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Synthesis and evaluation of substituted oxazolyl/Thiazolyl Thiazolidines and Azetidines derivatives for central nervous system depressant activity

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Abstract

Heterocyclic derivatives has been found in a large number of compounds which shows antibacterial, antifungal, anti-inflammatory, anti-tuberculosis, anticonvulsant activity. There is a close relation between the biological activity of the compounds on their molecular structures .The compounds containing thiazole, thiadiazole, oxazole, oxadiazole, imidazole, pyrimidine, pyridine and benzothiazoles rings have been found to exhibit broad spectrum of biological activities.

In the present work, Oxazolyl/Thiazolyl-2`-(4-phenyl-3-Chloro-2-oxo-Azetidine) and Oxazolyl/Thiazolyl-2`-(5-phenyl-2-oxo-Thiazolidine) were synthesized. The different heterocyclic moieties were condensed with aromatic aldehyde in ethanol containing trace amount of glacial acetic acid which were converted into various azetidines and thiazolidines by reaction with thioglycolic acid and chloro acetyl chloride. The structures of the synthesized compounds were characterized on the basis of IR and HNMR spectral data. Among all synthesized selected compounds were screened for their CNS activity. Chlorpromazine hydrochloride is employed as a reference standard. From the results it is concluded that, synthesized compounds show more depressant activity than reference standard.

Keywords : Thiazolidine, Azetidine, thioglycolic acid, chloroacetyl chloride, Chlorpromazine hydrochloride, CNS activity.

Introduction

The drug which decreases the activity of some parts of brains or spinal cord is called central nervous depressants. CNS depressants, sometimes referred to as sedatives and tranquilizers are substances that can slow brain activity. This property makes them useful for treating anxiety and sleep disorders. The group of drugs with unique chemical properties that induce a behavioral depression produces relief from unconsciousness, anxiety, sleep and the predominant tendency of all these drugs is to inhibit the excitability of neurons.

CNS depressants slow normal brain function. In higher doses, some CNS depressants can become general anesthetics. Tranquilizers and sedatives are examples of CNS depressants. CNS depressants can be divided into two groups, based on their chemistry and pharmacology:

1. Barbiturates, such as mephobarbital (Mebaral) and pentobarbital sodium (Nembutal), which are used to treat anxiety, tension, and sleep disorders.

2. Benzodiazepines, such as diazepam (Valium), chlordiazepoxide HCl (Librium), and alprazolam (Xanax), which can be prescribed to treat anxiety, acute stress reactions, and panic attacks. Benzodiazepines that have a more sedating effect, such as estazolam (ProSom), can be prescribed for short-term treatment of sleep disorders.

Ragab *et al.,* (1997) synthesized thiazolidinones and thiadimidazolidinone derivatives for their anticonvulsant activity. Rao and Mittra (1978) reported CNS activity in various pyrazole and pyrazolone derivatives Rana *et al.*,(2007) reported N-{[(6-substituted-1,3, benzothiazole-2-yl)amino]carbonothioyl}-2,4-substituted benzamides as potential anti-convulsant [3]. Nassem *et al*. Synthesised, 2-(1H-indole-3-yl) acetyl-N- (substituted phenyl) hydrazine carbothiamides and reported as anticonvulsants (Nassem *et al.,* 2008). The literature survey shows that indoline derivatives which have a wide range of biological activities such as antimicrobial, anti-inflammatory, antihistamine, antioxidant, anti-proliferative and antidepressants (Canas and Leeming, 1969). Various indole derivatives are reported to be effective in CNS disorders such as convulsion and depression (Sareen *et al*, 1962). Chinnasamy Rajaram *et al.,* (2010) reported Anticonvulsant activity of Schiff bases of isatin derivatives (Katritzky A R., 1984). Substituted 1,3,4 oxadiazoles derivatives are reported to show broad spectrum of biological activities viz.

bactericidal, fungicidal, herbicidal, antiviral and CNS depressant (Doran and Schonle, 1938). Thiazolidinones are used as sedatives (Jones *et al.,*1946) hypnotics (Erlenmeyer and Meyonburg, 1937, Bhattacharjee *et al.,*2012), antipasmodic or anticonvulsant. Some Schiff Bases of 2-Amino-N-(O-Fluorophenylcarboxamido)-4-(P-Methoxyphenyl) Thiophenes were synthesized by Bhattacharjee et al.,and found to possess CNS depressant activity (Kashaw *et al.,* 2008). 1-(4-substituted-phenyl)-3-(4-oxo-2-propyl-*4H*-quinazolin-3-yl)-urea were synthesized by Kashaw *et al*., for CNS activity[13]. Christopher B. Chapleo *et al*. synthesized a series of 2-aryl-5-hydrazino-l,3,4-thiadiazole derivatives and evaluated them for anticonvulsant activity (Chapleo, 1986).

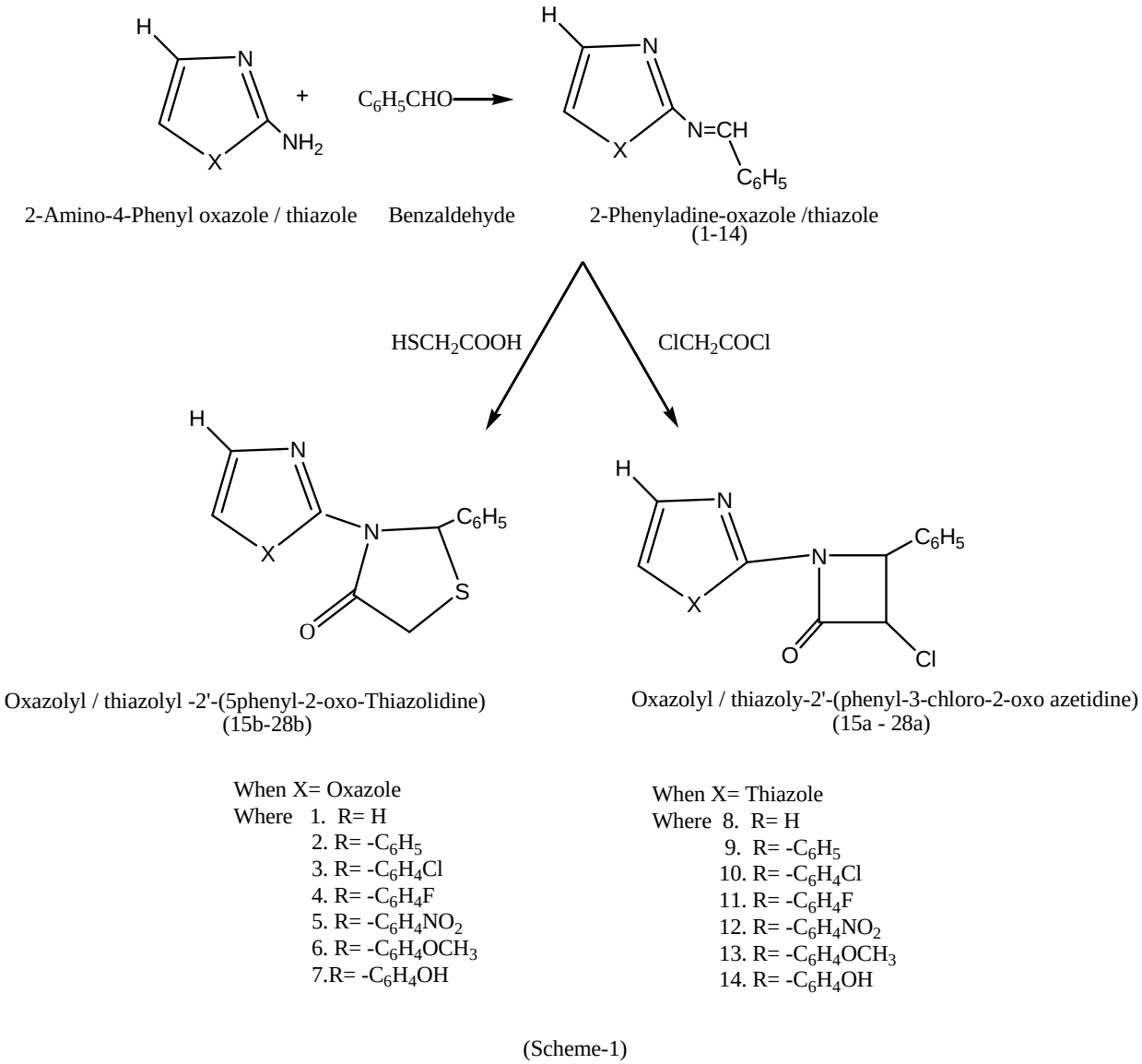
A survey of literature reveals that benzotriazoles derivatives possess immense biological properties such as anti-inflammatory, analgesic, anti-bacterial, hypertensive and CNS depressant activity. 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones were reported as CNS depressant and anticonvulsants by Jatav *et al.,(*2008). New 3-[(3-Substituted-5-methyl-4-thiazolidinon-2-ylidene) hydrazono]-1*H*-2-indolinones and 3-[(2-Thioxo-3-substituted-4, 5-imidazolidine-dion-1-yl)imino] - 1*H*-2-indolinones were synthesized by Karali *et al* and screened for CNS Depressant Activity (Karali *et al.,*1998). K. P. Harish *et al.* synthesized a series of 2-amino-5-sulphanyl-1,3,4-thiadiazole derivatives and evaluated for the anticonvulsant activity (Harish *et al.,* 2014). Saxena and Khan (1989) reported CNS depressant activity in quinazolone derivatives. John (1982 and 1986) reported that quinazoline and its synthetic analogue exhibit biological activities like anticonvulsant, anti-depressant and CNS stimulants.

A series of 3-substituted 5-methoxycarbonyl-5-methoxy-carbonylmethyl-1,4,2-dioxazoles was prepared by Ned D. Heinde et all for pharmacological screening as CNS depressant activity (Heinde *et al.,* 1977). 5-(2-Aminoethyl)-2-oxazolidinones with central nervous system depressant and anti-inflammatory activity were reported by Welstead *et al.,* (1973). Saxena *et al* reported that Substituted octahydro pyrazino pyrido indoles, a new class of central nervous system depressants (Saxena *et al.,* 1973) .5-(2-substituted alkyl)-2-oxazolidinones (Fielder *et al.,* 1973), oxaza heterocyclic amides (Pifferi *et al.,* 1972), trimethoxybenzoyloxazolidine were also reported to have CNS depressants by various workers. Recently N-[2-phenyl-4-oxo-1,3-thiazolidin-3-yl]-2-(2,4,6-trichlorophenoxy) acetamide showed depression of the central nervous system in mice. Compound with 4-OH, 3-OCH3 substitution on phenyl ring and hydrogen group on thiazolidine ring showed more promising CNS depressant reported by N.Sunitha *et al.,* (2016).

Sudheer Babu and Selvakumar (2013) co-relates structural activity relationship studies on synthesized compounds, 1-ortho phenyl carboxylic acid substituted and 1- phenyl substituted benzimidazolyl isoindolines, which showed good CNS depressant activity. Raghunandan Nerella *et al.,* (2011) synthesized a series of new 1-NSubstituted amino methyl-3-(3-phenyl quinazolin-4-one-methylene- 2-yl) indolin-2-one showed CNS depression activity. Bethi Srinivas *et al.*, (2011) synthesized a series of isatin derivatives containing 1, 2, 3, 4- tetrahydrocarbazole moiety, the synthesized compound exhibited central nervous system depression in the mice (Ganesh *et al.,* 2011). Some mannich bases of 1,3,4 oxadiazoles were prepared by screened for CNS depressant activity. Poonam Singh *et al.,* (2012) synthesized substituted diphenyl- 1,3,4-oxadiazole derivatives for central nervous system depressant activity and concluded that introduction of electron withdrawing group at C2 & C5 position of the oxadiazole nucleus increases the pharmacological activity (Deivanayagam *et al.,* 2015).

[1-(thiophen-2-yl] ethylidene] hydrazine and 4, 4'-(hydrazine-1,2- diylidenedimethylylidene) bis (N,N-dimethyl aniline) were synthesized and screened for CNS depressant activity by P. Deivanayagam *et al.,* (2015). 5-amino-1,3,4-thiadiazole-2-thiol possess anticonvulsant activity (Yusuf *et al.,* 2013). Rajesh Sharma et al (2014) reported 2-(2-(3-(4-chlorophenyl)-6-oxo-5,6-dihydropyridazin- 1(4H) yl)acetyl)hydrazine carbothioamide and 2-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-6-(4- chlorophenyl)-4,5- dihydropyridazin-3(2H)-one derivatives and found to possess anticonvulsant activity. Indulatha *et al.,* (2012) synthesized Novel N-4'-oxo-2'-(substituted phenyl)-thiazolidin-3'-yl]-3-carboxamido-2H-chromen-2-one and evaluated for their anticonvulsant activity. Xinghua Zhen *et al.,* (2015) synthesized 2-(5-methyl-2,3-dioxoindolin-1-yl) acetamide derivatives and reported for their anticonvulsant activity.

K. Swathi *et al.,* (2014) carried out synthesis and sedative-hypnotic activity of novel series of isatin hydrazone and isatin thiosemicarbazone derivatives by using potentiation of pentobarbitone induced Narcosis method against standard drug diazepam (50mg/kg) [36]. Lots of work has been done on thiazole & oxazole nucleus with potential biological activities. Various azetidinones and thiazolidinones are reported to possess CNS depressant activity. Keeping all these views and literature survey attempts were made to synthesize various azetidines and thiazolidines and screened for CNS depressant activity as given in Scheme-1)



(Scheme-1)

Fig: Scheme 1

Materials and Methods

All the melting points were determined in open capillary tubes. IR spectra were recorded in solid state using KBr pellet method. The spectra were recorded on Perkin Elmer FT-IR spectrophotometer (model RX-1). The PMR spectra were recorded in DMSO-d6 solvent at room temperature using TMS as reference compound. The spectra were recorded on Perkin Elmer Model 32 NMR spectrometer at 300MHz at CDRI Lucknow.

The reactions were monitored by TLC. The required 2-Amino-4-[p-subst/unsubst] phenyl thiazoles / oxazoles were prepared by know method. Procedure for one compound of each step has been described in sequel.

Synthesis of 2-Amino – Oxazole

A solution of 60 gm of urea in 200 ml of warm water is placed in 500 ml three necked flask equipped with dropping funnel ,mechanical stirrer and reflux condenser.143 gm of α,β-dichloroethyl ether is added and the mixture is heated under gentle reflux with stirring for 2 hrs. As the reaction proceeds, the two layers gradually merge. To the cold solution, sufficient solid NaOH is added to liberate 2-Amino oxazole from its salt. Ether is added to dissolve the product and ether is evaporated.2-Amino oxazole is recrystallized from ethanol.

M.P.: 90- 95^{0}C.

IR (KBr): 1255 cm-^{1} (due to C-N), 1475 - 1453 cm-^{1}(due to C=N), 3065-3005 cm-^{1} (due to C-H), 1565-1558 cm-^{1} (due to N=C-O), 3300-3135 cm-^{1} (due to N-H),

PMR: δ 6.7 (s, 1H, due to -CH), δ 7.2 (s, 1H, due to -CH), δ 5.12 (br, s, 2H, due to NH_2).

Synthesis of 2-Amino-4-phenyl Oxazole

In a round bottom flask, add 2-bromo-1-phenylethanone (1.0 m mol), urea (1.0 m mol) and PEG (0.5 ml) under reflux until the completion of reaction (monitored by TLC). The resultant compound was washed with water (4mL) then extracted with ethyl acetate (3 X 15 ml). The organic phase was separated & passed through anhydrous sodium sulphate, and filtered. The excess solvent was removed under vacuum. The crude mixture was purified by using standard silica gel column chromatography in ethyl acetate & petroleum ether in the ratio of 1:1. After extraction with ethyl acetate, H_2O and PEG 400 were removed by heating mixture to its boiling point.

B.P: 113-115^{0}C

IR (KBr): 1255 cm-^{1} (due to C-N), 1475 - 1453 cm-^{1}(due to C=N), 3065-3005 cm-^{1} (due to C-H), 1565-1558 cm-^{1} (due to N=C-O), 3300-3135 cm-^{1} (due to N-H), 1155-1103 cm-^{1} (due to C-O-C)

NMR: (300 MHz, CDCl3): δ 7.52–7.47 (m, 2H, ArH), 7.33–7.28 (m, 2H, ArH), 7.09 (m, 1H, ArH), 6.74 (s, 1H, oxazole), 5.17 (br s, 2H, NH2)

Similarly, 2-Amino-4-p-chloro/ fluoro/ nitro /methoxy/ hydroxy phenyl oxazoles were prepared.[37-39]

Synthesis of 2-Amino – Thiazole

A solution of 76 gm of thiourea in 200 ml of warm water is placed in 500ml three necked flask equipped with dropping funnel, mechanical stirrer and reflux condenser. 143 gm of α,β-dichloroethyl ether is added and the mixture is heated under gentle reflux with stirring for 2 hrs. As the reaction proceeds, the two layers gradually merge. To the cold solution, sufficient solid NaOH is added to liberate 2-Amino Thiazole from its salt. Ether is added to dissolve the product and ether is evaporated.2-Amino Thiazole is recrystallized from ethanol.

M.P.: 90- 91^0C.

IR (KBr): 1255 cm^{-1} (due to C-N), 694 cm^{-1} (due to C-S-C), 1615 & 1535 cm^{-1}(due to C=N)

PMR: δ 6.6 (s, 1H, due to -CH), δ 7.1 (s, 1H, due to -CH), δ 11.4 (d, 2H).

Synthesis of 2-Amino-4-phenyl Thiazole

A mixture of acetophenone (12.0gm, 0.1mol), thiourea (15.2gm, 0.2mol) and iodine (25.4gm, 0.1mol) was heated for 10 hours on a steam bath. The crude reaction mixture was cooled and repeatedly extracted with ether to remove unreacted acetophenone and iodine. The residue was then dissolved in hot water and filtered to remove sulphur and other impurities. The solution was then moderately cooled and made alkaline with conc. Ammonia.2-amino-4-phenyl thiazole, thus precipitated was collected and recrystallized from diluted ethanol as long colorless needles.

M.P.: 149^0C.

IR (KBr): 1255 cm^{-1} (due to C-N), 694 cm^{-1} (due to C-S-C), 1615 & 1535 cm^{-1}(due to C=N)

PMR: δ 6.6 (s, 1H, due to -CH), δ 7.5 (m, 5H, Aromatic), δ 11.35 (d, 2H,-NH_2).

Synthesis of 2-Phenyladine-Oxazole [1-14]

A mixture of 2-amino oxazole (0.01mol) and benzaldehyde (0.015mol) in absolute EtOH (30 ml) in presence of glacial acetic acid was refluxed for 10 hours on a steam bath. The solvent was removed under pressure. The solid thus obtained was washed with EtOAc-Hexane (1:1) then with cold water and recrystallized from methanol.

Yield = 52%

M.P = 179°C

IR (KBr): 1690 – 1625 cm^{-1} (due to C=N), 1252 – 1225 cm^{-1} (due to C-N), 3065-3005 cm^{-1} (due to C-H), 1565-1558 cm^{-1} (due to N=C-O), 1155-1103 cm^{-1} (due to C-O-C).

PMR: δ 6.6 (s, 1H, due to -CH), δ 6.9 – 7.7.9 (m, 5H, due to Ar-H), δ 8.52 (s, 1H, due to -CH).

Similarly various 2-Phenyladine -4-(p-subst/unsubst)-phenyl thiazole / oxazole were synthesized by using similar reaction procedure.

Synthesis of Oxazolyl/Thiazolyl-2`-(4-phenyl-3-Chloro-2-oxo-Azetidine) [15a-28a]

To the compound [1-14] (0.01mol) in dioxane (50ml) was added chloro acetyl chloride (0.01 mol) and Et_3N at 0°C with stirring. The mixture was left at room temperature for 3 hours, then refluxed for 10 hours; excess of solvent distilled off and the residue was poured over crushed ice. The resulting solid was crystallized from proper solvent.

Yield = 45%

M.P = 209°C

IR (KBr): 740 cm^{-1} (due to C-Cl), 1685 cm^{-1} (due to cyclic C=O), 1690 – 1625 cm^{-1} (due to C=N), 1252 – 1225 cm^{-1} (due to C-N), 3065-3005 cm^{-1} (due to C-H), 1565-1558 cm^{-1} (due to N=C-O), 1155-1103 cm^{-1} (due to C-O-C).

PMR: δ 4.45-4.6 (1H, d, N-CH), δ6.95-7.1 (1H, d, CH-Cl), δ 6.8 (1H, s, due to -CH), δ 7.3 – 7.8 (10H, m, due to Ar-H).

Similarly, various 4`-(p-subst / unsubst)-phenyl oxazolyl / Thiazolyl-2`-(4-phenyl-3-chloro-2-oxo-azetidines) were synthesized by using similar reaction.

Synthesis of Oxazolyl/Thiazolyl-2`-(5-phenyl-2-oxo-Thiazolidine) [15b-28b]

To the compound [1-14] (0.01 mol) in DMF (30 ml) was added in thioglycolic acid (0.01 mol) and $ZnCl_2$ in traces. The reaction mixture was refluxed for 10 hours, then cooled and poured over crushed ice. The resulting solid was crystallized from DMF/water.

Yield = 49%

M.P = 213°C

IR (KBr): 1705 cm^{-1} (due to C=O), 1690 – 1625 cm^{-1} (due to C=N), 1252 – 1225 cm^{-1} (due to C-N), 3065-3005 cm^{-1} (due to C-H), 1565-1558 cm^{-1} (due to N=C-O), 1155-1103 cm^{-1} (due to C-O-C).

PMR: δ 5.6 (1H, s, N-CH, thiazolidine ring), δ 6.8 (1H, s, due to -CH), δ 7.38 – 7.86 (10H, m, due to Ar-H), δ 3.6-3.75 (2H, s, $CO-CH_2-S$)

Similarly, various 4`-(p-subst/unsubst)-phenyl oxazolyl/Thiazolyl-2`-(5-phenyl-2-oxo-thiazolidine) were synthesized by using similar reaction procedure. The analytical data of all the synthesized compounds are incorporated in Table 1 respectively.

Table 1: Physical Data of Synthesized Compounds

Comp'd No.	Nature of R	Molecular Formula	MP°(C)	Yield (%)
1.	2-Amino- oxazole	$C_{10}H_9N_2O$	110 - 112	75
2.	2-Amino-4-phenyl oxazole	$C_{16}H_{13}N_2O$	118 - 120	72
3.	2-Amino-4-(p-chloro) phenyl oxazole	$C_{16}H_{12}N_2OCl$	119 -121	75
4.	2-Amino-4-(p-fluoro) phenyl oxazole	$C_{16}H_{12}N_2OF$	120-122	69
5.	2-Amino-4-(p-nitro) phenyl oxazole	$C_{16}H_{12}N_3O_3$	126-128	70
6.	2-Amino-4-(p-methoxy) phenyl oxazole	$C_{17}H_{15}N_2O_2$	124-126	68
7.	2-Amino-4-(p-Hydroxy) phenyl oxazole	$C_{16}H_{13}N_2O_2$	122-124	70
8.	2-Amino- Thiazole	$C_{10}H_9N_2S$	111-113	77
9.	2-Amino-4-phenyl Thiazole	$C_{16}H_{13}N_2S$	119-121	73
10.	2-Amino-4-(p-chloro) phenyl Thiazole	$C_{16}H_{12}N_2SCl$	121-123	72
11.	2-Amino-4-(p-fluoro) phenyl Thiazole	$C_{16}H_{12}N_2SF$	125-127	70

12.	2-Amino-4-(p-nitro) phenyl Thiazole	$C_{16}H_{12}N_3O_2S$	123-125	69
13.	2-Amino-4-(p-methoxy) phenyl Thiazole	$C_{17}H_{15}N_2O_S$	127-129	73
14.	2-Amino-4-(p-Hydroxy) phenyl Thiazole	$C_{16}H_{13}N_2OS$	124-126	65
15a	2-Amino- oxazole	$C_{12}H_9N_2O_2Cl$	134-136	66
16a	2-Amino-4-phenyl oxazole	$C_{18}H_{13}N_2O_2Cl$	140-142	69
17a	2-Amino-4-(p-chloro) phenyl oxazole	$C_{18}H_{12}N_2O_2Cl_2$	139-141	65
18a	2-Amino-4-(p-fluoro) phenyl oxazole	$C_{18}H_{12}N_2O_2ClF$	141-143	62
19a	2-Amino-4-(p-nitro) phenyl oxazole	$C_{18}H_{12}N_3O_4Cl$	147-149	65
20a	2-Amino-4-(p-methoxy) phenyl oxazole	$C_{19}H_{15}N_2O_3Cl$	151-153	55
21a	2-Amino-4-(p-Hydroxy) phenyl oxazole	$C_{18}H_{13}N_2O_3Cl$	155-157	53
22a	2-Amino- Thiazole	$C_{12}H_9N_2OSCl$	136-138	62
23a	2-Amino-4-phenyl Thiazole	$C_{18}H_{13}N_2OSCl$	142-144	60
24a	2-Amino-4-(p-chloro) phenyl Thiazole	$C_{18}H_{12}N_2OSCl_2$	147-149	52
25a	2-Amino-4-(p-fluoro) phenyl Thiazole	$C_{18}H_{12}N_2OSFCl$	145-147	53
26a	2-Amino-4-(p-nitro) phenyl Thiazole	$C_{18}H_{12}N_3O_3SCl$	149-151	50
27a	2-Amino-4-(p-methoxy) phenyl Thiazole	$C_{19}H_{15}N_2O_2SCl$	155-157	55
28a	2-Amino-4-(p-Hydroxy) phenyl Thiazole	$C_{18}H_{13}N_2O_2SCl$	153-155	52
15b	2-Amino- oxazole	$C_{12}H_{10}N_2O_2S$	155-157	50
16b	2-Amino-4-phenyl oxazole	$C_{18}H_{14}N_2O_2S$	159-161	52
17b	2-Amino-4-(p-chloro) phenyl oxazole	$C_{18}H_{13}N_2O_2SCl$	163-165	47
18b	2-Amino-4-(p-fluoro) phenyl oxazole	$C_{18}H_{13}N_2O_2SF$	162-164	50
19b	2-Amino-4-(p-nitro) phenyl oxazole	$C_{18}H_{13}N_3O_4S$	165- 167	50
20b	2-Amino-4-(p-methoxy) phenyl Thiazole	$C_{19}H_{16}N_2O_3S$	169-171	42
21b	2-Amino-4-(p-Hydroxy) phenyl oxazole	$C_{18}H_{14}N_2O_3S$	175-177	46
22b	2-Amino- Thiazole	$C_{12}H_{10}N_2OS_2$	153-155	48
23b	2-Amino-4-phenyl Thiazole	$C_{18}H_{14}N_2OS_2$	159-161	49
24b	2-Amino-4-(p-chloro) phenyl Thiazole	$C_{18}H_{13}N_2OS_2Cl$	163-165	42
25b	2-Amino-4-(p-fluoro) phenyl Thiazole	$C_{18}H_{13}N_2OS_2F$	162-164	35
26b	2-Amino-4-(p-nitro) phenyl Thiazole	$C_{18}H_{13}N_3O_3S_2$	165- 167	39
27b	2-Amino-4-(p-methoxy) phenyl Thiazole	$C_{19}H_{16}N_2O_2S_2$	169-171	37
28b	2-Amino-4-(p-Hydroxy) phenyl Thiazole	$C_{18}H_{14}N_2O_2S_2$	175-177	35

Results and Discussions

Central Nervous system (CNS) Activity

The 18 animals (mice) divided in to 3 groups containing 6 animals each. The CNS activity was studied by using mice through oral route using cannula insertion via mouth. The decrease in count in comparison to corresponding control was compared after 30 minutes by digital Actophotometer and was tabulated before and after drug administration. The mean % score for a group was plotted and chart for dose of drug (10mgm/kg) were drawn. The Pharmacological

screening of the synthesized compounds and the effect of CNS activity in mice is summarized in Table 2- 4.

The mean value of corresponding control was compared with synthesized compounds and it shows more depressant activity than chlorpromazine hydrochloride. When compared synthesized compounds, Thiazolyl/oxazoly-2'-(phenyl-3-chloro-2-oxo azetidine) showed average mean 60.53 % & Thiazolyl /oxazolyl -2'-(5phenyl-2-oxo-Thiazolidine) showed average mean 58.47 %, indicates thiazolidine were slightly more CNS depressant than azetidines derivatives. The Pharmacological screening of synthesized compounds are given in Table 2, 3, 4 and graph for comparative study with standard drug given in Figure 1, respectively.

Table 2: CNS Study of Chlorpromazine hydrochloride

Control Drug	Dose mg/kg	Activity after 60 minutes (in activity cage recorder)		
		Before treatment	After Treatment	% Change in activity
Chlorpromazine hydrochloride	10mg/kg	341	110	67.74
		344	130	62.20
		325	105	67.69
		330	135	59.09
		355	98	72.39
		365	120	67.12
			Mean	66.03

Table 3: CNS Study of Thiazolyl/oxazoly-2'-(phenyl-3-chloro-2-oxo azetidine)

Compound No.	Dose mg/kg	Activity after 60 minutes (in activity cage recorder)		
		Before treatment	After Treatment	% Change in activity
16a	10mg/kg	360	140	61.11
17a		345	150	56.52
20a		330	125	62.12
23a		300	110	63.33
25a		289	105	63.66
28a		310	135	56.45
			Mean	60.53

Table 4: CNS Study of Thiazolyl /oxazolyl -2'-(5phenyl-2-oxo-Thiazolidine)

Compound No.	Dose mg/kg	Activity after 60 minutes (in activity cage recorder)		
		Before treatment	After Treatment	% Change in activity
16b	10mg/kg	320	150	46.87
17b		302	100	66.88
20b		324	110	66.04
23b		310	130	58.06
25b		280	130	53.57
28b		345	140	59.42
			Mean	58.47

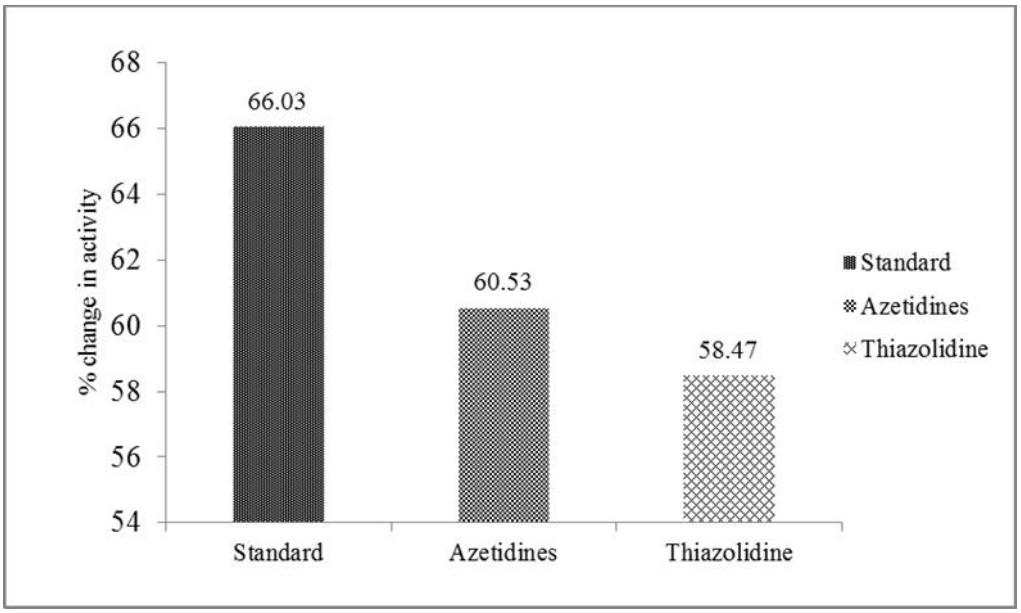


Figure 1: Comparative study with standard drug

Conclusion

The mean value of corresponding control was compared with synthesized compounds and it shows more depressant activity than chlorpromazine hydrochloride. When compared synthesized compounds, Thiazolyl/oxazoly-2'-(phenyl-3-chloro-2-oxo azetidine), average mean 60.53% & Thiazolyl /oxazolyl -2'-(5phenyl-2-oxo-Thiazolidine), average mean 58.47 %, indicates

thiazolidine were slightly more CNS depressant than azetidines derivatives. The pharmacological data showed that compound No 17a & 28a were more effective compared with other azetidines, similarly compound number 16b & 25b were more effective than compared with other thiazolidines. The Pharmacological screening of synthesized compounds are given in Table 2, 3, 4 and graph for comparative study with standard drug given in Figure-1, respectively.

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