Research Article

SUBSTITUTED 3, 4-DIHYDRO-1*H*-QUINOLIN-2-ONE DERIVATIVES AS POTENTIAL ANTIDEPRESSANT, SEDATIVE AND ANTI-PARKINSON AGENTS

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ABSTRACT

This study aimed at evaluating the Antidepressant and Sedative activity of structurally diverse derivatives of lead compound 7-[4-{4-(2, 3-dichlorophenyl) piperazine-1-yl} butoxy]-3, 4-dihydro-1*H*-quinolin-2-one; 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. All compounds showed significant antidepressant activity in the forced-swimming test at two doses (50 or 100 mg/kg). Also, all tested compounds (at 50 or 100 mg/kg) produced a significant decrease in locomotor activity of mice during a 30 min observation period. The most potent antidepressant and sedative effect was produced by compound 6, 6b followed by 6j. The anti-Parkinson activity of these derivatives in reversing the reserpine-induced catalepsy in rats was evaluated and compared with Rasagiline drug. The test compounds showed promising effects with compound 6b and 6j being most potent.

Keywords: antidepressant, sedative, locomotor, anti-Parkinson, reserpine.

INTRODUCTION

Heterocyclic antidepressant drugs have greatly improved the outcome of depression. However, a considerable proportion of patients show only partial or no response, regardless of the treatment received[1]. 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.[2-4] In the scope of a research program aimed at the development of new alternatives to treat neurological disorders[5-7] in the present study, evaluation of systemic antidepressant and sedative activity of the newly synthesized analogs of lead compound 7-[4-{4-(2, 3-dichlorophenyl) piperazine-1-yl}butoxy]-3,4-dihydro-1*H*-quinolin-2-one; 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 reserpine-induced catalepsy in mice, indicating potential anti-Parkinson activity. The anti-Parkinson properties of these derivatives, as determined by reversal of reserpine-induced catalepsy[8] 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 6, 6b, and 6j 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. The most promising candidates were identified and recommended for further studies.

MATERIALS AND METHODS

Chemistry: Our target compounds are structurally diverse analogs of lead compound 7-[4-{4-(2, 3-dichlorophenyl) piperazine-1-yl}butoxy]-3,4-dihydro-1H-quinolin-2-one (6a-6k) as in Table 1, were prepared using the process described in Scheme 1.

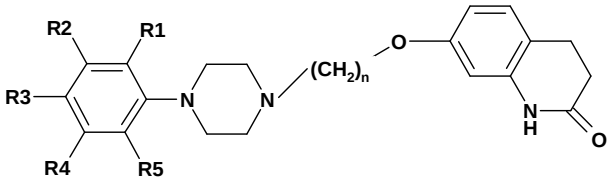
Melting points (M. P.) were determined using a Thomas Hoover capillary apparatus and are uncorrected (Table 2). Infrared spectral data was acquired using Perkin Elmer FTIR (Table 2). A Bruker, 300 MHz spectrophotometer was used to acquire 1H-NMR spectra; chloroform-d and DMSO-d6 were used as solvents (Table 3). All chemicals and laboratory grade (LR) reagents were obtained from Rankem (India) and were used without further purification.

Detailed synthetic process

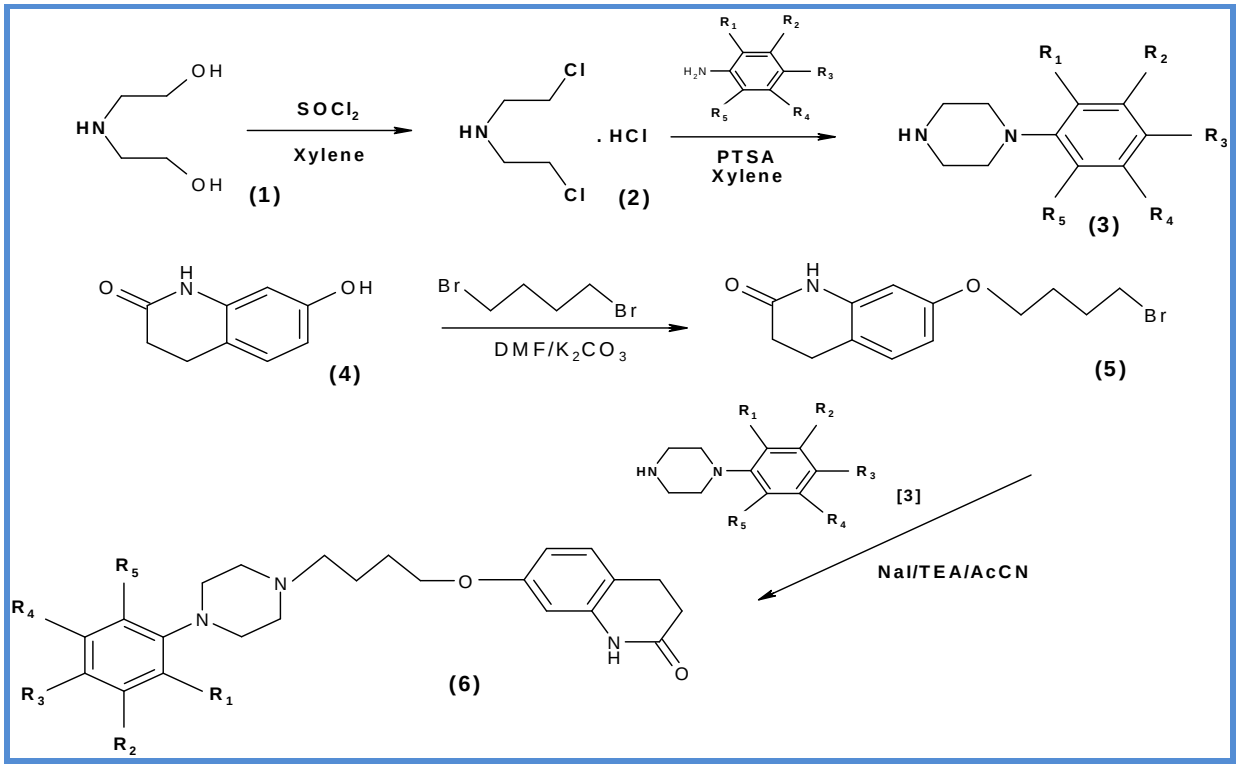
Standard procedure for the preparation of bis-(2-chloroethylamine) hydrochloride (2)

To the mixture of diethanolamine (1) (100 gm, 0.95 mol), *p*-toluenesulphonic acid (PTSA) (3 gm, 3%) and Chloroform (250 mL) was added thionyl chloride (104.7 gm, 1.42 mol) at 25-30^{o}C under stirring. After complete addition, the reaction mass is heated to 75-80^{o}C when a mild reflux was observed. The reaction continued for 2 hours to ensure completion and cooled to 25^{o}C when product crystallizes out of solution. The white crystalline product is isolated by filtration and dried under vacuum at 30^{o}C. Product Yield: 94.10 gm, 94.1 %.

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

Lead Compound "6"						
						
Compounds	**R^1**	**R^2**	**R^3**	**R^4**	**R^5**	**n**
6	Cl	Cl	H	H	H	4
6a	Cl	Cl	H	H	H	2
6b	Cl	Cl	H	H	H	3
6c	H	H	$CH(CH_3)_2$	H	H	1
6d	H	H	$CH(CH_3)_2$	H	H	2
6e	H	H	$CH(CH_3)_2$	H	H	3
6f	1-naphthyl					1
6g	1-naphthyl					2
6h	2-naphthyl					1
6i	2-naphthyl					2
6j	6H-indolo[2,3-B]quinoxaline: indoloquinoxiline					2
6k	6H-indolo[2,3-B]quinoxaline: indoloquinoxiline					1

Scheme 1: Synthetic route for the preparation of Lead Compound (6) and its derivatives (6a-6k)



Standard procedure for the preparation of 1-(2, 3-dichlorophenyl)-piperazine hydrochloride (3) and its derivatives

The mixture of bis-(2-chloroethylamine) hydrochloride (2) (100 gm, 0.56 mol), 2, 3-dichloro-aniline (98 gm, 0.61 mol), *p*-toluenesulphonic acid (PTSA) (3 gm, 3%) in xylene (300 mL) was heated to reflux (140-145^{o}C, 27 h.) and progress of the reaction was monitored by TLC using chloroform: methanol (8:2) solvent system. On completion the reaction mass was cooled to 30^{o}C and further chilled to 0-5^{o}C when product crystallizes as off-white crystals. The product is isolated by filtration and washed with chilled xylene (5^{o}C, 75 mL) followed by acetone (5^{o}C, 75 mL) for removal of aniline traces before drying in oven under reduced pressure (100 mm/Hg) at 40^{o}C for 8 hours. Product Yield: 122 gm, 82.0 %

Standard procedure for preparation of 7-(4-bromobutoxy)-2(1*H*)-quinolinone (5) and its derivatives

A mixture of 7-hydroxy-2(1*H*)-quinolinone (4) (163 g, 1.0 mol), 1, 4-dibromobutane (648 g, 3.0 mol), and K_2CO_3 (138 g, 1.0 mol) in DMF (2500 mL) were stirred for 4 h at 60 °C and then diluted with water (2500 mL). An organic layer was extracted with ethyl acetate (AcOEt), and the extract was washed, dried, and evaporated to dryness in vacuum. Recrystallization from EtOH gave the product as a white powder.

Product Yield: 190 gm, 64%

Standard procedure for preparation of 7-[4-{4-(2, 3-dichlorophenyl) piperazine-1-yl} butoxy]-3, 4-dihydro-1H-quinolin-2-one and its analogs [6a-6k]

A mixture of 7-(4-Bromobutoxy)-2(1*H*)-quinolinone (5) (297 g, 1.0 mol), NaI (234 g, 1.56 mol), triethylamine (173.7 g, 1.72 mol) and 1-(2, 3-dichlorophenyl)-piperazine hydrochloride (3) (381 g, 1.43 mol), in acetonitrile (750 mL) was refluxed for 4 h with stirring. Progress of reaction was monitored by TLC; using benzene: ethyl acetate (7:3) solvent system. The reaction mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was extracted with CHCl3, and the extract was washed, dried, and evaporated in vacuo. Recrystallization from MeOH-CHCl3 gave the desired product as colorless needles.

Product Yield: 407.0 g, 84 %

PHARMACOLOGY

For Testing Sedative and Antidepressant activity

Animals

Swiss albino mice of either 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 maintained 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.[9,10] 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 forced-swimming 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 22–38^{0}C. 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 despair[11] 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 saline-treated 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 solution15 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 7-[4-{4-(2, 3-dichlorophenyl) piperazine-1-yl}butoxy]-3,4-dihydro-1H-quinolin-2-one (6a-6k) as listed in Table 1, were prepared using the process described in Scheme 1. To examine structure-activity relationships (SAR) of structural modifications on the nucleus portion in the lead compound, structurally diverse analogs of intermediate; 1-(2, 3-dichlorophenyl)-piperazine hydrochloride were synthesized and reacted with various analogs of intermediate; 7-(4-bromobutoxy)-2(1*H*)-quinolinone and indoloquinoxiline to achieve novel derivatives of the lead compound desired for the study. 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 2: Melting Range and IR spectral data of Synthesized Compound (6a-6k)

Product	M. P. ^{0}C	IR (cm^{-1})
"6"	139-139.5	3368 (N-H stretching), 3109 (aromatic C-H stretching), 2944 (aliphatic C-H stretching), 1677 (C=O stretching), 1594-1445 (aromatic region), 1174 (C-N stretching), 779 (C-Cl stretching).
6a	140-143	3193 (N-H stretching), 3124 (aromatic C-H stretching), 2947 (aliphatic C-H stretching), 1681 (C=O stretching), 1596-1465 (aromatic region), 1180 (C-N stretching), 756 (C-Cl stretching).
6b	170-171	3201 (N-H stretching), 3047 (aromatic C-H stretching), 2947 (aliphatic C-H stretching), 1689 (C=O stretching), 1596-1519 (aromatic region), 1195 (C-N stretching), 748 (C-Cl stretching).
6c	167-168	3193 (N-H stretching), 3047 (aromatic C-H stretching), 2800 (aliphatic C-H stretching), 1674 (C=O stretching), 1581-1465 (aromatic region), 1188 (C-N stretching)
6d	148-151	3201 (aromatic C-H stretching), 3055 (aliphatic C-H stretching), 2947 (aliphatic C-H stretching), 1674 (C=O stretching), 1589-1481 (aromatic region), 1380 (C-N stretching), 1272 (C-O stretching)
6e	151-153	3193 (N-H stretching), 2947 (aliphatic C-H stretching), 1674 (C=O stretching), 1519-1450 (aromatic region), 1380 (C-N stretching), 1195 (C-O stretching)
6f	125-127	3109 (aromatic C-H stretching), 2947 (aliphatic C-H stretching), 1674 (C=O stretching), 1589-1481 (aromatic region), 1380 (C-N stretching), 1272 (C-O stretching)
6g	121-123	3193 (aromatic C-H stretching), 2947 (aliphatic C-H stretching), 1681 (C=O stretching), 1596-1465 (aromatic region), 1380 (C-N stretching), 1265 (C-O stretching)
6h	178-179	3193 (aromatic C-H stretching), 3047 (aliphatic C-H stretching), 1674 (C=O stretching), 1581-1465 (aromatic region), 1326 (C-N stretching), 1188 (C-O stretching)
6i	156-159	3201 (aromatic C-H stretching), 2947 (aliphatic C-H stretching), 1689 (C=O stretching), 1596-1519 (aromatic region), 1380 (C-N stretching), 1272 (C-O stretching)
6j	137-141	3193 (aromatic C-H stretching), 3055 (aliphatic C-H stretching), 1681 (C=O stretching), 1589-1465 (aromatic region), 1319 (C-N stretching), 1188 (C-O stretching)
6k	187-190	3201 (aromatic C-H stretching), 3062 (aliphatic C-H stretching), 1674 (C=O stretching), 1388 (C-N stretching), 1188 (C-O stretching)

Table 3: ^{1}H NMR spectral data of Synthesized Compound (6a-6k)

Product	^{1}H NMR (ð)
"6"	ð 1.77-1.72 ppm (t, 2H, -CH_2), 1.83-1.79 (t, 2H, -CH_2), 2.50-2.45 (t, 2H, -CH_2), 2.63-2.58 (m, 6H, CO-CH_2-CH_2 of carbostyryl, CH_2 of piperazine), 2.91-2.86 (m, 2H, -CH_2 of piperazine), 3.06 (s, 4H, -CH_2 of piperazine), 6.30-6.29 (s, 1H, -ArH), 6.53-6.50 (d of d, 1H,-ArH), 6.98-6.93 (m, 1H, -ArH), 7.05-7.02 (d, 1H, -ArH), 7.16-7.10 (d, 2H, -ArH), 7.79 (s, 1H, -NH)
6a	ð 2.34-2.00 (m, 2H, CO-CH_2 of carbostyryl), 2.50-2.35 (m, 4H, CH_2-N-CH_2 of piperazine), 2.78-2.59 ppm (t, 2H, -CH_2), 2.99-2.75 (m, 2H, -CH_2 of carbostyryl), 3.58-3.39 (m, 4H, CH_2-N-CH_2 of piperazine), 4.06-3.85 (t, 2H, -CH_2), 6.61-6.38 (m, 2H, -ArH), 6.99-6.87 (m, 2H,-ArH), 7.16-7.00 (d, 2H, -ArH), 10.65 (s, 1H, -NH)
6b	ð 1.99-1.83 ppm (t, 2H, -CH_2), 2.52-2.32 (m, 4H, CO-CH_2 of carbostyryl, -CH_2), 2.67-2.58 (m, 4H, CH_2-N-CH_2 of piperazine), 2.98-2.86 (m, 2H, -CH_2 of carbostyryl), 3.55-3.44 (m, 4H, CH_2-N-CH_2 of piperazine), 4.17-4.02 ppm (t, 2H, -CH_2), 6.50-6.36 (m, 2H, -ArH), 7.13-6.89 (m, 2H, -ArH), 7.24-7.14 (d, 2H, -ArH)
6c	ð 1.29-1.20 ppm (d, 6H, -CH_3), 2.55-2.47 (m, 2H, CO-CH_2 of carbostyryl), 2.75-2.61 (m, 4H, CH_2-N-CH_2 of piperazine), 3.13-2.80 (m, 3H, -CH_2 of carbostyryl, -CH), 3.64-3.39 (m, 4H, CH_2-N-CH_2 of piperazine), 5.01 ppm (s, 2H, -CH_2), 6.21-6.46 (d, 1H, -ArH) , 6.79-6.55 (m, 2H, -ArH), 7.00-6.80 (m, 1H, -ArH), 7.13-7.01 (d, 2H, -ArH) 7.36-7.13 (m, 1H, -ArH), 10.50 (s, 1H, -NH)
6d	ð 1.22-1.15 ppm (d, 6H, -CH_3), 2.60-2.43 (m, 2H, CO-CH_2 of carbostyryl), 2.70-2.60 (m, 4H, CH_2-N-CH_2 of piperazine), 2.84-2.71 (t, 2H, -CH_2), 3.10-2.86 (m, 3H, -CH_2 of carbostyryl, -CH), 3.66-3.44 (m, 4H, CH_2-N-CH_2 of piperazine), 4.26-4.06 ppm (t, 2H, -CH_2), 6.61-6.46 (d, 1H, -ArH), 6.71-6.62 (m, 2H, -ArH), 7.00-6.73 (d, 1H, -ArH), 7.39-7.13 (m, 3H, -ArH), 10.60 (s, 1H, -NH)
6e	ð 1.29-1.05 ppm (d, 6H, -CH_3), 1.92-1.75 (t, 2H, -CH_2), 2.60-2.40 (m, 4H, CO-CH_2 of carbostyryl, -CH_2), 2.80-2.60 (m, 4H, CH_2-N-CH_2 of piperazine), 3.29-2.95 (m, 3H, -CH_2 of carbostyryl, -CH), 3.82-3.48 (m, 4H, CH_2-N-CH_2 of piperazine), 4.25-4.04 (t, 2H, -CH_2), 6.59-6.26 (d, 1H, -ArH), 6.95-6.70 (m, 2H, -ArH), 7.21-7.04 (d, 3H, -ArH), 7.39-7.21 (m, 1H, -ArH), 10.67 (s, 1H, -NH)
6f	ð 1.95-1.86 (t, 2H, CO-CH_2 of piperazine), 2.47-2.38 (m, 4H, CH_2-N-CH_2 of piperazine), 2.80-2.75 (m, 2H, -CH_2 of carbostyryl), 3.49-3.16 (m, 4H, - CH_2-N-CH_2 of piperazine), 4.98-4.76 (t, 2H, -CH_2), 6.51-6.44 (m, 2H, -ArH), 7.06-7.03 (d, 1H, -ArH), 7.15 (s, 1H, -ArH), 7.27-7.22 (t, 1H, -ArH), 7.40-7.35 (d, 2H, -ArH), 7.75-7.69 (m, 3H, -ArH), 9.98 (s, 1H, -NH)
6g	ð 1.90-1.65 (m, 2H, CO-CH_2 of carbostyryl), 2.21-2.19 (m, 4H, CH_2-N-CH_2 of piperazine), 2.70-2.28 (m, 2H, -CH_2 of carbostyryl), 2.88-2.71 (t, 2H, -CH_2), 3.44-3.25 (m, 4H, - CH_2-N-CH_2 of piperazine), 4.12-3.82 (t, 2H, -CH_2), 6.65-6.35 (t, 2H, -ArH) 7.38-7.27 (m, 2H, -ArH), 7.71-7.46 (m, 4H, -ArH), 7.94-7.86 (d, 1H, -ArH), 8.12-8.11 (d, 1H, -ArH), 10.04 (s, 1H, -NH)
6h	ð 1.95-1.86 (m, 2H, CO-CH_2 of carbostyryl), 2.43-2.38 (m, 4H, CH_2-N-CH_2 of piperazine), 2.55-2.50 (m, 3H, -CH_2 of carbostyryl, CH of piperazine), 2.80-2.75 (m, 3H, -CH_2 of piperazine), 4.98-4.80 (t, 2H, -CH_2), 6.52-6.45 (t, 2H, -ArH), 7.11-7.03 (m, 2H, -ArH), 7.59-7.38 (m, 4H, -ArH), 7.88-7.85 (d, 1H, -ArH), 8.11-8.08 (d, 1H, -ArH), 10.01 (s, 1H, -NH)
6i	ð 1.65-1.55 (t, 2H, CO-CH_2 of carbostyryl), 1.82-1.69 (t, 2H, -CH_2), 2.66-2.43 (m, 4H, CH_2-N-CH_2 of piperazine), 2.80-2.75 (m, 2H, CH_2 of carbostyryl), 3.65-3.44 (m, 4H, CH_2-N-CH_2 of piperazine), 3.95-3.90 (t, 2H, -CH_2), 6.51-6.44 (m, 2H, -ArH), 7.05-7.02 (d, 1H, -ArH), 7.14-7.13 (s, 1H, -ArH), 7.27-7.22 (t, 1H, -ArH), 7.40-7.34 (m, 2H, -ArH), 7.75-7.69 (m, 3H, -ArH), 9.99 (s, 1H, -NH)
6j	ð 2.42-2.38 (t, 2H, -CH_2 of carbostyryl), 2.78-2.71 (m, 2H, -CH_2 of carbostyryl), 3.99-3.93 (t, 2H, -CH_2), 4.70-4.64 (t, 2H, -CH_2), 6.36-6.33 (m, 2H, -ArH) 6.96-6.92 (d, 1H, -ArH), 7.43-7.36 (t, 1H, -ArH), 7.99-7.59 (m, 4H, -ArH), 8.03-7.99 (t, 1H, -ArH), 8.25-8.03 (d, 1H, -ArH), 8.39-8.25 (t, 1H, -ArH), 9.93 (s, 1H, -NH)
6k	ð 2.49-2.44 (t, 2H, -CH_2 of carbostyryl), 2.85-2.80 (m, 2H, -CH_2 of carbostyryl), 5.07-5.29 (t, 2H, -CH_2), 6.51-6.48 (m, 2H, -ArH) 7.07-7.05 (d, 1H, -ArH), 7.52-7.47 (t, 1H, -ArH), 7.87-7.81 (m, 1H, -ArH), 7.93-7.88 (m, 3H, -ArH), 8.21-8.17 (d, 1H, -ArH), 8.36-8.33 (m, 1H, -ArH), 8.48-8.46 (m, 1H, -ArH), 10.04 (s, 1H, -NH)

PHARMACOLOGY

The antidepressant and sedative activity of the novel synthesized analogs (6a-6k) 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 4).

The lead compound 6 at 50 mg/kg and derivative 6b at 50 mg/kg and at 100 mg/kg are equipotent to Imipramine (15 mg/kg). Derivatives 6j and 6k at 50 and at 100 mg/kg respectively were more potent then rest of test series (6d-6i) with effect comparable to Imipramine (15 mg/kg). The effect of compounds 6d (100 mg/kg), 6e (100 mg/kg) and 6f (50 mg/kg) was comparable with that of compounds 6j (100 mg/kg) and 6k (50 mg/kg).

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 6 at 100 mg/kg followed by 6b and 6j at both dose levels. Lead compound 6 at 50 mg/kg dose level is equipotent to Imipramine (100 mg/kg). Compound 6f (100 mg/kg) and 6k (100 mg/kg) displayed a significant sedative effect compared with Imipramine (100 mg/kg). Compound 6j has displayed most potent effect in series of test compounds and higher than Imipramine.

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
"6"	50	224.05 ± 12.2
	100	220.12 ± 6.8
6a	50	254.02 ± 10.6
	100	240.17± 22.0
6b	50	227.15 ± 11.0
	100	225.16 ± 9.5
6c	50	255.20 ± 18.2
	100	248.11 ± 12.3
6d	50	240.08 ± 7.2
	100	239.20 ± 10.5
6e	50	248.40 ± 12.6
	100	235.33 ± 8.4
6f	50	230.43 ± 22.2
	100	253.43 ± 6.6
6g	50	250.32 ± 17.9
	100	259.22 ± 16.8
6h	50	258.05 ± 9.5
	100	249.27 ± 10.0
6i	50	244.05 ± 30.6
	100	243.88 ± 20.4
6j	50	229.05 ± 33.7
	100	239.17 ± 6.4
6k	50	230.05 ± 8.6
	100	227.40 ± 18.3

Note: Significant difference compared with saline treated control group ($p < 0.05$)

Table 5: Sedative Activity Test Results

Treatment	Dose (mg/Kg)	Number 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
"6"	50	198.3 ± 11.1	60.3
	100	165.5 ± 7.5	69.3
6a	50	255.7 ± 10.7	51.6
	100	215.9 ± 19.3	55.8
6b	50	185.2 ± 20.1	60.0
	100	175.35 ± 7.7	62.3
6c	50	318.6 ± 10.2	39.3
	100	305.3 ± 22.6	41.7
6d	50	295.7 ± 16.3	46.5
	100	290.4 ± 17.6	48.7
6e	50	395.3 ± 25.2	33.2
	100	385.5 ± 11.2	38.6
6f	50	208.8 ± 31.9	52.4
	100	195.6 ± 16.6	62.9
6g	50	225.1 ± 10.1	51.2
	100	199.4 ± 19.2	58.7
6h	50	335.3 ± 10.3	34.6
	100	325.5 ± 9.8	38.4
6i	50	281.1 ± 11.1	49.9
	100	265.8 ± 20.6	50.5
6j	50	175.4 ± 19.5	63.3
	100	169.3 ± 13.3	65.7
6k	50	195.5 ± 17.7	57.6
	100	180.8 ± 18.8	60.0

Note: Significant difference compared with saline treated control group ($p < 0.05$)

Table 6: Anti-parkinson Activity Test Results

Reversal of Reserpine Catalepsy Test[a]		
Compound No.	**20 mg/Kg po**	**40 mg/Kg po**
Rasagiline	**++**	**+++**
"6"	**++**	**++**
6a	***0***	±
6b	**+**	**+++**
6c	***0***	***0***
6d	±	±
6e	***0***	±
6f	**+**	**+**
6g	**+**	**++**
6h	±	±
6i	***0***	±
6j	**+**	**++**
6k	±	**+**

Note: [a] Symbols represent activity as follows: ***0*** = no effect; **±** = marginal effect; **+** = significant effect; **++** = marked effect; **+ + +** = approaching complete reversal.

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 6 and when 2, 3-dichlorophenyl is replaced with α-napthyl (6f, 6g). The activity appears to diminish with replacement of β-napthyl (6h, 6i). When phenyl ring was substituted in the 4- position by isopropyl group and methyl, ethyl or propyl linker incorporated as in 6c, 6d and 6e; compounds showed no effect or marginal potency. Compound 6b was found to be most active. Compound 6j showed marked effect while marginal effect is seen with compound 6k when ethyl linker is replaced with methyl in the structural framework of molecule.

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 linkers like methyl, ethyl and propyl in the structural framework of lead compound. Replacing substituted phenylpiperazine with indoloqunoxiline has provided encouraging results. The compound 6b with propyl linker incorporation and compound 6j with indoloqunoxiline replacement are the most effective than the compounds with isopropyl substitution on phenyl ring and with methyl or ethyl linker incorporated. Also, the results were confirmed with sedative and anti-Parkinson activity test results of compounds 6b and 6j 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, alkyl linker and incorporation of indoloqunoxiline moiety for the antidepressant, sedative and anti-Parkinson activities. Further studies should be made to establish the mechanism-of-action with the possibility to formulate a potent antidepressant and sedative prescription.

CONCLUSION

In conclusion, we have investigated the importance of incorporating functional group substitution on phenyl ring, methyl, ethyl, propyl or butyl linker and indoloqunoxiline moiety for the 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 namely 6, 6b, and 6j 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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