Top Heterocycl Chem (2017) 48: 235–266
DOI: 10.1007/7081_2015_176

Published online: 6 October 2015

Thiazoles in Peptides and Peptidomimetics

Jeffrey Y.W. Mak, Weijun Xu, and David P. Fairlie

Abstract The natural occurrence of the thiazole ring in chemistry and biology has inspired its widespread use in synthetic peptidomimetics as structural templates, biological probes, and pharmaceuticals. Thiazole can be viewed as a dehydrated cyclized derivative of cysteine, incorporated into peptide sequences through chemical synthesis or ribosomal biosynthesis. Thiazoles are planar heterocycles and valuable synthetic templates with a strong hydrogen bond accepting nitrogen, a sulfur atom with extended lone pair electron orbitals, and an aromatic π-cloud. These properties can influence molecular conformation and direct interactions with proteins, leading to development of thiazole-containing peptidomimetics as protein mimicking scaffolds, modulators of cell surface proteins like G protein-coupled receptors (GPCRs), inhibitors of enzymes, and agonists or antagonists of protein–protein interactions. The thiazole ring is the most common five-membered heterocycle present in pharmaceuticals. This perspective article describes important properties of thiazoles in synthetic peptidomimetics and highlights key examples, including some from the last 5 years.

Keywords Amino acid · Conformation · Cyclic peptide · Cysteine · Drug · Heterocycle · Peptidomimetic · Pharmaceutical · Protein structure · Thiazole

Contents

J.Y.W. Mak, W. Xu, and D.P. Fairlie (✉)
Division of Chemistry and Structural Biology, Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD 4072, Australia
e-mail: d.fairlie@imb.uq.edu.au

Abbreviations

CCK	Cholecystokinin
CRF	Corticotropin-releasing factor
cSRC	Proto-oncogenic (sarcoma) protein tyrosine-protein kinase
FDA	Food and drug administration (USA)
NSAID	Non-steroidal anti-inflammatory drug
SAR	Structure–activity relationships

1 From Cysteine to Thiazoles and Peptidomimetics

Thiazole (C_3H_3NS) is a five-membered heterocyclic aromatic compound found in many natural products [1–4] including vitamin B1 and has been widely incorporated into synthetic molecules including pharmaceuticals [5], catalysts [6], and dyes [7]. Indeed, thiazole is a more common component of FDA-approved pharmaceuticals than related five-membered heterocycles such as isothiazole, thiophene, furan, isoxazole, and oxazole (Fig. 1). This perspective briefly summarizes thiazole chemistry [8] and focuses on current knowledge of thiazole peptidomimetics and their interactions with proteins.

From a peptidomimetic perspective, thiazole can be viewed as a derivative of cysteine, in much the same way as oxazole can be considered a derivative of serine or threonine (Scheme 1). Within a peptide sequence, a thiazole can be considered to represent a net condensation between the thiolate side chain of cysteine (e.g., in **1**) and the C-terminus of an adjacent amino acid with elimination of water to produce a dipeptide surrogate (Scheme 1). This heterocyclization with dehydration forms a thiazoline (e.g., **3**) that may undergo dehydrogenation to provide the thiazole (e.g., **5**). This set of reactions occurs in both ribosomal and non-ribosomal biosynthesis. The consequences of this condensation include the following: (1) the C-terminal

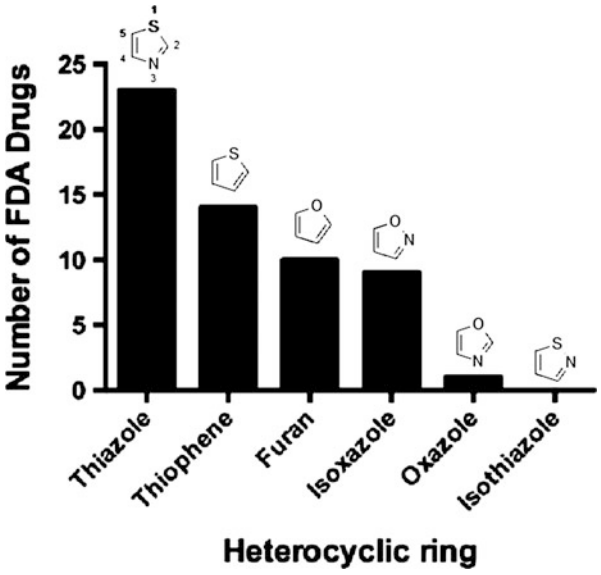
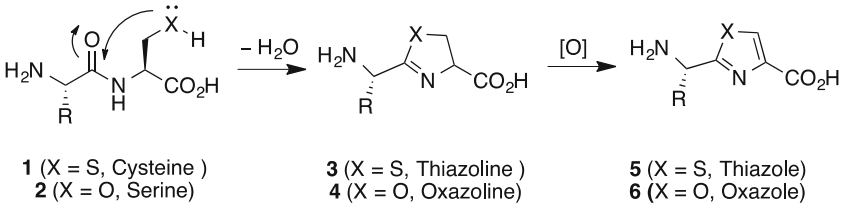


Fig. 1 Number of FDA-approved pharmaceuticals containing a single heterocyclic ring. The FDA1216 database [9] was searched for each heterocyclic ring using the ligand filtering module within Schrödinger software. Numbering convention shown for thiazole



Scheme 1 Condensation of the cysteine (X = S, **1**) and serine (X = O, **2**) side chains to give, respectively, thiazoline **3** and oxazoline **4**, followed by dehydrogenative aromatization to thiazole **5** and oxazole **6** dipeptide surrogates [10]

carboxylate is reoriented due to attachment to the sp^2 carbon of thiazole versus an sp^3 carbon in cysteine; (2) replacement of the N-terminal amide and cysteine thiol by the thiazole reduces polarity and hydrogen bond donors; (3) the cysteine stereochemical center is removed; (4) overall, this cyclization rigidifies the peptide backbone and favors turn conformations that may facilitate peptide cyclization.

The thiazole ring in dipeptide surrogates (e.g., **5**) may be reduced to the thiazoline (one double bond) or thiazolidine (no double bonds) to provide a range of conformational and stereochemical influences on the spatial disposition of the N- and C-terminus of the mimetic, to alter the capacity of the heterocycle to fit into hydrophobic binding sites in proteins, and to modify the hydrogen bonding properties of the heteroatoms. We shall return to peptidomimetics after briefly summarizing the chemistry of the thiazole heterocycle.

2 Chemistry of Thiazoles

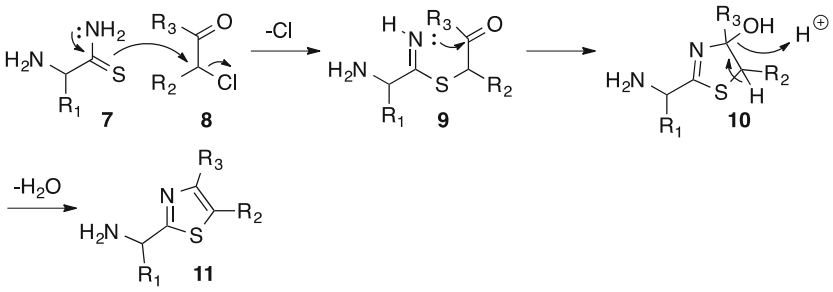
2.1 Syntheses of Thiazoles

The reactivity and synthesis of thiazoles has been previously reviewed [8, 11–16], and only such chemistry relevant to their use as peptidomimetics is presented below. Thiazoles have been traditionally prepared from open-chained components by a number of methods, among which the Hantzsch synthesis is preferred (Scheme 2) [17]. Thioamides (e.g., **7**) and α-halocarbonyls (e.g., **8**) combine to form thiazoles (e.g., **11**) via halide displacement (to give **9**) and subsequent condensation (e.g., **10**) [18]. All three carbons of the components may possess alkyl and aryl substituents, such that various substituted thiazoles may be synthesized [19]. For example, the thioamide component can be replaced by a thiourea to give the corresponding 2-aminothiazole [20].

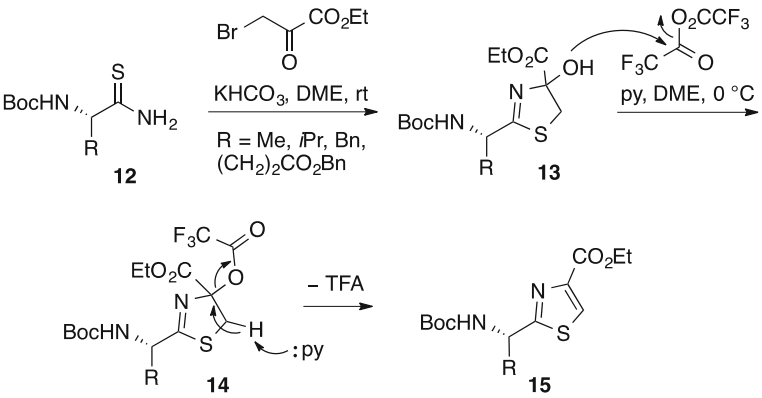
Racemization in the synthesis of thioamides derived from enantiomerically pure α-amino acids has been reported due to base-promoted epimerization [21]. Furthermore, application of α-amino acid-derived thioamides in the Hantzsch synthesis has been suggested to cause racemization from acid-catalyzed imine to enamine equilibrium during cyclization prior to aromatization [22, 23]. A modified Hantzsch synthesis protocol was developed to obtain enantiomerically pure α-amino acid-derived thiazoles (e.g., **15**) [23, 24]. After alkylation of thioamide **12** with ethyl bromopyruvate gave **13**, the hydroxyl group was trifluoroacetylated (to give **14**) and then eliminated in one pot using trifluoroacetic anhydride and pyridine at low temperature (Scheme 3).

The practicality of the Hantzsch synthesis was demonstrated by the preparation of orthogonally protected thiazole diamino acids **21**. β-Alanines **16** were converted to β-keto esters **18** by acylation with Meldrum's acid (**17**) and solvolytic decarboxylation. α-Chlorination of **19** with sulfuryl chloride followed by condensation with thiourea gave 2-aminothiazoles **20**, which were suitably *N*-protected and saponified to give **21** (Scheme 4) [25].

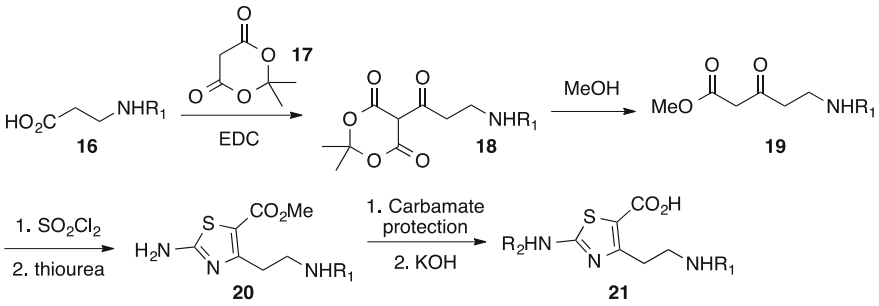
The Hantzsch reaction has also demonstrated utility for peptide macrocyclization (Fig. 2). In the case of macrocycle **22**, the Hantzsch synthesis



Scheme 2 Mechanism of the Hantzsch thiazole synthesis



Scheme 3 Modified Hantzsch thiazole synthesis for production of enantiomerically pure α-amino acid-derived thiazoles



Scheme 4 Synthesis of orthogonally protected thiazole diamino acids **21**

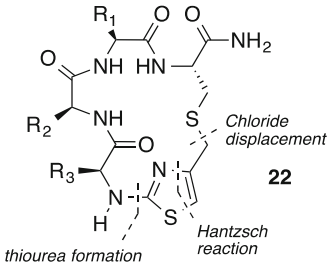
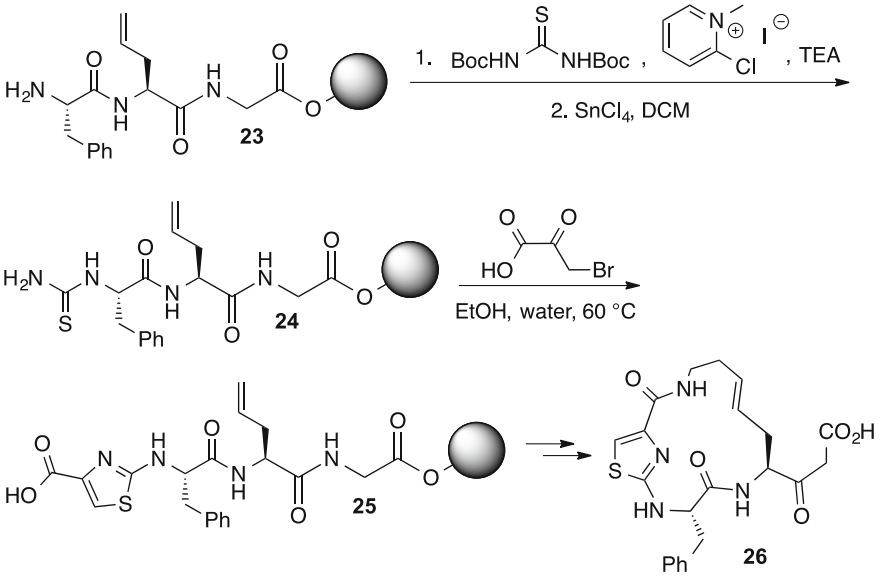


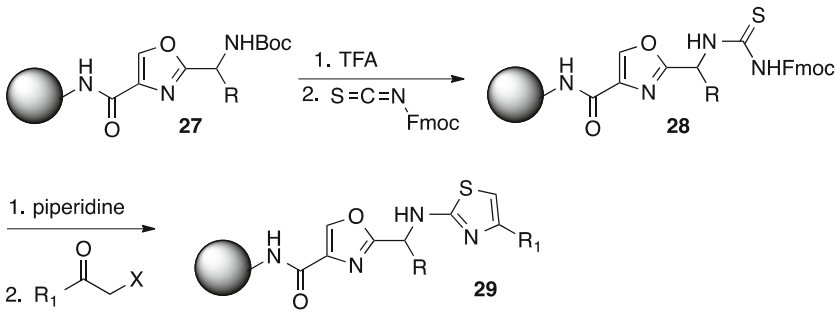
Fig. 2 Hantzsch strategy for the synthesis of peptide macrocycle **22**

installed a cysteine mimetic in the form of a thiazole ring, possessing a 4-position alkyl chloride, which was displaced by the thiol of a cysteine residue in the macrocyclization step [26].

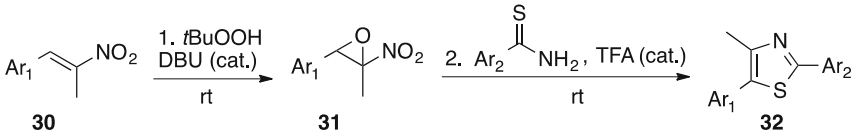
The Hantzsch synthesis has been conducted on solid phase to synthesize thiazole-containing peptide macrocycles [27]. The N-terminus of peptide **23** on solid support was reacted with *N*,*N*′-di-Boc-thiourea and Mukaiyama's reagent to



Scheme 5 Hantzsch thiazole formation in solid phase macrocycle synthesis



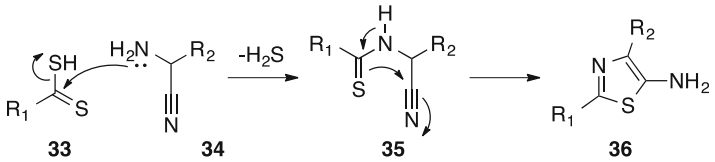
Scheme 6 Solid phase Hantzsch thiazole synthesis with *N*-Fmoc-NCS



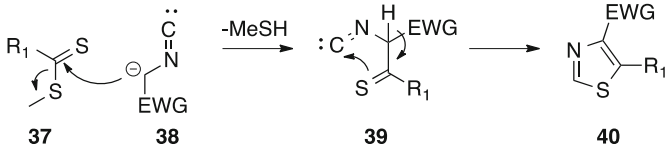
Scheme 7 One-pot synthesis of 2,5-diaryl thiazoles from nitrostyrenes **30**

give thiourea **24**. Subsequent treatment of **24** with α-bromopyruvic acid gave thiazole **25** en route to macrocycle **26** (Scheme 5).

Alternatively, *N*-Fmoc-isothiocyanate has been used to prepare thioureas **28** for solid phase Hantzsch syntheses of thiazoles **29** (Scheme 6) [28].



Scheme 8 Thiazole formation from dithioacid **33** and α-aminonitrile **34** in the Cook–Heilbron synthesis



Scheme 9 Modified Cook–Heilbron synthesis of 4,5-disubstituted thiazoles **40** using activated methylene isocyanides **38**

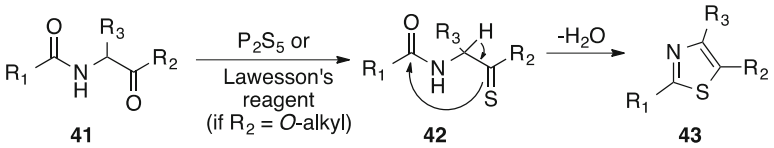
A one-pot formation of 1,3-thiazoles from nitrostyrenes **30** (Scheme 7) was developed based on a Hantzsch strategy [29]. Oxidation of nitrostyrenes **30** gave α-nitro-epoxides **31**, which serves as the α-halocarbonyl equivalent in condensations with thioamides to give the thiazoles **32**, albeit the reaction scope was limited to the formation of 2,5-diaryl thiazoles.

The Cook–Heilbron synthesis gives access to 5-aminothiazoles (e.g., **36**) with 2-position substituents [30–32]. Thioamidation of α-aminonitrile **34** with thiocarbonyl electrophiles, such as carbon disulfide, dithioesters, dithioacids (as exemplified by **33**), and isothiocyanates, provides thioamide intermediate **35**, which cyclizes to 5-aminothiazole **36** (Scheme 8).

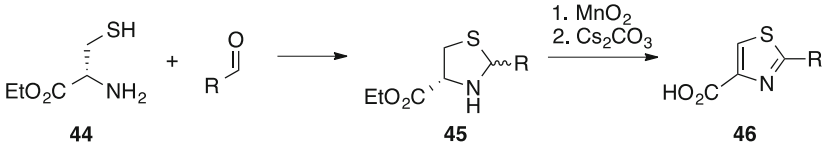
Employment of activated methylene isocyanide **38**, instead of the aminonitrile, in the condensation with dithioester **37** gave access to 4,5-substituted thiazoles **40** by way of thioketone intermediate **39** (Scheme 9) [33].

The Gabriel synthesis features conversion of α-acylamino ketones **41** into the corresponding thioketones **42**, which undergo intramolecular condensation to thiazole **43** [34, 35]. Substitution of Lawesson's reagent in place of phosphorus pentasulfide as thionating agent has expanded the approach to α-amido esters to make 5-alkoxythiazoles (Scheme 10) [36].

2,4-Disubstituted thiazoles **46** have also been synthesized from cysteine. For example, cysteine ethyl ester (**44**) has been condensed with aldehydes to give thiazolidines **45**, which were oxidized with manganese dioxide to give the corresponding substituted thiazoles **46** on multi-gram scale (Scheme 11) [37].



Scheme 10 Simplified mechanism of the Gabriel synthesis of thiazoles



Scheme 11 Synthesis of 2,4-disubstituted thiazoles from cysteine ethyl ester

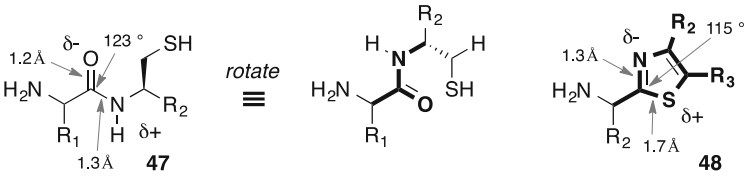


Fig. 3 Selected bond lengths and angles of amide **47** and thiazole **48** with coplanar atoms in *bold*. Bond angles and lengths correspond to unsubstituted thiazole [38]

2.2 *Stereoelectronic Properties of Thiazoles*

Thiazoles possess a number of stereoelectronic properties that may impact on their peptidomimetic derivatives. Thiazoles are planar aromatic heterocycles in which the relative connectivity of the heteroatoms, the bond lengths, and the bond angles all compare favorably with the planar amide bond in peptides, except that the C–S bond is considerably longer than the carbonyl C=O bond (Fig. 3) [38]. Replacement of a cysteine residue by a thiazole ring forces three additional atoms into the same plane as the amide (Fig. 3, shown in bold). Furthermore, a 5-position substituent (R_3) may be introduced, occupying space inaccessible by the cysteine residue.

The thiazole ring structure satisfies Hückel's rule ($n = 1$) courtesy of the delocalization of the lone pair of the sulfur atom. Relative to oxazole, which has little aromatic character, thiazole is considered to be aromatic, due in part to π-electron delocalization of the lone pair on the sulfur atom [39]. Calculations of the electron density distribution in thiazole by many different methods indicate the sulfur and nitrogen atoms have, respectively, net positive and negative charges, and C-2 and C-5 are, respectively, slightly positive, but close to neutral, and slightly negative [40]. The computational results are consistent with experiments indicating nucleophiles attack preferentially at C-2 and electrophiles react with C-5 (Fig. 4).

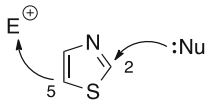


Fig. 4 The 2- and 5-positions of thiazole react preferentially with nucleophiles and electrophiles, respectively

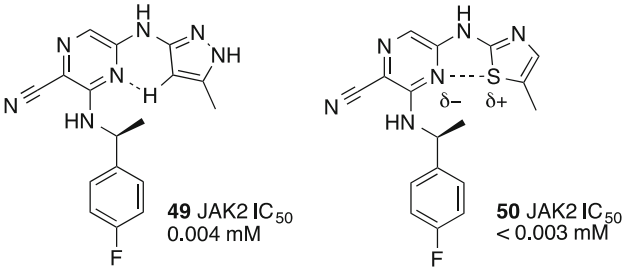


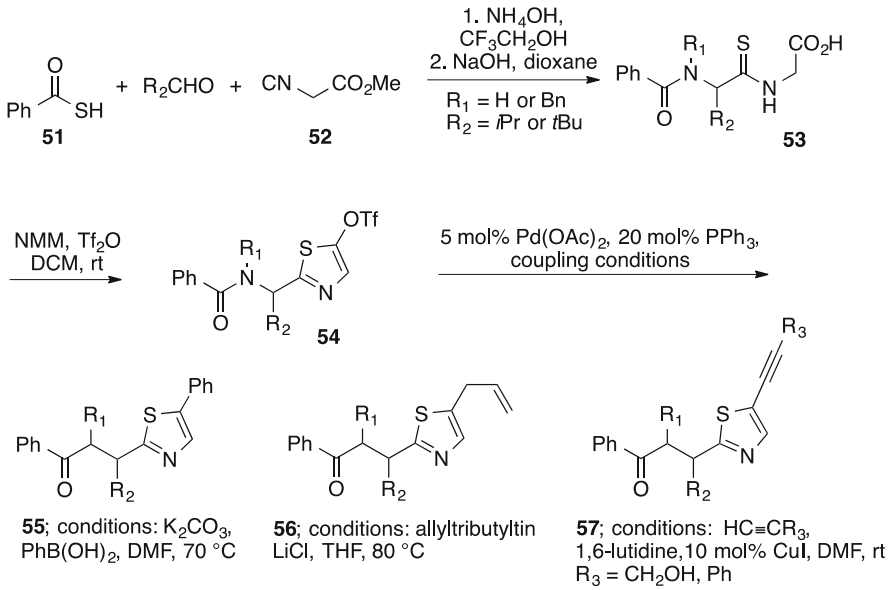
Fig. 5 The predicted N–HC hydrogen bond in pyrazole **49** was successfully replaced by a N–S electrostatic interaction in thiazole **50**

The thiazole sulfur has been suggested to form non-covalent interactions with electron-rich regions of molecules [41]. For example, replacement of a thiazole for the pyrazole ring in Janus kinase 2 inhibitor **49** gave analogue **50**, which exhibited similar potency (Fig. 5). Based on the predicted binding mode, a co-planar electrostatic interaction between the nitrogen (δ−) of the pyrazine and the sulfur (δ+) of the thiazole of inhibitor **50** was presumed to replace the hydrogen bond between the pyrazine and 5-position proton of the pyrazole in **49** [41].

The thiazole sp^2 nitrogen is basic. With lone pair electrons sitting outside of the aromatic π-system, the thiazole nitrogen may act as a moderately strong hydrogen bond acceptor, similar to the oxygen of an amide. With a pK_a of 2.5 for the protonated form of unsubstituted thiazole, the nitrogen is typically not protonated under physiological conditions; however, thiazole basicity is affected by ring substitution [42]. Typically, 2-, 4-, and 5-position alkyl groups increase basicity with decreasing potency. For example, the pK_a values of protonated 2-, 4-, and 5-methylthiazoles are 3.4, 3.2, and 3.1, respectively. Protonated 2-aminothiazole has a pK_a of 5.4, due to resonance between the exocyclic amine and the conjugated π system. Protonated benzothiazole and electron-deficient thiazoles, such as nitrothiazole, are relatively more acidic than thiazole.

2.3 Chemical Reactivity of Thiazoles

Unlike their structurally related oxazole counterparts, thiazoles do not usually react in cycloaddition reactions, due to their greater aromaticity [43–45]. Unless activated by electron donating groups (e.g., amino or hydroxyl groups) [46], similar to



Scheme 12 Synthesis of 5-substituted thiazole peptides via the Ugi reaction

π-deficient pyridines, thiazoles typically resist electrophilic attack, due in part to deactivation by the nitrogen [40]. For example, thiazoles are resistant to nitration, sulfonation, and halogenation in strongly acidic media, because nitrogen protonation depletes ring electron density. The C-2 proton possesses greater kinetic and thermodynamic acidity [40], relative to those at C-4 and C-5, and may be deprotonated with alkyl lithium bases [47] and lithium diisopropylamide [48]. Together with thiazole Grignard reagents [47], *C*-lithiated species have been reacted with various carbon electrophiles. The C-2 position is prone to nucleophilic attack and becomes even more reactive to nucleophiles upon alkylation of the thiazole nitrogen to give the corresponding thiazolium salts [19].

Appropriately functionalized thiazole derivatives have been substrates in palladium-catalyzed reactions, such as Suzuki, Stille, Negishi, Sonogashira, as well as Heck coupling reactions [49, 50], albeit few examples of the latter have been reported [19]. The thiazole tin and zinc reagents serve, respectively, as nucleophilic partners in Stille and Negishi cross-coupling reactions. In Suzuki cross-couplings, however, halothiazoles act typically as the electrophilic component, because of the instability of thiazole boronates, especially those with boron at C-2 [19, 51]. Scalable syntheses of 2-bromothiazole, as well as 2,4- and 2,5-dibromothiazoles from inexpensive commercially available starting materials, have facilitated the use of metallation and palladium-catalyzed reactions [52].

The Ugi reaction has been exploited for the synthesis of thiazole-containing peptides, albeit without stereochemical control [53, 54]. After the Ugi reaction and ester hydrolysis afforded thioamide **53**, treatment with triflic anhydride in CH_2Cl_2 gave thiazole triflate **54**, which was employed in a series of palladium-catalyzed

cross-coupling reactions to prepare thiazoles possessing proton, allyl, acetylenyl and aryl 5-position substituents (e.g., **55**, **56**, and **57**, Scheme 12) [55].

3 Thiazoles as Peptide Surrogates and Synthetic Building Blocks

3.1 Thiazoles as Synthetic Building Blocks

There are many useful thiazole synthetic blocks that are commercially available (e.g., **58–66**, Fig. 6). Thiazoles have found wide application within peptidomimetics, due in part to effective methods for installing substituents at each of the ring carbons [6, 56–58].

3.2 Thiazoles as Capping Groups in Peptidomimetics

Thiazoles have been used to cap the N- and C-termini of peptides and peptidomimetics, such as in the anticancer agent dolastatin-10 (**68**, Fig. 7) [59, 60]. In the PAR2 agonist 2at-LIGRL-NH_2 (**67**, Fig. 7 2at=2-aminothiazol-4-oyl), the aminothiazoyl group was used as a metabolically stable N-terminus cap [61], which may confer additional chemical and biological stability to the peptide [62, 63]. Frequently, the thiazole fits neatly into an indentation in the surface of a protein target, offering interactions with its π cloud or its hydrogen bond accepting nitrogen (see Sect. 5).

2-Aminothiazole was used as a heterocyclic cysteine surrogate in the development of Ras protein C-terminal *CAAX* tetrapeptide mimetics for the inhibition of

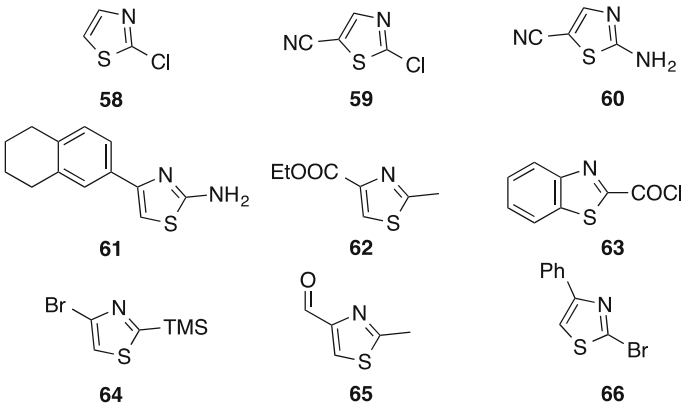


Fig. 6 Useful thiazole-containing synthetic building blocks

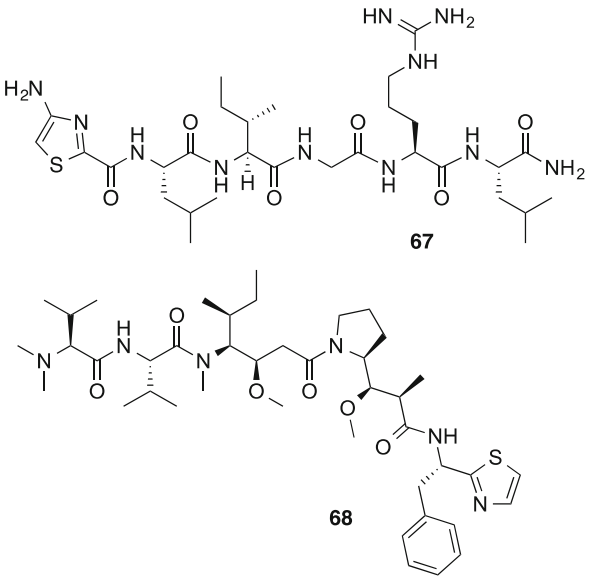


Fig. 7 PAR2 agonist 2at-LIGRL-NH_2 (**67**, 2at=2-aminothiazol-4-oyl) and dolastatin-10 (**68**)

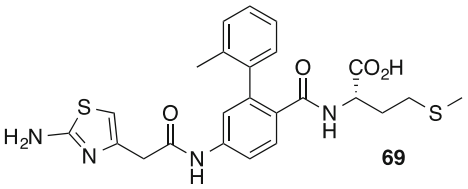
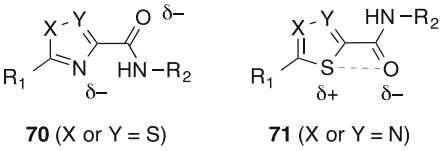


Fig. 8 Based on the C-terminal Ras protein tetrapeptide CAAX sequence, 2-aminothiazole served as a cysteine mimetic in FTase inhibitor **69**

the zinc metalloenzyme farnesyltransferase (FTase, Fig. 8) [64]. In previous studies, a pyridine group had been successfully employed as a metabolically stable cysteine mimetic. The 2-aminothiazole was tested as an alternative, because of its comparable basicity to pyridine, and pronounced properties for forming metal complexes. Thiazole peptidomimetic **69** inhibited FTase activity (IC_{50} 49 nM) and rat smooth muscle cell proliferation (IC_{50} 107 μM). Described as a potentially promiscuous scaffold [65], 2-aminothiazole is a component of some drugs and has gained significant consideration for employment in drug discovery.

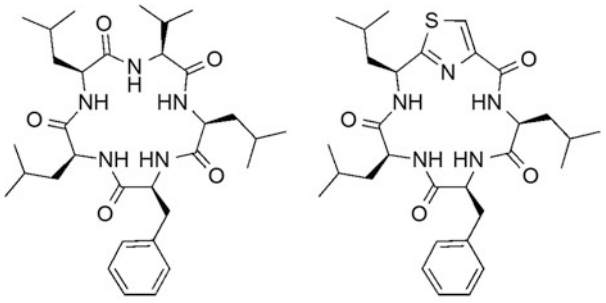
3.3 Thiazole Influences Conformation in Peptidomimetics

Thiazoles exert stereoelectronic effects on adjacent carboxamides that dictate their conformation [66, 67]. The solid-state structures of six thiazole-5-carboxamide analogues have been deposited in the Cambridge crystallographic database. The four thiazole-5-carboxamides **71** possessing a 1,4-relationship between the sulfur and carbonyl oxygen atom exhibited a S–C–C–O dihedral angle value between



70 (X or Y = S) **71** (X or Y = N)

Fig. 9 The dipole moment of the thiazole ring can dictate the conformation of the neighboring amide



Sansalvamide A (**72**) **73**

Fig. 10 Sansalvamide A (**72**) and its thiazole analogue **73**

11° and 37° and S–O distances that were less than the sum of the van der Waal radii, suggesting an attractive interaction (Fig. 9). On the other hand, the two thiazole-5-carboxamides **70** with a 1,4-relationship between the thiazole nitrogen and the amide carbonyl oxygen had N–C–C–O torsion angle values of 165° and 173°. On switching locations of the nitrogen and sulfur heteroatoms in thiazole-5-carboxamides **70** and **71** (Fig. 9), the altered dipole and orbital alignments result in opposite amide orientations with different three-dimensional electrostatic surfaces. These differences translated into opposing agonist versus antagonist activity in activating a G protein-coupled receptor (GPCR, i.e., the complement C-3a receptor) on human macrophages [66]. The influence of the heteroatom was confirmed by locking the heterocyclic amide conformation using fused bicyclic rings.

Toward the development of potential anticancer agents, peptidomimetics of the cytotoxic cyclic pentapeptide sansalvamide A (**72**) were prepared employing triazole, oxazole, and thiazole rings as amide bond isosteres (Fig. 10) [68]. Replacement of the Leu-Val residue with thiazole (**73**) gave an analogue with equal cytotoxicity to the parent sansalvamide A (**72**). The relative cytotoxicity of the heterocycle analogues was rationalized on their ability to adopt backbone conformation and side chain presentations similar to the native peptide [68].

4-Amino(methyl)-1,3-thiazole-5-carboxylic acids have served as turn-inducing constraints in peptides such as an analogue of gramicidin S that maintained strong antibacterial activity with reduced hemolytic activity [69]. Oligomers of the 4-amino(methyl)-1,3-thiazole-5-carboxylic acids in γ-peptides adopted a right-handed 9-helix structure [70]. Potent examples of thiazole GPCR ligands include cholecystokinin-1 (CCK1) agonist SR146131 (**74**) and antagonist SR27897 (**75**, $IC_{50} > 0.58$ nM CCK; 489 nM CCK2), orally active corticotropin-releasing factor

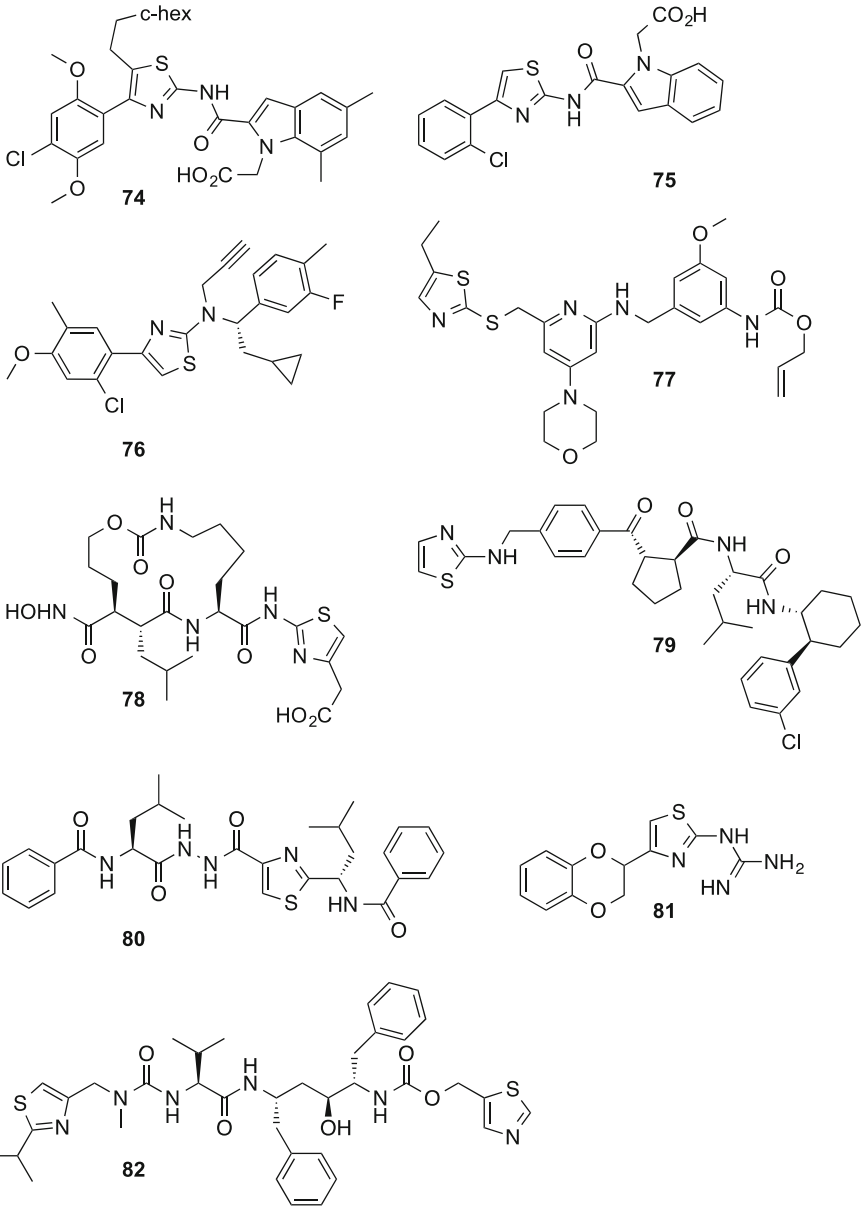


Fig. 11 Thiazole-containing GPCR modulators (**74**–**77**) and enzyme inhibitors (**78**–**82**)

(CRF) antagonist SSR-125543A (**76**, $K_i = 2$ nM, CRF1), and orally active and brain permeable neuropeptide Y antagonist J-104870 (**77**, Y1 < 1 nM; Y2,Y4 > 10 μM; Y5 6 μM) (Fig. 11) [71].

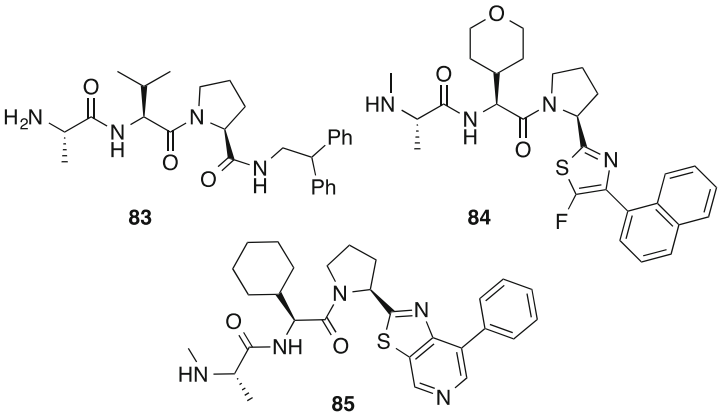


Fig. 12 Thiazoles as amide replacements in IAP antagonists

Thiazoles have served as linkers and capping groups in peptide-mimicking ligands that inhibit enzymes, for example, in tumor necrosis factor-α converting enzyme inhibitor **78** (IC_{50} 0.08 μM), cyclin-dependent kinase inhibitor **79** (IC_{50} 40 nM, CDK2), cathepsin K inhibitor **79** (K_i 10 nM), ERK inhibitor **81** (K_d 16 μM, ERK2), and the HIV protease inhibitor ritonavir (**80**, $IC_{50} \sim 1$ nM, HIV-1 protease) [72].

3.4 Thiazoles as Amide Bond Replacements

Thiazoles have been used as amide bond isosteres. For example, in the development of inhibitors of apoptosis protein (IAP) antagonists, the proline amide bond of lead peptide **83** did not make any specific interactions with the target protein (Fig. 12) [73]. Thus, the amide bond was replaced with thiazole and benzothiazole surrogates to fine-tune the physicochemical properties. The most potent of these thiazole analogues (e.g., **84** and **85**) had K_i values of 20–60 nM against targeted IAPs.

Thiazoles were used as amide bond replacements in the development of peptidomimetic oligomers that modulate the activity of human *p*-glycoprotein [74]. Linear and cyclic trimer oligomers of (*S*)-valine-derived thiazole units **5** (R = *i*-Pr, Scheme 1) exhibited low micromolar inhibition of human *p*-glycoprotein. Consistent with being effective amide bond replacements, thiazole-based amino acids have also been used to construct peptide secondary structures analogous to those of natural amino acids, such as helical oligomers [70, 75], β-strand mimics [72], and turn mimics [69, 71].

Bi-thiazoles (Fig. 13) may be considered peptide mimics and have served in enzyme inhibitors, protein-binding motifs, and natural products. For example, bi-thiazole-2,2′-diamines (**86** and **87**, Fig. 13) compete against peptide substrates that bind cJun N-terminal kinases (JNKs) [76]. When incorporated into peptide

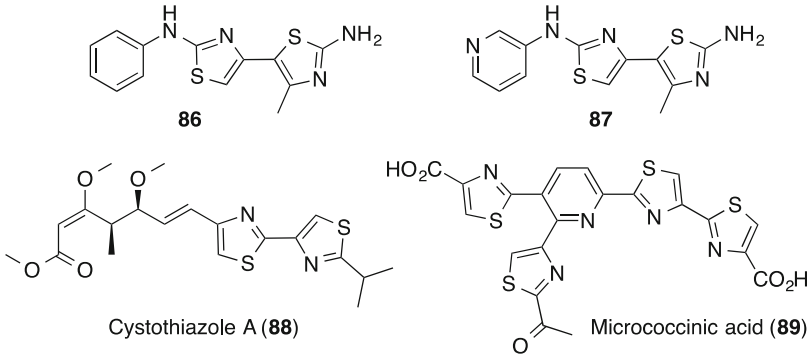


Fig. 13 Bithiazole-2,2′-diamines **86** and **87** and bithiazole natural products cystothiazole A (**88**) and micrococcinic acid (**89**)

sequences, these scaffolds can restrict conformation. The bi-thiazole natural product antibiotic cystothiazole A (**88**) kills human colon cancer and leukemia cells (Fig. 13) [77, 78]. Bi-thiazoles occur in other natural products such as micrococcinic acid (**89**) and macrocyclic peptides (see section below).

4 Thiazoles in Peptidomimetics and Cyclic Peptides

Thiazoles are present in numerous classes of natural products, particularly alkaloids and cyclic peptides [1, 3, 79–81]. Only a few thiazole macrocycles can be accommodated within the size constraints of this article. The first to be considered here is largazole (**90**, Fig. 14), a metabolite from a cyanobacterium that potently inhibits the growth of triple-negative human breast cancer cells ($GI_{50} = 7.7$ nM) [82–86]. Largazole features a macrocycle containing a thiazole fused to a 4-methylthiazoline. An octanoyl moiety is attached to the macrocycle by way of a thioester to the 3-hydroxy-7-mercaptohept-4-enoic acid subunit and serves to produce a prodrug, which on thioester hydrolysis releases the thiolate that potently inhibits histone deacetylase enzymes. The thiazole–thiazoline bicyclic unit serves primarily as a scaffold that orients the other components of the molecule for protein binding.

Bistratamides (e.g., **91**–**93**, Fig. 15) are a family of thiazole-containing hexapeptide analogues, which were isolated from the aplouso-branch ascidian *Lissoclinum bistratum* [87]. Bistratamides have exhibited antitumour activity against human colon cancer cells [87]. Their cytotoxicity and that of related macrocycles are contingent on the variety of L-amino acid, oxazole, oxazoline, and thiazole components, which leads to different conformational restrictions [88].

Sanguinamides A and B (**94** and **96**, Fig. 16) are thiazole-containing cyclic hepta- and octa-peptide analogues. Sanguinamide A has inspired analogues exhibiting membrane permeation and oral absorption [89–91]. Sanguinamide B

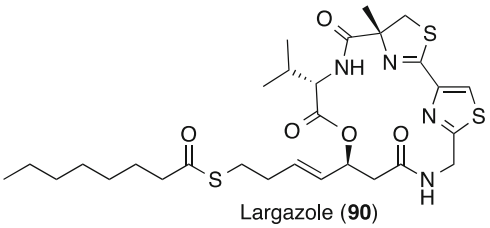


Fig. 14 Largazole (**90**), a thiazole-containing cyclic peptide natural product

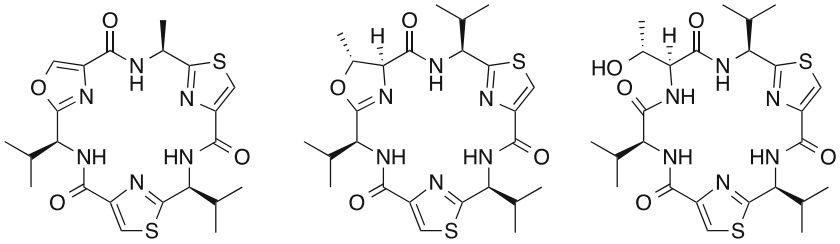


Fig. 15 Bistratamides C (**91**), E (**92**), and J (**93**)

analogues have been the subject of synthetic efforts, due in part to their cytostatic activity [92, 93]. Originally isolated from the sea slug *H. sanguineus* [91], sanguinamide A (**94**) features an isoleucine-thiazole dipeptide surrogate in a 21-member cyclic heptapeptide, *cyclo*-[Ile(Thz)AlaPheProIlePro]. The total synthesis of **94** enabled NMR studies, which revealed two strong intramolecular hydrogen bonds between Ala^2 and Leu^5 rigidify the cyclic peptide, which adopts a predominant conformation possessing a prolyl amide *cis*-isomer between Phe^3 and Pro^4 [90]. Replacement of the thiazole constraint by Ala gave a more flexible cyclic peptide with conformers due to *cis–trans* isomerization about the Ile^5-Pro^6 peptide bond, both retaining the amide *cis*-isomer between Phe^3 and Pro^4 [89]. Guided by amide H–D exchange rates and NMR structures, Ala^2 was replaced by the bulkier *t*BuGly (i.e., **95**, Fig. 16) to shield solvent-exposed polar atoms, substantially increasing oral bioavailability in rats (7–50%) [89]. Sanguinamide B (**96**, *cyclo*-[Pro-Val-(Ala-Thz)Ile-(ProThzOx)]) was also isolated from *H. sanguineus*. Featuring two prolyl amide *trans*-isomers and an unusual 4,2-oxazole-thiazole unit in a 24-member cyclic octapeptide [92], **96** has exhibited antibacterial (*P. aeruginosa*) and anticancer activity [92–94].

Other thiazole-containing 24-member cyclic octapeptide derivatives include urukthapelstatin A (**97**), patellamide D (**98**), and ascidiacyclamide (**99**) (Fig. 17). Urukthapelstatin A (**97**) was isolated from *Mechercharimyces asporophorigenens* YM11-542 and was characterized by crystallography. The 24-member cycle of **97** contains a sequential oxazole–thiazole moiety that has also been observed in mechercharstatin and telomestatin [95]. Urukthapelstatin A is a potent inhibitor of human cancer cell growth (e.g., IC_{50} 12 nM, A549 lung fibroblasts).

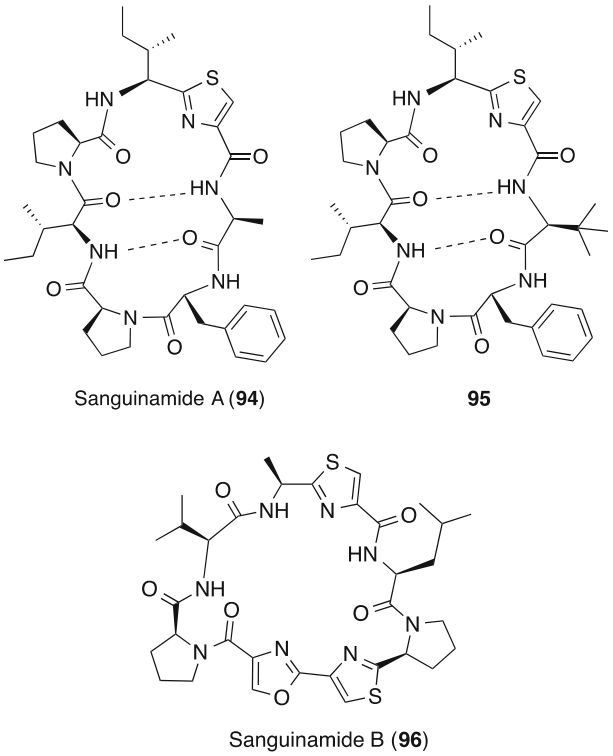


Fig. 16 Sanguinamide A (**94**), *t*BuGly analogue **95**, and sanguinamide B (**96**)

The patellamides are a diverse class of cyclic peptides that exhibit cancer cell cytotoxicity. Biosynthetically produced by enzymes, they possess various oxazoline, oxazole, thiazoline, and thiazole moieties [96–98]. For example, patellamide D (**98**) and ascidiacyclamide (**99**) were isolated from *Lissoclinum patella*, and both have two thiazole and two oxazoline components that create a saddle-shaped conformation that bestows metal binding capability [99]. Each thiazole nitrogen in the cyclic peptide can coordinate to copper, zinc, calcium, and potassium to form one or two metal ion complexes [100]. In complexes with two copper ions, the cyclic peptide can trap carbon dioxide from solution to form a carbonate bridge between the two metal ions [101]. These cleft-forming thiazole peptides can also trap small organic molecules in their cavities [2]. Removal of two of the heterocycles from an ascidiacyclamide analogue completely altered the cleft structure [102] and inspired the use of thiazoles, oxazoles, and their reduced analogues to generate other shapes, including cylindrical and conical structures [103], as well as the preparation of very large macrocycles containing as many as 19 thiazoles and 76 amino acids [104].

There are many larger macrocycles of varying sizes containing thiazoles (Figs. 18 and 19) that are ribosomally derived from complex gene clusters. Most

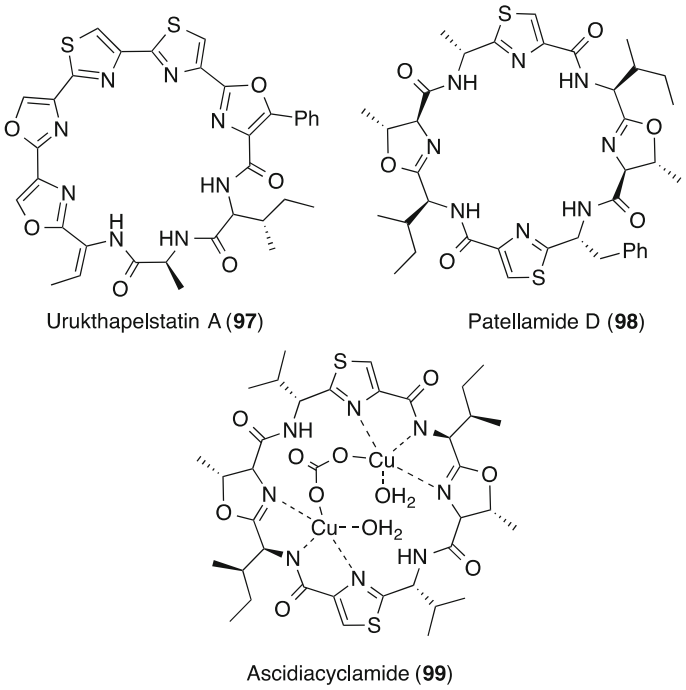
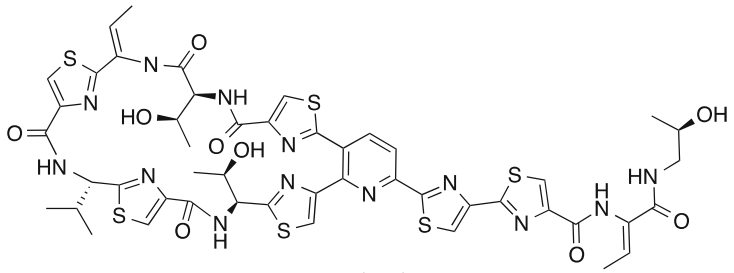
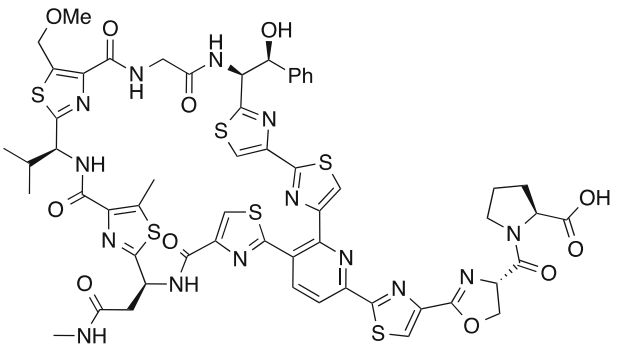


Fig. 17 Thiazole-containing cyclic octapeptide derivatives urukthapelstatin A (**97**), patellamide D (**98**), and ascidiacyclamide (**99**)

notable are the thiopeptide antibiotics, which typically have antibacterial activity against Gram-positive bacteria, and sometimes anticancer, antimalarial, immunosuppressive, and cytotoxic activities at low micromolar concentrations [105]. For example, micrococcin P1 (**100**, Fig. 18) incorporates the four-thiazole unit micrococcinic acid (**89**, Fig. 13), in a 26-member ring that exhibits antimalarial, antiprotozoal, antibacterial, and cytotoxic activities [106]. The natural product GE2270A (**101**) contains five thiazoles and exhibits potent antibacterial activity [107]. The antibiotic GE37468A (**102**) inhibits bacterial protein synthesis. Containing three thiazoles, a thiazoline, an oxazole, and a proline in a 29-member ring, **102** inhibits the growth of a number of bacteria including *Clostridium difficile*. An analogue LFF571 [108] is in clinical trials for treating bacterial infections in the GI tract. Micrococcin P1 (**100**), GE2270A (**101**), and GE37468A (**102**) all have a central pyridine ring. Thiostrepton A (**103**, Fig. 19) is a bis-macrocycle possessing a dehydropiperidine core linked to one macrocycle comprising of three thiazoles and a thiazoline, a second cycle containing a quinaldic acid macrocycle, and a bis-dehydroalanine tail. Biosynthesis of **103** involves 21 separate genes. Thiostrepton A has also been made by chemical synthesis [109]. Demonstrated to be active against breast cancer cells and Gram-negative bacteria, **103** is an inhibitor of 50S ribosome and 20S proteasome [110], as well as a valuable tool in molecular biology for gene selection in nucleotide metabolism.





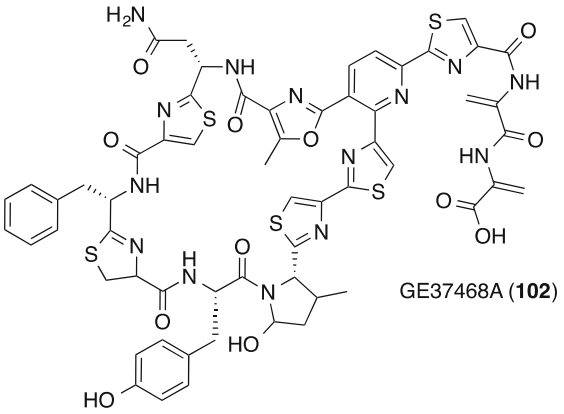


Fig. 18 Micrococcin P1 (thiocillin, **100**), GE2270A (**101**), and GE37468A (**102**)

Although **103** had limited solubility, thiostrepton A is marketed as a drug for treating mastitis and skin infections in domestic animals. The related bis-macrocycle, nosiheptide (**104**, Fig. 19), is a thiopeptide antibiotic from a marine *actinomycete* strain that has exhibited potency (MIC 0.25 mg/L) against methicillin-resistant *Staphylococcus aureus* (MRSA), drug-resistant clinical isolates, and a virulent strain of *Clostridium difficile*, but was inactive against most

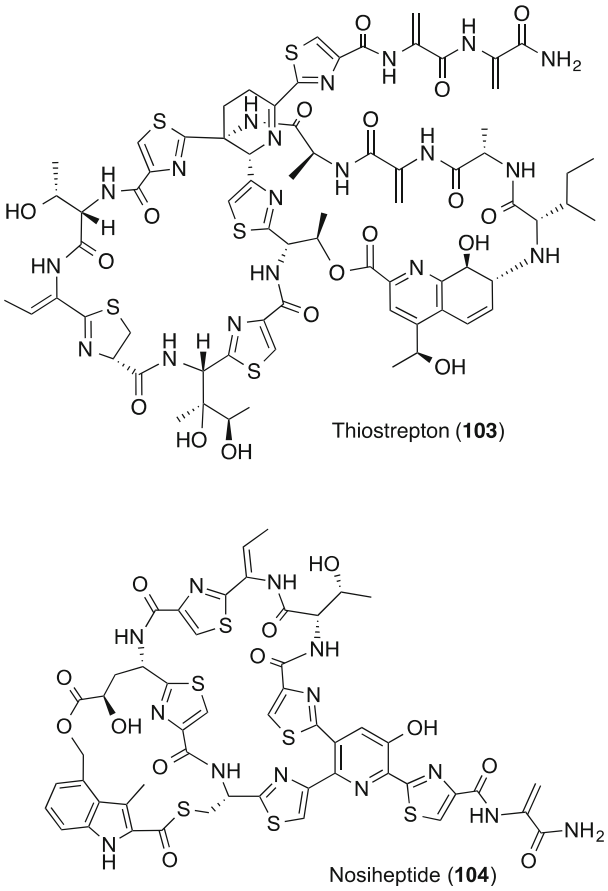


Fig. 19 Thiostrepton (**103**) and nosiheptide (**104**)

Gram-negative strains tested [111]. With negligible cytotoxicity against mammalian cells and in vivo activity in a murine model of MRSA infection, nosiheptide is marketed for veterinary use as an antibiotic, as well as a food preservative.

5 Protein-Binding Thiazoles and Thiazole Drugs

The thiazole ring is present in biologically active molecules and pharmaceuticals that interact with various proteins [112–114], in part due to the hydrogen bond acceptor ability and aromatic character of the heterocycle. A search of the protein data bank found over 200 crystal structures that feature thiazole–protein interactions exhibiting aromatic π–π, π-cation and π-halogen attractive forces. To exemplify key molecular interactions that underpin biological properties of thiazole

peptidomimetics, eight specific thiazole–protein crystal structures are discussed below including six inhibitors of kinases, a protease inhibitor, and one example of a thiazole bound to DNA: 2GQG [115], 3G5D [116], 2Y6O [117], 3BX5 [118], 3IW8 [119], 3QXP [120], 1A61 [121], and 2R2U [122].

5.1 Kinase Inhibition by Dasatinib

Dasatinib (**105**, Fig. 20a–c) is a kinase inhibitor used to treat chronic myelogenous leukemia (CML) and other cancers. It features a central 2-amido thiazole-5-carboxamide component derived from amino acid **111** (Fig. 21).

Dasatinib (**105**) has been crystallized with several human kinases including BCR-ABL kinase, the human kinase domain of cSrc, erythropoietin-producing hepatocellular EphA4 kinase, Lyn protein kinase [123], and Bruton's tyrosine kinase [124]. A common feature of most dasatinib structures is that the thiazole nitrogen acts as a hydrogen bond acceptor that binds to a protein backbone amide NH, often from a methionine (Fig. 20).

BCR-ABL kinase is activated in chronic myeloid leukemia [115] and inhibited by the drug imatinib (Gleevec); however, kinase mutation leads to resistance. Dasatinib (**105**) is 325-fold more potent than imatinib against wild-type and most mutant forms of BCR-ABL and interacts in the ATP binding site (Fig. 21a, PDB: 2GQG) flanked by the two classical kinase sub-lobes. The 2-amino thiazole component occupies a site normally occupied by the adenine group of ATP. The 2-chloro-6-methyl phenyl moiety binds within a hydrophobic site formed by M290, V299, T315, and K217. The thiazole nitrogen and the proton of its 2-amido nitrogen form respectively hydrogen bonds with the amide and carbonyl oxygen of Met318. A hydrogen bond is also made between the hydroxyl oxygen of Thr315 and the thiazole 5-carboxamide NH of dasatinib. The terminal hydroxyethyl group contacts the backbone carbonyl oxygen of Tyr320 via a hydrogen bond. Comparison of the crystal structures of dasatinib and imatinib bound, respectively, to BCR-ABL led to the suggestion that the higher kinase affinity of the former was due to its ability to recognize multiple states of the enzyme [115].

The kinase cSrc is overexpressed in certain tumors such as glioblastoma, gastrointestinal, and prostate cancers [125–127]. The duration of action of cSrc inhibitors is compromised by the development of drug resistance due to the buildup of substrate pressure on the kinase. Crystallographic analysis of dasatinib (**105**) bound to the human kinase domain of cSrc facilitated development of more effective kinase inhibitors by showing that a T388M mutation, involving a change from a hydrogen bond acceptor side chain to a larger hydrophobic side chain, abolished an important hydrogen bond and caused a steric clash with the known inhibitors (Fig. 21b, PDB: 3G5D) [116].

Erythropoietin-producing hepatocellular kinase EphA4 is associated with axon growth and angiogenesis [128, 129]. Among fourteen known human Eph receptors,

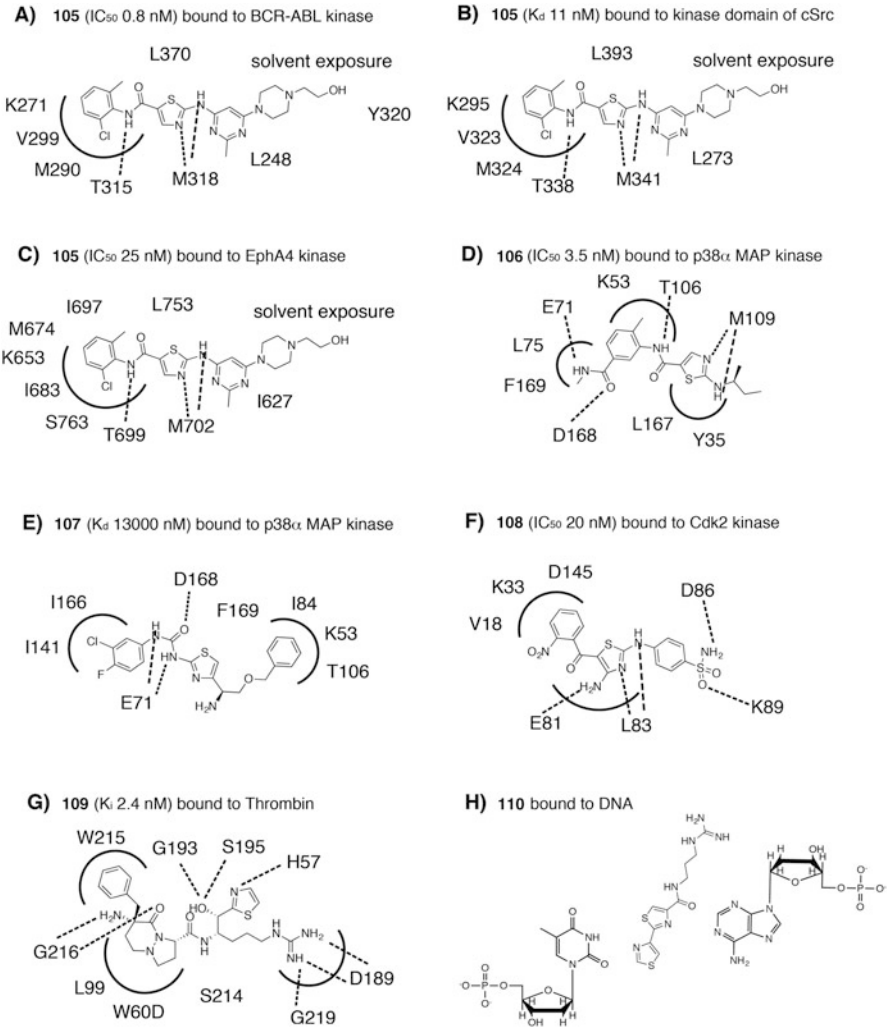
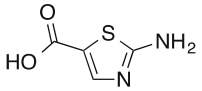


Fig. 20 Interactions between thiazole-containing molecules and their targets in crystal structures: (**a–c**) dasatinib (**105**) bound to BCR-ABL kinase (PDB: 2GQG), the human kinase domain of cSrc (PDB: 3G5D), and human EphA4 kinase (PDB: 2Y6O); (**d**) inhibitor **106** bound to p38α MAP kinase (PDB: 3BX5); (**e**) inhibitor **107** bound to p38α MAP kinase (PDB: 3IW8); (**f**) inhibitor **108** bound to Cdk2 kinase (PDB: 3QXP); (**g**) inhibitor **109** bound to thrombin (PDB: 1A61); (**h**) intercalating agent **110** bound to DNA (PDB: 2R2U)



111

Fig. 21 The central thiazole amino acid of dasatinib

EphA4 is overexpressed in a range of malignant carcinomas, including gastric cancer [130], prostate cancer [131], and cutaneous lymphomas [132]. Crystallographic analysis of the broad-spectrum kinase inhibitor dasatinib (**105**) bound to EphA4 revealed a network of hydrogen bonds between the thiazole ring nitrogen and Met702 amide NH, between the thiazole 2-amido NH with the carbonyl oxygen of Met702, and between the thiazole 5-carboxamide NH and the side chain hydroxyl oxygen of Thr699 (Fig. 21c, PDB: 2Y6O) [117]. Similar to the binding modes of the kinases described above, the 2-chloro-6-methyl phenyl ring is accommodated in a hydrophobic pocket, and the hydroxyethyl piperazine is mainly solvent exposed.

5.2 p38α Kinase Inhibitors

Mitogen-activated protein kinase p38α (MAPK14) plays an important role in inflammatory stress and conditions such as rheumatoid arthritis, by causing the up-regulation of pro-inflammatory cytokines, such as TNFα and IL-1β [133]. Iterative structure-activity relationship studies have led to the development of a potent and selective MAPK14 inhibitor BMS-640994 (**106**, IC_{50} 3.5 nM, [118]) [134]. Crystallographic analysis of the inhibitor-kinase structure has revealed the importance of the amido thiazole carboxamide moiety for the binding of **106** to MAPK14. Stationed in a small hydrophobic pocket lined by Y35 and L167, the thiazole engages in a hydrogen bond with its ring nitrogen to the backbone NH of Met109, and with the amide at its 2-position with the carbonyl of Met109. The linker amide H forms a hydrogen bond with side chain hydroxyl oxygen of T106. In addition, the C-terminal carboxamide of **106** interacts in hydrogen bonds with Glu71 and Asp168 (Fig. 21d, PDB: 3BX5). From such information, orally bioavailable inhibitors were designed exhibiting anti-inflammatory activity in rodent models of inflammatory disease.

Thiazole urea **107** binds an allosteric site of human p38α MAP kinase in a way that stabilizes an inactive conformation (Fig. 21e, PDB: 3IW8). In the crystal structure, the thiazole ring of **107** does not contribute to hydrogen bonding interactions with p38α MAP kinase, but forms a π–π contact with F169 [119]. Moreover, the thiazole serves as a pivot that orients the 3-chloro-4-fluoro-phenyl ring toward a hydrophobic pocket, the urea moiety to form two hydrogen bonds with backbone NH of Asp168 and Glu71, and the benzyl ether into a second pocket surrounded by I84, T106 and K53, which are proximal to the gatekeeper residues.

5.3 Cyclic Dependent Kinase Inhibitor

Cyclin-dependent kinases (CDK) are a group of Ser/Thr protein kinases that are cell cycle regulators and targets for drug design [135]. Diaminothiazole **108** (IC_{50}

20 nM) proved to be a potent inhibitor of CDK2. In the crystal structure of **108** bound to CDK2, the diamino thiazole is anchored by hydrogen bonds to Glu81 and Leu83; places the *ortho*-nitro phenyl ketone into a hydrophobic pocket consisting of Val18, Ala31, and Lys33; and serves as a hinge-binding scaffold that extends the benzenesulfonamide residue outward to engage in polar interactions in a pocket composed of Gln85, Asp86, and Lys89 (Fig. 21f, PDB: 3QXP).

5.4 Thrombin Inhibitor

Thiazoles have been incorporated into inhibitors of many proteases. For example, thrombin is a serine protease involved in blood coagulation. In the crystal structure of thrombin bound to inhibitor **109,** the thiazole occupies the S1′ pocket surrounded by side chains of Cys42, His57, Try60A, Trp60D, and Lys60F (Fig. 21g, PDB: 1A61) [121].

5.5 DNA-Binding Thiazole

A crystal structure for of **110** bound to the 5′-GT containing oligonucleotide d $(ATTTAGTTAACTAAAT)_2$, the bithiazole moiety intercalates between T7 and T9, interfering with stacking of DNA bases, and plays an essential role in DNA cleavage (Fig. 21h, PDB: 2R2U). Thiazoles are often components of DNA-intercalating dyes and other fluorescent dyes, especially when conjugated with aromatic rings that impart useful fluorescence properties [136].

5.6 Thiazole-Containing Drugs

Among FDA-approved drugs that contain thiazole (**105**, **112**–**133**, Figs. 22 and 23 show twenty-three representative examples), about half are β-lactams that target a penicillin-binding protein, and the remainder target a variety of human and viral enzymes, GPCRs and DNA. Relatively stable from a biological perspective, thiazole drugs have been found to be prone to ring oxidation, as illustrated by the oxidative epoxidation across the C-4–C-5 double bond of **134** (Scheme 13) [137]. Metabolism proceeds by spontaneous rupture of epoxide **135** to form diol **136**, which further ring opens to give dicarbonyl **137** and thioamide **138**, both of which may be further metabolized [138–140].

Ring oxidation was retarded by the addition of substituents at the thiazole C-4 and C-5 positions [141, 142]. For example, the metabolism of the thiazole-containing drug sudoxicam (**139**, Fig. 24) caused oxidative ring opening in vivo

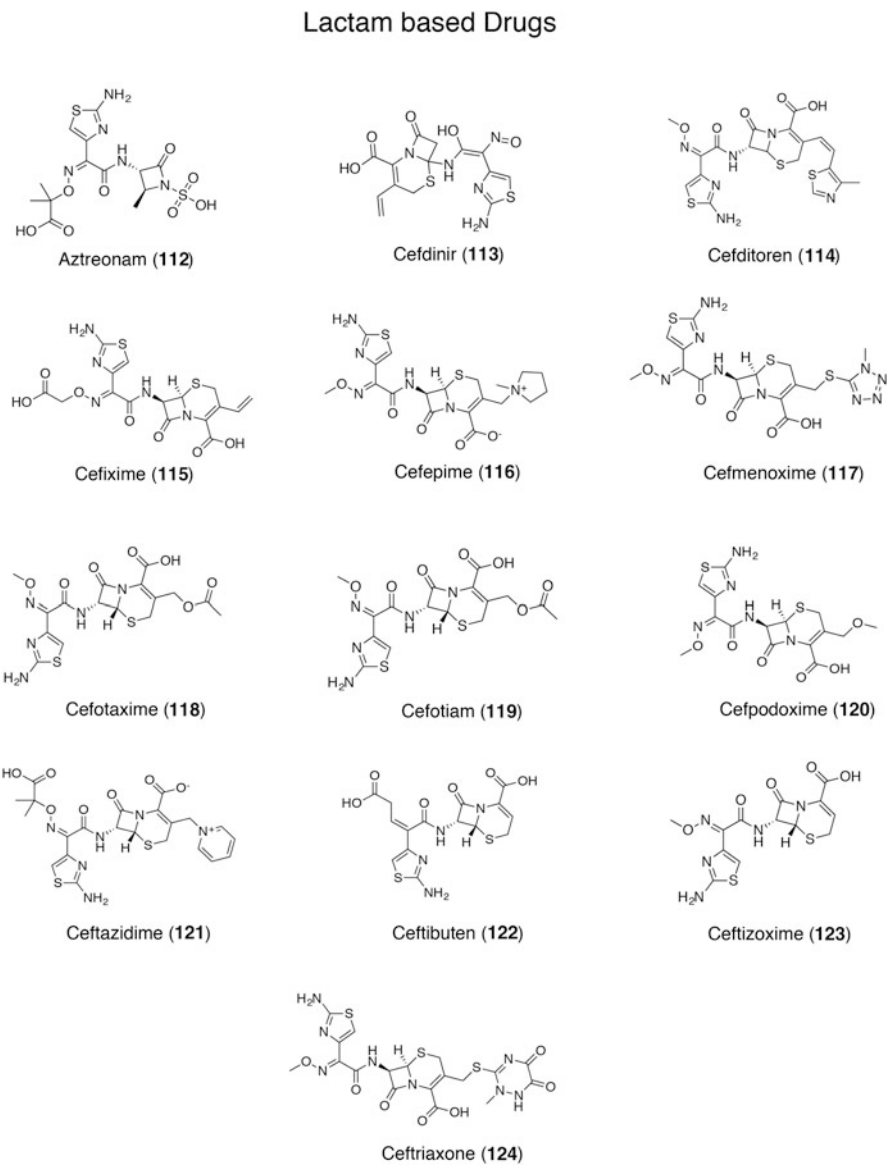


Fig. 22 Lactam-based thiazole-containing antibiotics (**112**–**124**) that target penicillin-binding protein in bacteria cell walls

in rat, dog, and monkey [143]. The addition of a methyl group to the thiazole 5-position of **139** gave meloxicam (**128**) and switched the oxidative metabolism to the methyl group without epoxidation of the heterocycle leading to little to no ring-opened metabolites [144, 145].

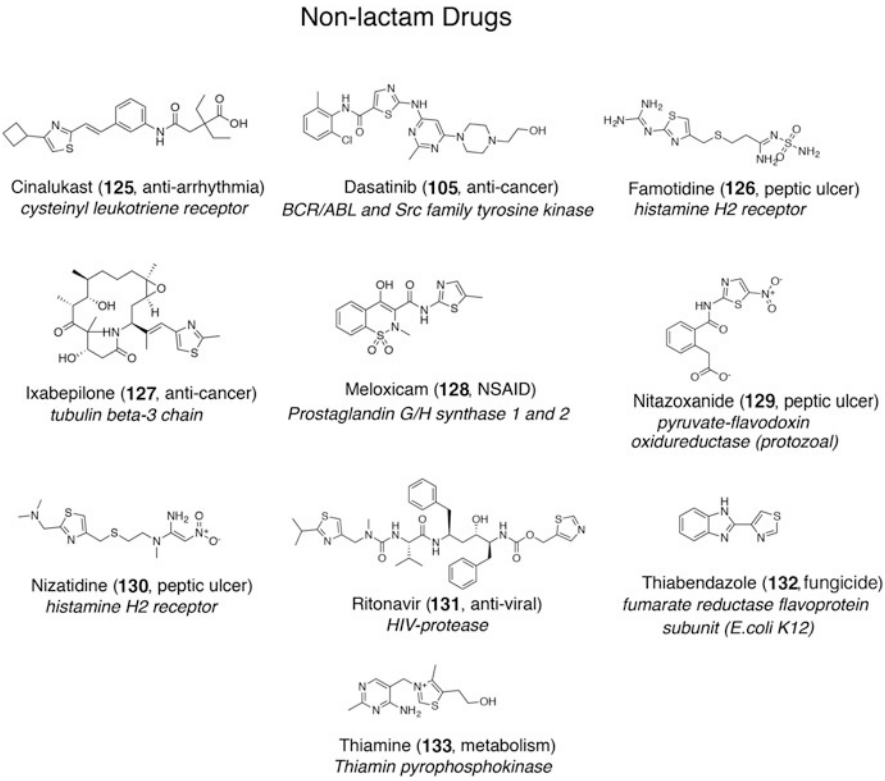
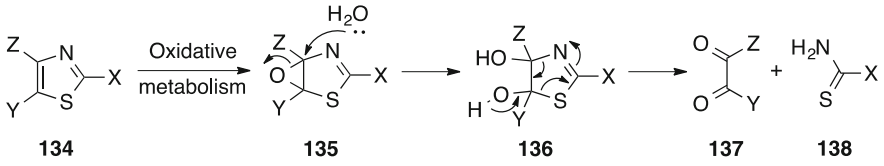


Fig. 23 Non-lactam thiazole-containing drugs (**105**, **125**–**133**), their uses (in *parentheses*), and protein targets (in *italics*) gathered from http://www.drugbank.ca/



Scheme 13 Oxidative metabolism of thiazoles to give dicarbonyl and thioamide metabolites

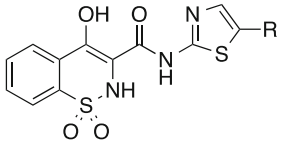


Fig. 24 Sudoxicam (**139**) and 5-methyl analogue, meloxicam (**128**)

6 Concluding Remarks

The thiazole ring is present in many peptidic natural products and peptidomimetics. This article has illustrated commonly used approaches to synthesize thiazole derivatives, described their key electronic properties, and highlighted their most important chemical reactivities. A particular focus has been on uses of thiazoles in synthetic peptidomimetics, for example, as a peptide capping group, an amide bond replacement, or a conformational constraint. Importantly, the thiazole ring is the most common five-membered heterocycle present in FDA-approved drugs, strongly supporting future development of additional thiazole-based peptidomimetics. To this end, this perspective assessment of currently known thiazole analogues provides a valuable platform for building new thiazole-based peptidomimetics for the future.

Acknowledgments We acknowledge support from the Australian Research Council (DP130100629, DP150104609, CE140100011) and the National Health and Medical Research Council of Australia (APP1084018). DF is an NHMRC Senior Principal Research Fellow (APP1027369).

References

1. Davyt D, Serra G (2010) Mar Drugs 8:2755
2. Donia MS, Schmidt EW (2010) Cyanobactins – ubiquitous cyanobacterial ribosomal peptide metabolites. In: Liu H-W, Mander L (eds) Comprehensive natural products II. Elsevier, Oxford, p 539
3. Jin Z (2013) Nat Prod Rep 30:869
4. Melby JO, Nard NJ, Mitchell DA (2011) Curr Opin Chem Biol 15:369
5. Leoni A, Locatelli A, Morigi R, Rambaldi M (2014) Expert Opin Ther Pat 24:201
6. Dondoni A (2010) Org Biomol Chem 8:3366
7. Powell RS (1969) In: Kirk-Othmer encyclopedia of chemical technology, 2nd ed, vol 20, p 185
8. Dondoni A, Merino P (1996) Thiazoles. In: Katritzky AR, Rees CW, Scriven EFV (eds) Comprehensive heterocyclic chemistry II. Pergamon, Oxford, 373 p
9. Matthews EJ, Kruhlak NL, Benz RD, Contrera JF, Rogers BA, Wolf MA, Richard AM (2008) DSSTox FDA maximum (recommended) daily dose database (FDAMDD): SDF files and documentation, updated version: FDAMDD_v3b_1216_15Feb2008
10. Geyer A, Enck S (2013) Approaches to thiazole dipeptides for the synthesis of thiopeptide antibiotics In: Attanasi OA, Spinelli D (eds) Targets in heterocyclic systems: chemistry and properties, vol 16. Royal Society of Chemistry, p 113
11. Wu Y-J, Yang BV (2011) Five-membered ring systems: with N and S (Se) atoms. In: Gordon WG, John AJ (eds) Progress in heterocyclic chemistry, vol 23. Elsevier, Oxford, p 267
12. Wu Y-J, Yang BV (2012) Five-membered ring systems: with N and S (Se) atoms. In: Gordon WG, John AJ (eds) Progress in heterocyclic chemistry, vol 24. Elsevier, Oxford, p 281
13. Wu Y-J, Yang BV (2013) Five-membered ring systems: with N and S (Se) atoms. In: Gordon WG, John AJ (eds) Progress in heterocyclic chemistry, vol 25. Elsevier, Oxford, p 257
14. Wu Y-J, Yang BV (2014) Five-membered ring systems: with N and S (Se) atoms. In: Gordon WG, John AJ (eds) Progress in heterocyclic chemistry, vol 26. Elsevier, Amsterdam, p 279

15. Wu YJ, Yang BV (2011) Five-membered ring systems: with N and S (Se) atoms. In: Gordon G, John AJ (eds) Progress in heterocyclic chemistry, vol 22. Elsevier, Oxford, p 259
16. Xu Z, Ye T (2011) Thiazoline and thiazole and their derivatives. In: Majumdar KC, Chattopadhyay SK (eds) Heterocycles in natural product synthesis. Wiley-VCH, Weinheim, p 459
17. Hantzsch A, Weber JH (1887) Chem Ber 20:3118
18. Snyder NL, Boisvert CJ (2011) Hantzsch synthesis. Wiley, Hoboken, p 591
19. Ambhaikar NB (2013) Thiazoles and benzothiazoles. In: Li JJ (ed) Heterocyclic chemistry in drug discovery. Wiley, Hoboken, p 283
20. Lu J-Y, Riedrich M, Wojtas KP, Arndt H-D (2013) Synthesis 45:1300
21. Shalaby MA, Grote CW, Rapoport H (1996) J Org Chem 61:9045
22. Holzapfel CW, Pettit GR (1985) J Org Chem 50:2323
23. Bredenkamp MW, Holzapfel CW, van Zyl WJ (1990) Synth Commun 20:2235
24. Aguilar E, Meyers AI (1994) Tetrahedron Lett 35:2473
25. Butler JD, Coffman KC, Ziebart KT, Toney MD, Kurth MJ (2010) Chem Eur J 16:9002
26. Nefzi A, Arutyunyan S, Fenwick JE (2010) J Org Chem 75:7939
27. Cohrt AE, Nielsen TE (2013) ACS Comb Sci 16:71
28. Murru S, Nefzi A (2014) ACS Comb Sci 16:39
29. Weiss KM, Wei S, Tsogoeva SB (2011) Org Biomol Chem 9:3457
30. Cook AH, Heilbron IM, Levy AL (1947) J Chem Soc 1594
31. Cook AH, Heilbron I, Macdonald SF, Mahadevan AP (1949) J Chem Soc 1064
32. Ahmad NM (2005) Cook-Heilbron 5-aminothiazole synthesis. Wiley, Hoboken, p 275
33. Lingaraju GS, Swaroop TR, Vinayaka AC, Kumar KSS, Sadashiva MP, Rangappa KS (2012) Synthesis 44:1373
34. Gabriel S (1910) Ber Dtsch Chem Ges 43:134
35. Gabriel S (1910) Ber Dtsch Chem Ges 43:1283
36. Kiryanov AA, Sampson P, Seed AJ (2001) J Org Chem 66:7925
37. Di Credico B, Reginato G, Gonsalvi L, Peruzzini M, Rossin A (2011) Tetrahedron 67:267
38. Nygaard L, Asmussen E, Hoeg JH, Maheshwari RC, Nielsen CH, Petersen IB, Rastrup-Andersen J, Soerensen GO (1971) J Mol Struct 8:225
39. Beker W, Szarek P, Komorowski L, Lipiński J (2013) J Phys Chem A 117:1596
40. Metzger JV, Vincent EJ (1979) Properties and reactions of thiazoles. In: Metzger JV (ed) Thiazoles and its derivatives, vol 1, The chemistry of heterocyclic compounds. Wiley, New York
41. Ioannidis S, Lamb ML, Almeida L, Guan H, Peng B, Bebernitz G, Bell K, Alimzhanov M, Zinda M (2010) Bioorg Med Chem Lett 20:1669
42. Phan-Tan-Luu R, Surzur JM, Metzger J, Aune JP, Dupuy C (1967) Bull Soc Chim Fr 3274
43. Grandberg II, Kost AN (1959) Zh Obshch Khim 29:1099
44. Acheson RM, Foxton MW, Miller GR (1965) J Chem Soc 3200
45. Reid DH, Skelton FS, Bonthrone W (1964) Tetrahedron Lett 1797
46. Zahradnik R, Koutecky J (1961) Collect Czech Chem Commun 26:156
47. Metzger J, Koether B (1953) Bull Soc Chim Fr 708
48. Florio S, Troisi L, Capriati V (1998) Tetrahedron Lett 39:7951
49. Schnürch M, Flasik R, Khan AF, Spina M, Mihovilovic MD, Stanetty P (2006) Eur J Org Chem 2006:3283
50. Schröter S, Stock C, Bach T (2005) Tetrahedron 61:2245
51. Schnuerch M, Haemmerle J, Mihovilovic MD, Stanetty P (2010) Synthesis 837
52. Grubb AM, Schmidt MJ, Seed AJ, Sampson P (2012) Synthesis 44:1026
53. Thompson MJ, Chen B (2009) J Org Chem 74:7084
54. Dömling A (2005) Chem Rev 106:17
55. Kazmaier U, Persch A (2010) Org Biomol Chem 8:5442
56. Just-Baringo X, Albericio F, Alvarez M (2014) Curr Top Med Chem 14:1244
57. Nefzi A, Fenwick JE (2011) Tetrahedron Lett 52:817

58. Valdomir G, Padrón JI, Padrón JM, Martín VS, Davyt D (2014) Synthesis 46:2451
59. Maderna A, Doroski M, Subramanyam C, Porte A, Leverett CA, Vetelino BC, Chen Z, Risley H, Parris K, Pandit J, Varghese AH, Shanker S, Song C, Sukuru SCK, Farley KA, Wagenaar MM, Shapiro MJ, Musto S, Lam M-H, Loganzo F, O'Donnell CJ (2014) J Med Chem 57:10527
60. Pettit GR, Hogan F, Toms S (2011) J Nat Prod 74:962
61. Boitano S, Flynn AN, Schulz SM, Hoffman J, Price TJ, Vagner J (2011) J Med Chem 54:1308
62. Hershko A, Heller H, Eytan E, Kaklij G, Rose IA (1984) Proc Natl Acad Sci 81:7021
63. Hollebeke J, Van Damme P, Gevaert K (2012) N-terminal acetylation and other functions of Nα-acetyltransferases. Biol Chem 393:291
64. Bolchi C, Pallavicini M, Bernini SK, Chiodini G, Corsini A, Ferri N, Fumagalli L, Straniero V, Valoti E (2011) Bioorg Med Chem Lett 21:5408
65. Devine SM, Mulcair MD, Debono CO, Leung EWW, Nissink W, Lim SS, Chandrashekaran IR, Vazirani M, Mohanty B, Simpson JS, Baell JB, Scammells PJ, Norton RS, Scanlon MJ (2015) J Med Chem. doi:10.1021/jm501402x
66. Reid RC, Yau MK, Singh R, Lim JX, Fairlie DP (2014) J Am Chem Soc 136:11914
67. Mali SM, Schneider TF, Bandyopadhyay A, Jadhav SV, Werz DB, Gopi HN (2012) Cryst Growth Des 12:5643
68. Davis MR, Singh EK, Wahyudi H, Alexander LD, Kunicki JB, Nazarova LA, Fairweather KA, Giltrap AM, Jolliffe KA, McAlpine SR (2012) Tetrahedron 68:1029
69. Legrand B, Mathieu L, Lebrun A, Andriamanarivo S, Lisowski V, Masurier N, Zirah S, Kang YK, Martinez J, Maillard LT (2014) Chem Eur J 20:6713
70. Mathieu L, Legrand B, Deng C, Vezenkov L, Wenger E, Didierjean C, Amblard M, Averlant-Petit M-C, Masurier N, Lisowski V, Martinez J, Maillard LT (2013) Angew Chem Int Ed 52:6006
71. Blakeney JS, Reid RC, Le GT, Fairlie DP (2007) Chem Rev 107:2960
72. Loughlin WA, Tyndall JDA, Glenn MP, Hill TA, Fairlie DP (2010) Chem Rev 110(6):PR32
73. Cohen F, Koehler MFT, Bergeron P, Elliott LO, Flygare JA, Franklin MC, Gazzard L, Keteltas SF, Lau K, Ly CQ, Tsui V, Fairbrother WJ (2010) Bioorg Med Chem Lett 20:2229
74. Singh S, Prasad NR, Kapoor K, Chufan EE, Patel BA, Ambudkar SV, Talele TT (2014) ChemBioChem 15:157
75. Dewal MB, Firestine SM (2011) Curr Med Chem 18:2420
76. Ngoei KRW, Ng DCH, Gooley PR, Fairlie DP, Stoermer MJ, Bogoyevitch MA (2013) Biochim Biophys Acta 1834:1077
77. Ojika M, Suzuki Y, Tsukamoto A, Sakagami Y, Fudou R, Yoshimura T, Yamanaka S (1998) J Antibiot 51:275
78. Iwaki Y, Akita H (2007) Chem Pharm Bull (Tokyo) 55:1610
79. Bertram A, Pattenden G (2007) Nat Prod Rep 24:18
80. Walsh CT, Malcolmson SJ, Young TS (2011) ACS Chem Biol 7:429
81. Jin Z (2011) Nat Prod Rep 28:1143
82. Bowers A, West N, Taunton J, Schreiber SL, Bradner JE, Williams RM (2008) J Am Chem Soc 130:11219
83. Diness F, Nielsen DS, Fairlie DP (2011) J Org Chem 76:9845
84. Taori K, Paul VJ, Luesch H (2008) J Am Chem Soc 130:1806
85. Taori K, Paul VJ, Luesch H (2008) J Am Chem Soc 130:13506
86. Ying Y, Taori K, Kim H, Hong J, Luesch H (2008) J Am Chem Soc 130:8455
87. Foster MP, Concepcion GP, Caraan GB, Ireland CM (1992) J Org Chem 57:6671
88. Bertram A, Maulucci N, New OM, Mohd Nor SM, Pattenden G (2007) Org Biomol Chem 5:1541
89. Nielsen DS, Hoang HN, Lohman R-J, Hill TA, Lucke AJ, Craik DJ, Edmonds DJ, Griffith DA, Rotter CJ, Ruggeri RB, Price DA, Liras S, Fairlie DP (2014) Angew Chem Int Ed 53:12059
90. Nielsen DS, Hoang HN, Lohman R-J, Diness F, Fairlie DP (2012) Org Lett 14:5720

91. Dalisay DS, Rogers EW, Edison AS, Molinski TF (2009) J Nat Prod 72:732
92. Singh EK, Ramsey DM, McAlpine SR (2012) Org Lett 14:1198
93. Wahyudi H, Tantisantisom W, McAlpine SR (2014) Tetrahedron Lett 55:2389
94. Wahyudi H, Tantisantisom W, Liu X, Ramsey DM, Singh EK, McAlpine SR (2012) J Org Chem 77:10596
95. Matsuo Y, Kanoh K, Yamori T, Kasai H, Katsuta A, Adachi K, Shin-Ya K, Shizuri Y (2007) J Antibiot 60:251
96. Donia MS, Hathaway BJ, Sudek S, Haygood MG, Rosovitz MJ, Ravel J, Schmidt EW (2006) Nat Chem Biol 2:729
97. Koehnke J, Bent A, Houssen WE, Zollman D, Morawitz F, Shirran S, Vendome J, Nneoyiegbe AF, Trembleau L, Botting CH, Smith MC, Jaspars M, Naismith JH (2012) Nat Struct Mol Biol 19:767
98. Koehnke J, Bent AF, Houssen WE, Mann G, Jaspars M, Naismith JH (2014) Curr Opin Struct Biol 29c:112
99. Comba P, Dovalil N, Gahan LR, Hanson GR, Westphal M (2014) Dalton Trans 43:1935
100. van den Brenk AL, Tyndall JDA, Cusack RM, Jones A, Fairlie DP, Gahan LR, Hanson GR (2004) J Inorg Biochem 98:1857
101. van den Brenk AL, Byriel KA, Fairlie DP, Gahan LR, Hanson GR, Hawkins CJ, Jones A, Kennard CHL, Moubaraki B, Murray KS (1994) Inorg Chem 33:3549
102. Abbenante G, Fairlie DP, Gahan LR, Hanson GR, Pierens GK, van den Brenk AL (1996) J Am Chem Soc 118:10384
103. Singh Y, Sokolenko N, Kelso MJ, Gahan LR, Abbenante G, Fairlie DP (2000) J Am Chem Soc 123:333
104. Sokolenko N, Abbenante G, Scanlon MJ, Jones A, Gahan LR, Hanson GR, Fairlie DP (1999) J Am Chem Soc 121:2603
105. Just-Baringo X, Albericio F, Alvarez M (2014) Mar Drugs 12:317
106. Ciufolini MA, Lefranc D (2010) Nat Prod Rep 27:330
107. Heckmann G, Bach T (2005) Angew Chem 117:1223
108. Trzasko A, Leeds JA, Praestgaard J, Lamarche MJ, McKenney D (2012) Antimicrob Agents Chemother 56:4459
109. Nicolaou KC, Zak M, Safina BS, Estrada AA, Lee SH, Nevalainen M (2005) J Am Chem Soc 127:11176
110. Zhang F, Kelly WL (2015) ACS Chem Biol. doi:10.1021/cb5007745
111. Haste NM, Thienphrapa W, Tran DN, Loesgen S, Sun P, Nam SJ, Jensen PR, Fenical W, Sakoulas G, Nizet V, Hensler ME (2012) J Antibiot 65:593
112. Huber RG, Margreiter MA, Fuchs JE, von Grafenstein S, Tautermann CS, Liedl KR, Fox T (2014) J Chem Inf Model 54:1371
113. Feher M, Schmidt JM (2003) J Chem Inf Comput Sci 43:218
114. Li JJ (2013) Heterocyclic chemistry in drug discovery. Wiley, Hoboken
115. Tokarski JS, Newitt JA, Chang CY, Cheng JD, Wittekind M, Kiefer SE, Kish K, Lee FY, Borzillerri R, Lombardo LJ, Xie D, Zhang Y, Klei HE (2006) Cancer Res 66:5790
116. Getlik M, Grutter C, Simard JR, Kluter S, Rabiller M, Rode HB, Robubi A, Rauh D (2009) J Med Chem 52:3915
117. Farenc C, Celie PH, Tensen CP, de Esch IJ, Siegal G (2011) FEBS Lett 585:3593
118. Hynes J Jr, Wu H, Pitt S, Shen DR, Zhang R, Schieven GL, Gillooly KM, Shuster DJ, Taylor TL, Yang X, McIntyre KW, McKinnon M, Zhang H, Marathe PH, Doweyko AM, Kish K, Kiefer SE, Sack JS, Newitt JA, Barrish JC, Dodd J, Leftheris K (2008) Bioorg Med Chem Lett 18:1762
119. Simard JR, Grutter C, Pawar V, Aust B, Wolf A, Rabiller M, Wulfert S, Robubi A, Kluter S, Ottmann C, Rauh D (2009) J Am Chem Soc 131:18478
120. Schonbrunn E, Betzi S, Alam R, Martin MP, Becker A, Han H, Francis R, Chakrasali R, Jakkaraj S, Kazi A, Sebti SM, Cubitt CL, Gebhard AW, Hazlehurst LA, Tash JS, Georg GI (2013) J Med Chem 56:3768

121. St Charles R, Matthews JH, Zhang E, Tulinsky A (1999) J Med Chem 42:1376
122. Goodwin KD, Lewis MA, Long EC, Georgiadis MM (2008) Proc Natl Acad Sci U S A 105:5052
123. Williams NK, Lucet IS, Klinken SP, Ingley E, Rossjohn J (2009) J Biol Chem 284:284
124. Marcotte DJ, Liu YT, Arduini RM, Hession CA, Miatkowski K, Wildes CP, Cullen PF, Hong V, Hopkins BT, Mertsching E, Jenkins TJ, Romanowski MJ, Baker DP, Silvian LF (2010) Protein Sci 19:429
125. Chang YM, Bai L, Liu S, Yang JC, Kung HJ, Evans CP (2008) Oncogene 27:6365
126. Du J, Bernasconi P, Clauser KR, Mani DR, Finn SP, Beroukhim R, Burns M, Julian B, Peng XP, Hieronymus H, Maglathlin RL, Lewis TA, Liau LM, Nghiemphu P, Mellinghoff IK, Louis DN, Loda M, Carr SA, Kung AL, Golub TR (2009) Nat Biotechnol 27:77
127. Yeatman TJ (2004) Nat Rev Cancer 4:470
128. Cheng N, Brantley DM, Chen J (2002) Cytokine Growth Factor Rev 13:75
129. Pasquale EB (2008) Cell 133:38
130. Gong J, Morishita A, Kurokohchi K, Tani J, Kato K, Miyoshi H, Inoue H, Kobayashi M, Liu S, Murota M, Muramatsu A, Izuishi K, Suzuki Y, Yoshida H, Uchida N, Deguchi K, Iwama H, Ishimaru I, Masaki T (2010) Int J Oncol 36:101
131. Ashida S, Nakagawa H, Katagiri T, Furihata M, Iiizumi M, Anazawa Y, Tsunoda T, Takata R, Kasahara K, Miki T, Fujioka T, Shuin T, Nakamura Y (2004) Cancer Res 64:5963
132. van Doorn R, Dijkman R, Vermeer MH, Out-Luiting JJ, van der Raaij-Helmer EM, Willemze R, Tensen CP (2004) Cancer Res 64:5578
133. Kumar S, Boehm J, Lee JC (2003) Nat Rev Drug Discov 2:717
134. Choy EH, Panayi GS (2001) N Engl J Med 344:907
135. Hall M, Peters G (1996) Adv Cancer Res 68:67
136. Sonar MV, Wampole ME, Jin Y-Y, Chen C-P, Thakur ML, Wickstrom E (2014) Bioconjug Chem 25:1697
137. Dalvie DK, Kalgutkar AS, Khojasteh-Bakht SC, Obach RS, O'Donnell JP (2002) Chem Res Toxicol 15:269
138. Mizutani T, Yoshida K, Kawazoe S (1994) Drug Metab Dispos 22:750
139. Mizutani T, Suzuki K (1996) Toxicol Lett 85:101
140. Kalgutkar AS, Driscoll J, Zhao SX, Walker GS, Shepard RM, Soglia JR, Atherton J, Yu L, Mutlib AE, Munchhof MJ, Reiter LA, Jones CS, Doty JL, Trevena KA, Shaffer CL, Ripp SL (2007) Chem Res Toxicol 20:1954
141. Blagg J (2010) Structural alerts for toxicity. In: Abraham DJ, Protella DP (eds) Burger's medicinal chemistry, drug discovery and development, vol 2. Wiley, Hoboken, p 301
142. Barreiro EJ, Kümmerle AE, Fraga CAM (2011) Chem Rev 111:5215
143. Hobbs DC, Twomey TM (1977) Drug Metab Dispos 5:75
144. Schmid J, Busch U, Trummlitz G, Prox A, Kaschke S, Wachsmuth H (1995) Xenobiotica 25:1219
145. Obach RS, Kalgutkar AS, Ryder TF, Walker GS (2008) Chem Res Toxicol 21:1890