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BENZOPYRAN: A BIOLOGICALLY ACTIVE SCAFFOLD

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ABSTRACT

Many natural products (including hesperidin, warfarin, and genistein) as well as synthetic products have the benzopyran ring system. It demonstrates biological features of anticoagulants, anti-HIV, antimicrobials, anti-inflammatory, antitumor, and anti-cancer. chromene moiety can be able of reacting at the cellular level which results in their diverse functions, which include anticonvulsant, anti-HIV, antitubercular, anti-HIV, and anti-herbicide. analgesic effect. A vast spectrum of cellular targets (receptors) interacts with benzopyran derivatives which may be responsible for their various biological effects. It focuses on research into naturally occurring pyrans as anticancer medicines. Structure-activity connections, Pharmacological insights give us a deep understanding of how medications work on a molecular level. The most promising compounds for treating cancer have certain structures that allow them to fight cancer cells effectively. These compounds can target different types of cancer cells, and they can work in different ways to kill the cells. These scaffolds made of pyran promising effects undoubtedly position them at the forefront of pharmacological research. Therefore, this review aims to highlight the biological importance of major benzopyran analogues with biological activity.

Keywords: **Benzopyran, Importance of chromene, biological activity, Anticancer Activity**

1. INTRODUCTION:

In medicinal chemistry, the bicyclic heterocyclic system known as benzopyran has a privileged place, α-tocotrienol, γ-tocotrienol, and tocopherol (Vitamin E) are important nutrients that help keep our bodies healthy. They can be found in many foods, including nuts, seeds, and leafy greens, are among the natural chemicals that include the benzopyran unit, which bears a phytyl chain on the pyran ring. Benzopyran is a heterocyclic organic formed when a pyran ring with oxygen as a hetero element and a benzene ring connect, also known as chromene. It is known as chromenes in the IUPAC nomenclature system.

According to the literature, benzopyrans are significant chemical synthons connected to numerous biological activities Antioxidant, anti-HIV, neuroprotective, antiepileptic, antibacterial, antidiabetic, antihypertensive, and anticancer agents are examples of such compounds. As a result, various benzopyrans are involved. in the quest for innovative anti-breast cancer medications.

1.1. Breast Cancer:

According to the National Cancer Institute, the most frequently diagnosed cancer in women is breast cancer. It is also the second leading cause of cancer death in women. India is breast cancer. Despite the fact that chemotherapy is widely accepted as the foundation of cancer treatment **[1]**.

Breast and ovarian cancers are the principal factors of cancer mortality between women in the United States. According to studies, there were 555,000 national cancer deaths in India in 2010 **[2]**.

1.2. Selective estrogen receptor modulators (SERMs):

Estrogens are thought to be important in the onset and spread of breast cancer, consequently, it is acknowledged that ERs and oestrogens are important molecular targets for breast cancer.

Drugs classified as SERMs Some tissues respond to xenoestrogens as if they are estrogen, while others respond to them as if they are the opposite of estrogen. Genistein is a SERM that is being researched as a breast cancer preventative.

Long-term estrogen exposure may have major negative effects, including a greater risk of breast and uterine cancer as a result, ER blockers are the primary mode of treatment for breast cancer.

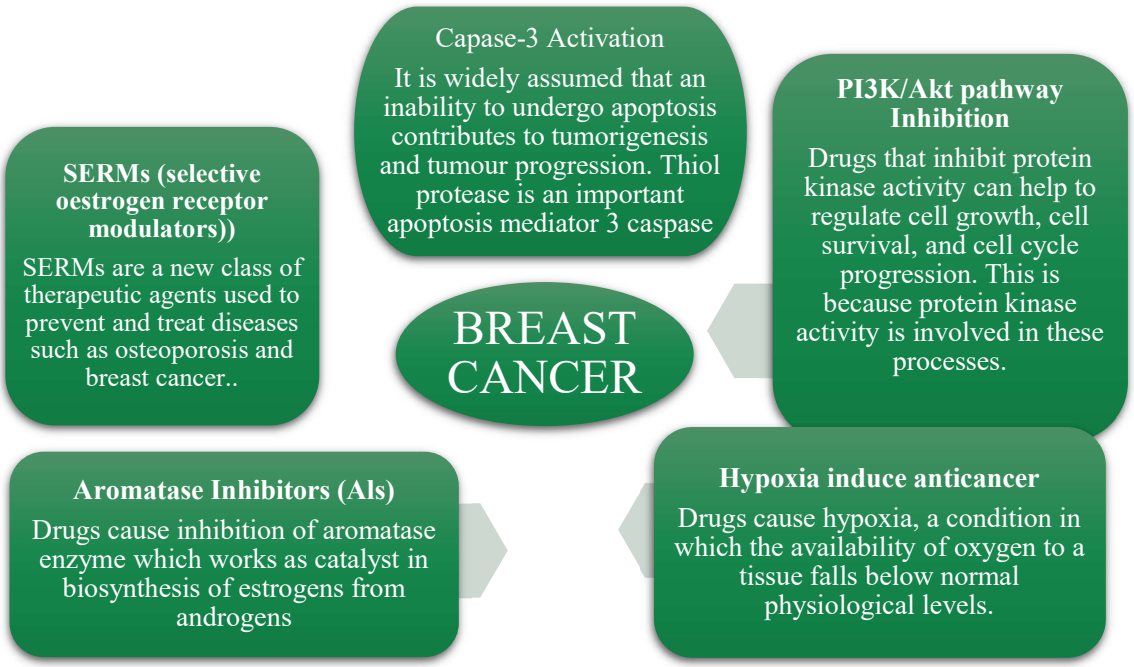


Figure 1: The Anti-Breast Cancer Drug's Mechanism of Action

1.3. Aromatase inhibitors (AIs): Aromatase, an enzyme complex of cytochrome P450, is inhibited during the manufacture of estrogen. The aromatase gene CYP19 encodes for this. Lower level of estrogen, production has an impact on AI. The production of estrogens from androgens uses the aromatase enzyme as a helpful catalyst. A considerable impact on the progression and spread of hormone-dependent breast tumors could be had by inhibiting the aromatase enzyme.

Benzopyrone is an excellent scaffold for the discovery of new adenosine A1/A2A receptor antagonists. Adenosine receptor antagonists are being researched as prospective therapeutic options for the treatment of some malignancies, neurological diseases, depression, and maybe improving tumor immunotherapy **[3]**.

1.4. Anticancer scaffolds based on pyran: The essential structural component of benzopyran, chromone, flavonoids, coumarin, flavonoids, and naphthoquinones, which have a range of pharmacological actions, is the pyran ring. Pyran heterocycles are prevalent in both natural and synthetic compounds. The medicinal properties of certain naturally occurring substances, such as pyrans and benzopyrans are fascinating, their structure, reactivity, synthesis, and biological characteristics set them apart, and they have raised substantial interest in the synthetic area.

The existence of the pyran scaffold (2H or 4H) determines pyran heterocyclic classification compounds **(Figure 1)** As a consequence, 2H-1-benzopyran is 2H-chromene, 4H-benzo[b]pyran-4-one (more commonly known as 4H-chromene) is the benzo analogue of 4H-pyran. 2H-naphtho [1,2, b] Interrelated naphthyl derivatives include pyran and xanthenes. Pyranones (also known as pyrones) are ketones produced from pyrans, with pyran-2-one and pyran-4-one being the parent molecules **[4]**.

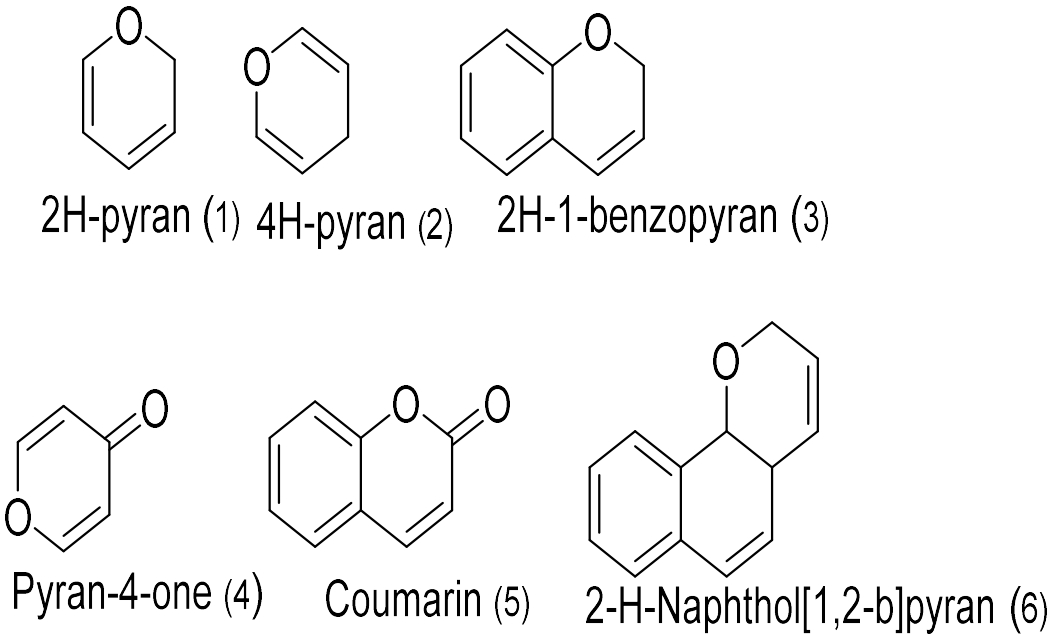


Figure 1: (Pyran-based heterocycle)

It is widely accepted that structural frames are preferred and modest heterocyclic molecules are the primary building blocks for physiologically active substances. Pyran skeletons are significant structural components that can be found in many natural products, such as sugars, coumarins, flavonoids, anthraquinones, etc Flavonoid-based pyran derivatives **Figure 2**) detected from Alpinia blepharocalyx seeds include epicalyxins F and G, as well as calyxes F, G, L, and I. Epicalyxin F is the most efficient anticancer medication In the human HT-1080 fibrosarcoma and murine 26-L5 carcinoma, researchers found that the addition of a small molecule inhibitor increased the sensitivity of the tumor cells to radiation treatment **[4]**.

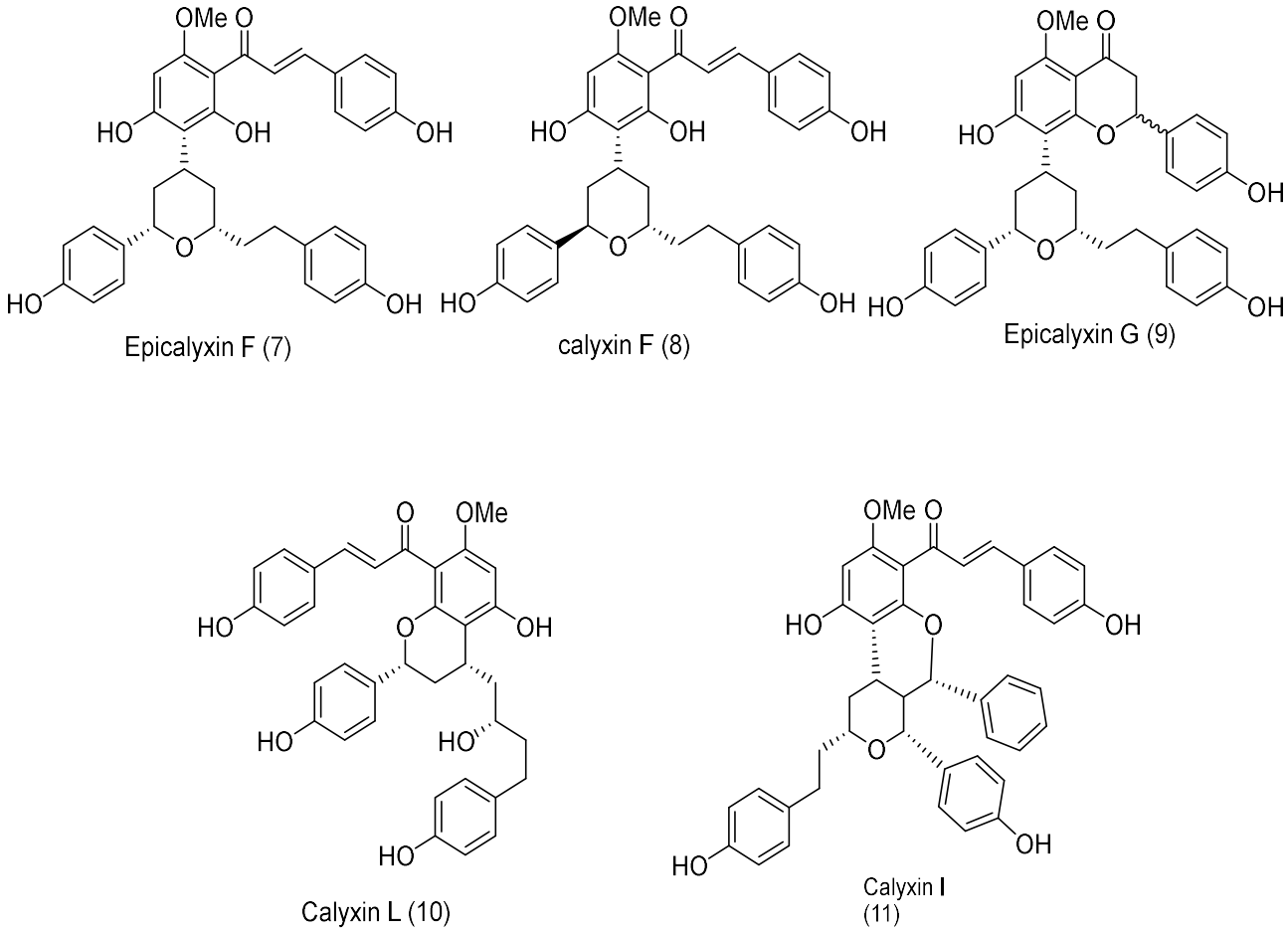


Figure 2: Natural pyran-based derivatives with the potential to cause cell damage

Lapachone (20, **Figure 3**), a bioactive metabolite with a variety of biological functions, is a classic example of a pyran derivative for instance anti-inflammatory, anti-bacterial, and anti-cancer properties. As a result, it is critical for therapeutic growth. Zanamivir **(Figure 3)**.

Furthermore, zanamivir was the first neuraminidase inhibitor to be produced for commercial use. GlaxoSmithKline is now selling this medication under the brand name "Relenza." A prodrug of is zanamivir octanoate **(Figure 3)**, which is given orally and shares structural similarities with zanamivir

Figure 3 shows commercially available pyran-based medicines available or undergoing preclinical or clinical evaluation. Many commercially available medicinal drugs include the pyran unit, according to a literature review. As a result of their extensive spectrum of biological activities, including their anticancer characteristics, benzopyrans and pyran-based chemicals have been fused a

significant group of structural motifs seen in many natural and manmade medications that have high levels of activity.

2-(2-benzofuranyl)-3-nitro was produced Anticancer activity of 4h (1)-benzopyran-4-ones. According to the literature, molecules with 3-nitro-4-hydroxycoumarins are examples of carbonyls flanked by nitro groups demonstrate effective anaphylactic action. The resulting chemicals are tested for anti-cancer properties **[5]**.

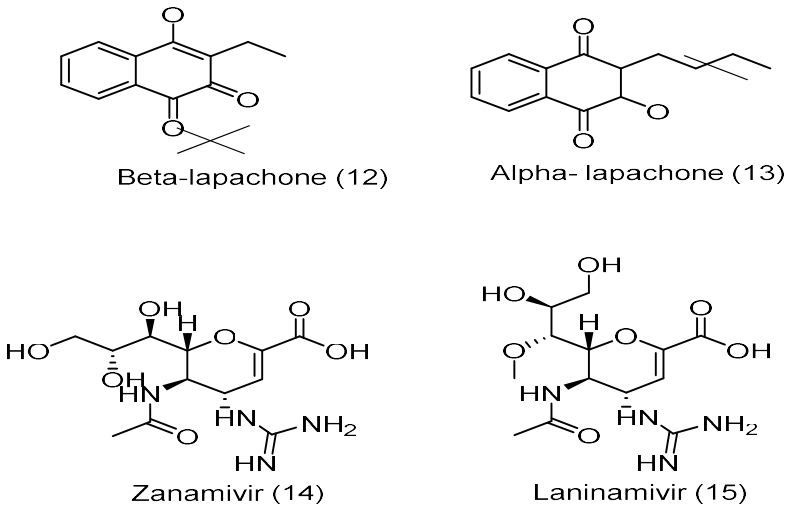
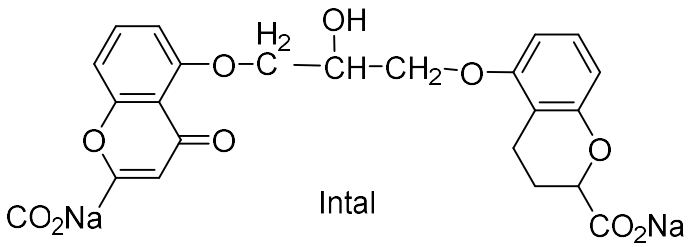


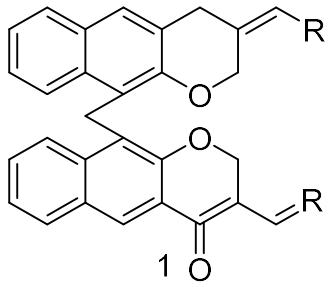
Figure 3: Natural and synthetic commercialized pyran-based medications in preclinical/clinical studies

2. The Biological Importance of Chroman Derivatives:

Chromans are incredibly essential in biology, particularly as potential pesticides and drugs**.** Disodium cromoglycate, also known as Intal or Cromolyn sodium, is structurally similar to khelin, a component of spasmolysis Ammivisnaga seeds. Intal is one of the most widely used effective asthma medications for avoiding attacks, however it is inefficient for treating acute asthma attacks.



A number of antiallergic 3-(1H-tetrazol-5-yl) chromones were synthesized and created a variety of insecticidal chromanones and chromone analogs from diacylhydrazine derivatives. These substances were tested Aphis medicagini, Nilaparvata legen, Mythima separata, and Tetranychus cinnabarinus are all susceptible to this new treatment. for their insecticidal action and others. Calophyllum brasiliense, isolated Cambers chromanone acids from *Staphylococcus epidermidis* with *Bacillus cereus*. Bis-chromanones found to be efficient against *Staphylococcus aureus* and *Staphylococcus faecalis* **[6]**.



Created a novel class of compounds including chromone and chromanone that can suppress HIV-1. Some new chroman and chromanone compounds have antitubular and antibacterial properties **[7]**. Generated and tested several new A classes of 4H-chromeno[2,3-d] pyrimidines were synthesized and evaluated for their antitubercular and antibacterial activities. The results showed that some of these compounds had good activity against both bacteria and tuberculosis. These findings suggest that 4H-chromeno[2,3-d] pyrimidines have potential as new antitubercular and antibacterial agents. 2-amino-4-phenyl-4H-chromene-3-carbonitriles are a new class of compounds that have a wide range of potential applications. The results of the study showed that these new compounds show promise as potential antitubercular and antibacterial agents **[7-8]**.

Isolated chromene derivatives and found to modulate the carcinogen metabolizing enzyme CYP1A (P-450 1A Cytochrome) in summary, the findings point to chroman's strong inhibitory capabilities against CYP1A activity in murine hepatoma cells. In tests, chroman was able to lower CYP1A activity by up to 60%, as well as dramatically lower GST (Glutathione S transferases) levels. The isolated chroman has strong selective DNA

damage was produced by the radical scavenging activity against hydroxyl radicals **[9]**. The anti-platelet activity of the compounds was evaluated and found to be these chromenes possessed inhibitory activity against rabbit blood platelet aggregation induced by ADP *in vitro* **[10]**.

The 6-bromo-2-methyl-2H-chromene substructure is a typical anticancer drug that has the best cytotoxicity profile, comparable to cisplatin **[11]**.

The primary nucleus of the naturally occurring chemical family known as flavonoids is the chromane structure. Flavonoids are a group of chemicals that contribute to the taste, smell, and nutritional value of many plants and fruits. Furthermore, they have been linked with HIV prevention, tumor reduction, cancer prevention, antioxidant properties, anti-aging effects, inflammation reduction, and bacteria prevention. activities, certain Flavonoids are crucial nutraceutical components that help protect against chronic diseases

Because of their biological and pharmacological properties, chromene, benzochromene, and their derivatives have received substantial research. The benzochromene nucleus has emerged as an intriguing framework for the production of powerful anticancer drugs **[12]**. A number of novel Two-amino-four-hydroxy-benzochromene derivatives were synthesized in order to investigate their potential use as antiproliferative agents against three human cancer cell lines - MCF-7, HepG-2, and HCT-116 **[13]**.

3. Chromene derivatives and pharmacological activities:

Chromens are a unique class of phytochemicals that have distinct therapeutic properties that can be utilized for pharmacological purposes. Some of the derivatives and their associated pharmacological effects are detailed below

3.1. Anticancer Activity of Chromene:

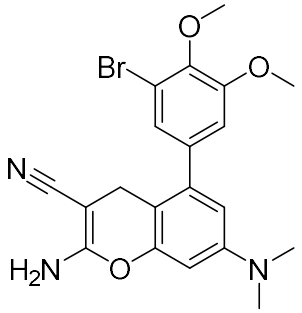
Cancer is a major health problem worldwide that requires serious attention and care. Thus, for decades, researchers have been charged with devising viable cancer therapy treatments. Aside from in addition to surgery and radiation, chemotherapy is an essential cancer treatment option. Despite the fact that chemotherapy medications Cancer treatment often involves the use of 5-fluorouracil, cisplatin, paclitaxel, and docetaxel. These drugs work to kill cancer cells or stop their growth, the disease remains tenacious and lethal **[11]**.

Chromene moieties have been linked to anticancer action in a variety of natural substances. These substances come from

naturally existing herbal plants as well as animals like aquatic creatures **[14-15]**.

Some of the natural anticancer medicines that contain the chromene ring include Tephrosin, Calanone, Acronycine, and Seselin. These drugs have been tested for their potential use in treating various types of cancer, including lung cancer, leukaemia, cervical carcinoma, colon cancer, and ovarian cancer.

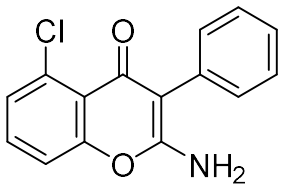
Four-aryl-4Hchromene compounds are a subclass of microtubule inhibitors. Attachment of the aryl group at the fourth position of a molecule enhances its potential to fight cancer, according to the National Institutes of Cancer (NIOC) laboratory in Bethesda, Maryland **[16]**.



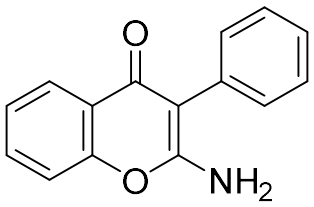
2-amino-5-(3-bromo-4,5-dimethoxyphenyl)-7-(dimethylamino)-4H-chromene-3-carbonitrile

A new method for synthesizing 4H-chromeno[2,3-d] pyrimidines has been developed. These compounds have shown antitubercular and antibacterial activity *in vitro* **[8]**.

Produce and test 2-amino-3-phenyl-4H-chromene-4-ones for carbonic anhydrase inhibition. These compounds are extremely active **[17]**.



chloro-2-amino-3-phenyl-4H-chromen-4-one



2-amino-3-phenyl-4H-chromen-4-one

3.2. Antitumor Activity of fused chromones

No	Name	Source
1	Coniochaetone	*H Fimetariella sp. (fungus)*
2	Oxalicumone A	*Penicillium oxalicum (fungus)*
3	Oxalicumone b	*Penicillium oxalicum (fungus)*
4	Oxalicumone D	*Penicillium oxalicum (fungus)*
5	Oxalicumone E	*Penicillium oxalicum (fungus)*
6	3,3-Dimethylallylspatheliachromene	*Cneorum tricoccum, Dictyoloma vandellianum A. Juss*
7	Pulverochromenol	*Cneorum tricoccum*
8	methyl ether of 3,3-dimethylallylspatheliachromene	*Dictyoloma vandellianum A. Juss*

4. Antitubercular Activity: Tuberculosis is a serious, contagious disease caused by Mycobacterium bacteria. It usually attacks the lungs, but it can also damage the brain and other parts of the body such as the digestive system, urinary system, reproductive organs,gastrointestinal system, and more **[16]**. coumarin-based acylhydrazones are effective against Mycobacterium TB H37Rv, and compares favorably to existing antituberculosis medicines such as isoniazid and ethambutol. Coumarin-based acylhydrazones were tested against Mycobacterium TB H37Rv, a reference strain, for in vitro antimycobacterial efficacy The three compounds displayed antimycobacterial action sub micromolar concern and were compared to the first-line antituberculosis medicines, isoniazid (INH) and ethambutol (EMB). These compounds, (R = Ph, Ar = 4-MeOPh; MIC 0.13 M), (R = Ph, Ar =2-furyl; MIC 0.15 M), and (R = Me, Ar = 4-pyridyl; MIC 0.17 M) could potentially be used as new antituberculosis medicines **[18]**.

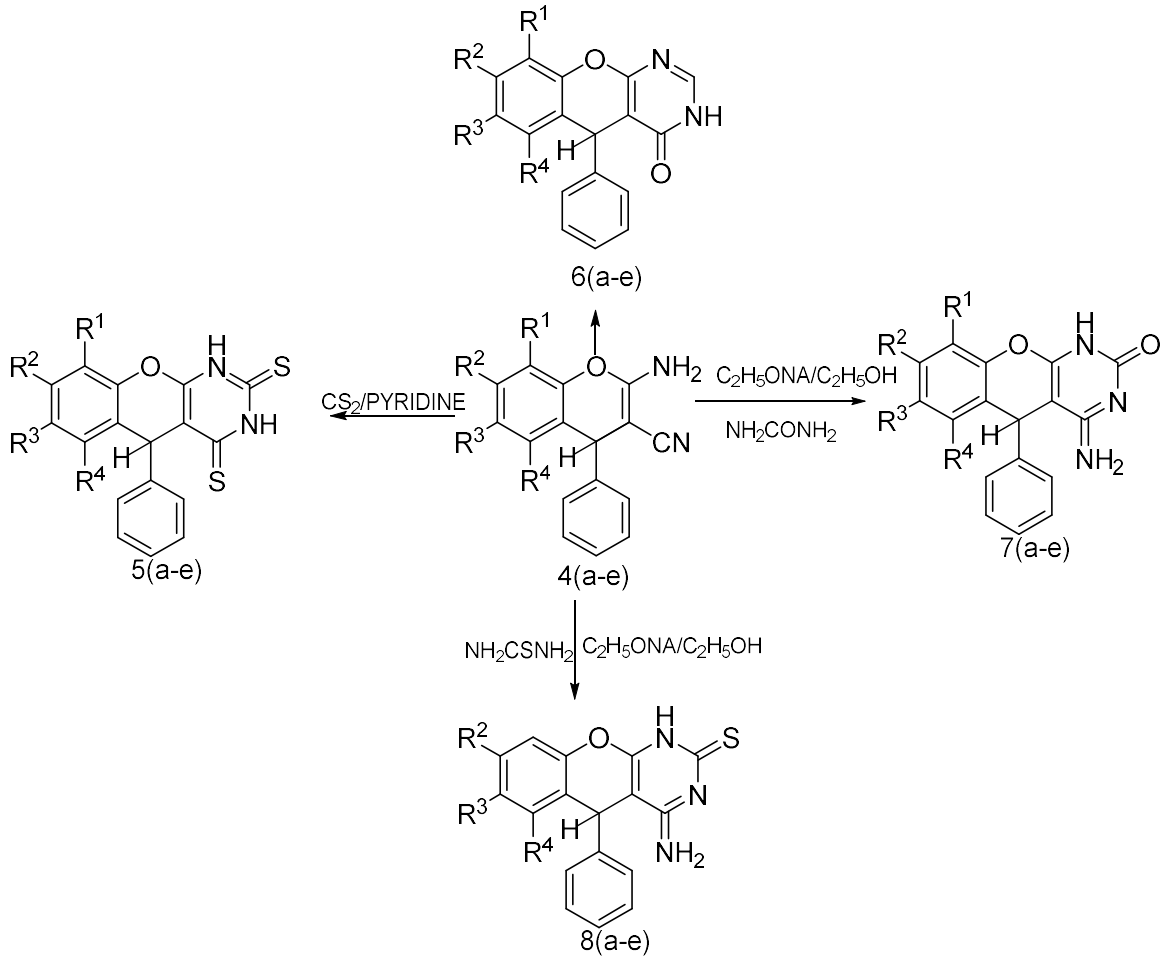
The agar dilution technique to synthesis a variety of the objective of this study was to investigate the in vitro antimycobacterial activity of 4H-chromen-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives against Mtb H37Rv **[19]**. The

results showed that these compounds have potential for the treatment of tuberculosis **[19]**.

4.1. Antitubercular and antibacterial activities of certain new 4H-chromeno[2,3-d] pyrimidines synthesized through 2-amino-4-phenyl-4H-chromene-3-carbonitrile:

Chromene derivatives have lately received a lot of interest due to their pharmacological and biological relevance The purpose of this study was to initiate the synthesis of chromene-pyrimidine hybrids with substituted chromene-3-carbonitrile 4(a-e) by cyclization using carbon disulfide 5(a-e), formic acid 6(a-e), urea 7(a-e), and thiourea 8(a-e).

Scheme 1 Compounds 5, 6, 7, 8 (a-e) synthetic route:



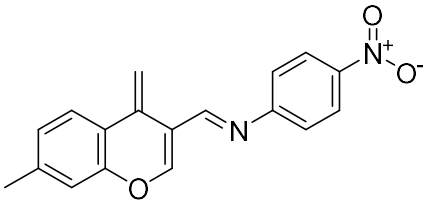
All of the chemicals synthesized in this investigation were evaluated for possible biological properties Antitubercular, antibacterial, and antifungal properties are only a few examples. Antitubercular activity against Mycobacterium tuberculosis H37Rv

was shown (ATCC-27294). Out of all the compounds tested, pyrimidine-4-one 6b had the highest activity against mycobacteria (62.5 lg/ml) **[16]**.

4.3 Antimicrobial activity of a chromene derivative: Antimicrobials are drugs that kill or inhibit the growth of germs **[21]**.

Antibacterial activity of the synthesized Schiff bases and chalcones was investigated against *Staphylococcus aureus* and *Bacillus subtilis* as well as two Gm-ve species *Escherichia coli* and *Pseudomonas aeruginosa* **[16, 20]**.

The in vitro evaluation of novel hydrazide-hydrazone compounds with a 2H-chromene and coumarin scaffold has shown them to have antimycobacterial action **[22]**.



12E-N-((7-methyl-4-methylene-4H-chromen-3-yl)methylene)-4-nitrobenzenamine

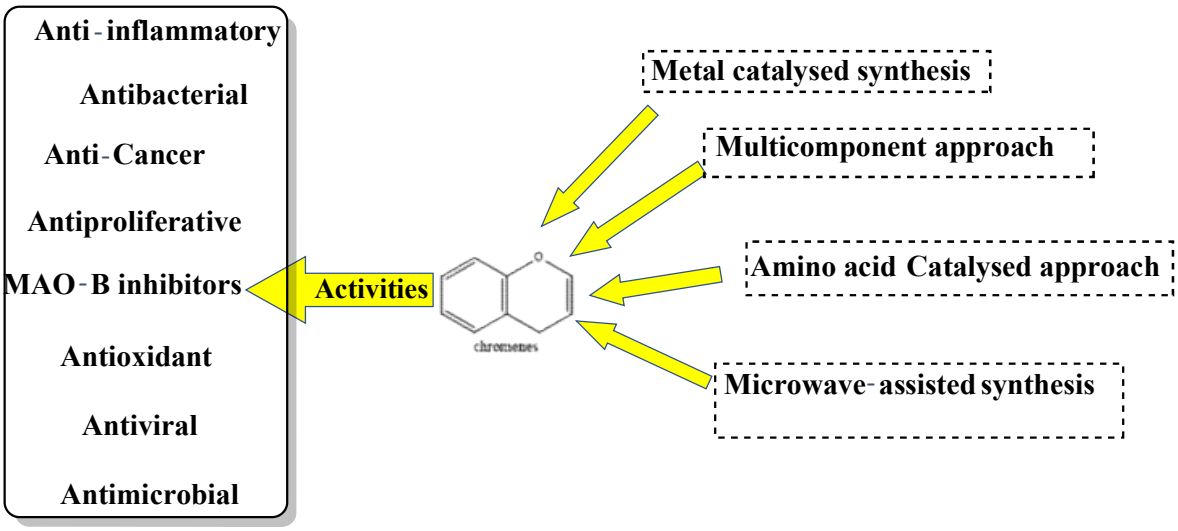


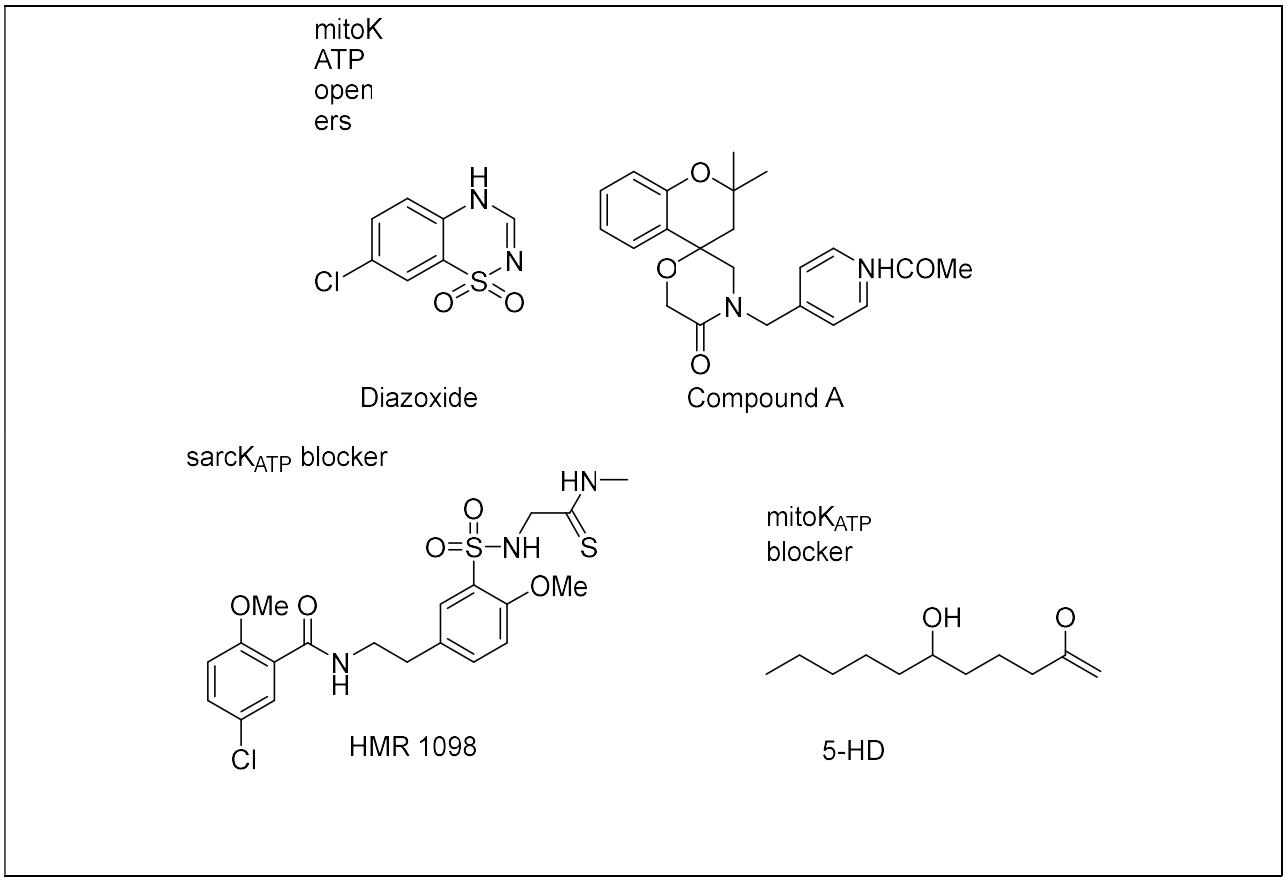
Chart 1: Shows the activity of chromen

Life-threatening ventricular arrhythmias are particularly common in patents with ischemic heart disease. Following a myocardial infarction, antiarrhythmic drugs are administered, as well as reperfusion (reoxygenation) of the ischemic heart tissue **[23]**.

However, antiarrhythmic medications have shown little efficacy in suppressing arrhythmias and preventing sudden cardiac death, Antioxidants such as C-tocopherol have been shown to reduce membrane-related alterations produced by ischemia and reperfusion **[24]**.

As a result, it would be useful to produce bifunctional drugs that act as antiarrhythmic antioxidants. These bifunctional medicines should preferentially segregate in the membrane and exert antiarrhythmic effects while also preserving the membrane lipids by scavenging free radicals **[25]**.

5. A novel spiro-cyclic benzopyran that activates ATP-dependent potassium channels in the heart exhibits antiarrhythmic properties.:



SarcKATP may also be exploited as a pharmaceutical target to reduce Arrhythmias of the ventricle during ischemia and reperfusion (Billman 2008). Recent research has shown that blocking sarcKATP with HMR 1098 (a specific sarcKATP blocker) and activating mitoKATP with diazoxide are both effective. A specific mitoKATP activator) decreasing the duration of ventricular arrhythmias. The antiarrhythmic activity of HMR 1098 on sarcKATP inhibition is possibly due to the maintenance of electrical stability between ischemic and nonischemic myocardium. The antiarrhythmic effects of sarcKATP inhibition and mitoKATP activation are thought to be based on separate pathways, we anticipated that combining these two distinct impulses at the same time would result in a greater antiarrhythmic impact. If this idea is right, it might lead to the development and use of combination antiarrhythmic medications with both mitoKATP activation and sarcKATP inhibition capabilities. The combination of diazoxide and compound A, both of which activate mitoKATP, with HMR 1098, a selective sarcKAT. The resulting effect on I/R-induced ventricular arrhythmias was studied **[26]**.

6. CONCLUSION:

TB remains the number one cause of death from a single pathogen, and is projected to infect one million children in 2017. This high number is a motivation for the global scientific community to continue research and development to find a cure for this illness. Benzopyrans are a common type of natural compound with a wide range of medicinal uses. The benzopyran scaffold is a key building block for many chroman and coumarin molecules found in nature and in pharmaceuticals. Benzopyran is a widely studied class of molecule due to its diverse range of potential biological applications, particularly against cancer.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

7. REFERENCES:

[1] Kumar Piyush, Singh Kuldeep, Rahman Md. Azizur, Hasan Syed Misbahul, Wal Pranay., 2018. A Review of Benzopyran Derivatives In

Pharmacotherapy Of Breast Cancer, Asian J Pharm Clin Res, Vol 11, Issue 7, pp.43-46.

[2] Polu, Picheswararao, Udupa Nayanabhirama, and Saleemulla Khan., 2015."Herbal medicinal plants as an anticancer agent." Annals of Phytomedicine 4.1 pp.37-45.

[3] M.M. van der Walt, G. Terre'Blanche., 2018. Benzopyrone represents a privilege scaffold to identify novel adenosine A1 / A2A receptor antagonists, Bioorganic Chemistry.

[4] Dinesh Kumar, Pooja Sharma, Harmanpreet Singh, Kunal Nepali, Girish Kumar Gupta, Subheet Kumar Jaina and Fidele Ntie-Kang., 2017. The value of pyrans as anticancer scaffolds in medicinal chemistry, RSC Adv, pp.36977–36999

[5] Chebrolu, Papa Rao; Masna, Rakesh., 2005. Synthesis and anti-cancer activity of 2-(2-benzofuranyl)-3-nitro-4h (1)-benzopyran-4-ones, m Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States.

[6] Tapas Kumar Mandal., 2015. Biological importance of 4H-1-benzopyran and derivatives, Prajnan O Sadhona Vol. 2, pp.180.

[7] Park, J. H.; Lee, S. U.; Kim, S. H.; Shin, S. Y.; Lee, J. Y.; Shin, C.-G.; Yoo, K. H.; Lee, Y. S., 2008. Chromone and Chromanone Derivatives as Strand Transfer Inhibitors of HIV-1 Integrase. Arch. Pharm. Res 31.

[8] Nimesh R. Kamdar, Dhaval D. Haveliwala, Prashant T. Mistry, Saurabh K. Patel., 2011. Synthesis and evaluation of in vitro antitubercular activity and antimicrobial activity of some novel4H-chromeno[2,3-d] pyrimidinevia2-amino-4-phenyl-4H-chromene-3-carbonitriles, Medicinal chemistry Research volume 20, pp.854–864

[9] AmiraM.Gamal-Eldeen,AhmedAbdel-Lateff,TatsufumiOkino.,2009.Modulationof carcinogen metabolizing enzymes by chromanone A; a new chromone derivative from algicolous marine fungus Penicillium sp. Environmental Toxicology and Pharmacology pp. 317.

[10] Hu, Chun Qiu, Zhiyuan, Wang, Yongyong Xiao, Gaokeng; Song, Liyan; Pang, Yan., 2010. Synthesis and anti-platelet aggregation activity of Mannich base derivatives of 4-chromanones, ingxi Huagong Zhongjianti, 40(2), pp. 18-21.

[11] Mohammad Aziz Mohammadi, Mehdi Khoobi, Ali Ramazani, Saeed Emami, Abdolhossein Zarrin, Omidreza Firuzi, Ramin Miri, Abbas Shafiee., 2013. 2H-chromene derivatives bearing thiazolidine-2,4-dione, rhodanine or hydantoin moieties as potential anticancer agents, European Journal of Medicinal Chemistry, pp. 15-22.

[12] Meng, L.; Wang, J.J., 2018. Recent Progress on Asymmetric Synthesis of Chiral Flavanones, Chromanones, and Chromenes. In Advances in Organic Synthesis; Atta-ur-Rahman, Ed.; Bentham Science: Sharjah, UAE, Volume 11, pp. 1–42.

[13] Hamed, Hany M. Fouda, Ahmed M. Khattab, Essam S. A. E. H., El-Agrody, Ahmed M., 2017. Synthesis, Molecular Properties and Evaluation of the Antitumor Activity of 2-Amino-6-Methoxy-4H-Benzo[h]Chromenes, 6-Methoxy-2-Oxo-2HBenzo [h] Chrome, Current Bioactive Compounds, pp.356-369

[14] K. Kanagalakshmi, M. Premanathan, R. Priyanka, B. Hemalatha, A. Vanangamudi(2010) .Synthesis, anticancer and antioxidant activities of 7-methoxyisoflavanone and 2,3-diarylchromanones, European Journal of Medicinal Chemistry **,**pp**.**2447-2452.

[15] D.H. Nama, K.Y. Lee, C.S. Moon, Y.S. Lee., 2006. Synthesis and anticancer activity of chromone-based analogs of lavendustin A, European Journal of Medicinal Chemistry pp.4288-4292.

[16] Ravi Kant Kushwaha, Kuldeep Singh, Piyush Kumar, Dinesh Chandra (2019). Review on Chromen derivatives and their Pharmacological Activities, Research J. Pharm. and Tech. 12(11): November pp. 5570-5571.

[17] Gianfranco Balboni a, Cenzo Congiu a, Valentina Onnis a, Alfonso Maresca b, Andrea Scozzafava b,Jean-Yves Winumc, Annalisa Maietti d, Claudiu T. Supuran b., 2012. Flavones and structurally related 4-chromenones inhibit carbonic anhydrases by a different mechanism of action compared to coumarins; Bioorganic & Medicinal Chemistry Letters ,pp. 3063–3066

[18] Angelova, Violina T., Valcheva, Violeta Vassilev, Nikolay G.Buyukliev, Rosen Momekov, Georgi; Dimitrov, Ivan; Saso, Luciano; Djukic, Mirjana, Shivachev, Boris ., 2017. Antimycobacterial activity of novel hydrazide-hydrazone derivatives with 2H-chromene and coumarin scaffold, Bioorganic & Medicinal Chemistry Letters pp. 223-227.

[19] Raju CB, Nageswara R, Suman P, Yogeeswari P, Sriram D, et al., 2011. Synthesis, structure–activity relationship of novel substituted 4H-chromen-1,2,3,4-tetrahydropyrimidine-5-carboxylates as potential anti-mycobacterial and anticancer agents. Bioorg Med Chem Lett, pp. 2855–2859

[20] Golus J, Sawicki R, Widelski J, Ginalska G., 2016. The agar microdilution method - a new method for antimicrobial susceptibility testing for essential oils and plant extracts. J Appl Microbiol 121(5), pp. 1291-1299

[21] H.M. E1-Shaaer, P. Foltfnova, M. Lacova, Chovancova, H. Stankovicova., 1998. Synthesis, antimicrobial activity and bleaching effect of some reaction products of 4-oxo-4H-benzopyran-3- carboxaldehydes with aminobenzothiazoles and hydrazides, II Farmaco pp. 224-232

[22] Violina T. Angelovaa, Violeta Valchevab, Nikolay G. Vassilevc, Rosen Buyuklieva, Georgi Momekovd, Ivan Dimitrova, Luciano Sasoe, Mirjana Djukicf, Boris Shivachev., 2017. Antimycobacterial activity of novel hydrazide-hydrazone derivatives with 2*H*-

chromene and coumarin scaffold Bioorganic & Medicinal Chemistry Letters page no 1-16.

[23] Maria Koufaki, Athens (GR): Theodora Calogeropoulou, Athens (GR); Alexandros Makriyannis, Boston, MA (US)., 2002. Preparation of substituted benzopyrans as bifunctional agents possessing antioxidant and antiarrhythmic activity, PCT Int. Appl

[24] Woosley R. L., 1991. "Antiarrhythmic drugs' Annu. Rev. Pharmacol. Toxikol., 31, pp.427.

[25] Michael J. Shattock Peter S. Haddock., 1995. 4 - Oxidant Stress and the Heart: Modulation of Ion Transport Mechanisms During Ischaemia and Reperfusion, Handbook of Immunopharmacology**,** pp.53-72.

[26] Ecrsoz Gonca, Simona, Rapposelli, Faruk, Darıcı, Maria Digiacomo & Zehra Yılmaz., 2016. Antiarrhythmic activity of a new spiro-cyclic benzopyran activator of the cardiac mitochondrial ATP dependent potassium channels Archives of Pharmacal Research volume 39, pp.1212–1222.