

PASS assisted search and evaluation of some azetidin-2-ones as C.N.S. Active agents.

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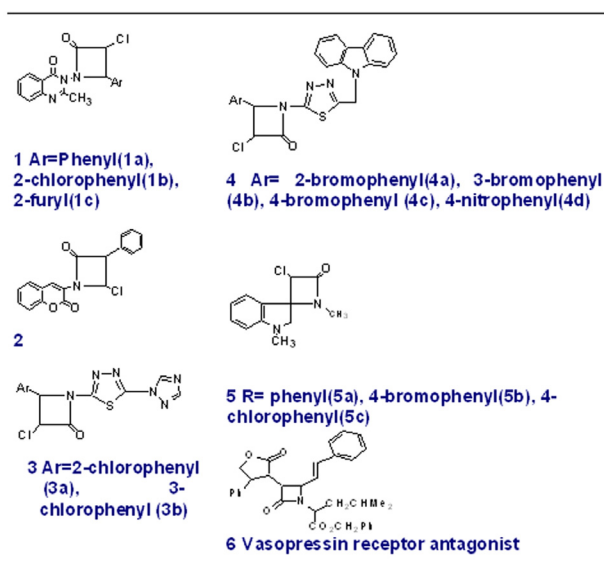
Abstract Purpose: The present study evaluates some azetidin-2-ones derivatives for their central nervous system (CNS) modulating activities. The compounds were chosen from a series (5a-o) which were previously synthesized and evaluated for hypolipidemic and anti-hyperglycemic activity based on the predictions made by the computer software "Prediction of Activity Spectra for Substances (PASS)". **Material and Methods:** The test compounds were predicted to have a variety of biological activities but those with the best potential for CNS modulating activity were selected for evaluation of a particular CNS activity as 5a for anti-anxiety, 5b, 5n and 5j for nootropic activity and compound 5c anti-catatonic and anti-dyskinetic activities. Test compound 5a was evaluated for anti-anxiety activity in mirrored chamber model and for pentobarbitone induced sleep potentiation in mice. Test compounds 5b, 5n and 5j were evaluated for nootropic activity in mice by examining the effect on transfer latency on elevated plus maze (EPM) in mice and compound 5c was tested for anti-catatonic activity in perphenazine-induced catatonia and anti-dyskinetic effects in reserpine induced orofacial dyskinesia in rats, respectively. **Results and Discussion:** The test compound 5a showed significant anxiolytic activity in the mirror chamber paradigm and showed potentiation of the pentobarbitone-induced hypnosis, which was comparable to diazepam. The nootropic activity of compounds 5b, 5n and 5j were found to be significant in elevated and maze test. The test compound 5c significantly prevented the perphenazine-induced catalepsy in a dose dependent manner. Potentiation of anti-catatonic effect of sub-effective dose of L-dopa and reversal of sulphiride-induced catalepsy was also observed by compound 5c. It indicated that the test compound

might be showing anticatatononic effect by dopaminergic stimulation probably through D2 dopaminergic receptors. Compound 5c significantly reduced the vacuous chewing movements, tongue protrusions and jaw tremors induced by reserpine. It further supports the dopaminergic agonism by the test compound as reserpine induces oral dyskinetic features by depleting catecholamine (dopamine and nor-epinephrine). **Conclusion:** It was concluded that azetidionones possess considerable CNS activities and can be further explored to find additional CNS active compounds.

INTRODUCTION

Azetidin-2-ones (monocyclic-β-lactams) have not been reported so far as CNS active agents, However the presence of this moiety in a variety of heterocyclic biologically active compounds has been reported to increase the CNS activity of parent structures [Table 1]. Substitution of quinazolinones at 3-position with 2-azetidione has resulted in compounds of structure 1, where compounds 1 a, b and c were potent against oxotremorine-induced tremors. The active compounds have phenyl, 2-chlorophenyl and 3-furyl group respectively at the C₄ position of the azetidione ring (1). Substitution of benzopyran-2-ones at position 3 by azetidion-2-ones has been carried out to develop CNS active agents (2). One of these compound 2 exhibited CNS depressant activity in both gross behavioral studies as well as in its effect on spontaneous motor activity measured by using an actophotometer. Carbazole 3 and 1, 2, 4-triazole 4 derivatives of 2-azetidionones have also been explored for anticonvulsant properties (3, 3a). Carbazole derivatives (3 a-b) and 1,2,4-triazole derivatives (4 a-d) were reported to be protective in pentylenetetrazole-induced convulsions. Spiroazetidionones 5 derived from 3-(N-substituted) imino-1-methylindol-2-ones had been reported as anticonvulsants.

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Table 1: Azetidinone substituted CNS active heterocyclic compounds.

The basis of developing these compounds was anticonvulsant activity of indol derivatives (4). Recently azetidinone derivatives have been reported for the treatment of Alzheimer's disease (5). Azetidinones are supposed to exert this effect because of their ability to regulate the production of amyloid-b-peptides. The formation of amyloid-b-peptides depends upon the levels of esterified cholesterol and azetidinones decrease the esterification of cholesterol (6).

With these literature reports test compounds **5a-o** [Table 2], previously synthesized and evaluated for cholesterol absorption inhibitory activity (7) and anti-hyperglycemic activity (7a), were evaluated for potential CNS modulating activities using computer software PASS (Prediction of Activity Spectra for Substances) (8).

Computer software PASS predicts simultaneously several hundreds of biological activities depending upon the chemical structures of compounds. This software determines the predicted activity spectrum of a compound as probable activity (P_a) and probable inactivity (P_i). Prediction of this spectrum by PASS is based on SAR analysis of the training set containing more than 35,000 compounds, which correlates with more than 500 kinds of biological activity. PASS predicted some of our compounds with probable CNS activity viz: 5a for anti anxiety 5b, 5j and 5n for nootropic and 5c for anti-catatonic.

The present study was carried out to evaluate the selected compounds for the above-mentioned CNS activities.

Table 2: Structure of compounds 5a-o.

COMPOUND	R ¹	R ²	R ³
5a			
5b			
5c			
5d			
5e			
5f			
5g			
5h			
5i			
5j			
5k			
5l			
5m			
5n			
5o			

MATERIALS AND METHODS

Animals –Wistar rats (150-200 g) and Laka mice (20-25 g) of either sex bred in Central Animal House facility of the Panjab University were used in these studies. The animals were housed under standard laboratory conditions, maintained on a natural light and dark cycle and had free access to food and water.

Animals were acclimatized to laboratory conditions before the experimentation. All experiments were carried out between 0900 and 1500 h. The experimental protocols were approved by the Institutional Ethics Committee and conducted according to the Indian National Science Academy Guidelines for the use and care of experimental animals.

Drugs: Diazepam (Ranbaxy research laboratories, India), l-dopa (Hi media, Mumbai, India), carbidopa (Sun Pharmaceuticals, Mumbai, India), sulpiride, pentobarbitone, reserpine (Loba chemicals, Mumbai) piracetam (Torrent laboratories, India) perphenazine (Searle India). Test compounds 5a, 5b, 5c, 5j and 5n were suspended in 0.5% carboxy methyl cellulose solution and were administered *per orally* (p.o) in all the experiments.

Evaluation of anti-anxiety activity: The anti-anxiety effect of test compound 5_a was assessed using the mirrored chamber paradigm in Laka mice (9). This mirror chamber paradigm measures approach-conflict behavior of animals. Group-housed mice were brought into the testing room and allowed to acclimate to the new environment for 30 min. The mice were placed in the mirror chamber and scored once. Mice dosed with vehicle or drug, were placed at a single, fixed starting point in a corner of the chamber. The mouse was allowed to explore the chamber for 5 min. The three parameters recorded are transfer latency (the time in seconds for the first entry into the chamber of mirrors), the number of entries, and the total time in seconds spent in the chamber during the test. The criterion for the entry into the chamber was all four feet being placed on to the floor panel of the mirrored chamber. The test compound 5a (1.0, 2.5, 5.0 mg/kg, p.o) and diazepam a reference standard [2.0 mg/kg intra peritoneally (i.p)] were given to mice 30 min before the start of the experiment. Data for vehicle, diazepam and test compound 5a treated groups were compared.

Evaluation of effect on pentobarbitone induced sleep: Pentobarbitone (45 mg/kg, i.p) was injected to Laka mice to induce sleep. The mice treated with the test compound 5a (5.0 mg/kg, p.o) and diazepam (1.0 mg/kg i.p) 30 min before the injection of pentobarbitone were observed for loss and regain of righting reflex to note the onset and duration of sleep respectively. Values observed for vehicle, diazepam and test compound 5a treated groups were compared.

Evaluation of nootropic activity: An elevated plus maze consisting of two open arms (16 x 5 cm) and two enclosed arms (16 x 5 x 12 cm) was used in the present study (10). The maze was elevated at the height of 25 cm. The animal was placed at the corner of an open

arm facing away from center of maze and the time taken by the animal to enter in closed arm was noted as transfer latency (TL), one hour before and 24 hours after administering the test drugs. Test compounds 5j, 5b and 5n (5.0 mg/kg) and reference standard piracetam (3mg/kg) were administered orally in the form of suspension in 0.5% CMC solution.

Evaluation of anti-catatonic effect in perphenazine-induced catatonia: The bar test was used for evaluating anti-catatonic effect of test compound 5c (11). In the bar test, front paw of the mice were gently placed on a horizontal metal bar with 2 mm diameter and placed 4 cm above ground level and the length of time the mouse maintained this abnormal posture with at least one paw was measured. The test was terminated when the paw of animal touched the ground or 180 sec had passed. If the animal did not hold on to the bar after three attempts, it received the score of 0 seconds. The test compound was dosed per orally at 25, 50 and 100 mg/kg and l-dopa (100 mg/kg) in combination with carbidopa (10mg/kg) was used as standard anti-catatonic drug. To explore the mechanism of action, the potentiation of anti catatonic effect of l-dopa (100mg/kg) with sub-effective dose of test compound 5c (50 mg/kg) and reversal of sulpiride (100 mg/kg) induced catatonia was also observed in two different protocols.

Induction and Behavioral assessment of orofacial dyskinesia: Reserpine (1.0 mg/kg i.p) was administered to rats on day 1, day 3 and day 5 of the study to induce oral dyskinesia (12). All the behavioral assessments were carried out 24 h after the last dose of reserpine. Test compound 5c was administered once daily at the doses of 50 and 100 mg/kg per orally in two different treatment groups. The rats were placed individually in a small (30 x 20 x 30 cm) Plexiglas observation chamber for the assessment of oral dyskinesia. Animals were allowed 10 min to get used to the observation chamber before behavioral assessments. The number of vacuous chewing movements and tongue protrusions and jaw tremors were scored by the observer with the help of hand operated counter. In the present study vacuous chewing movements are referred to as single mouth opening in the vertical plane not directed toward physical material. If tongue protrusion, vacuous chewing movements occurred during a period of grooming, they were not taken into account. Counting was

stopped whenever the rat began grooming, and restarted when grooming stopped. Mirrors were placed under the floor and behind the back wall of the chamber to permit observation of oral dyskinesia when the animal was faced away from the observer. The behavioral parameters of oral dyskinesia were measured continuously for a period of 5 min. In all the experiments the scorer was unaware of the treatment given to the animals. The data for vehicle treated and compound 5c were compared.

Statistical analysis: One specific group of rats was assigned to one specific drug treatment condition and each group comprised of 6 rats (n=6). Each score was expressed mean ± SEM. The data were analyzed using Student's "t" test. In all the tests the criterion for the statistical significance was p < 0.05.

RESULTS

Anti-anxiety effect of compound 5a: Compound 5a (1.0 mg/kg, 2.5 mg/kg and 5.0 mg/kg p.o.) dose dependently produced a significant (p < 0.05) increase in time spent and number of entries in the mirror chamber as compared to vehicle treated control mice. Similarly there was a significant (p < 0.05) decrease in transfer latency in the mirror chamber (Table 3 and Figure 1, 2, 3). Further test compound 5a significantly increased the duration of pentobarbitone induced sleep as compared to control animals. (Table 4 and Figure 4)

Nootropic activity of compounds 5j, 5b, and 5n: Test compounds 5j, 5b and 5n showed a significant (p < 0.05) decrease in transfer latency on second day comparable to that exhibited by the reference drug piracetam. (Table 5 and Figure 5).

Anti-catatonic activity of compound 5c: Perphenazine (5 mg/kg), produced full catatonia in animals as indicated by a significant (p < 0.05) increase in time spent on the bar in the bar test. Test compound 5c dose dependently (25-100 mg/kg p.o.) reversed perphenazine-induced catatonia as evidenced by a significant (p < 0.05) decrease time spent on the bar in bar test. (Table 6, Figure 6).

Table 3: Antianxiety effect of 5a in mirror chamber test.

S.No.	Group(mg/kg)	n	Transfer latency (Sec)	In mirror chamber	
				No. of entries	Time spent (Sec)
1	Control	6	122.65±5.36	5.62±1.23	79.49±6.15
2	Compound 5a(1.0)	6	116.5±8.25	8.69±0.32 ^a	120.6±4.75 ^a
3	Compound 5a(2.5)	6	89.89±10.25 ^a	10.28±1.28 ^a	142.3±2.58 ^a
4	Compound 5a(5.0)	6	78.90±5.68 ^a	13.25±1.24 ^a	182.6±11.23 ^a
5	Diazepam(2.0)	6	65.23±5.23 ^a	11.65±1.65 ^a	165.8±11.87 ^a

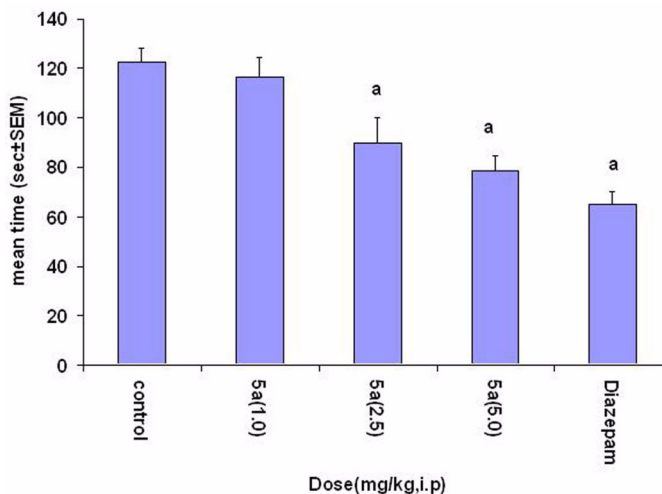


Figure 1: Effect of compound 5a on transfer latency in mirror chamber test in mice (n=6) a= p<0.05 as compared to control group.

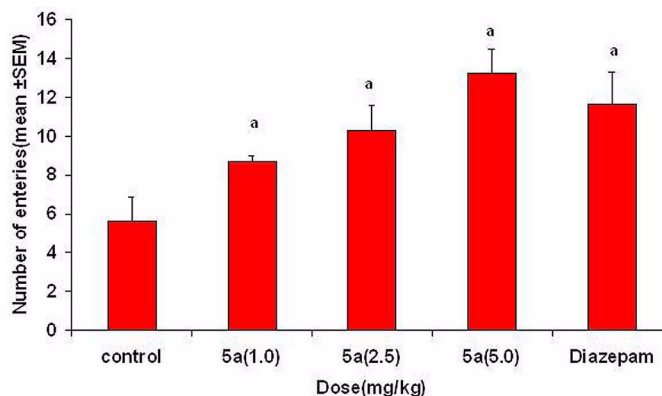


Figure 2: Effect of compound 5a on number of entries in mirror chamber test in mice (n=6) a= p<0.05 as compared to control group.

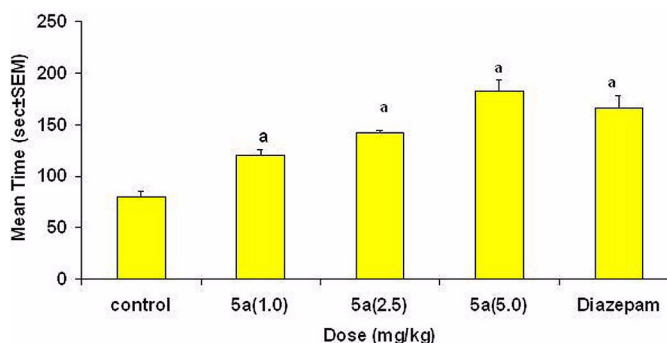


Figure 3: Effect of compound 5a on time spent in mirror chamber test in mice (n=6-8) a= p<0.05 as compare to control group.

Table 4: Effect of test compound 5a on pentobarbitone induced sleep.

S.No.	Treatment Group(mg/kg)	n	Onset sleep(min)	Duration of sleep(min)
1	Control	6	3.0±0.2	42.0±1.8
2	Compound 5a(5)	6	2.2±0.4	70.4±5.4 ^a
3	Diazepam(1.0)	6	3.1±0.5	107.1±6.6 ^a

a= p<0.05 as compare to control group

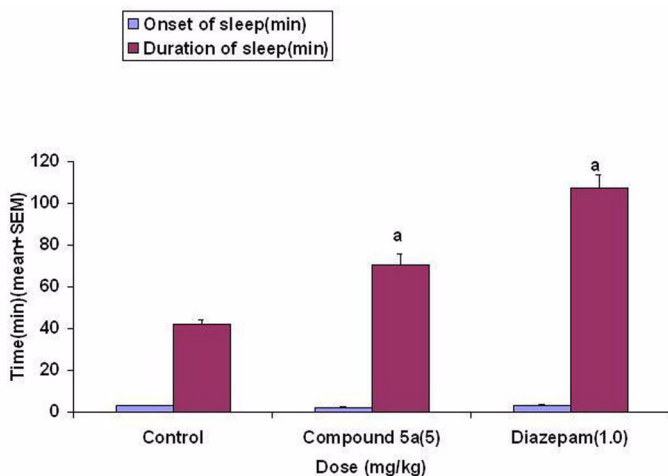


Figure 4: Effect of test compound 5a on pentobarbitone induced sleep in mice (n=6-8) a= p<0.05 as compared to control group.

Table 5: Nootropic effect of compounds 5j, 5b, and 5n in mice as tested on elevated plus maze.

S.No.	Group(mg/kg)	n	Transfer latency (Sec) (day1)	Transfer latency (Sec)(day 2)	Percent decrease
1	Control	6	59.4±9.8	44.2±4.52	25.5
2	Piracetam (3.0)	6	57.0±12.13	10.4±1.2	81.75 ^a
3	Compound 5j(5.0)	6	38.75±2.8	13.25±1.89	65.8 ^a
4	Compound 5b(5.0)	6	37.25±4.89	23.12±7.52	37.9 ^a
5	Compound 5n(5.0)	6	33.25±2.7	13.0±1.25	60.9 ^a

a= p<0.05 as compare to control group

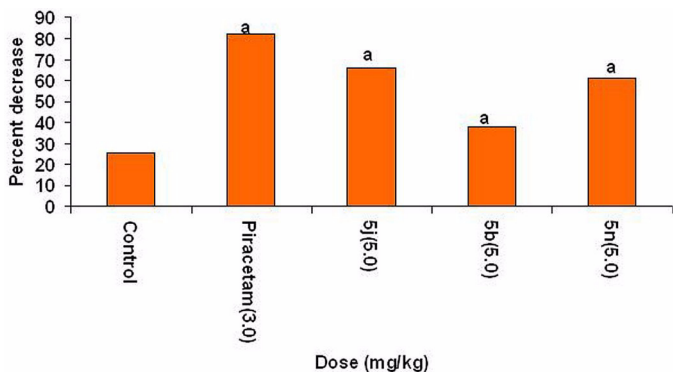


Figure 5: Effect of compounds 5j, 5b, 5n on transfer latency in elevated plus maze in mice (n=6-8) a= p<0.05 as compared to control group.

Table 6: Anticatatonic effect of compound 5c against perphenazine-induced catatonia in rats.

S.No.	Group (Dose mg/kg)	n	Mean fall off time (sec) at					
			0min	30min	60min	120min	180min	240min
1	PPZ(control)	6	0	98.9±6.3	169.0±5.36	186.8±05.3	173.0±4.1	174.25±1.99
2	5c(25)	6	0	80.4±5.7 ^a	117.2±12.5 ^a	122.8±13.8 ^a	124.8±13.4 ^a	145.2±12.56 ^a
3	5c(50)	6	0	61.0±4.6 ^a	57.4±3.87 ^a	107.6±05.8 ^a	112.4±05.6 ^a	111.23±6.09 ^a
4	5c(100)	6	0	15.6±3.1 ^a	22.22±1.55 ^a	027.6±02.8 ^a	028.2±01.2 ^a	21.35±2.56 ^a

a= p<0.05 as compare to control group

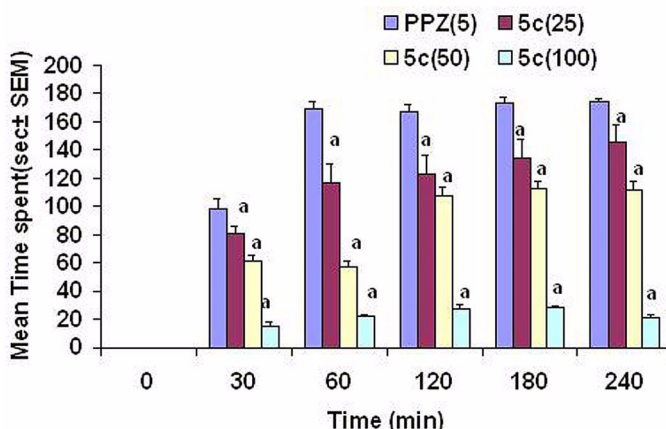


Figure 6: Anti catatonic effect of compound 5c in perphenazine-induced catatonia in rats (n=6-8) a= p<0.05 as compared to control group (perphenazine treated).

L-dopa (100 mg/kg p.o.) plus carbidopa (10 mg/kg p.o.) offered significant protection against perphenazine-induced catatonia. Compound 5c (50 mg/kg), when combined with sub-effective dose of L-dopa (100 mg/kg p.o.) + carbidopa (10 mg/kg p.o.), potentiated the motor stimulating effect of threshold dose of L-dopa as indicated by complete reversal of catatonia in bar tests (Table 7 and Figure 7).

Table 7: Modification of the anticatatonic effect of L-dopa by compound 5c against perphenazine-induced catatonia in rats.

S.No.	Group (Dose mg/kg)	n	Mean fall off time (sec) at					
			0min	30min	60min	120min	180min	240min
1	Sulpiride(100)	6	0	64.2±3.95	110.0±3.8	119.0±4.2	100.2±3.7	96.21±4.89
2	5c(100) +Sulpiride (100)	6	0	57.2±6.34 ^a	67.9±6.1 ^a	70.6±6.6 ^a	71.2±6.3 ^a	73.65±5.56 ^a

a= p<0.05 as compare to sulpiride per se treated group

Sulpiride (100 mg/kg i.p.) produced a significant catatonia. Compound 5c (100 mg/kg p.o.) offered significant (p < 0.05) blockade to sulpiride-induced catatonia (Table 8 and Figure 8).

Antidyskinetic effect of compound 5c: Reserpine (1mg/kg) treatment on alternate days for 3 days signifi-

cantly produced the vacuous chewing movements, tongue protrusions and jaw tremors (JT) in rats. The animals of vehicle treated control did not exhibit such behaviors.

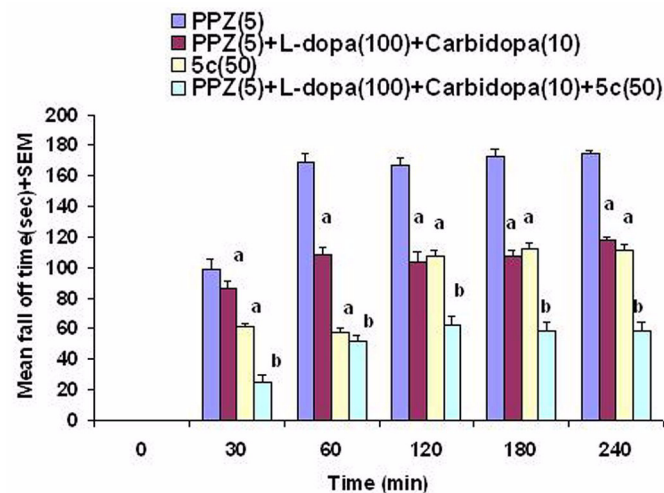


Figure 7: Modification of l-dopa effect of on perphenazine induced catatonia by compound 5c in rats (n=6-8). a= p<0.05 as compared to control group (perphenazine treated), b= p<0.05 as compared to groups treated with compound 5c (50mg/kg) and l-dopa (100 mg/kg).

Table 8: Modification of on sulpiride-induced catatonia by compound 5c in rat.

S.No.	Group (Dose mg/kg)	n	Mean fall off time (sec) at					
			0min	30min	60min	120min	180min	240min
1	Sulpiride(100)	6	0	84.2±3.95	110.0±3.8	119.0±4.2	100.2±3.7	86.21±4.89
2	5c(100) +Sulpiride (100)	6	0	57.2±6.34 ^a	67.9±6.1 ^a	70.6±6.6 ^a	71.2±6.3 ^a	73.65±5.56 ^a

a= p<0.05 as compare to sulpiride per se treated group

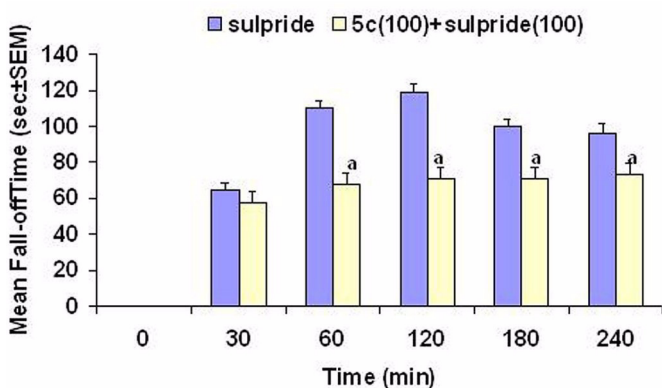


Figure 8: Effect of compound 5c on sulpiride-induced catatonia in rats (n=6-8) a= p<0.05 as compared to sulpiride per se treated group.

Table 9: Effect of 5c pretreatment on reserpine-induced orofacial dyskinesia in rat.

S.No.	Treatment group (Dose mg/kg)	n	Vacuuous Chewing Movements	Toung Protrusions	Jaw Tremors
1	Saline	6	0	0	0
2	Reserpine(control)	6	87.6±2.26	24.0±2.78	17.0±1.94
3	5c(50)	6	67.33±1.42 ^a	15.0±1.17 ^a	9.67±0.25 ^a
4	5c(100)	6	42.25±1.06 ^a	9.0±0.5 ^a	6.0±0.56 ^a

a= p<0.05 as compare to control group

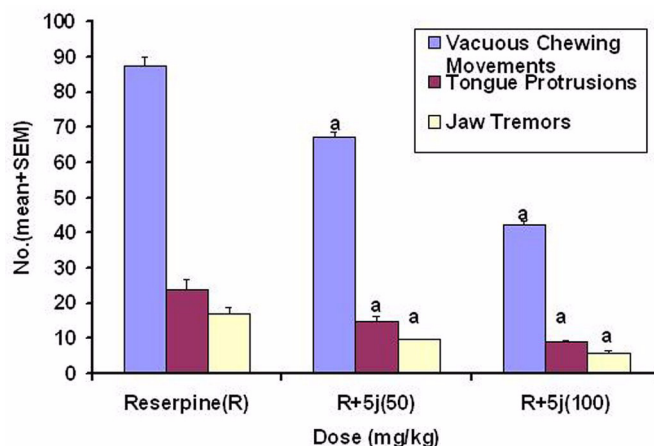


Figure 9: Effect of 5c on reserpine induced orofacial dyskinesia in rats (n=6-8) a= p<0.05 as compared to reserpine only treated group (control group).

Chronic co-administration of compound 5c along with reserpine, significantly (p < 0.05) and dose dependently (50 and 100 mg/kg) suppressed the reserpine-induced vacuous chewing movements, tongue protrusions and jaw tremors (Table 9 and Figure 9).

DISCUSSION

Anti anxiety activity of compound 5a: Compound 5a showed anti anxiety activity as evidenced by dose dependent significant increase in number of entries and total time spent in mirrored chamber and also by decreased transfer latency. The effect of the compound was comparable with diazepam used as a reference drug in the study. The CNS depressant action of 5a was further verified as it potentiated the pentobarbitone induced sleep significantly.

The vasopressin V2 receptor antagonism has been reported to exert antianxiety effect (13). Compound 5a has structural similarity with the 2-azetidinone 6 reported with vasopressin inhibitory activity (14). (Table I) Thus it is proposed that compound 5a may be exerting anti-anxiety effect via vasopressin V2 receptor antagonism.

Nootropic activity of test compounds 5b, 5j and 5n: Test compounds showed a significant decrease in transfer latency on second day indicating the improvement in cognitive function. As the β -lactam analogues retain the biological activity of α -lactam bioactive compounds (15), so it is proposed that the nootropic activity of these compounds may be due to the presence of monocyclic beta lactam ring, as compounds containing suitably substituted monocyclic gamma lactam ring (piracetam, etiracetam, pramirastam, aniracetam etc.) are known to possess the nootropic activity.

Anti-catatonic activity of test compound 5c: Perphenazine induced catalepsy has been ascribed to its ability to block dopamine D2 receptors in the striatum (16). The catatonic effect of phenothiazines in animals is considered as representative of the extra pyramidal motor effects seen in Parkinsonian patients. In Parkinson's disease the decreased dopamine levels due to loss of dopaminergic neurons, removes the inhibitory effect of dopamine D2 receptors towards indirect pathway, whose increased activity leads to the disinhibition of excitatory influence to the cortex and the cardinal symptoms of bradykinesia (17, 18). Test compound 5c showed dose dependent decrease in mean fall-off time in bar test indicating anticatatonic activity. Test compound also showed the potentiation of anticatatonic activity of sub-effective dose of L-dopa. Further studies, showed reversal of catatonic effect of sulphiride a specific D2-receptor antagonist by the test compound. These findings suggest that anti catatonic activity of test compound may be mediated through D2 receptor activation.

Antidyskinetic activity of test compound 5c: Reserpine is a monoamine-depleting agent that depletes dopamine and norepinephrine non-selectively and its repeated administration in rats produced spontaneous oral dyskinesia similar to tardive dyskinesia and this may be due to decreased dopaminergic transmission (19). Test compound 5c showed significant antidyskinetic activity by decreasing reserpine-induced orofacial dyskinetic behaviors in rats. This effect of test compound may be attributed to its dopaminergic agonistic activity.

CONCLUSION

The present study concluded that the azetidionones possess considerable CNS modulating activities, and can be explored further to find the additional CNS active compounds.

REFERENCES

- [1] Srivastva VK, Singh S, Gulati A, Shankar K. Antiparkinsonian agents from quinazolinyl thiazolidinones and azetidionones. *Indian J Chem(B)* 1987;26: 652-656
- [2] Kulkarni YD, Srivastva D, Bishnoi A, Dua PR. Synthesis of 3-(a(3-chlor-2-oxo-4-substitued-phenyl)/furfuryl-1-azetidiny)-2-H-1-benzopyran-2-ones and 3-(a-(2-substitued-phenyl)/furfuryl thiazolidinyl)-2-H-1-benzopyran-2-ones as CNS active agents. *J Indian Chem Soc* 1996; 73: 173-175
- [3] Srivastava SK, Srivastava S, Srivastava SD. Synthesis of new carbazoyl-thiazol-2-oxo-azetidines antimicrobial anticonvulsant and anti-inflammatory agents. *Indian J Chem (B)* 1999; 8: 183-187.
- [3a] Srivastava SK, Srivastava S, Srivastava SD. Synthesis of 1, 2, 4-triazolo-thiadiazoles and its 2-oxoazetidines as antimicrobial, anticonvulsant and anti-inflammatory agents. *Indian J Chem (B)* 2002; 41: 2357-2363
- [4] Singh GS, Siddiqui N, Pandeya SN. Synthesis and anticonvulsant activity of new 1-substituted 1'-methyl-3-chloro-2-oxospiro (azetidin-3',4'-indol-2'-ones). *Boll Chim Farmaceutico* 1994;133 : 76-79
- [5] Davis HR, Parker EM, Magaret VH, Tse WH, Markel LB. *Chemical abstracts* 2003, (138) : 375 :14002 g
- [6] Puglielli L, Konopka G, Pack Chung E, Ingano LA, Berezovska O, Hyman BT, Chang TY, Tanzi RE, Kovacs DM. Acyl-coenzyme A cholesterol acyltransferase modulates the generation of the amyloid-b-peptide. *Nat Cell Biol* 2001; 10: 905-912
- [7] Goel RK, Mahajan MP, Kulkarni SK. Hypocholesterolemic activity of some novel 2-azetidionones in diet and diabetes induced hypercholesterolemia in rats. *Die Pharmazie* (in press).
- [7a] Goel RK, Mahajan MP, Kulkarni SK. Evaluation of anti-hyperglycemic activity of some novel monocyclic beta lactams *J Pharm Pharmaceut Sci* 2004;7(1):76-78
- [8] Filimonov DA, Poroikov VV, Karaicheva EI, Kazaryan RK, Boudunova AP, Mikhailovsky EM, Rudnitskih AV, Goncharenko LV, Burov Yu. *Exp Clin Pharmacol (Rus)* 1995,8, 56-62 and www.ibmh.msk.su/pass/predict
- [9] Reddy DS, Kulkarni S K. Differential anxiolytic effects of neurosteroids in the mirrored chamber behavior test in mice. *Brain Res* 1997;287 : 61-71
- [10] Kumar S, Kulkarni SK. Influence of antidepressant drugs on learning and memory paradigms in mice. *Indian J Exp Biol* 1996;5: 431-435
- [11] Costall B, Naylor RJ. On catalepsy and catatonia and the predictability of the catalepsy test for neuroleptic activity. *Psychopharmacologia*. 1974;34(3):233-241

- [12] Kulkarni SK, Naidu PS. Animal models of tardive dyskinesia--a review. *Indian J Physiol Pharmacol* 2001;5(2): 148-160
- [13] Griebel G, Simiand J, Serradeil-le Gal C, Wagnon J, Pascal M, Scatton B, Maffrand JP, Soubrie P. *PNAS* 2002; 99:6370-6375
- [14] Bruns RF, Cooper DJ, Dreessman BA, Hunden DC, Kaldol SW, Gray AR, John RS. *Chemical abstracts* 1997;127(11): 607: 234215s
- [15] Nilsson BM, Ringdahl B, Hacksell U. Beta-lactam analogues of oxotremorine 3- and 4-methyl-substituted 2-azetidinones. *J Med Chem* 1990;33 (2): 580-584
- [16] Kulkarni SK, Arzi A, Kaul PN. Modification of drug-induced catalepsy and tremors by quizapine in rats and mice. *Jpn J of Pharmacol* 1980; 30: 129-135
- [17] Shukla VK, Garg S K, Kulkarni SK. Yohimbine potentiate the anticataleptic action of clonidine against perphenazine-induced catalepsy in rats. *Archives Internationales de Pharmacodynamie et de Therapie* 1986; 282(1): 44-49
- [18] Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Lanciego JL, Artieda J, Gonzalo N, Olanow W. Pathophysiology of the basal ganglia in Parkinson's disease. *Trends in Neurosci* 2000;23 (3): S8-S19
- [19] Neisewander JL, Lucki I, McGonigle P. Neurochemical changes associated with the persistence of spontaneous oral dyskinesia in rats following chronic reserpine treatment. *Brain Res* 1991; 558(1):27-35