

Review

# An Overview on the Synthesis of Fused Pyridocoumarins with Biological Interest

Matina D. Douka and Konstantinos E. Litinas \* 

Laboratory of Organic Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece

\* Correspondence: klitinas@chem.auth.gr; Tel.: +30-231-099-7864; Fax: +30-231-099-7679

**Abstract:** Pyridocoumarins are a class of synthetic and naturally occurring organic compounds with interesting biological activities. This review focuses on the synthetic strategies for the synthesis of pyridocoumarins and presents the biological properties of those compounds. The synthesis involves the formation of the pyridine ring, at first, from a coumarin derivative, such as aminocoumarins, hydroxycoumarins, or other coumarins. The formation of a pyranone moiety follows from an existing pyridine or piperidine or phenol derivative. For the above syntheses, [4 + 2] cycloaddition reactions, multi-component reactions (MCR), as well as metal-catalyzed reactions, are useful. Pyridocoumarins present anti-cancer, anti-HIV, antimalarial, analgesic, antidiabetic, antibacterial, antifungal, anti-inflammatory, and antioxidant activities.

**Keywords:** fused pyridocoumarins; 4-hydroxycoumarins; aminocoumarins; multi-component reactions; [4 + 2] cycloaddition reaction; Povarov reaction



**Citation:** Douka, M.D.; Litinas, K.E. An Overview on the Synthesis of Fused Pyridocoumarins with Biological Interest. *Molecules* **2022**, *27*, 7256. <https://doi.org/10.3390/molecules27217256>

Academic Editor: Petko Petkov

Received: 30 September 2022

Accepted: 24 October 2022

Published: 26 October 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

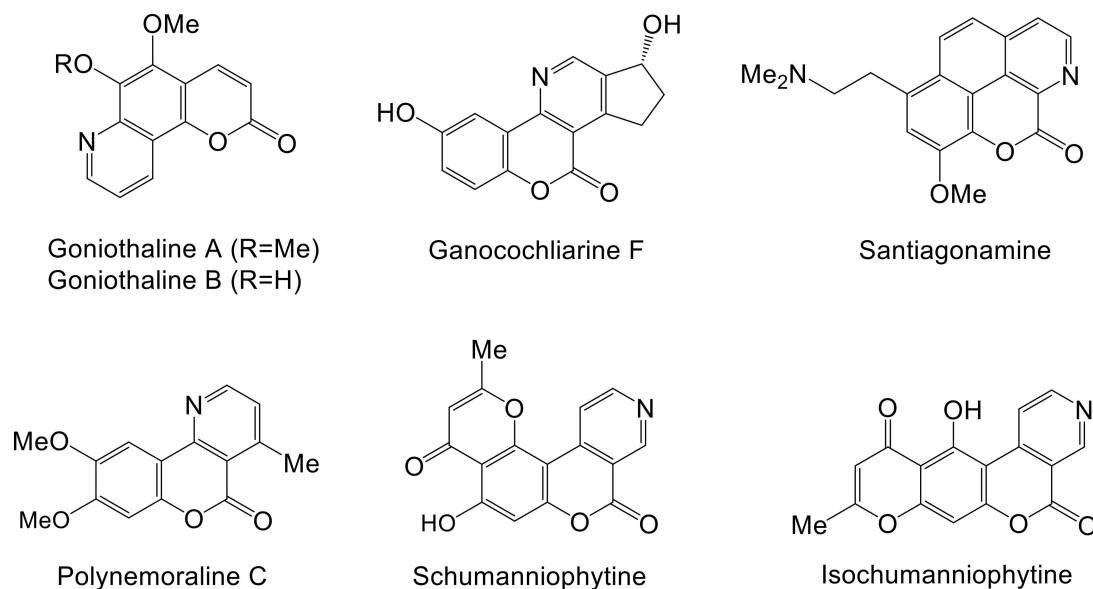


**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Coumarin derivatives are extensively distributed in plants and trees in nature [1–8]. Natural or synthetic coumarins display a vast array of biological and/or pharmacological activities [9–12], such as anticoagulant [13–15], anti-inflammatory [16,17], anti-HIV and antiviral [18–21], anticancer [22–25], antibiotic [26–28], antioxidant [29–31], antidiabetic [29,32,33], antimicrobial [30,34–36], antitubercular [35,37,38], multitarget agents on neurodegenerative diseases [39], etc. Fused coumarins also present biological activity, and many of them, including pyranocoumarins [40], furocoumarins [41,42] and pyrrolo-coumarins [41,42], have been isolated from natural sources. Fused pyridocoumarins exhibit varied biological activities, such as antibacterial [43–45], antifungal [43–45], cytotoxic [46,47], antiproliferative [48], anti-inflammatory [49], analgesic [49], antimalarial [50], antidiabetic [51,52], etc. Some of the fused pyridocoumarins have been extracted from plants. Especially, goniothaline A and goniothaline B (Figure 1) have been isolated from the aerial parts of the Australian rainforest plant *Goniothalamus Australis* and evaluated for in vitro antimalarial activity [53–55]. Ganocochliarine F has been isolated from the fruiting bodies of the Chinese fungus *Ganoderma cochlear* and evaluated for inhibition effects on proliferation of fibroblasts NRK-49F [56]. Santiagonamine has been extracted from the stems and branches of *Berberis darwinii* Hook, a South American shrub, and shows wound-healing activity [57]. Polynemoraine C has been isolated from the ethanol extracts of the branches and leaves of *Polyalthia nemoralis* A DC, collected from Hainan province in China [58]. Pharmacokinetic study of polynemoraine C in mouse plasma has been performed for its further preclinical investigation [59]. Schumanniphytine and the isomer isoschumanniphytine have been isolated from the rootbark of *Schumanniphyton magnificum* Harms. (Rubiaceae), a tree found in west central Africa, and possess anti-HIV activity [60–63]. Even though several reviews referring the chemistry and biological aspects of coumarins and fused coumarins have been published to date, there are few reviews containing topics

on the chemistry and biological activity of fused pyridocoumarins [11,42,64–67]. In this review, we present an overview of the advances described in the literature on the synthesis and biological evaluation of fused pyridocoumarins. The design and synthesis of those derivatives will be presented, accompanied by their biological properties.



**Figure 1.** Representative fused pyridocoumarins found in nature.

## 2. Synthetic Strategies for the Preparation of Fused Pyridocoumarins

The synthesis of fused pyridocoumarins has been achieved by two main routes. One is the formation of a pyridine moiety from a coumarin derivative. The other is the formation of a pyranone moiety from a pyridine or piperidine or phenol derivative.

### 2.1. Pyridine-Ring Formation

The coumarin precursors for the formation of a pyridine ring are aminocoumarins, hydroxycoumarins or other coumarin derivatives.

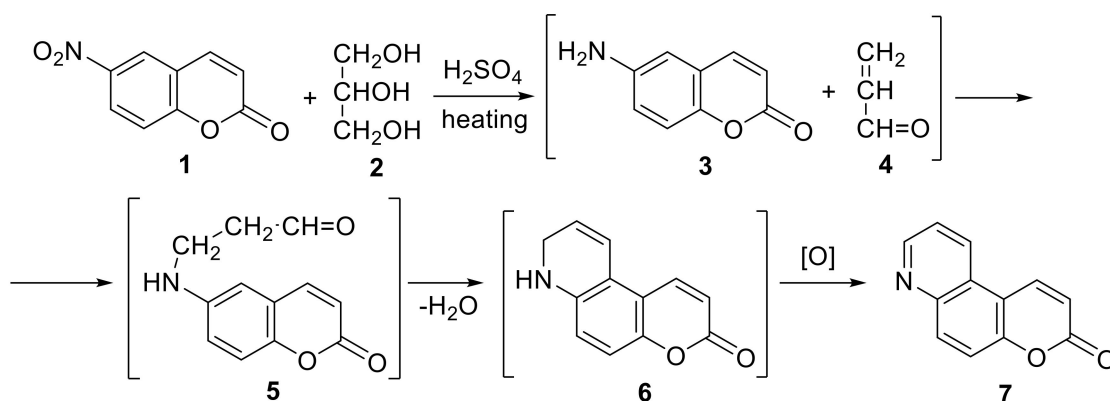
#### 2.1.1. Synthesis from Aminocoumarins

##### Skraup Reaction

The Skraup reaction is used for the synthesis of quinolines [68,69]. The 3*H*-pyrano [3,2-*f*]quinoline-3-one (**6**) was the first fused pyridocoumarin, prepared in 1919 under the Skraup reaction [70], upon heating of 6-nitrocoumarin (**1**) with glycerol (**2**) in the presence of concentrated sulfuric acid at 145–150 °C and then at 160–170 °C for 6 h in 14% yield [71]. During this reaction, an oxidation of **2** to acrolein (**4**), in parallel to the reduction of **1** to 6-aminocoumarin (**3**), occurred (Scheme 1), followed by the addition of **3** to **4**, the formation of the intermediate aldehyde **5**, cyclization of this and dehydration to dihydro pyridocoumarin **6**, which oxidized to give pyridocoumarin **7** [69].

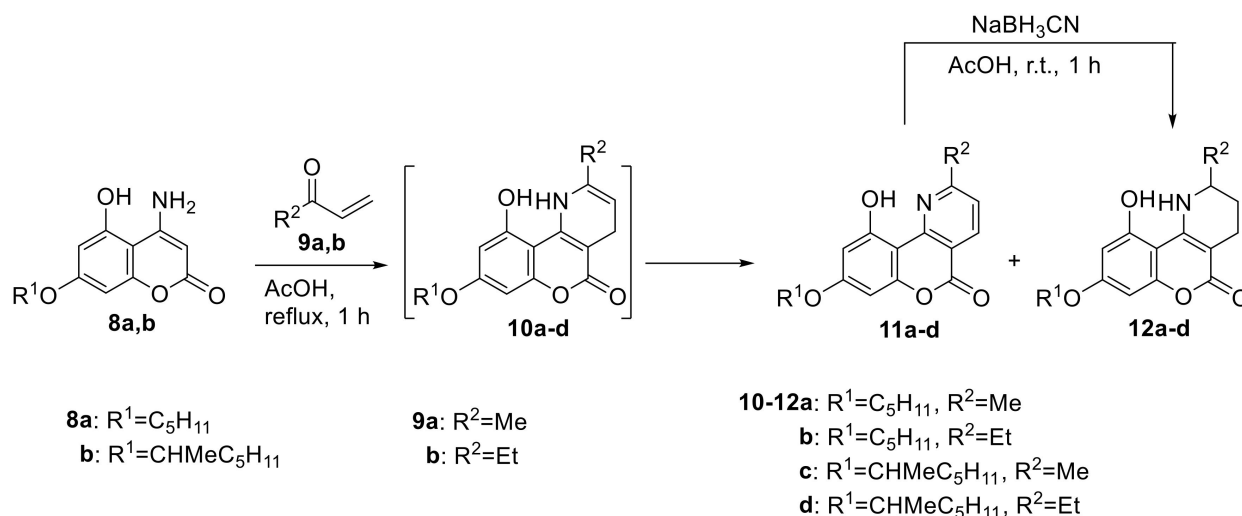
##### Reaction with $\alpha,\beta$ -Unsaturated Carbonyl Compounds (Skraup–Doebner–von Miller Reaction)

The yield of the above Skraup reaction is relatively low. Doebner and von Miller, by replacing glycerol with  $\alpha,\beta$ -unsaturated ketones in the presence of an acid catalyst, increased the yield of the resulted quinoline derivatives [72,73]. The Skraup–Doebner–von Miller reaction of anilines with 3-substituted  $\alpha,\beta$ -unsaturated carbonyl compounds in the presence of protic acids or Lewis acids resulted mainly in 2-substituted quinolines. Introducing an electron-withdrawing group in the  $\alpha,\beta$ -unsaturated carbonyl (as is the case for 3-substituted  $\alpha,\beta$ -unsaturated esters), in the presence of TFA, reversed the regioselectivity to give 4-substituted quinolines [73].



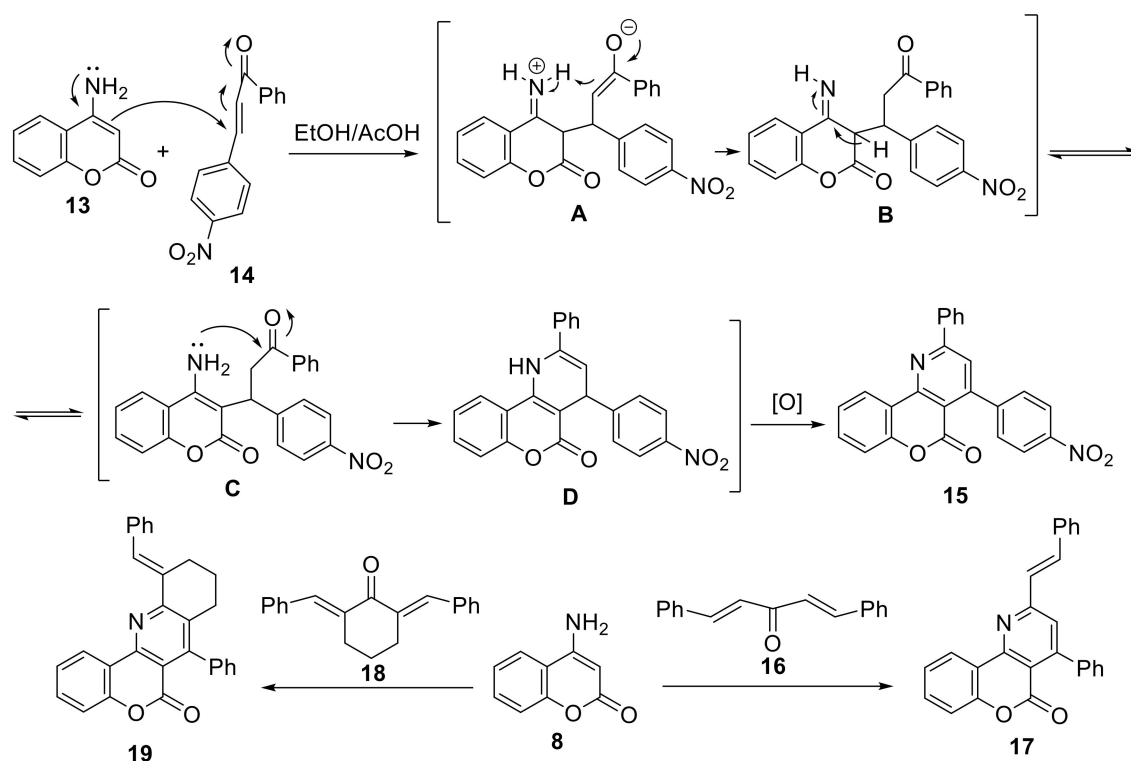
**Scheme 1.** Synthesis of pyridocoumarin **7** under a Skraup reaction.

In 1994, Heber and Berghaus reported the synthesis of fused pyridocoumarins **11a–d** and the azacannabinoidal tetrahydro derivatives **12a–d** [74]. The Michael reaction of 4-aminocoumarin moiety of **8a,b** with the double bond of arylvinylketone **9a,b** gave an intermediate enamino, which underwent an internal cyclization to form the 1,4-dihydro-adduct **10a–d**. The disproportionation of the latter under the applied conditions afforded the mixture of **11a–d** (26–36% yield) and **12a–d** (23–45% yield) (Scheme 2). The reduction of **11a–d** with  $\text{NaBH}_3\text{CN}$  in glacial acetic acid led to the tetrahydropyrido [3,2-*c*]coumarins **12a–d** in 70–85% yield.



**Scheme 2.** Synthesis of fused pyridocoumarins **11a–d** and the azacannabinoidal tetrahydropyrido [3,2-*c*]coumarin derivatives **12a–d**.

In 2014, Hamama et al., studied the reactions of 4-aminocoumarin (**13**) with  $\alpha,\beta$ -unsaturated ketones in ethanol/acetic acid (1:1) under reflux [47]. The outcome of those reactions is a regiochemistry reversal to Skraup–Doebner–von Miller reaction (Scheme 3). The reaction started from a Michael addition of **13** to  $\alpha,\beta$ -unsaturated ketone **14** to give **A** and **B**, tautomerization of the latter to **C**, followed by cyclization of **C** and removal of water to dihydropyridocoumarin **D**, which by oxidation led to pyridocoumarin **15** in 58% yield. The synthesis of **17** was achieved in 76% yield by the reaction of **13** with dibenzylideneacetone (**16**). The similar reaction of 2,6-dibenzylidenecyclohexanone (**18**) resulted in pyridocoumarin **19** in 73% yield. The new compounds were tested for their antitumor activity in vitro against Ehrlich ascites carcinoma cells (EAC) and were found to be three times more toxic than 5-fluorouracile 5-FU.

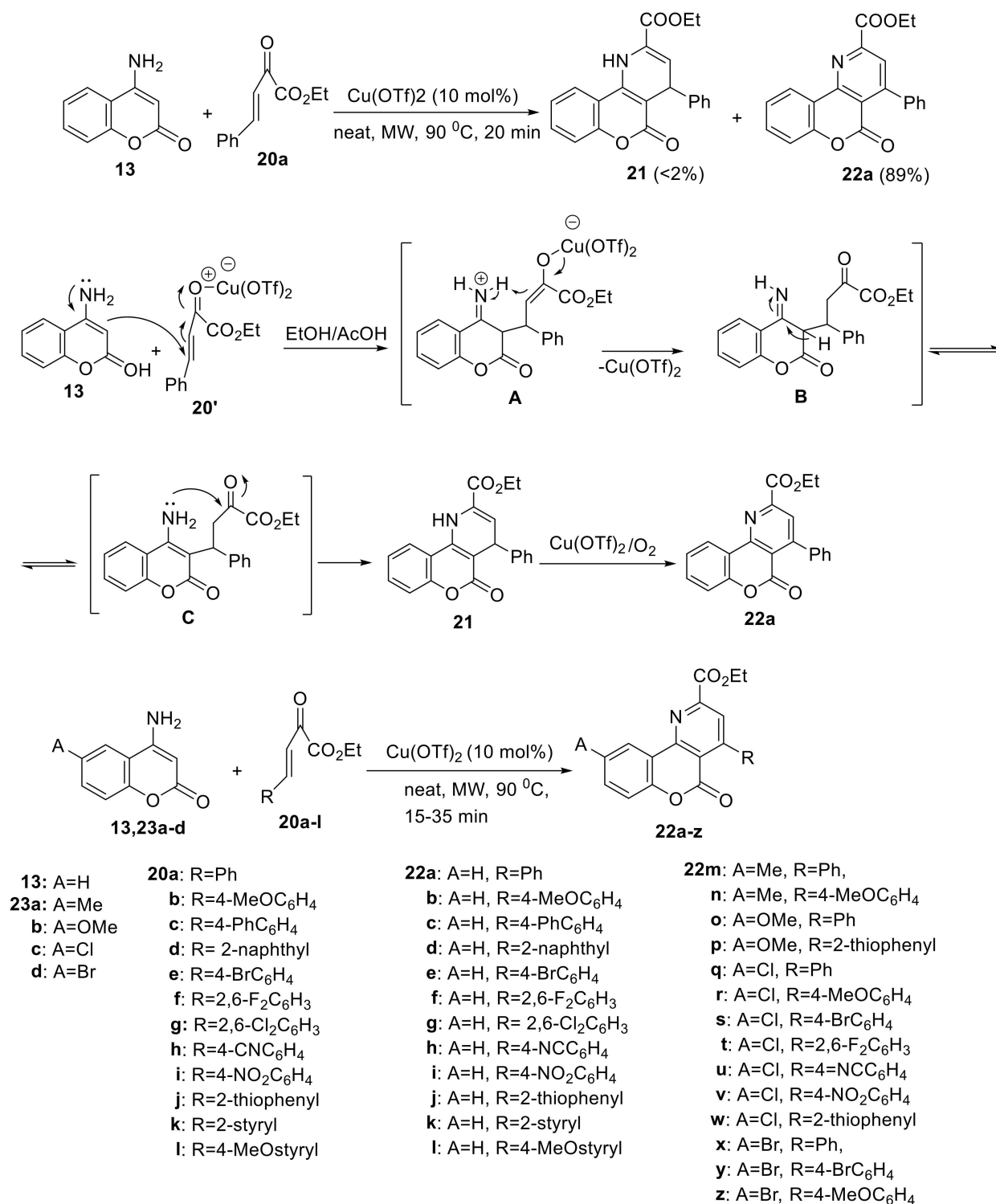


**Scheme 3.** Reactions of 4-aminocoumarin (13) with the  $\alpha,\beta$ -unsaturated ketones 14, 16, 18 for the synthesis of pyridocoumarins 15, 17, 19.

In 2017, Samanta and coworkers reported the  $\text{Cu}(\text{Otf})_2$  (10 mol%)-catalyzed synthesis of fused pyridocoumarins **22a–z** from aminocoumarins **13**, **23a–d** and  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters **20a–l** under solvent-free conditions, microwave irradiation and open atmosphere [75]. The reaction mechanism was similar with the above applied. A Michael addition of 4-aminocoumarin (**13**) to the Lewis acid,  $\text{Cu}(\text{Otf})_2$ , activated **20'**, led to the Michael adduct **C** (Scheme 4). The 1,4-dihydropyridocoumarin **21** was formed by the cyclization of the latter and water elimination. Oxidation of **21** in the presence of  $\text{Cu}(\text{Otf})_2$  under the reaction conditions afforded the pyridocoumarin **22a**. It must be mentioned that the yield of this conversion was only 19% without the presence of the catalyst.

The following year, Adib et al., synthesized a series of fused pyridocoumarins **26a–p** by the reactions of 4-aminocoumarins **13**, **24a** (prepared in situ from 4-hydroxycoumarin and ammonium acetate) with  $\alpha$ -azidolactones **25a–j** in the presence of NaOH under heating at 60 °C for 20 min [52]. According to the mechanism proposed (Scheme 5), the aminocoumarin **13** deprotonated by NaOH and the conjugate base **A** added in a Michael addition to the  $\alpha$ -azidolactone **25a** to give the intermediate **B** under removal of a nitrogen molecule. An imine–enamine tautomerization of the latter followed by cyclization led to tricyclic intermediate **C**, which by water elimination and tautomerization of imine resulted in amino-substituted pyridocoumarin **26a**. The synthesized compounds were evaluated for their  $\alpha$ -glucosidase inhibitory activity and exhibited in vitro yeast  $\alpha$ -glucosidase inhibition with  $\text{IC}_{50} = 101.0\text{--}227.3 \mu\text{M}$ , better than the standard drug acarbose ( $\text{IC}_{50} = 750.0 \mu\text{M}$ ). Compound **26i** was the most potent.

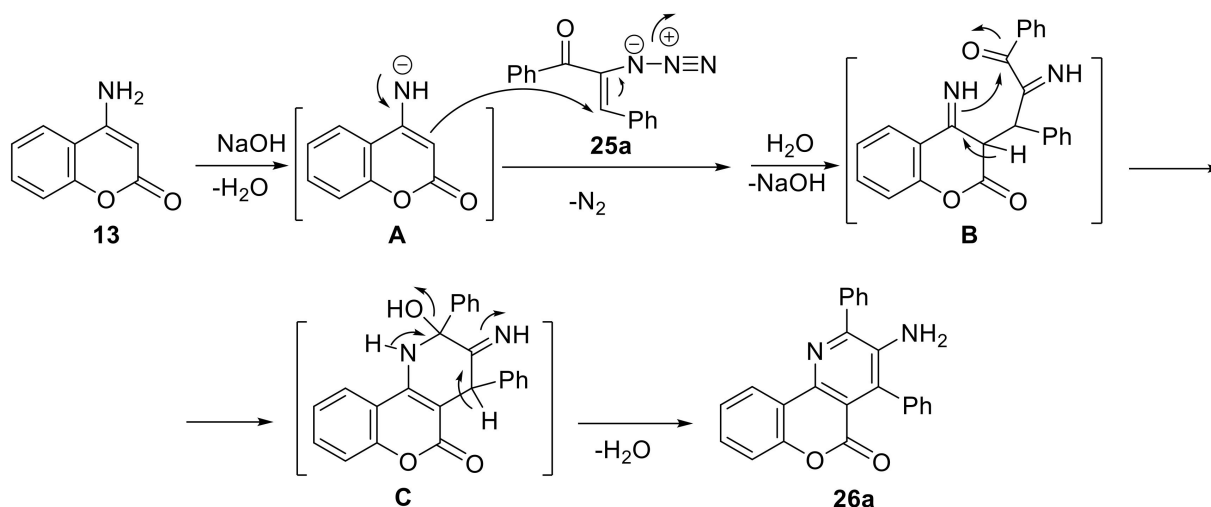
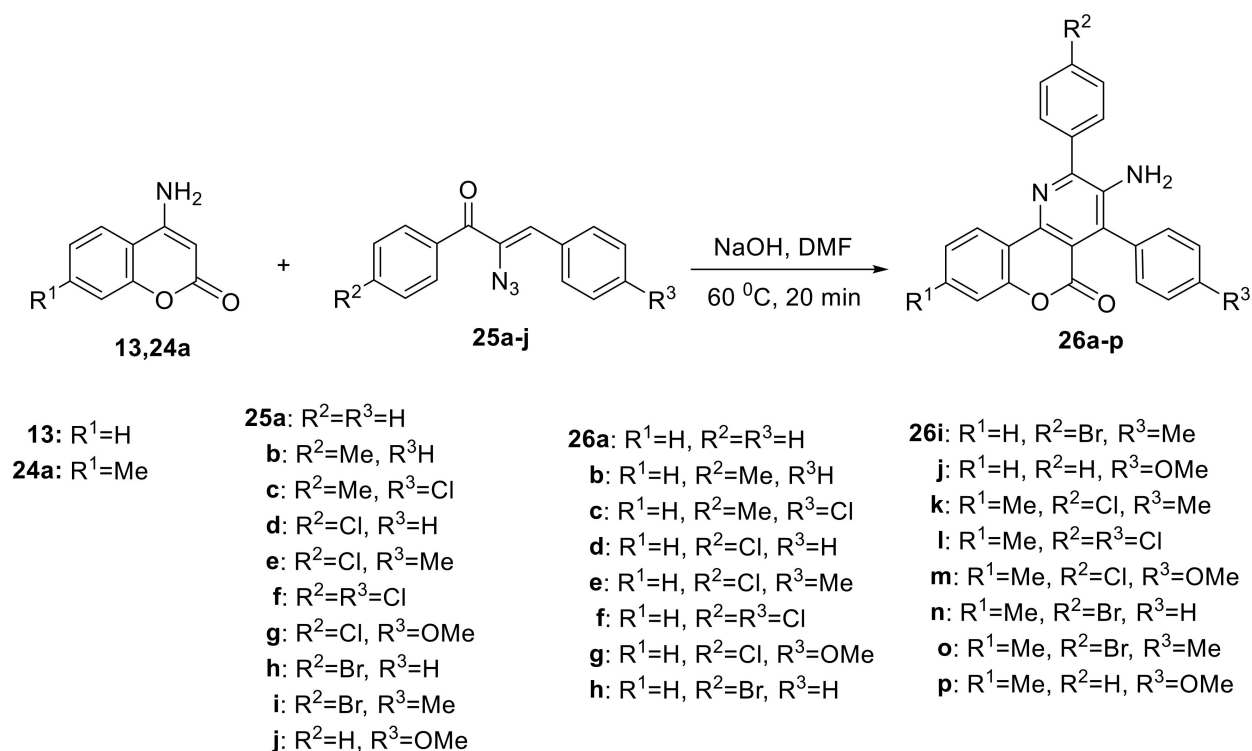
In 2019, Osyanin and coworkers received regioselectively the 3-substituted pyridocoumarins **28a–l** by the reaction of 4-aminocoumarin (**13**), with the  $\beta$ -formyl substituted 4*H*-chromenes **27a–i** in 52–74% yield [76]. The reaction proceeds through a Michael addition of **13** to the  $\alpha$ -carbon of chromene carbaldehyde, e.g., **27i**, leading to the Michael adduct **A**, according to their former work [77]. The condensation of the latter under cyclization possibly led to dihydropyridine **B** (Scheme 6). Aromatization of the pyridine ring under opening of the pyran ring furnished the final product **28i**.



**Scheme 4.** Synthesis of pyridocoumarins **22a–z** by the reactions of aminocoumarins **13**, **23a–d** with  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters **20a–l** in the presence of  $\text{Cu}(\text{Otf})_2$  under MW irradiation.

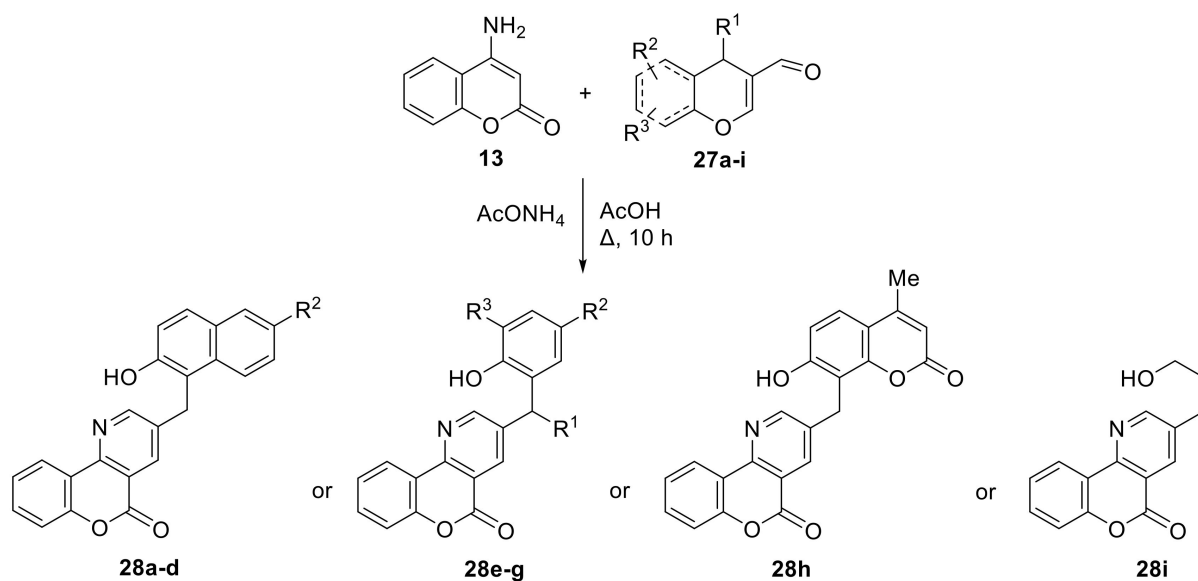
#### Povarov Reaction

A Povarov reaction is a Diels–Alder reaction between an *N*-aryl imine and an electron-rich dienophile in the presence of Lewis acid as catalyst, used for the synthesis of quinolines [78–82]. The reaction is an inverse electron demand Diels–Alder (IEDDA). The one-pot synthesis using aromatic amine, aldehyde, and electron-rich alkene as a MCR is an advance of the Povarov reaction, leading to quinolines [83,84].



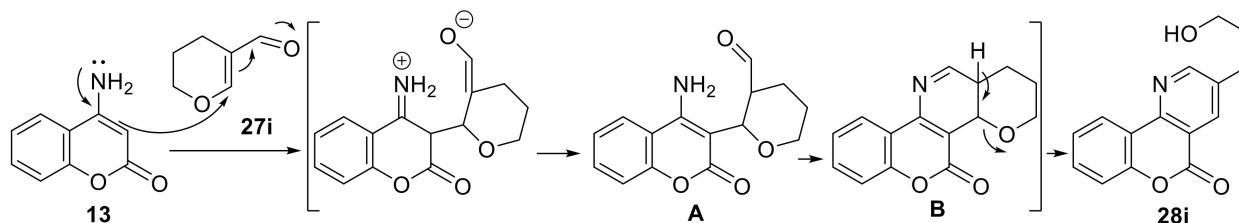
**Scheme 5.** Synthesis of fused pyridocoumarins **26a–p** by the reactions of 4-aminocoumarins **13, 24a** with  $\alpha$ -azidochalcones **25a–j**.

In 2008, Bodwell and coworkers prepared the 1,2,3,4-tetrahydropyridocoumarins **33a,b** (36:64) from the Povarov reaction of imine **31**, synthesized by the reaction of 3-aminocoumarin (**29**) with *p*-nitrobenzaldehyde (**30**), and the 3,4-dihydro-2*H*-pyran (**32**) in the presence of Yb(OTf)<sub>3</sub> as a catalyst (Scheme 7). Similar reactions of **31** with various electron-rich dienophiles resulted in the corresponding tetrahydropyridocoumarins in good yields and variable diastereomeric ratios [85]. They also prepared some of the products, such as **33a,b**, by the one-pot three component version of this reaction. The reaction proceeds by an IEDDA [4 + 2] cycloaddition reaction of alkene to the imine **A**, catalyzed by Yb(OTf)<sub>3</sub>, to **B**, which upon tautomerization gave the products **34**. Oxidation of these products led to the pyridocoumarins, e.g., **35** resulted in **36** by oxidation with bromine.



**27a:** =CH---CH=:naphtho[2,1], R<sup>1</sup>=H, R<sup>2</sup>(6-)=H  
**b:** =CH---CH=:naphtho[2,1], R<sup>1</sup>=H, R<sup>2</sup>(6-)=Br  
**c:** =CH---CH=:naphtho[2,1], R<sup>1</sup>=H, R<sup>2</sup>(6-)=t-Bu  
**d:** =CH---CH=:naphtho[2,1], R<sup>1</sup>=H, R<sup>2</sup>(6-)=adamantan-1-yl  
**e:** =CH---CH=:benzo[1,2], R<sup>1</sup>=R<sup>3</sup>=H, R<sup>2</sup>=NO<sub>2</sub>  
**f:** =CH---CH=:benzo[1,2], R<sup>1</sup>=H, R<sup>2</sup>=Me, R<sup>3</sup>=adamantan-1-yl  
**g:** =CH---CH=:benzo[1,2], R<sup>1</sup>=Ph, R<sup>2</sup>=R<sup>3</sup>=H  
**h:** =CH---CH=:4-methylcoumarin[7,8], R<sup>1</sup>=H  
**i:** =CH---CH=: 2H, 2H, R<sup>1</sup>=H

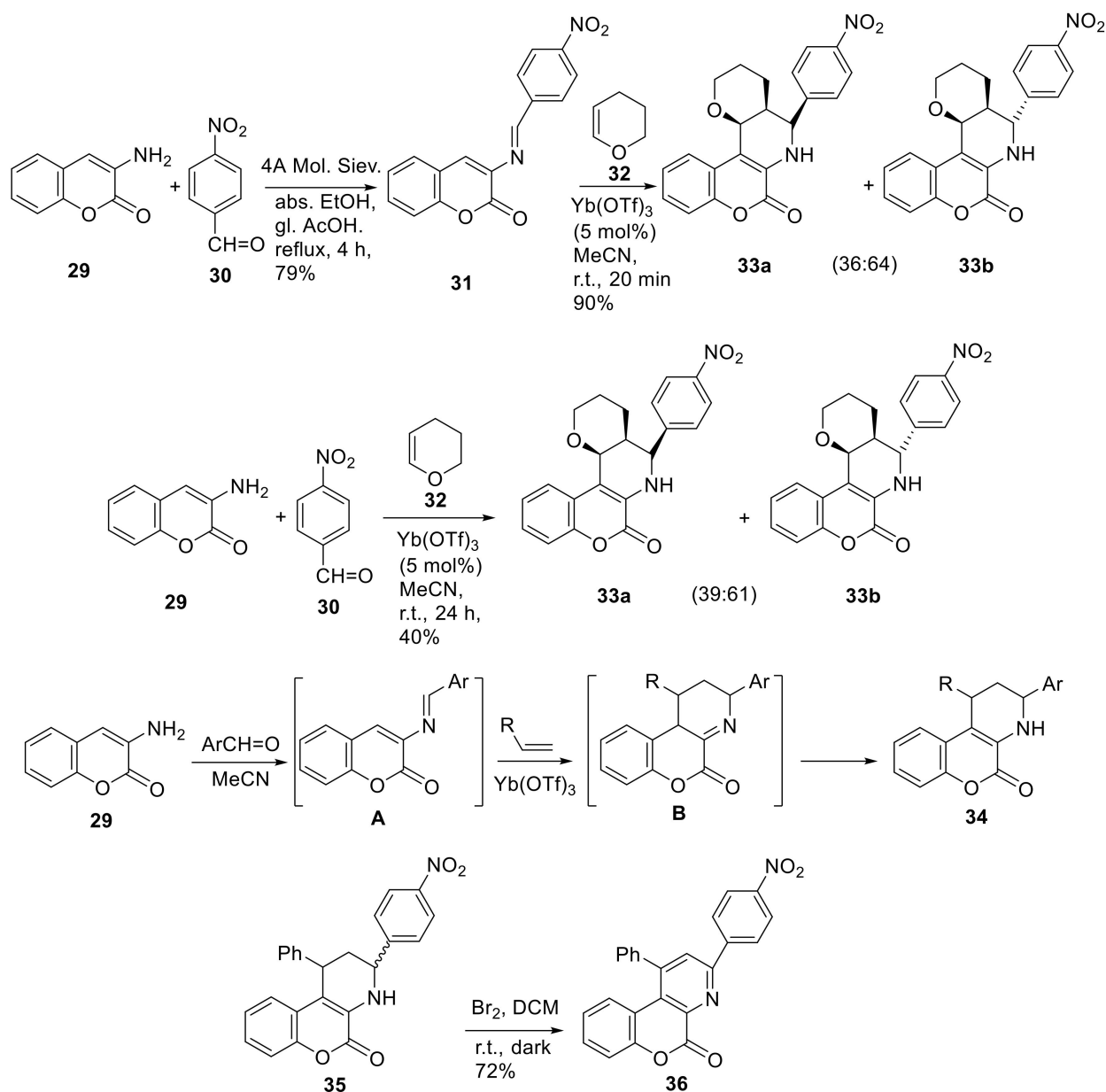
**28a:** R<sup>2</sup>=H  
**b:** R<sup>2</sup>=Br  
**c:** R<sup>2</sup>=t-Bu  
**d:** R<sup>2</sup>=adamantan-1-yl  
**e:** R<sup>1</sup>=R<sup>3</sup>=H, R<sup>2</sup>=NO<sub>2</sub>  
**f:** R<sup>1</sup>=H, R<sup>2</sup>=Me, R<sup>3</sup>=adamantan-1-yl  
**g:** R<sup>1</sup>=Ph, R<sup>2</sup>=R<sup>3</sup>=H



**Scheme 6.** Synthesis of fused pyridocoumarins **28a–i** by the reaction of 4-aminocoumarin (**13**) with  $\beta$ -formyl substituted 4H-chromenes **27a–i**.

The same group, in 2011, synthesized the fused pyridocoumarins **40**, **45** by the intramolecular Povarov reaction of 3-aminocoumarin (**29**) and the unsaturated ethers of salicylaldehyde **37**, **42**, respectively, in the presence of 5 mol% Yb(OTf)<sub>3</sub> [86]. In the case of **37** the *cis*-tetrahydropyridocoumarin **39** was isolated along with the reduction product **41** of the intermediate imine **38**. The reactions of 3-aminocoumarin derivatives with *O*-cinnamylsalicylaldehydes, e.g., **46**, resulted in the *trans,trans*-tetrahydropyridocoumarins, such as **47**, in the presence of 10 mol% Yb(OTf)<sub>3</sub> at r.t. (Scheme 8). In the case of *N*-cinnamyl-2-pyrrolcarbaldehyde **48**, the *cis,trans*-adduct **49** with [5,6] fused ring system was obtained.

In 2015, Khan and coworkers utilized the 10 mol% Yb(OTf)<sub>3</sub> in an one-pot three component Povarov reaction of 3-aminocoumarins, aldehydes and 5,6-unsubstituted 1,4-dihydropyridine derivatives [87]. The products, hexahydro-1H-chromeno [3,4-*h*] [1,6]naphthyridine-3-carboxylate derivatives **53a–y**, isolated in 72–91% yield, have the *exo*-conformation, as is suggested by <sup>1</sup>H-NMR spectra and X-ray diffraction analysis of compound **53a** (Scheme 9).

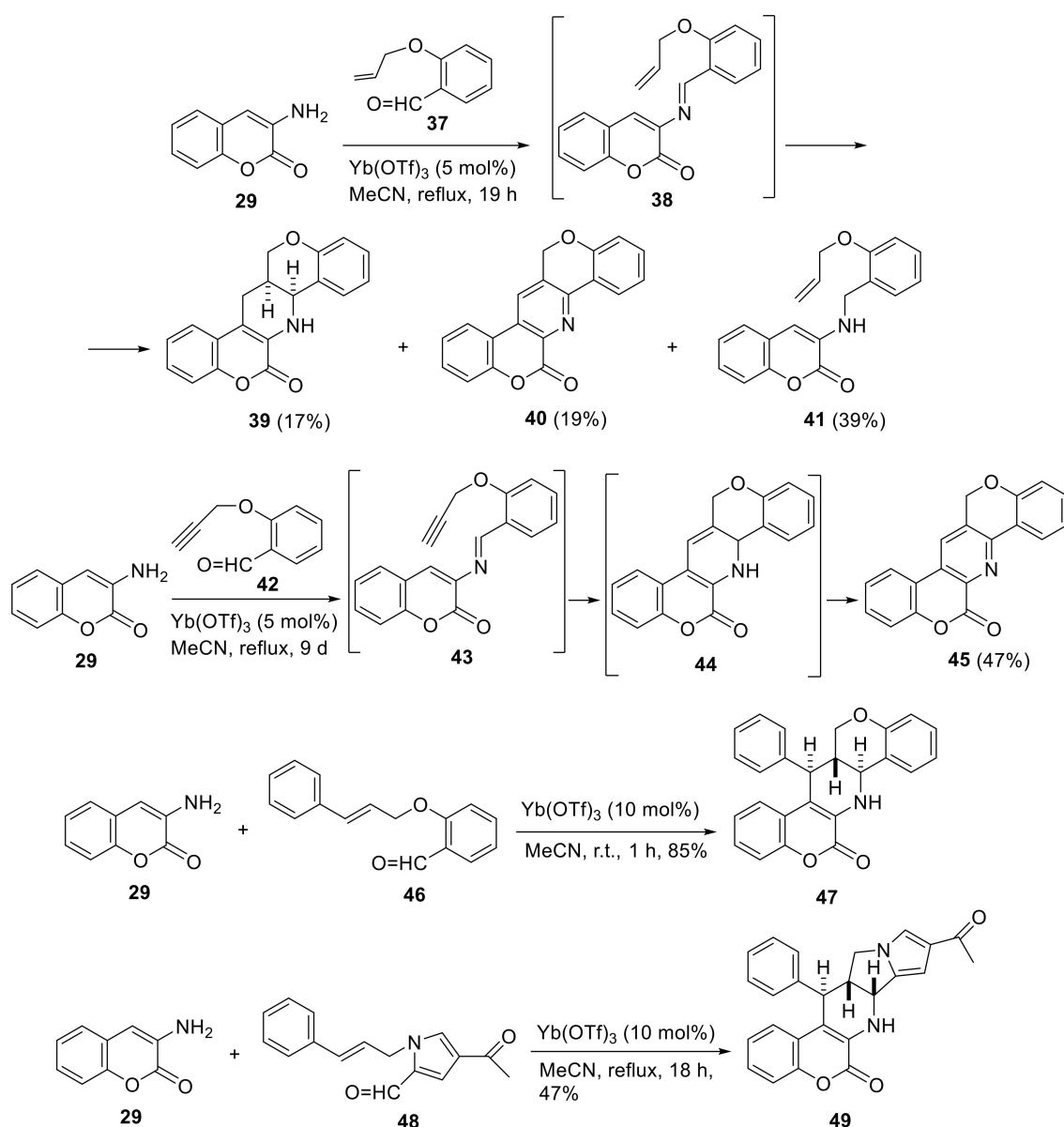


**Scheme 7.** Synthesis of fused pyridocoumarins **33a,b** by a Povarov reaction and a one-pot three component Povarov reaction.

The same group, in 2012, prepared the pyrido [2,3-*c*]coumarin derivatives **36**, **55a–n** by the molecular iodine catalyzed one-pot Povarov reaction of 3-aminocoumarins **29**, **50a,c** with aromatic aldehydes **30**, **51a–c,e–h,m** and alkynes **54**, **56a–e** [88]. The condensation reaction of **29** with **51a** led to the formation of imine **A**. The [4 + 2] Povarov reaction of **A** with alkyne **56** gave 1,4-dihydropyridocoumarin **B**, which upon tautomerization to **C** and oxidation by air resulted in the pyridocoumarin **55** (Scheme 10).

In 2011, Majumdar and coworkers used the  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (10 mol%) as a catalyst for the Povarov three-component reaction of 6-aminocoumarin (**57a**) with aromatic aldehydes **51** and phenylacetylene (**54**) to prepare the angular pyrido [3,2-*f*]coumarins **58a–c** [89]. The similar reaction of 7-amino-4-methylcoumarin (**59a**) with the anisaldehyde **51c** and **54** resulted in linear pyridocoumarin **60** (Scheme 11). The intermediate imine **A** underwent a Diels–Alder reaction with **54** to give the dihydropyridine **B**. Tautomerization of the latter to **C** followed by oxidation by the air afforded the final product **58**.

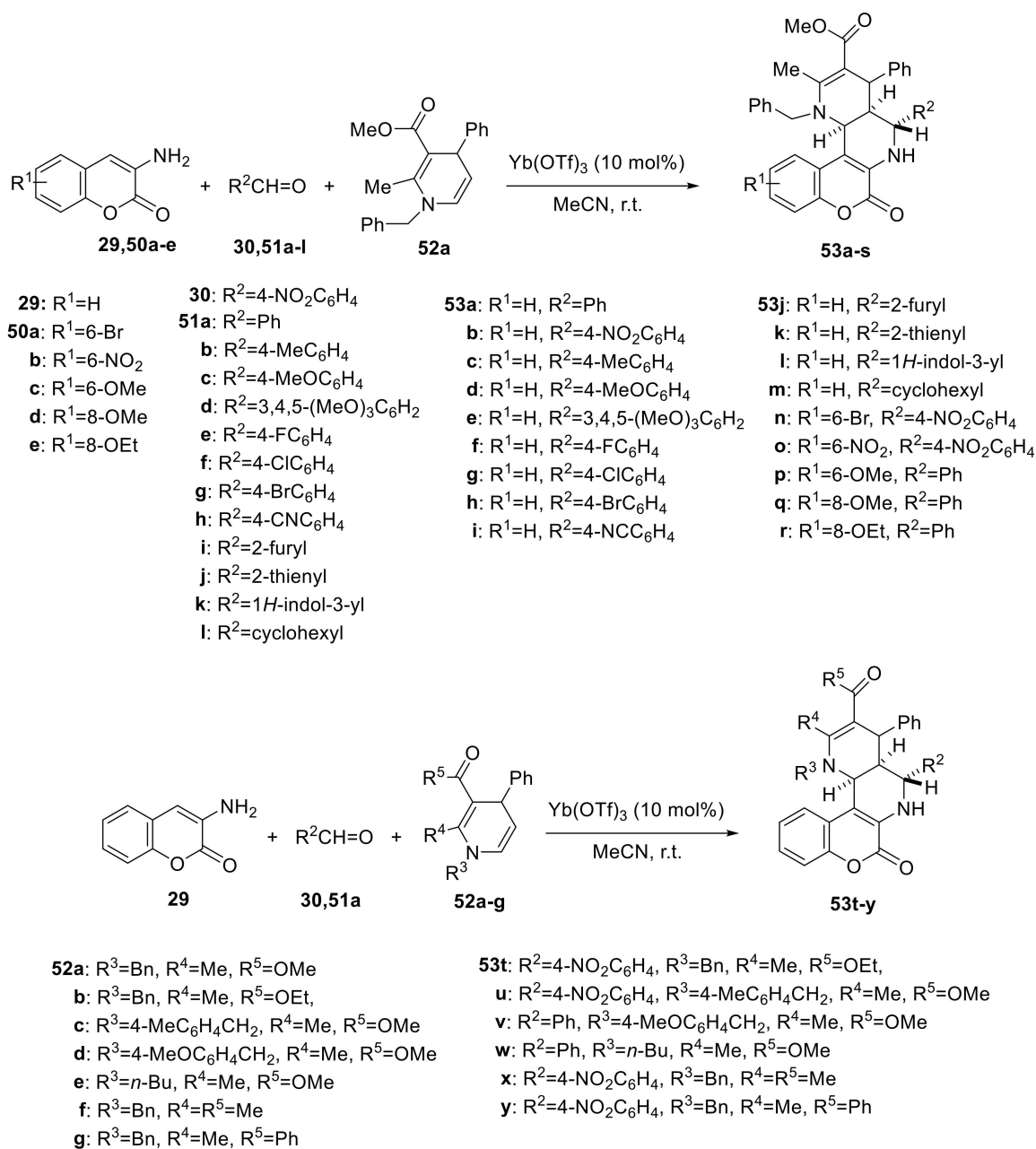




**Scheme 8.** Intramolecular Povarov reaction for the synthesis of pentacyclic fused pyridocoumarins.

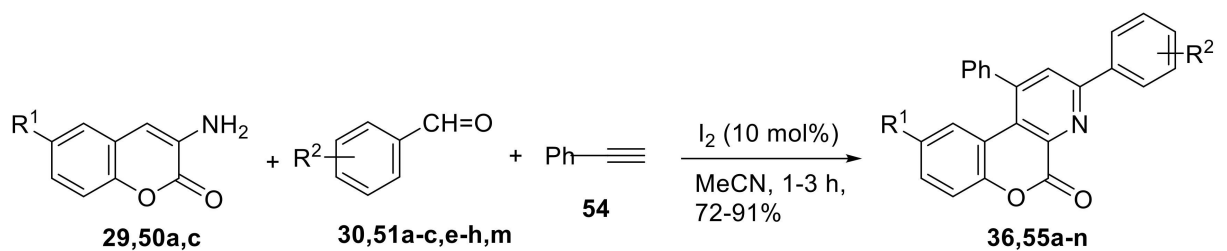
In 2013, our group reported the synthesis of fused pyridocoumarins **62a–f**, **63a,b** and **64** under a three component Povarov-type reaction of 6- or 7-aminocoumarins **57a–f**, **59a,b** with *n*-butyl vinyl ether (**61**) in the presence of 10 mol% molecular iodine [90]. Iodine, a mild Lewis acid, catalyzes the reaction of **61** with the aminocoumarin **57b** for the formation of the intermediate imine **A** (Scheme 12). The intermediate **B** is formed by an aza-Diels–Alder reaction of **A** with a second molecule of **61**, under iodine catalysis, and tautomerization. Elimination of *n*-butanol resulted in 1,2-dihydropyridocoumarin **C**, which upon oxidation led to the final product **62b**.

In 2014, Ganguli and Chandra synthesized the [5,6]- and [6,7]-fused pyridocoumarins **66a–i**, **67a–f**, respectively, under an iodine-catalyzed three-component reaction of 6-aminocoumarin (**57a**), aldehydes and styrene (**65**) in aqueous micellar conditions in the presence of sodium dodecyl sulfate (SDS) [91]. During this process, the 6-benzylaminocoumarins **68a–i** were isolated. The intermediate aldimine **A** reacted with **65** in an inverse electron demand Diels–Alder reaction to give the Povarov adducts **B** and **C** (Scheme 13). These adducts aromatized to pyridocoumarins **66** and **67**, respectively, by a hydrogen transfer to aldimine **A**, which gave the benzylaminocoumarin **68**.



**Scheme 9.** Synthesis of *exo*-hexahydro-1*H*-chromeno [3,4-*h*][1,6]naphthyridine-3-carboxylate derivatives **53a–y** from 3-aminocoumarins, aldehydes and 1,4-dihydropyridines via an one-pot Povarov reaction.

In 2014, our group used FeCl<sub>3</sub> as a catalyst for the three component domino reactions of 6- or 7-aminocoumarins **57** or **59** with benzaldehyde (**51a**) and phenylacetylene (**54**). The reactions were performed in toluene under reflux or under microwave irradiation at 170 °C in the presence of air or *p*-benzoquinone leading to the synthesis of 2,4-diphenyl-substituted fused pyridocoumarins **66**, **67**, **69** or **71**, **72** [92]. The intermediate imine **A** underwent nucleophilic addition from alkynylated complex **B** to give propargylamine complex **C**. The **C**, through intramolecular arylation afforded the vinyl complex **D**, which on decomposition resulted in 1,4-dihydropyridocoumarin **E**. Tautomerization of the latter and oxidation by air led to pyridocoumarin **66a** (Scheme 14). We had tested the new compounds as inhibitors of lipid peroxidation. Compound **66a**, **67a**, **69b** presented 100% inhibition of antilipid peroxidation at 0.1 mM.

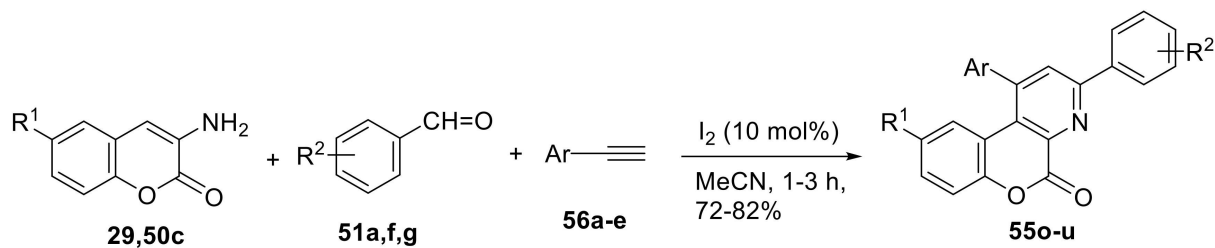


**29:** R<sup>1</sup>=H  
**50a:** R<sup>1</sup>=6-Br  
**c:** R<sup>1</sup>=6-OMe

**30:** R<sup>2</sup>=4-NO<sub>2</sub>  
**51a:** R<sup>2</sup>=H  
**b:** R<sup>2</sup>=4-Me  
**c:** R<sup>2</sup>=4-OMe  
**e:** R<sup>2</sup>=4-F  
**f:** R<sup>2</sup>=4-Cl  
**g:** R<sup>2</sup>=4-Br  
**h:** R<sup>2</sup>=4-CN  
**m:** R<sup>2</sup>=2-Cl

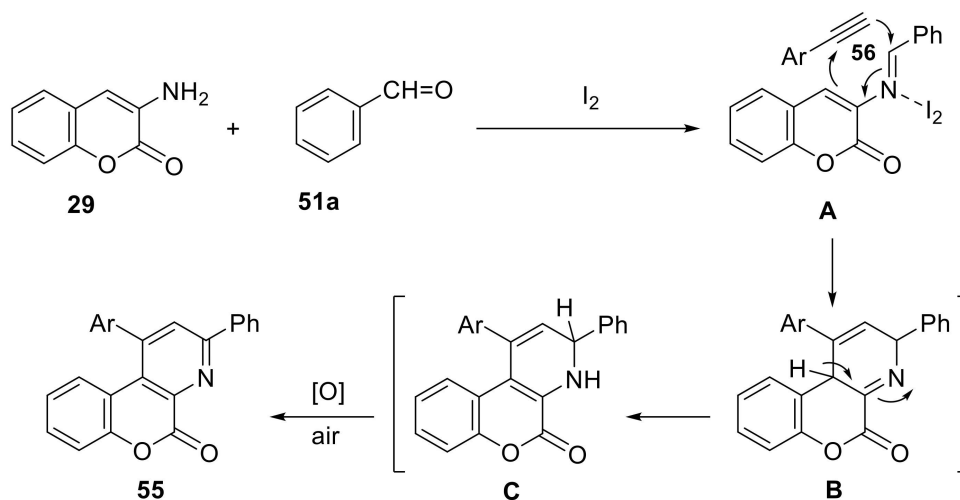
**36:** R<sup>1</sup>=H, R<sup>2</sup>=4-NO<sub>2</sub>  
**55a:** R<sup>1</sup>=H, R<sup>2</sup>=H  
**b:** R<sup>1</sup>=H, R<sup>2</sup>=4-Me  
**c:** R<sup>1</sup>=H, R<sup>2</sup>=4-OMe  
**d:** R<sup>1</sup>=H, R<sup>2</sup>=4-F  
**e:** R<sup>1</sup>=H, R<sup>2</sup>=4-Cl  
**f:** R<sup>1</sup>=H, R<sup>2</sup>=4-Br

**55g:** R<sup>1</sup>=H, R<sup>2</sup>=4-NC  
**h:** R<sup>1</sup>=H, R<sup>2</sup>=2-Cl  
**i:** R<sup>1</sup>=Br, R<sup>2</sup>=4-Cl  
**j:** R<sup>1</sup>=Br, R<sup>2</sup>=4-Br  
**k:** R<sup>1</sup>=Br, R<sup>2</sup>=4-Me  
**l:** R<sup>1</sup>=Br, R<sup>2</sup>=4-OMe  
**m:** R<sup>1</sup>=OMe, R<sup>2</sup>=4-Cl  
**n:** R<sup>1</sup>=OMe, R<sup>2</sup>=4-Me

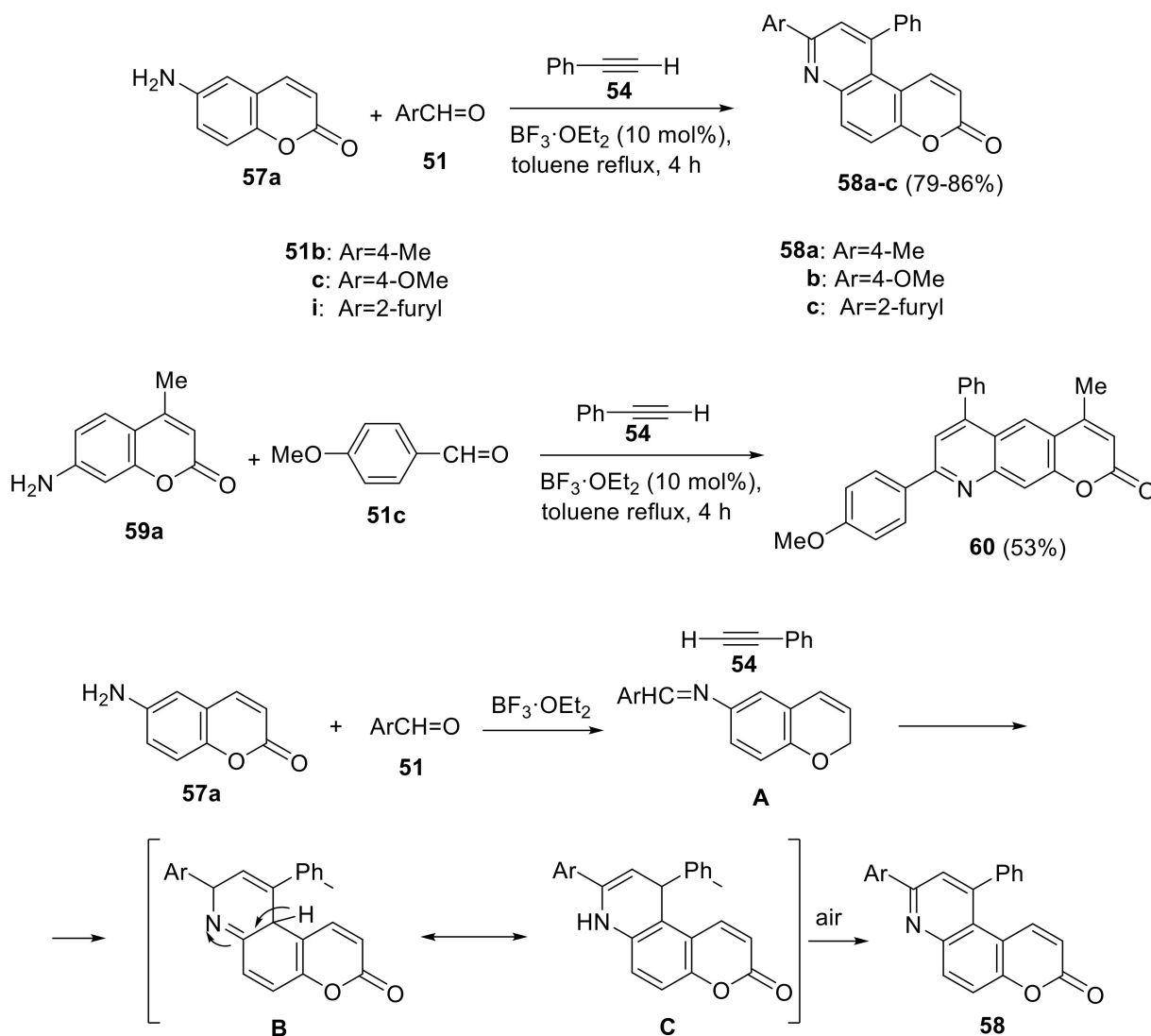


**56a:** Ar=4-MeC<sub>6</sub>H<sub>4</sub>  
**b:** Ar=3,4-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>  
**c:** Ar=3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>  
**d:** Ar=4-*tert*-BuC<sub>6</sub>H<sub>4</sub>  
**e:** Ar=1-C<sub>10</sub>H<sub>7</sub>

**55o:** R<sup>1</sup>=H, R<sup>2</sup>=4-Cl, Ar=4-MeC<sub>6</sub>H<sub>4</sub>  
**p:** R<sup>1</sup>=OMe, R<sup>2</sup>=H, Ar=4-MeC<sub>6</sub>H<sub>4</sub>  
**q:** R<sup>1</sup>=OMe, R<sup>2</sup>=4-F, Ar=4-MeC<sub>6</sub>H<sub>4</sub>  
**r:** R<sup>1</sup>=H, R<sup>2</sup>=4-Cl, Ar=3,4-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>  
**s:** R<sup>1</sup>=H, R<sup>2</sup>=4-Cl, Ar=3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>  
**t:** R<sup>1</sup>=H, R<sup>2</sup>=4-Cl, Ar=4-*tert*-BuC<sub>6</sub>H<sub>4</sub>  
**u:** R<sup>1</sup>=H, R<sup>2</sup>=4-Cl, Ar=1-C<sub>10</sub>H<sub>7</sub>



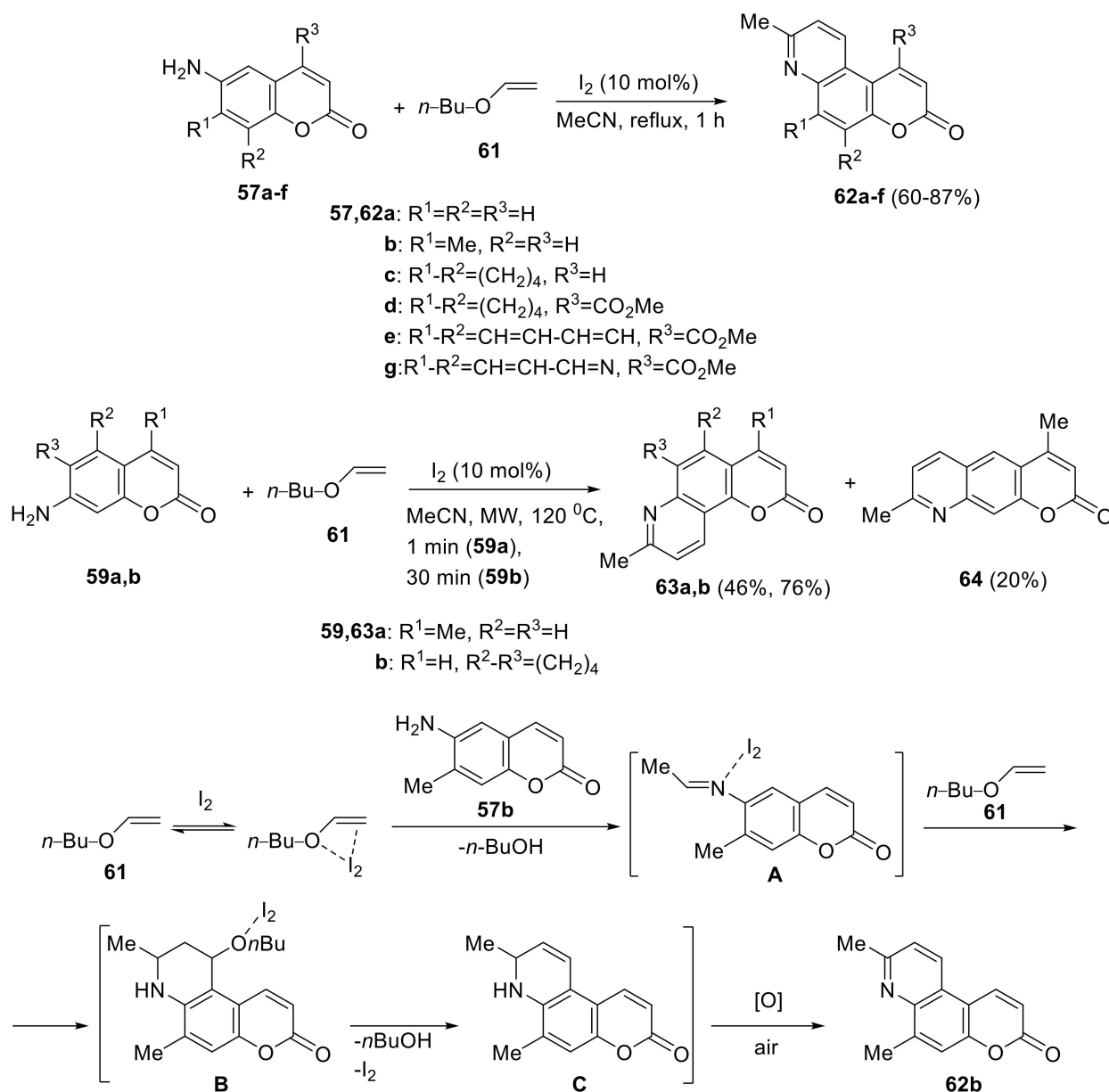
**Scheme 10.** Synthesis of pyrido [2,3-*c*]coumarins **36**, **55a–u** by a molecular iodine catalyzed three component Povarov reaction.



**Scheme 11.** Synthesis of fused pyridocoumarins **58a–c**, **60** by a  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  catalyzed Povarov reaction of aminocoumarins **57a**, **59a** with aldehydes **51** and phenylacetylene (**54**).

The same year, Khan and coworkers synthesized furo- and pyrano-tetrahydropyrido [2,3-*c*]coumarin derivatives by the one-pot three-component reactions of 3-aminocoumarin (**29**) with aromatic aldehydes **30**, **51** and 2,3-dihydrofuran or 3,4-dihydropyran (**32**) in the presence of  $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$  in refluxing acetonitrile [93]. The reactions with 3,4-dihydropyran (**32**) resulted in tetrahydropyridocoumarins **74a–j** and **75a–j** as *endo–exo* and *endo–endo* diastereomeric products, respectively (Scheme 15). The **74** were the major products, while the **75** were the minor products, as established by the coupling constants of the  $^1\text{H-NMR}$  spectra. The XRD crystallographic data of **74e** revealed the *endo–exo* configuration. From the performed docking studies, it was found that most of the derivatives **75** present inhibition activity against human dopamine D3 receptor. The blockage of this receptor is effective for potential pharmacotherapy of several neuropsychiatric disorders.

In 2015, the same group reported an intramolecular Povarov reaction of 2-propargyloxybenzaldehydes **42**, **76a–d** with 3-aminocoumarins **29**, **50a–f** catalyzed by triflic acid (10 mol%) in acetonitrile under reflux for the synthesis of fused pyridocoumarin derivatives **45**, **77a–p** (Scheme 16). The structure of **45** and **77m** was confirmed by X-ray diffraction analysis [94]. The plausible mechanism for this reaction is similar to the mechanism proposed in Scheme 7 with formation of intermediate imine, intramolecular Diels–Alder reaction, tautomerization and aromatization through air oxidation.

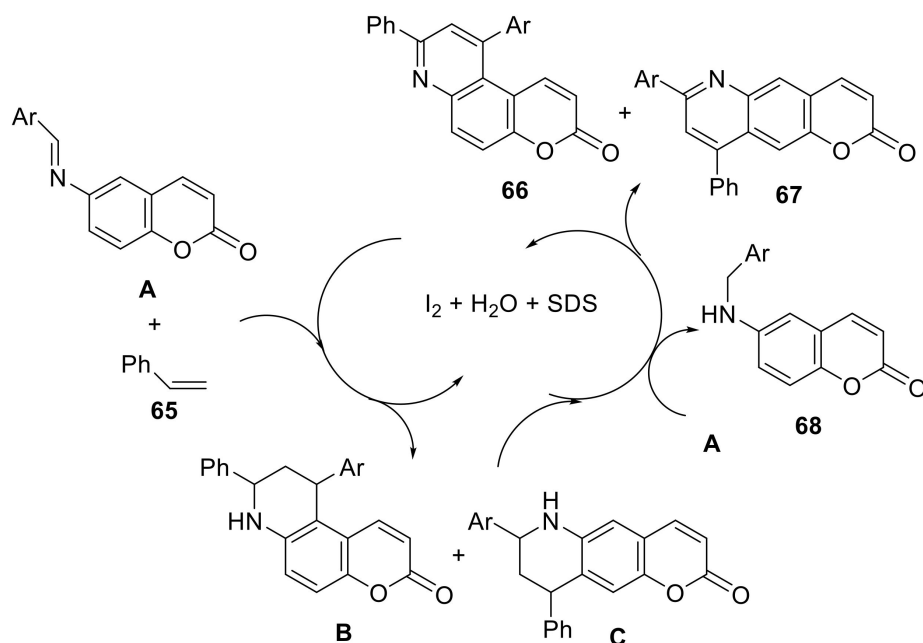
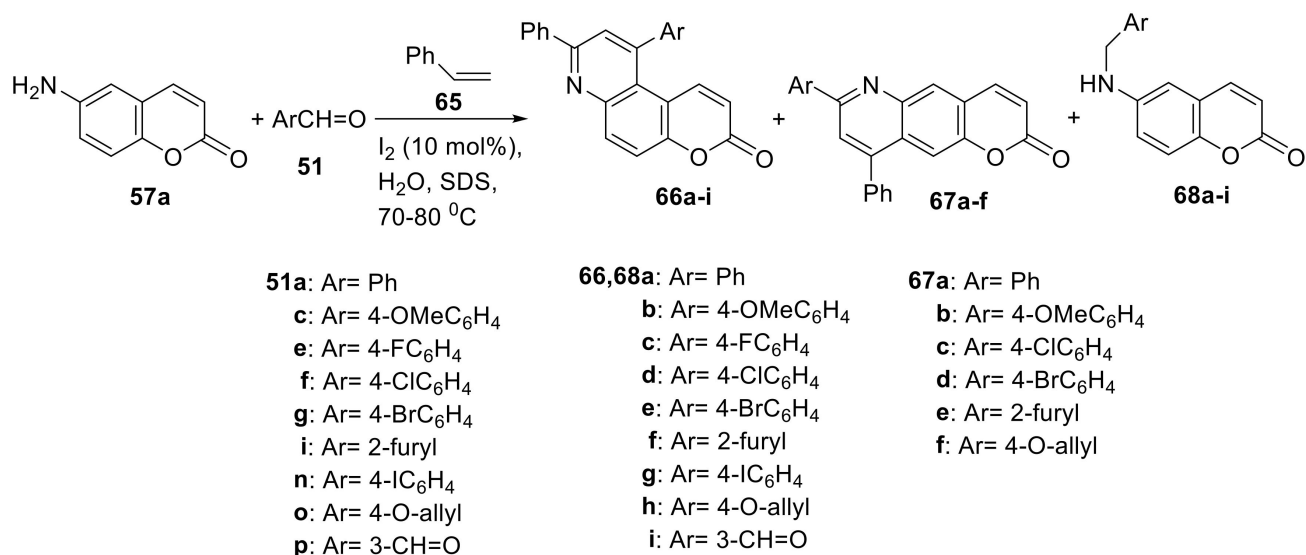


**Scheme 12.** Synthesis of [5,6]- or [7,8]-fused pyridocoumarins **62a–f**, **63a,b** from the reaction of aminocoumarins **57a–f**, **59a,b** and *n*-butyl vinyl ether (**61**) under molecular iodine catalysis.

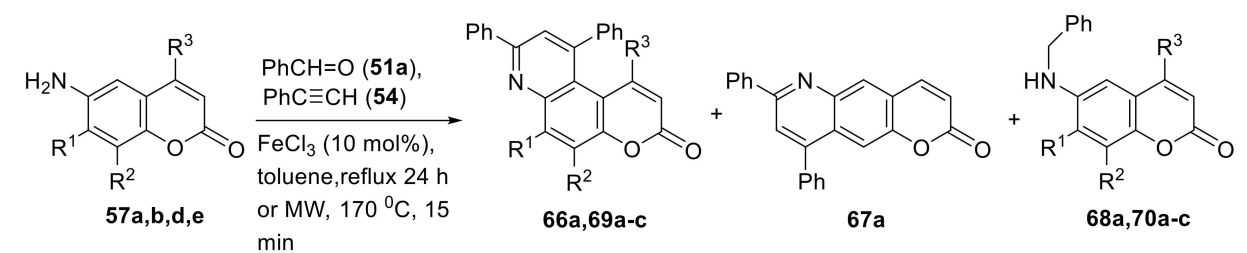
In 2015, Xi and Liu synthesized ferrocenyl-substituted pyrido [3,2-*g*]coumarins **80a–o** by Povarov three-component reaction of 7-amino-4-methylcoumarin (**59a**) with aromatic aldehydes **51,78** and ferrocenylacetylene (**79**) in the presence of  $Ce(OTf)_3$  as a catalyst [95] under refluxing toluene (Scheme 17). They studied the antioxidant activity of the ferrocenylcoumarin derivatives and it was found that these compounds can trap radicals and inhibit DNA oxidation. Derivatives with electron-donating group at 8-position, such as **80d**, **80n**, **80o**, possess higher inhibitory effect on AAPH-induced oxidation of DNA.

In 2016, Gurumurthy et al., synthesized tetrahydropyrido [2,3-*c*]coumarin derivatives **74** and dihydropyrido [2,3-*c*]coumarin derivatives **82a,b**, **84a–c** by the one-pot three component Povarov reaction of 3-aminocoumarin (**29**) with aromatic aldehydes **30**, **51**, **78** and 3,4-dihydropyran (**32**) or 2-vinylnaphthalene (**81**) or diethylacetylenedicarboxylate (**83**) under  $BiCl_3$  catalysis in acetonitrile at room temperature [96]. The reactions gave, stereoselectively, the *endo–exo* products **74**, as it was established by  $^1H$ -NMR experiments. The similar reaction with diisopropylidiazodicarboxylate (**85**) resulted in the fused

triazinocoumarin derivatives **86a–d**. A stepwise mechanism has been proposed for this reaction (Scheme 18). By the electrophilic interaction of 3,4-dihydropyran (**32**) to the intermediate imine **A**, activated as **B** by the Lewis acid,  $\text{BiCl}_3$ , the intermediate **C** was formed. The latter underwent a ring closure in *anti*-mode via an intermolecular attack by the carbon-4 of coumarin ring to give the *endo–exo* product **74a**. The synthesized compounds were evaluated for their antioxidant activity, determined by the DPPH radical scavenging activity. Compounds **84b** and **86a** exhibited good free radical scavenging activity, but lower than the reference compounds  $\alpha$ -tocopherol and butylated hydroxytoluene (BHT).



**Scheme 13.** Synthesis of [5,6]- and [6,7]-fused pyridocoumarins through three-component reaction of 6-aminocoumarin (**57a**), aldehydes and styrene (**65**) under iodine catalysis in aqueous micellar conditions.



**57a:**  $\text{R}^1=\text{R}^2=\text{R}^3=\text{H}$

**b:**  $\text{R}^1=\text{Me}, \text{R}^2=\text{R}^3=\text{H}$

**d:**  $\text{R}^1-\text{R}^2=(\text{CH}_2)_4, \text{R}^3=\text{CO}_2\text{Me}$

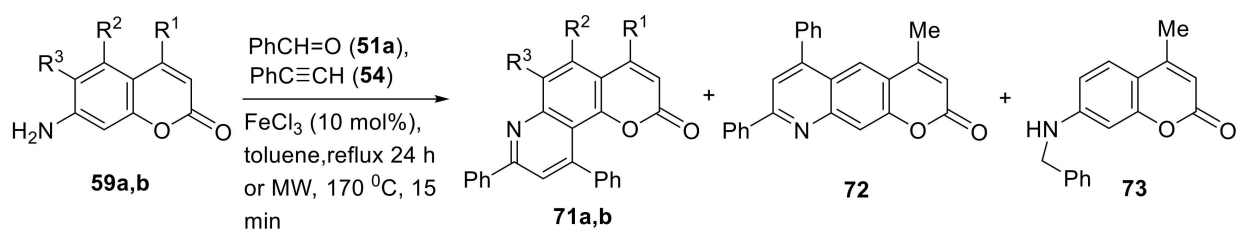
**e:**  $\text{R}^1-\text{R}^2=\text{CH}=\text{CH}-\text{CH}=\text{CH}, \text{R}^3=\text{CO}_2\text{Me}$

**66,68a:**  $\text{R}^1=\text{R}^2=\text{R}^3=\text{H}$

**69,70a:**  $\text{R}^1=\text{Me}, \text{R}^2=\text{R}^3=\text{H}$

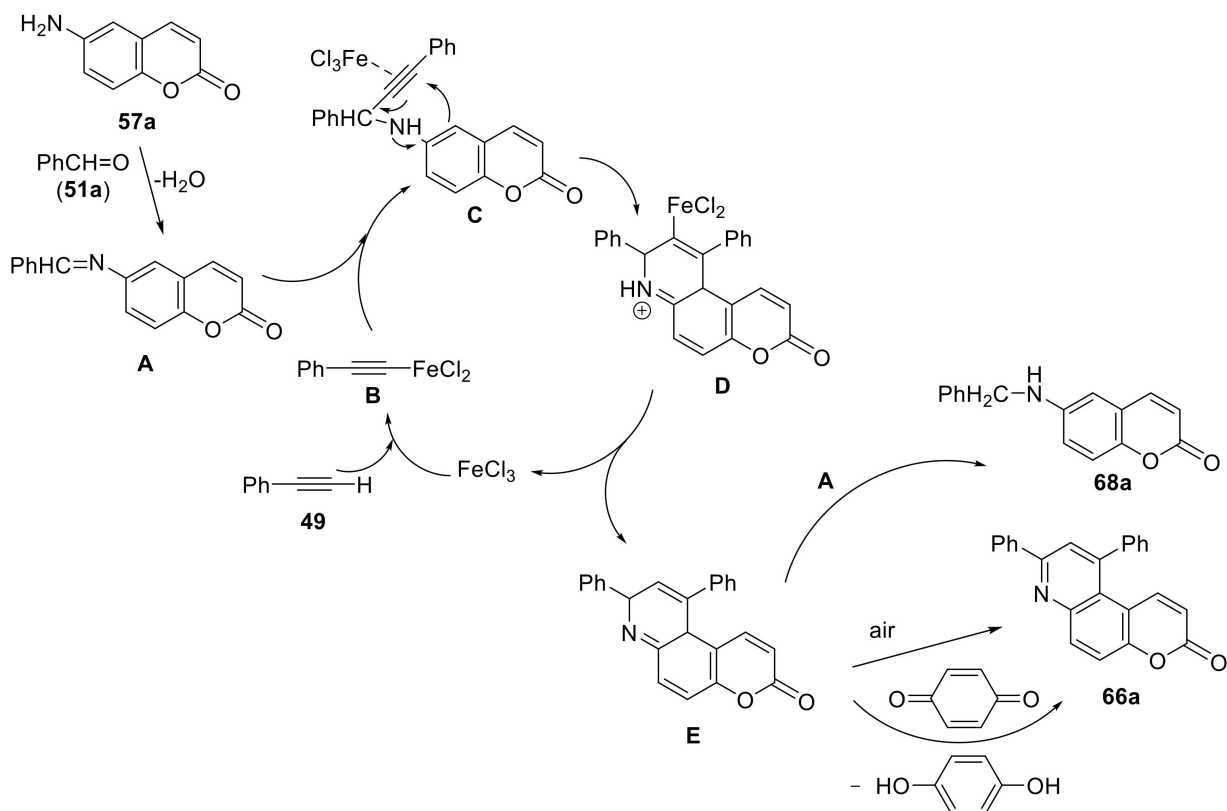
**b:**  $\text{R}^1-\text{R}^2=(\text{CH}_2)_4, \text{R}^3=\text{CO}_2\text{Me}$

**c:**  $\text{R}^1-\text{R}^2=\text{CH}=\text{CH}-\text{CH}=\text{CH}, \text{R}^3=\text{CO}_2\text{Me}$

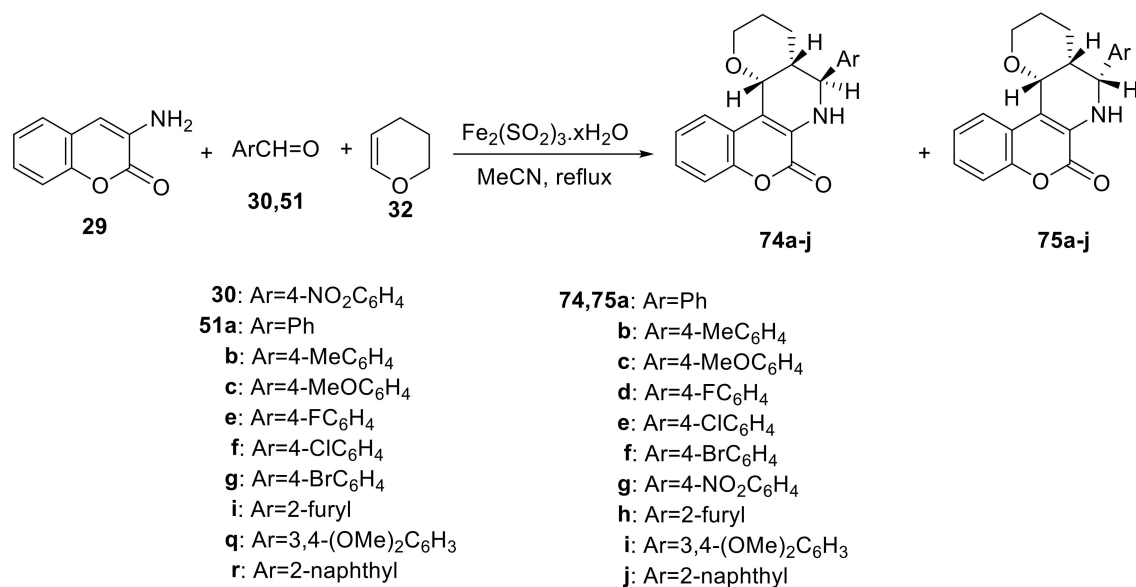


**59,71a:**  $\text{R}^1=\text{Me}, \text{R}^2=\text{R}^3=\text{H}$

**b:**  $\text{R}^1=\text{H}, \text{R}^2-\text{R}^3=(\text{CH}_2)_4$

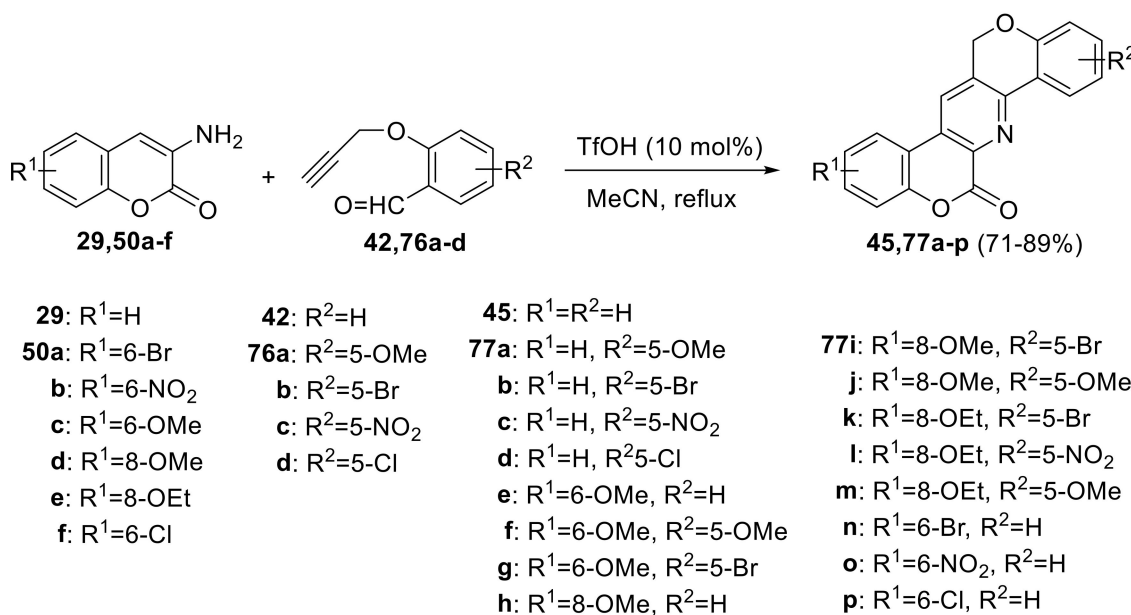


**Scheme 14.**  $\text{FeCl}_3$ -catalyzed three-component reaction of aminocoumarins with benzaldehyde and phenylacetylene to 2,4-diphenyl substituted fused pyridocoumarins.



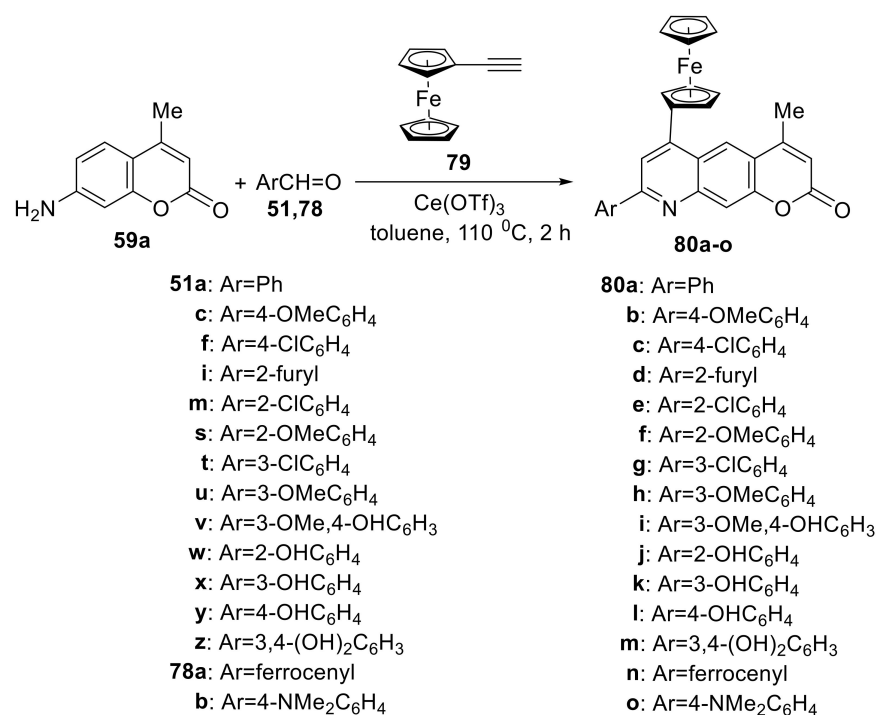
**Scheme 15.** Synthesis of pyrano-tetrahydropyrido [2,3-c]coumarin derivatives by three-component reactions of 3-aminocoumarin (**29**), aldehydes **30**, **51** and 3,4-dihydropyran (**32**) in the presence of hydrated ferric sulfate.

In 2016, Chen et al., reported the synthesis of substituted pyrido [2,3-c]coumarins **55a**, **88a–x** by a one-pot three-component reaction of acetophenones (mainly), aromatic aldehydes and 3-aminocoumarin (**29**) in the presence of equimolar amount methanesulfonic acid in refluxing acetonitrile [97]. As a plausible mechanism, they proposed the addition of enol **87a'**, formed in the presence of acid by the tautomerization of acetophenone **87a**, to the intermediate imine **A**, the condensation product from **29** and benzaldehyde **51a**, in an asynchronous [4 + 2] cycloaddition reaction. Subsequently, the coumarin ring of **B** added to the ketone carbonyl to give the intermediate **C**. The latter by tautomerization, elimination of water and oxidation under air resulted in the product **55a** (Scheme 19).

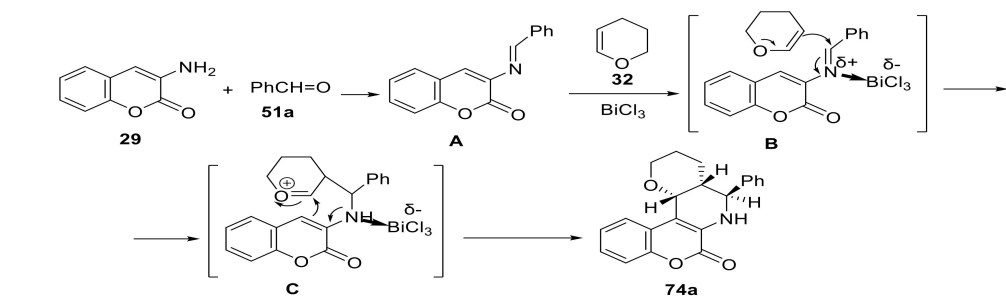
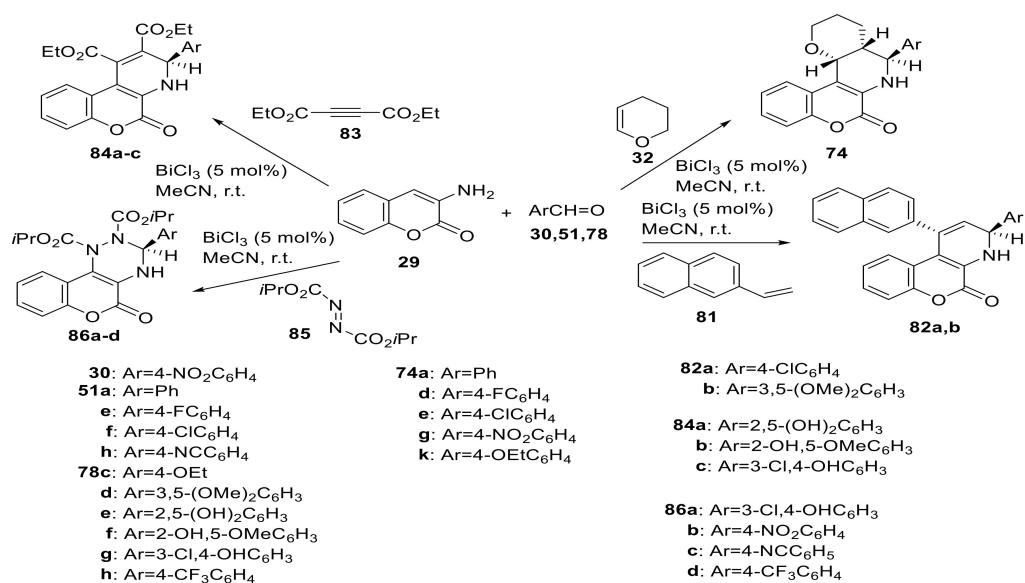


**Scheme 16.** Synthesis of the substituted pyrido [2,3-c]coumarin derivatives **45**, **77a–p** by an intramolecular Povarov reaction.

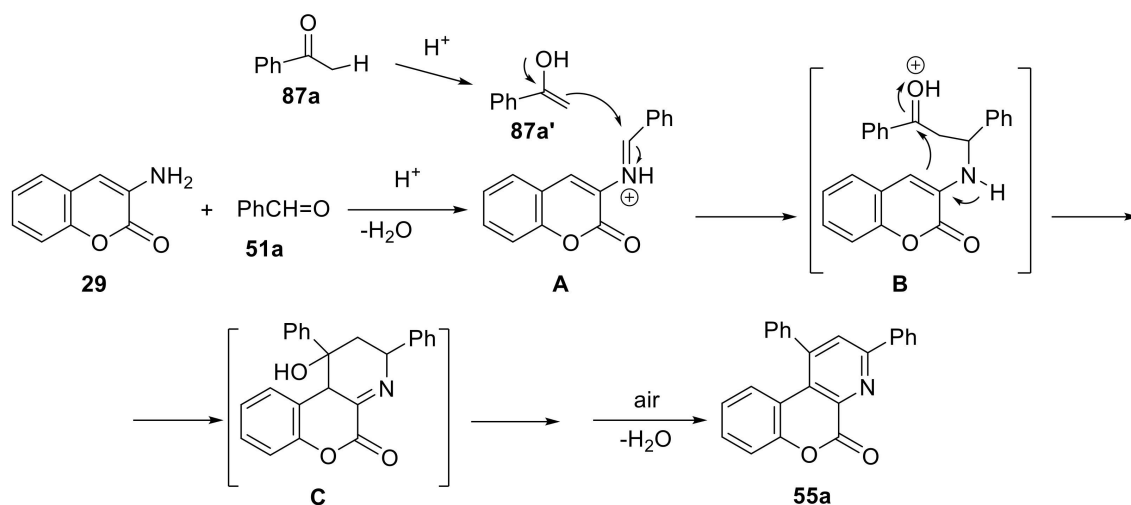
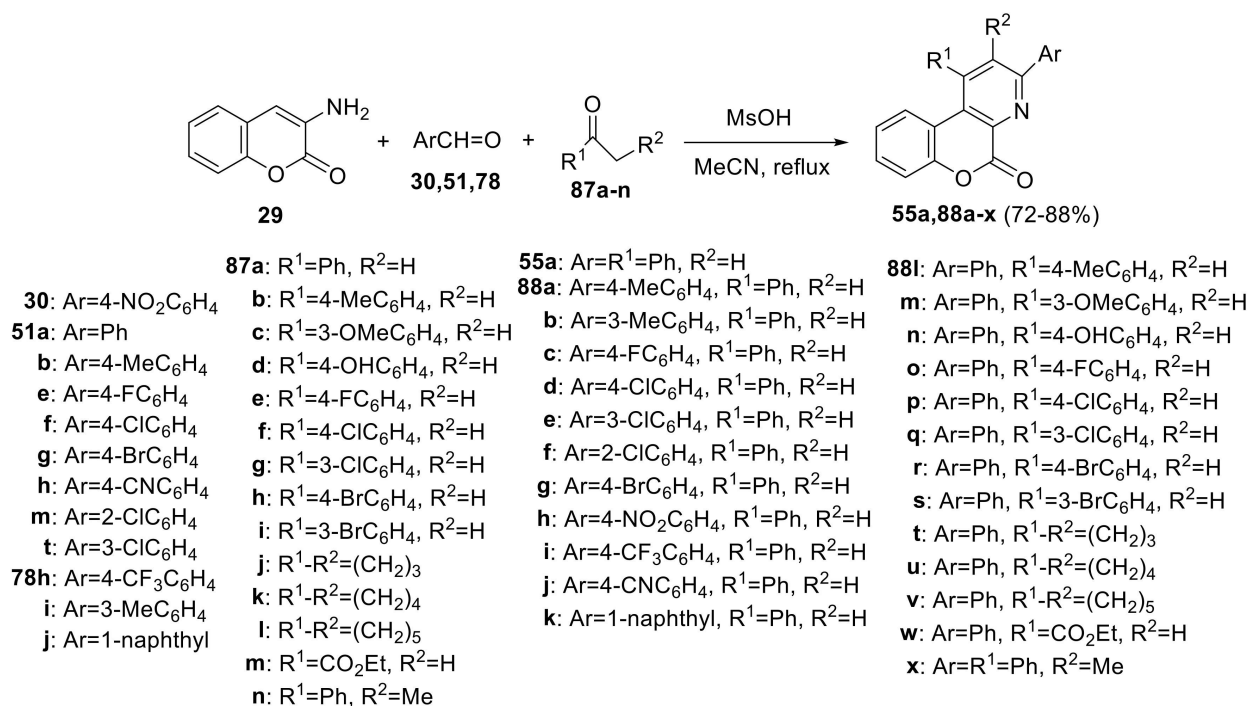




**Scheme 17.** Synthesis of ferrocenyl-substituted pyrido [3,2-g]coumarins **80a–o** by Povarov reaction in the presence of Ce(OTf)<sub>3</sub> as a catalyst.



**Scheme 18.** Synthesis of dihydro- and tetrahydropyrido [2,3-c]coumarin derivatives via a one-pot three-component Povarov reaction catalyzed by BiCl<sub>3</sub>.



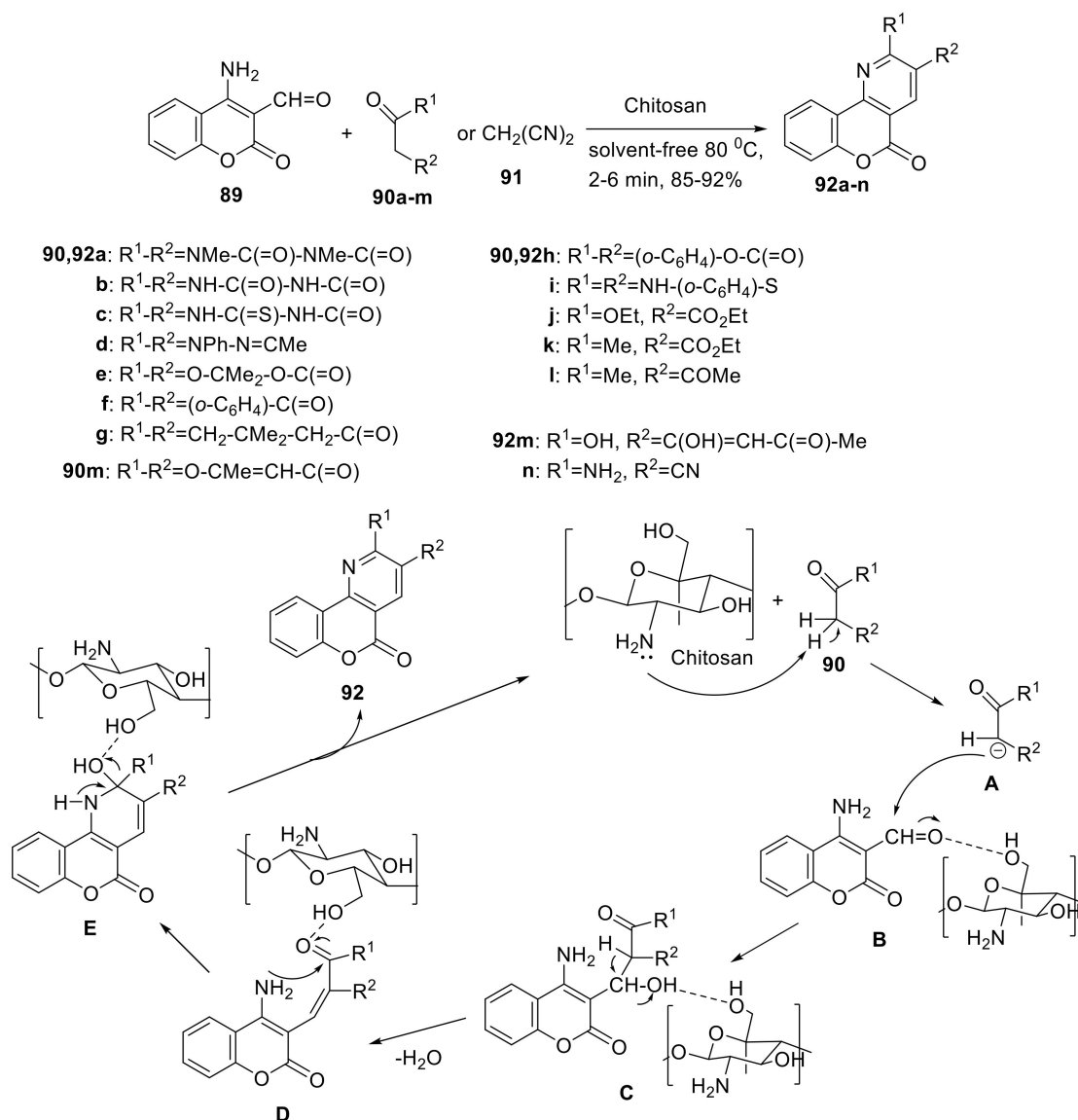
**Scheme 19.** Synthesis of substituted pyrido [2,3-*c*]coumarins **55a**, **88a–x** by a one-pot three-component reaction of 3-aminocoumarin (**29**) with aromatic aldehydes and acetophenones **87a–n** in the presence of methanesulfonic acid.

### Friedlander Reaction

Friedlander reaction is the reaction of *o*-aminobenzaldehydes with carbonyl compounds containing  $\alpha$ -methylene group in the presence of base or acid, or without catalyst under heating, leading to the synthesis of quinolines [98–100]. For the mechanism of this reaction two routes are accepted, Schiff base formation or intermolecular aldol reaction. In both cases, a cyclodehydration follows to give quinoline.

In 2013, Siddiqui and Khan applied the Friedlander reaction of 4-amino-3-formylcoumarin (**89**) with active methylene carbonyl compounds **90a–m** or malononitrile (**91**) under solvent-free conditions at 80 °C in the presence of chitosan as a green catalyst to get the fused pyrido [3,2-*c*]coumarin **92a–n** [101]. Barbituric acid (**90b**), Meldrum's acid (**90e**), 1,3-indandione (**90f**), dimedone (**90g**), 4-hydroxycoumarin (**90h**), ethyl acetoacetate (**90k**), acetylacetone (**90l**) were between the active methylene carbonyls. As a plausible mechanism the chitosan

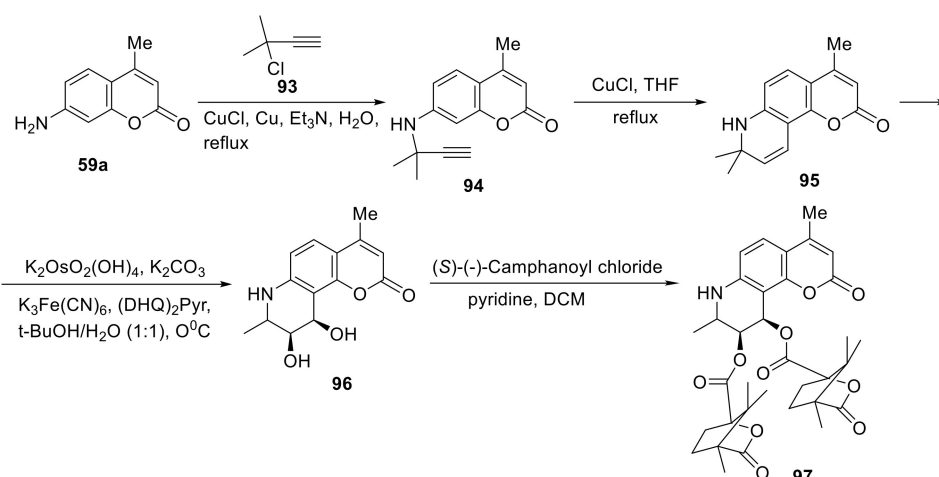
abstracted a hydrogen to give carbanion **A**, which added to the electrophilic carbon of formyl-group of **B** (Scheme 20). Elimination of water from the resulted specie **C** led to unsaturated coumarin intermediate **D**. A 1,2-Addition of the 4-NH<sub>2</sub> group to the carbonyl of **D** and elimination of water from the intermediate **E** afforded the product **92**.



**Scheme 20.** Synthesis of pyrido [3,2-*c*]coumarins **92a–n** by the Friedlander reaction of 4-amino-3-formylcoumarin (**89**) with active methylene carbonyl compounds **90a–m**, **91**.

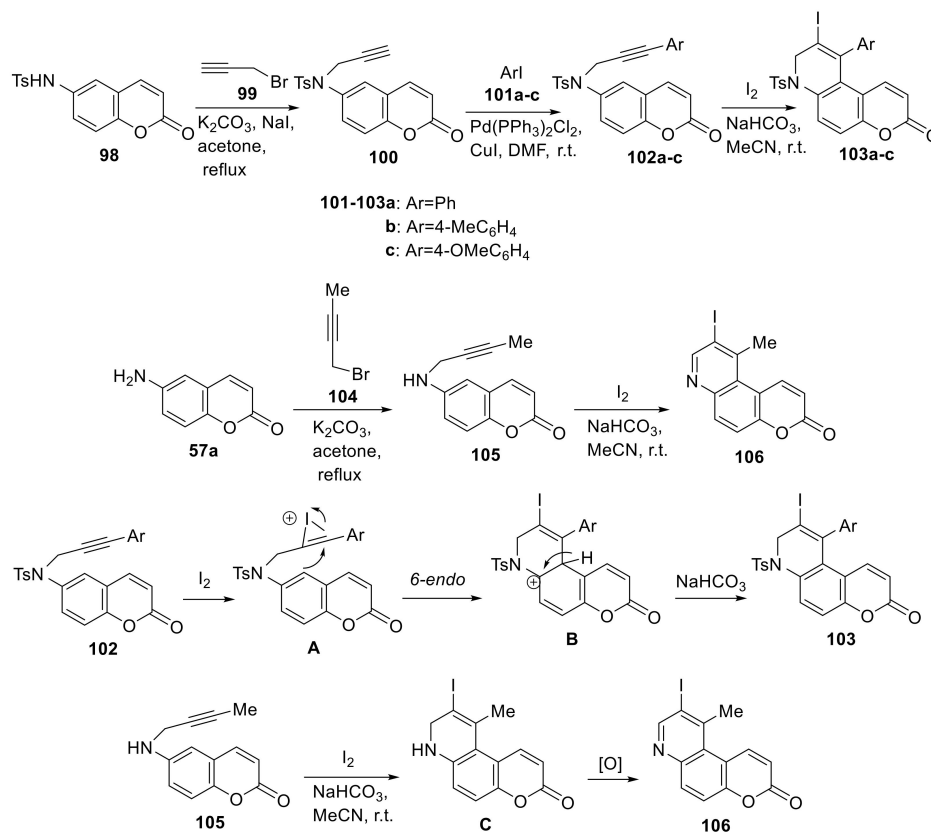
#### From Propargylaminocoumarins

In 2007, Lee and coworkers synthesized 9,10-Di-*O*-camphanoyl-4,8,8-trimethyl-7,8,9,10-tetrahydro-2*H*-pyrano [2,3-*f*]quinolin-2-one (**97**) by the esterification of aza-*cis*-khellactone **96** with (*S*)-(-)-camphanoyl chloride [102]. The latter was prepared by the asymmetric Sharpless dihydroxylation with AD-mix- $\alpha$  of 4-methyl-1'-azaseselin (**95**), which was formed by the aza-Claisen rearrangement and cyclization of propargylaminocoumarin **94** in the presence of CuCl in refluxing THF (Scheme 21). The substitution of 3-chlorobutynes **93** by the aminocoumarin **59a** resulted in adduct **94**. Compound **97** as well as analog pyran derivatives have been studied for their anti-HIV activity using the HIV-1 IIB strain in H9 lymphocytes. It was found that **97** has an anti-HIV activity with EC<sub>50</sub> = 0.77  $\mu$ M and therapeutic index (TI) > 42.



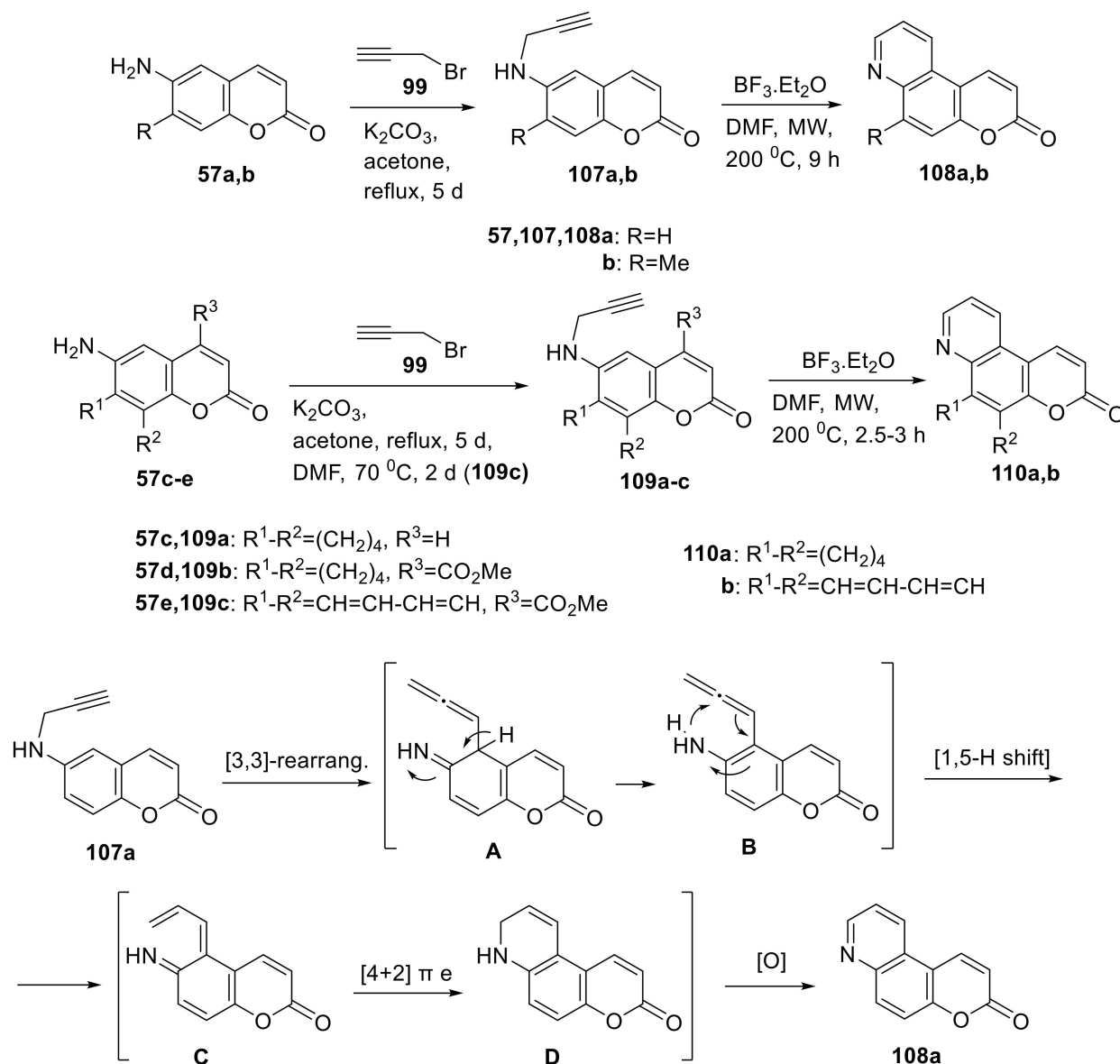
**Scheme 21.** Synthesis of dihydropyridocoumarin **95** from the aza-Claisen rearrangement-cyclization of propargylaminocoumarin **94** under heating in the presence of  $\text{CuCl}$ .

In 2011, Majumdar and coworkers used iodine for the Claisen rearrangement and cyclization of 6-propargylaminocoumarins **102a–c** and **105** to obtain selectively the angular dihydropyridocoumarins **103a–c** and the pyridocoumarin **106**, respectively [103]. For the mechanism, they suggested an initial formation of the iodonium intermediate **A**, followed by the nucleophilic attack of the 5-carbon of aromatic ring to the activated triple bond. Hydrogen abstraction by the base from the intermediate **B** led to the final product **103** (Scheme 22). In the case of non-*N*-substituted dihydro-intermediate **C** the oxidation by the iodine might be responsible for the synthesis of pyridocoumarin **106**.



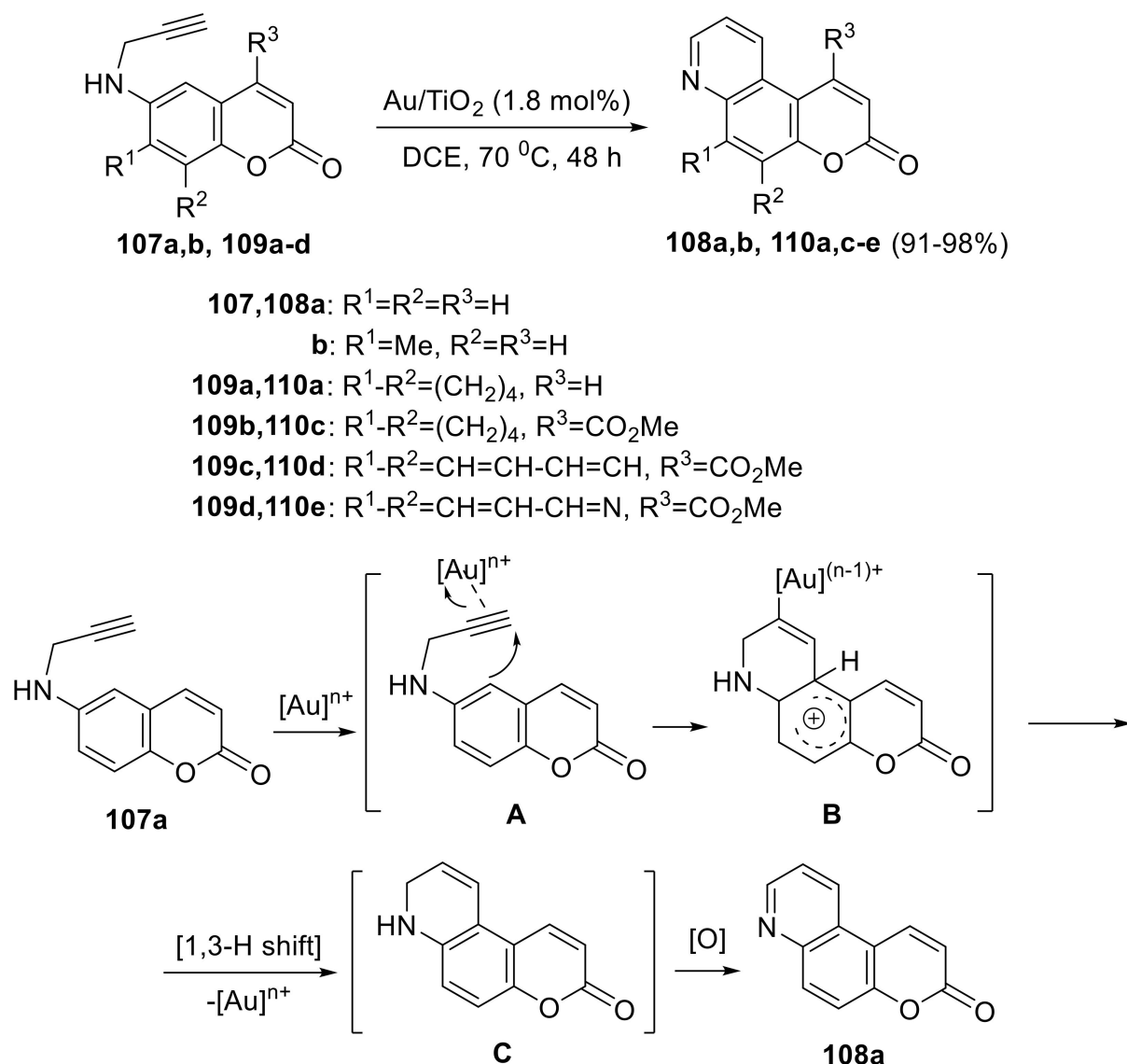
**Scheme 22.** Synthesis of dihydropyridocoumarins **103a–c** and pyridocoumarin **106** from the propargylaminocoumarins **102a–c** and **105**, respectively, under treatment by iodine and  $\text{NaHCO}_3$ .

The same year, our group using  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  under microwave irradiation obtained, also selectively, the angular [5,6]-fused pyridocoumarins **108a,b** through the aza-Claisen rearrangement of propargylaminocoumarins **107a,b** [104]. The pyridocoumarins **110a,b** were isolated similarly from the propargylaminocoumarins **109a–c**. The imino-adduct **A** was formed through the aza-Claisen rearrangement of **107a**, followed by tautomerization to **B** (Scheme 23). 1,5-H Shift of the latter gave the intermediate **C**, which by a Diels–Alder intramolecular reaction furnished the 1,2-dihydropyridocoumarin **D**. Oxidation of **D** led to the final product **108a**.



**Scheme 23.** Synthesis of [5,6]-fused pyridocoumarins through aza-Claisen rearrangement of the corresponding propargylaminocoumarins in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  under microwave irradiation.

In 2013, our group utilized the Au-NPs for the catalyzed synthesis of the pyridocoumarins **108a,b** and **110a,c–e** in excellent yields from the propargylaminocoumarins **107a,b** and **109a–d**, respectively [105]. A plausible mechanism with electrophilic aromatic substitution of the benzene ring of coumarin with the activated alkyne- $\pi$  complex of **A** to the vinyl-Au intermediate **B** through a 6-*endo-dig* cyclization is presented in Scheme 24. 1,3-H Shift under regeneration of the catalyst gave 1,2-dihydropyridocoumarin **C**, which by air-oxidation resulted in the isolation of [5,6]-fused pyridocoumarin.



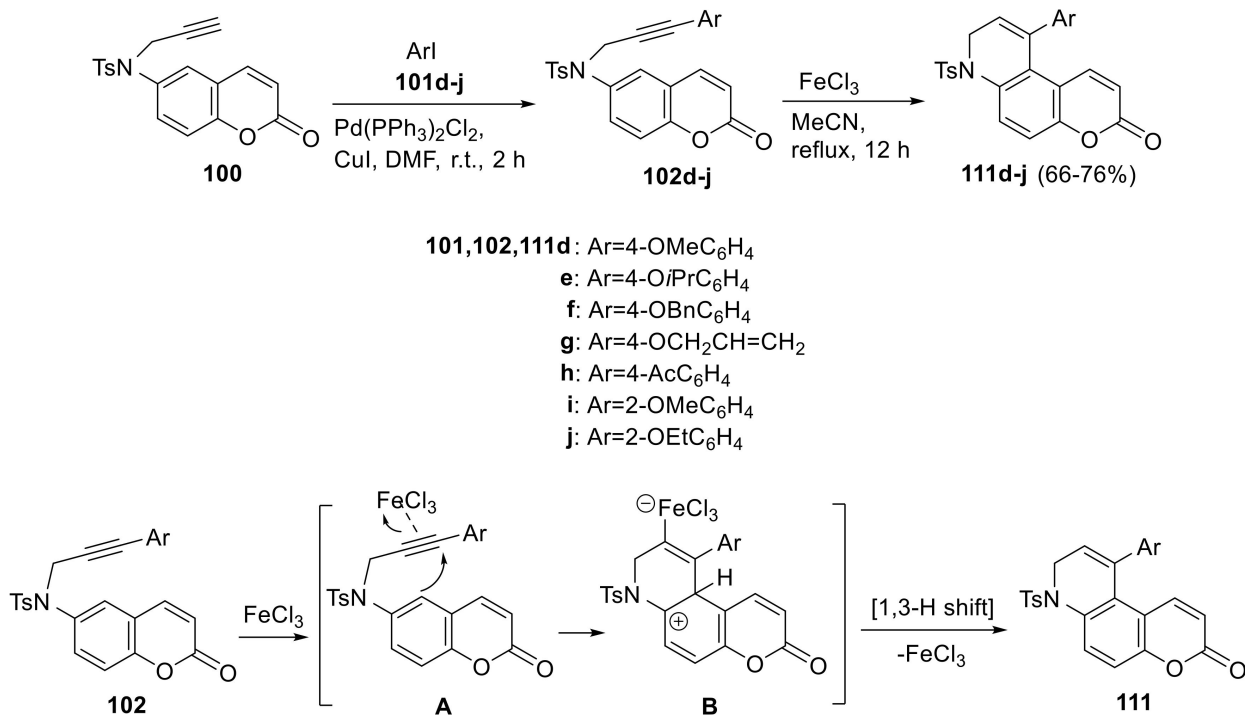
**Scheme 24.** Synthesis of [5,6]-fused pyridocoumarins from propargylaminocoumarins under Au-NPs catalysis.

In 2014 Majumdar and Ponra synthesized the dihydropyrido [3,2-*f*]coumarins **111d–j** from the propargylaminocoumarins **102d–j** in the presence of  $\text{FeCl}_3$  [106]. The expected pyrido [3,2-*f*]coumarins were not isolated during the above reactions. For the proposed mechanism,  $\text{FeCl}_3$  activates the alkyne moiety of **102** to give the intermediate  $\pi$ -complex **A** (Scheme 25). An intramolecular 6-*endo-dig* cyclization of **A** produced the charged species **B**. Upon deprotonation of the latter, followed by an 1,3-H shift and elimination of  $\text{FeCl}_3$  the final product **111** was formed.

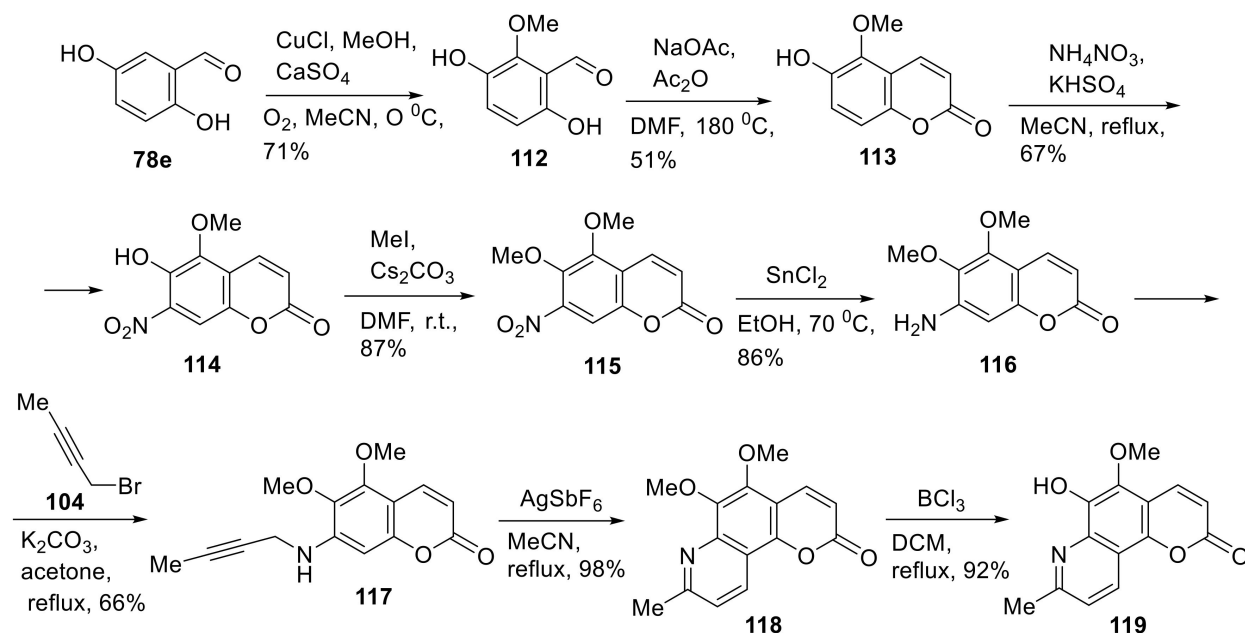
In 2019, Han and coworkers prepared goniothaline **A** (**118**) through the Ag-catalyzed cycloisomerization of propargylaminocoumarin **117**, while by the following regioselective demethylation due to neighboring pyridine nitrogen goniothaline **B** (**119**) was obtained [53]. Propargylamino-compound **117** has been synthesized by propargylation of aminocoumarin **116**, which has been prepared via a five-step procedure starting from 2,5-dihydroxybenzaldehyde (**78e**) (Scheme 26).

In continuation of their work, the same group reported the synthesis of pyrido [3,2-*c*]coumarins **124a–i** by the  $\text{AgNO}_3$  catalyzed cycloisomerization of 4-propargylaminocoumarins **123a–i** [107]. Propargylaminocoumarins have been synthesized by the nucleophilic sub-

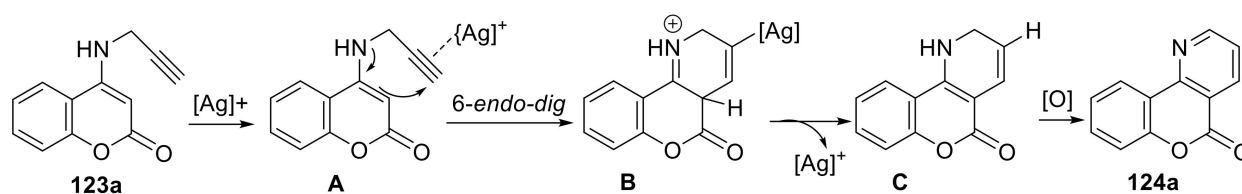
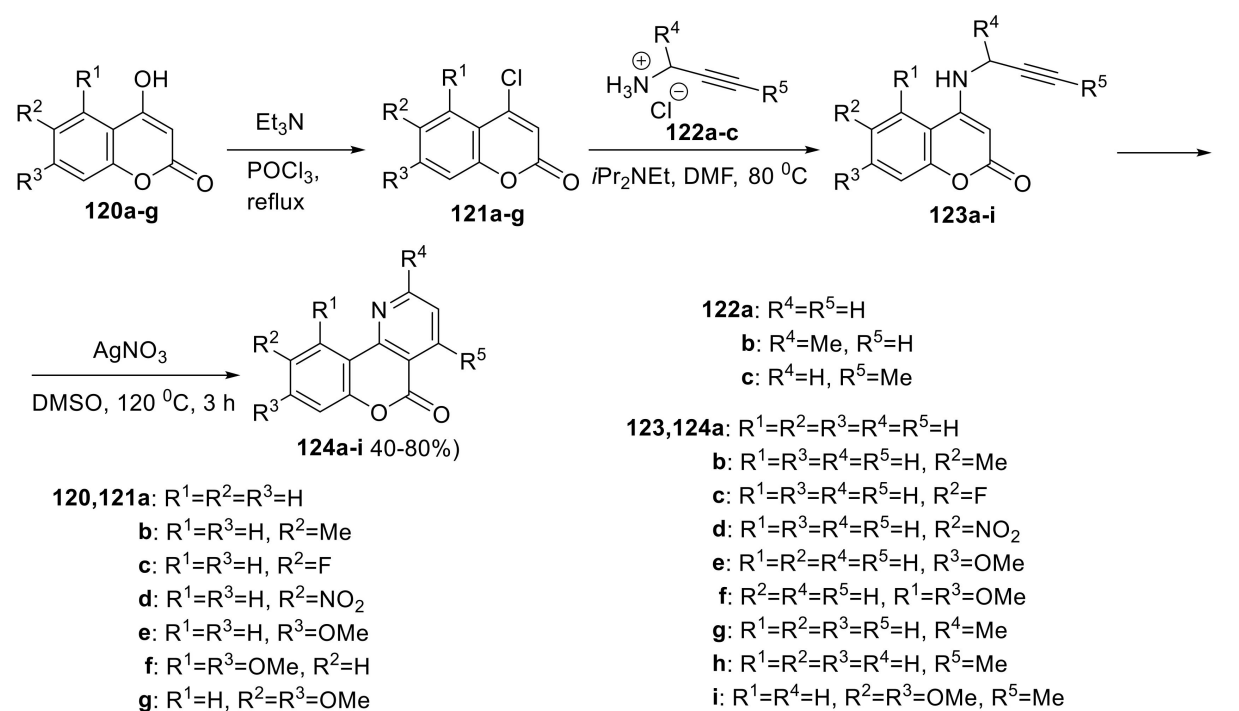
stitution of 4-chlorocoumarins **121a–g** with the propargylamine salts **122a–c** (Scheme 27). Polynemoraline C (**124i**) is a natural product synthesized by this method. As a plausible mechanism, the alkyne moiety of **123a** coordinated with silver catalyst to give intermediate **A**. An intramolecular attack of the enamine carbon atom to the electrophilic alkyne bond of **A** via a 6-*endo-dig* cyclization resulted in the 6-membered **B**. 1,3-H Shift under demetallation gave the 1,2-dihydro pyridocoumarin **C**, which oxidized to afford the final product **124a**.



**Scheme 25.** Synthesis of dihydropyrido [3,2-*f*]coumarins **111d–j** from the propargylaminocoumarins **102d–j** in the presence of FeCl<sub>3</sub>.



**Scheme 26.** Synthesis of goniotalines A (**118**) and B (**119**).



**Scheme 27.** Synthesis of pyrido [3,2-*c*]coumarins **124a–h** and polynemoraline C (**124i**).

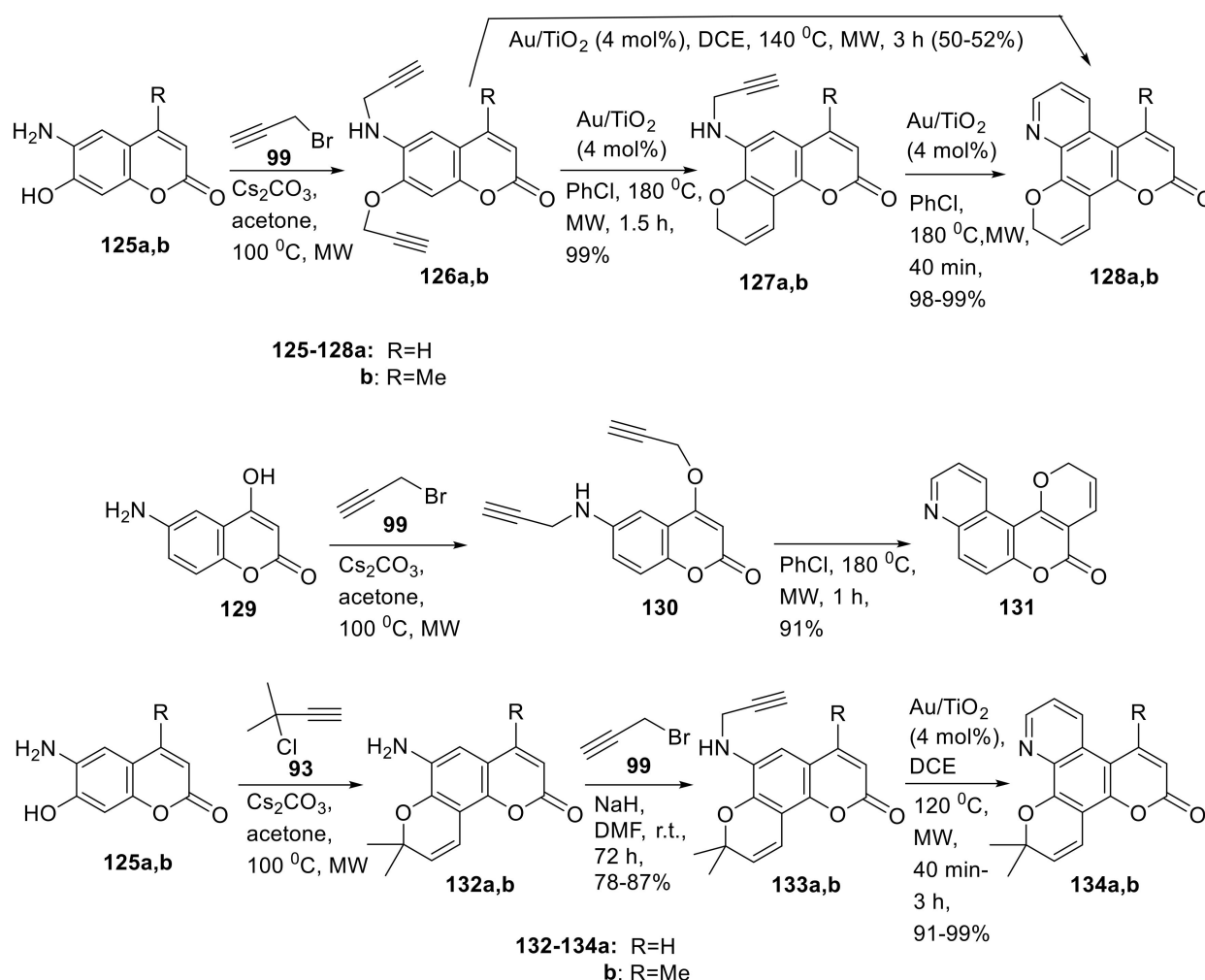
Very recently, our group synthesized bis-fused pyridopyranocoumarins **128a,b**, **131**, **134a,b** from the propargylaminocoumarin derivatives **126a,b**, **127a,b**, **120**, **133a,b** in excellent yields under Au-NPs catalyzed cycloisomerization reaction followed by air oxidation [108]. The propargylaminocoumarins have been synthesized from aminohydroxycoumarins **125a,b** and **129** under propargylation with propargyl bromide (**99**) or 3-chloro-3-methylbutyne (**93**) (Scheme 28). The compounds were tested for their antioxidant and anti-AChE activities. The derivatives **128a**, **132a**, **134a,b** presented promising anti-lipid peroxidation and anti-AChE activities.

#### Multi Component Reactions (MCR) of Aminocoumarin

Multicomponent reactions (MCRs) are an important method for the one-pot synthesis of organic compounds under atom economy of the three or more participating starting materials [109–113]. Povarov reaction, as we have mentioned earlier, is an application of MCRs for the synthesis of pyridocoumarins.

In 2012, Khan and Das utilized the MCR of 3-aminocoumarins **29**, **50a,b**, aldehydes **30**, **51**, **78** and cyclic 1,3-diketones **90m**, **135a,b** to prepare 1,4-dihydropyrido[2,3-*c*]coumarin derivatives **136a–s** in the presence of catalytic amount (20 mol%) of *p*-toluenesulfonic acid (*p*-TSA) [114]. The Knoevenagel condensation of benzaldehyde (**51a**) with dimedone (**90g**) gave the adduct **A**, which underwent a Michael addition of 3-aminocoumarin (**29**) leading to the intermediate **C** (Scheme 29). An intramolecular ring closure reaction of the latter followed by dehydration of the intermediate **D** resulted in the final product **136a**.

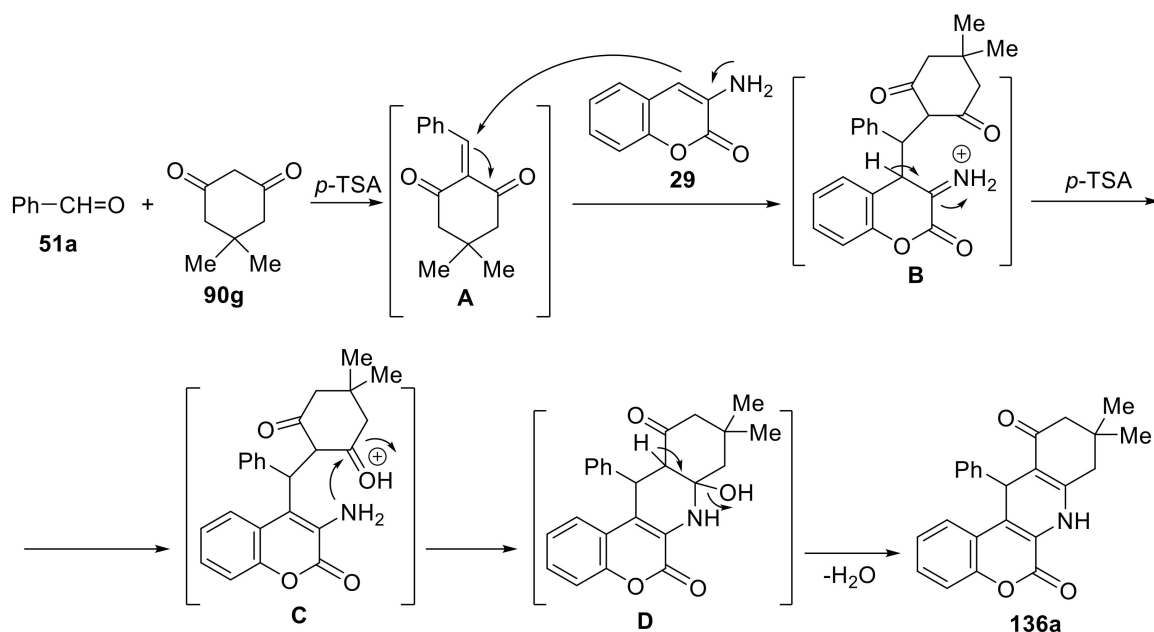
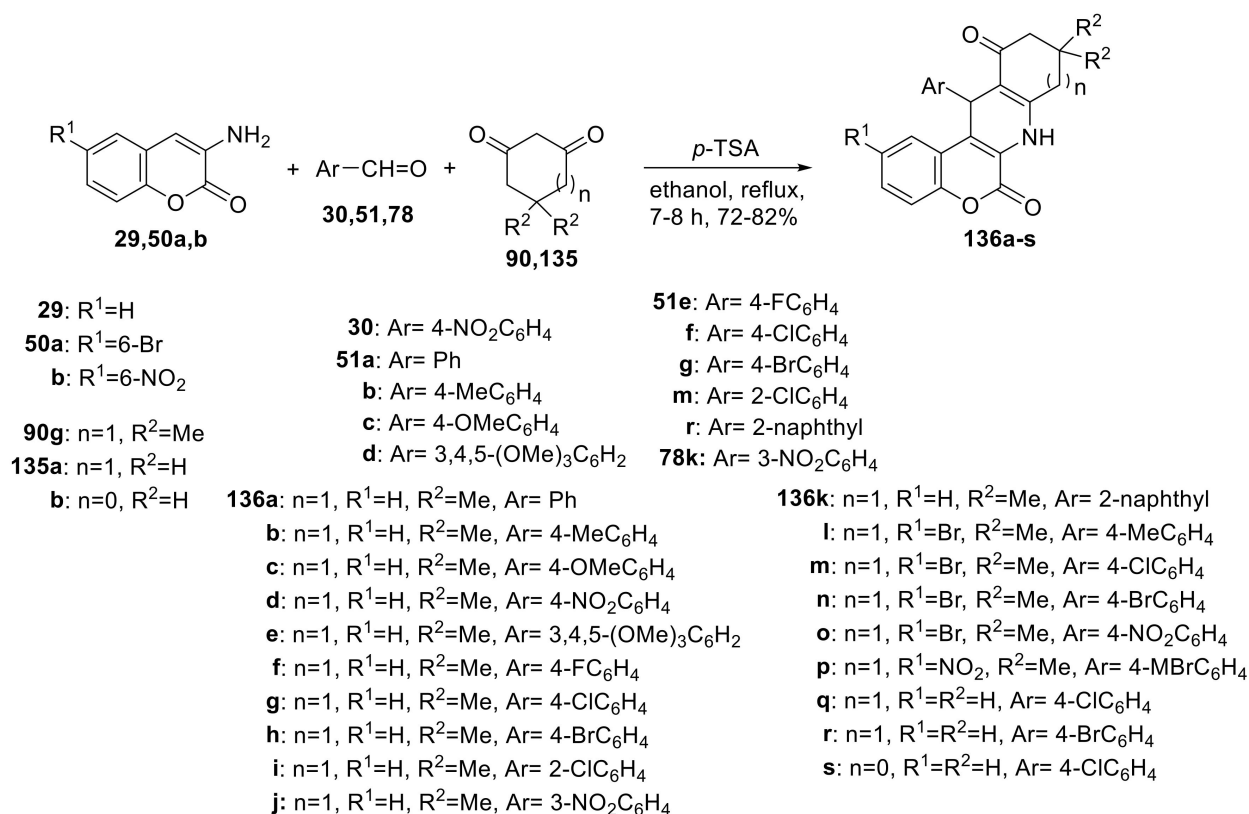




**Scheme 28.** Synthesis of fused dipyranoquinolinones **128a,b**, **131**, **134a,b**.

The same year, Paul and Das via a MCR of 4-aminocoumarin (**13**), aromatic aldehydes **30**, **51** and indandione (**90f**) or dimedone (**90g**) in the presence of the organic catalyst, ( $\pm$ )-lactic acid, in a green solvent, ethyl-*L*-lactate, obtained the 1,4-dihydropyrido [3,2-*c*]coumarin derivatives **137a–h** and **138a–h**, respectively [115]. At first, a Knoevenagel condensation led to the intermediate **A**. The formation of a H-bond between lactic acid and the carbonyls of **A** may increase the electrophilicity of the carbonyls, accelerating the Michael addition of 4-aminocoumarin (**13**) (Scheme 30). The intermediate **B** formed, upon tautomerization to adduct **C** and elimination of water, resulted in the final products **137** or **138**.

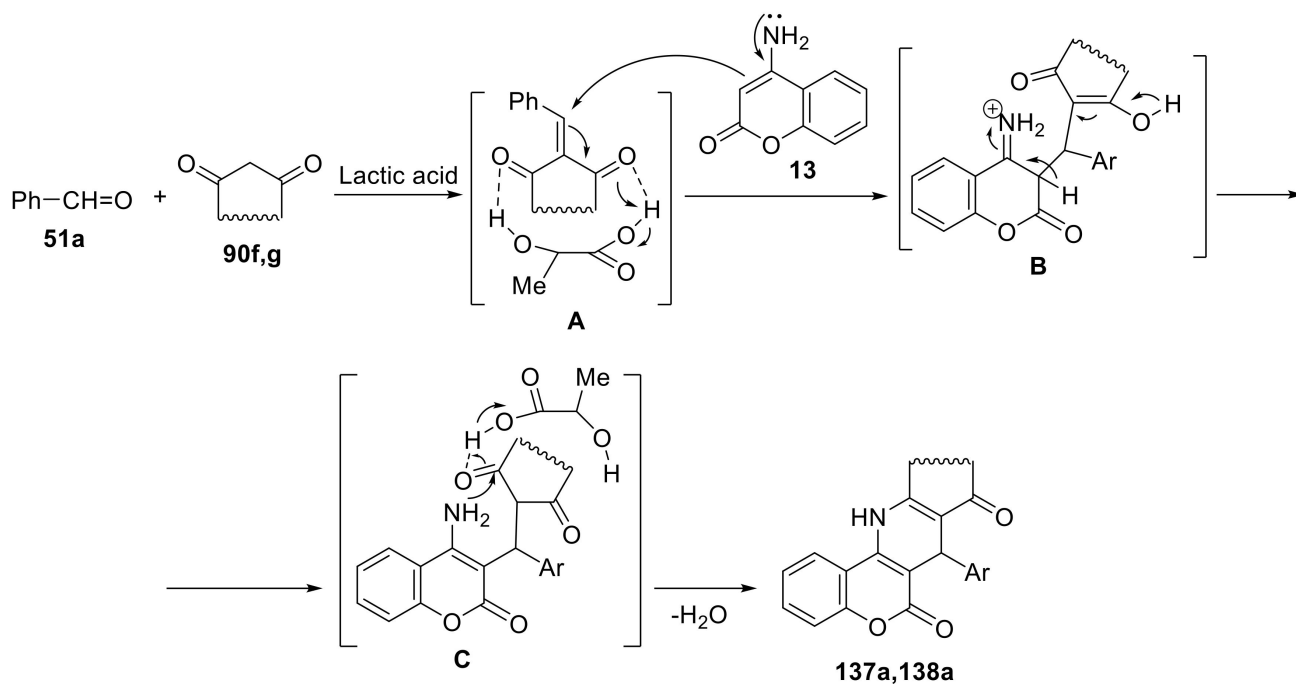
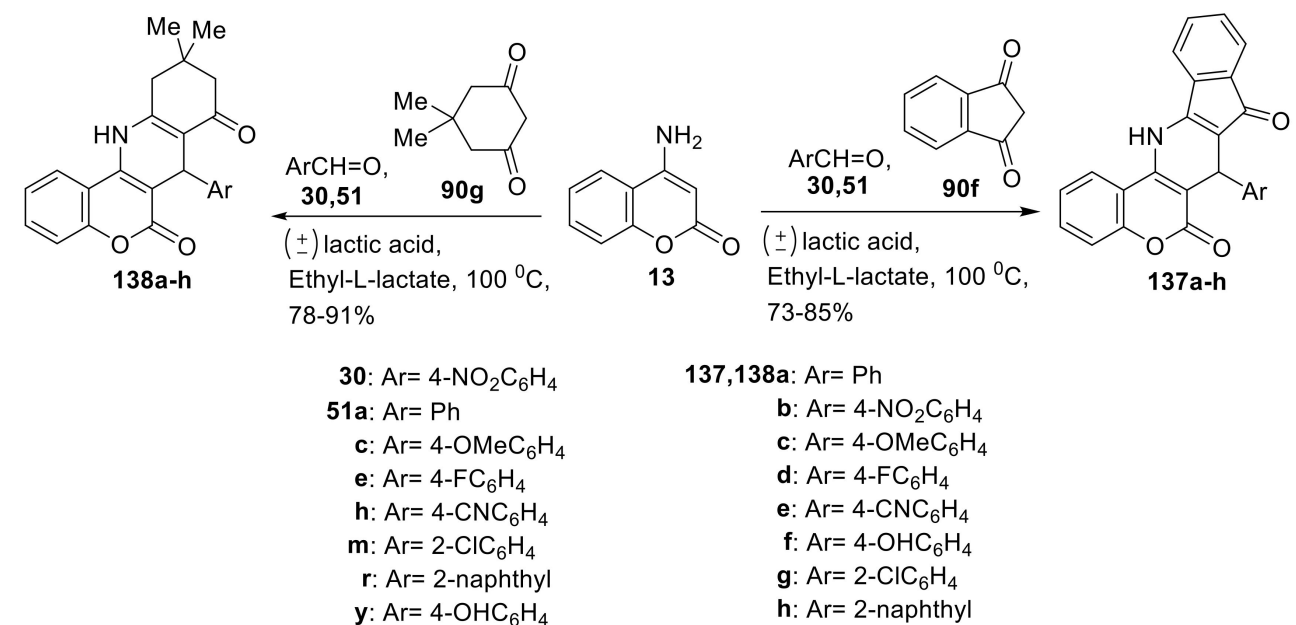
In 2013, the same group prepared the pyrido [3,2-*c*]coumarin derivatives **139a–d** by a MCR domino process from 4-aminocoumarin (**13**), aldehydes and malononitrile (**91**) under heating in water at 80 °C in the presence of triethanolamine, a Lewis-base-surfactant combined catalyst (LBSC), which acted as a catalyst to activate the substrates and as a surfactant forming colloidal particles [116]. A Knoevenagel condensation of aldehyde **51a** with **91** gave the  $\alpha,\beta$ -unsaturated nitrile **A**, which upon Michael addition of 4-aminocoumarin (**13**) afforded the intermediate **B** (Scheme 31). Tautomerization of the latter to **C** followed by intramolecular cyclization, catalyzed by triethanolamine, led to the intermediate **D**. Air oxidation resulted in the final product **139a**.



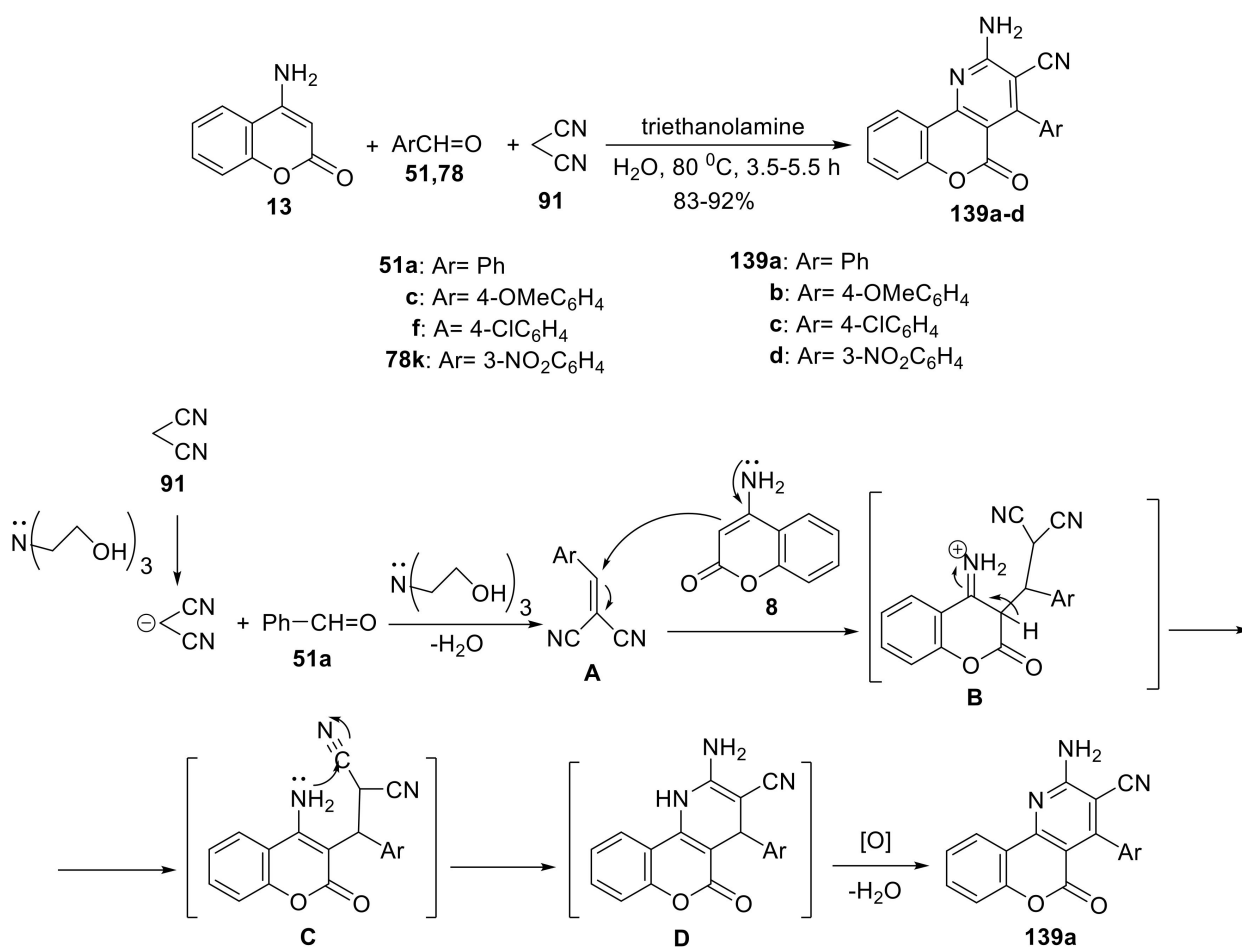
**Scheme 29.** Synthesis of 1,4-dihydropyrido [2,3-c]coumarins via MCRs of aldehydes, 1,3-cyclic diketones and 3-aminocoumarins.

In 2014, Kar and coworkers reported the synthesis of pyranoquinolin-3-ones **142a,b**, **143a,b**, **149** and pyranoacridin-3-ones **146a–c** by the thermolysis of enamino imine hydrochloride derivatives of 7-aminocoumarin **141a,b**, **148** and **145a–c**, respectively [117]. These derivatives were prepared by the three-component reaction of 7-aminocoumarin (**57a**) with  $\beta$ -chloroacrolein derivatives **140a,b** or 1-chloro-3,4-dihydronaphthalene-2-carbaldehydes **144a–c** or 2-chloroacenaphthylene-1-carbaldehyde **147** (Scheme 32). Oxidation of compounds

**146a–c** with DDQ resulted in the fully aromatic 3*H*-benzo[*h*]pyrano [3,2-*a*]acridine-3-one derivatives **150a–c**. A few years later, in 2017, Patra performed a modification of the above three-component reaction by using only one equivalent of 7-aminocoumarin (**57a**) and  $\beta$ -chloro- $\alpha,\beta$ -unsaturated aldehydes in methanol at 15 °C without the presence of hydrochloric acid [118]. This procedure led to the preparation of the intermediate chlorovinyl imine derivatives **151a,b** and **152a–d** (Scheme 33). Thermolysis of the latter at 230–260 °C resulted in the synthesis of pyranoquinoline-3-one derivatives **142a,b** and pyranoacridine-3-one derivatives **146a–d** with better yields.



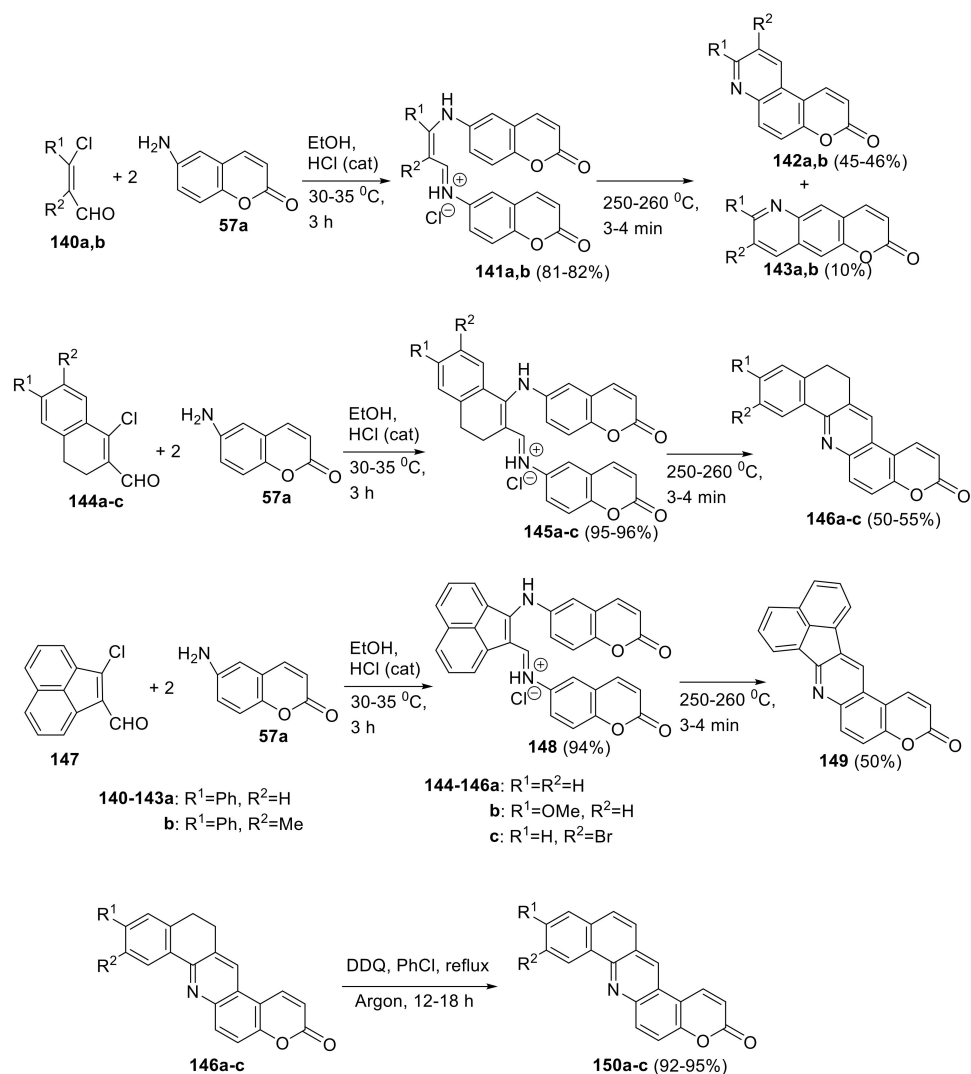
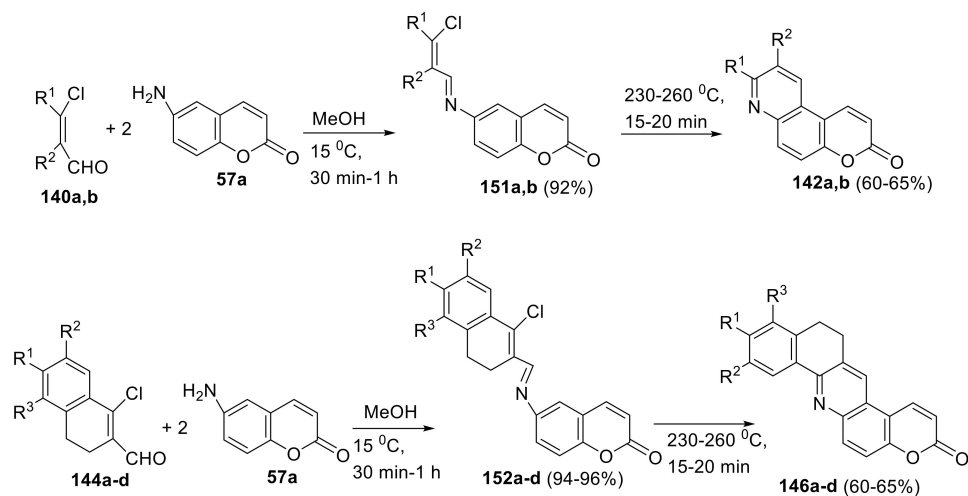
**Scheme 30.** Synthesis of 1,4-dihydropyrido [3,2-*c*]coumarin derivatives **137a–h** and **138a–h** via a MCR of aldehydes and indandione or dimedone.

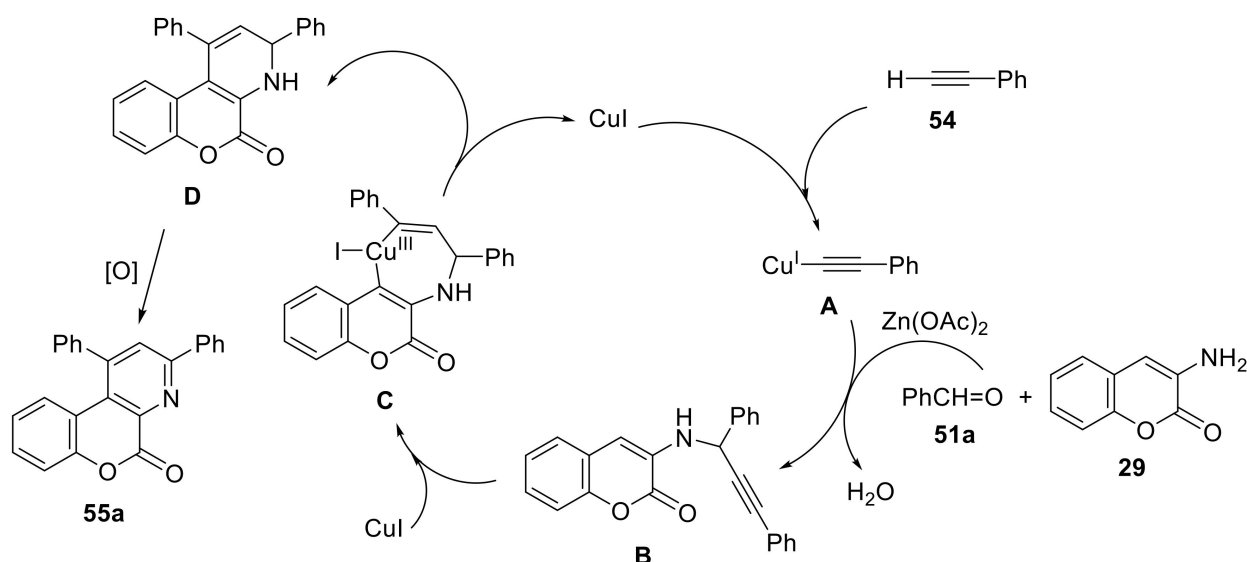
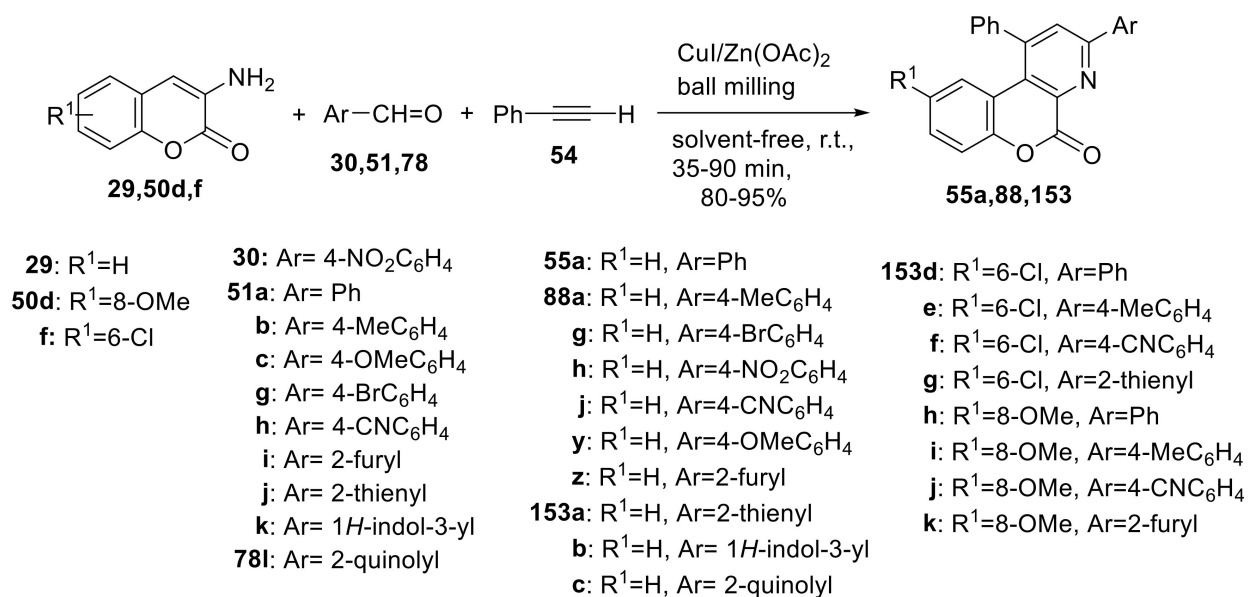


**Scheme 31.** Synthesis of pyrido [3,2-*c*]coumarin derivatives **139a–d** by a MCR domino process from 4-aminocoumarin (**13**), aldehydes and malononitrile (**91**).

In 2017, Kausar and Das reported the synthesis of pyrido [2,3-*c*]coumarin derivatives using the three-component reaction of 3-aminocoumarins, aldehydes and phenylacetylene in the presence of CuI-Zn(OAc)<sub>2</sub> as catalyst without solvent, under ball milling green conditions [119]. The reaction involves one C-N coupling and two C-C couplings in a combo-catalysis cycle (Scheme 34) in the proposed mechanism. The activation of terminal alkyne produced the copper carbide **A**. By a C-C and C-N bond formation between aminocoumarin (**29**), benzaldehyde (**51a**) and carbide **A** under the Lewis acid Zn(OAc)<sub>2</sub> catalysis the propargylamino intermediate **B** was formed. Oxidative C-H insertion after the activation of triple bond, and the  $\pi$ -bond of **B** by CuI, led to the seven-membered intermediate **C**, which underwent a C-C coupling under reductive elimination to give CuI and the 1,2-dihydropyrido [3,2-*c*]coumarin **D**. Oxidation of the latter resulted in the final product **55a**.

Recently, Rad-Moghadam and coworkers obtained the spiro 1,4-dihydropyrido [3,2-*c*]coumarin derivatives **156a–f** via a three-component reaction of 4-aminocoumarin (**13**), isatin derivatives **154a–f** and 3-methyl-1*H*-pyrazol-5-amine (**155**) in the presence of *p*-TSA in ethanol under sonication or heating [120]. They proposed two possible pathways (Scheme 35). In each path, A or B condensation of isatin (**154a**) with **13** or **155** led to the formation of the corresponding intermediates **A** or **E**. Nucleophilic addition of **155** or **13** to the **A** or **E**, respectively, gave the adducts **B** or **F**. The [3,3]-Sigmatropic rearrangement to **C** or **G**, followed by elimination of ammonia, afforded **D** or **H**. Tautomerization of both intermediates resulted in the final spiro compound **156a**.

Scheme 32. Synthesis of pyranoquinolin-3-ones **142a,b**, **143a,b**, **149** and pyranoacridin-3-ones **146a-c**.Scheme 33. Synthesis of pyranoquinoline-3-one and pyranoacridine-3-one derivatives **142a,b** and **146a-d**, respectively, via the intermediate chlorovinyl imine derivatives **151a,b** and **152a-d**.



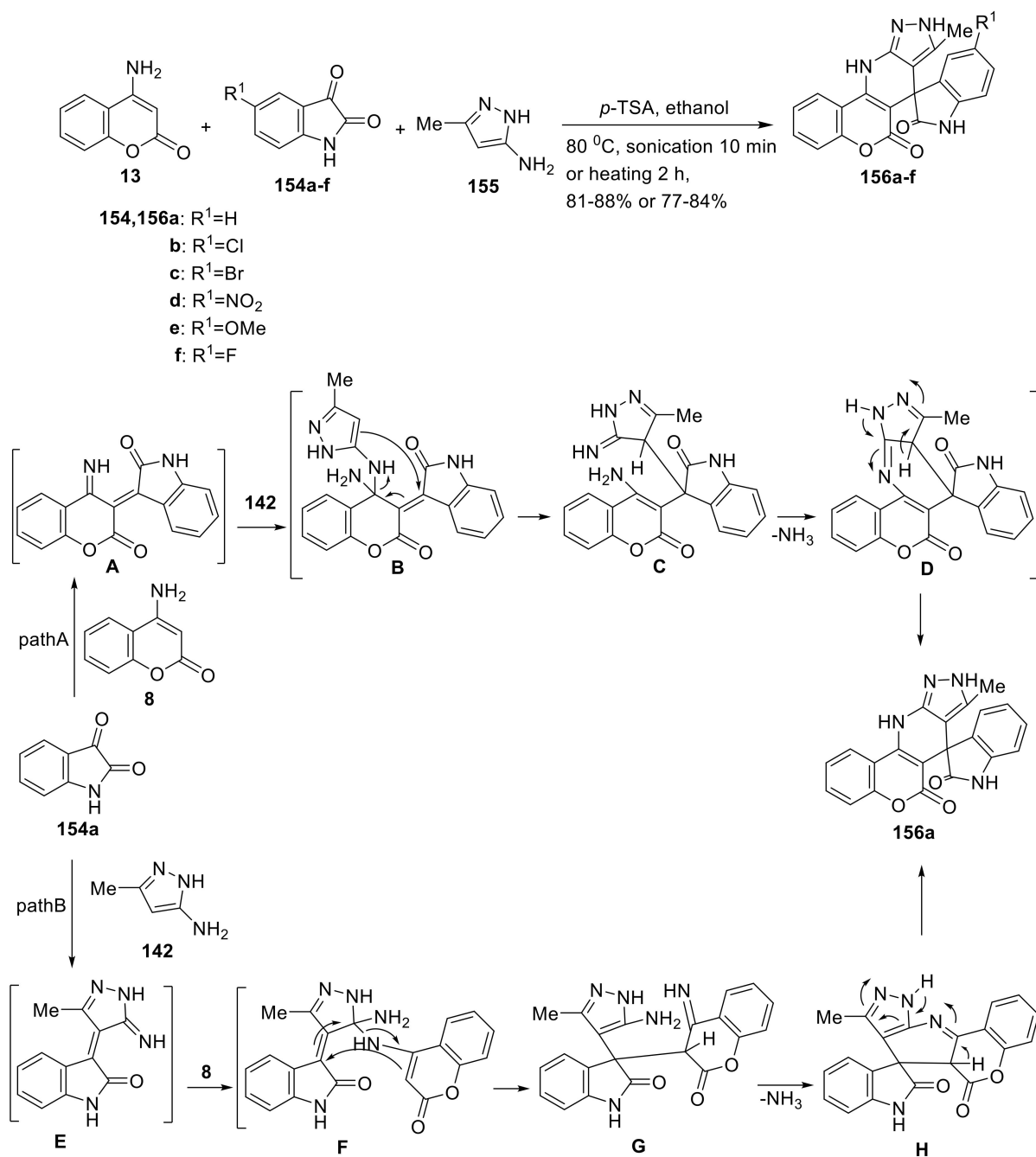
**Scheme 34.** Synthesis of pyrido [2,3-*c*]coumarin derivatives 3-aminocoumarins, aldehydes and phenylacetylene in the presence of  $\text{CuI-Zn(OAc)}_2$  as catalyst without solvent under ball milling.

The same year, Bregadiolli and coworkers synthesized chromeno [4,3-*b*]pyridine derivatives **158a–i** from a MCR between 4-aminocoumarin (**13**), aromatic benzaldehydes and ethyl benzoylacetate (**157**) catalyzed by  $\text{NbCl}_5$  [121]. In the proposed mechanism, a Knoevenagel condensation occurred between the enolic form of ethyl benzoylacetate (**157**) and benzaldehyde complexed with niobium, leading to the unsaturated intermediate **B** (Scheme 36). The complexation of  $\text{NbCl}_5$  with carbonyl-oxygen of **C** reduced the electron density of the double bond facilitating the attack of  $\text{NH}_2$ -group of **13** to give the intermediate **D**. After removing of a proton from the ammonium group and cyclization of the resulting **E** under elimination of water to **F**, followed by deprotonation, the 1,4-dihydropyrido [3,2-*c*]coumarin **158a** was formed.

#### Metal-Catalyzed Reactions of Aminocoumarin Derivatives

In 2008, Majumdar and coworkers utilized the Pd-catalyzed intramolecular Heck reaction of 6- or 7-benzoylaminocoumarins **162a–c** or **164a–c** for the regioselective synthesis of angular 3*H*-pyrano [3,2-*a*]phenanthridine-3,8(7*H*)-diones **165a–c** or linear 11-methyl-5*H*-

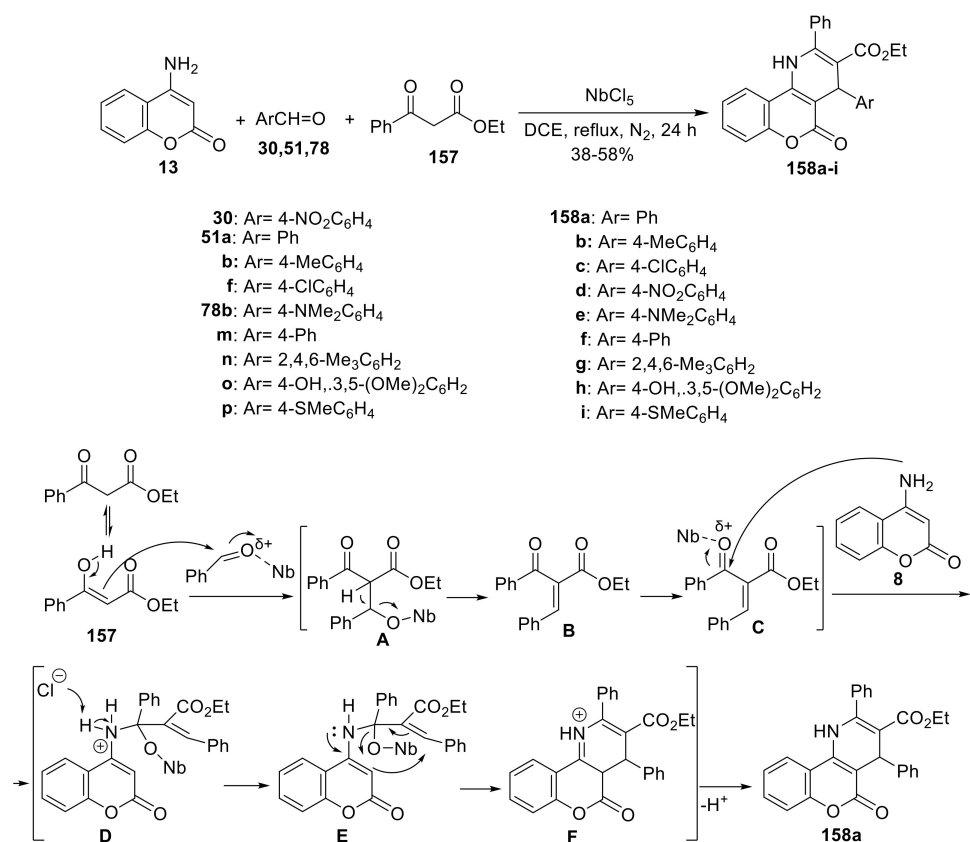
pyrano [3,2-*b*]phenanthridine-5,9(6*H*)-dione **166a–c**, respectively [122]. In the case of no *N*-substituted amides **162a** and **164a** the  $\text{Ag}_2\text{CO}_3$  was used as a base in the place of KOAc at 160 °C (Scheme 37).



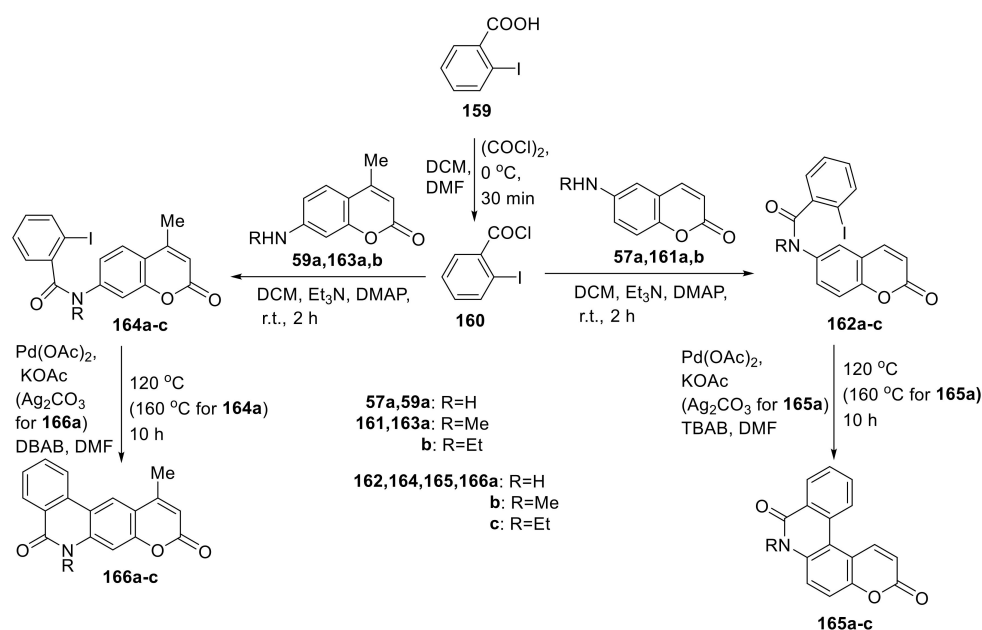
**Scheme 35.** Synthesis of spiro 1,4-dihydropyrido [3,2-*c*]coumarin derivatives **156a–f** via a three-component reaction of 4-aminocoumarin (**13**), isatin derivatives **154a–f** and 3-methyl-1*H*-pyrazol-5-amine (**155**) in the presence of *p*-TSA.

In 2012, Majumdar et al., reported the synthesis of pyrido [3,2-*f*]coumarins **168a–f** by the Indium (III) chloride-catalyzed reaction of 5-allyl-6-aminocoumarin (**167**) with benzaldehydes **51** [123]. In the proposed mechanism, the imine **A** formed from **167** and **51a** in the presence of  $\text{InCl}_3$  at first, followed by an 1,5-*H* shift to the intermediate **B**. The aromatization of benzene ring to **C** via an 1,7-*H* shift followed by an  $6\pi$ -electrocyclization

to intermediate **D** and a subsequent 1,5-H shift to **E**, which was oxidized, led to the final product **168a** (Scheme 38).

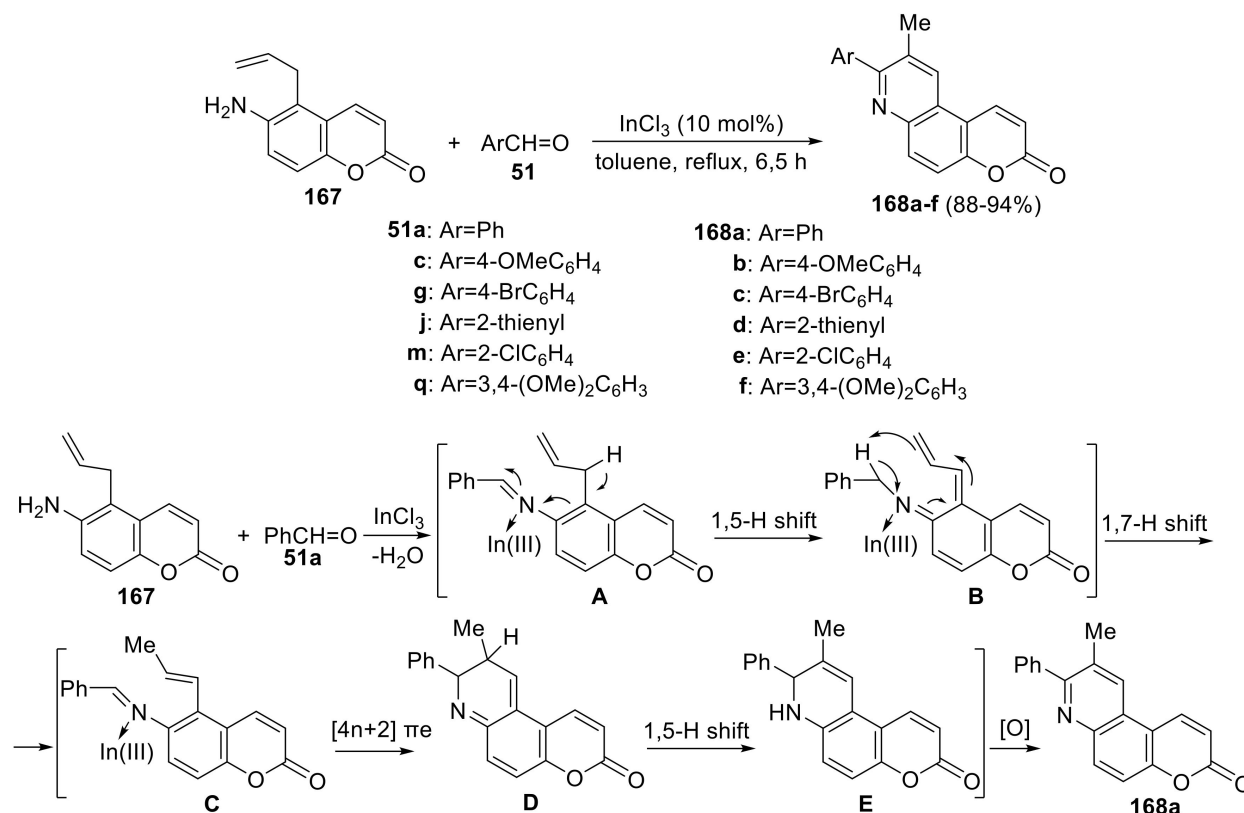


**Scheme 36.** Synthesis of chromeno [4,3-*b*]pyridines **158a–i** via a MCR of 4-aminocoumarin (**13**), aromatic benzaldehydes and ethyl benzoylacetate (**157**) catalyzed by NbCl<sub>5</sub>.



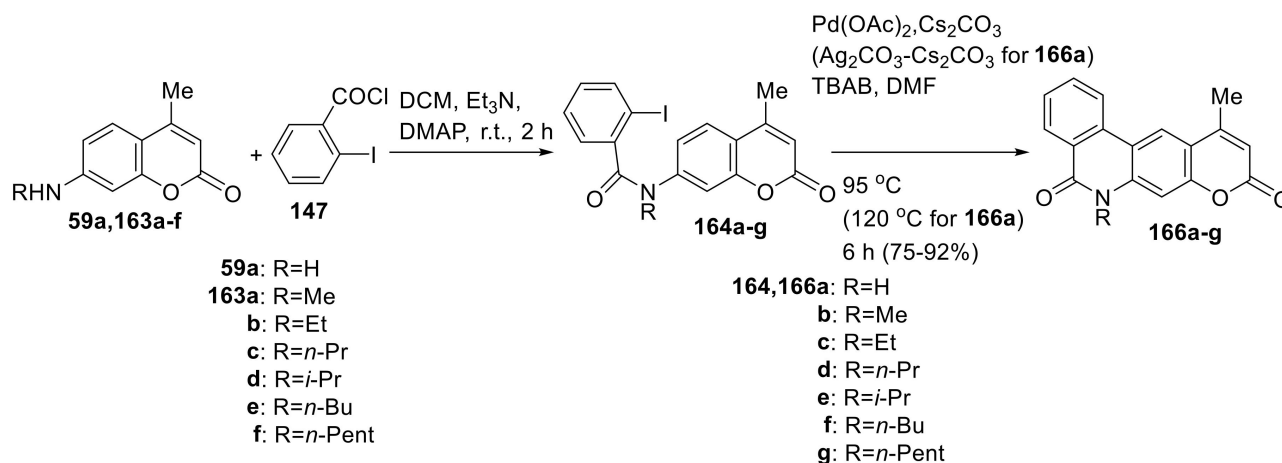
**Scheme 37.** Synthesis of 3*H*-pyrano [3,2-*a*]phenanthridine-3,8(7*H*)-diones **165a–c** and 11-methyl-5*H*-pyrano [3,2-*b*]phenanthridine-5,9(6*H*)-dione **166a–c** by an intramolecular Heck reaction.





**Scheme 38.** Indium (III) chloride catalyzed synthesis of pyrido [3,2-*f*]coumarins **168a-f**.

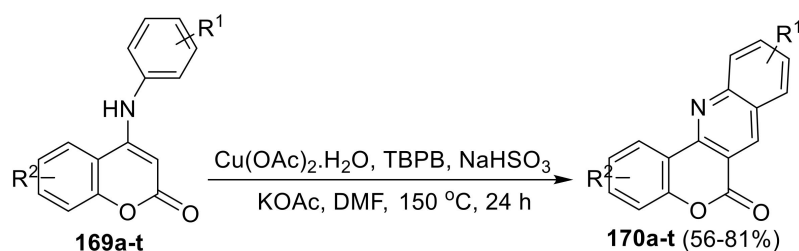
In 2017, Nath, a coworker of Majumdar, extended the former [66] regioselective Pd-catalyzed synthesis of linear 11-methyl-5*H*-pyrano [3,2-*b*]phenanthridine-5,9(6*H*)-diones **166a-g** using Cs<sub>2</sub>CO<sub>3</sub> as a base at lower temperature, 95 °C for 6 h [124]. In the case of amidocoumarin **164a**, the base was a mixture of Ag<sub>2</sub>CO<sub>3</sub> (2 equivalents) and Cs<sub>2</sub>CO<sub>3</sub> (2 equivalents) and the intramolecular Heck reaction performed at the elevated temperature of 120 °C (Scheme 39).



**Scheme 39.** Synthesis of 11-methyl-5*H*-pyrano [3,2-*b*]phenanthridine-5,9(6*H*)-dione **166a-g** by a Pd-catalyzed intramolecular Heck reaction.

In 2017 also, Xie, Su and coworkers synthesized 6*H*-chromeno [4,3-*b*]quinoline-6-ones **170a-t** by a copper-catalyzed cyclization of 4-arylamino coumarins **169a-t** using the *N*-methyl moiety of DMF as the source of methine group [125]. They tested *N,N*-

dimethylacetamide and *N,N*-dimethylaniline as a possible source of methine moiety, obtaining low yields of the product, while *N,N*-diethylformamide did not give any conversion. A possible mechanism has been proposed with addition of 4-phenylaminocoumarin (**169a**) to the iminium salt **A**, generated from DMF (Scheme 40). The intermediate **B** formed after elimination of MeNHCH=O gave the  $\alpha,\beta$ -unsaturated imine **D**, which upon attack from NaHSO<sub>3</sub> to adduct **E** followed by intramolecular cyclization generated the dihydropyridine intermediate **F** (path A). Another possibility is the 6 $\pi$  electrocyclicization of **D** to afford intermediate **F** (path B). Oxidation, next, of **F** led to the final product **170a**.



**169,170a:** R<sup>1</sup> = H, R<sup>2</sup> = H

**b:** R<sup>1</sup> = 4-Br, R<sup>2</sup> = H

**c:** R<sup>1</sup> = 4-Me, R<sup>2</sup> = H

**d:** R<sup>1</sup> = 4-Et, R<sup>2</sup> = H

**e:** R<sup>1</sup> = 4-OMe, R<sup>2</sup> = H

**f:** R<sup>1</sup> = 4-OEt, R<sup>2</sup> = H

**g:** R<sup>1</sup> = 4-Cl, R<sup>2</sup> = H

**h:** R<sup>1</sup> = 4-F, R<sup>2</sup> = H

**i:** R<sup>1</sup> = 4-CO<sub>2</sub>Et, R<sup>2</sup> = H

**j:** R<sup>1</sup> = 2-Me, R<sup>2</sup> = H

**169,170k:** R<sup>1</sup> = 2-OMe, R<sup>2</sup> = H

**l:** R<sup>1</sup> = 2,4-Me<sub>2</sub>, R<sup>2</sup> = H

**m:** R<sup>1</sup> = 1-2:CH=CH-CH=CH, R<sup>2</sup> = H

**n:** R<sup>1</sup> = 1-2:(CH<sub>2</sub>)<sub>4</sub>, R<sup>2</sup> = H

**o:** R<sup>1</sup> = H, R<sup>2</sup> = 6-Me

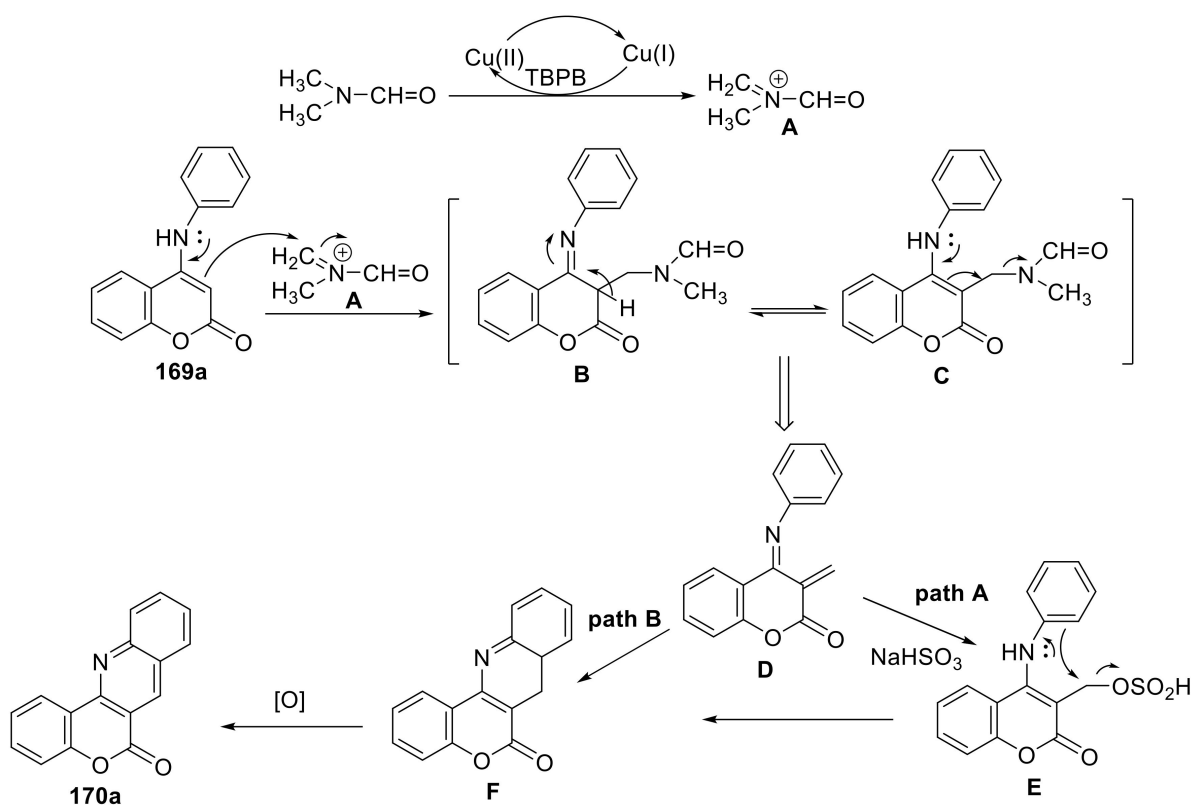
**p:** R<sup>1</sup> = H, R<sup>2</sup> = 6-OMe

**q:** R<sup>1</sup> = H, R<sup>2</sup> = 6-Cl

**r:** R<sup>1</sup> = 4-Me, R<sup>2</sup> = 6-Me

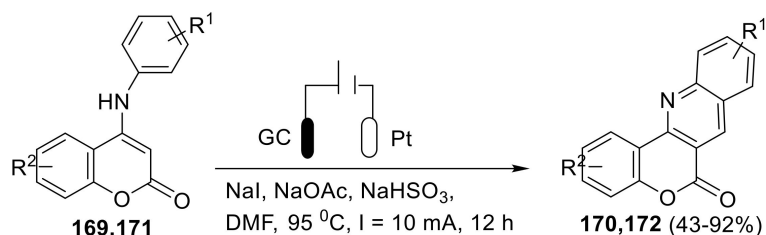
**s:** R<sup>1</sup> = 4-Cl, R<sup>2</sup> = 6-Me

**t:** R<sup>1</sup> = 4-Me, R<sup>2</sup> = 6-Cl



**Scheme 40.** Synthesis of 6*H*-chromeno [4,3-*b*]quinoline-6-ones **157a–t** by a copper-catalyzed cyclization of 4-arylamino coumarins **156a–t** in the presence of DMF.

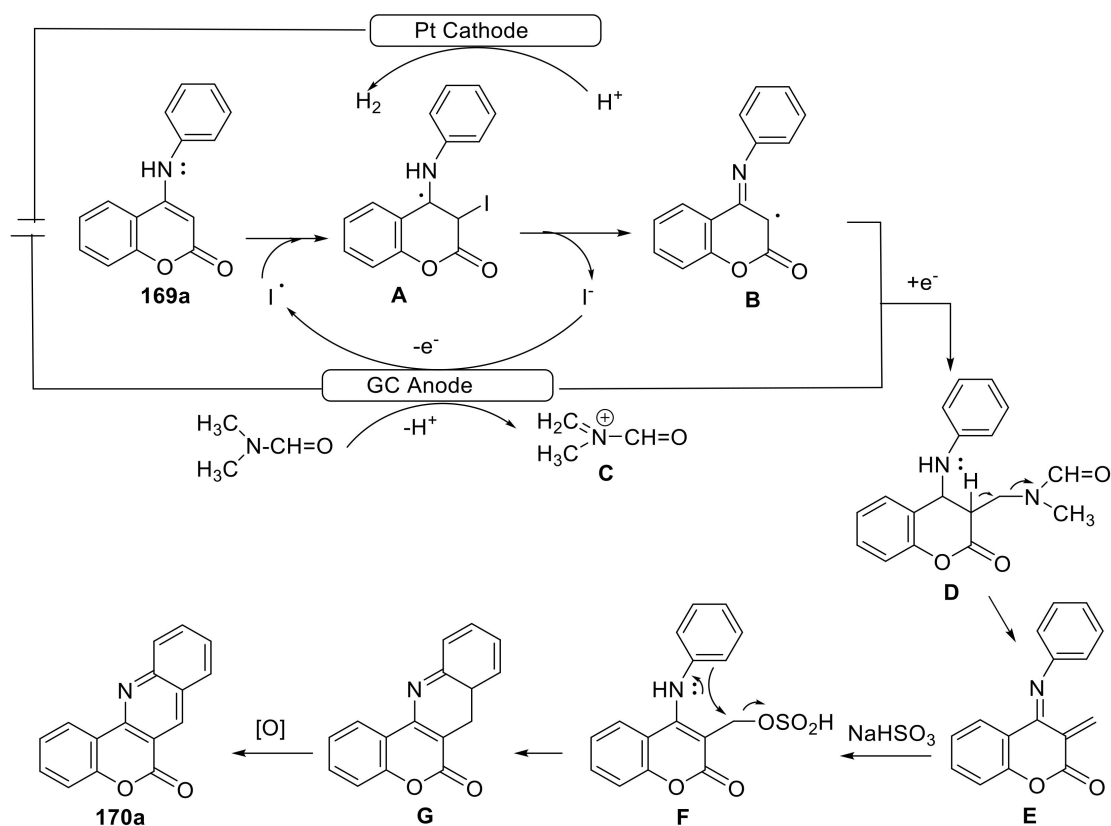
Recently, Ackermann and coworkers utilized 4-arylamino coumarins **169**, **171** for the synthesis of 6*H*-chromeno [4,3-*b*]quinoline-6-ones **170**, **172** through electro-oxidative cyclization in the presence of DMF as a methine source in a glassy carbon (GC) anode and a platinum (Pt) cathode [126]. In the proposed mechanism, iodine radicals, generated anodically, afforded intermediate **A** from **169a**, which is converted to radical **B**, releasing iodine anion (Scheme 41). The iminium intermediate **C**, formed by anodic oxidation of DMF, reacted as an electrophile with **B** to give intermediate **D**. Elimination of MeN-HCHO furnished the imine **E**, which was attacked by NaHSO<sub>3</sub> to afford intermediate **F**. Intramolecular cyclization to **G**, followed by oxidation, led to the final product **170a**.



**169,170a:** R<sup>1</sup> = H, R<sup>2</sup>=H  
**b:** R<sup>1</sup> = 4-Br, R<sup>2</sup>=H  
**c:** R<sup>1</sup> = 4-Me, R<sup>2</sup>=H  
**d:** R<sup>1</sup> = 4-Et, R<sup>2</sup>=H  
**e:** R<sup>1</sup> = 4-OMe, R<sup>2</sup>=H  
**g:** R<sup>1</sup> = 4-Cl, R<sup>2</sup>=H  
**h:** R<sup>1</sup> = 4-F, R<sup>2</sup>=H  
**j:** R<sup>1</sup> = 2-Me, R<sup>2</sup>=H

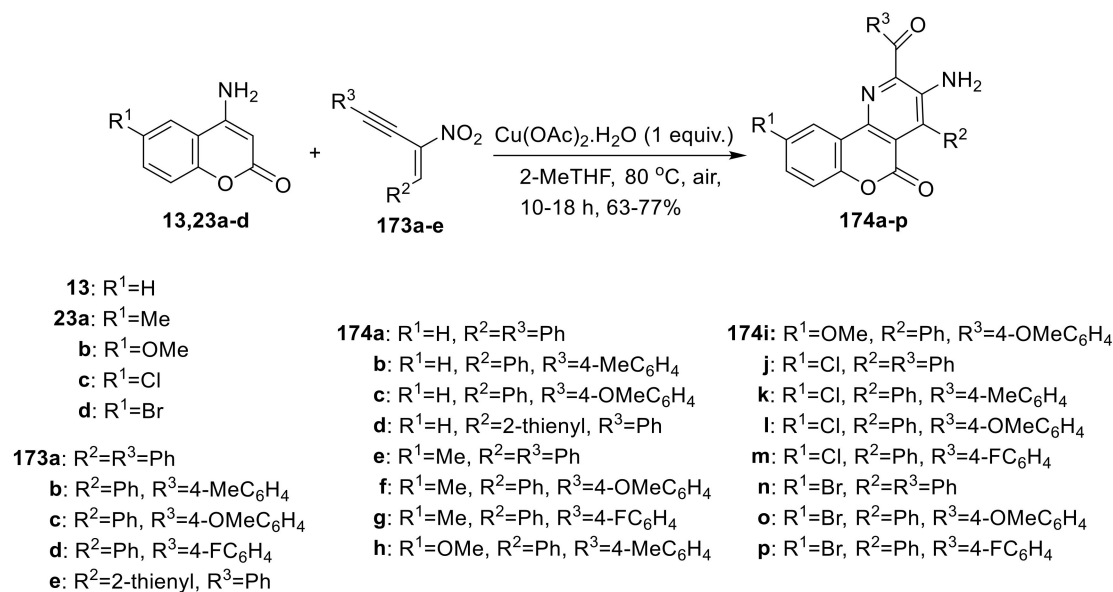
**169,170 l:** R<sup>1</sup> = 2,4-Me<sub>2</sub>, R<sup>2</sup>=H  
**o:** R<sup>1</sup> = H, R<sup>2</sup>=6-Me  
**p:** R<sup>1</sup> = H, R<sup>2</sup>=6-OMe  
**q:** R<sup>1</sup> = H, R<sup>2</sup>=6-Cl  
**r:** R<sup>1</sup> = 4-Me, R<sup>2</sup>=6-Me  
**s:** R<sup>1</sup> = 4-Cl, R<sup>2</sup>=6-Me  
**t:** R<sup>1</sup> = 4-Me, R<sup>2</sup>=6-Cl  
**u:** R<sup>1</sup>=4-*t*Bu, R<sup>2</sup>=H

**169,170v:** R<sup>1</sup>=4-Ph, R<sup>2</sup>=H  
**w:** R<sup>1</sup>=2,5-Me<sub>2</sub>, R<sup>2</sup>=H  
**x:** R<sup>1</sup>=4-Br, R<sup>2</sup>=6-Me  
**y:** R<sup>1</sup>=4-Me, R<sup>2</sup>=6-OMe  
**z:** R<sup>1</sup>=H, R<sup>2</sup>=7-Me  
**171,172a:** R<sup>1</sup>=4-Me, R<sup>2</sup>=7-Me  
**b:** R<sup>1</sup>=4-Me, R<sup>2</sup>=7-OMe  
**c:** R<sup>1</sup>=H, R<sup>2</sup>=7-Br



**Scheme 41.** Synthesis of 6*H*-chromeno [4,3-*b*]quinoline-6-ones **170**, **172** through electrooxidative cyclization of 4-arylamino coumarins **169**, **171**.

In 2019, Samanta, Kumar and coworkers reported the synthesis of substituted chromeno [4,3-*b*]pyridines **174a–p** from 4-aminocoumarins **13**, **23a–d** and  $\alpha$ -alkynyl- $\beta$ -aryl nitroolefins **173a–e** in the presence of copper acetate by heating in 2-methyltetrahydrofuran, as a green solvent, under aerobic conditions [127]. This reaction is a domino protocol via a [3 + 3] annulation reaction promoted by Cu(OAc)<sub>2</sub>, as is suggested by the authors (Scheme 42). The compounds were tested against CAG repeat RNAs that cause Huntington's disease. Derivatives **174c** and **174o** presented higher affinity (nanomolar) and selectivity for diseased r(CAG)<sup>exp</sup> RNA compared to regular duplex AU-paired RNA.



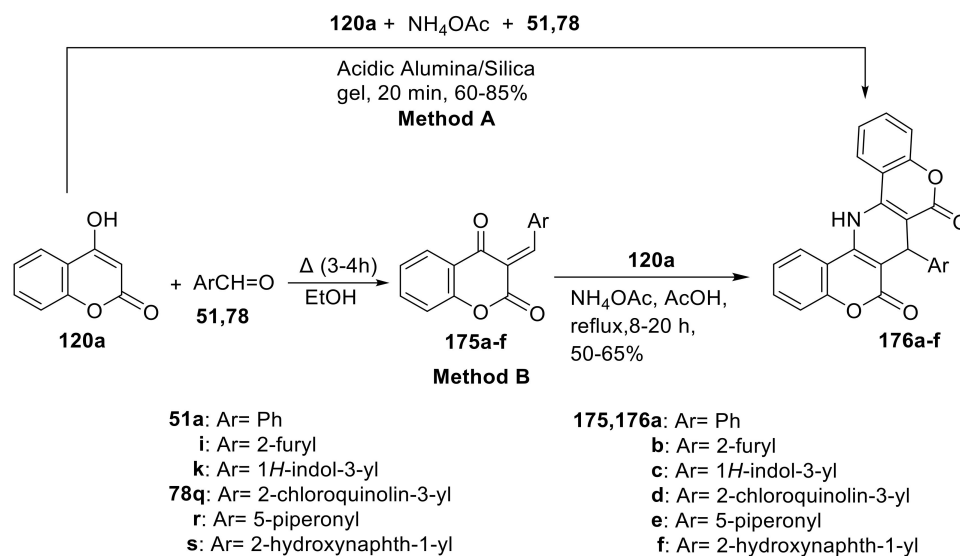
**Scheme 42.** Synthesis of pyrido [3,2-*c*]coumarins **174a–p** from 4-aminocoumarins and  $\alpha$ -alkynyl- $\beta$ -aryl nitroolefins **173a–e**.

### 2.1.2. Synthesis from Hydroxycoumarins

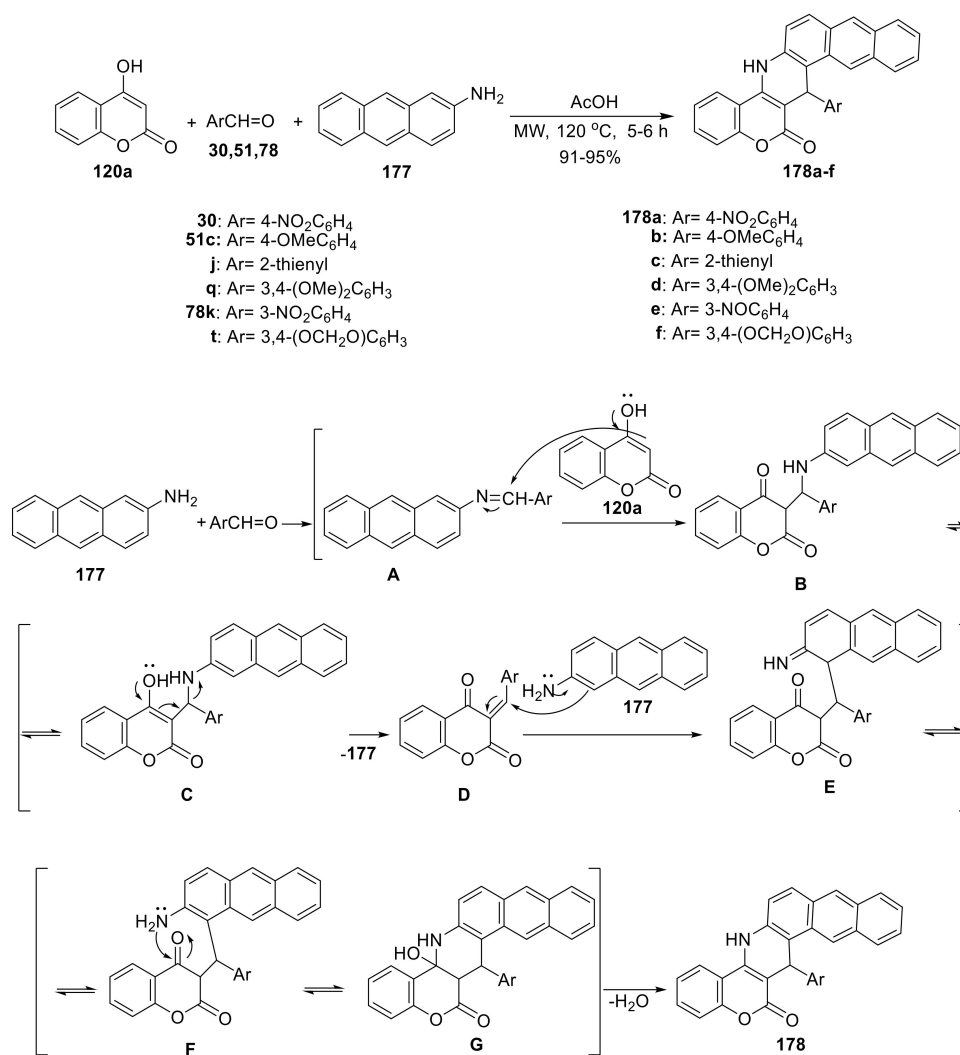
#### Multi Component Reactions (MCR) of Hydroxycoumarins

In 2004, Kidwai et al. synthesized the bis(benzopyrano) fused 1,4-dihydropyridines **176a–f** by a three-component reaction of 4-hydroxycoumarin (**120a**), aromatic aldehydes **51**, **78** and ammonium acetate under one-step procedure using acidic alumina and silica gel as solid support under MW irradiation (Method A) [128]. This method was faster and had better yields than the two-step procedure (Method B) (Scheme 43). In method B, the arylidene compounds **175a–f** were formed at first and reacted under reflux in acetic acid with **120a** in the presence of NH<sub>4</sub>OAc. It seems that 4-hydroxycoumarin (**120a**) reacted with NH<sub>4</sub>OAc to give 4-aminocoumarin, which then added to **175a–f** in a Michael addition reaction type, followed by cyclization via dehydration to give the 1,4-dihydro pyridine derivatives **176a–f**.

In 2009 Tu et al., prepared naphtho [2,3-*f*]quinoline derivatives by a one-pot three-component reaction of 2-aminoanthracene (**177**), aromatic aldehydes and 1,3-diketones under microwave irradiation in order to test their luminescent properties [129]. The derivative 4-Hydroxycoumarin (**120a**) resulted in the fused coumarin derivatives **178a–f**. These compounds exhibited good luminescent properties (Scheme 44). In the mechanism proposed [130], a condensation of **177** with aldehyde gave imine intermediate **A**, which underwent addition of 4-hydroxycoumarin (**120a**) to the adduct **B**. The latter after tautomerization to **C**, and removing of amine **177**, led to  $\alpha,\beta$ -unsaturated intermediate **D**. Addition of amine **177** to **D** and cyclization of the tautomer **F** of **E** resulted in adduct **G**. Water was eliminated from the latter and the final product **178** was obtained. Compounds **178a–f** exhibited good luminescent properties in ethanol solution and could be used as organic electroluminescent media.

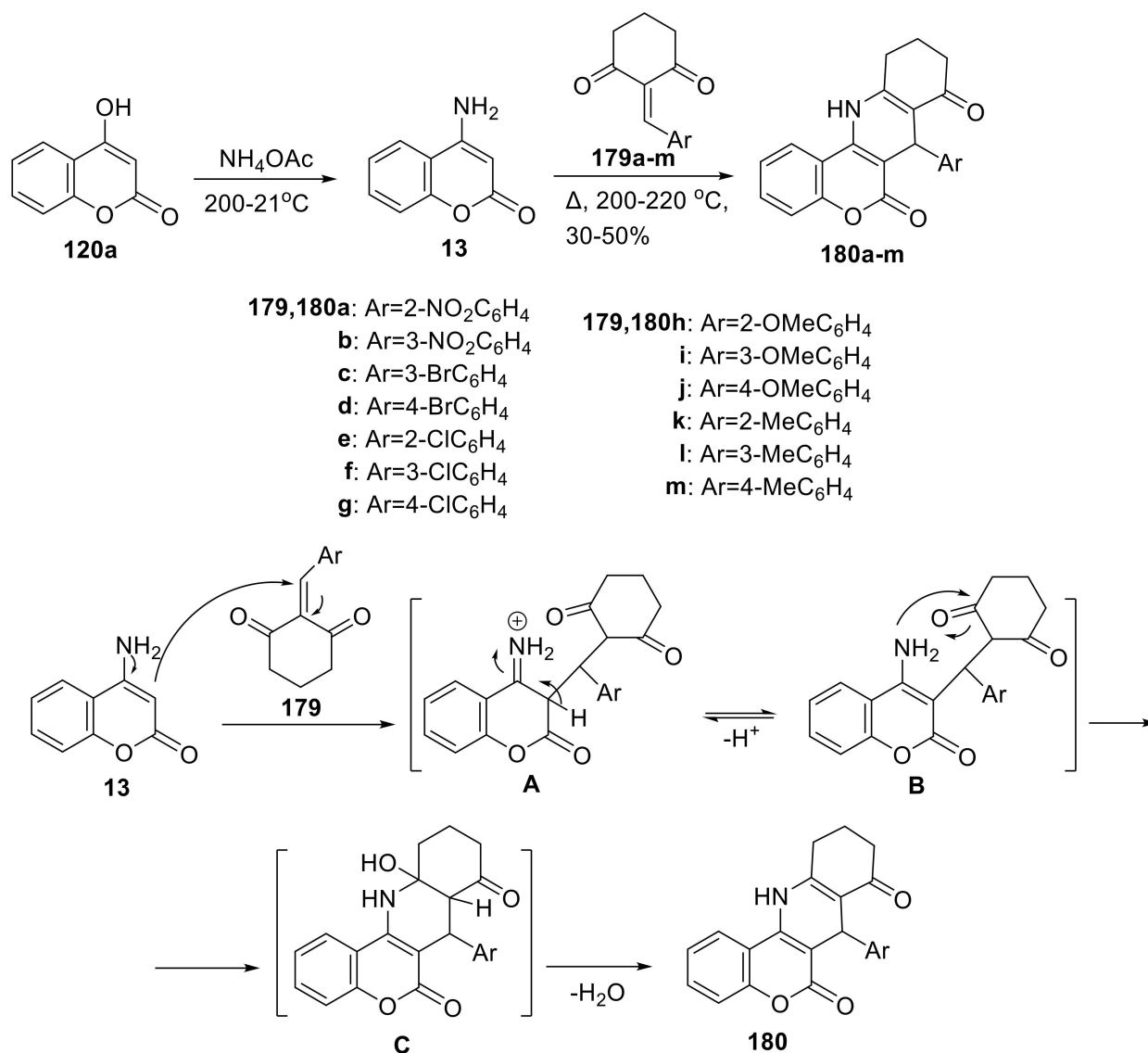


**Scheme 43.** Multicomponent synthesis of bis(benzopyrano) fused dihydropyridines using solid support media.



**Scheme 44.** Synthesis of coumarin derivatives **178a-f** by the one-pot reaction of 2-aminoanthracene (**177**), aldehydes and 4-hydroxycoumarin (**120a**) under MW irradiation.

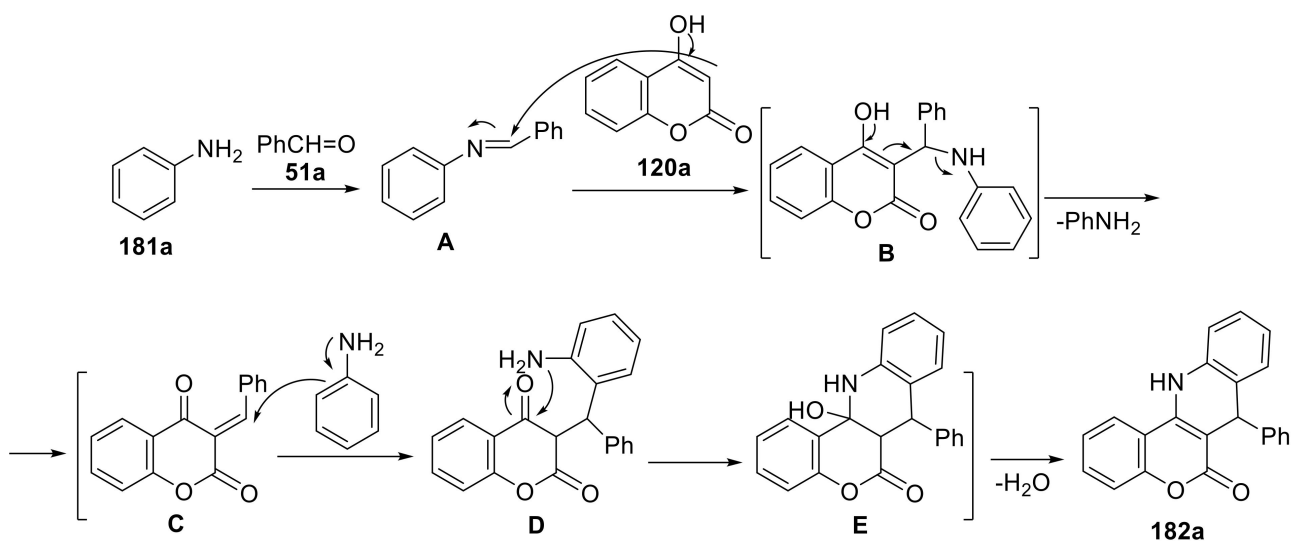
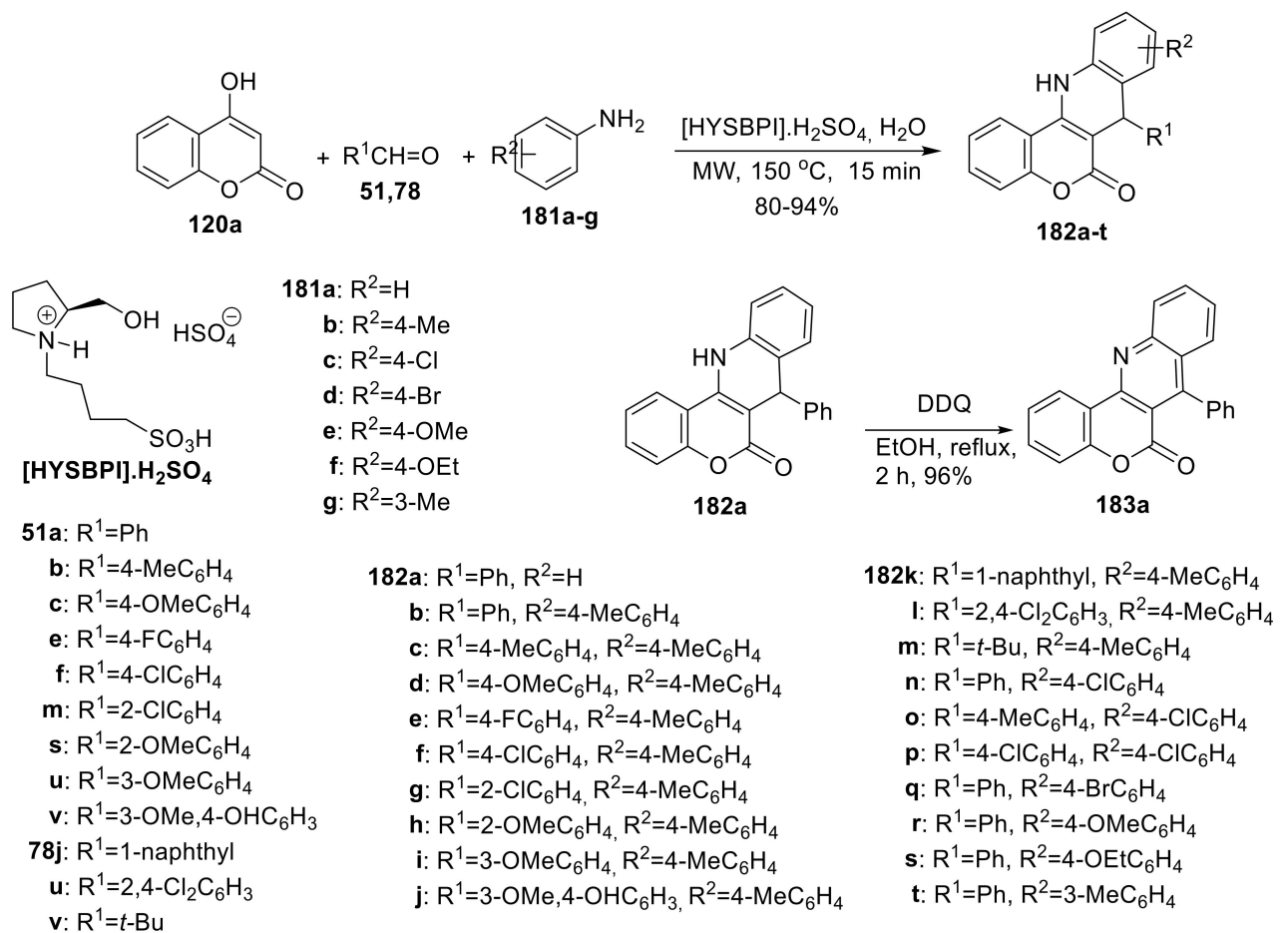
In 2011, Shafiee and coworkers prepared 4-aminocoumarin (**13**) by melting of 4-hydroxycoumarin (**120a**) in the presence of ammonium acetate. Then, they synthesized the chromeno [4,3-*b*]quinoline derivatives **180a–m** by the reaction of **13** with 2-arylidencyclohexano1,3-dione derivatives **179a–m** under heating at high temperature without solvent [131]. The Michael addition of 4-aminocoumarin (**13**) to  $\alpha,\beta$ -unsaturated compound **179** gave the intermediate **A**, according to the proposed mechanism (Scheme 45). Isomerization of **A** to **B**, followed by intramolecular cycloaddition to **C** and subsequent elimination of water resulted in the final 1,4-dihydropyridocoumarin derivatives **180**. The synthesized compounds were tested for their cytotoxic activity in human cancer cell lines (Hela, K562, LS180 and MCF-7). Some of them showed moderate cytotoxic capacity and, in parallel, very low calcium channel antagonist activity. Compound **180a** presented the highest antitumoral activity ( $IC_{50} = 25.4\text{--}58.6 \mu\text{M}$ ).



**Scheme 45.** Synthesis of chromeno [4,3-*b*]quinoline derivatives **180a–m**.

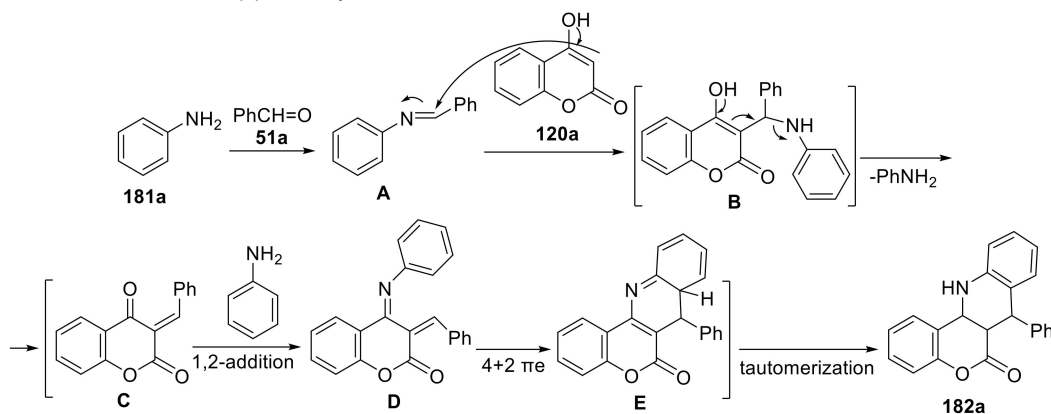
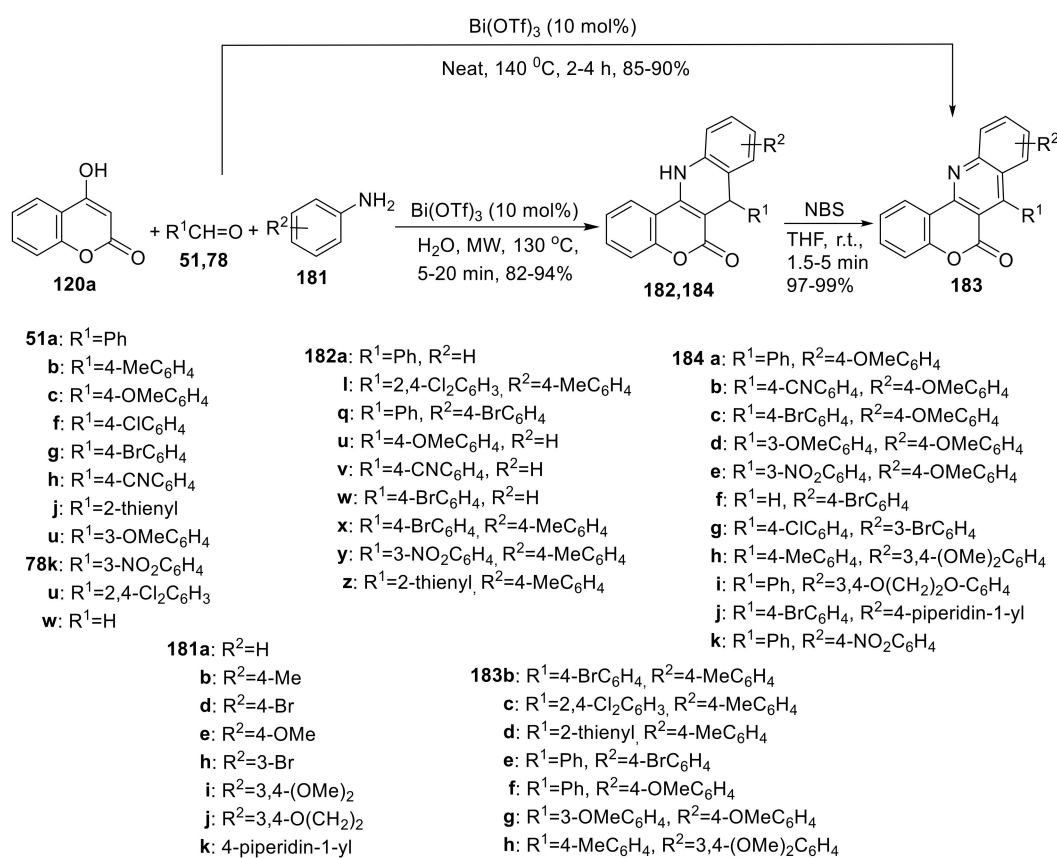
In 2013, Su and coworkers prepared the dihydrochromeno [4,3-*b*]quinoline derivatives **182a–t** via the three-component reaction of 4-hydroxycoumarin (**120a**) with aldehydes and anilines **181a–g** catalyzed by the ionic liquid *L*-2-(2-hydroxymethyl)-1-(4-sulfobutyl)pyrrolidinium hydrogen sulfate ([HYSBPI].H<sub>2</sub>SO<sub>4</sub> in water under microwave irradiation [132]. In the proposed mechanism, according to reference [130], a condensation of aniline (**181a**) with benzaldehyde (**51a**) gave the imine **A**. The intermediate **B** was formed by the addition of

**120a** to **A**, followed by the removal of aniline to give the benzylidene intermediate **C**. Addition of aniline to **C**, followed by intermolecular cyclization, led to the cyclized adduct **E**. Elimination of water from the latter resulted in the final product **182a** (Scheme 46). Oxidation of **182a** with DDQ afforded the pyridocoumarin **183a**. The antitumor activity of the prepared compounds was evaluated in human cancer cell lines (A-549 and MCF-7). They exhibited moderate antitumor activities with  $IC_{50} = 0.05\text{--}100\ \mu\text{mol/L}$ .



**Scheme 46.** Synthesis of dihydrochromeno [4,3-*b*]quinoline derivatives **182a-t**.

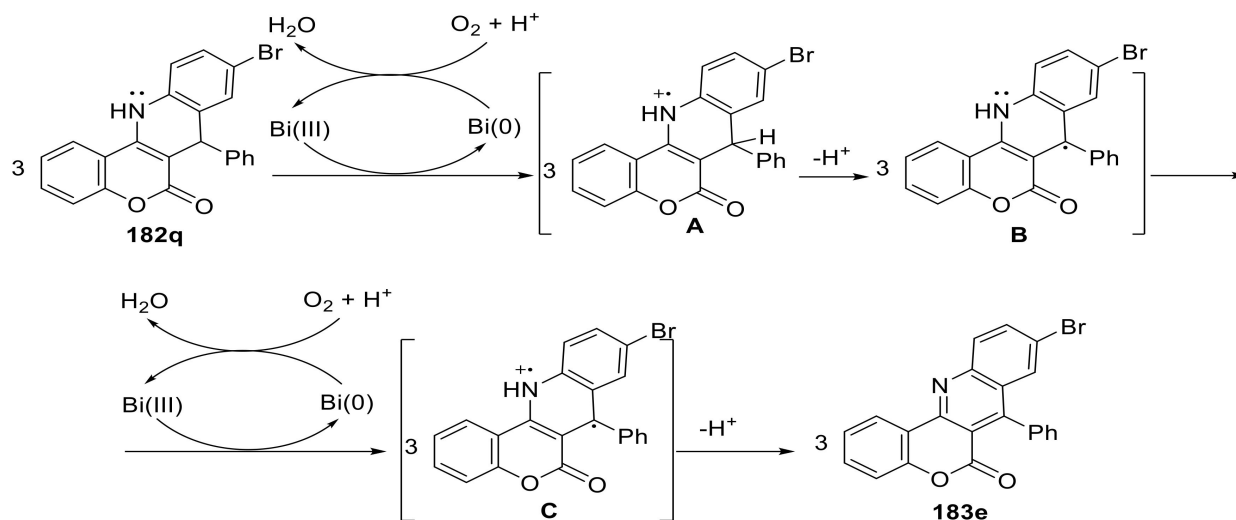
Next year, Choudhury and coworkers prepared similar dihydrochromeno [4,3-*b*]quinoline derivatives by the multi-component reaction of 4-hydroxycoumarin (**120a**) with aldehydes and anilines in water catalyzed by Bi(OTf)<sub>3</sub> (10 mol%) under microwave irradiation [133]. For the mechanism, they proposed the 1,2-addition of aniline to the alkylidene intermediate **C**, for the formation of imine **D**, followed by 6  $\pi$  electrocyclicization to the intermediate **E**. Tautomerization of the latter led to the dihydropyridine derivative **182a** (Scheme 47). When some of the above reactions were performed without solvent by conventional heating at 140 °C, for 2–4 h the chromeno [4,3-*b*]quinoline-6-ones **183** were received, possibly by a radical mechanism. Treatment of some of the dihydropyridocoumarin derivatives with NBS at room temperature resulted rapidly in a more clean reaction to the chromeno [4,3-*b*]quinoline-6-ones **183**. The fluorescent properties of the synthesized compounds were studied in different solvents. It was found that derivatives **182**, **184** are more fluorescent than the corresponding **183** analogs.



**Scheme 47.** Synthesis of dihydrochromeno [4,3-*b*]quinoline derivatives **182**, **184** and chromeno [4,3-*b*]quinoline-6-ones **183**.



For the transformation of the above referred solvent-free oxidation of compounds **182**, **184** to the chromeno [4,3-*b*]quinoline-6-ones **183**, the authors suggested that a radical mechanism is taking place with the parallel reduction of Bi(III) to Bi(0), as depicted in Scheme 48.

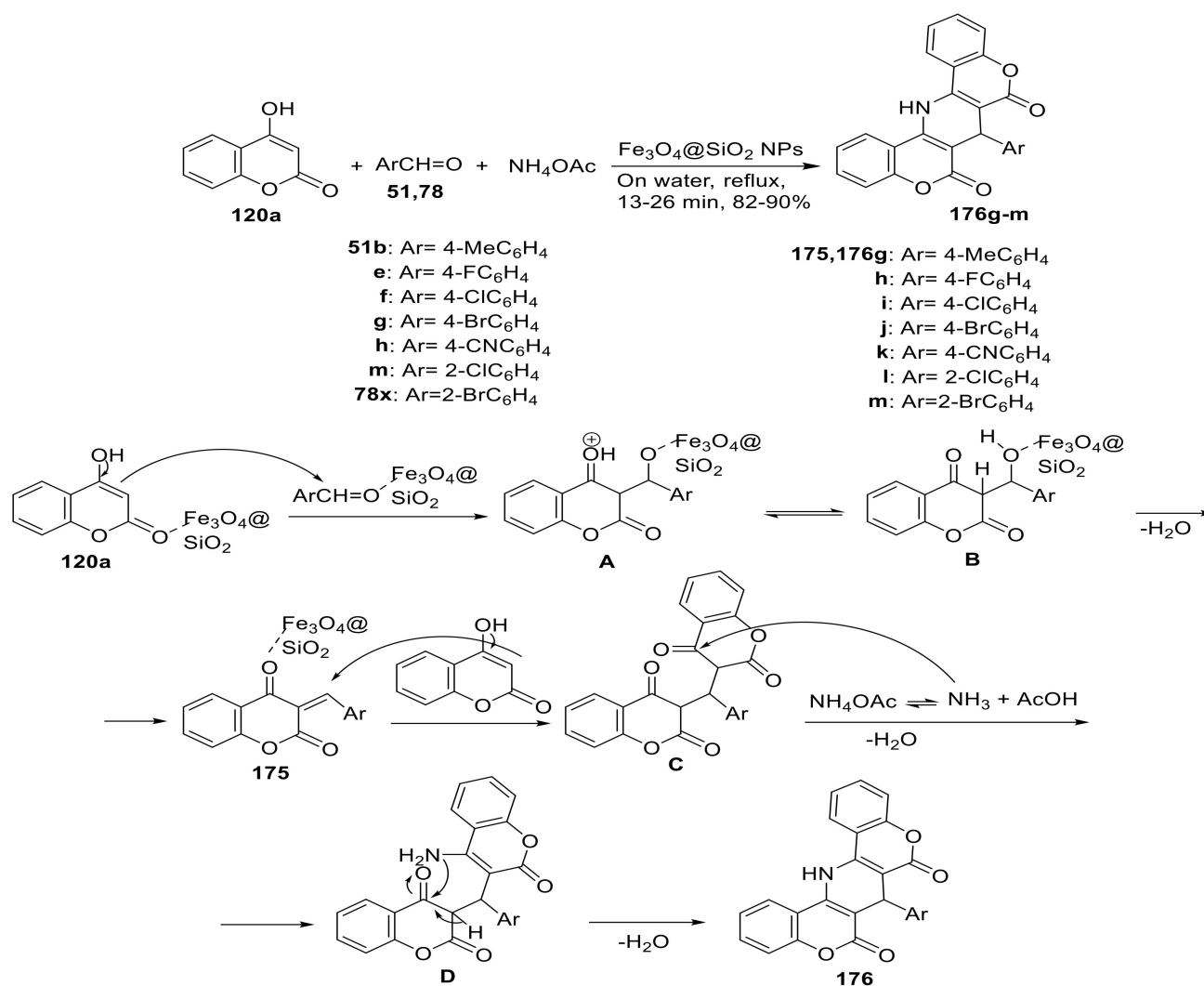


**Scheme 48.** Mechanism for the solvent-free transformation of dihydrochromeno [4,3-*b*]quinoline derivatives **182** to chromeno [4,3-*b*]quinoline-6-ones **183** in the presence of Bi(OTf)<sub>3</sub>.

The same year, Pal and coworkers utilized Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub> nanoparticles as catalyst for the synthesis of 1,4-dihydropyridocoumarins **176g–m** from the one-pot multi-component reaction of 4-hydroxycoumarin (**120a**), aldehydes and NH<sub>4</sub>OAc on water [134]. The catalyst could be removed with a magnet and reused further. A plausible mechanism is depicted in Scheme 46. By the binding of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub> nanoparticles to the carbonyl oxygen, the carbonyl activity increased, facilitating the nucleophilic attack to the aldehyde and the formation of the intermediate Knoevenagel alkylidene product **175** (Scheme 49). This adduct underwent a Michael addition from another molecule of **120a** to give intermediate **C**. Then ammonia reacted with **C** and amino-intermediate **D** was obtained, which under cyclization and elimination of water resulted in the desired product **176**.

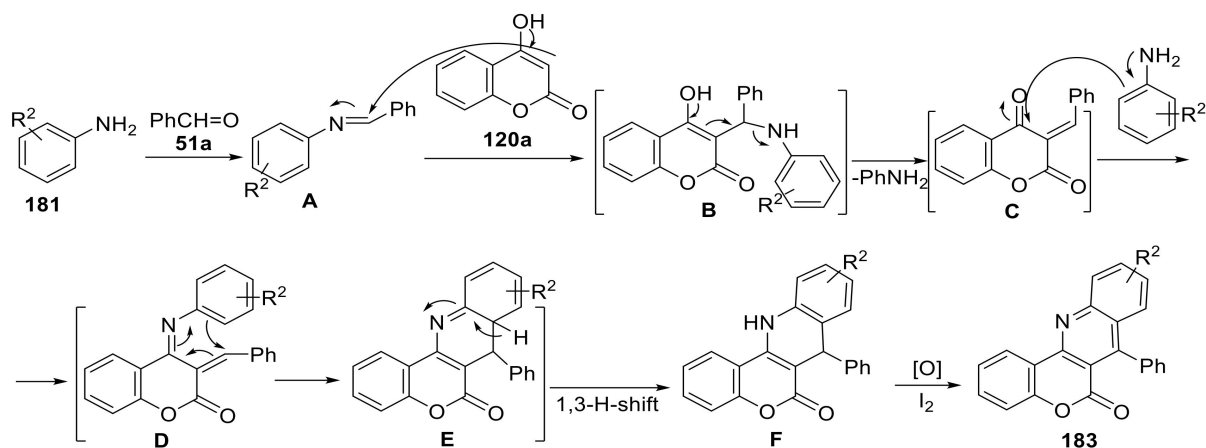
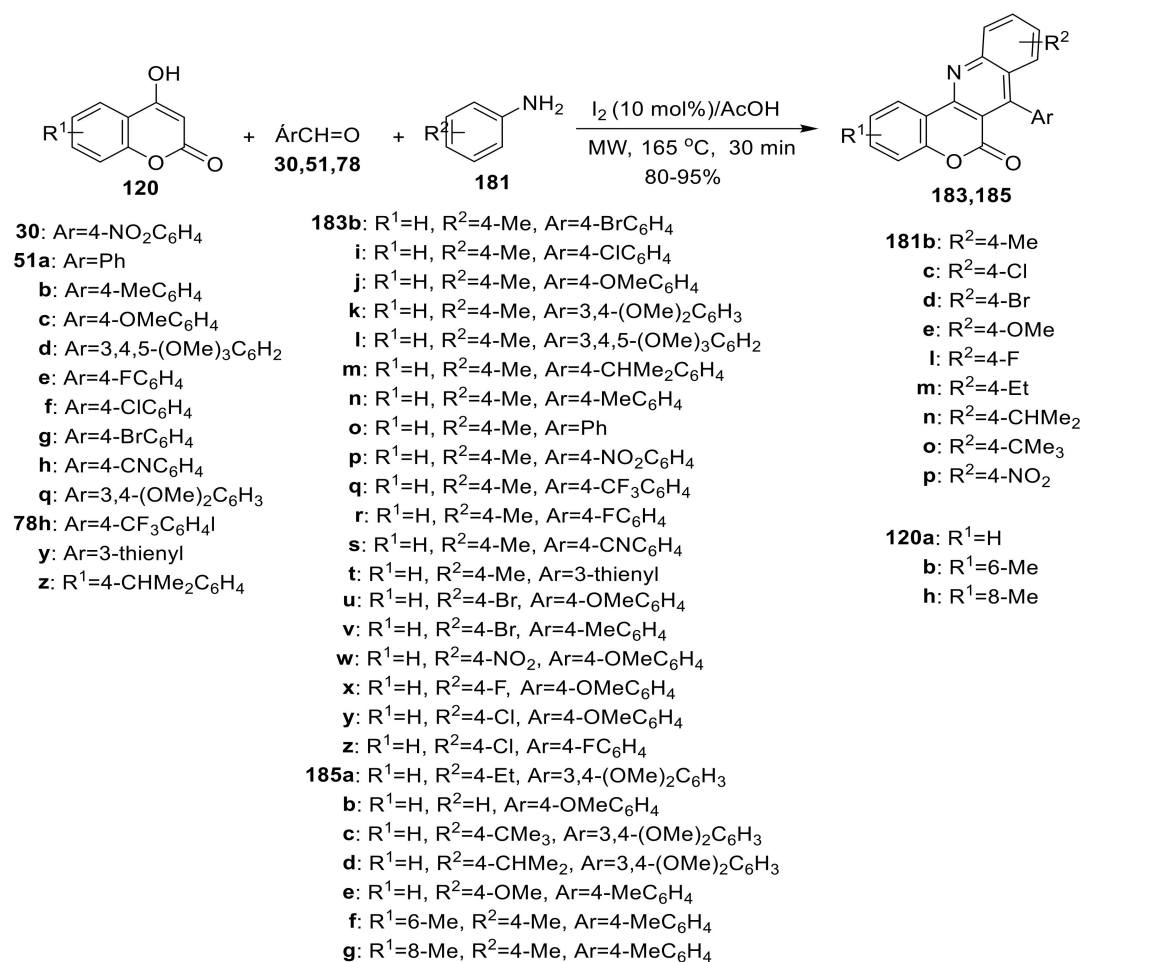
In 2015, Sashidhara et al., demonstrated a one-pot procedure for the synthesis of chromeno [4,3-*b*]quinoline-6-ones **183**, **185** under microwave irradiation in the presence of molecular iodine (10 mol%) via a three-component reaction of 4-hydroxycoumarin (**120a**), aromatic aldehydes and anilines [135]. Condensation of aldehydes with aniline led to the Schiff base **A**. Nucleophilic attack of 4-hydroxycoumarin on imine **A** gave unstable adduct **B**, which then underwent rearrangement to afford the intermediate **E** via the transition states **C** and **D** (Scheme 50). A 1,3-H shift resulted in the 1,4-dihydropyridocoumarin **F**, which upon oxidation in the presence of iodine furnished the final product **183**.

In 2016, Yin and coworkers presented the three component synthesis of dihydrochromeno [4,3-*b*]pyrazolo [4,3-*e*]pyridines **188a–n** or chromeno [4,3-*b*]pyrazolo[4,3-*e*]pyridines **189a–g** from 4-hydroxycoumarin (**120a**), aldehydes and 5-amino-3-methyl-*N*-phenylpyrazole (**187a**)/5-amino-3-methylisoxazole (**187b**), depending on the conditions, refluxing in AcOH-MeCN or heating at 140 °C in AcOH-DMSO [136]. According to the proposed mechanism, a Knoevenagel reaction of 4-hydroxycoumarin (**120a**) with benzaldehyde (**51a**) gave the benzylidene-adduct **A**, which reacted **187a** in a Michael reaction furnishing intermediate **B** (Scheme 51). Intramolecular cyclization by the addition of amine group to the coumarin 4-carbonyl and elimination of water resulted in the intermediate **C**. Tautomerization of the latter gave dihydro derivative **188a**, which upon oxidation led to the pyridocoumarin product **189a**.



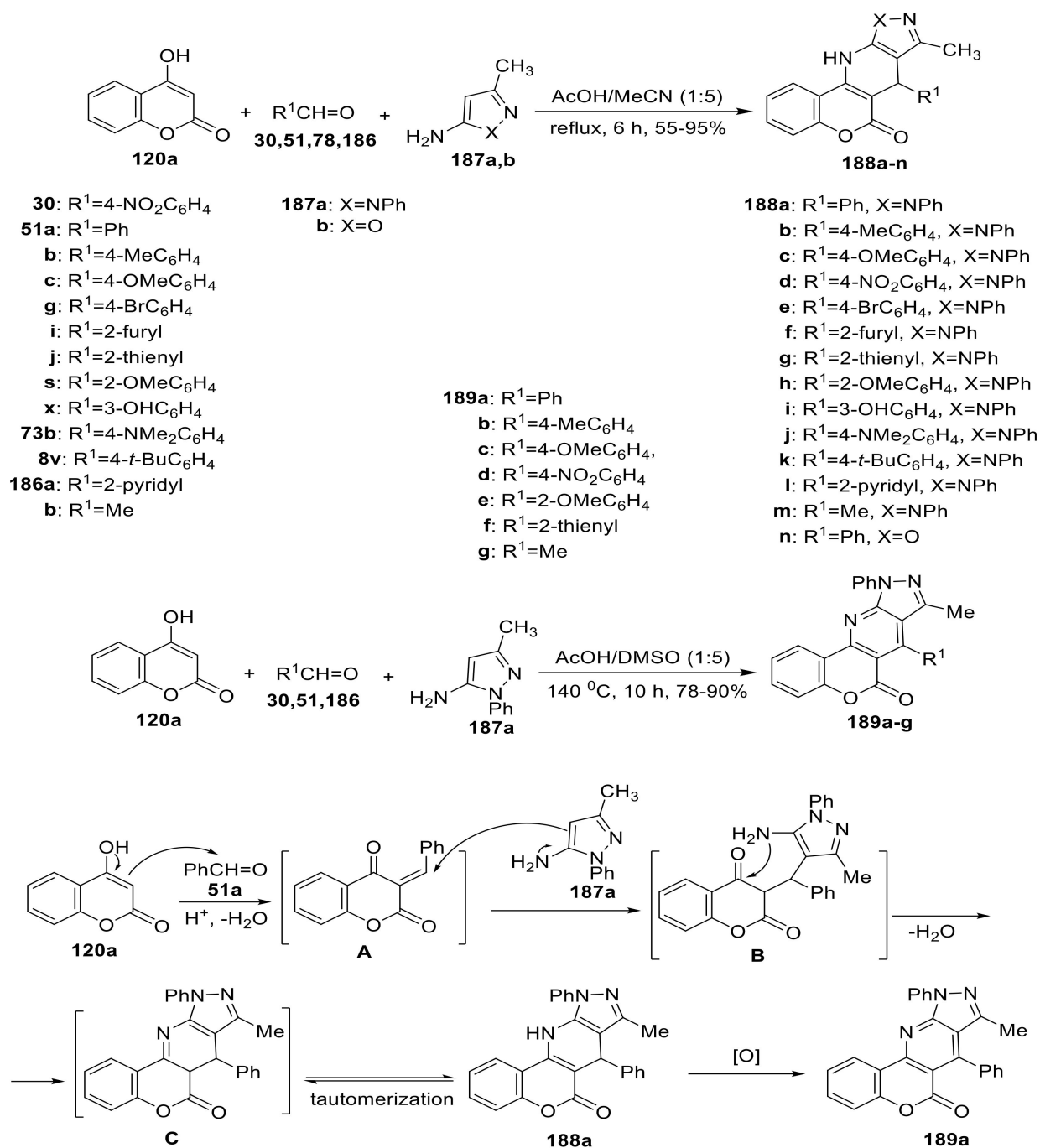
**Scheme 49.** Synthesis of 1,4-dihydropyridocoumarin derivative on water using Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub> nanoparticles as catalyst.

The same year, Khurana and coworkers reported an analogous synthesis of dihydrochromeno [3,4-*e*]isoxazolo [5,4-*b*]pyridine-6-ones **188n**, **190a–n** in excellent yields via a one-pot three-component reaction of 4-hydroxycoumarin (**120a**), aldehydes and 5-amino-3-methylisoxazole (**187b**) in the ionic liquid 1-butyl-3-methylimidazolium hydrogen sulfate ([C4mim] [HSO<sub>4</sub>]) under heating at 80 °C or ultrasonic irradiation at room temperature [137]. For the mechanism, a different approach has been proposed, in comparison to the above reaction. The iminium intermediate **A** was formed by the condensation of 5-amino-3-methylisoxazole (**187b**) with benzaldehyde (**51a**) in the presence of acidic ionic liquid. Nucleophilic addition of **120a** to **A** gave the unstable transition state **B**, which underwent cleavage furnishing the benzylidene intermediate **C** (Scheme 52). A 1,3-Addition of 5-amino-3-methylisoxazole (**187b**) to **C** resulted in the intermediate **D**, which under intramolecular cyclization led to the intermediate **E**. By the 1,3-H shift of the latter the final product **188n** was obtained. The authors confirmed the above mechanism performing the reaction of preformed alkylidene compound **A** with **187b**, which resulted in the expected final product **188n**.



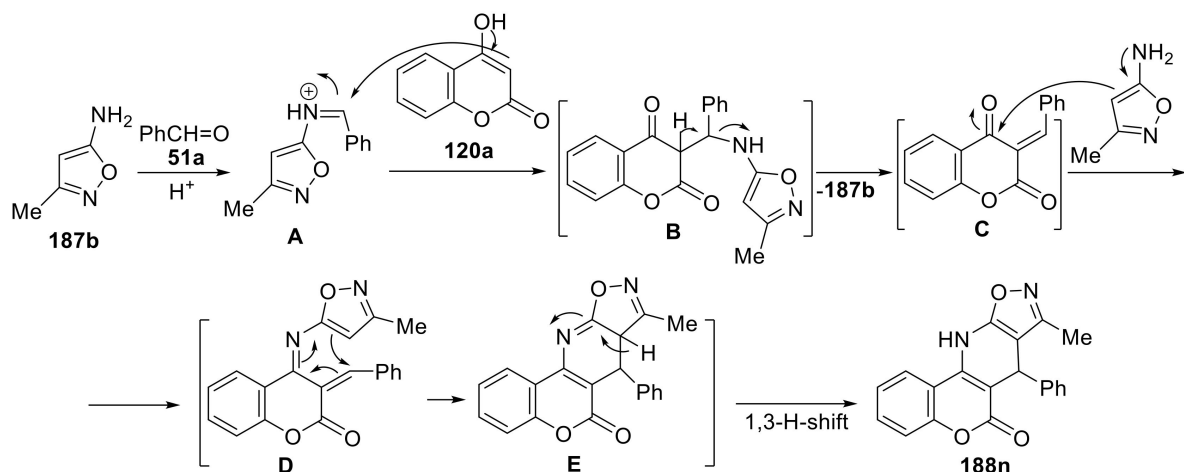
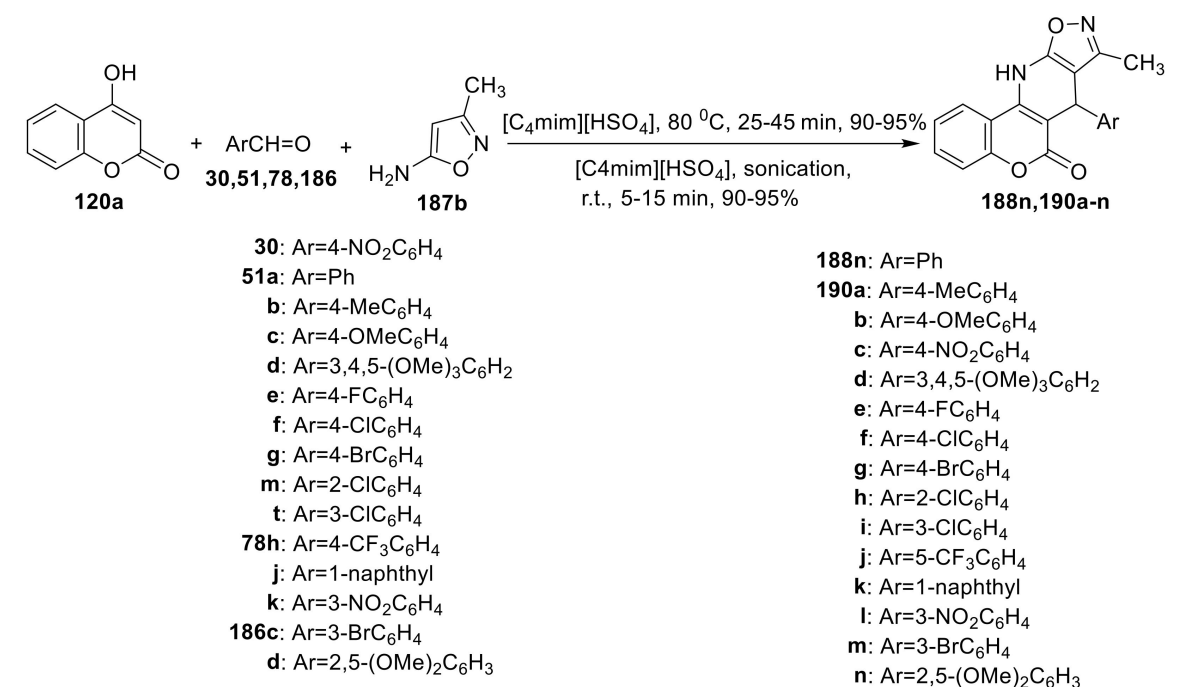
**Scheme 50.** Synthesis of chromeno [4,3-*b*]quinoline-6-ones catalyzed by molecular iodine under MW irradiation.

Ionic liquid, functionalized by silica@ $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticles (MNP), was used also by Mahdavi and coworkers as a catalyst for the synthesis of 6*H*-chromeno [4,3-*b*]quinoline-6-ones **182**, **184** via multi-component reaction of 4-hydroxycoumarin (**120a**), aromatic aldehydes and aromatic amines (Scheme 53). The catalyst (IL-SiO<sub>2</sub>@MNP) was prepared by the reaction of 1-butyl-3-(3-(trimethoxysilyl)propyl)-1*H*-imidazol-3-ium chloride with iron oxide nanoparticles coated by silica. The nanocatalyst could be separated after the completion of the reaction by a magnet and showed activity up to 10 times [138].



**Scheme 51.** Three-component synthesis of chromeno [4,3-*b*]pyrazolo [4,3-*e*]pyridines **189a-g**.

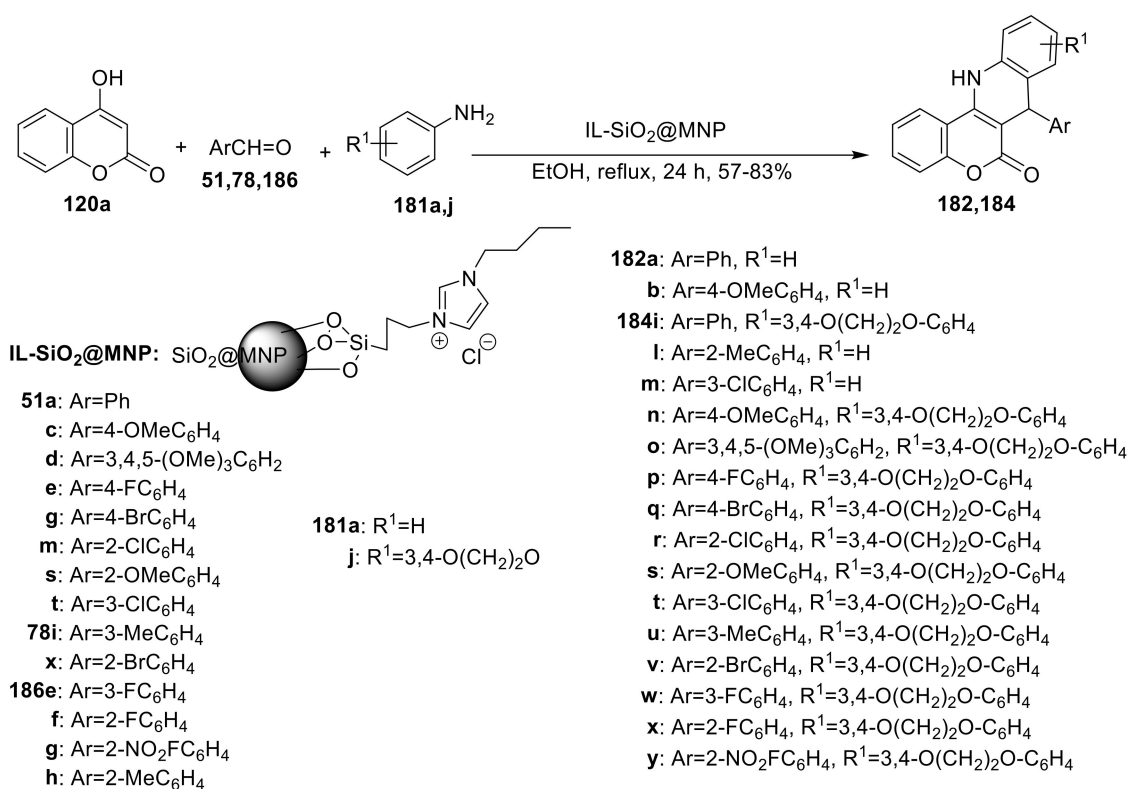
The same year, Foroumadi and coworkers synthesized the coumarin-fused dihydropyridinones **192a-i** via a multi-component reaction of 4-hydroxycoumarin (**120a**), ammonia, aromatic aldehydes, and Meldrum's acid (**90e**) in refluxing propan-1-ol [139]. In the proposed mechanism, the benzylidene intermediate **A** was formed by the Knoevenagel reaction of Meldrum's acid (**90e**) with aldehyde **51a** (Scheme 54). The amination reaction of 4-hydroxycoumarin with ammonia generated the 4-aminocoumarin (**13**), which by a Michael reaction to **A** led to the intermediate **B**. Intramolecular cyclization of the latter under loss of acetone and CO<sub>2</sub> resulted in the final product **192a**.



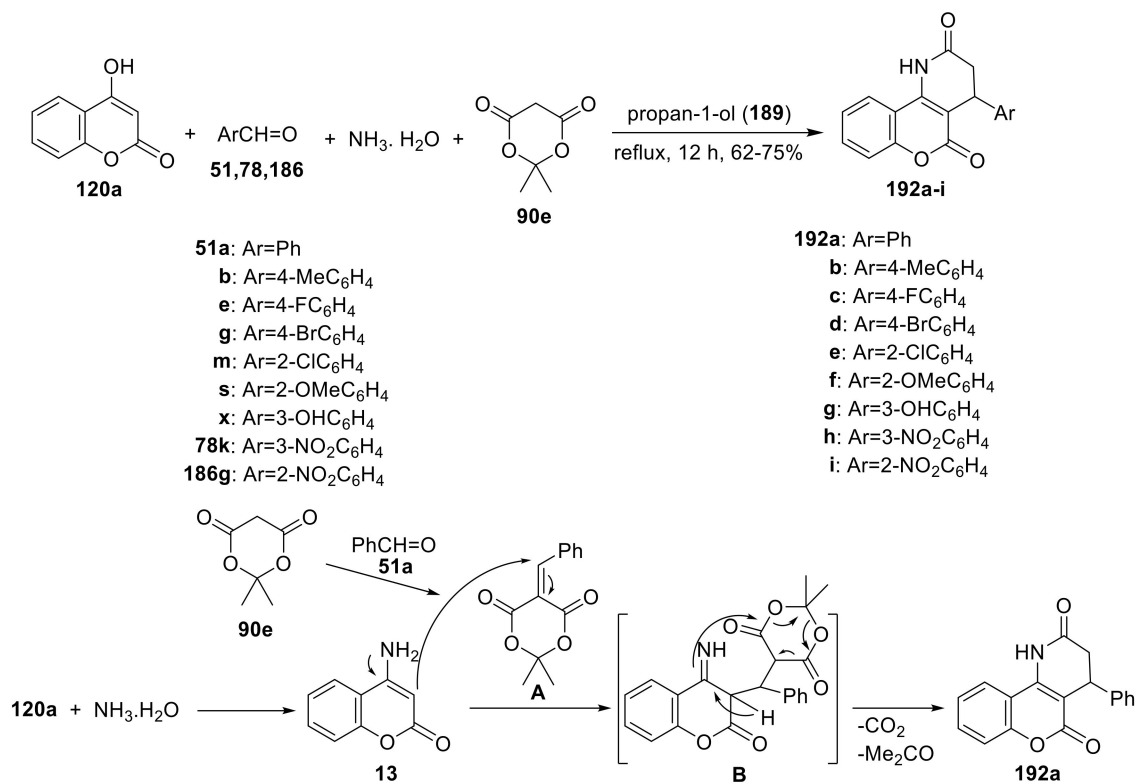
**Scheme 52.** Synthesis of dihydrochromeno [3,4-*e*]isoxazolo [5,4-*b*]pyridine-6-ones **188n**, **190a–n** in ionic liquid [C4mim][HSO<sub>4</sub>].

In 2018, Sayahi et al., demonstrated the same multi-component reaction for the synthesis of coumarin-fused dihydropyridinones **192a–h** in the presence of SBA-15-SO<sub>3</sub>H, a mesoporous material with nanochannels, as catalyst [140]. This reaction completed in less reaction time with better yield than in the former work (Scheme 55).

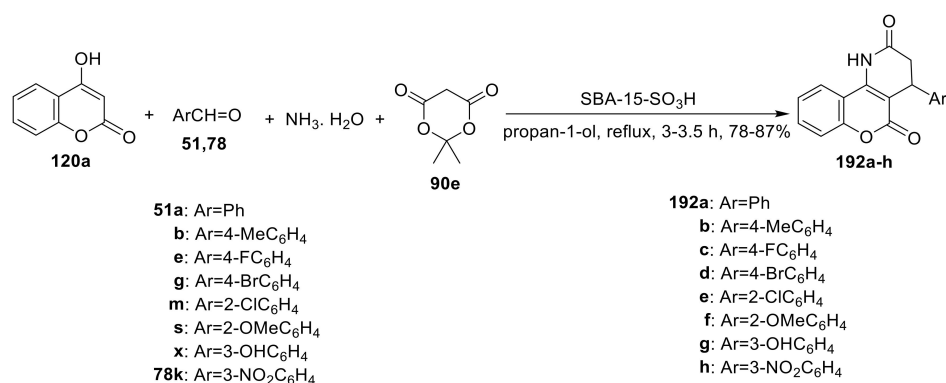
In 2019, Mohammadpoor-Baltork and coworkers demonstrated the synthesis of chromeno [4,3-*b*]quinoline-6-one derivatives **183**, **185** via a one-pot three-component reaction of 4-hydroxycoumarin (**120a**) with aldehydes and anilines catalyzed by halloysite nanoclay under solvent-free conditions [141]. Except for the products presented in Scheme 56, they also prepared analogous derivatives using two different anilines with aldehydes, or two different aldehydes with aniline or aromatic diamines with aldehydes or dialdehydes with anilines. In the proposed mechanism, the activated benzaldehyde **A** condensed with aniline to give imine **B**. The nucleophilic attack of **120a** afforded the intermediate **C**, which upon elimination of aniline resulted in the benzylidene intermediate **D**. Recondensation with aniline led to **E**. Electrocyclisation afforded **F**, and by an 1,3-H shift, dihydro-adduct **G** was formed. Anomeric-based oxidation in the presence of the catalyst, through **H**, resulted in the final product **185i**.



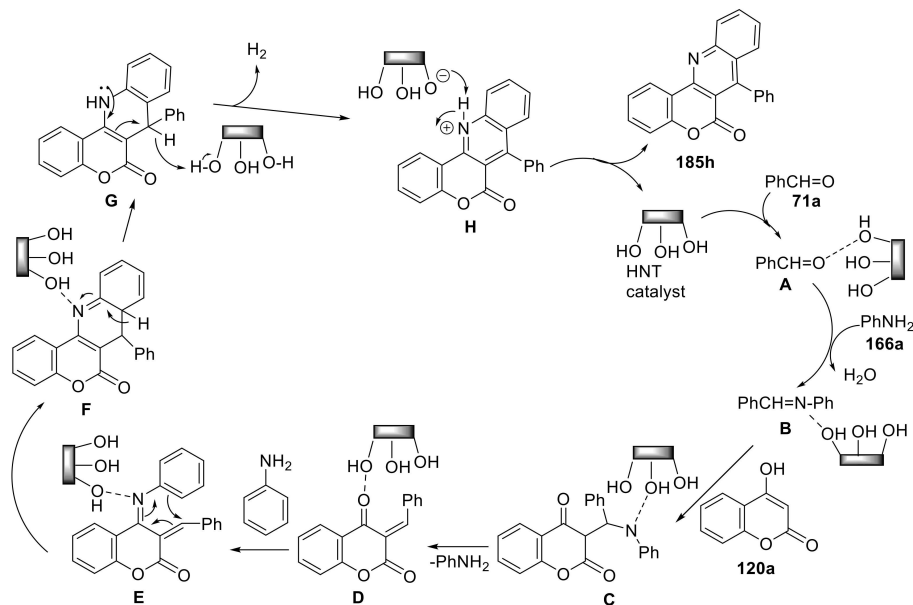
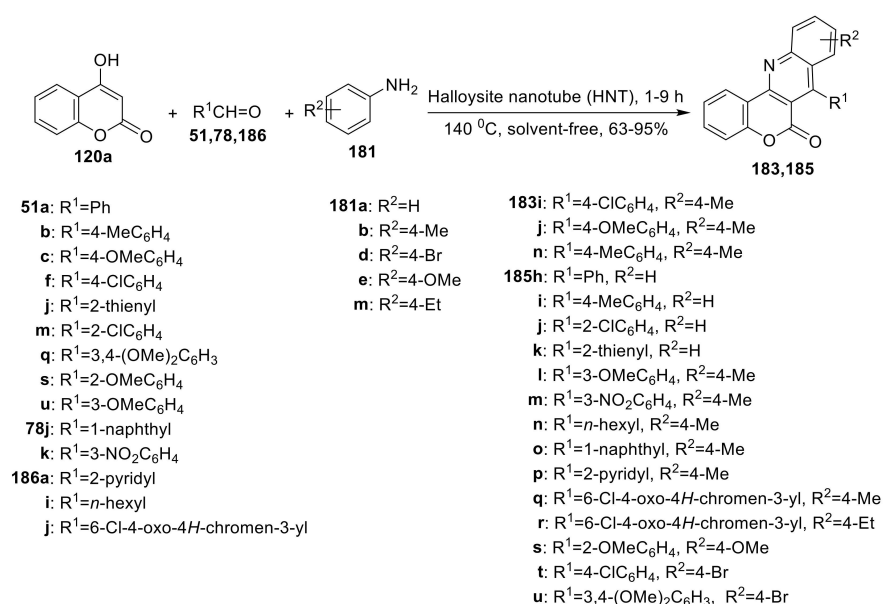
**Scheme 53.** Synthesis of 6H-chromeno [4,3-b]quinoline-6-ones catalyzed by ionic liquid immobilized on magnetic nanoparticles.



**Scheme 54.** Synthesis of coumarin-fused dihydropyridinones **192a-i** by a multi-component reaction in refluxing propan-1-ol.

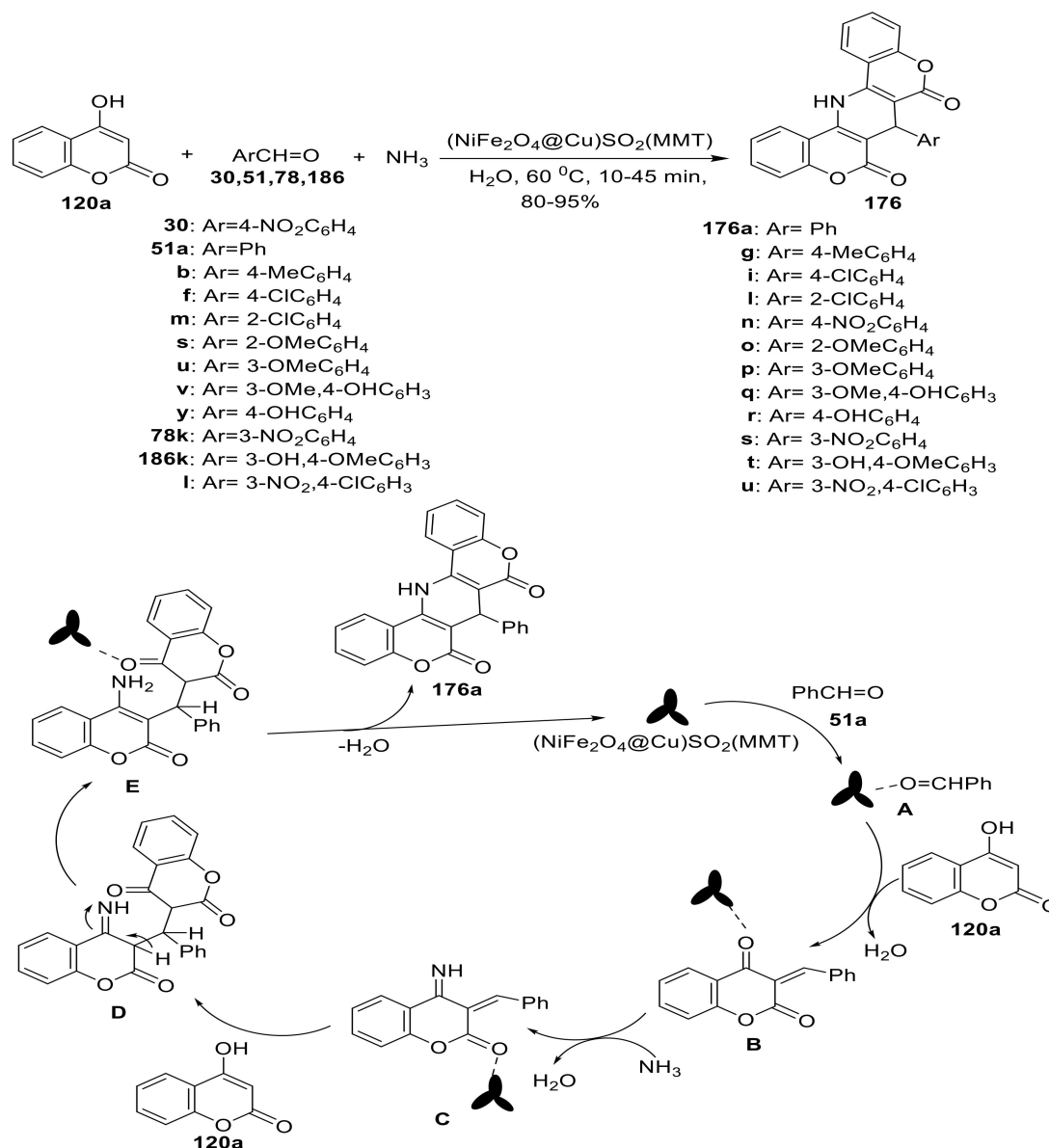


**Scheme 55.** Synthesis of coumarin-fused dihydropyridinones **192a–i** by a multicomponent reaction in refluxing propan-1-ol in the presence of SBA-15-SO<sub>3</sub>H.



**Scheme 56.** Synthesis of chromeno [4,3-*b*]quinoline-6-one derivatives via a three-component reaction catalyzed by halloysite nanotubes.

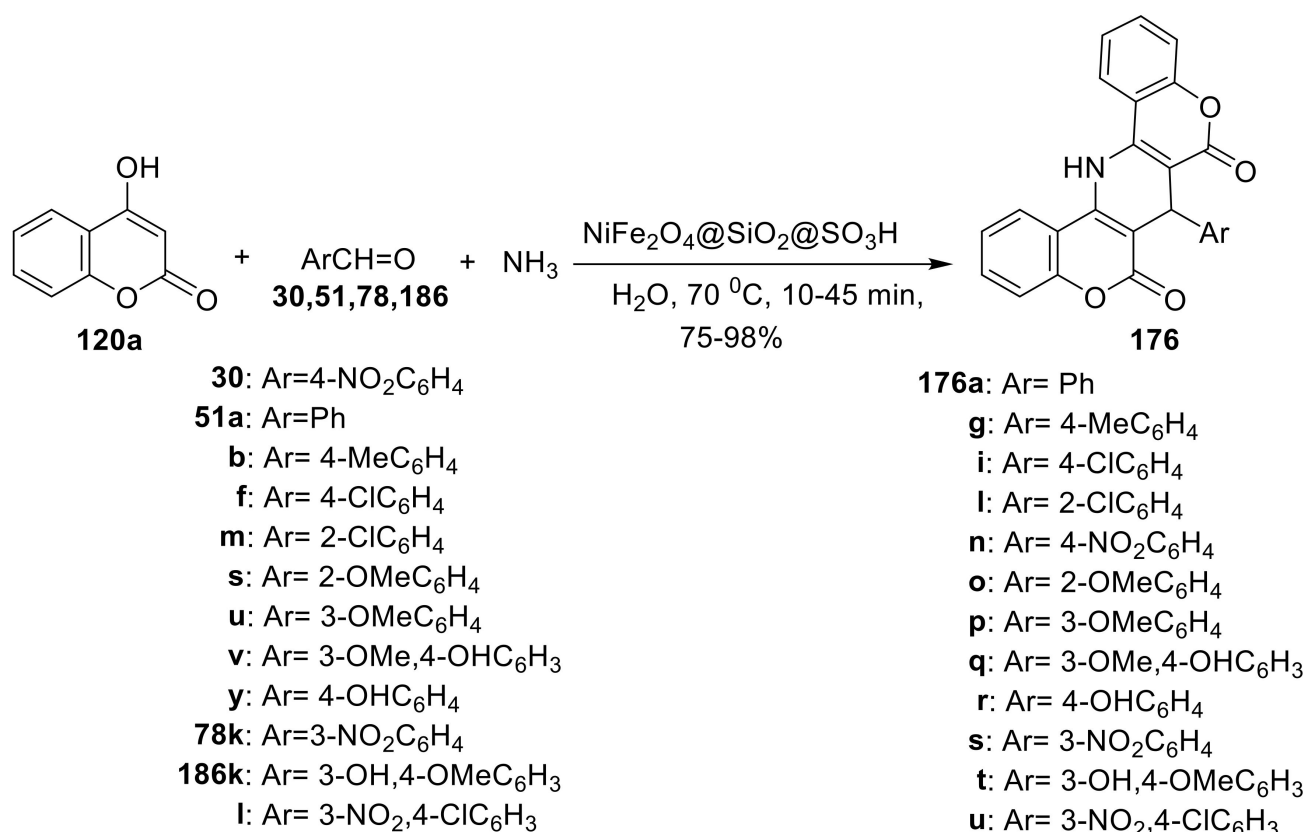
The same year, Zeynizadeh and Rahmani reported the Hantzsch synthesis of 1,4-dihydropyridocoumarin derivatives **176**, via the multi-component reaction of 4-hydroxycoumarin, aromatic aldehydes and ammonia, in the presence of a clay magnetic nanocatalyst [(NiFe<sub>2</sub>O<sub>4</sub>@Cu)SO<sub>2</sub>(MMT)] resulted from the reaction of sulfonated montmorillonite SO<sub>2</sub>(MMT) with copper immobilized nickel ferrite (NiFe<sub>2</sub>O<sub>4</sub>@Cu) [142]. The activated with clay nanocatalyst benzaldehyde **A** reacted in a Knoevenagel reaction with **120a** to the benzylidene adduct **B**, which reacted with ammonia to give the imine **C**. This by activation with clay reacted with a second molecule of **120a** and furnished the Michael adduct **D**. Tautomerization of the latter led to the enamine **E**, which under cyclization resulted in the final product **176a** (Scheme 57).



**Scheme 57.** Hantzsch synthesis of 1,4-dihydropyridocoumarins via multi-component reaction catalyzed by the clay magnetic nanocatalyst [(NiFe<sub>2</sub>O<sub>4</sub>@Cu)SO<sub>2</sub>(MMT)].

The same research group reported, in 2019, the use of another magnetic nanocatalyst, the sulfonated Ni-nanocatalyst NiFe<sub>2</sub>O<sub>4</sub>SiO<sub>2</sub>@SO<sub>3</sub>H, for the Hantzsch synthesis of the same 1,4-dihydropyridocoumarins **176** (Scheme 58) [143]. A similar mechanism such as Scheme 53 was proposed under activation with the sulfonated Ni-nanocatalyst.

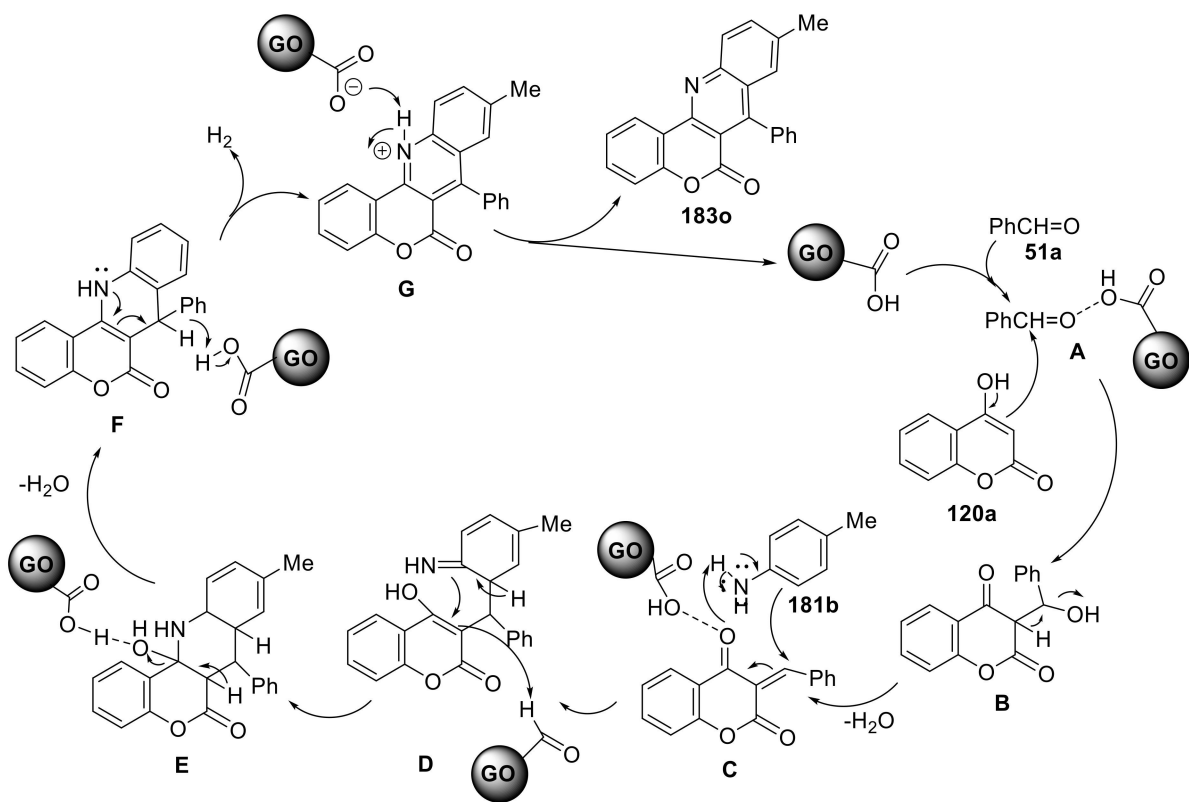
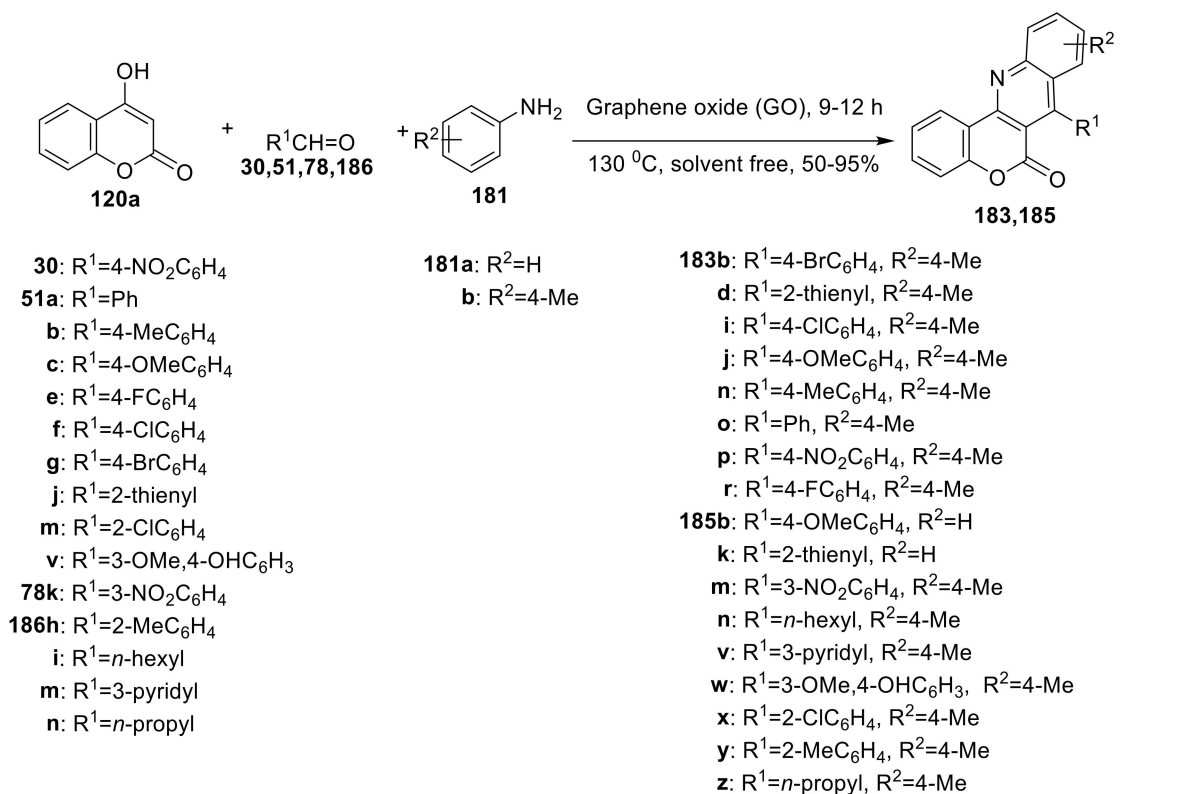




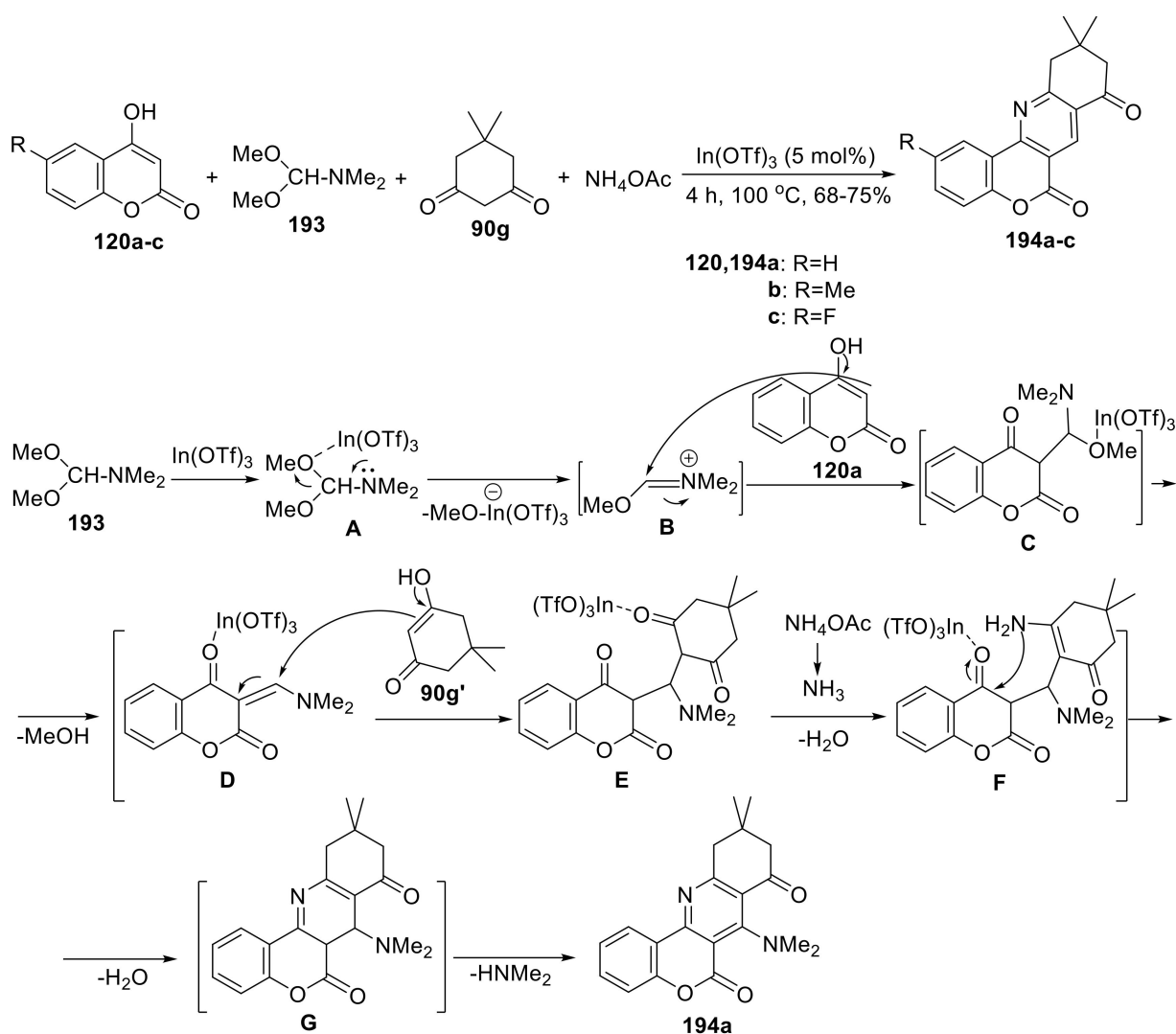
**Scheme 58.** Hantsch synthesis of the 1,4-dihydropyridocoumarins **176** catalyzed by the sulfonated Ni-nanocatalyst NiFe<sub>2</sub>O<sub>4</sub>SiO<sub>2</sub>@SO<sub>3</sub>H.

Recently, Ghosh and coworkers utilized graphene oxide (GO) as a catalyst for the one-pot three component synthesis of chromeno [4,3-*b*]quinoline-6-one derivatives **183**, **185** from 4-hydroxycoumarin (**120a**), aldehydes and anilines under solvent-free conditions [144]. GO could be recovered and reused up to five runs without losing the catalytic activity. In the proposed mechanism, the condensation of the activated benzaldehyde **A** with 4-hydroxycoumarin (**120a**) furnished after dehydration the unstable adduct **C**, which underwent nucleophilic attack from *p*-toluidine (**181b**) to give intermediate **D** (Scheme 59). After cyclization to **E** and dehydration, the intermediate **F** oxidized in the presence of GO and finally resulted in 9-methyl-7-phenyl-6*H*-chromeno [4,3-*b*]quinoline-6-one (**183o**).

The same year, Lee and coworkers reported the synthesis, between other fused pyridine derivatives, of pyrido [3,2-*c*]coumarin derivatives **194a–c** via the one-pot multi-component reaction of 4-hydroxycoumarin (**120a**), *N,N*-dimethylformamide dimethyl acetal, dimedone and ammonium acetate catalyzed by In(OTf)<sub>3</sub> under solvent-free conditions [145]. The derivatives were tested for their photophysical properties as photoluminescent probes. 4-Hydroxycoumarin (**120a**) attacked the iminium ion **B** generated from **193** under In(OTf)<sub>3</sub> catalysis (Scheme 60). Elimination of methanol from the intermediate **C** formed led to the intermediate **D**, which was isolated by the authors in the control experiment. Nucleophilic addition of the enol **90g'** gave Michael's reaction adduct **E**. The latter reacted with ammonia, generated from ammonium acetate, to afford intermediate **F**. Intramolecular condensation furnished the dihydro-intermediate **G**. Elimination of dimethylamine resulted in the final product **194a**.



**Scheme 59.** Synthesis of chromeno [4,3-*b*]quinoline-6-one derivatives **183**, **185** via three-component reaction catalyzed by graphene oxide.

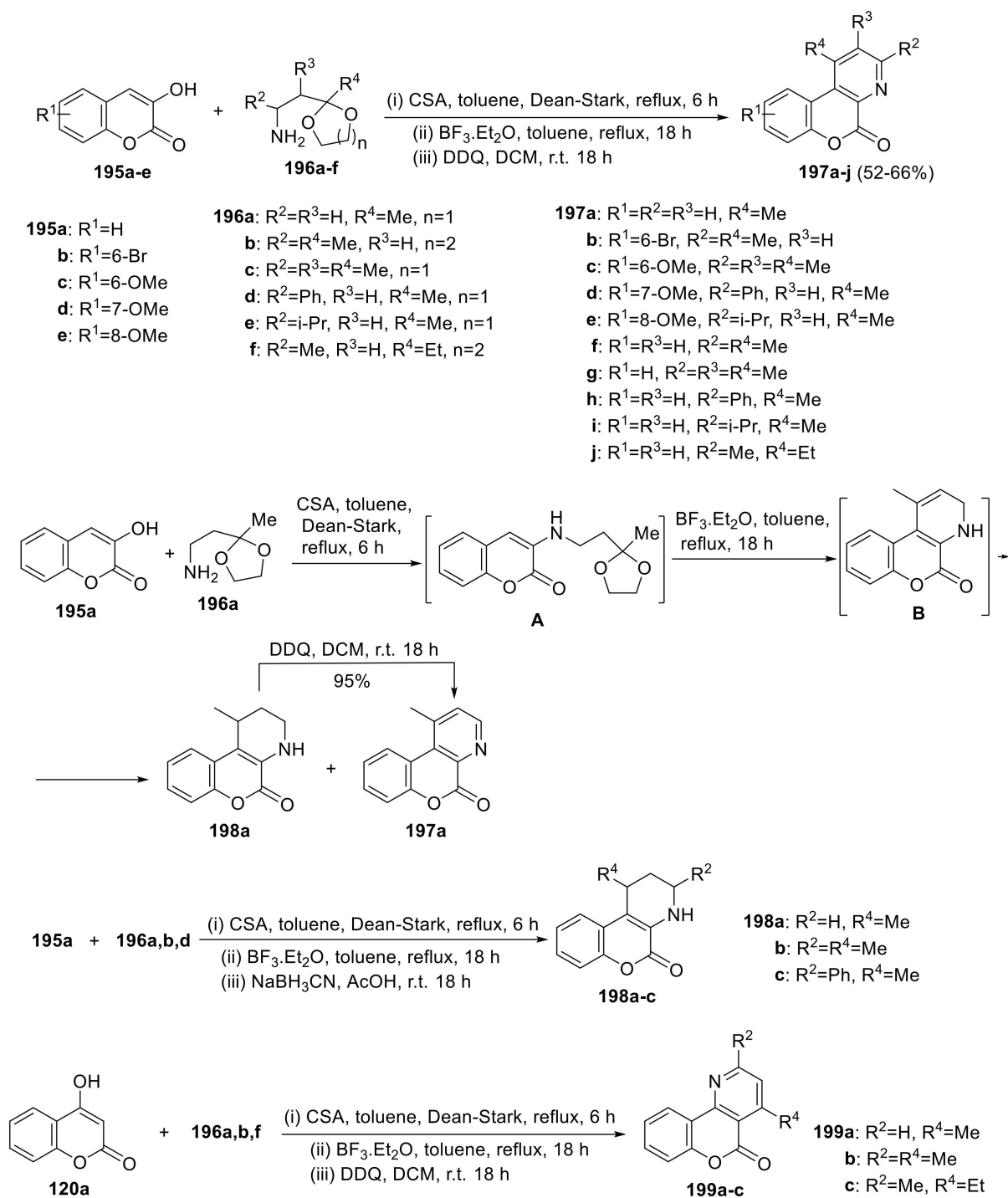


**Scheme 60.** Synthesis of pyrido [3,2-c]coumarin derivatives via one-pot multi-component reaction catalyzed by  $\text{In}(\text{OTf})_3$ .

In 2003, Guillaumet and coworkers synthesized pyrido [2,3-c] and pyrido [3,2-c]coumarins by the reactions of 3-hydroxycoumarins **195a–e** or 4-hydroxycoumarin (**120a**) with  $\beta$ -aminoketones **196a–f**, having the carbonyl group protected [146]. Condensation of **195a** with the amine **196a** in the presence of catalytic amount of camphorsulfonic acid (CSA) in toluene under reflux and Dean–Stark apparatus gave the intermediate **A** (Scheme 61). Cyclization in the presence of  $\text{BF}_3$  etherate under reflux led to intermediate **B**, which under disproportionation resulted in a mixture of **197a/198a** (56:44). The similar reactions of **120a** with **196a,b,f** afforded the pyrido [3,2-c]coumarins **199a–c**. When **198a** was treated with DDQ, this furnished pyrido [2,3-c]coumarin (**197a**). When the reactions of **195a** with protected aminoketones, **196a,b,d**, were treated in the third step with  $\text{NaBH}_3\text{CN}$ , the tetrahydropyrido [2,3-c]coumarins **198a–c** were isolated.

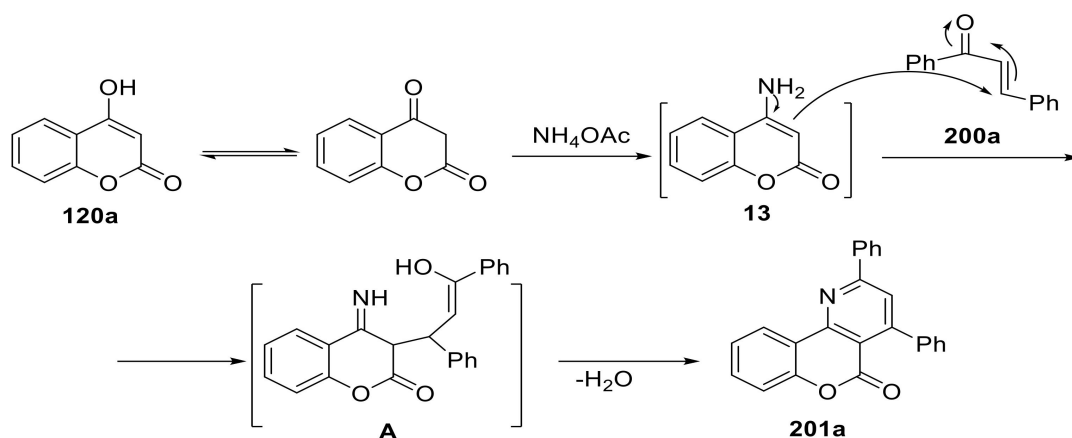
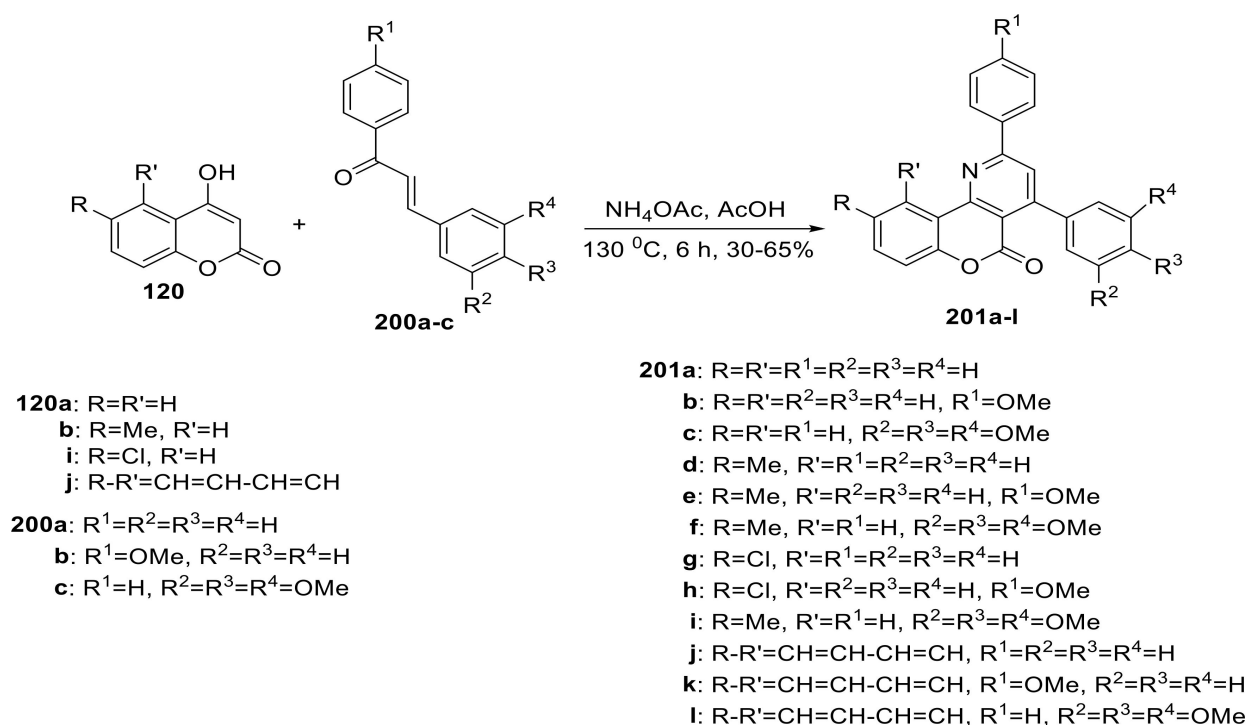
#### Synthesis with Krohnke’s-Type Reaction

Krohnke’s reaction is the reaction of  $\alpha$ -pyridinium methyl ketone salts with  $\alpha,\beta$ -unsaturated ketones in the presence of ammonium acetate in acetic acid for the synthesis of substituted pyridines [147–149]. 1,3-Dicarbonyl compounds are used also in place of pyridinium salts for the synthesis of pyridines under these reactions [149].



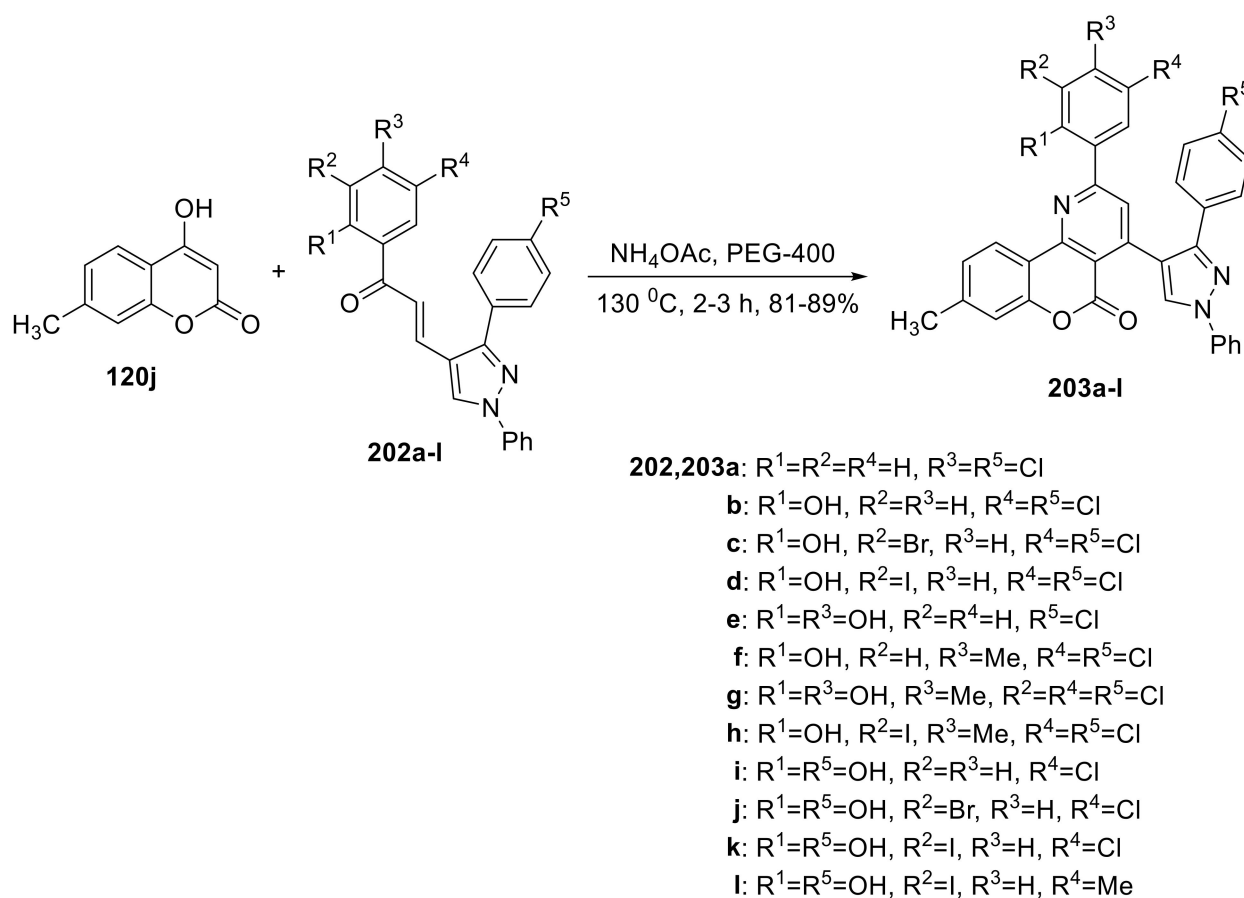
**Scheme 61.** Synthesis of pyrido [2,3-*c*] and pyrido [3,2-*c*]coumarin derivatives.

Application of Krohnke's reaction in the case of 4-hydroxycoumarins **120** as a one-pot reaction with chalcones **200** and ammonium acetate resulted in the fused pyrido [3,2-*c*]coumarins **201** [150]. In this reaction, the enamine **13**, in situ formed from **120a** and ammonium acetate, added in a Michael reaction to the chalcone **200a** and gave the intermediate **A** (Scheme 62). Tautomerization of the latter, dehydration and aromatization furnished the final product **201a**.



**Scheme 62.** Synthesis of diaryl pyrido [3,2-*c*]coumarins **201** by the Krohnke's reaction of 4-hydroxycoumarins with chalcones.

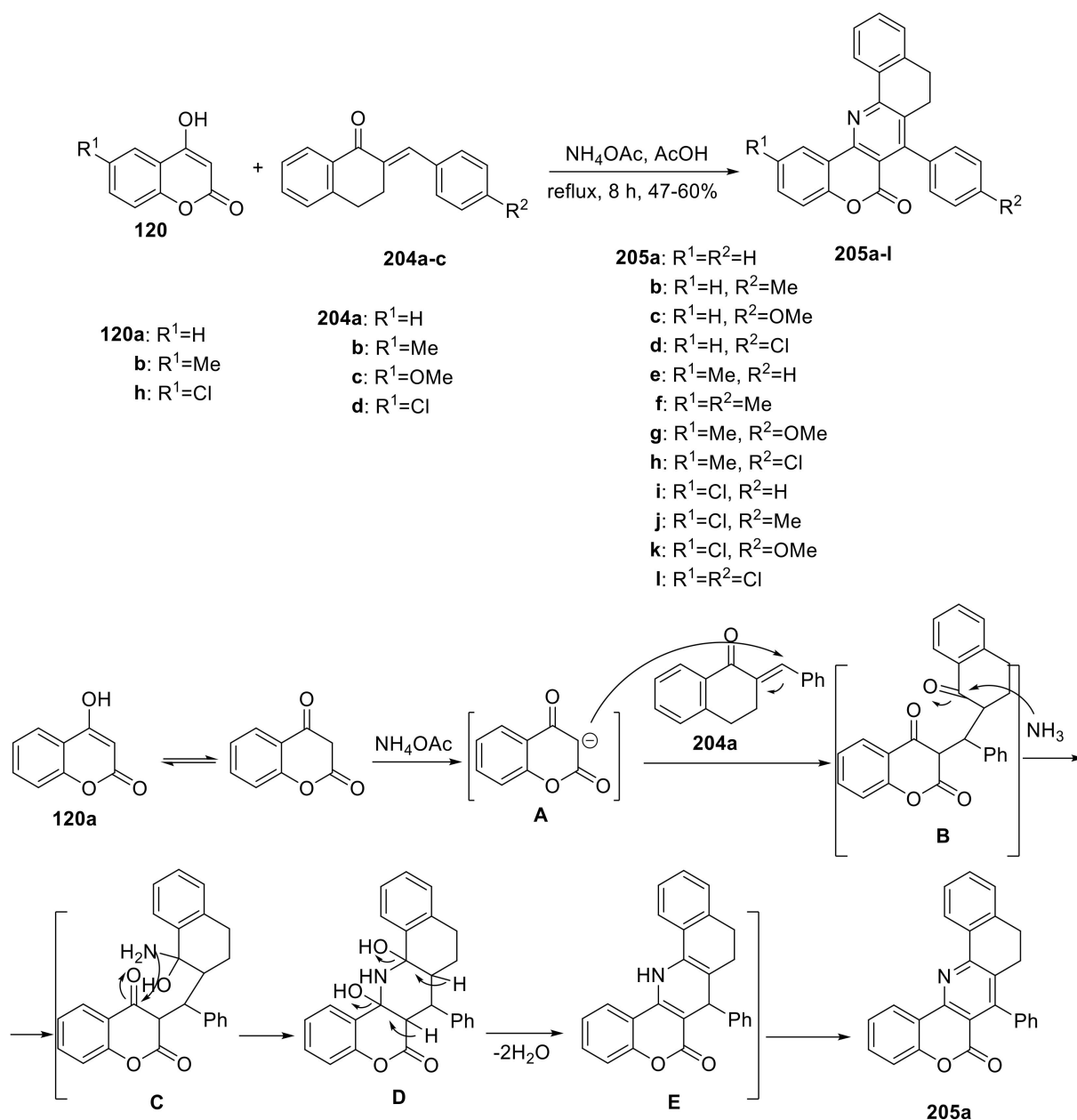
In 2010, Dawane, Konda and coworkers reported an analogous Krohnke's reaction of 4-hydroxy-7-methylcoumarin (**120j**) with chalcones **202**, containing a pyrazole moiety, in poly(ethylene glycol) (PEG-400) in the presence of ammonium acetate for the synthesis of the pyrido [3,2-*c*]coumarins **203** (Scheme 63) [45]. The proposed mechanism for this reaction was the same as that presented in Scheme 62. The synthesized derivatives were evaluated for their antimicrobial properties. The antibacterial activity was checked against bacteria *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus* and *Bacillus subtilis*. *Salmonella typhimurium*, Antifungal activity was tested against *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum*, and *Fusarium moniliforme*. Compounds **203b**, **203d-f**, **203h**, **203j**, **203l** showed good antibacterial activity against one or more bacteria. Most of the compounds presented inhibitory effect against fungi.



**Scheme 63.** Synthesis of aryl, pyrazolyl pyrido [3,2-*c*]coumarins **203** by the Krohnke's reaction of 4-hydroxycoumarins with chalcones.

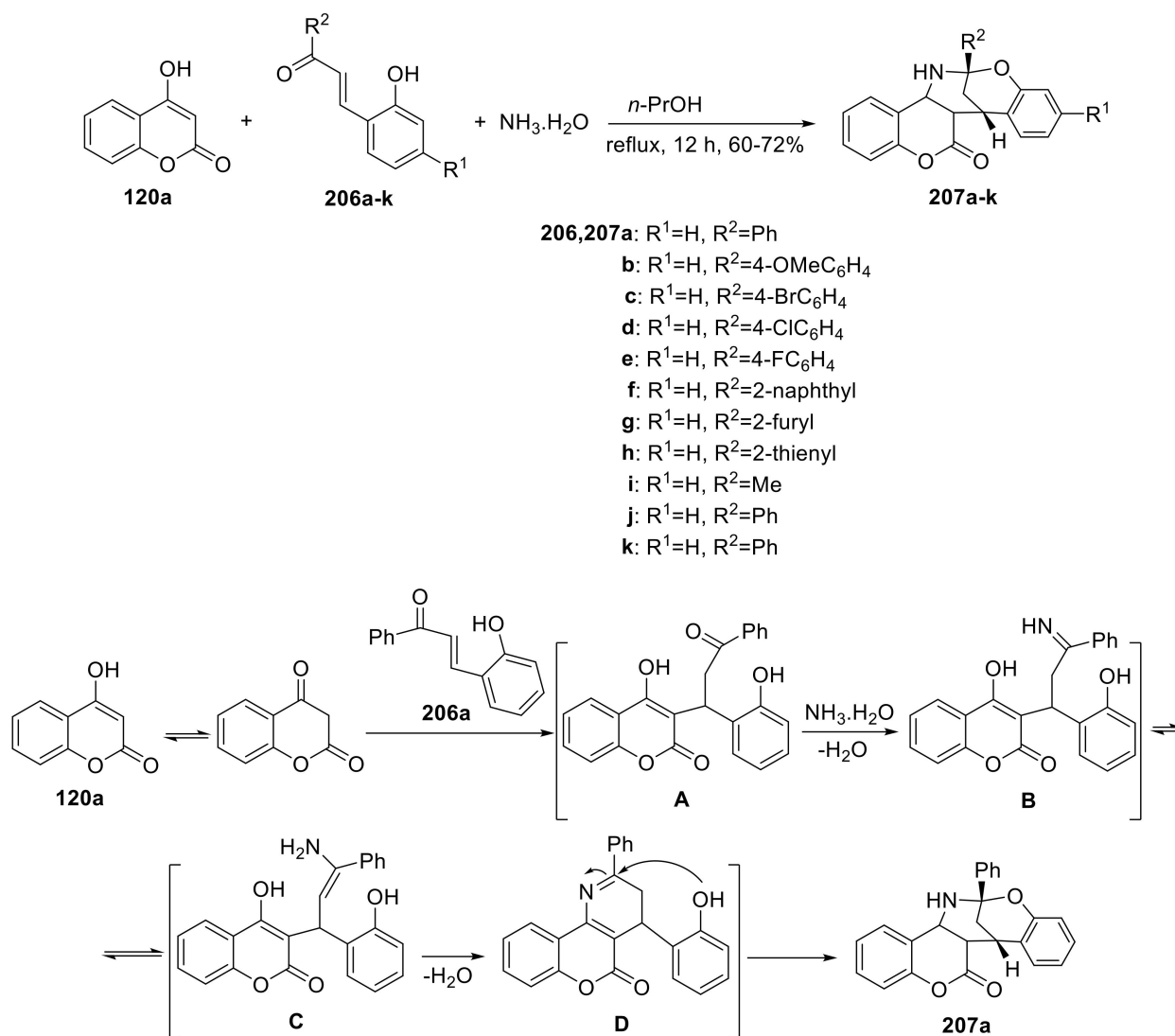
In 2011, Brahmhadtt and coworkers applied Krohnke's reaction, changing the chalcone to 2-arylidene tetralones **204a–c**, and synthesized the fused aza-phenanthrocoumarins **205a–l** [151]. According to the proposed mechanism, the anion **A** formed from 4-hydroxycoumarin (**120a**) and ammonium acetate reacted with **204a** in a Michael addition to give intermediate **B** (Scheme 64). Addition of ammonia furnished the adduct **C**, which cyclized to **D**, through the addition of amine-group to the coumarin carbonyl. Dehydration led to the 1,4-dihydro intermediate **E**. Oxidation of the latter resulted in the final product **205a**. Recently, the same group demonstrated the crystal structure of compound **205a** [152]. All the compounds were tested for their antibacterial activity against *Escherichia coli* (gram – ve bacteria) and *Bacillus subtilis* (gram + ve bacteria) and antifungal activity against *Candida albicans* (Fungi). Compounds **205i–l**, with chlorine atom in coumarin moiety, showed better activity against *E. coli* and *B. subtilis*. All the compounds presented moderate activity against fungi *C. albicans*, except compound **205e** with poor activity and **205b** with no activity.

In 2014, Yin and coworkers demonstrated the one-pot synthesis of pentacycle coumarin derivatives **207a–k** from the multi-component reaction of 4-hydroxycoumarin (**120a**), 2-hydroxychalcones **206a–k** and aqueous ammonia in refluxing *n*-propanol under catalyst-free conditions [153]. In the proposed mechanism, the intermediate **A** was formed by a Michael reaction of **120a** to the chalcone **206a** (Scheme 65). Amination with ammonia furnished the intermediate **B**, which through the tautomer **C** cyclized to dihydropyridocoumarin **D** under elimination of water. Intramolecular addition of a hydroxyl group to the imino moiety resulted in the final pentacycle product **207a**.



**Scheme 64.** Synthesis of fused aza-phenanthrocoumarins **205a-l** via a Krohnke's reaction.

In 2019, Giri and Brahmhadtt synthesized bipyridyl-fused coumarins **209a-l** by the Krohnke' reaction of 4-hydroxycoumarins **120** with chalcones **208a-c** and ammonium acetate in glacial acetic acid [154]. In the proposed plausible mechanism, the intermediate **B** was formed by the Michael reaction of carbanion **A** to the chalcone **208a**. Addition of ammonia to the 4-carbonyl of coumarin (Scheme 66), and not to the benzoyl carbonyl as in Scheme 62, gave the intermediate **C**, which cyclized to **D** upon nucleophilic addition of amine to the benzoyl carbonyl. Dehydration of the latter gave 1,4-dihydropyridocoumarin **E**, which by oxidation resulted in the final product **209a**. The synthesized compounds were tested for their antimicrobial activity against gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and gram-negative bacteria (*Escherichia coli* and *Salmonella typhimurium*) and antifungal activity against *Aspergillus niger* and *Candida albicans*. Compounds **209c**, **209f**, **209i** exhibited the better antimicrobial activity.



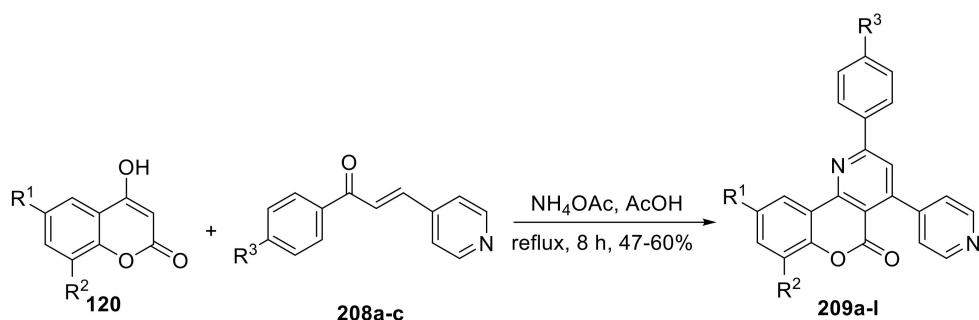
**Scheme 65.** Synthesis of pentacycle coumarin derivatives **207a–k** by a catalyst-free three-component reaction.

### 2.1.3. Synthesis from Various Coumarin Derivatives

In 1994, Heber and Berghaus reported the synthesis of pyridocoumarins **212a–c** by the treatment of 4-aminocoumarin derivatives **210a–c** with a mixture of DMF and phosphorus oxychloride under Vilsmeier conditions [74]. Reduction of **212b,c** with sodium cyanoborohydride resulted in azacannabinoids **213b,c** (Scheme 67).

In 2003, Al-Omran et al., synthesized coumarin derivative **215** by the reaction of 3-cyano-4-methylcoumarin (**214**) with dimethylformamide dimethylacetal (DMFDMA) under reflux in xylene [155]. Coumarin derivative **215** reacted with benzotriazole-1-ylacetic acid hydrazide under fusion to give the triazolo-fused pyridocoumarin **217** through the intermediates **A** and **B** (Scheme 68). The reaction of **215** with hydrazine hydrate resulted in *N*-aminopyridine derivative **216**. Treatment of **216** with chloroacetylacetone led to pyridotriazine derivative **218**. The reaction of **215** with 2-aminopyridine, urea, glycine, 2-aminocrotonitrile or cyanothioacetamide resulted in the pyridocoumarin derivatives **219–223**. The compounds were tested for their antifungal activity against *Aspergillus niger* and for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*. Most of the products showed antibacterial and fungicidal activities.

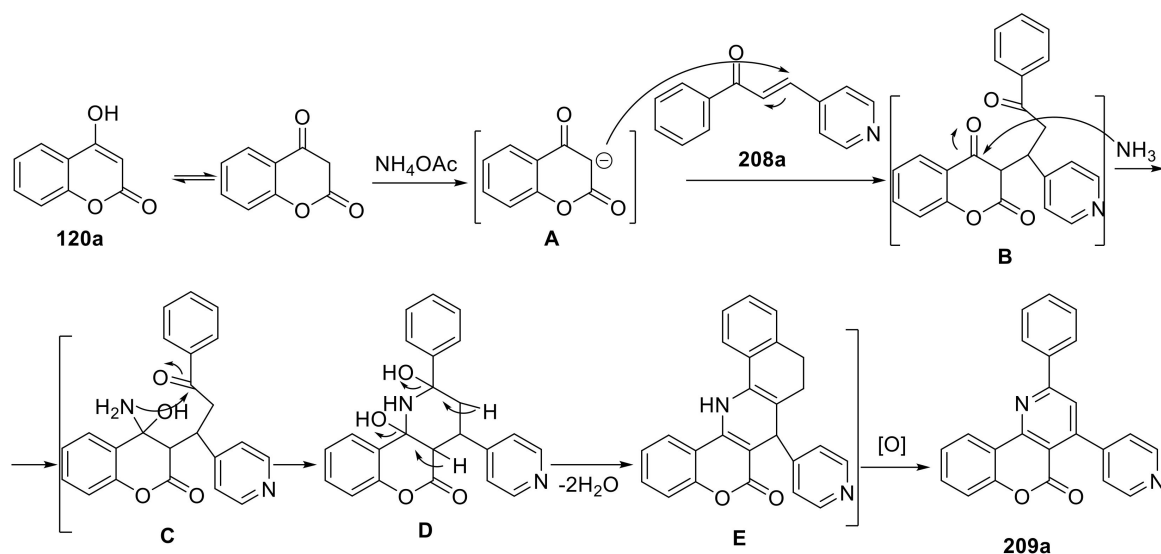




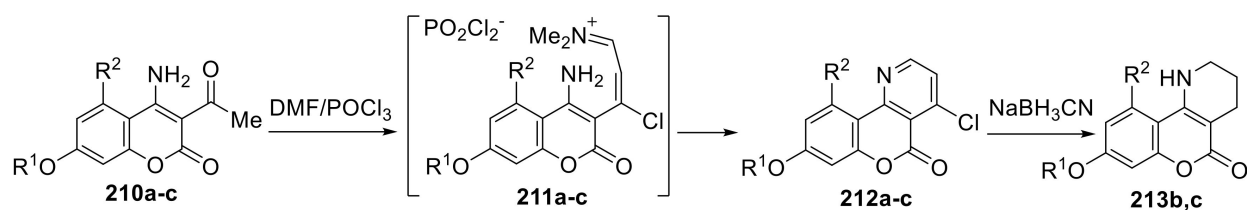
**120a:** R<sup>1</sup>=R<sup>2</sup>=H  
**b:** R<sup>1</sup>=Me, R<sup>2</sup>=H  
**h:** R<sup>1</sup>=Cl, R<sup>2</sup>=H  
**k:** R<sup>1</sup>=H, R<sup>2</sup>=Me

**208a:** R<sup>3</sup>=Me  
**b:** R<sup>3</sup>=OMe  
**c:** R<sup>3</sup>=Cl

**209a:** R<sup>1</sup>=R<sup>2</sup>=H, R<sup>3</sup>=Me  
**b:** R<sup>1</sup>=R<sup>2</sup>=H, R<sup>3</sup>=OMe  
**c:** R<sup>1</sup>=R<sup>2</sup>=H, R<sup>3</sup>=Cl  
**d:** R<sup>1</sup>=R<sup>3</sup>=Me, R<sup>2</sup>=H,  
**e:** R<sup>1</sup>=Me, R<sup>2</sup>=H, R<sup>3</sup>=OMe  
**f:** R<sup>1</sup>=Me, R<sup>2</sup>=H, R<sup>3</sup>=Cl  
**g:** R<sup>1</sup>=H, R<sup>2</sup>=R<sup>3</sup>=Me  
**h:** R<sup>1</sup>=H, R<sup>2</sup>=Me, R<sup>3</sup>=OMe  
**i:** R<sup>1</sup>=H, R<sup>2</sup>=Me, R<sup>3</sup>=Cl  
**j:** R<sup>1</sup>=Cl, R<sup>2</sup>=H, R<sup>3</sup>=Me  
**k:** R<sup>1</sup>=Cl, R<sup>2</sup>=H, R<sup>3</sup>=OMe  
**l:** R<sup>1</sup>=R<sup>3</sup>=Cl, R<sup>2</sup>=H

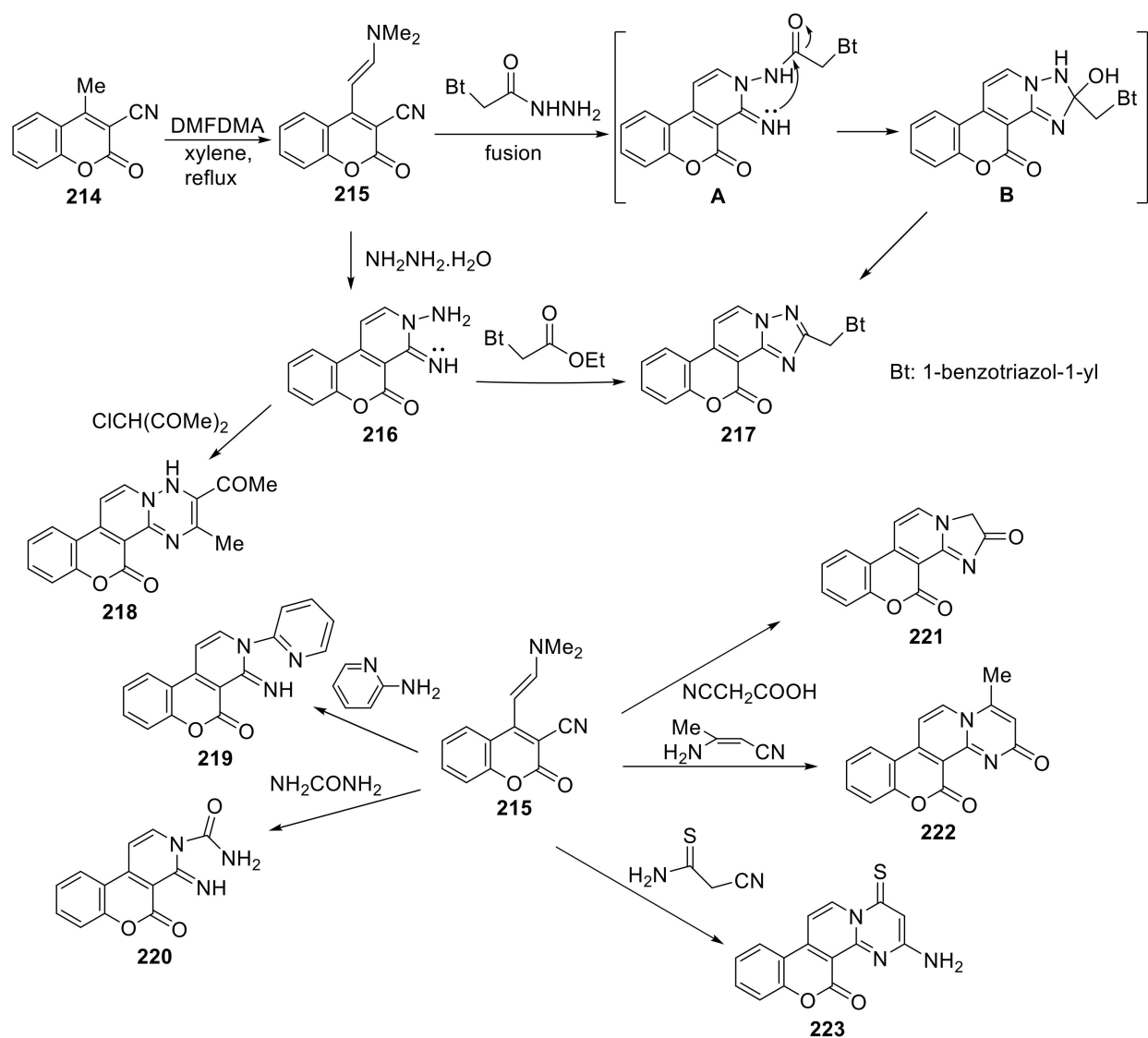


**Scheme 66.** Synthesis of bipyrindyl-fused coumarins **209a-l** by the Krohnke' reaction.



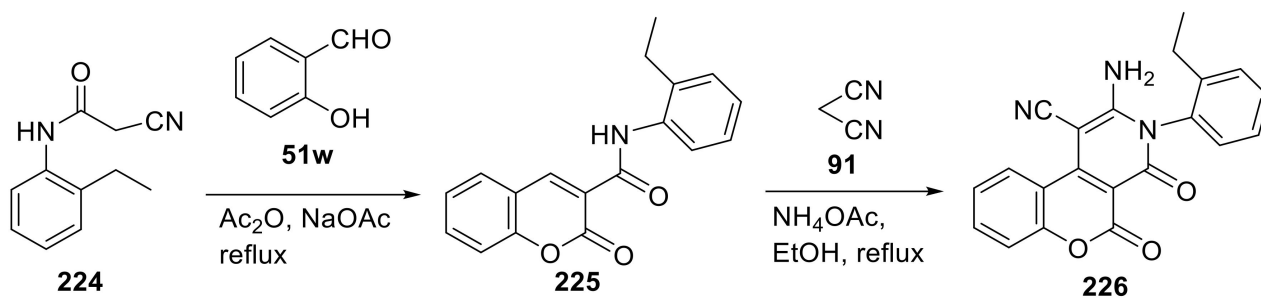
**210-213a:** R<sup>1</sup>=Me, R<sup>2</sup>=H  
**b:** R<sup>1</sup>=C<sub>5</sub>H<sub>11</sub>, R<sup>2</sup>=OCOMe  
**c:** R<sup>1</sup>=CHMeC<sub>5</sub>H<sub>11</sub>, R<sup>2</sup>=OCOMe

**Scheme 67.** Synthesis of pyridocoumarins **212a-c** and azacannabinoids **213b,c**.



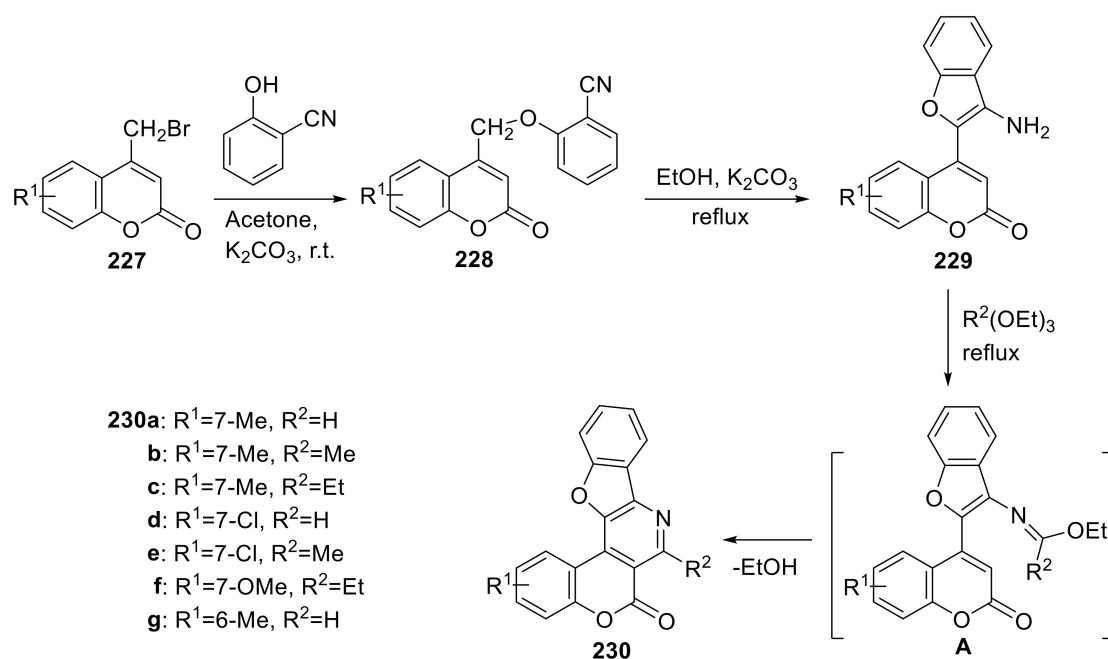
**Scheme 68.** Synthesis of fused pyridocoumarins **216–223**.

In 2005, Ismail and Noaman synthesized the chromeno [3,4-*c*]pyridone **226** by the treatment of 3-carboxamidocoumarin **225** with malonitrile (**91**) in the presence of ammonium acetate in refluxing ethanol [156]. Coumarin derivative **225** was obtained by the Perkin reaction of 2-ethyl cyanoacetanilide (**224**) with salicylaldehyde (**51w**) in acetic anhydride and sodium acetate under reflux (Scheme 69). The compound **226** was tested for antifibrotic activity, but it showed high fibrotic potential.



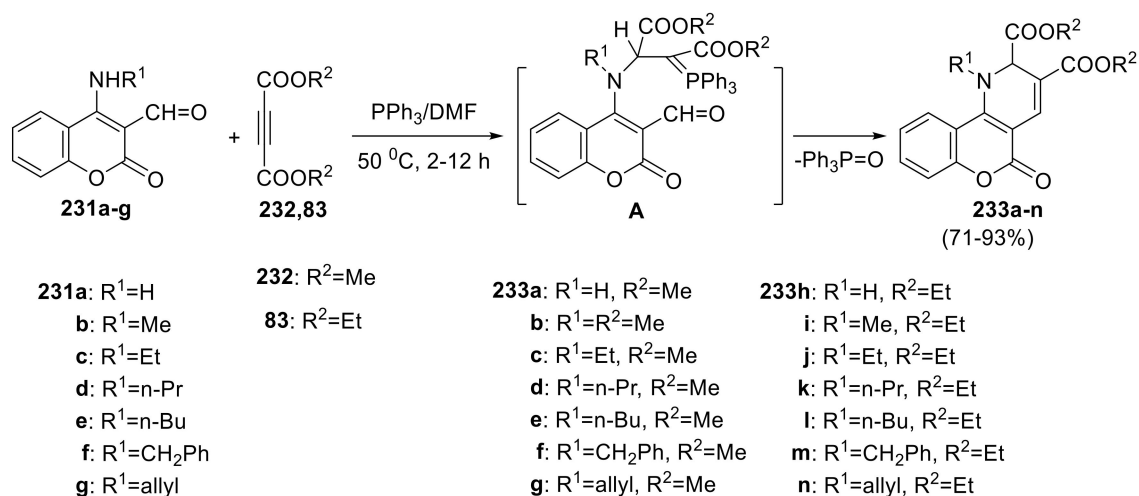
**Scheme 69.** Synthesis of chromeno [3,4-*c*]pyridone **226**.

The same year, Sun and coworkers isolated, in a three-step procedure, the angularly-fused benzofuopyridinocoumarins **230** in 70–80% yield by refluxing of 2'-cyano-4-phenoxy-coumarins **229** with excess of orthoesters [157]. The reaction proceeded through the imine **A** (Scheme 70). The products **230a–g** were tested for their anti-inflammatory, analgesic and anti-microbial activities. Compounds **230b** and **230f** showed significant inhibition of inflammation (78–97%), whereas compounds **230a**, **230b**, **230f**, **230g** presented interesting analgesic activity (one-third of the protection caused by acetylsalicylic acid). Compound **230f** was the most promising.



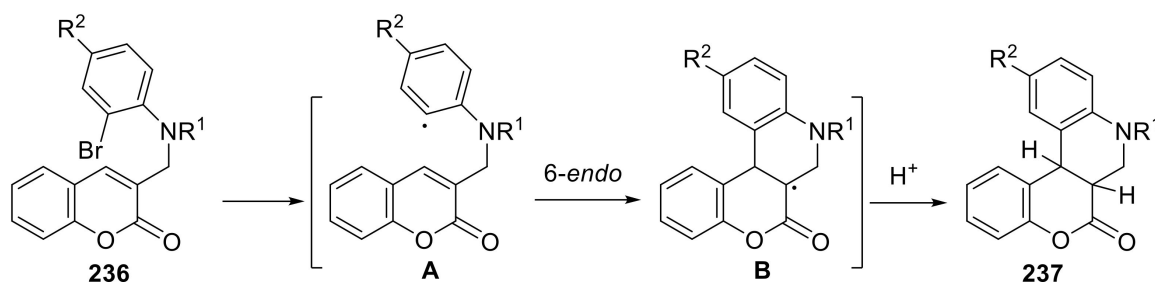
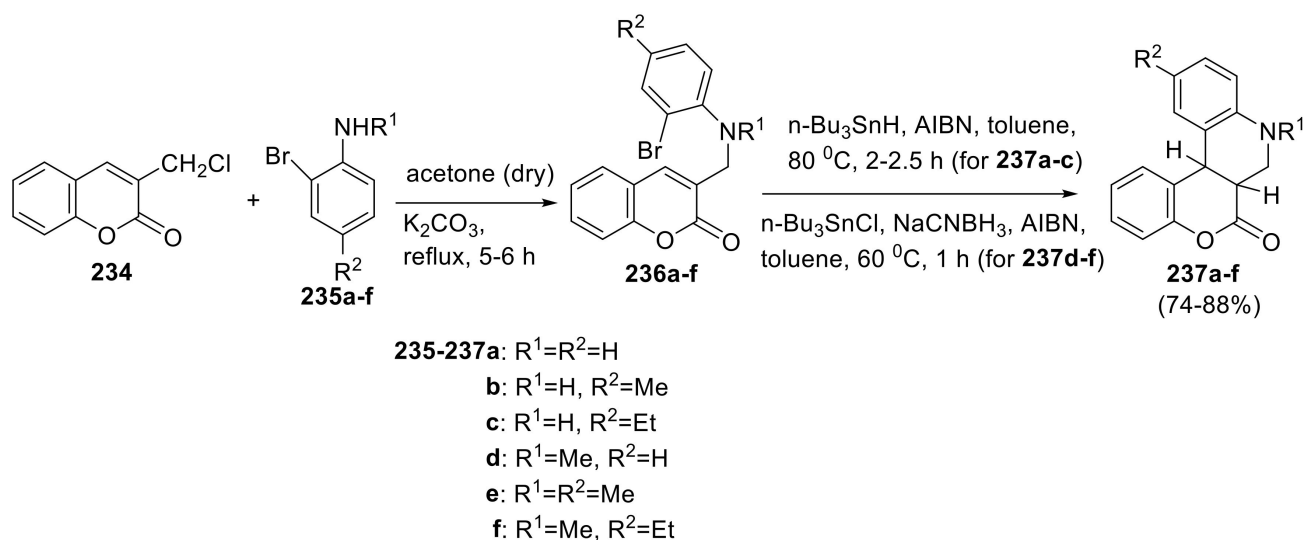
**Scheme 70.** Synthesis of angularly-fused benzofuopyridinocoumarins **230**.

In 2008, Glasnov and Ivanov synthesized dimethyl and diethyl 5-oxo-1,2-dihydro-5*H*-chromeno [4,3-*b*]pyridine-2,3-carboxylates **233a–n** by the reaction of 4-amino-3-formylcoumarins **231a–g** with acetylenedicarboxylates **232** and **83** in the presence of triphenylphosphine [158]. The final products were formed by an intramolecular Wittig reaction of the intermediate **A** (Scheme 71).



**Scheme 71.** Synthesis of dimethyl and diethyl 5-oxo-1,2-dihydro-5*H*-chromeno [4,3-*b*]pyridine-2,3-carboxylates **233a–n**.

The same year, Majumdar et al., reported the synthesis of 6a,7,8,12b-tetrahydro-6H-chromeno [3,4-c]quinolin-6-ones **237a–f** from 3-(2-bromoanilinomethyl)coumarins **236a–f** [159]. The latter were prepared by the reaction of 2-bromoanilines **235a–f** with 3-chloromethylcoumarin (**234**). The formation of products **237** could be explained by the generation of aryl radical **A**, which by a 6-endo trig cyclization produce the radical **B**, stabilized by the adjacent carbonyl (Scheme 72). Protonation of **B** led to the final compound **237**.

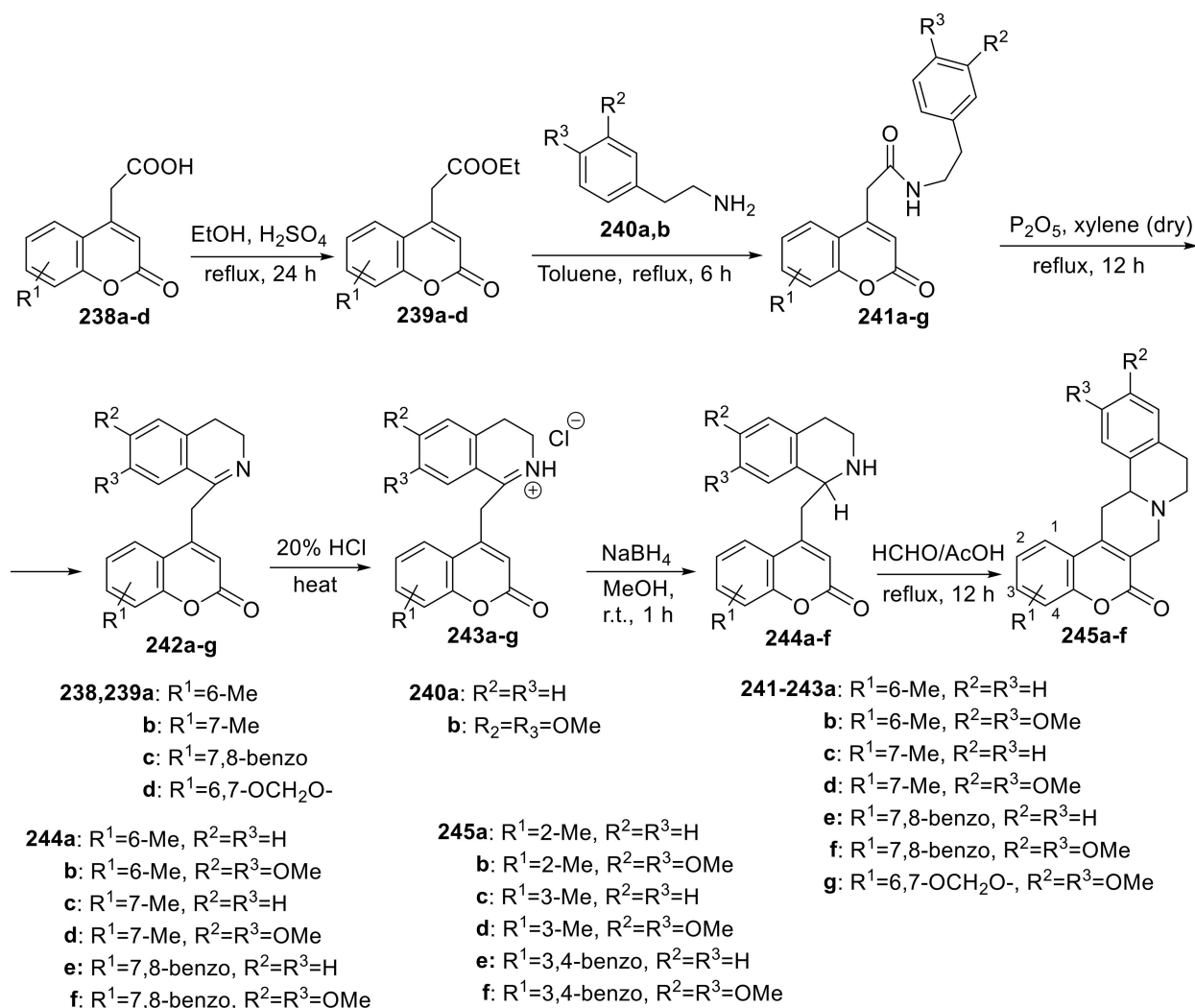


**Scheme 72.** Synthesis of 6a,7,8,12b-tetrahydro-6H-chromeno [3,4-c]quinolin-6-ones **237a–f**.

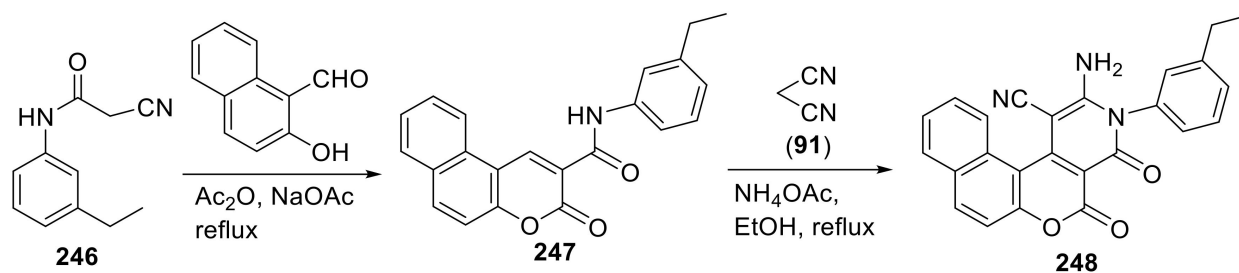
In 2010, Kulkarni and coworkers synthesized the coumarin analogues of protoberberine alkaloids **245a–f** by a Mannich reaction of 1,2,3,4-tetrahydroisoquinoline derivatives of coumarin **244a–f** [160]. Compounds **244** were obtained by the reduction of hydrochloric acid salts **243** with NaBH<sub>4</sub>. A Bischler–Napieralski reaction of amides **241** had furnished dihydroisoquinoline derivatives **242** (Scheme 73). Compounds **244** and **245** were tested for their antibacterial activity. Compounds **244e,f** and **245e,f** presented selectivity towards gram-positive bacteria *Staphylococcus aureus* and *Aspergillus niger*.

In 2012, Ghorab and coworkers reported the synthesis of benzo-fused chromeno [3,4-c]pyridone **248** by the treatment of 3-carboxamidocoumarin derivative **247** with malonitrile (**91**) [161] following the above presented similar work [99]. A Perkin reaction of 3-ethyl cyanoacetanilide (**246**) with 2-hydroxy-1-naphthaldehyde furnished the coumarin derivative **247** (Scheme 74). Compound **248** presented low anticancer activity (IC<sub>50</sub> = 245.7 μM) against Ehrlich Ascites carcinoma (EAC).

In 2017, Shi and coworkers utilized silica sulfuric acid (SSA) as a catalyst to synthesize the coumarin derivatives **250a–g** with hetero [5]helicene-like conformation [162]. This synthesis was achieved by the reaction of 3-ketobenzo[f]coumarin derivatives **249a–e** with aminopyrazoles **187** in the presence of DDQ in DMF under microwave irradiation (Scheme 75).

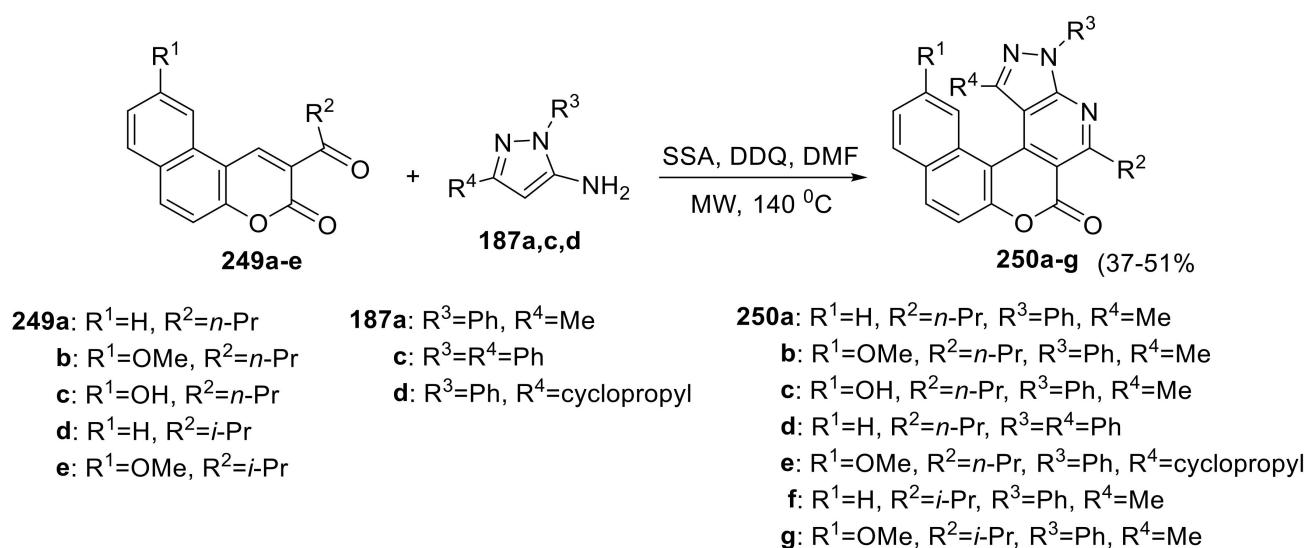


**Scheme 73.** Synthesis of 1,2,3,4-tetrahydroisoquinolinocoumarin derivatives **244a–f** and protoberberines **245a–f**.

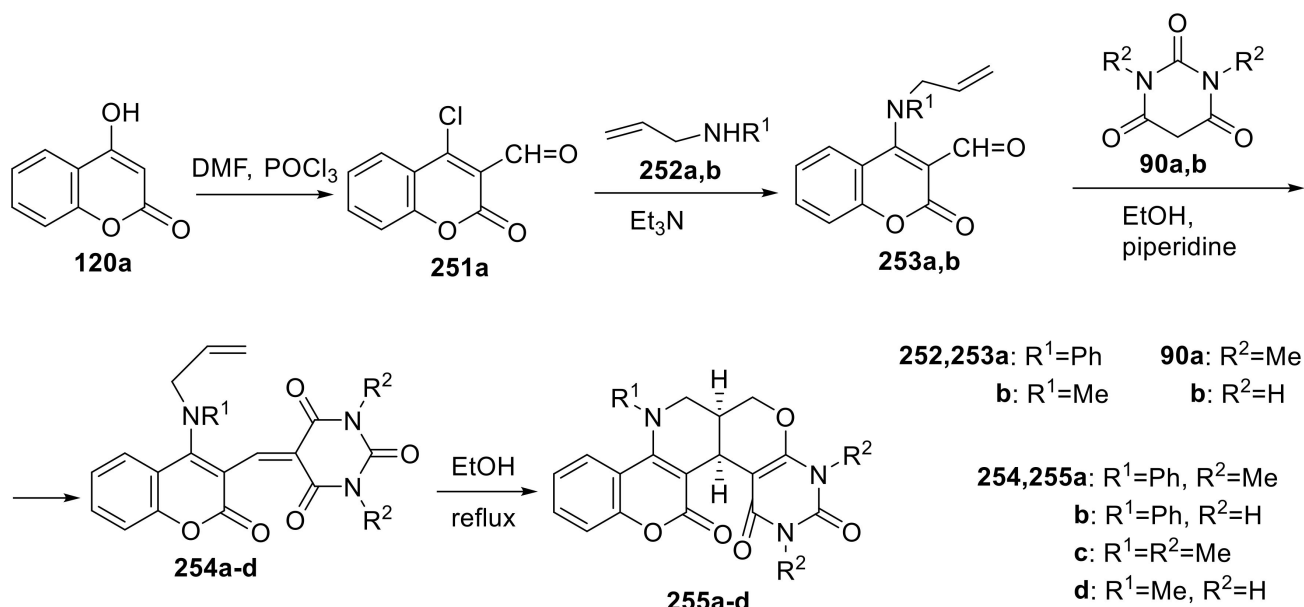


**Scheme 74.** Synthesis of benzo-fused chromeno [3,4-*c*]pyridone **248**.

In 2018, Borah synthesized the fused 1,2,3,4-tetrahydropyridocoumarin derivatives **255a–d** using the hetero Diels–Alder strategy [163]. The hetero Diels–Alder reaction of the Knoevenagel condensation adducts **254a–d** under reflux resulted in the final products **255a–d**. Compounds **254a–d** were achieved from the reaction of 3-allylamino-3-formyl coumarins **253a,b** with *N,N*-dimethylbarbituric acid (**90a**) and barbituric acid (**90b**) in the presence of piperidine as a base (Scheme 76). The 3-allylamino-3-formylcoumarins **253a,b** were prepared from the reaction of 4-chloro-3-formylcoumarin (**251a**) with allylamines **252a,b**.



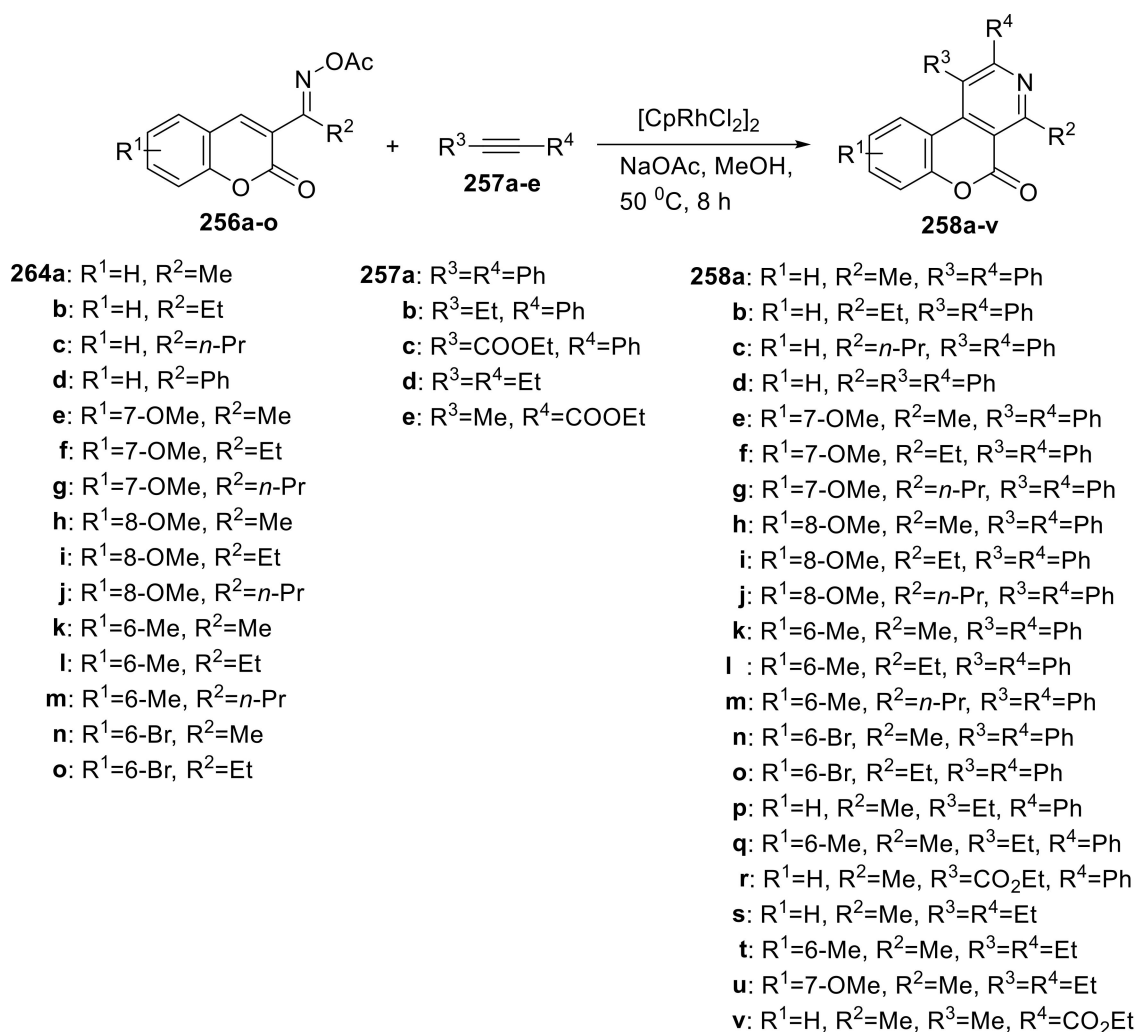
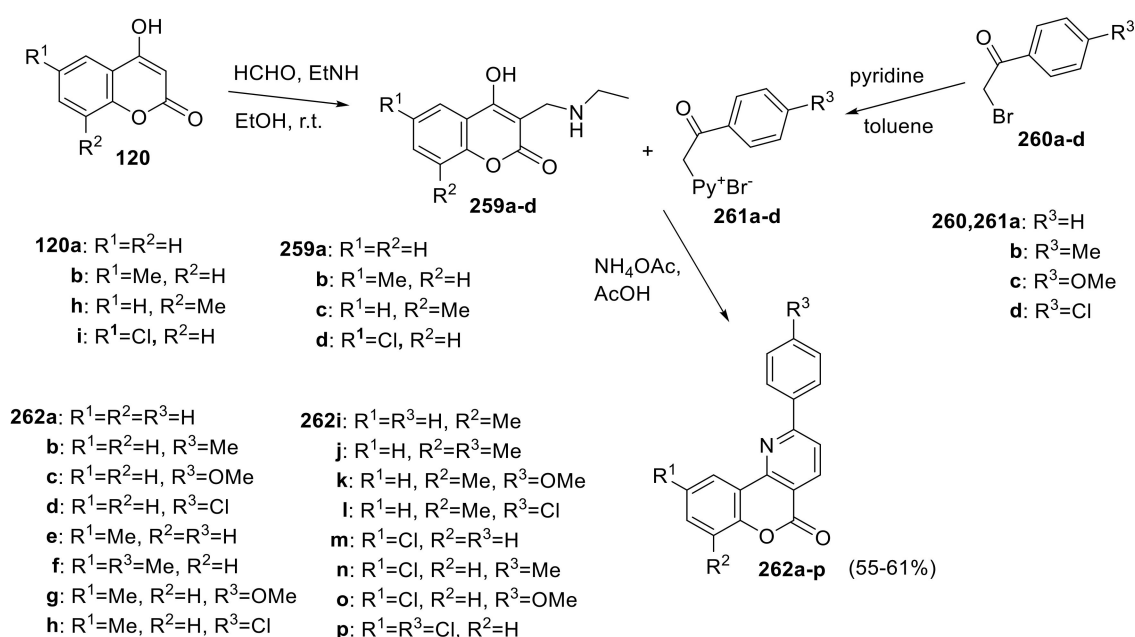
**Scheme 75.** Synthesis of hetero [5]helicene-like coumarin derivatives **250a–g**.



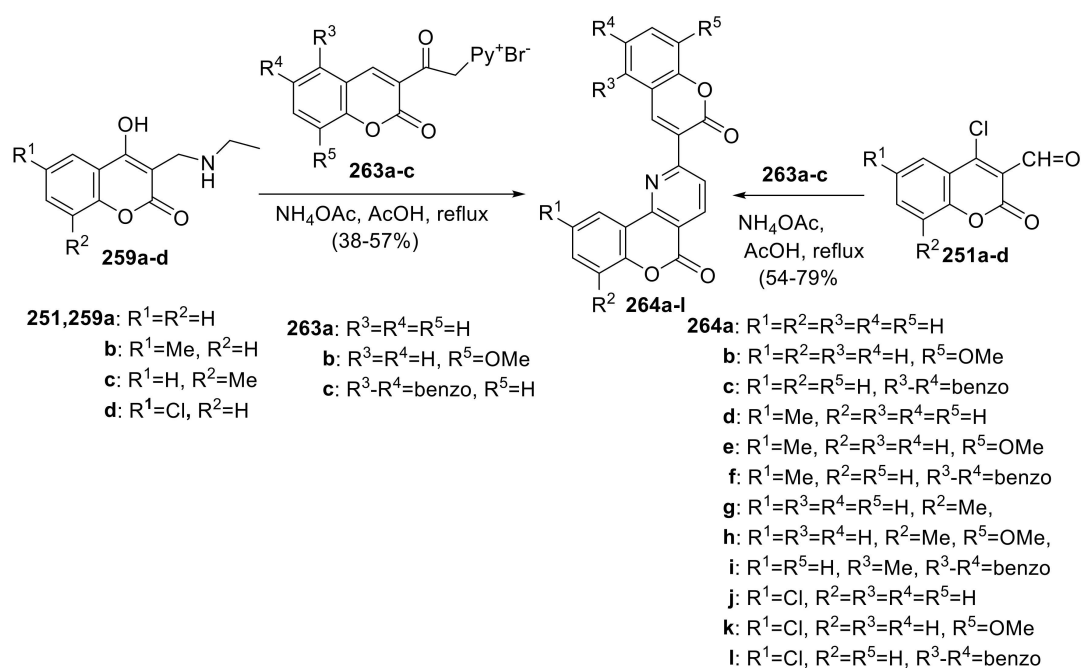
**Scheme 76.** Synthesis of fused 1,2,3,4-tetrahydropyridocoumarin derivatives **255a–d** using the hetero Diels–Alder reaction.

In a Chinese patent of 2019 [164], Li, Yang and Chen referred the synthesis of pyrido [3,4-*c*]coumarins **258a–v** by the Diels–Alder reaction of 3-acetoxyiminocoumarins **256a–o** with intermediate alkynes **257a–e** in the presence of dichloro(pentamethylcyclopentadienyl)rhodium(III) dimer as a catalyst (2.5 mol%) (Scheme 77).

In 2020, Vala and coworkers performed the reaction of 3-ethylaminomethyl-4-hydroxycoumarins **259a–d** with aroylmethyl pyridinium salts **261a–d** in the presence of ammonium acetate and acetic acid and synthesized the 2-arylpyrido [3,2-*c*]coumarins **262a–p** [165]. Compounds **259** were prepared by a Mannich reaction of 4-hydroxycoumarins **120** with formaldehyde and ethylamine, while the pyridinium salts **261** were obtained by treating phenacyl bromides **260** with pyridine (Scheme 78).

Scheme 77. Synthesis of pyrido [3,4-*c*]coumarins **258a–v**.Scheme 78. Synthesis of 2-aryl]pyrido [3,2-*c*]coumarins **262a–p**.

In 2013, Brahmabhatt and coworkers utilized, also, the 3-ethylaminomethyl-4-hydroxycoumarins **259a–d** to synthesize in moderate yields 2-(2-oxo-2H-chromen-3-yl)-5H-chromeno [4,3-b]pyridin-5-ones **264a–l** through the reaction with the pyridinium salts **263a–c**, in the presence of ammonium acetate and acetic acid [43]. For the reaction pathway, decomposition of **259a** resulted in the intermediate coumarin methide **A**, which then reacted with **263a** in the presence of  $\text{NH}_4\text{OAc}$  and  $\text{AcOH}$  to give the 1,5-dicarbonyl intermediate **B**. The latter was converted to the final product **264a** via a Krohnke's-type reaction (Scheme 79). The new compounds **264a–l** were tested for their antibacterial activity and presented potent inhibitory activity against gram-positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus*. They showed also appreciable activity against gram-negative bacteria, *Escherichia coli* and *Salmonella typhimurium*, as well as antifungal activity against *Aspergillus niger* and *Candida albicans*. Compounds **264e**, **264f**, **264i**, **264k**, **264l** were found to be the more proficient.

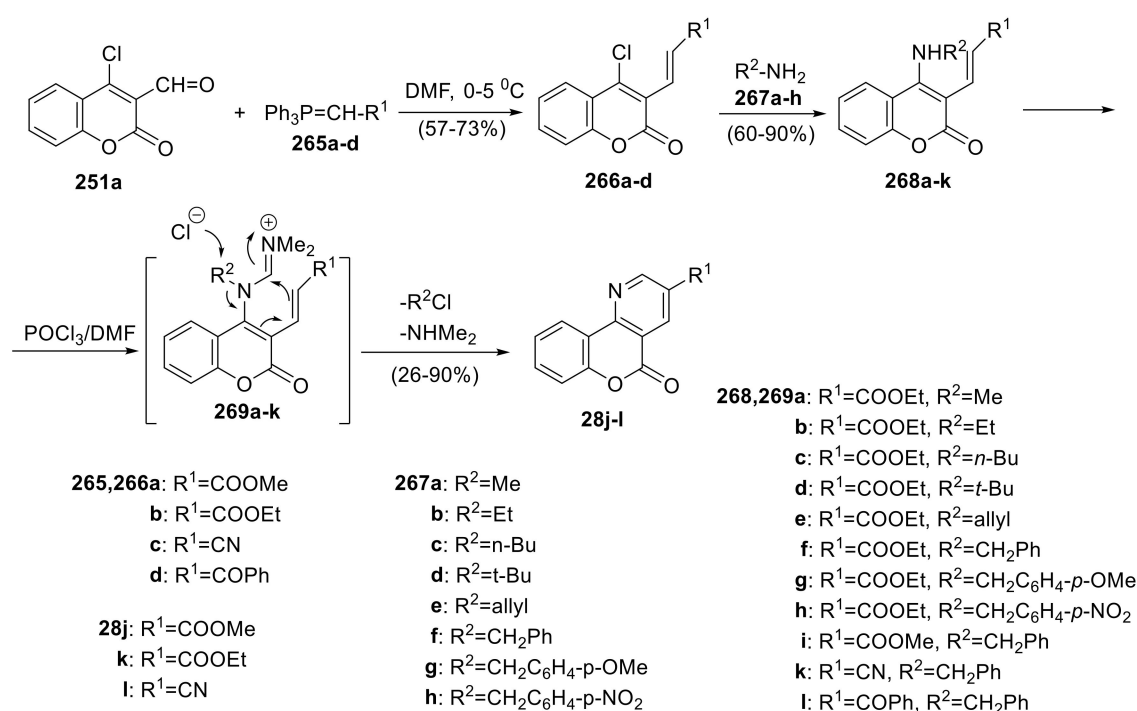


**Scheme 79.** Synthesis of 2-(2-oxo-2H-chromen-3-yl)-5H-chromeno [4,3-b]pyridine-5-ones **264a–l** by two methods.



In the same presentation, Brahmabhatt and coworkers used another route for the synthesis of compounds **264a–l** with the 4-chloro-3-formylcoumarins **251a–d** and pyridinium salts **263a–c** as starting materials [43]. The reaction of **251a** and **263a** resulted in the intermediate **C**, which then was converted to the final product **264a** (Scheme 79).

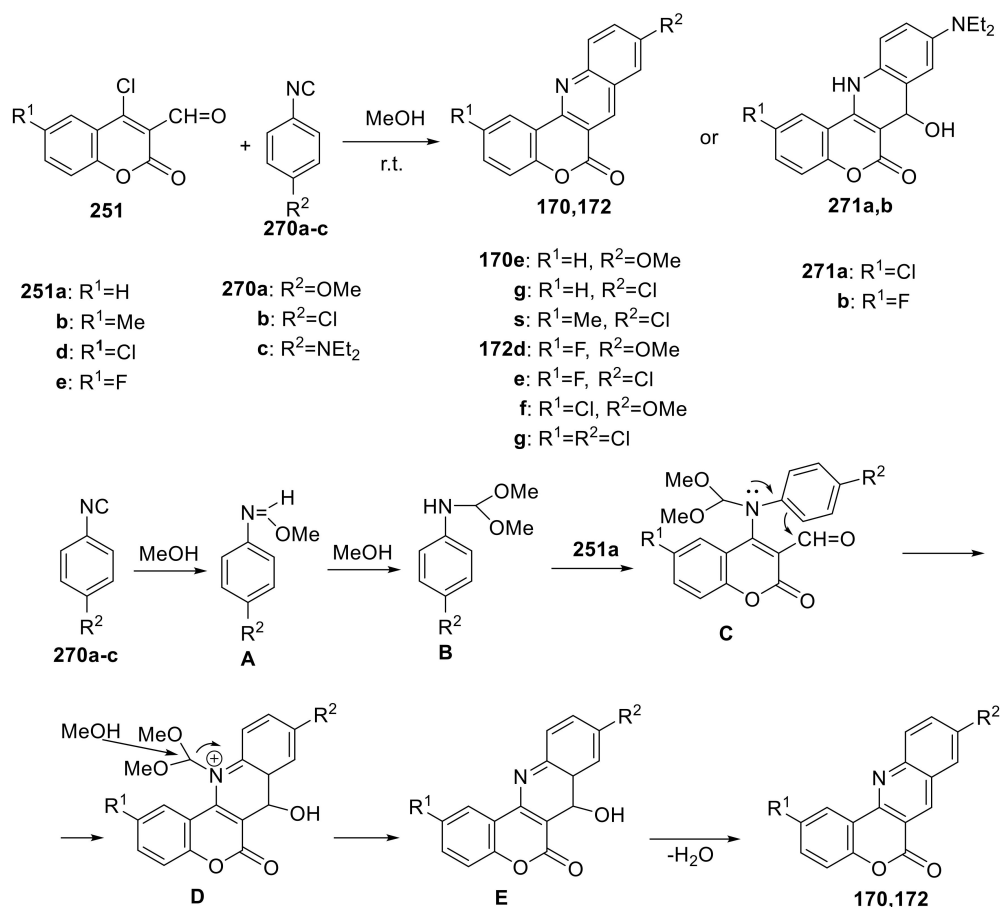
The 4-chloro-3-formylcoumarins **251**, used in the above reactions, are very versatile tools for the synthesis of fused pyridocoumarins [67]. In 1995, Heber et al., synthesized 3-substituted [1]benzopyrano [4,3-*b*]pyridine-5-ones **28j–l** from the treatment of 4-alkylamino-3-alkenylcoumarins **268a–k** under Vilsmeier conditions [166]. This reaction proceeded probably via the intermediate dimethyliminium salt **269**, followed by a nucleophilic attack of chloride anion to the *N*-alkyl moiety with subsequent electrocyclicization and elimination of alkyl chloride and dimethylamine (Scheme 80). Compounds **268a–k** were obtained by the conjugated addition–elimination reaction of 3-alkenyl-4-chlorocoumarins **266a–d** with alkylamines **267a–h**. The coumarin derivatives **266a–d** were prepared by the Wittig reaction of **251a** with the ylides **265a–d**.



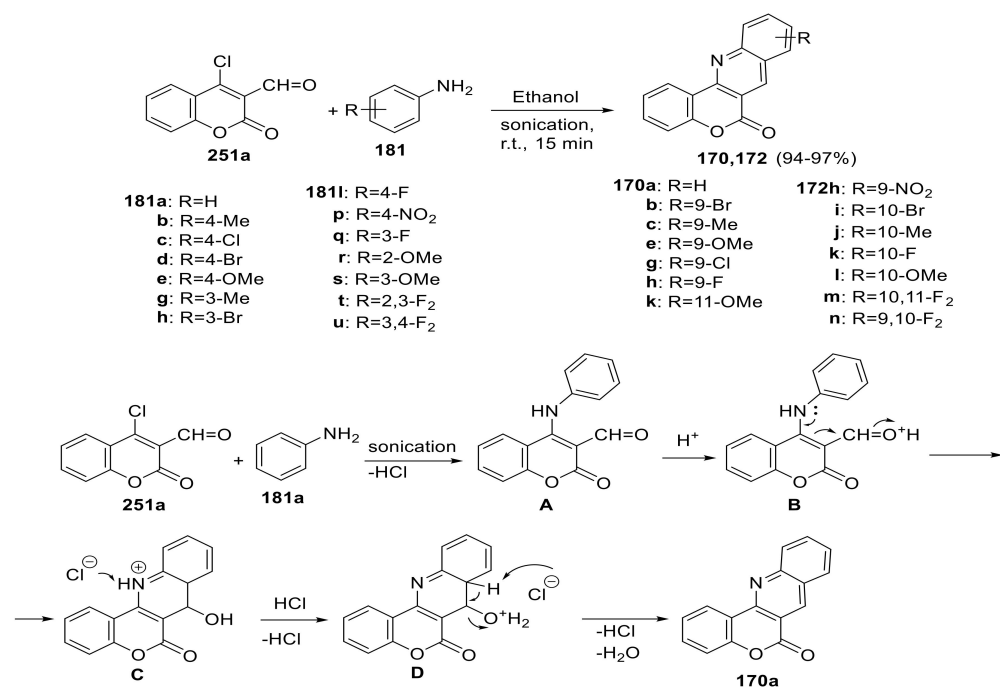
**Scheme 80.** Synthesis of 3-substituted [1]benzopyrano [4,3-*b*]pyridine-5-ones **28j–l**.

In 2006, Wu et al., reported that the reaction of 4-chloro-3-formylcoumarin **251** with aryl isocyanides **270a–c** led to the synthesis of chromeno [4,3-*b*]quinolin-6-ones **170**, **172** [167]. A possible mechanistic pathway was proposed according to Scheme 81. The amine **B** was formed from the addition of methanol to isocyanide **270**. 1,4-Addition of **B** to **251**, followed by elimination of the chloride anion, gave the intermediate **C** (Scheme 81). After cyclization through attack to aldehyde moiety the intermediate **D** was formed, which led to the alcohol derivative **E**. Elimination of water resulted in the products **170**, **172**. In the case of 4-diethylaminophenyl isocyanide (**270c**) the dihydro derivatives **271a,b** were isolated possibly via 1,3-H shift from the intermediate **E**.

In 2011, Gopikrishna and coworkers reported the synthesis of fused chromeno [4,3-*b*]quinolin-6-ones **170**, **172** by the one-pot reaction of anilines **181** with 4-chloro-3-formylcoumarin (**251a**) [168]. In the plausible proposed mechanism, the nucleophilic addition of aniline (**181a**), followed by elimination of chlorine, furnished *N*-aryl intermediate **A** (Scheme 82). Activation of the formyl group with the in-situ generated HCl gave through the **B** the cyclization intermediate **C**. Elimination of water from the isomerization intermediate **D** led to the final product **170a**.

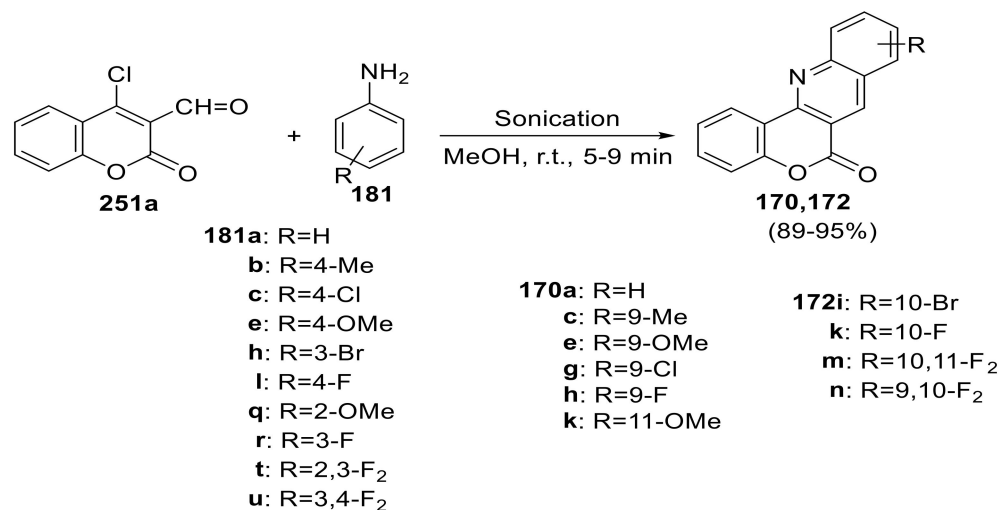


**Scheme 81.** Synthesis of chromeno [4,3-*b*]quinolin-6-ones **170**, **172** from the reaction of 4-chloro-3-formylcoumarin **251** with aryl isocyanides **270a-c**.



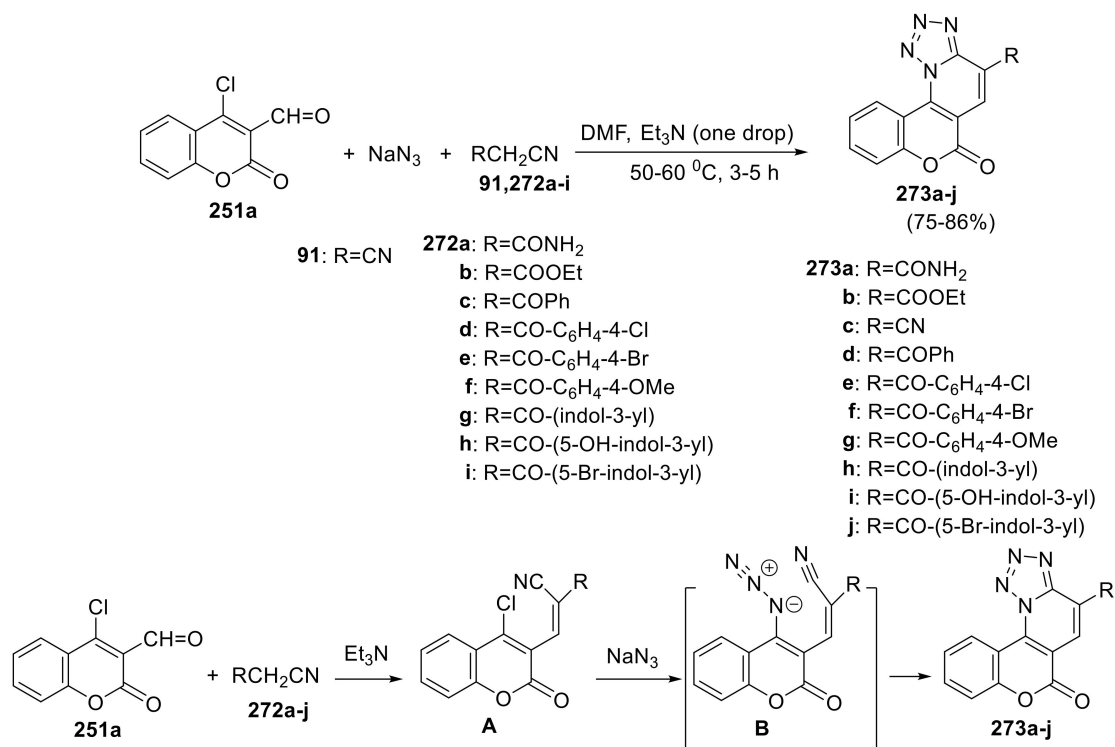
**Scheme 82.** Synthesis of chromeno [4,3-*b*]quinolin-6-ones by the one-pot reaction of anilines **181** with 4-chloro-3-formylcoumarin (**251a**).

One year later, Pal and coworkers performed an analogous reaction preparing the 6*H*-1-benzopyrano[[4,3-*b*]quinolin-6-ones **170**, **172** by sonication in methanol (Scheme 83). Compounds **170**, **172** were tested for their antiproliferative properties against human chronic myeloid leukemia cells, human colon carcinoma cells, breast cancer cells and human neuroblastoma cells, and some of them were found to be active [48].



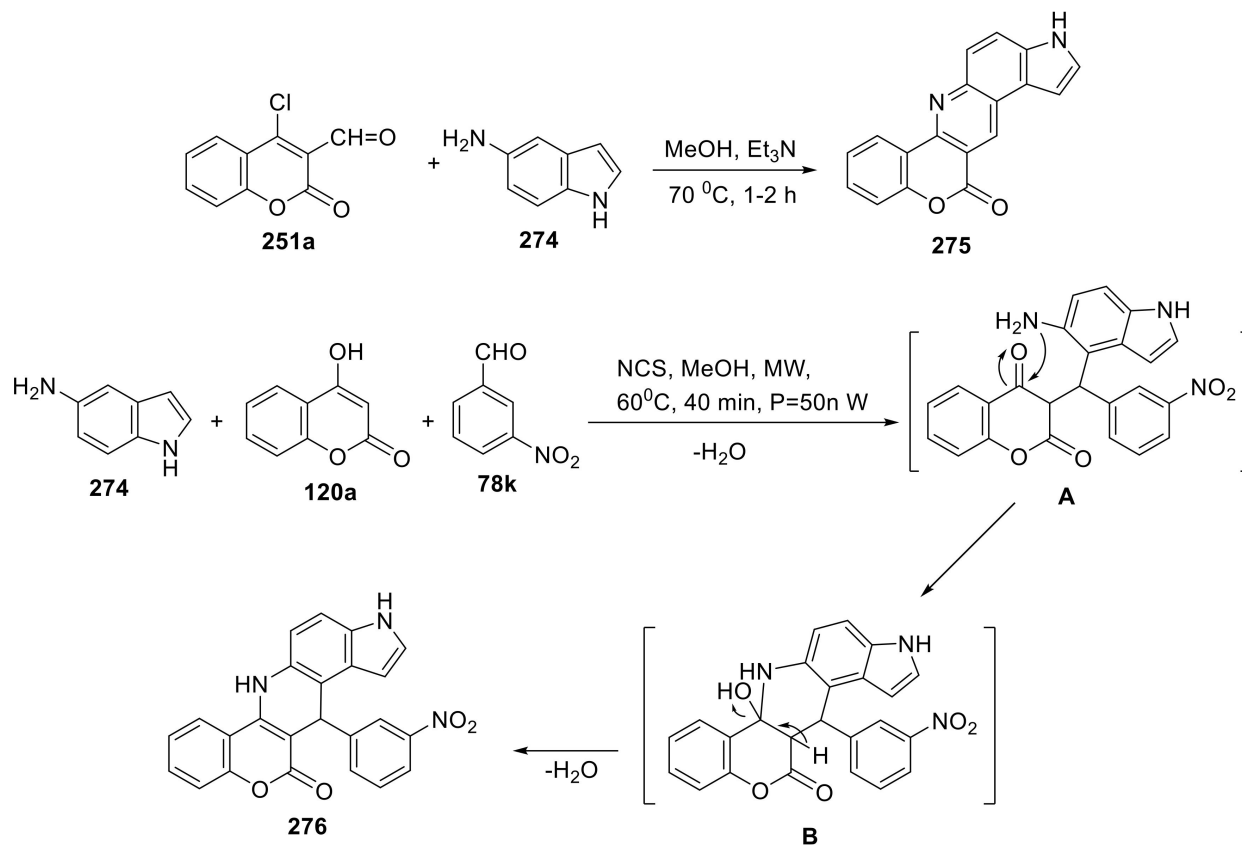
**Scheme 83.** Preparation of 6*H*-1-benzopyrano[[4,3-*b*]quinolin-6-ones **170**, **172** by sonication.

The same year, Bhuyan and coworkers prepared the tetrazole-fused pyrido [3,2-*c*]coumarin derivatives **273a–j** by the one-pot three-component reaction via the intramolecular 1,3-cycloaddition reaction of azides to nitriles [169]. The intermediate azides **B** was obtained by the reaction of sodium azide with 3-alkenyl-4-chlorocoumarin **A** (Scheme 84). The reaction of 4-chloro-3-formylcoumarin (**251a**) with the nitriles **91**, **271a–i** led to the intermediates **A**.



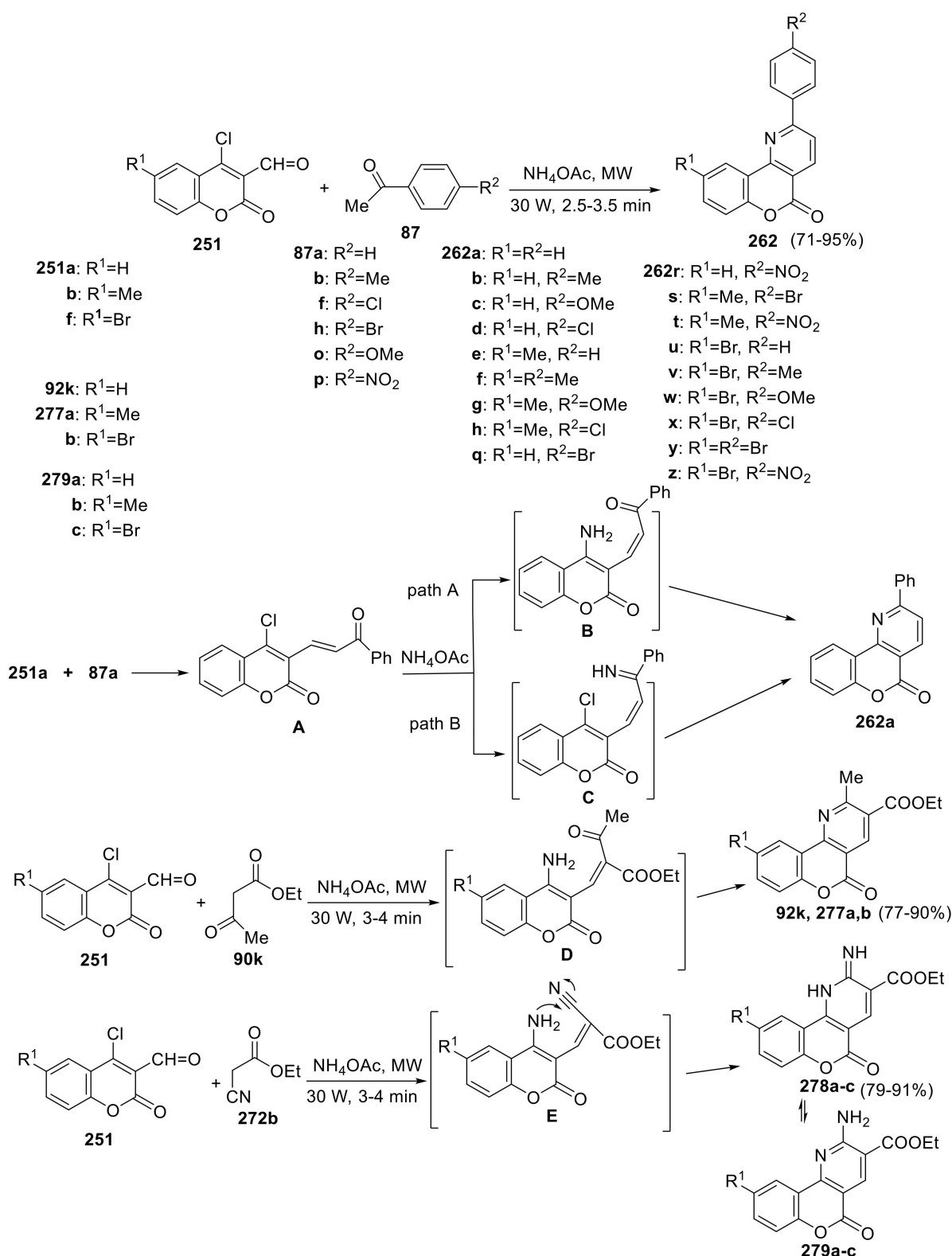
**Scheme 84.** Synthesis of tetrazole fused pyrido [3,2-*c*]coumarin derivatives **273a–j**.

In 2018, El-Agrody and coworkers synthesized derivatives containing indole fused with coumarin moiety such as **275** and **276** (Scheme 85). The reaction of **251a** with 5-aminoindole (**274**) in the presence of Et<sub>3</sub>N under heating resulted in the synthesis of chromeno [4,3-*b*]pyrrolo [3,2-*f*]quinoline-12(3*H*)-one (**275**). The three-component reaction of **274** with 4-hydroxycoumarin (**120a**) and *m*-nitrobenzaldehyde (**78k**) in the presence of *N*-chlorosuccinimide under microwave irradiation led to 13-(3-nitrophenyl)-6,13-dihydrochromeno [4,3-*b*]pyrrolo [3,2-*f*]quinoline-12(3*H*)-one (**276**). The synthesized compounds were screened for their cytotoxic activity against the human cervix carcinoma cell line (KB-3-1) [170]. Compound **276** presented higher potent activity (IC<sub>50</sub> = 7.9 μM) in comparison to the positive control compound (+)-Griseofulvin (IC<sub>50</sub> = 19.2 μM).



**Scheme 85.** Synthesis of fused coumarin derivatives containing indole and pyridine moieties.

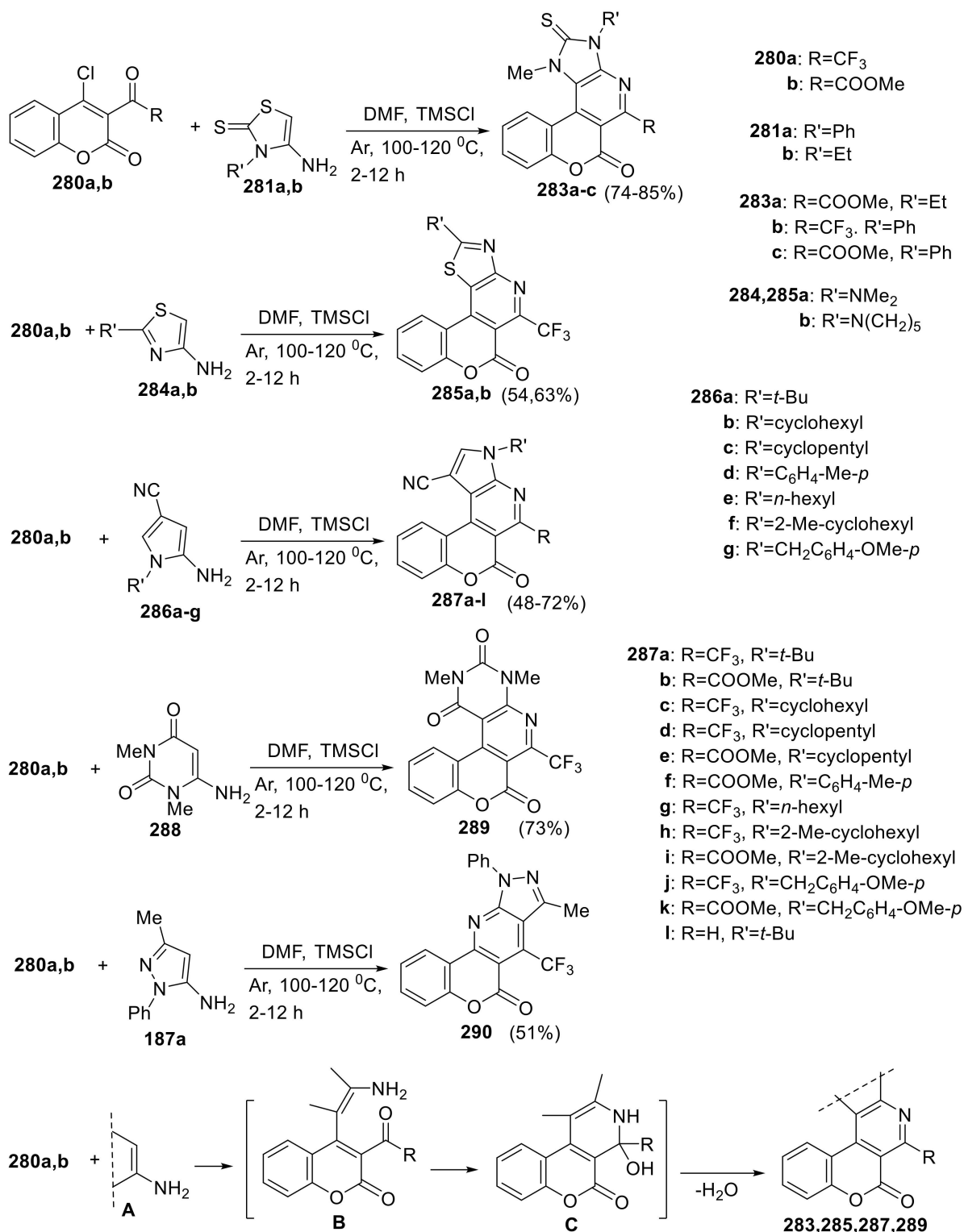
The same year, Kolita and Bhuyan demonstrated the synthesis of pyrido [3,2-*c*]coumarins **262**, or **92k**, **277a,b** or **279a–c** from the reaction of 4-chloro-3-formylcoumarin (**251a**) with aryl methyl ketones **87** or ethyl acetoacetate (**90k**) or ethyl cyanoacetate (**272b**), respectively, in the presence of NH<sub>4</sub>OAc under microwave irradiation and solvent-free conditions [171]. An aldol condensation between **251a** and **87a** possibly occurred to give the intermediate **A**. The latter in the presence of NH<sub>4</sub>OAc furnished the 4-aminocoumarin intermediate **B** (path A) or the imine intermediate **C** (path B). Intramolecular condensation of **B** or intramolecular *N*-substitution of **C** led to the pyrido [3,2-*c*]coumarin **262a** (Scheme 86). In the case of ethyl acetoacetate (**90k**), a Knoevenagel condensation to intermediate **D** followed by a condensation of amine group with carbonyl resulted in the final products **92k** or **277a,b**. When ethyl cyanoacetate (**272b**) was used, a condensation intermediate **E** again might have been formed. Addition of amide to cyanide group of **E** afforded via cyclization the products **278a–c**. There was evidence from the H<sup>1</sup>-NMR for the imine tautomeric form of those compounds and not for the amine tautomers **279a–c**.



**Scheme 86.** Synthesis of pyrido [3,2-*c*]coumarins under microwave irradiation and solvent-free conditions.

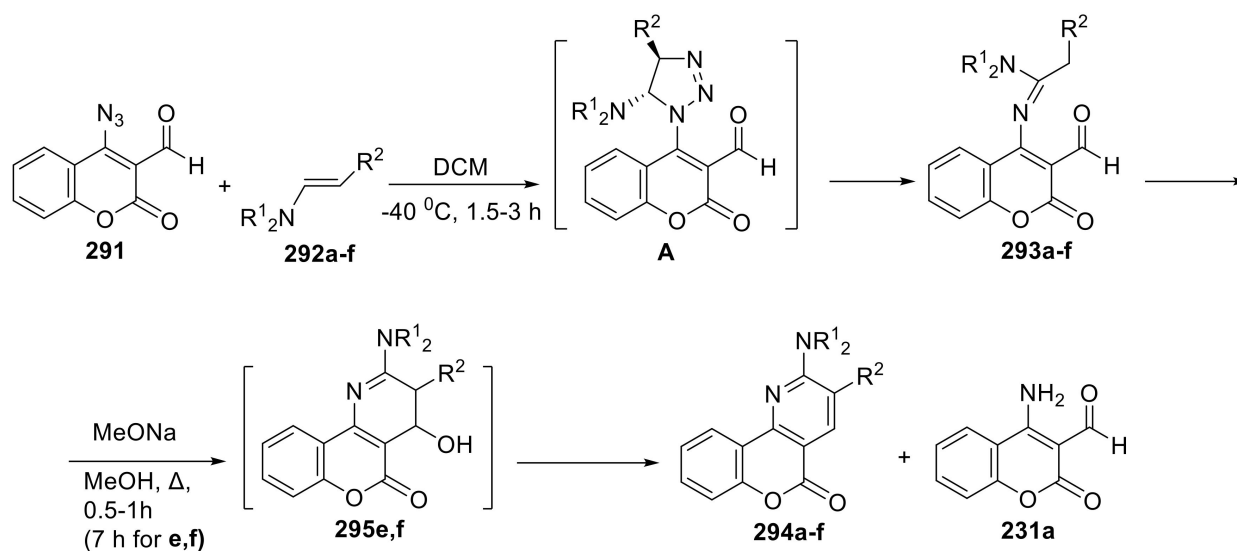
In 2011, Iarosenko, Langer and coworkers used an analogue of **251a**, the 3-acyl-4-chlorocoumarins **280a,b**, for the synthesis of 3,4-fused pyridocoumarins **283a-c**, **285a,b**, **287a-l**, **289**, **290** by cyclocondensation with electron-rich aminoheterocycles [172]. The reactions of amines **281a,b**, **284a,b**, **286a-g**, **288** resulted in fused pyrido [2,3-*c*]coumarin

derivatives via an attack of the internal enamine  $\beta$ -carbon of **A** for the formation of intermediate **B** (Scheme 87). Intramolecular attack of amine to the carbonyl of **B** led, under cyclization, to **C** and elimination of water to the final products. In the case of 5-amino-3-methyl-1-phenylpyrazole (**187a**), the regio-isomer of the fused pyrido [3,2-*c*]coumarin derivative **290** was synthesized probably due to the more aromatic character of amine.



Scheme 87. Synthesis of 3,4-fused pyridocoumarins **283a-c**, **285a,b**, **287a-l**, **289**, **290**.

Earlier in 2004, Trimarco and coworkers utilized another 3-formylcoumarin derivative, the 4-azido-3-formylcoumarin (**291**), for the synthesis of fused pyrido [3,2-*c*]coumarin derivatives **294a–f** [173]. The reaction of **291** with the enamines **292a–f** resulted in the amidines **293a–f** via the 1,3-cycloaddition intermediate **A** (Scheme 88). The amidines, by treating with catalytic amount of MeONa in refluxing MeOH, led to the final products **294a–f**. The intermediates **295e,f** (30%) were isolated in 2 h in the case of **293e,f**, along with the hydrolysis adduct, 4-amino-3-formylcoumarin (**231a**) (35%) and then refluxed for an additional time of 2 h to give **294e,f**.



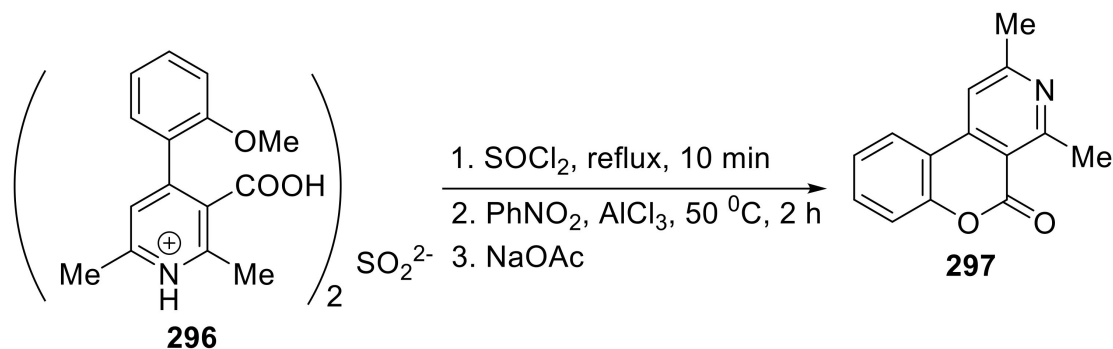
**Scheme 88.** Synthesis of fused pyrido [3,2-*c*]coumarin derivatives **294a–f** from 4-azido-3-formylcoumarin (**291**).

## 2.2. Pyranone Ring Formation

The formation of a pyranone ring could be obtained using the cyclization of suitable aryl-substituted pyridine or piperidine derivatives. Phenol derivatives, also, as well as salicylaldehydes could be the starting material, resulting in the construction of the pyranone ring.

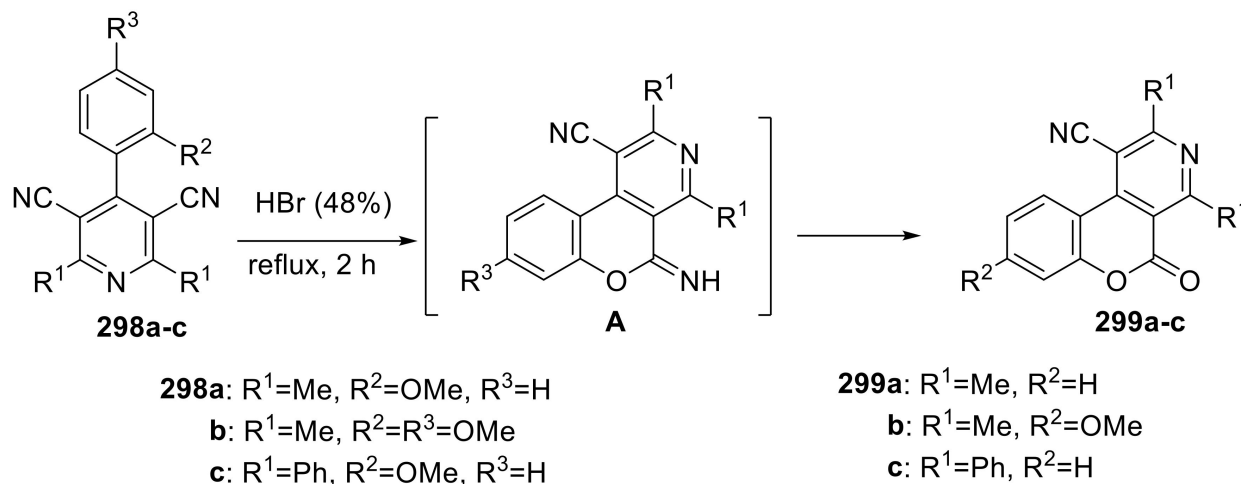
### 2.2.1. Synthesis from Pyridine or Piperidine Derivatives

Khan et al., isolated the pyrido [3,4-*c*]coumarin **297** via the cyclization of the chloride of 4-(*o*-methoxyphenyl)lutidine-3-carboxylic acid sulfate **296** with aluminum chloride in nitrobenzene at  $50\text{ }^{\circ}\text{C}$  for 2 h [174], in an attempt to prepare 2-azafluorenone derivatives. The intermediate chloride was prepared by refluxing **296** in thionyl chloride for 10 min (Scheme 89).



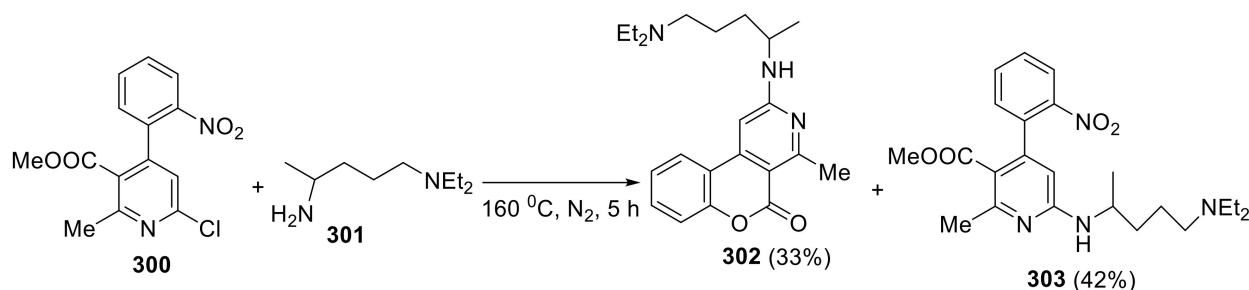
**Scheme 89.** Synthesis of pyrido [3,4-*c*]coumarin **297** by the formation of pyranone ring.

An analogous starting material, the 3,5-dicyano-4-(*o*-methoxyphenyl) pyridines **298a–c**, were used by Courts and Petrow for the synthesis of pyrido [3,4-*c*]coumarin **299a–c** [175]. The cyclization was performed by refluxing in hydrobromic acid for 2 h via the intermediate imine **A** (Scheme 90).



**Scheme 90.** Synthesis of pyrido [3,4-*c*]coumarin **299a–c** by the cyclization of 3,5-dicyano-4-(*o*-methoxyphenyl)pyridines **298a–c**.

Gorlinger and coworkers, in 2006, utilized the pyridine derivative **300** to synthesize the pyrido [3,4-*c*]coumarin **302** by the reaction with novaldiamine (**301**) (Scheme 91). These compounds together with other prepared were tested for *in vitro* antimalarial activity against *Plasmodium falciparum* strain Dd2 and 3D7 [50]. Compounds **302** and **303** presented quite good activity with IC<sub>50</sub> = 1.1 μM, 3.4 μM and 6.2 μM, 7.0 μM, respectively.

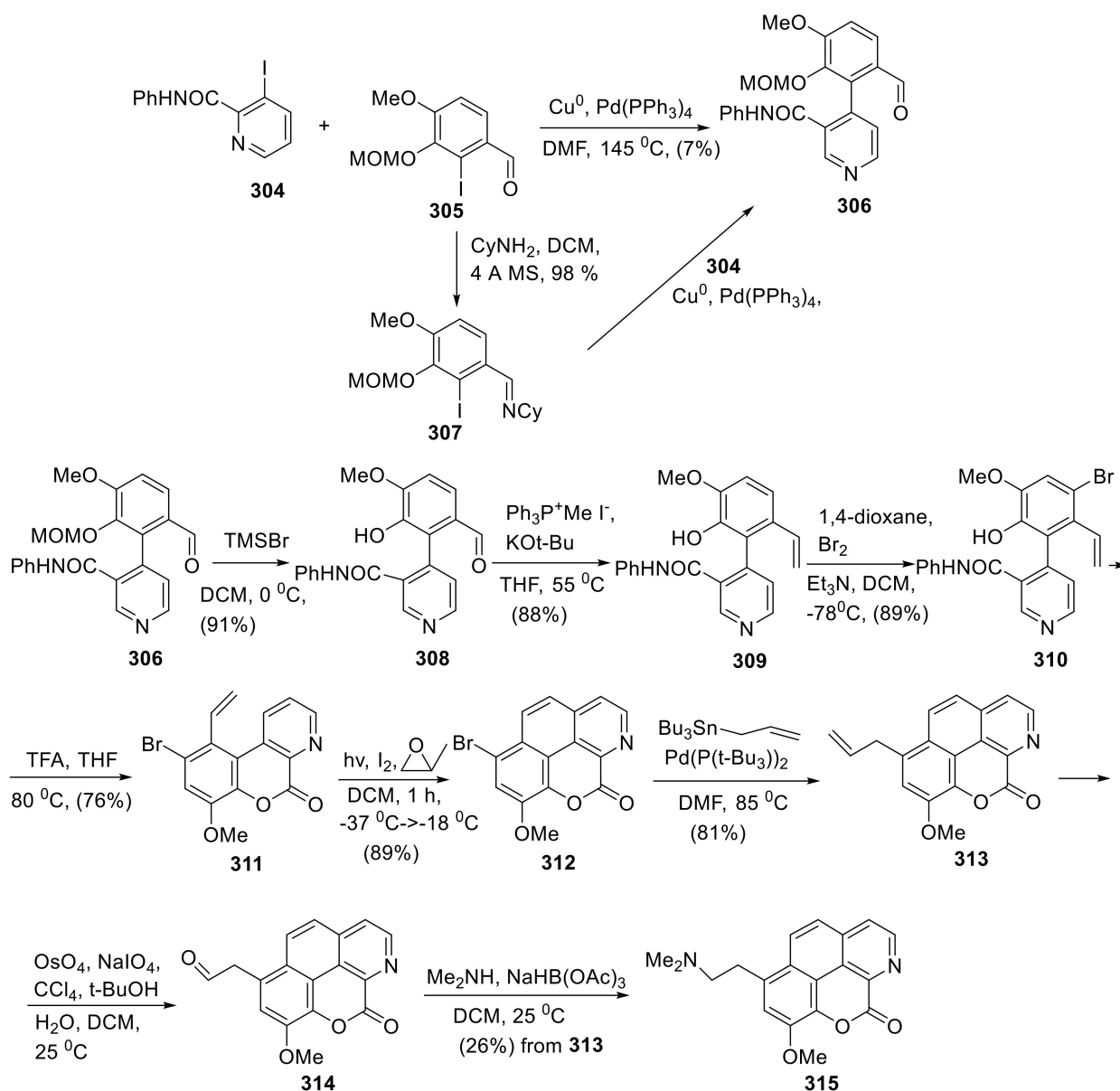


**Scheme 91.** Synthesis of pyrido [3,4-*c*]coumarin derivative **302**.

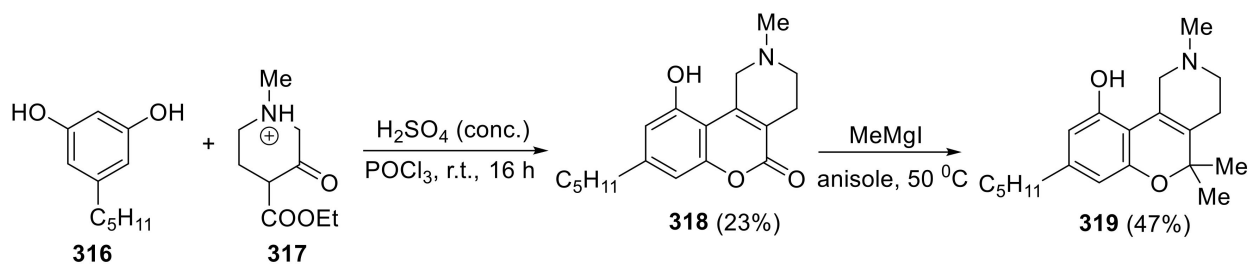
In 2007, Kelly and coworkers synthesized the natural product santiagonamine (**315**) using the pyridine derivative **304** (prepared from pyridine-3-carboxylic acid) as starting material, and benzaldehyde derivatives **305** or **307** (prepared from isovanillin) via a Pd-catalyzed Ullmann cross-coupling reaction [57]. After deprotection of **306**, Wittig reaction of **308** to **309**, bromination to **310**, cyclization in the presence of TFA to the pyrido [2,3-*c*]coumarin **311**, the **312** was obtained by photocyclization. Stille reaction of **312** with allyl tributyltin gave the allyl derivative **313**. Transformation of the latter with OsO<sub>4</sub> and sodium periodate afforded aldehyde **314**, which under reductive amination with dimethylamine led to santiagonamine (**315**) (Scheme 92). This was the first total synthesis of santiagonamine in 12 steps from isovanillin and 2.6% overall yield.

In 1966, Pars et al., synthesized the nitrogen analogs of tetrahydrocannabinol **319** [176]. The Pechmann-type reaction of olivetol (**316**) with 4-carbethoxy-*N*-methyl-piperid-3-one hydrochloride (**317**) in the presence of concentrated sulfuric acid and phosphorus oxychloride resulted in the tetrahydropyrido [4,5-*c*]coumarin **318** (Scheme 93). Treatment of the latter with MeMgI in anisole led to **319**.





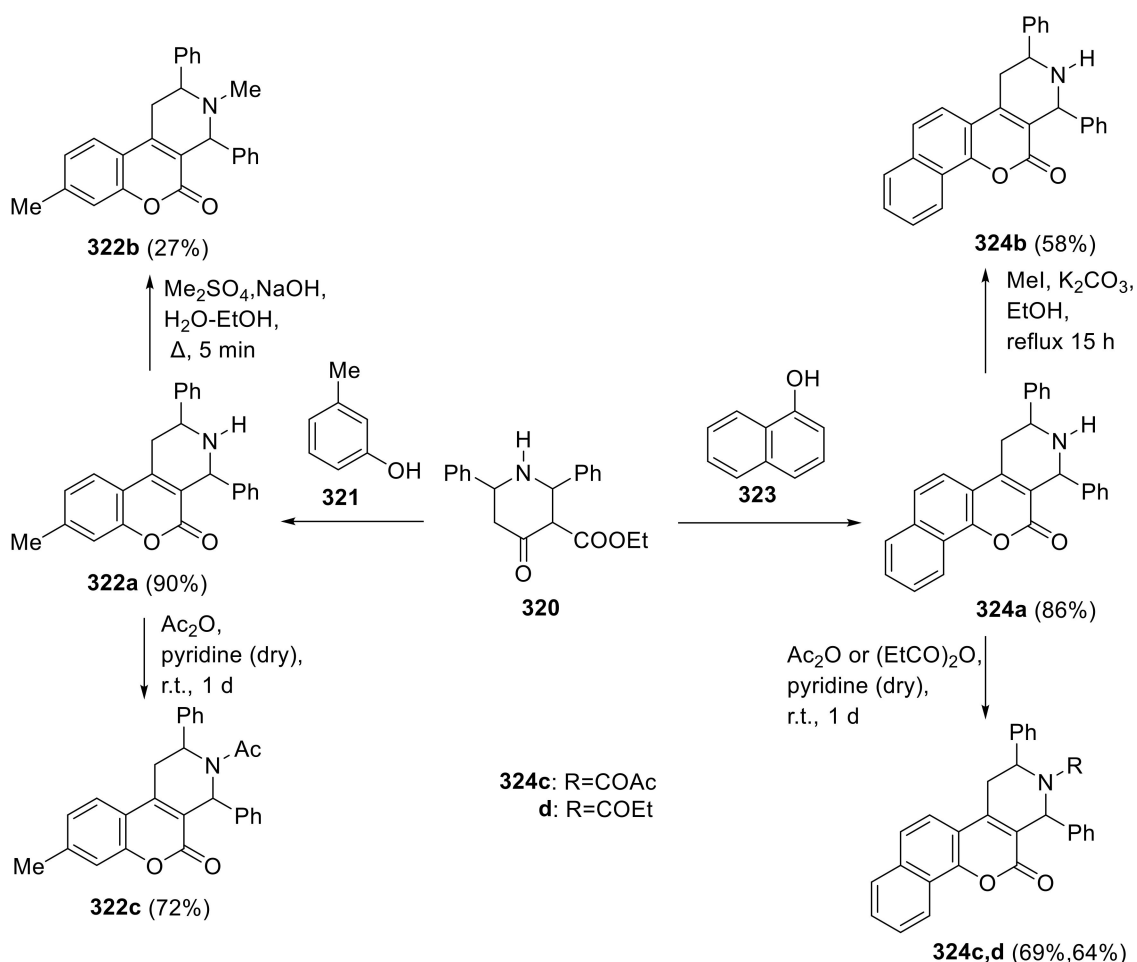
Scheme 92. Synthesis of santiagonamine (315).



Scheme 93. Synthesis of tetrahydrocannabinol analog 319.

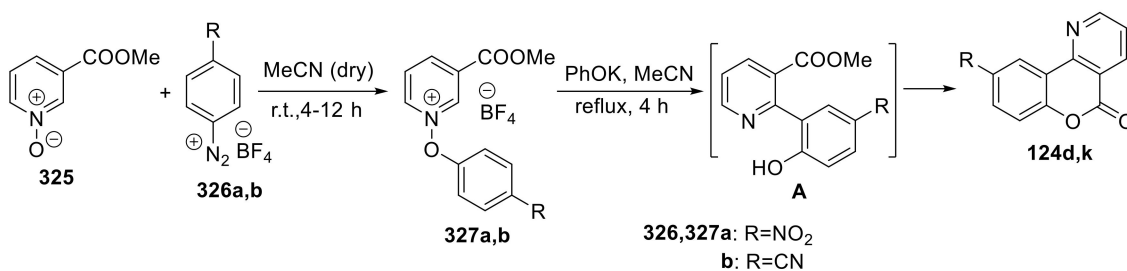
Mandal et al., used the piperidin-4-one derivatives **320** for the synthesis of fused tetrahydropyrido [3,4-*c*]coumarin derivatives **322a–c** and **324a–d** in order to study their fungicidal activity against *Xanthomonas malvacearum*, *Fusarium maniliform*, *Rhizoctonia solanis*, *Powdery mildew* of cucumber, *Phytophthora* infection of tomatoes and grey mold of beans [177]. The Pechmann reaction of **320** with *m*-cresol (**321**) or *a*-naphthol (**323**) led to the fused coumarin derivatives **322a** and **324a**, respectively (Scheme 94). Methylation of them with

$\text{Me}_2\text{SO}_4$  or MeI resulted in the *N*-methyl derivatives **322b** or **324b**, while *N*-acylation with acetic anhydride or propionic anhydride gave *N*-acyl derivatives **322c** or **324c,d**, respectively. Tetrahydrobenzopyridinocoumarins **324** presented higher fungicidal activity than compounds **322**. The substituents in the amine group led to a lowering of the fungicidal action in green plants.



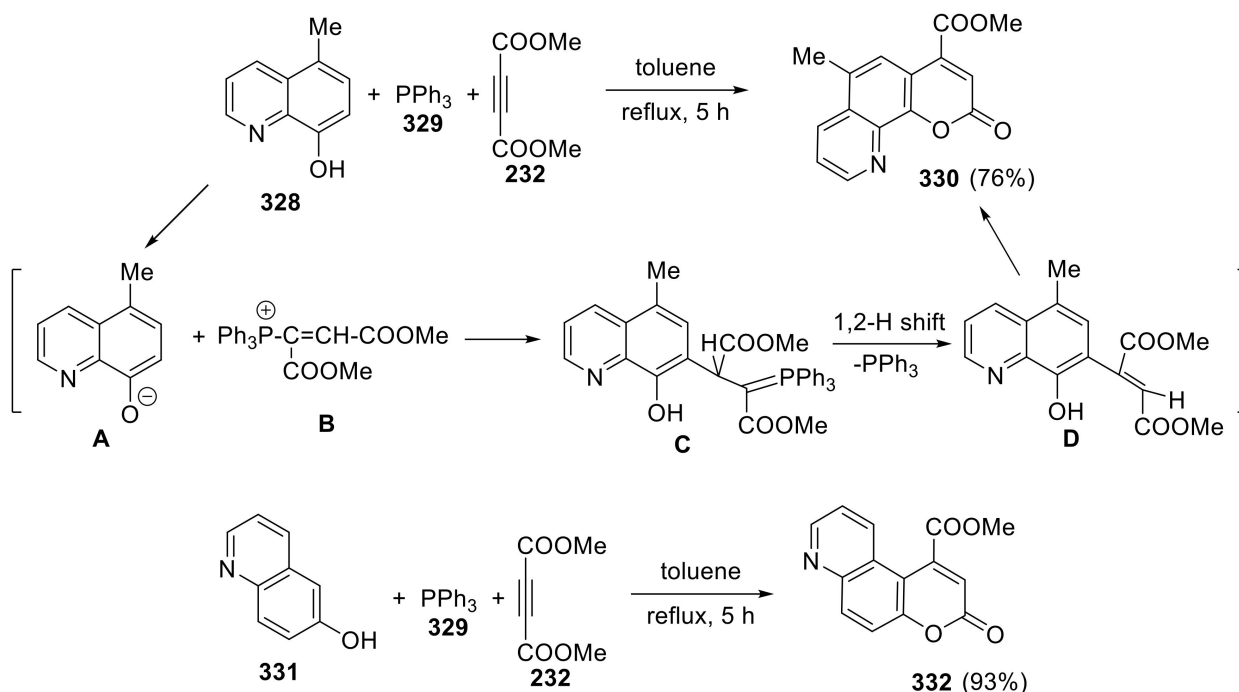
**Scheme 94.** Synthesis of fused tetrahydropyrido [3,4-c]coumarin **322a-c** and **324a-d** from the piperidin-4-one derivatives **320**.

The phenols **A** derived after the base-catalyzed rearrangement of 3-carbomethoxy *N*-(aryloxy) pyridinium tetrafluoroborate **327a,b** cyclized spontaneously to the fused pyrido [3,2-c]coumarins **124d,k**, according to Abramovitch and coworkers [178]. The *N*-(aryloxy) pyridinium salts **327a,b** were prepared by the reaction of pyridine-*N*-oxide **325** with the diazonium salts **326a,b** in dry acetonitrile (Scheme 95).



**Scheme 95.** Synthesis of fused pyrido [3,2-c]coumarins **124d,k** from 3-carbomethoxy *N*-(aryloxy)pyridinium tetrafluoroborate **327a,b**.

In 2007, the fused pyrido [3,2-*h*]coumarin **330** and pyrido [3,2-*f*]coumarin **332** were prepared by our group from the reaction of triphenylphosphine (**329**) and DMAD (**232**) with quinolinol-8 (**328**) and quinolinol-6 (**331**), respectively, as starting material [179]. The coumarin skeleton is possibly produced by lactonization of the intermediate **D**, according to an analogous reaction of phenols by Yavari et al. [180]. Intermediate **D** was achieved by an 1,2-H shift and elimination of PPh<sub>3</sub> from **C**, which was formed by the reaction of intermediates **A** and **B** (Scheme 96).

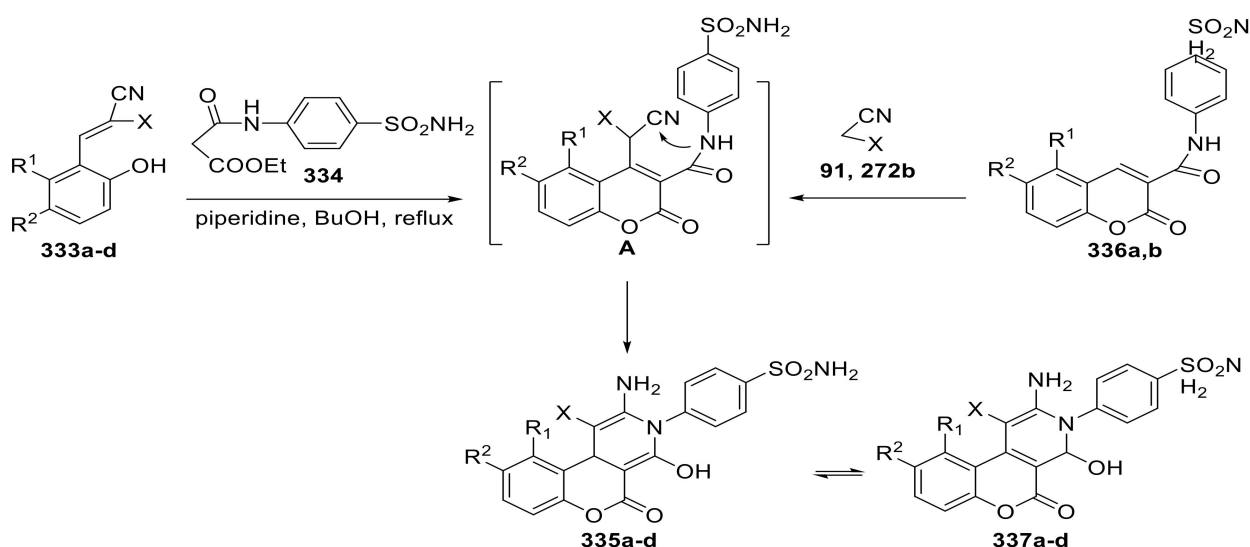


**Scheme 96.** Synthesis of fused pyrido [3,2-*h*]coumarin **330** and pyrido [3,2-*f*]coumarin **332** from the reaction of quinolinols with DMAD (**232**) and PPh<sub>3</sub> (**329**).

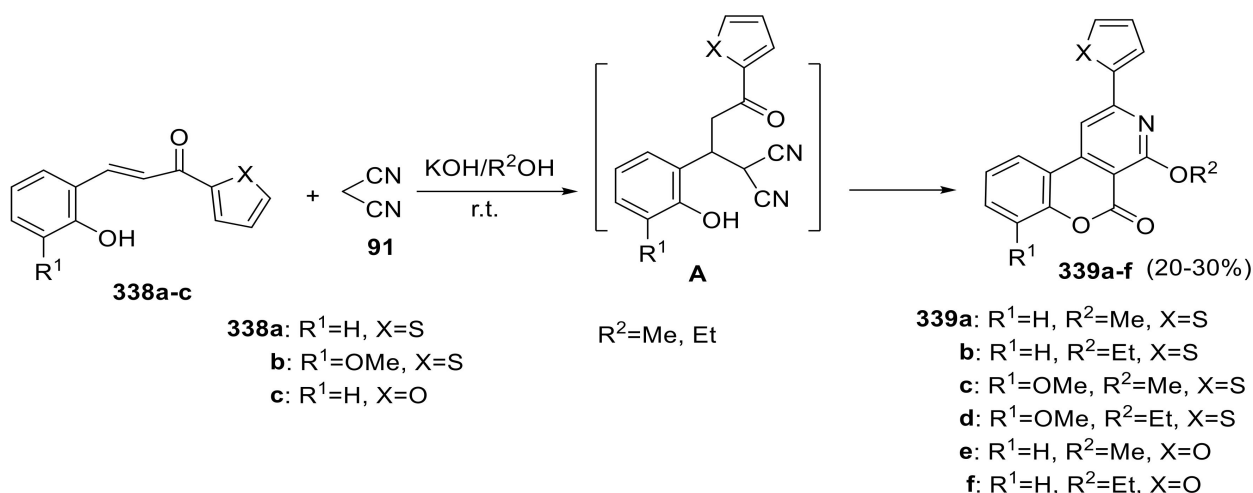
### 2.2.2. Synthesis from Phenol or Salicylaldehyde Derivatives

In 1998, El-Saghier et al. reported the synthesis of dihydro pyrido [3,4-*c*]coumarin derivatives **335a–d** starting from *o*-hydroxyarylidene malononitrile **333a,c** or *o*-hydroxyarylidene cyanoester **333b,d** and ethyl 2-(4-aminosulfonylcarbanilide)acetate (**334**) in the presence of piperidine [181]. A transesterification of **334** with phenol followed by addition of the produced carbanion to the vinyl group is probably responsible for the formation of intermediate **A**. Addition of amine of benzanilide moiety to the cyano group led to the product **335a–d**, as referred in the reference (Scheme 97). Possibly, these products are in the tautomeric form of **337a–d**, due to the proton peak of the dihydropyridine moiety at 4.50–5.10 ppm. The same products were synthesized, also, by the reaction of coumarin-3-(4-aminosulfonyl) carbanilide (**336a**) or benzo[*f*] coumarin-3-(4-aminosulfonyl) carbanilide (**336b**) with malononitrile (**91**) or ethyl cyanoacetate (**272b**). Analogous coumarin derivatives were obtained also in this work from the reaction of **336a,b** with some active methylene compounds.

Hosni et al., synthesized the fused pyrido [3,4-*c*]coumarins **339a–f** with thienyl or furyl substituents and studied their anti-inflammatory and analgesic activity [49]. The stirring of propenones **338–c** and malononitrile (**91**) in alcoholic potassium hydroxide at room temperature resulted in **338a–f** via the intermediate **A** (Scheme 98). The compounds showed moderate potency in anti-inflammatory activity. They exhibited also analgesic activity more than the diclofenac, the standard reference. Compounds **339f** and **339e** were safer than diclofenac, having higher LD<sub>50</sub>.



**Scheme 97.** Synthesis of dihydro pyrido [3,4-c]coumarin derivatives **335a–d** starting from *o*-hydroxyarylidene malononitrile **333a,c** or *o*-hydroxyarylidene cyanoester **333b,d**.

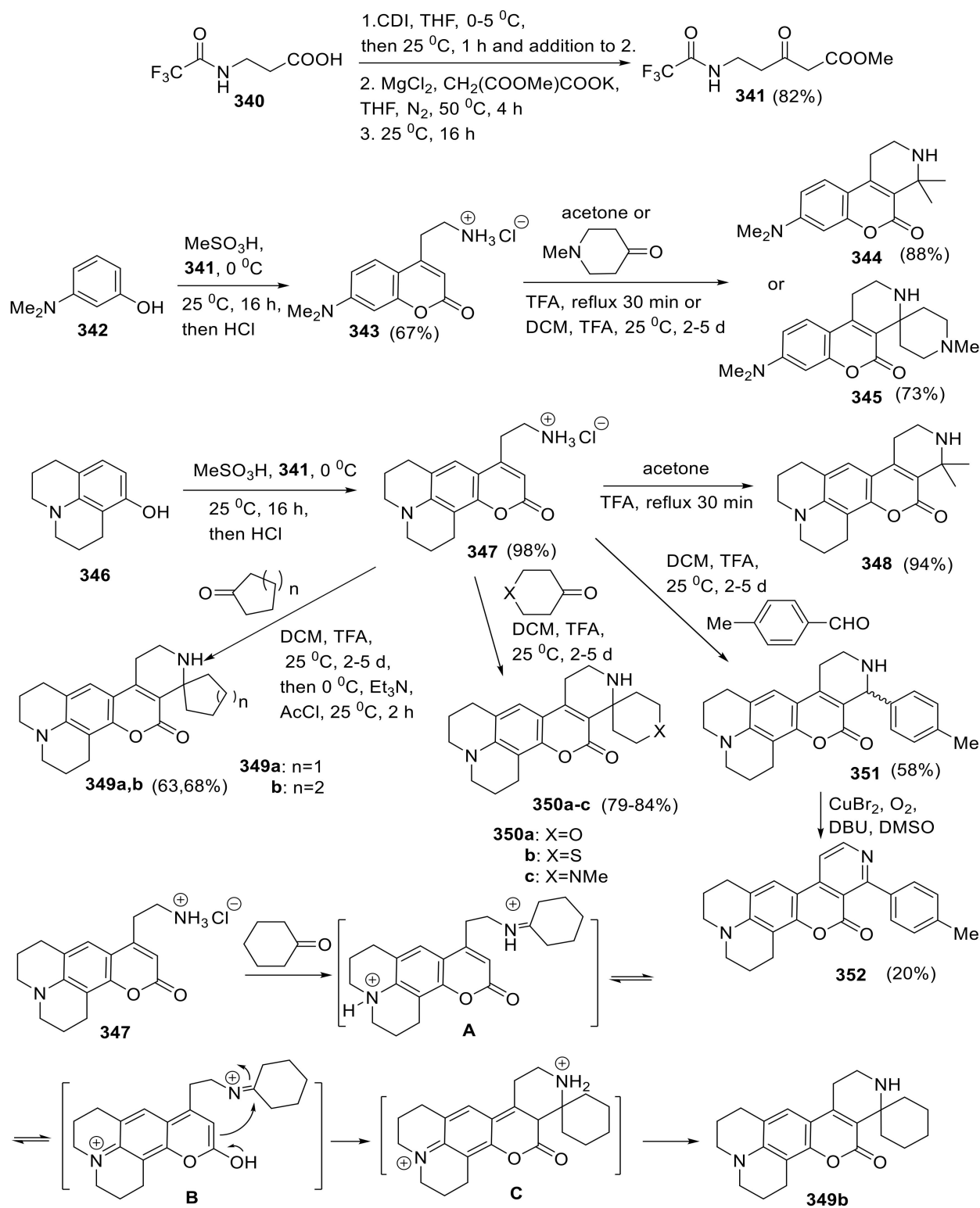


**Scheme 98.** Synthesis of fused pyrido [3,4-c]coumarins **338a–f** with thienyl or furyl substituents.

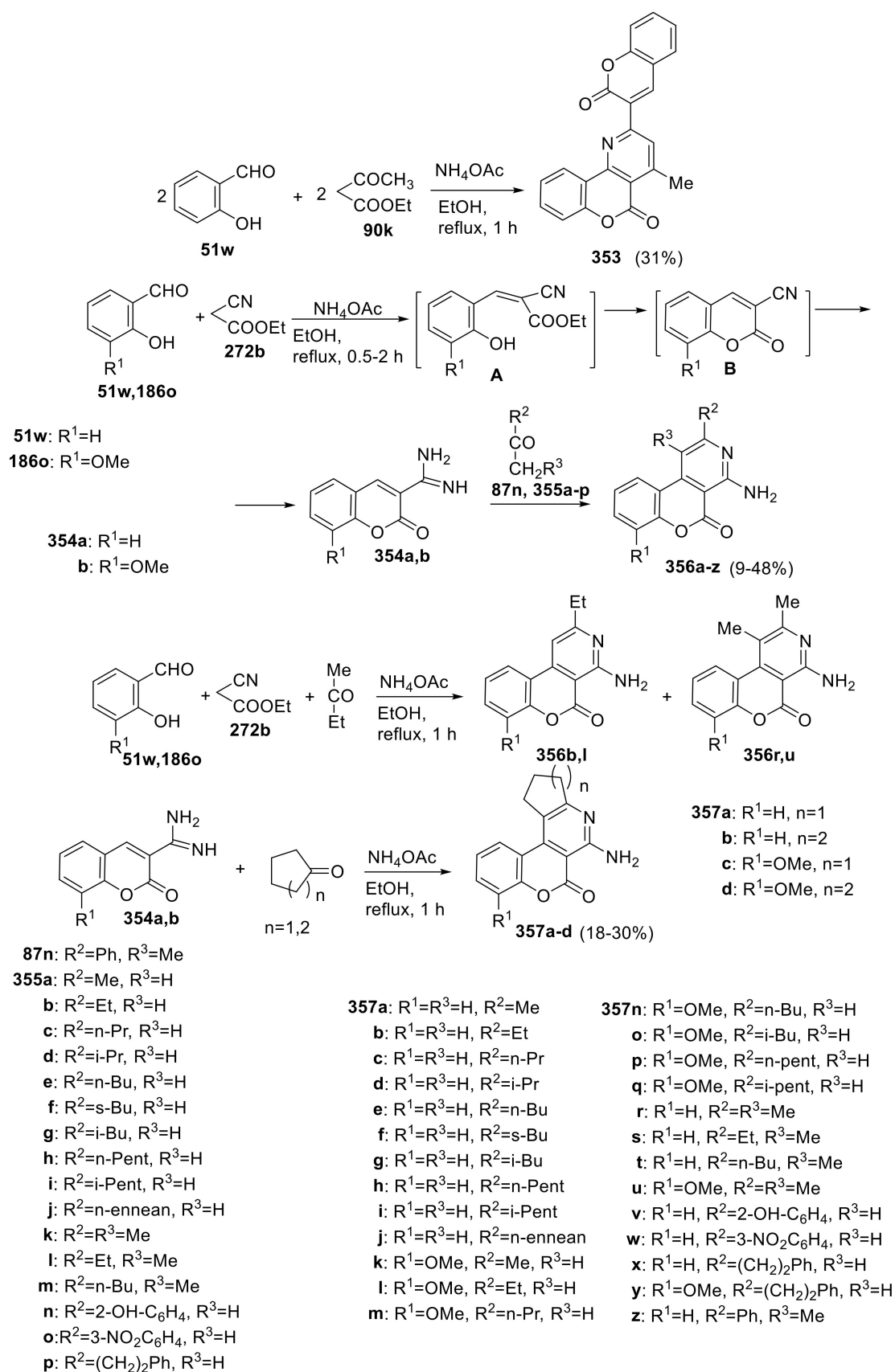
Sviripa et al., prepared fused tetrahydropyrido [3,4-c]coumarins, such as **344**, **345**, **348**, **349a,b**, **350a–c**, **351** via a Pictet–Spengler condensation of 4-(2-aminoethyl)coumarins, such as **343**, **347**, which have a C-7 activating amino or *N,N*-dialkylamino group [182]. 4-(2-Aminoethyl)coumarins were prepared from the corresponding phenols by treating with methyl sulfonic acid and methyl ester **341** (Scheme 99). They studied, also, reactions of **343**, **347** with 5 $\alpha$ -androstane-3-ones. Computational modelling has been used for the new molecules, analogs to 5 $\alpha$ -dihydrotestosterone, as a tool to study 17-oxidoreductases for intracrine, androgen metabolism. The mechanism of the Pictet–Spengler reaction is interpreted for the case of cyclohexanone with **347** through the intermediates **A**, **B** and **C** for the synthesis of **349b** (Scheme 99).

In 1969, Sakurai and Midorikawa utilized the condensation of salicylaldehydes with active methylene compounds for the synthesis of fused benzoquinazoline derivatives [183]. In the case of ethyl acetoacetate (**90k**) they have synthesized the fused pyrido [3,2-c]coumarin **353** from salicylaldehyde (**51w**) in the presence of ammonium acetate (Scheme 100). Sakurai et al., also, synthesized the pyrido [3,4-c]coumarins **356a–z** and **357a–d** by the reaction of salicylaldehydes with ethyl cyanoacetate (**272b**) and aliphatic ketones **355** [184]. Salicylaldehydes and **272b** via the condensation intermediate **A** and the cyclization intermediate **B** resulted in 3-amidinocoumarin **354**, isolated during the heating for several min. When the

heating was performed for 0.5–2 h, the reaction led to the final products **356a–z** and **357a–d**, through condensation with ketones, reaction of methylene group with C-4 of coumarin and subsequent dehydrogenation (Scheme 100).

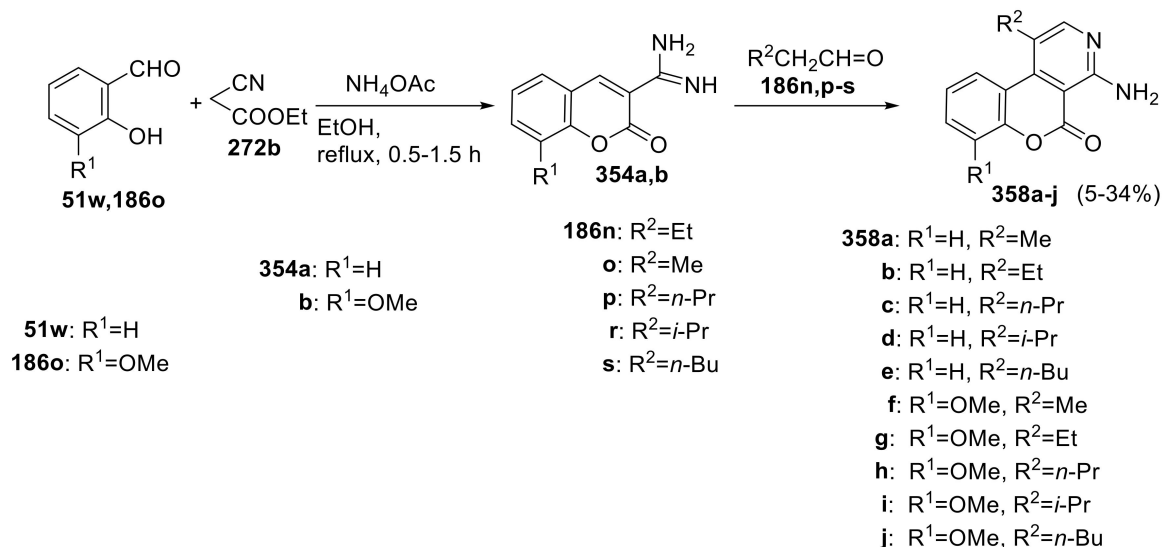


**Scheme 99.** Synthesis of fused tetrahydropyrido [3,4-*c*]coumarins by a Pictet–Spengler condensation of 4-(2-aminoethyl)coumarins.



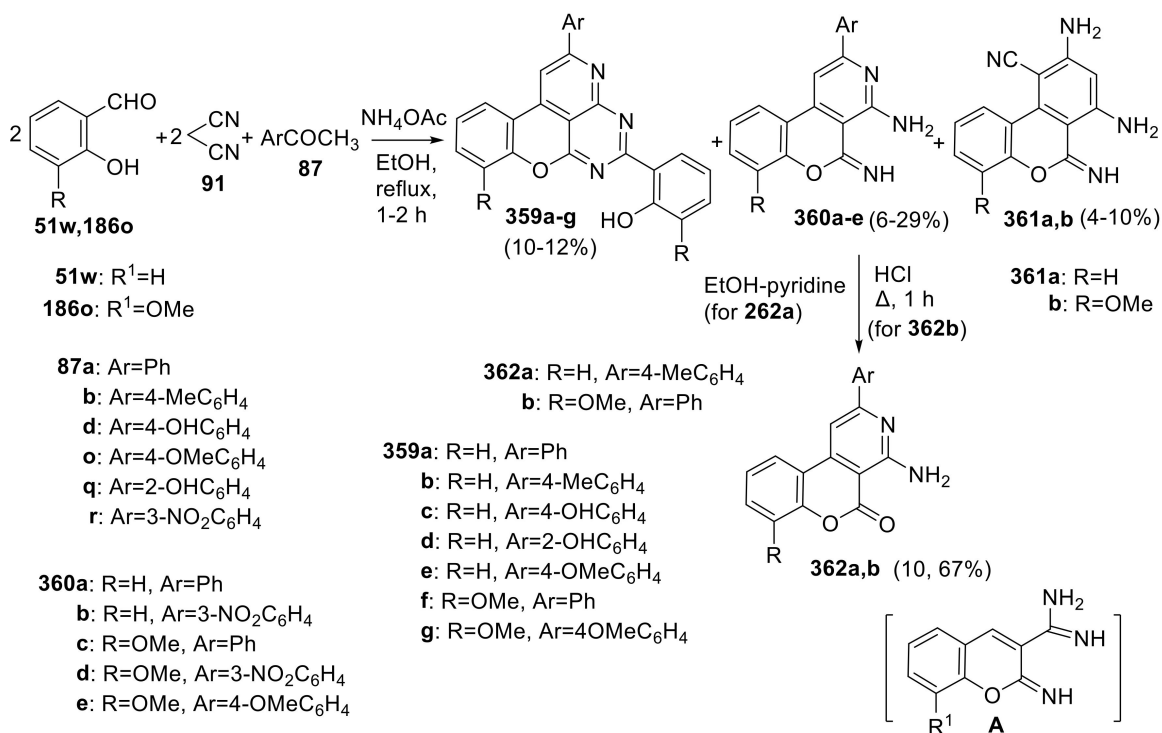
**Scheme 100.** Synthesis of fused pyrido [3,2-*c*]coumarin 353 and pyrido [3,4-*c*]coumarins 356a–z and 357a–d.

The same group studied the reaction of salicylaldehydes with ethyl cyanoacetate (**272b**) in the presence of aldehydes **186** and ammonium acetate to obtain the amino-substituted pyrido [3,4-*c*]coumarins **358a–j** [185]. The reflux in ethanol was for 0.5–1.5 h. 3-Amidinocoumarin **354** was the intermediate for the reaction (Scheme 101).



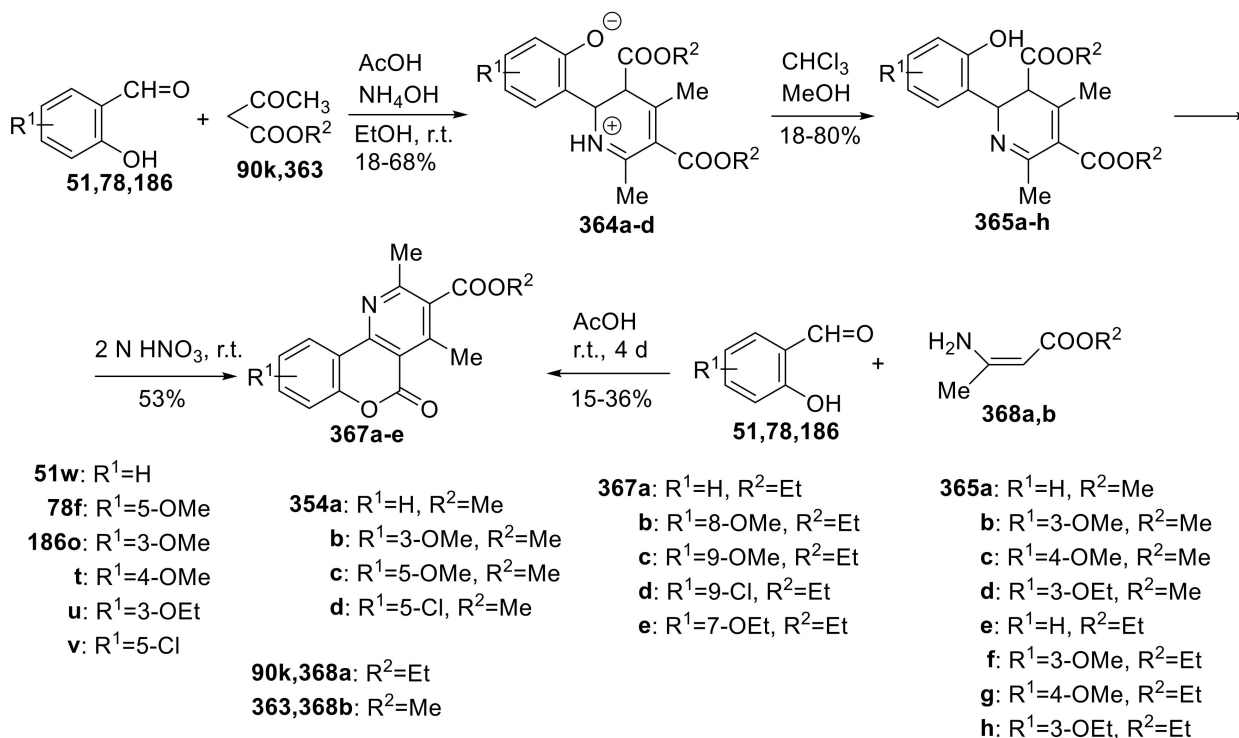
**Scheme 101.** Synthesis of amino-substituted pyrido [3,4-*c*]coumarins **358a–j**.

Sakurai et al., using malononitrile (**91**) with salicylaldehydes and acetophenones **87** in the presence of ammonium acetate, also synthesized benzopyrido [3,4-*c*]coumarinimides **360a–e** and benzopyranopyridopyrimidines **359a–g** [186]. The 3-Amidinocoumarinimide (**A**), analogous to the abovementioned **354**, was the proposed intermediate for these reactions (Scheme 102).



**Scheme 102.** Synthesis of amino-substituted pyrido [3,4-*c*]coumarins **362a,b** from salicylaldehydes malononitrile and acetophenones.

In 1987, O'Callaghan studied the reaction of salicylaldehydes with alkyl acetoacetate and excess of ammonia in acetic acid at room temperature, which yielded the dihydropyridine derivatives **365a–h** and their zwitterions **364a–d**. Zwitterions in solution changed slowly to the hydroxy derivatives [187]. Mild oxidation of them with 2 N HNO<sub>3</sub> resulted in pyrido [3,2-*c*]coumarin derivatives **367a–e**. The same derivatives were obtained by the reaction of salicylaldehydes with alkyl 3-aminocrotonate (Scheme 103).



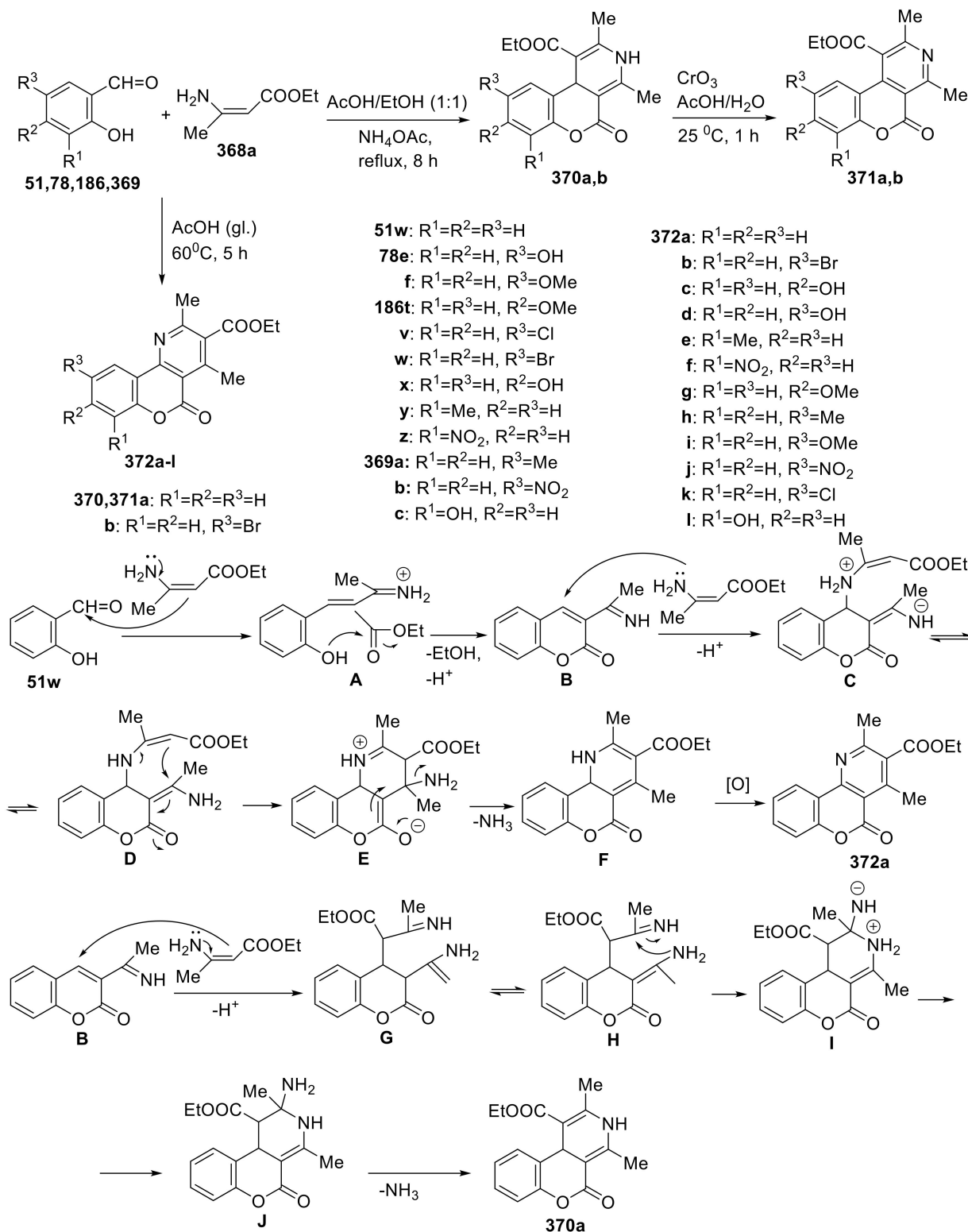
**Scheme 103.** Synthesis of pyrido [3,2-*c*]coumarin derivatives **367a–e** by mild oxidation of dihydropyridine derivatives **365a–h**.

Navarrete-Encina et al., performed, also, the reaction of salicylaldehydes with ethyl 3-aminocrotonate (**368a**) to get pyrido [3,4-*c*]coumarin **371a,b** or pyrido [5,6-*c*]coumarin derivatives **372a–l** [188]. Using acetic acid in ethanol they obtained dihydropyridocoumarin derivatives **370a,b**, which upon oxidation with CrO<sub>3</sub> led to **371a,b**. With glacial acetic acid and heating, they synthesized the pyridocoumarins **372a–l**. In the proposed mechanism, a condensation of carbonyl group of salicylaldehyde (**51w**) with the 3-aminocrotonate **368a** gave the intermediate **A**, which upon cyclization led to coumarin intermediate imine **B** (Scheme 104). In glacial acetic acid 1,4-addition of amine group of **368a** to the coumarin **B**, followed by intramolecular cyclization of the isomer **D** of intermediate **C** to **E** and elimination of ammonia afforded to the dihydropyridine moiety **F**. Oxidation of the latter furnished the pyridocoumarin **372a**. Upon 1,4-addition of the  $\alpha$ -carbon of 3-aminocrotonate to **B** in acetic acid/ethanol with decreased acidity the intermediate **G** was formed. Intramolecular cyclization of its isomer **H** to tetrahydropyridine **I**, followed by elimination of ammonia from intermediate **J**, led to dihydropyridocoumarin **370a**.

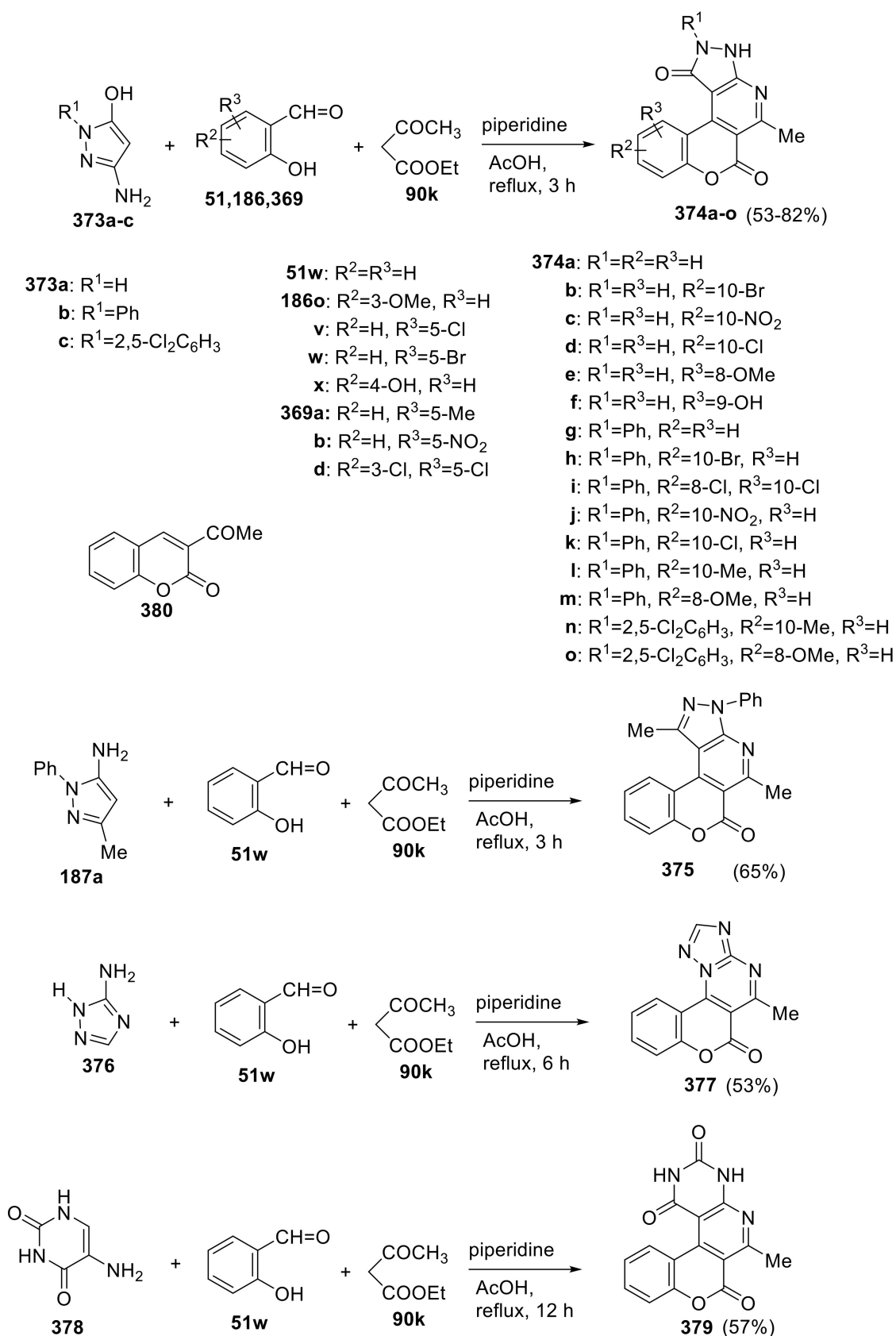
In 2011, Magedov and coworkers utilized a multi-component reaction of salicylaldehydes with 3-aminopyrazol-5-ones **373a–c** and ethyl acetoacetate for the formation of 2,3-dihydrochromeno [4,3-*d*]pyrazolo [3,4-*b*]pyridine-1,6-diones **374a–o**, in order to study their antibacterial properties [189]. They synthesized, also, fused pyrido [3,4-*c*]coumarin derivatives **375, 379** and the pyrimidino [3,4-*c*]coumarin **377** using as heterocyclic amines 3-amino-5-methyl-2-phenylpyrazole (**187a**), 6-aminouracil (**378**) and 3-amino [1,2,4]triazole (**376**), respectively (Scheme 105). In the proposed mechanism, 3-acetylcoumarin (**380**) was formed in situ from salicylaldehyde and ethyl acetoacetate followed by a condensation with aminopyrazole. The



compounds were tested for their antibacterial activity against gram(+)-strains. Compounds **374i** and **374o** inhibited the growth of *Staphylococcus epidermidis* with MIC = 6.3 and 25  $\mu\text{M}$ , respectively. Derivative **374i** was also active against methicillin-resistant *Staphylococcus aureus*, inhibiting the growth of this pathogen with MIC = 25  $\mu\text{M}$ .

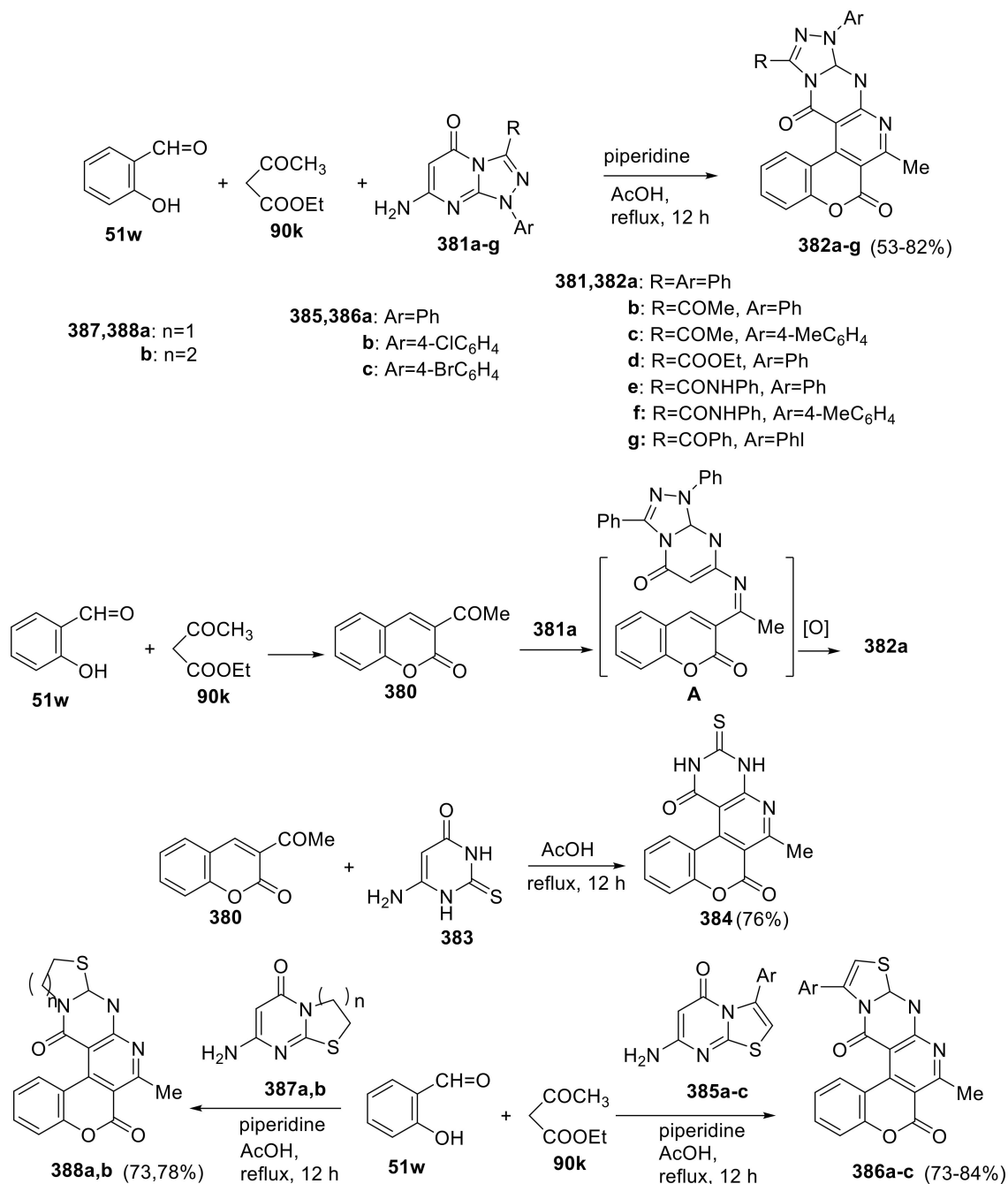


**Scheme 104.** Synthesis of pyrido [3,4-c]coumarin **371a,b** and pyrido [5,6-c]coumarin derivatives **372a-I** from salicylaldehydes and ethyl 3-aminocrotonate (**368a**).



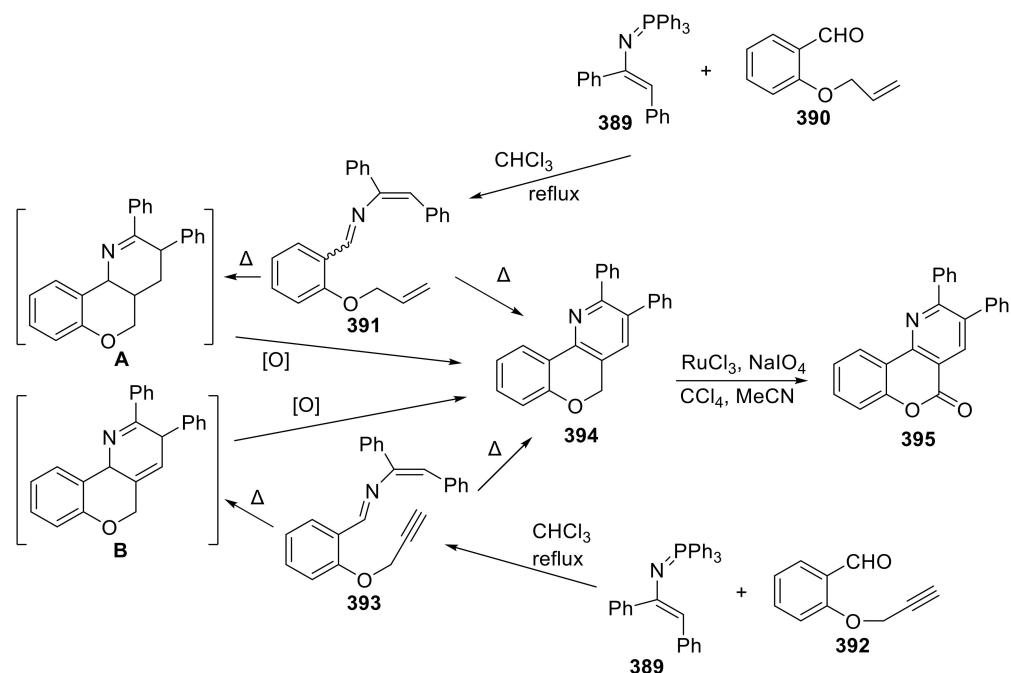
**Scheme 105.** Multicomponent synthesis of 2,3-dihydrochromeno [4,3-*d*]pyrazolo [3,4-*b*]pyridine-1,6-diones **374a–o**.

Gomha and Riyadh reported analogous reactions of salicylaldehyde (**51w**) and ethyl acetoacrylate (**90k**) with heterocycle amines such as **381a–g**, **385a–c** and **387a,b** [190]. They had isolated the intermediate 3-acetylcoumarin (**380**), which reacted further with pyrimidine derivative **383** to give the fused compound **384** (Scheme 106).



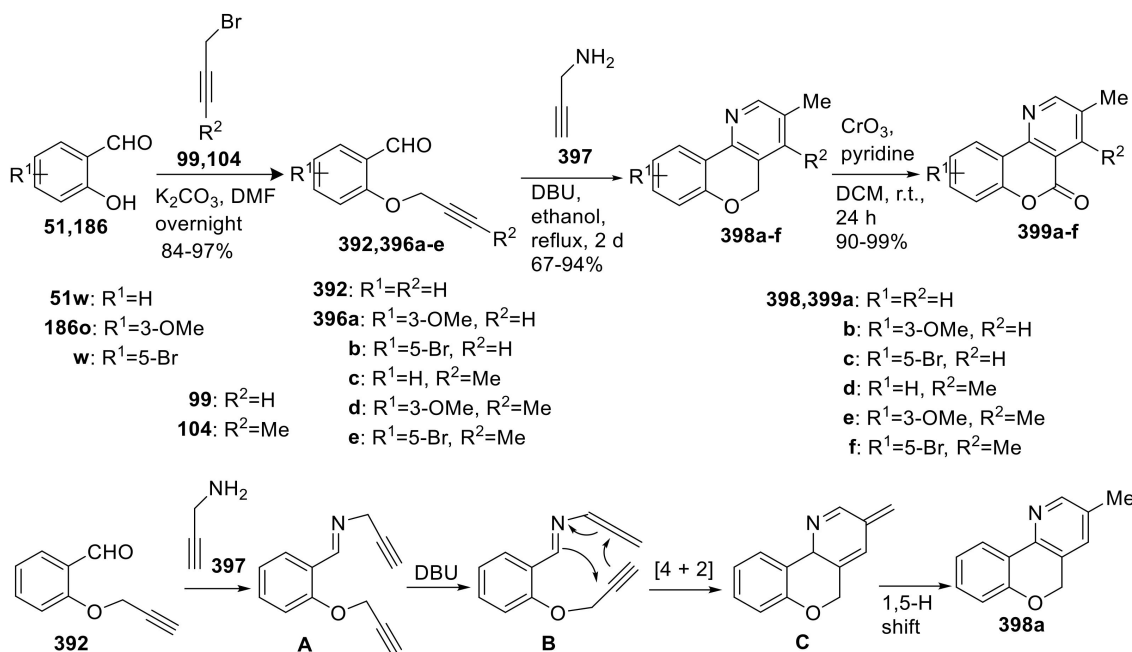
**Scheme 106.** Synthesis of chromen [4',3':4,5]pyrido [2,3-d][1,2,4]triazolo [4,3-a]pyrimidine-6,14-diones **382a–g**.

Palacios et al., synthesized the pyrido [3,2-*c*]coumarin **395** by oxidation of 5*H*-benzopyrano [4,3-*b*]pyridine **394** with ruthenium chloride in the presence of sodium periodate [191]. A Diels–Alder reaction of allyloxy-derivative **391** or propargyloxy-derivative **393** furnished the compound **394** (Scheme 107). Derivatives **391** and **393** were obtained by a Wittig reaction of aza-ylide **389** with the derivatives of salicylaldehyde **390** and **392**, respectively.



**Scheme 107.** Synthesis of benzopyrido [3,2-c]coumarin **395** by oxidation of **394** with  $\text{RuCl}_3$  in the presence of  $\text{NaIO}_4$ .

Keskin and Balci used an oxidation with  $\text{CrO}_3$  for the synthesis of pyrido [3,2-c]coumarins **399a–f** from the chromenopyridines **398a–f** [192]. A [4 + 2] Diels–Alder cycloaddition reaction of the adduct **A** from the reaction of 2-propargyloxybenzaldehyde (**392**) with propargylamine (**397**) resulted in **398a** (Scheme 108). A base-catalyzed isomerization of the terminal alkyne of the imine moiety by DBU resulted to the intermediate allene **B**, followed by a Diels–Alder reaction to the dihydropyridine intermediate **C**. 1,5-H shift of the latter afforded **398a**.



**Scheme 108.** Synthesis of pyrido [3,2-c]coumarins **399a–f** via oxidation with  $\text{CrO}_3$  of chromenopyridines **398a–f**.

### 3. Conclusions

From the literature review, pyridocoumarins, naturally occurring or synthetic, were found to have interesting biological activities. The synthetic strategies for the synthesis of pyridocoumarins involve two main routes. The formation of the pyridine ring in one route is achieved from a coumarin derivative, such as aminocoumarins, hydroxycoumarins, or other coumarins. In the other route, the pyranone moiety is formed from an existing pyridine or piperidine or phenol derivative. [4 + 2] Cycloaddition reactions, multi-component reactions (MCR), as well as metal-catalyzed reactions are useful for the above syntheses. Name reactions, such as Skraup, Skraup–Doebner–von Miller, Povarov, Friedlander, and Krohnke, are useful for these syntheses.

Pyridocoumarins present anti-cancer, anti-HIV, antimalarial, analgesic, antidiabetic, antibacterial, antifungal, antioxidant, and anti-inflammatory activities. Especially, pyrido [3,4-*c*]coumarin **302** presented good antimalarial activity. Some pyrido [3,2-*c*]coumarins had better antitumor activity than 5-fluorouracil, while dihydrochromeno [4,3-*b*]quinoline derivatives exhibited very good antitumor activity. Pyrido [3,2-*c*]coumarin and pyrido [3,4-*c*]coumarin derivatives showed antibacterial and antifungal activities. Pyrano [2,3-*f*]quinolin-2-one **97** had excellent anti-HIV activity.

We hope that this review will benefit researchers, not only in the field of pyridocoumarin derivatives, but generally, in the area of coumarins.

**Author Contributions:** The contribution of the authors is equal investigation, writing, original draft preparation, review, and editing. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

### References

1. Abdelmohsen, U.R.; Albohy, A.; Abdulrazik, B.S.; Bayoumi, S.A.L.; Malak, L.G.; Khallaf, I.S.A.; Bringmann, G.; Farag, S.F. Natural coumarins as potential anti-SARS-CoV-2 agents supported by docking analysis. *RSC Adv.* **2021**, *11*, 16970–16979. [[CrossRef](#)] [[PubMed](#)]
2. Stringlis, I.A.; de Jonge, R.; Pieterse, C.M.J. The age of coumarins in plant-microbe interactions. *Plant Cell Physiol.* **2019**, *60*, 1405–1419. [[CrossRef](#)] [[PubMed](#)]
3. Voges, M.J.E.E.; Baic, Y.; Schulze-Lefert, P.; Sattely, E.S. Plant-derived coumarins shape the composition of an *Arabidopsis* synthetic root microbiome. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 12558–12565. [[CrossRef](#)] [[PubMed](#)]
4. Matos, M.J.; Santana, L.; Uriarte, E.; Abreu, O.A.; Molina, E.; Yord, E.G. Coumarins—An Important Class of Phytochemicals. In *Phytochemicals: Isolation, Characterisation and Role in Human Health*; Rao, V.A., Rao, L.G., Eds.; IntechOpen: Rijeka, Croatia, 2015; Chapter 5.
5. Venugopala, K.N.; Rashmi, V.; Odhav, B. Review on natural coumarin lead compounds for their pharmacological activity. *BioMed. Res. Intern.* **2013**, *2013*, 963248. [[CrossRef](#)] [[PubMed](#)]
6. Awe, S.; Mikolasch, A.; Schauer, F. Formation of coumarines during the degradation of alkyl substituted aromatic oil components by the yeast *Trichosporon asahii*. *Appl. Microbiol. Biotechnol.* **2009**, *84*, 965–976. [[CrossRef](#)] [[PubMed](#)]
7. Su, X.-H.; Zhang, M.-L.; Li, L.-G.; Huo, C.-H.; Gu, Y.-C.; Shi, Q.-W. Chemical Constituents of the Plants of the Genus *Calophyllum*. *Chem. Biodivers.* **2008**, *5*, 2579–2608. [[CrossRef](#)] [[PubMed](#)]
8. Murray, D.H.; Mendez, J.; Brown, S.A. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*; John Wiley & Sons: New York, NY, USA, 1982.
9. O’Kennedy, R.; Thornes, R.D. *Coumarins: Biology, Applications and Mode of Action*; John Wiley & Sons: Chichester, UK, 1997.
10. Kontogiorgis, C.; Detsi, A.; Hadjipavlou-Litina, D. Coumarin-based drugs: A patent review (2008–present). *Expert Opin. Ther. Pat.* **2012**, *22*, 437–454. [[CrossRef](#)] [[PubMed](#)]
11. Medina, F.G.; Marrero, J.G.; Macías-Alonso, M.; González, M.C.; CórdovaGuerrero, I.; Teissier García, A.G.; Osegueda-Robles, S. Coumarin heterocyclic derivatives: Chemical synthesis and biological activity. *Nat. Prod. Rep.* **2015**, *32*, 1472–1507. [[CrossRef](#)] [[PubMed](#)]

12. Borah, B.; Dwivedi, K.D.; Kumar, B.; Chowhan, L.R. Recent advances in the microwave- and ultrasound-assisted green synthesis of coumarin-heterocycles. *Arab. J. Chem.* **2022**, *15*, 103654. [[CrossRef](#)]
13. O'Reilly, R.; Aggeler, P.M. Studies on Coumarin Anticoagulant Drugs. Initiation of Warfarin Therapy Without a Loading Dose. *Circulation* **1968**, *38*, 169–177. [[CrossRef](#)] [[PubMed](#)]
14. Lowenthal, J.; Birnbaum, H. Vitamin K and coumarin anticoagulants: Dependence of anticoagulant effect on inhibition of vitamin K transport. *Science* **1969**, *164*, 181–183. [[CrossRef](#)] [[PubMed](#)]
15. Fisher, P.; Campbell, K.J.; Howald, G.R.; Warburton, B. Anticoagulant Rodenticides, Islands, and Animal Welfare Accountancy. *Animals* **2019**, *9*, 919. [[CrossRef](#)] [[PubMed](#)]
16. Fylaktakidou, K.C.; Hadjipavlou-Litina, D.J.; Litinas, K.E.; Nicolaidis, D.N. Natural and synthetic coumarin derivatives with anti-inflammatory/antioxidant activities. *Curr. Pharm. Des.* **2004**, *10*, 3813–3833. [[CrossRef](#)] [[PubMed](#)]
17. Kontogiorgis, C.; Hadjipavlou-Litina, D.J. Synthesis and antiinflammatory activity of coumarin derivatives. *J. Med. Chem.* **2005**, *48*, 6400–6408. [[CrossRef](#)] [[PubMed](#)]
18. Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S.L.; Lee, K.H. Recent progress in the development of coumarin derivatives as potent anti-HIV agents. *Res. Rev.* **2003**, *23*, 322–345. [[CrossRef](#)]
19. Wang, L.; Ma, T.; Liu, G. Recent progress in calophyllum coumarins as potent anti-HIV agents. In *Medicinal Chemistry of Bioactive Natural Products*; Liang, X.T., Fang, W.S., Eds.; John Wiley & Sons: Hoboken, NJ, USA, 2006; p. 326.
20. Xu, Z.; Chen, Q.; Zhang, Y.; Liang, C. Coumarin-based derivatives with potential anti-HIV activity. *Fitoterapia* **2021**, *150*, 104863. [[CrossRef](#)] [[PubMed](#)]
21. Zhao, L.; Hu, D.; Wu, Z.; Wei, C.; Wu, S.; Song, B. Coumarin Derivatives Containing Sulfonamide and Dithioacetal Moieties: Design, Synthesis, Antiviral Activity, and Mechanism. *J. Agric. Food Chem.* **2022**, *70*, 5773–5783. [[CrossRef](#)]
22. Lacy, A.; O'Kennedy, R. Studies on coumarins and coumarin-related compounds to determine their therapeutic role in the treatment of cancer. *Curr. Pharm. Des.* **2004**, *10*, 3797–3811. [[CrossRef](#)]
23. Promsuwan, P.; Yenjai, C. Synthesis and Cytotoxicity of Coumarin Derivatives and Nordentatin. *Asian J. Chem.* **2013**, *25*, 3629–3632. [[CrossRef](#)]
24. Thakur, A.; Singla, R.; Jaitak, V. Coumarins as anticancer agents: A review on synthetic strategies, mechanism of action and SAR studies. *Eur. J. Med. Chem.* **2015**, *101*, 476–495. [[CrossRef](#)]
25. Rubab, L.; Afroz, S.; Ahmad, S.; Hussain, S.; Nawaz, I.; Irfan, A.; Batool, F.; Kotwica-Mojzych, K.; Mojzych, M. An Update on Synthesis of Coumarin Sulfonamides as Enzyme Inhibitors and Anticancer Agents. *Molecules* **2022**, *27*, 1604. [[CrossRef](#)] [[PubMed](#)]
26. May, J.M.; Owens, T.W.; Mandler, M.D.; Simpson, B.W.; Lazarus, M.B.; Sherman, D.J.; Davis, R.M.; Okuda, S.; Masefski, W.; Ruiz, N.; et al. The Antibiotic Novobiocin Binds and Activates the ATPase That Powers Lipopolysaccharide Transport. *J. Am. Chem. Soc.* **2017**, *139*, 17221–17224. [[CrossRef](#)]
27. Madeiro, S.A.L.; Borges, N.H.P.B.; Souto, A.L.; de Figueiredo, P.T.R.; Siqueira-Junior, J.P.; Tavares, J.F. Modulation of the antibiotic activity against multidrug resistant strains of coumarins isolated from Rutaceae species. *Microb. Pathogen.* **2017**, *104*, 151–154. [[CrossRef](#)] [[PubMed](#)]
28. Zou, J.; Liu, Y.; Guo, R.; Tang, Y.; Shi, Z.; Zhang, M.; Wu, W.; Chen, Y.; Hou, K. An in-vitro coumarin antibiotic combination treatment of *Pseudomonas aeruginosa* biofilms. *Nat. Prod. Commun.* **2021**, *16*, 1–7. [[CrossRef](#)]
29. Basile, A.; Sorbo, S.; Spadaro, V.; Bruno, M.; Maggio, A.; Faraone, N.; Rosselli, S. Antimicrobial and Antioxidant Activities of Coumarins from the Roots of *Ferulago campestris* (Apiaceae). *Molecules* **2009**, *14*, 939–952. [[CrossRef](#)] [[PubMed](#)]
30. Domínguez-Mendoza, E.A.; Cornejo-Garrido, J.; Burgueño-Tapia, E.; Ordaz-Pichardo, C. Antidiabetic effect, antioxidant activity, and toxicity of 3',4'-Di-O-acetyl-cis-khellactone in Streptozotocin-induced diabetic rats. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4086–4091. [[CrossRef](#)] [[PubMed](#)]
31. Alshibl, H.M.; Al-Abdullah, E.S.; Haiba, M.E.; Alkahtani, H.M.; Awad, G.E.A.; Mahmoud, A.H.; Ibrahim, B.M.M.; Bari, A.; Villinger, A. Synthesis and Evaluation of New Coumarin Derivatives as Antioxidant, Antimicrobial, and Anti-Inflammatory Agents. *Molecules* **2020**, *25*, 3251. [[CrossRef](#)] [[PubMed](#)]
32. Arumugam, S.; Kavimani, S.; Kadalmani, B.; Ahmed, A.B.A.; Akbarsha, M.A.; Rao, M.V. Antidiabetic activity of leaf and callus extracts of *Aegle marmelos* in rabbit. *Sci. Asia* **2008**, *34*, 317–321. [[CrossRef](#)]
33. Li, H.; Yao, Y.; Li, L. Coumarins as potential antidiabetic agents. *J. Pharm. Pharmacol.* **2017**, *69*, 1253–1264. [[CrossRef](#)]
34. Ojala, T.; Remes, S.; Haansuu, P.; Vuorela, H.; Hiltunen, R.; Haatela, K.; Vuorela, P. Antimicrobial activity of some coumarin containing herbal plants growing in Finland. *J. Ethnopharmacol.* **2000**, *73*, 299–305. [[CrossRef](#)]
35. Giri, R.R.; Lad, H.B.; Bhila, V.G.; Patel, C.V.; Brahmabhatt, D.I. Modified pyridine-substituted coumarins: A new class of antimicrobial and antitubercular agents. *Synth. Commun.* **2015**, *45*, 363–375. [[CrossRef](#)]
36. Al-Majedy, Y.K.; Kadhun, A.A.H.; Al-Amiery, A.A.; Mohamad, A.B. Coumarins: The Antimicrobial. *Rev. Pharm.* **2017**, *8*, 62–70. [[CrossRef](#)]
37. Hu, Y.-Q.; Xu, Z.; Zhang, S.; Wu, X.; Ding, J.-W.; Lv, Z.S.; Feng, L.S. Recent developments of coumarin-containing derivatives and their anti-tubercular activity. *Eur. J. Med. Chem.* **2017**, *136*, 122–130. [[CrossRef](#)] [[PubMed](#)]
38. Reddy, D.S.; Kongot, M.; Kumar, A. Coumarin hybrid derivatives as promising leads to treat tuberculosis: Recent developments and critical aspects of structural design to exhibit anti-tubercular activity. *Tuberculosis* **2021**, *127*, 102050. [[CrossRef](#)] [[PubMed](#)]
39. Stefanachi, A.; Leonetti, F.; Pisani, L.; Catto, M.; Carotti, A. Coumarin: A Natural, Privileged and Versatile Scaffold for Bioactive Compounds. *Molecules* **2018**, *25*, 250. [[CrossRef](#)]

40. Vlachou, E.-E.N.; Litinas, K.E. An overview on pyranocoumarins: Synthesis and biological activities. *Curr. Org. Chem.* **2019**, *23*, 2679–2721. [[CrossRef](#)]
41. El-Sawy, E.R.; Abdelwahab, A.B.; Kirsch, G. Synthetic Routes to Coumarin (Benzopyrone)-Fused Five-Membered Aromatic Heterocycles Built on the  $\alpha$ -Pyrone Moiety. Part 1: Five-Membered Aromatic Rings with One Heteroatom. *Molecules* **2021**, *26*, 483. [[CrossRef](#)]
42. Salehian, F.; Nadri, H.; Jalili-Baleh, L.; Youseftabar-Miri, L.; Bukhari, S.N.A.; Foroumadi, A.; Küçükkilinç, T.T.; Sharifzadeh, M.; Khoobi, M. A review: Biologically active 3,4-heterocycle-fused coumarins. *Eur. J. Med. Chem.* **2021**, *212*, 113034. [[CrossRef](#)] [[PubMed](#)]
43. Patel, A.A.; Lad, H.B.; Pandya, K.R.; Patel, C.V.; Brahmabhatt, D.I. Synthesis of a new series of 2-(2-oxo-2H-chromen-3-yl)-5H-chromeno[4,3-*b*]pyridin-5-ones by two facile methods and evaluation of their antimicrobial activity. *Med. Chem. Res.* **2013**, *22*, 4745–4754. [[CrossRef](#)]
44. Patel, M.A.; Bhila, V.G.; Patel, N.H.; Patel, A.K.; Brahmabhatt, D.I. Brahmabhatt Synthesis, characterization and biological evaluation of some pyridine and quinoline fused chromenone derivatives. *Med. Chem. Res.* **2012**, *21*, 4381–4388. [[CrossRef](#)]
45. Dawane, B.S.; Konda, S.G.; Bodade, R.G.; Bhosale, R.B. An efficient one-pot synthesis of some new 2,4-diaryl pyrido[3,2-*c*]coumarins as potent antimicrobial agents. *J. Heterocycl. Chem.* **2010**, *47*, 237–241. [[CrossRef](#)]
46. Goswami, L.; Gogoi, S.; Gogoi, J.; Baruah, R.K.; Boruah, R.; Gogoi, P. Facile Diversity-Oriented Synthesis of Polycyclic Pyridines and Their Cytotoxicity Effects in Human Cancer Cell Lines. *ACS Comb. Sci.* **2016**, *18*, 253–261. [[CrossRef](#)] [[PubMed](#)]
47. Hamama, W.S.; Ibrahim, M.E.; Metwalli, A.E.; Zoorob, H.H. New synthetic approach to coumarino[4,3-*b*]pyridine systems and potential cytotoxic evaluation. *Med. Chem. Res.* **2014**, *23*, 2615–2621. [[CrossRef](#)]
48. Mulakayala, N.; Rambabu, D.; Raja, M.R.; Chaitanya, M.; Kumar, C.S.; Kalle, A.M.; Krishna, G.R.; Reddy, C.M.; Rao, M.V.B.; Pal, M. Ultrasound mediated catalyst free synthesis of 6H-1-benzopyrano[4,3-*b*]quinolin-6-ones leading to novel quinoline derivatives: Their evaluation as potential anti-cancer agents. *Bioorg. Med. Chem.* **2012**, *20*, 759–768. [[CrossRef](#)]
49. Hosni, H.M.; Abdulla, M.M. Anti-inflammatory and analgesic activities of some newly synthesized pyridinedicarbonitrile and benzopyranopyridine derivatives. *Acta Pharm.* **2008**, *58*, 175–186. [[CrossRef](#)] [[PubMed](#)]
50. Görlitzer, K.; Enge, C.; Jones, P.G.; Jomaa, H.; Wiesner, J. Benzo[*c*][2,7]naphthyridine-2-yl-, 5-yl- and 2,5-diyl novaldiamines—synthesis and investigation of anti-malarial activity. *Pharmazie* **2006**, *61*, 975–980. [[PubMed](#)]
51. Heber, D. Reaktionen an Heterocyclen mit 2-Acyl-2-propenon-Teilstruktur, 3. Mitt. Pyrido[3,2-*c*]coumarine aus 3-substituierten 1-Benzopyranen und Enaminen. *Arch. Pharm.* **1987**, *320*, 402–406. [[CrossRef](#)]
52. Adib, M.; Peytam, F.; Rahmanian-Jazi, M.; Mohammadi-Khanaposhtani, M.; Mahernia, S.; Bijanzadeh, H.R.; Jahani, M.; Imanparast, S.; Faramarzi, M.A.; Mahdavig, M.; et al. Design, synthesis and in vitro  $\alpha$ -glucosidase inhibition of novel coumarin-pyridines as potent antidiabetic agents. *New J. Chem.* **2018**, *42*, 7268–17278. [[CrossRef](#)]
53. Ahn, S.; Yoon, J.A.; Han, Y.T. Total Synthesis of the Natural Pyridocoumarins Goniotaline A and B. *Synthesis* **2019**, *51*, 552–556. [[CrossRef](#)]
54. Aslam, M.S.; Ahmad, M.A.; Mamat, A.S.; Ahmad, M.Z.; Salam, F. Goniotalamus: Phytochemical and Ethnobotanical Review. *Rec. Adv. Biol. Med.* **2016**, *2*, 34–47. [[CrossRef](#)]
55. Levrier, C.; Balastrier, M.; Beattle, K.D.; Carroll, A.R.; Martin, F.; Choomuenwai, V.; Davis, R.A. Pyridocoumarin, aristolactam and aporphine alkaloids from the Australian rainforest plant *Goniotalamus australis*. *Phytochemistry* **2013**, *86*, 121–126. [[CrossRef](#)]
56. Wang, X.-L.; Dou, M.; Luo, Q.; Cheng, L.-Z.; Yan, Y.-M.; Li, R.-T.; Cheng, Y.-X. Racemic alkaloids from the fungus *Ganoderma cochlear*. *Fitoterapia* **2017**, *116*, 93–98. [[CrossRef](#)] [[PubMed](#)]
57. Markey, M.D.; Fu, Y.; Kelly, T.R. Synthesis of Santiagonamine. *Org. Lett.* **2007**, *9*, 3255–3257. [[CrossRef](#)] [[PubMed](#)]
58. Lu, Z.M.; Zhang, Q.J.; Chen, R.Y.; Yu, D.Q. Four new alkaloids from *Polyalthia nemoralis* (Annonaceae). *J. Asian Nat. Prod. Res.* **2008**, *10*, 656–664. [[CrossRef](#)]
59. Pang, M.; Lee, J.; Jeon, J.-H.; Song, I.-S.; Han, Y.T.; Choi, M.-K. Development of a Sensitive Analytical Method of Polynemoraleine C Using LCMS/MS and Its Application to a Pharmacokinetic Study in Mice. *Mass Spectrom. Lett.* **2021**, *12*, 200–205. [[CrossRef](#)]
60. Houghton, P.J.; Woldemariam, T.Z.; Khan, A.I.; Burke, A.; Mahmood, N. Antiviral activity of natural and semi-synthetic chromone alkaloids. *Antivir. Res.* **1994**, *25*, 235–244. [[CrossRef](#)]
61. Houghton, P.J.; Hairon, Y. Further chromone alkaloids from *Schumanniphyton magnificum*. *Planta Med.* **1987**, *53*, 262–264. [[CrossRef](#)]
62. Houghton, P.J. Revision of structures of some *Schumanniphyton* alkaloids. *Planta Med.* **1987**, *53*, 264–266. [[CrossRef](#)] [[PubMed](#)]
63. Houghton, P.J.; Hairong, Y. Novel Chromone Alkaloids from *Schumanniphyton magnificum*. *Planta Med.* **1985**, *51*, 23–27. [[CrossRef](#)]
64. Darbavar, M.; Sundaramurthy, V. Synthesis of Coumarins with 3:4-Fused Ring Systems and their Physiological Activity. *Synthesis* **1982**, *1982*, 337–388. [[CrossRef](#)]
65. Rawat, A.; Reddy, A.V.B. Recent advances on anticancer activity of coumarin derivatives. *Eur. J. Med. Chem. Rep.* **2022**, *5*, 100038. [[CrossRef](#)]
66. Patra, P. A Concise Review on Pyridocoumarin/Azacoumarin Derivatives: Synthesis and Biological Activity. *Chem. Sel.* **2019**, *4*, 2024–2043. [[CrossRef](#)]
67. Patra, P. 4-Chloro-3-formylcoumarin as a multifaceted building block for the development of various bio-active substituted and fused coumarin heterocycles: A brief review. *New J. Chem.* **2021**, *45*, 14269–14327. [[CrossRef](#)]
68. Manske, R.H. The chemistry of quinolines. The Chemistry of Quinolines. *Chem. Rev.* **1942**, *30*, 113–144. [[CrossRef](#)]

69. Manske, R.H.F.; Kulka, M. *The Skraup Synthesis of Quinolines in Organic Reactions*; John Wiley & Sons: New York, NY, USA, 1953; Volume 7, pp. 59–98.
70. Dey, D.B.; Goswami, M.N. XXXIX.  $\psi$ -1:8-isoNaphthoxazone. *J. Chem. Soc.* **1919**, *115*, 531–541. [[CrossRef](#)]
71. Liska, K.J.; Fentiman, A.F., Jr.; Foltz, R.L. Use of tris-(dipivalomethanato)europium as a shift reagent in the identification of 3-*H*-pyrano[3,2-*f*]quinoline-3-one. *Tetrahedron Lett.* **1970**, *53*, 4657–4660. [[CrossRef](#)]
72. Denmark, S.E.; Venkatraman, S. On the Mechanism of the Skraup–Doebner–Von Miller Quinoline Synthesis. *J. Org. Chem.* **2006**, *71*, 1668–1676. [[CrossRef](#)]
73. Wu, Y.-C.; Liu, L.; Li, H.-J.; Wang, D.; Chen, Y.-J. Skraup–Doebner–Von Miller Quinoline Synthesis Revisited: Reversal of the Regiochemistry for  $\gamma$ -Aryl- $\beta,\gamma$ -unsaturated  $\alpha$ -Ketoesters. *J. Org. Chem.* **2006**, *71*, 6592–6595. [[CrossRef](#)] [[PubMed](#)]
74. Heber, D.; Berghaus, T. Synthesis of 5*H*-[1]benzopyrano[4,3-*b*]pyridin-5-ones containing an azacannabinoid structure. *J. Heterocycl. Chem.* **1994**, *31*, 1353–1359. [[CrossRef](#)]
75. Yadav, A.; Biswas, S.; Mobin, S.M.; Samanta, S. Efficient Cu(OTf)<sub>2</sub>-catalyzed and microwave-assisted rapid synthesis of 3,4-fused chromenopyridinones under neat conditions. *Tetrahedron Lett.* **2017**, *58*, 3634–3639. [[CrossRef](#)]
76. Osipov, D.V.; Artyomenko, A.A.; Osyanin, V.A.; Klimochkin, Y.N. The reaction of 4-aminocoumarin with  $\beta$ -carbonyl-substituted 4*H*-chromenes: Synthesis of 5*H*-chromeno [4,3-*b*] pyridin-5-one derivatives. *Chem. Heterocycl. Comp.* **2019**, *55*, 261–265. [[CrossRef](#)]
77. Osipov, D.V.; Osyanin, V.A.; Klimochkin, Y.N. Synthesis of  $\beta$ -(*o*-hydroxybenzyl) pyridines by three-component condensation of ammonia, carbonyl-substituted 4*H*-chromenes, and CH acids. *Chem. Heterocycl. Comp.* **2018**, *54*, 1121–1126. [[CrossRef](#)]
78. Povarov, L.S.  $\alpha,\beta$ -Unsaturated ethers and their analogues in reactions of diene synthesis. *Russ. Chem. Rev.* **1967**, *36*, 656–670. [[CrossRef](#)]
79. Kouznetsov, V.V. Recent synthetic developments in a powerful imino Diels–Alder reaction (Povarov reaction): Application to the synthesis of *N*-polyheterocycles and related alkaloids. *Tetrahedron* **2009**, *65*, 2721–2750. [[CrossRef](#)]
80. Wang, X.-S.; Yin, M.-Y.; Wang, W.; Tu, S.-J. A Stereoselective Povarov Reaction Leading to *exo*-Tetrahydroindolo[3,2-*c*]quinoline Derivatives Catalyzed by Iodine. *Eur. J. Org. Chem.* **2012**, *2012*, 4811–4818. [[CrossRef](#)]
81. Domingo, L.R.; Aurell, M.J.; Saez, J.A.; Mekelleche, S.M. Understanding the mechanism of the Povarov reaction. A DFT study. *RSC Adv.* **2014**, *4*, 25268–25278. [[CrossRef](#)]
82. Clerigué, J.; Ramos, M.T.; Menéndez, J.C. Enantioselective catalytic Povarov reactions. *Org. Biomol. Chem.* **2022**, *20*, 1550–1581. [[CrossRef](#)]
83. Kobayashi, S.; Ishitani, H.; Nagayama, S. Lanthanide Triflate Catalyzed Imino Diels–Alder Reactions; Convenient Syntheses of Pyridine and Quinoline Derivatives. *Synthesis* **1995**, *1995*, 1195–1202. [[CrossRef](#)]
84. Ma, Y.; Qian, C.; Xie, M.; Sun, J. Lanthanide Chloride Catalyzed Imino Diels–Alder Reaction. One-Pot Synthesis of Pyrano[3,2-*c*] and Furo[3,2-*c*]quinolines. *J. Org. Chem.* **1999**, *64*, 6462–6467. [[CrossRef](#)]
85. Kudale, A.A.; Kendall, J.; Miller, D.O.; Collins, J.L.; Bodwell, G.J. Povarov Reactions Involving 3-Aminocoumarins: Synthesis of 1,2,3,4-Tetrahydropyrido[2,3-*c*]coumarins and Pyrido[2,3-*c*]coumarins. *J. Org. Chem.* **2008**, *73*, 8437–8447. [[CrossRef](#)]
86. Kudale, A.A.; Miller, D.O.; Dawe, L.N.; Bodwell, G.J. Intramolecular Povarov reactions involving 3-aminocoumarins. *Org. Biomol. Chem.* **2011**, *9*, 7196–7206. [[CrossRef](#)]
87. Islam, K.; Das, D.K.; Akram, E.; Khan, A.T. Exploration of C5–C6-Unsubstituted 1,4-Dihydropyridines for the Construction of *exo*-Hexahydro-1*H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylates Using a Stereoselective Povarov Reaction. *Synthesis* **2015**, *47*, 2745–2755. [[CrossRef](#)]
88. Khan, A.T.; Das, D.K.; Islam, K.; Das, P. A simple and expedient synthesis of functionalized pyrido[2,3-*c*] coumarin derivatives using molecular iodine catalyzed three-component reaction. *Tetrahedron Lett.* **2012**, *53*, 6418–6422. [[CrossRef](#)]
89. Majumdar, K.C.; Ponra, S.; Ghosh, D.; Taher, A. Efficient one-pot synthesis of substituted 4, 7-phenanthroline, pyrano-[3, 2-*f*] quinoline and pyrano [3, 2-*g*] quinoline derivatives by aza-diels-alder reaction. *Synth. Lett.* **2011**, *1*, 104–110. [[CrossRef](#)]
90. Symeonidis, T.S.; Litinas, K.E. Synthesis of methyl substituted [5,6]- and [7,8]-fused pyridocoumarins via the iodine-catalyzed reaction of aminocoumarins with *n*-butyl vinyl ether. *Tetrahedron Lett.* **2013**, *54*, 6517–6519. [[CrossRef](#)]
91. Ganguli, N.C.; Chandra, S. One-pot access to pyridocoumarins via Povarov-hydrogen transfer cascade under auto-tandem catalysis of iodine in aqueous micelles. *Tetrahedron Lett.* **2014**, *55*, 1564–1568. [[CrossRef](#)]
92. Symeonidis, T.S.; Hadjipavlou-Litina, D.J.; Litinas, K.E. Synthesis Through Three-Component Reactions Catalyzed by FeCl<sub>3</sub> of Fused Pyridocoumarins as Inhibitors of Lipid Peroxidation. *J. Heterocycl. Chem.* **2014**, *51*, 642–647. [[CrossRef](#)]
93. Das, D.K.; Sarkar, S.; Khan, A.T.; Saravanan, P.; Patra, S. Synthesis of fused tetrahydropyrido[2,3-*c*]coumarin derivatives as potential inhibitors for dopamine d3 receptors, catalyzed by hydrated ferric sulfate. *RSC Adv.* **2014**, *4*, 3581–3590. [[CrossRef](#)]
94. Belal, M.; Das, D.K.; Khan, A.T. Synthesis of Pyrido[2,3-*c*]coumarin Derivatives by an Intramolecular Povarov Reaction. *Synthesis* **2015**, *47*, 1109–1116. [[CrossRef](#)]
95. Xi, G.-L.; Liu, Z.-Q. Coumarin sharing the benzene ring with quinoline for quenching radicals and inhibiting DNA oxidation. *Eur. J. Med. Chem.* **2015**, *95*, 416–423. [[CrossRef](#)]
96. Gurumurthy, C.; Fatima, N.; Reddy, G.N.; Kumar, C.G.; Sabitha, G.; Ramakrishna, K.V.S. A diastereoselective synthesis of tetrahydro- and dihydro-pyrido[2,3-*c*]coumarin derivatives via a one-pot three-component Povarov reaction catalyzed by bismuth(III) chloride. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5119–5125. [[CrossRef](#)] [[PubMed](#)]
97. Chen, Z.; Hu, L.; Peng, F. Efficient Synthesis of Functionalized Pyrido[2,3-*c*]coumarin Derivatives by a One-Pot Three-Component Reaction. *Synth. Lett.* **2016**, *27*, 1888–1892. [[CrossRef](#)]



98. Cheng, C.-C.; Yan, S.-J. *The Friedlander Synthesis of Quinolines in Organic Reactions*; John Wiley & Sons: New York, NY, USA, 1982; Volume 28, pp. 37–201.
99. Marco-Contelles, J.; Pérez-Mayoral, E.; Samadi, A.; do Carmo Carreiras, M.; Soriano, E. Recent Advances in the Friedländer Reaction. *Chem. Rev.* **2009**, *109*, 2652–2671. [[CrossRef](#)] [[PubMed](#)]
100. Ghobadi, N.; Nazari, N.; Gholamzadeh, P. The Friedlander reaction: A powerful strategy for the synthesis of heterocycles. *Adv. Heterocycl. Chem.* **2020**, *132*, 85–134. [[CrossRef](#)]
101. Siddiqui, Z.N.; Khan, K. Friedlander synthesis of novel benzopyranopyridines in the presence of chitosan as heterogeneous, efficient and biodegradable catalyst under solvent-free conditions. *New J. Chem.* **2013**, *39*, 1595–1602. [[CrossRef](#)]
102. Suzuki, M.; Yu, D.; Morris-Natschke, S.L.; Smith, P.C.; Lee, K.-H. Anti-AIDS agents 66: Syntheses and anti-HIV activity of phenolic and aza 3',4'-di-O(-)-camphanoyl-(+)-cis-khellactone (DCK) derivatives. *Bioorg. Med. Chem.* **2007**, *15*, 6852–6858. [[CrossRef](#)]
103. Majumdar, K.C.; Ansary, I.; Samanta, S.; Roy, B.; Ansary, I.; Samanta, S.; Roy, B. Regioselective synthesis of pyridoquinolones and pyridocoumarins via molecular iodine-mediated 6-endo-dig electrophilic cyclization. *Tetrahedron Lett.* **2011**, *52*, 411–414. [[CrossRef](#)]
104. Symeonidis, T.S.; Kallitsakis, M.G.; Litinas, K.E. Synthesis of [5,6]-fused pyridocoumarins through aza-Claisen rearrangement of 6-propargylaminocoumarins. *Tetrahedron Lett.* **2011**, *52*, 5452–5455. [[CrossRef](#)]
105. Symeonidis, T.S.; Lykakis, I.N.; Litinas, K.E. Synthesis of quinolines and fused pyridocoumarins from *N*-propargylanilines or propargylaminocoumarins by catalysis with gold nanoparticles supported on TiO<sub>2</sub>. *Tetrahedron* **2013**, *69*, 4612–4616. [[CrossRef](#)]
106. Majumdar, K.C.; Ponra, S. Regioselective Synthesis of Dihydropyridocoumarin and Phenanthroline Derivatives via Iron(III) Chloride Mediated Intramolecular Cyclization. *Synthesis* **2014**, *46*, 1413–1420. [[CrossRef](#)]
107. Yoon, Y.A.; Ha, Y.T. Efficient Synthesis of Pyrido[3,2-*c*]coumarins via Silver Nitrate Catalyzed Cycloisomerization and Application to the First Synthesis of Polyneomarine C. *Synthesis* **2019**, *51*, 4611–4618. [[CrossRef](#)]
108. Vlachou, E.-E.N.; Fotopoulos, I.; Gabriel, C.; Pontiki, E.; Hadjipavlou-Litina, D.J.; Litinas, K.E. Synthesis and biological evaluation of fused dipyranoquinolinones as inhibitors of acetylcholinesterase with antioxidant properties. *Eur. J. Med. Chem. Rep.* **2022**, *5*, 100063. [[CrossRef](#)]
109. Zhu, J.; Bienaymé, H. (Eds.) *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005.
110. Dömling, A.; Wang, W.; Wang, K. Chemistry and Biology of Multicomponent Reactions. *Chem. Rev.* **2012**, *112*, 3083–3135. [[CrossRef](#)]
111. da Silveira Pinto, L.S.; Couri, M.R.C.; de Souza, M.V.N. Multicomponent Reactions in the Synthesis of Complex Fused Coumarin Derivatives. *Curr. Org. Synth.* **2018**, *15*, 21–37. [[CrossRef](#)]
112. Bhaskaruni, S.V.H.S.; Maddila, S.; Gangu, K.K.; Jonnalagadda, S.B. A review on multi-component green synthesis of *N*-containing heterocycles using mixed oxides as heterogeneous catalysts. *Arab. J. Chem.* **2020**, *13*, 1142–1178. [[CrossRef](#)]
113. John, S.E.; Gulati, S.; Shankaraiah, N. Recent advances in multi-component reactions and their mechanistic insights: A triennium review. *Org. Chem. Front.* **2021**, *8*, 4237–4287. [[CrossRef](#)]
114. Khan, A.T.; Das, D.K. Michael Initiated Ring Closure (MIRC) reaction on in situ generated benzylidenecyclohexane-1,3-diones for the construction of chromeno[3,4-*b*]quinoline derivatives. *Tetrahedron Lett.* **2012**, *53*, 2345–2351. [[CrossRef](#)]
115. Paul, S.; Das, A.R. An efficient green protocol for the synthesis of coumarin fused highly decorated indenodihydropyridyl and dihydropyridyl derivatives. *Tetrahedron Lett.* **2012**, *53*, 2206–2210. [[CrossRef](#)]
116. Bhattacharyya, P.; Paul, S.; Das, A.R.E. Facile synthesis of pyridopyrimidine and coumarin fused pyridine libraries over a Lewis base-surfactant-combined catalyst TEOA in aqueous medium. *RSC Adv.* **2013**, *3*, 3203–3208. [[CrossRef](#)]
117. Patra, P.; Kar, G.K.; Khatua, B. Thermolysis of *N*-Aryl Enaminoimine Hydrochloride Derivatives: A Short and General Method for the Synthesis of Pyranoquinolin-3-one and Pyranoacridin-3-one Derivatives. *J. Heterocycl. Chem.* **2014**, *51*, 1306–1310. [[CrossRef](#)]
118. Patra, P. Thermolysis of Chlorovinyl Imines as an Alternate Route for the Synthesis of Pyranoquinolin-3-one and Pyranoacridin-3-one Derivatives. *J. Heterocycl. Chem.* **2017**, *54*, 3656–3662. [[CrossRef](#)]
119. Kausar, N.; Das, A.R. Cu<sup>I</sup>-Zn(OAc)<sub>2</sub> catalyzed C(sp<sup>2</sup>)-H activation for the synthesis of pyridocoumarins through an uncommon Cu<sup>I</sup>-Cu<sup>III</sup> switching mechanism: A fast, solvent-free, combo-catalytic, ball milling approach. *Tetrahedron Lett.* **2017**, *58*, 2602–2607. [[CrossRef](#)]
120. Najafzadeh, F.; Rad-Moghadam, K.; Kalurazi, S.Y. A derivatization-directed three-component synthesis of fluorescent spiro [dihydropyridine-4,3'-indoline]s. *J. Chem. Res.* **2020**, *44*, 527–531. [[CrossRef](#)]
121. Oshiro, P.B.; Bregadiolli, B.A.; da Silva-Filho, L.C. A facile one-step synthesis of chromeno[4,3-*b*]pyridine derivatives promoted by niobium pentachloride. *J. Heterocycl. Chem.* **2020**, *57*, 2795–2800. [[CrossRef](#)]
122. Majumdar, K.C.; Chattopadhyay, B.; Nath, S. New Heck coupling strategies for the arylation of secondary and tertiary amides via palladium-catalyzed intramolecular cyclization. *Tetrahedron Lett.* **2008**, *49*, 1609–1612. [[CrossRef](#)]
123. Majumdar, K.C.; Nandi, R.K.; Ponra, S. Indium (III) Chloride Catalyzed Convergent, Regioselective Synthesis of Annulated Quinoline and Pyridine Derivatives. *Synth. Lett.* **2012**, *23*, 113–119. [[CrossRef](#)]
124. Nath, S. Synthesis of pyridocoumarin derivative by arylation of tertiary and secondary amide via Palladium catalyzed intramolecular cyclization. *J. Appl. Chem.* **2017**, *10*, 80–85. [[CrossRef](#)]
125. Weng, Y.; Zhou, H.; Sun, C.; Xie, Y.; Su, W. Copper-Catalyzed Cyclization for Access to 6*H*-Chromeno[4,3-*b*]quinolin-6-ones Employing DMF as the Carbon Source. *J. Org. Chem.* **2017**, *82*, 9047–9053. [[CrossRef](#)] [[PubMed](#)]
126. Weng, Y.; Chen, H.; Li, N.; Yang, L.; Ackermann, L. Electrooxidative Metal-Free Cyclization of 4-Arylamino-coumarins with DMF as C1-Source. *Adv. Synth. Catal.* **2021**, *363*, 2773–2777. [[CrossRef](#)]

127. Khan, E.; Biswas, S.; Mishra, S.K.; Mishra, R.; Samanta, S.; Mishra, A.; Tawani, A.; Kumar, A. Rationally designed small molecules targeting toxic CAG repeat RNA that causes Huntington's disease (HD) and spinocerebellar ataxia (SCAs). *Biochimie* **2019**, *163*, 21–32. [[CrossRef](#)]
128. Kidwai, M.; Rastogi, S.; Mohan, R. A Novel Route to New Bis(benzopyrano) Fused Dihydropyridines Using Dry Media. *Bull. Korean J. Chem.* **2004**, *25*, 119–121. [[CrossRef](#)]
129. Tu, S.; Wu, S.; Yan, S.; Hao, W.; Zhang, X.; Cao, X.; Han, Z.; Jiang, B.; Shi, F.; Xia, M.; et al. Design and Microwave-Assisted Synthesis of Naphtho[2,3-*f*]quinoline Derivatives and Their Luminescent Properties. *J. Comb. Chem.* **2009**, *11*, 239–242. [[CrossRef](#)]
130. Tu, S.; Zhang, Y.; Zhang, J.; Jiang, B.; Jia, R.; Zhang, J.; Ji, S. A Simple Procedure for the Synthesis of 4-Aza-podophyllotoxin Derivatives in Water under Microwave Irradiation Conditions. *Synlett* **2006**, *17*, 2785–2790. [[CrossRef](#)]
131. Miri, R.; Motamedi, R.; Rezaei, M.R.; Firuzi, O.; Javidnia, A.; Shafiee, A. Design, Synthesis and Evaluation of Cytotoxicity of Novel Chromeno[4,3-*b*]quinoline Derivatives. *Arch. Pharm. Chem. Life Sci.* **2011**, *2*, 111–118. [[CrossRef](#)]
132. Chen, Z.; Bi, J.; Su, W. Synthesis and Antitumor Activity of Novel Coumarin Derivatives via a Three-component Reaction in Water. *Chin. J. Chem.* **2013**, *31*, 507–514. [[CrossRef](#)]
133. Khan, M.N.; Pal, S.; Karamthulla, S.; Choudhury, L.H. Multicomponent reactions for facile access to coumarin-fused dihydroquinolines and quinolines: Synthesis and photophysical studies. *New J. Chem.* **2014**, *38*, 4722–4729. [[CrossRef](#)]
134. Dam, B.; Nandi, S.; Pal, A.K. An efficient 'on-water' synthesis of 1,4-dihydropyridines using Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub> nanoparticles as a reusable catalyst. *Tetrahedron Lett.* **2014**, *55*, 5236–5240. [[CrossRef](#)]
135. Sashidhara, K.V.; Palnati, G.R.; Singh, L.R.; Upadhyay, A.; Avula, S.R.; Kumara, A.; Kant, R. Molecular iodine catalysed one-pot synthesis of chromeno[4,3-*b*]quinolin-6-ones under microwave irradiation. *Green Chem.* **2015**, *17*, 3766–3770. [[CrossRef](#)]
136. Liu, M.; Yin, G.; Zhu, C.; Yao, C. Selective Synthesis of New Tetracyclic Coumarin-fused Pyrazolo[3,4-*b*]pyridines and Pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones. *J. Heterocycl. Chem.* **2016**, *53*, 1617–1625. [[CrossRef](#)]
137. Kumari, S.; Rajeswari, M.; Khurana, J.M. A Green Approach for the Synthesis of Novel 7, 11-Dihydro-6*H*-chromeno [3, 4-*e*]isoxazolo [5,4-*b*] pyridin-6-one Derivatives Using Acidic Ionic Liquid [C4mim][HSO<sub>4</sub>]. *Aust. J. Chem.* **2016**, *69*, 1049–1053. [[CrossRef](#)]
138. Rahimzadeh, G.; Bahadorikhalili, S.; Kianmehr, E.; Mahdavi, M. Ionic liquid-functionalized magnetic nanostructures as an efficient catalyst for the synthesis of 6*H*-chromeno[4,3-*b*]quinolin-6-ones. *Mol. Divers.* **2017**, *21*, 597–609. [[CrossRef](#)] [[PubMed](#)]
139. Firoozpour, L.; Nikookar, H.; Moghimi, S.; Mahdavi, M.; Asadipour, A.; Ranjbar, P.R.; Foroumadi, A. An efficient approach to the synthesis of coumarin-fused dihydropyridinones. *J. Heterocycl. Commun.* **2017**, *23*, 305–308. [[CrossRef](#)]
140. Sayahi, M.H.; Saghanezhad, S.J.; Mahdavi, M. SBA-15-SO<sub>3</sub>H-assisted preparation of 4-aza-phenanthrene-3, 10-dione derivatives via a one-pot, four-component reaction. *Res. Chem. Interm.* **2018**, *44*, 739–747. [[CrossRef](#)]
141. Ataee-Kachouei, T.; Nasr-Esfahani, M.; Mohammadpoor-Baltork, I.; Mirkhani, V.; Moghadam, M.; Tangestaninejad, S.; Kia, R. Facile and Green One-Pot Synthesis of Fluorophore Chromeno[4,3-*b*]quinolin-6-one Derivatives Catalyzed by Halloysite Nanoclay under Solvent-free Conditions. *ChemistrySelect* **2019**, *4*, 2301–2306. [[CrossRef](#)]
142. Zeynizadeh, B.; Rahmani, S. Sulfonyl-bridged (copper-immobilized nickel ferrite) with activated montmorillonite, [(NiFe<sub>2</sub>O<sub>4</sub>@Cu)SO<sub>2</sub>(MMT)]: A new class of magnetically separable clay nanocomposite systems towards Hantzsch synthesis of coumarin-based 1,4-dihydropyridines. *RSC Adv.* **2019**, *9*, 8002–8015. [[CrossRef](#)]
143. Zeynizadeh, B.; Rahmani, S.; Eghbali, E. Anchored sulfonic acid on silica-layered NiFe<sub>2</sub>O<sub>4</sub>: A magnetically reusable nanocatalyst for Hantzsch synthesis of 1,4-dihydropyridines. *Polyhedron* **2019**, *168*, 57–66. [[CrossRef](#)]
144. Singha, R.; Islam, A.; Ghosh, P. One-pot three-component tandem annulation of 4-hydroxycoumarine with aldehyde and aromatic amines using graphene oxide as an efficient catalyst. *Sci. Rep.* **2021**, *11*, 19891. [[CrossRef](#)]
145. Jamshaid, S.; Mohandoss, S.; Lee, Y.R. Indium(III)-catalyzed solvent-free multicomponent [2 + 2 + 1 + 1]-annulation to polycyclic functionalized fused pyridines as potential optical chemosensors. *Green Chem.* **2021**, *23*, 5113–5119. [[CrossRef](#)]
146. Pave, G.; Ghalard, P.; Viaud-Massuard, M.-C.; Troin, Y.; Guillaumet, G. New efficient synthesis of pyrido [2, 3-*c*] and pyrido [3, 2-*c*] coumarin derivatives. *Synlett* **2003**, *7*, 987–990. [[CrossRef](#)]
147. Zecher, W.; Krohnke, F. Eine neue Synthese substituierter Pyridine, I. Grundzüge der Synthese. *Chem. Ber.* **1961**, *94*, 690–697. [[CrossRef](#)]
148. Krohnke, F.; Zecher, W.; Kurtze, J.; Drechsler, D.; Pfléghar, K.; Schnalke, K.E.; Weis, W. Syntheses Using the Michael Addition of Pyridinium Salts. *Angew. Chem. Internat. Edit.* **1962**, *1*, 626–632. [[CrossRef](#)]
149. Krohnke, F. The Specific Synthesis of Pyridines and Oligopyridines. *Synthesis* **1976**, *1976*, 1–24. [[CrossRef](#)]
150. Pandya, S.; Pandya, U.R.; Hirani, B.R.; Brahmhatt, D.I. One pot synthesis of diarylpyrido[3,2-*c*]coumarins. *J. Heterocycl. Chem.* **2006**, *43*, 795–798. [[CrossRef](#)]
151. Brahmhatt, D.I.; Patel, N.H.; Patel, A.K.; Patel, M.A.; Patel, V.G. Synthesis and antimicrobial activity of some 7-aryl-5,6-dihydro-14-aza[1]benzopyrano[3,4-*b*]phenanthren-8*H*-ones. *J. Heterocycl. Chem.* **2011**, *48*, 840–844. [[CrossRef](#)]
152. Sharma, D.; Sharma, N.; Patel, N.H.; Brahmhatt, D.I.; Gupta, V.K. Crystal Structure of 7-Phenyl-5, 6-Dihydro-14-Aza-[1]benzopyrano [3, 4-*b*] phenanthren-8*H*-One. *Crystallogr. Rep.* **2021**, *66*, 1223–1226. [[CrossRef](#)]
153. Rao, Y.; Liu, M.; Wu, L.; Yin, G. Catalyst-free one-pot domino reactions for selective synthesis of functionalized 2,8-oxazabicyclo[3.3.1]-nonanes and 5*H*-indeno[1,2-*b*]pyridin-5-ones. *RSC Adv.* **2014**, *4*, 64551–64558. [[CrossRef](#)]
154. Giri, R.R.; Brahmhatt, D.I. A Convenient Synthesis of Bipyrido-Fused Coumarins and Their Biological Evaluation. *J. Heterocycl. Chem.* **2019**, *56*, 2630–2636. [[CrossRef](#)]

155. Al-Omran, F.; Elassar, A.-Z.A.; ElKhair, A.A. Synthesis and biological effects of new derivatives of azines incorporating coumarin. *J. Heterocycl. Chem.* **2003**, *40*, 249–254. [[CrossRef](#)]
156. Ismail, M.M.F.; Noaman, E. Novel Pirfenidone Analogs as Antifibrotic Agents: Synthesis and Antifibrotic Evaluation of 2-Pyridones and Fused Pyridones. *Med. Chem. Res.* **2005**, *14*, 382–403. [[CrossRef](#)]
157. Khan, I.A.; Kulkarni, M.V.; Gopal, M.; Shahabuddin, M.S.; Sun, C.-M. Synthesis and biological evaluation of novel angularly fused polycyclic coumarins. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3584–3587. [[CrossRef](#)] [[PubMed](#)]
158. Glasnov, T.N.; Ivanov, I.C. A Convenient Approach to the Synthesis of Dialkyl 5-Oxo-1,2-dihydro-5H-chromeno [4,3-*b*]pyridine-2,3-dicarboxylates. *Synth. Commun.* **2008**, *38*, 1579–1588. [[CrossRef](#)]
159. Majumdar, K.C.; Debnath, P.; Chottopadhyay, S.K. Aryl Radical Cyclization: Regioselective Synthesis of 6a,7,8,12*b*-Tetrahydro-6*H*-chromeno[3,4-*c*]quinolin-6-one. *Synth. Commun.* **2008**, *38*, 1768–1777. [[CrossRef](#)]
160. Jadhav, V.B.; Nayak, S.K.; Guru Row, T.N.; Kulkarni, M.V. Synthesis, structure and DNA cleavage studies of coumarin analogues of tetrahydroisoquinoline and protoberberine alkaloids. *Eur. J. Med. Chem.* **2010**, *45*, 3575–3580. [[CrossRef](#)] [[PubMed](#)]
161. El-Said, M.S.; El-Gazzar, M.G.; Al-Dosari, M.S.; Ghorab, M.M. Synthesis, anticancer activity and radiosensitizing evaluation of some new 2-pyridone derivatives. *Arzneimittelforschung* **2012**, *62*, 149–156. [[CrossRef](#)] [[PubMed](#)]
162. Lin, W.; Hu, X.; Song, S.; Cai, Q.; Wang, Y.; Shi, D. Microwave-assisted synthesis of novel hetero[5]helicene-like molecules and coumarin derivatives. *Org. Biomol. Chem.* **2017**, *15*, 7909–7916. [[CrossRef](#)]
163. Borah, P. Synthesis of some novel annulated coumarins by exploring intramolecular Hetero Diels-Alder reaction strategy. *J. Appl. Fundam. Sci.* **2018**, *4*, 81–83.
164. Li, J.; Yang, Q.; Chen, G. Synthesis method of (3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-6-yl)methanol. Patent No. CN 110283180 (A), 27 September 2019.
165. Pandya, M.K.; Parekh, T.H.; Chhasatia, M.R.; Vala, N.D. Synthesis and characterization of some novel coumarin based various 2-aryl-pyrido [3,2-*c*] coumarins. *J. Drug Deliv. Therap.* **2020**, *10*, 158–163. [[CrossRef](#)]
166. Heber, D.; Ivanov, I.C.; Karagiosov, S.K. The vilsmeier reaction in the synthesis of 3-substituted [1]benzopyrano[4,3-*b*]pyridin-5-ones. An unusual pyridine ring closure. *J. Heterocycl. Chem.* **1995**, *32*, 505–509. [[CrossRef](#)]
167. Wu, J.; Wang, X. Facile synthesis of chromeno[4,3-*b*]quinolin-6-ones from unexpected reactions of aryl isocyanides with 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde. *Org. Biomol. Chem.* **2006**, *4*, 1348–1351. [[CrossRef](#)]
168. Prasad, J.V.; Reddy, J.S.; Kumar, N.R.; Solomon, K.A.; Gopikrishna, G. An efficient ultrasound promoted catalyst-free protocol for the synthesis of chromeno[4,3-*b*]quinolin-6-ones. *J. Chem. Sci.* **2011**, *123*, 673–679. [[CrossRef](#)]
169. Borah, P.; Naidu, P.S.; Bhuyan, P.J. Synthesis of some tetrazole fused pyrido[2,3-*c*]coumarin derivatives from a one-pot three-component reaction via intramolecular 1,3-dipolar cycloaddition reaction of azide to nitriles. *Tetrahedron Lett.* **2012**, *53*, 5034–5037. [[CrossRef](#)]
170. Halawa, A.H.; El-Gilil, S.M.A.; Bedair, A.H.; Eliwa, E.M.; Frese, M.; Sewald, N.; Shaaban, M.; El-Agrody, A.M. Synthesis of diverse amide linked bis-indoles and indole derivatives bearing coumarin-based moiety: Cytotoxicity and molecular docking investigations. *Med. Chem. Res.* **2018**, *27*, 796–806. [[CrossRef](#)]
171. Kolita, S.; Bhuyan, P.J. An Efficient Synthesis of Pyrido[3,2-*c*]coumarins under Microwave Irradiation in Solvent-Free Conditions. *ChemistrySelect* **2018**, *3*, 1411–1414. [[CrossRef](#)]
172. Iarohsenko, V.O.; Erben, F.; Mrktchyan, S.; Hakobyan, A.; Vilches-Herrera, M.; Dudkin, S.; Bunescu, A.; Villiger, A.; Sosnovskikh, V.Y.; Lange, P. 4-Chloro-3-(trifluoroacetyl)- and 4-chloro-3-(methoxalyl)coumarins as novel and efficient building blocks for the regioselective synthesis of 3,4-fused coumarins. *Tetrahedron* **2011**, *67*, 7946–7955. [[CrossRef](#)]
173. Becalli, E.M.; Contini, A.; Trimarco, P. New synthetic approach to [1]benzopyrano[4,3-*b*]pyridin-5-one derivatives. *Tetrahedron Lett.* **2004**, *45*, 3447–3449. [[CrossRef](#)]
174. Khan, H.J.; Petrow, V.; Rewald, E.L.; Sturgeon, B. 452. Some derivatives of 1:3-dimethyl-2-azafluorenone. *J. Chem. Soc.* **1949**, *452*, 2128–2134. [[CrossRef](#)]
175. Courts, A.; Petrow, V. 69. New syntheses of heterocyclic compounds. Part XV. 9: 10-Dihydro-10-keto-1:3-dimethyl-2-aza-9-oxaphenanthrenes. *J. Chem. Soc.* **1952**, *200*, 334–337. [[CrossRef](#)]
176. Pars, H.G.; Grancelli, F.E.; Keller, J.K.; Razdan, R.K. Physiologically Active Nitrogen Analogs of Tetrahydrocannabinols. Tetrahydrobenzopyrano[3,4-*d*]pyridines. *J. Am. Chem. Soc.* **1966**, *88*, 3664–3665. [[CrossRef](#)]
177. Mandal, T.K.; Soldatenkov, A.T.; Ageev, E.A.; Stashenko, E.V.; Denisov, E.N.; Andreeva, E.I.; Prostakov, N.S. Synthesis and fungicidal activity of substituted tetrahydro-[3,4-*c*]- and benzo[*h*]tetrahydropyrido[3,4-*c*]coumarins. *Pharm. Chem. J.* **1990**, *24*, 145–149. [[CrossRef](#)]
178. Abramovitch, R.A.; Inbasekaran, M.N.; Kato, S.; Radzikowska, T.A.; Tomasik, P. Base-catalyzed rearrangement of *N*-(aryloxy)pyridinium salts. Effect of a 3-substituent in the pyridine ring upon orientation. Synthesis of novel tricyclic rings. *J. Org. Chem.* **1983**, *48*, 690–695. [[CrossRef](#)]
179. Galariniotou, E.; Fragos, V.; Makri, A.; Litinas, K.E.; Nicolaides, D.N. Synthesis of novel pyridocoumarins and benzo-fused 6-azacoumarins. *Tetrahedron* **2007**, *63*, 8298–8304. [[CrossRef](#)]
180. Yavari, I.; Adib, M.; Hojabri, L. Vinyltriphenylphosphonium salt mediated synthesis of 1,4-benzoxazine and coumarin derivatives. *Tetrahedron* **2002**, *58*, 6895–6899. [[CrossRef](#)]
181. El-Saghier, A.M.; Mo, E.-J.I.; Al-Afaleq, E.-J.I. Synthetic Reactions of Coumarin-3-(4-Aminosulfonyl)-Carbanilide Derivatives With Reactive Methylene Compounds. *Phosphorus Sulfur Silicon* **1998**, *139*, 67–75. [[CrossRef](#)]

182. Sviripa, V.M.; Fiandalo, M.V.; Begley, K.L.; Wyrebek, P.; Kril, L.M.; Balia, A.G.; Parkin, S.R.; Subramanian, V.; Chen, X.; Williams, A.H.; et al. Pictet–Spengler condensations using 4-(2-aminoethyl)coumarins. *New J. Chem.* **2020**, *44*, 13415–13429. [[CrossRef](#)] [[PubMed](#)]
183. Sakurai, A.; Midorikawa, H. Condensation of active methylene compounds with hydroxybenzaldehydes by ammonium acetate. *J. Org. Chem.* **1969**, *34*, 3612–3615. [[CrossRef](#)]
184. Sakurai, A.; Midorikawa, H.; Hashimoto, Y. The cyclization of ethyl cyanoacetate and salicylaldehyde or 3-methoxysalicylaldehyde with ketones by means of ammonium acetate. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2925–2933. [[CrossRef](#)]
185. Sakurai, A.; Midorikawa, H.; Hashimoto, Y. Substituted Benzopyranopyridine and Pyrimidine Ring Syntheses by the Ternary Condensation of Ethyl Cyanoacetate, Salicylaldehyde, and Certain Aldehydes in the presence of ammonium acetate. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1677–1682. [[CrossRef](#)]
186. Sakurai, A.; Motomura, Y.; Midorikawa, H. Substituted benzopyranopyridopyrimidine ring syntheses by the ternary condensation of malononitrile, salicylaldehyde, and aromatic ketones in the presence of ammonium acetate. *J. Org. Chem.* **1972**, *37*, 1523–1526. [[CrossRef](#)]
187. O’Callaghan, M. Synthesis of Dialkyl 2-(2-Hydroxyphenyl)-4,6-dimethyl-1,2-dihydropyridine-3,5-dicarboxylates and Alkyl 2,4-Dimethyl-5-oxo-5H-[1]benzopyrano[4,3-*b*]-pyridine-3-carboxylates. *Synthesis* **1987**, *1987*, 499–503. [[CrossRef](#)]
188. Navarrete-Encina, P.; Salazar, R.; Vega-Retter, C.; Perez, K.; Squella, J.A.; Nunez-Vergara, L.J. On the one pot syntheses of chromeno [4, 3-*b*] pyridine-3-carboxylate and chromeno [3, 4-*c*] pyridine-3-carboxylate and dihydropyridines. *J. Braz. Chem. Soc.* **2010**, *21*, 413–418. [[CrossRef](#)]
189. Frolova, L.V.; Malik, I.; Uglinskii, P.Y.; Rogelj, S.; Kornienko, A.; Magedov, I.V. Multicomponent synthesis of 2,3-dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine-1,6-diones: A novel heterocyclic scaffold with antibacterial activity. *Tetrahedron Lett.* **2011**, *52*, 6643–6645. [[CrossRef](#)] [[PubMed](#)]
190. Gomha, S.M.; Riyadh, S.M. Multicomponent Synthesis of Novel Penta-Heterocyclic Ring Systems Incorporating a Benzopyranopyridine Scaffold. *Synthesis* **2014**, *46*, 258–262. [[CrossRef](#)]
191. Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. Synthesis of Aza Polycyclic Compounds Derived from Pyrrolidine, Indolizidine, and Indole via Intramolecular Diels–Alder Cycloadditions of Neutral 2-Azadienes. *J. Org. Chem.* **2002**, *67*, 1941–1946. [[CrossRef](#)] [[PubMed](#)]
192. Keskin, S.; Balci, M. Intramolecular Heterocyclization of *O*-Propargylated Aromatic Hydroxyaldehydes as an Expedient Route to Substituted Chromenopyridines under Metal-Free Conditions. *Org. Lett.* **2015**, *17*, 964–967. [[CrossRef](#)] [[PubMed](#)]