Research Journal of Chemical Sciences _____ ISSN 2231-606X
Vol. **3(10),** 51-55, October **(2013)** *Res. J. Chem. Sci.*

Synthesis and Characterization of a New Series of2-(5-bromothiophen-2-yl)-5-Substituted-1, 3, 4-Oxadiazoles

Namratha B., Shetty Nitinkumar S., D'Souza Janice N. and Gaonkar Santosh L.
Department of Chemistry, Manipal Institute of Technolgy, Manipal University, Manipal-576014, Karnataka, INDIA

Available online at: www.isca.in, www.isca.me
Received 31st August 2013, revised 17th September 2013, accepted 15th October 2013

Abstract

A novel series of 2-(5-bromothiophen-2-yl)-5-substituted-1, 3, 4-oxadiazoleswere synthesized by oxidative cyclization of schiff bases derived from5-bromo-2-thiophene-carboxaldehyde and aromatichydrazides using Chloramine-T as an efficient oxidant. Structural elucidation was accomplished by ^{1}H NMR, ^{13}C NMR, elemental analysesand IR of synthesized compounds.

Keywords: Synthesis; chloramine-T; 1, 3, 4-oxadiazoles.

Introduction

Nitrogen containing heterocycles, especially 5-membered rings, have grabbed attention as they are found in natural products and are used often in medicinal chemistry. There has been a considerable development in the study of compounds with oxadiazole moiety. 1, 3, 4-oxadiazole is observed to be extensively manipulated in the fields of chemical and pharmaceutical sciences. The capacity of this isomer to undergo an array of chemical reactions has made it the medicinal backbone on which a number of potential molecules can be constructed.

Raltagravir**,** potent PDF inhibitor BB-83698 and furamizole are just few instances of oxadiazole therapeutic agents. A choice of compounds with 1, 3, 4-oxadiazoles are effective against bacterial strains[1], fungi[2], inflammation[3-4], body ache[5] and convulsion[6-7]. A range of similar compounds have also shown good activities against different insects[8]. This isomer is the active ingredient in compounds that can bring about muscle relaxation[9].

In order to avoid the harsh conditions and side reactions that the classical oxidants offer, milder reagents have been developed[10]. Chloramine-T[11-12] is one such oxidant. Its mild quality affords fine yield and excellently pure 2, 5-disubstituted-1, 3, 4-oxadiazoles.

The great potential for different pharmacological activities of 1, 3, 4-oxadiazole derivatives, the underlined chemistry and our continued interest[13-15] impelled us to carry out the Chloramine-T mediated synthesis of a series of 2-(5-bromothiophen-2-yl)-5-substituted-1, 3, 4-oxadiazoles.

Results and Discussion

The target compounds were synthesized as per scheme 1. All the experiments were carried out in Orbit 6 parallel synthesizer. Different aromatic acids 1 were esterified in the presence of acid catalyst. The esters 2 were converted to corresponding hydrazides by reacting with hydrazine. The resulting Aryl hydrazides 3 were further reacted with 5-bromo-2-thiophene-carboxaldehyde 4 to afford aryl hydrazones 5, which were oxidatively cyclized by using the catalyst Chloramine-T to the desired oxadiazoles 6 in good yield. Nuclear Magnetic Resonance spectra, Infrared spectra and elemental analyses characterized the synthesized compounds. The Infrared spectrum of oxadiazoles showed the absence of amide carbonyl peak at1600-1760 cm^{-1} and disappearance of the -NH peak at 3100-3300 cm^{-1}, which could be observed in aryl hydrazones, the intermediate stage. ^{1}H NMR and ^{13}C NMR showed the exact number of protons and carbons respectively in the expected region for the predicted structures of the oxadiazoles. The formation of the products was confirmed by correct elemental analyses.

Material and Methods

Experiments were carried out in an Orbit 6 parallel synthesizer. Melting points were established on a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 MHz spectrometer using DMSO as solvent and tetramethylsilane as internal standard. Chemical shifts were expressed in δ and the following abbreviations were used: s = singlet, d = doublet, t = triplet and m = multiplet. IR (KBr) spectra were recorded on Shimadzu 8300 spectrometer. Thin layer chromatography was facilitated on precoated silica gel G plates.

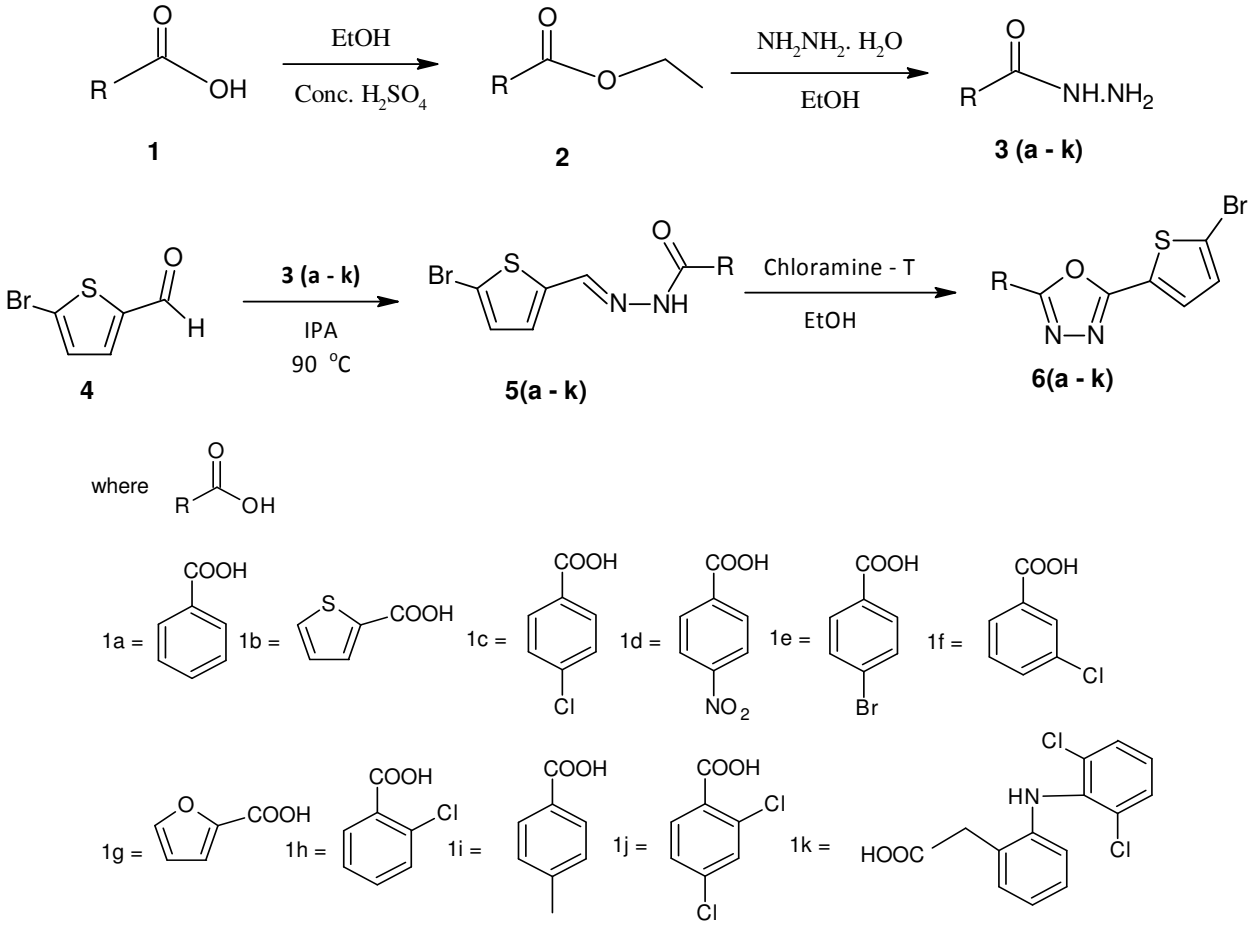
Representative procedure for the synthesis of aromatic hydrazides3 (a-k): A parallel synthesis equipment, set with a magnetic stirrer was charged with the respective aromatic acid **1** (1 g), ethanol (5 mL) and catalytic amount of conc. H_2SO_4. The mixture was refluxed for 3 h. The progress of the reaction was supervised by TLC (toluene: ethyl acetate = 7.5: 2.5). After

completion of reaction, aqueous layer was subjected to diethyl ether extraction. Ether layer was washed with 5 % sodium bicarbonate solution and thereafter evaporated to yield corresponding aromatic ester **2,** which was refluxed with 98 % hydratedhydrazine (2 mL) in ethanol (2 mL) for 2 h. The progress of the reaction was monitored by TLC (toluene: ethyl acetate: diethylamine = 7.5: 2.5:1). After completion of the reaction, reaction mixture was cooled and the solid formed was filtered and washed with chilled ethanol (1 mL) to get **3 (a-k)** which were directly used for next stage.

Representative procedure for the synthesis of aryl hydrazones 5 (a-k): An equimolar mixture of aromatic hydrazide 3 (a-k) and 5-bromo-2-thiophene-carboxaldehyde**4**was refluxed in IPA (10 vol.) for 2 h. The progress of the reaction was monitored by TLC (toluene: ethyl acetate: DEA= 7.5: 2.5: 1). After completion of the reaction, the mass was cooled and the solid formed was filtered to give 5 (a-k).

Representative procedure for the sythesis of 2, 5-disubstituted -1, 3, 4 oxadiazoles6 (a-k): A mixture of aryl hydrazone**5 (a-k**) (1 mmol) and Chloramine-T. $3H_2O$ (1.19 mmol) in ethanol (10 vol.) was refluxed under stirring for 2 h. The progress of the reaction was monitored by TLC ($CHCl_3$: ethyl acetate= 1:1). The reaction mass was then concentrated under reduced pressure and the residue was extracted into diethyl ether. Ether layer was washed with 10% NaOH solution, water, finally with brine solutions and dried (anhy. Na_2SO_4). Ether was evaporated to get the solid **6 (a-k)**. The hydrazone was recrystallized from ethanol.

The same procedure was used in all cases.



Scheme-1
Synthesis of 2-(5-bromothiophen-2-yl)-5-substituted-1, 3, 4-oxadiazole library

2-(5-bromothiophen-2-yl)-5-phenyl-1,3,4-oxadiazole 6a: Acquired from **5a** (1.0 g, 3.23 mmol) and Chloramine-T.$3H_2O$ (1.07 g, 3.84mmol) as a brown crystalline solid (0.91 g, 92 %), m.p. 124-126°C.IR (KBr pellets cm^{-1}) *v* 817, 972, 1200, 1488, 1596.^{1}H NMR DMSO: δ 7.855-7.297 (m, 5H-Ar), 7.932 (d, 1H-Thiophene), 8.579 (d, 1H-Thiophene).^{13}C NMR DMSO: δ 123.80(2C-Ar), 126.33(2C-Ar), 127.2(1C-Ar), 129.72(1C-Thiophene), 131.77(1C-Thiophene), 132.70(1C-Thiophene), 132.72 (1C-Thiophene), 144.01 (1C-Ar), 159.77(1C-Oxadiazole), 164.08 (1C-Oxadiazole). Anal.Calcd.for $C_{12}H_7BrN_2OS$: C, 46.92; H, 2.30; N, 9.12 %. Found: C, 46.96; H, 2.32; N, 9.14 %.

2-(5-bromothiophen-2-yl)-5-(thiophen-2-yl)-1,3,4-oxadiazole 6b: Acquired from **5b** (1.0 g, 3.17mmol) and Chloramine-T.$3H_2O$ (1.05 g, 3.76mmol) as a brown crystalline solid (0.85 g, 86 %), m.p. 136-138°C.IR (KBr pellets cm^{-1}) *v*817, 1040, 1141, 1488, 1561.^{1}H NMR DMSO: δ7.748-7.319 (m, 3H-Thiophenewithout-Br), 7.758 (d, 1H-Thiophene), 8.80(d, 1H-Thiophene).^{13}C NMR DMSO: δ 117.64 (1C-Thiophene), 124.31(1C-Thiophene), 126.08(1C-Thiophene), 129.31(1C-Thiophene), 131.23(1C- Thiophene with Br attached), 131.71(1C- Thiophene with Br attached), 132.48 (1C- Thiophene with Br attached), 132.73 (1C-Thiophene with Br attached), 159.36 (1C-Oxadiazole), 160.43 (1C-Oxadiazole). Anal.Calcd.for$C_{10}H_5BrN_2OS_2$: C, 38.35; H, 1.61; N, 8.94 %. Found: C, 38.33; H, 1.60; N, 8.96 %.

2-(5-bromothiophen-2-yl)-5-(4-chlorophenyl)-1,3,4-oxadiazole 6c: Acquired from **5c** (1.0 g, 2.91mmol) and Chloramine-T.$3H_2O$ (0.96 g, 3.45mmol) as a yellow crystalline solid (0.78 g, 79 %), m.p. 128-129°C.IR (KBr pellets cm^{-1}) *v*802, 1087, 1265, 1481, 1599.^{1}H NMR DMSO: δ7.705-7.128 (m, 4H-Ar), 7.822 (d, 1H-Thiophene), 8.112(d, 1H-Thiophene).^{13}C NMR DMSO: δ128.2 (2C-Ar), 129.80 (1C-Thiophene), 129.86(2C-Ar), 131.94(1C-Thiophene), 132.51(1C-Thiophene), 133.86 (1C-Ar), 137.41(1C-Thiophene), 139 (1C-Ar), 159.30(1C-Oxadiazole), 163.34(1C-Oxadiazole).Anal.Calcd.for$C_{12}H_6BrClN_2OS$: C, 42.19; H, 1.77; N, 8.20 %. Found: C, 42.16; H, 1.72; N, 8.18 %.

2-(5-bromothiophen-2-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole 6d: Acquired from **5d** (1.0 g, 2.82 mmol) and Chloramine-T.$3H_2O$ (0.93 g, 3.34 mmol) as a yellow crystalline solid (0.74 g, 75 %), m.p. 140-142 °C.IR (KBr pellets cm^{-1}) *v*856, 1519, 1324, 1427, 1589.^{1}H NMR DMSO: δ7.882-7.427 (4H-Ar), 8.116 (d, 1H-Thiophene), 8.831(d, 1H-Thiophene).^{13}C NMR DMSO: δ 123.6 (2C-Ar), 128.01 (2C-Ar), 129 (1C-Thiophene), 131.94(1C-Thiophene), 132.51(1C-Thiophene), 137.41(1C-Thiophene), 145.3 (1C-Ar), 147 (1C-Ar), 159.27 (1C-Oxadiazole), 163.35 (1C-Oxadiazole).Anal.Calcd.for$C_{12}H_6BrN_3O_3S$: C, 40.81; H, 2.00; N, 11.90 %. Found: C, 40.78; H, 1.99; N, 11.94 %.

2-(5-bromothiophen-2-yl)-5-(4-bromophenyl)-1,3,4-oxadiazole 6e: Acquired from **5e** (1.0 g, 2.57mmol) and Chloramine-T.$3H_2O$ (0.93 g, 3.04mmol) as a cream crystalline solid (0.83 g, 84 %), m.p. 134-136°C.IR (KBr pellets cm^{-1}) *v*833, 1100, 1481, 1589.^{1}H NMR DMSO: δ7.643-7.277 (m, 4H-Ar), 8.127 (d, 1H-Thiophene), 8.654(d, 1H-Thiophene).^{13}C NMR DMSO: δ 122 (1C-Ar), 129.04 (2C-Ar), 129 (1C-Thiophene), 131.94(1C-Thiophene), 132.3 (2C-Ar), 132.51(1C-Thiophene), 137.41(1C-Thiophene), 140 (1C-Ar), 159.3(1C-Oxadiazole), 163.3 (1C-Oxadiazole). Anal.Calcd. for $C_{12}H_6Br_2N_2OS$: C, 37.33; H, 1.57; N, 7.26 %. Found: C, 37.29; H, 1.56; N, 7.24 %.

2-(5-bromothiophen-2-yl)-5-(3-chlorophenyl)-1,3,4-oxadiazole 6f: Acquired from **5f** (1.0 g, 2.92 mmol) and Chloramine-T.$3H_2O$ (1.05 g, 3.45 mmol) as a brown crystalline solid (0.77 g, 78 %), m.p. 132-133°C.IR (KBr pellets cm^{-1}) *v* 766, 1033, 1200, 1427, 1512.^{1}H NMR DMSO: δ 7.92-7.15 (m, 4H-Ar), 8.01 (d, 1H-Thiophene), 8.123(d, 1H-Thiophene).^{13}C NMR DMSO: δ125.2 (1C-Ar), 127.4 (1C-Ar), 127.9 (1C-Ar), 129.75 (1C-Thiophene), 129.86(1C-Ar), 131.94(1C-Thiophene), 132 (1C-Thiophene), 135.11 (1C-Ar), 137.41(1C-Thiophene), 141.1 (1C-Ar), 159.2(1C-Oxadiazole), 163.11 (1C-Oxadiazole).Anal.Calcd.for $C_{12}H_6BrClN_2OS$: C, 42.19; H, 1.77; N, 8.20 %. Found: C, 42.15; H, 1.76; N, 8.17 %.

2-(5-bromothiophen-2-yl)-5-(furan-2-yl)-1,3,4-oxadiazole 6g: Acquired from **5g** (1.0 g, 3.34 mmol) and Chloramine-T.$3H_2O$ (1.20 g, 3.94 mmol) as a yellow crystalline solid (0.79 g, 80 %), m.p. 222-224 °C.IR (KBr pellets cm^{-1}) *v* 799, 901, 1133, 1473, 1555.^{1}H NMR DMSO: δ7.86-7.467 (m, 3H-Furan), 7.94 (d, 1H-Thiophene), 8.79 (d, 1H-Thiophene).^{13}C NMR DMSO: δ 119.05 (1C-Thiophene), 124.9 (1C-Thiophene), 126.12 (1C-Thiophene), 127.2 (1C-Furan), 127.4 (1C-Furan), 128.9 (1C-Furan), 129.25 (1C-Thiophene), 154.7 (1C-Furan), 159.10 (1C- Oxadiazole), 160.2 (1C-Oxadiazole). Anal.Calcd.for $C_{10}H_5BrN_2O_2S$: C, 40.42; H, 1.70; N, 9.43 %. Found C, 40.39; H, 1.75; N, 9.41 %.

2-(5-bromothiophen-2-yl)-5-(2-chlorophenyl)-1,3,4-oxadiazole 6h: Acquired from **5h** (1.0 g, 2.91mmol) and Chloramine-T.$3H_2O$ (1.04 g, 3.43mmol) as a brown crystalline solid (0.77 g, 78 %), m.p. 148-150 °C.IR (KBr pellets cm^{-1}) *v* 802, 848, 1164, 1272, 1488, 1589.^{1}H NMR DMSO: δ7.845-7.39 (m, 4H-Ar), 8.16 (d, 1H-Thiophene), 8.287 (d, 1H-Thiophene).^{13}C NMR DMSO: δ 125.2 (1C-Ar), 127.4 (1C-Ar), 127.9 (1C-Ar), 129.75 (1C-Thiophene), 129.86 (1C-Ar), 131.94(1C-Thiophene), 132 (1C-Thiophene), 135.11 (1C-Ar), 137.41(1C-Thiophene), 141.1 (1C-Ar), 159.2 (1C-Oxadiazole), 163.11 (1C-Oxadiazole).Anal.Calcd.for $C_{12}H_6BrClN_2OS$: C, 41.19; H, 1.77; N, 8.20 %. Found C, 41.16; H, 1.79; N, 8.17 %.

2-(5-bromothiophen-2-yl)-5-(4-methylphenyl)-1,3,4-oxadiazole 6i: Acquired from **5i** (1.0 g, 3.09mmol) and Chloramine-T.$3H_2O$ (1.10 g, 3.64mmol) as a yellow crystalline solid (0.85 g, 86 %), m.p. 137-138°C.IR (KBr

pellets cm^{-1}) *v* 813, 1062, 1372, 1466, 1591.^{1}H NMR DMSO: δ 2.39 (s, 3H, CH_3), 7.64-7.48 (m, 4H-Ar), 8.157 (d, 1H-Thiophene), 8.27 (d, 1H-Thiophene). ^{13}C NMR DMSO: δ 21.1 (1C-CH_3), 127.1 (2C-Ar), 129 (1C-Thiophene), 129.6 (2C-Ar), 131.94(1C-Thiophene), 132.1(1C-Thiophene), 136.5 (1C-Ar), 137.21(1C-Thiophene), 138.1 (1C-Ar), 159.4(1C-Oxadiazole), 163.7 (1C-Oxadiazole).Anal.Calcd.for $C_{13}H_9BrN_2OS$: C, 48.61; H, 2.82; N, 8.72 %. Found C, 48.64; H, 2.83; N, 8.68 %.

2-(5-bromothiophen-2-yl)-5-(2, 4-dichlorophenyl)-1,3,4-oxadiazole6j: Acquired from **5j** (1.0 g, 2.64 mmol) and Chloramine-T.$3H_2O$ (0.93 g, 3.10 mmol) as a brown crystalline solid (0.78 g, 79 %), m.p. 137-138 ^{o}C.IR (KBr pellets cm^{-1}) *v* 789, 824, 914, 1103, 1457, 1578.^{1}H NMR DMSO: δ 7.94-7.77 (m, 3H-Ar), 8.39 (d, 1H-Thiophene), 8.68 (d, 1H-Thiophene).^{13}C NMR DMSO: δ 126.2 (1C-Ar), 127.1 (1C-Ar), 129.1(1C-Thiophene), 129.3 (1C-Ar), 131.82(1C-Thiophene), 32.05(1C-Thiophene), 134.6 (1C-Ar), 134.8 (1C-Ar), 137.32 (1C-Thiophene), 139.3(1C-Ar), 159.5(1C-Oxadiazole), 162.9 (1C-Oxadiazole).Anal.Calcd.for $C_{12}H_5BrCl_2N_2OS$: C, 38.33; H, 1.34; N, 7.45 %. Found C, 38.36; H, 1.29; N, 7.48 %.

***N*-(2-{[5-(5-bromothiophen-2-yl)-1,3,4-oxadiazol-2-yl]methyl}phenyl)-2, 6-dichloroaniline6k:** Acquired from **5k** (1.0 g, 2.06 mmol) and Chloramine-T.$3H_2O$ (0.72 g, 2.41 mmol) as a brown crystalline solid (0.71 g, 72 %), m.p 80-82^{o}C.IR (KBr pellets cm^{-1}) *v* 762, 813, 905, 1108, 1347, 1480, 1598.^{1}H NMR DMSO: δ 2.32 (s, 2H, CH_2), 3.73 (s, 1H, NH), 6.5-6.7 (m, 4H, ArH), 6.93 (s, 1H, ArH), 7.12 (s, 2H, ArH), 8.39 (d, 1H-Thiophene), 8.68 (d, 1H-Thiophene).^{13}C NMR DMSO: δ 50.7 (1C-CH_2), 116.5 (1C-Ar), 119.4 (1C-Ar), 121.5 (1C-Ar), 124 (1C-Ar), 125.9 (1C-Ar), 127.1 (1C-Ar), 127.9 (1C-Ar), 128.4 (1C-Ar), 129 (1C-Thiophene), 131 (1C-Ar), 131.57 (1C-Thiophene), 132.32 (1C-Thiophene), 134.7 (1C-Ar), 137.31 (1C-Thiophene), 145.4 (1C-Ar), 147.2 (1C-Ar), 158.9 (1C-Oxadiazole), 162 (1C-Oxadiazole). Anal.Calcd.for $C_{19}H_{12}BrCl_2N_3OS$: C, 47.42; H, 2.51; N, 8.73 %. Found C, 47.38; H, 2.55; N, 8.70 %.

Conclusion

Chloramine-T, a novel oxidant, mediated the synthesis of a new series of 2-(5-bromothiophen-2-yl)-5-substituted-1, 3, 4-oxadiazoles by oxidative cyclization pathway. Chloramine-Tis desired as it is commercially available, inexpensive, water-tolerant, non-toxic, easy to handle and could be used without further purification. Acquired compounds were characterized based on their physical and spectral data. Synthesis of oxadiazole derivatives which have proven to be having great biological activities is found to be further advantageous. This work is intended to evaluate the anti-microbial activities of synthesized compounds in future.

Acknowledgement

Manipal Institute of Technology, Manipal has been gratefully acknowledged for the post doctoral research grant to SLG and for the laboratory facilities offered.

References

1. Patel N.B. and Patel J.C., Synthesis and antimicrobial activity of 3-(1, 3, 4-oxadiazol-2-il)quinazolin-4(3*H*)-ones, *Sci. Pharm.,* **78**, 171–193**(2010)**

2. Sangshetti J.N., Chabukswar A.R. and Shinde D.B., Microwave assisted one pot synthesis of someNovel 2, 5-disubstituted 1, 3, 4-oxadiazoles as antifungal agents, *Bioorg. Med. Chem. Lett.,* **21**, 444–448**(2011)**

3. Husain A., Ahmad A., Alam M.M., Ajmal M. and Ahuja P., Fenbufen based 3-[5-(substitutedaryl)-1, 3, 4-oxadiazol-2-yl)]-1-(biphenyl-4-yl)propan-1-ones as safer anti-inflammatory and analgesic agents, *Eur. J. Med. Chem.,* **44**, 3798–3804**(2009)**

4. Manjunatha K., Poojary B., Lobo P.L., Fernandes J. and Kumari N.S., Synthesis and biologicalevaluation of some 1, 3, 4-oxadiazole derivatives, *Eur. J. Med. Chem.* **45**, 5225–5233**(2010)**

5. 5.Amir M. and Kumar S., Synthesis and evaluation of anti-inflammatory, analgesic ulcerogenic andlipid peroxidation properties of ibuprofen derivatives, *Acta Pharm.,* **57**, 31–45 **(2007)**

6. Kashaw S.K., Gupta V., Kashaw V. and Mishra P. et al., Anticonvulsant andsedative-hypnotic activity of some novel 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazoline-4(3*H*)-ones, *Med. Chem. Res,* **19**, 250–261**(2010)**

7. Rajak H., Deshmukh R., Veerasamy R., Sharma A.K., Mishra, P. et al., Novelsemicarbazones based 2, 5-disubstituted-1, 3, 4-oxadiazoles: One more step towards establishingfour binding site pharmacophoric model hypothesis for anticonvulsant activity, *Bioorg. Med.Chem. Lett.,* **20,** 4168–4172 **(2010)**

8. Xiumian Z., Zhong L., Yanli W., Weidong C., et al., Syntheses and insecticidal activities of novel 2, 5 disubstituted 1, 3, 4-oxadiazoles, *J. Fluorine Chem.,* **123(2)**, 163-169 **(2003)**

9. Almasirad A., Vousooghi N., Tabatabai S.A., Kebriaeezadeh A. et al., Synthesis, Anticonvulsant and Muscle Relaxant Activities of Substituted 1, 3, 4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole, *Acta Chimica Slovenica*, **54 (2),** 317**(2007)**

10. Cledualdo S., Bruno F. L., Jose Maria B., Jorge G. F. L. and Petronio F., Synthetic Approaches and Pharmacological Activity of1, 3, 4-Oxadiazoles: A Review of the Literature from 2000–2012, *Molecules,* **17**, 10192-10231**(2012)**

11. Li X. and He D., Synthesis and optical properties of novel anthracene-based stilbene derivativescontaining an 1, 3, 4-oxadiazole unit, *Dyes Pigm.,* **93,** 1422–1427 **(2012)**

12. Gaonkar S. L., Lokanatha Rai K.M. and Prabhuswamy B., Synthesis and anti-microbial studies of a new series of 2-{4-[2-(5-ethylpyridin-2-ylethoxy] phenyl}-5-substituted-1, 3, 4-oxadiazoles, *Eur. J. Med. Chem.*, **41**, 841**(2006)**

13. Gaonkar S. L., Mahendra M., Nanjunda Swamy S. and Shetty Nitinkumar S., Synthesis and Crystal structure studies of Diethyl-(6-chloro-2-carbazolyl) Methyl malonatean intermediate in the synthesis of Anti-inflammatory drug Carprofen, *Res. J. Pharmaceutical Sci*, **1(1),** 16-22 **(2012)**

14. Kumar A., D'Souza S.S., Mysore Nagaraj S.R., Gaonkar S.L., Salimath B.P. and Rai K.M.L., Antiangiogenic and antiproliferative effects of substituted-1, 3, 4-oxadiazole derivatives is mediated by down regulation of VEGF and inhibition of translocation of HIF-1α in Ehrlich ascites tumor cells, *Cancer chemotherapy and pharmacology,* **64 (6),** 1221-1233 **(2009)**

15. Gaonkar S.L. and Rai K.M.L., A new method for the generation of azoalkenes from ketohydrazones and its application to the synthesis of tetrahydropyridazine derivatives, *Tetrahedron letters,* **46 (35),** 5969-5970 **(2005)**