Review Article

Thiazoles: A Retrospective Study on Synthesis, Structure-activity Relationship and Therapeutic Significance

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ABSTRACT

Thiazole or 1,3-thiazole is a distinct heterocyclic compound which incorporates sulphur and nitrogen atoms. It is a vital framework present in numerous pharmacologically active compounds, be it of natural origin or of synthetic nature. Many thiazoles having antitumor and antiviral activities, originate from microbes and marine organisms. A variety of synthetic drugs, having thiazole group, like antimicrobial sulfathiazole, antibiotic penicillin, antidepressant pramipexole, antineoplastic agent bleomycin, antiretroviral drug ritonavir, histamine H_2 receptor antagonist nizatidine, anti-inflammatory drug meloxicam, antifungal stilbene derivatives have been in the markets for quite some time. Hofmann and Hantzsch laid the groundwork for further development in the field of thiazole chemistry. The interaction of α-haloketones or α-halogenaldehyde and thioamide to obtain thiazoles is beautifully described by Hantzsch. Various studies have reported methods for the synthesis of the thiazoles; thioforamide, thiourea, α-thiocyanotoketones, and vinyl bromide have been extensively employed to synthesize thiazoles. The thiazoles have immense potential and this study tries to enlighten the crucial role of thiazoles for the betterment of society. The review provides different directions in the synthesis of novel thiazoles and also reveals diverse targets for augmentation in the field of designing of novel thiazoles.

Keywords: Thiazoles, Synthesis, QSAR, Molecular Docking, Biological Activity.

INTRODUCTION

Thiazole, a five-member ring has molecular formula C_3H_3NS, indicating the presence of sulphur and nitrogen atoms amidst the ring. Thiazoles or the compounds containing thiazole ring play a very crucial and important role amongst heterocyclic compounds. Thiazoles can be synthesized by using the well-known Hantzsch process. In this process α-haloketone is condensed with a thioamide and trisubstituted thiazole is synthesized.[1] Because of their enhanced importance in the synthesis of therapeutically useful compounds, there is a continuous effort to synthesize N-heteroimino-1,2,3-dithiazole derivatives. Considering a wide diversity in their chemical nature, the 1,2,3-dithiazoles have been given due importance among five-member sulphur-nitrogen heterocyclic compounds.[2]

Thiazoles are extensively present in nature. Practically in all organisms, the α-keto acids are decarboxylated with the help of coenzyme thiamine pyrophosphate, which contains the thiazolium ring serving as electron sink. The derivatives of thiamine, and enzymes for which the presence of Vitamin B_1 is essential for activity, are virtually present in all the human cells.[3] The thiazoles are utilized to synthesize N-S free carbenes and complexes with transition metals. The thiazoles, because of their versatile chemistry, can undergo alkylation reaction to give thiazolium cation. Various chemical compounds are possible by virtue of Benzoin condensation and Stetter reaction, in which the thiazolium salts serve as catalyst.[4] Thiazoles containing compounds have different biological

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activities like antibacterial,[5] anticancer,[6] antimalarial,[7] antifungal,[8] anti-inflammatory,[9] antiepileptic,[10] and anti-oxidants.[11]

STRUCTURE OF THIAZOLE

Resonance hybrid in the thiazole ring is considered in the following ways by resonating structure. However, various resonating structure are also possible with the attachment of d-orbital of sulfur, as described in Figure 1. The molecular orbital methods calculated the p-bond order that indicates aromatic thiazole molecule having a little diene character. Localization energies of the electrophilic reactivites have been predicted in decreasing order as, 5 > 2 > 4 and the nucleophilic reactivites arranged in following order, 2 > 5 > 4. In thiazole ring, the decreasing order of acidity of hydrogen atoms is predicted to be as, H2 >> H5 > H4.

Physical properties

Physical properties of the heterocyclic compound thiazole are described below in Table 1.[12]

Thiazole containing marketed drugs

Numbers of formulations are available in the market with international brand name that contains thiazole moiety having different pharmacological activities as described as below in Table 2.[13-21]

SYNTHETIC METHODS FOR PREPARATION OF THIAZOLES

Various methods of preparation of thiazoles are described below

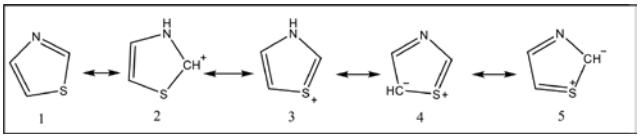
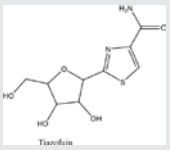
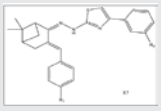
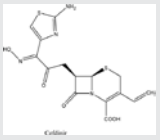
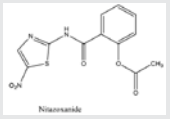
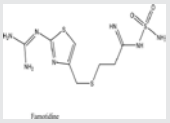
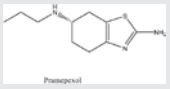
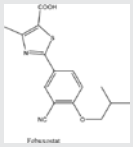
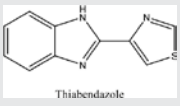
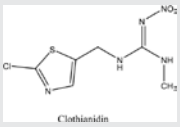
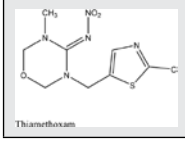


Figure 1: Resonance of thiazole structures.

Table 1: Physical properties of thiazole.

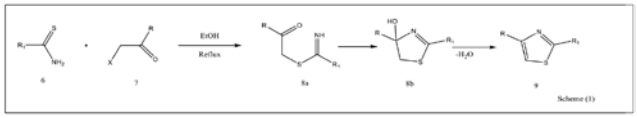
Chemical Formula	C_3H_3NS
Color	Pale yellow
Odour	Like pyridine
Solubility	Soluble in alcohol, ether, acetone; slightly soluble in water and sparingly soluble in dyes and solvents of organic origin.
Boiling Point	116-118°C
Relative Density	1.1998
Refractive Index	1.5969

Table 2: Marketed formulations having thiazole nucleus.

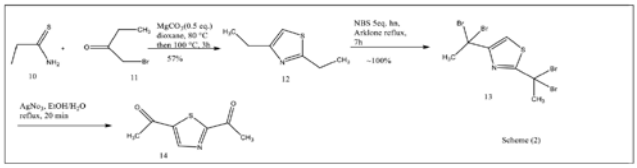
Drug	Uses	Brand	Company
	Anticancer agent	Tiazole	Valeant Pharmaceutical International
	Anti- HIV agent	Ritomax	Alkem Laboratories Ltd
	Antibacterial agent	Cefrine	Macleod's Pharmaceutical Ltd.
	Antiprotozoal agent	Nizonide	Lupin Pharmaceutical Ltd
	Antiulcer agent	Famocid	Sun Pharma Ltd.
	Anti-Parkinson agent	Pramipex	Sun Pharma Ltd.
	Antigout agent	Febutaz	Sun Pharma Ltd.
	Insecticidal agent	Mintezol	MERCK & Co.
	Insecticidal agent	Poncho	Bayer Pharmaceutical Ltd
	Insecticidal agent	Evident	Biostadt Pharmaceutical Ltd

Hantzsch Methods

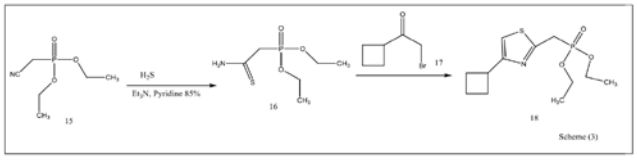
Guernon and Wu[22] accomplished the synthesis by adopting Hantzsch method of condensation of α-haloketones 7 and thioamides 6. An intermediate 8a or a cyclic hydroxyl isomer 8b was formed. Dehydration of compound 8b for the synthesis of 2,4-dialkylthiazole 9 is described below in Scheme 1.



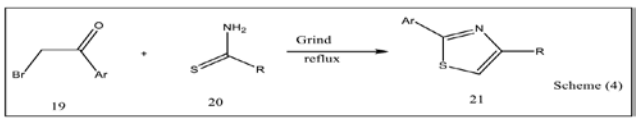
Aitken and Aitken[23] synthesized 2,4-diacetylthiazole 14 for the first time by tetrabromination and action of silver nitrate on the corresponding diethylthiazole. First step led to the formation of diethylthiazole 12 using Hantzsch method by the reaction of thiopropionamide 10 and Phosphorus pentasulfide with bromocarbonyl 11 compounds. Second step involved tetra bromination in Arklone by stirring under reflux. In the final step, tetrabromonated 13 compound was immediately converted to the final product 2,4-diacetylthiazole 14 by reacting with silver nitrate in aqueous ethanol as described below in scheme 2.



Maehr and Yang[24] obtained crystalline residue of diethylisobutylphosphonate 16 by adding hydrogen sulfide to a mixture of triethylamine, pyridine and diethyl cyanomethyl 15. The mixture was stirred at room temperature for 16 hr, evaporated at 55°C under reduced pressure. Bromoacetylcyclobutane 17 was added in the solution and after that bromine was added drop wise to this solution over a 10 min period, at 5°C temperature. After 4 hr the solution was cooled by adding a mix of ice and water and was stirred for 45 min at ambient temperature. Thioamide was added and the solution was stirred with the help of stirrer at room temperature overnight and final product ethyl methyl((4-cyclobutylthiazol-2-yl)methyl)phosphonate 18 was obtained as described below in Scheme 3.

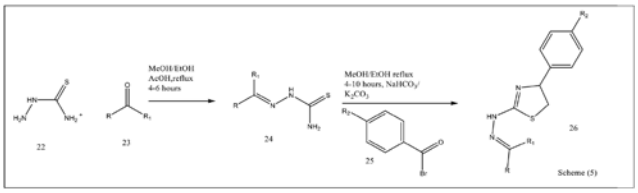


Heravi *et al.*[25] synthesized 2,4-disubstituted thiazoles 21 by condensation reaction between α-halo carbonyl compounds 19 and thiaurea 20 at room temperature, just after 15-20 min of grinding and refluxing as represented below in scheme 4.

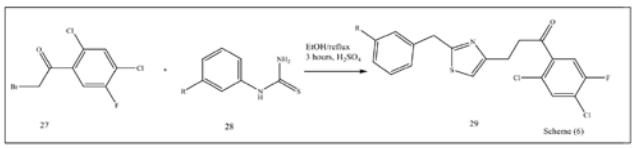


From thiosemicarbazides and thiosemicarbazones

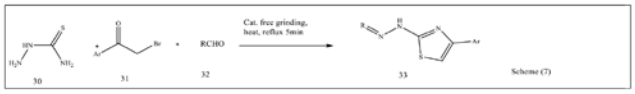
Bharti *et al.*[26] prepared some Schiff bases 26 having antibacterial and antifungal activities by reacting hydrazinecarbothioamide 22 and ether 23 in the presence of methanol/ethanol or AcOH and refluxed. Schiff bases were obtained by cyclization of thiosemicarbazones 24 with substituted phenyl bromide 25 in alcohol and then refluxed for 4-10 hr in the presence of $NaHCO_3/K_2CO_3$ as shown below in scheme 5.



Holla *et al.*[27] synthesized N-substituted thiazoles with the help of condensation reaction between aldehydes and thiasemicarbazide 28 in the presence of ethanol and concentrated H_2SO_4, and then reacted with 2,4-dichloro-5-flurophenylbromide 27 to give 2-substituted 4-(2,4-dichloro-5-flurophenyl) thiazoles 29 as described below in scheme 6.



Ding *et al.*[28] synthesized N-(substituted)-4-phenylthiazole compound 33 by a one-pot reaction of aldehydes 32 and α-bromoketones 31 with thiasemicarbazide 30 by grinding under catalyst and without using any solvents at room temperature as demonstrated below in scheme 7.



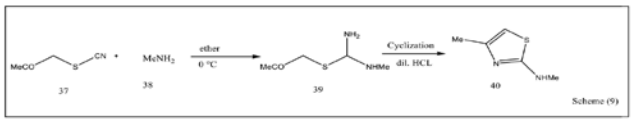
Synthesis by rearrangement of thiacyanoketone: tcherniac's synthesis

Action of labile sulfur

Dains and Krober[29] reacted thioacids 35 and α-thiocyanoketonacetophenone 34 by heating with dilute acid to obtained 2-mercapto-4-phenylthiazole 36. Various other sulfur containing compounds like, thiourea, ammonium dithiocarbamate or H_2S can also be used to produce 2-mercaptothiazoles as shown below in Scheme 8.

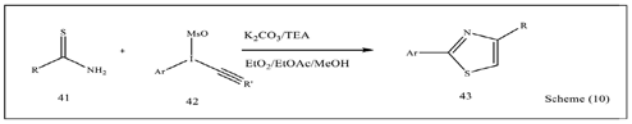
Action of labile nitrogen

Watt[30] synthesized initial product S-actonyl-N-methlisothiourea 39 by reacting α-thiocyanoacetone 37 and methyl amine 38 along with ether at 0°C temperature. The synthesized product was cyclized either by heating or by using dilute HCl, resulting in formation of 4-methyl-2-methylaminothiazole 40 as shown below in scheme 9.



From iodanes

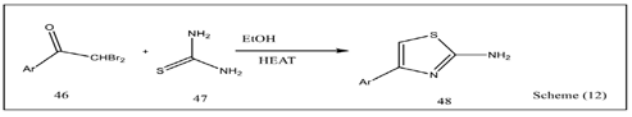
Wipf and Venkatraman[31] prepared novel thiazole by the cyclo-condensation of hypervalent alknyliodonium salts 42 and thioamides 41 in the presence of solid K_2CO_3/triethylamine, the final thiazole 43 was formed after 3 hr as shown below in scheme 10.



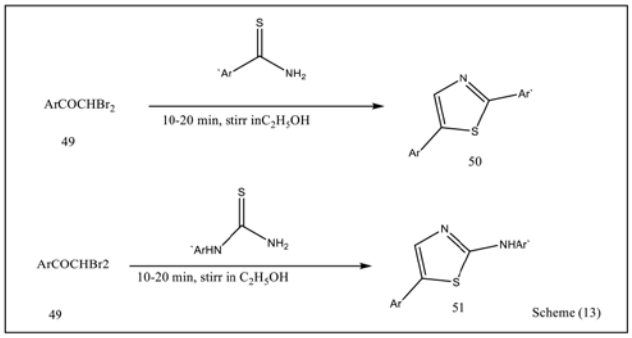
Ochiai *et al.*[32] synthesized 2,4-disubstituted thiazole 45 from (Z)-(2-acetoxy-1-alkenyl) phenyl-λ-3-iodanes 44 by reacting thiourea or thioamide in MeOH in the presence of triethylamine as described below in Scheme 11.

From α, α-dibromoketones

Ahluwalia *et al.*[33] reported that the condensation of α,α-dibromoketones 46 with thiourea 47 gives 2-amino-4-arylthiazoles 48 rather than the expected 5-bromothiazole derivative as shown below in scheme 12.

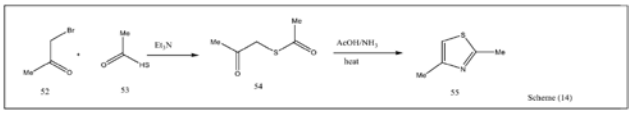


Parkash *et al.*[34] further elaborated the work, by demonstrating the superiority of α,α-dibromoketones as compared to the conventionally used α-dibromoketones for performing the Hantzch thiazole synthesis. 2,4-disubsitiutedthiazole 50, 51 were synthesized by stirring ethanolic solution of α,α-dibromoketones 49 and aryl thiourea/thioamide at room temperature for 10-20 min as described below in scheme 13.



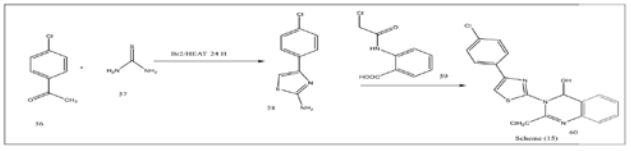
By cyclising dehydration of α-acylamino-carbonyl compounds

Kulkarni and Ganesan[35] synthesized 2,4-dimethylthiazole 55 by cyclizing dehydration of α-acylamino-carbonyl-compound. The process preceded by the reaction of 1-bromopropan-2-one 52 and ethanethioic S-acid 53 in the presence of triethylamine to obtain S-(2-oxopropyl) ethanethioate 54 which reacts with ammonia to gives thiazoles as demonstrated below in scheme 14.



Through 2-aminothiazole

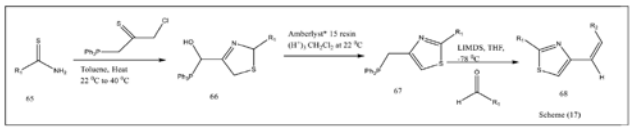
Pattan *et al.*[36] synthesized 2-(chloromethyl)-3(4-(4-chlorophenyl)thiazol-2-yl)-3,4-dihydrolin-4-ol 60 and their derivatives; p-acetophenone 56 and thiourea 57 mixtures were taken in ethanol and bromine was added drop-wise to form 4-(4-chlorophenyl) thiazol-2-amine 58. Compound 58 was reacted with 2-(2-chloroacetamido)benzoic acid 59 by heating and the filtrate was then cooled to obtain final thiazole 60 as described below in scheme 15.



From dehydrogenation

Sowinski and Toogood[37] synthesized tetrahydrothiazole 64 by reacting cystine methyl ester 61 with a chiral aldehyde 62 in the presence of PhH and refluxed to from 2-(1-methoxypropan-2-yl)-4-methylthiazolidine 63. Dehydrogenation of thiazole system was done by using various catalyst like nickel peroxide, manganese (IV) oxide, copper (II) bromide, base and bromotrichloromethane/diazabicycloundecane leading to the formation of tertrahydrothiazole 64 as demonstrated below in scheme 16.

Williams *et al.*[38] altered Hantzch thiazole method, which was initiated by the S-alkylation of thioamide 65 using α-chloroacetonyl triphenylphosphorane and warming at 40°C temperature in dry toluene. (2-N-subsitutied-2,5-dihydrothiazol-4-yl)(triphenyl-λ⁴-phosphanyl)methanol 66 undergoes dehydration with anhydrous Amberlyst-15 resin. Witting reaction of the yield (2-N-subsitutied-4-((triphenyl-λ⁴-phosphanyl)methyl)-2,5-dihydrothiazole 67 was undertaken by deprotonation with LiHMDS in THF at -78°C with aldehyde to get final product 2-N-subsitutied-4-vinyl-2,5-dihydrothiazole 68 as described below in scheme 17.

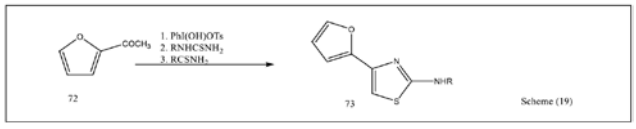


Charette Synthesis

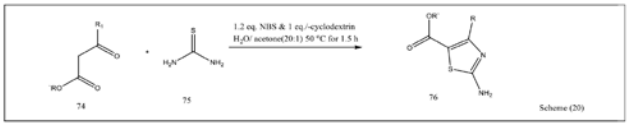
DeRoy and Charette[39] synthesized thiazole from thiazoline via an electrophilic activation of amide 69 using traflic anhydride (Tf_2O). Addition of L-cysteine HCl afforded thiazoline 70 and oxidation of the thiazoline ring using bromotrichlomethane ($BrCCl_3$) in existence of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) obtained thiazole ring 71 as shown below in scheme 18.

Miscellaneous

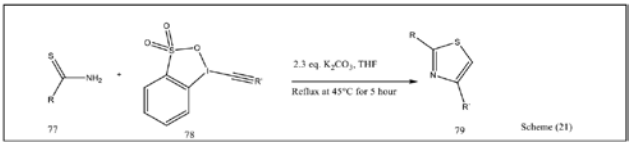
Singh *et al.*[40] synthesized 4-(2-subsitituted) thiazole 73 by hypervalent iodine oxidation of 2-acetylfuran 72 using hydroxyl(tosyloxy) benzene by stirring in dichloromethane for 24 hr, then by refluxing the reaction mixture with appropriate thioureas/thioamides for 3-4 hr to get final product 73 as described below in scheme 19.



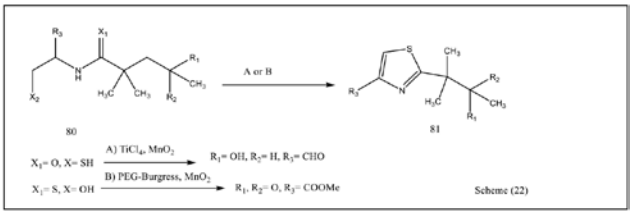
Narender *et al.*[41] synthesized 2-Amino-4-arylthiazole-5-carboxylates 76 and their selenazole derivatives by reacting esters 74 with thiourea 75 in the presence of N-bromosuccinimide in the existence of β-cyclodextrin in H_2O at 50°C temperature as described below in scheme 20.



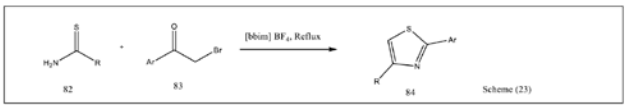
Ishiwata and Togo[42] prepared thiazoles by reacting thioamides 77 with 1H-1-(1'-alkynyl)-5-methyl-1,2,3-benziodoxanthiole 3,3-dioxides 78 to obtain 2,4-disubstituted thiazole 79 under reflux at 45°C temperature for 5 hr as depicted below in scheme 21.



Serra *et al.*[43] synthesized 2,4-disubstituted thiazole analogs by the cyclodehydration of amides 80 with $TiCl_4$ and cyclodehyderation of β-hydroxythioamides with Polyethylene glycol associated with Burgess reagents to obtain 2,4-disubstituted thiazole rings 81 as depicted below in scheme 22.



Potewar *et al.*[44] synthesized 2-methyl-4-arylthiazole 84 from α-bromoketone 83 and thiourea/thioamide 82 in ionic liquid 1,3-di-n-butylimidazoliumtetrafluorobor ate [(bbim) BF_4] at ambient temperature as shown in scheme 23.



THIAZOLES AND THEIR DOCKING TARGETS

Various studies have been done on thiazoles for computer aided drug designing and the docking targets are illustrated below in Table 3.

BIOLOGICAL ACTIVITY OF THIAZOLE CONTAINING COMPOUNDS

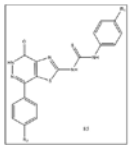
Anti-cancer activity

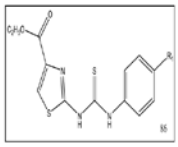
Ewida *et al.*[65] prepared and evaluated 2-thioureido compounds for DHFR inhibition. Compound 85a was most active against the breast cancer cell line HS 578T with IC_{50} data 0.8 μM and as DHFR inhibitor with IC_{50} value 0.06 μM. Compounds 85a and 85b

Table 3: Docking targets for thiazoles.			
Sl. No.	**Target**	**PDB: ID**	**Activity**
1	DNA gyrase and glucosamine-6-Phosphate synthase (GlcN-6-P)[45]	3U2D; 2vF5	Antimicrobial activity
2	GlcN-6-P synthase[46]	1jxa	Antibacterial activity
3	Dihydrofolate reductase (DHFR) and Hepatoma G2 (HepG2)[47]	1BID	Antimicrobial and Anticancer activities
4	Tyrosinase/tyrosine hydroxylase[48]	2toh	Antioxidant activity
5	DNA gyrase[49]	4BAE	Anti-Tuberculosis activity
6	Tryptophanyl-tRNA synthase[50]	P67592-I16K	Antibacterial and Antioxidant activities
7	Lipoxygenase (5-LOX)[51]	3O8Y; 3V99	Anti-inflammatory activity
8	Non-structural protein (NS5B)-polymerase[52]	3TYV	Antiviral activity
9	Gamma-Aminobutyric acid (GABA) AT enzyme[53]	1OHV	Antiepileptic activity
10	Cyclo-oxygenase (COX II)[54]	1CX2	Antiproliferative activity
11	COX I and COX II[55]	1eqg.C; 4m11	Anti-inflammatory activity
12	Selective COX II and Epidermal growth factor receptor (EGFR)[56]	3LN1;1M17	Anti-inflammatory and anticancer activities
13	COX I and COX II[57]	4PH9	Anti-inflammatory activity
14	COX II[58]	4COX	Anti-inflammatory activity
15	Cannabinoial (CB_2)[59]	5XRA	Anti-inflammatory
16	(Monoamine oxidase) hMAO-A and hMAO-B[60]	2Z5X; 2V5Z	Parkinson's Disease
17	Fructose-1,6-bisphosphatase[61]	1fta	Type II Diabetic activity
18	Human rhinovirus 3C protease (HRV 3C protease)[62]	ICQQ	Antiviral activity
19	12 human carbonic anhydrase[63]	5IPZ	Anticancer activity
20	Butyrylcholinesterase (BChE) and Acetylcholinesterase (AChE)[64]	4BDS; 4BDT	Anticancer
21	DHFR[65]	1U70	Anticancer

and 86 were *in vitro* tested and showed the antitumor activity against HT29 colon cancer, compounds 85a and 85c were active against SK-OV-3 ovarian cancer, and 85b was active against TK-10 renal cancer cell lines. Molecular modeling studies indicated the importance of Phenylalanine-31 and Arginine-22 for binding with DHFR enzyme.

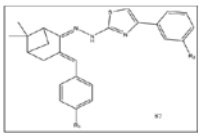
No.	R1	R2
85a	Cl	H
85b	OCH3	H
85c	OCH3	OCH3
86	Cl	-





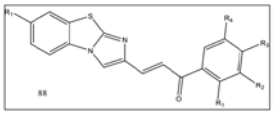
Wang *et al.*[66] prepared β-pentene based thiazole derivatives and performed *in vitro* evaluation for anticancer activity. Diverse cancer cells lines were taken and most of the compounds displayed high anticancer activity. Compounds 87a and 87b showed potent anticancer action against HeLa cell, SSMC-7721 and CT-26 with IC_{50} values as 3.48 ±0.14, 6.99 ± 0.15 and 8.84 ± 0.16 μM respectively. SAR study confirmed that presence of hydroxyl group on benzene ring enhances the activity while fluorine group decrease the activity.

No.	R1	R2
87a	NO2	OH
87b	Cl	OH

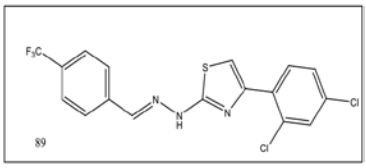


Sultana *et al.*[67] prepared benzo[d]imidazo [2, 1-b] thiazole-chalcone based derivatives and estimated the anticancer activity by using lungs, breast, prostate and colon cancer cell lines. Compounds 88a and 88b showed activity against MDA MB-231 breast cancer cell lines with IC_{50} values 1.3 and 1.2 μM.

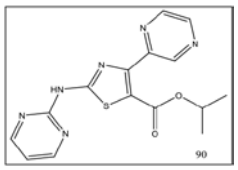
No.	R	R1	R2	R3	R4
88a	O	H	OH	OMe	H
88b	H	H	H	OMe	H



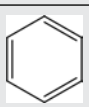
De Santana *et al.*[68] prepared new thiazole analogs and estimated their antitumor activity. Around 22 derivatives were prepared with two types of moiety, *i.e.*, thiosemicarbazones and thiazoles, with the motive of synthesizing novel antitumor active compounds with less toxicity. Eight compounds were active against at least three types or more than 5 types of cancer cell lines and their IC_{50} values were measured within 72 hr. Compound 89 proved to be a compound with potent anticancer activity which causes mitochondrial depolarization and DNA fragmentation.

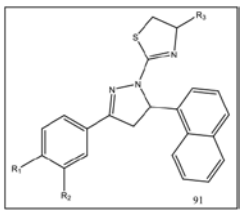


Frija *et al.*[69] prepared new aminothiazole derivatives as highly selective anti-hepatocellular carcinoma agents. Majority of the prepared derivatives showed good anti-heptocelluar activity. Derivative 90 was most active that reduced multiplication of several liver cancer cells with EC_{50} value of 0.11 μM.

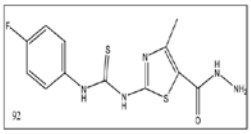


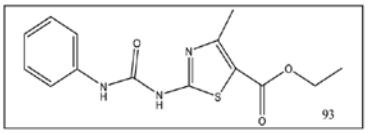
Yuan *et al.*[70] prepared compounds containing pyrazole, naphthalene and thiazole rings and evaluated for antitumor activity. Compounds 91a and 91b showed maximum inhibitory activity towards different cancer cell lines with values IC_{50} = 0.86, 0.95 μM for Hela, IC_{50} = 8.49 and 7.37 μM for HpeG2 and IC_{50} = 6.02, 6.57 μM for EGFR respectively. SAR study confirmed that methoxy group leads to higher activity than the halogen group. Docking study evaluated the simulation of compound 91a into EGFR active site, and came to the conclusion that there is formation of two p–p bonds in between LYS721 and naphthalene ring of compound 91a which may lead to enhanced anticancer activity.

No.	R1	R2	R3
91a	CH_3	CH_3	
91b	CH_3	CH_3	O

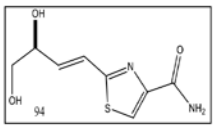


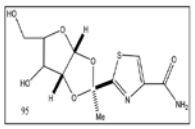
Rostom *et al.*[71] prepared novel derivatives containing ethyl 2-amino-4-methylthiazole-5-carboxylate moiety and by using *in vitro* method evaluated for anticancer and antimicrobial activity. The assay indicated thirty compounds bearing chemotherapeutically-active pharmacophores showing good antimicrobial activity, with specific bactericidal activity toward gram +ve bacteria and few other compounds gave medium anti-fungal activity toward fungal species *Candida albicans*. Compound 92 showed potent bifunctional antimicrobial and moderate anti-fungal activity whereas compound 93 displayed broad spectrum anticancer activity.

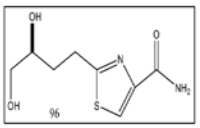




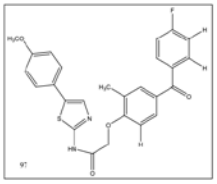
Popsavin *et al.*[72] prepared 2-substituted thiazole-4-carboxamide analogs and evaluated as anti-cancer agents by *in vitro* testing. All prepared compounds showed potent anti-cancer action against different cancer cell lines. Compounds 94, 95, and 96 were most potent towards K562 cell line having IC_{50} values of 0.11, 0.95 and 1.02 μM toward K562 cell line respectively; 0.05, 1.01, and 1.11μM towards HL-60 cell line respectively; 0.59, 0.04 and 0.61 μM towards Jurkat cell line respectively; 2.64, 14.02 and 4.01μM towards Raji cell line respectively; 9.21, 0.04 and 0.02 μM towards MCF-7 cell line respectively; 0.06, 2.51 and 1.51 μM towards Hela cell line respectively and > 100 μM towards MRC-5.



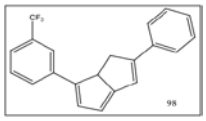




Prashanth *et al.*[73] prepared analogs containing benzophenone-thiazole and evaluated as potent VEGF-A inhibitors. Analog 97 was found to inhibit the activity in the EAC and DLA cancer cell lines with IC_{50} values (5.2 and 5.4 μM respectively). SAR study confirmed that presence of -CH_3 and -F group at benzophenone and CH_3O- group at phenyl ring enhances the anticancer activity.

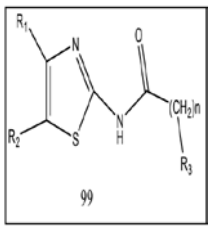


Koppireddi *et al.*[74] investigated a novel derivatives of 3-aryl-6-phenylimidazo [2, 1-b] thiazoles and evaluated for anticancer action by using various cancer cell lines. Analog 98 showed high cytotoxic activity having IC_{50} values of 6.5± 0.56 (HeLa), 8.9 ± 0.46(A549), 10.9 ± 0.44(MDA-MB-231), 17.4 ± 1.34(THP1) in μM.



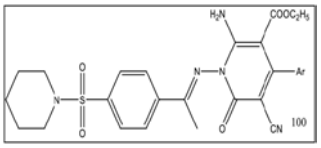
El-Messery *et al.*[75] prepared novel analogs containing of 2-acetamido- and 2 or 3-propanamido-thiazole moieties and evaluated for antitumor activity. Compounds were studied with single dose of 10 μM, by NCI *in vitro* assay for antitumor activity. Analogs 99a and 99b showed broad spectrum activity whereas two analogs 99c and 99d proved lethal while 99e, 99f, 99g and 99h displayed GI data 75.5, 69.3, 96.2 and 92.7% respectively in CCRF-CEM blood cancer cell lines.

No.	R1	R2	R3	N
99a	Phenyl	H	Cl	2
99b	Phenyl	H	N-phenyl-piperazino	1
99c	H	CH_3	N-phenyl-piperazino	2
99d	CH_3	$COOC_2H_5$	Cl	1
99e	H	CH_3	N-methyl-piperazino	1
99f	H	CH_3	N-phenyl-piperazino	1
99g	CH_3	$COOC_2H_5$	N-methyl-piperazino	2
99h	Phenyl	H	Cl	2



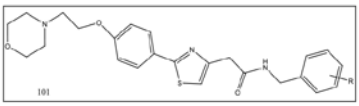
Al-Said *et al.*[76] prepared 1,2-dihydropyridine, thiophene and thiazole moiety analogs and evaluated anticancer activity by *in vitro* testing. Compounds 100a and 100b showed high potential by obtaining IC_{50} values of 20.6, 25.5 μM respectively against MCF7 breast cancer cell lines as correlated to reference drug Doxorubicin with IC_{50} value 32.02 μM.

No.	Ar
100a	C_6H_4Cl-4
100b	C_6H_4OH-4



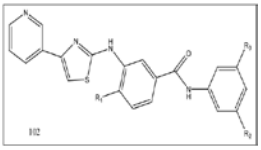
Fallah-Tafti *et al.*[77] prepared a new series of analogs containing thiazolyl N-benzyl-substituted acetamide moiety and estimated Src kinase inhibitory and antitumor activity. Analog 101a displayed inhibitory activity of c-Src kinase with GI_{50} values 1.34 μM and 2.30 μM in NIH3T3/c-Src527F and SYF/c-Src527F cells. Analogs 101b and 101c suppressed the multiple growth of breast cancer cell (BT-20), blood cancer (CCRF-CEM) cells and human colon carcinoma (HT-29). SAR study confirmed that for the maximum anticancer activity, substitution at 4 position of benzyl ring (4-fluoro, 3,4-dicholor or 4-methyl) is most essential.

No.	R
101a	CH_3
101b	4-F
101c	4-di-Cl



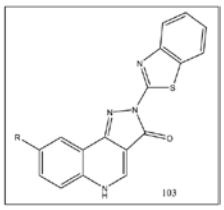
Wang *et al.*[78] synthesized novel analogs of 2,4-disubstituted thiazole and evaluated for anticancer activity by utilizing Bcr/Abl kinase. Analog 102a showed potent activity against Bcr/Abl kinase having IC_{50} value 0.67 μM. Analog 102b potently suppressed the production of K562 and Ku812 cells with IC_{50} values 10 and 11 μM respectively.

No.	R1	R2	R3
102a	Me	CF_3	
102b	Me	i-Pr	
102c	Me	t-Bu	



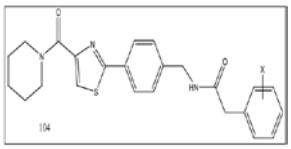
Reis *et al.*[79] prepared novel analogs consisting of 2-(benzo[d]thiazol-2-yl)-8-substituted-2H-pyrazolo[4,3-c]quinolin-3(5H)-ones and evaluated as anticancer activity against four types of cancer cell lines "i.e." MDA-MB-435, HL-60, HCT-8 and SF-295. Analogs 103a and 103b were displayed good anticancer activity towards MDA-MB-435 cell lines with IC_{50} values lower than 3 mg/mL.

No.	R
103a	CH_3
103b	Br



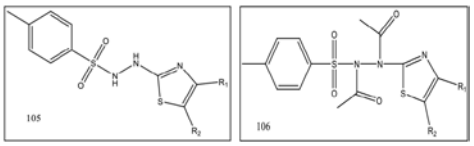
Aliabadi *et al.*[80] prepared analogs containing 2-phenylthiazole-4-carboxamide and evaluated for antitumor activity. Analogs 104a, 104b were observed as most active compounds against HT-29 cells having activity against colon cancer cells with IC_{50} = (¼ 4.46 - 0.98 μg/ml). Analog 104c showed potent activity against T47D cells with IC_{50} = (¼ 2.0 - 0.67 μg/ml). SAR studies were conducted to study the role of electron withdrawing groups, like halogens and electron gaining groups like methoxy.

No.	X
104a	4-OCH_3
104b	2-OCH_3
104c	3-F



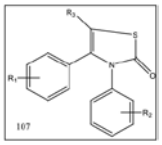
Zaharia *et al.*[81] prepared p-toluenesulfonyl-hydrazinothiazoles and hydrazino-bis-thiazoles analogs and evaluated for anticancer activity. Compounds 105a, 105b, 105c, 105d and 106 were found to be active against prostate cancer cell line DU-145 and liver cancer cell line Hep-G2 with IC_{50} value less than 10 μM.

No.	R1	R2
105a	CH_3	H
105b	C_6H_5	H
105c	CH_3	$COCH_3$
105d	CH_3	$COOC_2H_5$
106	CH_3	H



Liu *et al.*[82] prepared analogs containing 3,4-diarylthiazol-2(3H), 3,4-diarylthiazol-2(3H)-imines and evaluated for anticancer activity by *in vitro* testing. Analogs 107a, 107b were screened for antitumor action against human CEM cell line and found IC_{50} values to be 0.12 and 0.24 μM respectively.

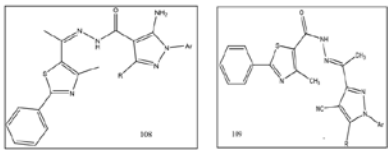
No.	R1	R2	R3
107a	3-NH_2-4-OMe	3',4',5'-$(OMe)_3$	H
107b	3-NH_2-4-OMe	3',4',5'-$(OMe)_3$	Cl



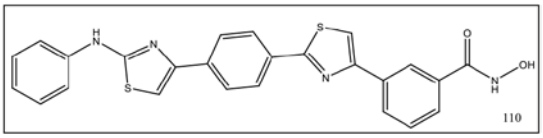
Anti-bacterial activity

Abu-Melha *et al.*[83] prepared thiazole based heterocyclic derivatives and estimated their antitumor and antimicrobial potential. In order to reduce the co-production of unhealthy and unsafe compounds, eco-friendly method of synthesis was employed. All prepared compounds showed different pharmacological activities like antitumor, antimicrobial and hepatoprotective. The SAR studies confirmed that chloride moiety gives potential anticancer activity. Few derivatives displayed broad spectrum antibacterial activity and hepatoprotective activity. Compounds 108a, 108b and 109a, 109b were screened for potent cyctotoxic activity.

No.	R	Ar
108a	$COCH_3$	4-ClC_6H_4
108b	COOEt	2,4-$(Cl)_2C_6H_3$
109a	Ph	4-ClPh
109b	4-MePh	Ph



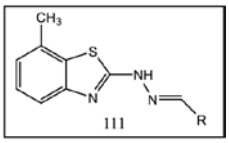
Bikobo *et al.*[5] prepared 2-phenylamino-thiazole derivatives as antimicrobial agent. Compound 110 showed potent actions against gram positive and gram-negative bacteria with MIC values 31.25 and 7.81 μM respectively.



Zha *et al.*[84] prepared new derivatives of benzothiazaole hydrazone and estimated their antibacterial and antifungal potential. The docking studies estimated that most of the synthesized compounds have better antibacterial activity as compared to the standard drugs like chloramphenicol and rifampicin. Also, few other compounds showed better antifungal activity as compared to standard drug ketoconazole. Structure Activity Relationship estimated that the antimicrobial activity depends upon the phenyl ring substituent.

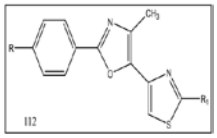
It was seen that electron donating groups increases the antibacterial activity whereas the electron withdrawing groups increases the antifungal activity. On the basis of docking study, it was confirmed that compounds 111a, 111b and 111c displayed better glide G-score.

No.	111a	111b	111c
R			

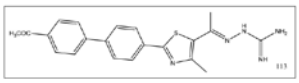


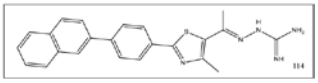
Abhale *et al*.[85] prepared novel analogs containing 4-methyl-2-aryl-5-(2-aryl/benzyl thiazol-4-yl)oxazole and estimated their antimicrobial, anti-tuberculosis and anticancer activities. Compound 112e was found to be very active against *M. tuberculosis* H37Ra cell line and *M. bovis* BCG strains. Compounds 112a, 112b, 112c, 112d and 112e displayed good anti-tubercular activity. SAR studies confirmed that anti-tubercular activity was enhanced by the replacement of H-atom with -F at phenyl ring A and ring B by substituents like halogen and -CH_3.

No.	R	R1
112a	H	3-$ClC_6H_4CH_2$
112b	H	4-$ClC_6H_4CH_2$
112c	4-F	$C_6H_5ClH_2$
112d	4-F	3-$ClC_6H_4CH_2$
112e	4-F	4-$FC_6H_4CH_2$

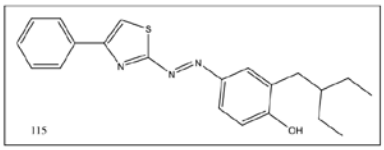


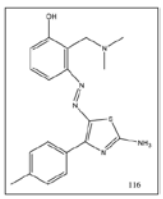
Mohammad *et al*.[86] prepared phenylthiazole analogs and estimated their antimicrobial activity. In this study, 2,5-disubstituted thiazole compounds were formed from a lead compound which showed high antimicrobial activity towards MRSA. *In vitro* MTS assay estimated that compounds 113 and 114 were active against microbial single strain of MRSA with MIC values 1.6 and 6.3 μg/ml respectively.



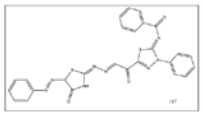


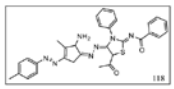
Abdellatif *et al*.[87] prepared benzothiazole and thiazole derivatives substituted with dialkylaminoalkyl-o-cresols and evaluated for antimicrobial activity. A good anti-microbial activity was displayed by the compounds 115 and 116. Compound 116 showed broad spectrum antibacterial and antifungal activity.

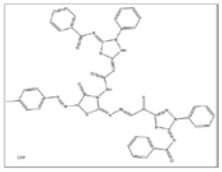




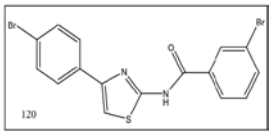
Farghaly *et al*.[88] synthesized novel 1,3-thiazole derivatives and analyzed them for antimicrobial activity using *in vitro* method. The study confirmed that majority of the derivatives displayed antimicrobial activity against some fungi species like, *A. flavus*, *S. racemosum*, *G. candidum* and broad-spectrum antibacterial activity against some bacteria. Compounds 117, 118 and 119 showed potent antimicrobial activity. The antimicrobial activity was tested at 125 μg/ml concentration.



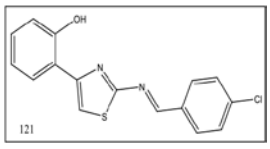




Li *et al*.[89] prepared thiazole analogs and analyzed their FabH-inhibition action. The synthesized derivatives were evaluated for antibacterial activity using MTT assay. Derivative 120 displayed more potent antibacterial activity and E. *coli* FabH inhibitory activity having MIC value in between 1.56 – 6.25μM.



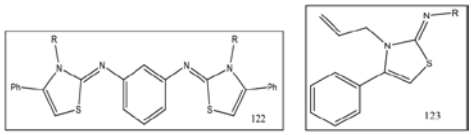
Gupta *et al*.[90] prepared 2-aminothiazole analogs and evaluated antimicrobial activity. By using disk diffusion method, antibacterial and antifungal activities of newly formed derivatives were evaluated against species like, *S. aureus, E. coli, P. aeruginosa, C. albicans, A. flavus and A. fumigatus*. Compound 121 showed more activity and highest zone of inhibition. SAR study confirmed that activity increases due to presence of -OH group at meta-position of phenyl ring A and -Cl group at para-position of ring B.



Shiran *et al*.[91] prepared new analogs containing 3-allyl-2-(substituted imino)-4-phenyl-3H-thiazole by reacting allyl-thioureas and 2-bromoacetophenone and evaluated for antibacterial activity. Compounds 122a, 122b and 123a, 123b displayed good broad spectrum antibacterial activity. With the help of structure activity relationship

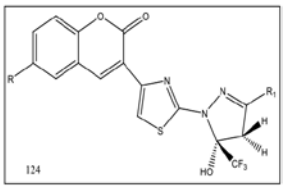
studies it was confirmed that due to the availability of alkyl group and allyl group increased antibacterial activity was observed.

No.	R
122a	Me
122b	Allyl group
123a	3,4-Dimethoxyphenyl
123b	1-Naphthyl

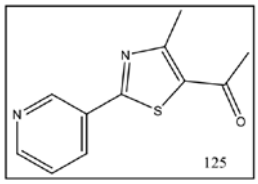


Aggarwal *et al.*[92] prepared new analogs containing thiazole moiety and evaluated for anti-inflammatory and antibacterial activity. Derivatives 124a, 124b displayed good anti-inflammatory as well as antibacterial activities. SAR studies confirmed that antibacterial and anti-inflammatory activities were enhanced due to presence of -Cl group at coumarin ring and trifluoromethyl group at position 3 and 5 of pyrazoline ring.

No.	R	R1
124a	H	CF_3
124b	Cl	CF_3

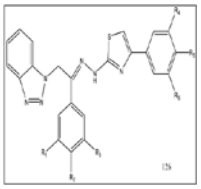


Bondock *et al.*[93] synthesized 2-(3-pyridyl)-4,5-disubstituted thiazole derivatives and evaluated for antimicrobial activity. Majority of the synthesized derivatives displayed both antibacterial and antifungal activity as per *in vitro* studies using disc diffusion assay. Compound 125 displayed potent antibacterial activity by suppressing the multiplication of *S. epidermidis* with MIC value 0.24 μg/ml and antifungal action against *Geotricum candidum* with MIC value 0.48 μg/ml. SAR study confirmed that as the number of methyl group substituent at position 4 or 5 of thiazole ring increases, there is reduction in antimicrobial activity.

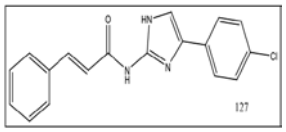


Gaikwad *et al.*[94] synthesized novel thiazoles and benzotriazoles derivatives and estimated their antimicrobial and antifungal potential. Compounds 126h, 126i and 126j substituted with fluorine and chlorine group displayed potent action against *A. niger* at 16 μg/ml. Analogs 126a, 126b, 126c, 126d, 126e, 126f and 126g showed acceptable activity at 32 μg/ml and few of them displayed moderate activity at 64 μg/ml. SAR study confirmed that substitution of halogen and nitro groups at phenyl ring would yield moderate to high active compounds whereas some of synthesized compounds were less active against *C. albicans and A. niger*.

No.	R_1	R_2	R_3	R_4	R_5	R_6
126a	H	F	H	H	NO_2	H
126b	H	F	H	CF_3	H	CF_3
126c	H	Cl	H	H	Cl	H
126d	H	Br	H	H	F	H
126e	H	NO_2	H	H	F	H
126f	H	NO_2	H	CF_3	H	CF_3
126g	CF_3	H	CF_3	H	F	H
126h	H	F	H	H	F	H
126i	H	F	H	H	Cl	H
126j	H	Cl	H	H	F	H

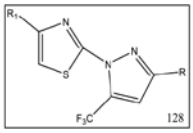
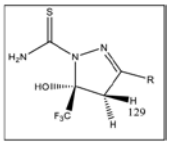


Padmavathi *et al.*[95] prepared a series of amido-linked derivatives containing pyrrolyl/pyrazolyl-oxazoles, thiazoles and imidazoles and evaluated for antimicrobial activity. Compound 127 showed potent antimicrobial activity. SAR study confirmed that monoheterocyclic with extended conjugation is more effective than bis-heterocyclic system. The derivatives having thiazole and imidazole rings are more active as compared to oxazole unit.

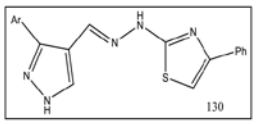
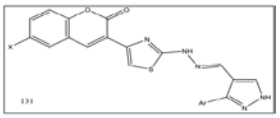


Aggarwal *et al.*[96] synthesized novel pyrazolylthiazoles derivatives and estimated their antimicrobial action. The derivatives 128a and 128b showed broad spectrum antibacterial activity as per *in vitro* testing. Compounds 129a, 129b and 129c displayed moderate antibacterial activity against gram positive bacteria *Bacillus pumilus*.

No.	R	R1
128a	CH3	p-$CH_3OC_6H_4$
128b	C6H5	C_6H_5
129a	CH_3	–
129b	CF_3	–
124c	p-ClC_6H_4	–

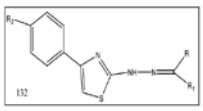
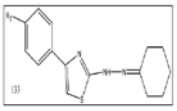
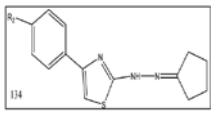



Vijesh *et al.*[97] prepared novel 2,4-disubstituted thiazoles, substituted with pyrazole ring and estimated their antimicrobial activity by *in vitro* testing. The derivatives 130, 131a, 131b, 131c and 131d showed broad spectrum antibacterial activity against various species. Two compounds 131c and 131d showed more potent antimicrobial activity at concentration of 1.6125 μg/ml as compared to standard drug Ceftriaxone, against various species of the micro-organism.

No.	Ar	X
130	2,5-dichlorothiophene	2,4-Dichlorophenyl
131a	2,4-Dichlorophenyl	H
131b	2,4-Dichlorophenyl	Br
131c	2,5-dichlorothiophene	H
131d	2,5-dichlorothiophene	Br

Bharti *et al.*[98] prepared 2,4-disubstituted thiazoles and estimated their antimicrobial activity by *in vitro* testing. Few derivatives displayed medium to high antibacterial activity whereas few analogs showed excellent antifungal activity. Analogs 132a, 132b, 132c, 133a, 133b, 134a and 134b were effective against fungal strains like *C. albicans, C. neoformans*. Compounds 132c and 132d showed good antibacterial activity.

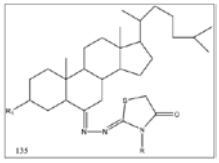




No.	132a	132b	132c	132d
R1	H	H		
R2				
R3	Br	OCH_3	OCH_3	Br

No.	R1
133a	OCH_3
133b	Br
134a	OCH_3
134b	Br

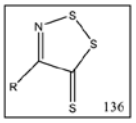
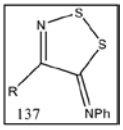
Khan and Yusuf[99] prepared a series of analogs containing thiazolidinone moiety of steroid and evaluated these for antibacterial activity. Disk diffusion assay was used to determine the antibacterial activity of prepared compounds and the minimum inhibitory concentration of compounds was also determined. Two compounds 135a and 135b showed potent antibacterial activity as compared to standard drug Amoxicillin. The SAR study confirmed that, substitution of chloro and acetoxy group at position-3 of steroidal thiazolidione ring is essential for antibacterial action.

No.	R1	R
135a	CH_3COO	
135b	Cl	



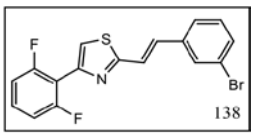
Konstantinova *et al.*[2] prepared new analogs containing 5-phenylimino, 5-thienoand and 5-oxo-1,2,3-dithiazoles and evaluated antimicrobial and antitumor activity. Two compounds 136a and 136b showed potent antibacterial and antifungal activity and compound 137 showed anticancer action against cell lines MCF-7 and MDA-MB-231.

No.	R
136a	2-Pyridinyl
136b	CO_2Et
137	2-Furanyl

Anti-fungal activity

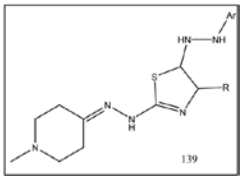
Lu *et al.*[100] prepared new stillbene derivatives with thiazole moiety and estimated their antifungal activity. Compound 138 displayed high inhibitory action while few compounds displayed medium antifungal activity against *F. graminearum, M. melonis*. SAR study confirmed that substitution by the electron withdrawing group at benzene ring would display more antifungal action as compared to electron donating group.



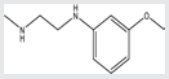
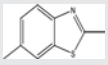
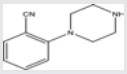
Ouf *et al.*[101] synthesized benzothiazole and aryhydrazothiazole derivatives and analyzed their antifungal activity. Two compounds 139a and 139b displayed more effective antifungal activity in the

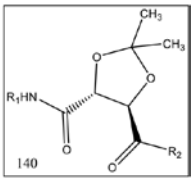
skin infection with MIC value 2 μg/ml and standard drug MIC value 8 μg/ml in case of *C. albicans*. These compounds displayed superior antifungal action in comparison to fluconazole.

No.	Ar	R
139a	4-$CH_3OC_6H_4$	Ph
139b	Ph	O



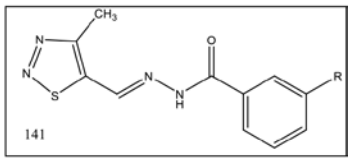
Zhang *et al.*[62] prepared novel series of 2,2-dimethyl-1,3dioxolane analogs and evaluated inhibition of human rhinovirus 3C protease by *in vitro* activity testing. Compound 140a and 140b showed good protease inhibitor activity. Most effective binding site in the treatment of the HRV infection is 3C protease. Compound 140b was most effective against HRV 3C protease with IC_{50} value 2.50 ± 0.7 μm.

No.	R1	R2
140a		
140b		



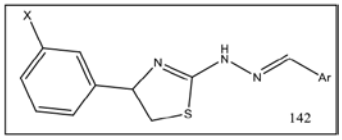
Zhang *et al.*[102] prepared new analogs containing 4-methyl-1,2,3-thiadiazole-5-carboxaldehyde benzoyl hydrazones and evaluated for antifungal activity. Compound 141a showed broad spectrum antifungal activity against fungi species *V. mali, B. cinerea, P. aphanidermatum, R. solani, F. moniliforme and A. solani* with IC_{50} values 8.20, 24.42, 15.80, 40.53, 41.48, and 34.16 μg/ml respectively. Two compounds 141b and 141c were highly effective against *V. mali* with EC_{50} values 1.64 and 1.87 μg/ml respectively; which is less than the standard drug Tiadinil. SAR study confirmed that substitution of halogen atom at p–position in phenyl ring observed higher activity against fungal species.

No.	R
141a	2, 4-Cl_2
141b	4-Br
141c	4-CF_3



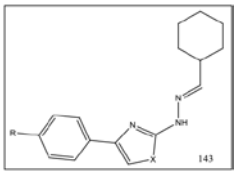
Kauthale *et al.*[103] prepared new derivatives containing thiazolyl hydrazones and analyzed their antifungal and antioxidant activities by *in vitro* testing. Compounds 142a and 142b showed good antioxidant and broad-spectrum antifungal activity. Majority of the synthesized compounds showed enhanced activity against fungi species when compared to fluconazole with MIC values in between 3.12 - 25 μg/ml.

No.	Ar	X
142a	2,4 dichlorophenyl	H
142b	2,4 dichlorophenyl	4-Cl

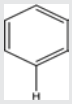


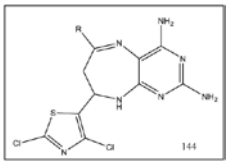
Laczkowski *et al.*[104] prepared new thiazoles and selenazoles derivatives and estimated their antimicrobial activity. Derivatives 143a, 143b, 143c and 143d displayed potent activity against various fungi species with MIC values in between 0.24 -15.62 μg/ml. Two compounds 143e and 143f were active against gram-positive bacteria likes *S. aureus* and *S. cocci* with MIC values in between 31.25 - 125 μg/ml.

No.	X	R
143a	S	F
143b	S	OCH_3
143c	S	CH_3
143d	S	2,4-di-F
143e	Se	NO_2
143f	Se	CH_3



Ramirez *et al.*[105] prepared new analogs containing 8,9-dihydro-7H-pyrimido[4,5-b][1,4]diazepines and evaluated for antifungal and anticancer properties. All prepared compounds were *in vitro* tested against 60 different types of cancer cell lines. Two compounds, 144a and 144b displayed GI_{50} with MIC values 1.28 ± 2.98 μM and 0.35 ± 2.78 μM and these compounds also showed antifungal activity against *C. neoformans* with MIC_{100} = 15.6-62.5 μg/ml and MIC_{80} = 15.6-31.2 μg/ml.

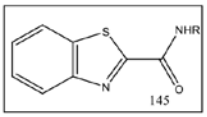
No.	R
144a	
144b	



Anti-inflammatory activity

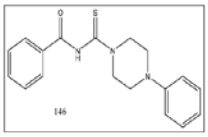
Ghonim *et al.*[59] prepared novel analogs, containing thiazole and benzothiazole, and selective cannabinoid CB2 agonists and analyzed their anti-inflammatory action by *in vivo* testing. Compounds 145a, 145b and 145c showed high affinity to activate the agonists CB2 and inhibit NKH-477 and to activate cAMP accumulation in cells, with EC_{50} values of 57 μM, 68 μM and 306 μM respectively.

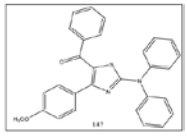
No.	R
145a	Adamantan-1-yl
145b	Naptha-1-yl
145c	3-triflurobenzyl



Khanfar *et al.*[106] prepared novel analogs containing oxadiazole and thiazole. H_3 receptor antagonists are useful in neurotransmitter disorder, inflammatory and gastro-intestinal diseases. Numbers of analogs were prepared, SAR study concluded that the compounds having oxadiazole moiety is less active as compared to thiazole-based moiety.

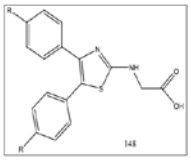
Sinha *et al.*[107] prepared new analogs containing 2-amino thiazole and evaluated for anti-inflammatory activity. Chronic inflammation is very complicated in various diseases including respiratory tract, asthma, cancer, cardiovascular, allergy and arthritis disorders. Two compounds 146 and 147 showed potent action with IC_{50} values of 0.9 ± 0.1 μM, 1.4 ± 0.1 μM, to inhibit 5-LOX. Compound 146 inhibit 5-LOX enzyme by competitive method whereas compound 147 inhibits by non-competitive method.

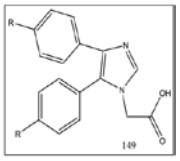




Abdelazeem *et al.*[108] synthesized novel analogs containing diarythiazole and diaryimidazole and *in vitro* evaluated for selective COXs- inhibitory activity and *in vivo* for the analgesic activity. Diphenylthiazole analogs 148a and 148b and diaryimidazole analogs 149a and 149b were highly active against COX-1 over COX-2. Derivative 148b exhibited high activity against COX-1 having IC_{50} value 0.32 μM and selective index 28.84.

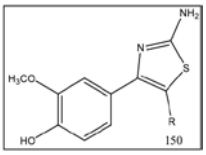
No.	R
148a	H
148b	OCH_3
149a	H
149b	OCH_3





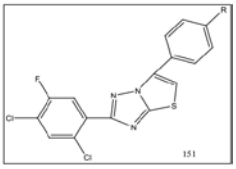
El-Achkar *et al.*[109] prepared novel diazole analogs and estimated their anti-inflammatory activity. Two compounds 150a and 150b displayed potent anti-inflammatory activity having IC_{50} values 9.01 ± 0.01 μM and 11.65 ± 6.20 μM respectively. By *in vivo* study it was confirmed that compound 150a inhibited both COX-1 and COX-2 while derivative 150b inhibited only COX-2 enzyme.

No.	R
150a	C_4H_9
150b	$CH_2C_6H_5$



Karthikeyan[110] prepared a series of analogs containing 2,4-dichloro-5-fluorophenyl thiazolotriazoles and estimated their analgesic, anti-inflammatory and antimicrobial activity by *in vitro* testing. Compounds 151a, 151b, 151c and 151d displayed anti-inflammatory activity and the derivatives 151c, 151d, 151e and 151f displayed higher antibacterial activity. Compounds 151c, 151d and 151f showed good antifungal activity.

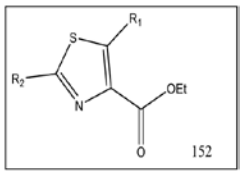
No.	151a	151b	151c	151d	151e	151f
R	4-F	4-Cl	2,4-Cl_2-5-F	4-Br	4-OCH_3	4-F



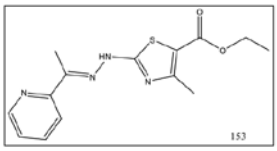
Anti-tuberculosis activity

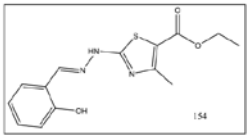
Karale *et al.*[111] synthesized 2,4,5-trisubstituted thiazole derivatives and evaluated for anti-tuberculosis activity. The derivatives 152a and 152b displayed high activity having MIC values less than 4.2 μg/ml in the *in vitro* test using H37Rv cell lines and toxicity against CHO-KI cells. Compound 152b was found to be harmless to the CHO cells at a dose 8 μg/mL and given data supported the compound to be very useful as agonist of the MDR-TB.

No.	R1	R2
152a		
152b		



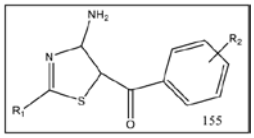
Makam *et al.*[112] synthesized 2-(2-hydraziyl) thiazole derivatives and estimated their anti-mycobacterial activity. Two compounds 153 and 154 displayed more potent inhibitory action towards *M. tuberculosis* H37Rv having MIC values of 12.5 and 25 μM respectively. Docking studies evaluated binding interactions of the compounds with β-ketoacyl-ACP synthase protein. The inhibition constant for derivatives 153 and 154 were measured to be 1.46 μM and 0.177 μM respectively.





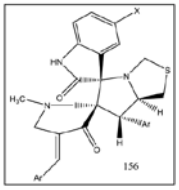
Romagnoli *et al.*[113] prepared new analogs containing 2-pyrrolidinyl-4-amino-5-(30,40,50-trimethoxybenzoyl) thiazole and evaluated for anti-microtubule activity. Compound 155 showed potent activity against cancer cell by inhibiting cancer cell lines at submicromolar concentration and also inhibited tubulin polymerization. SAR studies confirmed that substitution at C-2 position (pyrrolidin-1-yl) moiety and at C-5 (30,40,50-trimethoxybenzoyl) moiety were essential for their potent activity.

No.	R1	R2
155	Pyrrolidin-1-yl	3',4',5',$(OCH_3)_3$



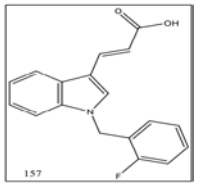
Karthikeyan *et al.*[114] prepared new analogs containing spiro-pyrrolothiazole and estimated their anti-tubercular activity. Agar dilution *in vitro* testing method was used to determine activity against H37Rv (MTB) and multi-drug resistant (MDR-TB) cell lines. Compound 156f displayed more potent activity with MIC 0.6 μM against MTB and MDR-TB. It was more effective in comparison to ethambutol having MIC value 7.6 μM. Six compounds 156a, 156b, 156c, 156d, 156e, and 156f showed maximum activity against MTB and MDR-TB with MIC values in between 0.6 to 2.8 μM.

No.	Ar	X
156a	4-FC_6H_4	Cl
156b	2,4-$Cl_2C_6H_3$	Cl
156c	4-FC_6H_4	NO_2
156d	4-BrC_6H_4	NO_2
156e	2-ClC_6H_4	NO_2
156f	2,4-$Cl_2C_6H_3$	NO_2



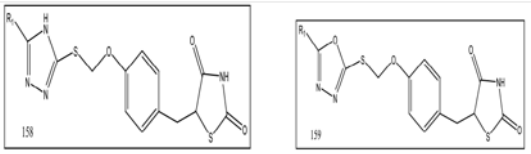
Anti-diabetic activity

Xu *et al.*[115] prepared new analogs containing thiazoles and indoles and estimated their anti-diabetic activity. Most of prepared analogs displayed inhibitory action in the formation of LPS-stimulated TNF-a. Compound 157 showed more binding affinity to the ligand A-FABP/ap2 with possible Ki value of 33 μM and showed potent anti-diabetic activity.

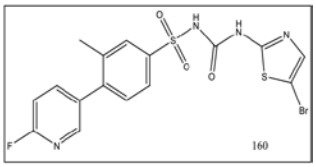


Iqbal *et al.*[116] prepared new series of analogs containing thiazolidinedione thiazole/triazole/oxadiazole and evaluated for hypoglycemic and hypolipidemic activity. Compounds 158, 159a and 159b displayed hypoglycemic and hypolipidemic activity. These analogs reduced the plasma glucose level and triglyceride level. Hence, these analogs were useful in the treatment of the complications of hyperglycemia and cardiovascular.

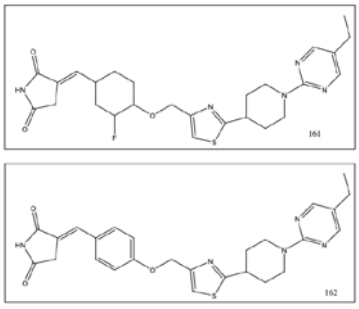
No.	R1
158	p-OMe-phenyl
159a	3-pyridyl
159b	4-pyridyl



Kitas *et al.*[61] synthesized sulfonylureido thiazole derivatives and analyzed their inhibitory effect on fructose-1,6-bisphosphatase for the cure of non-insulin dependent diabetes. Compound 160 showed good activity in the inhibition of fructose-1,6-bisphosphatase for the cure of type-2 diabetes with IC_{50} HL 0.13, HL IC_{50} F2 0.09, ML EC_{50} value 10.

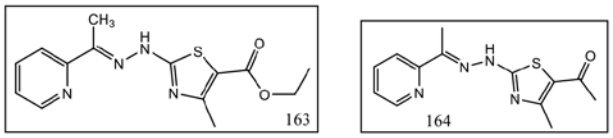


Kim *et al.*[117] synthesized new analogs containing 4-(phenoxymethyl) thiazole and analyzed these for anti-diabetic activity. Using *in vitro* method, two derivatives 161 and 162 were screened for anti-diabetic activity taking GPR119 into consideration. These compounds were found to have EC_{50} value of 49 μM and 18 μM respectively.

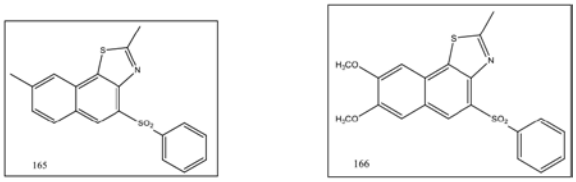


Anti-malarial activity

Makam *et al.*[118] synthesized 2-(2-hydrazinyl) thiazole derivatives and analyzed these for anti-malarial activity. Compounds 163 and 164 displayed potent anti-malarial activity by inhibiting NF54, against *P. falciparum* with IC_{50} values of 0.725 μM and 0.648 μM respectively.

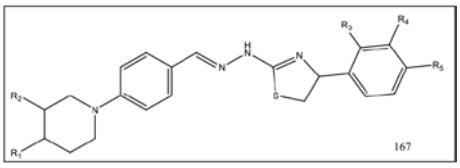


Cohen *et al.*[119] synthesized naphtho [2,1-d] thiazole derivatives and evaluated for anti-malarial activity. Compounds 165 and 166 showed activity against K1 *P. falciparum* strain. SAR of the analogs confirmed that H-atom at R1 and presence of an electron releasing group as R4 substituent aid both the absence of cytotoxicity and enhanced antiplasmodial action.



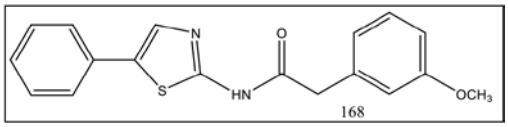
Miscellaneous

Saglik *et al.*[60] prepared novel thiazoles based derivatives and evaluated as MAO inhibitors. Compounds 167a and 167b displayed good inhibition of MAO-A and MAO-B with IC_{50} values 0.134 ± 0.004 μM and 0.123 ± 0.005 μM, 0.027 ± 0.001 μM and 0.025 ± 0.001 μM respectively. These derivatives were effective and safe in the neurological disease.

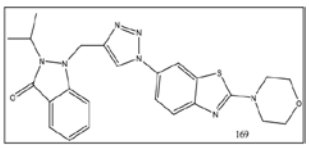


No.	R1	R2	R3	R4	R5
167a	CH_3	H	H	OH	OH
167b	H	CH_3	H	OH	OH

Sun *et al.*[120] prepared new analogs containing thiazole acetamide and evaluated for anticholinesterase activity for the treatment of the Alzheimer's disease. Compound **168** displayed high activity against AChE inhibition with MIC value IC_{50} = 3.14 ± 0.16 μM, SI value against (BuChE) = 2.94. Further testing found that prepared analogs have anti-cholinesterase activity by inhibition of Ab-aggregation and b-secretase.



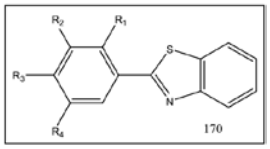
Avila *et al.*[121] prepared novel series of analogs containing Triazolbenzo[d]thiazoles and evaluated for neuroprotective activity. Compound 169 demonstrated neuroprotective activity in human neuroblastoma (SH-SY5Y) cells.



Ha *et al.*[122] prepared novel series of analogs containing alkoxy and /or hydroxy substituted phenyl-benzo[d] thiazole by reacting with 2-aminothiophenol in MeOH and benzaldehydes and evaluated for anti-tyrosinase activity. Two compounds 170a and 170b showed high action against tyrosinase enzyme (45.36–73.07% and 49.94–94.17% at 0.01–20 μM, respectively) and IC_{50}

values 1.14 ± 0.48 and 0.01 ± 0.0002 μM, than standard drug kojic acid (9.29-50.80% at 1.25-20 μM). SAR study confirmed that substitutions of hydroxyl group at R3 and R1 or both of the position of phenyl ring played vital role in the inhibition of tyrosinase.

Sr.	R1	R2	R3	R4
170a	H	H	OH	H
170b	OH	H	OH	H



CONCLUSION

Thiazoles are extremely reactive compounds. There are abundant reaction procedures to synthesize thiazoles. Most of the thiazole derivatives can be conveniently synthesized. Thiazole nucleus holds a very crucial place in the heterocyclic chemistry and the thiazoles will yield a far-reaching effect on the society because of its diverse pharmacological activities like anti-inflammatory, anti-tubercular, antimicrobial, anti-diabetic, anti-malarial and anticancer. Thiazole nucleus is a perfect candidate to explore lead compounds and other drug molecules for variety of disorders. The availability of many thiazole bearing drugs like sulfathiazole, bleomycin, ritonavir, nizatidine, meloxicam, cefrine, febutaz, pramipex has excited medicinal chemists to design and develop more of such versatile compounds. Thiazole analogs show better therapeutic effect and less toxicity. The review provides different directions in the synthesis of novel thiazoles and also reveals diverse targets for augmentation in the field of designing of novel thiazoles.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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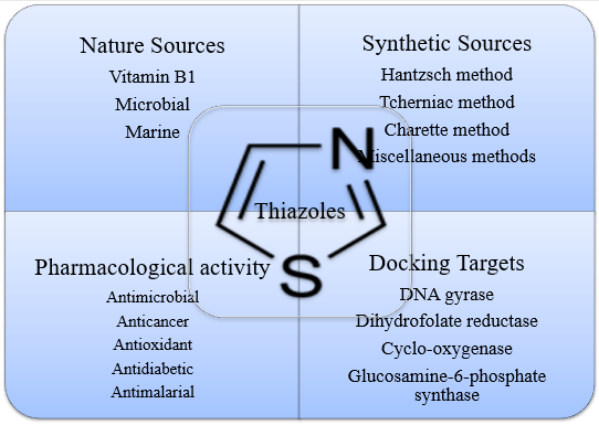
PICTORIAL ABSTRACT



SUMMARY

Thiazoles are very prominent heterocyclic compounds. Hantzsch was pioneer in the development of synthetic route of thiazoles from α-haloketones or α-halogenaldehyde and thioamide. There are numerous ways to synthesize thiazoles; thioforamide, thiourea, α-thiocyanotoketones, and vinyl bromide play a salient role in the synthesis of thiazoles. Thiazoles demonstrate an extensive pharmacological activity, *viz.* antimicrobial, antidepressant, antineoplastic, antiretroviral, antifungal, antidiabetic, and anti-inflammatory. The thiazoles have a lot of potential to generate biological active compound for the betterment of society.

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