Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 7, Issue 4, 2015

Review Article

A REVIEW ON THE VARIOUS BIOLOGICAL ACTIVITIES OF THIADIAZOLE

DINESH MEHTA*, POONAM TAYA, NEETU

M. M College of pharmacy, M. M. U, Mullana, 133207, India.
Email: neetuchopra057@gmail.com

Received: 20 Sep 2014 Revised and Accepted: 25 Oct 2014

ABSTRACT

Thiadiazole and their derivatives have been studied colossally because of their wide range of biological activity. They are found to be effectual as antibacterial, antimalarial, antiviral, antiinflammatory, anticancer and antianthelminthic agents. Distinct biological activities, such as antibacterial, anti-inflammatory, and antiviral have been consort with 1, 3, 4-thiadiazole derivatives. The substituted 1, 3, 4 Thiadiazole nucleus is particularly ubiquitous, and found in some marketed drugs such as acetazolamide, Methazolamide and antibacterial such as Sulphamethazole, antibiotic like Cefazoline. The synthesis of 1, 3, 4 Thiadiazole derivatives has allured widespread attention due to their diverse biological activities, including antimicrobial, anti-inflammatory, analgesic, and antianthelmintic. These reviews focused on various biological activities consorted with thiadiazole nucleus.

Keyword: Thiadiazole, Anti-inflammatory, Antimicrobial, Antihelminthics, Anticancer, Antibacterial and antiviral.

INTRODUCTION

Mostly five membered aromatic systems having three heteroatoms at symmetrical position have been studied because of their physiological properties [1]. 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 [2]. Thiadiazole contains the five-membered diunsaturated ring structure having molecular structure formula $C_2H_3N_2S$ containing two carbon atoms, three hydrogen, two nitrogen and one sulphur [3].

The incorporation of oxygen, nitrogen, and sulfur donor atoms in the macrocycles markedly affect their complexing properties because of the hard (O, N) and soft (S) character of the donor atoms and the exodentate tendency of the sulfide linkages [4]. During recent years there has been intense investigation of different classes of thiadiazole compounds, many of which known to possess interesting biological properties such as antimicrobial [5] antituberculosis, anticonvulsants, anti-inflammatory, antihypertensive[6]antioxidant, human adenosine A3 antagonist[7], anticancer [8, 9] and antifungal activity [10]. Thiadiazole play a prominent role in nature. For example, the thiazolium ring present in vitamin B1 serves as an electron sink and its coenzyme form is important for the decarboxylation of α-keto acids [11].

Chemistry of thiadiazole

Thiadiazoles and their derivatives can be considered as simple five membered heterocycles possessing one sulhur and two nitrogen atoms. The thiadiazoles exist in different isomeric forms such as1, 2, 4-, 1, 2, 5-, 1, 2, 3-and 1, 3, 4-thiadiazoles as showed in figure. 1(a-d)[12]. (fig. 1)

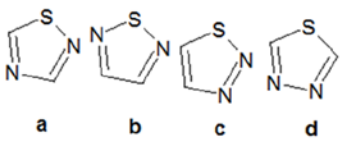


Fig. 1

The fig. 1 represents π-excessive ring system as the two adjacent N atoms of the ring carry a lone pair of electrons each. Actually 1, 3, 4-thiadiazole molecule does not display a true aromatic behavior as do benzene, pyridine and thiophene. Bak *et al.* have made analysis of microwave spectra of this molecule and calculated bond lengths, bond angles and bond orders [13]. They concluded that the aromatic character as measured by the π-electron delocalization decreases in the order of 1, 2, 5-thiadiazole>thiophene>thiazole>1, 3, 4-thiadiazole [14]. 1, 3, 4-thiadiazole core skeletons are subjected to various substitution reactions with alkyl halides, acid chlorides, and sulfonyl chlorides to afford various drug like 2-amino-substituted 1, 3, 4-thiadiazole derivatives [15].

Tautomerism

2-Hydroxy-1, 3, 4-thiadiazole, 2-mercapto-1, 3, 4-thiadiazole and 2-amino thiadiazole have been reported to exist in the tautomeric forms as shown below [16]. (fig. 2)

Fig. 2

Spectral properties of thiadiazoles

IR spectra provide sufficient findings about the chemical structure of the compounds. All the synthesized compounds are characterized by their IR and NMR Spectra. According to Mahendrasinh et al the IR peaks of 2, 5 di substituted thiadiazole derivatives are perceived at 750 (C-S str), 1333 (C-N str), 1670 (C=N str), 1630 (N-N str). [17]S. K. Srivastava evaluated structure 2-(2-Chloroacetyl)-mercapto-5-methyl-1, 3, 4-thiadiazole by ^{1}HNMR that revealed singlet of three methyl protons at 2. 42 (s, 3H,-CH_3) and singlet of two methylene protons at 4. 40(s, 2H,-CH_2). [18](fig. 3)

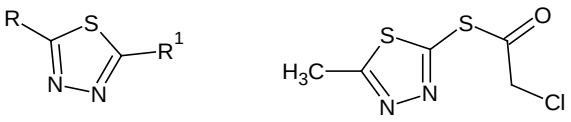


Fig. 3

Structure activity relationship

Structure-activity studies showed that optimum activity resulted when the thiadiazole ring was substituted with a 2-methylphenyl group and a guanidine moiety and analogues were found to lower blood pressure in meta corticoid (DOCA) hypertensive rats. [19]Christopher B. Chapleo et al stated that the unsubstituted guanidine was found to possess potent anticonvulsant properties;

considerable reduction or loss of activity however was observed with the majority of the substituted guanidines [20] (fig. 4)

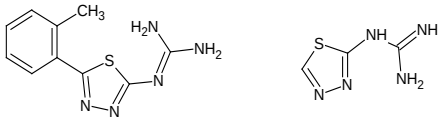
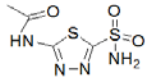
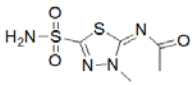


Fig. 5:

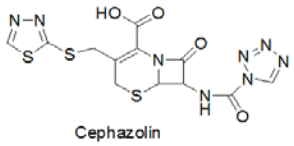
Marketed drugs containing thiadiazole nucleus [21] (fig. 5)



Acetazolamide



Methazolamide



Cephazolin

Synthetic methods of thiadiazoles

The method commonly employed for the synthesis of 1, 3, 4-thiadiazole is the cyclisation of thiosemicarbazide derivatives incorporating the basic structural unit and other method involve the use of isothiocyanate carbondisulphide.

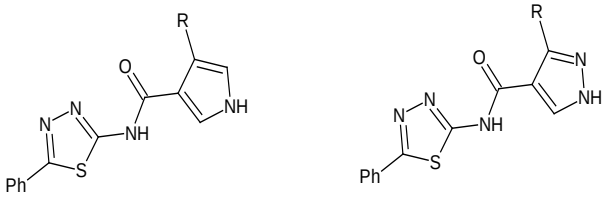
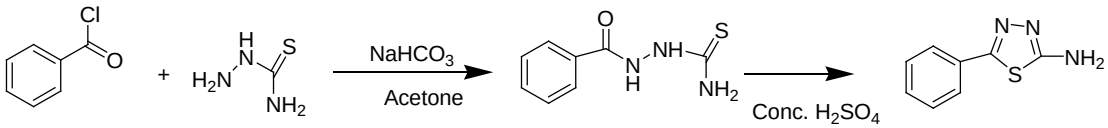


Fig.6.

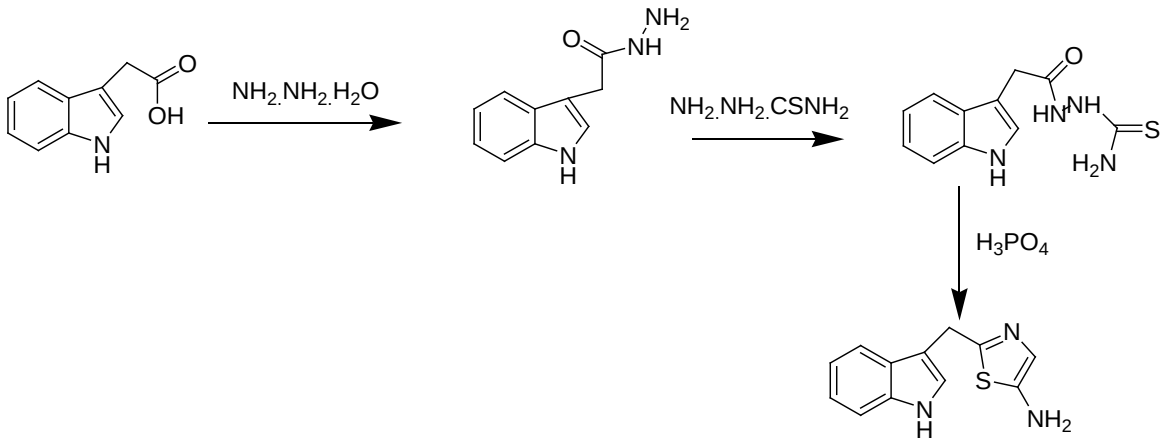
From thiosemicarbazides

Ilkay Kuçukguzel synthesized the thiadiazoles from aroyl thiosemicarbazide and this is prepared by reacting benzoyl chloride with thiosemicarbazide and then subjected to cyclization



Scheme 1

According to U Misra, indole-3-acetohydrazide reacted with thiosemicarbazide and the product in acidic medium gives thiadiazoles. [23] (Scheme 2)



Scheme 2

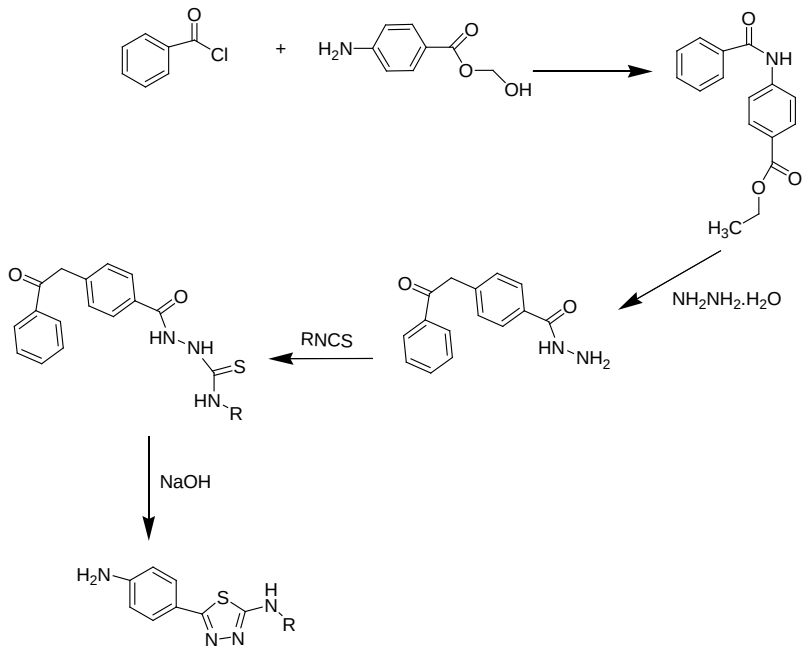
From isothiocyanate and hydrazine

Sevim Rollas et al synthesized the 1, 3, 4 thiadiazoles from Benzocaine and Benzoyl chloride and the intermediate ethyl 4-(benzoylamino)benzoate was added with hydrazine hydrate, which was then refluxed with isothiocyanate and then neutralized to get the final product, where R may be methyl, ethyl, propyl, 4-methylphenyl, 4-methoxyphenyl [24]. (Scheme 3)

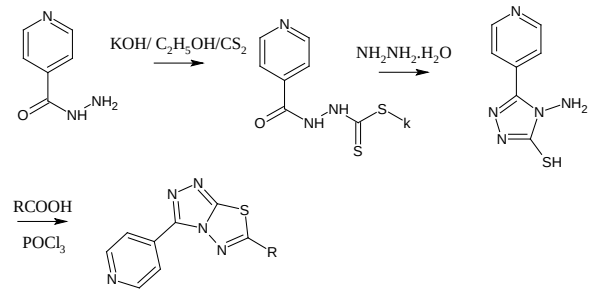
From the reaction of hydrazine and carbon disulfide

Sadaf J. Gilani gives the another method for synthesizing 1, 3, 4thiadiazoles is by reacting dithiocarbazinate with 99% hydrazine hydrate to give the 4-amino-5-(pyridin-4-yl)-4H-1, 2, 4-triazole-3-thiol and triazole is converted into thiadiazoles, by condensation with aromatic acids in the presence of $POCl_3$. [25](Scheme 4)

Seung-Ju Yang et al gave a regioselective, reagent-based method for the cyclization reaction of 2-amino-1, 3, 4-thiadiazole in which thiosemicarbazide intermediate was reacted with p-TsCl, triethylamine in N-methyl-2-pyrrolidone to give the corresponding 2-amino-1, 3, 4-thiadiazoles through regioselcective cyclization processes, where $R_1$is 4-methoxy-Ph and R_2 is 4-NO_2-Ph. [26] (Scheme 5)



Scheme 3:

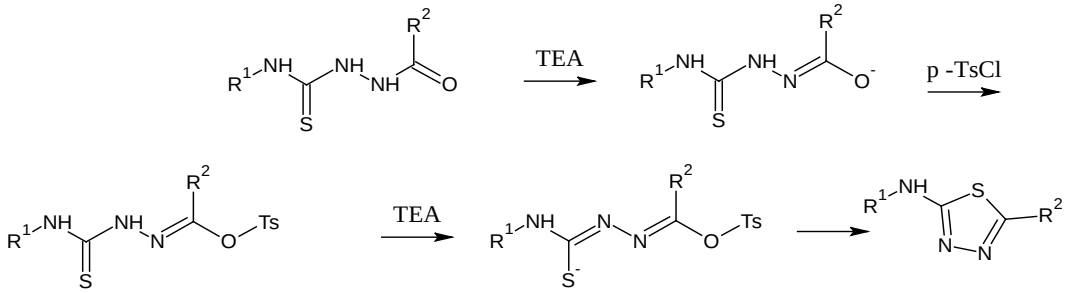


Scheme 4

R = a) C_6H_5; (b) R = 2-C_6H_4Cl; (c) R = 2, 4-$C_6H_3Cl_2$; (d) R = 2-$C_6H_4CH_3$;

(e) R = 2-$C_6H_4OCOCH_3$; (f) R = OC_6H_5 (phenoxy);

g) R = 4-$C_6H_4NO_2$.



Scheme 5

Biological activities associated with thiadiazoles

Anti-inflammatory activity

S. Maddila et al (2012) reported a new series of 1, 3, 4-thiadiazole with pyrazole-3-carboxamides and pyrrole-3-carboxamide and seven compounds were found to exhibit significant anti-inflammatory activity with inhibition in paw edema compared to the standard drug indomethacin. [27] (fig. 6) (table. 1)

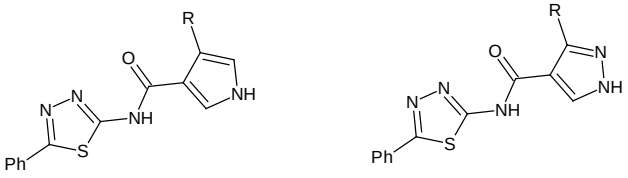


Fig.6.

R= C_6H_5, 4-NO_2-C_6H_4,

4-Br-C_6H_4, 4-F-C_6H_4,

4-Cl-C_6H_4, 4-I-C_6H_4

R	Ar
CH_3	C_6H_5
CH_3	4-MeC_6H_4
CH_3	4-ClC_6H_4
OC_2H_5	C_6H_5
OC_2H_5	4-MeC_6H_4
OC_2H_5	4-ClC_6H_4

Mohd. Amir et al (2008) synthesized a series of 3, 6-disubstituted-1, 2, 4-triazolo-[3, 4-b]-1, 3, 4-thiadiazoles by condensation of 4-amino-5-substituted-3-mercapto-(4H)-1, 2, 4-triazoles with various substituted aromatic acids and aryl/alkyl isothiocyanates through a one-pot reaction. These compounds were investigated for their anti-inflammatory, analgesic, ulcergenic, lipid peroxidation, antibacterial and antifungal activities and found to be more active than their standard drugs. [28] (fig. 7)

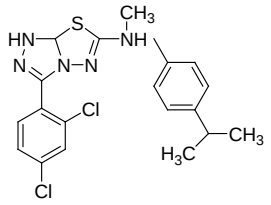


Fig. 7

Mohamed A. A. Radwan (2007) reported the synthesis of new substituted hydrazones, 1, 3, 4-thiadiazole derivatives as anti-inflammatory agents. The 3-substituted indole derivatives played a very important role as anti-inflammatory and analgesic agents and considering the interesting pharmacological profile of tenidap. [29] (fig. 8)

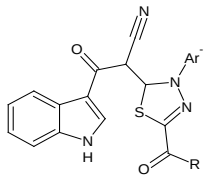


Fig. 8

Kamal M. Dawood (2006) reported the new series of derivatives of pyrazole and 1, 3, 4 thiadiazole. The newly synthesized compounds were found to possess anticonvulsant and anti-inflammatory activities with the same mechanism of action of selective COX-2 inhibitors. [30] (fig. 9) (table. 2)

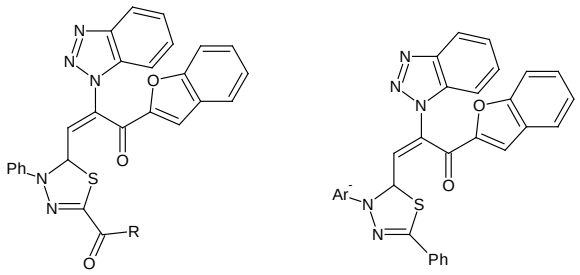
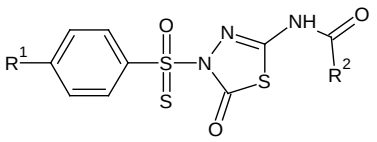


Fig. 9:

Table 2

Substituents	R	Ar
A	CH_3	C_6H_5
B	CH_3	4-MeC_6H_4
C	CH_3	4-ClC_6H_4
D	OC_2H_5	C_6H_5
E	OC_2H_5	4-MeC_6H_4
F	OC_2H_5	4-ClC_6H_4

Silvia Schenone et al (2006) synthesized the two series of N-[5-oxo-4-(arylsulfonyl)-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl]-amides and evaluated for in vivo analgesic and anti-inflammatory activities. All the new compounds possess good analgesic action in the acetic acid writhing test and some compounds also showed fair anti-inflammatory activity in the carrageenan rat paw edema test. [31] (fig. 10) (table. 3)



Compound	R^1	R^2	Compound	R^1	R^2
A	H	Phenyl	l	CH_3	4-methyl phenyl
B	H	4-methyl phenyl	m	CH_3	4-methoxy phenyl
C	H	4-methoxy phenyl	n	CH_3	4-chloro phenyl
D	H	4-chloro phenyl	o	CH_3	4-Fluorophenyl
E	H	4-fluoro phenyl	p	CH_3	Fuorophenyl
F	H	2-fluoro phenyl	q	CH_3	3-Fluorophenyl
G	H	3-fluoro phenyl	r	CH_3	2, 4-Difluorophenyl
h	H	2, 4di fluoro phenyl	s	CH_3	4-Trifluoromethylphenyl
I	H	4di fluoro phenyl methyl	t	CH_3	2-Furoyl
J	H	4-furoyl			
K	CH_3	Phenyl			

Antimicrobial activity

Kuldipsinh P. Barot et al (2013) synthesized a series of novel 1, 3, 4-thiadiazole; 1, 2, 4-triazole-5-thione and 1, 3-thiazolan-4-one derivatives of benzimidazole were synthesized by nucleophilic substitution reaction of 2-substituted-1[H] benzimidazole and these compounds were evaluated by spectral and elemental methods of analysis for antibacterial and antifungal activities. [32](fig. 11). Tomasz Plech et al (2012) synthesized eight derivatives of 1, 2, 4-triazolo [3, 4-b]1, 3, 4-thiadiazole and evaluated for their in vitro antimicrobial activity. Compounds with different substitutents as listed in table indicated high activity towards Gram-positive bacteria, which were up to 16 times more than currently used antibiotics.

The influence of an aryl fragment at position C-3 of the 1, 2, 4-triazolo [3, 4-b] 1, 3, 4-thiadiazole system, seems the most beneficial for the anti-MSSA and anti-MRSA activity is the presence of chlorine atom at the meta position of the phenyl ring. [33] (fig. 12) (table. 4)

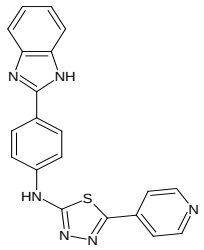


Fig. 11

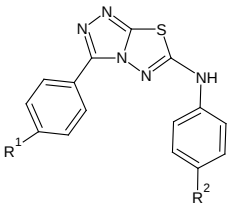


Fig. 12

compound	R^1	R^2
A	H	-Cl
B	H	-Br
C	2-Cl	-Cl
D	2-Cl	-Br
E	3-Cl	-Cl
F	3-Cl	-Br
G	4-Cl	-Cl
H	4-Cl	-Br

Amandeep Kaur(2012) reported the synthesis of some novel heterocyclic derivatives comprising imidazole and 1, 3, 4-thiadiazole containing biphenyl moiety. Structures of the compounds were elucidated by spectral studies and evaluated for antibacterial activity against various strains of Escherichia coli, Pseudomonas aeruginosa and Bacillus subtilis, and antifungal activity against *Candida albicans, Saccharomyces cerevisiae* and *Aspergillus niger*. [34] (fig. 13)

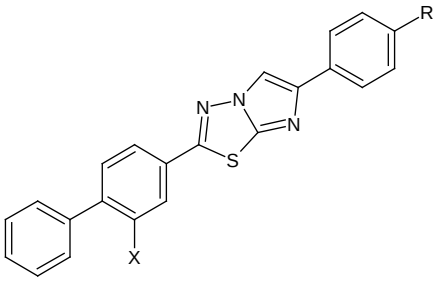


Fig. 13

Mahendrasinh M. Raj et al (2011) synthesized the Morpholine, Phthalimide and Piperidene derivatives of 1, 3, 4-Thiadiazole. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H NMR, and nitrogen estimation.

These compounds were screened for antibacterial such as *Staphylococcus aureusATCC* 9144, *Becillus Cereus ATCC* 11778, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853 and anti-fungal *Aspergillus niger* ATCC 9029 and *Aspergillus fumigates* ATCC 46645 by paper disc diffusion technique [35]. (fig. 14)

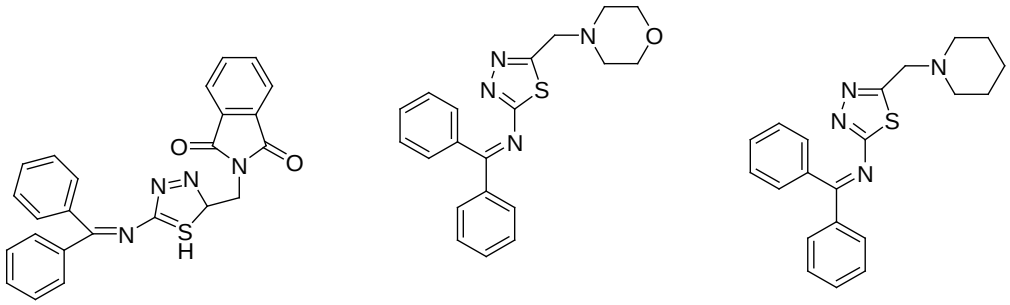


Fig. 14

Arvind k. singh et al (2011) reported the synthesis of 2, 5-Disubstituted 1, 3, 4-thiadiazoles and evaluated for various pharmacological activities such as antibacterial, anti-inflammatory and antihypertension activities. [36] (fig. 15)

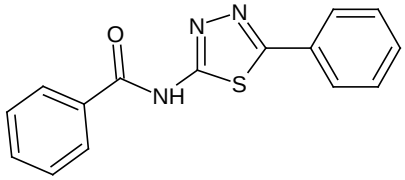
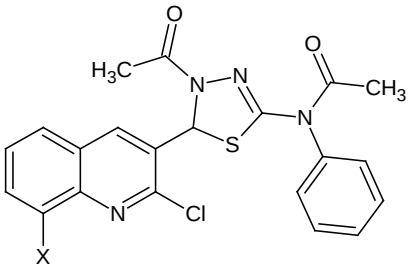


Fig. 15

Abdul R. Bhat et al (2011) synthesized a new series of thiadiazoles and intermediate thiosemicarbazones from the chloroquinone molecule and evaluated the compounds for their in vitro anti-microbial activity was performed against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Salmonella typhimurium*, and *Escherichia coli.* [37] (fig. 16)



X=H, Cl, CH_3

S. Nanjunda Swamy (2006) synthesized the two series of 4, 6-disubstituted 1, 2, 4-triazolo-1, 3, 4-thiadiazole derivatives and were

checked for their efficacy as antimicrobials in vitro. Compounds showed significant inhibition against all the strains of *Bacillus subtilis*, *Escherichia coli, Pseudomonas fluorescens, Xanthomonas campestris*, *Xanthomonas oryzae*, when compared to standard drugs. [38] (fig. 17) (table. 5)

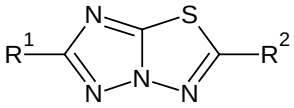


Fig. 17

Antitubercular activity

S. Talath and A. K. Gadada (2006) synthesized a series of 7-[4-(5-amino-1, 3, 4 thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolonic derivatives and characterized by IR, ^{1}H-NMR, ^{13}C NMR, FAB Mass spectral and elemental analyses. The compounds were evaluated for their preliminary in vitro antibacterial activity against some Gram-positive and Gram-negative bacteria and selected compounds were screened for antitubercular activity against *Mycobacterium tuberculosis H37Rv* strain by broth dilution assay method. [39] (fig. 18)

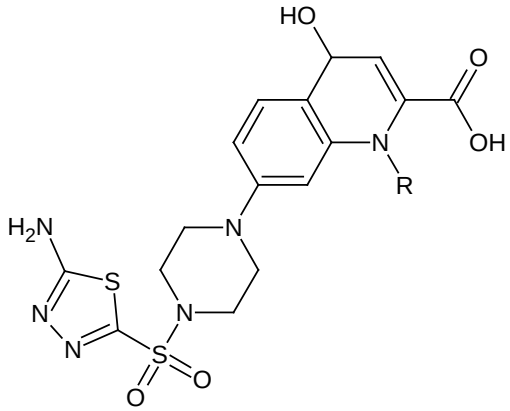


Fig. 18

R= Cyclopropyl,-CH_2CH_3

Anticancer activity

Hai-Chuan Zhao et al (2013) represented a novel series of 1, 3-selenazole-containing 1, 3, 4-thiadiazole derivatives bearing Schiff base moieties and evaluate for their in vitro antiproliferative activities against human breast cancer *cell MCF-7* and mouse lymphocyte leukemia cell L1210 by CCK-8 assay. [40] (fig. 19)

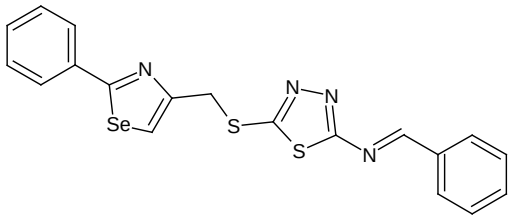


Fig. 19

Negar Mohammadhosseini et al (2013) synthesized a new series of 1-(substituted benzyl)-4-(5-(5-nitroaryl-2-yl)-1, 3, 4-thiadiazol-2-yl) piperazine derivatives and the most potent nitrofuran derivative containing 3-methoxybenzyl piperazine pendant at the C-2 position of 1, 3, 4 thiadiazole ring demonstrated strong *anti-H. pylori.* [41] (fig. 20)

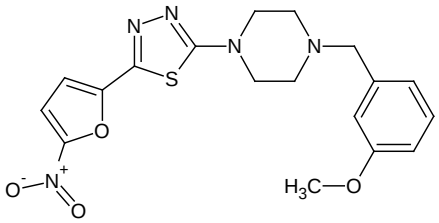


Fig. 20

Omaima M. Abdelhafez et al (2012) synthesized the new series of 4-methyl and 3, 4-dimethyl-7-oxycoumarin derivatives of thiadiazoles and evaluated for their monoamine oxidase (MAO) A and B inhibiting effect. The docking experiments carried out on MAO-A and MAO-B structures proved new information about the enzyme–inhibitor interaction and the potential therapeutic application of 7-oxycoumarin scaffold. [42](fig. 21)

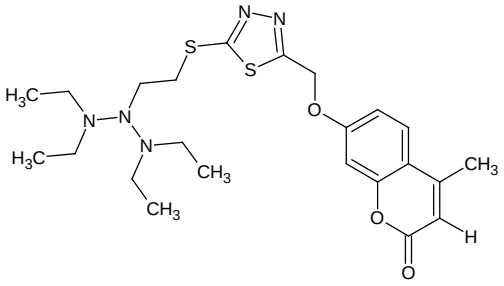


Fig. 21

C. Lopez-Cara (2012) synthesized the new compounds of 1, 3, 4-thiadiazole structure, and there in vitro biological evaluation as inhibitors of both neuronal and inducible Nitric Oxide Synthase (nNOS and iNOS) is done. These compounds have been designed by an isosteric modification of a series of 4, 5-dihydro-1H-pyrazole derivatives, previously described as the nNOS inhibitors.

Docking studies conclude that the stronger interaction between the inhibitor and the enzyme is the reinforced hydrogen bond formed between the guanidinium moiety of the inhibitor and Glu592 (Glu371 in iNOS) carboxylate. The insertion of the S atom in the heterocyclic ring induces a selective inhibition of the iNOS isoform. [43] (fig. 22)

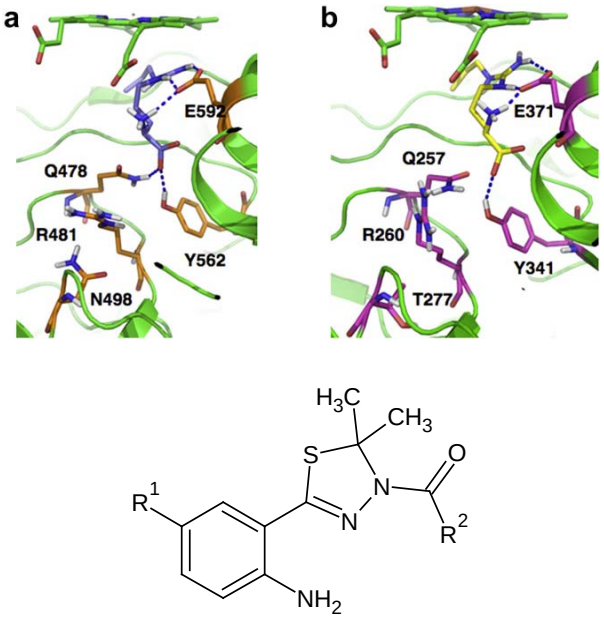


Fig. 22

Xin Jian Song (2011) et al synthesized novel fluorinated pyrazolo [3, 4-d] pyrimidine derivatives containing 1, 3, 4-thiadiazole. Their antitumor activities were evaluated against HL-60 by an MTT assay. The preliminary results indicated that some title compounds exhibit more potent antitumor inhibitory activity than doxorubicin (DOX). [44] (fig. 23)

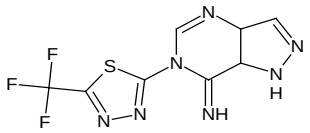


Fig. 23

Rahmi Kasmo gullar (2010) synthesized a new series of Pyrazole carboxylic acid derivatives of 5-amino-1, 3, 4-thiadiazole-2-sulfonamide from ethyl 3-(chlorocarbonyl)-1-(3-nitrophenyl)-5-phenyl-1H-pyrazole-4-carboxylate and studied the in vitro inhibitory effects on hydratase and esterase activities of carbonic anhydrase isoenzymes (HCA-I and HCA-II). [45] (fig. 24)

D. A. Ibrahimre presented (2009)a new series of 3, 6-disubstituted triazolo [3,4-b] thiadiazole derivatives and evaluated for their cytotoxic activity against a panel of 60 human cancer cell lines by the National Cancer Institute (NCI) and some of them demonstrated inhibitory effects on the growth of a wide range of cancer cell lines [46] (fig. 25).

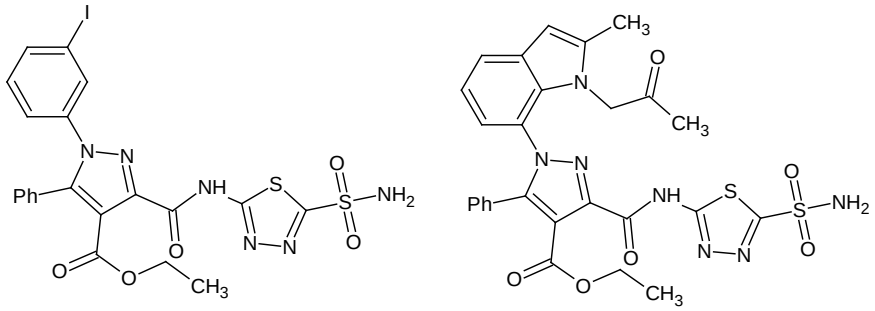


Fig. 24

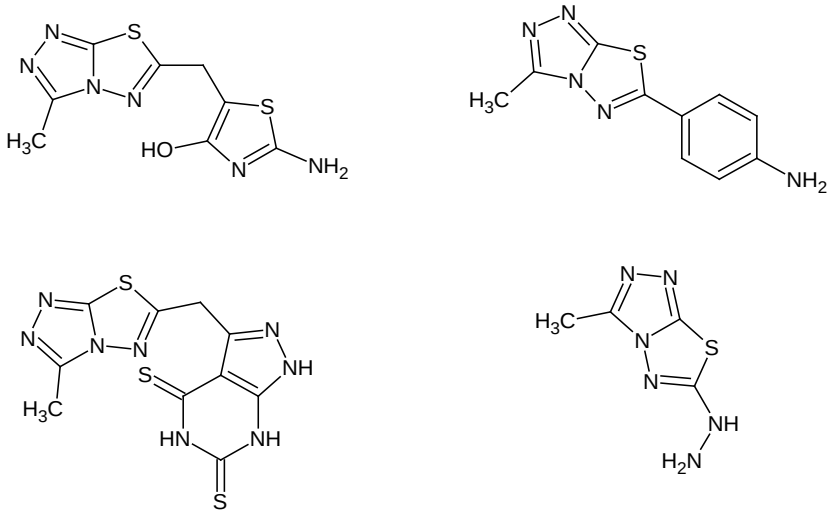


Fig. 25

Mohammad Yusuf et al (2008) synthesized a number of new imine derivatives of 5-amino-1, 3, 4-thiadiazole-2-thiol. Two compounds namely 5-{[1-(4-chlorophenyl)-3-(4-methoxy-phenyl)prop-2-en-1-ylidene]-amino}-5-benzylthio-1, 3, 4 –thiadiazole and 5-{[1-(4-chlorophenyl)-3-(4-dimethyl-aminophenyl)-prop-2-en-1-ylidene]amino}-5-benzylthio-1, 3, 4-thiadiazole have shown significant anti-depressant activity. [47] (fig. 26)

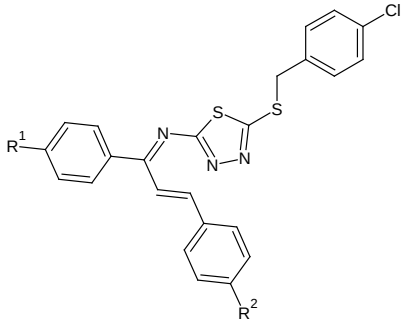


Fig. 26

R_1= H, OCH_3, $(CH_3)_2N$, Cl, OH, R_2= H, Cl

Nalan Terzioglu and Aysel Gursoy (2003) synthesized some novel 2, 6-dimethyl-N-substituted phenylmethylene-imidazo[2, 1-b][1, 3, 4]thiadiazole-5-carbohydrazides derivatives from 2, 6-dimethylimidazo-[2, 1-b][1, 3, 4]thiadiazole-5-carbohydrazide. The newly synthesized compounds were evaluated against human tumor cell line [48]. (fig. 27) (table. 7)

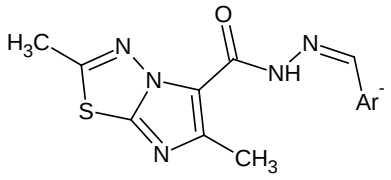


Fig. 27

Table 6

compound	Ar
A	C_6H_5
B	4-CH3C_6H_4
C	2-OHC_6H_4
D	4-$CH_3OC_6H_4$
E	4-BrC_6H_4
F	4-ClC_6H_4
H	4-$NO_2C_6H_4$

Stephen Turner et al (1988) synthesized a series of 2-aryl-5-guanidino-(or N-substituted guanidino)-1, 3, 4-thiadiazoleas and closely related analogues were found to lower blood pressure in meta corticoid (DOCA) hypertensive rats, in the 2-methylphenyl series, the iminoimidazolidine was of comparable activity to that of the unsubstituted guanidine. The iminoimidazolidine showed a somewhat longer duration of actionthan the guanidine derivatives. Preliminary studies in a pithed rat preparation indicated that these thiadiazole derivatives lowered blood pressure by a direct relaxant effect on vascular smooth muscle [49]. (fig. 28)

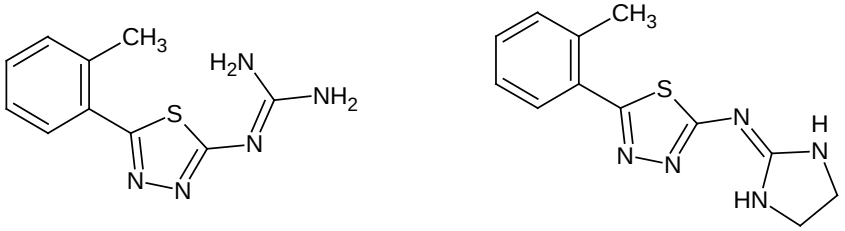


Fig. 28

CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Singh AK, Parthsarthy R, Kshitiz J, Mishra G. Synthesis, characterization and antibacterial activity of 1, 3, 4-thiadiazole derivatives. IJSID 2011;3:353-61.
2. Siddiqui N, Ahuja P, Ahsan W, Pandeya SN, Alam SM. Thiadiazoles: Progress report on biological activities. J Chem Pharm Res 2009;1:19-30.
3. Jalhan S, Jindal A, Gupta A, Hemraj. Synthesis, biological activities and chemistry of thiadiazole derivatives and schiff bases. Asian J Pharm Clin Res 2012;3:199-208.
4. Foroughifar N, Mobinikhaledi A, Ebrahimi S, Moghanian H, Bodaghi Fard MA, *et al*. Synthesis of a new class of azathia crown macrocycles containing two1, 3, 4-thiadiazole rings as subunits. Tetrahedron Lett 2009;50:836–9.
5. Bhat RA, Tazeem Amir A, Choi I, Athar F. 3-(1, 3, 4-Thiadiazole-2-yl) quinoline derivatives: Synthesis, characterization and anti-microbial activity. Eur J Med 2011;46:3158-66.
6. Chapleo BC, Myers M, Myers PL, Saville JF, Smith ACB, Stillings MR, *et al*. Substituted 1, 3, 4-Thiadiazoles with anticonvulsant activity Hydrazines. J Med Chem 1986;29:2273-80.
7. Jung KY, Kim SK, Gao ZG, Gross AS, Melman N, Jacobsonb KA, *et al*. Structure–activity relationships of thiazole and thiadiazole derivatives as potent and selective human adenosine A3 receptor antagonists. Bioorg Med Chem 2004;12:613–23.
8. Shen HL, Yu Li, H Shang HX, Tian S, Lai YS, Liu LJ. Synthesis and cytotoxic evaluation of new colchicine derivatives bearing 1, 3, 4-thiadiazole moieties. Chin Chem Lett 2013;24:299–302.
9. Juszczak M, Matysiak J, Szeliga M, Zarowski P, Niewiadomy N, Albrecht J, *et al*. 2-Amino-1, 3, 4-thiadiazole derivative (FABT) inhibits the extracellular signal-regulated kinase pathway and induces cell cycle arrest in human non-small lung carcinoma cells. Bioorg Med Chem Lett 2012;22:5466–9.
10. Kumar AK, Kumar VG, Renuka N. Thiadiazoles: molecules of diverse applications-a review. Int J Chem Tech Res 2013;5:239-48.
11. Mahendrasinh MR, Patel HV, Lata MR, Patel NK. Synthesis and biological evaluation of some new 1, 3, 4-thiadiazole derivatives for their antimicrobial activities. IJPCBS 2013;3:814-9.
12. Kamal M, Shakya AK, Jawid T. 1, 3, 4-Thiadiazole as Antimicrobial agent: a review. IJBR 2011;1:41-61.
13. Bak B, Nygaard L, Pedersen EJ, Anderson RJ. A mathematical contribution to structure-activity studies. Mol Spectra 1996;19:283.
14. Paul F, Jasont B, Mark H, jean MJF. Synthesis, antibacterial and antifungal activities of triazine derivatives. J Am Chem Soc 2003;125:13165.
15. Yang SJ, Lee SH, Kwak HJ, Gong YD. Regioselective Synthesis of 2° Amino-Substituted 1, 3, 4-Oxadiazoleand 1, 3, 4-Thiadiazole

Derivatives via Reagent-Based Cyclization of Thiosemicarbazide Intermediate. J Org Chem 2013;78:438−44.
16. Katritzky R, Logowski R. Synthesis and antifungal activity of some 2-aryl-3-hydroxymethylbenzo[b]thiophenes. Int J Chem Tech Res 1963;2:27.
17. Mahendrasinh MR, Patel HV, Lata M, Patel NK. Synthesis, Characterization and Antimicrobial Evaluation of some 5-(substituted)-2-amino-Thiadiazoles. Int J Res Chem Environ 2013;3:9-15.
18. Srivastava SK, Vermaand S, Srivastava SD. Synthesis, characterization and biological activity of 1, 3-thiazolidin-4-one derivatives of 2-mercapto-5-methyl-1, 3, 4-thiadiazole. J Chem Pharm Res 2010;5:270-6.
19. Turner S, Myers M, Gadie B, Hale SA, Horsley A, Nelson AJ, *et al*. Antihypertensive thiadiazoles-vasodilator activity of Some2-Aryl-5-guanidino-1, 3, 4-t hiadiazoles. J Med Chem 1988;31:906-13.
20. Chapleo BC, Myers PL, Smith CBA, Tulloch IF, Walter DS. Substituted 1, 3, 4-thiadiazoles with anticonvulsant activity. J Med Chem 1987;30:951-4.
21. Rushda P, Ahmad S, Mishra R, Alam S. Potential review on thiadiazoles. Int J Chem Tech Res 2006;6:2917-23.
22. Kucukguzel G, Satılmıs G, Nichols DB, Talele TT, Gurukumar KR, Basu NK, *et al*. 2-Heteroarylimino-5-arylidene-4-thiazolidinones as a new class of non-nucleoside inhibitors of HCV NS5B polymerase. Eur J Med Chem 2013;69:931-41.
23. Misra U, Hitkari A, Saxena AK, Gurtu S, Shanker K. Biologically active indolylmethyl-1, 3, 4-oxadiazoles, 1, 3, 4-thiadiazoles, 1, 3, 4-triazoles and 1, 2, 4-triazines. Eur J Med Chem 1996;31(7-8):629-34.
24. Rollas S, Kokyan S, Kaymakioglu KB, Turan SO, Akbuga J. Synthesis and evaluation of cytotoxic activities of some substituted isoxazolone derivatives. Eur J Med Chem 2011;15:94-9.
25. Gilani SJ, Khan SA, Siddiqui N. Synthesis and pharmacological evaluation of condensed heterocyclic 6-substituted 1, 2, 4-triazolo-[3, 4-b]-1, 3, 4-thiadiazole and 1, 3, 4 oxadiazole derivatives of isoniazid. Bioorg Med Chem Lett 2010;20:4762–5.
26. Yang SJ, Lee SH, Kwak HJ, Gong YD. Regioselective synthesis of 2amino-substituted 1, 3, 4-oxadiazole and 1, 3, 4-thiadiazole derivatives via reagent-based cyclization of thiosemicarbazide intermediate. J Org Chem 2013;78:438−44.
27. Maddila S Gorle, Sampath C, Lavanya P. Synthesis and anti-inflammatory activity of some new 1, 3, 4-thiadiazoles containing pyrazole and pyrrole nucleus. J Saudi Chem Soc 2012;3:16-25.
28. Amir M, Kumar H, Javed SA. Condensed bridgehead nitrogen heterocyclic system: Synthesis and pharmacological activities of 1, 2, 4-triazolo-[3, 4-b]-1, 3, 4-thiadiazole derivatives of ibuprofen and biphenyl-4-yloxy acetic acid. Eur J Med Chem 2008;43:2056-66.
29. Radwan MAA, Ragab EA, Sabrya NM, Shenawy El SM. Synthesis and biological evaluation of new 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents, Bioorg Med Chem 2007;15:3832–41.
30. Dawood KM, Gawad HA, Rageb EA, Ellitheyc M, Mohamed HA. Synthesis, anticonvulsant, and anti-inflammatory evaluation of some new benzotriazole and benzofuran-based heterocycles. Bioorg Med Chem 2006;14:3672–80.
31. Schenone S, Brullo C, Bruno O, Bondavalli F, Ranise A, Filippelli W, *et al*. New 1, 3, 4-thiadiazole derivatives endowed with analgesic and anti-inflammatory activities. Bioorg Med Chem 2012;14:1698–705.
32. Kuldipsinh P, Barot KS, Manjunath DG. Design, synthesis and antimicrobial activities of some novel 1, 3, 4-thiadiazole, 1, 2, 4-triazole-5-thione and 1, 3-thiazolan-4-one derivatives of benzimidazole. J Saudi Chem Soc 2013;6:1725-34.
33. Plech T, Wujec M, Kosikowska U, Barbara K. Studies on the synthesis and antibacterial activity of 3, 6-disubstituted 1, 2, 4-triazolo[3, 4-b]1, 3, 4-thiadiazoles. Eur J Med Chem 2012;47:580-4.
34. Kaur A, Kumar R, Kalidhar U. Synthesis, spectral studies and biological activity of some novel biphenyl imidazo[2, 1-b][1, 3, 4]thiadiazole derivatives. RJPBCS 2012;2:1085-6.
35. Mahendrasinh MR, Patel H, raj LM, Patel NK. Synthesis and biological evaluation of some new 1, 3, 4-thiadiazole derivatives for their antimicrobial activities. IJPCBS 2013;3:814-9.
36. Singh AK, Parthsarthy RK, shitiz J, Mishra M. Synthesis, Characterization and antibacterial activity of 1. 3. 4-thiadiazole derivatives. IJSID 2011;3:353-61.
37. Bhat AR, Tazeem Azam A, Choi I, Athar F. 3-(1, 3, 4-Thiadiazole-2-yl)quinoline derivatives: Synthesis, characterizationand anti-microbial activity. Eur J Med Chem 2011;46:3158-66.
38. Swamy SN, Basappa BS, Prabhuswamy B, Doreswamy BH, Prasad JS, Rangappa S. Synthesis of pharmaceutically important condensed heterocyclic 4, 6-disubstituted-1, 2, 4-triazolo-1, 3, 4-thiadiazole derivatives as antimicrobials. Eur J Med Chem 2006;41:531–8.
39. Talath S, Gadad AK. Synthesis, antibacterial and antitubercular activities of some 7-[4-(5-amino-[1, 3, 4]thiadiazole-2-sulfonyl)-piperazin-1-yl] fluoroquinolonic derivatives. Eur J Med Chem 2006;41:918–24.
40. Zhao HC, Shi YP, Liu YM, Li CW, Xua LN, Wang P, *et al*. Synthesis and antitumor-evaluation of 1, 3-selenazole-containing 1, 3, 4-thiadiazole derivatives. Bioorg Med Chem Lett 2013;23:6577–9.
41. Mohammadhosseini N, Parastoo SA, Aryapour H, Afshar F, Edraki N, Siavoshi F, *et al*. Synthesis and biological evaluation of novelbenzyl piperazine derivatives of 5-(5-nitroaryl)-1, 3, 4-thiadiazoles as Anti-Helicobacter pylori agents. J Pharm Sci 2013;21:66-73.
42. Omaima M, Abdelhafez KM, Ali AH, Mohamed M, Batran ARZ. Synthesis of new 7□Oxycoumarin derivatives as potent and selective monoamine oxidase inhibitors. J Med Chem 2012;55:10424−36.
43. Cara L, Carrion MD, Entrena A, Gallo AM, Espinosa A, Lopez A, *et al*. 1, 3, 4-Thiadiazole derivatives as selective inhibitors of iNOS versus nNOS: Synthesis and structure-activity dependence. Eur J Med Chem 2012;50:129-39.
44. Song XJ, Dong XSY. Microwave-assisted synthesis of some novel fluorinated pyrazolo[3, 4-d]pyrimidine derivatives containing 1, 3, 4-thiadiazole as potential antitumor agents. Chin Chem Lett 2012;22:1036–8.
45. Gullar RK, Metin B, Arslan BS, Gokce AK. Synthesis, characterization and antiglaucoma activity of some novel pyrazole derivatives of 5-amino-1, 3, 4-thiadiazole-2-sulfonamide. Eur J Med Chem 2010;45:4769-73.
46. Ibrahim DA. Synthesis and biological evaluation of 3, 6-disubstituted [1, 2, 4]triazolo[3, 4-b][1, 3, 4]thiadiazole derivatives as a novel class of potential anti-tumor agents. Eur J Med Chem 2009;44:2776–81.
47. Yusuf M, Khan RA, Ahmed B. Synthesis and anti-depressant activity of 5-amino-1, 3 4-thiadiazole-2-thiol imines and thiobenzyl derivatives. Bioorg Med Chem 2008;16:8029–34.
48. Terzioglu N, Gursoy A. Synthesis and anticancer evaluation of some new hydrazine derivatives of 2, 6-dimethylimidazo [2, 1-b]-[1, 3, 4] thiadiazole-5-carbohydrazide. Eur J Med Chem 2003;38:781-6.
49. Stephen T, Myers M, Gadie B, Stafford AH, Horsley A, Nelson AJ, *et al*. Antihypertensive Thiadiazoles. 2. ' Vasodilator Activity of Some 2-Aryl-5-guanidino-1, 3, 4-t hiadiazoles J Med Chem 1988;31:906-13.