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Chapter

Thiazole Moiety: An Interesting Scaffold for Developing New Antitumoral Compounds

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Abstract

Currently, cancer is one of the major health problems of the human population and prominent cause of death. Thiazole ring has demonstrated many pharmacological activities including anticancer. This scaffold has been found alone or incorporated into the diversity of therapeutic active agents such as tiazofurin, dasatinib, and bleomycin, which are well-known antineoplastic drugs. Recently, most of the compounds isolated from natural sources containing thiazole moiety exhibit notable cytotoxicities and present antitumor potential. In this context, several structural changes have been made in the original structure, such as the incorporation of different substituents or the fusion with other carbo- and heterocycles, in order to increase the antitumoral potency. Related to mechanism of action of these derivatives, some of them act through kinase modulation, polymerization inhibition of microtubule, pro-matrix metalloproteinase activation, signal transducer activation of transcription 3, histone deacetylase inhibition, etc.

Keywords: cancer, thiazole, MDM2 inhibitors, mechanism of action, metal complexes, peptides, sulfur

1. Introduction

Cancer is a generic term, which encompasses a wide group of diseases characterized essentially by an uncontrolled growth and propagation of cells with errors in the division mechanisms known as cell cycle. Cancer constitutes a major public health problem worldwide, since it is the second leading cause of death globally, with 9.6 million deaths estimated in 2018 [1]. Due to the limitations and side effects associated with available cancer treatments nowadays, it is an urgent challenge for medicinal researchers to develop more safe and selective anticancer drugs.

Among the design strategies in drug discovery, special attention has been paid to molecules containing sulfur heterocycles in their structures. Several studies have been carried out with plenty of sulfur heterocycles, including thiophene, thione, benzothiophene, and thiazine, towards different pathologies.

Thiazole ring is present in several anticancer drugs, such as bleomycin, sulfathiazole, thiazofurine, and dasatinib, and its derivatives present excellent pharmacological profiles, making this skeleton an ideal candidate to develop more potent and
safer drugs, especially in cancer. Herein, an extensive revision of the most relevant research published in the past 5 years is gathered.

2. Thiazole rings decorated with different fragments

2.1 Thiazole derivatives with \textit{in vitro} efficacy

\textbf{Aminothiazoles}: Aminothiazoles have been widely used in drug discovery research due to its biological properties. Commercial drugs, such as famotidine, sudoxicam, or cefdinir, contain an aminothiazole core in their structures (Figure 1) [2].

Aminothiazole scaffold can be modified by derivatization of the amino group at position 2 of the thiazole ring. Rostom et al. [3] reported a study based on structural modifications including azomethine, \textit{N}-formyl, \textit{N}-acyl, sulfonamide, ureido, and thioureido functionalities. Nine derivatives were evaluated by the NCI \textit{in vitro} screening panel assay, displaying most of them a promising antitumor activity against particular cell lines.

Sun et al. [4] synthesized a series of \textit{N},4-diaryl-1,3-thiazole-2-amines containing three aromatic rings with an amino linker. Compound 1 (Figure 2) was the most cytotoxic agent with IC$_{50}$ values at the submicromolar level. A further biological evaluation showed that this compound inhibited polymerization and disrupted tubulin microtubule dynamics in a similar way to the natural product combretastatin A-4, besides effectively inducing SGC-7901 cell cycle arrest at the G2/M phase.

In other study, a series of tri-substituted aminothiazoles were designed by Lu et al. [5] in order to obtain new antitumoral agents. Compound 2 (Figure 2) displayed a EC$_{50}$ value of 0.11 \mu M in hepatocellular carcinoma along with a selectivity towards nontumoral cells greater than 450 times.

A dysregulation of sirtuin 2 (Sirt2) plays an important role in the pathogenesis of cancer, among other diseases. Schiedel et al. [6] designed a series of novel aminothiazole derivatives with the aim of establishing a well-defined SAR model of sirtuin ligands. These thiazole-bearing compounds behaved as selective human sirtuins (hSirt2) inhibitors.

\textbf{Chalcones}: Chalcones are naturally biarylpropenones, which are classified as a subgroup of flavonoids with a broad spectrum of biological activities, including antimicrobial, anti-inflammatory, and anticancer properties [7].

A series of 4-amino-5-cinnamoylthiazoles as chalcone-like structures were synthesized and evaluated as antitumor agents, showing most of them significant cytotoxic activity against MCF-7, HepG2, and SW480 cell lines [8]. The most promising analog, compound 3 (Figure 2), revealed that it could prevent the proliferation of HepG2 cells by blocking cell cycle at the G2 phase and by inducing apoptosis.

\textbf{Coumarins}: Another strategy of design is the incorporation of a coumarin moiety in molecules containing thiazole. Many coumarin-bearing compounds are reported to have significant therapeutic potential, including anticancer activity.
through different mechanisms. Jashari et al. [9] reported the synthesis of new derivatives by combining this coumarin core with different heterocycles. The results showed that the compounds containing thiazoles in the structure had the most promising activity against the cancer cell lines tested.

This strategy can be complementary with the inclusion of other structures with recognized biological activities. A series of indole-incorporated thiazolylcoumarins were synthesized and evaluated against a wide range of tumor cell lines [10]. Among the tested compounds, structure 4 (Figure 2) exhibited a broad spectrum of growth inhibition activity with average GI_{50} values of 1.18–2.44 μM against nine cell lines.

Ayati et al. [11] also reported the synthesis of a series of new coumarin-containing compounds developed from the chalcone-like cinnamoylthiazoles mentioned above. Biological evaluations on the most cytotoxic compound 5 (Figure 2) against MCF-7 cells revealed the induction of apoptosis and blockage of the cell cycle distribution at the G1-phase.

2.2 Thiazole derivatives with in vivo efficacy

For the past 5 years, few examples of scaffolds bearing a thiazole ring have been reported with potent efficacy in xenograft models of various types of cancer. Figure 3 encompasses the most relevant examples gathered in the literature that are going to be discussed herein.

Attending to their structure, the thiazole analogs can be grouped as follows.

**Diaminothiazoles:** In 2015, several diaminothiazole derivatives were evaluated _in vitro_ against wild-type and resistant colon, breast, and uterine cancer cells lines. All of them showed potent activity in all cell lines with IC_{50} values in the nanomolar range. Among them, DAT1 (4-amino-5-benzoyl-2-(4-methoxyphenylamino)thiazole) (Figure 3) also demonstrated _in vivo_ tumor growth inhibition of around 60% in a taxol-resistant colon cancer model at a dose of 20 mg/kg [12]. More recently, DAT1 has also demonstrated its capacity 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) [13]. All these findings have placed DAT1 as a candidate to be tested in clinical trials.

**Thiazole-2-yl)hydrazones:** Di Martile et al. reported that a novel pCAF and GCN5 histone deacetylase inhibitor, named CPTH6 (3-methylcyclopentylidene-[4-(4′-chlorophenyl)thiazol-2-yl) hydrazone] (Figure 3), was able to reduce tumor growth in a spheroid patient-derived lung cancer stem cells (LCSCs) xenograft model.
accompanied by apoptosis induction and inhibition of α-tubulin acetylation [14]. Likewise, two 2-pyridyl-2,3-thiazole derivatives, TP-07 and TAP-07 (Figure 3), possess cytotoxic activity towards several cancer cell lines without antiproliferative effects to normal cells (IC\textsubscript{50} > 30 μM) along with \textit{in vivo} efficacy against a hepatocellular xenograft cancer model [15]. Thus, both compounds achieved 47% and 73% tumor mass reduction, respectively [15].

**Spiroimidazothiazolidines**: This class of compounds has demonstrated to be potent inhibitors of the Murine Double Minute-2 (MDM2)-p53 interaction, which ultimately leads to induction of apoptosis. Two analogs withstand in this class of compounds: a) ISA27 (Figure 3), which not only presented tumor growth inhibition \textit{in vivo} alone in a glioblastoma xenograft model but also a synergistic effect with temozolomide, a first-line treatment drug against brain cancers [16], and b) SM13 (Figure 3), an analog that reduced tumor growth in a human thyroid cancer xenograft model in the absence of p53 transcriptional activity [17].

**Piperidinone analogs**: Based on previous morpholine and piperidone MDM2 inhibitors, Gonzalez et al. introduced a thiazole ring decorated with a carboxylic acid over the piperidone scaffold. The resulting hit compound, termed AM-6761 (Figure 3), maintained the MDM2 inhibition efficacy and presented an ED\textsubscript{50} value of 11 mg/kg in SJSA-1 osteosarcoma xenograft model [18].

**Oridonin derivatives**: Oridonin is a complex ent-kaurane diterpenoid isolated from the traditional Chinese herb \textit{Isodon rubescens}, with well-known cytotoxic activity against various human cancers. In 2013, Ding et al. designed a series of novel nitrogen-enriched oridonin derivatives with thiazole-fused A-ring. The hit compound, CYD0618 (Figure 3), induced a threefold shrinkage of the tumor volume in a triple-negative breast cancer MDA-MB-231 xenograft model at a dose of 5 mg/kg, showing much higher efficacy than parent oridonin [19]. Later, Zhou et al. reported another oridonin analog, CYD-6-17 (Figure 3), which significantly inhibited renal cell carcinoma tumor growth \textit{in vivo} by targeting 3-phosphoinositide-dependent protein kinase 1 (PDPK1) and its downstream pathways [20].
3. Fused thiazole rings decorated with different fragments

**Benzothiazoles**: In the last few years, benzothiazoles have attracted considerable interest due to their broad spectrum of pharmacological activities, such as antitubercular, antimicrobial, analgesic, and antitumor properties [21].

This moiety can be functionalized with several structural modifications. Novel methylsulfonyl benzothiazoles were synthetized and evaluated against HeLa cell line, with compounds 6 and 7 (Figure 4) showing GI50 values of 0.1 μM or below [22].

Xie et al. [23] reported a new series of benzothiazole derivatives, with in vitro efficacy against HCT116, MCF-7, U87 MG, and A549 cell lines. Compound 8 (Figure 4) was proved to retain the antiproliferative activity and the inhibitory activity against PI3K (phosphoinositide 3-kinase) and mTORC1 (mammalian target of rapamycin), which are abnormally active in many tumor cells.

Benzothiazole derivatives bearing pyrimidine moiety were synthetized and evaluated for anticancer activity against MCF-7, A549, and A375 cancer cell lines, with significant antitumor activity. A further study of the most promising compounds indicated an effect on the expression of proteins that cause abnormal cell proliferation, such as ERK1/2, NF-kB, and survivin [24].

This moiety can also be used in the design of new molecules with a chalcone-like structure, as it has been mentioned before. Imidazole bearing benzothiazoles were synthetized by Sultana et al. [25] and evaluated against several cancer cell lines. Compounds 9 and 10 (Figure 4) exhibited good cytotoxicity against human breast cancer (MDA MB-231) with IC50 values of 1.3 and 1.2 μM, respectively. These compounds were revealed to induce cell cycle arrest in G2/M phase and to inhibit microtubule assembly.

**Imidazoles**: Imidazole-based compounds have achieved great progress in medicinal chemistry, since they have showed anticancer, antifungal, antibacterial, and antiparasitic activities, among others [26]. Their use as heterocycles merged with thiazole has attracted great attention in the last years [27, 28] due to its therapeutic properties.

A series of imidazo[2,1-b]thiazole derivatives were evaluated against different tumor cell lines, showing that compounds 11 and 12 (Figure 4) had a significant cytotoxic activity against A549 with IC50 values of 0.92 and 0.78 μM, respectively. These derivatives had proven to induce cell cycle arrest in G2/M phase and apoptosis in this cell line [29]. Ali et al. [30] synthesized a series of imidazo[2,1-b]thiazoles decorated with pyrazoles that turned out to be promising leads to further develop.
Due to the pharmacological properties of the imidazo[2,1-b]thiazole derivatives and coumarin compounds already mentioned, it has been reported a design that embodied both the active pharmacophores in a single molecule in order to evaluate their synergic activity against a series of tumor cell lines [31], showing some of them prominent cytotoxic activity.

Kamal et al. [32] also designed a novel series of imidazole merged with thiazole as chalcone-like derivatives and evaluated their cytotoxic activity against MCF-7, A549, HeLa, DU-145, and HT-29 cell lines. Among the compounds tested, structure 13 (Figure 4) with a pyridyl ring was the most active. This compound also disrupted microtubule dynamics, induced cell cycle arrest in G2/M phase and ultimately trigger apoptosis.

Pyrimidines: Compounds with fused rings can also be formed by merging other heterocyclic moieties with thiazole core. Li et al. [33] reported a novel series of thiazolo[5,4-d]pyrimidine derivatives, which were evaluated against three cancer cell lines. Compound 14 (Figure 4) showed the most potent antiproliferative activity with good selectivity when compared to normal cells (IC$_{50}$ values of 1.03 μM against MGC803 and 38.95 μM against GES-1). Biological studies indicated that this compound could inhibit the cell colony formation and migration by inducing apoptosis on MGC803 cells.

A series of thiazolo[3,2-a]pyrimidines were synthetized and evaluated in the NCI-60 cell lines panel assay, achieving significant cytotoxicity against some of the cell lines tested [34].

4. Miscellaneous structures bearing thiazole ring

Diazepines: Heterocyclic compounds 1,4-diazepines are considered an interesting moiety in drug research due to their broad range of pharmacological activities, including antibacterial, anti-HIV, anticonvulsant, and anticancer [35]. Ramírez et al. designed a series of novel thiazole-based compounds by fusing this structure with pyrimidine, which has also showed biological properties. The results indicated that some compounds showed promising antitumoral activity, with GI$_{50}$ values below 2 μM against NCI’s in vitro cell line screening [35].

Pyrazoline: Another heterocyclic structure used in combination with thiazole moiety is the pyrazoline ring. New thiazolyl-pyrazoline derivatives were synthetized, and their cytotoxicity was evaluated against A549 human lung adenocarcinoma and NIH/3 T3 mouse embryonic fibroblast cells, presenting in some cases similar IC$_{50}$ values to cisplatin [36].

Curcumins: Bayomi et al. [37] synthetized and evaluated a series of new curcumin analogs bearing thiazole as antitumoral and antioxidant agents, showing similar behavior than that of cisplatin and ascorbic acid, respectively.

Thiazolines: Thiazolines are the reduced form of thiazole and also have attracted interest in drug research due to its biological activity. Altintop et al. [38] evaluated a series of new thiazoline-based derivatives bearing a hydrazone moiety. The results showed that some of the compounds were potent inhibitors of DNA synthesis against C6 tumor cells.

5. Thiazole and metal complexes

There is a great variability of transition metals that in combination with different ligands have been reported as antitumoral agents acting through different mechanisms. The literature revealed the considerable interest in the thiazole
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pharmacophore alone [39], fused to other rings [40], or incorporated into different structures [41] for cancer therapy.

On the other hand, among the most effective and well-studied class of chemotherapeutic agents are the platinum-based drugs, which comprise cisplatin, carboplatin, and oxaliplatin. Given the clinical success of the platinum-based drugs, extensive research efforts have been made to develop alternative metal ions, that is, ruthenium, copper, zinc, and nickel, with antitumor activity.

**Copper complexes:** Copper complexes have attracted a vast interest due to their bioavailability, increased uptake in cancerous tissues, role in angiogenesis and photophysical properties, among others. The most common types of copper complexes are those incorporating 1,10-phenanthroline (phen) ligands. Planarity of the intercalative ligand is crucial in the binding of these complexes with DNA. The complexes containing nonplanar ligands favored groove binding [42].

Besides, Shakir et al. [43] have reported several Cu (II) complexes derived from benzothiazole and thiazole, which showed greater antioxidant and anticancer activities than the corresponding free ligands in various cell lines.

Studies carried out with several Cu (II) complexes with 2,2,6,2′,2′′-terpyridines revealed that these complexes are able to promote the generation of reactive oxygen species (ROS) in the presence of mild reducing agents. This feature has been exploited to oxidatively break the DNA strands, hence inhibiting the proliferation of tumor cells. In this context, the replacement of two pyridine rings by two thiazole nuclei (compound 15 in Figure 5) also achieved efficient DNA cleavage in several tumor cell lines [44]. Later, Czerwinska et al. corroborated an increase in the antiproliferative effect of these complexes against ovarian carcinoma cells by apoptosis [45].

In addition, the copper complexes have been recognized as promising drugs for metastatic tumors. For example, copper complexes of pyrrolidine dithiocarbamate (Cu(PDTC)₂) possessed potent anticancer activity on cisplatin-resistant neuroblastoma cells. Additionally, two copper thiosemicarbazone complexes showed similar effect on cisplatin-resistant neuroblastoma cells and prostate cancer. Xie et al. [46] reported the synthesis and antitumoral activity of two copper complexes of (4R)-2-thioxo-4-thiazolidinecarboxylic acid (TTDC) and 3-rhodaninepropionic acid (RDPA) against prostate cancer, presenting both of them variable potency, likely

![Figure 5](https://example.com/figure5.png)

*Figure 5.*
Some thiazole-metal complexes with antitumor activity.
related to different functional groups on TTDC and RDPA ligands. Owing to the presence of sulfur and amino groups in CuTTDC and CuRDPA, these complexes had emerged as ligands to attach to delivery vehicles, such as peptides or monoclonal antibodies for targeted delivery.

It is notably that a number of copper (II) complexes have been shown to present antitumor activity, through inhibition of human topoisomerase IIα. Recently, Sandhaus et al. [47] have identified a new complex (compound 16 in Figure 5) with potent antiproliferative activity towards colon cancer cell lines (HTC-116, Caco-2, and HT-29) and aggressive breast cancer cell lines (HCC 1500, HCC 70, HCC 1806, and HCC 1395).

**Ruthenium complexes**: Currently, ruthenium complexes are found to be a promising alternative for platinum because of favorable properties as anticancer drugs. Among the ligands, 2,6-di(thiazol-2-yl)pyridine combined with phenanthrones have demonstrated to act as DNA intercalative agents along with topoisomerase I and IIα inhibitors (compound 17 in Figure 5) [48]. The assays with other ligands, such as 1,3-thiazolidine-2-thione, with 1,4-bis(diphenylphosphino)butane or 2,2’-bipyridine, displayed strong cytotoxicity against breast and prostate cancer cell lines [49].

**Platinum and palladium complexes**: Platinum and palladium have similar chemical properties and modes of coordination, but the palladium compounds are more labile from a thermodynamic and a kinetic point of view with relation to platinum derivatives.

Rubino and co-workers [50] have reported two new mono-Pt(II) and binuclear chloro-bridged Pd(II) complexes with 2,2’-dithiobis(benzothiazole) as ligand. Only platinum derivative has emerged as an effective inductor of apoptotic death on HepG2 and MCF-7 cells and caused cell cycle arrest at G0/G1 phase while palladium was inactive. On the other hand, the inclusion of 2-(4-substituted)benzothiazoles (compound 18 in Figure 5) as ligands resulted in potent cytotoxic agents through tubulin polymerization in A549 and HeLa cell lines [51].

In addition, thiazolidinone-derived complexes, specifically with (Z)-2-((E)-(1-(pyridin-2-yl)ethylidene)hydrazono)thiazolidin-4-one, were markedly cytotoxic to MCF-7, HepG2, and NCI-H460 and presented better profile than cisplatin [52]. Other relevant strategy is the combination with scaffold with proven anticancer activity. In this context, the coumarin-thiazole analogs complexed with platinum or palladium showed that the Pd complex had higher antitumor effects than its Pt analogs in several cancer cell lines [53].

**Other metal complexes and applications**: Manganese is a metal that plays a critical role in cell development, and it is required for mitochondrial function. As novelty, Islam et al. [54] have described a new Mn-EDTA complex (compound 19 in Figure 5) incorporating a benzothiazole that has been investigated as potential agents for diagnosis of liver cancer by magnetic resonance.

Cobalt (II) complexes are one of the most studied, and they have been reported as cytotoxic agents in vitro against breast cancer cell lines [55]. However, the cobalt (III) complexes are less known, although a new Co(III)sulfathiazole complex have been reported as cytotoxic compound without genotoxic effects [56].

In recent years, lanthanum (III) complexes are emerging as promising agents due to their more physiological activities and lower toxicities after coordination with ligands. The main mechanism of action associated is the interaction with DNA by intercalation mode. Likewise, these compounds are useful as clinical biomarkers for early diagnosis of the presence of prostate cancer. One of the most relevant lanthanum (III) derivative is 2,3-dihydro-1H-indolo[2,3-b]phenazin-4-(5H)-yldene)benzothiazole-2-amine (compound 20 in Figure 5) that showed excellent anticancer activity in PC-3 cells [57].
Another relevant option is the gold(I) compounds that can act as prodrugs. Thus, 2-mercapto thiazoline as ligand by reaction with $\text{K[Au(CN)$_2$]}$ resulted in the nitrogen-coordinated complex [NCAu(N-ntz)]. On the other hand, reaction with $\text{[(Ph$_3$P)AuCl]}$ yielded the sulfur-coordinated complex [Ph$_3$P(Au(S-ntz)). Both of them inhibited the growth of tumorigenic cell lines such as the human ovarian carcinoma (A2780), human colon carcinoma (HCT116), and human breast adenocarcinoma (MCF7) [58].

Finally, another strategy to design new complexes as antitumoral agents is the combination of anti-inflammatory derivatives with metals. In this approach, the 1,2-benzothiazines nuclei, which are present in meloxicam and piroxicam, were complexed with ruthenium and osmium to obtain new derivatives with potent activity against cancer cell lines [59].

6. Peptidic thiazoles

Thiazoles and thiazolines are quite common motifs present in peptides isolated from natural sources, many of them known for having biological activity, typically antibacterial. These peptides are biosynthesized from nonribosomal peptide synthase (NRPS) or ribosomally produced and post-translationally modified. Both processes involve cyclodehydrations of cysteine residues to yield thiazolines and subsequent dehydrogenations to give thiazoles [60]. In this context, marine organism (cyanobacteria, fungi, sponges, tunicates, ascidians, etc.) provide an endless source of new structures with biological potential, cancer included [61]. Many isolated thiazole-containing peptides from nature have anticancer properties per se, but more efforts are continuously needed by scientific community to enhance and modulate its anticancer activity through structure modifications. Recent developments in this area are included here and listed by its cyclic/acyclic nature.

6.1 Linear peptides

Cyanobacteria-derived bisebromoamide was isolated and tested against HeLa S3 cells, showing a very low IC$_{50}$ [62]. It was also shown to induce apoptosis through ERK and mTOR inhibition in renal carcinoma cell lines [63]. A modification of central thiazoline of bisebromoamide by a thiazole and alanine scanning [64] provided new analogs, getting insights in the structural dependence of the cytotoxicity. Four analogs showed nanomolar cytotoxicity activity against human colon tumor cell line HCT116.

P-glycoprotein (P-gp, multidrug resistance protein 1) is overexpressed in patients suffering from chemotherapy resistance. In this sense, cyclic and acyclic (S)-valine-derived thiazole peptide dimers, trimers, and tetramers were found to be potent P-gp efflux transport inhibitors [65]. Based on this hit, further derivatization led to peptidomimetic TTT-28 (Figure 6), which was found to be a potent P-gp transport inhibitor and superior to parent compound in reversal of resistance to placitaxel in SW620/Ad300 and HEK/ABCB1 cell lines [66]. In vivo study [67] showed TTT-28 enhanced intratumoral concentration of placitaxel, inhibiting the growth of ABCB1 overexpressing tumors. Additional extensive derivatizations of TTT-28 in terminal groups and central thiazole building block side chain helped to understand the drug/substrate interactions with P-gp [68]. Modifications on these sites led to divergent effects in ATPase efflux pump, from initial stimulation in TTT-28 to inhibition.

Polyamides based on 2 and 3 repeating units of 2-aminothiazole-4-carboxylic acid were synthetized [69] and proved to bind selectively to c-MYC quadruplex
over other G-quadruplex and duplex DNA and therefore inhibiting c-MYC onco-gene transcription. Antiproliferative activity of the tripeptide was found in HeLa cells, caused by apoptotic pathway.

Thiazole scaffold is also present in short peptides known for inhibiting tubulin polymerization. Dolastatin 10 was firstly isolated from *Dolabella auricularia* and is composed of five unnatural amino acids with a thiazole ring in C-terminal (Figure 6). It was demonstrated as very potent in cell proliferation assays (IC$_{50}$ < 5.0 nM), but due to its high toxicity at maximum tolerated dose, new analogs have been developed. N-Terminal modified dolastatin analog (PF-06380101) bearing a quaternary amino acid was found to have improved potency and suitable ADME properties for antibody-drug conjugates [70]. Modified dolastatins at thiazole moiety by addition of new functionalities as alcohols, amines, and thiols have also been reported [71]. These analogs also showed low IC$_{50}$ for several cancerous cell lines.

Another thiazole-containing peptides targeting to tubulin polymerization are the tubulysins (Figure 6), isolated first from myxobacteria. Great number of modifications have been attempted to date, and numerous SAR studies have shed light into tubulysin mode of action (for a review, see ref. [72]). In this context, a pretubulysin (tubulysin biosynthetic precursors) lacking of C$_{11}$ acetate and bearing a methyl group at N$_{14}$ showed efficacy against various *in vivo* metastatic bladder, breast, and lung cancer models [73]. New tubulysin derivative KEMTUB10 with a N$_{14}$-benzyl-Tuv and 4-fluorophenyl moiety in Tuv exhibited activity in the picomolar range in the main breast cancer cell lines [74]. It blocks cells in G2/M phase of the cell cycle and stimulates apoptosis. In line with these results, attachment of alkyl groups at mentioned Tuv N$_{14}$ as benzyl, 4-fluorobenzyl, and cyclopropylmethyl in tubulysins also led to superpotent cytotoxic activity [75]. More Tuv modifications have been reported, like the incorporation of tetrahydropyran ring by Diels-Alder reaction for conformational restriction of tubulysin [76], but rigidification seemed to affect negatively to polymerization inhibition. Systematic derivatization by substitution of each subunit of tubulysin by diverse moieties, including three-dimensional structural motifs such as cubane and [1.1.1]-bicyclopentane, was reported [77]. A profound structure-activity study indicated that thiazole in Tuv unit cannot be substituted by 3D motifs but can be replaced by aromatics such as pyridine without significant loss of activity.

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*Figure 6. Thiazole/thiazoline containing peptides and peptidomimetics with anticancer activity.*
One objective for researchers working with tubulysins is the improvement of their therapeutic efficacy by the targeted cancer therapy as antibody-drug conjugation (ADC) or small molecule drug conjugates (SMDC), acting the tubulysins as payloads. This represents a very powerful tool, which is already being applied to all class of tubulin inhibitors [78]. Tubulysin warheads are therefore being used in ADC; one of them (AZ1399185) is in phase I clinical trials targeting HER2 receptors, involved in breast cancer development [79]. Following this trend, the modifications of tubulysins for an easier linking to conjugates is a new goal. New derivatizations at C-terminal Tup showed broad tolerance with no loss of activity, enabling more opportunities to conjugate to biomolecules and receptor ligands [80]. Another issue that arose during ADC conjugation of tubulysins to trastuzumab is the metabolism of C\textsubscript{11} acetate \textit{in vivo}, inactivating the payload [81, 82]. The problem was solved replacing the acetate ester by a more inert functionality to esterases like carbamates, retaining the activity. Tubulysin warheads have also been applied in a SMDC strategy in conjugation with folic acid to address folate receptor (FR), expressed in many cancers [83]. The EC1456 conjugate was tested in mice bearing FR-positive xenografts leading to cure of 100%. Results against human vintafolide-resistant xenografts were also positive.

### 6.2 Cyclic peptides

Cyclic depsipeptide largazole was discovered from cyanobacteria \textit{Symploca} sp. [84], and its distinctive structural feature is the presence of a thiazole fused linearly to a 4-methylthiazoline and a labile thioester (Figure 6). Largazole possesses great activity as inhibitor of class I histone deacetylase (HDAC) metalloenzymes [85], a promising target for chemotherapy. Many largazole structure-activity relationship studies have been reported. Among multiple sites of modification performed, thiazole-thiazoline fragment located in the macrocycle seems to be the most promising to achieve more potent and selective analogues. Substitution of thiazole by pyridyl residues and depsipeptide framework alteration to peptide isostere led to equipotent largazole analogues but with improved selectivity for different HDACs [86]. The replacement of thiazole and thiazoline by bipyridyl fragments led to derivatives with a similar activity of largazole, but with an improved selectivity for class I HDAC [87].

Largazole inhibition of HDAC is actually attained by largazole thiol derived from thioester hydrolysis. The thiol forms a thiolate-Zn\textsuperscript{2+} complex [88], a critical binding for the activity, since substitution by other poorer Zn-binding groups correlated to less HDAC inhibition and lower cytotoxicity [89]. The octanoyl side chain on the thioester allows good cell permeability. Thus, modifications can be made for a better membrane permeability and thiol liberation inside the cell. In this sense, controlled release of largazole thiol from an isobutylene-caged largazole thiol derivative, which possesses a high permeability, has been achieved by UV light photoactivation of a thiol-ene triggering reaction [90].

Cyclic thiazole- and oxazoline-containing octapeptides and patellamides, isolated from marine tunicates, have also been an object of modification. It has been shown that changes in the position of thiazoles and oxazolines in ascidiacyclamide can influence their cytotoxic activity, obtaining inactive derivatives and 10 times more active compounds depending on the conformations attained [91].

Apratoxin- and thiazoline-containing depsipeptides are known potent cytotoxins isolated from marine cyanobacteria. Apratoxins are known for being potent anticancer agents and co-translational translocation inhibitors. Different derivatives have been synthetized, involving thiazoline stereogenic configuration change at C\textsubscript{30} and substitution in C\textsubscript{34} [92] (Figure 6). A new derivative, apratoxin S10 with
(R)-C$_{30}^{30}$ thiazoline and the addition of a methyl group at C$_{34}^{34}$, shows potent in vitro angiogenesis and vascularized tumor cell growth inhibition [93]. It showed antipancreatic cancer activity, including in orthotopic pancreatic patient-derived xenograft mouse model [94]. Other derivatizations consisting of thiazoline substitution by piperidinecarboxylic acid moiety have been developed [95]. Apratoxins M16 showed comparable cytotoxicity to apratoxin A in HCT116 cancerous cells.

7. Conclusion

Incorporation of thiazole ring into different molecules have demonstrated to be a novel and promising approach to design more potent and safer antitumor drugs. The results of this chapter might help to enlighten other researchers to better design bioactive molecules. This thiazole ring can be incorporated as part of mono- or fused-cycles, metal complexes, or as a part of peptides. In many of these cases, the deletion of thiazole ring entails the loss of the bioactivity pointing out the importance of this ring for the anticancer activity. Thus, we consider this class of compounds and excellent starting point to achieve future drug candidates to treat cancer.
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