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Review Article

Thiazole Core: A Restorative Target in the Discovery of Potent Anti-cancer Agents

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ABSTRACT

In the past few decades, cancer has been one of the crucial health issues and protruding reason of deaths to humans. An appreciable advancement has been made in anti-cancer drugs development and various new anticancer agents that have natural as well as synthetic origin have been generated so far. Out of different heterocyclic compounds, thiazole which is 5-membered unique heterocyclic ring containing sulfur as well as nitrogen atoms has an eminent function in several medicinally significant organic compounds. Thiazole moiety has displayed several therapeutic actions which also include anticancer activities and has been an elementary part of clinically applied anticancer pharmaceutical drugs. Lately, majority of the compounds extracted from natural sources that contain thiazole component manifest significant cytotoxicities and showcase antitumor capabilities as well. In this background, variety of structural modifications has been made in the original structure, which includes the inclusion of variety of substituents or the incorporation with several other carbo- and also heterocycles, to elevate the antitumoral efficacy. Moreover, these thiazole compounds are less toxic and have been clinically proven to be highly effective and have excellent potency for anticancer activity. This review showcases the present phenomenal research on thiazoles and illuminates their biological significance in the discovery of anticancer drugs. The findings of this review article may help the researchers in the cogent design of anti-cancer drug molecules that are way more potent and bio-target specific in action.

Key words: Heterocyclic compounds, Thiazole, Drug discovery, Cancerous cells, Anticancer agents.

1. INTRODUCTION

Cancer can be regarded as a multifactorial ailment, in which both genetic as well as environmental factors play a significant role. It can be considered as one of the most dangerous ailment in the world with severity and deadliness that come as an outcome from incompatibility between cell growth and proliferation [1]. When normal cells are exposed to different factors and conditions, they get transformed into cancerous cells by changing the normal function of a broad spectrum of regulatory, apoptotic, and signal transduction pathways. This is known as loss of differentiation. Numerous efforts have been made to find appropriate methodology for cancer treatment and various strategies have been developed and tested so far. Chemotherapy is the fundamental and vital approach in the treatment of cancer in which a plethora of natural and synthetic compounds is utilized to completely dismantle cancer cells [2].

In spite of the expeditious progression in the science of drugs and chemotherapeutic agents, treating cancers still remain a paramount issue mainly due to the toxicity, resistance, and inefficiency of selectivity of the anticancer drugs that are currently available [3].

Advancement of our understanding about cancer cells and cell cycle dysregulation has successfully devised various new opportunities for target therapy of cancers and has led to the discovery of selective anticancer agents [4]. During the past few decades, synthesis of numerous compounds with specific molecular targets has taken place. They have proved to serve as extraordinary candidates in the treatment and diagnosis of cancer.

Thiazole is considered as an engrossing building block in the field of medicinal chemistry for the design and synthesis of several biologically active derivatives and has marked its presence in numerous clinically available drugs of anticancer [5].

The biological activities of several thiazoles are mainly determined by their molecular structures. Many heterocycle compounds such as azoles play an impactful role in the present branch of medicinal chemistry because of their enormous range of applications that they have in the fields of drug design and discovery [6,7].

Thiazole finds its utility in different areas of medicine in particular as a potential anticancer drug. In the recent times, thiazole which is a five membered sulfur and nitrogen containing heterocyclic ligand has inscribed substantial interest due to their effectual biological properties [8]. Thiazole and its derivatives are undoubtedly among the most active classes of compounds that are well known for their immensely wide range of activities, for example, antibacterial activity [9], antifungal activity [10], antimalarial activity [11], antitubercular activity [12], antiviral activity, anti-inflammatory activity, antidiabetic activity [13], anthelmintic activity, anticonvulsant activity [14], antioxidant activity [15], anticancer activity, and cardiovascular activity (Figure 1). Moreover, thiazole-containing

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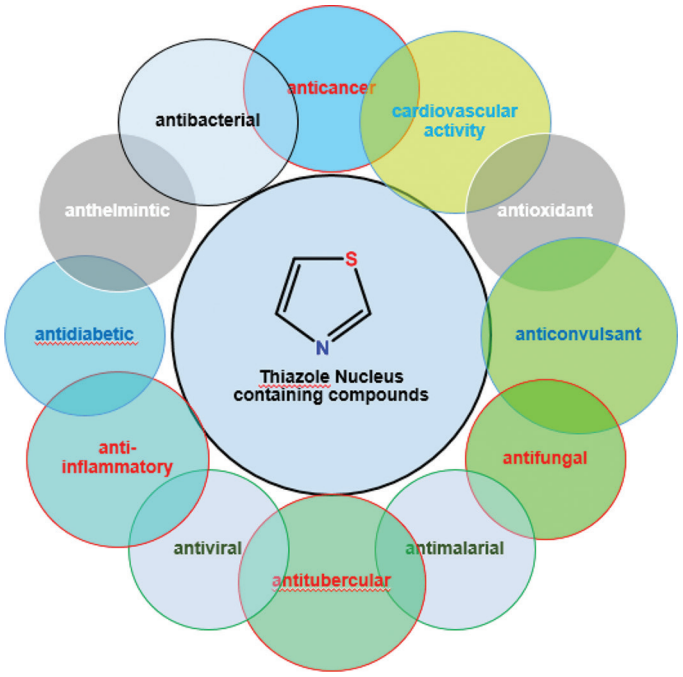

Figure 1: Biological activities shown by thiazole core containing compounds.

compounds are present in numerous clinically available anti-cancer drugs as well. Derivatives of thiazole have been classified on the basis of their molecular targets and/or pathological condition. The anticancer activity profile of thiazole containing compounds through diverse mechanism such as inhibition of different enzymes, diverse targets, and cytotoxicity assessment has been specifically depicted and illustrated in this review article [16-20].

Several Food and Drug Administration (FDA) approved drugs are available which possess thiazole core [5-9] including **Meloxicam (1)**, an anti-inflammatory drug, **Dabrafenib (2)**, a potent anticancer drug, **Cefdinir (3)**, an antibiotic, **Ritonavir (4)**, an effective antiviral agent, **Pramipexole (5)**, clinically used for the treatment of Parkinson's disease, **Thiabendazole (6),** as an antifungal drug, **Famotidine (7)**, a very good antiulcer agent, and **Febuxostat (8)**, clinically used as anti-arthritis agent. These drugs are shown in Figure 2.

There are various other recently FDA approved drugs containing thiazole nucleus (Figure 3) [21-23] **Isavuconazonium sulfate (9)**, sold under the brand name **Cresemba**, is a systemic antifungal medication used to treat invasive aspergillosis and mucormycosis which were approved in the year 2015. Thiazole derivative, **alpelisib (10)** under the brand name **Pigray**, which was approved in the year 2019, successfully provides effective treatment for certain types of breast cancer [12]. Another thiazole based drug is **cobicistat (11)**, which is used for treating human immunodeficiency virus infection. This drug was approved by FDA in 2018. **Lusutrombopag (12),** under the brand name **Mulpleta**, was also approved in 2018. It is a medication that has been developed for treating thrombocytopenia such as thrombocytopenia associated with chronic liver disease in patients [24].

Thus, these findings reveal that when a thiazole nucleus is incorporated into the molecular structure of various lead compounds, it results in enhanced biological activities of the molecules that are generated.

2. COMPOUNDS CONTAINING THIAZOLE CORE WITH THEIR ANTITUMOR ACTIVITIES

A series of N, 4-diaryl-1, and 3-thiazole-2-amines were synthesized by Sun *et al*. [25a] among which compound **13,** (Figure 4) shown promising cytotoxicity with IC_{50} values at the sub-micromolar level. Further studies showed that this compound acts similar action as combretastatin.

The compound **14** (Figure 4) showed an EC_{50} value of 0.11 μM in hepatocellular carcinoma and was selective toward normal cells >450 times.

A series chalcone-like structures were synthesized and evaluated their anticancer activity. Compounds were shown promising cytotoxic activity against MCF-7, HepG2, and SW480 cell lines [25b]. The most promising analog was compound **15**, (Figure 4) which prevents the proliferation of HepG2 cells by blocking cell cycle at the G2 phase.

A series of indole-thiazolylcoumarins hybrids were synthesized and tested against a wide range of tumor cell lines [26]. Among the tested compounds, molecule **16**, (Figure 4) showed growth inhibition activity with average GI_{50} values of 1.18–2.44 μM against nine tumor cell lines.

In 2015, several diaminothiazole derivatives were synthesized and *in vitro* studies were done against resistant colon, breast, and uterine cancer cells lines. All of them showed potent activity in all cell lines with IC_{50} values in the nM range. Among them, **DAT1 (17**; Figure 5) was selected for *in vivo* study. It showed tumor growth inhibition of about 60% in a taxol-resistant colon cancer model at a dose of 20 mg/kg [27].

More recently, **DAT1** has also shown its ability to induce apoptosis both *in vitro* and *in vivo* against colon cancer models with mutated p53 through ERK-mediated upregulation of death receptor 5 (DR5) [27]. These promising findings make DAT1 as a candidate to be tested in clinical trials.

Di Martile *et al*. reported that a novel pCAF and GCN5 histone deacetylase inhibitor, named **CPTH6 (18**; Figure 5), was shown its ability to reduce tumor growth in a spheroid patient-derived lung cancer stem cells. Compound showed its activity by inhibition of α-tubulin acetylation [28a,b]. Similarly, two compounds, **TP-07 (19)** and **TAP-07 (20**; Figure 5), also possessed cytotoxic activity against several cancer cell lines without antiproliferative effects to normal cells (IC_{50} > 30 μM) along with *in vivo* efficacy against a hepatocellular xenograft cancer model [29].

In this sequence, benzothiazoles also exhibited promising biological activities, such as antitubercular, antimicrobial, analgesic, and antitumor properties. Thus, this core nucleus was modified for potent antitumor activity. For anticancer activity, different methylsulfonyl benzothiazoles derivatives were synthetized and evaluated against HeLA cell line, the compounds **21** and **22** (Figure 6) were showing GI_{50} values of 0.1 μM or even low value.

Xie *et al*. [29] synthesized a new series of compounds having benzothiazole core, *in vitro* studies showed that these compounds have potent activity against HCT116, MCF-7, U87 MG, and A549 cell lines. The compound **23** (Figure 6) was active and showed anticancer activity and the inhibitory activity against PI3K (phosphoinositide 3-kinase) and mTORC1. The compound **24** (Figure 6) also disrupted microtubule dynamics and induces cell cycle arrest in G2/M phase and thus initiate apoptosis.

In this sequence, Braga *et al*. [30] synthesized a series of thiazole derivatives and evaluated them against three human cancer cell lines: HL-60 (promyelotic leukemia), Jurkat (acute lymphoblastic leukemia), and MCF-7 (breast cancer) as well as normal (Vero cells) cell lines. The compounds **25a, 25b,** and **25c** (Figure 7) were shown their ability to inhibit the viability of breast carcinoma cells (MCF-7) with IC_{50} values of 54, 43, and 76 μM, respectively, while derivative **25c** was found to be active against promyelocytic leukemia cells (HL-60) with an IC_{50} value of 43 μM.

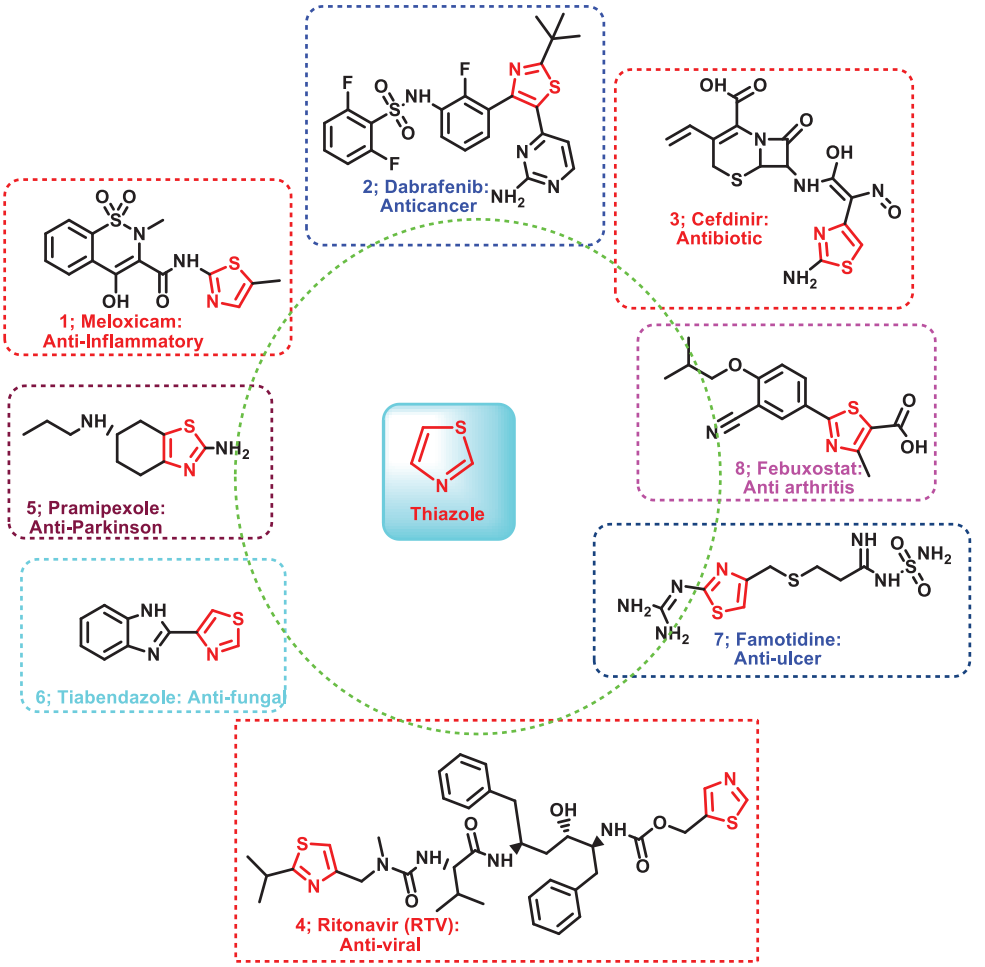

Figure 2: Examples of thiazole core containing FDA approved drug molecules.

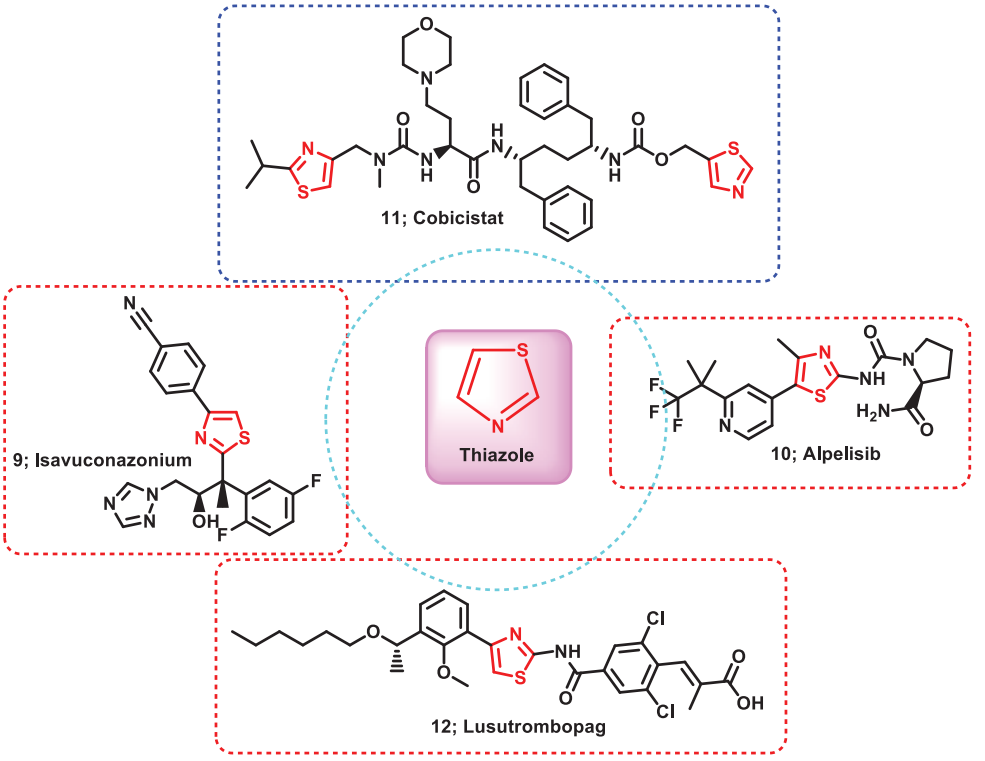

Figure 3: Examples of recently FDA approved thiazole- containing drug molecules.

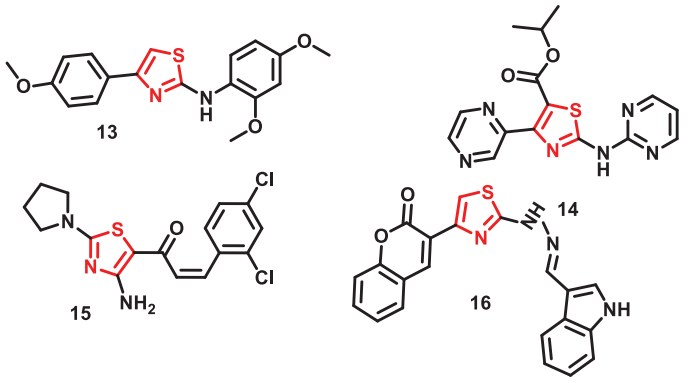

Figure 4: Structures of compounds 13–16 showing anticancer activity with thiazole core.

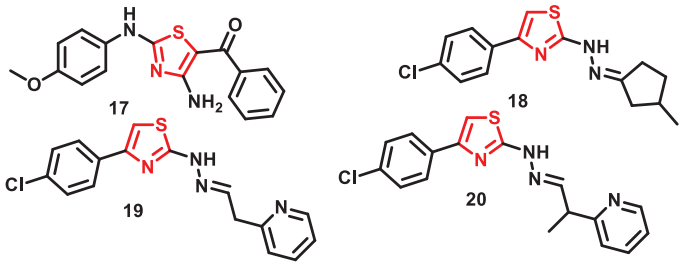

Figure 5: Structures of compounds 17-20 showing anticancer activity with thiazole core.

Mohareb *et al*. [31] synthesized a series of compounds containing thiazole nucleus and synthesized compounds were tested against six human cancer cell lines, namely: Human gastric cancer (NUGC), human colon cancer (DLD-1), human liver cancer (HA22T and HEPG-2), human breast cancer (MCF-7), and nasopharyngeal carcinoma (HONE-1) as well as against normal fibroblast cells (WI-38). It was interesting to note that compounds were showing different activity against different cancerous cell lines. The compound **29** was active against the NUGC cell line with an IC_{50} value of 23 ± 80 nmol/L, while compound **30** was 10 times more active than **29** (IC_{50} = 120 ± 38 nmol/L) against HEPG-2 **(**Figure 8) with respect to reference drug used. Among them, compound **30** (IC_{50} = 24 ± 18 nmol/L) was found to be more active than the reference drug (IC50 + 2315 ± 13 nmol/L) against DLD-1. The compound **28** showed activity at IC_{50} = 55 nmol/L and the synthesized thiazole derivative **27** (IC_{50} = 59 ± 22 nmol/L) was phenomenal and was 35 folds more active than the reference drug against HA22T.

Further in 2018, Ayati *et al*. designed and synthesized compounds of benzoylthiazole-chalcone hybrids. The synthesized compounds were evaluated for their antitumor activity against three cancerous cell lines: MCF-7, HepG2, and SW480 and etoposide were taken as reference drug. Compounds showed very good anticancer activity. Among them, compound **33** (Figure 9) was the most active with an IC_{50} value of 12.6 mM and 10.6 mM against MCF-7 and HepG2, respectively [32].

In the same year (2018), De Santana *et al*. synthesized thiazole derivatives and tested them against different cancerous cell lines:

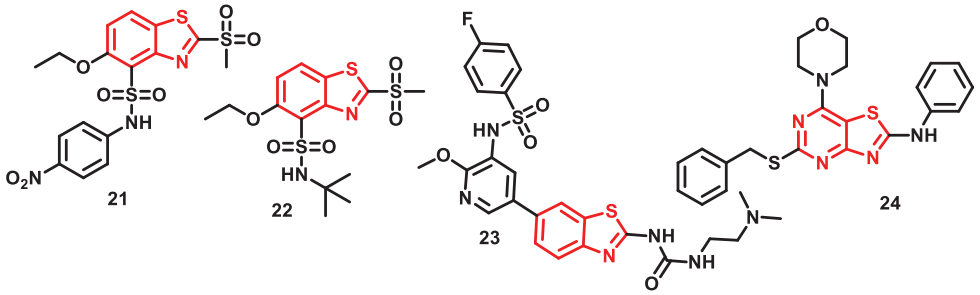

Figure 6: Structures of compounds 21-24 showing anticancer activity with benzothiazole core.

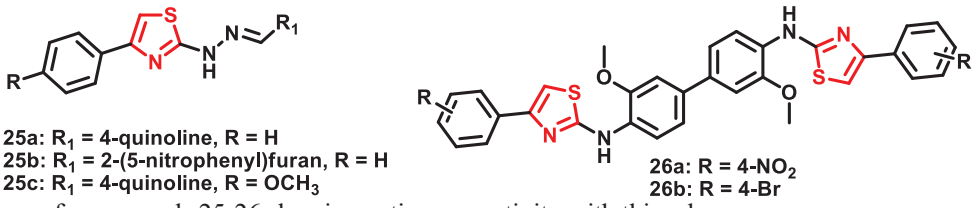

Figure 7: Structures of compounds 25-26 showing anticancer activity with thiazole core.

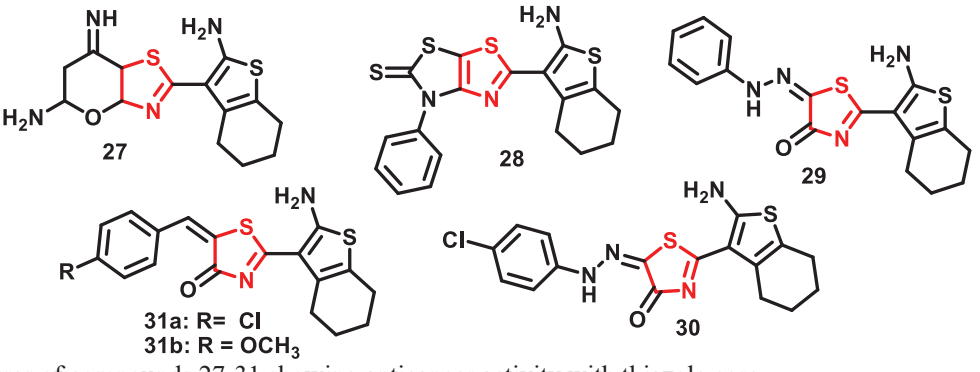

Figure 8: Structures of compounds 27-31 showing anticancer activity with thiazole core.

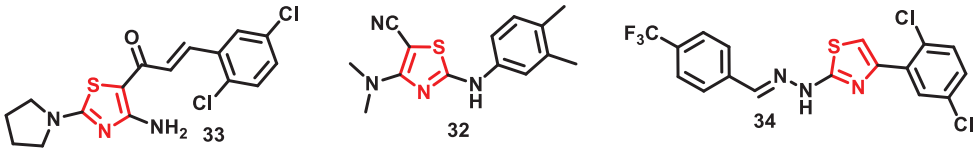

Figure 9: Structures of compounds 32-34 showing anticancer activity with thiazole core.

NCIeH292, HEp-2, HT-29, HL-60, and K562. Among all the synthesized compounds, compound **34** (Figure 9) was found to be most active with an IC_{50} ¼ 5.48 mM against K562 cells in comparison to Doxorubicin, a reference drug with an IC_{50} ¼ 1.38 mM [33-36].

3. CONCLUSION

These important findings revealed that thiazoles nucleus has a major importance and highly studied heterocyclic core in the field of medicinal chemistry with a plethora of biological effects. This core nucleus is connected with treating the body or a part of it to repair it against cancer, that is, this core is a "Restorative Target" in the discovery of potent anticancer molecules.

Hence, it is very well evident from the above article that the compounds containing thiazole possess wide range of applications in the development of drugs for providing treatment against the lethal cancer disease and also find tremendous applications in the design of new anticancer drugs which have an outstanding potency and selectivity both in cellular and molecular levels. Various studied thiazole derivatives were found to have more potency than the reference drugs used in the experiment and thus being good candidates for further moderation and development of various new and safe derivatives. This can be done on the basis of structure–activity relationships and relevant preclinical.

Although there have been many remarkable accomplishments in the study of thiazole-containing compounds, still some concerted research endeavors are required.

- Developing appropriate synthesis protocols involving the applications of green chemistry to provide a vital driving force for the development of future thiazole-containing compounds. The detailed explanation of biological activity through examination of mode of action especially on animals of laboratory followed by clinical investigation for the potent compounds.
- A detailed examination on pharmacodynamic and pharmacokinetic properties of listed potent compounds for anticancer activities.
- Another appealing aspect is to study identification and isolation of various naturally occurring thiazole-containing compounds and antibiotics that are obtained from plant and marine sources.

Hence, development of better analogs with higher efficiency, more selectivity, and also lesser side effects would be an outstanding contribution for the betterment of human beings. Thus, it is the need that more research should be done for exploration of this wonderful heterocyclic core.

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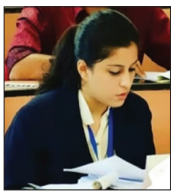

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