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A facile synthesis of 8-chloro-11-(4-fluorophenyl)-6, 11-dihydro-5*H-benzo* [5, 6] cyclohepta [1, 2-b] pyridin-11-ol

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ABSTRACT

This study aimed at evaluating the Sedative activity of structurally diverse derivatives of lead compound 8-chloro-11-(4-fluorophenyl)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-ol; synthesized via straightforward and efficient synthetic process. The structures of the compounds were characterized by spectral data (IR and 1H-NMR). The work was extended to study the potential role of the novel derivatives as anti-Parkinson agents.

Keywords: Antidepressant, sedative, anti-Parkinson.

INTRODUCTION

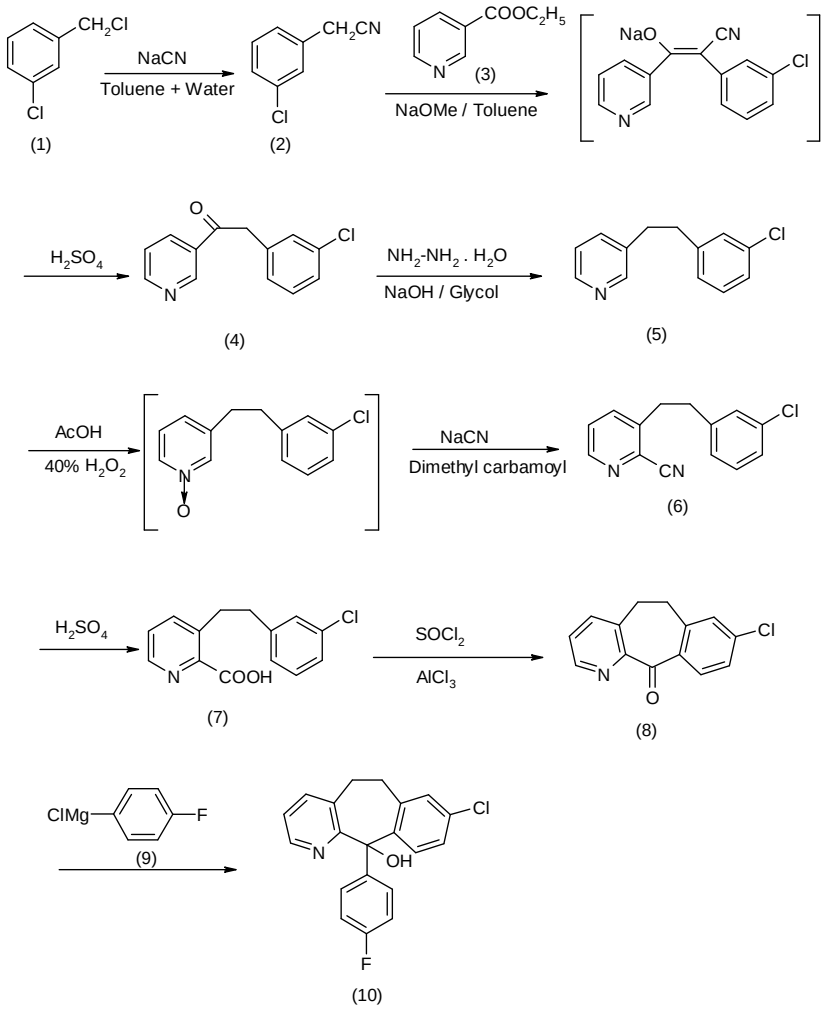
The heterocyclic antidepressants are the mainstay of antidepressant treatment and the development of new synthetic heterocyclic compounds as antidepressant, sedative, or analgesic agents has progressed considerably during the past decade. [1-3] In the scope of a research program aimed at the development of new alternatives to treat neurological disorders [4-6] in the present study, evaluationof systemic antidepressant and sedative activity of the newly synthesized analogs of lead compound 8-chloro-11-(4-fluorophenyl)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-ol; was investigated in comparison with Imipramine. The present paper describes the synthesis of structurally diverse analogs of lead compound and evaluation of antidepressant and sedative properties, in terms of reserpine antagonism, of these compounds.While screening derivatives for antidepressant activity, it was found that certain derivatives antagonized reserpineinduced catalepsy in mice, indicating potential anti-Parkinson activity. The anti-Parkinson properties of these derivatives, as determined by reversal of reserpineinduced catalepsy [7] in rats, are also described. All compounds showed significant antidepressant,sedative and anti-Parkinson activities at two doses (50 or 100 mg/kg). The compounds namely 10, 10a, and 10b showed even better antidepressant, sedative and anti-Parkinson activities which exceed that of the parent reference. Based on the results a definite structure-activity relationship (ASR) is established and discussed.

MATERIALS AND METHODS

Chemistry: Our target compounds are structurally diverse analogs of lead compound 8-chloro-11-(4-fluorophenyl)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ol (10a-10e) as in Table 1, were prepared using the process described in Scheme 1.Melting points (M. P.) were eterminedusing a Thomas Hoover capillary apparatus and are uncorrected (Table 2).Infrared spectral data was acquired using Perkin Elmer FTIR (Table 2). A Bruker, 300 MHz spectrophotometer was used to acquire 1H-NMR spectra; chloroform-d and DMSO-d6 were used as solvents (Table

3). All chemicals and laboratory grade (LR) reagents were obtained from Rankem (India) and were used without further purification.

Scheme 1: Synthetic route for the preparation of Lead Compound (10) and its derivatives (10a-10e)



Detailed synthetic process

Standard procedure for the preparation of 3-Chlorobenzylcyanide. (2)

3-Chlorobenzyl chloride (1) 100g is reacted with sodium cyanide (39 g) in a biphasic mixture of water (300 ml) and toluene (100 ml) in presence of tetrabutyl ammonium bromide under refluxing. Reaction mass is washed thoroughly with water to remove any sodium cyanide contents. Oily product obtained after recovery of toluene.

Standard procedure for the preparation of 3-pyridyl-3-chlorobenzyl ketone. (4)

3-chlorobenzyl cyanide (100g) as oil is added slowly to a mixture of sodium methoxide (58g) and ethyl nicotinate (3) 110g in toluene (100ml) at 65-70^{o}C . The reaction mixture is stirred at the same temperature for 5 hrs. Reaction mass is cooled to room temperature and product extracted in water. Aqueous solution of product is preceded as such for the preparation of 3-pyridyl-3-chlorobenzyl ketone. Aqueous solution of α-cyano-β-hydroxy-β-(3-pyridyl)-3-chlorostyrene sodium is cooled to 0-5^{o}C and sulfuric acid is slowly added at < 60^{o}C. Reaction mass is heated to 120-125 ^{o}C and stirring is continued for reaction completion. Reaction mass is quenched in water followed by basification to get crystallization mass filtered and washed with water to obtained solid with melting point 66^{o}C[8]

Standard procedure for preparation of 3-(3- Chlorophenethyl) pyridine. (5)
3-pyridyl-3-chlorobenzyl ketone is reacted with hydrazine hydrate (45g) and sodium hydroxide (10.8g) in ethylene glycol at 140-145 ^{o}C. Reaction mass after cooling and dilution with water is extracted with dichloromethane. Dichloromethane layer is washed with water and distilled to give title compound as oil

Standard procedure for preparation of 2-Cyano-3-(3- Chlorophenethyl) pyridine. (6)
3-(3- Chlorophenethyl) pyridine (30g) is heated with acetic acid (25g) and 40% hydrogen peroxide (40g) at 65-70 ^{o}C for 15-18 hrs.The reaction mixture is basified with caustic solution to pH 8-10 . 3-(3- Chlorophenethyl) pyridine-N-oxide (30g) obtained is reacted with N, N-dimethyl carbamoyl (29.8g) in Acetonitrile (60g) at 140-145 ^{o}C for 3 hrs followed by reaction with aqueous sodium cyanide (9.5g in 60 ml water) at -5 to 0^{o}C for 5 hrs. Caustic solution (6g in 90ml water) is added to the reaction mixture and stirred for 2 hrs. Organic layer is separated and evaporated to get crude 2-Cyano-3-(3- Chlorophenethyl) pyridine followed by purification in methanol to get title compound with yield of 74% with melting point 72^{o}C [9]

Standard procedure for preparation of 3-(3- Chlorophenethyl) picolinic acid. (7)
2-Cyano-3-(3- Chlorophenethyl) pyridine (20.8g) is heated with conc.sulfuric acid (31g) and water (17 ml) at 120-122 ^{o}C for 12 hrs.Reaction mixture is cooled to 90 ^{o}C and poured to cold water(165ml) . Adjust the pH of reaction mixture to 3 to 3.5 using 20% sodium hydroxide solution to obtain title compound with a yield of 21 g (94 %).

Standard procedure for preparation of 8-chloro-5H-benzo [5, 6] cyclohepta [1, 2-b] pyridine-11 (6H)-one. (8)
75 g of 3-(3- Chlorophenethyl) picolinic acid hydrochloride are suspended in 300ml of thionylchloride.The reaction mass is stirred at 40-50oC.After evaporation of the excess of thionylchloride 79.5g of carboxylic acid chloride are obtained. To the carboxylic acid chloride added 1,2-dichloromethane and 70g of AlCl3 and the mixture is stirred at 0-5oC.After acidification with diluted HCl the aqueous phase is separated and re-basified with 30% NaOH.The product is extracted with toluene and re-crystallised from diisopropyl ether gives 39.5g (65%) of a pale yellow solid with melting point 92^{o}C.

Standard procedure for preparation of 8-chloro-11-(4-fluorophenyl)-6, 11-dihydro-5*H*-benzo [5, 6] cyclohepta [1, 2-b] pyridin-11-ol and its analogs (10)
To a cool solution of 8-chloro-5H-benzo [5, 6] cyclohepta [1, 2-b] pyridine-11 (6H)-one in THF was added 1.2 M solution of 4-fluoro phenyl magnesium chloride (9). The reaction temperature increase gradually to ambient temperature. Mass is stirred at ambient temperature for 30 minutes and then reaction was quenched with NH4Cl solution. The reaction mixture was extracted with ethyl acetate and washed once with brine. The solvent was removed under vacuum to give a crude product. The crude product was recrystallized from ethylacetate and diisopropyl ether (80:20) to give the compound of 8-chloro-11(4-fluorophenyl)-6, 11-dihydro-5H-benzo [5, 6] cyclohepta [1, 2-b] pyridine-11-ol with melting point 141 - 143°C

Pharmacology
For Testing Sedative and Antidepressant activity
Animals
Swiss albino mice of sex, weighing 20–25 g (body weight), aged 6 to 8 weeks, were used for antidepressant and sedative tests. The anti-Parkinson test of reversal of reserpine-induced catalepsy was carried out using male Wistar rats weighing 148-250 g. Animals were maintaine under a 12/ 12 h light/dark cycle at 20- 28^{0}C and fed with standard laboratory diet and water ad libitum. Equal groups of six mice per group were used in all experiments. All animal procedures were performed after approval from the “Ethics Committee” and in accordance with the recommendations for the proper care and use of laboratory animals.

Preparation of test samples:
All tested compounds and Imipramine in 50 or 100 mg/kg concentration were dissolved using a few drops of Tween 80 and further dilutions were done using saline to get the necessary doses. [10, 11] The vehicle solution (Tween 80 in saline) was used as negative control, and Imipramine (15 mg/kg) was used as a reference drug in the antidepressant screening. All tested samples were given intraperitoneally (i.p.). The control-group animals received the same experimental handling as those of the test groups except for the drug treatment.

Screening for antidepressant activity:
The effects of the tested compounds at two doses (50 or 100 mg/kg,administered i.p. in Swiss albino mice (of either sex) as antidepressants were studied using Porsolt's forcedswimming test in comparison using the tricyclic antidepressant drug, imipramine (15 mg/kg, i.p.) as a reference drug. Porsolt's forced-swimming test each mouse was placed individually in a glass cylinder (diameter 12 cm, height 24 cm) filled with water at a height of 12 cm; the water temperature was maintained at 22–380C. The animal was forced to swim and after being in the water for 5 min, they were removed and allowed to dry for 15 min in a heated container before being returned to their home cages. They were placed in the cylinders 24 h later, and the total duration of immobility was measured during a five-minute test. An animal was judged to be immobile whenever it remained passively floating in the water in a slightly hunched but upright position, its head just above the surface. The floating time, which was the measure of despair11 was recorded 60 min after treatment with each test compound, saline, or imipramine (15 mg/kg, i.p.). The results are recorded in Table 4.

Screening for sedative effect:
The effects of the tested compounds at two doses (50 or 100 mg/kg, i.p.) as sedative agents were studied compared with the salinetreated group of mice. Spontaneous locomotor activity and exploratory movements in mice was measured in the commercially available motor-activity apparatus. The investigated compounds were injected i.p. at a dose 50 or 100 mg/kg. Thirty minutes after the injection, mice were placed in the activity monitor, in which the activity was monitored for 30 min. The results are recorded in Table 5.

Statistical Analyses:
Data are expressed as mean ± S.E. Differences between vehicle control and treatment groups were tested using one-way ANOVA followed by multiple comparisons by the Duncan's multiple comparison test. A probability value less than 0.05 was considered statistically significant.

Screening of Anti-Parkinson activity (Reserpine- Induced Catalepsy)
The rats (female Wistar), weighing 180-200 g, were injected subcutaneously with 5 mg/kg of reserpine Solution 15 on the evening prior to the test. Later (17 hr) they were tested for catalepsy using the following methods. 8

I) One hind leg was placed on a 3-cm high cork.
II) One hind leg was placed on a 9-cm high cork.
III) Rats were placed with their feet on parallel bars.
IV) Rats were placed with their feet on a vertical grid (318 in. mesh).

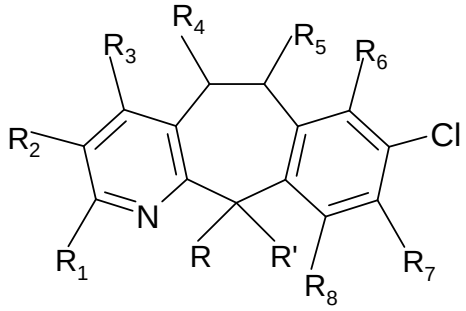
The rats were considered cataleptic if no movement occurred within about 20 sec and each rat was given a score of 2 on each test. If a rat moved immediately after being placed on an object, as mentioned above, but then remained immobile, a score of 1 was given. Rats showing a high degree of catalepsy (score 7 or 8) were split into groups of four and each group dosed orally with the compounds, using a dose volume of 1 ml per rat. The rats were retested for catalepsy at intervals over the following 5.5 hr. The degree of reversal of the catalepsy induced by the compounds was assessed from the time course of the catalepsy over the 5.5 hr period. Rasagiline drug was also tested in a similar manner for comparative purposes. The results are recorded in Table 6.

RESULTS AND DISCUSSION

Chemistry
As stated earlier the target compounds are structurally diverse derivatives of lead compound 8-chloro-11-(4-fluorophenyl)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ol (6a-6k) as listed in Table 1, were prepared using the process described in Scheme 1. The structures of the compounds were characterized by spectral data (MP, IR and 1H-NMR) and results are presented in Table 2 and 3.

Table 1: Structurally diverse novel analogs of lead Molecule synthesized for study

Lead Compound "10"



Analogs of Lead Compound with respective structural modifications

Compounds	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R'	R
10	H	H	H	H	H	H	H	H	OH	C_6H_4F
10a	H	H	H	H	H	H	H	H	OH	C_7H_7O
10b	H	H	H	H	H	H	H	H	OH	C_7H_7
10c	H	H	H	H	H	H	H	H	OH	C_3H_7
10d	H	H	H	H	H	H	H	H	OH	C_4H_9
10e	H	H	H	H	H	H	H	H	OH	$C_8H_{10}N$

Table 2: Melting Range and IR spectral data of Synthesized Compound (10-10e)

Product	Melting Point °C	IR
10	141 - 143°C	3256.87 cm^{-1} (O-H stretching), 3067.92 cm^{-1} (aromatic C-H stretching), 2949.94 cm^{-1} (aliphatic C-H stretching), 1597.74-1455.70 cm^{-1} (aromatic region), 1221.65 cm^{-1} (C-F stretching), 839.61 cm^{-1} (C-Cl stretching)
10a	162-165°C	3342.05 cm^{-1} (O-H stretching), 2965.21 cm^{-1} (aromatic C-H stretching), 2933.29 cm^{-1} (aliphatic C-H stretching), 1578.47-1458.70 cm^{-1} (aromatic region), 1134.05 cm^{-1} (C-O stretching), 838.20 cm^{-1} (C-Cl stretching)
10b	135-139°C	3345.76 cm^{-1} (O-H stretching), 2965.05 cm^{-1} (aromatic C-H stretching), 2933.12 cm^{-1} (aliphatic C-H stretching), 1578.46-1453.22 cm^{-1} (aromatic region), 1364.06 cm^{-1} (C-N stretching), 838.18 cm^{-1} (C-Cl stretching)
10c	146-148°C	3256.87 cm^{-1} (O-H stretching), 2979.69 cm^{-1} (aromatic C-H stretching), 2868.71 cm^{-1} (aliphatic C-H stretching), 1557.46-1450.95 cm^{-1} (aromatic region), 1137.70 cm^{-1} (C-N stretching), 856.61 cm^{-1} (C-Cl stretching)
10d	126-128°C	3307.90 cm^{-1} (O-H stretching), 3078.33 cm^{-1} (aromatic C-H stretching), 2957.22 cm^{-1} (aliphatic C-H stretching), 1542.16-1450.19 cm^{-1} (aromatic region), 849.06 cm^{-1} (C-Cl stretching)
10e	115-117°C	3320 cm^{-1} (O-H stretching), 3068 cm^{-1} (aromatic C-H stretching), 2945 cm^{-1} (aliphatic C-H stretching), 1597-1455cm^{-1} (aromatic region), 837 cm^{-1} (C-Cl stretching)

Table 3: 1H NMR spectral data of Synthesized Compound (10-10e)

Product	^{1}H NMR
10	2.9(m,4H,-CH2-CH2-), 3.45 (s, 1H,–OH), 6.7 (t,1H,-ArH), 7.1-7.3 (m,4H,-ArH) 7.6 (d-d, 2H,-ArH), 7.8 (s,1H,-ArH), 8.1(d,1H,-ArH) and 8.4 (d,1H,- ArH) .
10a	2.8 (m,4H,-CH2-CH2-), 3.6 (s,1H,–OH),3.9 (s,3H,–CH_3 from anisole), 6.7-7.0 (m,3H,-ArH), 7.2 (d,4H,-ArH), 7.7 (s,1H,-ArH), 7.8(d,1H,- ArH) 8.6(d,1H,- ArH).
10b	2.4(s,3H, methyl substitution on phenyl),2.8 (m,4H,-CH2-CH2-), 3.9 (s,1H,–OH), 6.6 (m,1H,-ArH), 7.1(d,2H,- ArH) 7.4(d,4H,-ArH), 7.7 (s,1H,-ArH), 7.9(d,1H,- ArH), 8.8(d,1H,- ArH)
10c	2.8 (m,4H,-CH2-CH2-),3.3(s,6H, methyl attached to nitrogen), 3.7 (s,1H,–OH), 6.5 (d,2H,-ArH), 6.9(m,1H,- ArH), 7.2(d,2H,- ArH), 7.5(d,2H,- ArH), 7.7 (s,1H,-ArH), 7.9(d,1H,- ArH), 8.9(d,1H,- ArH)
10d	0.9 (d,6H,-CH3-),1.7(m,1H,-CH),2.1(d,2H,-CH2), 2.9 (m,4H,-CH2-CH2-),3.7 (s,1H,–OH), 6.8 (m,1H,-ArH), 7.2(s,2H,- ArH), 7.6(s,1H,- ArH), 7.9(d,1H,- ArH), 8.6(d,1H,- ArH)
10e	0.9 (d,6H,-CH3-),2.6(m,1H,-CH), 3.0 (m,4H,-CH2-CH2-),3.5 (s,1H,–OH), 6.8 (m,1H,-ArH), 7.2(s,2H,- ArH), 7.6(s,1H,- ArH), 7.9(d,1H,- ArH), 8.8(d,1H,- ArH)

PHARMACOLOGY

The antidepressant and sedative activity of the novel synthesized analogs (10a-10e) were investigated individually. Anti-Parkinson activity of some of the relevant interesting compounds was assessed using the reversal of reserpine-induced catalepsy.

Results of Antidepressant Activity

The effects of the tested compounds as antidepressants were studied using Porsolt's forced-swimming test in comparison with an antidepressant drug, imipramine (15 mg/kg.) as a reference drug. 60 min after the administration, all tested compounds displayed a significant antidepressant effect compared with the control group (Table 6).The lead compound 10 at 50 mg/kg and derivative 10a at 50 mg/kg and at 100 mg/kg are equipotent to Imipramine (15 mg/kg). Derivatives 10b and 10c at 50 and at 100 mg/kg respectively were more potent then rest of test series (10d-10e) with effect comparable to Imipramine (15 mg/kg).

Table 4: Antidepressant Activity Test Results

Treatment	Dose (mg/Kg)	Duration of immobility ±SEM (s)
Saline		295.35 ± 1.21
Imipramine	15	221.00 ± 24.0
10	50	224.05 ± 12.2
	100	220.12 ± 6.8
10a	50	227.15 ± 11.0
	100	225.16 ± 9.5
10b	50	229.05 ± 33.7
	100	239.17 ± 6.4
10c	50	230.05 ± 8.6
	100	227.40 ± 18.3
10d	50	240.08 ± 7.2
	100	239.20 ± 10.5
10e	50	248.40 ± 12.6
	100	235.33 ± 8.4

Table 5: Sedative Activity Test Results

Treatment	Dose (mg/Kg)	Munber of movements ± SEM during 30 min	% inhibition of locomotor activity
Saline		495.1 ± 0.51	
Imipramine	50	205.3 ± 9.2	56.4
	100	188.5 ± 18.2	60.1
10	50	198.3 ± 11.1	60.3
	100	165.5 ± 7.5	69.3
10°	50	185.2 ± 20.1	60.0
	100	175.35 ± 7.7	62.3
10b	50	175.4 ± 19.5	63.3
	100	169.3 ± 13.3	65.7
10c	50	195.5 ± 17.7	57.6
	100	180.8 ± 18.8	60.0
10d	50	295.7 ± 16.3	46.5
	100	290.4 ± 17.6	48.7
10e	50	281.1 ± 11.1	49.9
	100	265.8 ± 20.6	50.5

Table 6: Anti-parkinson Activity Test Results

Reversal of Reserpine Catalepsy Test[a]		
Compound No.	**20 mg/Kg po**	**40 mg/Kg po**
Rasagiline	++	+++
10	++	++
10°	+	+++
10b	+	++
10c	±	+
10d	±	±
10e	*0*	±

Results of Sedative activity

The effects of the tested compounds at two doses as sedative agents were studied compared with the saline-treated group of mice (Table 5). All tested compounds produced a significant decrease in locomotor activity of mice during a 30-min observation period. The sedative effect of all the tested compounds was dose dependent. The potent effect was produced by Lead compound 10 at 100 mg/kg followed by 10a and 10b at both dose levels. Lead compound 10 at 50 mg/kg dose level is equipotent to Imipramine (100 mg/kg). Compound 10c (100 mg/kg) displayed a significant

sedative effect compared with Imipramine (100 mg/kg). Compound 10b has displayed most potent effect in series of test compounds and higher then Imipramine.

Results of Anti-Parkinson Activity

Potential anti-Parkinson activity of some of the relevant interesting compounds was assessed using the reversal of reserpine-induced catalepsy (Table 6). The results of the reversal of reserpine-induced catalepsy in rats show that lead compound and its some of the derivatives possess activity which is equivalent to or better than Rasagiline. In most of the cases, significant activity was only observed in lead compound 10 and when flurobenzene is replaced with methyl benzene (10b). When benzene ring was substituted in the 4- position by isopropyl group (10e) compounds showed marginal potency. Compound 10a was found to be most active. Compound 10c and 10d showed marked effect.

Structure-activity relationship

Analysis of the structure-activity relationship indicates that the activity of the tested compounds seems to be linked to the presence of functional group substitutions on phenyl ring and incorporation of various groups like anisol, tolyl, N,N-dimethylaniline, isobutyl and isopropyl in the structural framework of lead compound. The compound 6a with anisol incorporation and compound 10b with tolyl replacement are the most effective than the compounds with isopropyl substitution. Also, the results were confirmed with sedative and anti-Parkinson activity tests of compounds 10a and 10b as they exhibited promising results. Directed by the structure of the tested compounds it is likely that these compounds have a multiple mechanism-of-action for their antidepressant, sedative and anti-Parkinson activities. The results verified the importance of the presence of functional group substitution on phenyl ring. Further studies should be made to establish the mechanism-of-action with the possibility to formulate a potent antidepressant and sedative prescription

CONCLUSION

We investigated the importance of functional group substitutions, in the structural framework of the compounds for their antidepressant, sedative and anti-Parkinson activities. All compounds showed significant antidepressant, sedative and anti-Parkinson activities at two doses (50 or 100 mg/kg). The compounds “10”, “10a”, and “10b” showed even better antidepressant, sedative and anti-Parkinson activities which exceed that of the parent reference. Finally, the encouraging result of the antidepressant, sedative and anti-Parkinson activities 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, sedative and anti-Parkinson prescription.

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