NEW INSIGHTS INTO THE ORIGIN AND THERAPEUTIC IMPLICATIONS OF BENZOPYRAN AND THEIR DERIVATIVES: A REVIEW

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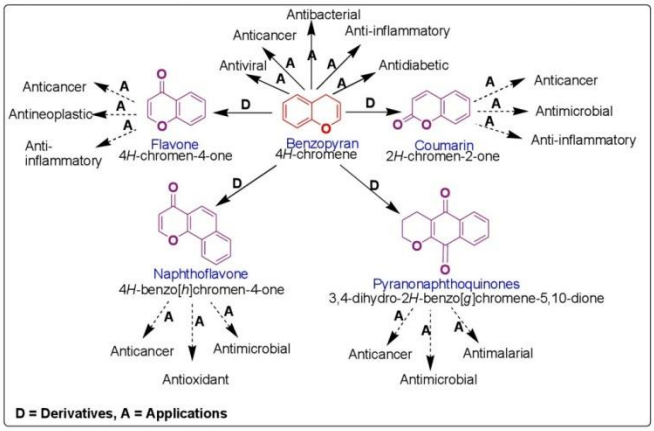
ABSTRACT

Benzopyran derivatives are essential for life and are found abundantly in nature. The benzopyran compounds and their derivatives play an essential role in medicinal chemistry. The various benzopyran derivatives have been used for therapeutic effects. The benzopyran derivatives can be proficient in various pharmaceutical applications for cellular markers. The basic structure of benzopyran is an efficient class of synthetic products and an emerging attention area of research. Therefore, impactful information on benzopyran and its derivatives has been compiled in the last several years. Recently, the development of novel benzopyran and its applications are attracting interested readers, chemists, and forthcoming researchers.

Keywords: Benzopyran, Scaffolds drugs, Therapeutic, Pharmaceutical, Derivatives.

Graphical Abstract:



1. Introduction

Benzopyran derivatives possess a significant role in wide research fields such as medicinal chemistry, biological chemistry, materials chemistry, and agriculture chemistry. In several natural products such as tocopherols, α- tocotrienol, and γ-tocotrienol containing the phytyl chain on the pyran ring, the benzopyran core unit is present [1]. Benzopyran derivatives promote their medical properties, which seem to be determined by their structural characteristics associated with physiochemical applications [2]. The derivatives of benzopyran have fortunate medicinal moieties which appear as a structural unit in various natural and artificial components. Benzopyran derivative shows facilitating penetration nature due to its lipophilicity [3]. Literature shows that the diversity of substituted benzopyran is a major chemical synthon that served as a bioactive agent [4], [5], [6], [7]. Trigger the immunity of the living system required bioactive benzopyran derivatives as a therapeutic agent for numerous diseases.

The word “pyran” is used for a heterocyclic ring bearing oxygen atom with carbons. Hetero-ring fused with a benzene ring known as “benzopyran”. Pyran heterocyclic compounds are the predominating building block of natural and artificial drugs. Natural drugs extract from plants and animals while artificial drugs synthesize by a pharmaceutical company [8]. According to the literature, our focused on

the therapeutic activity of benzopyran derivatives which shows broad biological activities, including anticancer [9], [10], antibacterial [11], antidiabetic and anti-inflammatory [12], [13], antitumor, antimicrobial [14], anticoagulant [15], antioxidant [16], anti-spasmolytic, antifungal [17], antiviral [16], anti-helminthic, antitubercular [18], and anticonvulsant [19]. Moreover, in the reported literature, some more activities are available like a diuretic, estrogenic, hypothermal, anti-HIV [20], analgesic, and vasodilatory properties. SARS and corona spike protein structure are almost the same proteinase is M^{pro} is called as SARS-CoV- M^{pro} [21]. Anti-viral properties encourage researchers to apply benzopyran moiety-bearing drugs against the pandemic corona [22]. The benzopyran-bearing compounds get great attention in research due to their vast biological activities [23]. The compounds of pentacyclic naphthoquinones derivatives act as a promising drug against antimalarial [24], antitumoral, and anti-leishmanial [25]. They promote awareness for the synthesis of novel pyran moiety-containing compounds with the green protocol. Benzopyran molecular orbital exhibited energy level as shown in **Figure 1 [35]**.

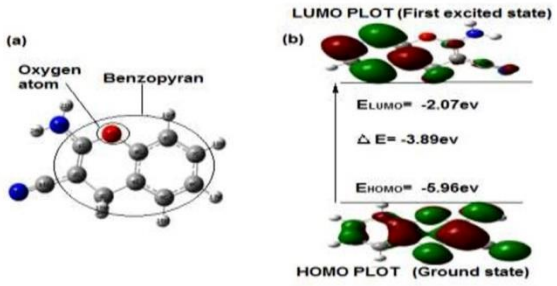


Figure 1 Benzopyran derivative (a) The optimized structure (b) Molecular orbital structure for the HOMO and LUMO [31].

Benzopyran derivatives nomenclature

Natural products like alkaloids, flavonoids, tocopherols, and anthocyanins have the basic structure of benzopyran. [26] Pyran moiety-bearing heterocyclic compounds were classified based on the source of

origin, and the position of the hydrogen atom [27]. The pyran ring is the basic structural unit of chromane, chromene, chromenone (eg. Coumarin, and Flavone), benzochromene (eg.Napthopyran), benzochromenone, xanthenes, and xanthenone (eg. Napthoflavone, Pyranonaphthoquinones) compounds have vast medicinal properties. The word "benzo" used before pyran as a prefix indicated a benzene ring fused with a pyran structure. If 2H-pyran fused with benzene is called 2H-benzopyran and if 4H-pyran fused with benzene is called 4H-benzopyran [28]. The word "naphtho" used before pyran as a prefix indicated two aromatic fused rings named naphthalene fused with pyran structure. If 2H-pyran fused with naphthalene is called 2H-naphthopyran and if 4H-pyran fused with naphthalene is called 4H-naphthopyran. The pyran ring contains the carbonyl group named pyranone. The 2^{nd} position of the ketone group is named pyran-2-one and the 4^{th} position is named pyran-4-one **Figure 2** [29], [30]. Benzo and naptho ring attached with pyranone same as pyran. Pyranone and its derivatives are chromone, chromanone, chromenone, coumarin, dihydrocoumarin, xanthone, and flavones.

Myriad benzopyran derivatives, a synthetic process have been produced by cyclization via alkyne π-activation. Benzopyran synthesis methods are challenging due to the restriction of substitution addition [32], [33], [34], [35]. Chromium complex tridentate chiral catalyst shows Schiff base property to form Oxa[4+2] Cycloaddition and allylboration by the reaction of 2-Substituted Enol Ether with 1,3-dienylboronates. Produced cyclic allylic boronates further react with substituted aldehyde up to 110^{o}C to form pyran derivatives [36]. In Aldol condensation, the reaction of two carbonyl compounds one is substituted aldehyde and the second is substituted ketone reacts together in presence of innocuous solvent ethanol and water at room temperature to give good yielding chalcones (enone). It further performed cyclization with nitrile derivatives (malononitrile or methyl cyanoacetate) within the sight of an organic base (triethylamine) in the same alcoholic condition at room temperature [37]. A Synthetic scheme of tricyclic pyran derivative compounds was obtained from a one-pot reaction. All compounds mix with dilute alcohol as a solvent at 89^{o}C. In the reaction mixture, hydroxy-naphthoquinone was added to form dimer pyranonaphthoquinone while hydroxy-coumarin was added to formed dimer pyranocoumarin [38]. In this review, the block diagram indicates benzopyran/derivatives and their therapeutic activity in published articles. Our analysis reports on published research articles giving a signal of awareness and attention to researchers/chemists on heterocyclic compounds especially oxygen-bearing ring-like pyran, benzopyran, napthopyran, and their derivatives. The numerical value on the block expresses the total of published articles every year and the interest of researchers gradually increases. We have collected the literature about benzopyran derivatives and applications from Google Scholar and Pub Med.

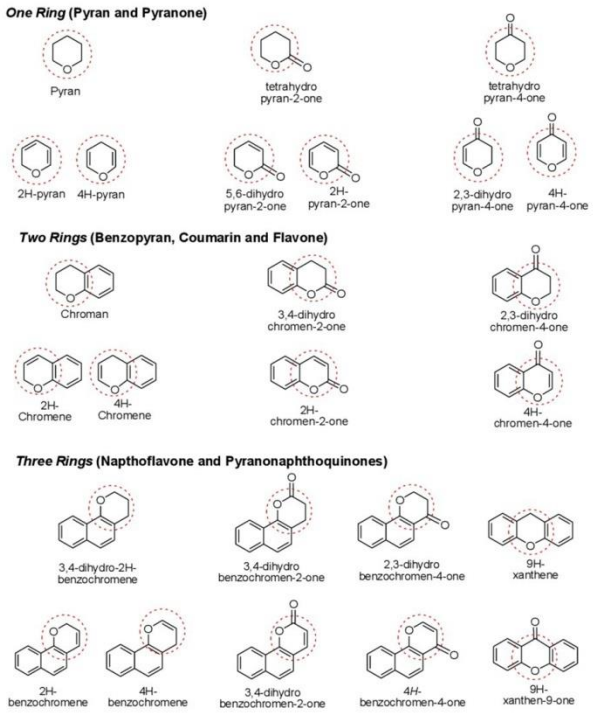


Figure 2 Basic core skeleton structure of benzopyran

Natural pyran compounds

Natural compounds possessed pyran basic unit moiety compounds such as vitamin E (01) [78], saccharides (02), coumarins (03) [79] flavonoids (04) [80], and pyranonapthoquinone's (05) [81], etc. Some large natural compound structure has antioxidant properties. Vitamin E is the perfect evidence of a large structure pyran moiety compound **Table 1**.

Table 1 A list of isolated compounds from plants

Plant isolated Compound	Plant	Family	References
Coumarin	Ammi majus L.	Apiaceae	[39]
	Ruta graveolens L.	Rutaceae	[40]
	Coriandrum sativum L.	Apiaceae	[41]
	Conyza sumatrensis (S.F.Blake) Pruski&G.Sancho	Compositae	[42]
	Myroxylon balsamum (L.) Harms	Leguminosae	[43]
Luteolin	Capsicum frutescens L.	Solanaceae	[44]
	Averrhoa bilimbi L.	Oxalidaceae	[45]
	Abutilon indicum (L.) Sweet	Malvaceae	[46]
	Balbisia calycina (Griseb.) Hunz. &Ariza	Ledocarpaceae	[47]

	Leontodon duboisii Sennen	Asteraceae	[48]
Apigenin	Petroselinum crispum (Mill.) Fuss	Apiaceae	[49]
	Elsholtzia rugulosa Hemsl.	Lamiaceae	[50]
	Chamomilla recutita (L.) Rauschert	Asteraceae	[51]
	Turnera aphrodisiaca Ward	Turneraceae	[52]
	Justicia gendarussa Burm.f.	Acanthaceae	[53]
Quercetin	Tridax procumbens (L.) L.	Compositae	[54]
	Tussilago farfara L.	Compositae	[55]
	Opuntia ficus-indica (L.) Mill.	Cactaceae	[56]
	Allium cepa L.	Amaryllidaceae	[57]
	Calluna vulgaris (L.) Hull	Ericaceae	[58]
Catechin	Camellia sinensis (L.) Kuntze	Theaceae	[59]
	Uncaria gambir (Hunter) Roxb.	Rubiaceae	[60]
	Nicotiana tabacum L.	Solanaceae	[61]
	Centaurea maculosa Noë ex Nyman	Asteraceae	[62]
	Arbutus unedo L.	Ericaceae	[63]
Kaempeferol	Fragaria × ananassa (Duchesne ex Weston) Duchesne ex Rozier	Rosaceae	[64]
	Morus alba L.	Moraceae	[65]
	Persicaria tinctoria (Aiton) H.Gross	Polygonaceae	[66]
	Bryophyllum pinnatum (Lam.) Oken	Crassulaceae	[67]
	Medicago truncatula Gaertn.	Leguminosae	[68]
Galangin	Helichrysum abietifolium Humbert	Compositae	[69]
	Alnus sieboldiana Matsum.	Betulaceae	[70]
	Lychnophora pohlii Sch.Bip	Compositae	[71]
	Alpinia officinarum Hance	Zingiberaceae	[72]
	Alpinia calcarata (Haw.) Roscoe	Zingiberaceae	[73]
Naphthoquinones	Tabebuia avellanedae Lorentz ex Griseb.	Bignoniaceae	[74]
	Rhinacanthus nasutus (L.) Kurz	Acanthaceae	[75]
	Avicennia *spp.*	Avicenniaceae	[76]
	Triphyophyllum peltatum (Hutch. & Dalziel) Airy Shaw	Dioncophyllaceae	[77]

Origin based pyran derivatives:

Epicalyxin F **(06)** are derivatives of flavonoids, the source of flavonoids is seeds of *Alpinia blepharocalyx* which is used as an anticancerous agent against human HT-1080. Calyxin F **(07)**, Epicalyxin G **(08)** and Calyxin G **(09)** are also the similar type of derivatives obtained from the same seeds with almost similar properties but the efficiency of Epicalyxin F has promising anticancer activities [82], [83]. Naturally occurring fused form of furanone and pyranonaphthoquinone are the basic frame to play a smart role in medicinal chemistry. Kalafungin **(10)** natural exiting compounds bearing the above-mentioned pharmacophore were tested for the treatment of leukemic cells and AKT kinase [84], [85]. Naturally occurring pyranonapthoquinone's derivatives possessed biological activities were obtained from various living organisms, including fungi, bacteria and higher plants. Many compounds of pyranonapthoquinones like eleutherin **(11)**,psychorubicin**(12)** and pentalongin **(13)** have been used worldwide, for the treatment of antibacterial, antiviral, anti-parasitic and anticancer [86] α- lapachone **(14)** and β-lapachones **(15)** are natural compounds, it was extracted from the heartwood of the *Bignoniaceae* trees [87] α- and β-lapachone used for vast treatment, including anticancer, [88] antibacterial and anti-inflammatory [89] activities β-lapachone were used for the treatment of NADH quinone oxidoreductase tumours [90]. The compounds exist in level II clinical trials to cure a pancreatic tumour [91], [92]. Myriad natural product compounds such as2-deoxy-KDC **(16)**, (5R, 6S)-6-acetoxy-5-hexadecanoide **(17)**, goniodiol **(18)**, psymberin (Irciniastatin A) **(19)**, thiomarinol **(20)** containing alpha-hydroxy alkyl pyran moiety structure to shows wide biological spectrum activities including antibacterial and anticancer **Figure 3 [93], [94]**. The essential oil was isolated from the leaves of *Calyptranthestricona* which contains some derivatives of benzopyran. 5,7-dimethoxy-2methyl-2H-chromene**(21)**and5,7-dimethoxy-2,8-dimethyl-2H-chromene **(22)** are possessed efficient antifungal properties. Similarly, biologically active 4H-benzopyran compounds are available in nature. The flower of *Wisteria sinensis*, extract having 7-hydroxy-6-methoxy-4H-chromene [95] **(23)** and it exhibits organoleptic property [96]. The stems of *Uvariaufielii* plant, extracted product uvafzlelin **(24)** (4H-benzopyran derivatives) were possessed broad-spectrum activity against both Gram-positive and Gram-negative bacteria. The *Millettiaconraui* tree bark extracted oil containing naturally fused pyran ring conrauinone-A **(25)** (4H-benzopyran derivatives) were used for the treatment of intestinal parasites. The bark of *Erythrina senegalensis* tree isolated product erysenegalensein C **(26)** (benzopyran-4-one derivative) was used to give the potential treatment of female infertility and gonorrhea [97]. It is also used for stomach pain. Derivatives of 2H-benzopyran are classified the class of ATP "Sensitive Potassium Channel Opener" drugs which have antihypertensive and anti-ischemic property. The Cromakalim **(27)** is one of the antihypertensive drugs to provide smooth vascular muscle relaxation due to the activation of the potassium ion (K^+ion) channel [98], [99]. Substituted-2 H-chromene compounds with 5-HT_{1A} receptor having higher affinity. As a Na+-glucose co-

transporter inhibitor, it has potent anti-diabetic properties. According to the research literature studied, compound [N-(2-(6-fluoro-2H-chromen-8-yloxy)ethyl)-4-(4-methoxyphenyl)butanamine] **(28)** were synthesized and the structural modification of the benzopyran. The heterocyclic compounds 4,5-dihydropyranochromenes **(29)** are the important family of pharmaceutical chemistry used as a therapeutic agent in neurodegenerative diseases, Parkinson's disease, Alzheimer's disease, Down's syndrome, Huntington's disease, amyotrophic lateral sclerosis, AIDS-associated dementia. Moreover, it's also used for the treatment of myoclonus and schizophrenia [100]. The diarylheptanoids pyran core containing molecules possessed bioactive properties such as Diospongin B **(30) [101]** and Centrolobine **(31)**. Hall and his team recently synthesized a stereospecific and regioselective cross-coupling of pyran and piperidine-derived compounds followed Suzuki-Miyaura [102]. The cross-coupling possessed in the alkylboronates, enhanced optically active property [103]. 2-amino-4-aryl-4H- chromene regulates aminopeptidase inhibitor which has a wide range of therapeutic activities. The substituent benzopyran 4-(pyridine-3yl) or 4-(isoquinolin-3-yl) and 2-amino or 2-acetamido like (E)-ethyl 2-amino-4-(1-aminobuta-1,3-dien-2-yl)-7-hydroxy-4H-chromenes-3-carboxylate (HF1-142) **(32)**,(E)-ethyl2-acetamido-4-(1-aminobuta-1,3-dien-2-yl)-7-hydroxy-4H-chromene-3-carboxylate (HF1-419) **(33)**, ethyl 2-amino-7-hydroxy-4-(quinolin-3-yl)-4H-chromene-3-carboxylate (HF1-435) **(34)**, ethyl 2-acetamido-7-hydroxy-4-(quinolin-3-yl)-4H-chromene-3-carboxylate (HF1-437) **(35)** are used as a most potential IRAP inhibitors [104]. Moreover, derivatives of amino benzopyran possessed vast application in various fields such as pigments, cosmetic and biodegradable agrochemicals **Figure 4**.

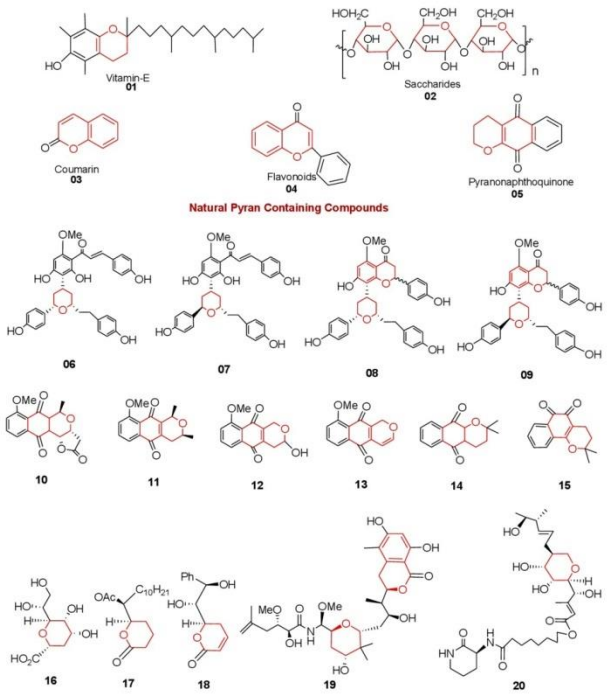


Figure 3 Natural Pyran compounds and their origin

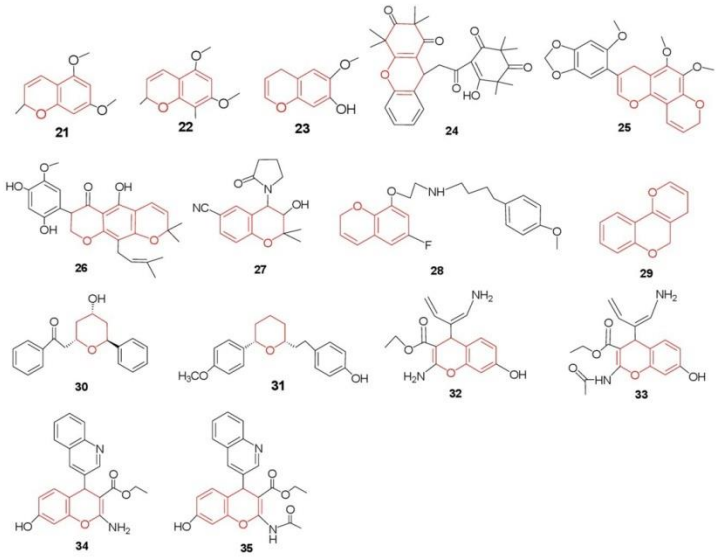


Figure 4 Natural and synthetic benzopyran derivatives

Life-Threatening Pharmaceutical Applications

Last twenty-year data for benzopyran and its derivatives', myriad published articles were analyzed having an anti-disease property such as anticancer, anti-inflammatory, antibacterial and anti-diabetics **Figure 5**. All the diseases reported in articles increases gradually every year because of their wide bioactive nature. Maximum article on inflammatory activity reported in a published article at every five-year duration, then anticancer, then antibacterial and finally anti-diabetic. The aim of the block diagram represents the significant property of benzopyran bearing compounds and the compression study of compounds against above mention diseases. We have collected the literature about benzopyran derivatives and applications from Google Scholar and Pub Med.

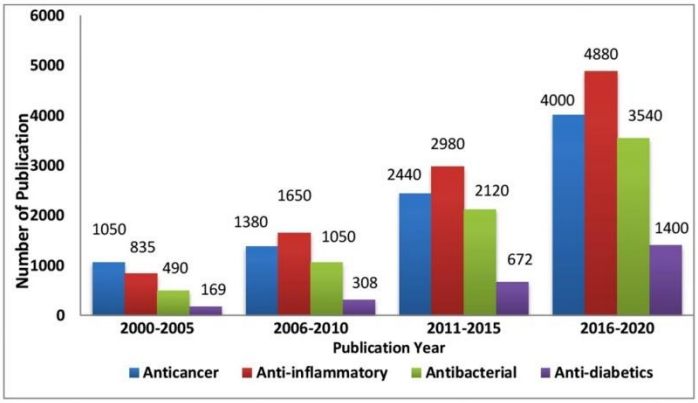


Figure 5 Benzopyran derivatives analysis data for life-threatening diseases.

1. Anticancer activity of benzopyran

Cancer constitutes the high mortality rate causing disease in the whole world. Uncontrolled growth of abnormal cells potentially spread in parts of the living body to form tumours. It's widely reported in the article, which describes the cytotoxic anticancer agents which induce programmed cell death [105]. Currently, heterocyclic compounds like benzopyran possessed wide biological activities. Benzopyran

moiety is the influencing structure due to reported potential anticancer activities, so try to design and develop some more relevant compounds [106]. Past two decay analyses of benzopyran derivatives anticancerous activity. We have collected the literature about benzopyran derivatives and applications from Google Scholar and Pub Med **Figure 6**.

Some natural compounds have benzopyran moiety and they are used for the treatment of life-threading diseases such as acronycine **(36)** for the treatment of lung, ovary, and colon cancer [107]. Calanone **(37)** is used treatment of cervical carcinoma and leukemia [108], [109]. Seselin **(38)** for the treatment of skin cancer tephrosin **(39)** is used for the treatment of lung cancer [110]. Zanamivir **(40)** was approved for the treatment of influenza A and B. The first clinically developed drugs were neuraminidase inhibitor drugs and laninamivir (**41)** structure is similar to zanamivir and its pro-drug is laninamivir octanoate [111], [112]. Pyran- skeleton containing drugs are commercially available for clinical trials. The 4H-pyranonaphtoquinone's moiety structure is an analogous structure of some naturally occurring anticancer potential compounds [113]. Asian medicinal plant *Rhinocanthusnasutus*, natural product srhinacanthin O **(42)** and pyranokunthone B **(43)** extracted from a marine actinomycete were used as an anti-cancerous agent due to its efficient treatment against the tumour. Griseusin **(44)** and granaticin **(45)** are shown biological properties including antibacterial, antiprotozoal and cytotoxic activities [114], [115]. edermycin **(46)** have been wide biological properties against K562 human myeloid leukaemia, P-388 murine leukaemia and murine lymphoblastoma cell lines [116], [117]. The substituted synthesized 4-aryl-4 H-benzopyran compound belongs to microtubule inhibitors and enhanced the activity of the anti-cancerous compounds [118]. The synthesized compounds are substituted-4H-chromene-3-carbonitrile derivatives **(47, 48 and 49)**. The compounds (47) and (48) are efficient anticancer alkaloid that promotes caspase-mediated programmed cell death in tumour cells and possessing vascular targeting activities [119]. The methods of preparation of these compounds were simple, potent cytotoxic and efficient vascular disrupting active. Tubulin is the potential therapeutic properties which are used for cancer therapy [120]. Antitumour agents can binds to tubulin and inhibit tubulin polymerization and responsible for discovery of colchicines binding site of tubulin. They dislocate α, β-dimer of tubulin which inhibits the tubulin assembly into microtubules leading to programmed cell death [121]. Some synthesized compounds were examined on breast non-neoplastic cells (MCF-10A) [122], and cancer cells (Hs578T and MCF-7 [123], [124]. After the purpose of IC50 value, precise assays were applied to analyze the efficiency of the synthesized compounds and their derivatives. The bromine atom performed better output and promising bioactivity. Enone compounds work as cell migration inhibitory agents and triggered regulated cells death. Moreover, it's also used as an anti-proliferative and antitumor agent [125], [126]. The synthesized compounds were compared with the standard drug doxorubicin. Substituted-4H-

chromene-3-carbonitrile derivatives **(50**, **51** and **52)** are anticancerous agents. Some synthetic compounds of substituted α-β-pyran naphthoquinones also possessed cytotoxic activities against tumour cell lines **Figure 7 [127]**.

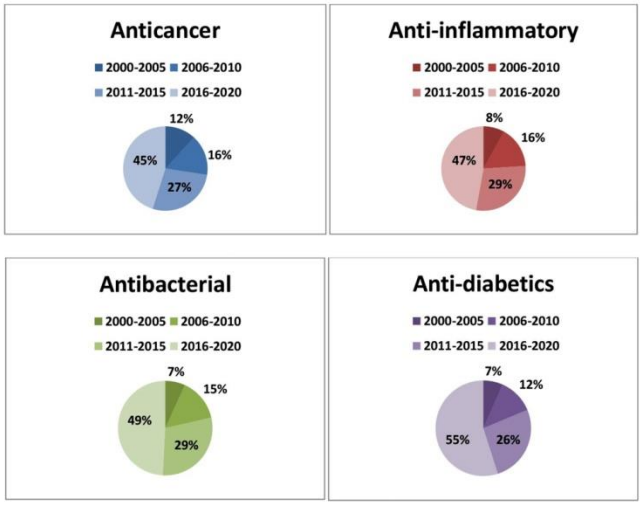


Figure 6 Anticancer, Anti-inflammatory, Antibacterial and Anti-bacterial published articles in last twenty years

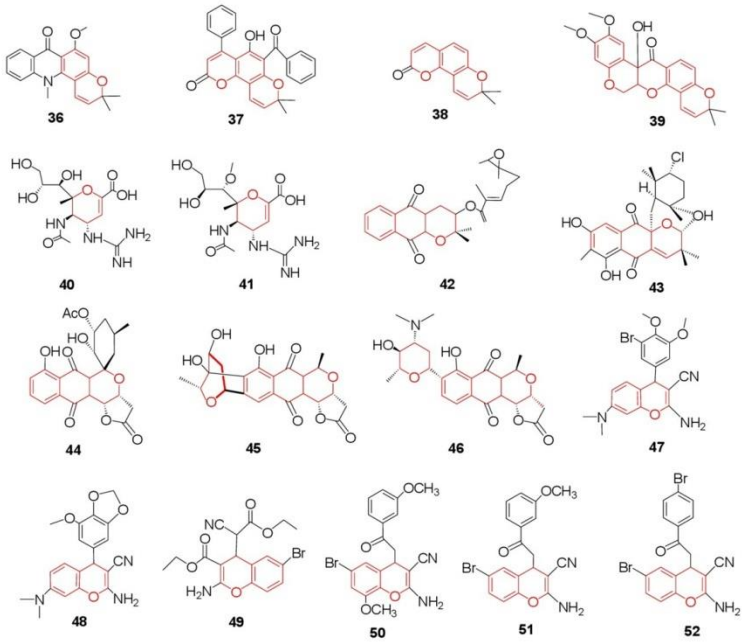


Figure 7 Synthesized benzopyran based anticancerous drugs

1. Anti-inflammatory activity of benzopyran

Inflammation is the initial response of the body immune system to irritation, infection or foreign substances [128]. The benzopyran pharmacophore possessed compounds that performed higher selectivity, efficiency, and potency treatment which provide COX-2 selective inhibitors (COXibs) under non-steroidal anti-inflammatory drugs (NSAIDs) for the inflammation. Some important inflammatory drugs like valdecoxib, celecoxib, etoricoxib and rofecoxib etc. Coxib clinical compounds like SC-75416 and SD-8381 bearing benzopyran moiety which provides quick action with higher efficiency. Past two decay analysis of benzopyran derivatives anti-inflammatory activity. We have collected the literature about benzopyran derivatives and applications from Google Scholar and Pub Med **Figure 6**.

In the evaluation test, SC-75416 was the superior anti-inflammatory to standard ibuprofen [129]. Benzopyran cyclooxygenase-2 selective inhibitors are substituted-2H-chromenes-3-carboxylic acid **(53**, **54**, **55** and **57)**. Special properties of substituted-4H-chromen-4-one **(56)** due to pyran moiety with nitrile functionality compounds to prohibited to binding TNF-α to its receptor. The potential of this compound help in the treatment of TNF-α caused disease [130]. Pro-inflammatory cytokine (Tumor Necrosis Factors Alpha (TNF-α)) secreted due to the multiple inflammatory stimuli response. TNF- α to its receptors

initiates the activation of transcription factors. The transcription factor regulates the secretion of multiple pro-inflammatory cytokines (TNF-α) and related proteins. Inhibition of transcription factor activation or falling in TNF-α level has been performed to cure various disease like rheumatoid arthritis, inflammatory bowel diseases and psoriasis etc [131]. The design and discovery of drugs play an important role, they help to inhibit the level of TNF-α due to TNF-α inhibition, zinc metalloproteinase also inhibits [132]. The benzopyran moiety structural compound plays an important role to block the production of TNF-α. All methoxy groups and pyran in the structure act as TNF-α production inhibitory agent [133]. This synthesized compound plays such activities7-methoxy-2-(3,4,5-trimethoxyphenyl)-2H-chromene **(58)**, The thiosemicarbazide with benzopyran structure (E)-1-[(4-chloro-2,2-dimethyl-2H-chromen-3-yl)methylene]thiosemicarbazide **(59)** enhanced anti-inflammatory mode of action, The natural compound, Cannabichromene(CBC) 2-methyl-2-(4-methylpent-3-enyl)-7-pentyl-2H-chromen-5-ol **(60)** is the cannabinoids extracted from *Cannabis sativa* have been vast medicinal activities such as anti-inflammatory diseases, hypothermia and antimicrobial. In the evaluation test, CBC performed better result as compared to pheylbutazone **Figure 8 [134]**.

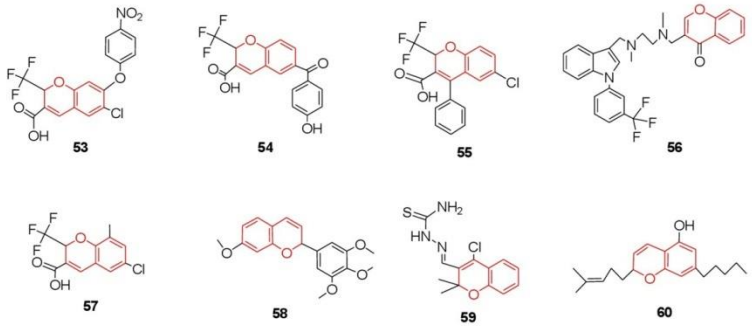


Figure 8 Synthesized benzopyran used as an anti-inflammatory compound

2. Antibacterial activity of benzopyran

The benzopyran synthesized compounds have multiple activities that were studied in the literature. Derivatives of its compounds have vast applications in various fields. Past two decay analysis of benzopyran derivatives antibacterial activity. We have collected the literature about benzopyran derivatives and applications from Google Scholar and Pub Med **Figure 7**.

1. The benzopyran organo-ligand derivative bearing CN and NH_2 binds with various metals to form organometallic compounds. The efficient inhibition activities of bacterial were belonged to the copper and cobalt complex. MIC-value of compounds against *E. coli* and *S.aureus* were 16 and 32μg/ml [135]. Antibacterial activity of the synthesized compounds is pyran ligand ($C_{18}H_{17}O_2N_2Cl$) **(61)** were attached with various metals to formed organometallic compounds. Synthesized organic compound electron-rich elements formed co-ordinate bond with metals. Such as ligands with Co ($C_{37}H_{37}O_4N_4Cl_2Co$), a ligands with Zn ($C_{37}H_{37}O_4N_4Cl_2Zn$**)**, a ligand with Mn ($C_{37}H_{37}O_4N_4Cl_2Mn$**)**, a ligand with Cu ($C_{37}H_{37}O_4N_4Cl_2Cu$**)**, a ligand with Ni ($C_{37}H_{37}O_4N_4Cl_2Ni$**) (62)**.The MIC(μg/ml) value data were reported on two bacterial strain *E.coli* and *S.aureus*, MIC value on Ligand against *E.coli* and *S.aureus* are 64,128, a ligand with Co are 16, 32, ligand with Zn are 64,64.ligand with Mn are 32, 128, a ligand with Cu are 16, 32, a ligand with Ni are 32, 64. All synthesized benzopyran and napthopyran compounds **(63)** and **(65)** were examined on various bacterial strains. The synthesized method of the compound was ecofriendly which follows green protocol. The in vitro antibacterial activity was tested on such bacterial strains (*Pseudomonas aeruginosa, Escherichia coli* and *Staphylococcus aureus*). Moreover, the synthesized technique of compounds used only water. The simplest structure of benzopyran is 2-amino-7-hydroxy-4-methyl-4H-chromene-3-carbonitrile **(64)** and the simplest structure of napthopyran is 3-amino-1-methyl-1H-benzochromene-2-carbonitrile **(66) [136].** The novel synthesized compounds **(67)** were reported in the article for the good antimicrobial mode of action. The 4H-pyran structural moiety has broad biological activities. In this article synthesized compounds **(68)** tested against bacteria and fungi. In Gram-positive bacteria (*M. Tuberculosis, M. Luteus, MRSA, B. Subtilis, B. Cereus*), Gram-negative bacteria (*P. Aerginosa, K. Pneumonia, E. Coli, P. Vulgoris, S. Typhi*), Dermatophytes (*M. Canis, M. Gypseums, T. Rubrum, T. Interdigitale*) **Figure 9 [137]**. Activation of Nrf2/HO-1 signaling and upregulation of PPARγ with the help of the cardioprotective effect of VIS [141]. 7,8-dihydroxy-3-(4-nitrophenyl)coumarin (3j) was more reactive against MAO-A (inhibition concentration [IC50] = 6.46 ± 0.02 μM) and MAO-B (IC50 = 3.8 ± 0.3 μM) enzymes [142]. In human liver (HepG2), prostate (LNCap), and pancreatic (BxPC3) cancer cells are cytotoxicity of 3-arylcoumarin derivatives (6a-f and 7a-f). More toxicity cytotoxicity in the HepG2 cell by 7,8-dihydroxy-3-(4-nitrophenyl) coumarin (7b) compound [143]. Glutamate plays important role in brain metabolism [144].

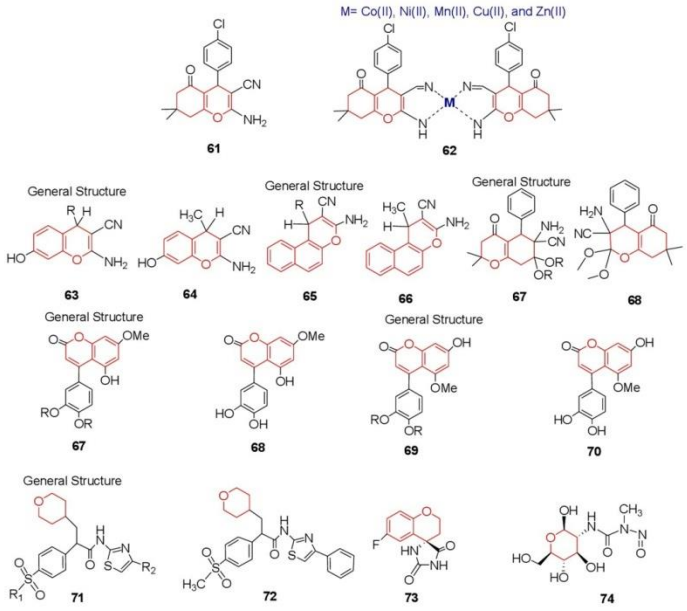


Figure 9 Synthesized benzopyran antibacterial agents

3. Antidiabetics activity of benzopyran

Diabetics is a widely spread disease. It's found most probably in all family. Patient of diabetics suffers sugar problem may be hypo or hyper. Diabetes is also 2 types (Type-1, Type-2). Some compounds of pyran/benzopyran or derivatives used for the treatment of diabetics. Past two decay analysis of benzopyran derivatives anti-diabetics activity. We have collected the literature about benzopyran derivatives and applications from Google Scholar and Pub Med **Figure 6**.

The neoflavonoid compounds **(67)** and **(69)** were reported in literature against diabetes. In this article, the extracted natural product from *Hintoniae latiflorae* cortex (copalchi bark) containing coutareagenin (benzopyranone) which is used to cure sugar level in the blood, extracting product were tested on rats from the inbred strain F>28. Copalchi extract gave through oral or intragastric and analyzed data, demonstrating the reduction of diabetic prominent blood sugar levels. The native extract of copalchi bark used as an antidiabetic agent and it's was induced to tested in various hyperglycemic animals' species by

different methods. The simplest derivatives structure of neoflavonoid **(68)** and **(70) [138].** The design and synthesized derivative of N-thiazole substituted arylacetamides **(71)** were reported in the article. Synthesized compounds **(72)** were used to activate glucokinase (GK) to the balancing of blood sugar level especially, for the treatment of diabetes mellitus. Instead of synthesized compounds were possessed the greatest GK activation strength with an EC50 of 0.026lM. Significantly such compounds enhanced both synthesis and uptake of glucose in rat primary hepatocytes. In addition, single oral administration of compound R-9k was used reduced blood sugar levels in both ICR and ob/ob. This derivative gives promising results to active Gk activator and anti-diabetic agent [139]**.** In the research article reported the treatment of diabetic rats. Streptozotocin **(74)** injected in rats collected data after 14 days due to recorded information of the changed level of glucose in the blood. Sorbinil **(73)** used as an anti-diabetic agent but according to recorded data it's not an efficient tool for aldose-reductase inhibition within the vascular system of the rat **Figure 9 [140]**.

CONCLUSION

The broad therapeutic applicability of benzopyran and its derivatives is essentially covered in this short article. As evidenced by several cited studies, the benzopyran scaffold is the building block of many chromanes, xanthones, and flavonoids found in various natural plants and pharmaceutical products. The ultimate conclusion is that benzopyran has demonstrated a diverse spectrum of biological activity, as one of the preferred heterocycles. We need to create new agents to relieve patient pain and cure myriad diseases, and molecular biologists, pharmacologists, medicinal chemist, and others need to work together. Computer-aided drug design was delivered through pharmaceutical chemists with high–throughput screening. Benzopyran moiety has received much attention area to discover more additional benzopyran derivatives with novel structures in the field of academic and pharmaceutical.

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