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Synthesis and biological significance of 2*H*-chromene analogs: A Review

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Abstract:

This review presents an overview of literature survey on the synthesis and biological significance of 2*H*-chromene substituted analogs. Present literature focuses on the biological significance and synthesis of these derivatives in the last 33 years from 1982 to 2015. The present survey captures the information on so many chromene scaffold containing analogs.

Keywords: Synthesis of 2*H*-chromene, Anti-HIV Activity, anticancer, antioxidant, Anti Inflamatory activity, Antimycobacterial activity, Antiproliferative activity

Introduction:

Chemistry of 2*H*-Chromenes

Chromene well known as the benzopyran is a polycyclic organic compound that results from the fusion of a benzene ring to a heterocyclic pyran ring. According to IUPAC nomenclature, it is called chromene. There are two isomers of benzopyran that vary by the orientation of the fusion of the two rings compared to the oxygen, resulting in 1-benzopyran (chromene,) and 2-benzopyran (isochromene), the number denotes where the oxygen atom is located by standard naphthalene like nomenclature. The structural isomers of 2*H*-chromens (Fig.1) are

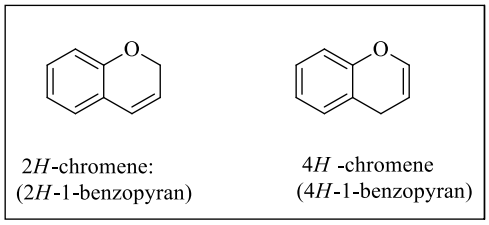


Fig. 1

Structural isomers of Iso-chromene (**Fig. 2**) are

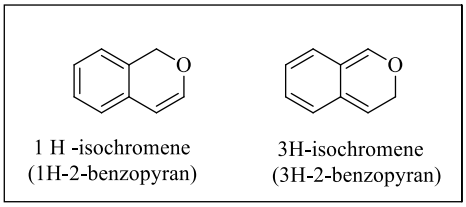


Fig. 2

Some novel 2*H*-chromene substituted 1,2,4- (Fig.3) and 1,3,4- (Fig.4) oxadiazoles and pyrimidine substituted ureide structural units are found in a large number of drugs and in natural products[1]. Chroman derivatives exhibit various useful biological activities[2], such as antioxidant[3], antiestrogen[4], anticonvulsion[5], and neuroprotection[6]. Many synthetic methods for chromans have been developed[2, 7].

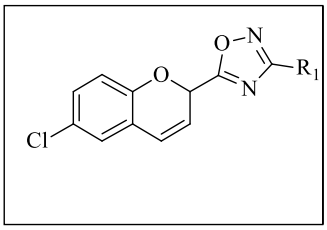


Fig.3.

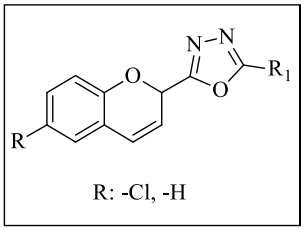


Fig.4

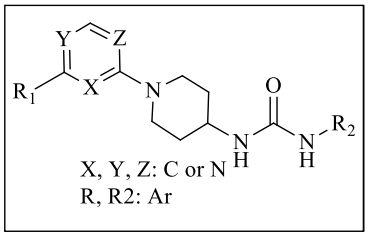


Fig.5

Part-A: Biological significance of 2*H*-Chromene ring system

The 2*H*-chromene moiety is a common structural feature of numerous biologically active molecules, as the derivatives of 2H-chromens are found to have, anticancer, anti inflammatory, antioxidant.etc activities. Several modes of activities are described as follows.

Anti-HIV Activity

The following is a natural product, isolated from the roots of *Pentas bussei*, a plant found in Kenya. The decoction of the roots is used as a remedy for gonorrhea, syphilis, and dysentery. Conocurvone (8,8':9',8"-Ter-3H-naphtho(2,1-b)pyran)-7,7',7",10,10',10" -hexone, 9, 9" -dihydroxy-3, 3', 3"-trimethyl-3,3',3" -tris(4-methyl-3-pentenyl)-(3R, 3'R, 3"R)-) (Fig.6) is a unique natural product in that it contains three naphtha-pyrandione units, and this fact was related to its remarkable anti-HIV activity[8] .

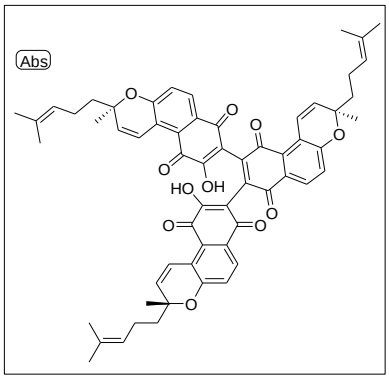


Fig.6

Anti-Cancer Activity

Mohammad. A. *et al.*[9] reported a series of 2*H*-chromene derivatives (Fig.7) bearing thiazolidine-2, 4-dione, in which the following series of molecules are reported as potential anticancer agents.

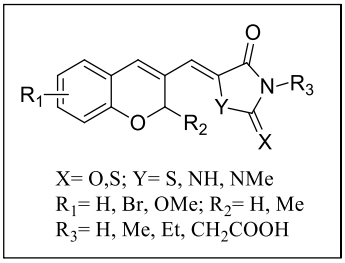


Fig.7

Jiyoung. M. *et al.*[14] developed a series of substituted N-[(2, 2-dimethyl-2H-chromen-6-yl) methyl]-N-phenylbenzenesulfonamides in which N-[(2,2-dimethylchromen-6-yl)methyl]-N-isopropyl-3,4-dimethoxy-benzenesulfonamide (Fig.8) was found to play an important role as an anti-cancer agent.

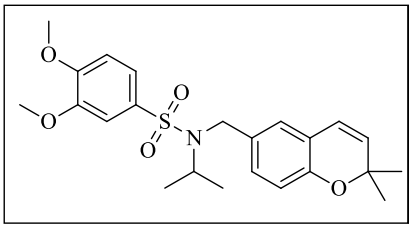


Fig.8

Anti Inflamatory activity

Nozaki. C. *et al.*[10] discovered selective, and orally bioavailable delta opioid receptor agonists. The lead derivative, N, N-diethyl-4-(5-hydroxyspiro [chromene-2,4'-piperidine]-4-yl)benzamide (Fig.9) is currently in phase II proof-of-concept studies for the management of pain. Further structure activity relationship exploration has led to the discovery of N, N-diethyl-3-hydroxy-4-(5-hydroxyspiro[chromene-2,4'-piperidine]-4-yl)benzamide (Fig.10), which is approximately 50-fold more potent than the other, was selected as a clinical candidate for the treatment of pain.

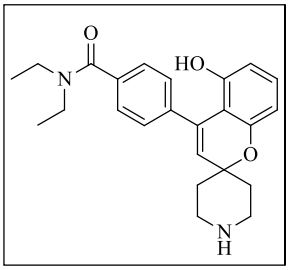


Fig.9

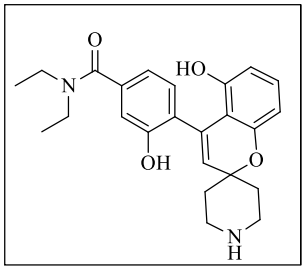


Fig.10

Antioxidant activity

Okram. M. S. *et al*[11]. synthesized a series of novel 3-substituted-2*H*-chromene-2-thiones, in which (8-methoxy-2-thioxo-chromen-3-yl)-(2-thienyl) methanone (Fig.11) was found to exhibit the best antioxidant activity.

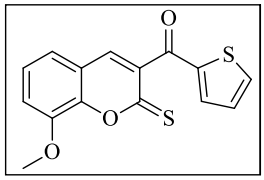


Fig.11

Cytotoxicity activity

Subba Reddy. B. V. *et al.*[12] developed the synthesis of novel polycyclic chromene derivatives and they were found to have considerable cytotoxic activity. Among the developed series of molecules, the following compound (Fig.12) is found to have considerable inhibitory concentration (IC_{50}= 1.67) and the best among the developed series.

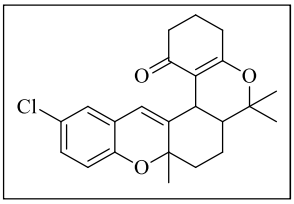


Fig.12

Anti-tumor activity

Eugene. *et al.*[13] described the biological importance of some chromene derivatives, as 1-(ethylamino)-3-[4-[7-[3-(ethylamino)-2-hydroxy-propoxy]-2H-chromen-3-l]phenoxy]propan-2-ol (Fig.13) and 1-(hexylamino)-3-[4-[7-[3-(hexylamino)-2-hydroxy-propoxy]-2*H*-chromen-3-yl]phenoxy]propan-2-ol (Fig.14) had shown considerable anti-tumor activity.

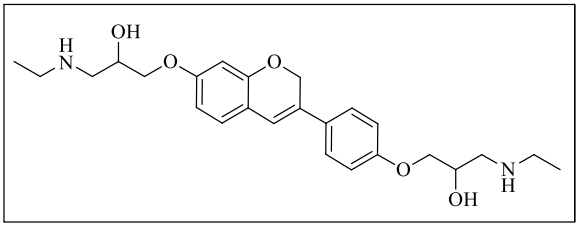


Fig.13

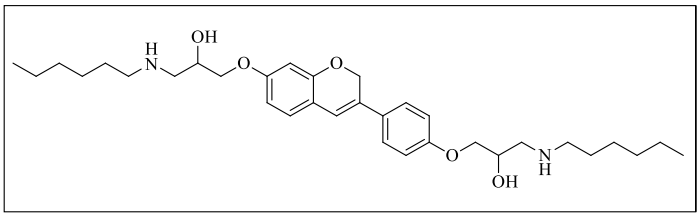


Fig.14

Jiyoung. M. *et al.*[14] proposed that 3, 4-dimethoxy-N-[(2, 2-dimethyl-2*H*-chromen-6-yl) methyl]-N-phenylbenzene sulfonamide (Fig.15) was found to play an important role as an anti-tumor agent.

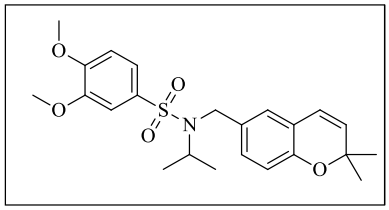
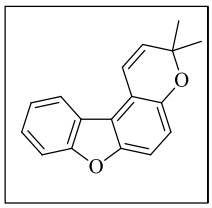


Fig.15

Antimycobacterial activity

Prado. S. *et al.*[15] discovered a selective *in-vitro* inhibitor of mycobacterial growth and designed a series of molecules, in which 3,3-dimethylbenzofuro[3,2-f]chromene (Fig.16), 3,3-dimethyl-1,2-dihydrobenzofuro[3,2-f]chromene (Fig.17). These compounds were found to have considerable anti-mycobacterial activity.



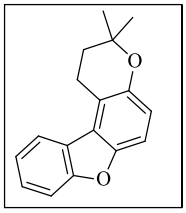


Fig.16 Fig.17

Anti -diabetic

Nowakowska. Z. *et al.*[16] described N- [2- [4-(azepan-1-yl carbamoylsulfamoyl) phenyl]ethyl]-6-chloro-2H-chromene-8-carboxamide (Fig.18) which was tested for potential antidiabetic activity as a Na^+-glucose co-transporter inhibitor.

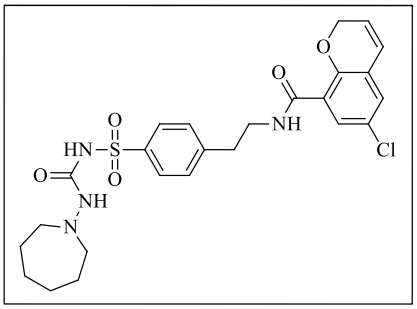


Fig.18

NF-kB inhibitory activity[17]

In 2014 Choi et al.[17], made a novel class of substituted chromenes using KL-1156 and examined their activity against a nuclear factor kappa B (NF-kB) and targeted cancer cell lines. From the SAR studies, it was found that among four modified parts of KL-1156 the new N-aryl, 3,4-dihydro substituted 2*H*-benzo[h]chromene-2-carboxamides were found to have excellent inhibitory activity against NF-kB and consequently showed better anti-proliferative activities than original KL-1156 molecule.

Antiproliferative activity[18]

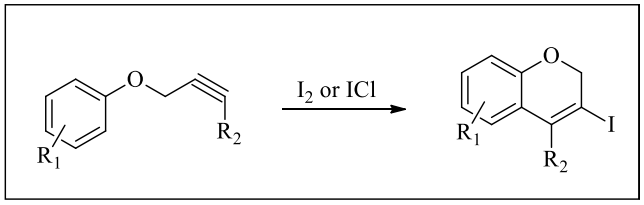
Lima *et al.*[18]synthesized a series of chromene containing fused imidazo[1,2-a] pyridine derivatives and tested their antiproliferative effects on HCT116 human cancer cell line[18]. The authors found that compound with carbamate group at 8th position of pyridine ring was observed to be most-effective among the series and showed the cell death by the apoptosis.

Part B: Important Methods for the synthesis of 2*H*-Chromenes

Synthesis of 2*H*-chromene derivatives have been described using several reactive species, some of these methods have been briefly discussed here.

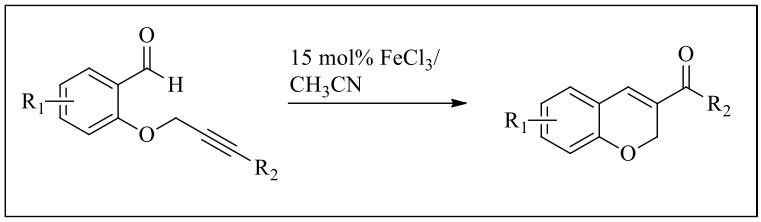
From O-Propargyl Phenols

The electrophilic cyclization of substituted propargylic aryl ethers by I_2, ICl, and PhSeBr produces 3,4-disubstituted 2H-benzopyrans[19] (Scheme-**1)** in excellent yields was reported by Larock. R. C. *et al.* This methodology results in vinylic halides or selenides under mild reaction conditions and tolerates a variety of functional groups, including methoxy, alcohol, aldehyde, and nitro groups.



Scheme-1

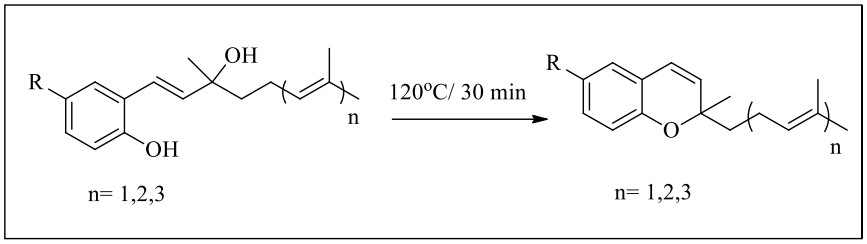
Iron-Catalyzed synthesis of functionalized 2*H*-Chromenes through intramolecular Alkyne-Carbonyl Metathesis was reported by Umasish. J. *et al* , works under mild reaction conditions to produce the functionalized 2*H*-chromene derivatives[20] (Scheme-**2**), compatible toward a wide range of functional groups, such as methoxy, fluoro, chloro, bromo.



Scheme-2

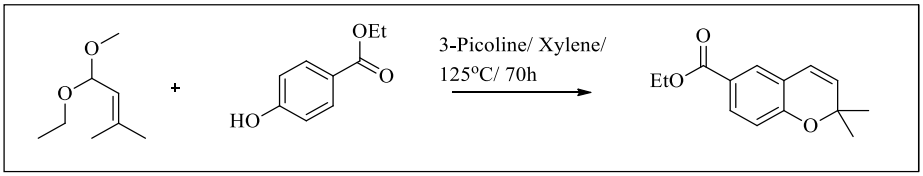
From Phenols

The catalyst free preparation of 2*H*-benzopyrans from bromophenols and tertiary allylic alcohols is described by Goujon. J. *Y. et al.*[21] (Scheme-**3**). The reaction is characterized by its mildness, good yields and ease of work-up.



Scheme-3

The following retinoic acid receptor alpha antagonist lead compound has been synthesized by the practical synthesis of a chromene by reacting corresponding phenol derivative with 3-methyl but-2-enol diethyl acetal in presence of 3-picoline and in xylene obtained considerable yields, reported by Mohammad. A. *et al.*[22] (Scheme-**4**).



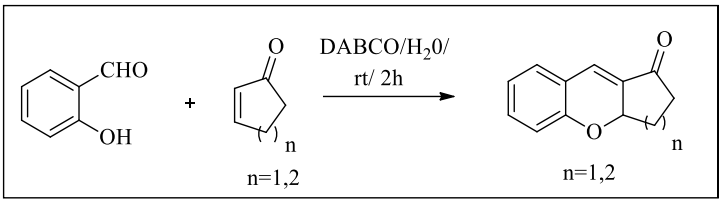
Scheme-4

From Salicyladehyde

Salicylaldehyde upon reacting with potassium vinyl trifluoroborates in presence of dibenzylamine afforded 2-substituted 2*H*-chromenes described by Bhaskar. *et al.* [23] Potassium vinyl trifluoroborates react with salicylaldehyde at 80 °C in the presence of dibenzylamine, produced 2-substituted 2*H*-chromene derivatives with a 70–90% yield (Scheme-**5**).

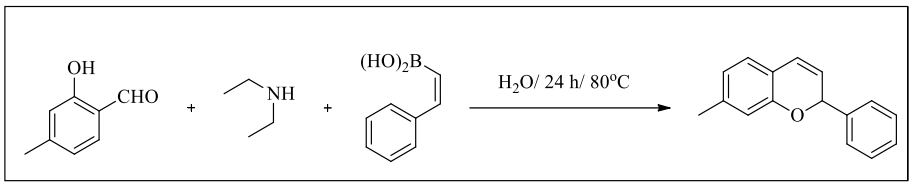
Scheme-5

The reaction of salicylaldehyde with 2-cyclohexen-1-one/2-cyclopenten-1-one in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) obtained condesed chromene derivatives in high yields as described by Ravichandran. S. *et al.* [24] (Scheme-**6**).



Scheme-6

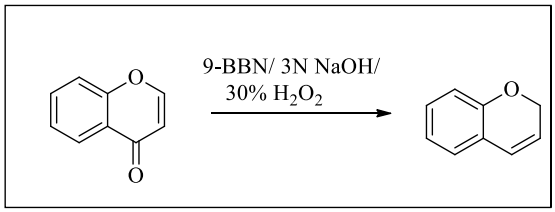
Candeias. N. R. *et al.* [25] developed water mediated synthesis of *2H*-Chromene derivatives by reacting salicylaldehyde, glyoxalic acid, glycoaldehyde and glyoxal with several boronic acids and different amines affording alkyl aminophenols, 2*H*-chromenes, *α*-amino acids, α-amino alcohols and 2-hydroxylmorpholines in good to high yields (Scheme -**7**).



Scheme-7

From Chromones

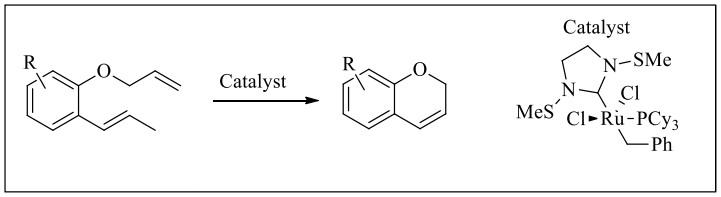
The reduction of chromones with 9-BBN at room temperature afforded 2*H*-chromenes in high yields was described by Eguchi. T. *et al.* [26] (Scheme-**8**).



Scheme-8

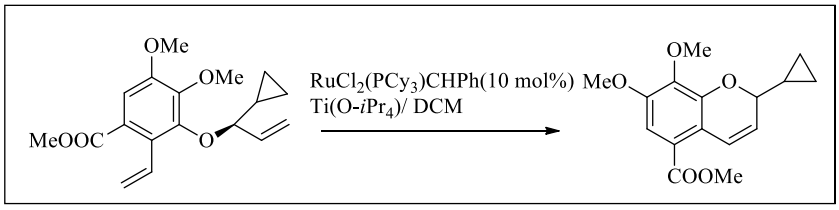
From olefinated phenols ring closing metathesis

Aryl allyl isomerization followed by RCM afforded 2*H*-chromenes from phenolic precursors[27] (Scheme -**9**) using Grubbs catalyst-2.



Scheme-9

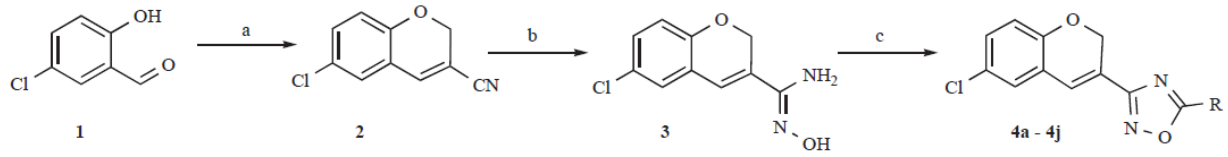
The enantiomeric ring closing metathesis of di-alkenyl derivatives of phenols afforded (+)-2-Cyclopropyl-7,8-dimethoxy-2H-chromene-5-carboxylic acid methyl ester, an advanced intermediate of a Dihydrofolate Reductase Inhibitor using Grubbs metathesis concept described by Wipf. P. *et al.* [28] (Scheme-**10**).



Scheme-10

Ratnakar Reddy *et al*.[29] in 2014, reported a series of isoxazole and 2-(1,2,3-triazolylmethoxy), functionalized 2*H*-chromenes by a cyclization reaction between ethyl-4,4,4-trifluoroacetoacetate and salicylaldehyde. All the compounds were examined for the cytotoxic evaluation toward four different targeted human cancer cells and found good results with a promising anticancer activity IC_{50} of 20 μM.

In 2012 Siva Nagi Reddy *et al*[30], developed a method for a series of 3,5-disubstituted 1,2,4-oxadiazoles (**4a-4j)** from commercial chlorosalicylaldehyde and tested their cytotoxicity by brine shrimp (Artemia salina) bioassay and compared with the standard podophyllotoxin. Among them four oxadiazoles exhibited good cytotoxicity.



Conclusion:

In summary, authors briefed up the syntheses literature and focus on the biological significance of 2H-Chromene derivatives from the last 32 years from 1982 to 2015. The present survey is highly useful for developing new approaches for the titled compounds and provides idea of motif's with various substitutions.

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