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Biological and medicinal significance of 2-aminothiazoles

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ABSTRACT

This article emphasizes on the importance of 2-aminothiazole as a biologically relevant heterocycle. Article includes most of the physiologically as well as medicinally important compounds containing 2-aminothiazole moiety. This article also covers marketed drugs containing 2-aminothiazole moiety.

Keywords: 2-Aminothiazole, biological significance, drugs, medicinal significance, pharmacological activities, standard drug

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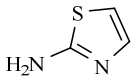
INTRODUCTION

Thiazole is classified under five-membered heterocyclic class of compounds and is found in many natural and synthetic agents. Naturally, thiazole is available in a large number of terrestrial and marine compounds with different pharmacological activities. Thiazole is also present in the vitamin B1 (Thiamine).

In synthetic substituted thiazole derivatives, 2-aminothiazoles (**1**) have shown a variety of biological activities such as antibacterial, antifungal, antitubercular, anti-HIV, anti-inflammatory, anticancer, anticonvulsant, antidiabetic, antihypertensive, antiprotozoal, dopaminergic, plasminogen activator inhibitor-1, neuroprotective and antioxidant. This broad spectrum of activities makes 2-aminothiazole as an attractive moiety in medicinal chemistry.



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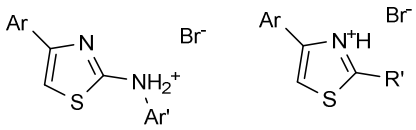
In this review, we focused on 2-aminothiazole derivatives with their brief profile of a number of biological activities as well as drug molecules containing 2-aminothiazole moiety.

Reported biological activities of 2-aminothiazoles

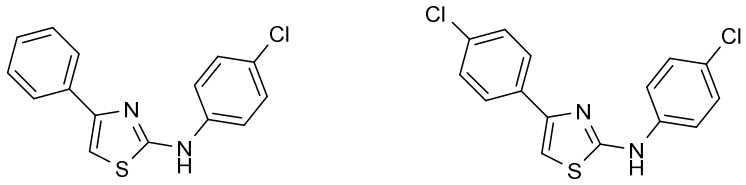
1) 2-Aminothiazoles as antibacterial agents:-

a) Joshi *et al.*,[1] have synthesized 16 flourine containing 2-(N-arylamino)- **2** / 2-methyl-4-arylthiazoles **3** and screened for their bactericidal activity.



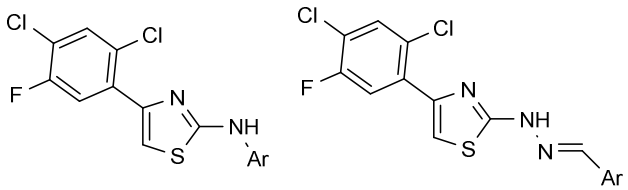
2 **3**

b) Dighe, S. N. *et al.*,[2] have reported 2-amino-4-arylthiazoles and studied their antibacterial properties. Among the synthesized compounds, compound 4 and 5 showed good activity than standard drug (Nitrofurantoin).



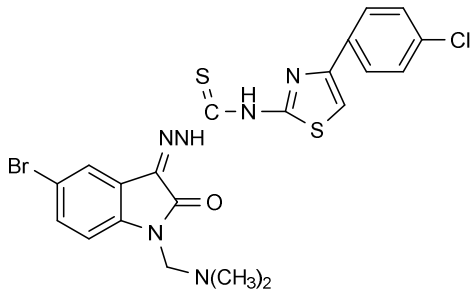
4 5

c) Hola B.H. *et al,*[3] have synthesized arylaminothiazoles **6** and arylidine/5- aryl-2-furfurylidinehydrazinothiazole **7** and were screened for antibacterial activity.



6 **7**

d) Pandeya *et al*.,[4] synthesized Schiff bases and the N-Mannich bases by the reaction of Isatin derivatives with N-[4-(49-chlorophenyl)thiazol-2-yl]thiosemicarbazide. The synthesized compounds were tested for antibacterial activity against 28 pathogenic bacteria using agar dilution method. Compound **8** was found most active compound in the synthesized series.



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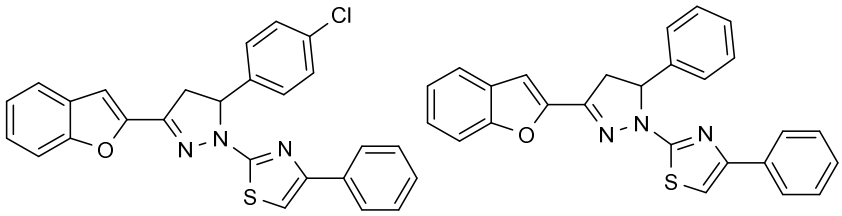
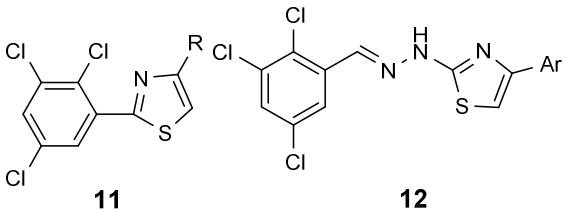
e) Abdel-Wahab *et al*.,[5] evaluated a series of 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones and 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles for antimicrobial activity. Within these series, compounds **9** and **10** showed higher activity against E. coli and S. aureus respectively than standard drug (Amoxicillin).



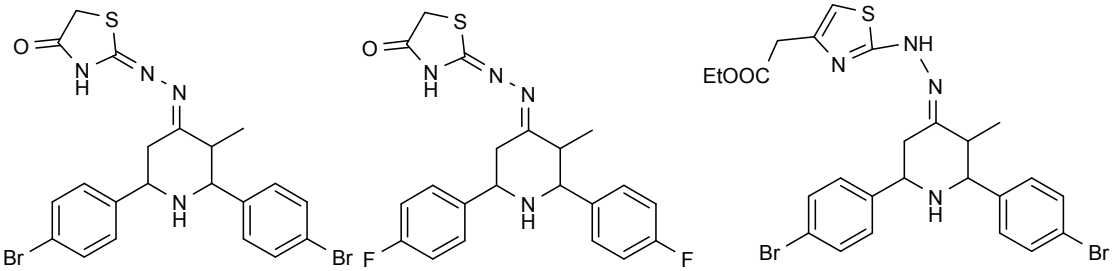
9 **10**

f) Karegoudar *et. al.*,[6] synthesized series of 4-aryl/chloroalkyl-2-(2,3,5-trichlorophenyl)-1,3-thiazoles **11** and 4-aryl-2-(2,3,5-trichlorophenylidenehydrazino)-1,3-thiazoles **12**. These compounds were tested for antibacterial activity. Among the synthesized compounds, most of the compounds showed comparable activity with standard drug (Ciprofloxacin).



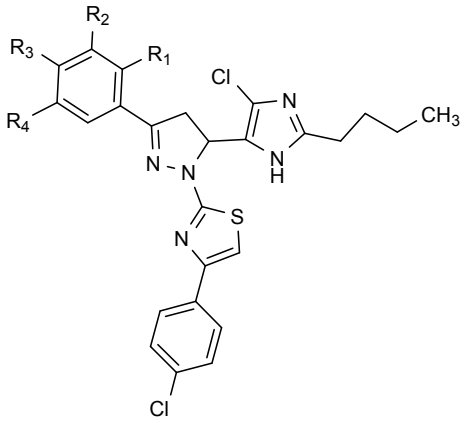
11 **12**

g) Aridoss *et. al.*,[7] synthesized stereospecific series of thiazolidinones and thiazoles derivatives and evaluated for antibacterial activity. Compound **13**, **14**, **15** showed comparable activity against standard drug (Ciprofloxacin)



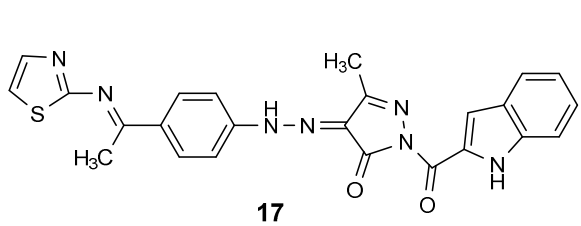
13 **14** **15**

h) Dawane B. S. *et al.*,[8] synthesized series of several 1-(4-(4'-chlorophenyl)-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1H-imidazol-5yl)-2-pyrazoline analogues and evaluated for antibacterial activity. Among the synthesized compounds, compound (**16a-e**) showed potent activities than standard drug (Tetracycline) against 4 species of bacteria.



16a, R_1 = OH, R_2 = I, R_3 = H, R^4 = Cl
16b, R_1 = OH, R_2 = Br, R_3 = H, R^4 = Cl
16c, R_1 = OH, R_2 = I, R_3 = H, R^4 = Cl
16d, R_1 = OH, R_2 = Br, R_3 = H, R^4 = Br
16e, R_1 = OH, R_2 = Cl, R_3 = H, R^4 = Cl

i) Mostafa, M. S. *et. al.*,[9] reported the synthesis of thiazole and indole substituted 3-methyl- 2-pyrazolin-5-one derivatives and their antibacterial evaluation aginst six bacterial and three fungal species. In this series, compound **17** and **18** showed good activities against bacterial and fungal species respectively.



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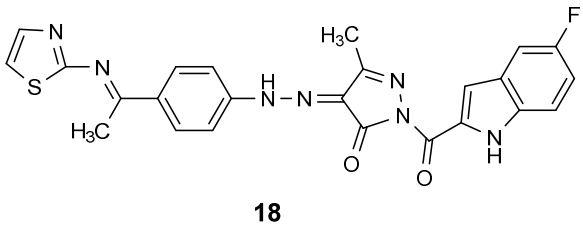
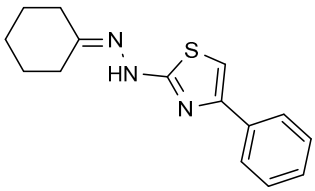


18

2) 2-Aminothiazoles as antifungal agents:-

a) Logu A.D. *et al.*,[10] have investigated *in vitro* antifungal activity cyclohexylidenehydrazo-4- phenylthiazole **19** against isolates of *candida* spp. including fluconazole-resistant *candida albicans.*



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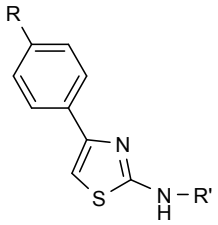
b) R. H. *et al.*,[11] have reported 2-amino-4-flouroarylthiazoles **20** as antifungal agents. These are synthesized by the reaction of various fluorinated phenacyl bromides with arylthioureas. Among the synthesied compounds many showed good antifungal activity.



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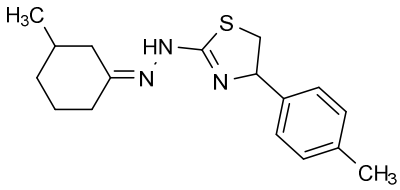
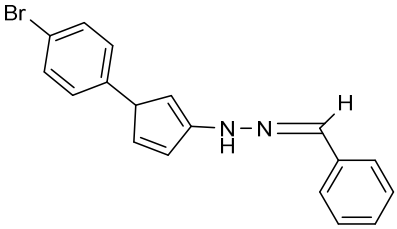
c) Chimenti F. *et al.*,[12] reported the synthesis of some new 2-sulfonamidothiazoles derivatives and evaluated for antifungal activity against candida species. In this series, compound **21** showed good activity against variety of candida species.



21

d) Bharti *et. al.*,[13] synthesized series of arylidene-2-(4-(4-methoxy/bromophenyl)thiazol-2-yl)hydrazine and 1-(4-(4-methoxy/bromophenyl)-thiazol-2-yl)-2-cyclohexylidene/cyclopentylidene hydrazine and screened for antifungal activity. Among the synthesized compounds, compounds **22**, **23**, **24**, **25** showed potent activity against four fungus species than standard drug (Fluconazole).



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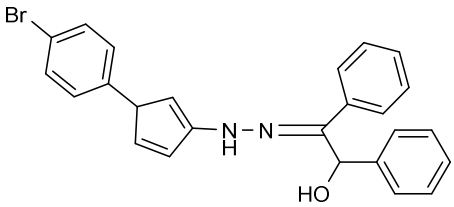

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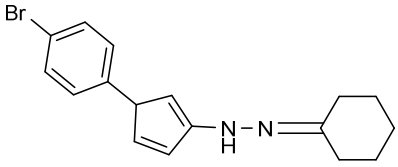

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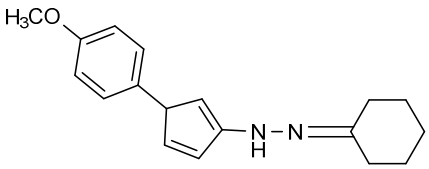
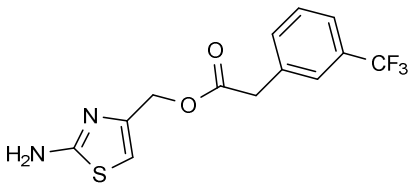


25

3) 2-Aminothiazoles as antitubercular agents:-

a) Karuvalam R. P. *et al.*,[14] reported the preparation of series of (2-aminothiazol-4-yl)methylester derivatives which have been screened against *M. tuberculosis* (H_{37}Rv strain), Mycobacterium smegmatis (ATCC 19420), Mycobacterium fortuitum (ATCC 19542). Among the synthesized compounds, compound **26, 27, 28** have shown a good antitubercular activity then standard drugs (Isoniazid and Rifampicin).



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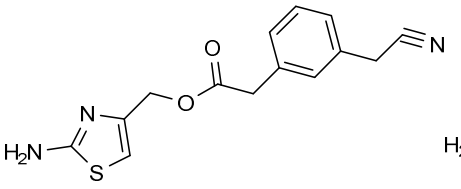

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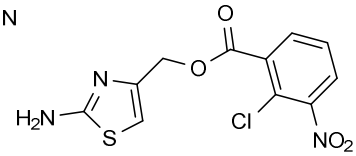
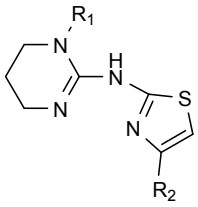


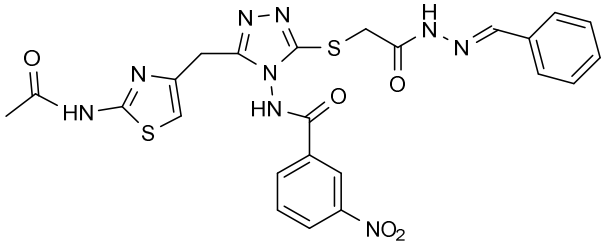
28

b) In U.S. patent,[15] 2-aminothiazole derivatives **29** have been reported as antitubercular agents. These compounds are prepared by the reaction of tetrahydro- pyrimidinylthiourea with ω-hydroxy-3-substitutedmethylacetophenones.



29

c) Shiradkar M. R. *et. al.*,[16] reported synthesis and antitubercular evaluation of series of N-{4-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-1,3-thiazol-2-yl}-2-substitutedamide derivatives (**30, 31**). Some compounds showed comparable activity with standard drug (Rifampin).



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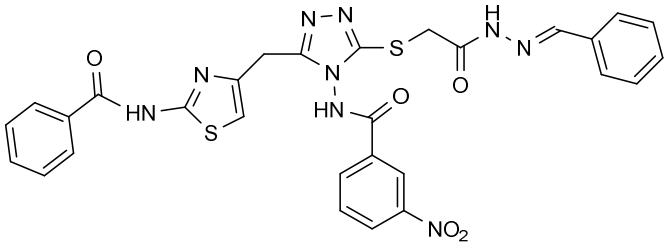
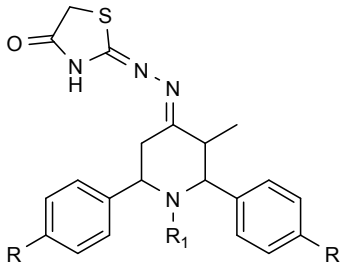
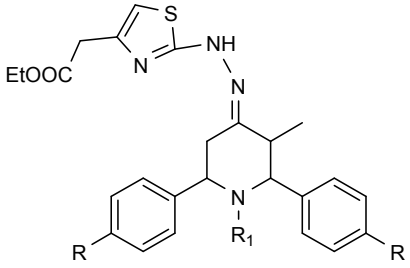


32

d) Aridoss G. *et al.*, [7] synthesised some new thiazolidinone and thiazole compounds and evaluated them for antimycobacterial activity. Among the series of the compounds, six compounds (33, 34, 35, 36, 37, 38) showed good activity than standard drug (Rifampicin).



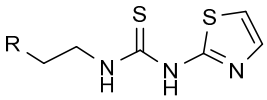


33, R = Cl, R_1 = H
34, R = Br, R_1 = H
35, R = H, R_1= Me

36, R = F, R_1 = H
37, R = OMe, R_1 = H
38, R = H, R_1= Me

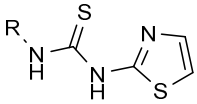
4) 2-Aminothiazoles as Anti-HIV agents:-

a) Bell W. F. *et al.*,[17] have reported phenylthiazolylthioureas **39** as anti-HIV agents. The lead compound in the series, N-(2-phenethyl)-N'-(2-thiazolyl)thiaourea inhibits HIV-1 RT using rCdG as the template with an IC_{50} of 0.9 µM.. In MT-4 cells the compound inhibits HIV-1 with ED_{50} of 1.3 µM.



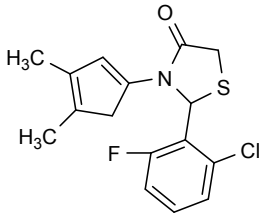
39

b) Venkatachalam T. K. *et al.*,[18] have reported aromatic and heterocyclic thiazolylthioureas **40** as an anti-HIV agents. Among these derivatives and some compounds showed subnanomolar IC_{50} values for the inhibition of HIV replication and were minimally toxic to human peripheral blood mononuclear cells (PBMC) with CC_{50} values ranging from 28 to > 100 µM. They exhibited remarkably high selectivity indices ranging from 28,000 to >100,000.



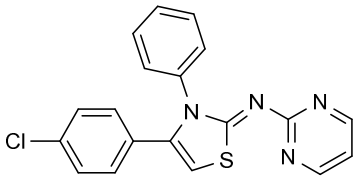
40

c) Rawal R. K. *et. al.*,[19] synthesized 2-aryl-3-heteroaryl-1,3- thiazolidin-4-ones derivatives and evaluated for anti-HIV activity by in-vitro assay. Compound **41** was found to be most active analogue among the synthesized compounds. It showed good EC50 value and low toxicity as compared to the standard drug (thiazobenzimidazole).



41

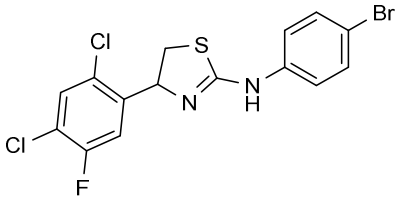
d) Turan-Zitouni *et. al.*,[20] synthesized and evaluated 3,4-diaryl-3Hthiazol-2-ylidene)pyrimidin-2-yl amine derivatives for anti-HIV activity. In this series, compound 42 showed potent activity.



42

5) 2-Aminothiazoles as anti-inflammatory agents:-

a) Hola B.H. *et al.*,[3] have synthesized arylaminothiazoles and screened for anti-inflammatory activity. Compound **43** and **44** showed comparable activity with that of standard drug (Ibuprofen).



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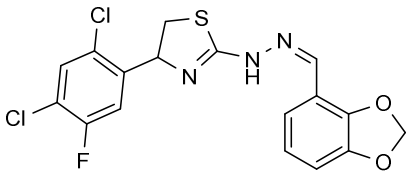
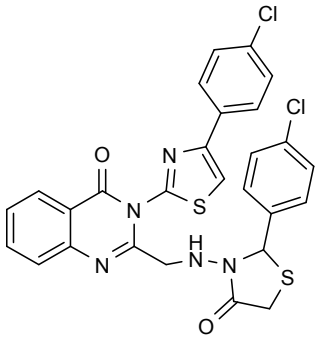


45

b) Kumar A. *et al.*,[21] reported synthesis of series of 3-[40-(p-chlorophenyl)-thiazol-20-yl]-2-[(substitutedazetidinone/thiazolidinone)-aminomethyl]-6-bromoquinazolin-4-ones. These compounds evaluated for anti-inflammatory activity by using rat paw oedema model. Compound **46** was found to be most active compound in this series and activity was comparable to that of standard drug (Phenyl-butazone).



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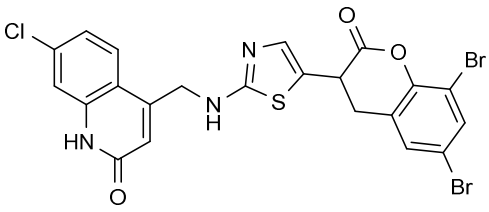
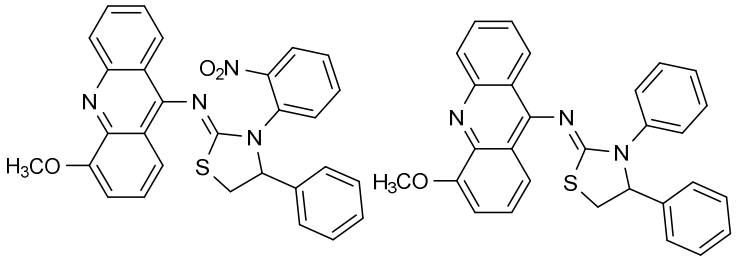
c) Kalkhambkar *et al.*,[22] reported synthesis of tricyclic thiazoles and their anti-inflammatory evaluation by using formalin induced paw oedema model. Compound **48** showed comparable activity with standard drug (Phenyl butazone).



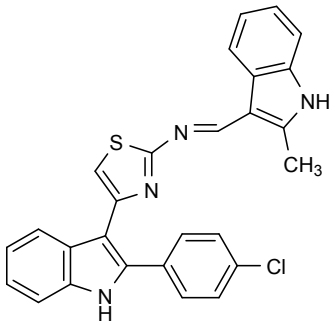
48

d) Sondhi *et. al.*,[23] synthesized acridinyl-thiazolino derivatives and subjected for anti-inflammatory activity using carrageenan induced paw oedema model. Compounds **49** and **50** showing comparable activity than standard drug (Ibuprofen).



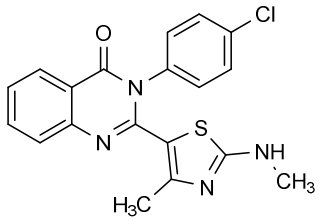
49 **50**

e) Singh N. *et. al.*,[24] reported synthesis of thiazolylformazanylindoles and their anti-inflammatory activity studies using carrageenan induced oedema model. Among the synthesized compounds, compound **51** was most potent compound with low toxicity.



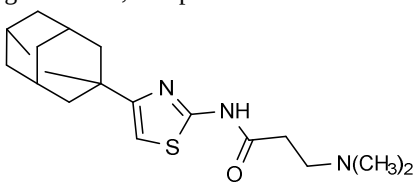
51

f) Giri S. *et. al.*,[25] reported series of 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazoline-4-one derivatives and evaluated for anti-inflammatory activity by carrageenan induced rat paw edema model. Compound **52** was found to be most active compound in this series and found to be more active than standard drug (Ibuprofen).



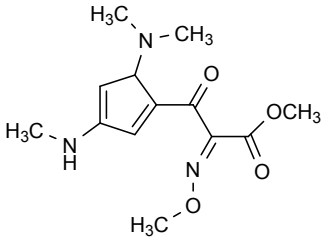
52

g) Kouatly O. *et. al.*,[26] reported synthesis of adamantane derivatives of thiazolyl-N-substituted amides derivatives and their evaluation as anti-inflammatory agents. The anti-inflammatory activity was measured by using carrageenin induced rat paw oedema model. Among the series, compound **53** found to be most potent active compound.



53

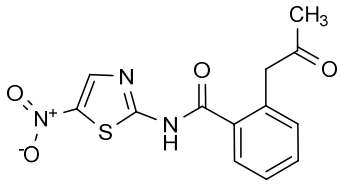
h) Franklin P. X. *et. al.*,[27] synthesized 2-amino thiazole derivative with different structural features and evaluated for anti-inflammatory activity. Anti-inflammatory activity was measured by rat paw edema model and chronic formalin induced rat paw edema model. Compound **54** showed comparable activity with standard drug (Dexamathasone).



54

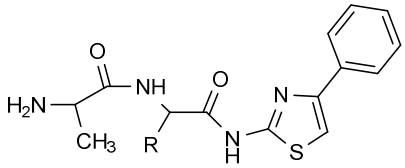
7) 2-Aminothiazoles as antiprotozoal agents:-

a) Warhurst D. C. *et al.*,[28] have reported Nitazoxanide **55** as an antiprotozoal agent. This compound and its metabolite tizoxanide were compared with metronidazole *in vitro* in microplates against six axenic isolates of *Giardia intestinalis*. Tizoxanide was eight times more active than metronidazole susceptible isolates and two times more active than metronidazole against the resistant isolates.



55

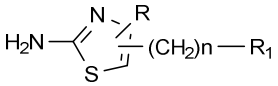
b) Himaja M. N. *et. al.*,[29] reported N-methylated thiazolylamino acids and peptide and investigated for its antihelmintic activity. Among the synthesized compound, compound **56** showed potent activity when compared with standard drug (Mebendazole).



56

7) 2-Aminothiazoles as dopaminergic agents:-

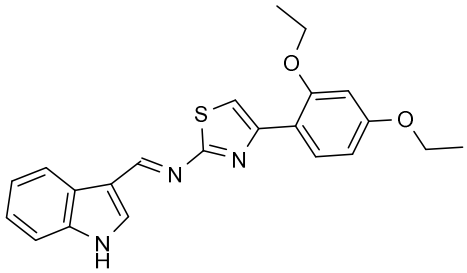
a) In W.O. patent[30] substituted 2-aminothiazole derivatives **57** has been reported as dopaminergic agents.



57

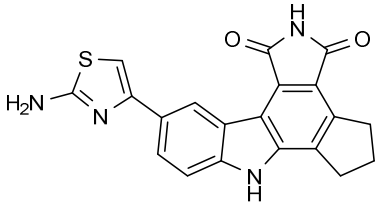
8) 2-Aminothiazoles as potent poly(ADP-ribose)polymerase-1 inhibitors:-

a) Zhang W. T. *et al.*,[31] have reported 2–aminothiazole derivatives as poly (ADP-ribose) polymerase-1 inhibitors. The inhibitory effect on PARP-1 activity and the cytoprotective action of these compounds were tested and evaluated on PC 12 cells. Among them, **58** appeared to be potent PARP-1 inhibitors with IC_{50} values less than 1µM.



58

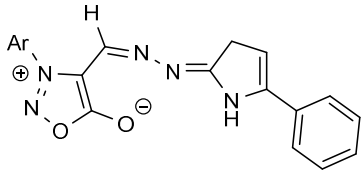
b. Dunn, D. *et. al.*,[32] reported synthesis of 4-thiazolyl substituted analogs of novel pyrrolocarbazole and their biological evaluation as poly(ADP-ribose) polymerase-1-(PARP-1) inhibitors. Among this series, compound **59** was found to be more potent.[32]



59

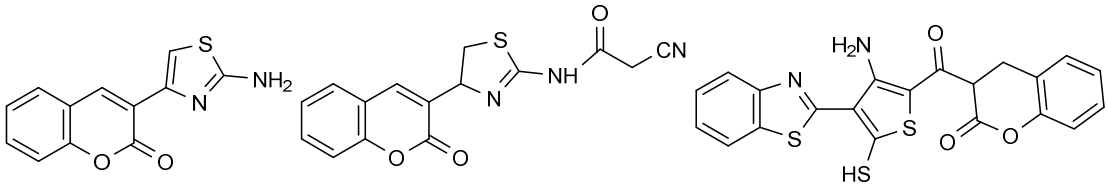
9) Neuroprotective and antioxidant activity

a) Shih M. H. *et. al.*,[33] reported synthesis of sydnonyl substituted thiazolidinone and thiazoline derivatives and their antioxidant evaluation. The antioxidant activity was measured by DPPH assay. Among these series, compound **60 e-h** represented potent antioxidant activity than standard compound (Vitamin E).



60 e-h

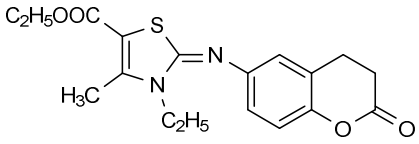
b) Gauda M. A. *et. al.*,[34] reported coumarine incorporated thiazole derivatives as antioxidant agents. Compounds **61**, **62** and **63** showed promising antioxidant activity comparable to standard (Ascorbic acid).



61 **62** **63**

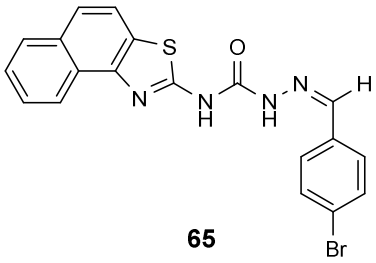
10) Anticonvulsant activity

a) Amin K. A. *et. al.*,[35] reported some thiazole substituted coumarine derivatives as an anticonvulsant agents. The anticonvulsant activity was measured by using PTZ induced seizures test. Compound **64** was most active compound among the synthesized series.



64

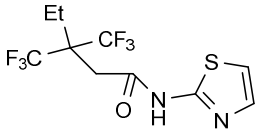
b) Azam F. *et. al.*,[36] reported synthesis of a series of N^4-(naphtha[1,2-d]thiazol-2-yl)semicarbazides and evaluated them for anticonvulsant activity by using maximal electroshock (MES) and pentylenetetrazole (PTZ)- induced seizure test. It was found that most of the compounds showed broad spectrum activity. Structure **65** represents general structure of the series.



65

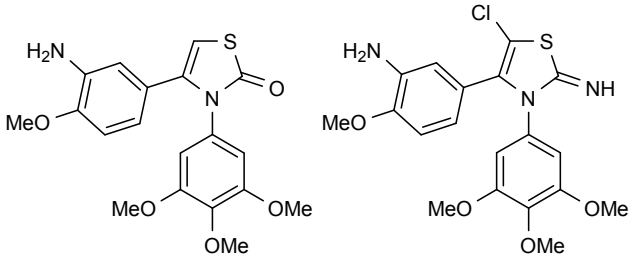
11) Anticancer activity

a) Luzina E. L. *et. al.*,[37] synthesized some N-bis(trifluoromethyl)alkyl-N′-thiazolylureas derivatives and evaluated for anticancer activity against human cancer cell lines. Among the synthesized compounds, compound **66** showed good activity against cancer cell PC-3 (prostate cancer, log GI50 −7.10).



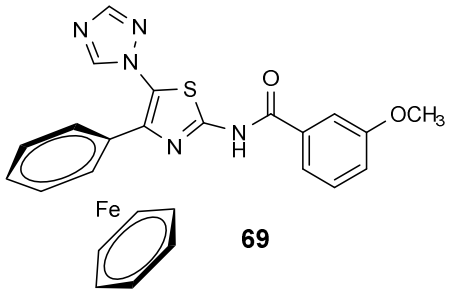
66

b) Liu *et. al.*,[38] reported synthesis of 3,4-diarylthiazol-2(3H)-ones and three 3,4-diarylthiazol-2(3H)-imines derivatives and evaluated for cytotoxicity against cancer cell lines. It was found that compound **67** (IC_{50}= 0.12 μM) and **68** (IC_{50} = 0.24 μM) showed potent activity against human CEM cells.



67 **68**

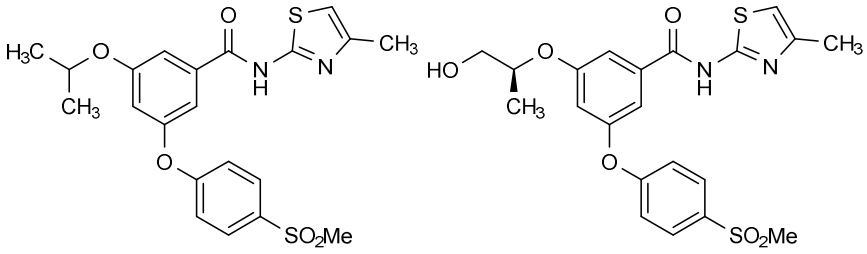
c) Shao *et al.*, [39] reportedsynthesis of ferrocenyl thiazole derivatives and their evaluation against human cancer cell lines. Compound **69** showed good activity against HL-60 (Leukemia), BGC-823 (gastric) and Hep-2 (Laryngic) cancer cell lines.



69

12) Antidiabetic activity

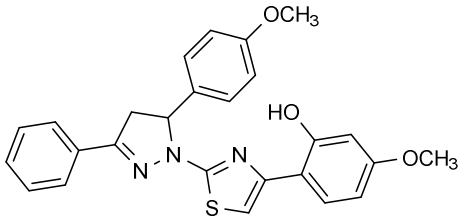
a) Iino T. *et al.*,[40] reported some thiazolylbenzamide derivatives as Glucokinase inhibitors. They synthesized series of compounds by modifying prototype of the compounds. Alkoxy and phenoxy substituents were inserted and their effect on Glucokinase inhibitor activity was checked. It was found that in the new series, compound **70** showed good activity than prototype of the compound. In another study[41], group further modified structure to yield more potent analogue **71** of the series.



70 **71**

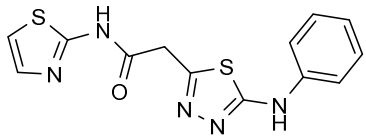
13) Antihypertensive activity

a) Turan-Zitouni G. *et. al.*,[42] reported some 1-(4-arylthiazol-2-yl)-3,5-diaryl-2-pyrazoline derivatives and evaluated them for hypotensive activity. All the synthesized compounds showed good activity than standard drug (Clonidine). Structure **72** represents the general structure of the series of the compounds.



72

b) Abdel-Wahab *et al.*,[43] synthesized thiazolylmalonamide, tetrachloroisoindolylimide, and triazole derivatives and evaluated for antihypertensive activity. Among the synthesized compounds many compounds showed good activity than standard drug (Minoxidil). These compounds were also investigated for acute toxicity study. Within these series, compound **73** showed good activity with low toxicity.

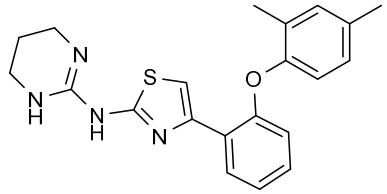


73

Drug containing 2-aminothiazole moiety:

1)Abafungin

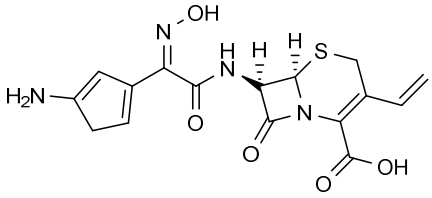
Abafungin **74** is an antimicrobial agent used for the treatment of dermatomycoses. It prevents the conversion of lanosterol to ergosterol by inhibiting cytochrome P450 enzyme 14α-demethylase and also acts on fungal cell membrane.[44]



74

2)Cefdinir

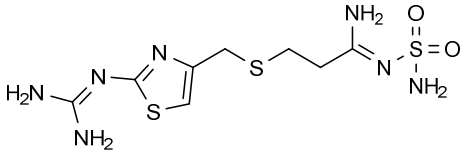
Cefdinir**75** is a third generation broad spectrum cephalosporin antibiotic used to treat some bacterial infections such as pneumonia, chronic bronchitis, sinusitis, pharyngitis, tonsillitis and some skin infections. It inhibits cell wall synthesis by acting on penicillin binding proteins (PBPs).[45]



75

3)Famotidine

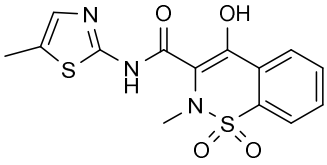
Famotidine **76** is a H_2-receptor antagonist used in the treatment of peptic ulcer disease and gastroesophageal reflux disease. It acts by inhibition of stomach acid production. Unlike other H_2 antagonist, it has no effect on cytochrome P450 enzyme system. It blocks histamine effects by binding competitively to H_2-receptors.[45,46]



76

4)Meloxicam

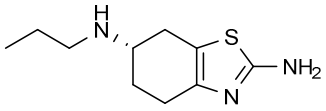
Meloxicam **77** is a nonsteroidal anti-inflammatory drug (NSAID) used in arthritis, dysmenorrhea and fever. It inhibits cyclooxygenase (COX) enzyme leading to inhibition of prostaglandin synthesis.[47]



77

5)Pramipexole

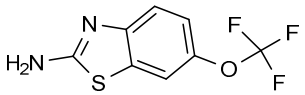
Pramipexole**78** used in the treatment of Parkinson's disease, restless legs syndrome and sometimes used in cluster headache. The mechanism action of Pramipexol is unknown but it is considered to act as dopamine receptor agonist.[47]



78

6)Riluzole

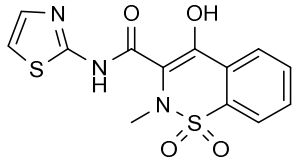
Riluzole**79** is used as an anticonvulsant drug. The mechanism of action of Riluzole is still unknown but it is considered that it indirectly prevents glutamate receptor activation.[47]



79

7)Sudoxicam

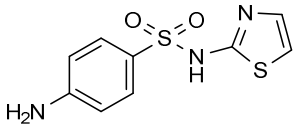
Similar to Meloxicam, Sudoxicam**80** is a nonsteroidal anti-inflammatory drug (NSAID) and it inhibits cyclooxygenase (COX) enzyme leading to inhibition of prostaglandin synthesis.[47]



80

8)Sulfathiazole:

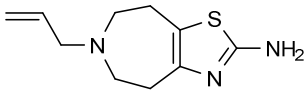
Sulfathiazole **81** is a sulpha drug used as an antimicrobial agent. It acts by inhibition of folic acid synthesis in prokaryotes. Now-a-days it is used in combination with sulfabenzamide and sulfacetamide to treat vaginal infections.[47, 48]



81

9)Talipexole

Talipexole **82** is a dopamine agonist used as an antiparkinson agent.[47]



82

CONCLUSION

2-Aminothiazole has great biological and medicinal interest. Some of the marketed drugs also possessed this heterocyclic moiety. The reported biological activities are antibacterial, antifungal, antitubercular, anti-HIV, antiprotozoal, anticancer, anti-inflammatory, dopaminergic, PARP-1 inhibitor, antioxidant, anticonvulsant, antidiabetic, antihypertensive activities. From all these activities, it is clear that 2-aminothiazoles moiety has really great interest in medicinal chemistry.

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