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COMPREHENSIVE REVIEW

Synthesis and pharmacological properties of polysubstituted 2-amino-4*H*-pyran-3-carbonitrile derivatives

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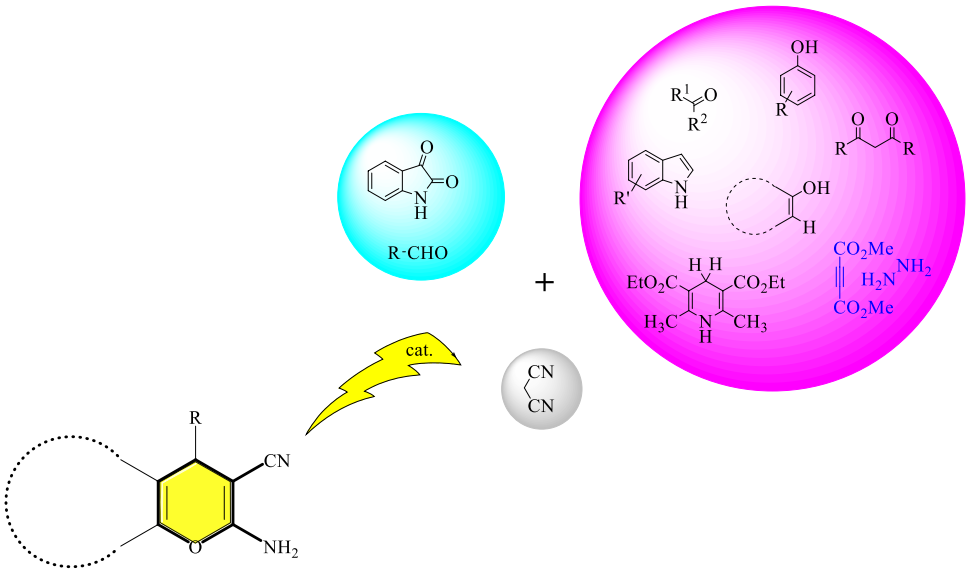
Abstract

2-Amino-3-cyano-4*H*-chromenes are structural core motifs that received increasing attention in the last years due to their interesting potential pharmacological properties. In this review, the synthetic methods for these compounds are classified based on the type of catalyst in the pertinent reactions. In addition, the wide range of pharmacological properties of these compounds is covered in a separate section.

Graphic Abstract



Keywords 2-Amino-4*H*-pyran-3-carbonitriles · Pharmacological properties · Polysubstituted · Malononitrile · Catalysts

Introduction

Polysubstituted 2-amino-4*H*-pyran-3-carbonitrile derivatives are among very important heterocyclic compounds with a wide range of interesting biological activities (Table 1) [1–9]. Their huge potential in drug discovery has inspired a wide array of synthetic work, and the conception of a new modified polycyclic framework based on this core structure has stimulated an extensive effort and attention. Furthermore, because of their orthogonal functional groups, these compounds can be considered as key intermediates for subsequent transformations.

Several strategies toward the synthesis of 2-amino-4*H*-pyran-3-carbonitriles in racemic or enantiomerically pure form have been described. The most useful and preferred

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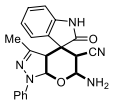
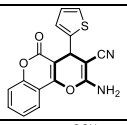
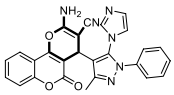
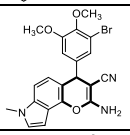
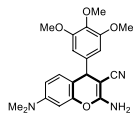
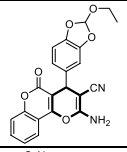
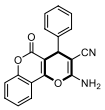
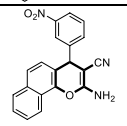
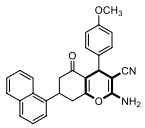
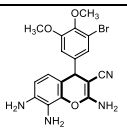
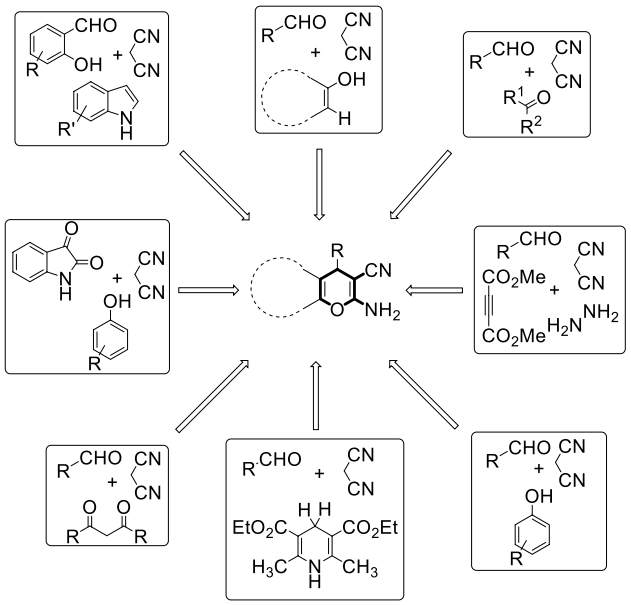
Table 1 Examples of biologically active molecules having 2-amino-4*H*-pyran-3-carbonitriles moieties

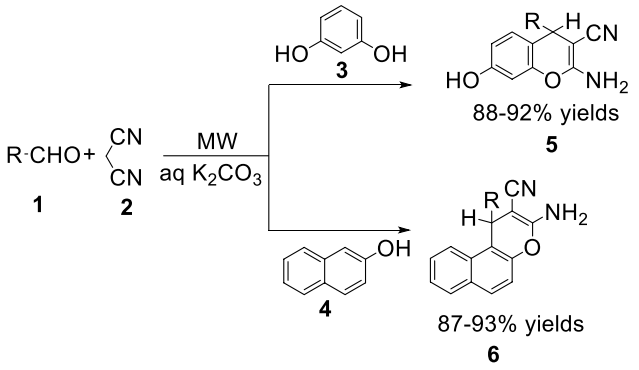
Structure	Effect	Structure	Effect
	Antibacterial, Anti-inflammatory [1]		Inhibitor of xanthine oxidase [6]
	Antibacterial, Antituberculosis, Antimalarial [2]		Apoptosis Inducer, Anticancer [7]
	Inducer apoptosis, Anticancer [3]		Antibacterial, Antifungal [8]
	Antibacterial [4]	 LY290181	Inhibitor of diabetic vascular dysfunction [9]
 (UCPH-101)	Inhibitor of the **E**xcitatory **A**mino **A**cid **T**ransporters (EAATs) [5]	 Crolibulin (EPC2407)	Drug: Anti **A**naplastic **T**hyroid **C**ancer (ATC)

method for the construction of these heterocyclic compounds is the multicomponent reaction (MCR) of aldehydes or isatin with malononitrile and *β*-ketoesters, diverse enolizable C-H-activated acidic compounds and phenols in the presence or absence of a catalyst (Scheme 1).

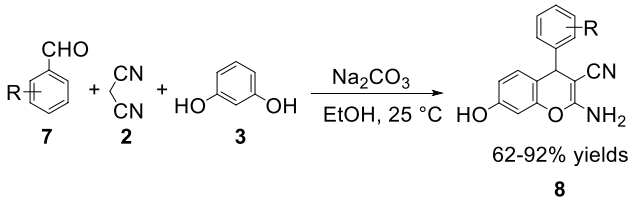
In 2015, a review article was published describing the different organocatalyzed synthetic strategies for the construction of chiral 2-amino-3-cyano-4*H*-chromene derivatives [10]. But despite their importance in synthetic, biological and medicinal chemistry, a comprehensive summary on the synthetic methodologies and different applications of polysubstituted 2-amino-4*H*-pyran-3-carbonitrile derivatives has not been reported. Hence, in this review, we aim to classify the existing synthetic methods for the construction of new 2-amino-4*H*-pyran-3-carbonitriles and their heterocyclic-fused analogs based on the type of the catalyst. In addition, the potential pharmacological or biological properties of these compounds will be discussed. In this regard, the content is divided into two main sections, namely description of catalytic synthesis strategies and evaluation of biological properties of scaffolds.



Scheme 1 Representative synthetic strategies for the preparation of 2-amino-4*H*-pyran-3-carbonitriles



Scheme 2 Synthesis of substituted 2-amino-4*H*-chromene and benzo[*e*]chromene derivatives (**5**, **6**) in aqueous K_2CO_3



Scheme 3 Synthesis of 2-amino-7-hydroxy-4*H*-chromene-3-carbonitriles **8** using sodium carbonate

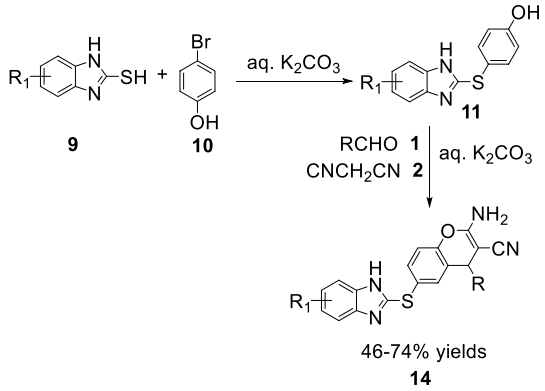
Synthetic entries for polysubstituted 2-amino-4*H*-pyran-3-carbonitriles based on the type of the catalyst

Common acid/base catalysts

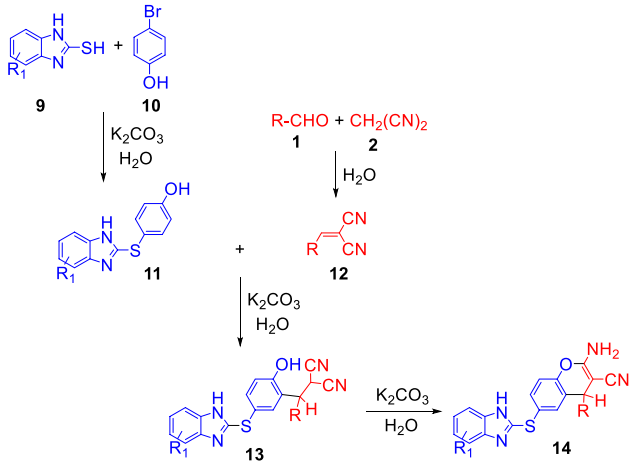
Kidwai et al. [11] reported a green synthesis of substituted 2-amino-4*H*-chromene and benzo[*e*]chromene derivatives (**5**, **6**) in good-to-high yields (87–93%). The condensation reaction of aldehydes **1**, malononitrile **2** and resorcinol **3**/*β*-naphthol **4** afforded the desired products **5**/**6**, respectively, in aqueous K_2CO_3 under microwave irradiation (Scheme 2).

In a similar work, Dinh Thanh et al. [12] synthesized 2-amino-7-hydroxy-4*H*-chromene-3-carbonitriles **8** in moderate-to-high yields (62–92%). These three-component reactions were carried out with aromatic aldehydes **7**, malononitrile **2** and resorcinol **3** using sodium carbonate as catalyst in ethanol (Scheme 3).

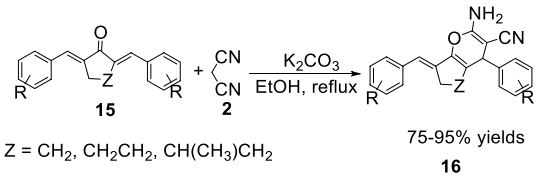
Kidwai et al. [13] in another paper reported the synthesis of 2-amino-6-(1*H*-benzo[*d*]imidazol-2-ylthio)-chromenes **14** in moderate-to-good yields (46–74%) by the multicomponent coupling of *p*-bromophenol **10** with 2-benzimidazolethiols **9**, malononitrile **2** and substituted aldehydes **1** (Scheme 4). The reaction is initiated by the in situ generation of 4-(1*H*-benzo[*d*]imidazol-2-ylthio) phenol **11** from the reaction of *p*-bromophenol **10** with 2-benzimidazolethiols **9** in aqueous K_2CO_3. The Knoevenagel condensation of malononitrile **2** and the substituted aldehydes **1**, the phenol ortho-C-alkylation and then subsequent nucleophilic attack by phenolic OH group to the CN affords the final 2-amino-2-chromenes **14** (Scheme 5).



Scheme 4 Synthesis of 2-amino-6-(1*H*-benzo[*d*]imidazol-2-ylthio)-chromenes **14** in aqueous K_2CO_3

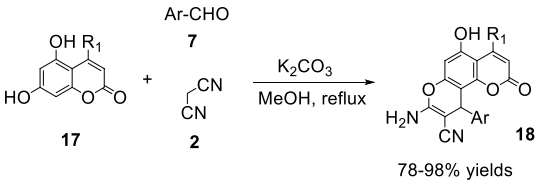


Scheme 5 The proposed mechanism for the synthesis of 2-amino-6-(1*H*-benzo[*d*]imidazol-2-ylthio)-chromenes **14** in aqueous K_2CO_3

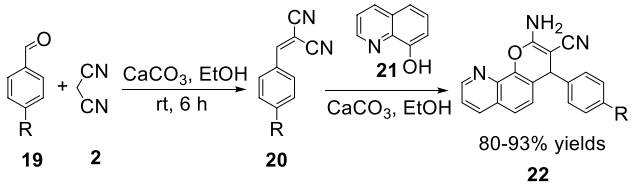


Scheme 6 The one-pot condensation of malononitrile **2** and *α*,*α*′-bis(arylidene) cycloalkanones **15** catalyzed by K_2CO_3

Karimi-Jaberi et al. [14] reported the synthesis of a new series of 2-amino-4*H*-pyran-3-carbonitriles **16**. In



Scheme 7 Synthesis of pyrano[2,3-*H*]coumarins **18** in the presence of K_2CO_3



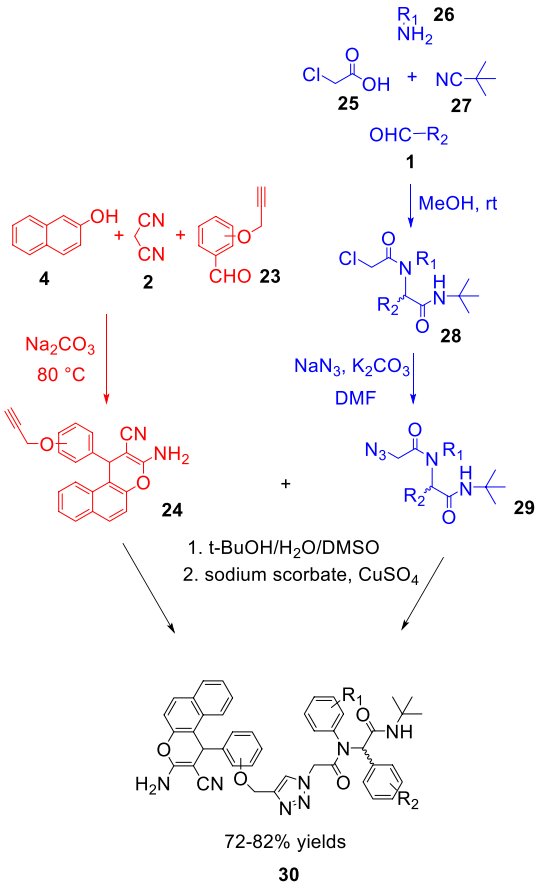
Scheme 8 Synthesis of a new pyran derivatives based on 8-hydroxyquinoline **22** in the presence of $CaCO_3$

their procedure, the reaction of malononitrile **2** and *α*,*α*´-bis(arylidene) cycloalkanones **15** in ethanol with K_2CO_3 as a catalyst led to the desired products **16** in good-to-excellent yields (75–95%) (Scheme 6).

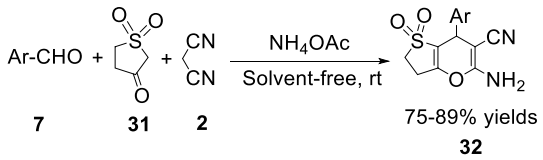
Karami et al. [15] reported a good procedure for the preparation of new pyrano[2,3-*H*]coumarin derivatives **18** from the reaction of 5,7-dihydroxy-4-substituted coumarins **17**, malononitrile **2** and aromatic aldehydes **7** in the presence of K_2CO_3 as a basic catalyst. The pyrano[2,3-*h*]coumarin derivatives **18** resulted in good-to-excellent yields (78–98%) (Scheme 7).

Rbaa et al. [16] reported the synthesis of new pyran derivatives based on 8-hydroxyquinoline **21** in good-to-high yields (80–93%). Initially, *p*-substituted benzaldehydes **19** reacted with malononitrile **2** in the presence of calcium carbonate ($CaCO_3$) in absolute ethanol to afford intermediates **20**. Then, 2-amino-4-aryl-4*H*-pyrano[3,2-h]quinoline-3-carbonitriles **22** was obtained from the reaction of 8-hydroxyquinoline **21** with intermediates **20** in the same conditions (Scheme 8).

Mohan and Bahulayan synthesized the triazole-linked chromene peptidomimetics **30** from the reaction of chromene alkynes **24** with *α*-acyl amino acetamide azides (Ugi azides) **29** [17]. The chromene alkynes **24** were synthesized initially with grinding of *β*-naphthol **4**, malononitrile **2** and propargylated aldehydes **23** in the presence of sodium carbonate in a solvent-free process. The *α*-acyl amino acetamide azides "Ugi azides" **29** were synthesized from Ugi four-component reaction of aldehydes **1**, 2-chloro acetic acid **25**, amines **26** and pivalonitrile **27** and then an azide substitution in the Ugi reaction product **28**. Finally, 1,4-disubstituted regioisomer of the triazole peptidomimetic **30** obtained in good yields (72–82%) from the click cycloaddition reactions between the alkynes **24** and azides **29** as shown in Scheme 9.



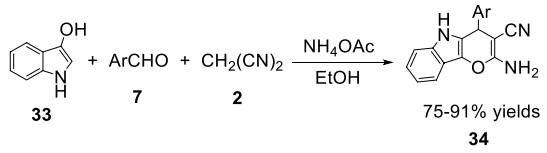
Scheme 9 The synthetic steps of triazole-linked chromene peptidomimetics **30**



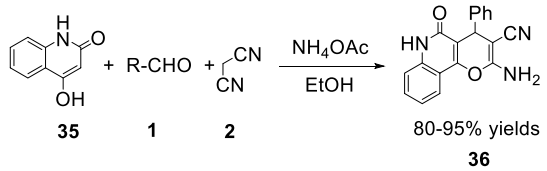
Scheme 10 Solvent-free synthesis of 7-aryl-1,1-dioxothieno[3,2-*b*]pyrans **32** in the presence of ammonium acetate

Yao et al. [18] reported an efficient procedure for the synthesis of 7-aryl-1,1-dioxothieno[3,2-*b*]pyrans **32** in good-to-high yields (75–89%). The reaction of aryl aldehydes **7**, tetrahydrothiophene-3-one-1,1-dioxide **31** and malononitrile **2** was carried out in the presence of ammonium acetate and led to the desired derivatives **32** under solvent-free conditions at room temperature (Scheme 10).

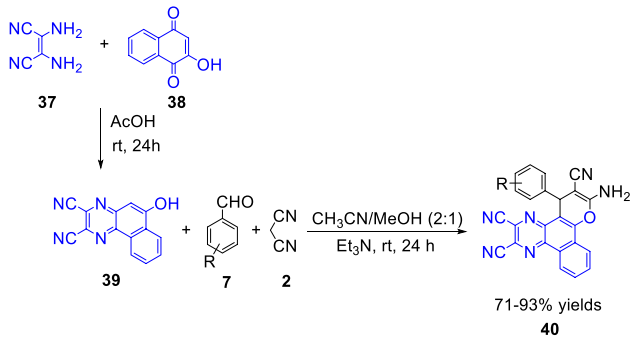
Damavandi [19] reported the reaction of aromatic aldehydes **7**, malononitrile **2** and indolin-3-one **33** in the presence of ammonium acetate as the catalyst in ethanol. As a result, 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]



Scheme 11 Synthesis of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*] indole-3-carbonitriles **34** catalyzed by ammonium acetate



Scheme 12 Condensation of 4-hydroxyquinolin-2(1*H*)-one **35**, aldehydes **1** and malononitrile **2** catalyzed by ammonium acetate

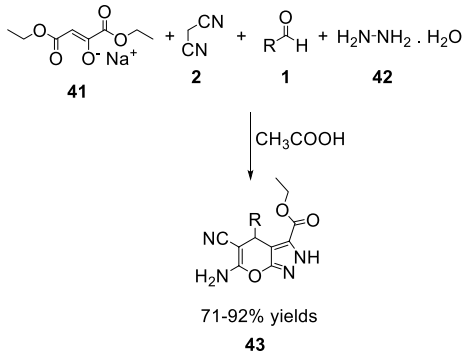


Scheme 13 Synthesis of functionalized pyrano[*f*]quinoxaline derivatives **40**

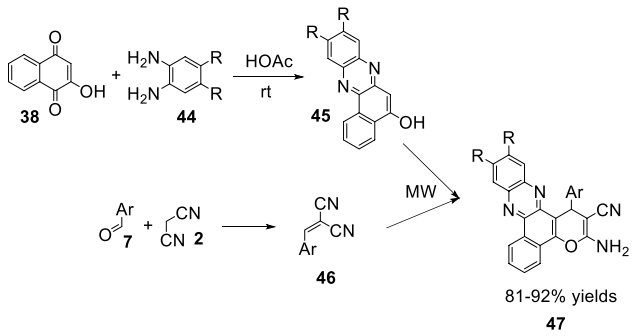
indole-3-carbonitriles **34** were obtained in good-to-high yields (75–91%) (Scheme 11).

Another example of the synthesis of 2-amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-*c*]quinolin-5-one derivatives **36** in good-to-excellent yields (80–95%) in the presence of ammonium acetate as the catalyst was reported by Lei et al. [20]. In this study, the products **36** were obtained from the one-pot condensation of 4-hydroxyquinolin-2(1*H*)-one **35**, aldehydes **1** and malononitrile **2** in refluxing EtOH in short reaction time and excellent yields (Scheme 12).

Ghadari et al. [21] reported an interesting stepwise procedure for the preparation of the functionalized pyranoquinoxaline derivatives **40** in the presence of trimethylamine. At the first step, quinoxaline derivatives **39** were synthesized from the reaction of diaminomaleonitrile **37** with 2-hydroxy-1,4-naphthoquinone **38** in acetic acid at room temperature. Subsequently, the three-component reaction of the synthesized quinoxaline **39** with aromatic aldehydes **7** and malononitrile **2** in the presence of triethylamine in



Scheme 14 Synthesis of ethyl 6-amino-4-aryl-5-cyano-2,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylates **43**



Scheme 15 Synthesis of polysubstituted benzo[*a*]pyrano-[2,3-*c*] phenazines **47** under microwave heating

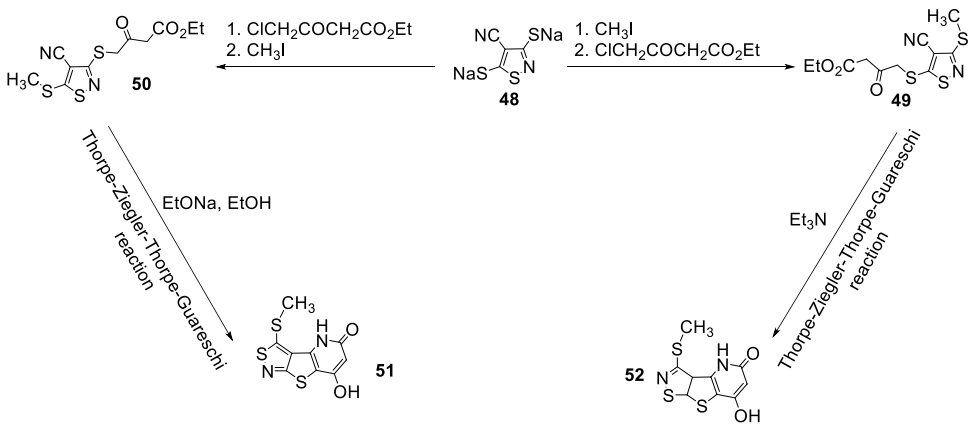
CH_3CN/EtOH (2:1) produced the functionalized pyrano[*f*] quinoxaline derivatives **40** in good-to-high yields (71–93%) (Scheme 13).

Gein et al. [22] reported the synthesis of ethyl 6-amino-4-aryl-5-cyano-2,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylates **43** through a four-component reaction of the sodium salt of diethyloxaloacetate **41**, aldehydes **1**, hydrazine hydrate **42** and malononitrile **2**. The products **43** were obtained in good-to-high yields (71–92%) in acetic acid (Scheme 14).

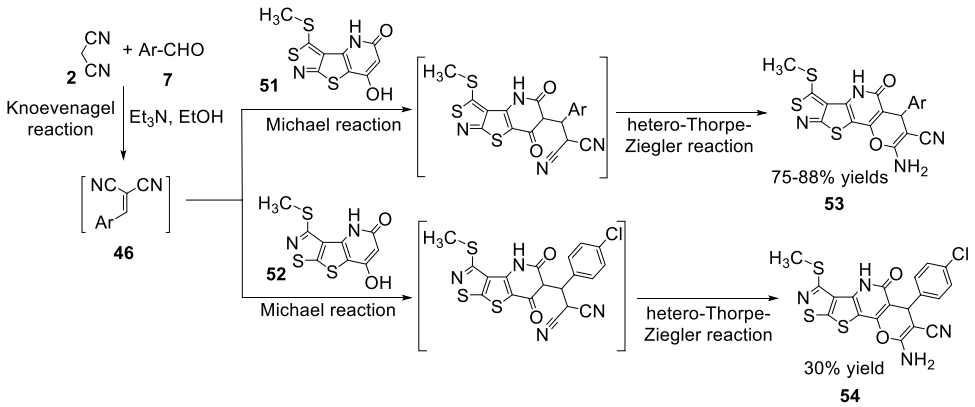
Wang et al. [23] devised two-step multicomponent tandem synthesis of highly functionalized benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **47** from microwave-assisted reaction of 2-hydroxynaphthalene-1,4-dione **38**, diamines **44**, aromatic aldehydes **7** and malononitrile **2** (Scheme 15). The reaction started by the condensation of 2-hydroxynaphthalene-1,4-dione **38** and diamine **44** to afford benzo[*a*]phenazin-5-ol **45**. Condensation of aromatic aldehydes **7** with malononitrile **2** produced 2-benzylidenemalononitriles **46** which after Michael addition with benzo[*a*]phenazin-5-ol **45** and subsequent cyclization afforded benzo[*a*]pyrano[2,3-*c*] phenazine derivatives **47** in good-to-high yields (81–92%).

Shestopalov et al. [24] developed an efficient procedure for the synthesis of isomeric

Scheme 16 Synthesis of isomers **51** and **52**



Scheme 17 Synthesis of isomeric isothiazolothieno-4*H*-pyranopyridines (**53**, **54**)

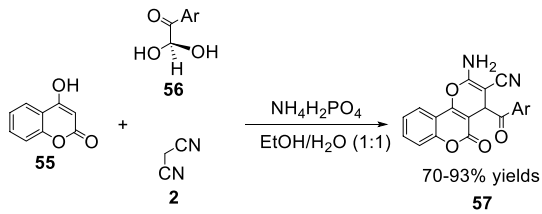


isothiazolothienopyranopyridines (**53**, **54**) through a two-step process (Scheme 17). The synthesis started from alkylation of dithiolate **48** by ethyl 4-chloroacetoacetate and then iodomethane to generate compound **50**. The reverse order of alkylation gives isomer **49**. The key thienopiridine **51** furnished by cyclization of **50** in the presence of sodium ethylate in refluxing ethanol and isomeric thienopiridine **52** also was obtained from cyclization of compound **49** in refluxing trimethylamine (Scheme 16).

The resulting isomeric compounds (**51**, **52**) were used in three-component reaction with the malononitrile **2** and aromatic aldehydes **7** to prepare a wide range of isomeric isothiazolothienopyranopyridines **53** and **54** in (75–88%) and 30% yields, respectively (Scheme 17).

Khodabakhshi et al. [25] reported a one-pot multicomponent process for the synthesis of pyrano[*c*]chromenes containing an aroyl group **57** in good-to-high yields (70–93%). In this process, the reaction of 4-hydroxycoumarin **55** with various aryl glyoxals **56** and malononitrile **2** in the presence of ammonium dihydrogen phosphate as a catalyst in EtOH/H_2O (1:1) afforded the corresponding products **57** (Scheme 18).

Han et al. [26] synthesized 2-amino-7-methoxy-4-aryl-4*H*-chromene-3-carbonitrile derivatives **59** in high yields

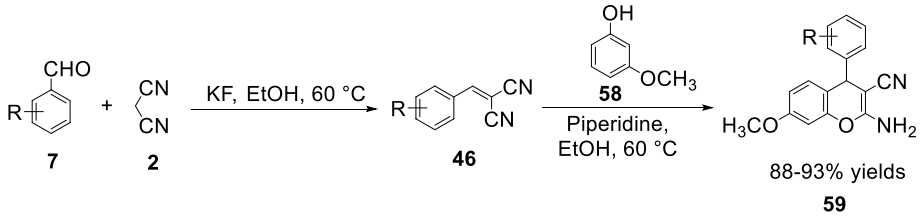


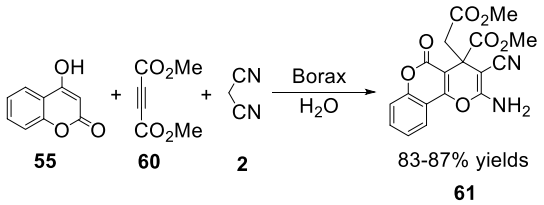
Scheme 18 Synthesis of 4-aroyl-pyrano[*c*]chromenes **57** using $NH_4H_2PO_4$

(88–93%) through condensation of *β*-dicyanostyrenes **46** with 3-methoxyphenol **58** in the presence of piperidine in absolute ethanol (Scheme 19). Precursor *β*-dicyanostyrenes **46** were prepared from the reaction of aromatic aldehydes **7** and malononitrile **2** in ethanol using KF.2H_2O as a catalyst.

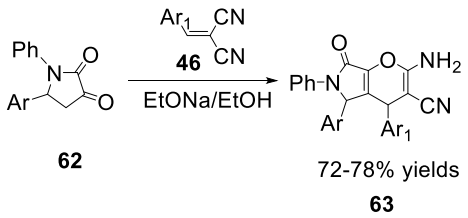
Molla and Hussain [27] successfully developed an efficient method for the synthesis of dihydropyrano[3,2-*c*]chromenes **61** in good yields (83–87%). These compounds **61** were synthesized through three-component reaction of 4-hydroxycoumarin **55**, dimethylacetylenedicarboxylate (DMAD) **60** and malononitrile **2** in refluxing water in the presence of borax as a catalyst (which upon hydrolysis in

Scheme 19 Synthesis of 2-amino-7-methoxy-4-aryl-4*H*-chromene-3-carbonitrile derivatives **59**

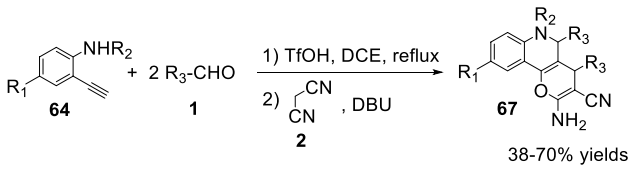




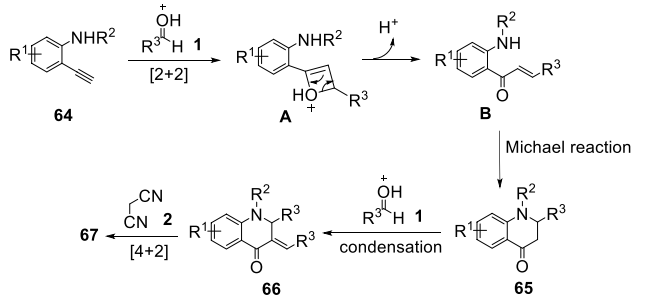
Scheme 20 Borax-catalyzed synthesis of dihydropyrano[3,2-*c*] chromene derivatives **61**



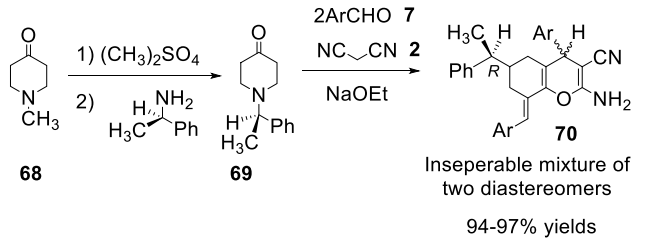
Scheme 21 Synthesis of new pyrano[2,3-*c*]pyrrole derivatives **63**



Scheme 22 Brønsted-acid-catalyzed synthesis of functionalized tricyclic pyranoquinolines **67**



Scheme 23 Proposed mechanism for the synthesis of the functionalized tricyclic pyranoquinolines **67**



Scheme 24 Synthesis of inseparable mixture of two diastereomeric 4(*H*)-pyrans **70**

water produces a hydroxyl anion (Brønsted base) and boric acid (Lewis acid) (Scheme 20).

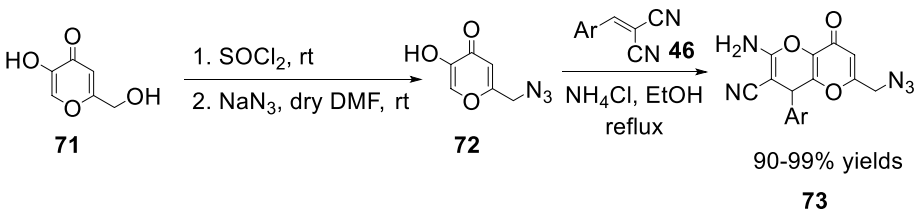
El-Ablak et al. [28] presented the synthesis of functionalized 2-amino-7-oxo-4,5,6,7-tetrahydropyrano[2,3-*c*]pyrrole-3-carbonitriles **63** in good yields (72–78%). The desired products **63** were obtained by the Michael addition of 1,5-diaryl-2,3-dioxopyrrolidines **62** with *α*-cyanocinnamonitriles **46** in the presence of sodium ethoxide as a catalyst (Scheme 21).

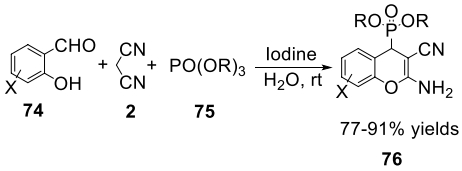
Wang et al. [29] disclosed a tandem annulation reaction of *o*-ethynylanilines **62**, aldehydes **1** and malononitrile **2**, affording functionalized tricyclic pyranoquinoline derivatives **65** with excellent functional groups in moderate-to-good yields (38–70%) (Scheme 22). The reaction starts with proton-activated highly selective [2 + 2] cycloaddition of C–C triple bond with C=O to afford 2*H*-oxete ion intermediate **A**. The ring opening of the resulting intermediate **A** produces enone **B** which after subsequent intramolecular Michael addition and aldol condensation with aldehydes **1** results in product **64**. The base-promoted [4 + 2] cycloaddition reaction of product **64** with nucleophilic malononitrile **2** affords pyranoquinoline derivatives **65** (Scheme 23).

Almansour et al. [30] reported a four-component reaction for the construction of an inseparable mixture of two diastereomeric 4(*H*)-pyrans **70** in excellent yields (94–97%). These diastereomers **70** were obtained from the reaction of (*R*)-1-(1-phenylethyl)tetrahydro-4(1*H*)-pyridinone **69**, aromatic aldehydes **7** and malononitrile **2** in the presence of solid sodium ethoxide under solvent-free conditions (Scheme 24).

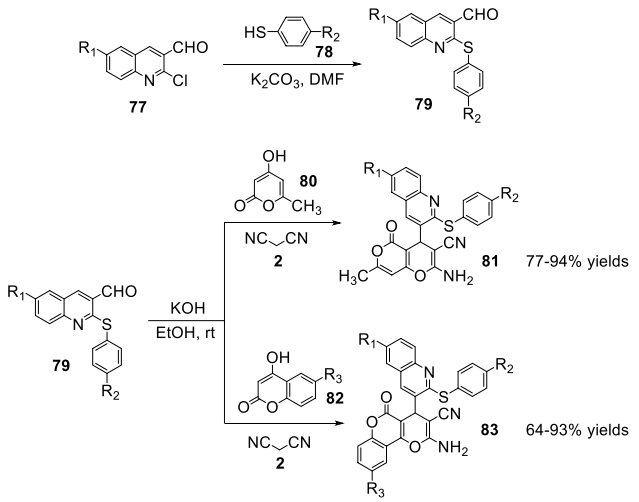
Aghbash et al. [31] synthesized derivatives of 2-amino-6-(azidomethyl)-8-oxo-4-aryl-4,8-dihydropyrano[3,2-*b*] pyran-3-carbonitrile **73** (Scheme 25). The reaction of **71**

Scheme 25 Synthesis of 2-amino-6-(azidomethyl)-8-oxo-4-aryl-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles **73**

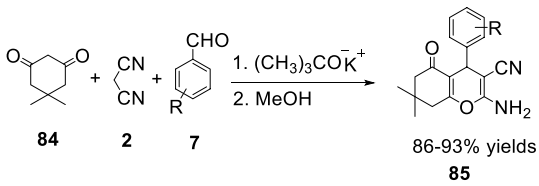




Scheme 26 Synthesis of 2-amino-3-cyano-4*H*-chromen-4-ylphosphonates **76**



Scheme 27 Synthesis of new pyrano[4,3-*b*]pyran **81** and pyrano[3,2-*c*]chromenes **83**



Scheme 28 Synthesis of tetrahydrobenzo[*b*]pyrans **85** in the presence of potassium tertiary butoxide

with thionyl chloride at room temperature followed by the reaction with sodium azide (NaN_3) in dry DMF formed 2-(azidomethyl)-5-hydroxy-4*H*-pyran-4-one **72**. The reaction of **72** with Knoevenagel adducts **46** afforded 2-amino-6-(azidomethyl)-8-oxo-4-aryl-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles **73** in high-to-excellent yields (90–99%).

Rajasekhar et al. [32] developed a new method for the preparation of 2-amino-3-cyano-4*H*-chromen-4-ylphosphonates **76** in high yields (77–91%). These compounds **76** were synthesized from the reaction of substituted salicylaldehyde **74**, malononitrile **2** and trialkyl phosphite **75** in the presence of iodine in water as a catalyst at room temperature (Scheme 26).

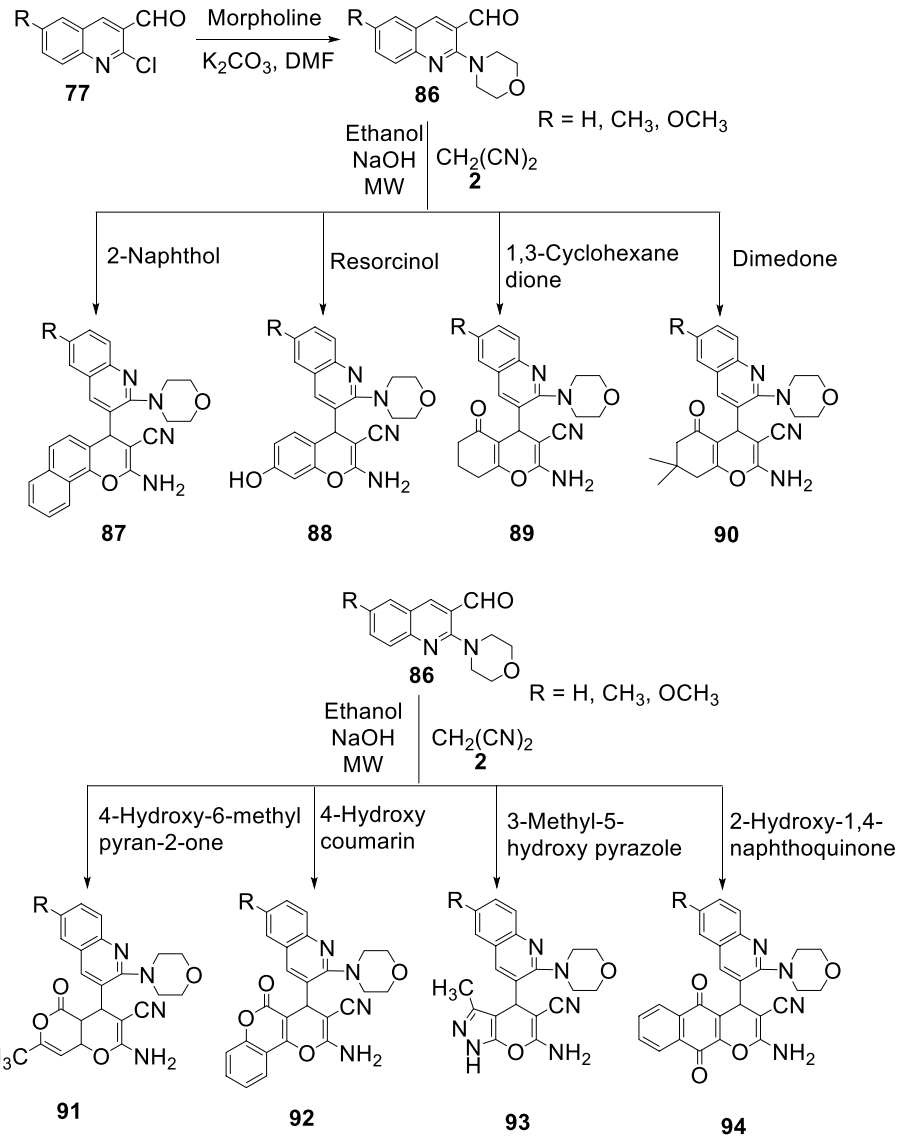
Makawana et al. [33] reported the synthesis of a new series of pyrano[4,3-*b*]pyran **81** and pyrano[3,2-*c*]chromene **83** derivatives bearing a 2-thiophenoxyquinoline nucleus in good-to-high yields (64–94%). This method was carried out via the reaction of 2-(thiophenoxyquinoline)-3-carbaldehydes **79**, 6-methyl-4-hydroxypyran-2-one **80**/4-hydroxy-6-(un)-substituted-2*H*-chromen-2-one **82** with malononitrile **2** at room temperature in the presence of KOH as a basic catalyst (Scheme 27). In this approach, 2-(thiophenoxy) quinoline-3-carbaldehydes **79** was generated by refluxing 2-chloroquinoline-3-carbaldehydes **77** and various thiophenols **78** in the presence of anhydrous potassium carbonate in dry DMF.

Rao et al. [34] described an efficient and convenient procedure for the synthesis of tetrahydrobenzo[*b*]pyrans **85** in good-to-high yields (86–93%). In their method, tetrahydrobenzo[*b*]pyrans **85** were produced from the reaction of substituted aromatic aldehydes **7**, dimedone **84** and malononitrile **2** in the presence of potassium tertiary butoxide as base in methanol at room temperature (Scheme 28).

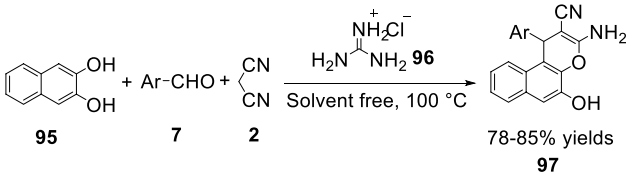
Makawana et al. [35] reported the synthesis of fused pyran derivatives bearing 2-morpholinoquinoline nucleus (**87**–**94**) from the reaction of 2-morpholinoquinoline-3-carbaldehydes **86** and malononitrile **2** with a variety of C–H-activated compounds. These reactions were conducted in the presence of NaOH as basic catalyst under microwave irradiation (Scheme 29). 2-Morpholinoquinolines **86** were synthesized through the reaction of 2-choloroquinolines **77** with morpholine catalyzed by K_2CO_3 in DMF.

Organo/organometal/natural catalysts

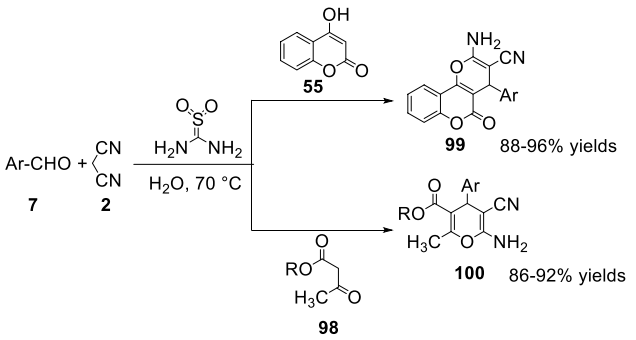
Olyaei et al. reported the synthesis of a new class of benzo[*f*]chromene derivatives **97** in good yields (78–85%) (Scheme 30). They introduced a one-pot three-component condensation reaction of 2,3-dihydroxynaphthalene **95**, malononitrile **2** and aromatic aldehydes **7** using guanidine



Scheme 29 Synthetic pathway for the fused pyran derivatives bearing 2-morpholinoquinoline nucleus (**87**-**94**)



Scheme 30 Synthesis of benzo[*f*]chromene derivatives **97** using guanidine hydrochloride **96**

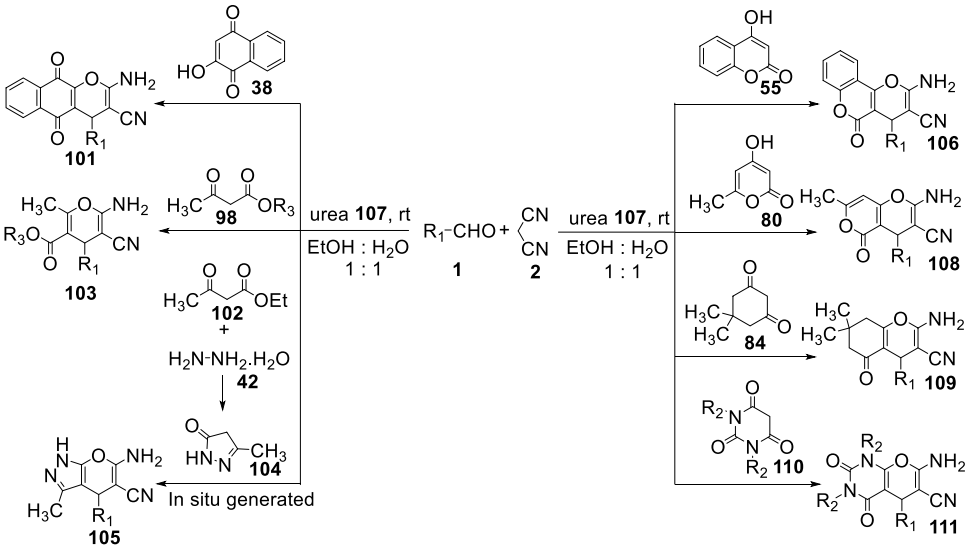


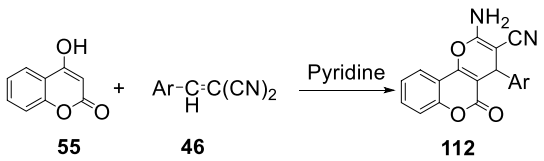
Scheme 31 Synthesis of 3,4-dihydropyrano[3,2-*c*]chromenes **99** and 6-amino-5-cyano-4-phenyl-2-methyl-4*H*-pyran-3-carboxylic acid ethyl esters **100** in the presence of thiourea dioxide

hydrochloride **96** as the catalyst under solvent-free conditions [36].

Mansoor et al. [37] described the synthesis of 3,4-dihydropyrano[3,2-*c*]chromenes **99** and 6-amino-5-cyano-4-phenyl-2-methyl-4*H*-pyran-3-carboxylic acid ethyl esters **100** in the presence of thiourea dioxide (an efficient,

Scheme 32 The reaction of aldehydes **1**, malononitrile **2** and a variety of C–H-activated acids catalyzed by urea





Scheme 33 Synthesis of Z-Amino-3-cyano-4-phenyl-5-oxo-γ-pyrano[3,2-*c*][*I*]benzopyranes **112**

reusable organic catalyst) in aqueous medium. The products **99**/**100** were obtained through one-pot, three-component reaction of aromatic aldehydes **7**, malononitrile **2** and 4-hydroxycoumarin **55**/alkyl acetoacetates **98**, respectively, in good-to-excellent yields (86–96%) (Scheme 31).

Brahmachari and Banerjee [38] conducted one-pot reaction of aldehydes **1**, malononitrile **2** and a variety of C–H-activated acids using urea as an inexpensive organocatalyst in aqueous ethanol at room temperature (Scheme 32). Accordingly, the functionalized 2-amino-3-cyano-4*H*-pyrans were synthesized in good-to-excellent yields (83–95%).

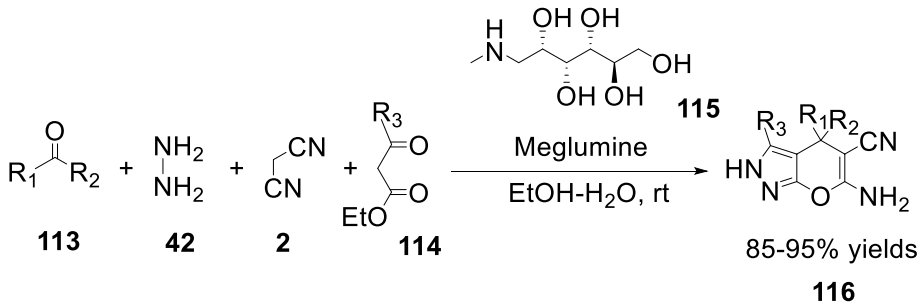
Wiener et al. [39] prepared *Z*-amino-3-cyano-4-phenyl-5-oxo-γ-pyrano[3,2-*c*][*I*]benzopyrane **112** from the reaction of 4-hydroxycoumarin **55** and benzylidenemalononitrile **46** in the presence of pyridine as a catalyst (Scheme 33).

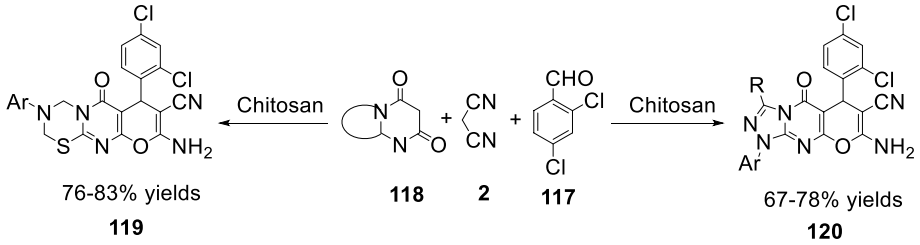
Zhang et al. [40] reported a four-component reaction of carbonyl compounds **113**, hydrazine hydrate **42**, malononitrile **2** and *β*-keto esters **114** catalyzed by meglumine **115** (an amino sugar derived from glucose) in EtOH-H_2O at room temperature (Scheme 34). Under these conditions, a series of dihydropyrano[2,3-*c*]pyrazole derivatives **116** were obtained in high yields (85–95%).

Abdelrazek and Gomha [41] synthesized a series of pyrano[2′,3′:4,5]pyrimido[2,1-*b*][1, 3, 5]thiadiazine **119** and pyrano[2,3-*d*][1, 2, 4]triazolo[4,3-*a*]pyrimidine **120** derivatives in good yields (67–83%). The treatment of 2,4-dichlorobezaldehyde **117**, malononitrile **2** and with appropriate active methylene compounds **118** (catalyzed by chitosan in refluxing dioxane) led to products **119** and **120** (Scheme 35).

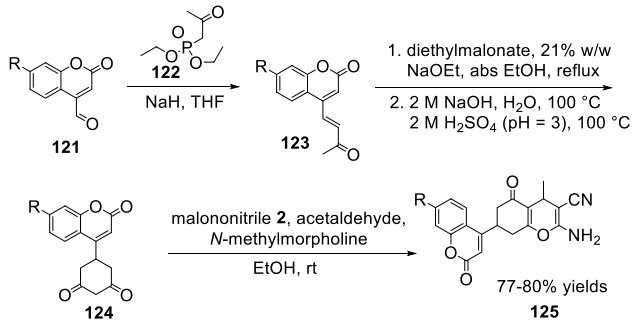
Huynh et al. [42] synthesized coumarin analogs **125** in good yields (77–80%) by three-component reaction of diketones **124** with malononitrile **2** and acetaldehyde in the presence of *N*-methylmorpholine in EtOH (Scheme 36). At first, for the synthesis of diketones **124**, diethyl-2-oxopropylphosphonate **122** reacted with aldehydes **121** in the presence of NaH in THF to generate the conjugated ketones **123**. The addition of diethylmalonate to conjugated ketones **123** in the presence of NaOEt in abs EtOH, followed by hydrolysis of

Scheme 34 Synthesis of dihydropyrano[2,3-*c*]pyrazoles **116** catalyzed by meglumine **115**

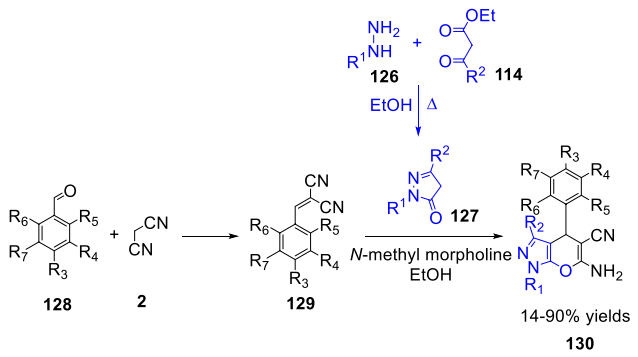




Scheme 35 A facile three-component reaction of 2,4-dichlorobezaldehyde **117**, malononitrile **2** and the appropriate active methylene compounds **118**



Scheme 36 The synthetic pathway for preparation of coumarin analogs **125**

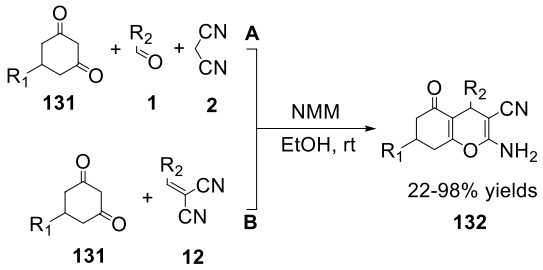


Scheme 37 Synthesis of 6-amino-1,3-disubstituted-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles **130**

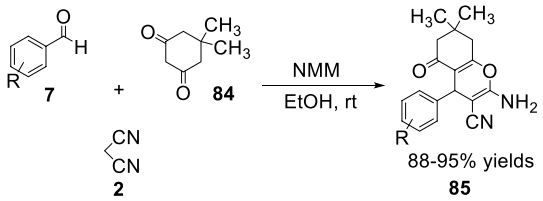
the ester in solution of NaOH and subsequent decarboxylation in H_2SO_4, afforded diketones **124**.

Yan et al. [43] synthesized 6-amino-1,3-disubstituted-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles **130** in low-to-high yields (14–90%). These compounds **130** were produced from the reaction of 1,3-disubstituted-1*H*-pyrazol-5(4*H*)-one **127**, various substituted aromatic aldehydes **128** and malononitrile **2** in the presence of *N*-methylmorpholine in EtOH at room temperature (Scheme 37). 1,3-Disubstituted-1*H*-pyrazol-5(4*H*)-one compounds **127** were produced by the reaction of hydrazines **126** with 3-oxo-esters **114** in EtOH.

Hansen et al. [44] reported the synthesis of 2-amino-4-(4-methoxyphenyl)-7-(naphthalen-1-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles **132**. In two-step



Scheme 38 One-pot and two-step reaction of 1,3-diones **131**, Malononitrile **2** and substituent aldehydes **1**

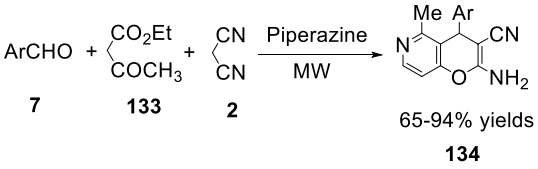


Scheme 39 Synthesis of 2-amino-4*H*-pyran derivatives **85** using *N*-methylmorpholine

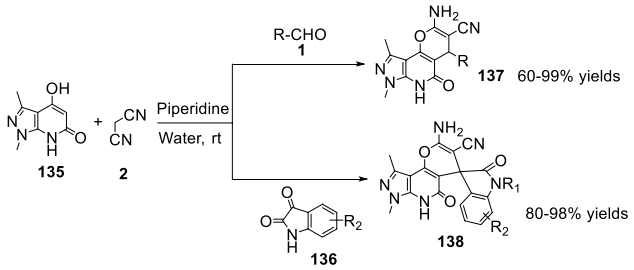
protocol **B**, the aldehydes **1** and malononitrile **2** generated an intermediate condensation products **12**, which then reacts with the 1,3-diones **131** to form the final product **132**, whereas in one-pot protocol **A**, three-component reaction of 1,3-diones **131**, malononitrile **2** and substituent aldehydes **1** provided the final product **132** in low-to-excellent yields (22–98%). The reactions were carried out in the presence of *N*-methylmorpholine in EtOH at room temperature (Scheme 38).

Mahdavi et al. [45] synthesized 2-amino-4*H*-Pyran derivatives **85** in high yields (88–95%) from the three-component reaction of dimedone **84**, aromatic aldehydes **7** and malononitrile **2** under the similar conditions (Scheme 39).

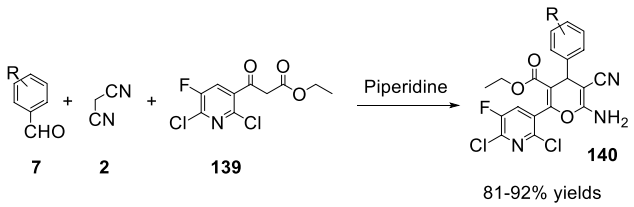
Jirandehi and Mirzaiean [46] reported the synthesis of pyrano[3,2-*c*]pyridines derivatives **134** in moderate-to-excellent yields (65–94%). The one-pot condensation of malononitrile **2**, ethyl acetoacetate **133** and aryl aldehydes **7** in the presence of piperazine as a catalyst under solvent-free media conditions by a microwave-assisted process afforded the desired products **134** (Scheme 40).



Scheme 40 Synthesis of pyrano[3,2-*c*]pyridines **134** in the presence of piperazine under microwave irradiation



Scheme 41 Three-component synthesis of polycyclic/spirocyclic heterocyclic compounds (**137**, **138**) catalyzed by piperidine

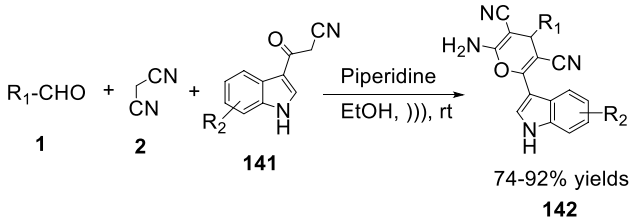


Scheme 42 One-pot synthesis of polyfunctionalized 4*H*-pyran derivatives containing fluorochloro pyridyl moiety **140** catalyzed by piperidine

Jayarajan and Vasuki [47] synthesized skeletally diverse polycyclic/spirocyclic heterocyclic compounds (**137**, **138**) in moderate-to-excellent yields (60–99%) using piperidine as the catalyst in water at room temperature. Piperidine efficiently catalyzed the reaction of malononitrile **2**, 4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)-one **135** (a novel heterocyclic active methylene compound) and aldehydes **1**/isatin derivatives **136** to afford **137**/**138,** respectively (Scheme 41).

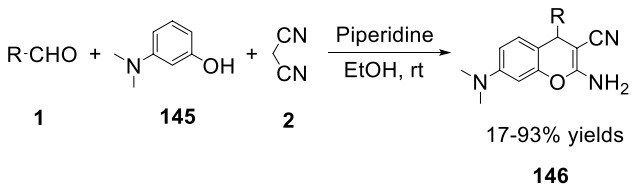
Using one-pot multicomponent reaction of ethyl 3-(2,6-dichloro-5-fluoropyridin-3-yl)-3-oxopropanoate **139**, malononitrile **2** and substituted aromatic aldehydes **7**, Ye et al. [48] were able to prepare polyfunctionalized 4*H*-pyran derivatives bearing fluorochloro pyridyl moiety **140**. These products **140** were isolated in good-to-high yields (81–92%) in the presence of piperidine (Scheme 42).

Ji et al. [49] described the one-pot multicomponent reaction of aldehydes **1**, malononitrile **2** with 3-cyanoacetyl indoles **141** in the presence of piperidine under ultrasonic



Scheme 43 Synthesis of indol-3-yl-substituted pyran derivatives **142** under ultrasonic irradiation

Scheme 44 Synthesis of pyrano[2,3-*a*]carbazoles **144** using of piperidine



Scheme 45 Synthesis of 2-amino-3-cyano-7-(dimethylamino)-4*H*-chromenes **146**

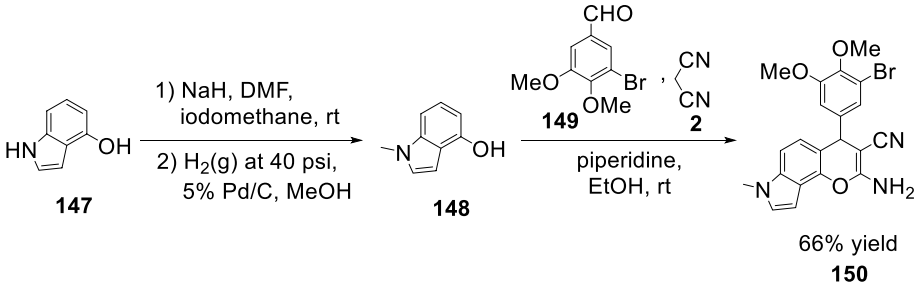
irradiation. As a result, a series of polysubstituted indol-3-yl-substituted pyran derivatives **142** were synthesized in good-to-high yields (74–92%) (Scheme 43).

Murali et al. [50] reported a facile and efficient, three-component synthesis of pyrano[2,3-*a*]carbazoles **144** in moderate-to-excellent yields (65–95%). The reaction of 2,3,4,9-tetrahydro-1*H*-carbazol-1-ones **143**, malononitrile **2** and aromatic/heteroaromatic aldehydes **7** with catalytic amount of piperidine in refluxing DMF produced the desired products **144** (Scheme 44).

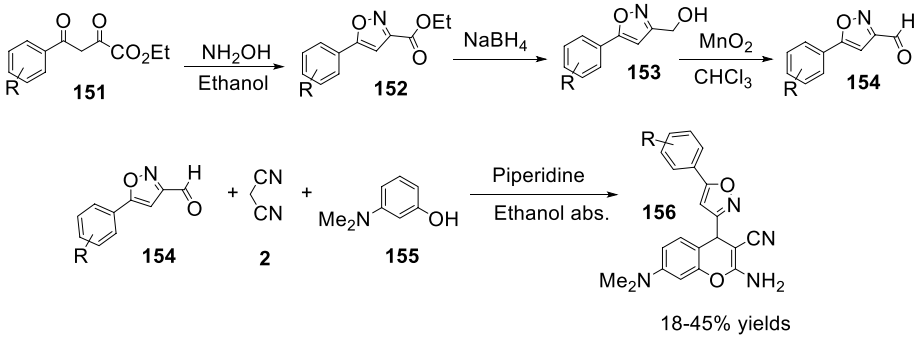
Kemnitzer et al. [51] synthesized the 2-amino-3-cyano-7-(dimethylamino)-4*H*-chromenes **146** in low-to-high yields (17–93%). Aldehydes **1** were treated with 3-dimethylaminophenol **145** and malononitrile **2** in the presence of piperidine in EtOH at room temperature to afford the corresponding products **146** (Scheme 45).

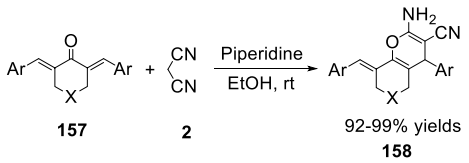
Cai et al. [7] also reported the synthesis of 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-4,7-dihydro-7-methyl-pyrano[2,3-*e*]indoles **150** in moderate yields (66%) as another derivatives of 4-aryl-4*H*-chromene (Scheme 46). These compounds **150** were synthesized from one-pot reaction of substituted 3-bromo-4,5-dimethoxybenzaldehyde **149**

Scheme 46 Synthesis of 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-4,7-dihydro-7-methyl-pyrano[2,3-*e*] indoles **150**

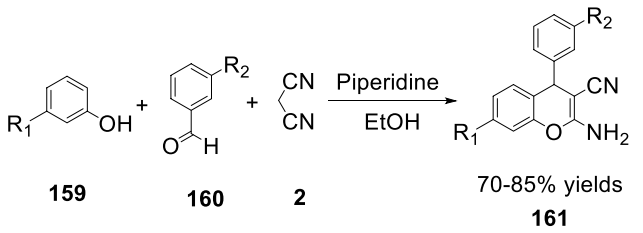


Scheme 47 One-pot synthesis of 4-(5-arylisoxazol-3-yl)-4*H*-chromenes **156**





Scheme 48 Synthesis of racemic 2-aminopyranopyridine-3-carbonitriles **158**



Scheme 49 One-pot reaction of substituted benzaldehydes **7**, malononitrile **2** and substituted phenols **159**

and 4-hydroxy-1-methyl-1*H*-indole **148** with malononitrile **2** which was catalyzed by piperidine in EtOH at room temperature. 4-Hydroxy-1-methyl-1*H*-indole **148** was produced by methylation and then deprotection of 4-Hydroxy-1*H*-indole **147**.

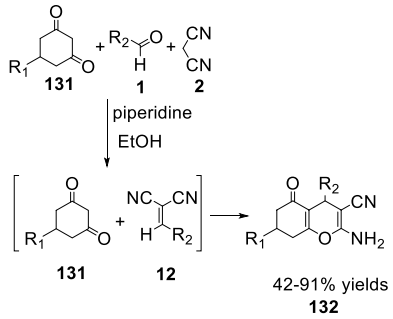
Later on, Akbarzadeh et al. [52] reported the synthesis of a new series of 4-aryl-4*H*-chromenes bearing a 5-arylisoxazol-3-ylmoiety at the C-4 position **156** (Scheme 47). Initially, ethyl 5-arylisoxazole-3-carboxylates **152** was formed from the reaction of ethyl-2,4-dioxo-4-arylbutanoate derivatives **151** with hydroxylamine hydrochloride. Addition of sodium borohydride to **152** produced 5-arylisoxazol-3-ylmethanol derivatives **153**. Oxidation of 5-arylisoxazol-3-ylmethanols **153** by MnO_2 led to 5-arylisoxazole-3-carboxaldehydes **154** which its reaction with malononitrile **2** and 3-(dimethylamino) phenol **155** in the presence of piperidine in EtOH gave 2-amino-7-dimethylamino-4-(5-arylisoxazol-3-yl)-4*H*-chromene-3-carbonitriles **156** in low-to-moderate yields (18–45%).

Chen et al. [53] used piperidine as a catalyst for the synthesis of racemic 2-aminopyranopyridine-3-carbonitriles **158** in excellent yields (92–99%). These products **158** were prepared from the reaction of dienones **157** and malononitrile **2** in EtOH at room temperature (Scheme 48).

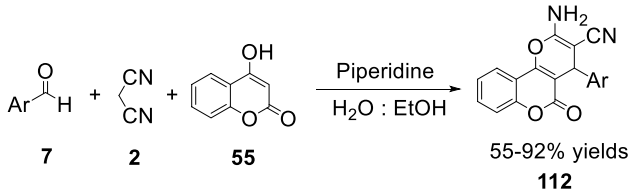
Ramani et al. [54] reported the synthesis of other derivatives of 4-aryl-4*H*-chromene-3-carbonitrile **161** from a one-pot reaction of *m*-substituted benzaldehydes **160**, malononitrile **2** and substituted phenols **159**. The products **161** were isolated in good yields (70–85%) using piperidine at 60–80 °C in ethanol (Scheme 49).

Once again, piperidine was used as a catalyst in a one-pot three-component synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles **132** by Erichsen et al. [5]. The reaction of aldehydes **1** and malononitrile **2** generates an intermediate condensation product **12**, which then reacts with the diketones **131** to form 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles **132** in moderate-to-high yields (42–91%) (Scheme 50).

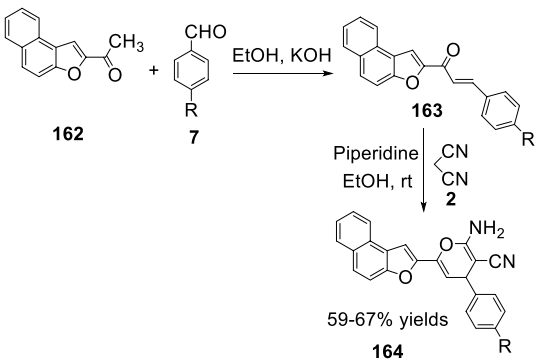
Balalaie et al. [55] described a simple procedure for the synthesis of dihydropyrano[3,2-*c*]chromene derivatives **112** in moderate-to-high yields (55–92%) by a three-component



Scheme 50 The reaction of diketones **131**, aldehydes **1** and malononitrile **2** for the preparation of the 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles **132**



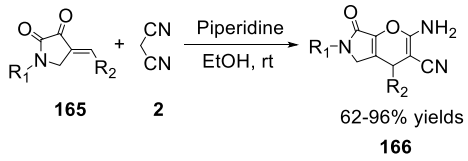
Scheme 51 Synthesis of dihydropyrano[3,2-*c*]chromenes **112** from the reaction of aromatic aldehydes **7**, malononitrile **2** and 4-hydroxycoumarin **55**



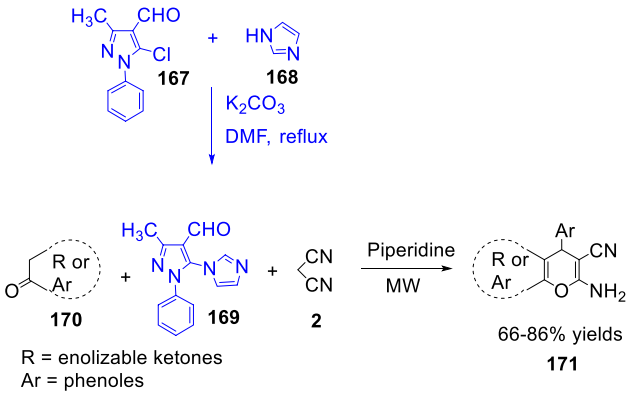
Scheme 52 The reaction of substituted chalcones **163** with malononitrile **2** catalyzed by piperidine

reaction of aromatic aldehydes **7**, malononitrile **2** and 4-hydroxycoumarin **55**. These reactions were carried out in the presence of three different catalysts, namely piperidine, triethylamine and sodium carbonate, in aqueous media in H_2O: EtOH(1:1) (Scheme 51).

Gaikwad et al. [56] synthesized 2-amino-4-(-4-substituted phenyl)-6-(naphtho[2,1-*b*]furan-2-yl)-4*H*-pyran-3-carbonitriles **164** from the reaction of substituted chalcones **163** with malononitrile **2** catalyzed by piperidine (Scheme 52). Initially, 3-(4-hydroxyphenyl)-1(naphtha[2,1-b]furan-2yl) prope-2-en-1-ones **163** was synthesized from Claisen–Schmidt condensation of 2-acetylnaphtho[2,1-*b*]



Scheme 53 Synthesis of fused bicyclic 4*H*-pyranes **166** catalyzed by piperidine



Scheme 54 Synthesis of 4-(5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*pyrazol-4-yl)-4*H*-pyran-2-amine derivatives **171** catalyzed by piperidine

furan **162** and substituted benzaldehydes **7** in ethanol and aqueous solution of potassium hydroxide. In the next step, the reaction of synthesized 3-(4-hydroxyphenyl)-1(naphtha[2,1-*b*]furan-2yl)prope-2-en-1-ones **187** with malononitrile **2** in ethanol in the presence of piperidine at room temperature afforded 2-amino-4-(-4-substituted phenyl)-6-(naphtho[2,1-*b*]furan-2-yl)-4*H*-pyran-3-carbonitriles **164** in moderate yields (59–67%).

Li et al. [57] developed the synthesis of functionalized 4*H*-pyrans **166** in moderate-to-excellent yields (62–96%). These compounds **166** were achieved by the reaction of α,*β*-enones **165** and malononitrile **2** catalyzed by piperidine in ethanol at room temperature (Scheme 53).

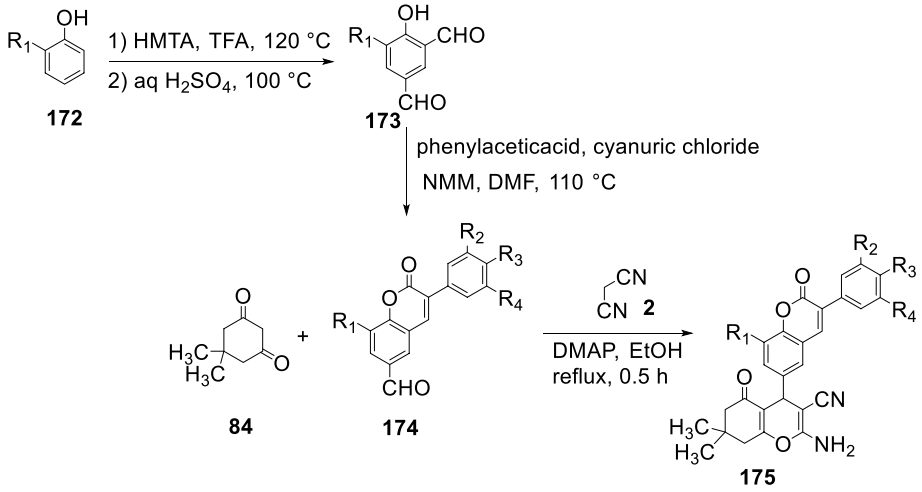
Kalaria et al. [2] synthesized 4-(5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-4*H*-pyran-2-amine derivatives **171** in moderate-to-good yields (66–86%) from the cyclocondensation reaction of 5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **169**, malononitrile **2** and enolizable ketones/phenols **170** in the presence of piperidine under microwave irradiation (Scheme 54). The starting material 5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **169** was prepared by nucleophilic displacement of the chloro group in 5-chloro-3-methyl-1-phenyl-1*H*pyrazole-4-carbaldehyde **167** with nitrogen atom of imidazole **168** in refluxing DMF with anhydrous potassium carbonate as a catalyst.

Sashidhara et al. [58] developed the synthesis of a new class 3-aryl coumarin-based aminopyran derivatives **175**. Firstly, the Duff reaction on *o*-substituted phenols **172** in the presence of hexamethylenetetramine (HMTA) and TFA at 120 °C generated aromatic dicarbaldehydes **173**. Reaction of the resulting dicarbaldehyde **173** with different substituted phenyl acetic acids in the presence of cyanuric chloride and *N*-methylmorpholine (NMM) in DMF afforded the corresponding 3-aryl coumarin aldehydes **174**. Finally, the multicomponent reaction of 3-aryl coumarin aldehydes **174** with malononitrile **2** and dimedone **84** in DMAP in refluxing EtOH furnished 3-aryl coumarin-based aminopyran derivatives **175** in good yields (Scheme 55).

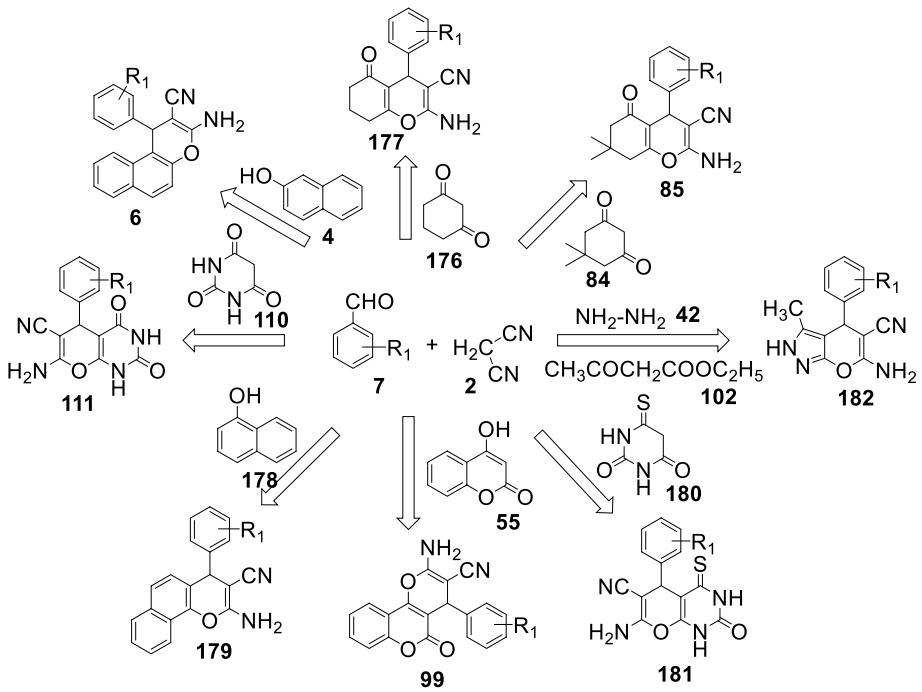
Kaur et al. [6] used DMAP for the synthesis of 4-aryl/heteroaryl-4*H*-fused pyrans in moderate-to-high yields (57–88%). The multicomponent reaction of aromatic aldehyde **7**, malononitrile **2** and C-H-activated acidic compounds under microwave irradiation afforded the desired products as shown in Scheme 56.

Mungra et al. [59] prepared *β*-aryloxyquinoline-3-carbaldehydes **184** by Vilsmeiere–Haack reaction of 2-chloro-3-formylquinolines **77** with phenols **183** using anhydrous potassium carbonate as a base in refluxing dimethylformamide. Subsequent one-pot three-component

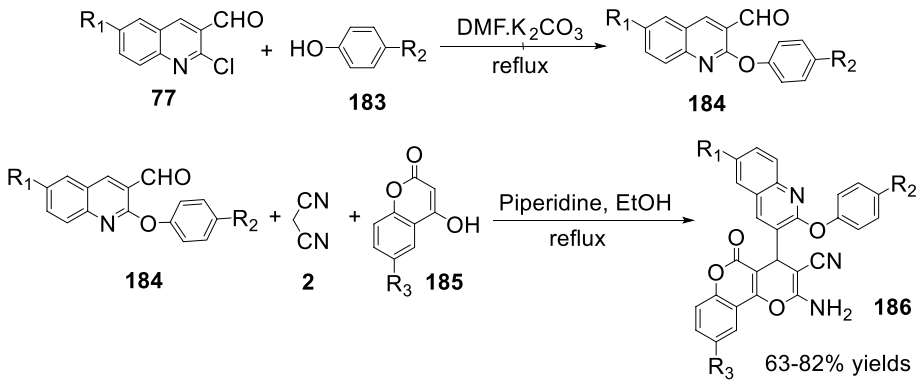
Scheme 55 Synthesis of 3-aryl coumarin-based aminopyran derivatives **175**

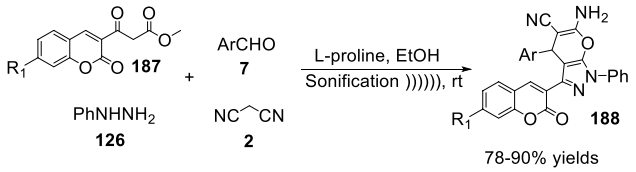


Scheme 56 The reaction of aromatic aldehyde **7**, malononitrile **2** and C-H-activated acidic compounds

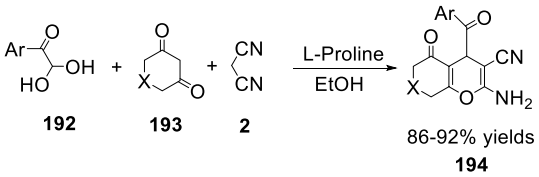


Scheme 57 Synthesis of *β*-aryloxyquinolines **184** and their pyrano[3,2-*c*]chromene derivatives **186**

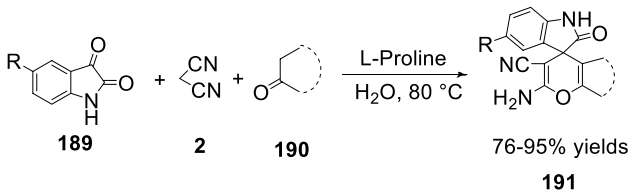




Scheme 58 L-Proline-catalyzed one-pot four-component synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives **188**



Scheme 60 L-Proline-catalyzed reaction of arylglyoxal monohydrates **192**, 1,3-diketones **193** and malononitrile **2**



Scheme 59 Synthesis of spirooxindole derivatives **191** in aqueous medium catalyzed by L-proline

cyclocondensation of *β*-aryloxyquinoline-3-carbaldehydes **184** with malononitrile **2** and 4-hydroxycoumarins **185** in ethanol which was catalyzed by piperidine afforded pyrano[3,2-*c*]chromene derivatives **186** in moderate-to-good yields (63–82%) (Scheme 57).

Seydimemet et al. [60] reported a simple approach to the synthesis of coumarin-containing dihydropyrano[2,3-*c*]pyrazoles **188** via four-component reaction of *β*-dicarbonyl compound **187**, phenylhydrazine **126**, aromatic aldehydes **7** and malononitrile **2**. The products **188** were obtained in good-to-high yields (78–90%) in the presence of L-proline as organocatalyst in EtOH under ultrasonic irradiation (Scheme 58).

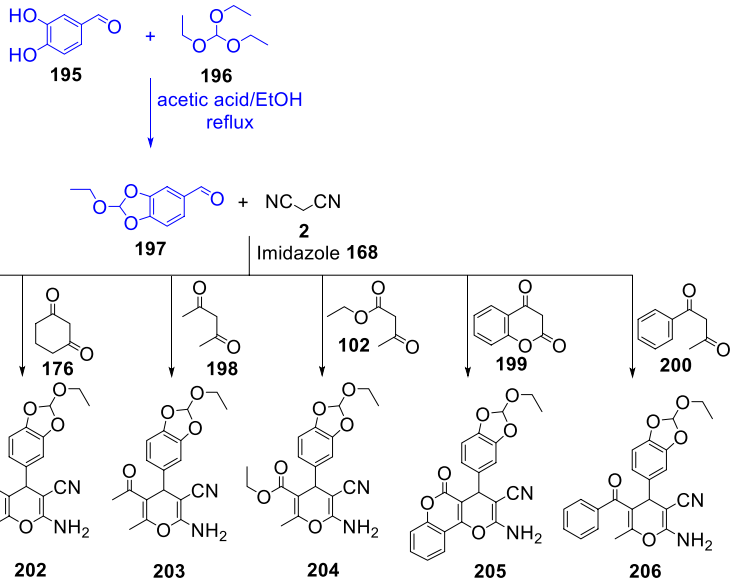
Li et al. [61] also used L-proline in the synthesis of spirooxindole derivatives **191** in good-to-high yields (76–95%) by three-component reaction of isatins **189**, malononitrile **2** (cyanoacetic ester) and 1,3-dicarbonyl compounds **190** in water (Scheme 59).

In another L-proline-catalyzed reaction, Poursattar Marjani et al. [62] synthesized 2-amino-4-aroyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles **194** in high yields (86–92%) from the reaction of arylglyoxal monohydrates **192**, 1,3-diketones **193** and malononitrile **2** in ethanol (Scheme 60).

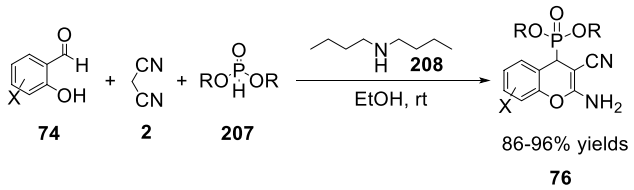
Baitha et al. [8] employed imidazole **168** as a catalyst to promote one-pot three-component coupling reaction of 2-ethoxybenzo[*d*][1, 3]dioxole-5-carbaldehyde **197**, malononitrile **2** and different active methylene groups in mixture of EtOH and H_2O (1:1) at room temperature. Under these circumstances, a new class of substituted 2-amino-4-(2-ethoxybenzo[*d*][1, 3]dioxol-5-yl)-4*H*-pyran-3-carbonitriles (**201**–**206**) were produced in high yields (88–92%) (Scheme 61). 2-Ethoxybenzo[d][1, 3]dioxole-5-carbaldehyde **197** was synthesized via treatment of 3,4-dihydroxybenzaldehyde **195** with triethyl orthoformate **196** in the presence of acetic acid in refluxing ethanol.

Kalla et al. [63] described for the first time the use of dibutylamine as a highly efficient organocatalyst in a multicomponent reaction of substituted salicylaldehydes **74**, malononitrile **2** and dialkylphosphites **207** in ethanol at ambient temperature. In this process, 2-amino-3-cyano-4*H*-chromen-4-ylphosphonates **76** were synthesized in good-to-excellent yields (86–96%) (Scheme 62).

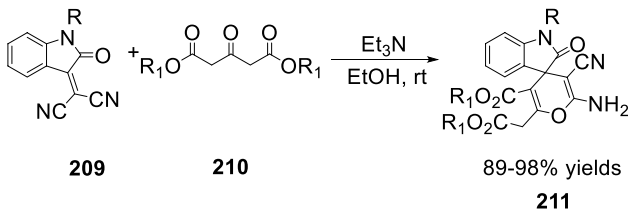
Satheesh et al. [64] reported the synthesis of spirooxindoles incorporating 2-aminopyran-3-carbonitrile unit **211** from the reaction of isatilidenes **209** and diethyl 1,3-acetone dicarboxylates **210** using triethylamine as an organic base in ethanol at room temperature. The desired products **211** were isolated in high-to-excellent yields (89–98%) (Scheme 63). A one-pot reaction of diethyl 1,3-acetone dicarboxylate **210**,



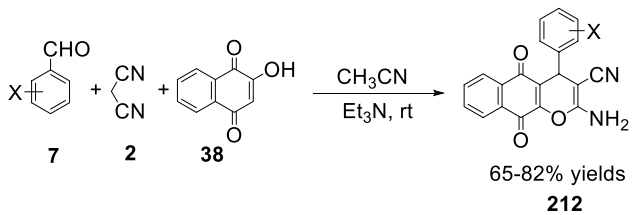
Scheme 61 Synthesis of 2-amino-4-(2-ethoxybenzo[*d*][1,3]dioxol-5-yl)-4*H*-pyran-3-carbonitriles (**201**–**206**) catalyzed by imidazole **168**



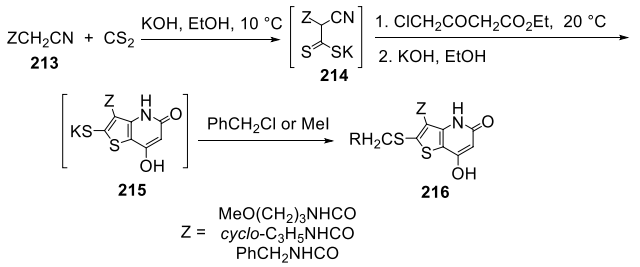
Scheme 62 Synthesis of 2-amino-3-cyano-4*H*-chromen-4-ylphosphonates **76** catalyzed by dibutylamine



Scheme 63 Synthesis of spirooxindoles incorporating 2-aminopyran-3-carbonitrile unit **211** using triethylamine



Scheme 64 Synthesis of functionalized benzo[*g*]chromene derivatives **212** in the presence of Et_3N

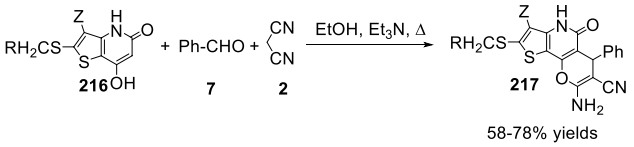


Scheme 65 Synthesis of substituted thieno[3,2*b*]pyridines **216**

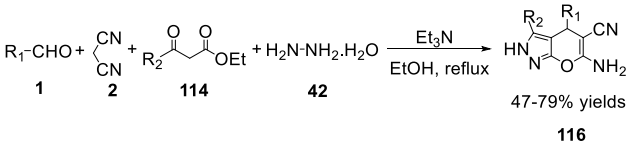
malononitrile **2** and isatin **136** was also conducted which resulted in the same product **211** (R = H, R_1 = Et).

Shaabani et al. [65] reported an efficient method for the synthesis of highly functionalized benzo[*g*]chromene derivatives **212** through addition and subsequent cyclization of 2-hydroxynaphthalene-1,4-dione **38** to the condensation product of the aromatic aldehydes **7** with malononitrile **2** in the presence of a catalytic amount of Et_3N. Various aldehydes **7** with electron-withdrawing and electron-donating groups afforded the corresponding benzo[*g*]chromene derivatives **212** in moderate-to-good yields (65–82%) at room temperature, without any undesirable by-product (Scheme 64).

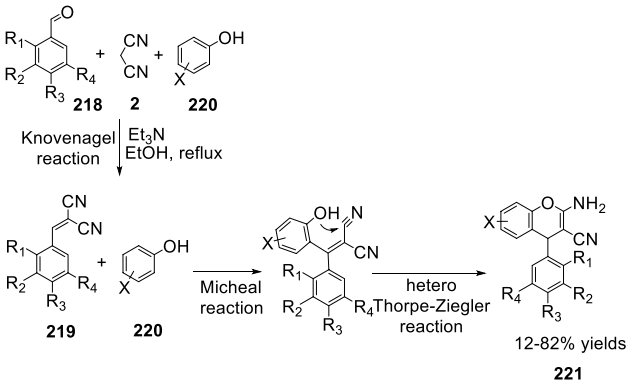
Larionova et al. [66] reported an original approach for the synthesis of substituted 5*H*-pyrano[2,3-*d*]-thieno[3,2-*b*]pyridines **217** from the substituted thieno[3,2-*b*]pyridines **216**. The synthesis started by the reaction of cyanoacetic acid amides **213** and carbon disulfide to generate monopotassium salt of carbamoylcyanodithioacetic acid **214**. Subsequently, regioselective alkylation of compound **214** with ethyl 4-chloroacetoacetate and then consecutive Thorpe–Ziegler and Thorpe–Guareschi reactions in the presence of an excess of KOH in ethanol produced thieno[3,2-*b*]-pyridine potassium salt **215**. Finally, alkylation with alkyl halides afforded



Scheme 66 Synthesis of 5*H*-pyrano[2,3-*d*]thieno[3,2-*b*]pyridines **217** from substituted thieno[3,2*b*]pyridines **216**



Scheme 67 Synthesis of substituted pyrano[2,3-*c*]pyrazoles **116** catalyzed by trimethylamine



Scheme 68 Synthesis of polyalkoxy 4-aryl-4*H*-chromenes **221**

compounds **216** (Scheme 65). The three-component reaction malononitrile **2** and aromatic aldehydes **7** with the synthesized thienopyridines **216** in the presence of trimethylamine-produced 5*H*-pyrano[2,3-*d*]thieno[3,2-*b*]pyridines **217** in moderate-to-good yields (58–78%) (Scheme 66).

Litvinov et al. [67] described a new four-component reaction of aldehydes **1**, malononitrile **2**, ketoesters **114** and hydrazine hydrate **42** (Scheme 67). The reaction was performed in the presence of trimethylamine in refluxing ethanol to afford substituted 6-amino-2*H*,4*H*-pyrano[2,3-*c*]pyrazol-5-carbonitriles **116** in moderate-to-good yields (47–79%).

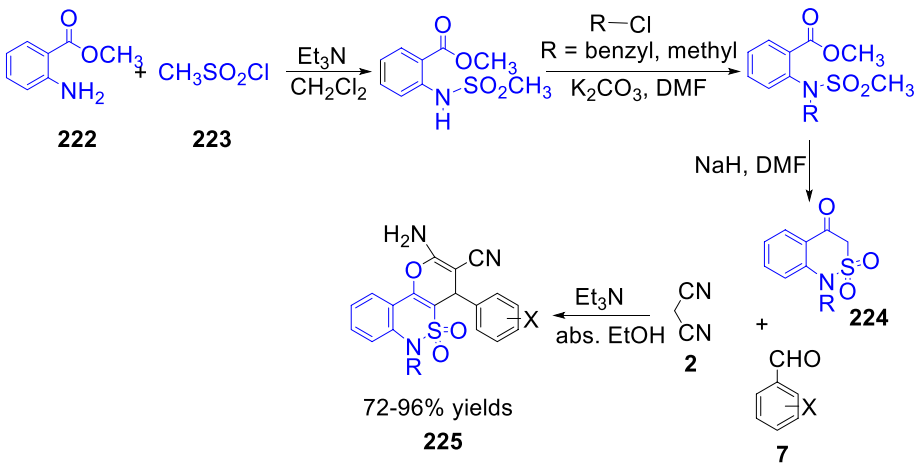
Preparation of polyalkoxy 4-aryl-4*H*-chromenes **221** via the three-component domino reaction of polyalkoxybenzaldehydes **218**, malononitrile **2** and phenols **220** was reported by Shestopalov et al. [68]. Initially, polyalkoxybenzylidene malononitriles **219** were obtained from the reaction of polyalkoxybenzaldehydes **218** with malononitrile **2** catalyzed by trimethylamine in refluxing EtOH. Michael reaction of polyalkoxybenzylidene malononitriles **219** and phenols **220** and then hetero-Thorpe–Ziegler reaction produced polyalkoxy 4-aryl-4*H*-chromenes **221** in low-to-good yields (12–82%) (Scheme 68).

Ahmad et al. [69] utilized MCR technique to get pyrano[1, 2]benzothiazines **225** in good-to-excellent yields (72–96%) through the reaction of benzothiazineenolates **224** with malononitrile **2** and various substituted benzaldehydes **7** in the presence of triethylamine as a catalyst (Scheme 69). The mesylation reaction of methyl anthranilate **222** with **223** and then *N*-benzylation/*N*-methylation reaction followed by cyclization with sodium hydride provide the required benzothiazineenolates **224**.

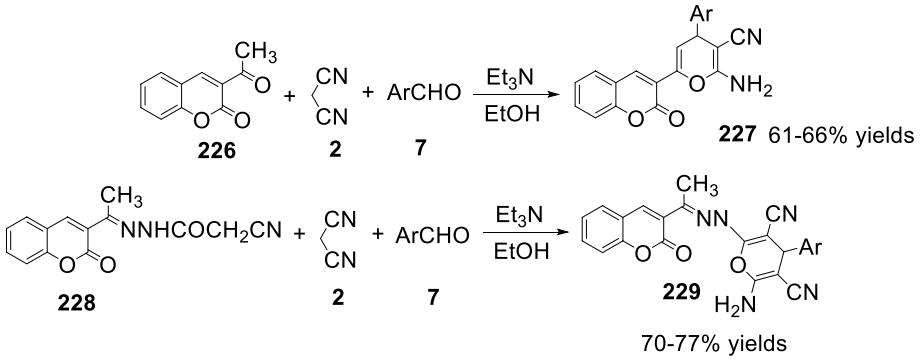
Abdo and Mohareb [70] reported the synthesis of a series of (2-oxo-2*H*-chromen-3-yl)-4*H*-pyran derivatives (**227**, **229**) in moderate-to-good yields (61–77%). These products **227**/**229** were prepared from a trimethylamine-catalyzed treatment of 3-acetylcoumarin **226**/compound **228**, malononitrile **2** and various benzaldehydes **7** in ethanol (Scheme 70).

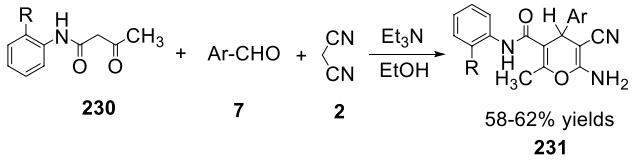
Azzam and Mohareb [71] reported the multicomponent reaction of acetoacetanilide derivatives **230** with aromatic aldehydes **7** and malononitrile **2**. Reactions catalyzed by

Scheme 69 Synthesis of pyrano[1, 2]benzothiazines **225**

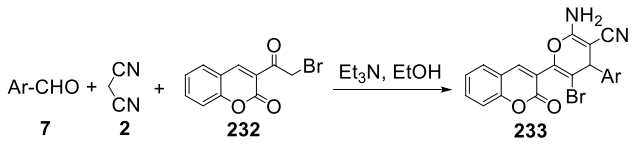


Scheme 70 Synthesis of derivatives of 2-oxo-2*H*-chromen-3-yl)-4*H*-pyran (**227**, **229**)

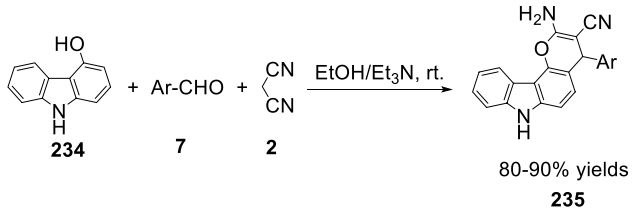




Scheme 71 Synthesis of 4*H*-pyran derivatives **231**



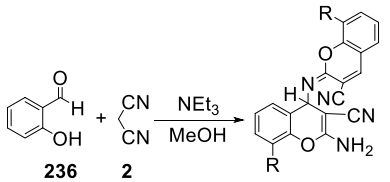
Scheme 72 Synthesis of 3-(2-bromoacetyl)-2*H*-chromen-2-ones **233** catalyzed by trimethylamine



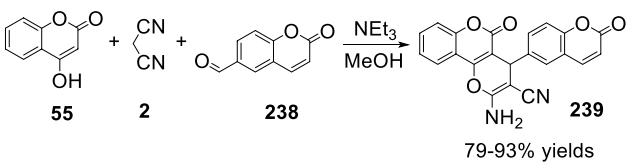
Scheme 73 Synthesis of novel pyrano[3,2-*c*]carbazoles **235**

triethylamine were conducted in absolute ethanol which led to 4*H*-pyran derivatives **231** in moderate yields (58–62%) (Scheme 71).

Mohareb and MegallyAbdo [72] used 3-bromoacetylcoumarin **232** for the synthesis of 2-amino-3-cyano-pyran derivatives **233**. 3-(2-Bromoacetyl)-2*H*-chromen-2-ones **233** were synthesized using three-component reaction of 3-bromoacetylcoumarin **232** (prepared from 3-bromoacetylcoumarin and potassium cyanide) with aromatic aldehydes **7** and malononitrile **2** in the presence of trimethylamine, respectively (Scheme 72).



Scheme 74 Synthesis of novel 2-iminochromene dimers **237**



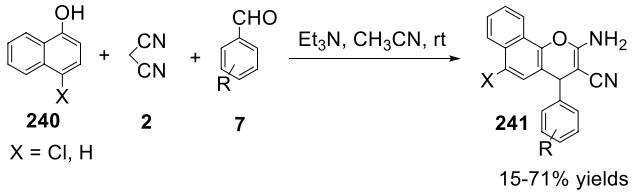
Scheme 75 Synthesis of biscoumarin fused with dihydropyran ring **239**

Padmaja et al. [73] conducted a simple one-pot, three-component reaction of aromatic aldehydes **7**, malononitrile **2** and 4-hydroxycarbazoles **234** catalyzed by trimethylamine in ethanol at room temperature. As they reported, pyrano[3,2-*c*]carbazole derivatives **235** were obtained in high yields (80–90%) under these circumstances (Scheme 73).

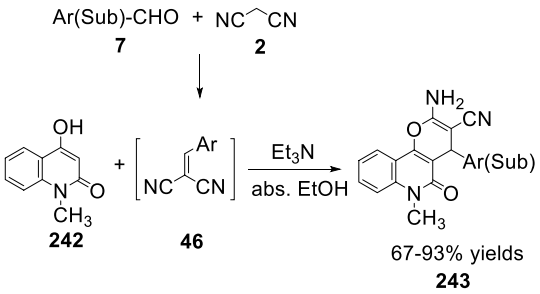
Costa et al. [74] reported the synthesis of novel 2-iminochromene dimers **237** in good yields (76–85%) from the combination of salicylaldehyde **236** with 2 equiv of malononitrile **2** in the presence of triethylamine in methanol at room temperature (Scheme 74).

Kalalbandi et al. [75] developed a synthetic route for the synthesis of biscoumarin fused with dihydropyran ring **239** in good-to-high yields (79–93%). The one-pot multicomponent reaction of 4-hydroxy coumarin **55**, formyl coumarin **238** and malononitrile **2** was carried out in the presence of catalytic amount of triethylamine in refluxing methanol (Scheme 75).

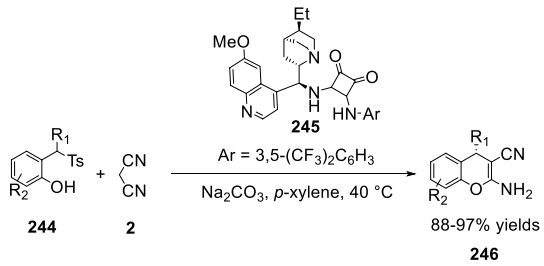
Schmitt et al. [9] prepared naphthopyran analogs of LY290181 **241** in low-to-good yields (15–71%). These



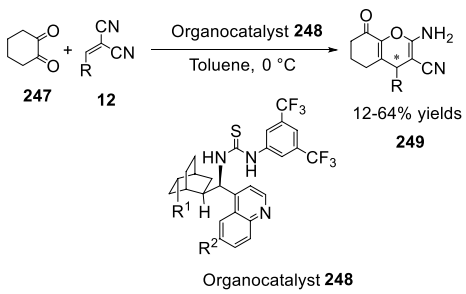
Scheme 76 Synthesis of naphthopyrans **241** in the presence of triethylamine



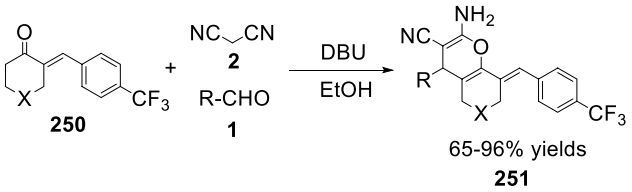
Scheme 77 Synthesis of pyrano[3,2-*c*]quinoline analogs **243**



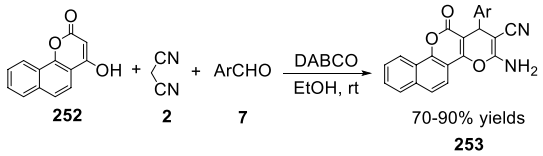
Scheme 78 Synthesis chiral 2-amino-4*H*-chromenes **246**



Scheme 79 Enantioselective synthesis of 2-amino-8-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles **249**



Scheme 80 Synthesis of novel 2-amino-4*H*-pyran derivatives **251** in the presence of DBU



Scheme 81 Synthesis of novel dihyrobenzo[*h*]pyrano[3,2-*c*]chromenes **253** in the presence of DABCO

compounds 100 were synthesized from a trimethylamine-catalyzed one-pot reaction of malononitrile **2** with benzaldehydes **7** and 1-naphtholes **240** in acetonitrile at room temperature (Scheme 76).

Upadhyay et al. [76] prepared pyrano[3,2-*c*]quinoline analogs **243** in good-to-high yields (67–93%) from the reaction of 2,4-dihydroxy1-methylquinolin **242**, aromatic aldehydes **7**, malononitrile **2** which was catalyzed by triethylamine in refluxing absolute ethanol (Scheme 77). Initially, the base-catalyzed Knoevenagel condensation between un(substituted) aromatic aldehydes **7** and malononitrile **2** results into cinnamic nitrile derivative **46**. The reaction of prepared cinnamic nitriles **46** in situ with 2,4-dihydroxy-1-methylquinolin **242** and then Michael addition and cyclization produced pyrano[3,2-*c*]quinolones **243**.

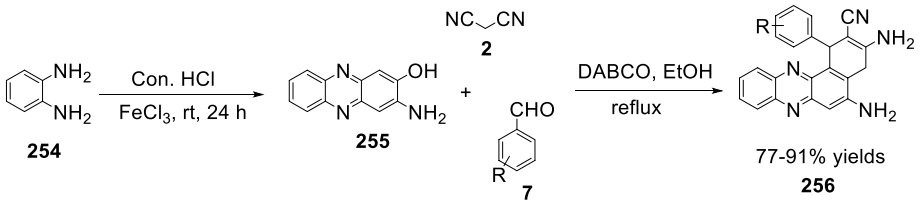
Wu et al. [77] synthesized chiral 2-amino-4*H*-chromenes **246** in high-to-excellent yields (88–97%) with excellent enantioselectivities. These compounds **246** were produced by the reaction of 2-(1-tosylalkyl)phenols **244** and malononitrile **2** under basic conditions catalyzed by asymmetric bifunctional squaramide **245** (Scheme 78).

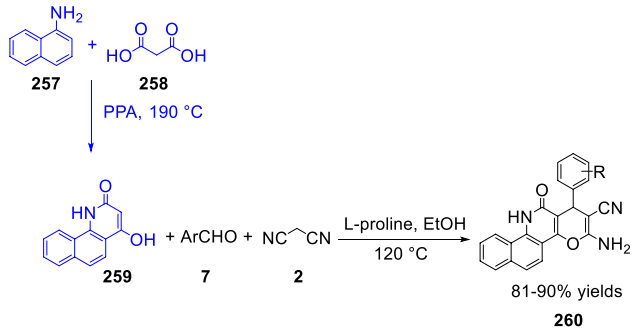
Ding and Zhao [78] reported the first enantioselective synthesis of 2-amino-8-oxo-tetrahydro-4*H*-chromene-3-carbonitriles **249** in low-to-moderate yields (12–64%). The tandem Michael addition–cyclization reaction between cyclohexane-1,2-dione **247** and benzylidenemalononitriles **12** in the presence of chiral cinchona alkaloid-derived thiourea organocatalysts **248** produced the desired products **249** (Scheme 79).

Wang et al. [79] reported a DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) mediated three-component reaction of aldehydes **1**, malononitrile **2** and *α*,*β*-unsaturated ketone derivatives **250** for the synthesis of a series of novel 2-amino-4*H*-pyran derivatives **251** in moderate-to-excellent yields (65–96%) (Scheme 80).

Esmati et al. [80] successfully accessed novel dihyrobenzo[*h*]pyrano[3,2-*c*]chromene derivatives **253** in good-to-high yields (70–90%). The DABCO (1,4-diazabicyclo[2.2.2]octane) mediated three-component reaction of 4-hydroxy-2*H*-benzo[*h*]chromen-2-one **252**, aromatic

Scheme 82 Facile synthesis of novel pyrano[3,2-*a*]phenazine derivatives **256**





Scheme 83 Synthesis of dihydropyrano[3,2-*c*]quinoline-2-carbonitrile derivatives **260**

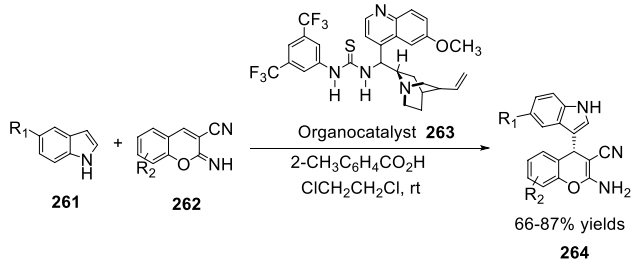
aldehydes **7** and malononitrile **2** in ethanol at room temperature resulted into the products **253** (Scheme 81).

Lu et al. [81] synthesized hybrid molecules of phenazine and pyran **256** in good-to-high yields (77–91%) in two steps. In the first step, 2-amino-3-hydroxyphenazine **255** was easily prepared by benzene-1,2-diamine **254** in the presence of $FeCl_3$ in acidic conditions. Subsequently, the resulting 2-amino-3-hydroxyphenazine **255** was reacted with malononitrile **2** and aromatic aldehydes **7** to afford a series of novel pyrano[3,2-*a*]phenazine derivatives **256** in the presence of DABCO under reflux conditions in ethanol (Scheme 82).

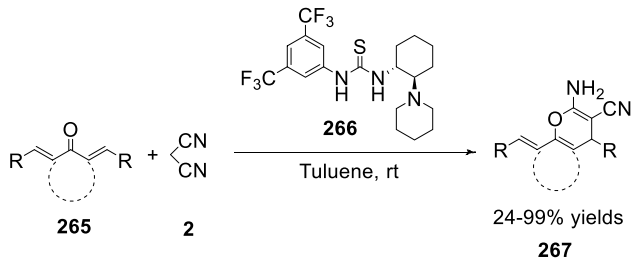
Nikookar et al. [82] synthesized dihydropyrano[3,2-*c*] quinoline-2-carbonitrile derivatives **260** in good-to-high yields (81–90%). Initially, the reaction of 1-naphthyl amine **257** and malonic acid **258** in the presence of PPA produced benzo[*h*]quinolin-2(1*H*)-one **259**. Then, the resulting benzo[*h*]quinolin-2(1*H*)-one **259** was reacted with various aromatic aldehydes **7** and malononitrile **2** using DABCO in EtOH to obtain dihydropyrano[3,2-*c*]quinoline-2-carbonitriles **260** (Scheme 83).

Gao and Du [83] succeeded in developing an efficient enantioselective method for preparation of functionalized 2-amino3-cyano-4-(indol-3-yl)-4*H*-chromenes **264**. Friedel–Crafts alkylation of indoles **261** with iminochromenes **262** were carried out in the presence of a thiourea organocatalyst **263** to afford the desired products **264** in moderate-to-good yields (66–87%) (Scheme 84).

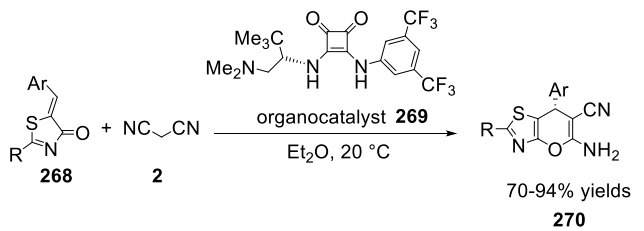
Hu et al. [84] described a cascade conjugate addition–intramolecular cyclization pathway for the synthesis of chiral pyran derivatives **267**. The reaction of malononitrile **2** with conformationally restricted dienones **265** catalyzed by



Scheme 84 Enantioselective synthesis of 2-amino-4-(indol-3-yl)-4H-chromenes **264**



Scheme 85 Synthesis of chiral pyran derivatives **267** catalyzed by piperidine-based thiourea–tertiary amine **248**

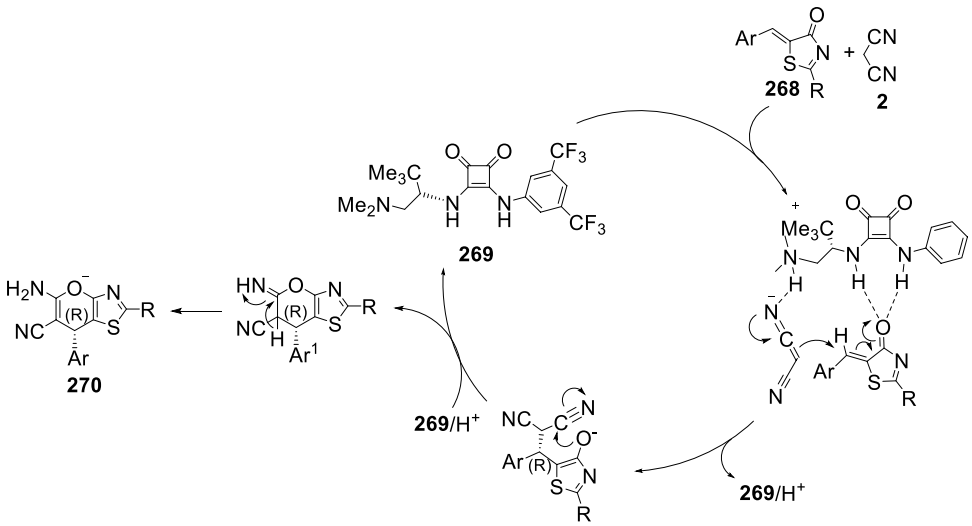


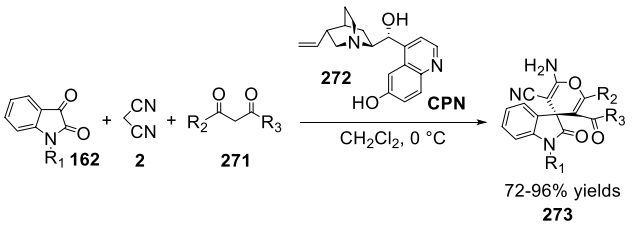
Scheme 86 [4 + 2] annulation of malononitrile **2** and 5-ylidenethiazol-4-ones **268**

piperidine-based thiourea-tertiary amine **266** afforded chiral pyran derivatives **267** in low-to-excellent yields (24–99%) with excellent enantioselectivities (Scheme 85).

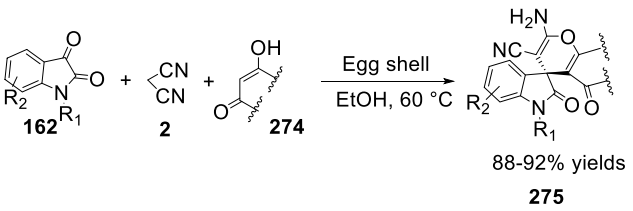
Cui et al. [85] developed the enantioselective synthesis of 7*H*-pyrano[2,3-*d*]thiazoles **270** in good-to-excellent yields (70–94%) from the reaction of malononitrile **2** with a wide range of 5-ylidenethiazol-4-ones **268**. The reaction was catalyzed by bifunctional squaramide derived from L-*tert*-leucine **269** as a chiral organocatalyst (Scheme 86). Proposed

Scheme 87 Proposed mechanism for the synthesis of 7*H*-pyrano[2,3-*d*]thiazoles **270**

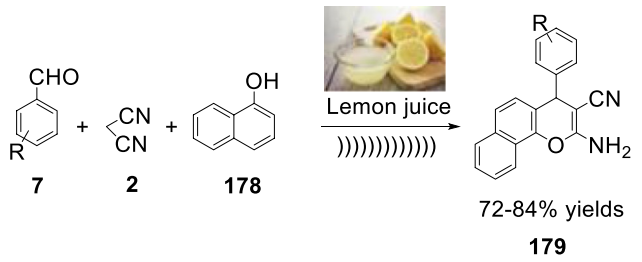




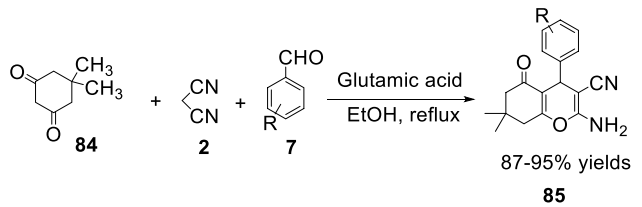
Scheme 88 Synthesis of optically active spiro[*4H*-pyran-3,3′-oxindoles] **273** catalyzed by cupreine (**CPN**)



Scheme 89 Synthesis of spiro[4*H*-pyran-oxindole] derivatives **275** catalyzed by egg shell



Scheme 90 The reaction of malononitrile **2**, aromatic aldehyde **7** and α-naphthol **178** catalyzed by lemon juice



Scheme 91 The reaction of dimedone **84**, aromatic aldehydes **7** and malononitrile **2** catalyzed by glutamic acid

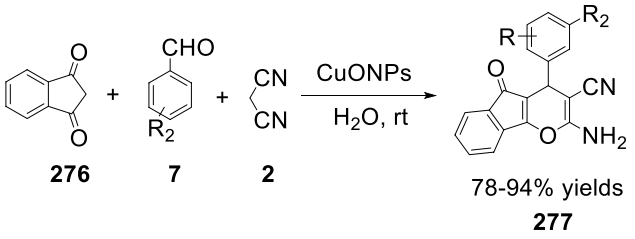
mechanism for this [4 + 2] cyclization reaction is shown in Scheme 87.

Chen et al. [86] developed the first enantioselective organocatalytic three-component reaction via a domino Knoevenagel/Michael/cyclization sequence. Cupreine (**CPN**) **272** as an organocatalyst was used for the synthesis of optically active spiro[*4H*-pyran-3,3′-oxindoles] **273** via the reaction of malononitrile **2**, isatins **162** and 1,3-diones **271** (Scheme 88). In this CPN-catalyzed method, the products **273** were obtained in good-to-excellent yields (72–96%).

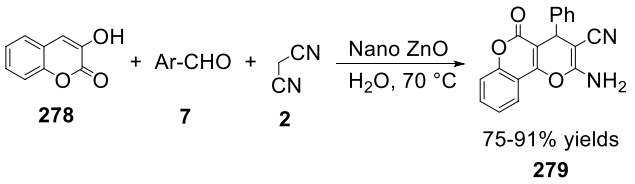
Youseftabar-Miri [87] utilized egg shell as a natural, green catalyst for the synthesis of spiro[4*H*-pyran-oxindole] derivatives **275** in high yields (88–92%) by one-pot multicomponent reaction of 1,3-diketones **274**, isatins **162** and malononitrile **2** (Scheme 89).

Bhosale et al. [88] synthesized 2-amino-4*H*-chromenes **179** in good yields (72–84%) by mixing malononitrile **2**, aromatic aldehyde **7** and *α*-naphthol **178** in lemon juice (as a natural catalyst) using ultrasound waves (Scheme 90).

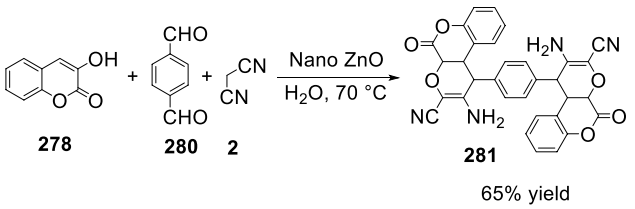
Hatamjafari [89] demonstrated glutamic acid as an efficient catalyst for the synthesis of 4*H*-chromenes **85** in good-to-excellent yields (87–95%) via a multicomponent reaction



Scheme 92 Synthesis of indeno-pyran derivatives **277** in one-pot reaction using CuO nanoparticles



Scheme 93 Synthesis of dihydropyrano[2,3-*c*]chromene derivatives **279** over nano ZnO



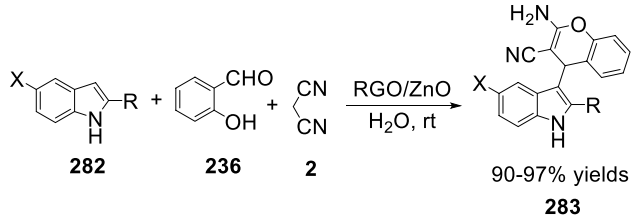
Scheme 94 Synthesis of compound **281** via reaction of terephthaldehyde **280**, malononitrile **2** and 3-hydroxycoumarin **278**

of dimedone **84**, aromatic aldehydes **7** and malononitrile **2** (Scheme 91).

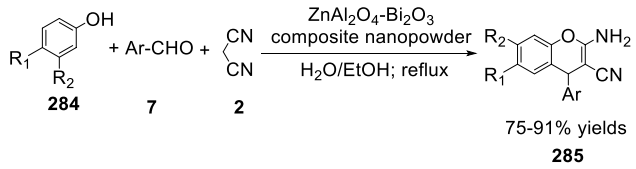
Nanoparticle/composite catalysts

Valekar et al. [90] synthesized indeno-pyran derivatives **277** in good-to-high yields (78–94%). Here, CuO nanoparticles catalyzed the one-pot reaction of malononitrile **2**, aromatic aldehydes **7** and indane 1,3-dione **276** in water at an ambient temperature (Scheme 92).

An efficient and green protocol for the synthesis of dihydropyrano[2,3-*c*]chromene derivatives **279** in good-to-high yields (75–91%) was reported by Paul et al. [91]. In this protocol, a one-pot, three-component coupling reaction of aromatic aldehyde **7**, malononitrile **2** and 3-hydroxycoumarin **278** using nanostructured ZnO as the catalyst produces the desired products **279** (Scheme 93). In this reaction, when terephthalaldehyde **280** is employed,



Scheme 95 RGO-/ZnO-catalyzed synthesis of 2-amino-4-(indol-3-yl)-*4H*-chromenes **283**



Scheme 96 Preparation of 4*H*-chromene-3-carbonitriles **285** using $ZnAl_2O_4$–Bi_2O_3 composite nanopowder

compound **281** with self-aggregating property is generated in moderate yield (65%) (Scheme 94).

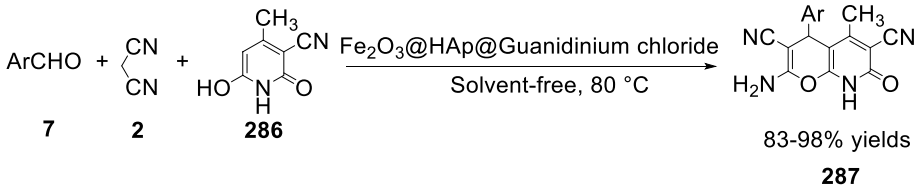
Rajesh et al. [92] introduced a nanocomposite consisting of reduced graphene oxide and zinc oxide nanoparticles (RGO/ZnO). They used this composite as an amphiphilic heterogeneous catalyst in the reaction of substituted indols **282**, malononitrile **2** and salicylaldehyde **236** in water to afford various indolyl-4*H*-chromenes **283** in high-to-excellent yields (90–97%) (Scheme 95).

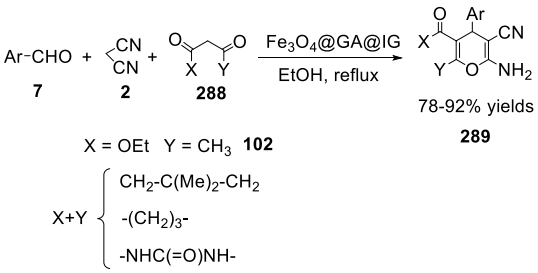
Ghashang [93] succeeded in developing a $ZnAl_2O_4$–Bi_2O_3 composite nanopowder-catalyzed one-pot synthesis of 2-4*H*-chromene-3-carbonitriles **285** in good-to-high yields (75–91%). The reaction of disubstituted phenols **284**, aromatic aldehydes **7** and malononitrile **2** in refluxing ethanol/water afforded the corresponding products **285** (Scheme 96).

Azarifar et al. [94] reported the synthesis of new pyranopyridine derivatives (2-amino-4-aryl-5-methyl-7-oxo-7,8-dihydro-4*H*-pyrano[2,3-*b*]pyridine-3,6-dicarbonitriles) **287** in good-to-excellent yields (83–98%). They carried out a one-pot three-component reaction between aromatic aldehydes **7**, malononitrile **2** and 3-cyano-6-hydroxy-4-methylpyridin-2(1*H*)-one **286** in the presence of guanidinium chloride-functionalized γ-Fe_2O_3/HAp magnetic nanoparticles under solvent-free conditions to afford the desired products **287** (Scheme 97).

Pourian et al. [95] reported a one-pot synthesis of 4*H*-pyran derivatives **289** in good-to-high yields (78–92%) by three-component reaction of various aromatic aldehydes **7**, malononitrile **2** and 1,3-dicarbonyl compounds **288**. These reactions were conducted in the presence of bionanocatalyst Fe_3O_4@GA@IG under ultrasonic irradiation in refluxing ethanol (Scheme 98).

Scheme 97 γ-Fe_2O_3@HAP-GndCl MNPs-catalyzed synthesis of new pyranopyridine derivatives **287**



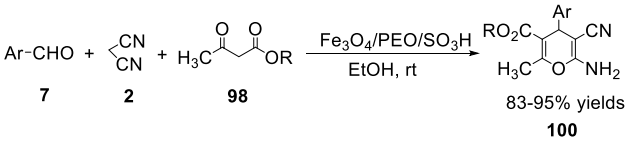


Scheme 98 The reaction of various aromatic aldehydes **7**, malononitrile **2** and 1,3-dicarbonyl compounds **288** catalyzed by Fe_3O_4@GA@IG

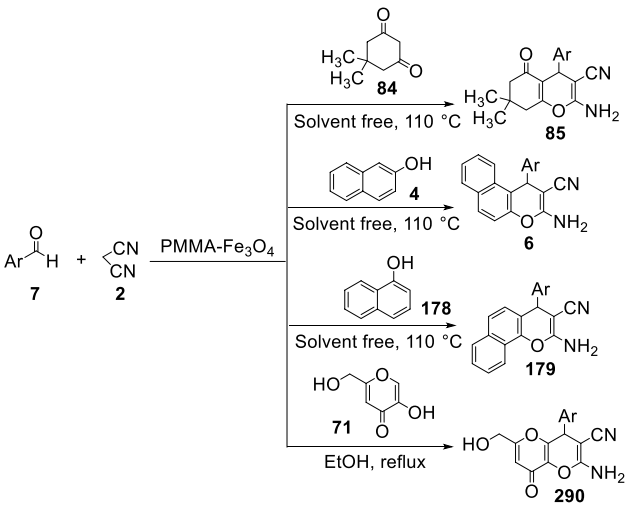
Azarifar et al. [96] used a Cu(II)-based Lewis acid as a heterogeneous nanocatalyst for the synthesis of new pyranopyridine derivatives **287** in excellent yields (82–98%). Fe_3O_4@SiO_2-acac-2ATP-Cu(II) catalyzed the one-pot three-component reaction of aromatic aldehydes **7**, malononitrile **2** and 3-cyano-6-hydroxy-4-methylpyridin-2(1*H*)-one **286** to afford 4*H*-pyrano[2,3-*b*]pyridine-3,6-dicarbonitriles **287** under solvent-free conditions (Scheme 99).

Maleki et al. [97] introduced a green protocol for multi-component synthesis of 2-amino-3-cyano-4*H*-pyranes **100** in good-to-excellent yields (83–95%). For this purpose, Fe_3O_4/PEO/SO_3H nanocatalyst was used in the reaction of aromatic aldehydes **7**, malononitrile **2** and methyl/ethyl acetoacetate **98** in absolute EtOH at room temperature (Scheme 100).

Eftekhari-Sis et al. [98] reported the synthesis of various chromene and pyran derivatives in moderate-to-excellent yields (61–96%) (Scheme 101) through a three-component reaction. In this method malononitrile **2**, substituted benzaldehydes **7** and phenolic or enolic components such as α-naphthol **178**, *β*-naphthol **4**, dimedone **84**



Scheme 100 Synthesis of 2-amino-3-cyano-4*H*-pyranes **100** catalyzed by Fe_3O_4/PEO/SO_3H

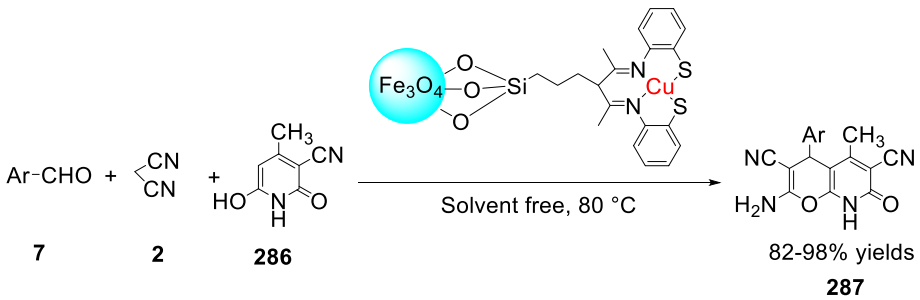


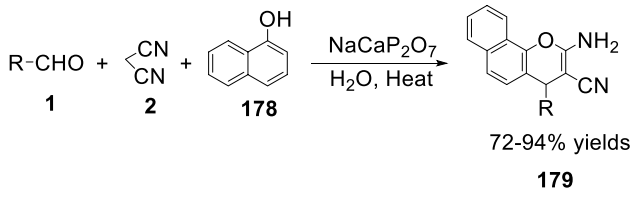
Scheme 101 The three-component reaction of malononitrile **2**, substitute benzaldehydes **7** and phenolic or enolic components catalyzed by PMAA-Fe_3O_4 nanorods

or kojic acid **71** were reacted in the presence of 2-[(2-pyridylmethyl)amino]acetic acid (PMAA)-functionalized Fe_3O_4 superparamagnetic nanorods as a catalyst.

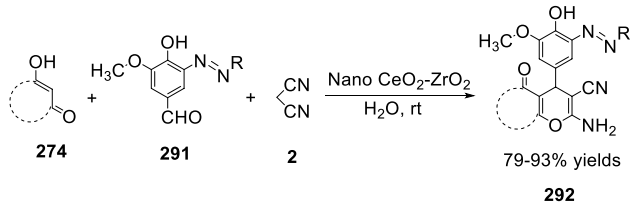
Solhy et al. [99] repeated this three-component reaction (between malononitrile **2**, α-naphthol **178** and various

Scheme 99 Synthesis of new pyranopyridine derivatives **287** catalyzed by Fe_3O_4@SiO_2-acac-2ATP-Cu(II)

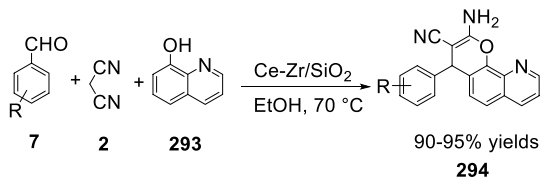




Scheme 102 The reaction of malononitrile **2**, α-naphthol **178** and various aldehydes **1** in the presence of $Na_2CaP_2O_7$



Scheme 103 Synthesis of 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted phenyldiazenyl)-chromene-3 carbonitriles **292** using nano-CeO_2–ZrO_2



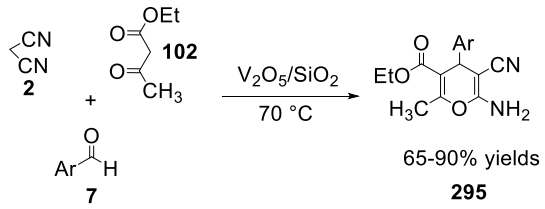
Scheme 104 Synthesis of pyranoquinolines **294** catalyzed by Ce-Zr/SiO_2

aldehydes **1**) using nanostructured diphosphate $Na_2CaP_2O_7$ (DIPH) as a basic catalyst. This aqueous green synthesis method successfully synthesized a series of 2-amino-chromenes **179** in good-to-excellent yields (72–94%) (Scheme 102).

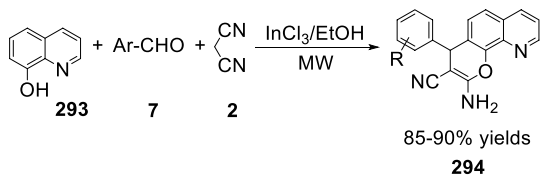
Sagar Vijay Kumar et al. [100] synthesized 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted phenyldiazenyl)-chromene-3-carbonitrile **292** in good-to-high yields (79–93%) from the reaction of 1,3-dicarbonyl compounds **274** (substituted phenyl-diazenyl) benzaldehydes **291** and malononitrile **2**. These reactions were catalyzed by nano-$CeO_2 - ZrO_2$ in water at room temperature (Scheme 103).

Transition metal catalysts

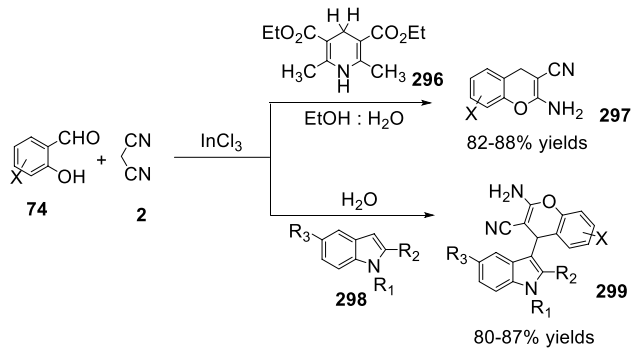
Baghbanian et al. [101] reported a one-pot three-component reaction between aromatic aldehydes **7**, malononitrile **2** and 8-hydroxyquenoline **293** in the presence of Ce-Zr/SiO_2 in ethanol that affords pyranoquinolines **294** in high yields (90–95%) (Scheme 104).



Scheme 105 The reaction of ethyl acetoacetate **102**, malononitrile **2** and aromatic aldehydes **7** in the presence of V_2O_5/SiO_2



Scheme 106 $InCl_3$-promoted synthesis of pyrano[3,2-*h*]quinolines **294** under microwave irradiation



Scheme 107 Synthesis of 2-amino-3-cyano-chromenes **297** and indolyl chromenes **299** catalyzed by $InCl_3$ in aqueous media

Mostafa and Khatab [102] obtained 4*H*-pyran derivatives **295** in moderate-to-high yields (65–90%) under solvent-free conditions. The desired products 295 were obtained through a one-pot reaction between ethyl acetoacetate (EAA) **102**, malononitrile **2** and aromatic aldehydes **7** in the presence of silica-supported V_2O_5 (V_2O_5/SiO_2) as a catalyst at 80 °C (Scheme 105).

An indium trichloride-catalyzed synthesis of pyrano[3,2-*h*]quinolines **294** in high yields (85–90%) was reported by the Kumar et al. [103]. The products **294** were produced by the reaction of malononitrile **2**, aromatic aldehydes **7** and quinolin-8-ol **293** in ethanol under microwave irradiation (Scheme 106).

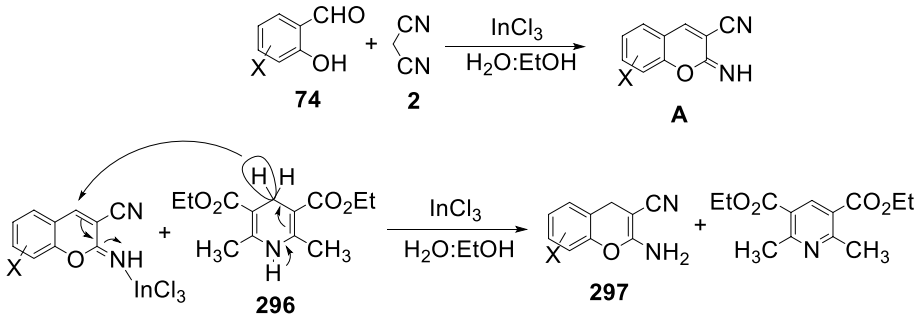
Perumal and Shanthi [104] reported another indium trichloride-catalyzed reaction of salicylaldehydes **74**, malononitrile **2** and Hantzsch dihydropyridine ester **296**

for the synthesis of new 2-amino-3-cyano-chromenes **297** in high yields (82–88%) in aqueous media (Scheme 107). Reaction of salicylaldehydes **74** with malononitrile **2** produced 2-imino-3-cyanocoumarin intermediate **A**. Hydride transfer from Hantzsch ester **296** to the electrophilic position of this intermediate **A** formed the final product **297** (Scheme 108). In this protocol, replacing the Hantzsch dihydropyridine ester **296** with indoles **298** under the same conditions led into the construction of novel indolyl chromenes **299** in high yields (80–87%) (Scheme 107).

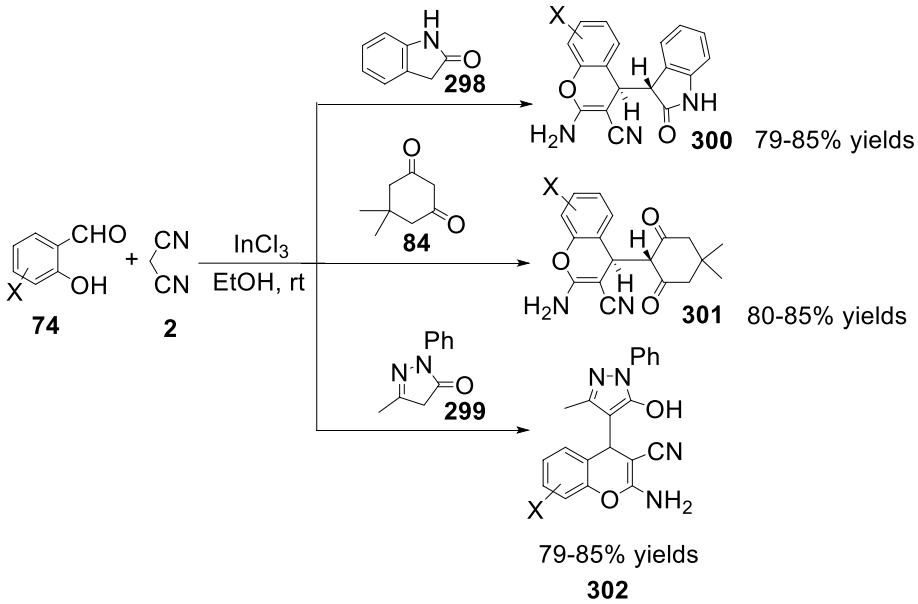
When Lakshmi et al. [105] examined the cyclic nucleophiles involving 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **299**, oxindole **298** and dimedone **84** under similar reaction conditions. Accordingly, a series of 4-substituted 2-amino-4*H*-chromenes (**300**–**302**) were synthesized in good yields (79–85%) and short reaction times (Scheme 109).

Yamuna and Rajendra Prasad [106] showed that pyrano[2,3-*a*]carbazoles (**304**, **305**) could be synthesized in high yields (90–95%) with a one-pot multicomponent reaction of benzaldehyde **7**/isatin **136** with malononitrile **2** and 1-hydroxycarbazoles **303** in the presence of $InCl_3$ as a catalyst in acetonitrile at 70 °C (Scheme 110).

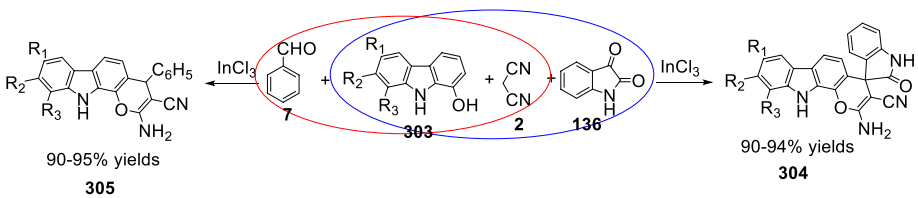
Heravi and Daraie [107] developed basic alumina-catalyzed synthesis of 6-amino-8-aryl-7-cyano-8*H*-[1, 3] dioxolo[4,5-*g*]chromenes **307** in high-to-excellent yields (92–97%). These compounds **307** were obtained from the condensation of 3,4-(methylenedioxy)phenol **306**,



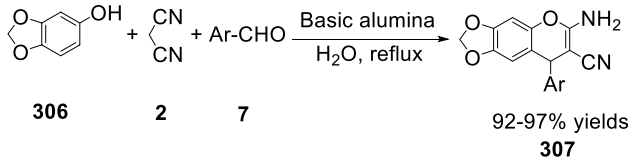
Scheme 108 Proposed mechanism for the synthesis of new 2-amino-3-cyano-chromenes **297** catalyzed by indium trichloride



Scheme 109 The reaction of salicylaldehydes **74** and malononitrile **2** with the cyclic nucleophiles catalyzed by indium trichloride

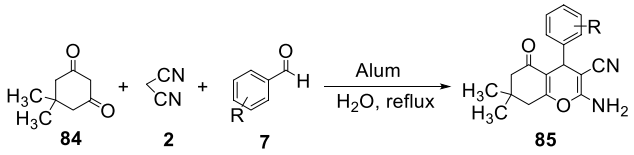


Scheme 110 Synthesis of pyrano[2,3-*a*]carbazoles (**304**, **305**) catalyzed by $InCl_3$



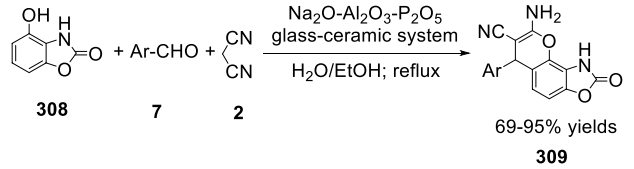
306 2 7 307

Scheme 111 Synthesis of 6-amino-8-aryl-8*H*-[1, 3]dioxolo[4,5-*g*] chromene-7-carbonitriles **307** catalyzed by basic alumina



84 2 7 85

Scheme 112 Synthesis of tetrahydro chromone derivatives **85** in the presence of potassium alum



308 7 2 309

Scheme 113 Preparation of 8-amino-6-aryl-1,2-dihydro-2-oxo-6*H*-pyrano[2,3-*e*]benzoxazole-7-carbonitriles **309** using Na_2O-Al_2O_3-P_2O_5 glass–ceramic system

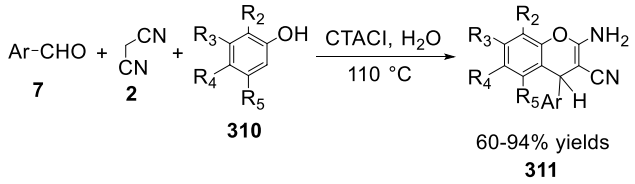
aromatic aldehydes **7** and malononitrile **2** in refluxing water (Scheme 111).

Pasdar et al. [108] synthesized tetrahydrochromone derivatives **85** by three-component condensation of benzaldehydes **7**, malononitrile **2** and dimedone **84** in the presence of potassium alum in refluxing water. The synthesized tetrahydrochromone derivatives **85** were used as ligand in the synthesis of metal complexes (Scheme 112).

Jabbarzare and Ghashang [109] demonstrated that glass–ceramic catalytic system (Na_2O–Al_2O_3–P_2O_5) can effectively catalyze the three-component coupling reaction, aromatic aldehydes **7**, malononitrile **2** and 4-hydroxy-2(3*H*)-benzoxazolone **308**. These reactions afforded 8-amino-6-aryl-1,2-dihydro-2-oxo-6*H*-pyrano[2,3-*e*]benzoxazole-7-carbonitrile derivatives **309** in good-to-excellent yields (69–95%) under reflux conditions in aqueous media (Scheme 113).

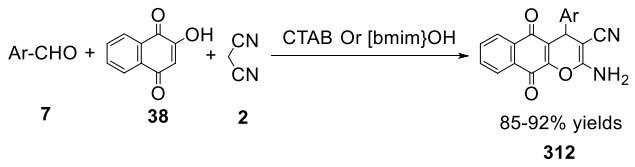
Phase transfer catalysts

Ballini et al. [110] reported a three-component one-pot reaction among aromatic aldehydes **7**, malononitrile **2** and phenols **310** to prepare 2-amino3-cyano-2-chromenes **311**



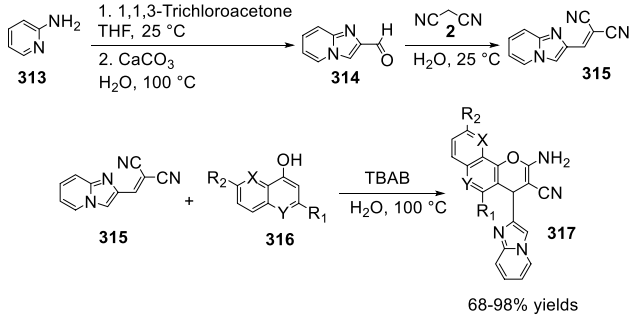
7 2 310 311

Scheme 114 Synthesis of 2-amino-3-cyano-2-chromenes **311** in aqueous media catalyzed by CTACl



7 38 2 312

Scheme 115 Synthesis of 4*H*-benzo[*g*]chromenes **312**



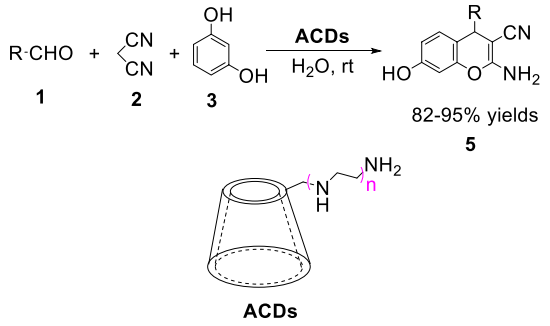
313 314 315 315 316 317

Scheme 116 Synthesis of imidazo[1,2-*a*]pyridine derivatives **317** catalyzed by TBAB

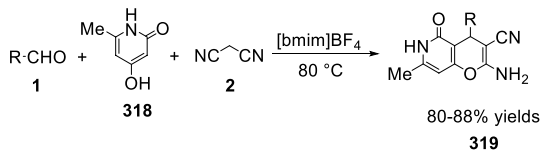
in moderate-to-excellent yields (60–94%). These reactions were carried out in the presence of cetyltrimethylammonium chloride (CTACl) in 110 °C in water (Scheme 114).

Khurana et al. [111] reported the synthesis of 4*H*-benzo[*g*]chromenes **312** in high yields (85–92%) through one-pot condensation of aromatic aldehydes **7**, malononitrile **2** and 2-hydroxy-1,4-naphthoquinone **38** using catalytic amount of cetyltrimethylammonium bromide (CTAB) in refluxing water under neat conditions. This reaction was also carried out in 1-butyl-3-methyl imidazolium hydroxide ([bmim]OH) ionic liquid as a catalyst (Scheme 115).

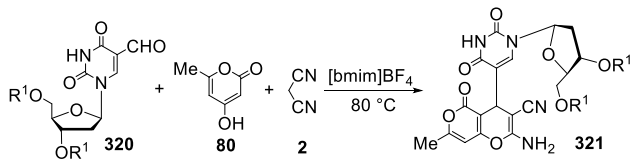
Haouchine et al. [112] synthesized imidazo[1,2-*a*]pyridine derivatives bearing 2-aminonicotinonitrile or 2-aminochromene moiety **317** using 2-(imidazo[1,2-*a*]pyridin-2-ylmethylene)malononitriles **315** as starting materials (Scheme 116). 2-(Imidazo[1,2-a]pyridin-2-ylmethylene) malononitriles **315** prepared from the reaction of 2-aminopyridine **313** and 1,1,3-trichloroacetone using the Chichibabin method followed by the reaction with malononitrile **2**



Scheme 117 The reaction of substituted aldehydes **1**, malononitrile **2** and resorcinol **3** catalyzed by ACDs



Scheme 118 Preparation of pyrano[3,2-*c*]pyridone **319**



Scheme 119 Synthesis of pyrano[3,2-*c*]pyridone nucleoside hybrids **321**

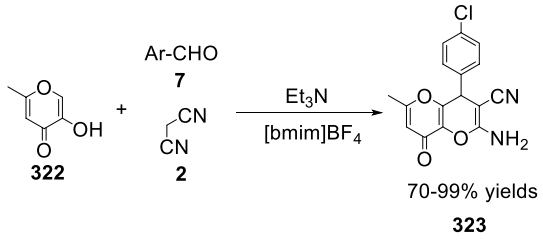
in water. The resulting 2-(imidazo[1,2-*a*]pyridin-2-ylmethylene)malononitriles **315** reacted with quinolinol derivatives **316** catalyzed by TBAB in water to afford the imidazo [1,2-*a*] pyridine derivatives **317** in good-to-excellent yields (68–98%).

Ren et al. [113] used a supramolecular catalyst for the synthesis of 2-amino-4*H*-chromenes **5** in good-to-excellent yields (82–95%). These compounds **5** were synthesized from the reaction of substituted aldehydes **1**, malononitrile **2** and resorcinol **3** catalyzed by amino-appended *β*-cyclodextrins (ACDs) in water at room temperature (Scheme 117).

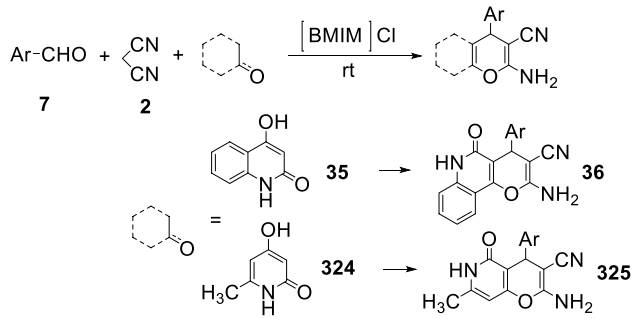
Ionic liquids

Fan et al. [114] reported [bmim]BF_4 mediated and promoted multicomponent reaction of aldehyde **1**, 4-hydroxypyridin-2(1*H*)-one **318** and malononitrile **2** for preparation of pyrano[3,2-*c*]pyridone derivatives **319** in good yields (80–88%) (Scheme 118).

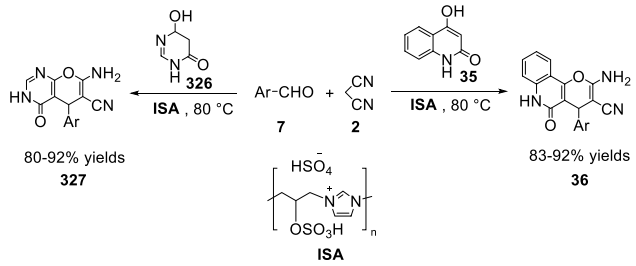
Fan et al. [114] following this general procedure, several pyrimidine nucleoside-pyrano[3,2-*c*]pyridone hybrids **321** synthesized from 5-formyl-20-deoxyuridine **320**, 4-hydroxy-6-methyl-2-pyranone **80** and malononitrile **2** in [bmim]BF_4 in 80 °C (Scheme 119).



Scheme 120 The reaction of aromatic aldehydes **7**, malononitrile **2** and 5-hydroxy-2-methyl-4*H*-pyran-4-one **323**



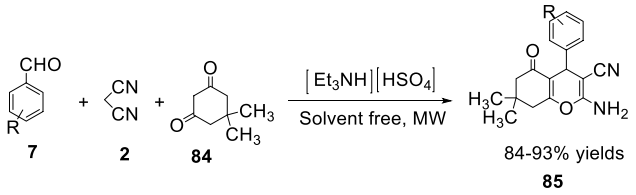
Scheme 121 ([BMIm]Cl) catalyzed synthesis of pyran motifs compounds (**36**, **325**)



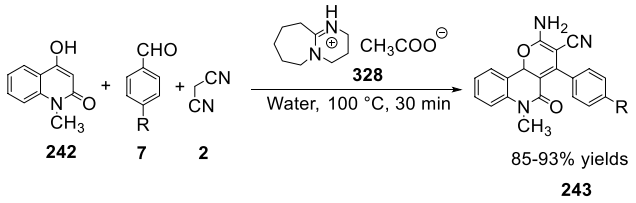
Scheme 122 Synthesis of pyrano[3,2-*c*]quinolines **36** and pyrano[2,3-*d*]pyrimidines **327** catalyzed by **ISA**

Li et al. [115] reported the synthesis of a series of 2-amino-4-aryl-4*H*,8H-6-methyl-8-oxo-pyrano[3,2-*b*]pyran derivatives **323** in good-to-excellent yields (70–99%). The Et_3N-catalyzed reaction of aromatic aldehydes **7**, malononitrile **2** and 5-hydroxy-2-methyl-4*H*-pyran-4-one **322** in [bmim]BF_4 as solvent afforded the desired products **323** (Scheme 120).

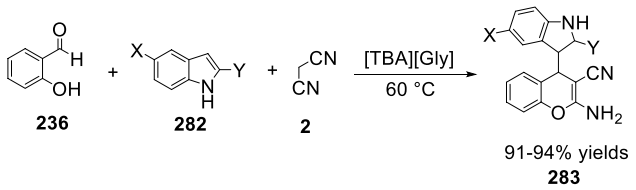
Abbaspour-Gilandeh et al. [116] advanced ([BMIm] Cl)-catalyzed synthesis of pyran motifs compounds (**36**, **325**) without using any solvent or additional catalyst. This protocol was carried out by multicomponent condensation of malononitrile **2**, aromatic aldehydes **7** and



Scheme 123 The reaction of aromatic aldehydes **7**, dimedone **84** and malononitrile **2** in the presence of $[Et_3NH][HSO_4]$



Scheme 124 Synthesis of dihydropyrano[3,2-*c*]quinolones **243** catalyzed by [DBU][Ac]



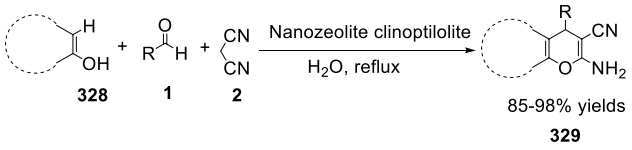
Scheme 125 One-pot synthesis of indol-3-yl-4*H*-chromenes **283** in the presence of [TBA][Gly]

4-hydroxy-6-methylpyridin-2(1*H*)-one **324**/4-hydroxyquinolin-2(1*H*)-one **35** (Scheme 121).

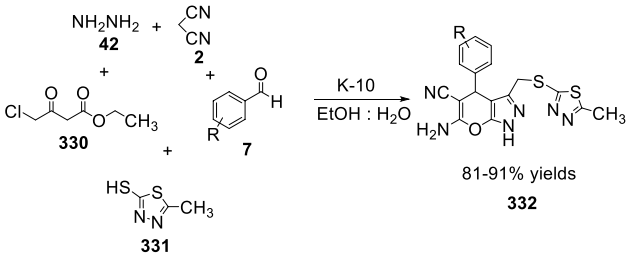
Tashrifi et al. [117] also planned and used ionene sulfuric acid **ISA** as both acidic catalyst and solvent in the synthesis of pyrano[3,2-*c*]quinolines **36** and pyrano[2,3-*d*]pyrimidines **327** in high yields (80–92%). The synthesis of these compounds **36**/**327** was performed by the three-component reaction of 4-hydroxyquinolin-2-one **35**/6-hydroxytetrahydropyrimidin-4-one **326** with malononitrile **2** and substituted aromatic aldehydes **7**, respectively (Scheme 122).

Mane et al. [118] synthesized 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(3,4-substituted phenyl)-5-oxo-4*H*-chromene-3-carbonitrile derivatives **85** in good-to-high yields (84–93%) utilizing triethylamine hydrogen sulfate $[Et_3NH][HSO_4]$ as ionic liquid catalyst under solvent-free conditions and microwave irradiation. The synthesis was successfully carried out via one-pot multicomponent cyclocondensation reaction of aromatic aldehydes (3, 4-substituted) **7**, dimedone **84** and malononitrile **2** (Scheme 123).

Bhupathi et al. [119] prepared a wide range of dihydropyrano[3,2-*c*]quinolones **243** in high yields



Scheme 126 Synthesis of 2-amino-4*H*-chromene derivatives **329** in the presence of nanozeolite clinoptilolite



Scheme 127 Synthesis of new derivatives of dihydropyranopyrazoles **332** catalyzed by K-10

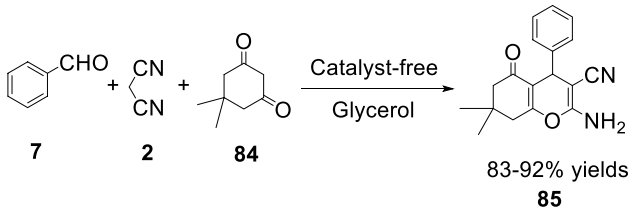
(85–93%) in the presence of {(1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate)}[DBU][Ac] **328** under mild reaction conditions. These products **243** were obtained by treatment of 1-methylquinoline-2,4(1*H*,3*H*)-dione **242**, aromatic aldehydes **7** and malononitrile **2** (Scheme 124).

Rajesh et al. [120] used a biodegradable organocatalyst [TBA][Gly] for the synthesis of 2-amino3-cyano-4-(indol-3-yl)-4*H*-chromenes **283** in high yields (91–94%). The reaction of malononitrile **2**, salicylaldehyde **236** and indoles **282** in the presence of tetrabutylammonium glycinate [TBA][Gly] at 60 °C under solvent-free conditions generated indolyl-4*H*-chromenes **283** in excellent yield (Scheme 125).

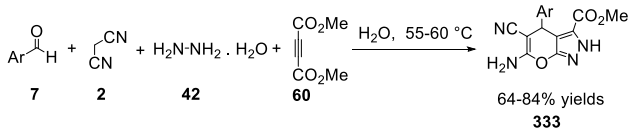
Zeolites

Using nanopowder of natural clinoptilolite (CP) zeolite as a green and reusable catalyst, Baghbanian et al. [101] reported the synthesis of a wide range of 2-amino-3-cyano-4*H*-chromene derivatives **329**. These products **329** were obtained in high-to-excellent yields (85–98%) via reaction of aldehydes **1**, malononitrile **2** and a variety of enolizable C–H-activated acidic compounds **328** (Scheme 126).

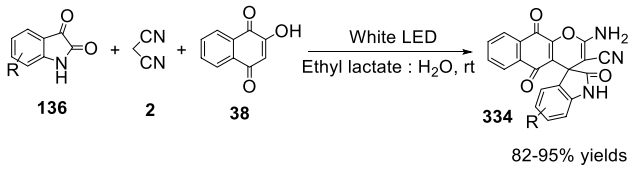
Reddy et al. [121] applied montmorillonite K10 clay as a green acid catalyst in the multicomponent reaction of ethyl 4-chloro-3-oxobutanoate **330**, 5-methyl-1,3,4-thiadiazole-2-thiol **331**, hydrazine hydrate **42**, malononitrile **2** and aryl aldehydes **7** in mixture of solvents ($EtOH:H_2O$). In this method, the new derivatives of dihydropyranopyrazoles **332** were generated in high yields (81–91%) (Scheme 127).



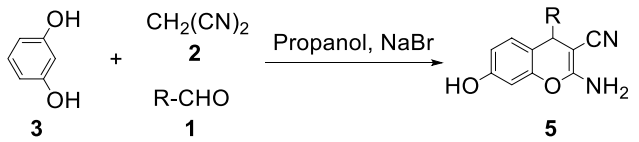
Scheme 128 The catalyst-free condensation reaction between benzaldehydes **7**, dimedone **84** and malononitrile **2**



Scheme 129 Four-component synthesis of 3-methyl carboxylate-substituted pyrano[2,3-*c*]pyrazoles **333** in water



Scheme 130 The visible-light-promoted reaction of isatins **136**, malononitrile **2** and 2-hydroxynaphthalene-1,4-dione **38**

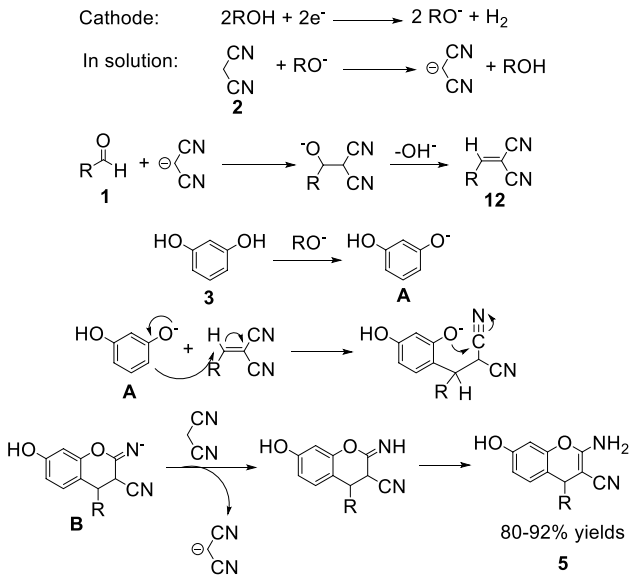


Scheme 131 A multicomponent electro-organic synthesis of 2-amino-3-cyano-4*H*-chromenes **5**

Catalyst-free

Safaei et al. [122] developed a green and versatile method for the synthesis of 4*H*-pyrans **85** in good-to-high yields (83–92%) under catalyst-free conditions using glycerol as a biodegradable medium. Under this condition, the desired products **85** were obtained from the reaction of aromatic aldehydes **7**, dimedone **84** and malononitrile **2** (Scheme 128).

Zonouz et al. [123] developed a four-component reaction of dimethyl acetylenedicarboxylate **60**, hydrazine hydrate **42**, malononitrile **2** and aromatic aldehydes **7** in water. In their green and facile method, methyl



Scheme 132 Proposal mechanism for the electro-organic synthesis of 2-amino-3-cyano-4*H*-chromenes **5**

6-amino-5-cyano-4-aryl-2,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylates **333** were synthesized in good yields (64–84%) (Scheme 129).

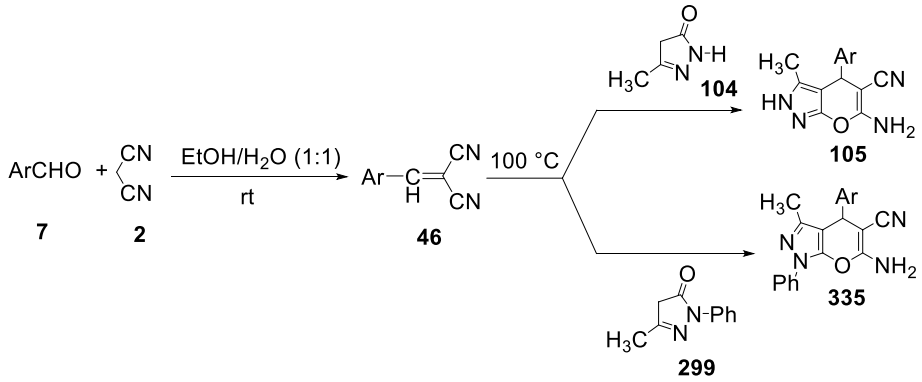
Zhang et al. [124] reported a novel visible-light-promoted three-component reaction of isatins **136**, malononitrile **2** and 2-hydroxynaphthalene-1,4-dione **38** in aqueous ethyl lactate at room temperature that affords spirooxindole-pyran derivatives **334** was obtained in good-to-excellent yields (82–95%) (Scheme 130).

Makarem et al. [125] prepared 2-amino-4*H*-chromenes **5** from the multicomponent condensation of resorcinol **3**, malononitrile **2** and various aldehydes **1** in an undivided cell in the presence of NaBr as an electrolyte (Scheme 131).

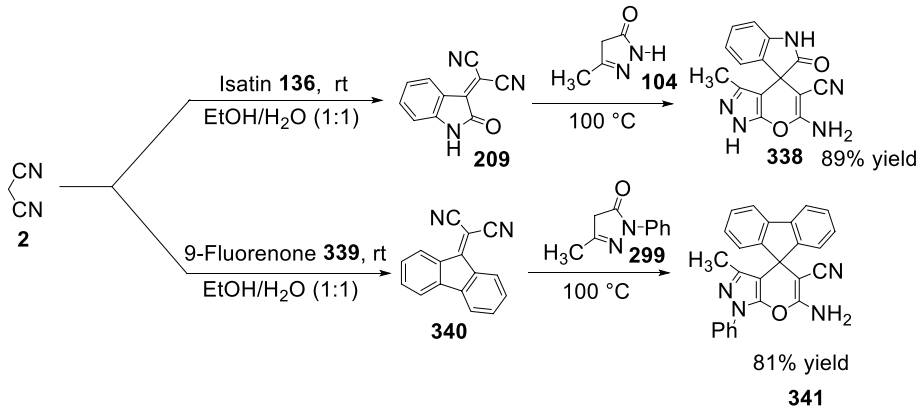
Based on the proposed mechanism shown in Scheme 132, deprotonation of alcohol **3** and malononitrile **2** at the cathode leads to the formation of an alkoxide **A** and malononitrile anion, respectively [125]. Next, 2-benzylidenemalononitrile intermediate **12** is generated from the condensation of the aldehyde **1** with malononitrile anion **2** through elimination of hydroxide. Then, phenol **3** C-alkylation and cyclization through nucleophilic attack of the alkoxide on the cyano moiety produces **B**. Finally, the desired 2-amino-4*H*-chromenes **5** is produced in good-to-high yields (80–92%) from protonation and rearrangement of **B**.

Mandha et al. [1] reported a green approach for the construction of substituted pyrano[2,3-*c*]pyrazoles (**305**, **335**) under non-catalytic conditions (Scheme 133). Initially, the Knoevenagel condensation of aromatic aldehydes **7** with malononitrile **2** in EtOH at room temperature gave intermediate **46**. A Michael addition reaction and subsequent

Scheme 133 Synthesis of various substituted pyrano[2,3-*c*] pyrazoles (**105**, **335**)

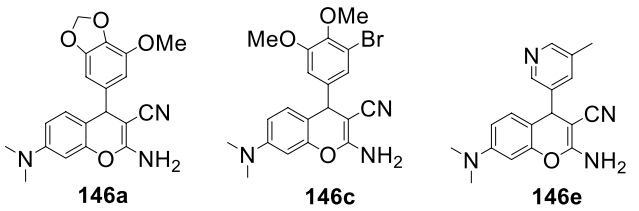


Scheme 134 Synthesis of spiroindoline and spirofluorene-substituted pyrano[2,3-*c*] pyrazoles (**338**, **341**)



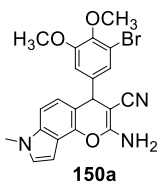
intramolecular cyclization of 3-methyl-1*H*-pyrazol-5(4*H*)-one 104/5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **299** with intermediate **46** afforded various substituted pyrano[2,3-*c*]pyrazoles **105**/**335** in moderate-to-high yields (64–93%).

Mandha et al. [1] with the same method also successfully synthesized spiroindoline- and spirofluorene-substituted pyrano[2,3-*c*]pyrazoles (**338**, **341**) in high yields (89 and 81%) with isatin **136** and 9-fluorenone **339**, respectively (Scheme 134).



Scheme 135 Structure of 2-1amino-3-cyano-4-aryl-4*H*-chromenes **146a**, **146c** and **146e**

Scheme 136 Structure of 4-Aryl-4*H*-chromene **150a**



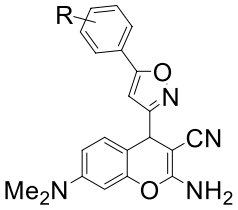
Biological activities of the synthesized polysubstituted 2-amino-4*H*-pyran-3-carbonitriles

Anticancer activity

Kemnitzer et al. [51] tested the synthesized 2-amino-3-cyano-4-aryl-4*H*-chromenes **146** for anticancer activities against T47D breast cancer cells. 2-Amino-3-cyano-7-(dimethylamino)-4-(3-methoxy-4,5-methylenedioxyphenyl)-4*H*-chromene **146a** induced apoptosis as determined by the flow cytometry analysis assay in multiple human cell lines (e.g., Jurkat, T47D). Compounds **146c** and **146e** had good activity in the caspase activation assay against T47D breast cancer cells with EC_{50} values of 19 and 11 nM, respectively. Compound **146c** was found to be a potent inhibitor of tubulin polymerization and effectively inhibited the binding of colchicine to tubulin (Scheme 135).

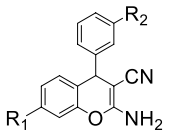
2-Amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-4,7-dihydro-7-methyl-pyrano[2,3-*e*]indole **150a** was explored by Cai et al. [7] as a novel anticancer agent.

Scheme 137 The general structure of 4-(5-arylisoxazol-3-yl)-4*H*-chromenes **156**



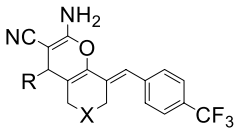
156c R=4-F
156j R=3-CH_3
156k R=4-CH_3

Scheme 138 The general structure of 4-aryl-4*H*-chromene-3-carbonitriles **161**



161c R_1=OCH_3 R_2=Br
161d R_1=OCH_3 R_2=Cl
161e R_1=OCH_3 R_2=F

Scheme 139 The general structure of 2-amino-4*H*-pyran derivatives **251**

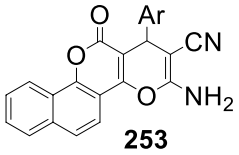


251a R=2-naphyhyl
251b R=3-NO_2-C_6H_5

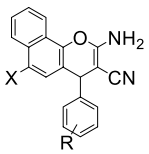
Compound **150a** also showed low nanomolar or subnanomolar inhibition of cell growth, and inhibited tubulin polymerization. Moreover, structure **150** was recognized as a highly potent apoptosis inducer with an EC_{50} (loss of half of the microtubuli) value of 2 Nm and a highly potent inhibitor of cell growth with a GI_{50} value of 0.3 nM in T47D cells (Scheme 136).

Shafiee et al. [52] reported a new series of 4-aryl-4*H*-chromenes bearing a 5-arylisoxazol-3-yl moiety at the C-4 position **156** as potential anticancer agents. These compounds **156** were tested against a panel of tumor cell lines including MCF-7 (breast cancer), KB (nasopharyngeal epidermoid carcinoma), Hep-G2 (liver carcinoma), MDA-MB-231 (breast cancer) and SKNMC (human neuroblastoma) using the MTT colorimetric assay, and their IC_{50} values were measured. Doxorubicin, a well-known anticancer drug, was used as the positive standard drug. Compounds **156c**, **156j** and **156 k** were the most potent of the series and displayed good activity against all tested cell lines with IC_{50} values of 6.5 ± 1.4 to 12.3 ± 0.5 mM. SAR studies showed that 3-methylphenyl-substituted analog **156j** was the most potent compound of this series against all tested cell lines (Scheme 137).

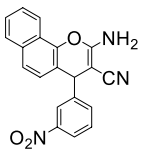
Scheme 140 The general structure of dihyrobenzo[*h*]pyrano[3,2-*c*]chromenes **253**



253



241



LY290181

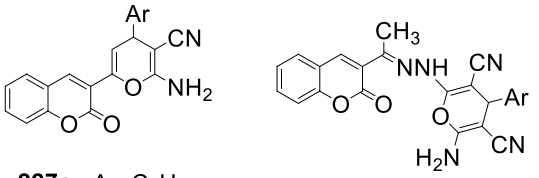
Scheme 141 Structure of naphthopyrans **241** and **LY290181**

Thomas et al. [54] tested the synthesized new 4-aryl-4*H*-chromene-3-carbonitrile derivatives **161** for anticancer activities in vitro. Compounds **161c–e** showed good anticancer activity against MCF-7 cell lines (CTC50 less than 62.5 µg/m) as compared to other derivatives of the series (Scheme 138).

Wang et al. [79] reported the synthesis of a series of novel 2-amino-4*H*-pyran derivatives **251** in excellent yields (Scheme 139). All derivatives were tested for antitumor activity against three human tumor cell lines, including human colon cancer (HCT116), human cervical cancer (Hela) and non-small cell lung cancer (H1975). At concentrations of 20 µmol/L, compounds **251a**, **251b** displayed noticeable growth inhibitory activity against the subtotal tested subpanel tumor cell lines; although other compounds exhibited some antitumor activity at concentrations of 10 µmol/L or lower, none of them came up with a profound inhibitory effect.

Esmati et al. [80] tested the novel dihyrobenzo[*h*]pyrano[3,2-*c*]chromene derivatives **253** for in vitro cytotoxic activity. Most of the synthesized compounds have no effect on HL-60 and MOLT4 cell lines (the IC50 of these analogs was higher than 50 or 100 mM), and their inhibitory activity levels against tumor cell line are mainly low, i.e., at micromolar concentrations range (Scheme 140).

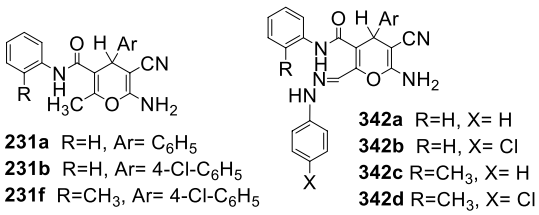
Schmitt et al. [9] synthesized 2-amino-4-phenyl-4*H*-naphtho(1,2-*b*)pyran-3-carbonitriles **241** and observed the best activities for the compounds that bear small substituents at the meta position of the phenyl ring. Sterically more demanding substituents such as benzyl or SF_5 probably obstruct naphthopyran–tubulin approach. **LY290181** caused a mitotic catastrophe leading to apoptosis in 518A2 melanoma cells, whereas naphthopyrans **241** induced a disruption of the vasculature in the chorioallantoic membrane (CAM) of fertilized chicken eggs as well as in xenograft tumors in mice (Scheme 141).



227a Ar=C_6H_5
227c Ar=4-Cl-C_6H_5

229c Ar=4-Cl-C_6H_5

Scheme 142 The general structure of 4*H*-pyrans **227** and **229**

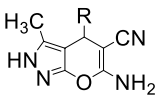


231a R=H, Ar= C_6H_5
231b R=H, Ar= 4-Cl-C_6H_5
231f R=CH_3, Ar= 4-Cl-C_6H_5

342a R=H, X= H
342b R=H, X= Cl
342c R=CH_3, X= H
342d R=CH_3, X= Cl

Scheme 143 The general structure of 4*H*-pyran derivatives **231** and **342**

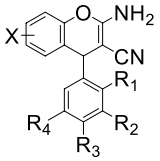
Scheme 144 The general structure of substituted pyrano[2,3-*c*] pyrazole **105**



105i R=3-OC_6H_5-C_6H_5

Mohareb and Abdo [70] evaluated in vitro anticancer activity of 4*H*-pyrans **227** and **229** against six human cancer cell lines including cells derived from human gastric cancer (NUGC), human colon cancer (DLD1), human liver cancer (HA22T and HEPG2), human breast cancer (MCF), nasopharyngeal carcinoma (HONE1) and normal fibroblast cells (WI38). Among the 4*H*-pyran derivatives **227**, compounds **227a**, **227c** were the most potent. The compound **227c** exhibited high potency toward six cancer cell lines, while compound **227a** analog was only potent against four cancer cell lines, namely NUGC, DLD1, HA22T and MCF with IC50 values of 48, 59, 122 and 480 nM, respectively. Similarly, among the 4*H*-pyran derivatives **229**, the highest activities were found for compound **229c** with remarkable activity against six human cancer cell lines (Scheme 142).

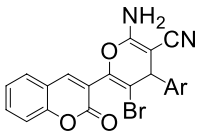
Azzam et al. [71] reported 4*H*-pyran derivatives **231** and **342** with antitumor activities. These compounds **231** and **342** were tested for antitumor activity against six human cancer and normal cell lines including cells derived from human gastric cancer (NUGC), human colon cancer (DLD1), human liver cancer (HA22T and HEPG2), human breast cancer (MCF) and nasopharyngeal carcinoma (HONE1) as well as a normal fibroblast cells (WI38). The results showed that compounds **231a**, **231b**, **231f** and most of **342** analogs had optimal cytotoxic effect against cancer cell lines as they had $IC_{50} < 550$ nM. Compounds **231f** and **342a**–**d** showed no toxicity against shrimp larvae (Scheme 143).



221a X=7-OCH_3 R_1=H R_2, R_3, R_4=OCH_3
221b X=7-NH_2 R_1=H R_2=OCH_3 R_3, R_4=H
221c X=7-N(C_2H_5)$_2$ R_1=H R_2=OCH_3, R_3, R_4=OCH_2O
221d X=6,7-OCH_2O R_1=H R_2=OCH_3 R_3, R_4=H
221e X=6,7-OCH_2O R_1=H R_2=OCH_3, R_3, R_4=OCH_2O

Scheme 145 The general structure of polyalkoxy-substituted 4-aryl-4*H*-chromenes **221**

Scheme 146 The general structure of 2-amino-3-cyano-pyran derivatives **233**



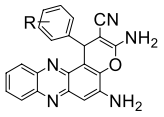
233a Ar=2-furyl
233b Ar=4-Cl-C_6H_5

Alla et al. synthesized substituted pyrano[2,3-*c*]pyrazoles **105** and evaluated their cytotoxic activity against MCF-7 (breast cancer cell line) by MTT assay with Taxol as a standard Ref. [1]. Among all synthesized compounds, compound **105i** was the most effective one with IC50 = 1.630 lg/mL (Scheme 144).

Shestopalov et al. [68] evaluated the synthesized 4-aryl-4*H*-chromenes **221** in a phenotypic sea urchin embryo assay for antimitotic- and microtubule-destabilizing activity. Compounds **221a-e** exhibited strong cytotoxicity in the NCI60 human tumor cell line. The results suggest that synthetically feasible polyalkoxy-substituted 4*H*-chromenes **221** may prove to be advantageous for further design as anticancer agents (Scheme 145).

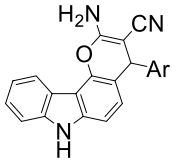
Mohareb et al. [72] synthesized 2-amino-3-cyano-pyran derivatives **233** and evaluated them for anticancer activity against six different human cancer cell lines: human liver cancer (HA22T and HEPG2), human gastric cancer (NUGC), human colon cancer (DLD1), nasopharyngeal carcinoma (HONE1), human breast cancer (MCF) and normal fibroblast cells (WI38). The best results were obtained with 4-chlorophenyl and furan substituents as they were active against most cancer cell lines. Compound **233a** with IC_{50} of 29 nM was almost equipotent to the standard CHS 828 (IC_{50} = 25 nM) against human gastric cancer NUGC, and **233b** with IC_{50} = 89 nM revealed the highest cytotoxicity among the four derivatives against MCF. The other derivatives of the series were less potent (Scheme 146).

Scheme 147 The general structure of pyrano[3,2-*a*]phenazines **256**



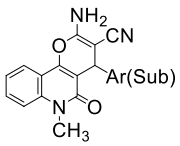
256a R=3,4-Cl_2
256b R=4-Cl

Scheme 148 The general structure of pyrano[3,2-*c*]carbazoles **235**



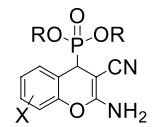
235a R=3-NO_2-C_6H_5
235c R=4-CN-C_6H_5
235g R=C_6H_5
235i R=3-OCH_3-C_6H_5

Scheme 149 The general structure of pyrano[3,2-*c*]quinolines **243**



243c Ar = 3-Cl-C_6H_5
243f Ar = 3-NO_2-C_6H_5
243i Ar = 3-Br-C_6H_5
243j Ar = 3-OC_6H_5-C_6H_5

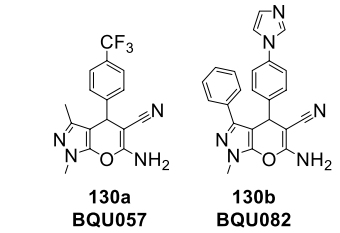
Scheme 150 The general structure of 2-amino-3-cyano-4*H*-chromen-4-ylphosphonates **76**



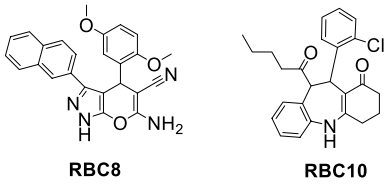
76a X=H R=Et
76b X=Br R=Et

Lu et al. [81] indicated that their synthesized novel pyrano[3,2-*a*]phenazines **256** exhibited cytotoxicity against HCT116, MCF7, HepG2 and A549 cancer cell lines in vitro. In particular, compounds **256a** and **256b** were found to have an excellent antiproliferative activity against the HepG2 cancer cell line. In particular, compound **256a** showed more potent than positive control drug both in vivo and in vitro (Scheme 147).

Padmaja et al. [73] reported the synthesis and biological evaluation of novel pyrano[3,2-*c*]carbazole derivatives **235** as antitumor agents inducing apoptosis via tubulin polymerization inhibition. The antiproliferative activity of these compounds was tested against various cancer cell lines such as MDA-MB-231, K562, A549 and HeLa. Compounds **235a**, **235c**, **235g** and **235i** showed superior antiproliferative activity over other derivatives with IC_{50} values ranging from 0.43 to 8.05 μM and significantly induced apoptosis by inhibiting tubulin polymerization (Scheme 148).



130a BQU057 **130b** BQU082



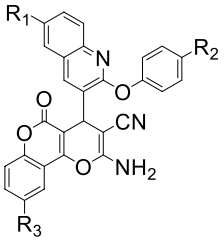
RBC8 RBC10

Scheme 151 The general structure of compounds **130** and parent drug **RBC8** and **RBC10**

Upadhyay et al. [76] evaluated the synthesized pyrano[3,2-*c*]quinolines **243** for their anti-inflammatory and cytotoxic activity at inhibiting TNF-α production in human peripheral blood mononuclear cells (hPBMC) assay. The results showed that compounds **243c**, **243f**, **243i** and **243j** were most active as both anti-inflammatory and anticancer. The structure–activity relationship suggests that the 3-substitution on the aryl ring at C4 position of the pyrano[3,2-*c*] quinolone structural motif is essential for both TNF-α and IL-6 inhibition and anticancer activity as well (Scheme 149).

Kalla et al. [63] synthesized 2-amino-3-cyano-4*H*-chromen-4-ylphosphonates **76**. All synthesized compounds showed moderate activity at 20 and 40 mM concentrations, while compounds **76a** and **76b** showed remarkable activity against the A549 and KB cell lines (Scheme 150).

Yan et al. [43] successfully produced a series of 6-amino-1,3-disubstituted-4-phenyl-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile compounds **130** and tested their Ral inhibitory potential in vitro and in vivo on human lung cancer cell line H2122. Ral GTPase is an enzyme that has two isoforms, RalA and RalB, which interact with a variety of downstream effectors and play distinct key roles in both normal and neoplastic cell physiology including regulation of vesicular trafficking, migration and invasion, tumor formation, metastasis and gene expression. Among the tested derivatives, compounds **130a** (**BQU057**) and **130b** (**BQU082**) displayed a dose-dependent effect on RalA and RalB activity in H2122 spheroids. Indeed, similar to a parent drug, e.g., RBC8 or RBC10, the two compounds **130a** and **130b** were observed in the mouse xenograft model in a good distributed manner (Scheme 151).



186f R_1=CH_3 R_2=Cl R_3=H
186l R_1=H R_2=Cl R_3=CH_3
186p R_1=OCH_3 R_2=H R_3=CH_3
186q R_1=OCH_3 R_2=CH_3 R_3=CH_3

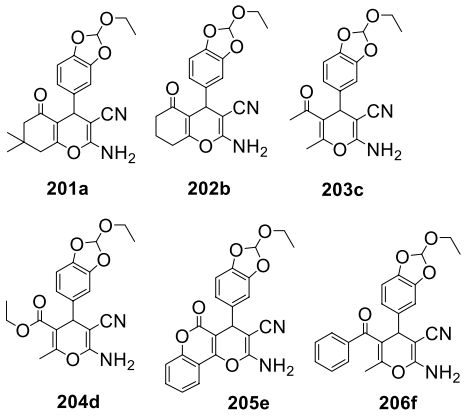
Scheme 152 The general structure of pyrano[3,2-*c*]chromene derivatives containing *β*-aryloxyquinolines **186**

Antimicrobial activity

Mungra et al. [59] developed a new class of *β*-aryloxyquinolines and their pyrano[3,2-*c*]chromene derivatives **186** incorporating a validated molecular target and evaluated their antimicrobial activities. Compounds **186f**, **186l** and **186q** displayed excellent in vitro antimicrobial activity against a representative panel of pathogenic strains specifically *Bacillus subtilis*, *Clostridium tetani*, *Streptococcus pneumoniae*, *Escherichia coli*, *Salmonella typhi*, *Vibrio cholera*, *Aspergillus fumigatus* and *Candida albicans*, while compound **186p** displayed more potent antifungal activity than the standard drug griseofulvin. Also, compound **186f** was a promising antimicrobial member, and majority of the compounds **186** possessed better antimicrobial activity compared to the standard bactericidal ampicillin (Scheme 152).

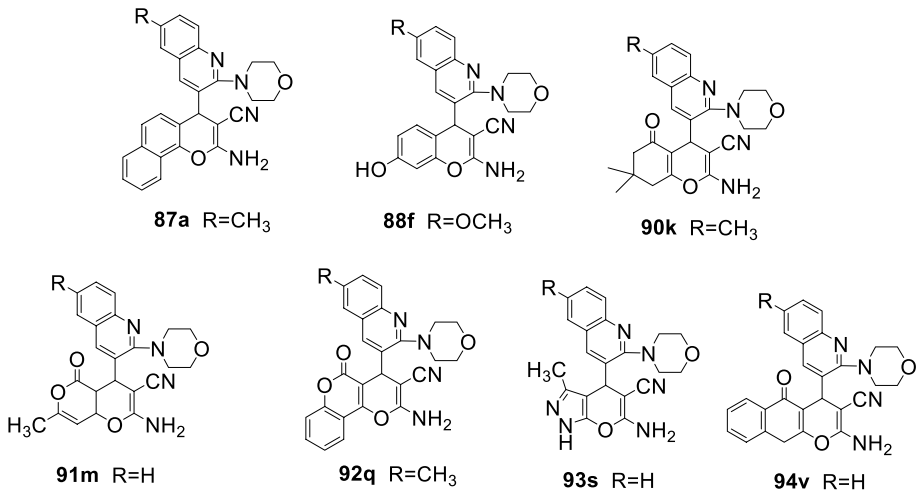
Makawana et al. [35] evaluated antimicrobial activity of a novel series of fused pyran derivatives which bear 2-morpholinoquinoline nucleus **87–94**, against three Gram-positive bacteria (*Streptococcus pneumoniae*, *Clostridium tetani* and *Bacillus subtilis*), three Gram-negative bacteria (*Salmonella typhi*, *Vibrio cholerae* and *Escherichia coli*) and two fungi (*Aspergillus fumigatus* and *Candida albicans*) based on minimal inhibitory concentrations (MIC) values. Among all compounds **87–94**, the best results were obtained with compounds that are shown in Scheme 153.

Baitha et al. [8] synthesized a new class of substituted 2-amino-4-(2-ethoxybenzo[d][1, 3]dioxol-5-yl)-4H-pyran-3-carbonitriles **201–206** as antifungal and antibacterial agents. Among the tested compounds, **201a**, **202b** and **205e** were found to be potent antibacterial agents at the MIC of 100 µg/mL, while compounds **203c**, **204d** and **206f** were moderately active at the MIC of 100 µg/mL against all tested bacteria. The compounds **201a**, **203c** and **205e** showed one to two orders of magnitude more antifungal activity almost against all tested fungi as compared with the standard miconazole at the same level of concentration (MIC of 10 µg/mL). Compounds **202b**, **203d** and **206f** also

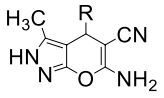


Scheme 154 Structure of 2-amino-4-(2-ethoxybenzo[*d*][1, 3]dioxol-5-yl)-4*H*-pyran-3-carbonitriles **201–206**

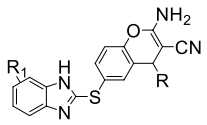
Scheme 153 The general structure of fused pyran derivatives bearing 2-morpholinoquinoline nucleus **87–94**



Scheme 155 The general structure of pyrano[2,3-*c*]pyrazoles **105**

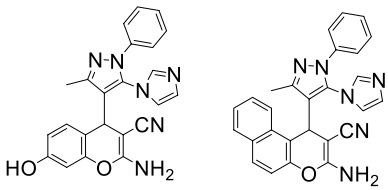


105i R=3-OC_6H_5-C_6H_5



14b R=2-thiophyl R_1=H
14c R=4-Cl-C_6H_5 R_1=H
14e R=4-NO_2-C_6H_5 R_1=H
14g R=5-benzo[*d*][1,3]dioxole R_1=H
14h R=3-indolyl R_1=H
14i R=2-Cl-quinoline R_1=H

Scheme 156 The general structure of 2-amino-6-benzothiazol-2-yl-sulfanyl-chromenes **14**



171s **171q**

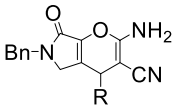
Scheme 157 Structure of compounds **171 s**, **171q**

were moderately active at the MIC of 100 ppm; 100 mg/L (Scheme 154).

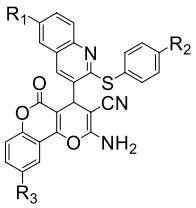
Mandha et al. [1] synthesized substituted pyrano[2,3-*c*]pyrazoles **105** and then evaluated them for antibacterial activity against two Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*), two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) with ciprofloxacin as a standard. Of all compounds **105** tested, compound **105i** with 3-phenoxyphenyl substitution was found to be the most potent compound (Scheme 155).

Kidwai et al. [13] synthesized 2-amino-6-benzothiazol-2-ylsulfanyl-chromenes **14** and screened their antibacterial activity in vitro, against standard strains of *P aeruginosa*, *E. coli*, *S. aureus* and *S. epidermidis*. They used QSAR analysis for the synthesized compounds to find a statistically reliable model for explaining their antibacterial activities. One of the main conclusions was that compounds **14h** and **14c** showed maximum and minimum MIC against *Escherichia coli*, respectively, where the lower MIC of **14c** was attributed to the presence of indole ring. For *Staphylococcus aureus*, **14e/14i** had the maximum/minimum MIC, respectively. The higher MIC of **14e** is due to the presence of a strong electron-withdrawing NO_2 group which lowers electron density in chromene ring. Similarly for *Staphylococcus epidermidis*, **14g/14b** had the highest/lowest MIC, respectively (Scheme 156).

Scheme 158 The general structure of fused bicyclic 4*H*-pyranes **166**



166k R=3-Cl-C_6H_5
166m R=2-OMe-C_6H_5
166q R=2-naphthyl
166r R=2-thionyl



83b R_1=CH_3 R_2=H R_3=H
83e R_1=CH_3 R_2=Cl R_3=H
83g R_1=H R_2=CH_3 R_3=H
83o R_1=OCH_3 R_2=Cl R_3=CH_3
83p R_1=H R_2=CH_3 R_3=CH_3

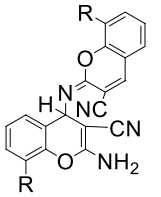
Scheme 159 The general structure of pyrano[3,2-*c*]chromenes **83**

Kalaria et al. [2] designed and synthesized 4-(5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*pyrazol-4-yl)-4*H*-pyran-2-amines **171**. The biological activity of these compounds was attributed to imidazole and pyrazole nuclei, which are present in the synthesized **171**. They screened the final motifs for their preliminary in vitro antibacterial activity against a panel of pathogenic strains of bacteria (*C. tetani*/*B. subtilis*) and fungi (*C. albicans*). For antifungal and antibacterial activity, compounds **171q** and **171 s** showed excellent activity compared to standards griseofulvin and ampicillin, respectively (Scheme 157).

Li et al. [57] synthesized of functionalized 4*H*-pyrans **166** and evaluated them for in vitro antibacterial activity against three ATCC-bacterial strains *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853) and *Enterococcus faecalis* (ATCC 29212). The MIC values of these compounds were between 16 and 128 µg/mL and exhibited their promising antibacterial activity. Among these functionalized 4*H*-pyrans **166**, compounds **166k**, **166 m**, **166q** and **166r** have shown antibacterial activity against the three ATCC-bacterial strains. In general, compounds with substitutions such as *meta*-chlorobenzene, naphthalene or thiophene displayed strong antibacterial activity at relatively low concentrations (Scheme 158).

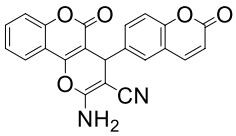
Makawana et al. [33] synthesized a new series of pyrano[3,2-*c*]chromene derivatives **83** bearing a 2-thiophenoxyquinoline nucleus and evaluated them as antimicrobial agents using the broth microdilution MIC method against

Scheme 160 The general structure of 2-iminochromene dimers **237**



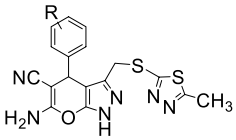
237a R=H
237b R=CH_3

Scheme 161 Structure of biscoumarin fused with dihydropyran ring **239**



239

Scheme 162 The general structure of hiadiazol-attached pyranopyrazole derivatives **332**

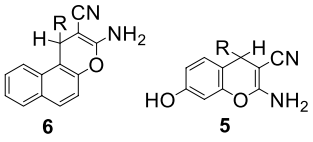


332f R= 4-NO_2
332j R= 2-CH_3
332k R= 4-CH_3

three Gram-positive bacteria (*Streptococcus pneumoniae*, *Clostridium tetani* and *Bacillus subtilis*), three Gram-negative bacteria (*Escherichia coli*, *Salmonella typhi* and *Vibrio cholerae*) and two fungi (*Aspergillus fumigatus* and *Candida albicans*). Among all compounds **83**, **83e** against *B. subtilis*, **83o** against *E. coli* and **83p** against *S. pneumoniae* proved to be most efficient antimicrobial members. Compounds **83b** and **83 g**, bearing methyl group either at the 6th position of the quinoline ring or at the 4th position of the thiophenol ring showed remarkable activity against most of the species tested (Scheme 159).

Costa et al. [74] synthesized novel 2-iminochromene dimers and evaluated their antifungal activity. Among all 2-iminochromene dimers **237**, compound **237a** presented significant antifungal activity, when tested on four Aspergillus species *A. alliaceus*, *A. carbonarius*, *A. niger* and *A. ochraceus* at concentrations of 2 mM. The analogous structure **237b** showed a poor antifungal activity that was attributed to its instability in dilute solution (Scheme 160).

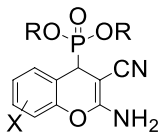
Kalalbandi et al. [75] developed a synthetic route for the synthesis of biscoumarin fused with dihydropyran ring **239**. All the newly synthesized compounds were screened for their antibacterial and antifungal activities in vitro against *Enteroccocus faecalis* (MTCC 3382), *Staphylococcus aureus* (MTCC 3160), *Pseudomonas aeruginosa* (MTCC 1034) and *Escherichia coli* (MTCC 1089). Majority of the compounds



6 **5**

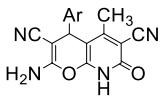
Scheme 163 The general structure of 2-amino-4*H*-chromenes **6** and benzo[*e*]chromenes **5**

Scheme 164 The general structure of compounds **76**



76

Scheme 165 The general structure of pyranopyridine derivatives **287**



287

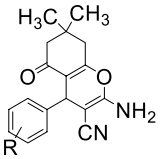
exhibited promising antimicrobial activities. In comparison with ciprofloxacin, compound **239** was found to be more potent against *S. aureus* and *P. Aeruginosa* (Scheme 161).

Reddy et al. [121] generated thiadiazole-attached pyranopyrazole derivatives **332**. The synthesized compounds **332** were tested for their antimicrobial activity against six medically significant bacterial and fungal species: Gram-positive/Gram-negative bacteria, *Staphylococcus aureus*, *Bacillus subtilis*/*Proteus vulgaris, Escherichia coli* and fungi strains (*Aspergillus flavus*, *Aspergillus niger*). All synthesized compounds except two possess higher to low antibacterial property against whole bacteria used in this screening. Compound **332f** showed outstanding activity against all six pathogens due to the presence of nitro substituent, while the compounds **332j** and **332 k** had no effect on the bacterial strains (Scheme 162).

Kidwai et al. [11] reported green synthesis of substituted 2-amino-4*H*-chromenes **6** and benzo[*e*]chromenes **5**. It was shown that all synthesized compounds **5**, **6** possess antibacterial activity as tested in vitro against standard strains of *Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853)* and *Staphylococcus aureus (ATCC 25923)* (Scheme 163).

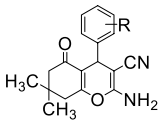
Rajasekhar et al. [32] prepared 2-amino-3-cyano-4*H*-chromen-4-ylphosphonates **76** and screened their antibacterial and antifungal activity by disk diffusion method against the growth of *Staphylococcus aureus* (ATCC 25923) (Gram positive) and *Escherichia coli* (ATCC 25922) (Gram negative) in comparison with penicillin as reference compound. All the compounds **76** showed moderate-to-good activity against both strains. Antifungal activity of the synthesized compounds was also screened against *Aspergillus*

Scheme 166 The general structure of 2-amino-4*H*-pyran derivatives **85**



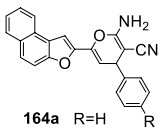
85a R=4-NO_2
85f R=2-Cl

Scheme 167 The general structure of tetrahydrobenzo[*b*] pyrans **85**



85

Scheme 168 The general structure of compounds **164**



164a R=H
164b R=CH_3
164c R=OH
164d R=OCH_3
164e R=Cl
164f R=F

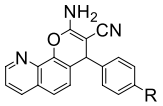
niger (ATCC 16404) and *Helminthosporium oryzae* (ATCC 11000) species in comparison with fungicide griseofulvin. All the compounds **76** showed good activity against both fungi (Scheme 164).

Azarifar et al. [94] developed synthesis and biological evaluation of new pyranopyridine derivatives **287**. These compounds **287** were evaluated for antifungal capacity against the fungus *Fusarium oxysporum*, and most of them showed excellent antifungal activity against this fungus (Scheme 165).

Mahdavi et al. [45] synthesized 2-amino-4*H*-pyrans **85** and tested their antimycobacterial and antifungal activities. The results demonstrated that the majority of the synthesized compounds **85** were active against *M. bovis* and poorly active against *C.albicans*. The compounds **85a** and **85f** showed the highest antimycobacterial activity. It was concluded that the position of substituents in the aromatic ring and their electron-donating capacity affected the activity of compounds **85** (Scheme 166).

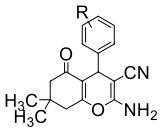
Rao et al. [34] synthesized tetrahydrobenzo[*b*]pyrans **85** and examined their antibacterial/antifungal activities against five pathogenic bacterial strains (Gram-negative bacteria: *Escerichia coli*, *Pseudomonas aeruginosa* and Gram-positive bacteria: *S. ureas*, *B. substills*)/the organism of *Aspergillus niger* and *Candida ablicans* in comparison with standard drugs amoxicillin/ketoconazole, respectively. Among all the tested compounds **85**, the compounds having halogens showed excellent activity. Generally, compounds possessing electron-donating groups showed moderate activity compared to those with electron-withdrawing groups (Scheme 167).

Scheme 169 The general structure of pyran derivatives based on 8-hydroxyquinoline **22**



22a R=H
22b R=OCH_3
22c R=NO_2
22d R=Cl

Scheme 170 The general structure of 4*H*-chromenes **85**

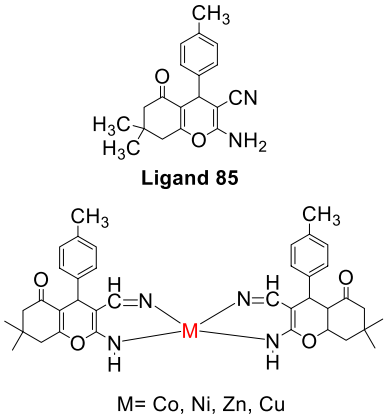


85b R=H
85c R=2-F
85d R=4-CH_3
85e R=4-Cl
85f R=2-Cl
85g R=3-OMe

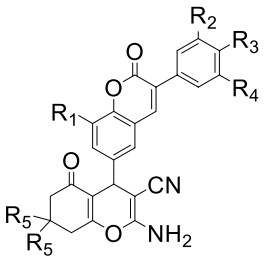
Gaikwad et al. [56] synthesized 2-amino-4-(-4-substituted phenyl)-6-(naphtho[2,1-*b*]furan-2-yl)-4*H*-pyran-3-carbonitriles **164** and evaluated their in vitro antimicrobial activity by cup-plate method against two bacteria (*Salmonua typhi* and *Staphylococcus aureus*) and two fungi (*Aspergillus niger* and *Candida albicans*). All the compounds **164** showed significant antibacterial and antifungal activities at 20 mg/ml concentration levels compared to penicillin and griseofulvin as standards, respectively. Among, compounds **164b,c** and **164e** were more potent on the bacterial strain, whereas all compounds showed maximum antifungal activity (Scheme 168).

Rbaa et al. [16] evaluated and screened new pyran derivatives based on 8-hydroxyquinoline **22** in vitro by the disk diffusion technique against Gram-positive and Gram-negative bacterial strains (*E. coli (ATCC35218), S. aureus (ATCC29213), V. parahaemolyticus (ATCC17802)* and *P. aeruginosa (ATCC27853)*). All the compounds **22** displayed a potential antibacterial activity against all the tested four Gram bacteria. The two products **22b**, **22c** showed antibacterial activity against the Gram-positive and Gram-negative strains compared to the standard antibiotic penicillin G. Among the tested compounds **22**, compound **22a** showed no effect against the strain and compound **22d** showed the most important antibacterial activity at MIC values comparable to the control (penicillin G). The molecules with electron-withdrawing substituents (acid function, nitro, etc.) have shown a lower activity than those having electron-donating substituents (O-alkyl, O-aryl, chlorophenyl, etc.) (Scheme 169).

Hatamjafari et al. [89] screened the synthesized 4*H*-chromenes **85** for antimicrobial activity. The majority of the compounds exhibited significant activity against selected bacteria (*V. cholerae, E. coli, B. subtillus, S. aureus*) and



Scheme 171 Structure of ligand **85** and the related complexes



175a R_1=isopropyl R_2=H R_3=OCH_3 R_4=OCH_3 R_5=CH_3

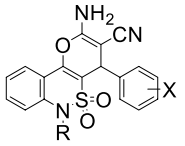
Scheme 172 The general structure of 3-aryl coumarin-based aminopyran derivatives **175**

fungi (*Chrysosporium sp., Trichoderma sp., A. niger, A. parasitica*). For antibacterial activity, *V. cholera, B. subtillus, S. aureus, Trichoderma sp.* and *E. coli* were highly vulnerable to compounds **85c–g** compared with ciprofloxacin as standard, at 100 μgmL^{-1}. For antifungal activity, *Chrysosporium sp.* and *Trichoderma sp.* were highly active for compounds **85d**, **85e** compared with clomatrimazole as standard at 100 μgmL^{-1}, respectively (Scheme 170).

Pasdar et al. [108] synthesized 2-amino-7,7-dimethyl-5-oxo-4-methylbenzen5,6,7,8-tetrahydro-4*H*-chromone-3-carbonitriles **85** and evaluated in vitro antibacterial effect of this compound both ligand and Cu (II), Ni (II), Co (II) and Zn (II) complexes by disk diffusion and micro-broth dilution methods. The results showed that the complexes have higher antibacterial activity in comparison with the ligand. Among, the most effective complex was the Cu complex with MIC value of 62.5 μg/mL against *E. coli* and 125 μg/mL against *S. aureus* (Scheme 171).

Antidepressant-like activity

Sashidhara et al. [58] synthesized and evaluated a new series of coumarin–aminopyran hybrids **175**. Among all



Inhibitores MAO-A

225d X=2,4-Cl_2 R=$CH_2C_6H_5$

225q X=4-NO_2 R=CH_3

Inhibitores MAO-B

225h X=4-OMe R=$CH_2C_6H_5$

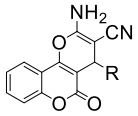
225r X=2,4-$(OH)_2$ R=CH_3

dual inhibitores MAO-A and MAO-B

225l X=H R=CH_3

Scheme 173 The general structure of the active pyranobenzothiazines **225** against MAO-A and MAO-B

Scheme 174 The general structure of 4-aryl/heteroaryl-4*H*-fused pyrans **99**

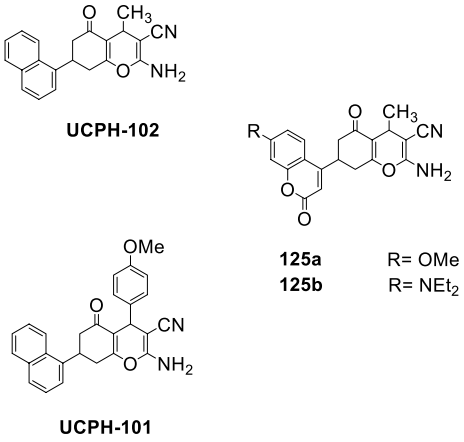


99a R=2-thionyl

synthesized coumarin-based aminopyran derivatives **175**, compound **175a** at a very low dose of 0.5 mg/kg caused a reduction in immobility time comparable to the standard drugs fluoxetine (FXT) and imipramine (IMI). This confirms that these prototypes exhibited antidepressant-type activity and may be a potential antidepressant drug for the treatment of mental depression (Scheme 172).

Ahmad et al. [69] reported the synthesis and in vitro biological evaluation of pyranobenzothiazine derivatives **225** for the inhibition of monoamine oxidases (A and B). Most of the tested pyranobenzothiazines **225** inhibited MAO-A and MAO-B isozymes with an IC50 values in the lower micromolar range. Monoamine oxidase involved in a number of psychiatric and neurological diseases and monoamine oxidase inhibitors (MAOIs) are best known as powerful antidepressants.

Among the tested compounds **225**, compound **225d** and **225q** are the selective inhibitors of monoamine oxidase A; however, the selective and potent inhibitors of monoamine oxidase B included compounds **225 h** and **225r**. Moreover, compound **225 l** as a dual inhibitor showed more inhibitory activity toward both the isozymes (Scheme 173).



Scheme 175 Structure of compounds **UCPH-101/102** and their synthesized analogs **125**

Enzyme inhibitory activity

Xanthine oxidase inhibitory activity

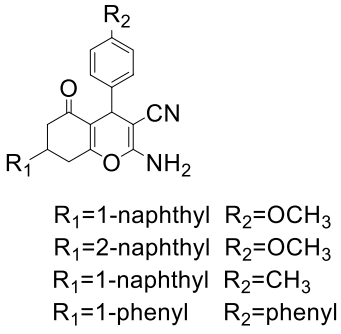
Xanthine oxidase is a type of enzyme that generates reactive oxygen species and leads to many diseases such as gout and symptoms of other diseases such as oxidative damage to the tissue. The selective inhibition of xanthine oxidase would be an appropriate treatment for these diseases [126, 127].

Kaur et al. [6] reported the synthesis and biological evaluation of 4-aryl/heteroaryl-4H-fused pyrans **99** for xanthine oxidase inhibition. All of the synthesized compounds **99** were screened for in vitro xanthine oxidase inhibition and compound **99a** was the most potent one, exhibiting significant inhibition against the enzyme with an IC_{50} value of 0.59 lM. Enzyme kinetic study showed that the compound **99a** was a mixed-type inhibitor. The docking study of **99a** confirmed that S-enantiomer of **99a** fits well in the binding site, while R-enantiomer was not able to get into the cavity (Scheme 174).

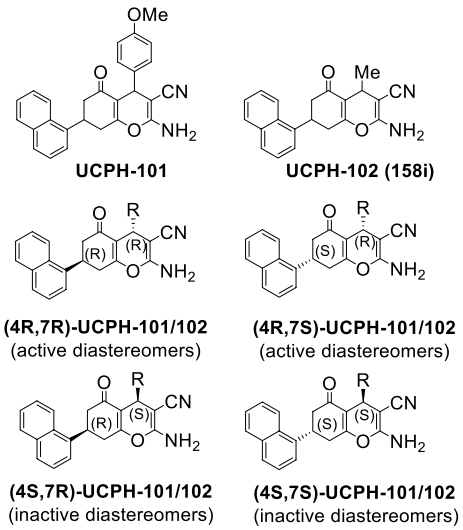
EAAT1 inhibitory activity

The excitatory amino acid transporters (EAATs) are glutamate transporters that remove glutamate from the synaptic cleft and extrasynaptic site via glutamate reuptake into glial cells and neurons. Thereby, the transporters play a central role in regulating the synaptic as well as extrasynaptic concentration of glutamate below levels of neurotoxicity.

Huynh et al. [42] synthesized and evaluated a series of coumarin-based fluorescent analogs of **UCPH-101/102** as subtype-selective inhibitors at EAAT1. Among synthesized compounds **125**, the analogs **UCPH-101** (IC50 = 0.66 lM) and **UCPH-102** (IC50 = 0.43 lM) were the most potent inhibitors of the series, whereas **125a** and **125b** inhibited

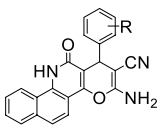


Scheme 176 The general structure of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles **132**



Scheme 177 The general structure of four stereoisomers of analog (**UCPH-101/102**) **132i**

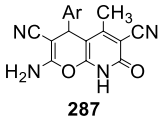
Scheme 178 The general structure of dihydropyrano[3,2-*c*] quinoline derivatives **260**



EAAT1 with IC50 values in the medium micromolar range (17 lM and 14 lM, respectively) (Scheme 175).

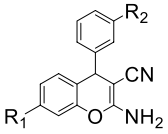
Erichsen et al. [5], in another similar work, designed, synthesized and evaluated the analogs of 2-amino-4-(4-methoxyphenyl)-7-(naphthalen-1-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**UCPH-101**). The SAR studies showed that potency was largely influenced by the chemical nature of the R_1 substituent. The presence of an aromatic ring in the 7-position (R_1) and an alkyl or aryl substituent in the 4-position (R_2) of the parental skeleton was mandatory and essential for the inhibitory activity of

Scheme 179 The general structure of 2-amino-4-aryl-5-methyl-7-oxo-7,8-dihydro-4*H*-pyrano[2,3-*b*]pyridine-3,6-dicarbonitrile **287**



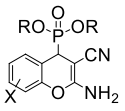
287

Scheme 180 Structure of compounds **161c** and **161e**



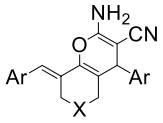
161c R_1=OCH3 R_2=F
161e R_1=OCH3 R_2=Br

Scheme 181 Structure of compound **76e**

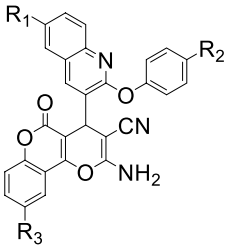


76e X=5-Cl R=Et

Scheme 182 The general structure of racemic 2-aminopyranopyridine-3-carbonitriles **158**



158



186f R_1=CH_3 R_2=Cl R_3=H

Scheme 183 Structure of compound **186f**

the analogs **132** at EAAT1. Accordingly, compounds **132b**, **132h**, **132i** and **132j** showed high inhibitory activity at EAAT1 (Scheme 176).

In a complementary contribution, they made further investigations on the structure–activity requirements of the (EAAT1) inhibitor, 2-amino-4-(4-methoxyphenyl)-7-(naphthalen-1-yl)-5-oxo-5,6,7,8-tetrahydro-4Hchromene-3-carbonitrile (**UCPH-101**) [44]. Separation of the four stereoisomers of analog **132i** was unequivocally confirmed that stereochemistry at C4 was mandatory for EAAT1 inhibitory activity, but the stereochemistry at C7 was not vital. Accordingly, only diastereomers with R configuration at C4 and both of the C7 diastereomers were active as EAAT1 inhibitors (Scheme 177).

Antidiabetic activity

Nikookar et al. [82] synthesized dihydropyrano[3,2-*c*]quinoline derivatives **260** and evaluated in vitro α-glucosidase inhibitory activities. All synthesized compounds **260** displayed excellent activity in the range of 10.3 ± 0.3 mM–172.5 ± 0.8 mM against the yeast α-glucosidase enzyme compared to the standard drug acarbose (IC50 = 750.0 ± 1.5 mM). Among, compounds **260e** and **260d** displayed the most potent α-glucosidase inhibitory activity (IC50 = 10.3 ± 0.3 and 15.7 ± 0.5 mM, respectively) (Scheme 178).

Antioxidant activity

Azarifar et al. [94] developed synthesis and biological evaluation of new pyranopyridine derivatives **287**. The obtained pyranopyridine derivatives **287** were evaluated as antioxidants by using a 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging assay. Most of the synthesized compounds **287** showed excellent antioxidant bioactivity with an IC_{50} value of 0.140 ± 0.003 to 0.751 ± 0.008 mg mL^{-1} (Scheme 179).

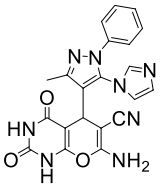
Thomas et al. [54] reported the synthesis of 4-aryl-4*H*-chromene-3-carbonitrile derivatives **161**, and in vitro antioxidant activity of all the synthesized compounds was assessed by nitric oxide and hydrogen peroxide free radical scavenging methods using ascorbic acid and butylated hydroxytoluene as references. All the synthesized compounds **161** showed significant-to-moderate activities in both the methods. Among, the analog **161e** (IC50 30.0 µg/mL) exhibited higher nitric oxide-scavenging activity, while compounds **161c** (IC50 = 26.8 µg/mL) and **161e** (IC50 = 24.2 µg/mL) showed maximum hydrogen peroxide-scavenging activity compared to ascorbic acid and butylated hydroxytoluene as standard references (Scheme 180).

Rajasekhar et al. [32] prepared 2-amino-3-cyano-4*H*-chromen-4-ylphosphonates **76** and screened their antioxidant activity. All the synthesized compounds showed a good activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH), nitric oxide (NO) scavenging power. Among the synthesized compounds **76**, **76e** exhibited the highest activity (Scheme 181).

Antitubercular activity

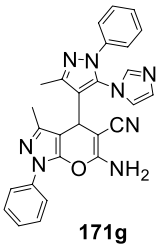
Chen et al. [53] synthesized racemic 2-aminopyranopyridine-3-carbonitriles **158** and investigated their antitubercular activities against autoluminescent *M. tuberculosis* H37Ra and standard strain *M. tuberculosis* H37Rv. Isoniazid and rifampicin were used as the positive controls. The

Scheme 184 Structure of compound **171o**



171o

Scheme 185 Structure of compound **171 g**



171g

synthesized racemic compounds **158** did not show obvious antitubercular activities (MIC > 10 µg/mL) (Scheme 182).

Mungra et al. [59] synthesized a new class of *β*-aryloxyquinolines and their pyrano[3,2-*c*]chromene derivatives **186** and evaluated their antitubercular activities. Majority of the compounds possessed poor antitubercular activity. Compound **186f** showed better antitubercular activity against *Mycobacterium tuberculosis* H37Rv in vitro (250 mg/ml) (Scheme 183).

Kalaria et al. [2] screened in vitro antituberculosis activity of synthesized 4-(5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*pyrazol-4-yl)-4*H*-pyran-2-amines **171** against *Mycobacterium tuberculosis* H37Rv. Among tested compounds, compound **171o** exhibited good better antituberculosis activity compared with rifampicin and isoniazid as the standard drugs (95% inhibition at 250 µg/mL concentration and 92% inhibition at 20, 100 µg/mL concentration). Accordingly, compounds **171o** may become new class of antitubercular agents in the future (Scheme 184).

Antimalarial activity

Kalaria et al. [2] screened antimalarial activity of novel 5-imidazopyrazole nucleus-bearing fused pyran derivatives **171** against *Plasmodium falciparum*. Almost one-third of the synthesized compounds have shown excellent activity against strains of *P. falciparum* as compared to quinine (IC50 = 0.268) as the reference drug; compound **171 g** was found to possess moderate activity (IC50 = 0.034) compared to chloroquine (Scheme 185).

Conclusions

In this review, the existing methods for the synthesis of 2-amino-3-cyano-4*H*-chromenes and their fused heterocyclic analogs were classified according to the type of catalyst used in the pertinent reactions. The wide range of potential pharmacological applications and biological activities of these compounds were also addressed in a separate section with focus on recently published articles.

In summary, the synthesis of 2-amino-3-cyano-4*H*-chromenes could be facilitated with various conventional and advanced catalysts, and even in the absence of any catalysts. In addition, these compounds are good candidates for a wide range of biological applications including anticancer, antimicrobial, antifungal, antidepressant-like, enzyme inhibition, antitubercular, antimalarial, antioxidant and antidiabetic activities.

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