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Review article on 1, 3, 4-Thiadiazole derivaties and it's Pharmacological activities.

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Abstract: Heterocyclic compounds occupy a central position among those molecule that makes life possible. The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Heterocyclic nucleus 1,3,4-thiadiazole constitutes constitutes an important class of compounds for new drug development. The synthesis of novel thiadiazole derivatives and investigation of their chemical and biological behavior have gained more importance in recent decades. During the recent years there has been intense investigation of different classes of thiadiazole compounds, many of which possess extensive pharmacological activeties. Among of these compounds having 1,3,4,_thiadiazole nucleus are known to exhibit unique anti-inflammatory, analgesic, antimicrobial, antitumor, antifungal, antimycobacterial , anticonvulsant, antI-diabetic, antiviral, activities. So far, modification of the thiadiazole ring have proven highly effective with improved potency and lesser toxicity. The present review highlights the recently synthesized thiadiazole possessing important biological activities.
Keywords : Thiadiazole, Biological activities.

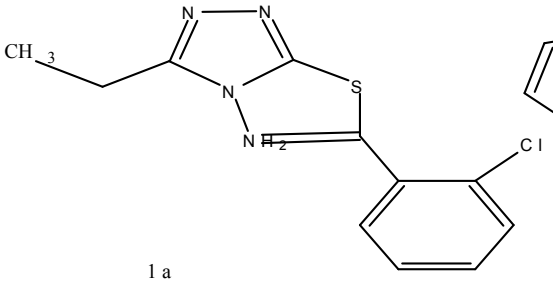
INTRODUCTION:

Heterocyclic compounds are cyclic compound with the ring containing carbon and other element, the component being oxygen, nitrogen and sulphur. The simplest of the five membered heterocyclic compound are pyrrole, furan and thiophene, each of which contains a single heteroatoms. The five membered ring containing more than one or two heteroatoms also such as azole, pyrrole, thiazole, thiadiazole, oxadiazole, triazene etc.

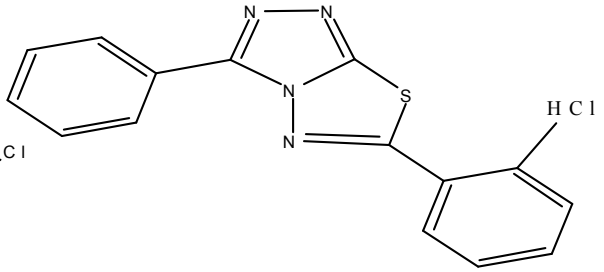
Thiadiazole is a heterocyclic compound featuring both two nitrogen atom and one sulfur atom as part of the aromatic five-membered ring. Thiadiazole and related compounds are called 1, 3, 4-thiadiazole (two nitrogen and one other heteroatom in a five-membered ring). They occur in nature in four isomeric forms as. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole. 1, 3, 4-thiadiazole are important because of their versatile biological actions. In particular, compounds bearing the 1, 3, 4-thiadiazole nucleus is known to have unique antibacterial and anti-inflammatory activities. Differently substituted thiadiazole moieties have also been found to have other interesting activities such as analgesic , antimicrobial, antitubercular , anticonvulsant and anti-hepatitis B viral activities . In this review article different compounds having heterocyclic nucleus have been shown to possess different activity. It was found that among the important pharmacophores responsible for various activities. A summarise review of thiadiazoles associated with large number of biological activities is presented below.

ANTIMICROBIAL ACTIVITY:

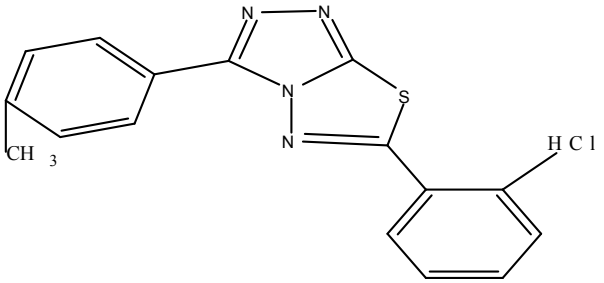
Swamy et al [1] synthesise a series of 4,6-disubstituted 1,2,4-triazolo-1,3,4-thiadiazole derivatives **1(a–f)** tested for *in vitro* antimicrobial activity against Bacillus subtilis, Escherichia coli, Pseudomonas fluorescens, Xanthomonas campestris pvs, Xanthomonas oryzae, Aspergillus niger, Aspergillus flavus, Fusarium oxysporum, Trichoderma sp. and Fusarium monaliforme, etc. and found them to be active with these compounds having maximum activity. The presence of chloro substituent enhances the activity of the compound.



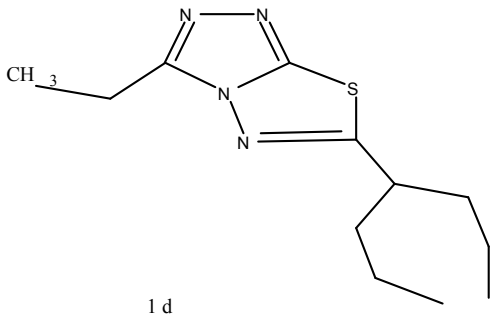
1 a



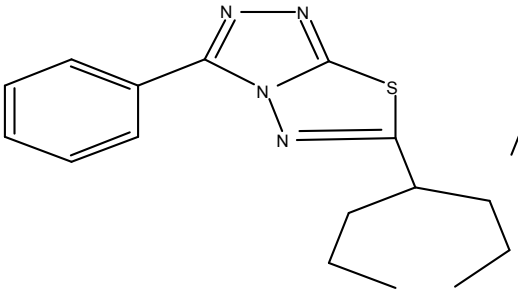
1 b



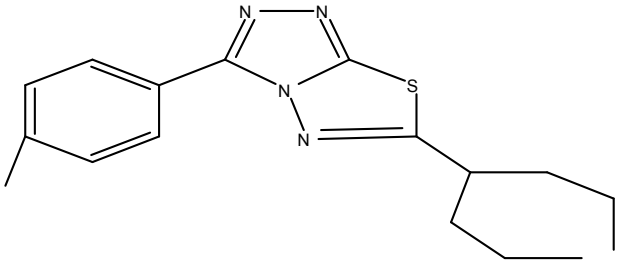
1 c



1 d

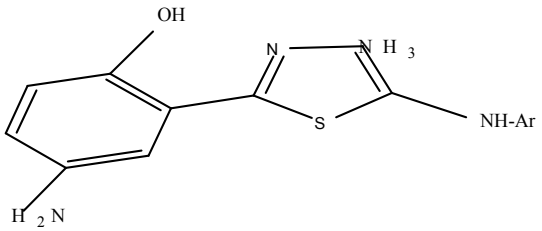


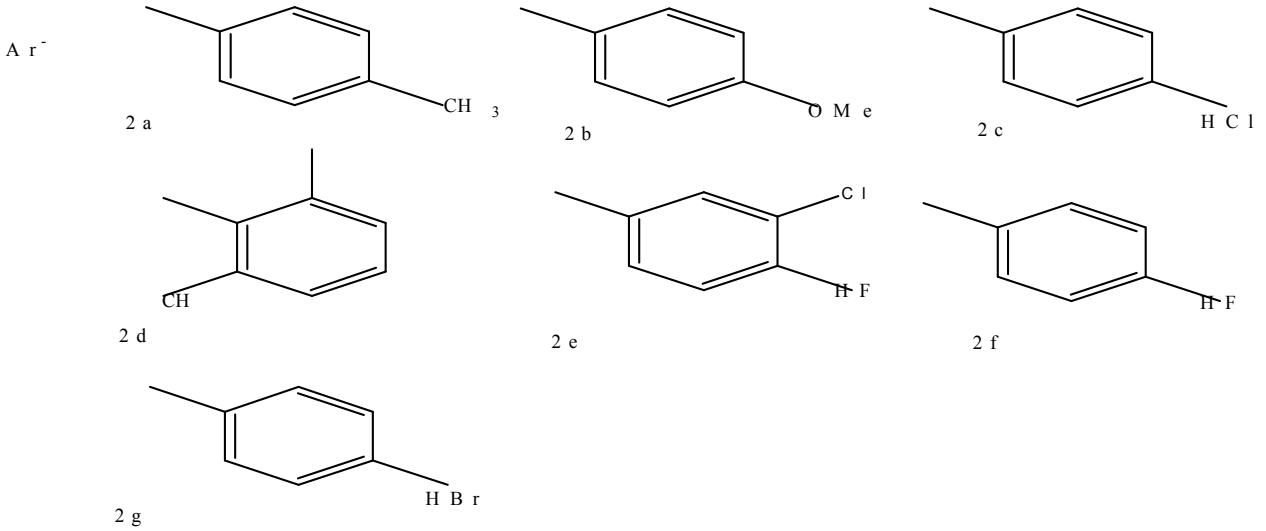
1 e



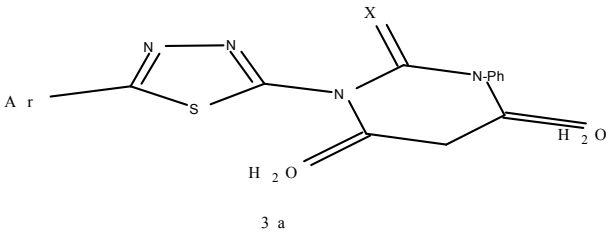
1 f

Some new 4-amino-2-{5-[(4-substituted phenyl)amino]-1,3,4-thiadiazole-2-yl} phenol **2(a-g)** were synthesized by Hussain et al [2] and evaluated for their antibacterial and antifungal activity. The compounds showed significant antibacterial and antifungal activity due to the presence of chloro and fluorophenylgroup against *S. aureus* (gram-positive) and *E.coli* (gram-negative) bacteria and antifungal activity against *A. niger* fungi.





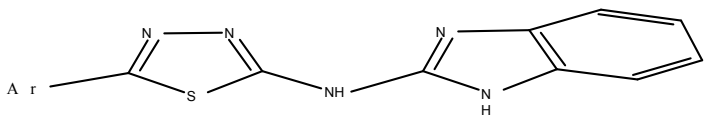
Various condensed N-[5-(3-Chlorobenzo[b]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-1H-benzo[d]imidazol-2-ylamine **3(a-c)** were synthesized by Aly et al [3] and evaluated for their antimicrobial activity against different gram positive and gram negative bacteria.



3 a

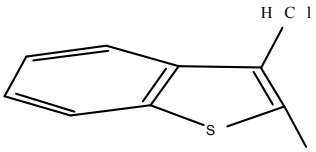
(X = O)

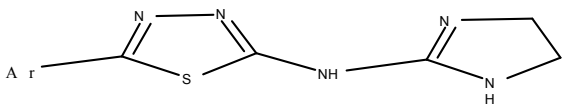
(X = S)



3 b

A r =

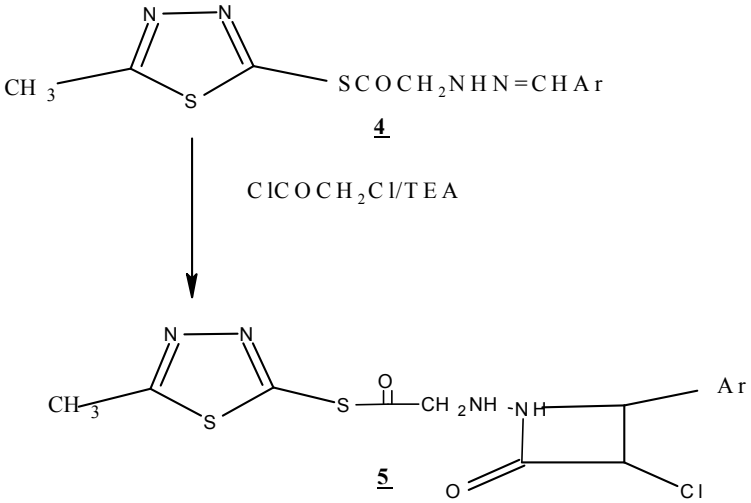




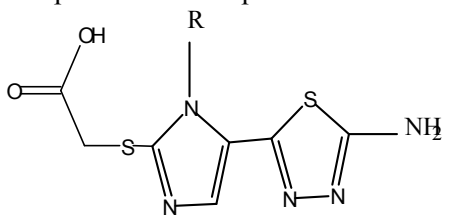
3 c

Various substituted mercapto-1,3,4-thiadiazole derivatives, 2-(2'-benzylidene-hydrazino-acetyl-mercapto)-5-methylmethyl-1,3,4-thiadiazoles, **4(a-n)** and 2-[2'-{4-substituted-aryl-3-chloro-2-oxo-azetidine} acetylamino mercapto]-5- 1,3,4-thiadiazoles **5(a-n)** were reported by DUA et al [4]. Activity of the compounds were enhanced

due to the substitution of chlorophenyl, bromophenyl, nitrophenyl, methoxyphenyl groups in compounds and screened for their antibacterial activity *substilis, E. coli, S. aureus* and *K. pneumoniae* bacteria and *antifungal activity against A. niger, A. flavus, F. oxisporium* and *T. viride* fungi.



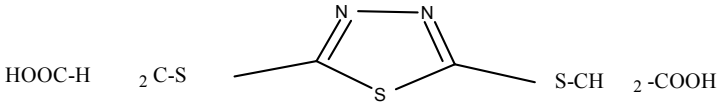
Synthesis of some new □□-[5-(5-amino-1,3,4-thiadiazol-2-yl)-imidazol-2-ylthio]acetic acids (**6a,b**) were reported by Hadizadeh et al [5]. The compounds were tested against *Mycobacterium tuberculosis* strain H37Rv in comparison to rifampicin.



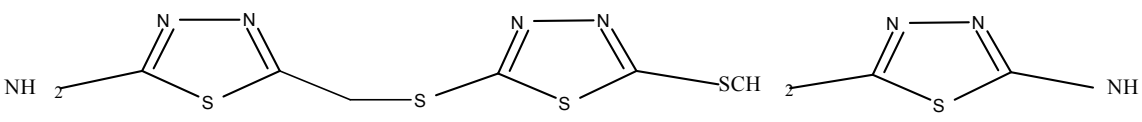
5a– R=CH_3

5b– R=$CH_2C_6H_5$

Salimon et al [6] introduced some new 2,5-(dithioacetic acid)-1,3,4-thidiazole **7(a)** and 2,5-di-[5-amino-1,3,4-thiadiazole-2-thiomethyl]-1,3,4-thiadiazole **7(b)** which were screened for their in vitro antibacterial activities against the Gram-positive (S. aureus, S. cerevisiae and C. diphtheriae) and the Gram-negative, (*E.coli* and *P. aeruginosa*) bacteria.

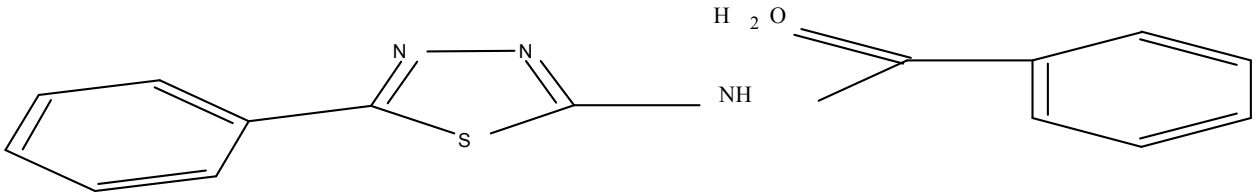


7 a



7 b

Quandil et al [7] prepared several 2-benzoylamino-5-(dihydroxyphenyl)-1,3,4-thiadiazoles derivative **8(a-e)** . All the synthesized compound were evaluated for their antimicrobial activity. These compounds have shown the selective activity against gram-positive *S.aureus.*



(a - e)

a ; - 2 , 3 - d ih y d r o x y

b ; - 2 , 4 - d ih y d r o x y

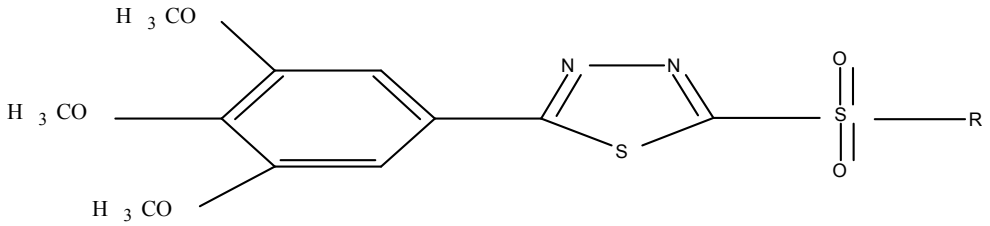
c ; - 2 , 6 - d ih y d r o x y

d ; - 3 , 4 - d ih y d r o x y

e ; - 3 , 5 - d ih y d r o x y

ANTIFUNGAL ACTIVITY:

Jun-Chen et al [8] introduced a series of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole **9(a-i)** derivatives. In this series of compound **9-h** possess higher antifungal activities against three kind of fungi Gibberella zeae, Botrytis cinerea, and Sclerotinia sclerotiorum, in vitro.



R =

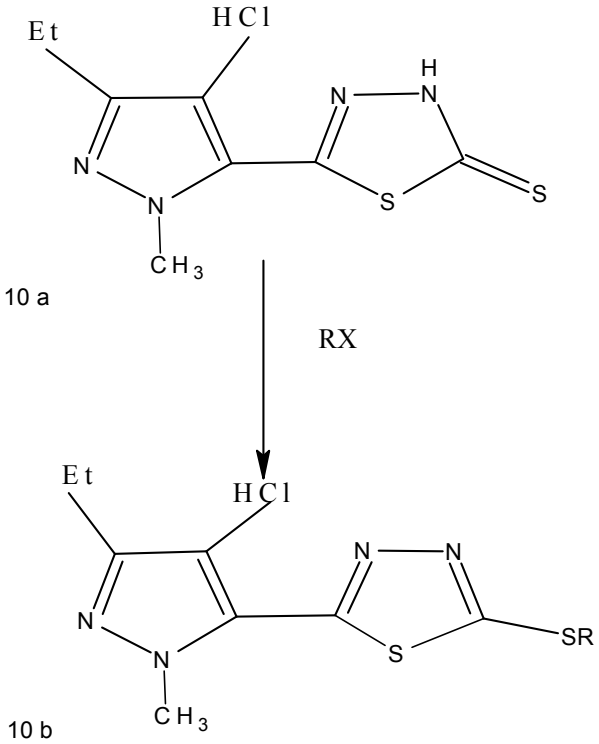
9 (a) = H 2 C = C H - C H 2

9 (b) = O 2 N - C 6 H 6 - C H 2 -

9 (c) = C 6 H 6 - C H 2

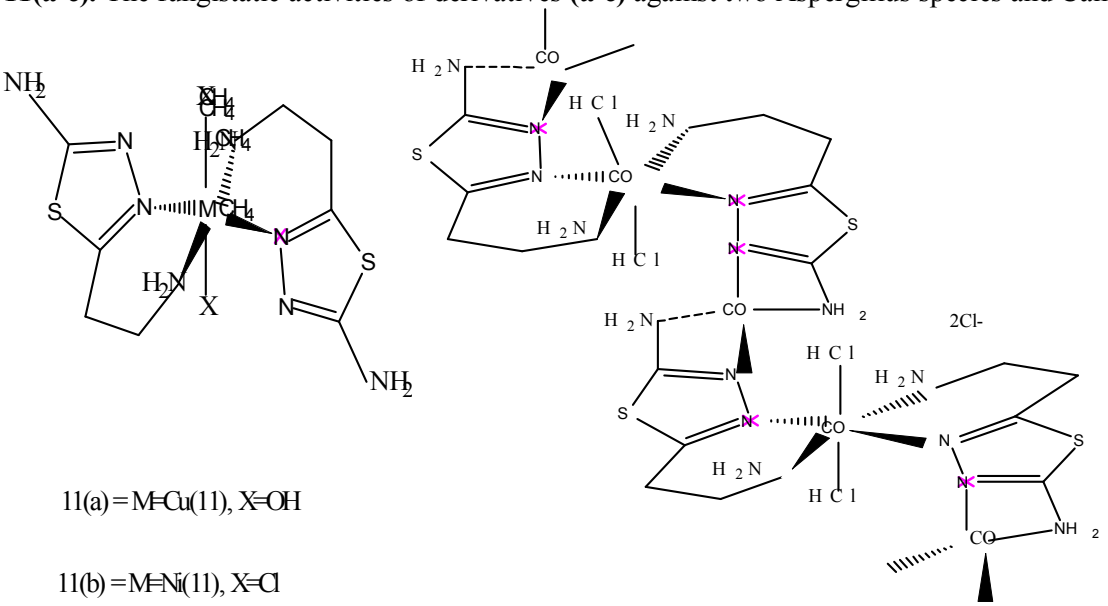
9 (d) = H 3 C -

Song CHEN et al [9] prepared a series of Pyrazolyl-Substituted 1,3,4-Thiadiazole derivative **10(a-e)** . The most active compound was 5-pyrazolyl-1,3,4-thiadiazole-2-thione **(a)** and 2-alkylthio-5-pyrazolyl-1,3,4-thiadiazole **(b)** and possess fungicidal activity against *Rhizoctonia solani* (Sheath blight on rice).



R = Me, Pr, Allyl, Amyl

Barboiu et al [10] have been introduced a series of metal complexes 5-(2-aminoethyl)-2-amino-1,3,4-Thiadiazole **11(a-c).** The fungistatic activities of derivatives **(a-c)** against two Aspergillus species and Candida albicans.

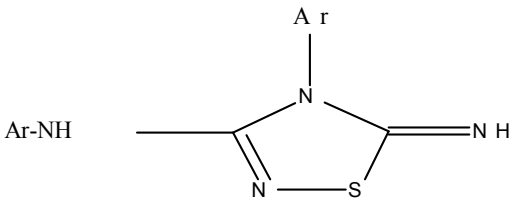


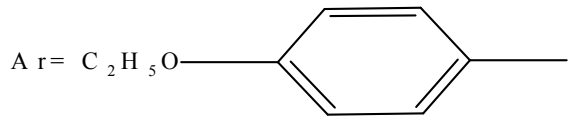
11(a) = M=Cu(11), X=OH

11(b) = M=Ni(11), X=Cl

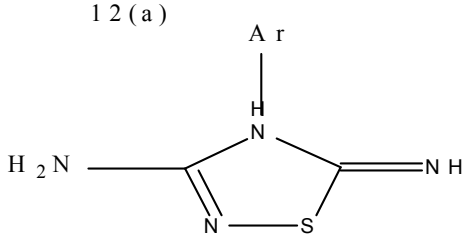
ANTICONVULSANT ACTIVITY:

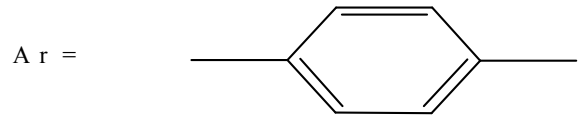
Gupta et al [11] have been synthesized a series of 3-aryl amino/amino-4-aryl-5-imino-D2-1,2,4-thiadiazoline . The anticonvulsant activity of all the synthesized compounds **12(a-b)** was evaluated against maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (ScPTZ) induced seizure models in mice.





12(a)

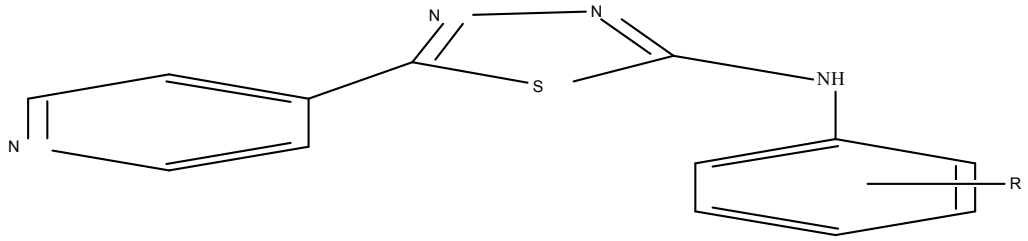




12(b)

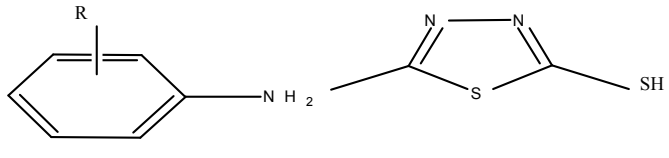
Shahar Yar et al [12] have been synthesized 2-Phenylamino-5-(4-pyridyl)-1,3,4-thiadiazole derivatives . All the newly synthesized compounds were evaluated for their anticonvulsant activity by MES method. Among of these Compounds **13(a-f)** showed maximal activity whereas compounds **13a** showed good activity.

2

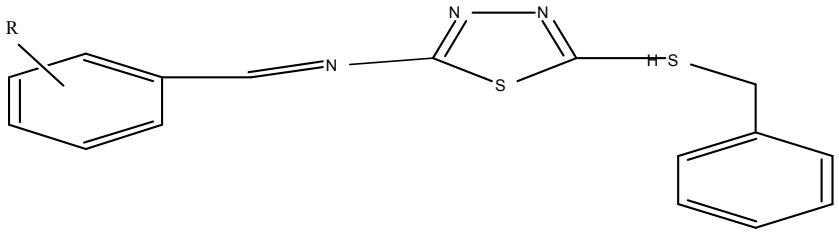


13(a) = O-CH3
13(b) = P-CH3
13(c) = O-OC2H5
13(d) = P-OC2H5
13(e) = Cl

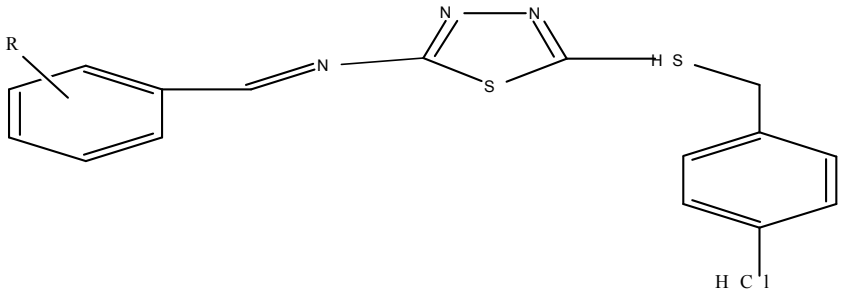
A series of aromatic aldehyde imine derivative of 2-thiobezyl-1,3,4-Thiadiazole were synthesized by Ahmed et al [13]. These derivatives **14(a-e),14(ia-ie), 14(iia-iie)** show good anticonvulsant activity. Among of these compounds chlorobenzyl substituted compound show the potent anticonvulsant activity against MES method.



14(a - b)

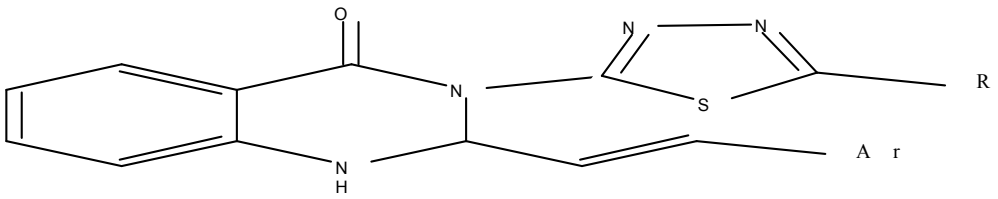


14(ia - ib)



14(iia - iib)

Jatav et al [14] produced a series of new 3-[5-substituted phenyl-1,3,4-thiadiazol-2-yl]-2-styryl quinazoline-4(3*H*)-ones and evaluated for anticonvulsant activity .Compounds were examined in the maximal electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (scPTZ)-induced seizure models. Compound 15 (**a-c**) showed good anticonvulsant activity in the test models.



R

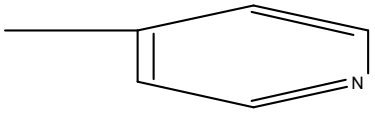
15(a) = C_6H_5

15(b) = m-ClC_6H_4

15(c) = b-ClC_6H_4

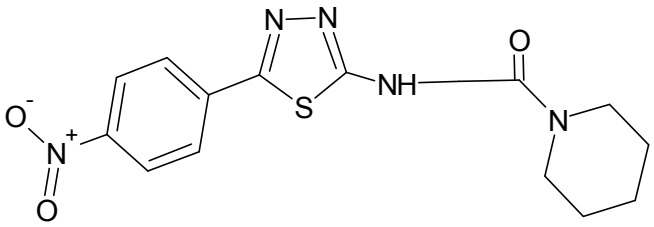
Ar

b-ClC_6H_4



ANTIDIABETIC ACTIVITY:

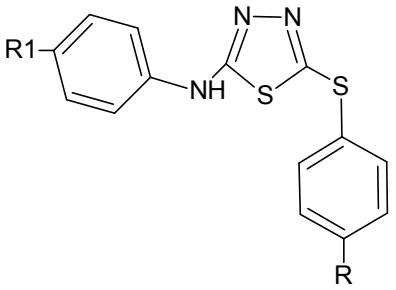
Pattan et al [15] have been itrroduced the synthesis of various compounds **16(a-d)** and evaluated for antidiabetic activity. Among of these compounds **16-d** has shown significant antidiabetic activity and compound **16 a-c** have shown moderate antidiabetic activity.



16d

ANTIINFLAMMATORY ACTIVITY:

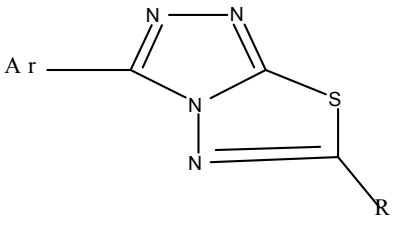
A new series of selective cox-2 inhibitors with 2-amino-5-sulfanyl-1,3,4-thiadiazole Derivatives **17(a-d)** were synthesized by Sharma et al [16] . These compound were selective inhibitiors of COX-2 and potentiated the activity of COX-1 enzyme. The presence of sulphonamide group is a required pharmacophore for selective inhibition of COX-2 enzyme.



17

	R	R1
a =	-F	$-SO_2NH_2$
b =	$-CH_3$	$-SO_2NH_2$
c=	$-CF_3$	$-SO_2NH_2$
d=	$-SO_2NH_2$	$-SO_2NH_2$

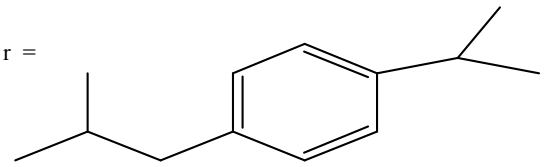
Amir et al [17] introduced the synthesis of compounds **18 (a-b**) and were evaluated for its anti-inflammatory activity . Due to the presence of 2,4-dichlorophenyl, 4-chloroprene, n-butyl amino and 4-aminophenyl groups of triazolo-thiadiazole ring have high anti-inflammatory activity.

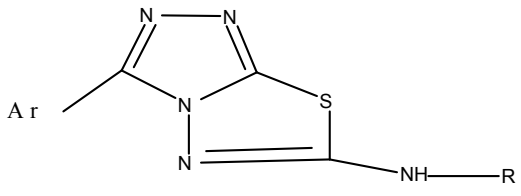


18 a

R = $2,4\text{-}Cl_2C_6H_3$

Ar =

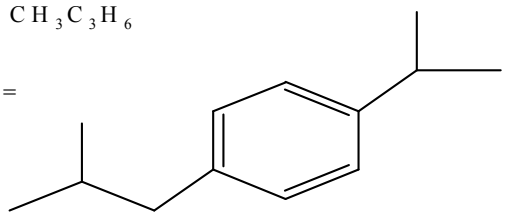




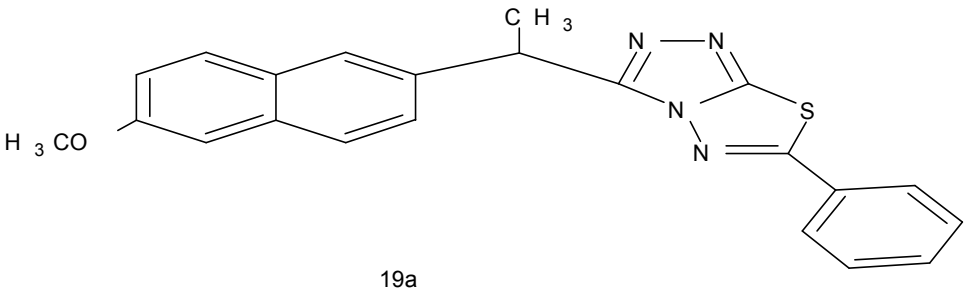
18 b

R = $CH_3C_3H_6$

Ar =

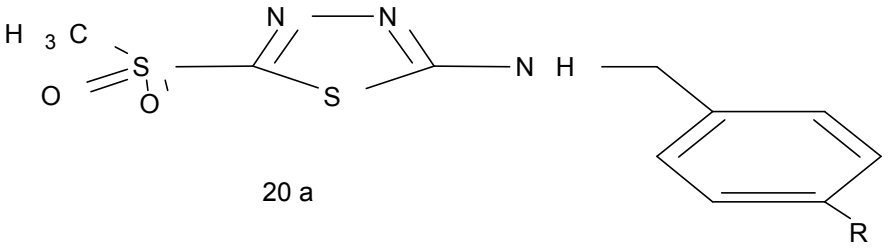


A series of aromatic acids and aryl/ alkyl isothiocyanates substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives **19(a-f)** have been synthesized by Amir et al [18] and evaluated for anti-inflammatory activity . Among of these compounds **19a** have showed higher antiinflammatory activity.

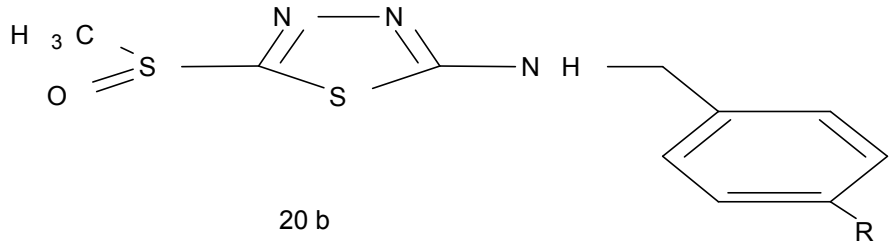


19a

Varandas et al.[19] were synthesized the compound **20(a)** by the compelte S-oxidation of correspounding methylsulfide derivatives performed by hydrogen per oxide and titanium trichloride and on the other hand oxidation of sulfide derivatives with m-choloro benzoic acid furnished the sulphoxide derivatives **20(b)** and evaluates the activity of anti-inflammatory, analgesic, and antiplatelet properties.

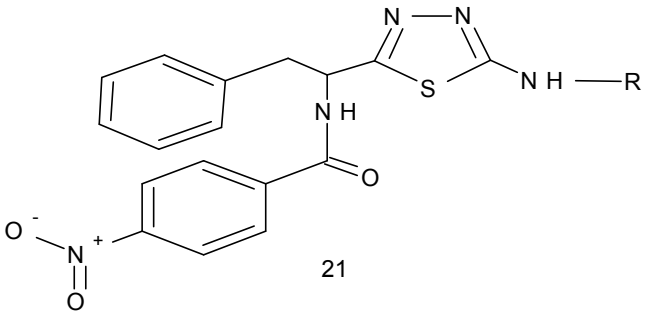


20 a



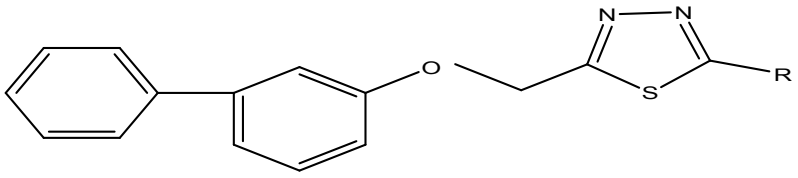
20 b

Moise et al [20] were showed the 1,3,4-thiadiazole, that containing a phenylalnine moiety were synthesized by intramolecular cyclization of 1,4-thiosmicrbazides **21** ,in acid and alkaline media and the synthesized compounds was evaluated by anti-inflammatory activity.



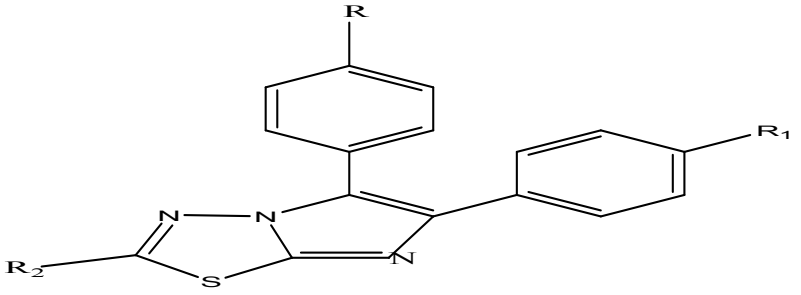
21

Harish et al [21] were synthesized the drug that contained the 1,3,4-thiadiazole and these are derivatives of biphenyl-4-yloxy acetic acid **22** that are evaluated by anti-infalmmatory activity , analgesic activity.



22

Aandanappa et al [22] were showed the series of 2-trifluoromethyl/sulphonamido-5,6-diarylsubtituted imidazo[2,1-b-]-1,3,4-thiadiazole derivatives **23** have been synthesized by the reaction of 2-amino-5-trifluoromethyl/sulphonamido-1,3,4-thiadiazoles and substituted by a-bromo-1,2-(p-subsitued)diaryl-1-ethanones and the compound were evaluated by the vitro cyclooxgenage inhibitory activity against COX-2 & COX-1 enzyme.

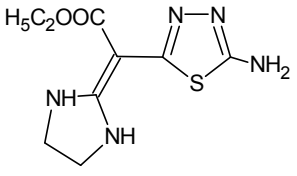


23

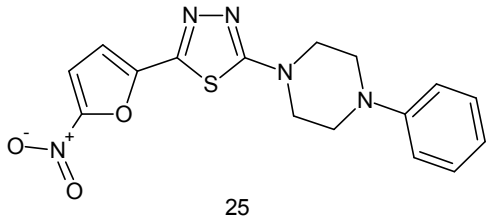
ANTILEISMANIAL ACTIVITY:

A series of 2-(5-nitro-2-furyl) and 2-(5-nitro-2thienyl)-5-substituted-1,3,4-thiadiazole **(24)** derivatives were synthesized by Shafiee et al [23]. The most active compound 8a was found to be active with an IC50 0.1 µM against *Leishmania major* promastigotes.

Ram *et al* [24] synthesized 2,4 disubstituted 1,3,4 thiadiazole **(25)** derivatives and evaluated for *invitro* antileishmanial activity. Among these, compound 7a showed 73% *in-vitro* inhibition of promastigote of *Leishmania donovani*.

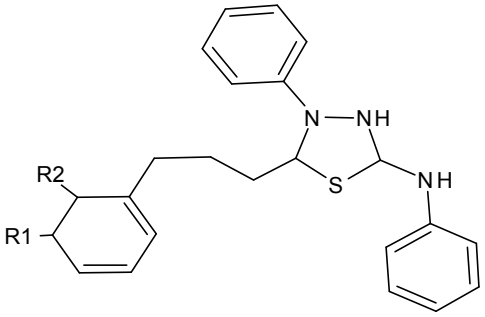


24



25

Echeavarria *et al* [25] introduced a series of 1,3,4-thiadiazolium-2-phenylamine **(26)** derivatives. These compounds were evaluated against *Leishmania amazonensis*. Compound 9a and 9b were more active than pentamidine against promastigote forms with IC50 value 0.17 and 0.04 µM respectively. Compound 9c and 9d were more effective against amastigotes with IC50 value 5.37 5.48 µM.



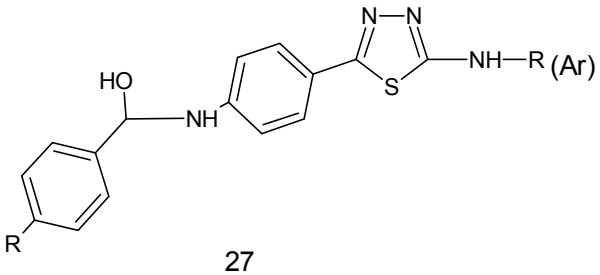
R_1 - H,OCH_3, H, Br

R_2 - OCH_3, H, F,H

26

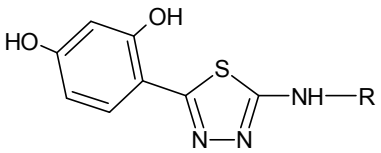
CYTOTOXIC ACTIVITY:

Sevgi et al [26] were synthesized 5-[-4-(4fluorobezoylolamino)phenyl]-2-subsitutedamino-1,3,4-thiadiazole **27** and evaluate the cytotoxic activity.



27

Matysiak et al [27] , introduced a series of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles **28** were synthesized and evaluated for their antiproliferative activities against human cancer cell lines. The cytotoxicity in vitro against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung), and T47D (breast) was determined. The highest antiproliferative activity was found for 2-(2,4-dichlorophenylamino) 5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole, with ID_{50} two times lower (SW707, T47D) than for cisplatin studied comparatively as the control compound.



R = alkyl,aryl, morpholinoalkyl

28

REFERENCES:

1. S. Nanjunda Swamy , Basappa , B.S. Priya , B. Prabhuswamy , B.H. Doreswamy, J. Shashidhara Prasad, Kanchugarakoppal S. Rangappa , Synthesis of pharmaceutically important condensed heterocyclic 4,6-disubstituted-1,2,4-triazolo-1,3,4-thiadiazole derivatives as antimicrobials; European journal of medicinal chemistry, 41, 2006, 531-538.
2. Sabir Hussain, Jyoti Sharma and Mohd. Amir, Synthesis and Antimicrobial Activities of 1,2,4-Triazole and 1,3,4-Thiadiazole Derivatives of 5-Amino-2-Hydroxybenzoic

Acid; E-Journal of Chemistry Vol. 5, No.4, 2008, 963-968.

3. A. A. ALY and R. EL-SAYED; Synthesis and Biological Activity of New 1,3,4-Thiadiazole Derivatives, Chem. Pap. 60 (1)56—60 (2006).
4. Rajiv Dua, and S.K. Srivastava, Synthesis , Characterization And Antimicrobial Activity Of 2-(2'-Substituted - Benzylidine - Hydrazino -Acetyl) – Mercapto -5-Methyl - 1, 3, 4-Thiadiazole And 2 -[2'- {4 - Substituted -Aryl - 3 - Chloro - 2 - Oxo –Azetidine } –Ac etyl-Aminomercapto]- 5-Methyl - 1, 3, 4 – Thiadiazole; International Journal of Pharma and Bio Sciences; V1(2)2010.
5. Farzin Hadizadeh , Rahil Vosooghi; Synthesis of □□-[5-(5-Amino-1,3,4-thiadiazol-2-yl)-2-imidazolylthio]acetic acids; Journal of Heterocyclic Chemistry, 45, (2008). Vol 45 1-3.
6. Jumat Salimon, Nadia Salih, Ayad Hameed, Hiba Ibraheem, Emad Yousif; Synthesis and Antibacterial Activity of Some New 1,3,4-Oxadiazole and 1,3,4-Thiadiazole Derivatives; Journal of Applied Sciences Research, 6(7), 866-870, 2010.
7. Amjad. M. Qandil , Haitham. N. Tumah and Mohammad. A. Hassan . Synthesis and Antibacterial Activity of N^4-Benzoyl-N^1-dihydroxy-benzoylthiosemicarbazides and Their Cyclic 1,3,4-thiadiazole Derivatives ; Acta Pharmaceutica Sciencia 48: 95-107 (2006).
8. Cai-Jun Chen, Bao-An Song, Song Yang, Guang-Fang Xu, Pinaki S. Bhadury, Lin-Hong Jin, De-Yu Hu, Qian-Zhu Li, Fang Liu, Wei Xue, Ping Lu and Zhuo Chen; Synthesis and antifungal activities of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole and 5- (3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives ; Bioorganic & Medicinal Chemistry 15 (2007) 3981–3989 .
9. Han Song CHEN, Zheng Ming LI , Yu Feng HAN, Zhong Wen WANG; New Fungicidally Active Pyrazolyl-Substituted 1,3,4-Thiadiazole Compounds and Their Preparation ; Chinese Chemical Letters Vol. 10, No. 5, pp. 365–366, 1999.
10. Mihai Barboiu, Marilena Cimpoesu, Cornelia Guran, and Claudiu T. Supumn; 1,3,4-Thiadiazole Derivatives Synthesis And Biological Activity Of Metal Complexes Of 5-(2-Aminoethyl)-2-Amino-1,3,4-Thiadiazole, 1996 vol-3 ,no-5 , 227-232.
11. A Gupta; P Mishra; SK Kashaw; V Kashaw; JP Stables; Synthesis of 3-aryl amino/amino-4-aryl-5-imino-D2-1,2,4-thiadiazoline and evaluated for anticonvulsant activity; European Journal of Medicinal Chemistry, 2008, 43, 749-754.
12. Mohammad Shahar Yar, and Mohammad Wasim Akhter, Synthesis And Anticonvulsant Activity Of Substituted Oxadiazole And Thiadiazole derivatives, Acta Poloniae Pharmaceutica and Drug Research, Vol. 66 No. 4 pp. 393 and 397, 2009.
13. Bahar Ahamad and Mohd. Yusuf , synthesis of aromatic aldehyde imine derivative of 2-thiobenzyl-1,3,4-thiadiazole and evaluation of their anticonvulsant activity; Indian Journal Of Chemistry; vol.49B, 2010 , 241-246.
14. Varsha Jatav , Pradeep Mishra , Sushil Kashaw , J.P. Stables , CNS depressant and anticonvulsant activities of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones ; European Journal of Medicinal Chemistry 43 (2008) 1945e1954.
15. Shashikant R Pattan , Prajact kekare, Nachiket S Dighe, Sunil A Nirmal, Deepak S Musmade, Smita K Parjane and Aarti V Daithankar , Synthesis and biological evaluation of some 1, 3, 4-thiadiazoles Journal of Chemical and Pharmaceutical Research, 2009, 1(1):191-198.
16. Rajesh Sharma, Jitendra Sainy Subhash Chandra Chatuvedi, 2-Amino-5-sulfanyl-1,3,4-thiadiazoles: A new series of selective cyclooxygenase-2 inhibitors ; Acta Pharm. 58 (2008) 317–326 Short communication 10.2478/v10007-008-0011-6.
17. Mohd. Amir, Harish Kumar, S.A. Javed; 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; European Journal of Medicinal Chemistry 43 (2008) 2056e2066.
18. Mohammad Amir, Harish Kumar and Sadique A. Javed; Synthesis and pharmacological evaluation of condensed heterocyclic 6-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives of naproxen; Bioorganic & Medicinal Chemistry Letters 17 (2007) 4504–4508.

19. L.S. Varandas, C.A.M. Fraga, A.L.P. Miranda1 and E.J. Barreiro, Design, Synthesis and Pharmacological Evaluation of New Nonsteroidal Antiinflammatory 1,3,4-Thiadiazole Derivatives; Letters in Drug Design & Discovery, 2005, 2, 62-67**.**
20. Mihaela Moise , Valeriu Sunel , Lenuta Profire , Marcel Popa , Jacques Desbrieres and Cristian Peptu ; Synthesis and Biological Activity of Some New 1,3,4-Thiadiazole and 1,2,4-Triazole Compounds Containing a Phenylalanine Moiety; Molecules 2009, 14, 2621-2631.
21. Harish Kumar, Sadique A. Javed, Suroor A. Khan, Mohammad Amir; 1,3,4-Oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid: Synthesis and preliminary evaluation of biological properties; European Journal of Medicinal Chemistry 43 (2008) 2688e2698.
22. Andanappa K. Gadad,a,b, Mahesh B. Palkar,b K. Anand,b Malleshappa N. Noolvi,b Thippeswamy S. Boreddyc and J. Wagwadec; Synthesis and biological evaluation of 2-trifluoromethyl/ sulfonamido-5,6-diaryl substituted imidazo[2,1-b]-1,3,4-thiadiazoles: A novel class of cyclooxygenase-2 inhibitors; Bioorganic & Medicinal Chemistry 16 (2008) 276–283.
23. VJ Ram, A Goel, M Kandpal. Biorganic Medicinal Chemistry, Lett., 1997, 7, 651.

    A Foroumadi; S Pournourmohammadi; F Soltani; S dabri; A Kharazmi; A Shafiee; M Asgharian-Rezaee. Biorganic Medicinal Chemistry , Lett., 2005, 15, 1983.
24. EF da Silva, MM Canto-Cavalheiro, VR Braz, L Cysne-Finkelstein, LL Leon, A Echevarria. European Journal Medicinal Chemistry, 2002, 37, 979.
25. Sevgi Karakuş1, Ufuk Çoruh2, Bilgehan Barlas-Durgun; 1, Ezequiel M. Vázquez-López3, Suna Özbaş-Turan1, Jülide Akbuğa1, Sevim Rollas1 Synthesis and cytotoxic activity of some 1,2,4-triazoline-3-thione and 2,5-disubstituted-1,3,4-thiadiazole derivatives , Marmara Pharmaceutical Journal 14: 84-90, 2010.
26. Joanna Matysiak, and opolski, synthesis and proliferative activity of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole, 2006.