

A REVIEW ON THE SYNTHETIC METHODOLOGIES OF CHROMONES

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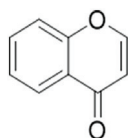
ABSTRACT

Chromones group of compounds and their derivatives form the essential component of pharmacophores in many biologically active molecules. They exhibit a wide range of biological activities such as antibiotic, antitumor, antiviral, antioxidant, antipsychotic, and antihypoxic activities. These applications have stimulated a continuous search for the synthesis of new compounds in this field and are being extensively investigated. The various methodologies so far reported for the synthesis of these compounds with the compounds biological applications are discussed in this communication

Keywords: Chromones, Synthesis, Biological activities.© 2018 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2018.v11i12.27960>

INTRODUCTION

Chromones and their structural analogs have motivated a great interest because of their usefulness as biologically active agents. The chromone moiety is the essential component of pharmacophores of a large number of bioactive molecules.



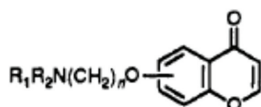
Chromone Nucleus

Chromone (1,4-benzopyrone) is a derivative of benzopyran with a substituted keto group on the pyran ring. Chromone, benzopyran, and coumarin possess a similar structure (Douglas *et al.*, 2003) [1]. The first chromone to be used in pure form in clinical practice was Khellin extracted from the seeds of plant *Ammi visnaga*. Khellin was first prepared in impure form (Edwards and Howell, 2000) [2].

SYNTHESIS

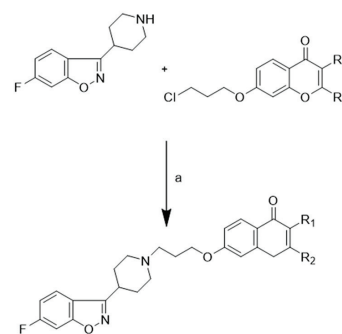
Chromone may be synthesized under either acidic/basic conditions. The classical 2,3-disubstituted benzopyranone (c). Synthesis utilizes acidic conditions and is by far the most common method [3]. It proceeds through an intramolecular condensation of molecules such as (b), which are usually obtained through a Baker-Venkataraman rearrangement of compound (a), or through a Claisen ester condensation.

Jaen *et al.* [4] (1991) described the synthesis of novel type of [(aryl piperazinyl)alkoxy]-4H-1-benzopyran-4-ones.

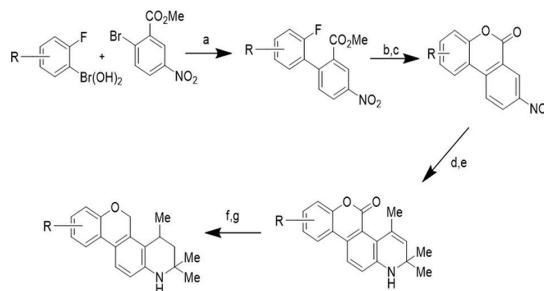


[(aryl piperazinyl)alkoxy]-4H-1-benzopyran-4-ones

Bass reported synthesis of chromones by cyclization of 2-hydroxyphenyl ketones with boron trifluoride-diethyl ether and methanesulfonyl chloride [5]. Bolos *et al.* [6] (1998) designed a series of novel 7-[3-(1-piperidinyl)propoxy]chromenones

a= K₂CO₃, CH₃CN; RefluxR₁=R₂= HR₁=CH₃, R₂=HR₁=CH₂OH, R₂=HR₁=COOH, R₂=HR₁=H, R₂=CH₂OH

Zhi *et al.* (2003) [7] synthesized 1,2-dihydro chromeno[3,4-f] quinoline derivatives.

a= 3mol % Pd(PPh₃)₄, Na₂CO₃, Toluene/EtOH/H₂O, Reflux, 18h, 90%

b= NaOH, THF, rt, 2h, 95%

c= NaH, DMF, 80°C, 2h, 85%

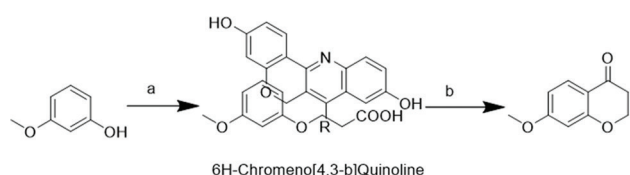
d= SnCl₂, AcOEt, Reflux, 2h, 95%

e= Acetone, 12, sealed tube, 130°C, 18h, 50%

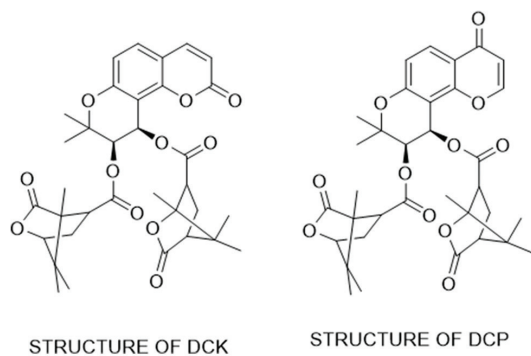
f= DIBAL-H, Toluene, -40°C, 60-95%

g= BF₃·OEt₂, Et₃SiH, CH₂Cl₂, rt, 2h, 70-90%

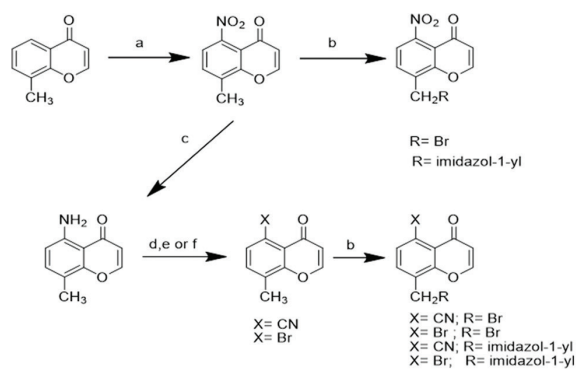
A new class of estrogen receptor beta (ER β) ligands based on the 6H-chromeno [4,3-b] quinoline scaffold were reported by Vu *et al.* (2007) [8].



Yu *et al.* (2003) [9] reported synthesis of 3' R,4' R-Di-O(-)-camphanoyl-2',2'-dimethyl dihydro pyrano-[2,3-f]chromone on the basis of a structure-activity relationship study of 3' R,4' R-Di-O(-)-camphanoyl-(+)-cis-Khellactone and its analogs.



Recanatini *et al.* (2001) [10] designed and synthesized chromone and xanthone derivatives.



a= HNO₃/H₂SO₄, 0-50°C

b= N-bromosuccinimide, CCl₄, reflux 5h

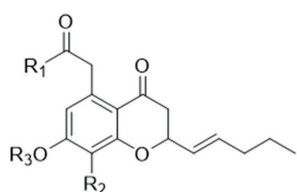
c= H₂, Pd/CaCO₃

d= NaNO₂, HCl, 0-50°C

e= NaCN/ CuCN, 100°C, 20 min

f= CuBr, rt, 12h

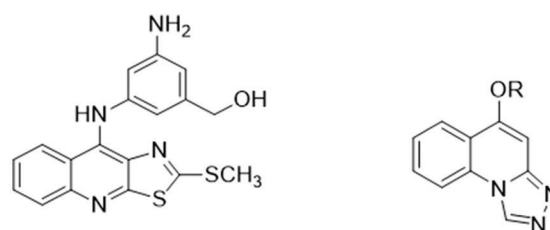
A new series of novel 2-vinyl chroman-4-ones (Albrecht *et al.*, 2005) [11] were synthesized which were analogs of natural products aposphaerin A and B.



Aposphaerin A: R₁= R₂= OH, R₃= Me

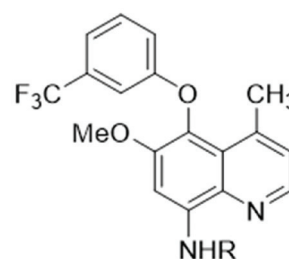
Aposphaerin B: R₁= OEt, R₂= R₃= H

A new group of 2-phenyl naphthalene type structures of 11 H-indolo[3,2-c] quinoline derivatives was designed by He *et al.* [12] (2003). Loaiza *et al.* [13] (2004) synthesized new 9-anilinothiazolo [5,4-b] quinoline derivatives. Guo *et al.* [14] (2009) synthesized a series of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives.

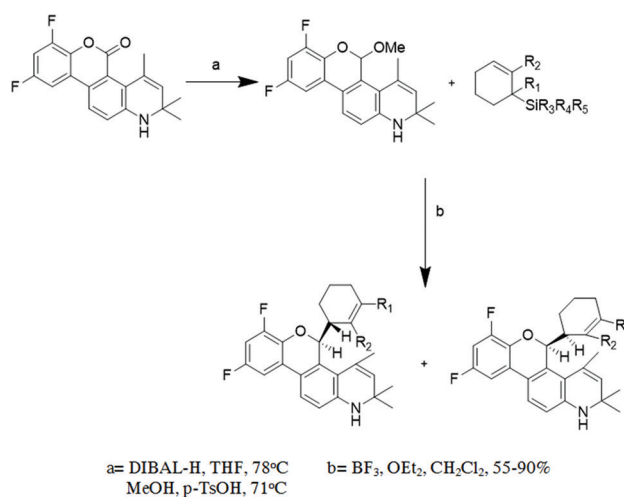


5-Alkoxy-[1,2,4] Triazolo [4,3-a] quinoline derivative

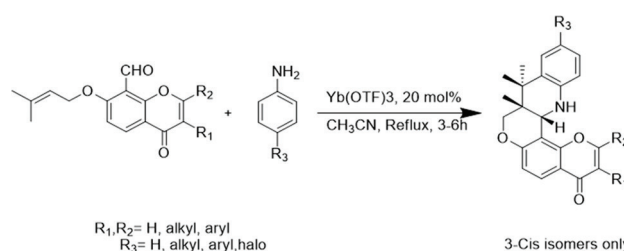
Shi *et al.* [15] (2008) synthesized substituted quinolines.



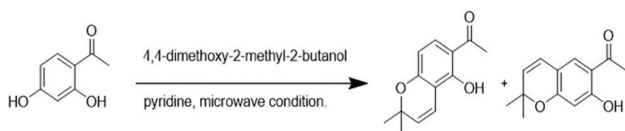
Pedram *et al.* [16] (2008) described the discovery of a new selective progesterone receptor modular which was the lead compound, 7,9-difluoro-5-(3-methyl cyclohex-2-enyl)-2,3,4-trimethyl-1,2-dihydro chromeno[3,4-f]quinoline



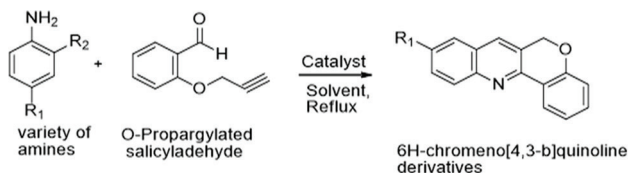
Nagaiah *et al.* (2010) [17] synthesized new cis-fused tetra hydro chromeno[4,3-b] quinolines by intramolecular [4+2] imino diels-alder reactions of 2-azadienes.



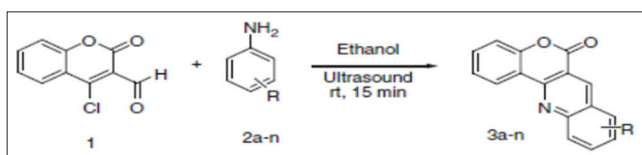
2,2-dimethyl-2H-chromone containing compounds were synthesized using microwave method by Zhou *et al.* [18] (2010)



Ramesh and Nagarajan (2010) [19] synthesized chromenoquinolines through cyclization of different substituted anilines/naphthyl amine with O-Propargylated salicylaldehydes using $\text{CuI}/\text{La}(\text{OTf})_3$ as a catalyst.

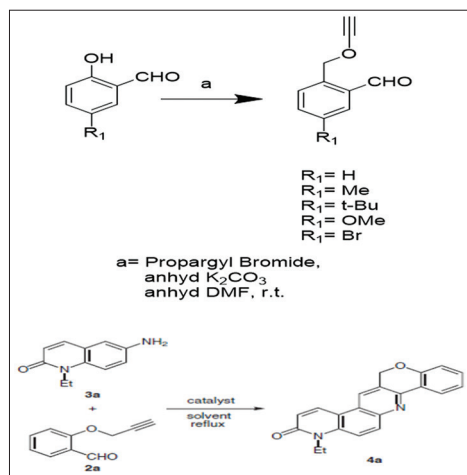


Prasad *et al.* (2011) [20] synthesized fused chromeno [4,3-b]quinolin-6-ones by ultrasound irradiation using 4-chloro-3-formyl coumarin. (Scheme 1)



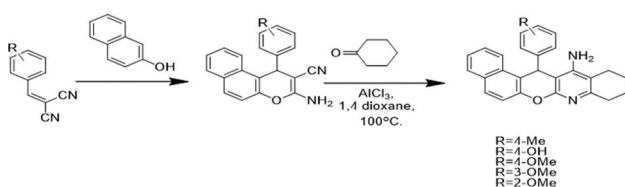
Scheme:1 Synthesis of fused chromeno-quinolines

Majumdar *et al.* (2011) [21] synthesized dihydro-3H-chromeno[3,4-b][4,7]phenanthrolin-3-one and chromeno [4,3-b] pyrano [3,2-f]quinolin-3(13H)-one derivatives by aza Diels-Alder reaction. (Scheme 2)

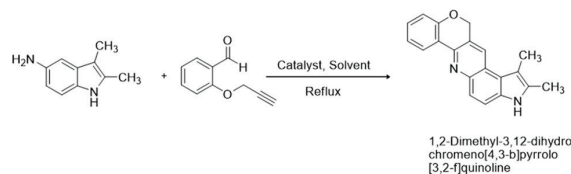


Scheme:2 Aza-Diels-Alder reaction

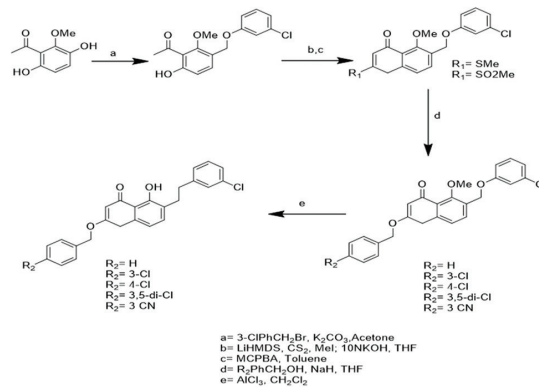
Synthesis of racemic 14-aryl-10,11,12,14-tetrahydro-9H-benzo[5,6]-chromeno[2,3-b]quinoline-13-amines by Friedlander reaction of 3-amino-1-aryl-1H-benzo[f]chromene-2-carbonitriles with suitable cycloalkanones is described by Maalej *et al.* (2011) [22].



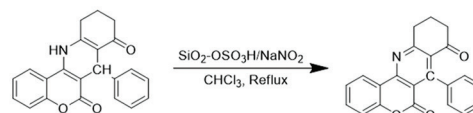
A one-pot intra molecular aza Diels-Alder approach for the synthesis of dihydrochromeno[4,3-b] pyrrolo [3,2-f]quinolines was reported by Ramesh and Nagarajan (2011) [23].



Substituted chromones such as 5-hydroxy chromones with two aryl methoxy substituent's were reported by Kim *et al.* (2011) [24].

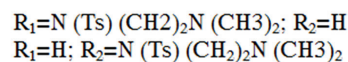
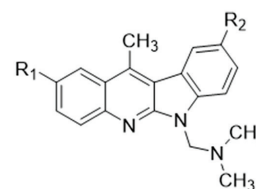


Motamedi *et al.* (2012) [25] combined silica sulfuric acid and sodium nitrite in the presence of wet SiO_2 for the oxidative aromatization of novel tetrahydrochromeno[4,3-b] quinolines to their corresponding pyridine derivatives.

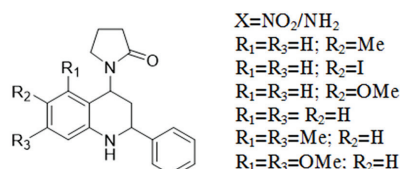


OXIDATIVE AROMATISATION OF TETRAHYDRO CHROMENO[4,3-b]QUINOLINES

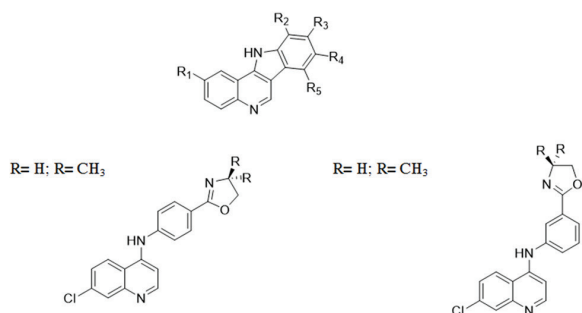
Luniewski *et al.* [26] (2012) synthesized novel indolo-[2,3-b] quinoline derivatives substituted at N-6 and C-2 or C-9 positions with (di methyl amino) ethyl chains linked to heteroaromatic core by ether, amide or amine bonds.



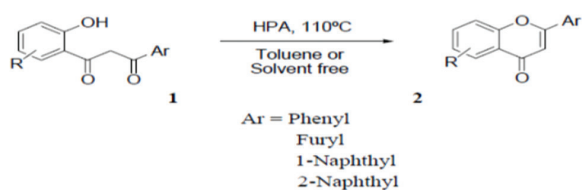
Bedoya *et al.* [27] (2012) synthesized 18-quinoline-based compounds containing quinoline/tetrahydroquinoline rings.



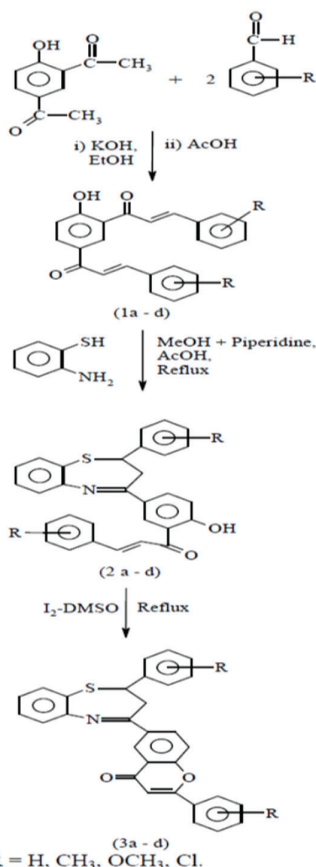
Godrey *et al.* [28] (2011) carried out Pd-mediated coupling for the synthesis of quinoline-oxazole hybrid compounds.



Bennardi *et al.* [29] (2008) carried out synthesis of substituted flavones and chromones using a Wells-Dawson heteropolyacid as a catalyst.

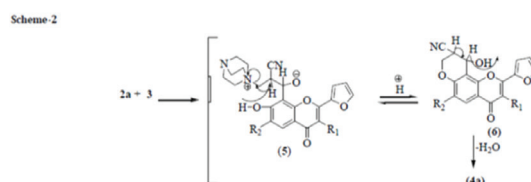
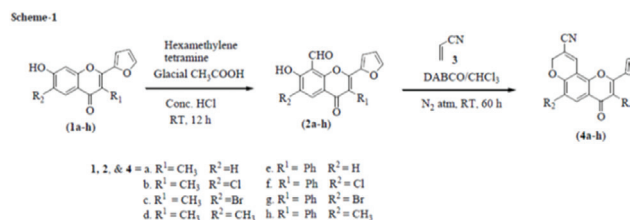


Dengle *et al.* [30] (2013) carried out synthesis and antimicrobial evaluation of chromones bearing

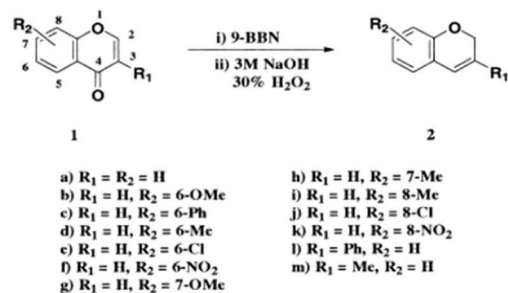


1, 5-benzo thiazepinyl moiety.

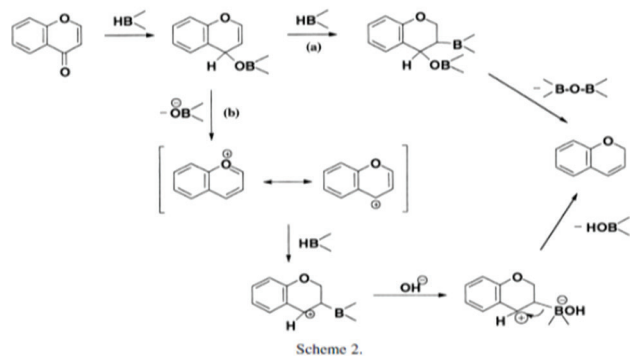
Suryanarayana and Anuradha [31] (2013) reported that new series of hetroannulated chromene-9-carbonitrile derivatives have been synthesized from 4-diazobicyclo [2, 2, 2]-octane catalyzed Baylis-Hillmann reaction of diversely substituted 7-hydroxy-8-formyl-2-furylchromones under a nitrogen atmosphere at room temperature in good yields.



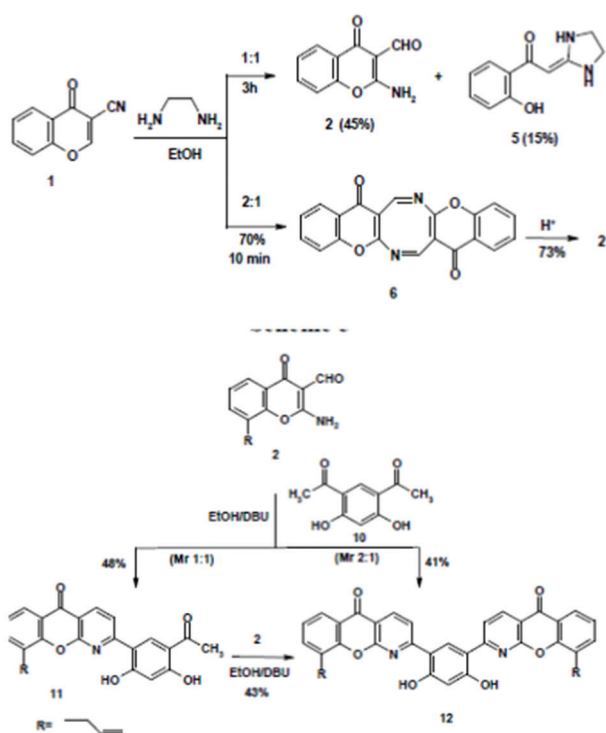
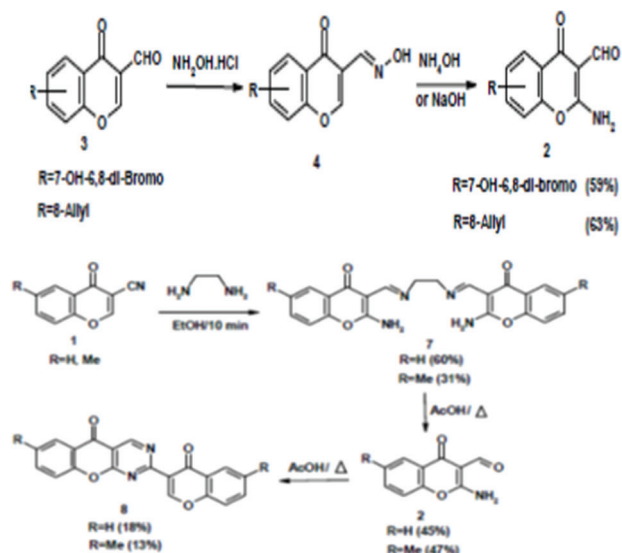
Yanhui Guo *et al.* [32] (2017) reported the reactions between *o*-hydroxyphenyl-functionalized enaminones and sulfonyl hydrazines providing 3-sulfonylated chromones through domino chromone ring construction and C(sp²)-H bond sulfonylation has been achieved under transition-metal-free conditions using KIO₃ as the only catalyst. Tetsuya Eguchi and Yukio Hoshino [33] (2001) reported chromones regioselectivity reduced to 2*H*-1-benzopyrans through the 1, 2-addition of 9-borabicyclo-[3.3.1] nonane.



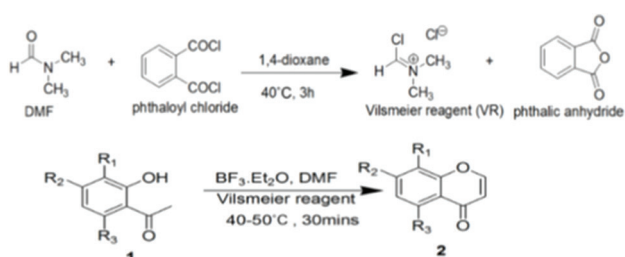
Scheme 1.



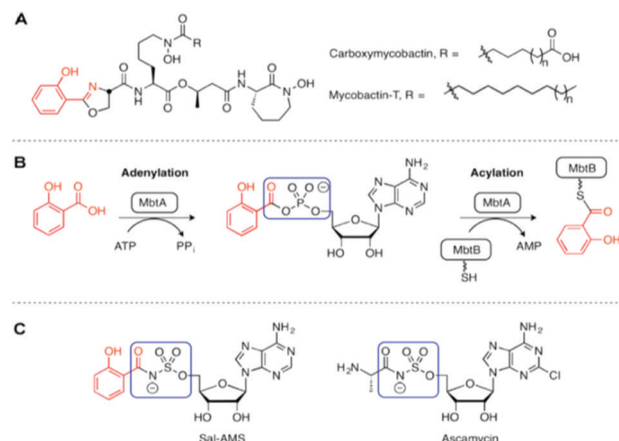
Ibrahim *et al.* [34] (2017) presented a review which discusses the methods developed for the synthesis and reactions of 2-aminochromone-3-carboxaldehydes.



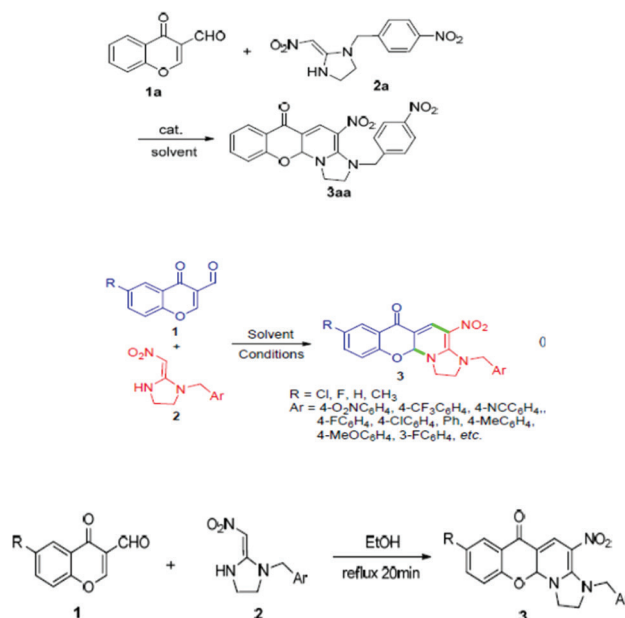
Santosh [35] (2014) reported the process for the preparation of chromones, isoflavones, and homoisoflavones using vilsmeier reagent generated from phthaloyl dichloride and DMF.



Engelhart *et al.* [36] (2013) reported the synthesis of chromone, quinolone, and benzoxazinone sulfonamide nucleosides as conformationally constrained inhibitors of adenylating enzymes required for siderophore biosynthesis.

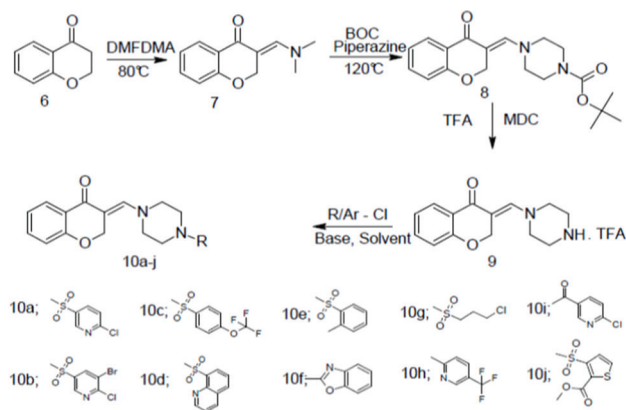


Chen *et al.* [37] (2017) reported that a concise and environment-friendly route for the synthesis of multisubstituted chromone-fused bicyclic pyridine for the synthesis of multisubstituted chromone-fused bicyclic pyridine compounds through one-step reaction of chromone-3-carboxaldehyde **1** and *N*-benzyl nitro ketene amins (NBKAs, **2**) in ethanol media has been developed.

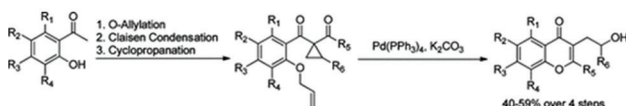
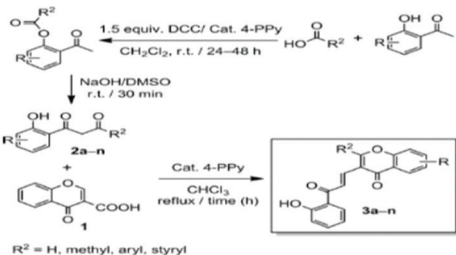


Gang Cheng *et al.* [38] (2017) developed an efficient synthesis of aza-chromones from 3-iodo-4-(1*H*)-pyridones and terminal acetylenes through a cascade carbonylation-Sonogashira-cyclization reaction. By controlling the use of bases, both 6-aza-chromones **5** and 3-(4-oxo-1,4-dihydroquinoline-3-carbonyl)-4*H*-pyrano[3,2-*c*]quinolin-4-ones **6** could be selectively obtained in moderate to good yields.

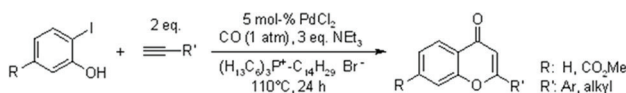
Patel *et al.* [39] (2011) reported that novel (3*E*)-3-[[4-(Aryl or Alkyl sulfonyl, Aryl carbonyl and Heteroaryl) piperazin-1-yl]methylene] chroman-4-one and *N*-[1-(Aryl or Alkyl sulfonyl, Aryl carbonyl and Heteroaryl)-4-piperidyl]-6-methyl-4-oxo-chromene-3-carboxamide was synthesized and antibacterial good activity against the bacterial strains.



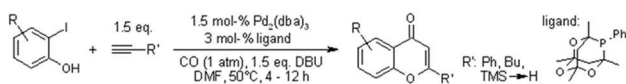
Talhi *et al.* [40] (2016) reported a one-pot synthesis of novel benzopyran-4-ones is organo base-catalyzed Michael addition on chromone-3-carboxylic acid led to decarboxylation and pyran-4-one ring opening of the latter. This was followed by chromone - and/or chromanone ring closure of the resulting Michael adducts when R1 is an *ortho*-hydroxyaryl group.



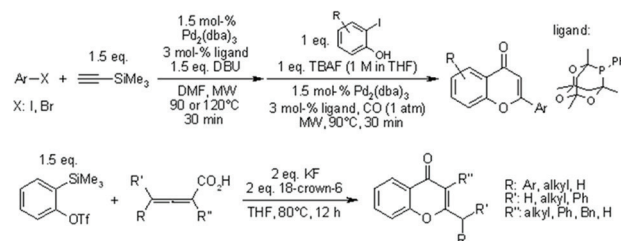
A tandem deprotection-cyclization reaction of 1,1-diacetylcyclopropanes is described which allows rapid access to structurally diverse 2,3-disubstituted chromones in good yields, and with straightforward purification. The utility of this reaction is showcased by the construction of the potent antibacterial marine natural product bromophycoic acid E scaffold (Robert *et al.*, 2017) [41].



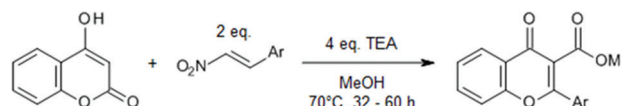
A highly efficient and selective palladium-catalyzed ligand-free cyclocarbonylation reaction of *o*-iodophenols with terminal acetylenes under atmospheric CO pressure affords diversified chromones in very good yields [42]. The use of a phosphonium salt ionic liquid as the reaction medium enhances the efficiency of the cyclocarbonylation reaction.



A palladium complex of 1,3,5,7-tetramethyl-2,4,8-trioxo-6-phenyl-6-phosphaadamantane is an effective catalyst for a sequential microwave-assisted Sonogashira and carbonylative annulation reaction to give substituted flavones [43].

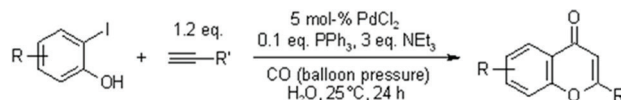


Chromone derivatives were synthesized from 2,3-allenoic acids and benzynes in good yields under mild conditions. The benzyne intermediate undergoes 1,2-addition with the carbonyl group, followed by ring opening, conjugate addition, and protonolysis to afford chromone derivatives. This protocol allows the diversity due to the substituent-loading capability of 2,3-allenoic acids as well as benzynes [44].

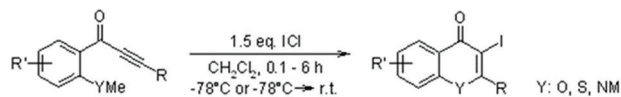


The unusual alcohol-mediated reaction of 4-hydroxycoumarins and β -nitroalkenes leads to 4-oxo-2-aryl-4H-chromene-3-carboxylate (flavone-3-carboxylate) derivatives. The transformation occurs through the *in situ* formation of a Michael adduct, followed by the alkoxide ion mediated rearrangement of the intermediate. The effects of different media on the reaction were investigated [45].

A Pd-catalyzed copper-free carbonylative Sonogashira coupling reaction at room temperature was achieved using water as a solvent under balloon pressure of CO with Et₃N as a base [46]. The developed method was successfully applied to the synthesis of flavones.



A mild ICl-induced cyclization of heteroatom-substituted alkynes provides a simple, highly efficient approach to various 3-iodochromones, iodochromenones, iodoquinolinones, and analogs in good to excellent yields. Subsequent palladium-catalyzed transformations afford a rapid increase in molecular complexity [47].



Apart from the above, cytotoxicity studies of 2-vinylchromone derivatives on human breast cancer cell lines were also investigated for their biological activity [48]. Endophytic fungi seem to be a major resource for naturally occurring chromones [49-51].

Chromones group of compounds and their derivatives form the essential component of pharmacophores in many biologically active molecules. They exhibit a wide range of biological activities such as antibiotic, antitumor, antiviral, antioxidant, antipsychotic, and antihypoxic activities. These applications have stimulated a continuous search for the synthesis of new compounds in this field and are being extensively investigated.

AUTHOR'S CONTRIBUTION

MV and SG conceived the present idea and collected literature about chromones. RM and EL developed and analyzed the collected literature.

MV and SG wrote the manuscript in consultation with RM and EL. RM and EL supervised the work and discussed the final draft and contributed to the final manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

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