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Chapter

Thiazole Moiety: An Interesting Scaffold for Developing New Antitumoral Compounds

Sandra Ramos-Inza, Carlos Aydillo, Carmen Sanmartín and Daniel Plano

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 *in vitro* efficacy

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, *N*-formyl, *N*-acyl, sulfonamide, ureido, and thioureido functionalities. Nine derivatives were evaluated by the NCI *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 *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.
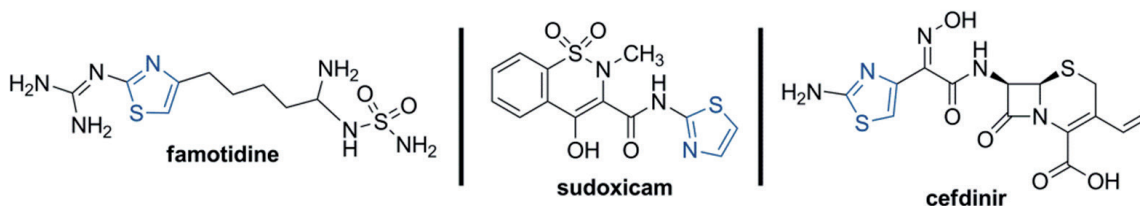
In other study, a series of tri-substituted aminothiazoles were designed by Lu et al. [5] in order to obtain new antitumoral agents. Compound **2** (**Figure 2**) displayed a EC_{50} value of 0.11 μM in hepatocellular carcinoma along with a selectivity towards nontumoral cells greater than 450 times.

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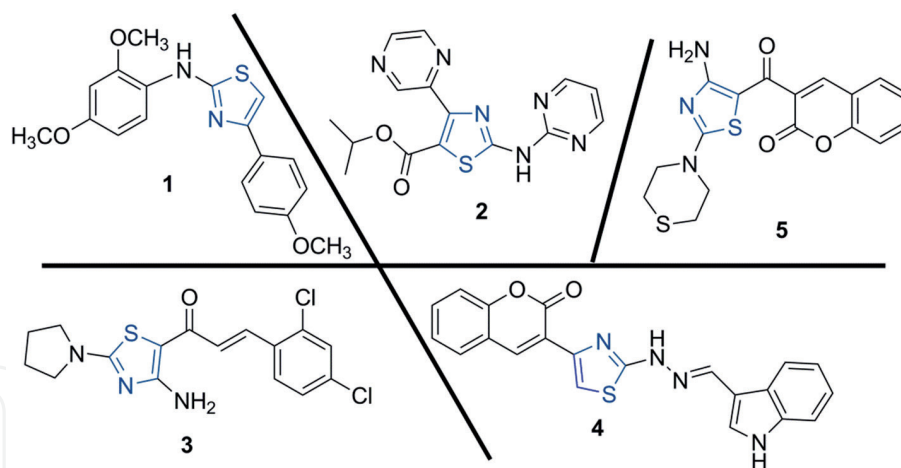
Chalcones: Chalcones are naturally biarylpropenones, which are classified as a subgroup of flavonoids with a broad spectrum of biological activities, including antimicrobial, anti-inflammatory, and anticancer properties [7].

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.

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

Figure 1.
Some aminothiazole as commercial drugs.

Figure 2.
Thiazole derivatives as potential antitumor agents.

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.

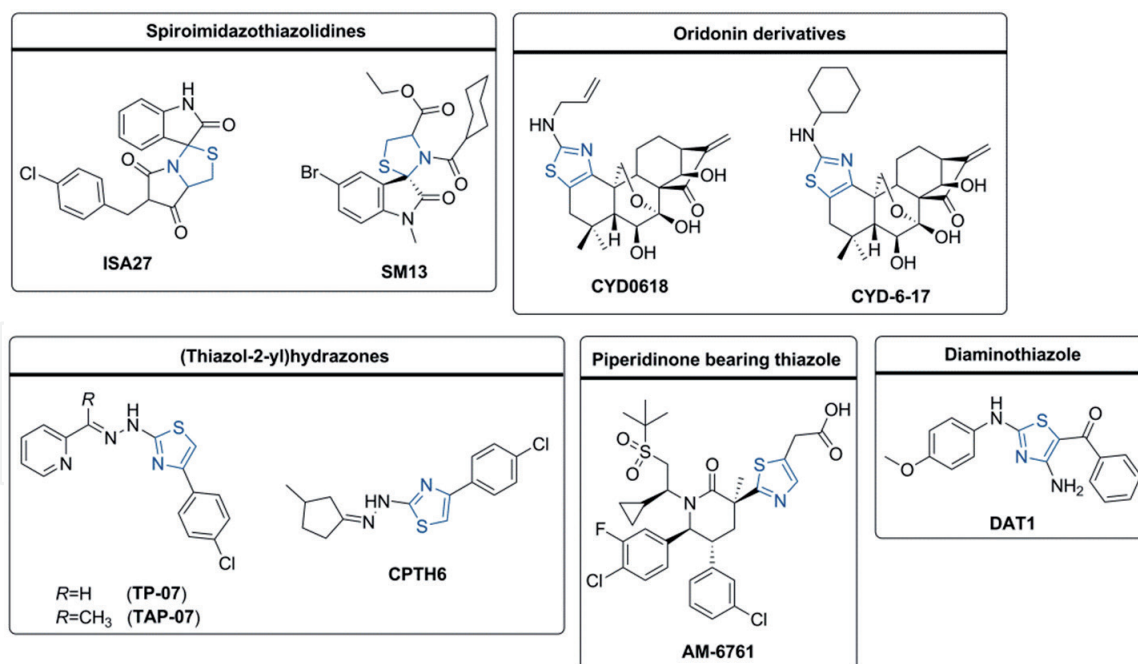### 2.2 Thiazole derivatives with *in vivo* efficacy

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

Figure 3.
Representative scaffolds containing thiazole ring with proven in vivo efficacy towards several cancer xenograft models.

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$_{50}$ > 30 μM) along with *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 *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$_{50}$ 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 *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 *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 GI$_{50}$ values of 0.1 µM or below [22].
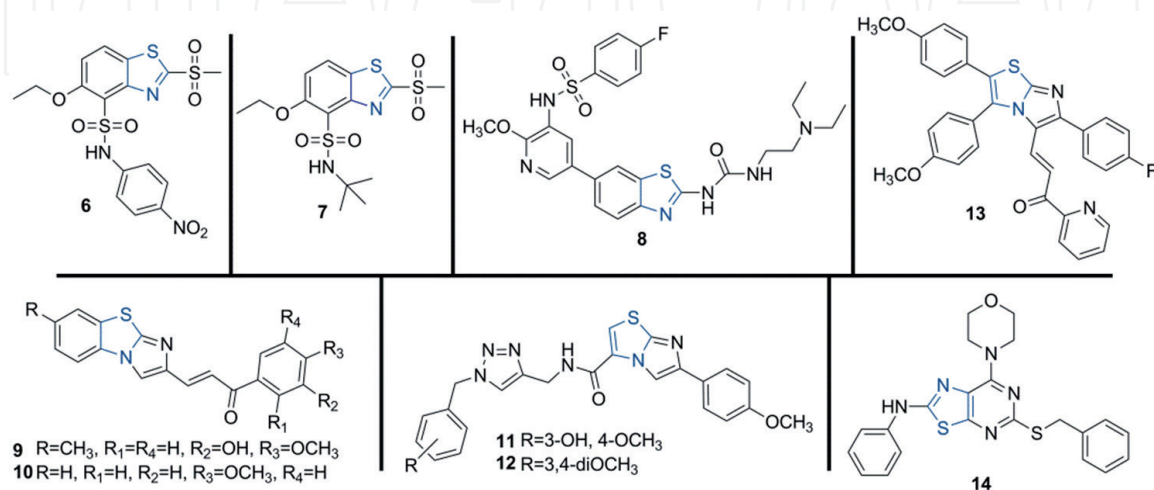
Xie et al. [23] reported a new series of benzothiazole derivatives, with *in vitro* efficacy against HCT116, MCF-7, U87 MG, and A549 cell lines. Compound **8** (**Figure 4**) was proved to retain the antiproliferative activity and the inhibitory activity against PI3K (phosphoinositide 3-kinase) and mTORC1 (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 IC$_{50}$ 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 IC$_{50}$ 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.

Figure 4.
Some thiazole-fused compounds with antitumor activity.

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

pharmacophore alone [39], fused to other rings [40], or incorporated into different structures [41] for cancer therapy.
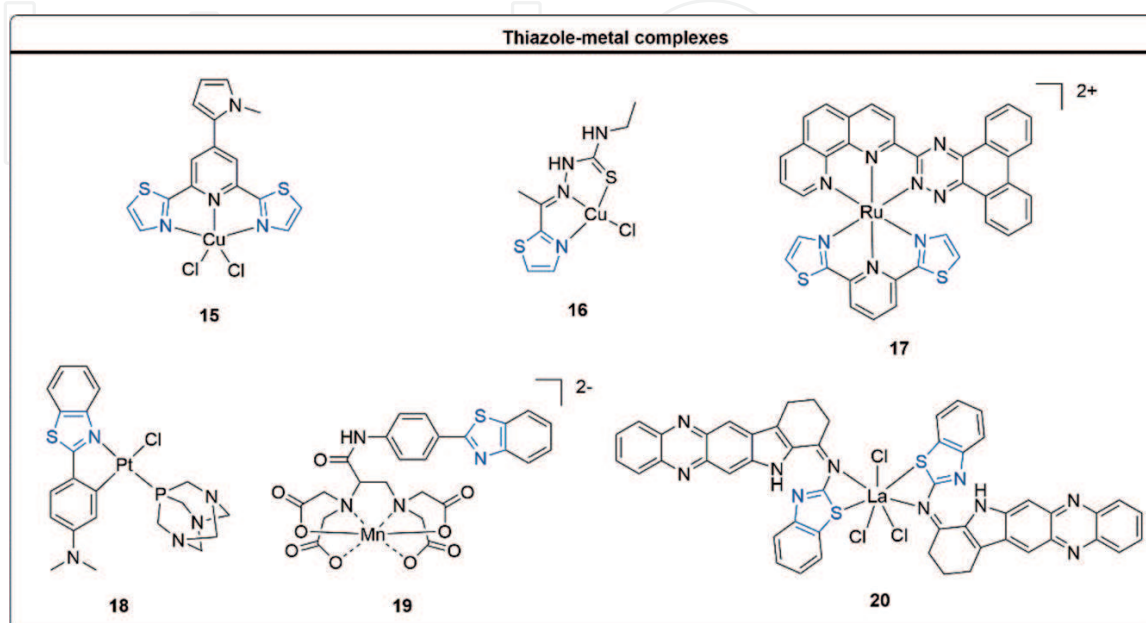
On the other hand, among the most effective and well-studied class of chemotherapeutic agents are the platinum-based drugs, which comprise cisplatin, carboplatin, and oxaliplatin. Given the clinical success of the platinum-based drugs, extensive research efforts have been made to develop alternative 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′′-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 (4*R*)-2-thioxo-4-thiazolidinecarboxylic acid (TTDC) and 3-rhodaninepropionic acid (RDPA) against prostate cancer, presenting both of them variable potency, likely

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 phenantrolines 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-1*H*-indolo[2,3-*b*]phenazin-4-(5*H*)-ylidene)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 $K[Au(CN)_2]$ resulted in the nitrogen-coordinated complex [NCAu(N-mtz)]. On the other hand, reaction with $[(Ph_3P)AuCl]$ yielded the sulfur-coordinated complex $[(Ph_3P)Au(S-mtz)]$. 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].
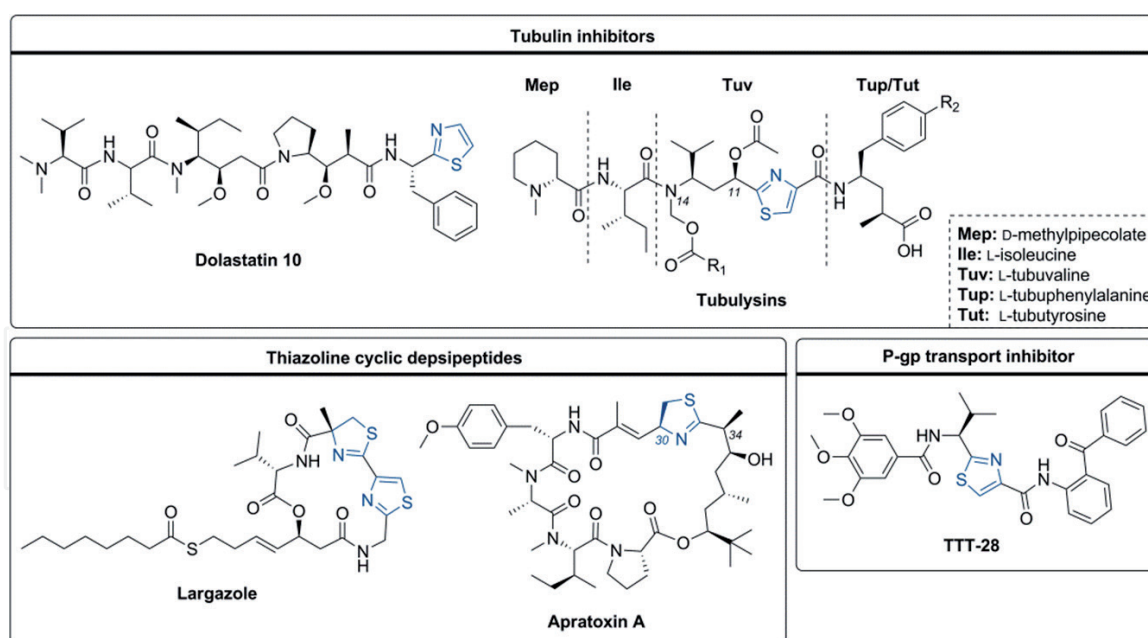
6. Peptidic thiazoles

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

Figure 6.
Thiazole/thiazoline containing peptides and peptidomimetics with anticancer activity.

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 Tup 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 tetrahydropyranyl 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.

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 (AZ13599185) 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^{11} acetate *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 curation of 100%. Results against human vintafolide-resistant xenografts were also positive.

6.2 Cyclic peptides

Cyclic depsipeptide largazole was discovered from cyanobacteria *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^{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^{30} and substitution in C^{34} [92] (**Figure 6**). A new derivative, apratoxin S10 with

(R)-C^{30} thiazoline and the addition of a methyl group at C^{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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References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018;**68**:394-424. DOI: 10.3322/caac.21492

[2] Das D, Sikdar P, Bairagi M. Recent developments of 2-aminothiazoles in medicinal chemistry. European Journal of Medicinal Chemistry. 2016;**109**:89-98. DOI: 10.1016/j.ejmech.2015.12.022

[3] Rostom SA, Faidallah HM, Radwan MF, Badr MH. Bifunctional ethyl 2-amino-4-methylthiazole-5-carboxylate derivatives: Synthesis and in vitro biological evaluation as antimicrobial and anticancer agents. European Journal of Medicinal Chemistry. 2014;**76**:170-181. DOI: 10.1016/j.ejmech.2014.02.027

[4] Sun M, Xu Q, Xu J, Wu Y, Wang Y, Zuo D, et al. Synthesis and bioevaluation of N,4-diaryl-1, 3-thiazole-2-amines as tubulin inhibitors with potent antiproliferative activity. PLoS One. 2017;**12**:e0174006. DOI: 10.1371/journal.pone.0174006

[5] Lu H, Rogowskyj J, Yu W, Venkatesh A, Khan N, Nakagawa S, et al. Novel substituted aminothiazoles as potent and selective anti-hepatocellular carcinoma agents. Bioorganic & Medicinal Chemistry Letters. 2016;**26**:5819-5824. DOI: 10.1016/j.bmcl.2016.10.015

[6] Schiedel M, Rumpf T, Karaman B, Lehotzky A, Olah J, Gerhardt S, et al. Aminothiazoles as potent and selective Sirt2 inhibitors: A structure-activity relationship study. Journal of Medicinal Chemistry. 2016;**59**:1599-1612. DOI: 10.1021/acs.jmedchem.5b01517

[7] Singh P, Anand A, Kumar V. Recent developments in biological activities of chalcones: A mini review. European Journal of Medicinal Chemistry. 2014;**85**:758-777. DOI: 10.1016/j.ejmech.2014.08.033

[8] Ayati A, Esmaeili R, Moghimi S, Oghabi Bakhshaiesh T, Eslami SZ, Majidzadeh AK, et al. Synthesis and biological evaluation of 4-amino-5-cinnamoylthiazoles as chalcone-like anticancer agents. European Journal of Medicinal Chemistry. 2018;**145**:404-412. DOI: 10.1016/j.ejmech.2018.01.015

[9] Jashari A, Imeri F, Ballazhi L, Shabani A, Mikhova B, Drager G, et al. Synthesis and cellular characterization of novel isoxazolo- and thiazolohydrazinylidene-chroman-2, 4-diones on cancer and non-cancer cell growth and death. Bioorganic & Medicinal Chemistry. 2014;**22**: 2655-2661. DOI: 10.1016/j. bmc.2014.03.026

[10] Gali R, Banothu J, Gondru R, Bavantula R, Velivela Y, Crooks PA. One-pot multicomponent synthesis of indole incorporated thiazolylcoumarins and their antibacterial, anticancer and DNA cleavage studies. Bioorganic & Medicinal Chemistry Letters. 2015;**25**:106-112. DOI: 10.1016/j. bmcl.2014.10.100

[11] Ayati A, Oghabi Bakhshaiesh T, Moghimi S, Esmaeili R, Majidzadeh AK, Safavi M, et al. Synthesis and biological evaluation of new coumarins bearing 2,4-diaminothiazole-5-carbonyl moiety. European Journal of Medicinal Chemistry. 2018;**155**:483-491. DOI: 10.1016/j.ejmech.2018.06.015

[12] Vasudevan S, Thomas SA, Sivakumar KC, Komalam RJ, Sreerekha KV, Rajasekharan KN, et al. Diaminothiazoles evade multidrug resistance in cancer cells and xenograft tumour models and develop transient

specific resistance: Understanding the basis of broad-spectrum versus specific resistance. Carcinogenesis. 2015;**36**: 883-893. DOI: 10.1093/carcin/bgv072

[13] Thamkachy R, Kumar R, Rajasekharan KN, Sengupta S. ERK mediated upregulation of death receptor 5 overcomes the lack of p53 functionality in the diaminothiazole DAT1 induced apoptosis in colon cancer models: Efficiency of DAT1 in Ras-Raf mutated cells. Molecular Cancer. 2016;**15**:22. DOI: 10.1186/s12943-016-0505-7

[14] Di Martile M, Desideri M, De Luca T, Gabellini C, Buglioni S, Eramo A, et al. Histone acetyltransferase inhibitor CPTH6 preferentially targets lung cancer stem-like cells. Oncotarget. 2016;**7**:11332-11348. DOI: 10.18632/oncotarget.7238

[15] Dos Santos Silva TD, Bomfim LM, da Cruz Rodrigues ACB, Dias RB, Sales CBS, Rocha CAG, et al. Anti-liver cancer activity in vitro and in vivo induced by 2-pyridyl 2,3-thiazole derivatives. Toxicology and Applied Pharmacology. 2017;**329**:212-223. DOI: 10.1016/j.taap.2017.06.003

[16] Costa B, Bendinelli S, Gabelloni P, Da Pozzo E, Daniele S, Scatena F, et al. Human glioblastoma multiforme: p53 reactivation by a novel MDM2 inhibitor. PLoS One. 2013;**8**:e72281. DOI: 10.1371/journal.pone.0072281

[17] Sorriento D, Del Giudice C, Bertamino A, Ciccarelli M, Gomez-Monterrey I, Campiglia P, et al. New small molecules, ISA27 and SM13, inhibit tumour growth inducing mitochondrial effects of p53. British Journal of Cancer. 2015;**112**:77-85. DOI: 10.1038/bjc.2014.577

[18] Gonzalez AZ, Li Z, Beck HP, Canon J, Chen A, Chow D, et al. Novel inhibitors of the MDM2-p53 interaction featuring hydrogen bond acceptors as carboxylic acid isosteres. Journal of Medicinal Chemistry. 2014;**57**: 2963-2988. DOI: 10.1021/jm401911v

[19] Ding C, Zhang Y, Chen H, Yang Z, Wild C, Chu L, et al. Novel nitrogen-enriched oridonin analogues with thiazole-fused A-ring: Protecting group-free synthesis, enhanced anticancer profile, and improved aqueous solubility. Journal of Medicinal Chemistry. 2013;**56**:5048-5058. DOI: 10.1021/jm400367n

[20] Zhou J, Yun EJ, Chen W, Ding Y, Wu K, Wang B, et al. Targeting 3-phosphoinositide-dependent protein kinase 1 associated with drug-resistant renal cell carcinoma using new oridonin analogs. Cell Death & Disease. 2017;**8**:e2701. DOI: 10.1038/cddis.2017.121

[21] Gill RK, Rawal RK, Bariwal J. Recent advances in the chemistry and biology of benzothiazoles. Archiv der Pharmazie (Weinheim). 2015;**348**: 155-178. DOI: 10.1002/ardp.201400340

[22] Lad NP, Manohar Y, Mascarenhas M, Pandit YB, Kulkarni MR, Sharma R, et al. Methylsulfonyl benzothiazoles (MSBT) derivatives: Search for new potential antimicrobial and anticancer agents. Bioorganic & Medicinal Chemistry Letters. 2017;**27**:1319-1324. DOI: 10.1016/j.bmcl.2016.08.032

[23] Xie XX, Li H, Wang J, Mao S, Xin MH, Lu SM, et al. Synthesis and anticancer effects evaluation of 1-alkyl-3-(6-(2-methoxy-3-sulfonylaminopyridin-5-yl)benzo[d]thiazol-2-yl)urea as anticancer agents with low toxicity. Bioorganic & Medicinal Chemistry. 2015;**23**: 6477-6485. DOI: 10.1016/j.bmc.2015.08.013

[24] Kumbhare RM, Dadmal TL, Ramaiah MJ, Kishore KS, Pushpa Valli

SN, Tiwari SK, et al. Synthesis and anticancer evaluation of novel triazole linked N-(pyrimidin-2-yl)benzo[d]thiazol-2-amine derivatives as inhibitors of cell survival proteins and inducers of apoptosis in MCF-7 breast cancer cells. Bioorganic & Medicinal Chemistry Letters. 2015;**25**:654-658. DOI: 10.1016/j.bmcl.2014.11.083

[25] Sultana F, Reddy Bonam S, Reddy VG, Nayak VL, Akunuri R, Rani Routhu S, et al. Synthesis of benzo[d]imidazo[2,1-b]thiazole-chalcone conjugates as microtubule targeting and apoptosis inducing agents. Bioorganic Chemistry. 2018;**76**:1-12. DOI: 10.1016/j.bioorg.2017.10.019

[26] Zhang L, Peng XM, Damu GL, Geng RX, Zhou CH. Comprehensive review in current developments of imidazole-based medicinal chemistry. Medicinal Research Reviews. 2014;**34**:340-437. DOI: 10.1002/med.21290

[27] Abdel-Maksoud MS, Kim MR, El-Gamal MI, Gamal El-Din MM, Tae J, Choi HS, et al. Design, synthesis, in vitro antiproliferative evaluation, and kinase inhibitory effects of a new series of imidazo[2,1-b]thiazole derivatives. European Journal of Medicinal Chemistry. 2015;**95**:453-463. DOI: 10.1016/j.ejmech.2015.03.065

[28] Romagnoli R, Baraldi PG, Prencipe F, Balzarini J, Liekens S, Estevez F. Design, synthesis and antiproliferative activity of novel heterobivalent hybrids based on imidazo[2,1-b][1,3,4]thiadiazole and imidazo[2,1-b][1,3]thiazole scaffolds. European Journal of Medicinal Chemistry. 2015;**101**:205-217. DOI: 10.1016/j.ejmech.2015.06.042

[29] Shaik SP, Nayak VL, Sultana F, Rao AVS, Shaik AB, Babu KS, et al. Design and synthesis of imidazo[2,1-b]thiazole linked triazole conjugates:

Microtubule-destabilizing agents. European Journal of Medicinal Chemistry. 2017;**126**:36-51. DOI: 10.1016/j.ejmech.2016.09.060

[30] Ali AR, El-Bendary ER, Ghaly MA, Shehata IA. Synthesis, in vitro anticancer evaluation and in silico studies of novel imidazo[2,1-b]thiazole derivatives bearing pyrazole moieties. European Journal of Medicinal Chemistry. 2014;**75**:492-500. DOI: 10.1016/j.ejmech.2013.12.010

[31] Gali R, Banothu J, Porika M, Velpula R, Bavantula R, Abbagani S. Synthesis and in vitro cytotoxic activity of novel coumarinylimidazo[2,1-b]thiazole derivatives. RSC Advances. 2014;**4**:53812-53819. DOI: 10.1039/C4RA11428K

[32] Kamal A, Balakrishna M, Nayak VL, Shaik TB, Faazil S, Nimbarte VD. Design and synthesis of imidazo[2,1-b]thiazole-chalcone conjugates: Microtubule-destabilizing agents. ChemMedChem. 2014;**9**:2766-2780. DOI: 10.1002/cmdc.201402310

[33] Li ZH, Zhang J, Liu XQ, Geng PF, Ma JL, Wang B, et al. Identification of thiazolo[5,4-d]pyrimidine derivatives as potent antiproliferative agents through the drug repurposing strategy. European Journal of Medicinal Chemistry. 2017;**135**:204-212. DOI: 10.1016/j.ejmech.2017.04.056

[34] Hassan GS, El-Messery SM, Abbas A. Synthesis and anticancer activity of new thiazolo[3,2-a]pyrimidines: DNA binding and molecular modeling study. Bioorganic Chemistry. 2017;**74**:41-52. DOI: 10.1016/j.bioorg.2017.07.008

[35] Ramirez J, Svetaz L, Quiroga J, Abonia R, Raimondi M, Zacchino S, et al. Synthesis of novel thiazole-based 8,9-dihydro-7H-pyrimido[4,5-b][1,4]diazepines as potential antitumor and antifungal agents. European Journal of

Medicinal Chemistry. 2015;**92**:866-875. DOI: 10.1016/j.ejmech.2015.01.053

[36] Altintop MD, Ozdemir A, Turan-Zitouni G, Ilgin S, Atli O, Demirel R, et al. A novel series of thiazolyl-pyrazoline derivatives: Synthesis and evaluation of antifungal activity, cytotoxicity and genotoxicity. European Journal of Medicinal Chemistry. 2015;**92**:342-352. DOI: 10.1016/j.ejmech.2014.12.055

[37] Bayomi SM, El-Kashef HA, El-Ashmawy MB, Nasr MN, El-Sherbeny MA, Abdel-Aziz NI, et al. Synthesis and biological evaluation of new curcumin analogues as antioxidant and antitumor agents: Molecular modeling study. European Journal of Medicinal Chemistry. 2015;**101**:584-594. DOI: 10.1016/j.ejmech.2015.07.014

[38] Altintop MD, Kaplancikli ZA, Ciftci GA, Demirel R. Synthesis and biological evaluation of thiazoline derivatives as new antimicrobial and anticancer agents. European Journal of Medicinal Chemistry. 2014;**74**:264-277. DOI: 10.1016/j.ejmech.2013.12.060

[39] Asati V, Mahapatra DK, Bharti SK. Thiazolidine-2,4-diones as multi-targeted scaffold in medicinal chemistry: Potential anticancer agents. European Journal of Medicinal Chemistry. 2014;**87**:814-833. DOI: 10.1016/j.ejmech.2014.10.025

[40] Kamal A, Syed MA, Mohammed SM. Therapeutic potential of benzothiazoles: A patent review (2010 - 2014). Expert Opinion on Therapeutic Patents. 2015;**25**:335-349. DOI: 10.1517/13543776.2014.999764

[41] Sovic I, Jambon S, Kraljevic Pavelic S, Markova-Car E, Ilic N, Depauw S, et al. Synthesis, antitumor activity and DNA binding features of benzothiazolyl and benzimidazolyl substituted isoindolines. Bioorganic & Medicinal Chemistry. 2018;**26**:1950-1960. DOI: 10.1016/j.bmc.2018.02.045

[42] Perontsis S, Hatzidimitriou AG, Begou OA, Papadopoulos AN, Psomas G. Characterization and biological properties of copper(II)-ketoprofen complexes. Journal of Inorganic Biochemistry. 2016;**162**:22-30. DOI: 10.1016/j.jinorgbio.2016.06.001

[43] Shakir M, Hanif S, Sherwani MA, Mohammad O, Azam M, Al-Resayes SI. Pharmacophore hybrid approach of new modulated bis-diimine Cu(II)/Zn(II) complexes based on 5-chloro Isatin Schiff base derivatives: Synthesis, spectral studies and comparative biological assessment. Journal of Photochemistry and Photobiology. B. 2016;**157**:39-56. DOI: 10.1016/j.jphotobiol.2016.01.019

[44] Li L, Du K, Wang Y, Jia H, Hou X, Chao H, et al. Self-activating nuclease and anticancer activities of copper(II) complexes with aryl-modified 2,6-di(thiazol-2-yl)pyridine. Dalton Transactions. 2013;**42**:11576-11588. DOI: 10.1039/c3dt50395j

[45] Czerwinska K, Machura B, Kula S, Krompiec S, Erfurt K, Roma-Rodrigues C, et al. Copper(ii) complexes of functionalized 2,2′:6′,2″-terpyridines and 2,6-di(thiazol-2-yl)pyridine: Structure, spectroscopy, cytotoxicity and catalytic activity. Dalton Transactions. 2017;**46**:9591-9604. DOI: 10.1039/c7dt01244f

[46] Xie F, Peng F. Anticancer activity of copper complex of (4R)-(−)-2-Thioxo-4-thiazolidinecarboxylic acid and 3-Rhodaninepropionic acid on prostate and breast cancer cells by fluorescent microscopic imaging. Journal of Fluorescence. 2018;**28**:89-96. DOI: 10.1007/s10895-017-2177-0

[47] Sandhaus S, Taylor R, Edwards T, Huddleston A, Wooten Y, Venkatraman R, et al. A novel copper(II) complex identified as a potent drug against colorectal and breast cancer cells and as a poison inhibitor for human topoisomerase IIalpha. Inorganic Chemistry Communications. 2016;**64**:45-49. DOI: 10.1016/j.inoche.2015.12.013

[48] Du K, Liang J, Wang Y, Kou J, Qian C, Ji L, et al. Dual inhibition of topoisomerases I and IIalpha by ruthenium(II) complexes containing asymmetric tridentate ligands. Dalton Transactions. 2014;**43**:17303-17316. DOI: 10.1039/c4dt02142h

[49] Correa RS, da Silva MM, Graminha AE, Meira CS, Santos JA, Moreira DR, et al. Ruthenium(II) complexes of 1,3-thiazolidine-2-thione: Cytotoxicity against tumor cells and anti-Trypanosoma cruzi activity enhanced upon combination with benznidazole. Journal of Inorganic Biochemistry. 2016;**156**:153-163. DOI: 10.1016/j.jinorgbio.2015.12.024

[50] Rubino S, Busa R, Attanzio A, Alduina R, Di Stefano V, Girasolo MA, et al. Synthesis, properties, antitumor and antibacterial activity of new Pt(II) and Pd(II) complexes with 2,2′-dithiobis(benzothiazole) ligand. Bioorganic & Medicinal Chemistry. 2017;**25**:2378-2386. DOI: 10.1016/j.bmc.2017.02.067

[51] Lalinde E, Lara R, Lopez IP, Moreno MT, Alfaro-Arnedo E, Pichel JG, et al. Benzothiazole-based cycloplatinated chromophores: Synthetic, optical, and biological studies. Chemistry. 2018;**24**:2440-2456. DOI: 10.1002/chem.201705267

[52] Song XQ, Liu YH, Shao J, Zhang ZL, Xie CZ, Qiao X, et al. Rapid induction of apoptosis in tumor cells treated with a new platinum(II) complex based on amino-thiazolidinone. European Journal of Medicinal Chemistry. 2018;**157**:188-197. DOI: 10.1016/j.ejmech.2018.07.075

[53] Sahin O, Ozdemir UO, Seferoglu N, Genc ZK, Kaya K, Aydiner B, et al. New platinum (II) and palladium (II) complexes of coumarin-thiazole Schiff base with a fluorescent chemosensor properties: Synthesis, spectroscopic characterization, X-ray structure determination, in vitro anticancer activity on various human carcinoma cell lines and computational studies. Journal of Photochemistry and Photobiology. B. 2018;**178**:428-439. DOI: 10.1016/j.jphotobiol.2017.11.030

[54] Islam MK, Kim S, Kim HK, Park S, Lee GH, Kang HJ, et al. Manganese complex of ethylenediaminetetraacetic acid (EDTA)-Benzothiazole aniline (BTA) conjugate as a potential liver-targeting MRI contrast agent. Journal of Medicinal Chemistry. 2017;**60**:2993-3001. DOI: 10.1021/acs.jmedchem.6b01799

[55] Vellaiswamy G, Ramaswamy S. Co(II) complexes of4-((3-ethoxy-2-hydroxybenzylidene)amino)-N-(thiazol-2-yl)benzenesulphonamide and 4-((pyridin-2-ylmethylene)amino)-N-(thiazol-2-tl)benzenesulfonamide: Synthesis, fluorescence properties and anticancer activity. Journal of Fluorescence. 2017;**27**:1559-1565. DOI: 10.1007/s10895-017-2096-0

[56] Pontoriero A, Mosconi N, Monti L, Bellu S, Williams PAM, Raimondi M, et al. Synthesis, characterization and biological studies of a cobalt(III) complex of sulfathiazole. Chemico-Biological Interactions. 2017;**278**:152-161. DOI: 10.1016/j.cbi.2017.10.004

[57] Neelima, Poonia K, Siddiqui S, Arshad M, Kumar D. In vitro anticancer activities of Schiff base and its lanthanum complex.

Spectrochimica Acta. Part A, Molecular and Biomolecular Spectroscopy. 2016;**155**:146-154. DOI: 10.1016/j.saa.2015.10.015

[58] Abbehausen C, Manzano CM, Corbi PP, Farrell NP. Effects of coordination mode of 2-mercaptothiazoline on reactivity of Au(I) compounds with thiols and sulfur-containing proteins. Journal of Inorganic Biochemistry. 2016;**165**:136-145. DOI: 10.1016/j.jinorgbio.2016.05.011

[59] Aman F, Hanif M, Kubanik M, Ashraf A, Sohnel T, Jamieson SM, et al. Anti-inflammatory oxicams as multi-donor ligand systems: pH- and solvent-dependent coordination modes of meloxicam and piroxicam to Ru and Os. Chemistry. 2017;**23**:4893-4902. DOI: 10.1002/chem.201700263

[60] Walsh CT, Acker MG, Bowers AA. Thiazolyl peptide antibiotic biosynthesis: A cascade of post-translational modifications on ribosomal nascent proteins. The Journal of Biological Chemistry. 2010;**285**:27525-27531. DOI: 10.1074/jbc.R110.135970

[61] Kang H, Choi M-C, Seo C, Park Y. Therapeutic properties and biological benefits of marine-derived anticancer peptides. International Journal of Molecular Sciences. 2018;**19**:919. DOI: 10.3390/ijms19030919

[62] Teruya T, Sasaki H, Fukazawa H, Suenaga K. Bisebromoamide, a potent cytotoxic peptide from the marine *Cyanobacterium lyngbya* sp.: Isolation, stereostructure, and biological activity. Organic Letters. 2009;**11**:5062-5065. DOI: 10.1021/ol9020546

[63] Suzuki K, Mizuno R, Suenaga K, Teruya T, Tanaka N, Kosaka T, et al. Bisebromoamide, an extract from Lyngbya species, induces apoptosis through ERK and mTOR inhibitions in renal cancer cells. Cancer Medicine. 2013;**2**:32-39. DOI: 10.1002/cam4.53

[64] Johnston HJ, Boys SK, Makda A, Carragher NO, Hulme AN. Naturally inspired peptide leads: Alanine scanning reveals an actin-targeting thiazole analogue of bisebromoamide. Chembiochem. 2016;**17**:1621-1627. DOI: 10.1002/cbic.201600257

[65] Singh S, Prasad NR, Kapoor K, Chufan EE, Patel BA, Ambudkar SV, et al. Design, synthesis, and biological evaluation of (S)-Valine Thiazole-derived cyclic and noncyclic peptidomimetic oligomers as modulators of human P-glycoprotein (ABCB1). Chembiochem. 2014;**15**:157-169. DOI: 10.1002/cbic.201300565

[66] Singh S, Prasad NR, Chufan EE, Patel BA, Wang YJ, Chen ZS, et al. Design and synthesis of human ABCB1 (P-glycoprotein) inhibitors by peptide coupling of diverse chemical scaffolds on carboxyl and amino termini of (S)-valine-derived thiazole amino acid. Journal of Medicinal Chemistry. 2014;**57**:4058-4072. DOI: 10.1021/jm401966m

[67] Wang Y-J, Patel BA, Anreddy N, Zhang Y-K, Zhang G-N, Alqahtani S, et al. Thiazole-valine peptidomimetic (TTT-28) antagonizes multidrug resistance in vitro and in vivo by selectively inhibiting the efflux activity of ABCB1. Scientific Reports. 2017;**7**:42106. DOI: 10.1038/srep42106

[68] Patel BA, Abel B, Barbuti AM, Velagapudi UK, Chen Z-S, Ambudkar SV, et al. Comprehensive synthesis of amino acid-derived Thiazole Peptidomimetic analogues to understand the enigmatic drug/substrate-binding site of P-glycoprotein. Journal of Medicinal Chemistry. 2018:61. DOI: 834-864. DOI: 10.1021/acs.jmedchem.7b01340

[69] Dutta D, Debnath M, Müller D, Paul R, Das T, Bessi I, et al. Cell penetrating thiazole peptides inhibit c-MYC expression via site-specific targeting of c-MYC G-quadruplex. Nucleic Acids Research. 2018;**46**:5355-5365. DOI: 10.1093/nar/gky385

[70] Maderna A, Doroski M, Subramanyam C, Porte A, Leverett CA, Vetelino BC, et al. Discovery of cytotoxic Dolastatin 10 analogues with N-terminal modifications. Journal of Medicinal Chemistry. 2014;**57**: 10527-10543. DOI: 10.1021/jm501649k

[71] Yokosaka S, Izawa A, Sakai C, Sakurada E, Morita Y, Nishio Y. Synthesis and evaluation of novel dolastatin 10 derivatives for versatile conjugations. Bioorganic & Medicinal Chemistry. 2018;**26**:1643-1652. DOI: 10.1016/j.bmc.2018.02.011

[72] Murray BC, Peterson MT, Fecik RA. Chemistry and biology of tubulysins: Antimitotic tetrapeptides with activity against drug resistant cancers. Natural Product Reports. 2015;**32**:654-662. DOI: 10.1039/c4np00036f

[73] Braig S, Wiedmann RM, Liebl J, Singer M, Kubisch R, Schreiner L, et al. Pretubulysin: A new option for the treatment of metastatic cancer. Cell Death & Disease. 2014;**5**:e1001. DOI: 10.1038/cddis.2013.510

[74] Lamidi OF, Sani M, Lazzari P, Zanda M, Fleming IN. The tubulysin analogue KEMTUB10 induces apoptosis in breast cancer cells via p53, Bim and Bcl-2. Journal of Cancer Research and Clinical Oncology. 2015;**141**: 1575-1583. DOI: 10.1007/s00432-015-1921-6

[75] Sani M, Lazzari P, Folini M, Spiga M, Zuco V, De Cesare M, et al. Synthesis and Superpotent anticancer activity of tubulysins carrying non-hydrolysable

N-substituents on tubuvaline. Chemistry - A European Journal. 2017;**23**:5842-5850. DOI: 10.1002/chem.201700874

[76] Park Y, Bae SY, Hah J-M, Lee SK, Ryu J-S. Synthesis of stereochemically diverse cyclic analogs of tubulysins. Bioorganic & Medicinal Chemistry. 2015;**23**:6827-6843. DOI: 10.1016/j.bmc.2015.10.003

[77] Nicolaou KC, Yin J, Mandal D, Erande RD, Klahn P, Jin M, et al. Total synthesis and biological evaluation of natural and designed tubulysins. Journal of the American Chemical Society. 2016;**138**:1698-1708. DOI: 10.1021/jacs.5b12557

[78] Chen H, Lin Z, Arnst K, Miller D, Li W. Tubulin inhibitor-based antibody-drug conjugates for cancer therapy. Molecules. 2017;**22**:1281. DOI: 10.3390/molecules22081281

[79] Li JY, Perry SR, Muniz-Medina V, Wang X, Wetzel LK, Rebelatto MC, et al. A Biparatopic HER2-targeting antibody-drug conjugate induces tumor regression in primary models refractory to or ineligible for HER2-targeted therapy. Cancer Cell. 2016;**29**:117-129. DOI: 10.1016/j.ccell.2015.12.008

[80] Colombo R, Wang Z, Han J, Balachandran R, Daghestani HN, Camarco DP, et al. Total synthesis and biological evaluation of tubulysin analogues. The Journal of Organic Chemistry. 2016;**81**:10302-10320. DOI: 10.1021/acs.joc.6b01314

[81] Leverett CA, Sukuru SCK, Vetelino BC, Musto S, Parris K, Pandit J, et al. Design, synthesis, and cytotoxic evaluation of novel tubulysin analogues as ADC payloads. ACS Medicinal Chemistry Letters. 2016;7:999-1004. DOI: 10.1021/acsmedchemlett.6b00274

[82] Tumey N, Leverett CA, Vetelino B, Li F, Rago B, Han X, et al. Optimization of tubulysin antibody-drug conjugates: A case study in addressing ADC metabolism. ACS Medicinal Chemistry Letters. 2016;**7**:977-982. DOI: 10.1021/acsmedchemlett.6b00195

[83] Reddy JA, Dorton R, Bloomfield A, Nelson M, Dircksen C, Vetzel M, et al. Pre-clinical evaluation of EC1456, a folate-tubulysin anti-cancer therapeutic. Scientific Reports. 2018;**8**:8943-8943. DOI: 10.1038/s41598-018-27320-5

[84] Ying Y, Taori K, Kim H, Hong J, Luesch H. Total synthesis and molecular target of largazole, a histone deacetylase inhibitor. Journal of the American Chemical Society. 2008;**130**:8455-8459. DOI: 10.1021/ja8013727

[85] Poli G, Di Fabio R, Ferrante L, Summa V, Botta M. Largazole analogues as histone deacetylase inhibitors and anticancer agents: An overview of structure-activity relationships. ChemMedChem. 2017;**12**:1917-1926. DOI: 10.1002/cmdc.201700563

[86] Clausen DJ, Smith WB, Haines BE, Wiest O, Bradner JE, Williams RM. Modular synthesis and biological activity of pyridyl-based analogs of the potent class I histone deacetylase inhibitor Largazole. Bioorganic & Medicinal Chemistry. 2015;**23**:5061-5074. DOI: 10.1016/j.bmc.2015.03.063

[87] Almaliti J, Al-Hamashi AA, Negmeldin AT, Hanigan CL, Perera L, Pflum MKH, et al. Largazole analogues embodying radical changes in the depsipeptide ring: Development of a more selective and highly potent analogue. Journal of Medicinal Chemistry. 2016;**59**:10642-10660. DOI: 10.1021/acs.jmedchem.6b01271

[88] Cole KE, Dowling DP, Boone MA, Phillips AJ, Christianson DW. Structural basis of the antiproliferative activity of largazole, a depsipeptide inhibitor of the histone deacetylases. Journal of the American Chemical Society. 2011;**133**:12474-12477. DOI: 10.1021/ja205972n

[89] Kim B, Ratnayake R, Lee H, Shi G, Zeller SL, Li C, et al. Synthesis and biological evaluation of largazole zinc-binding group analogs. Bioorganic & Medicinal Chemistry. 2017;**25**:3077-3086. DOI: 10.1016/j.bmc.2017.03.071

[90] Sun S, Oliveira B, Jiménez-Osés G, Bernardes GJL. Radical-mediated thiol-ene strategy for photoactivation of thiol-containing drugs in cancer cells. Angewandte Chemie, International Edition. 2018;**57**:15832-15835. DOI: 10.1002/anie.201811338

[91] Asano A, Yamada T, Taniguchi T, Sasaki M, Yoza K, Doi M. Ascidiacyclamides containing oxazoline and thiazole motifs assume square conformations and show high cytotoxicity. Journal of Peptide Science. 2018;**24**:e3120. DOI: 10.1002/psc.3120

[92] Chen Q-Y, Liu Y, Cai W, Luesch H. Improved total synthesis and biological evaluation of potent apratoxin S4 based anticancer agents with differential stability and further enhanced activity. Journal of Medicinal Chemistry. 2014;**57**:3011-3029. DOI: 10.1021/jm4019965

[93] Cai W, Chen Q-Y, Dang LH, Luesch H. Apratoxin S10, a dual inhibitor of angiogenesis and cancer cell growth to treat highly vascularized tumors. ACS Medicinal Chemistry Letters. 2017;**8**:1007-1012. DOI: 10.1021/acsmedchemlett.7b00192

[94] Cai W, Ratnayake R, Gerber MH, Q-y C, Yu Y, Derendorf H, et al. Development of apratoxin S10 (Apra S10) as an anti-pancreatic cancer agent and its preliminary evaluation in an orthotopic patient-derived

xenograft (PDX) model. Investigational New Drugs. 2018;**10**. DOI: 10.1007/s10637-018-0647-0

[95] Onda Y, Masuda Y, Yoshida M, Doi T. Conformation-based design and synthesis of apratoxin a mimetics modified at the α,β-unsaturated thiazoline moiety. Journal of Medicinal Chemistry. **2017**(60):6751-6765. DOI: 10.1021/acs.jmedchem.7b00833