Research Article

SCHIZOPHRENIC ACTIVITY OF 1,2,4-TRIAZOLO(4,3-A)-PYRIDINE-3-(2H)-ONE-2[3-{4-(3-SUBSTITUTED PHENYL)-1-PIPERAZINY}ALKYL] HYDROCHLORIDE DERIVATIVES.

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ABSTRACT

To study describe the actions of antipsychotics or neuroleptics on the behavioral effects elicitedby ketamine on open-field, rota rod and tail suspension tests in mice. A series of novel analogs of 2-[3-{4-(3-chlorophenyl)-1-piperazinyl} propyl]-1,2,4-triazolo [4,3-a] pyridine-3- (2H)-one hydrochloride, a potential psychoactive drug of the piperazine and triazolopyridine chemical classes that has antidepressant, anxiolytic, and hypnotic properties were synthesized. Male swiss albino mice (25–30g) were used for the study and compounds were administered alone (0.1 or 0.2 mg/kg) or thirty minutes before ketamine (10 mg/Kg, ip). ketamine increased (59.2 ± 3.2) the locomotor activity compared to control, while neuroleptics decreased it (28.3 ± 3.9). Pre treatment with neuroleptics, in both doses, blocked hyperlocomotion caused by ketmine. In rota rod test, ketamine decreased (Ketamine: 17.04 ± 3.7) the permanence time of the animalscompared to control (Control: 55.01 ± 0.5), but this effect was not observed when antipsychotics were administered alone. Pretreatment with antipsychotics reverted the effect of ketamine only in the rota rod. The action of antipsychotics or neuroleptics tested has exhibited encouraging results in the behavioral model induced by ketamine in mice and can be further evaluated as potential candidates for treatment of schizophrenia.

Keywords: Neuroleptic, Ketamine, Locomotor activity, Schizophrenia.

INTRODUCTION

Schizophrenia is a mental disorder characterized by a disintegration of the process of thinking and of emotional responsiveness.[1] It most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganised speech and thinking, and it is accompanied by significant social or occupational dysfunction. The onset of symptoms typically occurs in young adulthood, [2] with a global lifetime prevalence of around 1.5%.[3,4] Diagnosis is based on the patient's self-reported experiences and observed behavior. This hypothesis postulates that the dopaminergic hyperfunction is based on the following evidences: 1) psychotic symptoms presented by patients using drugs that induce dopamine release; 2) efficacy of typical antipsychotics in many patients via action on dopamine D2-like receptors[5,6]. However, the basis of the dopaminergic hypothesis has been questioned in some studies which demonstrated that a certain level (> 65%) of receptor blockade is necessary, but not sufficient to cause clinical results.

The purpose of this work is to understand the interaction between the dopaminergic and glutamatergic systems, analyzing the effects of series of antipsychotics of piperazine and triazolopyridine chemical classes in the behavioral model induced by ketamine in mice.

MATERIALS AND METHODS

Melting points (mp) were determined using a Thomas Hoover capillary apparatus and are uncorrected, and are mentioned in table no 6.

Infrared spectra were acquired on a Perkin Elmer FTIR, and are mentioned in table no 4.

Mass spectra were acquired with a Shimadzu Qp-2010 Mass spectrometer, and are mentioned in table no 4.

A Bruker, 300 MHz spectrophotometer was used to acquire ^{1}H-NMR spectra, and are mentioned in table no 5.

All chemicals and laboratory grade (LR) reagents were obtained from Rankem (India), merck, sigma, spectrochem and were used without further purification.

1-bromo -3-chloro-2 methyl propane was purchased from Japan.

Experimental

Synthetic process

Our synthesized molecules, 2-[3-{4-(substituted phenyl)-1-piperazinyl} alkyl]-1, 2, 4-triazolo [4, 3-a] pyridine-3-(2H)-one hydrochloride in listed table no. 1 are synthesized by following process which is described in figure no 1.

Stage 1 - General procedure for synthesis of 1-(aryl piperazine) Hydrochloide[7].

The mixture of bis-(2-chloroethylamine) hydrochloride (0.50 mol), substituted aromatic amines (0.61 mol), *para* toluenesulphonic acid (PTSA) in catalytic amount are taken in xylene, was heated to reflux till the completion of reaction (aniline gets completely consumed). Progress of the reaction was monitored by TLC. On completion the reaction mass was cooled to 30^{o}C and further chilled to 0-5^{o}C and solvent is decanted. The product is taken for

slurry washing with acetone to remove traces of un-reacted aniline. The product is washed with hexane and dried in oven under reduced pressure (100 mm/Hg) at 50°C for 8 hours.

Overall Product yield: 85%-90%

Stage 2 - General procedure for preparation of 1-(substituted phenyl)-4-(3-halo-alkyl) piperazine Hydrochloride[8].

To the mixture of 1-(substituted phenyl)-piperazine hydrochloride [1] (0.17 mol) in taken in acetone.20% NaOH is added into the mixture with constant stirring. Into the above mixture halo alkane is added (0.5mol) under stirring at 25-30°C. The reaction was further stirred for 24 hours at same temperature and progress was monitored by TLC. On completion of reaction the organic layer (acetone layer) is separated out and evaporated under reduced pressure below 50°C. The oily reaction mass is obtained is the crude base. 25% hydrochloric acid was added to this crude base. It is then stirred for a hour at 70°C-75°C. it is cooled and chilled at 0°C-5°C and stirred for half n hour. It is filtered and refluxed in hexane to removed un-reacted halo alkane. The product is washed with chilled acetone in 10:1(product: acetone) ratio. The halo alkanes used are 1-bromo-3-chloro-2-methyl propane and 1-bromo-3-chloro propane.

Overall Product yield: 70%-75%

Stage 3 - General procedure for preparation of sodium salt of 1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one[9].

A mixture of 2-chloropyridine (0.88 mol) and semicarbazide hydrochloride (1.79 mol) in 2-ethoxyethanol (200 mL) was heated to 145-150°C for 12 hours. Progress of the reaction was monitored by TLC. On completion the reaction mass was cooled to 60°C and water (400 mL) was added. The solution further cooled to 0°C and stirred for 0.5 hours. The precipitated product was isolated by filtration.

Product Yield: 90 %

The above solid was then dissolved in 30 % sodium hydroxide solution (100 mL) and warmed to 40°C when a clear solution was obtained. The solution was then slowly cooled to 0°C when product crystallizes as sodium salt and thick slurry was obtained. The sodium salt of the product was isolated by filtration and washed with chilled water (0°C, 200 mL) and dried at 70°C under reduced pressure (10 mm/Hg) for 12 hours.

Product Yield: 92.0 %

Stage 4 - General procedure for preparation of 2-[3-{4-(3-substited phenyl)-1-piperazinyl} alkyl]-1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one hydrochloride[9].

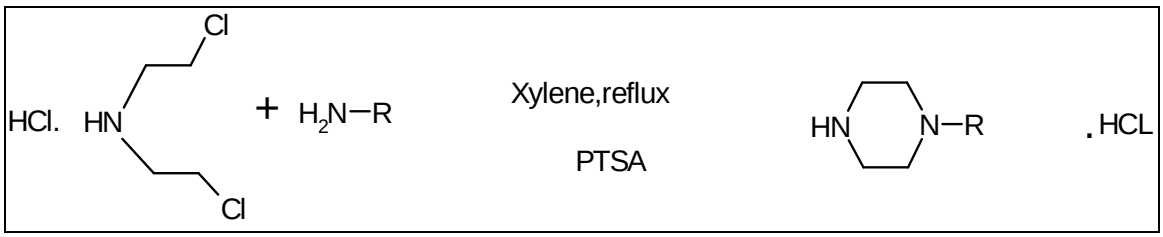
The hydrochloride salt of stage 3 was taken into water. It was dissolved into water at 75°C. It was filtered at the same temperature and cooled to 25°C. The pH was adjusted to 11-12 by caustic lye. This aqueous layer was washed with dichloromethane. Dichloromethane is evaporated under reduced pressure. This oily base (Stage 2 crude base) is taken for further reaction.

The mixture of 1-(substituted phenyl)-4-(3-haloalkyl) piperazine [2] (0.5 mol), 1, 2, 4-triazolo [4, 3-a] pyridine-3-(2H)-one[3] (1.15 mol) and para toluenesulphonic acid (PTSA) in catalytic amount in acetonitrile was refluxed at 80-82°C for 24 hours. Progress of the reaction was monitored by TLC to ensure formation of product and complete conversion of starting material 1-(substituted phenyl)-4-(3-haloalkyl) piperazine. On completion the reaction mass was cooled to 70°C and filtered. The acetonitrile was recovered by reduced pressure and toluene was added to residual reaction mass when a clear solution was obtained. The toluene solution was further washed twice with 20% sodium hydroxide solution (3x 15 mL) followed by 2% sodium chloride solution (2x 15 mL) at 60°C. To the toluene solution containing product as base, IPA HCl solution was added, salt starts precipitating out. The precipitated hydrochloride salt of target molecule was isolated by filtration and recrystallised using suitable solvent.

Overall Product Yield: 80%- 85. %

Figure 1 - Synthetic route

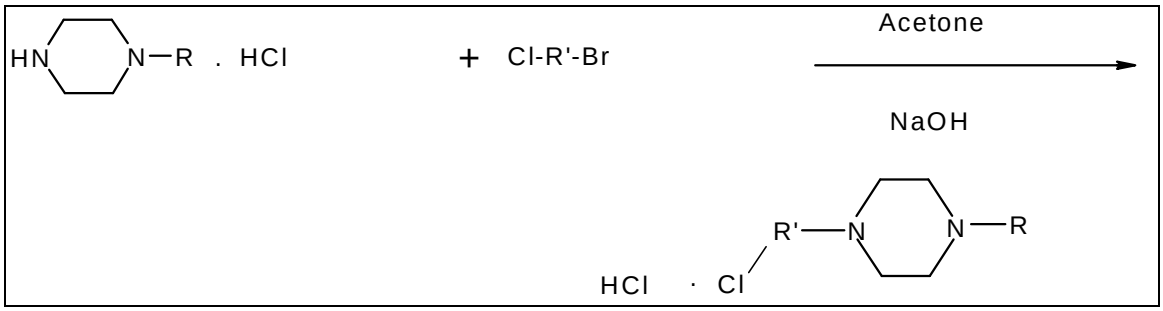
Stage 1-



1(a-f)

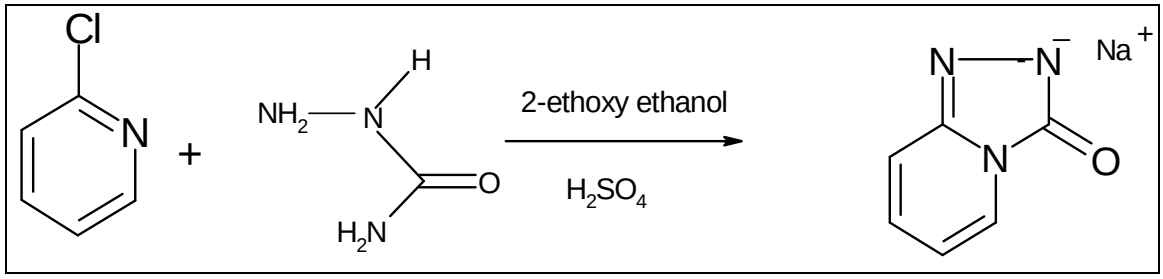
R= substituted benzene

Stage 2-



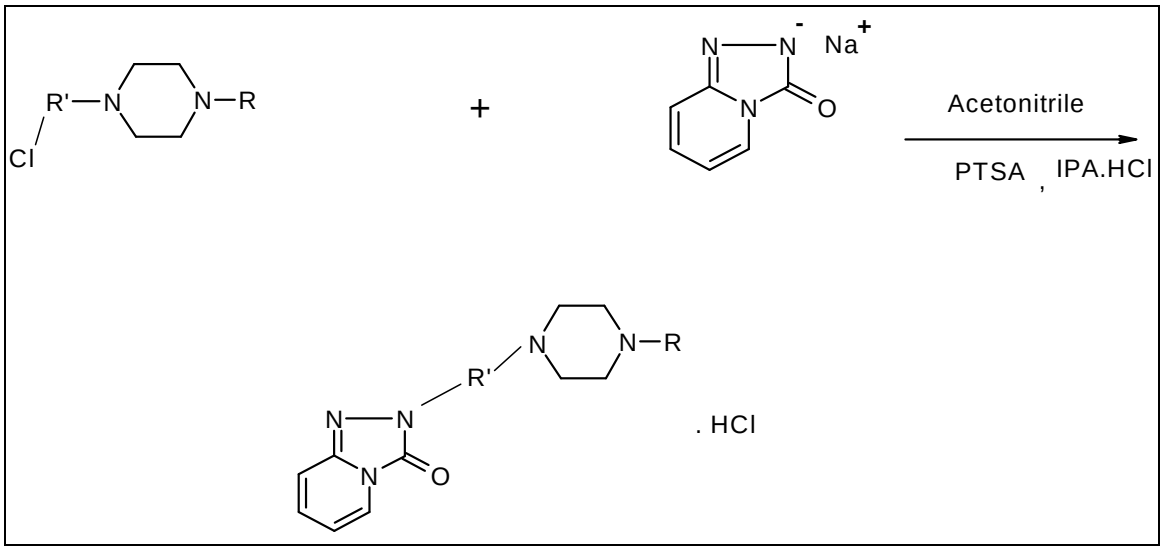
R'= alkyl group 2(a-f)

Stage 3-



3

Stage 4-



4(a-f)

Pharmacology

Anti-schrizophrenia Test Results:

Test Protocols:

Animals Used

Swiss albino male mice (*Mus musculus)* (22–35 g) were used for tests. The animals were maintained at a controlled temperature (25 ± 1 °C) with a 12h dark/light cycle and free access to water and food. All the experiments involving animals were performed as per the guidelines of Institutional Ethics Committee.

Drugs and treatment

Ketamine hydrochloride (50 mg/mL, ampoules) were used. Ketamine and all the drug analogs under test (Lead Compound & Analogs 1 - 6) were dissolved in distilled water and administered intraperitoneally (ip) in volumes of 10 mL/Kg body weight. All the compounds (0.1 mg/Kg or 0.2 mg/Kg) were administered alone or thirty minutes before ketamine (10 mg/Kg). Control animals received distilled water in the same period.

Procedure

Animals were tested during the light period and observed in a closed room, poorly illuminated, at a constant temperature of 25 ± 1 ºC. Immediately after treatment with ketamine or water, the tests were performed. First, animals were placed in the open field arena where the locomotor activities, such as number of grooming, rearing and stereotyped activity (repetitive movements) were measured. Subsequently, the same animals were placed on rota rod and on the tail suspension device straight afterward.

Open-field test (OF) (Results in Table 2)

The OF area was made of acrylic (transparent walls and black floor, 30 cm x 30 cm x 20 cm) divided into nine squares of equal area. The OF was used to evaluate the animals exploratory activity[10]. The observed parameters were: number of squares crossed (with the four paws) during three minutes after one minute for acclimatization (locomotor activity) and number of grooming and rearing. In this apparatus, behavioral changes, such as stereotyped behaviors (striking or preservative behaviors), walking in circles and ataxia were also observed and recorded.

Rota rod (RR) (Results in Table 3)

The method of Dunham and Miya[11] was used on rota rod test. Animals were placed with the paws on a 2, 5 cm diameter bar, 25 cm above the floor, which rotates 12 times per minute. The number of falls (up to three falls) and the time of permanence on the bar for one minute were registered.

Tail suspension test (TS)

In the tail suspension, a test used to analyze antidepressant activity of drugs in animals, the ketamine-treated group presented a reduced immobility time, revealing an antidepressant effect.

For the tail suspension test, the method described by Porsolt et al[12] was used. Mice were suspended by tail on the edge of a shelf 58 cm above a table top by adhesive tape placed approximately 1 cm from the tip of the tail. The duration of immobility was recorded during a period of five minutes.

Statistical analyses

All analyses were performed using one-way analysis of variance (ANOVA), at Prism 3.0 software. For significant results, multiple comparisons were made using Tukey as the post hoc test. Results were considered significant at $p < 0.05$, and presented as mean ± E.P.M.

Tail-suspension Test (TS)

The reduced immobility was reversed by all the Test Compounds (Lead Compound & Analogs 1 - 6) in all doses similar to the standard neuroleptic drugs (Risperidone or Haloperidol) used for comparison.

Table 1: Different derivatives of lead compound "4" synthesized for study

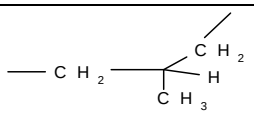
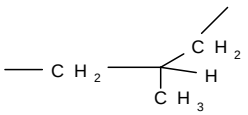
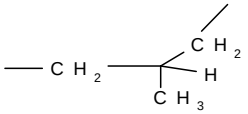
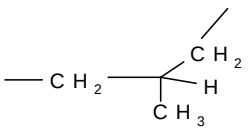
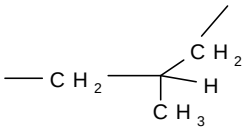
Synthesized compounds & it's reference number	R	R'
4a	3-Cl, C_6H_4	$-(CH_2)_3$
4b	3-Cl,4-F $-C_6H_4$	
4c	3,4-$(CH_3)_2$ $-C_6H_4$	
4d	2- C_2H_5 $-C_6H_5$	
4e	$C_{10}H_8$(α-position)	
4f	$C_{10}H_8$(β-position)	
4g	2-Cl,3-CH_3 $-C_6H_5$	$-(CH_2)_3$

Table 2: Effects of antipsychotic drugs and ketamine on the open-field test in mice

Group	Locomoter activity	Rearing	Grooming
Control	28.3 ± 3.9 (10)	12.55 ± 2.7 (11)	3.6 ± 0.5 (10)
Ketamine 10	59.2 ± 3.2 (10)	1.3 ± 0.6 (10)	0.3 ± 0.2(10)
Lead Compound	6.98 ± 1.7 (13)	6.1 ± 1.2 (11)	2.8 ± 0.6 (11)
1	6.1 ± 1.9 (12)	0.5 ± 0.5 (12)	0.8 ± 0.35 (12)
2	4.5 ± 0.2 (12)	0.9 ± 0.3 (12)	0.7 ± 0.2 (12)
3	2.1 ± 0.9 (10)	0.15 ± 0.3 (12)	0.09 ± 0.08 (12)
4	13.5 ± 3.1(10)	0.9 ± 0.2 (9)	0.7 ± 0.1 (10)
5	31.6 ± 4.2 (9)	1.2 ± 0.5 (10)	0.6 ± 0.1 (10)
6	4.5 ± 2.6 (10)	3.2 ± 0.2 (10)	1.8 ± 0.5 (9)

Note: Values are reported as means ± e.p.m. for the number of mice shown in parentheses. Analysis of variance and Tukey as the post-hoc test.

Table 3: Effects of antipsychotics drugs and ketamine on the Rota rod test in mice.

Group	Time of permanence (s)		N° falls
	Pretreatment with test compounds alone	Receipt of ketamine after treating with test compounds	
Control	55.01 ± 0.5 (10)		0.15 ± 0.05 (14)
Ketamine	17.04 ± 3.7 (10)a		1.9 ± 0.2(10)
Lead Compound	56.07 ± 1.5 (14)	37.03 ± 1.4 (14)	0.88 ± 0.1 (14)
1	46.02 ± 4.5 (14)	29.02 ± 5.1 (14)	2.2 ± 0.7 (20)
2	47 ± 2.6 (12)	30.25 ± 2.8 (12)	2.6 ± 0.5 (12)
3	47 ± 2.5 (12)	46 ± 6.5 (12)	2.7 ± 0.7 (12)
4	56 ± 2.8 (09)	30 ± 1.6 (09)	0.8 ± 0.2 (09)
5	50.1 ± 6.4 (10)	19.7 ± 5.3 (10)	2.9 ± 0.2 (10)
6	50.7 ± 2.3 (10)	32.1 ± 4.2 (10)	0.7 ± 0.9 (10)

Note: Values are reported as means ± e.p.m. for the number of mice shown in parentheses. Analysis of variance and Tukey as the post-hoc test.

Table 4: Spectral data of synthesized 4(a-f) compounds [I.R, Mass]

compounds	I.R(KBr)	Mass(m/z)
4 lead molecule	3000(Aromatic C-H stretching), 2954 (aliphatic C-H stretching), 1704(C=O stretching) ,1650 (C=N stretching), 1600(Aromatic C=C stretching), 1350.80 (C-N stretching), 750(C-Cl stretching)	371.87
4a	3000(aromatic C-H stretching), 2900(aliphatic C-H stretching),1700(C=O stretching), 1500(aromatic C=C stretching),1400(C-N stretching),1200(C-F stretching),700(C-Cl stretching)	405
4b	3000(aromatic C-H stretching),2980(aliphatic C-H stretching),1700(C=O stretching),1550(aromatic C=C stretching), 1350(C-N stretching)	379
4c	3101(aromatic C-H stretching),2839(aliphatic C-H stretching), 1700(C=O stretching), 1643(aromatic C=C stretching), 1380(C-N stretching)	379
4d	3100(aromatic C-H stretching),2975(aliphatic C-H stretching),1700(C=O stretching),1550(aromatic C=C stretching),1375(C-N stretching)	401
4e	3047(aromatic C-H stretching),2846(aliphatic C-H stretching), 1704(C=O stretching), 1512(aromatic C=C stretching), 1350(C-N stretching)	401
4f	3000(aromatic C-H stretching), 2850(aliphatic C-H stretching), 1700(C=O stretching), 1650(C=N stretching), 1495(aromatic C=C stretching), 1325(C-N stretching), 700(C-Cl stretching)	502

Table 5: Spectral data of synthesized 5(a-f) compounds [NMR]

Compounds	^{1}H NMR
4 lead molecule $Cdcl_3$	2.16-2.12 (m, 2H,CH_2) ,2.64-2.60 (t, 2H,-N-CH_2-), 2.73 (s,4H,piperazine), 3.09 (s, 4H,piperazine), 4.12-4.07 (t, 2H,O=C-N-CH_2), 6.51-6.46 (m, 1H, ArH), 7.02-6.93 (m, 2H, ArH), 7.09-7.08 (d, 2H, Ar H), 7.26-7.17 (m, 1H, ArH), 7.34-7.31 (d, 1H, ArH), 7.76-7.45 (d, 1H, ArH),11.10(s,1H,N-H)
4a	1.18-1.13(d,3H, [-{CH_2}$_2$-CH- CH_3]), 2.74(m,1H, [-{CH_2}$_2$-CH- CH_3]),2.97 -2.90(m,4H,piperazine, -N-CH_2), 3.41-3.37(d,2H,piperazine),3.71-3.66(m,4H,piperazine),4.05-4.00(dd,1H, [-{CH_2}-CH- CH_3]),4.14-4.09(dd,1H, [-{CH_2}-CH- CH_3]),6.50-6.45(t,1H,Ar-H),6.73-6,68(m,1H,Ar-H),6.98-6.86(m,1H,Ar-H),7.67-7.01(m,3H,Ar-H),7.70-7.68(d,1H,Ar-H), 12.50(s,1H ,N-H)
4b	1.22-1.20(d,3H, [-{CH_2}$_2$-CH- CH_3]), 2.20(s,3H,Ar- CH_3), 2.30(s,3H,Ar- CH_3),2.62-2,54(m,1H, [-{CH_2}$_2$-CH- CH_3]), 3.26-3.07(m,4H,piperazine),3.41-3.31(t,2H,piperazine),3.57-3.54(d,2H,piperazine),3.71-3.67(d,2H,-N- CH_2),3.92-3.85(dd,1H, [-{CH_2}-CH- CH_3]), 4.07-4.00(dd,1H, [-{CH_2}-CH- CH_3]), 6.67-6.61(m,1H,Ar-H),6.77-6.74(m,1H,Ar-H), 6.8593-6.8536(d,1H,Ar-H), 7.04-7.01(d,1H,Ar-H), 7.20(s,2H,Ar-H), 7.87-7.85(d,1H,Ar-H),10.89(s,1H,N-H)
4c	1.01-1.88(d,6H, Ar- CH_3, [-{CH_2}$_2$-CH- CH_3]), 2.65-2.63(m,1H, [-{CH_2}$_2$-CH- CH_3]), 2.30-2.31(m,2H,Ar-CH_2) 3.40(s,8H,piperazine),3.63 (s,2H,-N- CH_2), 4.06-3.90(dd,2H, [-{CH_2}-CH- CH_3]), 6.67-6.62 (m,1H,Ar-H), 7.27-7.16(m,1H,Ar-H),7.56-7.44(m,2H,Ar-H),7.68-7.65(d,1H,Ar-H), 8.09-7.88 (m,2H,Ar-H), 8.12-8.11(d,1H,Ar-H),10.57(s,1H,N-H)
4d	1.01-0.99(d,1H, [-{CH_2}$_2$-CH-CH_3]), 2.72-2.61(m,1H, [-{CH_2}$_2$-CH- CH_3]), 3.30-3.12(m,4H,piperazine),3.36(s,4H,piperazine),3.83-3.82(s,2H,-N- CH_2), 4.06-3.90(dd,2H, [-{CH_2}-CH-CH_3]), 6.69-6.62(m,1H,Ar-H), 7.22-7.16(m,1H,Ar-H),7.29(s,2H,Ar-H),7.53-7.44(m,3H,Ar-H),7.65-7.53(d,1H,Ar-H),7.93-7.88(t,2H,Ar-H),8.12-8.09(t,1H,Ar-H),10.57(s,1H,N-H)
4e	1.09-1.07(d,3H, [-{CH_2}$_2$-CH- CH_3]), 2.50-2.48(m,1H,[{CH_2}$_2$-CH- CH_3]),3.50(s,8H,piperazine), 3.60(s,2H,N- CH_2), 4.00(dd,2H,[-{CH_2}-CH- CH_3]), 6.50(m,1H,Ar-H),7.26-7.18(m,3H,Ar-H),7.53-7.45(m,3H,Ar-H),7.64(s,1H,Ar-H),7.90-7.87(t,2H,Ar-H),8.10(d,1H,Ar-H), 10.50(s,1H,N-H)
4f	2.25-2.18(m,3H,Ar-CH_3),3.06-2.98(m,2H,-CH_2),3.23-3.14(m,6H,piperazine),3.62-3.50(m,2H,piperazine), 4.03-3.99(m,2H,-N- CH_2), 4.03-3.99(t,2H, O=C-N-CH_2),6.67-6.62(m,1H,Ar-H),7.01-7.04(m,1H,Ar-H),7.28-7.15(m,4H,Ar-H),7.85-7.83(d,1H,Ar-H), 10.27(s,1H,N-H)

Table 6: Physical data of the synthesized compounds

compound	Molecular Formula	Nature	Melting Point
4 lead molecule Trazodone Hydrochloride	$C_{19}H_{22}N_5OCl$	White crystalline	223° C
4a	$C_{20}H_{23}N_5OClF$	White amorphous	>250^0 C
4b	$C_{22}H_{29}N_5O$	Light green amorphous	>250° C
4c	$C_{22}H_{29}N_5O$	White crystalline	>250° C
4d	$C_{24}H_{27}N_5O$	Pale green amorphous	210^{0}C-212^{0}C
4e	$C_{24}H_{27}N_5O$	White flakes	232^{0}C-234^{0}C
4f	$C_{20}H_{24}N_5OCl$	Dark blue amorphous	>250° C

RESULTS AND DISCUSSION

Chemistry

The target compounds, 2-[3-{4-(substitued phenyl)-1-piperazinyl} alkyl]-1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one hydrochloride derivatives (4a-f) mentioned above, wereprepared by the process described in Figure 1. To examine structure-activity relationships on the nucleus portion in the 2-[3-{4-(3-chlorophenyl)-1-piperazinyl} propyl]-1, 2, 4-triazolo [4,3-a] pyridine-3- (2H)-one derivatives, few analogs of process intermediate 1-(3-substituted phenyl)-piperazine hydrochloride and further 1-(substitued phenyl)-4-(3-chloroalkyl) piperazine were prepared by employing similar process and then reacted with 1, 2, 4-triazolo [4,3-a] pyridine-3- (2H)-one to achieve novel derivatives of the lead compound desired for the study.

Stage first is the condensation of bis-(2-chloro ethyl amine) hydrochloride is condesend with aromatic amines in xylene using PTSA as a catalyst.

In second part alkylation of these using 1-bromo-3-chloropropane and 1-bromo2-methyl-3-chloro propane in alkaline aqueous acetone (20 %) gave various analogs of 1-(substituted phenyl)-4-(3-chloroalkyl) piperazine intermediate.

The third part is synthesis of major intermediate i.e sodium salt of 1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one

is synthesized by condensation of 2-chloropyridine and semicarbazide hydrochloride using ethoxyehanol as solvent, which is further converted into its sodium salt.

In the fourth part of the process these various derivatives of 1-(3-substituted phenyl)-4-(3-chloroalkyl) piperazine intermediate were condensed with sodium salt of 1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one using acetonitrile as solvent which is finally converted into the hydrochloride form for the stability. These novel analogs were taken for studies.

CONCLUSION

The results showed that antipsychotics or neuroleptic test compounds, under the mentioned experimental conditions, attenuated the increase of locomotor activity and stereotyped behavior, reversed the motor incoordination and blocked the hypermobility induced by acute administration of ketamine. These results suggest that the ketamine mechanism of action may involve the dopaminergic system. This study concluded that the test compounds have exhibited encouraging results in the behavioral model induced by ketamine in mice and can be further evaluated as potential candidates for treatment of schizophrenia.

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