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REVIEW ARTICLE

Thioethers: An Overview

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Abstract: Spreading rapidly in recent years, cancer has become one of the causes of the highest mortality rates after cardiovascular diseases. The reason for cancer development is still not clearly understood despite enormous research activities in this area. Scientists are now working on the biology of cancer, especially on the root cause of cancer development. The aim is to treat the cancer disease and thus cure the patients. The continuing efforts for the development of novel molecules as potential anti-cancer agents are essential for this purpose. The main aim of this review was to present a survey on the medicinal chemistry of thioethers and provide practical data on their cytotoxicities against various cancer cell lines. The research articles published between 2001-2020 were consulted to prepare this review article; however, patent literature has not been included. The thioether-containing heterocyclic compounds may emerge as a new class of potent and effective anti-cancer agents in the future.

Keywords: Thioether, anticancer activity, antineoplastic, cytotoxicity, pharmacokinetics, cardiovascular diseases.

1. INTRODUCTION

Cancer, one of the most life-threatening diseases, is mainly identified as a disease with uncontrolled cell division; therefore, the impact of anti-proliferative compounds on the decline of tumor dimension is the major target of medicinal explorations. In the future, cancer will be one of the primary causes of death after cardiovascular diseases and will probably become the most widespread disease [1]. Effective prevention therapies need to be discovered because of the high mortality rate of cancer. Also, exploring anticancer agents and main treatments controlling the metastatic diffusion of cancer cells is vital in the field of cancer investigation [2]. At present, cancer treatment involves various techniques, including surgery, radiotherapy, immunotherapy, natural products, and chemotherapy. Even though anti-cancer drugs have the capability to destroy cancer cells, they also kill normal cells besides cancerous tissues. In the last several decades, the synthesis of new cytotoxic compounds has led to the improvement of anti-cancer therapeutics [3]. There are both opportunities and challenges in exploring anti-cancer drugs, which may mirror every part of drug improving protocols [4]. Despite a diversity of smartly designed molecules, gene-targeted drugs are in clinical use nowadays. They generally temporarily prevent the mortal destruction of central cancers such as those of the lung, colon, and breast that become metastasized and are beyond the reach of the experienced surgeon or radiotherapist [5]. The search for novel and more efficient chemotherapeutic agents is ongoing due to diverse side effects and drug resistance related to the existing ones [6].

Thioether is a functional group that consists of one sulfur atom settled between two carbon atoms. Thioethers are a class of organic compounds that have attracted the attention of medicinal chemists since they contain carbon-sulfur bonds. Sulfur-containing structures are abundantly found in compounds used for cancer disease. Among the various classes of sulfur-containing compounds, thioethers play a crucial role in medicinal chemistry because of their broad applications as drugs and drug intermediates. Thioether compounds possess many specific activities such as anticancer [7], anticonvulsant [8], antimicrobial [9, 10], antiplatelet [11], antifungal [12], and antimycobacterial [13]. Although thioether structures are generally used as transition groups, they are very efficient organic compounds. Sulfur molecules also represent an important group of sulfur compounds used for medical purposes. Recently, the chemistry of thioethers and their combined molecules has gained high importance due to their efficient biological benefits. Chemical agents are generally metabolized within a mammalian organism by the addition of oxygen atoms to the molecules. During metabolism, the sulfur of the thioether group is first converted into sulfone and then converted into sulfoxide. Oxidation of sulfide increases water solubility, and increased polarity allows for easy elimination of the compounds. The substrate specificity of the enzymes related to sulfur oxidation has been generally attributed to the cyto-

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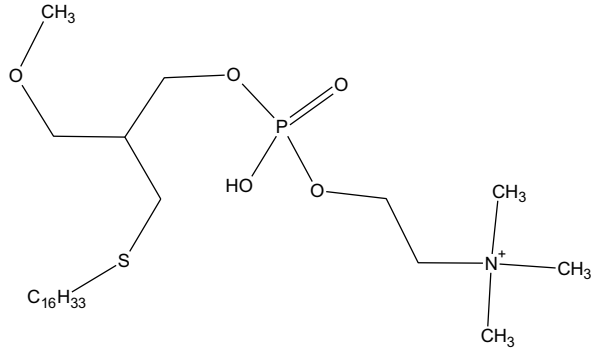
chrome P-450-dependent monooxygenase system [14]. The cytochrome P-450 system catalyzes the hydroxylation of nonnutritive alkyl and aryl hydrocarbons and dealkylation of ethers, thioethers, and *N*-substituted amines or amides [15]. Monooxygenase facilitates NADPH- and oxygen-connected oxygenations of compounds having nucleophilic sulfur or nitrogen [16]. In recent years, it has been found that the intermediate metabolism enzyme, phenylalanine monooxygenase (PAH; phenylalanine hydroxylase), plays a role in the sulfur oxygenation of xenobiotic thioethers [17]. Also, oxidation of thioethers to sulfoxide and subsequently sulfone induces an increase in hydrophilicity. GSH, which is abundant in the cell, is a thiol-containing tripeptide. Glutathione transferases, known as glutathione S-transferases, the Phase-II detoxification enzyme family, catalyze the conversion of endogenous and exogenous electrophilic and hydrophobic compounds with glutathione, generally catalyzing their conversion into less toxic metabolites. It has been reported that GSTP1-1, one of the GST isozymes, is secreted in large amounts in many different tumors of human origin (lung, colon, kidney, ovary, esophagus, and stomach). Prodrugs that are inactive on administration are converted preferentially and specifically into their toxins with GSTP, which is present at elevated levels in tumor cells. This strategy enables increased transport of the active compound into tumor tissues while reducing the toxicity of the compound to normal tissues. An example is azathioprine, a 6-mercaptopurine prodrug.

This review appraises the anti-cancer activity of thioethers and their complex compounds noticed in the 20th-21st century. However, the patent literature is not included in the content of this review. Molecules used in clinical applications are not included in this review. Thioether compounds that show selective effects in cancer cells are highlighted in the text.

Phase trials of the Ilmofosine molecule have been carried out. It is an anti-cancer drug carrying the thioether group known in history. Ilmofosine, BM 41.440 (1-hexadecylmercapto-2-methoxymethyl-*rac*-glycero-3-phosphocholine), is a cytotoxic thioether phospholipid analog that has recently entered phase I trials in cancer patients [18, 19]. In 1991, the antineoplastic activity of this compound was investigated *in vivo* in the [3]Lewis-lung carcinoma system [20].



Ilmofosine (BM 41.440)

H_2C--O--P--O--$(CH_2)_2$--N $(CH_3)_3$

2. PHARMACOKINETICS OF THIOETHER DERIVATIVES

Researchers have studied thioether bridges in detail to improve the pharmacokinetic effects and bioavailability. Kluskens *et al.* considered that the use of an intra-molecular thioether bridge is an effective way to protect peptides against proteolytic degradation. Thioether bridges are more stable compared to peptide bonds and disulfide bridges [21]. Philips *et al.* described the effects, pharmacokinetics, and toxicity of trastuzumab-maytansinoid conjugates *in vitro* and *in vivo* using thioether and disulfide binders. Trastuzumab linked to maytansinoid through a nonreducible thioether linkage showed high activity compared to unconjugated trastuzumab or trastuzumab linked to other maytansinoids through disulfide linkers [22, 23]. Sahu *et al.* synthesized different thioether derivatives of quinoxaline derivatives. Pharmacokinetic parameters showed good results with respect to the efficient oral bioavailability of compounds [24]. Seto *et al*. evaluated the pharmacokinetic profile of thioethers before conducting *in vivo* experiments in diabetic mice. Although thioethers have a short half-life, they showed nominal total clearance and moderate oral bioavailability, suggesting that thioether derivatives are orally bioavailable compounds [25]. In a non-enzymatic way, rabeprazole, a proton pump inhibitor (PPI), was reduced to the thioether of rabeprazole with small enzymes, CYP2C19 and CYP3A4. Pharmacokinetic interactions between rabeprazole and CYP3A4 have limited clinical importance [26]. For the improvement of antibacterial activity and pharmacokinetic profiles, Uno *et al*. conceived that tetrazolothioether could be found in the core of pyrrolidine. According to these data, the introduction of a suitable heteroaromatic thioether group into the pyrrolidine nucleus can have a strong impact on pharmacokinetics [27].

3. SYNTHESIS OF SOME THIOETHERS

Thioether structure is used both as a bridge to link functional groups and for pharmacological activity. The thioether functional group has attracted the attention of a lot of researchers in recent years. Researchers have synthesized the derivatives containing thioether in various ways.

Alanazi *et al.* synthesized the thioether compounds in their study at room temperature through a mixture of starting compounds containing a thiol group and an appropriate alkyl, aryl, and/or aralkyl halide in acetone, including anhydrous potassium carbonate. Alkyl/aralkyl halides incorporated into thiol groups in molecules are shown in Fig. (**1**) [28].

In the study of Eskandariyan *et al.*, following the addition of appropriate arylmethyl halides, the synthesis occurred with the starting compound having a thiol group. The solution was stirred at room temperature in 0.1 M NaOH in a methanol medium [11]. Hou *et al.* synthesized new thioethers by utilizing benzyl bromide derivatives. To a solution of 1,2,4-triazole-3-thione compound in acetonitrile, the corresponding benzyl bromide compounds were added, and the mixture was mixed under reflux in the presence of NaOH [29]. In their study, Klimesova *et al*. added 1,2,4-triazole-3-thiol/4-methyl-1,2,3-triazole-3-thiol in dry DMF

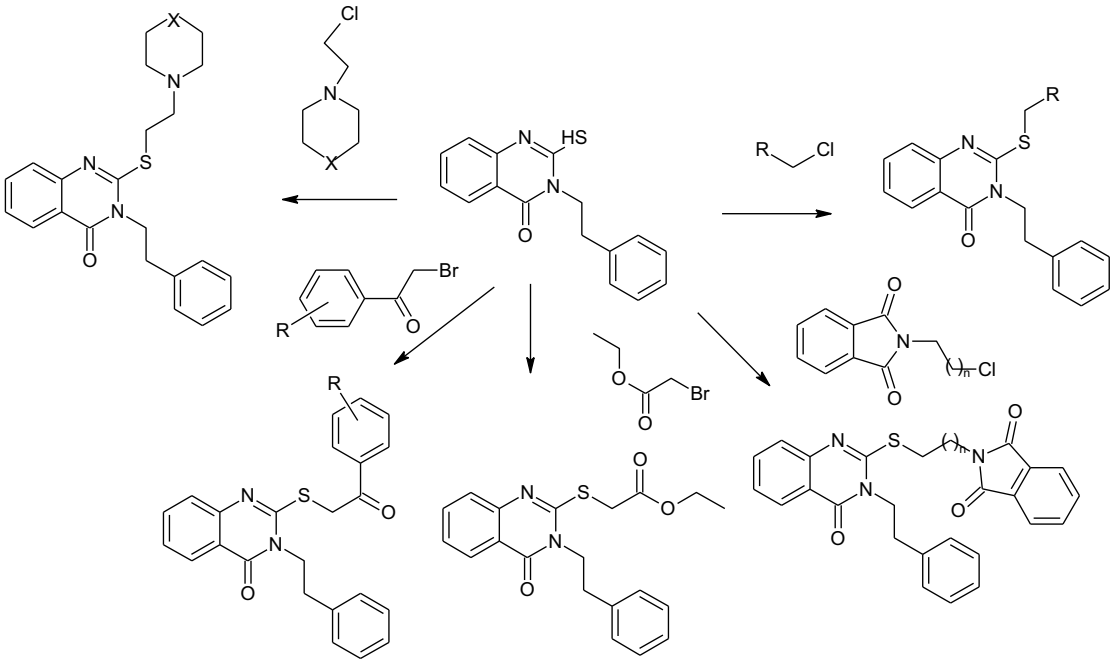


Fig. (1). Synthesis of thioether derivatives (Alanazi *et al.*) [28].

to a solution of sodium in dry methanol. After 10 min of stirring at room temperature, benzyl halide was added. The final suspension was stirred with $CaCl_2$ at room temperature [30]. Patel *et al.* designed and synthesized new thioether compounds using a mixture of 1,2,4-triazole-3-thiol compound bearing naphthalene molecules. Appropriate 2-chloro-*N*-substituted benzothiazoles and anhydrous potassium carbonate in acetone were refluxed in a water bath [31]. Popiolek *et al*. also synthesized thioether compounds using their method. Firstly, 4,5-diphenyl-4*H*-1,2,4-triazole-3-thione was dissolved in DMF. Subsequently, potassium carbonate and ethyl bromoacetate were added to the solution. The content of the flask was refluxed for 2 hours [32]. Thioethers can be synthesized using the Williamson ether synthesis route. In this method, firstly, thiol and sodium hydroxide were reacted, and thiol was transformed into a thiolate anion. Thiols are more acidic than water or alcohol because of the weak S-H bond. Conversion of thiol into a thiolate anion occurs by the reaction of a hydroxide ion and thiol function. Thioethers are formed by the reaction of the thiolate anion with an alkyl halide or sulfonate ester.

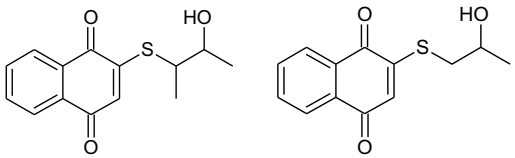
4. ANTI-CANCER ACTIVITY OF THIOETHERS

Cancer has recently become a significant problem worldwide. Scientists have paid great attention to discovering new anti-cancer drugs. Many new organic compounds have been examined to find the perfect cure for diverse cancer types. In recent years, researchers have frequently used thioether groups as they possess transitional groups and efficient functions. Compounds with some thioether functions showing anti-cancer activity are given in Table **1**.

4.1. Breast Cancer

Breast cancer is the most commonly diagnosed cancer in females, and it is a multifactorial disease caused by hormones, reproductive status, genetic mutations, family history, and lifestyle. An association has been defined between breast cancer and environmental factors. Researchers are striving to develop and design new epigenetic biomarkers for breast cancer due to increased death rates [33].

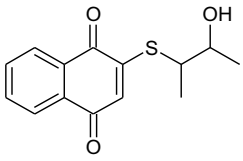
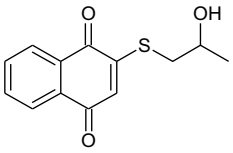
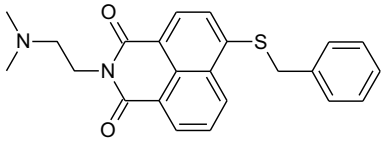
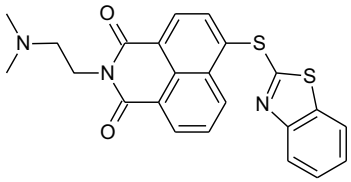
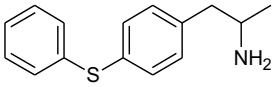
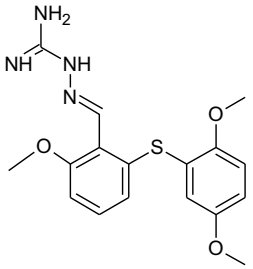
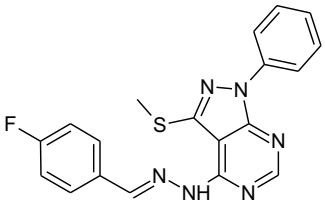
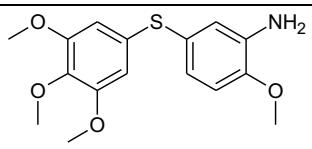
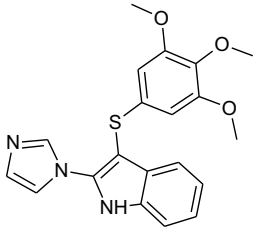
Chen *et al*. synthesized and evaluated new vitamin K3 analogs for anti-cancer activities. Towards the tumor cells of TW-039 (nasopharyngeal), MCF-7 (breast), MES-SA (uterine), A-549 (lung), SW-480 (colorectal), HepG2 (liver), MKN45 (gastric), and MES-SA/Dx5 (uterine), many molecules demonstrated robust inhibitory activity. Although they did not affect normal cells of WI-38, Detroit551, 2-[(3-hydroxybutan-2-yl)sulfanyl]naphthalene-1,4-dione **(1)**, they selectively influenced MCF-7 cells (IC_{50}: >1 μM), and 2-[(2-hydroxypropyl)sulfanyl]naphthalene-1,4-dione **(2)** (IC_{50}: >10 μM) showed strong tumor cell cytotoxicity. In this series of thioethers, analogs with a hydroxyl group would be included according to structure-activity relations [34].



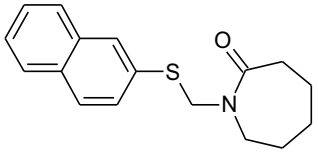
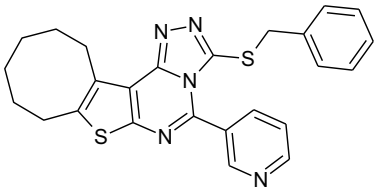
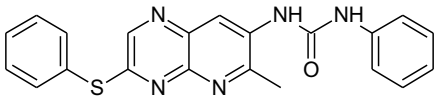
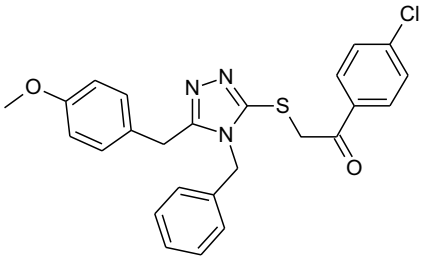
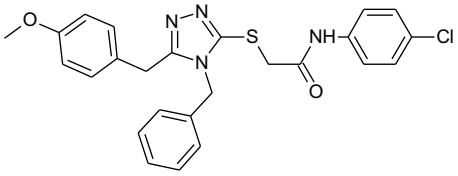
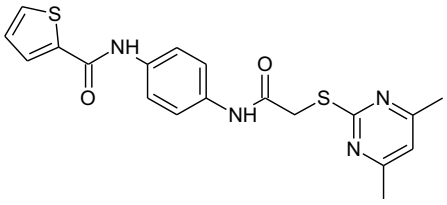
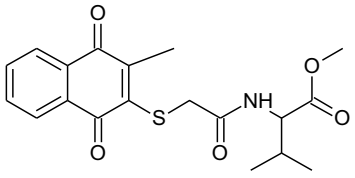
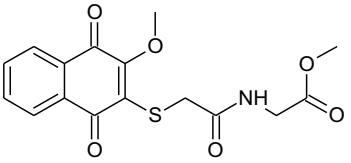
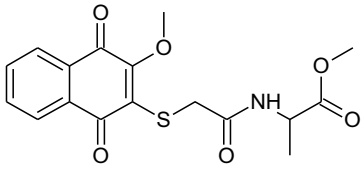
(1) **(2)**

Ott *et al.* synthesized and researched a series of sulfur-substituted naphthalimides. A relation between DNA and topoisomerase was proposed as the main goal of the agent's DNA interaction. Significant empirical setups of compounds 6-(benzylsulfanyl)-2-[2-(dimethylamino)ethyl]-1H-benzo[d, e]isoquinoline-1,3(2H)-dione **(3)** and 6-(1,3-benzothiazole-2-ylsulfanyl)-2-[2-(dimethylamino)ethyl]-1*H*-benzo[d,e]isoquinoline-1,3(2H)-dione **(4)** and a proportional assessment of their effects against proliferation showed significant phototoxic effects. Sulfur-substituted naphthalimides are avail-

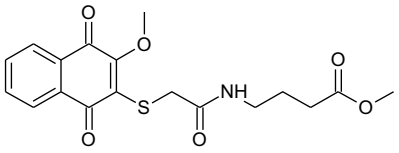
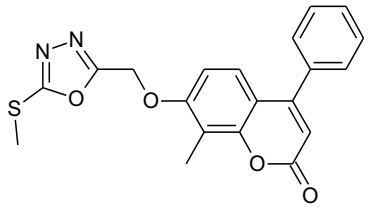
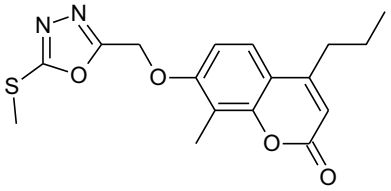
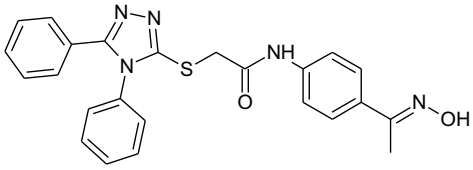
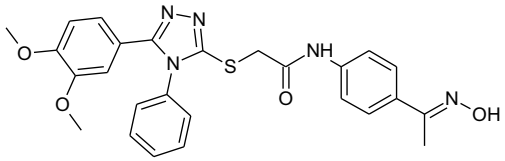
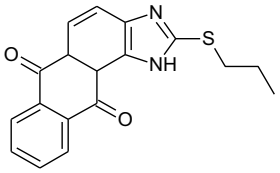
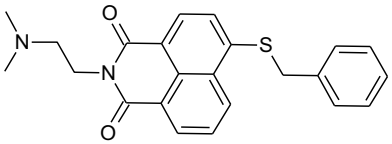
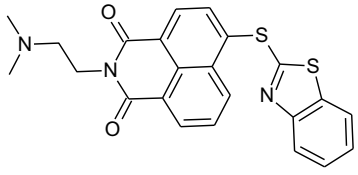
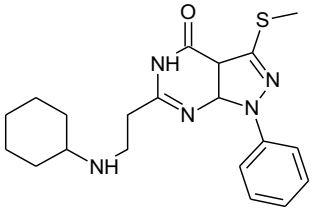
Table 1. Synthesized thioethers with anti-cancer effects.

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
1	2-[(3-hydroxybutan-2-yl) sulfanyl]naphthalene-1,4-dione		Breast Cancer	Chen *et al.* 2002 [34]
2	2-[(2-hydroxypropyl)sulfanyl] naphthalene-1,4-dione		Breast Cancer	Chen *et al.* 2002 [34]
3	6-(benzylsulfanyl)-2-[2-(dimethylamino)ethyl]-1H-benzo[de]isoquinoline-1,3(2H)-dione		Breast Cancer	Ott *et al.* 2008 [35]
4	6-(1,3-benzothiazol-2-ylsulfanyl)-2-[2-(dimethylamino)ethyl]-1H-benzo[de]isoquinoline-1,3(2H)-dione		Breast Cancer	Ott *et al.* 2008 [35]
5	1-[4-(phenylsulfanyl)phenyl]propan-2-amine		Breast Cancer	Cloonan *et al.* 2009 [36]
6	(2-(2,5-dimethoxyphenylthio)-6-methoxybenzylideneamino)guanidine		Breast Cancer	Zhang *et al.* 2009 [37]
7	4-[(2E)-2-(4-fluorobenzylidene) hydrazinyl]-3-(methylsulfanyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine		Breast Cancer	El-Hamid *et al.* 2012 [39]
8	2-methoxy-5-[(3,4,5-trimethoxyphenyl)sulfanyl]aniline		Breast Cancer	Dos Santos *et al.* 2013 [40]
9	2-(1H-imidazole-1-yl)-3-[(3,4,5-trimethoxyphenyl)sulfanyl]-1H-indole		Breast Cancer	Regina *et al.* 2013 [41]

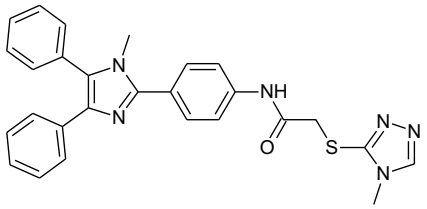
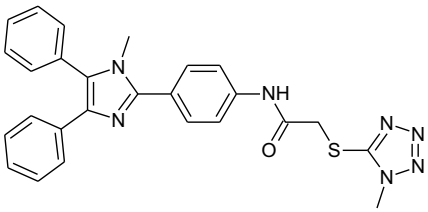
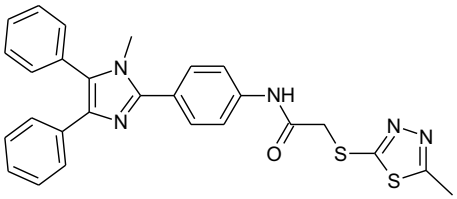
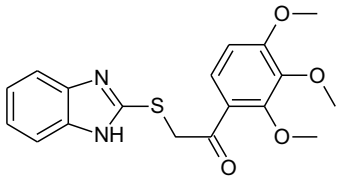
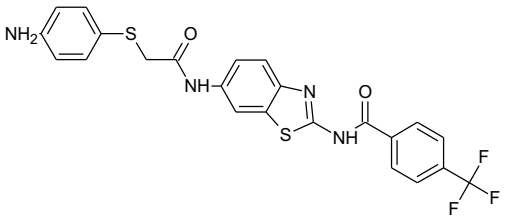
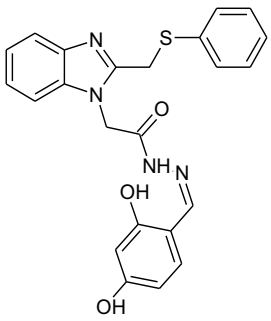
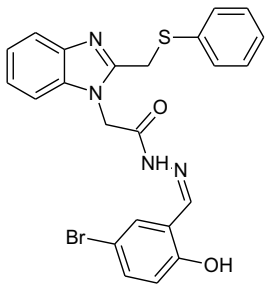
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
10	1-[(naphthalene-2-ylsulfanyl) methyl]azepan-2-one		Breast Cancer	Mudududdla *et al.* 2014 [43]
11	3-(benzylthio)-5-(3-pyridyl)-8,9,10,11,12,13-hexahydrocycloocta [4,5]thieno[3,2-e]-1,2,4-triazolo [4,3-c]pyrimidine		Breast Cancer	Kandeel *et al.* 2015 [44]
12	1-[6-Methyl-3-(phenylsulfanyl) pyrido[2,3-b]pyrazin-7-yl]-3-phenylurea		Breast Cancer	Argyros *et al.* 2017 [45]
13	2-{[4-Benzyl-5-(4-methoxybenzyl)-4H-1,2,4-triazol-3-yl]sulfanyl}-1-(4-chlorophenyl)ethanone		Breast Cancer	Rostom *et al.* 2017 [47]
14	2-{[4-Benzyl-5-(4-methoxybenzyl)-4H-1,2,4-triazol-3-yl]sulfanyl}-*N*-(4-chlorophenyl)acetamide		Breast Cancer	Rostom *et al.* 2017 [47]
15	*N*-[4-({[(4,6-dimethylpyrimidin-2-yl)sulfanyl]acetyl}amino)phenyl]thiophene-2-carboxamide		Breast Cancer	Yang *et al.* 2017 [48]
16	methyl 3-methyl-2-({[(3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)sulfanyl]acetyl}amino)butanoate		Cervical Cancer	Sreelatha *et al*. 2014 [50]
17	methyl ({[(3-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)sulfanyl]acetyl}amino)acetate		Cervical Cancer	Sreelatha *et al.* 2014 [50]
18	methyl 2-({[(3-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)sulfanyl]acetyl}amino)propanoate		Cervical Cancer	Sreelatha *et al.* 2014 [50]

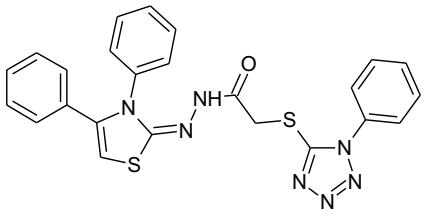
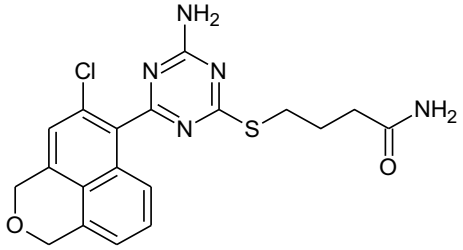
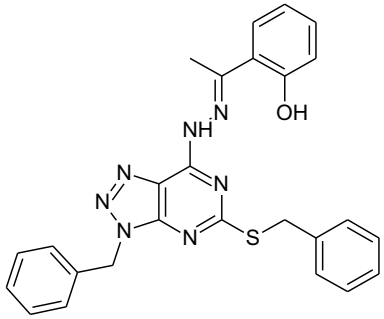
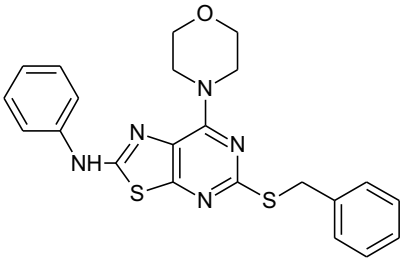
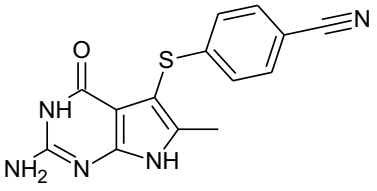
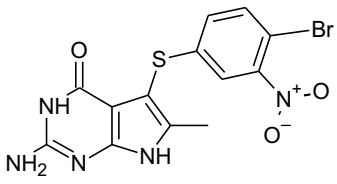
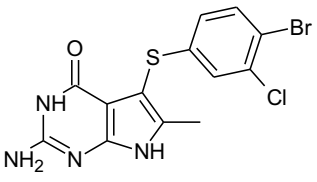
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
19	methyl 4-({[(3-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)sulfanyl]acetyl}amino) butanoate		Cervical Cancer	Sreelatha *et al.* 2014 [50]
20	8-methyl-7-{[5-(methylsulfanyl)-1,3,4-oxadiazol-2-yl]methoxy}-4-phenyl-2H-chromen-2-one		Central Nervous System (CNS) Cancer	İsmail *et al.* 2010 [52]
21	8-methyl-7-{[5-(methyl sulfanyl)-1,3,4-oxadiazol-2-yl]methoxy}-4-propyl-2H-chromen-2-one		Central Nervous System (CNS) Cancer	İsmail *et al.* 2010 [52]
22	2-(4,5-diphenyl-4H-[1,2,4]triazol-3-ylsulfanyl)-*N*-[4-(1-hydroxyimino-ethyl)phenyl]acetamide		Central Nervous System (CNS) Cancer	Abourahma *et al.* 2014 [53]
23	2-[5-(3,4-dimethoxyphenyl)-4-phenyl-4H-[1,2,4]triazol-3-ylsulfanyl]-*N*-[4-(1-hydroxyiminoethyl) phenyl]acetamide		Central Nervous System (CNS) Cancer	Abourahma *et al*. 2014 [53]
24	2-(propylthio)-1H-anthra[1,2-d]imidazole-6,11-dione		Central Nervous System (CNS) Cancer	Chen *et al*. 2013 [54]
25	6-(Benzylsulfanyl)-2-[2-(dimethylamino)ethyl]-1H-benzo[de]isoquinoline-1,3(2H)-dione		Colon Cancer	Ott *et al.* 2008 [35]
26	6-(1,3-benzothiazol-2-yl-sulfanyl)-2-[2-(dimethylamino)ethyl]-1H-benzo[de]isoquinoline-1,3(2H)-dione		Colon Cancer	Ott *et al.* 2008 [35]
27	6-(2-(cyclohexylamino)ethyl)-3-methylsulphanyl-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one		Colon Cancer	Elenany *et al.* 2010 [58]

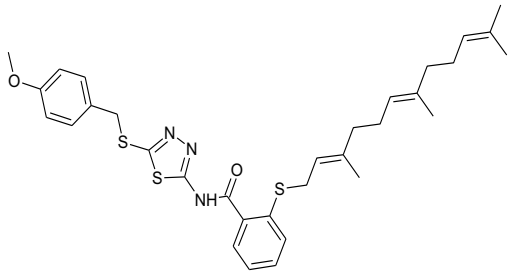
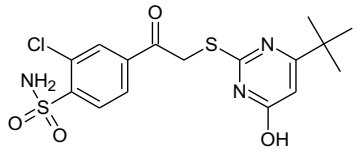
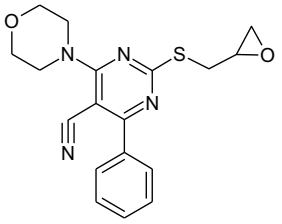
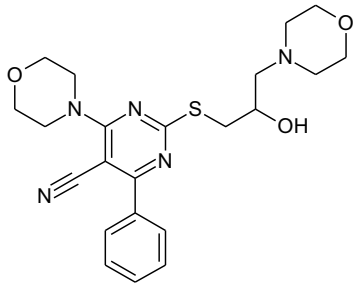
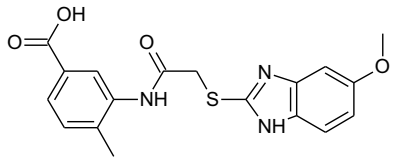
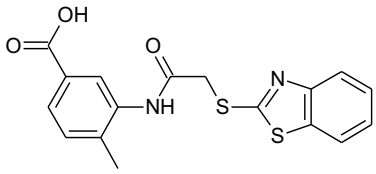
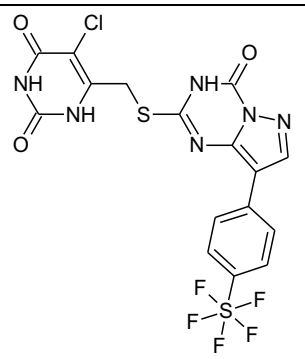
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
28	2-(4-Methyl-4H-1,2,4-triazole-3-yl)-sulfanyl-*N*-[4-(1-methyl-4,5-diphenyl-1H-imidazole-2-yl)phenyl]acetamide		Colon Cancer	Özkay *et al.* 2010 [59]
29	2-(1-methyl-1H-1,2,3,4-tetrazole-5-yl)-sulfanyl-*N*-[4-(1-methyl-4,5-diphenyl-1H-imidazole-2-yl)phenyl]acetamide		Colon Cancer	Özkay *et al.* 2010 [59]
30	2-(5-methyl-1,2,4-thiadiazole-3-yl)-sulfanyl-*N*-[4-(1-methyl-4,5-diphenyl-1H-imidazole-2-yl)phenyl]acetamide		Colon Cancer	Özkay *et al.* 2010 [59]
31	2-(1H-benzimidazole-2-ylsulfanyl)-1-(2,3,4-trimethoxyphenyl)ethanone		Colon Cancer	Abdelaziz *et al.* 2015 [62]
32	*N*-(6-(2-((4-aminophenyl)thio)acetamido) benzo[d]thiazol-2-yl)-4-(trifluoromethyl) benzamide		Colon Cancer	Ma *et al.* 2017 [63]
33	2-(phenylthiomethyl)-1H-benzo-[d]-imidazole pieces. Among them, 2-[(phenylsulfanyl)methyl]-1(*N*'-[(2,4-dihydroxy phenyl) methylidene] acetohydrazide)-benzimidazole		Colon Cancer	Liu *et al.* 2012 [64]
34	2-[(phenylsulfanyl)methyl]-1(*N*'-[(2-hydroxy-5-bromophenyl)methylidene] acetohydrazide)-benzimidazole		Colon Cancer	Liu *et al.* 2012 [64]

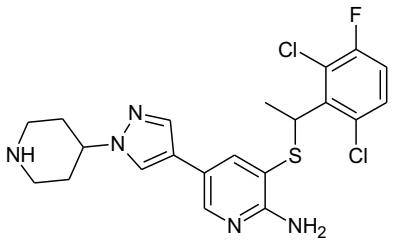
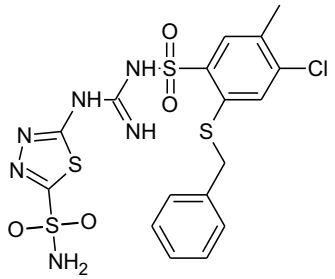
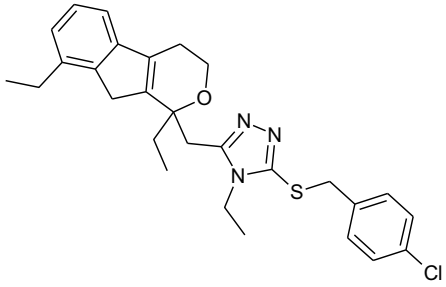
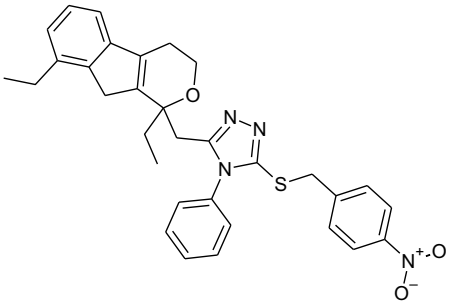
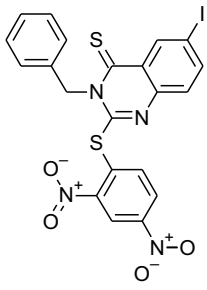
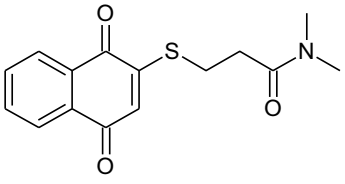
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
35	*N*'-[(3,4-diphenylthiazol-2(3H)-ylidene)]-2-[(1-phenyl-1H-tetrazole-5-yl)thio]acetohydrazide		Glioma cancer	Altıntop *et al.* 2014 [65]
36	4-{[4-Amino-6-(5-chloro-1H,3H-benzo[de]isochromen-6-yl)-1,3,5-triazin-2-yl]sulfanyl}butanamide		Gastric and Oesophagus Cancer	Suda *et al.* 2014 [69]
37	2-(1-(2-(3-benzyl-5-(benzylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)hydrazono)ethyl)phenol		Gastric and Oesophagus Cancer	Li *et al.* 2016 [70]
38	5-(benzylthio)-7-morpholino-*N*-phenylthiazolo[5,4-d]pyrimidin-2-amine		Gastric and Oesophagus Cancer	El-Gohary *et al.* 2017 [71]
39	4-[(2-Amino-6-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl) sulfanyl]benzonitrile		Inhibition of Macromolecular Targets	Gangjee *et al.* 2005 [74]
40	2-amino-5-[(4-bromo-3-nitrophenyl)sulfanyl]-6-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one		Inhibition of Macromolecular Targets	Gangjee *et al.* 2005 [74]
41	2-amino-5-[(4-bromo-3-chlorophenyl)sulfanyl]-6-methyl-3,7-dihydro-4H-pyrrolo [2,3-d]pyrimidin-4-one		Inhibition of Macromolecular Targets	Gangjee *et al.* 2005 [74]

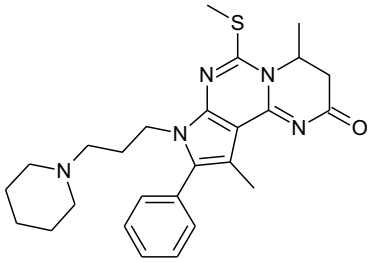
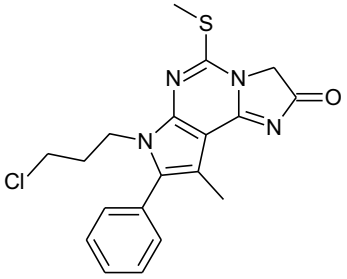
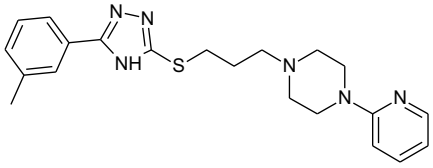
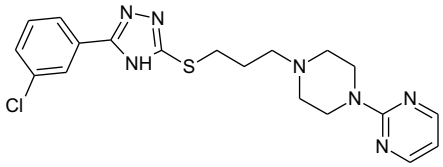
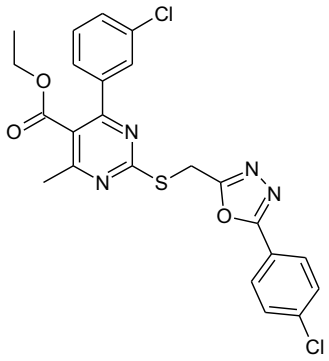
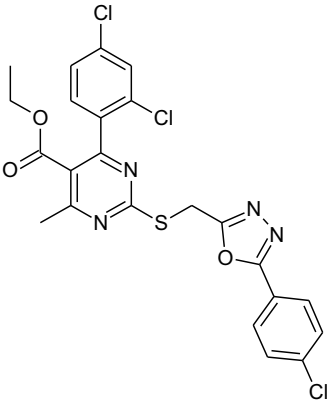
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
42	*N*-{5-[(4-methoxybenzyl)sulfanyl]-1,3,4-thiadiazol-2-yl}-2-(3,7,11-trimethyldodeca-2,6,10-triene-1-yl-thio)benzamide		Inhibition of Macromolecular Targets	Ling *et al.* 2012 [80]
43	4-{[(4-Tert-butyl-6-hydroxypyrimidin-2-yl)sulfanyl]acetyl}-2-chlorobenzene sulfonamide		Inhibition of Macromolecular Targets	Capkauskaite *et al.* 2013 [82]
44	4-(morpholine-4-yl)-2-[(oxirane-2-ylmethyl)sulfanyl]-6-phenylpyrimidine-5-carbonitrile		Inhibition of Macromolecular Targets	Fargualy *et al.* 2013 [83]
45	4-(morpholine-4-yl)-2-[(3-(morpholine-4-yl)propan-2-ol)sulfanyl]-6-phenylpyrimidine-5-carbonitrile		Inhibition of Macromolecular Targets	Fargualy *et al.* 2013 [83]
46	3-(2-(5-methoxy-1H-benzo[d]imidazol-2-ylthio)acetamido)-4-methylbenzoic acid		Inhibition of Macromolecular Targets	Rakse *et al.* 2013 [85]
47	3-(2-(5-methoxy-2-benzo[d]thiazol-2-ylthio)acetamido)-4-methylbenzoic acid		Inhibition of Macromolecular Targets	Rakse *et al.* 2013 [85]
48	5-chloro-6-[({4-oxo-8-[4-(pentafluoro-λ6-sulfanyl)phenyl]-3,4-dihydropyrazolo[1,5-a][1,3,5]triazin-2-yl}sulfanyl)methyl]pyrimidine-2,4(1H,3H)-dione		Inhibition of Macromolecular Targets	Sun *et al.* 2013 [86]

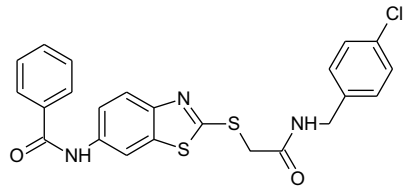
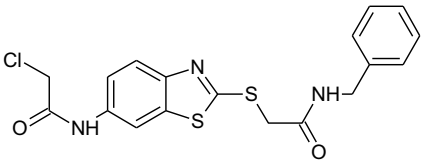
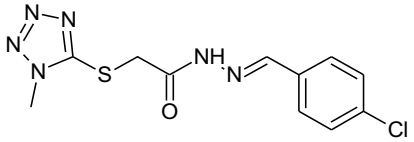
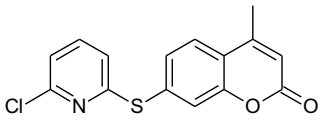
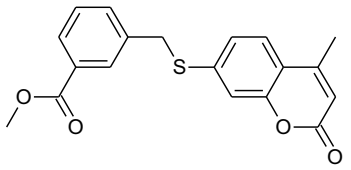
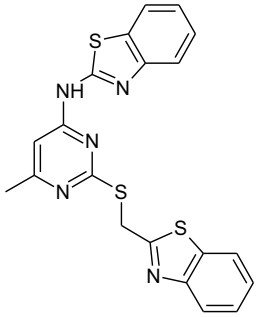
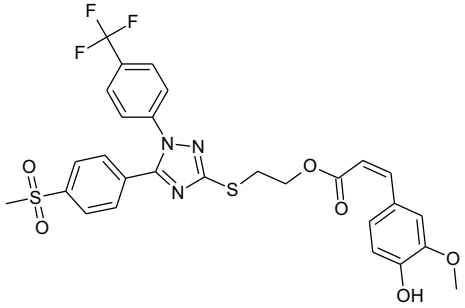
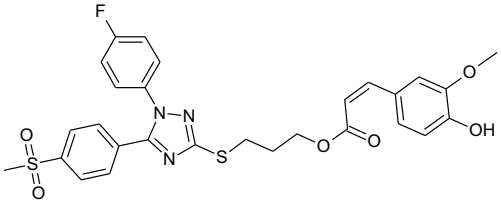
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
49	3-{[1-(2,6-dichloro-3-fluorophenyl)ethyl]sulfanyl}-5-[1-(piperidin-4-yl)-1H-pyrazol-4-yl]pyridin-2-amine		Inhibition of Macromolecular Targets	Zhang *et al.* 2013 [87]
50	1-(2-Benzylthio-4-chloro-5-methylbenzenesulfonyl)-3-(2-sulfamoyl-1,3,4-thiadiazol-5-yl)guanidine		Inhibition of Macromolecular Targets	Zolnowska *et al.* 2014 [88]
51	1-{[5-(4-Chlorobenzyl)sulfanyl-4-ethyl-4H-1,2,4-triazole-3-yl]methyl}-1,8-diethyl-tetrahydropyrano[3,4-b]indole		Inhibition of Macromolecular Targets	Çoruh *et al.* 2018 [89]
52	1-{[5-(4-nitrobenzyl)sulfanyl-4-phenyl-4H-1,2,4-triazole-3-yl]methyl}-1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole		Inhibition of Macromolecular Targets	Çoruh *et al.* 2018 [89]
53	3-benzyl-2-[(2,4-dinitrophenyl)sulfanyl]-6-iodoquinazoline-4(3H)-thione		Leukemia	Abdelhamed *et al.* 2001 [90]
54	3-[(1,4-dioxo-1,4-dihydronaphthalen-2-yl)sulfanyl]-*N,N*-dimethylpropanamide		Leukemia	Tandon *et al.* 2004 [92]

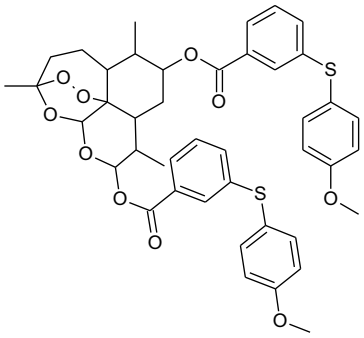
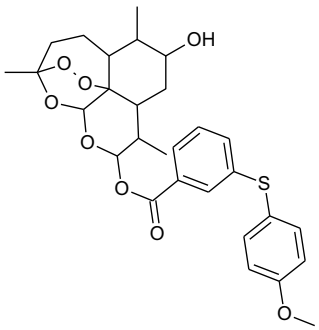
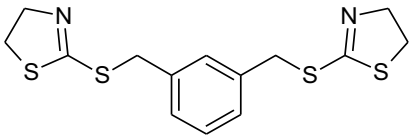
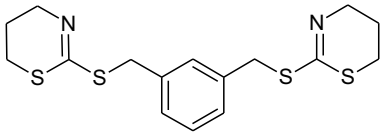
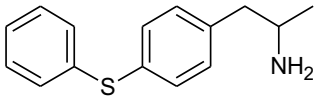
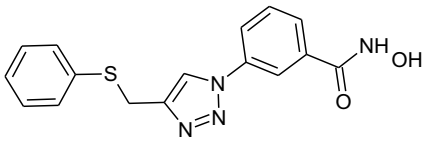
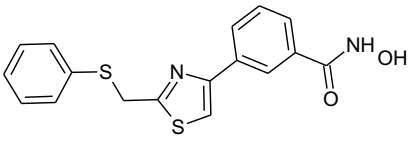
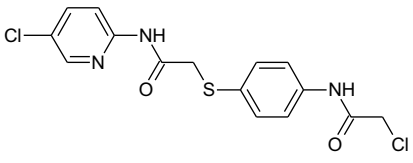
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
55	8-[3-(piperidino)propyl]-4,10-dimethyl-9-phenyl-6-(methylsulfanyl)-3,4-dihydropyrimido [1,2-c]pyrrolo[3,2-e]pyrimidin-2(8H)-one		Leukemia	Lauria *et al.* 2012 [93]
56	7-(3-Chloropropyl)-9-methyl-5-(methylsulfanyl)-8-phenyl-3H-imidazo[1,2-c]pyrrolo[3,2-e]pyrimidin-2(7H)-one		Leukemia	Lauria *et al.* 2012 [93]
57	5-(3-methylphenyl)-4H-1,2,4-triazol-3-yl 3-[4-(2-pyridyl)piperazino]propyl sulfide		Leukemia	Murty *et al.* 2012 [94]
58	5-(3-chlorophenyl)-4H-1,2,4-triazol-3-yl 3-[4-(2-pyrimidinyl)piperazino]propyl sulfide		Leukemia	Murty *et al.* 2012 [94]
59	ethyl 4-(3-chlorophenyl)-2-(((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)thio)-6-methyl-1,4-dihydropyrimidine-5-carboxylate		Leukemia	Regap *et al.* 2017 [96]
60	ethyl 2-(((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)thio)-4-(2,4-dichlorophenyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate		Leukemia	Regap *et al.* 2017 [96]

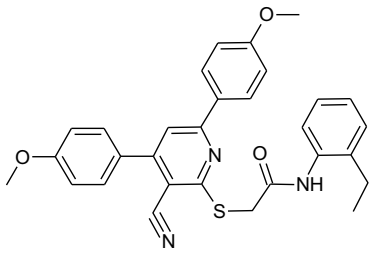
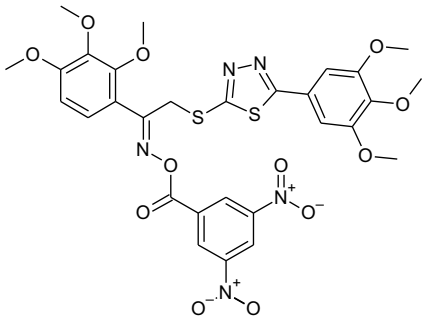
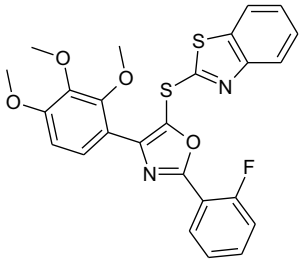
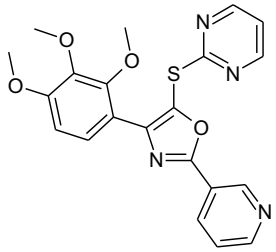
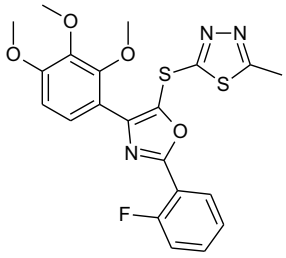
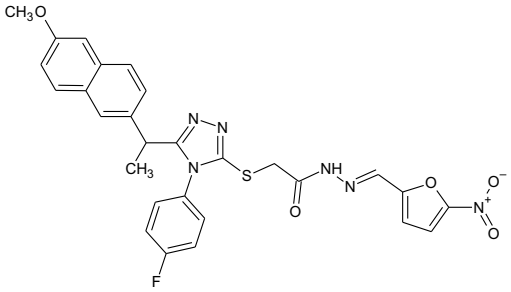
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
61	*N*-[2-({2-[(4-chlorobenzyl)amino]-2-oxoethyl}sulfanyl)-1,3-benzothiazol-6-yl]-2-methoxybenzamide		Liver Carcinoma	Wang *et al.* 2011 [99]
62	*N*-(2-{[2-(benzylamino)-2-oxoethyl]sulfanyl}-1,3-benzothiazol-6-yl)-2-chloroacetamide		Liver Carcinoma	Wang *et al.* 2011 [99]
63	*N*'-[(E)-(4-chlorophenyl)methylidene]-2-[(1-methyl-1H-tetrazol-5-yl)sulfanyl]acetohydrazide		Lung Carcinoma	Altıntop *et al.* 2012 [102]
64	7-[(6-chloropyridin-2-yl)sulfanyl]-4-methyl-2H-chromen-2-one		Lung Carcinoma	Chen *et al.* 2012 [103]
65	methyl 3-{[(4-methyl-2-oxo-2H-chromen-7-yl)sulfanyl]methyl}benzoate		Lung Carcinoma	Chen *et al.* 2012 [103]
66	bis benzothiazole *N*-(2-((benzothiazol-2-yl)methylthio)-6-methylpyrimidin-4-yl)benzo-thiazol-2-amine		Lung Carcinoma	Seeniah *et al.* 2014 [104]
67	2-((5-(4-(methylsulfonyl)phenyl)-1-(4-trifluoromethylphenyl)-1H-1,2,4-triazol-3-yl)thio)ethyl-3-(3,4-dihydroxyphenyl)acrylate		Lung Carcinoma	Cai *et al*. 2016 [105]
68	2-((5-(4-(methylsulfonyl)phenyl)-1-(4-fluorophenyl)-1H-1,2,4-triazol-3-yl)thio)ethyl-3-(3-methoxy-4-hydroxyphenyl)acrylate		Lung Carcinoma	Cai *et al.* 2016 [105]

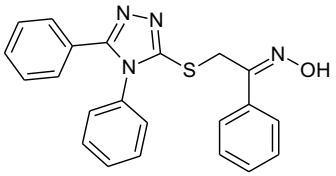
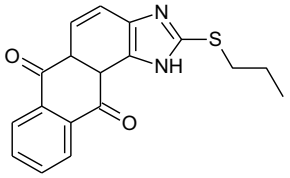
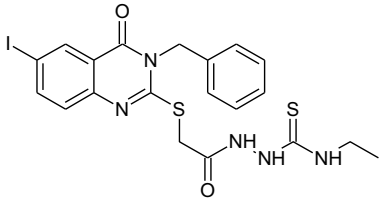
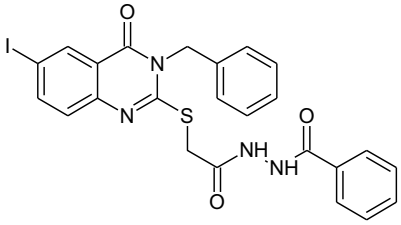
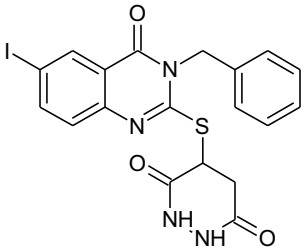
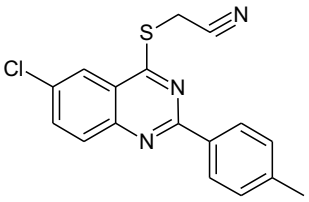
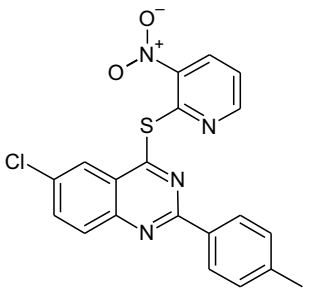
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
69	dihydroartemisinin 9α,12α-di-[3-(p-methoxyphenyl)thio]-benzoate		Lung Carcinoma	Xu *et al.* 2016 [106]
70	9α-hydroxy-dihydroartemisinin 12α-[3-(p-methoxyphenyl)thio]-benzoate		Lung Carcinoma	Xu *et al.* 2016 [106]
71	2,2'-[Benzene-1,3-diylbis(methanediylsulfanediyl)]bis(4,5-dihydro-1,3-thiazole)		Lung Carcinoma	Wang *et al.* 2012 [107]
72	2,2'-[benzene-1,3-diylbis(methanediylsulfanediyl)]bis(5,6-dihydro-4H-1,3-thiazine)		Lung Carcinoma	Wang *et al.* 2012 [107]
73	1-[4-(Phenylsulfanyl)phenyl] propan-2-amine		Lymphoma	Cloonan *et al.* 2009 [36]
74	*N*-hydroxy-3-{4-[(phenylsulfanyl) methyl]-1H-1,2,3-triazol-1-yl}benzamide		Lymphoma	Suzuki *et al.* 2014 [109]
75	*N*-hydroxy-3-{2-[(phenylsulfanyl) methyl]-1,3-thiazol-4-yl}benzamide		Lymphoma	Suzuki *et al.* 2014 [109]
76	2-chloro-*N*-[4-({2-[(5-chloropyridin-2-yl)amino]-2-oxoethyl}sulfanyl) phenyl]acetamide		Melanoma	Zhao *et al.* 2013 [110]

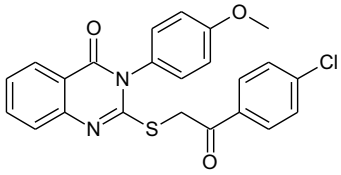
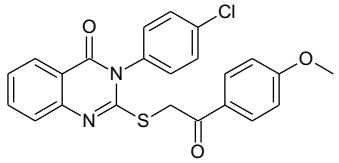
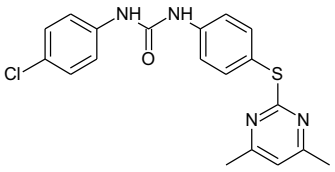
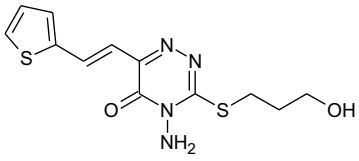
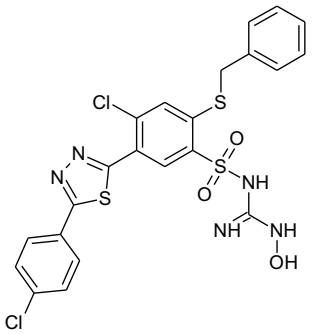
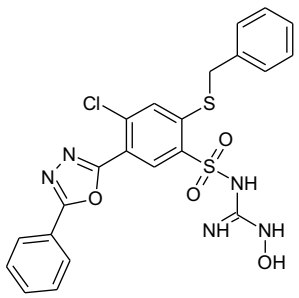
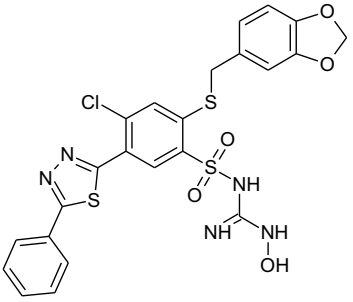
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
77	2-[(3-Cyano-4,6-bis(4-methoxyphenyl)pyridine-2-yl)sulfanyl]-*N*-(2-ethylphenyl)acetamide		Osteocarcinoma	Cui *et al.* 2016 [111]
78	1-(2,3,4-Trimethoxyphenyl)-2-{[5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazol-2-yl]thio}ethanone O-(3,5-dinitrobenzoyl)-oxime		Prostate Cancer	Xue *et al.* 2006 [114]
79	2-(2-(2-fluorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-yl-thio)benzo[d]thiazole		Prostate Cancer	Liu *et al.* 2009 [116]
80	2-(2-(pyridine-3-yl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-yl-thio)pyrimidine		Prostate Cancer	Liu *et al.* 2009 [116]
81	2-(2-(2-fluorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-yl-thio)-5-methyl-1,3,4-thiadiazole		Prostate Cancer	Liu *et al.* 2009 [116]
82	(S)-2- {[5- [1- (6-methoxynaphthalene-2-yl)ethyl]-4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl]sulfanyl}-*N*'-[(5-nitrofuran-2-yl)methylidene] acetohydrazide		Prostate Cancer	Han *et al.* 2019 [117]

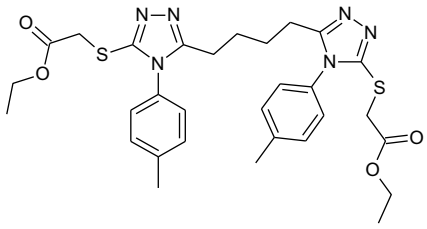
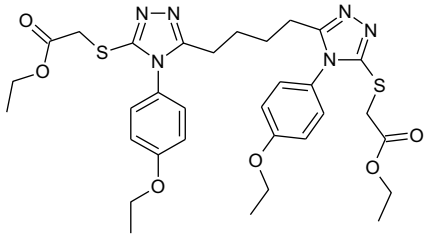
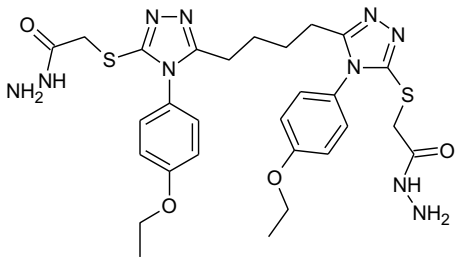
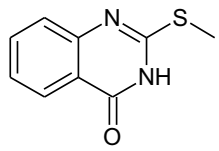
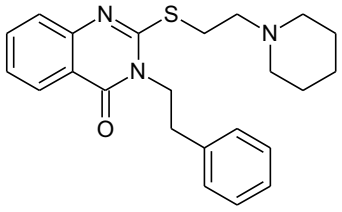
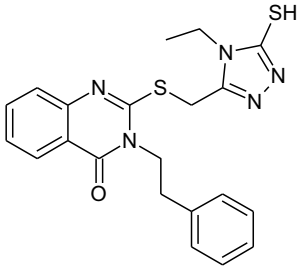
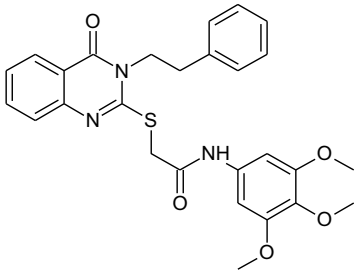
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
83	2-[(4,5-diphenyl-4H-1,2,4-triazol-3-yl)sulfanyl]-*N*-hydroxy-1-phenylethanimine		Renal Carcino-ma	Abdelaziz *et al.* 2013 [122]
84	2-(propylthio)-1H-anthra[1,2-d]imidazole-6,11-dione		Renal Carcino-ma	Chen *et al*. 2013 [54]
85	*N*'-[(3-Benzyl-4-oxo-6-iodo-3H-quinazoline-2-yl)thioacetyl]-N3-ethylthio semicarbazide		Anti-cancer effects for multi cancer cell lines	Khalil *et al*. 2003 [123]
86	*N*-benzoyl-N'-[2-(3-benzyl-4-oxo-6-iodo-3H-quinazoline-2-yl)thioacetyl] hydrazine		Anti-cancer effects for multi cancer cell lines	Khalil *et al.* 2003 [123]
87	2-[(3,6-dioxo-pyridazine-4-yl)thio]-3-benzyl-4-oxo-6-iodo-3H-quinazoline		Anti-cancer effects for multi cancer cell lines	Khalil *et al.* 2003 [123]
88	{[6-chloro-2-(4-methylphenyl)quinazolin-4-yl]sulfanyl}acetonitrile		Anti-cancer effects for multi cancer cell lines	El-Azab *et al.* 2010 [124]
89	6-chloro-2-(4-methylphenyl)-4-[(3-nitropyridin-2-yl)sulfanyl] quinazoline		Anti-cancer effects for multi cancer cell lines	El-Azab *et al.* 2010 [124]

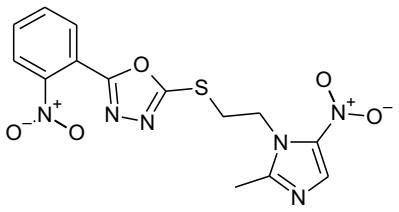
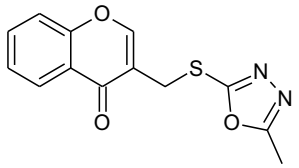
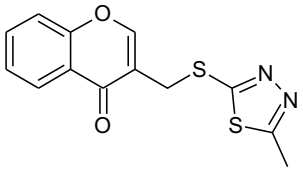
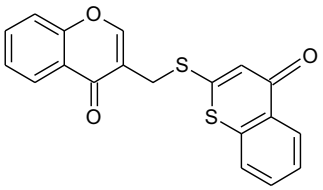
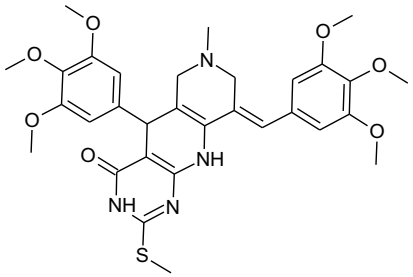
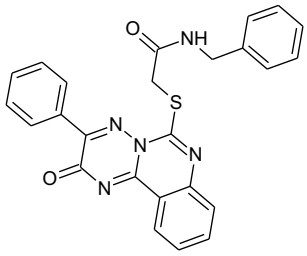
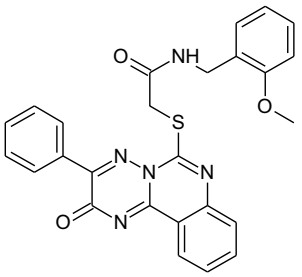
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
90	2-{[2-(4-chlorophenyl)-2-oxoethyl]sulfanyl}-3-(4-methoxyphenyl)quinazoline-4(3H)-one		Anti-cancer effects for multi cancer cell lines	Abdel-Gawad *et al.* 2010 [125]
91	3-(4-chlorophenyl)-2-{[2-(4-methoxyphenyl)-2-oxoethyl]sulfanyl}quinazolin-4(3H)-one		Anti-cancer effects for multi cancer cell lines	Abdel-Gawad *et al.* 2010 [125]
92	1-(4-chlorophenyl)-3-{4-[(4,6-dimethylpyrimidin-2-yl)sulfanyl]phenyl}urea		Anti-cancer effects for multi cancer cell lines	Jin *et al.* 2011 [126]
93	4-amino-3-[(3-hydroxypropyl)sulfanyl]-6-[(E)-2-(thiophene-2-yl)ethenyl]-1,2,4-triazin-5(4H)-one		Anti-cancer effects for multi cancer cell lines	Saad *et al*. 2011 [127]
94	1-{2-benzylthio-4-chloro-5-[5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl]benzenesulfonyl}-3-hydroxyguanidine		Anti-cancer effects for multi cancer cell lines	Brozewicz *et al.* 2012 [128]
95	1-[2-benzylthio-4-chloro-5-(3-phenyl-1,2,4-oxadiazol-5-yl)benzenesulfonyl]-3-hydroxyguanidine		Anti-cancer effects for multi cancer cell lines	Brozewicz *et al.* 2012 [128]
96	1-{2-[(1,3-benzodioxol-5-yl)methylthio]-4-chloro-5-(5-phenyl-1,3,4-thiadiazol-2-yl)benzenesulfonyl}-3-hydroxyguanidine		Anti-cancer effects for multi cancer cell lines	Brozewicz *et al.* 2012 [128]

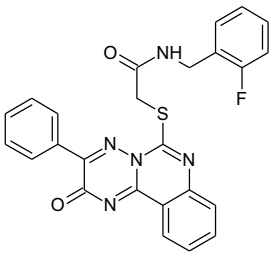
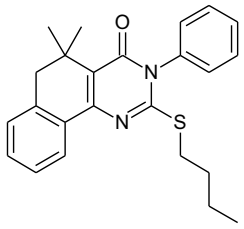
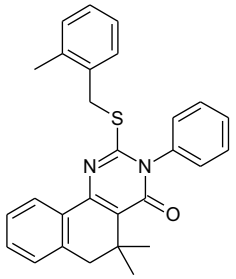
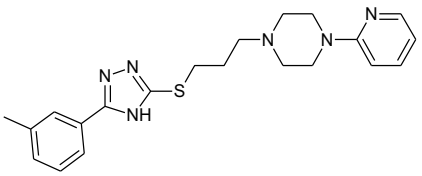
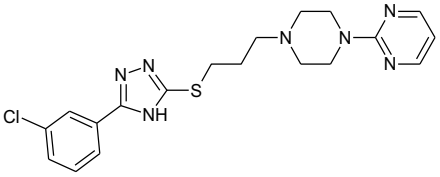
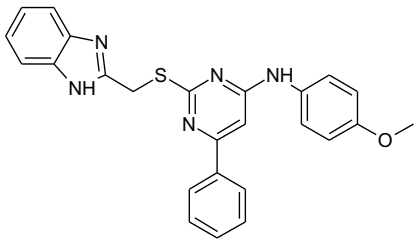
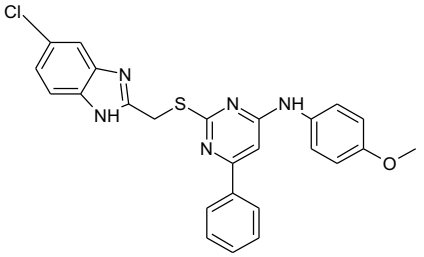
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
97	1,4-bis[5-(carbethoxy-methyl)-thio-4-(p-tolyl)-1,2,4-triazol-3-yl]-butane		Anti-cancer effects for multi cancer cell lines	Purohit *et al.* 2012 [129]
98	1,4-bis[5-(carbethoxy-methyl)-thio-4-(p-ethoxyphenyl)-1,2,4-triazol-3-yl]-butane		Anti-cancer effects for multi cancer cell lines	Purohit *et al.* 2012 [129]
99	1,4-bis(5-[hydrazinocarbonyl methylthio]-4-p-ethoxyphenyl-1,2,4-triazol-3-yl)butane		Anti-cancer effects for multi cancer cell lines	Purohit *et al.* 2012 [129]
100	2-(methylsulfanyl)quinazoline-4(3H)-one		Anti-cancer effects for multi cancer cell lines	Alanazi *et al.* 2013 [28]
101	3-Phenethyl-2-[2-(piperidin-1-yl)ethylthio]quinazoline-4(3H)-one		Anti-cancer effects for multi cancer cell lines	Alanazi *et al.* 2013 [28]
102	2-[(4-ethyl-5-mercapto-4H-1,2,4-triazol-3-yl)methylthio]-3-phenethylquinazolin-4(3H)-one		Anti-cancer effects for multi cancer cell lines	Alanazi *et al.* 2013 [28]
103	2-[(3-Phenylethyl-4-oxo-3,4-dihydroquinazolin-2-yl)sulfanyl]-*N*-(3,4,5-trimethoxyphenyl)acetamide		Anti-cancer effects for multi cancer cell lines	Alsuwaidan *et al.* 2013 [130]

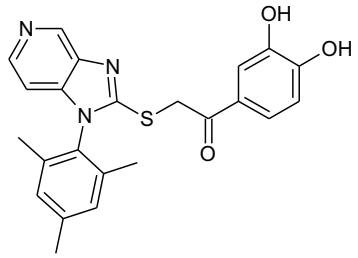
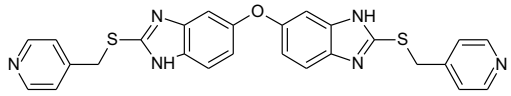
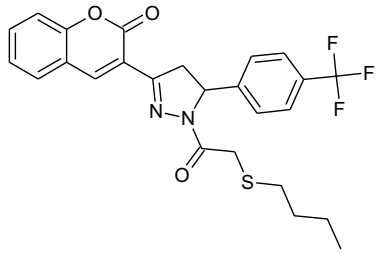
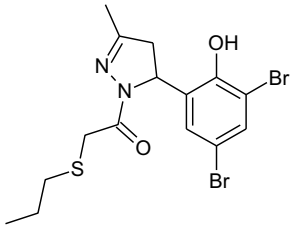
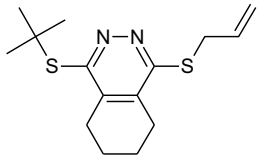
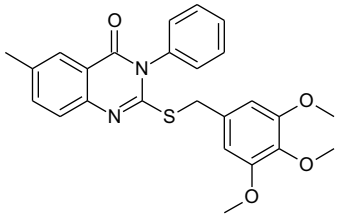
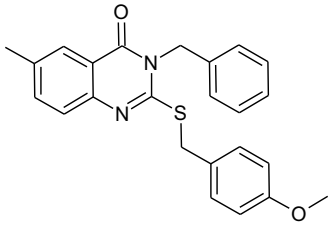
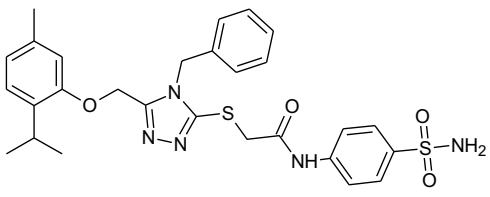
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
104	2-{[2-(2-methyl-5-nitro-1H-imidazole-1-yl)ethyl]sulfanyl}-5-(2-nitrophenyl)-1,3,4-oxadiazole		Anti-cancer effects for multi cancer cell lines	Du *et al.* 2013 [131]
105	3-{[(5-methyl-1,3,4-oxadiazol-2-yl)sulfanyl]methyl}-4H-chromen-4-one		Anti-cancer effects for multi cancer cell lines	Huang *et al.* 2013 [132]
106	3-{[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl}-4H-chromen-4-one		Anti-cancer effects for multi cancer cell lines	Huang *et al.* 2013 [132]
107	3-{[(4-oxo-4H-thiochromen-2-yl)sulfanyl]methyl}-4H-chromen-4-one		Anti-cancer effects for multi cancer cell lines	Huang *et al.* 2013 [132]
108	7-methyl-2-(methylthio)-9-(3,4,5-trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one		Anti-cancer effects for multi cancer cell lines	Insuasty *et al.* 2013 [133]
109	*N*-benzyl-2-[(3-phenyl-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazoline-6-yl)thio]acetamides		Anti-cancer effects for multi cancer cell lines	Kovalenko *et al.* 2013 [135]
110	*N*-(2-methoxybenzyl)-2-[(3-phenyl-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazoline-6-yl)thio]acetamides		Anti-cancer effects for multi cancer cell lines	Kovalenko *et al.* 2013 [135]

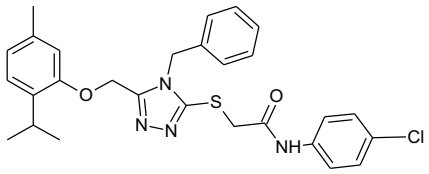
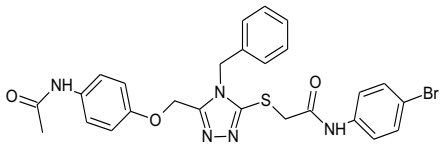
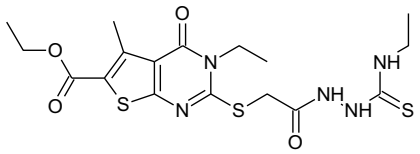
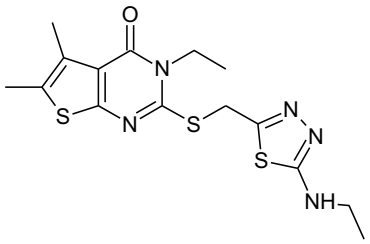
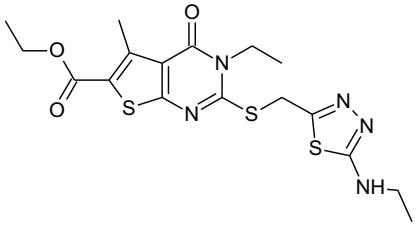
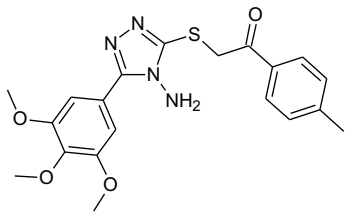
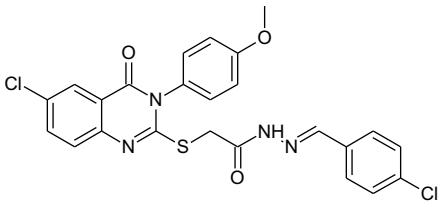
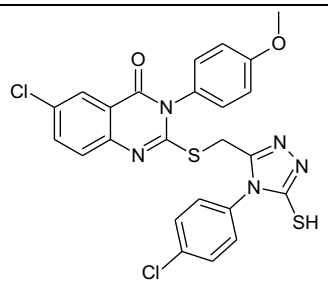
(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
111	*N*-(2-fluorobenzyl)-2-[(3-phenyl-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazoline-6-yl)thio]acetamides		Anti-cancer effects for multi cancer cell lines	Kovalenko *et al.* 2013 [135]
112	5,5-dimethyl-3-phenyl-2-sulfanylbuthyl-5,6-dihydrobenzo[h]quinazolin-4(3H)-one		Anti-cancer effects for multi cancer cell lines	Markosyan *et al.* 2014 [137]
113	5,5-dimethyl-3-phenyl-2-[(2-methylbenzyl)sulfanyl]-5,6-dihydrobenzo[h]quinazolin-4(3H)-one		Anti-cancer effects for multi cancer cell lines	Markosyan *et al.* 2014 [137]
114	5-(3-methylphenyl)-4H-1,2,4-triazol-3-yl-3-[4-(2-pyridyl)piperazino]propylsulfide		Anti-cancer effects for multi cancer cell lines	Murty *et al.* 2014 [138]
115	5-(3-chlorophenyl)-4H-1,2,4-triazol-3-yl-3-[4-(2-pyridyl)piperazino]propylsulfide		Anti-cancer effects for multi cancer cell lines	Murty *et al.* 2014 [138]
116	2-[(1H-benzimidazole-2-ylmethyl)sulfanyl]-6-phenyl-*N*-(4-methoxyphenyl)pyrimidine-4-amine		Anti-cancer effects for multi cancer cell lines	Shao *et al*. 2014 [139]
117	2-{[(5-chloro-1H-benzimidazole-2-yl)methyl]sulfanyl}-6-phenyl-*N*-(4-methoxyphenyl)pyrimidine-4-amine		Anti-cancer effects for multi cancer cell lines	Shao *et al*. 2014 [139]

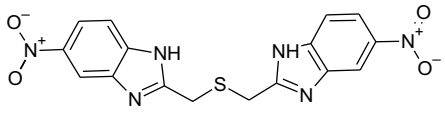
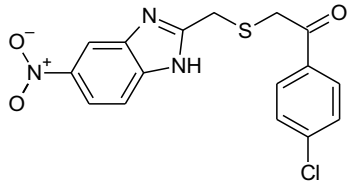
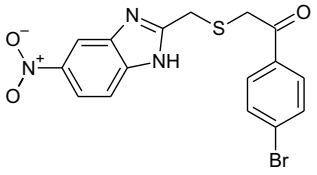
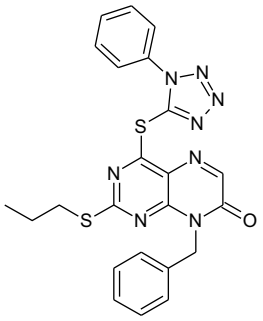
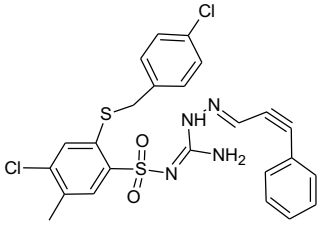
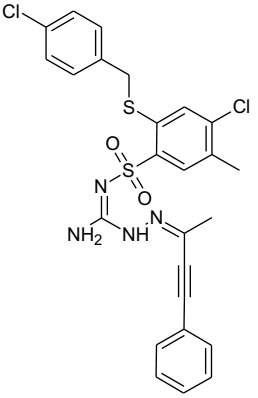
(Table 1) contd…

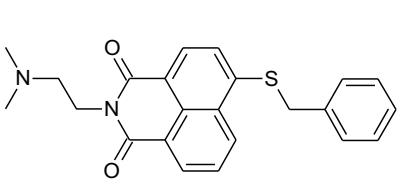
Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
118	1-(3,4-dihydroxyphenyl)-2-((1-mesityl-1H-imidazo[4,5-c] pyridin-2-yl)thio)ethanone		Anti-cancer effects for multi cancer cell lines	Song *et al.* 2014 [140]
119	2,2'-bis-pyrid-4-yl methylsulfanyl-5,5'-bis-1H,10H-benzimidazole ether		Anti-cancer effects for multi cancer cell lines	Wang *et al.* 2014 [141]
120	3-(1-(2-(butylthio)acetyl)-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-3-yl)-2H-chromen-2-one		Anti-cancer effects for multi cancer cell lines	Wu *et al.* 2014 [142]
121	1-(5-(3,5-dibromo-2-hydroxyphenyl)-3-methyl-4,5-dihydropyrazol-1-yl)-2-(propylthio)ethanone		Anti-cancer effects for multi cancer cell lines	Wu *et al.* 2014 [142]
122	1-(tert-butylsulfanyl)-4-(prop-2-en-1-ylsulfanyl)-5,6,7,8-tetrahydrophthalazine		Anti-cancer effects for multi cancer cell lines	Park *et al.* 2015 [143]
123	2-[(3,4,5-trimethoxybenzyl)-thio]-3-phenyl-6-methyl-quinazolin-4(3H)-one		Anti-cancer effects for multi cancer cell lines	El-Messery *et al.* 2016 [144]
124	2-[(4-methoxy-benzyl)-thio]-3-benzyl-6-methyl-quinazolin-4(3H)-one		Anti-cancer effects for multi cancer cell lines	El-Messery *et al.* 2016 [144]
125	2-{[3-[[5-methyl-2-(propan-2-yl)phenoxy]methyl)-4-benzyl-4,5-dihydro-1H-1,2,4-triazol-5-yl]sulfanyl}-*N*-(4-sulfamoylphenyl)acetamide		Anti-cancer effects for multi cancer cell lines	Kulabaş *et al.* 2016 [145]

(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
126	2-{[3-[[5-methyl-2-(propan-2-yl)phenoxy]methyl]-4-benzyl-4,5-dihydro-1H-1,2,4-triazol-5-yl] sulfanyl}-*N*-(4-chlorophenyl)acetamide		Anti-cancer effects for multi cancer cell lines	Kulabaş *et al.* 2016 [145]
127	2-[(3-{[4-(acetylamino)phenoxy]methyl}-4-benzyl-4,5-dihydro-1H-1,2,4-triazol-5-yl)sulfanyl]-*N*-(4-bromophenyl)acetamide		Anti-cancer effects for multi cancer cell lines	Kulabaş *et al.* 2016 [145]
128	Ethyl 3-ethyl-2-(((2-(2-(ethylamino)-2-thioxoacetyl)hydrazinyl)methyl)thio)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate		Anti-cancer effects for multi cancer cell lines	Mavrova *et al.* 2016 [146]
129	3-ethyl-2-(((5-(ethylamino)-1,3,4-thiadiazol-2-yl)methyl)thio)-5,6-dimethylthieno [2,3-d] pyrimidin-4(3H)-one		Anti-cancer effects for multi cancer cell lines	Mavrova *et al.* 2016 [146]
130	ethyl 3-ethyl-2-(((5-(ethylamino)-1,3,4-thiadiazol-2-yl)methyl)thio)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate		Anti-cancer effects for multi cancer cell lines	Mavrova *et al.* 2016 [146]
131	2-[(4-amino-5-(3,4,5-trimethoxyphenyl)-4H-1,2,4-triazol-3-yl)sulfanyl]-1-(4-methylphenyl)ethanone		Anti-cancer effects for multi cancer cell lines	Zhao *et al.* 2016 [149]
132	*N*'-[4-chlorobenzylidene]-2-[6-chloro-3-(4-methoxy-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl-thio]acetohydrazide		Anti-cancer effects for multi cancer cell lines	El-Gazzar *et al.* 2017 [151]
133	6-chloro-2-((4-(4-chlorophenyl)-5-mercapto-4H-1,2,4-triazol-3-yl)methylthio)-3-(4-methoxyphenyl)quinazolin-4(3H)-one		Anti-cancer effects for multi cancer cell lines	El-Gazzar *et al.* 2017 [151]

(Table 1) contd…

Comp. Number	Name of Compounds	Structure of Compounds	Cancer Activity	References
134	2,2'-(sulfanediyldimethanediyl)bis(5-nitro-1H-benzimidazole)		Anti-cancer effects for multi cancer cell lines	El-Gohary *et al.* 2017 [71]
135	1-(4-chlorophenyl)-2-{[(5-nitro-1H-benzimidazole-2-yl)methyl]sulfanyl}ethanone		Anti-cancer effects for multi cancer cell lines	El-Gohary *et al.* 2017 [71]
136	1-(4-bromophenyl)-2-{[(5-nitro-1H-benzimidazole-2-yl)methyl]sulfanyl}ethanone		Anti-cancer effects for multi cancer cell lines	El-Gohary *et al.* 2017 [71]
137	8-benzyl-4-[(1-phenyl-1H-tetrazol-5-yl)sulfanyl]-2-(propylsulfanyl)pteridine-7(8H)-one		Anti-cancer effects for multi cancer cell lines	Li *et al.* 2017 [152]
138	2-{4-chloro-2-[(4-chlorobenzyl)thio]-5-methylbenzenesulfonyl}-3-(3-phenylprop-2-ynylideneamino)guanidine		Anti-cancer effects for multi cancer cell lines	Pogorzelska *et al.* 2017 [153]
139	2-{4-chloro-2-[(4-chlorobenzyl)thio]-5-methylbenzenesulfonyl}-3-(1-methyl-3-phenylprop-2-ynylideneamino)guanidine		Anti-cancer effects for multi cancer cell lines	Pogorzelska *et al.* 2017 [153]



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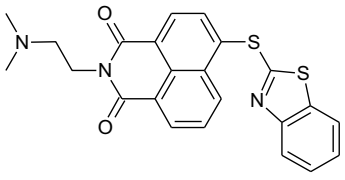
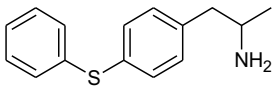


(4)

able as options to provide potential benefits in the treatment of photodynamic tumors. In MCF-7 breast cancer cells, the antiproliferative impacts of compounds have been evaluated. These compounds showed IC_{50} values between 1.9 and 4.6 μM, and were found to be extremely active [35].

Cloonan *et al*. synthesized a new category of anti-cancer agents in the serotonin-carrier activity of sulfur-substituted α-alkyl phenethylamines. In addition to various pharmacological applications in cancer treatment, it seems likely that some serotonin reuptake carriers (SERT) ligands may act as apoptotic agents. New, structurally diverse, various 4-MTA analogs have been synthesized. Their potential SERT-dependent antiproliferative and cytotoxic activities could be detected since many of the analogs showed SERT-binding activity. A few derivatives showed anti-tumor impacts on lymphoma, breast cancer, and leukemia cell lines. At the same time, there was no direct relationship found between these two activities, thus displaying the potential to be feasible chemotherapeutic agents. Antiproliferative activity of 1-[4-(phenylsulfanyl)phenyl]propan-2-amine **(5)** has been investigated. It demonstrated potent activity in three breast cancer cell lines with a 50 μM IC_{50} value [36]. Semicarbazide compounds have been explored as a strong apoptosis inducer *via* cell-based HTS analysis. Growth inhibition analysis of T47D cells, caspase activation analysis with 60 nM EC_{50} value, and SAR analysis value of 62 nM at GI_{50} led to exploring the aqueous soluble compounds. In an MX-1 breast tumor pattern, compound **(6)** was discovered to be an inhibitor of tubulin polymerization. In T47D breast cancer cells, EC_{50} of (2-(2,5-dimethoxyphenylthio)-6-methoxybenzylideneamino)guanidine **(6)** was 52 nM [37].



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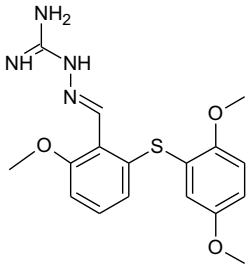
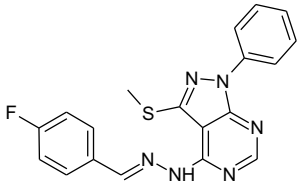


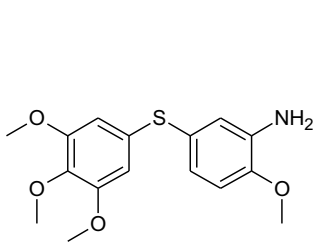
(6)

Alafeefy *et al.* synthesized a series of some novel quinazoline derivatives and evaluated their *in vitro* antitumor activity against four cancer cell lines, including HeLa (cervix), HepG2 (liver), HCT-8 (colon), and MCF-7 (breast). Twelve compounds showed good cytotoxicity against the MCF-7 cell line. The best cytotoxic results were obtained with compounds carrying the allyl and/or benzyl moiety in the 2 and/or 3 positions of the quinazoline nucleus, and some alkyl halides were found to afford suitable *S*-alkylthioether derivatives; the 2-mercapto function of the compounds was then alkylated with some selected α-halo ketones [38]. El-Hamid *et al.* synthesized a series of novel pyrazolo[3,4-d]pyrimidines derivatives having methylsulphanyl at 3rd positions. Against human breast cancer cell line MCF-7, they explored the cytotoxic activity of the synthesized analogs. Compared to that of doxorubicin, some of the test compounds displayed strong anti-cancer activity. 4-[(2*E*)-2-(4-fluorobenzylidene)hydrazinyl]-3-(methylsulfanyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine **(7)** was the most effective compound reported in the study with IC_{50} value of 7.5 μM [39].



(7)

Dos Santos *et al.* designed intermediate groups of combretastatin A-4 (CA-4) analogs in a certain way using selenium and sulfur atoms between the aromatic rings. They described the preparation of two sulfur analogs of CA-4. For the evaluation of cytotoxic activity in human cancer cells and inhibition of tubulin polymerization, as well as several synthetic mediators, they appraised all synthesized compounds. 2-Methoxy-5-[(3,4,5-trimethoxyphenyl)sulfanyl] aniline **(8)** showed the maximum activity at nM concentration (0.008 μM) against MCF-7 breast cancer cells [40]. In another study, 71 new arylthioindole/aroylindole compounds were synthesized as potential anti-cancer agents with different (hetero) cyclic substituents. As an inhibitor of cell expansion, 2-(1H-imidazole-1-yl)-3-[(3,4,5-trimethoxyphenyl)sulfanyl]-1H-indole **(9)** was found to be extremely effective. It displayed IC_{50} value of 1.0 nM in MCF-7 cells. It was quite active during the entire screening of cancer cells [41].



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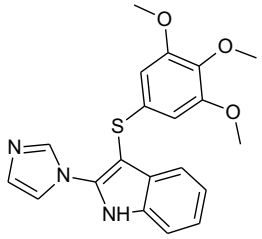
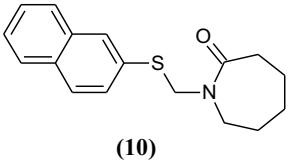


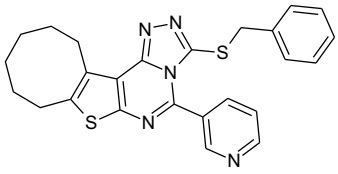
(9)

Marciniek *et al*. defined the synthesis of a novel group of halogenopropargylseleno, halogenopropargylthio, and dipropargylthio quinoline complexities. The activity of all synthesized molecules was defined by the WST-1 test to prevent the proliferation of MCF-7, T-47D, SNB-19, and MDA-MB-231 cell lines. Because of the existence of thiopropargyl groups in the 7- and 4-quinoline positions, dipropargylthioquinoline exhibited the highest antiproliferative activity than cisplatin in MCF-7 cells [42]. With formaldehyde and thiols in water, *via* three-component coupling (3CC), Mudududdla *et al.* defined an effective trifluoroacetic acid-catalyzed thioalkylmethylation and thiophenylmethylation of lactams, phenols, and isatins. The naphthyl 1-[(naphthalene-2-ylsulfanyl)methyl]azepan-2-one **(10)** showed considerable cytotoxic activity. It stimulated apoptosis in MCF-7 breast cancer cells [43].



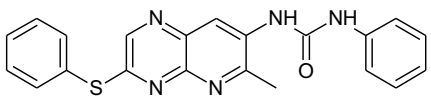
(10)

A novel series of twenty-four 2-substitutedhexahydrocycloocta[4,5]thieno[2,3-d]pyrimidine derivatives with distinct substituents at the C-4 position and hexahydrocycloocta[4,5]thieno[3,2-e]-1,2,4-triazolo[4,3-c]pyrimidines were synthesized and evaluated for anti-cancer activity. The anti-cancer activity of seventeen compounds was evaluated by using a two-stage protocol with 59 different human tumor cell lines. Against fifty-six human tumor cell lines, 3-(benzylthio)-5-(3-pyridyl)-8,9,10,11,12,13-hexahydrocycloocta [4,5]thieno[3,2-e]-1,2,4-triazolo[4,3-c]pyrimidine **(11)** showed strong anti-cancer activity, with a GI_{50} value ranging from 0.495 to 5.57 μM. The compound exhibited the highest selectivity towards the two cell lines belonging to breast cancer, MDA-MB-468 and T-47D, with GI_{50} values of 0.568 and 0.495 μM, respectively. This compound induced cell cycle arrest at the G2/M phase. It displayed the backlog of cells in the pre-G1 phase [44].



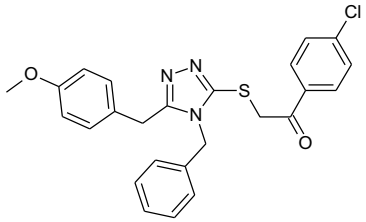
(11)

A series of newly substituted pyridopyrazine derivatives were designed and evaluated as multi-kinase inhibitors in the PI3K pathway. The targeted compounds were prepared from 6-amino-2-picoline, following nitration, and on reduction, they were transformed to substituted 6-methyl-7-aminopyrido[2,3-b]pyrazines. *In vitro*, against several breast cancer cell lines, appropriate manipulation of the former amines resulted in the described analogs. Breast cancer needs medical interventions despite the improvement in antibody therapies and protein kinase inhibitors. 1-[6-Methyl-3-(phenylsulfanyl)pyrido[2,3-b]pyrazin-7-yl]-3-phenylurea **(12)** was found to inhibit the growth of xenografted tumors. The specificity of the compound was detected in a panel of 31 kinases [45].



(12)

By incorporating diverse aromatic (or heteroaromatic) substituents into C-12 or 14-OH, a series of new thioether andrographolide analogs were synthesized and evaluated for inhibitory activity toward cancer cells bearing MCF-7, MDA-MB-231, and A549, *in vitro*. Against MCF-7, two compounds demonstrated perfect activity with an IC_{50} value of 0.7 and 0.6 μM, respectively. Liu *et al*. bound the aromatic (or heteroaromatic) thioether moiety to 14-OH utilizing an ester bond, as the esterification of 14-OH could increase anti-tumor activity. Heteroaromatic thioether displayed better activity compared to the aromatic thioether [46]. Twenty-nine novel 1,2,4-triazoles and some derived thiazolothiadiazoles were defined and synthesized by Rostom *et al.* 2-{[4-Benzyl-5-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}-1-(4-chlorophenyl)ethanone **(13)** exhibited a remarkable anti-tumor potential. The other four compounds displayed significant percentage growth inhibitory activity (GI%) of tumors in the normal breast epithelial cell line MCF-10A. The same active analogs were detected for their *in vitro* Cdc25A/B phosphatase inhibitory activity. 2-{[4-Benzyl-5-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl] sulfanyl}-*N*-(4-chlorophenyl)acetamide **(14)** showed an evident inhibitory affinity against the Cdc25B isozyme (6.7 and 8.4 μM, respectively). The anti-tumor potential of the active compounds was determined by the nature of the substituent on the 3-thioether functionality. These results are consistent with the fact that thioethers have diverse chemotherapeutic activities [47].



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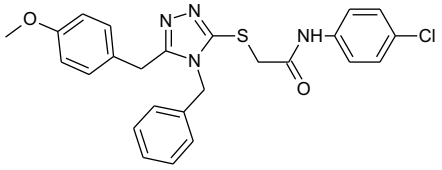
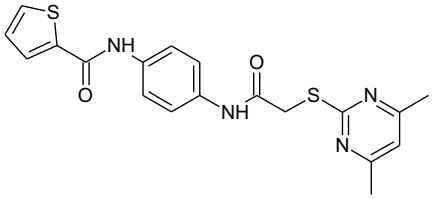


(14)

A structure-based optimization of SIRT2 inhibitors led to the synthesis of novel 2-((4,6-dimethylpyrimidin-2-yl) thio)-*N*-phenylacetamide derivatives. SAR analyses of novel synthesized derivatives led to the elucidation of several strong SIRT2 inhibitors. Dysregulation of SIRT2 is considered critical as it contributes to several human diseases, including cancer. Human sirtuin 2 (SIRT2) plays a critical role in multiple biological processes. *N*-[4-({[(4,6-dimethylpyrimidin-2-yl)sulfanyl]acetyl}amino)phenyl]thiophene-2-carboxamide **(15)** is the most active inhibitor with an IC_{50} value of 42 nM. The compound has a very good selectivity to SIRT2 over SIRT1 and SIRT3. The compound displayed a potent ability to inhibit human breast cancer cell line MCF-7. It improved the acetylation of α-tubulin in a dose-dependent manner [48].

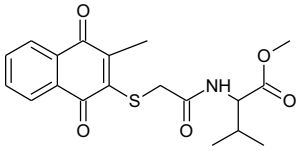


(15)

4.2. Cervical Cancer

Cervical cancer is the fourth leading cause of cancer-related mortality and the second most commonly diagnosed cancer in females after breast cancer worldwide. Chemotherapy, radical surgery, and radiotherapy are the only treatment options for women with cervical cancer [49]. With various amino acids together, a set of new naphthoquinone

amide derivatives of the bioactive quinones have been synthesized. All compounds were evaluated for their anti-cancer activity against SAS and HeLa cancer cell lines. 3D-QSAR studies showed that sulfur improved the activity against HeLa cells by closing the electron-donating group. Among the derivatives synthesized, methyl 3-methyl-2-({[(3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)sulfanyl] acetyl}amino)butanoate **(16)**, methyl ({[(3-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)sulfanyl]acetyl}amino) acetate **(17)**, methyl 2-({[(3-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)sulfanyl]acetyl}amino)propanoate **(18)** and methyl 4-({[(3-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)sulfanyl]acetyl}amino) butanoate **(19)** were the most active compounds with IC_{50} values of 16, 12, 14 and 24.5 μM, respectively. Sreelatha *et al.* designed the cytotoxic naphthoquinone amides to present thioether functionality as the side chain in the quinone ring. An amino acid moiety and the thioether group could be the cause of the activity of the derivatives. The main target was to synthesize derivatives with the amide and thioether linkage and analyze their cytotoxicity [50].



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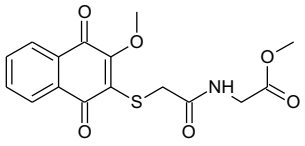

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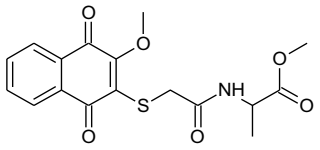

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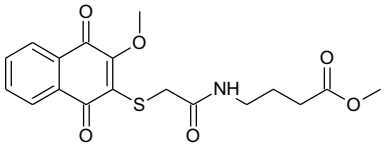
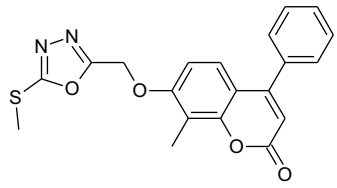


(19)

4.3. Central Nervous System (CNS) Cancer

Brain tumors continue to be one of the significant causes of mortality and morbidity worldwide. Different diseases affect the central nervous system (CNS). In the case of CNS tumors, current therapies are still not completely successful in killing tumor cells, restoring the damaged tissue, and in the case of stroke and spinal cord injury [51]. İsmail *et al*. synthesized a new series of 7-substituted-benzopyran-2-ones by associating heterocyclic rings with acetoxy or methyleneoxy linker. Against CNS Cancer (SF-295), 5-methyl thioether of 1,3,4-oxadiazole showed good activity with 21.89 % growth. In the active site with 5H links and with catalytic runs of top 1 (Arg488, Lys532 and Asn631) 5-methyl thioether, compounds 8-methyl-7-{[5-(methylsulfanyl)-1,3,4-oxadiazol-2-yl]methoxy}-4-phenyl-2H-chromen-2-one **(20)** and 8-methyl-7-{[5-(methyl sulfanyl)-1,3,4-oxadiazol-2-yl]methoxy}-4-propyl-2H-chromen-2-one **(21)** connected with each other in a significant manner [52].



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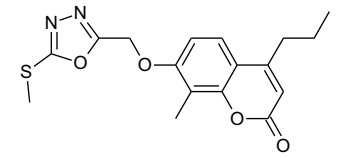
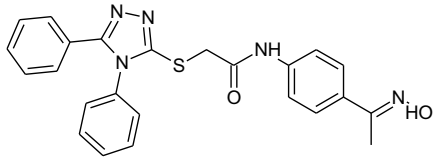


(21)

Abourahma *et al.* prepared a series of new nitric oxide (NO) donating triazole/oxime hybrids and evaluated their antiproliferative activity. When compared to their ketone intermediates and indomethacin, the prepared NO-donating oximes showed low ulcerogenic activity and were screened by histopathological investigation and calculation of the ulcer indices. Toward most of the tested cell lines, the NO-donating 2-(4,5-diphenyl-4H-[1,2,4]triazol-3-ylsulfanyl)-*N*-[4-(1-hydroxyimino-ethyl)phenyl]acetamide **(22)** and 2-[5-(3,4-dimethoxyphenyl)-4-phenyl-4H-[1,2,4]triazol-3-ylsulfanyl]-*N*-[4-(1-hydroxyiminoethyl) phenyl]acetamide **(23)** displayed notable cell growth inhibition activity. With a selectivity rate of 11.99 at the GI_{50} level towards the CNS subpanel, the compounds were found to have high selectivity. Against most of the tested cell lines bearing CNS cancer cell line SF-268, the NO-donating compound exhibited notable cell growth inhibition activity [53].



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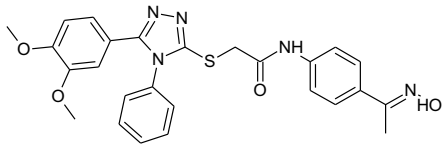
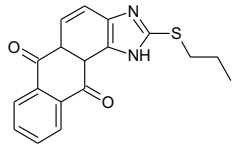


(23)

A series of 2-thio-substituted anthra[1,2-d]imidazole-6,11-diones were synthesized by utilizing fragment-based design strategies and evaluated for hTERT repressing activities and cell proliferation using NCI 60-cell panel assay. Only, 2-(propylthio)-1H-anthra[1,2-d]imidazole-6,11-dione **(24)** showed different selectivity to CNS cancer with IC_{50} value of 7.403 μM. As anti-cancer drugs, all the test compounds showed different cytotoxic and cytostatic activities exhibiting their potential application [54].

To perform anti-cancer activity screening, a novel class of tetrazole-hydrazone analogs bearing chloro-substituted phenyl derivative was synthesized. The anti-cancer activity of the compounds was evaluated against C6 and A549 tumor cell lines. For anti-cancer activity research, caspase-3

activation analysis and MTT analysis of DNA synthesis were performed. Three compounds displayed considerable anti-tumor activity [55].

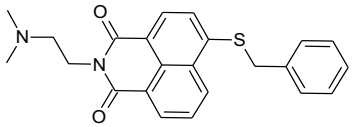


(24)

4.4. Colon Cancer

Colorectal cancer is one of the most common cancers diagnosed in males and females despite extensive screening and early diagnosis. Chemotherapy is the best among the most current therapies for colon cancer, and early-stage lesions are interrupted by surgery. More progressive lesions require both surgical and systemic cures [56].

Ott *et al.* synthesized and researched a series of sulfur-substituted naphthalimides. 6-(Benzylsulfanyl)-2-[2-(dimethylamino)ethyl]-1H-benzo[d,e]isoquinoline-1,3(2H)-dione **(25)** and 6-(1,3-benzothiazole-2-yl-sulfanyl)-2-[2-(dimethylamino)ethyl]-1H-benzo[d,e] isoquinoline-1,3(2H)-dione **(26)** were evaluated for the antiproliferative activity, and showed IC_{50} values between 1.9 and 4.6 μM in HT-29 colon carcinoma cells [36]. Zhao *et al.* drafted and synthesized twenty-two sulfur-containing shikonin compounds. Against three cancer cell lines, BEL-7402, SPC-A1, and HT-29, they studied their anti-tumor activities. Most of the synthesized analogs showed perfect cytotoxicity against HT-29 cells, according to pharmacological results. An increase in cytotoxicity was related to the entry of a thioether structure in the chain of shikonin [57].



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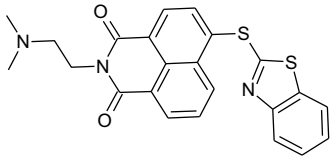

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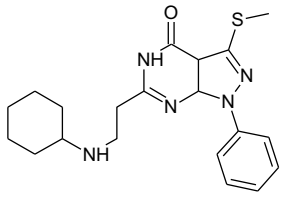
Elenany *et al*. synthesized a new series of pyrazolo[3,4-d]pyrimidine-4-one derivatives containing an aryl and an alkyl group at position 6. The anti-tumor activity of some of the recently synthesized molecules on the HCT116 human colon tumor cell line was examined *in vitro*. Most of the pilot compounds were screened for potent anti-tumor activity. Among the test compounds, particularly 6-(2-(cyclohexylamino)ethyl)-3-methylsulphanyl-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one **(27)** showed the highest activity with IC_{50} value equal to 0.47 μg/mL [58].

18 new imidazole-piperazine and imidazole-(benz)azole derivatives were synthesized for evaluation of possible anticancer activity. Toward colon (HT-29) and breast cancer (MCF-7) carcinoma cell lines, Özkay *et al.* performed the analysis of DNA synthesis, cytotoxicity (MTT), and apoptotic DNA to detect the anti-cancer activity of the analogs. 2-(4-Methyl-4H-1,2,4-triazole-3-yl)-sulfanyl-*N*-[4-(1-methyl-4,5-diphenyl-1H-imidazole-2-yl)phenyl]acetamide **(28),** 2-(1-methyl-1H-1,2,3,4-tetrazole-5-yl)-sulfanyl-*N*-[4-(1-methyl-4,5-diphenyl-1H-imidazole-2-yl)phenyl]acetamide **(29)** and 2-(5-methyl-1,2,4-thiadiazole-3-yl)-sulfanyl-*N*-[4-(1-methyl-4,5-diphenyl-1H-imidazole-2-yl)phenyl]acetamide **(30)** were the most active compounds in the series according to anti-cancer activity screening results. Towards both cancer cell lines, these compounds showed considerable cytotoxicity. These compounds caused DNA fragmentation of the HT-29 cells [59].



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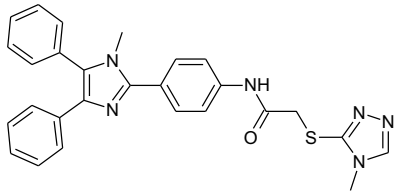

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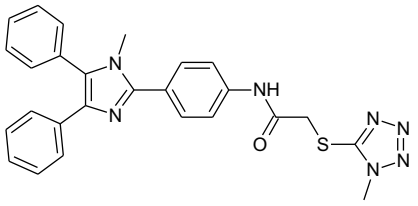

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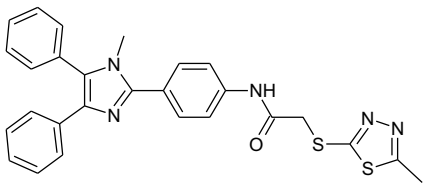

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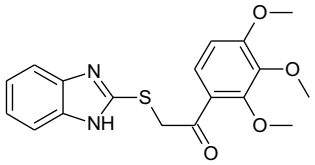
Due to the sulfur linker with heteroaryl substitution at the 5th position, novel pyrrolo[2,3-d]pyrimidines were designed and synthesized being associated with supposed pharmacophoric components as heteroaryl groups, such as benzothiazole and benzimidazole. Against the HCT116 colon cancer cell line, Tangeda *et al.* evaluated the cytotoxicity of all compounds. Through sulfur with nitrobenzimidazole and pyrimidyl heterocycles enclosed at 5th position, two compounds were found to be the strongest of all with IC_{50} values ~17.6 μM. Apoptosis induction activity among four compounds was assessed. The compounds were evaluated against colon cancer cell lines for cytotoxic activity, and their IC_{50} values were obtained. All compounds suppressed cell proliferation. In human colon cancer cell lines, a few of them induced apoptosis [60].

A series of new diaryl thiourea and thioether sorafenib derivatives were drafted and synthesized. Their antiproliferative activities were evaluated and identified against HCT116 and MDA-MB-231 cell lines. With IC_{50} = 1.8-80.4 μM, most compounds showed potent antiproliferative activity against HCT116 cells. Against two cancer cell lines, three compounds showed competitive antiproliferative activities compared to sorafenib [61]. Abdelaziz *et al.* synthesized a set of 2-((benzimidazole-2-yl)thio)-1-arylethan-1-ones to identify a powerful anti-tumor agent for cancer stem cells and a bulk of tumor cells. Against colon HT-29 cancer cell line, all compounds were evaluated for their antiproliferative activity. Flow cytometry was conducted to evaluate their inhibitory effect against cell surface expression of CD133 with a powerful cancer stem cells (CSCs) marker. 2-(1H-benzimidazole-2-ylsulfanyl)-1-(2,3,4-trimethoxyphenyl) ethanone **(31)** was found to be the most active anti-proliferative analog toward HT-29 with an IC_{50} value of 18.83 ± 1.37 μM [62].



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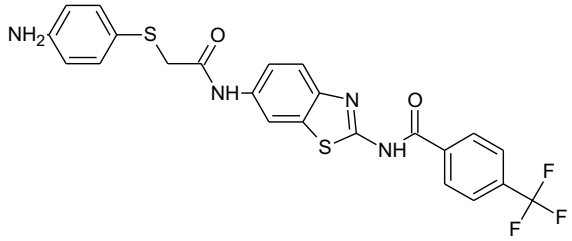
For strong non-covalent NAE inhibitors, a target-based initial screening was implemented to explore benzothiazoles. NEDD8 activating enzyme (NAE) plays a vital role in diverse cellular functions in cancers. Three compounds showed anti-tumor activity in the nanomolar range. With an IC_{50} value of 100 nM against HCT116 colon cancer cells, *N*-(6-(2-((4-aminophenyl)thio)acetamido)benzo[d]thiazol-2-yl)-4-(trifluoromethyl) benzamide (**32**) displayed excellent anticancer activity. For developing non-sulfamide NAE inhibitors, this scaffold symbolizes a promising lead. The benzyl substituted thioether was kept, and phenyl substitutions were presented on the amide side [63].



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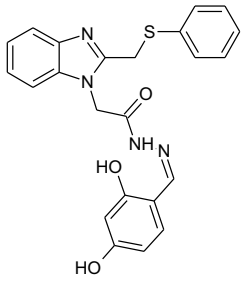
Liu *et al.* synthesized a new class of acetylhydrazone derivatives, including 2-(phenylthiomethyl)-1H-benzo-[d]-imidazole compounds. Among them, 2-[(phenylsulfanyl)methyl]-1(*N*'-[(2,4-dihydroxy phenyl) methylidene] acetohydrazide)-benzimidazole (**33**) and 2-[(phenylsulfanyl)methyl]-1(*N*'-[(2-hydroxy-5-bromophenyl)methylidene]acetohydrazide)-benzimidazole (**34**) showed perfect cancer inhibitory activity against the tested cancer cells (IC_{50} value 4-17 μM). These compounds showed inhibitory activity of 4.86 μM and 8.33 μM IC_{50} values, respectively, against the HCT116 cancer cell line [64].



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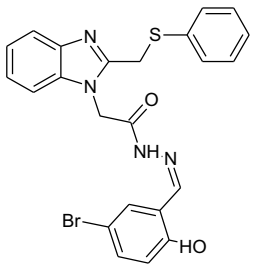

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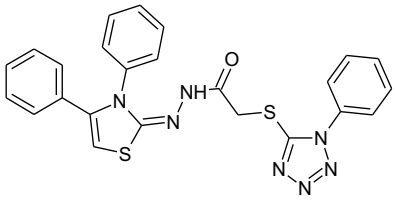
4.5. Glioma

N'-(3,4-diarylthiazol-2(3H)-ylidene)-2-(arylthio)acetohydrazides were designed, synthesized, and evaluated for their cytotoxicity against NIH/3T3 cells. For their cytotoxicity toward C6 glioma cells, the most efficient derivatives were evaluated. Against C6 glioma cells, *N*'-[(3,4-diphenylthiazol-2(3H)-ylidene)]-2-[(1-phenyl-1H-tetrazole-5-yl)thio] acetohydrazide (**35**) was found to be more efficient than cisplatin (IC_{50}=13.7 ± 1.2 μg/mL) with IC_{50} value of 8.3 ± 2.6 μg/mL. On C6 glioma cells, the compound showed DNA synthesis inhibitory activity and displayed less toxicity to NIH/3T3 cells (IC_{50} = 416.7 ± 28.9 μg/mL). While preparing the molecules, thio-linked triazole, tetrazole, thiadiazole, and pyrimidine were chosen as the side chain [65].



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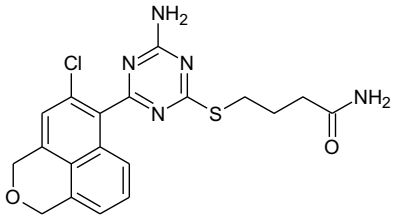
4.6. Gastric and Esophageal Cancer

Esophageal cancer has a very mild prognosis, and less than 20% of the patients survive for 5 years after diagnosis. Due to late clinical presentation with advanced disease, weak survival is imputable [66]. Ma *et al*. designed, synthesized, and evaluated a series of new 1,2,3-triazole-pyrimidine hybrids against four chosen cancer cell lines (EC-109, MGC-803, B16-F10, and MCF-7) for their anticancer activity. Against all selected cancer cell lines, most of the synthesized compounds demonstrated moderate to good activity. With single-digit micromolar IC_{50} values ranging between 1.42 to 6.52 μM, one compound displayed the best anti-cancer activity. By inducing apoptosis and arresting the cell cycle at the G2/M phase, this compound could inhibit the proliferation of EC-109 cancer cells [67]. Worldwide, gastric cancer (GC) is the fourth widespread tumor and the second major cause of cancer-related death. For advanced-stage gastric cancer, chemotherapy is the standard treatment. For targeting agents in front-line therapy, the challenges related to the procedure provide a framework to help detect the best single or combined chemotherapy cures [68].

Suda *et al.* designed a new series of 2-amino-1,3,5-triazines containing a tricyclic moiety such as heat shock protein 90 (Hsp90). 4-{[4-Amino-6-(5-chloro-1H,3H-benzo

[d,e]isochromen-6-yl)-1,3,5-triazin-2-yl]sulfanyl}butanamide (**36**) demonstrated high binding affinity for *N*-terminal Hsp90a (Kd=0.52 nM) and potent *in vitro* cell growth inhibition against human cancer cell lines HCT116 and NCI-N87 with IC_{50} values of 0.098 μM and 0.066 μM, respectively. It showed high oral bioavailability *in vitro* and strong anti-tumor impact in a human NCI-N87 gastric cancer xenograft model [69].



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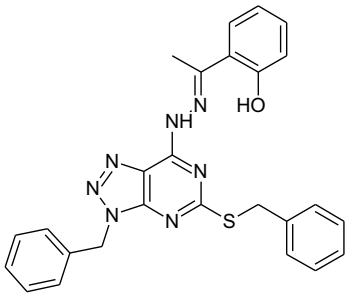
Li *et al.* described, synthesized, and evaluated a series of [1,2,3]triazolo[4,5-d]pyrimidine derivatives, including a hydrazone part, against a few cancer cell lines of distinct origins for their antiproliferative activity using MTT assay. Against the cancer cell lines selected, most of the synthesized compounds showed mild to good activity and good selectivity between normal and cancer cells against MGC-803 and GES-1 cell lines, with IC_{50} values of 0.85 and 56.17 μM, respectively. 2-(1-(2-(3-benzyl-5-(benzylthio)-3H-[1,2,3] triazolo[4,5-d]pyrimidin-7-yl)hydrazono)ethyl)phenol (**37**) displayed the strongest antiproliferative activity. The compound inhibited colony formation of MGC-803 cells with an IC_{50} value of 0.8 μM [70].



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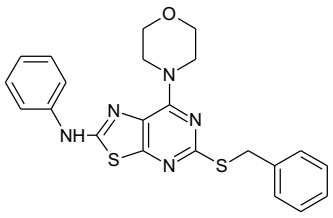

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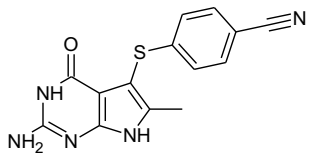
A series of thiazolo[5,4-d]pyrimidine derivatives were synthesized, and their antiproliferative activities were evaluated against three cancer cell lines (MGC803, H1650, and HGC27). Through the variation in three sides of the thiazolo-pyrimidine core, the structure-activity relationships were assessed. With IC_{50} values of 1.03 μM and 38.95 μM against MGC803 and GES-1 cancer cell lines, respectively, as well as selectivity between normal and cancer cells, 5-(benzylthio)-7-morpholino-*N*-phenylthiazolo[5,4-d]pyrimidin-2-amine **(38)** demonstrated the strongest anti-tumor activity. In addition to inducing apoptosis, this compound also inhibited colony formation and metastasis of MGC803 [71].

5. INHIBITION OF MACROMOLECULAR TARGETS

Many enzymes, proteins, or receptors play important roles in cancer. Researchers focus only on these pathways for not damaging normal cells. In recent years, macromolecular targets have gained the attention of researchers for cancer treatments. In general, active anti-tumor compounds, 5-diacetoxypentyldoxorubicin and morpholinodoxorubicin, and 6-maleimidocaproylhydrazone derivatives have been designed and synthesized. Molecules have been united to control IgG and monoclonal antibody BR96. *In vitro*, BR96 conjugates are rather active and antigen-specific. An IC_{50} of 0.03 μM was obtained for BR96-DAPDOX conjugate. However, it was 300-fold stronger than a non-binding IgG-DAPDOX checks conjugate. A few immunoconjugates which connect an absorbing MAb and DOX were synthesized using disulfide or thioether links to the MAb and hydrazone links to the DOX C-13 ketone. To transmit DAPDOX and MorphDOX compounds, the utilization of thioether/ hydrazone-based connection chemistry was defined. A reaction with 2-mercaptoethanol thioether analogs was performed for determining the hydrolytic stability of new linkers using a sample of the thioether contact to BR96 [72]. Leese *et al.* improved a resilient, straight, highly efficient synthesis of 2-alkylsulfanyl estrogens from estrone. While its 3-*O*-sulfamate compound was exposed to increased antiproliferative activity, 2-methylsulfanyl estradiol (2-MeSE2) showed a counterpart antiproliferative activity to 2-methoxyestradiol (2-MeOE2). An enzyme aiming at the therapy of hormone-dependent tumors was the basic route associated with significant inhibition of steroid sulfatase [73]. Using potential inhibitors of thymidylate synthase (TS) and as anti-tumor agents, a series of 17 new 2-amino-4-oxo-5-[(substituted phenyl)thio]pyrrolo[2,3-d]pyrimidines were designed and synthesized. The analogs included a diversity of electron retreat substituents on the phenyl ring of the side chain. The analogs were evaluated as inhibitors of human TS (hTS). 4-[(2-Amino-6-methyl-4-oxo-4,7-dihydro-3H-pyrrolo [2,3-d]pyrimidin-5-yl) sulfanyl]benzonitrile **(39)**, 2-amino-5-[(4-Bromo-3-nitrophenyl)sulfanyl]-6-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one **(40)** and 2-amino-5-[(4-Bromo-3-chlorophenyl)sulfanyl]-6-methyl-3,7-dihydro-4H-pyrrolo [2,3-d]pyrimidin-4-one **(41)** were found as strong inhibitors of hTS with IC_{50} values of 0.28, 0.21, and 0.22 μM, respectively [74].



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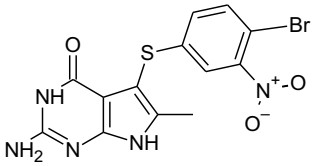

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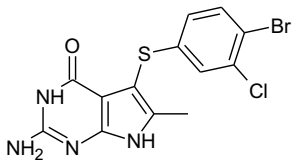
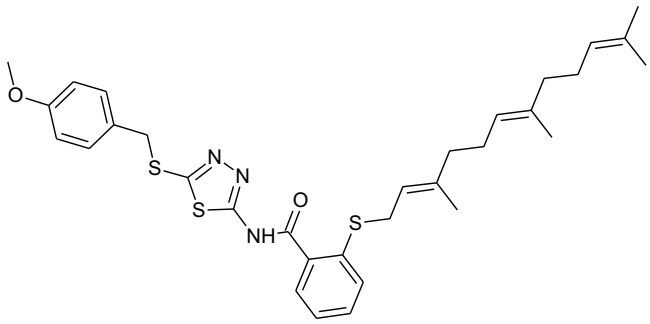


(41)

With diverse unsubstituted or substituted benzyl chlorides, alkylbromides, and chloracetamides, *via* co-action of 2-mercaptopyrimidines, a series of novel 2-*S*-substituted pyrimidine differentiations were synthesized according to reaction conditions. The synthesized molecules were examined according to anti-tumor activity. Three compounds showed good anti-tumor activity to diverse cancer cell lines [75]. Caspase 3 intervenes in apoptotic cell death, which is a cysteinyl protease. Caspase 3 inhibition may have a significant effect on the therapy of a few diseases. In the P3 zone, owing to solid-phase synthesis-led modification, thiobenzylmethylketone was appropriately processed. This method led to convenient derivatives with improved activity towards caspase 3. The power of these inhibitors was found out to be 146 nM with the novel derivatives [76]. Saczewski *et al.* synthesized a series of *S*-substituted-benzenesulfonamide derivatives qua inhibitors of four isoforms of the zinc enzyme carbonic anhydrase. Some of these molecules exhibited selectivity to the inhibition of the tumor-associated cells. Qua inhibitors of four CA isoforms associated with diverse ortho-substituents for the sulfamoyl moiety, a rather wide series of *S*-substituted 4-chloro-2-mercapto-5-methylbenzenesulfonamides, were examined [77]. Cuny *et al.* investigated and optimized the role of novel inhibitors in haspin kinase activity in mitosis and its potential in cancer. For haspin and DYRK2 inhibition, the structure-activity relationship (SAR) of the acridine sequence exhibited much resemblance. For both haspin and DYRK2 inhibition, a few structural properties of the compounds are essential. For instance,one or two methoxy groups, three or four methylene chains between the acridine and the thioether, three acridine aromatic rings, and a thioether or -CH_2- connection to the acridine could be obtained [78]. APN/CD13 is a member of the M1 family of aminopeptidases and a membrane-bound, zinc-dependent homodimeric enzyme. APN/CD13 is an active player in tumor metastasis and angiogenesis, according to most recent studies. Due to their property of inhibiting metalloaminopeptidase activities, racemic 5-substituted 7-aminobenzocyclohepten-6-ones were synthesized and evaluated. Toward APN/CD13, compared to the parent aminobenzosuberone, two compounds substituted with a sulfide piece were verified to be more active. For potent affinity to APN, sulfide was found critical when compared with the activities of some compounds. To a novel series of 7-aminobenzocyclohepten-6-one derivatives, a simple synthesis-led entry was designed successfully. Thio derivatives and the first samples of a novel chemotype of APN inhibitors reproduced from aminobenzosuberone scaffold displayed potent (60-83 nM) inhibitory activity [79]. With distinct substituted 1,3,4-thiadiazoles, Ling *et al*. synthesized novel farnesylthiosalicylic acid (FTA) derivatives. By linking the carboxyl group of FTA with dissimilar thioether-substituted 1,3,4-thiadiazoles, they synthesized and designed 13 target compounds. Against human hepatocellular carcinoma cells (Bel7402), human lung cancer cells (H520), human glioblastoma cells (U251), and human breast adenocarcinoma cells (MDA-MB-231), they appraised the cytotoxicity of individual compounds by MTT analysis utilizing FTA as a positive control. According to the results, *N*-{5-[(4-methoxybenzyl)sulfanyl]-1,3,4-thiadiazol-2-yl}-2-(3,7,11-trimethyldodeca-2,6,10-triene-1-yl-thio)benzamide **(42)** induced tumor cell apoptosis with high Bax and caspase 3 expression activities in cancer cells [80].



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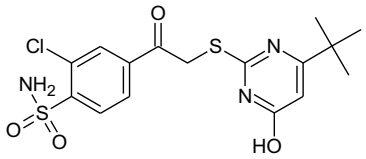
Zheng *et al.* synthesized a series of novel class compounds on the basis of the collation of the Bim BH3:Bcl-xL complex. In multiple tumor cell lines known to express Bcl-xL, Bcl-2, and Mcl-1 proteins at high grades, novel molecules were proven more efficient than ABT-737 in inhibiting growth. Two compounds exhibited the most potent anti-tumor activity among the compounds produced [81]. As inhibitors of carbonic anhydrases (CA), two groups of benzenesulfonamide derivatives, including pyrimidine compounds, were drafted and synthesized. The *S*-alkylated benzimidazoles were found to be more powerful CA binders than *N*-alkylated benzimidazoles and indapamide. The *S*-alkylated pyrimidines were designed for the catalytic field of recombinant human CA VI, and CA XII transmitted in cancer; increased binding measurements of compounds were obtained. Two new series of carbonic anhydrase inhibitors were synthesized and characterized. 4-{[(4-Tert-butyl-6-hydroxypyrimidin-2-yl)sulfanyl]acetyl}-2-chlorobenzene sulfonamide **(43)** showed subnanomolar affinity for CA I (Kd = 0.5 nM). It was found to be highly selective for CA I [82].



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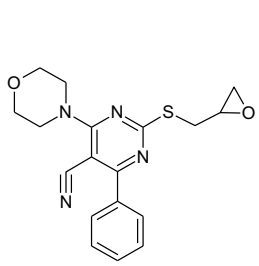
Fargualy *et al.* synthesized some new pyrimidine-5-carbonitrile derivatives, including diverse substituents. Some chosen agents of the synthesized compounds were investigated against specific human tumor cell lines for their cytotoxic potency. To dock the utilization of the MOE program on the 3D structure of dihydrofolate reductase and thymidylate synthase enzymes, five active anti-cancer compounds were considered. During the assessment of the entire panel and 5-dose *in vitro* anti-tumor screening, 4-(morpholine-4-yl)-2-[(oxirane-2-ylmethyl)sulfanyl]-6-phenylpyrimidine-5-carbonitrile **(44)** met the threshold inhibition criteria.

With dihydrofolate reductase enzyme, 4-(morpholine-4-yl)-2-[(3-(morpholin-4-yl)propan-2-ol)sulfanyl]-6-phenylpyrimidine-5-carbonitrile **(45)** showed potent interactions [83].



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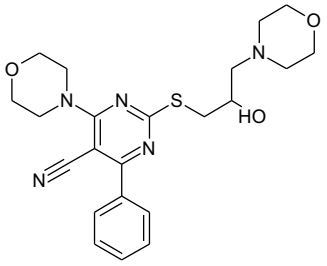

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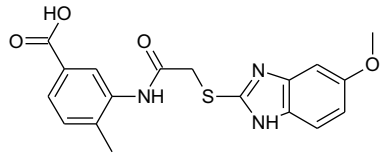
Hamdy *et al.* synthesized a series of substituted 1,2,4-triazol-4-amine derivatives. They investigated potential pro-apoptotic Bcl-2-inhibitory anti-tumor analogs *in vitro*. Under simple conditions *via* a cyclization reaction between carbon disulfide and indole-3-carboxylic acid hydrazide pursued by *S*-benzylation, synthesis of the desired analogs was achieved in good yields. In Bcl-2 revealing human cancer cell lines, active compounds were found to show sub-micromolar IC_{50} values. As a nominee molecule aiming to support anti-cancer activity, ELISA and molecular modeling studies were conducted on anti-apoptotic Bcl-2. The anti-cancer activity of the novel triazole-amines may be attributed to Bcl-2 [84]. Rakse *et al.* designed, synthesized, and screened a new series of 3-acetamido-4-methyl benzoic acid derivatives to evaluate PTP1B (protein tyrosine phosphatase 1B) inhibitory activity. The derivatives 3-(2-(5-methoxy-1H-benzo[d]imidazol-2-ylthio)acetamido)-4-methylbenzoic acid **(46)** and 3-(2-(5-methoxy-2-benzo[d]thiazol-2-ylthio) acetamido)-4-methylbenzoic acid **(47)** displayed maximum PTP1B inhibitory activity. To figure out the interplays ruling the binding mode of the synthesized molecules within the active site of the PTP1B enzyme, docking studies were conducted [85].



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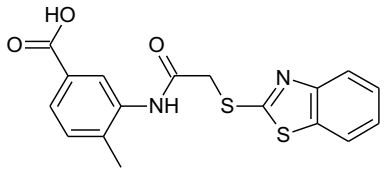

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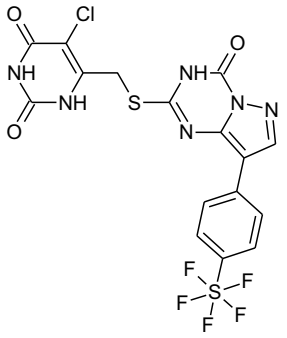
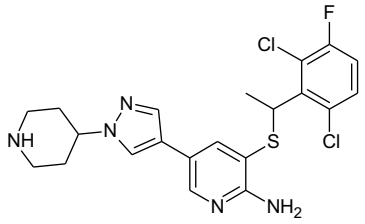
Novel thymidine phosphorylase inhibitors 5-chlorouracil-linked-pyrazolo[1,5-a][1,3,5]triazines were designed. To synthesize the compounds, multiple-step convex synthetic schemes were constructed. Pyrazolo[1,5-a][1,3,5]triazin-2-thioxo-4-one and 5-chloro-6-chloromethyluracil intermediates were coupled with methanol and sodium ethoxide to give the desired compounds. At the allosteric site and active site of the enzyme, in facilitating the interaction of the two fragments, the methylthio coupling spacer was found to be convenient. With an IC_{50} value of 0.36 ± 0.1 μM, the best coupled 5-chloro-6-[({4-oxo-8-[4-(pentafluoro-λ^6-sulfanyl) phenyl]-3,4-dihydropyrazolo[1,5-a][1,3,5]triazin-2-yl}sulfanyl)methyl]pyrimidine-2,4(1H,3H)-dione **(48)** inhibited thymidine phosphorylase. The compound showed a mixed-type of enzyme inhibition kinetics. It might bind to two dissimilar parts of the enzyme. The resilient methylthio linker was found to be a convenient spacer to bridge the 5-chlorouracil moiety with the pyrazolo[1,5-a][1,3,5]triazine scaffold [86].



(48)

Through the medium of bioisosteric replacement and docking assay, against c-Met, a series of 2-amino-3-benzylthiopyridines, 2-amino-*N*-benzylpyridine-3-carboxamides, and 2-amino-*N*-benzylpyridine-3-sulfonamides were designed. Optimization of the 2-amino-3-benzylthiopyridine scaffold led to the synthesis of 3-{[1-(2,6-dichloro-3-fluorophenyl)ethyl]sulfanyl}-5-[1-(piperidin-4-yl)-1H-pyrazol-4-yl]pyridin-2-amine **(49)**, which showed c-Met inhibition with an IC_{50} value up to 7.7 nM. The compound efficiently inhibited c-Met activation-mediated cell metastasis and the proliferation of c-Met addictive human cancer cell lines (IC_{50} ranging from 0.19 to 0.71 μM). The compound efficiently inhibited the proliferation of several human cancer cell lines, such as MKN45, SNU-5, and EBC-1 cell lines, during cytotoxicity evaluation [87].



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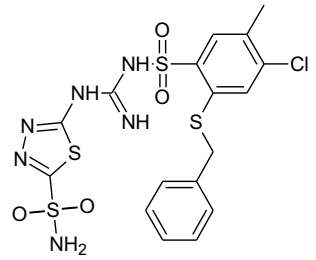
Zolnowska *et al.* synthesized a set of new *N*-substituted-*N'*-(2-arylmethylthio-4-chloro-5-methylbenzenesulfonyl) guanidines as inhibitors of four isoforms of zinc enzyme carbonic anhydrase. 1-(2-Benzylthio-4-chloro-5-methylbenzenesulfonyl)-3-(2-sulfamoyl-1,3,4-thiadiazol-5-yl)guanidine **(50)** was observed as the most potent inhibitor of hCA I, hCA IX, and hCA XII with K_I values of 87 nM, 4.7 nM, and 0.96 nM, respectively [88].

Çoruh *et al*. designed and synthesized a series of new etodolac thioether derivatives with benzyl chlorides and etodolac 1,2,4-triazole-3-thiones. All compounds were evaluated for anti-cancer activity towards SKOV3 (ovarian), HepG2 (liver), PC3 and DU145 (prostate), and MCF7 (breast) cell lines using the MTT colorimetric method. Some compounds demonstrated the best anti-cancer activity with

IC_{50} values of 7.22 and 5.10 μM against the SKOV3 cancer cell line. Many compounds displayed the strongest anti-cancer activity against the PC3 cancer cell line. The active compounds were evaluated for caspase -3, -9, and -8 protein expression and activation in the apoptosis pathway for 6, 12, and 24 h. 1-{[5-(4-Chlorobenzyl)sulfanyl-4-ethyl-4*H*-1,2,4-triazole-3-yl]methyl}-1,8-diethyl-tetrahydropyrano[3,4-b]indole **(51)** and 1-{[5-(4-nitrobenzyl)sulfanyl-4-phenyl-4*H*-1,2,4-triazole-3-yl]methyl}-1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole **(52)** were investigated for molecular modeling and apoptotic mechanism on the methionine aminopeptidase (type II) enzyme active site [89].



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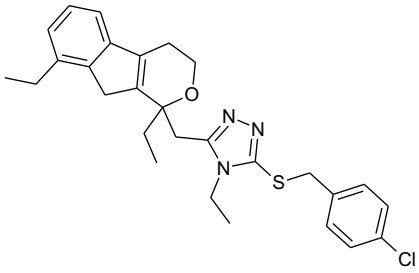

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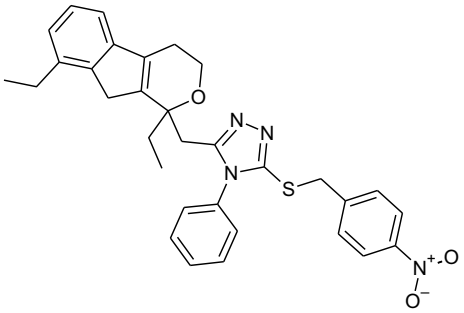
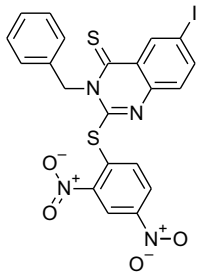


(52)

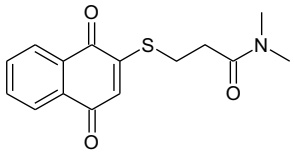
6. LEUKEMIA

Leukemia is a type of cancer in the blood-forming tissues of the body, including the bone marrow and the lymphatic system, and is followed by the formation of a large number of abnormal white blood cells. Many factors may pave the way for developing some types of leukemia. The most known risk factors are genetic disorders and environmental factors. Abdelhamed *et al*. synthesized a novel series of quinazolinone analogs with 6-iodo and 2-thioether *in vitro* and assessed their anti-tumor activity. They detected eight active anti-cancer compounds. The thioether compound was verified as the most active compound. The compound demonstrated $LC_{50,}$ MG-MID GI_{50} (Mean-graph midpoint), TGI values of 38.7, 2.7, and 12.3 μM, respectively. In the anti-tumor activity evaluation with almost five layers, initial material and 2,4-dinitrochlorobenzene granted thioether 3-benzyl-2-[(2,4-dinitrophenyl)sulfanyl]-6-iodoquinazoline-4(3H)-thione **(53)** provided successful results. The extent of activity was reduced, changing the nitrobenzene moiety of the compound by nitropyridine. To achieve an active anti-tumor activity against cancerous cells and low toxicity against ordinary cells, the practice of synthesizing these hybrids was tested [90].



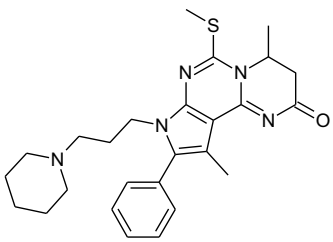
(53)

On the catalytic site, polysubstituted thioanalogs of merbarone treated the topoisomerase II inhibitor. Ranise *et al.* synthesized three series of 5-substituted 1,3-diphenyl-6-(ω-dialkyl- and ω-cyclo-aminoalkyl)thio-2-thiobarbiturates. The fourth series of forced analogs was equipped to better figure out pharmacophore necessities. In the nominal micromolar concentration series with IC_{50} value 3.3-4.3 μM, some involutions were active. Some compounds displayed IC_{50} values between 10 and 15.5 μM. Against leukemia cell lines with GI_{50} up to 0.01 μM, with strong antiproliferative activity, separated compounds were demonstrated [91]. Tandon *et al.* synthesized and evaluated a series of 2-substituted 1,4-naphthoquinones, including sulfur atoms. They evaluated their anti-tumor activities towards the Lymphoid Leukaemia P-388 cell line. Among the synthesized compounds, 3-[(1,4-dioxo-1,4-dihydronaphthalen-2-yl)sulfanyl]-*N*,*N*-dimethylpropanamide **(54)** displayed significant anti-cancer activity [92].



(54)

To anticipate the development of the biological activity of pyrrolo-pyrimidine derivatives, the chemometric process VLAK was implemented by utilizing the NCI ACAM Database as a depository of anti-tumor drugs with a familiar mechanism of action as anti-cancer agents. A good rise in the anti-tumor activity of the two chosen compounds was observed. These novel pyrrolo-pyrimidine compounds exhibited anti-tumor activity against the complete panels of NCI DTP tumor human cell lines. Toward the leukemia subpanel, 8-[3-(piperidino)propyl]-4,10-dimethyl-9-phenyl-6-(methylsulfanyl)-3,4-dihydropyrimido[1,2-c]pyrrolo[3,2-e]pyrimidin-2(8H)-one **(55)** showed effective anti-cancer activity. Especially, the RPMI cell line concluded the maximum precision (pGI_{50} = 6.68). 7-(3-Chloropropyl)-9-methyl-5-(methylsulfanyl)-8-phenyl-3H-imidazo[1,2-c]pyrrolo [3,2-e]pyrimidin-2(7H)-one **(56)** displayed good anti-cancer activity against leukemia cancer cell line [93].



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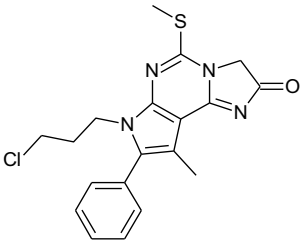

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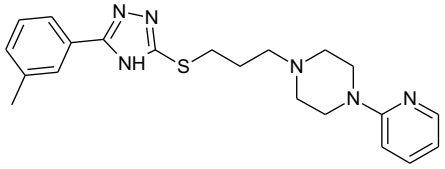
Starting with efficient carboxylic acids, a series of 3-[3-[4-(Substituted)-1-cyclicamine]propyl]thio-5-substituted[1,2,4]triazoles were synthesized. The cytotoxicity effect of these derivatives was examined against five dissimilar human cancer cell lines. Three compounds showed good anti-cancer activity. Against U937 and HL-60 (leukemia) cells, the triazole derivatives 5-(3-methylphenyl)-4H-1,2,4-triazol-3-yl 3-[4-(2-pyridyl)piperazino]propyl sulfide **(57)** and 5-(3-chlorophenyl)-4H-1,2,4-triazol-3-yl 3-[4-(2-pyrimidinyl)piperazino]propyl sulfide **(58)** were found to be the strongest. As feasible factors of their biological activity, the cytotoxic activity of the compounds altered between the cell lines [94].



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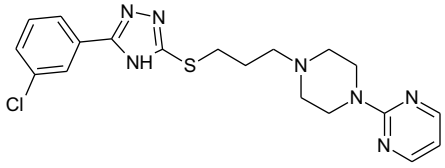

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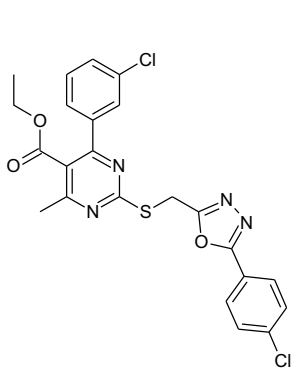
Antypenko *et al.* synthesized new molecules using the thione structure. For *N,N*-dialkylethylamines, antixcalkyls, 1-(alkyl)aryl-2-ethanols, 1-aryl-2-ethanones, esters, and carboxylic acids, they altered the potassium salt of the tetrazolo[1,5-*c*]quinazoline-5-thione with proper halogen involutions. US National Cancer Institute (NCI) selected the molecules by scanning their ability to inhibit 60 different human tumor cell lines. Many compounds exhibited fatal antitumor activity (1.0 μM) against severe lymphoblastic leukemia cell lines. Two compounds showed mild anti-cancer features hindering the expansion of leukemia HL06-(TB) and MOLT-4 cell lines [95]. Regap *et al.* designed and synthesized a series of dihydropyrimidine (DHPM) derivatives containing 1,3,4-oxadiazole moiety as monastrol analog. The novel compounds were screened for their cytotoxic activity against 60 cancer cell lines. Against the most sensitive cell lines, leukemia HL-60(TB) and MOLT-4, seven compounds were investigated. The most active compounds were ethyl 4-(3-chlorophenyl)-2-(((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)thio)-6-methyl-1,4-dihydropyrimidine-5-carboxylate **(59)** against HL-60(TB) (IC_{50} = 56 nM) and ethyl 2-(((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)thio)-4-(2,4-dichlorophenyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate **(60)** against MOLT-4 (IC_{50} value = 80 nM) [96].



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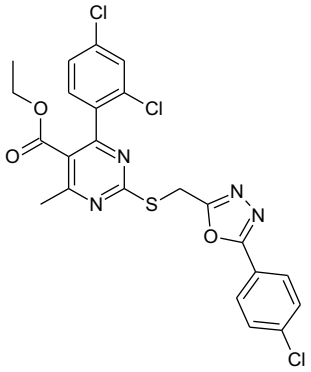

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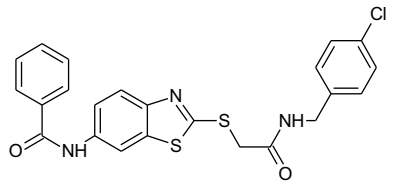
7. LIVER CARCINOMA

Among tumors, liver cancer is an uncommonly heterogeneous malignant disease and has a high incidence of death. Environmental and genetic susceptibilities such as aflatoxin, HBV, and/or HCV infections, metabolic syndrome, abusive alcohol intake, obesity, and diabetes are risk factors in liver cancer. Due to the outcomes of anti-cancer agents and lack of consistent conventional therapies, new molecularly aimed drugs and combined cures have become an important option in liver cancer therapy [97]. Li *et al.* drafted and synthesized a series of new 1-anilino-4-(arylsulfanylmethyl)phthalazines. When two dissimilar cancer cell lines were examined using the MTT assay, two compounds displayed advanced activity compared to cisplatin *in vitro*. Next, the results could be achieved from biological test conclusions regarding their structure-activity relationships, which were firstly compared to that of an unsubstituted thiophenol to improve the anti-cancer activity association of a displaced thiophenol group at the 4-position of the phthalazine ring. Moreover, anti-tumor activity was reduced by changing a sulfanyl with sulfonyl or sulfinyl groups. By the MTT method and measuring cell viability, anti-cancer activities of molecules were evaluated against Bel-7402 (Human Liver Cancer cell lines) *in vitro* [98]. Wang *et al.* synthesized a series of new benzothiazole-2-thiol derivatives and studied their anti-cancer activities on MCF-7 and HepG2 cells. Most compounds had inhibitory impacts on cell growth. Some of the compounds were more efficient than cisplatin. Against distinct types of human cancer cell lines, *N*-[2-({2-[(4-chlorobenzyl)amino]-2-oxoethyl}sulfanyl)-1,3-benzothiazol-6-yl]-2-methoxybenzamide **(61)** and *N*-(2-{[2-(benzylamino)-2-oxoethyl]sulfanyl}-1,3-benzothiazol-6-yl)-2-chloroacetamide **(62)** showed good inhibitory activities with IC_{50} values in the nominal micromolar range. In cultures of MCF-7 and HepG2 cells, twenty-four benzothiazole-2-thiol derivatives were evaluated by examining the cell growth inhibitory activities (IC_{50}) and SAR utilizing the MTT assay [99].

8. LUNG CARCINOMA

Lung cancer is the main cause of cancer-related mortality among males and is second in rank to the incidence of breast cancer in females. The main risk factor known is the

use of tobacco. Chemotherapy with or without radiotherapy remains the main therapy of choice for a more advanced phase of the disease or inoperable tumors [100]. Thomson *et al.* synthesized a new bioreductive prodrug of 6-thioguanine, including a gem-dimethyl thioether connection. They compared it with the unsubstituted analog. With the relayed prodrug only, researchers observed hypoxia selective extrication of 6-thioguanine in A549 cell tests. Using chemical hydrogenation, by isolating the reduction produced, 6-(4-aminobenzyl)thioguanine showed that the thioether connection was steady for fragmentation. While benefitting from the inferior toxicity of 6-alkyl analogs, they utilized the gem-disubstitution technology to develop thioguanine [101]. Altıntop *et al.* synthesized novel hydrazone derivatives using the nucleophilic addition elimination reaction of 2-[(1-methyl-1H-tetrazol-5-yl)thio)]acetohydrazide with aromatic aldehydes/ketones. Whole molecules were also investigated for their cytotoxic impacts on the A549 cell line. Because of its inhibitory effect on the A549 cell line, *N*'-[(E)-(4-chlorophenyl)methylidene]-2-[(1-methyl-1H-tetrazol-5-yl) sulfanyl]acetohydrazide **(63)** was detected as the most potent anti-cancer agent with an IC_{50} value of 0.1 μM [102].



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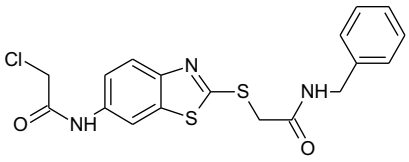

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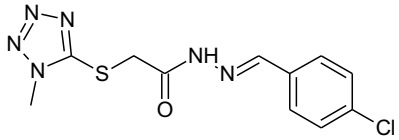

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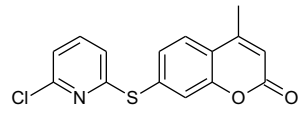
Against four human tumor cell lines, including KB-vin (vincristine-resistant subline), KB (nasopharyngeal), DU145 (prostate), and A549 (lung), thirty-five *S*- and *O*-substituted 7-mercaptocoumarin were designed, synthesized, and evaluated with paclitaxel as the positive control *in vitro*. Many of the synthesized compounds displayed strong cytotoxic activity. Among them, 7-[(6-chloropyridin-2-yl)sulfanyl]-4-methyl-2H-chromen-2-one **(64)** and methyl 3-{[(4-methyl-2-oxo-2H-chromen-7-yl)sulfanyl]methyl}benzoate **(65)** exhibited a wide spectrum of activity, with GI_{50} values ranging from 0.92-2.11 μM and 2.06-14.07 μM, respectively [103].

Seeniah *et al.* prepared a variety of pyrimidinyl benzimidazoles, benzoxazoles, and benzothiazoles linked by amino, thio, and methylthio moieties and evaluated their cytotoxic activities. Compounds were subjected to the MTT assay to detect growth-inhibitory and cytotoxic activities. The amino linked pyrimidinyl bis benzothiazole *N*-(2-((benzothiazol-2-yl)methylthio)-6-methylpyrimidin-4-yl)benzo-thiazol-2-amine **(66)** showed cytotoxic activity against A549 cells with an IC_{50} value of 10.5 μM [104].



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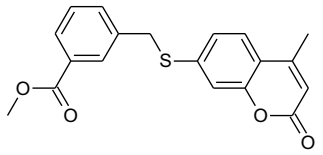

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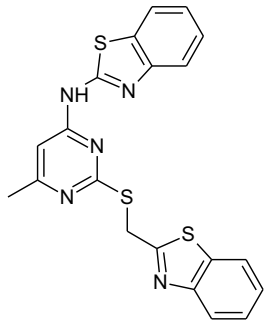
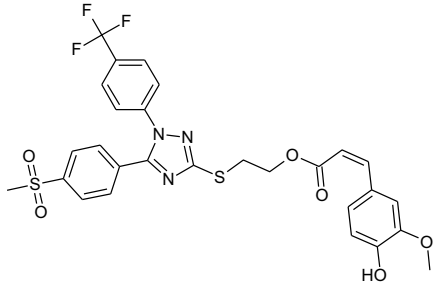


(66)

Inflammation has an important role in cancer induction and spread. 5-Lipoxygenase (5-LOX), and Cyclooxygenase-2 (COX-2), two significant enzymes, are up-regulated in diverse tumor types during inflammatory responses. For an increased security profile, to describe more efficient anti-tumor agents, dual inhibition of 5-LOX and COX-2 provides a reasonable concept. Cai *et al.* hybridized diaryl-1,2,4-triazoles with caffeic acid (CA), affording a new class of 5-LOX/COX-2 dual inhibitors as anti-tumor drug nominees, which were evaluated for 5-LOX/COX-2 inhibitory and anti-tumor activities. *In vitro*, some of these compounds showed strong 5-LOX/COX-2 inhibitory and antiproliferative activities. *In vivo,* most active 2-((5-(4-(methylsulfonyl)phenyl)-1-(4-trifluoromethylphenyl)-1H-1,2,4-triazol-3-yl)thio)ethyl-3-(3,4-dihydroxyphenyl)acrylate **(67)** could inhibit tumor growth. This compound inhibited tumor growth in the ratio of 58.9% at the dose of 40 mg/kg. In human non-small cell lung cancer A549 cells, 2-((5-(4-(methylsulfonyl) phenyl)-1-(4-fluorophenyl)-1H-1,2,4-triazol-3-yl)thio)ethyl-3-(3-methoxy-4-hydroxyphenyl)acrylate **(68)** inhibited cell cycle in the G2 phase and induced apoptosis in a dose-dependent manner. With these results, COX-2/5-LOX dual inhibitors suggested new hints for cancer cure [105].



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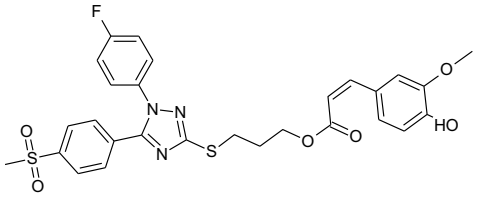
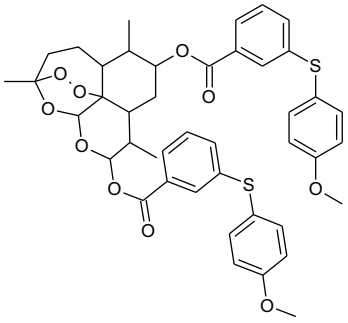


(68)

Xu *et al.* drafted and synthesized ten new artemisinin derivatives bearing sulfur atoms. *In vitro* cytotoxicity of these derivatives against SGC-7901, PC-3, MDA-MB-435S, and A549 cancer cell lines was evaluated by the MTT assay. With IC_{50} values ranging from 1.6 to 30.5 μM against PC-3, SGC-7901 and A549 cells, dihydroartemisinin 9α,12α-di-[3-(p-methoxyphenyl)thio]-benzoate **(69)** and 9α-hydroxy-dihydroartemisinin 12α-[3-(p-methoxyphenyl)thio]-benzoate **(70)** showed strong anti-tumor activity. The compounds displayed potent specificity with the selectivity index of 16.1 and 50.1 towards human lung cancer A549 cells and normal human hepatic L-02 cells, respectively [106].



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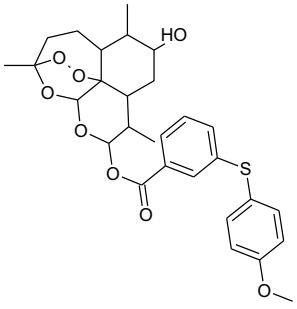

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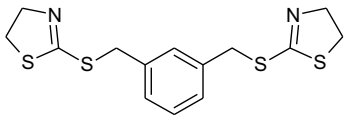
Together with dibromides, a series of new multi-thioether derivatives were synthesized by the composition of thiazine and thiazoline. Initially, the starting materials 1,3-thiazinane-2-thione and thiazolidine-2-thione were synthesized. After that, under varied reaction conditions, starting materials were reacted with different dibromides. To evaluate the anti-tumor activity, the synthesized derivatives were tested against A-549 (human lung cancer cell). Standard MTT assay was used for *in vitro* anti-tumor activity studies. 2,2'-[Benzene-1,3-diylbis(methanediylsulfanediyl)]bis(4,5-dihydro-1,3-thiazole) **(71)** and 2,2'-[benzene-1,3-diylbis(methanediylsulfanediyl)]bis(5,6-dihydro-4H-1,3-thiazine) **(72)** demonstrated the highest anti-tumor activities [107].

Yun *et al.* synthesized thioether-based 2-aminobenzamide derivatives considering their antiproliferative efficiency, better metabolic stability, and HDAC inhibitory effects, and therefore evaluated their anti-cancer activity against A549 cancer cells *in vitro* and *in vivo* [108].



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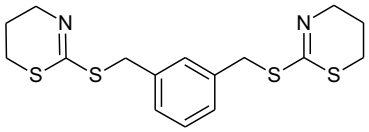

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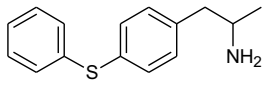
9. LYMPHOMA

Lymphoma is a type of blood cancer advancing from lymphocytes that are part of the body's immune system. Lymphoma therapy may concern one or more of chemotherapy, radiation therapy, targeted therapy, and surgery. Cloonan *et al.* synthesized a new category of anti-cancer agents with serotonin transporter activity of sulfur-substituted α-alkyl phenethylamines. The effect of pro-apoptotic agents on serotonin reuptake transporter (SERT) ligands was investigated in cancer treatment. New structurally various 4-MTA analogs were synthesized, and their potential SERT-dependent antiproliferative activity as well as cytotoxic activity were detected. Many analogs showed SERT-binding activity. A few derivatives showed anti-tumor effects on lymphoma, breast cancer, and leukemia cell lines. There was no direct relationship observed between these two activities, which displays their potential to be developed as feasible chemotherapeutic agents. 1-[4-(Phenylsulfanyl) phenyl]propan-2-amine **(73)** was researched for antiproliferative activity. It demonstrated potent activity in two Burkitt's lymphoma with IC_{50} values of 10 μM and 50 μM, respectively [34].



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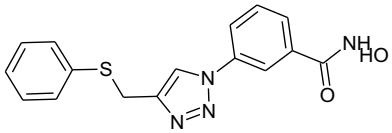
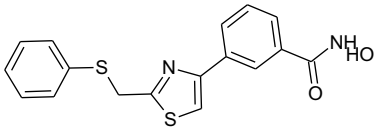


(74)

Suzuki *et al.* detected new strong HDAC8-selective inhibitors. Theysynthesized a series of NCC149 (*N*-hydroxy-3-[1-(phenylthio)methyl-1H-1,2,3-triazol-4-yl]benzamide) derivatives having diverse aromatic linkers. Among these derivatives, *N*-hydroxy-3-{4-[(phenylsulfanyl)methyl]-1H-1,2,3-triazol-1-yl}benzamide **(74)** displayed the most potent HDAC8 inhibitory activity, and *N*-hydroxy-3-{2-[(phenylsulfanyl)methyl]-1,3-thiazol-4-yl}benzamide **(75)** showed potent T-cell lymphoma cell growth inhibitory activity [109].



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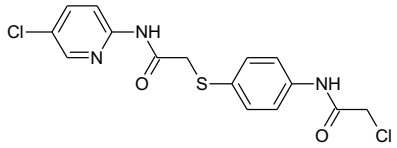
10. MELANOMA

Melanoma is the most dangerous form of skin cancer. This type of cancer generally develops when unrepaired DNA harms skin cells. Many environmental risk factors such as ultraviolet radiation from sunlight or tanning beds start mutations that lead skin cells to multiply rapidly and form malignant tumors. Accomplishing cancer-inducing apoptosis is a hopeful therapeutic treatment for melanoma. Zhao *et al.* synthesized and evaluated 30 compounds for their antiproliferative activity against three tumor cell lines, H460, A875, and Hela cancer cells, using the MTT assay. With an IC_{50} value of 98 nM, the most potent analog 2-chloro-*N*-[4-({2-[(5-chloropyridin-2-yl)amino]-2-oxoethyl} sulfanyl)phenyl]acetamide **(76)** inhibited the proliferation of A875 cells. Through G2/M cell cycle arrest, the compound exhibited potential anti-cancer activity according to morphological analysis and flow cytometry analysis [110].



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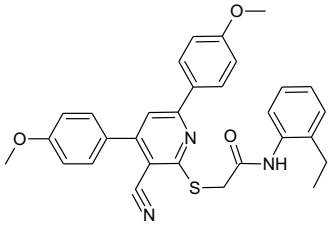
11. OSTEOSARCOMA

Osteosarcoma is the most widespread type of bone cancer. Osteosarcoma could spread to parts of the skeleton, unlike other types of cancer. Osteosarcoma starts in the bones, while sometimes it spreads to the other bones or lungs through metastasis. With 2-((3-cyanopyridin-2-yl) thio)acetamide, Cui *et al.* explored effective LDHA inhibitors by imaging and biological validation. 2-[(3-Cyano-4,6-bis(4-methoxyphenyl)pyridine-2-yl)sulfanyl]-*N*-(2-ethylphenyl)acetamide **(77)** was evaluated by *in vitro* antiproliferation analyses and enzymatic work. The compound induced apoptosis of MG-63 cancer cells in dose-response and time-dependent manners according to the flow cytometry study. This compound with antiproliferative activity was reported for the first time as a compound targeting LDHA. Against LDHA with an IC_{50} value of 1.24 μM, the compound showed good inhibitory potency and inhibited the proliferation of MG-63 cancer cells (EC_{50}=0.98 μM). With such anti-proliferative potency, this compound could be used to develop a more potent LDHA inhibitor [111].



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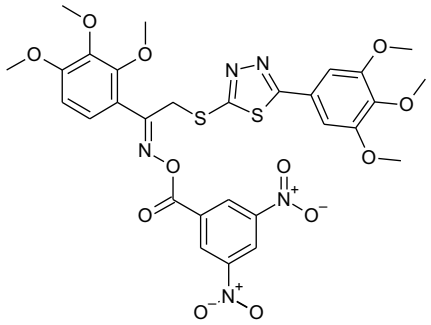
12. PROSTATE CANCER

In most industrialized countries, prostate cancer (PC) is the most common cancer among males. Overdiagnosis is the main adverse impact of prostate cancer screening. However, in the absence of screening, cases that have not been presented clinically are common [112, 113]. Ranise *et al.* synthesized three series of thiobarbiturate derivatives. Some compounds displayed IC_{50} values between 10 and 15.5 μM. Selected compounds showed potent antiproliferative activity against prostate cell lines with GI_{50} up to 0.01 μM [92]. Starting from gallic acid, Xue *et al.* drafted and synthesized a series of new oxime esters containing the 1,3,4-thiadiazole group. The main aim was to enhance biological properties and diverse bioactivity spectrum to explore novel fungicide and anti-cancer agents. The thioetherification reactions of 5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazole-2-thiol with 2-Bromo-1-(2,3,4-trimethoxyphenyl) ethanone were achieved by using catalyzer indium to optimize the reaction. 1-(2,3,4-Trimethoxyphenyl)-2-{[5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazol-2-yl]thio}ethanone *O*-(3,5-dinitrobenzoyl)-oxime **(78)** was the final compound in this study. Some of the compounds showed specific activities against the PC3 cancer cell line *in vitro* [114].



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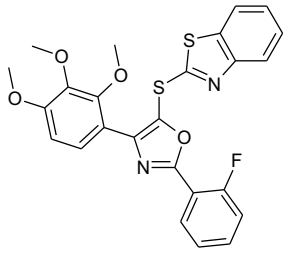
Using thiol compounds, the thioetherification reaction of 4-chloroquinazolines was refluxed, and some S'-substituted 4-alkyl(aryl)thioquinazoline derivatives were synthesized. The compounds were evaluated for their anti-tumor activities towards some cancer cells by the MTT method *in vitro*. Against PC3 cells, five compounds were highly active. The IC_{50} values of the compounds were 5.6, 1.8, 8.1, 8.7, and 8.9 μM, respectively, against PC3 cells. Against Bcap37 and BGC823 cells, all synthesized compounds displayed low activity [115]. Twenty new 2,4,5-trisubstituted oxazole derivatives, including heterocycle moiety, were synthesized and evaluated for their antiproliferative activity. Only three compounds showed good antiproliferative activity in the bioassay experiments *in vitro*. Against the two adjusted cell lines with IC_{50} much less than the positive control, 2-(2-(2-fluorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-yl-thio) benzo[d]thiazole **(79)**, 2-(2-(pyridine-3-yl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-yl-thio)pyrimidine **(80)** and 2-(2-(2-fluorophenyl)-4-(2,3,4-trimethoxyphenyl)oxazol-5-yl-thio)-5-methyl-1,3,4-thiadiazole **(81)** demonstrated potent inhibitory activity. It was concluded that the fluorophenyl group had a significant impact on antiproliferative activity. It was noted that these compounds had *S*-containing groups displaying advanced inhibitory activity than the latter ones [116].



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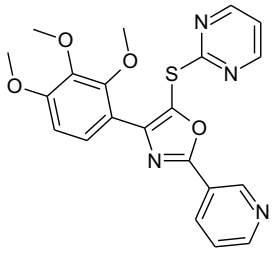

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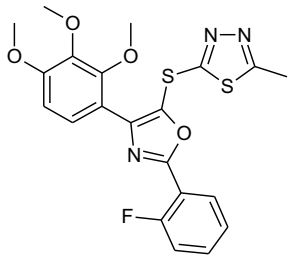
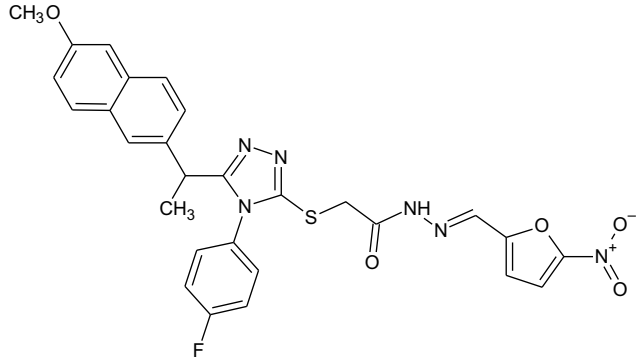


(81)

Han *et al.* designed, synthesized, and characterized thirteen new naproxen hydrazide-hydrazone compounds containing the 1,2,4-triazole ring and thioether moiety. All compounds were checked for anti-cancer activity against DU-145, PC-3, and LNCaP prostate cancer cell lines. Eight compounds showed anti-cancer activity against some cell lines. (*S*)-2- {[5- [1- (6-methoxynaphthalene-2-yl)ethyl]-4-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}-*N*'-[(5-nitrofuran-2-yl)methylidene] acetohydrazide **(82)** displayed anti-cancer activity against all three cell lines with IC_{50} values of 26.0, 34.5, and 48.8 μM, respectively [117, 118].



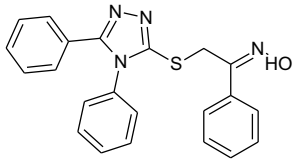
(82)

Yılmaz *et al*. designed and synthesized novel flurbiprofen thioether compounds. They evaluated these compounds against MetAP-2 *in vitro* and *in silico* to gain new specific and efficient anti-cancer agents against prostate cancer. Many compounds showed the most potent anti-cancer activity against PC3 cancer cell line (IC_{50}= 27.1 μM, and 5.12 μM, respectively), DU-145 cancer cell line (IC_{50}= 11.55 μM, 6.9 μM, and 9.54 μM, respectively) and LNCaP cancer cell line (IC_{50}= 11.45 μM and 26.91 μM, respectively). This study demonstrated that some of the synthesized thioether compounds have anti-cancer and apoptotic activities against prostate cancer cells [119].

Birgül *et al.* synthesized new triazole-thioether hybrid compounds. These compounds were evaluated to inhibit methionine amino peptidase-2 (MetAP2) enzyme in prostate cancer. Some of the compounds showed anti-cancer activity against the prostate cancer cell lines PC-3, DU-145, and LNCaP. Also, these compounds can be potent small molecules against prostate cancer. Molecular docking and dynamics simulation of compounds were conducted. The results of the *in vitro* and *in vivo* anti-cancer activity studies determined (S)-3-((2,4,6-trimethylphenyl)thio)-4-(4-fluorophenyl)-5-(1-(6-methoxynaphtalen-2-yl)ethyl)-4H-1,2,4-triazole as a candidate molecule in prostate cancer treatment [120].

13. RENAL CARCINOMA

In recent decades, the incidence of renal cell carcinoma (RCC) has risen steadily. Today, it is a widespread urologic tumor that accounts for about 2-3% of all human malignancies. In both males and females, the incidence of renal cancer is rising tremendously. Renal cell cancer (RCC) contains a different group of solid tumors stemming from renal parenchyma [121]. A series of new nitric oxide (NO) donating triazole/oxime hybrids were prepared and evaluated for their antiproliferative activity. Primary one dose anti-cancer analysis was conducted in full NCI 60 cell lines derived from nine tumor subpanels, including melanoma, leukemia, colon, lung, ovarian, CNS, prostate, renal, and breast cancer cell lines *in vitro*. NO-donating 2-[(4,5-diphenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-*N*-hydroxy-1-phenylethanimine **(83)** showed potent growth inhibitory activity against renal cancer A498 cell line with 50.52(%) cell growth inhibition [122].



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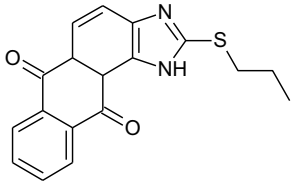
A series of 2-thio-substituted anthra[1,2-d]imidazole-6,11-diones were synthesized by utilizing fragment-based design strategies, and using the NCI 60-cell panel assay, hTERT repressing activity and cell proliferation activity were evaluated. Among all the synthesized compounds, six showed moderate selectivity against leukemia cancer. Only 2-(propylthio)-1H-anthra[1,2-d]imidazole-6,11-dione **(84)** showed different selectivity for renal cancer. All the test compounds showed different cytotoxic and cytostatic activities and can be considered anti-cancer drugs for developing a potential application [54].



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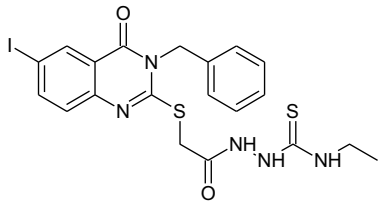
14. ANTI-CANCER EFFECTS ON MULTI CANCER CELL LINES

In medicinal chemistry, synthesized molecules are screened for anti-cancer activity against diverse cancer cell

lines. With similar pathways, the same molecules could impact different cancer cell lines. Khalil *et al*. synthesized a novel series of 2-substituted mercapto-3H-quinazolines, including 2-heteroarylthio and 6-iodo moieties, in such a way that the 5-thioether moiety remained on position 2. Thioether is a functional group recognized for increasing anti-tumor activity. Analogs were screened as active anti-cancer agents *in vitro*, and eighteen molecules were evaluated for their anti-tumor activity. In this study, *N*'-[(3-Benzyl-4-oxo-6-iodo-3H-quinazoline-2-yl)thioacetyl]-*N*^{3}-ethylthio semicarbazide **(85)**, *N*-benzoyl-*N*'-[2-(3-benzyl-4-oxo-6-iodo-3H-quinazoline-2-yl)thioacetyl] hydrazine **(86)** and 2-[(3,6-dioxo-pyridazine-4-yl)thio]-3-benzyl-4-oxo-6-iodo-3H-quinazoline **(87)** demonstrated to be the most active compounds displaying GI_{50} values of 12.8, 11.3, and 13.8 μM, respectively. To manufacture the desired thioethers, *via* $-CH_2-$ or $-CH_2CO-$ bridges or only tied to the sulfur atom to the 2-SH of the quinazoline ring, a diversity of heterocycles were connected. Utilizing three cancer cell lines, including SF-268 (CNS), NCIH460 (lung), and MCF-7 (breast), the synthesized molecules were exposed to one dose prime anti-tumor analysis *in vitro* [123].



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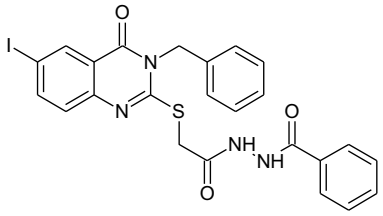

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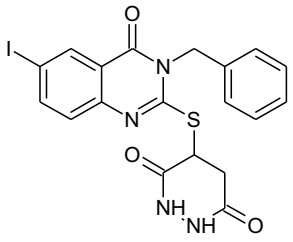

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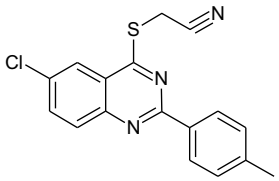
New derivatives of quinazoline were synthesized and evaluated for their anti-tumor activity against three tumor cell lines, including HeLa (cervix), MCF-7 (breast), and HEPG2 (liver). Against all tumor cell lines, with IC_{50} values in the range of 3.35-5.59 μg/ml, thioether molecules {[6-chloro-2-(4-methylphenyl)quinazolin-4-yl]sulfanyl}acetonetrile **(88)** and 6-chloro-2-(4-methylphenyl)-4-[(3-nitropyridin-2-yl)sulfanyl] quinazoline **(89)** displayed strong anti-tumor activity. Strong inhibitory activity of the molecules compared to other equivalent series and molecular docking studies assisted in figuring out the diverse interplays between the ligands and enzyme active sites [124].



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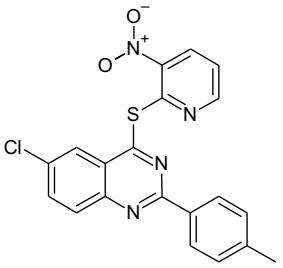
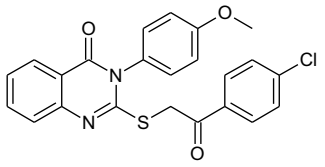


(89)

Some novel quinazoline derivatives were synthesized and their biological assessment as anti-tumor agents was performed using anti-tumor scanning processes. 2-{[2-(4-chlorophenyl)-2-oxoethyl]sulfanyl}-3-(4-methoxyphenyl) quinazoline-4(3H)-one **(90)** and 3-(4-chlorophenyl)-2-{[2-(4-methoxyphenyl)-2-oxoethyl]sulfanyl}quinazolin-4(3H)-one **(91)** were the most active members which exhibited broad-spectrum anti-tumor activity against myriad cell lines that belong to distinct tumor subpanels. In future developments, these two quinazoline analogs could be considered as stronger anti-tumor agents. In addition to the 6-substituted quinazolinone derivatives, their *S*-methyl thioether counterparts and 2-thioxo-3-substituted quinazolinones displayed considerable anti-tumor potency [125].



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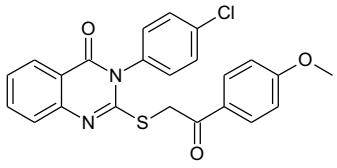
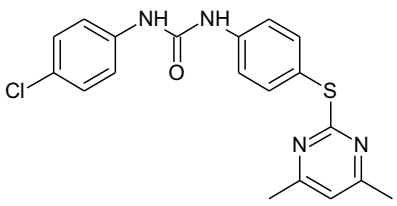


(91)

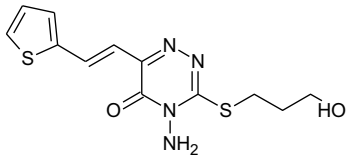
Jin *et al.* synthesized a new set of ureas, including the pyrimidinyl group. Some of the synthesized molecules demonstrated potential cytotoxicity against several human cancer cell lines. The entry of a sulfide bridge between pyrimidinyl and phenyl rings plays a key role in their biological activities. The researchers came to this conclusion regarding structure-activity relationships when four cancer cell lines, CNE2 (nasopharyngeal), KB (oral carcinoma cell), MCF-7 (breast), and MGC-803 (gastric), were analyzed using the MTT method, that an ether bond increased anti-cancer activity through the entry of a sulfide bridge. For instance, four compounds bearing sulfide bridges showed IC_{50} values of 20.0 μM, 32.1 μM, 10.2 μM, and 15.5 μM, respectively. With IC_{50} values of 10.2 μM and 13.5 μM, 1-

(4-chlorophenyl)-3-{4-[(4,6-dimethylpyrimidin-2-yl)sulfanyl]phenyl}urea **(92)** displayed the best inhibitory activity against KB and CNE2 cell lines [126].



(92)

A series of *S*-alkyl and *S*-glycosyl derivatives of 1,2,4-triazine-5(4H)-one were synthesized utilizing distinct halo compounds. Some of the synthesized compounds were investigated as anti-cancer agents. In some members of the series, important anti-tumor activities were screened *in vitro*. 4-amino-3-[(3-hydroxypropyl)sulfanyl]-6-[(*E*)-2-(thio-phene-2-yl)ethenyl]-1,2,4-triazin-5(4*H*)-one **(93)** was the most active cytotoxic agent against dissimilar cancer cell lines, including HCT-116 (colon), MCF-7 (breast) and Hep-G2 (liver) [127].



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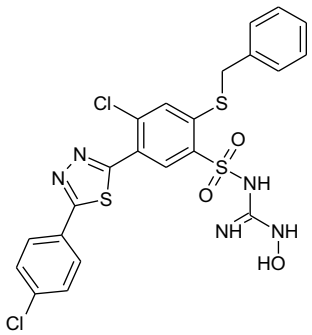
Twenty-four 1-[2-alkylthio-5-(azol-2 or 5-yl)-4-chlorobenzenesulfonyl]-3-hydroxyguanidines were synthesized, and some of the compounds were tested for their *in vitro* anti-cancer activity. Three compounds, 1-{2-benzylthio-4-chloro-5-[5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl]benzenesulfonyl}-3-hydroxyguanidine **(94)**, 1-[2-benzylthio-4-chloro-5-(3-phenyl-1,2,4-oxadiazol-5-yl)benzenesulfonyl]-3-hydroxyguanidine **(95)** and 1-{2-[(1,3-benzodioxol-5-yl)methylthio]-4-chloro-5-(5-phenyl-1,3,4-thiadiazol-2-yl)benzenesulfonyl}-3-hydroxyguanidine **(96)** demonstrated the highest *in vitro* anti-cancer activity with TGI mean values of 3.72-4.47 μM and GI_{50} average value in the range of 1.62-1.86 μM. The remaining compounds displayed a wide spectrum of anti-cancer activity at nominal micromolar GI_{50} values against all the tested cancer cell lines, such as non-small cell lung cancer, leukemia, colon, melanoma, breast, CNS, prostate, ovary, and renal cancer [128].



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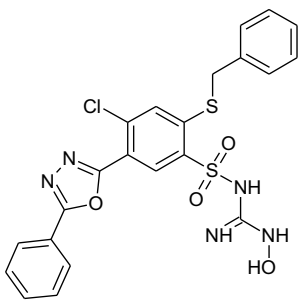

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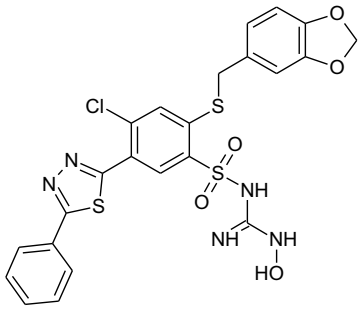
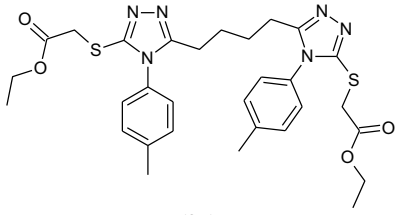


(96)

Purohit *et al.* evaluated the cytotoxicity of novel derivatives containing thioether functionality and other pharmacophore alterations. Against three human cancer cell lines, A-549, HT-29, and MDA MB-231, the compounds were evaluated for *in vitro* cytotoxicity potential utilizing the standard MTT analysis. Eighteen bis-1,2,4-triazole derivatives, including diethylcarbamoyl, thioester, and hydrazide functional groups, were synthesized and characterized. The triazoles substituted with p-tolyl and p-ethoxy phenyl groups displayed greater cytotoxicity than other compounds. The triazole compounds that had thioether bridge, such as 1,4-bis [5-(carbethoxy-methyl)-thio-4-(p-tolyl)-1,2,4-triazol-3-yl]-butane **(97)**, 1,4-bis[5-(carbethoxy-methyl)-thio-4-(p-ethoxyphenyl)-1,2,4-triazol-3-yl]-butane **(98)**, and 1,4-bis(5-[hydrazinocarbonyl methylthio]-4-p-ethoxyphenyl-1,2,4-triazol-3-yl)butane **(99)**, were found to possess strong cytotoxicity. Among the synthesized compounds, the triazoles with diethylcarbamoyl and thioester functionality were found to be more efficient than their acid hydrazide counterparts because of their higher lipophilicity and higher membrane penetrating power [129].



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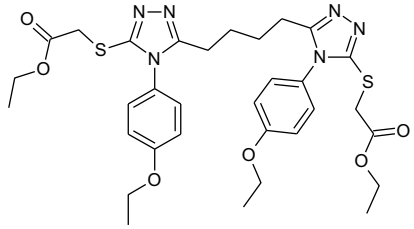

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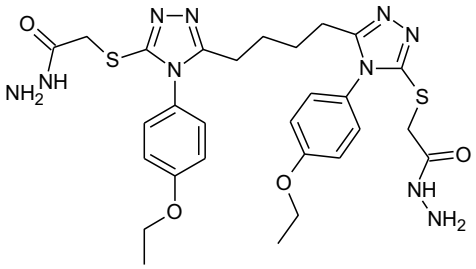
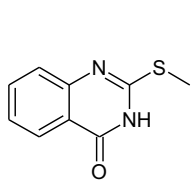


(99)

Alanazi *et al.* synthesized and evaluated a new series of 2-([5-mercapto-4-(substituted)-4*H*-1,2,4-triazol-3-yl)methylthio]-3-phenethylquinazolin-4(3H)-ones and 2-(substituted-thio)-3-phenethylquinazolin-4(3H)-ones because of their *in vitro* anti-tumor activity. A thiol group was used as a starting material. Novel molecules were synthesized by researchers using the thiol group, and all synthesized molecules had a thioether group. 2-(methylsulfanyl)quinazoline-4(3H)-one **(100)** demonstrated anti-tumor activity against breast and renal cancer cell lines. 3-Phenethyl-2-[2-(piperidin-1-yl)ethylthio]quinazoline-4(3H)-one **(101)** displayed mild activity against breast cancer cell lines and compound 2-[(4-ethyl-5-mercapto-4*H*-1,2,4-triazol-3-yl)methylthio]-3-phenethylquinazolin-4(3H)-one **(102)** demonstrated good activity toward non-small cell lung cancer cell and leukemia lines [28].



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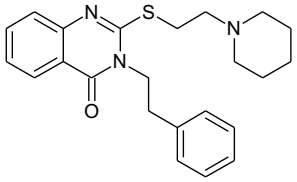

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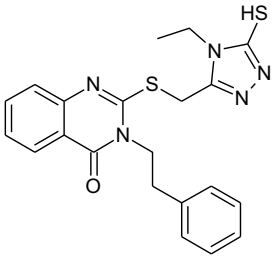

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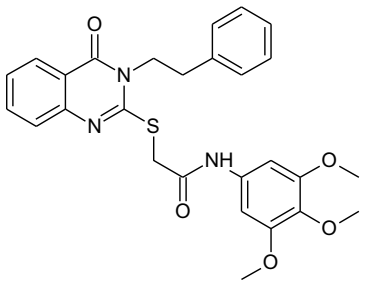
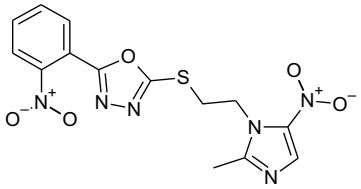


(103)

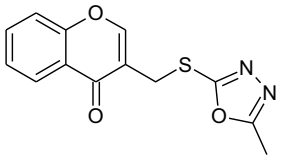
Alsuwaidan *et al.* designed, synthesized, and evaluated a new series of 2-(3-phenethyl-4(3H)quinazoline-2-ylthio)-*N*-substituted anilides and substituted phenyl 2-(3-phenethyl-4(3H) quinazoline-2-ylthio) acetates for their *in vitro* anti-tumor activity. 2-[(3-Phenylethyl-4-oxo-3,4-dihydroquinazolin-2-yl)sulfanyl]-*N*-(3,4,5-trimethoxyphenyl)acetamide **(103)** showed notable broad-spectrum anti-tumor activity. Compound **(103)** showed notable growth inhibitory activity against colon cancer (GI_{50}=2.02 μM), renal cancer (GI_{50}=1.77 μM), breast cancer (GI_{50}=2.77 μM), non-small cell lung cancer (GI_{50}=2.04 μM), melanoma cancer (GI_{50}=3.30 μM) and ovarian cancer (GI_{50}=2.55 μM). For compound **(103)**, the researchers conducted a docking study into the ATP binding site of EGFR-TK. Molecular docking studies demonstrated the inhibitory activity of compound **(103)** and aided in figuring out the diverse interactions between the active sites of the enzyme and the ligands [130].

A series of new 1,3,4-oxadiazole thioether derivatives were synthesized as anti-cancer agents and potential inhibitors of thymidylate synthase (TS). The anti-cancer activities of these compounds against three cancer cell lines were evaluated *in vitro* by the MTT method. All compounds showed strong inhibition activities toward HepG2 cell lines. 2-{[2-(2-methyl-5-nitro-1H-imidazole-1-yl)ethyl]sulfanyl}-5-(2-nitrophenyl)-1,3,4-oxadiazole **(104),** including a nitro substituent, showed stronger *in vitro* anti-cancer activities against HepG2 (liver), SGC-7901 (gastric), and MCF-7 (breast) cell lines with IC_{50} values of 0.7 ± 0.2, 30.0 ± 1.2, and 18.3 ± 1.4 μM, respectively. The compound can be chosen as a dual antibacterial/anti-tumor agent according to molecular docking and 3D-QSAR studies. A few 1,3,4-oxadiazole thioether derivatives displayed significant anti-cancer activities [131].



(104)

With the benefits of good output, short time periods, mild conditions, and ready isolation of the crops, new thioether substituted flavonoids with various heterocyclic groups were synthesized *via* a microwave-assisted process. The antiproliferative activities of these flavonoids were evaluated against six cancer cell lines, including Hela, HCCLM-7, SW-480, MDA-MB-435S, MCF-7, and Hep-2 by the MTT-based assay. Compared with the positive control 5-fluorouracil, 3-{[(5-methyl-1,3,4-oxadiazol-2-yl)sulfanyl]methyl}-4*H*-chromen-4-one **(105)**, 3-{[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl} -4*H*-chromen-4-one **(106)** and 3-{[(4-oxo-4H-thiochromen-2-yl)sulfanyl]methyl}-4*H*-chromen-4-one **(107)** were successfully detected as the most potent agents due to their higher potency and broad-spectrum bioactivity with IC_{50} values in the range of 0.43-6.7 μM. This study showed that functional thioether groups could increase the anti-tumor activity of candidate compounds. Huang *et al.* concluded that the entry of heterocyclic groups with a resilient thiomethyl linkage into the chromene scaffold as new anti-cancer drugs is an efficient strategy for the future improvement of flavonoids [132].



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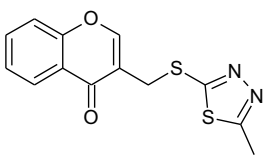
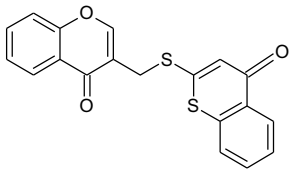


(106)

Insuasty *et al.* proposed a cyclocondensation reaction between 6-amino-2-methylthiopyrimidin-4(3H)-one and bis-(benzylidene)piperidones for the formation of pyrimidonaphthyridines. In the absence of acid or basic catalysts, in the reaction medium, microwave irradiation was utilized as an energy resource. 7-methyl-2-(methylthio)-9-(3,4,5-

trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one **(108)** was detected as a potent compound among eighteen pyrimidonaphthyridines against different cancer cell lines, with important GI_{50} values against melanoma and leukemia cells, according to anti-cancer screening information. With the most significant GI_{50} values ranging from 1.48 to 9.92 μM, the compound showed significant activity against 57 cancer cell lines in *in vitro* analysis [133].



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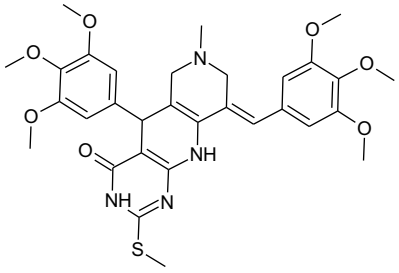
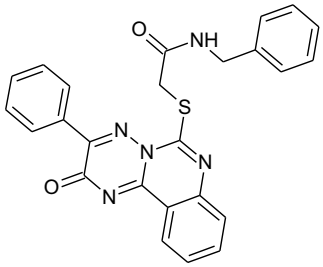


(108)

Through the extra production of thiophenol conjugates, at the C17 location having both aryl and alkyl-substituted α,β-unsaturated ketones, the synthesis of a novel class of 3-methoxyestrone analogs was defined. Combining β-substituted thioethers with 4-methylthiophenol, both aromatic and alkyl-substituted enones were synthesized and evaluated. The biological activity of these novel estrone-derived analogs was examined. The previously described reaction sequence and advantage of the synthesized enone structure were reported. The benefits of the enones are due to β-substituted aromatic thioethers through a thiol addition to alkyl and phenyl β-substituted enones [134]. A series of new *N*-aryl(alkaryl)-2-[(3*R*-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazoline-6-yl)thio]acetamides were obtained by the reaction of *N*-aryl-2-chloroacetamides with alkylation of potassium salts and aminolysis of activated acids. For assessing the GI_{50} level ($logGI_{50}$ is from -7.57 to -4.05 for dissimilar cell lines), the most effective five compounds in micromolar concentrations were screened *in vitro*. *N*-benzyl-2-[(3-phenyl-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazoline-6-yl)thio] acetamides **(109)** exhibited a different selectivity against renal cancer, *N*-(2-methoxybenzyl)-2-[(3-phenyl-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazoline-6-yl)thio]acetamides **(110)** showed anti-cancer activity against colon cancer and melanoma, and *N*-(2-fluorobenzyl)-2-[(3-phenyl-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazoline-6-yl)thio]acetamides **(111)** showed anti-cancer activity against renal cancer. Compound **(109)** displayed the highest susceptibility to renal cancer cell line A498 ($logGI_{50}$ = -7.57) [135].

Yurttaş *et al.* synthesized and designed some novel 1-(aryl)ethanone derivatives and evaluated their anti-cancer activities. For the success of the synthesis of new similar compounds for nontoxic, more selective, and more active derivatives, the ongoing studies have been supported by findings from the study of toxicity and activity [136]. Condensation of isothiocyanates with ethyl-2-cyano-3,3-dimethyl-4-phenylbutanoate, 3-substituted 5,5-dimethyl-2-thioxo-2,3,5,6-tetrahydrobenzo[*h*]quinazolin-4(1H)-ones was cyclized in 1-amino-3,3-dimethyl-3,4-dihydronaphthalene-2-ethylcarboxylate. Markosyan *et al.* studied antineoplastic features of the synthesized compounds. The plurality of tetra-substituted derivatives showed significant EAC growth inhibition (50-71%, $p < 0.05$). Substituted compounds 5,5-dimethyl-3-phenyl-2-sulfanylbuthyl-5,6-dihydrobenzo[h]quinazolin-4(3H)-one **(112)** and 5,5-dimethyl-3-phenyl-2-[(2-methylbenzyl)sulfanyl]-5,6-dihydrobenzo[h]quinazolin-4(3H)-one **(113)**, in tests against sarcoma 180, showed modest activity [137].



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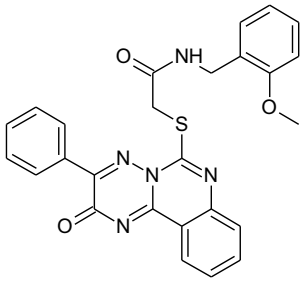

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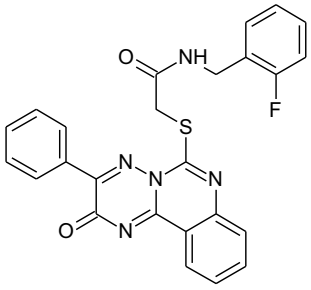

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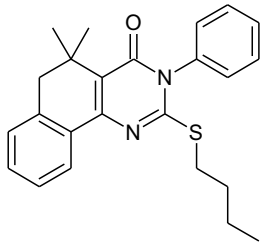

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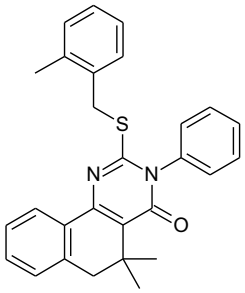
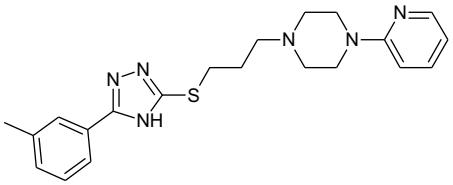


(113)

Murty *et al.* synthesized a series of 5-(substituted)- 1,2, 4-triazole-3-thione derivatives with good output, beginning from suitable carboxylic acids utilizing two different protocols. The cytotoxicity assays of these derivatives were studied against five distinct human cancer cell lines (THP-1, U937, Colo205, HL-60, and MCF7). Six compounds displayed potent anti-cancer activity. The triazole derivatives 5-(3-methylphenyl)-4*H*-1,2,4-triazol-3-yl-3-[4-(2-pyridyl) piperazino]propylsulfide **(114)** and 5-(3-chlorophenyl)-4*H*-1,2,4-triazol-3-yl-3-[4-(2-pyridyl)piperazino]propylsulfide **(115)** were the most efficient thioethers against U937 (28.19 μM, 49.13 μM, and 52.33 μM) and HL-60 (6.67 μM, 18.51 μM, and 29.36 μM) cell lines. As a feasible determinant of their biological activity, the cytotoxic potency of the derivatives changed among the cell lines [138].



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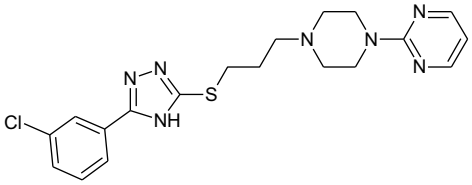
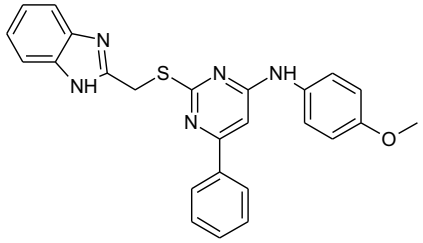


(115)

A series of pyrimidine-benzimidazole hybrids were designed, synthesized, and evaluated for anti-cancer activity against four human cancer cell lines, including MGC-803, MCF-7, SMMC-7721, and EC-9706. Some of the synthesized compounds showed mild to strong activity against MGC-803 and MCF-7. Against all four tested human cancer cell lines, 2-[(1H-benzimidazole-2-ylmethyl)sulfanyl]-6-phenyl-*N*-(4-methoxyphenyl)pyrimidine-4-amine **(116)** and 2-{[(5-chloro-1H-benzimidazole-2-yl)methyl]sulfanyl}-6-phenyl-*N*-(4-methoxyphenyl)pyrimidine-4-amine **(117)** were more cytotoxic than 5-fluorouracil, with IC_{50} values ranging from 2.03 to 10.55 μM and 1.06 to 12.89 μM, respectively. Due to an increase in apoptotic cell death, compounds led to cell cycle arrest in the G2/M phase in the MGC-803 cell line [139].

As efficient CDC25 inhibitors, a new series of imidazopyridine derivatives were synthesized and screened for their anti-tumor activity. In addition to inhibiting the proliferation of diverse types of cancer cell lines, the strongest one among all the compounds inhibited the activities of CDC25A/B enzymes, which involved cell division cycle (CDC) of 25 proteins and key phosphatases arranging proliferation and cell cycle transition. In MCF-7, HepG2 and HT-29 cell lines, 1-(3,4-dihydroxyphenyl)-2-((1-mesityl-1H-imidazo[4,5-c] pyridin-2-yl)thio)ethanone **(118)** started S-phase cell cycle arrest, along with generation of ROS, apoptosis and mitochondrial dysfunction. Oral management of the molecule specifically inhibited xenografted human liver tumor growth [140].



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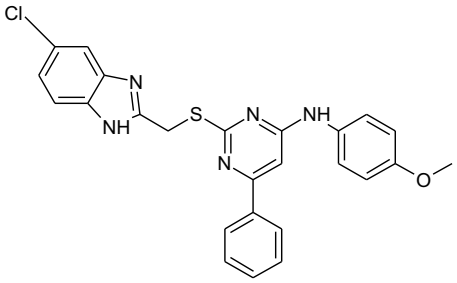

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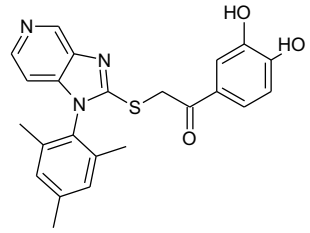
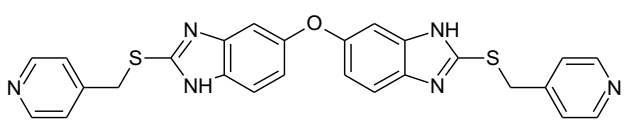


(118)

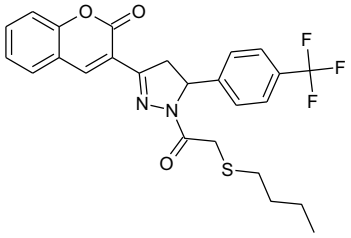
Wang *et al.*synthesized a novel series of bis-benzimidazole derivatives. Toward the chosen tumor cells, these compounds, especially 2,2'-bis-pyrid-4-yl methylsulfanyl-5,5'-bis-1H,10H-benzimidazole ether **(119)**, showed high activity according to *in vitro* cytotoxicity assessment. The compound exhibited IC_{50} values of 5.58 μmol/L (cervical cancer cell (HeLa)) and 5.95 μmol/L (mononuclear tumor cell line (U937)), respectively [141].



(119)

As potential telomerase inhibitors, a series of new derivatives were designed and synthesized. Five compounds showed high anti-tumor activity against MGC-803, SGC-7901, HEPG-2, and Bcap-37 cell lines. Through inducing cell cycle arrest in the G0/G1 phase, 3-(1-(2-(butylthio)

acetyl)-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-3-yl)-2H-chromen-2-one **(120)** and 1-(5-(3,5-dibromo-2-hydroxyphenyl)-3-methyl-4,5-dihydropyrazol-1-yl)-2-(propylthio)ethanone **(121)** could suppress cell proliferation. The 3D structure appeared more stable and formed mainly straight-chain thioether moiety composed of ATP-binding pocket and hydrophobic-hydrophobic interaction, resulting in the higher anti-tumor activity of compounds [142].



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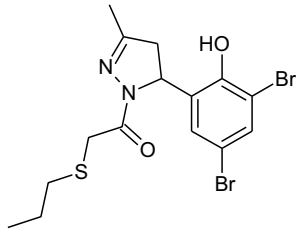
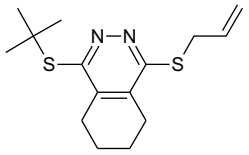


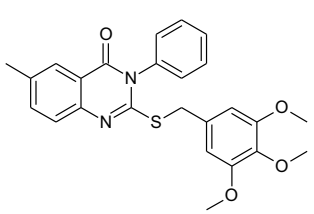
(121)

For the development of novel anti-cancer agents, a new series of 1-allylthio-4-alkylthio-5,6,7,8-tetrahydrophthalazine and 6-allylthio-3-aralkylthio-4,5-dimethylpyridazines were synthesized from maleic anhydride derivatives. These obtained derivatives included the formation of phthalazine and pyridazine rings, aralkylthiolation, dichlorination, and allylthiolation. In CCK-8 analyses against breast cancer (MCF-7) and hepatocarcinoma (Hep3B) cells, these novel compounds displayed antiproliferative activities. Compared to 5-FU, five compounds displayed higher potency for inhibiting the growth of the cell line. Among the five compounds, 1-(tert-butylsulfanyl)-4-(prop-2-en-1-ylsulfanyl)-5,6,7,8-tetrahydrophthalazine **(122)** displayed the highest activity towards Hep3B and MCF-7 cells. In that study, aryl halides were reacted with thiols to give suitable thioethers. The nucleophilic substitution reaction of an aryl halide with a thiol is both efficient for the synthesis of thioethers and important for the preparation of pharmaceuticals [143].



(122)

A novel series of quinazoline derivatives were designed, synthesized, and evaluated for their *in vitro* anti-tumor activities. Against several tumor cell lines, 2-[(3,4,5-trimethoxybenzyl)-thio]-3-phenyl-6-methyl-quinazolin-4(3H)-one **(123)** and 2-[(4-methoxy-benzyl)-thio]-3-benzyl-6-methyl-quinazolin-4(3H)-one **(124)** displayed a wide spectrum of anti-tumor activity. With GI_{50} MG-MID values of 2.2 and 2.4 μM, respectively, the compound proved to be ten-fold more active than 5-FU [144].



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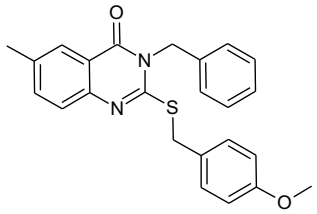
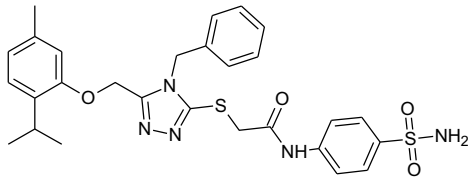


(124)

Beginning from phenolic compounds, Kulabaş *et al.* synthesized a set of thiosemicarbazide derivatives, 1,2,4-triazol-3-thione derivatives, and compounds including 2-(4*H*-1,2,4-triazole-3-ylthio)acetamide structure. From these compounds, 2-{[3-[[5-methyl-2-(propan-2-yl)phenoxy]methyl)-4-benzyl-4,5-dihydro-1H-1,2,4-triazol-5-yl]sulfanyl}-*N*-(4-sulfamoylphenyl)acetamide **(125)**, 2-{[3-[[5-methyl-2-(propan-2-yl)phenoxy]methyl]-4-benzyl-4,5-dihydro-1H-1,2,4-triazol-5-yl] sulfanyl}-*N*-(4-chlorophenyl)acetamide **(126)** and 2-[(3-{[4-(acetylamino)phenoxy]methyl}-4-benzyl-4,5-dihydro-1H-1,2,4-triazol-5-yl)sulfanyl]-*N*-(4-bromophenyl) acetamide **(127)** were selected and evaluated against 60 human cancer cell lines derived from nine distinct cancer types. In human tumor cell lines K-562, A549, and PC-3, antiproliferative activity of the chosen compounds was observed. These compounds showed anti-cancer activity against PC-3 cells, A549/ATCC cells, and K-562 cells, with IC_{50} values of 5.96, 7.90, and 7.71 μM, respectively. Caspase activation and Bcl-2 activity of the chosen compounds were investigated after the cell viability assay. In a dose-dependent manner, these three compounds displayed a distinct increase in caspase-3 activity [145].



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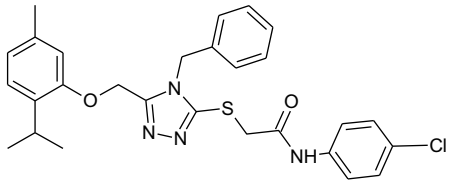

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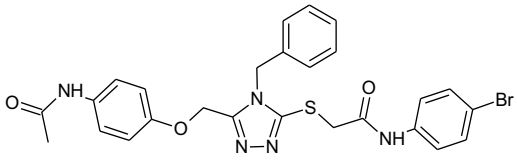
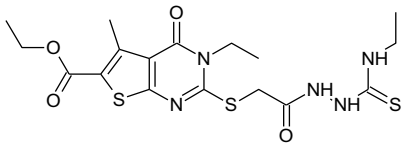


(127)

Some derivatives of 3-ethyl-2-mercapto-thieno[2,3-d]pyrimidin-4(3H)-ones were designed and synthesized by researchers as precursors to predict their cytotoxicity and proliferative activity, utilizing ethyl 2-aminothiophene-3-carboxylates. Thienopyrimidinones, including thiosemicarbazide and 1,3,4-thiadiazole moieties, were evaluated for

their cytotoxic impact on cancer cell lines, namely MDA-MB-231, HT-29, HepG2, HeLa as well as human diploid cell line Lep-3. Ethyl 3-ethyl-2-(((2-(2-(ethylamino)-2-thioxoacetyl)hydrazinyl)methyl)thio)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate **(128)**, 3-ethyl-2-(((5-(ethylamino)-1,3,4-thiadiazol-2-yl)methyl)thio)-5,6-dimethylthieno [2,3-d] pyrimidin-4(3H)-one **(129)** and ethyl 3-ethyl-2-(((5-(ethylamino)-1,3,4-thiadiazol-2-yl)methyl)thio)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate **(130)** demonstrated cytotoxicity against the studied cancer cell lines [146].



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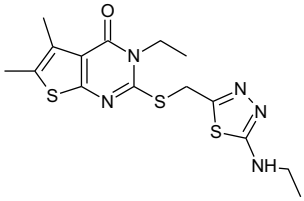

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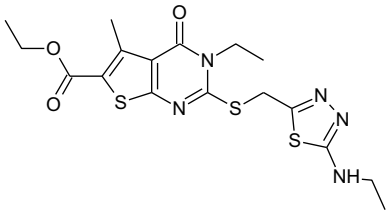
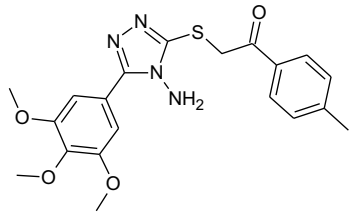


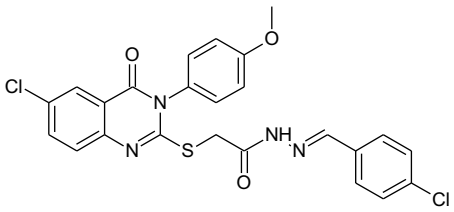
(130)

Ferrociphenols (FCs) and their oxidized electrophilic quinone methide metabolites (FC-QMs) were described as organometallic compounds. Wang *et al.* investigated the reaction of chosen thiols with cellular nucleophiles to evaluate the reactivity of FC-QMs. They synthesized and characterized FC-SR compounds, which are a series of novel compounds resulting from the supplement of these nucleophiles. Against hormone-resistant cancer cells, some of the FC-SR compounds displayed antiproliferative effects [147]. In several pathogen protections, cancer, and immunological diseases, the complex created between flagellin and host toll-like receptor 5 (TLR5), a spherical protein that is the major component of a bacterial flagellum, plays an important role. In addition to primary human PBMCs in both cultured cell lines, a series of new small-molecule inhibitors for flagellin-induced TLR5 signaling with high selectivity and inhibitory activity were synthesized using pyrimidine, triazole, and thioether derivatives [148]. A set of new 3-alkylsulfanyl-4-amino-1,2,4-triazole derivatives were designed, synthesized, and evaluated for their antiproliferative activities. Some compounds showed effective antiproliferative activities against four cancer cell lines, namely HCT116, HepG2, Hela, and PC-3. With IC_{50} values of 0.37, 2.94, and 31.31 μM, in inhibiting HCT116, Hela and PC-3 cell proliferation, respectively, the most potent compound 2-[(4-amino-5-(3,4,5-trimethoxyphenyl)-4*H*-1,2,4-triazol-3-yl)sulfanyl]-1-(4-methylphenyl)ethanone **(131)** showed 184-, 18-, and 17-fold increase compared to fluorouracil. The compound did not affect normal human embryonic kidney cells, HEK-293. In a dose-dependent manner, the compound induced apoptosis and inhibited the cell cycle in the G2/M phase in HeLa cells [149].



(131)

Abuelizz *et al.* synthesized a novel series of quinazoline derivatives. The cytotoxicity of all compounds was evaluated *in vitro* against the HeLa and MDA-MB231 cancer cell lines. With the IC_{50} range of 1.85-2.81 μM, three compounds were considered potential anti-cancer agents. These compounds utilizing aromatic and hetero substituents of the quinazoline core could be considered a beneficial template [150]. El-Gazzar *et al.* designed, synthesized, and evaluated a novel series of 2-mercapto-quinazolin-4-one analogs for their *in vitro* antitumor activity. *N*'-[4-chlorobenzylidene]-2-[6-chloro-3-(4-methoxy-phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl-thio]acetohydrazide **(132)** and 6-chloro-2-((4-(4-chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-3-yl)methylthio)-3-(4-methoxyphenyl)quinazolin-4(3H)-one **(133)** displayed anti-tumor activity with IC_{50} values of 9.5 and 25.4 μg/ml against human MCF-7 breast tumor and Caco-2 colon cell lines, respectively [151].



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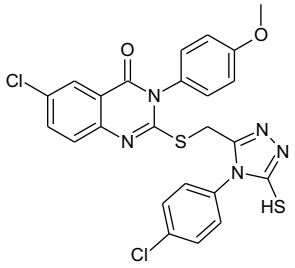
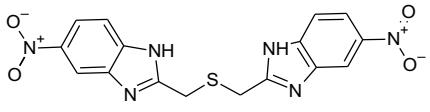


(133)

Gohary *et al.* prepared and reported novel benzimidazole analogs. 2,2'-(sulfanediyldimethanediyl)bis(5-nitro-1H-benzimidazole) **(134)**, 1-(4-chlorophenyl)-2-{[(5-nitro-1H-benzimidazole-2-yl)methyl]sulfanyl}ethanone **(135)** and 1-(4-bromophenyl)-2-{[(5-nitro-1H-benzimidazole-2-yl)methyl] sulfanyl}ethanone **(136)** were the most active analogs against HepG2, HCT-116 and MCF-7 cancer cell lines, respectively, according to the *in vitro* anti-tumor screening of the analogs. These three potent anti-tumor analogs were also evaluated for cytotoxicity against the W138 normal cell line and *in vivo* anti-tumor activity against EAC in mice. Com-

pounds **134** and **136** showed remarkable ILS (% Increase in lifespan) of mice injected with EAC cells, with IC_{50} values of 224.14 μM and 212.42 μM, respectively [72].



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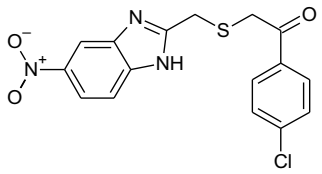

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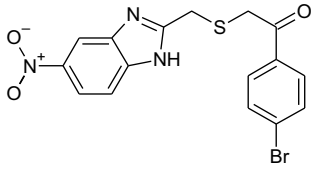
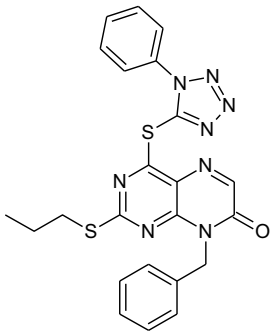


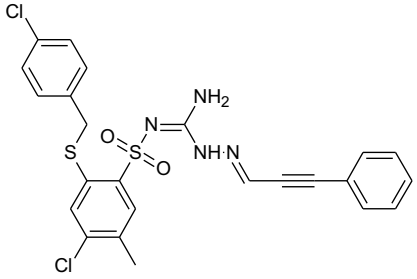
(136)

A series of novel diheteroaryl thioether analogs were designed, prepared, and screened against MKN-45, MGC-803, H1650, and EC-109 cancer cell lines. Most of the targeted compounds showed mild to good antiproliferative activities. Towards the tested cell lines with IC_{50} values below 10 μM, 8-benzyl-4-[(1-phenyl-1H-tetrazol-5-yl)sulfanyl]-2-(propylsulfanyl)pteridine-7(8*H*)-one **(137)** demonstrated the best anti-tumor activity. The compound enhanced Bax expression, down-regulated the expression of Bcl-2, and divided caspases-3/9. For preparing anti-tumor agents or biological probes, the diheteroaryl thioethers are a class of arising chemotypes. The compound could serve as a fine starting point to draft novel apoptosis inducers. The synthesis of a series of novel diheteroaryl thioether derivatives was reported which were evaluated for their anti-cancer activity and inception mechanisms of inducing cancer cell death [152].



(137)

Pogorzelska *et al.* synthesized and evaluated a series of novel 2-(2-alkylthiobe1nzenesulfonyl)-3-(phenylprop-2-ynylideneamino)guanidine derivatives for their anti-tumor activity towards cell lines of cervical cancer HeLa, colon cancer HCT-116, and breast cancer MCF-7 *in vitro* by MTT assays. Derivatives, such as 2-{4-chloro-2-[(4-chlorobenzyl) thio]-5-methylbenzenesulfonyl}-3-(3-phenylprop-2-ynylideneamino)guanidine **(138)** and 2-{4-chloro-2-[(4-chlorobenzyl)thio]-5-methylbenzenesulfonyl}-3-(1-methyl-3-phenylprop-2-ynylideneamino)guanidine **(139)**, showed the best anti-cancer properties with IC_{50} values of 6-18 μM and 8-14 μM, respectively. The new series of derivatives displayed good metabolic stability among the pharmacologically active compounds [153].



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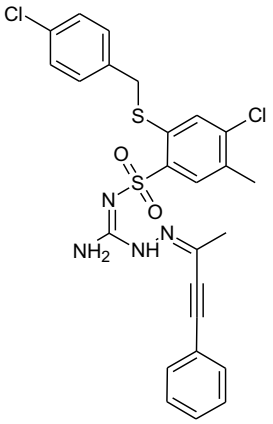

(139)

15. FUTURE PERSPECTIVE

Cancer is one of the biggest problems faced by humanity. Solving this problem is a multi-step and complex process. Many doctors and scientists around the world are developing and testing a variety of methods for the treatment of cancer and cancer-related diseases. Over time, with the development of new technologies, hopefully, cancer will not be a problem for humanity. In the next decade, further developments based on the accumulated medicinal chemistry knowledge and functional studies, together with new approaches, will lead to eventual success in developing anticancer agents to treat cancer. With the development of selective and targeted anti-cancer agents, the side effects of cancer drugs will also be minimized. In particular, pathological, histological, genetic, and radiological tests performed in cancer screening are very significant in diagnosing cancer. Also, biochemical and histological scans of pathology tissues obtained by biopsy may assist in developing new molecules.

Additionally, the recent identification of newly synthesized compounds as new therapeutic targets in various types of cancer will stimulate further development efforts. It is thought that thioether-bearing compounds will be among the new chemotherapeutics that will be used in cancer treatment. Further studies on structure-activity relationships will better explain that thioether structure is an effective group against cancer.

Executive Summary

• Cancer is a complex disease caused by the uncontrolled division and proliferation of cells, and under the influence of genetic and environmental conditions, SHP2 and Lyp have gained significant attention as drug targets for cancer and autoimmune diseases, respectively.

•Although there are more than 100 types of cancer and standard approaches developed, cancer is still a personal devastating disease.

• • In addition to chemotherapy, radiotherapy, and surgery, which are accepted as standard treatments, grafts, and biological, hormonal, targeted, and gene therapies are being used increasingly.

• • Many doctors and scientists around the world are developing and testing a variety of methods for the treatment of cancer and cancer-related diseases.

• In recent years, drugs for macromolecular targets have been used to treat cancer types.

• In recent years, researchers have been synthesizing thioether derivatives for targeted macromolecules to treat various cancer types.

• Researchers are also working to obtain promising thioether compounds.

CONCLUSION

Cancer is a disease associated with the division of cells controlled by genes. Biological therapies, such as radiotherapy, chemotherapy, surgery, immunotherapy, hormone therapy, targeted therapies, and gene therapy, can be used alone or together to treat cancer. Chemotherapy, like radiotherapy, can be administered as neoadjuvant therapy or alone to reduce tumor size before surgery. In recent years, the development of selective new chemotherapeutic agents targeting cancer cells has been implicated in the goals of medicinal chemists. Thioethers are significant functional groups with a lot of biological activities. They have been used for the synthesis of biologically active molecules by researchers. Many methods and protocols support the synthesis of thioether compounds successfully. Even though stereotyped synthetic methods are used in laboratory conditions, different processes are also accepted for the synthesis of diverse thioether derivatives. In recent years, anti-cancer activity studies of thioether compounds have also been carried out.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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