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

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.

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-arylamo)- 2 / 2-methyl-4-arylthiazoles 3 and screened for their bactericidal activity.
b) Dighe, S. N. et al., 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).

c) Hola B.H. et al., have synthesized arylaminothiazoles 6 and aryldine/5-aryl-2-furfuryldinehydrazinothiazole 7 and were screened for antibacterial activity.

d) Pandeya et al., 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.

e) Abdel-Wahab et al., 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).
f) Karegoudar et al., 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).

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

h) Dawane B. S. et al., synthesized series of several 1-(4-(4'-chlorophenyl)-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1H-imidazol-5-yl)-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.
i) Mostafa, M. S. et al., reported the synthesis of thiazole and indole substituted 3-methyl-2-pyrazolin-5-one derivatives and their antibacterial evaluation against six bacterial and three fungal species. In this series, compound 17 and 18 showed good activities against bacterial and fungal species respectively.

2) 2-Aminothiazoles as antifungal agents:

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

b) R. H. et al., 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 synthesized compounds many showed good antifungal activity.
c) Chimenti F. et al.,\textsuperscript{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.

d) Bharti et al.,\textsuperscript{13} synthesized series of arylidene-2-(4-(4-methoxy/bromophenyl)thiazol-2-yl)hydrazine and 1-(4-(4-methoxy/bromophenyl)-thiazol-2-yl)-2-cyclohexyldene/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).

3) 2-Aminothiazoles as antitubercular agents:-

a) Karuvalam R. P. et al.,\textsuperscript{14} reported the preparation of series of (2-aminothiazol-4-yl)methylester derivatives which have been screened against \textit{M. tuberculosis} (H\textsubscript{3}Rv strain), \textit{Mycobacterium smegmatis} (ATCC 19420), \textit{Mycobacterium fortuitum} (ATCC 19542). Among the synthesized compounds, compound 26, 27, 28 have shown a good antitubercular activity then standard drugs (Isoniazid and Rifampicin).
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.

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\begin{align*}
26 & \begin{array}{c}
\text{H}_2\text{N} \\
\text{N} \\
\text{S} \\
\text{O} \\
\text{C}\text{F}_3
\end{array} \\
27 & \begin{array}{c}
\text{H}_2\text{N} \\
\text{N} \\
\text{S} \\
\text{O} \\
\text{R}
\end{array} \\
28 & \begin{array}{c}
\text{H}_2\text{N} \\
\text{N} \\
\text{S} \\
\text{O} \\
\text{Cl} \\
\text{NO}_2
\end{array}
\end{align*}
\]

29

R₁

R₂

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).

\[
\begin{align*}
30 & \begin{array}{c}
\text{O} \\
\text{N} \\
\text{S} \\
\text{N} \\
\text{O} \\
\text{R}
\end{array} \\
31 & \begin{array}{c}
\text{O} \\
\text{N} \\
\text{S} \\
\text{N} \\
\text{O} \\
\text{R}
\end{array} \\
32 & \begin{array}{c}
\text{O} \\
\text{N} \\
\text{S} \\
\text{N} \\
\text{O} \\
\text{R}
\end{array}
\end{align*}
\]

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

a) Bell W. F. et al., have reported phenylthiazolylthioureas as anti-HIV agents. The lead compound in the series, N-(2-phenethyl)-N'-(2-thiazolyl)thiourea 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.

b) Venkatachalam T. K. et al., have reported aromatic and heterocyclic thiazolylthioureas 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.

c) Rawal R. K. et al., 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 EC_{50} value and low toxicity as compared to the standard drug (thiazobenzimidazole).

d) Turan-Zitouni et al., 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.
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).

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).

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).

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

f) Giri S. et al.,\textsuperscript{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).

g) Kouatly O. et al.,\textsuperscript{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 carrageenan induced rat paw oedema model. Among the series, compound 53 found to be most potent active compound.

h) Franklin P. X. et al.,\textsuperscript{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).
7) 2-Aminothiazoles as antiprotozoal agents:-
   a) Warhurst D. C. et al., have reported Nitazoxanide 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.

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

7) 2-Aminothiazoles as dopaminergic agents:-
   a) In W.O. patent substituted 2-aminothiazole derivatives has been reported as dopaminergic agents.

8) 2-Aminothiazoles as potent poly(ADP-ribose)polymerase-1 inhibitors:-
   a) Zhang W. T. et al., 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, appeared to be potent PARP-1 inhibitors with IC<sub>50</sub> values less than 1µM.
b. Dunn, D. et al.,\textsuperscript{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.\textsuperscript{33}

9) Neuroprotective and antioxidant activity

a) Shih M. H. et al.,\textsuperscript{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).

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

10) Anticonvulsant activity

a) Amin K. A. et al.,\textsuperscript{35} reported some thiazole substituted coumarine derivatives as anticonvulsant agents. The anticonvulsant activity was measured by using PTZ induced seizures test. Compound 64 was most active compound among the synthesized series.
b) Azam F. et al., reported synthesis of a series of N^2-(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.

11) Anticancer activity
a) Luzina E. L. et al., synthesized some N-bis(trifluoromethyl)alkyl-N'-thiazoylureas 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).

b) Liu et al., 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 \mu M) and 68 (IC_{50} = 0.24 \mu M) showed potent activity against human CEM cells.

c) Shao et al., reported synthesis 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.
12) Antidiabetic activity

a) Iino T. et al., reported some thiazolylbenzamide derivatives as Glucokinase inhibitors. They synthesized series of compounds by modifying prototype of the compound. 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, group further modified structure to yield more potent analogue 71 of the series.

b) 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.

13) Antihypertensive activity

a) Turan-Zitouni G. et al., 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.

b) Abdel-Wahab et al., synthesized thiazolylmalonamide, tetrachloroisoindolylimide, and triazole derivatives and evaluated for antihypertensive activity. These compounds were also investigated for acute toxicity study. Within these series, compound 73 showed good activity with low toxicity.
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

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

3) Famotidine
Famotidine 76 is a H2-receptor antagonist used in the treatment of peptic ulcer disease and gastroesophageal reflux disease. It acts by inhibition of stomach acid production. Unlike other H2 antagonist, it has no effect on cytochrome P450 enzyme system. It blocks histamine effects by binding competitively to H2-receptors.45,46

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

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.48
6) Riluzole
Riluzole\textsuperscript{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.\textsuperscript{47}

7) Sudoxicam
Similar to Meloxicam, Sudoxicam\textsuperscript{80} is a nonsteroidal anti-inflammatory drug (NSAID) and it inhibits cyclooxygenase (COX) enzyme leading to inhibition of prostaglandin synthesis.\textsuperscript{47}

8) Sulfathiazole:
Sulfathiazole\textsuperscript{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.\textsuperscript{47, 48}

9) Talipexole
Talipexole\textsuperscript{82} is a dopamine agonist used as an antiparkinson agent.\textsuperscript{47}

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.

REFERENCES
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