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.

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 (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 benzopyrone (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.

Zhi et al. [7] synthesized 1,2-dihydro chromeno[3,4-f] quinoline derivatives.
A new class of estrogen receptor beta (ERβ) 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′,4′-R-Di-O-(-)-camphanoyl-Z,2′-dimethyl dihydro pyrano-[2,3-f]chromone on the basis of a structure-activity relationship study of 3′,4′-R-Di-O-(-)-camphanoyl-(+)-cis-Khellactone and its analogs.

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

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.

A new group of 2-phenyl naphthalene type structures of 11H-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.

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.

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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 Cul/La(OTf)3 as a catalyst.

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

Majumdar et al. (2011) [21] synthesized dihydro-3H-chromeno[4,7]phenanthroline-3-one and chromono [4,3-b]pyran-3,2-fquinolin-3(13H)-one derivatives by aza Diels-Alder reaction. (Scheme 2)

Motamedi et al. (2012) [25] combined silica sulfuric acid and sodium nitrite in the presence of wet SiO2 for the oxidative aromatization of novel tetrahydrochromeno[4,3-b] quinolines to their corresponding pyridine derivatives.

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 thiazepiny moiety.

Suryanarayana and Anuradha [31] (2013) reported that new series of heteroannulated 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.

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Yanhui Guo et al. [32] (2017) reported the reactions between o-hydroxyphenyl-functionalized enamiones and sulfonyl hydrazines providing 3-sulfenylated chromones through domino chromone ring construction and C(sp²)-H bond sulfenylation 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 2H-1-benzopyrans through the 1, 2-addition of 9-borabicyclo-[3.3.1] nonane.

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 benzoazinone sulfonamide nucleosides as conformationally constrained inhibitors of adenylylating enzymes required for siderophore biosynthesis.

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

Gang Cheng et al. [38] (2017) developed an efficient synthesis of aza-chromones from 3-iodo-4-(1H)-pyridones and terminal acetylenes through a cascade carbonylation-Sonogashira-cyclization reaction. By controlling the use of bases, both 5-aza-chromones 5 and 3-(4-oxo-1,4-dihydroquinoline-3-carbonyl)-4H-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 (3E)-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-piperidinyl]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 R is an ortho-hydroxyaryl group.

A tandem deprotection–cyclization reaction of 1,1-diacylcyclopropanes 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-alkenonic acids and benzenes 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-alkenonic acids as well as benzenes [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 Br₂ as a base [46]. The developed method was successfully applied to the synthesis of flavones.

A mild ICl-induced cyclization of heteroatom-substituted alkynones provides a simple, highly efficient approach to various 3-iodochromones, iodothiochromenones, 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 pharmacoaphores in many biologically active molecules. They exhibit a wide range of biological activities such as antibiotic, antitumor, antiviral, antioxidant, antipsychotic, and anthypoxic 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.
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