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Indole Derivatives as Anticancer Agents for Breast Cancer Therapy: A Review

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Abstract: Breast cancer (BC) is the second most common cause of cancer-related deaths in women throughout the world. Multiple drugs have been approved by US-FDA for breast related malignancies. Frequent emergence of resistances creates the severe need of newer moieties that are free from such problems. Drugs targeting breast cancer have been observed to be based on the multiple mechanisms of action, and various indole based anticancer agents have also been explored. Moreover, indoles have promising anti-cancer potential; there has been the emphasis on the synthesis of indole derivatives to overcome problems faced by existing therapeutic agents. Taking into consideration the above-mentioned facts we have analyzed in detail the possible role of indole based anticancer agents typically for breast related malignancies. This is the first exhaustive review that jointly covers various synthetic anticancer indole derivatives and related signaling pathways by which these derivatives have shown promising anti-breast cancer potential.

Keywords: Anticancer, apoptosis, breast cancer, indole, mTOR, resistance, signaling

INTRODUCTION

Breast cancer (BC) is a heterogeneous disease, which may be classified as adeno, ductal, lobular and nipple carcinoma on the basis of its origin. Estrogen receptor (ER), progesterone receptor (PR) and ERBB2/HER2 are highly upregulated in different cancer stages in BC due to multiple genetic alterations [1, 2]. This is the second most prevalent cause of cancer-related deaths, and there is a need of permanent cure of this disease [3]. In US, the expected numbers of BC cases in 2014 are 235,030 in both sexes together and 232,670 in females, which indicates that women are most affected [4]. Environmental factors and dietary habits are the primary source of BC induction with some secondary factors like virus-mediated genetic disturbances and many more [5]. During the development of cancer, multiple signaling cascades get deregulated which result in increased cell proliferation, cell survival, as well as the emergence of resistance towards several anticancer drugs. The deregulation mainly recognized in BC are the inactivation of tumor suppressor genes and hyperactivation of proto-oncogenes [6]. Several deregulations involving aromatase, NFkB kinase, estrogen transduction pathway, and imbalance of pro and anti-apoptotic proteins have been associated with BC. Above-mentioned proteins are thus important targets in BC for the chemotherapeutic agent to inhibit the progression of breast related malignancies [7].

For the treatment of BC, fulvestrant, lapatinib, eribulin mesylate, pertuzumab, everolimus and numerous other agents have been approved by the FDA. The occurrence of resistance that is faced by these drugs has restricted their use, and we still need some alternates for a full proof treatment option against BC. Thus, there is a need to develop a new group of anticancer agents targeting BC cells [8]. Nowadays a large number of potent bioactive entities originating from natural sources as well as derived by synthetic methodology exist as potent anticancer agents that can be used for BC chemotherapy [9]. Among these entities, indole is one of the fascinating moiety that is a part of potent natural compounds along with synthetic derivatives. These derivatives have shown a broad spectrum of biological activities such as antibiotic, anticancer, anti-inflammatory, anticonvulsant and specifically anticancer activity. Anticancer activity of various indole derivatives has been examined on diverse human BC cell lines, and impressive results were obtained. The captivating results ignited interest among the several group of researchers for developing indole derivatives as active chemotherapeutic agents [10, 11]. Here we have tried to compile all these indole based agents (**2-16** apoptosis-inducing factor, **17-35** tubulin inhibitor, **36-44** NFkB kinase inhibitor, **45-46** estrogen receptor regulator, **47-50** aromatase inhibitor, **51-51** AhR regulator and **53-78** miscellaneous anticancer agents) with special privilege to BC chemotherapy.

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INDOLES AS ANTICANCER AGENTS

Indoles, firstly isolated from an indigo dye, are heterocyclic aromatic compounds consisting of six-membered benzene ring and five-membered pyrrole ring which fused together. Indole nucleus is usually present in the biological system and also found in many plants belonging to the cruciferous family such as broccoli, cauliflower, cabbage and brussels sprouts [12, 13].

Complex indole containing anticancer agents such as vinca alkaloids were first obtained in 1950 from *Catharanthus roseus* plant. Initially, vinca alkaloids were identified for their hypoglycemic properties but later on their ability to suppress the bone marrow, and inhibition of microtubule formation provided a way to target many forms of cancers [14]. Currently, indole derivatives have been used clinically in cancer chemotherapy such as vincristine, vinblastine, vinorelobine and sunitinib that target different cellular signaling cascades for arresting disease progression [15]. Simplified and prospective mechanism associated with indole based anti-cancer agents is represented in Fig. **1** [16, 17].

Induction of Apoptotic Factor and Cell Cycle Arrest

Apoptosis is an energy dependent programmed cell death without oligonucleosomal DNA fragmentation. It begins through the activation of caspases in which aged cells die by a natural physiological process without affecting normal cells [18]. Induction of apoptosis regulated by pro-apoptotic BCL-2 associated X proteins (Bax), Bcl-2 antagonist of cell death (Bad), Bcl-2 antagonist killer 1, anti-apoptotic B cell lymphoma proteins Bcl -2, Bcl-xL 2, Mcl-1, Bcl-w, Bcl-b and A1 in the cells [19]. Induction of apoptotic cell death commences by two signaling transduction pathways, extrinsic and intrinsic molecular pathway. The extrinsic pathway is triggered by extracellular pro-apoptotic stimuli, which upon binding to their receptor activates procaspases 8 and 10. Caspases 8 and 10 amplify the extrinsic pathways proteins BH-3 only. Activated caspases 8 and 10 stimulate the caspases 3, 6 and 7 to induce apoptotic cell death. Activated caspases 8 cleaves the Bid

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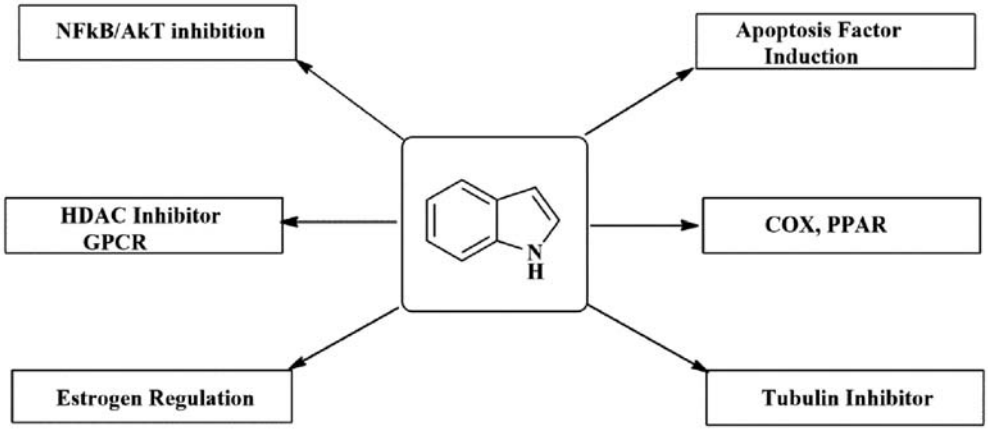

Fig. (1). Targets of indole in breast cancer.

to tBid belongs to BH-3 protein. BH3-only protein subgroup such as Bim, Bid, and Puma directly or other BH-3 only proteins known as sensitizers indirectly activate the Bax and Bak adapter molecules. Activated adapter molecules enter into the mitochondria and oligomerize, resulting in the release of cytochrome c from the mitochondria. Released cytochrome c in turn activates Apaf1, which stimulates caspases 9 and 3 by inducing apoptotic cell death as shown in Fig. **2** [20, 21, 22].

Indole-3-carbinol (I3C) (Fig. **3**) is an important natural indole derivative obtained from the glucobrassicin belonging to *Brassica* genus, which showed impressive outcome *in vitro* and *in vivo* anticancer activity in various tissues. I3C upon acid condensation generate a series of compounds such as Diindolylmethane (DIM), indolo[3,2b]-carbazole (ICZ), a linear trimer (LTr1), a cyclic trimer (CTr) and cyclic tetramer indole (CTet) (Fig. **3**). They inhibited the estrogen-mediated tumor growth, induced apoptotic cell death in BC cells and arrested G1/S phase of cell cycle [23, 24, 25]. I3C inhibited insulin-like Growth Factor Receptor-1 (IGFR-1) and downstream signaling cascades in BC [26].

3-Methoxymethyl (**2**) and 3-ethoxymethyl indole (**3**) exhibit activity almost similar to I3C for arresting cell cycle. The N-Alkoxy derivative of I3C has been found to be more potent compared to I3C for halting the cell cycle in G1phase. As the alkoxy group bulkiness increases from methoxy to butoxy, GI_{50} concentration for methoxy, ethoxy, propoxy and butoxy derivatives decreases 23, 50, 217 and 470-fold lower than I3C, respectively [27, 28].

9-[(6-Chloropyridin-4-yl)methyl]-9H-carbazole-3-carbinol (HYL-6d) (**4**) blocks cell cycle in G1 and S phase. It promotes apoptosis by increasing the level of pro-apoptotic Bcl-XS along with decreasing the level of anti-apoptotic Bcl-2 and Bcl-XL proteins in MCF-7 cell lines [29]. 3-(Benzoylthio)-5-(1H-indol-3-yl)-4H-1,2,4-triazol-4-amine (**5**) substituted compound showed Bcl-2 inhibitory activity when tested on MDA-MB-231 cells (IC_{50} 0.31 μM). It acts by competing with Bcl-2 homology domain (BH-3) for binding with Bcl-2 at the hydrophobic groove and showed interaction of 4-amino and sulfur atom with Tyr67 [30]. Li *et al.* synthesized a series of indolylquinone from 2-substituted indole and tested for their antiproliferative activity against BC cell lines. Among the series, compound (**6**) and (**7**) exhibit most potent antiproliferative activity by inducing apoptosis cell death in V-FTIC positive cells. Compound (**6**) showed IC_{50} value of 6.46 μM (MCF-7) and 12.59 μM) (MDA-MB231) while compound (**7**) has IC_{50} value of 7.23 μM (MCF-7) and 11.27 μM (MDA-MB-231) cell lines [29].

Instability of I3C in acidic environment of stomach was one of the drawbacks associated with it, which can be overcome by its tetrameric derivate (Fig. **3**). A tetrameric derivative was found to be 5 times more effective than I3C in BC cell lines and was highly selective towards tumorigenic cells. These derivatives were responsible for inhibiting the growth of ER-positive as well as ER-negative BC cells by arresting G1 phase of cell cycle through inhibiting the expression of cyclin-dependent kinase 6 and increase the level of p27 protein. Other kinases present in G1 phase remain intact indicating no participation of other proteins. Higher expression of apoptotic death receptor was also observed in tetramer treated cells and causes apoptotic cell death [31]. Galluzi *et al*. reported that C tet induce the endoplasmic reticulum stress in ER-positive MCF-7 as well as ER-negative MDA-MB-231 BC cell lines [32]. 6-bromoindirubin-3-oxime (6-BIO) (**8**) and 7-bromoindirubin-3-oxide (7-BIO) (**9**) induce apoptosis in MDA-MB-231-TXSA BC cell line with the IC_{50} value of 9.2 ± 3.5 and 2.3 ± 4.6 μM respectively.

7-BIO increases the level of p21 that inhibits the activity of cyclin B1/CDC-2 complex and increase the expression of death receptor 4 and 5 proteins resulting in arresting of cells in G2/M phase. Whereas 6-BIO activates caspases 9 and 3 associated with apoptotic cell death [33]. Li *et al*. reported that I3C derived 5-hydroxy tetraindole (SK228) (**10**) induce apoptotic cell death in the MCF-7 cell line with IC_{50} value of 0.00088 ± 0.00004 μM and MDA-MB-231 cell line with IC_{50} value of 0.00045 ± 0.00003 μM. They concluded that 5-hydroxy tetraindole arrest the cell cycle at G2/M phase which is associated with increased expression of phosphorylated CDC-2, cyclin B1 and causes apoptotic cell death by intrinsic (bcl-2/bak) and extrinsic pathway [34].

It has been found that cell cycle progression is strictly regulated by cyclin-dependent kinases such as CDK2, CDK4 and CDK6 which are the family members of serine/threonine kinase. CDK2 is a major cyclin-dependent kinase of the G_1 phase of the cell cycle which is stimulated by cyclins and inhibited by p21. Cyclin D activates CDK2 by binding with CDK4. CDK4 partially inactivates retinoblastoma (RB1) along with stimulation of cyclin E to activate the CDK2. Activated CDK2 regulates the promotion of cell cycle from G1 to S phase [35]. Wherever, I3C comes in contact with the acidic environment of the stomach, it dimerizes into several condensation products that have been found to show distinctive anticancer activity. DIM (Fig. **3**) a condensation product of I3C possesses anticancer activity in various tumor types such as breast, colon, and pancreas. It acts by inhibiting proliferation of estrogen-dependent as well as independent BC by suppressing anti-apoptotic and inducing the pro-apoptotic protein along with fixing cells cycle in G1 phase. DIM increases the expression of p21 related transcriptions through estrogen-independent manner. It also causes binding of specific transcription factor (Sp1 and Sp3) to consensus element and increases the ratio of Bax to Bcl-2 in breast cancer

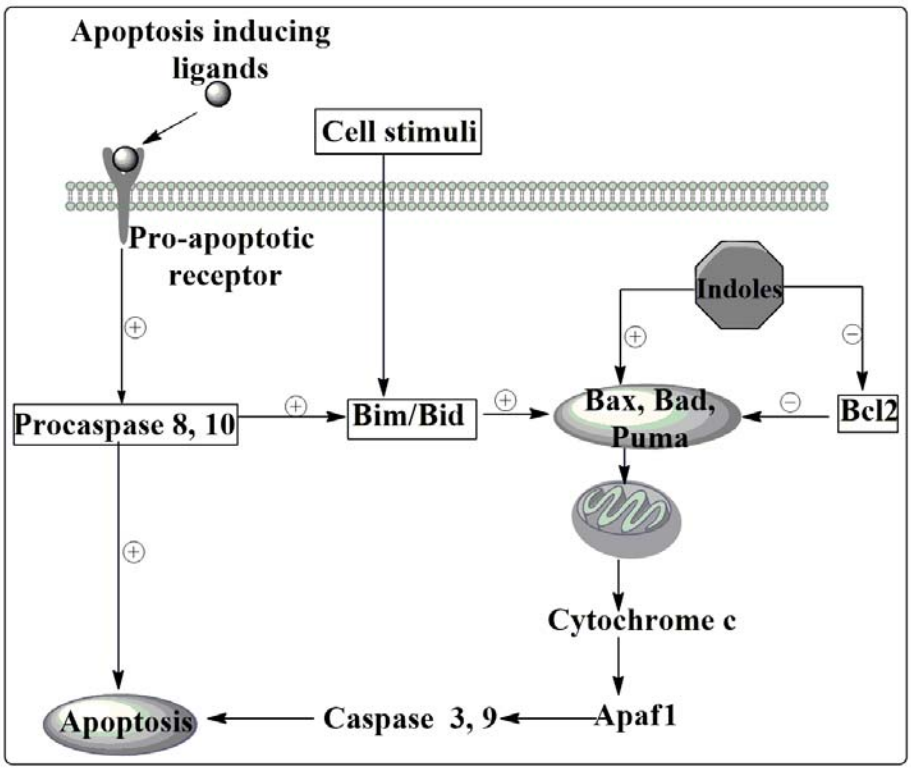

Fig. (2). Apoptosis signaling pathway.

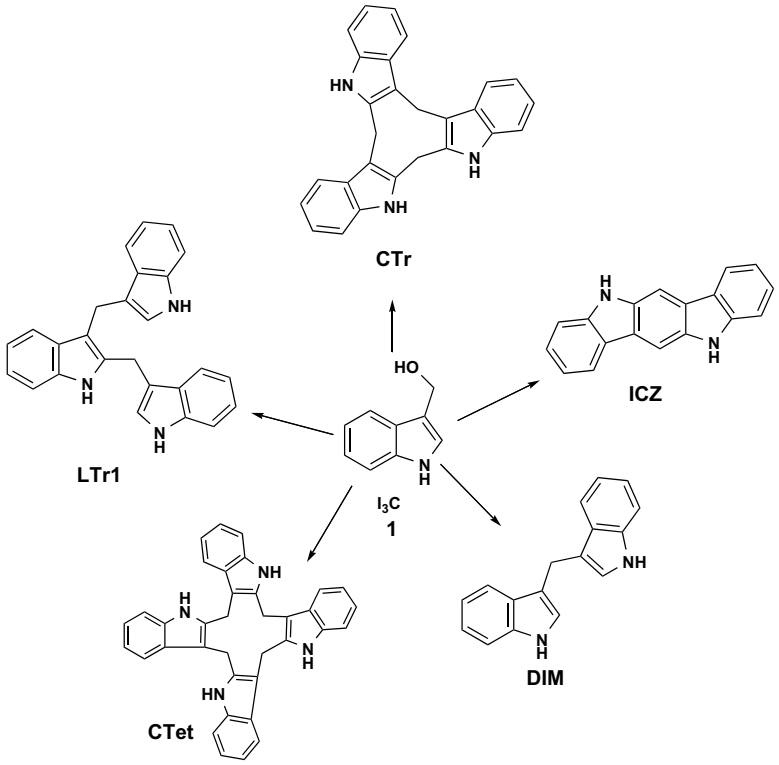

Fig. (3). I3C and its metabolic products.

cells [36]. 1-Benzyl-I3C (**11**), analogs of I3C was found to be thousand times more potent in comparison to I3C in suppression of both estrogen dependent and independent BC cells by inhibiting phosphorylation of retinoblastoma protein (Rb). It acts on CDK and leads to the stimulation of p21 and p27, CDK inhibition resulted in arresting the G1 phase of cell cycle and showed a significant effect in *in vivo* growth of BC in athymic mice.

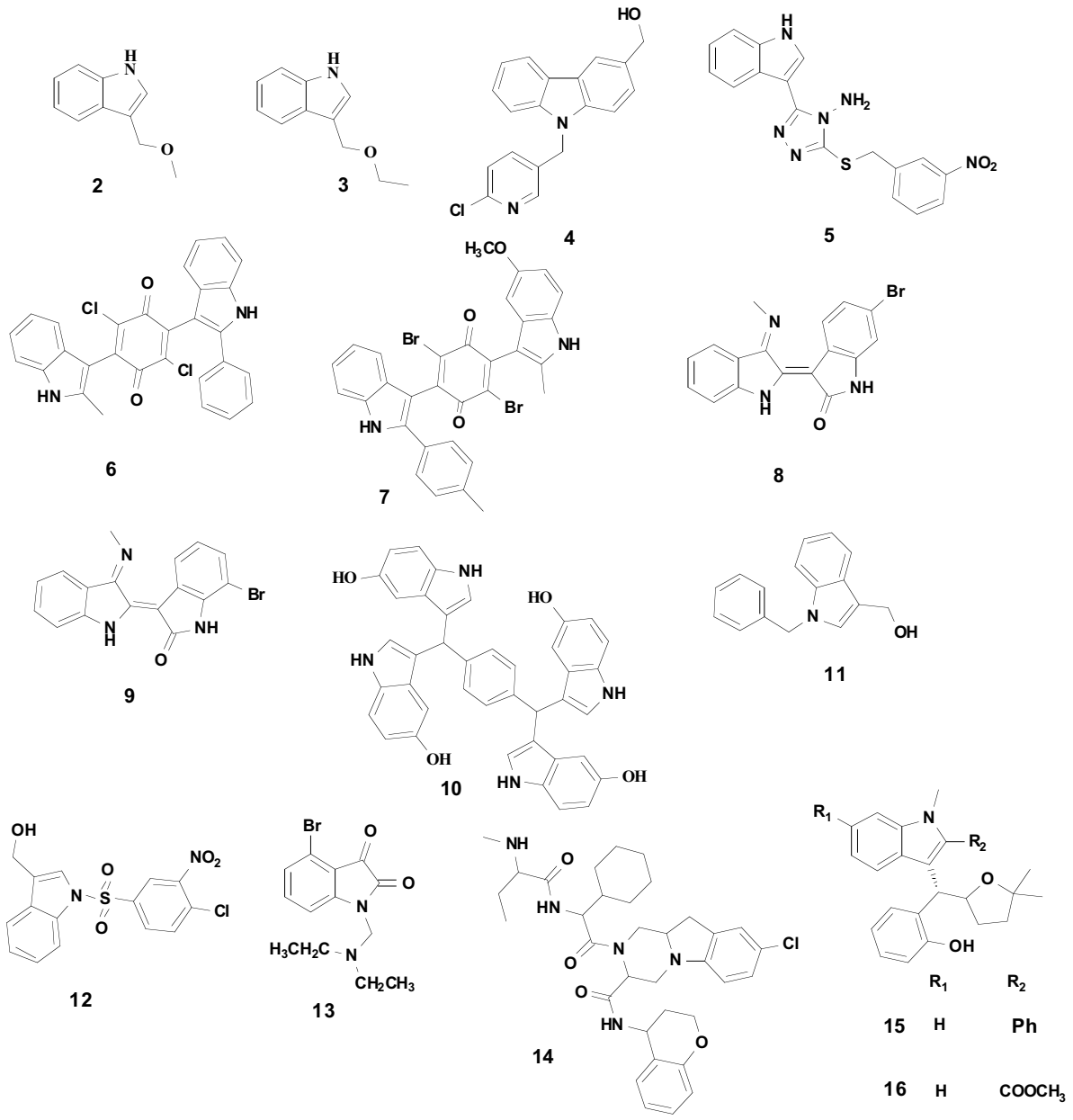

Fig. (4.) Structure of apoptotic factor inducing compounds.

Another derivative, OSU-A9 (**12**) was found to be hundred folds more potent than I3C in the induction of apoptotic cell death in prostate cancer [37]. Solomon *et al*. reported that isatin–benzothiazole analogs (**13**) have 10-15 times more selectivity towards the cancerous than normal cells and inhibit cell cycle in G2/M phase with GI_{50} of 93.72 ± 1.59, 49.02 ± 1.42, 57.64 ± 0.98, 67.78 ± 1.01 μM in case of MDA-MB231, MDA-MB468, MCF7, MCF10A cell lines respectively [38]. Furthermore, X-chromosome linked inhibitor of interacts with caspases 3 as well as 9 and inhibits the process of apoptosis. Compound **14** hexahydropyrrazin[1,2-a]indole derivative which targets X-linked inhibitor of apoptosis protein (XIAP) and cellular IAP protein in MDA-MB-231 cells (IC_{50} 0.023 μM and 0.0011 μM respectively and GI_{50} for MDA-MB-231 cells 0.0028 μM). It also exhibits less substrate like the potential for MDR1 [39]. Palladium catalyzed 3-substituted indole (**15**) and (**16**) arrests cell cycle in G1 and G2 phase respectively similar to taxol in MCF-7 cell lines. The structure of apoptosis factors inducing indole derivatives is shown in Fig. **4** [40, 41].

Tubulin Inhibitors

Tubulin protein consists of α and β heterodimers which is a critical assembly for cells that perform various cellular functions such as mitosis and vascularization. Targeting these proteins with anti-cancer drugs, disturb the normal tubulin protein assembly and arrests growth of cancer cells. Two categories clinically used anti-tubulin drugs, vinca alkaloids and taxane which suffer from the major drawback of resistance that limits their use [41]. Thus, there is a need for the newer class of tubulin based anticancer agents. Multiple indole derivatives (Fig. **5**) can be suitable alternative in this scenario as they have shown promising anticancer ability by blocking tubulin based physiology. 2-phenylindole derivatives developed from the 4-(1-Indol-2-yl) phenol have shown significant anticancer potential against MCF-7 and MDA-MB-231 BC cell lines. N-(2-(4-hydroxyphenyl)-1H-indol-3-yl)-4-nitrobenzohydrazide (**17**) with IC_{50} 0.00160 ± 0.0002 μM, 0.03250 ± 0.00018 μM was found to be active against MDA-MB-231and MCF-7 cells respectively. N-(2-(4-hydroxyphenyl)-1H-indol-3-yl)-4-nitrobenzohydrazide was

found to be the most potent among the series of 2-phenyl indole derivatives. It acts by binding to the colchicine binding site of tubulin through hydrogen bond interaction between 'NH' of indole and Asnα101 of tubulin [42]. Arylthioindole derivative (**18**) acts in a similar manner by binding at colchicine binding site of tubulin and arresting the cell cycle in G2/M phase in the MCF-7 cells with IC_{50} 0.001 μM, tubulin IC_{50} 0.95 μM and have superior activity to that of colchicine and combrestatin. Replacement of sulfur atom of **18** with ketone drastically reduced activity while hydroxyl group instead of ketone, exhibit equipotent activity to ketonic one. Five membered heterocyclic ring at 2 position of indole showed better results compared to six member cyclic ring. Interestingly they were found to be comparatively more active in P-glycoprotein expressing NCI/ADR-RES and Messa/Dx5 cell line than that of vinorelbine, vinblastine and paclitaxel [43]. Similar activity has also been shown by compounds **19**, **20** and **21** (IC_{50} 0.020 ± 0, 0.039 ± 0.001 and 0.036 ± 0.006 μM against MCF-7 cell lines) having five-membered heterocyclic at 2 position of indole. They showed hydrophobic interaction with Lys254 and Leu248. 7-methoxy-2-(1*H*-pyrrol-2-yl)-3-((3,4,5-trimethoxyphenyl)thio-1*H*-indole (**19**) was reported to have low systematic clearance and thus excellent bioavailability [44]. N4-(substituted phenyl)-N4-alkyl/desalkyl-9H-pyrimido[4,5-b]indole-2,4-diamines derivatives were quite effective in tumor cell that exhibiting elevated expression of Pgp, β3 or acquire resistance to the anticancer drug. Gangjee *et al*. found that **22**, **23** and **24** when tested on MCF-7 cancer cells showed promising anticancer activity with IC_{50} of 0.0147 ± 0.0015, 0.0235 ± 0.0012 and 0.014 ± 0.0005 μM respectively. *In silico* study predicted that the interaction of 4'–OCH_3 oxygen with Cysβ241 and N4-CH_3 is essential for the activity of compound **22**. Chloride salt of **22** solved the solubility problem which is prominent in case of paclitaxel-based agents. N-4-desalkyl substituted of these agents with –OCH_3 group on phenyl ring, inactivate them towards cancerous cells due to lack of hydrogen bonding interaction as compared to **22** [45]. 2-(3,4,5-trimethoxybenzoul)-2-aminoindole derivative **25** (IC_{50} 0.015 μM against FM3A cells) was synthesize by the introduction of NH group instead sulfur present in benzo[b]thiophene moiety of some previously synthesized anti-tubulin agents. It binds to the colchicine binding site thereby arresting the cell cycle in G2/M phase and inducing apoptotic cell death at 0.030 μM. Electrons withdrawing group at 6 position of indole of this series are less active in comparison to electron donating groups at the same position. Docking study of **25** suggested that –OCH_3 group interact in similar manner as 'C' ring of colchicine interacts with tubulin protein. N-methyl moiety interacts with βLeu255 and βMet259 through hydrophobic interaction while unsubstituted 'N' of indole ring losses this interaction, making it less active even after trimethoxy phenyl moiety overlaps on colchicine 'A' ring [46]. Azaindole derivatives **26** and **27** reversible depolarize the microtubule assembly and show the cytostatic action in various cancerous cells of MDR. Compounds **26** and **27** have shown IC_{50} of 1.2, 12.7 μM and 0.1, 0.2 μM respectively against MCF-7, MDA-MB-231 cell lines. SAR study demonstrated the importance of methoxy group for their activity while '**z**' does not have much influence on the activity [47]. Compound **28** is a pyranochalcone derivative, containing indole moiety which binds to colchicine binding site of tubulins and inhibit proliferation of MCF-7 BC cell with IC_{50} 1.5 ± 0.02 μM. *In vivo* study of compound **28** in hepatocarcinoma mice has been reported to reduce the tumor growth by 56.8% at 30 mg/kg dose which is significantly better than 5-flurouracil which showed only 25.93% reduction [48]. 2-phenylindole-3-carbaldehydes compounds were synthesized and evaluated by Kaufmann *et al*. They predicted that compound **29** had potent antimitotic activity in MDA-MB-231 (IC_{50} 0.006 μM), and MCF-7 (IC_{50} 0.021 μM) cell lines compared to aldehydic group containing **30**. This is due to the higher binding affinity of imine of **29** with microtubules than the aldehyde one [49]. A series of indole containing novel combretastatins analogs were synthesized and evaluated for their anticancer activity on various cell lines by Kumar *et al*. They demonstrated that (Z)-2-(1-Acetyl-1H-indol-3-yl)-3-(4-(dimethylamino)phenyl)acrylic acid (**31**) induce the apoptosis in MCF-7 cells (IC_{50} 0.37 μM) by binding at colchicine binding site of tubulin, which was predicted by molecular docking technique [50]. Kishnegowda *et al*. describes the inhibition of tubulin polymerization by the 5, 7-dibromoisatin analog compound **32** in BC cell lines in same extent as that of vinblastine sulfate. Other related derivatives **33** and **34** showed overall more effectiveness than vinblastine sulfate. *In-vitro* evaluation has shown that these derivatives were less active in MCF-7 than HT29 human colon cancer cell lines. Additionally these derivatives have shown suppression of AkT phosphorylation [51]. Indomethacin and sulinidac analogs were synthesized and evaluated by Chennamaneni *et al*. They found that the compound **35** was the most potent anti-tubulin agent from their series of synthesized compounds. Compound **35** binds at the colchicine and taxoid binding site of tubulin. Interestingly, it promotes tubulin polymerization at low concentration and enhances the same at higher concentration [52].

NFkB/PI3K/AKT/mTOR Pathway Inhibitors

NFkB/PI3K/AKT/mTOR pathway plays a vital role in BC progression. Receptors like EGFR and ERα activate phosphatidylinositol 3-kinase (PI3K) that catalyzes the conversion of phosphatidylinositol (4,5) diphosphate into phosphatidylinositol (3,4,5) triphosphate. These further activate downstream signal by phosphorylating Akt at Thr308 [53]. Activated AkT then detaches itself from the plasma membrane and suppresses the inhibitory activity of tuberous sclerosis complex-2 (Tuberin) on mTOR (mammalian target of rapamycin). mTOR in turn regulates phosphorylation of AkT at Ser473. mTOR is a negative regulator of Akt, which influences cell survival, cell cycle progression, cell growth and cell metabolism. It also suppresses cell cycle inhibitor p21 and p27, pro-apoptotic Bad, and Bim, which, as a result, degrade tumor suppressor protein p53 and phosphorylate the NFkB. NF-kB is a transcriptional factor consisting of five subunits (p50, p52, RelA, RelB, c-Rel) but p50/RelA is an essential subunit involved in transcription. NFkB remains in the cytosol in association with protein IkB, which retains NFkB in the cytoplasm in deactivated form. Inhibitors of nuclear factor kappa-B kinase (IKK) dependent phosphorylation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IkBα) and subsequent degradation by proteosome, reliefs NFkB. Free NFkB gets translocated in the nucleus and regulates the genes for normal growth of lubolalveolar cell in breast tissues as shown in Fig. **6** [54]. Its hyperactivity is associated with cell proliferation, metastasis, angiogenesis and drug resistance of BC. To target this pathway is an important aspect to inhibit the progression of related cancers [2].

The structure of NFkB inhibitors shown in Fig. **7**. Evodiamine, (**36**) a natural indole alkaloid obtained from Chinese herb *Evodiarutaecarp* induces apoptosis in the BC cell lines by inhibiting activation of NFkB and related genetic transcriptions. It also enhances the anticancer potential of doxorubicin on cancerous cells showing resistance towards doxorubicin related treatment [55, 56]. 5-Benzylated 4-oxo-3, 4-dihydro-5H-pyridazino[4,5-b]indole derivative (**37**) showed significant anti-proliferative activity in BC. Docking study of **37** suggested that pyridazinone ring form hydrogen bonding with Val1882 of PI3K hinge region, 'cyano' group with hydroxyl group at Ser806 and bromine interacts with deeper pocket and carboxylate terminal of Asp841 of PI3K [57]. Zhang *et al*. disclosed that flouro group containing 5-ureidobenzofuranone indole (IC_{50} 0.0002, 0.0003, and <0.003 μM against PI3K, mTOR, MDA-MB-361 respectively) acts as a potent PI3K and mTOR inhibitor in BC. *In vivo* study of 3**8** predicted that at dose of 25 mg/kg iv, shrinks the tumor size in MDA-MB-361 efficacy nude mice [58]. Orally bioavailable **6,** a multi-targeted chemotherapeutic agent used in BC, inhibits NFkB and increase the ERβ/ERα ratio. Up-regulation of AhR is also observed with OSU-A9 (**12**) [59]. 4-hydroxy-3,3-dimethyl-*2H*

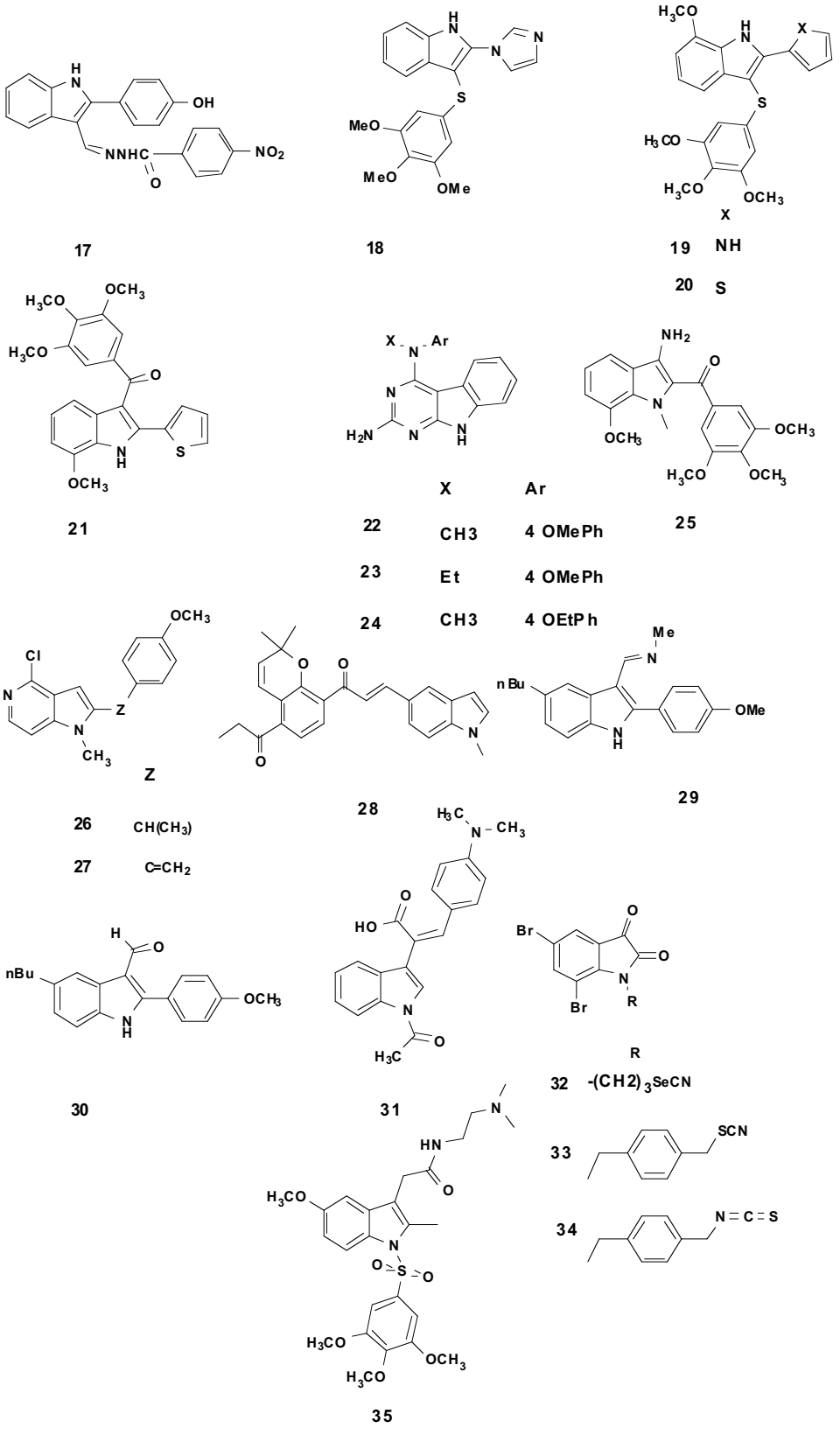

Fig. (5). Structure of tubulin inhibitor compounds.

benzo[*g*]indole-2,5(*3H*)-dione (BVT948) (**39**), a novel compound inhibit BC cell proliferation through inhibition of MMP-9 expression by down-regulating protein tyrosine phosphatases (PTP), along with NFkB inactivation [60].

Tropomycin related tyrosine kinase A (Trk A) is a family member of receptor tyrosine kinases which maintains peripheral nervous system and is also involved in metastasis and proliferation of cancer of various tissues like breast, colon, pancreatic, thyroid,

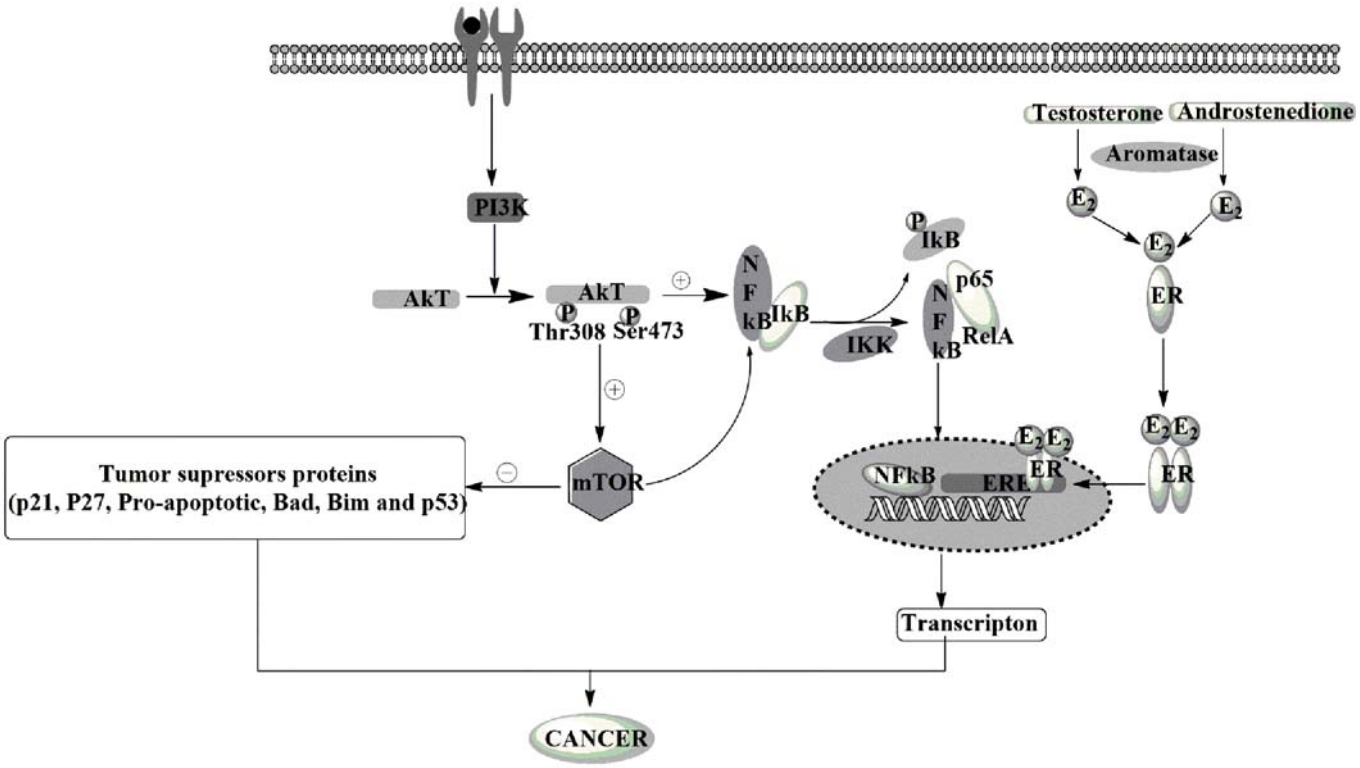

Fig. (6). Cellular signaling pathway in breast cancer.

prostate and lung cancer. Azaindole derivative **40** inhibits the Trk A with IC_{50} value of 0.0016 μM by formation of five hydrogens, one π-π stacking and one hydrophobic interaction at the ATP binding site of the Trk in the MCF-7 cell lines. They reduce the growth rate by 40 to 70% and induces the apoptotic cell death by regulating the pro and anti-apoptotic factor [61]. DIM also blocks the human growth factor (HGF) induced activation of AkT in MDA-MB-231 cell lines but not in non-tumorigenic MCF-10AT cells up to 46% by decreasing the phosphorylation of HGF receptor and c-Met at Tyr1234 and 1235 [62].

3-substituted derivative of 2-indoline was synthesized by Mokhtari *et al*. and investigated for their cytotoxicity against MCF-7 cell line. They predicted that Compound **41** possessed enough high activity and inhibited c-Src tyrosine kinase and showed cytotoxicity against MCF-7 cell line with IC_{50} 6 μM [63]. 2, 2-diphenyl-3, 3'diindolylmethane (**42**) induces the apoptosis in MDA-MB-231 cells through the inhibition of EGFR that regulate the downstream activity of STAT, AKT and ERK1/2 and many other signaling molecules. Further, it has been demonstrated that **42** specifically binds at the ATP binding site of the EGFR and also increases the Bcl-XL proteins to induce apoptotic cell death [64]. One of FDA approved indole derivative sunitinib (**43**) used for the treatment of advanced renal cell carcinoma act through the regulation of kinases [65].

Estrogen Signaling Regulation

Estrogen Receptor Regulation

Estrogen is an essential hormone that plays a vital role in various physiological functions. In case of women, estrogen regulates multiple physiological functioning such as proper development of breast tissues, menstruation regulation and preserve of pregnancy. Furthermore, unbalanced level of estrogen acts as a carcinogen [66]. In premenopausal women, ovaries are the primary source of estrogen but in post-menopausal women adipocyte tissues produce estrogen with the help of aromatase and sulfatase enzymes. Inhibiting the action of endogenous estrogen or blocking its biosynthesis by targeting the aromatase or sulfatases are the recent approaches to treating hormonal dependent breast cancers (HDBC) [67, 68]. ERs are mainly present in the cytosol, binding of estradiol to ER trigger the activation results in dimerization. Then it gets translocate into the nucleus to form complex with an estrogen-responsive element on estrogen-responsive genes to control the cellular function (Fig. **6**) [66]. Along with Estrogen, BC susceptible gene 1(BRCA1) is also responsible for ER-mediated activity by means of decreasing the expression of ER. Meng *et al*. reported that I3C showed the chemo-preventive activity by repressing the estrogen-dependent ERα activity, up-regulating BRCA1 in dose-dependent manner. Thereby preventing cell proliferation, cell migration, and cell invasion [69]. Telomerase is ribonucleoproteins containing a reverse transcriptase enzyme. It consists of two subunits, hTR RNA subunit, and hTERT catalytic subunit that are present in inactive form in a somatic cell for regulating cell proliferation. The activity of the hTERT unit is controlled by the hTERT promoter. hTERT promoter gene contains estrogen receptor binding site, estrogen response element (ERE) and Sp1 that forms a dimer and binds with the ERE-Sp1 composite element essential for its activity. I3C down-regulate the ERα by degrading the ERα through stimulation of ubiquitin and decrease the interaction of ERα and Sp1 towards composite element [70]. It also blocks the estrogen-mediated activation of insulin-like growth factor-1 in BC [26]. 1-benzyl-I3C (**11**) inhibits the expression of ER. In combination with tamoxifen, it inhibits ER_{α} to a greater extent [37]. SERM class of compound has acquired important consideration over the hormonal replacement therapy in BC, in spite they suffer from some drawbacks of their selectivity. 2-arylindle derivative (**44**) (Fig. **8**) showed 130 fold selectivity towards the ERα (human ERα/β IC_{50} 0.002/0.259 μM). It antagonize the action of estradiol in MCF-7 (IC_{50} 0.030 μM) cancer cells and uterus tissues [71]. ER923 (**45**) is an indole derivative anti-estrogenic compound, equally

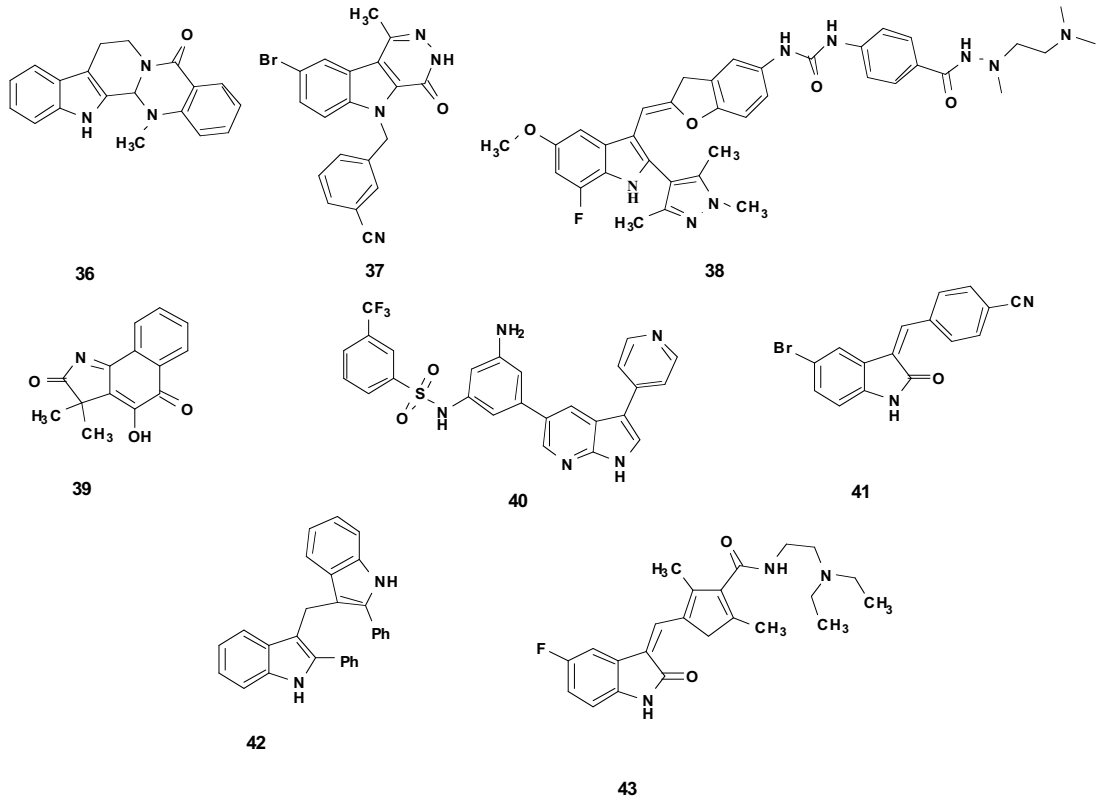

Fig. (7). Structure of NFkB inhibitor compounds.

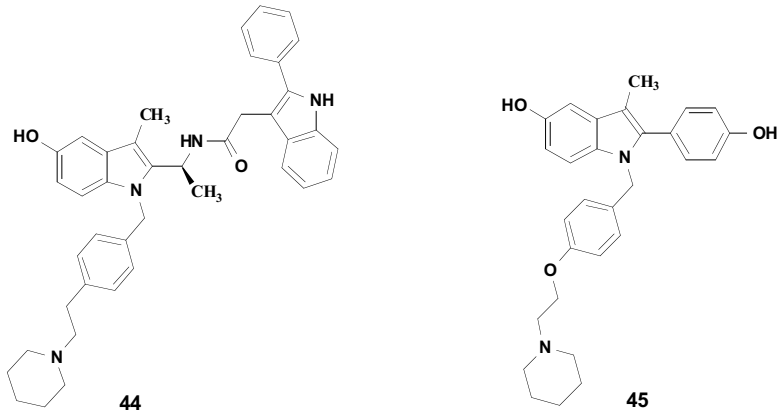

Fig. (8). Structure of estrogen receptor regulator compounds.

effective as tamoxifen and overcome the resistance associated with tamoxifen, tested *in vitro* and *in vivo* [72].

Aromatase Inhibitors

Cytochrome P450 and NADPH reductase constitute the aromatase enzyme, containing haeme group at substrate binding site. Aromatase is located in ovarian cells of premenopausal women and in postmenopausal, aromatase is present in skin, adipose tissues, brain, blood vessels and breast tissues [73, 74]. It catalyzes the hydroxylation of C19 androstenedione and testosterone in three step biosynthetic processes into C18 estrone and estradiol respectively, which is involved in tumorigenesis of breast shown in Fig **6**. Several studies suggested that there is a higher expression of aromatase in BC cells [75]. It has been reported that I3C and DIM reduce the expression of a CYP19 transcript and proteins in estrogen-positive MCF-7 cells, but up-regulation also observed in estrogen negative MDA-MB-231 cells [76].

Wang *et al.* synthesized and studied the SAR of large number of 1-aryl-2-(1H-imidazol-1-yl)methyl)-6-substituted-1*H*-indole derivatives to target aromatase and compared their aromatase inhibitory activity against letrozole. Compound **46** (IC_{50} 0.0049 μM) was found three times more potent than letrozole (IC_{50} 0.016 μM). Triflouromethyl group at C-4 position of **46** increase its interaction towards aromatase as well as metabolic stability. Aromatase inhibitor compounds shown in Fig. **9** [77] Marchand *et al*. reported that indole derivative 1-ethyl-5-[(imidazol-1-yl)(4-chlorophenyl)-methyl]-1*H*-indole (**47**) (Fig. **9**) possesses maximum activity with relative potency 336 in comparison to non-steroidal anti-aromatase aminoglutethimide with relative potency 1 [78]. Benzonitrile derivative of indole at 4 and 6 position synthesized by Leimgruber-Batcho reaction were tested

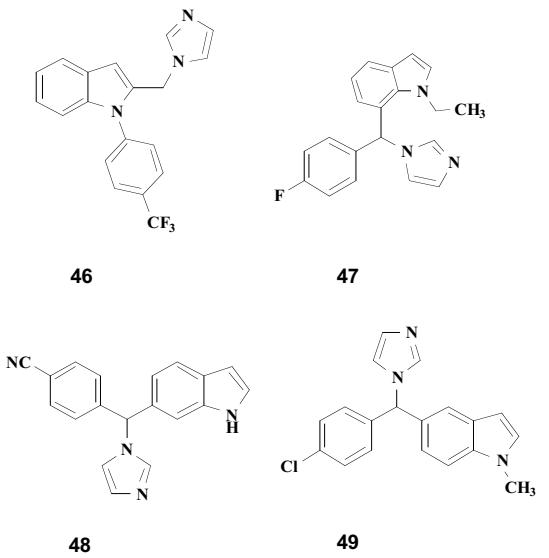

Fig. (9). Structure of aromatase inhibitor compounds.

against aromatase activity that have shown good results as compared to aminoglutethimide. Among benzonitrile derivatives, racemic mixture of **48** (IC_{50} 0.0115 μM) inhibit >10 % of CYP17 superior to aminoglutethimide (IC_{50} 29.75 μM) and comparable to fadrazole (IC_{50} 0.03 μM) [79]. 5-[(aryl)(imidazol-1-yl)methyl]-1*H*-indole derivative (**50**) assessed for CYP19 inhibitory activity and compared their anticancer potency with reference drug aminoglutethimide emerged as a superior chemical entity. Whereas (+) enantiomer of **49** (IC_{50} 0.009 μM) was more potent to its (-) enantiomer and racemic form (IC_{50} 0.0153 μM) [80].

Arylhydrocarbon Receptor (AhR)

Arylhydrocarbon receptors are present in cytoplasm that regulates estrogen metabolism by binding with polycyclic aromatic hydrocarbon ligand. Upon binding with ligand, the receptor translocates into the nucleus where it dimerizes with arylhydrocarbon receptor nuclear translocator protein. It regulates the estrogen metabolizing genes CYP1A1, CYP1A2, and CYP1B1. CYP1A1 and CYP1A2 produce non-carcinogenic 2-hydroxyestradiol by metabolizing the estradiol, whereas CYP1B1 metabolizes the estradiol to carcinogen 4-hydroxyestradiol. Effect of DIM has been investigated on these Receptors. In basal condition ratio of CYP1B1 : CYP1A1 mRNA was high, but it decreased significantly when cell were treated with DIM while the level of CYP1A2 remains unaltered [81] [82]. AhR catalyzes the oxidative conversion of estrone to 2-hydroxy estrone that competes with estradiol to bind at the estrogen receptor, results in abrogation of the estrogen-related effect on its receptor. It also degrades the estrogen receptor, so inhibition the estrogen positive breast cancer with AhR agonist has been designed. Synthetic derivative 5-5-diMe-DIM (**50**) (Fig. **10**) has been shown high selectivity towards AhR [23].

McDougal *et al*. synthesized dihalo derivative (**51**) of DIM exhibiting weak AhR agonistic and anti-estrogenic activity tested on T47D and MCF-7 breast cancer cells. They showed that 5,5-dichloro, 5,5-dichlor-2,2-dimethyl and 4,4-dichloro-DIM to inhibit the T47D cancer cells line but MCF-7 cancer cells were less sensitive to 0.1 μM concentration. *In vivo* study suggested that DIM inhibits 7,12-dimethylbenz[a]anthracene (DMBA) induced breast tumor at dose of 5 mg/Kg but dihalo derivative 5,5-dibromo-, 6,6-dichloro- and 4,4-dichloroDIM significantly inhibits the tumor growth at a dose of 1.0 mg/kg, whereas the 5,5-dichloro-2,2-dimethyl-, 5,5-dichloro and 5,5-difluoroDIM were inactive at the same dose concentration [83].

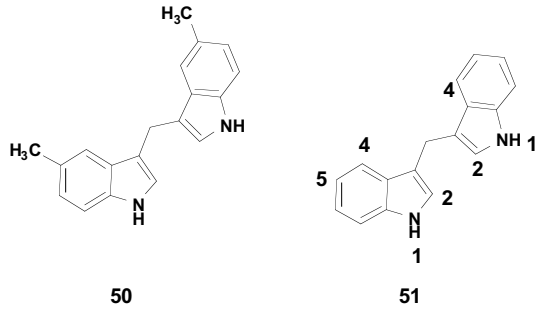

Fig. (10). Structure of AhR regulator compounds.

Miscellaneous

A series of bisindolylalkane derivatives 3, 3'-(thiochroman-4,4-diyl)bis1-*H*-indole were synthesized by Song *et al*. possessing anticancer activity against various cell lines by inhibiting topoisomerase II. Out of these series, 3,3'-(8-chlorothiochroman-4,4-diyl)bis(1H-indole) (**52**) (Fig. **11**) was most active against MCF-7 cells with IC_{50} 18.83 μM and showed comparable activity to VP-16 at 100 μM concentration [84].

Compounds **53, 54** and **55** are weak inhibitors of the topoisomerase I / II in the BC cell lines but how they show cytotoxic effect is not yet clear. IC_{50} value of **53**, **54** and **55** for MCF-7 were 7.1 ± 1.2, 4.7 ± 1.0, 5.1 ± 0.4 μM respectively [85]. Gallic acid is a natural polyphenolic compound possessing various biological properties including anticancer activity. Khaledi *et al*. disclosed the cytotoxic and antioxidant activity of indole derivative of gallic acid in BC cells. From series of synthesized molecules, compounds **56** and **57** were more potent cytotoxic candidates with IC_{50} 19.2 and 13.3 μM against MCF-7 BC cell line [86]. Some hybrids of indole and barbituric acid synthesized on the basis of docking study at active sites of COX-2, thymidyl synthase and ribonucleotide reductase for evaluating their anticancer activity by Singh *et al*. They demonstrated that compounds **58** (GI_{50} 0.1 μM, TGI 0.38 μM and LC_{50} >100 μM) and **59** (GI_{50} 0.02 μM, TGI 0.06 μM and LC_{50} 0.69 μM) showed better activity than the indomethacin and 5-flourouracil in case of MDA-MB-231 cell lines [87]. N-[1-(tert-Butoxycarbonyl)indol-3-yl]methyl-N-phenylthiourea (**60**) was synthesized by Budovska *et al*. and showed anticancer activity (IC_{50} 0.72 ± 1.3 $\mu molL^{-1}$) quite comparative to that of doxorubicin (IC_{50} 0.5 ± 0.024 $\mu molL^{-1}$) as tested on MCF-7 BC cell line [88]. Kumar *et al*. synthesized and evaluated the bis(indolyl) hydrazide–hydrazones derivative compounds for their anticancer activity. They reported that **61** has potent activity against MDA-MB-231 cell line (IC_{50} 1.0 μM) while **62** is active against MCF-7 cell lines (IC_{50} 3.1 μM), but their target by virtue of which they show anticancer activity is not clear [89]. Peroxisome proliferator-activated receptor γ (PPARγ) is a nuclear hormone receptor which is highly up-regulated in tumor state. 1,1-Bis(3'-indolyl)-1-(p-trifluoromethylphenyl)methane (**63**) is a modulator of PPARγ resulting in inhibition of growth of BC by halting the cell in G_0/G-S phase. It was ultimately causing cell death by down-regulating cyclin D1 [90].

1,1-Bis (3'-indolyl)-1-(p-biphenyl) methane (**64**) is another PPARγ based agent that increases the level of p27 and caveolin-1. It has been found to arrest the growth of basal-like BC cells in animal model at 64 mg/kg dose and reduced the tumor growth by 67% and 87% at the 11th and 35th day of treatment respectively [91]. Aplysinopsins analogs **65** and **66** synthesized by Reddy *et al*. have shown significant activity against MCF-7 BC cell lines with IC_{50} value of 4.4 μM and 5.2 μM respectively which is comparatively better than 5-flourouracil (IC_{50} 15.2 μM) [92]. 3-[(4-substitutedpiperazin-1-yl)methyl]-1*H*-indole derivative (**67**) synthesized and evaluated

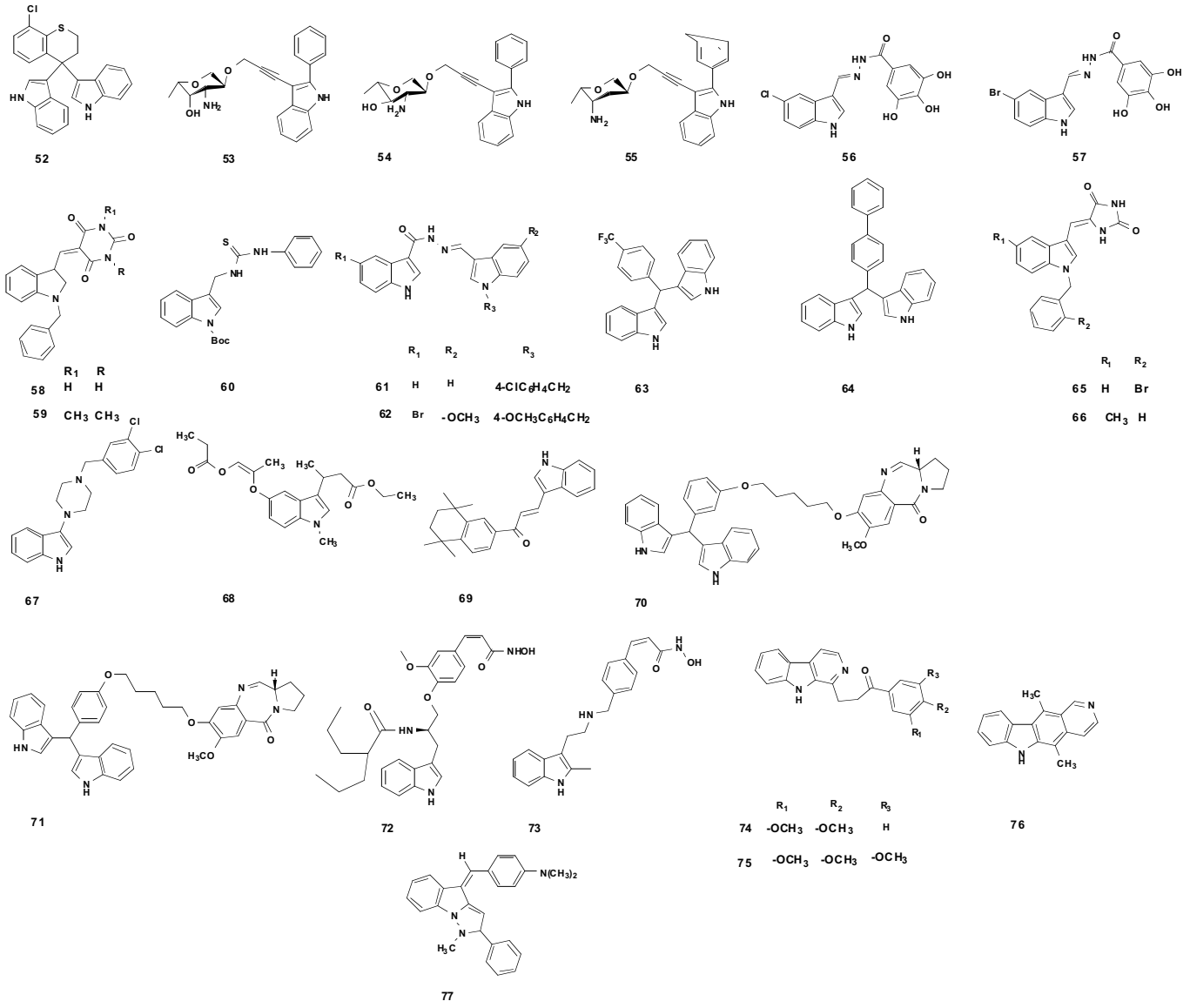

Fig. (11). Structure of miscellaneous anticancer compounds.

for cytotoxic activity against various cancer lines. In case of MCF-7 BC cell lines, **67** showed the IC_{50} value of 2.92 μM that significantly is better than that of 5-flourouracil showing the IC_{50} value of 3.50 μM [93].

GPR30/GPER is G-protein coupled receptor which is responsible for multiple biological responses such as cell proliferation, migration and formation of fibroblast in cancer cells in response to estrogen, and by cross-talk of multiple kinase related activities associated with it. Lappano *et al*. discussed that MIBE (Methyl-3-[5-(2-ethoxycarbonyl-1-methylvinyloxy)-1-methyl-1H-indol-3-yl]but-2-enoate) (**68**) inhibits the GPER and ERα mediated proliferation of BC cells [94]. Compound **69,** an indole retinoid derivative, inhibit Retinoid X receptor alpha (RXRα) and RXRγ as predicted by docking study and had shown anticancer activity in triple negative MBA-MD-231 BC cell line, IC_{50} value was found to be 1.8 μM and found minimum toxic effect on normal epithelial MCF-12A cells [95]. Bisindol-pyrrolobenzodiazepine also conjugates exhibit a significant anticancer activity in BC cell lines by inducing apoptosis cell death through inhibition of histone deacetylase protein by increasing the level of their inhibitor protein p21. Pyrrolo[2,1-c][1,4]benzodiazepines are DNA minor groove binding anticancer agents that are currently in a clinical trial. They served basis for the synthesis of hybrid bisindole-pyrrolobenzodiazepine (**70**) (GI_{50} 0.19 μM) and **71** (GI_{50} 0.14 μM) and evaluated for their anticancer activity on estrogen-positive MCF-7 cell lines. The results indicated that compound **70** and **71** have shown anticancer potential by down-regulating histone deacetylase 1, 2, 3, 9 and the level of p21 increases. It also inhibit tubulin polymerization and inducing cell cycle arrest by damaging DNA [96]. Compound **72** had moderate intracellular and nuclear HDAC inhibitory activity in case of MDA-MB-231 cell lines (IC_{50} 3.1 μM). Inhibition of class 1 HDAC was comparatively inferior to that of SAHA but decrease the level of histone acetylation at 1 μM was found better than SAHA after the treatment of 24 h [97]. Panabinostat (**73**) is a multitargeted drug specifically, HDAC inhibitor developed by the Novartis tested for treatment of BC is in phase II clinical trial [28, 98]. Another important compounds **74** and **75** had shown cytotoxic activity against MCF-7 cell lines with IC_{50} 2.25 and 3.29 μM, respectively. **75** damage the DNA most probably by inducing fragmentation in DNA as observed by Chauhan *et al.* [99]. Another compound Ellipticine (**76**) isolated from the plants *Ochrosiaborbonica* and *Excavatiacoccine*, form an adduct with DNA on metabolism by CYP450 and seems useful in the BC [100]. Pyrazolo[1,5 a] indole

derivate GS-2 (**77**) displays anticancer activity in various types of cancer. It increase the level of reactive oxygen species in the MDA-MB-231cancer cell line and subsequently causes the destruction of DNA and activation of the caspases to induce cell death [101]. All the miscellaneous compounds are represented in Fig. **11**.

CONCLUSION

Indole is a typical nucleus that is found in natural products as well as part of scaffolds synthesized in laboratories possessing the broad spectrum of biological activity. In BC, indole derivatives seem to be quite competent and acting through an assorted mechanism that are well established in the case of BC, thus, making them valuable BC particular framework. In recent years, researchers have synthesized numerous indole derivatives as potent and efficacious molecules for exploring anti-cancer activity. Exhaustive literature survey indicated that indoles are associated with properties of inducing apoptotic factor, disturbing tubulin assembly. It is also associated with inhibition of NFkB/mTOR/kinase and regulating estrogen-mediated activity thus, active in the combat against breast related malignancies. Furthermore, critical targets such as topoisomerase, HDAC, COX, PPAR, GPCR, histone acetylase are well investigated in BC. These indole derivatives have been found to modulate them and seem to be expedient to treat BC. It is a much-noted point that these derivatives have shown significant activity against cancer cells that were otherwise resistant to standard drugs. This further adds to the possibility of indoles being a template for the development of next generation BC, specific chemotherapeutic agents. Currently, quite a few of them are under clinical trial for the treatment of a several type of cancer. But this is just a start and this review has cleared that indole derivatives can further be explored for the betterment of BC chemotherapy. A lot of potential is still hidden which demands to be discovered for the much-required upgrading of BC chemotherapy.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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