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Biological Evaluation and Synthesis, Characterization of Heterocyclic Compounds



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ABSTRACT

Chromenes and their derivatives exhibit characteristic IR, UV, ¹H NMR, ¹³C NMR and mass spectral data, which are extremely useful in monitoring the course of reactions as well as identification of the products of the synthesis. Some salient features of the spectral characteristics of chromene are summarized here. Heterocyclic compounds are very important branch of organic and medicinal chemistry. Among these widespread heterocyclic compounds; oxygen heterocycles occupies a discrete position because of their natural abundance and large biological as well as pharmaceutical significance.



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INTRODUCTION

Heterocyclic compounds are very important branch of organic and medicinal chemistry.¹ Among these widespread heterocyclic compounds; oxygen heterocycles occupy a discrete position because of their natural abundance and large biological as well as pharmaceutical significance.² In this particular class of *o*-heterocyclic's, '*Chromene*' heterocyclic scaffolds signify a "privileged" structural design and are well-distributed in natural products with a broad spectrum of potent biological activities that contain anti-microbial,³ anti-viral,⁴ anti-inflammatory,⁵ antimalarial,⁶ sex-hormonal,⁷ anti-tumor,⁸ anti-cancer,⁹ anti- Alzheimer, anti-Parkinson,¹⁰ estrogenic¹¹ and many more.

Bicyclic oxygen heterocycles resulting from combination of benzene ring with 5,6-positions of either 2H- or 4H-pyran ring system are designated as 2H-chromene (2H-1-benzopyran) (**1**) and 4H-chromene (4H-1-benzopyran) (**2**) (**Figure-1**).

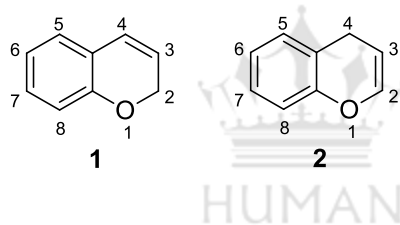


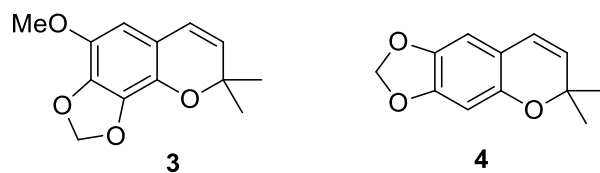
Figure 1. 2H-chromene (2H-1-benzopyran) (**1**), 4H-chromene (4H- 1-benzopyran) (**2**). This chapter presents a summary of a literature survey on the synthesis and biological significance of 2H-chromene fused derivatives. The present assessment captures the information on so many chromene derivatives as synthetic tools for our research work.

1. Biological significance of 2H-Chromene ring system

2H-Chromenes and their derivatives are widely distributed in nature isolated from different medicinal plants and found useful in the healing of different ailments.

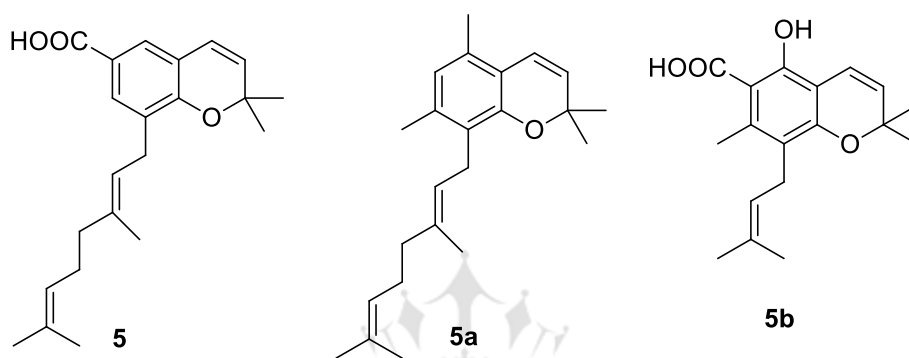
Anticancer activity

Two new myriachromene (**3**) and 2, 2-dimethyl-6, 7-methylenedioxy-2H-chromene (**4**) were synthesized and reported as potential anticancer agents.¹²



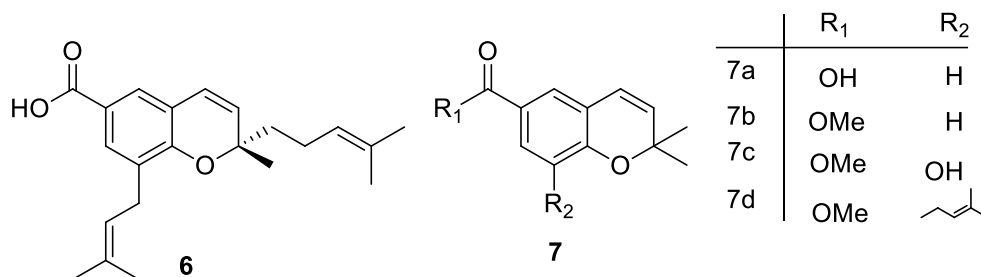
Antifungal activity

A new chromene cumanensic acid (**5**) and its derivatives (**5a**, **5b**) have been isolated¹³ from *Piper cf. cumanense* Kunth. (*Piperaceae*). The compounds **5**, **5a**, **5b** displayed antifungal activity against *Fusarium oxysporum* f. sp. *dianthi*.



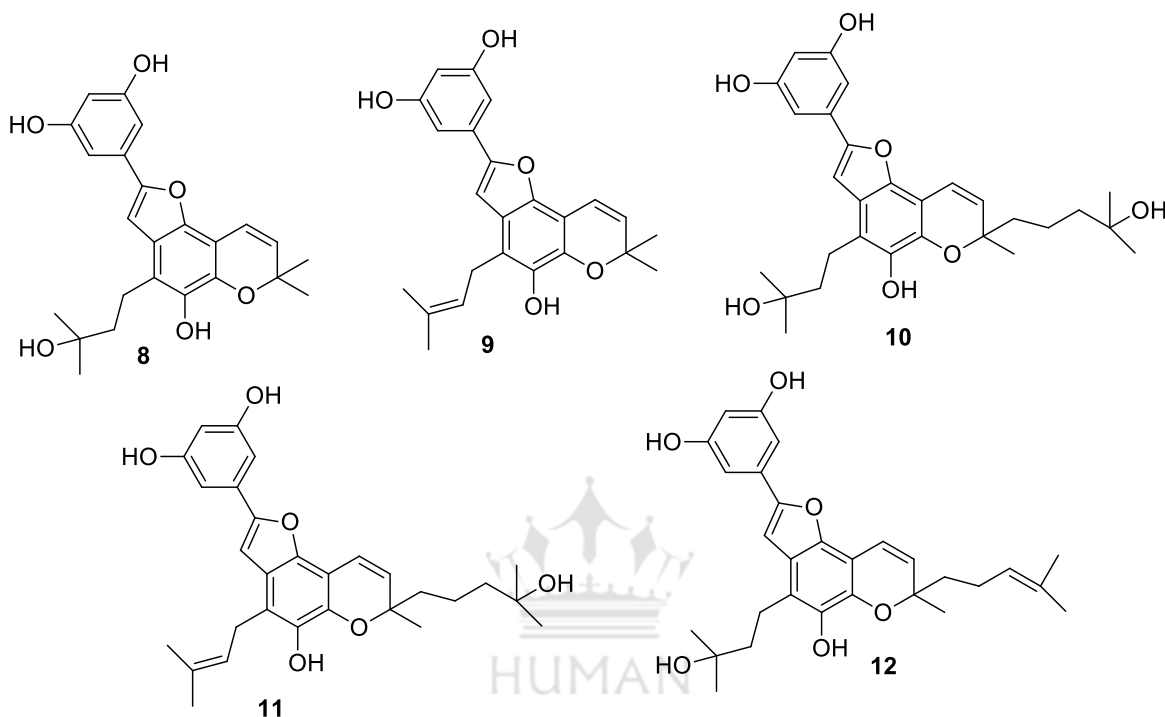
Cytotoxicity against -Antitumor activity

Several biologically active chromenes have been isolated from species of the *genus Piper*, including the prenylated chromene (**6**) from *Piper gaudichaudianum* and chromenes (**7a-d**) from *P. aduncum*, these chromenes show antitumor properties.^{14, 15, 16}



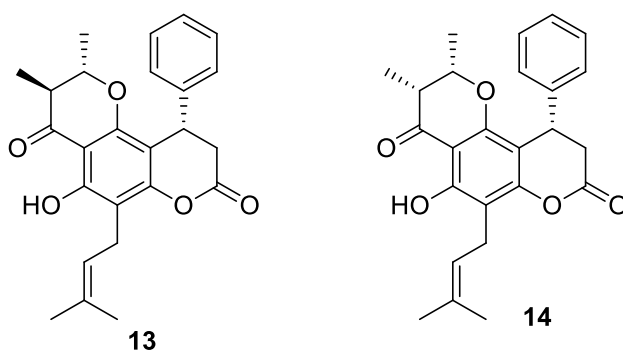
Antioxidant and anti-inflammatory activity

Five new furo[f]chromenes known as Wittifurans A–C, F, and G (**8-12**) have been isolated from the stem bark of *Morus wittiorum* and exhibited their antioxidant and anti-inflammatory activities.¹⁷



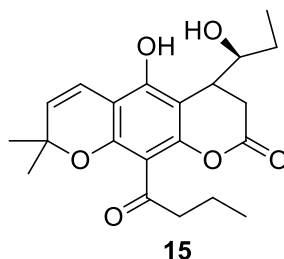
Anti-HIV activity

The anti-HIV compounds calopolyanolide C (**13**) and calopolyanolide D (**14**) were isolated from *C. polyanthum wall*.¹⁸



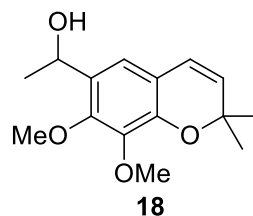
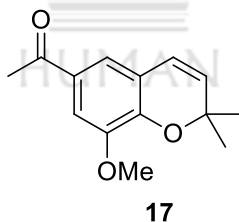
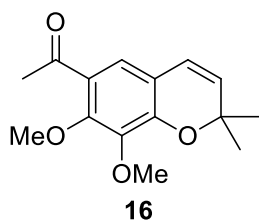
Antimalarial activity

A linearly pyrano-fused coumarin, Theraphin C (**15**) was synthesized and examined for its antimalarial activity against the chloroquine sensitive and resistant strains of *Plasmodium falciparum*.¹⁹



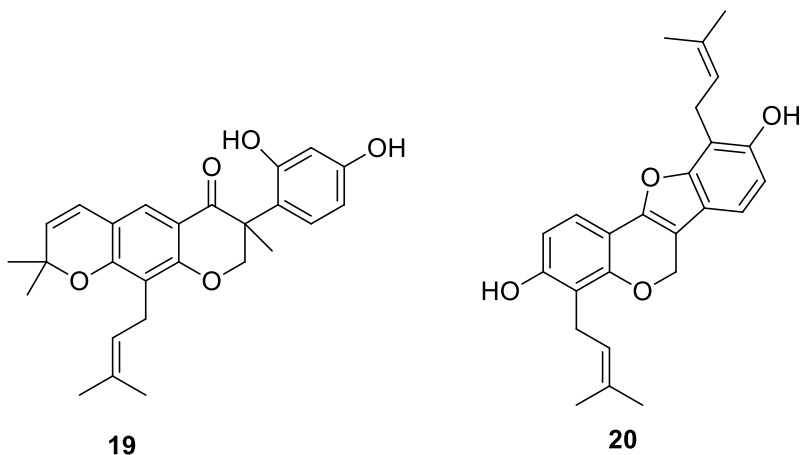
Hypertension and diabetes

Three 2H-chromenes methylripario chromene A (**16**), acetovanillo chromene (**17**) and ortho chromene A (**18**) are isolated from the leaves of *Orthosiphon aristatus* have been used as traditional prescriptions for the treatment of hypertension and diabetes.²⁰



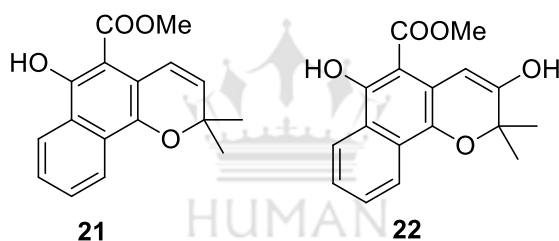
Antibacterial activity

Two new fused chromenes (**19**, **20**) have been isolated from the roots of *Erythrina variegata* and their structures have been elucidated by spectroscopic analyses. The new chromenes have shown antibacterial activity against methicillin-resistant *Staphylococcus aureus*.²¹



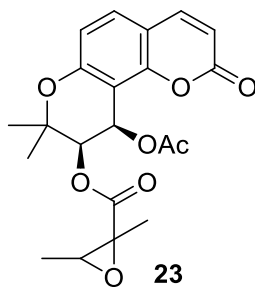
Antiviral activity against hepatitis B

Mollugin (21) and its derivatives (22) were prepared and demonstrated potential antitumor, antimutagenic as well as antiviral activity against hepatitis B virus.^{22, 23}



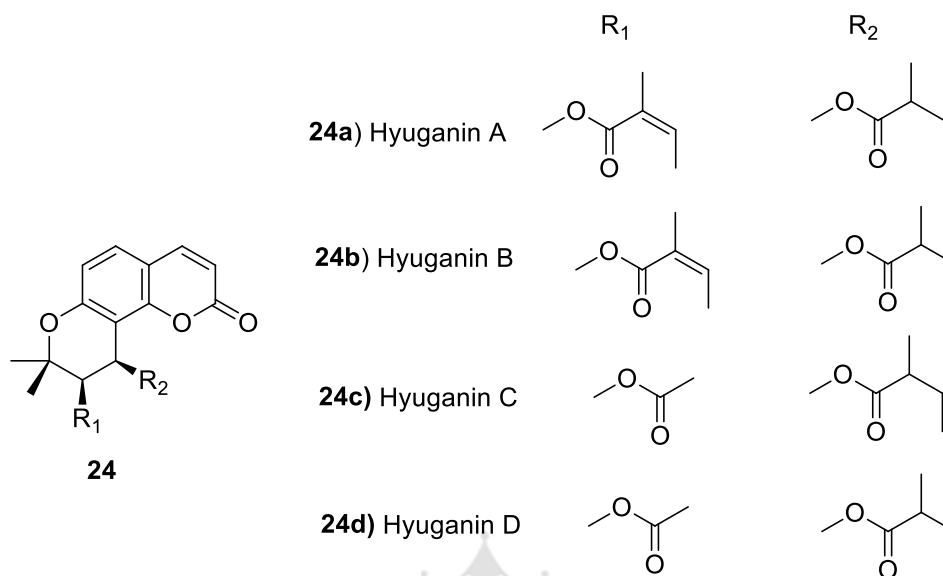
For treating allergies and inflammations

(3'R,4'R)-3'-Epoxyangeloyloxy-4'-acetox-3',4'- dihydroseselin (23) was extracted from the leaves of *Angelica shikokiana* and purified for treating allergies and inflammations, especially bronchitis and skin allergies.²⁴



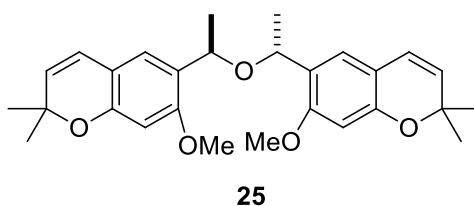
Vasorelaxant activity

From the methanolic extract of *Angelica furcula* KITAGAWA, four new khellactone-type coumarins Hyuganins A, B, C, and D were isolated and displayed vasorelaxant activity.²⁵



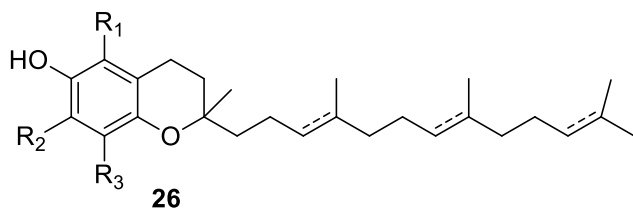
Anti-ulcer activity

An anti-ulcer chromene (25) was isolated from *Eupatorium aschenbornianum* and also reported its synthetic route.²⁶



In Vitamin-E

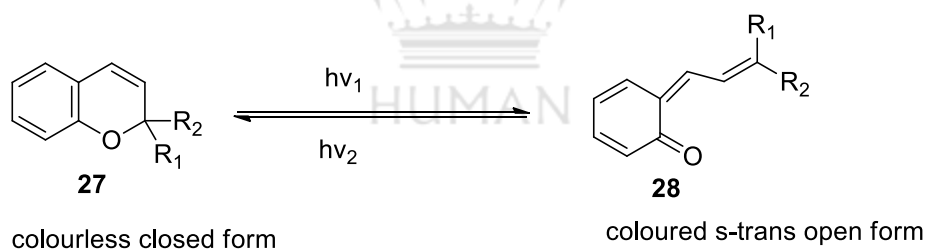
The chromane ring can also be found in vitamin E constituents, tocopherols, and tocotrienols. The tocopherols and tocotrienols have α , β , γ , and δ forms, named based on the number and position of the methyl groups on the chromane ring.²⁷



	R ₁	R ₂	R ₃
α	CH ₃	CH ₃	CH ₃
β	CH ₃	H	CH ₃
γ	H	H	CH ₃
δ	H	CH ₃	CH ₃

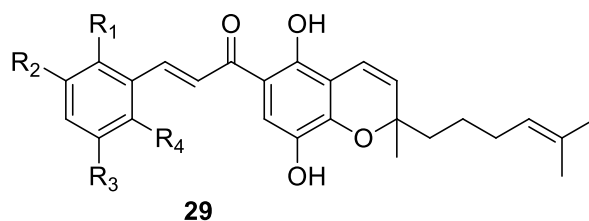
Photochromism^{28, 29}

Photochromism is one of the properties of 2H-chromene that has drawn attention among Scientists. The reversible action of rapid color changing of a compound when irradiated with light containing ultraviolet rays such as sunlight or light of a fluorescent lamp and resumption of the initial colour when placed in a dark place is called photochromism. It is the result of the ability of this compound to undergo a reversible cleavage of the alkylic C-O bond, leading to a quasi-planar 'open form' with a distinct absorption spectrum, *i.e.* different colours.



As dyes and cosmetic³⁰

The natural products (**29a-c**) of the flemingin series are important as they are among the few natural 2H-chromenes without 2, 2-dimethyl substituent. They are found in the seedpods of a *Leguminosae* (*Flemingia rhodocarpa* Baker), and its powder is used as dye a cosmetic and a drug called wars, which is sold in East Africa.



29a) $R_1 = OH$, $R_2 = R_3 = R_4 = H$, Flemigin A

29b) $R_1 = R_4 = OH$, $R_2 = R_3 = H$, Flemigin B

29c) $R_1 = R_3 = OH$, $R_2 = R_4 = H$, Flemigin C

Since several substituted chromenes have a diverse range of biological activities. The present work is planned to synthesize several new and biologically active novel chromene derivatives. The results of the present study are discussed in 3 chapters.

2. Biological evaluation and Synthesis, Characterization of heterocyclic compounds. **General methods for the synthesis of chromene derivatives**

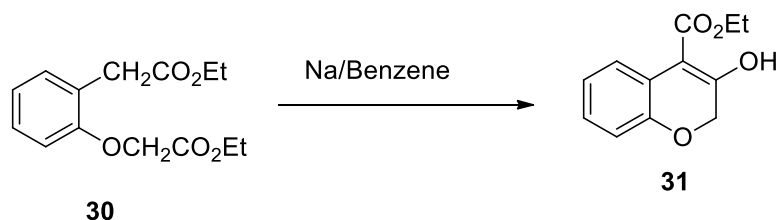
In general, it is observed that chromenes with an alkyl, aryl, heteryl moiety substituted at 3 or 4 positions or a fused heterocycle at 3, 4-position of chromenes have greater biological activity compared to the presence of substituent or fused heterocycle in the aromatic ring of the chromene.

2.1. *Synthesis of substituted chromenes*

1. *By Dieckmann reaction*³¹

Intermolecular condensation of diester in the presence of sodium in benzene or toluene resulted in 3-hydroxy-4-ethoxycarbonyl-2H-chromene (**31**) (Scheme 1).

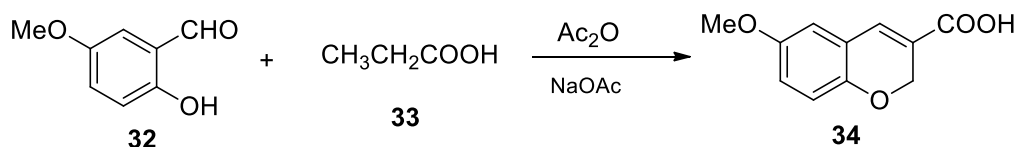
Scheme-1:



2. By Perkin reaction³²

A reaction of substituted salicylaldehyde (**32**) in the presence of acetic anhydride and sodium acetate produced chromene with carboxylic acid at position 3 of the lactones ring (**34**) (Scheme 2).

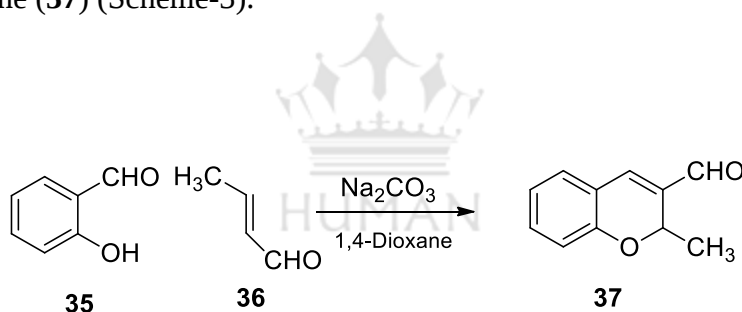
Scheme-2:



3. Reaction of salicylaldehyde with 3-methyl-acrolein³³

Reaction of salicylaldehyde (**35**) with 3-methyl-acrolein (**36**) in Na_2CO_3 gives 2-methyl-3-formyl-2H-chromene (**37**) (Scheme-3).

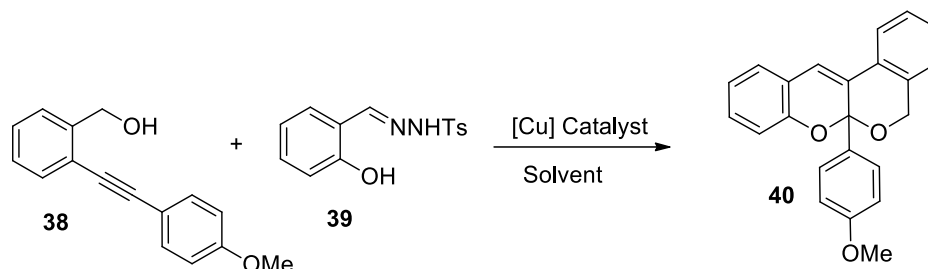
Scheme-3:



4. Copper-Catalyzed 2H-Chromene Synthesis

Liu and co-workers³⁴ were reported a copper-promoted tandem reaction of internal alkynol (**38**) and salicyl-N-tosylhydrazone (**39**) to produce isochromeno [3, 4-b] chromene (**40**) (Scheme- 4). This methodology works best with copper (II) perchlorate as the catalyst in a toluene/dioxane (1:4) solvent mixture at 60 °C.

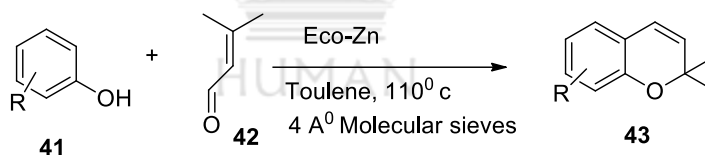
Scheme-4:



5. Eco-Zn-Catalyzed Synthesis of 2H-Chromenes from Biomass:

Escande et al., reported³⁵ a general and efficient method to synthesize 2H-chromenes based on the concept of Eco-catalysis, which involves the use of biomass-derived metallic elements for chemical synthesis. In this process, phyto extraction processes are used to obtain valuable metals. The Eco-Zn was extracted from Zn-hyper accumulating plant leaves derived from *Noccaea caerulescens* (*Brassicaceae*) (Scheme-5).

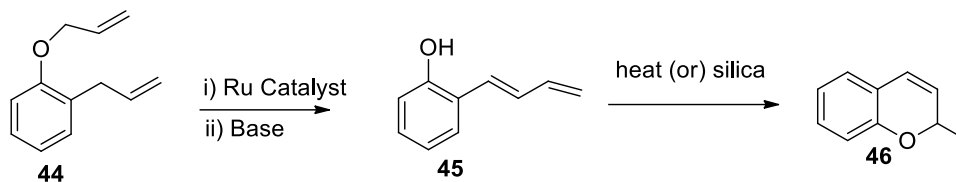
Scheme-5:



6. Synthesis of Chromenes via RCM/Base-Induced Ring-Opening Reaction

Ram chary et al. reported³⁶ a new method for the synthesis of highly substituted (Z)-2-(buta-1, 3-dienyl) phenols from highly substituted dienes by a combination of ring-closing metathesis (i) and base-induced ring-opening (ii). The corresponding phenol then transformed to the desired 2-methyl-2H-chromenes via a [1, 7]-sigma tropic H-shift reaction followed by electro cyclic ring closure (Scheme-6).

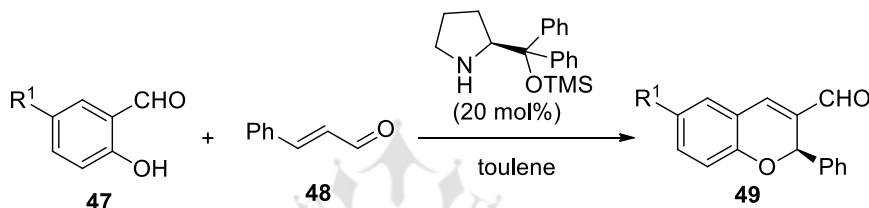
Scheme-6:



7. Enantioselective Domino Oxa-Michael/Aldol Condensation

Cordova and co-workers³⁷ independently developed almost the same organocatalytic methodology for the synthesis of optically active chromenes as described (scheme-7).

Scheme-7:

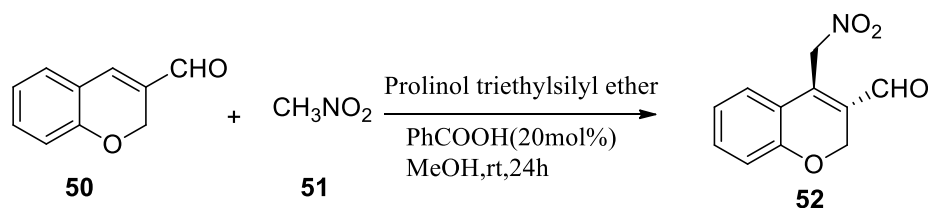


2.2. Synthesis of chromene derivatives

1. Organocatalytic conjugate addition of nitroalkanes to 2H-chromene-3-carbaldehydes:

The conjugate addition of nitroalkanes to 2H-chromene-3-carbaldehydes (**50**) was studied in the presence of prolinol triethylsilyl ether catalyst. This reaction provides a new method for the preparation of highly functionalized chroman derivatives (Scheme-8).³⁸

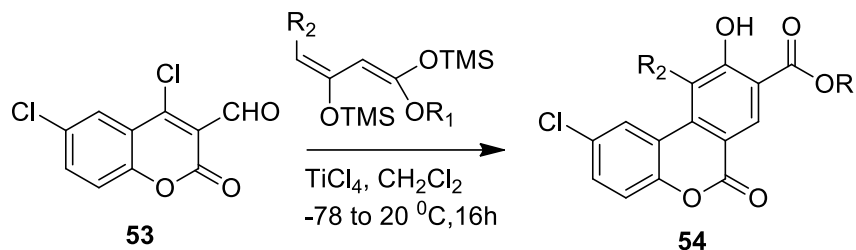
Scheme-8:



2. Synthesis of benzo[c]chromen-6-ones:

The cyclocondensation of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde (**53**) with 1,3-bis(silyloxy)-1,3-butadienes provides a convenient synthesis of benzo[c]chromen-6-ones (**56**) (Scheme-9).³⁹

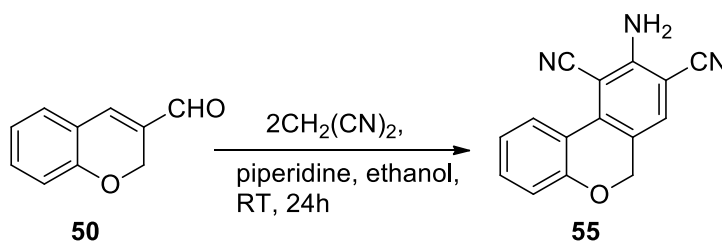
Scheme-9:



3. Reaction of chromene-3-carbaldehyde with malononitrile:

A simple and efficient method was developed for the reaction of 2H-chromene-3-carbaldehydes (**50**) with malononitrile in the presence of piperidine gave 9-amino-6H-benzo[c]chromene-8, 10-dicarbonitriles (**55**) in good yields. (Scheme-10).⁴⁰

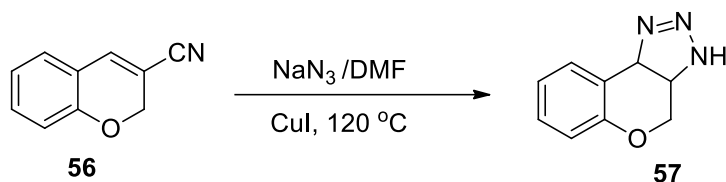
Scheme-10:



4. copper catalyzed reactions of cyanochromenes and sodium azide:

Gawande et al. reported the synthesis of chromenotetrazoles (**57**) derivatives from cyanochromenes (**56**) and sodium azide under copper catalyst conditions (Scheme-11).⁴¹

Scheme-11:



4. Spectral characteristics of chromene scaffold:

Chromenes and their derivatives exhibit characteristic IR, UV, ^1H NMR, ^{13}C NMR and mass spectral data, which are extremely useful in monitoring the course of reactions and identifying the products of the synthesis. Some salient features of the spectral characteristics of chromene are summarized here.

4.1) UV spectral data⁴²

The UV spectrum of 2H-chromene (**1**) displays two bands of λ_{max} (hexane) 266.5 and 314.0 nm, of which the former is a conjugation band (K) while the latter at 314.0 nm is a B band that arises due to the $\pi-\pi^*$ transition. The most prevalent absorption of 2H-chromene is their B band, which appears both in parent and its derivatives in the region 260–279 nm with $\log \epsilon$ of 3.15–4.30. When absorption in this region is absent, the B band is found at 280–299 nm with $\log \epsilon$ of 3.68–4.01. The higher wavelength absorption of 2H-chromenes generally appears at either 304–316 nm or 324–340 nm. The presence of functional groups such as hydroxyl and carbonyls on the benzene ring enhances absorption at higher wavelengths.

4.2) IR Spectral data^{42,43}

The IR spectrum of 2H-chromene (**1**) is reported^{42, 43} at 3040 (w), 2970 (w), 1644 (m), 1613 (m), 1480, 1495 (s), and 1230 cm^{-1} (aromatic ether). The diagnostic peaks are C=C stretching of the pyran ring at 1644 cm^{-1} and C–O stretch of the aromatic ether of the pyran ring at 1230 cm^{-1} .

4.3) ^1H NMR spectral data⁴³

In the ^1H NMR (CDCl_3) spectrum of **50** the 2-OCH_2 appears as singlet at δ 5.04, H-4 appears at δ 7.26 as a singlet, H-7 at d 7.30 (t, $J = 7.8$ Hz, 1H), H-5 at δ 7.20 (d, $J = 7.6$ Hz, 1H), H-6 at δ 6.96 (t, $J = 10.8$ Hz, 1H) and the H-8 at δ 6.87 (d, $J = 8.4$ Hz, 1H).

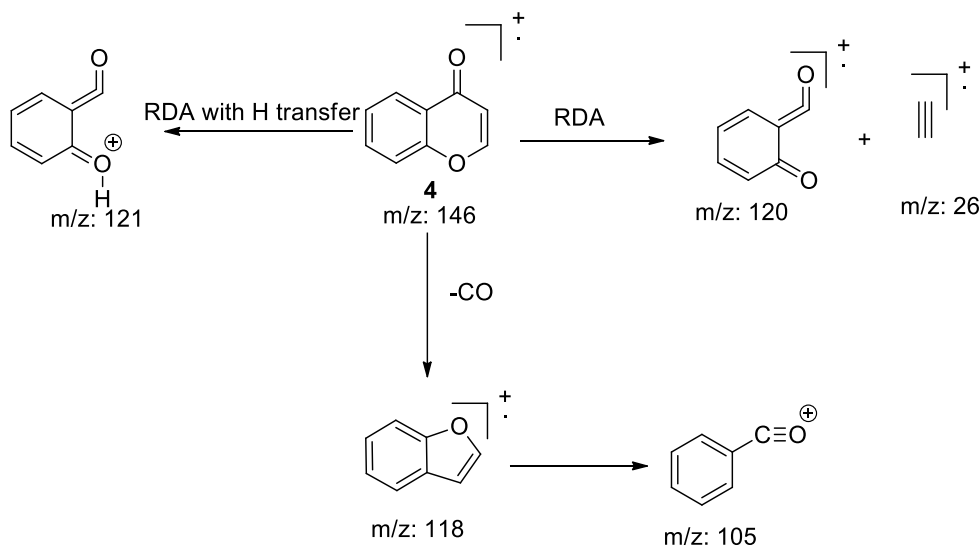
4.4) ^{13}C -NMR Spectral data⁴³

In the ^{13}C NMR (CDCl_3) of **52**, the aldehyde carbon resonates at δ 169.2, OCH_2 at δ 68.2, C-4 at δ 139.2 and C-3 at δ 106.3. The aromatic signal assignments are δ 156.1 (C-8a), 133.5 (C-7), 1289.2 (C-5), 123.2 (C-6), 121.0 (C-4a), 117.3 (C-8).

4.5) Mass spectral data⁴⁴

The electron impact (EI) mass spectra of oxygen heterocyclics afford valuable clues in the identification of the ring system and the position of the substituents⁴⁴. In the simple 4H-chromene (**4**), the molecular ion is intense and generally appears as the base peak. Elimination of carbon monoxide from the molecular ion of 146 gives the benzofuran ion at m/z 118. Fragmentation by retro Diels-Alder (RDA) pathway gives RDA ion (m/z 120) and ionized acetylene (m/z 26) (Scheme-12). The RDA with proton transfer is also observed in 4H-Chromene.

Scheme-12



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