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1, 3, 4-Thiadiazoles: An Overview

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Abstract

Many of the pharmaceutically important compounds possessed 1,3,4-thiadiazoles as its heterocyclic moiety. They have shown many of the activities like anti-inflammatory, anticonvulsant, antimicrobial, anticancer, antihypertensive. In this review some of the recent work done on the moiety with their activity was given.

Keywords: Biological Activities; 1,3,4-Thiadiazoles

Introduction

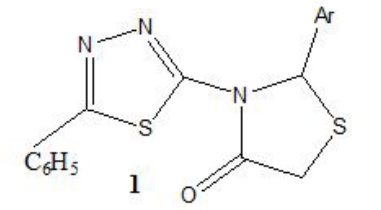
A large number of biologically active compounds were having heterocyclic moieties and the molecular framework of the compounds determines the biological activity. Heterocyclic nucleus containing nitrogen atoms were having a special interest because they are in an important class of natural and non-natural products, many of them exhibits usual biological synthesis. Thiadiazoles had an important place in the drug industries. Among that, 1,3,4-thiadiazoles have wide uses in many fields. In the earlier days, they were used in the pharmaceutical area as an antibacterial with known sulphonamides. Then, in later days some of them were used as antitumour, anti-inflammatory agents, pesticides, dyes, lubricants and analytical agents.

1, 3, 4-thiadiazole derivatives is possessing biological activities probably conferred because of strong aromaticity of the ring system, that leads to great *in vivo* stability and generally, a lack of toxicities for higher vertebrates, including humans. When different functional groups are attached to nucleus it may interact with biological receptors and produce an outstanding property. 1,3,4- Thiadiazoles exhibits various biological activities and find a great use in the fields of pharmaceuticals, acetazolamide, the first non-mercurial diuretic drug [1-4], antitumor agents [5], agrochemicals [6]. Some antibacterial sulphonamides which are not used clinically but possessed historical [7] importance. However, this molecules Thiadiazoles (e.g. 1,3,4-thiadiazoles) exhibit a number of extremely interesting spectroscopic properties, which are also worth mentioning. One of the very interesting spectroscopic properties of Thiadiazoles is the dual fluorescence effect (which can hardly be associated with the ESIPT or TICT effects) [8-11]. Herewith a brief account of various alterations done on the Thiadiazoles nucleus and their biological activities was given.

Biological Activities

Antimicrobial activity

A.A. Aly, et al. [12] had synthesized a variety of heterocyclic compounds from 2-amino Thiadiazoles like 3-[5-(3-chlorobenzo[b] thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-2-arylthiazolidin-4-ones **1**, 1-[5-(3-chlorobenzo[b]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-3-phenyldihydropyrimidine-2,4,6-trione **2**, N-(4,5-dihydro-1*H*-imidazol-2-yl)-5-(3-chlorobenzo[b]thiophen-2-yl)-1,3,4-thiadiazol-2-ylamine **3**, N-[5-(3-chlorobenzo[b]thiophen-2-yl)-1,3,4-thiadiazol-2-yl]-1*H* benzo[d]imidazol-2-ylamine **4**. The compounds were screened for antibacterial activity against *Bacillus cereus, Escherichia coli* and for antifungal activity against *Aspergillus niger* and *Penicillium notatum*. All the compounds have shown a remarkable activity towards the selected strains.

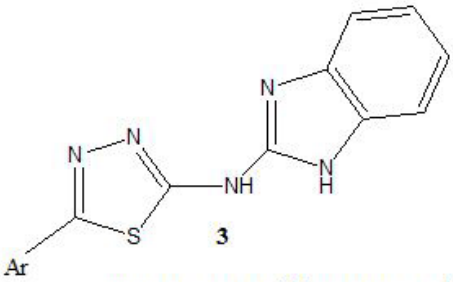


1

Ar=C_6H_5, C_6H_4Cl(p), $C_6H_4OCH_3$(p)

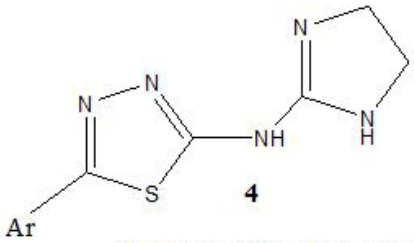
2

Ar=C_6H_5, C_6H_4Cl(p), $C_6H_4OCH_3$(p)
X=O,S



3

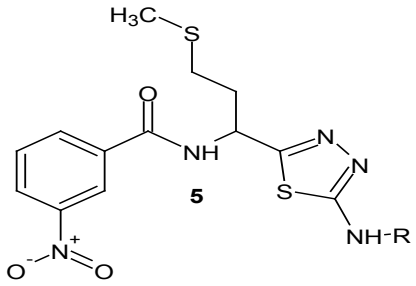
Ar=C_6H_5, C_6H_4Cl(p), $C_6H_4OCH_3$(p)



4

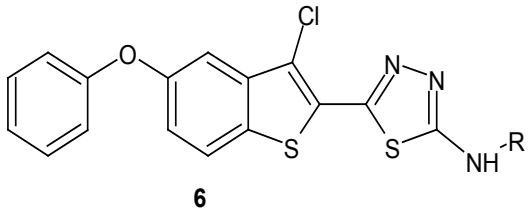
Ar=C_6H_5, C_6H_4Cl(p), $C_6H_4OCH_3$(p)

2-[1-(3-nitrobenzoylamino)-3-(methylthio)]-propyl-5-(substituted amino)-1,3,4-thiadiazoles **5** were prepared by Lenuta profire, et al. [13]. All the compounds were tested for antimicrobial activities against *Staphylococcus aureus, Bacillus antracis, Bacillus cereus, Sarcina lutea, Escherichia coli*. On MIC determination, only the compound containing R=4-CH_3 C_6H_4 had showed good activity at low concentration upon *Bacillus aureus* and *Bacillus cereus*. They were also investigated for toxicities and were found to have less toxicity.



5

R=CH_3, C_6H_5, $C_6H_4Cl_3$(4), C_6H_4Br(4), $CH_2CH=CH_2$

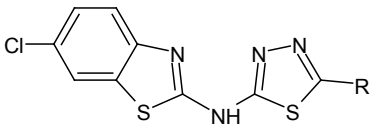


6

R=C_6H_5, 3-Cl C_6H_4, 4-Cl C_6H_4, 2-$CH_3C_6H_4$
4-$CH_3C_6H_4$, 2-$OCH_3C_6H_4$, 4-$OCH_3C_6H_4$, 2-$NO_2C_6H_4$

H.S Joshi, et al. [14] had synthesized a series of 2-(3'-chloro-5'-phenoxy-benzo[*b*]thiophen-2'-yl)-5-arylamino-1,3,4-thiadiazoles **6** and tested their antimicrobial activity. They found that when R=4-Cl C_6H_4 and R=4-CH_3 C_6H_4, the compound showed good activity against *Escherichia coli* and R=3-Cl C_6H_4, 4-Cl C_6H_4 they showed good activity against *Bacillus megaterium* and with R=C_6H_5 and R=2-NO_2 C_6H_4 it showed good activity against *Staphylococcus aureus*. When the compound possessed R=C_6H_5, 3-Cl C_6H_4, 4-Cl C_6H_4 a good activity against *Aspergillus niger* was found. All the other compounds have shown mild activity against other organisms.

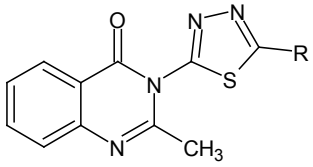
Some 2-aryl-5-(6'-chloro-1',3'-benzothiazol-2-yl-amino)-1,3,4-thiadiazoles **7** were screened for antibacterial activity against *E coli, Staphylococcus aureus, Pseudomonas aeruginosa* and for antifungal activity against *Aspergillus niger, Candida albicans* by Mohd Amir, et al. [15]. Acetoxy phenyl derivative showed potent activity against *Staphylococcus aureus* and when R=2-naphthylmethyl, it showed good activity against *E. Coli* and with R=2,4-dichlorophenyl containing compound showed significant activity against bacterial strains. When R=2-aminophenyl and R=2, 4-dichloro phenoxy methyl gave good antifungal activity against *Aspergillus niger* and *Candida albicans* respectively.



7

R=C_6H_5, 4-ClC_6H_4, 2,4-$(Cl)_2C_6H_3$, 4-$NO_2C_6H_4$
2-$NH_2C_6H_4$, 2,4-$(Cl)_2C_6H_3OCH_2$, 4-$OCH_3C_6H_4$,
2-Acetoxy phenyl, 3-pyridinyl, 2-napthyl methyl

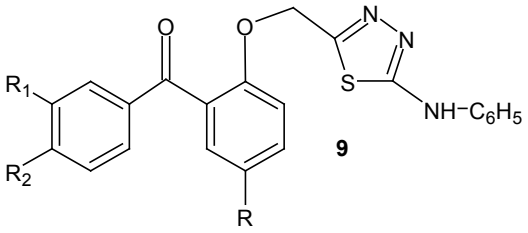
P. Mishra et al. [16] prepared some new 2-methyl-3-(1,3,4-thiadiazoyl)-4-(3*H*) quinazolinones **8** and screened them for them *in vitro* antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, E Coli* and *Candida albicans, Aspergillus niger, Curvularia lunata* for antifungal activity. All the compounds have shown mild to moderate activity. They also determined MIC for the synthesized compounds and found that they had better fungi toxic than bacteriotoxic. Compound with 4-Cl C_6H_4 had a potent antibacterial and antifungal activity.



8

R=CH_3, C_3H_7, C_4H_9, C_6H_5, C_6H_4(p)CH_3, C_6H_4(p)Cl

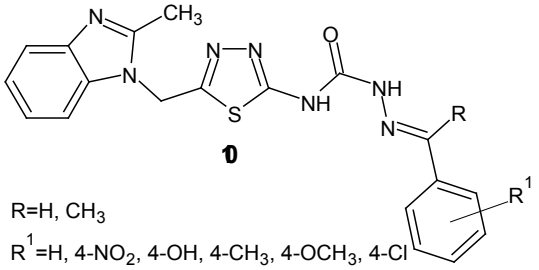
Sheena Shashikanth, et al. [17] prepared few 2-(2-aroylaryloxy) methyl-5-*N*-phenylamino-1,3,4-thiadiazoles **9** and found some active compounds when screened them against *Bacillus cereus, Staphylococcus aureus, E coli* for antibacterial and *Penicillium nigricans, Aspergillus fumigatus, Fusarium solani* for antifungal activity. The chloro substitution has shown good activity.



9

R=CH_3
R_1=Cl, H, CH_3
R_2=H, Cl, OCH_3

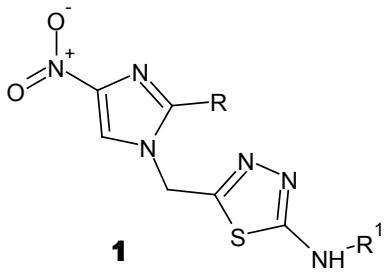
A series of 2,5-disubstituted 1,3,4-thiadiazoles **10** were synthesized by H. Rajak, etal. [18] and found a mild to moderate antimicrobial activity when screened against *Staphylococcus aureus, Bacillus aureus, Proteus mirabilis, Pseudomonas aeruginosa* and for antifungal activity against *Aspergillus niger* and *Candida albicans*. The compound with 4-$NO_2C_6H_4$ substituent found to be more active compound, showing a broad spectrum of activity.



10

R=H, CH_3
R^1=H, 4-NO_2, 4-OH, 4-CH_3, 4-OCH_3, 4-Cl

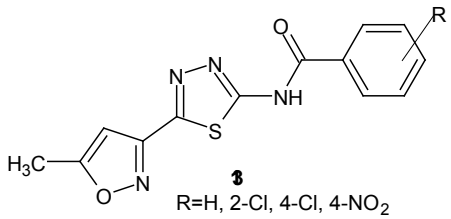
Various 1,3,4-thiadiazole derivatives **11** were synthesized by A. Shafiee, et al. [19] and found to be active against *Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Bacillus subtilis, Clostridium difficile, Aspergillus niger* and *Cryptococcus neoformans*. They found that most of the compounds were active against *Bacillus subtilis* and *Clostridium difficile*. 2-butylamino-5-[(4-nitro-1*H*-imidazol-1-yl) methyl]-1,3,4-thiadiazole had shown good activity against most organisms.



11

R=H, CH_3
R^1=$CH_3(CH_2)_3$, 4-CH_3O $_6H_4$, 4-$NO_2C_6H_4$

Zi yi Zhang, et al. [20] had synthesized some derivatives of 1,3,4-thiadiazole **13** and screened the compounds for *in vitro* antibacterial activity at 100 ppm concentration against *E coli, Staphylococcus aureus, Pseudomonas aeruginosa* and the unsubstituted and 4-Cl substituted compound were found to have moderate active compounds and others were inactive against *Staphylococcus aureus*.



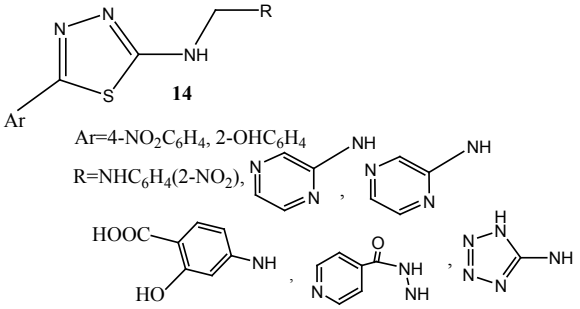
13

R=H, 2-Cl, 4-Cl, 4-NO_2

Antitubercular activity

H.S. Joshi, et al. [14] had synthesized a series of 2-(3'-chloro-5'-phenoxy-benzo[*b*]thiophen-2'-yl)-5-arylamino-1,3,4-

thiadiazoles **6** and tested for antitubercular activity and found that p-methoxy derivative showed good inhibition at 0.25µg/ml than other compounds. Shashikant R Pattan et al [21] prepared some of N'-substituted-N'-[5-(4-nitrophenyl)-[1,3,4] thiadiazol-2-yl]-methanediamines **14** and screened for antitubercular activity. Most of the compounds have shown significant activity.

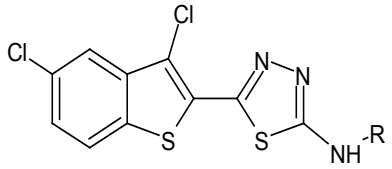


14

Ar=4-$NO_2C_6H_4$, 2-OHC_6H_4

R=$NHC_6H_4(2\text{-}NO_2)$,

2 - (3', 5' - dichlorobenzo[b]thiophen - 2' -yl) - 5 - arylamino - 1,3,4 - Thiadiazoles **15** were synthesized by H.S. Joshi and K.M. Thaker [22]. They had evaluated all the synthesized compounds and found that the compound with nitro phenyl shown good inhibition against *Mycobacterium tuberculosis* $H_{37}Rv$ with 98% inhibition among all compounds. The compounds for antitubercular activity were conducted on organism at 6.25 µg/ml in primary screening and those that have shown >90% inhibitions were compared with standard at 0.25 µg/ml.



15

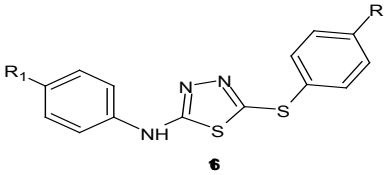
R=C_6H_5, 2-Cl C_6H_4, 3-Cl C_6H_4, 2-Cl-5-$CH_3C_6H_3$,

2,3-$(CH_3)_2C_6H_3$, 4-$OCH_3C_6H_4$, 2-$CH_3C_6H_4$

4-$CH_3C_6H_4$, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$

Anti-inflammatory activity

Rajesh Sharma, et al. [23] synthesized a series of diaryl substituted 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives **16** and evaluated for anti-inflammatory activity using Carrageenean induced rat paw oedema method. The compound with R=SO_2NH_2, R_1=SO_2Cl showed highest selective COX-2 inhibitory activity. Some of the compounds have shown both COX-1 and COX-2 inhibition and some with only on COX-1. They found that some compounds have shown non selective COX inhibitors.

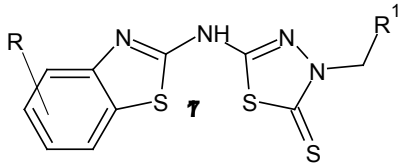


16

R=SO_2NH_2, SO_2Cl

R_1=Cl, Br, F, CH_3, CF_3, CCl_3, SO_2Cl, SO_2NH_2

K.M. Basavaraja, et al. [24] prepared few 2-[3-substituted-2-thione-1,3,4-thiadiazole-5-yl] amino bezothiazoles **17** and found a high significant anti-inflammatory activity when R'=diphenylamino, R'=morpholino, R'=diethylamino group.

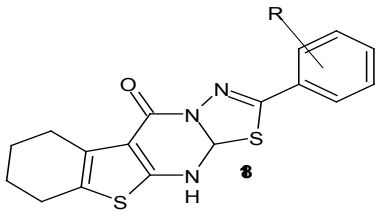


17

R=Cl, F

R_1=$N(CH_3)_2$, $N(C_2H_5)_2$, $N(C_6H_5)_2$,

Some new substituted thiadiazolothieno-pyrimidinones **18** were prepared by Amit Kumar Das et al. [25] and found to have some active compounds when evaluated for anti-inflammatory activity. Some thiadiazolopyrimidinones (R= o-methoxy, m-methoxy, p-methoxy, o-methyl, m-methyl, p-methyl, p-amino, p-chloro) were synthesized. Among these, p-methoxy, o-methyl, m-methyl, p-chloro showed activity after 3 h and o-methoxy, m-methoxy had shown after 2 h from time of administration. p-Amino has shown least activity.

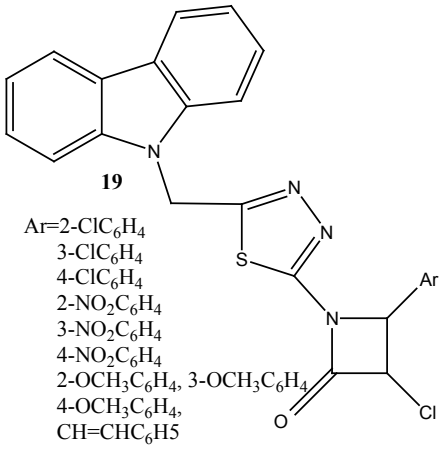


18

R=o-OCH_3, m-OCH_3, p-OCH_3, o-CH_3

m-CH_3, p-CH_3, p-NH_2, p-Cl

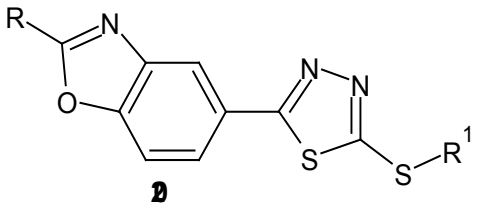
S.K.Srivastava, et al.[26] synthesized new carbazolyl-thiadiazol-2-oxo-azetidines **19** and evaluated their anti-inflammatory activity. Only the compound with Ar=2-Cl C_6H_4 had shown good activity when compared to other derivatives and all the other compounds have given mild to moderate activity.



19

Ar=2-ClC_6H_4
3-ClC_6H_4
4-ClC_6H_4
2-$NO_2C_6H_4$
3-$NO_2C_6H_4$
4-$NO_2C_6H_4$
2-$OCH_3C_6H_4$, 3-$OCH_3C_6H_4$,
4-$OCH_3C_6H_4$,
$CH{=}CHC_6H5$
C_4H_3O

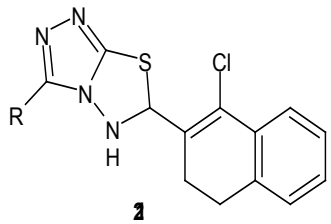
B. Gopal Krishna, et al. [27] worked on the synthesis of 5-(2-substituted benzoxazol-5-yl)-2-methyl thio/ benzylthio/ arylamino carbonyl methylthio-1,3,4-thiadiazoles **20** and studied their anti-inflammatory activity. They found that only compound with R=CH_2 C_6H_5 has shown 65.39% inhibition of edema.



20

R=H, CH_3

A new series of compounds containing 3-alkyl/aryl-6-(1-chloro-3,4-dihydronaphth-2-yl)-5,6-dihydro-s-triazolo[3,4-b] [1,3,4] thiadiazoles **21** were synthesized by Rajive gupta, et al. [28]. They had evaluated their compounds for anti-inflammatory activity and found that all compounds showed mild anti-inflammatory activity of about 3- 12% against acute Carrageenean-induced oedema in rat paw method.



21

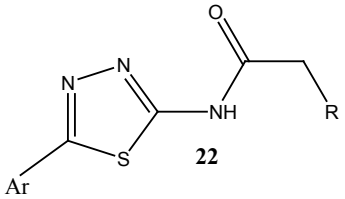
R=CH_3, C_2H_5, C_3H_7, C_6H_5, $CH_2C_6H_5$

4-$OCH_3C_6H_4$, 2-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 2-Cl C_6H_4

E. Palaska, et al. [29] prepared few derivatives of 2-(2-naphthyloxymethyl)-5-substitutedamino-1,3,4-thadiazoles. They had evaluated the compounds for anti-inflammatory activity and ulcerogenic activities. None of the compounds showed significant side effects.

Antidiabetic activity

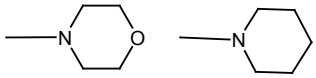
Shashikant R Pattan, et al. [30] worked on a few Thiadiazoles derivatives **14** and found some moderate to good active compounds when evaluated for antidiabetic activity. The compound with 4-carboxy-3-hydroxy phenyl amino has shown maximum antidiabetic activity than other derivatives. Some new series of 1,3,4-thiadiazoles **22** were synthesized and they were screened for antidiabetic activity by Shashikant R Pattan, et al. [31]. They had synthesized of about eight compounds of which the compound with R=piperidinyl had shown maximum antidiabetic activity and R=diphenylamino derivative showed moderate activity.



22

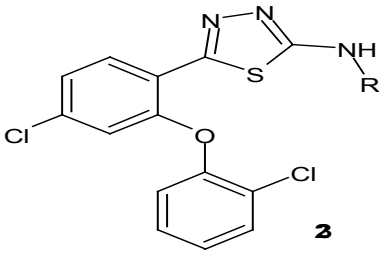
Ar=4-NO_2 C_6H_4
$C_6H_5CH{=}CH$

R=$N(C_2H_5)$, $N(C_6H_5)_2$



Anticonvulsant activity

A. Foroumadi, et al. [32] reported some novel 2-amino-5-[4-chloro-2-(2-chlorophenoxy) phenyl]-1,3,4-thiadiazole derivatives **23** and studied their anticonvulsant activity using MES and PTZ method. They had synthesized four compounds of which the compound with R=C_2H_5 had shown good anticonvulsant activity by both methods. While R=CH_3 has given the activity only with MES method.

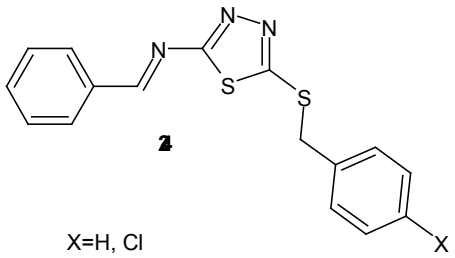


23

R=H, CH_3, C_2H_5, C_6H_5

Bahar Ahmed, et al. [33] synthesized various compounds of 2-thiobenzyl-1,3,4-thiadiazoles **24** and studied their anticonvulsant activity and neurotoxicity test. They synthesized chlorobezylated

imines and benzylated imines. Among these, chlorobenzylated imines have shown 100% protection towards MES induced hind limb extension method with fast recovery and without neurotoxicity whereas benzylated imines showed less protection than chlorobenzylated imines towards MES induced hind limb extension with slow recovery and without neurotoxicity.



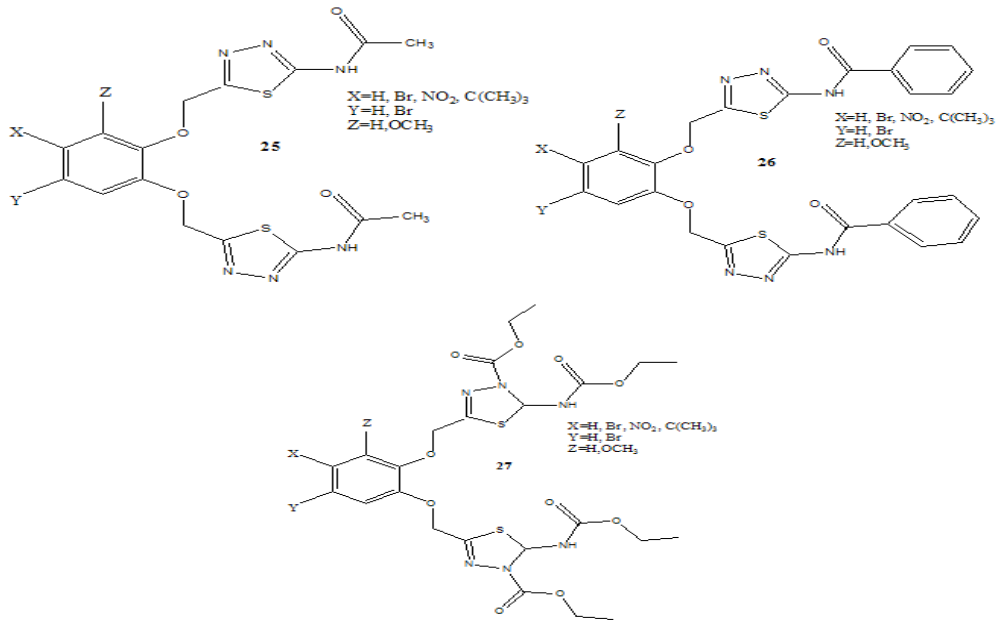
Some of the new carbazolyl thiadiazol-2-oxo azetidines **19** had been synthesized by S.K.Srivastava, et al. [34]. They also studied for their anticonvulsant activity and found only the chloro derivatives had given good active compounds than other derivatives.

Analgesic activity

A new series of 4-[5-chlorophenylamino)-1,3,4-thiadiazole-2-yl-sulphanyl]-benzene sulphonamide **16** were synthesized by Rajesh Sharma, et al. [35]. They had synthesized about 15 compounds and evaluated for analgesic activity using tail flick method. They found that compound with R=SO_2NH_2 and SO_2Cl has shown a significant analgesic activity compared to Tramadol HCl. K.M. Basavaraja, et al. [24] prepared a series of 2-[3-substituted-2-thione-1,3,4-thiadiazole-5-yl] aminobenzothiazoles **17** and tested for analgesic activity by using Eddys hot plate method. They had synthesized eight compounds, among which the compound with chloro and morpholino substitution showed higher potency with faster onset of action.

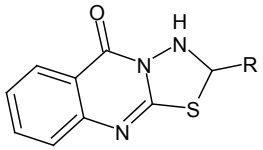
Anticancer activity

Kemal Sancak, et al. [34] prepared a series of *N*-[5-({2-[(5-acetylamino-1,3,4-thiadiazole-2-yl) methoxy] substituted phenoxy} methyl)-1,3,4-thiadiazole-2-yl] acetamides **25**, N-[5-({2-[(5-acetylamino-1,3,4-thiadiazole-2-yl)methoxy]substituted phenoxy}methyl)-1,3,4-thiadiazole-2-yl]benzamine **26**, Ethyl-5-({2-[(4-{ethoxy carbonyl-5-({ethoxy carbonyl}imino)-4,5-dihydro-1,3,4-thiadiazole-2-yl) methoxy] substitutedphenoxy} methyl)-2-[(ethoxycarbonyl)imino]-2,3-dihydro-1,3,4-thiaiazole-3-carboxylate **27**. All the new compounds were tested for cytostatic activity on tumor cell lines like breast cancer, on small cell lung cancer and CNS. The best activity was found with compounds containing acetyl an d ethoxy carbonyl groups.



Antihypertensive activity

V. Alagarsamy, et al. [35] had synthesized few 2-substituted [1,3,4] Thiadiazoles [2,3-b] quinazolin-5(4H)-ones **28**. The compounds were tested for *in vivo* antihypertensive activity. They found that compound containing R=$NHCH_2CH{=}CH_2$ has reduced BP significantly when compared to prazocin, the standard.

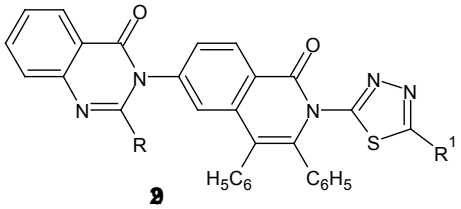


28

R=H, $NHCH_3$, $NHCH_2CH=CH_2$, NHC_6H_5, $NH(3\text{-Cl } C_6H_4)$, $NH(3\text{-}CH_3C_6H_4)$

Antiviral activity

V.K. Pandey, et al. [36] had synthesized few derivatives of 2-aryl-3-[5'-aralkyl-1',3',4'-thiadiazolyl-{2'(2",4"-dipenyl-1"-oxo isoquinolinyl}]-4-oxo-3*H*-quinazolinones **29** and screened for antiviral activity against influenza virus. The compound with p-chlorophenyl group at 2nd position of quinazolone and methyl group at 5th position of thiadiazole ring showed maximum activity.

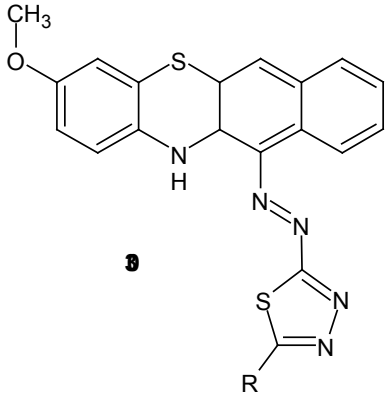


29

R=C_2H_5, $C_6H_5CH=CH$, $p\text{-Cl } C_6H_4$, $p\text{-}NO_2C_6H_4$, $m\text{-}C_6H_3(NO_2)_2$

R^1=CH_3, C_2H_5

V.K. Pandey, et al. [37] prepared few derivatives of 1-(2'-diazo-5'-aralkyl-1',3',4'-thiadiazolyl)-6-methoxy[2,3-*b*] benzophenothiazines **30**. They screened the compounds for antiviral activity against Japanese encephalitis (JEV) and Herpes Simplex Virus Type-I (HSV-I). They found that only one compound has shown activity against JEV upto 50% *in vitro* and also against HSV-I upto 8% *in vitro*. The compounds that had shown activity had phenyl group as its substitution.

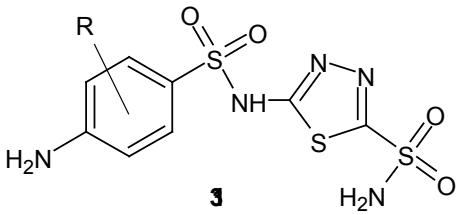


30

R=H, CH_3, C_2H_5, CH_2Cl, C_6H_5

Antioxidant activity

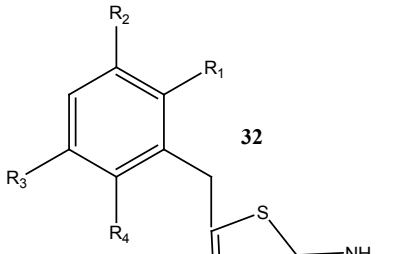
A.S. Mundey, et al. [38] synthesized 5-(4-amino) substituted benzene sulphonamido-1,3,4-thiadiazol-2-sulphonamides **31** and screened their free radical scavenging activity by using 2,2-Diphenyl-1-Picrylhydrazyl (DPPH) method. They found that the unsubstituted derivative has shown moderate activity.



31

R=H, 5-OCH_3, 2-NO_2

B.K. Karale, et al. [39] had screened the antioxidant activity of some of the synthesized Thiadiazoles derivatives **32**. They had evaluated using DPPH method and found only some active compounds among the synthesized derivatives.



32

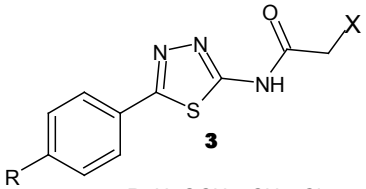
R_1=H,F
R_2=Cl,F
R_3=Cl,F
R_4=H,F
Ar=C_6H_5, $2\text{-}CH_3C_6H_4$, $3\text{-}CH_3C_6H_4$ $4\text{-}CH_3C_6H_4$, $3\text{-}OCH_3C_6H_4$

Rajive gupta [28] synthesized a series of 3-alkyl/aryl-6-(1-chloro-3,4-dihydronaphth-2-yl)-5,6-dihydro-s-triazolo[3,4-*b*] [1,3,4] Thiadiazoles **21** and evaluated their antioxidant activity. They had evaluated against sodium nitroprusside induced nitric oxide production, measured by Griess reaction. Among all the synthesized compounds, only the compound containing the substituent like propyl, phenyl, 4-methylphenyl showed significant effect.

Diuretic activity

Few derivatives of some 1,3,4-thiadiazoles **33** were synthesized by Sanmati K Jaim [40] and also studied their diuretic action. They found that the compound having R=H with X=di-n-propyl/di-isopropyl amino substituent and compound with R=CH_3 with X=pyrrolidino substituent showed good activity. The compound having R=CH_3O, CH_3 and X=2-pyrrolidino substituent showed moderate activity. From the results of compounds on

diuretic activity it was found that di-iso propyl amino derivatives are more active than di-n-propyl amino derivatives.



3

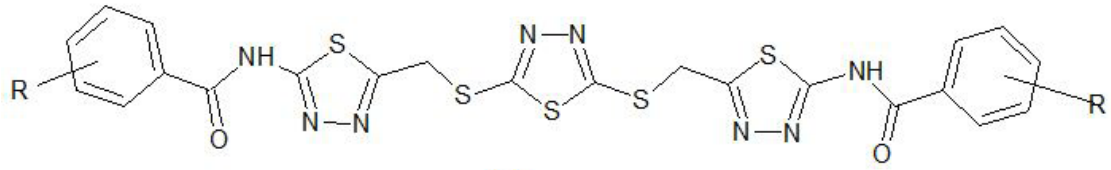
R=H, OCH_3, CH_3, Cl

X=Di-n-propyl amino, di-n-isopropyl amino

pyrrolidine, 2-pyrrolidinone

Plant growth regulators

Some of the 2,5-bismercapto-1,3,4-thiadiazole heterocyclic derivatives **34** were synthesized by Tai Bao Wei, et al. [41]. They evaluated the compounds for the plant growth promoters and found some active compounds. They evaluated on the wheat seeds and recorded the length of seedlings and roots by taking the concentration of compounds from 0.001 to 100 ppm. The compounds having the substituent like 2-chloro, 3-chloro and 4-methyl groups had good promoting effects.



34

R=H, 4-OCH_2CH_3, 2-Cl, 3-Cl, 4-Br, 4-F, 4-OCH_3, 4-CH_3

Conclusion

The literature reveals that 1,3,4-thiadiazoles has diverse biological potential, and the easy synthetic routes for synthesis have been attention of the chemists, pharmacologists and researchers. The anticancer and antiviral activities were the most encouraging activities for the pharmacists. Also the research on antitubercular activity has given positive results. In conclusion, a wide variety of biological activity of 1,3,4-thiadiazoles has been described.

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