Breast Cancer (2017) 24:191–219
DOI 10.1007/s12282-016-0732-1

REVIEW ARTICLE

Recent development of targeted approaches for the treatment of breast cancer

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Received: 24 March 2016 / Accepted: 18 September 2016 / Published online: 31 October 2016

Abstract Breast cancer is the most prominent cause of cancer death in women worldwide. The highlights of this review are to provide an overview of the targeted therapeutic agents, challenges with metastatic breast cancer (MBCa), mechanisms of action through Hedgehog/Gli 1 signaling pathway and future prospective. Over a decade of success, several drugs have been approved and are in the advanced stages of clinical trials that target the receptors such as estrogen receptor, growth factor receptor, receptor activator of nuclear factor kappa-B, etc. Currently, several monoclonal antibodies are also used for the treatment of breast cancer. Advances in understanding tumor biology, particularly signaling pathways such as Notch signaling pathway, Hedgehog/Gli 1 signaling pathway, and inhibitors are considered to be important for bone metastasis. These studies may provide vital information for the design and development of new strategies with respect to efficacy, reduction of the side effects, and treatment strategies.

Keywords Breast cancer · Estrogen receptor · Hedgehog/Gli 1 signaling · Immunomodulators · Angiogenesis · Growth factor receptor inhibitors

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Introduction

Cancer is one of the most dreaded diseases worldwide. Unfortunately, enhancements in socioeconomic circumstances are associated with increasing cancer incidences such as breast, blood, lung, oral, prostate cancer, etc. [1, 2]. Of these, breast cancer (BCa) is one of the most common cancers endangering women [3, 4], constituting 14.6 % of all cancers [5]. National Cancer Institute (NCI) has estimated that the diagnosis of 246,660 new cases and 40,450 deaths due to BCa in the United States in 2016 and still the incidence is rising [5]. There are several types of BCa, such as ductal carcinoma in situ, invasive ductal carcinoma, triple negative breast cancer (TNBC), inflammatory breast cancer, MBCa, and other types. The efficacy of developing therapeutic options for BCa patients is time-limited and non-curative. These treatments are provided by a single agent or in combination that dependent on disease stages, histology and molecular subtypes, and menopausal status [6]. These treatments have numerous side effects and often unsuccessful to remove the tumor completely. Hence, to overcome these drawbacks, perpetual screening for extremely safer drugs has been ongoing numerous decades, resulting in the finding of new anticancer drugs and vaccines significantly.

Estrogen receptor as pharmacological target

The relation between hormones and malignancy growth has been recognized more than a century. Estrogens play a major role in promoting the proliferation both the normal and neoplastic breast epithelium [7]. Estrogen receptor (ER) is a member of the nuclear hormone family of intracellular receptors translocating into the nucleus and bind to DNA then regulate the activity of different genes

[8]. ERα and ERβ are two different forms of ER produced from two separate genes that are differentially expressed in the tissue [9]. ERs are over-expressed in around 70 % of breast cancer cases, referred to as ER-positive (ER+), and can be demonstrated in such tissues using immunohistochemistry. In the mammary gland, estradiol (E2) binds to ERα and ERβ that control cell proliferation and differentiation [10]. They are coded by two distinct genes located on chromosomes 6 and 14 that produce two proteins with 595 and 530 amino acids, respectively [11]. The ER comprises of five main regions that include the N-terminal domain (NTD), a conserved DNA-binding domain (DBD), variable hinge region, a conserved ligand binding domain (LBD) and variable C-terminal region with diverse roles in signaling [12]. ER+ breast cancers are estrogen-dependent and include luminal types A and B. ER-negative

(ER−) breast cancers are estrogen independent and include subtypes in which human epidermal growth factor receptor 2 (HER2) also known as ErbB2 is over-expressed

Current treatment options

Various types of BCa treatment are currently available to treat pre- and postmenopausal women including surgery, brachytherapy, endocrine therapy, chemotherapy, vaccine treatment and targeted therapy, bone directed treatment, etc. Of these, Surgery (mastectomy) and radiotherapy play an important role in the treatment of BCa in earlier stages. Systemic therapy may be used for almost all BCa patients predominantly for those with advanced stage [13]. Hormone receptor-positive cancers are often treated with hormone-blocking therapy. Aromatase inhibitors (AIs) are the preferred option for postmenopausal women. The monoclonal antibodies or other immune-modulators may be administered in certain cases of MBCa. Several therapeutic targets and signaling pathways are explained in Fig. 1.

Notch signaling pathway

Notch signaling pathway is a potential therapeutic target for the treatment of BCa that involves in the cell proliferation, differentiation, and apoptosis [14]. There are different types of Notch receptors and ligands that have different effects on the development of tissues and organs. This pathway is one of the more sensitive targets to inhibit BCa stem cell subset, which is resistant to standard treatments such as chemotherapy and radiation [15]. Even if Notch inhibitors alone do not yield major responses and cures, there is growing evidence that synergy can result from combining Notch inhibition with already-existing treatment modalities such as chemotherapy, radiation, and other pathway inhibitors. The first Notch pathway inhibitors used both experimentally and clinically were the γ-secretase inhibitors which prevent cleavage of NEXT and therefore the release of NCID from the plasma membrane [15]. The γ-secretase inhibitors, SAHM1, and TR4 have the benefit that can disrupt signaling by all four Notch receptors [16]. In addition, there are several approaches specifically GSIs, dnMAML1, and inhibitory antibodies available to block Notch signaling. While γ-secretase inhibitors are already in clinical trials as Notch-inhibiting agents and are clinically promising, they are highly non-specific. Other experimental means of Notch inhibition include γ-secretase inhibitors, peptide or antibody blockers, stapled peptides, and genetic strategies such as RNA interference [17]. The detailed structural information of the drugs targeting Notch pathway is given in Table 1.

Hedgehog/gli1 signaling pathway

The hedgehog (Hh) signaling pathway plays an essential role in the regulation of embryonic development and tissue homeostasis of diverse adult tissues, and its deregulation has been implicated in the tumorigenesis and metastasis of various malignancies including BCa. This pathway is a highly coordinated and orchestrates the network involving in the inhibition of twelve transmembrane protein, Pathed1 (Ptch1) by binding Hh protein, activation of the seven-transmembrane protein, Smoothened (SMO), release of a five-zinc finger transcription factor, Gli from a large protein complex, nuclear translocation of Gli, and transcription of target genes [18]. In the absence of Sonic Hh (Shh), Glisorganize a large protein complex with Costal2, fused and suppressor fused (SUFU) and are sequestered in the cytoplasm [18]. In the presence of Shh, a full-length Gli3 released from the large protein complex is transported into the nucleus to activate Hh target genes [19]. Gli1 is one of target genes of Gli3. Therefore, Gli1 is a marker of the Hh pathway activation [20]. Recently, Targeting the Hh pathway has been recognized to be one of the promising therapies for BCa.

Cyclopamine is the first Hh inhibitor, identified from naturally occurring plant alkaloids [21, 22]. It has poor oral bioavailability and suboptimal pharmacokinetics and thus more potent derivatives have been synthesized. This led to the development of Hh modulators with improved potency and druggability, such asvismodegib (GDC-0449), IPI-926, sonidegib (LDE-225), BMS-833923, PF-04449913, and LY2940680 [22]. The agents inhibiting the Hh are also being tested in women with advanced breast cancer in early clinical trials. Several synthetic, small-molecule SMO antagonists have been developed with higher potency than cyclopamine such as SANT1-SANT4, CUR-61414,

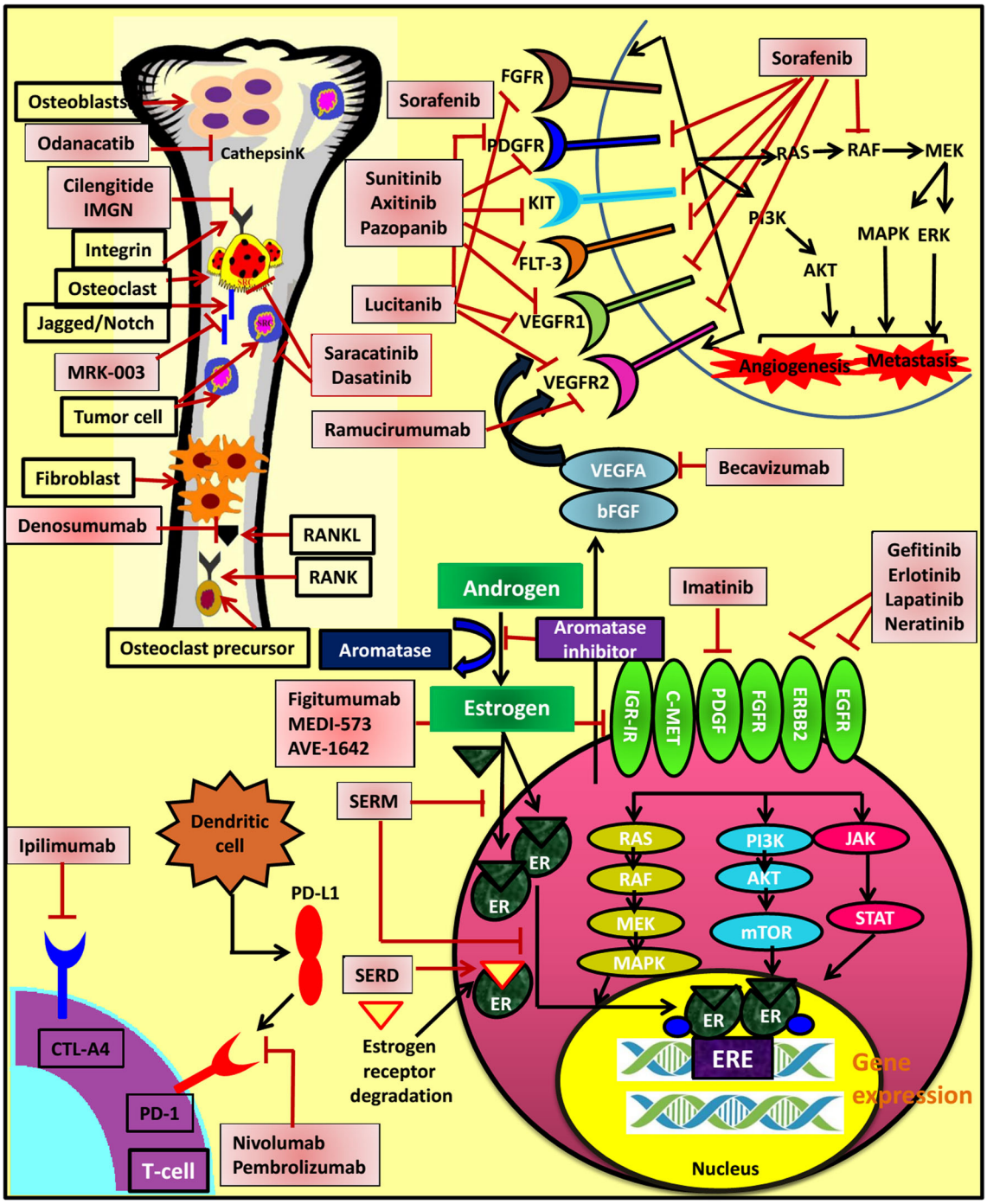


Fig. 1 Schematic diagram of the therapeutic targets and signaling pathways of the active drugs

HhAntag-691, and GDC-0449 which have been tested in preclinical models against a variety of solid tumors [23].

Recently, the in vitro anticancer activities of GANT-61 was reported at the dose ranges from 5 to 20 μM, which significantly reduced the survival of 7/8 tested cell lines after 48 h and in all cell lines after 72 h of treatment relative to the vehicle control [21]. GDC-0449 significantly decreased cell survival in all cell lines only at the highest dose (12 μM) after 72, 96 or 6 days of treatment [21]. Cyclopamine and CUR0199691 have been used successfully in vivo to treat Hh network-induced cancers [22]. Recent in vitro cell line studies provide more insight into the association of Hh signaling with breast cancer. Gli-1 mRNA level was increased in a number of breast cancer cell lines, including MDA-MB-453 (TN), MDA-MB-231 (TN and basal type B), BT20 (basal type A), MCF10A

Table 1 The details of the drugs targeting Notch and Hedgehog/Gli signaling pathways

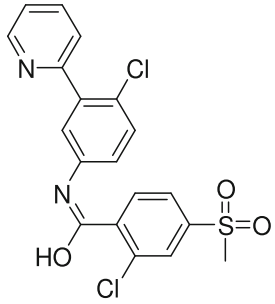
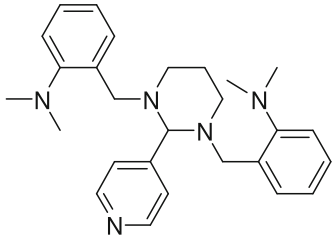
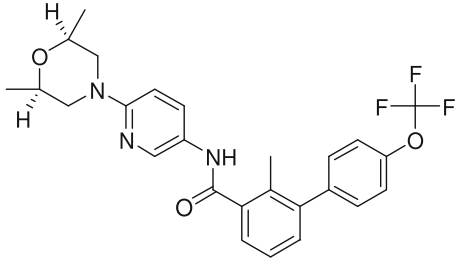
S. no	Structure/name/ composition of compound	Targets/ approval/ study phase	Properties	Drug information	References
1a	 GDC-0449 (Vismodegib/Erivedge) Formula: $C_{19}H_{14}Cl_2N_2O_3S$ Mass: 421.30	SMO, Approved 2012 for basal cell carcinoma	Roche/ Genentech/ Curis, Antagonist, ChemSpider ID: 23337846 Route of administration: Oral	The substance acts as a cyclopamine-competitive antagonist of the SMO which is part of the hedgehog signaling pathway. The drug is also undergoing clinical trials for SMO inhibition causes the transcription factors GLI1 and GLI2 to remain inactive, which prevents the expression of tumor mediating genes within the hedgehog pathway	[22]
1b	 GANT-61 Formula: $C_{27}H_{35}N_5$ Mass: 429.60	Gli	Antagonist, ChemSpider ID: 373207	GLI antagonist that inhibits GLI1 and GLI2-induced transcription (IC_{50} ~5 μM). Inhibits the hedgehog (Hh) signaling pathway downstream of SMO and SUFU causing GLI1 nuclear accumulation. Displays antiproliferative and antitumor activity in vitro and in vivo	[22]
1c	 LDE-225 (Erismodegib/ Sonidegib/Odomzo®) Formula: $C_{26}H_{26}F_3N_3O_3$ Mass: 485.498	SMO, Approved 2015 for basal cell carcinoma	Novartis, Antagonist, ChemSpider ID: 25027390 Route of administration: Oral	It is an orally bioavailable SMO antagonist created by Novartis. This drug induces cell cycle arrest and apoptosis in a variety of cancer cell line. Several phase I/II trial for erimodegib as a monotherapy and in combination are underway, treating both solid tumors and hematological malignancies	[18]

Table 1 continued

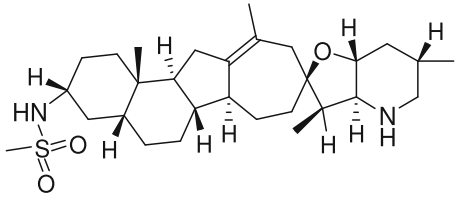
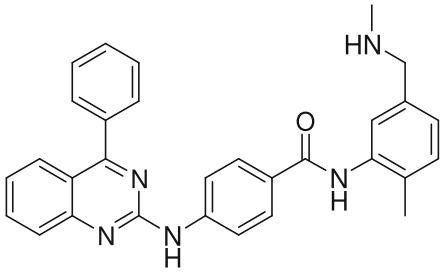
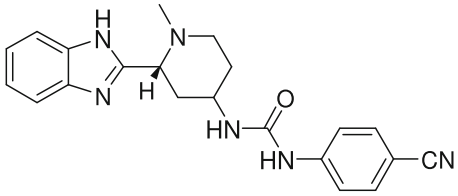
S. no	Structure/name/ composition of compound	Targets/ approval/ study phase	Properties	Drug information	References
1d	 IPI-926 (Saridegib) Formula: $C_{29}H_{48}N_2O_3S$ Mass: 504.768	SMO	Infinity, Antagonist, ChemSpider ID: 26353073 Route of administration: Oral	It is a cyclopamine-derived inhibitor of the Hh pathway with potential antineoplastic activity. Specifically, saridegib binds to and inhibits the cell membrane-spanning G-protein coupled receptor SMO, which may result in the suppression of Hh pathway signaling and a decrease in tumor cell proliferation and survival	[18]
1e	 BMS-833923 Formula: $C_{30}H_{27}N_5O$ Mass: 473.568	SMO	Bristol Myers Squibb/ Exelixis, Antagonist, ChemSpider ID: 29785288 Route of administration: Oral	BMS-833923 is an orally bioavailable small-molecule inhibitor of SMO with IC_{50} values of 6–35 nM	[19]
1f	 PF-04449913 (Glasdegib) Formula: $C_{21}H_{22}N_6O$ Mass: 374.438	SMO	Pfizer, ChemSpider ID: 28518072 Route of administration: Oral	PF-04449913 is also known as Glasdegib. It is a potent and orally bioavailable small-molecule inhibitor of SMO	[20]

Table 1 continued

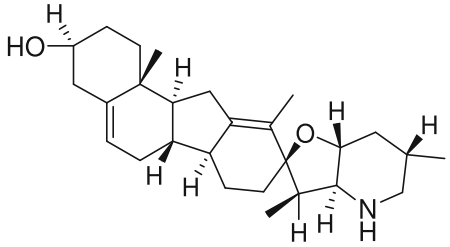
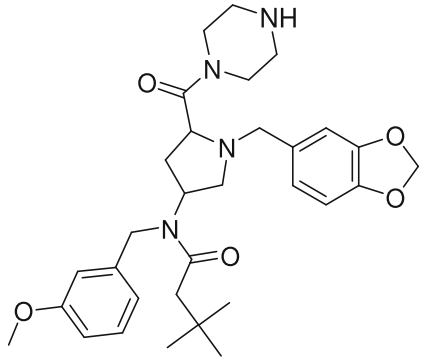
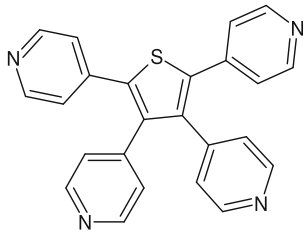
S. no	Structure/name/ composition of compound	Targets/ approval/ study phase	Properties	Drug information	References
1g	 Cyclopamine Formula: $C_{27}H_{41}NO_2$ Mass: 411.314	Hh signaling inhibitor	ChemSpider ID: 391275	It is a naturally occurring chemical. Cell-permeable inhibitor of Hh signaling, via direct inhibition of SMO, the accessory protein to the putative Hh receptor. Anticancer and teratogenic activity in in vivo	[21]
1h	 CUR-61414 Formula: $C_{31}H_{42}N_4O_5$ Mass: 550.688	Hh signaling inhibitor, SMO	Antagonist, ChemSpider ID: 8004752	CUR-61414 is a small-molecule member of the aminoproline class of compounds that was identified in a high throughput screen for inhibitors of the Hh signaling pathway	[23]
1i	 GANT-58 Formula: $C_{24}H_{16}N_4S$ Mass: 392.475	GLI	Antagonist, ChemSpider ID: 221795	It is a more potent in inducing growth arrest and apoptosis compared to cyclopamine in a number of cancer cells	[22]

Table 1 continued

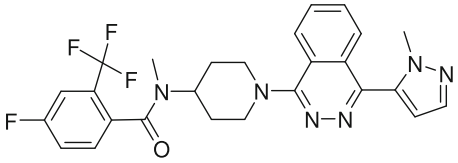
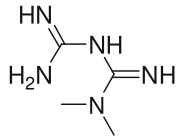
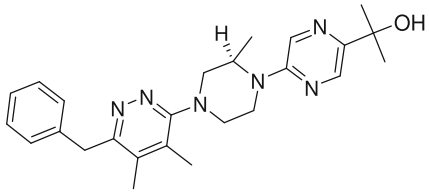
S. no	Structure/name/ composition of compound	Targets/ approval/ study phase	Properties	Drug information	References
1j	 LY-2940680 (Taladegib) Formula: $C_{26}H_{24}F_4N_6O$ Mass: 512.501	SMO receptor-specific Hh signaling inhibitor	ChemSpider ID: 26323626 Route of administration: Oral	It is also known as Taladegib inhibits signaling that is mediated by the Hh pathway protein SMO, which may result in a suppression of the Hh signaling pathway and may lead to the inhibition of the proliferation of tumor cells in which this pathway is abnormally activated. The Hh signaling pathway plays an important role in cellular growth, differentiation and repair	[23]
1k	 Metformin Formula*:* $C_4H_{11}N_5$ Mass*:* 129.163	Shh inhibitor	ChemSpider ID: 3949 Route of administration: Oral	Metformin is an oral biguanide agent the downregulation of Shh signaling by metformin inhibited the proliferation of cancer cells both in vitro and in vivo, impaired cellular migration and invasion and reduced breast cancer stem cells survival and self-renewal capacity	[22]
1l	 LEQ506 Formula: $C_{25}H_{32}N_6O$ Mass: 432.56	SMO	Antagonist, ChemSpider ID: 34222891 Route of administration: Oral	LEQ506, also known as NPV-LEQ506, is a n orally bioavailable SMO antagonist with potential antineoplastic activity	[24]

Table 1 continued

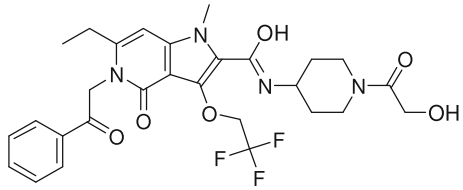
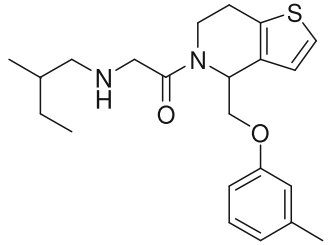
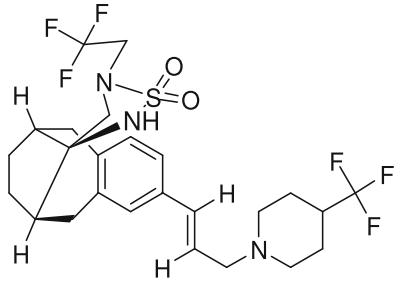
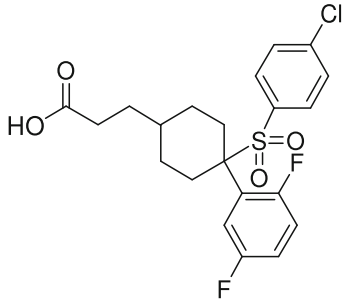
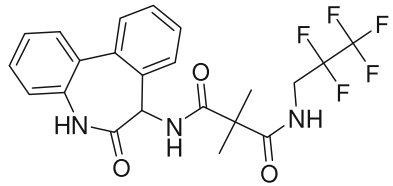
S. no	Structure/name/ composition of compound	Targets/ approval/ study phase	Properties	Drug information	References
1m	 TAK-441 Formula: $C_{28}H_{31}F_3N_4O_6$ Mass: 576.564	SMO	Millennium, Antagonist, PubChem CID: 44187367 Route of administration: Oral	TAK-441 is a potent inhibitor of Hh signaling pathway, TAK-441 is also a novel pyrrolo[3,2-c]quinoline-4-one derivative. TAK-441 is currently in clinical trials for the treatment of advanced solid tumors	[22]
1n	 RU-SKI 43 Formula: $C_{22}H_{30}N_2O_2S$ Mass: 386.550	Hedgehog acyltransferase (Hhat) inhibitor	ChemSpider ID: 22624820	RU-SKI 43 is a small molecule inhibitor of Hhat reduced cancer cell proliferation and Gli-1 activation through Smoothened-independent non-canonical signaling. Also, RU-SKI 43 treatment inhibited two key proliferative pathways regulated by Akt and mTOR	[24]
1o	 MRK003 Formula: $C_{25}H_{31}F_6N_3O_2S$ Mass: 551.587	γ-secretase in Notch pathway	PubChem CID: 56841621	MRK-003, a potent and selective γ-secretase inhibitor, treatment resulted in the downregulation of nuclear Notch1 intracellular domain, inhibition of anchorage-independent growth, and reduction of tumor-initiating cells capable of extensive self-renewal	[14]

Table 1 continued

S. no	Structure/name/ composition of compound	Targets/ approval/ study phase	Properties	Drug information	References
1p	 MK 0752 Formula: $C_{21}H_{21}ClF_2O_4S$ Mass: 442.903	γ-secretase in Notch pathway	PubChem CID: 9803433 Route of administration: Oral	A synthetic small molecule with potential antineoplastic activity. MK0752 inhibits the Notch signaling pathway, which may result in induction of growth arrest and apoptosis in tumor cells in which the Notch signaling pathway is overactivated	[15]
1q	 RO4929097 Formula: $C_{22}H_{20}F_5N_3O_3$ Mass: 469.404	γ-secretase in Notch pathway	PubChem CID: 49867930 Route of administration: Oral	An orally bioavailable, small-molecule γ-secretase inhibitor with potential antitumor activity. γ-secretase inhibitor RO4929097 binds to γ-secretase and blocks activation of Notch receptors, which may inhibit tumor cell proliferation	[16]

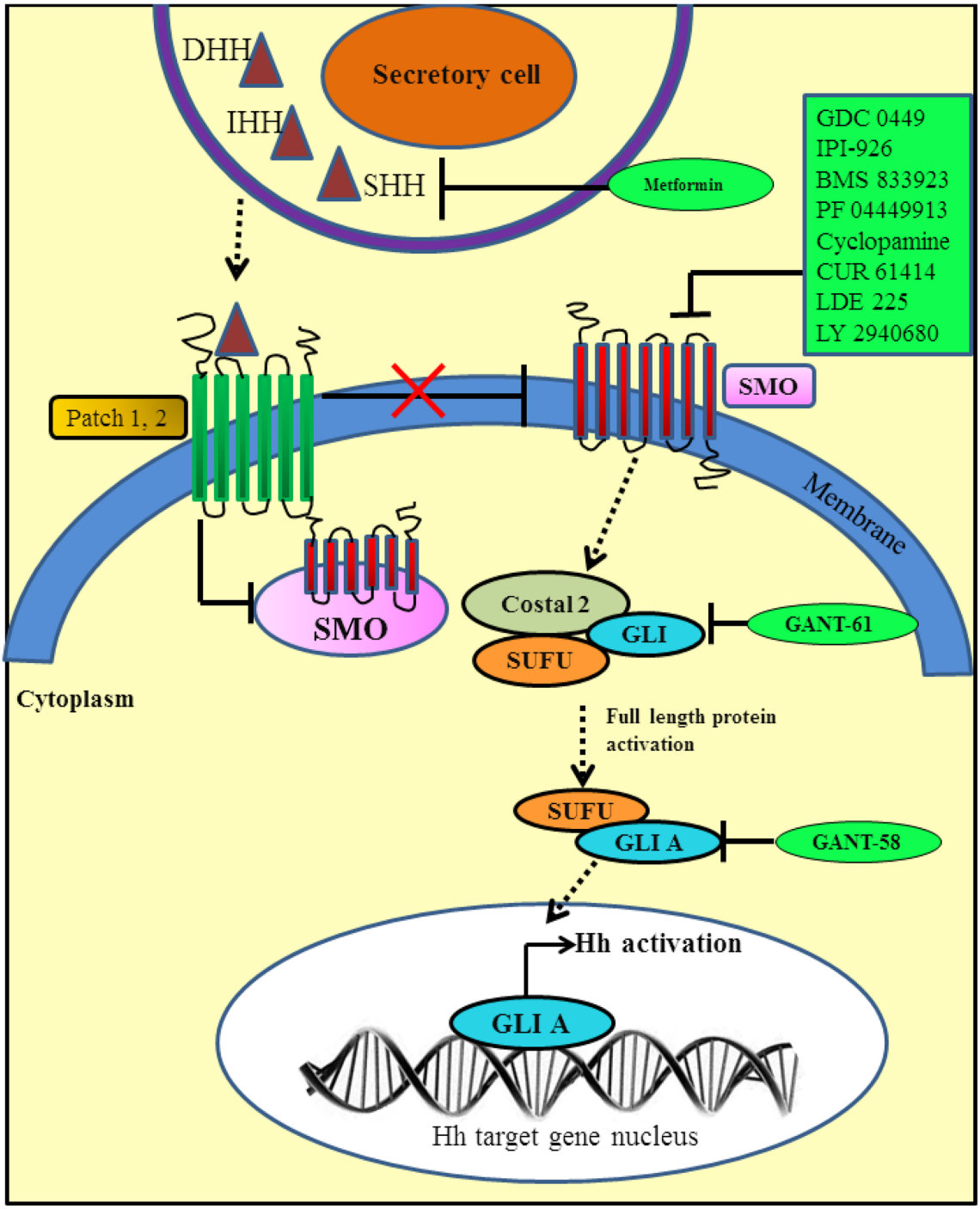


Fig. 2 Schematic diagram of the Hedgehog/gli1 signaling pathways

(benign breast cancer cell line), and SKBR3 (HER2+) in comparison to a primary human mammary epithelial cells (HMEC) [19]. RU-SKI 43 is as selective small molecule inhibitor of Hedgehog acyltransferase (Hhat) recently identified and also reduced the growth of ER+ cell proliferation, whereas a structurally related, inactive compound had no effect. Overexpression of Hhat in ER+ cells not only rescued the growth defect in the presence of RU-SKI 43 but also resulted in increased cell proliferation in the absence of drug [24]. Furthermore, the depletion or inhibition of Hhat reduced proliferation of HER2 amplified as well as tamoxifen-resistant cells. Inhibition of Smoothened had no effect on proliferation, indicating that canonical Shh signaling was not operative. If this pathway continues to be of interest, targeting the Hh signaling would be successful in breast cancers (Fig. 2) [24]. The

structure, chemical composition, and properties of Hh targeting drugs are given in Table 1.

Drugs targeting bone metastasis and environment

Strategies to target bone metastases have included bisphosphonate therapy, receptor activator of nuclear factor kappa-B ligand (RANK-L) directed monoclonal antibody (mAbs) therapy, and palliative radiation in addition to systemic therapy [25]. The recent preclinical study showed that radium-223 alone or in combination with doxorubicin or zoledronic acid increased survival and reduced serum bone biomarkers in a mouse model of BCa bone metastasis [26]. Cathepsin K is a lysosomal cysteine protease highly expressed in osteoclasts, plays a major role in bone resorption. Odanacatib is a promising compound under phase II clinical investigation in women with BCa and bone metastases [27]. Cilengitide is an RGD-mimetic cyclic pentapeptide inhibitor of both αvβ3 and αvβ5 integrins, inhibits bone metastasis in animals and tested in patients [28]. Saracatinib, a dual inhibitor of Src/Abl, has been shown to decrease levels of bone resorption markers in a phase I study in patients with solid tumors [29]. Dasatinib is a potent, orally available inhibitor by blocking the activity against of multiple oncogenic novel tyrosine kinase inhibitors (TKIs) such as the Src/Ab1 family kinases, a non-receptor or receptor tyrosine kinase that has been recently implicated in MBCa to the bone [30]. The structure, chemical composition, and properties of above mentioned drugs are given in Table 2.

Immunotherapy and immunomodulators

Modern anticancer therapy involves the use of mAbs which is once administered to the patient will selectively target a particular protein involved in the proliferation of tumor cells [31]. A synthetic sialyl-Tn (STn) antigen was generated for use as a therapeutic cancer vaccine antigen, and tests in the animal model and human studies showed the antigen to be safe and to produce a strong immune response [32]. Nivolumab is a fully human IgG4 programmed cell death 1 (PD-1) immune checkpoint inhibitor antibody. It boosts the body's immune system by targeting a protein on white blood cells called PD-1 [33]. It is currently under investigation in phase II study in randomized, non-comparative trial of Nivolumab after induction treatment in TNBC patients have been started (NCT02499367) [33]. Ipilimumab is an anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) mAb. Pembrolizumab is a human antibody used in cancer immunotherapy. It targets the programmed cell death 1 (PD-1) receptor [34]. The structures, properties, and function of immunomodulators are given in Table 3.

Inhibition of angiogenesis

Angiogenesis has a key role to play in tumor growth and progression [35]. It switches the shift of the balance between proangiogenic and antiangiogenic in favor of proangiogenesis, applies to all types of solid tumors [36]. Tumor cells enhance local vascular endothelial growth factor (VEGF) production to stimulate the outgrowth of new blood vessels; moreover elevated vascular endothelial growth factor receptor (VEGFR) levels are associated with cancer progression and poor survival rates. Several approaches are employed to inhibit the VEGF pathway. Bevacizumab is a mAb that inhibits VEGFR signaling through attaching and counteracting VEGF-A. It increases response rate (RR) and progression-free survival (PFS) of patients with MBCa when added to first-line chemotherapy in three randomized phase III trials [37]. Ramucirumab is a fully human immunoglobulin G1 mAb (IgG1) developed for the treatment of solid tumors [38]. Sorafenib is an oral multikinase inhibitor that targets Raf-1, wild-type B-Raf, tyrosine kinases acting on VEGFR, platelet-derived growth factor receptor (PDGFR), Flt-3, and c-Kit [39]. Sunitinib malate (SM) is an inhibitor of receptor tyrosine kinases (RTKs) that include VEGFR, PDGFR, stem cell factor receptor (KIT), and colony stimulating factor-1 receptor (CSF1R) [40]. Pazopanib is an oral small molecule TKI of VEGFR, PDGFR, and KIT [41]. Lucitanib is a potent, oral inhibitor of the tyrosine kinase activity of FGFR, PDGFR, and VEGFR [42]. Regorafenib, masitinib, and imatinib mesylate may prove to be clinically useful in inhibiting breast cancer cell migration and metastasis [42]. Axitinib is an oral, potent, selective TKI of VEGFR1, VEGFR2, and VEGFR3 with antiangiogenic and antitumor properties [43]. Aflibercept is an inhibitor of VEGFR. It is a recombinant, decoy receptor fusion protein, rationally designed to block angiogenesis by targeting VEGF-A, VEGF-B, and placental growth factor [44]. The clinically available drugs against angiogenesis are given in Table 4.

Growth factor receptor inhibitors

Growth factors bind to activate RTKs on the high affinity cell surface, which triggers the intracellular signaling pathways [45]. Palbociclib is an oral, small-molecule inhibitor of cyclin-dependent kinases (CDKs) 4 and 6 with preclinical evidence of growth-inhibitory activity in ER+ breast cancer cells and synergy with anti-estrogens [46]. Ado-trastuzumab emtansine and pertuzumab have been

Table 2 Comparative study of drug targeting bone metastasis and environment

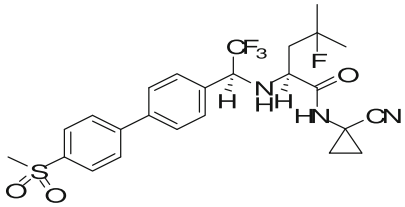
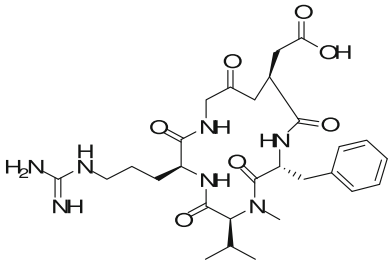
S. no	Structure/name/composition of compound	Targets/Approval/ Study phase	Properties	Drug Information	References
2a	Denosumab Formula: $C_{6404}H_{9912}N_{1724}O_{2004}S_{50}$ Mass: 144.7 kDa	RANKL/Yes/ Approved 2010	Antibody	Denosumab is a monoclonal antibody that targets the receptor activator of Nf-κb (RANKL). It is used to treatpatients with bone metastases from breast cancer, cancer treatment-induced bone loss	[25]
2b	 Odanacatib Formula: $C_{25}H_{27}F_4N_3O_3S$ Mass: 525.559 Da	Cathepsin K/No/ Phase III	Merck & Co/ChemSpider ID: 8328162 Route of administration: Oral	Odanacatib is a cathepsin K inhibitor, in reducing markers of bone remodeling in women with breast cancer and metastatic bone disease	[27]
2c	 Cilengitide Formula: $C_{27}H_{40}N_8O_7$ Mass: 588.656 Da	Integrin, FAK/src/ AKT/No/ Phase II	Technical University/ChemSpider ID: 154046	Cilengitide is a cyclic pentapeptide, has an ability to enhance radiation response in preclinical models of breast cancer	[28]

Table 2 continued

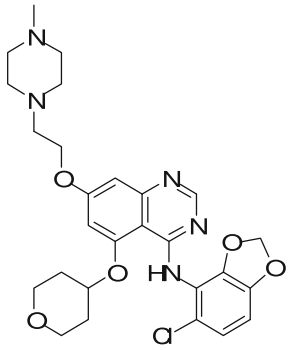
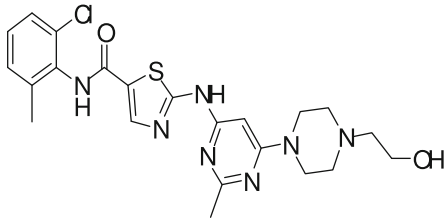
S. no	Structure/name/composition of compound	Targets/Approval/ Study phase	Properties	Drug Information	References
2d	 Saracatinib Formula: $C_{27}H_{32}C_lN_5O_5$ Mass: 542.026 Da	C-src/No/Phase II	AstraZeneca/ChemSpider ID: 477917 Route of administration: Oral	Saracatinib is an oral aniline-quinazoline, It is also known as AZD0530, is a dual tyrosine kinase inhibitor administered orally as a monotherapy, did not induce meaningful responses in patients with hormone receptor-negative metastatic breast cancer	[29]
2e	 Dasatinib Formula: $C_{22}H_{26}ClN_7O_2S$ Mass: 488.005 Da	C-src/No/Phase II	Bristol-Myers Squibb/Trade name: Sprycel Protein binding: 96 % ChemSpider ID: 2323020 Route of administration: Oral	Dasatinib is a novel tyrosine kinase inhibitor with activity against the Src family kinases Phase II studies shown limited responses to dasatinib among breast cancer patients	[30]

Table 3 Comparative study of monoclonal antibody

S. no	Structure/name/composition of compound	Targets/ approval/study phase	Drug information	References
3a	Synthetic sialyl-Tn (STn)	Immune cells/ No/Phase III	It is used to treat MBCa. STn-KLH was well tolerated in this largest to date metastatic breast cancer vaccine	[32]
3b	Nivolumab	PD-1/No/Phase II	Nivolumab is a mAbthat blocks the PD-1 receptor on T cells. Inhibiting the interaction between PD-1 and the PD-1 ligand and CD80 enhances T cell response, potentiate immune response	[33]
3c	Ipilimumab	CTLA-4/No/ Phase I, II	Ipilimumab is used to treat cancer patients with reduced CTLA-4 expression. It inhibits CD80 and CD86 on antigen presenting cells forms binding to CTLA-4 on T cells	[34]
3d	Pembrolizumab	PD-1/No/Phase I, II	Pembrolizumab is used to inhibit PD-1 in patients with advanced TNBC. It is one of a number of closely related therapies called checkpoint therapy	[34]

FDA-approved for HER2-positive breast cancer [47]. Currently, EGFR (ERB1) and ErbB2 (HER2) oral dual TKI lapatinib reduces tyrosine phosphorylation, as well as activation of extracellular signal-regulated kinase 1/2-mitogen-activated protein kinase (MAPK) and PI3K/AKT, affecting downstream effectors of both proliferation and survival [48]. Afatinib is a novel, orally bioavailable, anilinoquinazoline compound. This agent acts as a potent, irreversible, highly selective inhibitor of EGFR/HER1, HER2, and HER4 tyrosine kinase activity [49]. Gefitinib is an EGFR TKI. Neratinib is an oral irreversible inhibitor of endothelial growth factor receptor and HER2 tyrosine kinases [50]. Panitumumab is a fully human mAb specific to the EGFR [51]. Cetuximab binds to EGFR and prevents its intracellular signaling [52]. Figitumumab, a fully human IgG2α–IGF-IR mAb, generated enthusiasm in a randomized phase II clinical study [53]. Imatinib mesylate (IM) inhibits several protein tyrosine kinases, including PDGFR and c-kit, which are preferentially expressed in tumor cells [42]. MEDI-573, amAb with high binding affinity for both IGFs selectively inhibits the activation of both the IGF1R and IR-A signaling pathways and in mouse models without disrupting glucose metabolism mediated by insulin and IR interaction [54]. AVE1642, a humanized IgG1 antibody, showed promising data in preclinical studies but failed in its phase II clinical trials in breast cancer patients [55]. Ganitumab, a fully humanized IgG1 antibody, is being tested in combination with cytotoxic chemotherapy, mTOR inhibitors, and hormonal therapies in various diseases, including NSCLC, colorectal, pancreatic, ovarian, and breast cancer [56]. Dalotuzumab, another humanized IgG1 antibody with promising preliminary profiles [57], is currently being studied with AIs and the mTOR antagonist in advanced breast cancer. Ruxolitinib inhibits dysregulated Janus kinase (JAK) signaling associated with myelofibrosis. A randomized, double-blind, study of ruxolitinib or placebo in combination with capecitabine in subjects with advanced or metastatic HER2-negative breast cancer is in phase II clinical trial (NCT02120417). Temsirolimus, an inhibitor of mTOR, has clinical activity as intravenous (IV) monotherapy in heavily pretreated locally advanced breast cancer or MBCa [58]. The structures, chemical composition, and properties of the GFR inhibitors are given in Table 5.

Selective estrogen receptor downregulators (SERDs)

SERD is a novel class of compound that modulates the level and activity of the ER and displays the tissue selective activation of estrogenic signaling. It improves the normal function and bone strength without affecting the breast and endocrine system outcomes. These ligands should behave as a potent antagonist in the ER+ cell proliferation with no agonist effects. SERD provides treatment options in a variety of diseases, including resistance to endocrine therapies for ER+ BCa in postmenopausal women [59]. Fulvestrant is an SERD that competitively binds to ER, with a binding affinity approximately 100 times greater than that of tamoxifen [60]. In preclinical studies, fulvestrant has been shown to inhibit the in vitro growth of human breast carcinoma cells and was also effective in tamoxifen-resistant breast carcinoma xenografts in in vivo mouse models. GDC-0810 or ARN-810 is currently in phase II clinical trials. It is an orally active and robust activity in models of tamoxifen-sensitive and tamoxifen-resistant BCa with locally advanced or metastatic ER+ BCa [61]. AZD 9496 is a small molecule that can antagonist activity of ERα and induces receptor degradation in the MCF-7 Xenograft model. Recently, SS5020 has been reported to downregulate the ER with antitumor effects against chemically induced memory tumors [62]. A closely related analog of

Table 4 Comparative studies of inhibitors in angiogenesis

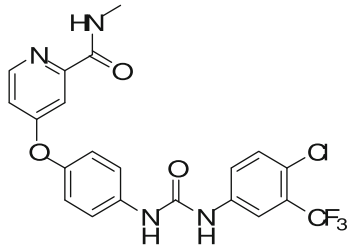
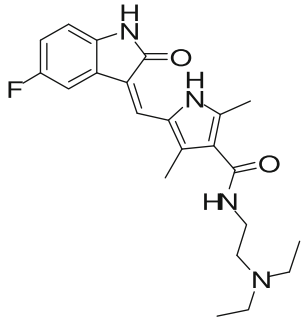
S. no	Structure/name/ composition of compound	Targets/approval/study phase	Properties	Drug information	References
4a	Bevacizumab	VEGFA/Yes/Approved 2011	Antibody	It is a monoclonal antibody against circulating VEGF. It is an angiogenesis inhibitor, a drug that slows the growth of new blood vessels	[37]
4b	Ramucirumab	VEGFR2/No/Phase III	Antibody	It works as a receptor antagonist blocking the binding of VEGF. It is selected for a further preclinical evaluation. Because it did not meaningfully improve important clinical outcomes. It has different side effects such as fatigue, hypertension, febrile neutropenia and stomatitis	[38]
4c	 Sorafenib Formula: $C_{21}H_{16}ClF_3N_4O_3$ Mass: 464.825 Da	VEGFR, Raf, PDGF, Flt3, c-kit/No/Phase III	Bayer and Onyx Pharmaceuticals/Trade name: Nexavar Bioavailability: 38–49 % Protein binding: 99.5 % ChemSpider ID: 187440 Route of administration: Oral	It is an orally available multikinase inhibitor that inhibits the growth of negative breast cancer	[39]
4d	 Sunitinib malate Formula: $C_{22}H_{27}FN_4O_2$ Mass: 398.474 Da	PDGFR, VEGFR/No/Phase III	Pfizer/Trade name: Sutent Protein binding: 95 % ChemSpider ID: 4486264 Route of administration: Oral	It is also known as SU11248, is a multitarget RTKs, SM significantly inhibits the growth of TNBC but increases breast cancer stem cells and Notch-1 expression. Sunitinib is effective at inhibiting both migration and proliferation of breast cancer cells	[40]

Table 4 continued

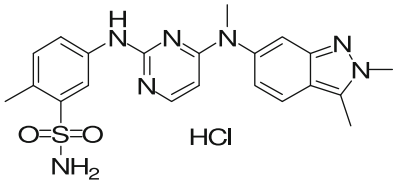
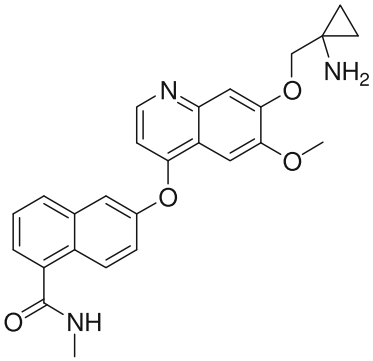
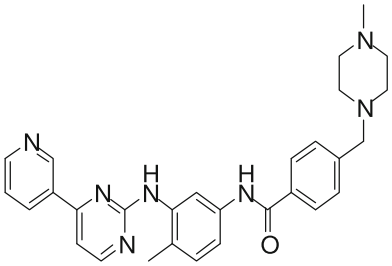
S. no	Structure/name/ composition of compound	Targets/approval/study phase	Properties	Drug information	References
4e	 Pazopanib Formula: $C_{21}H_{24}ClN_7O_2S$ Mass: 473.979 Da	VEGFR, PDGFR/No/Phase II	Trade name: Votrient Protein binding: >99 % ChemSpider ID: 9700526 Route of administration: Oral	It is a potent TKI, that block tumor growth and inhibits angiogenesis	[41]
4f	 Lucitanib Formula: $C_{26}H_{25}N_3O_4$ Mass: 443.494 Da	FGFR, VEGFR, PDGFR/ No/Phase II	ChemSpider ID: 28189586 Route of administration: Oral	Lucitanib is a selective, orally available TKI, recently it has been used in phase II clinical trials for MBC, 10 mg of lucitanib daily in patients with FGFR1 amplified and non-amplified MBC patients. Result in this studies drug response is partial	[42]
4g	 Imatinib Formula: $C_{29}H_{31}N_7O$ Mass: 493.603 Da	PDGFR, c-kit/No/Phase II	Novartis/Trade name: Gleevec, Glivec Bioavailability: 98 % Protein binding: 95 % ChemSpider ID: 5101 Route of administration: Oral	Imatinib combined with radiotherapy leads in breast cancer cell lines to a significant benefit which might be influenced through inhibition of PDGFR phosphorylation. Combining imatinib with chemotherapy enhances cytoreductive effects	[43]

Table 4 continued

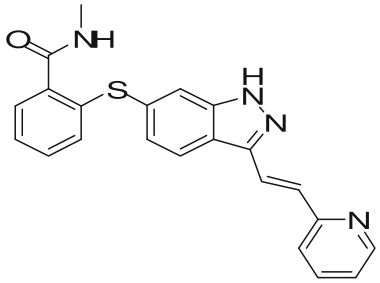
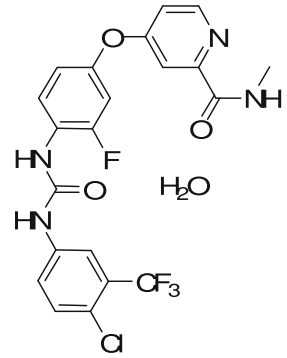
S. no	Structure/name/ composition of compound	Targets/approval/study phase	Properties	Drug information	References
4h	 Axitinib Formula: $C_{22}H_{18}N_4OS$ Mass: 386.470 Da	VEGFR/No/Phase I	Pfizer/Trade name: Inlyta Bioavailability: 58 % Protein binding: >99 % ChemSpider ID: 4953153 Route of administration: Oral	It is an oral, potent, selective TKI of VEGFR1, VEGFR2, and VEGFR3 with antiangiogenic and antitumor properties. A phase I study of single-agent axitinib in solid tumors identified 5 mg twice daily as the therapeutic starting dose and provided evidence of clinical activity and safety	[43]
4i	Aflibercept Formula: $C_{4318}H_{6788}N_{1164}O_{1304}S_{32}$	VEGFR2/No/Phase I	Regeneron Pharmaceuticals/Trade names: Eylea, Zaltrap Route of administration: injection	It is an novel VEGF targeted agent and used for the treatment of anti-angiogenic therapy for multiple tumors. VEGF-Trap (Aflibercept) and trastuzumab has greater inhibition effect than either alone, especially in tumors overexpression HER2	[44]
4j	 Regorafenib hydrate Formula: $C_{21}H_{17}ClF_4N_4O_4$ Mass: 500.831 Da	VEGFR2 PDGFR Ret, Kit and Raf/No/Phase I	Bayer/Trade name: Stivarga Bioavailability: 69–83 % Protein binding: 99.5 % ChemSpider ID: 28295228 Route of administration: Oral	It is also known as BAY 73-4506, is a TKI targeting angiogenic, stromal and oncogenic receptor kinases administered orally. BAY 73-4506 possesses higher affinity and more potent anticancer agent	[45]

Table 4 continued

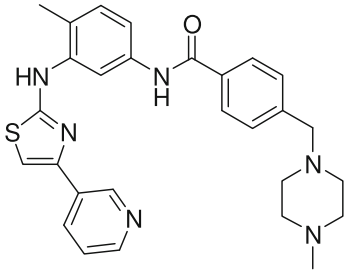
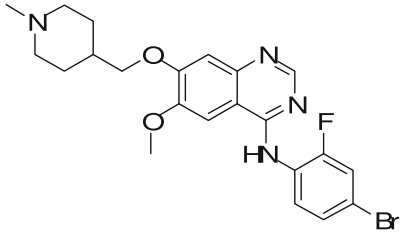
S. no	Structure/name/ composition of compound	Targets/approval/study phase	Properties	Drug information	References
4k	 Masitinib Formula: $C_{28}H_{30}N_6OS$ Mass: 498.642 Da	PDGFR1,2 Kit and Lyn/No/Phase I	Trade name: Masivet, Kinavet ChemSpider ID: 8250179 Route of administration: Oral	It is a new orally administered TKI inhibitor that targets mast calls and macrophages, important cells for immunity, through inhibiting a limited number of kinases	[42]
4l	 Vandetanib Formula: $C_{22}H_{24}BrFN_4O_2$ Mass: 475.354 Da	VEGFR,EGFR/No/Phase II	AstraZeneca/Trade name: Caprelsa Protein binding: 90–96 % ChemSpider ID: 2338979 Route of administration: Oral	It is also known as ZD6474 was originally developed as a second generation TKI, but subsequently found to have more potent inhibitory effect against VEGF and RET receptors	[42]

Table 5 Comparative study of growth factor receptor inhibitors

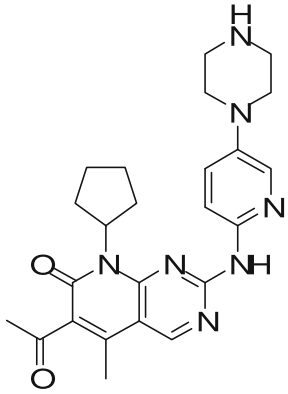
S. no	Structure/name/composition of compound	Targets/approval/study phase	Properties	Drug information	References
5a	 Palbociclib Formula: $C_{24}H_{29}N_7O_2$ Mass: 447.533 Da	ErbB2 CDK 4,6/Yes/Approved 2015	Pfizer/Trade name: Ibrance ChemSpider ID: 4487437 Route of administration: Oral	Palbociclib with fulvestrant resulted in longer PFS and a relatively higher quality of life than fulvestrant alone in patients with advanced hormone-receptor positive breast cancer that had progressed during prior endocrine therapy, regardless of the patient's menopausal status	[46]
5b	Ado-trastuzumabemtansine Whole antibody	ErbB2/Yes/Approved 2013	Trade name: Kadcyla, Bioavailability: N/A Protein binding: 93 % Route of administration: Intravenous infusion	It consists of the monoclonal antibody linked to a potent microtubule inhibitor (emtansine), allowing a targeted delivery of chemotherapy to cells that overexpress HER2	[47]
5c	Pertuzumab Whole antibody	ErbB2/Yes/Approved 2013	Trade name: Perjeta, Omnitarg Route of administration: Intravenous	It is a HER2/neu receptor antagonist, it is used for the treatment of breast cancer given before surgery as part of a complete treatment course combination with herceptin and docetaxel as neoadjuvant treatment of patient with HER2-positive, locally advanced, inflammatory or early stage (tumor is greater than 2 cm in diameter or node positive) breast cancer	[47]

Table 5 continued

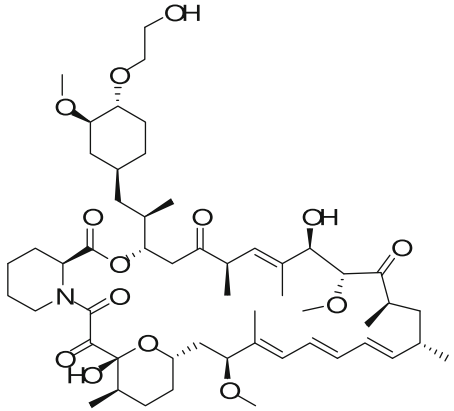
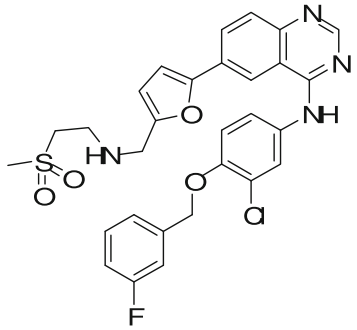
S. no	Structure/name/composition of compound	Targets/approval/ study phase	Properties	Drug information	References
5d	 Everolimus Whole antibody Formula: $C_{53}H_{83}NO_{14}$ Mass: 958.224 Da	mTORC1/Yes/ Approved 2012	Novartis/Trade name: Afinitor ChemSpider ID: 21106307 Route of administration: Oral	It is mTOR inhibitor in combination with exemestane, has been approved for patients with advanced hormone positive/HER2-negative breast cancer who progress on prior nonsteroidal aromatase inhibitor therapy based on results reported in the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study	[48]
5e	 Lapatinib Formula: $C_{29}H_{26}ClFN_4O_4S$ Mass: 581.057 Da	EGFR, ErbB2/Yes/ Approved 2007	GlaxoSmithKline/Trade name: Tykerb, Bioavailability: Variable, Protein binding: >99 %, ChemSpider ID: 181006 Route of administration: Oral	It is anorally active, dual, small-molecule, potent reversible TKI inhibitor. Lapatinib for use in combination with capecitabine in the treatment of advanced HER2-amplified (HER2-positive) breast cancer	[48]

Table 5 continued

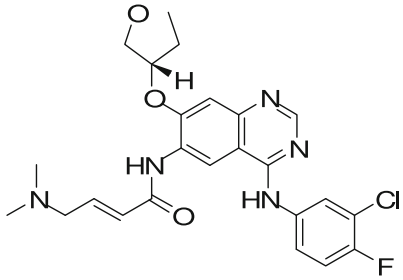
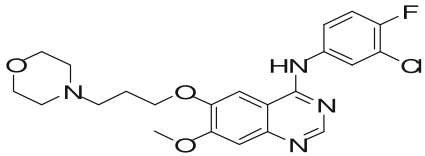
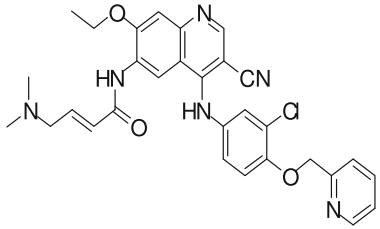
S. no	Structure/name/composition of compound	Targets/approval/study phase	Properties	Drug information	References
5f	 Afatinib Formula: $C_{24}H_{25}ClFN_5O_3$ Mass: 485.938 Da	EGFR, HER1,2 & 4/No/ Phase III	BoehringerIngelheim/Trade name: Gilotrif, Giotrif Protein binding: 65 % ChemSpider ID: 8360155 Route of administration: Oral	It is a novel, orally bioavailable, anilinoquinazoline compound. It is higher affinity and more potent inhibitor ErbB receptors (Trastuzumab) with afatinib would improve clinical outcomes compared with HER2 inhibition alone in patients who had progressed on previous trastuzumab treatment	[49]
5g	 Gefitinib Formula: $C_{22}H_{24}ClFN_4O_3$ Mass: 446.902 Da	EGFR/No/Phase II	AstraZeneca and Teva/Trade name: Iressa Bioavailability: 59 % Protein binding: 90 % ChemSpider ID: 110217 Route of administration: Oral	It is an EGFR TKI. It has been shown that combining Gefitinib with endocrine therapy can delay the development of drug resistance. Gefitinib has been downregulate the expression of molecules involved in the MAPK pathway and demonstrated that Gefitinib at a low dose could reverse tamoxifen resistance	[50]
5h	 Neratinib Formula: $C_{30}H_{29}ClN_6O_3$ Mass: 557.043 Da	EGFR, ErbB1, 2, 4/No/ Phase II	ChemSpider ID: 8091392 Route of administration: Oral	It is a potent, irreversible,oral TKI. Neratinib inhibits EGFR and HER2 at IC_{50} values of 92 and 59 nM in cell-free autophosphorylationassay respectively	[50]

Table 5 continued

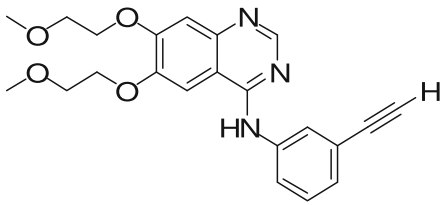
S. no	Structure/name/composition of compound	Targets/approval/ study phase	Properties	Drug information	References
5i	 Erlotinib Formula: $C_{22}H_{23}N_3O_4$ Mass: 393.436 Da	EGFR/No/Phase II	Genentech and OSI Pharmaceuticals/Trade name: Tarceva Bioavailability: 59 % Protein binding: 95 % ChemSpider ID: 154044 Route of administration: Oral	It is an orally available quinazolinamine that competes with ATP for binding with the intracellular catalytic domain of EGFR-TK to inhibit the phosphorylation of EGFR-TK. This action blocks downstream signal transduction and inhibits the tumorigenic effects associated with ligand-dependent and ligand-independent EGFR activation. Down-regulation of CDK2 after treatment with erlotinib	[49]
5j	Panitumumab Whole antibody Formula: $C_{6398}H_{9878}N_{1694}O_{2016}S_{48}$	EGFR/Yes/Phase II	AbgenixInc/Trade name: Vectibix Route of administration: Intravenous	It is an anti-EGFR monoclonal antibody or TKI. It is used to improve the pathologic complete response rate as neoadjuvant treatment for women with TNBC	[51]
5k	Cetuximab Formula: $C_{6484}H_{10042}N_{1732}O_{2023}S_{36}$ Mass: 145781.6	EGFR/No/Phase II	Antibody	The EGFR monoclonal antibody Cetuximab is used for the treatment of TNBC. Cetuximab, in combination with Ixabepilone, is more effective in eliminating cancer stem cells populations compared to chemotherapy alone in TNBC. Anti-EGFR MAbs substantially enhance the effects of doxorubicin against well-established xenografts of tumor cells expressing high levels of EGFR	[52]
5l	Figitumumab Formula: $C_{6462}H_{9948}N_{1736}O_{2020}S_{54}$ Mass: 146.0 kDa	IGF-IR/No/Phase II	Antibody	It is also known as CP-751,871, a human monoclonal antibody that blocks IGF1R ligand binding, alone and in combination with the therapeutic anti-HER2 antibody trastuzumab and the pan-HER family tyrosine kinase inhibitor neratinib, using in vitro and in vivo breast cancer model systems	[53]
5m	MEDI-573	IGF-IR/No/Phase II	Antibody	It is a dual-targeting human MAb that neutralizes the IGFI and IGFII ligands, resulting in inhibition of IGF signaling through both IGF1R and insulin receptor isoform A in a number of cancer cell lines	[54]
5n	AVE1642	IGF-IR/No/Phase II	Antibody	It is a humanised version of the murine mAb, binds the human IGF-1R specifically and with high affinity. AVE1642 is well tolerated as a single agent and combined with docetaxel. Promising activity was proved in sarcoma and breast cancer patients.	[55]

Table 5 continued

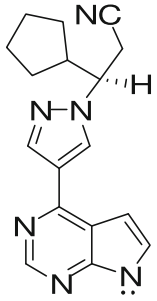
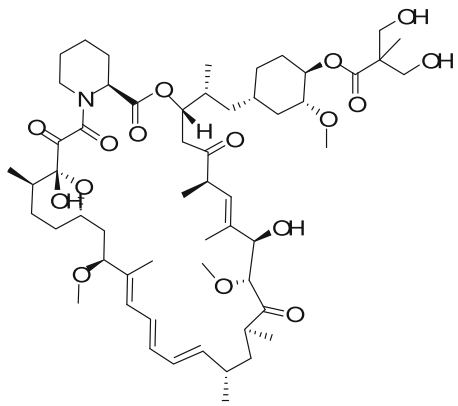
S. no	Structure/name/composition of compound	Targets/approval/study phase	Properties	Drug information	References
5o	 Ruxolitinib Formula: $C_{17}H_{18}N_6$ Mass: 306.365 Da	JAK1,2/No/Phase II	Incyte Pharmaceuticals and Novartis/Trade name: Jakafi, Jakavi Bioavailability: 95 %, Protein binding: 97 % Chem Spider ID: 25027389 Route of administration: Oral, topical	It is an oral inhibitor of JAK1 and JAK2. Combination of Ruxolitinib plus Trastuzumab is safe and effective in stopping breast tumor growth in patients with HER2 positive metastatic breast tumors	[56]
5p	Ganitumab Formula: $C_{6472}H_{10028}N_{1728}O_{2020}S_{42}$ Mass: 145.7 kDa	mTORC1/No/Phase II	Antibody	It is a mAb IGF-1 receptor antagonist. Ganitumab is used to endocrine treatment for patients with hormone-receptor positive breast cancer	[56]
5q	Dalotuzumab Formula: $C_{6528}H_{10086}N_{1730}O_{2018}S_{40}$ Mass: 146.4 kDa	IGF1R/No/Phase I	Antibody	It is a fully humanized mAb, it is a IGF1R antagonist activity	[56]
5r	 Temsirolimus Formula: $C_{56}H_{87}NO_{16}$ Mass: 1030.287 Da	mTORC1/No/Phase II	Wyeth/Trade name: Torisel ChemSpider ID: 21468899	It is an inhibitor of the mTOR. It inhibited the proliferation of breast cancer cell lines that were estrogen dependent, overexpressed HER2 and inhibited growth of Phosphatase and tensin homolog (PTEN)-deficient cells in a nude mouse xenograft mode	[58]

Table 6 Comparative studies of SERD

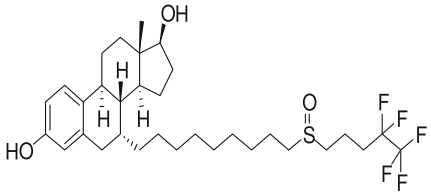
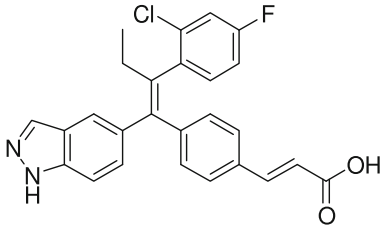
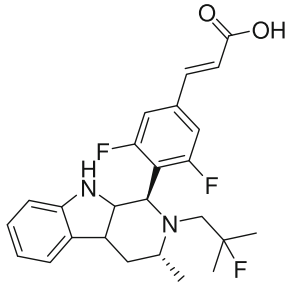
S. no	Structure/name/composition of compound	Targets/approval/ study phase	Properties	Drug information	References
SERD					
6g	 Fulvestrant Formula: $C_{32}H_{47}F_5O_3S$ Mass: 606.772 Da	ER/Yes/ Approved 2002	Trade name: Faslodex Protein binding: 99 % ChemSpider ID: 94553 Route of administration: Intramuscular injection	It is a steroid-based novel ER antagonist originally selected for development due its lack of agonism across all tissue types. It binds competitively to the ER, with high affinity and downregulates ER by functional blockade and increased turnover	[56]
6h	 ARN-810 Formula: $C_{26}H_{20}C_lFN_2O$ Mass: 446.90 Da	ER/No/Phase II	AK Scientific, Inc. (AKSCI) PubChem CID: 9874874 ChemSpider: 8050563	It is a potent ER-α binder (IC_{50} = 6.1 nM), a full transcriptional antagonist with no agonism and displays good potency and efficacy in ER-α degradation (EC_{50} = 0.7 nM) and MCF-7 breast cancer cell viability (IC_{50} = 2.5 nM) assays	[61]
6i	 AZD 9496 Formula: $C_{25}H_{25}F_3N_2O_2$ Mass: 444.489 Da	ER/No/Phase I	AstraZeneca orally bioavailable selective estrogen receptor downregulator (Ki = 0.7 nM)	It is a potent and orally bioavailable SERD (IC_{50} = 0.7 nM(Ki)) and antagonist. It can induce ERα degradation in BCa cell lines at picomolar concentrations. AZD9496 is used for the treatment of ER+ BCa or ER downregulator	[62]

Table 6 continued

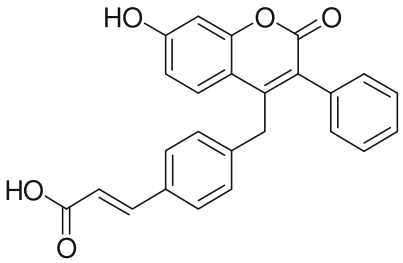
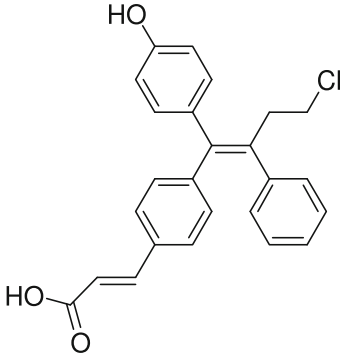
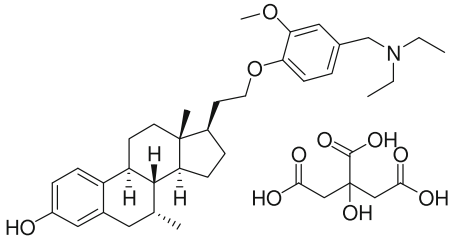
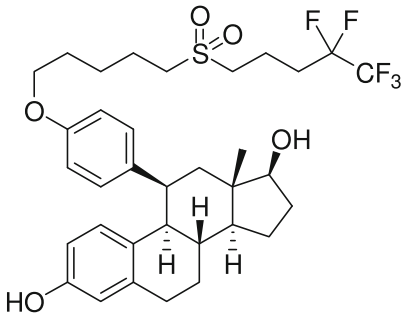
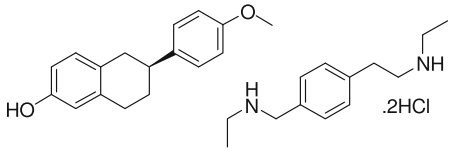
S. no	Structure/name/composition of compound	Targets/ approval/study phase	Properties	Drug information	References
6j	 SS5020 Formula: $C_{25}H_{18}O_5$ Mass: 398.407 Da	ER/No/ Preclinical	AstraZeneca lacks estrogenic and genotoxic actions Route of administration: Oral	It is a novel benzopyran antiestrogen. The growth of human MCF-7 breast cancer xenograft implanted into athymic nude mice was also effectively suppressed by SS5020. SS5020, lacking genotoxic and estrogenic actions, could be a safer and stronger antiestrogen and used for breast cancer therapy and prevention.	[66]
6k	 SS1020 Formula: $C_{25}H_{21}ClO_3$ Mass: 404.885 Da	ER/No/ Preclinical	New triphenylethylene antiestrogen	It is an ER downregulator and higher antitumor potential against MCF-7 BCa xanograft model was stronger activity	[67]
6l	 TAS-108 Formula: $C_{39}H_{55}NO_{10}$ Mass: 697.855 Da	ER/No/Phase II	Anderson Cancer Center, Tolerated at doses ranging from 40 to 160 mg/day	It is a novel steroidal ERα antagonist activity and partial ERb agonist activity, potentially providing TAS-108 with bone-protective effects. TAS-108 may be effective against estrogen-dependent, tamoxifen-resistant tumors in vitro, it may have a beneficial effect on bone-mineral density and it may have less of an agonist effect on the endometrium compared with tamoxifen in animal studies	[68]

Table 6 continued

S. no	Structure/name/composition of compound	Targets/approval/ study phase	Properties	Drug information	References
6m	ZK191703	ER/No/Preclinical	Pure antiestrogen, single injection of 5 mg/kg	It is a new orally bioavailable pure antiestrogen have equivalent or superior potency in patients to intramuscularly administered fulvestrant	[69]
6n	 RU58668 Formula: $C_{34}H_{43}F_5O_{15}S$ Mass: 658.759 Da	ER/No/Phase I	Tocris Bioscience3224 ChemSpider ID5293467	It is a pure antiestrogen that downregulates ER expression (IC_{50} = 0.04 nM). Displays potent antiproliferative activity in vitro (IC_{50} = 0.035-0.09 nM in MCF-7 cells) and causes long term regression of tamoxifen-resistant MCF-7 xenografts in vivo	[70]
6o	 RAD1901 Formula: $C_{30}H_{40}Cl_2N_2O_2$ Mass: 531.56 Da	ER/No/Phase II	IRIX Pharmaceuticals Inc. (Florence, South Carolina, USA) ClinicalTrials.gov #:NCT02338349, good oral bioavailability	It is a novel, non-steroidal, orally bioavailable SERD. It is used for the treatment of hormone-driven or hormone-resistant MBCa.RAD1901 is currently being investigated in postmenopausal women with advanced ER+, HER2-negative BCa, the most common form of the disease. The compound has the potential for use as a single agent or in combination with other therapies to overcome endocrine resistance in metastatic breast cancer	[71]

SS1020 was also reported to be a selective ER down-regulator by the same group. At present, SERD such as SR16234, ZK191703, ZD164384, RU58668, RAD1901, GDC0810 or ARN-810, TAS-108 showed potent bioavailability and good activity in clinical trials (Table 6).

Natural antiestrogen

Thymoquinone (TQ) is isolated from *Nigella Sativa* that inhibits the growth of cancer cell and induces apoptosis in both ER− and ER+ cancer cell lines [63]. Tehranolide is a natural sesquiterpene lactone isolated from *Artemisia annua*. It inhibits cell proliferation by affecting PI3K/AKT/cyclin D signaling [63]. Deoxybouvardin is a natural cyclopeptide derived from *Rubia Yunnanensis* that exhibits a variety of biological activities, including anti-neoplastic. Subglutinol A is an immunosuppressive α-pyrone diterpenoid that can be isolated from *Fusarium Subglutinans,* an endophytic fungus. It has been proven to be an ER antagonist [64]. The natural effects of I3C are attributable to DIM, which shows evidence of anti-tumorigenic activities in vivo and in vitro by reducing the growth of breast cancer cells [65].

Conclusion

In summary, there are several types of drugs having different pharmacological properties, administration route, and targeting site that have already marketed for the treatment of breast cancer. Many therapeutic options and their mode of activation have been elaborately discussed herewith. The discovery of new targets and expression in breast cancer has been developed and reported by the researchers all over the world, but also further development is ongoing to reduce or minimize the riskiness or side effects. Therefore, further investigation will be important to focus on the design of drugs and new agents acting on targets for validating the concept of the underlying single or combined treatment strategy. Ultimately, the comparative studies of carrier-linked prodrugs with current chemotherapeutic regimens will also be needed for their market approval. This review is to focus on the availability of multiple agents with different ways of mechanisms of activation possessing the challenges and may also be useful for further innovation.

Acknowledgments Thanks are attributable to DST &DBT, Govt. of India for financial support and Bioinformatics Infrastructure facility, IASST.

Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

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