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An insight into the therapeutic potential of piperazine-based anticancer agents

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Abstract: The piperazine ring system is among the medicinally important nitrogen-containing heterocyclic ring systems and is exploited for the synthesis of various drug molecules. A number of FDA-approved anticancer drugs contain piperazine rings and thus it is considered as an attractive scaffold having extraordinary potential for the development of new anticancer agents. In recent decades there has been an alarming increase in the number of people suffering from cancerous diseases all over the world, which resulted in an extraordinary increase in research reports on new anticancer drug candidates. The aim of this article is to highlight the structural parameters imparting anticancer activity to piperazine derivatives and to indicate future perspectives for the discovery of new anticancer agents.

Key words: Piperazine chemistry, structural features, anticancer activity

1. Introduction

Cancer is an uncontrolled proliferation of cells and has become a public health concern all over the world. Cancer cells have the ability to invade through blood or lymph and spread to other parts of the body.[1] Cancer can affect almost every tissue in the body and is one of the major causes of mortalities each year.[2] According to the World Health Organization, about 8.8 million deaths were reported due to cancer in 2015.[3] Deaths due to cancer are increasing continuously and it is estimated that about thirteen million people will die of cancer in 2030.[4,5] Chemotherapy is one of the important methods for the treatment of cancer besides surgery and radiation therapy. There are many effective cytotoxic drugs available for the treatment of cancer, but their lower selectivity for tumor cells than normal cells is responsible for severe adverse effects.[6] Chemotherapeutic agents are now used in combination so that the toxicity due to the overexpression of single agents can be prevented.[7] The emergence of drug resistance to the existing anticancer agents is increasing, which is the major cause of failure of anticancer chemotherapy.[8] Therefore, discovery and development of novel efficacious, selective, and less toxic anticancer molecules is urgently needed. Piperazine is a vital heterocycle for most bioactive compounds.[9] Piperazine-containing molecules have presented various biological activities like antibacterial,[10] antifungal,[11] antimalarial,[12] antidepressant,[13] antitumor,[14] alpha adrenoceptor antagonist,[15] and 5-HT7 receptor antagonist activities.[16] Buspirone (antianxiety) and trazodone (antidepressant) are recently approved drug molecules that contain pyrimidinylpiperazine and 3-chlorophenylpiperazine respectively in their structures.[17,18] The piperazine ring system has earned special attention in the discovery of a wide range of drugs, especially for the development of anticancer agents. In 2016, a review of anticancer piperazine was published.[19] However, there still remains

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a need to summarize the research publications in the field. This article comprehensively deals with the recent research work on piperazine derivatives having anticancer activity and highlights the structural parameters responsible for their bioactivity.

2. Review of the literature

2.1. FDA-approved piperazine-based anticancer drugs

The piperazine ring is present in a number of FDA-approved anticancer agents. More than 200 approved anticancer agents by National Cancer Institute USA were checked; among these, the piperazine-based anticancer agents include abemaciclib **1**, bosutinib **2**, brigatinib **3**, dexrazoxane **4**, dosatinib **5**, imatinib **6**, leucovorin **7**, olaparib **8**, palbociclib **9**, ponatinib **10**, rociletinib **11**, venetoclax **12**, and trabectidin **13** (Figure 1).[20]

Abemaciclib **1** was reported as a D-cyclin dependent kinase (CDK4/6) inhibitor to treat different cancer types.[21] Bosutinib **2** was found effective for the cure of breast cancer[22] while brigatinib **3** is effective against oncogenic anaplastic lymphoma kinase.[23] Bates and coworkers described the use of dexrazoxane **4** in stage IIIB or IV of metastatic breast cancer as a cost-effective treatment preventing anthracycline-induced cardiotoxicity.[24] Dasatinib **5** is an orally active drug for the treatment of chronic myelogenous leukemia and acute lymphoblastic leukemia,[25] and imatinib **6** is a potential protein kinase inhibitor.[26] Leucovorin **7** plus fluorouracil is used for the cure of colon cancer.[27] Olaparib **8** is applicable in ovarian and breast cancer treatment[28] and palbociclib **9** in combination with endocrine agents is approved for treatment of patients with estrogen receptor-positive breast cancer.[29,30] Ponatinib **10** is an excellent inhibitor of RET kinase and has activity in models of RET-driven medullary thyroid carcinoma.[31] Rociletinib **11** is an effective inhibitor of epidermal growth factor receptor (EGFR) and is effective against non-small-cell lung cancer.[32] Venetoclax **12** and trabectidin **13** are effective for the treatment of chronic lymphocytic leukemia[33] and liposarcoma or leiomyosarcoma, respectively.[34]

2.2. Chemistry and pharmacology of new piperazine-containing anticancer compounds

Piperazine derivatives with anticancer activities are categorized below on the basis of their chemical structures.

2.2.1. Piperazine-containing polymeric anticancer agents

In 2016, organo-iron complexes containing 1,4-dipiperazinobenzene-cyclopentadienyliron hexafluorophosphate were synthesized and were evaluated against two breast cancer cell lines, HTB26 and MCF7. Compound **14** (Figure 2) exhibited prominent activity against the HTB26 and MCF7 cell lines, having IC_{50} values of 14 µM for both.[35] In the same year, the same authors synthesized organo-iron melamine dendrimers capped with piperazine molecules. The anticancer activity of the dendrimers was evaluated and significant efficacy was observed for piperazine-terminated organo-iron dendrimers against HTB26 and MCF7 cancer cell lines with IC_{50} values of 3.6 µM and 2.5 µM, respectively. Piperazine-terminated dendrimers exhibited significant inhibitory activities as compared to the dendrimers having chloro or hydroxy terminal groups.[36]

2.2.2. Metal complexes of piperazine derivatives

The metal-containing anticancer drugs cisplatin and carboplatin are effective in the treatment of testicular, ovarian, and colorectal cancer.[37,38] Al-Asbahy et al. synthesized a new dinuclear copper(II) complex having a piperazine bridge ligand as an anticancer agent. The cytotoxicity of compound **15** (Figure 3) was evaluated on different tumor cell lines and showed GI_{50} values below 10 µg/mL against MCF7, K562, and A2780 cancer cell

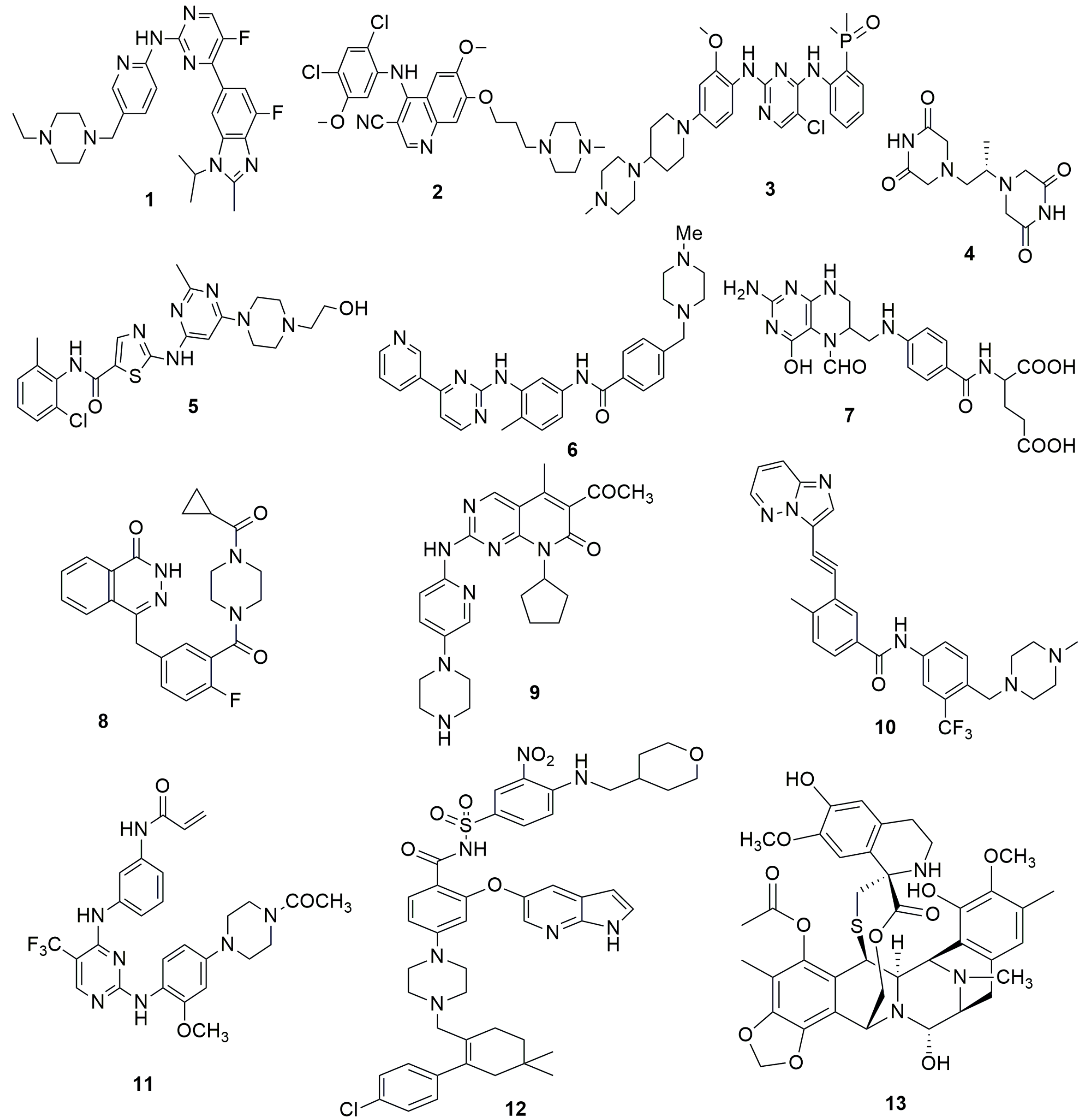

Figure 1. Structures of FDA-approved anticancer drugs based on piperazine rings.

lines. This compound also showed prominent telomerase inhibitory activity, having an IC_{50} value of 17.1 µM.[39] Heteroleptic palladium(II) complexes of 4-(2-methoxyphenyl)piperazine 1-dithiocarbamates with diphenyl-p-tolylphosphine and tri-p-tolylphosphine (**16** and **17**) were prepared. Compound **16** exhibited promising cytotoxic activity against MCF7, having an IC_{50} value of 9.1 ± 2.3 µM. Compound **17** showed prominent activity in this series, having an IC_{50} value of 2.3 ± 0.2 µM against MDA-MB-231. The higher activity of compound **17** was possibly due to its higher stability as compared to **16**, as determined by density functional theory.[40] Arjmand et al. designed and synthesized tin iminodiacetate conjugated with piperazinediium cation **18** as a potential antitumor agent. Conjugate **18** showed significant cytotoxic activity versus HCT15, HOP62, MCF7, and

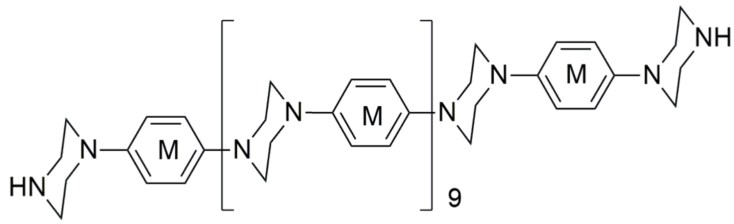

Figure 2. Piperazine-containing organo-iron complex.

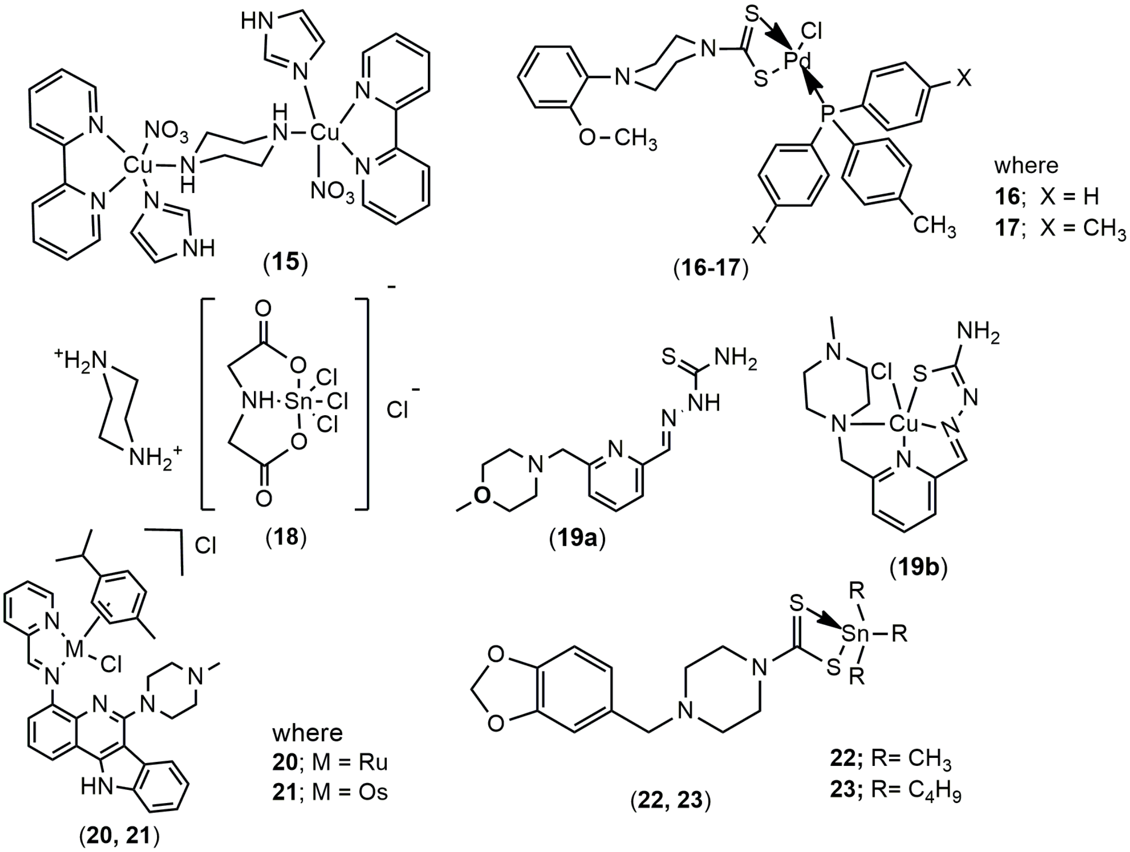

Figure 3. Piperazine-containing anticancer agents having metal complexes.

SK-OV-3 cancer cell lines, having GI_{50} values of less than 10 µg/mL. It also inhibited topoisomerase-1, having an IC_{50} value of 30 µM. The new complex showed less systemic toxicity on the livers and kidneys of rats. This compound interacted with c-DNA through electrostatic interaction.[41] The conjugates of thiosemicarbazone-piperazine and thiosemicarbazone-morpholine along with their copper(II) complexes were studied as anticancer agents. Compound **19b** showed activity against LS174 (colon cancer) cancer cells, having IC_{50} values of 16.4 ± 4.2 µM. The compounds without the metal complexation showed no anticancer activity, having IC_{50} values of greater than 300 µM.[42] The coordination complexes of indoloquinoline-methyl piperazine hybrids with ruthenium and osmium metal were evaluated for their cytotoxic activity. The position of metal complexes with indoloquinoline-piperazine was altered to see the effect on water solubility and anticancer activity. Compounds **20** and **21**, the ruthenium and osmium complexes, were more active, having IC_{50} values of 18.41 ± 2.22 µM and 19.40 ± 1.22 µM, respectively, as evaluated against SK-N-MC neuroepithelioma cells. In these derivatives the metal complexes' binding sites are at position #4 of the indoloquinoline.[43] Shaheen and coworkers synthesized organotin derivatives of 4-(benzo[d][1,3]dioxo-5-ylmethyl) piperazine 1-carbodithioates and evaluated them against a human ovarian cancer cell line by MTT (3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide) assay. Diorganotins were found to be more active compounds, which suggest a lipophilic role of these compounds. Compounds **22** and **23** were found to be more toxic, having IC_{50} values of 0.11 and 0.35 µM, respectively, compared to the standard drug cisplatin.[44]

2.2.3. Natural compounds hybridized with piperazines

Natural products have been a source of new drugs since ancient times. Hybridization of natural and synthetic compounds is a very significant approach to design new lead compounds for therapeutic applications.[45] Natural compounds have contributed significantly to the discovery of new anticancer agents.[46] A series of novel hybrid compounds comprising piperazine and chalcones were screened for anticancer activity. In this series, compound **24** (Figure 4) showed prominent activity against A549, HeLa, and SGC7901 cell lines, having IC_{50} values of 5.24 ± 1.01 µM, 0.19 ± 0.13 µM, and 0.41 ± 0.26 µM, respectively.[47] Mistry et al. synthesized a series of $N-$Mannich bases of berberine having piperazine rings as new anticancer agents. These compounds demonstrated excellent anticancer activities as compared to doxorubicin and berberine as standard drugs. Compounds **25** and **26** were prominent agents, having IC_{50} values of 7.340 ± 0.04 µM and 5.755 ± 0.17 µM for **25** and 7.327 ± 0.08 µM and 7.606 ± 0.08 µM for **26** against cervical cancer lines HeLa and CaSki, respectively.[48] Mistry et al. synthesized N-Mannich bases of berberine with substituted phenyl piperazine molecules and reported their antitumor activities. Compound **27** exhibited promising anticancer effects against HeLa cell lines with IC_{50} values of 4.243 ± 0.03 µg/mL. Compound **28** was most potent against the CaSki cell line, having IC_{50} values of 4.353 ± 0.10 µg/mL. Compounds **27** and **28** showed less toxicity for the cell line MDCK (Madin-Darby canine kidney) having CC_{50} values of 194.2 ± 1.92 µg/mL and 147.8 ± 1.53 µg/mL and presenting a good therapeutic index. Both compounds have shown better anticancer activities than the reference drug, berberine.[49] Singh et al. synthesized colchicine derivatives and screened them for antiproliferative activities against two colon cancer cell lines, HCT-116 and Colo-205. P-glycoprotein (P-gp) induction activity of these agents was also evaluated. Piperazine-containing derivative **29** presented anticancer activity against HCT-116 (IC_{50} value of 3.0 µM) and Colo-205 (IC_{50} value of 1.0 µM) cancer cell lines.[50] Sun et al. synthesized podophyllotoxin and piperazine acetate esters as new anticancer agents. Compound **30** displayed prominent activity, having IC_{50} values of 2.78 ± 0.15 µM against a human breast cancer cell line. Further analysis showed that these compounds produced their effect by occupying the colchicine binding pocket of tubulin.[51] Amujuri et al. synthesized novel schizandrin derivatives and tested their anticancer properties. Among the synthesized compounds, piperazine analogs **31** and **32** of schizandrin were found to have moderate anticancer activities against the DU-145 cancer cell line, having IC_{50} values of 15.31 and 9.657 µM, respectively, with reference to doxorubicin as a standard drug.[52] Chen et al. reported the synthesis of novel series of estrone derivatives and investigated in vitro cytotoxic activities against human prostate cancer cell lines, i.e. PC3, LNCaP, and DU145. Piperazine derivative **33** showed prominent activity against the PC-3 cell line, having IC_{50} values of 3.41 ± 0.21 µM, while **34** was most active against LNCaP, having IC_{50} values of 0.78 ± 0.34 µM. Compound **35** presented prominent activity against DU145 with IC_{50} values of 0.55 ± 0.25 µM. These compounds exhibited greater cytotoxic efficacies against individual carcinoma cell lines than the reference drug, finasteride.[53]

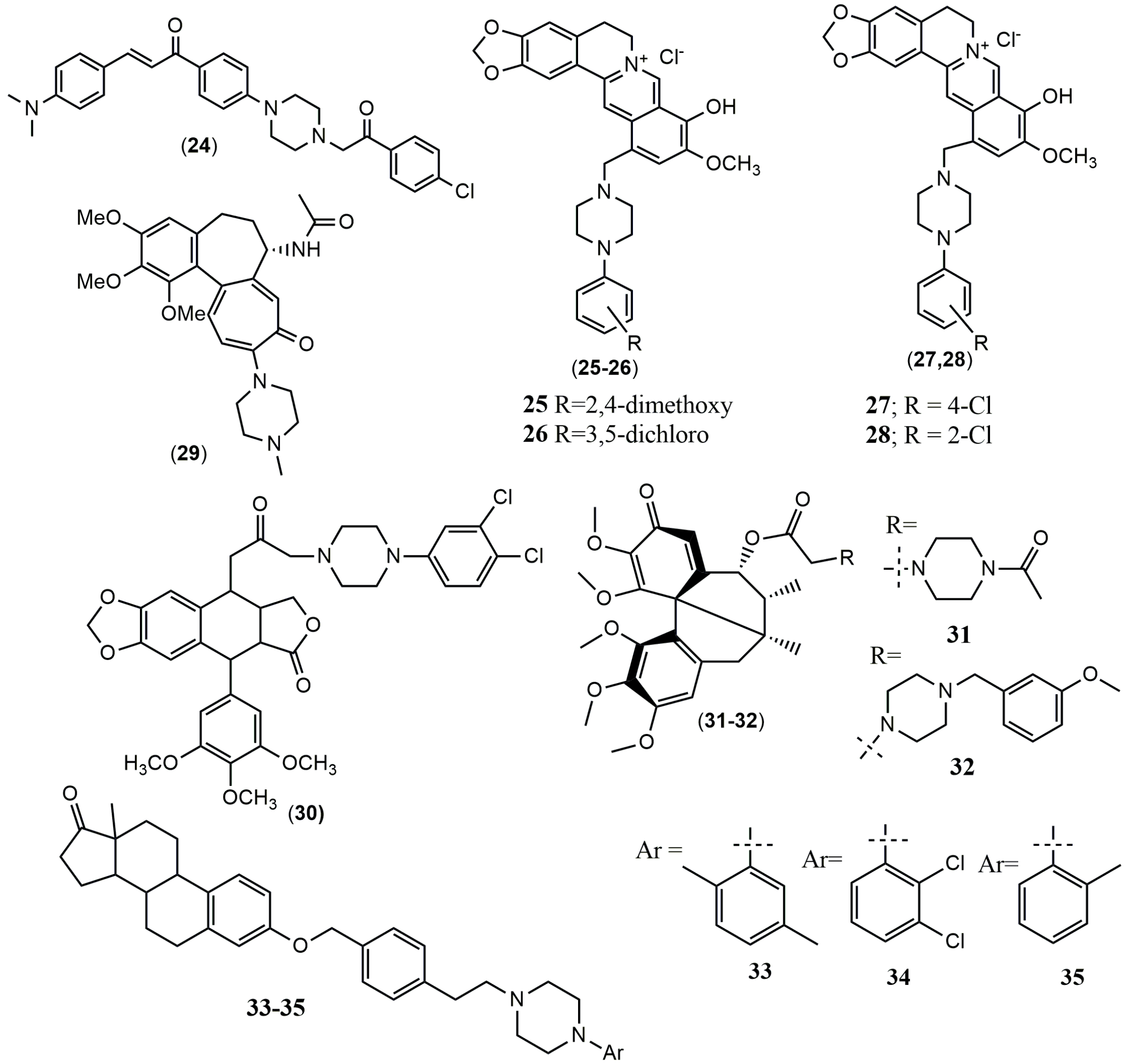

Figure 4. Structures of anticancer piperazine derivatives of natural compounds.

Varchi et al. designed and synthesized a molecular conjugate consisting of a photosensitizer (pheophorbide a) and it was attached to a piperazine containing an antiandrogen molecule via a small pegylated linker. Compound **36** (Figure 5) showed good activity against the PC3 cell line, having an IC_{50} value of 35.1 nM upon irradiation of cells with white light and 98 nM when irradiated with red light. This is due to the reactive oxygen species generated by the photosensitizer part after light irradiation while the antiandrogen molecule releases nitric oxide to produce the overall phototoxic effect. This approach is very interesting and should be developed further.[54] Yang et al. reported the synthesis of cyclic polyamine dehydroabietylamine derivatives and evaluated in vitro anticancer activity against MCF7 and HepG-2 (liver carcinoma) cancer cell lines while using 5-fluorouracil as a standard drug. Piperazine-containing compound **37** was found to have good tumor inhibition effects on HepG-2, having an IC_{50} value of 23.56 µM, and showed selectivity for this cell line compared to MCF7 cells having an IC_{50} value of 62.55 µM. The addition of a benzene ring as a linker in these conjugates led to the formation of less active compounds.[55] Mustafa et al. carried out the synthesis of *N1*-(coumarin-

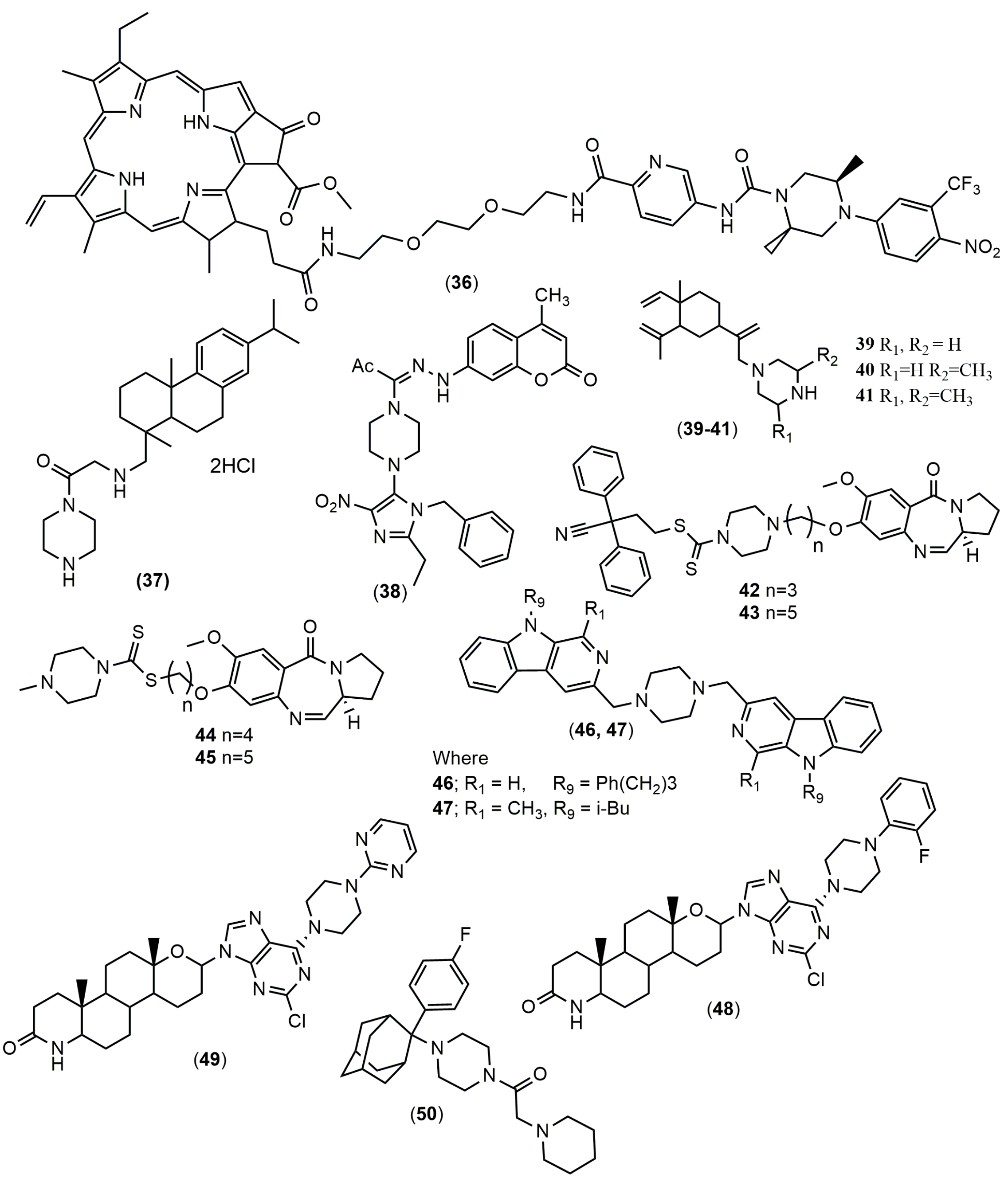

Figure 5. Piperazine derivatives of natural compounds with anticancer activity.

7-yl) piperazineamidrazone derivatives. Evaluation of antitumor activities of these derivatives was performed by MTT assay. The introduction of heterocyclic rings at position 4 of piperazine significantly influenced the anticancer activities. Compound **38** was more active against MCF7 and K562 cell lines, having IC_{50} values of 20.2 ± 3.7 and 9.2 ± 2.8 µM, respectively. This compound reduced the viability of these cells to less than 50% after 72 h. Pyrimidyl and ethyl carboxylate derivatives at position 4 of piperazine also produced compounds with prominent activities.[56] Yu et al. synthesized new piperazine-derived compounds of β-elemene. Compound

39 was found to have promising antiproliferative activity, having IG_{50} values of 4.9 ± 0.6 and an IC_{50} value of 8.3 µM against HL-60 cells. Compounds **40** and **41** were also active, having IC_{50} values of 9.2 ± 0.5 µM and 11.3 ± 0.9 µM. Further evaluation of the mechanism of action revealed that the new derivatives caused apoptosis by the production of ROS and decreasing the c-FLIP (FLICE inhibitory protein) levels.[57] Kamal et al. reported the synthesis, cytotoxic activity, and DNA-binding affinity of dithiocarbamate/piperazine bridged pyrrolo[2,1c][1,4]benzodiazepines. Compound **42** displayed cytotoxic potency against 33 cell lines, having GI_{50} values of <0.99 µM. Furthermore, compounds **43**, **44**, and **45** showed excellent cytotoxic activity, having GI_{50} values of 0.10–1.7 µM against different human cancer cell lines. These derivatives showed good interaction with DNA as determined by molecular docking studies and compound **45** was most prominent, having E_{int} = –114.56 kcal/mol.[58] Sun et al. synthesized bivalent β-carbolines having a piperazine group as the spacer. The introduction of different groups at position #1 and position #9 significantly improved the antiproliferative activities. Compounds **46** and **47** exhibited promising cytotoxic activities. Compound **46**, having an IC_{50} value of 3.02 µM, was most active against the 769-P (renal carcinoma) tumor cell line as compared to standard drug cisplatin (IC_{50} value of 14.7 µM). Compound **47**, having an IC_{50} value of 7.16 µM, was most potent against MCF7, and it also showed antiangiogenic activity.[59] Piperazine-substituted purine 4-aza steroid-nucleoside derivatives (**48** and **49**) exhibited significant cytotoxicities on PC-3 cell lines, having IC_{50} values of 5.13 µM and 1.84 µM, respectively. Compounds **48** and **49** contain chlorine atoms at position #6 of the purine ring and phenyl and pyrimidyl-substituted piperazine rings at position #4.[60] Fytas et al. synthesized 2-aryl-2-dialkyl adamantane derivatives substituted with piperazine. Compound **50** showed excellent activities against HeLa and MDA MB 231 cell lines, having IC_{50} values of 8.4 µM and 6.8 µM, respectively. This compound was also found to be selective as it showed less toxicity to normal human cell lines, which is encouraging for drug development. Therefore, the combination of piperidine acetyl and 4-substituted benzene significantly increased the activity of the derivatives.[61]

2.2.4. Structural hybrids of piperazine with other pharmacophores

Molecular hybridization is a technique in which two or more pharmacophores are attached by a chemical bond. Natural or synthetic bioactive compounds can be combined to produce new molecules with increased activity and less toxicity. The technique of hybrid molecules is also being used while synthesizing new derivatives.[62] Among the series of novel phenanthridinylpiperazinetriazole hybrid molecules, compound **51** has shown promising activity against the THP1 (human acute monocytic leukemia) cell line, having IC_{50} values of 9.73 ± 4.09 µM, while compound **52** was most potent against HL60 (human promyelocytic leukemia), having IC_{50} values of 7.22 ± 0.32 µM as compared to the standard drug etoposide (14.10 ± 0.54 µM). Therefore, the introduction of an aryl sulfonyl group to the triazole ring significantly improved the anticancer activities of these derivatives (Figure 6).[63] The hybrid molecules of 4-piperazinylquinoline-derived isatin compounds, **53** and **54** (Figure 6), exhibited prominent activity and caused apoptosis of MCF7 cancer cells, having GI_{50} values of 15.12 ± 0.34 and 21.56 ± 0.69 µM, respectively, but not to MCF10A noncancer cells. The lipophilic group at the isatin ring produced more active compounds while the trifluoromethyl group at position #7 of quinoline produced less active compounds as compared to the chloride or bromide group.[64] Murty et al. synthesized a series of piperazinylbenzothiazole/benzoxazole derivatives, which were attached to 1,3,4-oxadiazole-2-thiol via propyl chain. Compound **55**, having an IC_{50} value of 36.9 µM, was most prominent against the A431 (skin) cell line. Compound **55** was also active against the MCF7 cell line with an IC_{50} value of 52.7 µM but the most potent

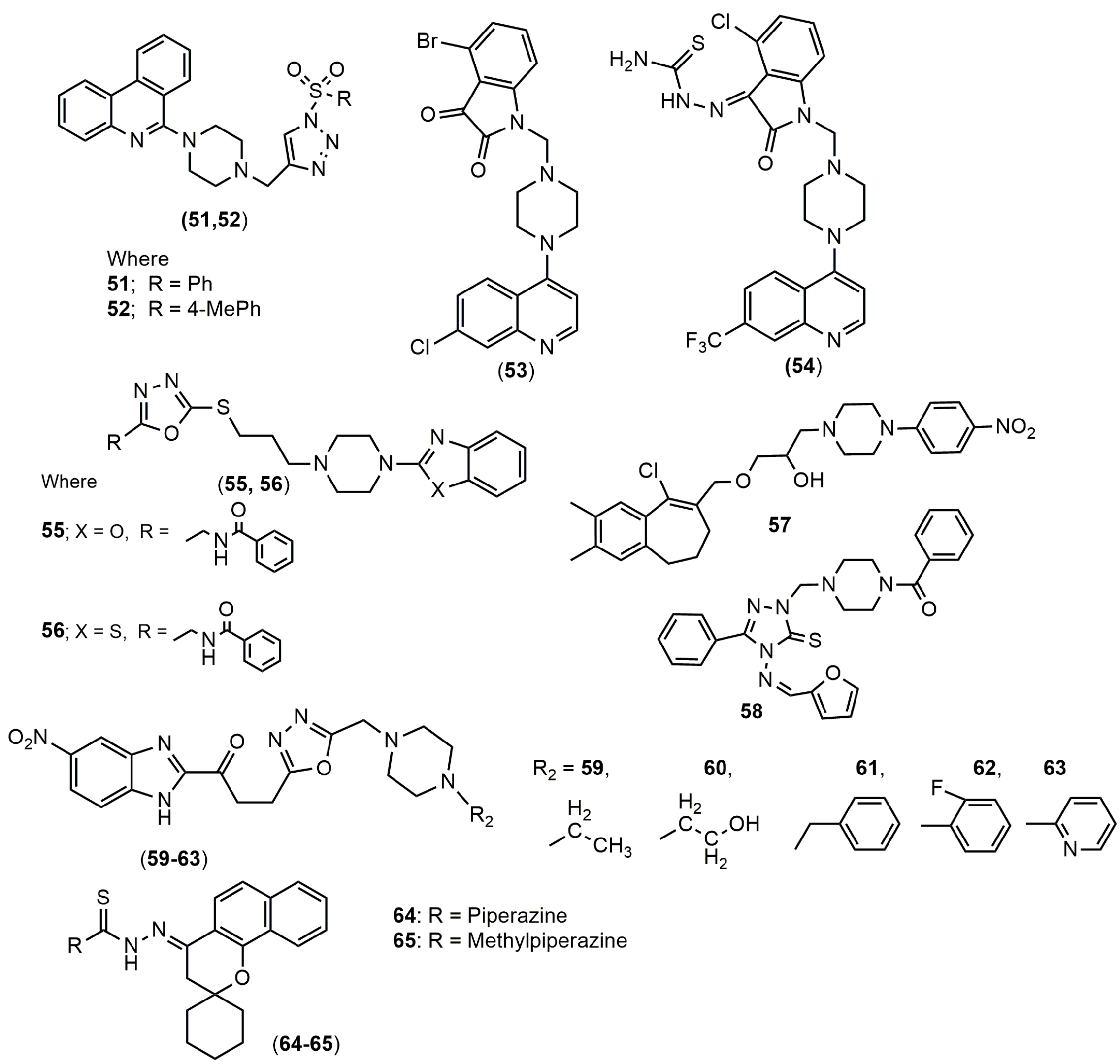

Figure 6. Piperazine-containing synthetic hybrid anticancer agents.

compound against the MCF7 cell line was **56**, having an IC_{50} value of 39.0 µM. Compound **56** also exhibited excellent activity against A431, having an IC_{50} value of 55.9 µM.[65] Vanguru et al. combined benzosuberone, beta-aminoalcohol, and piperazine in a single molecule to produce hybrid molecules. Compound **57** was found to be most potent, having GI_{50} values of 0.010–0.097 µM against HeLa, MDA-MB-231, A549, and MIAPACA cell lines. This molecule also showed better binding interaction (–108.626 kcal/mol) with the binding site of colchicine at β-tubulin.[66] In the triazole and piperazine hybrids reported by Mishra and coworkers, compound **58** showed prominent anticancer activity, having an IC_{50} value of 1.92 µM, and the compound disrupted the G2/M phase of the cancer cell cycle. Upon in vivo evaluation, this compound slowed the progression of tumors, leading to the enhanced life span, and showed less toxicity.[67] Ibrahim et al. carried out the molecular docking simulation, synthesis, and evaluation of anticancer activities of hybrid molecules of 2-substituted-5-nitro-benzimidazole with oxadiazole and piperazine compounds (Figure 6). Compounds **59**, **60**, and **61** showed promising anticancer potentials against the A549 cancer cell line, having IC_{50} values of 8.39 ± 0.11 µM, 8.38 ±

0.09 µM, and 27.80 ± 0.08 µM, respectively. Compounds **61**, **62**, and **63** exhibited activity against the HCT116 cancer cell line with IC_{50} values of 3.28 ± 0.08, 2.56 ± 0.10, and 4.19 ± 0.10 µM, respectively, as compared to reference drug 5-fluorouracil.[68] Among the novel analogs of spirobenzo[*h*]chromene and spirochromane, piperazine-containing spirobenzo[h]chromenes analogs **64** and **65** were found to have moderate anticancer activities against the HT-29, A549, and MCF7 cell lines; however, **65** had better activity against the HT-29 cell line, having IC_{50} values of 8.17 ± 1.23 µM.[69]

2.2.5. Anticancer piperazine derivatives of existing drug molecules

Some existing drug molecules have also been modified by introducing piperazine rings to produce new compounds. Vianello et al. synthesized tranylcypromine derivatives as inhibitors of KDM1A (lysine specific demethylases). The piperazine derivatives of tranylcypromine, compounds **66** and **67**, having IC_{50} values of 0.1885 ± 0.104 µM and 0.0890 ± 0.02 µM against KDM1A, were found to be the most effective agents. Compound **66** (Figure 7) showed more selectivity for KDM1A as compared to MAO-A. The enantiomers of compound **66** were also synthesized because it showed in vivo activity as well as good pharmacokinetic properties. The (*1S*, *2R*) enantiomer **68** (IC_{50} = 0.084 ± 0.003 µM) was more active than its analogue (*1R*, *2S*). It also showed activity upon in vivo evaluation, where it increased the survival time of mice with leukemia.[70] Li et al. synthesized derivatives of imatinib by replacing the amide bond with 1,2,3-triazole and 1,3,4-oxadiazole (Figure 7). Compounds **69**, **70**, and **71** showed excellent anticancer activities, having IC_{50} values of 0.03 and 0.02 µM for **69**, 0.04 and 0.02 µM for **70**, and 0.3 and 0.02 µM for **71** against the K562 and HL60 cell lines, respectively, compared to the reference drug imatinib (0.38 and 0.03 µM for K562 (human chronic myeloid leukemia) and HL60 (acute myeloid leukemia)). The introduction of trifluoromethyl and piperazine ring significantly increased the antiproliferative activities of new derivatives. Since trifluoromethyl is a lipophilic group, it possibly increases the penetration across the cancer cell membrane.[71] Li et al. synthesized novel artemisinin derivatives and evaluated their in vitro anticancer properties. The anticancer activity of 7**2** against MCF7 was excellent with IC_{50} values of 2.1 ± 0.2 µM with reference to artemisinin, dihydroartemisinin, doxorubicin, and temozolomide.[72] Kassab and Gedawy synthesized novel ciprofloxacin hybrids and evaluated their anticancer and antibacterial studies. Five compounds, 7**3**, 7**4**, 7**5**, 7**6**, and 7**7**, demonstrated potent in vitro anticancer activities against different cell lines with IC_{50} values ranging between 0.72 and 4.92 µM, which were 1.5-fold to 9-fold more active than doxorubicin.[73]

2.2.6. Piperazine substituted by aromatic and aliphatic systems

Organic compounds are mostly composed of aromatic and aliphatic rings, which influence their conformation and properties. *N*−Alkylated piperazine derivative **78** acts as an antitumor agent to induce apoptosis in human prostate carcinoma (PC-3) by reactive oxygen species-mediated RhoB expression. This compound (Figure 8) showed higher cytotoxicity against the PC-3 and NUGC-3 (stomach carcinoma) cell lines as compared to HCT-116 and exhibited cell line specificity. Upon in vivo evaluation for antitumor activity, compound **78** demonstrated growth inhibition of PC-3 tumors by up to 74.7% in a mouse at the daily dose of 30 mg/kg, therefore suggesting potential for cancer therapeutics.[74] REV-ERBβ is a nuclear receptor that plays a role in cancer cell survival. In 2015, Torrente et al. reported the synthesis of dual inhibitors of REV-ERBβ and autophagy. Upon anticancer evaluation, compound **79** was found to have good cytotoxicity against a breast cancer cell line (BT-474), having IC_{50} values of 9.41 ± 0.62 µM. It showed no toxicity to the normal HMEC

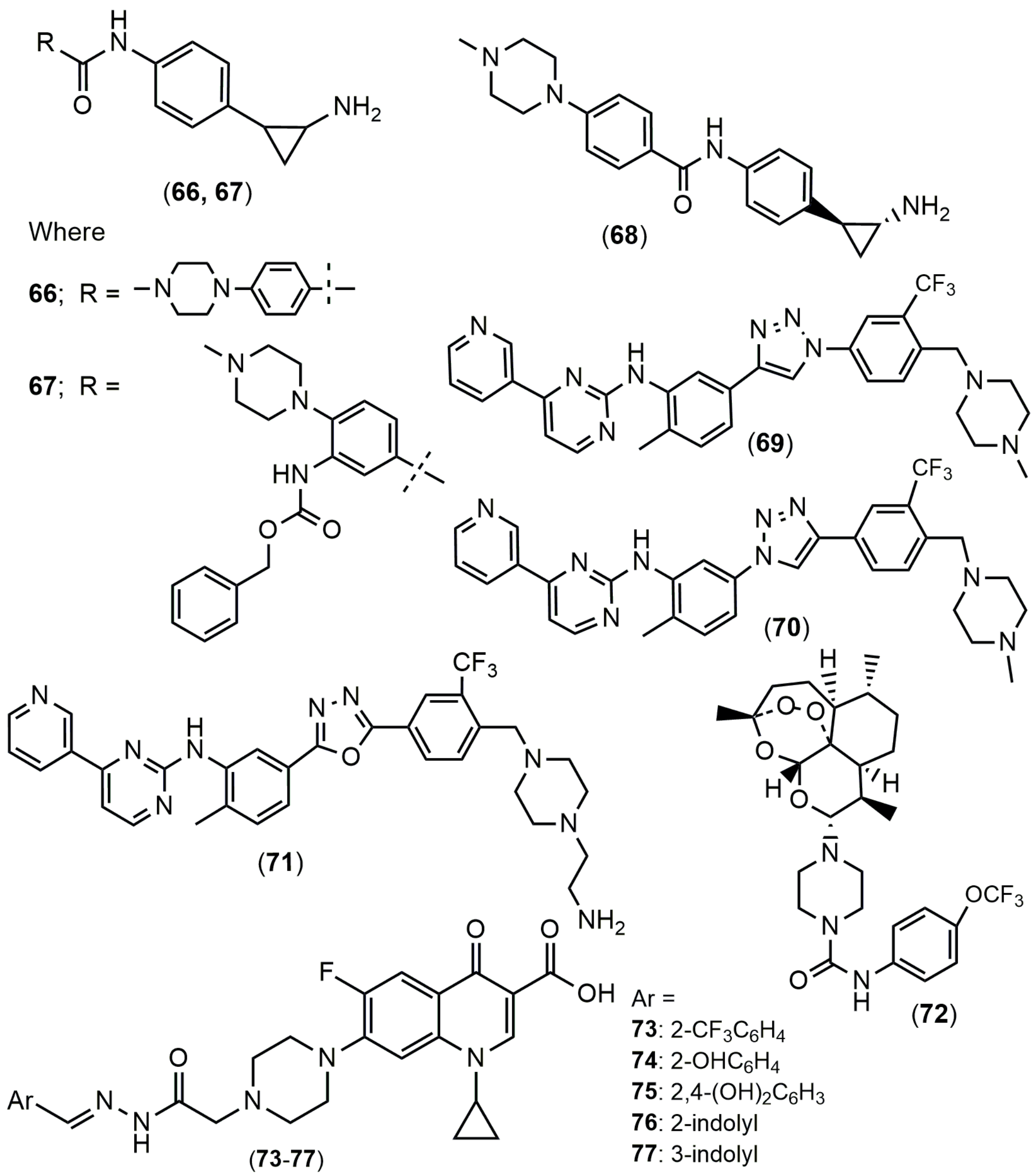

Figure 7. Piperazine derivatives of existing drug molecules.

(human mammary epithelial cell) cell line, having an IC_{50} value of greater than 100 µM.[75] Gurdal et al. synthesized novel benzhydrylpiperazinecarboxamide and thioamide derivatives. 4-Chlorobenzhydryl derivatives were more active as compared to the unsubstituted and disubstituted benzhydryl derivatives. Thioamide derivatives were also more potent than carboxamide derivatives (Figure 8). Compounds **80** and **81** were most active against HUH-7 (hepatocellular) cells, having GI_{50} values of 1.29 µM and 5.97 µM, respectively. The majority of derivatives displayed higher cytotoxicities against HUH-7 as compared to the standard drug 5-fluorouracil (30.66 µM). Compounds **82** and **83** were most active against MCF7, having GI_{50} values of 6.14 µM and 4.94 µM, respectively. Compound **83** was less toxic to a normal breast cell line (MCF-12A), having a GI_{50} value of 8.5 µM. Against the HCT-116 cell line, **84** and **80** were most active, having GI_{50} values of

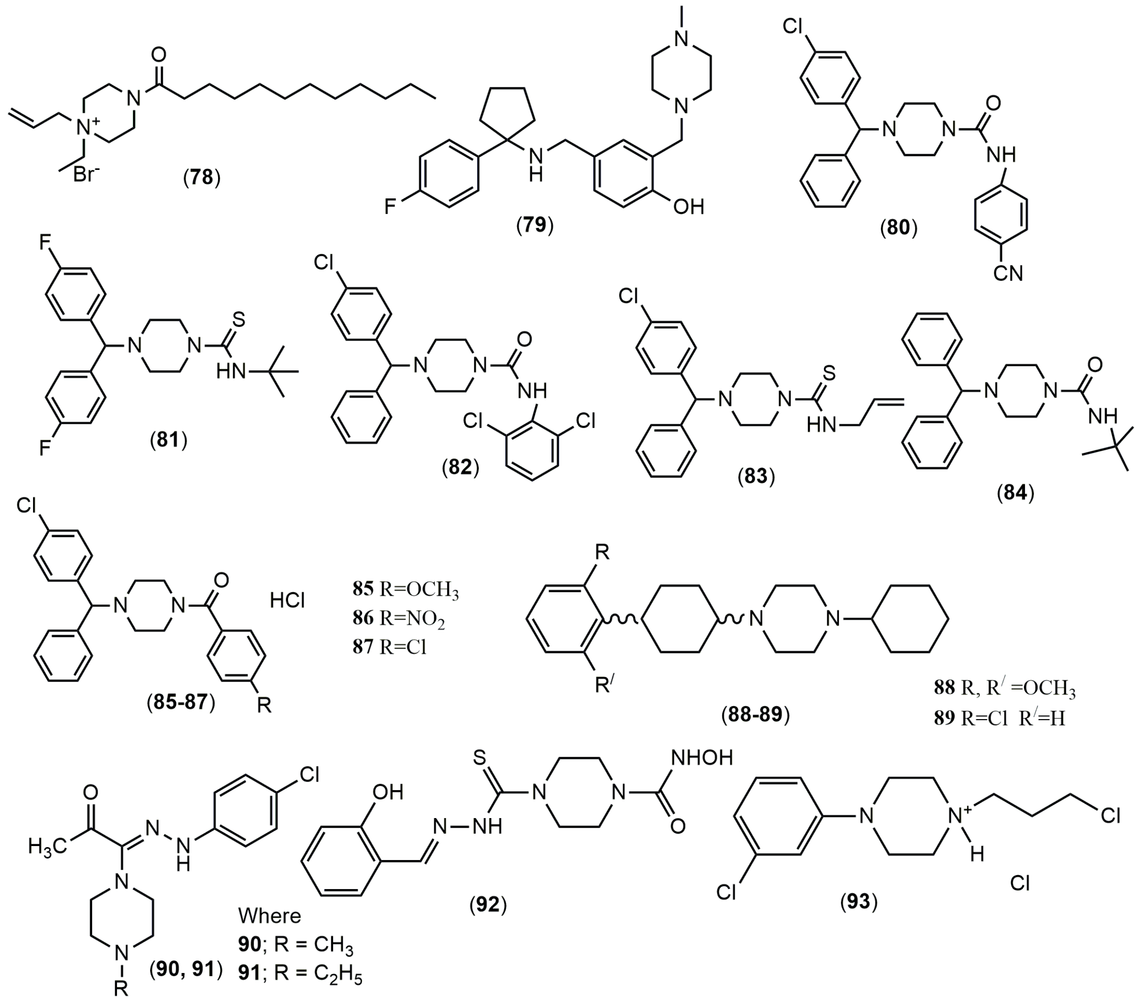

Figure 8. Piperazine derivatives having aromatic and aliphatic systems.

1.01 µM and 1.81 µM.[76] Yarim et al. reported the cytotoxic activity of benzhydryl piperazine derivatives. Many compounds demonstrated good activities but compounds **85** and **86** (Figure 8) were excellent, having GI_{50} values of 0.44 µM and 0.31 µM for T47D (breast) and 1.67 and 2.59 µM for HEP3B (liver). Compound **87** was also found to be a prominent antiproliferative agent with GI_{50} values of 1.91, 2.49, 4.15, and 4.64 µM for the T47D, HEP3B, FOCUS, and HUH7 (liver) cell lines. Further evaluation of compound **87** showed that it produced long-term and irreversible growth inhibitory effects at higher concentrations.[77] Abate et al. synthesized cyclohexylpiperazine derivatives. Compound **88** displayed activities against the PC-3 (IC_{50} = 31.3 ± 8.4 µM) and SK-N-SH (IC_{50} = 32.5 ± 1.9 µM) cell lines. Compound **89** was also active against the PC-3 and SK-N-SH cell lines, having IC_{50} values of 22.6 ± 4.6 and 13.8 ± 0.7 µM. Compound **88** displayed the best antiproliferative activities at 30 and 50 µM when administered in combination with an IC_{50} value of 0.1 µM doxorubicin in MDCK-MDR1 (Madin-Darby canine kidney multidrug resistance) cells. The derivatives in this series exhibited affinities for the sigma receptor and human sterol isomerase (HSI) binding site and have the potential for p-glycoprotein (P-gp) inhibitory activity.[78] Piperazine-containing amidrazone derivatives (**90** and **91**) (Figure 8) showed prominent anticancer activities. It was noted that the methyl-piperazine (4.81 µM)-

substituted compounds had lower mean growth inhibition (MGI) as compared to ethyl-substituted compounds (4.92 µM). Compound **90** showed prominent activity against leukemia (GI_{50} 4.73 µM), non-small-cell lung, colon (GI_{50} 4.76 µM), and CNS cancer (GI_{50} 4.77 µM) cell lines. Compound **91** was most active against the CNS cancer cell line, having a GI_{50} value of 4.68 µM.[79] Piperazine-containing hydroxamates (**92**) appeared potent against NCIH-460 and HCT-116, having GI_{50} values of 5.15 µM and 8.6 µM respectively. They also inhibited hHDAC8 (histone deacetylase) at higher concentrations, having an IC_{50} of 33.67 µM, and this compound has hydrogen bond interaction with this enzyme with a docking score of –7.67. Compound **92** showed encouraging activity against the HL60 cell line, having an IC_{50} value of 0.6 µM. In this cell line there is overexpression of ribonucleotide reductase (RR) and it is possibly inhibited by this compound.[80] Bhat et al. synthesized disubstituted piperazine derivatives having a 3-chlorophenyl group on one side and a 3-chloropropyl group on the other side. Upon screening for cytotoxic potential, compound **93** (Figure 8) was found to have good activity against PC-3, having an IC_{50} value of 16 µM.[81]

2.2.7. Piperazine-containing anticancer agents having other heterocyclic rings

1,4-Dihydropyridine derivatives appeared as another class of anticancer agents. Piperazine-containing compound **94** displayed activities in the range of 8–35 µM against different cancer cell lines. Promising anticancer activities were observed against the M14 (melanoma) and HT29 (colon carcinoma) cell lines, having IC_{50} values of 8 ± 6 µM and 11 ± 3 µM (Figure 9).[82] 5-Fluoro-N^2,N^4-diphenylpyrimdine-2,4-diamines were disclosed as inhibitors of cyclin-dependent kinases CDK2 and CDK9. Compound **95** showed good antitumor activity against DU145 and KBvin (vincristine-resistant KB subline), having GI_{50} values of 0.91 µM. Compounds **96** and **97** displayed prominent activity against A549, having GI_{50} values of 9.07 µM and 12.22 µM. Compound **96** also exhibited better inhibition of CDK9/cyclinT1, having an IC_{50} value of 11.30 µM, as compared to CDK2/cyclinE1.[83]

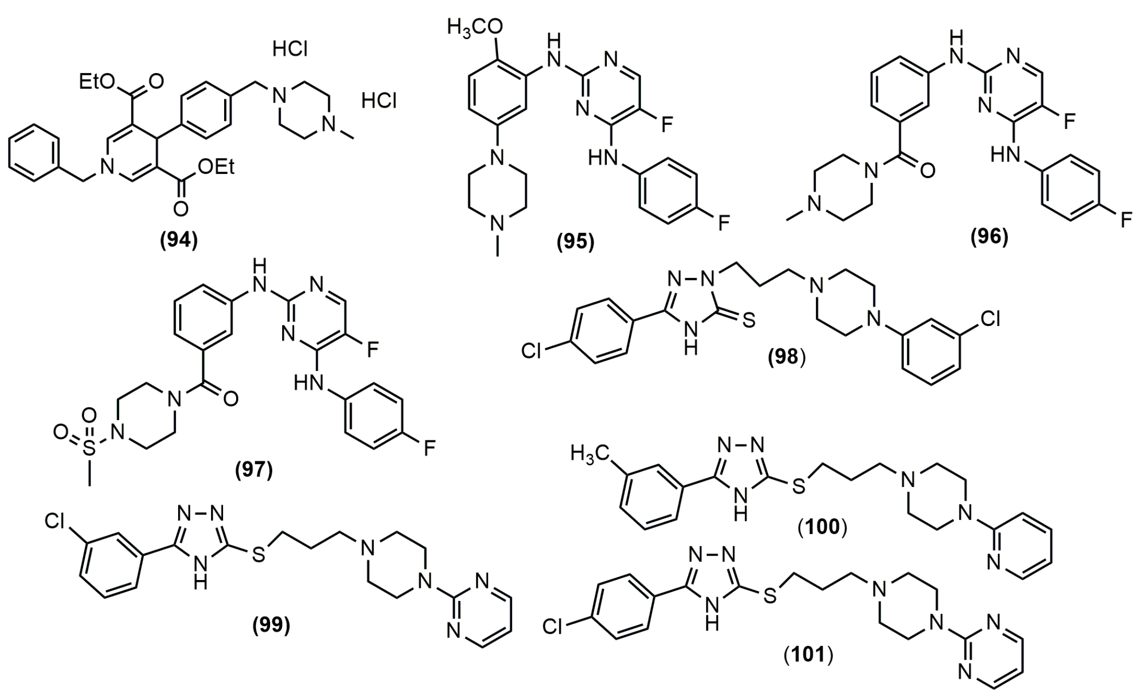

Figure 9. Piperazine derivatives having heterocyclic substitutions.

Among S and N alkyl piperazine derivatives of mercapto-1,2,4-triazole derivatives (Figure 9), compounds **98**, **99**, **100**, and **101** exhibited antiproliferative activities against U937 (human leukemic monocytic lymphoma) cells, having IC_{50} values of 28.19, 49.13, 52.33, and 102.24 µM, respectively. Compounds **98**, **99**, **100**, and **101** also showed activity against HL-60 cells with IC_{50} values of 6.67, 18.51, 29.36, and 105.06 µM, respectively. It was also observed that the compounds with chloro groups at the 3rd and 4th positions of the phenyl ring of the triazole ring and piperazine group substituted with N-3 chlorophenyl, *N*-2-pyrimidyl, and *N*-2-pyridyl groups were most active.[84]

Abadleh et al. reported the synthesis of N^2-(thien-3-yl)amidrazones having piperazine, morpholine, piperidine, and thiomorpholine heterocyclic molecules. Amidrazone **102** with *N*-piperazine moiety exhibited prominent activity against MCF7 and K562, having IC_{50} values of 7.26 µM and 9.91 µM, respectively (Figure 10).[85] Sharathkumar et al. synthesized and evaluated the antiproliferative activity of 4-thiazolidinone-pyridine and piperazine-based conjugates on human leukemia cells. Compound **103** showed potent activity, having IC_{50} values of 9.71, 15.24, and 19.29 µM against Nalm6, K562, and Jurkat cells, respectively. Cytotoxicity of compound **103** was also tested by cell cycle analysis and mitochondrial membrane potential. The possible mechanism of action of compound **103** to produce cell death is the depolarization of mitochondrial membrane potential.[86] Yurttas et al. synthesized triazine derivatives having piperazine amide groups and determined their in vitro antitumor activities on MCF7 cells and NIH/3T3 (mouse embryonic fibroblast cells). Compounds **104** and **105** (Figure 10) showed prominent activity, having IC_{50} values of 56.3 ± 8.1 µM and 56.3 ± 6.9 µM, respectively, against the MCF7 cell line. Compound **105** also showed more activity against normal NIH/3T3 cell lines, having IC_{50} values of 112.8 ± 8.8 µM as compared to cisplatin (1294 ± 15.7 µM).[87] Arnatt et al. reported the synthesis of a piperazine-containing chemokine receptor (CCR5) antagonist effective against

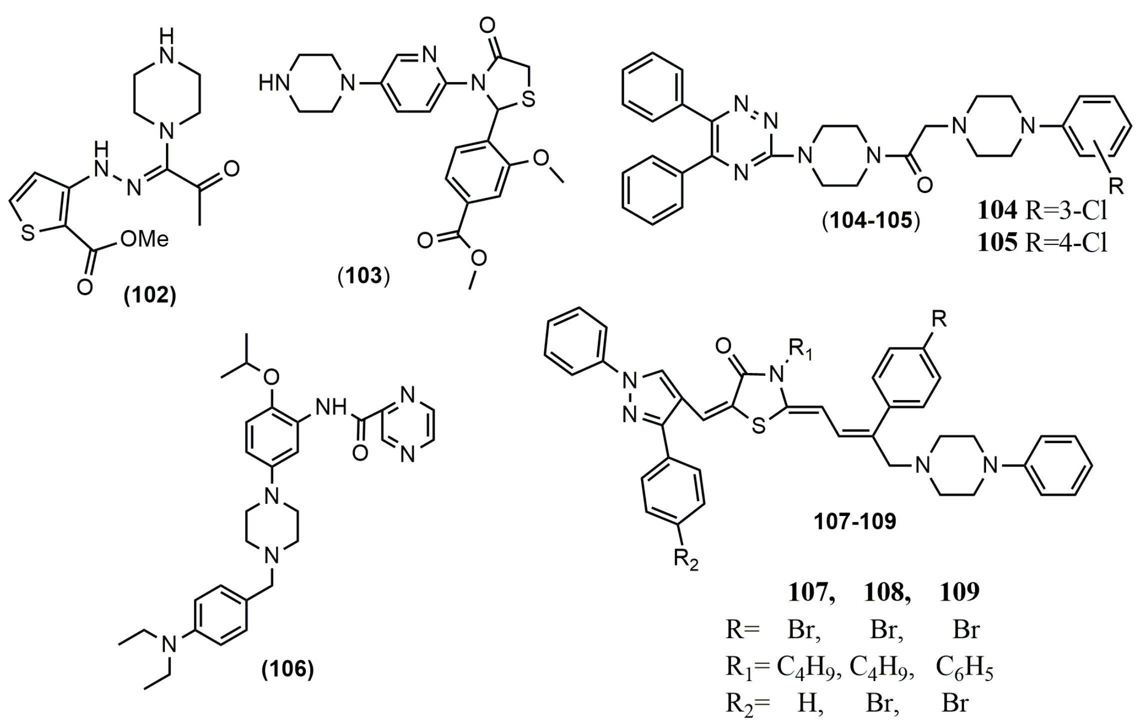

Figure 10. Piperazine derivatives having other heterocycles.

prostate cancer. Compound **106** displayed activity against both the M12 and PC-3 cell lines with IC_{50} values of 11.4 µM and 6.5 µM, respectively. It also showed less toxicity against the normal NIH 3T3 cell line, having a TC_{50} value of 31.9 µM, which indicates that it is cytoprotective in nature. Compound **106** contains a p-diethylamino-substituted benzyl group attached to a piperazine ring.[88] Piperazine-based thiazolidinones and 1,3-diaryl pyrazoles were attached to produce new VEGFR2 tyrosine kinase inhibitors by El-Miligy et al. These compounds were evaluated for anticancer activity and tyrosine kinase inhibitory activity. Among these derivatives, **107**, **108**, and **109** (Figure 10) were the most active agents against the HepG-2 cancer cell line, having IC_{50} values of 0.06, 0.03, and 0.06 µM respectively. Molecular docking studies showed prominent tyrosine kinase inhibitory activity (binding energy = –10.79, –10.23, and –8.56 kcal/mol for 11, 13, and 16, respectively) by the inactive enzyme conformation stabilization.[89]

2.2.8. Piperazine derivatives containing condensed heterocyclic rings as anticancer agents

Condensed heterocyclic rings are important structures that are used in the synthesis of drug molecules. 1,4-Disubstituted piperazines derivatives having indole rings displayed prominent cytotoxicities against liver and colon cancer cell lines, having IC_{50} values of less than 10 µM. Compound **110** was the most potent compound against HUH-7 and MCF7 cell lines with IC_{50} values of 3.42 µM and 2.92 µM, respectively (Figure 11). It has a 3,4-dichlorobenzyl group as a substituent on the piperazine ring system. The most potent compound

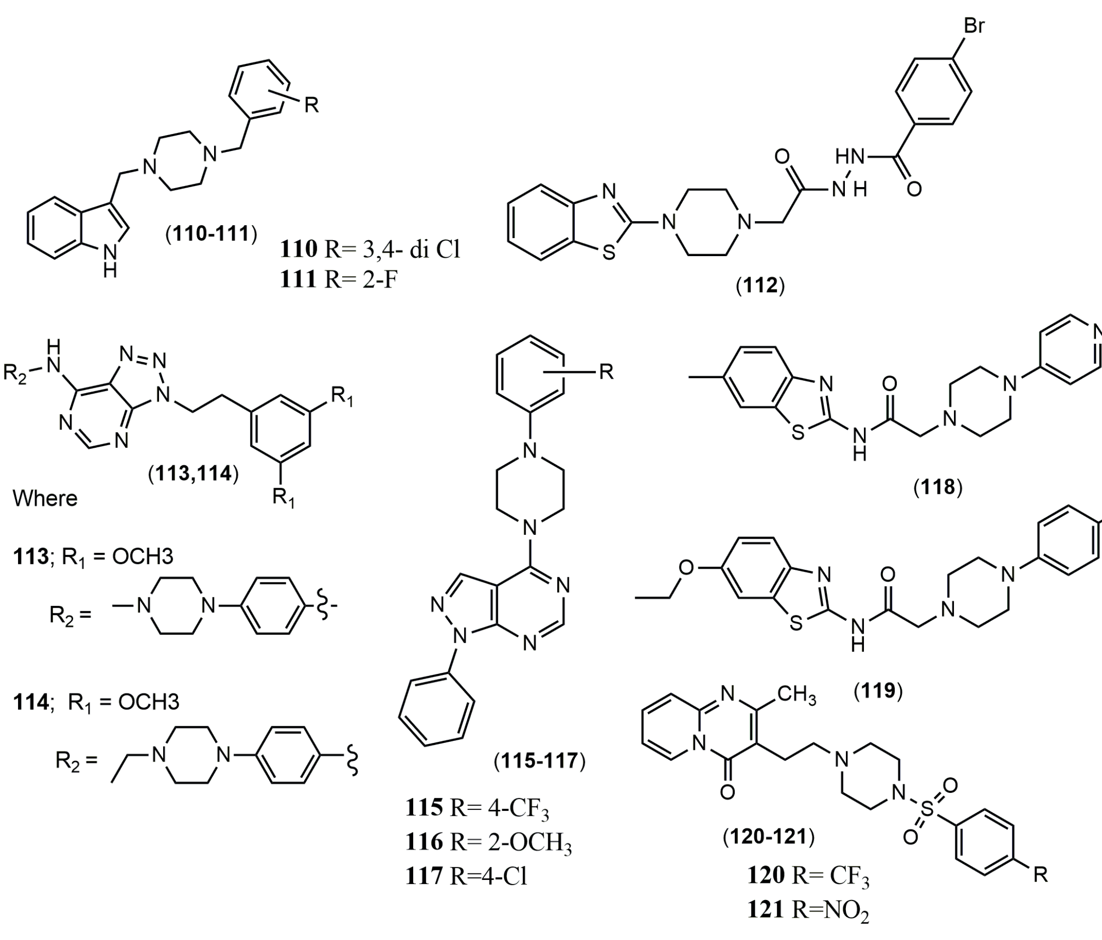

Figure 11. Anticancer piperazine derivatives having condensed heterocyclic rings.

against the HCT116 cell line was **111**, having an IC_{50} value of 6.38 µM. Attachment of a disubstituted benzyl group to piperazine produced more active derivatives as compared to the monosubstituted benzyl group.[90] Al-Ghorbani et al. synthesized novel piperazine-benzothiazole analogues. Trypan blue dye exclusion assay was used for antiproliferative activity evaluation. Compound **112**, having IC_{50} values of 25.0 ± 0.3 µM, showed promising antiproliferative efficacy in this series against the DLA (Dalton's lymphoma ascites) cell line as compared to the reference drug, 5-fluorouracil, having an IC_{50} value 12.7 µM. It contains a bromo benzoyl group attached to acetic hydrazine. Upon in vivo evaluation, it was found that compound **112** inhibited tumor growth by inhibiting the process of angiogenicity.[91] [1,2,3]Triazole[4,5-d]pyrimidine derivatives exhibited good activity against non-small-cell lung cancer (HOP-92) and colon cancer (HT29) cell lines. Piperazine-containing compound **113** showed moderate activity against HOP-92, having a growth percentage (GP %) value of 35.41%, while compound **114** was moderately active against HT29, having a growth percentage value of 57.89% using a single dose of 10 µM concentration.[92,93] Among a series of pyrazolopyrimidine derivatives, piperazine-containing compound **115** displayed antitumor activity against breast and lung cancer cell lines, having IC_{50} values of 0.70 µmol/mL and 0.88 µmol/mL, respectively. Compounds **116** and **117** (Figure 11) showed excellent antitumor activities against a lung cell line, having IC_{50} values of 0.16 µmol/mL for each compound. Docking studies of these derivatives with epidermal growth factor receptor protein (EGFR) showed the involvement of hydrogen bonding through the N^1 of pyrimidine or N^2 of pyrazole with the receptor.[94] Gurdal et al. prepared benzothiazole-piperazine derivatives. Derivatives in this series showed cytotoxic activity against MCF7, HCT-116, and HUH-7 cell lines. The liver cancer cell line (HUH-7) was most sensitive to these compounds because the IC_{50} values for most of the compounds were in the range of 3–10 µM. Derivative **118** was most active, having a GI_{50} value of 3.1 µM against this cell line. It also showed good activity against the MCF7 cell line, having a GI_{50} value of 9.2 µM. Compound **119**, a 4-phenyl-substituted compound, was prominently active against the HCT-116 cell line, having a GI_{50} value of 4.5 µM.[95] Mallesha et al. designed and synthesized a different pyrido pyrimidine-4-one and it was connected to substituted piperazine. Compound **120** was the most potent against IMR-32 (neuroblastoma) and MDA-MB-231 cell lines, showing 85.45% and 65.58% inhibition at doses of 10 µM, respectively. It contains a trifluoromethyl phenyl sulfonyl group attached to the piperazine. Nitro-substituted compound **121** also showed promising cell proliferation inhibition of 64.38% and 62.27% at a dose of 10 µM.[96]

In 2010, Lee et al. reported the synthesis and anticancer activities of new quinoxalinylpiperazine derivatives. Compound **122** displayed significant activity against eleven cancer cell lines, having IC_{50} values ranging from 0.011 to 0.021 µM. It contains a 3,5-dimethoxyphenyl group attached to piperazine (Figure 12). Therefore, the introduction of an electron-donating group in the aryl piperazine ring produced active compounds, while in the quinoxaline ring a fluorine atom at position #6 resulted in the formation of more active compounds as compared to chlorine or bromine atoms. Compound **122** was active against the HCT116 cell line and drug-resistant HCT-15, having IC_{50} values of 29 ± 1.4 nM and 21 ± 0.98 nM. This compound has the potential for further development as an anticancer agent.[97] Anderson et al. investigated the cytotoxicity and mechanism of action of piperazine derivatives of quinoxaline di-N-oxide compounds. Aerobic cytotoxicities were more prominent and compound **123** was found to be the most potent against HT29, SiHa, and SiHa-POR, having IC_{50} values of 0.28 ± 0.009, 0.25 ± 0.01, and 0.08 ± 0.03 µM, respectively.[98] Wu et al. synthesized piperazine-containing quinazolinone derivatives having substituents at positions 3, 6, and 7. Upon evaluation of the antitumor activities, compounds **124** and **125** showed promising activities, having GI_{50} values of 0.11–2.01 µM.

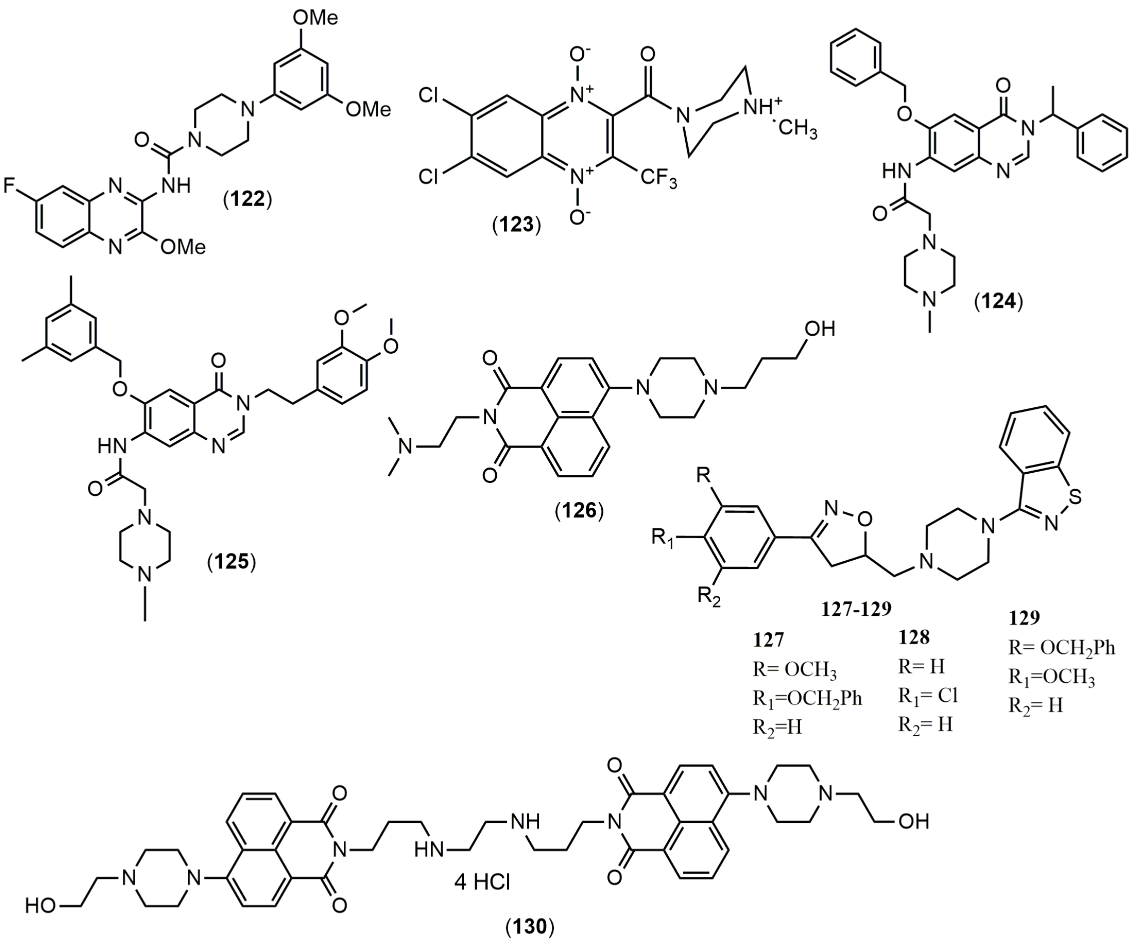

Figure 12. Piperazine hybrids with condensed heterocyclic rings.

Compounds **124** and **125** were most potent against the HOP-92 cancer cell line, having GI_{50} values of 0.11 and 1.70 µM. Therefore, the introduction of piperazinyl acetamide at position 7 of quinazoline influenced the activity of these compounds.[99] Wang et al. synthesized a series of novel naphthalimide derivatives containing piperazine and a piperidine ring. Piperazine-containing compound **126** showed good cytotoxic activity against the A549 cell line, having an IC_{50} value of 2.19 µM. The derivatives in this series showed strong interaction with Ct-DNA (calf thymus DNA) as DNA intercalators.[100] Benzo[*d*]isothiazole-derived compounds having piperazine, isoxazoline, and benzoisothiazole rings (**127**, **128**, and **129**) (Figure 12) exhibited high cytotoxicity, having IC_{50} values of 30, 75, and 95 µM/mL. These compounds showed a time-dependent decrease in treated cells. Removal of the benzyloxy group resulted in decreased activity of the compounds.[101] Rong et al. synthesized novel derivatives of bis-naphthalimide and investigated their anticancer properties. Compound **130** (Figure 12) modified with piperazine showed significant anticancer activities against HeLa and MGC-803 cells, having IC_{50} values of 2.73 ± 0.18 and 1.60 ± 0.37 µM, respectively, and it was better than the control drug, amonafide.[102]

Piperazine and benzothiazine hybrids exhibited excellent anticancer activity. Compound **131** (Figure 13) showed prominent antiproliferative activity against the HeLa, MDA-MB-231, and IMR32 cancer cell lines, having GI_{50} values of 0.12, 0.63, and 0.83 µM. Compounds **132** and **133** (Figure 13) also exhibited GI_{50} values of less than 0.01 µM against breast cancer and neuroblastoma cell lines. Molecular docking studies were

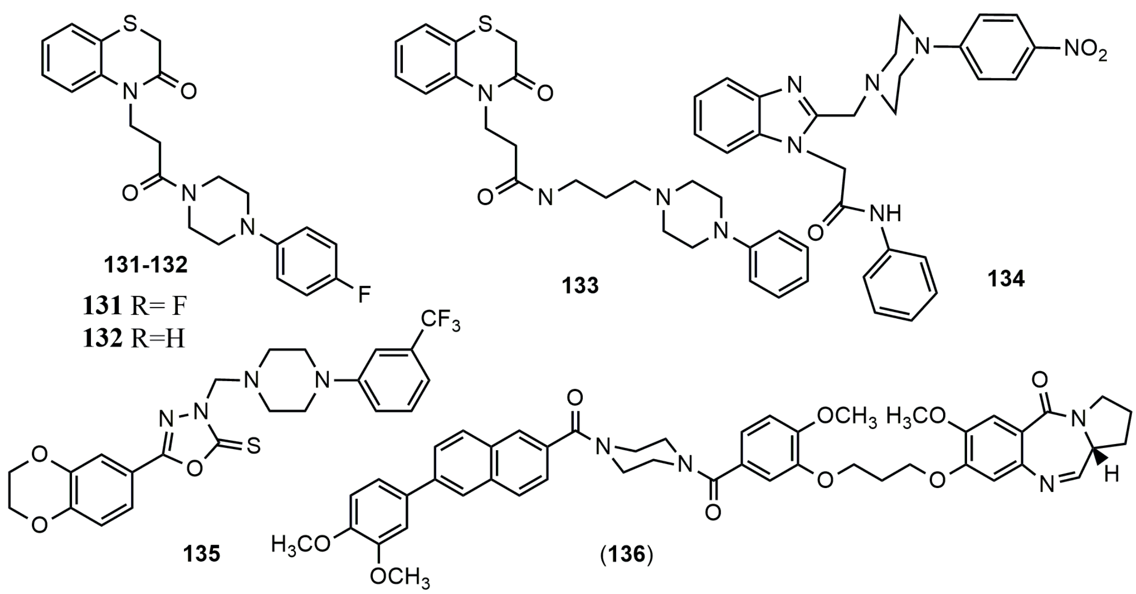

Figure 13. Piperazine linkage with condensed heterocycles.

also carried out and were in accordance with experimental results.[103] Boddu et al. synthesized a new series of benzimidazole 1-acetamide derivatives having phenyl piperazine at position #2 of the benzimidazole. Among the new compounds, **134** showed the highest activity against the HeLa and MCF7 cell lines with IC_{50} values of 14.05 ± 3.40 and 17.64 ± 3.29 µM, respectively.[104] Sun et al. synthesized piperazine derivatives of 1,3,4-oxadiazole-2-thione-substituted 1,4-benzodioxan and evaluated them for anticancer activities. Anticancer activities of these compounds ranged from 5.78 to 50 µM. Compound **135** exhibited prominent anticancer activity, having an IC_{50} value of 5.78 µM against the HepG2 cell line and showing more activity than fluorouracil (IC_{50} = 13.31 µM for HepG2). This compound was also the most potent inhibitor of focal adhesion kinase (FAK) enzyme, having an IC_{50} value of 0.78 µM. Molecular docking evaluation also showed good binding of this compound into the active site of FAK.[105] An aryl-substituted naphthalene ring was attached to pyrrolobenzodiazepine via piperazinyl isovanillin as the coupling agent. These conjugates showed promising anticancer potentials, having GI_{50} values ranging from 0.01 to 3.41 µM. Among all synthesized compounds, piperazine-containing conjugate **136** exhibited significant anticancer activities by inducing apoptosis against MCF7, A549, and Colo205 cell lines with GI_{50} values of 0.02, 0.01, and 0.03 µM, respectively, with reference to adriamycin (ADR) and DC-81.[106]

3. Conclusion

Piperazine is a part of many natural and synthetic molecules that exhibit significant pharmacological properties. Piperazine is also a main pharmacophore of many drugs under development. In the present review anticancer properties of piperazine-containing molecules have been discussed. Organo-iron complexes linked via piperazine and organo-iron melanin dendrimers having piperazine showed anticancer activities against breast cancer cell lines. Metal complexes such as copper, tin, palladium, ruthenium, and osmium with piperazine-containing organic compounds also displayed anticancer activities. Copper complexes linked via piperazine and tin complexes with piperazine were found to be the inhibitors of telomerase and topoisomerase-1, respectively. Plant-derived natural molecules such as chalcones, alkaloids, terpenes, coumarins, and constituents of essential oil have potential anticancer activities. Hybrid molecules of these phytochemical compounds with substituted and unsubstituted piperazines demonstrated excellent anticancer activities. Some piperazine conjugates with natural molecules such as β-elemene and pheophorbide produced anticancer activities by the release of reactive oxygen species and nitric oxide molecules. Piperazine was used as a linker in some new anticancer compounds derived from natural substances, such as beta carbolines and pyrrolobenzodiazepines. Piperazine was also used as a linker/bridge between hybrid molecules of quinolines–isatins and phenanthridine–triazoles. Piperazine was a terminal substituent in dihydropyridines, diphenylpyrimidines, diphenyl amine, thienylamidrazones, and thiazolidinone pyridine derivatives with promising anticancer activities. Some highly active anticancer compounds have been produced in which piperazine served as a part of the main pharmacophore. Benzhydrylpiperazine, cyclohexylpiperazine, piperazinehydroxamate, and piperazine-containing alkyl compounds are examples of these derivatives. Condensed heterocyclic derived compounds having piperazine also displayed anticancer activities. These rings are benzothiazole, triazolopyrimidine, pyridopyrimidine, quinoxaline, quinoxaline di-n-oxide, quinazolinone, and naphthalimide. There are many cytotoxic heterocyclic molecules tethered with piperazine. In this review some recent research in the field of synthesis of anticancer piperazine derivatives has been summarized. It can provide useful information for future research in this area.

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