



THE ANTI-BREAST CANCER THERAPEUTIC APPLICATIONS OF SULFONAMIDE-SIX-MEMBERED HETEROCYCLE HYBRIDS: A MINI REVIEW

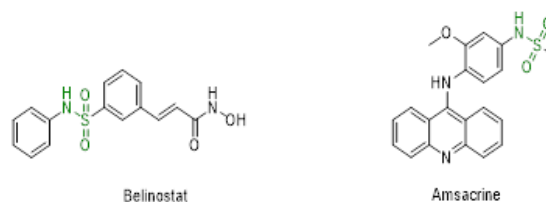
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Nowadays, breast cancer ranks among the most commonly diagnosed malignancies and stands as the primary cause of cancer-related mortality in women globally. Chemotherapy remains the cornerstone of breast cancer treatment. However, multidrug resistance and severe adverse effects pose significant challenges to the efficacy of chemotherapy, thereby necessitating urgent exploration of novel anti-breast cancer agents. Sulfonamides and six-membered heterocycles, including pyridines, quinolines, tetrahydroquinolines, pyrimidines, fused pyrimidines, pyrimidinones, carbazoles, coumarins, quinoxalines, and triazines, have been shown to exhibit anti-breast cancer activity *via* distinct mechanisms of action. Consequently, sulfonamide-six-membered heterocycle hybrid molecules hold the potential to tackle drug resistance and mitigate adverse effects, leveraging their ability to target dual or multiple biological pathways in breast cancer cells simultaneously. This review aims to highlight the therapeutic potential of sulfonamide-six-membered heterocycle hybrid compounds against breast cancer, focusing on studies published from 2020 onwards. The goal is to pave the way for the development of novel, effective, and low-toxic anti-breast cancer candidates.



INTRODUCTION

Breast cancer, capable of spreading or metastasizing to other parts of the body via blood and lymph vessels, ranks as the most commonly diagnosed cancer and the primary cause of cancer-related mortality among women globally.^{1,2} According to estimates by the World Health Organization (WHO), approximately 2.3 million new breast cancer cases were diagnosed in 2022, accounting for 11.6% of all new cancer cases globally.^{3,4} Additionally, the disease caused

approximately 670,000 deaths worldwide during the same period. The incidence and mortality of breast cancer are expected to continue rising for an extended period. Projections indicate that by 2050, there will be approximately 2.64 million new cases and 1.70 million deaths from breast cancer worldwide.^{5,6} Chemotherapy is the mainstay of breast cancer therapy. Still, multidrug resistance and severe adverse events are surmountable obstacles to effective chemotherapy of breast cancer,

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creating an urgent need to develop novel anti-breast cancer agents.^{7,8}

Sulfonamide derivatives have been shown to induce cancer cell cycle arrest, trigger apoptosis, inhibit angiogenesis, and disrupt cell migration. Notably, several sulfonamide-containing agents, including Belinostat and Amsacrine, have already been approved for clinical use in cancer therapy or are currently under clinical evaluation.^{9,10} Six-membered heterocycles, including coumarin,

pyridine, quinoline, tetrahydroquinoline, pyrimidine, fused pyrimidine, pyrimidinone, quinoxaline, ethacrynic acid, and triazine, serve as potential inhibitors of diverse proteins, enzymes, and receptors in cancer cells. Accordingly, these six-membered heterocycles represent privileged and pivotal templates for the discovery of novel anticancer therapeutics. Therefore, rational hybridization of sulfonamide with six-membered heterocycles may generate novel anti-breast cancer candidates.

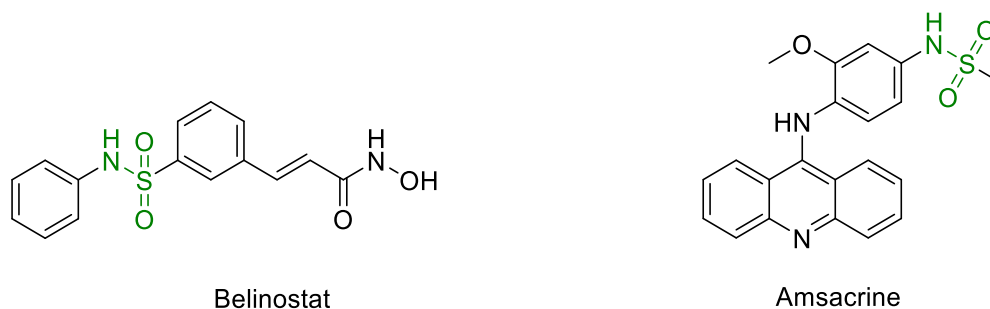


Fig. 1 – Chemical structures of Belinostat and Amsacrine.

This review highlights the therapeutic potential of sulfonamide-six-membered heterocycle hybrids against breast cancer, focusing on studies published from 2020 onward. It also delves into the structure-activity relationships (SARs) and mechanisms of action, with the aim of guiding the rational design of more effective and less toxic anti-breast cancer candidates.

SULFONAMIDE-PYRIDINE/QUINOLINE/ TETRAHYDROQUINOLINE

Pyridine/quinoline/tetrahydroquinoline derivatives have shown potential in inhibiting tumor proliferation, invasion, and metastasis *via* a variety of mechanisms on various molecular targets, inclusive of inhibition of topoisomerase, tyrosine kinases, heat shock protein 90 (Hsp90), histone deacetylases (HDACs), tubulin, and induction of cell cycle arrest and apoptosis, and inhibition of polymerization.^{11,12} Moreover, several pyridine/quinoline/tetrahydroquinoline-based agents such as Foretinib, and Talazoparib have already been applied for breast cancer therapy.^{13,14} Therefore, sulfonamide-pyridine/quinoline/tetrahydroquinoline hybrids represent useful scaffolds for developing therapeutic interventions against breast cancer.

HoAn20 (Fig. 2; **1a**, IC₅₀: 0.674 and 1.34 μM, MTT assay) and **HoAn32** (**1b**, IC₅₀: 0.431 and

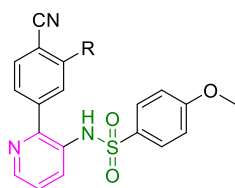
1.19 μM), sulfonamide-pyridine hybrids, were not inferior to ABT-751 (IC₅₀: 0.143 and 8.39 μM) against SK-BR-3 and BT474 breast cancer cell lines.¹⁵ Mechanistically, **HoAn32** could suppress colony formation, arrest cell cycle at the G2/M phase, induce cancer cell apoptosis, and elevate the generation of reactive oxygen species (ROS). Moreover, no significant change in body weight or injury in the major organs (heart, liver, spleen, lung, and kidney) was observed in the **HoAn32** (25 mg/kg, oral administration) treated mice group, demonstrating its excellent safety profile.

Sulfonamide-pyridine hybrid **2** (GI₅₀: 18.62 μM, MTT assay) showed moderate antiproliferative activity against MCF-7 breast cancer cells and could effectively inhibit the migration potential of breast cancer cells with high expression of Rab27a through down-regulation of focal adhesion kinase (FAK) and c-Jun *N*-terminal kinase (JNK) signaling pathways.¹⁶ Tumor growth or metastasis was not influenced by hybrid **2** in the MDA-MD-231 xenografted mouse model and the spontaneous metastasis model of 4T1/luc cells, but tumor growth in mice transplanted with Rab27a-overexpressing cells was greatly delayed compared to that of the parental control cells.

Naphthoquinone-containing sulfonamide-pyridine hybrids **3** (IC₅₀: 1.79-4.65 μM, MTT assay) exhibited promising antiproliferative activity against MCF-7 cancer cells, and the SAR elucidated that the methyl group on the pyridine moiety was beneficial

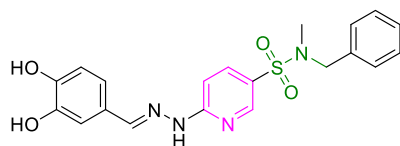
for the activity.¹⁷ The representative hybrids **3a,b** (IC_{50} : 1.91 and 1.79 μM) were comparable to PI-083

(IC_{50} : 1.96 μM) and doxorubicin (IC_{50} : 0.93 μM) against MCF-7 cancer cells.



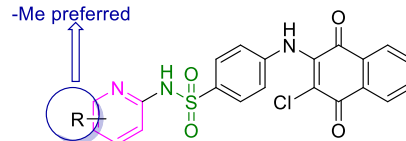
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1a: R = H; 1b: R = F.



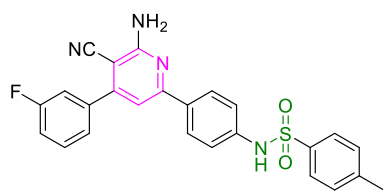
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-Me preferred

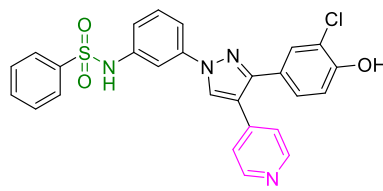


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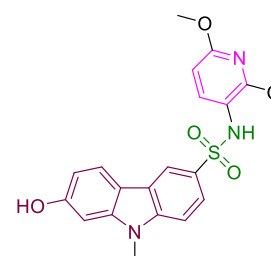
3a: R = 3-Me; 3b: R = 5-Me.



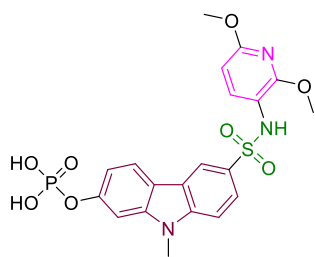
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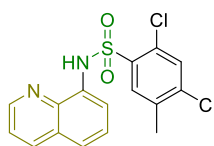
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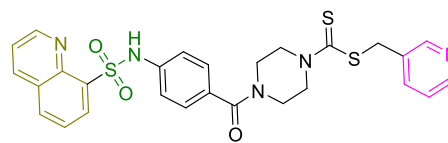
6a



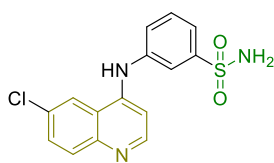
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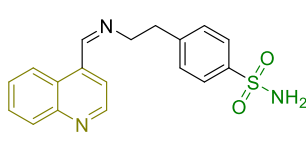
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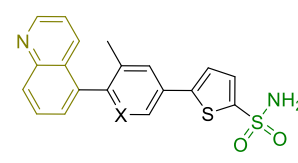
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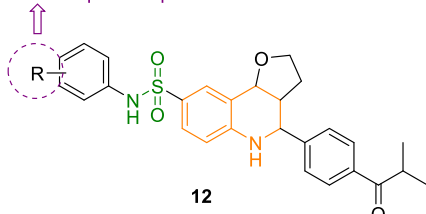


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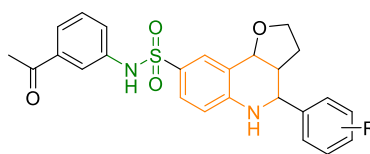


11

11a: X = CH; 11b: X = N.

Substituent at *meta*-position preferred

12

12a: R = Ac; 12b: R = 3-Et;
12c: R = 3-*i*-Pr; 12d: R = 3-NMe₂.

13

13a: R = H; 13b: R = 4-*i*-Pr.

Fig. 2 – Chemical structures of sulfonamide-pyridine/quinoline/tetrahydroquinoline hybrids **1-13**.

Incorporation of urea between sulfonamide and pyridine moieties as a linker reduced the antiproliferative activity against breast cancer cells,¹⁸ whereas a phenyl ring could serve as a linker.^{19–21} Phenyl tethered sulfonamide-pyridine hybrid **4** (GI₅₀: 1.35–2.32 μ M, SRB assay) showed promising antiproliferative activity against MCF-7, HS 578T, BT-549, T-47D, MDA-MB-231 and MDA-MB-468 breast cancer cell lines and displayed higher inhibitory effect (IC₅₀: 3.62 μ M) than sorafenib (IC₅₀: 4.85 μ M) in inhibition of VEGFR-2.¹⁹ Mechanistically, hybrid **4** arrested the cell cycle at the G2/M phase and induced apoptosis through upregulating Bax, Caspase 3, and P53 and downregulating the expression of Bcl-2. Further study revealed that incorporation of pyrazole between sulfonamide and pyridine motifs was also tolerated, and sulfonamide-pyrazole-pyridine hybrid **5** (IC₅₀: 16.05 μ M, MTT assay) was comparable to cisplatin (IC₅₀: 16.14 μ M) against MCF-7 cancer cells and displayed low cytotoxicity (IC₅₀: 392.1 μ M) towards normal BHK-21 cells.²²

Sulfonamide-carbazole hybrid **6a** (IC₅₀: 14 nM, SRB assay) and its sodium phosphate prodrug **6b** (IC₅₀: 16 nM) were highly potent against MCF-7 cancer cells, and prodrug **6b** also showed low acute toxicity with an LD₅₀ value of 273 mg/kg.²³ Moreover, prodrug **6b** (2.5 mg/kg, intravenous injection) possessed acceptable pharmacokinetic properties in rats: AUC_{0–last} was 18449 ng·h/mL, and t_{1/2} was 0.72 h. The SAR indicated that the introduction of the cycloalkylamino group into the sulfonamide fragment decreased the activity.²⁴

Sulfonamide-quinoline hybrid **7** (GI₅₀: 1.71–4.48 μ M, SRB assay) was comparable to vemurafenib (GI₅₀: 1.00–5.49 μ M) against MCF-7, HS 578T, BT-549, T-47D, MDA-MB-231 and MDA-MB-468 breast cancer cell lines,²⁵ whereas quinoline-sulfonamide-pyridine hybrid **8** (IC₅₀: 970 nM, MTS assay) was highly active against MCF-7 cancer cells.²⁶ Besides, hybrid **8** (IC₅₀: > 40 μ M) was non-toxic towards normal BJ cells, and SI was > 41.2, revealing its excellent selectivity profile. Mechanistically, hybrid **8** could inhibit the colony formation of MCF-7 cells, as well as reduce the pyruvate kinase M2 isoform (PKM2) nuclear localization and block the downstream signaling pathways of PKM2, resulting in inhibition of tumor cell proliferation.

Sulfonamide-quinoline hybrid **9** (IC₅₀: 0.43 and 1.03 μ M, MTT assay) was more potent than doxorubicin (IC₅₀: 3.04 and 1.67 μ M) against MCF-7 and MDA-MB-231 breast cancer cell lines and

increased the expression levels for pro-apoptotic markers Bax and active Caspase-3 proteins, while decreasing anti-apoptotic Bcl-2 protein.²⁷ The SARs demonstrated that replacement of amino linker by imine linker was permitted, and hybrid **10** (IC₅₀: 1.56 and 15.0 μ M, MTT assay) was comparable to staurosporine (IC₅₀: 4.45 and 7.02 μ M, MTT assay) against MCF-7 and MDA-MB-231 breast cancer cell lines;²⁸ incorporation of thiophene between sulfonamide and quinoline enhanced the antiproliferative activity, and hybrids **11a,b** (IC₅₀: 32.0 and 16.5 nM, MTT assay) possessed pronounced antiproliferative activity against MCF-7 cancer cells.²⁹

Sulfonamide-tetrahydroquinoline hybrids **12** (IC₅₀: 1.1–3.8 μ M, MTT assay) and **13** (IC₅₀: 0.6–2.2 μ M) exhibited excellent antiproliferative activity against MDA-MB-231 cancer cells.³⁰ The SAR elucidated that (1) for hybrids **12**, substituent at *meta*-position of phenyl ring was favorable to the activity, and hybrids **12a–d** (IC₅₀: 1.1–1.6 μ M) were found to be most active in this series; (2) for hybrids **13**, *iso*-propyl group at *para*-position of phenyl ring enhanced the activity, and hybrids **13a,b** (IC₅₀: 900 and 600 nM) were highly potent against MDA-MB-231 cancer cells. In particular, hybrid **13a** could inhibit both human murine double minute 2 (MDM2) and X-linked inhibitor of apoptosis protein (XIAP) without causing loss of body weight in the mouse model at the dose of 60 mg/kg through intraperitoneal injection.

SULFONAMIDE-PYRIMIDINE/FUSED PYRIMIDINE/PYRIMIDINONE HYBRIDS

Pyrimidine/fused pyrimidine/pyrimidinone derivatives have the potential to inhibit cancer cell growth, differentiation, migration, and metabolism through targeting EGFR, PI3K, CDKs, DNA, tropomyosin-related kinase receptor (TRK), dihydrofolate reductase (DHFR), and thymidylate synthase (TS).^{31,32} Several pyrimidine/fused pyrimidine/pyrimidinone-containing agents such as tucatinib, lapatinib, palbociclib, and ribociclib have already been applied in clinics for the treatment of breast cancers.^{33,34} Therefore, the hybridization of sulfonamide with pyrimidine/fused pyrimidine/pyrimidinone may provide valuable scaffolds for the discovery of novel anti-breast cancer agents.

Sulfonamide-pyrimidine hybrids **14a,b** (Fig. 3; IC₅₀: 1.61 and 1.41 μ M, MTT assay) were not inferior to doxorubicin (IC₅₀: 1.03 μ M) against

MDA-MB-231 cancer cells,³⁵ whereas hybrids **15a-c** (IC_{50} : 22.97–42.22 μ M, MTT assay) were comparable to 5-fluorouracil (IC_{50} : 18.13 μ M) against MCF-7 cancer cells.³⁶ Further study showed that hybrid **16** (IC_{50} : 2.40–2.50 μ M, MTT assay) exhibited excellent antiproliferative activity against MCF-7, T-47D, and MDA-MB-231 breast cancer cell lines, and the activity was superior to that of 5-fluorouracil (IC_{50} : 2.46–6.70 μ M).³⁷ The SAR demonstrated that the 2,5-dimethoxyphenyl ring at the C-6 position of the pyrimidine moiety was vital for the high activity,³⁷ while cyclization of C-5 and C-6 positions was tolerated, and hybrid **17** (IC_{50} : 3.93 μ M, MTT assay) possessed promising antiproliferative activity against T-47D cancer cells.³⁸ Mechanistically, hybrid **16** caused cell cycle arrest at the G2/M phase and induced late apoptosis and necrotic cell death.

Pyrimidine-sulfonamide-thiazole-fluorene hybrid **18a** (IC_{50} : 21.57 μ M, MTT assay) was more potent

than pyrimidine-sulfonamide-fluorene hybrid **18b** (IC_{50} : 37.11 μ M) against MCF-7 cancer cells, revealing that the thiazole fragment was favorable to the activity.³⁹ Mechanistic studies indicated that hybrid **18b** effectively inhibited the colony-forming and cell migratory ability and exhibited significant early apoptosis induction ability. Pyrimidine-sulfonamide-diazepam hybrids **19a-c** (IC_{50} : 6.99–8.65 μ M, MTT assay) were comparable to sorafenib (IC_{50} : 7.26 μ M) and doxorubicin (IC_{50} : 6.75 μ M) against MCF-7 cancer cells and exhibited profound inhibitory activity (IC_{50} : 100–140 nM) against VEGFR-2.⁴⁰ The SAR illustrated that the methyl group on the pyrimidine moiety was favorable to the activity, and the antiproliferative activity was positively correlated with the number of methyl groups. In addition, hybrids **19a-c** (IC_{50} : 49.88–66.67 μ M) displayed low cytotoxicity towards normal VERO cells, and SI values were 5.7 to 9.5, revealing their good selectivity profiles.

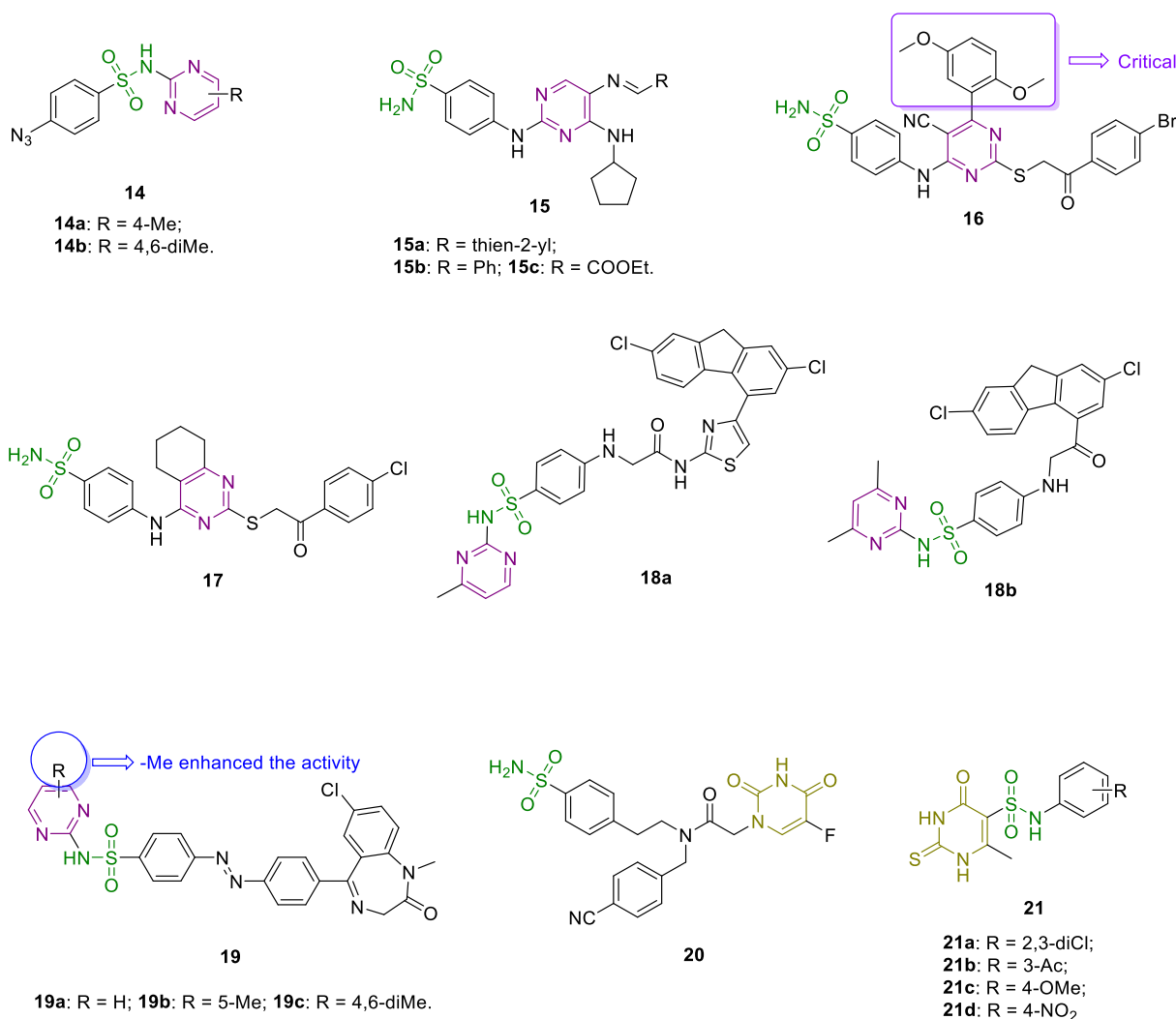


Fig. 3 – Chemical structures of sulfonamide-pyrimidine/pyrimidinone hybrids **14-21**.

Sulfonamide-pyrimidinone hybrid **20** (IC_{50} : 2.45 and 6.86 μM , SRB assay) was comparable to staurosporine (IC_{50} : 4.52 and 4.25 μM) against T-47D and MDA-MB-231 breast cancer cell lines and could arrest cell cycle in the G2/M phase and induce apoptosis.⁴¹ Hybrids **21a-e** (IC_{50} : 1.67–2.34 μM , MTT assay) demonstrated potent antiproliferative activity against MCF-7 cancer cells, and the activity was 2.2–3.0 times superior to that of 5-fluorouracil

(IC_{50} : 5.15 μM).⁴² Additionally, hybrids **21a-e** (IC_{50} : 60.21–84.43 μM) displayed low cytotoxicity towards normal WI-38 cells, and SI values were in a range of 28.06 to 36.05, revealing their good selectivity profiles. Mechanistically, hybrid **21a** stimulated the apoptotic death of cancer cells and induced cell growth arrest at S phase indirectly through enhanced expression of cell cycle inhibitors p21 and p27.

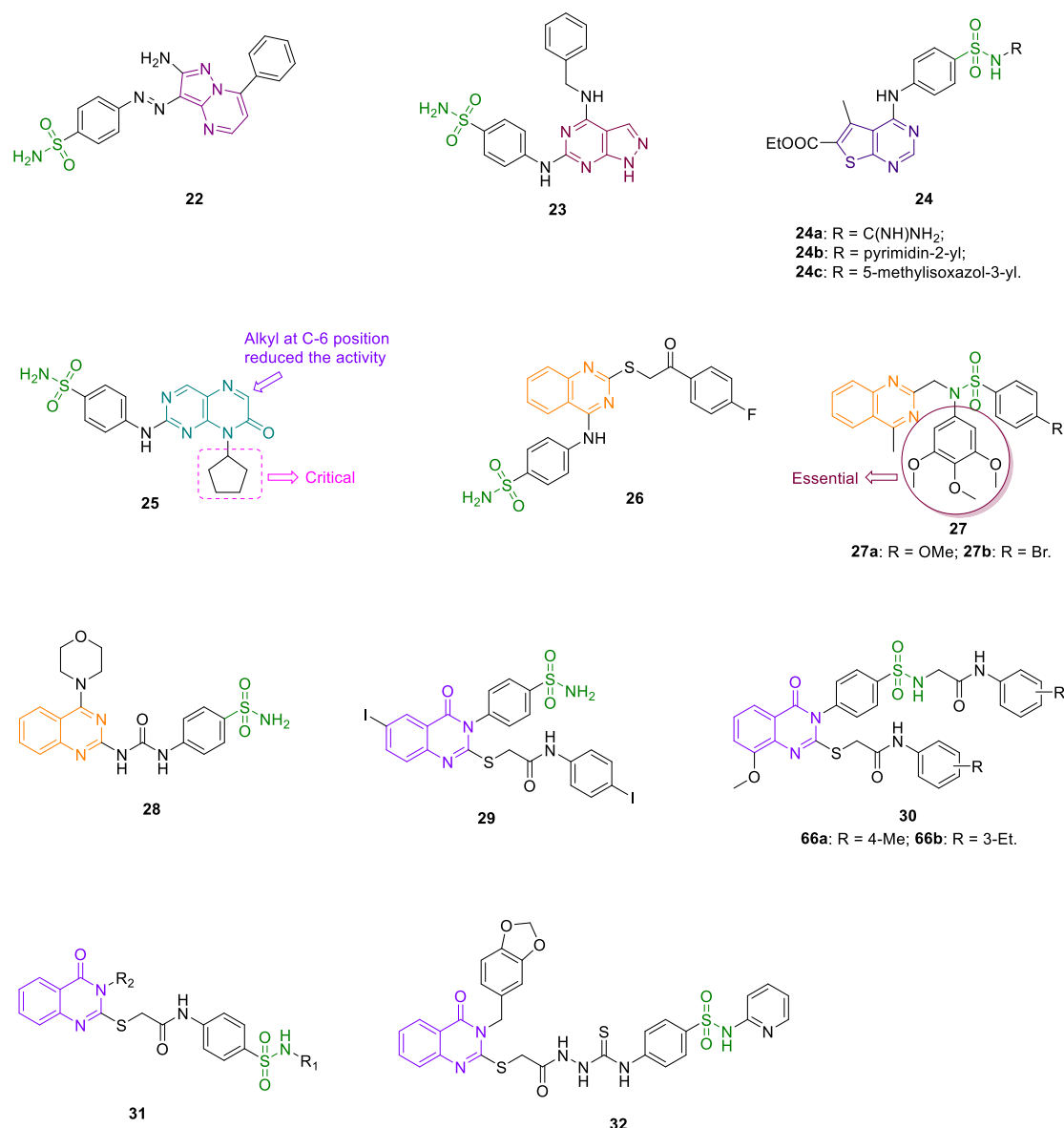


Fig. 4 – Chemical structures of sulfonamide-fused pyrimidine hybrids **22-32**.

Sulfonamide-pyrazolo[1,5-a]pyrimidine hybrid **22** (Fig. 4; IC_{50} : 0.96 and 1.07 μM , MTT assay) was 9.5 and 6.0-fold more potent than staurosporine (IC_{50} : 9.20 and 6.46 μM) against MCF-7 and MDA-MB-468 breast cancer cell lines.⁴³ Mechanistically, hybrid **22** disrupted the MCF-7 cell cycle *via* alteration of

the sub-G1 phase and arrest of the G2-M stage and induced apoptosis. Sulfonamide-pyrazolo[3,4-d]pyrimidine hybrid **23** (IC_{50} : 1.58–5.58 μM , MTT assay) showed higher antiproliferative activity than centrinone (IC_{50} : 2.88–13.01 μM) against MCF-7, BT474, and MDA-MB-231 breast cancer cell lines

and displayed low cytotoxicity towards HUVECs (IC_{50} : 30.21 μ M).⁴⁴ Sulfonamide-thieno[2,3-d]pyrimidine hybrids **24a-c** (IC_{50} : 6.17–17.64 μ M, MTT assay) exhibited promising antiproliferative activity against MCF-7 and MDA-MB-231 breast cancer cell lines, and the most active hybrid **24a** (IC_{50} : 6.17 and 8.68 μ M) was not inferior to doxorubicin (IC_{50} : 1.6 and 2.2 μ M).⁴⁵ Further study indicated that hybrid **24a** (IC_{50} : 277.05 μ M) displayed low cytotoxicity towards normal MCF-10A breast cells, and SI values were 173.1 and 125.9. However, sulfonamide-purine hybrids and sulfonamide-[1,2,4]triazolo[4,3-a]pyrimidine hybrids only showed weak to moderate antiproliferative activity against breast cancer cell lines and still need further structural modifications.^{46,47}

The antiproliferative SARs of sulfonamide-pteridin-7(8*H*)-one hybrids (IC_{50} : 0.39–79.1 μ M, MTT assay) against MDA-MB-231 cancer cells revealed that (1) introduction of alkyl group into C-6 position of pteridin-7(8*H*)-one moiety decreased the activity significantly; (2) the cyclopentyl group at C-8 position of pteridin-7(8*H*)-one moiety was more favorable than cyclopropyl and linear alkyl group.⁴⁸ In particular, hybrid **25** (IC_{50} : 390 nM) was 11.6 times superior to palbociclib (IC_{50} : 4.54 μ M) against MDA-MB-231 cancer cells and manifested excellent inhibitory activities towards both CDK4/cyclin D3 and CDK6/cyclin D3 (IC_{50} : 34.0 and 65.1 nM, respectively). Mechanistically, hybrid **25** caused cell cycle arrest at G2/M phase and induced apoptosis.

Sulfonamide-quinazoline hybrid **26** (IC_{50} : 2.54 and 4.14 μ M, MTT assay) showed potent antiproliferative activity against MCF-7 and T-47D breast cancer cell lines, and the activity was comparable to that of 5-fluorouracil (IC_{50} : 2.46 and 6.70 μ M).⁴⁹ Mechanistically, hybrid **26** induced G2/M phase arrest in MCF-7 cells and promoted both early and late apoptotic stages, along with necrotic cell death. The antiproliferative SARs of sulfonamide-quinazoline hybrids **27** (IC_{50} : 0.81–34.2 μ M, MTT assay) against MCF-7 cancer cells indicated that (1) the 3,4,5-trimethoxyphenyl ring was essential for the activity; (2) replacement of the sulfonamide moiety by an amide fragment led to loss of activity.⁵⁰ Amongst them, hybrids **27a,b** (IC_{50} : 0.81 and 1.40 μ M) were 14.9 and 8.6-fold more potent than 5-fluorouracil (IC_{50} : 12.1 μ M) against MCF-7 cancer cells, and hybrid **27a** (IC_{50} : 26.19 μ M) also displayed low cytotoxicity towards normal HUEVC cells. The mechanistic studies revealed that hybrid **27a** arrested the cell cycle in the G2/M phase, induced intrinsic apoptosis, and

inhibited cell colony formation. Further structural modifications demonstrated that the installation of urea between sulfonamide and quinazoline was permitted, as evidenced by that hybrid **28** (IC_{50} : 200 nM, CellTiterGlo®3 assay) was highly potent against MCF-7 cancer cells.⁵¹ Moreover, hybrid **28** (IC_{50} : 3.4 and 95.1 nM) was a dual PI3K α and mTOR inhibitor and merited further investigations.

Sulfonamide-quinazolinone hybrid **29** (IC_{50} : 2.98 μ M, MTT assay) was more active than erlotinib (IC_{50} : 4.27 μ M) and doxorubicin (IC_{50} : 9.78 μ M) against MCF-7 cancer cells and displayed low cytotoxicity (IC_{50} : 35.17 μ M) towards normal MCF-10A breast cells with an SI value of 11.8.⁵² Hybrids **30a,b** (IC_{50} : 2.5 and 5.0 μ M, MTT assay) were not inferior to doxorubicin (IC_{50} : 1.4 μ M) against MCF-7 cancer cells and could mediate apoptosis and arrest cell cycle growth at G1 phase.⁵³ The SARs elucidated that (1) alkyl group on the phenyl ring was favorable to the activity;⁵³ (2) movement of sulfonamide fragment from phenyl ring at N-3 position of quinazolinone moiety to phenyl ring at C-2 position of quinazolinone moiety resulted in significant loss of antiproliferative activity, and hybrids **31** (IC_{50} : 12.69–91.71 μ M, MTT assay) showed moderate activity against MCF-7 cancer cells.⁵⁴ Pyridine-containing sulfonamide-quinazolinone hybrid **32** (IC_{50} : 3.87 μ M, MTT assay) was superior to erlotinib (IC_{50} : 12.40 μ M) and doxorubicin (IC_{50} : 9.34 μ M) against MCF-7 cancer cells and merited further evaluations.⁵⁵

MISCELLANEOUS SULFONAMIDE HYBRIDS

Sulfonamide-coumarin hybrids **33a,b** (Fig. 5; IC_{50} : 2.01 and 2.39 μ M, MTT assay) exhibited potent antiproliferative activity against MCF-7 cancer cells and displayed low cytotoxicity (IC_{50} : 35.44 and 27.81 μ M) towards normal WI-38 cells.⁵⁶ Mechanistically, hybrid **33a** caused cancer cell arrest at the G0/G1 phase, promoted apoptosis, and blocked colony formation in MCF-7 cancer cells. Hybrids **34a,b** (IC_{50} : 7.78–17.94 μ M, MTT assay) showed moderate to excellent antiproliferative activity against MCF-7 and MDA-MB-231 breast cancer cell lines and induced apoptosis by upregulating pro-apoptotic protein marker Bax and downregulating anti-apoptotic protein marker Bcl2.⁵⁷

Sulfonamide-1,3,4-oxadiazole-quinoxaline hybrids **35** (IC_{50} : 4.30–14.07 μ M, MTT assay) showed

considerable antiproliferative activity against MCF-7 cancer cells.⁵⁸ The SAR illustrated that replacement of 1,3,4-oxadiazole by 1,2,4-triazole was tolerated, and hybrids **36** (IC_{50} : 3.10–14.30 μ M, MTT assay) also possessed promising antiproliferative activity against MCF-7 cancer cells.⁵⁹ Amongst them, the representative hybrids **35a-c** (IC_{50} : 4.30–5.31 μ M) and hybrids **36a,b** (IC_{50} : 3.10 and 4.02 μ M) not only were comparable to etoposide (IC_{50} : 4.32 μ M) against MCF-7 cancer cells, but also were not inferior to etoposide (IC_{50} : 350–440 nM vs 390 nM) in inhibition of EGFR. Sulfonamide-[1,2,4]triazolo[4,3-a]quinoxaline hybrids **37** (IC_{50} : 2.18–14.14 μ M, MTT assay) demonstrated moderate to excellent

antiproliferative activity against MCF-7 cancer cells, and hybrids **37a,b** (IC_{50} : 2.18 and 2.66 μ M) were as potent as etoposide (IC_{50} : 2.44 μ M).^{60,61} Sulfonamide-[1,3]dithiolo[4,5-b]quinoxaline-2-ylidene hybrid **38** (IC_{50} : 3.82 and 2.26 μ M, MTT assay) showed higher antiproliferative activity than doxorubicin (IC_{50} : 4.17 and 3.18 μ M) against MCF-7 and MDA-MB-231 breast cancer cell lines and displayed low cytotoxicity (IC_{50} : 81.64 μ M) towards normal WI-38 cells.⁶² In addition, hybrid **38** (IC_{50} : 190, 121, and 420 nM) exhibited great inhibitory effects against wild-type EGFR, EGFR^{L858R}, and VEGFR2 and could cause cell cycle arrest at the S phase and induce apoptosis.

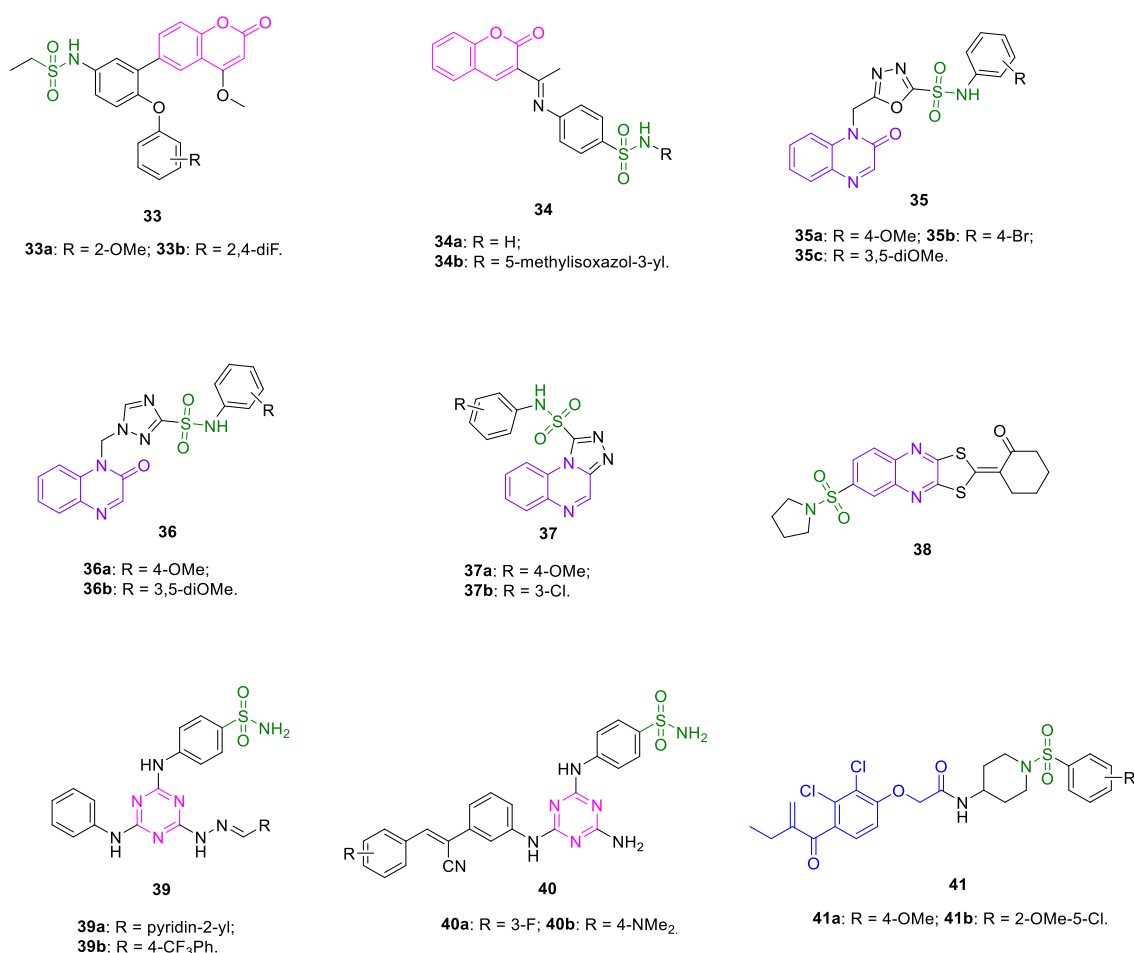


Fig. 5 – Chemical structures of sulfonamide hybrids **33-41**.

Sulfonamide-1,3,5-triazine hybrids **39a,b** (GI_{50} : 0.31–1.10 μ M and 1.73–3.07 μ M, respectively, SRB assay) were not inferior to 5-fluorouracil (IC_{50} : 0.07–10.60 μ M) against MCF-7, HS 578T, BT-549, T-47D, MDA-MB-231, and MDA-MB-468 breast cancer cell lines.⁶³ The SAR revealed that the hydrazone group was critical for the activity,^{64,65} while free amine was tolerated, as evidenced by that hybrids **40a,b** (IC_{50} :

1.48 and 3.99 μ M, MTT assay) were more potent than staurosporine (IC_{50} : 6.07 μ M) against MDA-MB-468 cancer cells.⁶⁶ Mechanistically, hybrid **39a** caused cell cycle arrest at S phase, altered the sub-G1 phase, and induced apoptosis, whereas hybrid **40a** arrested MDA-MB-468 cell cycle in G0-G1 and S phases and induced apoptosis through increasing the level of cleaved caspases 3 and 9.

Sulfonamide-ethacrynic acid hybrids **41a,b** (IC₅₀: 97 and 128 nM, MTT assay) were not inferior to doxorubicin (IC₅₀: 120 nM) against MCF-7 cancer cells, and the SAR implied that the methoxy group on the phenyl ring was favorable to the activity.⁶⁷ In addition, hybrids **41a,b** (IC₅₀: 0.90 and 4.32 μM) displayed relatively low cytotoxicity towards normal MRC5 cells, and SI values were 9.2 and 33.7, revealing their excellent selectivity profile. Hence, hybrids **41a,b** could serve as promising candidates for further investigations.

CONCLUSIONS

Multidrug resistance and severe side effects are surmountable obstacles to effective chemotherapy of breast cancer, highlighting the urgent need to explore novel anti-breast cancer chemotherapeutics. Sulfonamides and six-membered cycles with structural and mechanism diversity demonstrated potential activity against breast cancers, and some of their derivatives have already been applied in clinics for breast cancer therapy or under clinical evaluations, demonstrating that sulfonamide and six-membered cycles are useful anti-breast cancer pharmacophores. Accordingly, rational hybridization of sulfonamides with six-membered cycles is a promising approach for the discovery of novel therapeutic agents for clinical deployment in the control and eradication of breast cancers.

The purpose of this review is to summarize the current scenario of anti-breast cancer therapeutic potential, structure-activity relationships, and mechanisms of action of sulfonamide-six-membered cycle hybrids, covering articles published from 2020 onwards. It can be concluded that sulfonamide and six-membered cycles are useful anti-breast cancer pharmacophores, and rational design of sulfonamide-six-membered cycle hybrids has the potential to enhance the anticancer activity, reduce side effects, and overcome drug resistance.

Abbreviations

Akt: alpha serine/threonine-protein kinase;
 AUC_{0-∞}: area under the concentration-time curve;
 Bcl-2: anti-apoptotic B-cell lymphoma-2;
 BET: bromodomain and extra-terminal proteins;
 CA: carbonic anhydrase;
 CCK-8 assay: cell counting kit-8 assay;
 CDKs: cyclin-dependent kinases;
 CL: plasma clearance;
 C_{max}: maximum concentration;
 COX-2: cyclooxygenase-2;

c-kit: v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog;
 DHFR: dihydrofolate reductase;
 E_r: estrogen receptor α;
 ESR1: estrogen receptor 1;
 F%: bioavailability;
 FAK: focal adhesion kinase; JNK:
 GI₅₀: concentration that inhibits cell growth by 50%;
 hCA: human carbonic anhydrases;
 HDACs: histone deacetylases;
 HIF-1α: hypoxia inducible factor-1α;
 Hsp90: heat shock protein 90;
 HUVEC: human umbilical vein endothelial cells;
 IC₅₀: half maximal inhibitory concentration;
 JNK: c-Jun N-terminal kinase;
 LD₅₀: median lethal dose;
 15-LOX: 15-lipoxygenase;
 MDM2: human murine double minute 2;
 mTOR: mammalian target of rapamycin;
 MMP-2: matrix metalloproteinase-2;
 NFATc: nuclear factor of activated T-cells;
 MTT assay: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay;
 PI3K: phosphatidylinositol 3-kinase;
 PKM2: pyruvate kinase M2 isoform;
 SARs: structure-activity relationships;
 SI: selectivity index;
 SRB assay: Sulforhodamine B assay;
 system X_c⁻: cystine/glutamate antiporter;
 t_{1/2}: half-life time;
 t_{max}: peak time;
 TRK: tropomyosin related kinase receptor;
 TS: thymidylate synthase;
 VEGFR-2: vascular endothelial growth factor receptor 2;
 WHO: World Health Organization;
 XIAP: X-linked inhibitor of apoptosis protein.

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