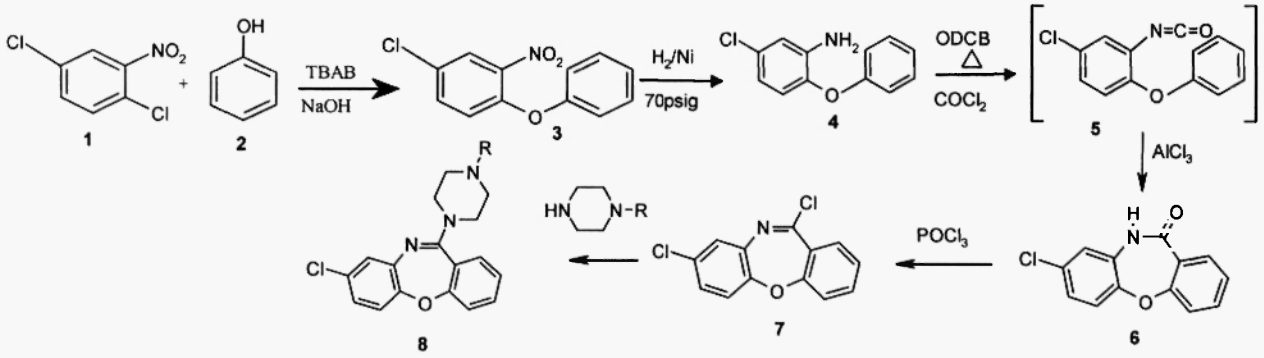
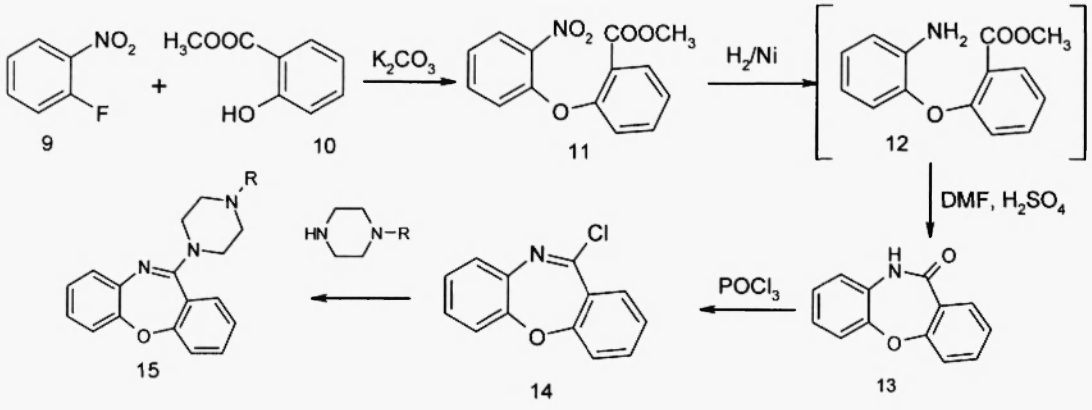
SYNTHESIS AND EVALUATION OF ANTIPSYCHOTIC ACTIVITY OF 11- (4-ARYL-1-PIPERAZINYL)-DIBENZ [b, f][1,4] OXAZEPINES AND THEIR 8-CHLORO ANALOGUES

B.S.Wagh†, B. P. Patil, M. S. Jain, S. S. Harak and S. B. Wagh*
*Department of Pharmaceutical Chemistry,
N. D. M. V, P'S College of Pharmacy, Gangapur road, Nashik- 422 002
e- mail: sbwagh_nsk@sancharnet.in
†University Institute of Chemical Technology,
Matunga, Mumbai.

Abstract : Atypical drugs reduce positive and negative symptoms of schizophrenia, without inducing EPS, but they exert other undesirable side effects. We have gone for synthesis of novel derivatives of Loxapine which are devoid of catalepsy and have decreased metabolic demethylation which is the prominent factor for bioavailability of the drug. While doing so we have also been successful in retaining the antipsychotic activity of the drug. Condensation of 8,11-dichlorodibenzoxazepine and 11-chlorodibenzoxazepine with 1-aryl piperazines was carried to give 8-chloro-11-(4-aryl-1-piperazinyl)-dibenz[b,f][1,4]oxazepines and 11-(4-aryl-1-piperazinyl)-dibenz[b,f][1,4]oxazepines respectively. These derivatives were found as active as Clozapine.



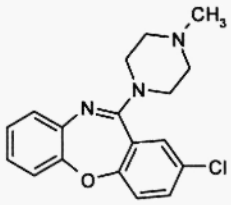
Scheme-1



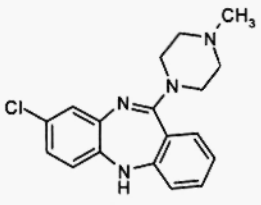
Scheme-2

Introduction

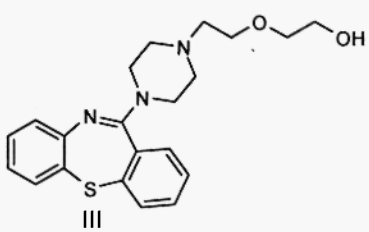
Schizophrenia is a chronic, complex neuropsychiatric illness, afflicting approximately 1% of the population (1,2). In general, schizophrenia involves alteration in cognitive and emotional functioning, and the symptoms can be grouped as positive (altered behavior, such as delusions, hallucination, extreme emotions, excited motor activity, and incoherent speech.) or negative (lack of behavior, such as poverty of speech, social withdrawal, avolition, anhedonia and affective blunting and are resistant to typical antipsychotics (1-3).



I



II



III

It has been shown that increase in the electron density in the tricyclic ring reduces affinity for dopamine receptors and increases its selectivity for the receptors. Loxapine **I** is effective against positive symptoms of schizophrenia, but has EPS, where as Clozapine **II**, shows notably low production of EPS and is effective against both positive and negative symptoms. However incidences of aggranulocytosis were observed in some patients on clozapine. The only difference in both is the relative position of chlorine to N-methyl piperazino group. Quetiapine **III** has similar antipsychotic profile and minimal propensity to elicit EPS. Structurally only the 8-chloro group is absent in quetiapine. Based upon this we have synthesized two series of dibenzoxazepine derivatives with certain logical modifications, in first the 2-chloro group is absent and in the second series the substitution at 2^{nd} is shifted to 8^{th} position. We further have replaced the N-methyl group by an aryl group as it was observed that the aryl piperazine group itself has potency to act as a noble antipsychotic agent with unique nondopaminergic mechanism (4-6).

Experimental

Melting points were determined in open capillaries and are uncorrected. Precoated TLC plates were used to check the identity of reactant and intermediates. Iodine chamber and UV (254nm) chamber were used to visualize spots on TLC plates. Liquid intermediates were checked for their purity using Gas chromatography. (Pack column SE-30, OV-101, and capillary column BP-5). I.R. spectra were recorded on SHIMADZU IR 408 Spectrophotometer. H^1 NMR spectra were recorded on 300MHz spectrophotometer and chemical shift (δ) were expressed in parts per million (δppm), downfield from TMS as an internal standard.

4-Chloro-2-nitro diphenyl ether 3:

Phenol 2 (4gm, 0.26mole) was dissolved in a solution of 11gm sodium hydroxide in 225ml water, when the exotherm was over, TBAB 83gm (0.26mole) and DCNB 1 50ml (0.26mole) was added. The reaction mixture was refluxed for 30hrs with vigorous stirring. The oily layer was taken in 200ml toluene and aqueous layer was extracted with 100ml toluene. The combined toluene extract was washed with 5% sodium hydroxide, dried over anhydrous sodium sulphate and distilled under vacuum. The oily residue weighs 6.1gm (81%) which was sufficiently pure for the next step.

4-Chloro-2-amino diphenyl ether 4: In a stainless steel hydrogenation bottle, 4-chloro-2-nitro-diphenyl ether **3** (8g, 0.032mole, 50ml methanol were taken and Raney nickel W-2 1gm was added, the reaction mixture hydrogenated at 70psi pressure, the reaction monitored by TLC. The catalyst was then filtered and methanol was distilled off to give almost pure 4-chloro-2-amino diphenyl ether, 6g (85%) m. p. 39-40^{0}C (by freezing) was obtained upon distillation under reduced pressure using kugelhor distillation apparatus (1mm of Hg, and 110-120^{0}C air bath temperature).

11-Oxa-8-chlorodibenz [b, f][1,4] oxazepine 6:

Step 1 : A slurry of 4-chloro-2-aminodiphenyl ether hydrochloride (5g, 0.022mole) in 40ml 1,2-Dichlorobenzene (ODCB) was heated to 160 – 170°C. A solution of triphosgene (4g) in 20ml ODCB was delivered with a dip tube drop-wise over **a** period of 2-3 hrs. When the addition was completed, the mixture was then diluted with 15ml ODCB and protected from moisture (solution A).

Step 2 : Slurry of 3.3g anhydrous aluminum chloride in 30ml ODCB was heated to 90-100^{0}C in an oil bath under nitrogen atmosphere. Solution A from step I was added slowly (15min), when addition was completed the temperature was raised to 150^{0}C and maintained at the same temperature for 2 hrs. It was cooled to room temperature and 200ml ice water was added. The ODCB was removed by steam distillation, which is continued to no more oil is separated in the distillate. An off-white residue obtained was extracted with 2 x 200ml boiling acetone, decolourised with active charcoal, which was filtered, the filtrate was then concentrated and cooled to 0°C. White crystalline 11-oxa-8-chlorodibenzoxazepine 6 (yield 2.15g, 38% m. p. 287-290^{0}C) was obtained upon filtration.

8,11-Dichlorodibenz[b, f][1,4]oxazepine 7: 11-oxa-8-chlorodibenzoxazepine 5 (2g, 0.0203mole), 16 ml freshly distilled phosphorus oxychloride and 0.6ml N,N-dimethyl aniline were mixed and refluxed for five hrs. The excess phosphorous oxychloride was then distilled under vacuum. The residue then extracted with 2 x 50ml toluene, which was washed with 3 x 100ml cold water and distilled under reduced pressure to give 8,11-Dichlorodibenzoxazepine 7 (1.17g, 51%) as a pink solid having m. p. 118-119^{0}C.

8-Chloro-11-(4-chlorophenylpiperazinyl)dibenzoxazepine: 8,11-Dichlorodibenzoxazepine 7 (0.70gm, 0.0026mole) was dissolved in 40 ml xylene and 4-chlorophenylpiperazine (1gm, 0.0052mole) was added and reaction mixture was refluxed for 7hrs. The reaction was monitored by TLC. and after completion solid 4-chlorophenylpiperazine hydrochloride was separated by filtration. Xylene layer was extracted with 3 x 50ml 10% HCl, the aqueous layer was then cooled and basified to pH 11-12 with addition of 5% ammonia solution, extracted with 2 x 50ml diethyl ether. Ether was distilled off to give 8-chloro-11-(4-chlorophenyl piperazinyl) dibenzoxazepine. Yield 0.74gm 83% and m. p. 154-156^{0}C.

2-Nitro-2'-methyl diphenyl ether carboxylate 9: o-Fluoro nitrobenzene (10gm, 0.070mole), anhydrous potassium carbonate (14.7gm, 0.1066mole) and methyl salicylate (16.2gm, 0.1066mole) were refluxed for 10hrs. The reaction was monitored by GC. The reaction mixture was dumped in water, extracted with toluene, the extract washed with 10% solution of cold sodium hydroxide. Toluene was then distilled off to give thick liquid of 2-nitro-2'-methyl diphenyl ether carboxylate 11 (yield 18gm, 93%)

2-Amino-2'-methyl diphenyl ether carboxylate 11: In a stainless steel hydrogenation bottle, 2-nitro-2'-methyl-diphenyl ether carboxylate 11 (8g, 0.0293mole), 50ml methanol were taken and Raney nickel W-2 1gm was added, the reaction mixture hydrogenated at 70psi pressure, the reaction monitored by TLC. The catalyst was filtered and methanol was distilled off to give almost pure 2-amino-2'-methyldiphenyl ether carboxylate 12, (6g, 82%) as a residue which was used as such for the next step.

11-Oxadibenz[b,f][1,4]oxazepine 13: 2-amino-2'-methyldiphenyl ether carboxylate 12 (5gm, 0.0205mole) in 40ml DMF, added 1ml sulphuric acid and refluxed for 15hrs, monitored the reaction by TLC. Added 200ml water to the reaction mixture and filtered the solid 11-Oxadibenz[b,f][1,4] oxazepine 13 (yield 3.4gm, m.p.210 - 212).

11-Chlorodibenz[b,f][1,4]oxazepine 14: 11-oxadibenzoxazepine 13 (3g, 0.0142mole) and 18 ml freshly distilled phosphorus oxychloride were mixed. An identical procedure was followed as for 8,11-Dichlorodibenz[b, f][1,4]oxazepine 7. 11-Chlorodibenzoxazepine 14 (1.3g, 40%) was distilled at 150 – 160°C at 2mm of Hg as a thick liquid, which solidifies below room temperature.

8-Chloro-11-(3-chlorophenylpiperazinyl)dibenzoxazepine 15: 11-Chlorodibenzoxazepine 14 (1gm, 0.0043mole) was dissolved in 40 ml xylene and 3-chlorophenylpiperazine (0.9gm, 0.0043mole) were taken and procedure followed as per 8-chloro-11-(3-chlorophenyl piperazinyl) dibenzoxazepine to give 11-(4-chlorophenyl piperazinyl) dibenzoxazepine. Yield 1.4gm, 80% and m. p. 157 - 160^{0}C.

Pharmacological screening (12,13)

Catalepsy was induced and determined at 5, 15, 30, 60, 90, &120 min. intervals by means of Bar test using Loxapine as standard. The duration of catalepsy were transformed to logarithmic values in order to normalize the data. Foot shock induced aggression was used for anti-aggressive activity. Each pair of mice was dosed and tested without previous exposure. The test compound and standard compound were administered three minutes before the mice were placed in a box with a grid floor consisting copper wire with a distance of 6mm. A constant current of 1.2 μA was supplied through grid floor by a constant current shocker-using electrode. Latency for first attack was determined for one min. All observations were given as mean ± SEM for each group. The data was analyzed by students't' test, $p<0.05$ was considered significant. **(Figure I&II)**

Result and Discussion

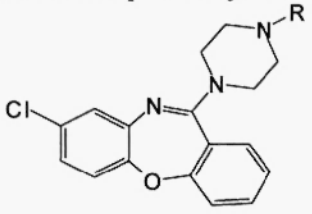
Condensation of 2,5-dichloronitrobenzene 1 and phenol 2 was carried out by using phase transfer catyalyst (7). This method is found to be superior to Ulman condensation as per literature report (8). The low melting DCNB 1 acts as an oil phase at elevated temperature and potassium phenoxide as aqueous phase, which is ideal situation for phase transfer catalysis. Phenol is used in excess (0.5 moles), to avoid contamination of any unreacted DCNB in final product. At 100 – 110°C the reaction gives 75 – 85% yield of nitro diphenyl ether. Excess phenol is removed by washing with aqueous alkali. The crude product is sufficiently pure for hydrogenation. Scale up of this process is simple because of efficient heat transfer conditions.

The nitro diphenyl ether 3 thus produced was hydrogenated to amino diphenyl ether 4. The conversion to isocyanate 5 was achieved by using triphosgene. We have developed a novel phosgenation method which is convenient for laboratory and bulk scale phosgenation. A solution of triphosgene in o-dichlorobenzene is added to slurry of amino

diphenyl ether hydrochloride at 160 – 170°C. This is an excellent alternative to hazardous gaseous phosgene. A molar excess of phosgene in form of triphosgene was used. Quantitative conversion to isocyanate was observed, the reaction was monitored by IR (9-11). The cyclisation of isocyanate to dibenzoxazepinone was insitu carried out using anhydrous aluminium chloride. This upon treatment with phosphorus oxychloride gave 8,11-dichlorodibenzoxazepine 7. Condensation of 7 with 1-aryl piperazines yielded desired 8-chloro-11-(4-aryl-1-piperazinyl)-dibenz[b,f][1,4] oxazepines P1-P9 (Table 1).

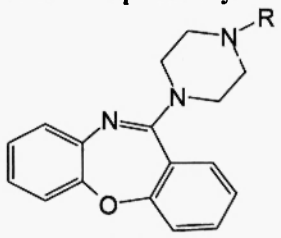
Since o-fluoro nitrobenzene is easily available we have not followed the phase transfer catalysis for the synthesis of dibenzoxazapine. The dibenzoxazpines were synthesized by condensation of o-fluoronitrobenzene 9 and methyl salicylate 10. The reaction smoothly works with excellent yields in presence of potassium carbonate. The resulting nitro diphenyl ether 11 was reduced to amino diphenyl ethers 12 by catalytic hydrogenation. The crude product was directly subjected to cyclisation by refluxing with DMF in presence of catalytic amounts of sulphuric acid to lactum 13. An identical process was followed as for the 8-chloro-11-(4-aryl-1-piperazinyl)-dibenz[b,f][1,4]oxazepines to give finally 11-(4-aryl-1-piperazinyl)-dibenz[b,f][1,4]oxazepines ($P_{10\text{-}P23}$). The structures of the compounds were established by spectral data (Table-2).

Table-1 : Physical and Spectral data for compounds synthesized by method A.



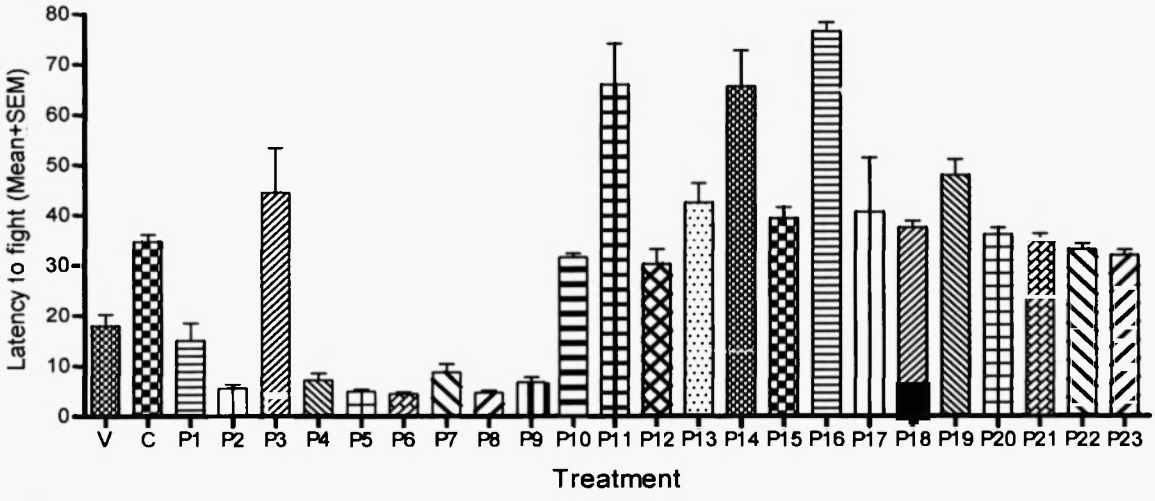
Sr.No.	R	Yield %	M.P. ^{0}C	Spectral Data
P1	4-ClC_6H_4	83	154-156	IR: 1603 C=N, 1499 C-H,1231 C-O PMR:3.25,s, 4H Ar-CH3, 3.72,s, 4H, 6.8to7.5 cm, 11H Ar-H
P2	-C_6H_5	80	157-158	IR: 1586 C=N, 1250 C-O, 3100-2800 C-H
P3	3-ClC_6H_4	70	124-125	IR: 1557 C=N, 1280 C-O, 1231 C-N, 2982 C-H
P4	4-$CH_3C_6H_4$	70	175-178	IR: 1280 C-O, 1590 C=N, 1310 C-N
P5	3-$CH_3C_6H_4$	70	125-128	IR: 1292 C-O, 1605: C=C, 1557 C=N, 1183 C-C, 781 C-Cl PMR: 2.31,s,3H Ar-CH_3, 3.26,s,4H, 3.69,s, 4H, 6.72-7.47 CM,11H Ar-H
P6	2-$CH_3C_6H_4$	65	156-158	IR: 1586 C=N, 1179 C-N,1295 C-O PMR: 3.21,s,3H, CH_3, 3.01,s,4H, 3.62,s,4H,6.88-7.47cm,11H,Ar-H
P7	2-ClC_6H_4	72	153-154	1586 C=N, 1148 C-N, 1228 C-O
P8	2-$OCH_3C_6H_4$	60	170-173	IR: 1610 C=C, 1250 C-N, 1110 C-O PMR: 3.18,s, 4H, 3.72,s, 4H, 3.85,s, 3H, O-CH_3 6.86-7.39cm,11H,Ar-H
P9	4 -$OCH_3C_6H_4$	80	160-162	IR: 1251 C-O, 1601 C=N, 1333 C-N PMR: 3.74,s, 4H, 3.78,s, 4H, 3.78,s, 3H, O-CH_3, 6.85-7.49 cm,1H,Ar-H

Table II : Physical and Spectral data for compounds synthesized by method B.



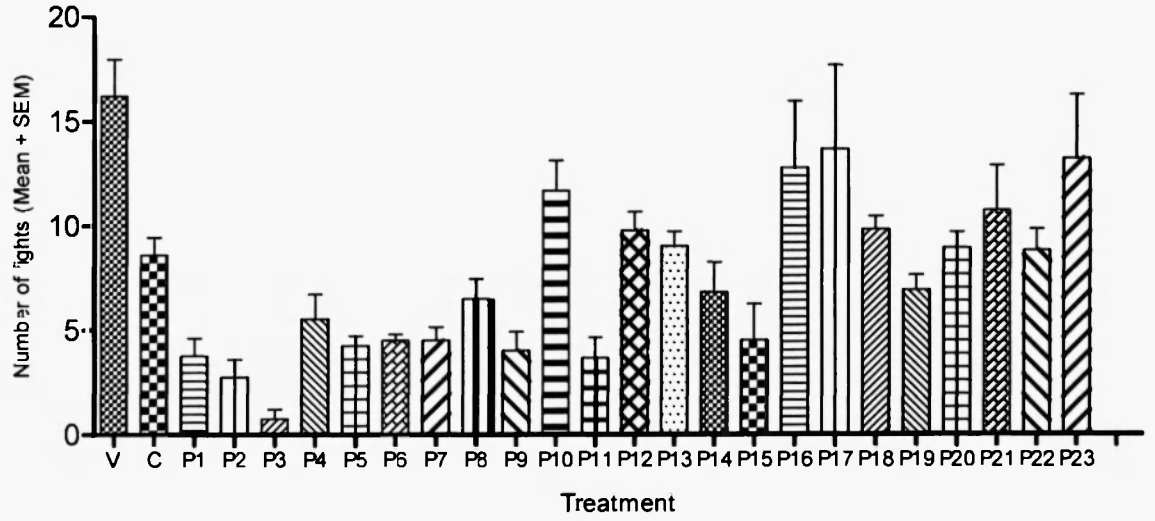
Sr.No.	R	Yield %	M.P. ^{0}C	Spectral Data
P10	3-$CF_3C_6H_5$	62	235 - 136	IR: 3062.7:C-H, 1605:C=N, 2853:C-H; 1250:C-O
P11	4-$OCH_3C_6H_4$	78	172 - 173	IR: 3028:C-H, 1593:C=N, 2822:C-H; 1238:C-O, 1124:C-O-C
P12	-$CH_2C_6H_4$	68	115 – 118	IR:2841.3:C-H, 1592:C=N, 2813:C-H; 1225;C-O; 1354: C-N
P13	3-ClC_6H_4	89	157 – 160	IR:1587:C=N, 2829:C-H; 1232:C-O; 1374:C-N; PMR: 7.45,m,4H, Ar-H, 7.16,m,4H, Ar-H, 7.01,m,4H, Ar-H, 3.67,s,4H, pip. H 3.30,s,4H,pip.H ^{13}C NMR: C_1-126.58, C_2-129.05,C_3-123.47,C_4-131.56, C_6& C_7-134.9, C_8-118.22, C_9-122.33, C_{10}.127.67, C_{11}-126.96 C_{12}-142.43, C_{13}-163.026, C_{14} & C_{17}-47.61, C_{15} & C_{16}-54.91, C18-138.324, C19-114.21, C_{20}-130.23 , C_{21}-129.573, C_{22}-132.1, C_{23}-115.21
P14	3-$CH_3C_6H_4$	83	192 – 196	IR : 1592:C=N, 1238:C-O; 1290:C-N
P15	2-$OCH_3C_6H_4$	73	172 – 175	IR: 1591:C=N, 2813:C-H; 1239:C-O; 1101:C-O-C; 1304: C-N; PMR: 7.43,m,4H,Ar-Hphenyl 7.15,m,4H,Ar-H (diphenyl), 6.99, m,4H, Ar-H (diphenyl), 3.87,s,3H, C-H(OCH_3), 3.79,s,4H,piperazine H, 3.18,s,4H, piperazine H ^{13}C NMR: C_1-124.133, C_2-129.638, C_3-123.27, C_4-124.133, C_5-121.289, C_6 & C_7- 132.584, C_8-121.033, C_{10}-126.932, C_{11}-125.517, C_{12}-141.578, C_{13}-162.9.6, C_{14} & C_{17}-50.697, C_{15}& C_{16}-55.393,C_{18}-134.63, C_{19}-115.32,C_{20}-118.355, C_{21}-120.184, C_{22}-111.348, C_{23}-160.45, C_{24}-47.600
P16	4-n-$C_3H_7C_6H_4$	68	157 – 159	IR: 1620:C=N, 2790:C-H, 1190:C-O; 1285: C-N
P17	3,4-$Cl_2C_6H_5$	65	175 – 177	IR: 1524:C=N, 2820:C-H, 1224:C-O; 1305: C-N
P18	2-ClC_6H_5	83	161 – 162	IR: 1596:C=N, 2819:C-H, 1203:C-O; 1325: C-N
P19	2,3-$Cl_2C_6H_5$	74	122 – 126	IR: 1580:C=N, 2797:C-H, 1213:C-O; 1320: C-N
P20	-CHO	60	205 – 207	IR: 1592:C=N, 2810:C-H, 1210:C-O; 1321: C-N
P21	-C_2H_5	68	172 – 174	IR: 1610:C=N, 2800:C-H, 1203:C-O; 1335: C-N
P22	H	88	128 – 130	IR: 1575:C=N, 2824:C-H, 1220:C-O; 1350: C-N
P23	-C_6H_5	72.	131 - 133	IR: 1620:C=N, 2839:C-H, 1210:C-O; 1315: C-N

FIGURES



*p< 0.05 was considered significant

Figure I: Effect of dibenzoxazepines on latency to fight in mice using foot shocked induced aggression model



*p< 0.05 was considered significant

Figure II: Effect of dibenzoxazepines and 8-chloro analogues on number of fights in mice using foot shocked induced aggression model

Conclusion

Usage of phase transfer catalyst eased the synthesis process. All Compounds showed significant decrease in catalepsy after five min. as compared to Loxapine. P5 and P8 showed non-significant decrease in catalepsy. In fighting behavior studies the compounds P2,P3,P4,P5,P6,P7,P9,P10,P11,P12,P13,P14,P17,P18,P19,P20,P22,P23 were found to posses antipsychotic activity equivalent to clozapine while compounds P1,P8,P14,P15,P16,P17,P21 were found to be moderately active as compared to Clozapine..

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