CHEMISTRY OF ANTICANCER THIAZOLE COMPOUNDS

Chawla Amit*, Sheelmani, Arashdeep Singh, Chawla Payal, Dhawan R K
Khalsa College of Pharmacy, Amritsar, Punjab, India

ABSTRACT:
In recent years heterocyclic compounds analogues and derivatives have attracted strong interest due to their biological and pharmacological properties. A vast variety of thiazole derivatives having excellent broad spectrum activity forms an invaluable part of the present research for researchers. The present review focus on the different methods of synthesis of substituted thiazoles with potential activities that are now in developing phase. The search for new biologically active thiazole analogues continues to be an area of intensive investigation in medicinal chemistry. The present review describes ongoing research in search for new thiazole compounds that can prove usefulness for the design of future target and development of new drug molecules. Most of the compounds showed moderate to good anticancer activity which are described in this review.

Keywords: Thiazole; Anticancer; Heterocyclics

INTRODUCTION
Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways\cite{1}. The heterocyclic molecules which possess indole, pyrazole and azetidine moieties exhibit wide range of biological activities\cite{2}. Synthesis of the basic nucleus is well established and the proposed derivatives can be synthesized based upon the literature available about the reaction involved\cite{3}.
Indoles are one of the most important alkaloids molecules found extensively in biological systems, which play vital role in many of the biochemical process. Indole ring constitutes an important basic skeleton and development of the drug\cite{4}.
Thiazoles are a class of organic compounds related to azoles with a common thiazole functional group\cite{5}. Thiazole was first described by Hantzsch and Waber in 1887. Popp confirmed its structure in 1889\cite{6}.

Thiazole is aromatic, heterocyclic organic compound that has a five-membered molecular ring structure,\( \text{C}_3\text{H}_3\text{N} \). The numbering starts from the sulphur atom. Thiazole are well represented in biomolecules\cite{7}.

Thiazoles molecules containing a thiazole amine-moiety exhibit interesting biological activities depending on the substitution pattern at the thiazole ring\cite{8}.

Proposed work is based upon the development of some newer structurally related compounds of benzothiazoles and evaluation of biological activity. Benzothiazoles are fused membered rings, which contain the heterocycles bearing thiazole. The basic structure of benzothiazole consist of benzene ring fused with 4, 5 position of thiazole. The two rings together constitute the basic nucleus 1, 3-benzothiazle. Benzothiazoles show antitumor activity, especially the phenyl-substituted benzothiazoles\cite{9}.

Recently thiazolidinone research area unexpectedly became interesting and promising
for oncology. In-depth study of PPARs allowed putting forward and validating the concept of anticancer potential existence of PPAR agonists including thiazolidinedione. While applying the research strategy through the past few years we succeeded in gaining a number of interesting synthetic results that make possible to extend the field of the chemistry of thiazolidinone and related heterocycles, especially in the scope of drug-like molecules design\textsuperscript{[10]}. Anticancer activity evaluation of 4-thiazolidinones and related heterocyclic systems and efficient approaches to interpretation of structure–activity correlation\textsuperscript{[11]}.

**THIAZOLE ANTICANCER DRUGS**

Kini S, \textit{et al}\textsuperscript{[12]} refluxed o-aminophenols with substituted benzoic acid in presence of polyphosphoric acid at higher temperature to get aryl substituted benzothiazoles and evaluated them against Human Cervical Cancer cell lines as anticancer drugs.

![Fig. 1](image1.png)

Stanton HLK, \textit{et al} synthesized benzothiazole containing phthalimide and studied their anti-cancer activity on human carcinoma cell lines\textsuperscript{[13]}.

![Fig. 2](image2.png)

A number of N-bis(trifluoromethyl)alkyl-N′-thiazolyl and benzothiazolylureas have been synthesized and evaluated by Luzina \textit{et al} against the human cancer cell lines\textsuperscript{[14]}. The most sensitive cell lines relative to the tested compound was: (3) PC-3 (prostate cancer, log GI50 −7.10), and SR (leukemia, log GI50 −5.44) human cancer cells. Synthesis and activity of a series of 4-thiazoyl substituted analogs of novel pyrrolocarbazole as poly(ADP-ribose) polymerase-1-(PARP-1) inhibitors have been disclosed by Dunn \textit{et al}\textsuperscript{[15]}. Among these compounds, (4) found to be more potent.

![Fig. 3](image3.png)

All the synthesized compounds showed remarkable antitumor activity against human MCF7 cell line. Compound 5b was the most potent one comparing with the standard drug DXR\textsuperscript{[16]}.

![Fig. 4](image4.png)

a, Ar = C6H5; b, Ar = C6H4-Cl-p; c, Ar = C6H4-Br-p

![Fig. 5](image5.png)
N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl] -amino]-1,3-thiazole-5-carboxamide is a novel multi-targeted kinase inhibitor recently approved in several countries for the treatment of chronic myelogenous leukemia (CML) as well as Philadelphia chromosome-positive acute lymphocytic leukemia (ALL). Dasatinib exhibits greater potency than imatinib mesylate and inhibits the majority of kinase mutations in imatinib-resistant CML\textsuperscript{17-20}. Unlike imatinib, which binds to the inactive conformation of Bcr-Abl, dasatinib binds to the active form of the enzyme\textsuperscript{21}. The ability to inhibit SRC-family kinases such as Hck and Lyn, in addition to binding to the active conformation of BCR-ABL, may both contribute to the effectiveness of dasatinib against imatinib-resistant tumors\textsuperscript{22}.

Ten new aryl imidazoles incorporated with chemotherapeutic pharmacophores have been synthesized and evaluated for their anti bacterial and short term anti cancer activity. Compound 7 showed the best anti cancer activity with CTC50 value of 98.56 and 31.25 $\mu$g mL$^{-1}$ against DLA and EAC cell line\textsuperscript{17}\textsuperscript{23}.

Compound 8 exhibited highest activity against cervical cancer\textsuperscript{24}.

![Fig. 8](image)

Compound 9 was found to be non-selective (SR were between 0.66–2.06 and 0.84–1.66 at the GI50 and TGI levels respectively).

![Fig. 9](image)

All the synthesized compounds showed moderate cytotoxic activity towards both the cell lines. Among the APTOM-4c exhibited significant activity against MCF-7 and DLA cell lines\textsuperscript{26}.

![Fig. 10](image)

Compound 11 showed high inhibitory effects against non-small cell lung cancer (NCI-H460) and breast adenocarcinoma MCF-7), respectively\textsuperscript{27}.

![Fig. 11](image)
Lester R. Marrison et al used Suzuki cross-coupling for synthesis of 3- and 5-substituted 2-pyrones, which show remarkable inhibitory activity against bacteria, yeast and fungi, and 3-Octenyl and 5-octanyl 2-pyrones shows anti cancer activity against human ovariun carcinoma and human chronic myelogenous leukaemia cell lines at the micromolar level\textsuperscript{[28]}.

Fig. 12

Fahmy et al \textsuperscript{[40]} synthesized a series of novel fluorinated thiazolo[4,5-d]pyrimidine derivatives and screened their anticancer activity against 60 human tumor cell lines. Compounds 13 and 14 showed better anticancer activity against tumor cell lines\textsuperscript{[29]}.

Fig. 13

Gududuru et al. tested a series of 2-arylthiazolidine-4-carboxylic acid amides for possible cytotoxic activity in prostate cancer. Compound 15 was found to be most potent and selective cytotoxic agent with IC50 of 0.55 \( \text{LM} \) and 38-fold selectivity in PPC-1 cells\textsuperscript{[30]}.

Fig. 15

Compounds were evaluated against five human prostate cancer cell lines. They reported that increase in the alkyl chain enhanced the antiproliferative activity while replacement of the alkyl chain with aryl group reduced the biological activity\textsuperscript{[31]}.

Fig. 16

Compound 17 was screened against nine types of human cancer cells and showed significant cytotoxic activity in case of lung cancer, melanoma and renal cancer, where the reduction in growth was found to be 75%, 97% and 84%, respectively, at the concentration of 1.0 \( \times 10^{-4} \) \( \text{LM} \)\textsuperscript{[32]}.  

Fig. 14
Compound 18 was screened against three human cancer cell lines (HT-29, H460 and MDA-MB-231) by MTT assay and exhibited IC50’s of 0.025, 0.075 and 0.77 lM, respectively. The SAR study showed that substitution with smaller electron-withdrawing fluorine atom at 5-position of the indolin-2-one ring and 3-(diethylamino) propyl group at the 3-position of 4-thiazolidinone ring had positive contribution for increasing antitumor activity.\[33\]

The SAR study revealed that anticancer activity of compound 19 was affected by the nature of substituent in position 5 of 4-thiazolidinone cycle and introduction of 4-chlorophenoxy-N-(4-methoxyphenyl)-acetamide group in 5-position of 4-thiazolidinone core enhanced potency.\[34\]

A number of 5-bromo-3-[(3-substituted-5-methyl-4-thiazolidinone-2-ylidene hydrazono]-1H-2-indolinones (20) had been investigated for their primary cytotoxic activity against 3-cell line panel consisting of NCI-H460 (Lung), MCF7 (Breast), and SF-268(CNS). It was observed that thiosemicarbazone derivatives of indolinones showed promising cytotoxicity activity.\[35\]

ACKNOWLEDGEMENT

Authors are thankful to Hon. Secretary, Khalsa College Charitable Society, Amritsar and Director-Principal, Khalsa college of Pharmacy, Amritsar for providing facilities to carry out this project work.

REFERENCES

1. Achson A. An introduction to the chemistry of heterocyclic compounds., Willy-Intersciences;India; 2009 3rd ed.


30. Abhishek Kumar Jain a, Ankur Vaidya a, Veerasamy Ravichandran b, Sushil Kumar Kashaw a, Ram Kishore Agrawal. Recent developments and biological activities of thiazolidinone derivatives. Bioorganic & Medicinal Chemistry.


