ISSN- O: 2458-868X, ISSN –P : 2458 – 8687

International Journal of Medical Science and Innovative Research (IJMSIR)

IJMSIR : A Medical Publication Hub

Available Online at: www.ijmsir.com

Volume – 1, Issue – 4, November – December 2016, Page No. : 12 - 18

Synthesis and anticonvulsant activity of some potential 5-acetyl-2, 3-diarylthiazolidin-4-ones derivatives

Davinder Kumar[1], Virender Kumar[1], Sandeep Jain[2], Ritu Saini[2], Ruchi*[1]

[1]College of Pharmacy, Pt. B.D. Sharma University of Health Sciences, Rohtak, Haryana 124001

[2]Department of Pharmaceutical Sciences, Guru Jambeswhar University of Science & Technology, Hisar Haryana, 125001

Corresponding Author: Ruchi Poria, Asstt. Professor, College of Pharmacy, Pt. B.D. Sharma University of Health Sciences, Haryana, Rohtak, 124001

Abstract: A series of 5-acetyl-2,3-diarylthiazolidin-4-one were synthesized from Schiff base 1 of substituted benzaldehyde and substituted aniline which on treatment with thioglycolic in presence of zinc chloride undergo cyclization to give 2,3-diarylthiazolidin-4-one 2. Which on further reaction with acetyl chloride in presence anhydrous sodium acetate furnished the title compounds 3. These compounds were characterized by IR, 1H NMR spectral data. The synthesized compounds were evaluated for their in vivo anticonvulsant activity using maximal electroshock seizure (MES) model in mice. Standard drug Phenytoin was administered intraperitoneally at a dose of 25 mg/kg. The test compounds were active at a dose of 30 mg/kg. The abolition of hind limb tonic extensor phase was recorded as measures of anticonvulsant activity and failure to extend limb to an angle greater than 90° is defined as protection. Out of tested compounds 3j was the most active compound of the series.

Keywords: Schiff base derivatives, Thiazolidinone, anticonvulsant activity, Maximal Electro Shock method.

1. Introduction

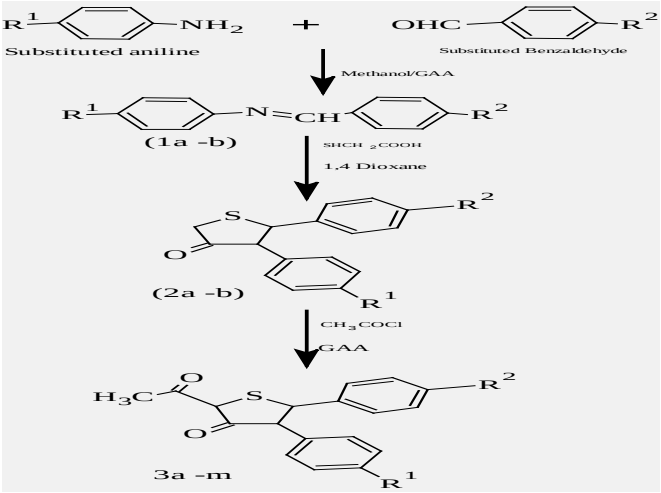
Heterocyclic substances are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances. Today, the major challenge of modern drug discovery is the design of highly efficient chemical reaction sequences which provide a maximum of the structural complexity and biological diversity with just a minimum number of synthetic steps to assemble compounds with interesting properties. [1] Thiazolidinone, a saturated form of thiazole with carbonyl group on fourth carbon, has been considered as magic moiety (wonder nucleus) which possesses almost all types of biological activity. Thiazolidinone is an important and versatile scaffold that has occupied a prominent position in medicinal chemistry field. 4-Thiazolidinone and rhodanine derivatives have attracted continuing interest over the years because of their diverse biological activities, such as Thiazolilidinone posses anti-HIV [2], antibacterial activity [3], anti-inflammatory [4], anticonvulsant activity [5-7], antitumor [8-10], antitubercular [11], antimicrobial [12-14], antiviral [14], Antihelmintics[15] and antidiabetic activity [16-18] Also, structural modification of this scaffold offers a high degree of diversity that has proven useful for the search of new therapeutic agents. Moreover, compounds such as ralitoline (anti-convulsant), etozoline (antihypertensive), pioglitazone (hypoglycemic) and thiazolidomycin (activity against streptomyces species), containing this pharmacophore are already available in the market.[19]

The present study was undertaken to investigate the anticonvulsant activity of thiazolidinones derivatives using maximal electroshock induced seizure method. The anticonvulsant is a diverse group of pharmaceuticals used in the prevention of epileptic seizures. The goal of an anticonvulsant is to suppress the rapid and excessive firing

of neurons that starts a seizure. An anticonvulsant would prevent the spread of seizure within the brain and offer protection against possible excitotoxic effect that may result in brain damage. Thiazolidinone has sodium channel blocking effect. It has also showed anticonvulsant effect in different screening model [20-22]. The synthesized compounds were characterized by TLC, M.P, IR and ^{1}HNMR. The compounds were evaluated for anticonvulsant activity by maximal electroshock seizure method.

2. Chemistry

The syntheses of 5-acetyl-2,3-diarylthiazolidin-4-ones were prepared by the following steps Schiff base 1 were prepared by the reaction of substituted benzaldehyde with substituted aniline in ethanol few drops of glacial acetic were added and the reaction mixture was refluxed for 3 hours. Schiff base1 was treated with thioglycolic acid in dry dioxane in presence of anhydrous $Zncl_2$ refluxed for 8-10 hours. Then formation of 2,3-diarylthiazolidin-4-one 2. Then 2 was treated with acetyl chloride in presence of anhydrous sodium acetate in glacial acetic acid stirred on a magnetic stirrer for 6-8h gave 5-acetyl-2,3-diarylthiazolidin-4-one 3. The IR and ^{1}HNMR spectral data of the compounds were found in agreement with the assigned molecular structure. IR spectra aromatic showed =C-H stretch at 3033 cm^{-1} C=O stretch gave pick at 1710 cm^{-1} and the presence of methyl group showed by C-H bending at 1400 cm^{-1}. C-Cl str, aromatic showed peak at 1036.10cm^- , C-F str, aromatic showed peak at 1250 cm^{-1}. ^{1}HNMR proton of C-H_3 was observed at 2.023 ppm and peak of C-H in thiazolidinones was seen at about 5.622ppm and Aromatic protons appeared as multiplet (m) in the assigned value of 7.015-7.524δ (ppm).



Scheme 1- Synthetic route followed to obtain target compounds (Synthesis of 5-acetyl-2, 3-diarylthiazolidin-4-ones) from different reactants

3. Experimental

The purity of all the synthesized compounds were checked by thin layer chromatography on silica gel G as stationary phase and different solvent systems as mobile phase using iodine vapors as detecting agent. Melting points were determined by the Tempo melting point determination apparatus in open capillary tubes and are uncorrected. Infrared spectra were recorded on Perkin Elmer IR spectrophotometer using KBr pellets. Proton nuclear magnetic spectra (^{1}HNMR) were recorded on Bruker Avance-II 400 NMR Spectrophotometer. Schiff base derivatives 1a-b and 2, 3 diaryl thiazolidin-4-ones 2a-b were prepared according to the procedure described in the literature and finally 5-acetyl-2,3-diarylthiazolidin-4-one derivatives [23] listed in Table -1

3.2Procedure for the synthesis of 5-acetyl-2,3-diarylthiazolidin-4-one: [23]

3.2.1Procedure for the preparation of benzylidene aniline

In a solution of 0.01 mol of the substituted benzaldehyde in 15ml of methanol, 0.01 mol of aniline and a few drops of glacial acetic acid were added and the reaction mixture

refluxed for 3h. The reaction mixture was cooled, poured into ice cold water, and the separated solid was filtered, dried and recrystallized from ethanol.

3.2.2Procedure for the preparation of 2,3-diaryl-1,3-thiazolidin-4-one. Then, this solution of 0.01 mol benzylidenaniline derivative in 15 ml of dry dioxane, 0.01 mol of freshly distilled thioglycolic acid and anhydrous $ZnCl_2$ (0.2 g) was added and the mixture refluxed for 8-10 h. The solvent was removed (reduced pressure) and the residue washed with 5% sodium bicarbonate and with cold water dried, and recrystallized from ethanol. 3.2.3 Preparation of 5-acetyl-2,3-diarylthiazolidin-4-one

0.01 mol of 2,3-diarylthiazolidinone derivative dissolved in 20 ml glacial acetic acid and anhydrous sodium acetate and 0.01 acetyl chloride added and stirred on a magnetic stirrer for about 6-8 hrs and reaction completion was monitored by TLC and then filtered and washed thoroughly with cold distilled water and re-crystallized from ethanol. The physical and analytical data of synthesized compounds 3a-m are given as follows.

4. Result and Discussion

4.1 Spectral analysis

1. 5-acetyl-2,3-diphenyl-1,3-thiazolidin-4-one (3a). Yield: 65.35; m.p.: 270-274^oC; IR (KBr, cm^{-1}): 3100 (C-H), 1710 (C=O), 1560 (C=C), 1380 (C-H, bending), 1380(CH_3), 1310 (C-N), ^1H NMR, (300.131MHz, DMSO): δ (ppm): 5.324(s, 1H, -CH in thiazolidinone), 4.48(s, 1H, -CH-in thiazolidinone), 7.015-7.524(m, 10H, aromatic), 2.047(s, 3H, CH_3).

2. 5-acetyl-2-(4-bromophenyl)-3-phenylthiazolidin-4-one (3b). Yield: 58.16%; m.p.: 234-238 ^oC; IR (KBr, cm^{-1}): 3137.09 (C–H), 1742.73(C=O), 1598.69 (C=C), 1400 (CH_3), 1067.05(C-Br); ^1H NMR, (300.131MHz, DMSO): δ (ppm): 5.622(s, 1H, -CH- thiazolidinones), 7.014-7.139(m, 9H, aromatic) 2.023(s, 3P, CH_3), 4.067(s, 1H, -CH- thiazolidinone).

Table 1 Physicochemical characteristics of synthesized 5-acetyl-2,3-diarylthiazolidin-4-ones derivatives.

Compounds	R_1	R_2	Molecular Formula	Molecular weight	Melting point (^oC)	*Rf value	% yield
3a	H	H	$C_{17}H_{15}NO_2S$	297.08	270-274	0.54	65.35
3b	p-Br	H	$C_{17}H_{14}BrNO_2S$	375.27	234-238	0.64	58.16
3c	H	p-Cl	$C_{17}H_{14}ClNO_2S$	331.04	230-235	0.44	73.51
3d	p-OCH_3	H	$C_{18}H_{17}NO_3S$	327.40	240-245	0.71	59.21
3e	H	3,4-$(OCH_3)_2$	$C_{19}H_{19}NO_4S$	357.42	232-236	0.57	69.23
3f	p-F	H	$C_{17}H_{14}FNO_2S$	315.36	219-224	0.45	47.52
3g	p-Cl	p-Cl	$C_{17}H_{13}Cl_2NO_2S$	366.26	230-235	0.52	51.61
3h	p-Br	p-NO_2	$C_{17}H_{13}BrN_2O_4S$	421.27	190-195	0.65	71.31
3i	p-NO_2	p-Cl	$C_{17}H_{13}ClN_2O_4S$	376.80	249-254	0.67	65.38
3j	p-OCH_3	p-OCH_3	$C_{19}H_{19}NO_4S$	357.42	241-245	0.53	73.41
3k	p-NO_2	H	$C_{17}H_{14}N_2O_4S$	342.37	260-264	0.71	69.52
3l	H	p-OH	$C_{17}H_{15}NO_3S$	313.57	180-185	0.56	77.27
3m	p-Br	p-Cl	$C_{17}H_{13}BrClNO_2S$	410.95	230-234	0.65	57.53

***TLC Mobile Phase – Hexane: ethyl acetate (3:1)**

3. 5-acetyl-2,3-bis(4-chlorophenyl)thiazolidin-4-one (3g). Yield: 51.65%; m.p.: 234-238 oC; IR (KBr, cm-1): 2913.35 (C–H), 1700 (C=O), 1597.16 (C=C), 1408 (CH3), 1300.42(C-N), 1070 (C-Cl); 1H NMR, (300.131MHz, DMSO): δ (ppm): 7.344-7.744(m, 8P, aromatic), 1.194(s, 3P, CH3), 4.00(s, 1H, -CH-thiazolidinone).
4. 5-acetyl-2,3-bis(4-methoxyphenyl)thiazolidin-4-one

(3j). Yield: 71.31%; m.p.: 241-245 oC; IR (KBr, cm-1): 3050 (C-H), 1686.16 (C=O), 1513.49 (C=C), 1410.71 (CH3), 1236 and 1036.40(Ar-O-CH3)

5. 5-acetyl-2-(4-chlorophenyl)-3-(4-fluorophenyl) thiazolidin-4-one (3). Yield: 48.30%; m.p.: 223-227 oC; IR (KBr, cm-1): 3000 (C-H), 1710 (C=O), 1508.16 (C=C), 1402.60 CH3, 1237.66 (Ar-F), 1072.37 (Ar-Cl); 1H NMR, (300.131MHz, DMSO): δ (ppm): 7.158-7.256 (m, 8H, aromatic), 2.503(s, 3H, CH3), 5.696(s, 1H, -CH-thiazolidinone).
6. 5-acetyl-2(4-bromophenyl)-3-(4-nitrophenyl) thiazolidin-4-one (3h). Yield: 71.31%; m.p.: 190-195 oC; 1H NMR, (300.131MHz, DMSO): δ (ppm): 7.011-7.458(m, 8H, aromatic), 4.109(s, 1H, -CH-thiazolidinone), 2.003(s, 3H, CH3).

4.2 Evaluation of anticonvulsant activity [24]

The synthesized derivatives were evaluated for their anticonvulsant activity using Maximal Electroshock Seizure (MES) method wherein electroshocks were applied via ear-lip electrodes using an electro convulsiometer. Phenytoin used as a standard drug. Maximal Electroshock Seizure method was used for the study of anticonvulsant activity. The abolition of hind limb tonic extensor phase was recorded as measures of anticonvulsant activity and failure to extend limb to an angle greater than 90̊ is defined as protection. The animals were randomly allocated into 15 groups of 6 animals each and were fasted for 24hr before the experiment with free access to water. Control group received only 1% carboxymethyl cellulose suspension. Standard drug Phenytoin was administered intraperitoneally at a dose of 25 mg/kg. The test compounds were administered at a dose of 30 mg/kg. Both the test compounds and standard drug were administered through intraperitoneally route by dissolving in 20% solution of Tween 80. Maximal electroshock of current intensity 42mA was given for 0.2 sec duration after the administration of test and standard drug. The anticonvulsant activity was assessed after 30min. of standard and test compound administration. The abolition of hind limb tonic extensor spasm was recorded as a measure of anticonvulsant activity. The duration was measured in seconds. The criterion for anticonvulsant activity and protection against MES induced seizures is abolishing HLTE, which is taken as the end point of the test. Phenytoin showed 82.95% protection from the convulsion. Results of MES test are presented in Table 2 and figure-1. The anticonvulsant activity of the title compounds containing electron withdrawing groups like bromo, chloro were found somewhat less than the compounds containing electron releasing groups like methoxy and hydroxyl. 3j was the most active compound that showed 71% protection against the seizures. All the compounds showed less activity than standard drug Phenytoin. The entire tested compound showed protection against MES test indicative of their ability to inhibit seizure spread. The abolition of hind limb tonic extensor spasm measured percentage protection. The Percentage protection was calculated according to the following equations:

% protection of the compound = (MCT of the compound-MCT of the control)/ MCT of the control x 100.

Where MCT is mean convulsion threshold. The result is presented in Table 2, which shows the mean convulsion threshold.

Table 2- Anticonvulsant activity of synthesized 5-acetyl-2, 3-diarylthiazolidin-4-ones derivatives

S.NO.	Compound No.	Tonic extensor phase time in sec	% Protection
1.	3a	11.61±0.68	62
2.	3b	12.05±0.41	61
3.	3c	11.14±0.51	63.5
4.	3d	10.83±0.42	65
5.	3e	9.89±0.67	67
6.	3f	10.53±0.76	66
7.	3g	13.31±0.44	56
8.	3h	15.9±0.72	48
9.	3i	12.53±0.87	59
10.	3j	8.95±1.28	71
11.	3k	16.09±1.25	47
12.	3l	10.65 ±1.68	65
13.	3m	13.01±1.29	57
14.	Phenytoin	5.22±0.67	82.95
15.	control	30.63±1.12	0

The results were expressed as mean ± SEM (n=6). Significance was calculated by using One-way ANOVA with Dunnett's test. The difference in results was considered significant when P<0.05 ***P<0.001 vs control.

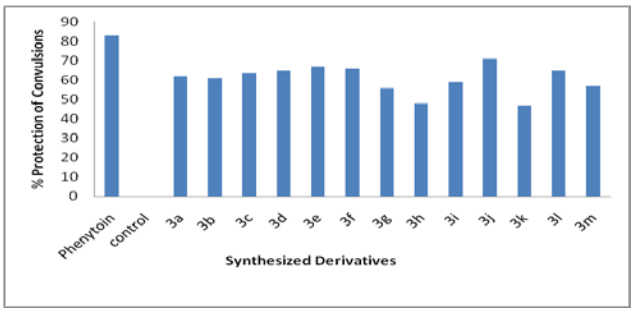


Figure 1: Effect of synthesized compounds on MES induced seizures

5. Conclusion

Present study describes the synthesis of a series of 5-acetyl-2,3-diarylthiazolidin-4-one Starting from substituted benzaldehyde and substituted aniline. The compounds were characterized by modern analytical techniques such as IR, proton NMR spectra. All the title compounds were screened for their in vivo anticonvulsant activity against Phenytoin as a standard drug and their percentage protection from convulsion were determined. The anticonvulsant activity of the title compounds containing electron withdrawing groups like bromo, chloro were found somewhat less than the compounds containing electron releasing groups like methoxy and hydroxyl. 3j was the most active compound that showed 71% protection against

the seizures and 3e, 3f and 3l of the series has moderate action towards prevention and protection against the seizures. These results suggest that some more compounds using different derivative of benzaldehyde and aniline should be synthesized and screened for their anticonvulsant activity to explore the possibility of 5-acetyl-2,3-diarylthiazolidin-4-ones as a novel series of anticonvulsant.

Acknowledgement

The authors are thankful to Principal and senior teachers, College of Pharmacy PGIMS Rohtak, for providing necessary facilities and supporting to write my Research work.

7. Reference

1. James R. LaSalle, Do. FAAFP management of type 2 diabetes Focus on the thiazolidineones. Hospital Physician. October 2005: 46.
2. Rao A., Balzarini J., Carbone A., Chimirri A., Clercq E., Monforte A.M., Monforte P., Pannecouque C., Zappala M. (2004). Synthesis of new 2,3-diaryl-1,3-thiazolidin-4-ones as anti-HIV agents. Farmaco. 59:33–39.
3. Sayyed M., Mokle S., Bokhare M., Mankar A., Surwase S., Bhusare S., Vibhutea Y. Synthesis of some new 2, 3-diaryl-1, 3-thiazolidin-4-ones as antibacterial agents. (2006). ARKIVOC. ii: 187-192.
4. Sh Vazzana I., Terranova E., Mattioli F., Sparatore F. (2004). Aromatic Schiff bases and 2,3-disubstituted-1,3-thiazolidin-4-onederivatives as anti-inflammatory agents. ARKIVOC. V: 364-374
5. Sindikar A.V., Khan F., Viswanathan C. L. (2006). Design, synthesis and in vivo anticonvulsant screening in mice of novel phenylacetamides. Eur. J. Med. Chem., 41(6): 786-792.
6. Aysel G., Nalan T. (2005). Synthesis and Isolation of New Regioisomeric 4-Thiazolidinones and their Anticonvulsant Activity. Turk J Chem. 29:247-254.
7. D. Kumar, V. Kumar, J. Mundlia, D. Pradhan and S. Malik,Thiazolidin-4-one Derivatives as Central Nervous System Potential Agents, Central Nervous System Agents in Medicinal Chemistry, 23-27, 2015, 15.
8. Thuan TN, Dung MTD, Que ND, Dung PTP, Yu KT, Hahn H, Han WB, Kim Y, Han BS, Nam HB, Medicinal Chemistry Research, synthesis and bioevaluation of new 5-benzyliedenethiazolidine-2,4-diones bearing benzenesulfonamide moiety. Med Chem Research. 2015; 24: 3803-12.
9. Li SN, Xu YY, Gao YJ, Yin RH, Hang LS, Li QH. Combination of 4-anilinoquinazoline and rhodanine as novel epidermal growth factor receptor tyrosine kinase inhibitors. Bioorg Med Chem 2015 Jul 29; 23(13): 3221-7
10. Cardoso MV, Moreira DR, Oliveira Filho GB, Cavalcanti SM, Coelho LC, Espíndola JW, Gonzalez LR, Rabello MM, Hernandes MZ, Ferreira PM, Pessoa C, Alberto de Simone C, Guimarães ET, Soares MB, Leite AC. Design, synthesis and structure activity relationship of phtalimides endowed with dual antiproliferative and immunomodulatory activities. Eur J Med Chem. 2015; 96: 491-503.
11. Sardari S, Kohanzad H, Ghavami G. Artificial neural network modeling of antimycobacterial chemical space to introduce efficient descriptors employed for drug design. Chemometr Intell Lab Syst. 2014; 130: 151-158.
12. Patel AB, Chikhalia KH, Kumari P. An efficient synthesis of new thiazolidin-4-one fused *s*-triazines as potential antimicrobial and anticancer agents. J Saudi Chem Soc. November 2014; 24: 646–56.
13. Liu JC, Zheng CJ, Wang MX, Li YR, Ma LX, Hou

SP, Piao HR. Synthesis and evaluation of the antimicrobial activities of 3-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-2-thioxothiazolidin-4-one derivatives. Eur J Med Chem. 2014; 74: 405-10.

14. Shaikh MF, Patel BN, Sanna G, Busonera B, Colla LP, Rajani PD , Synthesis of some new 2-amino – 6-thiocyanoto benzothiazole derivatives veering 2,4-thiazolidinediones and screening of the invitro antimicrobial antitubercular and antiviral activities. med chem res. August 2015; 24: 3129–42
15. Kumar, V., Satyanarayana, D., Subrahmanyam. Synthesis and anthelminitic evaluation of 2-aryl-3-substituted benzamido-1,3-thiazolidin-4-Ones. E.V.S., Ind. J. Het. Chem. 251-252, 2002, 11.
16. Jawale D V, Pratap U R, Rahuja N, Srivastava A K, Man R A. Synthesis and antihyperglycemic evaluation of new 2,4- thiazolidinediones having biodynamic aryl sulfonylurea moieties. Bioorg Med Chem Lett, 436–49, 2012;22.
17. Nazreen S, Alam M S, Hamid H, Yar S Shafi S, Dhula A, Haider S. Design, synthesis, in silico molecular docking and biological evaluation of novel oxadiazole based thiazolidine-2, 4-diones bis-heterocycles as PPAR-γ agonists. Eur J Med Chem 175-85, 2014;87.
18. Zhou L, Zhong Y, Xue M Z, Kuang D, Cao X W, Zhao Z J et al. Design, synthesis and evaluation of PPAR gamma binding activity of 2-thioxo-4-thiazolidinone derivatives. Chinese Chem Lett, 63-8, 2015;26(1).
19. Tripathi AC, Gupta SJ, Fatima GN, Sonar PK, Verma A, Saraf SK. 4-Thiazolidinones: The advances continue. Eur J Med Chem. 2014; 72: 52-77.
20. Farghaly AR, Esmail S, Abdel-Zaher A, Abdel-Hafez A, El-Kashef H. Synthesis and anticonvulsant activity of some new pyrazolo [3,4-*b*]pyrazines and related heterocycles. Bioorg Med Chem. 2014; 22: 2166-75.
21. Nikalje APG, Khan FK, Ghodke M. Design and synthesis of 2-(1,3-dioxoisoindolin-2-yl)-*N*-(4-oxo-2-substitutedthiazolidin-3-yl)acetamide derivatives as potential anticonvulsant agents. Eur J Med Chem. 2011; 46: 5448-55.
22. Senthilraja M Alagarsamy V. Synthesis and pharmacological investigation of 2-(4-Dimethylaminophenyl)-3,5-disubstituted thiazolidin-4-ones as anticonvulsants. Arch Pharm Chem Life Sci. 2012; 345: 827-33.
23. Sayyed, M., Mokale, S., Bokhare, M., Mankar, A., Surwase, S. Synthesis and antibacterial evaluation of 2,3-diaryl- 1,3-thiazollidin-4-ones derivatives. *ARKIVOC*. 2006, (ii), 187-192.
24. Singh, T., Kumar, P. Sharma, S. Mondalc, C. and Kumar, N. synthesis, anticonvulsant evaluation and spectral characterization of thiazolidinone derivatives. *J.Chem. Pharm. Res*., 2011, 3(5), 609-615.