (Aromatic) 3002.15, C=C (Aromatic) 1470.00, C=C (Alkenyl) 1605.70, C=N (Imines) 1680.14, C-O-C (stretch) 1145.78, C-N (Amines) 1303.32, C-Cl 715.12; ^{1}H NMR(delta ppm): Methylene attached to oxygen atoms (Doublet) 3.7, Alkenic (Quadruplet) 4.03-4.15, Aromatic (Triplet) 7.45-7.52, Aromatic attached to oxadiazole ring (Multiplet) 6.61-6.95.

4g: 2-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-5-(4-fluorophenyl)-1,3,4-oxadiazole

Molecular Formula: $C_{19}H_{13}FN_2O_3$; Molecular Weight:336.31g/mol; Percentage yield: 30.3%; Rf value: 0.79; IR(cm-1) C-O 1123.13, C-H (Alkane) 2975.39, C-H (Aromatic) 3006.18, C=C (Aromatic) 1489.19, C=C (Alkenyl) 1610.81, C=N (Imines) 1685.40, C-O-C (stretch) 1158.78, C-N (Amines) 1303.32, C-F 1239.12; ^{1}H NMR(delta ppm): Methylene attached to oxygen atoms (Doublet) 3.4, Alkenic (Quadruplet) 4.10-4.23, Aromatic (Triplet) 7.0-7.31, Aromatic attached to oxadiazole ring (Multiplet) 6.5-6.8.

4h: 2-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-5-(4-methylphenyl)-1,3,4-oxadiazole

Molecular Formula: $C_{20}H_{16}N_2O_3$; Molecular Weight:332.35264g/mol, Percentage yield: 52%; Rf value: 0.89; IR(cm-1) C-O 1112.10, C-H (Alkane) 2990.68, C-H (Aromatic) 3019.02, C=C (Aromatic) 1479.00, C=C (Alkenyl) 1620.30, C=N (Imines) 1698.21, C-O-C (stretch) 1128.08, C-N (Amines) 1309.22, C-H (Bending) 1373.39; -CH_3 (Methyl) 1465.45; ^{1}H NMR(delta ppm): Methylene attached to oxygen atoms (Doublet) 3.2, Alkenic (Quadruplet) 4.02-4.13, Aromatic (Triplet) 7.43-7.51, Aromatic attached to oxadiazole ring (Multiplet) 6.2-6.7.

4i: 2-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-5-(4-methoxyphenyl)-1,3,4-oxadiazole

Molecular Formula: $C_{20}H_{16}N_2O_4$; Molecular Weight: 348.35204 Percentage yield: 48.2%; Rf value: 0.85; IR(cm-1) C-O(stretching) 1125.30, C-H (stretching-methyl group) 2989.32, C-H (Aromatic) 3002.15, C=C (Aromatic) 1470.00, C=C (Alkenyl) 1605.70, C=N (Imines) 1680.14, C-O-C (stretch) 1145.78, C-N (Amines) 1303.32; ^{1}H NMR(delta ppm): Methylene attached to oxygen atoms (Doublet) 3.5, Alkenic (Quadruplet) 4.20-4.34, Aromatic (Triplet) 7.53-7.58, Aromatic attached to oxadiazole ring (Multiplet) 6.4-6.6.

4j: 2-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-5-(4-ethoxyphenyl)-1,3,4-oxadiazole

Molecular Formula: $C_{21}H_{18}N_2O_4$;Molecular Weight: 362.37862 Percentage yield: 54.3% Rf value: 0.65; IR(cm-1) C-O 1128.31, C-H (Alkane) 2991.02, C-H (Aromatic) 3015.05, C=C (Aromatic) 1475.00, C=C (Alkenyl) 1608.70, C=N (Imines) 1680.14, C-O-C (stretch) 1148.78, C-N (Amines) 1309.38; ^{1}H NMR(delta ppm): Methylene attached to oxygen atoms (Doublet) 3.30, Alkenic (Quadruplet) 4.10-4.18, Aromatic (Triplet) 7.51-7.58, Aromatic attached to oxadiazole ring (Multiplet) 6.1-6.4.

The compounds 3, 4a-4j are obtained as semi-solids and hence their melting points could not be determined.

PHARMACOLOGICAL STUDIES

The experiments were conducted as per the guidelines of CPCSEA, Chennai, India (185/CPCSEA) and institutional ethical committee clearance no. DCD/GCP/20/E.C/ADM/2017-18. Permission was accorded only for three of the synthesized compounds. Swiss albino mice of either sex weighing between 15 to 30g were procured from the animal house of the drug testing laboratory, Bengaluru, Karnataka. The animals were kept in well ventilated spacious animal house with 12 ± 1 hr day and night schedule in the animal house of Government college of Pharmacy, Bengaluru, Karnataka. The animals were lodged in large and hygienically maintained spacious cages during the course of the experimental period. The room temperature was maintained at 27 ± 1 ^{0}C. The animals were fed with standard mice feed and water adlibitum.

Preparation of Suspension

The suspensions of synthesized compounds were prepared using 1 % tween 80 as suspending agent in distilled water by triturating both in equal ratio. The prepared suspension was used for acute toxicity studies and pre-clinical studies of antidepressant activity.

Acute toxicity studies

Acute toxicity studies were carried out on Swiss albino mice maintained at normal laboratory condition. The animals were divided into 3 groups containing 6 mice in each group. On the day of the experiment, the animals were fasted overnight. Group I, II, and III, received 2000, 300, 50mg/kg b.w oral dose of synthesized compound suspended in 1 % tween 80. The suspension was found to be safe at 50mg/kg b.w of animals. The dose of 40mg/kg b.w of animals was considered as effective dose. Therefore each compounds at the dose of 40mg/kg b.w of animals was used to evaluate anti-depressant activity. The compounds were triturated in equal ratio along with 1 % tween 80 in the preparation of suspension for 40mg/kg b.w of animals. The same dose was used for the evaluation of anti-depressant activity[12].

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 8s, 2025
https://www.theaspd.com/ijes.php

ANTIDEPRESSANT ACTIVITY

Forced swimming test

Swiss albino mice of either sex weighing 20-35g was selected for studies. This model consist of 5 group, each group consist of 6 mice. The first group received 1 % Tween 80 (Control group), the second group received standard (Piperine 40mg/kg) b.w and the other three groups received respective compounds (40mg/kg) b.w of animals for 2 weeks for the evaluation of anti-depressant activity[13].

Evaluation of Antidepressant activity

Mice were individually forced to swim inside a vertical Plexiglas cylinder (40cm; diameter: 18cm, containing 15cm of water maintained at 25˚C). Mice placed in cylinder for the first time were initially highly active, vigorously swimming in circles, trying to climb the wall or diving to the bottom (Figure 1). After 2-3 min activity begins to subside and to be interspersed with phases of immobility or floating of increasing length. After 5-6 min immobility reaches to a plateau where the mice remain immobile for approximately 80% of the time(Figure 2). The mice were removed and allowed to dry in heated enclosures (32 ˚C) before being returned to their home cages. The evaluation was done on 7^{th} and 14^{th} day from the day of drug dosing. They were placed in cylinder and the total duration of immobility is measured during 6 min test. Floating behavior during 6 min period has been found to be reproducible in different groups of mice. An animal is judged to be immobile whenever it remains floating passively in the water in a slightly hunched but upright position, its nose just above the surface[14].

Statistical evaluation

The swimming duration of the mice in control group (Table 1) and standard group(Table 2) was observed and noted. This was compared with the swimming duration of mice in test groups i.e groups administered with synthesized (Table 3, 4,5) compounds (4a, 4b, 4c) . The treated groups showed lesser swim duration when compared to control and standard group. The difference in the mean values between treated, control and standard groups were compared. (Table 6)

RESULTS AND DISCUSSION

Evaluation of Anti-depressant activity by Forced swimming test

Table 1: Effect of 1 % Tween 80- Control group

Sl. No.	Weight (grams)	Dose (ml)	Duration of immobility on 7^{th} day (sec)	Duration of immobility on 14^{th} day (sec)
1	29	1.16	208	190
2	30	1.20	240	300
3	24	0.96	126	240
4	28	1.12	263	270
5	20	0.80	120	150
6	28	1.12	242	240

Table 2: Effect of Piperine (40mg/kg) –Standard group

Sl. No.	Weight (grams)	Dose (mg)	Duration of immobility on 7^{th} day (sec)	Duration of immobility on 14^{th} day (sec)
1	24	0.96	84	78
2	27	1.08	105	91
3	21	0.84	90	72
4	24	0.96	89	80
5	28	1.12	112	160
6	26	1.04	95	116

Table 3: Effect of compound-4a 40mg/kg : Benzoic acid derivative

Sl. No.	Weight (grams)	Dose (mg)	Duration of immobility on 7th day (sec)	Duration of immobility on 14th day (sec)
1	29	1.16	66	98
2	28	1.12	98	102
3	27	1.08	88	68
4	28	1.12	101	90
5	27	1.08	81	83
6	23	0.92	73	75

Table 4: Effect of Compound-4b 40mg/kg : p-Hydroxy benzoic acid derivative

Sl. No.	Weight (grams)	Dose (mg)	Duration of immobility on 1st Day (sec)	Duration of immobility on 14th day (sec)
1	26	1.04	120	96
2	25	1.0	91	91
3	22	0.88	78	85
4	30	1.20	75	65
5	23	0.92	82	95
6	25	1.0	97	98

Table 5: Effect of Compound-4c 40mg/kg : p-Nitro benzoic acid derivative

Sl. No.	Weight (grams)	Dose (mg)	Duration of immobility on 1st Day (sec)	Duration of immobility on 14th day (sec)
1	28	1.12	100	64
2	32	1.28	78	75
3	26	1.04	84	80
4	30	1.20	75	79
5	28	1.12	81	89
6	23	0.92	65	93

Table 6: Evaluation report of forced swimming test

Group	Treatment	Duration of immobility on 1st day (sec)	Duration of immobility on 14th day (sec)
1	Vehicle(1% Tween 80)	199.83 ± 25.34	231.66 ± 22.12
2	Piperine (40mg/kg)	95.83 ± 4.3	99.5 ± 13.66
3	Compound-4a (40mg/kg)	84.5 ± 5.63	86 ± 5.38
4	Compound-4b (40mg/kg)	90.5 ± 6.78	88.33 ± 5.03
5	Compound-4c (40mg/kg)	80.5 ± 4.72	80 ± 4.21

Values expressed as mean ± SEM (n=6) $p < 0.0001$

Each compound at dose of 40mg/kg b.w of animals was evaluated for anti-depressant activity by forced swimming test model.

Figure 1: Mice during rigorous swimming

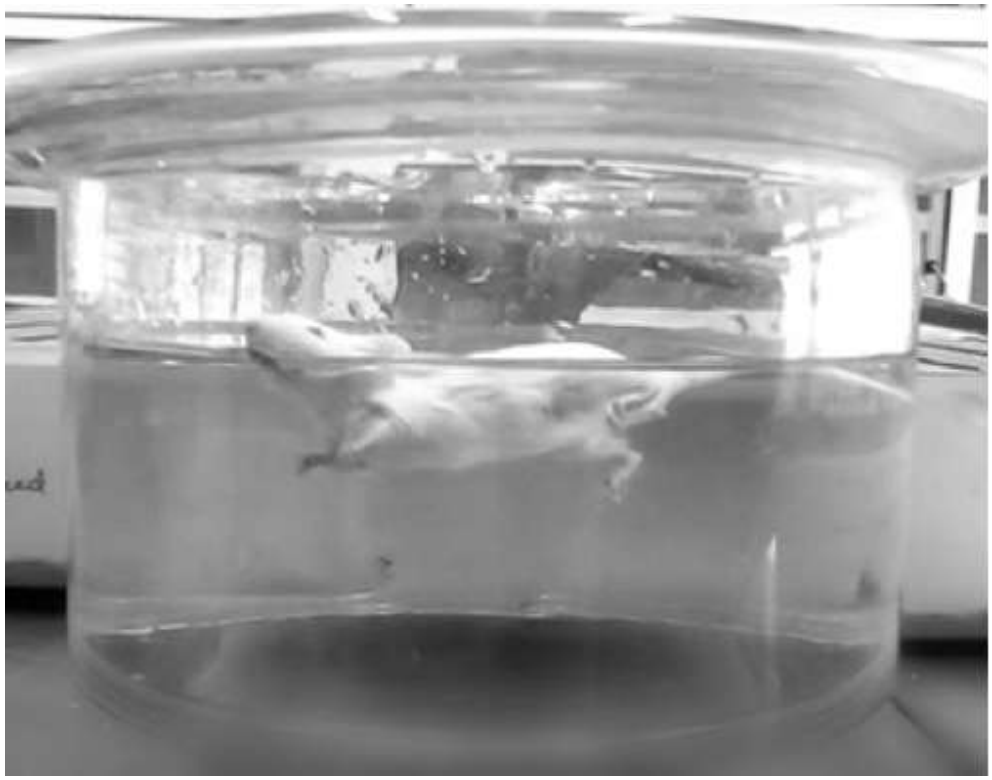
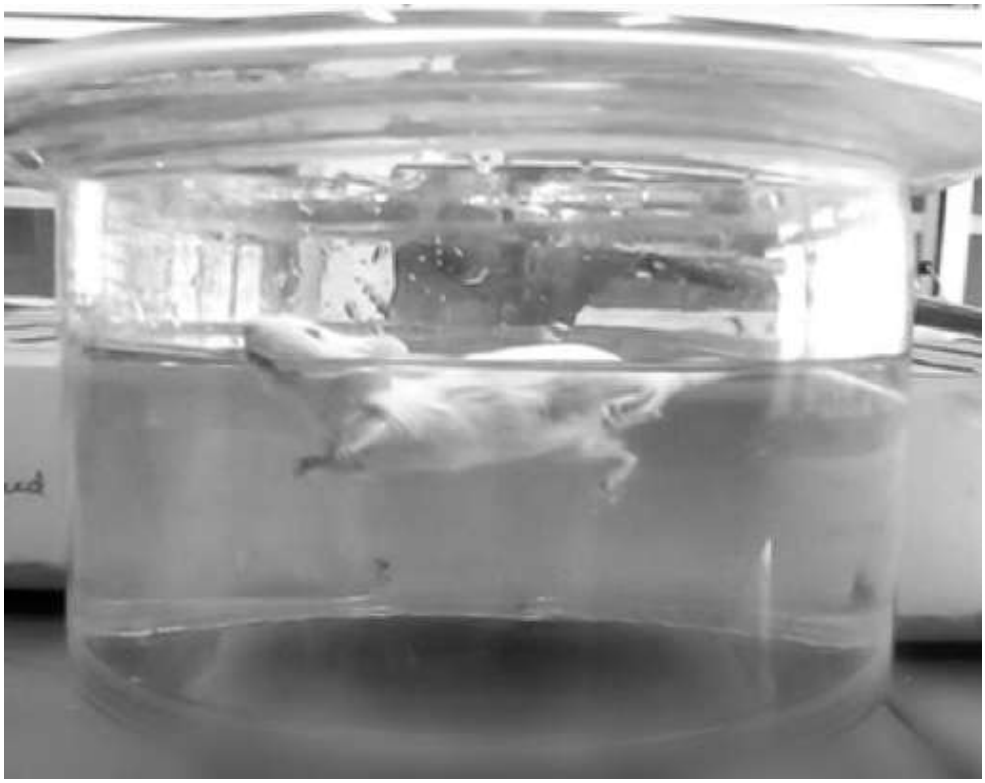


Figure 2: Mice floating after rigorous swimming



International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 8s, 2025
https://www.theaspd.com/ijes.php

Figure 3: Effect of Piperine and synthesized compounds in Forced Swim Test on 7th day

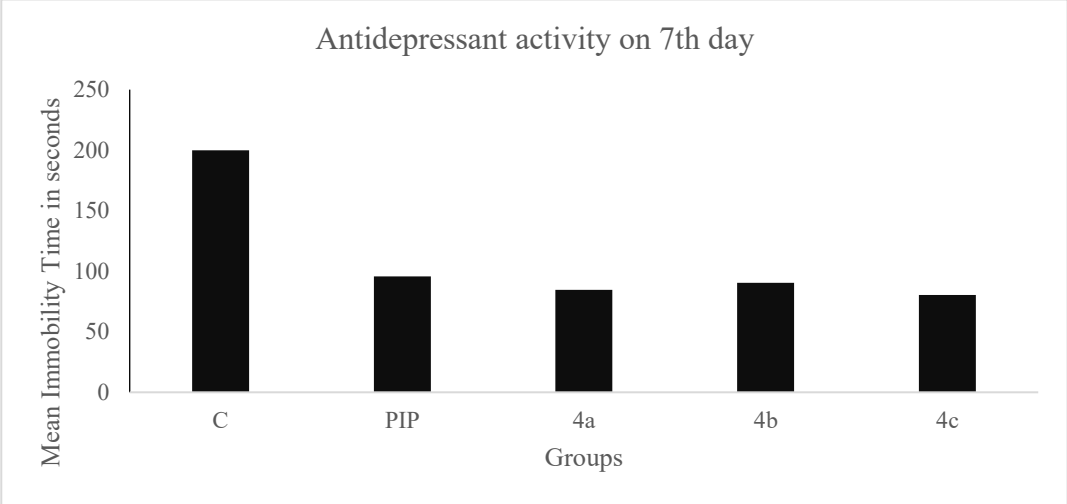
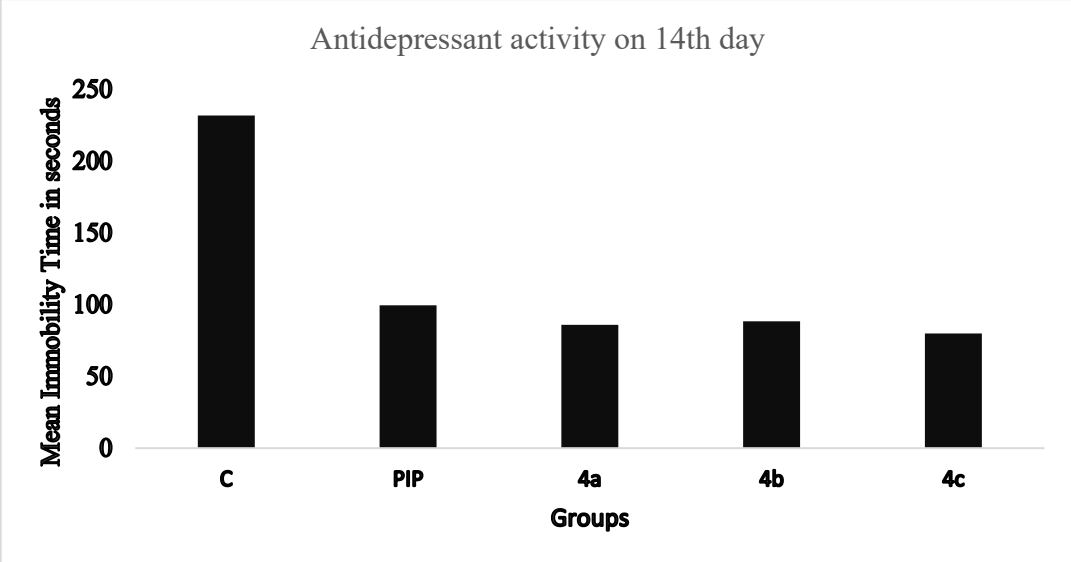


Figure 4: Effect of Piperine and synthesized compounds in Forced Swim Test on 14th day



DISCUSSION

Substituted 2-[(1E,3E)-4-(1,3-benzodioxol-5-yl)buta-1,3-dien-1-yl]-5-phenyl-1,3,4-oxadiazole (4a-4e) were synthesized by a series of reactions from Piperine (synthetic scheme). Piperine was converted to (2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienoic acid (1) in presence of alcoholic KOH. The structure was confirmed by the appearance of a broader peak at 3161 cm^{-1} and 1725 cm^{-1} corresponding to hydroxyl group and carbonyl group of acid confirming the hydrolytic reaction. This acid is converted to its ester i.e. methyl (2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienoate(2). The structure was supported by the presence of peak at 1734 cm^{-1} corresponding to ketonic ester group. The ester was then converted to (2E,4E)-5-(1,3-benzodioxol-5-yl)penta-2,4-dienehydrazide (3) upon reaction with hydrazine hydrate. The peak observed at 3332.99 cm^{-1} confirms the presence of the group N-H indicating the formation of compound 3. The derivatives(4a-4j) of 3 were prepared by its reaction with substituted benzoic acid in the presence of phosphorous oxychloride in ethanol. The appearance of a sharp peak at 1651 cm^{-1} corresponds to C=N and peak at 1068cm^{-1} for C-O in 1, 3, 4-oxadiazole ring confirms its formation. The confirmation of 4a compound was shown by a peak for aromatic C-H at 3078 cm^{-1} and alkene C=C at 1485 cm^{-1}. Further the 4b compound was confirmed by the presence of 3633.89 cm^{-1}. The appearance of peak for C-N 1232.51cm^{-1} and N-O 1544.98 cm^{-1} confirms the 4c compound. 4d

compound was confirmed by the peaks for N-H stretch at 3103.46 cm^{-1} and C-N at 1062 cm^{-1}. The derivative 4e was confirmed by a sharp peak for C-Br at 644.2 cm^{-1}. The compound 4f was confirmed by the peak for C-Cl at 715.12 $cm^{-1.}$ Peak at (C-F) 1239.12 cm^{-1} confirms 4g derivative. The peak at -CH_3 (Methyl) 1465.45 cm^{-1} confirms the compound 4h. The derivative 4i confirms the compound by the peak at C-H (stretching-methyl group) 2989.32 cm^{-1}. Derivative 4j were confirmed by peaks at C-H (Alkane) 2989.32. Further the derivatives formed were confirmed by ^1H NMR. It shows a singlet at δ 3.5-3.8 indicating the presence of 2 protons of Methylene attached to oxygen atoms. A doublet observed at δ 4.0-5.8 confirms the presence of 4 protons in alkene chain. Multiplet peaks were observed at δ 7.4-8.0 indicating the presence of aromatic protons.
Among the derivatives screened, 4c has an electro negative nitro group substitution at para position on the phenyl ring attached to 1,3,4-oxadiazole moiety at 40mg/kg dose demonstrated the anti-depressant activity comparable to that of standard Piperine at 40mg/kg. While it was interesting to note that the anti-depressant activity shown by 4a and 4b compounds were also comparable to standard as these are substituted with lesser electronegative atoms. Further investigation on acute toxicity studies and pharmacological evaluation of remaining compounds needs to be carried out to establish the Structure activity relationship among synthesized derivatives.

ACKNOWLEDGEMENT
It is with immense gratitude and regards we the authors are thankful to the principal, Government college of Pharmacy, Bengaluru and KLE college of Pharmacy Hubballi, for providing the laboratory facilities to carry out the present research work. The authors are also thankful to Director, NMR studies, IISc, Bengaluru for providing spectral facilities.

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