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Diverse synthesis of pyrrolo/indolo[3,2-*c*]coumarins as isolamellarin-A scaffolds: a brief update

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This paper reviews a vast body of literature on diverse synthetic methodologies, biological, and fluorescence activities of pyrrolo/indolo[3,2-c]coumarin derivatives published during last 20 years. Synthesized pyrrolo/indolo[3,2-c]coumarins have been reported in the literature by the construction of either pyrrole, indole, or coumarin ring *via* classical reaction protocols including metal-catalyzed reactions, and green reaction protocols starting from suitable precursors.

Introduction

The chemistry of coumarin derivatives (natural, as well as synthetic) has occupied a significant position in the field of synthetic and medicinal chemistry due to various biological activities[1–6] that include anti-microbial,[7–9] anti-depressant,[10] anti-oxidant,[11–13] anti-leishmanial,[14] anti-inflammatory,[15] anti-coagulant,[16] and anti-cancer[17] reported over the last 50–60 years. On the other hand, pyrrole and indole derivatives are also important for their robust biological interests.[18–20]

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Prasanta Patra

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When different substituted pyrrole and indole rings are fused to the coumarin ring, separately, a synergistic effect of both rings may be achieved in target systems. Thus, the synthesis, biological evaluation and fluorescence studies of pyrrole and indole-fused coumarins have immense interest from synthetic organic as well as pharmaceutical chemists. Pyrrole-fused coumarin derivatives such as lamellarins[21–23] isolated from diverse marine organisms, such as molluscs, ascidians, and sponges, are well known for their antitumor,[24,25] reversal of multidrug resistance,[26,27] and anti-HIV,[28,29] activities. Many synthetic lamellarins related to pyrrole-fused coumarin derivatives display diverse biological activities, including multidrug-resistant (MDR) reversal,[30,31] *Topoisomerases* I inhibitory,[32] DYRK1A inhibitory,[33–35] anti-retroviral activities,[36] and act as neuroimaging[37] and anti-cancer agents[38–43] (Fig. 1). On the other hand, isolamellarins, *i.e.*, pyrrolo/indolo[3,2-*c*]coumarin derivatives are also known for their excellent anti-cancer activity[44] and are also efficient against tumour angiogenesis,[45] which is a key step for spreading cancer cells. These compounds exhibit antitumor activity, *in vitro* cytotoxicity against HepG-2 and MCF-7,[46] and excellent antioxidant and inhibitory activity of lipoxygenase.[47] In addition, these compounds are used as angiogenesis inhibitors,[48] benzodiazepine receptor ligand[49] and act as outstanding fluorescent probes.[50–52] Moreover, these synthesized compounds have potential applications in asymmetric organic synthesis. All these observations establish the importance of pyrrolo/indolo[3,2-*c*]coumarins. Diverse synthetic methodologies with biological activities of different types pyrrole or indole fused coumarins (Fig. 1) have been reported in the literature by various groups of scientists over two to three decades. However, only three groups[21,53,54] of scientists have elaborately explained the synthesis and biological properties of marine alkaloid lamellarins, *i.e.*, pyrrolo/indolo[2,3-*c*]coumarin derivatives along with other 3,4-heterocycle-fused coumarins in their reports (reviews and book) but no review has been reported yet on pyrrolo/indolo [3,2-*c*]coumarins despite their various stupendous biological and fluorescence activities. Here, we highlight a different synthetic approach and their applications in organic synthesis by taking the help of classical as well as modern methodology using different transition metal catalysis. To the best of our knowledge, this is the first of its kind review on pyrrolo/indolo[3,2-*c*]coumarins.

Gandhi Kumar Kar

Prof. Gandhi Kumar Kar was born in district Bankura, of West Bengal, India in 1958. He did his MSc (Chemistry/1980) and PhD (Synthetic Organic Chemistry/1986) under the supervision of Prof. B. G. Chatterjee and Prof. J. K. Ray from I. I. T. Kharagpur, WB, India. He is currently working as a Professor of Chemistry at the Department of Chemistry, Presidency University. His research interest includes synthesis of biologically important small molecules like β-lactams and γ-lactams, furo-natural products polycyclic and aza-arenes as well as their oxidative metabolites as suspected carcinogens. Prof. Kar has almost 57 publications in reputed national and international journals.

Different techniques for the synthesis of pyrrolo/indolo[3,2-*c*]coumarin derivatives

Pyrrolo[2,3-*c*]coumarins are the main cores of the fused pentacyclic lamellarins and pyrrolo/indolo[3,2-*c*]coumarins are the isomers containing substituted pyrrole or indole, and coumarin moiety fused together. The core structure suggests that these derivatives could be synthesized either by the creation of pyrrole/indole, coumarin, or both rings in any step of the synthesis. In fact, most of the syntheses reported in the literature mainly involved the construction of pyrrole or indole ring starting from 4-substituted coumarin precursors following traditional methods such as Knorr, Paal–Knorr, and Hantzsch reaction protocols as well as transition metal-catalyzed and microwave-assisted green synthetic protocols. While surveying the literature, we found only limited reports on the synthesis and biological evaluation of pyrrolo/indolo[3,2-*c*]coumarin derivatives prior to 2010. However, a large number of syntheses of such derivatives have been reported by various groups of scientists after 2010, indicating the gradual increase in the interest in the synthesis and biological evaluation of such compounds. Our review work is classified into five sections according to the creation of the different rings and starting materials. These are: (i) from α-aminocarbonyl compounds and activated ketones *via* Knorr synthesis, (ii) from β-ketoesters with ammonia and α-haloketones or ketones/aldehydes having an electrophilic centre in the α-position under heating conditions *via* Hantzch synthesis, (iii) from Michael acceptors and by rearrangements, (iv) using nitrene intermediates and lastly (v) using transition metal catalysis.

Thomas Kappe and his co-workers[55] were pioneer chemists for the synthesis of pyrrolo/indolo[3,2-*c*]coumarin derivatives. In 1984, they synthesized these compounds from 3-phenyl-4-amino coumarin derivatives in the presence of palladium-charcoal as a catalyst and diphenyl ether as a solvent at 250 °C (Scheme 1). They reported that only two entries and *N*-phenyl indolocoumarin derivative were obtained in excellent yield, but in the case of *N*-unsubstituted indole derivative, the yield was very low. Later on, many other scientists modified their different methods starting from suitable precursors.

From α-aminocarbonyl compounds and activated ketones *via* Knorr synthesis

The Knorr pyrrole synthesis has been widely used to construct substituted pyrroles that engage the reaction of an α-amino-ketone and a compound containing an active methylene group (Scheme 2). The protocol of the reactions involves the formation of an imine between amine and ketone. The substituted pyrrole is formed by intramolecular cyclization of imine by the elimination of water and is followed by isomerisation.

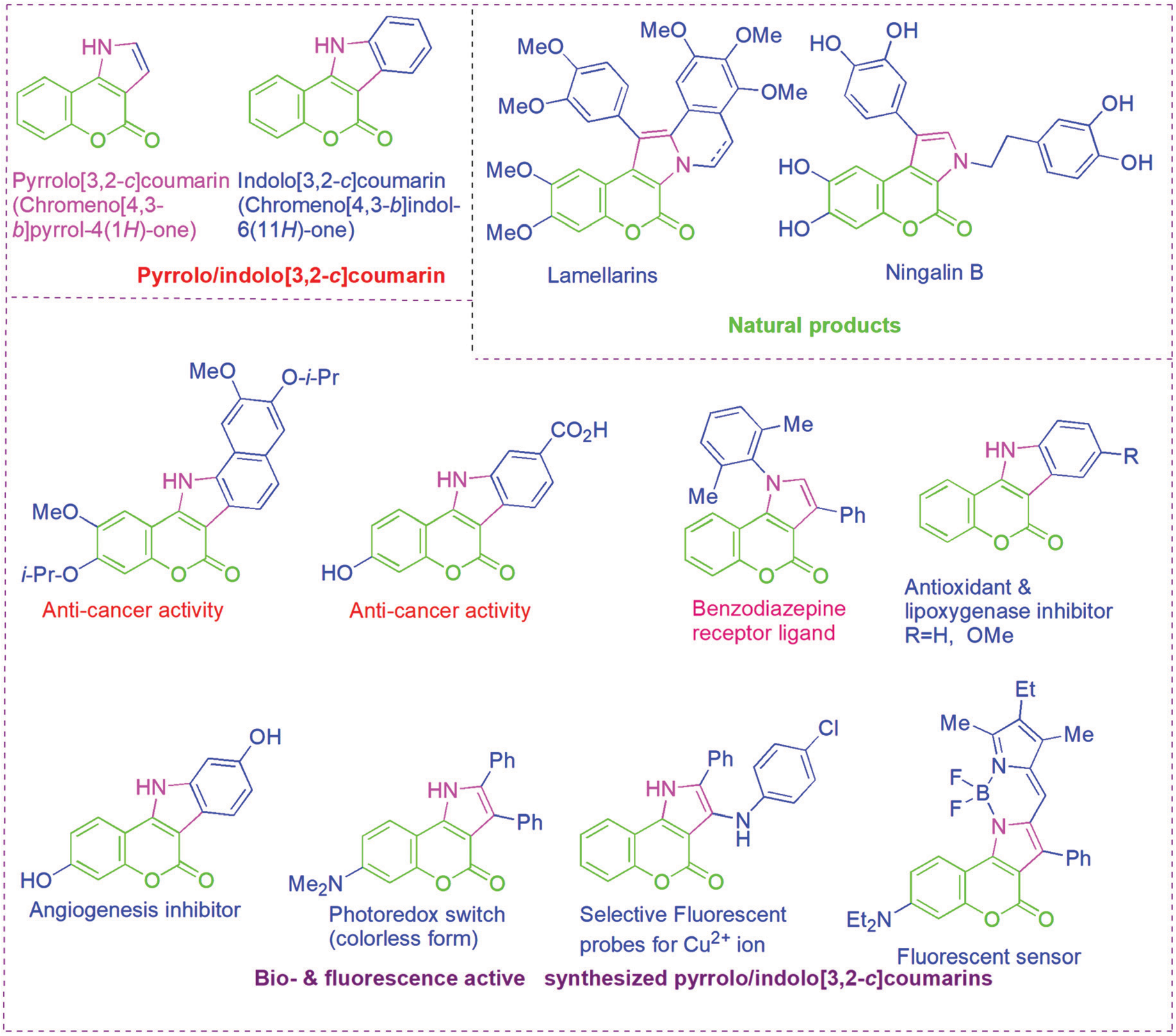
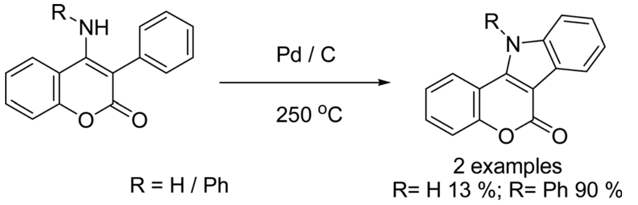


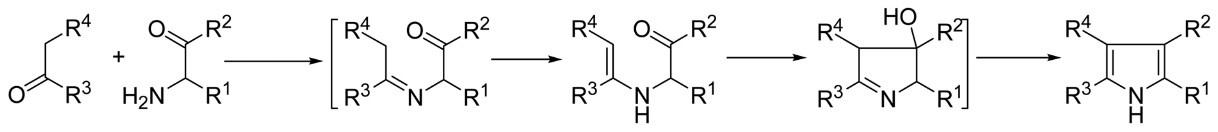
Fig. 1 Representative pyrrolo/indolocoumarins.



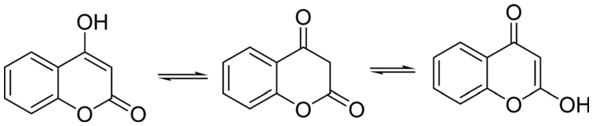
Scheme 1 First synthesis of chromeno[4,3-b]indol-6(11H)-ones using palladium–charcoal as a catalyst.

4-Hydroxycoumarin can exist in three tautomeric keto–enol forms (Scheme 3). These three possible prototropic transformations have been intensively examined through various chemical reactivities, and spectral, thermochemical and computational methods. Thus 4-hydroxy or 4-substituted coumarins have been used as a precursor in Knorr pyrrole synthesis to construct a condensed pyrrole ring upon a reaction with α-amino-ketones.

Alberola *et al.*[56] reported the synthesis of pyrrolo[3,2-*c*] coumarin from 4-*N*-(acylmethyl)-aminocoumarins or its ketal analogue in the presence of an acid or a base (Scheme 4). The synthesis of 4-*N*-(acylmethyl)-aminocoumarins or its ketal analogue was achieved by the reaction between 4-chloro/amino/hydroxycoumarin and α-amino ketones or its chlorohydrates or ketal derivatives in the presence of triethylamine in ethanol under



Scheme 2 Knorr synthesis of substituted pyrrole derivatives.



Scheme 3 Different keto-enol forms of 4-hydroxy coumarin.

reflux. These intermediates on $TiCl_4$ or acid/base-catalyzed cyclization furnished the functionalized pyrrolocoumarins in excellent yields (Scheme 4).

Ortega and his co-workers[57] reported the synthesis of a similar type of pyrrolo[3,2-*c*]coumarins from Weinreb amides (Scheme 5). Weinreb amides were prepared *via* two different pathways from 4-chlorocoumarin. The reaction of Weinreb-α-amino acid with *N*,*O*-dimethylhydroxylamine in the presence of DCC or BOP [((benzotriazol-1-yloxyl)tris(dimethylamino)-phosphonium hexafluorophosphate)] yielded Weinreb amide. The authors reported that BOP was used instead of DCC when the R^2 alkyl group in Weinreb-α-amino acid was bulky (*e.g.*, R^2 = ^{i}Pr). It was reported that the percentage of yields of Weinreb amides *via* path 1 is better than that in path 2 as the use of DCC leads to the formation of the DCU derivative of Weirneb amide as a side product (Scheme 5). Finally, the desired pyrrolocoumarin derivatives were obtained by the reaction of the Weinreb amides with organometallic reagent (*e.g.*, RLi or RMgBr) followed by acid, base or silica gel catalyzed cyclization of the resulting α-aminoketone [4-(*N*-alkyl-*N*-(2-oxoalky)amino)-coumarin derivatives] (Scheme 5).

Angel Alberol and coworkers[58] reported the substrate-dependent synthesis of different types of pyrrolo[3,2-*c*]coumarins from 4-chloro-3-formylcoumarin and different reactive masked α-amino carbonyl derivatives. In presence of triethylamine 4-chloro-3-formylcoumarin and various α-amino carbonyl acetal/ketal derivatives, the reaction resulted in the formation of the 4-(*N*-(2,2-dialkoxyalky)-*N*-alkyamino)-coumarin derivatives *via* the addition–elimination process. Acid-mediated cyclization ($AcOH/H_2O$) of these compounds formed two types of products in a different ratio depending on the nature of masked carbonyl functionality of α-amino carbonyl derivatives (Scheme 6). The formation of these two types of products has successfully been explained with proper mechanisms. These synthesized compounds are widely used as precursors for the synthesis (on treatment with organometallic compounds) of bio-active highly substituted pyrrole[59] as well as pyrano pyrrole derivatives (Fig. 2).

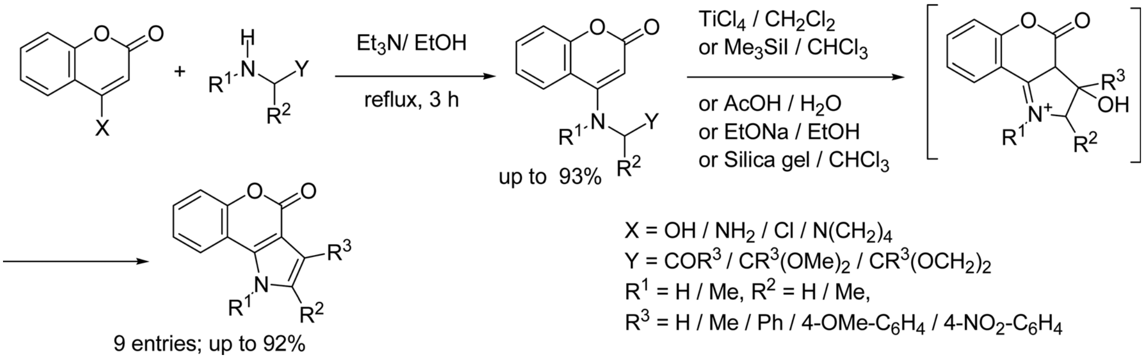
In another approach, Yang *et al.*[60] used a similar route to synthesize various trisubstituted pyrrolo[3,2-*c*]coumarins derivatives as possible potential benzodiazepine-like receptor ligands in moderate yields starting from 4-hydroxycoumarin over six steps (Scheme 7). Base-promoted intramolecular cyclization of enamine, followed by dehydration is the key step for the synthesis of the target compound. In all cases, the products were isolated in moderate yields.

Yang and coworkers[61] synthesized and studied the photochemical and redox-switching properties of pyrrolo[3,2-*c*] coumarins. Microwave-promoted coupling of 4-substituted 3-acylcoumarins and 1-amino-1-phenylpropan-2-one hydrochloride in the presence of diisopropylethylamine (DIPEA) as a base in dichloroethane (DCE) afforded the 4-amino substituted coumarin derivatives. These derivatives on refluxing with catalytic TsOH in methanol subsequently furnished the target pyrrolocoumarin in 95–98% yields by intramolecular cyclization (Scheme 8).

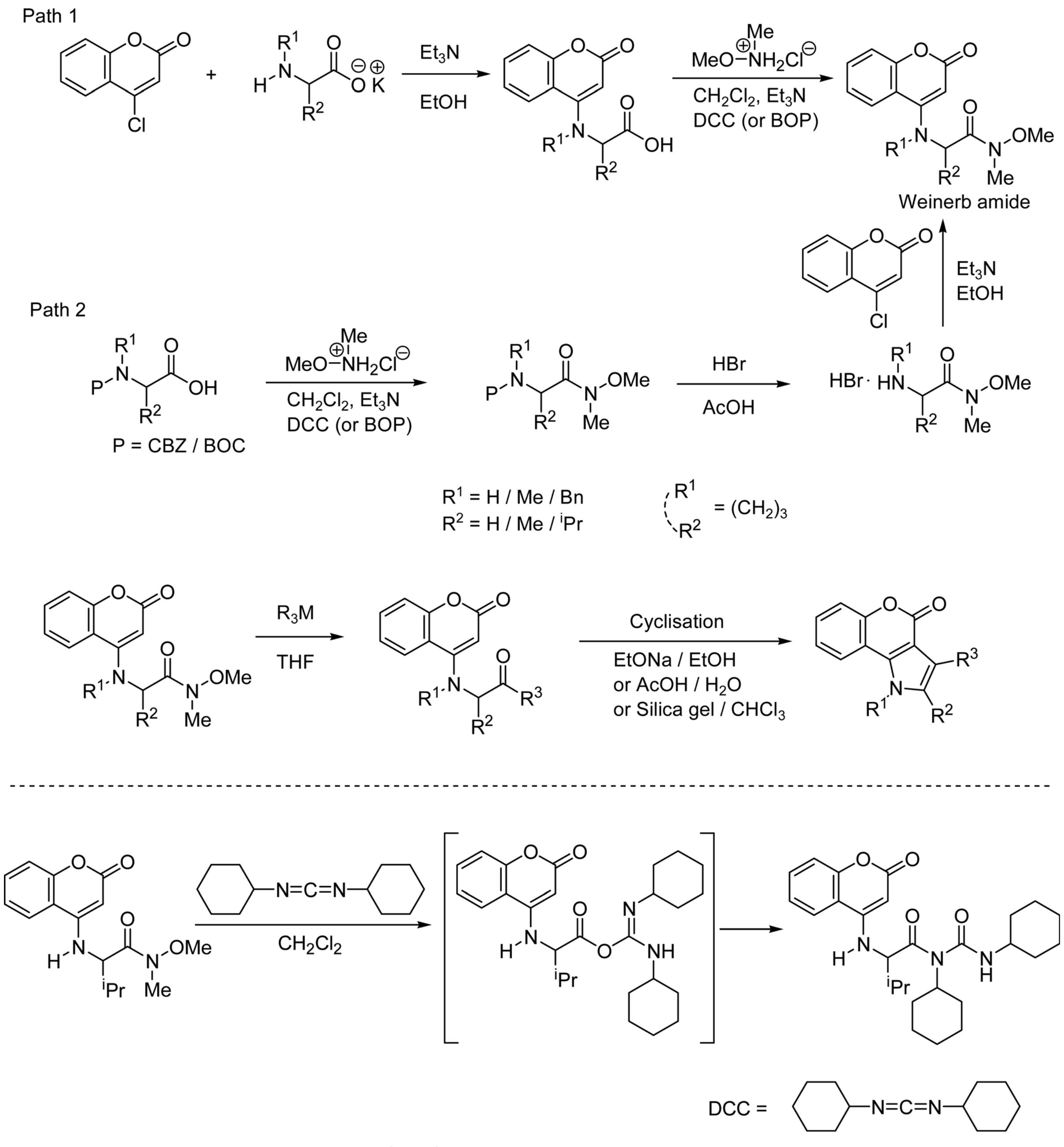
From β-ketoesters with ammonia and α-haloketones or ketones/aldehydes with an electrophilic centre in the α-position under heating conditions *via* Hantzch synthesis

The Hantzsch Pyrrole Synthesis is a well-known organic name reaction for the construction of substituted pyrrole ring from β-ketoesters, ammonia and α-haloketones or ketones/aldehydes with an electrophilic centre in the α-position under heating conditions (Scheme 9). Recently, this well-known reaction has been modified by reagents, catalysts, use of microwave and varying the starting material mainly in α-haloketones to synthesize pharmaceutically important more challenging polycyclic pyrrole derivatives.

Using this protocol, Das *et al.*[62] developed a one-pot multicomponent, reusable cheap tin oxide (SnO_2) quantum dot (QD) catalyzed the synthesis of pentacyclic dihydroxy pyrrolo[3,2-*c*] coumarins derivatives in an aqueous medium in excellent yield without traditional chromatographic separation (Scheme 10). The SnO_2 QD catalyst was prepared using a simple solvothermal method and characterized using X-ray diffraction and transmission electron spectroscopy techniques. Here the catalyst acts as a Lewis acid and activates the dicarbonyl



Scheme 4 Knorr synthesis of polyfunctionalized pyrrolo[3,2-c]coumarins from 4-substituted coumarin.

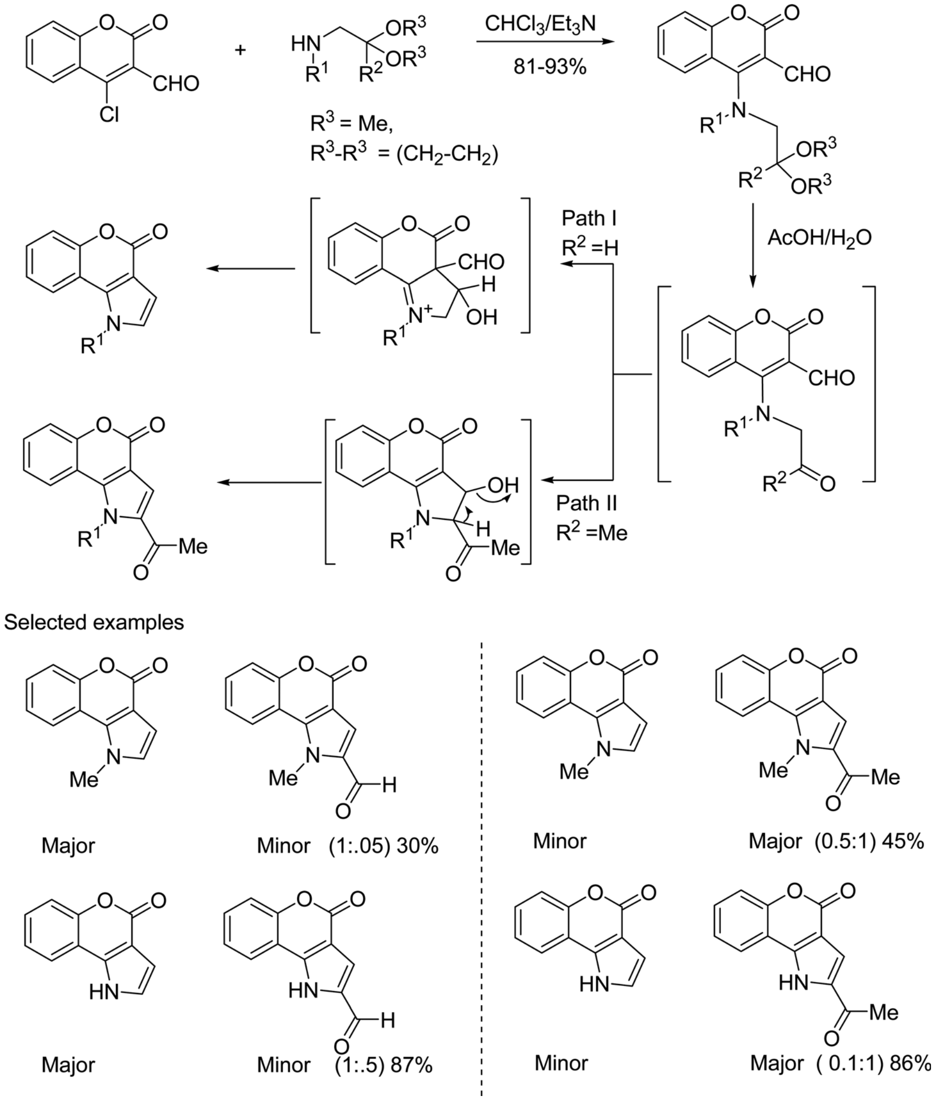


Scheme 5 Knorr synthesis of polyfunctionalized pyrrolo[3,2-*c*]coumarins from 4-chlorocoumarin.

compounds towards electrophilic addition and subsequent *N*-cyclization.

Chen *et al.*[63] reported a one-pot two-step synthesis of 3-alkoxy pyrrolo[3,2-*c*]coumarins, without the separation of intermediates, by the reaction of 4-aminocoumarin with arylglyoxal monohydrates and *p*-toluenesulfonates as an alkylating agent in moderate to good yields (Scheme 11). At first, 3-hydroxypyrrolo[3,2-*c*]coumarin intermediates were obtained from arylglyoxal monohydrates and 4-aminocoumarin by refluxing in AcOH. Then, the desired product was obtained on heating of the *in situ* formed title compounds with *p*-toluenesulfonates in the presence of DBU catalyst under refluxing toluene. The authors also used *N*-substituted 4-aminocoumarins instead of 4-aminocoumarins as reactants, the desired products 1,2,3-trisubstituted pyrrolo[3,2-*c*]coumarins were achieved in low yields due to steric hindrance.

Chen and coworkers[64] developed KHSO$_4$ promoted concise, efficient, one-pot high yielding synthetic approach for the synthesis of functionalized 2-aryl-3-arylamino pyrrolo[3,2-*c*]coumarins *via* the three-component reaction of 4-aminocoumarin, arylglyoxal monohydrates and aromatic amines in toluene under reflux conditions with short reaction time (Scheme 12). The proposed mechanism of the reaction goes through the formation of the imine intermediate *via* the condensation between amine and aryl glyoxal monohydrate, then the imine intermediate is immediately attacked by the Michael donor C-3



Scheme 6 Substrate-dependent Knorr synthesis of pyrrolo[3,2-c]coumarins from 4-chloro-3-formylcoumarin.

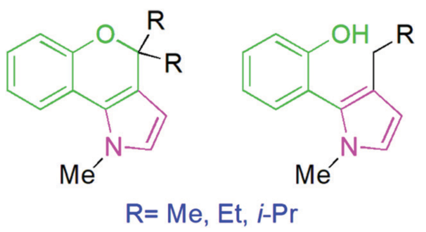


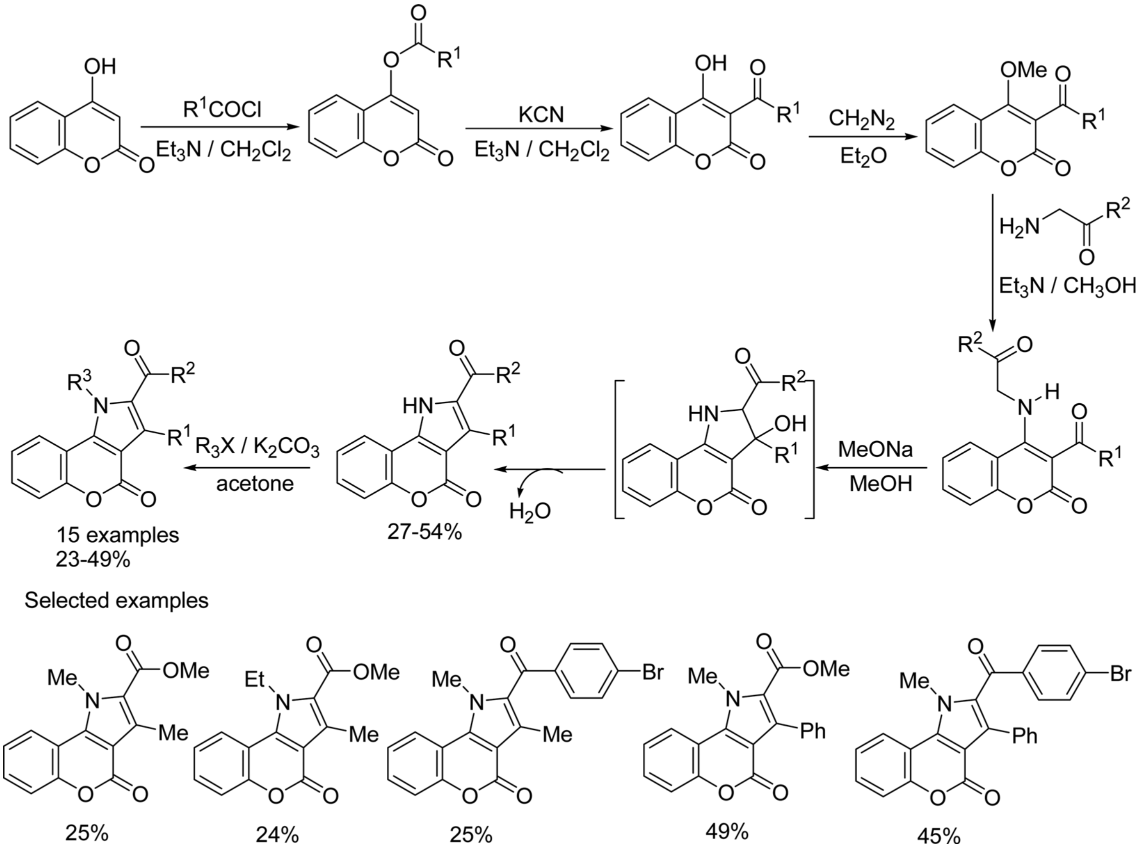
Fig. 2 Synthesis of pyrano and pyrrole derivatives from pyrrolo[3,2-c]coumarins.

centre of 4-amino coumarin to generate another intermediate having keto and amine functionality, which then instantaneously cyclizes intramolecularly by the removal of water to afford pyrrolo[3,2-*b*]coumarin derivatives.

In that next year, a similar kind of protocol was reported by Das and co-workers.[65] They reported reusable nanocrystalline $CuFe_2O_4$ catalyzed one-pot three-component synthesis of 2-aryl-3-arylamino pyrrolo[3,2-*c*]coumarins from glyoxal monohydrate along with aromatic or heteroaromatic amine and 4-aminocoumarin in aqueous medium at 70 °C in good to excellent yields (Scheme 13). Both Cu^{2+} and Fe^{3+} accelerated the reaction by activating the electrophilic addition as well as the cyclization process. The magnetic nanocrystalline catalyst $CuFe_2O_4$ was prepared by a simple and effective citric acid complex method and characterized using XRD, FT-IR, EDX and TEM, and HRTEM techniques.

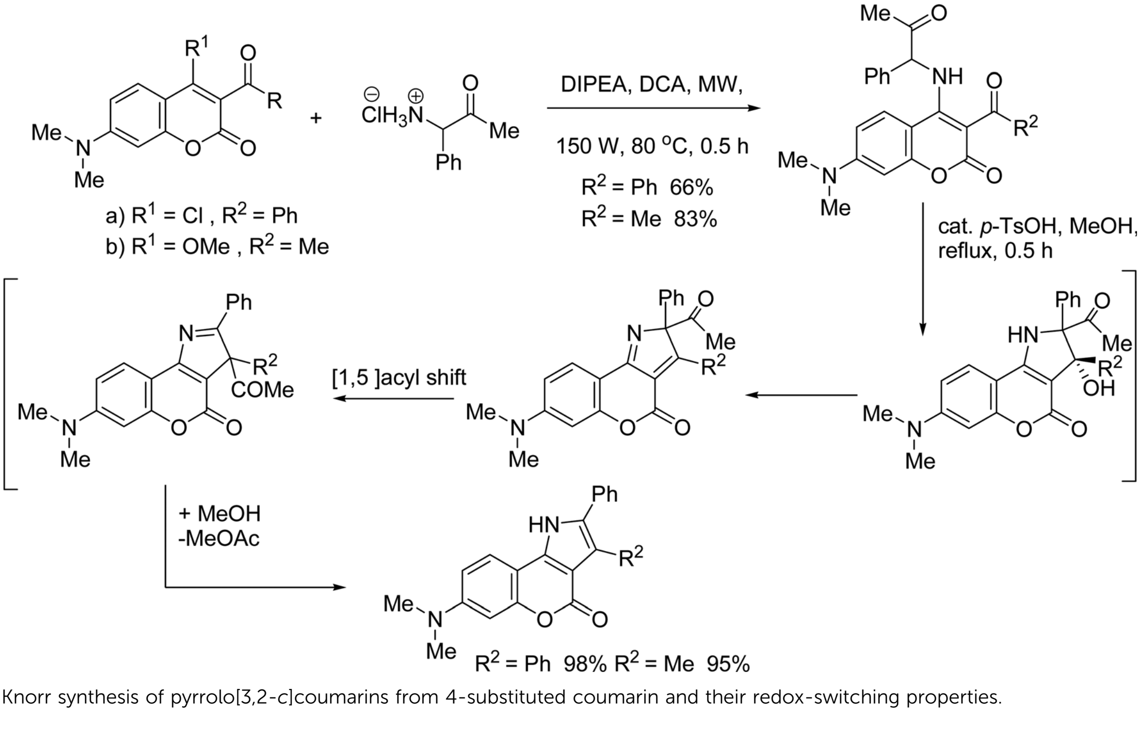
After that, Chen *et al.*[66] also followed a similar type of protocol for the synthesis of functionalized 3-indolylpyrrolo[3,2-*c*]coumarins in moderate to good yields *via* a one-pot, three-component reaction of 4-aminocoumarins, arylglyoxal monohydrates, and indole instead of amine in the presence of *p*-TSA in ethanol at 0 °C, within one hour (Scheme 14).

Pramanik and coworkers[67] developed environmentally benign, one-pot three-component domino condensation for the library synthesis of biologically significant pyrrolo[3,2-*c*] coumarins derivatives from 4-aminocoumrins, arylglyoxal

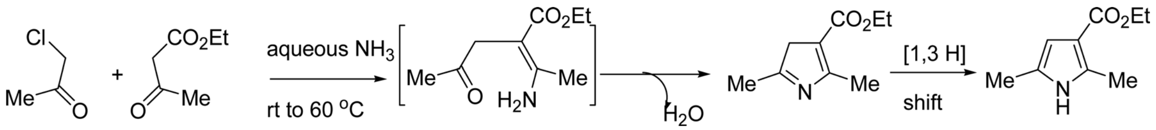


Scheme 7 Multi-step synthesis of pyrrolo[3,2-*c*]coumarins from 4-hydroxycoumarin.

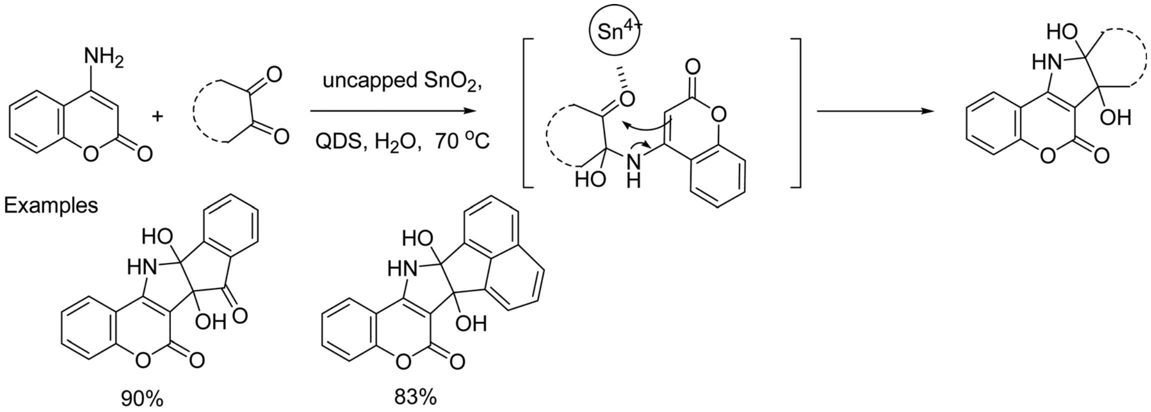
monohydrates and various nucleophilic substrates, such as arylamines, malononitrile, ethyl cyanoacetate and cyanoacetamide in the presence of magnetically separable $Fe_3O_4@SiO_2–SO_3H$ nanoparticles as a solid acid catalyst under solvent-free conditions



Scheme 8 Knorr synthesis of pyrrolo[3,2-c]coumarins from 4-substituted coumarin and their redox-switching properties.



Scheme 9 Hantzsch synthesis of substituted pyrrole.



Scheme 10 One-pot multi-component, reusable cheap tin oxide (SnO$_2$) quantum dot (QD) catalyzed modified Hantzsch synthesis of fused pentacyclic dihydroxy pyrrolo[3,2-*c*]coumarins in an aqueous medium.

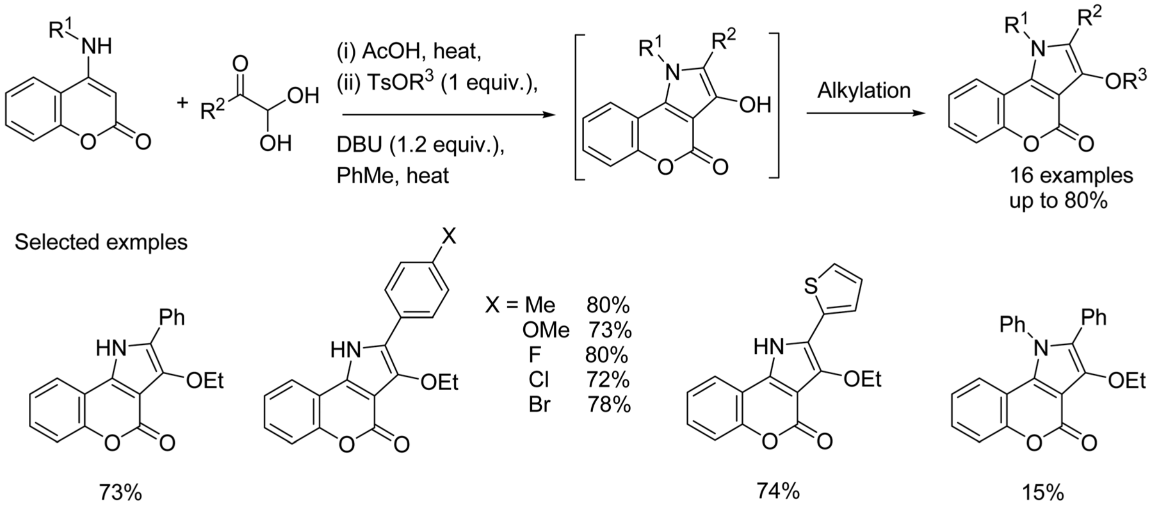
(Scheme 15). The protocol of the reactions involved a condensation reaction, Michael addition, *N*-cyclization, and 1,3 H shift.

On the other hand, when active methylene compounds, such as malononitrile, ethyl cyanoacetate and cyanoacetamide, instead of arylamines, were employed in the preceding reactions a new series of pyrrolocoumarin derivatives substituted with the –CH(CN)Y group (where Y = CN/CO$_2$Et/CONH$_2$) were produced with satisfactory yields (Scheme 16).

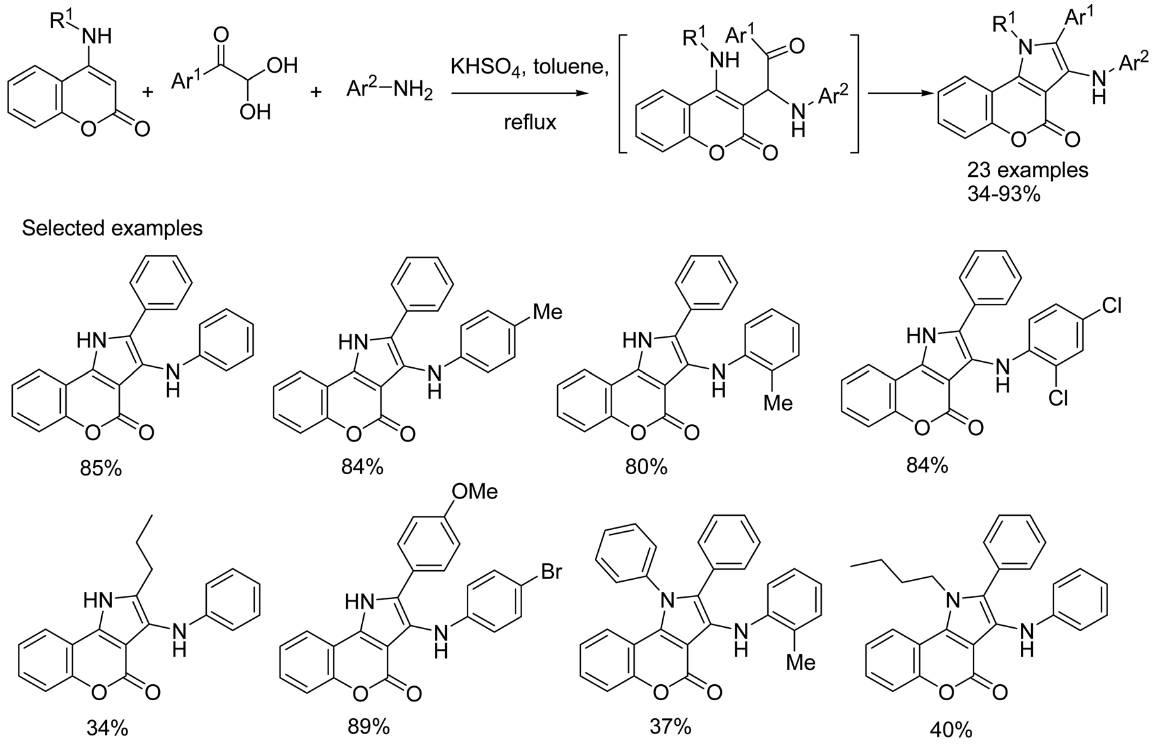
Furthermore, 3-hydroxypyrrolo[3,2-*c*]coumarins were obtained in 73–80% yield when 4-aminocoumrins were treated with arylglyoxal monohydrates in the absence of any nucleophilic substrates, such as arylamines, malononitrile, ethyl cyanoacetate, or cyanoacetamide under similar reaction conditions (Scheme 17).

The synthesized pyrrolo[3,2-*c*]coumarin derivatives have further been converted to biologically important indolo[3,2-*c*] coumarin derivatives as a possible anticancer agent, antitumor angiogenesis and estrogenic agent in good yields within 15 minutes in the presence of diphenyl ether as a solvent without using any catalyst through intramolecular thermal cyclization and subsequent aromatization (Scheme 18).

Pramanik *et al.*[50] designed and executed synthesis of some novel 2,3-disubstituted pyrrolo[3,2-*c*]coumarin based simple and practicable molecular probe (having an aryl amino group



Scheme 11 One-pot multi-component DBU catalyzed modified Hantzsch synthesis of 3-alkoxy pyrrolo[3,2-c]coumarins under refluxing toluene.



Scheme 12 $KHSO_4$ promoted one-pot three-component modified Hantzsch synthesis of 2-aryl-3-arylamino pyrrolo[3,2-*c*]coumarins and their derivatives in toluene.

in position 3) *via* one-pot two-step reaction under metal-free green conditions (Scheme 19). At first, an intermediate was formed by the condensation between an equimolar mixture of arylglyoxal monohydrate and arylamine at 60 °C under neat conditions and then the final compounds were achieved by Michael addition between the intermediates and 4-aminocoumarin in the presence of PEG-OSO3H at 60 °C under solvent-free conditions.

From Michael acceptors and by rearrangements

Michael addition is one of the most helpful methods for the creation of a C–C bond involving the nucleophilic addition to an α,β-unsaturated carbonyl compound containing an electron-withdrawing group. Many groups of scientists developed mild reaction conditions for the synthesis of pyrrolo/indolo[3,2-*c*] coumarin derivatives using mainly 4-aminocoumarin derivatives and Michael acceptors in the presence of various catalysts under different reaction conditions.

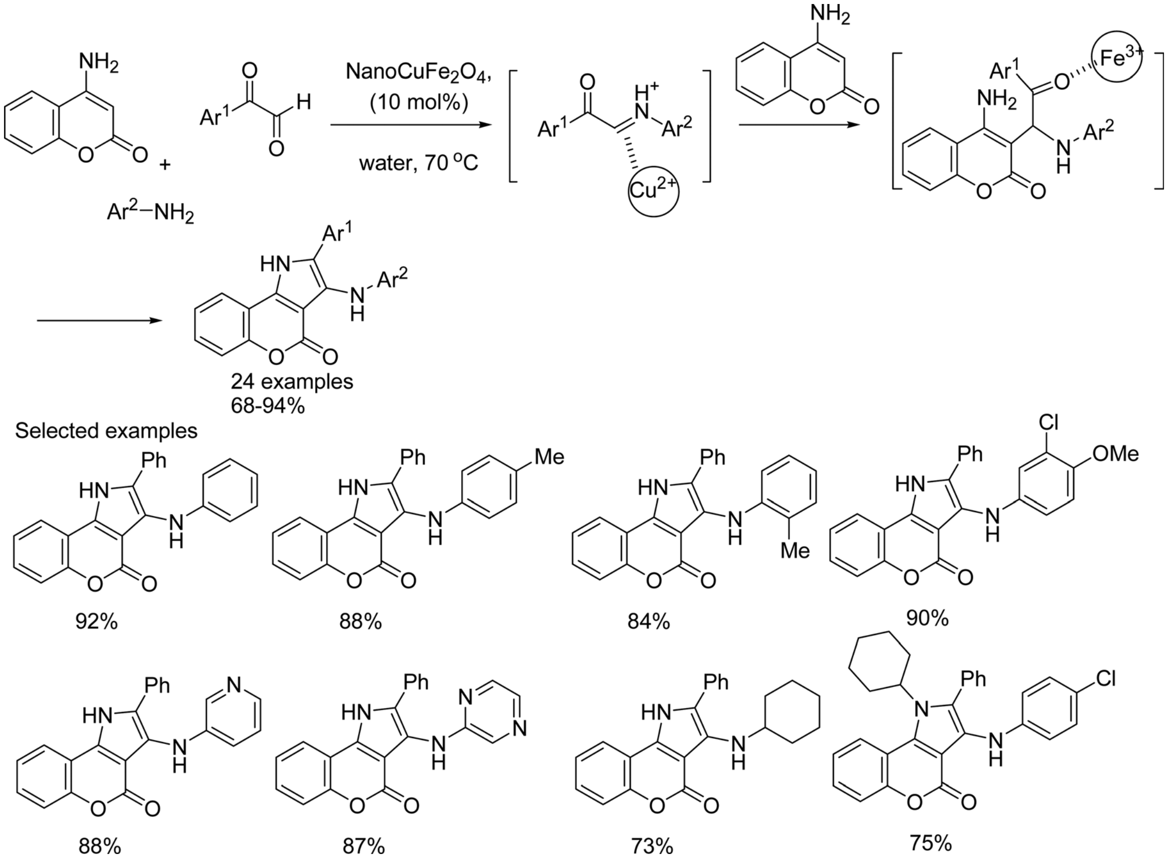
Das and *et al.*[68] developed a simple but efficient high-yielding synthetic protocol for the synthesis of 3-aryl-pyrrolo[3,2-*c*] coumarin derivatives using reusable, biodegradable, polymer-supported catalyst PEG–SO_3H. The authors used the coupling of 4-aminocoumarin as a Michael donor and α,β-unsaturated nitroalkene as a Michael acceptor in MeOH under reflux conditions (Scheme 20). Other than Michael addition, intramolecular cyclization with the concomitant removal of the nitro group is another important step for the construction of the pyrrole ring. In all cases, the catalyst activated the reactions by donating the proton from the PEG–SO_3H catalyst.

In the very next year, the process was modified by the same group[69] using $CuFe_2O_4$ catalyst instead of the PEG–SO_3H catalyst to report a highly convergent, efficient, one-pot three-component domino practical hetero-annulation protocol for the synthesis of a series of 3-aryl-pyrrolo[3,2-*c*]coumarins derivatives involving the coupling of 4-aminocoumarin, various aldehydes and nitromethane (Scheme 21). The use of magnetic nanoparticles $CuFe_2O_4$ is more attractive with respect to high yields and easy separation of the products.

Padilha and coworkers[51] developed a new solvent-free approach toward the synthesis of *N*-aryl-3-aryl-pyrrolo [3,2-*c*]coumarin derivatives from 4-phenylaminocoumarins with β-nitroalkenes in the presence of $TsOH{\cdot}H_2O$ at 120–160 °C (Scheme 22). A short reaction time, ease of product purification, and use of solvent-free conditions are attractive features of this protocol that makes the procedure more economic and eco-friendly.

The synthesized *N*-aryl-3-aryl-pyrrolo[3,2-*c*]coumarins could be converted to coumarin fused pentacyclic heterocycles, the backbone of isolamellarin-A with moderate to good yields when it was treated with diphenylacetylene in the presence of 10 mol% $Pd(TFA)_2$ as a catalyst in combination with NaOAc and LiCl as additives and DMF as a solvent at 100 °C for 24 hours (Scheme 23). Here more sustainable and environmentally-benign molecular oxygen acts as an oxidant for the regeneration of the catalyst from Pd(II) to Pd(0) state. This compound also showed intense absorption in the region of 250 nm.

Catalyst-free, rapid, efficient, atom economic, clean, and simple multi-component reaction of arylglyoxal, 4-hydroxycoumarin



Scheme 13 Nanocrystalline CuFe$_2$O$_4$ catalyzed one-pot three-component modified Hantzsch synthesis of 3-aryl amino pyrrolo[3,2-*c*]coumarins in aqueous media.

and 4-aminocoumarin in an acetic acid medium under microwave heating conditions gave pyrrolo[3,2-*c*]coumarins instead of six-membered N-heterocycles in very good yields as reported by Choudhury and co-workers[70] (Scheme 24). The proposed mechanism goes through Michael addition, *N*-cyclization by the elimination of water and hydrogen shift, and the mechanism for the construction of the pyrrole ring was explained using DFT calculations.

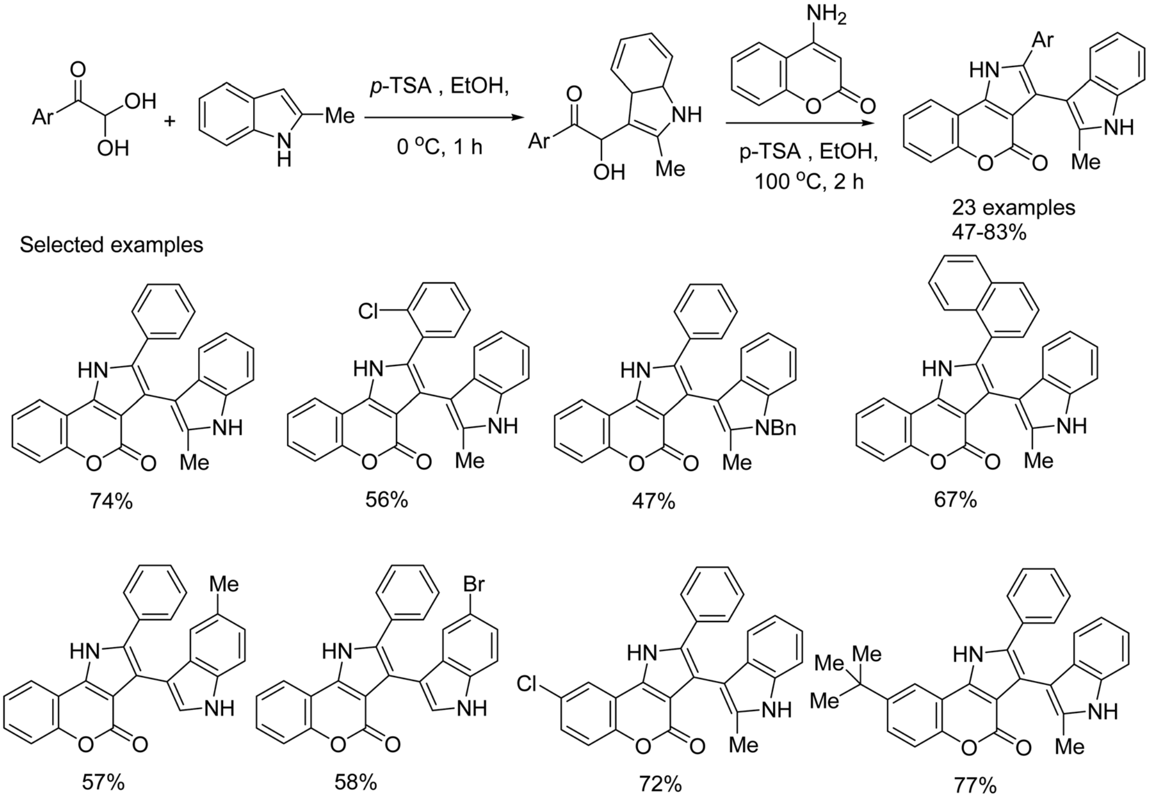
Polycyclic pyrrolo/indolo coumarin has been synthesized by a convergent route based on a cascade benzannulation–lactonization from α-carboxypyrolyl/indolylacrylates and phthalide in the presence of lithium hexamethyldisilazide (LiHMDS) in THF at very low temperature in moderate yields as developed by Mal and his co-workers[71] (Scheme 25). The typical mechanism for the formation of unexpected carboxylate derivatives of polycyclic pyrrolo/indolo[3,2-*c*]coumarins is shown in the following Scheme 25.

Mohamed and coworkers[46] used 2-(bromoacetyl)-3*H*-benzo[*f*]coumarin as a precursor for the synthesis of pyrrolo coumarins and when it reacted with different substituted aromatic amines in refluxing dimethylformamide (DMF) formed the desired pyrrolo coumarin derivatives (Scheme 26). The key step of the reaction proceeds through intramolecular Michael addition, auto-oxidation and tautomerization.

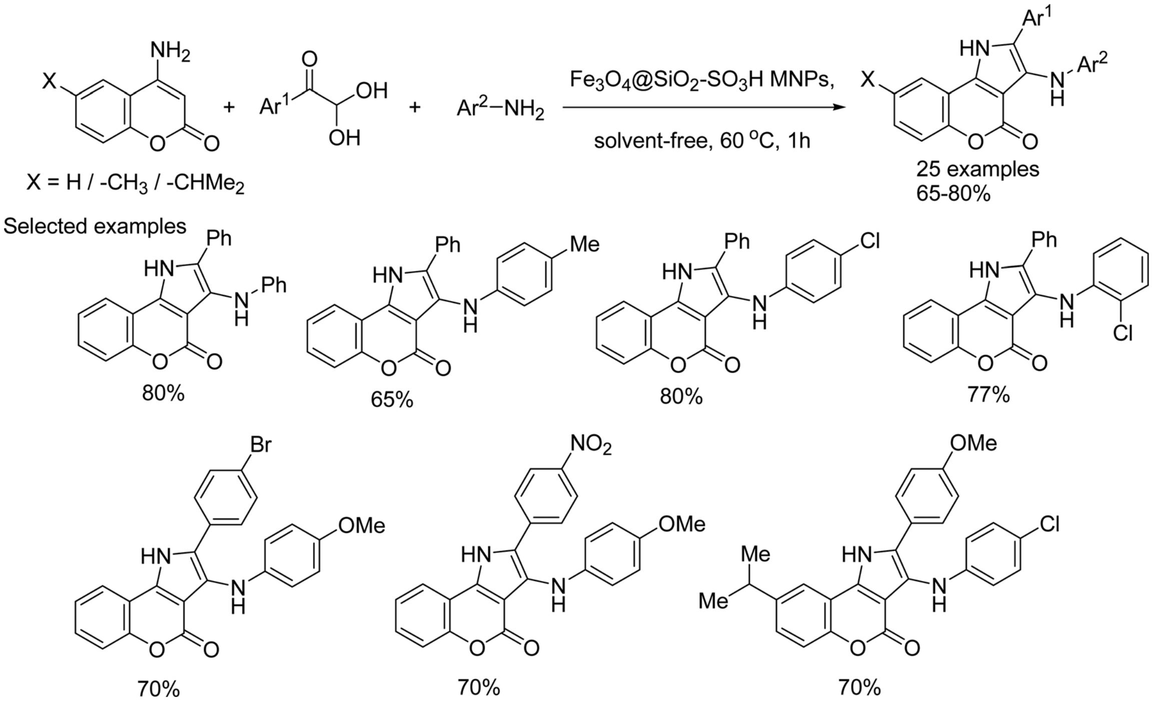
Yang *et al.*[72] established a mild, efficient, and environmentally-benign one-pot synthesis of functionalized 2,3-disubstituted pyrrolo [3,2-*c*]coumarins starting from 4-aminocoumarin derivatives, arylglyoxal monohydrates, and 1,3-dicarbonyl compounds *via* a three-component domino reaction involving Michael addition and *N*-cyclization with the elimination of water in refluxing green solvent ethanol with no catalyst (Scheme 27). This protocol has many advantages like operational simplicity, short reaction time, good yields, use of no catalyst, the scope of use of large substrates and use of non-aqueous workup, and no chromatographic separation.

In the same year, applying the same reaction protocol, H. Yahyavi and coworkers[73] reported a simple and facile strategy for the synthesis of 2,3-disubstituted pyrrolo[3,2-*c*] coumarins *via* one-pot three-component domino reactions by the use of aryl methyl ketones instead of arylglyoxal monohydrates, (het)arylglyoxals with active methylene compounds in the presence of molecular iodine as a catalyst and DMSO as a solvent at 100 °C (Scheme 28). The process involved *in situ* Kornblum oxidation reaction of acetophenones, Knoevenagel condensation between (het)arylglyoxals with active methylene compounds, Michael addition and followed by *N*-cyclization with a hydrogen shift.

Yadav and coworkers[74] have developed superior indium triflate-catalyzed and microwave-assisted, facile, solvent-free, one-pot quick method for the synthesis of novel 2,3-disubstituted pyrrolo[3,2-*c*]coumarins through Michael addition and *N*-cyclization reaction between 4-amino coumarin and a group of α-aroyl/heteroaryl/acetylidene malonates at 90 °C

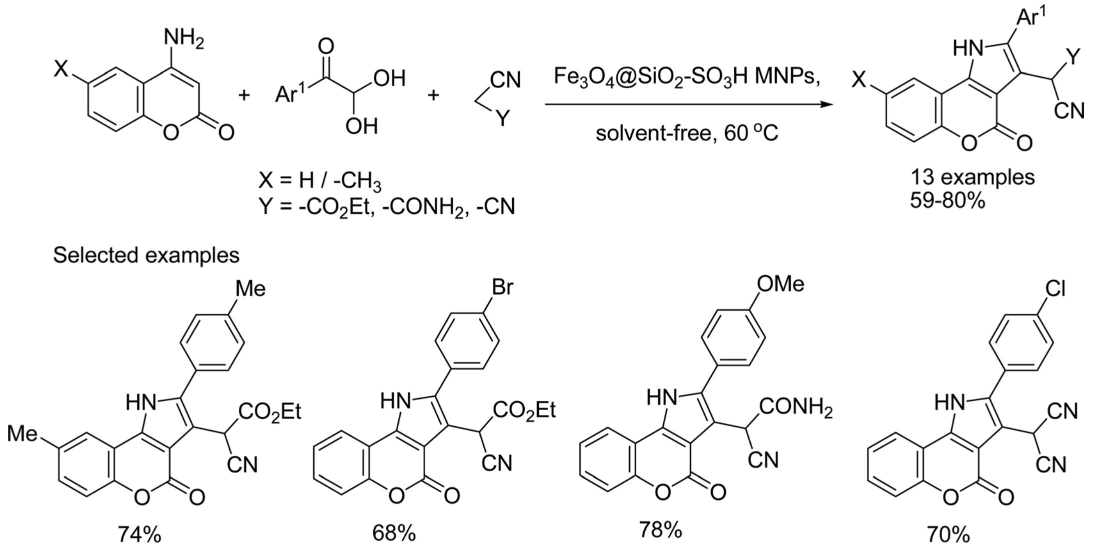


Scheme 14 *p*-TSA catalyzed one-pot three-component modified Hantzsch synthesis of 3-indolyl pyrrolo[3,2-*c*]coumarins in ethanol at 0 °C.

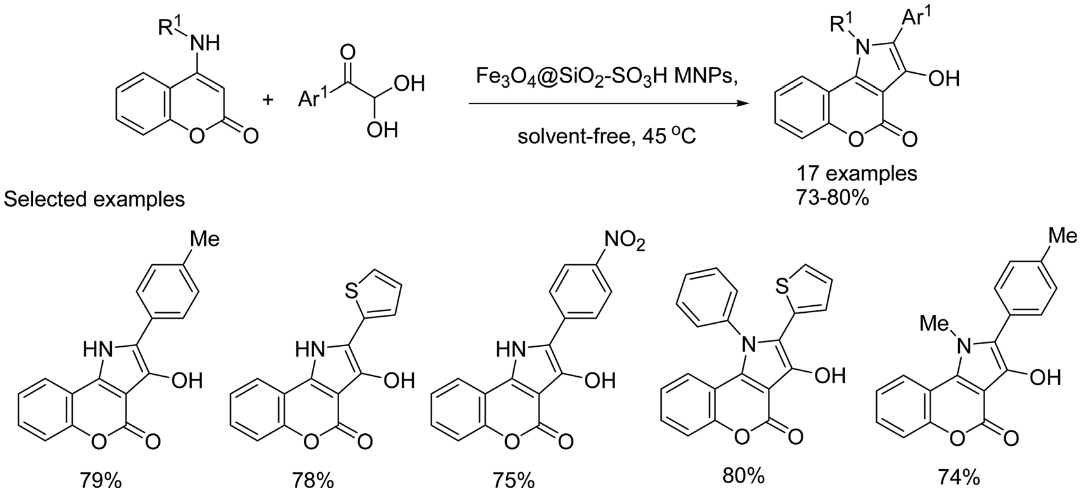


Scheme 15 Solvent-free magnetically separable $Fe_3O_4@SiO_2-SO_3H$ nanoparticles catalyzed synthesis of pyrrolo[3,2-*c*]coumarins using amines as nucleophilic substrates.

(Scheme 29). Here, $In(OTf)_3$ acts a powerful Lewis acid catalyst than other AgOTf, $Cu(OTf)_2$, $Zn(OTf)_2$, $B(C_6F_5)_3$, I_2, PTSA, and CSA. Though rare-earth metal(III) triflates $M(OTf)_3$ (M = Nd, Gd, Yb) were found to be equipotent, however, considering the cost



Scheme 16 Solvent-free magnetically separable Fe_3O_4@SiO_2–SO_3H nanoparticles catalyzed the synthesis of pyrrolo[3,2-*c*]coumarins using cyano acetate as nucleophilic substrates.



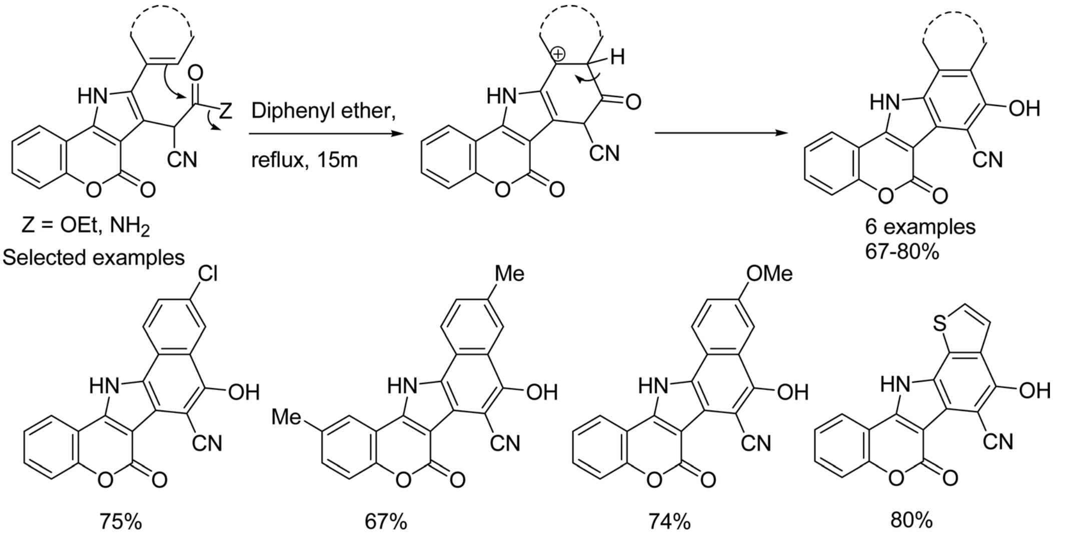
Scheme 17 Solvent-free magnetically separable Fe_3O_4@SiO_2–SO_3H nanoparticles catalyzed the synthesis of 3-hydroxypyrrolo[3,2-*c*]coumarin derivatives without any external nucleophilic substrates.

of In(OTf)$_3$, it was selected as the best catalyst for this conversion.

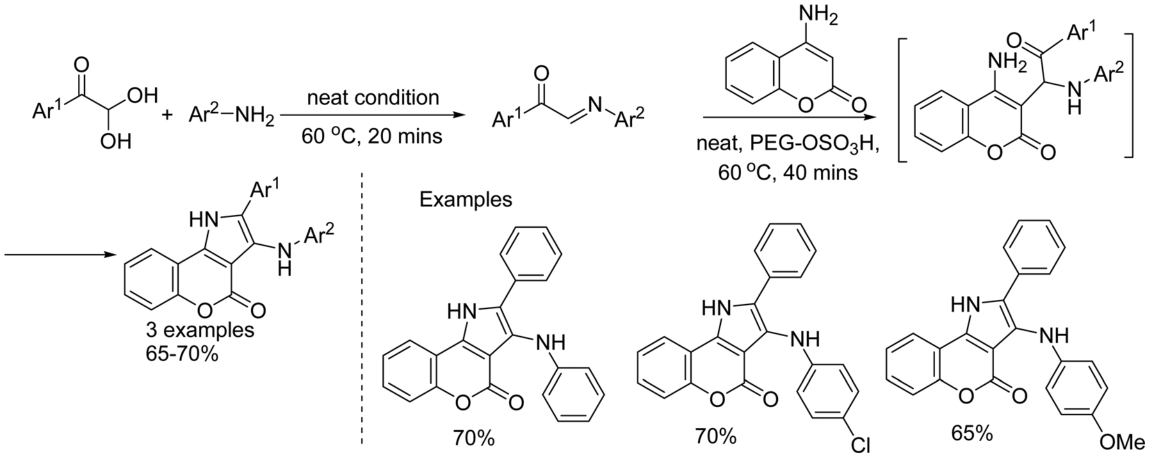
The above-synthesized compounds were successfully applied in the synthesis of chiral 3-hydroxy-3-pyrrolocoumarinyl-2-oxindole derivatives[75] as possible anti-cancer agents *via* selective C(sp^3)–H hydroxylation reaction of 3-substituted-2-oxindoles in the presence of molecular O_2 as an oxidant and TBAF (30 mol%) as a catalyst at room temperature for 6 hours and obtained 81–89% yields (Scheme 30).

Tetrahydro pyrrolo[3,2-*c*]coumarins derivatives with more than one chiral centres have been extensively used for the development of human drug designing.[76] Li and his co-worker[77] developed an NHC-catalyzed cascade cycloaddition reaction for the construction of a sterically congested tetrasubstituted chiral tetrahydro pyrrolo[3,2-*c*]coumarin derivatives in good yields with excellent enantio- and diastereoselectivities through MCR reactions, involving Michael addition between α,β-unsaturated acylazolium intermediate and imine derivatives of 2-hydroxy acetophenone and *p*-nitro benzylamine, intramolecular Mannich reaction and followed by cyclization (Scheme 31). Here, 5 mol% of NHC was used as the reaction catalyst in combination with DABCO as the base, and a mixture of EtOAc/toluene = 1/2 as the reaction solvent. The α,β-unsaturated acylazolium precursor was prepared from different substituted α-bromocinnamaldehyde and N-heterocyclic carbene (abbreviated as NHC or carbene) in the presence of base DABCO.

The lactone ring of the synthesized tetrahydropyrrolo[3,2-*c*] coumarin derivatives was converted to a highly substituted pyrroline derivative in moderate yields with the retention of the excellent optical purity and diastereomeric ratio by a trans-



Scheme 18 Synthesis of indolo[3,2-*c*]coumarin derivatives as a possible anticancer agent from pyrrolo[3,2-*c*]coumarin derivatives.



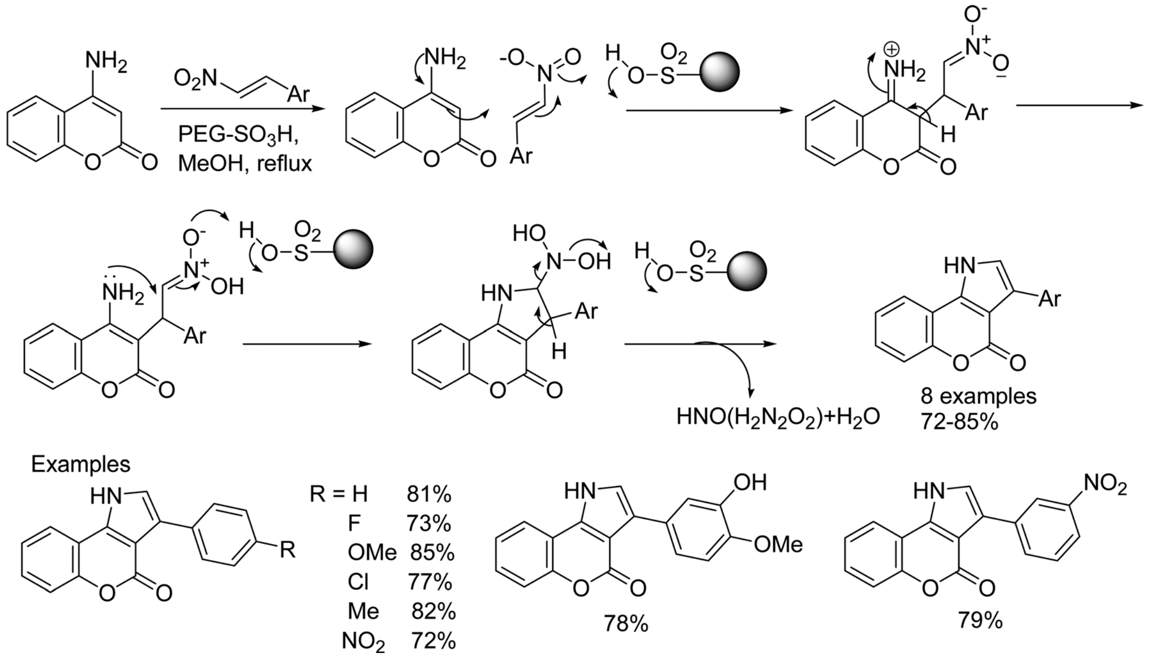
Scheme 19 Solvent- and catalyst-free synthesis of 2,3-disubstituted pyrrolo[3,2-*c*]coumarin under neat conditions.

esterification process in the presence of sulphuric acid and methanol at room temperature (Scheme 32). These chiral pyrroline derivatives have been generally applied as an efficient organic catalyst in asymmetric secondary amine-catalyzed reactions. When the chiral pyrrolo[3,2-*c*]coumarin derivative was treated with RANEY® Ni under an H_2 atmosphere, the nitro group of the above compound was reduced to amine along with trans-esterification in 96% yield without erosion of the product stereo-selectivities. This chiral primary amine of the corresponding compound was transformed to a thiourea derivative in good yields with retention of the optical purity as a single diastereomer on treatment with aromatic isothiocyanate in dichloromethane at room temperature. The thiourea derivative has potential applications in asymmetric organic synthesis.

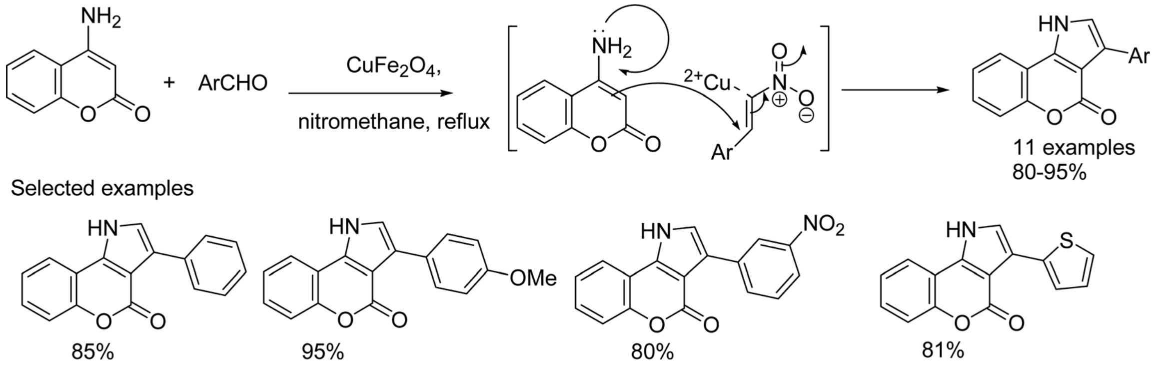
Recently, a series of pentacyclic isolamellarin scaffolds have been synthesized by Vyasamudri *et al.*[78] 4-Chloro-3-formylcoumarin and tetrahydroisoquinoline on refluxing in toluene in the presence of Cs_2CO_3 as a base produced the scaffolds *via* 1,4 addition–elimination, followed by cyclization with the removal of water (Scheme 33).

The synthesized pentacyclic derivatives are designed for the synthesis of isolamellarin-A through successive reactions with *N*-bromosuccinimide (NBS) in THF at 0 °C for 5 minutes and then Pd(0) catalyzed Suzuki coupling of brominated pentacycle with phenylboronic acid in combination with potassium carbonate as a base in refluxing THF and afforded in 88% yield (Scheme 34).

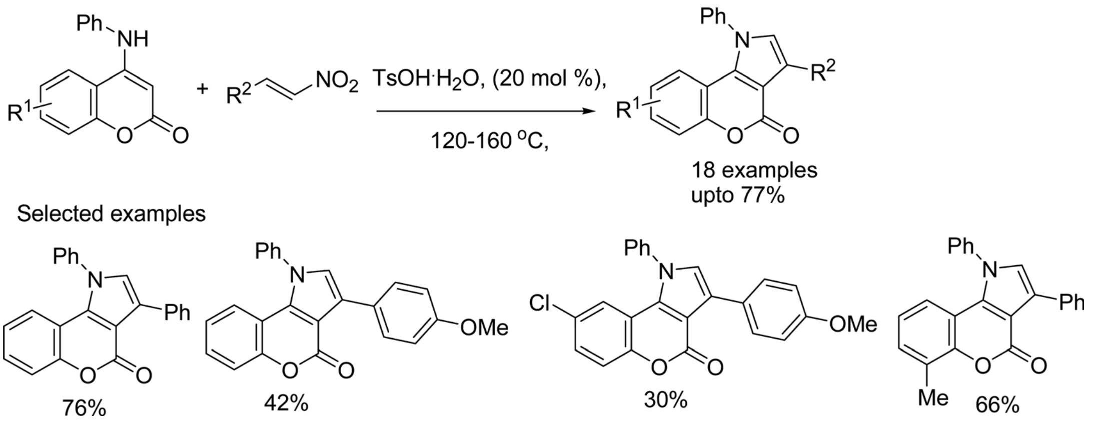
Very recently, Li and his co-workers[79] have developed *p*-TSA catalyzed protocol for the synthesis of a series of novel biologically fascinating pyrrolo[3,2-*c*]coumarins starting from coumarin 3-carbaldehydes with isocyanides and anilines in moderate to good yields *via* sequential multi-component reaction, intramolecular Michael cyclization, and auto-oxidation in the presence of *p*-TSA as a catalyst (Scheme 35). The authors also reported that electron-deficient anilines provided better yields compared to those with the electron-rich ones, and also reported that when *tert*-butyl



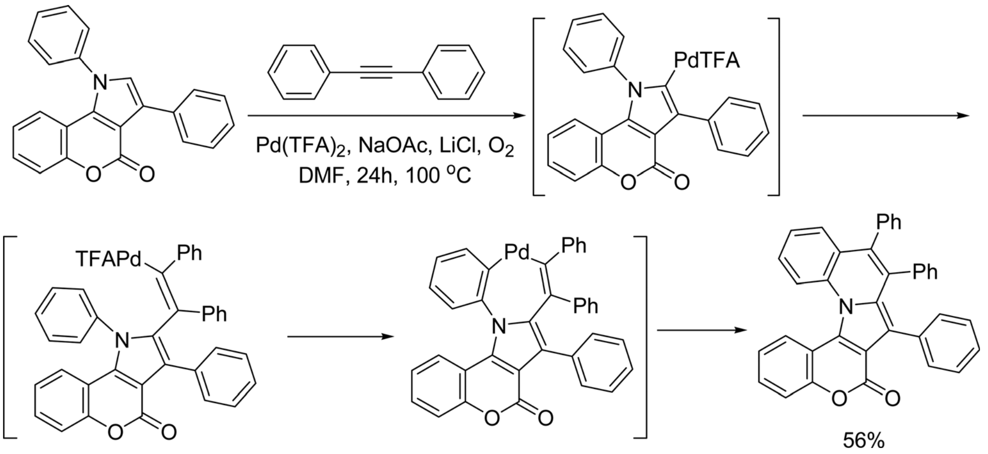
Scheme 20 PEG–SO_3H catalyzed Michael addition for the synthesis of 3-aryl-pyrrolo[3,2-*c*]coumarins from α,β-unsaturated nitroalkene.



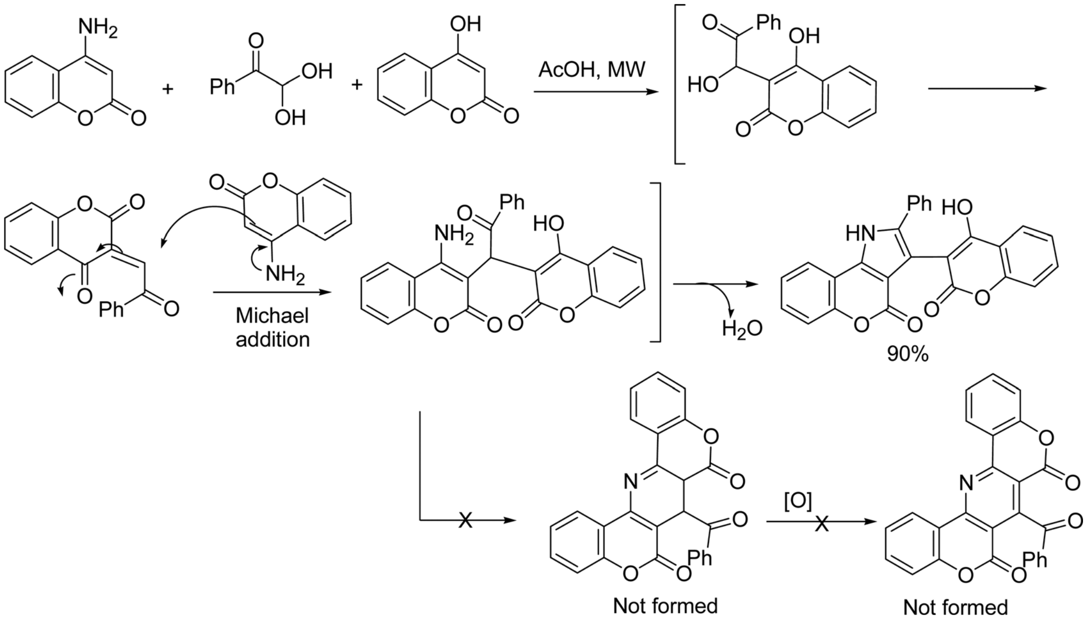
Scheme 21 $CuFe_2O_4$ catalyzed Michael addition for the synthesis of 3-aryl-pyrrolo[3,2-*c*]coumarins from α,β-unsaturated nitroalkene.



Scheme 22 TsOH·H_2O catalyzed Michael addition for the synthesis of *N*-aryl-3-aryl-pyrrolo[3,2-*c*]coumarins from α,β-unsaturated nitroalkene.



Scheme 23 Application of *N*-aryl-3-aryl-pyrrolo[3,2-*c*]coumarins for the synthesis of pentacyclic isolamellerin-A using a palladium catalyst.



Scheme 24 Microwave-assisted synthesis of pyrrolo[3,2-*c*]coumarins from arylglyoxal by Michael addition in the presence of acetic acid.

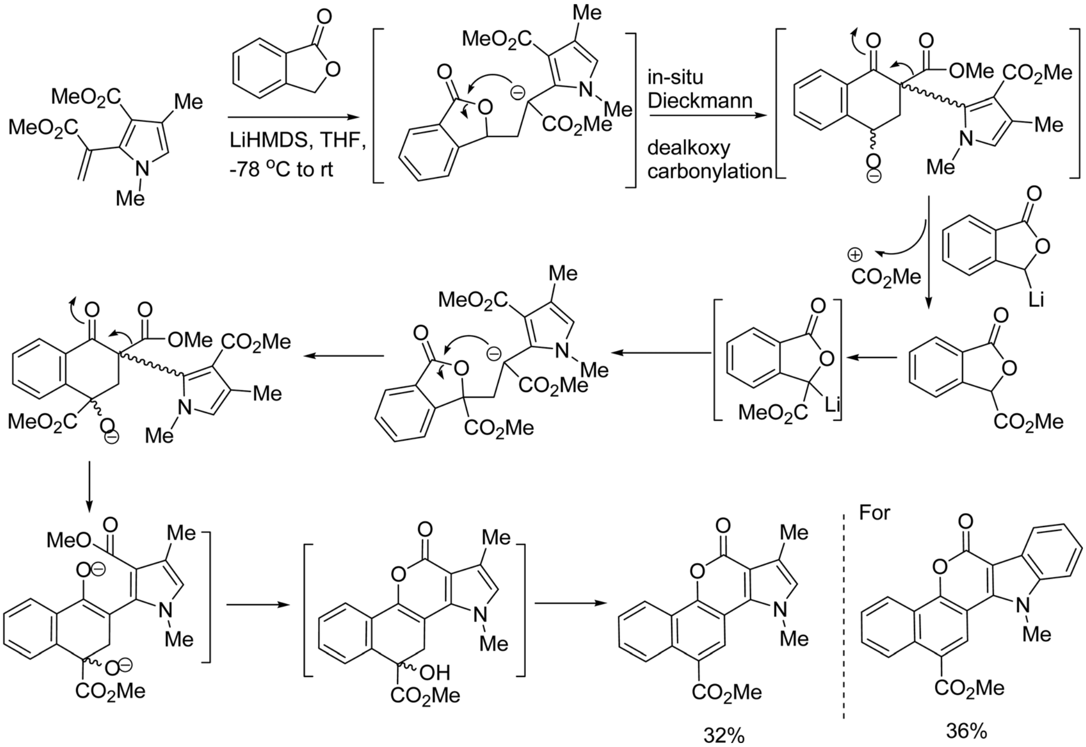
isocyanide was replaced by cyclohexyl isocyanide, the corresponding products were obtained in relatively lower yields.

The authors also constructed tetracyclic new imidazole derivatives by the condensation of two amino functionalities of pyrrolo[3,2-*c*]coumarins scaffolds with various benzoic acids in the presence of PPA at 180 °C (Scheme 36).

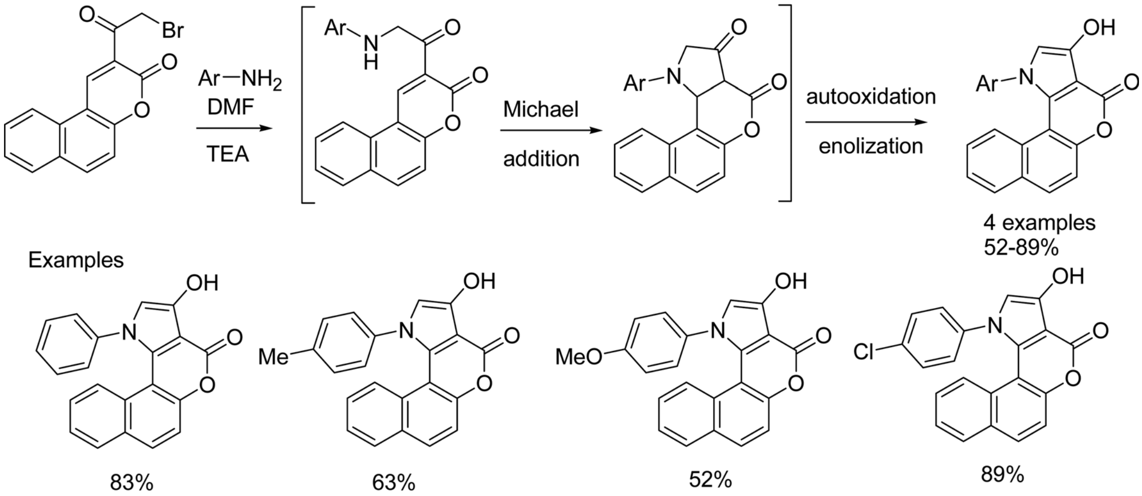
Dihydro pyrrolo[3,2-*c*]coumarinquinoxalin-one derivative could be synthesized using the above synthesized *o*-iodo derivative of pyrrolo[3,2-*c*]coumarins by Pd(0) catalyzed intramolecular Buchwald–Hartwig reaction in combination with 2-dicyclohexylphosphino-2′-methylbiphenyl as a ligand and Cs_2CO_3 as a base by refluxing in 1,4-dioxane (Scheme 37).

Majumdar *et al.*[80] developed a versatile approach for the synthesis of pyrrolo[3,2-*c*]coumarin in 70–75% yields from 4-*N*-(4′-aryloxybut-2′-ynyl)-*N*-methylaminocoumarins and one equivalent of 3-chloroperoxybenzoic acid (*m*CPBA) at 0–5 °C (10 minutes) followed by stirring at room temperature for further 10 hours (Scheme 38). The proposed mechanism goes through the formation of *N*-oxides, subsequent [2,3] and [3,3] sigmatropic rearrangements, tautomerization, *N*-cyclization, and then a nucleophile attack by water. The treatment of (4-aryloxybut-2-ynyl)*N*-methylamine with 4-tosyloxycoumarin in refluxing ethanol for 10–12 hours gave the starting material for the synthesis of pyrrolo[3,2-*c*]coumarin. 4-Tosyloxycoumarin could be prepared from 4-hydroxy coumarin with tosyl chloride in pyridine in satisfactory yield.

$FeCl_2 \cdot 4H_2O$ catalyzed isomerization of 4-vinylisoxazoles at 65 °C in acetonitrile solvent towards the synthesis of pyrrolo[3,2-*c*]coumarin was first observed by Khlebnikov and co-workers[81] (Scheme 39). Mild reaction conditions, short reaction time, and the use of cheap and available catalysts make the protocol more accessible for the synthesis of such



Scheme 25 Unexpected synthesis of carboxylate derivatives of pyrrolo/indolo[3,2-*c*]coumarins from α-carboxypyrolyl/indolylacrylates by Michael addition.



Scheme 26 Synthesis of 3-hydroxyl pyrrolo[3,2-*c*]coumarins from 2-(bromoacetyl)-3*H*-benzo[*f*]coumarin *via* intramolecular Michael addition.

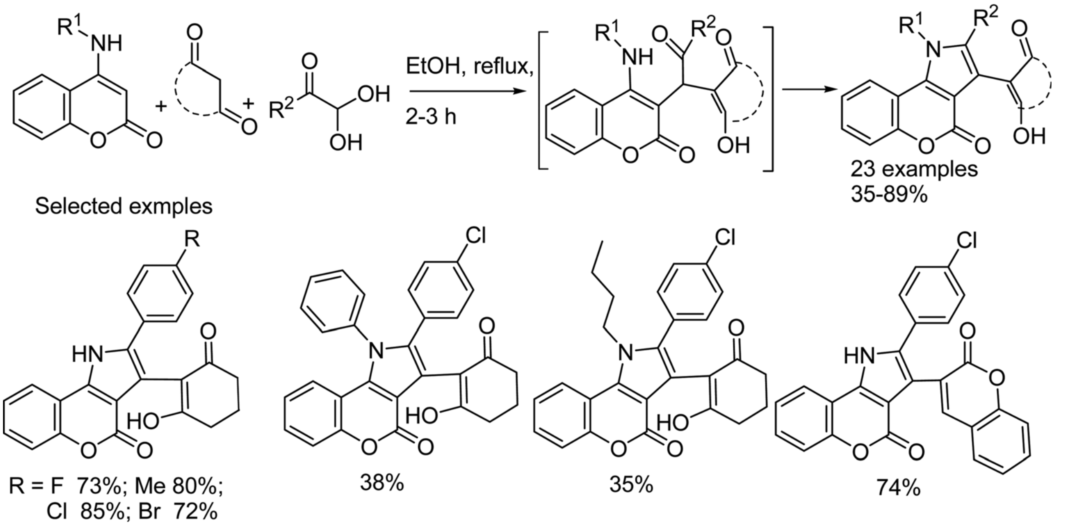
types of compounds. The authors elucidate a probable mechanism of isomerization by DFT calculations. According to the calculations, the isomerization involves the formation of Fe(II)–isoxazole complex by ring-opening of isoxazole ring, Fe(II)–nitrene complex and 1,5-cyclization to afford fused pyrrole derivatives.

Using nitrene intermediate protocols

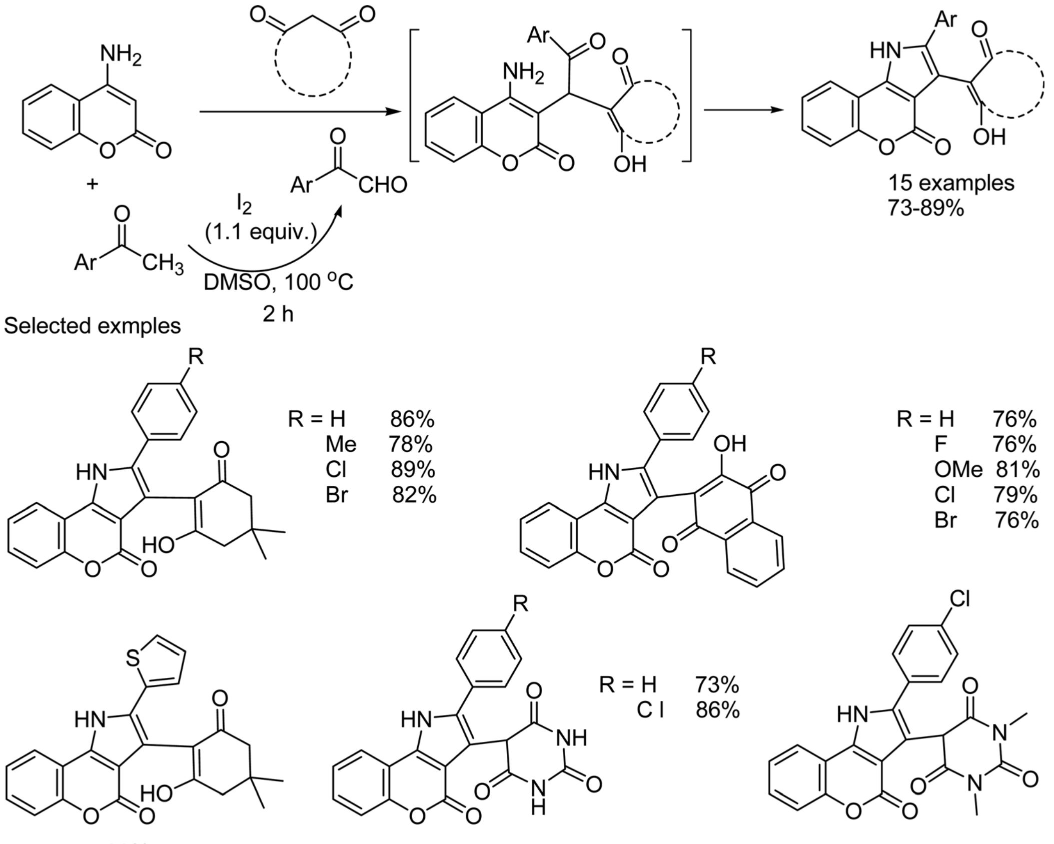
Nitrene is a reactive intermediate and is considered an electrophile due to an unsatisfied octet. It is *in situ* generated in a reaction by heating, photon irradiation, or by a reaction with $R_3P(R = Ph, OEt)$.

Kappe *et al.*[82] reported the synthesis of indolo[3,2-*c*]coumarins derivatives[2] from 3-phenyl 4-hydroxycoumarin. They described the easy synthesis of indolo[3,2-*c*]coumarin derivatives by photocyclization of 4-azido-3-phenyl coumarin derivatives (Scheme 40), which was prepared from 4-hydroxy-3-phenyl coumarin derivatives following a well-known literature procedure. The key step of the reaction involves a nitrene intermediate generated by the photon.

Coumestrol is a natural phytochemical with biological importance due to its estrogenic properties. Kappe and his co-workers extended their previous work[55] to synthesize



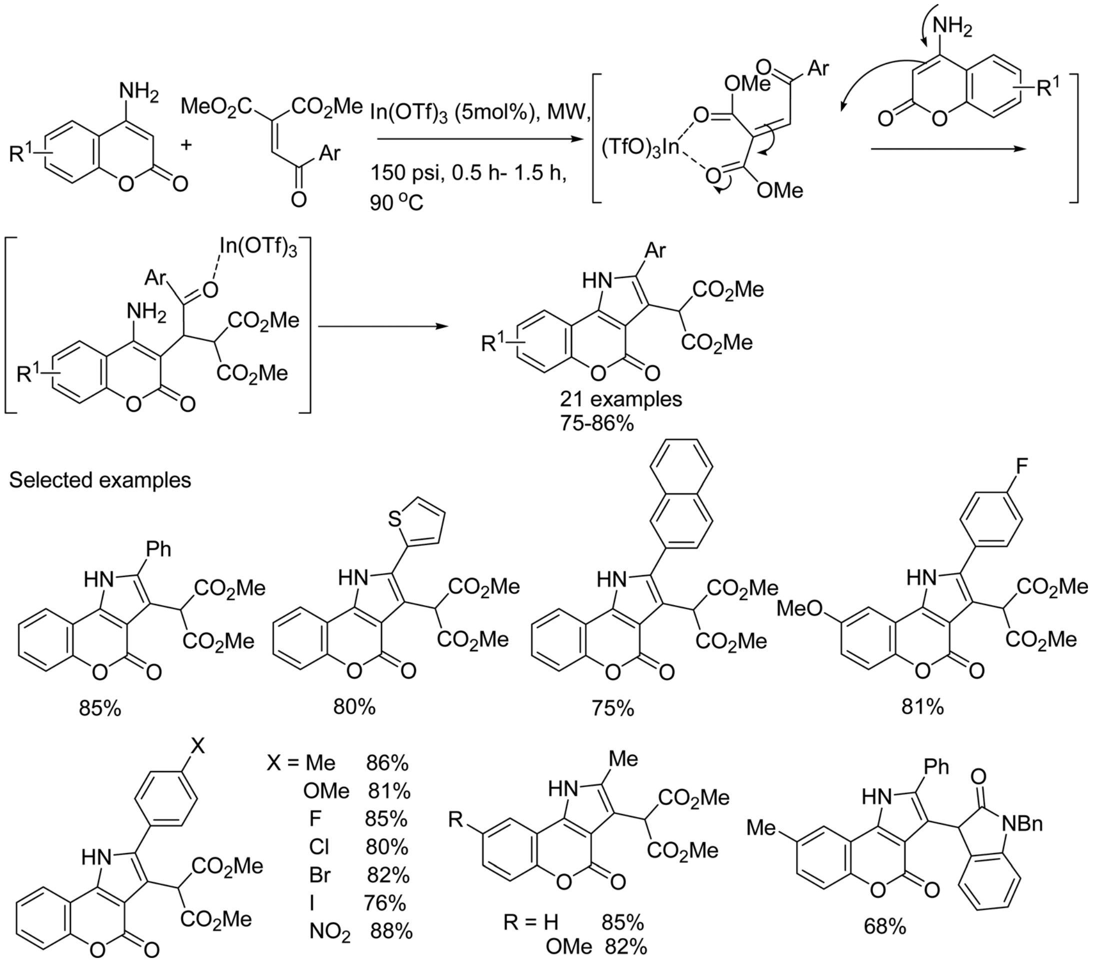
Scheme 27 Catalyst-free synthesis of 2,3-disubstituted pyrrolo [3,2-*c*]coumarins in ethanol as a green solvent by Michael addition.



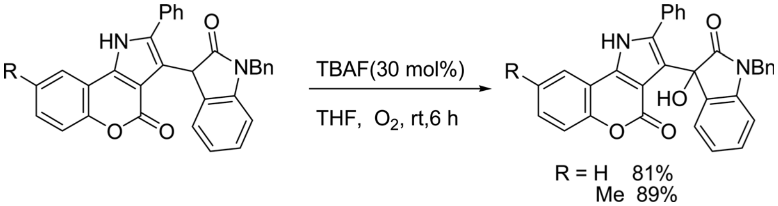
Scheme 28 Molecular iodine catalyzed synthesis of 2,3-disubstituted pyrrolo[3,2-*c*]coumarins by Michael addition.

monoazo coumestrol derivatives[83] (Scheme 41). Monoazo coumestrol derivatives are indolo-coumarins in a broad sense pyrrolocoumerin, which is of interest in this review and we focus mainly on the synthesis of monoazo coumestrol. Monoazo coumestrol-dimethylether was achieved by refluxing 4-chloro-3-arylcoumarins or 4-tosyl-3-arylcoumarins in the presence of sodium azide in DMF and the latter was prepared following their previous method. Finally, monoazo coumestrol and their diacetyl derivatives were obtained from monoazo coumestrol–dimethyl ether.

In 2013, Bochkov and coworkers[52] reported the synthesis of 2-benzoyl pyrrolo[3,2-*c*]coumarin starting from commercially



Scheme 29 Microwave-assisted synthesis of 2,3-disubstituted pyrrolo[3,2-*c*]coumarins catalyzed by indium(III) triflate.

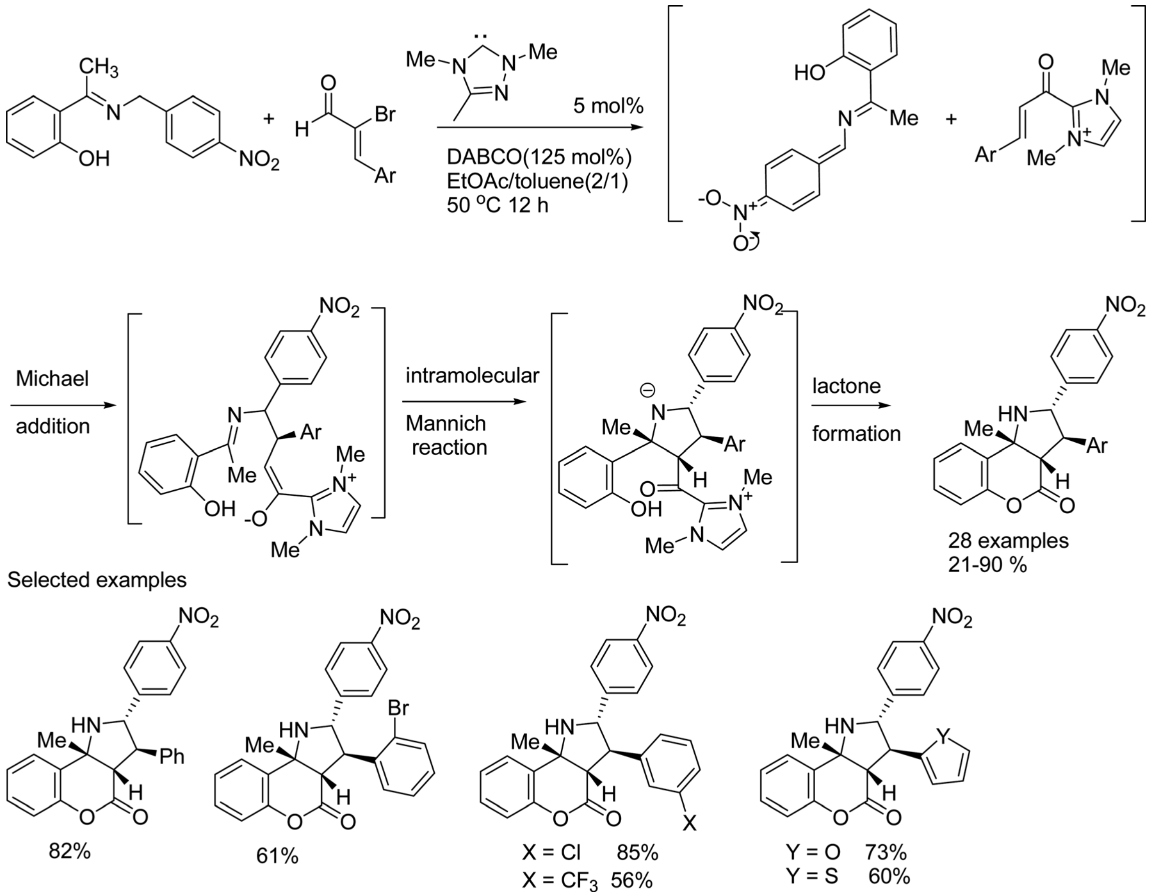


Scheme 30 TBAF catalyzed synthesis of chiral 3-hydroxy-3-pyrrolocoumarinyl-2-oxindole derivatives *via* selective C(sp^3)–H hydroxylation in the presence of molecular O_2.

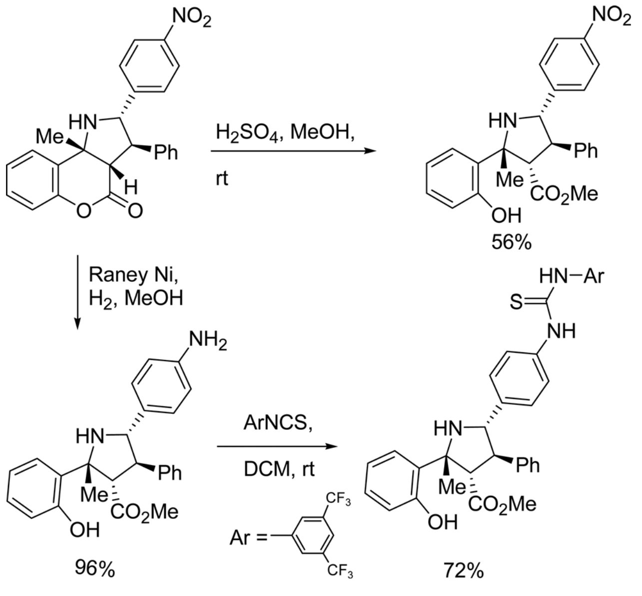
available 4-hydroxy coumarin in four steps *via* nitrene intermediate (Scheme 42). Initially prepared, 4-chloro 3-formyl coumarin (prepared from 4-hydroxy coumarin with $POCl_3$/DMF using Vilsmeier reaction) was treated subsequently with Wittig reagent, sodium azide in acetone, and then refluxing in toluene for one hour provided pyrrolocoumarin derivatives by thermal cyclization in satisfactory yield.

The synthesized 2-benzoyl pyrrolo[3,2-*c*]coumarins were used as precursors for the synthesis of a series of novel non-symmetrical coumarin-fused BODIPY dyes in two steps without isolation of the dipyrromethene intermediate in 30–58% yield, as shown in Scheme 43.

Charushin and coworkers[84] developed a new microwave-assisted Cadogan cyclization for the synthesis of polyfunctionalized indolo[3,2-*c*]coumarins in good to excellent yields from 3-(4,5-dimethoxy-2-nitrophenyl)coumarins bearing various substituents on the benzene ring of the coumarin system *via in situ* generated nitrene intermediate followed by electrophilic cyclization in the presence of triphenyl phosphine or triethyl phosphite in diglyme at 200 °C (Scheme 44). However, the use of triethyl phosphite instead of triphenylphosphine is a more effective reagent for cyclization. The reaction between salicylaldehydes and 2-(4,5-dimethoxy-2-nitrophenyl)acetonitrile with ethanol under heating conditions followed by acidification through



Scheme 31 NHC-Catalyzed synthesis of chiral tetrahydropyrrolo[3,2-c]coumarin derivatives.



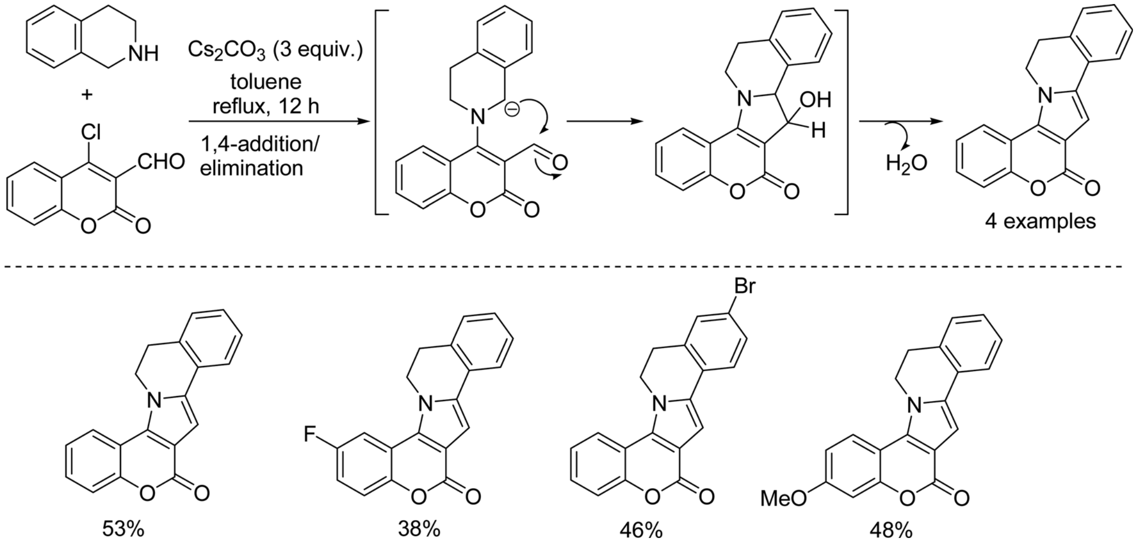
Scheme 32 Synthesis of chiral pyrroline derivatives from chiral tetrahydro pyrrolo[3,2-c]coumarin derivative.

Perkin condensation afforded required starting materials 3-(4,5-dimethoxy-2-nitrophenyl)coumarins. The high yields, use of microwave irradiation, easily available starting materials and introduction of a wide range of functionality make this strategy quite attractive for the synthesis of indolocoumarin derivatives.

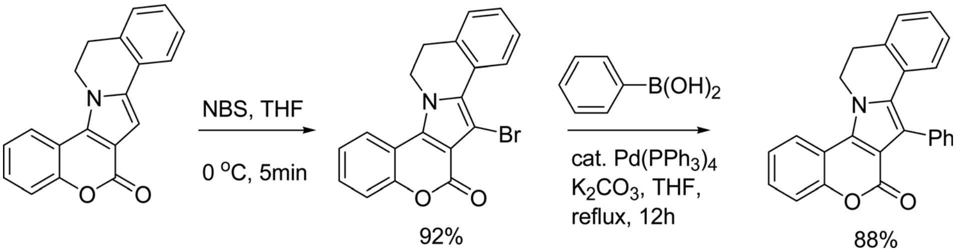
They also modified the synthesized compound in two ways, one is demethylation with 48% hydrobromic acid under reflux to give the corresponding dihydroxy derivative and another one is N–H alkylation of indolo[3,2-*c*]coumarin with an alkyl halide in DMF at room temperature in the presence of sodium *tert*-butoxide as the base (Scheme 45). In both cases, they obtained moderate yields.

Using transition metal catalysis

A number of very helpful traditional methods such as Knorr, Paal–Knorr, and Hantzsch reactions have been reported to construct pyrrole rings for the synthesis of pyrrolo/indolo coumarins. Because of some significant drawbacks such as low availability of starting materials, multiple synthetic steps, low compatibility of functional groups, and harsh reaction conditions, organic chemists try to develop novel synthetic methods to build differentially substituted or fused pyrrole derivatives. Aside from traditional methods, one of the most attractive modern approaches for the direct synthesis of pyrrolo/indolo coumarin is the transition metal-catalyzed reaction.



Scheme 33 Synthesis of pentacyclic isolamellarin scaffolds from 4-chloro-3-formylcoumarin and tetrahydroisoquinoline *via* 1,4 addition–elimination and cyclization.



Scheme 34 Design of isolamellarin-A scaffold *via* palladium(0) catalyzed Suzuki coupling reaction.

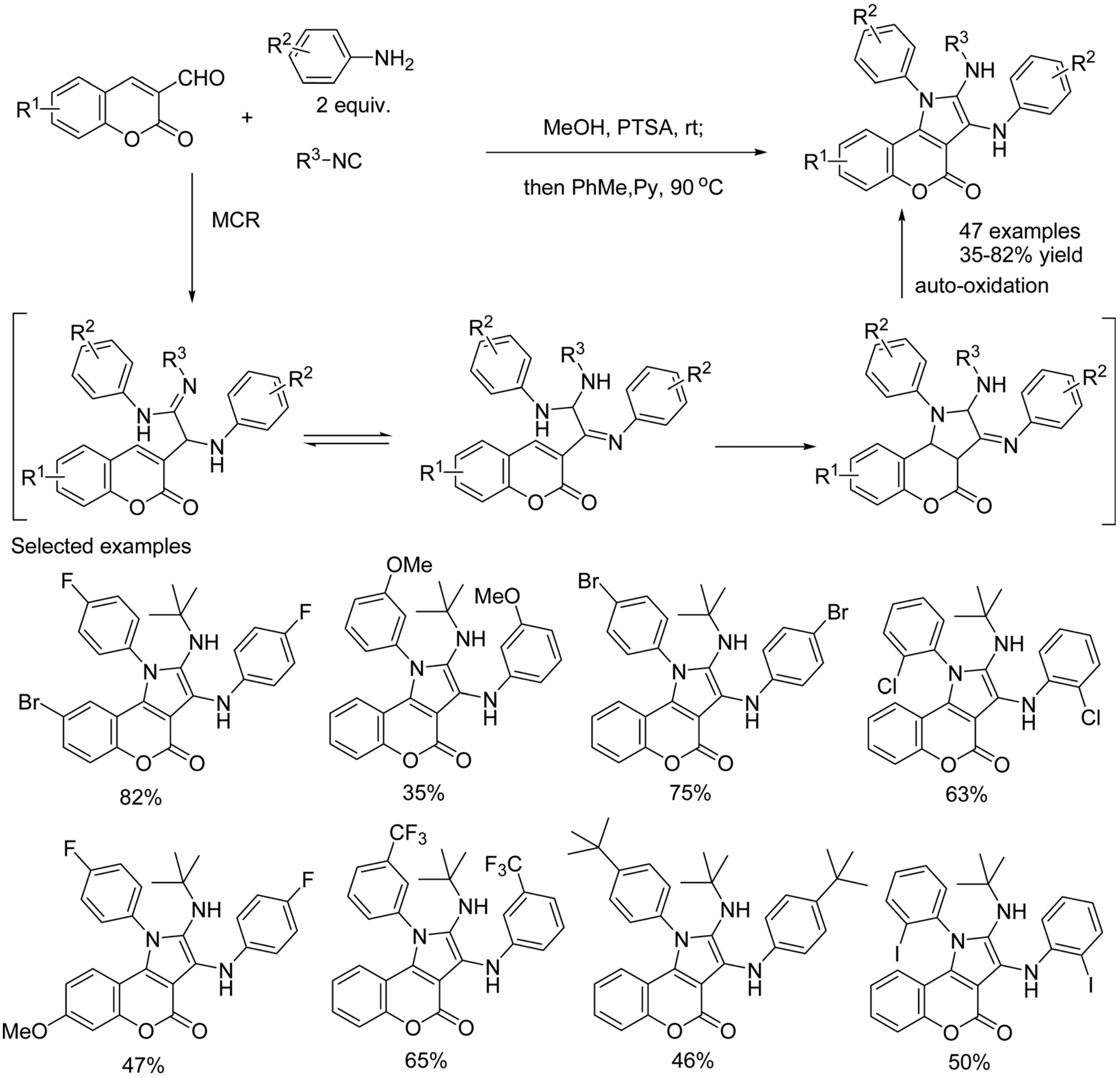
Pd catalyzed reaction

Organopalladium chemistry has found extensive use in organic synthesis over the past 40–50 years. Palladium catalysts can assist distinctive organic transformations that cannot be easily achieved using traditional classical techniques under normal reaction conditions. Mild reaction conditions and tolerance of a broad range of functional groups motivate the use of this catalyst for the synthesis of important, biologically active, and more challenging heterocyclic compounds. Here we highlight mainly two types of palladium-catalyzed reactions, one is Pd(0) catalyzed reaction with a base under an inert atmosphere and another is Pd(II) catalyzed reaction in combination with oxidant for the synthesis of pyrrolo/indolocoumarins.

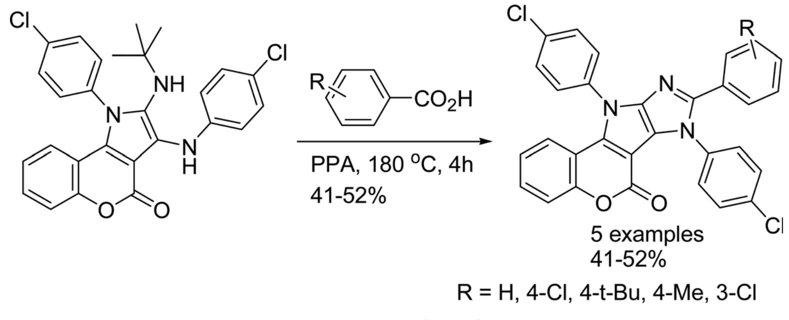
James and coworkers[85] demonstrated a concise synthesis of indolo[3,2-*c*]coumarin by the LDA-induced migration of heterobiaryl *O*-carbamates, which, were prepared sequentially from aryl boronic acid and 2-iodoindole derivative by Pd(0)-catalyzed Suzuki cross-coupling reaction in toluene under reflux conditions with satisfactory yields (Scheme 46). It is a two-step process so the overall yield is not excellent. The mechanism of the reaction in the first step goes through oxidative addition and subsequent trans metallation to produce heterobiaryl *O*-carbamates and in the second step, the desired product is obtained *via* lactone formation.

Chang and coworkers[86] designed and characterized a cobalt-sandwich diphosphine chelated palladium complex, [(*g*5-cyclopentadienyl)(*g*4-1,2-diphenyl-3,4-bis(diphenylphosphino-jP) cyclobutadiene)cobalt(I)]palladium(II)dichloride, from the reaction of a cyclobutadiene-substituted CpCoCb diphosphine, (*g*5-cyclopentadienyl) (*g*4-1,2-diphenyl-3,4-bis-diphenylphosphinocyclobutadiene)cobalt(I), with one molar equivalent of Pd(COD)Cl_2. Using this catalyst, they reported the synthesis of indolocoumarin from 4-(2-bromophenylamino)-coumarin in combination with DABCO in dioxane at 100 °C with almost quantitative yield (Scheme 47). The reaction between 4-hydroxycoumarin and 2-bromoaniline derivatives under solvent-free neat conditions at 200 °C afforded the starting material 4-(2-bromophenylamino)-coumarin derivatives in moderate yields.

Peng *et al.*[87] prepared a large number of diversely substituted pyrrolo[3,2-*c*]coumarins *via* a palladium(II) catalyzed oxidative annulation of 4-aminocoumarin to various internal alkynes in the absence of a directing group (essential for Rh(III)- or Ru(II)-catalyzed oxidative couplings) in combination with copper(II)acetate as an oxidant, molecular oxygen for the regeneration of Cu(II) in DMSO solvent at room temperature and up to 99% yield (Scheme 48). In some cases, a mixture of products of region-isomers was isolated in case of unsymmetrical

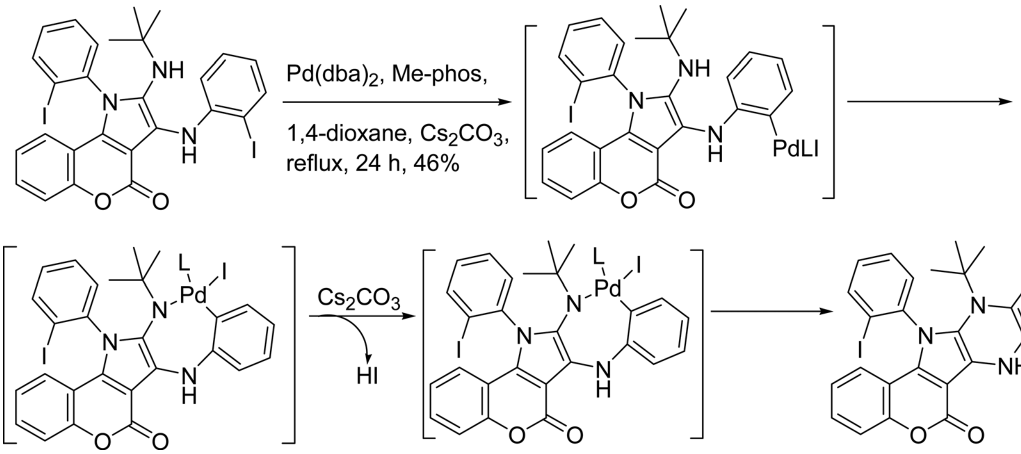


Scheme 35 *p*-TSA catalyzed synthesis of sterically hindered pyrrolo[3,2-*c*]coumarins starting from coumarin 3-carbaldehydes with isocyanides and anilines.

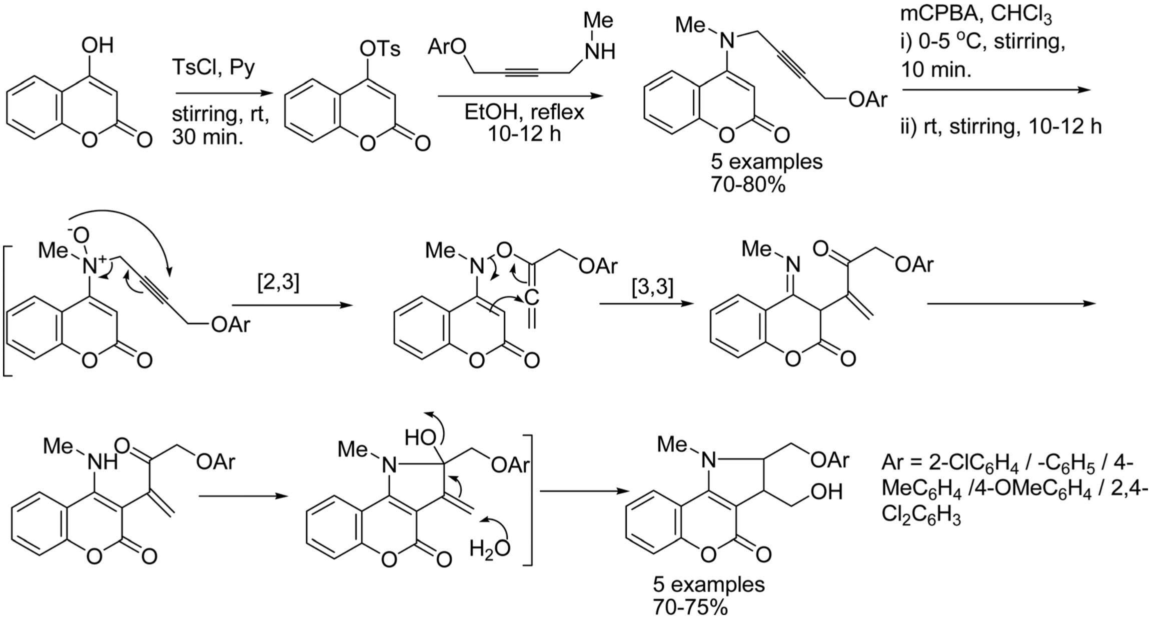


Scheme 36 Synthesis of fused tetracyclic imidazole derivatives from pyrrolo[3,2-*c*]coumarins by the condensation of two amino functionalities and various benzoic acids.

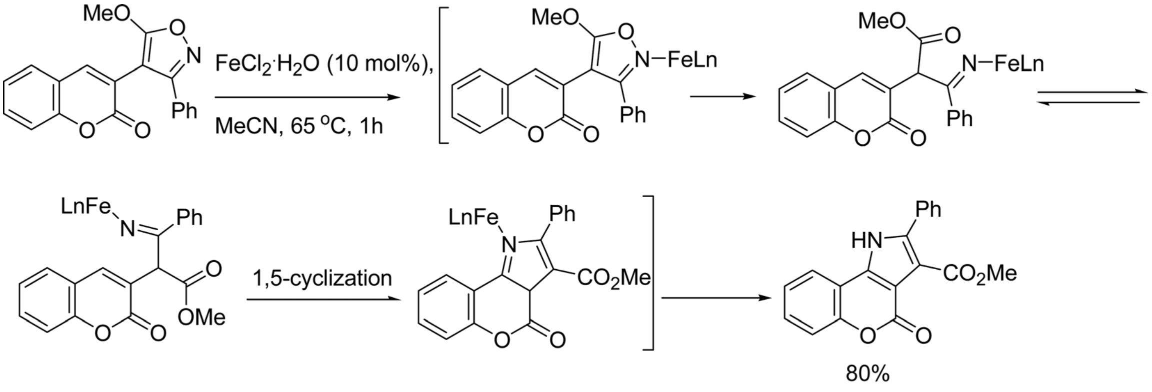
alkynes. Electron-donating alkynes are more favored for oxidative annulation than electro-withdrawing alkynes. The proposed mechanism of reactions protocol involves the formation of palladium intermediate between 4-aminocoumarin and a



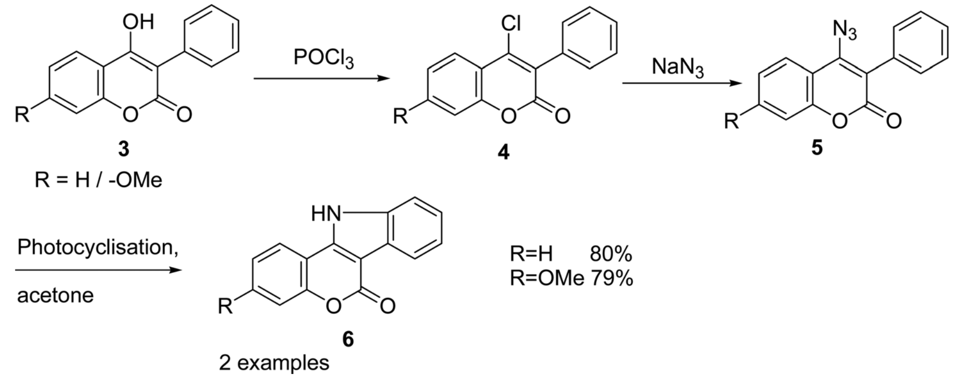
Scheme 37 Design of pyrrolo[3,2-*c*]coumarins by Pd(0) catalyzed intramolecular Buchwald–Hartwig reaction.



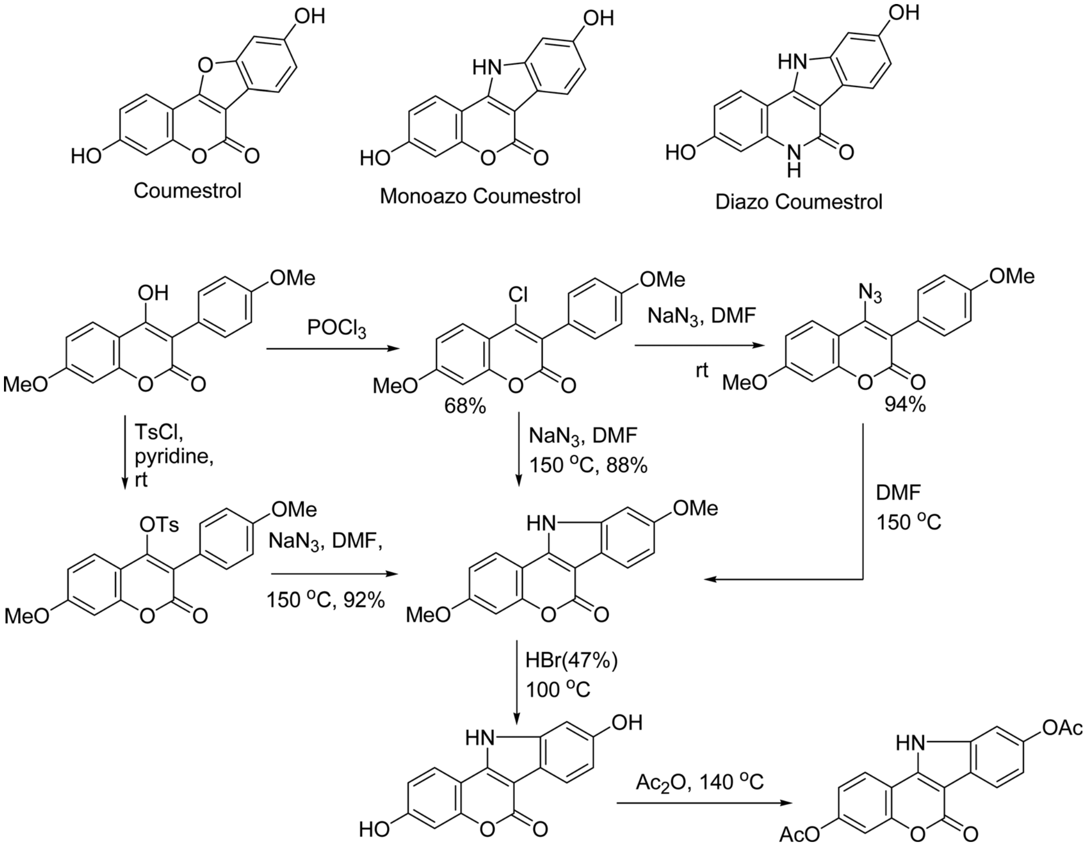
Scheme 38 Synthesis of polyfunctionalized pyrrolo[3,2-c]coumarins *via* sigmatropic rearrangement from 4-hydroxycoumarin.



Scheme 39 Synthesis of substituted pyrrolo[3,2-c]coumarins *via* isomerization of 4-vinylisoxazoles.



Scheme 40 Synthesis of indolo[3,2-*c*]coumarin from 3-phenyl 4-hydroxycoumarin *via* nitrene intermediate.

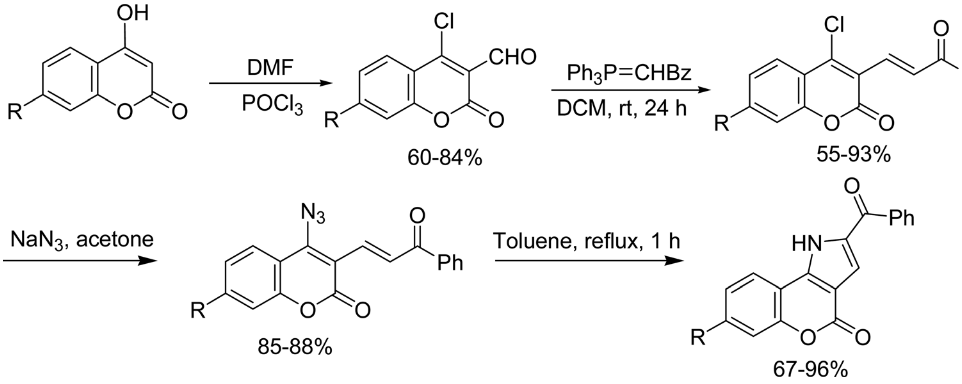


Scheme 41 Multi-step synthesis of monoazo Comestrol *via* nitrene intermediate.

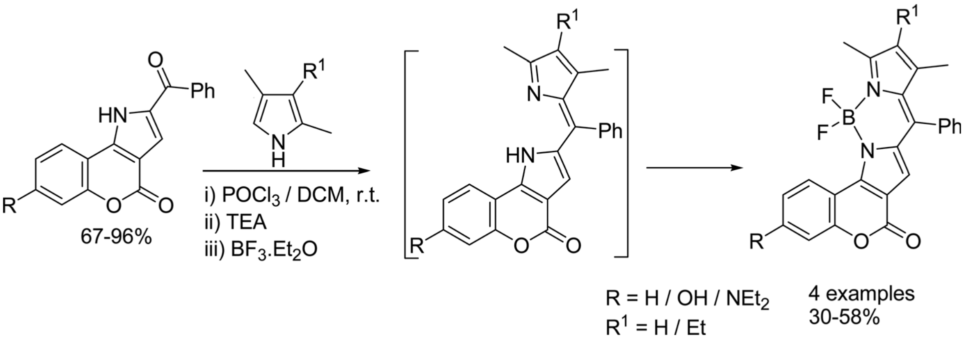
palladium catalyst, vinylpalladium intermediate by syn addition of this intermediate and alkyne, and the subsequent construction of pyrrole ring by reductive elimination.

The above Pd(II)-catalyzed oxidative annulations with diphenyl acetylene are also applicable for N-protected 4-aminocoumarin for the synthesis of the corresponding pyrrolo coumarin with satisfactory yield under similar reaction conditions (Scheme 49).

The oxidative intramolecular cyclization reaction between two arenens involves a loss of H_2 molecules promoted by Pd(II) species that were regenerated by the use of oxidant. This intramolecular cyclization reaction is a special type of typical electrophilic aromatic substitution between σ-arylpalladium(II) complex by direct palladation at the *ortho*-position of one arene with another arene. The palladium(II)-catalyzed C–C coupling reactions are more accessible than Pd(0)-catalyzed C–C coupling reactions due to the absence of prefunctionalized halo substituent on the starting material and inert atmosphere. Cheng and coworkers[88] developed palladium(II)-catalyzed highly efficient and atom-economical cross dehydrogenative coupling (CDC) reactions for the synthesis of indolo[3,2-*c*]coumarins in combination with cesium acetate as a base, silver acetate as an oxidant, and phenol as a solvent at 100 °C and



Scheme 42 Synthesis of 2-benzoyl pyrrolo[3,2-*c*]coumarins non-symmetrical coumarin-fused BODIPY dyes from 4-hydroxy coumarin.



Scheme 43 Application of 2-benzoyl pyrrolo[3,2-c]coumarins for the synthesis of non-symmetrical coumarin-fused BODIPY.

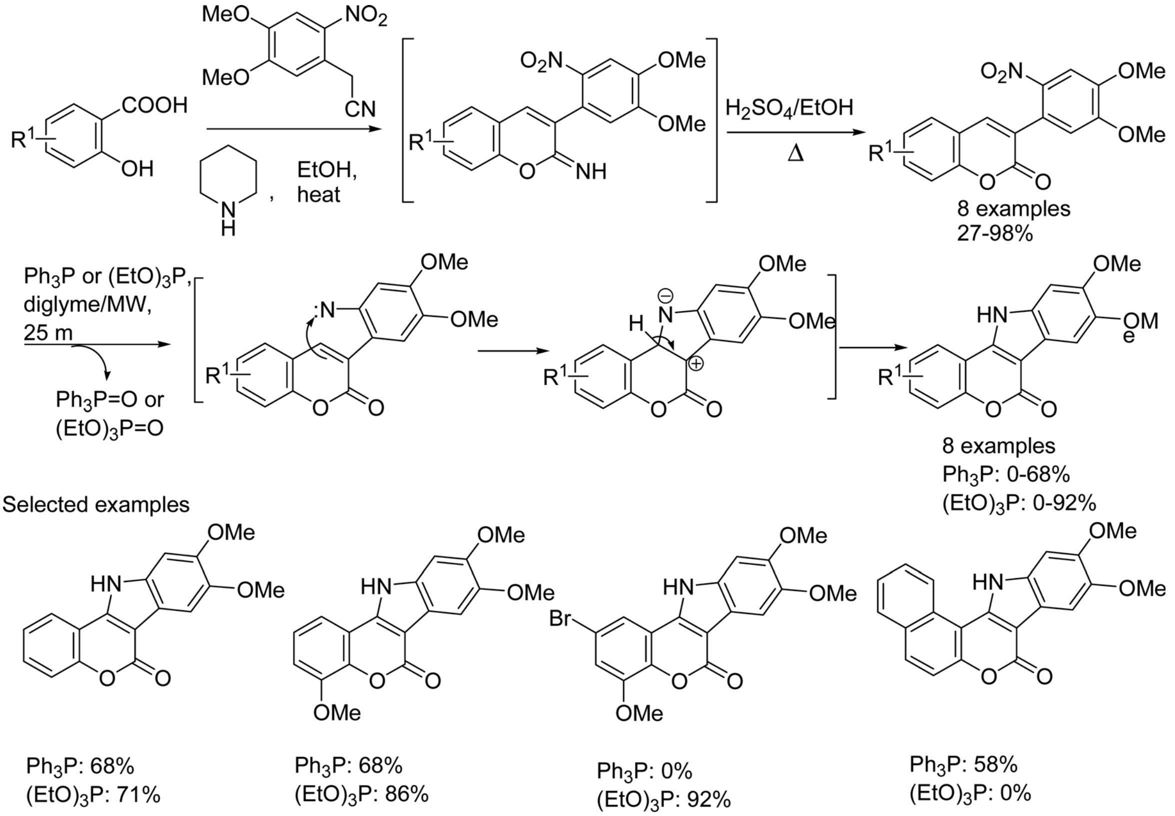
afforded up to 99% yield (Scheme 50). In the absence of a base, the above reaction proceeded smoothly but afforded lower yields under similar conditions. The reaction goes through σ-bond metathesis *via* C–H activation of C–H bond in the 3 position in the lactone ring of the coumarin ring of 4-(arylamino) coumarins followed by reductive elimination.

In that same year, a similar kind of protocol was reported by the same group.[89] They developed an efficient, atom-economic, base-free palladium-catalyzed reaction for the synthesis of indolo[3,2-*c*]coumarin derivatives in good to excellent yields (up to 99%) *via* intramolecular cross dehydrogenative coupling (CDC) reaction of *N*-aryl aminocoumarins in the presence or absence of silver acetate using acetic acid as a solvent at 100 °C (Scheme 51). They also reported a comparative study in the presence or absence of silver acetate with respect to yields and the requirement of time for the formation of the desired products. In most cases, the use of silver acetate as an additive increases the effectiveness of the reaction with respect to the time of the reaction and yield of the products.

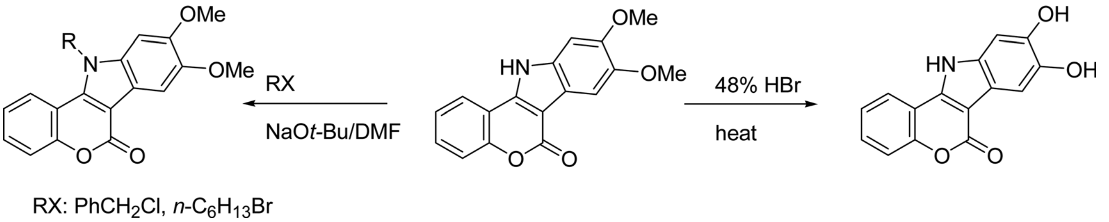
In the next year, Litinas *et al.*[47] reported the same types of indolo[3,2-*c*]coumarin derivatives under microwave irradiation within half an hour. They used Pd(II)–acetate in combination with $Cu(OAc)_2$ as an oxidant without any base in acetic acid under microwave irradiation for the synthesis of azacoumestans in excellent yields from 4-(arylamino)coumarins (Scheme 52). The role of acetic acid in such oxidative cyclization processes is to increase the electrophilicity of Pd(II) species by protonating one of the acetate ligands, which affords to promote the initial electrophilic palladation of the aromatic ring. The required 4-(arylamino)coumarins were prepared up to almost quantitative yield by the reaction of arylamines with 4-bromocoumarin under microwave irradiation in water or by Pd-catalyzed C–N coupling under heating conditions. However, the reaction of 4-bromocoumarin and nitro-aniline failed to produce corresponding 4-(arylamino)coumarins under microwave irradiation. So the use of Pd-catalyst for C–N coupling is more effective for the preparation of 4-(arylamino)coumarins from 4-bromocoumarin instead of 4-hydroxycoumarin.

In the same year, Hajra and coworkers[90] developed a simple, mild and efficiently-modified one-step reaction protocol for the synthesis of indolocoumarin by the construction of pyrrole ring *via* simultaneous coupling of C–N bond between 4-hydroxycoumarins and different substituted anilines and a C–C bond by similar C–H activation of 4-(arylamino)coumarins intermediate in the presence of Pd(II)acetate in combination with more sustainable and environmentally-benign molecular oxygen as an oxidant and DMF as a solvent at 140 °C for 16 hours (Scheme 53). The use of molecular oxygen as an oxidant makes the protocol more sustainable and environmentally-benign.

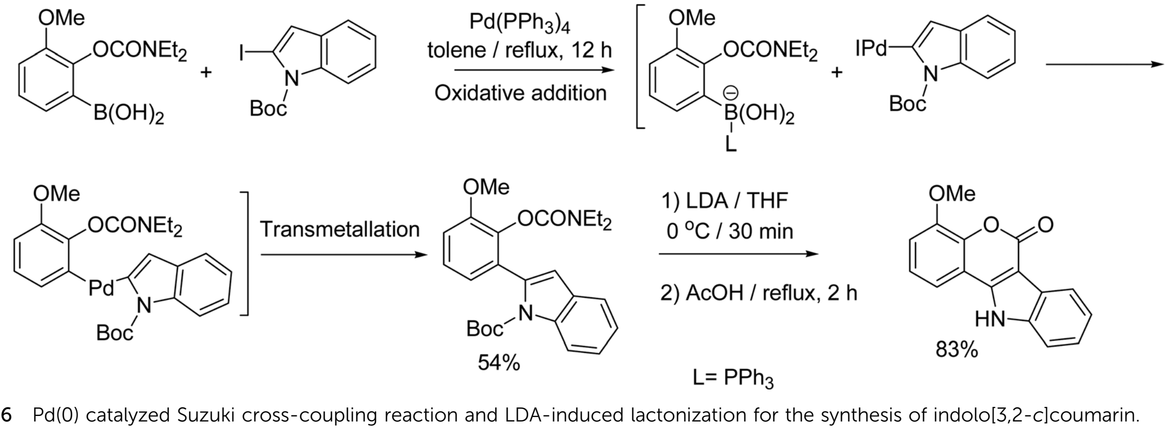
Palladium-catalyzed lactonization to construct coumarin ring is another attractive and popular method for the synthesis of indolo[3,2-*c*]coumarin derivatives.



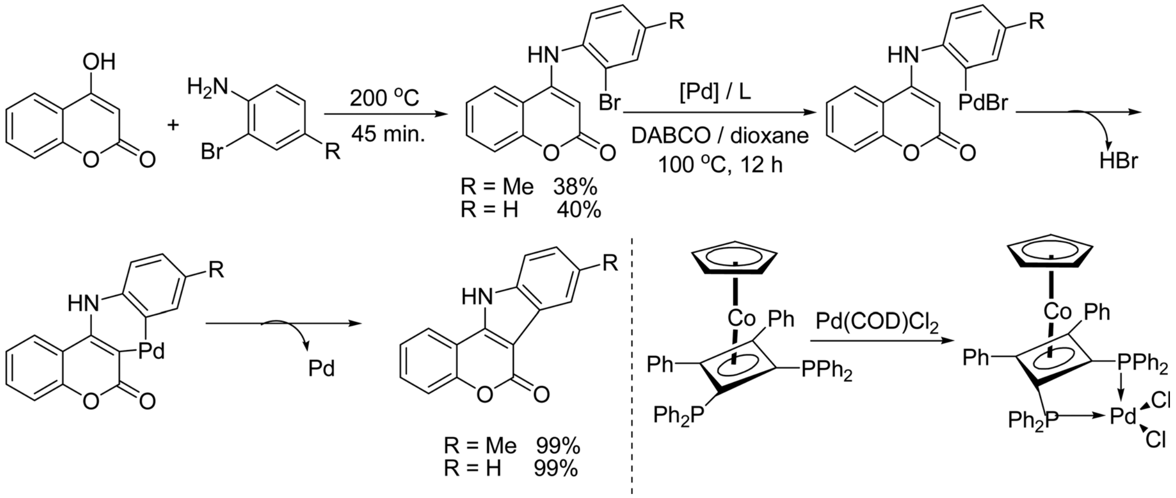
Scheme 44 Microwave-assisted synthesis of polyfunctionalized indolo[3,2-c]coumarins from salicylic acid.



Scheme 45 Demethylation and N–H alkylation of polyfunctionalized indolo[3,2-c]coumarins.



Scheme 46 Pd(0) catalyzed Suzuki cross-coupling reaction and LDA-induced lactonization for the synthesis of indolo[3,2-c]coumarin.



Scheme 47 Cobalt-sandwich diphosphine chelated palladium-catalyzed coupling reaction for the construction of indolo[3,2-c]coumarins.

Yao *et al.*[91] developed palladium-catalyzed lactonization *via* CO insertion for the synthesis of indolo[3,2-*c*]coumarin derivatives from 2-(3-iodo-1-methyl-1*H*-indol-2yl)phenyl acetate in combination with K_2CO_3 as a base in DMF as a solvent at 90 °C in 75% yield (Scheme 54). When 2-(2-(2-(dimethylamino)phenyl)ethynyl)phenylacetate was treated with molecular iodine in DCM, it afforded 2-(3-iodo-1-methyl-1*H*-indol-2yl)phenyl acetate in 78% yield *via* a bridge iodonium ion and consequent intramolecular nucleophilic attack by nitrogen.

Recently, Chen and coworkers[92] elucidated the mechanism and origins of the ligand-controlled Pd-catalyzed regiodivergent carbonylation of alkynes with the help of DFT (density functional theory) calculations. The competitive nucleophilic attack, either by nitrogen or oxygen existing in the substrate leads to two possible reaction pathways. *O*(*N*)-Cyclization, CO insertion, N–H(O–H) cleavage, C–N(C–O) reductive elimination, and oxidation of Pd(0) by BQ are involved in the key steps in the catalytic cycles. The rate-determining step of the overall reaction is reductive elimination and irreversible cyclization determines the chemoselectivity. The sterically bulky and electron-rich ligand L2 favours the formation of the products and stronger aromaticity is another factor for the formation of indolo[3,2-*c*]coumarin derivatives (Scheme 55).

Wu *et al.*[93] reported an efficient intramolecular oxidative C–H/C–H coupling protocol for the synthesis of indolo[3,2-*c*] coumarins from aryl indole 3-carboxylate by Pd(II) catalyzed reaction in combination with AgOAc as an oxidant, K_2CO_3 as a base, PivOH as an additive in DMA at 120 °C in satisfactory yields (Scheme 56). The required aryl indole 3-carboxylate was achieved *via* Pd-catalyzed C–H carbonylation of indole with aryl formats in the presence of Pd(II)acetate, molecular iodine potassium carbonate in DMF solvent at 100 °C. In both cases, a relatively wide range of functional groups could be introduced. The use of solid or liquid formate esters instead of highly toxic, flammable, explosive, and difficult handling of gaseous CO for the carbonylation makes the protocol greener and easy to handle in the laboratory.

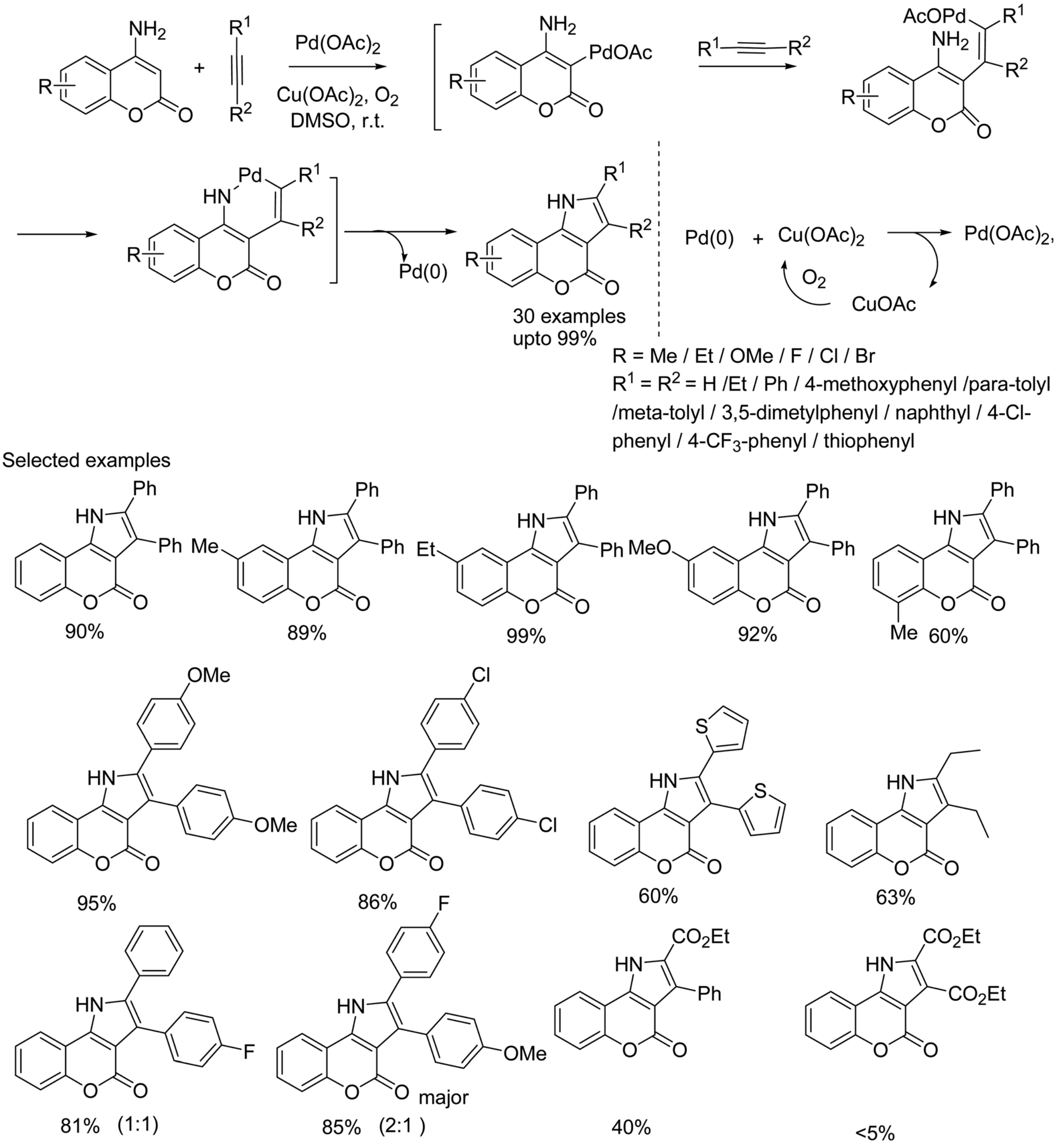
Cu-catalyzed reaction

The transition metal Cu has also the properties which are responsible for catalytic activities, such as larger surface area, partially-filled d-orbital or filled d-orbital and variable oxidation states. Moreover, due to low cost, less toxic, and ease to handle Cu-catalyzed reactions have been widely used in organic synthesis for C–C or C–heteroatom coupling.

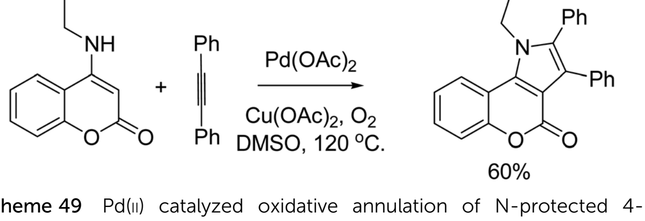
Ruchirawat and coworkers[94] developed a simple, ligand- and base-free copper(I) salt catalyzed and highly effective C–O carboxylic lactonization method for the synthesis of indolo[3,2-*c*]coumarin from 2-haloaryl-indole-3-carboxylic acids by means of microwave irradiation in the presence of DMF solvent at 200 °C (Scheme 57). Catalyst CuTC was more effective than CuI in C–O carboxylic lactonization under similar conditions and a higher amount of yields was obtained from bromo derivatives than from chloro derivatives. The required 2-haloaryl-indole-3-carboxylic acids were prepared from iodoaryl carboxylate esters and 2-haloarylboronic acids by the Pd(0) catalyzed Suzuki cross-coupling reaction and subsequent hydrolysis using potassium hydroxide as a base in methanol.

Using the same protocols pentacyclic pyrroloisoquinoline alkaloids (isolamellarins) were synthesized effectively (Scheme 58). An alternative method for the synthesis of the same isolamellarin was also investigated using lead tetraacetate in the presence of EtOAc under reflux conditions but afforded a lower yield.

CuTC (copper(I) thiophene-2-carboxylate)-catalyzed reaction of 2-(2-halophenyl)-1-methyl-1*H*-indole-3-carboxylate derivatives *via* lactone formation under microwave irradiation in ideal green solvent water for the synthesis of indolo[3,2-*c*]coumarin (Scheme 59) has been reported by Nealmongkol and his coworkers.[95] N-Protected indole derivatives gave better yield under similar conditions. One-pot lactone formation from biaryl esters instead of biaryl acids under microwave irradiation with a



Scheme 48 Pd(II) catalyzed oxidative annulation of 4-aminocoumarin with various internal alkynes in the absence of a directing group for the synthesis pyrrolo[3,2-*c*]coumarin derivatives.

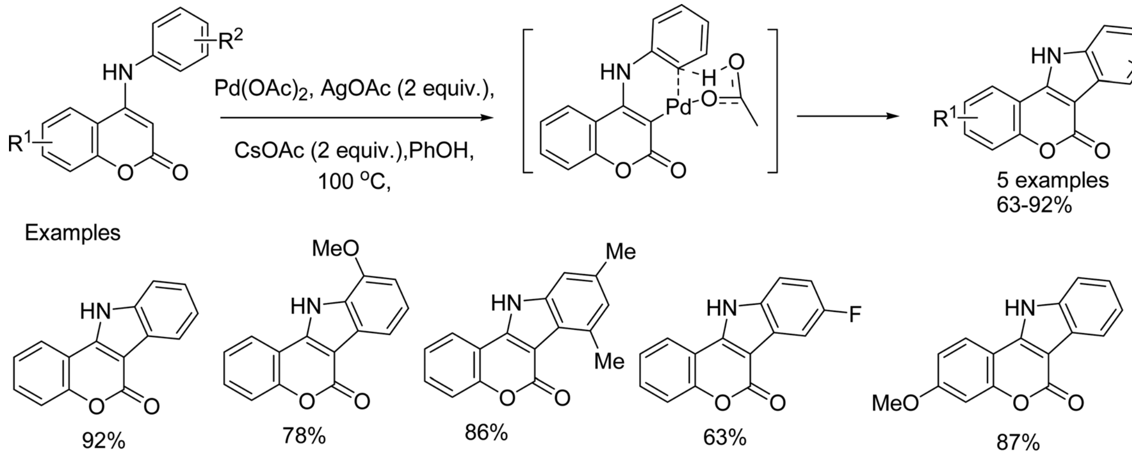


Scheme 49 Pd(II) catalyzed oxidative annulation of N-protected 4-aminocoumarin with various internal alkynes in the absence of a directing group for the synthesis pyrrolo coumarin.

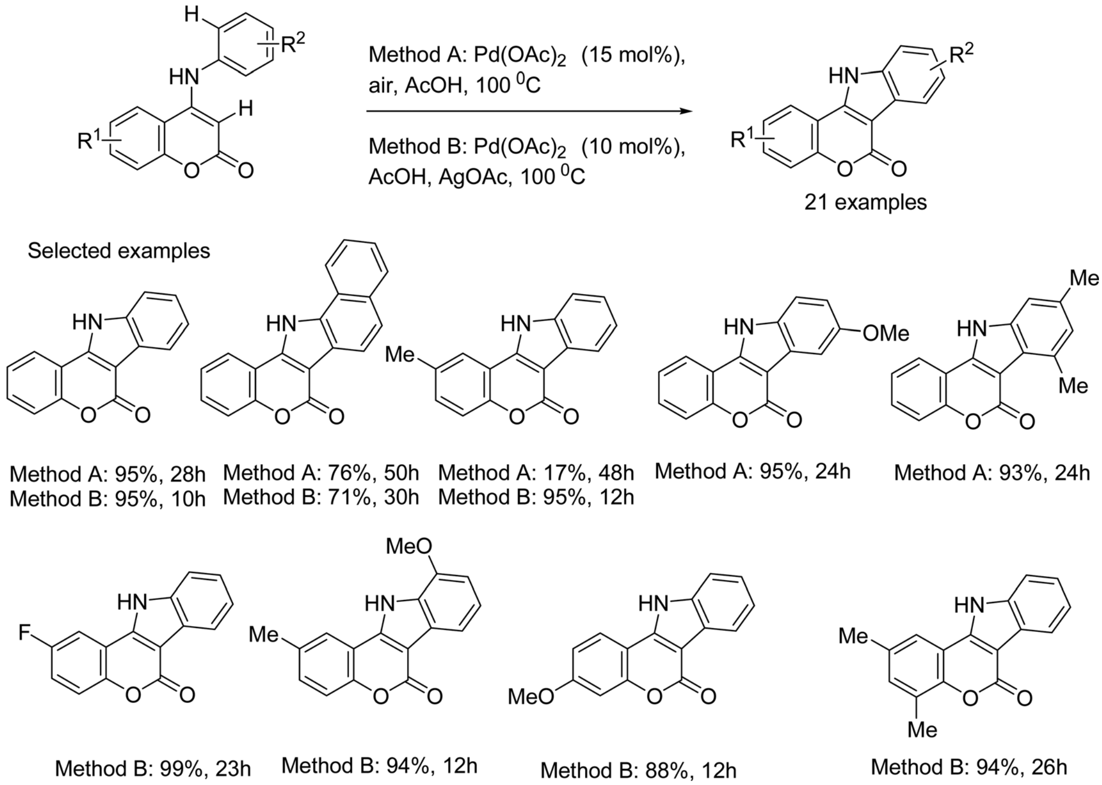
catalytic amount of CuTC in combination with Cs_2CO_3 as a base and TMEDA as a ligand.

Biological activities

Mohamed and coworkers[46] evaluated the cytotoxic study of the synthesized indolo[3,2-*c*]coumarins derivatives against HepG2 (hepatoma cells or human liver hepatocellular carcinoma cell line) and MCF7 (human breast adenocarcinoma cell line) and evaluation study revealed that the compounds with chlorine substituent at the 4-position of the phenyl ring in the



Scheme 50 Pd(II) catalyzed oxidative annulation in the presence of cesium acetate as a base, silver acetate as an oxidant for the synthesis indolo[3,2-c]coumarin derivatives.



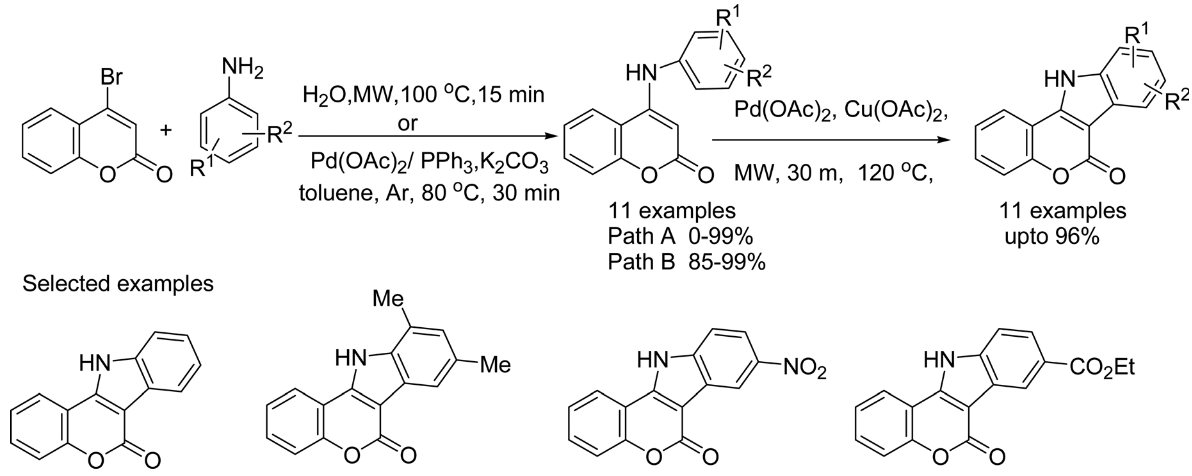
Scheme 51 Pd(II) catalyzed oxidative annulations of *N*-aryl aminocoumarins absence of a base for the synthesis indolo[3,2-*c*]coumarin derivatives.

N-aryl part of the pyrrolo[3,2-*c*]coumarins possessed the best cytotoxic activity reflected in IC_{50} ($\mu g\ mL^{-1}$) values (Table 1).

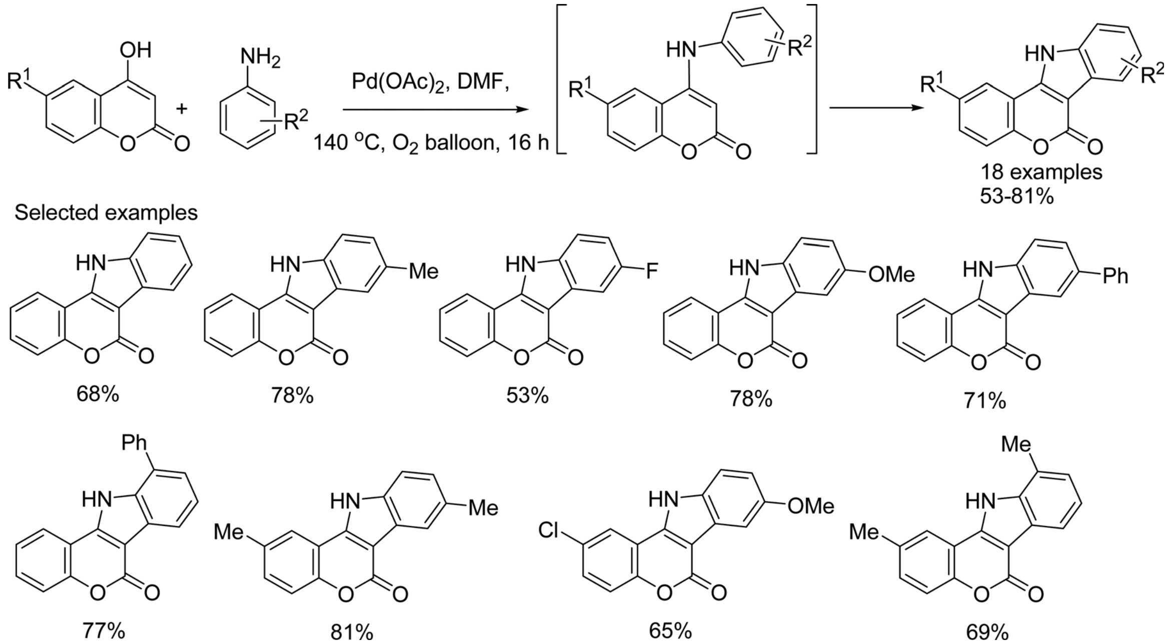
Litinas *et al.*[47] performed biological tests on azacoumestans (indolo[3,2-*c*]coumarin derivatives) as inhibitors of soybean lipoxygenase and inhibitors of lipid peroxidation. From IC_{50} ($\mu g\ mL^{-1}$) values, it indicated that azacoumestans having R = H or OMe exhibited excellent inhibition of soybean lipoxygenase activity whereas azacoumestans having $R{=}NO_2$ (3 or 4 positions) showed exceptional inhibition of lipid peroxidation activity (Table 2).

Iwao *et al.*,[44] reported the synthesis of indo[3,2-*c*]coumarin derivatives (Fig. 3) and designed them to evaluate their bioactivity against cell growth inhibitory activity on uterine cancer cells HeLa. The excellently observed IC_{50} values of all the designed compounds were found to be comparable or higher than that of lamellarin D which has a higher growth inhibitory activity than the control drug mitomycin C.

Wang and Shenqing,[45] evaluated the bio-activity of indo[3,2-*c*] coumarin derivatives as an efficient inhibitor of tumour vascular growth, which can be used for researching and treating or



Scheme 52 Microwave-assisted Pd(II) catalyzed two steps synthesis of indolo[3,2-*c*]coumarin derivatives from 4-bromocoumarin.



Scheme 53 One-step Pd(II) catalyzed synthesis of indolo[3,2-*c*]coumarin derivatives molecular oxygen as an oxidant from 4-hydroxycoumarin and aromatic amines.

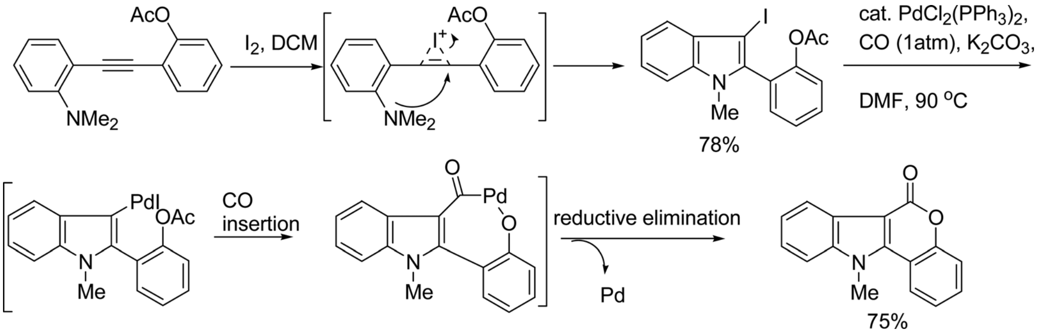
preventing malignant cell growth diseases. These compounds and their derivatives showed promising activity as inhibitors of such diseases (Fig. 4).

Dakshanamurthy *et al.*[48] evaluated the azacoumestan derivatives for their ability to block angiogenesis progression in the *in vitro* angiogenesis assay using human umbilical vein endothelial cells (HUVEC) and the HUVEC assay. The compounds exhibited noticeably inhibitory activity. Anti-angiogenesis therapy is a significant cancer treatment option to inhibit the growth of tumours directly (Fig. 5).

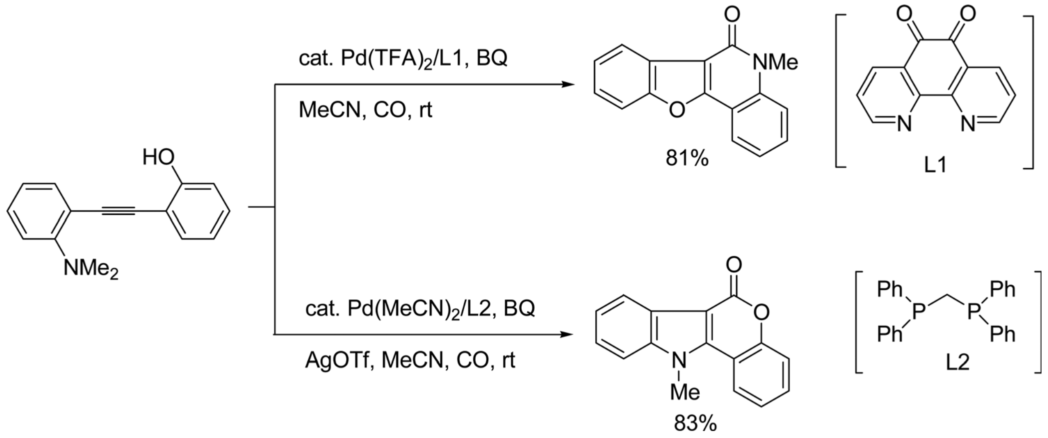
Azacoumestan derivatives were used as a benzodiazepines receptor–ligand as reported by Thakur *et al.*[49] in their topological modeling study. Hydrophobic and steric parameters of benzodiazepine-receptor (BZR) ligands play dominating role in developing a quantitative structure–activity relationship (QSAR) model. BZR is a uniquely complex receptor that is associated with a diverse biological activity profile. Azacoumestan derivatives having R$=$3,5-Me_2 or R$=$3-Cl substituents of the aryl moiety of the *N*-aryl part showed good receptor binding affinity (pIC_{50}) that indicates the presence of the hydrophobic contribution and steric effects favouring the exhibition of pIC_{50} (Table 3).

Fluorescence activities

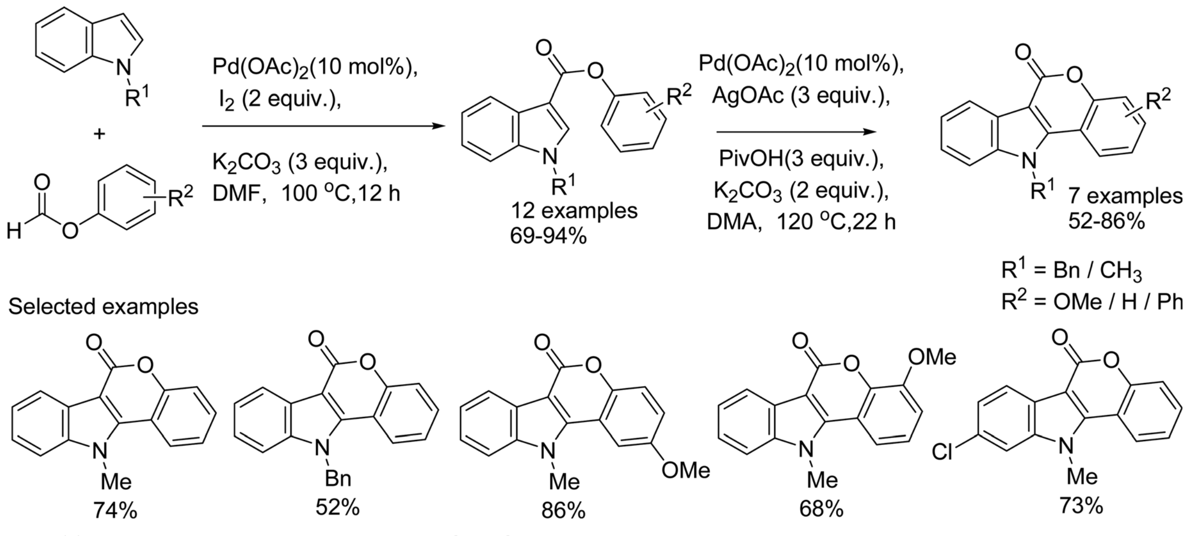
Yang and coworkers[61] investigated the photochemical and redox-switching properties of both 7-dimethylamino pyrrolo [3,2-*c*]coumarins on the coumarin moiety (R^2 = Ph, Me).



Scheme 54 Pd(II) catalyzed synthesis of indolo[3,2-*c*]coumarin derivatives *via* CO insertion by the construction of lactone ring.

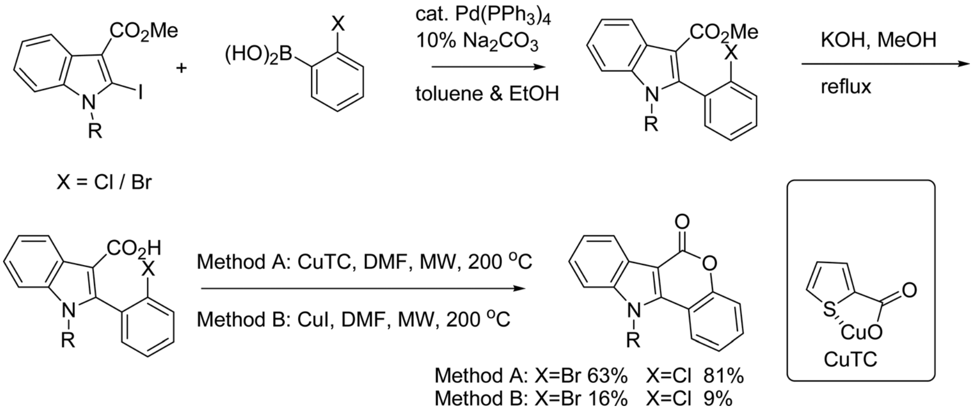


Scheme 55 Ligand controlled Pd-catalyzed regiodivergent carbonylation of alkynes explained by DFT calculations.

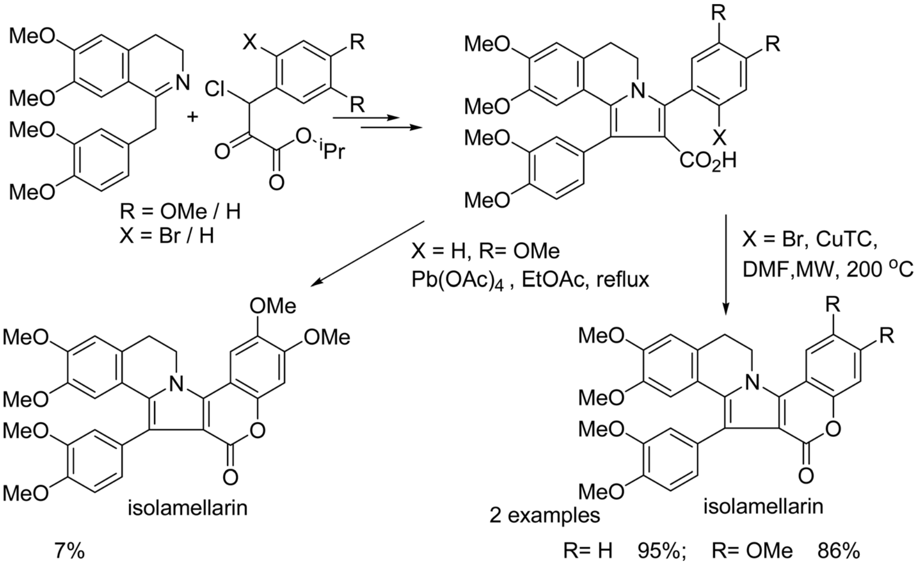


Scheme 56 Pd(II) catalyzed two-steps synthesis of indolo[3,2-*c*]coumarin by the construction of lactone ring *via* carbonylation with formate esters instead of CO.

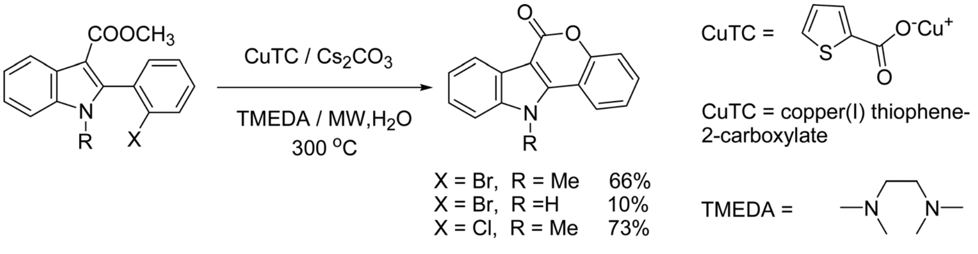
The synthesized compounds were highly light-sensitive and exhibited colors upon UV irradiation within a second by photooxidation of the colorless diphenyl-substituted pyrrolocoumarin resulting in a distinct change to red and a sharp decrease in fluorescence intensity. The photo-oxidized product can be quickly reverted to the original form by reduction with NaCNBH$_3$ or hydrogenation. However, no photooxidation product was observed when pyrrolo[3,2-*c*]coumarins were



Scheme 57 Microwave-assisted ligand- and base-free CuTC catalyzed synthesis of indolo[3,2-*c*]coumarin by the construction of lactone ring from 2-haloaryl-indole-3-carboxylic acids.



Scheme 58 Microwave-assisted CuTC catalyzed synthesis of isolamellarin by the construction of coumarin ring.



Scheme 59 Microwave-assisted CuTC catalytic synthesis of indolo[3,2-*c*]coumarins by the construction of lactone ring from 2-haloaryl-indole-3-carboxylic esters.

subjected to prolonged irradiation under the same conditions that suggest a crucial role in photochemical properties of the strong electron-donating properties of the 7-dimethylamino group. This assumption was supported by the cyclic voltammetry (CV) of the compounds (Fig. 6).

Pramanik *et al.*[50] reported 2,3-disubstituted pyrrolo[3,2-*c*] coumarins as a molecular probe that exhibited fluorescence quenching through selective binding with Cu^{2+} through the formation of a stable 6-membered cyclic chelate complex with the aryl-substituted –NH group and the ester carbonyl group of

Table 1 Relative cytotoxic activity of the compounds

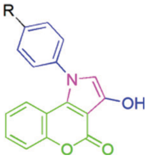
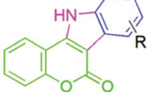
Compounds	*In vitro* cytotoxicity IC$_{50}$ (μg mL^{-1})	
	HePG-2	MCF-7
R=H	58.98 ± 0.89	71.55 ± 2.91
R=Me	49.60 ± 2.03	63.48 ± 2.11
R=OMe	49.65 ± 2.08	62.41 ± 2.23
R=Cl	44.71 ± 1.92	43.81 ± 1.83

Table 2 Relative biological results [*in vitro* inhibition of soybean lipoxygenase (LOX%) or (IC$_{50}$) μM;% inhibition of lipid peroxidation (AAPH%)]

Compounds	*In vitro* inhibition of LOX% and AAPH%; IC$_{50}$ (μg mL^{-1})	
	(LOX%)	(AAPH%)
R=H	26.5	66
R=4-OMe	26	100
R=4-NO$_2$	42.5	40
R=3-NO$_2$	22%	33
R=4-Cl	47	100
R=3-Me	36%	100
R=2-Me	55	68
R=4-COOEt	41.5	100
NDGA	5.5(94%)	—
Trolox	—	88

coumarins over other competitive metal ions like Na$^+$, K$^+$, Mn^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, Ag$^+$, Fe^{2+}, Fe^{3+}, Cr^{3+}, and As^{3+} in acetonitrile solvent. Thus, the compounds were selected as the fluorescent probe for bio-imaging of human cervical cancer (HeLa) cells in the presence of Cu^{2+} ions. Changing the solvent from acetonitrile to MeOH (polar and protic), the fluorescence quantum yields (Φ_F) for all the compounds (R = H, Cl, OMe) were found to be much lower due to extensive solvation through intermolecular hydrogen bonding with MeOH. So, acetonitrile was selected as a better solvent for showing the fluorescence activity and the fluorescence quantum yield (Φ_F) for compound (R=Cl) in that solvent was found to be more than that of other compounds (R = H, OMe) (Fig. 7).

Padilha and coworkers[51] evaluated the photophysical and electrochemical (cyclic voltammetry) properties of some of *N*-aryl 3-aryl pyrrolo[3,2-*c*]coumarins derivatives and their pentacyclic derivatives. Both compounds exhibited intense absorption in the region of 250 nm in their electronic excitation spectra, taken in dilute chloroformic solutions. The emission spectra of tricyclic and pentacyclic compounds were found in rather low intensity, in the blue region, and displayed essentially the same shape and position of their maxima (467 and 468 nm, with half bandwidths of 74 and 84 nm, respectively), indicating that the different organic moieties in coumarin did not play a fundamental role in the excited state of these compounds (Fig. 8).

Bochkov and coworkers[52] reported a series of novel non-symmetrical coumarin-fused BODIPY dyes and their spectral properties were studied. Absorption and fluorescence maxima of compound (X = H; R = NEt$_2$) have slightly longer wavelengths

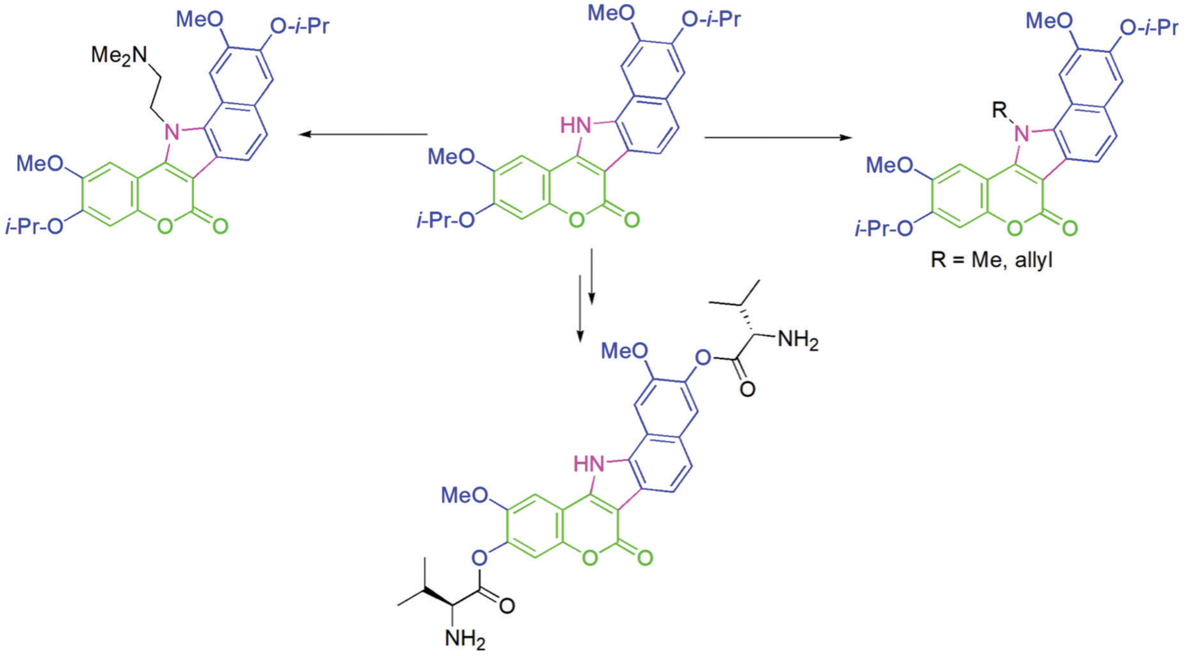


Fig. 3 Designed indo[3,2-c]coumarin derivatives as anti-cancer agents.

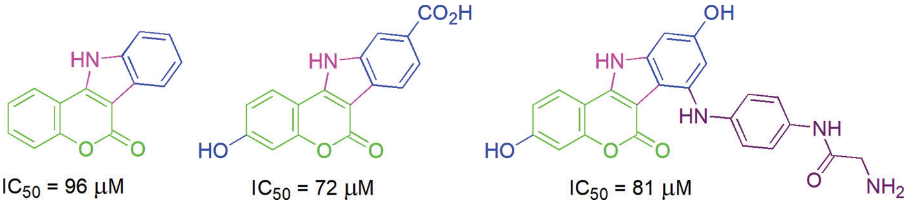


Fig. 4 Designed indo[3,2-*c*]coumarin derivatives as an efficient inhibitor of tumour vascular growth.

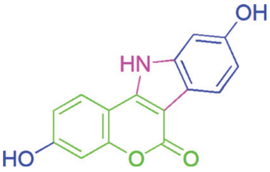
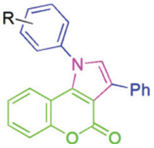
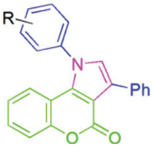


Fig. 5 Azacoumestan derivatives as an anti-angiogenesis agent.

Table 3 Structural details of benzodiazepine receptor ligands and their biological activity (pIC_{50})

Compounds 	Receptor binding affinity pIC_{50}	Compounds 	Receptor binding affinity pIC_{50}
R=H	7.19	R=4-Cl	7.40
R=3-Me	7.60	R=3,5-Me_2	8.07
R=4-Me	6.76	R=3-OMe	7.32
R=3-Cl	8.00	R=4-OMe	7.21

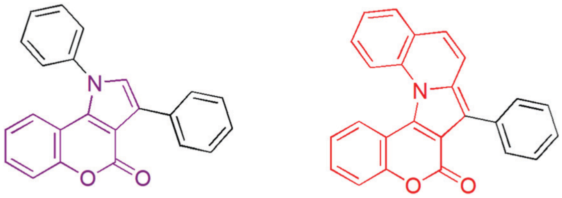


Fig. 8 Fluorescence active pyrrolo[3,2-*c*]coumarins and their pentacyclic derivatives.

as compared to the compound (X = Et; R = NEt_2). The replacement of the 2-ethyl-substituent with hydrogen (H) in the pyrrole ring of the coumarin fused BODIPYs causes a blue shift of the absorption and emission bands of about 20–25 nm. Their absorption and emission properties are strongly influenced by substitution in the coumarin moiety as well as pyrrole moiety. Coumarin containing diethylamine functionality of the dyes showed near-IR emission with large Stokes shifts (up to 144 nm) and good fluorescence quantum yields. So, coumarin-fused BODIPY is a useful scaffold for the design of

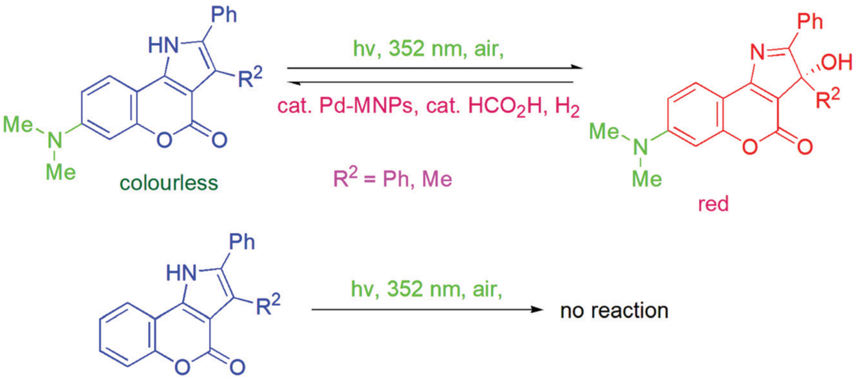


Fig. 6 Redox-switching properties 7-dimethylamino pyrrolo[3,2-c]coumarins upon UV irradiation.

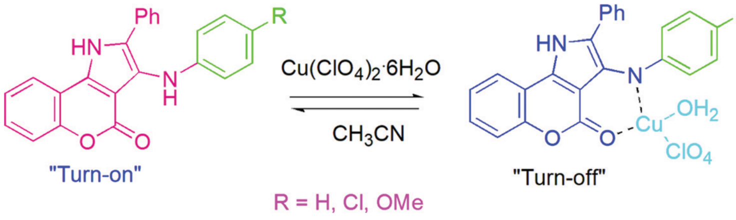


Fig. 7 Sensing mechanism of synthesized pyrrolo[3,2-c]coumarins with Cu^{2+}.

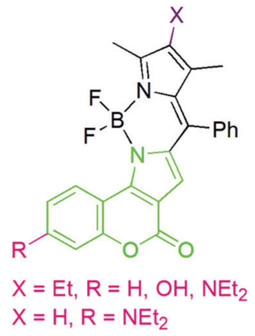


Fig. 9 Complex derivatives of pyrrolo[3,2-c]coumarins as fluorescence dyes.

new efficient NIR-emitting dyes with large Stokes shifts for various applications (Fig. 9).

Conclusions and perspectives

From time to time, different novel methods with their advantages and disadvantages are employed for the construction of both coumarins as well as pyrrole or indole rings. Among them, researchers will choose the most appropriate greener and eco-friendly methods for the synthesis of coumarin fused pyrrole and indole derivatives that increase research interest of pyrrolo/indolo[3,2-*c*]coumarins and other lamellarin-related molecules for further modifications. This work brings out contributions on different classical methods, including Knorr synthesis, Hantzsch synthesis, Michael addition, Wittig reaction, sigmatropic rearrangement, cyclization *via* nitrene intermediates with a green approach, transition metal-catalyzed mainly palladium-catalyzed Suzuki, Heck, and Oxidative Heck reactions for the construction of pyrrole or coumarin rings and their applications in organic synthesis and pharmaceutical chemistry. From the above-mentioned synthetic methodologies, it is concluded that the C–H bond in the 3-position in the lactone ring of the coumarin moiety and the C–H bond in the 2-position of the pyrrole ring could be activated *via* C–H activation to form the C–C bond without prefunctionalization by halogens producing new pyrrolo/indolo[3,2-*c*]coumarin in many cases.

In the future, depending upon the significant contribution of the existing library of related reports, our review article will help to give confidence to synthetic organic chemists for further development of more challenging coumarin fused pyrrole or indole and other 3,4-heterocycle-fused coumarins through the exploration of copper and palladium catalyst and with the help of other green synthetic approaches. As the existing and reported pyrrolo/indolo[3,2-*c*]coumarin derivatives and related compounds possess mainly anti-tumor and anti-cancer activities, which will assist medicinal chemists and pharmacists for further developments. Coumarin derivatives are a great platform for designing varieties of small molecule-based fluorescent probes because of their strong fluorescence, good structural flexibility, and excellent biocompatibility. These attractive properties explore the application of pyrrolocoumarin-fused-based fluorescence sensors in the fields of chemical sensors, molecular recognition, analytical chemistry, bioorganic chemistry, bio-imaging and materials chemistry.

Conflicts of interest

The authors declare no conflict of interest.

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References

1 F. Borges, F. Roleira, N. Milhazes, L. Santana and E. Uriarte, *Curr. Med. Chem.*, 2005, **12**, 887–916.
2 K. C. Fylaktakidou, D. J. Hadjipavlou-Litina, K. E. Litinas and D. N. Nicolaides, *Curr. Pharm. Des.*, 2004, **10**, 3813–3833.
3 F. G. Medina, J. G. Marrero, M. Macias-Alonso, M. C. Gonzalez, I. Cordova-Guerrero, A. G. T. Garcia and S. Osegueda-Roblesa, *Nat. Prod. Rep.*, 2015, **32**, 1472–1507.
4 G. Melagraki, A. Afantitis, O. Igglessi-Markopoulou, A. Detsi, M. Koufaki, C. Kontogiorgis and D. J. Hadjipavlou-Litina, *Eur. J. Med. Chem.*, 2009, **44**, 3020–3026.
5 A. Lacy and R. O'Kennedy, *Curr. Pharm. Des.*, 2004, **10**, 3797–3811.
6 P. Patra, G. K. Kar, A. Sarkar, J. K. Ray, T. Dasgupta, M. Ghosh and S. Bhattacharya, *Synth. Commun.*, 2012, **42**, 3031–3041.
7 D. A. Ostrov, J. A. Hernandez-Prada, P. E. Corsino, K. A. Finton, N. Le and T. C. Rowe, *Antimicrob. Agents Chemother.*, 2007, **51**, 3688–3698.
8 F. Chimenti, B. Bizzarri, A. Bolasco, D. Secci, P. Chimenti, A. Granese, S. Carradori, D. Rivanera, A. Zicari, M. M. Scaltrito and F. Sisto, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4922–4926.
9 D. Feng, A. Zhang, Y. Yang and P. Yang, *Arch. Pharm.*, 2020, **353**, 1900380, DOI: 10.1002/ardp.20190038.
10 K. V. Sashidhara, A. Kumar, M. Chatterjee, K. B. Rao, S. Singh, A. K. Verma and G. Palit, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1937–1941.
11 I. Kostova, S. Bhatia, P. Grigorov, S. Balkansky, V. S. Parmar, A. K. Prasad and L. Saso, *Curr. Med. Chem.*, 2011, **18**, 3929–3951.
12 G.-L. Xi and Z.-Q. Liu, *J. Agric. Food Chem.*, 2015, **63**, 3516–3523.
13 T. Kund and A. Pramanik, *Bioorg. Chem.*, 2020, **98**, 103734, DOI: 10.1016/j.bioorg.2020.103734.
14 G. A. Gonçalves, A. R. Spillere, G. M. das Neves, L. P. Kagami, G. L. von Poser, R. Faria, S. Canto and V. L. Eifler-Lima, *Eur. J. Med. Chem.*, 2020, **203**, 112514.

15 Y. Bansal, P. Sethi and G. Bansal, *Med. Chem. Res.*, 2013, **22**, 3049–3060.

16 X. M. Peng, G. L. Damu and C. Zhou, *Curr. Pharm. Des.*, 2013, **19**, 3884–3930.

17 T. U. Kumar, Y. Bobde, S. Pulya, K. Rangan, B. Ghosh and A. Bhattacharya, *ChemistrySelect*, 2019, **4**, 10726–10730.

18 Z. Chen, X. Wang, W. Zhu, X. Cao, L. Tong, H. Li, H. Xie, Y. Xu, S. Tan, D. Kuang, J. Ding and X. Qian, *J. Med. Chem.*, 2011, **54**(11), 3732–3745.

19 I. A. Pullar, S. L. Carney, E. M. Colvin, V. L. Lucaites, D. L. Nelson and S. Wedley, *Eur. J. Pharmacol.*, 2000, **407**, 39–46.

20 V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman and P. Sharma, *RSC Adv.*, 2015, **5**, 15233–15266.

21 D. Imbri, J. Tauber and T. Opatz, *Mar. Drugs*, 2014, **12**, 6142–6177.

22 H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264–287.

23 P. Krishnaiah, V. L. N. Reddy, G. Venkataramana, K. Ravinder, M. Srinivasulu, T. V. Raju, K. Ravikumar, D. Chandrasekar, S. Ramakrishna and Y. J. Venkateswarlu, *Nat. Prod.*, 2004, **67**, 1167–1168.

24 C. Bailly, *Mar. Drugs*, 2015, **13**, 1105–1123.

25 J. Kluza, M.-A. Gallego, A. Loyens, J.-C. Beauvillain, J.-M. F. Sousa-Faro, C. Cuevas, P. Marchetti and C. Bailly, *Cancer Res.*, 2006, **66**, 3177–3187.

26 F. Plisson, X. C. Huang, H. Zhang, Z. Khalil and R. J. Capon, *Chem. – Asian J.*, 2012, **7**, 1616–1623.

27 M. Vanhuyse, J. Kluza, C. Tardy, G. Otero, C. Cuevas, C. Bailly and A. Lansiaux, *Cancer Lett.*, 2005, **221**, 165–175.

28 M. V. R. Reddy, M. R. Rao, D. Rhodes, M. S. T. Hansen, K. Rubins, F. D. Bushman, Y. Venkateswarlu and D. J. J. Faulkner, *Med. Chem.*, 1999, **42**, 1901–1907.

29 C. P. Ridley, M. V. R. Reddy, G. Rocha, F. D. Bushman and D. J. Faulkner, *Bioorg. Med. Chem.*, 2002, **10**, 3285–3290.

30 D. L. Boger, D. R. Soenen, C. W. Boyce, M. P. Hedrick and Q. Jin, *J. Org. Chem.*, 2000, **65**, 2479–2483.

31 A. R. Quesada, M. D. G. Grávalos and J. L. F. Puentes, *Br. J. Cancer*, 1996, **74**, 677–682.

32 C. Neagoie, E. Vedrenne, F. Buron, J. Y. Mérour, S. Rosca, S. Bourg, O. Lozach, L. Meijer, B. Baldeyrou, A. Lansiaux and S. Routier, *Eur. J. Med. Chem.*, 2012, **49**, 379–396.

33 K. A. Koo, N. D. Kim, Y. S. Chon, M.-S. Jung, B.-J. Lee, J. H. Kim and W.-J. Song, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2324–2328.

34 A. Foucourt, D. Hedou, C. Dubouilh-Benard, L. Desire, A.-S. Casagrande, B. Leblond, N. Loaec, L. Meijer and T. Besson, *Molecules*, 2014, **19**, 15546–15571.

35 H. Falke, A. Chaikuad, A. Becker, N. Loaec, O. Lozach, S. Abu Jhaisha, W. Becker, P. G. Jones, L. Preu, K. Baumann, S. Knapp, L. Meijer and C. Kunick, *J. Med. Chem.*, 2015, **58**, 3131–3143.

36 M. V. R. Reddy, M. R. Rao, D. Rhodes, M. S. T. Hansen, K. Rubins, F. D. Bushman, Y. Venkateswarlu and D. J. Faulkner, *J. Med. Chem.*, 1999, **42**, 1901–1907.

37 P. A. Vadola and D. Sames, *J. Org. Chem.*, 2012, **77**, 7804–7814.

38 T. Fukuda, F. Ishibashi and M. Iwao, *Heterocycles*, 2011, **83**, 491–529.

39 M. Chittchang, P. Batsomboon, S. Ruchirawat and P. Ploypradith, *ChemMedChem*, 2009, **4**, 457–465.

40 M. Vanhuyse, J. Kluza, C. Tardy, G. Otero, C. Cuevas, C. Bailly and A. Lansiaux, *Cancer Lett.*, 2005, **221**, 165–175.

41 N. Zhang, D. Wang, Y. Zhu, J. Wang and H. Lin, *Asian Pac. J. Cancer Prev.*, 2014, **15**, 9915–9919.

42 M. Facompre, C. Tardy, C. Bal-Mahieu, P. Colson, C. Perez, I. Manzanares, C. Cuevas and C. Bailly, *Cancer Res.*, 2003, **63**, 7392–7399.

43 J. Kluza, M.-A. Gallego, A. Loyens, J.-C. Beauvillain, J.-M. F. Sousa-Farco, C. Cuevas, P. Marchetti and C. Bailly, *Cancer Res.*, 2006, **66**, 3177–3187.

44 M. Iwao, F. Ishibashi, T. Fukuda and H. Hasegawa, *PCT Int. Appl.*, WO2012/099129, 2012.

45 W. Wang and F. Z. Shenqing, CN102321090, 2012.

46 K. S. Mohamed and E. E. Elbialy, *J. Heterocycl. Chem.*, 2018, **55**, 893–898.

47 T. Balalas, A. Abdul-Sada, D. J. Hadjipavlou-Litina and K. E. Litinas, *Synthesis*, 2017, 2575–2583.

48 S. Dakshanamurthy, M. Kim, M. L. Browna and S. W. Byers, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4551–4556.

49 A. Thakur, M. Thakur and P. Khadikar, *Bioorg. Med. Chem.*, 2003, **11**, 5203–5207.

50 S. Mukherjee, S. Hazra, S. Chowdhury, S. Sarkar, K. Chattopadhyay and A. Pramanik, *J. Photochem. Photobiol., A*, 2018, **364**, 635–644.

51 G. Padilha, B. A. Iglesias, D. F. Back, T. S. Kaufman and C. C. Silveira, *ChemistrySelect*, 2017, **2**, 1297–1304.

52 A. Y. Bochkov, I. O. Akchurin, O. A. Dyachenko and V. F. Traven, *Chem. Commun.*, 2013, **49**, 11653–11655.

53 F. Salehian, H. Nadri, L. Jalili-Baleh, L. Youseftabar-Miri, S. N. Abbas Bukhari, A. Foroumadi, T. T. Küçükkilin, M. Sharifzadeh and M. Khoobi, *Eur. J. Med. Chem.*, 2020, 113034, DOI: 10.1016/j.ejmech.2020.113034.

54 T. Fukuda, F. Ishibashi and M. Iwao, *Alkaloids*, 2020, **83**, 1–112.

55 W. Stadlbauer and T. Kappe, *Monatsh. Chem.*, 1984, **115**, 467–475.

56 A. Alberola, R. Álvaro, J. M. Andrés, B. Calvo and A. González, *Synthesis*, 1994, 279–281.

57 A. Alberola, R. Álvaro, A. G. Ortega, M. L. Sádaba and M. C. Sañudo, *Tetrahedron*, 1999, **55**, 13211–13224.

58 A. Alberola, L. Calvo, A. González-Ortega, A. P. Encabo and M. C. Sañudo, *Synthesis*, 2001, 1941–1948.

59 R. A. Navarro, L. C. Bleye, A. González-Ortega and M. C. S. Ruiz, *Heterocycles*, 2001, **55**, 2369–2386.

60 Y.-X. Liao, P.-Y. Kuo and D.-Y. Yang, *Tetrahedron Lett.*, 2003, **44**, 1599–1602.

61 C.-H. Lin and D.-Y. Yang, *Org. Lett.*, 2013, **15**, 2802–2805.

62 K. Pradhan, S. Paul and A. R. Das, *RSC Adv.*, 2015, **5**, 12062–12070.

63 X. Yang, L. Jing and Z. Chen, *Chem. Heterocycl. Compd.*, 2018, **54**, 1065–1069.

64 Z. Chen, X. Yang and W. Su, *Tetrahedron Lett.*, 2015, **56**, 2476–2479.

65 M. Saha, K. Pradhan and A. R. Das, *RSC Adv.*, 2016, **6**, 55033–55038.

66 Z. Chen, S. Ye and X. Zhang, *Heterocycles*, 2018, **96**, 501–508.

67 S. Mukherjee, S. Sarkar and A. Pramanik, *ChemistrySelect*, 2018, **3**, 1537–1544.

68 S. Paul and A. R. Das, *Catal. Sci. Technol.*, 2012, **2**, 1130–1135.

69 S. Paul, G. Pal and A. R. Das, *RSC Adv.*, 2013, **3**, 8637–8644.

70 R. Mishra, A. Kumar Panday, L. H. Choudhury, J. Pal, R. Subramanian and A. Verma, *Eur. J. Org. Chem.*, 2017, 2789–2800.

71 K. Ghosh, R. Karmakar and D. Mal, *Eur. J. Org. Chem.*, 2013, 4037–4046.

72 X. Yang, L. Zheng, Z. Chen and W. Zhong, *Synth. Commun.*, 2018, **48**, 929–935.

73 H. Yahyavi, M. M. Heravi, M. Mahdavi and A. Foroumadi, *Tetrahedron Lett.*, 2018, **59**, 94–98.

74 A. Yadav, S. K. Gudimella and S. Samanta, *ChemistrySelect*, 2019, **4**, 12768–12773.

75 S. Peddibhotla, *Curr. Bioact. Compd.*, 2009, **5**, 20–38.

76 T. O. Painter, K. Kaszas, J. Gross, J. T. Douglas, V. W. Day, M. J. Iadarola and C. Santini, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 963–968.

77 T. Li, J. Wang, J. Xu, J. Jin, Y. R. Chi and Z. Jin, *Org. Lett.*, 2020, **22**, 326–330.

78 S. Vyasamudri and D.-Y. Yang, *J. Org. Chem.*, 2019, **84**, 3662–3670.

79 X. Lai and C. Che, *ACS Omega*, 2020, **5**, 21968–21977.

80 K. C. Majumdar and S. K. Samanta, *Tetrahedron Lett.*, 2002, **43**, 2119–2121.

81 E. E. Galenko, V. A. Bodunov, A. V. Galenko, M. S. Novikov and A. F. Khlebnikov, *J. Org. Chem.*, 2017, **82**, 8568–8579.

82 H. W. Stadlbauer, A.-S. Karem and T. Kappe, *Monatsh. Chem.*, 1987, **118**, 81–89.

83 W. Stadlbauer, R. Laschober and T. Kappe, *Monatsh. Chem.*, 1991, **122**, 853–861.

84 R. A. Irgasheva, A. A. Karmatskya, P. A. Slepukhina, G. L. Rusinova and V. N. Charushin, *Tetrahedron Lett.*, 2013, **54**, 5734–5738.

85 C. A. James, A. L. Coelho, M. Gevaert, P. Forgione and V. Snieckus, *J. Org. Chem.*, 2009, **74**, 4094–4103.

86 C.-P. Chang, S. V. Pradiuldi and F.-E. Hong, *Inorg. Chem. Commun.*, 2009, **12**, 596–598.

87 S. Peng, L. Wang, J. Huang, S. Sun, H. Guo and J. Wanga, *Adv. Synth. Catal.*, 2013, **355**, 2550–2557.

88 C. Cheng, W.-W. Chen, B. Xua and M.-H. Xu, *Org. Chem. Front.*, 2016, **3**, 1111–1115.

89 C. Cheng, W.-W. Chen, B. Xu and M.-H. Xu, *J. Org. Chem.*, 2016, **81**, 11501–11507.

90 A. Dey, Md A. Ali, S. Jana, S. Samanta and A. Hajra, *Tetrahedron Lett.*, 2017, **58**, 313–316.

91 T. Yao, D. Yue and R. C. Larock, *J. Org. Chem.*, 2005, **70**, 9985–9989.

92 J. Liu, X. Zhang, Y. Tian, X. Wang, X. Zhu and D. Chen, *Dalton Trans.*, 2019, **48**, 15059–15067.

93 J. Wu, J. Lan, S. Guo and J. You, *Org. Lett.*, 2014, **16**, 5862–5865.

94 N. Thasana, R. Worayuthakarn, P. Kradanrat, E. Hohn, L. Young and S. Ruchirawat, *J. Org. Chem.*, 2007, **72**, 9379–9382.

95 P. Nealmongkol, K. Tangdenpaisal, S. Sitthimonchai, S. Ruchirawat and N. Thasana, *Tetrahedron*, 2013, **69**, 9277–9283.