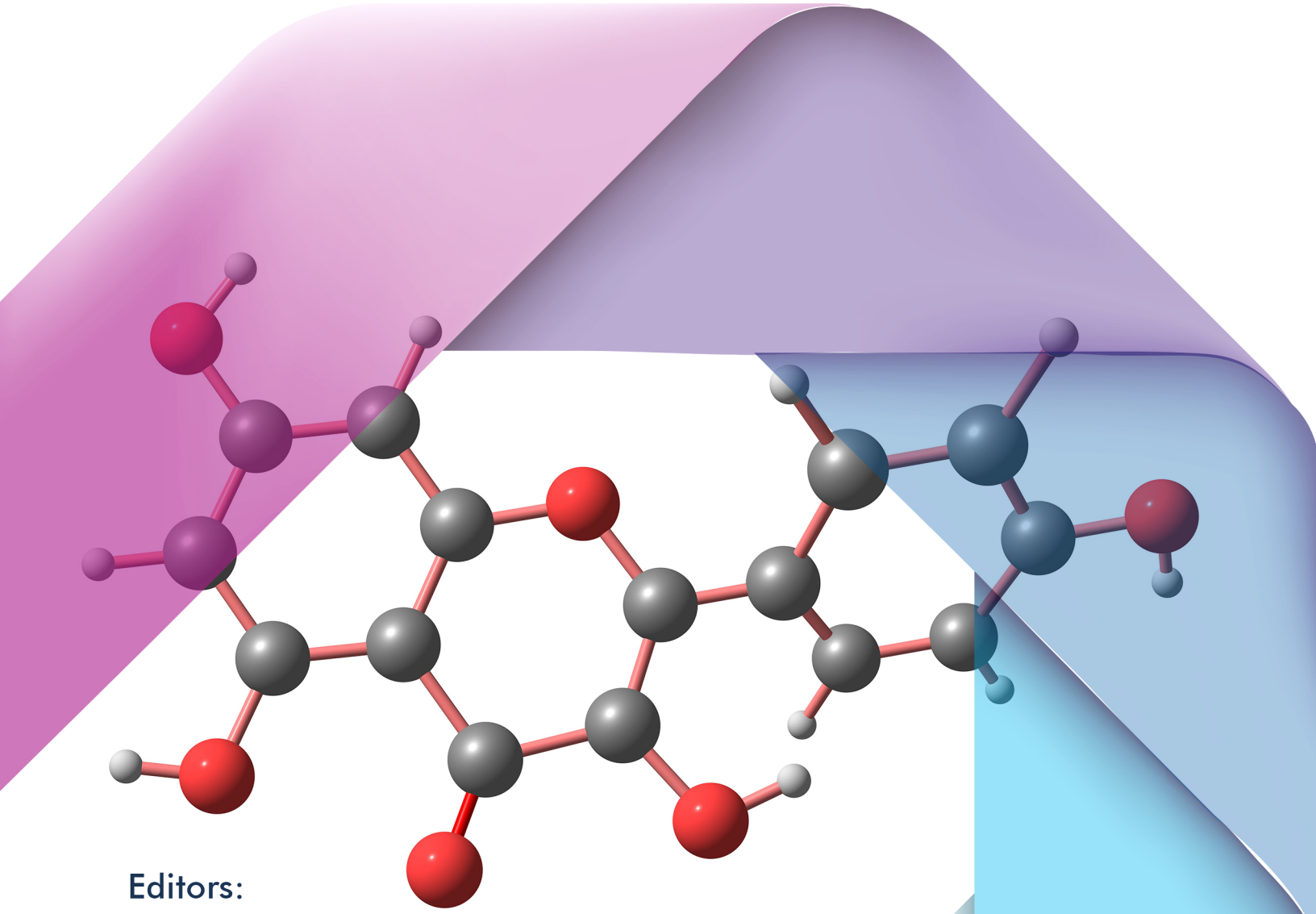
THE ROLE OF CHROMENES IN DRUG DISCOVERY AND DEVELOPMENT



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The Role of Chromenes in Drug Discovery and Development

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PREFACE

Chromene is a natural compound together with a synthetic scaffold that epitomizes a privileged structural motif rampant in many biologically active compounds.. This framework is present in more than 5000 compounds including natural products and synthetically designed structures. The contribution of nature to these molecules is quite enormous. It can be metamorphosed into several other forms such as flavones, flavonoids, flavans, flavonols, isoflavonoids, rotenoid isoflavones, anthocyanidins, coumarins, *etc.* Several studies proclaimed that chromenes/flavones/benzopyrans exhibit various biological activities such as excellent anticancer and antioxidant activites.

The antioxidant capacity of these molecules can be attributed to the presence of various functional groups and the detailed reason can be explained as follows. The ortho hydroxyl group attached to the phenyl ring at 2-carbon can interact with a free hydrogen radical and make an intermolecular hydrogen bond, thus scavenging the activity of the free radical. 2,3-Olefinic bond with 4-keto functional group delocalizes an electron resulting in a semiquinone radical. Tocopherol or ascorbic acid may interact synergistically and thus increase antioxidant activity. Chromenes can chelate oxidizing metal ions by preventing oxidation. Besides this, chromene fused with sugar moieties called chromene glycosides is also discussed.

Based on the high importance of the chromene scaffold, we will discuss its synthetic approaches with diversity-orientation. Chromene as a drug/drug-like/bioactive molecule will be the prime focus of the book, and is studied with relevance to several human health issues. Naturally present chromene glycosides and their applications with nutraceutical values will be discussed. The book will also shed light on corona virus with respect to chromenes.

The proposed book “The role of Chromenes in drug discovery and development” is an outstanding collection of contemporary research on chromenes as well as their versatile applications. This book will provide a comprehensive scientific advancement that has taken place in the field of organic and medicinal chemistry. This book will serve as a reference for professionals, students, scientists, research scholars, and academicians in drug discovery and development.

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CHAPTER 1

Chromene and its Importance: Chemistry and Biology

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Abstract: Chromene (benzopyrans) is one of the privileged scaffold molecules that are widely distributed in natural products and possesses a wide variety of pharmacological activities such as anticoagulant, antioxidant, anti-inflammatory, anti-spasmolytic, antitumor, antihepatotoxic, diuretic, estrogenic, antiviral, antifungal, antimicrobial, anthelminthic, anti-HIV, antitubercular, herbicidal, anticonvulsant and analgesic. Their low toxicity combined with their broad pharmacological properties has inspired researchers to obtain new chromenes and derivatives possessing considerable pharmacological action. The present review article attempts to summarize the natural source of chromene and its derivatives along with updated knowledge on its biological activities.

Keywords: Benzpyrans, Biological activity of Chromenes, Chemistry of Chromenes, Chromenes, Natural compounds.

INTRODUCTION

Chromene belonging to the family of lactones is a well-known, naturally occurring aromatic bicyclic heterocyclic compound. It consists of a benzene ring that is fused to an oxygen-containing pyran heterocyclic ring. It exists as mainly four structural isomers (Fig. **1**) resulting from the multiple relative positions of the oxygen atom and the tetrahedral carbon atom, namely, 2H-chromene, 4H-chrome-

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ne, 1H-isochromene, and 3H-isochromene [1]. Out of these isomeric forms of chromenes, 2H-chromene and its benzo fused derivatives are widely distributed in various plant species including fruits and vegetables and seem to be important for the chemical defense of plants as well as for the treatment of a wide range of pharmacological activities like anti-inflammatory, antipyretics, antioxidant, bronchodilator, vasodilator, anti-amoebic, antibacterial and antifungal activities as well as for the management of neurodegenerative disorders including Alzheimer's and Schizophrenia [2, 3]. For thousands of years, various chromenes and chromene derivatives have been used in different traditional systems of medicine. This important chemical moiety encompasses the fundamental skeleton structure for various phytoconstituents such as natural alkaloids, coumarins, flavonoids, polyphenols, anthocyanins, and tocopherols [4, 5]. The published literature review states that, to date, several bioactive chromenes and their various derivatives have been isolated and separated from various natural sources as well as have been well studied for their biogenetic pathway and biosynthesis. This chemical moiety has been recognized by research scientists due to its low toxicity profiles in addition to broad biological activities [6, 7].

CHROMENE-CONTAINING PLANTS

Table **1** indicates the list of various plant sources from which chromenes and their derivatives were separated and isolated and were found to possess marked pharmacological activities. Fig. (**1**) shows the structure of some important chromenes derived from plants.

Table 1. List of plants containing chromenes and their derivatives.

S. No	Botanical Source (Common Name)	Family	Plant Part	Example	Refs.
1.	*Ageratin aadenophora*	Asteraceae	Leaves	Demethoxyencecalin, encecalinanddemethylencecalin	[8]
2.	*Ageratum conyzoides* L.	Asteraceae	Whole plant	2,2-dimethylchromene-7-methoxy-6-O-β-D-glucopyranoside	[9]
3.	*Ageratum conyzoides* Linn	Asteraceae	Essential oil	Precocene I, II 2-(1′-oxo-2′-methylpropyl)-2- methyl-6,7-di methoxy-chromene2-(1′-oxo-2′-methyl propyl)-2-methyl-6,7-dimethoxy-chromene;2-(2′-methylprop-2′-enyl) -2-Methyl-6,7-dimethoxychroman-19-on	[10]
4.	*Alternanthera sessilis*	Amaranthaceae	Leaves	3,3'-(propane-2,2-diyl)-bis-(3,4,5,6,7,8-hexahydro-1*H*-isochromene	[11]

(Table 1) cont.....

S. No	Botanical Source (Common Name)	Family	Plant Part	Example	Refs.
5.	*Amoorarohituka* (Roxb.) Wight &Arn. *Dysoxylumbinectariferum* (Roxb.) Hook. F. ex Hiern *Schumanniophyton magnificum* Harms *Schumanniophy-tonproblematicum* (A. Chev.)	Meliaceae Meliaceae Rubiaceae Rubiaceae	leaves and stem stem bark Bark Bark	Rohitukine	[12 -15]
6.	*Bourreriapulchra*	Boraginaceae	Root	6,6-dimethyl-2-methoxy-6*H*-benzo (c) chromen-9-yl)methanol; 2-methoxy-6,6-dimethyl-6*H*-benzo (c) chromen-9-carbaldehyde	[16]
7.	*Caleahispida*	Asteraceae	Essential oil from leaves	6-acetyl-7-hydroxy-2,2-dimethylchromene	[17]
8.	*Caleapinnatifida* (R. Br.) Less.	Asteraceae	Leaves	6-acetyl-7-hydroxy2,2-dimethylchromene; 6-(1-hydroxyethyl)-7-methoxy-2, 2-dimethyl chromene;6-(1-ethoxyethyl)-7-methoxy-2,2 dimethylchromene	[18]
9.	*Calophyllum cordatooblongum*	-----	Stem bark	Isocordato-oblongic acid	[19]
10.	*Calophyllum dispar*	Clusiaceae	fruits and stem-bark	isodispar A, disparinol D, disparpropylinol B, dispardiol B, mammea A/AB cyclo E, mammea A/AB dioxalanocyclo F	[20]
11.	*Calyptranthestricona*	Myrtaceae	Essential oil of leaves	Chromene I and II	[21]
12.	*Cannabis sativa*	Cannabaceae	-----	Δ9-Tetrahydrocannabinol, cannabichromene, and cannabinol	[22]
13.	*Cassia sieberiana*DC	Fabaceae	Leaves	2-(4- hydroxylphenyl)-7'-1, 2-dihydroxy-1-phenylpropyl)-4', 6'-dihydroxy [1] phenylbenzofuro (2, 3-c)-7'-chromene	[23]
14.	*Eupatorium toppingianum*	Compositae	Leaves	6-acetyl-7, 8-dimethoxy-2,2- dimethylchromene	[24]
15.	*Flemingiagrahamiana* Wight&Arn	Leguminosae	Leaves	Flemingins A-C, G-N	[25]
16.	*Dasymaschalonrostratum*	----	Alternaria sp.ZG22 (fungal strain)	Alternapyran	[26]
17.	*Koeberliniaspinose*Zucc.	Koeberliniaceae	Stems, twigs, and roots	(3E,7E)-9-hydroxy-1-[(R)-6-hydroxy-2,8-dimethyl 2H-chromen-2-yl]-4,8-dimethylnona-3,7-dien-2-one (2R)-2-[(3E,7E)-9-hydroxy-4,8-dimethylnona 3, 7-dien-1-yl]-2,8-dimethyl-2H-chromen-6-ol.	[27]
18.	*Mallotus apelta* (Lour.) Müll. Arg	Euphorbiaceae	----	Malloapelta A-F	[28]

CHAPTER 2

Recent Trends of Chromene Syntheses

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Abstract: 2H/4H-chromenes (2H/4H-Ch) structural scaffolds have been widely employed in the synthesis of many natural products and medicinal agents. 2H/4H-Ch have attracted considerable attention due to their various pharmacological activities, such as anticonvulsant, anticholinesterase, anticancer, anti-tuberculosis, antimicrobial, and inhibitory activity against monoamine oxidase (MAO), and anti-diabetic activities. In literature, the synthesis of 4H-chromenes was performed by one-pot Knoevenagel condensation of resorcinol, aryl aldehydes, and malononitrile in the presence of basic catalysts. Also, 2H-Ch analogs were performed by the Wittig-Horner-Emmons and Suzuki-Miyaura cross-coupling reactions. A description of recent advances in the syntheses of chromenes is presented in this chapter. The strategies for the synthesis of 2H/4H-Ch discussed in this chapter are organocatalysts, organometallic or metal catalysts, heterogeneous base catalysts, enzymatic catalysts, and green chemistry-based approaches.

Keywords: 2H/4H-chromenes, Enzymatic catalyst, Green chemistry approaches, Heterogeneous base catalyst, Knoevenagel condensation, Organo-base-catalyst, Pharmacological activities, Wittig-Horner-Emmons.

INTRODUCTION

Chromene and its derivatives are some of the most important structural motifs found in nature that are widely being used to discover and develop novel drug candidates. These scaffolds play essential roles in bioorganic, medicinal, and pharmaceutical chemistry [1]. Chromenes and chromanes contain a benzopyran ring system, with varying degrees of oxidation and saturation, and exhibit unique biological attributes [2]. The structural class of chromenes consists of two subclasses, namely, 2H-chromene (**1**) and 4H-chromene (**2**), differentiated by sp3

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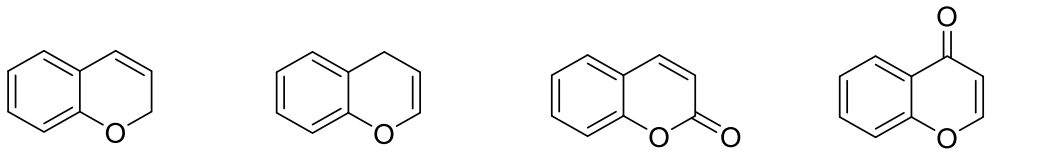
carbon arrangement linked to the ring oxygen. Two other subclasses may be formed when the sp3 carbon is replaced with a carbonyl function, which gives rise to the formation of 2H-chromen-4-one (**3**) and 4H-chromen-2-one (**4**) motifs (Fig. **1**). There has been a consistent attraction towards the synthesis of chromenes as they possess properties, such as anticancer activity [3], anticonvulsant profile [4], antibacterial activity [5], anti-juvenile hormone activity, anti-anaphylactic activity, anti-allergic and anti-inflammatory properties, anti-tubercular, anti-diabetic, parasympathomimetic and monoamine oxidase (MAO) inhibitory profiles [2, 6, 7].



2*H*-chromene **4*H*-chromene** **2*H*-chromen-2-one** **4*H*-chromen-4-one**

(1) **(2)** **(3)** **(4)**

Fig. (1). Basic structural moieties of chromene class of compounds.

Chromenes have been identified as strong cytotoxic agents with several mechanistic approaches, like tubulin depolymerization at metaphase, cell cycle arrest at G2, or M-phase caspase-dependent apoptotic pathways. Chromenes are also involved in vascular targeting and thus disrupt freshly formed capillary tubes, which results in a rapid collapse in the blood flow to the tumorogenic tissues, and a prolonged span of such vascular shutdown results in tumor cell necrosis [8]. Compound **5** was found to exhibit potent cytotoxic activities against six human tumor cells with an IC_{50} value of less than 1μM [9]. Compound **6** demonstrated a weak inhibitory effect on tubulin polymerization with a very strong cytotoxicity against A172 glioma cells with IC_{50} of 7.4 nM [10]. Compound **7**, belonging to a class of 4-aryl-4H-chromene derivatives, act against MCF-7 cancer breast cell lines by microtubule-interfering properties and has activity comparable to colchicine [11]. Compound **8**, formed by functionalization of 2H-chromenes with isoxazole and 2-(1,2,3-triazolylmethoxy), was tested for its cytotoxic activity against four different targeted human cancer cells. It exhibited a very potent activity of IC_{50} less than 20μM [12]. Compound **9**, made of chromene fused with imidazo [1,2-a] pyridine motif was evaluated for its antiproliferative properties in human colon HCT116 cancer cell lines. Compound **9** was found to be the most effective due to its cell cycle detention capabilities at both G2 and S phases due to the carbamate group's inhibitory effect attached to the pyridine ring on the cell cycle, ultimately leading to cell death by apoptosis (Fig. **2**) [13 - 15].

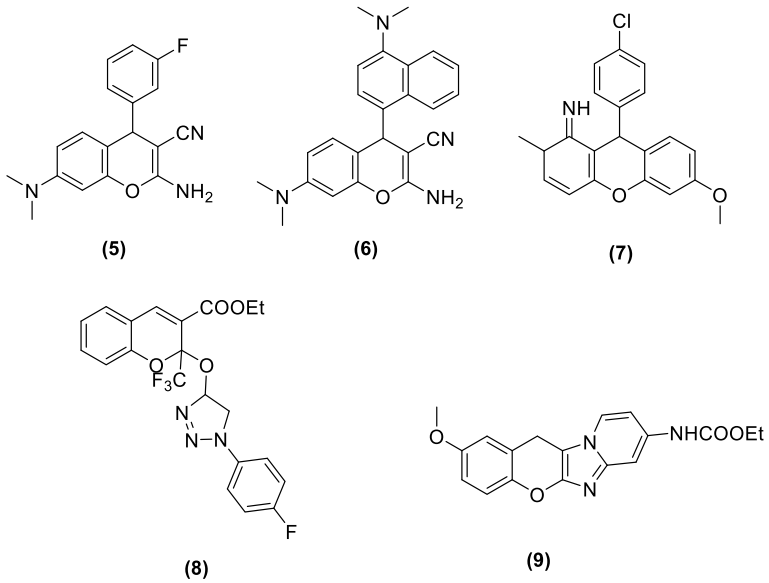


Fig. (2). Chromene based compounds active as anticancer agents.

Chromenes are well-established as antimicrobial agents. 2-cyano-4-oxo-3-p-enyl-3,4-dihydro-2H-furo [3,2-c]chromene-2-carboxylates class of compounds were synthesized and tested for their antimicrobial efficacy *in vitro* against several strains of Gram(+)ve and Gram(-)ve bacteria. Out of all the congeners synthesized, compound 10 showed inhibition on the growth of *Micrococcus luteus* MTCC 2470 and *Klebsiella planticola* MTCC 530 strains, whereas, compound11 was found to be extremely active against *B. subtilis* MTCC 121, *M. luteus* MTCC 2470, *E. coli* MTCC 739, and *K. planticola* MTCC 530 bacterial strains [16]. Compounds **12** and **13**, belonging to the chemical class of indolyl-4H-chromene-phenyl prop-2-en-1-one showed antibacterial activity comparable to the standard drug against *S. aureus* (both having MIC of 9.3µg/mL) (Fig. **3**).

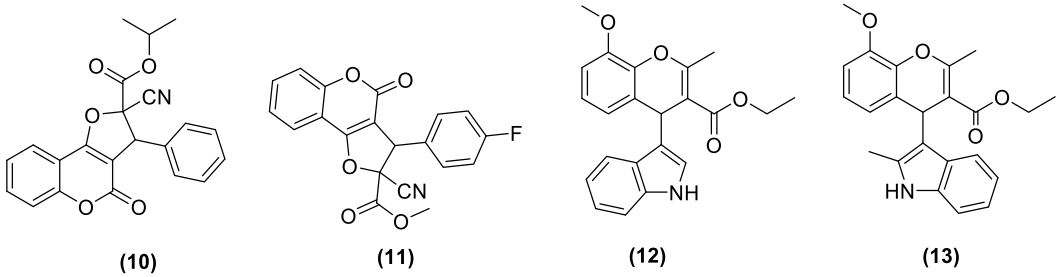


Fig. (3). Chromene based compounds active as antimicrobial agents.

CHAPTER 3

Diversity-Oriented Synthesis of Chromenes

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Abstract: Diversity-oriented synthesis (DOS) plays an important role in the construction of various natural products and the development of diverse small-molecules of biological significance. In recent years, numerous diversity-oriented approaches have been demonstrated to furnish complex structures with molecular diversity from readily accessible starting materials. This chapter summarizes the recent diversity-oriented approaches based on metal-free, transition metal-catalyzed, and organocatalyzed reactions for the synthesis of chromene derivatives.

Keywords: Chromenes, Diversity-oriented synthesis, Heterocycles, Metal-free synthesis, Organocatalyzed reactions, Transition metal-catalyzed reactions.

INTRODUCTION

Diversity Oriented Synthesis (DOS) provides a requisite perspective for the construction of small molecular libraries of biologically active molecules and is considered to be an important alternative to shape skeletal, stereochemical, and overall functional diversity [1]. Diversity-oriented synthesis involves the deliberate, simultaneous, and efficient synthesis of more than one target compound in a diversity-driven approach to answering a complex problem. The term 'diversity' has been divided into four important components: appendage, functional group, stereochemical, and skeletal or scaffold diversities [2]. The scaffold diversity describes the production of various divergent molecular skeletons that could be achieved from a reagent-based approach or a substrate-based approach [3]. The DOS strategy has been employed for the generation of chromene-based motifs, an important class of heterocyclic compounds that has an indispensable demand in the field of drug discovery and chemical biology [4]. For instance, cannabichromene**1** shows anti-inflammatory, antiviral, and analgesic properties [5]; tuberatolide B **2** is an effective antagonist against farnesoid X

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receptor [6], and acolbifene**3** and OP-1074**4** act against breast cancer [7]. Furthermore, compound **5** is an adrenergic receptor [8]; and warfarin **6** is used for the treatment of thromboembolic disease (Fig. **1**) [9].

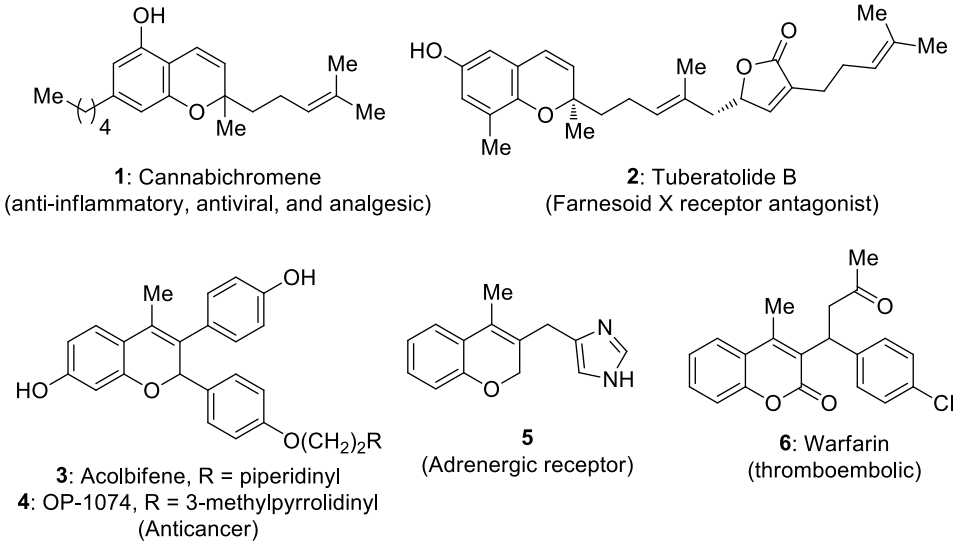

Fig. (1). Biologically active 2*H*-chromene derivatives.

Owing to the enormous biological significance of chromenes, various efficient methods have been developed for their synthesis. This chapter summarizes the recent approaches involving metal-free, transition metal-catalyzed, and organocatalyzed synthesis of chromenes.

METAL-FREE SYNTHESIS OF CHROMENES

Gharpure and co-workers devised a novel method for the synthesis of 1,4-heterocycle-fused chromenes (**9** and **10**) in moderate to excellent yields. This cascade reaction occurs between salicylaldehyde **7** and alkyl or aryl-substituted alkynols **8** in the presence of TMSOTf in DCM at 0ºC and proceeds through 7-*endo* or 7-*exo*-mode of hydroalkoxylation followed by [4+2] cycloaddition to deliver 1,4-heterocycle-fused linear chromenes **9** or 1,4-heterocycle-fused spiro chromenes products **10** (Fig. **2**) [10].

Chen and co-workers reported an efficient approach for the synthesis of 2-amin--4*H*-chromenes **13** from 2-halomethyl phenols **11** and ynamides **12** under catalyst-free conditions (Fig. **3**) [11]. Both electron-donating and electron-withdrawing groups present on phenyl-terminated ynamides **12** afforded the desired products 2-amino-4*H* chromenes **13** in good yields under the optimized

conditions. This [4+2] cycloaddition reaction proceeds through an *o*-methylene quinone intermediate.

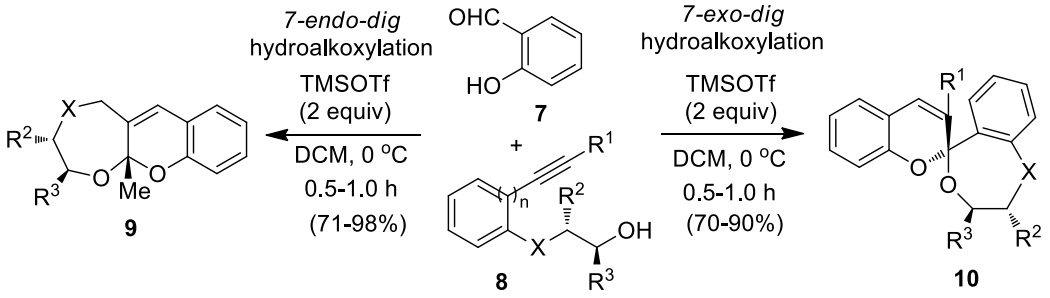

Fig. (2). Synthesis of 1,4-heterocycle-fused and spiro chromenes.

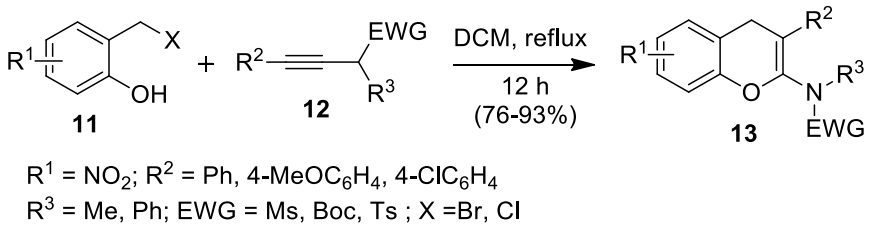

Fig. (3). Synthesis of 2-amino-4*H*-chromenes under catalyst-free conditions.

Song and co-workers demonstrated a one-pot cascade reaction for the synthesis of 2*H*-chromenes **15** starting from epoxides **14** in the presence of DDQ in toluene under refluxing conditions (Fig. **4**) [12]. The mechanism of this reaction involves Claisen and Meinwald rearrangements. The intermediate formed during the reaction undergoes oxidative oxa-6π-electrocyclization to afford *2H*-chromenes **15** in good to excellent yields.

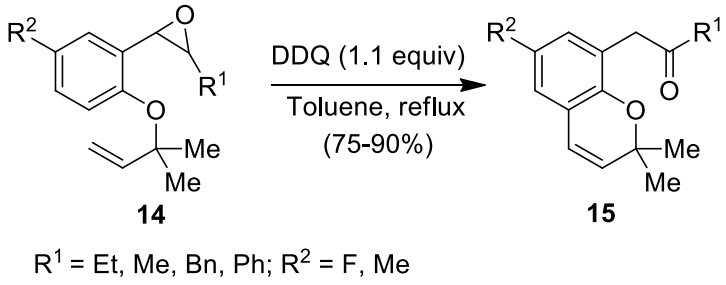

Fig. (4). DDQ-mediated synthesis of 2*H*-chromenes.

CHAPTER 4

Role of Chromene in the Cure of Different Kinds of Human Disease

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Abstract: A variety of chemicals were being used by us for the treatment of human and animal diseases from the early beginning of civilization. These chemicals may be from a natural or synthetic source. Here the choice of discussion is being focused on the chemical name Chromene and its derivatives that have a significant effect on various health diseases of human beings. Over the past few years, various natural, as well as synthetic derivatives of chromene, have shown several fascinating features. These chromene derivatives were being used in the treatment of Alzheimer's disease and Chagas disease. These possess antimicrobial and antiviral properties, used as anticancer agents, showing antileishmanial properties along with antifungal properties. In this review, we have focused on the importance of chromene and its derivatives for the betterment of human beings by finding such studies that describe the use of chromene and derivatives obtained from natural as well as synthetic sources.

Keywords: Alzheimer's disease, Anti-cancer, Antileishmanial, Chromene derivatives, Galanthamine.

INTRODUCTION

Chromenes are heterocyclic chemicals that are found in nature and a six-membered ring is linked to a six-membered oxygen-containing ring, known as (the pyran ring). Derivatives of chromene are important organic molecules that can be found all over nature. These compounds have a variety of pharmaceutical and biological properties, including anti-neurodegenerative, anti-HIV effects,

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anti-microbial, and anticancer [1, 2]. Furthermore, they are used as natural pesticides. Chromene derivatives are extensively used as intermediates in the manufacture of both natural as well as in synthetic commodities. Chemists face a huge challenge in designing and developing novel synthetic methods, as well as offering systematic and eco-friendly methodologies to synthesize such valuable heterocycles. Synthetic chemists are now working on developing solvent-free, ecologically friendly, catalyst-free, and single-step synthesis methods. Some of the benefits of solvent-free procedures include quicker reaction durations and basic preparation and purification procedures [3 - 5].

CHROMENE AND ITS DERIVATIVES IN VARIOUS PROBLEMS

Chromene derivatives popularly known as essential elements are physiologically active chemicals in both artificial and natural conformations. Over the past few years, various natural and synthetic chromene counterparts have demonstrated a variety of fascinating features. When it comes to the vast majority of people's health complications that the nation's population is currently facing, cancer and contagious diseases are now at the top of the list. To check out all these mentioned activities, some of them are discussed here [1, 6].

ALZHEIMER'S DISEASE

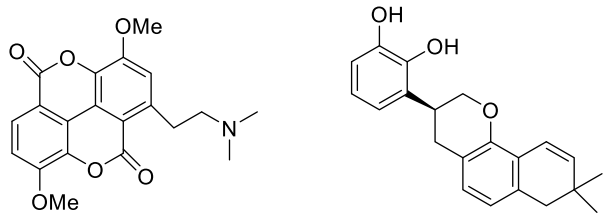
Taspine 56 was discovered for the first time in *Magnolia x soulangiana* leaves. In an enzyme assay, this chemical was found to inhibit AChE with an IC_{50} value of 0.33 mM and illustrating the higher activity of this chromene derivative as compared with the Galanthamine (IC_{50} of 3.20 mM). Glabrindin 57 an isoflavone isolated from the root part of *Glycyrrhiza glabra* was used to examine its activity on cholinesterase activity and cognitive abilities in mice. According to the study, this isolated molecule appears to be promising as a possible memory enhancer that should be further investigated for the treatment of Alzheimer's patients. Glabridin is a popular ingredient in cosmetics and has recently been labeled as an anti-obesity agent (Fig. **1**) [7].

For Alzheimer's disease treatment, fragments that had fascinating and complementary properties are a new class of chromene hybrids. These chromene hybrids were synthesized, developed, and tested physiologically for justification of the activity [8]. For the study of cholinesterase inhibitory characteristics, tacrine fragments were chosen. To study the flavonoid framework produced for its radical activity, 4-oxo-4H-chromene was selected, as well as inhibitory characteristics for beta-secretase 1 (BACE-1). The new tacrine4-oxo-4H-chromene hybrids are more powerful than tacrine by the suppression of acetyl and butyrylcholinesterase in humans at the nano and picomolar doses. They are also more effective than the parent apigenin, flavonoid for inhibiting human BACE-1.

Tacrine derivative of chromene was one of the hybried investigated. It showed significant ChEs and back-I inhibition in humans. along with CNS-permeable cpapbilities. It was used as a good antioxidant also [9].

Using a modified Ellman's approach, N-alkyl/alkyl aryl amide moieties present in several novels fused tricyclic coumarins were synthesized and examined for inhibitory actions of AChE and BuChE. The findings revealed that the majority of the chemicals that are being studied had only potent anti-AChE action. Chromene derivatives, which have an attached bromobenzyl amide-containing group, had the highest AChE inhibitory activity (IC50 1.4 nM), which was 51 times higher than galantamine. In an antioxidant experiment, these synthesized compounds showed strong ABTS radical scavenging action. Derivative molecule revealed inhibition of mixed types, engaging concurrently with both the catalytic anionic site (CAS) and peripheral anionic site (PAS) of AChE and producing a significant enzyme inhibition *via* two binding sites, based on inhibitory kinetic analysis and molecular docking studies [10, 11].

Production and assessment of acetylcholinesterase and butyrylcholinesterase inhibitory action of chromenes fused to an N-benzylpyridinium frame. The anti-AChE activity with (IC50 = 0.038 M) and 1-(4-fluorobenzyl)pyridinium derivatives are the best ones for AChE/BuChE response [3, 12].



Taspine Glabridin

Fig. (1). Structure of some compounds acting against Alzheimer's disease.

ANTI-TRYPANOSOMAL

Piper aduncum and *Piper gaudichaudianum* were used to isolate five natural chromene and chromene derivatives having anti-trypanocidal properties by using standard acetylation methylation and reduction procedures by which another seven derivatives were synthesized. *In-vitro* activity of the parasite *Trypanosoma cruzi* was performed against epimastigote forms to confirm the anti-trypanosomal properties of the compounds. *Trypanosoma cruzi* is responsible for Chagas disease. The majority of compounds from the study had potent trypanocidal activity, which is specific to the electron-donating class of compounds, and could be replaced on the aromatic ring. From the study, the extremely effective

CHAPTER 5

Naturally Occurring Chromene Containing Molecules and their Isolation Protocols

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Abstract: Natural products have been used as major sources of therapeutic agents in drug discovery since the ancient eras. Natural products have been widely studied in the physical and biological sciences, including nutrition, health, bio-medical, and other interrelated sciences. Because of their unique chemical diversity and bioactivity, they have continued to offer templates for the development of novel forms of drugs. In the field of traditional medicine, natural products have been used for a very long time in the form of decoctions, medicinal extracts, infusions, or other therapeutic preparations. Chromene is one of the essential chemical constituents, derived from the conversion of multiple biosynthetic pathways present in the plant as well as animal kingdoms, which represents a remarkable group of structurally varied secondary metabolites. The scaffold is considered an important class of oxygenated heterocyclic compounds as two forms of 2H/4H-chromene (2H/4H-Ch) with versatile biological profiles. Chromenes are the basic backbone of various polyphenols, alkaloids, tocopherols, anthocyanins, *etc.* Crotin, Crotaramine, Dysoline, Malachromone, Oxalicumones A-C, Khellin, Baicalin, Diosmin, *etc.* are some examples of naturally isolated chromene fused compounds that are reported for the treatment of diverse health ailments. Their unique structure and varied pharmacological activities may provide new leads for the discovery of drugs with their action. In recent years, the need to develop effective and selective methods for the extraction and isolation of new natural products has been increasingly felt. This chapter presents the extraction, isolation, and characterization processes of the chromenes by the natural sources, illumination of the structures of purified chromenes, and their bioactivity.

Keywords: Chemical constituent, Chromene, Isolation, Natural product, Plant extract.

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INTRODUCTION

Natural product chemistry was initiated from human curiosity about color, odor, taste, nutritional value, and most important cures for many human, animal, and plant diseases. Products that are derived from plants, vertebrates, microorganisms, and biochemical factories for the biosynthesis of primary and secondary metabolites are known as "natural products". Over the centuries, natural products (NPs) have been considered the best and most reliable source of drugs and drug leads [1, 2]. Medicinal plants and microorganisms have been considered an essential source of therapeutic agents, and nowadays many of the drugs are plant-derived NPs or their derivatives [3]. However, some practical hitches in procurement, free availability, and time coverage to work on plant or microbial source raises numerous difficulties in natural product-based drug discovery. Hence pharmaceutical industry has shifted its main focus towards synthetic compound libraries for the discovery of new drug leads. Despite the high complexity, this circumstance rejuvenated the interest in "natural product-based drug discovery", which in turn necessitated a broad interdisciplinary research approach to address the multiple issues [4]. From the beginning of the medicinal history, plants and their various parts were only applied on an experimental basis considering traditional uses and effectiveness, without a thorough knowledge of their pharmacological activities or active constituents. During the 18th century, Anton von Storck investigated that, poisonous herbs (aconite and colchicum), and William Withering, studied foxglove for the treatment of edema, and this laid the basis for the rational clinical investigation of medicinal herbs [5].

Chromene (Benzopyran) is one of the renowned medicinal pharmacophores that may appear as an important chemical moiety in natural compounds and has garnered great attention due to its numerous interesting biological activities. Chromene is a fusion of 5,6-positions of a benzene ring and 2H- or 4H-pyran ring and makes a bicyclic oxygen heterocyclic ring system in the form of 2H-chromene (2H-1-benzopyran) and 4H-chromene (4H-1-benzopyran) and known asbenzopyrans [6, 7]. It is a basic skeleton for various types of polyphenols and is extensively found in natural tocopherols, alkaloids, anthocyanins, and flavonoids. Chromenes, the secondary metabolites, have been the focus because of their interesting biological and pharmacological properties and their wide presence in the animal and plant kingdom in the form of isolated and fused ring systems [8].

This heterocycle is widely distributed in several species of natural plants as well as in notable amounts synthesized from nature-derived chromone molecules. They have been used as traditional medicine since ancient times and are well-known for their miscellaneous pharmacological activities, such as anti-inflammatory, antiallergic, antimicrobial, antibacterial, insecticidal, antidiabetic, antitumor,

fungicidal, antivascular, TNF-α inhibitor, antioxidant, antispasmolytic, anticoagulant [9], estrogenic, anti-helminthic, anti-HIV, anticancer, and cytotoxic [10]. Due to its multiple biological activities, chromone is an admirable template in medicinal chemistry for pharmaceutical industries or research organizations to perform structural modifications. Thereby, presently synthesis of a large library of compounds is being initiated that are also considered privileged scaffolds in finding out various target-based drug discoveries against fastidious diseases [11].

Benzopyran is a fusion of an oxygen-containing pyran ring with a benzene ring and can be of 1-benzopyran or 2 –benzopyran. The level of saturation and oxidation in benzopyran is again classified into Chroman, 2*H*-chromene, and 4*H*-chromene as shown in (Fig. **1**). Their widespread availability in the plant kingdom can be useful for various physiological properties of plants as well as humans for their potential activity as a drug. Benzopyran derivatives are lipophilic compounds, and this is a key feature that helps them to cross the cell membrane easily. Oxygen heterocycles constitute a special class due to their broad pharmaceutical significance and their wide occurrence in nature. Universally, benzopyran nucleus is well known for its diverse biological significance towards diseases and the basic structural skeleton generally includes 2*H*-chromene and 4*H*-chromene. Several similar classes of compounds are derived from benzopyran or chromene scaffolds *e.g*. flavones, isoflavones, flavanols, coumarins, *etc.* in which aromatic rings or carbonyl group is attached to C-2 or C-3 position of benzopyran (Fig. **2**) [7].

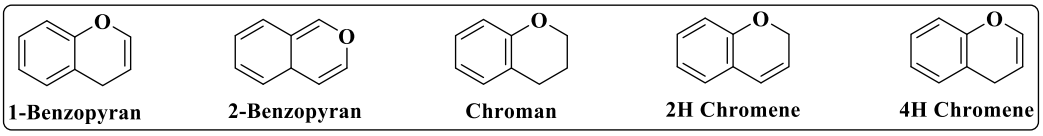

Fig. (1). Types of benzopyran and chromenes.

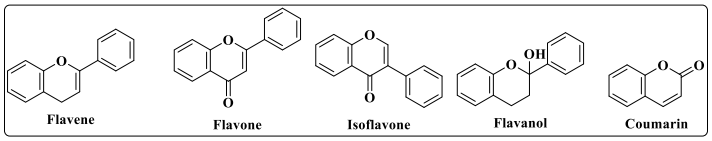

Fig. (2). Structure of similar classes of compounds derived from benzopyran or chromene scaffold.

Vitamin E possesses antioxidant activity, an evident example of the naturally occurring chromane [12]. Similarly, Cannabichromene is also noticeably available in various plant species (Fig. **3**).

CHAPTER 6

Chromenes and Nutraceuticals

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Abstract: Nutraceuticals have received tremendous interest in the treatment or prevention of multiple diseases in modern times. Chromenes (Benzopyran), phytochemicals that are polyphenolic secondary metabolites, are one of the privileged scaffolds that occur in various natural products as essential structural components and also have beneficial nutraceutical properties. Chromenes are more correctly referred to as ‘nutraceuticals' due to their variety of pharmacological activities in the mammalian body. A better understanding of their mechanisms and biological activities suggests their ability as therapeutic agents and also for predicting and monitoring food quality due to their significance in food organoleptic properties and human health. In this chapter, the discussion will be on the diverse therapeutic actions of chromenes as well as the probable mechanisms of action that are responsible for their therapeutic activity. The origins of these chromenes, their extraction from these sources, and their use as nutraceutical components in various food items will also be discussed. The pharmacological relevance of chromenes, which may be added to staple foods to create various nutraceutical products, will also be discussed. As shall be evident after reading this chapter, chromenes as pharmacological agents have a wide range of targets. As a result, medicinal chemistry and quantitative structure-activity relationships should be used to focus on their specific biological action when developing new congeners of chromenes to be used as drugs.

Keywords: Anti-cancer activity, Anti-microbial activity, Antioxidant activity, Anti-viral activity, Cardioprotective activity, Chromenes, Nutraceutical property, Pharmacological property, Polyphenols, Secondary metabolite.

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INTRODUCTION

Derivatives of natural chemistry evolved from mankind's fascination with color, flavor, and odor and the quest for remedies for human, animal, and plant diseases [1]. Natural products have long been regarded as the greatest source of medicines and drug leads. Since 1981, approximately 80% of small-molecule drugs have been inspired by natural products, with 53% being either natural products or derivatives thereof [2, 3]. The term “natural product” refers to substances obtained from plants, microorganisms, mammals, and birds, all of which function as biological warehouses for the biosynthesis of both primary and secondary metabolites [4]. Secondary metabolism generates compounds that are thought to be critical for plants' interactions with their biotic and abiotic environments. High genetic plasticity and variability of bioactive secondary metabolites enable plants to adapt to the changing demands of their climate [2, 3]. The ability of a community to foster interactions with beneficial organisms while reducing interactions with non-beneficial organisms such as predators, pathogens, and parasites is crucial to its survival. Though the structure of these biotic interactions is very complex, multidisciplinary teams of scientists are now starting to understand the molecular structure of these interactions using modern instruments in chemistry and biology [5, 6].

Dietary supplements and interventions comprising high quantities of chromenes (4H-benzopyran-4-one), flavonoids (2-phenyl-1,4-benzopyrone), or coumarins (1,2-benzopyrone) are becoming increasingly popular owing to the massive consumer demand for healthy practices and disease management [7]. Though not classified as vital nutrients, plant-produced chemicals (phytochemicals) are believed to have wellness properties due to their action as chain-breaking antioxidants that scavenge or reduce free radical creation [7, 8]. Phenolic compounds such as phenolic acids, anthocyanins, coumarins, tannins, chromenes, and flavones seem to be the most abundant group of antioxidants [9 - 11]. For years, scientists have searched for novel antioxidants from natural sources due to their numerous applications as anticancer agents, as a cure for metabolic diseases such as cardiovascular diseases, as nutraceutical agents, and in antimicrobial drug resistance [12 - 14].

Chromenes are heterocyclic compounds with a benzene ring bonded to a pyran nucleus (Fig. **1**). The carbon atom in the 2-position of 2H-chromenes I either forms a double bond with oxygen (Z =O, 2-oxo-2H-chromene; widely known as coumarin), nitrogen (Z = NH, 2-imino-2H-chromene) or sulfur (Z =S, 2H-chromene-2-thione) or forms two single bonds with separate substituents, X and Y. In the 4-position, 4H-Chromenes III and IV have an sp3 hybridized carbon atom or a double bond to a heteroatom [15]. Chromenes (Benzopyran) are

uncommon scaffolds that may be found in a range of natural products and have excellent photochemical characteristics. They are known to display antitumor, anti-hepatotoxic, antioxidant, anti-inflammatory, diuretic, anticoagulant, anti-spasmolytic, estrogenic, antiviral, antifungal, antimicrobial, anti-helminthic, hypothermic, vasodilator, anti-HIV, anti-tubercular and herbicidal activities [13 - 15]. The development of numerous additional active and significant chemicals was motivated by the therapeutic use of these pharmacophores in the treatment of cancer, inflammation, and other disorders. The structure-activity relationship (SAR) results show that replacing certain groups in the chromenes nucleus enhances the molecule's ability to fight illness [16, 17].

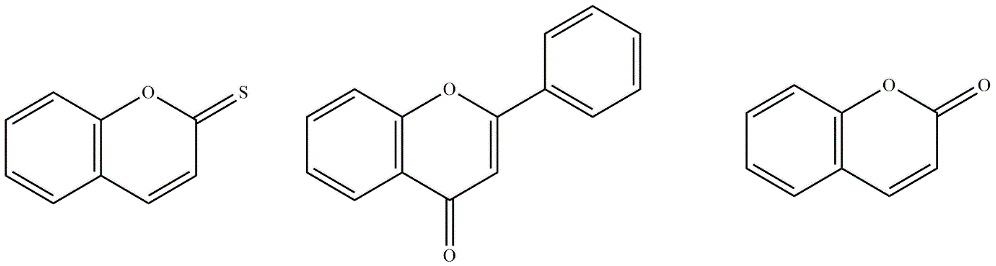

Fig. (1). Structure of chromenes.

Nearly seven decades ago, a review study emphasized the broad distribution of chromenes in plants and discussed the numerous techniques for their synthesis. From 1988 to 1994, another review on natural coumarins focused on their identification and separation from plant extracts as well as on their chemical synthesis [16, 17]. Today, natural compounds are highly rated by medicinal chemists owing to their low toxicity and a wide variety of pharmacological characteristics. Such compounds serve as a source of inspiration for the development of novel therapies. The pharmaceutical industry is already familiar with this critical framework in the search for prospective medication candidates [2, 3].

In this chapter, we have endeavored to cumulate the origins of chromenes, their isolation from various sources, and their application as nutraceutical ingredients in various food items. The pharmacological value of chromenes, which can be added to staple foods to create various nutraceutical items, is also discussed. After reading the chapter, it shall be evident that chromenes are a pharmacological agent with a broad range of goals and that complex biological methodologies must be devised by using medicinal chemistry and quantitative structure-activity interactions for the development of new congeners of chromenes that can be used as medicines.

CHAPTER 7

Pharmacokinetic Aspects of Chromenes

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Abstract: Unfavourable pharmacokinetics is the major hurdle for the new chemical entity (NCE) to become a drug during the drug discovery and development process. Early evaluation of absorption, distribution, metabolism, and excretion (ADME) characteristics for the promising candidates not only speed up the drug development stages but also lower the attrition rate in clinical phases which can save resource and time. Furthermore, pharmacokinetic behavior is helpful for a better understanding of efficacy, toxicity, and safety. The present chapter deals with ADME information on chromene-based molecules, which have gained significant importance nowadays due to their wide range of pharmacological actions, including anticancer activities. Comprehensive ADME data based on the available information on *in-vitro* and *in-vivo* profiles will pave the way towards understanding for discovery and development of new therapeutics in this scaffold from bench to bedside.

Keywords: 14n, ADL5859, ADME, Chromene, Crolibulin, C-8 hydroxychromene, Dihydropyrimidinone, Glabridin, IND8541, Methoxsalen, mHA11, Pharmacokinetics.

INTRODUCTION

The discovery of new chemical entities (NCEs) is a lingering and expensive endeavor burdened with various evident failures during clinical trials [1, 2]. One of the main reasons for attrition during the drug development process is thought to be their poor pharmacokinetic behavior which has been playing a vital role in drug discovery and development [3, 4]. A good candidate entails a balance among efficacy, safety, and pharmacokinetics properties [3]. Pharmacokinetic exposure of NCE plays a crucial role in achieving the therapeutic goals for unmet medical needs. Various *in-silico*, *in-vitro/ex-vivo,* and *in-vivo* models are available to inve-

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stigate the key absorption, distribution, metabolism, and excretion (ADME) characteristics for the development of NCE to become a drug [5 - 7].

Over the years, chromene-based molecules (Fig. **1**) have been broadly explored in the drug discovery and development process. Chromene is a heterocyclic scaffold where a benzene ring is fused with a pyran nucleus. Chromenes are also known as benzopyrans [8, 9]. These compounds are reported to have diverse pharmacological activities, including anticancer, anti-vascular, apoptotic, neuroprotective, cardioprotective, anti-inflammatory, and selective δ-opioid receptor agonists to regulate pain, *etc.* [10 - 18]. Methoxsalen, a natural chromene, is a United States Food and Drug Administration (USFDA) approved drug used for the treatment of several skin diseases [11]. Crolibulin is another 4*H*-chromene analog that is now under clinical trials (Phase I/II) to treat anaplastic thyroid cancer. There are also chromene-linked compounds like chromones, chromanones, chromandioane, *etc.* which also have several useful pharmacological activities *viz.* neuroprotective, cardioprotective, anticancer, analgesic, anti-inflammatory, antiviral, *etc.* [19 - 22]. Natural chromones like quercetin and genistein are currently in Phase I/II clinical trials to treat prostate cancer and lung cancer, respectively [23]. However, the present chapter deals with ADME perspectives of chromene molecules in particular (Fig. **2**) based on the available *in-vitro/ex-vivo* and *in-vivo* pharmacokinetic data.

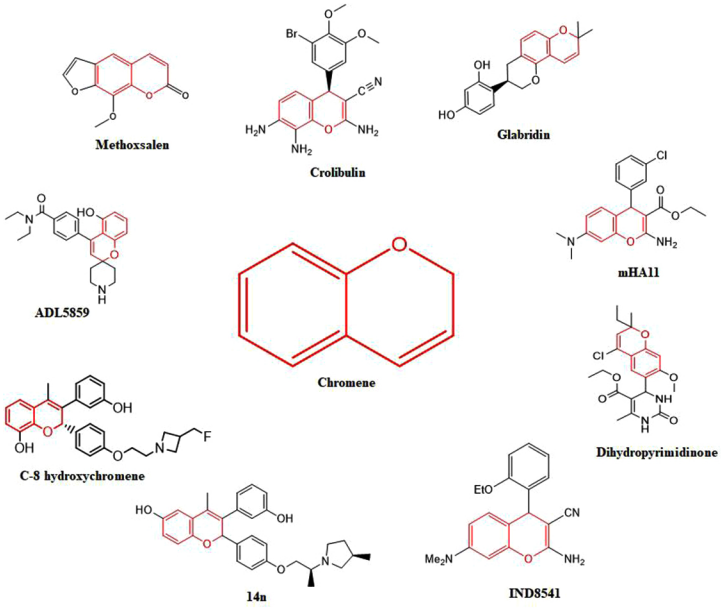

Fig. (1). Chemical Structure of chromene and chromene-based drug, clinical candidates, and preclinical candidates.

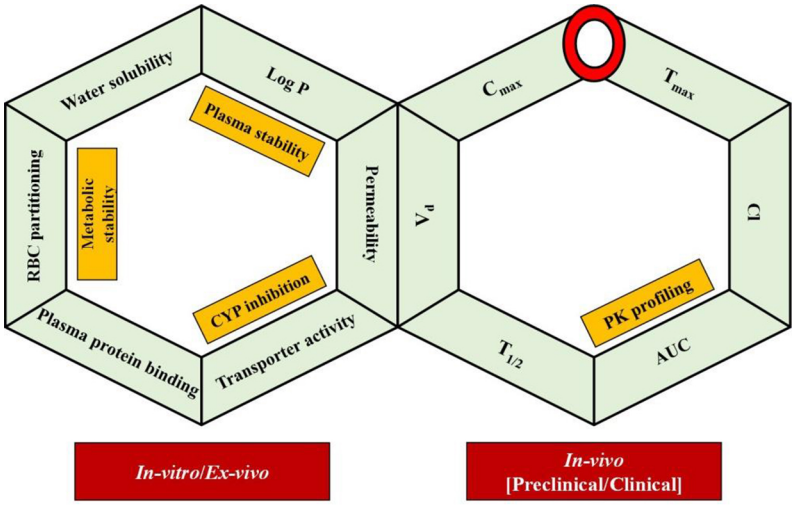

Fig. (2). Available data on *in-vitro* and *in-vivo* pharmacokinetics of chromene and chromene-based drugs, clinical candidates, and preclinical candidates.

PHARMACOKINETICS OF CHROMENE-BASED DRUG

Methoxsalen

Methoxsalen is a naturally occurring chromene and is also called xanthotoxin or8-methoxypsoralen. It is approved by USFDA to treat skin ailments *viz.* eczema, psoriasis, and cutaneous T-cell lymphomas [11]. Methoxsalen is a naturally occurring derivative of furocoumarin. It is prevalently present in the plants of the Rutaceae and Umbelliferae family, as well as in various edible species, including parsnips, celery, limes, and figs [24, 25]. The aqueous solubility of methoxsalen is found to be 47.6 µg/mL [26, 27]. Busch *et al.* reported 88 to 91% of serum protein binding by methoxsalen [28]. A similar report on high binding affinity with human serum albumin and human serum was also reported at 84% and 90%, respectively [27]. However, Artuc *et al.* observed plasma protein binding of 75 to 80%, which is slightly lower than earlier reports [29]. In *in-vitro* metabolic studies, methoxsalen is metabolized minimally in the mouse hepatocytes, but it was transformed in rat hepatocytes. Increased metabolism of methoxsalen was observed upon activation of cytochrome enzymes, including cytochrome-448 and cytochrome-450 (CYP) [30, 31]. During pharmacokinetics in psoriatic patients, methoxsalen attained a maximum plasma concentration (C_{max}) in the range of 50 to 250 µg/L and the time to reach $C_{max,}$ (T_{max}) was from 1 to 2 h after oral administration of standard-dose at 0.5 to 0.7 mg/kg. Oral pharmacokinetic parameters of methoxsalen were significantly affected in the presence of food. Ehrsson *et al.* demonstrated that the C_{max} and area under the curve for plasma concentration (AUC) of methoxsalen were considerably raised in non-fasting

CHAPTER 8

Chromene and its Derivatives in the Treatment of SARS-COV- 2 Virus Infection

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Abstract: Coronavirus pandemics are characterizing the 21st century in itself. In 2002-03, the first coronavirus SARS-CoV caused Severe Acute Respiratory Syndrome (SARS); in 2012, the Middle East Respiratory Syndrome (MERS-CoV) made its appearance, and in 2019, a new human beta coronavirus strain, the SARS-CoV-2 led to COVID-19 pandemic that took over the entire globe under its rollout. The scientific research and medical challenges to save lives have revealed the biochemistry and genetic evolution of an important cycle of the new pathogen, which has steered us to new preventive and therapeutic approaches to treat SARS-CoV-2. Until now, there is a scant resource of vaccines available, and therefore, it is very challenging to dose huge mass around the world. Moreover, there are other various difficulties in producing, distributing, and storing vaccines; the allopathic drug is always a thrust in this situation. Various *in-silico* and *in-vitro* studies have helped to prove that natural molecules containing chromene have shown their effectiveness in the treatment of SARS-CoV-2. Pleiotropic activities and the absence of systemic toxicity of natural chromene and its derivatives represent potential target compounds in clinical trials to enrich the drug armament against coronavirus infections. In this chapter, efforts are being made to discuss the recent investigation of the progress of chromenes in treating SARS-COV-2 virus infection and various treatments involving the possible use of poly-substituted chromene compounds of modern and natural medicines for the treatment of COVID-19.

Keywords: Anti-viral, Chromene, COVID-19, 3CLpro and PLpro inhibitors, Herbal medicines, Proteases, SARS COV-2.

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INTRODUCTION

The bursting spread of the SARS-CoV-2 virus through inter-human transmission has made a significant change in humans that has to be addressed with appropriate health etiquette standards, including therapy protocols to counter this viral infection with an immediate effect. Some of the already existing drugs have proved as a remedy for SARS-CoV-2. Chromene (benzopyran) is one of the entitled medicinal scaffolds that appear as an integral part of natural compounds, generating great awareness because of its potent anti-viral activity. It is a significant class of heterocyclic compounds having various biological activities along with a simplified chemical structure having mild to moderate adverse effects. There is an urgent need for a treatment method for COVID-19 infection that firmly emphasizes drug repurposing strategies that can effectively result in novel and effective treatments with computational, experimental, and pharmacokinetic proficiency. The corona-viral proteases, 3C-like protease (3CLpro) and papain-like protease (PLpro) are striking anti-viral targets since they are vital proteins for corona-viral replication. This chapter credits the research progress on chromene as a modern and herbal medicine explored from various sources and seeks to offer an inclusive description to treat SARS-CoV-2 infections [1 - 4].

A GENERAL OUTLINE OF CORONAVIRUS

Origin and Transmission

Coronavirus was grouped into four categories such as α-CoV, β-CoV, γ-CoV and δ-CoV. In these four categories, two were found to infect mammals and the other two were found to infect birds. COVID-19 or SARS-CoV-2 the cause of the current pandemic, belongs to β-coronavirus group which consists of an enveloped positive-sense RNA virus belonging to the subgenus sarbecovirus and subfamily Orthocoronavirinae [5, 6]. Earlier also this β-coronavirus group comprising SARS-CoV and MERS-CoV was reported to cause life-threatening diseases [7]. It has also been reported that the SARS-CoV-2 genome sequence is found to be 96.2% similar to CoV RaTG13 and 79.5% found to be similar to SARS-CoV which shows the possibility of common ancestry and bat as the natural host of the virus. Moreover, it is implied that COVID-19 uses angiotensin-converting enzyme-2 receptor (ACE-2) similar to SARS-CoV [8]. Protein sequence alignment and genome sequencing reported by Lui *et al.* [9] exhibited that many species have common residues of receptors in pangolins, turtles, and snakes. Wrapp *et al.* [10] reinforced the possibility of the existence of more than one intermediate host. The binding affinity of SARS-CoV-2 spike protein to ACE-2 is far stronger than that witnessed by SARS-CoV.

From the studies, it has been speculated that the transmission of this virus is very fast and it is an inter-human type transmission that occurs within social events and public places [11]. Droplet transmission has been considered a primary mode of inter-human transmission [12]. It is observed that the infection also spreads*via* direct contact and also *via* exposure of the nose, eyes, and mouth by touching contaminated objects. Besides this, coming in contact with asymptomatic carriers is also supposed to be the cause of SARS-CoV-2 infection. As the infection is spreading at an unparalleled momentum, infection *via* air warrants a moral decision [13, 14].

Structure of COVID-19 (SARS-CoV-2)

The specific feature of coronaviruses is the presence of club-shaped spike projections on their surfaces. SARS viruses mainly consist of 4 essential structural proteins as follows:

- Spike protein is a class I fusion protein that is cleaved at S1/S2 and is triggered by human protease which contains a receptor-binding domain along with the S20 portion, which is responsible for the attachment of the virus to the cell membrane [15].
- M protein has approximately 25–30 kDa size which provides shape to the virus and can adjust for 2 different conformers that help membrane curvature to attach with the nucleocapsid.
- E protein having approximately 8–12 kDa size is a trans-membrane protein. Viruses with an absence of E protein are considered to be non-pathogenic and have an important function in the assembly as well as the release of viruses.
- N protein forms a nucleocapsid and has an affinity for viral RNA. This has a role in the packing of the encapsidated genome to viral particles [16 - 18]. The virus also contains a hemagglutination-esterase (HE) dimer part that binds to sialic acid and is responsible for esterase activity that enables viral S protein cell entry and thus helps in the spread of the virus [19].

SARS-COV-2 GENOME, PROTEIN STRUCTURE AND BIORHYTHM

SARS-CoV-2 is identified as the seventh contagious coronavirus (CoV) that can infect humans [20]. With a diameter of 150–160 nm, the virus is pleomorphic or spherical and contains positive single-strand RNA, capsid, matrix, nucleoprotein, and S-protein (Fig. **1**). An envelope protein (E), membrane glycoproteins (M), nucleocapsid proteins (N), and spike glycoprotein (S) are all part of a typical virus protein [21]. SARS-CoV-2 is different from other CoVs in that it has an extra glycoprotein with acetyl esterase and hemagglutination capabilities. The 50 untranslated regions (UTR), S, E, M, and N genes, 30 UTR, and additional open

CHAPTER 9

Chromenes as Anticancer Agents

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Abstract: Heterocyclic compounds hold an important place in the realm of medicinal chemistry due to their vast pharmacological and therapeutic significance. Worldwide, cancer is the leading cause of death, and developing an appropriate treatment for the management of cancer is a challenge. Efforts are being made continuously to search for a suitable medicinal agent to treat cancer. Chromene (benzopyran) is an important scaffold and is also considered a privileged pharmacophore. This scaffold also appears as an important structural component in various natural products. The various substituted and fused chromenes display propitious activity against various types of cancer. This chapter highlights the latest advancements from the year 2015 to date on chromene-based molecules that have anticancer activities. A subpart briefing natural chromenes containing anticancer potential is also incorporated.

Keywords: Cancer, Cell line, Chromene, Cytotoxicity, Heterocycle, IC_{50}.

INTRODUCTION

Cancer is the second leading cause of death globally and is responsible for about 10 million deaths in 2020 as per the latest report of the World Health Organization. It is a major devastating disease in which there is uncontrolled proliferation of the body's cells. This mass of cells is called a tumor which may be cancerous or benign. A cancerous tumor is malignant which means it can grow and spread to other parts of the body. Cancer is the Latin word for 'Crab' because of the crab-like tenacity of the malignant tissues. Management of different types of cancer is done with help of many anti-cancer agents. Failure in the management of cancer may be observed while using these agents due to the occurrence of resistance. Therefore, it is very much essential for the development

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of novel anticancer agents to overcome the problem of long-term resistance and toxicity [1]. Recently few agents were found to have potent anticancer activity. Crolibulin, which is a chromene analog, has anticancer activity and is in phase II clinical trial (Fig. **1**) [2, 3].

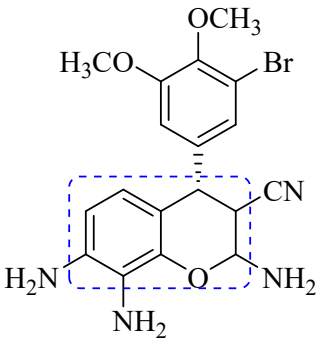

Fig. (1). Structure of Crolibulin.

Benzopyran is a chromene analog and was found to have very good biological activity having a heterocyclic ring system with a combination of benzene ring which is fused to a pyran ring. Chromene analog is found in anthocyanins, alkaloids, flavonoids, and tocopherols [4]. Various structure skeletons like 4H-chromene, 2H-chromene, and chromene have benzopyran nuclei (Fig. **2**).

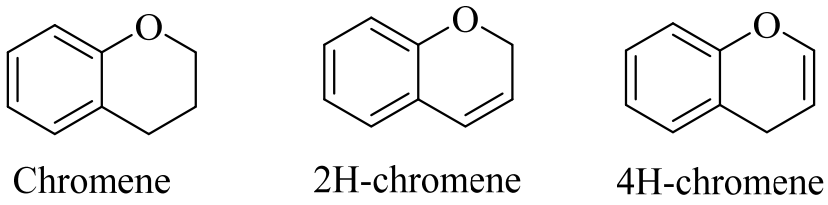

Fig. (2). Structural skeletons of benzopyran nucleus.

Colchicine binding sites are the main target sites for different classes of chromene to show chemotherapeutic activity. Chromene has shown anti-cancer activity against different types of human cancer cells. Also, these agents have shown vascular targeting activity as they cause a fast breakdown of the flow of tumor blood [5]. Therefore, these agents specifically focus on tumor blood vessels that inhibit the formation of blood vessels [6]. The prime purpose of this chapter is to present detailed information about the natural as well as synthetic-based chromenes that are found to have potent anti-cancer activity.

Detailed information about these anticancer agents is available with the help of various published articles available on search engines like SciFinder, PUBMED,

Google Scholar, and science direct from the year 2015 to 2020. The main focus of this five-year review is on the potential anticancer activity of chromene and its application against various types of tumors.

NATURAL CHROMENE BASED ANTI-CANCER DERIVATIVES

Chromene moiety is present in various natural products that are found to have potent anticancer activity. Various plants, sea fish, *etc.* are the main source of these chromenes. Examples of few natural origin anticancer agents are calanone (cervical and leukemia carcinoma), tephrosin used in lung cancer, seselin used in skin cancer, and acronycine used in ovary, lung, and colon cancer (Fig. **3**) [7 - 10].

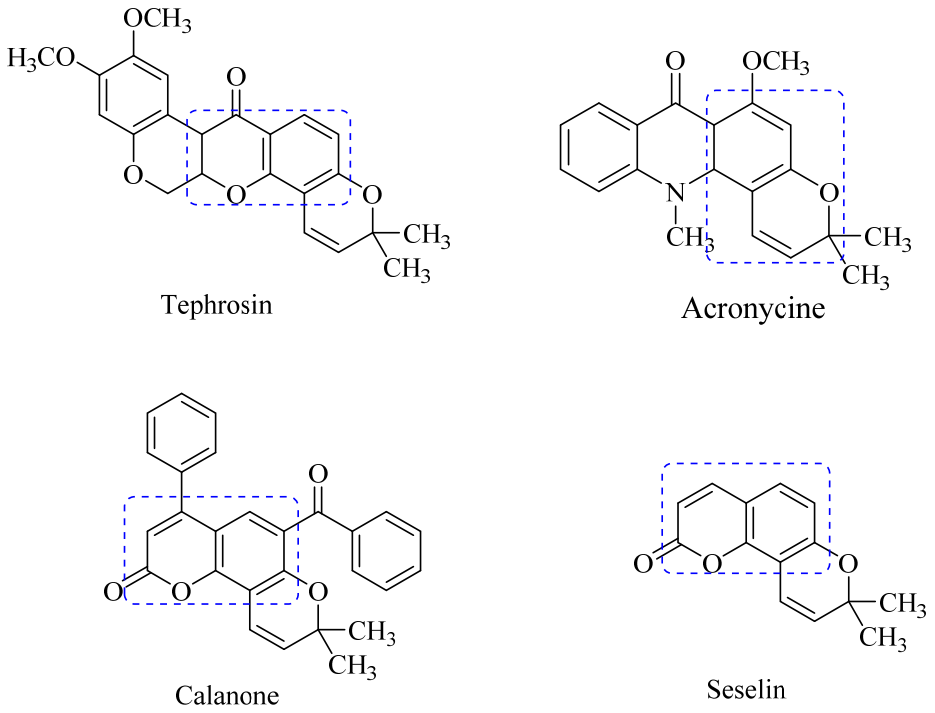

Fig. (3). Structure of natural-based derivative of chromene.

SYNTHETIC CHROMENE BASED ANTI-CANCER DERIVATIVES

A series of five mitochondrion-targeted novel Pt(II) complexes have been prepared and characterized by XRD (single-crystal) and elemental techniques. These synthesized compounds were checked for cytotoxicity against cisplatin-resistant A549/DDP cells. Among all synthesized complexes, compound (**1**) was observed to exhibit a 525.5-fold higher activity with an IC_{50} (μM) value of 0.13 ± 0.04. Compound (**1**) shows a significant decrease in the membrane of

CHAPTER 10

Chromene as Antioxidants

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Abstract: Chromene is a heterocyclic compound that contains oxygen in its ring. It is widely obtained naturally from both animals and plants, and it is an integral part of alkaloids, tocopherol, anthocyanins, and flavonoids. The 2-oxo-2H-chromene is called coumarins, and coumarins have excellent antioxidant potential due to the presence of the phenol group, more than 1300 coumarins have been identified to date. The chromene scaffold in coumarins has the structural modification ability that makes it the structure of choice for medicinal purposes. Various medicines can be synthesized by using a chromene scaffold *e.g.* asthma, hypertension, antifungal, and antimicrobial. Chromene shows a good antioxidant potential that depends on its hydrogen ion-releasing capacity and stabilizes hydrogen with the help of a high resonating structure. The bond length between bonds also enhances the free radical scavenging function. In this chapter, we have discussed some chromene derivatives and their antioxidant potential, and the effect of cyclic structure on the antioxidant's function.

Keywords: Antioxidant, Benzopyran, Chromene, Coumarins, Free radical scavenging, Keto-enol tautomerism.

INTRODUCTION

Chromene is a heterocyclic skeleton that contains oxygen and represents a favored structural design for medicinal purposes [1]. It has a 4H-pyran ring that is linked with a benzene ring. Chromene (benzopyran) is a structural component found in biological or natural compounds, it is an integral part of alkaloids, tocopherol, anthocyanins, and flavonoids [2]. The carbon of chromenes at position 2 shares the double bond with oxygen (2- oxo-2H-chromene), which is called coumarins [3]. The hydroxyl-coumarins show antioxidant properties due to the phenol group which reacts with free radicals, and break the initiation or propagation of chain re-

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action [4]. The hydroxy-7-methoxy-4-chromanone and chroman-2-carb-x-amiddes, a chromene scaffold, show good antioxidant properties. Chromene scaffold is used to synthesize various drugs utilized for treating various diseases *e.g.* asthma, and hypertension, with some other functions such as antifungal, antimicrobial, antioxidant [3], antiproliferative [5], anti-inflammatory, antiallergenic central nervous system activities, and cyclooxygenase-2 (COX-2) inhibition [2].

ANTIOXIDANTS AND FREE RADICALS

Various environmental factors generate oxidative stress inside the body. Oxidative stress initiates the process of free radical generation; cellular health depends on the equilibrium between the generation and removal of free radicals [6, 19]. Free radicals are responsible for lipid peroxidation, and cellular, protein, and DNA damage [7]. A free radical is an unstable molecule that is formed in the biotransformation of oxygen in the respiratory chain. This unstable molecule scavenges electrons from nearby molecules of cells and causes damage to cells, DNA, and cellular protein or cell death [8]. To prevent the operation of these atoms, the body must have a protective barrier with antioxidants [9]. Our body strives to compensate for the free radicals but the overproduction of free radicals causes irreversible harm that is responsible to cause various diseases like hepatic disorder, diabetes, cancer, hypertension, Alzheimer's, and Parkinson's diseases [8]. Antioxidants are agents that can neutralize free radicals. These antioxidants include nutrient antioxidants, vitamins A, C, and E, and the minerals copper, zinc, and selenium. Other dietary food compounds, such as the phytochemicals in plants are believed to have greater antioxidant effects than vitamins or minerals [10], based on their mechanism as free radical scavenger function, chain terminator, and chelating agent [11]. The antioxidant function of compounds obtained either from a biological system or chemically synthesized depends on their H^+ releasing capability, or showing the keto-enol tautomerism, and the bond length between single and double bonds increases the radical scavenging potential. Furthermore, low Bond Dissociation Enthalpies (BDE) values are often attributed to the high antioxidant potential [8].

CHROMENE AS ANTIOXIDANTS

2-H Chromene or 2- oxo-2H-chromene are called coumarins [3], which are found in several green plants. To date, more than 1300 coumarins have been identified. Various natural products containing coumarin scaffold exhibit antioxidant properties, these coumarins contain a benzopyrone scaffold in them [4]. In China, *Magnolia fargesii* is traditionally used as an anti-inflammatory plant that contains scopoletin, a coumarin that exhibits good antioxidant properties and suppresses

diabetic cataracts [12]. The two coumarins evodione and leptonol isolated from *Melicope lunu-ankenda* show antipyretic, analgesic, antioxidant activities, and anti-inflammatory [13]. The benzo[h]-chromene scaffold (Fig. **1**) isolated from *Aristolochia brevipes*, on di or tri substitution exhibits anti-arthritis, and anti-diarrheal properties [14]. The naturally occurring chromene scaffold has extensive employability in synthesizing drugs for various diseases, and the structural properties of Chromene scaffold also favor the substation, this structural modification ability made the scientist more eager for making various kinds of derivatives. Various synthetic treatments of Chromene scaffold have been performed so far. In this chapter, we have focused on the various alterations in the basic chromene scaffold for enhancing antioxidant function.

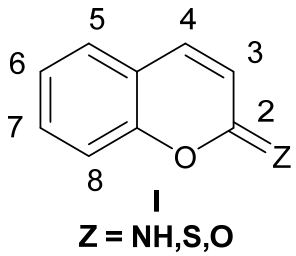

Fig. (1). Representing the basic structure of the coumarins scaffold.

CHROMENE DERIVATIVES AS ANTIOXIDANTS

In the quest for more safe and effective synthetic drugs, researchers and synthetic chemists are working on various chromene derivatives for synthesizing new drugs because the plant origin Chromene or coumarins exhibited excellent properties against various diseases. Here we are discussing various Chromene derivatives and their antioxidants.

Sorkhi *et al.* synthesized two substituted 6-methoxy-2*H*-chromanene derivatives chalcones by using the Chromene scaffold, and the antioxidant potential was determined with a comparison to Trolox using the DPPH and FRAPS method. Four derivatives 1, 2, 3, and 4 were prepared, among them compounds 3, and 4 have shown good antioxidant potential [15] (Table **1**).

Table 1. IC_{50} value of compounds.

Compound	DPPH µM	FRAPS µM
3	69 ± 0.38	89 ± 0.37
4	67 ± 0.44	102 ± 0.41
trolox	36.4 ± 0.53	49.3 ± 0.27

CHAPTER 11

The Implication of Chromene Derivatives in Bioactive Admixtures

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Abstract: Chromene is a heterocyclic scaffold and can be obtained from the natural origin (from different fractions of the plant extracts), synthetic origin as well as mineral origin. The nucleus of the scaffold possesses the ability to interact with different biological targets and thus is medicinally active. Chromene derivatives obtained from different origins are reported to possess pharmacological activities such as antitumor, antibacterial, anti-inflammatory, antithrombotic, and antipsychotic activities. Many chromene-based admixtures are reported to possess different bioactivities. Many derivatives of chromene, such as isomiroestrol, deoxymiroestrol, and miroestrol have been investigated as phytoestrogens. Along with therapeutic potencies, chromene glycosides have safety, efficacy, and stability in the form of herbal drugs and cosmetics. So, the chapter focuses on chromene derivatives, their biological sources, respective bioactivities, and recent advancements.

Keywords: Admixtures, Chromenes, Extracts, Heterocyclic scaffold, Phytoestrogens, *Staphylococcus aureus*.

INTRODUCTION

Chromene glycosides are heterocyclic compounds of natural origin that contain oxygen as a part of the heterocyclic ring system [1]. Some of the chromene glycosides along with their biological source are listed in Table **1**. The high therapeutic potency with minimum toxic nature makes these phytoconstituents widely acceptable and applicable for treating several ailments [2]. Flavones, the

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nucleus of the Chromenes are the key moiety for their therapeutic potential. 6-acetyl-2,2-dimethylchromene-8-*O*-β-D-glucoside is identified as a chromene compound obtained from the extract of *Tithoniadiversifolia* [3]. Asteraceae is one of the largest chromenes glycoside-containing family and around fifty chromene compoundd have been identified as a member of this family [4]. *H. japonicum* is widely used in China for the management of diseases associated with bacteria. A recent data unfolds a new chromene glycoside (2,2-dimethyl- 3′,7-dihydroxy-6-phenyl-2′,5-chromene-carbolactone) possessing antibacterial activity [5]. 2-chromene facsimiles, such as 2,2,6-trihydroxychromene and 2,2-dihydroxy-6-methoxychromene were obtained from the hydro-alcoholic extract (ethyl-acetate fraction) of *Artemisia annua*. Sargaol glycoside has been isolated from the *Dimocarpusfumatus* and is reported with cytotoxic potential [6]. 1H-benzo chromenes and 4H-chromenes can be synthesized from the pioneer of the o-quinone method [7]. The antineoplastic activity of 4H-Chromene is higher than the 2H-chromenes. Extraction with chloroform and phytochemistry of *Paramignyatrimera* has confirmed several phenol-containing compounds. The isolated compounds from the chloroform fraction of the extract resemble the 1,2,4,6-tetra-substituted subordinate [8]. Plant extracts and isolated chromene derivatives show antidiabetic, analgesic, anti-inflammatory, anti-cancer, and anti-microbial activities [9].

Table 1. Compounds related to chromene glycosides along with the species.

Chromene Glycosides	Species	References
3′-Methoxycarpachromene	*Pinus monophylla*	[10]
6-(2-Hydroxyethyl)-2,2-dimethyl-2H-1-benzopyran	*P. trimera P. Grithii*	[11, 12]
Daedalin A	*Paramignyatrimera*	[13]
Ostruthin	*P. trimera*	[14, 15]
7-Hydroxycoumarin	*P. trimera*	[16]
7-Methoxycoumarin	*P. trimera*	[17]
Ninhvanin(8-Methoxyostruthin)	*P. trimera*	[18]

In nature, chromene glycosides have been found in various forms like anthocyanins, flavone, catechins, flavones, and flavanones and accumulatively established as isoflavonoids and flavonoids and possess various biological effects [19 - 21]. Glycosides are sugar-containing molecules that are bounded to some other functional groups by way of glycosidic bonds [22]. They have a crucial cardinal impact on the human body. Based on aglycone moieties, glycosides are classified into different classes, namely alcoholic glycosides, anthraquinone glycosides, coumarin glycosides, chromone glycosides, cyanogenic glycosides,

flavonoid glycosides, phenolic glycosides, saponins [23, 24]. Due to polarity and ionized aromaticity, the chromene glycoside ameliorates the pharmacokinetic features of principal molecules [25]. Thusly, the consolidation of chromene molecules is a significant synthetic approach in the new drug revelation. Better medicinal effects of chromene-associated medications have urged analysts to incorporate novel chemotherapeutic agents [26]. Several cellular components have interacted with the chromene derivate and could be accountable for wide-pharmacological activities.

By and large, chromenes are utilized as restorative specialists, food-added substances, and potential decomposable agrochemicals [27]. The chromene glycoside has numerous therapeutic values such as anti-angiogenic, anti-coagulant, anti-HIV, diuretics, antimalarial, anti-proliferative, anti-microbial, anti-leukemic, and anti-anaphylaxis properties [28]. In addition to chromene, a glycoside is the ingredient of various herbal products such as calophyllolides, calanone, and calanolides, which could be exploited as Nootropics for neurodegenerative complications such as Lou Gehrig's disease, Alzheimer's, Huntington's, and Parkinson's disease [29, 30]. It is also useful in dementia associated with AIDS. Additionally, it is useful in myoclonus and schizophrenia [31]. Herbal products having chromene glycosides have mostly been explored in the last 20 years. Chromene which has 2-oxo-2H is termed as coumarin (Fig. **1**). A few instances of 2-oxo-2H-chromenes are distinguished [32].

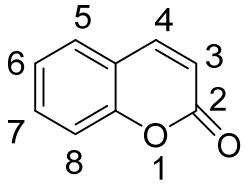

Fig. (1). Structure of coumarin.

Some chromene glycosides have been found in *Calophyllum dispar*. Few chromene derivatives have been obtained from the fungus *Aspergillus glaucus* (found in marine) [33], *Ocimum sanctum* contains ocimarin [34] and Lysilactones A-C is obtained from Lysimachiaclethroides, abundantly used as an indigenous medicine in China. *Streptomyces polyformus* extract contains polycarcin [35]. Arahypin-5 has been found in peanut seeds. Few derivatives have been found in citrus sinensis like atalaphyllidine, xanthyletin, seselin, and xanthoxyletin [36]. Calanones are obtained from the *Calophyllum teysmannii*. *Perithalia capillaris* algae extract contains prenylated chromene such as seselin [37].

CHAPTER 12

Chromene Derivatives as Potassium Channel Openers or Inhibitors

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Abstract: This overview depicts the voltage-regulated potassium channel, which is found in the CNS, and the emerging therapeutic applications of potassium channel modulators. It also discusses the recent developments in our understanding of the mechanisms, that control the activity of a series of channels, that are selective for potassium ions. It has been long recognized that the excitability of cells is mediated by proteins, which can modulate the ability of potassium ions to travel across the cell membrane. Going back ten years, it has become increasingly clear that, potassium ion channels represent an excellent target for novel drug design. Investigating the role of potassium channels in treating human diseases continues to be a growing field of research. The ability of potassium channels to regulate membrane potential accords a central role in varied cellular processes that govern excitability, action potential characteristics, stimulus secretion coupling, cell volume regulation, and epithelial electrolyte transport. Attention from medicinal chemists to potassium channels as drug targets has grown with the realization that a variety of potassium channel openers offer significant therapeutic opportunities in cardiac, smooth muscle, neuronal, immune, and secretary systems. Progressive improvements in molecular biology have enabled regular cloning of potassium channels of interest, and defined families of these channels have facilitated a comprehensive understanding of their function. Importantly many families of increasingly selective small molecules have emerged as target validation and clinical proof of principle. Many reviews have appeared summarizing the synthesis and therapeutic potential of these channels. The scope of this report is to make you aware of potassium channel biology, which leads to a more expedient identi-

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fication of agents for the treatment of CNS disorders, emphasizing developments in medicinal chemistry based on potassium channels where modulators would have considerable clinical potential. While every effort has been made to include all relevant reports in this discussion, any omission is inadvertent and we apologize for the same.

Keywords: Benzopyran, Cromakalim, K_{ATP}, Nicorandil.

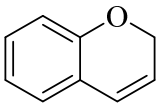
INTRODUCTION

Diseases of mankind have been treated by natural products including plants and their extracts for hundreds of years. Several potential compounds have been extracted that have shown potential therapeutic values. It seems that almost every plant could have medicinal properties, therefore few of them find a place in the modern system of medicine and the present official pharmacopoeial system. Until the middle 19th century, plants and their products were chief medicinal materials for the treatment of ailments. Rig Veda is probably the oldest repository of medicinal plants used for the treatment of various diseases. However, the passage of time and development in sciences leads to the systematic study of plant-based drugs resulting in the evolvement of disciplines like the chemistry of natural products, and organic and medicinal chemistry.

The key role of potassium channels involves resting membrane potential maintenance and action potential repolarization. Cell excitability, regulation of different functions of smooth and cardiac muscles, and the central nervous system are affected by membrane potential fluctuations. The regulation of potassium channels is mainly affected by calcium, cell metabolism, voltage, and receptor-mediated processes. Calcium and sodium channels are relatively unique, but different types of potassium channels are generally found in the same tissue. However, there is limited knowledge about the biological functions which are affected by various types of potassium channels. However, openers or inhibitors of potassium channels may play a significant role in the treatment of various ailments of smooth and cardiac muscles and the nervous system. On the other hand, diverse potassium channel modulators are being revealed at a faster pace by using modern methods of research [1, 2]. Development of newer compounds generally takes place on the existing prototype structures.

CHROMENES

Chromene (benzopyran) (Fig. **1**) is a heterocyclic organic compound resulting from the fusion of pyran with a benzene ring. Chromene ring system has been found to be present in several natural products such as hesperidin, warfarin, and genistein [3].



[Chromene (benzopyran)]

Fig. (1). Structure of chromene (benzopyran).

Heterocyclic chromenes form an extremely important class of compounds with diverse promising biological activities including antitubercular, anticancer, anticonvulsant, antimicrobial, antihyperglycemic, monoamine oxidase (MAO) inhibitor, formyl peptide receptor 1 (FPR1) antagonist and antiacetylcholinesterase. Particularly, the 2H/4H-Ch ring system has been used as a scaffold for designing compounds with potential antitumors and other medicinal activities. It has been found that various C3-ester substituted and C4-modified arty ethers at chromenes have better antagonistic activity against estrogen receptors, principally for Erα. On the other hand, 4H-benzo[h]chromenes incorporated with halogen-substituted benzene resulted in better antitumor activity and particular selectivity for c-Src kinase inhibition. The Methoxy group or halogen at the C-6 of the 2H-Ch scaffold is important for the antitumor activity [4].

HOW DOES THE POTASSIUM CHANNEL OPENER WORK?

The functions of potassium channels are regulated by alteration in the intracellular levels of ATP (adenosine triphosphate), thereby linking the membrane potential to the metabolic state of the cell, allowing the passage of potassium ions out of the cell, causing trans membrane hyperpolarization and repolarization. These effects result in the relaxation of smooth muscle by the reduction of intracellular calcium release [5, 6].

ATP-sensitive Channel

ATP-sensitive K_{ATP} channels, which are inhibited by the levels of intracellular ATP are found to be present in various tissues like pancreas beta cells, heart, skeletal and smooth muscles, and the central nervous system and are associated with numerous different cellular functions like insulin secretion, shortening of action potential duration and loss of cellular K^+ ions in the heart, regulating the excitability of skeletal muscles, relaxation of smooth muscles and release of neurotransmitters [7 - 13]. This is by far an extensively studied potassium channel probably by the availability of chemical agents modulating its activity. The opening of K_{ATP} has been found to be associated with the process of vasodilation. Out of all the potassium channels known today, 4-pyrrolidine benzopyran

CHAPTER 13

Miscellany of Chromene

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Abstract: Chromenes (Benzopyran) comprise a major class of pharmacophores widely distributed in various natural products, synthetic drugs, and therapeutic leads. They have been able to fascinate scientists due to the diverse pharmacological activities they possess and the variety of interesting chemical reactions they exhibit. This chapter critically reviews and highlights the general spectroscopic characteristics of chromenes, the diversity of naturally available chromenes as well as various strategies and mechanisms to develop synthetic chromenes. Recent biological application of chromenes of both natural and synthetic origin is also summarized here.

Keywords: Applications, Chromenes, Natural source, Synthetic strategies.

INTRODUCTION

Chromenes, also known as benzopyrans, are a crucial group of pharmacophores that occur naturally in a wide variety of products, as well as in synthetic pharmaceuticals and therapeutic leads. They possess numerous pharmacological properties that have captured significant attention and exhibit a plethora of notable chemical interactions. Chromenes are bicyclic oxygen heterocycles that feature a benzene ring with 5,6-positions of either a 2H-(**I**) or 4H-pyran (**II**) ring system as shown in (Fig. **1**). Both forms of the molecule - the 2H and 4H - are referred to as chromene, and contain a nine-carbon ring structure. Eight of these carbons are sp^2 hybridized, while one is sp^3 hybridized. The naming convention for 2H- and 4H-chromenes is determined by the relative position of the sp^3 carbon atom with the oxygen ring. The nomenclature method for 2H-chromene-2-one (**III**) and 4H-chromene-4-one (**IV**) is the same in which the sp^3 carbon is substituted by a carbonyl functional group (Fig. **1**).

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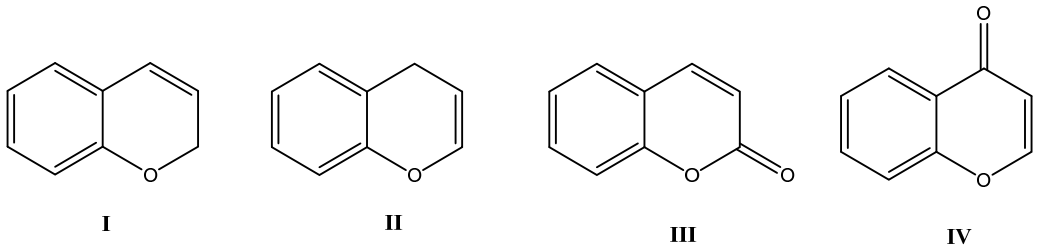

Fig. (1). 2H-Chromene (**I**), 4H-chromene (**II**), 2H-chromen-2-one (**III**), and 4H-chromen-4-one (**IV**).

Chromenes are the building blocks of distinct types of benzo- and naphthochromenes that arise from fusing the benzene or naphthalene rings to different parts of the chromene skeleton. The 2H-chromene scaffold can bond to the benzene ring in four different positions (c, f, g, h), generating four different forms of benzochromenes - benzo[c]chromene (**V**), benzo[f]chromene (**VI**), benzo[g]chromene (**VII**), and benzo[h]chromenes (**VIII**) Fig (as depicted in **2**). Similarly, fusing 2H-chromene with naphthalene leads to four distinct naphthochromenes (Fig. **2**). Additionally, a range of dibenzochromenes, such as dibenzo[c,f]chromene (**IX**), dibenzo[c,g]chromene (**X**), dibenzo[c,h] chromene (**XI**), *etc*., have been reported in Fig. (**2**).

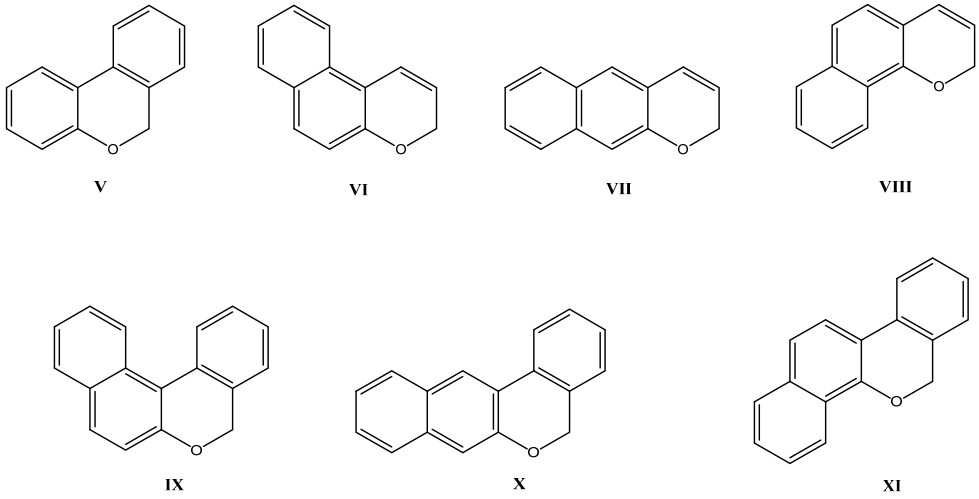

Fig. (2). 2H-Benzo[c]chromene (**V**), 2H-benzo[f]chromene (**VI**), 2H-benzo[g]chromene (**VII**), and 2H-benzo[h]chromene (**VIII**), dibenzo[c,f] cheomene (**IX**), dibenzo[c,g] chromene (**X**),dibenzo[c,h] chromene (**XI**).

Chromenes have been the subject of study for nearly five decades, and numerous chromene scaffolds containing natural products have been identified for their

pharmacological effects. Biogenetic pathways and synthesis have been thoroughly explored [1]. They are components of various naturally occurring polyphenols, alkaloids, coumarins, flavonoids, tocopherols, anthocyanins, rotenoids, stilbenoids, flavonoids, and chromene glycosides. They have demonstrated anticancer [2 - 6], anti-convulsant [7, 8], anti-inflammatory [9 - 14], analgesic [15], anti-microbial [16 - 23], anti-viral [24 - 27], anticholinesterase [28 - 31], antioxidant [11, 32 - 36], oestrogenic [37 - 39], and inhibitory activity against monoamine oxidase (MAO) [40 - 46], among other benefits. They have a higher degree of lipophilic characteristics, which allow them to cross cell membranes [47]. Their comparatively low toxicity profile, along with higher potency against a large number of diseases has sparked interest among medicinal chemists looking for new therapeutic drugs.

Over the years, various synthetic approaches have been employed to produce different chromene derivatives, including multi-component reactions [48], heterogeneous catalytic methods [49], electro-catalytic processes [50], green synthesis routes using aqueous media [51, 52], microwave [4], and ultrasound techniques [53]. Chromene derivatives are also used to create high-performance fluorescent dyes for synthetic fibers, daylight fluorescent pigments, electrophotographic and electroluminescent devices [54], as well as in lasers, optical brighteners, fluorescence markers, and cosmetics [55].

The present work has been conceived to highlight the importance and diversity of chromene derivatives reported from various natural sources, as well as distinct strategies and mechanisms to develop synthetic chromenes. General spectroscopic characteristics and recent biological applications of both 2H and 4H chromenes are also summarized here. The study is expected to aid researchers in their efforts to develop potent 2H and 4H chromenes as lead molecules for the treatment of a variety of life-threatening diseases as well as other industrial applications.

GENERAL SPECTROSCOPIC CHARACTERISTICS OF CHROMENES

The UV spectrum of 2H-chromene is characterized by two bands at λmax (hexane) 266.5 and 314.0 nm. The band at λmax 266.5 nm corresponds to a conjugation band (K), while the band at λmax 314.0 nm arises due to the $\pi-\pi^*$ transition (B band) [56]. 2H-chromenes and their derivatives typically absorb strongly at the B band and in the 260-279 nm range. Absorption at higher wavelengths in the 304-316 nm or 324-340 nm range is also observed, particularly with the addition of functional groups like hydroxyl and carbonyls to the benzene ring. Since the C=C bond in 4H-chromenes is not in conjugation with the benzene ring, their UV spectrum is similar to that of substituted benzene derivatives, and typically appears in the region of 275-285 nm [57]. Benzo fused chromene such

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Ashutosh Kumar Dash

Ashutosh Kumar Dash: Dr. Ashutosh Kumar Dash is proficient in medicinal chemistry/ organic chemistry/ basic chemistry/pharmaceutical sciences with an experience of 12 years in research and academic sectors. Over the years, he developed expertise in basic as well as applied research (medicinal/ pharmaceutical chemistry; natural product based medicinal chemistry and carbohydrate chemistry) as an assistant professor and researcher in the Natural Product Chemistry division of CSIR-Indian Institute of Integrative Medicine, (IIIM) Jammu. In natural product chemistry, he has expertise in isolation of secondary metabolites from microbial and plant sources, DOS, semi-synthetic modifications, and medicinal chemistry against specific targets in cancer, diabetics, inflammation, etc. He has expertise in the drug development process from synthesizing and optimizing to its detailed pharmacology. Sincere efforts for synthesizing new drug discovery targeting these vital aspects of cancer and having a good working experience with methodologies in organic chemistry has been achieved. He has extensively published in peer-reviewed and book chapters with Springer and Elsevier publishers. He has successfully accomplished 4 major projects including BIRAC, ICMR and Institutional projects. Dr. Dash has 9 patents to his credit. He mentored Ph.D. and doctoral research scholars as well as M. Pharm and B. Pharm students in their dissertations. He is a board member in a number of journals.

Deepak Kumar

Deepak Kumar: Prof. Deepak Kumar serves as professor in the department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences. He received Ph.D. from South Korea under the prestigious Brain Korea 21 Plus fellowship. Prior to that, he did M Pharm from Sikkim Central University, Sikkim. He has been invited as a chairperson, keynote and session speaker in reputed national and international conferences. He has been honoured with the High impact factor Research Award 2022 by the governor of Himachal Pradesh; Excellence Research Award 2022; International Scientist Awards 2021; Young Scientist Award 2020; etc. He is also serving as reviewer in several scientific journals, consultant to industries, and committees of various universities. Prof. Kumar is an active member of the American Chemical Society, Association of Pharmacy Profession and member of Chemical and Pharmaceutical Society from India and S. Korea. His research areas include medicinal chemistry and drug discovery, bioorganic chemistry, drug delivery, nanomedicine, chemical biology, etc.