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3-[2-OXO-2H-CHROMEN-3(6)(8)-YL]-1-ARYL/HETEROARYL-1H-PYRAZOLE-4-CARBALDEHYDES: SYNTHESIS, REACTIONS AND APPLICATIONS

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Abstract – The chemistry of 3-(2-oxo-2H-chromen-3(6)(8)-yl)-1-aryl/heteroaryl-1H-pyrazole-4-carbaldehydes has gained increased interest in both synthetic organic and biological fields, since a large number of developments in the use of such compounds seem to be of considerable value. This review describes all the available synthetic methods for diverse 3-(2-oxo-2H-chromen-3(6)(8)-yl)-1-aryl/heteroaryl-1H-pyrazole-4-carbaldehydes in the literature survey. It also summarizes their chemical behaviors as building blocks towards a variety of chemical reagents to construct related compounds as well as their biological applications.

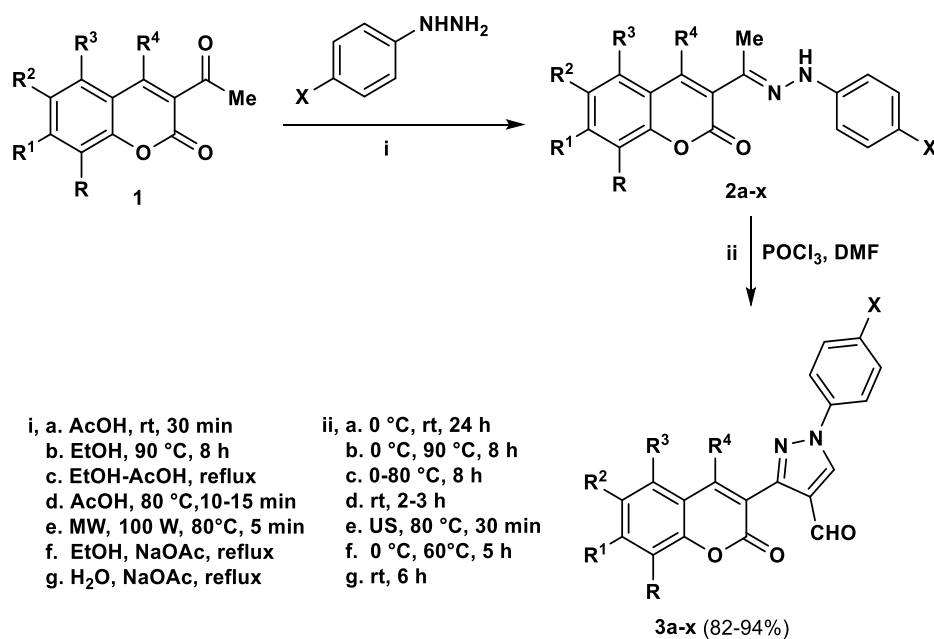
1. INTRODUCTION

Heterocycles are the principal structural motif of life because of their widespread distribution in nature and essential roles in numerous chemical processes. All living creatures are provided by heterocycles, which serve as the primary building blocks of their DNA and RNA. In addition, heterocyclic compounds demonstrated great physiological and pharmacological activities.¹ Nitrogen and oxygen heterocycles are fundamental building blocks of many physiologically active molecules, which have various uses in chemistry and biology.² Particularly, coumarin derivatives are essential components of fruits and crops and have antifungal and phytotoxic properties. In addition, coumarin compounds exhibited prominent biological properties such as antidepressant,³ antioxidant,^{4,5} antiviral,⁶ antimicrobial,⁷ antibiotic,⁸ muscle relaxant,⁹ anti-inflammatory,¹⁰ antinociceptive,¹¹ antitumor¹² and anti-HIV.¹³ On the other hand, pyrazoles are aromatic heterocycles with two nitrogen atoms in their five-membered rings.¹⁴ They form a significant

heterocyclic family that contains a variety of synthetic and natural compounds with a wide pharmacological and agrochemical effects.¹⁵ Further, they have an importance in medicinal chemistry due to their wide range of pharmacological activities such as anticonvulsant,¹⁶ antifungal,¹⁷ antitubercular (anti-TB),¹⁸ antimicrobial,¹⁹ anti-inflammatory,²⁰ antiproliferative,²¹ anticancer²² and anti-HIV.²³ When pyrazole ring was incorporated with coumarin moiety, the merged structure showed a significant change in pharmacological properties. Moreover, different biochemical and synthetic studies confirmed the hypothesis that the coumarinyl-pyrazole moiety is a basic structural motif for producing bioactive components in drug discovery. Coumarinyl-pyrazole compounds exhibited biologically properties such as anti-TB,²⁴ antioxidant,^{25,26} anticancer,^{27,28} antihyperglycemic agents,²⁵ antimicrobial,^{29,30} antibacterial,³¹ antiproliferative,^{28,32} and PDE inhibitor.³³ With a part of our ongoing studies on biologically active relevant heterocycles,³⁴⁻⁴⁰ we make a serious effort to present concise review focusing on the synthesis, reactions and applications of diverse 3-(2-oxo-2*H*-chromen-3(6)(8)-yl)-1-aryl/heteroaryl-1*H*-pyrazole-4-carbaldehydes and related compounds.

2. THE SYNTHETIC METHODS

The synthetic methods of 3-(2-oxo-2*H*-chromen-3-yl)-4-formylpyrazoles (**3**) were described. 3-Acetyl-coumarins (**1**) were reacted with arylhydrazines using different reaction conditions to afford the corresponding arylhydrazones **2a-x**. Upon subjection of these hydrazones **2a-x** to Vilsmeier-Haack reaction afforded a series of 1-aryl-4-formyl-3-(2-oxo-2*H*-chromen-3-yl)-1*H*-pyrazoles (**3a-x**) (Scheme 1 and Table 1).⁴¹⁻⁵⁶



Scheme 1

Table 1. The specific reaction conditions for the formation of products **3a-x**

Product	R	R ¹	R ²	R ³	R ⁴	X	Reaction conditions I	Reaction conditions II
3a	H	H	H	H	H	H	1. AcOH, rt, 30 min 2. EtOH-AcOH, reflux 3. MW, 100 W, 80 °C, 5 min 4. H ₂ O, NaOAc, reflux	1. 0 °C, rt, 24 h 2. US, 80 °C, 30 min 3. 0 °C, 60 °C, 5 h
3b	H	H	Cl	H	H	H	EtOH-AcOH, reflux	0-80 °C, 8 h
3c	H	H	Br	H	H	H	EtOH, 90 °C, 8 h	0-80 °C, 8 h
3d	H	H	F	H	H	H	EtOH, 90 °C, 8 h	0-80 °C, 8 h
3e	H	H	NO ₂	H	H	H	EtOH, NaOAc, reflux	0 °C, 60 °C, 5 h
3f	H	H	H	H	OH	H	AcOH, rt, 30 min	0 °C, 90 °C, 8 h
3g	MeO	H	H	H	H	H	AcOH, rt, 30 min	0 °C, 90 °C, 8 h
3h	Cl	H	H	H	H	H	AcOH, rt, 30 min	0 °C, 90 °C, 8 h
3i	Br	H	H	H	H	H	AcOH, rt, 30 min	0 °C, 90 °C, 8 h
3j	Br	H	Br	H	H	H	AcOH, rt, 30 min	0 °C, 90 °C, 8 h
3k	H	H	Br	H	H	Br	EtOH-AcOH, reflux	rt, 2-3 h
3l	H	NEt ₂	H	H	H	H	AcOH, rt, 30 min	0 °C, 60 °C, 5 h
3m	H	H	H	H	H	NO ₂	AcOH, 80 °C, 10-15 min	rt, 2-3 h
3n	H	H	H	H	H	Cl	AcOH, 80 °C, 10-15 min	rt, 2-3 h
3o	H	H	H	H	H	F	AcOH, 80 °C, 10-15 min	rt, 2-3 h
3p	H	H	Br	H	H	Cl	AcOH, 80 °C, 10-15 min	rt, 2-3 h
3q	H	H	H	H	H	Me	AcOH, 80 °C, 10-15 min	rt, 2-3 h
3r	H	H	Br	H	H	MeO	AcOH, 80 °C, 10-15 min	rt, 2-3 h
3s	H	H	H	Br	H	CO ₂ H	EtOH, 90 °C, 8 h	0-80 °C, 8 h
3t	H	H	H	Cl	H	CO ₂ H	EtOH, 90 °C, 8 h	0-80 °C, 8 h
3u	H	OH	H	H	H	CO ₂ H	EtOH, 90 °C, 8 h	0-80 °C, 8 h
3v	H	H	H	H	H	CO ₂ H	EtOH, 90 °C, 8 h	0-80 °C, 8 h
3w	H	Benzo		H	H	H	EtOH-AcOH, reflux	rt, 6 h
3x	H	H	Benzo		H	H	EtOH-AcOH, reflux	rt, 6 h

Also, 3-(2-oxo-2*H*-chromen-3-yl)-1-(4-arylthiazol-2-yl)-1*H*-pyrazole-4-carbaldehydes (**5a-n**)⁴¹ and 3-(2-oxo-2*H*-chromen-3-yl)-1-(benzothiazol-2-yl)-1*H*-pyrazole-4-carbaldehydes (**8**)⁵⁷ were synthesized by a sequential Hantzsch thiazole synthesis and Vilsmeier–Haack reaction. An equimolar mixture of α -halo-ketone and thiosemicarbazide in ethanol, was added to the substituted 3-acetylcoumarins (**1**) under refluxing to give the non-isolated hydrazones **4** (Scheme 2). Similarly, the acetyl derivatives **1** condensed with 2-hydrazinobenzothiazole (**6**) in ethanol to afford the hydrazones **7** (Scheme 3). Applying of Vilsmeier-Haack formylation of the latter hydrazones **4** and **7** gave the target compounds **5** (Table 2) and **8**, respectively (Scheme 2 and 3).

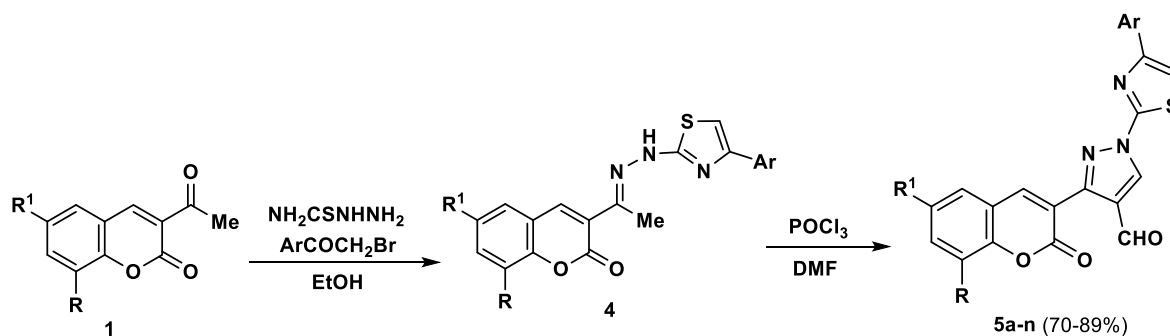
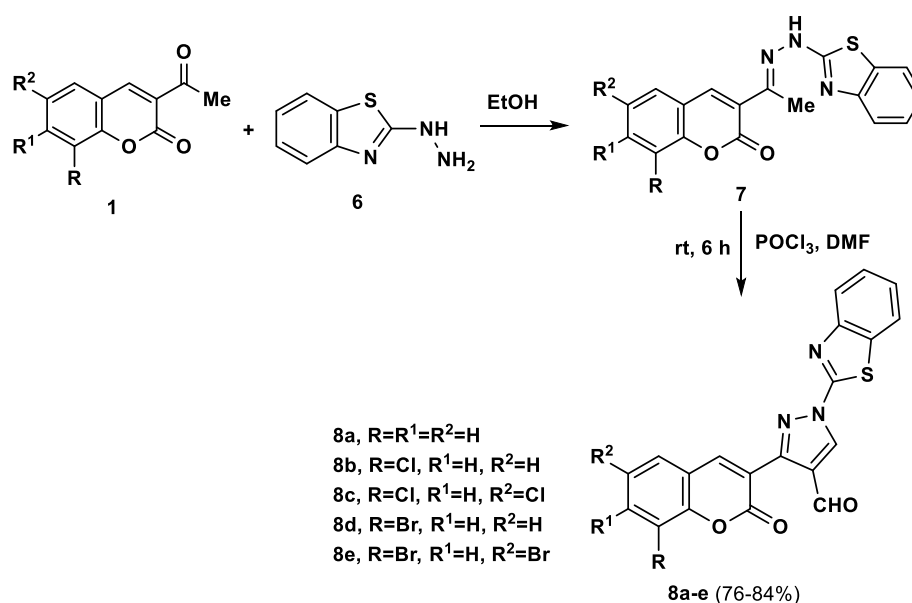


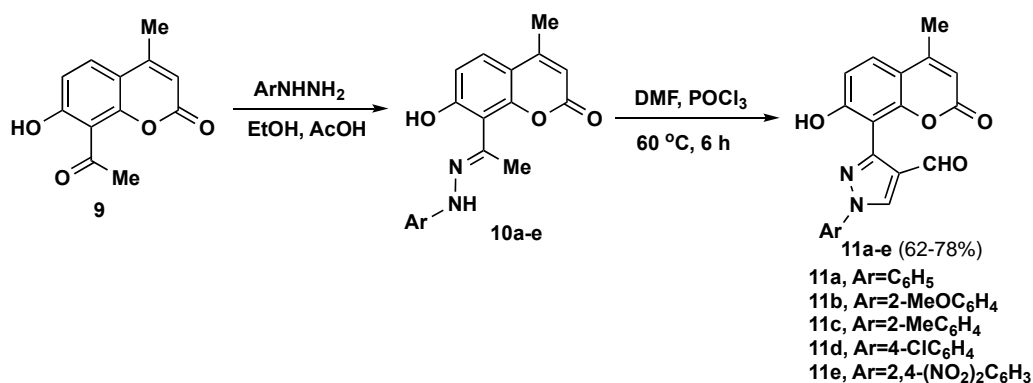
Table 2. The derivatives of 3-(2-oxo-2*H*-chromen-3-yl)-1-(4-arylthiazol-2-yl)-1*H*-pyrazole-4-carbaldehydes (**5a-n**)

Product	R	R ¹	Ar	Product	R	R ¹	Ar
5a	H	H	Ph	5h	H	H	4-MeOC ₆ H ₄
5b	H	Cl	Ph	5i	H	Cl	4-MeOC ₆ H ₄
5c	Cl	Cl	Ph	5j	Cl	Cl	4-MeOC ₆ H ₄
5d	H	Br	Ph	5k	H	Br	4-MeOC ₆ H ₄
5e	Br	Br	Ph	5l	Br	Br	4-MeOC ₆ H ₄
5f	OMe	H	Ph	5m	OMe	H	4-MeOC ₆ H ₄
5g	OMe	Br	Ph	5n	OMe	Br	4-MeOC ₆ H ₄



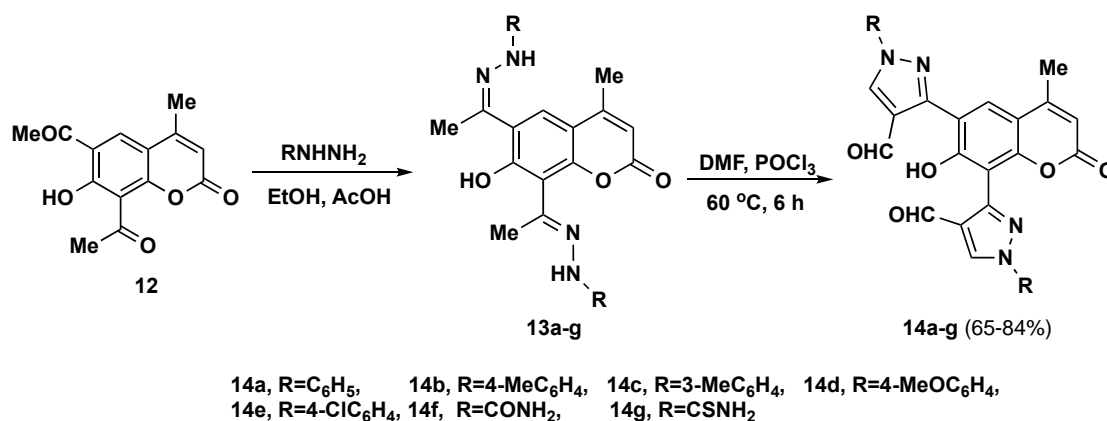
Scheme 3

In 2013, Nagamallu *et al.*⁵⁸ applied the similar strategy to synthesize new coumarinyl-pyrazole derivatives. The starting material, 8-acetyl-7-hydroxy-4-methyl-2*H*-chromen-2-one (**9**), was heated with different arylhydrazines under reflux in ethanol and a catalytic acetic acid to yield the corresponding hydrazones **10a-e**. The aimed 1-aryl-3-(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)-1*H*-pyrazole-4-carbaldehydes (**11a-e**) were obtained in 62-78% yields by Vilsmeier-Haack formylation of the hydrazones **10a-e** (Scheme 4).



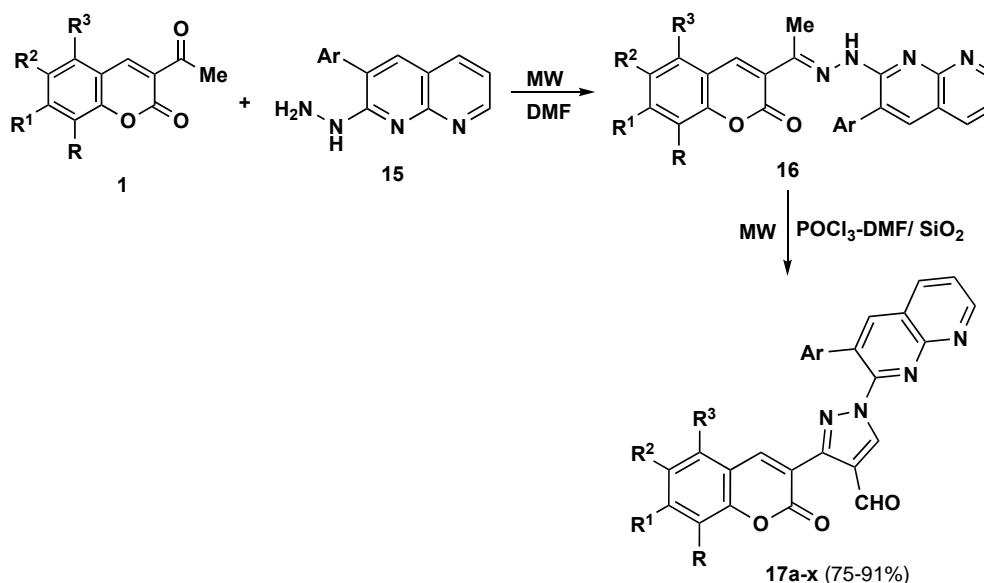
Scheme 4

In continuation, Nagamallu *et al.*⁵⁹ used a similar route for the synthesis of 3,3'-(7-hydroxy-4-methyl-2-oxo-2*H*-chromene-5,8-diyl)-bis-(1-aryl/alkyl-1*H*-pyrazole-4-carbaldehydes) (**14a-g**). Initially, treatment of different alkyl/aryl-hydrazines with 6,8-diacetyl-7-hydroxy-4-methylcoumarin (**12**) at refluxing conditions produced the respective hydrazone derivatives **13a-g**. Subsequently, Vilsmeier-Haack formylation on hydrazone intermediates **13a-g** led to the formation of desired coumarin bis-(4-formylpyrazoles) **14a-g** as shown in Scheme 5.



Scheme 5

Similarly, condensation of 1-(3-aryl-1,8-naphthyridin-2-yl)hydrazines (**15**) with different 3-acetyl-coumarins (**1**) in the presence of a catalytic amount of DMF under MW irradiation afforded the corresponding 3-{1-[2-(3-aryl-1,8-naphthyridin-2-yl)hydrazinyldene]ethyl}-2*H*-chromen-2-ones (**16**) in excellent yields. When the hydrazones **16** were subjected to the Vilsmeier-Haack reaction with POCl₃-DMF/SiO₂ under MW irradiation, the respective 1-[3-(3-aryl-1,8-naphthyridin-2-yl)]-3-(2-oxo-2*H*-chromen-3-yl)-1*H*-pyrazole-4-carbaldehydes (**17a-x**) were isolated (Scheme 6 and Table 3).⁶⁰⁻⁶⁸



Scheme 6

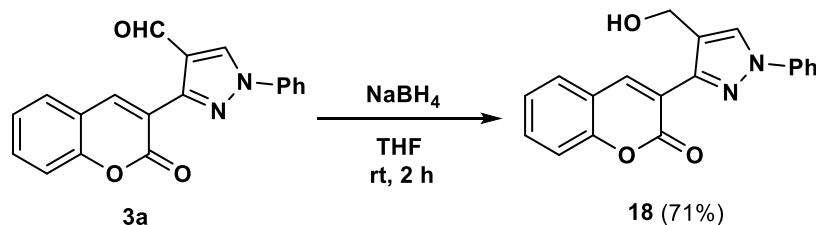
Table 3. The derivatives of 1-[3-(3-aryl-1,8-naphthyridin-2-yl)]-3-(2-oxo-2*H*-chromen-3-yl)-1*H*-pyrazole-4-carbaldehydes (**17a-x**)

Product	R	R ¹	R ²	R ³	Ar	Product	R	R ¹	R ²	R ³	Ar
17a	H	H	H	H	1-naphthyl	17m	Br	H	H	H	3-MeOC ₆ H ₄
17b	H	H	H	H	3-MeOC ₆ H ₄	17n	Br	H	H	H	4-FC ₆ H ₄
17c	H	H	H	H	4-FC ₆ H ₄	17o	Br	H	H	H	3-FC ₆ H ₄
17d	H	H	H	H	3-FC ₆ H ₄	17p	Br	H	H	H	4-MeOC ₆ H ₄
17e	H	H	H	H	4-MeOC ₆ H ₄	17q	Br	H	H	H	2-ClC ₆ H ₄
17f	H	H	H	H	2-ClC ₆ H ₄	17r	NO ₂	H	H	H	3-MeOC ₆ H ₄
17g	OMe	H	H	H	1-naphthyl	17s	Cl	H	Cl	H	1-naphthyl
17h	OMe	H	H	H	3-MeOC ₆ H ₄	17t	Cl	H	Cl	H	3-MeOC ₆ H ₄
17i	OMe	H	H	H	4-FC ₆ H ₄	17u	Br	H	Br	H	4-MeOC ₆ H ₄
17j	OMe	H	H	H	3-FC ₆ H ₄	17v	NO ₂	H	NO ₂	H	1-naphthyl
17k	OMe	H	H	H	4-MeOC ₆ H ₄	17w	H	H	Benzo		4-FC ₆ H ₄
17l	OMe	H	H	H	2-ClC ₆ H ₄	17x	H	H	Benzo		3-FC ₆ H ₄

3. CHEMICAL REACTIONS

3.1. Reaction with sodium borohydride

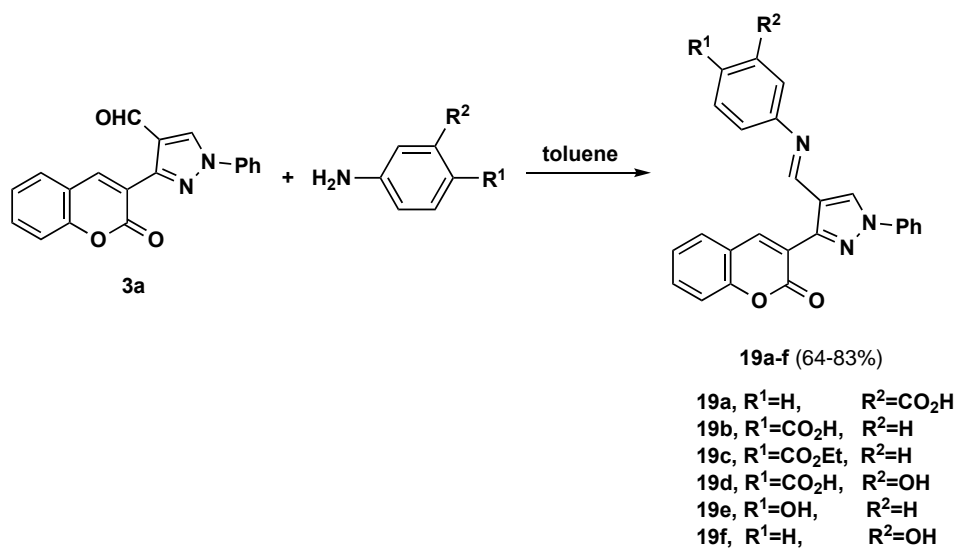
Srikrishna and Dubey²⁸ studied the reduction of 3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3a**) with sodium borohydride in tetrahydrofuran to result in the formation of 3-(4-(hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one (**18**) (Scheme 7).



Scheme 7

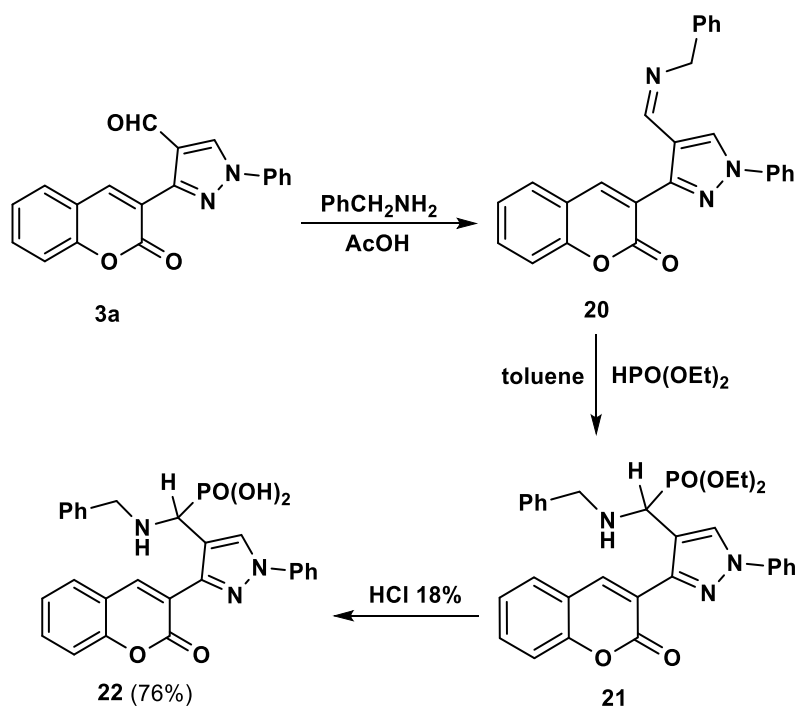
3.2. Reaction with amines

In 1999, Bratenko and others synthesized a series of 3-aryl-(heteroaryl)pyrazoles containing azomethine fragments in position 4, bearing carboxyl, hydroxyl and ethoxycarbonyl groups in *N*-aryl substituents. Thus, 1-phenyl-3-(2-oxo-2*H*-chromen-3-yl)pyrazol-4-ylideneaminobenzoic acids and their esters (**19a-f**) were formed by condensation of aniline derivatives with aldehyde **3a** in toluene (Scheme 8).⁶⁹



Scheme 8

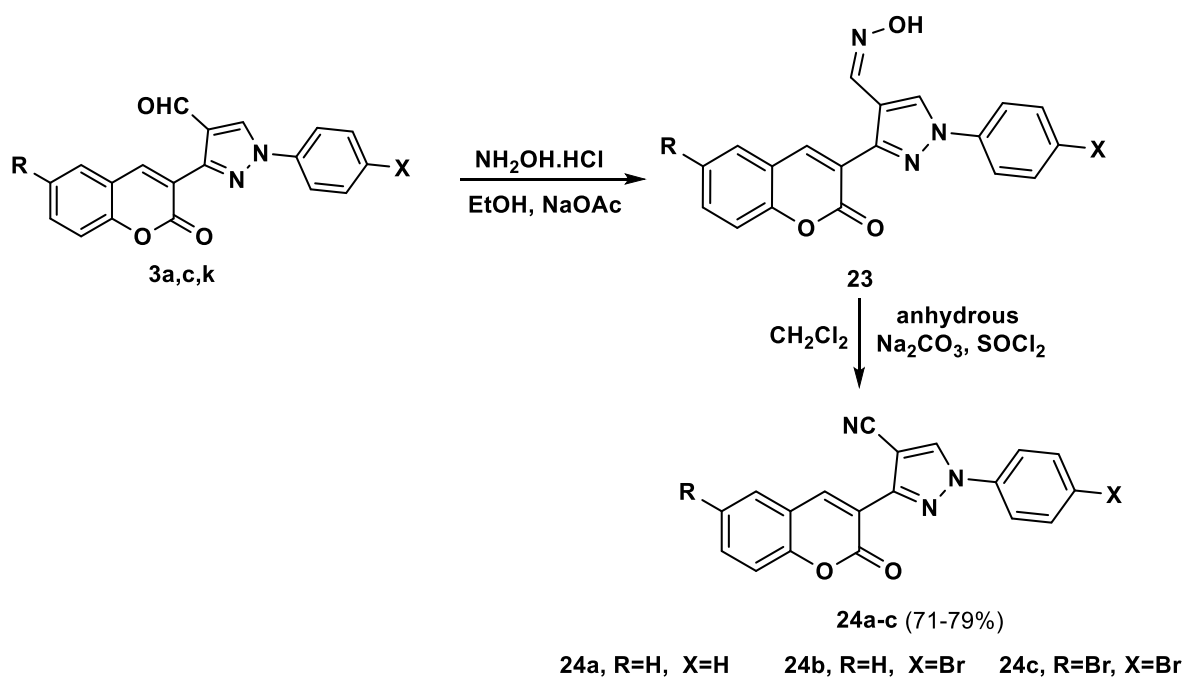
Preparation of the pyrazolyl-coumarinyl-methylphosphonic acid **22** was achieved by Bratenko in 1990. The synthesis of aldimine **20** was performed by heating aldehyde **3a** with benzylamine in boiling benzene in the presence of acetic acid. Addition of diethyl phosphite to azomethine **20**, was carried out in toluene to form diethyl {[(benzylamino)(3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methyl]-phosphonate (**21**) in high yield. The acid hydrolysis of the latter ester with hydrochloric acid afforded the corresponding α -aminophosphonic acid **22** (Scheme 9).⁷⁰



Scheme 9

Treatment of the aldehydes **3a,c,k** with hydroxylamine hydrochloride in the presence of anhydrous sodium

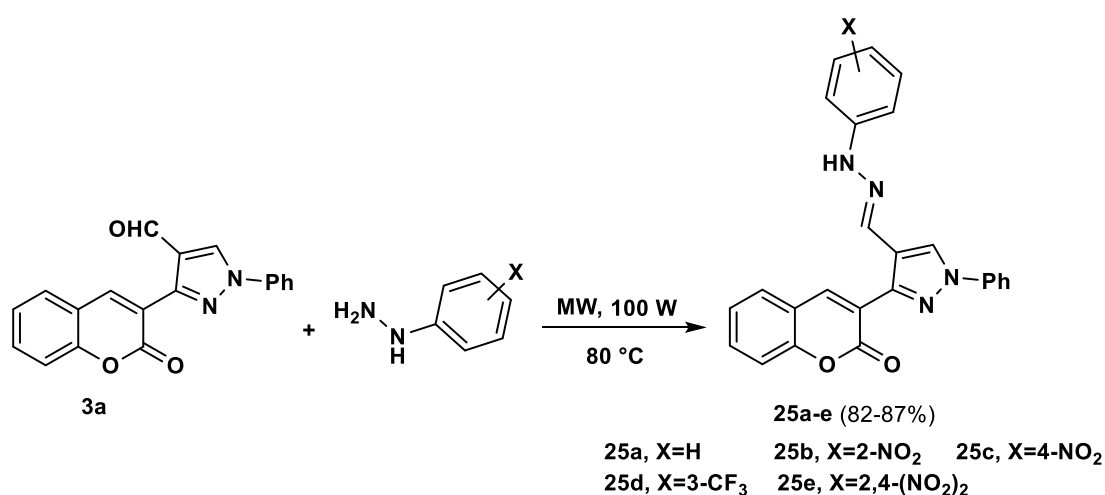
acetate under reflux for one hour gave the corresponding oximes **23**. The dehydration of the latter oximes gave the corresponding nitrile products **24a-c** (Scheme 10).⁷¹



Scheme 10

3.3. Reaction with hydrazines

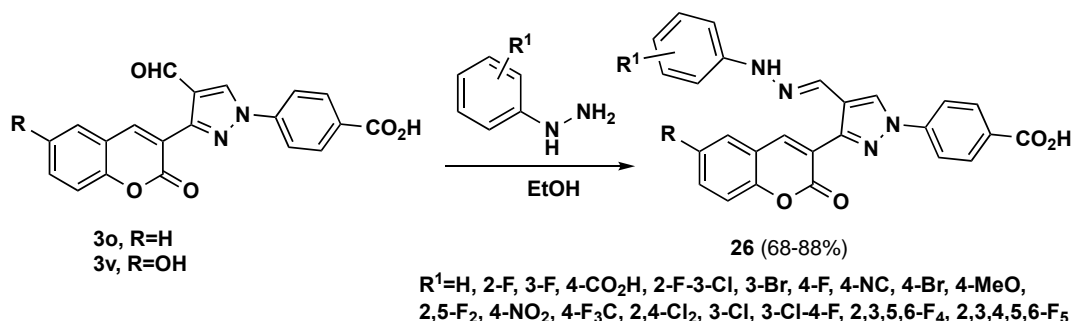
The target products 3-{4-[(2-arylhydrazinylidene)methyl]-1-phenyl-1*H*-pyrazol-3-yl}-2*H*-chromen-2-ones (**25a-e**) were obtained in 82-87% yields under effect of microwave at 80 °C by treatment of the aldehyde **3a** with substituted phenylhydrazine (Scheme 11).²⁷



Scheme 11

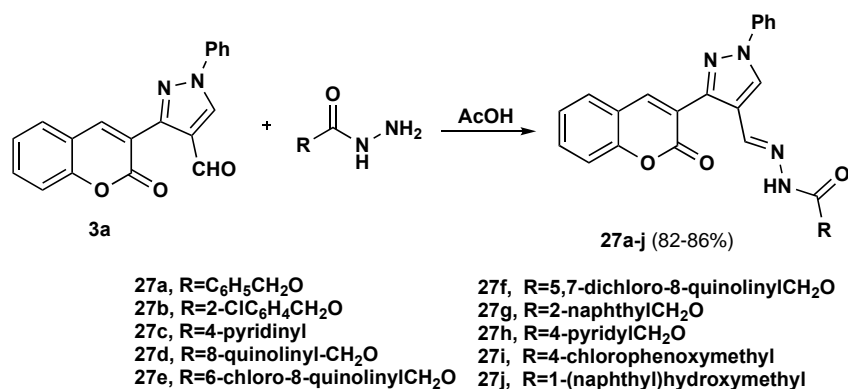
Whitt *et al.*^{45,47} designed 4-[3-(2-oxo-2*H*-chromen-3-yl)-4-((2-arylhydrazono)methyl)-1*H*-pyrazol-1-yl]-

benzoic acids (**26**). In this, different hydrazines underwent reaction with aldehydes **3o,v** by conventional method in ethanol using a catalytic acetic acid to afford the corresponding hydrazones **26** in 68-88% yields (Scheme 12).



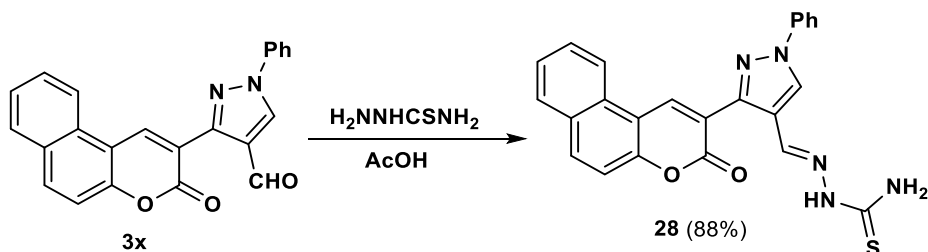
Scheme 12

Several synthetic protocols were reported to construct the hydrazone functionalization of coumarinyl-pyrazole scaffold. Condensation of a variety of acyl hydrazines with 3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3a**) in the presence of amount of glacial acetic acid under reflux furnished the corresponding hydrazones **27a-j** in good to excellent yields (Scheme 13).^{31,72,73}



Scheme 13

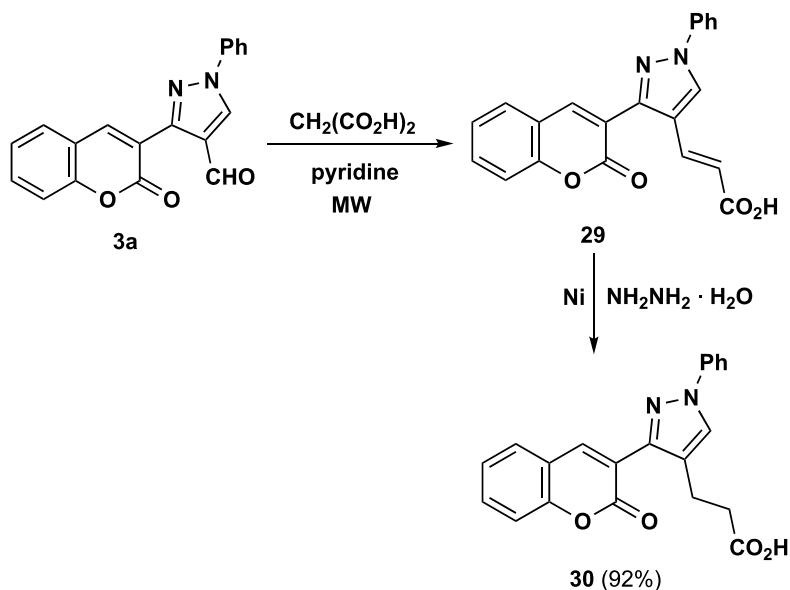
In 2012, Zaki *et al.*²⁶ reported that the aldehyde **3x** condensed with thiosemicarbazide in acetic acid affording the corresponding thiosemicarbazone (**28**) (Scheme 14).



Scheme 14

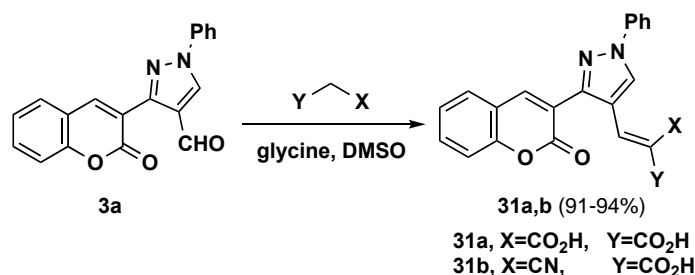
3.4. Reaction with active methyl and methylene compounds

4-Formyl-3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole (**3a**) condensed with malonic acid in pyridine under conventional heating or microwave irradiation to afford 3-[3-(2-oxo-2*H*-chromen-3-yl)-1-phenylpyrazol-4-yl]propenoic acid (**29**). In the presence of raney nickel, the latter acid **29** was reduced with hydrazine hydrate to furnish 3-[3-(2-oxo-2*H*-chromen-3-yl)-1-phenylpyrazol-4-yl]propanoic acid (**30**) in high yield (Scheme 15).^{74,75}



Scheme 15

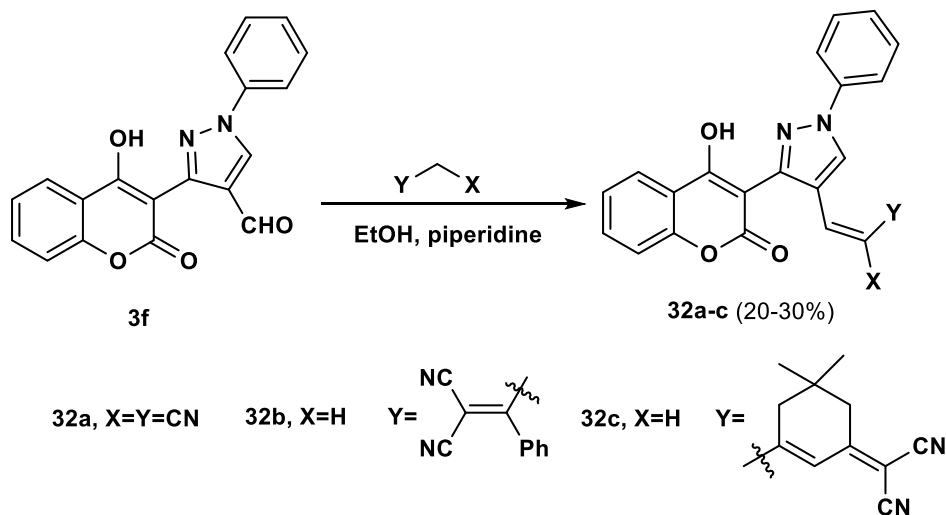
An efficient, eco-friendly glycine catalyzed Knoevenagel condensation route for the synthesis of coumarinyl arylidenes was demonstrated by Chaudhry *et al.*³² Malonic acid and cyanoacetic acid were used as acyclic active methylene compounds to react with the aldehyde **3a** to yield the corresponding arylidene derivatives **31a,b**. These valuable green reactions resulted in excellent yields of the target compounds in DMSO solvent at room temperature by using glycine as a catalyst (Scheme 16).



Scheme 16

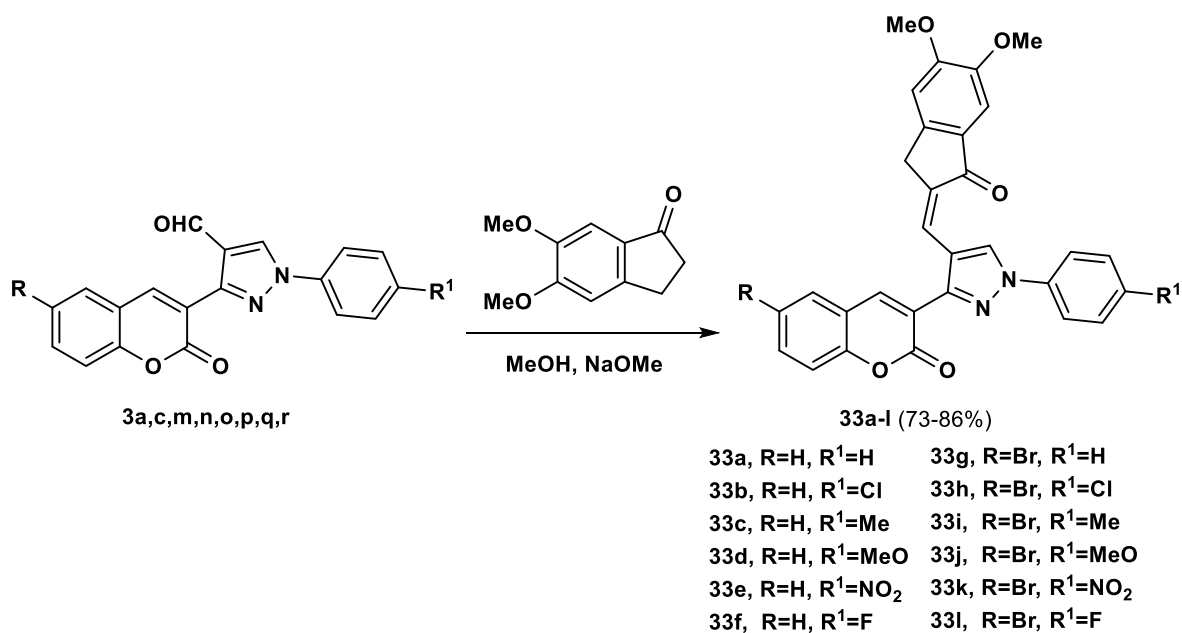
In addition, the aldehyde **3f** underwent reaction with other active methylene compounds. Thus, the aldehyde

3f was treated with malononitrile, 2-(1-phenylethylidene)malononitrile and 2-(3,5,5-trimethylcyclohex-2-en-1-ylidene)malononitrile in ethanol and piperidine to give the corresponding arylidenes **32a-c** (Scheme 17).⁵⁴



Scheme 17

Claisen-Schmidt condensation reaction of 3-(6-substituted-2-oxo-2*H*-chromen-3-yl)-1-(4-substituted phenyl)-1*H*-pyrazole-4-carbaldehydes (**3a,c,m,n,o,p,q,r**) with 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one in methanolic sodium methoxide led to the formation of corresponding 6-substituted-3-{1-(4-substituted phenyl)-4-[(5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl]-1*H*-pyrazol-3-yl}-2*H*-chromen-2-ones (**33a-l**) (Scheme 18).⁷⁶



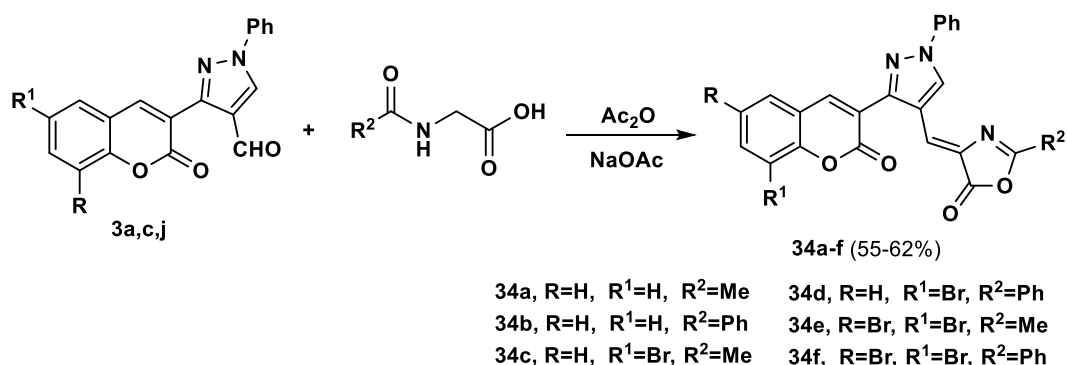
Scheme 18

3.5. Construction of heterocycles containing coumarin-pyrazole moiety

3.5.1. Five-membered heterocycles containing coumarin-pyrazole moiety

3.5.1.1. Formation of oxazoles

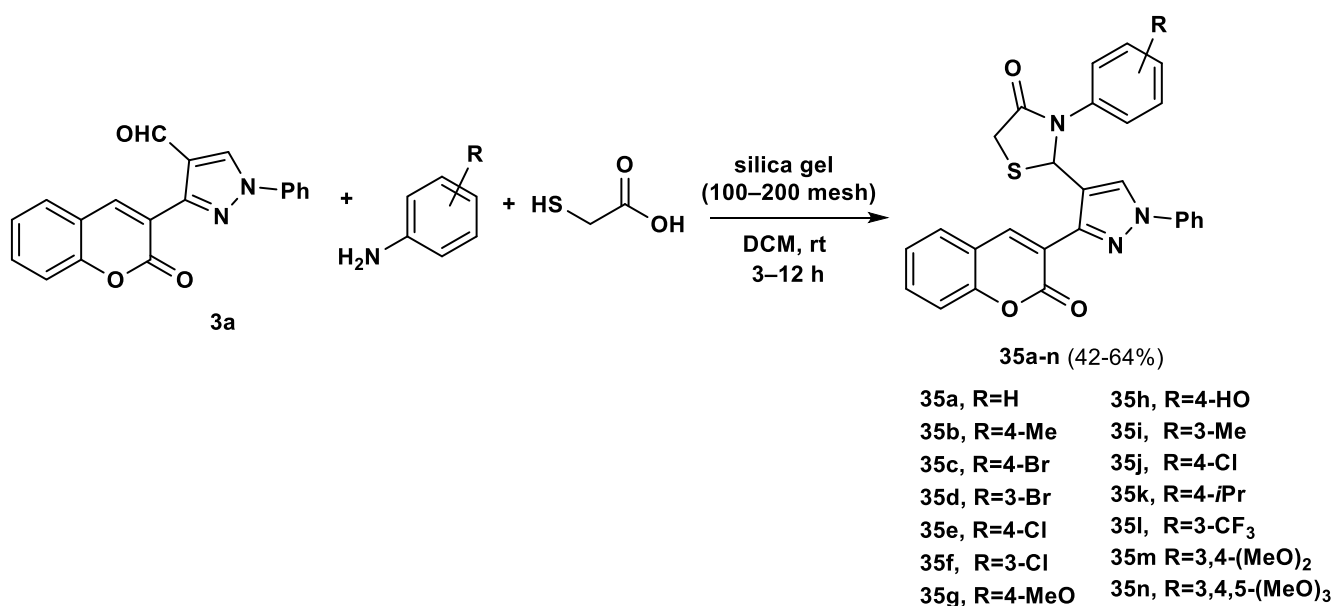
The 2-alkyl(aryl)oxazolone heterocycles affixed coumarin-pyrazole moiety **34a-f** were reported by Patel *et al.*³⁰ The reaction of aldehydes **3a,c,j** with *N*-acetyl or *N*-benzoylglycine in acetic anhydride and sodium acetate afforded the desired azalactone products, namely 2-alkyl/aryl-4-[(3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene]oxazol-5(4*H*)-ones (**34a-f**) in 55-62% yields (Scheme 19).



Scheme 19

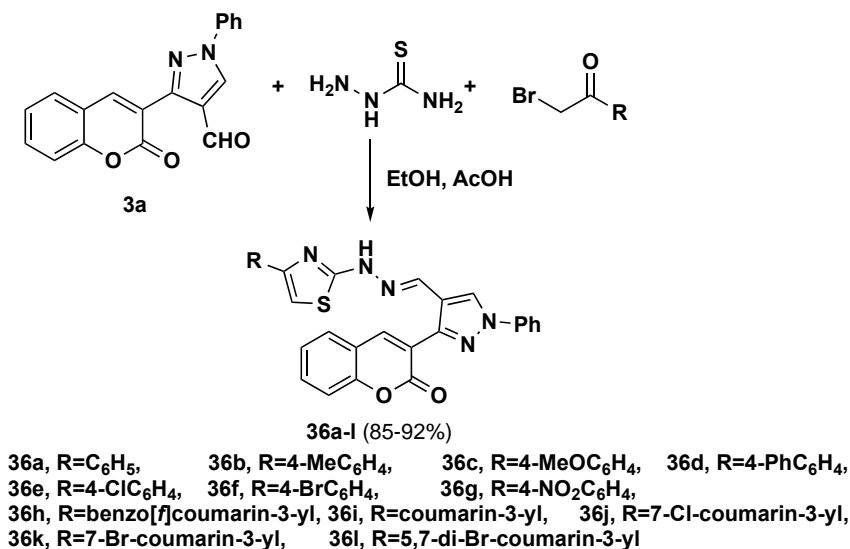
3.5.1.2. Formation of thiazoles

Thacker and co-workers reported a series of coumarin-linked to thiazolidinone **35a-n** through pyrazole linker.⁴² The aldehyde **3a** reacted with various anilines and thioglycolic acid in the presence of silica gel (100–200 mesh) and dichloromethane as a solvent to afford the 1-phenyl-3-(2-oxo-2*H*-chromen-3-yl)-4-thiazolidinonylpyrazoles (**35a-n**) (Scheme 20).



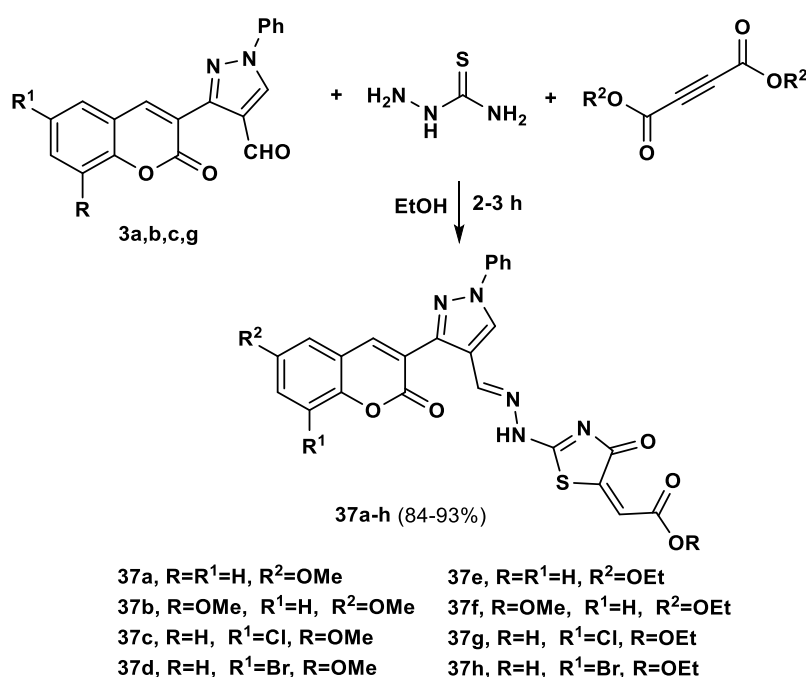
Scheme 20

One-pot three-component synthesis of new coumarin-pyrazole affixed substituted thiazole, namely 3-{1-phenyl-4-[(2-(4-arylthiazol-2-yl)hydrazono)methyl]-1*H*-pyrazol-3-yl}-2*H*-chromen-2-ones (**36a-l**) was done by Gondru *et al.*⁷⁷ Three-component reactions of the aldehyde **3a**, thiosemicarbazide and 1-aryl-2-bromoethan-1-ones under reflux in ethanol using a catalytic acetic acid furnished the final products **36** in good to excellent yields (Scheme 21).



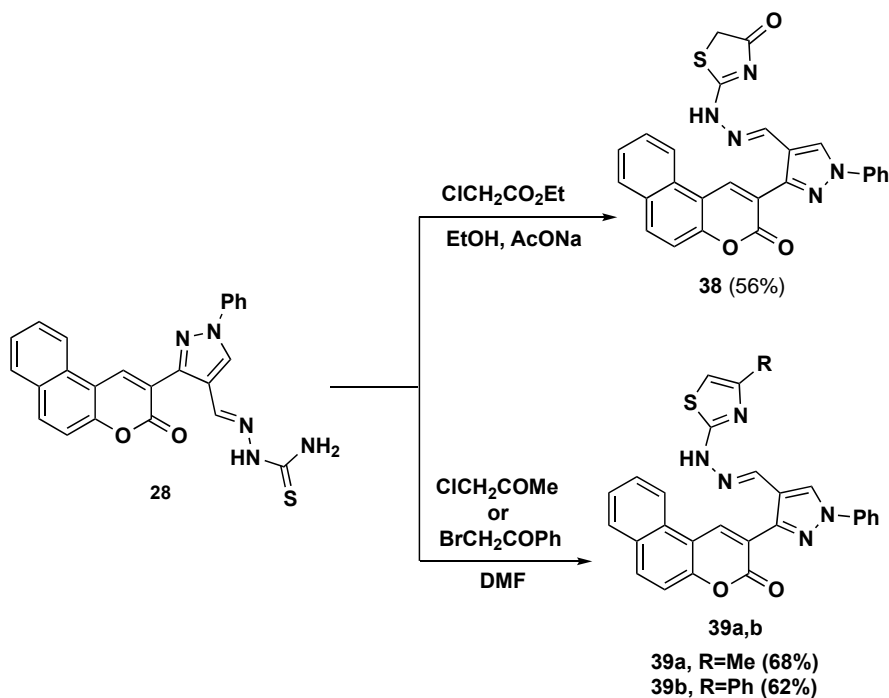
Scheme 21

One-pot multicomponent reaction of the substituted aldehydes **3a,b,c,g**, thiosemicarbazide and dialkyl acetylenedicarboxylates in ethanol under reflux for 2-3 h gave the corresponding coumarinyl-pyrazolyl-thiazolidinones **37a-h** with good to excellent yields (Scheme 22).⁴³



Scheme 22

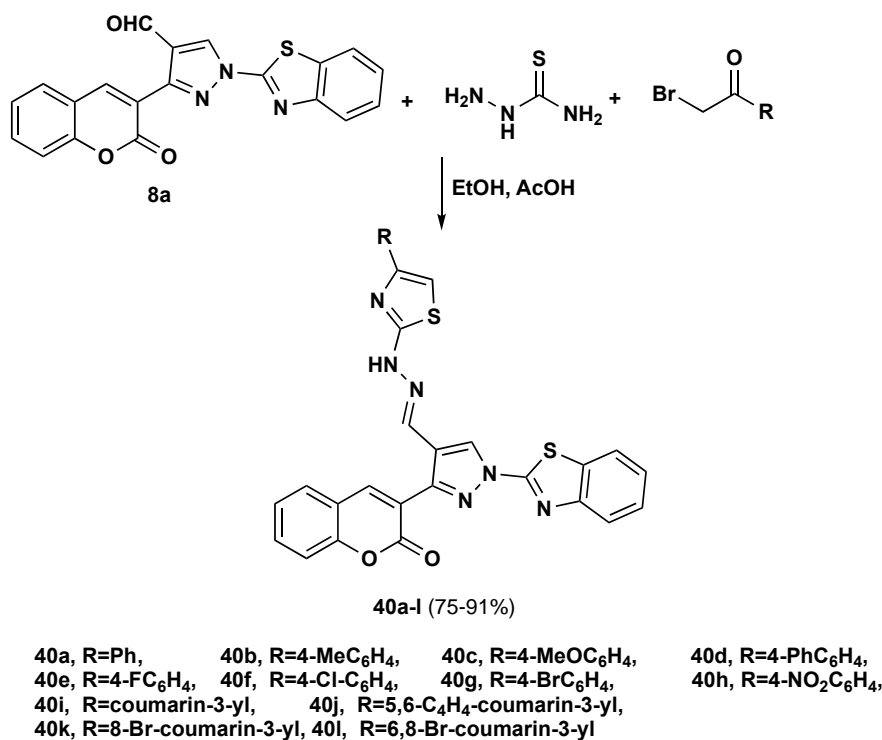
Zaki *et al.*²⁶ have reported synthesis of the thiazolyl-pyrazoles **38** and **39a,b** derivatives containing a coumarin ring as shown in Scheme 23. Refluxing of the thiosemicarbazone **28** with ethyl chloroacetate or different α -bromoketones in the presence of ethanolic sodium acetate, led to the desired thiazoles **38** and **39a,b**, respectively, with 56-68% yields.



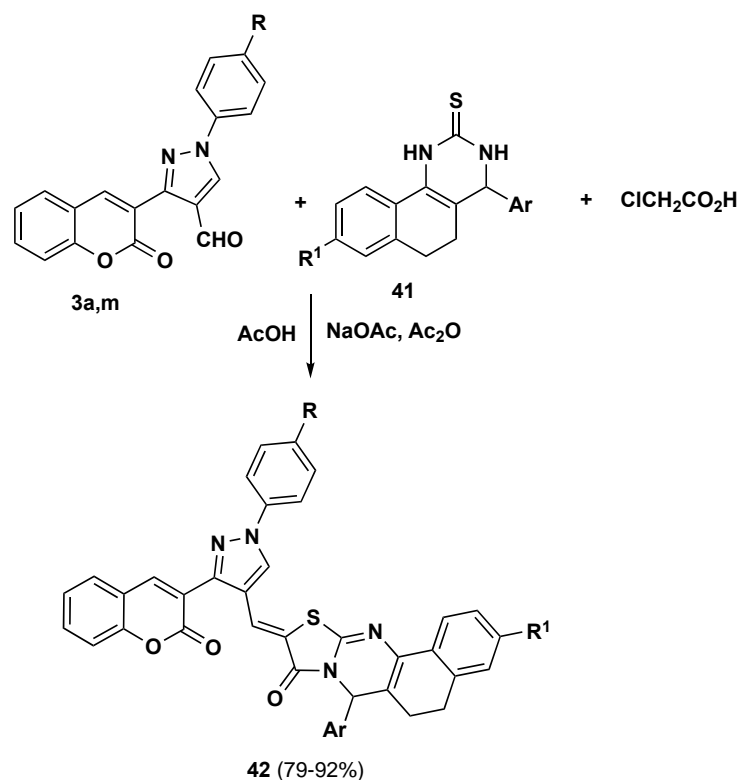
Scheme 23

In the same way, reaction of 1-(benzothiazol-2-yl)-3-(2-oxo-2*H*-chromen-3-yl)-1*H*-pyrazole-4-carbaldehyde (**8a**) with thiosemicarbazide and various α -bromoketones by refluxing in ethanol in the presence of a catalytic amount of glacial acetic acid led to formation of 3-{1-(benzothiazol-2-yl)-4-[(2-(4-arylthiazol-2-yl)hydrazono)methyl]-1*H*-pyrazol-3-yl}-2*H*-chromen-2-ones (**40a-l**) (Scheme 24).⁵⁷

One-pot three-components reaction of 3,4-dihydropyrimidine-2(1*H*)-thiones (**41**), chloroacetic acid and 3-(2-oxo-2*H*-chromen-3-yl)-1-aryl-1*H*-pyrazole-4-carbaldehydes (**3a,m**) in acetic acid and in the presence of acetic anhydride and anhydrous sodium acetate afforded 10-[(3-(2-oxo-2*H*-chromen-3-yl)-1-aryl-1*H*-pyrazol-4-yl)methylene]-7-aryl-5,7-dihydro-6*H*-benzo[*h*]thiazolo[2,3-*b*]quinazolin-9(10*H*)-one derivatives **42** (Scheme 25).⁷⁸



Scheme 24

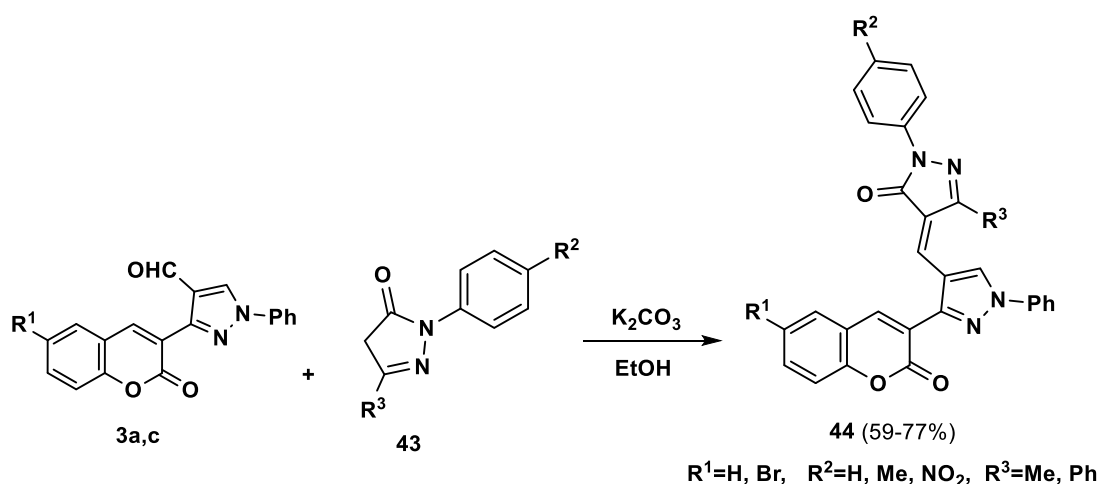


R=H, NO₂ R¹=H, MeO
 Ar=Ph, 1-naphthyl, 4-ClC₆H₄, 4-MeOC₆H₄, 3,4-(MeO)₂C₆H₃,
 2,3,4-(MeO)₃C₆H₂, 3-HO-4-MeOC₆H₃, 4-FC₆H₄, 4-BrC₆H₄,
 4-HOC₆H₄, 3-MeO-4-HOC₆H₃, 3-EtO-4-HOC₆H₃, 2-ClC₆H₄

Scheme 25

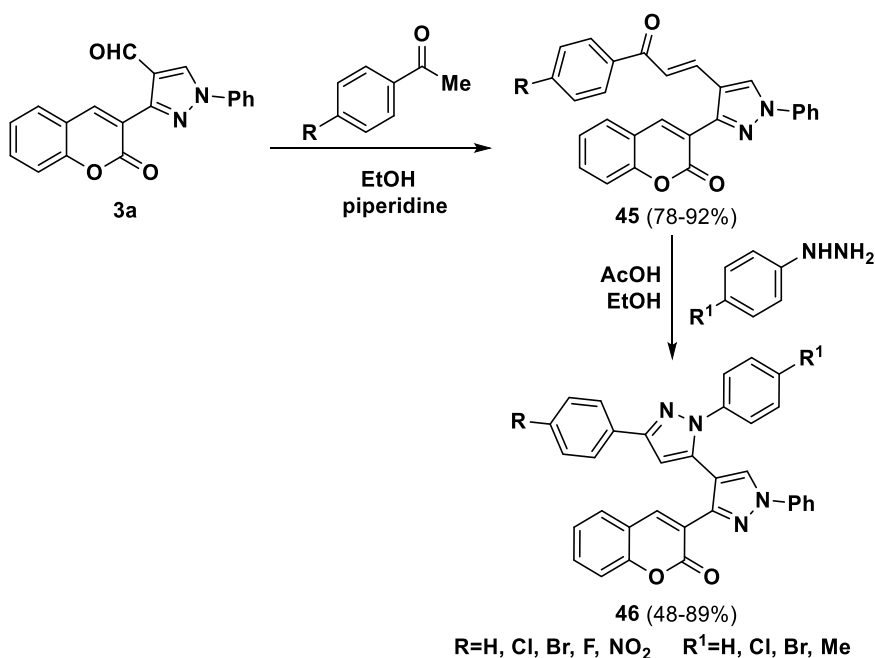
3.5.1.3. Formation of pyrazoles

Chaudhry *et al.*⁷⁹ suggested potassium carbonate as green catalyst for the synthesis of 5-alkyl/aryl-4-{[3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl]methylene}-2-aryl-2,4-dihydro-3*H*-pyrazol-3-one (**44**) by reaction of the aldehydes **3a,b** with 2-aryl-5-substituted-2,4-dihydro-3*H*-pyrazol-3-one (**43**) in ethanol as shown in Scheme 26.



Scheme 26

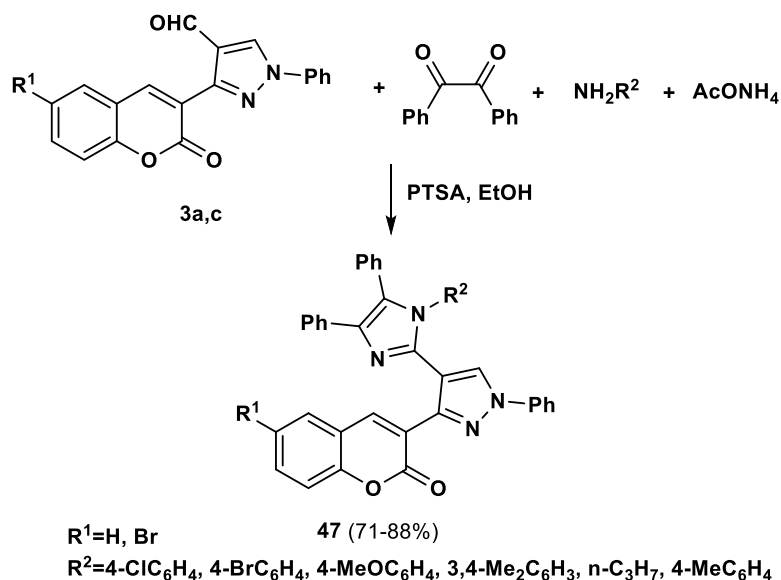
The aldehyde **3a** was treated with different acetophenone derivatives in ethanol and in the presence of piperidine to afford the corresponding chalcones **45**. These chalcones were readily cyclized by reaction with 4-substituted phenylhydrazines in the presence of ethanol and glacial acetic acid affording the coumarinyl-bis-pyrazole derivatives **46** (Scheme 27).⁸⁰



Scheme 27

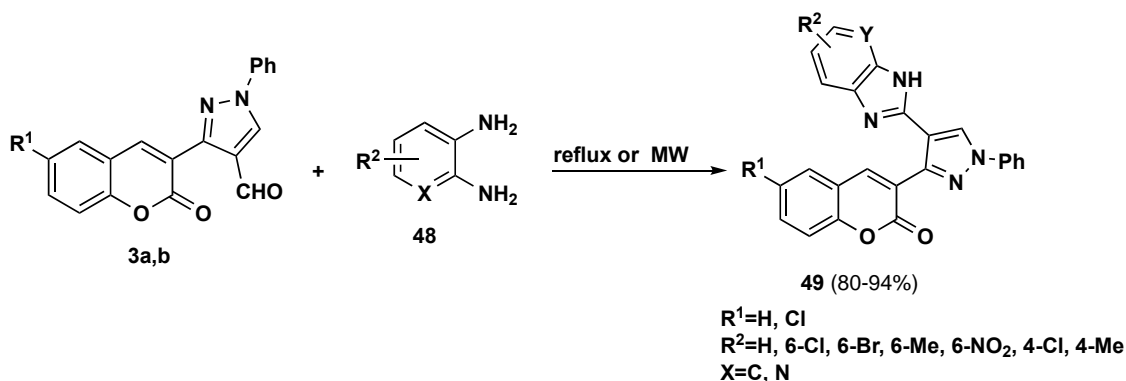
3.5.1.4. Formation of imidazoles

Treatment of the aldehydes **3a,c** with a mixture of benzil, ammonium acetate and different amines led to construct structurally diversified 3-(2-oxo-2*H*-chromen-3-yl)-4-imidazolylpyrazoles **47**. This cyclization reaction was successfully carried out with catalytic amount of *p*-toluenesulfonic acid (PTSA) by refluxing in ethanol for 2 h (Scheme 28).^{81,82}



Scheme 28

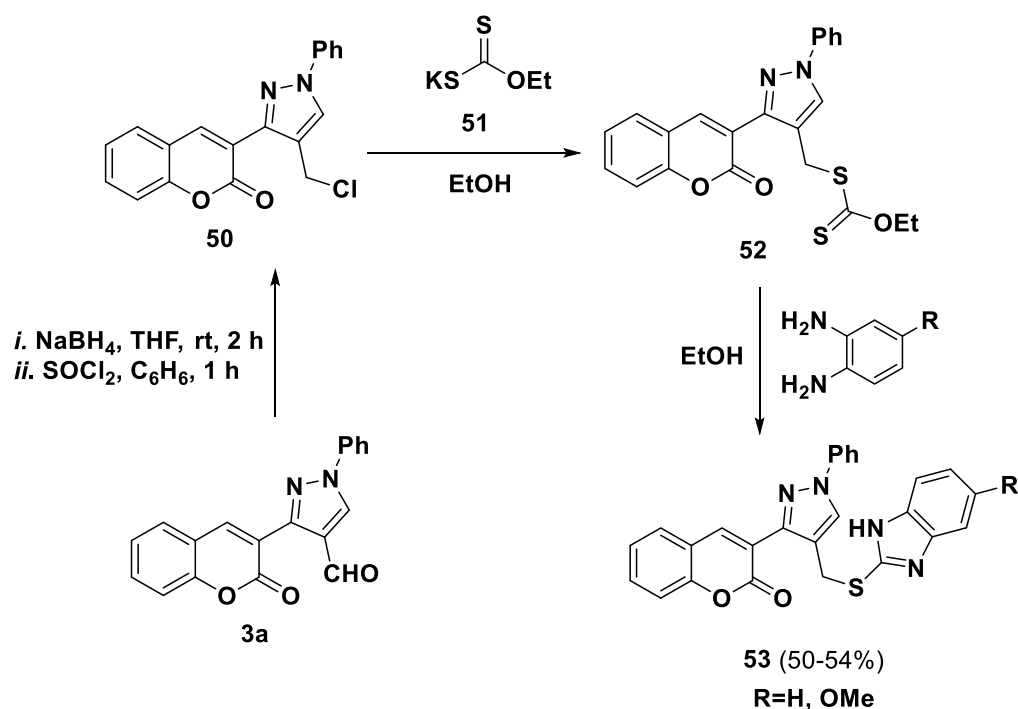
One-pot synthetic methodology was performed by Kumbar and co-workers⁸³ to synthesize 3-(4-(1*H*-benzo[*d*]imidazol-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one and 3-[4-(3*H*-imidazo[4,5-*b*]pyridin-2-yl)-1-phenyl-1*H*-pyrazol-3-yl]-2*H*-chromen-2-one derivatives **49**. In this protocol, the conventional heating and microwave irradiation assisted reaction of the aldehydes **3a,b** with substituted aryl-1,2-diamine compounds **48** to afford the desired products **49** in excellent yields 80-94% (Scheme 29).



Scheme 29

Srikrishna *et al.*⁸⁴ disclosed the different strategies to synthesize biologically active coumarin-pyrazole affixed benzimidazole scaffold. In this protocol, the aldehyde **3a** was reduced by sodium borohydride,

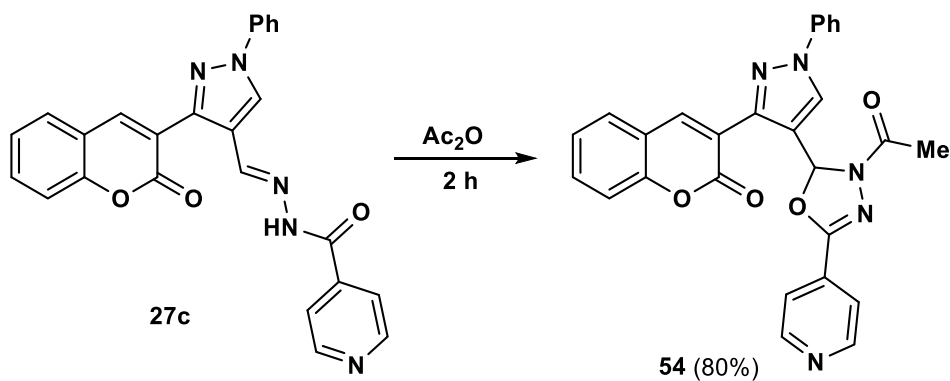
followed by refluxing with thionyl chloride in benzene to afford 3-[4-(chloromethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2*H*-chromen-2-one (**50**). Then, on the reaction of compound **50** with *O*-ethyl carbonodithioate (**51**) provided the intermediate **52**, which on refluxing with the substituted 1,2-phenylenediamine furnished the desired 3-{4-[(1*H*-benzo[*d*]imidazol-2-ylthio)methyl]-1-phenyl-1*H*-pyrazol-3-yl}-2*H*-chromen-2-ones (**53**) (Scheme 30).



Scheme 30

3.5.1.5. Formation of oxadiazoles

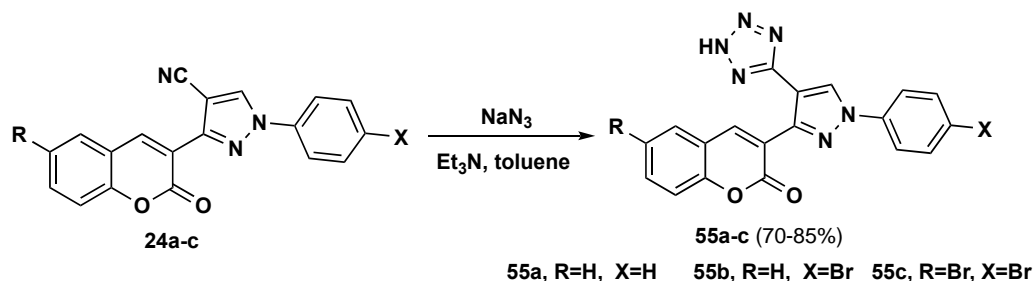
3-{4-[3-Acetyl-5-(pyridin-4-yl)-2,3-dihydro-1,3,4-oxadiazol-2-yl]-1-phenyl-1*H*-pyrazol-3-yl}-2-oxo-2*H*-chromene (**54**) was synthesized in good yield by an intramolecular oxidative cyclization of the hydrazone **27c** in acetic anhydride (Scheme 31).⁷²



Scheme 31

3.5.1.6. Formation of tetrazoles

1,3-Dipolar cyclization of 3-(6-substituted-2-oxo-2*H*-chromen-3-yl)-1-aryl-1*H*-pyrazole-4-carbonitriles (**24a-c**) with sodium azide in the presence of triethylamine in toluene gave 3-[1-aryl-4-(1*H*-tetrazol-5-yl)-1*H*-pyrazol-3-yl]-2*H*-chromen-2-ones (**55a-c**) in 70-85% yields (Scheme 32).⁷¹

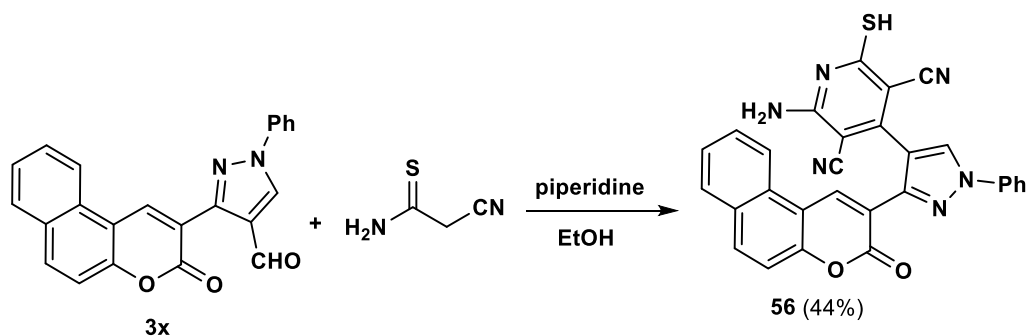


Scheme 32

3.5.2. Six-membered heterocycles containing coumarin-pyrazole moiety

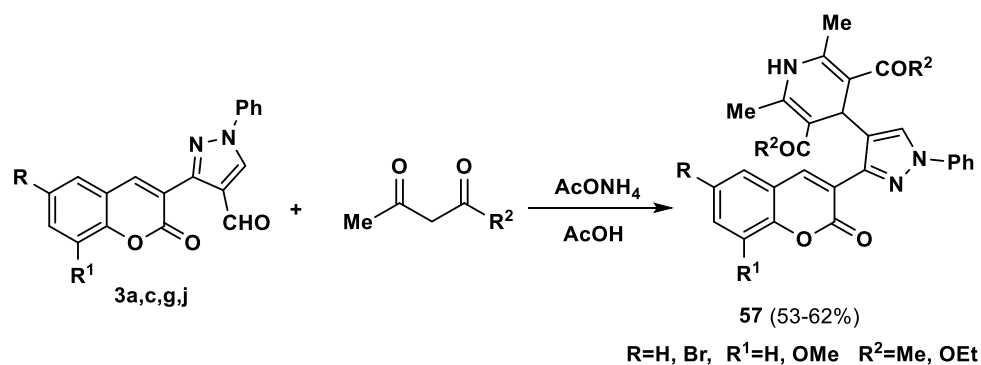
3.5.2.1. Formation of pyridines

Zaki *et al.*²⁶ developed a route for synthesis of 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 (**56**) in good yield by reaction of 3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3x**) with cyanothioacetamide in ethanol containing a catalytic amount of piperidine under reflux (Scheme 33).



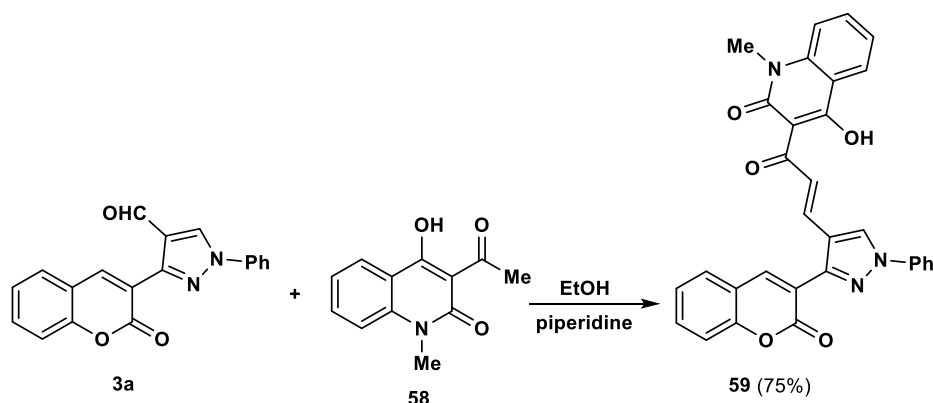
Scheme 33

Patel *et al.* in 2008, reported Hantzsch reaction for the synthesis of 3-[1-phenyl-4-(2,6-dimethyl-3,5-disubstituted-1,4-dihydropyridin-4-yl)-pyrazol-3-yl]coumarins (**57**). When a mixture of the aldehydes **3a,c,g,j**, 1,3-dicarbonyl compound and ammonium acetate, was heated under reflux in acetic acid, the target products **57** were obtained in 53-62% yields (Scheme 34).³⁰



Scheme 34

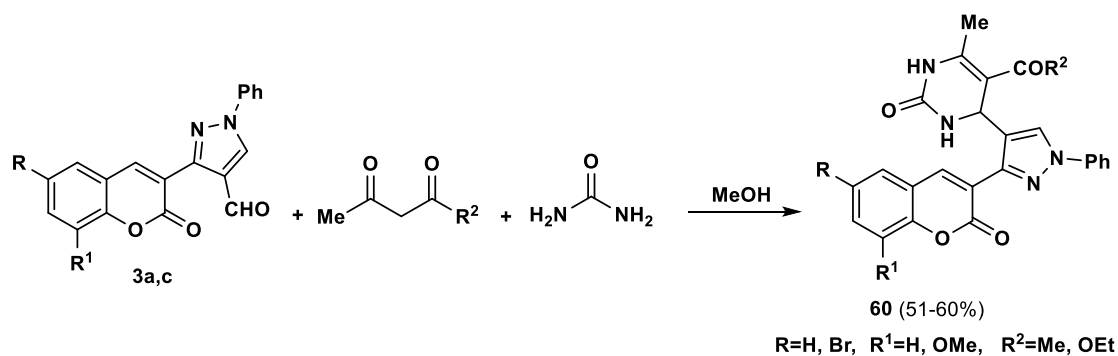
It was also found that condensation of the aldehyde **3a** with 3-acetyl-4-hydroxyquinolin-2-(1*H*)-one (**58**) in ethanol and piperidine gave the corresponding chalcone system 4-hydroxy-1-methyl-3-[4-(2-oxo-2*H*-chromen-3-yl)prop-2-enoyl]-1-phenyl-1*H*-pyrazol-4-yl)quinolin-2(1*H*)-one (**59**) (Scheme 35).⁴⁴



Scheme 35

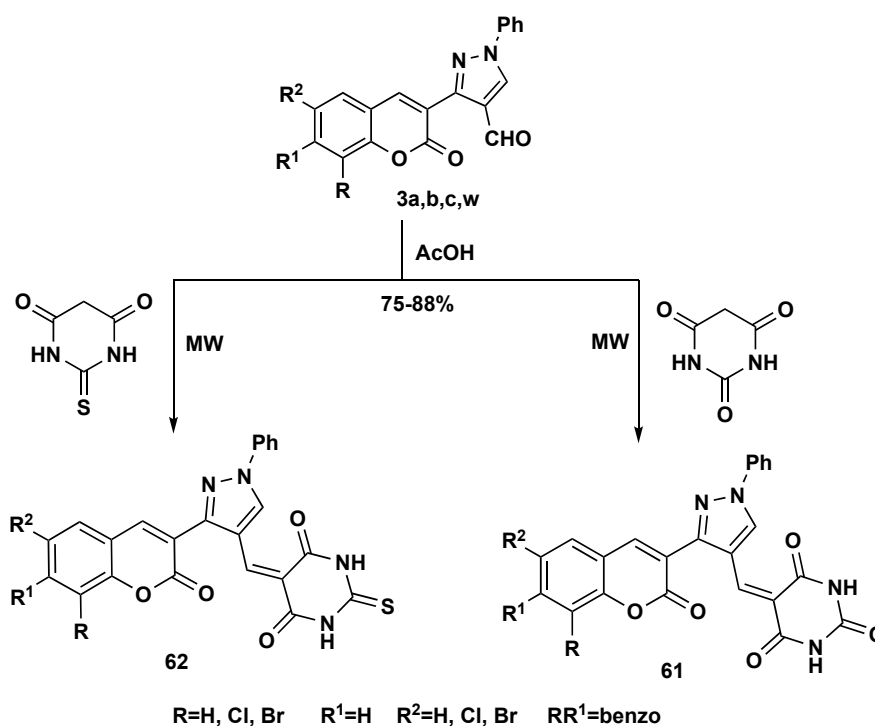
3.5.2.2. Formation of pyrimidines

One-pot, three-components reaction of the aldehydes **3a,c**, 1,3-dicarbonyl compound and urea in methanol under reflux according to Biginelli reaction conditions furnished 3-[1-phenyl-4-(6-methyl-5-substituted-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)pyrazol-3-yl]-2-oxo-2*H*-chromenes (**60**) (Scheme 36).³⁰



Scheme 36

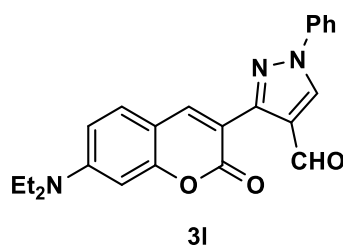
Microwave-assisted condensation route for the preparation of 5-{{[3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl]methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones (**61**) and 5-{{[3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl]methylene}-2-thioxodihydropyrimidine-4,6-(1*H*,5*H*)-diones (**62**), was achieved by Vijaya Laxmi and co-workers.³³ Thus, reaction of the aldehydes **3a,b,c,w** with barbituric acid and thiobarbituric acid in acetic acid under microwave irradiation produced the corresponding products **61** and **62**, respectively, in good to excellent yields (Scheme 37).



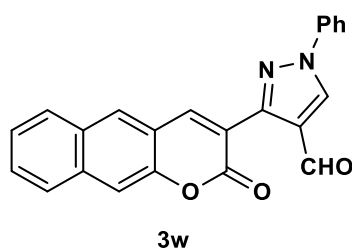
Scheme 37

4. THE APPLICATIONS

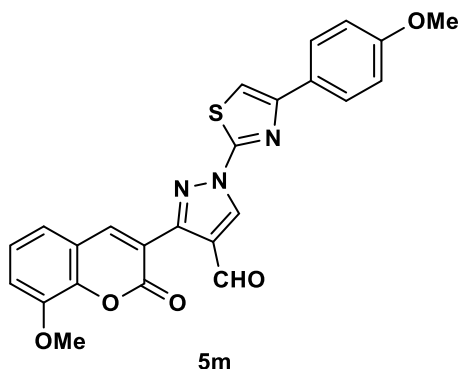
The laser efficiency and spectra related to the aldehyde **3I** was studied, and compared with a common coumarin laser dye, C_{515} , in several solvents. The aldehyde **3I** decomposed fast in chloroform. Further, the integrated intensity was very low in dichloromethane and DMF as compared to standard. The range covered was also to shorter wavelength side where many other standard dyes are available.⁵²



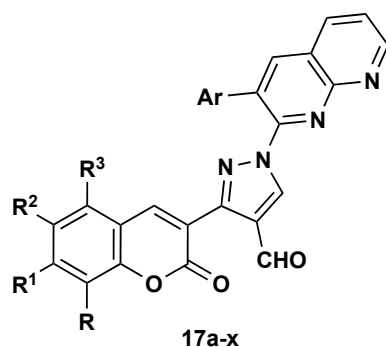
3-(2-Oxo-2*H*-benzo[*g*]chromen-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3w**) has little absorption-emission characteristics and whitening/dyeing properties on polyester.⁵¹



3-(8-Methoxy-2-oxo-2*H*-chromen-3-yl)-1-[4-(4-methoxyphenyl)thiazol-2-yl]-1*H*-pyrazole-4-carbaldehyde (**5m**) has shown significant antiproliferative activity against different human cancer cell lines such as cervical cancer (HeLa), breast cancer (MCF7), and adenocarcinoma (A549) cell lines by using Nocodazole as a positive control.⁴¹

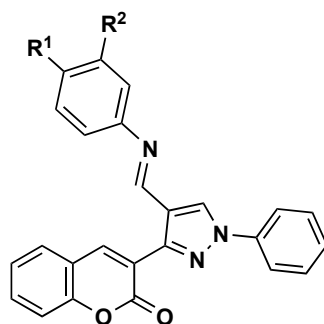


The 1-(1,8-naphthyridin-2-yl)-3-(2-oxo-2*H*-chromen-3-yl)-1*H*-pyrazole-4-carbaldehydes (**17a-x**) showed acceptable antibacterial activities against *Bacillus subtilis* and *Escherichia coli*. However, the derivatives **17k** and **17w** displayed the high effects.^{60-63,66}



17k, R=OMe, R¹=R²=R³=H, Ar=4-MeOC₆H₄
17w, R=R¹=H, R²R³=benzo, Ar=4-FC₆H₄

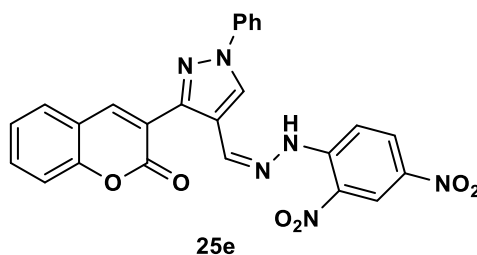
1-Phenyl-3-(2-oxo-2*H*-chromen-3-yl)-pyrazol-4-ylideneaminobenzoic acids and their esters **19c,d** have moderate bactericidal properties.⁶⁹



19c,d

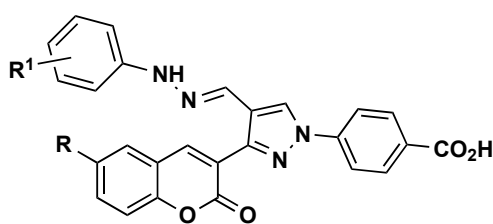
19c, R¹=CO₂Et, R²=H19d, R¹=CO₂H, R²=OH

Jain *et al.*²⁷ described an unprecedented 3-{4-[(2,4-dinitrophenyl)hydrazonomethyl]-1-phenyl-1*H*-pyrazol-3-yl}-chromen-2-one (**25e**) as colorimetric receptor R1 which can help with the semi-quantitative detection of inorganic fluoride in actual samples without being interfered with by other anions.



25e

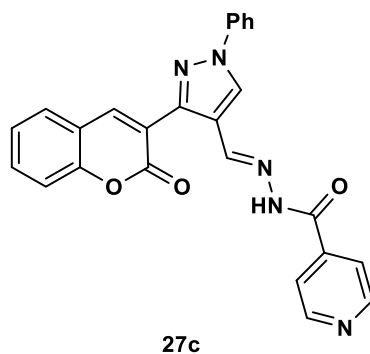
Some of the coumarinyl-pyrazole-hydrazones **26** were tested against several bacterial strains. Several molecules showed promising results with MIC values as low as 1.56 μg/mL. It was found that fluoro-substituted compounds are most potent than the hydroxy-substituted compounds.⁴⁵



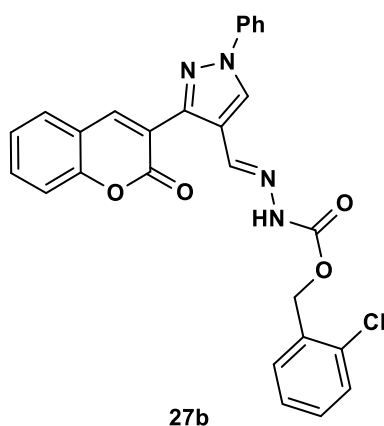
26

Ar=H, 2-F, 3-F, 4-HO₂C, 2-F-3-Cl, 3-Br, 4-F, 4-NC, 4-Br, 4-MeO, 2,5-F₂, 4-NO₂, 4-F₃C, 2,4-Cl₂, 3-Cl, 3-Cl-4-F, 2,3,5,6-F₄, 2,3,4,5,6-F₅

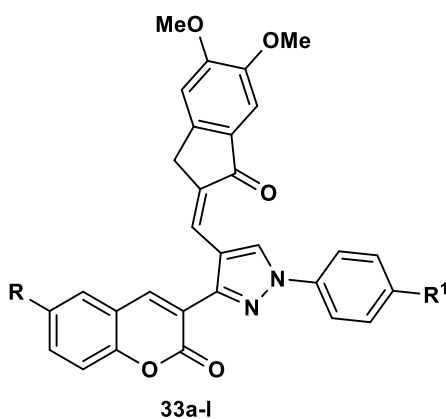
The coumarinyl-pyrazole-hydrazones **27a-j** exhibited weak bacteriostatic effects. The maximum activity among these compounds, was observed for *N*-acylhydrazone containing the isonicotinoyl fragment **27c**.³¹



Also, 2-chlorobenzyl {2-[(3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene]hydrazine-1-carboxylate (**27b**) showed a high docking score *in silico* studies exhibiting good antibacterial properties against *S. aureus*.⁷³

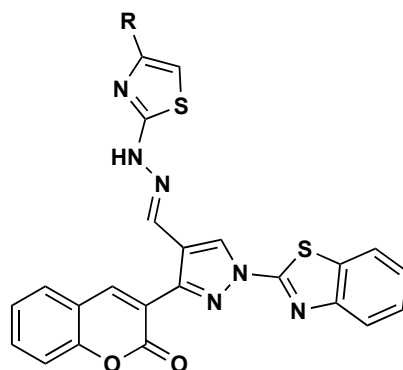


6-Substituted-3-[1-(4-substituted)-4-[(5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl]-1H-pyrazol-3-yl]-2H-chromen-2-ones (**33a-l**) were screened for their antioxidant activity. It was discovered that the presence of compounds with halogen substituents and electron-withdrawing groups as **33b,e,f,k,l** demonstrated strong antioxidant properties. Compounds **33c,d** ($R^1 = \text{Me}$ and 4-MeO) had strong antidiabetic action when was screened to antihyperglycemic activity.⁷⁶



33a, R=H, R ¹ =H	33b, R=H, R ¹ =Cl	33g, R=Br, R ¹ =H	33h, R=Br, R ¹ =Cl
33c, R=H, R ¹ =Me	33d, R=H, R ¹ =MeO	33i, R=Br, R ¹ =Me	33j, R=Br, R ¹ =MeO
33e, R=H, R ¹ =NO ₂	33f, R=H, R ¹ =F	33k, R=Br, R ¹ =NO ₂	33l, R=Br, R ¹ =F

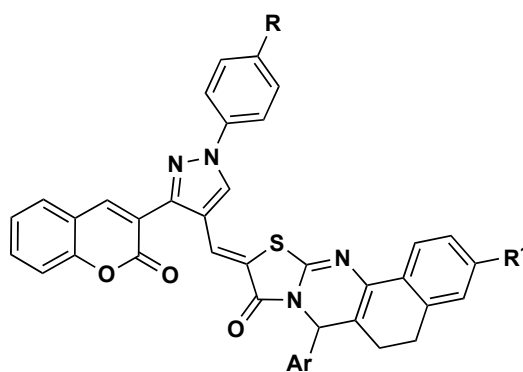
A series of coumarin-pyrazolyl-thiazole frameworks **40a-l** were evaluated for their antibacterial activities. Compounds **40b,g,k,l** exhibited promising inhibitory activities against the tested bacterial strains with minimum inhibitory concentration (MIC)/minimum bactericidal concentration (MBC) spectrum of 1.9/7.8 $\mu\text{g/mL}$ to 3.9/7.8 $\mu\text{g/mL}$.⁵⁷



40a-l

40a, R=Ph, 40b, R=4-MeC₆H₄, 40c, R=4-MeOC₆H₄, 40d, R=4-PhC₆H₄,
 40e, R=4-FC₆H₄, 40f, R=4-Cl-C₆H₄, 40g, R=4-BrC₆H₄, 40h, R=4-NO₂C₆H₄,
 40i, R=coumarin-3-yl, 40j, R=5,6-C₄H₄-coumarin-3-yl,
 40k, R=8-Br-coumarin-3-yl, 40l, R=6,8-Br-coumarin-3-yl

The derivatives of 7-aryl-10-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-7,10-dihydro-5*H*-benzo[*h*]thiazolo[2,3-*b*]quinazolin-9(6*H*)-one derivatives **42** were investigated for their *in vitro* antiproliferative and antibacterial activities. The derivatives which have Ar=4-ClC₆H₄, and Ar=3-MeO-4-HOC₆H₃, displayed better antiproliferative activity against HepG2 (hepatocellular carcinoma) cell line. Also, some of these compounds showed broad and excellent antibacterial efficacy comparable to that of the standards.⁷⁸

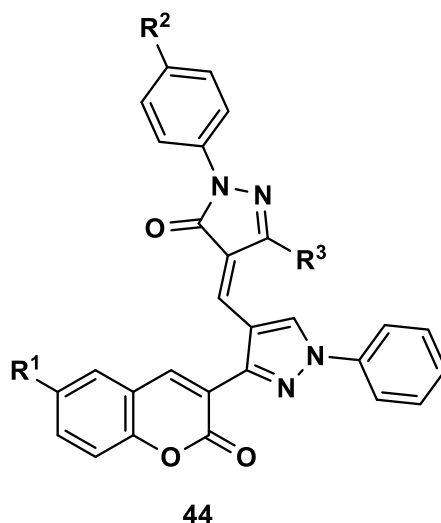


42

R=H, NO₂ R¹=H, MeO
 Ar=Ph, 1-naphthyl, 4-ClC₆H₄, 4-MeOC₆H₄, 3,4-(MeO)₂C₆H₃,
 2,3,4-(MeO)₃C₆H₂, 3-HO-4-MeOC₆H₃, 4-FC₆H₄, 4-BrC₆H₄,
 4-HOC₆H₄, 3-MeO-4-HOC₆H₃, 3-EtO-4-HOC₆H₃, 2-ClC₆H₄

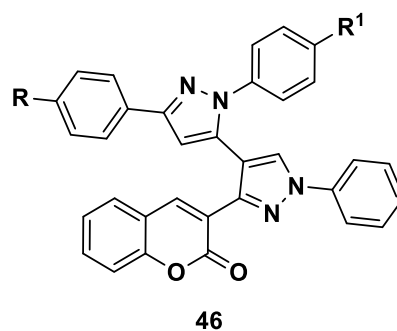
The derivatives of 5-alkyl/aryl-4-[[3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl]methylene]-2-aryl-2,4-dihydro-3*H*-pyrazol-3-one (**44**) were evaluated against the α -glucosidase enzyme. The derivative

$R^1=\text{Br}$, $R^2=\text{NO}_2$, $R^3=\text{Me}$ showed excellent results of IC_{50} in comparison to clinical drug acarbose.⁷⁹



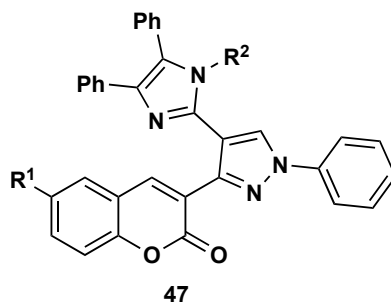
$R^1=\text{H, Br}$, $R^2=\text{H, Me, NO}_2$, $R^3=\text{Me, Ph}$

The coumarinyl-bis-pyrazole derivatives **46** were evaluated for their *in vitro* antibacterial, antitubercular and antimalarial activities. The biological screens of **46** provided real insight into how to modify the basic nucleus and substitution patterns to increase effectiveness. The fluorine and chlorine derivatives played very important role to achieve significant change in antimicrobial and antitubercular activities while the nitro and bromo derivatives showed better antimalarial activity.⁸⁰



$R=\text{H, Cl, Br, F, NO}_2$ $R^1=\text{H, Cl, Br, Me}$

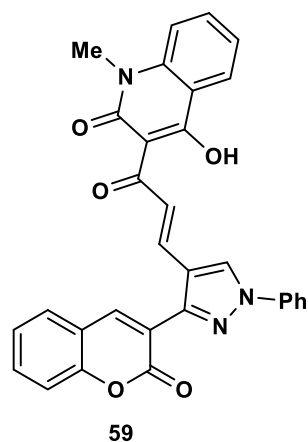
The coumarin-pyrazolyl-imidazoles **47** were evaluated for their α -glucosidase inhibition potentials. All of the derivatives showed effects that ranged from good to exceptional and were on par with or even superior to those of the medication acarbose. The most effective one was the derivative $R^1=\text{Br}$, $R^2=4\text{-ClC}_6\text{H}_4$.^{81,82}



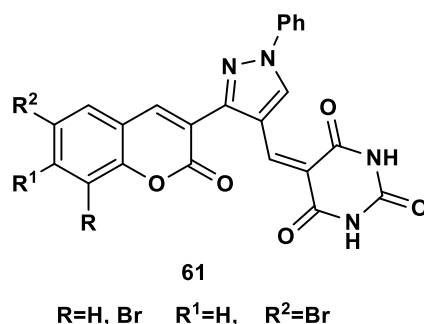
$R^1 = \text{H, Br}$

$R^2 = 4\text{-ClC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 3,4\text{-Me}_2\text{C}_6\text{H}_3, n\text{-C}_3\text{H}_7, 4\text{-MeC}_6\text{H}_4$

Hassan *et al.*⁴⁴ studied the effects of some chalcones of coumarinyl-pyrazoles on the growth of a few types of plants such as hibiscus, mint, and basil. The results indicated that 4-hydroxy-1-methyl-3-{3-[3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl]acryloyl}quinolin-2(1*H*)-one (**59**) has the ability to promote the growth of particular agricultural crop plants.



Compounds **61** ($R = \text{H, R}^1 = \text{H, R}^2 = \text{Br}$) and ($R = \text{Br, R}^1 = \text{H, R}^2 = \text{Br}$) exhibited high effects against *Aspergillus niger*. Structure–activity relationship studies revealed that the presence of bromo at position 6 on the coumarin ring enhanced the activity.³³



CONCLUSION

The constantly increasing number of papers describing synthesis of heterocyclic compounds based on 3-(2-oxo-2*H*-chromen-3(6)(8)-yl)-1-aryl/heteroaryl-1*H*-pyrazole-4-carbaldehydes indicates their growing

importance as building blocks with high synthetic potential. The aim of this review is to demonstrate the widespread applications of 3-(2-oxo-2H-chromen-3(6)(8)-yl)-1-aryl/heteroaryl-1H-pyrazole-4-carbaldehydes in organic synthesis and the outlook for potential future developments. Due to their chemical reactivity and versatility, these aldehyde derivatives constitute valuable synthetic units giving rise to a number of useful classes of organic compounds.

ACKNOWLEDGMENT

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