Organic Chemistry: An Indian Journal

Organic Chemistry
ISSN: 0974-7516

Research | Vol 12 Iss 6

Synthesis and Anti Convulsant Activity of Novel Oxadiazole Substituted Phenothiazine Derivatives

Dighe NS[1*], Bankar AA[1], Musmade DS[2] and Nirmal SA[3]

[1]Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Loni, MS, India

[2]Department of Pharmaceutical Chemistry, Sanjivani College of Pharmaceutical Education and Research, Kopergaon, MS, India

[3]Department of Pharmacognosy, Pravara Rural College of Pharmacy, Loni, MS, India

[*]**Corresponding author:** Dighe NS, Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Loni, MS, India, Tel: 02422 273 528; E-mail: nachiket1111@rediffmail.com

Received: December 07, 2016; **Accepted:** December 15, 2016; **Published:** December 28, 2016

Abstract

The research is directed towards the synthesis and evaluation of novel agents for the treatment of various neurological disorders. The phenothiazine nucleus has been well explored for the various biological activities in past. The oxadiazole substituted phenothiazine have been of keen interest as a drug candidate for the treatment of various neurological disorders. In view of these an attempt has been made to synthesize substituted phenothiazine and explore them for promising anti convulsant activity. The anti-convulsant activity of synthesized compounds had been done by using Strychnine induced and 4-amino pyridine induced models.

Keywords: ***Anticonvulsant activity; Strychnine induced model; Thiosemicarbazide induced model, 4-Amino pyridine induced model; Neurotoxicity screening***

Introduction

A convulsion is a medical condition where body muscles contract and relax rapidly and repeatedly, resulting in an uncontrolled shaking of the body. Because a convulsion is often a symptom of an epileptic seizure, the term convulsion is sometimes used as a synonym for seizures [1-3]. However, not all epileptic seizures lead to convulsion, and not all convulsions are caused by epileptic seizures. Convulsion is also consistent with an electric shock and improper Enriched Air scuba diving [4]. A seizure occurs when nerve cells in the brain send out sudden, excessive, uncontrolled electrical signals [5]. Everyone's brain has continuous electrical activity. When something goes wrong with this activity your child may have a seizure. Seizure can produce a variety of symptoms depending on what part of the brain is involved. Generalized and partial seizure are the main types of seizures [6]. Convulsion is caused by chemicals in the blood as well as infection like meningitis

Citation: Dighe NS, Bankar AA, Musmade DS, et al. Synthesis and Anti Convulsant Activity of Novel Oxadiazole Substituted Phenothiazine Derivatives. Org Chem Ind J. 2016;12(6):108.

or encephalitis. A very common cause of convulsion is fevers. Other possibilities include head trauma, stroke, or lack of oxygen to the brain. Sometimes convulsion can be caused by genetic defect or brain tumors.

Materials and Methods

Reagents

All the chemicals were purchased from Merck research chemicals pvt. Ltd. all are of synthesis grade.

Synthesis of 7, 8 or 9 substituted aniline Benzoic acid derivatives

Equimolar amount of substituted aniline was added to a chloro benzoic acid in 20 mL of DMF and 0.1% of potassium hydroxide solution and the reaction mixture was heated under refluxed at about 80°C temperature, for 2 h. TLC indicated the end of reaction. The mixture was cooled by addition of a water/ice mixture. The solid was filtered in excellent yield [I].

Synthesis of 7, 8 or 9 substituted 10 H-phenothiazine 1 carboxylic acid derivatives

Equimolar amount of 7, 8 or 9 substituted Anilino Benzoic acid was added to a solution of sulfur powder and iodine in 5 mL of ethanol. Reaction mixture was heated under reflux with stirring for about 2 h and poured into ice/water mixture. The precipitate was filtered and washed with cold water [II].

Synthesis of derivatives of ethyl 10H-phenothiazine-1-carboxylate: 0.01 mole of 10 H-phenothiazine-1-carboxylic acid was reflux with conc. H_2SO_4 using ethanol as solvent for 1 hour in 250 ml RBF. After which the resulting reaction mixture was kept in ice cold water [III].

Synthesis of derivatives of 10H-phenothiazine-1-carbohydrazide: 0.01 mole of compound A was reflux with 3 ml to 4 ml of hydrazine hydrate for 1 hour. After which the resulting reaction mixture was allow to cool in ice bath. The resulting precipitate was collected and dried (IV).

Synthesis of derivatives of N'-benzylidene-10H-phenothiazine-1- carbohydrazide

0.01 mole of compound B was reflux with 0.01 mole of substituted aromatic aldehyde for 1 hour. After which the resulting reaction mixture was allow to cool in ice bath. The resulting precipitate was collected and dried and recrystallized from ethanol (V).

Synthesis of derivative of 2-chloro-1-(1-(2,3-dihydro-1,3,4-oxidiazole carbonyl)-10H-phenothiazine-10yl)ehanone

0.01 mole of a compound VI (1,3,4-oxadiazol-3(2H)-yl) (10H-phenothiazin-1-yl) methanone was reflux with 0.01 mole of substituted 2-chloroacetyl chloride for 1 hour. After which the resulting reaction mixture was allow to cool in ice bath SCHEME 1**.** The resulting precipitate was collected and dried and recrystallized from ethanol (VII) [7-9] (TABLE 1).

SCHEME 1**. Synthesis of derivative of 2-chloro-1-(1-(2,3-dihydro-1,3,4-oxidiazole carbonyl)-10H-phenothiazine-10yl) ehanone.**

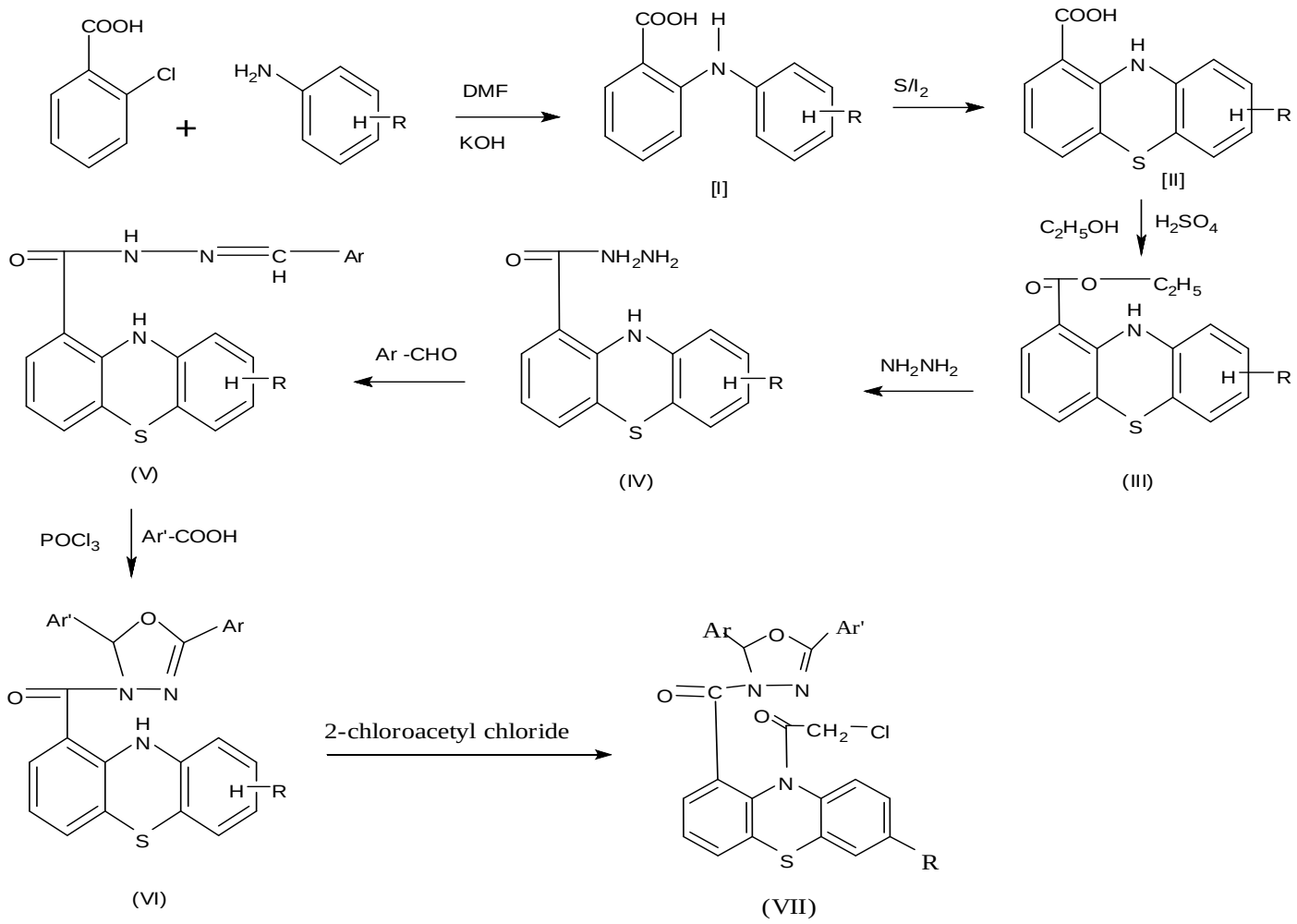
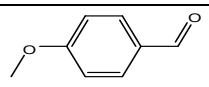
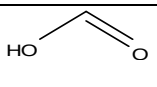
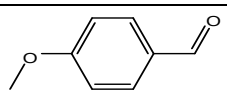
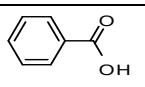
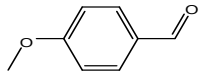
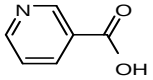
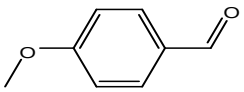
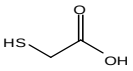
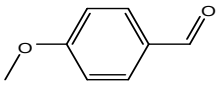
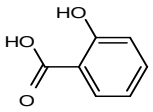
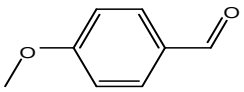
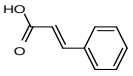
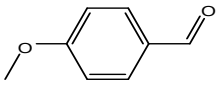
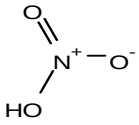
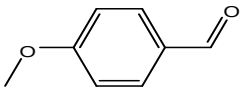
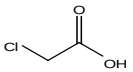
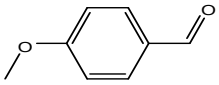
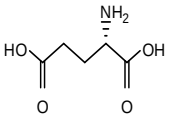
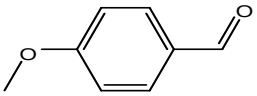
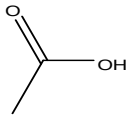
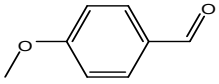
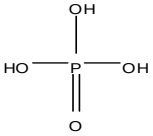
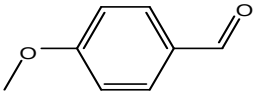
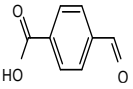


TABLE 1. **Compound codes for the different products.**

COMP CODE	**Ar**	**Ar'**	**R**	**COMP. CODE**	**Ar**	**Ar'**	**R**
A_1			P-CL M-CL	A_2			P-CL M-CL

A_3			P-CL M-CL	A_4			P-CL M-CL
A_5			P-CL M-CL	A_6			P-CL M-CL
A_7			P-CL M-CL	A_8			P-CL M-CL
A_9			P-CL M-CL	A_{10}			P-CL M-CL
A_{11}			P-CL M-CL	A_{12}			P-CL M-CL

Anti-Convulsant Activity

Strychnine induced model

The experimental animals are treated with test compound and standard drug respectively. The occurrence of clonic seizure, tonic seizures and death and recovery was recorded after 0.5 h, 1 h, 2h, and 4 h respectively.

Thiosemicarbazide induced model

The experimental animals are treated with test compound and standard drug respectively. the animals were injected with a subcutaneous dose of 20 mg/kg Thiosemicarbazide. The occurrence of clonic seizure, tonic seizures and death and recovery was recorded after 0.5 h, 1 h, 2h, and 4 h respectively.

4-Amino pyridine induced model neurotoxicity testing

The experimental animals are treated with test compounds and standard. Test drug were administered at a dose of 30 mg/kg body weight intraperitonially, 30 min prior to subcutaneous injection of 4-aminopyridine at a dose of 13.3 mg/kg. Control injection of 4-aminopyridine at a dose of 13.3 mg/kg. Controls treated with 4-aminopyridine only exhibit characteristic behavioral signs, such as hyper reactivity, trembling, intermitted forelimb/hind limb clones followed by hind limb extension, tonic seizures, opisthosomas and death. The standard drug phenytoin at a dose of 30 mg/kg body weight was taken for comparison.

Neurotoxicity screening

Activity of the drugs interfering with motor coordination was checked by the rotarod test. The mice were trained to say on an accelerating rotarod that rotate at 6 revolutions per minute. The rod diameter was 3.3 cm. neurotoxicity was indicated by the

inability of the animal to maintain equilibrium on the rod at least 1 min in each of three trials. The dose, at which the animals were unable to grasp the rotarod, was determined. The compounds were found to be non-neurotoxic at a dose of 30 mg/kg body weight [10,11].

The synthesized compounds show anti-convulsant activity using strychnine induced convulsions, 4-Amino pyridine induced convulsions. The controls protected only up to 15 min which was followed by death in all cases (TABLE 2).

TABLE 2. **Analytical and Physicochemical data of the synthesized compounds (A_1-A_{12}).**

Comp.	Mol. Formula	Mol. Wt.	M.P. °C	Yield %	Elemental analyses Calculated		
					C	H	N
A_1	$C_{24}H_{16}N_3O_5Scl_3$	563	242-246	61	65.58	3.67	11.37
A_2	$C_{29}H_{20}N_3O_5Scl_3$	627	230-235	56	63.57	4.00	10.59
A_3	$C_{29}H_{19}N_4O_5Scl_3$	640	263-265	62	62.42	3.61	7.53
A_4	$C_{25}H_{18}N_3O_5S_2CL_3$	609	265-270	59	56.36	3.26	11.33
A_5	$C_{30}H_{21}N_3O_6SCL_3$	656	252-255	63	56.50	2.81	12.20
A_6	$C_{32}H_{24}N_3O_5SCL_3$	667	265-270	49	55.13	3.30	6.89
A_7	$C_{23}H_{15}N_4O_5SCL_3$	564	220-225	58	59.09	3.08	9.50
A_8	$C_{25}H_{17}N_3O_5SCL_4$	611	245-250	60	60.16	3.43	10.02
A_9	$C_{28}H_{22}N_4O_7SCL_3$	663	252-255	57	60.79	3.40	10.50
A_{10}	$C_{26}H_{18}N_30_4SCL_3$	573	260-265	63	63.52	3.55	10.97
A_{11}	$C_{23}H_{15}N_3O_5SPCL_3$	581	253-257	55	56.74	3.00	12.25
A_{12}	$C_{31}H_{19}N_3SO_2CL_3$	650	235-242	51	62.92	4.19	12.62

Spectral Data (A_1-A_{12})

A_1: IR (cm^{-1}) : 822.50 (-C-CL str)3023.10 (Ar-CH str.), 1611.15 (-C=O str.),1532.11 (-C=N str.), 1236.60 (-C-N str.), 3223.50 (-N-H str.), 1321.21 (-C-O str.).; **^{1}HNMR:** CH 6.61 1.50 methine, CH 7.41 7.01 phenothiazine, CH 7.95 7.29 benzylidenimin, CH 7.38 7.26 1-benzene

A_2: IR (cm^{-1}) 823.50 (-C-CL str**.)** 3065.50 (Ar-CH str.),1611.11 (-C=O str.),1532.20 (-C=N str.), 1235.40 (-C-N str.), 3225.40 (-N-H str.), 1325.42 (-C-O str.); **^{1}HNMR:** CH 6.62 1.50 methine, CH 7.06 7.62 benzylidenimin, CH 7.11 7.26 1-benzene, CH3 3.83 0.86 methyl

A_3: IR (cm^{-1}) : 822.50 (-C-Cl str.), 3023.15 (Ar-CH str.), 1678.11 (-C=O str.), 1518.32 (-C=N str.), 1256.36 (-C-N str.), 3255.23 (-N-H str.), 1360.32 (-C-O str.); **^{1}HNMR:** CH 6.6 1.50 methine, CH 7.41 6.91 phenothiazine, 0.25 1 -C(=O)N from 1-benzene,CH 7.02 7.29 benzylidenimin

A_4 : IR (cm^{-1}): 823.50 (-C-CL str**)** 3110.25 (Ar-CH str.), 848.23(-C-Cl str.), 1625.12 (-C=O str.), 1492.2 (-C=N str.), 1260.16 (-C-N str), 3280.23 (-N-H str.), 1340.33 (-C-O str.); **^{1}HNMR:** 1.50 thiol , CH 6.61 1.50 methine, CH 7.00 6.99 phenothiazine, CH_2 2.56 1.37 methylene,CH 7.40 7.26 1-benzene

A_5: IR (cm^{-1}) 822.50 (-C-CL str.) 1255.36 (-N-O str.),3110.23 (Ar-CH str.),1615.11 (-C=O str.),1510.32 (-C=N str.), 1260.36 (-C-N str.),3250.23 (-N-H str.), 1360 (-N-O str.),1320.32 (-C-O str.); **^{1}HNMR:** 5.00 Aromatic C-OH **,**CH 6.61 1.50 methine, CH 8.19 7.26 1-benzene, CH 7.52 7.29 benzylidenimin, CH 7.42 6.91 phenothiazine

A_6 :IR (cm^{-1}) : 822.50(C-CL str.) 3056.23 (Ar-CH str.),1615.11 (-C=O str.),1520.32 (-C=N str.), 1254.36 (-C-N str.), 3260.23 (-N-H str.), 1329.32 (-C-O str.); **^{1}HNMR**: CH 5.25 1-ethyline**,** CH 7.06 7.29 benzylidenimin, CH 7.73 7.26 1-benzene, CH 7.41 6.91 phenothiazine, OH 9.68 5.00 aromatic C-OH

A_7 :IR (cm^{-1}): 822.50(-C-CL str) 3658.21 (-OH str.), 3010.23 (Ar-CH str.), 1615.11 (-C=O str.), 1520.32 (-C=N str.), 1255.36 (-C-N str.), 3250.23 (-N-H str.), 1320.32 (-C-O str.); **^{1}HNMR:** CH 6.01 1.50 methine, CH 8.09 7.62 benzylidenimin, CH 7.41 6.91 phenothiazine, CH 7.24 7.26 1-benzene

A_8 .IR (cm^{-1}): 822.50(-C-CL str**)** 3050.23 (Ar-CH str.), 3608.23 (-OH str.), 1715.11 (-C=O str.), 1510.32 (-C=N str.), 1258.36 (-C-N str.), 3275.23 (-N-H str.), 1320.32 (-C-O str.); **^{1}HNMR:** CH_3 3.83 methyl, 7.62 1-benzene, 1.50 methine, 7.00 phenothiazine,1.37 methylene

A_9 .IR (cm^{-1}): 822.50(-C-CL str**)** 3017.23 (Ar-CH str.), 1690.11 (-C=O str.), 1540.32 (-C=N str.), 1260.36 (-C-N str.), 3259.23 (-N-H str.), 1335.32 (-C-O str.); **^{1}HNMR:** CH_3 2.34 methyl, 1.37 methylene,2.00 amine 1.50 methine,11.00 carboxylic acid,6.70 phenothiazine, 7.76 benzylidenimin, 7.06 benzylidenimin

A_{10} . IR (cm^{-1}): 822.50(-C-CL str**)** 3018.23 (Ar-CH str.),1685.11 (-C=O str.),1510.32 (-C=N str.), 1250.36 (-C-N str.),3250.23 (-N-H str.), 1320.32 (-C-O str.); **^{1}HNMR:** 9.43 aromatic C-OH, 6.68 1-benzene, CH 7.41 phenothiazine, 7.62 benzylidenimin,1.37 methylene,1.50 methine.

A_{11}. IR (cm^{-1}): 3120.28 (Ar-CH str.),830.24(-C-Cl str.),1635.12 (-C=O str.),1590.2 (-C=N str.), 1270.16 (-C-N str),3270.25 (-N-H str.), 1340.35 (-C-O str.); **^{1}HNMR:** 6.94 1-benzene, 7.96 benzylidenimin, 9.43 aromatic C-OH,2.00 alcohol,1.37 methylene,0.86 methyl.

A_{12}. IR (cm^{-1}): 822.50(-C-CL str**)** 1613.05 (-C=O str.),1533.20 (-C=N str.), 1336.40 (-C-N str.),3331.50 (-N-H str.),1432.20 (-C-O str.),920.45 (-C-OH str.); **^{1}HNMR:** 11.00 Carboxylic acid, 0.86 methyl, 7.68 phenothiazine, 7.36 1- benzene,7.29 benzylidinimin. TABLE 3.

TABLE 3. **Anti-convulsant activity of compound (A_1-A_{12}).**

Compound code	Strychnine induced model			Thiosemicarbazide induced model			4-Amino pyridine induced model		Neurotoxicity testing	
	0.5 h	1 h	2 h	0.5 h	1 h	2 h	15 min	0.5 h	0.5 h	4 h
Control	30 mg	Death	Death	30 mg	Death	Death	30 mg	Death	30 mg	-
A1	30 mg	30 mg	30 mg	30 mg	30mg	Death	30 mg	Death	30 mg	-
A2	30 mg	30 mg	30 mg	30 mg	30 mg	Death	30 mg	Death	30 mg	-
A3	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	Death	30 mg	-

A4	30 mg	30 mg	30 mg	30 mg	Death	Death	30 mg	Death	30 mg	-
A5	30 mg	30 mg	30 mg	30 mg	30 mg	Death	30 mg	Death	30 mg	-
A6	30 mg	30 mg	Death	30 mg	Death	Death	30 mg	Death	30 mg	-
A7	30 mg	30mg	30mg	30mg	30mg	30mg	30mg	Death	30mg	-
A8	30 mg	Death	Death	30 mg	30 mg	Death	30 mg	Death	30 mg	-
A9	30 mg	30 mg	30 mg	30mg	30 mg	30 mg	30 mg	Death	30 mg	-
A10	30 mg	Death	Death	30 mg	30 mg	Death	30 mg	Death	30 mg	-
A11	30 mg	30 mg	Death	30 mg	Death	Death	30 mg	Death	30 mg	-
A12	30 mg	Death	Death	30mg	30mg	Death	30mg	Death	30mg	-
Diazepam	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg				-
Phenytoin							30 mg	Death	30mg	-

Result and Discussion

All the synthesized compounds were evaluated for their anticonvulsant activity using various chemical induced convulsion models on albino mice (20 g to 25 g). The vehicle and Standard drug Diazepam was used. All the synthesized compounds show significant anti-convulsant activity at a dose of 30 mg/kg body weight. The compounds A_3, A_5, A_7 and A_9 were found to be most active amongst all the screened compounds using strychnine induced model and against Thiosemicarbazide induced model respectively and none of the compound showed anticonvulsant activity using 4-amino pyridine.

Conclusion

The synthesized compounds show significant anti-convulsant activity due to presence of electron withdrawing groups like Chlorine as a substituent. The synthesized compounds can be proved as a potential candidate for the treatment of epilepsy and other disorders in future. These compounds can be used for ligand based drug designing purpose by which exact molecular mechanism responsible for showing anti-convulsant effect can be explored in future. The synthesized compounds also found to be non-neurotoxic at 30 mg/kg up to half an hour.

REFERENCES

1. Sinha S, Pandeya SN, Verma A, et al. Int J Res Ayu Pharm. 2011;2(4):1130-37.
2. Krall RL, Penry JK, White BG, et al. Epilepsiae. 1978;19:409-28.
3. Dighe NS, Shinde PS, Tambe P. American chemical society. Int J pharma chem. 116-22.
4. Jaiswal N, Jaiswal RK, Barthwal JP, et al. Synthesis and biological activity of some new 10-[(3,5-diaryl-2-pyrozolin-1-yl)acetyl] phenothiazines. Indian J Chem. 1981;20B:252-3.
5. Sharma S, Srivastava VK, Kumar A. Synthesis and anti-inflammatory activity of some derivatives of Phenothiazine. J Govi Verlag. 2005;60(1):18-22.
6. Srivastava SK, Srivastava SD, Srivastava SL. Synthesis of new 2-chloro-phenothiazinothiadiazol-2-oxoaze-tidines. Indian J chem. 2000;39B:464-7.
7. Trivedi AR, Siddiui AB, Viresh HS. Design, synthesis, characterization and antitubercular activity of some 2-heterocycle-substituted phenothiazines. ARKIVOC. 2008;ii:210-7.
8. Upadhyay RK, Upadhyay MS, Jain S. Synthesis and anti-microbial activity of 1-[2-(10-p-chlorobenzyl) phenothiazinyl]-3-substituted aryl-2-propen-1-ones. E J Chem. 2009;6(S1):S254-8.
9. Dighe NS. Design Synthesis and Evaluation of Antidepressant activity of some new oxidiazole derivatives of phenothiazine. Int J chem pharm sci.2016;4(1):2321-3132.
10. Laws ML, Roberts RR, Nicholson JM, et al. Synthesis characterization and anticonvulsant activity of enaminones. Bio org Med Chem Let.1998;6:2289-99.
11. Vogel HG. Drug discovery, and evaluation: Pharmacology assay. Berlin: Springer Verlag; 2002.