doi.org/10.1002/cbdv.202300836 Review CHEMISTRY & BIODIVERSITY

www.cb.wiley.com

Multicomponent Synthesis Strategies, Catalytic Activities, and Potential Therapeutic Potential of Pyranocoumarins: A Comprehensive Review

Jayalakshmi M,[a] Francis Joy,[a] Aatika Nizam,*[a] and Suresh Babu Naidu Krishna*[b]

Fused coumarins, because of their remarkable biological and therapeutic properties, particularly pyranocoumarins, have caught the interest of synthetic organic chemists, leading to the development of more efficient and environmentally friendly protocols for synthesizing pyranocoumarin derivatives. These compounds are the most promising heterocycles discovered in both natural and synthetic sources, with anti-inflammatory, anti-HIV, antitubercular, antihyperglycemic, and antibacterial properties. This review employed the leading scientific databases Scopus, Web of Science, Google Scholar, and PubMed up to the end of 2022, as well as the combining terms pyranocoumarins, synthesis, isolation, structural elucidation, and biological activity. Among the catalysts employed, acidic magnetic nanocatalysts, transition metal catalysts, and carbon-based catalysts have all demonstrated improved reaction yields and facilitated reactions under milder conditions. Herein, the present review discusses the various multicomponent synthetic strategies for pyranocoumarins catalyzed by transition metal-based catalysts, transition metal-based nanocatalysts, transition metal-free catalysts, carbon-based nanocatalysts, and their potential pharmacological activities.

1. Introduction

Catalysis has played a beneficent role in organic synthesis as it promotes chemical reactions effectively to synthesize the desired products with high efficiency and using modest reaction conditions.[1,2] In general, based on the phase in which the catalyst exists, they are divided into two categories: homogeneous and heterogeneous. In homogenous catalysis, both reactants and catalysts function in the same phase, whereas in heterogenous catalysis, reactants and catalysts operate in distinct phases; typically, the catalyst is solid, and the reactant is in the liquid or gaseous phase.[3] Homogeneous catalysts possess innumerable advantages, such as better yield and high selectivity.[3–6] A major disadvantage of homogeneous catalysis is the difficulty in the removal of catalyst from the reaction medium.[7] Since the catalyst and the reactants are in distinct phases during heterogeneous catalysis, the separation procedure is quicker and more effective. The availability of surface area on the catalyst is a limitation of heterogeneous catalysis. When the surface of the catalyst is entirely saturated with reactant molecules, (i.e., no more reactants can fit on the surface), the reaction cycle cannot continue until some of the product molecules leave the surface, providing some space for new reactant molecules to form. As a result, the adsorption stage in a heterogeneously catalyzed process is frequently the rate-limiting step.[8,9] The collision involving the reactants and the catalyst's surface affects the selectivity and activity of heterogeneous catalysts. Reduced coordination of the new reactants and the surface of the catalyst until the product leaves the surface would decrease the selectivity and activity of a heterogeneous catalyst. To overcome the above-mentioned facets faced by using homogeneous and heterogeneous catalysts, nanocatalysts were deployed, which pose to be an attractive and effective alternative to conventional catalysts. Nanocatalysis includes the usage of nanocatalysts whose average size is around 1–100 nm. Due to their nanosize, they find wide catalytic applications. These nanocatalysts are recovered from the reaction medium via filtration or centrifugation methods. Nevertheless, in some cases, the separation of these catalysts is a tedious task as their size reduces to nanoscale dimensions and recovery becomes impossible. To overcome such limitations magnetic separation technique could be employed. The insolubility and paramagnetic nature of magnetic nanocatalysts make their recovery easy and they can be reused till there is a decrease in the catalytic activity.[10] Transition metal-based nanomaterials serve a dual purpose: they provide a nanoscale support system while simulating metal surface activation. Metal based nanocatalysts could be employed to synthesize various biologically active molecules. Various reports have been mentioned in the literature for the synthesis of heterocycles mainly coumarin and its analogs.[11–14]

The innovation of affordable and effective medications against diseases is one of the primary goals of researchers in medicinal chemistry. In the recent past, coumarin and its derivatives have

[a] J. M, F. Joy, Dr. A. Nizam
Department of Chemistry, CHRIST (Deemed to be University), Bangalore (Karnataka)-560029, India
E-mail: aatika.nizam@christuniversity.in

[b] Dr. S. B. Naidu Krishna
Department of Biomedical and Clinical Technology, Durban University of Technology, Durban,
E-mail: sureshk@dut.ac.za

gained popularity due to its prevailing pharmacological activities, including antimicrobial, antiviral, anticancer, antioxidant, anti-inflammatory, anti-tuberculosis, anti-influenza, anti-alzheimer, and anti-hyperlipidemia.[15,16,25,26,17–24,27] Numerous plants and microorganisms have been identified to naturally produce the chemical coumarin as a secondary metabolite. Moreover, it is found that a significant increase in biological activity is observed upon combining the coumarin ring with varied heterocycles thereby providing a unique option to develop advanced multicyclic compounds.[28–31]

Fused coumarin systems, particularly pyranocoumarins, are significant in synthetic organic chemistry as a valuable intermediate for synthesizing several biologically active compounds.[32] Pyranocoumarins are naturally occurring oxygen-containing ring compounds known for their extensive range of biological activities. Some of the invaluable pyranocoumarins isolated from nature are xanthyletin (isolated from *Zanthoxylum americanum*), khellactone, urisugacins, decursin, seselin, calanolide A, inopyllum B, dipetalolactone, and pyripyropenes (Figure 1).[33–37]

Pyranocoumarins have received remarkable demand in bioorganic chemistry due to their nature and exhibition of pharmacological activities. As illustrated in (Figure 2), there are numerous scaffold designs for pyranocoumarin derivatives based on structural rearrangement between pyran rings and coumarins.[38] Using 4-hydroxy coumarin as a starting point, pyrano[3,2-*c*]coumarin is a well-known type of pyranocoumarin derivative that is affordable, easily accessible, and stable.[39] The reaction of 4-hydroxy coumarin with various electrophiles such as propargylic alcohols,[40,41] propargyl chloride, and propargyl bromide,[42–45] alkenes,[46,47] and α,β-unsaturated carbonyls are also some of the most popular synthetic schemes used to synthesize pyranocoumarins apart from multicomponent reaction strategy.[48–52]

This review focuses on the various methods reported for pyranocoumarin synthesis using various catalysts such as transition metal-based catalysts, transition metal-based nanocatalysts, transition metal-free catalysts, and carbon-based nanocatalysts.

2. Synthesis of Pyranocoumarin Derivatives

2.1. Catalyzed by transition metal-based catalysts

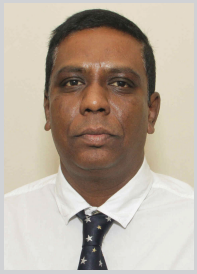
Transition metals in various forms are known to efficiently catalyze reactions for the synthesis of pyranocoumarins starting from coumarin. Haak and co-workers in 2010 established an approach for the synthesis of pyrano[3,2-*c*]coumarins (**3**) and these scaffolds were procured in good yields (22–82%), where propargyl alcohols (**2**) react with 4-hydroxy coumarin (**1**) catalyzed by ruthenium (2 mol-%) and trifluoroacetic acid (2 mol-%) in toluene at 100 °C (Scheme 1).[41]

Later, in 2011 Liu et al., outlined a specific design for the development of pyranocoumarin using much milder reaction conditions. This reaction utilizes 4-hydroxy coumarin (**1**) with α,β-unsaturated ketones (**4**) for the synthesis of pyranocoumar-

Jayalakshmi M is from Bangalore (Karnataka), India. She completed her B.Sc. from Vijaya Degree College, Bangalore University in 2018. She completed her M.Sc. Chemistry from Bangalore City University in 2020. In 2021 she joined Dr. Aatika Nizam group as a Ph.D. student at CHRIST (Deemed to be University). Her main research interest includes the synthesis of Heterocycles and, the synthesis of nano-catalyst and their application in Organic transformation reactions.

Francis Joy is from Kerala, India. He completed his B.Sc. from Mahatma Gandhi University, Kerala in 2017. In the same year, he worked as a project intern at the National Institute of Oceanography. He completed his M.Sc. Chemistry from CHRIST (Deemed to be University) in 2020. In 2021 he joined Dr. Aatika Nizam group as a Ph.D. student at CHRIST (Deemed to be University). His research interests are Organic Synthesis, Organic Photonic Materials for various applications like optical sensing, food spoilage and latent finger printing, and Organometallic Chemistry

Dr. Aatika Nizam received her M.Sc. degree in chemistry from Bangalore University, Karnataka, India in 2006. She finished her Ph.D. degree in Chemistry from Bangalore University, Karnataka, India, in 2012. Currently, she is an Associate Professor in the Department of Chemistry at CHRIST (Deemed to be University), Bangalore, India. Her research interests include Organic synthesis, Heterocyclic Chemistry, synthesis of nano-catalysts and their application in Organic transformation reactions, Photoluminescence studies, and, Spectroscopy.



Dr. Suresh Babu Naidu Krishna is a Research Fellow in the Department of Biomedical and Clinical Technology at Durban University of Technology, South Africa. He holds a Ph.D. in Biochemistry from SriKrishna Devaraya University. Dr. Krishna's research focuses on the optimization and development of scientific methods for the rapid diagnosis of antimicrobial resistance (AMR) and the applications of silver nanoparticles in biomedical applications. He is a registered member of the South African Council for Natural Scientific Professions (SACNASP) as a Natural Scientist. Additionally, Dr. Krishna is a member of the Royal Society of South Africa (MRSSAf), the South African Society for Microbiology (SASM), and the South African Society for Biochemistry and Molecular Biology (SASBMB).

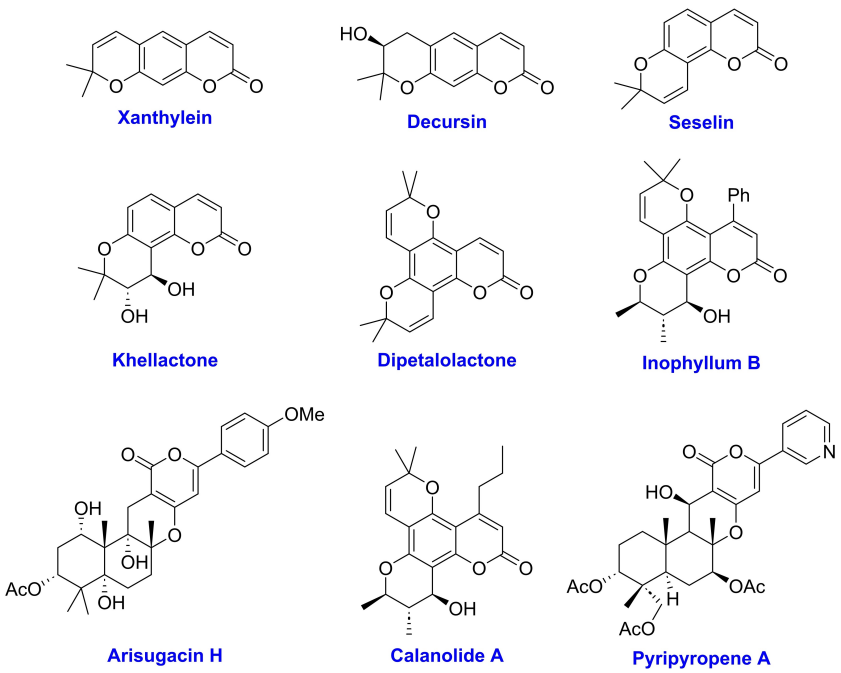


Figure 1. Natural products containing pyranocoumarin moieties.

ins (**5**) in high yields (58–98%) catalyzed by $AuCl_3$/AgOTf (3 mol-%). The developed methodology significantly generated numerous complimentary compounds when substituted 4-hydroxy coumarin combined with a wide range of unsaturated ketones (Scheme 2).[53]

Further, Nepali and his research group devised a technique under solvent-free conditions for 2,4-diarylpyrano[3,2-*c*]-chromen-5(4*H*)-one derivative (**5**) preparation in good yields (78–82%) mediated by SiO_2-$ZnCl_2$ via condensation of 4-hydroxy coumarin (**1**) with α,β-unsaturated ketones (**4**) at 100 °C. The synthesized derivatives were found to possess non-purine xanthine oxidase inhibition properties (Scheme 3).[54]

Extending the studies carried out by Nepali et al., utilizing neat conditions, Yaragorla et al., (2015) developed a novel synthetic methodology using $Ca(OTf)_2$ and Bu_4NF_6 as a catalyst for the reaction between 4-hydroxycoumarin (**1**) and chalcone (**4**) at 120 °C in 3–4 h (Scheme 4). The reaction proceeded via a one-pot, multicomponent, conjugate addition and annulation of different nucleophiles to carbonyl compounds that are unsaturated for the production of the desired product (**5**) which was found to be bioactive in good to excellent yields (80–92%).[55]

The reaction between 4-hydroxycoumarin (**1**) and secondary propargylic alcohols (**2**) catalyzed by iron at 80 °C gave Pyrano-

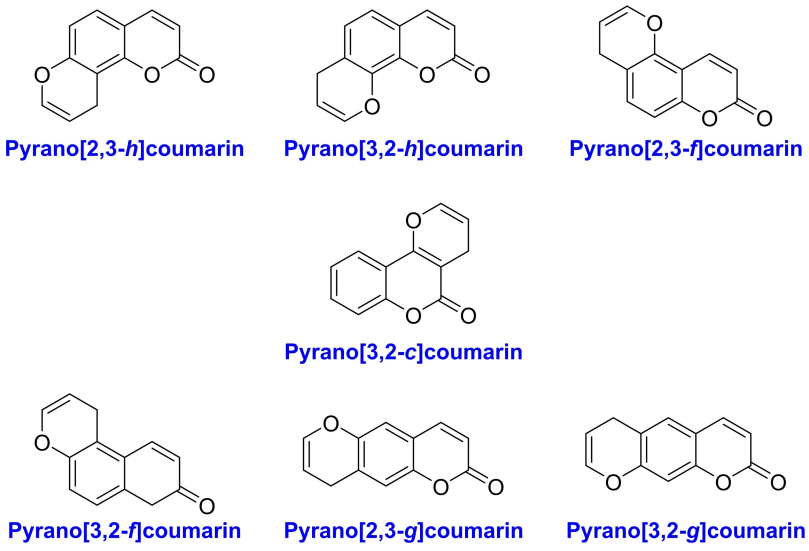
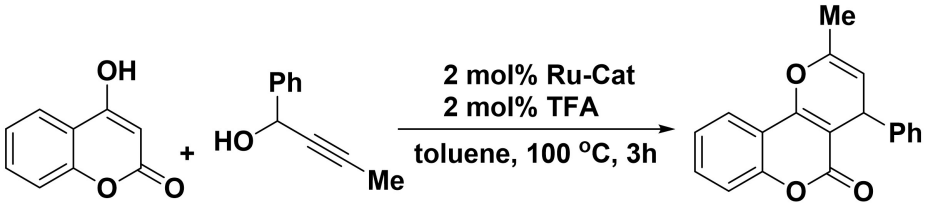
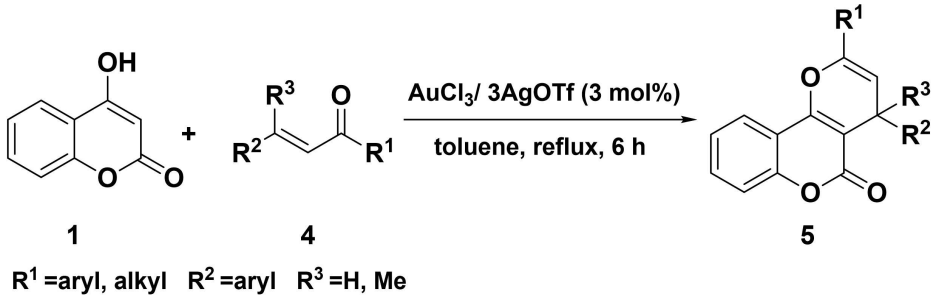


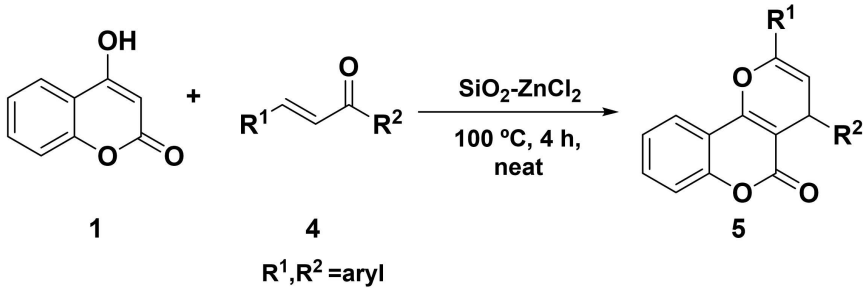
Figure 2. Scaffold patterns of pyranocoumarins.



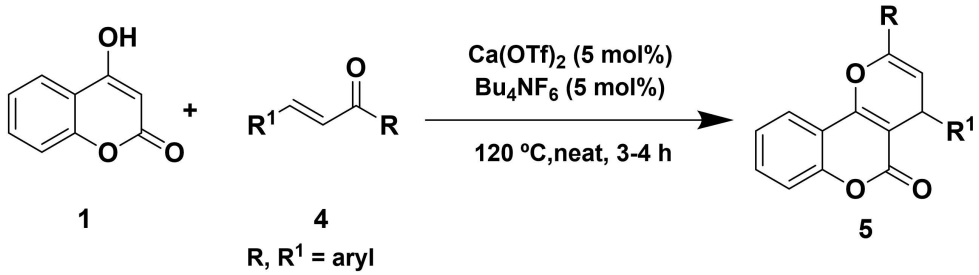
Scheme 1. Synthesis of pyrano[3,2-c] coumarins promoted by ruthenium salt.



Scheme 2. Transition metal-catalyzed synthesis of pyranocoumarins.



Scheme 3. Synthesis of 2,4-diarylpyrano[3,2-c]chromen-5-ones under neat conditions.

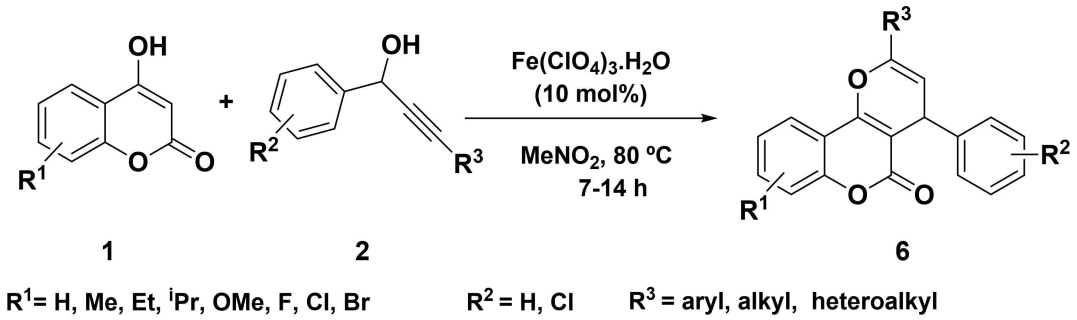


Scheme 4. Calcium metal catalyzed synthesis of pyranocoumarins.

[3,2-*c*]coumarins (**6**) via annulation to obtain good yields (40–75%). In addition to pyranocoumarin derivatives, furo[3,2-*c*]coumarins were also obtained in a regioselective manner (Scheme 5).[56]

In 2018, Priyanka et al. devised a simpler and an efficient method for the synthesis of pyranocoumarin derivatives starting from substituted phenols (**8**) and ethyl benzylidene oxobutanoates (**7**). This method involves the Michael addition of substituted phenols to ethyl benzylidene oxobutanoates thereby forming an intermediate (**9**), which was then treated with propiolic acid (**10**) at room temperature with the involvement of palladium acetate in TFA to get the anticipated products (**11** and **12**) in excellent yields (58–78%). The preliminary mechanistic analyses proved that an intermediate chroman derivative was generated first, followed by the formation of the end product after additional dehydration (Scheme 6).[57]

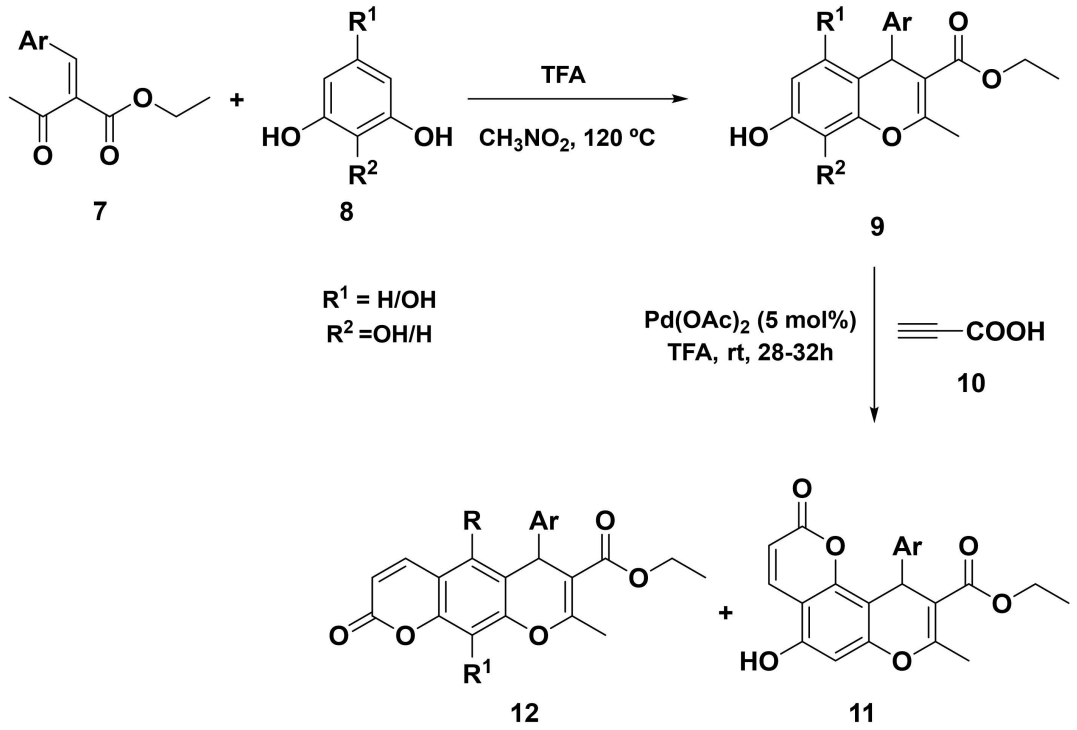
Tamimi et al. developed an approach to generate dihydropyrano[3,2-*c*]chromenes (**15**) in excellent yields (85–97%) which were synthesized using keggin-type polyoxomolybdate silver salt ($Ag_3[PMo_{12}O_{40}]$) as an effective heterogeneous



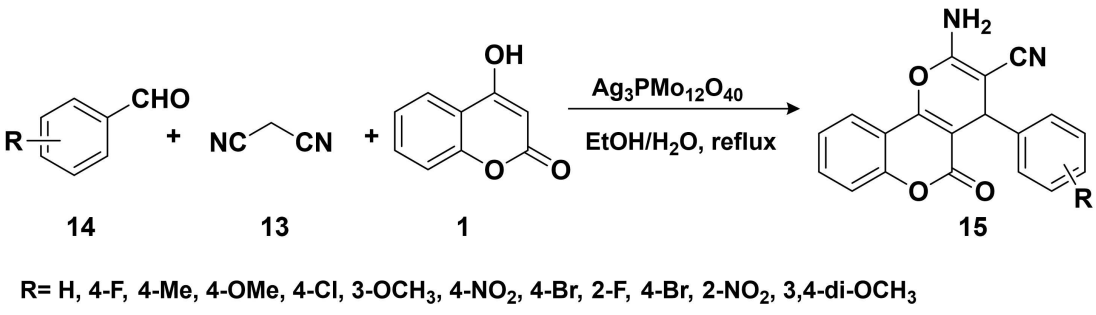
Scheme 5. Regioselective approach for pyrano[3,2-c]coumarins synthesis through iron-catalyzed annulation reactions.

catalyst. In a single pot using an ethanol-water solvent, the reaction proceeded *via* cyclo condensation reaction of C–H containing acid compounds such as 4-hydroxycoumarin (**1**) and dimedone, many aldehydes (**14**), and malononitrile (**13**) to obtain the desired product (Scheme 7).[58]

In 2020, a regioselective Bi-catalyzed synthesis process for Pyrano[3,2-*c*]coumarin analogs (**5**) through 6-*endo* mode was



Scheme 6. Synthesis of pyranocoumarins in the presence of palladium acetate catalyst under room temperature.



Scheme 7. Keggin-type polyoxomolybdate catalyzed dihydropyrano[3,2-c]chromenes preparation.

found when 4-hydroxy coumarins (**1**) reacted with propargyl alcohols (**2**) using CH_3NO_2 as solvent at 100 °C. The reaction was found to proceed *via* sequential propargylation and cyclization reactions. 5-*Exo* mode furochromones and furocoumarins were procured when terminal propargyl alcohols were used (Scheme 8). The desired products were obtained in good yields (50–78%).[59]

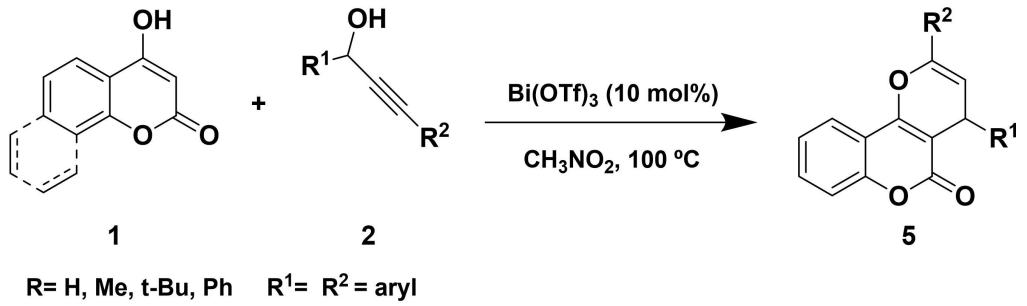
Benzaldehydes (**14**), malononitrile (**13**), and 4-hydroxycoumarin (**1**) were reacted in one pot, with the use of a transition metal-based catalyst to produce tetrahydro-4*H*-chromenes and dihydropyrano[3,2-c]chromenes (**15**) in excellent yields (65–92%) was developed by Sharghi et. al., The reported procedures were used to create a cobalt complex $[Co(MCG)(H_2O)_3]$ that was functionalized with a coumarin moiety (Scheme 9).[60]

Zinc sulfate ($ZnSO_4$) and triple superphosphate fertilizer ($Ca(H_2PO_4)$ were used to create an effective phosphate catalyst ($Zn_3(PO_4)_2.4H_2O$) by Hallaoui et al., (H_2PO_4). Dihydropyrano[3,2-*c*]chromenes (**15**) were furnished in good yields (81–87%) in one pot catalyzed by heterogeneous catalyst under reflux conditions from aldehydes (**14**), malononitrile (**13**), and 4-hydroxycoumarin (**1**) in (Scheme 10).[61]

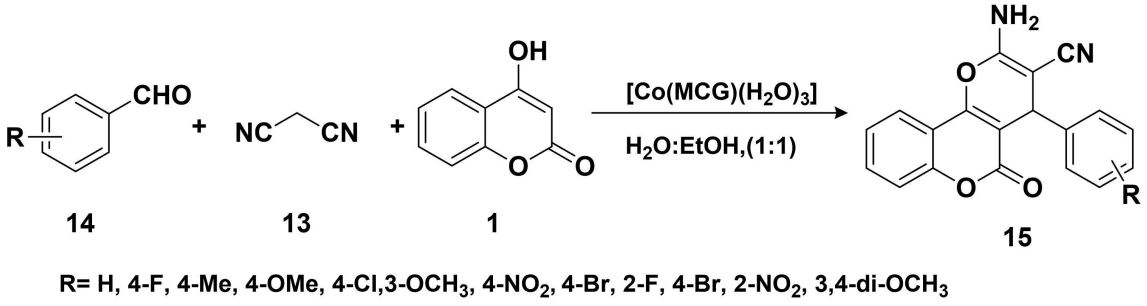
2.2. Catalyzed by transition metal-based nanocatalysts

Increasing interest has been devoted lately towards the synthesis of pyranocoumarin and its derivatives using transition metal-based nano-catalysts due to its high activity and selectivity thereby allowing greener and waste-minimized processes. Moreover, the utilization of transition metal nano-catalysts helps in carrying out the reaction in neoteric eco-friendly solvents.

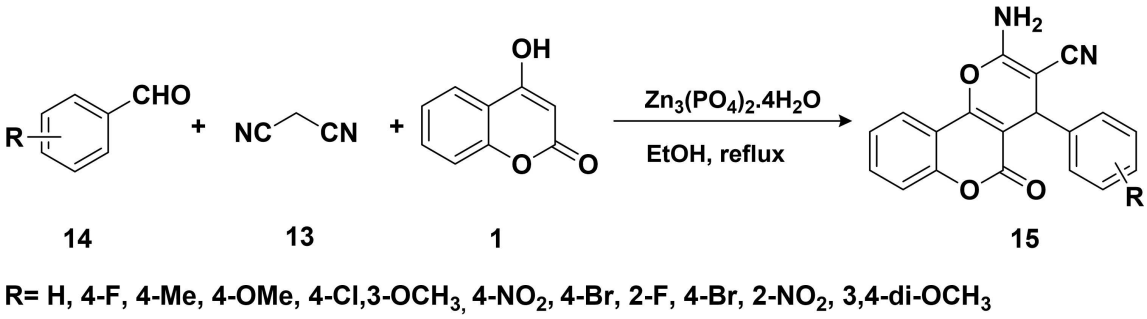
Another multi-component synthesis approach for dihydropyrano[3,2-*c*]chromenes (**15**) was put forth by combining a variety of aromatic aldehydes (**14**), 4-hydroxycoumarin (**1**), and malononitrile (**13**) in an aqueous environment at a higher temperature catalyzed by tetragonal ZrO_2 NPs (t-ZrO_2-NPs) gave excellent yields (88–92%). Tetragonal ZrO_2 NPs were shown by



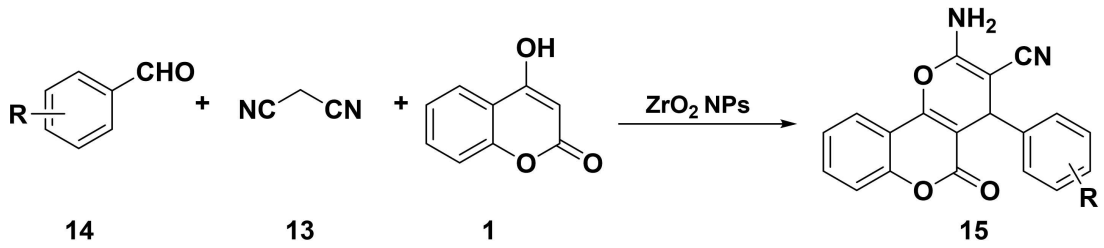
Scheme 8. Synthesis of pyrano[3,2-c]coumarins using propargyl alcohol and 4-hydroxy coumarin.



Scheme 9. Synthesis of pyranocoumarin analogs promoted by cobalt complex.



Scheme 10. Novel phosphate catalyst promoted dihydropyrano[3,2-c]chromenes synthesis under reflux conditions.



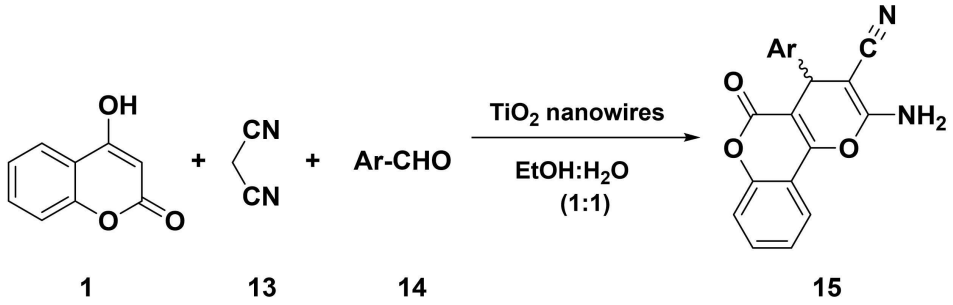
Scheme 11. Zirconium oxide nanoparticles catalyzed the synthesis of pyranochromenes.

catalytic analysis to be more effective than monocyclic ZrO_2 NPs (Scheme 11).[62]

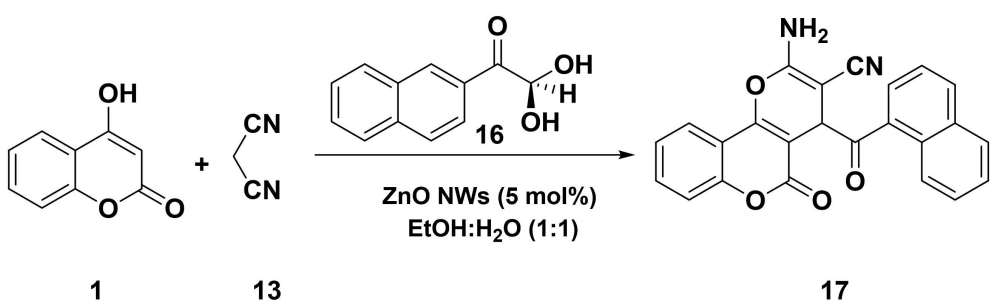
Khodabakshi et al., (2014) designed a multicomponent condensation of aldehydes (**14**), 4-hydroxy coumarin (**1**), and malononitrile (**13**) in EtOH:H_2O (1:1) to produce a series of pyranocoumarins derivatives (**15**), in great yields (80–90%) which were found to be biologically active. The synthesis was catalyzed by titanium dioxide nanowires. In the mechanism proposed by the authors, it is found that an aryl methylene intermediate was generated by aldehyde and malononitrile *via* Knoevenagel condensation catalyzed by TiO_2 NWs, which is found to be a viable process for the synthesis. The expected products are generated wherein the aryl methylene is generated via Knoevenagel condensation followed by a Michael-type addition and hetero-cyclization facilitated by TiO_2 NWs (Scheme 12).[63]

Later in 2014, Saeed Khodabakhshi using water as a solvent constructed a novel method for the green synthesis of naphthyloyl pyranocoumarins (**17**) *via* condensation reaction between 4-hydroxy coumarin (**1**), malononitrile (**13**), and naphthyl glyoxals (**16**) promoted by ZnO nanowires (ZnO NWs) under reflux conditions. The reaction proceeded in three steps wherein initially, the formation of the Knoevenagel intermediate takes place followed by condensation to produce pyranocoumarins (Scheme 13) in excellent yields (85–90%).[64]

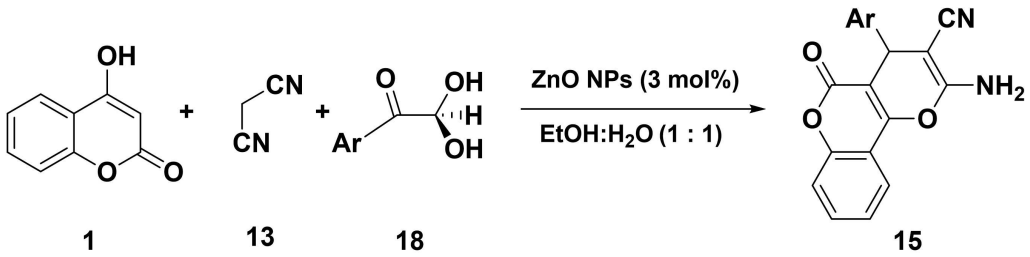
In the same year following the studies carried out using Zn-based nanomaterials, Khodabakhshi et al., (2014) demonstrated the preparation of an evolving family of pyrano[3,2-*c*]coumarins with an aryloyl group, malononitrile, 4-hydroxy coumarin in EtOH:H_2O (1:1) solvent catalyzed by zinc oxide nanoparticles (ZnO NPs) as an efficient and recyclable catalyst. The recovery of the catalysts in the reaction was carried out by recovering and reusing them almost three times without any loss of catalytic activity. The plausible mechanism stated involves initiation of the reaction with a Knoevenagel-type condensation of aryl glyoxal (**18**) and malononitrile (**13**) with 4-hydroxy coumarin (**1**) activated by ZnO NP, which is followed by a Michael-type addition of 4-



Scheme 12. TiO_2 NWs mediated synthesis of pyranocoumarins.



Scheme 13. Synthesis of pyranocoumarins using ZnO nanowires.



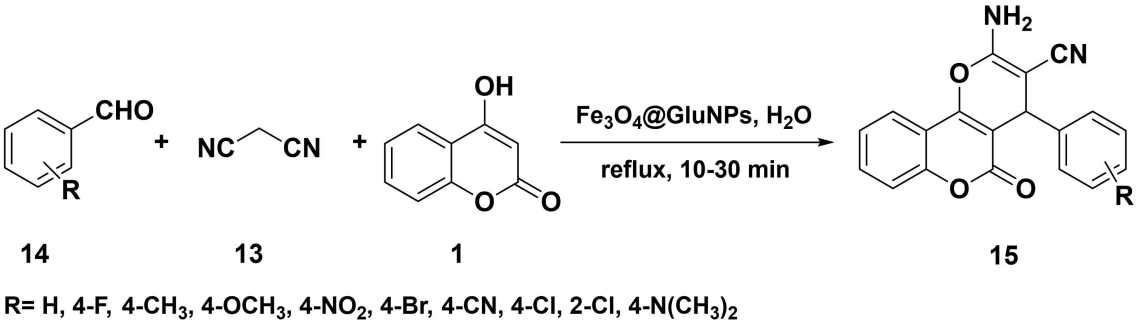
Scheme 14. Synthesis of pyranocoumarin via zinc catalyzed intermolecular hetero-cyclization reaction.

hydroxycoumarin to the corresponding aroylidene malononitrile. The aroylidene malononitrile undergoes an intermolecular hetero-cyclization reaction to yield the final product (15) in good to excellent yields (75–100%) (Scheme 14).[65]

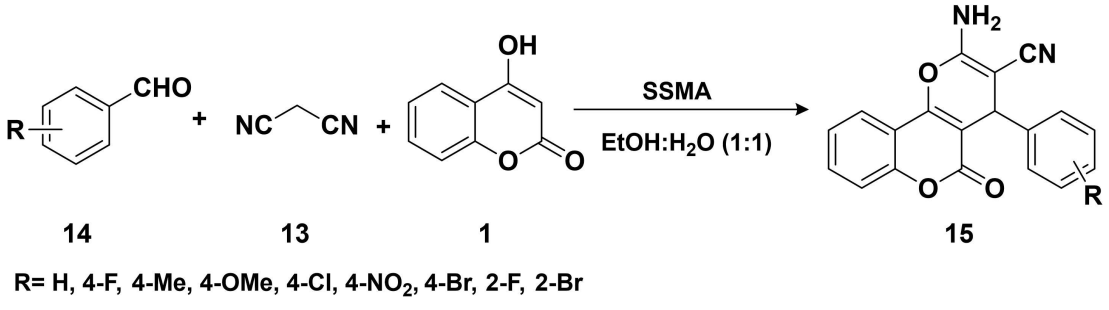
In a one-pot condensation of various aldehydes (**14**), malononitrile (**13**), and 1,3-dicarbonyl compounds, such as dimedone and 4-hydroxycoumarin (**1**), Gupta et al., demonstrated the synthesis of ferrite-supported glutathione as a green and magnetically recoverable nanocatalyst. They then utilized it to make tetrahydro-4*H*-chromene derivatives and dihydropyrano[3,2-*c*]chromenes in good yields (65–92%) (**15**). This approach worked well because of the nanocatalyst's reusability, the good to exceptional yields in the aqueous medium, and quick reaction times (Scheme 15).[66]

In 2016, Karami and his co-workers devised a one-pot multicomponent method to synthesize pyranocoumarins (**15**) by reacting malononitrile (**13**), aromatic aldehyde (**14**), and 4-hydroxycoumarin (**1**) catalyzed by silica-coated molybdic acid (SSMA) in EtOH:H_2O (1:1). It was observed that devoid of substantial reduction in product yields or catalytic activity, the catalyst was revived and reused for six cycles. FT-IR spectra were used to evaluate the synthesized catalyst's activity for six runs. All of the runs had the same spectral signature as the newly created catalyst, demonstrating the catalyst's high level of stability. The authors suggested a mechanistic three-step process for synthesizing pyranocoumarins. To create an intermediate called aryl methylene, SSMA first catalyzed the Knoevenagel condensation of aldehyde and malononitrile. Following this, the aryl methylene intermediate underwent a Michael-type addition, and then hetero-cyclization aided by SSMA produced the desired products in good yields (70–94%) (Scheme 16).[67]

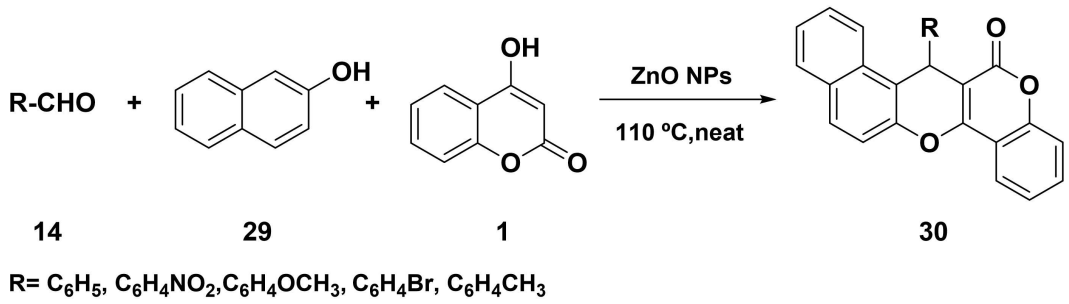
Banerjee and his co-workers (2017) described an efficient, multi-component, one-pot synthesis of pyranocoumarins (**30**) *via* a reaction between various aldehydes (**14**), β-naphthol (**29**), and 4-hydroxy coumarin (**1**) catalyzed by nano-ZnO at 110 °C in a solvent-free environment. This approach posed several advantages, including a short reaction time, wide substrate



Scheme 15. Fe_3O_4@GluNPs as a greener catalyst for pyranochromenes preparation.



Scheme 16. Silica-coated molybdic acid-catalyzed synthesis of pyranocoumarins.



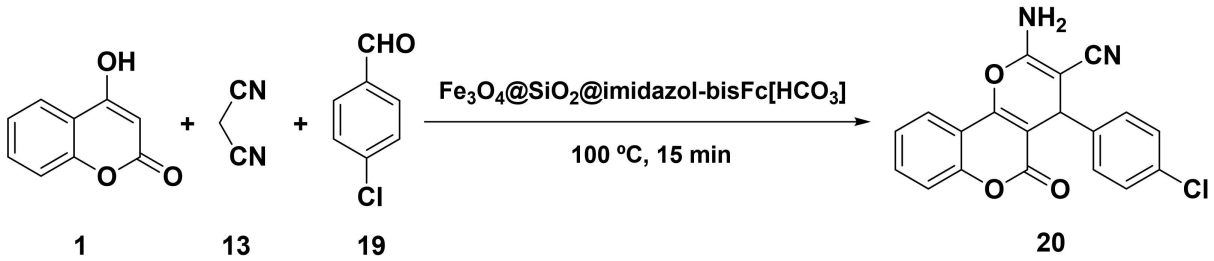
Scheme 17. Nano ZnO mediated synthesis of pyranocoumarins.

tolerance, catalyst reusability, great yields (80–90%), and a solvent-free environment (Scheme 17).[68]

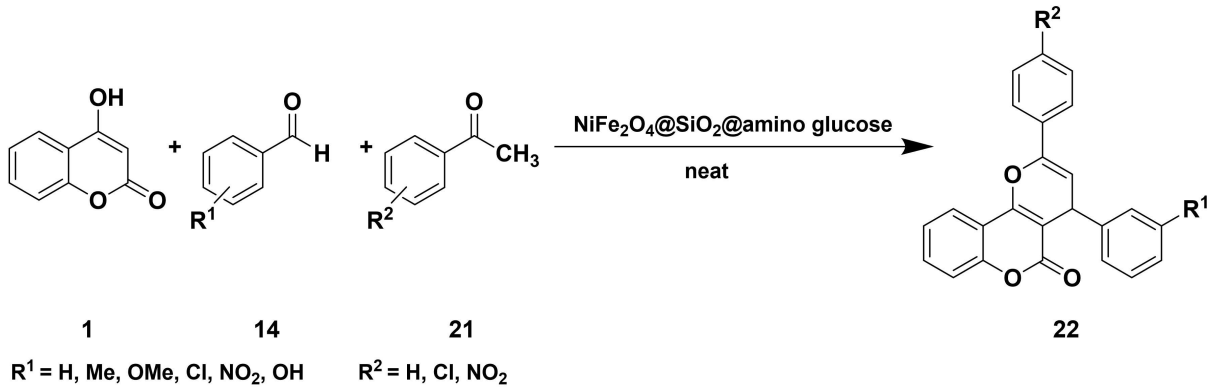
Analyzing the previous reports of metal NPs-catalyzed synthesis of pyranocoumarin derivatives, Teimuri, and his colleagues 2018 devised a one-pot multicomponent condensation process of different aromatic aldehydes (**19**), malononitrile (**13**), and 4-hydroxy coumarin (**1**) at 100 °C under solvent-free conditions to synthesize dihydropyrano[2,3-*c*]coumarin derivatives (**20**) in excellent yields (82–94%) using a nanoparticle composite. (Fe_3O_4@SiO_2@imidazol-bisFc[HCO_3]) synthesized proved to be a valuable catalyst in generating pyranocoumarin derivatives (Scheme 18).[69]

Later following the investigations carried out using iron-based nanocomposites, simultaneous synthesis of pyranocoumarin (**22**) was effectuated using aryl aldehydes (**14**), and acetophenones (**21**), and 4-hydroxy coumarin (**1**) promoted by amino glucose-functionalized silica-coated $NiFe_2O_4$ nanoparticles by Fekri and co-workers as an effective one-pot multicomponent process. $NiFe_2O_4$@SiO_2@glucose amine nano composite elevated the electrophilic character of the carbonyl species wherein the catalyst works as a Brönsted acid. A chalcone intermediate was generated via nucleophilic addition of the enolic form of the ketone followed by dehydration. Further, a Michael-type addition of 4-hydroxy coumarin with chalcone generates the desired product (Scheme 19) in excellent yields (90–98%).[70]

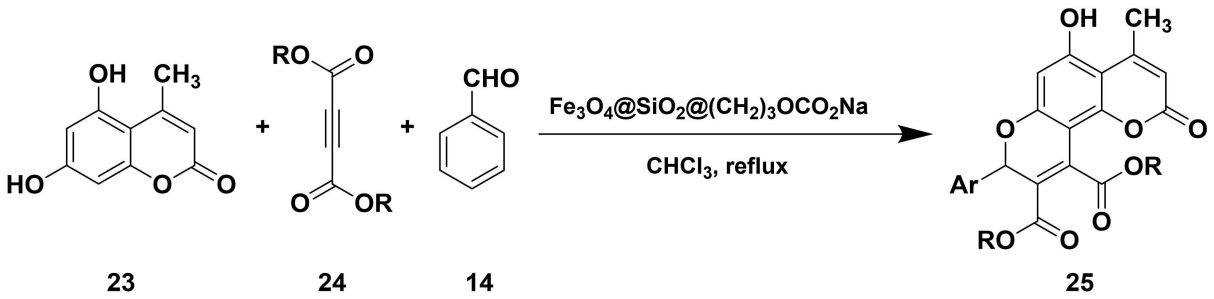
In continuation with the studies carried out using Fe-based nanocomposite as catalysts, to facilitate the synthesis of pyrano[2,3-*h*]coumarin derivatives, Tanuraghaj et. al., (2019) proposed a novel, three-component, heterogeneous basic nanocatalyst composed of sodium carbonate functionalized silica coated-iron oxide nanoparticles Fe_3O_4@SiO_2@-$(CH_2)_3OCO_2Na$ (**25**). The expected product is produced through a reaction involving dialkyl acetylene dicarboxylates (**24**), 5,7-



Scheme 18. Synthesis of dihydropyrano[2,3-*c*]coumarin derivatives promoted by the iron-based ionic liquid.



Scheme 19. $NiFe_2O_4$@SiO_2@glucose amine promoted multicomponent synthesis of pyranocoumarin derivatives.



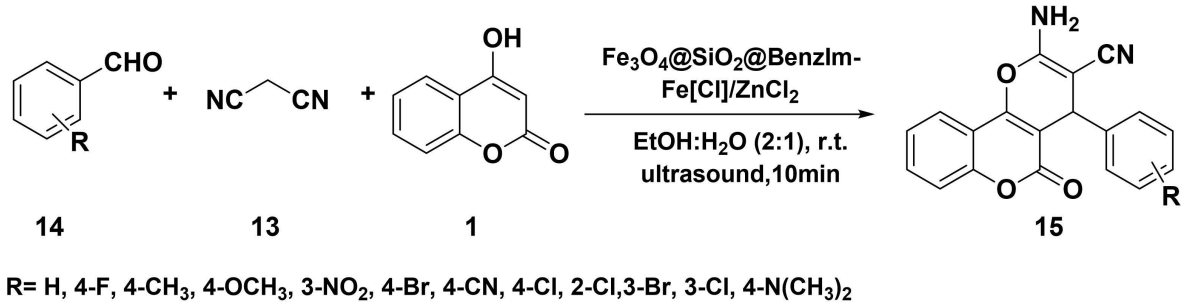
Scheme 20. $Fe_3O_4@SiO_2@(CH_2)_3OCO_2Na$ nanoparticles promoted the synthesis of pyrano[2,3-*h*]coumarin.

dihydroxy-4-methylcoumarin (**23**), and aromatic aldehydes (**14**). Without losing its catalytic activity, the nanocatalyst was retrieved utilizing an external magnetic field. To produce the intermediate, the basic nanocatalyst first deprotonates the hydroxy group of 5,7-dihydroxy-4-methyl coumarin. This is followed by an attack on acetylene dicarboxylate. The intermediate then attacks the aldehyde's carbonyl group, resulting in the formation of an adduct. Deprotonating the adduct was followed by intramolecular ring-closing with the removal of water to produce the final product in a high yield (70–92%) (Scheme 20).[71]

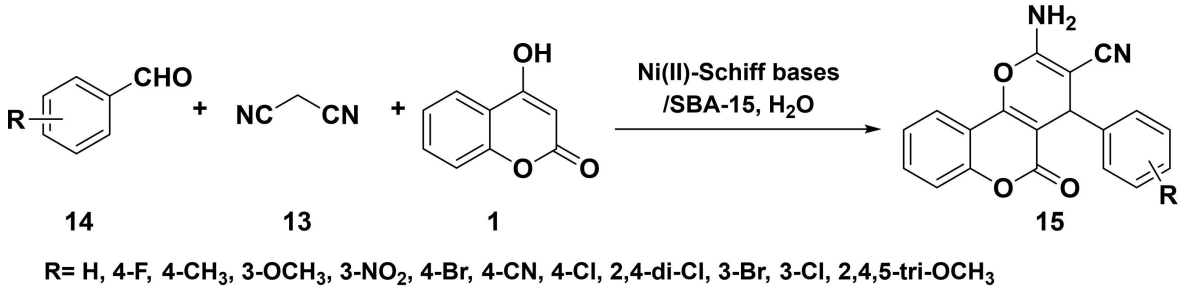
By using the chemical coprecipitation method, Gholamhosseini-Nazari et al. described the novelty in the synthesis of magnetically recoverable $Fe_3O_4@SiO_2$-BenzIm-Fc [Cl]/$ZnCl_2$ nanoparticles. They also evaluated the catalytic activity of $Fe_3O_4@SiO_2$-BenzIm-Fc [Cl]/$ZnCl_2$ nanoparticles by carrying out one-pot synthesis of dihydropyrano[3,2-*c*]chromene analogs (**15**) and other pyran ring fused heterocycles from aldehydes (**14**), malononitrile (**13**) and 4-hydroxy coumarin (**1**). This method had the benefits of quick reaction times with high yields (80–96%), environmentally friendly reaction conditions, simple purification, and recyclable catalysts (Scheme 21).[72]

Pesyan et al., produced the heterogeneous nanocatalyst, Ni(II)-Schiff base/SBA-15, by functionalizing mesoporous silica SBA-15 with the Ni(II)-Schiff base complex. Aldehydes (**14**), malononitrile (**13**), and 4-hydroxycoumarin (**1**) were cyclo condensed in a single pot with the catalyst to produce dihydropyrano[3,2-*c*]chromene analogs (**15**) (90–95%) as indicated in (Scheme 22).[73]

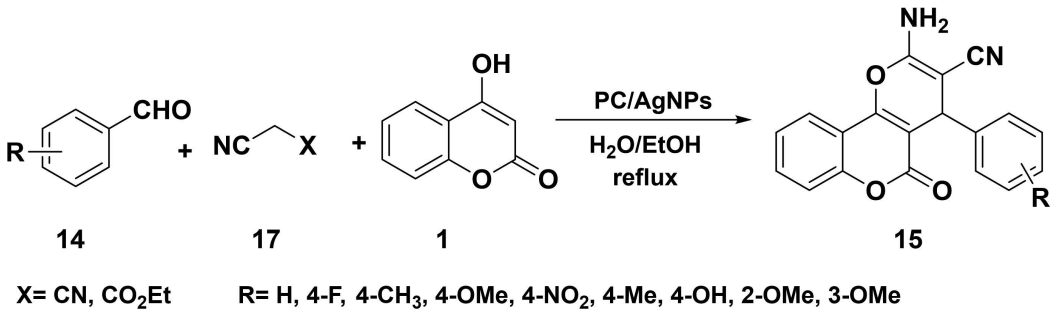
Saneinezhad et al. produced a silver-supported, Preyssler-functionalized cellulose nanocomposite by employing the Taguchi method. From aromatic aldehydes (**14**), malononitrile (**17**), and a range of C–H acid compounds like 4-hydroxy chromene (**1**), tetrahydro-4*H*-chromenes, pyrano[2,3-*d*]pyrimidines, dihydropyrano[3,2-*c*]chromenes (**15**), and ethyl-substituted 4*H*-pyran-3-carboxylates were procured in good to excellent yields (80–96%) (Scheme 23).[74]



Scheme 21. $Fe_3O_4@SiO_2$-BenzIm-Fc[Cl]/$ZnCl_2$ NPs catalysed dihydropyrano[3,2-*c*]chromene analogs synthesis.



Scheme 22. Ni (II)-Schiff base complex catalyzed cyclo condensation of aldehydes, malanonitrile, and 4-hydroxycoumarin.



Scheme 23. Synthesis of dihydropyrano[3,2-*c*]chromenes catalyzed by silver-supported cellulose nanocomposite.

Understanding the significant involvement of Fe-based nanocatalyst in pyranocoumarin synthesis, Fekri (2021) developed a novel, green, efficient, recyclable Lewis acid, nanomagnetic dapsone-Cu supported on silica-coated Fe_3O_4 (Fe_3O_4@SiO_2-pr@ dapsone-Cu) nanocomposite for the synthesis of pyrano[3,2-*c*]chromene-diones (**27**) via a multicomponent reaction of aromatic aldehyde (**14**), 4-hydroxy coumarin (**1**), and indandione (**26**) in water (Scheme 24). The synthesized catalyst exhibited potent recyclability wherein it was retrieved and reprocessed for six cycles without losing its catalytic activity. The reaction was initiated by the nanocatalyst by activating the aldehyde which was followed by the nucleophilic attack of C–H acid of indan-1,3-diones to form a chalcone. To obtain the desired product, Michael addition of 4-hydroxy coumarin takes place resulting in the formation of a chalcone followed by intramolecular cyclization, and finally, the removal of water takes place thereby affording the product in good yield (80–95 %).[75]

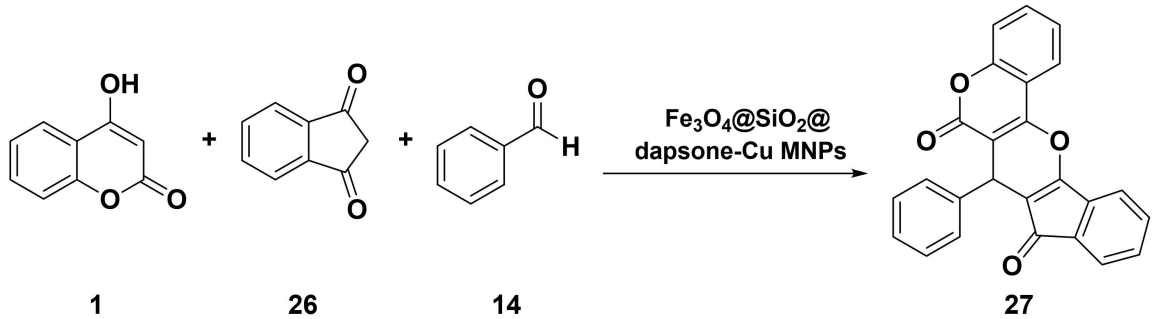
2.3. Catalyzed by organocatalyst

Even though transition metal-based catalysts posed significant attention in rendering pyranocoumarins, organic chemists started developing synthetic methodology devoid of transition metals considering the adverse effects of the same. In 2009, Renaud and co-workers demonstrated an approach catalyzed by phosphoric acid for the synthesis of pyranocoumarin derivatives (Scheme 25). The plausible mechanism involves the formation of a pyranone ring by reacting, unsaturated aldehydes (**4**) with 4-hydroxy coumarin (**1**) in toluene at 60 °C via a [3 + 3] cycloaddition process, yielding pyranocoumarins (**5**) in high yields (85–92 %).[76]

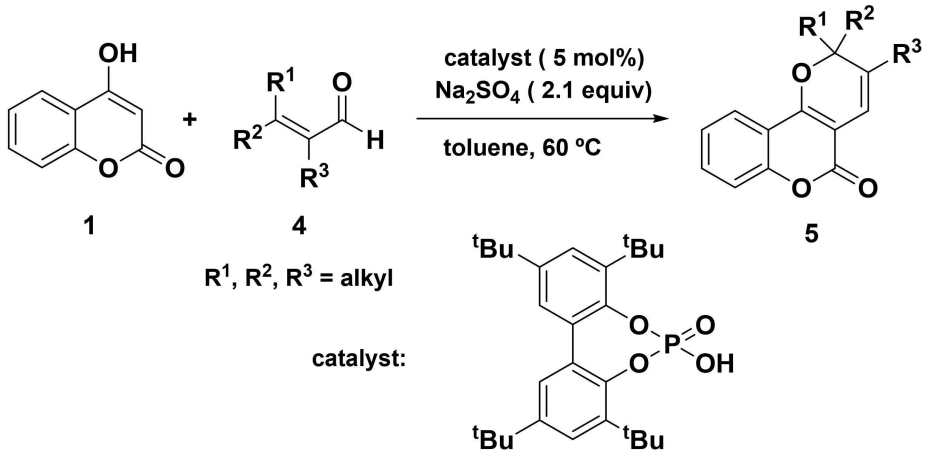
Later in 2012, Ahadi and his co-workers highlighted the potent involvement of an organocatalyst: DBU by devising a new diastereoselective synthetic process for making coumarins fused with pyrans (Scheme 26). The developed methodology involves a three-component tandem reaction catalyzed by DBU (30 mol-%) starting from 3-bromo-4-hydroxycoumarins as α-halo ketones (**33**), 4-hydroxy coumarin (**1**), and terepthaldehyde or isophthaldehyde (**32**) in AcOH to give good yields of the target product pyranocoumarin (**34**) in high yield (75–96 %).[77]

Zeba N. Siddiqui (2014) reported an effective one-pot pyranocoumarin synthesis employing sulfamic acid in aqueous media to condensate 4-chloro-3-formylcoumarin (**37**) with various active methylene compounds (**38**) under homogeneous catalytic conditions. Under catalytic conditions, the reaction proceeded via a Knoevenagel condensation followed by a Michael addition leading to a cyclization process rendering the desired products (**39**). The pyranocoumarin derivatives were afforded in excellent yields (88–94 %) wherein the catalyst was reused for almost 4 cycles without losing its catalytic activity (Scheme 27).[78]

Dihydropyrano[3,2-*c*]chromenes, Tetrahydro-4*H*-chromenes, pyrano[3,2-*c*]chromenes, and pyrano[2,3-*c*] pyrazoles are among the many pyran scaffolds. Pandit et. al., suggested synthesis using tris-hydroxymethyl aminomethane (THAM) as an efficient, available, and affordable organocatalyst under benign conditions using aryl aldehydes (**14**), dicyanomethane/malononitrile (**13**), and C–H acid substances like dimedone, 4-hydroxycoumarin (**1**), 4-hydroxy-



Scheme 24. Fe_3O_4@SiO_2-pr@ dapsone-Cu nanocomposite mediated synthesis using aromatic aldehyde, indanone, and 4-hydroxy coumarin.



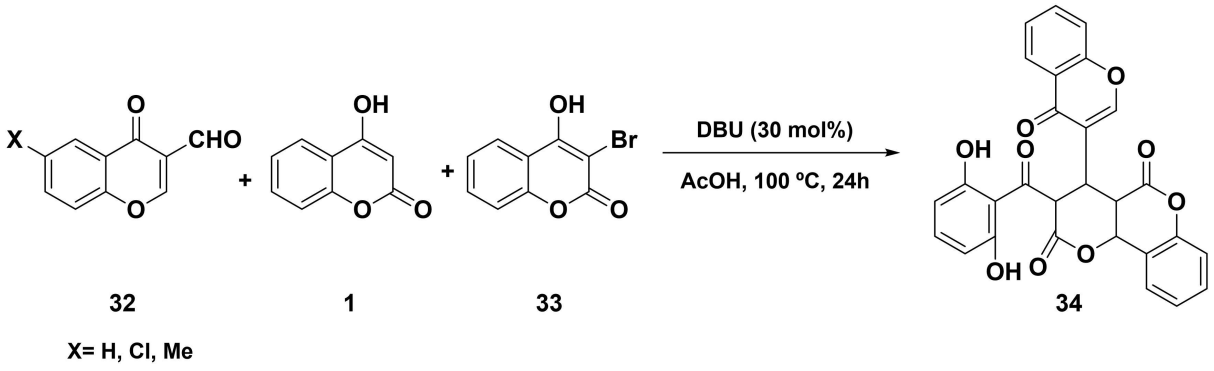
Scheme 25. Phosphoric acid-catalyzed synthesis of pyranocoumarins.

1-methylquinolin-2(1*H*)-one, ethyl acetoacetate and hydrazine hydrate to obtain desired products, respectively (Scheme 28).[79]

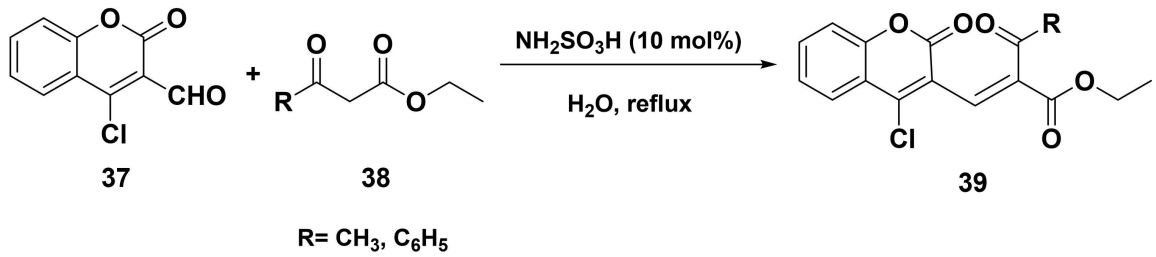
Thiourea dioxide was used by Mansoor et al., in their work as a useful and recyclable catalyst to promote the Knoevenagel condensation reaction of aromatic aldehydes (**14**), malononitrile (**17**), and 4-hydroxycoumarin (**1**) to produce analogs of the expected product (**18**) in excellent yields (50–96%). A similar approach was employed to prepare pyrano[2,3-*c*]pyrazoles which were promoted using thiourea dioxide (Scheme 29).[80]

Considering the greener alternatives to classical environmentally benign catalysts, ionic liquid has received momentous attention considering its green, recyclable, and ecologically friendly attributes. Brönsted acidic phosphonium-based ionic liquid functionalized SBA-15 was used as a catalyst by Saeedi et al., (2015) to develop pyrano[3,2-*c*]chromenone derivatives (**5**) in H_2O:EtOH (1:1) at 60 °C (Scheme 30). The proposed mechanism involves the addition of 4-hydroxy coumarin (**1**) to an activated chalcone derivative (**4**), which leads to the production of an intermediate that later effectuates intramolecular cyclization and water removal to yield the desired molecules (85–92%).[81]

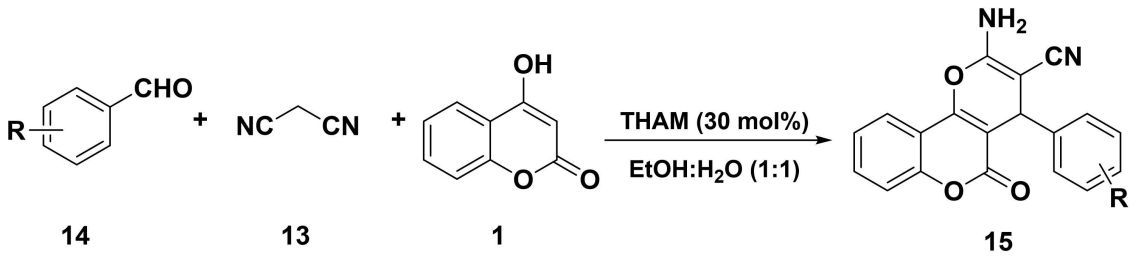
Metal triflates are found to be an emerging Lewis acid catalyst in many of the recently reported organic transformations. The increased activity and the high stability toward air and moisture place them on top of the hierarchy



Scheme 26. Diastereoselective methodology for the preparation of pyran fused coumarins catalyzed by DBU.



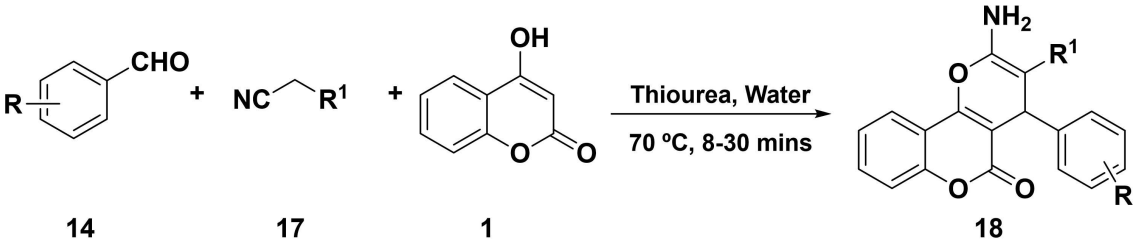
Scheme 27. One-pot pyranocoumarin synthesis catalyzed by sulfamic acid.



14 13 1 15

R= H, 4-F, 4-Me, 4-OMe, 3-NO_2,4-CN, 3,4,5-tri-OMe, 4-Me, 4-OH,2-OMe, 3-OMe,4-$CH(Me)_2$, 4-cyclohexyl, 3-pyridyl, 2,6-di-Me, 4-furanyl

Scheme 28. Synthesis of pyran fused heterocycles catalyzed by THAM



14 17 1 18

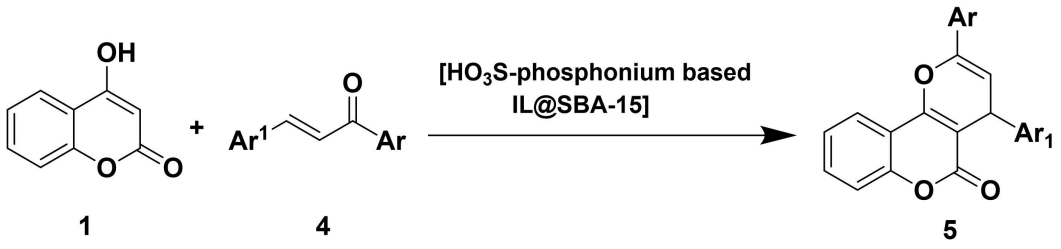
R^1 = CN, $COOC_2H_5$ R = H, 4-F, 4-Me, 4-OMe, 3-NO_2,4-CN, 3-Cl, 2-NO_2 4-Me, 4-OH,2-OMe, 3-OMe,2-F, 2-Br, 2,4-di Cl_2

Scheme 29. Pyrano[3,2-*c*]chromenes preparation via multicomponent approach catalyzed by thiourea.

overthrowing all the conventional Lewis acid catalysts. Considering the above-mentioned advantages of metal triflates as catalysts, Bezuidenhout et al., (2015) described a regioselective cyclization of 4-hydroxy-3-propargylic coumarins (**44**) to yield furo and pyrano[3,2-*c*]coumarins (**5**) promoted by Al $(OTf)_3$ (Scheme 31). It's a two-step process that starts with propargylic alcohols (**2**) reacting with 4-hydroxy coumarin (**1**) to produce 4-hydroxy-3-(prop-2-ynyl) coumarins (**44**) which are assisted by Al $(OTf)_3$. Following that, 4-hydroxy-3-(prop-2-ynyl)coumarins (**44**) are cyclized with the involvement of DBU or CuBr to produce furo[3,2-*c*]coumarin or pyrano[3,2-*c*]coumarin derivatives (**5**) in good yields (up to 94%).[82]

Yang and his co-workers (2015) in the presence of a primary amine/*N*-Boc-D-phenyl glycine system (BoC-D-Phg-OH), effectuated a novel, efficient, and enantioselective preparation of pyranocoumarins catalyzed by a quinine-derived primary amine. The reaction proceeded via a Michael/cyclodehydration between chalcones (**40**) and 4-hydroxy coumarin (**1**)/ 4-hydroxy-2-pyrone (**42**). Chiral pyranocoumarins were achieved with good enantioselectivities and great yields (up to 84%). The developed methodology was also the first report for developing chiral 2,4-diphenyl-4*H*-pyranocoumarin (**41**) and 2,4-diphenyl-7-methylpyrano-4*H*-[4,3-*b*]pyran-5-one (**43**) (Scheme 32).[83]

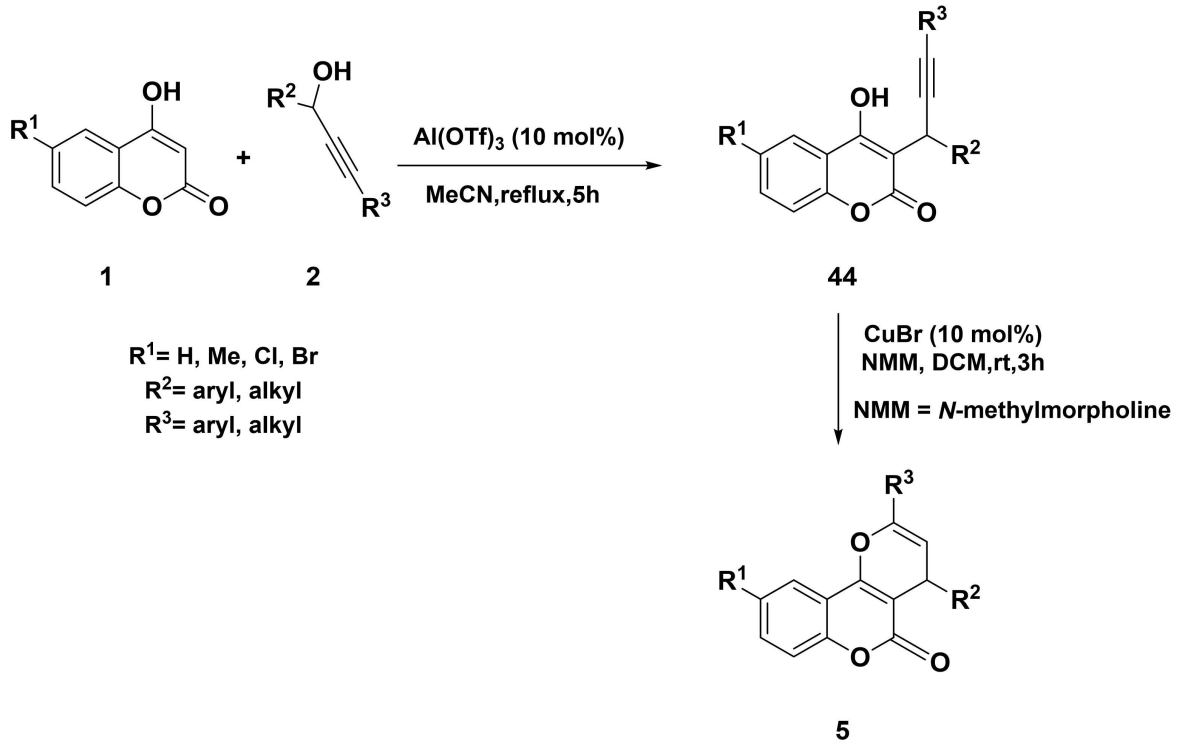
An efficient regioselective protocol was reported by coupling 4-hydroxycoumarin (**1**) with chalcones (**45**) to obtain pyranocoumarin derivatives (**46**) under neat conditions facilitated by [BSMIM]OTs (BAIL) (1-butane sulfonic acid-3-methylimidazolium tosylate). The plausible mechanism involves Michael addition followed by an annulation



1 4 5

Ar =Ph, $C_6H_4NO_2$, C_6H_4Cl, C_6H_4OMe Ar^1= Ph, C_6H_4OMe, C_6H_4Me, C_6H_4Cl

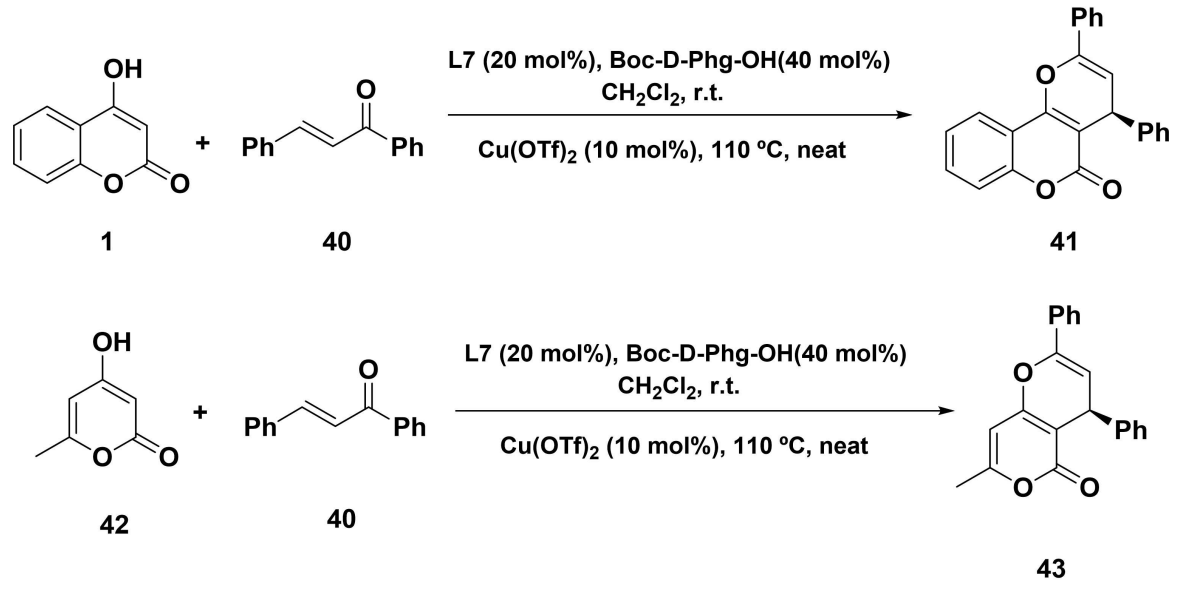
Scheme 30. [HO_3S-PhospIL@SBA-15] catalyzed pyrano[3,2-*c*]chromenone synthesis.



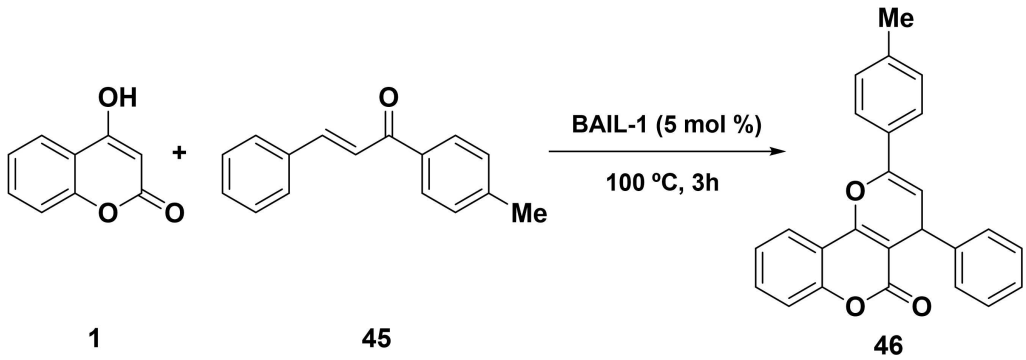
Scheme 31. Pyranocoumarin analogs synthesis involves two steps mediated by aluminum triflate.

reaction rendering pyranocoumarins in great yield (up to 90%) and water as a by-product. It turns out that, the catalyst could be recovered and reutilized multiple times devoid of any significant loss in its catalytic performance (Scheme 33).[84]

In 2017 Jhadav et al., reported condensation of 4-hydroxycoumarin (**1**), aldehydes (**48**), and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (**47**) with the assistance of a catalytic quantity of silica-supported tungstic acid (STA) resulting in a greener and solvent-free process. Knoevenagel condensation, Michael addition, intramolecular imine-enamine tautomerism, *O*-cyclization, and MeSH elimination are involved in chemical transformation. Lesser reaction time, an extensive range of functional group tolerance, an affordable heterogeneous catalyst, and high yields via a simple experimental and workup approach are all advan-



Scheme 32. Enantioselective synthesis of pyranocoumarins catalyzed by a quinine-derived primary amine.



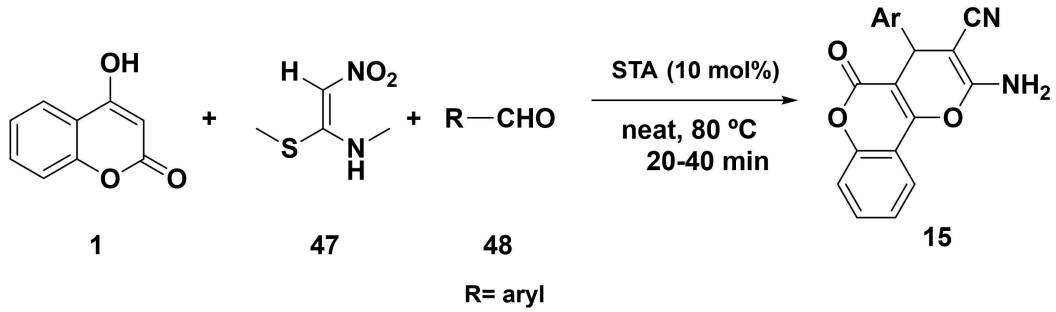
Scheme 33. Regioselective approach for pyranocoumarin derivatives mediated by BAIL.

tages of the current environmentally friendly protocol. The catalyst was revived and reutilized for at least four runs with not much remarkable reduction in product yield (first run: 94%, fourth run: 88%) (Scheme 34).[85]

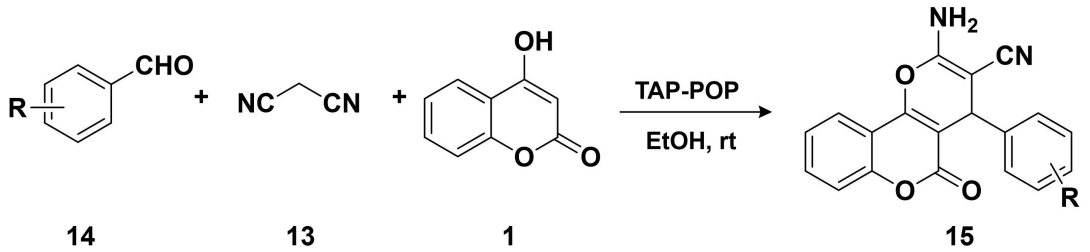
A nitrous-rich thiamin pyrimidine-based porous organic polymer (TAP-POP) was developed by Shunmughanathan et al., (2018), and it was then shown to have catalytic activity for the one-pot synthesis of dihydropyrano[3,2-*c*]chromenes from aldehydes (**14**), malononitrile (**13**), and C–H acid compounds, such as 4-hydroxycoumarin (**1**) and 4-OH-6-Me-2*H*-pyran-2-one under ambient conditions (Scheme 35).[86] The desired dihydropyrano[3,2-*c*]chromenes were obtained in excellent yields (78–97%).

In 2018, to synthesize 2-amino 5-oxo-4-aryl-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carboxamide (**51**), an environmentally benign approach was devised by Jhadav et. al., A mixture of 4-hydroxycoumarin (**1**), 4-chlorobenzaldehyde (**49**), cyanoacetamide (**50**), and polystyrene-supported *p*-toluenesulfonic acid (PS-PTSA) was agitated at 80 °C in EtOH to produce chromene-3-carboxamide. For four runs, the catalyst was revived and reused with the most negligible impact on product yields (first run: 94% and fourth run: 89%). The proposed mechanism is Knoevenagel condensation followed by intermolecular ring closure (Scheme 36).[87]

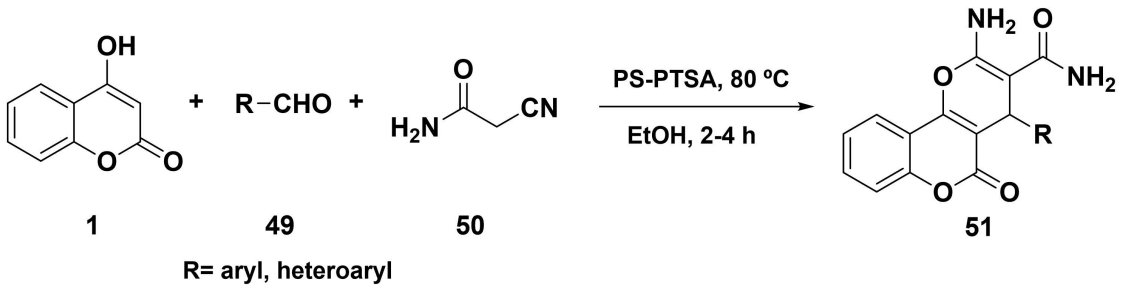
Ying Li and colleagues (2019) discovered a successful method for the synthesis of pyranocoumarins using an acid-catalyzed regio divergent annulation of isoprene (**53**) and 4-hydroxycoumarin (**1**) obtained from biomass. Pyranocoumarins were the only products of the strong Brönsted acid [2,4-$(NO_2)_2C_6H_3SO_3H$] (**54**), but pyranochromones (**55**) were produced in good yields (up to 60%) instead when $Sm(OTf)_3$ was present (Scheme 37).[46]



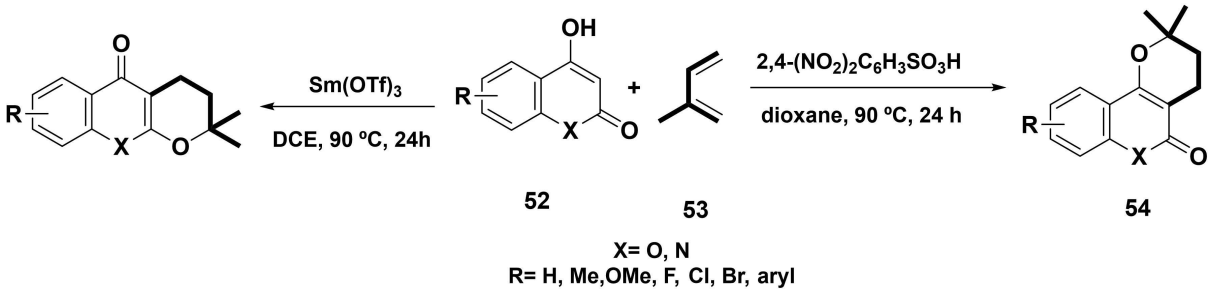
Scheme 34. silica-supported tungstic acid (STA) mediated multicomponent synthesis of pyranocoumarins.



Scheme 35. TAP-POP promoted the one-pot synthesis of pyranochromenes.



Scheme 36. PS-PTSA mediated pyranocoumarin synthesis using ethanol solvent under reflux conditions.



Scheme 37. Brönsted acid promoted the annulation of 4-hydroxy coumarins with isoprene.

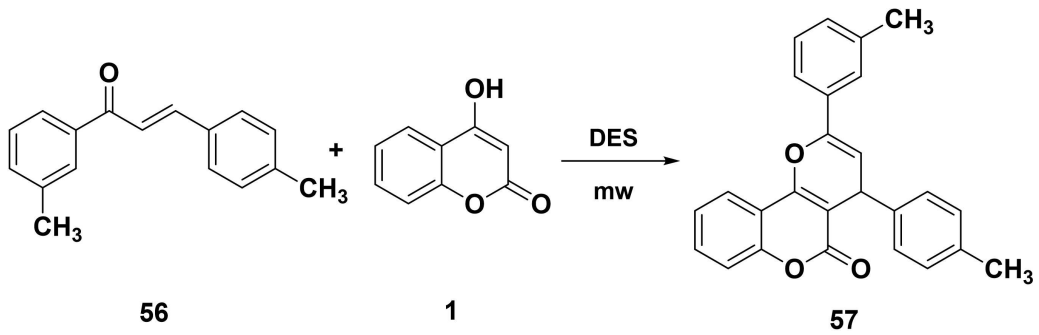
Teja Chitrala et al. proposed a metal-free technique for the pyranocoumarin derivatives (**57**) synthesis in the presence of easily recoverable catalysts such as Dimethyl Urea-Malonic acid DES (Deep Eutectic Solvent) under microwave irradiation (Scheme 38). The procedure involves Michael addition promoted by DES followed by subsequent intramolecular cyclization to produce a high yield of pyranocoumarins (Up to 94%).[88]

The reaction between 3-nitrobenzaldehyde (**14**), 4-chloro benzoyl acetonitrile (**59**), and dimedone (**60**) catalyzed by LUDOX HS-40 in ethanol at room temperature was developed by Mugada Sugunakara et al., (2021) as a simple, one-pot, step-economic (PASE) pyranocoumarin synthesis. Isatins/acenaphthoquinone was used as a substitute for aldehydes under mild conditions to expand the scope of this reaction. Good yields (60–70%) were obtained when the reaction was effectuated at 60 °C (Scheme 39).[89]

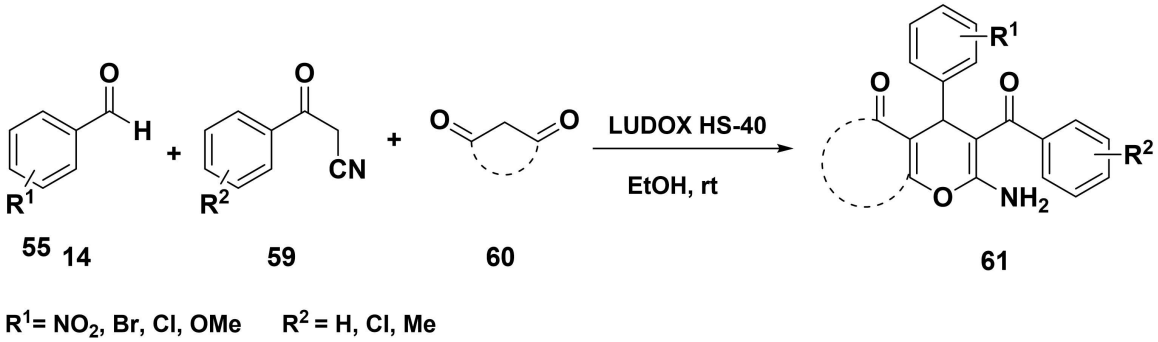
2.4. Catalyzed by carbon-based nanocatalysts

Khodabakshi and Karami established a pyranocoumarin (**15**) synthesis in 2014 using 4-hydroxycoumarin (**1**), malanonitriles (**13**), and aryl glyoxals (**17**) in H_2O:EtOH under metal-free conditions using 5 mg of GO nanosheets as a new, recyclable, and safe catalyst (1:1). Natural antifungal, antibacterial, and anticancer activities were found in the synthesized compounds. At room temperature, all aryl glyoxals with both electron-withdrawing and donating groups exhibited good-to-excellent yields (85–92%) affording the respective pyranocoumarin derivatives. The nanosheets were recovered and reutilized for almost four runs with a minuscule loss in the catalytic activity (Scheme 40).[90]

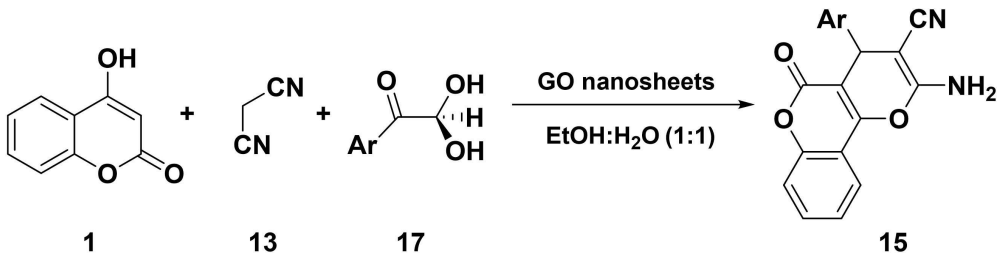
Michael cyclization reaction of 4-hydroxy coumarin (**1**), 4-hydroxypyrone, and 4-hydroxy-1-methylquinolinone with chalcone derivatives (**4**) in water was devised as an efficient methodology for the multicomponent union of pyranocou-



Scheme 38. DES catalyzed pyranocoumarin synthesis.



Scheme 39. LUDOX HS-40 mediated synthesis of pyranocoumarins.



Scheme 40. Synthesis of pyranocoumarins using GO nanosheets.

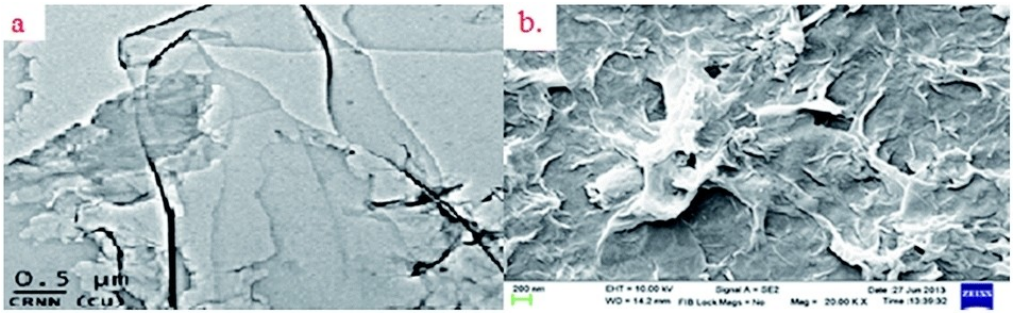
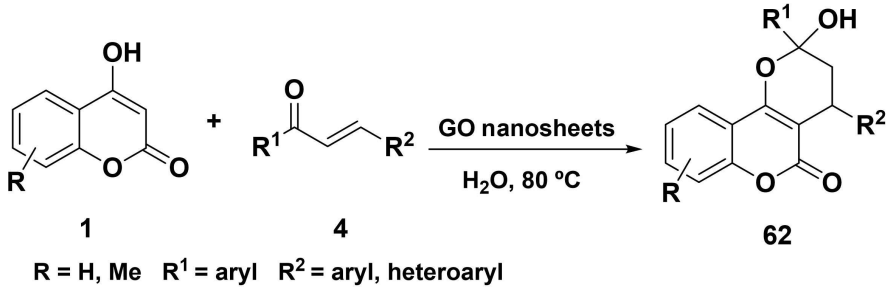


Figure 3. (a) TEM and (b) FESEM images of graphene oxide nanosheets. Reprinted from ref. [91], Copyright 2015, Royal Society of Chemistry.

marins (**62**) in 2015 at 80 °C using graphene oxide nanosheets as a heterogeneous carbocatalyst. Pyranocoumarins and pyranopyrans were obtained in yields of 84–92 % in 3–4 h and 88–95 % in 2–3 h, respectively (Scheme 41). The GO nanosheets were reused for five runs, with a mild performance decline (first run: 92 %, fifth run: 86 %) (Figure 3).[91]

In 2015, Khodabakhshi and colleagues developed a one-pot pyranocoumarin synthesis catalyzed by graphene oxide nanosheets which can be used as a recyclable catalyst. A greener method was developed where a three-component condensation of aryl aldehydes (**14**) and 4-hydroxy coumarin (**1**) with malononitrile (**13**) in the presence of GO nanocatalyst was



Scheme 41. GO Nanosheets catalyzed multicomponent synthesis of pyranocoumarins.

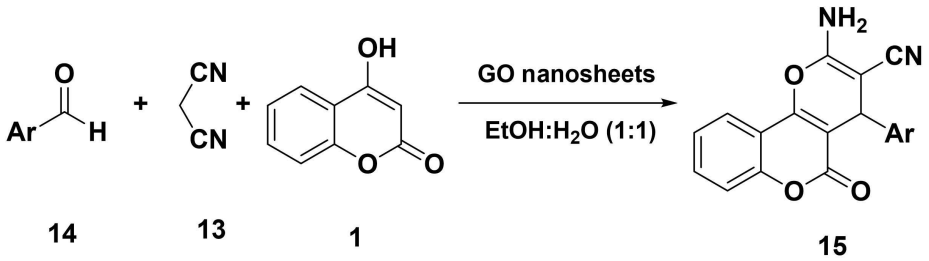
carried out thereby furnishing pyranocoumarins in excellent yields (88–95%). The catalyst retrieved could be used for four runs devoid of significant catalytic activity (Scheme 42).[92]

In 2020, Firouz Matloubi Moghaddam et al. described a multi-component, one-pot synthesis. Cysteic acid grafted to graphene oxide was employed as a solid acid catalyst for the developed methodology (Scheme 43). The coupling reaction of different aldehydes (**14**), malononitrile (**13**), and 4-hydroxy coumarin (**1**) catalyzed by cysteic acid grafted on graphene oxide in water and ethanol solvents yielded pyrano[3,2-*c*]chromenes derivatives in great yield (89–98%).[93]

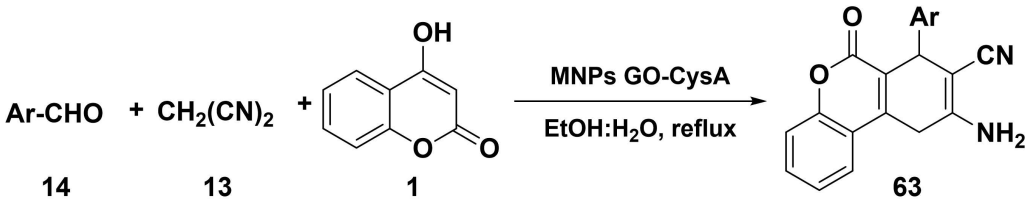
3. Other techniques

Extending the studies carried out using molecular iodine as a catalyst, Ahmed and Babu (2013) designed a regioselective protocol to prepare multi-substituted pyranocoumarins (**23**) at 100 °C using acetic acid and molecular iodine as a catalyst (Scheme 44). A wide range of substituted chalcones (**31**) was used which reacted with 4-hydroxy coumarin (**1**) to render high yields of the expected products (85–95%).[94]

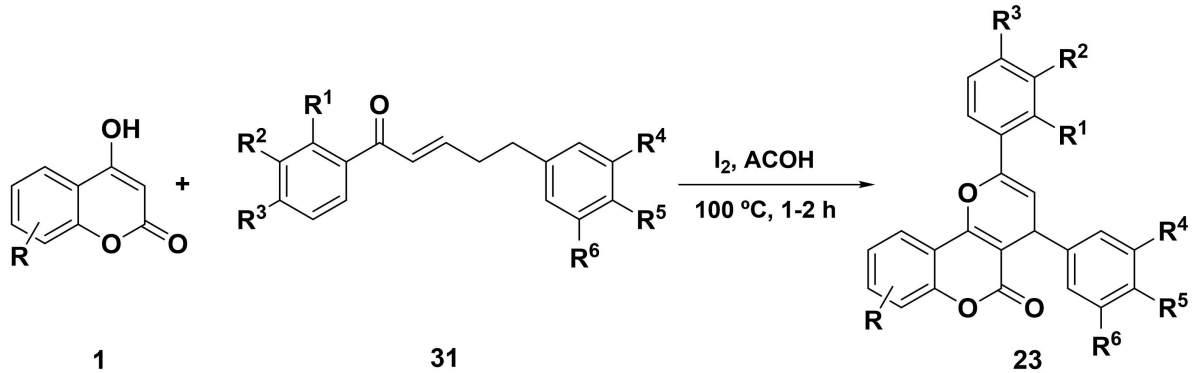
Lin and colleagues (2009) devised a method for producing multi-substituted pyranocoumarins (**5**) via a two-step synthetic procedure catalyzed by molecular iodine and sulfuric acid. The developed methodology is found to be a straightforward route to synthesizing the desired products in excellent yields (97%) (Scheme 45).[40]



Scheme 42. Synthesis of pyranocoumarins promoted by Graphene oxide nanosheets.



Scheme 43. pyrano[3,2-*c*]chromenes synthesis catalyzed by cysteic acid grafted on graphene oxide.



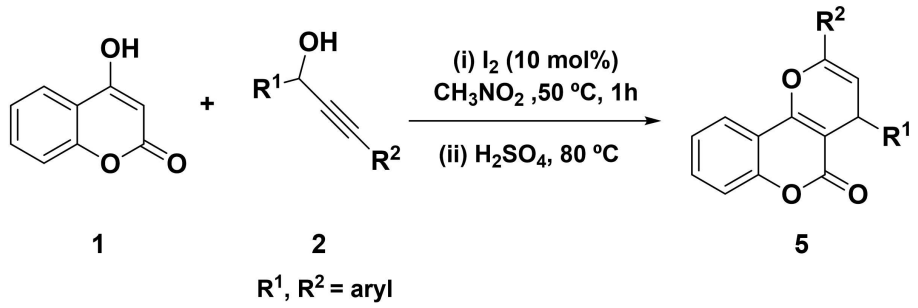
Scheme 44. Molecular iodine-mediated pyranocoumarin synthesis.

Borax is a naturally occurring and inexpensive catalyst found to efficiently catalyze a high-yielding one-pot synthesis of pyrano[3,2-*c*]chromenes (**36**), 4*H*-chromene, and 4*H*-pyran. Borax catalyzes the reactions between 4-chlorobenzaldehyde (**13**), malononitrile (**35**), and 4-hydroxy coumarin (**1**) in ethanol to generate pyranocoumarin derivatives in high yield (70–84%). To broaden the scope of the developed methodology, the reaction was carried out using benzaldehyde and malononitrile instead of 4-hydroxy coumarin. Interestingly, when cycloalkane-1,3-dione /1,3-diketoesters under similar conditions were used other pyran derivatives were obtained as the product. The catalyst was shown to be reusable for five reaction cycles with no significant loss of catalytic activity (Scheme 46).[95]

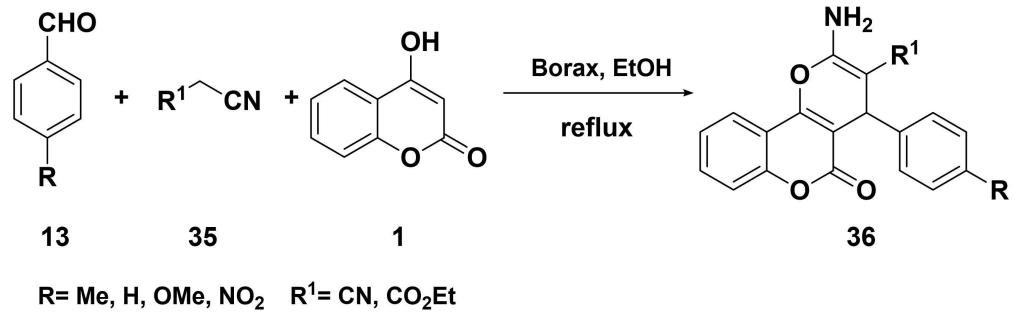
The usage of low-cost, environmentally friendly catalysts in ambient conditions provides a superior strategy for synthesizing a variety of heterocycles. Aldehydes can be transformed quickly and effectively using ammonium acetate. Aldehydes (**14**), malononitrile (**13**), and 1,3-dicarbonyl compounds such as 4-hydroxy-6-methyl-2*H*-pyran-2-one, 4-hydroxycoumarin (**1**), and 4-hydroxy-1-methylquinolin-2(1*H*)-one were used as starting materials in the PASE multicomponent method by Elinson et. al., to create dihydropyrano[4,3-*b*]chromenes in excellent yields (88–95%) using EtOH as a solvent in the presence of NH_4OAc (10 mol-%) (Scheme 47).[96]

By cyclo-condensing various benzaldehydes (**14**), malononitrile (**13**), and dimedone, 4-hydroxycoumarin (**1**) in ethanol/water under refluxing conditions, Heravi et al., synthesized tetrahydro-4*H*-chromenes and dihydropyrano[3,2-*c*]chromenes in excellent yield (50–98%). Strong Brönsted acid of the Keggin type, $H_5BW_{12}O_{40}$ (BWA), was employed (Scheme 48).[97]

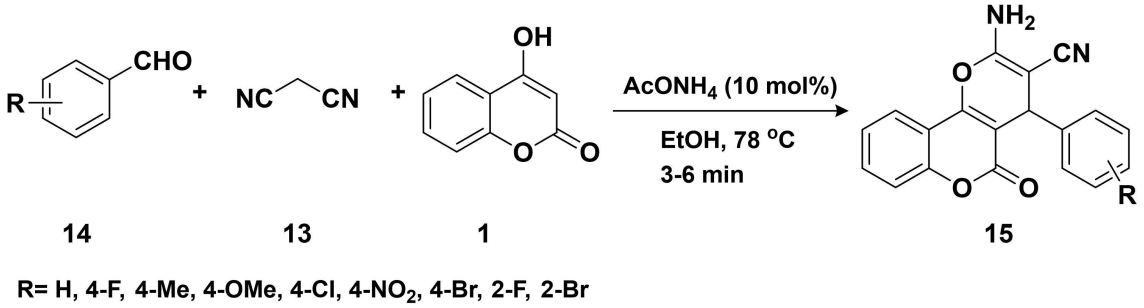
In their one-pot, multicomponent photocatalyzed synthesis of pyranocoumarins, Chen Lu et. al., (2020) used the photocatalyst 9-mesityl-10 methyl acridinium perchlorate (Acr +-Mes ClO_4−) to support the synthesis of 2-amino-4*H*-chromenes (**15**). Malononitrile (**13**) and ArOH-type structural



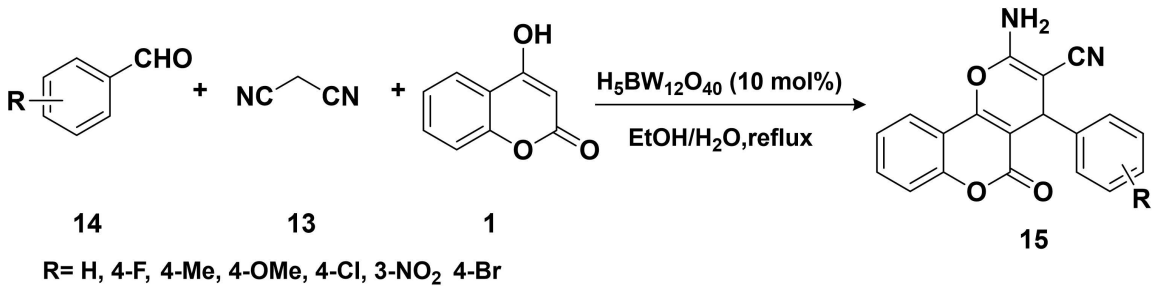
Scheme 45. Two-step synthetic method mediated by molecular iodine and sulfuric acid for pyranocoumarin synthesis.



Scheme 46. Borax promoted the synthesis of pyrano[3,2-c]chromenes.



Scheme 47. Synthesis of dihydropyrano[4,3-*b*]chromenes via PASE multicomponent method.



Scheme 48. Keggin-type hetero polyacid catalyzed pyranochromenes synthesis.

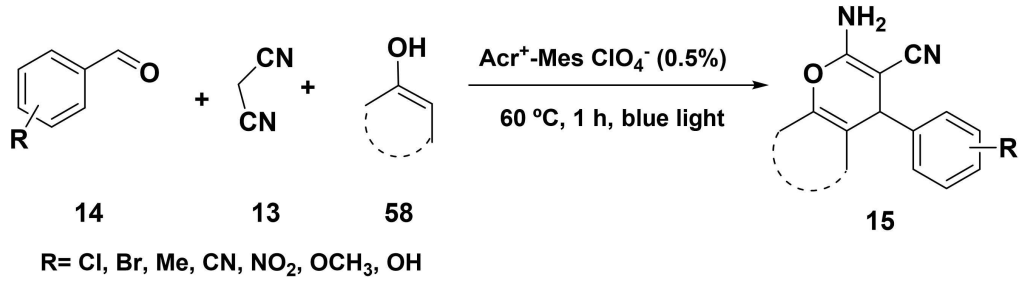
motifs (**58**) are used in the condensation of aromatic aldehydes (**14**) to produce the desired products in excellent yields (76–95%). This process offers various benefits, including the use of a green and sustainable solvent, great yields of the desired products, and the use of cheap catalysts with minimal catalyst loadings (Scheme 49).[98]

To produce dihydropyrano[3,2-*c*]chromenes in 2019, Mihiri and colleagues used ammonium acetate (15 mol-%) for multi-component condensation reaction of aromatic aldehydes (**14**) with 4-hydroxycoumarin (**1**) and malononitrile (**13**) in the presence of a flexible solvent Bmim [triflate] to obtain desired products in great yield (70–90%). The synthetic compounds' cation binding and antibacterial properties were evaluated (Scheme 50).[99]

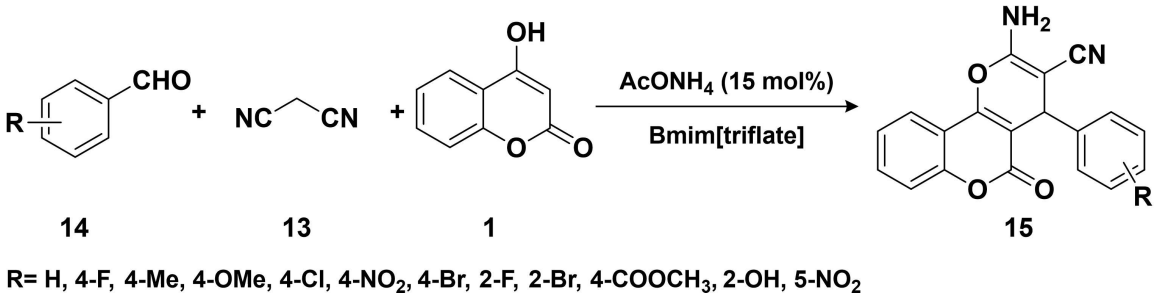
Zabihzadeh et al., used a one-pot method to affordgreat a variety of tetrahydrobenzo[*b*]pyran derivatives, such as pyrano[2,3-d]-pyrimidinone (thione) and pyrano[3,2-*c*]chromene, in good yield (86–95%) by three-component condensation of aldehydes (**14**), malononitrile (**13**), and other compounds, such as dimedone, barbituric acid, and 4-hydroxy coumarin (**1**). A DABCO-based bis-dicationic ionic salt ([(DABCO)$_2$C$_3$H$_5$OH].2Cl) was employed for this purpose in an aqueous medium (Scheme 51).[100]

4. Pharmaceutical applications of pyranocoumarins

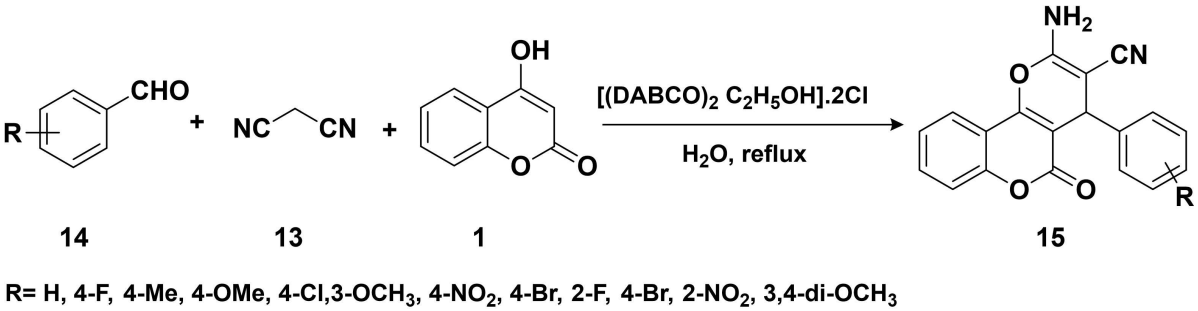
Pyranocoumarin and its derivatives as mentioned in (Table 1) possess an extensive range of pharmacological activities such as anti-HIV, anti-fungal, insecticidal, anti-cancer, anti-inflammatory, antioxidant, and anti-bacterial properties (Figure 4).[27,34,101–103] Furthermore, they are used to treat neurological disorders such as Huntington's disease, Schizophrenia, Myoclonus, Amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease as Cognitive enhancers.[104]



Scheme 49. Photocatalyzed one-pot multicomponent synthesis of pyranocoumarins.



Scheme 50. One-pot synthesis of dihydropyrano[3,2-c]chromenes in the presence of ammonium acetate.



Scheme 51. DABCO-based ionic salt promoted the synthesis of pyrano[3,2-c]chromenes.

Pyranocoumarins have demonstrated a variety of biological functions in pharmaceutical chemistry. Given that they can suppress the enzyme NADH: ubiquinone oxidoreductase (Pathogenesis for the onset of Parkinson's disease), they exhibit significant promise as cancer treatment agents.[105,106] Additionally, this enzyme inhibits phorbol ester-induced ornithine decarboxylase which is in charge of the biosynthesis of polyamine growth factors necessary for normal cellular proliferation; it may be used in cancer therapy.[105,106] It also exhibits some potential in preventing benzo(*a*)pyrene and hydrogen peroxide-induced mutagenesis and activates protein kinase C.[107] These substances also have a lot of potential as anti-HIV medications. Furthermore, dipyranocoumarins analogs from the Calophyllum genus have HIV-1-specific reverse transcriptase inhibitor action.[108] DCK has been reported to reduce HIV-1 replication in H9 lymphocytes.[109] Pyranocoumarins are used to produce smooth muscle relaxation (tracheal and pulmonary artery relaxation) as well as anti-malarial, anti-ulcer,[110] hemorrhagic toxin, anti-protozoan, and uterotonic activities.[111] Besides pyranocoumarins, such as selen, are also clinically employed as photoactive medicines in the treatment of vitiligo and sunburn prevention.[112] Also inhibited by this family of scaffolds include protein kinases, endothelin-converting enzymes, bone reabsorption by osteoclast-like cell lines, arachidonate 5-lipoxygenase, and interferon-induced nitric oxide production.[113]

Some pyranocoumarins were isolated from a wide variety of natural sources, and new pyranocoumarin analogs are found or synthesized regularly. As indicated in the table below, the documented biological properties such as antibacterial, anti-obesity, antiviral, cytotoxic, antiTB, and antifungal activity make them a unique class for therapeutic applications.[130] Diverse activities of pyranocoumarin mole-

Figure 4. Biological activities exhibited by pyranocoumarin analogs

Table 1. The structure, synthesis pathway, and biological activity of pyranocoumarins.

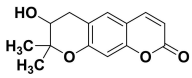
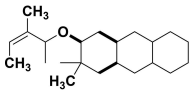
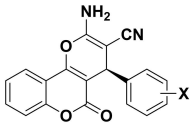
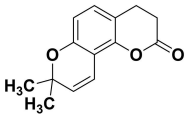
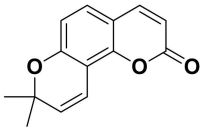
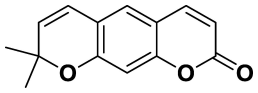
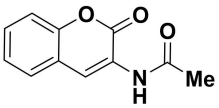
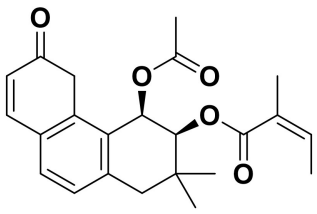
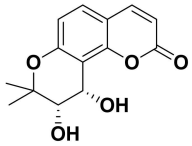
S. No	Compound Name	Structure	Synthetic Route	Biological activity	Ref
1	a) 7-hydroxy-8,8-dimethyl-7,8-dihydro-2*H*,6*H*-pyrano[3,2-*g*] chromen-2-one		Isolated from Zosima absinthifolia (Apiaceae)	Antibacterial activity against *Bacillus subtilis*	[114]
	b) (3S,4aR,9aS)-2,2-dimethyl-3-(((Z)-3-methyl pent-3-en-2-yl) oxy)tetradeca-hydroanthracene			*Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi.*	
2	2-amino-4*H*-chromenes		Organocatalytic Knoevenagel/ Michael/cyclization	Antibacterial	[115]
3	Dihydropyrano coumarins		Isolated from Peucedanum japonicum thunb (PJT)	Anti-Obesity	[116]
4	Seselin and Xanthyletin 3′,4′-dihydroxy-3′, 4′-dihydroseselin Derivatives	 	Catalytic Osmium Oxidation of Seselin and Xanthyletin	DNA-damaging agents; cytotoxic activity against P-388 lymphocytic leukemia.	[117]
5	Coumarino acetamides		By refluxing various chloroacetamides with 7-hydroxy-4-methyl chromen-2-one in acetonitrile and anhydrous K_2CO_3	Cytotoxic and Antitumor-promoting activity	[118]
6	(3S,4R)-4-acetoxy-2,2-dimethyl-6-oxo-1,2,3,4,5,6-hexahydrophenanthren-3-yl (Z)-2-methylbut-2-enoate (Angular coumarins)		Isolated from Radix peucedani, the dry root of Peucedanum praeruptorum Dunn, through bioassay-guided fractionation.	Cytotoxic and antitumor-promoting activity	[119]
7	Angular-type pyranocoumarins		Isolated from Peucedani Radix	Exhibited potential for use in the treatment of cancer and pulmonary hypertension.	[120]

Table 1. continued

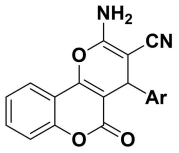
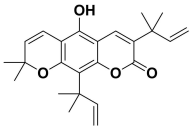
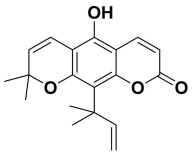
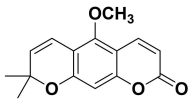
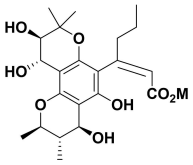
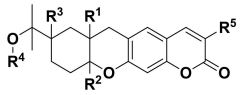
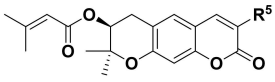
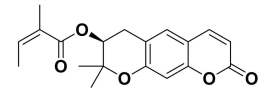
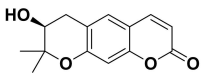
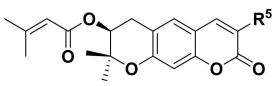
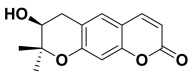
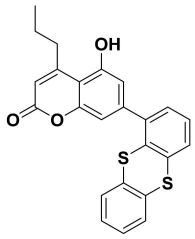
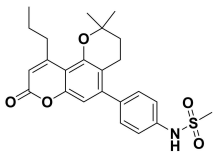
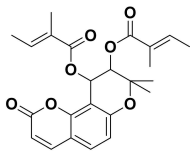
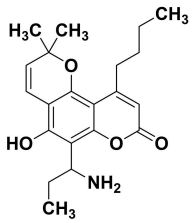
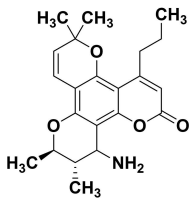
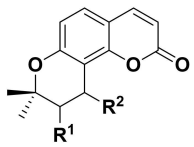
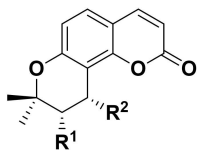
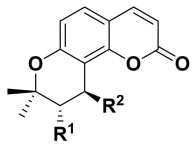
S. No	Compound Name	Structure	Synthetic Route	Biological activity	Ref
8	2-amino-4*H*-chromenes		Synthesis using natural feedstock coconut juice.	Anti-hyperglycemic as well as anti-dyslipidemic activities.	[121]
9	Clausenidin, Clausarin, Nordentatin and Xanthoxyletin		Isolated from medicinal plants. Synthesis of new pyranocoumarin derivatives were carried out by Hydrogenation, epoxidation and methylation techniques.	Anti-viral	[122]
					
					
11	Clauemarmarins		Isolated from the stems of *Clausena emarginata*	Hepatoprotective	[123]
					
12	Decursin, Decursinol Angelate and Decursinol		Isolated from *Angelica gigas Nakai*	Anti-cancer	[124]
					
					
13	Decursin		Isolated from *Angelica gigas*	Anti-cancer	[125]
14	Decursinol		Isolated from *Angelica gigas*	Exert in vivo inhibitory activity against LNCaP/AR-Luc xenograft growth and lung metastasis.	[126]

Table 1. continued

S. No	Compound Name	Structure	Synthetic Route	Biological activity	Ref
15	5-hydroxy-4-propyl-7-(thianthren-1-yl)-2*H*-chromen-2-one		Synthesized via silica sulfuric acid-catalyzed pechmann reaction and Pd (0) catalysed Suzuki coupling in tandem	Antiproliferative activities against breast cancer cells	[127]
	N-(4-(2,2-dimethyl-8-oxo-10-propyl-,4-dihydro-2*H*,8*H*-pyrano[2,3-*f*] chromen-5-yl)phenyl) methanesulfonamide				
16	Anomalin		Isolated from *Angelica anomala*	Remarkably reduced the increase in SNP-induced nuclear factor	[128]
17	(10R,11S)-12-amino-6,6,10,11-tetramethyl-4-ropyl-11,12-dihydro-*H*,6*H*,10*H*-dipyrano [2,3-*f*:2′,3′-*h*] chromen-2-one		Synthesized using different alkylating agents.	Anti-tuberculosis	[129]
	6-(1-aminopropyl)-10-butyl-5-hydroxy-2,2-dimethyl-2*H*,8*H*-pyrano[2,3-*f*] chromen-8-one				
18	(+)-Praeruptorin (Pra-C)		Isolated from the roots of *Peucedanum praeruptorum*	Muscle relaxant	[113]
					
					

cules have been explored by using them as drugs to treat various diseases. Norisoerlengieafusicol and Norpterophyllin are drugs possessing the pyranocoumarin moiety used to prevent coagulation and fungal diseases, respectively. Pyranocoumarins such as Pterophyllin III and Bothrioclinin are some of the widely known utreotonic drugs, as they are used during deliveries. Ureotonic drugs help in the expulsion of the placenta and reduce blood loss and the duration of the third stage of labor. On the other hand, Wedelolactone is most widely used for its anti-neoplastic properties.[131]

5. Conclusion and Future perspectives

Pyranocoumarins are the heterocyclic structures lately being of great interest in the development of novel lead structures possessing valuable biological properties. This review deals with the synthesis of pyranocoumarins catalyzed by transition metal-based and metal-free catalysts. Pyranocoumarins are useful intermediates in the synthesis of many biologically active drugs and are receiving prominence in synthetic organic chemistry. Even though few synthetic approaches reported in the literature involve environmentally friendly ways, there is a need to design a more efficient synthetic protocol that employs non-toxic reagents, cheaper catalyst/reactants, ambient reaction conditions, atom economy, excellent yields, and shorter reaction time. Most of the reported procedures involve 4-hydroxycoumarin as one of the coupling partners. Other coupling partners include alkenes, α, β-unsaturated carbonyls, propargylic alcohol, propargyl chloride, propargyl bromide, and carbonyl compounds. Pharmaceutical applications of pyranocoumarins have been discussed as they possess a wide range of biological activities. The mechanisms by which these pyranocoumarins act against bacteria, cancer, and various other causing agents are still to be explored. Considering the biological importance of pyranocoumarin molecules, more research is warranted to unravel the bioactivity of these molecules.

Author Contributions

Jayalakshmi M: Conceptualization, writing – original draft preparation and visualization. Francis Joy: Conceptualization, writing – review and editing. Aatika Nizam: Conceptualization, resources and supervision. SBN Krishna: Conceptualization, writing – review and editing.

Acknowledgements

The authors are thankful to the Centre for Research, CHRIST (Deemed to be University), for the research support and facilities. KSBN would like to thank Durban University of Technology for research fellowship.

Conflict of Interests

The authors declare no conflict of interest.

Keywords: carbon-based nanocatalyst · organocatalyst · pyranocoumarins · transition metal-based nanocatalyst · transition metal-based catalyst

[1] B. Banerjee, *Ultrason. Sonochem.* **2017**, *35*, 1–14.
[2] G. Brahmachari, B. Banerjee, *Curr. Green Chem.* **2015**, *2*, 274–305.
[3] R. Dalpozzo, *Green Chem.* **2015**, *17*, 3671–3686.
[4] V. Polshettiwar, R. Luque, A. Fihri, H. Zhu, M. Bouhrara, J.-M. Basset, *Chem. Rev.* **2011**, *111*, 3036–3075.
[5] A. Fadhel, P. Pollet, C. Liotta, C. Eckert, *Molecules* **2010**, *15*, 8400–8424.
[6] Y. Zhu, L. P. Stubbs, F. Ho, R. Liu, C. P. Ship, J. A. Maguire, N. S. Hosmane, *ChemCatChem* **2010**, *2*, 365–374.
[7] M. Kazemi, L Shiri, *Mini Rev. Chem.* **2018**, *15*, 86–104.
[8] L. Shiri, A. Ghorbani-Choghamarani, M. Kazemi, *Appl. Organomet. Chem.* **2017**, *31*, e3596, DOI: 10.1002/AOC.3596.
[9] L. Shiri, A. Ghorbani-Choghamarani, M. Kazemi, *Aust. J. Chem.* **2016**, *69*, 585–600.
[10] M. Kazemi, M. Ghobadi, A. Mirzaie, *Nanotechnol. Rev.* **2018**, *7*, 43–68.
[11] A. H. M. Elwahy, M. R. Shaaban, *RSC Adv.* **2015**, *5*, 75659–75710.
[12] T. Cheng, D. Zhang, H. Li, G. Liu, *Green Chem.* **2014**, *00*, 1–3.
[13] B. I. Kharisov, H. V. R. Dias, O. V. Kharissova, *Arab. J. Chem.* **2019**, *12*, 1234–1246.
[14] D. Wang, D. Astruc, *Chem. Soc. Rev.* **2017**, *46*, 816–854.
[15] A. Stefanachi, F. Leonetti, L. Pisani, M. Catto, A. Carotti, *Molecules* **2018**, *23*, 250.
[16] P. Anand, B. Singh, N. Singh, *Bioorg. Med. Chem.* **2012**, *20*, 1175–1180.
[17] B. Yuce, O. Danis, A. Ogan, G. Sener, M. Bulut, A. Yarat, *Arzneimittel-Forschung/Drug Res.* **2009**, *59*, 129–134.
[18] D. A. Ostrov, J. A. Hernández Prada, P. E. Corsino, K. A. Finton, N. Le, T. C. Rowe, *Antimicrob. Agents Chemother.* **2007**, *51*, 3688–3698.
[19] N. A. Gormley, G. Orphanides, A. Meyer, P. M. Cullis, A. Maxwell, *Biochemistry* **1996**, *35*, 5083–5092.
[20] Y. Shikishima, Y. Takaishi, G. Honda, M. Ito, Y. Takeda, O. K. Kodzhimatov, O. Ashurmetov, K. H. Lee, *Chem. Pharm. Bull.* **2001**, *49*, 877–880.
[21] M. E. Riveiro, A. Moglioni, R. Vazquez, N. Gomez, G. Facorro, L. Piehl, E. R. de Celis, C. Shayo, C. Davio, *Bioorg. Med. Chem.* **2008**, *16*, 2665–2675.
[22] K. Fylaktakidou, D. Hadjipavlou-Litina, K. Litinas, D. Nicolaides, *Curr. Pharm. Des.* **2005**, *10*, 3813–3833.
[23] Y. Bansal, P. Sethi, G. Bansal, *Med. Chem. Res.* **2013**, *22*, 3049–3060.
[24] J. Y. Yeh, S. M. Coumar, J. Horng, H. Y. Shiao, F. M. Kuo, H. L. Lee, I. C. Chen, C. W. Chang, W. F. Tang, S. N. Tseng, C. J. Chen, S. R. Shih, J. T. A. Hsu, C. C. Liao, Y. S. Chao, H. P. Hsieh, *J. Med. Chem.* **2010**, *53*, 1519–1533.
[25] M. Curini, F. Epifano, F. Maltese, M.C Marcotullio, S.P Gonzales, J.C Rodriguez, *Aust. J. Chem.* **2003**, *56*, 59–60.
[26] G. R. Madhavan, V. Balraju, B. Mallesham, R. Chakrabarti, V. B. Lohray, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2547–2551.
[27] Y. Kashman, K. R. Gustafson, R. W. Fuller, J. H. Cardellina, J. B. Mcmahon, M. J. Currens, R. W. Buckheit, S. H. Hughes, G. M. Cragg, M. R. Boyd, *J. Med. Chem.* **1992**, *35*, 2735–2743.
[28] S. Vilar, E. Quezada, L. Santana, E. Uriarte, M. Yanez, N. Friaz, C. Alcaide, E. Cano, F. Orallo, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 257–261.
[29] M. I. Hussain, S. Qamar Abbas, M. J. Reigosa, *Planta Daninha* **2018**, *36*, 1–13.
[30] H. Fan, J. Peng, M. T. Hamann, J. F. Hu, *Chem. Rev.* **2008**, *108*, 264–287.
[31] K. N. Venugopala, V. Rashmi, B. Odhav, *BioMed Res. Int.* **2013**, *2013*, 1–14.
[32] M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, P. A. Belyakov, A. O. Chizhov, G. I. Nikishin, *Tetrahedron* **2010**, *66*, 4043–4048.
[33] T. C. McKee, C. D. Covington, R. W. Fuller, H. R. Bokesch, S. Young, J. H. Cardellina, M. R. Kadushin, D. D. Soejarto, P. F. Stevens, G. M. Cragg, M. R. Boyd, *J. Nat. Prod.* **1998**, *61*, 1252–1256.
[34] E. Melliou, P. Magiatis, S. Mitaku, A. Skaltsounis, E. Chinou, *J. Nat. Prod.* **2005**, *68*, 78–82.
[35] A. Basile, S. Sorbo, V. Spadaro, M. Bruno, A. Maggio, N. Faraone, S. Rosselli, *Molecules* **2009**, *14*, 939–952.

[36] S. K. Kapoor, J. M. Kohli, Y. N. Sharma, A. Zaman, *Phytochemistry* **1972**, *11*, 477.
[37] K. Otoguro, K. Shiomi, Y. Yamaguchi, N. Arai, T. Sunazuka, R. Masuma, Y. Iwai, S. Omura, *J. Antibiot. (Tokyo)*. **2000**, *53*, 50–57.
[38] G. V. Z. Anindita Mukherjee, Sachinta Mahato, S. S. Nov, Adinath Majee, *New J. Chem.* **2020**, *00*, 1–3.
[39] A. K. Bagdi, A. Majee, A. Hajra, *Tetrahedron Lett.* **2013**, *54*, 3892–3895.
[40] X. Lin, X. Dai, Z. Mao, Y. Wang, *Tetrahedron* **2009**, *65*, 9233–9237.
[41] S. Berger, E. Haak, *Tetrahedron Lett.* **2010**, *51*, 6630–6634.
[42] J. Reisch, H. R. W. Dharmaratne, *Z. Naturforsch. B* **1985**, *40*, 636–638.
[43] K. C. Majumdar, A. T. Khan, R. N. De, *Synth. Commun.* **1988**, *18*, 1589–1595.
[44] K. C. Majumdar, P. Debnath, P. K. Maji, *Tetrahedron Lett.* **2007**, *48*, 5265–5268.
[45] K. C. Majumdar, B. Sinha, I. Ansary, S. Ganai, D. Ghosh, B. Roy, B. Sridhar, *Synth.* **2014**, *46*, 1807–1814.
[46] Y. Li, Y. C. Hu, H. Zheng, D. W. Ji, Y. F. Cong, Q. A. Chen, *Eur. J. Org. Chem.* **2019**, *2019*, 6510–6514.
[47] R. Sarma, M. M. Sarmah, K. C. Lekhok, D. Prajapati, *Synlett* **2010**, *4*, 2847–2852.
[48] G. Appendino, G. Cravotto, S. Tagliapietra, G. M. Nano, G. Palmisano, *Helv. Chim. Acta* **1990**, *73*, 1865–1878.
[49] J. Moreau, C. Hubert, J. Batany, L. Toupet, T. Roisnel, J.-P. Hurvois, J.-L. Renaud, *J. Org. Chem.* **2009**, *74*, 8963–8973.
[50] G. Zheng, W. Lu, J. Cai, *J. Nat. Prod.* **1999**, *62*, 626–628.
[51] Y. Jacquot, B. Refouvelet, L. Bermont, G. L. Adessi, G. Leclercq, A. Xicluna, *Pharmazie* **2002**, *57*, 233–237.
[52] Y. Liu, J. Zhu, J. Qian, B. Jiang, Z. Xu, *J. Org. Chem.* **2011**, *76*, 2–7.
[53] Y. Liu, J. Zhu, J. Qian, B. Jiang, Z. Xu, *J. Org. Chem.* **2011**, *76*, 9096–9101.
[54] H. S. Virdi, S. Sharma, S. Mehndiratta, P. M. S. Bedi, K. Nepali, *J. Enzyme Inhib. Med. Chem.* **2015**, *30*, 730–736.
[55] S. Yaragorla, P. L. Saini, G. Singh, *Tetrahedron Lett.* **2015**, *56*, 1649–1653.
[56] Q. Ren, J. Kang, M. Li, L. Yuan, R. Chen, L. Wang, *Eur. J. Org. Chem.* **2017**, *2017*, 5566–5571.
[57] Priyanka, R. K. Sharma, R. J. Butcher, D. Katiyar, *Tetrahedron Lett.* **2018**, *59*, 2347–2351.
[58] M. Tamimi, M. M. Heravi, M. Mirzaei, V. Zadsirjan, N. Lotfian, H. Eshtiagh-Hosseini, *Appl. Organomet. Chem.* **2019**, *33*, e5043.
[59] J. Kim, K. Lee, P. H. Lee, *Bull. Korean Chem. Soc.* **2020**, *41*, 709–718.
[60] F. Tavakoli, M. Shekouhy, H. Sharghi, Seyyede, F. Razavi, M. Aberi, *Chem. Sel.* **2020**, *5*, 2662–2671.
[61] A. El Hallaoui, S. Chehab, T. Ghailane, B. Malek, O. Zimou, S. Boukhriss, A. Souizi, R. Ghailane, *Polycycl. Aromat. Compd.* **2021**, *41*, 2083–2102.
[62] A. Saha, S. Payra, S. Banerjee, *RSC Adv.* **2013**, *00*, 1–3.
[63] S. Khodabakhshi, B. Karami, K. Eskandari, S. J. Hoseini, *Comptes Rendus Chim.* **2014**, *17*, 35–40.
[64] S. Khodabakhshi, *Polycycl. Aromat. Compd.* **2014**, *34*, 573–587.
[65] S. Khodabakhshi, K. Eskandari, B. Karami, *Heterocycles* **2014**, *89*, 1670.
[66] A. Gupta, R. Jamatia, A. Pal, *New J. Chem.* **2015**, *39*, 5636–5642.
[67] B. Karami, M. Kiani, *Monatsh. Chem.* **2016**, *147*, 1117–1124.
[68] B. Banerjee, *J. Nanostructure Chem.* **2017**, *7*, 389–413.
[69] R. Teimuri-Mofrad, S. Esmati, S. Tahmasebi, M. Gholamhosseini-Nazari, *J. Organomet. Chem.* **2018**, *870*, 38–50.
[70] L. Z. Fekri, M. Nikpassand, S. Pourmirzajani, B. Aghazadeh, *RSC Adv.* **2018**, *8*, 22313–22320.
[71] H. M. Tanuraghaj, M. Farahi, *RSC Adv.* **2018**, *8*, 27818–27824.
[72] M. Gholamhosseini-Nazari, S. Esmati, K. D. Safa, A. Khataee, R. Teimuri-Mofrad, *Res. Chem. Intermed.* **2019**, *45*, 1841–1862.
[73] N. Noroozi Pesyan, G. Rezanejade Bardajee, E. Kashani, M. Mohammadi, H. Batmani, *Res. Chem. Intermed.* **2020**, *46*, 347–367.
[74] S. Saneinezhad, L. Mohammadi, V. Zadsirjan, F. F. Bamoharram, M. M. Heravi, *Sci. Rep.* **2020**, *10*, 1–26.
[75] L. Zare Fekri, *Front. Chem.* **2021**, *9*, 1–11.
[76] J. Moreau, C. Hubert, J. Batany, L. Toupet, T. Roisnel, J. P. Hurvois, J. L. Renaudz, *J. Org. Chem.* **2009**, *74*, 8963–8973.
[77] S. Ahadi, M. Zolghadr, H. R. Khavasi, A. Bazgir, *Org. Biomol. Chem.* **2013**, *11*, 279–286.
[78] Z. N. Siddiqui, *Tetrahedron Lett.* **2014**, *55*, 163–168.
[79] K. S. Pandit, P. V. Chavan, U. V. Desai, M. A. Kulkarni, P. P. Wadgaonkar, *New J. Chem.* **2015**, *39*, 4452–4463.
[80] S. S. Mansoor, K. Logaiya, K. Aswin, P. N. Sudhan, *J. Taibah Univ. Sci.* **2015**, *9*, 213–226.
[81] M. Saeedi, M. Jeiroudi, L. Ma'mani, M. Mahdavi, E. Alipour, A. Shafiee, A. Foroumadi, *Iran. J. Chem. Chem. Eng.* **2015**, *34*, 39–45.
[82] M. Gohain, J. Van Tonder, *Synlett* **2015**, *26*, 745–750.
[83] S. Yang, L. Shen, Y.-J. Kim, J.-H. Jeong, *Org. Biomol. Chem.* **2016**, *14*, 623–630.
[84] S. Mahato, S. Santra, R. Chatterjee, G. V. Zyryanov, A. Hajra, A. Majee, *Green Chem.* **2017**, *19*, 3282–3295.
[85] A. M. Jadhav, S. K. Krishnammagari, J. T. Kim, Y. T. Jeong, *Tetrahedron* **2017**, *73*, 5163–5169.
[86] M. Shunmughanathan, N. Madankumar, K. Pitchumani, *ChemistrySelect* **2018**, *3*, 13743–13750.
[87] A. M. Jadhav, K. T. Lim, Y. S. Jeong, Y. T. Jeong, *Synth. Commun.* **2018**, *48*, 2232–2241.
[88] C. Teja, A. Garg, G. K. Rohith, H. Roshini, S. Jena, F. R. Nawaz Khan, *Polycycl. Aromat. Compd.* **2021**, *0*, 1–11.
[89] M. S. Rao, S. Hussain, *Polycycl. Aromat. Compd.* **2021**, *0*, 1–12.
[90] S. Khodabakhshi, B. Karami, *New J. Chem.* **2014**, *38*, 3586–3590.
[91] N. Kausar, P. P. Ghosh, G. Pal, A. R. Das, *RSC Adv.* **2015**, *5*, 60199–60207.
[92] S. Khodabakhshi, F. Marahel, A. Rashidi, M. K. Abbasabadi, *J. Chin. Chem. Soc.* **2015**, *62*, 389–392.
[93] F. Matloubi Moghaddam, M. Eslami, G. Hoda, *Sci. Rep.* **2020**, *10*, 1–14.
[94] N. Ahmed, B. V. Babu, *Synth. Commun.* **2013**, *43*, 3044–3053.
[95] A. Molla, E. Hossain, S. Hussain, *RSC Adv.* **2013**, *3*, 21517–21523.
[96] M. N. Elinson, F. V. Ryzhkov, R. F. Nasybullin, A. N. Vereshchagin, M. P. Egorov, *Helv. Chim. Acta* **2016**, *99*, 724–731.
[97] M. M. Heravi, M. Mirzaei, S. Y. S. Beheshtiha, V. Zadsirjan, F. Mashayekh Ameli, M. Bazargan, *Appl. Organomet. Chem.* **2018**, *32*, e4479.
[98] L. Chen, C. Lin, Y. Lan, Z. Li, D. Huang, W. Yang, Y. Li, *Environ. Chem. Lett.* **2020**, *18*, 2157–2163.
[99] L. Boubakri, R. Ternane, L. Mansour, A. H. Harrath, *J. Heterocycl. Chem.* **2019**, *57*, 291–298.
[100] M. Zabihzadeh, A. Omidi, F. Shirini, H. Tajik, M. S. N. Langarudi, *J. Mol. Struct.* **2020**, *1206*, 127730.
[101] Y. Kashman, K. R. Gustafson, R. W. Fuller, J. H. Cardellina, J. B. McMahon, M. J. Currens, R. W. Buckheit, S. H. Hughes, G. M. Cragg, M. R. Boyd, *J. Med. Chem.* **1992**, *35*, 2735–2743.
[102] R. S. Mali, P. P. Joshi, P. K. Sandhu, A. Manekar-Tilve, *J. Chem. Soc. Perkin Trans. 1* **2002**, *2*, 371–376.
[103] L. Xie, Y. Takeuchi, L. M. Cosentino, A. T. McPhail, K.-H. Lee, *J. Med. Chmistry* **2001**, *44*, 664–671.
[104] L. Andreani Lazzeri, E. Lapi, *Boll. Chim. Farm.* **1960**, *99*, 583–586.
[105] N. Fang, J. E. Casida, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 3380–3384.
[106] N. Fang, J. Casida, *J. Nat. Prod.* **1999**, *62*, 205–210.
[107] K. S. Ahn, W. S. Sim, I. H. Kim, *Planta Med.* **1996**, *62*, 7–9.
[108] T. Ishikawa, *Heterocycles* **2000**, *53*, 453–474.
[109] L. Xie, Y. Takeuchi, L. M. Cosentino, K. H. Lee, *J. Med. Chem.* **1999**, *42*, 2662–2672.
[110] R. Goel, R. Maiti, M. M. R. AB, *Indian J. Exp. Biol. Biol.* **1997**, *35*, 1080–1083.
[111] G. Cravotto, G. M. Nano, S. Palmisano, G. Pilati, T. Tagliapietra, *J. Heterocycl. Chem.* **2001**, *38*, 965–971.
[112] D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930.
[113] N. C. Zhao, W. B. Jin, X. H. Zhang, F. L. Guan, Y. Bin Sun, H. Adachi, T. Okuyama, *Biol. Pharm. Bull.* **1999**, *22*, 984–987.
[114] S. M. Razavi, G. Imanzadeh, F. S. Jahed, G. Zarrini, *Russ. J. Bioorganic Chem.* **2013**, *39*, 215–217.
[115] G. Zhang, Y. Zhang, J. Yan, R. Chen, S. Wang, Y. Ma, R. Wang, *J. Org. Chem.* **2012**, *77*, 878–888.
[116] N. Taira, R. Nugara, M. Inafuku, K. Takara, T. Ogi, T. Ichiba, H. Iwasaki, T. Okabe, H. Oku, *Journl Funct. Foods* **2017**, *29*, 19–28.
[117] P. Magiatis, E. Melliou, A. L. Skaltsounis, S. Mitaku, S. Léonce, P. Renard, A. Pierré, G. Atassi, *J. Nat. Prod.* **1998**, *61*, 982–986.
[118] S. Das, R. Das, S. Bhosale, A. Gawai, *Asian J. Res. Chem.* **2010**, *3*, 166–171.
[119] J. Y. C. Wu, W. F. Fong, J. X. Zhang, C. H. Leung, H. L. Kwong, M. S. Yang, D. Li, H. Y. Cheung, *Eur. J. Pharmacol.* **2003**, *473*, 9–17.
[120] Y. L. Song, Q. W. Zhang, Y. P. Li, R. Yan, Y. T. Wang, *Molecules* **2012**, *17*, 4236–4251.
[121] B. Halder, H. S. Maity, A. Nag, *Curr. Organocatalysis* **2019**, *6*, 20–27.
[122] C.-R. Su, S. F. Yeh, C. M. Liu, A. G. Damu, T.-H. Kuo, P.-C. Chiang, K. F. Bastow, K.-H. Lee, T.-S. Wu, *Bioorg. Med. Chem.* **2009**, *17*, 6137–6143.
[123] L. Zhu, L. Lu, D. Zhang, *Front. Environ. Sci. Eng. China* **2010**, *4*, 373–386.
[124] H. Lee, H. Lee, E. Lee, J. Lee, K. Lee, K. Kim, S. Kim, J. Lu, *Am. J. Chin. Med.* **2009**, *37*, 127–142.

[125] J. Guo, C. Jiang, Z. Wang, H. J. Lee, H. Hu, B. Malewicz, H. J. Lee, J. H. Lee, N. I. Baek, J. H. Jeong, D. K. Kim, K. S. Kang, S. H. Kim, J. Lu, *Mol. Cancer Ther.* **2007**, *6*, 907–917.
[126] W. Wu, S. N. Tang, Y. Zhang, M. Puppala, T. K. Cooper, C. Xing, C. Jiang, J. Lü, *Am. J. Chin. Med.* **2017**, *45*, 1773–1792.
[127] W. Mao, T. Wang, H. Zeng, Z. Wang, J. Chen, J. Shen, *Elsevier* **2009**, *19*, 4570–3.
[128] S. Khan, R. Choi, J. Lee, Y. Kim, *Eur. J. Pharmacol.* **2016**, *77*, 95–104.
[129] Z. Xu, K. Pupek, W. Suling, L. Enache, M. Flavin, *Bioorg. Med. Chem.* **2006**, *14*, 4610–4626.
[130] K. P. Beena, G. S. Pooja, *Asian J. Res. Chem.* **2022**, *15*, 176–181.
[131] G. S. Sorabad, D. Y. Yang, *J. Org. Chem.* **2023**, *88*, 4730–4742.

Manuscript received: June 9, 2023
Accepted manuscript online: September 13, 2023
Version of record online: ■■, ■■