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Diverse biological activities of Thiazoles: A Retrospect

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Abstract
Many compounds bearing five membered heterocyclic rings in their structure have an extensive spectrum of biological activities. The search for new biologically active thiazole analogues continues to be an area of intensive investigation in medicinal chemistry. The present review describes ongoing research in search for new thiazole compounds that can prove useful for the design of future target and development of new drug molecule.

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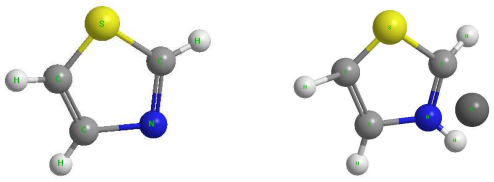
INTRODUCTION

Thiazoles are a class of organic compounds related to azoles with a common thiazole functional group. Thiazole is aromatic, heterocyclic organic compound that has a five-membered molecular ring structure, C_3H_3NS.

The thiazole moiety is a crucial part of vitamin B_1 (thiamine) and epothilone, benzothiazoles are important thiazoles example eluciferin. Thiazoles have been used to give N-S free carbenes and transition metal carbene complexes. The amino atom can be alkylated to create a thiazolium cation; thiazolium salts are catalysts in the Stetter reaction and the Benzoin condensation. Thiazole dyes are used for dying cotton. Thiazoles are well represented in bisomolecules.



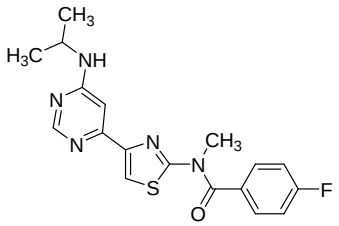
3D structure of thiazole and thiazolium salts

BIOLOGICAL ACTIVITIES

Anticonvulsant activity

Satoh *et al*[1] identified 4-fluoro-*N*-[4-[6-(isopropylamino)-pyrimidin-4-yl]-1,3-thiazol-2-yl]-*N*-methyl benzamide **(1)** as a potent mGluR1 antagonist as PET tracer, it would have great potential for elucidation of mGluR1 functions in human.

Agarwal *et al*[2] synthesized a series of 5-[(*N*-substituted benzylidenylimino)amino]-2-oxo/thio-barbituric acids and screened, *in vivo* for anticonvulsant and acute toxicity studies. The compounds **(2a)** and **(2b)** found to be more potent.



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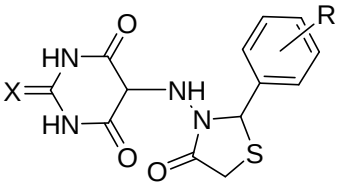
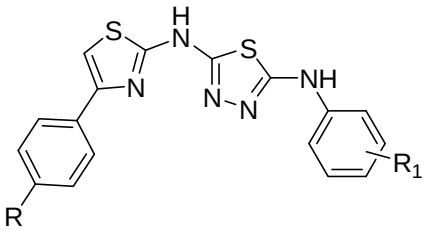


(2a & 2b)

2a, X = S, R = 4-OCH_3, **2b**, X = S, R = 3-OCH_3, 4-OH

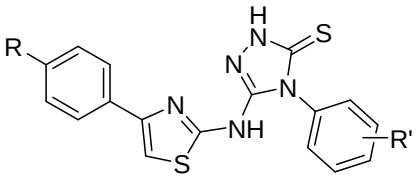
Siddiqui *et al*[3] synthesized a series of thiazole-substituted thiadiazole derivatives and screen for anticonvulsant activity *in vivo* by models such as MES and scPTZ. Three compounds **(3a-c)** were found to be potent.

Siddiqui *et al*[4] synthesized a series of 3-[4-(substituted phenyl)-1,3-thiazol-2-ylamino]-4-(substituted phenyl)-4,5-dihydro-1*H*-1,2,4-triazole-5-thiones and screened for *in vivo* anticonvulsant activity via MES and scPTZ. Compounds **(4a** and **4b)** showed significant anticonvulsant activity with ED_{50} values 23.9 mg/kg and 13.4 mg/kg respectively in MES screen and 178.6 mg/kg and 81.6 mg/kg respectively in scPTZ test.



(3a-c)

3a, R = Br, R_1= OCH_3
3b, R = NO_2, R_1= 4-CH_3
3c, R = NO_2, R_1 = 4-OCH_3

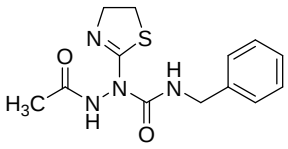


(4a & b)

4a, R = Cl, R'= Br
4b, R = 4-CH_3, R' = 2-CH_3

Banerjee *et al*[5] studied the SAR of over 250 compounds.1-acetyl-4-benzyl-2-(thiazol-2-yl)semicarbazide **(5)**, displayed moderate-excellent activity in mice (MES ip ED_{50} =22 mg/kg, PI = 5.4) and rat (MES po ED_{50} = 6.2 mg/kg, Tox TD_{50}> 250) which exceed that of phenytoin.

Siddiqui *et al*[6] prepared several heteroaryl semicarbazones and evaluated for anticonvulsant activity utilizing scPTZ and MES tests at 30, 100 and 300 mg/kg dose levels. Compounds **(6a-c)** exhibited significant anticonvulsant activity at 30 mg/kg dose level comparable to the standard drug phenytoin.



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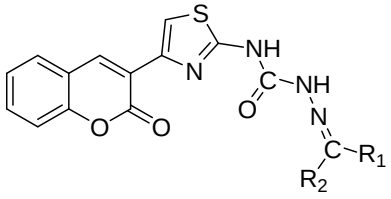


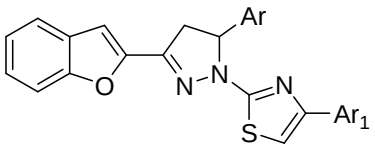
(6a-c)

6a, R_1 = 3,4-CH_3.C_6H_3, R_2 = CH_3
6b, R_1 = 2-OCH_3.C_6H_4, R_2 = CH_3
6c, R_1 = 4-Br.C_6H_4, R_2 = CH_3

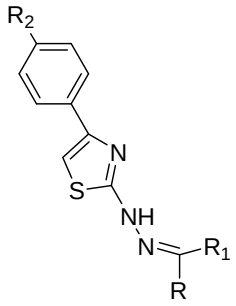
Antimicrobial activity

Abdel-Wahab *et al*[7] synthesized various pyrazoline incorporated thiazole derivatives **(7a-d)** and screened for antibacterial and antifungal activity against *Escherichia coli* and *Aspergillus niger*.

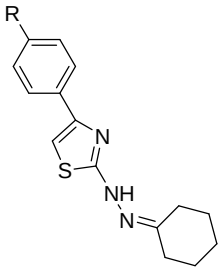
A series of arylidene-2-(4-(4-methoxy/bromophenyl) thiazol-2-yl)hydrazines and 1-(4-(4-methoxy/bromo phenyl)-thiazol-2-yl)-2-cyclohexylidene/cyclopentylidene hydrazines were synthesized, and screened for antimicrobial and anti-fungal activities by Bharti *et al*[8]. Among the tested compounds **(8a-c**, **9a-b**, **10a** and **10b)** were more potent.



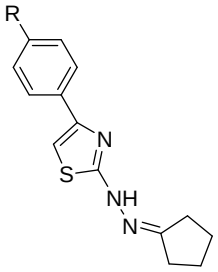
(7a-d)
7a, Ar = Ar_1 = Ph
7b, Ar = Ph, Ar_1 = 4-Br.C_6H_4
7c, Ar = 4-Cl.C_6H_4, Ar_1 = Ph
7d, Ar = 4-Cl.C_6H_4, Ar_1 = 4-Br.C_6H_4



(8a-c)
8a, R = H, R_1 = C_6H_5, R_2 = OCH_3
8b, R = H, R_1 = C_6H_5, R_2 = Br
8c, R = C_6H_5, R_1 = -CH(OH)C_6H_5, R_2 = Br



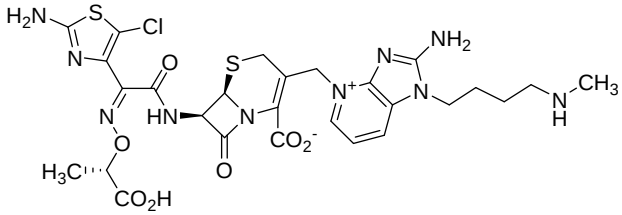
(9a & b)
9a, R = OCH_3, **9b**, R = Br



(10a & b)
10a, R = OCH_3, **10b**, R = Br

A novel series of 7*β*-[2-(2-amino-5-chlorothiazol-4-yl)-2(*Z*)-((*S*)-1-carboxy ethoxyimino)acetamido] cephalosporins bearing various pyridinium groups at the C-3′ position were synthesized by Yamawaki *et al*[9] . Among these cephalosporins, 2-amino-1-(3-methylamino-propyl)-1*H*-imidazo-[4,5-b]-pyridinium group at the C-3' position **(11)** showed potent and well-balanced antibacterial activities against *P. aeruginosa* and other Gram-negative pathogens.

Khalil *et al*[10] synthesized some 3-oxo-propiononitrile and thioamide derivatives for new thiazole, out of these compound **(12)** showed potent antibacterial activity.



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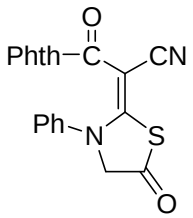
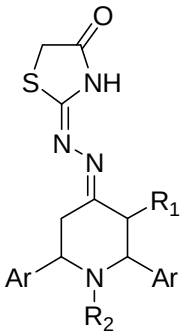


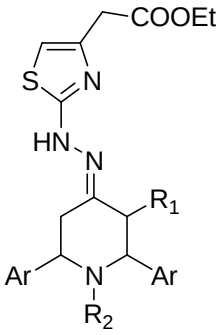
(12)

A stereospecific synthesis of some thiazolidinones and thiazoles was achieved conveniently by Aridoss *et al*[11] and Antimycobacterial activity were tested against *Mycobacterium tuberculosis* indicated that

some compounds **(13a-c)** and **(14a-c)** exhibited two fold enhanced potency than Rifampicin.

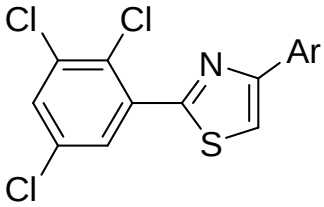


(13a-c)
13a, $R_1 = CH_3$ $R_2 = H$, Ar = C_6H_5
13b, $R_1 = C_2H_5$, $R_2 = H$, Ar = C_6H_5
13c, $R_1 = CH_3$, $R_2 = CH_3$, Ar = C_6H_5

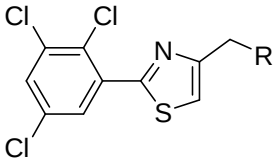


(14a-c)
14a, $R_1 = CH_3$ $R_2 = H$ Ar = 4-F-C_6H_4
14b, R_1= CH_3, $R_2 = H$, Ar = 4-OCH_3-C6H4
14c, $R_1 = CH_3$, $R_2 = CH_3$, Ar = C_6H_5

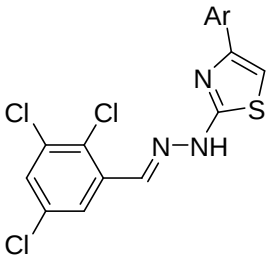
Karegoudar *et al*[12] reported a series of novel 4-aryl/chloroalkyl-2-(2,3,5-trichlorophenyl)-1,3-thiazoles and by condensing 2,3,5-trichlorobenzenecarbothioamide with phenacyl bromide afforded 4-aryl-2(2,3,5-trichlorophenylidene hydrazino) -1,3-thiazoles in good yield. Among these compounds **(15a-d), (16a-b)** and **(17a-b)** possessed potent activity.



(15a-d)
15a, Ar = 3-pyridyl, **15b**, Ar = biphenyl
15c, Ar = 4-NO_2-C_6H_4, **15d**, Ar = 4-Cl-C_6H_4



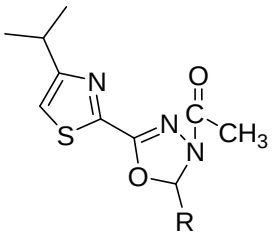
(16a-b)
16a, R = piperidino
16b, R = 4-mercaptopyrazolopyrimi



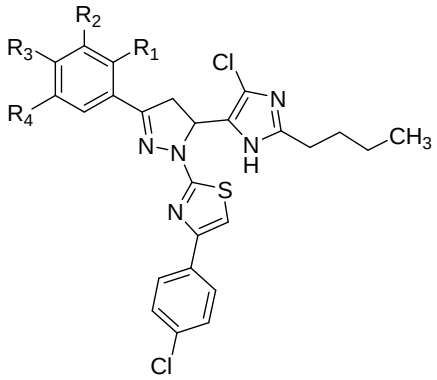
(17a-b)
17a, Ar = 3-pyperidyl, **17b,** Ar = 4-NO_2

Mallikarjuna *et al*[13] synthesized a series of 4-isopropylthiazole-2-carbohydrazide analogs, derived clubbed oxadiazole-thiazole and triazole-thiazole derivatives and evaluated them for *in vitro* antibacterial, antifungal and antitubercular activity against *Mycobacterium tuberculosis* H_{37}Rv strain by broth dilution assay method. The synthesized compounds **(18a-c)** showed potent antitubercular efficacy.

Several 1-(4-(4'-chlorophenyl)-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1*H*-imidazol-5yl)-2-pyrazoline derivatives were prepared by Dawane *et al*[14] and tested for antibacterial and antifungal activity. Among these compounds, **(19a-e)** exhibited stronger antifungal and antibacterial activities.



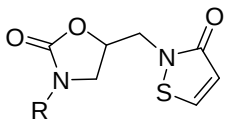
(18a-c)
18a, R = C_6H_5
18b, R = 3,4,5-$(OCH_3)_3$-C_6H_2
18c, R = 4-OH-C_6H_4



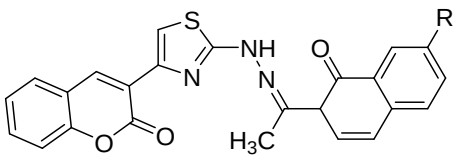
(19a-e)
19a, R_1 = OH, R_2 = I, R_3 = H, R_4 = Cl
19b, R_1 = OH, R_2 = Br, R_3 = H, R_4 = Cl
19c, R_1 = OH, R_2 = I, R_3 = H, R_4 = Cl
19d, R_1 = OH, R_2 = Br, R_3 = H, R4 = Br
19e, R_1 = OH, R_2 = Cl, R_3 = H, R_4 = Cl

Adibpour *et al*[15] reported the synthesis and antibacterial activity of several new 5-((3-oxoisothiazol-2(3*H*)-yl)methyl)-3-phenyloxazolidin-2-ones and analogous 2-(4-substituted phenyl)-3(2*H*)-isothiazolones substituted at 4 and/or 3-positions of the phenyl moiety with different groups of which some have shown to increase the antibacterial activity of both 3-aryl-2-oxazolidinones and 3(2*H*)-isothiazolones was described. The compounds **(20a-c)** showed potent activity.

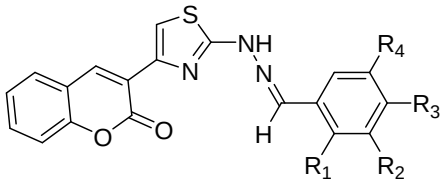
Arshad *et al*[16] synthesized two novel series of thiazolylcoumarin derivatives and screened *in vitro* for antibacterial activity against *Mycobacterium tuberculosis* and *Candida albicans*. The three compounds **(21a**, **21b** and **22)** exhibited very good activity.



(20a-c)
20a, R = C_6H_5, **20b**, R = 4-F-C_6H_4
20c, R = -CH_2-C_6H_4



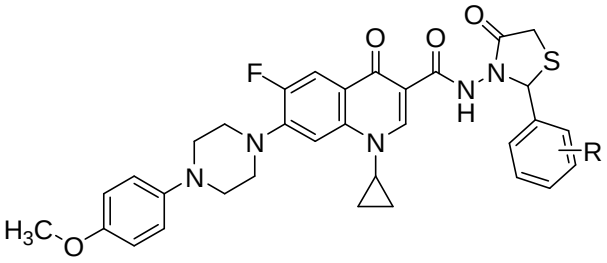
(21a & b)
21a, R= Br, **21b**, R = OH



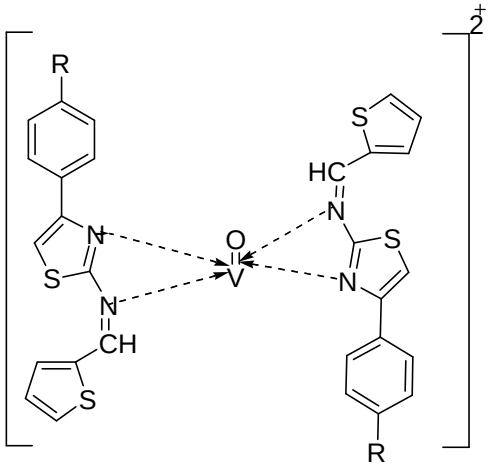
(22)
22, R_1 = OH, R_2 = H, R_3 = H, R_4 = Br

Patel *et al*[17] synthesized 2-substituted phenyl-3-{1-cyclopropyl-6-fluoro- 7-[4-(4-methoxyphenyl piperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-1,3-thiazolidin-4-ones and screened for antifungal and antibacterial activities. Compounds **(23a-c)** showed excellent activity against fungi, whereas compounds **(23d-f)** displayed against bacteria.

Sindhu *et al*[18] synthesized oxovanadium (IV) complexes of Schiff's bases **(24)**. These complexes were monomeric possessing a 1:2 (metal: ligand) stoichiometry and screened compounds evaluated for antibacterial activity.



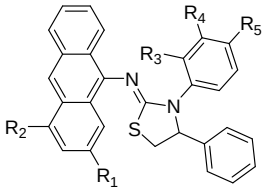
(23a-f)
23a, R = 3-OCH_3, **23b**, R = 4-OH, **23c**, R = OH
23d, R = 2-NO_2, **23e**, R = 2-Cl, **23f**, R = 4-Cl



(24)
24, R = H, OH, OCH_3, NO_2, Cl, Br, CH_3.

Anti-inflammatory activity

Sondhi *et al*[19] reported variety of *N*-(4-phenyl-3-(2′,3′,4′-(un)substituted phenyl)thiazol-2(3*H*)-ylidene)-2,4-(un)substituted acridin-9-amine and 1-[(2,4-(un)substituted acridin-9-yl)-3-(4-phenyl-3-(2′,3′,4′-(un)substituted phenyl)thiazol-2(3*H*)-ylidene)]isothiourea derivatives and screened for anti-inflammatory, analgesic and kinase (CDK1, CDK5 and GSK3) inhibition activities. Out of these compounds, **(25)** and **(26)** showed potent activity.



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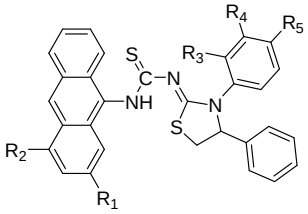
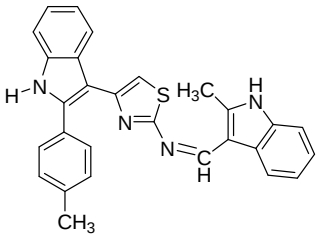


(26)

25, R_1 = H, R_2 = OCH_3, R_3 = CH_3, R_4 = CH_3, R_5 = H
26, R_1 = H, R_2 = CH_3, R_3 = R_4 = H, R_5 = CH_3

A series of 3-(2'-substituted indolidene aminothiazol-4'-yl)-2-(4-chlorophenyl)indoles were synthesized by Singh *et al*[20] and them evaluated for their anti-inflammatory activity against carrageenan induced edema in albino rats at a dose of 50 mg/kg p.o. The most active compound of this series **(27)** was found to show higher percent of inhibition of edema, lower ulcerogenic liability and acute toxicity than phenyl butazone.

Kalkhambkar *et al*[21] prepared tri heterocyclic thiazoles containing coumarin and carbostyril (1-aza coumarin) by the reaction of the *in situ* generated 4-thioureidomethyl carbostyril and 3-bromoacetyl coumarins and tested for *in vivo* analgesic and anti-inflammatory activities. Hence the compounds **(28a-f)** seem to be more effective as slow acting anti-inflammatory agents.



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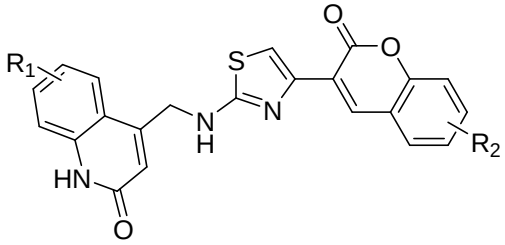


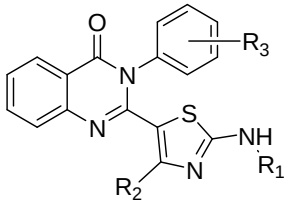
(28a-f)

28a, R_1 = 6-Cl, R_2 = 6-Br, **28b**, R_1 = 7-Cl, R_2 = 6-Br
28c, R_1 = 8-CH_3, R_2 = 6'-Br, **28d,** R_1 = 6-Cl, R_2 = 6',8'-Br
28e, R_1 = 7-Cl, R_2 = 6',8'-Br, **28f**, R_1 = 8-CH_3, R_2 = 6',8'-Br

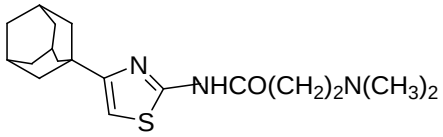
A series of 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3*H*-quinazoline-4-one derivatives were designed and synthesized by Giri *et al*[22] and evaluated for anti-inflammatory activity *in vivo* for acute inflammation. Two of the compounds **(29a)** and **(29b)** turned out to be the most promising dual inhibitors of NF-kB and AP-1 mediated transcriptional activation with an IC_{50} of 3.3 mM for both.

A series of adamantane derivatives of thiazolyl-*N*-substituted amides were synthesized by Koualty *et al*[23] and tested for anti-inflammatory activity as well as lipoxygenase and cycloxygenase inhibitory actions. Among the tested compounds, **(30)** showed potent activity.

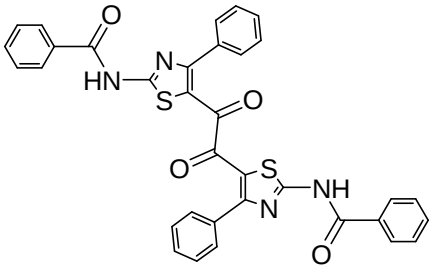
Substituted thiazoles with different structural features were synthesized and screened for their anti-inflammatory activity by Franklin *et al*[24] in acute carrageen in induced rat paw edema model and chronic formalin induced rat paw edema model. The compound **(31)** showed potent anti-inflammatory activity.



(29a & 29b)
29a, R_1 = CH_3, R_2 = CH_3, R_3 = 4-Cl
29b, R_1 = p-Cl-Ph, R_2 = CH3, R_3 = 4-Cl



(30)

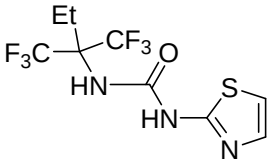


(31)

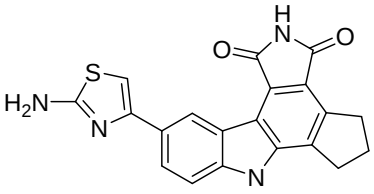
Anticancer activity

A number of *N*-bis(trifluoromethyl)alkyl-*N′*-thiazolyl and benzothiazolylureas have been synthesized and evaluated by Luzina *et al*[25] against the human cancer cell lines. The most sensitive cell lines relative to the tested compound was: **(32)** PC-3 (prostate cancer, log GI_{50} −7.10), and SR (leukemia, log GI_{50} −5.44) human cancer cells.

Synthesis and activity of a series of 4-thiazolyl substituted analogs of novel pyrrolocarbazole as poly (ADP-ribose) polymerase-1-(PARP-1) inhibitors have been disclosed by Dunn *et al*[26]. Among these compounds, **(33)** found to be more potent.

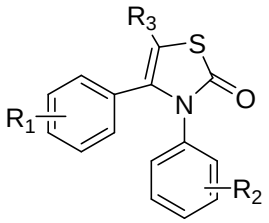


(32)



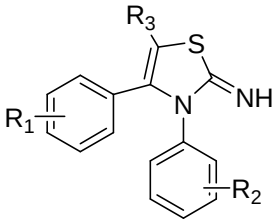
(33)

A series of 3,4-diarylthiazol-2(3*H*)-ones and three 3,4-diarylthiazol-2(3*H*)-imines were synthesized and evaluated by Liu *et al*[27] for their cytotoxicity in a panel of human cancer cell lines. Two compounds **(34)** and **(35)** showed potential anticancer activity against human CEM cells with IC_{50} values of 0.12 and 0.24 μM, respectively.



(34)

34, R_1 = 3-NH_2, 4-OMe, R_2 = 3',4',5'-$(OMe)_3$, R_3 = H



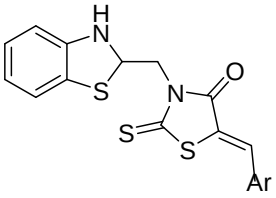
(35)

35, R_1 = 3-NH_2, 4-OMe, R_2 = 3',4',5'-$(OMe)_3$, R_3 = Cl

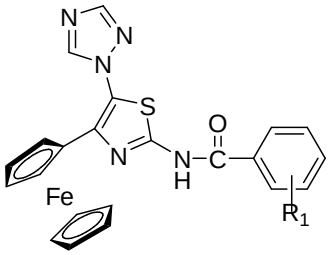
Havrylyuk *et al*[28] synthesized a series of 5-arylidene derivatives and evaluated them for antitumor activity. Among the tested compounds, 2-{2-[3-(benzothiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidene methyl]-4-chlorophenoxy}-*N*-(4-methoxyphenyl)acetamide **(36)** were found to be the most active with log GI_{50} and log TGI values 5.38 and 4.45 respectively.

Shao *et al*[29] synthesized novel ferrocenyl containing thiazole derivatives from 2-amino-4-ferrocenyl-5-(1*H*-1,2,4-triazole-1-yl)- 1,3-thiazole and substituted benzoyl chloride and evaluated of anticancer activities. Thiazole **(37a)** and **(37b)** showed good inhibition percentages against human cancer cell lines.

Marini *et al*[30] studied that incorporation of planar heterocyclic thiazole nucleus in place of one of the amine like clinically ineffective trans-$[PtCl_2(NH_3)_2]$ (transplatin) to obtained compound **(38)**. On the basis of results they concluded that such compounds significantly enhanced anticancer activity.

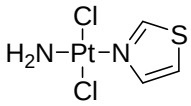


36, Ar = 2-(4-OMe-$C_6H_4NHCOCH_2O$)-5-Cl-C_6H_5



(37a-b)

37a, R_1 = *m*-OCH_3 **37b,** R_1 = *p*-OCH_3

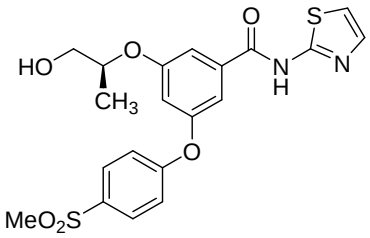


(38)

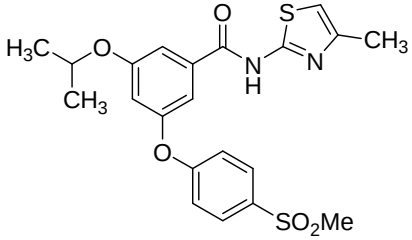
Antidiabetic activity

The optimization of the led GK activator to 3-[(1*S*)-2-hydroxy-1-methylethoxy]-5-[4-(methylsulfonyl) phenoxy]-*N*-1,3-thiazol-2-ylbenzamide **(39)**, a potent GK activator was described by Iino *et al*[31]. Following oral administration, this compound exhibited robust glucose lowering in diabetic model rodents.

Identification and synthesis of novel 3-alkoxy-5-phenoxy-*N*-thiazolyl benzamides as glucokinase activators were described by Iino *et al*[32]. Removal of an aniline structure of the prototype led and incorporation of an alkoxy or phenoxy substituent led to the identification of 3-isopropoxy-5-[4-(methylsulfonyl)phenoxy]-*N*-(4-methyl-1,3-thiazol-2-yl)benzamide **(40)** as a novel, potent, and orally bioavailable GK activator.



(39)

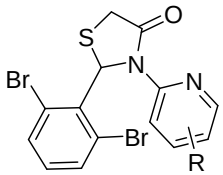


(40)

Anti-HIV activity

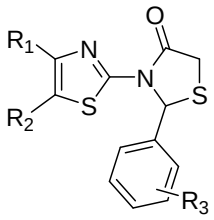
Rawal *et al*[33] synthesized a series of 2-(2,6-dibromophenyl)-3-heteroaryl-1,3-thiazolidin-4-one and evaluated as selective human immunodeficiency virus type-1 reverse transcriptase (HIV-1, RT) enzyme inhibitors. *In vitro* cell assay showed that eight compounds **(41a-h)** effectively inhibited HIV-1 replication at 20-320 nM concentrations with minimal cytotoxicity in MT-4 as well as in CEM cells.

Rawal *et al*[34] synthesized a series of 2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones. Compounds having isothiourea or thiourea functional group showed high anti-HIV-1 activity. *In vitro* tests showed that the compound **(42)** exhibited EC_{50} at 0.26 lM with minimal toxicity in MT-4 cells as compared to 0.35 µM for thiazobenzimidazole (TBZ).



(41a-h)

41a, R = furan-2ylmethyl, **41b**, R = pyridin-2yl
41c, R = 6-methyl-pyridin-2yl,
41d, R = pyrimidin-2yl
41e, R = 4-methyl-pyrimidin-2yl, \
41f, R = 4,6-dimethyl-pyridin-2yl
41g, R = 4-methyl-6-trifluoromethylpyrimidin-2-yl,
41h, R = 4,5,6-trimethylpyrimidin-2-yl



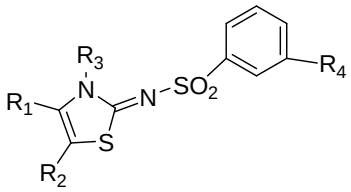
(42)

42, $R_1 = R_2 = CH_3$, R_3 = 2'-Cl, 6'-F

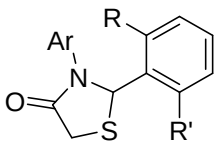
Masuda *et al*[35] synthesized various *N*-3-alkylated thiazolidene sulfonamide. The effects of different bases and solvents were investigated, and the NaH–THF combination was found to be the most effective at conferring high yields and *endo*-selectivity. Among the tested compounds an *endo*-alkylated compound **(43)** found to be showed more potent antiretroviral activity.

.Barreca *et al*[36] synthesized a series of 2,3-diaryl-1,3-thiazolidin-4-ones. They revealed that some potent compounds **(44a** and **44b)** are effective for inhibiting HIV-1 replication at nanomolar concentrations so considered as non-nucleoside HIV-1 RT inhibitors (NNRTIs).

Turan-Zitouni *et al*[37] synthesized 3,4-diaryl-3*H*-thiazol-2-ylidene)pyrimidin-2-yl amine derivatives and evaluated them for anti-HIV activity. Among the tested compounds the compound **(45)** showed excellent activity.



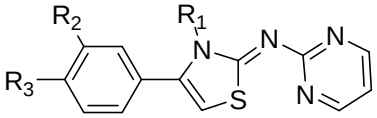
43, $R_1 = CH_3$, R_2 = t-Bu, $R_3 = CH_3$, $R_4 = NO_2$



(44a-b)

44a, R = F, R'= F, Ar = C_5H_4N

44b, R = Cl, R' = Cl, Ar = C_5H_4N

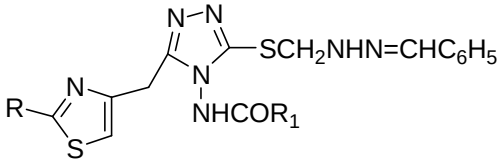


45, $R_1 = C_6H_5$, R_2 = H, R_3 = Cl

Anti-Alzheimer activity

A novel clubbed triazolylthiazole series of cdk5/p25 inhibitors, potentially useful for the treatment of Alzheimer's disease, was disclosed by Shiradkar *et al*[38]. Evaluation of the SAR of substitution within these series had allowed the identification of compounds **(46a)** and **(46b)** which significantly reduce brain cdk5/p25 and thus have potential as possible treatments for Alzheimer's disease.

Helal *et al*[39] used high-throughput screening with cyclin-dependent kinase 5 (cdk5)/p25 that led to the discovery of *N*-(5-isopropyl-thiazol-2-yl)isobutyramide **(47)**. This compound was an equipotent inhibitor of cdk5 and cyclin-dependent kinase 2 (cdk2)/cyclin E (IC_{50} = ca. 320 nM).



(46a-b)

46a, R = $NHCOCH_2Cl$, R_1 = 4-Cl-C_6H_4

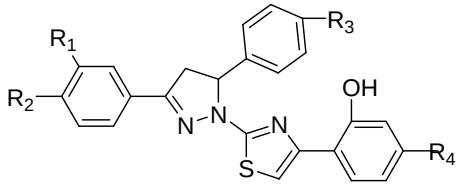
46b, R = $NHCOCH_3$ R_1 = 4-ClC_6H_4

Antihypertensive activity

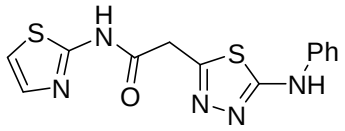
Some 1-(4-arylthiazol-2-yl)-3,5-diaryl-2-pyrazoline derivatives were synthesized by Zitouni *et al*[40] by reacting 1-thiocarbamoyl-3,5-diaryl-2-pyrazoline derivatives with phenacetylbromide. The hypotensive activities were evaluated by using the tail-cuff method. An increase in the hypotensive activity of the compounds **(48a-d)** has been observed.

Abdel-Wahab *et al*[41] synthesized potent derivative of thiazolylmalonamide, tetrachloroisoindolylimide, and triazole and evaluated for antihypertensive α-blocking activity and low toxicity. Among these compounds, **(49)** found to be more potent.

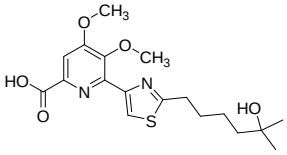
Dash *et al*[42] synthesized two potent compounds, WS75624 A **(50)** and WS75624 B **(51)** as endothelin converting enzyme (ECE) inhibitors and reported as potential antihypertensive agents.



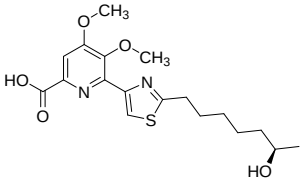
(48a-d)
48a, R_1 = H, R_2 = H, R_3 = H, R_4 = H
48b, R_1 = CH_3, R_2 = CH_3, R_3 = H, R_4 = OCH_3
48c, R_1 = H, R_2 = H, R_3 = OCH_3, R_4 = OCH_3
48d, R_1 & R_2 = -CH_2-, R_3 = H, R_4 = OCH_3



(49)



(50)



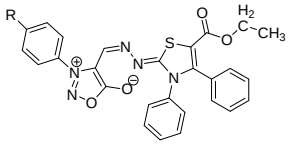
(51)

Antioxidant activity

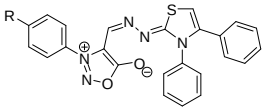
Shih *et al*[43] synthesized 3-aryl-4-heterocyclic sydnones derivatives. The antioxidant activity of synthesized compounds was evaluated, Among these compounds, 4-methyl-2-[(3-arylsydnon-4-yl-methylene)hydrazono]-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester **(52a-d)** and 4-phenyl-2-[(3-arylsydnon-4-yl-methylene)hydrazono]-2,3-dihydro-thiazoles **(53a-d)** exhibited the potent DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activity, comparable to that of vitamin E.

Bozdag˘-Du¨ndar *et al*[44] studied a series of 2,4-dichlorothiazolyl thiazolidine-2,4-dione and 4-chloro-2-benzylsulfanylthiazolyl-thiazolidine-2,4-dione derivatives and they were tested for their antioxidant properties by determining their effects on superoxide anion formation, and the 2,2-diphenyl-1-picrylhydrazyl (DPPH) stable free radical. Compound **(54)** showed the best superoxide anion scavenging activity.

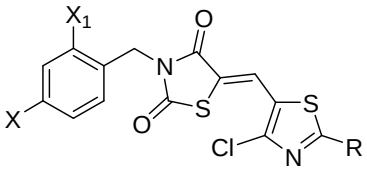
The antioxidant activity of the synthesized compounds (2-amino thiazole derivatives) was evaluated by Gouda *et al*[45] they reported that the three compounds **(55a-c)** showed potent antioxidant activity, after postulating the structure-activity relationship (SAR) of them.



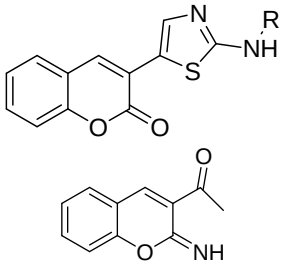
(52a-d)
52a, R = H, **52b**, R = 4-CH_3
52c, R = 4-OCH_3, **52d**, R = 4-OC_2H_5



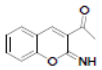
(53a-d)
53a, R = H, **53b**, R = 4-CH_3
53c, R = 4-OCH_3, **53d**, R = 4-OC_2H_5



(54)
54, R = Cl, X = Cl, X_1 = H



(55a-c)
55a, R = H, **55b**, R = $COCH_2CN$, **55c**, R =



Conclusion

Thiazoles can be easily synthesized and offer countless modifications by numerous reaction modes in various positions due to their high reactivity. This has been comprehensively documented. Apart from the synthetic interest, the known and expected biological or medicinal activities of the numerous derivatives deserve particular mentions. Thus the quest to explore many more modifications on thiazole moiety needs to be continued.

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