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A Brief Review: Some Interesting Methods of Synthesis Chromene Derivatives as Bioactive Molecules

Zainab Sallal Abdulsahib
Department of Chemistry, College of Education for Pure Science Ibn-Al Haitham, University of Baghdad, Baghdad, Iraq.
zainabsallal57@gmail.com

Raied Mustafa Shakir
Department of Chemistry, College of Education for Pure Science Ibn-Al Haitham, University of Baghdad, Baghdad, Iraq.
raiedalsayab@yahoo.co.uk

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Abstract

Chromene is considered a fused pyran ring with a benzene ring, which is found in many plants and is part of many important compounds such as anthocyanidins, anthocyanins, catechins, and flavanones. These compounds are included under the headings "flavonoids" and "iso-flavonoids." These compounds are well known as bioactive molecules with wide medicinal uses. According to these pharmacokinetic characteristics, many researchers are giving more attention to this type of compound and its derivatives. Many chromene derivatives have been synthesized to study their biological effects for the treatment of many diseases. Furthermore, the researcher displayed wide interest in finding new methods for synthesizing chromene derivatives. These methods depend on utilizing a new catalyst to increase the yield of this reaction or reduce the time of the reaction. On the other hand, new methods were found by using a new reactant and a new substrate. This review will present the most recent important methods for the synthesis of chromene derivatives as well as an examination of their biological activity.

Keywords: Chromene, Flavanones, Synthesis, Biomolecular,

Introduction

2H-1-benzopyran and 4H-1-benzopyrean are commonly known as chromene, and they can be realized as a fused result from merging the benzene ring with pyran, as depicted in Figure 1.

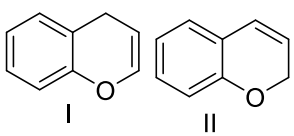

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Figure 1. Structure of 2H-1-benzopyran and 4H-1-benzopyrean.

Chromene and its derivatives exist in many plants [1]. For instance, *Koeberlinia spinosa* was found to contain nine compounds containing chromene as bioactive compounds [2]. Furthermore, chromene structure was found in polyphenolic compounds, which are known for their biological activity. Hesperidine derivatives, for example, demonstrated antitumor [3] and antioxidant activity [4, 5]. Furthermore, flavonoids demonstrated a broad range of biological activity [6, 7], with antioxidant being one of the major bioactivities. Chromene derivatives have also shown anticancer [8, 9], antioxidant [9], antibacterial [10], anticonvulsant [11], anti-inflammatory [12], and antitubercular [13] properties. Figure 2 displayed some natural and synthetic chromene known for their biological activity [14].

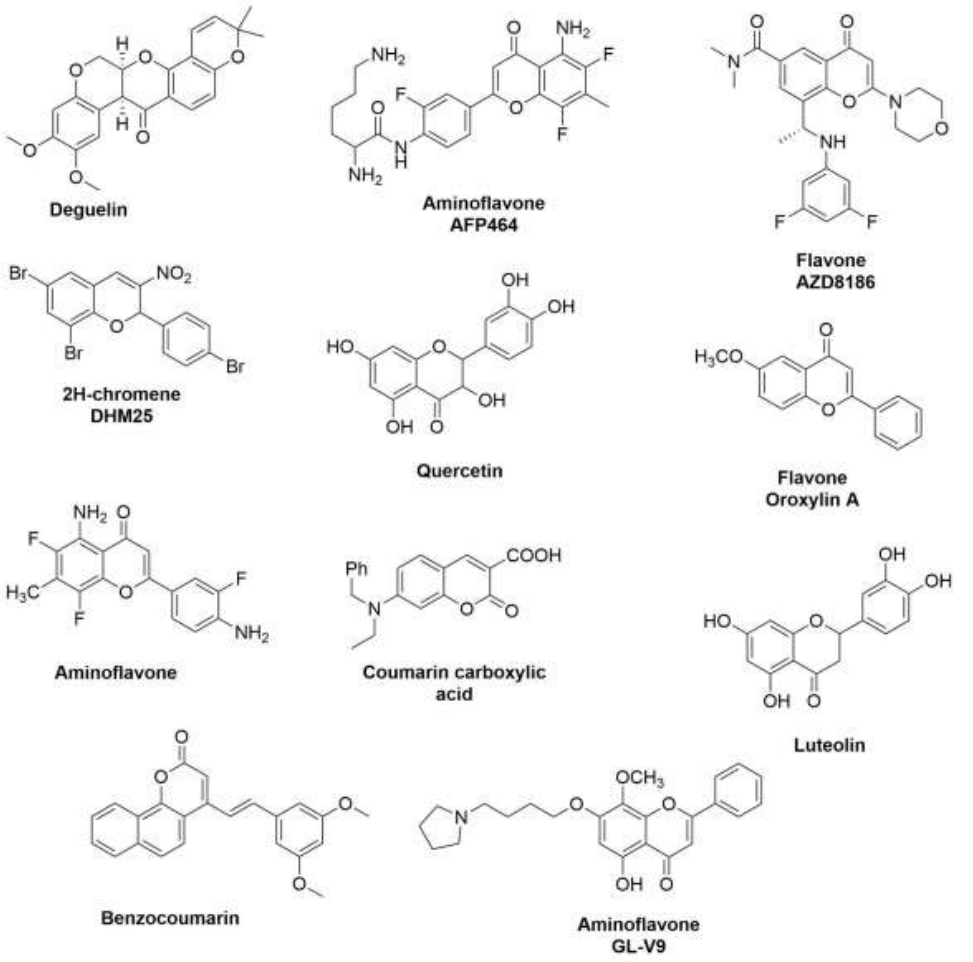


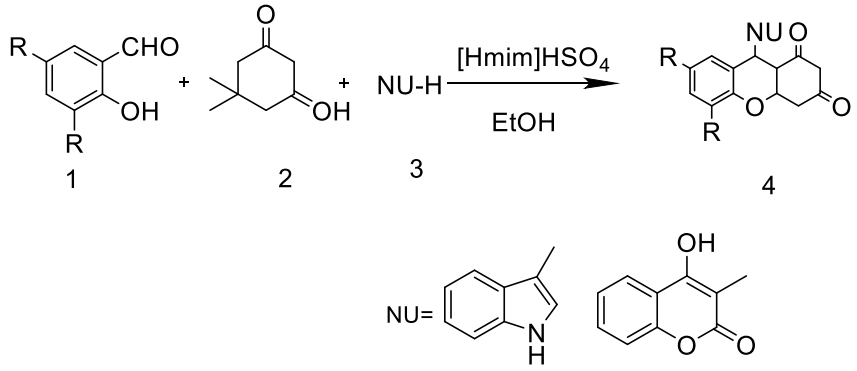
Figure 2. Natural and synthetic chromene derivatives with interesting biological activity.

These interesting and variable biological activities inspire the researcher to find new methods for the synthesis of chromene derivatives using either a new catalyst to increase the yield of these derivatives and reduce the time of synthesis or a new substrate and new conditions. This work will review the recently developed methods for synthesizing chromene derivatives and the biological activity of these compounds.

Methods of Synthesis of chromene

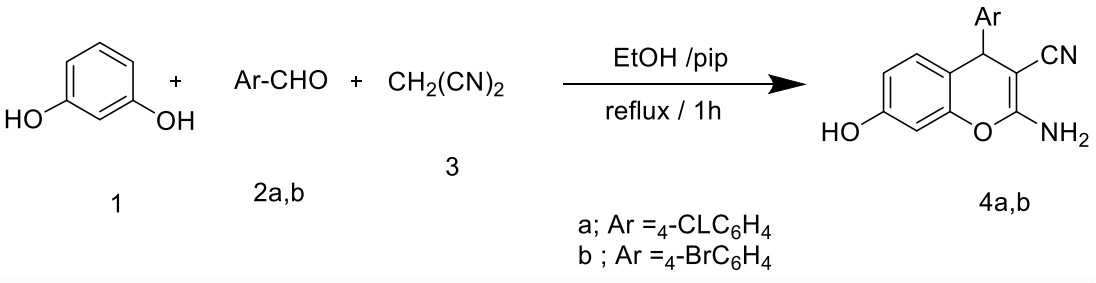
A large number of synthesis methods was found to synthesize 2H-chromene and 4H-chromene. These methods reflected the value of these derivatives. This section will discuss the most important methods for synthesis of chrome as well as the most intriguing catalysts that have been used.

i-Oxo-chromenyl xanthenone and indolyl xanthenone derivatives were synthesized and tested for anti-HIV-1 RT inhibitory activity using an ionic liquid ([Hmim] HSO4 as a catalyst) [15]. This reaction took 45-60 minutes at room temperature to produce a high yield, as shown in Scheme 1.



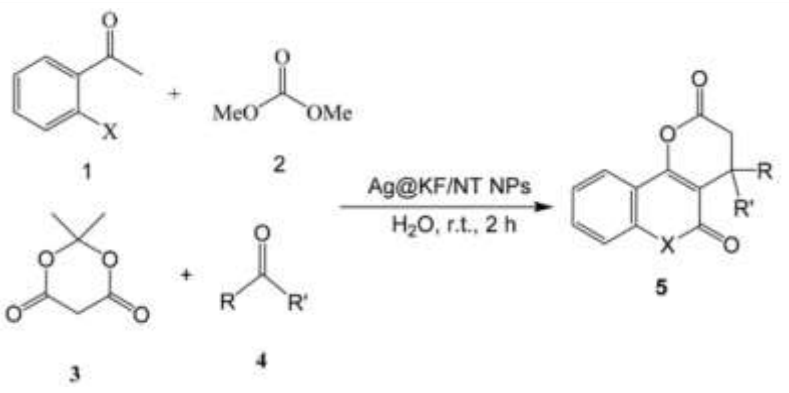
Scheme 1. Synthesis chromene by ionic liquid [Hmim]HSO_4 as catalyst.

ii- 2-Amino-the 4-(p-chloro or bromophenyl)-4H-chromene-3-carbonitri substituted of amine in position four and hydroxyl group at position seven were synthesized from a three-component subsetrate of resorcinol, chlorobenzaldehyde or 4-bromobenzaldehyde, and malononitrile in a mixture of ethanol and piperidine with reflux for one hour, as depicted in scheme 2. These compounds displayed anticancer activity. [16]



Scheme 2. Synthesis 2-Amino-4-(Aryl)-7-hydroxy-4H-chromene-3-carbonitri using piperidine and ethanol.

iii- The green method has been implemented by utilizing reactions between four compounds as displayed in Scheme 3. In this method, catalytic amounts of Ag@KF/Natrolite NPs were used as catalysts, and the reaction was performed at water and ambient temperature for two hours. These compounds were tested as antioxidants and antimicrobial agents [17].

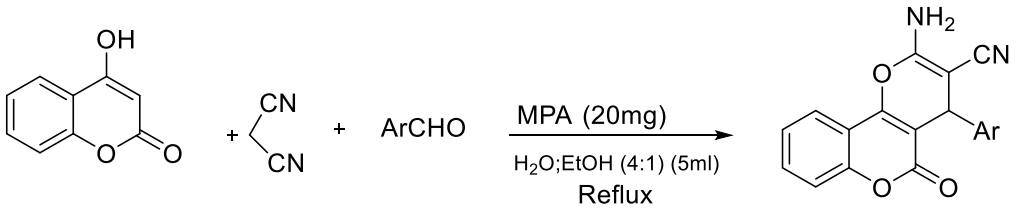


1 2 3 4 5

5	R	R'	X	Yield/% of 5
a	Ph	H	OH	92
b	3-Br-C_6H_4	H	OH	85
c	4-Me-C_6H_4	H	OH	95
d	4-MeO-C_6H_4	H	NH_2	95
e	4-Cl-C_6H_4	H	NH_2	87
f	2-Cl-C_6H_4	H	OH	85
g	2-Me-C_6H_4	H	NH_2	90
h	Me	Me	NH_2	97
i	Me	Et	OH	87
j	Me	^nPr	OH	87
k	Me	Me_2CHCH_2	OH	65

Scheme 3. Synthesis chromene derivatives by using Ag@KF/Natrolite NPs as catalyst

iv- Chromene derivatives were synthesized by a pot reaction utilizing nanoporous Na+-montmorillonite perchloric acid as an improved natural soil, as shown in Scheme 4. The antioxidant capacity was investigated. These compounds had significant antioxidant properties [18].



Scheme 4. Synthesis chromene derives by utilizing nanoporous Na+-montmorillonite perchloric acid.

v- 2- amino-4H-chromene-3-carbonitriles containing a 5-hydroxypyrazol ring were synthesized from the reaction of four compounds with a free catalyst. As shown in Scheme 5, this reaction was carried out in water at 30 °C for 5-10 mints [19].

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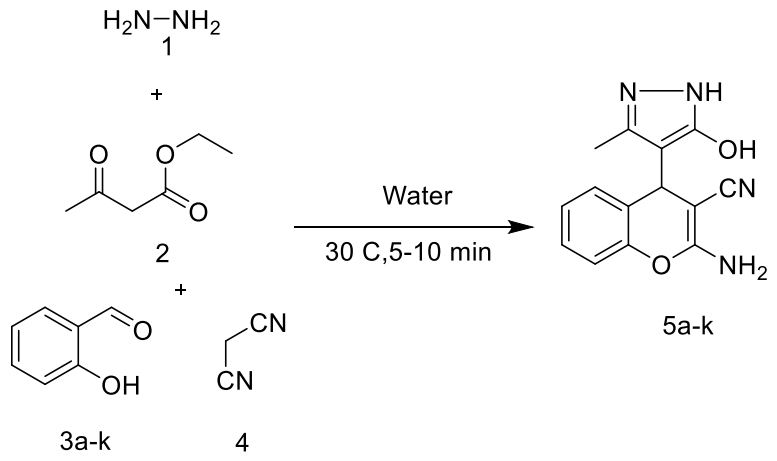


Scheme5.Without catalyst four-substrates synthesis of 4H-chromenes 4-pyrazolyl moity.

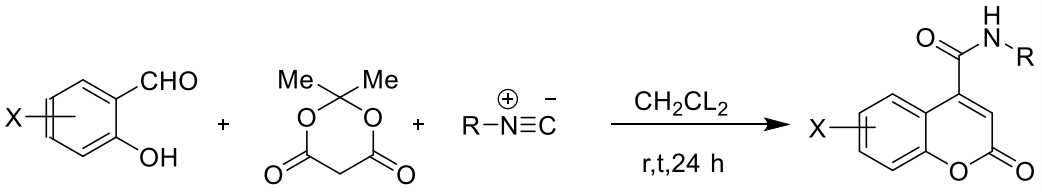
vi- A new efficient method for synthesizing ethyl 4-(2-oxo-2-arylethyl)-2-(trifluoromethyl)-4H-chromene was developed by using $BF_3.OEt_2$ (10 mol%) as a catalyst by [3, 3] sigmatropic rearrangement [20], as demonstrated in Scheme 6.

	X_1	X_2	R'
1a	H	H	Ethyl
1b	Br	H	Ethyl
1c	H	OCH_3	Ethyl
1d	Cl	H	Ethyl
1e	H	H	Methyl

R = Phenyl(**2a**),
4-Fluorobenzene(**2b**),
4-methylbenzene(**2c**).

Scheme 6. Synthesis chromene derivatives by using $BF_3.OEt_2$ (10 mol %) as catalyst.

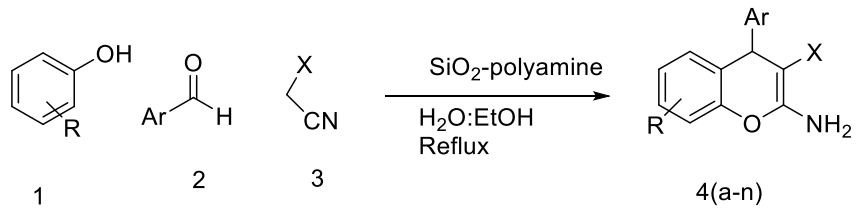
vii- A new one-pot method of synthesis of 3,4-dihydrocoumarin derivatives utilizing salicylaldehyde, Meldrum's acid, and isocyanides This condensation reaction is accomplished by a free catalyst in dichloromethane at room temperature [21], as displayed in Scheme 7.



Entry	R	X	Product	Yield (%)
1	Cyclohexyl	H	4a	80
2	tert-Butyl	H	4b	72
3	Benzyl	H	4c	70
4	Cyclohexyl	5-Br	4d	75
5	4-$CH_3C_6H_4CH_2SO_2$	5-Br	4e	65
6	tert-Butyl	5-Br	4f	70
7	Benzyl	5-Br	4g	71
8	Cyclohexyl	3-OMe	4h	80
9	Cyclohexyl	4-OMe	4i	81
10	tert-Butyl	4-OMe	4j	78
11	2,6-Dimethyl-phenyl	4-OMe	4k	79

Scheme 7: Synthesis chromene derivatives in DCM without catalyst.

viii- 2-amino-4H-chromene derivatives were synthesized using silica gel-supported polyamine as a heterogeneous catalyst [22]. This reaction was performed in aqueous ethanol with reflux for 2–3 hours to obtain a high yield. As displayed in Scheme 8.

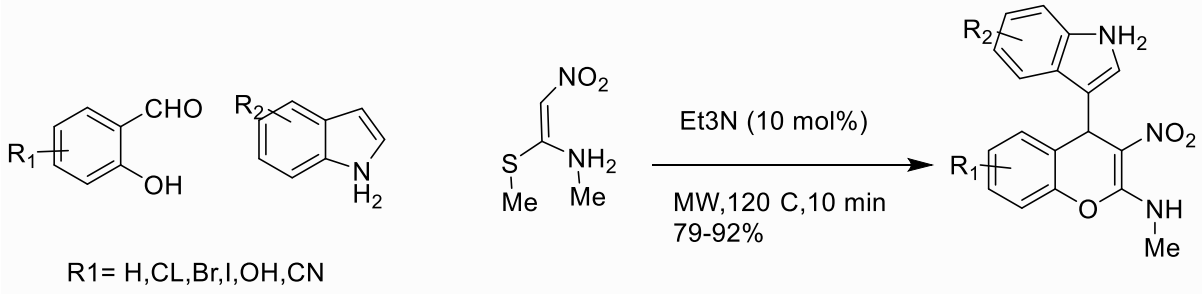


Entry	R	Ar	X	Product	Time (h)	Yield (%)
1	H	4-Cl	CN	4a	2:30	94
2	H	2,4-Cl	CN	4b	2:00	89
3	H	4-NO_2	CN	4c	3:00	90
4	H	3-NO_2	CN	4d	3:00	93
5	H	4-F	CN	4e	2:30	95
6	H	4-Me	CN	4f	3:20	90
7	H	3-OH	CN	4g	3:00	88
8	H	3-OH	CN	4h	3:40	91
9	4-Cl	4-Cl	CN	4i	4:00	89

Scheme 8: Synthesis chromene derivatives utilizing silica gel – polyamine.

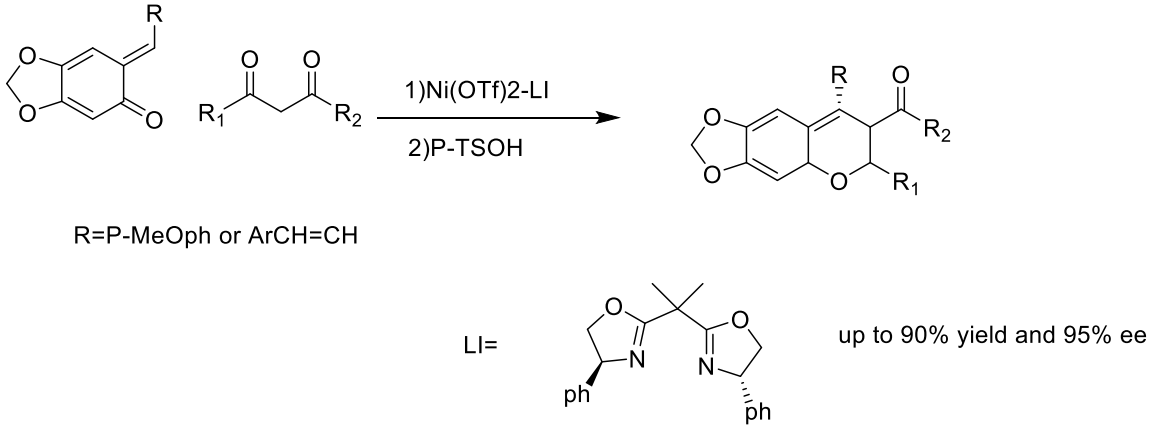
ix- Indolyl-4H-chromene derivatives were synthesized in a pot reaction using triethylamine as a catalyst, and the reaction was achieved under microwaves in the absence of solvent. The reactions

accord was between 2-hydroxybenzaldehyde, N-methyl-1-(methylsulfanyl)-2-nitroethenamine, and indoles [23], as depicted in Scheme 9.



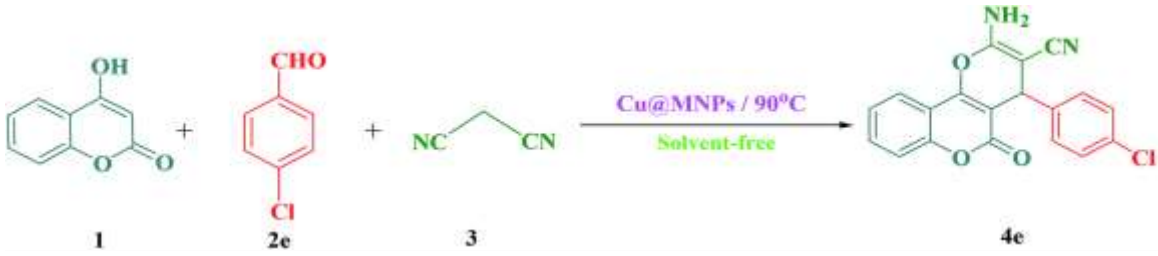
Scheme9. Synthesis chromene derivatives by using triethylamine(10%) in microwave.

x-4H-chromene derivatives were synthesized using Ni(II)–bis(oxazoline) complex with *p*-TsOH to obtain a yield of more than 90%[24], as depicted in Scheme 10.



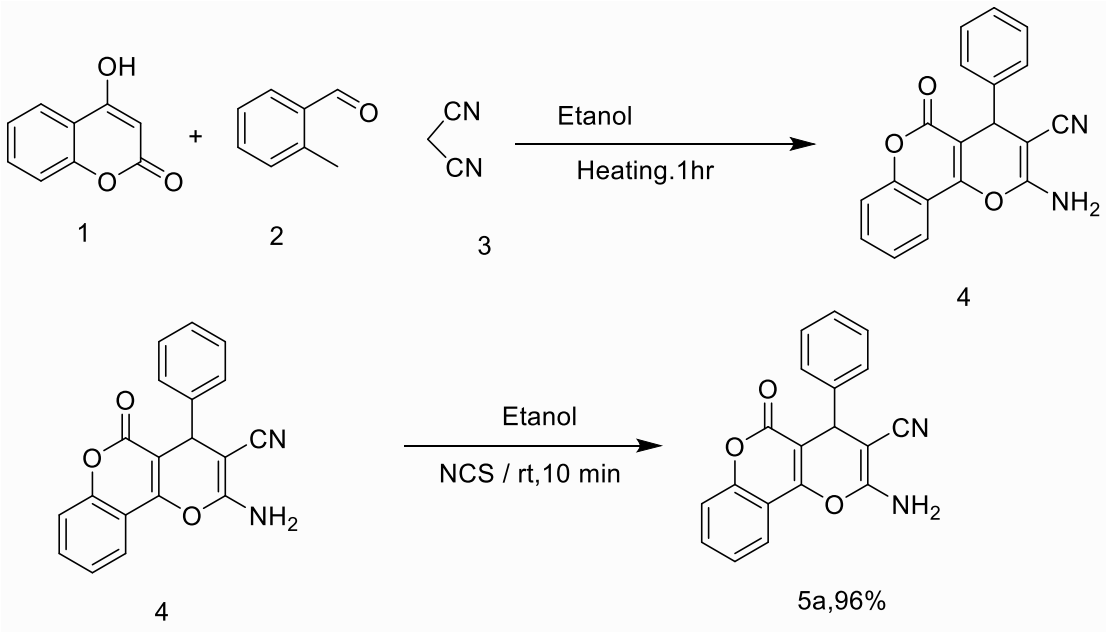
Scheme 10. Synthesis chromene derivatives by using Ni(II)–bis(oxazoline) and *P*-TsOH.

xi- As shown in Scheme 11, 2-amino-4H-chromene derivatives were synthesized in one-pot reactions between three compounds derived from 4-hydroxycoumarin using recyclable nanocatalyst (MNPs@Cu) in the absence of solvent [25].



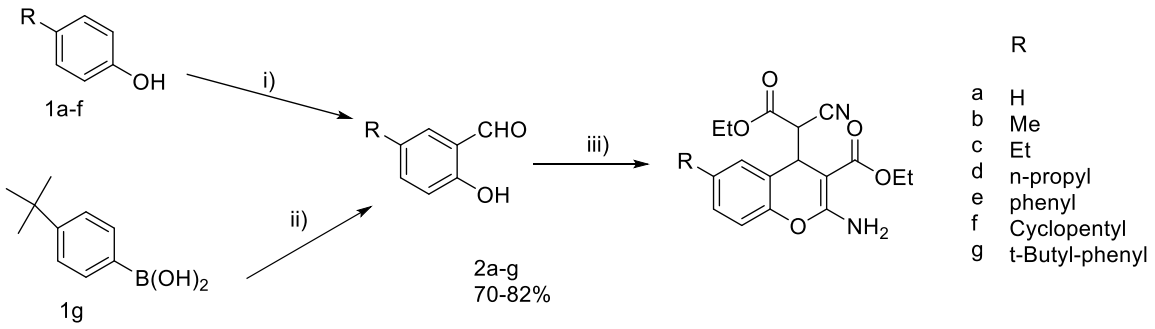
Scheme 11. Synthesis chromene derivatives by using nano catalyst (MNPs@Cu) in free of solvent.

xii-[3,2-c] chromenes were synthesized in two steps, the first one by refluxing 4-Hydroxy coumarin, Aryl aldehydes and Malononitrile in ethanol for one hour, and the second step was accomplished by treating the resulting product with N-chlorosuccinimide in ethyl alcohol at ambient temperature [26], as depicted in Scheme 12. The antimicrobial activity of compounds was screened, and most of these compounds showed extraordinary antimicrobial activity.



Scheme 12: Synthesis chromene derivatives by using N-chlorosuccinimide (NCS).

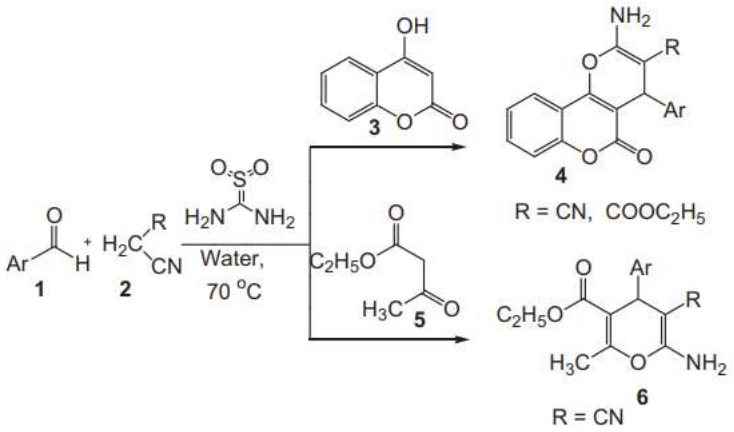
xiii- New 2-Amino-4H-chromene-3-carboxylate derivatives were synthesized by a reaction substituting salicylaldehyde with ethyl cyanoacetate in ethanol at room temperature in the presence of 3A molecular sieves [27], as depicted in Scheme 13. These compounds exhibited anticancer activity.



a Reagents and conditions: (i) $MgCl_2$, Et_3N, paraformaldehyde, dry CH_3CN, reflux; (ii) 5-bromosalicylaldehyde, $Pd(OAc)_2$, K_2CO_3, H_2O, room temp; (iii) ethyl cyanoacetate, EtOH, 3 Å molecular sieves, room temp. The asterisk (/) represents chiral centers

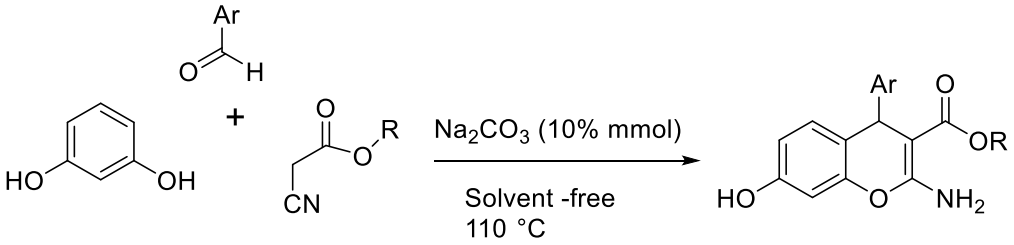
Scheme 13. Synthesis chromene derivatives by using 3A molecular sieves.

xiv- In an aqueous medium, thiourea dioxide was used as a catalyst to synthesize new 3,4-dihydropyrano[c]chromene and 6-amino-substituted-4H-pyrans [28]. as depicted in Scheme 14.



Scheme 14. Synthesis chromene derivatives by using thiourea dioxide in aqueous medium.

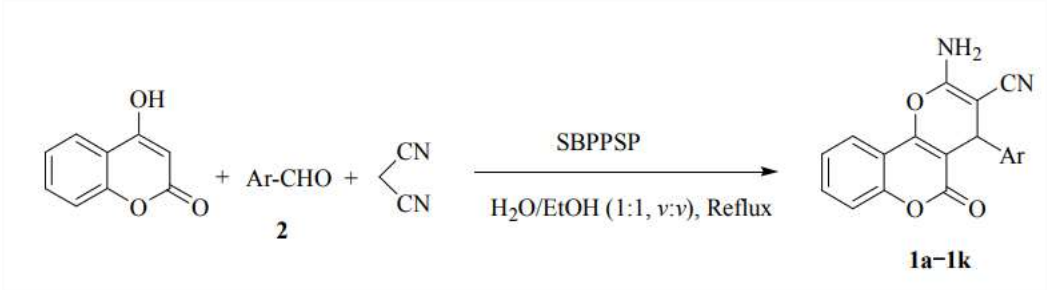
xv- As shown in Scheme 15, Sodium carbonate (10% mmol) was used as a catalyst in a fusion reaction at 110 °C in the absence of a solvent [29]. The synthesized compound showed antibacterial activity.



Entry	Product	Ar	R	Time, min	Yield%
1	4a	Ph	Et	20	95
2	4b	Ph	Me	15	98
3	4c	4-ClC_6H_4	Et	20	90
4	4d	4-ClC_6H_4	Me	15	92
5	4e	4-BrC_6H_4	Et	15	90

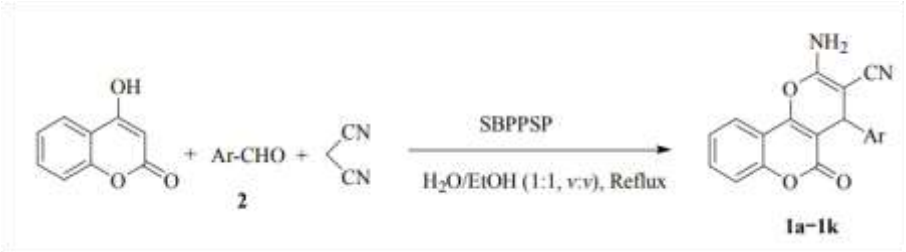
Scheme 15. Synthesis chromene derivatives by using Sodium carbonate (10% mmol) with out solvent.

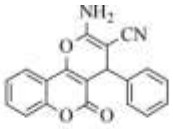
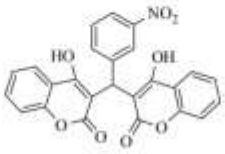
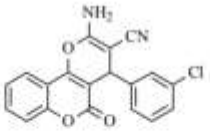
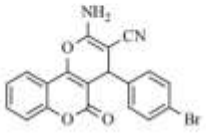
xvi- Silica linked with SBPPSP (sodium slot of *N*-propylpiperazine *n*-propionate) used as novel catalyst for synthesis 3,4-Dihydropyrano[*c*]chromene Derivatives and biscoumarins[30], as demonstrated in Scheme 16.



Scheme 16. Synthesis chromene derivatives by using SBPPSP.

xvii- Hexamethylenetetramine (10% mmol) was utilized to synthesize dihydropyrano [3,2-c] chromene derivatives with a high isolated yield [31]. as displayed in Scheme 17.



1	C_6H_5–		**1a**	12	92
2	4-Cl-C_6H_4–		**1b**	10	95
3	3-Cl-C_6H_4–		**1c**	10	91
4	4-Br-C_6H_4–		**1d**	10	90

Scheme 17. Synthesis chromene derivatives by using hexamethylenetetramine (10% mmol).

Conclusion

Seventeen methods were exhibited for the synthesis of either 2H-chromene or 4H-chromene or both of them. Most of these methods depend on reacted three or four components in one pot or in stages. The majority of these methods made use of a new catalyst to increase the yield of the reaction or shorten the reaction time.

Acknowledgement

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