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Chemistry

SYNTHESIS AND ANTICANCER ACTIVITY OF AMINOTHIAZOLE-TERMINAL PHENOXYCOMPOUNDS HYBRIDS AND THEIR ANALOGS: A SHORT REVIEW

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Abstract. 2-Aminothiazole and compounds with terminal phenoxy groups are privileged structures in medicinal chemistry. Compounds containing these two scaffolds are of interest for the design of new pharmaceuticals, particularly for treating malignant tumors. Hybridization, which is realized by combining both privileged fragments *via* the formation of covalent bonds, is a promising approach to finding lead compounds. The resulting conjugates can bind to a variety of receptors, and therefore, their synthesis and pharmacological screening is an actual task of modern medicinal chemistry. This review highlights the latest advances in the field of phenoxyalkylacylamino thiazoles and their analogs with anticancer potential, covering work published over the past two decades.

Keywords: 2-aminothiazole, terminal phenoxy group, molecular hybridization, anticancer activity.

1. Introduction

Cancer is a disease characterized by the uncontrolled proliferation of cells, leading either to the formation of a solid mass of cells known as a tumor or to the development of liquid cancer, which may originate in the blood or bone marrow.[1] This disease is a challenge for societies, public health, and the economy in the 21st century, responsible for almost one in six deaths (16.8%) and one in four deaths (22.8%) from non-communicable diseases (NCDs) worldwide. In 2022, there were nearly 20 million new cases of cancer and 9.7 million deaths from cancer.[2] In 2024, the projected number of deaths from cancer in the US alone was 611,000. This equates to over 1,600 deaths from cancer each day.[3]

Given the above fact, the search for new anticancer drugs is an important task of the present day. Heterocyclic compounds of both natural and synthetic origin are considered to be one of the most promising classes of compounds for the design of chemotherapeutic agents.[4-8]

The present review is devoted to the current state of the search for antitumor drugs among phenoxyalkylacylaminothiazoles of general formula **1** (Fig. 1). Examples of such compounds **2-4** are shown in Fig. 2.

The structure of this type of compound includes two privileged scaffolds – 2-aminothiazole fragment[6-13] and terminal phenoxy group.[14] According to DeSimone *et al.*[15] privileged structures are molecular scaffolds with versatile binding properties, such that a single scaffold can provide potent and selective ligands for a range of different biological targets through modification of functional groups.

The terminal phenoxy group is found in a large number of currently used drugs. Many studies have reported on its crucial importance for pharmacological activity. Some of the FDA-approved drugs presented in Fig. 3.[14] It should be noted that incorporation of a terminal phenoxy group into potential drug molecules can result in significant changes of the pharmacokinetic profile of investigated molecules.[14,16]

In particular, phenoxyaceticcarboxamides (Fig. 4) were the first antibiotics used for treating the infection diseases with high mortality.[17]

2-Aminothiazole also represents a significant and versatile scaffold within the domain of drug design and discovery. The 2-aminothiazole-based compounds have been demonstrated to exhibit diverse biological activities.[9-13] The structure of some pharmaceutical substrates are illustrated in Fig. 5.

2-Aminothiazole derivatives also include some of the most popular antimicrobials, such as the broad-spectrum semi-synthetic cephalosporin antibiotics Cefdinir, Cefotaxime, and the sulfamide drug Norsulfazole (Fig. 6).[18]

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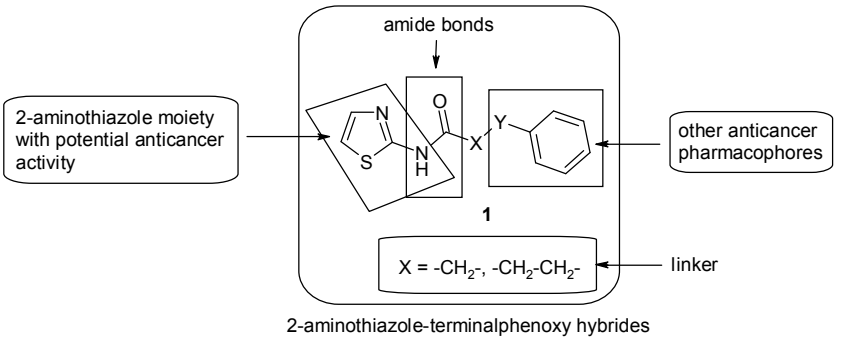


Fig. 1. 2-Aminothiazole-terminalphenoxy compounds hybrids

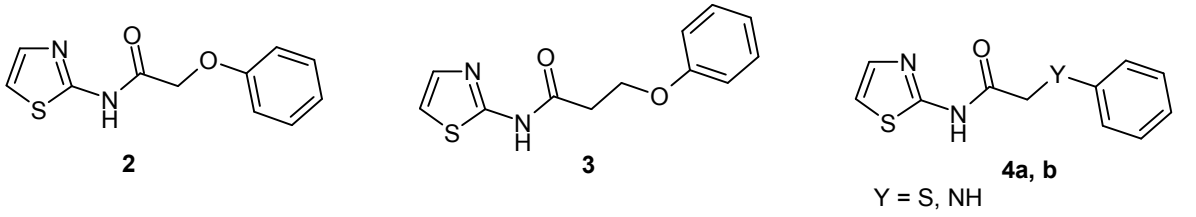


Fig. 2. Examples of 2-aminothiazole-terminalphenoxy hybrids

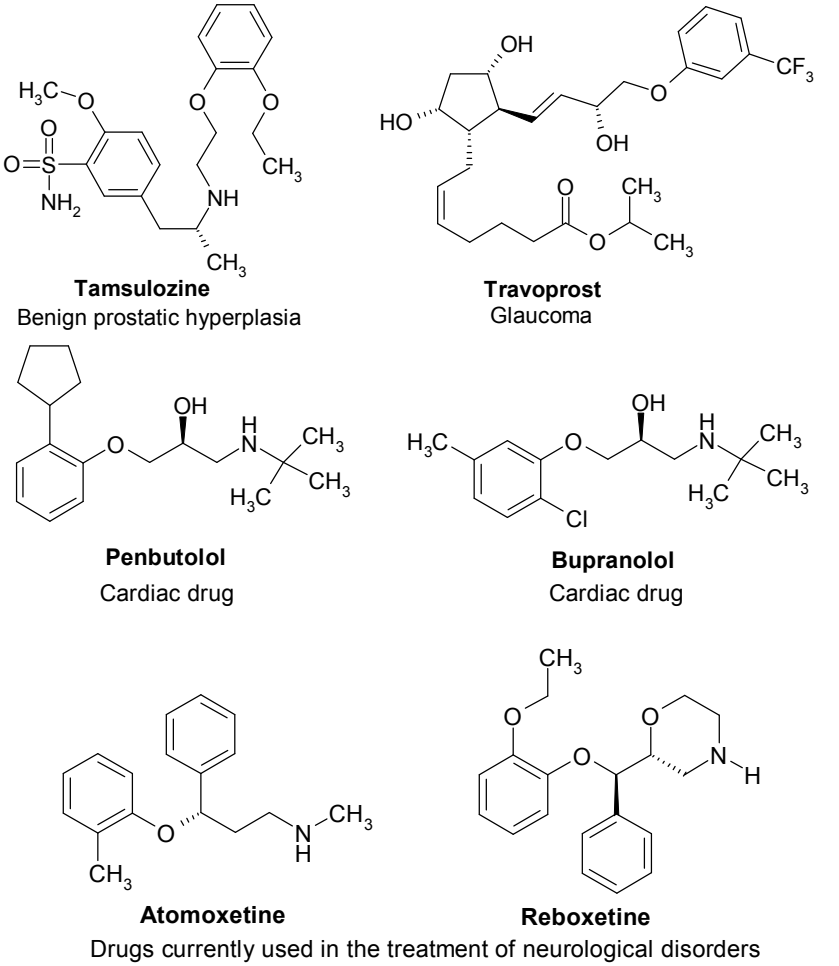


Fig. 3. Some of FDA-approved drugs with terminal phenoxy moiety

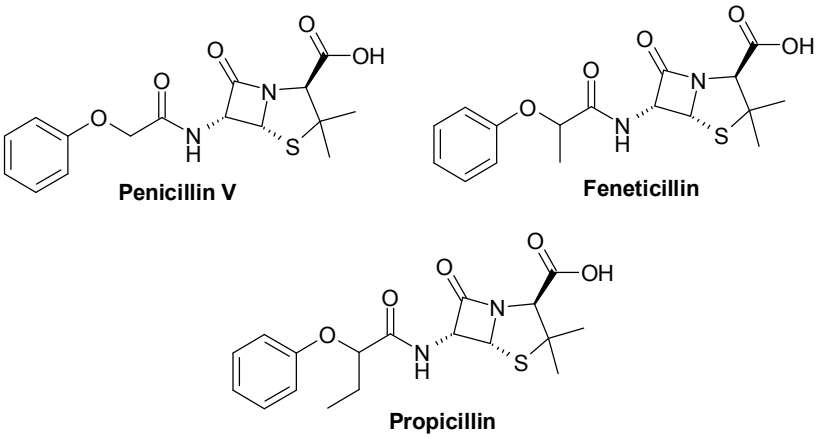


Fig. 4. First antibiotics phenoxyaceticcarboxamides series

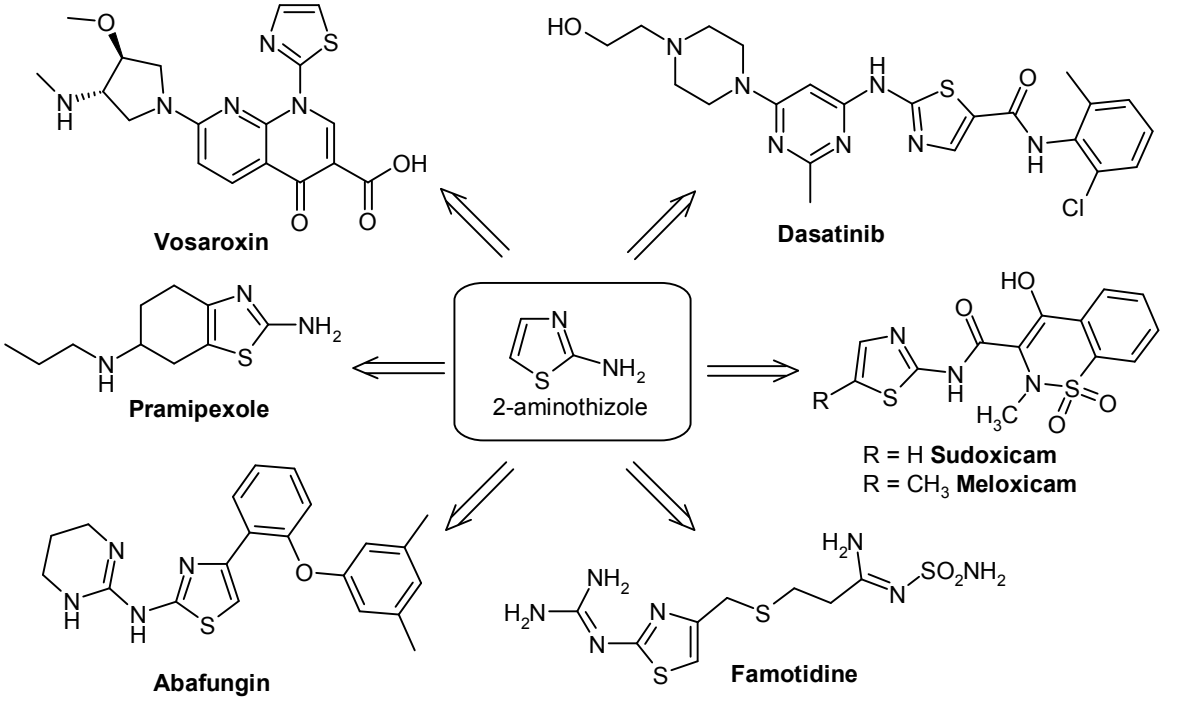


Fig. 5. Some of FDA-approved drugs with 2-aminothiazole moety

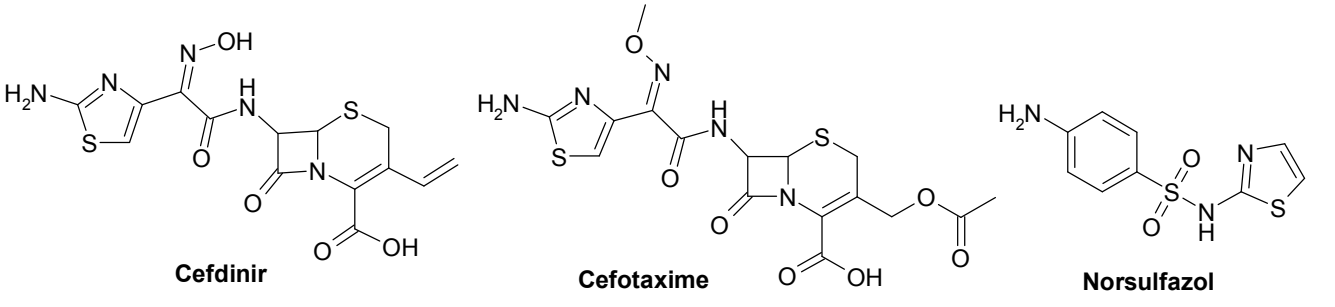
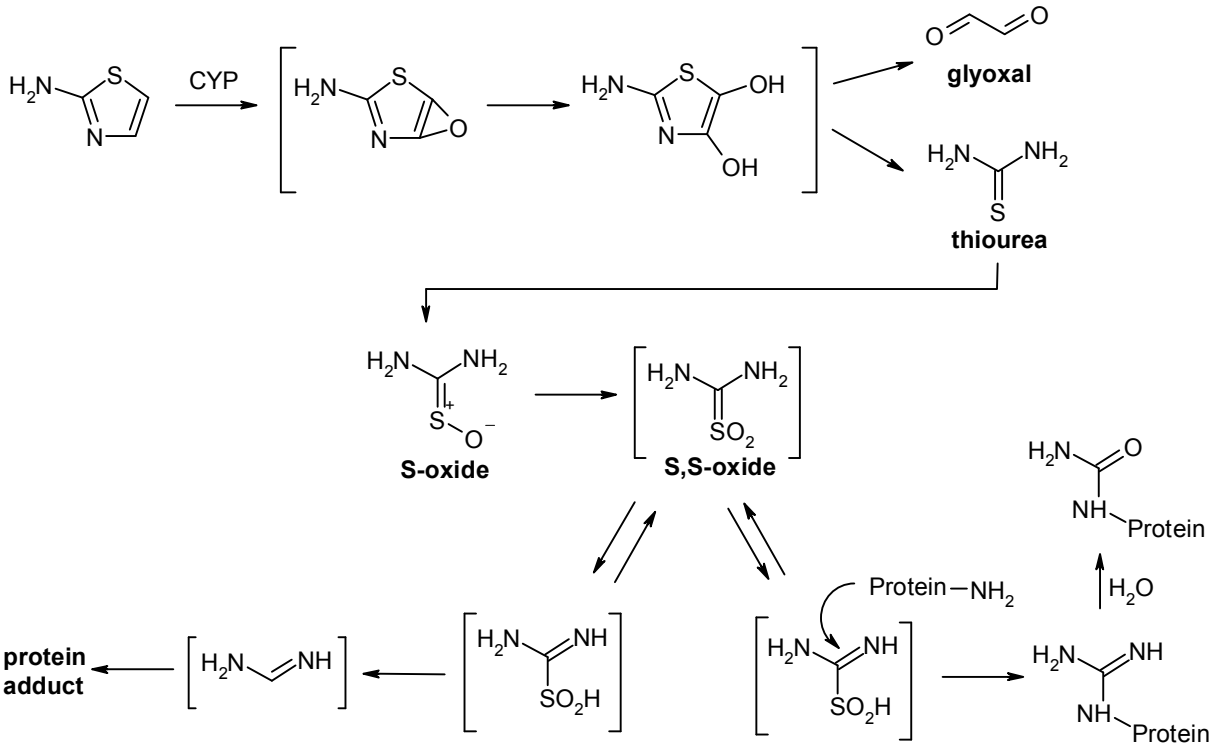


Fig. 6. Example of antimicrobials 2-aminothiazole series

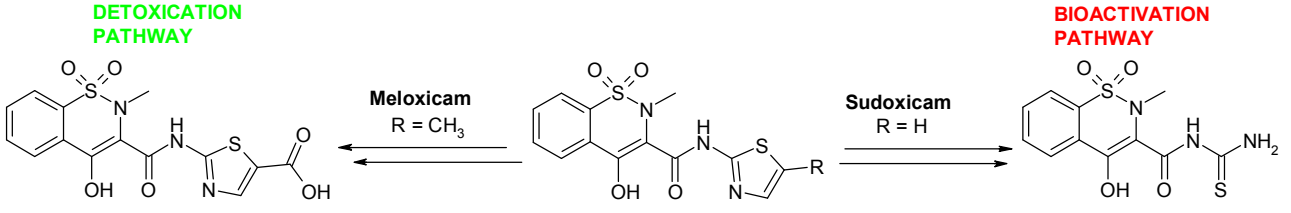
Information on the antitumor effect of 2-aminothiazole derivatives is summarised in reviews.[9,10]

Thiazole ring is a known toxicophore.[19] Toxic effect is realized *via* the C4–C5 epoxidation–diol pathway according scheme. Toxicophores are functional groups/substructures capable of forming electrophilic reactive metabolites that have been frequently associated with adverse drug reactions (ADR) occurring with certain marketed drugs/investigational drug candidates (Scheme 1).[19]

The presence of an aminothiazole moiety does not necessarily lead to the formation of reactive metabolites. For example, the presence of a substituent in position 4 or 5 makes epoxidation difficult and metabolism occurs with the formation of non-toxic intermediates (Scheme 2).[20]



Scheme 1. Mode of toxic action of 2-aminothiazole derivatives



Scheme 2. Metabolic pathway of Sudoxicam and Meloxicam

The linker also affects the biological activity of the hybrids. It can improve the pharmacological, pharmacokinetic, and physiochemical profiles of bioactive compounds.[21,22]

The molecular hybridization of two or more of previously characterized lead compounds is a strategy to enhance its usefulness as a drug. As mentioned above, scaffolds bearing a 2-amino thiazole privileged heterocycle and a terminal phenoxy group are promising in medicinal chemistry.[23,24]

We also predicted potential targets for basic compounds **2**-4.[25,26] The diagrams demonstrate the result (Fig. 6). It was predicted that kinase is a favorite target for mentioned compounds. Protein kinases are important therapeutic targets for the treatment of cancer. They regulate cell growth proliferation and modulate immune responses.[27,28]

The compounds described in this review also contain an amide group, and as found by Peter Ertl *et al.*[29] this functional group is the most common among medi-

cines and biologically active substances (40.2% of the analyzed substances).

Given the above facts, the compounds, the **2-4** structures of which are shown in Fig. 2, are promising for the development of new drugs. This review is aimed to summarise the current state of the art and prospects for the design of new anticancer agents based on phenoxyalkylacylamino thiazole derivatives. The *S*- and *N*-bioisosteres of these compounds and rigid benzofuran-2-carboxamides are also discussed.

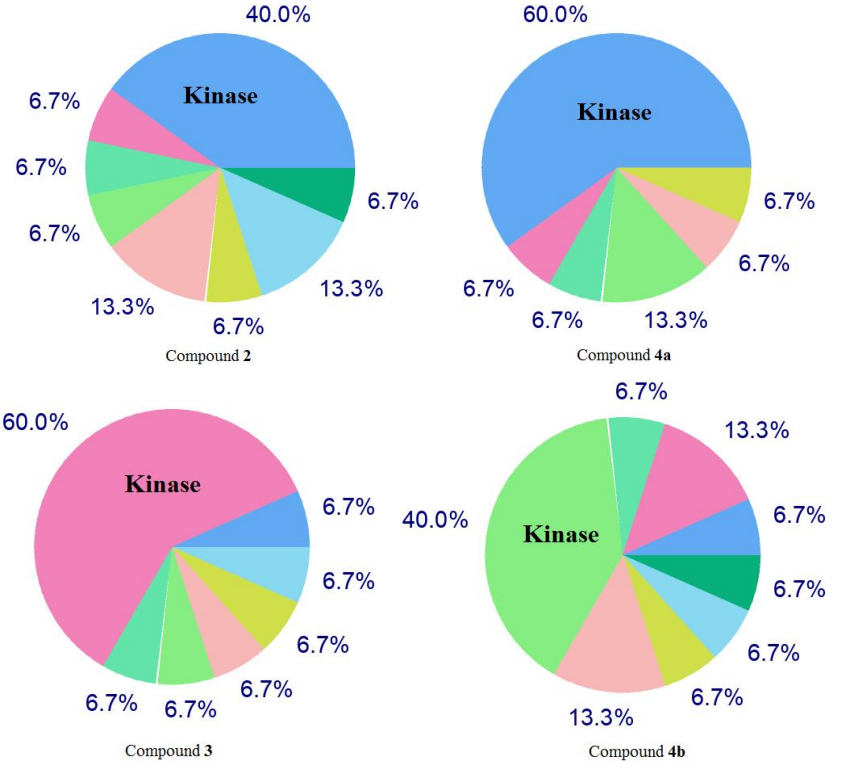


Fig. 6. Target prediction of the compounds **2**, **3**, **4a,b** using the SwissTargetPrediction Webtool

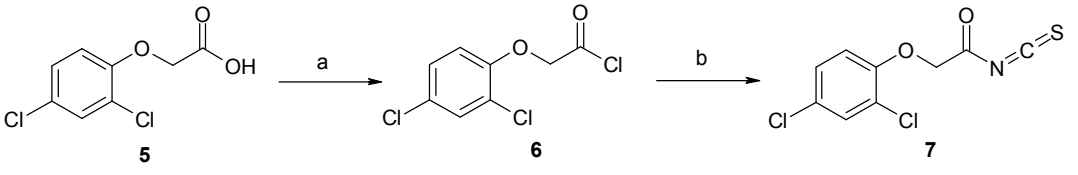
2. Aminothiazole-Terminal Phenoxy Compounds Hybrids and Their Analogs − Synthesis and Anticancer Activity

3.1. Synthesis of CCN at High Temperature

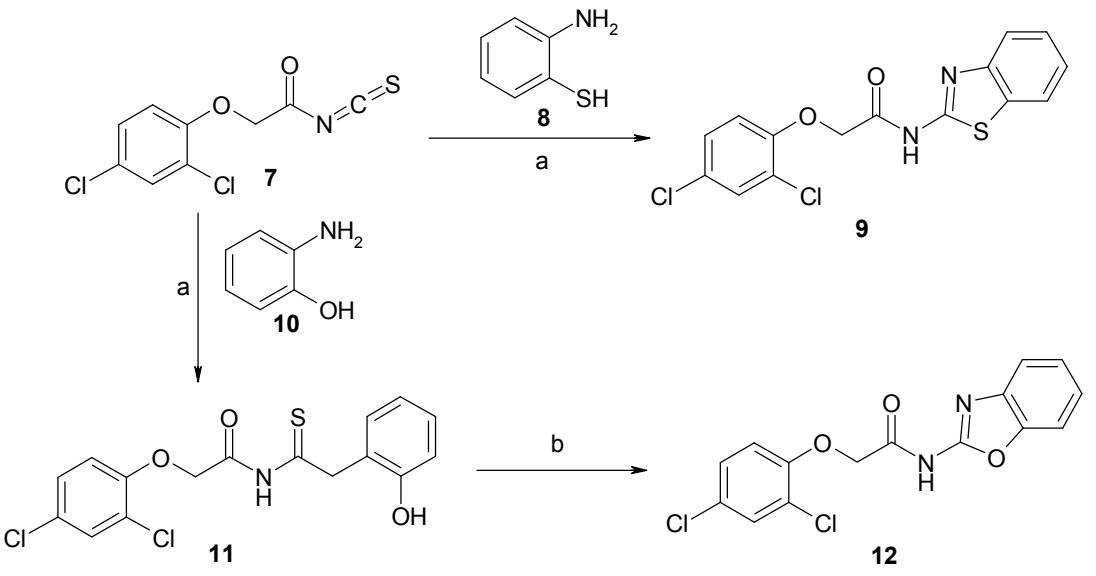
El-Sayed *et al.*[30] reported the synthesis and antitumor activity of *N*-benzothiazol-2-yl-2-(2,4-dichlorophenoxy)-acetamide **9** and bioizosteric *N*-benzo-oxazol-2-yl-2-(2,4-dichlorophenoxy)-acetamide **12** were investigated as potential CDK-2 inhibitors. This transformation was carried out using isothiocyanate **7**, which was obtained according to the following scheme (Scheme 3).

The cyclization of **7** with 2-mercaptoaniline **8** gave **9**. The oxygen bioisosteric derivative **12** was obtained through the formation of an intermediate acylthiourea **11**, which was cyclized when heated above the melting point (Scheme 4).

The new compounds were evaluated *in vitro* for their activity against colorectal carcinoma (HCT-116) and breast adenocarcinoma (MCF-7) cancer cell lines using the MTT assay, and compared to the standard drug doxorubicin. The antitumor effect of both compounds against the HCT-116 and MCF-7 cancer cell lines is comparable to the reference drug doxorubicin (see Table 1 for details).[30]



Scheme 3. Synthesis of (2,4-dichlorophenoxy)-acetyl isothiocyanate.
Reagents and conditions: (a) $SOCl_2$, dry benzene, reflux; (b) NH_4SCN / dry CH_3CN stir, rt.



Scheme 4. Synthesis of *N*-benzothiazol-2-yl-2-(2,4-dichlorophenoxy)-acetamide **9** and *N*-benzooxazol-2-yl-2-(2,4-dichlorophenoxy)-acetamide **12**. Reagents and conditions: (a) dry acetonitrile, reflux for 30 min; (b) fusion over m. p., 30 min

Table 1. *In vitro* cytotoxic activity of the synthesized compounds against HCT-116 and MCF-7 cell lines

Compound	*In vitro* cytotoxic activity against cancer cell lines, IC_{50}, μM		Enzyme activity, IC_{50}, μM
	HCT-116	MCF-7	CDK-2/cyclin A2
9	5.91	7.39	0.70
12	7.06	9.81	0.88
Doxorubicin	5.23	4.17	-
Roscovitine	-	-	0.35

To reveal the possible molecular anticancer mechanism of the new potential targets **9** and **12**, a kinase profiling analysis against CDK-2/cyclin A2 was performed using roscovitine as a standard drug. Benzo [d]thiazole **9** and benzo[d]oxazole **12** compounds exhibited notable activity, with IC_{50} values of approximately 0.70 ± 0.13 and 0.88 ± 0.10 μM, respectively, which is approximately half that of roscovitine.[30]

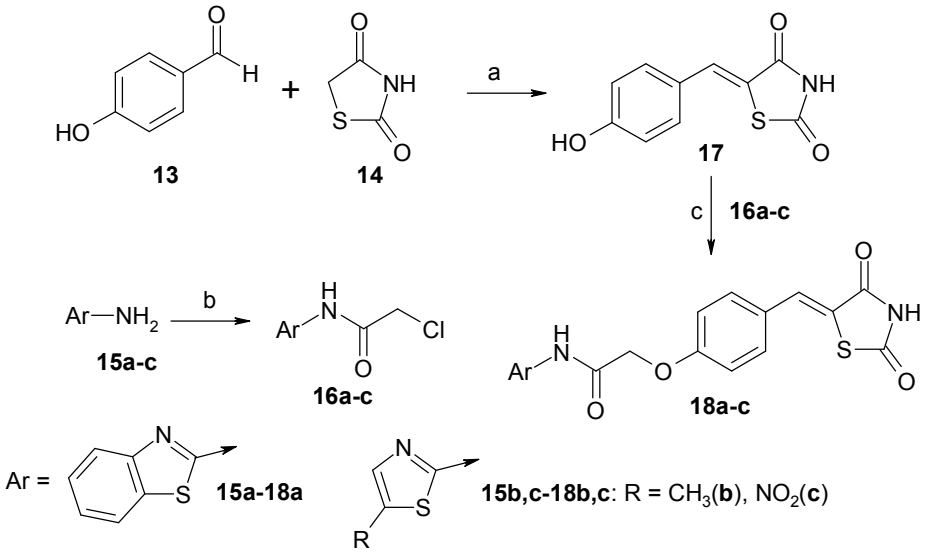
It is known that activation of PPARγ results in decreased serum glucose concentration in diabetes, which has led to the development of PPARγ agonists, thiazolidinediones containing glitazones such as pioglitazone, which are used clinically as antidiabetic drugs. In addition to their established antidiabetic effects, PPARγ agonists induce apoptosis, cell cycle arrest, and terminal differentiation in several malignant cell lines. In recent years, numerous studies have reported the anticancer effects of a range of PPARγ ligands on a multitude of tumor cell types. To search for new antitumor agents, Joshi *et al.*[31] and Patil *et al.*[32] synthesized a combinatorial library of compounds of the general formula **18a-c** (Scheme 5).

Among the obtained compounds, thiazole derivatives showed significant antitumor activity against a several cell lines of Leukemia, Breast cancer, Hepatoma, NSC lung cancer, Prostate cancer, Oral cancer, and Nasopharyngeal cancer. Joshi *et al.*[31] and Patil *et al.*[32] consider these compounds **18a, 18c** (Fig. 7) as promising for optimization to create innovative anticancer drugs.

PPARγ agonists are also HDAC inhibitors, which lead to a synergistic effect, enhance cytotoxic effects against various cancer cell lines, and cause proliferation arrest and apoptosis. In some cases, even low doses of a PPARγ ligand in combination with a weak HDAC inhibitor resulted in a deeper growth arrest than treatment with each drug alone.[33]

To apply a multi-pharmacophore approach to the treatment of malignant tumors, Tilekar *et al.*[33] designed compounds of a general formula (Fig. 8) that simultaneously affect HDAC and PPARγ, which are important targets in cancer therapy.

In particular, 2-aminothiazole derivatives **22a-c** (Scheme 6) were also synthesized.[33]



Scheme 5. Synthesis of 2-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)-phenoxy]-*N*-thiazol-2-yl-acetamides **18a-c**. Reagents and conditions: (a) toluene, piperidinium benzoate, reflux 5-6 hrs; (b) chloroacetyl chloride, DCM, K_2CO_3, stir rt.; (c) DMF, K_2CO_3, stir, rt. overnight

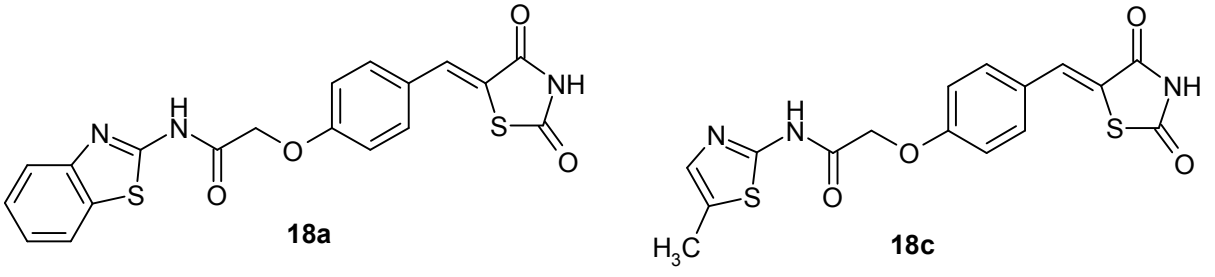


Fig. 7. *N*-Benzothiazol-2-yl-2-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)-phenoxy]-acetamide **18a** and 2-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-*N*-(5-methylthiazol-2-yl)-acetamide **18b** as potent anticancer agents

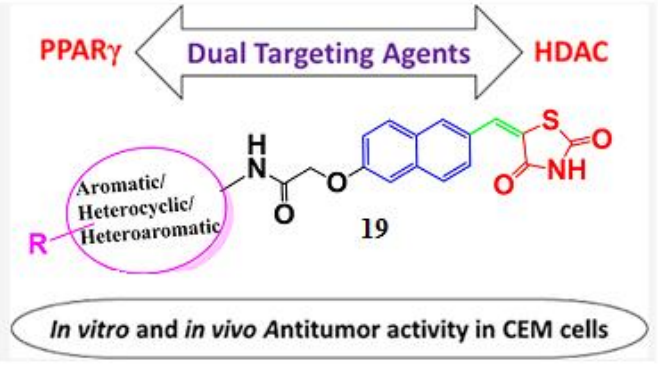


Fig. 8. HDAC/PPARγ dual targeting agents

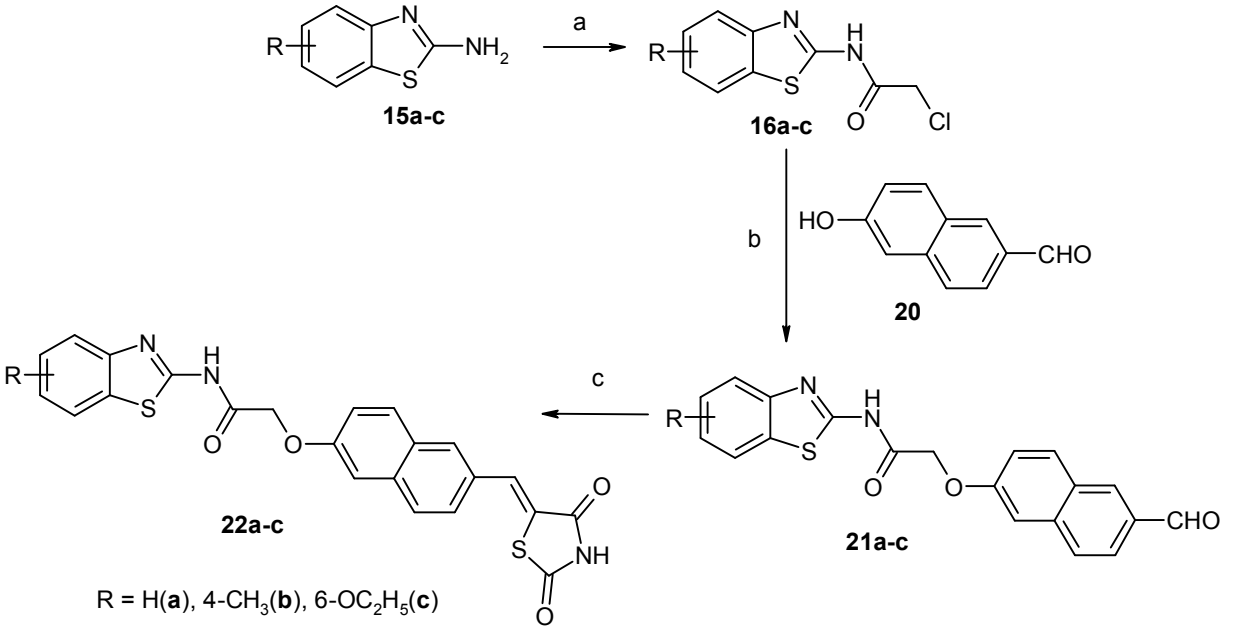
The results of the antitumor activity study[33] are shown in Table 2. Benzothiazole-containing compounds were compared, showing an unsubstituted benzothiazole **22a** ring preferred to alkyl **22b** and alkoxy substitution **22c**.

Ramos *et al.*[34] have investigated a large library of commercially available organic compounds. The interaction of these compounds with the human anti-apoptotic protein Bcl-2 was the subject of study using biophysical

and in silico methods. The compound **24** (Fig. 9) was identified as an active inhibitor. This finding could serve as a starting point for the development of more potent and safer anticancer molecules that modulate the Bcl-2 protein-protein interaction.

Mah *et al.*[35] described 3-heteroaryl coumarin **25** (Fig. 9) as a novel fluorescent anaplastic lymphoma kinase inhibitor. This result is useful for biological and pharmaceutical research as it allows the visualization of subcellular locations in mammalian cells using fluorescence microscopy.

Ankenbruck *et al.*[36] report the discovery of a new small molecule inhibitor of miR-21 and demonstrate its potential as an alternative approach to cancer therapy by a high-throughput screen of over 300,000 small molecules a new class of ether-amides **26-30** (Fig. 10) miR-21 inhibitors were identified. The authors obtained a line of cells that could be used for high-throughput screening, bioassay was carried out by the National Cancer Institute.



Scheme 6. Synthesis of *N*-benzothiazol-2-yl-2-[6-(2,4-dioxothiazolidin-5-ylidenemethyl)-naphthalen-2-yloxy]-acetamides **22a-c**. Reagents and conditions: (a) chloroacetyl chloride, chloroform, K_2CO_3, stir, 0-5°C, 1 hr; rt, 24-48 hrs; (b) 6-hydroxy naphthaldehyde, DMF, K_2CO_3, stir 48 hr; (c) 2,4-thiazolidinedione, DMF, piperidine, reflux 3-4 hrs

Table 2. IC_{50} values against HDAC4 and HDAC8

Cpd	Ar group	HDAC4, IC_{50}, μM	HDAC8, IC_{50}, μM
22a	benzo[d]thiazol-2-yl	0.42	2.7
22b	4-methylbenzo[d]thiazol-2-yl	1.2	5.8
22c	6-ethoxybenzo[d]thiazol-2-yl	3.6	17

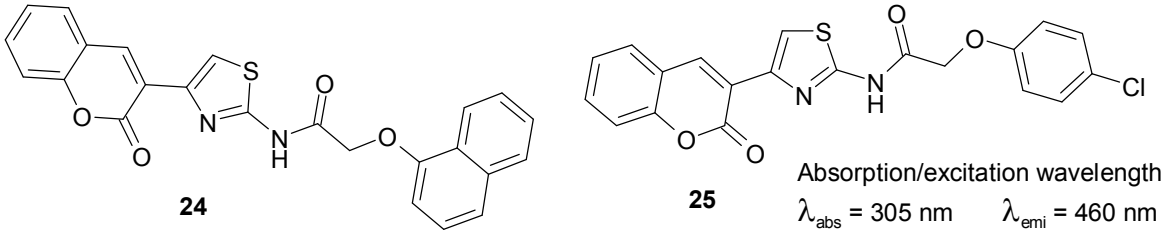


Fig. 9. Structure of coumarin derivatives **24** and **25** and absorption/excitation wavelength of compound **25**

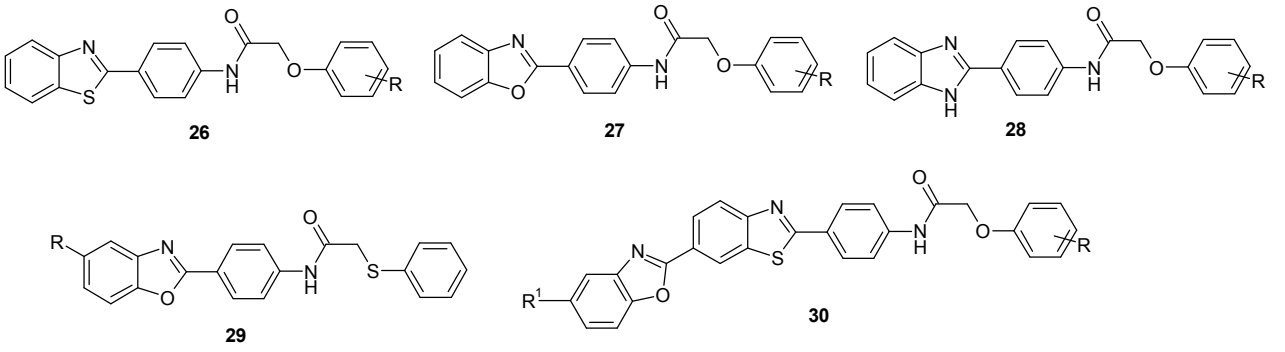


Fig. 10. New class of ether-amides **26-30** miR-21 inhibitors

2.2. Synthesis and Anticancer Activity of 2-Arylamino-*N*-Thiazol-2-yl-Acetamide and 2-Arylsulfanyl-*N*-Thiazol-2-yl-Acetamide

Amino or sulfur derivatives are bioisosteric analogs to 2-phenoxy-*N*-thiazol-2-yl-acetamides (Fig. 11).[37,38]

Bioisosteric replacement is a powerful tool for modulating the drug-like properties, altering ADME-Tox properties of chemical space of experimental therapeutics.[37,38]

The synthesis of a 2-aminothiazole sublibrary containing compounds with methyl, bromine, phenyl, or butylidene substituents at the 4- or 5-position of the core structure was described by Li *et al.*[39] The antitumor activities of all target compounds were evaluated against the human lung cancer cell line H1299 and the human glioma cell line SHG-44. Dasatinib and the derivative SNS-032 (BMS-387032)] as lead compounds optimization was used (Fig. 12).

The synthesis of 2-aminothiazoles with different hydrophobic substitution patterns, including methyl, bromo, phenyl, or butylidene at the 4- or/and 5-position of the core was illustrated in Scheme 7.[39]

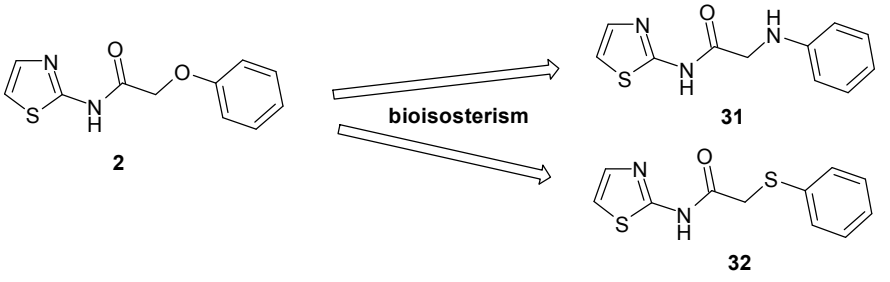


Fig. 11. Bioisosteric replacement

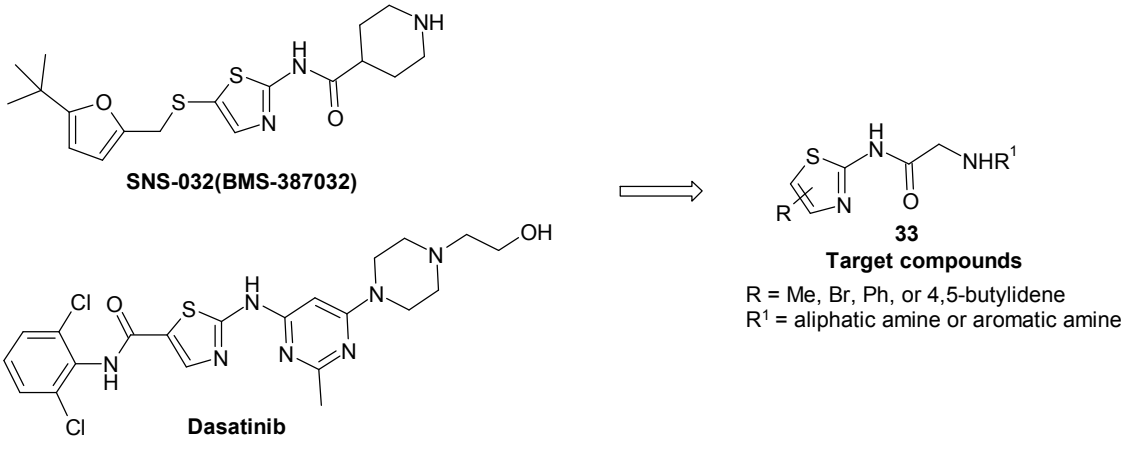


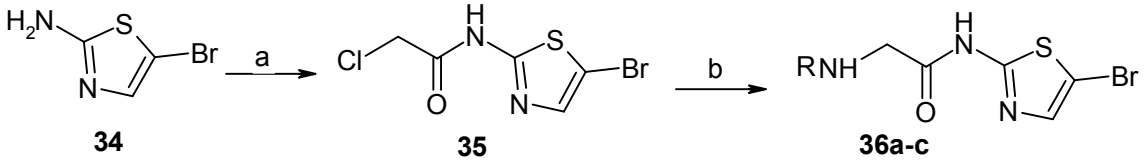
Fig. 12. Antitumor molecules encompassing 2-aminothiazole core

The target compounds **36a-c** were synthesized by sequential chloroacetylation of the amine **34** followed by nucleophilic chlorine substitution in chloracetamide **35** using aromatic amines.

The obtained arylamino derivatives **36a-c** showed moderate antitumor activity (Table 3).[39]

However, parallel studies using aliphatic amines allowed us to identify 3-(4-methylbenzylamino)-*N*-(4,5,6,7-tetrahydrobenzo[d]-thiazol-2-yl)propanamide **40**, which exhibited the most potent anticancer activities with IC_{50} values of 4.89 and 4.03 μmol/L (Scheme 8) against the two tested cell lines H1299 and SHG-44, respectively.[39] Compound **40** were prepared according to Scheme 8.

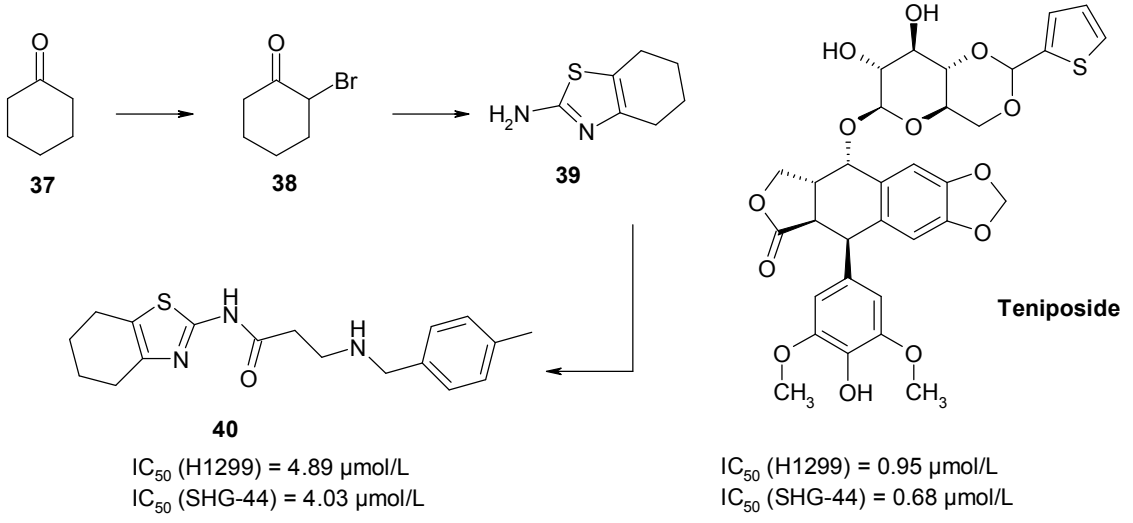
By the solvent-free/neat fusion reaction of *N*-benzothiazol-2-yl-2-chloroacetamide with different amines a series of novel 2-aminobenzothiazole derivatives were synthesized, and tested using various methods[40] (Scheme 9). Compounds **41-44** were evaluated for PI3Kγ inhibition at a concentration of 100 μM. Compound **42b** showed the highest PI3Kγ inhibition (48%) at a concentration of 100 μM. Electron acceptor substituents in the aryl cycle resulted in partial or complete loss of antitumor activity. For compounds **41**, **42a-d**, **44a-c**, the percentage of inhibition against A549 and MCF-7 in the MTT assay was determined. For the most potent compounds, **42d** and **43**, the anticancer activities were 64.15% and 90.59% on the lung cancer A549 cell line and 32.01% and 85.05% on the breast cancer MCF-7 cell line, respectively. IC_{50} values for **43** and **42d** ranged from 22.13 to 61.03 μM. For the reference compounds doxorubicin and gedatolisib, the IC_{50} against the A549 cancer cell line was 16.61 and 16.46 μM, respectively.[40]



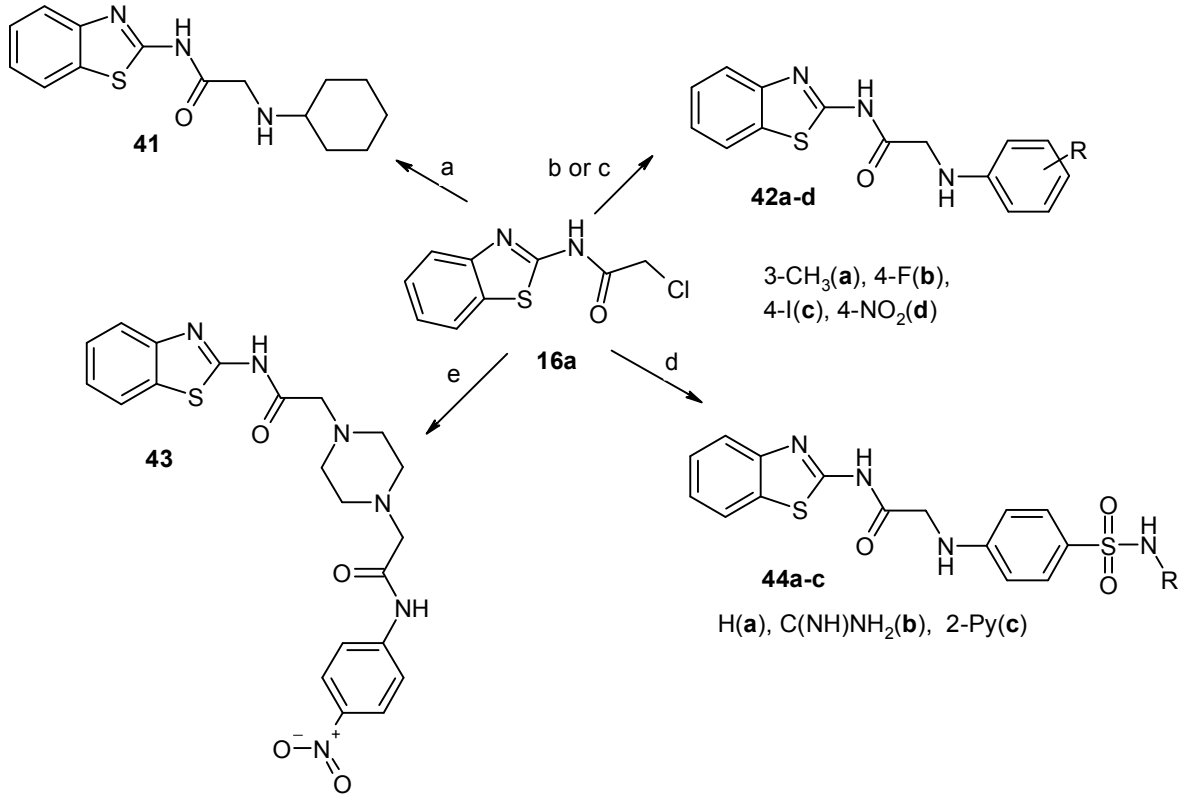
Scheme 7. Synthesis of target compounds **36a-c**. Reagents and conditions: (a) 2-chloroacetyl chloride, pyridine, DCM, 0°C, 4 hr; (b) aromatic amine, triethylamine, THF, reflux, 4 hr

Table 3. Antitumor activities of compounds **36a-c** against H1299 cell line and SHG-44 cell line

Compound	R	IC_{50}, μmol/L	
		H1299	SHG-44
36a	C_6H_5	9.31	14.29
36b	4-$CH_3OC_6H_4$	9.34	14.41
36c	4-ClC_6H_4	8.71	13.66
Teniposide	-	0.95	0.68



Scheme 8. Synthesis of 3-(4-methylbenzylamino)-*N*-(4,5,6,7-tetrahydrobenzothiazol-2-yl)-propionamide **40**. Reagents and conditions: (a) Br_2, Et_2O, 0°C, 3-4 hrs; (b) thiourea, EtOH, reflux, 2-3 hrs; (c) 2-chloroacetyl chloride or 3-chloropropionyl chloride, pyridine, DCM, 0°C, 4 hr; (d) aliphatic amine or aromatic amine, triethylamine, THF, reflux, 4 hr



Scheme 9. Synthesis of target compounds **41-44**. Reagents and conditions: (a) cyclohexylamine, dioxan, 100°C, 3 hr; (b) metatoluidine, DMF, 100°C, 3 hr; (c) corresponding aromatic amine, neat fusion, 165°C; (d) corresponding aromatic amine, neat fusion, 195°C; (e) 1-(4-nitrophenyl)piperazine, reflux, 200°C, 24 hr

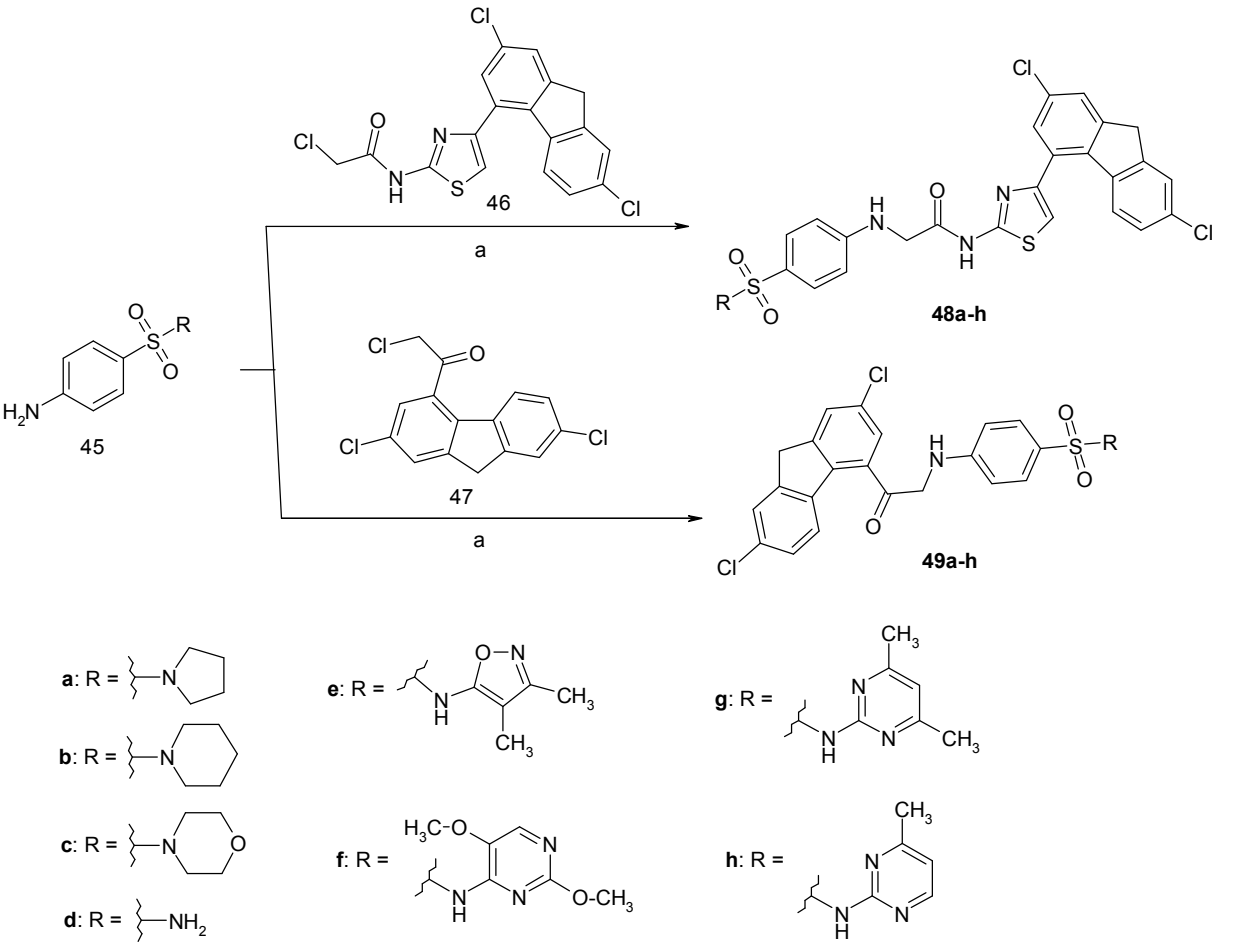
Hussein *et al.*[41] synthesized a series of new fluorene-aminothiazole sulfonamide conjugates as potential anticancer agents (Scheme 10). Similar compounds without a thiazole linker were also obtained. The synthetic conjugates were evaluated for anticancer activity against selected cancer cell lines MCF-7, HT-29, HCT-116, and MRC-5. It should be noted that conjugate **48g** with a 4,6-dimethylpyrimidinyl group showed excellent cytotoxicity of 5.6 μM (IC_{50}) and selectivity index of 10.14 against the HCT-116 cancer cell line, which was comparable and superior to the reference drug doxorubicin. Additional clonogenicity, cell migration, and apoptosis induction assays demonstrated that the conjugate **48g** effectively inhibits the colony forming and cell migratory ability of HCT-116 cancer cells with significant apoptosis induction.

Further clonogenic, cell migration, and apoptotic induction assays demonstrated that conjugate **48g** was effective in inhibiting HCT-116 cancer cell colonization and migration with significant apoptotic induction.[41]

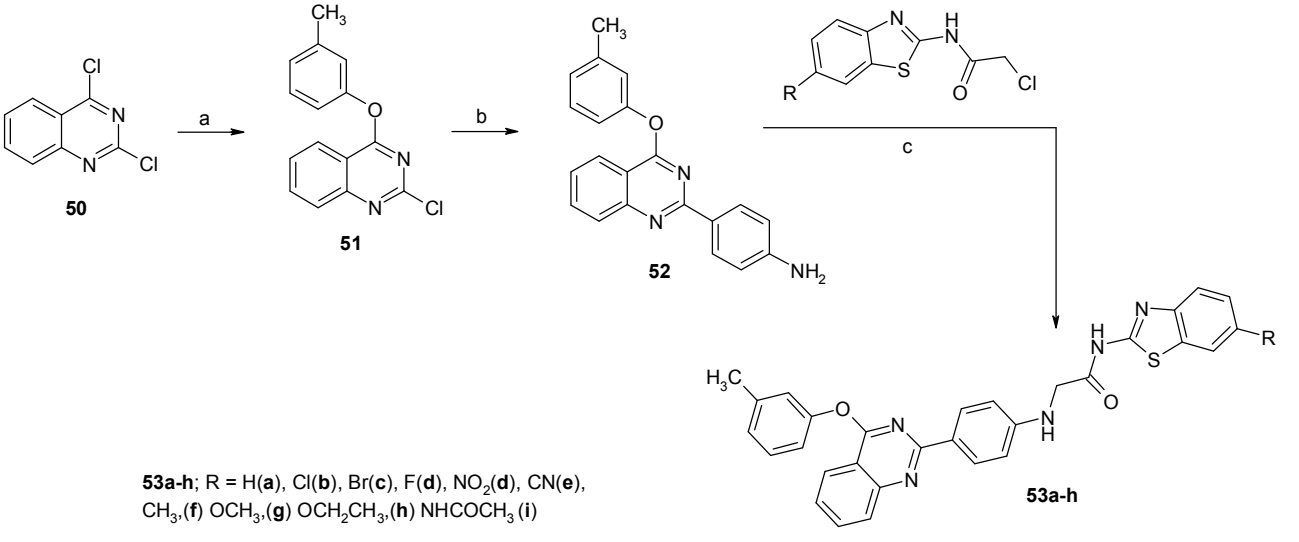
To investigate the antitumor activity of a series of various benzothiazolyl acetamide-fused quinazoline derivatives were synthesized according to Scheme 11. Quinazolines **52** were synthesized by using the Suzuki coupling reaction.[42] The target benzothiazolyl acetamide-fused quinazoline **53a-h** by the reaction of 2-chloracetavidobenzuthiazole with compound **52**.

The study of activity showed[42] that analogs **53c** and **53e** were active against prostate cancer (PC3) cell proliferation. In addition, *N*-benzothiazolyl acetamide-fused quinazolines substituted with electronwithdrawing groups – bromo (**53c**) and nitro (**53e**) showed moderate activity: inhibition of cell growth at 78.4 and 53.9 μg/mL, respectively. Furthermore, it was established that all the synthesized analogs were non-toxic, as evidenced by their LC_{50} values of 80 μg/mL.

These derivatives also demonstrated an exceptional *in vitro* antimycobacterial activity (MIC, 3.12–25 μg/mL) against *M. tuberculosis* H37Rv. Compounds represent new scaffolds that could be further optimized for the future development of more potent and selective antimycobacterial/ anticancer agents. This is important because epidemiological data have shown an association between tuberculosis and an increased risk of lung cancer. The incidence of combined forms of lung carcinoma and tuberculosis ranges from 1% to 16%.[43-46]



Scheme 10. Synthesis of target fluorene-aminothiazole derivatives **48** and **49**.
Reagents and conditions: (a) ethanol, triethylamine, reflux



Scheme 11. Synthetic protocol for the benzothiazolyl acetamide-fused quinazoline analogs **53**.
Reagents and conditions: (a) K_2CO_3, *m*-cresol, EtOH, 80°C; (b) 4-aminophenylboronic acid pinacol ester, $Pd(PPh_3)_4$, Na_2CO_3, DME, 90°C; (c) K_2CO_3, acetone, reflux

2.3. Benzofuran-2-Carboxamides as Rigid Analogs of Phenoxyalkylacyl-aminothiazoles

One of the strategies in drug discovery is the conformation restriction of the leader compound. The idea is to keep the molecule in the bioactive conformation while at the same time eliminating alternative conformations that might interact with other targets. Keeping molecules in a particular conformation can increase activity, improve binding site interactions, and/or reduce side effects. By locking the bonds within a ring, rigidification can be achieved.[47-49] This approach can also be implemented in the case of phenoxyalkylacylamino-thiazoles (Fig. 13).

A series of benzofuran-2-carboxamides have been described in the literature.[50-55] The targeted benzofuran-2-carboxamides **58**, **60** and **61a-e** were synthesized from chlorohydrides **56a, b** of commercially available benzofuran-2-carboxylic acids **55a, b** and 2-aminothiazole **57**, 2-aminobenzothiazole **16a** and 2-amino-5-aryl-methylthiazoles **59a-e**. The acylation reaction was carried out in dry dioxane at room temperature in the presence of triethylamine (Scheme 12).

5-R-benzyl-1,3-thiazol-2-amines **59a-e** (Scheme 13) were synthesized using diazonium salts **62a-e** as starting reagents. Diazonium salts **62a-e** react with acrolein **63** to form 3-aryl-2-chloropropanals **64a-e**.[50] These aldehydes were converted in high yields to 5-R-benzylthiazol-2-ylamines **59a-e**.

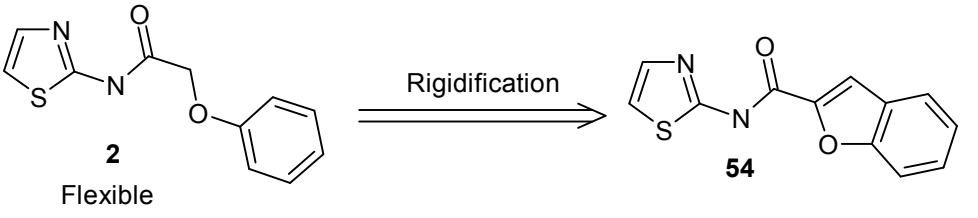
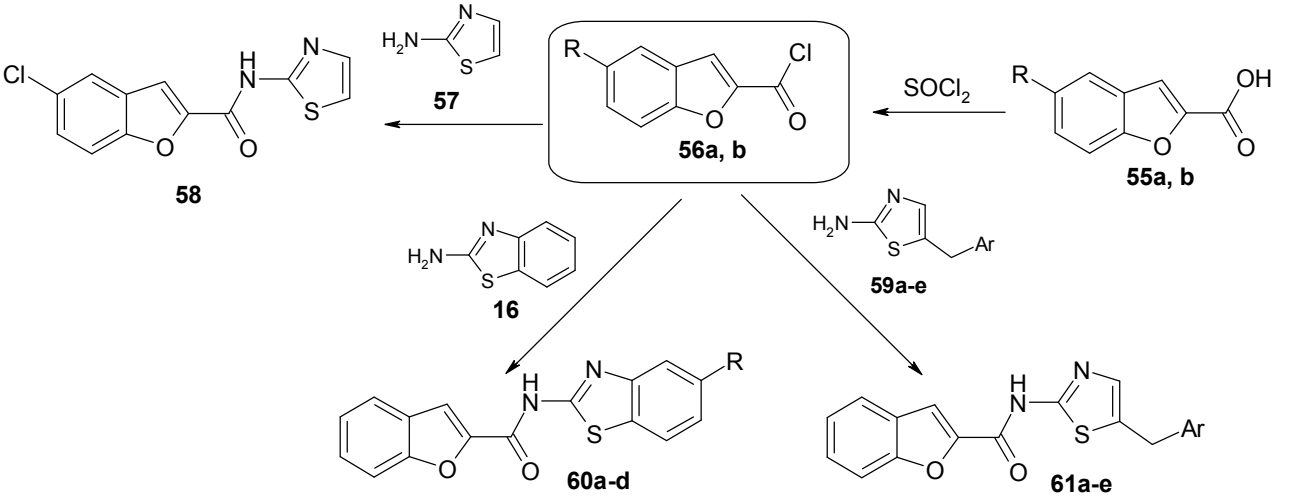


Fig. 13. Benzofuran-2-carboxamides as rigid analogs of phenoxyalkylacylaminothiazoles

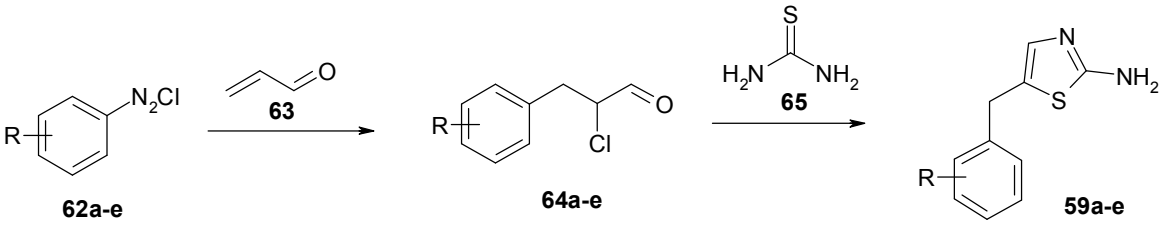


55, 56: R = H(**a**); 5-Cl(**b**)

60: R = H(**a**); CN(**b**); NO_2(**c**); (**d**)

59, 61: Ar = 3-$CH_3C_6H_4$(**a**); 2-ClC_6H_4(**b**); 2,3-$Cl_2C_6H_3$(**c**); 4-Cl-3-$CF_3C_6H_3$(**d**); 2-BrC_6H_4(**e**)

Scheme 12. Synthesis of benzofuran-2-carboxamides **58**, **60a-d**, **61a-e**



Scheme 13. Synthesis of 2-amino-5-arylmethylthiazoles

Table 4. Mean inhibitory concentration (GI_{50}, μM) of compounds **61a, c, d** in comparison with 5-FU, cisplatin and curcumin

Compound	Subpanel of tumor cell lines									
	L	NSCLC	ColC	CNSC	M	OV	RC	PC	BC	MG-MID
61a	1.01	2.23	0.87	3.80	1.18	2.68	2.33	2.78	1.36	2.03
61c	14.15	1.85	0.84	1.73	1.51	1.37	2.06	3.56	2.31	3.26
61d	41.23	4.96	4.29	2.68	4.95	5.96	4.81	5.67	6.01	8.95
5-FU	15.1	>100	8.4	72.1	70.6	61.4	45.6	22.7	76.4	52.5
Cisplatin	6.3	9.4	21.0	4.7	8.5	6.3	10.2	5.6	13.3	9.48
Curcumin	3.7	9.2	4.7	5.8	7.1	8.9	10.2	11.2	5.9	7.41

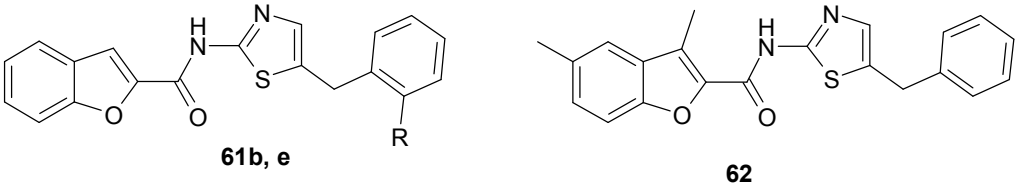
Antitumor activity studies for compounds **58, 60a, 61a-d** were conducted on 60 cell lines of the National Cancer Institute (NCI, USA) (Table 4). Compounds **61a, c, d** were the most effective against all cell lines. The MG-MID values, μM, for **61a, c, d** are lower than for 5-fluorouracil, curcumin, and cisplatin, tested under similar conditions.[50]

The significant antitumor effect of *N*-(5-(2-bromobenzyl)thiazol-2-yl)benzofuran-2-carboxamides **61b, e** (Fig. 28) on cell growth, apoptosis and angiogenesis in human hepatocellular carcinoma (HCC) cells was reported. The authors[51,52] suggest that these compounds can be a lead compound for development anticancer drugs against HCC.

Compound **62** (Fig. 14) demonstrated approximately 20-fold greater cytotoxicity against U251 and T98G cells than TMZ and approximately 2-fold greater activity than Dox. This compound induced apoptosis by cleaving PARP1 and caspase 3, increased Bax and Bim levels and decreased the levels of phosho-ERK1/2 kinase in treated U251 cells. Compound **62** was cytotoxic *via* ROS production and DNA single-strand breakage, but did not intercalate into a DNA molecule.[53]

In vitro biological evaluation of compounds **60b-d** showed that only 2-imidazolynyl substituted derivative **60d** exerted concentration-dependent antiproliferative effects on tumor cell lines at micromolar concentrations and showed selectivity on the SK-BR-3 cell line.[54]

A series of benzothiazolamide and urea derivatives linked to a privileged pyridylamide fragment (Fig. 15) were synthesized as sorafenib analogues and their antiproliferative activity was evaluated in a panel of 60 human cancer cell lines at a single concentration of 10 μM at the National Cancer Institute (NCI, USA). Among them, benzofuran derivative **65** showed comparable activity to sorafenib.[55]



61b: HS-111 R = Cl
61e: HS-113 R = Br

Fig. 14. Structure of *N*-(5-(2-bromobenzyl)thiazol-2-yl)benzofuran-2-carboxamides **61b**, **e** and **62**

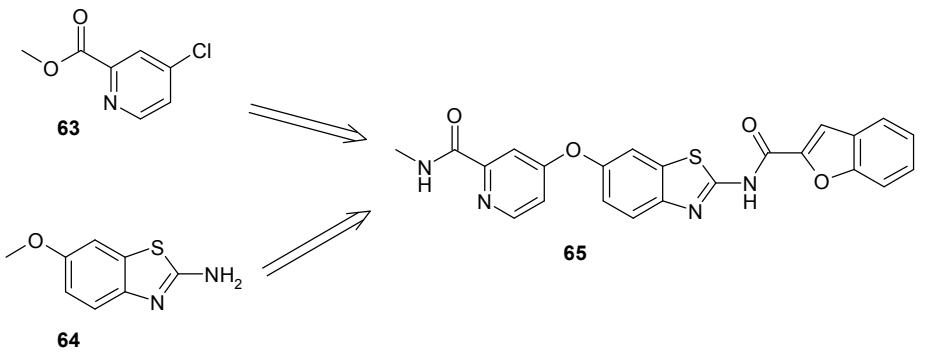


Fig. 15. Synthesis of 4-({2-[(1-benzofuran-2-ylcarbonyl)amino]-1,3-benzothiazol-6-yl}oxy)-*N*-methylpyridine-2-carboxamide **65**

Table 5. Growth inhibition of HCT-116 and SK-BR-3 cell lines

Compound	% Growth inhibition				ClogP
	HCT-116 (colon cancer)		SK-BR-3 (breast cancer)		
	100 μM	10 μM	100 μM	10 μM	
65	77.45	9.15	52.44	54.38	4.45
Sorafenib	97.32	48.41	93.12	48.87	5.46

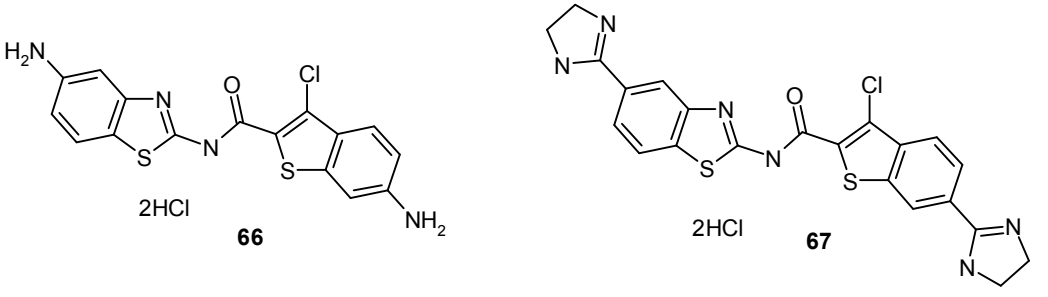


Fig. 16. Structures of 3-chlorobenzo[b]thiophene-2-carboxylic acid benzothiazol-2-ylamides dihydrochlorides **66, 67**

Cindrić *et al.*[56,57] obtained thioanalogs of amides **61** (compounds **66**, **67**) and studied their antitumor activity (Fig. 16).

The data of experimental biological studies[55] for compound **65** are given in Table 5.

Amino-substituted benzothiazole hydrochloride salt **66** showed the most potent and selective activity against the MCF-7 cell line with an of 40 nM.[56]

Benzothiazole derivative **67** with 2-imidazolinyl group showed the strongest selective activity against HeLa cells with IC_{50} = 1.16 μM.[57]

3. Conclusions

The intensification of cancer research in recent years put some molecules into clinical trials, but still, there is an urgent need to develop effective therapeutic molecules to combat these diseases. A large volume of research has been carried out on phenoxyalkylacylamino thiazoles derivatives, which has proved the pharmacological importance of this heterocyclic nucleus. Hybridization of privileged 2-aminothiazole and compounds with terminal phenoxy groups to form promising moiety as ligands of different molecular targets. The present review focuses on the anticancer profile of phenoxyalkylacylamino thiazoles and their *S*- and *N*-bioisosteres in the current literature with an update of recent research findings on this scaffold and the perspectives that they hold for future research. It is anticipated that this information would give rise to the design of better molecules with enhanced biological properties and higher specificity, and together with the development of novel synthetic strategies. The eventual development of new phenoxyalkylacylamino thiazoles and their *S*- and *N*-bioisosteres into drugs for cancer chemotherapy can have great relevance.

Funding

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СИНТЕЗ І ПРОТИПУХЛИННА АКТИВНІСТЬ ГІБРИДІВ «АМІНОТІАЗОЛ – ТЕРМІНАЛЬНА ФЕНОКСИСПОЛУКА» ТА ЇХНІХ АНАЛОГІВ: КОРОТКИЙ ОГЛЯД

Анотація. *2-Амінотіазол і сполуки з термінальними феноксигрупами належать до привілейованих структур у медичній хімії. Сполуки, що містять ці два скафолди, викликають інтерес для дизайну нових фармакологічних засобів, зокрема для терапії злоякісних пухлин. Гібридизація, яка реалізується комбінацією обох привілейованих фрагментів через утворення ковалентних зв'язків, є перспективним підходом до пошуку сполук-лідерів. Отримані кон'югати можуть зв'язуватися з різноманітними рецепторами, і тому їхній синтез і фармакологічний скринінг є актуальним завданням сучасної медичної хімії. У цьому огляді висвітлено останні досягнення в галузі феноксіалкілациламінотіазолів і їхніх аналогів з протиракovим потенціалом, що охоплює роботи, опубліковані за останні два десятиліття.*

Ключові слова: *2-амінотіазол, термінальна феноксигрупа, молекулярна гібридизація, протипухлинна активність.*