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REVIEW ARTICLE

Synthesis and Functionalization of Coumarin-Pyrazole Scaffold: Recent Development, Challenges, and Opportunities

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Abstract: Heterocycles are the main structural motif of DNA and RNA and play a crucial role in various chemical reactions of metabolisms. Therefore, heterocyclic compounds show good physiological and pharmacological properties. Coumarin and pyrazole scaffolds are present in many commercial drug molecules and natural products. This review overviews the progress made in the synthesis and functionalization of the coumarin-pyrazole hybrid heterocycle. It also includes discussion on the possible reactive sites of heterocycles, functionalization, and mechanistic pathways to incorporate pyrazole pharmacophore unit in synthesis. Several synthesis and biological studies reveal that the combination of the coumarin-pyrazole moiety is a prominent structural motif to find lead compounds in drug discovery.

Keywords: Coumarin-pyrazole, Vilsmeier-Haack, formylation, multicomponent reactions, heterocycles, DNA.

1. INTRODUCTION

Heterocycles are the main structural motif of life as they are widely distributed in nature and play a crucial role in various chemical reactions of metabolisms [1]. Heterocycles are the backbone of all living organisms as they are the main constituents of DNA and RNA. Therefore, heterocyclic compounds show good physiological and pharmacological properties. Nitrogen and oxygen-containing heterocycles are the core structures of numerous biologically active compounds and exhibit wide applications in chemistry, biology, and material sciences [2]. Particularly, coumarin and its derivatives are present in many pharmaceutically important molecules and natural products. Coumarins are chemically known as 2*H*-1-benzopyran-2-ones and were first isolated in 1820 as an oxygenated fused bicyclic heterocycle by Vogel [3, 4]. Coumarin moiety is present in a number of natural products, such as Alternariol (3,7,9-trihydroxy-1-methyl-6H benzo[c]chromen-6-one), a toxic metabolite of *Alternaria* fungi, Umbelliferone (7-hydroxy coumarin) which is found in Apiaceae [5], Osthole (7-methoxy-8-(3-methylbut-2-en-1-yl) coumarin) which is found in *Cnidium monnieri* [6-8], and Scoparone (6,7-dimethoxy coumarin) which is found in *Artemisia scoparia* [9]. Coumarins are also an important component in cereals and fruits exhibiting antifungal and phytotoxic activity. In addition, coumarin derivatives have shown prominent biological activities such as antioxidant [10, 11], antimicrobial [12-16], anti-HIV [17-21], antibiotic [22, 23], muscle relaxant [5], anti-inflammatory [24, 25], antidepressant [26], antinociceptive [27], antitumor [28], antiviral [29, 30] anti-influenza [31], anti-Alzheimer [32, 33], anti-asthmatic [34], antihyperlipidemic [35], antipyretic [36], anticoagulant [37, 38], antitubercular [39-48], and anticancer [49-52] activity. Further, they are widely used as perfumes, additives in food, laser dyes, optical brightening agents, and cosmetics [53, 54]. Therefore, coumarin scaffolds have attracted a great deal of attention from organic chemists because of their synthetic utility as building blocks for the synthesis of biologically potent molecules.

2. COUMARIN-PYRAZOLE BASED BIOLOGICALLY ACTIVE MOLECULES

Moreover, coumarin incorporated with other heterocycles also has shown prominent diversified activities such as anti-inflammatory (**I**) [55], cytotoxic-activity (**II-V**) [56-59], anticoagulant (**VI**) [60], vasorelaxing-activity (**VII**) [61], and as inhibitors of amyloid-*β*-aggregation (**VIII**) [62] activity as shown in Fig. (**1**).

Pyrazoles are well-known examples of aromatic heterocycles containing two nitrogen atoms in their five-membered rings [63]. They constitute an important heterocyclic family covering a broad range of synthetic as well as natural products that display innumerable chemical, biological, agrochemical, and pharmacological properties [64, 65]. Therefore, pyrazole is one of the key motifs and occupies prime importance in medicinal chemistry due to its wide range of pharmacological activities such as anti-fungal [66], anti-HIV [67, 68], anti-inflammatory [69], anti-proliferative [70], antimicrobial [71], anticancer [72], anticonvulsant [73], and anti-TB [74-79] activities.

Pyrazoles having a functional group like aldehyde or carboxylate at C-4 position have shown promising antimicrobial properties. Therefore, several blockbuster drugs have been developed from the substituted pyrazole (Fig. **1**) [73]. Pyrazole-containing molecule, **celecoxib** (**IX**), demonstrates anti-inflammatory effects and inhibits COX-2. **Rimonabant** (**X**) functions as a cannabinoid receptor and is used to treat obesity, **fomepizole** (**XI**) inhibits alcohol dehydrogenase, and **sildenafil** (**XII**) inhibits phosphodiesterase [80]. In addition, pyrazole derivatives have shown important applications in material chemistry [81] as brightening agents [82] having

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This paper is dedicated to Prof. Vinod K. Tiwari, Banaras Hindu University, Varanasi

1570-1794/21 $65.00+.00

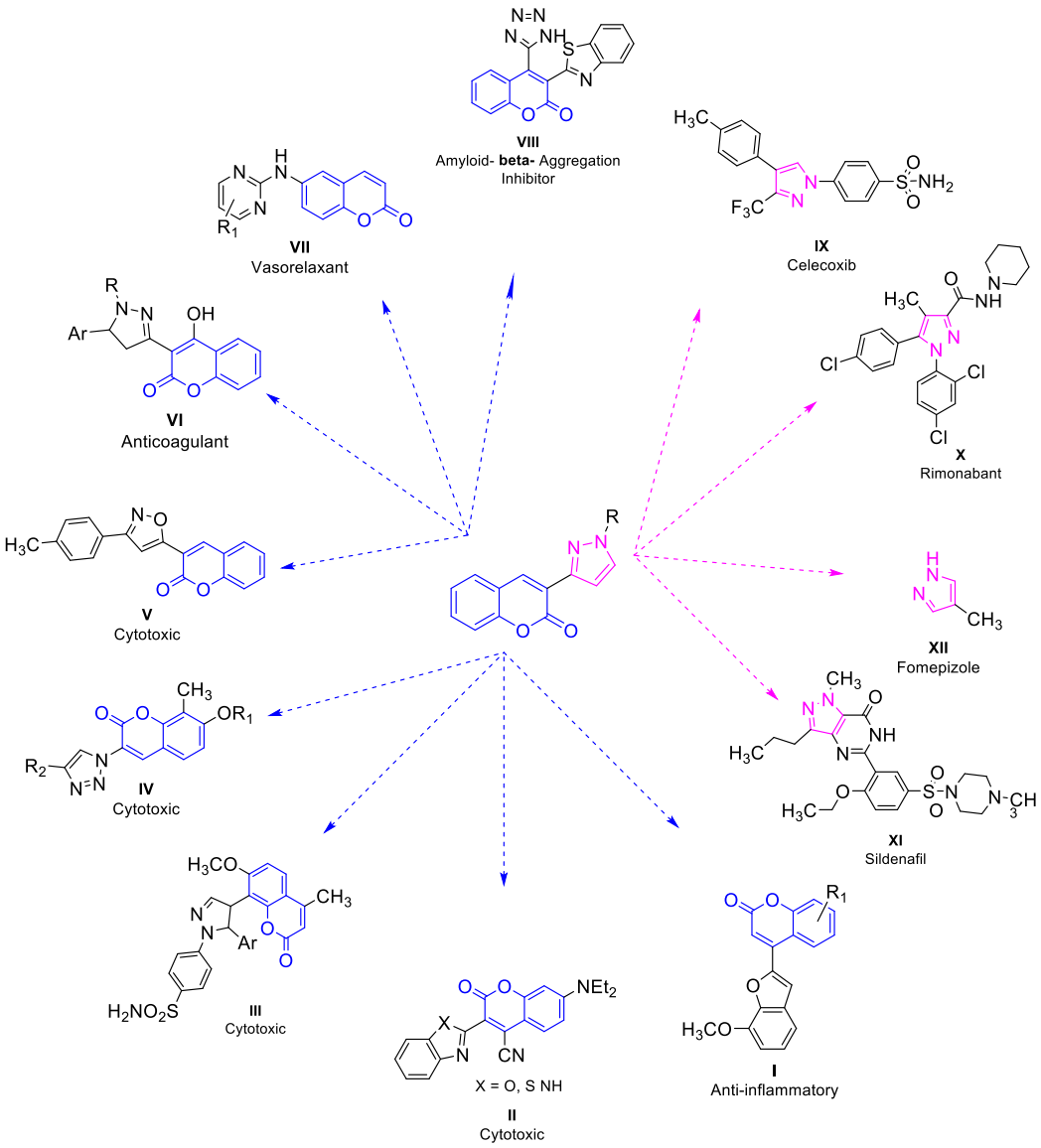


Fig. (1). Biologically important coumarin and pyrazole based heterocycles.

electroluminescence [83] and solvatochromic [84] properties. Moreover, they act as organic light-emitting diodes [85], liquid crystals [86], and semiconductors [87]. Heterocycles having pyrazole rings are also of considerable interest because of their synthetic utility as synthetic reagents in multicomponent reactions [88], guanylating agents [89], and chiral auxillaries [90]. It has also been found that various substituted pyrazoles are used as chelation and extraction reagents for many metal ions [91].

Pyrazoles incorporated with coumarin were synthesized, which showed a significant change in pharmacological properties. Furthermore, several synthesis and biological studies revealed that coumarin-pyrazole moiety is a prominent structural motif for finding lead compounds in drug discovery. Coumarin-pyrazole derivatives have shown prominent biological activities such as antioxidant (**XIII-XV**) [99, 100, 106, 109, 110, 119], anticancer (**XVI** and **XVII**) [113, 123, 128, 134], antimicrobial (**XVIII-XXI**) [99, 100, 104, 111, 112, 119, 121, 124, 126, 128, 131], anti-tubercular (**XXII**) [112], α-Glucosidase inhibitor (**XXIII** and **XXIV**) [130], antibacterial [99, 100, 119, 121, 126, 131], antiproliferative [122, 134], PDE inhibitor [132], and antihyperglycemic agents [106] (Fig. **2**).

To the best of our knowledge, in light of the significance of coumarin-pyrazoles derivatives, to date, a concise review is not reported covering synthesis and functionalization of coumarin-pyrazole building blocks for the generation of libraries of biologically active compounds. In continuation of our research interest in pharmacologically important heterocycles [92], this concise review focuses on the synthesis and functionalization of diverse coumarin-pyrazole derivatives.

3. MOLECULAR STRUCTURE AND PROPERTIES

Coumarin-pyrazole scaffold constitutes two heterocycles, viz. coumarin and pyrazole. Coumarin-pyrazole chemistry mainly constitutes the substituted 3-(1-phenyl or 1*H*-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one moiety. With respect to substitution of N-atom of pyrazole ring in the coumarin-pyrazole scaffold, two prominent derivatives **1** and **2** were reported in numerous protocols as shown in Fig. (**3**).

The corresponding spectral information, IR (KBr), ^{1}H NMR (400 MHz, DMSO-d_6/TMS), and ^{13}C NMR (100 MHz, DMSO-d_6/TMS) of coumarin-pyrazole derivatives **1** and **2** is shown in Table **1**.

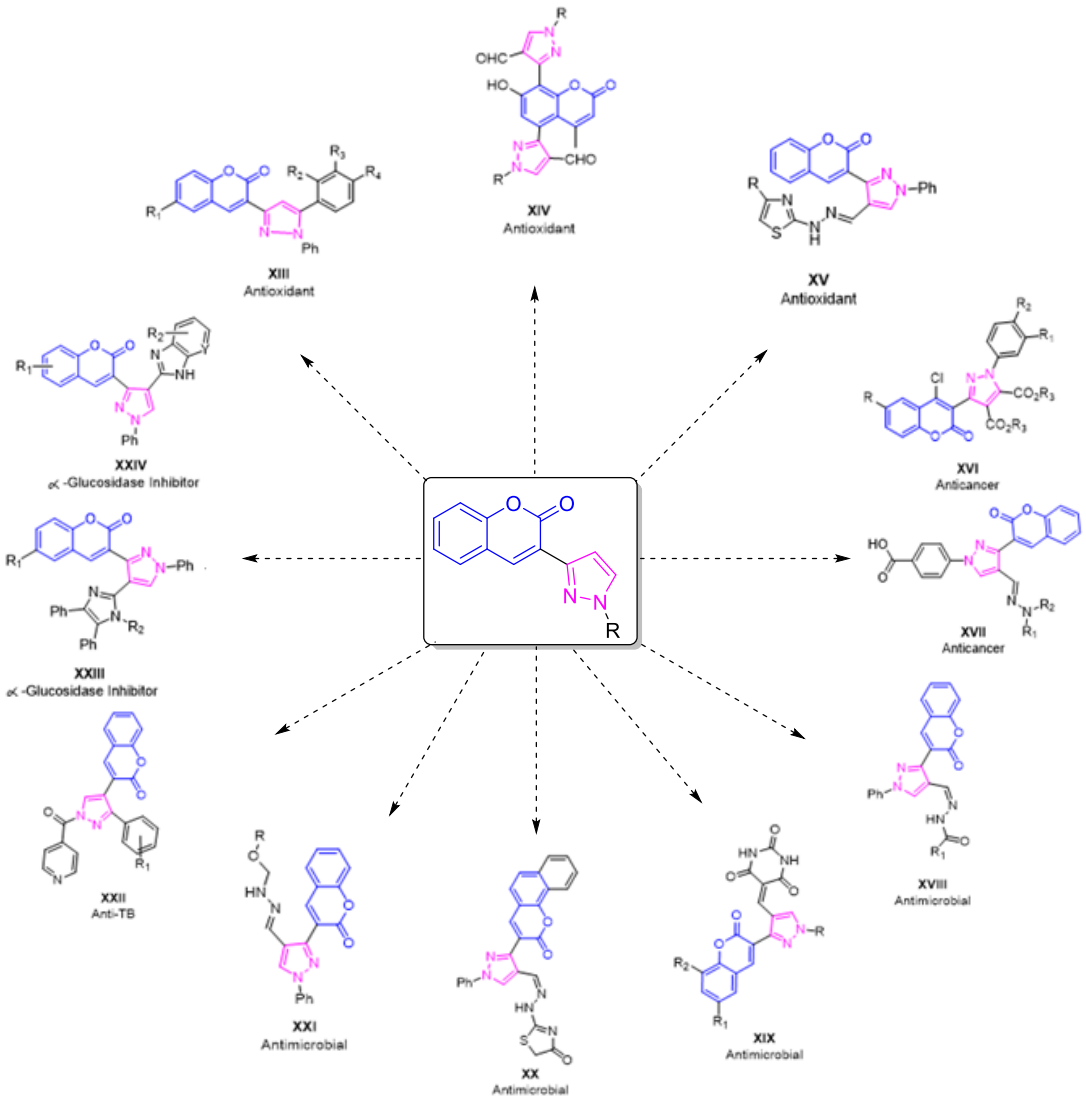


Fig. (2). Biologically active coumarin-pyrazole scaffold-based derivatives.

Fig. (3). Structure of Coumarin-pyrazole derivatives **1** and **2**.

4. SYNTHETIC STRATEGIES FOR COUMARIN-PYRAZOLE DERIVATIVES

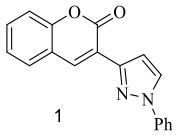
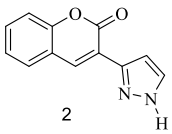
Chodankar and co-workers put forward a synthetic route for a series of 3-(1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one (i.e. coumarin-pyrazole **1**) [96]. In this protocol, intermediate coumarin carboxylic acid **5** was prepared from salicyaldehyde **3**, succinic anhydride **4**, sodium succinate, and catalytic conc. HCl. The second intermediate (*E*)-3-hydroxy-2-(2-oxo-2*H*-chromen-3-yl) acrylaldehyde **6** was obtained by Vilsmeier-Haack formylation of intermediate **5**. The desired coumarin-pyrazole product **1** was afforded in excellent (90-94%) yield by refluxing intermediate (*E*)-3-hydroxy-2-(2-oxo-2*H*-chromen-3-yl) acrylaldehyde **6** with phenyl hydrazine in ethanol under catalytic acetic acid (Scheme **1**).

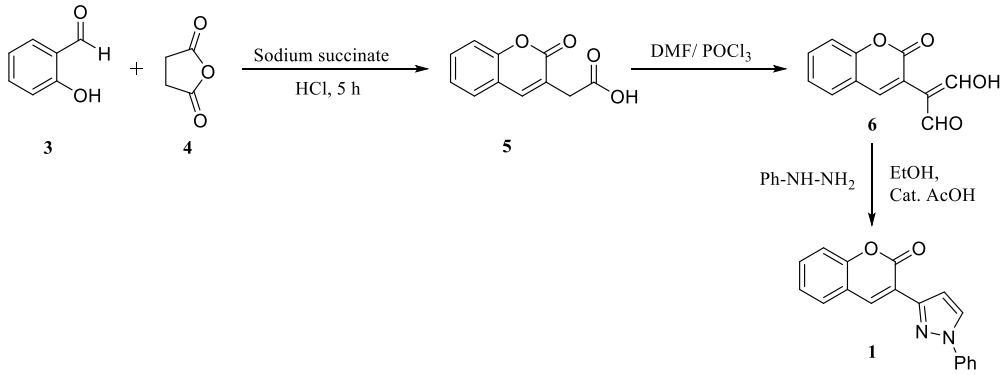
Trkovnik and co-workers reported the preparation of coumarin-pyrazole compound [93-95]. Furthermore, Chodankar *et al*. demonstrated an alternative novel efficient route for the synthesis of 4-formyl coumarin-pyrazole **11** in excellent yields (95-97%) as shown in Scheme **2** [97]. In this report, the synthesis was achieved in three steps. The intermediate 3-acetyl coumarin (3-acetyl-2*H*-chromen-2-one) **9** was prepared by Knovengeal condensation of salicyaldehyde **7** with ethyl acetoacetate **8** in ethanol and a catalytic amount of piperidine. The respective hydrazone derivatives **10** were obtained from 3-acetyl coumarin **9** by refluxing with various hydrazine in ethanol and adding catalytic acetic acid. Finally, these hydrazone derivatives **10** on Vilsmeier-Haack formylation furnish the intermediate 4- formyl coumarin-pyrazole **11**.

By employing a similar synthetic strategy, Srikrishna *et al*. in 2017 (Schemes **25** and **26**) [107], Zaki *et al*. in 2012 (Scheme **39**) [119], and Jain *et al*. in 2017 (Scheme **34**) [128] synthesized 4-formyl coumarin-pyrazole **11** in good to excellent yield.

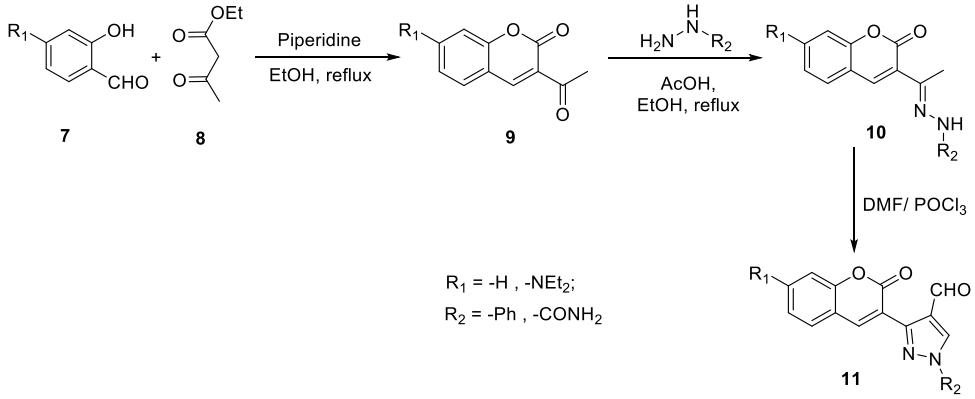
Catalytically, Srikrishna *et al*. developed a green protocol for the synthesis of 4-formyl coumarin-pyrazole scaffold **11** (Scheme **3**) [98]. In this protocol, *L*-Proline was used as a green catalyst for Knovengeal condensation of salicyaldehyde **7** with ethyl acetoacetate **8** to afford the 3-acetyl coumarin compound **9**. Further, synthesis of desired product **11** (4-formyl coumarin-pyrazole) was achieved from 3-acetyl coumarin **9** in a stepwise manner in the same way as described in Scheme **2**. Interestingly, intermediate

Table 1. Spectral (IR, ^{1}H, and ^{13}C NMR) information of coumarin-pyrazole derivatives 1 and 2.

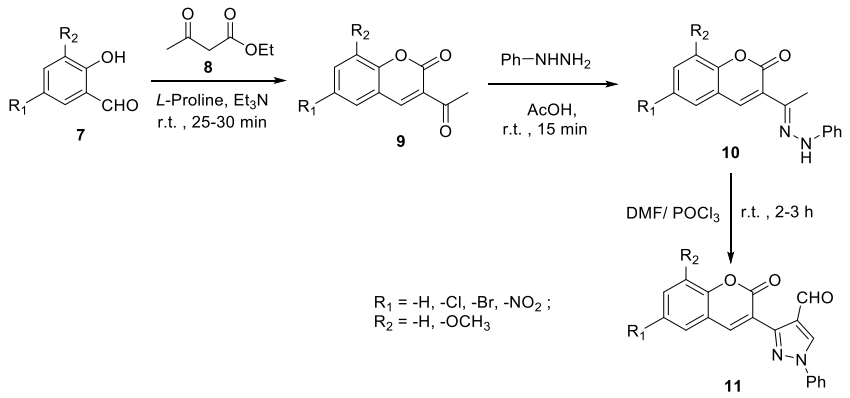
 1 3-(1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one				 2 3-(1*H*-pyrazol-3-yl)-2*H*-chromen-2-one			
IR (KBr) = 1736 cm^{-1} (strong, sharp, -CO of coumarin ring)				**IR (KBr) = 1736 cm^{-1} (strong, sharp, -CO of coumarin ring)**			
^{1}H-NMR			**^{13}C-NMR**	**^{1}H-NMR**			**^{13}C-NMR**
δ (ppm)	Multiplicity		δ (ppm)	δ (ppm)	Multiplicity		δ (ppm)
6.76	d	1H	114.8	6.3	d	1 H	104.8
7.28-7.72	m	9H	119.3	7.02-7.27	m	4 H	131.8
7.86	d	1H	119.9	10.7	d	1 H	142.4
8.20	s	1H	120.1	7.6	d d	1 H	129.4
-	-	-	123.4	7.72	s	1 H	146.1
-	-	-	124.8	-	-	-	122.3
-	-	-	127.8	-	-	-	126.8
-	-	-	129.7	-	-	-	125.5
-	-	-	132.6	-	-	-	128.4
-	-	-	138.5	-	-	-	121.5
-	-	-	142.8	-	-	-	150.2
-	-	-	143.3	-	-	-	162.0
-	-	-	146.4	-	-	-	-
-	-	-	147.3	-	-	-	-
-	-	-	159.0	-	-	-	-



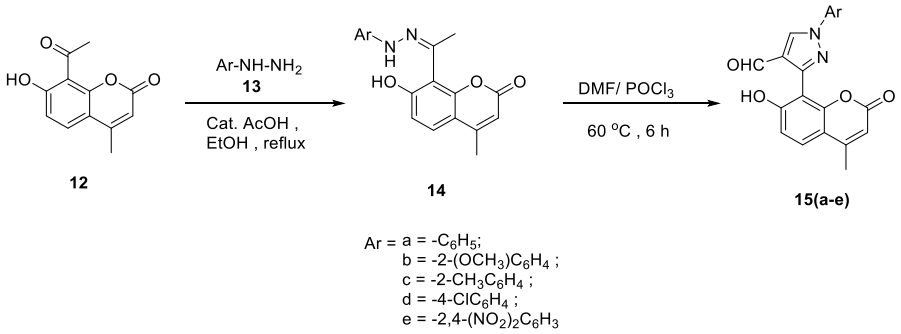
Scheme 1. Synthesis of coumarin-pyrazole using salicyaldehyde, succinic anhydride, and sodium succinate.



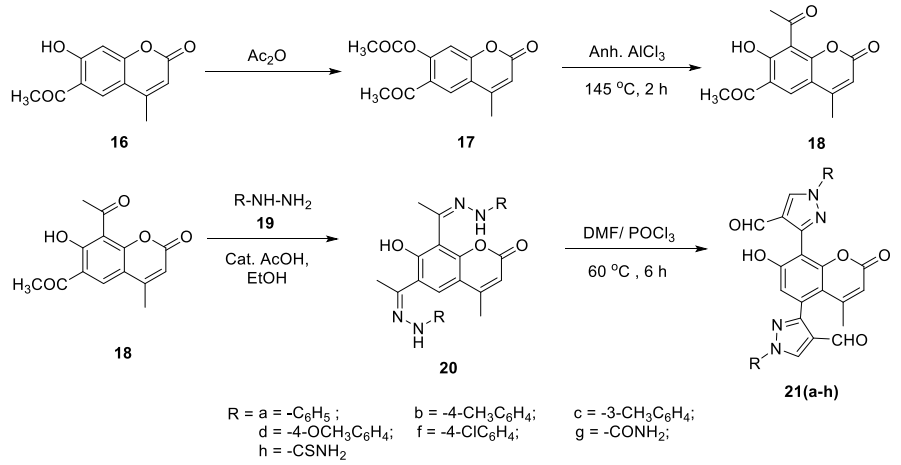
Scheme 2. Synthesis of coumarin-pyrazole using piperidine catalyst.



Scheme 3. Synthesis of coumarin-pyrazole using *L*-Proline catalyst.



Scheme 4. Synthesis of 3-(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)-1-aryl-1*H*-pyrazole-4-carbaldehyde.



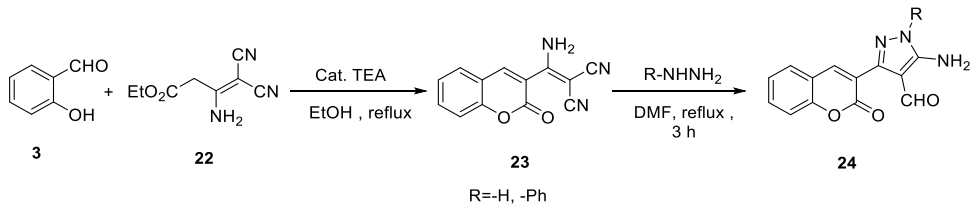
Scheme 5. Synthesis of coumarin appended bis (formyl pyrazoles).

hydrazone compound **10** and product **11** were obtained by stirring at room temperature with the same reagents which were used in Scheme **2**.

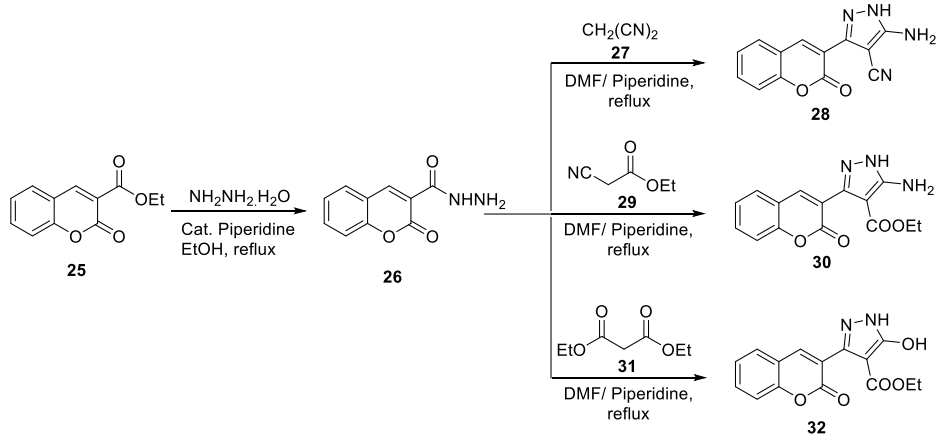
In 2013, Nagamallu *et al*. applied a similar strategy to synthesize new coumarin-pyrazole containing compound 3-(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)-1-aryl-1*H*-pyrazole-4-carbaldehyde **15(a-e)** derivatives [99]. The starting material 8-acetyl-7-hydroxy-4-methyl-2*H*-chromen-2-one **12** was converted to their corresponding hydrazones **14** by refluxing it with different phenyl hydrazine **13** in ethanol and under catalytic acetic acid. The targeted product derivatives **15(a-e)** were obtained in moderate to good yield (62-78%) by Vilsmeier-Haack formylation of intermediate (*Z*)-7-hydroxy-4-methyl-8-(1-(2-aryl hydrazono) ethyl)-2*H*-chromen-2-one **14** with DMF/$POCl_3$ as shown in Scheme **4**. The newly synthesized **15(a-e)** derivatives have shown good biological activity.

In continuation, Nagamallu *et al.* used a similar route for the synthesis of new biologically potent product 3,3'-(7-hydroxy-4-methyl-2-oxo-2*H*-chromene-5,8-diyl)bis(1-aryl/ alkyl-1*H*-pyrazole-4-carbaldehyde) **21(a-h)** in their second multistep synthetic report (Scheme **5**) [100]. Initially, coumarin substituted phenol **16** on acylation afforded the coumaryl ester compound **17** which on Fries rearrangement gave the second intermediate 1,1'-(7-hydroxy-4-methyl-2-oxo-2*H*-chromene-6,8-diyl)bis(ethan-1-one) compound **18**. Further, treatment of different aryl/ alkyl hydrazines **19** and intermediate compound **18** at refluxing conditions produced the respective hydrazone derivatives **20**. Subsequently, Vilsmeier-Haack formylation on hydrazone intermediate **20** leads to the formation of desired coumarin affixed bis (formyl pyrazoles) **21(a-h)** derivatives as shown in Scheme **5**.

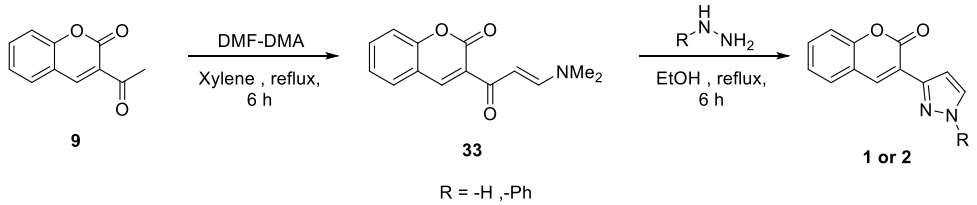
Novel synthetic approach to synthesize 5-amino-3-(2-oxo-2*H*-chromen-3-yl)-1-*H* or phenyl-1*H*-pyrazole-4-carbaldehyde



Scheme 6. Synthesis of 5-amino-3-(2-oxo-2*H*-chromen-3-yl)-1-*H* or phenyl-1*H*-pyrazole-4-carbaldehyde.



Scheme 7. Synthesis of coumarin-pyrazole derivatives using 2-Oxo-2*H*-coumarin-3-carbohydrazide.



Scheme 8. Synthesis of coumarin-pyrazole using 3-((*E*)-3-(dimethyl amino) acryloyl)-2*H*- chromen-2-one.

derivative **24** was reported by Soliman and a co-worker (Scheme **6**) [101]. The protocol describes the synthesis and applications of ethyl 3-amino-4,4-dicyanobut-3-enoate compound **22**, which was used as a starting material to synthesize the desired product **24**. Salicyaldehyde **3** and ethyl 3-amino-4,4-dicyanobut-3-enoate compound **22** when refluxed in ethanol afforded the intermediate 2-(amino(2-oxo-2*H*-chromen-3-yl) methylene) malononitrile **23.** Further, refluxing the intermediate **23** with substituted hydrazine furnished the desired product **24** in moderate to good yield (Scheme **6**).

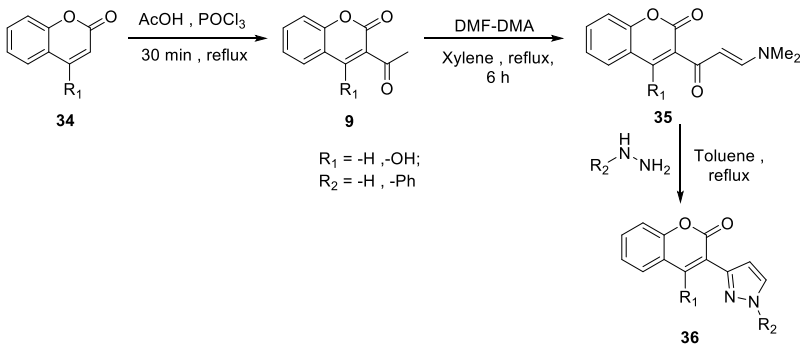
Latif and co-workers reported the synthesis of new coumarin-pyrazole derivatives as shown in Scheme **7** [102]. Initially, intermediate 2-Oxo-2*H*-coumarin-3-carbohydrazide **26** was synthesized by refluxing the hydrazine hydrate with ethyl 2-oxo-2*H*-chromene-3-carboxylate **25** using piperidine as a catalyst. Reaction of intermediate **26** with malanonitrile **27,** ethyl 2-cyanoacetate **29** and with diethyl malonate **31** afforded the 5-amino-3-(2-oxo-2*H*-chromen-3-yl)-1*H*-pyrazole-4-carbonitrile **28**, ethyl 5-amino-3-(2-oxo-2*H*-chromen-3-yl)-1*H*-pyrazole-4-carboxylate **30** and ethyl 5-hydroxy-3-(2-oxo-2*H*-chromen-3-yl)-1*H*-pyrazole-4-carboxylate **32** respectively.

Aziz El-Taweel *et al*. demonstrated the new methodology to synthesize coumarin-pyrazole scaffold **1** and **2** in 60-65 % yield [103]. Initially, the intermediate (*E*)-3-(3-(dimethyl amino) acryloyl)-2*H*-chromen-2-one **33** was obtained by condensation of 3-acetyl coumarin derivative **9** with DMF/ DMA. Further, refluxing enaminone intermediate **33** with different hydrazine led to the formation of 3-(1-phenyl or 1*H*-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **(1** and **2)** in good to excellent yield (Scheme **8**).

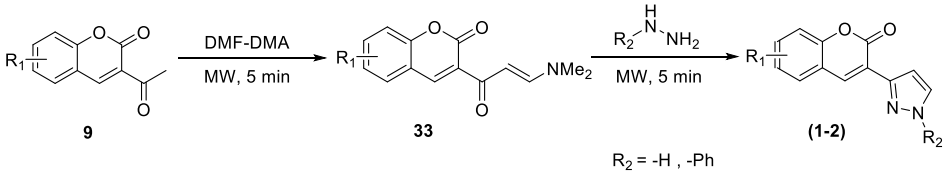
In continuation of these developed protocols, Hamdi *et al*. reported the synthesis of 4-hydroxy-3-(1-phenyl or *H*-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **36** derivatives by employing a similar strategy using 4-hydroxy coumarin **34** as shown in Scheme **9**. Acylation of 4-hydroxy coumarin **34** using AcOH/ $POCl_3$ afforded the corresponding 3-acetyl-4-hydroxy or *H*-2*H*-chromen-2-one **9** derivative, which subsequently on condensation with DMF-DMA, furnished (*E*)-3-(3-(dimethyl amino) acryloyl)-4-hydroxy or *H*-2*H*-chromen-2-one **35** derivatives. Further, the reaction of intermediate **35** with various substituted hydrazine led to the formation of desired products **36** in good to excellent yield (Scheme **9**) [104].

Microwave-assisted green and efficient synthetic protocols for the synthesis of coumarin-pyrazole **(1-2)** scaffolds were put forward by Khadijah and his co-workers, as shown in Scheme **10** [105]. In the present protocol, under microwave irradiation, condensation of 3-acetyl coumarin **9** with DMF/DMA furnished the corresponding product (*E*)-3-(3-(dimethyl amino) acryloyl)-2*H*-chromen-2-one **33** in good to excellent yield. The desired products **(1-2)** were obtained in 60-65% yield when the intermediate **33** compound was irradiated in microwave for 5 minutes as mentioned in Scheme **10**.

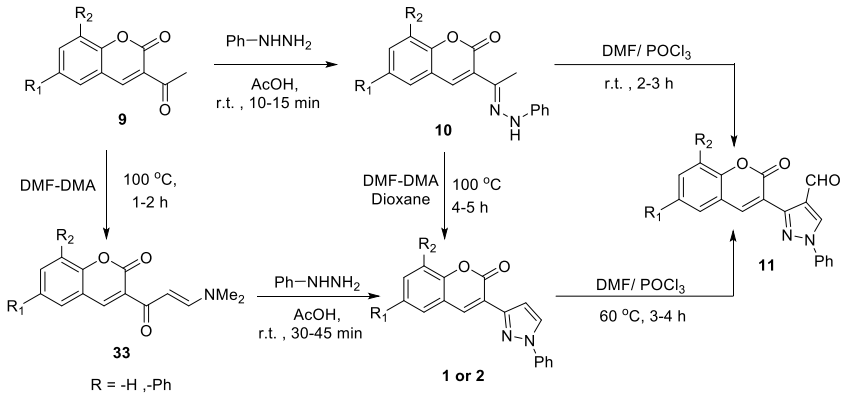
Microwave-assisted synthetic route was similarly applied by Gomha *et al*. to obtain coumarin-pyrazole **(1-2)** scaffolds as shown in Scheme **29** [106]. Condensation of 3-acetyl coumarin **9** derivatives with DMF-DMA followed by cyclization with (*E*)-3-(3-(dimethyl amino) acryloyl)-2*H*-chromen-2-one **33** using with various hydrazine furnished the desired products [106].



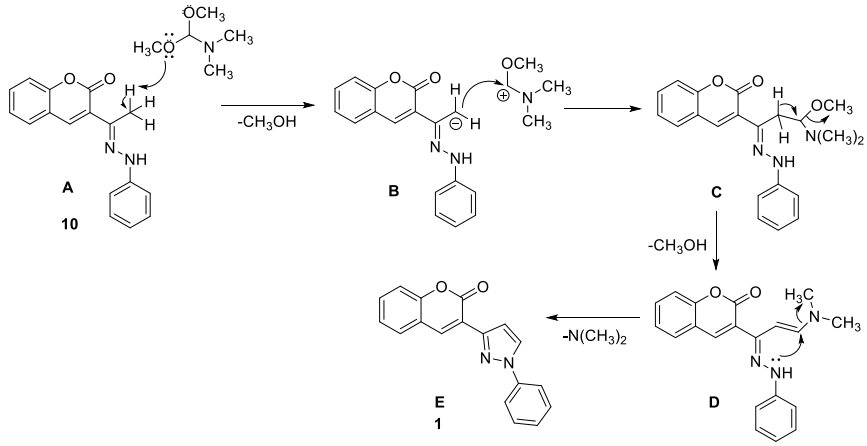
Scheme 9. Synthesis of 4-hydroxy-3-(1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one.



Scheme 10. Microwave-assisted green synthesis of coumarin-pyrazole scaffold.



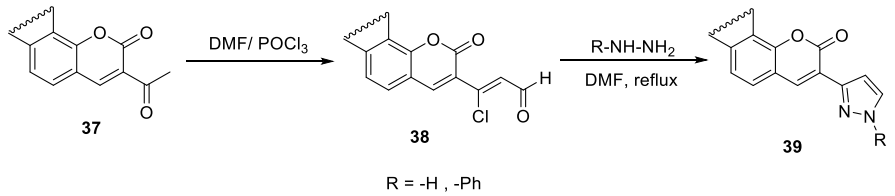
Scheme 11. Synthesis of coumarin-pyrazole using different condensation approach.



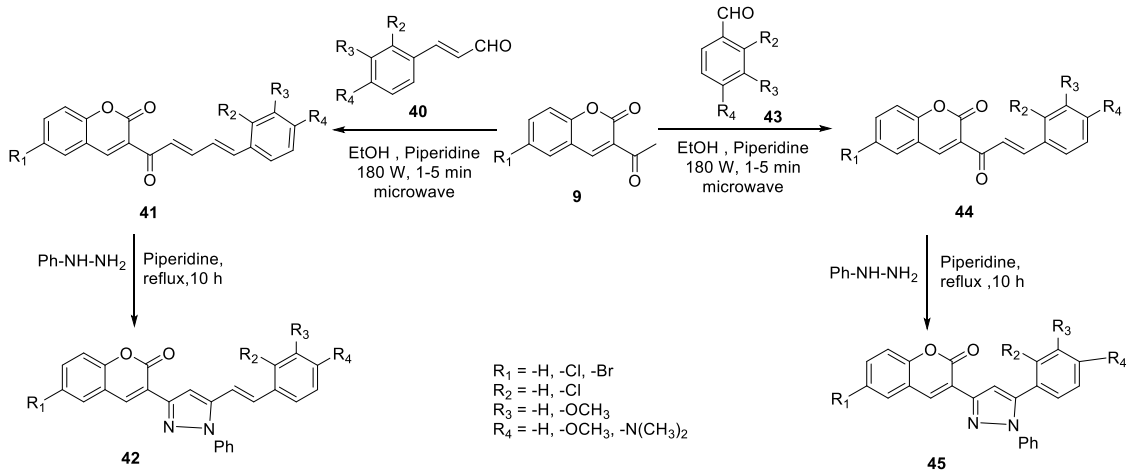
Scheme 12. Plausible mechanism for the synthesis of coumarin-pyrazole.

Srikrishna and co-workers demonstrated three different synthetic routes for the synthesis of 4-formyl coumarin-pyrazole [3-(2-oxo-2H-chromen-3-yl)-1- phenyl-1H-pyrazole-4-carbaldehyde] **11** using starting 3-acetyl coumarin derivative **9** as shown in Scheme **11** [107]. Among the developed methods, the synthesis of desired molecules was achieved efficiently in terms of overall yield and purity of the final product via a synthetic route from the reaction of **9-10-11**.

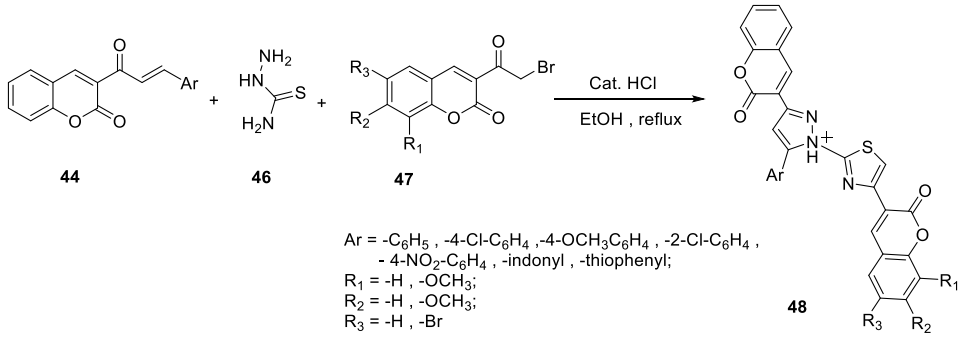
The detailed mechanism of conversion of intermediate hydrazone **A** to coumarin-pyrazole **E** in a stepwise manner is shown in the following Scheme **12**.



Scheme 13. Synthesis of coumarin-pyrazole scaffold by using (*Z*)-3-chloro-3-(2-oxo-7,8-dihydro-2*H*-cyclobuta[*h*]chromen-3-yl) acrylaldehyde.



Scheme 14. Microwave-assisted synthesis of coumarin-pyrazole derivatives.



Scheme 15. One pot, three-component synthesis of thiazolyl-pyrazole-biscoumarin derivative.

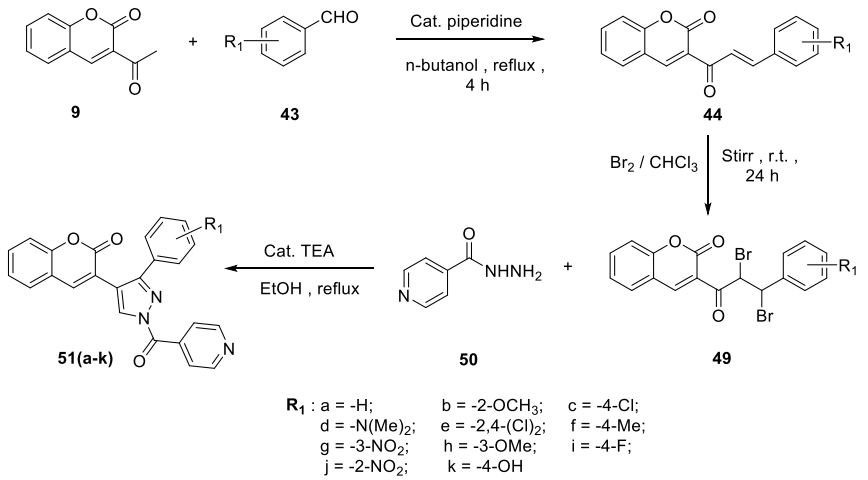
El-Deen *et al*. reported novel route for the synthesis of 3-(1-phenyl or *H*-1*H*-pyrazol-3-yl)-7,8-dihydro-2*H*-cyclobuta[*h*] chromen-2-one **39** using (*Z*)-3-chloro-3-(2-oxo-7,8-dihydro-2*H*-cyclobuta[*h*]chromen-3-yl) acrylaldehyde **38** derivative coumarin analogues (Scheme **13**). Initially, 3-acetyl-7,8-dihydro-2*H*-cyclobuta[*h*]chromen-2-one compound **37** was treated with DMF/ $POCl_3$ to afford the intermediate **38**, which on refluxing with various hydrazine derivatives results in the formation of desired product **39** with moderate to good yield (68-70%) [108].

Green microwave-assisted synthetic route for the condensation of 3-acetyl coumarin **9** with different aryl/ aliphatic aldehyde **(40 or 43)** to corresponding coumarin-chalcones **(41 or 44)** was demonstrated by Jayashree *et al.* [109]. In this protocol, intermediate coumarin-chalcone 3-((2*E*,4*E*)-5-arylpenta-2,4-dienoyl)-2*H*-chromen-2-one **41** was treated with phenyl hydrazine using catalytic amount of piperidine base to afford the desired product (*E*)-3-(1-aryl-5-styryl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **42.** Similarly, another coumarin-chalcone 3-cinnamoyl-2*H*-chromen-2-one **44** furnished the product 3-(1,5-diphenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **45** using similar condition as shown in Scheme **14**.

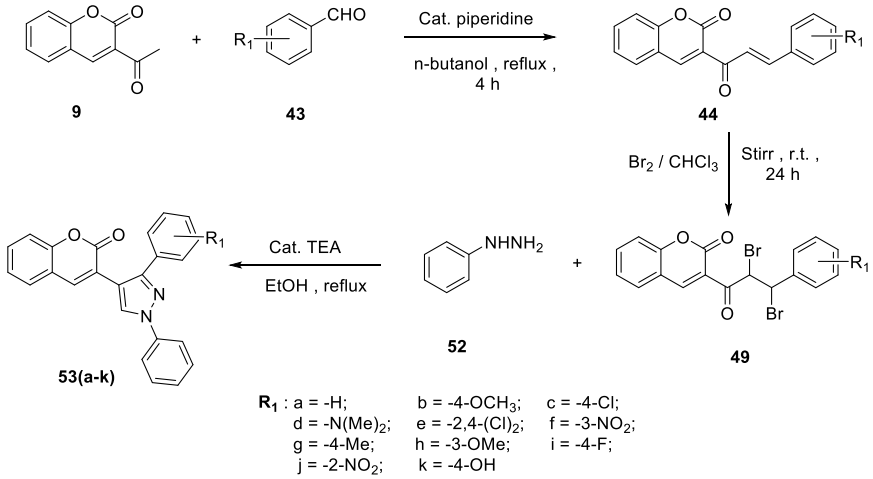
Mahmoodi and co-workers developed an efficient one-pot three-component method for the synthesis of 3-(2-oxo-2*H*-chromen-3-yl)-1-(4-(2-oxo-2*H*-chromen-3-yl) thiazol-2-yl)-5-aryl-1*H*-pyrazol-1-ium **48** [110]. Synthetic protocol demonstrated the one-pot reaction between coumarin-chalcone [3-cinnamoyl-2*H*-chromen-2-one] **44**, thiosemicarbazide **46** and coumarin-phenacyl bromide **47** under reflux conditions in ethanol and a catalytic amount of conc. HCl to furnish the desired product **48** with 70% yield (Scheme **15**).

Argade *et al*. developed a new synthetic route to synthesize biologically active, novel 3-(1-isonicotinoyl-3-phenyl-1*H*-pyrazol-4-yl)-2*H*-chromen-2-one compound **51(a-k)** derivatives with good to excellent (53-92%) yields [111]. The intermediate coumarin-chalcone **44** was obtained by the condensation reaction between 3-acetyl coumarin **9** and different aryl-aldehyde **43** under reflux condition and catalytic piperidine base. Next, synthesis of second intermediate dibromo compound 3-(2,3-dibromo-3-phenylpropanoyl)-2*H*-chromen-2-one **49** was achieved by reacting intermediate **44** with $Br_2/CHCl_3$ at room temperature condition. Further, the desired products **51(a-k)** were obtained by refluxing isonicotinic acid hydrazide **50** with intermediate dibromo derivative **49** using a catalytic amount of trimethylamine base as shown in Scheme **16**.

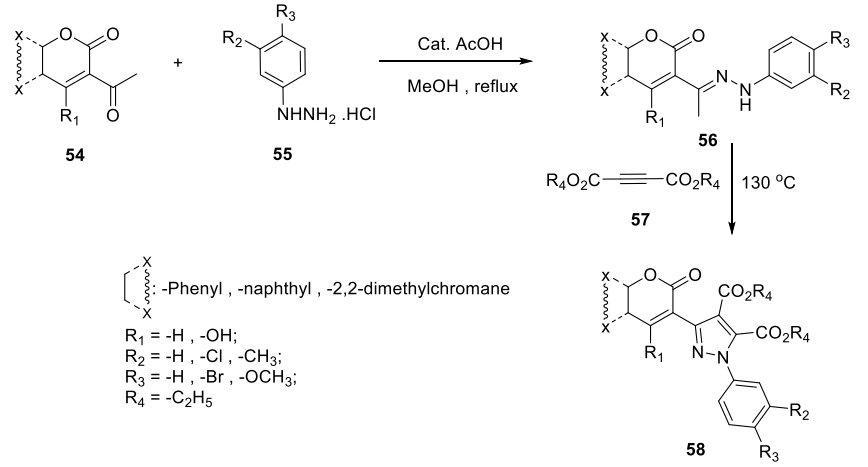
In continuation, Argade *et al*. reported the synthesis of 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2*H*-chromen-2-one **53 (a-k)** derivatives



Scheme 16. Synthesis of 3-(1-isonicotinoyl-3-phenyl-1*H*-pyrazol-4-yl)-2*H*-chromen-2-one.



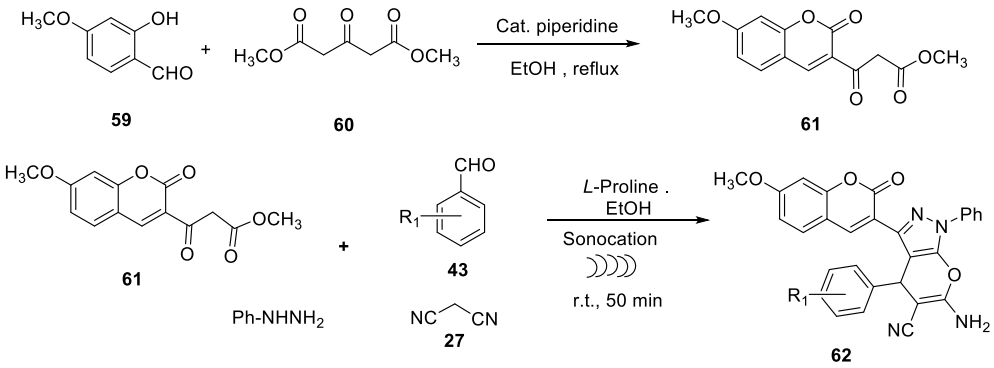
Scheme 17. Synthesis of 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2*H*-chromen-2-one.



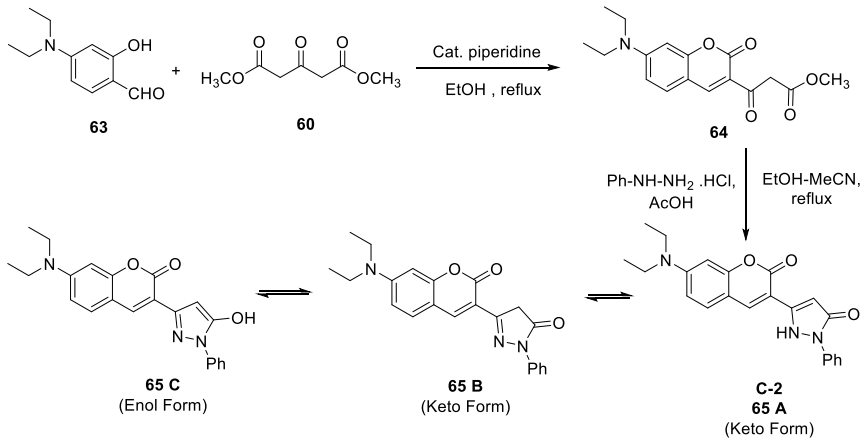
Scheme 18. Synthesis of coumarin-pyrazole functionalized scaffold using diethyl but-2-ynedioate intermediate.

by employing a similar synthetic strategy. In this protocol, the synthesis of second dibromo intermediate 3-(2,3-dibromo-3-phenylpropanoyl)-2*H*-chromen-2-one **49** derivatives from 3-acetyl coumarin **9** compound was obtained as shown in Scheme **16**. Finally, the reaction of dibromo derivatives **49** with phenyl hydrazine led to the formation of new desired coumarin-pyrazole derivatives **53 (a-k)** in 60-95 % yield as shown in Scheme **17** [112].

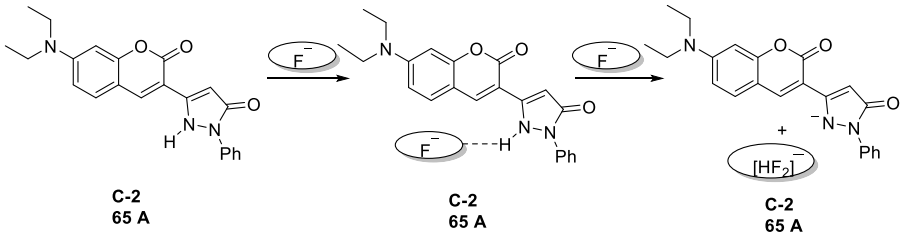
Considering the importance of coumarin-pyrazole scaffold, Kumar and co-workers developed another novel method for the synthesis of new diethyl 3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate **58** from (*E*)-4-hydroxy-3-(1-(2-phenyl hydrazono) ethyl)-2*H*-chromen-2-one **56** compound (Scheme **18**) [113]. Treatment of substituted phenyl hydrazine with different coumarin compounds **54** has afforded the intermediate **56**, which on



Scheme 19. Green ultrasonic mediated synthesis of coumarin-pyrazole scaffold.



Scheme 20. Synthesis of novel coumarin-pyrazolone based colorimetric and fluorimetric chemosensor.



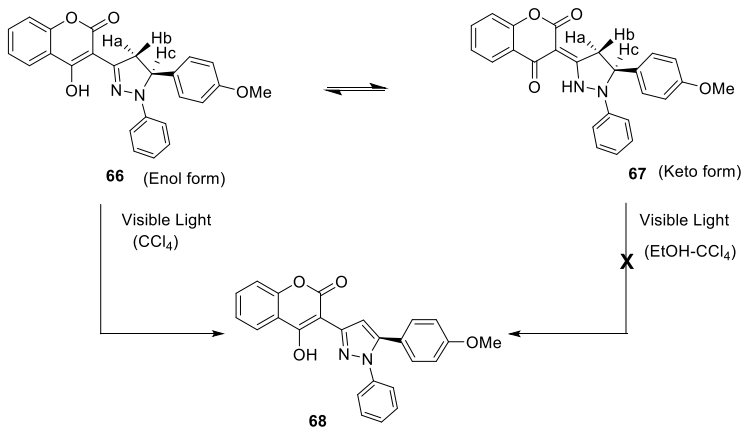
Scheme 21. Proposed receptor C-2 binding mode with F^- in DMSO solution.

refluxing with diethyl but-2-ynedioate **57** furnished the targeted coumarin-pyrazole functionalized product **58**.

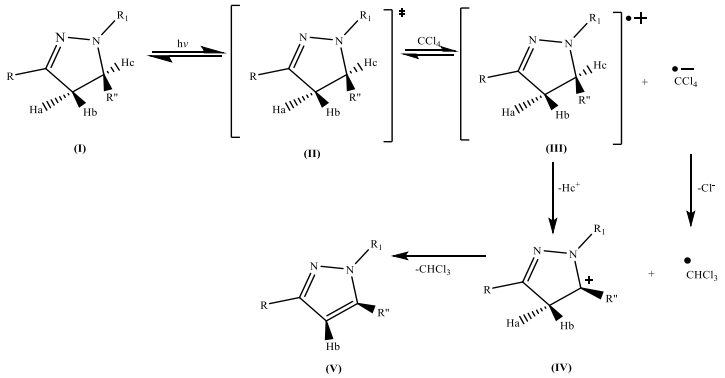
Green ultrasonic-assisted and the one-pot multicomponent synthetic route was demonstrated by Seydimemet *et al*. to synthesize functionalized coumarin-pyrazole scaffold using intermediate methyl 3-(7-methoxy-2-oxo-2*H*-chromen-3-yl)-3-oxopropanoate **61** [114]. The intermediate **61** was synthesized via condensation of 2-hydroxy-4-methoxybenzaldehyde **59** with dimethyl 3-oxopentanedioate **60** using a catalytic amount of piperidine base. Ultrasonic irradiation-assisted catalytic *L*-proline mediated four component reaction between intermediate **61**, phenyl hydrazine, aryl aldehyde **43,** and malanonitrile **27** and afforded the product 6-amino-3-(7-methoxy-2-oxo-2*H*-chromen-3-yl)-1,4-diphenyl-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile **62** in good to excellent yields as shown in Scheme **19**.

Babür and co-workers reported the synthesis of novel 7-(diethylamino)-3-(5-hydroxy-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **65** and explored their applications as new colorimetric and fluorimetric chemosensors. The desired product obtained by the condensation followed by cyclization between intermediate methyl 3-(7-methoxy-2-oxo-2*H*-chromen-3-yl)-3-oxopropanoate **64** and phenyl hydrazine under reflux condition in ethanol-acetonitrile solvent using acetic acid as a catalyst is shown in Scheme **20** [115]. Coumarin-pyrazolone-based colorimetric and fluorimetric chemosensor (C-2) was successfully synthesized for ratiometric sensing of F^- and AcO^- and it was found that chemosensor was more sensitive to F^- than AcO^- at the stoichiometric ratio of 1:1.

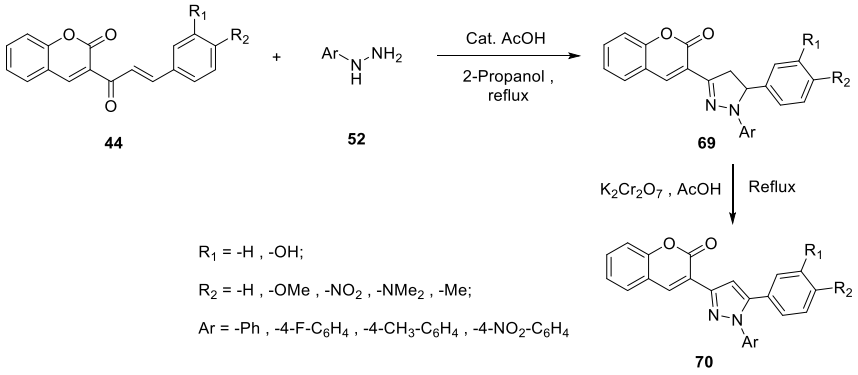
Traven *et al*. reported the quantitative photo-oxidation of 4-hydroxy-3-pyrazolinylcoumarins **66** into 4-hydroxy-3-(5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **68** (Scheme **22**) [116]. The present protocol demonstrated how the enol form of 4-hydroxy-3-pyrazolinylcoumarins **66** undergoes easy photo-oxidation reaction in CCl_4 under visible light, but its keto form **67** does not undergo the same. In another report, detailed mechanistic path with intermediate radicals about the photo-oxidation reaction of the enol form of 4-hydroxy-3-pyrazolinylcoumarins **66** to desired product **68** was demonstrated by the same research group of Traven *et al.* [117]. The photo-oxidation reaction and the stepwise mechanistic path is shown in Scheme **21**.



Scheme 22. Photo-oxidation reaction of 4-hydroxy-3-pyrazolinyl coumarins.



Scheme 23. Proposed mechanism of photo-oxidation reaction of 4-hydroxy-3-pyrazolinyl coumarins.



Scheme 24. Photo-dehydrogenation of coumarin-pyrazolines with $K_2Cr_2O_7$ in acetic acid.

In continuation, Traven and co-workers demonstrated different approaches for the dehydrogenation of coumarin-pyrazolines by using per-chloro alkanes [118]. Initially, coumarinyl-pyrazolines **69** compound was synthesized by refluxing chalcone derivatives **44** with different aryl hydrazine **52** using cat. AcOH. The desired products 3-(1-aryl-5-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **70** were obtained from intermediate **69** by treatment with $K_2Cr_2O_7$ in catalytic acetic acid (Scheme **24**).

5. FUNCTIONALIZATION OF COUMARIN-PYRAZOLE SCAFFOLD

In the coumarin-pyrazole scaffold, the pyrazole ring exhibits a predominant nucleophilic character. Therefore, aromatic electrophilic substitution (*ArSE*) reactions go very easily at the 4th position of the pyrazole ring. Due to this mode of reactivity, major functionalization reactions are reported on 4-formyl coumarin-pyrazole **11** and related derivatives of the coumarin-pyrazole moiety, as shown in Fig. (**4**).

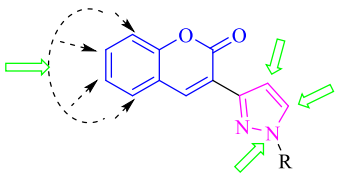
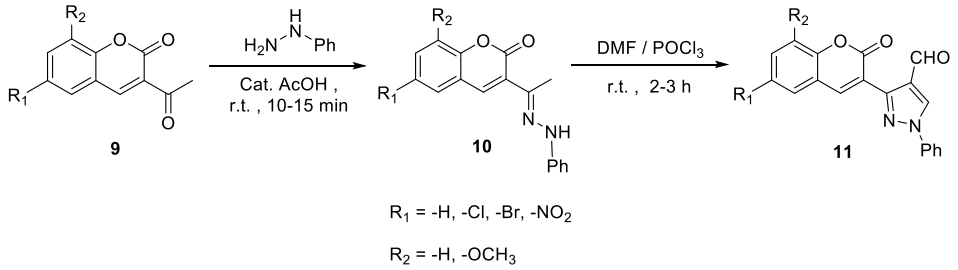


Fig. (4). Reactive sites of coumarin-pyrazole scaffold.

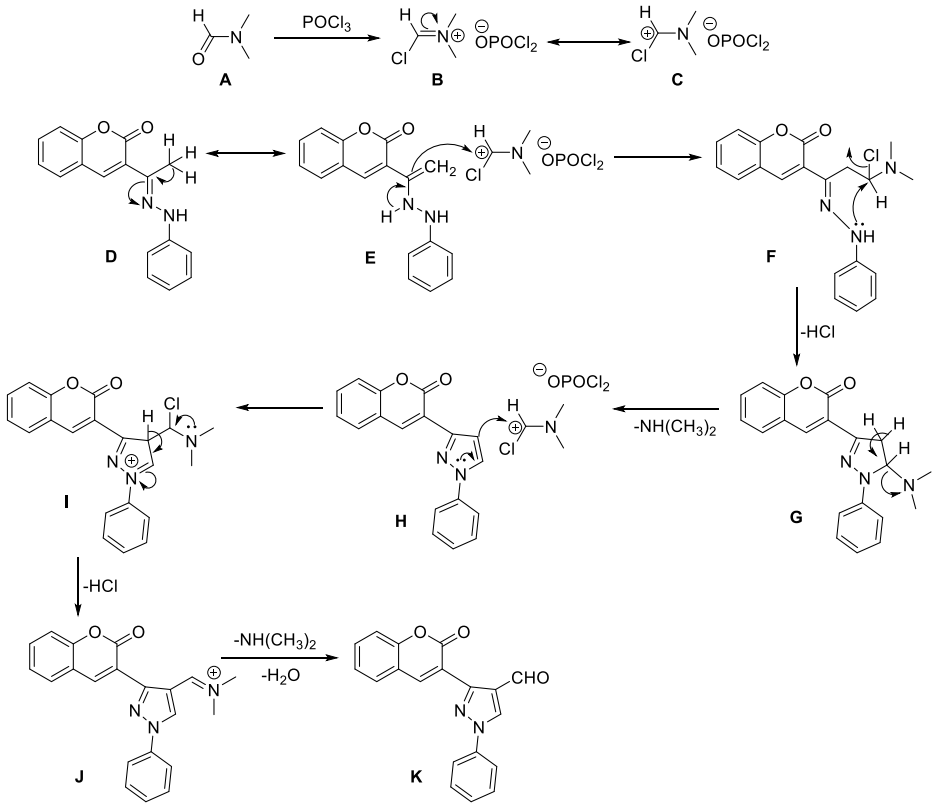
I) C-C Bond Formation Reactions

A) Synthesis of 4- formyl-Coumarin-pyrazole Derivatives

Due to predominant nucleophilicity, the formylation reactions, particularly Vilsmeier-Haack reaction using DMF/$POCl_3$, were



Scheme 25. Two-step synthesis of 4-formyl coumarin-pyrazole derivative.



Scheme 26. Proposed mechanism of formylation for the synthesis of 4-formyl coumarin-pyrazole derivative.

reported at the 4th position of the pyrazole ring of the coumarin-pyrazole scaffold. Numerous protocols were reported related to the synthesis of 4-formyl coumarin-pyrazole scaffold **11**. Chodankar and co-workers disclosed, for the first time, the synthesis of 4-formyl coumarin-pyrazole. Synthesis of 4-formyl coumarin-pyrazole **11** was achieved starting from salicyaldehyde **7** and ethyl acetoacetate **8** in three steps, as shown in Scheme **2** [97].

In continuation with Chodankar *et al*., several synthetic methods have been reported for the synthesis of 4-formyl coumarin-pyrazole **11** intermediate to explore the applications of couamrin-pyrazole heterocycle in medicinal and material chemistry. Therefore, selective functionalization with diverse substituents on the parent 4-formyl couamrin-pyrazole **11** scaffolds raised the interest among synthetic chemists.

Srikrishna *et al*. (2014) (Scheme **3**) [98], Nagamallu *et al*. (2013) (Scheme **4**) [99], Nagamallu *et al*. (2015) (Scheme **5**) [100], Zaki *et al*. (2012) (Scheme **39**) [119], Jain *et al*. (2017) (Scheme **34**) [128], and Whitt *et al*. (2019) (Scheme **36**) [129] reported the synthesis, functionalization, and derivatisation of 4-formyl coumarin-pyrazole scaffold **11**.

All above mentioned synthetic methods of 4-formyl coumarin-pyrazole have been reported by using Vilsmeier-Haack reagent ($DMF/POCl_3$) into the intermediate (*E*)-3-(1-(2-phenyl hydrazono) ethyl)-2*H*-chromen-2-one **10** in one-pot method (Scheme **25**) [107].

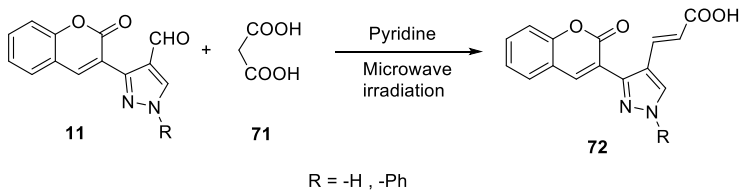
Mechanism of cyclization followed by formylation to obtain desired 4-formyl coumarin-pyrazole **11** product was put forth for the first time by Srikrishna and co-workers in their research protocol [107]. The detailed stepwise mechanism for the synthesis of 4-formyl coumarin-pyrazole **11** is shown in Scheme **26**.

B) Synthesis and Applications of Coumarin-pyrazole Cyano Derivatives

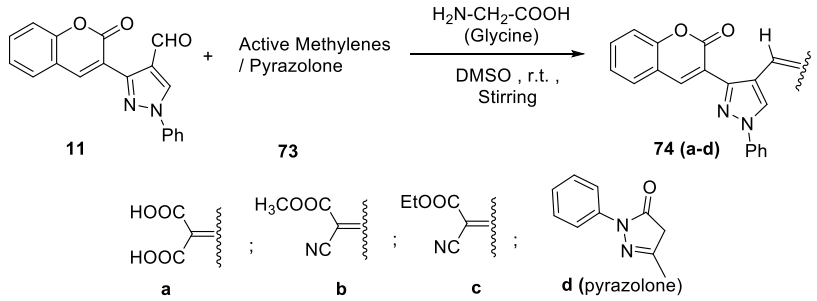
Zaki and co-workers, in their reported protocol, mentioned that 4-cyano coumarin-pyrazole [3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4-carbonitrile] **114** compound was one of the significant intermediates in 70-78% yield (Scheme **45**) [119]. Similarly, Padhye *et al*. and Kumbar *et al*. (Scheme **37**, compound **94**) also reported intermediate coumarin-pyrazole cyano compound in their synthetic protocols [120, 121].

C) Reactions Involving C=C Bond Formation

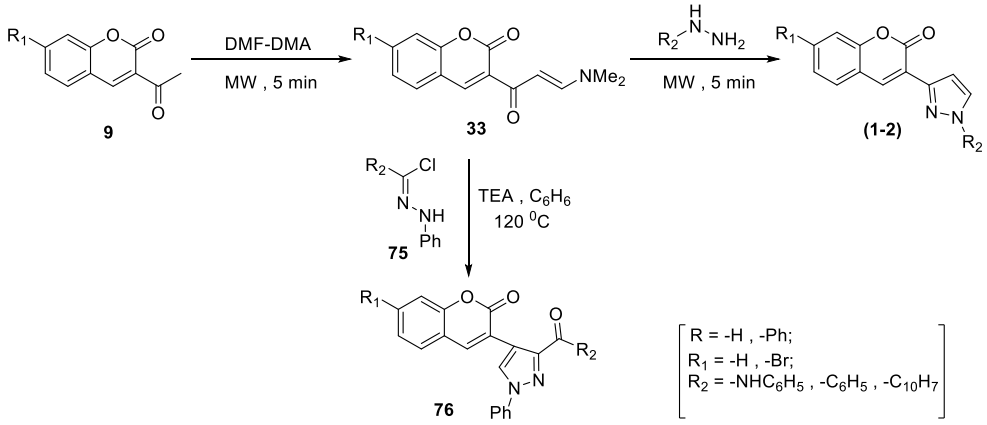
Chornous and co-workers developed a green, efficient microwave-assisted Doebner condensation reaction between 4-formyl coumarin-pyrazole **11**, malonic acid **71,** and pyridine used as a base



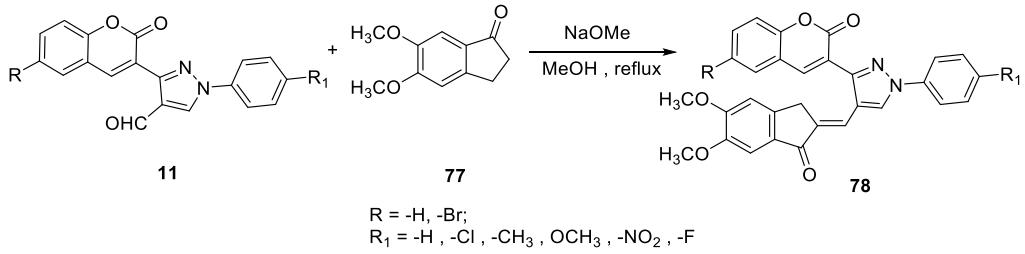
Scheme 27. Microwave-assisted Doebner reaction for 4-formyl coumarin-pyrazole.



Scheme 28. Glycine catalyzed the synthesis of coumarin pyrazole-acrylol analogues.



Scheme 29. Synthesis of 4-acyl coumarin-pyrazole.



Scheme 30. Claisen-Schmidt condensation reaction of 4-formyl coumarin-pyrazole and indenone.

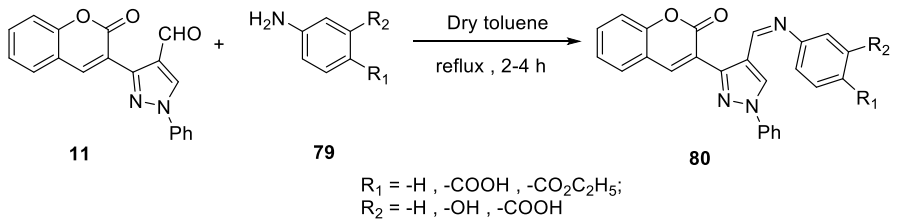
to afford novel (*E*)-3-(3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl) acrylic acid **72** in excellent yield (Scheme **27**) [122].

An efficient, eco-friendly glycine catalyzed Knoevengeal condensation route for the synthesis of coumarin pyrazole-acrylol analogues **74 (a-d)** was demonstrated by Chaudhry *et al*. [123]. The desired coumarin-pyrazole-acrylol derivatives **74 (a-d)** were obtained in excellent yields (82%) when 4-formyl coumarin-pyrazole **11** condensed with different active methylenes **73** under room temperature. They were stirred in DMSO in the presence of a catalytic amount of glycine (Scheme **28**).

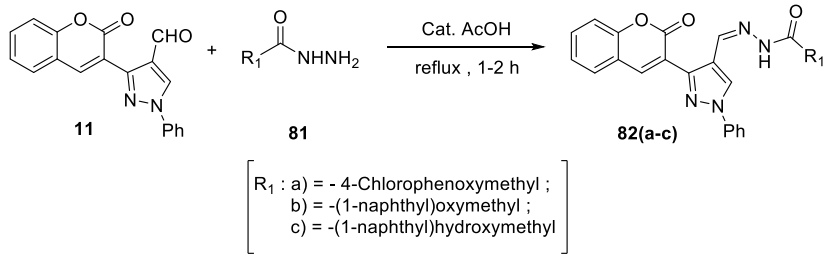
Few other reports also mentioned the condensation reaction with 4-formyl coumarin-pyrazole **11** to obtain the C=C bond containing moieties. Kenchappa *et al*. (2017) (Scheme **30**, compound **78**) [124], Vijaya Laxmi *et al*. (2012) (Scheme **46**, derivative **118** and **120**) [132], and Gondru *et al*. (2018) (Scheme **51**, compound **139**) [135] reported the protocols of similar condensation reactions.

D) Synthesis of Acyl Derivatives

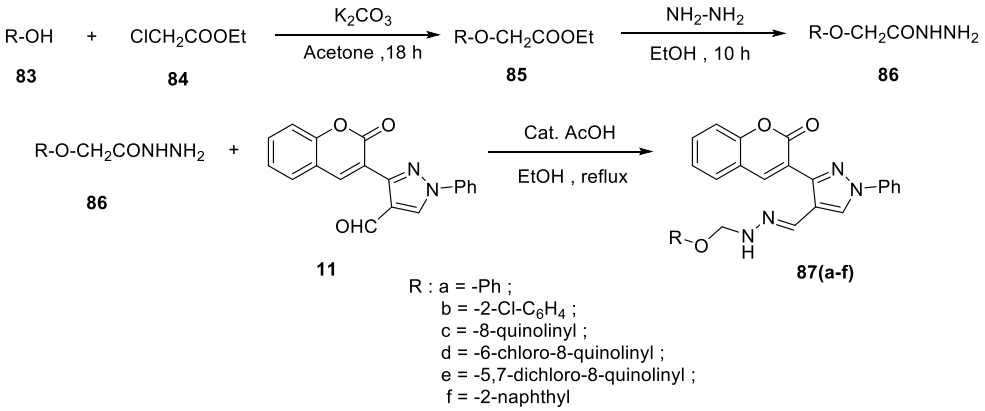
In 2015, Gomha *et al*. demonstrated the synthetic protocol for the acylation reaction of coumarin-pyrazole to yield the product [3-(3-benzoyl-1-phenyl-1*H*-pyrazol-4-yl)-2*H*-chromen-2-one] **76** with good to excellent yield [106]. Initially, intermediate 3-((*E*)-3-(dimethyl amino) acryloyl)-2*H*-chromen-2-one **33** obtained by condensation 3-acetyl coumarin **9** with DMF-DMA followed by treatment with (*Z*)-1-(1-chloroalkylidene)-2-phenylhydrazine molecule **75** led to the formation of the desired product **76** as shown in Scheme **29**.



Scheme 31. New azomethine synthesis from 4-formyl coumarin-pyrazole and primary arylamine.



Scheme 32. Synthesis of coumarin-pyrazole based new hydrazone derivatives.



Scheme 33. Synthesis of novel hydrazone derivatives using 2-aryloxyacetohydrazide.

E) Synthesis of Coumarin-pyrazole Containing α, β-unsaturated Carbonyl Derivatives

Kenchappa *et al*. developed a new series of compound (*E*)-3-(4-((5,6-dimethoxy-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene) methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **78** (68-82% yield) by the Claisen-Schmidt condensation reaction of 4-formyl coumarin-pyrazole **11** and 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one compound **77** in methanol and sodium methoxide base (Scheme **30**) [124].

In addition to the above-reported methods, Chaudhry *et al*. in 2016 (Scheme **28,** compound **74)** [123], Patel *et al*. in 2008 (Scheme **42**, compound **105**) [131], Vijaya Laxmi *et al*. in 2012 (Scheme **46**, compound **118** and **120**) [132], and Gondru *et al*. in 2018 (Scheme **51**, compound **139**) [135] also reported the functionalization of couamrin-pyrazole scaffold and synthesized various interesting coumarin-pyrazole containing *α, β*-unsaturated carbonyl derivatives.

II) Reactions of C-N Bond Formation

a) Reactions of Imine Bond Formation

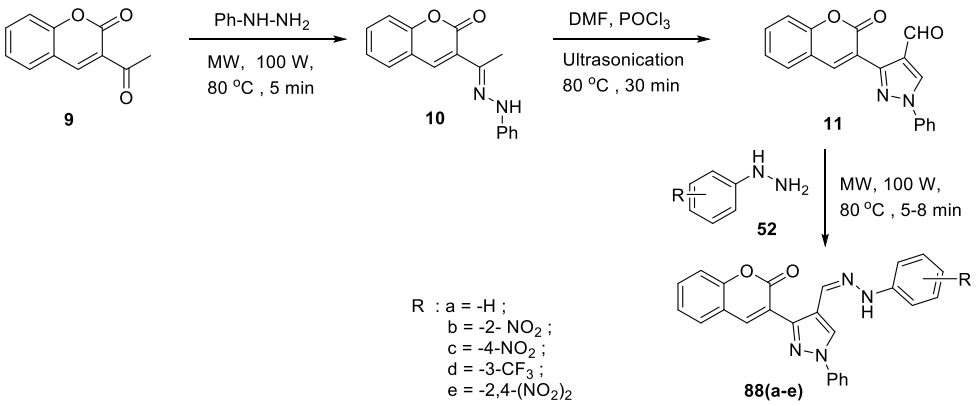
Bratenko and co-workers synthesized new (*Z*)-3-(1-phenyl-4-((phenylimino)methyl)-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **80** azomethine (imine) derivatives by reacting 4-formyl coumarin-pyrazole **11** using various primary arylamine **79** under reflux condition in toluene with 65 to 84% yield (Scheme **31**) [125].

b) Synthesis of Hydrazone Based Derivatives

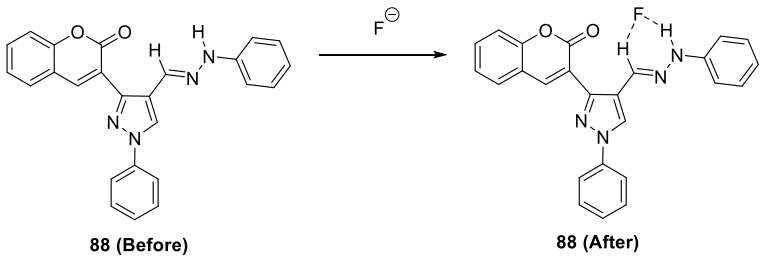
Several synthetic protocols have been reported allied to the hydrazone functionalization of the 4-formyl coumarin-pyrazole **11** scaffolds. Bratenko and co-workers reported a protocol of condensation of various acyl hydrazine **81** with 4-formyl coumarin-pyrazole **11** for the synthesis of a new series of hydrazone derivatives [(*Z*)-*N*'-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl) methylene)-2-phenoxy/aryloxyacetohydrazide] **82(a-c)** in good to excellent (82 to 86%) yields (Scheme **32**) [126].

Labudova *et al.* (2016) demonstrated a synthetic protocol to synthesize (*E*)-3-(4-((2-((aryl-2-yloxy)methyl)hydrazono)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **87 (a-f)** derivatives using intermediate 4-formyl coumarin-pyrazole **11** and different 2-aryloxyacetohydrazide **86** (Scheme **33**) [127]. The reaction of chloro ethyl acetate **84** with appropriate phenols in the presence of K_2CO_3 provided the first intermediate **85**, which on refluxing with hydrazine hydrate in ethanol furnished the second intermediate 2-aryloxyacetohydrazide **86**. Finally, condensation of 4-formyl coumarin-pyrazole **11** with intermediate **86** using reflux and catalytic acetic acid condition afforded the target product **87 (a-f)** in 56 to 65 % yield.

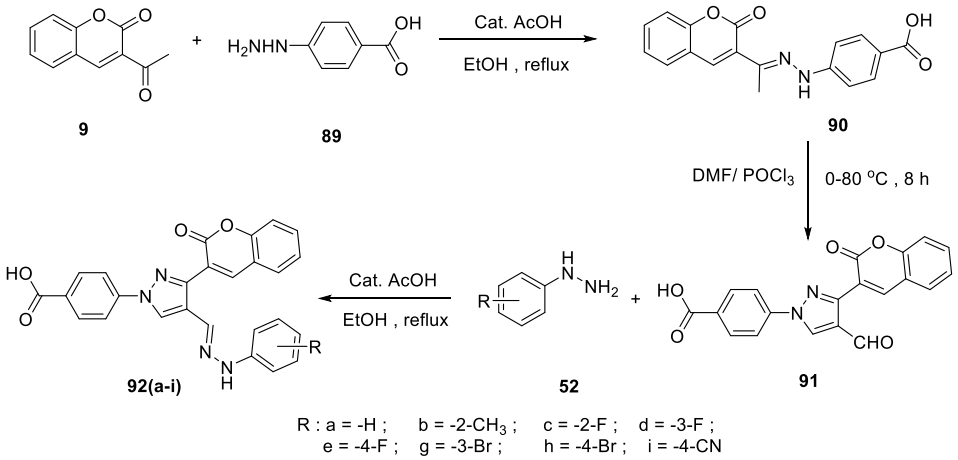
By applying similar reaction condition as in Scheme **33**, coumarin-pyrazole scaffold synthesis was reported by Zaki *et al*. in 2012 (Scheme **39** and **43**, compound **98**) [119]. Gondru *et al*. in 2015 (Compound **103**, Scheme **40)** [130] reported the synthesis of



Scheme 34. Microwave and ultra-sonic method for the synthesis of (*Z*)-3-(1-phenyl-4-((2-phenyl hydrazono)methyl)-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one.



Scheme 35. Fluoride ion detection using the sensor of coumarin-pyrazole-hydrazone molecule.



Scheme 36. Synthesis of new coumarin-pyrazole-hydrazone derivatives.

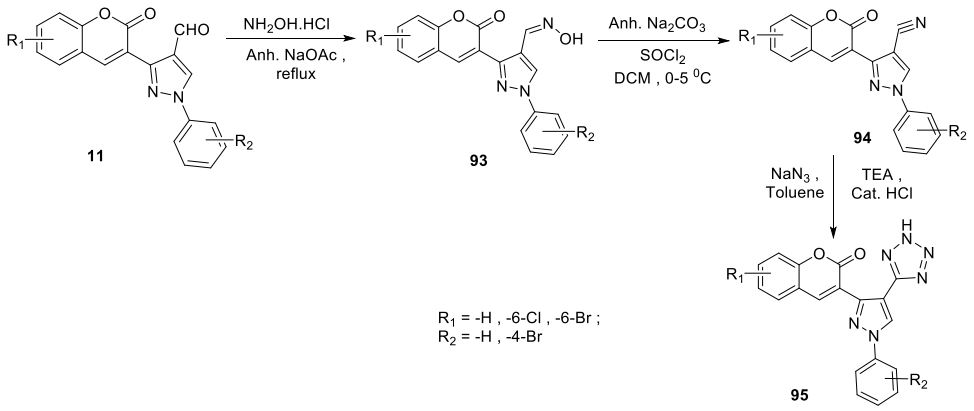
hydrazone derivatives of 4-formyl coumarin-pyrazole **11** using various hydrazine compounds.

Green, ultra-sonication, and microwave irradiation techniques were applied by Jain *et al.* to synthesize (*Z*)-3-(1-phenyl-4-((2-phenyl hydrazono)methyl)-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **88 (a-e)** derivatives via multistep reaction way as shown in Scheme **34** [128]. In this approach, 3-acetyl coumarin **9** and phenyl hydrazine were treated under microwave irradiation to give (*E*)-3-(1-(2-phenyl hydrazono)ethyl)-2*H*-chromen-2-one compound **10**, which on Vilsmeier-Haack formylation using ultrasonic technique yielded the 4-formyl coumarin-pyrazole **11**. The target molecules **88 (a-e)** were obtained in 82 to 87% yields by microwave irradiation of 4-formyl coumarin-pyrazole **11** with different aryl hydrazine **52**. The synthesized molecules have shown good applications as sensors for instantaneous and selective bare eye detection of fluoride (F^-) ion in an unknown sample. The following Scheme **35** shows the binding of fluoride (F^-) ion to the corresponding final product **88 (a-e)** derivatives [128].

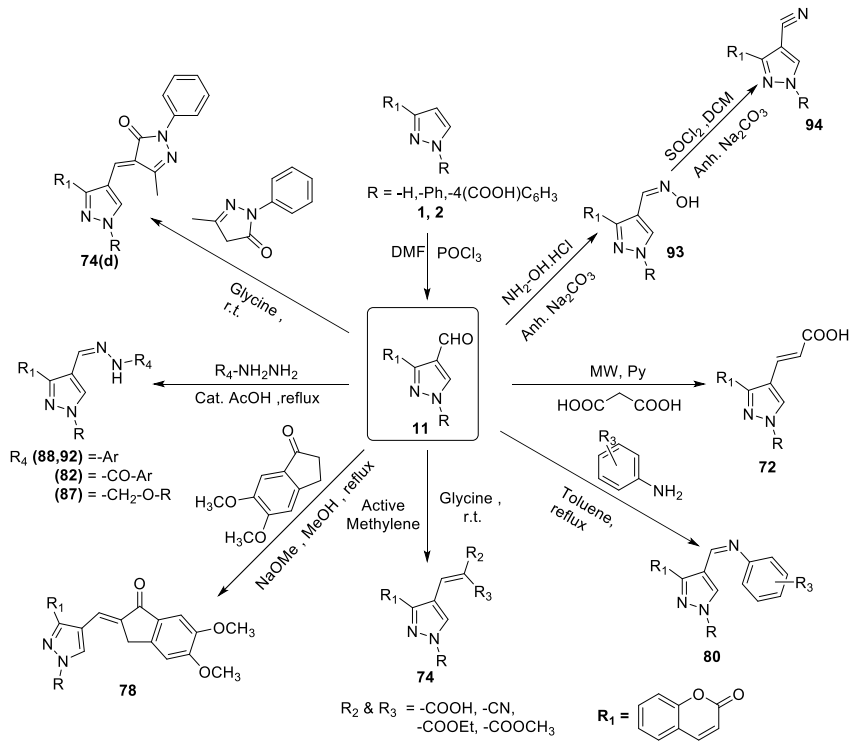
Recently, Whitt *et al*. applied the same synthetic strategy to synthesize different (*E*)-4-(3-(2-oxo-2*H*-chromen-3-yl)-4-((2-phenylhydrazono)methyl)-1*H*-pyrazol-1-yl)benzoic acid **92 (a-i)** derivatives of hydrazone. In this, starting material was 4-hydrazinylbenzoic acid **89** treated with 3-acetyl coumain **9** to afford the intermediate product (*E*)-4-(2-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazinyl)benzoic acid **90**. Then, intermediate **90** was converted into 4-(4-formyl-3-(2-oxo-2*H*-chromen-3-yl)-1*H*-pyrazol-1-yl)benzoic acid **91** via Vilsmeier-Haack formylation followed by reaction with various hydrazine **52** in ethanol using catalytic acetic acid which afforded the desired product **92 (a-i)** derivatives obtained in good to excellent (68-88%) yield (Scheme **36)** [129].

c) Synthesis of Oxime Derivatives

Kumbar *et al*. developed a new synthetic protocol for novel coumarin-pyrazole affixed tetrazole, i.e., 3-(1-phenyl-4-(2*H*-tetrazol-5-yl)-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **95** derivatives. Initially, oxime intermediate (*Z*)-3-(2-oxo-2*H*-chromen-3-yl)-



Scheme 37. Synthesis of coumarin-pyrazole affixed oxime derivatives.



Scheme 38. Miscellaneous C-C and C-N bond formation reactions of coumarin-pyrazole scaffold.

1-phenyl-1*H*-pyrazole-4-carbaldehyde oxime **93** was obtained by refluxing 4-formyl coumarin-pyrazole **11** with hydroxylamine hydrochloride in ethanol. Further, oxime intermediate **93** on treatment with $SOCl_2$ provides access to 3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4-carbonitrile **94** derivatives then reaction with sodium azide in toluene using cat. triethyl amine furnished the desired product with **95** good yields (70 to 85%), as shown in Scheme **37** [121].

Another research protocol of Zaki and co-workers also reported the formation of coumarin-pyrazole affixed oxime intermediate **113** in their entire Scheme **45** [119].

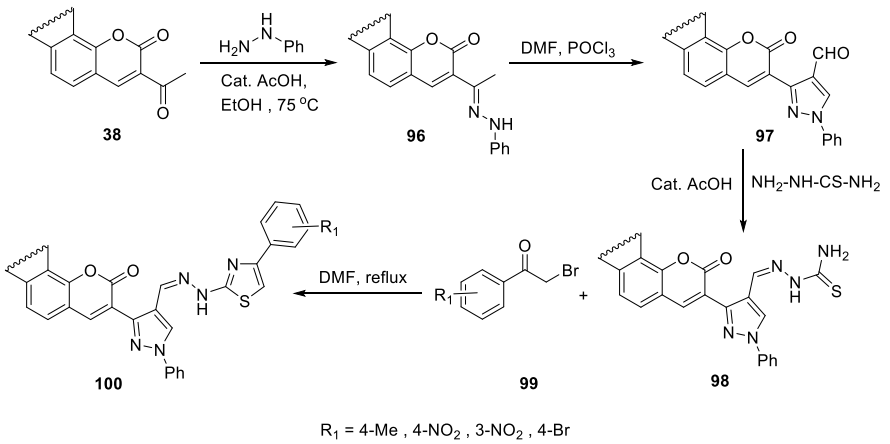
III) SYNTHESIS OF COUMARIN-PYRAZOLE AFFIXED HETEROCYCLES

A) Synthesis of Coumarin-pyrazole Affixed Five-membered Heterocycles

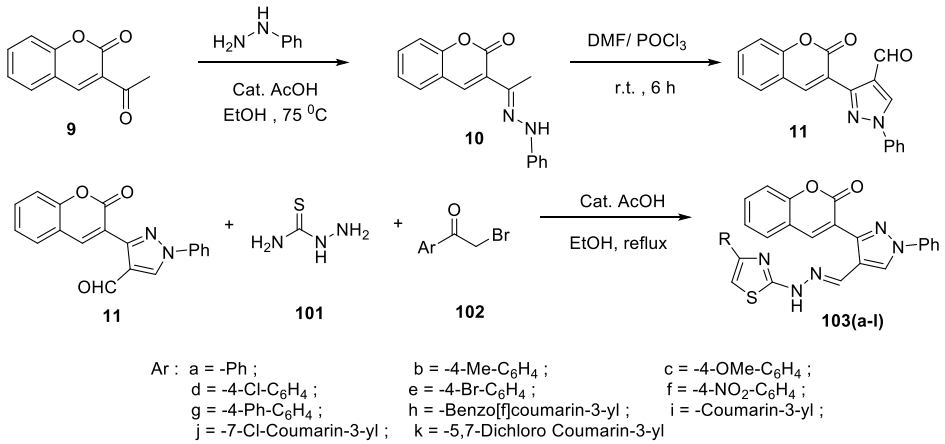
i) Formation of Coumarin-pyrzole Affixed Thiazole Molecule

Zaki *et al*. reported synthesis of (*Z*)-3-(1-phenyl-4-((2-(4-phenylthiazol-2-yl)hydrazono)methyl)-1*H*-pyrazol-3-yl)-2*H*-aryl[*h*]chromen-2-one **100** derivatives containing new thiazole heterocycle as shown in Scheme **39**. Initially, the 3-acetyl-7,8-dihydro-2*H*-aryl[*h*]chromen-2-one compound **38** on refluxing with phenyl hydrazine afforded the corresponding hyrazone **96,** which subsequently transformed into new 4-formyl coumarin-pyrazole derivative **97** by Vilsmeier-Haack formylation reaction. Further, the reaction of this new formyl **97** derivatives refluxed with thiosemicarbazide using catalytic acetic acid afforded the corresponding thiosemicarbazone **98** derivatives. Finally, refluxing in DMF with different phenacyl bromides **99** produced the desired thiazole-based **100** derivatives with 56-70% yield [119].

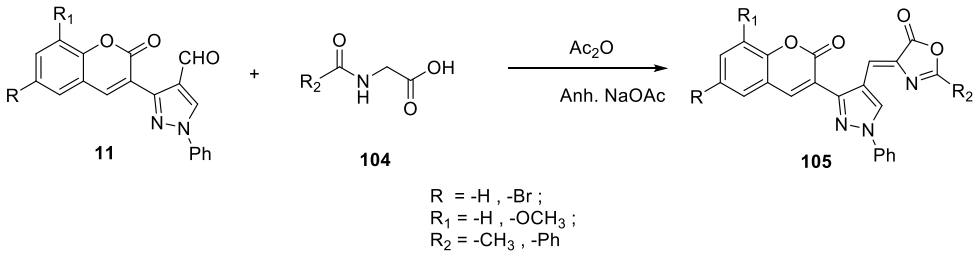
One-pot three-component synthesis of new coumarin-pyrazole affixed substituted thiazole (*E*)-3-(1-phenyl-4-((2-(4-phenylthiazol-2-yl)hydrazono)methyl)-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **103**(**a-l**) were developed by Gondru and co-workers. The stepwise conversion of 3-acetyl coumarin **9** to corresponding hydrazone **10** was achieved by reacting 4-formyl coumarin-pyrazole **11**. Three component reactions of 4-formyl coumarin-pyrazole **11**, thiosemicarbazide **101,** and 1-aryl-2-bromoethan-1-one **102** refluxed in ethanol using catalytic acetic acid condition furnished the final



Scheme 39. Synthesis of coumarin-pyrazole affixed thiazole compound derivatives.



Scheme 40. Three-component synthesis of thiazole based coumarin-pyrazole derivatives.



Scheme 41. Erlenmeyer-Plochl azlactone synthesis using *N*-acetylglycine or *N*-benzoylglycine.

product **103 (a-l)** in good to excellent (85-92%) yields (Scheme **40**) [130].

Mahmoodi *et al*. reported new series of thiazolyl-pyrazole-biscoumarin **48** by applying a one-pot multicomponent synthetic route as shown in Scheme **15**. Coumarinyl chalcone **44**, thiosemicarbazide **46** and coumarinyl phenacyl bromide **47** were refluxed in ethanol to access desired product 3-(2-Oxo-2*H*-chromen-3-yl)-1-(4-(2-oxo-2*H*-chromen-3-yl) thiazol-2-yl)-5-aryl-1*H*-pyrazol-1-ium **48** in good yields (Scheme **15**) [110].

ii) Formation of Novel Coumarin-pyrazole Affixed Tetrazole Compound

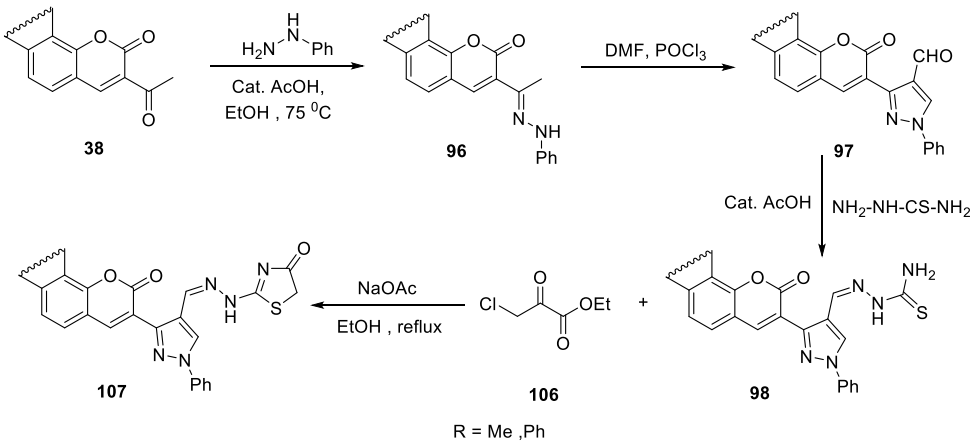
Kumbar *et al*. reported the synthesis of the desired product 3-(1-phenyl-4-(2*H*-tetrazol-5-yl)-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **95** from intermediate 3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4-carbonitrile **94** as shown in Scheme **37** with 70-85% yield [121].

iii) Formation of Coumarin-pyrazole Affixed Alkyloxazolone

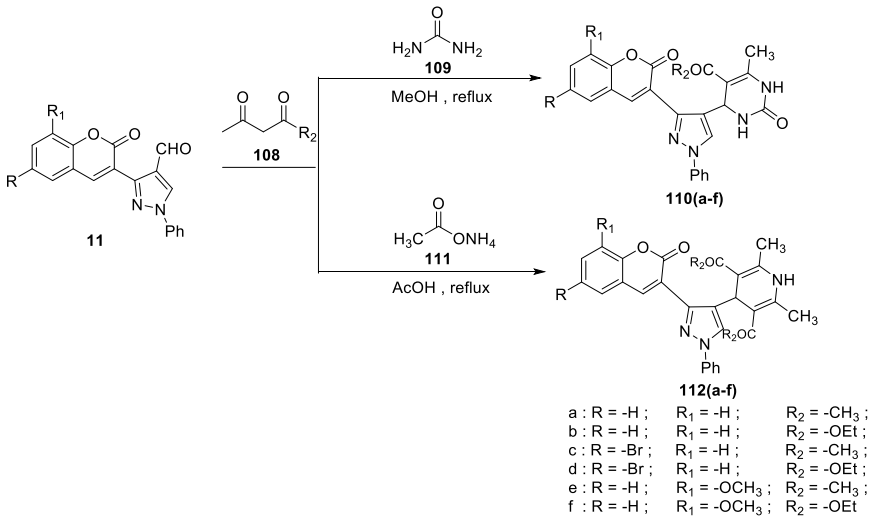
The heterocycle 2-alkyloxazolone affixed coumarin-pyrazole moiety **105** was reported by Patel *et al*. (Scheme **41**) [131]. Reaction of 4-formyl coumarin-pyrazole **11**, *N*-acetylglycine or *N*-benzoylglycine **104** in Ac_2O/ NaOAc afforded the desired Erlenmeyer-Plochl azlactone product i.e. (*Z*)-2-methyl-4-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) oxazol-5(4*H*)-one **105** in 55-65% yield (Scheme **41**).

iv) Formation of Coumarin-pyrazole Affixed Thiazolone

Zaki *et al*. demonstrated the synthesis of three linked heterocyclic (coumarin-pyrazole-thiazolone) compound **107** [*i.e.* (*Z*)-2-(2-((3-(2-oxo-2*H*-aryl[*h*]chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)thiazol-4(5*H*)-one] using intermediate thiosemicarbazone derivative **98** and ethyl 3-chloro-2-oxopropanoate **106** under reflux condition in ethanol with the addition of NaOAc base as shown in entire Scheme **42** [119]. The



Scheme 42. Synthesis of three linked heterocyclic (coumarin-pyrazole-thiazolone) compound.



Scheme 43. Biginelli and Hantzsch reactions using 4-formyl coumarin-pyrazole.

synthesis of intermediate thiosemicarbazone **98**, starting from 3-acetyl-7,8-dihydro-2*H*-aryl[*h*]chromen-2-one **38,** was performed in the same way as described in Scheme **39**.

B) Formation of Coumarin-Pyrazole Affixed Six-Membered Heterocycle Compounds

i) Synthesis of 5-acetyl-3,4-dihydro-6-methylpyrimidin-2(1H)-one

Biginelli reaction involving one-pot, three-component (4-formyl coumarin-pyrazole **11**, 1,3-diketo/ dicarbonyl compound **108** and urea **109** refluxing in methanol to furnish the product 5-acetyl-3,4-dihydro-6-methylpyrimidin-2(1*H*)-one **110 (a-f)** (50-60% yield) was reported in the research protocol of Patel *et al*. in 2008 (Scheme **43**) [131].

ii) Synthesis of 3,5-dicarbonyl-1,4-dihydro-2,4,6-trimethylpyridine

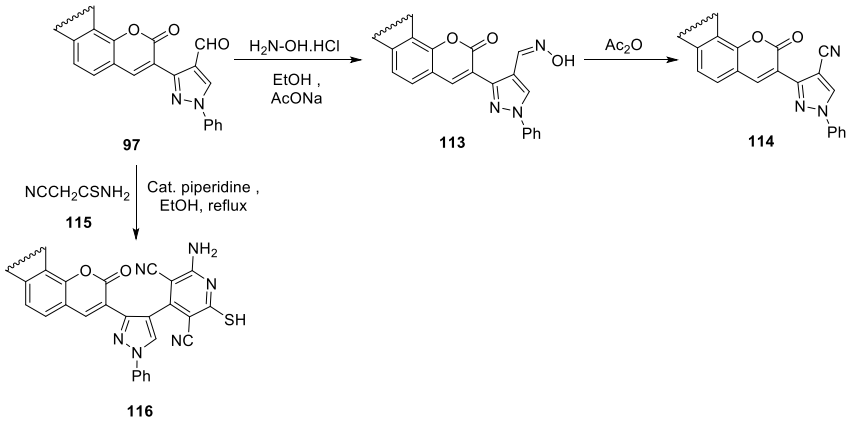
Patel *et al*. in 2008 also reported Hantzsch reaction for the synthesis of novel diethyl 2,6-dimethyl-4-(3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate compound **112 (a-f)** derivatives. The 4-formyl coumarin-pyrazole **11**, 1,3-diketo/ dicarbonyl compound **108** and ammonium acetate **111** were refluxed in acetic acid; the target product **112 (a-f)** derivatives were obtained in 53-63% yield (Scheme **43**) [131].

iii) Synthesis of 2-amino-6-mercaptopyridine-3,5-dicarbonitrile

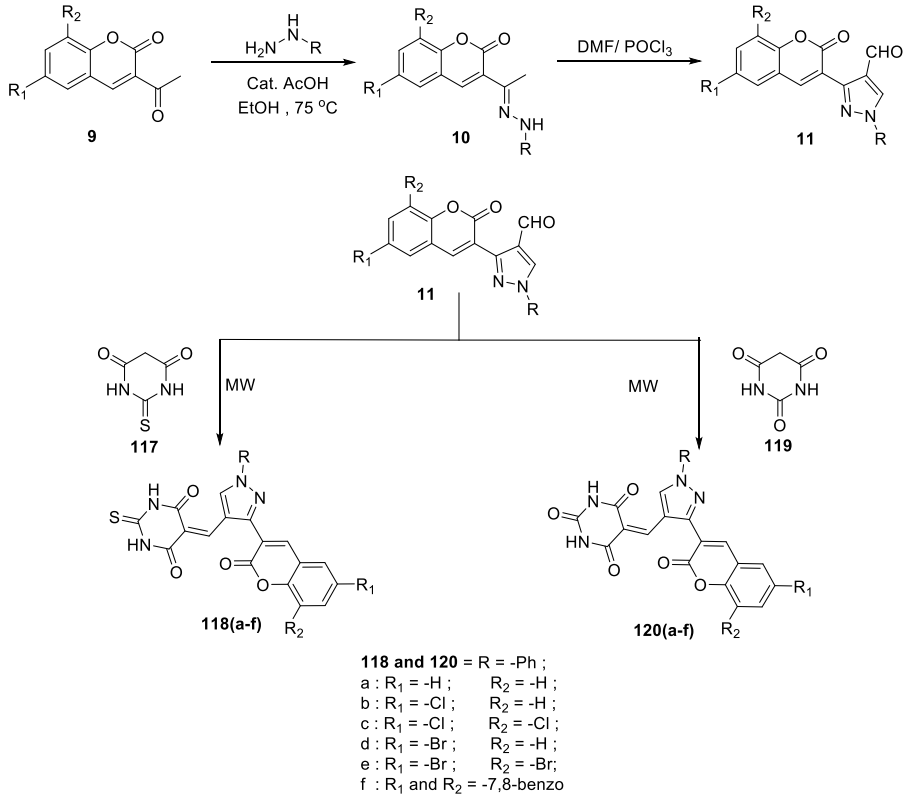
Zaki *et al*. developed the synthesis of novel 2-amino-6-mercapto-4-(3-(2-oxo-2*H*-aryl[*h*]chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)pyridine-3,5-dicarbonitrile **116** by reacting substituted 4-formyl coumarin-pyrazole **97** with 2-cyanoethanethioamide **115** in the refluxed condition in ethanol using cat. piperidine base to afford the product with moderate to good yields. In the next strategy, substituted 4-formyl coumarin-pyrazole **97** was treated with $NH_2OH.HCl$ to obtain the coumarin-pyrazole-oxime **113** and abnormal Beckmann rearrangement gave 4-cyano coumarin-pyrazole **114** product **116** (Scheme **44**) [119].

iv) Synthesis of Coumarin-pyrazole Affixed Pyrimidine 2,4,6(1H,3H,5H) Triones and Thioxopyrimidine 4,6(1H,5H) Diones

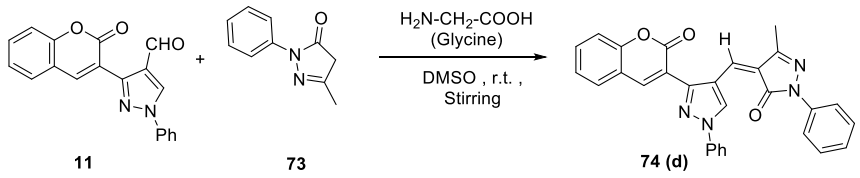
Green, microwave-assisted condensation route for the synthesis of new 5-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **118(a-f)** and 5-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **120(a-f)** from 4-formyl coumarin-pyrazole **11** was developed by Vijaya Laxmi and co-workers [132]. Initially, 3-acetyl coumarin **9** on treatment with phenyl hydrazine converted into corresponding hydrazone **10** followed by Vilsmeier-Haack reaction which gave 4-formyl coumarin-pyrazole **11**. Further, reaction of 4-formyl coumarin-pyrazole **11** with dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione **117** and pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (Barbituric acid) **119** under microwave irradiation produced the corresponding products **118 (a-f)** and **120 (a-f)** in good to excellent (75-90%) yield (Scheme **45**).



Scheme 44. Synthesis of pyridine and cyano containings coumarin pyrazole derivatives.



Scheme 45. Microwave assisted synthesis of novel coumarin-pyrazole affixed pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones and thioxopyrimidine-4,6(1*H*,5*H*) diones.



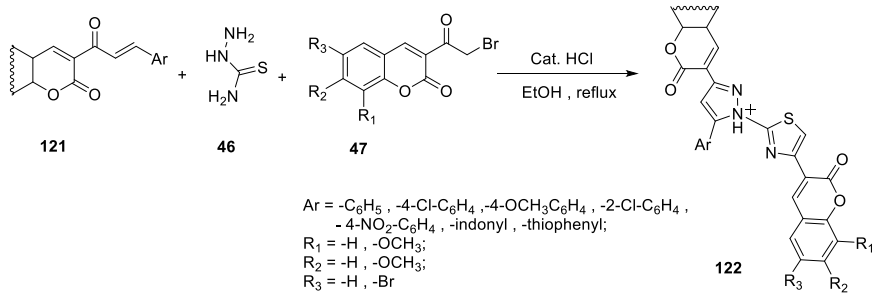
Scheme 46. Synthesis of coumarin-pyrazole affixed substituted 2,4-dihydropyrazolone.

v) Synthesis of Coumarin-pyrazole Affixed Substituted 2,4-Dihydropyrazolone

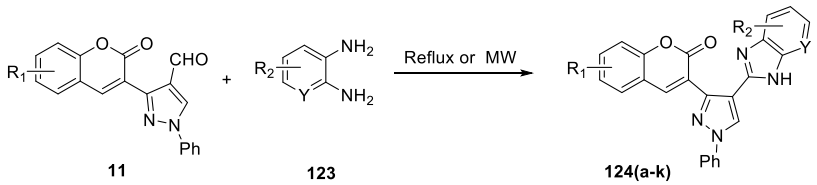
Chaudhry *et al.* developed green glycine catalyzed condensation for the synthesis of (*E*)-5-methyl-4-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **74 (d)** using 4-formyl coumarin-pyrazole **11** and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **73** as shown in Scheme **46** [123].

vi) Synthesis of New Thiazolyl-pyrazole-Biscoumarin Scaffold

In Scheme **47**, Mahamoodi and coworkers (2016) described an efficient, one-pot, three-component synthetic route for the synthesis of 3-(2-Oxo-2*H*-chromen-3-yl)-1-(4-(2-oxo-2*H*-chromen-3-yl) thiazol-2-yl)-5-aryl-1*H*-pyrazol-1-ium **122** containing thiazolyl-pyrazole-biscoumarin moiety [110].



Scheme 47. Synthesis of 3-(2-Oxo-2*H*-chromen-3-yl)-1-(4-(2-oxo-2*H*-chromen-3-yl) thiazol-2-yl)-5-aryl-1*H*-pyrazol-1-ium.



124 (a-k) :

a : R_1 = -H ; R_2 = -H ; Y = -C ;
b : R_1 = -H ; R_2 = -6-Cl ; Y = -C ;
c : R_1 = -H ; R_2 = -6-CH_3 ; Y = -C ;
d : R_1 = -H ; R_2 = -6-NO_2 ; Y = -C ;
e : R_1 = -H ; R_2 = -6-Br ; Y = -N ;
f : R_1 = -H ; R_2 = -5,5(Me)$_2$; Y = -C ;
g : R_1 = -6-Cl ; R_2 = -H ; Y = -C ;
h : R_1 = -6-Cl ; R_2 = -4-Cl ; Y = -C ;
i : R_1 = -6-Cl ; R_2 = -4-CH_3 ; Y = -C ;
j : R_1 = -6-Cl ; R_2 = -6-NO_2 ; Y = -C ;
k : R_1 = -6-Cl ; R_2 = -6-Br ; Y = -N ;

Scheme 48. Microwave-assisted efficient synthesis of coumarin-pyrazole attached benzimidazole.

C) Formation of Coumarin-pyrazole Fused Heterocycle

i) Synthesis of 6-amino-3-(7-methoxy-2-oxo-2H-chromen-3-yl)-1,4-diphenyl-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile

Seydimemet *et al*. disclosed ultrasonic irradiation assisted catalytic *L*-proline mediated four-component reaction between intermediate **61**, phenyl hydrazine, aryl aldehyde **43,** and malanonitrile **27,** affording the product 6-amino-3-(7-methoxy-2-oxo-2*H*-chromen-3-yl)-1,4-diphenyl-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile **62** in good to excellent yields as shown in Scheme **19** [114].

ii) Synthesis of Coumarin-pyrazole Affixed Benzimidazole Scaffold

Microwave-assisted, one-pot synthetic methodology was developed by Kumbar and co-workers to synthesize 3-(4-(1H-benzo[d]imidazol-2-yl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one and 3-(4-(3H-imidazo[4,5-b]pyridin-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **124(a-k)** derivatives. In this protocol, the comparative conventional and microwave-assisted reaction study was performed. The result revealed that microwave-assisted method was superior in terms of reaction yield, time, and work-up procedure. Synthesis was performed using 4-formyl coumarin-pyrazole **11** and substituted aryl 1,2-diamino compound **123** under microwave irradiation to afford the desired product **124 (a-k)** in excellent yields (90-97%) as shown in Scheme **48** [133].

Srikrishna *et al*. disclosed the different strategies to synthesize biologically active coumarin-pyrazole affixed benzimidazole scaffold **130** and their analogues **134 (**Scheme **49)** [134]. In this protocol, the 4-formyl coumarin-pyrazole **11** on reduction with $NaBH_4$ afforded the alcohol intermediate **125**, which subsequently converted into **126** by refluxing with $SOCl_2$ in benzene. Intermediate **126** on S_N^2 reaction with *O*-ethyl carbonodithioate **127** provided another intermediate **128** which on refluxing with different aryl 1,2-diamine **129** furnished the desired product 3-(4-((1*H*benzo[*d*]imidazol-2-ylthio)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-ones **130**.

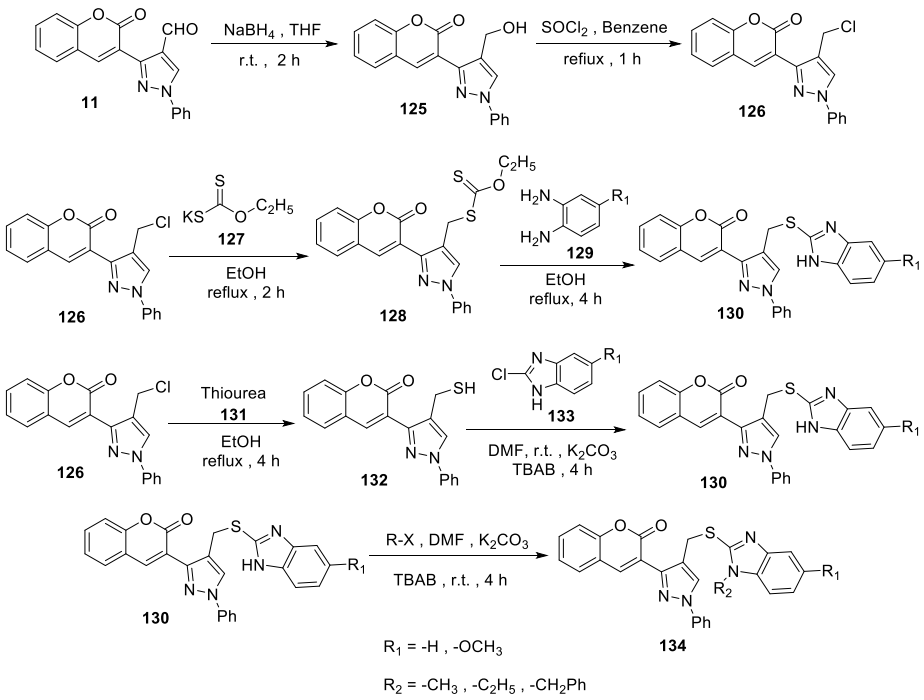
The intermediate **126** on treatment with thiourea **131** resulted in the formation of thiol **132,** which on refluxing with 2-chloro-1*H*-benzo[*d*]imidazole in presence of K_2CO_3/ TBAB afforded the product **130**. Further, N-alkylation of **130** gave the corresponding alkyl-substituted coumarin-pyrazole affixed benzimidazole 3-(4-(((1-methyl-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **134** by using K_2CO_3/ TBAB as shown in Scheme **49**.

iii) Synthesis of fused thiazolo[2,3-b]pyrimidinones bearing a pyrazolylcoumarin moiety:

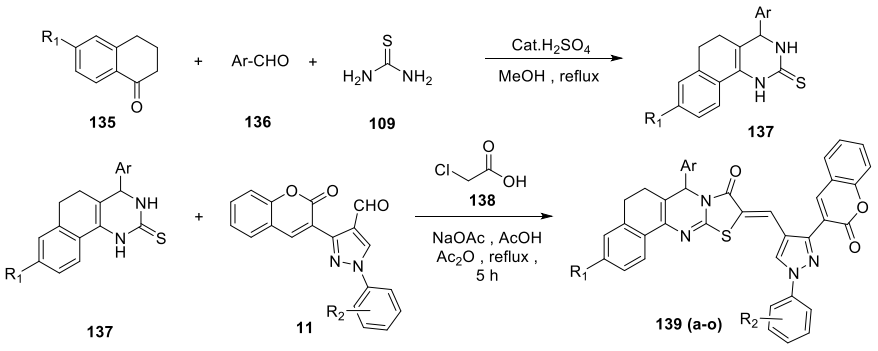
Gondru and coworkers demonstrated an efficient one-pot, four-component condensation reaction between 4-formyl coumarin-pyrazole **11**, chloroacetic acid **138**, thio-intermediate **137** and acetic anhydride in the presence of acetic acid with NaOAc base to afford the series of (*Z*)-7-aryl-10-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-5,7-dihydro-6*H*-benzo[*h*] thiazolo[2,3-b]quinazolin-9(10*H*)-one **139(a-o)** derivatives. The intermediate **137** [4-aryl-8-methyl-3,4,5,6-tetrahydrobenzo[*h*]quinazoline-2(1*H*)-thione] was synthesized *via* one-pot, three-component condensation reaction between 6-methyl-3,4-dihydronaphthalen-1(2*H*)-one **135**, aldehyde **136** and thiourea **109** using catalytic conc. H_2SO_4 (Scheme **50**) [135].

IV) Reactions at N-Atom of Coumarin-Pyrazole

The N-atom of coumarin-pyrazole derivative **2** showed decent nucleophilic character; therefore, various reactions such as nucleophilic substitution, addition, condensation reactions are reported in some research protocols of the coumarin-pyrazole scaffold. El-Deen *et al*. demonstrated, for the first time, the utility of reactions related to N-atom of pyrazole ring in synthesizing diverse compounds using coumarin-pyrazole scaffold as summarized in Scheme **51** [108].



Scheme 49. Synthesis of coumarin-pyrazole affixed benzimidazole using different strategies.



139 (a-o) =

a :	R_1 = -Ph ;	Ar = -4- Cl-C_6H_4 ;	R_2 = -H ;
b :	R_1 = -OMe ;	Ar = -4-Cl-C_6H_4 ;	R_2 = -2,4$(NO_2)_2$;
c :	R_1 = -OMe ;	Ar = -C_6H_5 ;	R_2 = -H ;
d :	R_1 = -OMe ;	Ar = -C_6H_5 ;	R_2 = -2,4$(NO_2)_2$;
e :	R_1 = -OMe ;	Ar = -4-OMe-C_6H_4 ;	R_2 = -H ;
f :	R_1 = -3,4-$(OMe)_2$;	Ar = -4-OMe-C_6H_4 ;	R_2 = -H ;
g :	R_1 = -3,4-$(OMe)_2$;	Ar = -4-OMe-C_6H_4 ;	R_2 = -2,4$(NO_2)_2$;
h :	R_1 = -3-OH,4-OMe ;	Ar = -4-OMe-C_6H_4 ;	R_2 = -H ;
i :	R_1 = -F ;	Ar = -4-OMe-C_6H_4 ;	R_2 = -H ;
j :	R_1 = -Me ;	Ar = -4-Cl-C_6H_4 ;	R_2 = -H ;
k :	R_1 = -OMe ;	Ar = -4-Br-C_6H_4 ;	R_2 = -H ;
l :	R_1 = -OMe ;	Ar = -4-Br- C_6H_4 ;	R_2 = -H ;
m:	R_1 = -OMe ;	Ar = -4-OH,3-Me-C_6H_3 ;	R_2 = -H ;
n :	R_1 = -OMe ;	Ar = -4-OH,3-Me-C_6H_3 ;	R_2 = -H ;
o :	R_1 = -OMe ;	Ar = -4-OH,3-Me-C_6H_3 ;	R_2 = -H

Scheme 50. Synthesis of fused thiazolo[2,3-b]pyrimidinone-pyrazolylcoumarin hybrids.

a) Amidation and co-related Substitution Reaction

Amidation of coumarin-pyrazole **2** was successfully carried out using acetyl chloride or benzoyl chloride, and chloro acetyl chloride **140** afforded the intermediate amide **141**. Further, the reaction of amide derivative of chloro acetyl chloride **141 (b)** with different amine **142** gave the substitution product **143**.

b) N-methylation Reaction

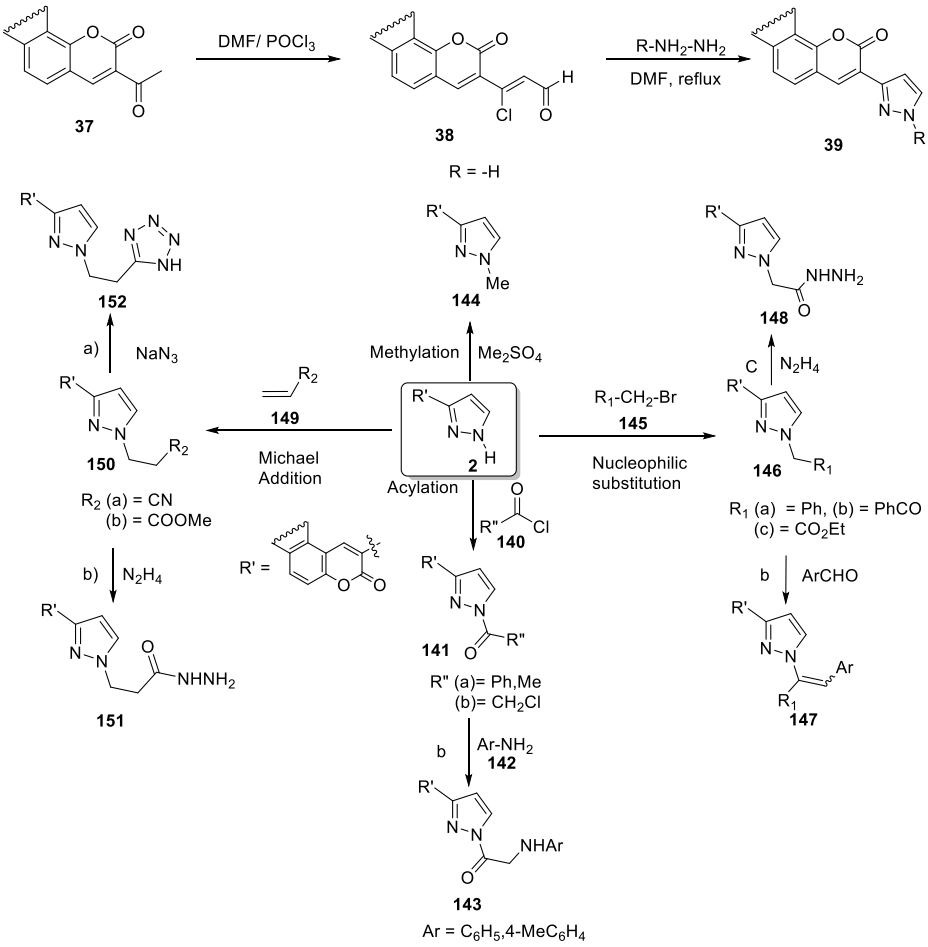
In the next protocol, *N*-methylation of coumarin-pyrazole **2** was performed using dimethyl sulphate to obtain the product **144**.

c) Nucleophilic Substitution and Related Reactions

Aliphatic nucleophilic substitution reactions at N-atom are more familiar and performed using benzyl chloride or phenacyl bromide **145** to obtain the intermediate **146**. This intermediate **146,** on treatment with various aldehydes, gave the chalcone derivative **147,** and with hydrazine hydrate, afforded the acyl hydrazide compound **148**.

d) Michael Addition and Related Reactions

Michael addition reactions also worked efficiently with coumarin-pyrazole **2** and afforded the coumarin-pyrazole based cyano **150**



Scheme 51. Miscellaneous reaction strategy of *N*-atom of pyrazole ring of the coumarin-pyrazole.

(a) and ester-based **150 (b)** derivatives. Further, treatment with hydrazine hydrate and NaN_3 furnished the acid-hydrazide derivative **151** and tetrazole affixed coumarin-pyrazole **152,** respectively, in good to excellent yield (Scheme **51**) [108].

CONCLUSION

In recent years, coumarin and pyrazole-containing pharmacophores have received considerable interest in finding new leads in drug discovery and exploring the applications in material chemistry. Thus, new methods have been developed for the synthesis and functionalization of coumarin-pyrazole-containing compounds. In the present review, we summarized the synthesis and functionalization of the pharmacologically important coumarin-pyrazole scaffold. Approaches include the synthesis of coumarin with various substitutions that can easily be further derivatized, as well as incorporating the pyrazole with or without substitution with addition, cyclization, and cascade reactions. Moreover, coumarin-pyrazole has been used to afford valuable chemical entities that are otherwise cumbersome to synthesize. The ease of synthetic access will encourage further use of coumarin-pyrazole building blocks in medicinal and material chemistry. It has been demonstrated that this combination of heterocycles can be introduced as a good surrogate to tune hydrophobic and lipophilic groups, such as the functionalization on the 4-formyl group, or a substitution on coumarin moiety can enhance the chemical and metabolic stability; therefore, this remarkable stability and other characteristic properties will stimulate their use not only in the pharmaceutical industry but also in material and agrochemical industry. It is expected that further methods will be devised for its easy incorporation and functionalization into desired target scaffolds, and continued studies will deepen the understanding of its impact on the properties of compounds. We believe that this review of the unique combination of coumarin-pyrazole heterocycles will encourage the scientists to use the coumarin-pyrazole scaffold to find new chemical entities within medicinal chemistry as well as other fields of chemistry.

CONSENT FOR PUBLICATION

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Eftekhari-Sis, B.; Zirak, M.; Akbari, A. Arylglyoxals in synthesis of heterocyclic compounds. *Chem. Rev.,* **2013**, *113*(5), 2958-3043. http://dx.doi.org/10.1021/cr300176g PMID: 23347156

[2] Li, X.; He, L.; Chen, H.; Wu, W.; Jiang, H. Copper-catalyzed aerobic C(sp^2)-H functionalization for C-N bond formation: Synthesis of pyrazoles and indazoles. *J. Org. Chem.,* **2013**, *78*(8), 3636-3646. http://dx.doi.org/10.1021/jo400162d PMID: 23547954

[3] Vogel, A. Darstellung von benzoesaure aus der tonka-bohne und aus den meliloten-oder steinklee-blumen. *Ann. Phy,* **1820**, *64*, 161-166. http://dx.doi.org/10.1002/andp.18200640205

[4] Stefanachi, A.; Leonetti, F.; Pisani, I.D. L.; Catto ID, M.; Carotti, A. Coumarin: A natural, privileged and versatile scaffold for bioactive compounds. *Molecules,* **2018**, *23*, 250-283. http://dx.doi.org/10.3390/molecules23020250

[5] Venugopala, K.N.; Rashmi, V.; Odhav, B. Review on natural coumarin lead compounds for their pharmacological activity. *BioMed Res. Int.,* **2013**, *2013*, 963248. http://dx.doi.org/10.1155/2013/963248 PMID: 23586066

[6] Matsuda, H.; Tomohiro, N.; Ido, Y.; Kubo, M. Anti-allergic effects of cnidii monnieri fructus (dried fruits of Cnidium monnieri) and its major component, osthol. *Biol. Pharm. Bull.,* **2002**, *25*(6), 809-812. http://dx.doi.org/10.1248/bpb.25.809 PMID: 12081154

[7] Yao, L.; Lu, P.; Li, Y.; Yang, L.; Feng, H.; Huang, Y.; Zhang, D.; Chen, J.; Zhu, D. Osthole relaxes pulmonary arteries through endothelial phosphatidylinositol 3-kinase/Akt-eNOS-NO signaling pathway in rats. *Eur. J. Pharmacol.,* **2013**, *699*(1-3), 23-32. http://dx.doi.org/10.1016/j.ejphar.2012.11.056 PMID: 23220709

[8] Hung, C.M.; Kuo, D.H.; Chou, C.H.; Su, Y.C.; Ho, C.T.; Way, T.D. Osthole suppresses hepatocyte growth factor (HGF)-induced epithelial-mesenchymal transition *via* repression of the c-Met/Akt/mTOR pathway in human breast cancer cells. *J. Agric. Food Chem.,* **2011**, *59*(17), 9683-9690. http://dx.doi.org/10.1021/jf2021489 PMID: 21806057

[9] 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*(30), 3797-3811. http://dx.doi.org/10.2174/1381612043382693 PMID: 15579072

[10] Kostova, I.; Bhatia, S.; Grigorov, P.; Balkansky, S.; Parmar, V.S.; Prasad, A.K.; Saso, L. Coumarins as antioxidants. *Curr. Med. Chem.,* **2011**, *18*(25), 3929-3951. http://dx.doi.org/10.2174/092986711803414395 PMID: 21824098

[11] Xi, G-L.; Liu, Z-Q. Coumarin-fused coumarin: antioxidant story from *N,N*-dimethylamino and hydroxyl groups. *J. Agric. Food Chem.,* **2015**, *63*(13), 3516-3523. http://dx.doi.org/10.1021/acs.jafc.5b00399 PMID: 25826201

[12] Ostrov, D.A.; Hernández Prada, J.A.; Corsino, P.E.; Finton, K.A.; Le, N.; Rowe, T.C. Discovery of novel DNA gyrase inhibitors by high-throughput virtual screening. *Antimicrob. Agents Chemother.,* **2007**, *51*(10), 3688-3698. http://dx.doi.org/10.1128/AAC.00392-07 PMID: 17682095

[13] Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Granese, A.; Carradori, S.; Rivanera, D.; Zicari, A.; Scaltrito, M.M.; Sisto, F. Synthesis, selective anti-Helicobacter pylori activity, and cytotoxicity of novel N-substituted-2-oxo-2H-1-benzopyran-3-carboxamides. *Bioorg. Med. Chem. Lett.,* **2010**, *20*(16), 4922-4926. http://dx.doi.org/10.1016/j.bmcl.2010.06.048 PMID: 20630755

[14] Lad, H.B.; Giri, R.R.; Brahmbhatt, D.I. An efficient synthesis of some new 3-bipyridinyl substituted coumarins as potent antimicrobial agents. *Chin. Chem. Lett.,* **2013**, *24*, 227-229. http://dx.doi.org/10.1016/j.cclet.2013.01.041

[15] Keri, R.S.; Hosamani, K.M.; Reddy, H.S.; Shingalapur, R.V. Synthesis, *in-vitro* antimicrobial and cytotoxic studies of novel azetidinone derivatives. *Arch. Pharm. (Weinheim),* **2010**, *343*(4), 237-247. PMID: 20205197

[16] Annunziata, F.; Pinna, C.; Dallavalle, S.; Tamborini, L.; Pinto, A. An overview of coumarin as a versatile and readily accessible scaffold with broad-ranging biological activities. *Int. J. Mol. Sci.,* **2020**, *21*(13), 4618-4698. http://dx.doi.org/10.3390/ijms21134618 PMID: 32610556

[17] Palmer, C.J.; Josephs, J.L. Synthesis of the *Calophyllum* coumarins. Part 2. *J. Chem. Soc. Perkin Trans,* **1995**, *1*, 3135-3152. http://dx.doi.org/10.1039/p19950003135

[18] Kashman, Y.; Gustafson, K.R.; Fuller, R.W.; Cardellina, J.H., II; McMahon, J.B.; Currens, M.J.; Buckheit, R.W., Jr; Hughes, S.H.; Cragg, G.M.; Boyd, M.R. The calanolides, a novel HIV-inhibitory class of coumarin derivatives from the tropical rainforest tree, *Calophyllum lanigerum*. *J. Med. Chem.,* **1992**, *35*(15), 2735-2743. http://dx.doi.org/10.1021/jm00093a004 PMID: 1379639

[19] Kostova, I. Coumarins as inhibitors of HIV reverse transcriptase. *Curr. HIV Res.,* **2006**, *4*(3), 347-363. http://dx.doi.org/10.2174/157016206777709393 PMID: 16842086

[20] Gu, Q.; Zhang, X. M.; Wang, R. R.; Liu, Q. M.; Zheng, Y. T.; Zhou, J.; Chen, J. J. Anti-HIV active constituents from Angelica apaensis. *Nat. Pro. Res. Dev.,* **2008**, *20*

[21] Patil, A.D.; Freyer, A.J.; Eggleston, D.S.; Haltiwanger, R.C.; Bean, M.F.; Taylor, P.B.; Caranfa, M.J.; Breen, A.L.; Bartus, H.R.; Johnson, R.K. The inophyllums, novel inhibitors of HIV-1 reverse transcriptase isolated from the Malaysian tree, *Calophyllum inophyllum Linn. J. Med. Chem.,* **1993**, *36*(26), 4131-4138. http://dx.doi.org/10.1021/jm00078a001 PMID: 7506311

[22] Guibourt, N. J. B. G. *Histoire Abrégée des Droques Simples (Abridged History of Simple Drugs)*; Paris, L. Colas., **1820**, 2, pp. 160-161.

[23] Heide, L. The aminocoumarins: Biosynthesis and biology. *Nat. Prod. Rep.,* **2009**, *26*(10), 1241-1250. http://dx.doi.org/10.1039/b808333a PMID: 19779639

[24] Bansal, Y.; Sethi, P.; Bansal, G. Coumarin: A potential nucleus for anti-inflammatory molecules. *Med. Chem. Res.,* **2013**, *22*, 3049-3060. http://dx.doi.org/10.1007/s00044-012-0321-6

[25] Zhu, J.-J.; Jiang, J.-G. Pharmacological and nutritional effects of natural coumarins and their structure-activity relationships. *Mol. Nutr. Food Res.,* **2017**, *62*(14), 1701073.

[26] Sashidhara, K.V.; Kumar, A.; Chatterjee, M.; Rao, K.B.; Singh, S.; Verma, A.K.; Palit, G. Discovery and synthesis of novel 3-phenylcoumarin derivatives as antidepressant agents. *Bioorg. Med. Chem. Lett.,* **2011**, *21*(7), 1937-1941. http://dx.doi.org/10.1016/j.bmcl.2011.02.040 PMID: 21377878

[27] Barros, T.A.A.; de Freitas, L.A.; Filho, J.M.B.; Nunes, X.P.; Giulietti, A.M.; de Souza, G.E.; dos Santos, R.R.; Soares, M.B.; Villarreal, C.F. Antinociceptive and anti-inflammatory properties of 7-hydroxycoumarin in experimental animal models: potential therapeutic for the control of inflammatory chronic pain. *J. Pharm. Pharmacol.,* **2010**, *62*(2), 205-213. http://dx.doi.org/10.1211/jpp.62.02.0008 PMID: 20487200

[28] Huang, X.Y.; Shan, Z.J.; Zhai, H.L.; Su, L.; Zhang, X.Y. Study on the anticancer activity of coumarin derivatives by molecular modeling. *Chem. Biol. Drug Des.,* **2011**, *78*(4), 651-658. http://dx.doi.org/10.1111/j.1747-0285.2011.01195.x PMID: 21791009

[29] Neyts, J.; De Clercq, E.; Singha, R.; Chang, Y.H.; Das, A.R.; Chakraborty, S.K.; Hong, S.C.; Tsay, S.C.; Hsu, M.H.; Hwu, J.R. Structure-activity relationship of new anti-hepatitis C virus agents: heterobicycle-coumarin conjugates. *J. Med. Chem.,* **2009**, *52*(5), 1486-1490. http://dx.doi.org/10.1021/jm801240d PMID: 19193060

[30] Olomola, T.O.; Klein, R.; Mautsa, N.; Sayed, Y.; Kaye, P.T. Synthesis and evaluation of coumarin derivatives as potential dual-action HIV-1 protease and reverse transcriptase inhibitors. *Bioorg. Med. Chem.,* **2013**, *21*(7), 1964-1971. http://dx.doi.org/10.1016/j.bmc.2013.01.025 PMID: 23415084

[31] Yeh, J. Y.; Coumar, M. S.; Horng, J. T.; Shiao, H. Y.; Lee, H. L. Anti-Influenza drug discovery: Structure-Activity relationship and mechanistic insight into novel angelicin derivatives. *J. Med. Chem.,* **2010**, *53*, 1519-1533.

[32] Sun, Q.; Peng, D.Y.; Yang, S.G.; Zhu, X.L.; Yang, W.C.; Yang, G.F. Syntheses of coumarin-tacrine hybrids as dual-site acetylcholinesterase inhibitors and their activity against butylcholinesterase, Aβ aggregation, and β-secretase. *Bioorg. Med. Chem.,* **2014**, *22*(17), 4784-4791. http://dx.doi.org/10.1016/j.bmc.2014.06.057 PMID: 25088549

[33] Piazzi, L.; Cavalli, A.; Colizzi, F.; Belluti, F.; Bartolini, M.; Mancini, F.; Recanatini, M.; Andrisano, V.; Rampa, A. Multi-target-directed coumarin derivatives: hAChE and BACE1 inhibitors as potential anti-Alzheimer compounds. *Bioorg. Med. Chem. Lett.,* **2008**, *18*(1), 423-426. http://dx.doi.org/10.1016/j.bmcl.2007.09.100 PMID: 17998161

[34] Vasconcelos, J.F.; Teixeira, M.M.; Barbosa-Filho, J.M.; Agra, M.F.X.P.; Nunes, X.P.; Giulietti, A.M.; Ribeiro-Dos-Santos, R.; Soares, M.B. Effects of umbelliferone in a murine model of allergic airway inflammation. *Eur. J. Pharmacol.,* **2009**, *609*(1-3), 126-131. http://dx.doi.org/10.1016/j.ejphar.2009.03.027 PMID: 19289114

[35] Yuce, B.; Danis, O.; Ogan, A.; Sener, G.; Bulut, M.; Yarat, A. Antioxidative and lipid lowering effects of 7,8-dihydroxy-3- (4-methylphenyl) coumarin in hyperlipidemic rats. *Arzneimittelforschung,* **2009**, *59*(3), 129-134. PMID: 19402343

[36] Keri, R.S.; Hosamani, K.M.; Shingalapur, R.V.; Hugar, M.H. Analgesic, anti-pyretic and DNA cleavage studies of novel pyrimidine derivatives of coumarin moiety. *Eur. J. Med. Chem.,* **2010**, *45*(6), 2597-2605. http://dx.doi.org/10.1016/j.ejmech.2010.02.048 PMID: 20356657

[37] Watzka, M.; Geisen, C.; Bevans, C.G.; Sittinger, K.; Spohn, G.; Rost, S.; Seifried, E.; Müller, C.R.; Oldenburg, J. Thirteen novel VKORC1 mutations associated with oral anticoagulant resistance: Insights into improved patient diagnosis and treatment. *J. Thromb. Haemost.,* **2011**, *9*(1), 109-118. http://dx.doi.org/10.1111/j.1538-7836.2010.04095.x PMID: 20946155

[38] Weigt, S.; Huebler, N.; Strecker, R.; Braunbeck, T.; Broschard, T.H. Developmental effects of coumarin and the anticoagulant coumarin derivative warfarin on zebrafish *(Danio rerio*) embryos. *Reprod. Toxicol.,* **2012**, *33*(2), 133-141. http://dx.doi.org/10.1016/j.reprotox.2011.07.001 PMID: 21798343

[39] Manvar, A.; Bavishi, A.; Radadiya, A.; Patel, J.; Vora, V.; Dodia, N.; Rawal, K.; Shah, A. Diversity oriented design of various hydrazides and their in vitro evaluation against *Mycobacterium tuberculosis* $H37_{Rv}$ strains. *Bioorg. Med. Chem. Lett.,* **2011**, *21*(16), 4728-4731. http://dx.doi.org/10.1016/j.bmcl.2011.06.074 PMID: 21752642

[40] Rezayan, A.H.; Azerang, P.; Sardari, S.; Sarvary, A. Synthesis and biological evaluation of coumarin derivatives as inhibitors of *Mycobacterium bovis* (BCG). *Chem. Biol. Drug Des.,* **2012**, *80*(6), 929-936. http://dx.doi.org/10.1111/cbdd.12044 PMID: 22943459

[41] Naik, R.J.; Kulkarni, M.V.; Sreedhara Ranganath Pai, K.; Nayak, P.G. Click chemistry approach for bis-chromenyl triazole hybrids and their antitubercular activity. *Chem. Biol. Drug Des.,* **2012**, *80*(4), 516-523. http://dx.doi.org/10.1111/j.1747-0285.2012.01441.x PMID: 22737986

[42] Cardoso, S.H.; Barreto, M.B.; Lourenço, M.C.; Henriques, Md.; Candéa, A.L.; Kaiser, C.R.; de Souza, M.V. Antitubercular activity of new coumarins. *Chem. Biol. Drug Des.,* **2011**, *77*(6), 489-493. http://dx.doi.org/10.1111/j.1747-0285.2011.01120.x PMID: 21414146

[43] Upadhyay, K.; Bavishi, A.; Thakrar, S.; Radadiya, A.; Vala, H.; Parekh, S.; Bhavsar, D.; Savant, M.; Parmar, M.; Adlakha, P.; Shah, A. Synthesis and biological evaluation of 4-styrylcoumarin derivatives as inhibitors of TNF-α and IL-6 with anti-tubercular activity. *Bioorg. Med. Chem. Lett.,* **2011**, *21*(8), 2547-2549. http://dx.doi.org/10.1016/j.bmcl.2011.02.016 PMID: 21396814

[44] Jeyachandran, M.; Ramesh, P.; Sriram, D.; Senthilkumar, P.; Yogeeswari, P. Synthesis and in vitro antitubercular activity of 4-aryl/alkylsulfonylmethylcoumarins as inhibitors of *Mycobacterium tuberculosis*. *Bioorg. Med. Chem. Lett.,* **2012**, *22*(14), 4807-4809. http://dx.doi.org/10.1016/j.bmcl.2012.05.054 PMID: 22726933

[45] Basanagouda, M.; Jambagi, V.B.; Barigidad, N.N.; Laxmeshwar, S.S.; Devaru, V.; Narayanachar, Synthesis, structure-activity relationship of iodinated-4-aryloxymethyl-coumarins as potential anti-cancer and anti-mycobacterial agents. *Eur. J. Med. Chem.,* **2014**, *74*, 225-233. http://dx.doi.org/10.1016/j.ejmech.2013.12.061 PMID: 24463645

[46] Zheng, P.; Somersan-Karakaya, S.; Lu, S.; Roberts, J.; Pingle, M.; Warrier, T.; Little, D.; Guo, X.; Brickner, S.J.; Nathan, C.F.; Gold, B.; Liu, G. Synthetic calanolides with bactericidal activity against replicating and nonreplicating *Mycobacterium tuberculosis*. *J. Med. Chem.,* **2014**, *57*(9), 3755-3772. http://dx.doi.org/10.1021/jm4019228 PMID: 24694175

[47] Keri, R.S.; Sasidhar, B.S.; Nagaraja, B.M.; Santos, M.A. Recent progress in the drug development of coumarin derivatives as potent antituberculosis agents. *Eur. J. Med. Chem.,* **2015**, *100*, 257-269. http://dx.doi.org/10.1016/j.ejmech.2015.06.017 PMID: 26112067

[48] Boerner, L.J.K.; Zaleski, J.M. Metal complex-DNA interactions: From transcription inhibition to photoactivated cleavage. *Curr. Opin. Chem. Biol.,* **2005**, *9*(2), 135-144. http://dx.doi.org/10.1016/j.cbpa.2005.02.010 PMID: 15811797

[49] El-Ansary, S.L.; Hussein, M.M.; Abdel Rahman, D.E.; Abdel Ghany, L.M.A. Synthesis, docking and *in vitro* anticancer evaluation of some new benzopyrone derivatives. *Bioorg. Chem.,* **2014**, *53*, 50-66. http://dx.doi.org/10.1016/j.bioorg.2014.02.003 PMID: 24607350

[50] Amin, K.M.; Eissa, A.A.; Abou-Seri, S.M.; Awadallah, F.M.; Hassan, G.S. Synthesis and biological evaluation of novel coumarin-pyrazoline hybrids endowed with phenylsulfonyl moiety as antitumor agents. *Eur. J. Med. Chem.,* **2013**, *60*, 187-198. http://dx.doi.org/10.1016/j.ejmech.2012.12.004 PMID: 23291120

[51] Saidu, N.E.B.; Valente, S.; Bana, E.; Kirsch, G.; Bagrel, D.; Montenarh, M. Coumarin polysulfides inhibit cell growth and induce apoptosis in HCT116 colon cancer cells. *Bioorg. Med. Chem.,* **2012**, *20*(4), 1584-1593. http://dx.doi.org/10.1016/j.bmc.2011.12.032 PMID: 22264758

[52] 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. http://dx.doi.org/10.1016/j.ejmech.2015.07.010 PMID: 26188907

[53] O'Kennedy, R.; Thornes, R.D. Coumarins: Biology applications and mode of action. Wiley, **1997**.

[54] Zabradnik, M. The production and application of fluorescent brightening agents. Wiley, **1992**.

[55] Zeydi, M.M.; Kalantarian, S.J.; Kazeminejad, Z. Overview on developed synthesis procedures of coumarin heterocycles. *J. Iranian Chem. Soc,* **2020**, *17*, 3031-3094. http://dx.doi.org/10.1007/s13738-020-01984-1

[56] Ghate, M.; Manohar, D.; Kulkarni, V.; Shobha, R.; Kattimani, S.Y. Synthesis of vanillin ethers from 4-(bromomethyl) coumarins as anti-inflammatory agents. *Eur. J. Med. Chem.,* **2003**, *38*(3), 297-302. http://dx.doi.org/10.1016/S0223-5234(03)00016-3 PMID: 12667696

[57] Lee, S.; Sivakumar, K.; Shin, W.S.; Xie, F.; Wang, Q. Synthesis and anti-angiogenesis activity of coumarin derivatives. *Bioorg. Med. Chem. Lett.,* **2006**, *16*(17), 4596-4599. http://dx.doi.org/10.1016/j.bmcl.2006.06.007 PMID: 16793260

[58] Abdellatif, K.R.A.; Abdelgawad, M.A.; Elshemy, H.A.H.; Kahk, N.M.; Amir, D.M.E. Design, synthesis, antioxidant and anticancer activity of new coumarin derivatives linked with thiazole. *Isoxazole or Pyrazole Moiety,* **2017**, *14*, 773-781.

[59] Peterson, L. B.; Blagg, B. S. J. Click chemistry to probe Hsp90: Synthesis and evaluation of a series of triazole-containing novobiocin analogues. *Bioorg. Med. Chem. Lett.,* **2010**, *20*(13), 3957-3960. http://dx.doi.org/10.1016/j.bmcl.2010.04.140 PMID: 20570149

[60] Parmar, V.S.; Sharma, N.K.; Husain, M.; Watterson, A.C.; Kumar, J.; Samuelson, L.A.; Cholli, A.L.; Prasad, A.K.; Kumar, A.; Malhotra, S.; Kumar, N.; Jha, A.; Singh, A.; Singh, I.; Himanshu, ; Vats, A.; Shakil, N.A.; Trikha, S.; Mukherjee, S.; Sharma, S.K.; Singh, S.K.; Kumar, A.; Jha, H.N.; Olsen, C.E.; Stove, C.P.; Bracke, M.E.; Mareel, M.M. Synthesis, characterization and *in vitro* anti-invasive activity screening of polyphenolic and heterocyclic compounds. *Bioorg. Med. Chem.,* **2003**, *11*(6), 913-929. http://dx.doi.org/10.1016/S0968-0896(02)00539-4 PMID: 12614877

[61] Abdelhafez, O.M.; Amin, K.M.; Batran, R.Z.; Maher, T.J.; Nada, S.A.; Sethumadhavan, S. Synthesis, anticoagulant and PIVKA-II induced by new 4-hydroxycoumarin derivatives. *Bioorg. Med. Chem.,* **2010**, *18*(10), 3371-3378. http://dx.doi.org/10.1016/j.bmc.2010.04.009 PMID: 20435480

[62] Amin, K.M.; Awadalla, F.M.; Eissa, A.A.M.; Abou-Seri, S.M.; Hassan, G.S. Design, synthesis and vasorelaxant evaluation of novel coumarin-pyrimidine hybrids. *Bioorg. Med. Chem.,* **2011**, *19*(20), 6087-6097. http://dx.doi.org/10.1016/j.bmc.2011.08.037 PMID: 21908192

[63] Kiyani, H.; Albooyeh, F.; Fallahnezhad, S. Synthesis of new pyrazolyl-1,3-diazabicyclo[3.1.0]hexe-3-ene derivatives. *J. Mol. Struct.,* **2015**, *1091*, 163-169. http://dx.doi.org/10.1016/j.molstruc.2015.02.069

[64] Lv, P-C.; Sun, J.; Luo, Y.; Yang, Y.; Zhu, H-L. Design, synthesis, and structure-activity relationships of pyrazole derivatives as potential FabH inhibitors. *Bioorg. Med. Chem. Lett.,* **2010**, *20*(15), 4657-4660. http://dx.doi.org/10.1016/j.bmcl.2010.05.105 PMID: 20594840

[65] Karrouchi, K.; Radi, S.; Ramli, Y.; Taoufik, J.; Mabkhot, Y.N.; Al-Aizari, F.A.; Ansar, M. Synthesis and pharmacological activities of pyrazole derivatives: A Review. *Molecules,* **2018**, *23*(1), 134-219. http://dx.doi.org/10.3390/molecules23010134 PMID: 29329257

[66] Shelke, S.N.; Mhaske, G.R.; Bonifácio, V.D.B.; Gawande, M.B. Green synthesis and anti-infective activities of fluorinated pyrazoline derivatives. *Bioorg. Med. Chem. Lett.,* **2012**, *22*(17), 5727-5730. http://dx.doi.org/10.1016/j.bmcl.2012.06.072 PMID: 22832312

[67] Saudi, M.; Zmurko, J.; Kaptein, S.; Rozenski, J.; Gadakh, B.; Chaltin, P.; Marchand, A.; Neyts, J.; Van Aerschot, A. Synthetic strategy and antiviral evaluation of diamide containing heterocycles targeting dengue and yellow fever virus. *Eur. J. Med. Chem.,* **2016**, *121*, 158-168. http://dx.doi.org/10.1016/j.ejmech.2016.05.043 PMID: 27240271

[68] Manvar, D.; Pelliccia, S.; La Regina, G.; Famiglini, V.; Coluccia, A.; Ruggieri, A.; Anticoli, S.; Lee, J.C.; Basu, A.; Cevik, O.; Nencioni, L.; Palamara, A.T.; Zamperini, C.; Botta, M.; Neyts, J.; Leyssen, P.; Kaushik-Basu, N.; Silvestri, R. New 1-phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-3-carboxamides inhibit hepatitis C virus replication via suppression of cyclooxygenase-2. *Eur. J. Med. Chem.,* **2015**, *90*, 497-506. http://dx.doi.org/10.1016/j.ejmech.2014.11.042 PMID: 25483263

[69] Abdellatif, K.R.A.; Abdelall, E.K.A.; Fadaly, W.A.A.; Kamel, G.M. Synthesis, cyclooxygenase inhibition, anti-inflammatory evaluation and ulcerogenic liability of new 1,3,5-triarylpyrazoline and 1,5-diarylpyrazole derivatives as selective COX-2 inhibitors. *Bioorg. Med. Chem. Lett.,* **2016**, *26*(2), 406-412. http://dx.doi.org/10.1016/j.bmcl.2015.11.105 PMID: 26691756

[70] Zhang, L.; Shan, Y.; Li, C.; Sun, Y.; Su, P.; Wang, J.; Li, L.; Pan, X.; Zhang, J. Discovery of novel anti-angiogenesis agents. Part 6: Multi-targeted RTK inhibitors. *Eur. J. Med. Chem.,* **2017**, *127*, 275-285. http://dx.doi.org/10.1016/j.ejmech.2016.12.059 PMID: 28068599

[71] Nasr, T.; Bondock, S.; Eid, S. Design, synthesis, antimicrobial evaluation and molecular docking studies of some new thiophene, pyrazole and pyridone derivatives bearing sulfisoxazole moiety. *Eur. J. Med. Chem.,* **2014**, *84*, 491-504. http://dx.doi.org/10.1016/j.ejmech.2014.07.052 PMID: 25050881

[72] Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. From 2000 to mid-2010: a fruitful decade for the synthesis of pyrazoles. *Chem. Rev.,* **2011**, *111*(11), 6984-7034. http://dx.doi.org/10.1021/cr2000459 PMID: 21806021

[73] Ansari, A.; Ali, A.; Asif, M. Review: Biologically active pyrazole derivatives. *New J. Chem.,* **2017**, *41*, 16-41. http://dx.doi.org/10.1039/C6NJ03181A

[74] Trivedi, A.; Dodiya, D.; Dholariya, B.; Kataria, V.; Bhuva, V.; Shah, V. Synthesis and biological evaluation of some novel 1,4-dihydropyridines as potential antitubercular agents. *Chem. Biol. Drug Des.,* **2011**, *78*(5), 881-886. http://dx.doi.org/10.1111/j.1747-0285.2011.01233.x PMID: 21895982

[75] Kompis, I.M.; Islam, K.; Then, R.L. DNA and RNA synthesis: Antifolates. *Chem. Rev.,* **2005**, *105*(2), 593-620. http://dx.doi.org/10.1021/cr0301144 PMID: 15700958

[76] Czaplinski, K.H.; Hänsel, W.; Wiese, M.; Seydel, J.K. New benzylpyrimidines: inhibition of DHFR from various species. QSAR, CoMFA and PC analysis. *Eur. J. Med. Chem.,* **1995**, *30*, 779-787. http://dx.doi.org/10.1016/0223-5234(96)88297-3

[77] So, S.S.; Richards, W.G. Application of neural networks: quantitative structure-activity relationships of the derivatives of 2,4-diamino-5-(substituted-benzyl)pyrimidines as DHFR inhibitors. *J. Med. Chem.,* **1992**, *35*(17), 3201-3207. http://dx.doi.org/10.1021/jm00095a016 PMID: 1507206

[78] Thomas, K.D.; Adhikari, A.V.; Chowdhury, I.H.; Sumesh, E.; Pal, N.K. New quinolin-4-yl-1,2,3-triazoles carrying amides, sulphonamides and amidopiperazines as potential antitubercular agents. *Eur. J. Med. Chem.,* **2011**, *46*(6), 2503-2512. http://dx.doi.org/10.1016/j.ejmech.2011.03.039 PMID: 21489660

[79] Ward, S.E.; Harries, M.; Aldegheri, L.; Austin, N.E.; Ballantine, S.; Ballini, E.; Bradley, D.M.; Bax, B.D.; Clarke, B.P.; Harris, A.J.; Harrison, S.A.; Melarange, R.A.; Mookherjee, C.; Mosley, J.; Dal Negro, G.; Oliosi, B.; Smith, K.J.; Thewlis, K.M.; Woollard, P.M.; Yusaf, S.P. Integration of lead optimization with crystallography for a membrane-bound ion channel target:

Discovery of a new class of AMPA receptor positive allosteric modulators. *J. Med. Chem.,* **2011**, *54*(1), 78-94.
http://dx.doi.org/10.1021/jm100679e PMID: 21128618

[80] Mert, S.; Kasımoğulları, R.; İça, T.; Çolak, F.; Altun, A.; Ok, S. Synthesis, structure-activity relationships, and *in vitro* antibacterial and antifungal activity evaluations of novel pyrazole carboxylic and dicarboxylic acid derivatives. *Eur. J. Med. Chem.,* **2014**, *78*, 86-96.
http://dx.doi.org/10.1016/j.ejmech.2014.03.033 PMID: 24681068

[81] Fu, H.; Yao, J. Size effects on the optical properties of organic nanoparticles. *J. Am. Chem. Soc.,* **2001**, *123*, 1434-1439.
http://dx.doi.org/10.1021/ja0026298

[82] Wang, M.; Zhang, J.; Liu, J.; Xu, C.; Ju, H. Intramolecular energy and charge transfer in 5-(9-anthryl)-3-(4-nitrophenyl)-1-phenyl-2-pyrazoline. *J. Lumin.,* **2002**, *99*, 79-83.
http://dx.doi.org/10.1016/S0022-2313(01)00204-6

[83] Gao, X.C.; Cao, H.; Zhang, L.Q.; Zhang, B.W.; Cao, Y.; Huang, C.H. Properties of a new pyrazoline derivative and its application in electroluminescence. *J. Mater. Chem.,* **1999**, *9*, 1077-1080.
http://dx.doi.org/10.1039/a900276f

[84] Karci, F.; Karci, F.; Demircali, A.; Yamac, M. Synthesis, solvatochromic properties and antimicrobial activities of some novel pyridone-based disperse disazo dyes. *J. Mol. Liq.,* **2013**, *187*, 302-308.
http://dx.doi.org/10.1016/j.molliq.2013.08.005

[85] Chou, P.T.; Chi, Y. Phosphorescent dyes for organic light-emitting diodes. *Chemistry,* **2007**, *13*(2), 380-395.
http://dx.doi.org/10.1002/chem.200601272 PMID: 17146830

[86] Kauhanka, U.M.; Kauhanka, M.M. Synthesis of new liquid crystalline isoxazole-, pyrazole-and 2-isoxazoline-containing compounds. *Liq. Cryst.,* **2006**, *33*, 121-127.
http://dx.doi.org/10.1080/02678290500429976

[87] Burschka, J.; Kessler, F.; Nazeeruddin, M.K.; Gratzel, M. Co(III) complexes as p-dopants in solid-state dye-sensitized solar cells. *Chem. Mater.,* **2013**, *25*, 2986-2990.
http://dx.doi.org/10.1021/cm400796u

[88] Tu, X.J.; Hao, W.J.; Ye, Q.; Wang, S.S.; Jiang, B.; Li, G.; Tu, S.J. Four-component bicyclization approaches to skeletally diverse pyrazolo[3,4-b]pyridine derivatives. *J. Org. Chem.,* **2014**, *79*(22), 11110-11118.
http://dx.doi.org/10.1021/jo502096t PMID: 25338160

[89] Castagnolo, D.; Schenone, S.; Botta, M. Guanylated diamines, triamines, and polyamines: Chemistry and biological properties. *Chem. Rev.,* **2011**, *111*(9), 5247-5300.
http://dx.doi.org/10.1021/cr100423x PMID: 21657224

[90] Molteni, G.; Del Buttero, P. A bicyclo[3.1.1]heptano[4,3-*c*]pyrazole derived chiral auxiliary for dipolar cycloadditions. *Tetrahedron Asymmetry,* **2005**, *16*, 1983-1987.
http://dx.doi.org/10.1016/j.tetasy.2005.04.014

[91] Singh, P.; Paul, K.; Holzer, W. Synthesis of pyrazole-based hybrid molecules: search for potent multidrug resistance modulators. *Bioorg. Med. Chem.,* **2006**, *14*(14), 5061-5071.
http://dx.doi.org/10.1016/j.bmc.2006.02.046 PMID: 16554161

[92] (a) Kale, R.R.; Prasad, V.; Mohapatra, P.; Tiwari, V.K. Recent developments in benzotriazole methodology for construction of pharmacologically important heterocyclic skeletons. *Monatsh. Chem.,* **2010**, *141*, 1159-1182.
http://dx.doi.org/10.1007/s00706-010-0378-1
(b) Prasad, V.; Kale, R.R.; Mishra, B.B.; Kumar, D.; Tiwari, V.K. Diacetoxyiodobenzene mediated one-pot synthesis of diverse carboxamides from aldehydes. *Org. Lett.,* **2012**, *14*(12), 2936-2939.
http://dx.doi.org/10.1021/ol3012315 PMID: 22630055
(c) Prasad, V.; Kale, R.R.; Kumar, V.; Tiwari, V.K. Carbohydrate chemistry and room temperature ionic liquids (RTILs): Recent trends, opportunities, challenges and future perspectives. *Curr. Org. Synth.,* **2010**, *1*, 506-531.
http://dx.doi.org/10.2174/157017910792246063
(d) Kale, R.R.; Prasad, V.; Hussain, H.A.; Tiwari, V.K. Facile route for N_1-aryl benzotriazoles from diazoamino arynes *via* CuI-mediated intramolecular N-arylation. *Tetrahedron Lett.,* **2010**, *51*(43), 5740-5743.
http://dx.doi.org/10.1016/j.tetlet.2010.08.083 PMID: 32287442
(e) Mane, V.; Pandey, J.; Ayyagari, N.; Dey, C.; Kale, R.; Namboothiri, I.N.N. Synthesis of hydrazinoheterocycles from Morita-Baylis-Hillman adducts of nitroalkenes with azodicarboxylates. *Org. Biomol. Chem.,* **2016**, *14*(8), 2427-2438.
http://dx.doi.org/10.1039/C5OB02656C PMID: 26810956
(f) Hosamani, B.; Kale, R.R.; Sharma, H.; Wachtel, E.; Kesselman, E.; Danino, D.; Friedman, N.; Sheves, M.; Namboothiri, I.N.N.; Patchornik, G. Membrane protein crystallization in micelles conjugated by nucleoside base-pairing: A different concept. *J. Struct. Biol.,* **2016**, *195*(3), 379-386.
http://dx.doi.org/10.1016/j.jsb.2016.06.021 PMID: 27368128
(g) Dhandapani, G.; Nair, D.K.; Kale, R.R.; Wachtel, E.; Namboothiri, I.N.N.; Patchornik, G. Role of amphiphilic [metal:chelator] complexes in a non-chromatographic antibody purification platform. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.,* **2019**, *1133*, 121830.
http://dx.doi.org/10.1016/j.jchromb.2019.121830 PMID: 31704445
(h) Kale, R.R.; Prasad, V.; Tiwari, V.K. Facile route for novel quinazolinone-fused azauracils through cyclodesulfurization of thioquinazolinones. *Synlett,* **2011**, *2*, 195-198.
(i) Tiwari, V.K.; Kale, R.R. A facile one-pot MW approach for 3-heteroaryl-2-thioxo-2, 3-dihydroquinazolin-4 (1H)-one. *ARKIVOC,* **2008**, *15*, 27-36.
http://dx.doi.org/10.3998/ark.5550190.0009.e04

[93] Trkovnik, M.; Kuld, M.; La-N, M.; Bobarevi, B. Notizen: Synthesis of Heterocyclic Comounds with 3-Acetoacetyl-4-hydroxy-coumarin, I. *Z. Naturforsch. B,* **1974**, *29*, 580-581.
http://dx.doi.org/10.1515/znb-1974-7-833

[94] Trkovnik, M.; La-N, M.; Stunic, Z.; Nahmijas, D. 4H-Benzopyrano [3,4-d]oxazol-4-ones and 3-[N, N-bis(carboxymethyl)amino]-4-hydroxycoumarin derivatives. *Org. Prep. Proced. Int.,* **1975**, *7*, 26-30.
http://dx.doi.org/10.1080/00304947509356810

[95] Trkovnik, M.; Kules, M.; Tabaković, I.; Zecević, M. Thin-layer chromatography of some coumarin derivatives. *J. Chromatogr. A,* **1976**, *128*(1), 227-230.
http://dx.doi.org/10.1016/S0021-9673(00)84060-1 PMID: 186472

[96] Chodankar, N.K.; Sheshadri, S. Studies in the vilsmeier-haack reaction: part XXV-synthesis of 3-hetarylcoumarins by the application of the vilsmeier-haack reaction. *Dyes Pigments,* **1985**, *6*, 313-319.
http://dx.doi.org/10.1016/0143-7208(85)85001-4

[97] Chodankar, N.K.; Sequeira, S.; Sheshadri, S. Synthesis of 3-hetarylcoumarins from 3-acetylcoumarinst. *Dyes Pigments,* **1986**, *7*, 231-236.
http://dx.doi.org/10.1016/0143-7208(86)85011-2

[98] Srikrishna, D.; Dubey, P.K. Synthesis of 3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes. *Der. Phar. Chem,* **2014**, *6*(4), 57-60.

[99] Nagamallu, R.; Kariyappa, A.K. Synthesis and biological evaluation of novel formyl-pyrazoles bearing coumarin moiety as potent antimicrobial and antioxidant agents. *Bioorg. Med. Chem. Lett.,* **2013**, *23*(23), 6406-6409.
http://dx.doi.org/10.1016/j.bmcl.2013.09.053 PMID: 24120538

[100] Nagamallu, R.; Srinivasan, B.; Ningappa, M.B.; Kariyappa, A.K. Synthesis of novel coumarin appended bis(formylpyrazole) derivatives: Studies on their antimicrobial and antioxidant activities. *Bioorg. Med. Chem. Lett.,* **2016**, *26*(2), 690-694.
http://dx.doi.org/10.1016/j.bmcl.2015.11.038 PMID: 26631319

[101] Soliman, A.Y.; Bakeer, H.M. Nitriles in heterocyclic synthesis: Studies on ethyl 3-amino-4,4-dicyano-3-butenoate. *Chin. J. Chem.,* **1991**, *9*(5), 461-466.
http://dx.doi.org/10.1002/cjoc.19910090515

[102] Latif, H.A.; Barsy, M.A.; Elrady, E.A. Simple synthesis of some novel polyfunctionally derivatives of 2h-coumarin-2-one. *IOSR J. Applied Chem,* **2017**, *10*, 27-29.
http://dx.doi.org/10.9790/5736-1005012729

[103] Aziz El-Taweel, F.M.A.; Mohamed, H.E. Studies with enaminones: synthesis of new coumarin-3-yl azoles, coumarin-3-yl azines, coumarin-3-yl azoloazines, coumarin-3-yl pyrone and coumarin-2-yl benzo[*b*]Furans. *J. Heterocycl. Chem.,* **2001**, *38*, 981-984.
http://dx.doi.org/10.1002/jhet.5570380428

[104] Hamdi, N.; Saoud, M.; Romerosa, A.; Hassen, R.B. Synthesis, spectroscopic and antibacterial investigations of new hydroxy ethers and heterocyclic coumarin derivatives. *J. Heterocycl. Chem.,* **2008**, *45*, 1835-1842.
http://dx.doi.org/10.1002/jhet.5570450644

[105] Khadijah, M. Al-Zayadi. Microwave assisted synthesis, Part 1: Rapid solventless synthesis of 3-substituted coumarins and benzocoumarins by microwave irradiation of the corresponding enaminones. *Molecules,* **2003**, *8*, 541-555.
http://dx.doi.org/10.3390/80700541

[106] Gomha, S.M.; Zaki, Y.H.; Abdelhamid, A.O. Utility of 3-Acetyl-6-bromo-2*H*-chromen-2-one for the synthesis of new heterocycles as potential antiproliferative agents. *Molecules,* **2015**, *20*(12), 21826-21839.
http://dx.doi.org/10.3390/molecules201219803 PMID: 26690106

[107] Srikrishna, D.; Dubey, P.K. Facile, stepwise and diversity oriented synthesis of 3-(2-oxo-2*h*-chromen-3-yl)-1-phenyl-1h-pyrazole-4-carbaldehydes. *J. Chem. Pharm. Res.,* **2017**, *9*(11), 99-108.

[108] El-Deen, I.M. Al-Wakeel, El-S. I.; El-Mawla, A.G. Syntheses of Some 3- [1′ (1′ *H*) -Substituent-pyrazol-5′-yl] benzo [5,6] coumarins. *Chin. J. Chem.,* **2002**, *20*, 670-675.
http://dx.doi.org/10.1002/cjoc.20020200709

[109] Jayashree, B.S.; Arora, S.; Venugopala, K.N. Microwave assisted synthesis of substituted coumarinyl chalcones as reaction intermediates for biologically important coumarinyl heterocycles. *Asian J. Chem.,* **2008**, *20*, 1-7.

[110] Mahmoodi, N.O.; Ghodsi, S. Thiazolyl-pyrazole-biscoumarin synthesis and evaluation of their antibacterial and antioxidant activities. *Res. Chem. Intermed.,* **2016**, *43*, 661-678.
http://dx.doi.org/10.1007/s11164-016-2644-2

[111] Aragade, P.; Maddi, V.; Khode, S.; Palkar, M.; Ronad, P.; Mamledesai, S.; Satyanarayana, D. Synthesis and antibacterial activity of a new series of 3-[3-(substituted phenyl)-1-isonicotinoyl-1*H*-pyrazol-5-yl]-2*H*-chromen-2-one derivatives. *Arch. Pharm. (Weinheim),* **2009**, *342*(6), 361-366.
http://dx.doi.org/10.1002/ardp.200800156 PMID: 19475595

[112] Aragade, P.; Narayanan, R.V.; Maddi, V.; Patil, P.; Shinde, P.; Agrawal, M. Synthesis and antibacterial activity of a new series of 3-[3-(substituted phenyl)-1-phenyl-1*H*-pyrazol-5-yl]-2*H*-chromen-2-one derivatives. *J. Enzyme Inhib. Med. Chem.,* **2012**, *27*(6), 849-853.
http://dx.doi.org/10.3109/14756366.2011.622270 PMID: 21988189

[113] Kumar, J.A.; Saidachary, G.; Mallesham, G.; Sridhar, B.; Jain, N.; Kalivendi, S.V.; Rao, V.J.; Raju, B.C. Synthesis, anticancer activity and photophysical

properties of novel substituted 2-oxo-2*H*-chromenylpyrazolecarboxylates. *Eur. J. Med. Chem.,* **2013**, *65*, 389-402. http://dx.doi.org/10.1016/j.ejmech.2013.03.042 PMID: 23748152

[114] Seydimemet, M.; Ablajan, K.; Hamdulla, M. Li. W.; Omar, A.; Obul, M. l-Proline catalyzed four-component one-pot synthesis of coumarin-containing dihydropyrano[2,3-*c*]pyrazoles under ultrasonic irradiation. *Tetrahedron,* **2016**, *72*, 7599-7605. http://dx.doi.org/10.1016/j.tet.2016.10.016

[115] Babur, B.; Seferoglu, N.; Seferoglu, N. A ratiometric fluorescence chemosensor based on a coumarin–pyrazolone hybrid: the synthesis and an investigation of the photophysical, tautomeric and anion binding properties by spectroscopic techniques and DFT calculations. *Tetrahedron Lett.,* **2015**, *56*(17), 2149-2154. http://dx.doi.org/10.1016/j.tetlet.2015.03.014

[116] Traven, V.F.; Ivanov, I.V.; Pavlov, A.S.; Manaev, A.V.; Voevodinaa, I.V.; Barachevski, V.A. Quantitative photooxidation of 4-hydroxy3-pyrazolinylcoumarins to pyrazolyl derivatives. *Mend Comm,* **2007**, *17*, 345-346. http://dx.doi.org/10.1016/j.mencom.2007.11.016

[117] Traven, V.F.; Ivanov, I.V. New reaction of photoaromatization of aryl- and hetarylpyrazolines. *Russ. Chem. Bull. Int. Edn,* **2008**, *57*, 1063-1069. http://dx.doi.org/10.1007/s11172-008-0135-3

[118] Traven, V.F.; Cheptsov, D.A.; Bulanova, M.V.; Solovjova, N.P.; Chibisova, T.A.; Dolotov, S.M.; Ivanov, I.V. On the mechanism of photodehydrogenation of aryl(hetaryl)pyrazolines in the presence of perchloroalkanes. *Photochem. Photobiol.,* **2018**, *94*(4), 659-666. http://dx.doi.org/10.1111/php.12918 PMID: 29526037

[119] Zaki, R.M.; Elossaily, Y.A. Kamal, EL-Dean, A. M. Synthesis and antimicrobial activity of novel benzo[*f*]coumarin compounds. *Russ. J. Bio. Chem,* **2012**, *38*, 639-646. http://dx.doi.org/10.1134/S1068162012040152

[120] Padhye, M.R.; Varadrajan, T.S.; Deshpande, A.V. Laser spectra and efficiencies of pyrazolo derivatives of coumarins. *Spectrosc. Lett.,* **1985**, *18*, 705-711. http://dx.doi.org/10.1080/00387018508062302

[121] Kumbar, M.N.; Sannaikar, M.S.; Shaikh, S.K.J.; Kamble, A.A.; Wari, M.N.; Inamdar, S.R.; Qiao, Q.; Revanna, B.N.; Madegowda, M.; Dasappa, J.P.; Kamble, R.R. Synthesis, photophysical and computational study of novel coumarin-based organic dyes. *Photochem. Photobiol.,* **2018**, *94*(2), 261-276. http://dx.doi.org/10.1111/php.12852 PMID: 29105763

[122] Chornous, V.O.; Bratenko, K.M.; Vovk, M.V. Microwave-assisted synthesis of 3-(4-pyrazolyl)propenoic acids. *syn. Comm,* **2004**, *34*, 79-83.

[123] Chaudhry, F.; Asif, N.; Shafqat, S.S.; Khan, A.A.; Munawar, M.A.; Khan, M.A. An efficient eco-friendly synthesis of pyrazole acryloyl analogues by amino acid catalysis. *Syn. Comm,* **2016**, *46*, 701-709.

[124] Kenchappa, R.; Bodke, Y.D.; Chandrashekhar, A.; Sindhe, M.A.; Peethambar, S.K. Synthesis of coumarin derivatives containing pyrazole and indenone rings as potent antioxidant and antihyperglycemic agents. *Arabian J. Chem.,* **2017**, *10*, S3895-S3906.

[125] Bratenko, M.K.; Sidorchuk, I.I.; Khalaturnik, M.V.; Vovk, M.V. Synthesis and antimicrobial activity of new azomethines synthesized from 4-formyl-1-phenyl-3-aryl(heteryl)pyrazoles. *Pharm. Chem. J.,* **1999**, *2*, 81-83.

[126] Bratenko, M.K.; Voloshin, N.P.; Petrunik, I.O.; Livak, D.M.; Vovk, M.V. Synthesis and antimicrobial activity of 4-formylpyrazole N-acylhydrazones. *Pharm. Chem. J.,* **1998**, *6*, 29-30. http://dx.doi.org/10.1007/BF02580517

[127] Labudova, K.; Sunil, D.; Kamath, P.R. Synthesis of Schiff bases as potent safab1 inhibitors and antibacterial agents. *Pharma Chem.,* **2016**, *8*, 493-498.

[128] Jain, A.; Gupta, R.; Agarwal, M. Instantaneous and selective bare eye detection of inorganic fluoride ion by coumarin–pyrazole-based receptors. *J. Heterocycl. Chem.,* **2017**, *54*(4), 2808-2816. http://dx.doi.org/10.1002/jhet.2884

[129] Whitt, J.; Duke, C.; Sumlin, A.; Chambers, S.A.; Alnufaie, R.; Gilmore, D.; Fite, T.; Basnakian, A.G.; Alam, M.A. Synthesis of hydrazone derivatives of 4-[4-formyl-3-(2-oxochromen-3-yl)pyrazol-1-yl]benzoic acid as potent growth inhibitors of antibiotic-resistant *staphylococcus Aureus* and *Acinetobacter baumannii. Molecules,* **2019**, *24*(11), 2051-2066. http://dx.doi.org/10.3390/molecules24112051 PMID: 31146470

[130] Gondru, R.; Banothu, J.; Thatipamula, R.K.; Althaf Hussain, S.K.; Bavantula, R. 3-(1-Phenyl-4-((2-(4-arylthiazol-2-yl)hydrazono)-methyl)-1H-pyrazol-3-yl)-2H-chromen-2-ones: one-pot three component condensation, *in vitro* antimicrobial, antioxidant and molecular docking studies. *RSC Adv.,* **2015**, *5*, 33562-33569. http://dx.doi.org/10.1039/C5RA04196A

[131] Patel, M.A.; Brahmabhatt, D.I. Synthesis of some oxazolyl - pyrazolyl; 1,4-Dihydropyridinyl-pyrazolyl and 1,2,3,4-tetrahydro pyrimidinyl-pyrazolyl coumarins. *J. Heterocycl. Chem.,* **2008**, *45*, 1051-1055. http://dx.doi.org/10.1002/jhet.5570450416

[132] Vijaya Laxmi, S.; Kuarm, B.S.; Rajitha, B. Synthesis and antimicrobial activity of coumarin pyrazole pyrimidine 2,4,6(1*H*,3*H*,5*H*)triones and thioxopyrimidine4,6(1*H*,5*H*)diones. *Med. Chem. Res.,* **2012**, *19*, 768-774.

[133] Kumbar, M.N.; Kamble, R.R.; Kamble, A.A.; Salian, S.R.; Kumari, S.; Nair, R.; Kalthur, G.; Adiga, S.K.; Prasad, D.J. Design and microwave assisted synthesis of coumarin derivatives as pde inhibitors. *Int. J. Med. Chem.,* **2016**, *2016*, 9890630. http://dx.doi.org/10.1155/2016/9890630 PMID: 26998358

[134] Srikrishna, D.; Dubey, P.K. Synthesis of novel substituted 3-(4-((1Hbenzo[d]imidazol-2-ylthio)methyl)-1-phenyl-1Hpyrazol-3-yl)-2H-chromen-2-ones: Various approaches. *Res. Chem. Intermed.,* **2018**, *44*, 4455-4468. http://dx.doi.org/10.1007/s11164-018-3397-x

[135] Gondru, R.; Peddi, S.R.; Manga, V.; Khanapur, M.; Gali, R.; Sirassu, N.; Bavantula, R. One-pot synthesis, biological evaluation and molecular docking studies of fused thiazolo[2,3-b]pyrimidinone-pyrazolylcoumarin hybrids. *Mol. Divers.,* **2018**, *22*(4), 943-956. http://dx.doi.org/10.1007/s11030-018-9845-0 PMID: 29968120