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Review Article

A REVIEW OF BENZOPYRAN DERIVATIVES IN PHARMACOTHERAPY OF BREAST CANCER

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ABSTRACT

One of the naturally occurring compounds containing oxygen moiety is benzopyran. Depending on its substitution pattern, different biological effects are shown. The benzopyran ring system is present in many natural products (such as genistein, hesperidin, and warfarin) as well as synthetic products. It displays pharmacological properties such as antitumor, anti-HIV, antimicrobials, anti-inflammatory, and anticoagulants. The sufficient literature support and the fact that benzopyran has potential as a pharmacophore particularly as anti-breast cancer, etc, current research seemed pertinent keeping in view the mechanism of anti-breast cancer activity. Therefore, the objective of this review is to focus on important benzopyran analogs with anti-breast cancer activity and highlight their mechanisms of action.

Keywords: Anticancer, Benzopyran, Breast cancer, Estrogen, Estrogen receptor.

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INTRODUCTION

Benzopyran, a bicyclic heterocyclic system, constitutes a privileged structure in medicinal chemistry. Benzopyran unit is present in many natural products as found in α-tocotrienol, γ –tocotrienol, δ-tocotrienol, and tocopherol (Vitamin E) carrying phytyl chain on the pyran ring [1]. They are present in pigments in leaves and in various food sources such as in olive oil, red wine, fruits, and tree [2]. Some naturally occurring benzopyran derivatives include warfarin (1), genistein (2), nebivolol (3), hesperidin (4), and umbelliferone (5). Thus, benzopyran constitutes the basic backbone of various compounds such as coumarins (6), chroman (7), xanthenes (8), polyphenols like flavonoid (9), and anthocyanin (10). The two isomers of benzopyran are present which differ by the orientation of the fusion of the two ring systems contrasted to the oxygen which results in 2H-1-benzopyran (chromene, 11) and 2-benzopyran (isochromene, 12; Fig. 1).

Literature reveals that benzopyrans are important chemical synthon, associated with a broad range of biological effects including antioxidant [3,4], anti-HIV [5,6], neuroprotective [7,8], antiepileptic [9,10], antimicrobial [11,12], antidiabetic [13,14], antihypertensive [15,16], and anticancer agents [17,18]. Among the diverse biological activities of benzopyrans, breast cancer is one of the most intriguing since the discovery of ormeloxifene [19], KBU2046 (Phase II) [20], and B43-genistein [21]. Therefore, many benzopyrans have contributed to the search for new anti-breast cancer agents.

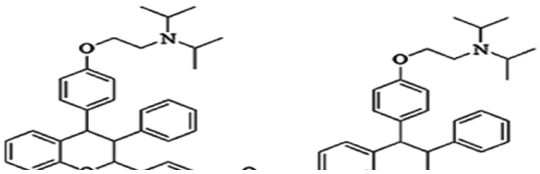
BENZOPYRAN AND BREAST CANCER

Breast cancer is considered as the most commonly diagnosed cancers and is the second leading cause of cancer death among women in India. The mechanism of breast cancer progression is related with cell proliferation and apoptotic cell death (Fig. 2) [22]. Although chemotherapy is widely recognized as the mainstay of cancer therapy, undesirable side effects limited the use of anticancer drugs in chemotherapeutics [23].

Selective estrogen receptor modulators (SERMs)

Estrogens considered playing a valuable role in the development and progression of breast cancer having hormone dependency. Therefore, estrogens and ERs are recognized as significant molecular targets for breast cancer. Estrogens have diverse positive effects on various body parts, especially on brain, heart, liver, bone, and vagina. The prolonged estrogen exposure may have some serious negative effects such as increased risk of breast and uterine cancers [24,25]. Therefore, ER blockers are the mainstay approach for breast cancer treatment.

SERMs include drugs which function as estrogen agonist in some target tissues whereas function as estrogen antagonists in others tissues. Genistein works as a SERM and also being tested as a preventive for breast cancer [26]. Kumar *et al.* synthesized a series of 2, 3, 4-triarylbenzopyrans and evaluated for its SERM activity. Compounds 13 and 14 displayed estrogen antagonistic activity having 73.91% and 69.24% inhibition, respectively. Compound 14 exhibited lowest inhibitory concentration (IC_{50}) at 6.97 μM against MCF-7 cell line, while compound 15 exhibited lowest IC_{50} value of 5.6 μM against MDA-MB-231 cell line despite they have low receptor binding affinity which may suggest that these compounds may possibly act by ER-independent mechanism. Compounds having free hydroxyl group at 2-position in phenyl ring resulted in increased estrogen antagonistic activity [27].



Aromatase inhibitors (AIs)

The synthesis of estrogen involves aromatase (a cytochrome P450 enzyme complex) inhibition. This is encoded by the aromatase gene *CYP*19. Therefore, to decrease the level of estrogen, production affects AI. The aromatase enzyme is useful catalyst in the biosynthesis of estrogens from androgens. Inhibition of the aromatase enzyme is responsive to have significant action on the progress and expansion of hormone-dependent breast cancers [24,28].

Bonfield *et al.* developed some new benzopyran derivatives (16 and 17) as potential AIs. Compounds 6-methoxy-3-phenylchroman-4-one (16) and 3-(pyridin-3-yl) chroman-4-one (17) showed potent activity with IC_{50} values of 2.4 μM and 5.8 μM, respectively, in contrast to aromatase enzyme. However, compounds with functional groups such

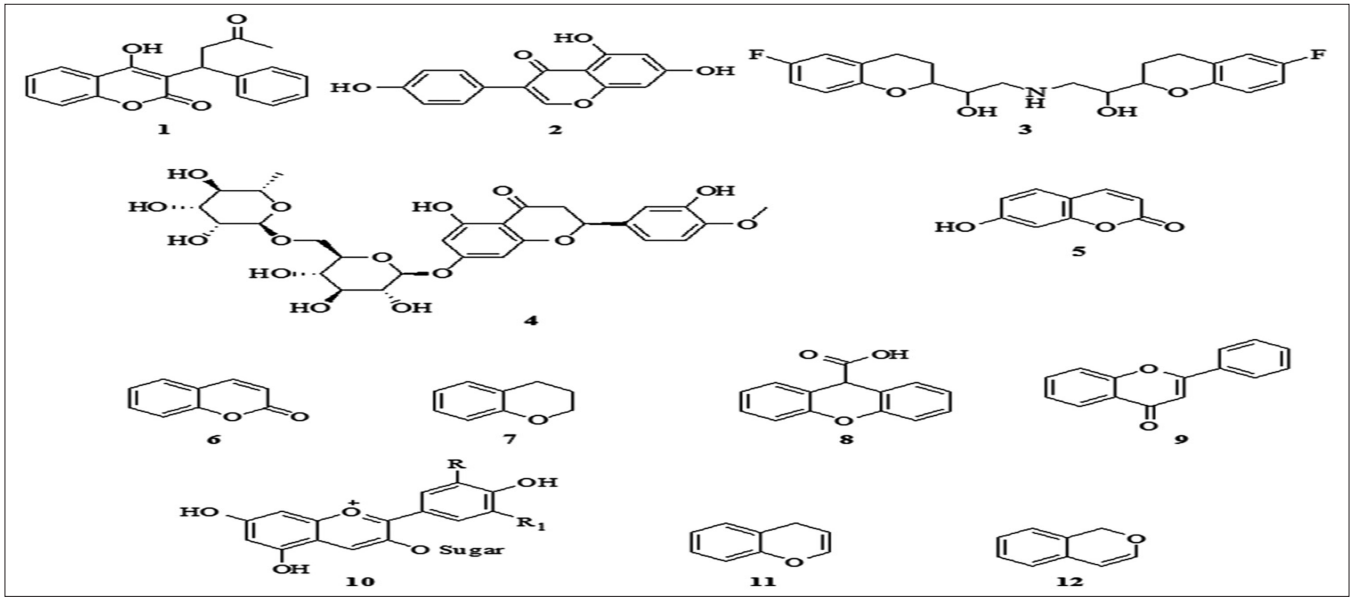


Fig. 1: Benzopyran-based heterocycles

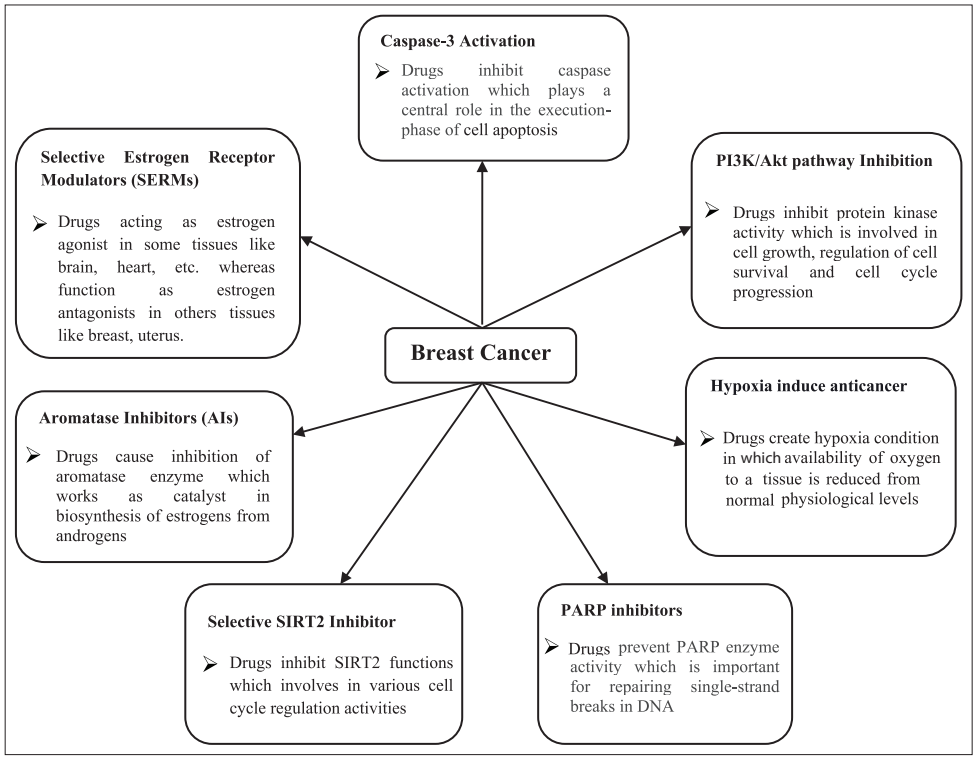
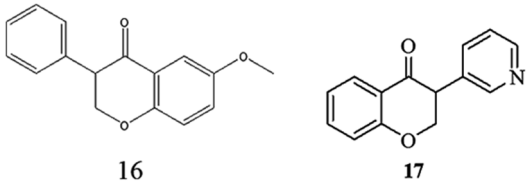


Fig. 2: The mechanism of action of anti-breast cancer drugs

as methoxy and pyridyl possessed potent activity against aromatase. It was proposed that non-planarity structural feature of the compound might involved in binding of enzyme and ligand. The binding mode analysis revealed that methoxy groups formed hydrogen bonds with aromatase molecule which might resulted in enhanced binding affinity [29].

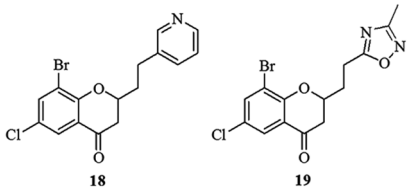


Selective SIRT2 inhibitor

SIRT2 belongs to the human sirtuin family and is responsible for NAD+ (nicotinamide adenine dinucleotide)-dependent deacetylase activity. It is implicated as a potential drug target to combat cancer, neurodegeneration, and inflammation [30].

Seifert *et al.* reported the synthesis of a series of benzopyran-4-ones having 2-position substitution by heterocyclic ring with increased hydrophilicity as SIRT2 inhibitors. Most active analogs (18 and 19) contained hydrogen bond accepting groups (pyridyl and 1,2,4-oxadiazole) and were recognized as selective SIRT2 inhibitors having low micromolar IC_{50} values. These compounds also exhibited antiproliferative activity in breast cancer and lung carcinoma in MCF-7

and A549 cell lines, respectively. They worked by increasing acetylation level of α-tubulin [31].



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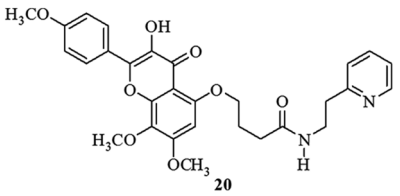
Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors

PARP inhibitors are also called as poly ADP ribose polymerase inhibitor. It represents a group of pharmacological inhibitors. They are important for repairing single-strand breaks in DNA. They endeavor by preventing PARP enzyme activity, thereby preventing DNA damage repairmen, followed by stimulation of mitochondria which release apoptosis-inducing factor and resulting in cell death. Therefore, PARP enzyme inhibition is becoming an attractive target for cancer therapy [32,33].

Singh *et al.* synthesized different 7,8-dimethoxy-3-hydroxy-2-(4-methoxyphenyl)benzopyran-4-one derivatives and tested for their anticancer activity against MCF-7 cell line using SRB assay. Compounds displayed anticancer activity within the range of IC_{50} 2.58–34.86 μM. The most promising compound 20 activated apoptosis in MCF-7 cells and interfered with kinetics of tubulin polymerization. The molecular docking study was also performed for compound 20 which showed that it binds with ER-α [34].



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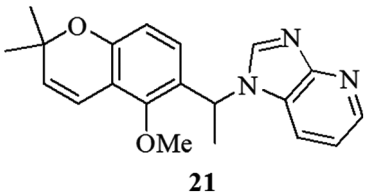
Hypoxia induce anticancer

Hypoxia is a condition in which the availability of oxygen to a tissue is reduced from normal physiological levels. The stimulation of the hypoxia-inducible factor (HIF-1) pathway is associated with several types of cancer. Therefore, inhibition of the HIF-1 pathway is recognized as a viable approach to the development of anticancer agents [35].

Tan *et al.* performed a literature on natural products containing 2, 2-dimethylbenzopyran structure and prepared a combinatorial library of products. These natural products were evaluated for their inhibitory effects on hypoxic activation of an alkaline phosphatase reporter in human glioma cells. Compound 103D5R (21) was found to decrease HIF-1α protein levels induced by hypoxia or cobaltous ions. Therefore, 103D5R works as an inhibitor of HIF-1α. The activity was also attributed on the duration of treatment. The mechanism involved the downregulation of HIF-1α mRNA translation by 103D5R [36].



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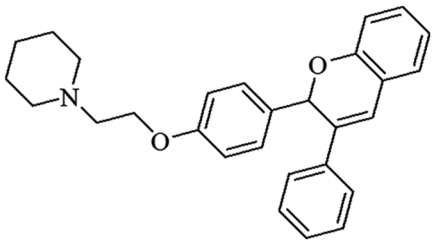
Phosphatidylinositol-3 kinase (PI3K)/protein kinase (AKT) pathway inhibition

PI3Ks belongs to a family lipid kinase. The inositol ring 3'-OH group in inositol phospholipids undergoes phosphorylation by PI3Ks. Then, AKT comes in contact with the particular phospholipids, leading to its translocation to the inner membrane, and it is then subjected to phosphorylation and activation by PDK1 and PDK2. This activated AKT regulates the activity of various substrates involved in the cell growth, regulation of cell survival, and cell cycle progression. Many newer anticancer agents act by mechanisms involving PI3K/AKT pathway [37,38].

Saxena *et al.* synthesized a series of benzopyran compounds and tested for its antiestrogen activity. The compound CDRI-85/287 (22) decreased the function of ERα-dependent proliferation markers and ERβ-dependent cell cycle progression markers. The EGFR activation was prevented by the compound 22, causing inhibition of PI-3-K/AKT pathway, leading to the induction of apoptosis. The mechanism of action included the antagonist effect of compound 22 with exogenous E2. The compound also showed low binding affinity due to the inexistence of hydroxyl group [39].



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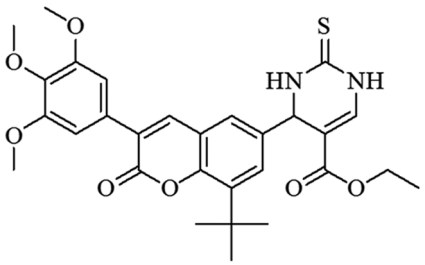
Caspase-3 activation

Caspase-3 is a caspase protein that interacts with caspase-8 and caspase-9. It is encoded by the *CASP3* gene. The *CASP3* protein is a member of cysteine-aspartic acid protease (caspase) family. Sequential activation of caspases plays a central role in the execution phase of cell apoptosis [40].

Sashidhara *et al.* synthesized coumarin-monastrol hybrid (23) and reported it as an anti-breast cancer agent. It was found that hybrid (23) was effective in breast cancer cells (MCF-7 and MDA-MB-231). It worked by inducing caspase-3 activation and followed by apoptosis in both cell lines [41].



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CONCLUSION

As evident from numerous cited papers, the benzopyran scaffold is the building block of various chromans, coumarins, xanthones, and flavonoids present in various natural plants and pharmaceutical products. The overall conclusion is that benzopyran being one of the privileged heterocycles has shown a wide array of biological activities, particularly against cancer.

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AUTHORS' CONTRIBUTION

Concept, collection of data, and writing of the article - Piyush Kumar. Critical review of article - Kuldeep Singh, Md. Azizur Rahman, and Pranay Wal. Final approval of the article - Syed Misbahul Hasan.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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