A REVIEW OF NOVEL BENZOPYRANS AND THEIR MEDICINAL APPLICATIONS

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Abstract

Introduction: *Benzopyran derivatives have different biological activity and behavior. Benzopyran derivatives may treat several illnesses. Their physicochemical structures appear to influence their biological action.*

Expert opinion: *Numerous benzopyran derivatives have biological effects in vivo and in vitro. To evaluate the therapeutic value of their clinical evaluation, it will be essential. It is generally known that the compounds having benzopyran moiety serve as lead compounds for the development of new, more promising molecules.*

Introduction

Natural compounds with diverse structural features affect chemical biology and drug development. Natural chemicals' pharmacological effects inspire many scientists to discover new molecules. It focused on the oxygen heterocycle-forming benzopyran and its derivatives. Anti-inflammatory, antibacterial, antimicrobial, antiviral, antioxidant, antiplatelet, and anticancer properties made benzopyran derivatives important compounds in the past. This study discusses benzopyran derivatives with anti-inflammatory, anti-cancer, anti-arthritis, anti-bacterial, anti-Alzheimer, anti-skin disease, antiviral, treatment type 2, and autosomal dominant polycystic kidney disease characteristics.

Benzopyran derivatives for anticancer

Brain tumors, melanomas, pancreatic cancers, NSCLC-type lung cancers, hormone-refractory prostate cancers, and triple-negative breast cancers cannot be treated. Antineoplastic medicines damage healthy and cancerous cells. Thus, new benzopyran derivatives examined novel antiproliferative treatments.

MCT inhibitors SLC-16 genes produce MCTs. Mammals contain 14 MCT isoforms, however only 4 (MCT1, 2, 3, 4) transport monocarboxylates proton-linked. Metabolic demands upregulate MCT1 in brain, breast, head, lung, and colon malignancies. It may extrude lactate from oxygenated and hypoxic tumor cells. MCT1 inhibition forces aerobic cancer cells to utilise glucose instead of lactate, straining and killing hypoxic ones. MCT1 may be an oncogene.

MCT1-prevention invention WO2013109972. Formula 2 and 2a showed six compounds (Figure 3, Compounds 7–12). Drugs helped breast cancer. Benzene ring and tertiary amine structure compound 9 exhibits a 48 nM cytotoxicity IC50.

Experts expanded compounds 11 and 12 with biological activity and structure similar to compound 9 in the invention. At 0.8 and 76 nM, non-benzopyran derivatives 11 and 12 inhibit breast cancer MCT1.

CYP1B1 inhibitors

The cytochrome P450 superfamily comprises heme-thiolate monooxygenase

(CYP1B1), CYP1A1, and CYP1A2. It regulates metabolizing and produces quinone metabolites, which are essential for cancer-causing DNA adducts. CYP1B1 protein is greater in breast, ovarian, and prostate cancers (PCa). Breast cancer cells proliferated when CYP1B1 reduced apoptosis and enhanced cell cycle transition. CYP1B1 may be a cancer catalyst, biomarker, and treatment target. WO2010125350 controls CYP1B1-mediated cancer. Figure 4 displays Formula 3 structures and seven compounds.

14 is benzopyran-coumarone. Experts expanded Compounds 16–19 by biological activity and structure. When 16 and 17 are active, CYP1B1 produces the phosphoramidate mustards N,N-bis (2-chloroethyl) phosphoramide (CI-IPM) and Br-IPM. In prodrugs 16 and 17, CYP1B1 activation lowers the toxicity of CI-IPM and Br-IPM, phosphoramidate mustards. Table 1 demonstrates the cytotoxicity IC50 values of Compounds 16–19 in cancer cells UT-SCC-14, 8, 9, and 10. According to evidence, compounds 16 and 17 reduce CYP1B1 expression and are nontoxic. These two chemicals may represent anticancer drug leads.

P-glycoprotein inhibitors

The earliest and best-described mammalian ATP-binding cassette (ABC) transporter protein was P-gp. Overexpression of P-gp is associated with chemotherapy-induced multidrug resistance (MDR). P-gp is a polypeptide with two nucleotide-binding and 12 transmembrane domains. It transports analgesics, anticancer drugs, HIV protease inhibitors, products, lipids, peptides, and more.

Table 1. The cytotoxicity IC50 values for SU025-04 and SU046-04 in the UT-SCC- 14, UT-SCC-8, UT-SCC-9 and UT-SCC-10 cancer cells.

Comp.	UT-SCC-14	UT-SCC-8	UT-SCC-9	UT-SCC-10
SU025-04	0.05 ± 0.01	0.31 ± 0.06	0.41 ± 0.07	0.22 ± 0.03
SU037-04	0.12 ± 0.07	0.56 ± 0.04	0.22 ± 0.08	0.21 ± 0.04
SU046-04	0.02 ± 0.01	0.06 ± 0.02	0.15 ± 0.02	0.09 ± 0.03
SU048-04	0.94 ± 0.02			

Normal cells hardly express P-gp, while cancer cells do. Even modest P-gp levels may make tumors resistant to cytotoxic drugs in animals. Modifying P-gp may reverse clinical MDR.

Thus, many experts studied P-gp modulators for years. Verapamil and cyclosporine are first-generation P-gp inhibitors. Elacridar, zosuquidar, and laniquidar are third-generation P-gp modulators. These drugs worked well in vitro. Clinical experiments failed. Novel, powerful, noncytotoxic P-gp modulators are urgently needed.

P-gp inhibitor CN201110051792. Inhibitors rule Figure 5. Formula 4 specifies structures with three model compounds (20–22).

This work employed P-gp-transfected MDA435/LCC6MDR breast cancer cells and their progenitor. LCC6MDR cells were 90.4 times more resistant to paclitaxel (PTX) than LCC6 (Table 2). P-gp modulating drugs were assessed using Relative Fold (RF), which compares the IC50 for PTX in LCC6MDR cells with

and without 1 M modulators.

Phosphatidylinositol 3-kinase/Akt inhibitors

PI3K-related protein kinases coordinate growth factor, food, and energy status signals to enhance cell growth, proliferation, and survival. PI3K/mTOR inhibitors treat cancer.

CN201210009328 covers PI3K/mTOR cancer inhibitors. Figure 6 illustrates Formula 5 and two compounds (YL201211 and YL201212). Formula 5: H or Br.

In vitro, the compounds or medicinal salts were anticancer. YL201211 and YL201212 reduced LP-1, OPM-2, K562, and Jurkat cancer cell proliferation. PARP and caspase-3 may kill tumor cells with YL201212.

AR-JunD inhibitors

Advanced hormone-refractory metastatic PCa kills the second most men in the US. Reactive oxygen species (ROS), which naturally damage DNA, RNA, lipids, and proteins, are increasingly being linked to PCa incidence, recurrence, and androgen independence.

Androgen signaling increases ROS in PCa tissue. Two factors produce these. Androgen-induced oxidative stress increases JunD in TFAP-1 human PCa cells. Testosterone boosts SSAT. SSAT oxidizes polyamines to H2O2. A recent research found that androgen receptor (AR)-JunD-induced SSAT expression boosts ROS levels, which stimulates NF-B overexpression, perhaps creating an autocrine feed-forward loop between SSAT-ROS-NF-B-SSAT that continues ROS generation.

Anti-JunD WO2011130692. Inhibitors rule Figure 7. Formula 6 explains Compounds 24 and 25. Parents found that the AR-JunD complex oxidizes polyamines to trigger SSAT gene expression. These results explain androgen-induced ROS generation in PCa cells and offer a prostate-specific target for PCa-chemopreventive/chemotherapeutic drug development.

In US2009326015, benzopyran derivatives (Compound 26) inhibited AR in PCa cells at transcriptional, protein, activity, and downstream targets KLK2 and PSA. Figure 8 shows Formulas 7 and 7a and three compounds (26–28). Compound 26 kills Hela, U266 and A549 cancer cells. Table 3 shows results. Compound 27 lowers PSA, KLK2, and NKX3-1 mRNA.

Others patent about anticancer

According to patents CN201410041573 and CN201210220626, sulfonyl hydrazones with the 8-ethoxy-3-nitro-2H-benzopyran structure and its analogues exhibit strong anticancer activity in vitro and in vivo.

In CN201510414085, 2H-1-benzopyran-2-ketone was found to inhibit sword bean protein A (ConA)-induced T cell proliferation, lipopolysaccharide-induced B cell proliferation, CD86 expression in first-generation dendritic cells, and B cell activating factor receptor expression in B lymphocytes. Thus, the chemicals are immunosuppressive, anti-inflammatory, and anti-cancer.

IC50 (M) fixes the problem after 72 hours while preserving SGLT2's selectivity. This led to type 2 diabetes, metabolic syndrome, and obesity inhibitors.

SGLT2 inhibitors may lower HbA1c by 0.5-1.5% without hypoglycemia.

WO2013045495 and EP2573088 treat type 2 diabetes. Figure 9 presents Formula 8 and five sample compounds (Compounds 29–33).

SGLT2 inhibitors, novel benzopyran

derivatives, might treat diabetes and other SGLT2-regulated disorders. Compound 29 inhibits SGLT1 and SGLT2 in stably transfected Chinese Hamster Ovary cells. SGLT2's IC50 is 0.1 M, whereas SGLT1's is above 10 M. Pyrano[3,2-c][2]benzopyran-6(2W)-one derivatives are also used to treat or prevent diabetes and other SGLT2-mediated diseases.

Benzopyran derivatives treating type 2 diabetes

WHO estimates 200 million diabetics globally. Nearly 360 million, largely in developing countries, are predicted by 2030. 90% of patients have type 2 diabetes, which causes higher hepatic glucose production, reduced insulin secretion, beta cell dysfunction, and insulin resistance. Type 2 diabetes treatment begins with weight loss and glycemic control, but as the condition advances, it becomes difficult to maintain the restricted lifestyle. Most diabetics need insulin or other treatments.

SGLT2 inhibitors

SGLT1 and SGLT2 belong to the sodium/glucose cotransporter family (SLCSA). Studies show that SGLT1 and SGLT2 enable proximal tubules resorb kidney-filtered glucose. The small intestine, trachea, heart, and plasma membranes express SGLT1, which resorbs 10% of kidney glucose. SGLT2, which is expressed in the renal cortex, resorbs 90% of glucose from the kidneys. Thus, blocking renal transporters slows glucose resorption, which may lower diabetics' blood glucose levels. Nonselective SGLT1 and SGLT2 inhibition may cause severe diarrhea.

α-Glucosaminidase inhibitors

-D-Glucoside Glucohydrolase (-glucosidases) enzymes govern quality, glycoprotein processing, and carbohydrate metabolism. Glycosidases fold and mature N-linked glycoproteins in the endoplasmic reticulum by catalyzing their oligo-saccharide chains. Inhibiting -glucosidase, which folds and matures glycoproteins, may impede cell-cell or cell-virus recognition by affecting glycoprotein maturation, transport, secretion, and function.

This invention, CN201210169320, treats type 2 diabetes using pharmaceuticals. -Glucosidase inhibition was evaluated with many benzopyran derivatives. Figure 10 shows nine example compounds (Compounds 34-42) and their structures (Formula 9).

-Glucosidases' IC50 values ranged from 59 to 69 nM for compounds 34 to 42. These drugs may benefit type 2 diabetes.

Benzopyran derivatives for anti-inflammation

Inflammation may cause asthma, rheumatoid arthritis (RA), atherosclerosis, inflammatory bowel diseases, and many cancers. In response to stimuli, inflammatory cells release nitric oxide, ROS, prostaglandins, and cytokines. Thus, various experts investigated new anti-inflammation compounds.

These results inspired several COX-2 inhibitor researchers. Selective COX-2 inhibitors include benzopyran compounds. CN201210202059 and WO2013189121 highlighted the benzopyran pharmacophore's 2-trifluoromethyl, 3-carboxy, and 4-H substituents. Figure 11 shows Formula 10 and nine sample compounds (Compounds 43-51).

GIBH1008 was found to be a selective COX-2 inhibitor (IC50 = 61.75 nM; selectivity index (SI) > 1619) with greater activity than the reference drug rofecoxib (IC50 = 0. In sequence, GIBH1016, 1014, and 1018 inhibited COX-2 (IC50 = 179.5

nM, 36.84 nM, SI = 862, and 63.74 nM, SI = 1569). The strongest COX-2 inhibitors in this category were 6-chloro or 6-bromo analogues.

Benzopyran derivatives treating arthritis

Arthritis affects millions. RA is arthritis. Analgesics, steroidal, and NSAIDs treat arthritis. These medications may treat pain and inflammation, not arthritis. These medicines produce gastrointestinal adverse effects with conventional NSAIDs and COX-2 inhibitors.

WO2009109230 offered a straightforward technique to produce novel 2-aryl and 2-heteroaryl-4H-1-benzopyran-4-one-6-amidino derivatives. Figure 12 shows four novel compounds (52–55). Compound 52 reduces inflammatory and neuropathic pain in vivo. Chemical 52 performed well in animal models of inflammatory pain, even with large dosages. Nimesulide ulcerated.

In animal models of neuropathic pain, Compound 52 showed remarkable effectiveness at doses of 10 and 30 mg/kg, with ED50 and ED100 values lower than 10 mg/kg, as in the Zymosan tests. Thus, chemical 52 prevents and treats arthritis.

Benzopyran derivatives treating skin diseases

Netherton syndrome (NS) is a severe autosomal recessive cutaneous condition caused by LKTI-1 deficiency. LEKTI-1 regulates KLK serine proteases. 15 mammalian serine proteases are KLKs. KLK5, KLK7, and KLK14 of the epidermal proteolytic cascade trigger pro-KLK5 and pro-KLK7 to activate the kallikrein activation cascade. Recently, matriptase and mesotrypsin activated pro-KLK5 and pro-KLK7.

LP73 inhibited KLK7 (IC50 = 0.063 M) and CFL33 KLK5 (IC50 = 7 M). CFL33 and LP73 impacted two NS patients' keratinocytes' pro-allergic and inflammatory cytokines. The invention is a compound of Formula 12, where N is 0 or 1, Z is O or S, R1 is one group chosen from hydrogen, C1-C7 alkyl, replaced, or not, by a halogen, hydroxyl, or O-R12 group, and R12 is a C1-C7 alkyl, CH2, or CH3. Both inhibit R1, R14, and R2 are selected from hydrogen, O-R14, a C1-C7 alkyl, a C3-C6 cycloalkyl, an aryl group, and a hetero alkyl group.

Benzopyran derivatives for treating Alzheimer's disease (AD)

Long-term central nervous system neurodegenerative illness AD affects more than 44 million individuals globally. Cognitive deterioration, behavioral abnormalities, and death result. Inflammation, oxidative/nitrosative stress, cholinergic transmission loss, tau protein buildup, metal ions, and amyloid (A) plaques cause AD. AD's origin is unknown.

These plaques are amyloid precursor protein peptide aggregates. Peptides vary. Brain fibrils occur more commonly than other aggregates from hazardous A1-42. AD clinical studies have reduced A production, increased A clearance, and prevented A aggregation.

CN201510402044 created AD medicines. A1-42 and MAO-A inhibitory benzopyran compounds were evaluated. Formula 13 and four compounds (67–70)

Compound 67 selectively inhibits MAO-A (673 nM) and MAO-B (714 nM) unlike Iproniazid. Three drugs exhibited A1-42 selectivity (60.1%, 20 M), whereas curcumin A showed 50.2%, 20 M.

Benzopyran derivatives treating the polycystic kidney disease

Genetic ADPKD. When tubule epithelial

cells grow abnormally, many fluid-filled cysts develop, enlarging the kidneys four to eight times normal and compromising renal function. Leakage and cyst-lining epithelial growth cause cysts. CFTR cysts. AMPK damaged CFTR chloride channel and mTOR signaling. mTOR regulates transcription, protein synthesis, cell development, and proliferation. Rapamycin inhibits mTOR. Rapamycin expands ADPKD animal cysts. LKBl directly activates AMPK. LKBl mutations activate mTOR and cancer.

WO2016073470 produced ADPKD medicines. Benzopyran derivatives. Figure 15 shows Formula 14 and compounds 71–74.

Compound 71 (BIT-11), a novel oxadiazole-based LKBl activator, increased p-AMPK/AMPK levels in human ADPKD cells, proving that the LBKl-AMPK pathway controlled energy metabolism. AMPK suppresses CFTR chloride channel and mTOR signaling. Compound 71 inhibits CFTR and mTOR by phosphorylating tuberous sclerosis protein 2 and raptor. Low ATP decreases energy-intensive transport, secretion, and development through AMPK. Compound 71 stimulates AMPK, inhibiting cyst development via secretory and proliferative pathways. 71–74 may work together. A novel LKBl activator suppresses human ADPKD cell mTOR-dependent proliferation and CFTR-mediated Cl secretion.

Benzopyran derivatives for antiviral

HBV kills 1.2 million people annually. Interferons and nucleoside analogs are used to treat HBV, however treatment resistance and high recurrence make them useless. notably Chirates. Innovative anti-HBV treatments are needed as Chinese drugs evolve. Chinese medicine has used physiologically active natural products for millennia.

CN201110208329 provides drug development benzopyran derivatives with diverse structures and bioactivities. Figure 16 shows Formulas 15, 15a, and 15b and 11 representative compounds (Compounds 75–85).

Benzopyran derivatives for antibacterial activity

Given the increased knowledge of the microbiome and the worldwide development of antibiotic-resistant pathogens, new infection-targeting methods are essential.

Anti-Helicobacter pylori activity

Helicobacter pylori, a gram-negative, S-shaped bacterium with polar flagella that lives near the stomach mucosa, is a WHO class 1 carcinogen. Chronic gastritis, gastroduodenal inflammation, and high infection rates connect H. pylori to stomach cancer and inflammation-related gastritis. Gastric illness may result. Clarithromycin and metronidazole-resistant H. pylori strains complicate therapy.

CN200910200178 created anti-H. pylori drugs. Figure 17 displays Formula 16 and six typical compounds, including Compound 86, which has anti-H. pylori activity and MIC values comparable to metronidazole, the positive control group (MIC = 0.5 g/ml).

Anti-methicillin-resistant Staphylococcus aureus (MRSA) activity

China, Japan, and Korea have hospital MRSA rates of 70%–80%. Jevons identified MRSA, a "superbug" associated to endocarditis, pneumonitis, toxic shock syndrome, and others, in 1961 in England. Its multidrug resistance to conventional medicines and global epidemiology of livestock-, community-, and healthcare-

associated illnesses make it notorious. Thus, MRSA-fighting drugs are urgently needed.

3. Expert opinion

Many biopolymer-interacting natural compounds contain a benzopyran motif. Bioactive benzopyran derivative synthesis has gained attention since Nicolaou and colleagues released a combinatorial library based on a new benzopyran template.

45 patents disclosed physiologically active benzopyran derivatives between 2009 and 2016. Physicochemical characteristics may affect benzopyran's biological effect. Methylation epigallocatechin (EGC) derivatives and gallocatechin derivatives are novel powerful, selective, noncytotoxic, and non-substrate P-gp modulators that exceed epigallocatechin gallate modulation.

Benzopyran-3-alcohol ester derivative P-gp inhibitors are less toxic and more effective against multiresistant malignancies. Anti-inflammatory and antioxidant benzopyran derivatives are well-known. Anti-inflammatory and anticancer benzopyran compounds rank high among physiologically active analogues. Anticancer activity by inhibiting MCT1, CYP1B1, P-gp, P13K/Akt, and AR-JunD, type 2 diabetes treatment, anti-inflammatory activity, arthritis, skin disease, AD, antimicrobial, antiviral, and polycystic kidney disease treatment are of interest.

Despite several substances to treat type 2 diabetes, cancer, and inflammation, metabolic issues, in vivo toxicity, and medication resistance persist. Drugs have slow-acting side effects. Twenty-plus SGLT2 inhibitors are in phase II and III trials. Europe authorized dapagliflozin in November 2012. Renal dysfunction prevents it. 2013 saw Europe and America approve canagliflozin. End-stage renal disease and severe renal impairment were warned against it.

We need molecular biologists, pharmacologists, medicinal chemists, and others to create novel drugs that heal and alleviate patient suffering. Pharmaceutical chemists create new benzopyran derivatives with unique structures using high-throughput screening and computer-aided drug design.

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