

SYNTHESIS, ANTICONVULSANT AND ANTIMICROBIAL EVALUATION OF SOME NEW 3-[5-(SUBSTITUTED-PHENYL)- [1,3,4]OXADIAZOLE-2-YL]-1-NAPHTHALEN-2-YL-PROPAN-1-ONE

Arvind Kumar*, Baby Rabiya Parveen and Vaishali

Department of Pharmaceutical Chemistry, S. D. College of Pharmacy and Vocational Studies,
Bhopa Road, Muzaffarnagar - 251001, India.

ABSTRACT

A series of 3-[5-(Substituted-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one were synthesized, and characterized by ¹HNMR, IR and Mass spectroscopy. All synthesized compounds were evaluated for anticonvulsant activity and antibacterial activity. The anticonvulsant activity was carried out on maximal electroshock seizure (MES) model. The compounds 3-[5-(4-Hydroxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-2) and 3-[5-(4-Flouro-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-3) showed comparable result of anticonvulsant activity as standard. Whereas Compound 3-[5-(4-Flouro-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-3) showed recognizable antimicrobial activity against MTCC-521 gram (-)ve bacteria.

Keywords: 1,3,4-Oxadiazole derivatives, Anticonvulsant activity and antibacterial activity.

INTRODUCTION

Epilepsy, derived from Greek word epilambanein, means to attack or seize. An epileptic seizure is a transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity in the brain¹. Epilepsy is one of the most common neurological conditions, occurring in about 1% of the global population. It is second most common disorder after stroke. Estimates suggest that available medication controls the seizures in only 50% of patients or decreases the incidence in only 75% of patients². The search for antiepileptic agents with more selectivity and lower toxicity continues to be an area of investigation in medicinal chemistry.³ The mechanisms of action of the antiepileptic drugs (AEDs) consist in the blockade of voltage-dependent Na⁺ channels or T-type Ca²⁺ channels, inhibition of glutamatergic transmission and facilitation of γ -aminobutyric acid (GABA) inhibitory neurotransmission.⁴

Oxadiazole, a heterocyclic nucleus with molecular formula C₂H₂N₂O. There are four possible isomers of oxadiazole depending on the position of nitrogen atom in the ring namely 1,2,3-, 1,2,4-, 1,2,5- and 1,3,4-oxadiazoles, out of these 1,3,4-oxadiazoles are found to be most potent biologically.^{5,6} 1,3,4-Oxadiazoles compounds are not intermediates, it is very effective organic compounds in their own right. It has become an important construction motif for the development of new drugs. Compounds containing 1,3,4-oxadiazole cores have a broad biological activity spectrum^{7,8} such as anticonvulsant,⁹ anti-inflammatory¹⁰⁻¹³ analgesic^{14,15} antimicrobial,¹⁶ anti-tubercular,¹⁷ antidepressant,¹⁸ anti-tumour,¹⁹ antioxidant,²⁰⁻²³ antimalarial,²⁴ antiviral²⁵ and hypoglycemic activities.²⁶⁻³¹

The aim of the present study was to synthesize new 1,3,4-Oxadiazole derivatives from 4-Naphthalen-2-yl-4-oxo-butyric acid hydrazide and

evaluate their anticonvulsant and antibacterial activities.

EXPERIMENTAL

Chemistry

All the chemicals and solvents, purchased from Merck (India), Spectrochem (India), Sigma-Aldrich (India), CDH (India) and S.D. Fine were used without further purification. Thin layer chromatographic analysis of compounds was performed on silica gel G coated glass plates. The adsorbent silica gel G was coated to a thickness of about 0.25 mm on previously cleaned TLC plates of 20x5 cm using conventional spreader. The plates were placed in hot air oven at 105°C for 30 min. The solutions of compounds were applied as a spot on the activated plate about 2 cm above from the lower edge. The mobile phases were selected according to the polarity of compounds. Melting points were determined by using open capillary melting point apparatus and are reported uncorrected. FT-IR spectra (KBr) were recorded on a Perkin-Elmer Spectrometer BX-II spectrophotometer. The ¹H-NMR and spectra were recorded on Bruker 400 MHz High Resolution NMR spectrometer using TMS as an internal standard. Chemical shifts were reported in ppm (δ) and signals were described as singlet (s), doublet (d), triplet (t) and multiplet (m) (Scheme - 1).

Synthesis of 4-Naphthalen-2-yl-4-oxo-butyric acid (3)

The compound 4-Naphthalen-2-yl-4-oxo-butyric acid were synthesized by the mixing of Naphthalene 12.8 g (0.1M) and Succinic anhydride 10.0 g (0.1M) in benzene (50 ml) and anhydrous Aluminium chloride 13.33 g (0.1M) and stirred on magnetic stirrer at room temperature for 48 hrs. After completion the reaction dilute HCl (2% v/v, 50 ml) was added. An excess solvent was removed by steam distillation; the hot solution was poured in to a beaker containing cold water (200 ml), and neutralized by sodium bicarbonate. The solid mass was separated, washed with cold water, dried and recrystallized from ethanol. The physico-chemical data was calculated: Rf value 0.54, % yield 67.12, melting point 110-112°C, creamy white color and powdered form.

Synthesis of 4-Naphthalen-2-yl-4-oxo-butyric acid ethyl ester (4)

4-Naphthalen-2-yl-4-oxo-butyric acid ethyl ester was prepared by the reaction of 4-Naphthalen-2-

yl-4-oxo-butyric acid (10 mmol) with ethanol under reflux for 24 h in the presence of concentrated H₂SO₄ (few drops). The resultant mixture was concentrated, cooled and poured into crushed ice. The oily matter thus separated out. The physico-chemical data was calculated: Rf value 0.62, % yield 52.19, brown color and oily in nature.

Synthesis of 4-Naphthalen-2-yl-4-oxo-butyric acid hydrazide (5)

4-Naphthalen-2-yl-4-oxo-butyric acid ethyl ester (50 mmol) and hydrazine hydrate 99% (50 mmol) in the presence of ethanol were refluxed for 20–24 h. This reaction was monitored with TLC. After the completion of reaction, excess solvent was removed under vacuum and the residue was filtered under suction, washed with water, and dried in air. The solid mass thus recrystallized from ethanol. The physico-chemical data was calculated: Rf value 0.66, % yield 48.10, melting point 142-144°C, greenish yellow color and powdered form.

Synthesis of 3-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one. 6a (AR-1)

3-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one was prepared by the reaction of 4-Methoxybenzaldehyde (0.1 mmol) in the presence of Phosphorous oxychloride in a 100-ml round bottle flask. The reaction mixture was refluxed for 3 h. The resultant mixture was cooled, poured into crushed ice and neutralize by dissolving in sodium bicarbonate. The solid mass thus separated out was dried and recrystallized from ethanol.

Light brown colored flakes, M.f. C₂₂H₁₈N₂O₃, m.p. 210-212 °C, Rf 0.42, % yield 45.61, IR (KBr, cm⁻¹, ν): 3055.11(-CH-); 1639.89(-C=O); 1509.57(-C-C); 1269.80(-O-). ¹H NMR (500 MHz, DMSO-*d*), δ 7.129-7.983 (m, 11H, Ar-H), 3.745 (s, 3H, -OCH₃), 2.216-3.238 (t, 4H, CH₂-CH₂). MS (m/z+) [M⁺1] 359.39

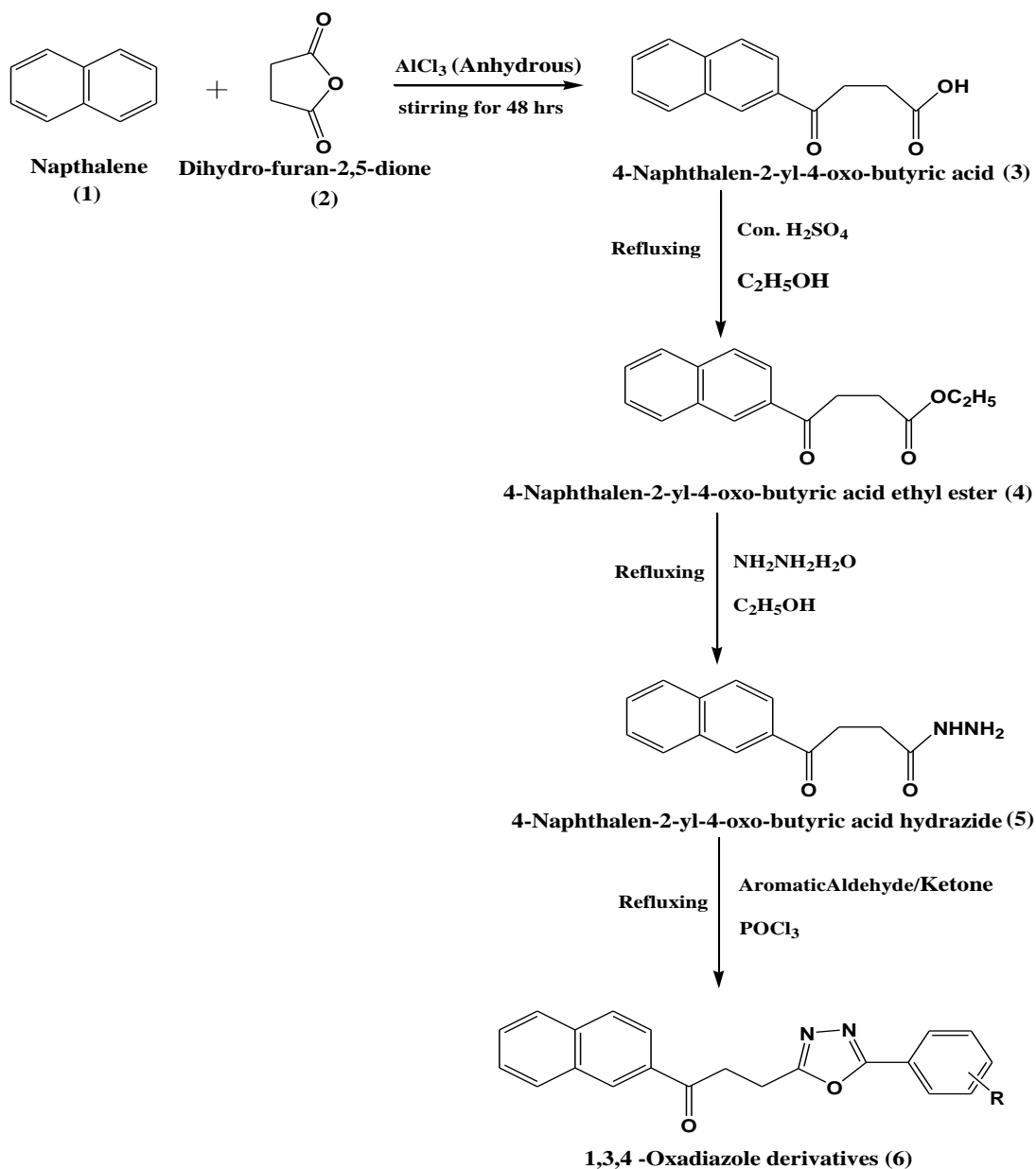
Synthesis of 3-[5-(4-Hydroxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one. 6b (AR-2)

3-[5-(4-Hydroxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one was prepared by the reaction of 4-Hydroxy benzaldehyde (0.1 mmol) in the presence of Phosphorous oxychloride in a 100-ml round bottle flask. The reaction mixture was refluxed for 3 h. The resultant mixture was cooled, poured into

crushed ice and neutralize by dissolving in sodium bicarbonate. The solid mass thus separated out was dried and recrystallized from ethanol.

Palish yellow colored flakes, M.f. $C_{21}H_{16}N_2O_3$, m.p. 205-207 °C, Rf 0.64, % yield 50.21, IR (KBr, cm^{-1} , ν): 2822.57(-CH-); 1690.12(-C=O); 1474.41(-C-C); 1439.08(O-H); 1265.41(-O-).

1H NMR (500 MHz, DMSO- d_6), δ 7.119-7.996 (m, 11H, Ar-H), 4.316 (s, 1H, -OH), 2.212-3.241 (t, 4H, CH_2-CH_2); MS (m/z+) [M^+] 345.36.



Compound No.	6a	6b	6c
R-	-OCH ₃ ,	-OH,	-F

Synthetic Scheme-1

Synthesis of 3-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one. 6c (AR-3)

3-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one was prepared by the reaction of 4-Fluorobenzaldehyde (0.1 mmol) in the presence of Phosphorous oxychloride in a 100-ml round bottle flask. The reaction mixture was refluxed for 3 h. The resultant mixture was cooled, poured into crushed ice and neutralized by dissolving in sodium bicarbonate. The solid mass thus separated out was dried and recrystallized from ethanol.

Brown colored flakes, M.f. $C_{21}H_{15}FN_2O_2$, m.p. 215-217 °C, Rf 0.54, % yield 54.44, IR (KBr, cm^{-1} , ν): 3049.22(-CH-); 1609.16(-C=O); 1521.06(-C-C); 1274.24(-O-); 904.06(-C-F). 1H NMR (500 MHz, DMSO- d_6), δ 7.121-7.980 (m, 11H, Ar-H), 2.210-3.232 (t, 4H, CH_2-CH_2). MS (m/z+) [M^+ 1]347.35

RESULT AND DISCUSSION

Anticonvulsant Activity

The synthesized compounds were showed protection against MES test, indicative of their

ability to inhibit the seizure spread. The results are shown in Table 1. The compounds AR-1, AR-2 and AR-3 were active in MES test. The compounds 3-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-1), 3-[5-(4-Hydroxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-2) and 3-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-3) show protection at a dose of 50 mg/kg. None of these compounds showed neurotoxicity in the highest administered dose (300 mg/kg).

Antibacterial activity

A series of 3-[5-(Substituted-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one were synthesized. The results are shown in Table 2. The compound AR-1, AR-2 and AR-3 showed very good inhibitory characteristics with stronger antimicrobial activity against MTCC-521 gram (-)ve bacteria were evaluated after Cup-plate method. The studied products are still under investigation. Their antibiotic properties have promising applications in the control of infections.

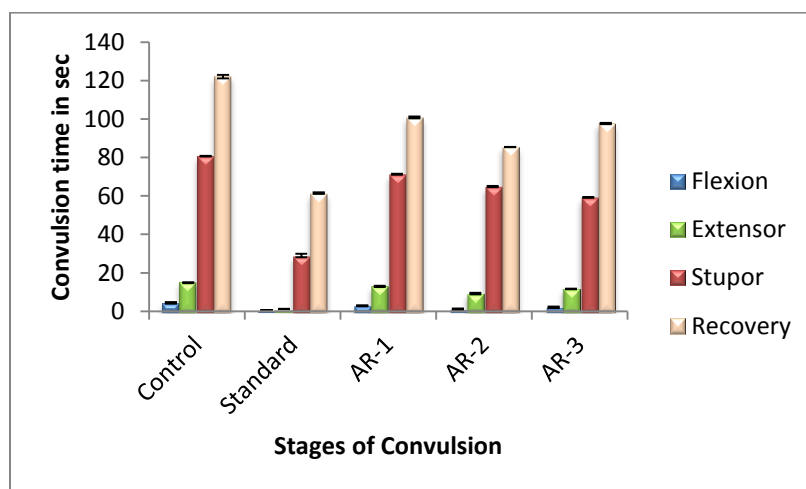
Table 1: Anticonvulsant activity of compounds

Treatment	Dose (mg/kg)	Various phase of convulsions (time in sec)				
		Flexion	Extensor	Stupor	Recovery	%Protection
Control	Tween 80	4.41±0.43	14.88±0.31	80.68±0.19	122.1±0.91	0
Std.	25	0.59±0.1***	1.22±0.13***	29.01±0.92***	61.47±0.46***	100
AR-1	50	2.92±0.30**	12.96±0.28**	71.25±0.24**	100.5±0.50**	66.66
AR-2	50	1.17±0.30**	9.22±0.40**	64.84±0.35**	85.48±0.10**	83.33
AR-3	50	2.12±0.42*	11.62±0.12*	59.23±0.23*	97.68±0.38*	83.33

Values represent the mean \pm SD of six animals each group (n=6), AR-1, AR-2, AR-3 test compounds.

*indicates $p < 0.05$, **indicates $p < 0.02$ and ***indicates $p < 0.01$ when compared to the control group.

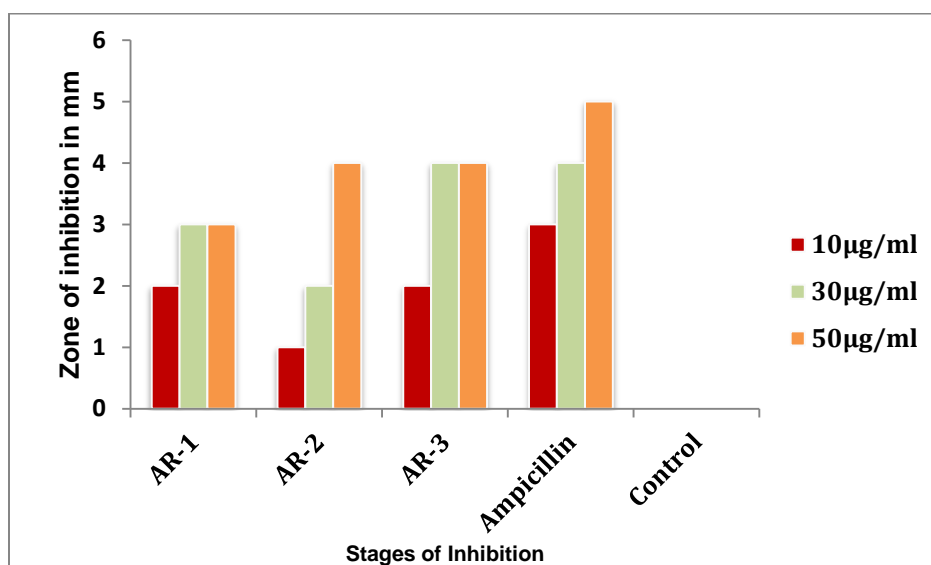
(The mean difference was considered significant at 0.01 level).



Graph 1.

Table 2: Antibacterial activity of compounds

COMPOUND CODE	Zone of inhibition in mm		
	<i>E. coli</i> (MTCC-521)		
	10 µg/ml	30 µg/ml	50µg/ml
AR-1	2	3	3
AR-2	1	2	4
AR-3	2	4	4
Ampicillin	3	4	5
Control	-	-	-

**Graph 2.****CONCLUSION**

A series of substituted 1,3,4-Oxadiazole derivatives were synthesized, their anticonvulsant activity were evaluated after oral administration on MES model. The compounds 3-[5-(4-Hydroxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-2) and 3-[5-(4-Flouro-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-3) displayed significant anticonvulsant activity and compound 3-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-1) shown mild activity. However, further studies need to be carried out to ascertain the precise mechanism of action of anticonvulsant activity of these compounds.

The Compound 3-[5-(4-Flouro-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-3) showed significant inhibitory characteristics with stronger antimicrobial activity against MTCC-521 gram (-)ve bacteria.

ACKNOWLEDGEMENT

The authors are thanks to animal house of S. D. College of Pharmacy & Vocational Studies, Muzaffarnagar to providing animals for pharmacological screening. Thanks are also due to JNU Delhi for recording the ¹HNMR and IR spectra of the synthesized compounds.

REFERENCES

1. Sharma Suruchi, Dixit Vaishali, Epilepsy a Comprehensive Review. International Journal of Pharma Research & Review. 2013; 2(12): 61-80.
2. Tripathi M, Jain DC, Devi MG, Jain S, Saxena V, Chandra PS, Need for a national epilepsy control program. Annals of Indian Academy of Neurology., 2012; 15: 89-93.
3. Mukhopadhyay Kumar Hirak, Kandar Charan Chandi, Das Sanjay Kumar, Ghosh Lakshmikanta, Gupta Kumar Bijan, Epilepsy and its Management a Review. Journal of Pharma Sci Tech., 2012; 1(2): 20-26.

4. Thiry A, Dogne JM, Supuran CT, Masereel B, Carbonic Anhydrase Inhibitors as Anticonvulsant Agents. *Curr. Top. Med. Chem.*, 2007; 7: 855-864.
5. Bachwanin M, Sharma V, Kumar R, Biological activities of 1,3,4-oxadiazole: A Review a. *Int researct journal of pharmacy.*, 2011; 2(12): 1.
6. Nagarj, Chaluvvaraju KC, Niranjan MS, Kiran S, 1,3,4-oxadiazole: A Potent Drug Candidate with Various Pharmacological Activities. *Int J pharm pharm sci.*, 2011; 3(3): 9-16.
7. Boström J, Hogner A, Llinàs A, Wellner E, Plowright AT, Oxadiazoles in Medicinal Chemistry. *J. Med. Chem.*, 2012; 55: 1817-1830.
8. Oliveira CS, Lira BF, Barbosa Filho JM, Lorenzo JGF, Athayde Filho PF, Synthetic approaches and Pharmacological Activity of 1,3,4-oxadiazoles: A review of the literature from 2000-2012 *Molecules.*, 2012; 17: 10192-10231.
9. Zarghi A, Tabatabai SA, Faizi M, Ahadian A, Navabi P, Zanganeh V, Shafiee A, Synthesis and anticonvulsant activity of new 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles. *Bioorg Med Chem Lett.*, 2005; 15: 1863-1865.
10. Kamble RR, Sudha BS, Synthesis and Pharmacological screening of 5-methyl-3-[p-(6'-aryl-2'-thioxo-1',2',5',6'-tetrahydro-pyrimidin-4'-yl)-phenyl]-3H-2-oxo-D4-1,3,4-oxadiazoles. *Indian J Pharm Sci.*, 2006; 6: 249-253.
11. Narayana B, Vijayraj KK, Ashalatha BV, Kumari NS, Synthesis of some new 2-(6-methoxy-2-naphthyl)-5-Aryl-1,3,4-oxadiazoles as possible Non-steroidal Antiinflammatory and Analgesic Agents. *Arch der Pharm.*, 2005; 338: 373-377.
12. Hussain A, Ahuja P, Sarafroz, Synthesis and Biological evaluation of β -aroylpropionic acid based 1,3,4-oxadiazole. *Indian J Pharm Sci.*, 2009; 71(1): 62-66.
13. Omar FA, Mahfouz NM, Rahman MA, Design, Synthesis and anti-inflammatory Activity of 1,3,4-oxadiazole derivatives. *Eur J Med Chem.*, 1996; 31: 819-825.
14. Ingole PS, Mohane SR, Berad BN, Synthesis and Antimicrobial activity of 2-alkyl/aryl-5-(pyrid-4-yl)-1,3,4-oxadiazole. *Asian J Chem.*, 2007; 19: 2683-2686.
15. Todeschini AR, Miranda AL, Silva CM, Parrini SC, Barreiro EJ, Synthesis and evaluation of analgesic, antiinflammatory and antiplatelet properties of new 2-pyridyl aryl hydrazone derivatives. *Eur J Med Chem.*, 1998; 33: 189-199.
16. Karthikeyan MS, Prasad DJ, Mahalinga M, Holla BS, Kumari NS, Antimicrobial studies of 2,4,-dichloro-5-fluorophenyl containing oxadiazoles. *Eur J Med Chem.*, 2008; 43: 25-31.
17. Somani RR, Shirodkar PY, Synthesis, Antibacterial and Anti tubercular Evaluation of some 1,3,4-Oxadiazole Analogues. *Asian J Chem.*, 2008; 20: 6189-6194.
18. Ergenc N, Gunay NS, Synthesis and antidepressant evaluation of new 3-phenyl-5-sulfonamidoindole derivatives. *Eur J Med Chem.*, 1998; 33: 143-148.
19. Holla BS, Poojary KN, Bhat KS, Ashok M, Poojary B, Synthesis and anticancer activity studies on some 2-chloro-1,4-bis-(5-substituted-1,3,4-oxadiazol-2-ylmethyleneoxy) phenylene derivatives. *Indian J Chem.*, 2005; 44B: 1669-1673.
20. Mohamed Jawed Ahsan, Sharma Jyotika, 1,3,4-Oxadiazole: A Versatile Therapeutic Heterocycle. *Adv. Biomed. Pharma.*, 2014; 1(1): 1-10.
21. Padmavathi V, Reddy G Dinneswara, Reddy S Nagi, Mahesh K, Synthesis and biological activity of 2-(bis((1,3,4-oxadiazolyl/1,3,4-thiadiazolyl)methylthio)methylene) malononitriles. *European Journal of Medicinal Chemistry.*, 2011; 46: 1367-1373.
22. Yang SJ, Lee SH, Kwak HJ and Gong YD, Regioselective Synthesis of 2-Amino-Substituted 1,3,4-Oxadiazole and 1, 3, 4-Thiadiazole Derivatives via Reagent-Based Cyclization of Thiosemicarbazide Intermediate. *J. Org. Chem.*, 2013; 78: 438-444.
23. Arvind Singh K, Vinay Sahu KR, Deepmala Yadav, Review article on 1,3,4-Oxadiazole derivatives and it's Pharmacological activities. *International Journal of ChemTech Research.*, 2011; 3(3): 1362-1372.
24. Walcourt A, Loyevsky M, Lovejoy DB, Gordeuk VR, Richardson DR, Novel arylhydrazone and thiosemicarbazone iron chelators with anti-malarial activity against chloroquine-resistant and sensitive parasites. *Int J Biochem Cell Biol.*, 2004; 36: 401-407.
25. Abdel-Aal MT, El-Sayed WA, El-Ashry EH, Synthesis and antiviral evaluation of some sugar aryl glycinoylhydrazones and their oxadiazoline derivatives. *Arch. Pharm. Chem. Life Sci.*, 2006; 339: 656-663.

26. Shivarama BH, Gonsalves R, Sheony S, Ibid, Synthesis of substituted 1,3,4-Oxadiazole, Journal of Science., 2000; 35: 267.
27. Shafiee A, Sayadi A, Roozbahani MH, Foroumadi A, Kamal F, Imidazole as an important moiety, Arch. Pharm. Med. Chem., 2002; 10: 495.
28. Hui X, Zhang Z, Synthesis of substituted 1,3,4-Oxadiazole, Ind. J. Chem., 1999; 38(B):1066.
29. Gulerman N, Rollas S, Kiraz M, Ekinci AC, Vidin A, Farmaco, Synthesis of substituted 4-([1,2,4]triazolo[3,4-b]-[1,3,4]thiadiazol-6-yl)quinolines, J. Med. Chem., 1997; 52:691.
30. Muhi-Eldeen Z, Nadir M, Aljobory NR, Hussein F, Stohs S, Synthesis of New biologically active Triazoles derivative, Eur. J. Med. Chem., 1991; 26: 237.
31. Saini R, Chaturvedi S, Kesari AN, Kushwaha S, Synthesis, Characterization and biological Evaluation of 1,3,4-Oxadiazole, Der. Pharm. Chemica., 2010; 2(2): 297-302.