International Journal of Engineering Research and General Science Volume 2, Issue 6, October-November, 2014
ISSN 2091-2730

A novel $POCl_3$ catalysed expeditious synthesis and antimicrobial activities of 5-subtituted-2-arylbenzalamino-1, 3, 4-thiadiazole

Shalini Jaiswal*, Shailja Sigh

Dr. Shalini Jaiswal
Department of Chemistry, AMITY UNIVERSITY
Greater Noida Campus, U.P. 201308
Email: shaliniajaiswal@gmail.com and sjaiswal@gn.amity.edu
Telephone: 09953217151

ABSTRACT : There is a growing need for more environmentally acceptable processes in the chemical industry. The fields of combinatorial and automated medicinal chemistry have emerged to meet the increasing requirement of new compounds for drug discovery. Microwave-assisted organic synthesis is an enabling technology for accelerating drug discovery and development processes.

In the family of heterocyclic compounds nitrogen containing heterocycles are an important class of compounds in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes. Thiosemicarbazide belongs to thiourea group, whose biological activity is due to the presence of aldehyde or ketone moiety. Thiosemicarbazide derivatives exhibit a great variety of biological activities, such as antitumor, antifungal , antibacterial , and antiviral.

Here we developed a, novel, solvent free, microwave assisted synthesis of hitherto unknown 5-subtituted-2aryl benzalamino-1, 3, 4-thiadiazole **4a-h** with excellent yield.

KEY WORDS

5-subtituted-2aryl benzalamino-1, 3, 4-thiadiazole, green chemistry, microwave irradiation, antibacterial activity, gram positive and gram negative bacteria.

INTRODUCTION

Conventional methods of organic synthesis are too slow to satisfy the demand for generation of such compounds. It is widely acknowledged that there is a growing need for more environmentally acceptable processes in the chemical industry .The fields of combinatorial and automated medicinal chemistry have emerged to meet the increasing requirement of new compounds for drug discovery

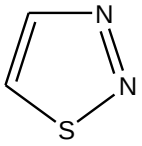
The microwave region of the electromagnetic spectrum lies between infrared and radio frequencies[1, 2]. Microwave-assisted organic synthesis is an enabling technology for accelerating drug discovery and development processes. Microwave instruments are used principally in three areas of drug research: the screening of organic drug, peptide synthesis, and DNA amplification. Microwave include following advantages, over the conventional heating.

- Uniform heating occurs throughout the material
- Process speed is increased
- High efficiency of heating
- Reduction in unwanted side reaction
- Purity in final product,
- Improve reproducibility
- Environmental heat loss can be avoided
- Reduce wastage of heating reaction vessel
- Low operating cost

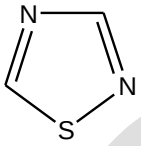
Resistance to antimicrobial agents has become an increasingly important and pressing global problem. Heterocyclic compounds are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, and antibiotics [1, 2].In the family of heterocyclic compounds nitrogen containing heterocycles are an important class of compounds in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes [3].

Thiosemicarbazide belongs to thiourea group, whose biological activity is due to the presence of aldehyde or ketone moiety. Thiosemicarbazide derivatives exhibit a great variety of biological activities[4, 5] , such as antitumor , antifungal , antibacterial , and antiviral. Thiosemicarbazide are potent intermediates for the synthesis of pharmaceutical and bioactive materials and thus, they are used extensively in the field of medicinal chemistry.

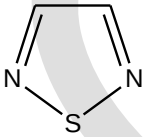
Thiadiazole is a 5-membered ring system containing two nitrogen and one sulphur atom. They occur in nature in four isomeric forms viz. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole. These different classes of thiadiazoles nucleus were known to possess various biological and pharmacological properties[6-9]



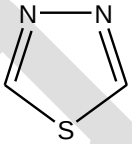
(1)1,2,3-Thiadiazole



(2)1,2,4-Thiadiazole



(3)1,2,5-Thiadiazole



(4)1,3,4-Thiadiazole

1,3,4-thiadiazole exhibit diverse biological activities, possibly due the present of =N-C-S moiety[10.] 1, 3, 4-thiadiazoles are very interesting compounds due to their important applications in many pharmaceutical, biological and analytical field [11, 12]. The naturally occurring B6-vitamins pyridoxine, pyrodoxal, pyridoxamine, and codecarbaxylase also contains thiadiazole nucleus.

Literature survey revealed that the 1, 3, 4-thiadiazole moiety have been widely used by the medicinal chemist in the past to explore its biological activities. 1, 3, 4-Thiadiazole are very interesting compounds due to their important applications in many pharmaceutical biological and analytical fields[13, 14].

1,3,4-thiadiazole derivatives have been of interest to the medicinal chemists for many years because of their anticancer[15,16],antitubercular[17], antibacterial[18], antifungal[19,20], anticonvulsant, analgesic[21] , antisecretory[22] ,antitumor[23] and anti-microbial[24]activities.

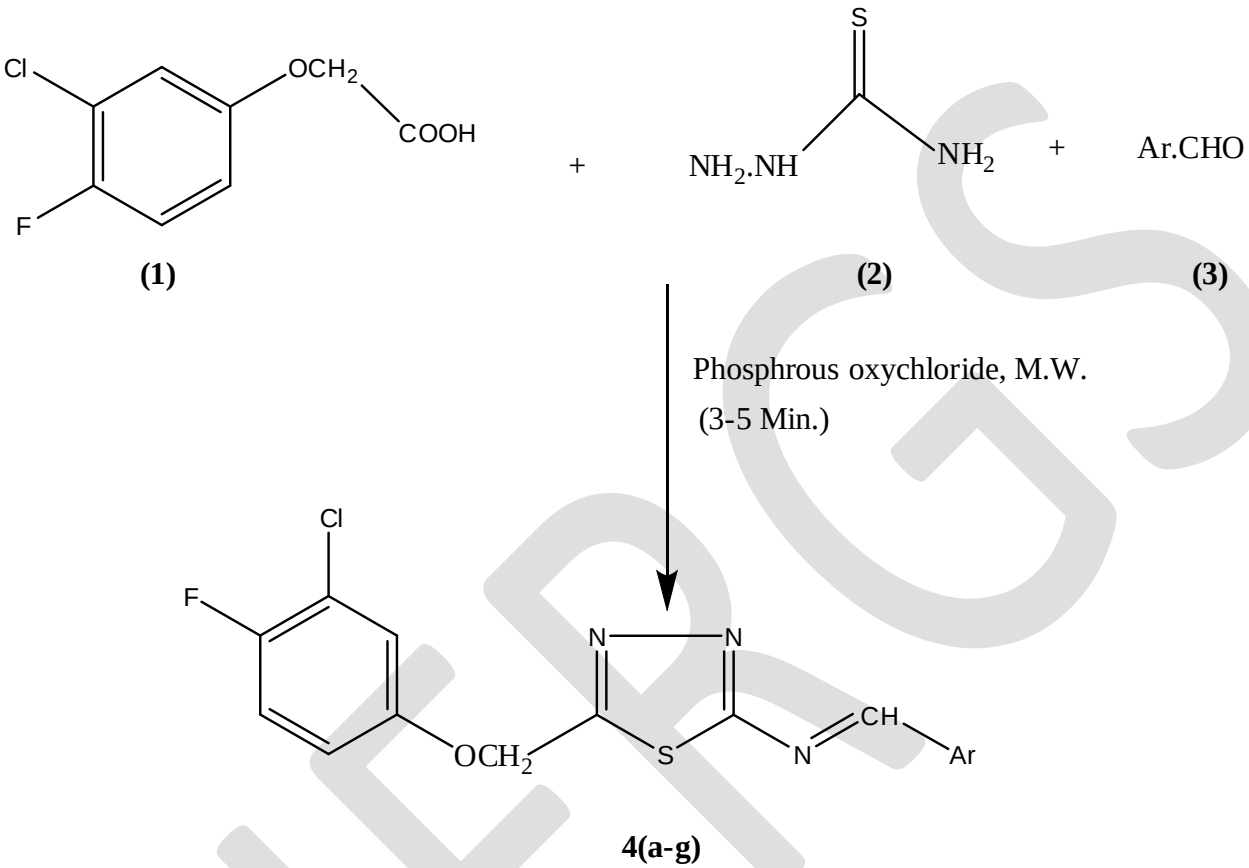
The solvent free reaction or dry media techniques under microwave irradiation are one of the main fields of our research. Encouraged by above reports and as part of our research programme for development of eco-friendly synthetic protocol for biologically active compounds as well as in pursuing of our work on new solvent-free synthesis we developed a, novel, solvent free, microwave activated synthesis of hitherto unknown 5-subtituted-2aryl benzalamino-1, 3, 4-thiadiazole **(Scheme 1)**.The reaction time, yield, and ^{1}HNMR spectra are summarized in **Table-1 and Table-2.**

EXPERIMENTAL SECTION

All chemicals used in this study were purchase from Aldrich Chemicals and were used without further purification. Melting points were determined by open glass capillary method and are uncorrected. A Laboratory Microwave Oven (Model BP 310/50) operating at 2450 MHz and power output of 600 W was used for all the experiments. The completion of reactions was monitored by TLC (Merk silica gel). IR spectra were recorded on a Shimadzu FTIR-420 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at

400^{o}C on a Bruker AVANCE DPX (400 MHz) FT spectrometer in $CDCl_3$ using TMS as an internal reference (chemical shift in δ, ppm). Mass spectra were recorded on JEOL SX-303 (FAB) mass spectrophotometer at 70ev. Elemental analyses were carried out using a Coleman automatic C, H, N analyser. The yield and melting point are given in **Table-1.**

Scheme-I



4(a-g)

GENERAL METHODS AND MATERIALS

Microwave assisted synthesis of 5-subtituted-2arylbenzalamino-1, 3, 4-thiadiazole 4_{a-h}:

(3-Chloro-4-flurophenoxy) acetic acid **1** (0.010 mol), thiosemicarbazide **2** (0.012 mol), aromatic aldehyde **3** (0.02 mol) and catalytic amount of POCl3 were mixed thoroughly in a beaker and the mixture was heated in household microwave oven, operating at medium power (600W) for the specified period (3-5 min) given in **Table-1**.

The completion of reaction was checked by TLC at every 30 sec. and after completion of reaction, the reaction-mixture was allowed to attain room temperature. The reaction-mixture was cooled and poured on crushed ice, cooled to 10 ^{0}C. The solid separated was filtered, treated with dil. NaOH to adjust PH 9-10. Finally resulting solid was washed with water and crystallized from DMF to obtain the crude product **4_{a-h}**.

Thermal synthesis of 5-subtituted-2arylbenzalamino-1, 3, 4-thiadiazole 4_{a-h}:

A mixture of (3-Chloro-4-flurophenoxy) acetic acid **1** (0.010 mol), thiosemicarbazide **2** (0.012 mol), and aromatic aldehyde **3** (0.02 mol) in 30 ml of ethanol (95%) was
Refluxed on a water bath at 90 ^{0}C for 4-5 hour. The completion of reaction was checked by TLC at every 1.5 hours and after completion of reaction, the reaction-mixture was allowed to attain room temperature. The reaction-mixture was cooled and poured on crushed ice, cooled to 10 ^{0}C. The solid separated was filtered, treated with dil. NaOH to adjust Ph 9-10. Finally resulting solid was washed with water and crystallized from DMF to obtain the crude product **4_{a-h}**.

RESULTS AND DISCUSSION

After the experiment it is concluded that the compounds which are synthesized in the project having good yield .The identification and characterization of the compound determined on the basis of their[1] melting Point ,TLC, ^{1}HNMR and mass Spectroscopy. The spectral and elemental analysis of newly synthesized compound is elaborated in Table-2, which confirms the structure of synthesized compounds.

The 5-subtituted-2arylbenzalamino-1, 3, 4-thiadiazole derivatives were assayed for their antimicrobial activity against selected species of gram-positive, gram negative bacteria .The antibacterial activity data reveals that the compounds *4c and 4d* exhibited good antibacterial activity against n gram positive *(S.aureus and B.cereus)* compared to standard drug. While all compound exhibited lowest activity against gram negative bacteria as compared to standard drug Streptomycin.

Table-1

Melting point and Yield of Compound 4_{a-f}

Compound	Ar	Time		Yield (%)		M. P. (^{0}C)
		MWI (min)	Thermal (hour)	MWI	Thermal	
4a	-C_6H_5	4	5	86	35	185
4b	2-HO- C_6H_4	3	4	80	37	225
4c	2-NO_2- C_6H_4	3	5	85	35	215
4d	2-Cl-C_6H_4	3	5	88	36	180
4e	3-Cl,4-Cl-C_6H_3	5	4	90	42	210
4f	3-MeO, 4-HO-C_6H_3	3	4	85	35	220
4g	3-NH2-C_6H_4	5	5	90	36	270
4h	3-MeO,4-MeO- C_6H_3	4	4	85	45	188

Table-2

Physical and ^{1}HNMR Spectra data of Compound 4_{a-h}

Compd	Mol.Formulla	1 H-NMR ($CDCl_3$, δ, ppm)	Elemental Analysis Found (Calculated)	MS (EI, *m/z* (M^+)
4a	$C_{16}H_{11}ClFN_3OS$	7.3-7.5(m,5H, ArH),8.1(s,1H,=CH),5.20(s, 2H,-CH_2),6.84-7.18(m.3H,ArH)	C, 55.25(54.95); H, 3.19(3.24); N, 12.08(12.12)	347
4b	$C_{16}H_{11}ClFN_3O_2S$	6.8-7.5(m,4H, ArH),8.1(s,1H,=CH),5.20(s, 2H, -CH_2),6.86-7.18(m.3H,ArH),5.0(s,1H,-OH).	C, 52.82(52.85); H, 3.05(3.10); N, 11.55(11.60)	363.
4c	$C_{16}H_{10}ClFN_4O_3S$	7.6-8.2(m, 4H, ArH),8.1(s,1H,=CH),5.20(s, 2H, -CH_2),6.89-7.16(m.3H,ArH).	C, 48.92(48.95); H, 2.57(2.60); N, 14.26(14.20)	392
4d	$C_{16}H_{10}Cl_2FN_3OS$	7.2-7.6(m,4H, ArH),8.1(s,1H,=CH),5.20(s, 2H, -CH_2),6.89-7.16(m.3H,ArH).	C, 50.28(50.25); H, 2.64(2.50); N, 10.99(10.85)	380
4e	$C_{16}H_9Cl_3FN_3OS$	7.2-7.6(m, 4H, ArH),8.1(s,1H,=CH),5.20(s, 2H, -CH_2),6.89-7.16(m.3H,ArH).	C, 46.12(45.95); H, 2.18(2.10); N, 10.08(10.15)	414
4f	$C_{17}H_{13}ClFN_3O_3S$	6.7-7.2(m, 3H, ArH),8.1(s,1H,=CH),5.20(s, 2H, -CH_2),6.88-7.16(m.3H,ArH),3.73(s,3H,-OCH_3),5.0(s,1H,-OH)	C, 51.85(52.10); H, 3.33(3.45); N, 10.67(10.58)	393
4g	$C_{16}H_{12}ClFN_4OS$	6.5-7.1(m, 4H, ArH),8.1(s,1H,=CH),5.20(s, 2H, -CH_2),6.84-7.18(m.3H,ArH),5.0(s,1H,-NH_2	C, 52.97(52.86); H, 3.33(3.26); N, 15.44(15.30)	362
4h	$C_{18}H_{15}ClFN_3O_3S$	6.7-7.0(m, 3H, ArH),8.1(s,1H,=CH),5.20(s, 2H, -CH_2),6.84-7.18(m.3H,ArH),3.73(s,6H,-OCH_3),	C, 53.01(52.96); H, 3.71(3.80); N, 10.30(10.28)	407

ANTIMICROBIAL ACTIVITY

The compound were screened for their antibacterial activity against the gram positive bacteria (*Bacillus cereus* and *Staphylococcus aureus*) and gram negative bacteria(*Eschertia coli* and P*seudomonas aeguginosa*) by measuring inhibition of zone in mm. Streptomycin (50µg/ml) was used as a standard drug for antibacterial activity.

All the compound exhibited significant to moderate activity against gram positive and gram negative bacteria as compared to standard drug Streptomycin. The Compounds 4c and 4d has exhibited higher activity against gram positive (*S.aureus* and *B.cereus*) .The higher antibacterial activity of 4c and 4d due to the presence of electron withdrawing group(Chloro and Nitro) at its ortho position .The compounds 4a and 4e has exhibited moderate activity against gram positive (*S.aureus* and *B.cereus)*.While all compound exhibited lowest activity against gram negative bacteria as compared to standard drug Streptomycin.

Table-3

Antibacterial data of 5-subtituted-2arylbenzalamino-1, 3,4-thiadiazole derivatives

Compound	**Antibacterial data in MIC (µg.ml)**			
	Gram + Bacteria		**Gram –Bacteria**	
	S.aureus	***B.cereus***	***E.coli***	***P.aeruginosa***
4a	**8**	**7**	**5**	**4**
4b	**7**	**6**	**7**	**6**
4c	**9**	**8**	**7**	**7**
4d	**9**	**8**	**6**	**7**
4e	**8**	**7**	**7**	**6**
4f	**7**	**6**	**7**	**6**
4g	**7**	**6**	**6**	**6**
4h	**7**	**6**	**7**	**7**
Streptomycin	**10**	**9**	**10**	**12**

CONCLUSION

In the recent year microwave assisted organic reaction has emerged as new tool in organic synthesis and this is considered as an important approach toward green chemistry. This growth of green chemistry holds significant potential for a reduction of the by product & waste production and a lowering of the energy costs. So as part of our research programme for development of eco-friendly synthetic protocol for biologically active compounds as well as in pursuing of our work on new solvent-free cyclisation process we developed a, novel, solvent free, microwave assisted synthesis of hitherto unknown 5-subtituted-2aryl benzalamino-1, 3,4-thiadiazole derivative which possess antimicrobial activities like antibacterial, antiviral and antifungal activities etc. The entire compound exhibited significant to moderate activity against gram positive and gram negative bacteria as compared to standard drug Streptomycin. The Compounds 4c and 4d has exhibited higher activity against gram positive (*S.aureus* and *B.cereus*) .

The compounds 4a and 4e has exhibited moderate activity against gram positive (*S.aureus* and *B.cereus)*.While all compound exhibited lowest activity against gram negative bacteria as compared to standard drug Streptomycin. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic thiadiazole nucleus. Although several method are available for synthesis of thiadiazole but all these method have some disadvantage like long reaction period, low yield and use of toxic organic solvents which pollute our environment.

ACKNOWLEDGEMENT

The authors would like to express their gratitude and thanks to Department of Chemistry, DIT, and School of Engineering (Part of AMITY Education Group) Greater Noida for necessary facilities to carry out this research work and RSIC, CDRI Lucknow for spectral analysis.

REFERENCES:

1.Varma RS, Aqueous N-heterocyclization of primary amines and hydrazines with dihalides: microwave-assisted syntheses of *N*-azacycloalkanes, isoindole, pyrazole, pyrazolidine, and phthalazine derivatives, Journal of Organic Chemistry, vol.71(1),135–141, (2006).

2. Kumar YD, and Varma RS, Revisiting nucleophilic substitution reactions: microwave-assisted synthesis of azides, thiocyanates, and sulfones in an aqueous medium, Journal of Organic Chemistry, vol. 71(17), 6697–6700, (2006).

3. Valverde MG and Torroba T,Special issue: sulphur nitrogen heterocycles, Molecules, 10(2), 318–320, (2008).

4. Shipman C ,Smith SH, Drach JC, and Klayman DL,Thiosemicarbazones of 2-acetylpyridine, 2-acetylquinoline,1-acetylisoquinoline, and related compounds as inhibitors of herpes simplex virus in vitro and in a cutaneous herpes guinea pig model, Antiviral Research, 6(4), 197–222, (1986).

5. Quiroga AG, Perez JM, Lopez-Solera I, et al.,Novel tetra nuclear orthometalated complexes of Pd(II) and Pt(II) derived from *p*-isopropylbenzaldehyde thiosemicarbazone with cytotoxic activity in *cis*-DDP resistant tumour cell lines. Interaction of these complexes with DNA, Journal of Medicinal Chemistry, 4199), 1399–1408, (1998).

6. Cleric F, Pocar D, synthesis of 2-amino-5-sulfanyl-1, 3, 4-thiadiazole derivatives and evaluation of their antidepressant and anxiolytic activity, J.Med.Chem, 44, 931-936 (2001).

7. Rajesh S, Jitendra S, and Subash Chandra C, 2-amino-5-sulfanyl-1, 3, 4-thiadiazole: a new series of selective cyclooxygenase-2-inhibitors, Acta Pharma, 58, 317-326 (2008).

8. Smith N, Garg SP, Pramilla S, synthesis of some pyrazoles, pyrazolones, and oxadiazoles bearing 2-arylamino-5-mercapto-1,3,4-thiadiazole nuclei as possible antimicrobial agents, Indian journal of heterocyclic chemistry, 12, 09-12 (2002).

9. Jitendra Kumar G, Rakesh Kumar Y,Rupesh D, Pramod Kumar S, Recent advancements in the synthesis and pharmacological evaluation of substituted 1,3,4-thaidiazole derivatives, international journal of pharma tech research, 2(2), 1493-1507, (2010).

10. Oruc E, Rollas S, Kandemirli F, Shvets N and Dimoglo A, 1,3,4-thiadiazole derivatives- synthesis, structure elucidation and structure antituberculosis activity relationship investigation. Journal of Medical Chemistry, 47, 6760-6767(2004).

11. Hadizadeh F and R Vosoogh. Synthesis of a-[5-(5-Amino-1, 3, 4-thiadiazol-2-yl)-2 imidazolylthio]-acetic acids. Journal of Heterocyclic Chemistry, 45: 1-3(2008).

12. Lu S M and R Y Chen, Facial and efficient synthesis aminophosphate derivatives of 1, 3, 4-oxadiazole and 1, 3, 4- thiadizaole, Organic Preparations and Procedures International, 32(3), 302-306,(2000).

13. Katritzky A, Rees CW and Potts KT (eds.), Comprehensive Heterocyclic Chemistry. Oxford-VCH, 6(1982).

14. Ahmed M, Jahan J and Banco S, A simple spectrophotometric Methods for the determination of copper in Industrial, Environmental, Biological and Soil, samples using 2, 5-dimercapto 1, 3, 4-thiadiazole, J anal Sci,18,805-810,(2002).

15. Terzioglu N and Gursoy A, Synthesis and anticancer evaluation of some new hydrazone derivatives of 2,6-dimethylimidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazide,Eur. J. Med. Chem. 38, 781-86, (2003).

16. Holla, B.S.; Poorjary, K.N.; Rao, B.S.; Shivananda, M.K. New bis-minomercaptotriazoles and bis-triazolothiadiazoles as possible anticancer agents, Eur. Journal of Medicinal Chemistry, 37, 511–517,(2002).

17. Gadad AK, Noolvi MN and Karpoormath RV, Synthesis and anti-tubercular activity of a series of 2-sulfonamide/trifluoromethyl-6-substituted imidazo [2, 1-b] [1, 3, 4] thiadiazole derivatives, Bioorg. Med Chem, 12,5651-59,((2004)).

18. Gadad AK, Mahajanshetti CS, Nimbalkar S and Raichurkar A, Synthesis and antibacterial activity of some 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide derivatives, Eur. J. Med. Chem, 35, 853-57, (2000).

19. Andotra CS, Langer TC and Kotha A, Synthesis and antifungal activity of some substituted 1,3,4-thiadiazolo[3,2-a]-s-triazin-5-phenyl-7-thiones and imidazo-[2,1-b]-1,3,4-thiadiazol-5-ones. J. Indian.Chem. Soc,74, 125-27, (1997).

20. Liu X, Shi Y, Ma Y, Zhang C, Dong W, Pan L,Wang B,Li Z, Synthesis, antifungal activities and 3D-QSAR study of N-(5-substituted-1, 3, 4-thiadiazol-2-yl) cyclopropanecarboxamides.Eur. J. Med Chem, 44, 2782–2786,(2009).

21. Khazi IAM, Mahajanshetti CS, Gadad AK, Tarnalli AD and Sultanpur CM, Synthesis and anticonvulsant and analgesic activities of some 6-substituted-imidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamides and their 5-bromo derivatives. Arzneim-Forsch. Drug. Res,46, 949-52,((1996)).

22. Andreani A, Leonia A, Locatelli A, Morigi R, Rambaldi M, Simon WA and Senn-Bilfinger J,Synthesis and antisecretory activity of 6-substituted 5-cyanomethyl imidazo[2,1-b]thiazoles and 2,6-dimethyl-5-hydroxymethylimidazo [2,1-b][1,3,4]thiadiazole. Arzneim-Forsch. Drug. Res,50,550-53,(2000).

23. Supuran, CT, Briganti F, Tilli S, Chegwidden WR, Scozzafava A, Carbonic anhydrase inhibitors: Sulphonamides as antitumor agents, Bioorg. Med. Chem, 9, 703–714,(2001).

24. Deminbas N, Karaoglu SA, Demirbas A, Sancak K, Synthesis and antimicrobial activities of some new 1-(5-phenylamino-[1,3,4]thiadiazol-2-yl)methyl-5-oxo-[1,2,4]triazole and 1-(4-phenyl-5-thioxo-[1,2,4]triazol-3-yl)methyl-5-oxo- [1,2,4]triazole derivatives, Eur. J. Med. Chem,39, 793–804,(2004)