Available online at www.jcpronline.in

Journal of Current Pharma Research 5 (3), 2015, 1578-1585.

Journal of Current Pharma Research

http://www.jcpronline.in

Original Article

Biological Potential of Thiadiazole Linked Heterocycles: An Overview.

Mayura Kale*, Kirtee Baheti

[1]Government College of Pharmacy, Osmanpura, Aurangabad-431005, Maharashtra, India.

Received 02 March 2015; received in revised form 15 May 2015; accepted 16 May 2015

Available online 28 June 2015

Abstract

There are a diverse group of pharmacologically active heterocyclic compounds most of which are in clinically used on regular basis. Heterocycles are also a part of important elements of our body such as nucleic acids and are present in nature too. One of these is thiadiazole heterocycle which along with its combinations with other heterocycles continue to draw attention of organic chemists and researchers due to their varied therapeutical potential to act as antihelmintic, insecticide, antibacterial, antitumor, anti-inflammatory, anti-oxidant, antifungal, potent HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTIs), antimicrobial, anticonvulsants, antihypertensive, anticancer agents. This review aims to highlight research reported on biological potential of thiadiazole linked heterocycles along with recent progressive findings about the pharmacological activities of it.

Keywords: Thiadiazole, Heterocycles, Biological Activities, Antihypertensive, Anticonvulsant.

Introduction

Heterocyclic compounds represent one of the most active classes of compounds possessing a wide spectrum of biological activities[1]. Thiadiazole is a five-membered ring structure existing as a clear to yellowish liquid with a pyridine like odour. It is parent functionality for chemical compounds such as biocides, fungicides, dyes and chemical reaction accelerators[2]**.** These also possess pharmaceutical, industrial and medicinal importance due to the presence of toxophoric moiety in it[3]. Of the various isomers, 1,3,4-thiadiazole and its derivatives possess interesting biological activities probably conferred to them due to strong aromaticity of the ring system which leads to great in vivo stability. These generally lack toxicity for higher vertebrates, including humans when substituted with varied functionalities on the aromatic ring which interact with biological receptors[4,5].

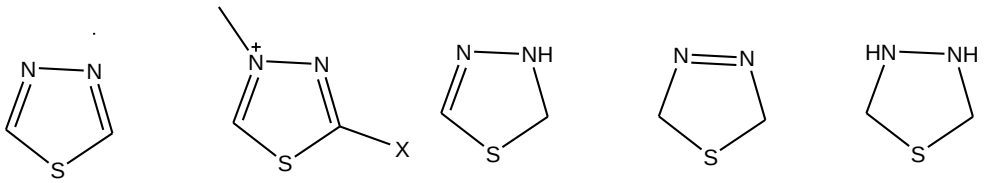
*Corresponding author.
E-mail address: kale_mayura@yahoo.com (Mayura Kale)

1,3,4-Thiadiazoles have been sub classified as aromatic systems which include the neutral thiadiazole**,** mesoionic systems which is defined as five-membered heterocycles which are neither covalent nor polar and non aromatic systems such as the 1,3,4-thiadiazolines, along with tetrahydo 1,3,4-thiadiazolidines. The four isomeric forms of thiadiazole viz. 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5- thiadiazole, and 1,3,4-thiadiazole are depicted as below[6].

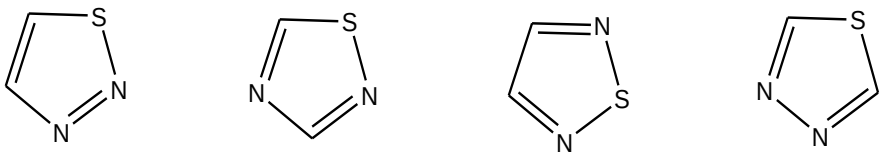
Biological Activities

Analgesic Activity

The biheterocyclics comprising 1,2,4-triazole 1,3,4-thiadiazole and thiadiazines have been found to exhibit promising pharmacological activities[16-20]. Of these, heterocyclic systems involving 3-nitronaphtho [2,1-b]furan, 1,2,4-triazole, 1,3,4-thiadiazolo thiadiazines (Figure No.-1) were synthesized and evaluated for analgesic activity. The newly synthesized compounds were characterized by analytical and spectral studies. All the compounds were evaluated for this activity by acetic acid-induced writhing method in Swiss albino mice Most of the compounds exhibited activity comparable to the standard[7,8,9].



1 **2** **3** **4** **5**



1,2,3-thiadiazole 1,2,4-thiadiazole 1,2,5-thiadiazole 1,3,4-thiadiazole

Physicochemical properties of thiadiazole

Molecular Formula	$C_2H_2N_2S$
Molecular Weight	86.116Da
pKa Value	4.9
Log P Value	0.79
Molar Refractivity	$20.8cm^3$
Boiling Point	110.8^0c
Density	$1.3gm/cm^3$
Surface Tension	55.9dyne/cm
Vapour pressure	27mm Hg at 25^0c

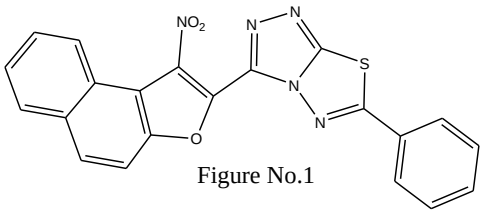


Figure No.1

Helicobacter Pyroli Activity

Novel hybrid molecules with nitro aryl and 1,3,4-thiadiazole moieties have been screened for their anti-*H. pylori* activity. These are 5-(5-nitroaryl)-1,3,4-thiadiazole derivatives bearing different bulky alkyl thio side chains at C-2 position of thiadiazole ring. The activity was determined against three different metronidazole resistant *H. pylori* isolates by paper disk diffusion method. Majority of synthesized compounds exhibit moderate to strong inhibitory response at 25µg/disk. The introduction of different alkyl thio moieties at C-2 position of thiadiazole ring was found to influence this inhibitory activity. The nitro group at C-5 altered the activity and among these, 5-nitrofuran and 5-nitroimidazole moieties were found to significantly raise the inhibitory activity[10]. On the other hand, the antibacterial property of 1,3,4-thiadiazole derivatives (Figure No.-2) against both gram positive and

gram negative bacteria has also been well established[11,12].

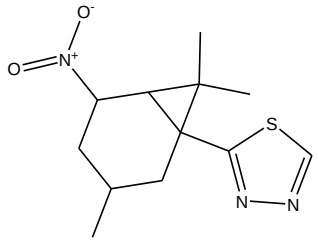


Figure No. 2

Anticancer Activity

A triazolo-thiadiazole system may be considered to be a cyclic analogue consisting of two components thiosemicarbazideand biguanide which show diverse biological activities[13,14]. Some novel 4-(3-substituted [1,2,4] triazolo[3,4- b][1,3,4] thiadiazol-6-yl) (Figure No.-3) derivatives have been evaluated for in-vitro anticancer activity. Of these, compound 43 exhibited best *in-vitro* antioxidant activity. MTT assay was performed in cultured Hela Cells(cervical cancer),B16F1 (Mouse melanoma cells) and in cultured normal Human Lung cells as V79 to confirm their *in-vitro* cytotoxic potency Most of the compounds have been shown to enhance the life span of tumor in mice, which is a reliable criterion for judging the importance of any anticancer agent[15].

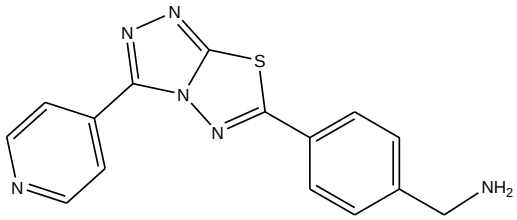


Figure No. 3

HIV Inhibitory Activity

Recently, literature survey has identified 1,2,3-thiadiazole derivatives as novel class of potent HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs). In this, it was found that the fluorine atom or trifluoromethyl group at a strategic position of an organic molecule significantly changes physicochemical and pharmacokinetic properties thus enhancing oral bioavailability and thereby transport mechanism. Based on these findings, a series of novel 4-trifluoromethyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide (Figure No.-4) Schiff's bases have been synthesized and screened successfully for HIV-inhibitory activity with promising results[16].

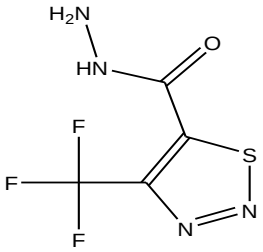


Figure No.4

Antihypertensive Activity

Thiadiazolyl quinazolones were assayed for their effects on cardio vascular system at two dose levels only one compound was found to show some noticeable antihypertensive activity. Thus compound (Figure No.-5) containing m-hydroxy phenyl substituent attached to the thiadiazole nucleus was found to cause depletion in blood pressure to the extent of 60 mm of Hg for more than 30min at 5.0mg/kg iv. However, the same compound at dose level of 1.0mg/kg iv decreased the blood pressure to the extent of 25mm of Hg [17].

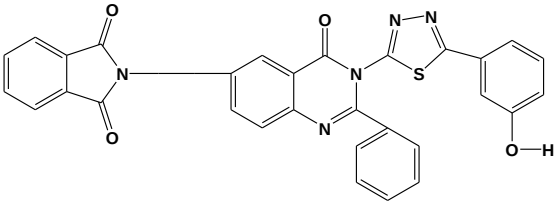


Figure No. 5

Antiinflammatory Activity

Some newer derivatives of thiadiazole linked with azetidinone and indole have been explored and evaluated for *in vivo* anti-inflammatory and analgesic activities. The characteristic feature of this series is substituted phenyl moiety at second position of indole nucleus. It was observed that the compound (Figure No.-6) showed maximum anti-inflammatory activity by significantly reducing the oedema and analgesic activity by inhibiting writhes. These activities were found

to be better than the standard drug phenyl butazone at all the graded doses [18].

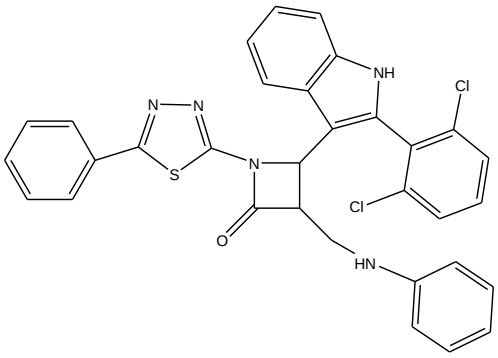


Figure No. 6

Anticonvulsant Activity

During the search for newer chemical entities for the treatment of epilepsy, a series of 3,6-disubstituted-1,2,4-triazolo-1,3,4-thiadiazole derivatives have been synthesized and evaluated for their anticonvulsant activity and their related neurotoxicity. Most of the synthesized compounds exhibited activity comparable to that of standard drugs; phenytoin and carbamazepine. The compounds passed the rotorod test showing no sign of neurological deficit. Among the various halosubstituted derivatives, compound (Figure No.-8) containing 2-bromophenyl attached to thiadiazole ring exhibited highest activity [19].

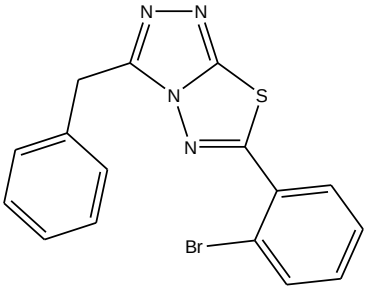


Figure No. 8

Wound Healing Activity

Thiadiazole and quinoline compounds constitute one of the major classes of nitrogen containing heterocycles. They have gained considerable attention of researchers as these possess significant biological a pharmacological properties. Some novel substituted N-aryl-5-phenyl 1,3,4-thiadiazoles have been prepared by the reaction of different substituted chloro-quinolines and hydroxy-quinolines with 2-amino-5-phenyl 1,3,4-thiadiazole in the presence of glacial acetic acid and ethanol. These exhibited good wound healing activities which was evident by increase in rate of wound contraction and marked reduction in epithelization period. The compound (Figure No.-9) showed significantly high wound healing property which was almost equal to that of standard drug povidine iodine[20].

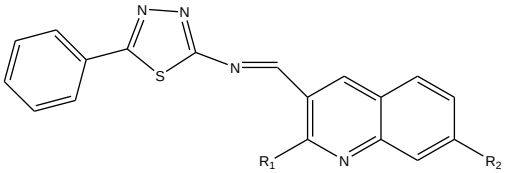


Figure No. 9

Antiproliferative Activity

A series of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles bearing an adamantly moiety have been synthesized by condensation of 4-amino-5-aryl-2*H*-1,2,4-triazole-3(4*H*)-thiones with adamantyl-1-carboxylic acid in the presence of $POCl_3$ and characterized by spectral techniques. The compounds were screened for their antiproliferative activity against a large panel of human cell lines. Introduction of methyl or fluoro residues in the *ortho* position of the aromatic ring (Figure No.-10) was found to enhance the potency [21].

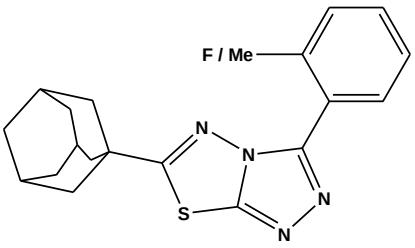


Figure No. 10

Antitubercular Activity

An Investigation on thiadiazole and imidazo [2, 1-b]-1, 3, 4-thiadiazole compounds, possess interesting biological properties such as Antitubercular Activity. Some member of imidazo (2, 1b)-1, 3, 4-thiadiazole family displayed good activity against M. Tuberculosis. A series of 6-aryl-3- (3,4–

dialkoxyphenyl) -[1,2,4]triazole [3,4-b][1,3,4] thiadiazole (Figure No.-11) were synthesized by condensing 4-amino-5-(3,4-dialkoxyphenyl)-4H-[1,2,4]- triazole-3-thiol (6) with various aromatic carboxylic acids in the presence of phosphorous oxychloride through one-pot reaction. The structures of such compounds were confirmed on the basis of IR, 1H NMR and mass spectral studies and they are screened for their antimicrobial activity against a variety of microorganisms. Among the newer analogues, three compounds, 3-(3,4-dimethoxyphenyl) -6- phenyl-[1,2,4]triazolo [3,4-b][1,3,4] thiadiazole 7a, 6-benzyl-3-(2,3 –dimethoxyphenyl) -[1,2,4]triazolo [3,4-b][1,3,4] thiadiazole 7d and 6-(p-bromophenyl) -3- (3,4-dimethoxyphenyl) -[1,2,4]triazolo [3,4-b][1,3,4] thiadiazole 7m exhibited promising antimicrobial activity[22].

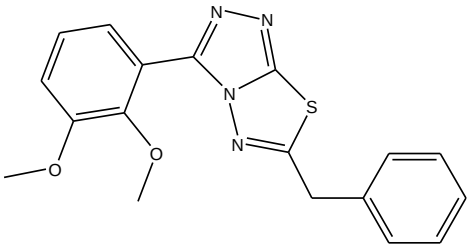


Figure No. 11

Antimicrobial Activity

It is known that triazole and thiadiazole rings make up the structure of various drugs. From these observations, new derivatives of 1,2,4-triazole-3-thiones and 2-amino-1,3,4-thiadiazoles have been prepared and screened as antibacterial agents. The synthesized compound biologically evaluated and the result showed that the compound in (Figure No.-12) showed the higher biological activity against *E.coli* than the standard drug amoxicillin & ceftriaxone. Compound structure shown in (Figure No.-13) exhibited antibacterial against *E.faecalis* higher than the same standard drugs [23].

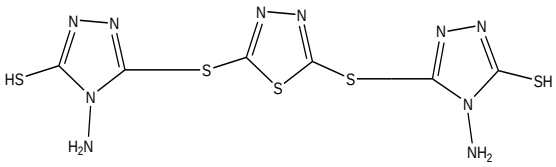


Figure No. 12

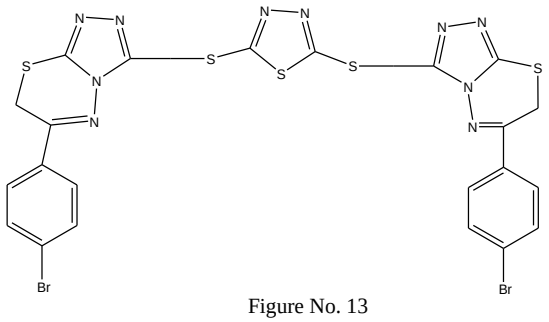


Figure No. 13

Antidiabetic Activity

The designs of some thiadiazole derivatives as anti-diabetic agents have been undertaken using docking studies. The designed molecules were synthesized and subjected to anti-diabetic activity by *in vitro* and *in vivo* method. (Figure No.-14) was found to show potent anti-diabetic activity in alloxan induced diabetes rat model and *in vitro* pancreatic α-amylase inhibition. Molecular docking studies have revealed that synthesized derivatives and target proteins were actively involved in binding and had significant correlation with biological activity[24].

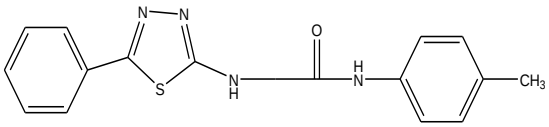


Figure No. 14

Antiepileptic Activity

An indirect type of molecular modelling study has been carried out to find out the 3D structural similarity between some reported antiepileptic drugs and the newly designed 1,3,4-thiadiazole derivatives. A novel series of 1,3,4-thiadiazole derivatives (Figure No.-15) have been prepared by both conventional and microwave irradiated methods. These were screened for their antiepileptic activity by MES model in rats [25].

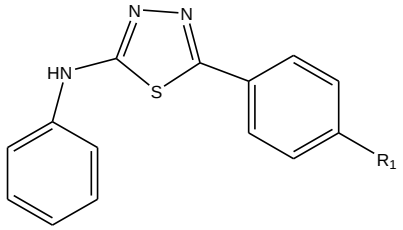


Figure No. 15

Muscle Relaxant Activity

A series of 5-[2-(phenylthio)phenyl]-1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole derivatives have been synthesized. These were screened for *in vivo* muscle relaxant activities using pentylenetetrazole (PTZ) and rotarod tests using diazepam as the standard drug. Most of the compounds were found to be active, of which compound shown in (Figure No.-16) was found to be most effective muscle relaxant [26].

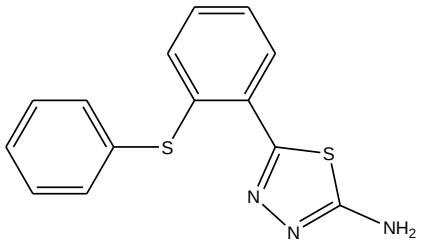


Figure No. 16

Diuretic Activity

Some Schiff bases of traded drug acetazolamide with salicyladehyde have been complexed with Zn (II) salt (Figure No.-17). The diuretic activity of these complexes has been taken on albino rats and compared with that of parent drug. The results have been found to be encouraging with metal chelates as compared to parent drug. It has been observed that about 90% of the dose gets excreted within 24 hours. The above results have also confirmed that zinc complex of acetazolamide Schiff base shows better diuretic activity than the parent drug[27].

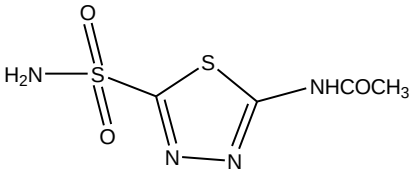


Figure No. 17

Conclusion

The biological potential of thiadiazole and its combination with many heterocycles has drawn special attention of medicinal chemists and hence thorough efforts are being carried out in the search of lead molecules related to it. The present review summarizes the biological activities of the lead thiadiazole fused with other heterocyclic systems such as triazolo-pyridines, triazolo-pyrimidines, triazolo-pyrazines, triazolo-triazines and triazolo- thiadiazines. We have also depicted the general structure of such potent fused heterocycles which shall be helpful to the researchers to further carry out various structural modifications in these heterocycles in order to improve the concerned biological activity.

Acknowledgement

The authors are thankful to the Principal, Government College of Pharmacy, Aurangabad, Maharashtra, India for providing literature survey facility to carry out this review work.

References

1. Kale M., Patwardhan K (2013) Synthesis of heterocyclic scaffolds with anti-hyperlipidemic potential. Der Pharma Chemica. 5(5), 213-222.
2. Jalhan S., Jindal A., Gupta A., Hemraj (2012) Synthesis, biological activities and chemistry of thiadiazole derivatives and Schiff bases. Asian J. Pharm. Clin. Res. 5(3), 199-208.
3. Sankangoud R., Chatni N., Goudanavar P (2010) Synthesis and evaluation of antibacterial activity of some new N,N'-(5-(6-(4-substitutedphenyl)imidazo[2,1-b][1,3,4]-thiadiazol-2-yl)-pyrimidine-2,4-diyl)diacetamide derivatives. Der Pharma Chemica. 2(2), 347-353.
4. Barboiu M., Cimpoesu M., Guran C., Supuran C (1996) synthesis and antifungal activity of metal complexes containing dichloro tetramorpholino cyclophosphazatriene. Metal based drug. 3(5), 227-232.
5. Kempegowda, Senthil Kumar G., Dev P., Mani T (2011) Thiadiazoles: Progress report on biological activities. Der Pharma Chemica. 3(2), 330-341.
6. Semwal A., Chaudhary B., Singh R., Bagchi A (2013) Report on biological activities of thiadiazole derivatives. Int. J. Recent Adv. Pharm. Res. 3(1), 1-13.
7. Singh G (2003) Recent progress in the synthesis and chemistry of

azetidinones. Tetrahedron. 59, 7631-7649.

8. Ravindra K.C., Vagdevi H.M., Vaidya V.P (2006) Synthesis, antimicrobial and antiinflamatory activities of 1,3,4-oxadiazoles linked 2-naphtho[2,1-b] furan. Indian J. Chem. 2006, 45(B), 2506-2511.

9. Shashikala Devi K., Ramaiah M., Vanita G.K., Veena K., Vaidya V.P (2011) Synthesis and analgesic activity of triazolothiadiazoles and triazolothiadiazines encompassing 3–nitronaphtho[2,1-b]furan. J. Chem. Pharm. Res. 3(1), 445-451.

10. Edwards D.I (1993) The influence of microaerophilia and anaerobiosis on metronidazole uptake in helicobacter pylori oxford journals medicine & health. J. of Antimicrobial Chemotherapy. 36(3), 453-461.

11. Amir M., Kumar H., Javed S.A (2008) Synthesis and antimalarial activity of carbamate and amide derivatives of 4-anilinoquinoline. Eur. J. Med. Chem. 43, 2056-2066.

12. Asadipoura A., Edrakib N., Nakhjirib M., Yahya-Meymandib A., Alipourd E., Sanieee P., Siavoshie F., Shafieea A., Foroumadia A (2013) Anti-helicobacter pylori activity and structure-activity relationship study of 2-alkylthio-5-(nitroaryl)-1,3,4-thiadiazole derivatives. Iranian J. of Pharm. Res. 12(3), 281-287.

13. Sharma M., Deekshith V., Semwal A., Sriram D., Yogeeswari P (2012) Discovery of fused triazolo-thiadiazoles as inhibitors of TNF-alpha: Pharmacophore hybridization for treatment of neuropathic pain. Pain and Therapy 1 (3), 1-17.

14. El Shehrya M.F., Abu-Hashemb A.A., El-Telbani E.M (2010) Synthesis of 3-((2,4-dichlorophenoxy)methyl)-1,2,4-triazolo (thiadiazoles and thiadiazines) as anti-inflammatory and molluscicidal agents. 45 (5), 1906–1911.

15. Reddy A., Kini S.G., Mubeen M (2013) Synthesis and biological evaluation of novel triazolo-thiadiazole derivatives. Der Pharma Chemica 5(6), 259-272.

16. Jain S.V., Ghate M., Bhadoriya K.S., Bari S.B., Chaudhari A., Borse J.S (2011) 2D and 3D-QSAR study on 4-anilinoquinozaline derivatives as potent apoptosis inducer and efficacious anticancer agent. Org. and Med. Chem. Lett. 2, 24-28.

17. Raghubir R., Dixit M., Joshi M.N., Bajpai S.K (2004) Thiadiazolyl quinazolones as potential antiviral and antihypertensive agents. Ind. J. Chem. 43(B), 180-183.

18. Singh I. (2014) Synthesis of some newer derivatives of thiadiazole as anti-inflammatory and analgesic agents. Int. J. Pharm. Chem. Sci. 3(4), 827-832.

19. Farghalya A. R., Clercq E. D., El-Kashefa H (2006) Synthesis and antiviral activity of novel [1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles, [1,2,4]triazolo[3,4-b] [1,3,4]thiadiazines and [1,2,4]triazolo[3,4-b][1,3,4] thiadiazepines . ARKIVOC. (x) 137-151.

20. Husain A., Naseer M. A., Sarafroj M (2009) Synthesis and anticonvulsant activity of some novel fused heterocyclic 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole derivatives. Drug Research 66(2), 135-140

21. Jayakumar B.H.M., Pramod N., Patel A.H., Rao N.R., Sanjay kumar D., Shiv kumar H (2012) Thiadiazole-quinoline derivatives as potential wound healing activity. Int. J. Phytopharmacol. 3(2), 157-162.

22. Khana M.H., Akhtara T., Yasina K. A., Al-Masoudib N. A., Jonesc P. G., Hameed S (2010) Synthesis crystal structure and antiproliferative activity of 6-adamantyl-3-aryl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles Z. Naturforsch. 65b, 178 – 184.

23. Sahu J. K., Ganguly S., Kaushik A (2014) Synthesis of some novel heterocyclic 1,2,4-triazolo [3,4-

b][1,3,4] thiadiazole derivatives as possible antimicrobial agents. J. Appl. Pharm. Sci. 4(2), 81-86.

24. Datar P.A., Deokule T.A (2014) Design and synthesis of thiadiazole derivatives as antidiabetic agents. Med. Chem. 4, 390-399.

25. Sahoo B.M., Dinda S.C., Ravikumar B.V.V (2012) Design, synthesis and antiepileptic evaluation of 5-(aryl)-N-phenyl-1,3,4-thiadiazol-2-amine. Int. J. Pharm. Pharmaceut. Sci. 4(3), 747-751.

26. Almasirada A., Vousooghib N., Tabatabaic S.A., Kebriaeezadehd A., Shafieee A (2007) Synthesis, anticonvulsant and muscle relaxant activities of substituted 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole. Acta Chim. Slov. 54, 317–324.

27. Ghosh S., Malik S., Jain B., Ganesh N (2009) Synthesis, characterization and biological studies of Zn(II) complex of schiff base derived from 5-acetazolamido-1,3,4 - thiadiazole-2-sulphonamide, a diuretic drug. Asian J. Exp. Sci. 23(1), 189-192.

****