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Review Article

A Review On Thiazole As Anticancer Agents

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Abstract

A study on heterocyclic compounds is of great interest in pharmaceutical area. This has catalyzed the discovery and development of much new heterocyclic chemistry and methods. In fact, one of the reasons for the wide spread use of heterocyclic compounds is that their structures can be suitably manipulated to achieve a required modification in function. Literature survey shows that the modifications of thiazole ring have highly effective to improve potency and lesser toxicity. The present review shows the important biological activity (Anticancer Activity) possesses by thiazole.

Keywords: Thiazole derivatives, Anticancer activity.

INTRODUCTION

Now a days, in the pharmaceutical area study on heterocyclic compounds is of great interest. The discovery and development of much new heterocyclic chemistry and methods is catalysed by this study. The main reasons for the wide spread use of heterocyclic compounds is that the structures of heterocyclic compounds can be suitably manipulated to achieve a required modification in functions. Knowledge of heterocyclic chemistry is benefit in biosynthesis and drug metabolism. So, pharmaceutical and agrochemical industries have made rapid and significant progresses to quench the quest of organic chemists in discovering and developing suitable heterocyclic compounds for the benefit of mankind. Thus, heterocyclic chemistry attracts scientists to working in the area of natural products as well as synthetic organic chemistry. The reason for the upsurge in the interest and development of these heterocyclic compounds is due to their pesticidal, potential chemotherapeutic, fungicidal and antiviral properties. A number of heterocyclic derivatives containing nitrogen have been used as versatile scaffolds in drug development.

Thiazoles are the class of organic compounds related to azoles containing thiazole as a functional group. Thiazoles are aromatic, heterocyclic organic compound which have a five-membered ring structure with molecular formula C_3H_3NS**[1]**.As the heterocyclic compounds are interest for its theoretical implications due to its synthetic procedure and physiological and industrial significance**[2]**.Thiazole and its derivatives are the most utilized heterocycles. Thiazole ring system plays an important role in the drug market with a wide spectrum of activity such as antibacterial, antifungal and antiviral **[3]**. Natural products having thiazole ring are known for their antibiotic and antifungal activities **[4]**. Marine products having thiazole ring exhibit antineoplastic, antifungal andinflammatory activity **[5]**. Naturally thiazole ring is found in essential vitamin B_1, bacitracin, and pencillins. Thiamine is a water soluble vitamin that helps the body release energy from carbohydrates during metabolism. It also helps in the normal functioning of the nervous system by its role in the synthesis of acetylcholine, a neurotransmitter. Thiamine is found mostly in pasta and breads made from refined flours. It is also found in ready-to-eat cereals and in navy and kidney beans. Other thiazole compounds include rhodanine and the dye rhodanine red derived from it, and the yellow dye primuline. Synthetic drugs belonging to the thiazole family include sulfathiazole, sulfasuxidine, and thiazolsulfone (Promizole). 2-Mercapto- benzothiazole (Mertax) is a thiazole derivative used for accelerating the vulcanization of rubber.

Thiazole derivatives were found to possess anticonvulsant, antimicrobial, anti-inflammatory, anticancer, anti-HIV, antidiabetic, anti-alzheimer,

antihypertensive and antioxidant activities. Due to its potent and significant biological activities it has great pharmaceutical importance; hence, synthesis of this compound is of considerable interest**[6,7]**.

- 4- Thiazolidone derivatives have found to show a very good antifungal activity.
- (1, 3 benzothiazol-2yl) amino 9-(10H) acridinone derivatives**[8]**have found to possess antileshmanial activity.
- 4-Substituted Methoxybenzoyl-aryl-thiazole has been found to possess a very good anticancer activity.

They have been studied extensively because of their ready accessibility, diverse chemical reactivity and broad spectrum of biological activity **[9]**.

Recently the applications of thiazoles were found in drug development for the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial, HIV infections**[10]**, hypnotics**[11]** and more recently for the treatment of pain**[12]**,as fibrinogen receptor antagonists with antithrombotic activity**[13]** and as new inhibitors of bacterial DNA gyrase B**[14]**. Thiazoles containing N=C=S moiety has been employed as antipsychotic and anti-bacterial activity.

The substituted thiazoles compounds have number of characteristics pharmacological features such as:

1. Relative stability
2. Ease of starting material.
3. Built biocidal unit.
4. Enhanced lipid solubility with hydrophilicity.
5. Easy metabolism of compounds.

CHEMISTRY

Thiazole is a heterocyclic compound containing both a nitrogen and sulphur atom as part of the aromatic five-member ring. Thiazoleand related compounds are 1,3-azoles. They are isomeric with the 1,2-azoles **Figure 1**, known as isothiazole. The numbering system is shown below for naming derivatives of thiazoles**[15]**.

STRUCTURE ACTIVITY RELATIONSHIP

From the literature review the structural activity relationship of the thiazole ring can be summarized as follows**Figure 2[16]**.

- ❖ The ester group at position 2 of thiazole ring is necessary to have higher antitumor activity than the acetyl and N-phenyl carboxamide groups.
- ❖ The presence of chlorine group at the position 2, 4 or 4 in the aryl moiety had high cytotoxic activity than halogen at position 3.
- ❖ 4-Substituted Methoxybenzoyl-aryl-thiazole has been found to possess a very good anticancer activity.
- ❖ Methyl substituted benzyl group at the 2nd position of the thiazole ring is more potent than the phenyl substitution.
- ❖ m-Phenylsulphanamido group at the 4th position shows antibacterial activity.
- ❖ The compounds with methyl substitution in the 5th position of the thiazole ring were found to be less active against M. Tuberculosis than the compound with no substitution in the 5th position.
- ❖ Different thiazole molecules when fused with pyrazole ring containing heterocycles presents antibacterial activity.
- ❖ Aryl amino thiazoles were found to possess effective antibacterial and antiinflammatory activity.
- ❖ Potent derivatives have highly electronegative part of sulfhydryl group, specifically Schiff bases, probably due to their ability to increase the penetration in the bacterial cell. Cyano group has no role.
- ❖ Optimization of sulfhydryl group reveals loss of activity.
- ❖ Free amino group have open area for the further modification.

BIOLOGICAL ACTIVITY

Thiazoles and fused thiazole derivatives are known to possess several biological activities including anticancer activity**[17,19]**. There are a variety of mechanisms for the antitumor action of thiazole and fused thiazole derivatives, acting on cancer biotargets, such as tumor necrosis factor TNF- α**[20]**,inosine monophosphate dehydrogenase (IMPDH) **[21]**and apoptosis inducers **[22]**.Tiazofurin**Figure 3[23]**the synthetic nucleoside analogue, is a potent inhibitor of inosine monophosphate dehydrogenase (IMPDH). Inhibition of this enzyme results in a decrease in gu-

anosine triphosphate (GTP) and deoxyguanosine triphosphate (dGTP) biosynthesis, producing inhibition of tumor cell proliferation.

Tiazofurin is a high-priority candidate for clinical trials with potential importance for treatment of lung tumours, metastases and acute myelogenous leukaemia**[24,26]**. To improve its biological properties, many analogues had been prepared, including a number of those with variations in the furanose ring for example compounds**Figure 4[27-29]**.

Some nicotinamide adenine dinucleotide (NAD) analogues were modified at the nicotinamide moiety and were identified as active antitumor and antiviral. For example thiazole-4-carboxamide adenine dinucleotide analogues were prepared as potential selective human (IMPDH) inhibitors**Figure 5[30]**.

Epothilones,**Figure 6** is a recent class of natural products which have been reported to exhibit extraordinarily potent cytotoxicity in a broad range of human cancer cell lines, in addition epothilones are known to induce mitotic arrest at the G2/M transition leading to apoptotic cell death. Epothilones are apoptosis inducers through one of two pathways, namely a receptormediated and a non receptor-mediated or chemical-induced pathway **[31,32]**. Thus epothilones, have much greater activity against multi-drug resistant cell lines[**33]**.

The position of the thiazole-containing side chain of epothilones was investigated. Among a tested series of hybrid compounds the one containing thiazole side chain at C_{15} (MSt-2) showed the maximum potency to induce apoptosis, while another containing thiazole side chain at C_3 (MSt-6) was less potent**Figure 7[34]**. Thus it was reported that the 16membered trilactone core structure with a thiazole-containing side chain of epothilones were promising apoptosis inducers**[35]**.

BIOLOGICAL ACTIVITY REVIEW

A. Grozav*et al.*,synthesized 2-(2-((1H-indol-5yl)methylene)-hydrazinyl)-thiazole derivatives-**Figure 8**. These derivatives evaluated for their in vitro cytotoxicity on two carcinoma cell lines; human ovarian cancer cells (A2780) and human cervical cancer cells (HeLa). Compounds **1a** and **1c** had a good inhibition on both A2780 and HeLa while derivative **1e** has been active only on HeLa cell lines **[36].**

B. Parrino*et al.*,synthesized new series of thiazolenortopsentin analogues**Figure 9**. The antiproliferative activity of the new derivatives was tested against different human tumor cell lines of the NCI full panel of approximately 60 human cancer cell lines derived from 9 human cancer cell types that have been grouped into disease subpanels including leukemia, non-small cell lung, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast tumor cell lines. The compounds **2a,o**showed antiproliferative activity in the micromolar to nanomolar range (GI50 0.03-98.0 μM). Compounds **2a** and **2o** were active against the total number of cell lines investigated, whereas compounds **2m** and **2n** were cytotoxic against a very high percentage of the tested cell lines (96% and 93% respectively) **[37]**.

Sadashiv*et al.*,synthesized a series of 2,4-disubstituted-1,3-thiazoles linked with pyrazoline scaffolds**Figure 10**. The compounds were evaluated for their anticancer activity against A549 and MCF-7 human cancer cell lines and in vitro antimicrobial activity against pathogenic microbial strains. The compounds **3a**,**3c** and **3d** , exhibited better activity than standard drug Cisplatin**[38]**.

S. P.Shaik*etal.*, synthesized a new class of 1,2,3-triazolo linked benzo[d]imidazo[2,1-b]thiazole conjugates**Figure 11** and evaluated for their cytotoxic activity. Among them, conjugates **4b**and **4d** showed significant cytotoxic activity against the human breast cancer cell line (MCF-7) **[39]**.

G. T.Zitouni*et al.*, synthesized new bis-thiazole derivatives**Figure 12**and investigated for their cytotoxic effects on A549 human lung adenocarcinoma, C6 rat glioma, 5RP7 H-ras oncogene transformed rat embryo fibroblast and NIH/3T3 mouse embryonic fibroblast cell lines and DNA synthesis inhibitory effects. The inhibitory effects of these compounds on AChE and BuChE were also evaluated. Among these compounds, compound **5e** was found to be the most promising anticancer agent due to its remarkable antiproliferative effects on A549 and C6 cell lines and low cytotoxicity against NIH/3T3 cells**[40]**.

G. Y. Yeap*et al.*,synthesized a new hydroxybenzene modified thiazole-azo derivative**Figure 13** and its chemosensing towards heavy metal ions (Na+, Al3+, K+, Ca2+, Mn2+, Fe2+, Ni2+, Cu2+, Zn2+, Ag+, Cd2+, Hg2+ and Pb2+) was characterized by UV–vis spectroscopy**[41]**.

F. I. Hamed*et al.*, synthesized and characterized

a series of new heterocyclic compounds with the thiazole nucleus**Figure 14**.The 2 amino-4-(4-chlorophenyl)-6-(4-phenylthiazol-2-yl)-4H-pyran-3, 5-dicarbonitrile **7b** showed the maximum cytotoxicity among the synthesized compounds towards the six cancer cell lines **[42]**.

T. A. R. Santos *et al.,* evaluated 1,3-thiazole and thiosemicarbazone compounds**Figure 15**for Antitumor and immunomodulatory activities The compounds **8a**, **8b**, and **8c** are most potent anticancer and immunomodulatory agent**[43]**.

S. Mirza*et al.,*synthesized substituted aryl thiazoles**Figure 16** and their in vitro cytotoxicity was evaluated against four cancer cell lines, MCF-7 (ER+ve breast), MDA-MB-231 (ER-ve breast), HCT116 (colorectal) and HeLa (cervical).Among them, compounds **9a-9e** were found to be toxic to all four cancer cell lines **[44]**.

W. X. Cai*et al.,* synthesized a series of novel 2-phenyl-4-trifluoromethyl thiazole-5-carboxamide derivatives**Figure 17** and evaluated for their anticancer activity against A-549, Bel7402, and HCT-8 cell lines. Compound **11a** (48%) and **11b** (40%), which is a little lower than that of control, while some of them exhibited low activity against A-549. Furthermore, compound **10a** and **10b** can increase the A-549 cell growth. All the title compounds exhibited no inhibition or low inhibitor effect against Bel7402 and HCT-8. Compound **10b** (40%) displayed moderate inhibitory against HCT-8 **[45]**.

S. M. Gomha*et al.,* synthesized new thiazole derivatives**Figure 18**. Compounds **12a**, **12b** and **12c** may have significant and promising anticancer efficiency for hepatocellular carcinoma with low IC50, 0.5 0.02, 0.52 0.03, and 0.84 0.04 μM, respectively **[46]**.

R. Ali *et al.,* synthesizeda series of imidazo[2,1-b]thiazoles bearing pyrazole moieties**Figure 19** and evaluated for anticancer activity. The in vitro anticancer evaluation revealed that compounds**13a, 13b, 13c** exhibitedincreased potency towards CNS SNB-75 and Renal UO-31 cancer cell lines**[47]**.

S. Koppireddi*et al.,*synthesized a series of new 3,6-diphenylimidazo[2,1-b]thiazole derivatives **Figure 20** and evaluated for their anticancer activity. Among the all synthesized compounds, **14c** were most potent anti-proliferative activity against HeLa, MDA-MB-231, A549 and THP1 human cancer cell lines **[48]**.

S. A. F. Rostom*et al.,*synthesized novel bifunctionalethyl 2-amino-4-methylthiazole-5-carboxylatederivatives**Figure 21**. Five cell lines namely; the non-small cell lung cancer Hop-92, NCI-H522, ovarian cancer IGROV1, colon cancer HCC-2998 and melanoma SK-MEL-2 exhibited remarkable sensitivity against most of the tested compounds. Compound **15** proved to possess a broad spectrum of anticancer activity against 29 of the tested 60 subpanel tumor cell lines **[49]**.

B. L. Zhang et al.,synthesized a series of steroidal[17,16-d]thiazole, steroidal[1,2-b]pyridine and steroidal[17,16-d]thiazole[2,1-b] imidazo products**Figure 22**. These compounds were evaluated for their anti-proliferation activity in vitro against EC109, EC9706 and MGC803 cell lines. Bioactivities test results showed that compound **16**series have a relatively goodactivity against the three cell lines, especially EC109 cell line **[50]**.

M. S. A. Saadi*et al.,*synthesized and evaluated two series of 2,4,5-polysubstituted thiazoles comprising the acid hydrazide functionality and some derived pharmacophores known to contribute to various chemotherapeutic activities**Figure 23**. Compounds were selected and tested for their preliminary in-vitro anticancer activity according to the current one-dose protocol of the NCI. Three cell lines, non-small cell lung cancer Hop-92, ovarian cancer IGROV1, and melanoma SK-MEL-2, exhibited some sensitivity against most of the tested compounds. Compound **17** proved to be the most active anticancer member with a broad spectrum of activity against most of the tested subpanel tumor cell lines **[51]**.

K. M.Dawood*et al.,* synthesized 2- (4-(pyrazol-4-yl)thiazol-2-ylimino)-1,3,4-thiadiazole derivatives**Figure 24**. Compounds **18a-c**, and**19a-b**were tested for their in-vitro antitumor activity against human hepatocellular carcinoma cell (HepG2), human breast cancer cells (MCF-7) and human lung cancer cells (A549) **[52]**.

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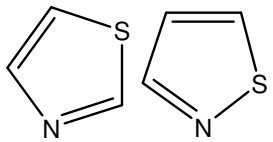


ThiazoleIsothiazole (1,3-azole) (1,2-azole)

Figure 1

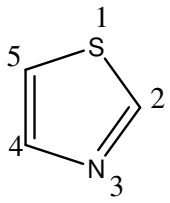
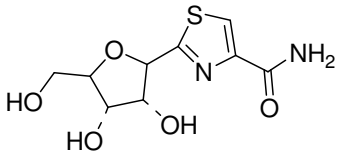
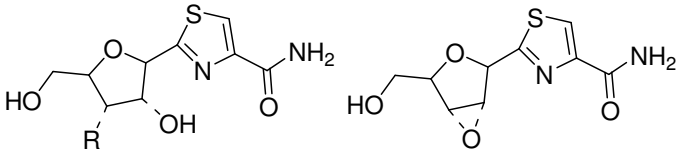


Figure 2



Tiazofurin

Figure 3



R = NHAc, NH_2

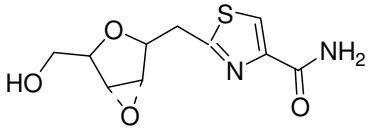
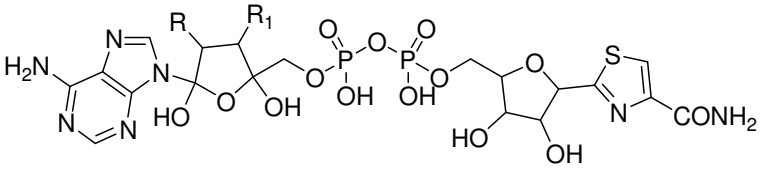
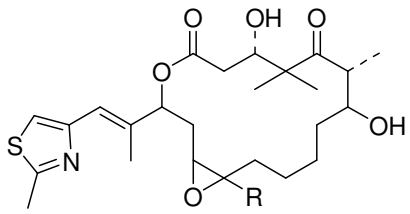


Figure 4



R, R_1 = H,CH_3

Figure 5



Compound	R
Epothilone A	H
Epothilone B	CH_3

Figure 6

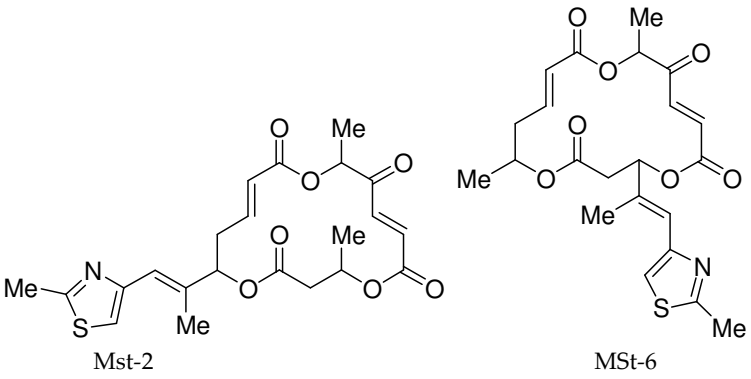
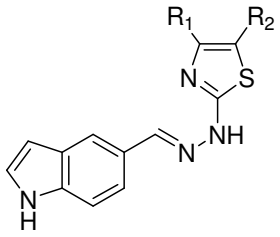


Figure 7

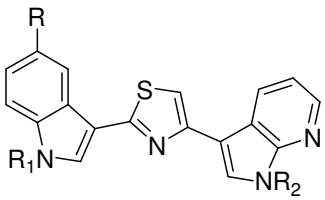
S.no.	R_1	R_2
1a	Me	H
1b	Me	COMe
1c	Ph	H
1d	Me	COOEt
1e	CH_2COOEt	H
1f	COOEt	H



1

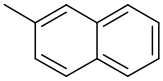
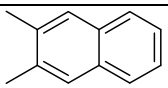
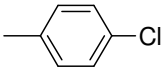
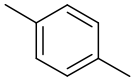
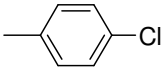
Figure 8

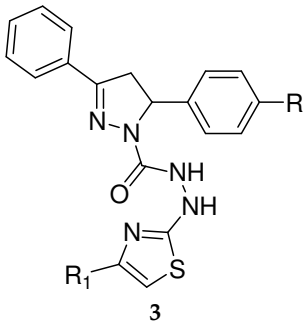
S.no.	R	R_1	R_2
2a	OMe	CH_2CH_2OMe	H
2b	OMe	CH_2CH_2OMe	Me
2c	OMe	CH_2CH_2OMe	CH_2CH_2OMe
2d	OMe	Me	CH_2CH_2OMe
2e	Br	CH_2CH_2OMe	H
2f	Br	CH_2CH_2OMe	Me
2g	Br	CH_2CH_2OMe	CH_2CH_2OMe
2h	Br	Me	CH_2CH_2OMe
2i	F	CH_2CH_2OMe	H
2j	F	CH_2CH_2OMe	Me
2k	F	CH_2CH_2OMe	CH_2CH_2OMe
2l	F	Me	CH_2CH_2OMe
2m	F	H	CH_2CH_2OMe
2n	H	H	CH_2CH_2OMe
2o	Br	H	CH_2CH_2OMe



2

Figure 9

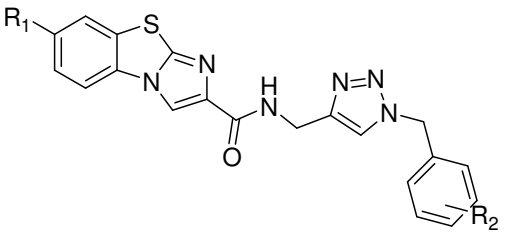
S.no.	R	R_1
3a	Cl	
3b	Cl	
3c	Cl	
3d	Cl	
3e	Cl	
3f	F	
3g	F	



3

Figure 10

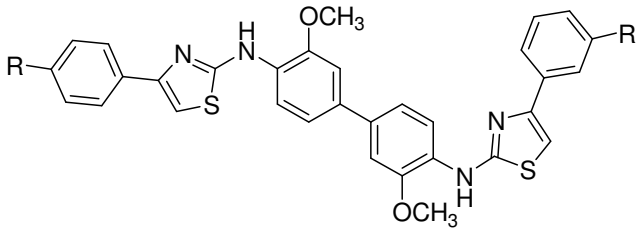
S.no.	R_1	R_2
4a	H	3-OH
4b	H	4-F
4c	OEt	4-OH
4d	Me	4-F
4e	H	3-OPh
4f	OMe	4-F



4

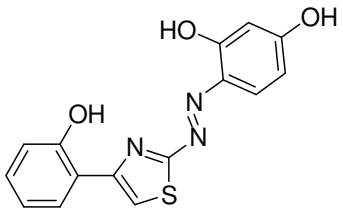
Figure 11

S.no.	R
5a	H
5b	4-NO_2
5c	4-CH_3
5d	4-OCH_3
5e	4-Br
5f	4-Cl



5

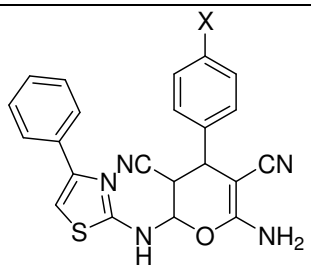
Figure 12



6

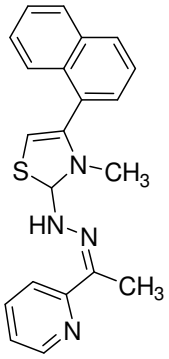
Figure 13

S.no.	X
7a	H
7b	Cl
7c	OCH_3

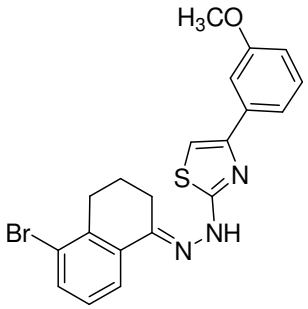


7

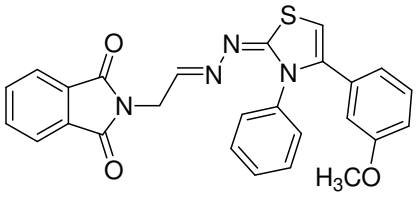
Figure 14



8a

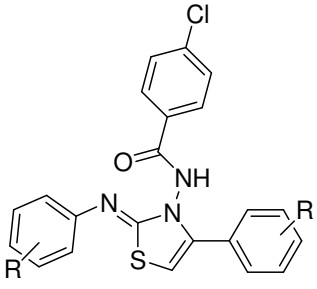


8b



8c

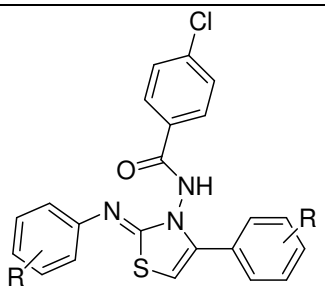
S.no.	R	R
9a	p-Bromo	p-NO_2
9b	p-Bromo	p-Bromo
9c	p-NO_2	p-Bromo
9d	p-NO_2	p-NO_2
9e	p-Bromo	p-Chloro



9

Figure 15

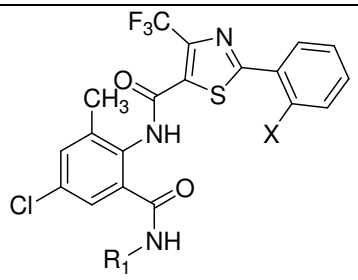
S.no.	R	R
9a	p-Bromo	p-NO_2
9b	p-Bromo	p-Bromo
9c	p-NO_2	p-Bromo
9d	p-NO_2	p-NO_2
9e	p-Bromo	p-Chloro



9

Figure 16

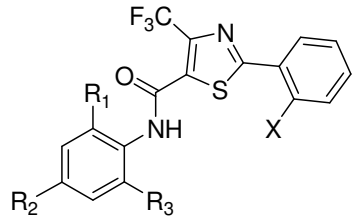
S.no.	R	X
10a	Cl	CH_3
10b	Cl	



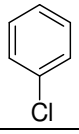
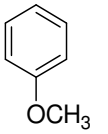
10

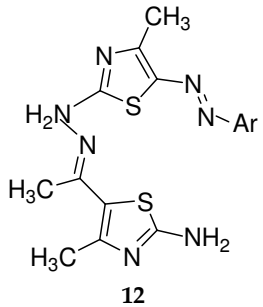
Figure 17

S.no.	X	R_1	R_2	R_3
11a	Cl	CH_3	Cl	H
11b	Cl	Cl	Cl	Cl



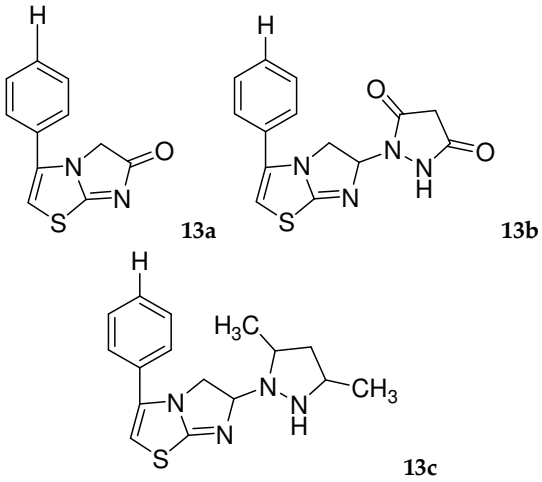
11

S.no	Ar
12a	
12b	
12c	



12

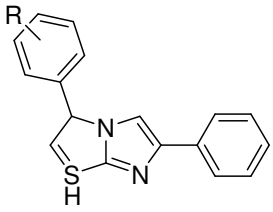
Figure 18



13a **13b** **13c**

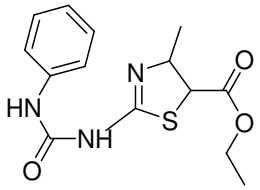
Figure 19

S.no.	R
14a	4-F
14b	4-Cl
14c	3-CF_3
14d	4-Br
14e	2-OMe



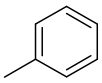
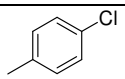
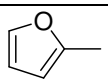
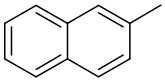
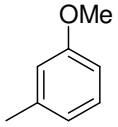
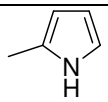
14

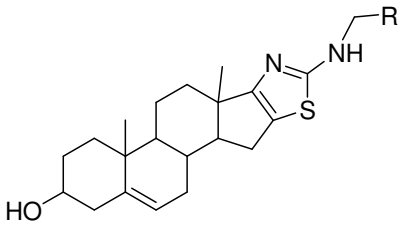
Figure 20



15

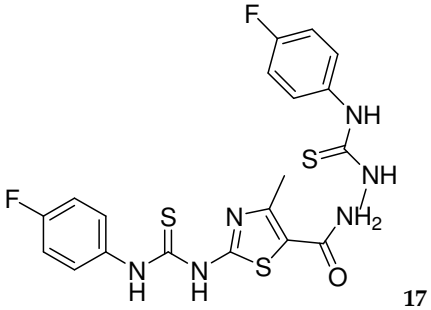
Figure 21

S.no.	R
16a	
16b	
16c	
16d	
16e	
16f	



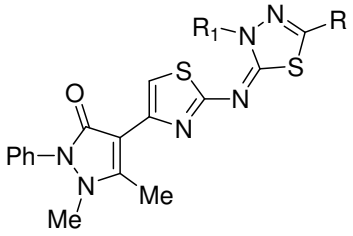
16

Figure 22



17

Figure 23

S.no	R	R_1	
18a	OCMe	4-MeC_6H_4	 **18**
18b	OCMe	4-$OMeC_6H_4$	
18c	OCOEt	4-$OMeC_6H_4$	

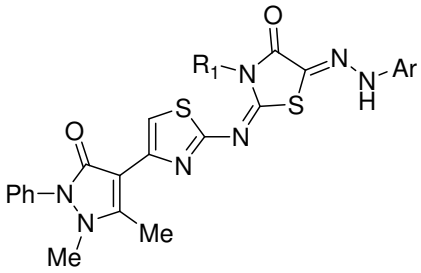
S.no	Ar	R_1	
19a	4-$OMeC_6H_4$	Ph	 **19**
19b	2-Furyl	Ph	

Figure 24