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## 3-(Bromoacetyl)coumarins: unraveling their synthesis, chemistry, and applications

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This review emphasizes recent developments in synthetic routes of 3-(bromoacetyl)coumarin derivatives. Also, chemical reactions of 3-(bromoacetyl)coumarins as versatile building blocks in the preparation of critical polyfunctionalized heterocyclic systems and other industrially significant scaffolds are described. Recent advances of 3-(bromoacetyl)coumarins as attractive starting points towards a wide scale of five and six-membered heterocyclic systems such as thiophenes, imidazoles, pyrazoles, thiazoles, triazoles, pyrans, pyridines, thiadiazins as well as fused heterocyclic systems have been reported. Additionally, this review covers a wide range of analytical chemistry, fluorescent sensors, and biological applications of these moieties, covering the literature till May 2021.

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### 1. Introduction

Coumarins are one of the most common host heterocyclic systems reported in the literature of organic chemistry.<sup>1,2</sup> Furthermore, coumarins and their derivatives are seen to be the pivotal components of a plethora of many natural products and pharmaceuticals<sup>3</sup> and synthetic dyes.<sup>4-9</sup> The pharmacological activities discovered amongst coumarin derivatives include the treatment categories of Alzheimer's<sup>10</sup> and haematopoietic necrosis (IHN);<sup>11</sup> they have shown potent anticoagulant, antibiotic, antiembolic, antioxidative, and anti-ischemic activities<sup>12-16</sup> (Fig. 1).

Among these compounds, 3-(bromoacetyl)coumarin **1** and its derivatives are a prominent structural class in the synthesis of various bioactive heterocyclic scaffolds,<sup>17,18</sup> they also are important components in drug discovery on account of their biological activities such as antiproliferative, antimicrobial activities,<sup>19</sup> and are promising inhibitors of type 2 diabetes mellitus.<sup>20</sup> In addition, numerous chemosensors are based on polyfunctional coumarin platforms used to detect multianalyte detection, such as different bioactive elements and various environmental pollutants.<sup>21,22</sup> There is no survey available on the biological and chemical applications achieved since the discovery of 3-(bromoacetyl)coumarins. The articles on this type of coumarin are scattered in scientific journals.

In continuation of our investigations on the chemistry of coumarins and their azo/thio isosteric analogs<sup>23-28</sup> and based on

the above mentioned interesting biological and chemical aspects, this survey mainly highlights the advances in the synthesis of 3-(bromoacetyl)coumarin and its derivatives, besides, their transformations for the construction of different fused heterocyclic systems in detail. Additionally, a wide range of analytical chemistry, fluorescent sensors, and biological applications of these moieties are summarized.

### 2. Spectral data

Many papers have reported the spectroscopic measurements (IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and Mass) of 3-(bromoacetyl)coumarin.<sup>29,30</sup> As IR spectrum of 3-(bromoacetyl)coumarin showed the characteristic ketonic group band at 1674, while C-H stretching vibrations at the aromatic region 3100–3000 cm<sup>-1</sup> (ref. 29) and two carbonyl characteristic peaks at  $\nu$  1674 and 1729 cm<sup>-1</sup> related to  $\alpha,\beta$ -unsaturated ketonic and lactonic, respectively.<sup>31</sup> <sup>1</sup>H NMR spectrum of parent 3-(bromoacetyl)coumarin **1** shows singlet signal of H-4 at  $\delta$  = 8.63 ppm, while the CH<sub>2</sub> group appears as singlet signal at  $\delta$  = 4.74 ppm. Also, <sup>13</sup>C NMR spectrum of 3-(bromoacetyl)coumarin exhibits characteristic signals at  $\delta$  = 188.9, 158.9, and 35.6 ppm corresponding to  $\alpha,\beta$ -unsaturated ketonic, lactonic and methylene carbons, respectively.<sup>30</sup> In the same context, HRMS/MS is mentioned as characteristic spectrometric data for 3-(bromoacetyl)coumarin **1** shows that  $m/z$  266.9665 (calcd. for C<sub>11</sub>H<sub>8</sub><sup>79</sup>BrO<sub>3</sub> [M + H]<sup>+</sup> 266.9657).<sup>30</sup>

In 1991, Vasudevan *et al.*<sup>32</sup> elucidated the structure 3-(bromoacetyl)coumarin **1** through its single-crystal X-ray, which showed that there are two conformers of the structure **1**, *S-cis* (I) or *S-trans* (II) (Fig. 2).

Moreover, Sparkes and coworkers<sup>33</sup> reported a polymorph of 3-(bromoacetyl)coumarin (Fig. 3). Whereas, Chennuru *et al.*<sup>34</sup>

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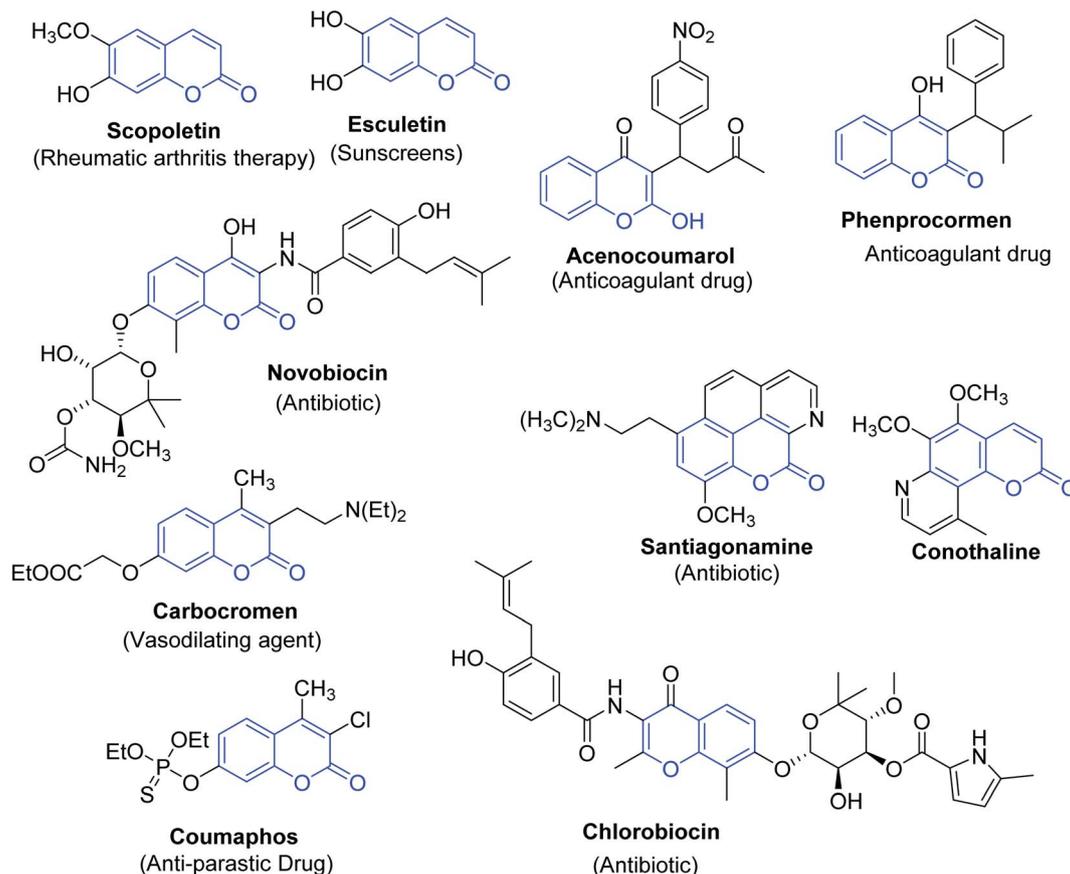



Fig. 1 Selected structures of coumarin derivatives in biological applications.

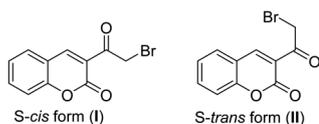


Fig. 2 *S-cis* (I) or *S-trans* (II) conformers of 3-(bromoacetyl)coumarin 1.

reported a single-crystal X-ray of 6-chloro-3-(bromoacetyl)coumarin (Fig. 4).

### 3. Synthesis

#### 3.1. Using 3-acetylcoumarins

The reaction of 3-acetylcoumarins **2** with numerous reagents represents a general approach to preparing 3-bromoacetyl coumarin derivatives **1**. Several brominating agents have been reported in the last two decades such as tetrabutylammonium tribromide (TBATB), bromine, phenyltrimethylammonium tribromide (PhTAPBr<sub>3</sub>), *N*-bromosuccinimide (NBS), and copper(II) bromide (CuBr<sub>2</sub>) (Scheme 1).<sup>35–47</sup>

### 4. Reactivity

On the treatment of 3-(bromoacetyl)coumarin **1** with various nucleophiles, four possible electrophilic positions are susceptible to attack: the exo-carbonyl group (position 1), bromomethane group (CH<sub>2</sub>Br) (position 2), lactonic carbonyl group

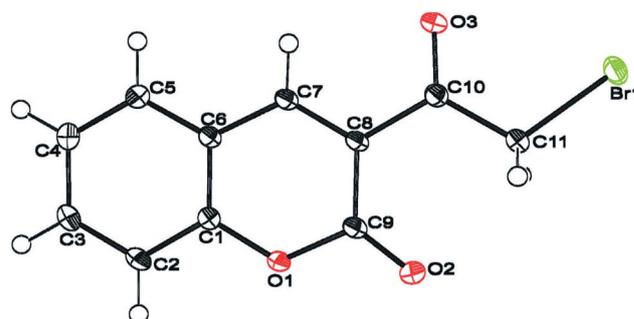


Fig. 3 ORTEP diagram of 3-(bromoacetyl)coumarin **1** [reprinted from ref. 33].

(position 3) and the bromo atom (position 4) susceptible to attack (Fig. 5). Besides, the typically nucleophilic position for attacking is carbon 4. The reactivity of  $\alpha$ -bromoacetyl coumarin towards oxygen, nitrogen, and sulphur nucleophiles is discussed in this review.

### 5. Reactions

#### 5.1. Amination

Sinnur *et al.*<sup>48</sup> reported a short and efficient synthesis for aminomethyl-3-coumarinyl ketone hydrochloride **4** *via*



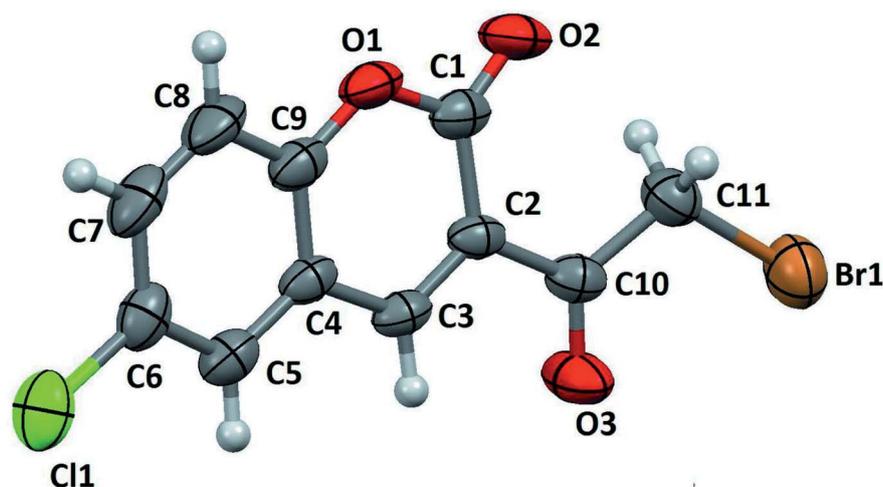


Fig. 4 ORTEP diagram of 6-chloro-3-(bromoacetyl)coumarin [reprinted from ref. 34].



**Condition A:** TBATB, AcOH, RT / 2h [35,36]

**Condition B:** Br<sub>2</sub> in CHCl<sub>3</sub> or AcOH, reflux [37-40]

**Condition C:** PhTAPBr<sub>3</sub>, THF, 25 °C, 15 min [41-42]

**Condition D:** NBS, *p*-TSA, 4h, reflux [43]

**Condition E:** CuBr<sub>2</sub>, EtOH, 80 °C [44]

**Condition F:** CuBr<sub>2</sub>, EtOH, 300W, 100 °C, 2 min [45]

**Condition G:** CuBr<sub>2</sub> in CHCl<sub>3</sub>/EtOAc [46, 47]

**1a, 2a:** R<sub>1</sub>=R<sub>2</sub>=R<sub>3</sub>=R<sub>4</sub>=H

**1c, 2c:** R<sub>1</sub>=H, R<sub>2</sub>=R<sub>3</sub>=R<sub>4</sub> CH=CH-CH=CH

**1e, 2e:** R<sub>1</sub>= OH, R<sub>2</sub>=R<sub>3</sub>=R<sub>4</sub>= H

**1g, 2g:** R<sub>1</sub>=R<sub>2</sub>=R<sub>3</sub>= H, R<sub>4</sub> = Cl;

**1i, 2i:** R<sub>1</sub>=R<sub>2</sub>=R<sub>3</sub>= H, R<sub>4</sub> = OCH<sub>3</sub>

**1b, 2b:** R<sub>1</sub>= NEt<sub>2</sub>, R<sub>2</sub>=R<sub>3</sub>=R<sub>4</sub>= H

**1d, 2d:** R<sub>1</sub>= OH, R<sub>2</sub>=R<sub>3</sub>=R<sub>4</sub>= H

**1f, 2f:** R<sub>1</sub>= OMe, R<sub>2</sub>=R<sub>3</sub>=R<sub>4</sub>= H

**1h, 2h:** R<sub>1</sub> = OMe, R<sub>2</sub> = CH<sub>2</sub>CH=CH<sub>2</sub>, R<sub>3</sub>=R<sub>4</sub>= H

**1j, 2j:** R<sub>1</sub> = OMe, R<sub>2</sub> = Cl, R<sub>3</sub>=R<sub>4</sub>= H

Scheme 1 Formation of 3-(bromoacetyl)coumarin derivatives 1.

refluxing 3-(bromoacetyl)coumarin **1** with hexamethylenetetramine **3** in drops of concentrated hydrochloric acid (Scheme 2).

Moreover, 3-(bromoacetyl)coumarin **1** was condensed with an amino group of various heterocyclic derivatives **5** such as 2-

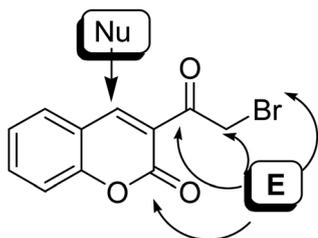


Fig. 5 Reactive sites in 3-(bromoacetyl)coumarin.

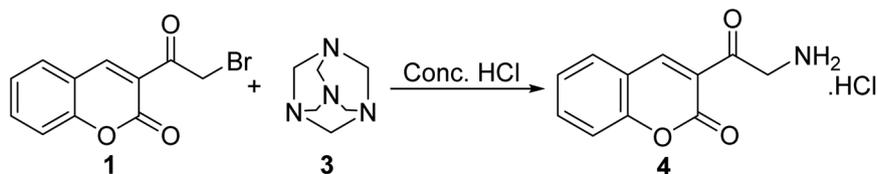
aminothiazole, 2-aminobenzothiazole, 2-amino-1,3,4-oxadiazole, 2-amino-1,3,4-thiadiazole, and 3-amino-4*H*-1,2,4-triazole derivatives in DMF to give the corresponding 2*H*-chromen-2-ones **6** (Scheme 3).<sup>49</sup>

Treatment of 3-(bromoacetyl)coumarin **1** with di(2-picolyl)amine **7** in chloroform under basic condition at room temperature afforded the corresponding 3-(bis(pyridin-2-ylmethyl)glycyl)-2*H*-chromen-2-one **8** (Scheme 4).<sup>50,51</sup>

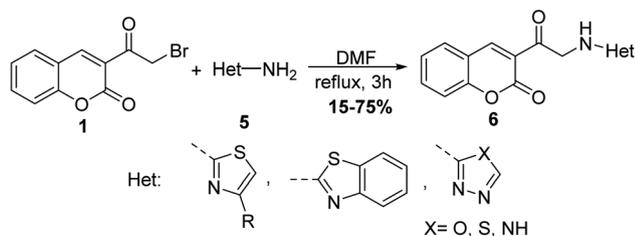
Selective nucleophilic substitution of 3-(bromoacetyl)coumarin **1** was accomplished through stirring with benzimidazole **9** in acetonitrile at ambient temperature afforded corresponding imidazole-1-carbonyl-chromenone **10** (Scheme 5).<sup>52</sup>

Valadbeigi *et al.*<sup>53</sup> reported the synthesis of thiazolidinedione derivatives **12** through heating of 3-(bromoacetyl)coumarin **1**





Scheme 2 Synthesis of aminomethyl-3-coumarinyl ketone hydrochloride 4.



Scheme 3 Condensation of 3-(bromoacetyl)coumarin 1 with various heterocyclic amino groups.

with thiazolidine-2,4-dione **11** in alcoholic potassium hydroxide (Scheme 6).

The reaction of the 3-(bromoacetyl)coumarin derivatives **1** with substituted arylamine **13** in ethanol in the absence<sup>54</sup> or the presence of sodium bicarbonate<sup>41,55,56</sup> or under solvent-free condition using  $K_2CO_3$  (ref. 57) yielded the corresponding 3-(2-(phenylanilino)acetyl)-2H-chromen-2-ones **14** (Scheme 7).

Whereas, refluxing of 3-(bromoacetyl)coumarin derivatives **1** with arylamines **13** in a mixture of ethanol and chloroform afforded the corresponding imino derivatives **15a-f** (Scheme 8).<sup>54</sup>

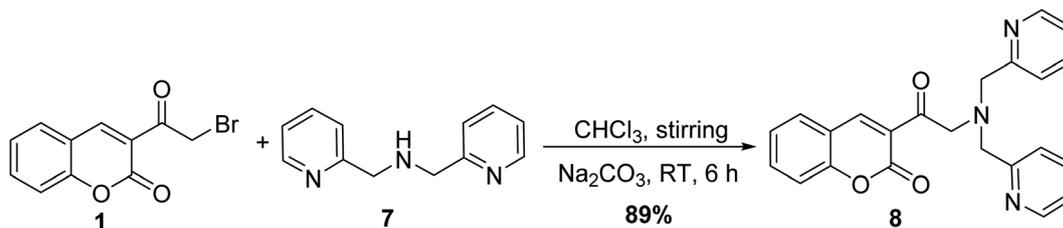
Coupling of 3-(bromoacetyl)coumarin derivatives **1** with amine hydrochlorides **16** such as hydroxylamine hydrochloride, methoxyamine hydrochloride, *o*-benzylhydroxylamine hydrochloride, and ethoxyamine hydrochloride in methyl alcohol to afford 3-(bromoacetyl) coumarin oximes **17** (Scheme 9).<sup>53,58-62</sup>

## 5.2. Azidation

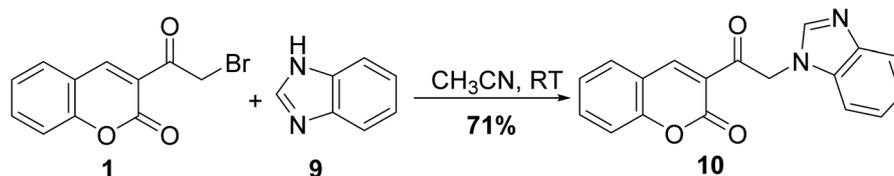
Evans and coworkers<sup>58</sup> reported the synthesis of coumarin fluorophore bearing an azidoacyl group **19** via the treatment of 3-(bromoacetyl)coumarin **1** with sodium azide ( $NaN_3$ ) **18** at tetrahydrofuran (Scheme 10).

## 5.3. Thiocyanation reaction

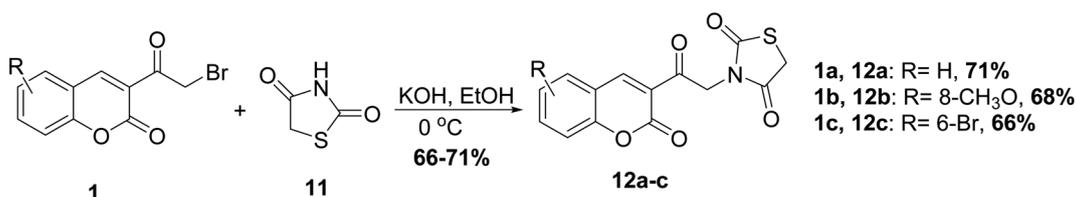
Ramanna *et al.*<sup>63</sup> reported the treatment of 3-(bromoacetyl) coumarin derivatives **1** with potassium thiocyanate (KSCN) **20**



Scheme 4 Reaction of 3-(bromoacetyl)coumarin **1** and di(2-picoly)amine **7**.

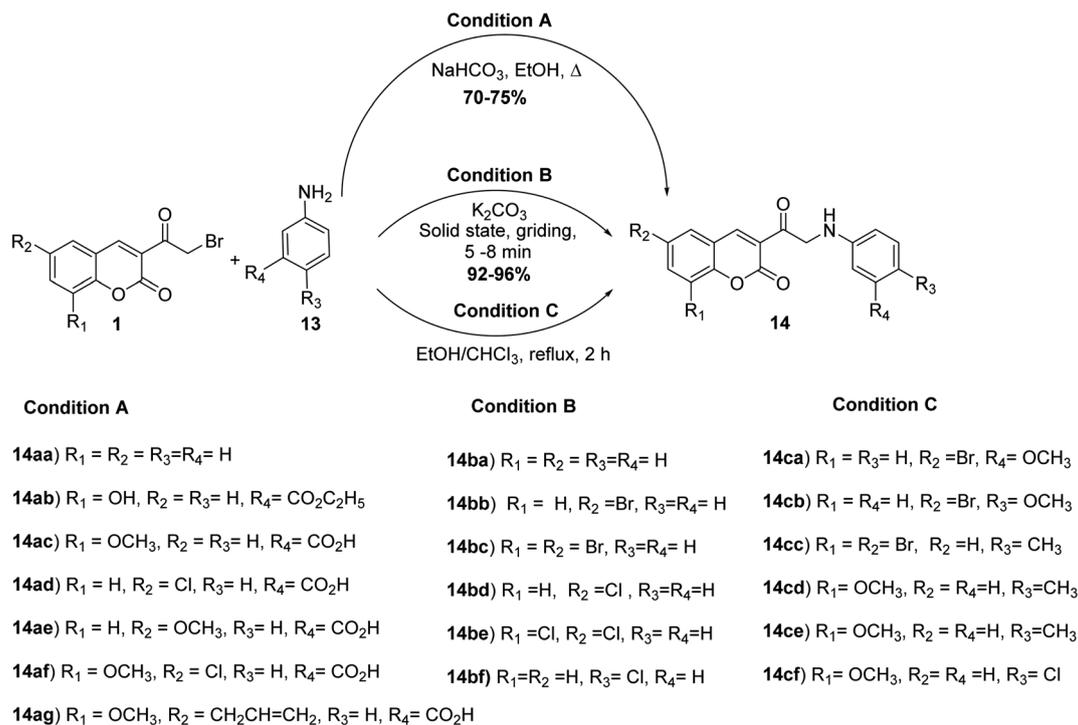


Scheme 5 Treatment of 3-(bromoacetyl)coumarin **1** with benzimidazole **9**.

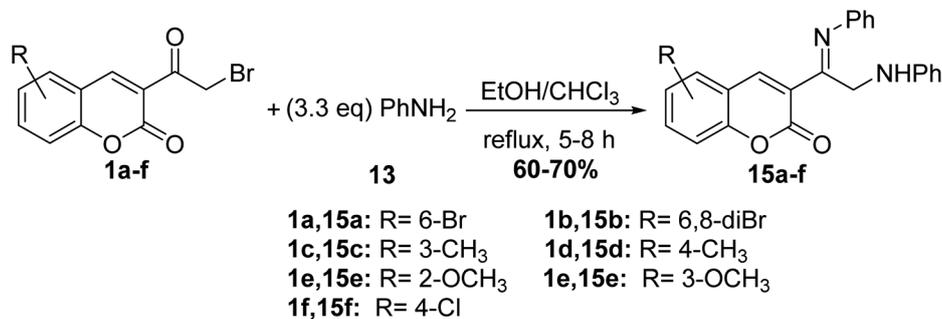


Scheme 6 Transformation of 3-(bromoacetyl)coumarin **1** to thiazolidine-2,4-dione **11**.

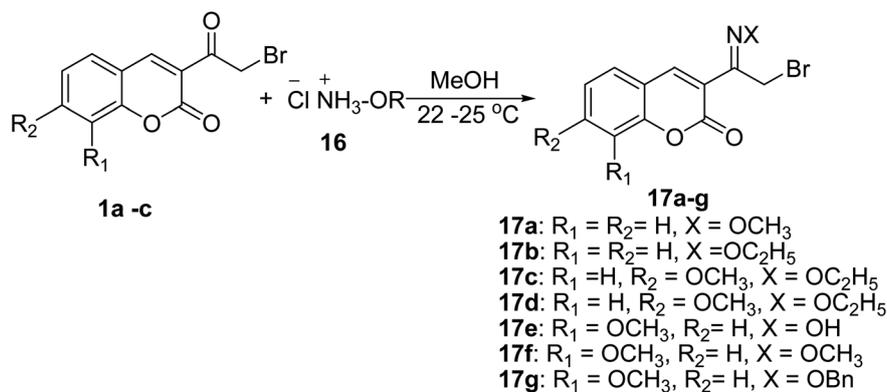




Scheme 7 Transformation of 3-(bromoacetyl)coumarins 1 to chromenones 14.

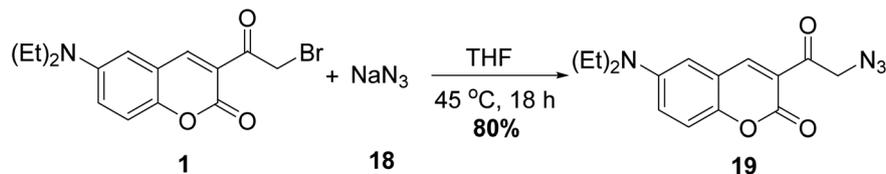


Scheme 8 Synthesis of imino derivatives 15.

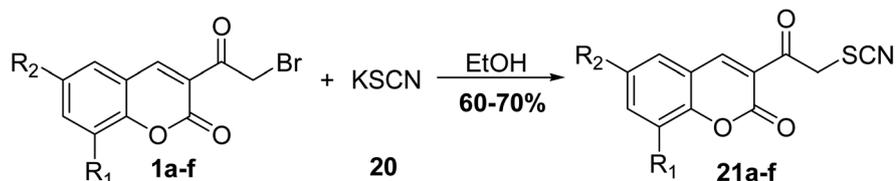


Scheme 9 Synthesis of bromoacetyl coumarin oximes 17.



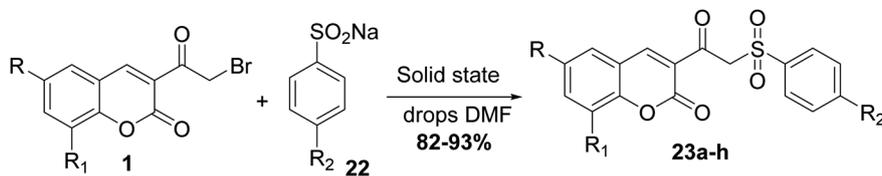


Scheme 10 Synthesis of 3-azidoacetyl coumarins 19.



**1a,21a:**  $R_1 = R_2 = H$ , **70%**  
**1b,21b:**  $R_1 = OCH_3$ ,  $R_2 = H$ , **68%**  
**1c,21c:**  $R_1 = Br$ ,  $R_2 = H$ , **70%**  
**1d,21d:**  $R_1 = Br$ ,  $R_2 = Br$ , **64%**  
**1e,21e:**  $R_1 = H$ ,  $R_2 = Cl$ , **62%**  
**1f,21f:**  $R_1 = C$ ,  $R_2 = Cl$ , **60%**

Scheme 11 Treatment of 3-(bromoacetyl)coumarins 1a-f with potassium thiocyanate 20.



**1a, 23a:**  $R = R_1 = R_2 = H$       **1e, 23e:**  $R = R_1 = H$ ,  $R_2 = CH_3$   
**1b, 23b:**  $R = Br$ ,  $R_1 = H$       **1f, 23f:**  $R = Br$ ,  $R_1 = H$ ,  $R_2 = CH_3$   
**1c, 23c:**  $R = R_1 = Br$ ,  $R_2 = H$       **1g, 23g:**  $R = R_1 = Br$ ,  $R_2 = CH_3$   
**1d, 23d:**  $R = Cl$ ,  $R_1 = R_2 = H$       **1h, 23h:**  $R = R_1 = Cl$ ,  $R_2 = CH_3$

Scheme 12 Alkylation of 3-(bromoacetyl)coumarin derivatives 1 via sulfonates metal salts 22.

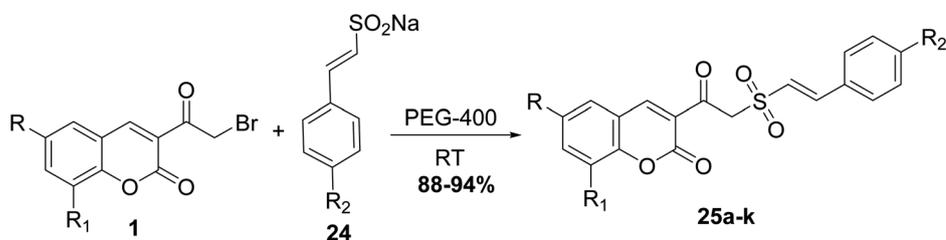
in ethanol furnished 3-thiocyanatoacetyl coumarin derivatives **21** in good yields (Scheme 11).

#### 5.4. Sulfonation reaction

Mixing of 3-(bromoacetyl)coumarins **1** with sodium arene sulfonates **22** in solid state in the presence of few drops of DMF furnished 3-(2-

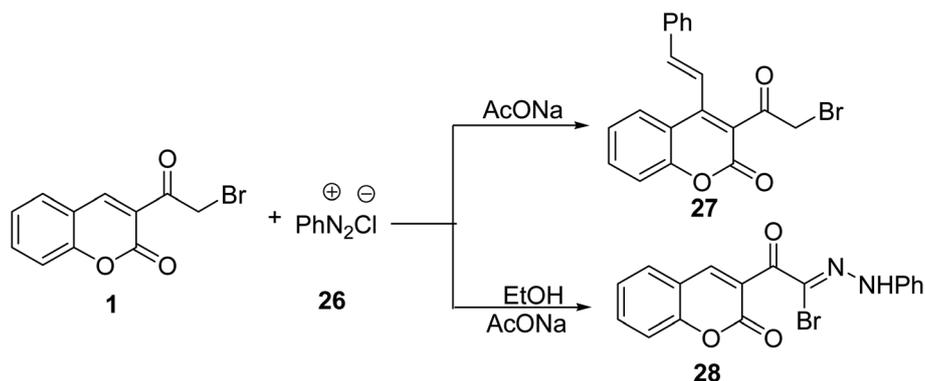
(phenylsulfonyl)acetyl)coumarin derivatives **23** (Scheme 12).<sup>64,65</sup> Furthermore, the reactions of this type were promoted under solvent-free conditions, as reported in literature.<sup>66,67</sup>

A facile synthesis (*E*)-styryl sulfones **25a-k** was accomplished via the reaction of 3-(bromoacetyl)coumarin derivatives **1** with sodium sulfonates **24** in the presence of polyethylene glycol

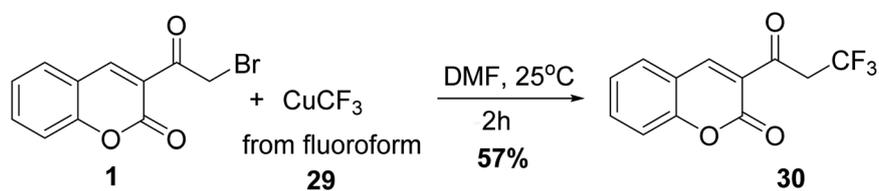


**25a:**  $R = R_1 = R_2 = H$       **25b:**  $R = R_1 = H$ ,  $R_2 = CH_3$   
**25c:**  $R = Br$ ,  $R_1 = R_2 = H$       **25d:**  $R = Br$ ,  $R_1 = H$ ,  $R_2 = CH_3$   
**25e:**  $R = R_1 = Br$ ,  $R_2 = H$       **25f:**  $R = R_1 = Br$ ,  $R_2 = CH_3$   
**25g:**  $R = Cl$ ,  $R_1 = R_2 = H$       **25h:**  $R = R_1 = Cl$ ,  $R_2 = CH_3$   
**25j:**  $R = Cl$ ,  $R = R_2 = CH_3$       **25k:**  $R = R_1 = Cl$ ,  $R_2 = CH_3$

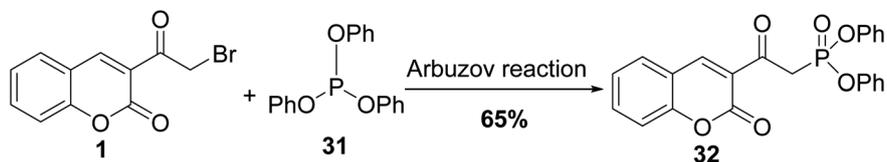
Scheme 13 Synthesis of heteryl (*E*)-styryl sulfone derivatives 25a-k.



Scheme 14 Coupling 3-(bromoacetyl)coumarin 1 with benzenediazonium chloride 26.



Scheme 15 Trifluoromethylation of 3-(bromoacetyl)coumarin 1.



Scheme 16 Formation of 2-oxophosphonates 32.

(PEG-400) for promoting the reaction at ambient temperature (Scheme 13).<sup>68</sup>

### 5.5. Coupling reactions

Coupling buffered solution of 3-(bromoacetyl)coumarin 1 with benzenediazonium chloride 26 yielded the corresponding 3-(2-bromoacetyl)-4-styryl-2H-chromen-2-one 27 (Scheme 14).<sup>69</sup> While the reaction of 3-(bromoacetyl)coumarin 1 with benzenediazonium chloride 26 under the influence of sodium acetate afforded *N*-phenylacetohydrazonyl bromide bearing coumarin moiety 28 (Scheme 14).<sup>70</sup>

### 5.6. Trifluoromethylation reaction

Novak and co-workers showed that trifluoromethylation of 3-(bromoacetyl)coumarin 1 with CHF<sub>3</sub> 29 derived CuCF<sub>3</sub> at room

temperature to give 2-trifluoromethylcoumarin 30 in yield 57% (Scheme 15).<sup>71</sup>

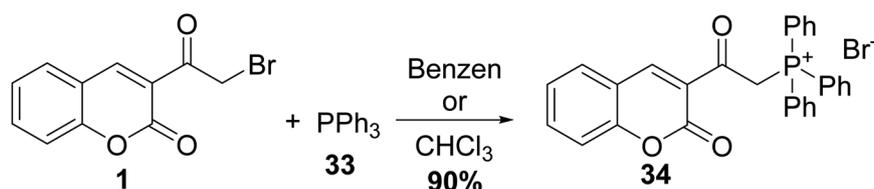
### 5.7. Phosphorylation reaction

3-(Bromoacetyl)coumarin 1 was transformed to 2-oxophosphonates 32 in xylene *via* Arbuzov reaction conditions with triphenyl phosphite 31 (Scheme 16).<sup>72–75</sup>

Wang *et al.* synthesized triphenylphosphonium 34 *via* the treatment of 3-(bromoacetyl)coumarin 1 with triphenylphosphine 33 in benzene or chloroform (Scheme 17).<sup>76</sup>

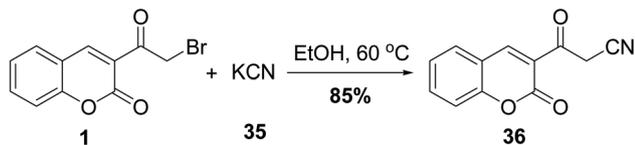
### 5.8. Cyanation reaction

3-(Cyanoacetyl)coumarin 36 was prepared based on cyanation of 3-(bromoacetyl)coumarin 1 by treatment with potassium cyanide (KCN) 35 under ethanolic condition (Scheme 18).<sup>70</sup>



Scheme 17 Treatment of 3-(bromoacetyl)coumarin 1 with triphenylphosphine 33.





Scheme 18 Treatment of 3-(bromoacetyl)coumarin **1** with potassium cyanide **35**.

## 5.9. Reaction with active methylene compound

2-Hydroxy-1-(2-oxo-2*H*-chromen-3-yl-ethylidene)malononitrile **39** was obtained through Knoevenagel condensation of 3-(bromoacetyl)coumarin **1** with cyanoacetonitrile, **37** in the presence of ammonium acetate **38** (Scheme 19).<sup>70</sup>

## 5.10. Synthetic approach toward heterocyclic hybrids

### 5.10.1. Synthesis of three-membered rings with one heteroatom

**5.10.1.1. Oxirane.** Oxirane phosphonates **41** were obtained via Michaelis–Becker reaction of 3-(bromoacetyl)coumarin **1** and dialkyl phosphites **40** using *N*-benzyl-*N,N,N*-triethylammonium chloride (BTEAC) as a phase-transfer catalyst (Scheme 20).<sup>77</sup>

### 5.10.2. Synthesis of five-membered rings with one heteroatom

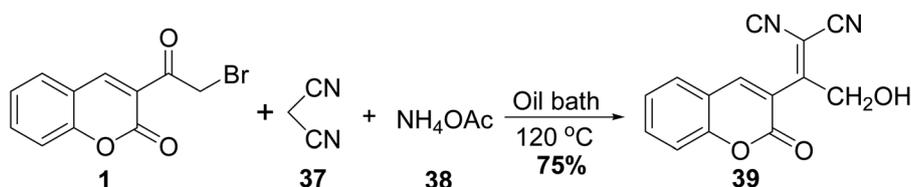
**5.10.2.1. Pyrroles.** An efficient synthesis of poly functionalized coumarin bearing pyrrolo[2,1-*a*]isoquinoline derivatives **44** was achieved via a multi-reaction of 3-(bromoacetyl)coumarin derivatives **1**, isoquinoline **42**, and dimethyl acetylenedicarboxylate **43** under the influence of triethylamine as catalyst (Scheme 21).<sup>78</sup>

Pal *et al.*<sup>79</sup> reported an eco-benign methodology for the preparation of coumarin-pyrrol hybrids **46** via three-component reactions of 3-(bromoacetyl)coumarin derivatives **1**, an alkyl/arylamine **13**, and acetylacetone **45** in the presence of optimized molarity of alum catalyst in water–PEG 400 (Scheme 22).

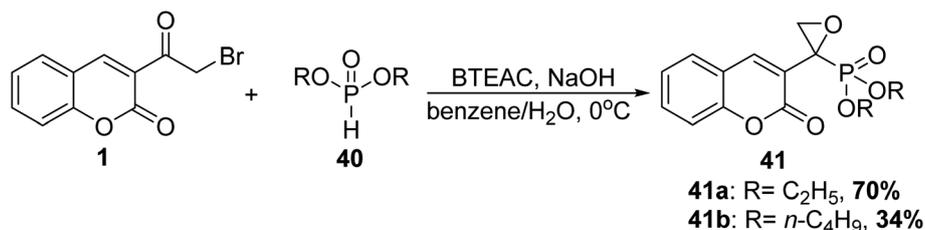
Pyrrole bis-coumarins **47** as fluorescent probes have been synthesized from the treatment of corresponding 3-(bromoacetyl)coumarin derivatives **1** with aniline **13** under catalytic condition (Zn–I<sub>2</sub>) (Scheme 23).<sup>80</sup>

**5.10.2.2. Dihydrofurans.** The synthesis of coumarin substituted dihydrofurans **50a-i** in good yields was performed via refluxing 3-(bromoacetyl)coumarins **1**, dimedone **48**, and aromatic aldehydes **49** in a mixture of acetonitrile and pyridine as a solvent containing a catalytic amount of triethylamine (Scheme 24).<sup>81</sup>

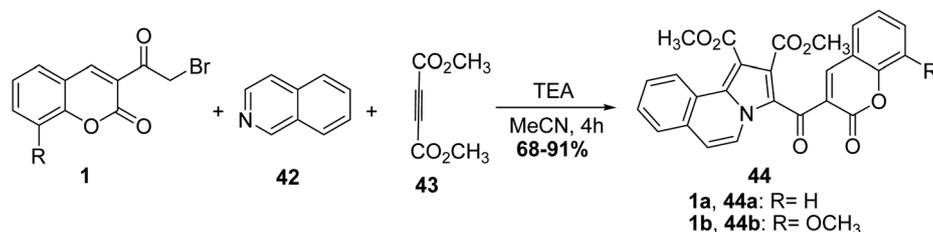
**5.10.2.3. Thiophenes.** Triethylamine-catalyzed heterocyclization of the ketene *N,S*-acetals **51** with 3-(bromoacetyl)coumarin **1** in ethanol has been employed to synthesize the corresponding 4-amino-2-phenylamino thiophenes **52a-c** (Scheme 25).<sup>82</sup>



Scheme 19 Formation of 2-hydroxy((2*H*-chromen-3-yl)ethylidene)malononitrile **39**.

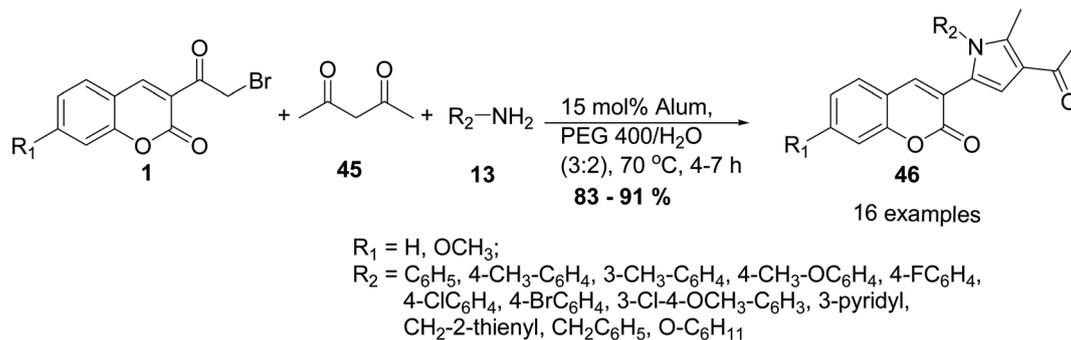
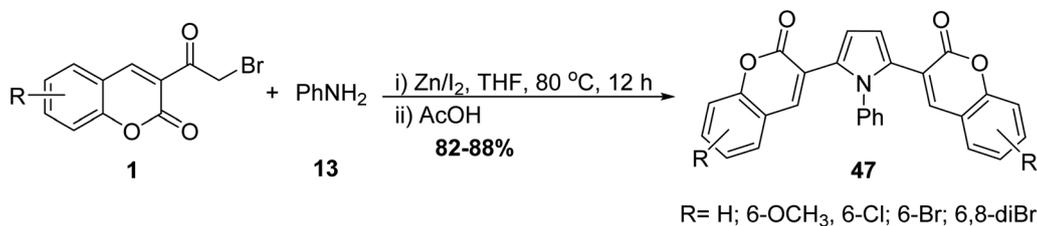
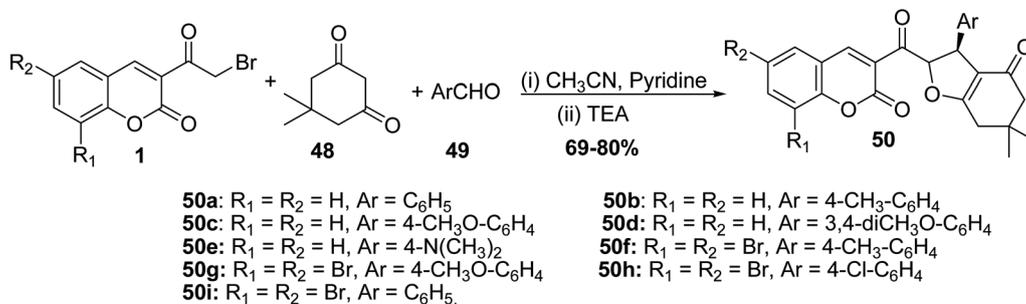


Scheme 20 Synthesis of enol phosphate **41**.



Scheme 21 Synthesis of coumarin bearing pyrrolo[2,1-*a*]isoquinolines **44**.



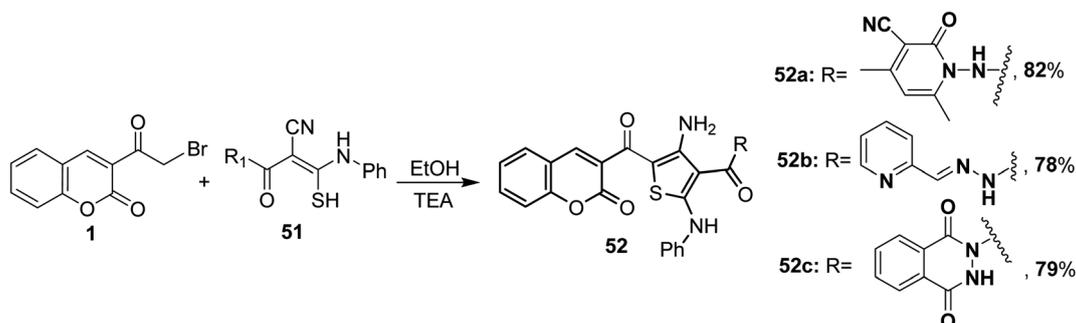
Scheme 22 MCR of coumarins **1**, an alkyl/arylamine **13**, and acetylacetone **45**.Scheme 23 Reaction of corresponding 3-(bromoacetyl)coumarins **1** with aniline **13**.

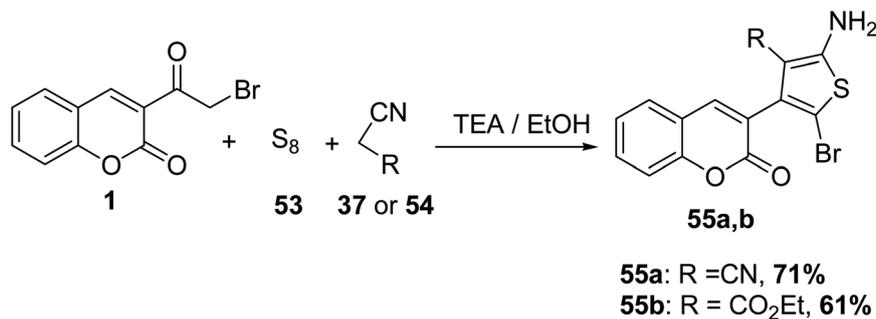
Scheme 24 Synthesis of coumarin bearing dihydrofurans.

Treatment of 3-(bromoacetyl)coumarin **1** with sulfur **53** and either malononitrile **37** or ethyl cyanoacetate **54** in the presence of triethylamine furnished the corresponding 2-amino thiophene derivatives **55a** and **55b**, respectively (Scheme 26).<sup>70</sup>

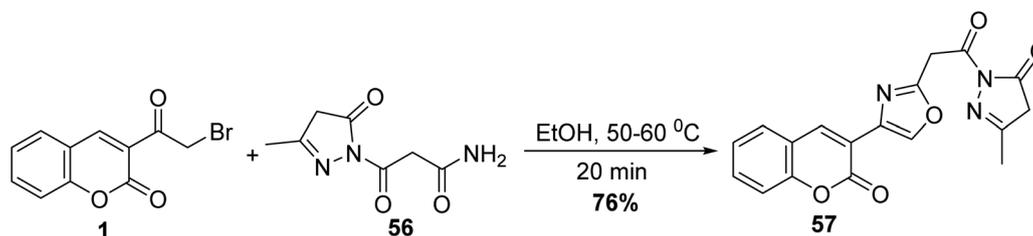
### 5.10.3. Synthesis of five-membered rings with two heteroatoms

5.10.3.1. *Oxazoles*. Eco-friendly approach to accesses 3-methyl-1-(2-(4-(2-oxo-2H-chromen-3-yl)oxazol-2-yl)acetyl)-1H-pyrazol-5(4H)-one **57** was carried out without using any

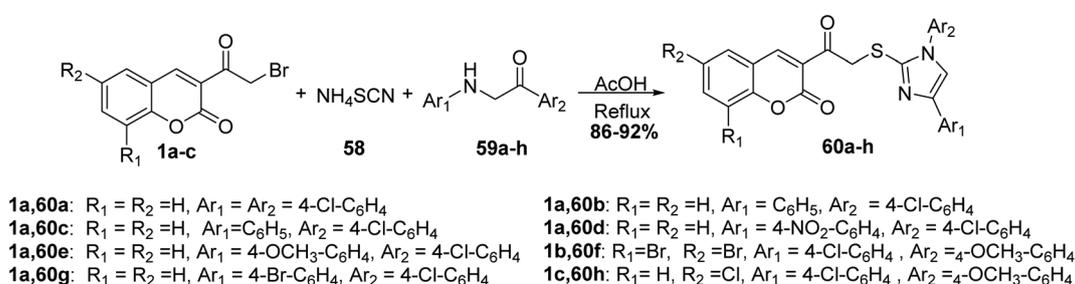
Scheme 25 Heterocyclization of the ketene *N,S*-acetals **51**.



Scheme 26 Formation of thiophene derivatives 55.



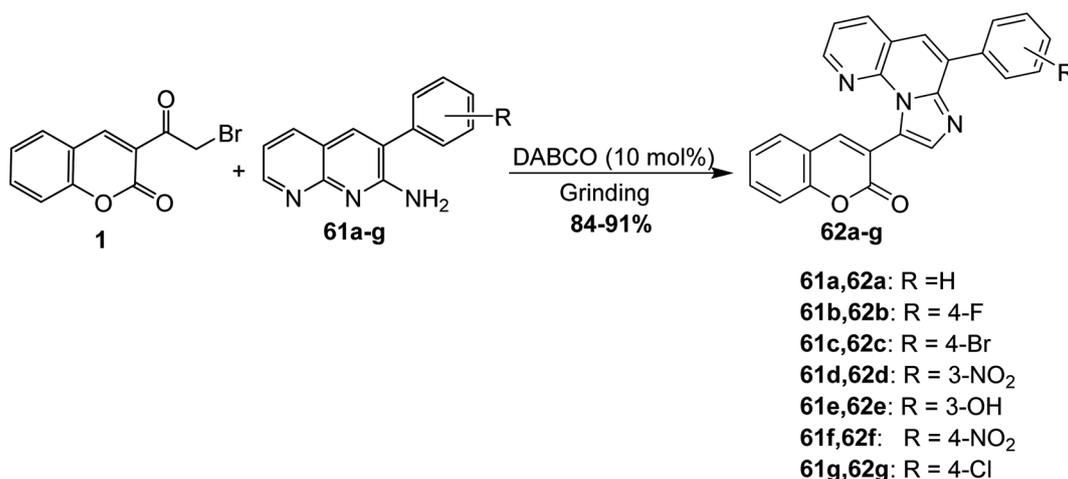
Scheme 27 Synthesis of tetracyclic heterocyclic systems 57.



Scheme 28 Preparation of substituted imidazole derivatives 60.

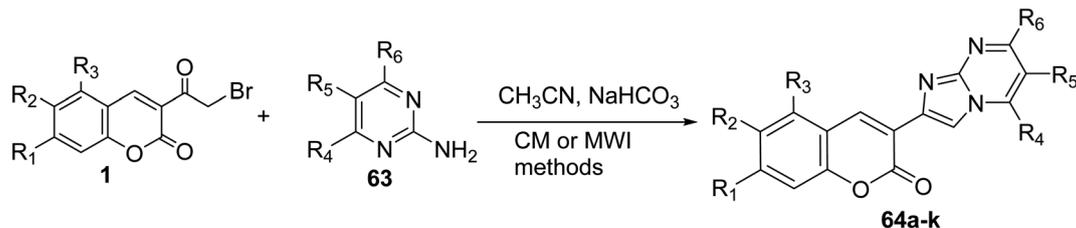
catalyst through the reaction of 3-(bromoacetyl)coumarin **1** with 3-oxopropanamide **56** in ethanol under heating (Scheme 27).<sup>83</sup>

**5.10.3.2. Imidazole derivatives.** A simple one-pot synthesis of novel substituted imidazoles **60** has been accomplished by three-component reaction of 3-(bromoacetyl)coumarin **1**,



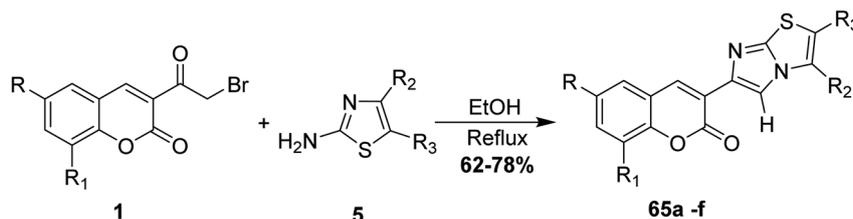
Scheme 29 Cyclocondensation of compound 1 and 2-amino-1,8-naphthyridines 61.





- 64a:** R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>5</sub> = R<sub>6</sub> = H  
**64b:** R<sub>1</sub> = N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>; R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>5</sub> = R<sub>6</sub> = H  
**64c:** R<sub>1</sub> = H; R<sub>2</sub> = R<sub>3</sub> = -CH=CH-CH=CH-; R<sub>4</sub> = R<sub>5</sub> = R<sub>6</sub> = H  
**64d:** R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H; R<sub>4</sub> = CH<sub>3</sub>; R<sub>5</sub> = H; R<sub>6</sub> = CH<sub>3</sub>  
**64e:** R<sub>1</sub> = N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>; R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = CH<sub>3</sub>; R<sub>5</sub> = H; R<sub>6</sub> = CH<sub>3</sub>  
**64f:** R<sub>1</sub> = H; R<sub>2</sub> = R<sub>3</sub> = -CH=CH-CH=CH-; R<sub>4</sub> = CH<sub>3</sub>; R<sub>5</sub> = H; R<sub>6</sub> = CH<sub>3</sub>  
**64g:** R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H; R<sub>4</sub> = CH<sub>3</sub>; R<sub>5</sub> = H, R<sub>6</sub> = Morpholinyl  
**64h:** R<sub>1</sub> = N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>; R<sub>2</sub> = R<sub>3</sub> = H; R<sub>4</sub> = CH<sub>3</sub>, R<sub>5</sub> = H; R<sub>6</sub> = Morpholinyl  
**64i:** R<sub>1</sub> = H; R<sub>2</sub> = R<sub>3</sub> = -CH=CH-CH=CH-, R<sub>4</sub> = CH<sub>3</sub>; R<sub>5</sub> = H; R<sub>6</sub> = Morpholinyl  
**64j:** R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub>; R<sub>4</sub> = H; R<sub>5</sub> = Br; R<sub>6</sub> = H  
**64k:** R<sub>1</sub> = N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>; R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H; R<sub>5</sub> = Br; R<sub>6</sub> = H

Scheme 30 Synthesis of coumarin-imidazo[1,2-a]pyrimidines 64.



- 65a:** R = H, R<sub>1</sub> = H, R<sub>2</sub> = CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, R<sub>3</sub> = H;  
**65b:** R = H, R<sub>1</sub> = H, R<sub>2</sub> = H, R<sub>3</sub> = CH<sub>3</sub>  
**65c:** R = Cl, R<sub>1</sub> = H, R<sub>2</sub> = CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>; R<sub>3</sub> = H;  
**65d:** R = Br, R<sub>1</sub> = H, R<sub>2</sub> = CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, R<sub>3</sub> = H;  
**65e:** R = Br, R<sub>1</sub> = H, R<sub>2</sub> = CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>; R<sub>3</sub> = CH<sub>3</sub>  
**65f:** R = Br, R<sub>1</sub> = Br, R<sub>2</sub> = CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>; R<sub>3</sub> = H

Scheme 31 Reaction of bromoacetyl coumarins 1 with thiazole derivatives 5.

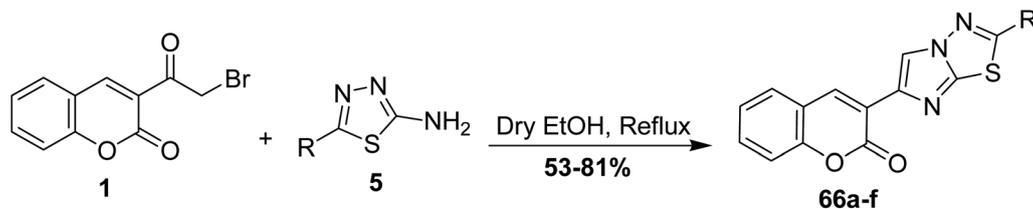
ammonium thiocyanate 58, and phenacyl aniline 59 (Scheme 28).<sup>84</sup>

Boda *et al.* reported the preparation of fused imidazo[1,2-*a*][1,8]naphthyridines 62a-g through the solvent-free reaction of 3-(bromoacetyl)coumarin 1 and 2-amino-1,8-naphthyridines 61a-g using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a catalyst (Scheme 29).<sup>85</sup>

The coumarin-imidazo[1,2-*a*]pyrimidine derivatives 64 as pH-sensitive fluorescent compounds were carried out through

thermal conventional (CM) or microwave irradiation (MWI) methods. Heating a mixture of 3-(bromoacetyl)coumarin 1 and 2-aminopyrimidine derivatives 63 in the microwave at 200 W at 100 °C afforded corresponding products in yields 5–90% compared by conventional thermal method (5–80%) (Scheme 30).<sup>37</sup>

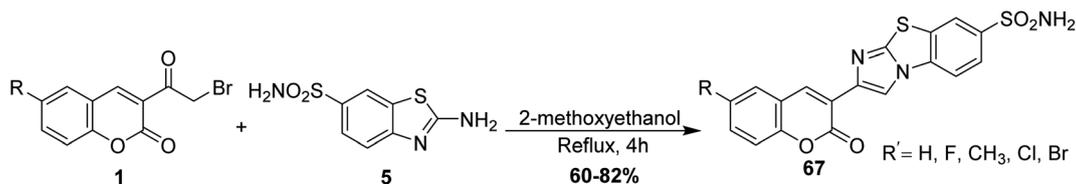
Rao and Reddy have repeated the cyclocondensation of 3-(bromoacetyl)coumarins 1 with 2-aminothiazoles 5 in refluxing ethanol yielded the corresponding imidazo[2,1-*b*]thiazol-5-2*H*-chromen-2-ones 65 (Scheme 31).<sup>86</sup>



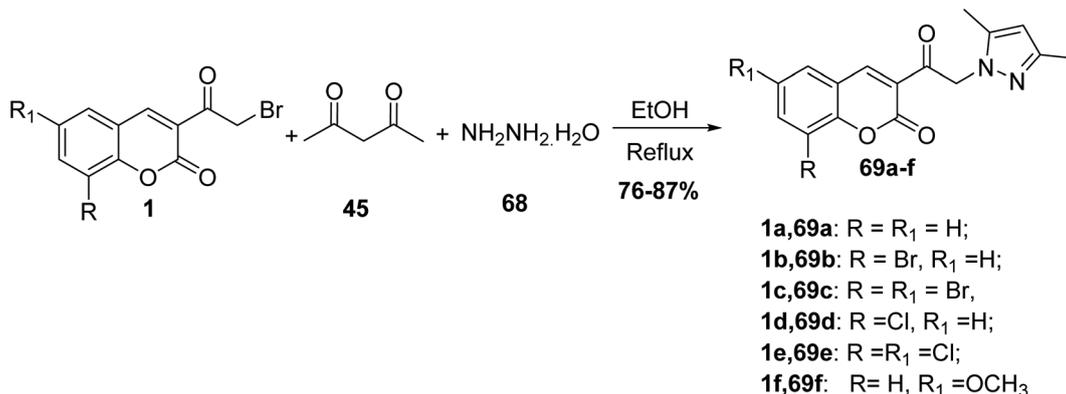
- 66a:** R = C<sub>2</sub>H<sub>5</sub>, **66b:** R = *n*-C<sub>3</sub>H<sub>7</sub>, **66c:** R = cyclohexyl,  
**66d:** R = C<sub>6</sub>H<sub>5</sub>, **66e:** R = 2-furyl, **66f:** R = 2-thienyl.

Scheme 32 Reaction of 3-(bromoacetyl)coumarin 1 and 1,3,4-thiadiazoles 5.





Scheme 33 Formation of imidazobenzothiazoles 67.



Scheme 34 Multi-component reaction of the synthesis of 3,5-dimethylpyrazoles 69.

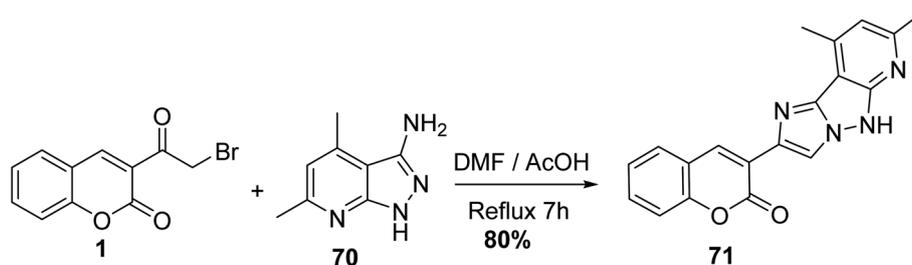
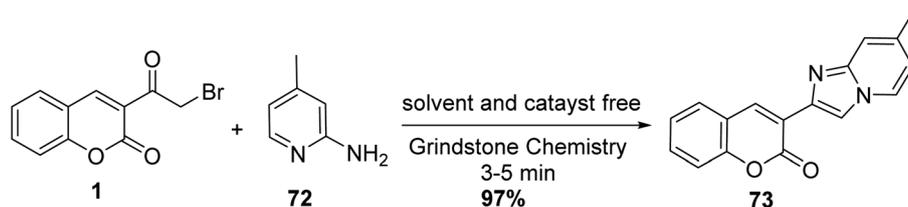
3-(2-Cyclohexylimidazo[2,1-*b*]-[1,3,4]thiadiazol-6-yl)-2*H*-chromen-2-ones **66a-f** was obtained as hydrobromide salt through the reaction of 3-(bromoacetyl)coumarin **1** with 2-amino-5-cyclohexyl-1,3,4-thiadiazole **5** in refluxing ethanol (Scheme 32).<sup>87,88</sup>

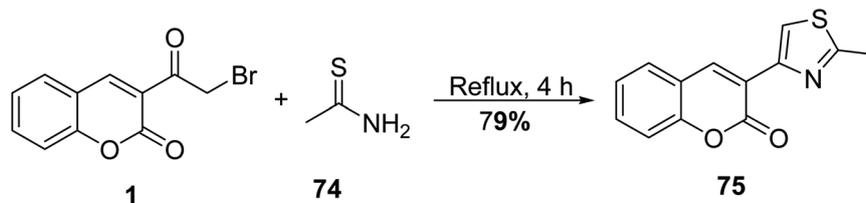
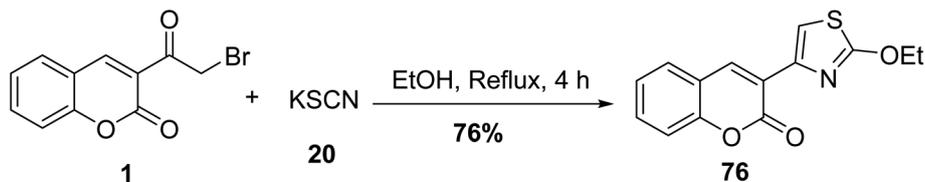
In refluxing 2-methoxyethanol, the reaction of 6-substituted-3-(bromoacetyl)coumarins **1** with 2-aminobenzo[*d*]thiazole-6-sulfonamide **5** was achieved, followed by neutralization using

ammonia solution afforded corresponding imidazobenzothiazoles **67** (Scheme 33).<sup>89</sup>

**5.10.3.3. Pyrazoles.** 3,5-Dimethylpyrazole derivatives **69** have been prepared through a one-pot multi-component reaction of 3-(bromoacetyl)coumarin derivatives **1**, acetylacetone **45**, and hydrazine hydrate **68** in refluxing ethanol (Scheme 34).<sup>90</sup>

Condensation of 3-(bromoacetyl)coumarin **1** with 3-amino-pyrazole **70** within DMF/AcOH yielded the corresponding imidazo[1,2-*b*]pyrazole **71** (Scheme 35).<sup>91</sup>

Scheme 35 Annulation of imidazo[1,2-*b*]pyrazole 71.Scheme 36 Synthesis of coumarin bearing imidazo[1,2-*a*]pyridine 73.

Scheme 37 Formation of 3-(2-methylthiazol-4-yl)-2H-chromen-2-one **75**.Scheme 38 Synthesis of 3-(2-ethoxythiazol-4-yl)-2H-chromen-2-one **76**.

Using grindstone chemistry, the synthesis of 3-(7-methylimidazo[1,2-*a*]pyridin-2-yl)-2H-chromen-2-one **73** was achieved through the reaction of 3-(bromoacetyl)coumarin **1** with 2-amino-4-methylpyridine **72** under neat condition and catalyst-free (Scheme 36).<sup>92</sup>

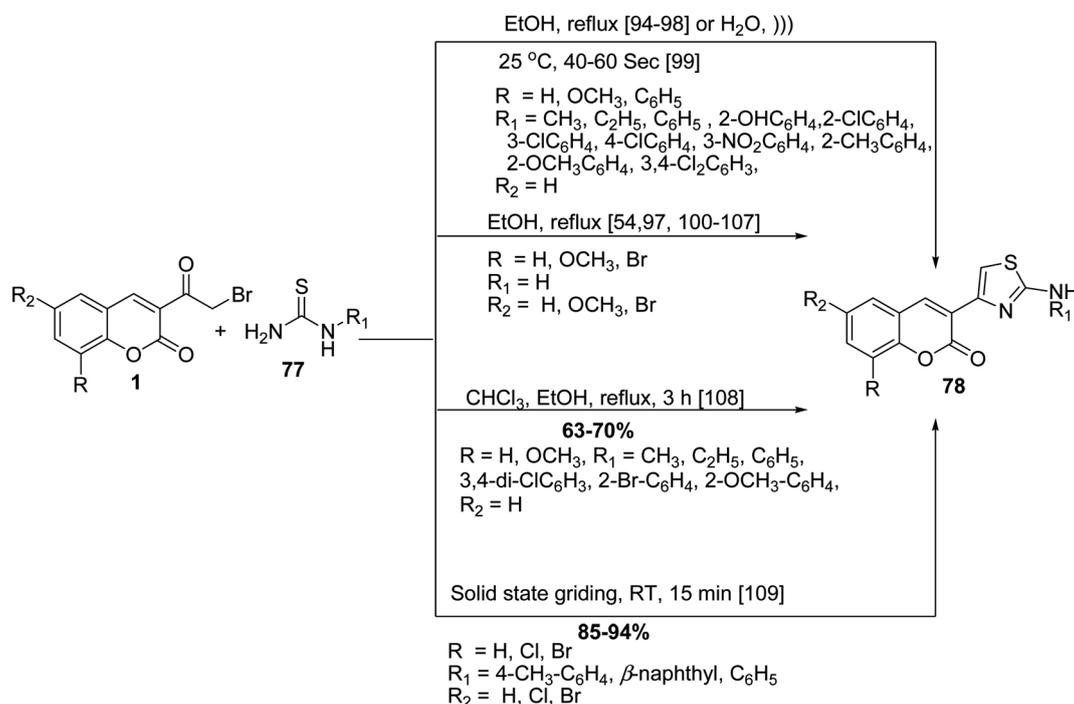
**5.10.3.4. Thiazole derivatives.** Gouda disclosed the reaction of 3-(bromoacetyl)coumarin **1** with thioacetamide **74** in methanol under reflux furnished 3-(2-methylthiazol-4-yl)-2H-chromen-2-one **75** (Scheme 37).<sup>93</sup>

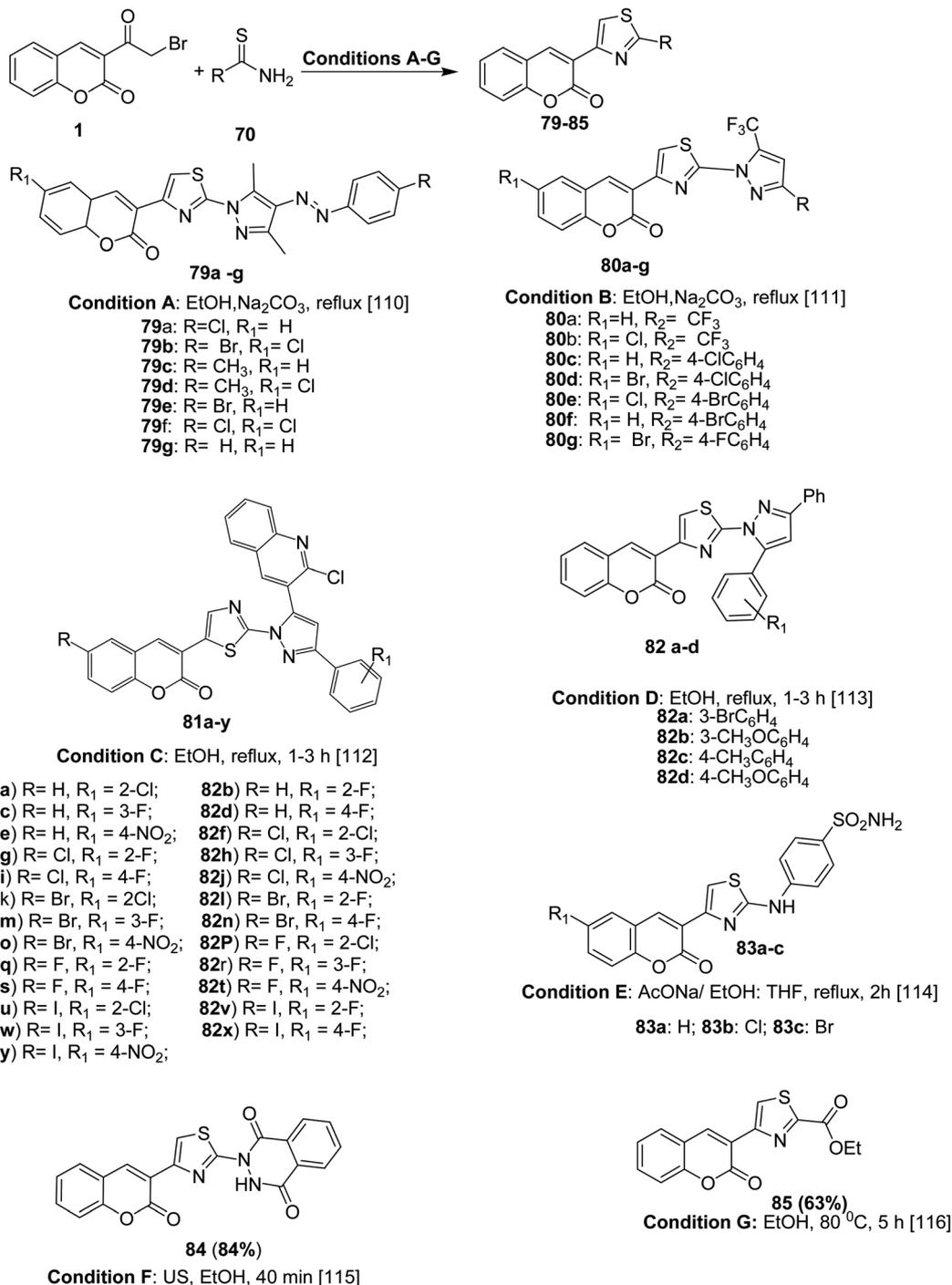
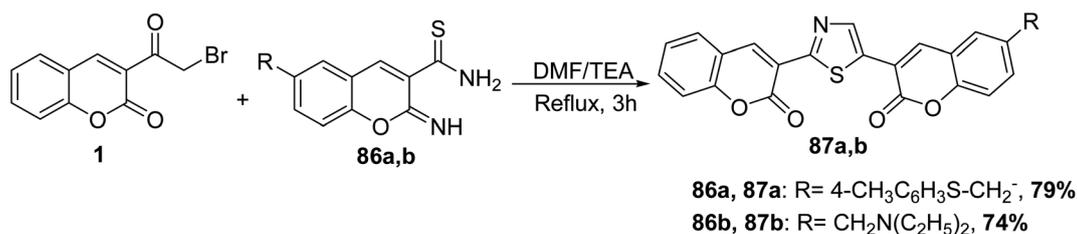
One of the most successful methods for the synthesis of 3-(2-ethoxythiazol-4-yl)-2H-chromen-2-one **76** is the refluxing 3-

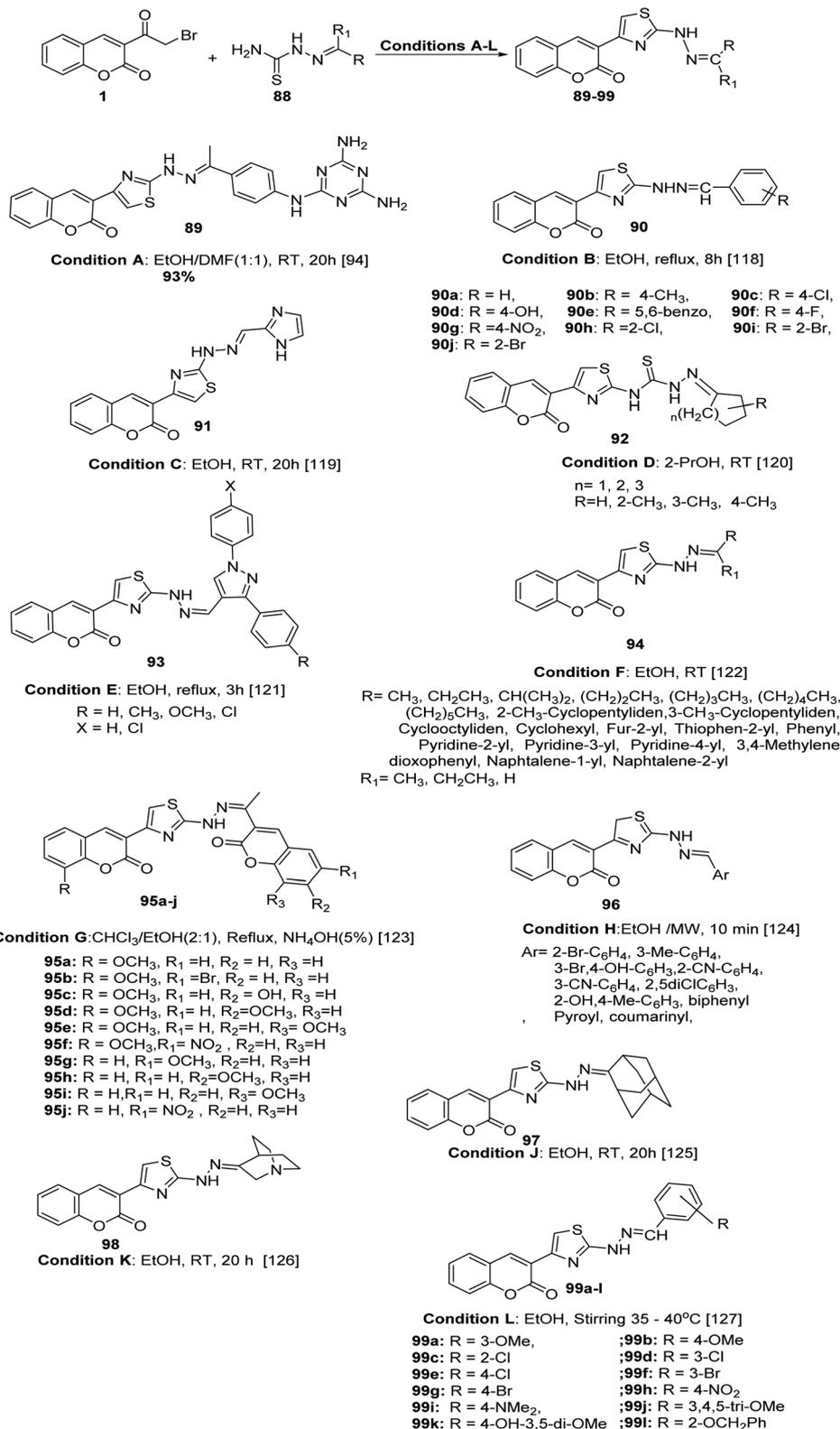
(bromoacetyl)coumarin **1** with potassium thiocyanate **20** in ethanol (Scheme 38).<sup>78</sup>

The Hantzsch thiazole synthesis of numerous 2-amino thiazolylcoumarins **78** was accomplished by cyclocondensation of 3-(bromoacetyl)coumarin derivatives **1** with various *N*-substituted thiourea **77** under various conditions (Scheme 39).<sup>54,94-109</sup>

Analogously, 4-coumarinylthiazole derivatives **79-85** were efficiently prepared under conventional method or ultrasound irradiation in short reaction and high yields *via* the condensation of various 3-(bromoacetyl)coumarin derivatives **1** with *N*-substituted thioamide **74** (*e.g.* 2,4-thioureido

Scheme 39 Hantzsch route for the synthesis of substituted 2-amino thiazolylcoumarins **78**.

Scheme 40 Treatment of various 3-(bromoacetyl)coumarins **1** with *N*-substituted thioamides **74**.Scheme 41 Synthesis of 3-(thiazol-2-yl)-2*H*-chromen-2-ones **87a,b**.

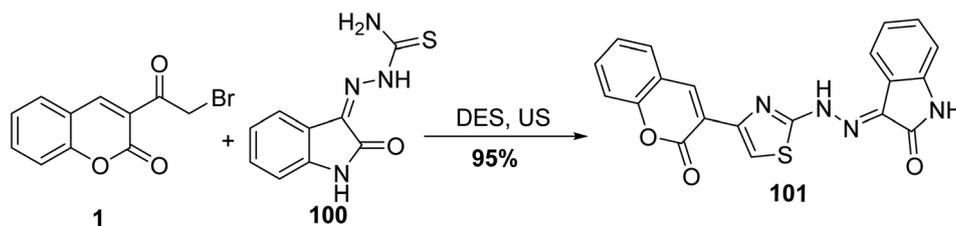
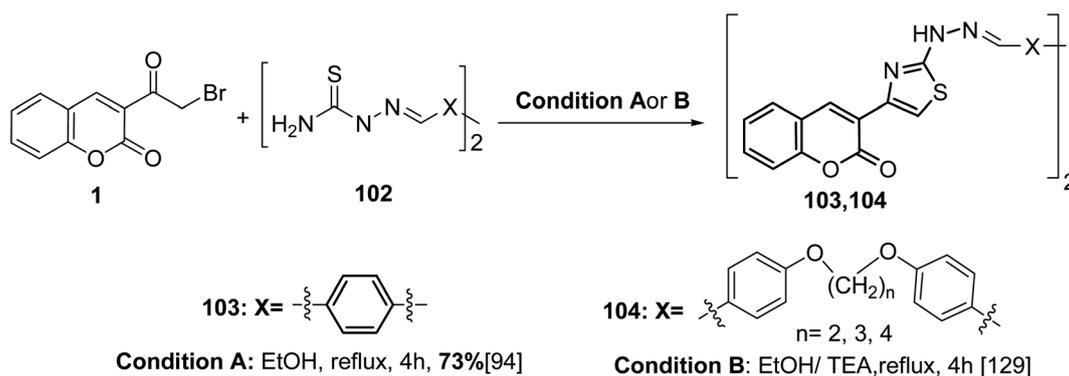
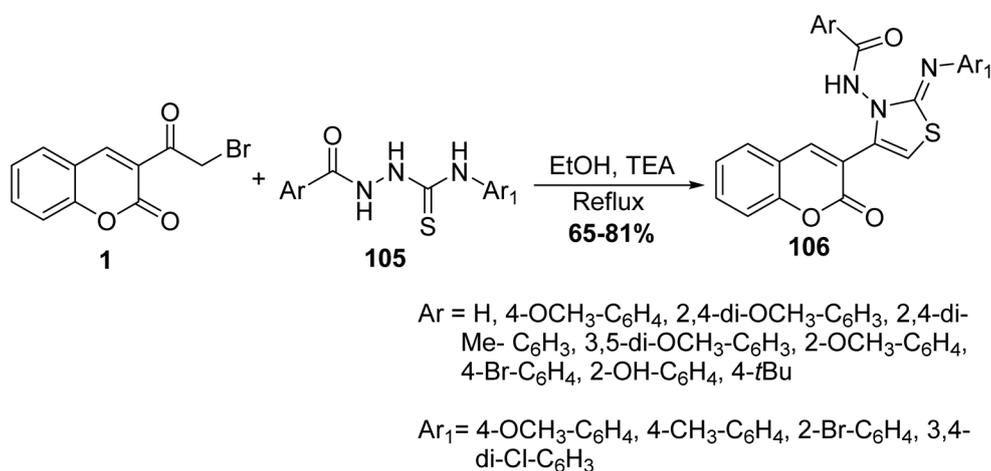
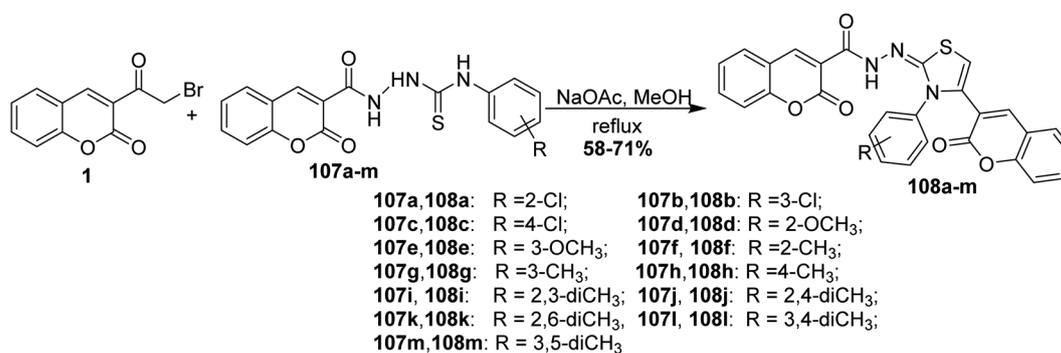


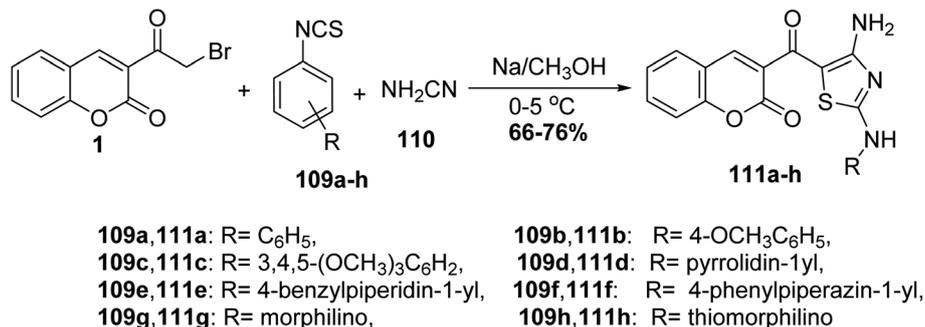
Scheme 42 Synthesis of series of hydrazinyl thiazolyl coumarin derivatives 89–99.

benzenesulfonamide, ethyl thiooxamate, dihydrophthalazine carbothioamide, and pyrazole carbothioamides) in refluxing ethanol or tetrahydrofuran under alkaline condition (sodium acetate and sodium carbonate) (Scheme 40).<sup>110–116</sup>

3-(Bromoacetyl)coumarin **1** was reacted with the appropriate carbothioamides **86** in DMF in the presence of triethylamine to give the corresponding 3,3'-(thiazole-2,4-diyl)bis-chromen-2-ones **87a,b** (Scheme 41).<sup>117</sup>



Scheme 43 The synthesis of 2-oxochroman-3-thiazol-2-hydrazone-indolin-2-one **101**.Scheme 44 Formation of bis(thiazole-4,2-diy)bis(2H-chromen-2-ones) **103** and **104**.Scheme 45 Synthesis of thiazolylcoumarin derivatives **106**.Scheme 46 Synthesis of bis-coumarin-iminothiazole hybrids **108a-m**.



Scheme 47 The synthesis of (4-aminophenyl-thiazole-5-carbonyl)-2H-chromenones 111.

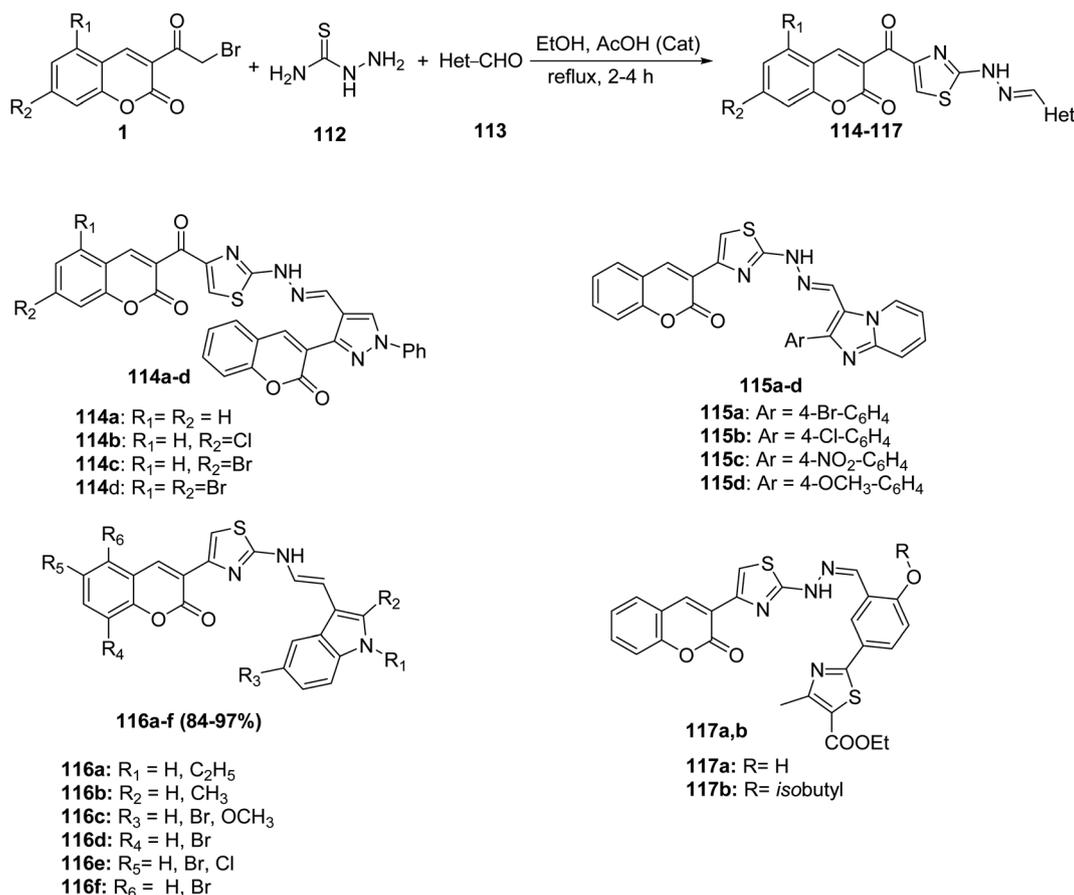
New sets of hydrazinyl thiazolyl coumarin derivatives **89–99** were accomplished in high and efficient yield from the one-pot Hantzsch reaction; the proposed mechanism of the reaction involves the cyclocondensation of the appropriate thiosemicarbazones **88** with 3-(bromoacetyl)coumarin **1** under various conditions (Scheme 42).<sup>94,118–127</sup>

Utilizing deep eutectic solvent (DES) and ultrasound for the preparation of 2-oxochroman-3-thiazol-2-hydrazono-indolin-2-one **101** *via* the reaction of **1** with hydrazinecarbothioamide **100** (Scheme 43).<sup>94,128</sup>

The bis(thiazole-4,2-diyl)bis(2H-chromen-2-ones) **103** and **104** were obtained *via* one-pot cyclisation reaction of bis(hydrazinecarbothioamides) **102** with 3-(bromoacetyl)coumarin **1** (Scheme 44).<sup>94,129</sup>

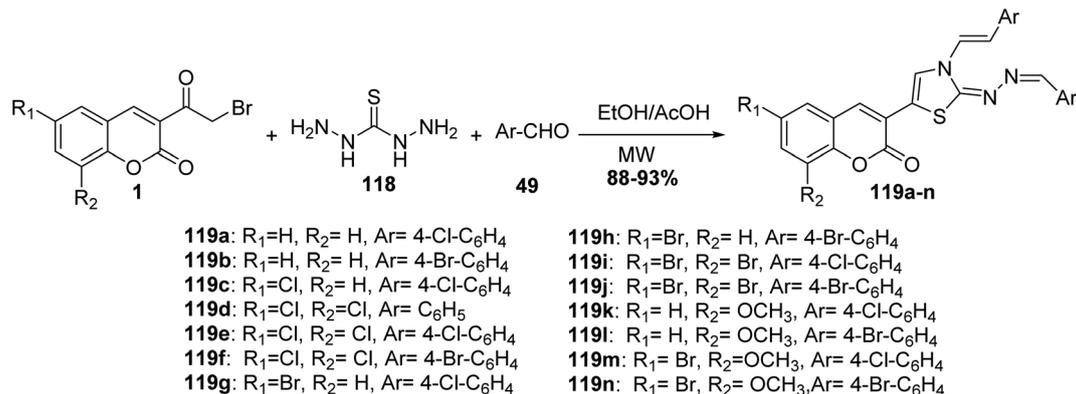
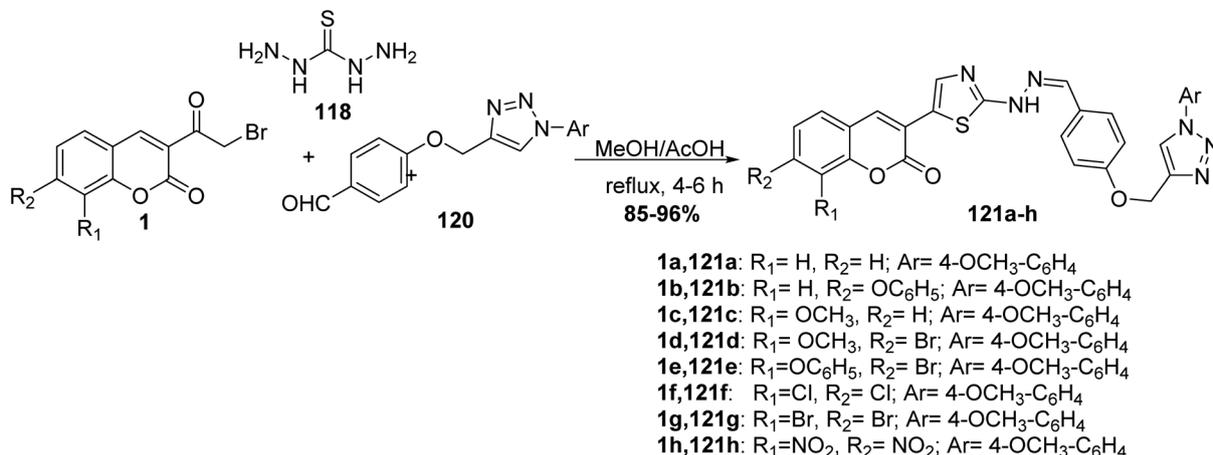
Cyclization reaction of 3-(bromoacetyl)coumarin **1** with thiosemicarbazides **105** in the presence of a catalytic amount of trimethylamine in ethanol yielded thiazolylcoumarin derivatives **106** (Scheme 45).<sup>130</sup>

Refluxing of 3-(bromoacetyl)coumarin **1** and coumarinothiosemicarbazides **107a–m** in methanol containing drops of



Scheme 48 Formation of annulated thiazolylcoumarins 114–117.



Scheme 49 Synthesis of coumarin based thiazoles **119a-n**.Scheme 50 Synthetic route for the formation of 1,2,3-triazole-thiazole systems **121a-h**.

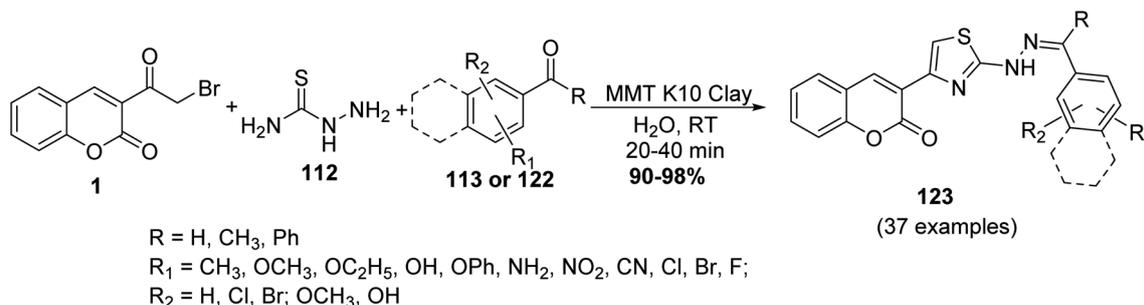
acetic acid as catalyst gave bis-coumarin-iminothiazole hybrids **108a-m** in good yields (Scheme 46).<sup>131</sup>

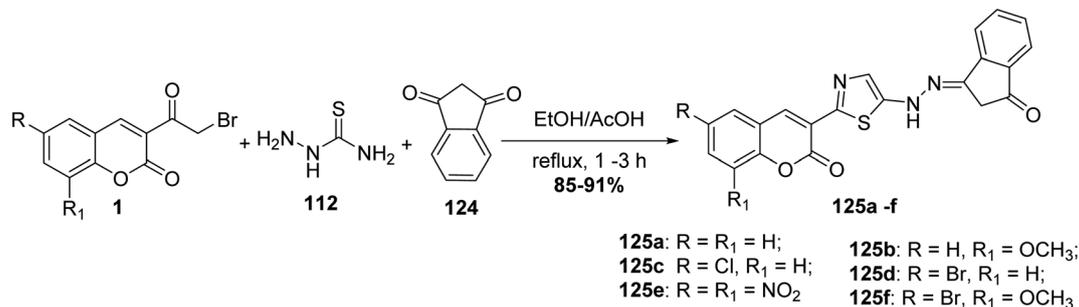
The multi-component reaction of 3-(bromoacetyl)coumarin derivatives **1**, phenylisothiocyanates **109a-h** with cyanamide **110** in freshly prepared sodium methoxide yielded annulated 3-(4-amino-2-(phenylamino)thiazole-5-carbonyl)-2H-chromen-2-one derivatives **111a-h** in moderate yields (Scheme 47).<sup>132</sup>

Novel series of thiazolylcoumarins **114-117** were prepared *via* multi-component condensation reaction of 3-(bromoacetyl)

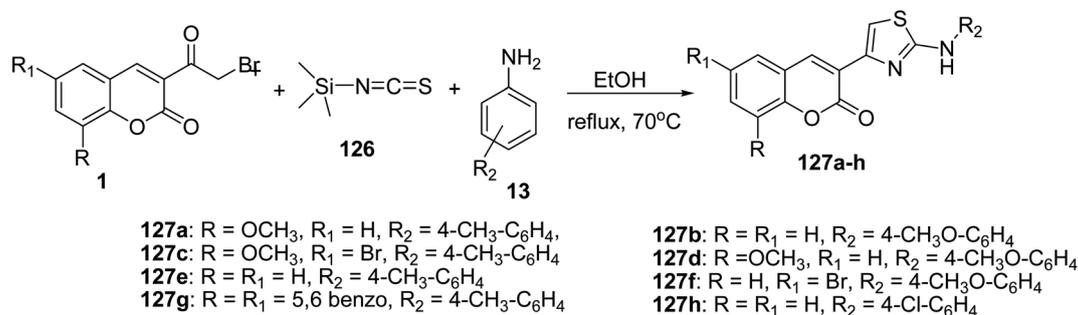
coumarin derivatives **1** thiosemicarbazide **112** and aldehydes **113** with different substitution patterns (aryl,<sup>133,134</sup> pyrazole,<sup>134</sup> imidazo[1,2-*a*]pyridine,<sup>135</sup> indole<sup>136</sup>) in ethanol with a catalytic amount of acetic acid (Scheme 48).

New series of coumarin based thiazoles **119a-n** were accomplished *via* mixing of substituted 3-(bromoacetyl) coumarins **1**, aldehydes **49**, and thiocarbonylhydrazide **118** in the presence of a catalytic amount of acetic acid in the microwave for 6–8 min (Scheme 49).<sup>137</sup>

Scheme 51 Formation of thiazolyl coumarins **123**.



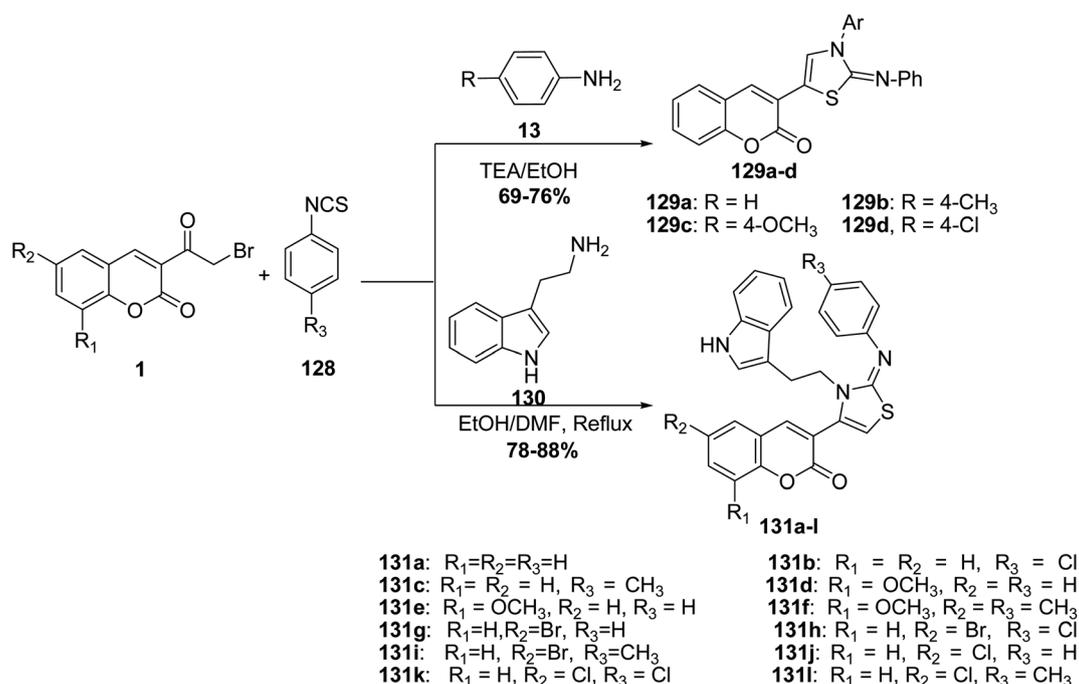
Scheme 52 Synthesis of novel thiazolyhydrazone derivatives 125.



Scheme 53 Synthesis of 3-(2-amino-4-thiazolyl)coumarins 127a-h.

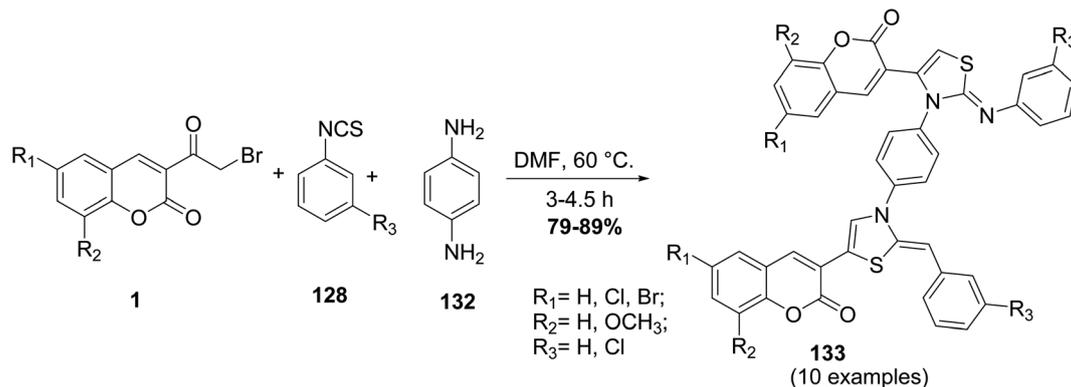
Three-component condensation of 3-(bromoacetyl)coumarin derivatives **1**, thiocarbonylhydrazide **118** and aldehyde **120** were carried out under refluxing condition in ethanol in the presence of a catalytic amount of acetic acid to afford novel series of substituted 1,2,3-triazole-hydrazinyl-1,3-thiazole scaffolds **121a-h** (Scheme 50).<sup>138</sup>

A water-mediated MCR protocol has been described for the synthesis of thiazolyl coumarins **123** from a three-component reaction of 3-(bromoacetyl)coumarin **1**, aldehydes **113** or ketones **122**, and thiosemicarbazide **112** catalyzed by montmorillonite K10 clay at ambient temperature (Scheme 51).<sup>139</sup>

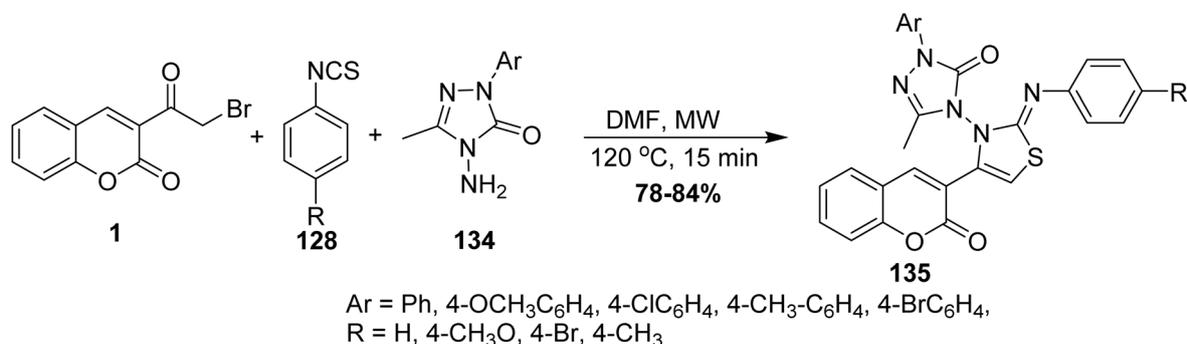


Scheme 54 Synthesis of 2-arylimino-3-thiazolines 129 and 131.





Scheme 55 Preparation of bis (thiazolyl-2H-chromene) systems 133.



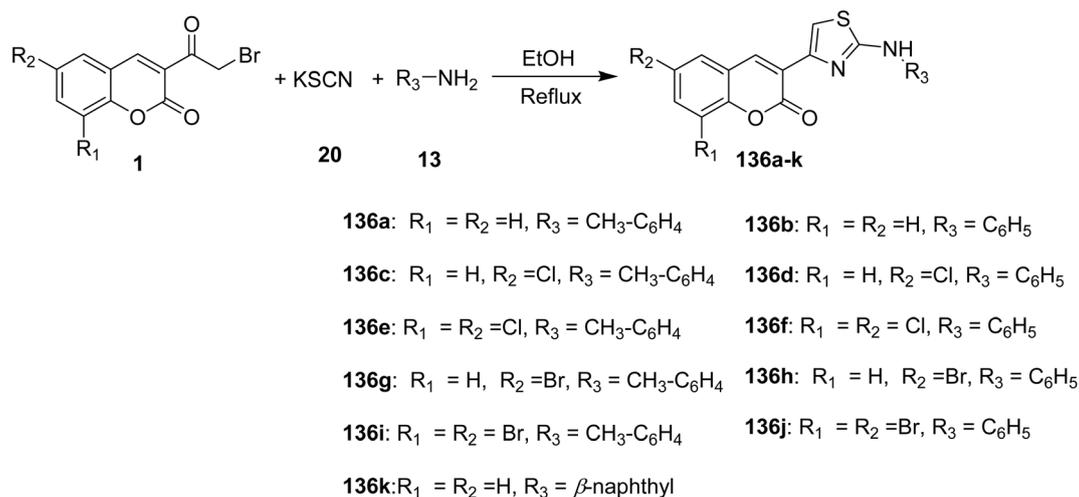
Scheme 56 Preparation of poly functionalized heterocyclic hybrids 135.

One-pot, synthesis of thiazolylhydrazone derivatives **125a-f** through multi-component condensation of 3-(bromoacetyl) coumarin derivatives **1**, thiosemicarbazide **112** and 1,3-indandione **124** in refluxing ethanol using a catalytic amount of acetic acid (Scheme 52).<sup>140</sup>

Multi-component synthesis of 3-(2-amino-4-thiazolyl) coumarins **127a-h** have been obtained in good yields by

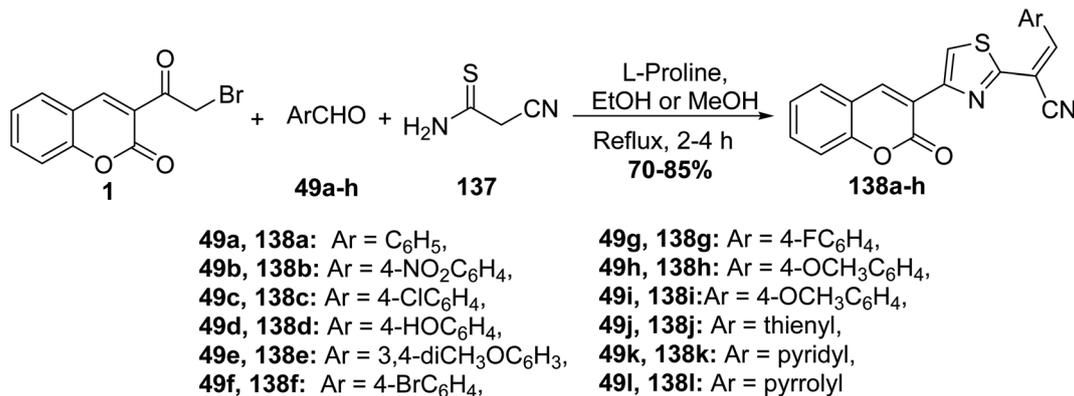
refluxing of 3-(bromoacetyl)coumarin derivatives **1**, trimethylsilyl isothiocyanate **126**, and different primary amines **13** in ethanol (Scheme 53).<sup>141</sup>

The reaction of 3-(bromoacetyl)coumarins **1** with phenylisothiocyanate **128** and aniline derivatives **13** afforded the thiazole derivatives **129a-d** (Scheme 54).<sup>70</sup> On the other hand, an efficient three-component synthesis of 2-arylimino-3-

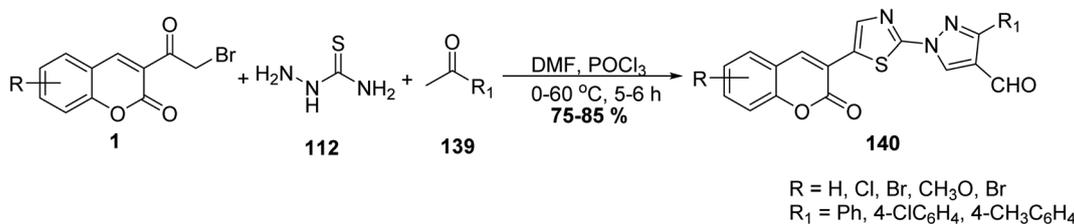


Scheme 57 Synthesis of 3-[2-(arylamino)thiazol-4-yl]coumarins 136a-k.

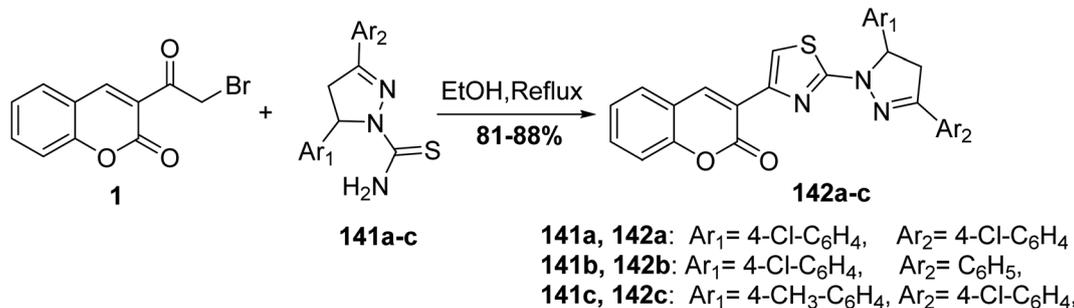




Scheme 58 Multi-component synthesis of chromen-3-thiazol-2-arylacrylonitriles 138.



Scheme 59 Vilsmeier-Haack reaction condition for the synthesis of products 140.



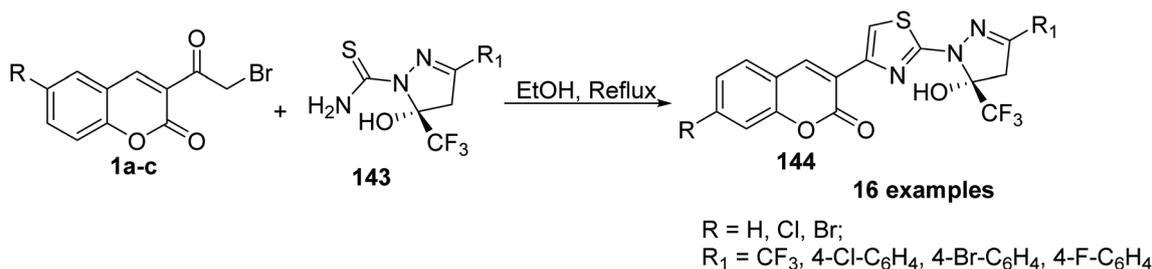
Scheme 60 Synthesis of 4,5-dihydropyrazolyl-thiazole-coumarin hybrids 142.

thiazolines **131** by the condensation of 3-(bromoacetyl) coumarin derivatives **1**, arylisothiocyanates **128**, and amine **130** (Scheme 54).<sup>142</sup>

A one-pot multi-component approach involving different substituted of 3-(bromoacetyl)coumarin derivatives **1**, phenyl

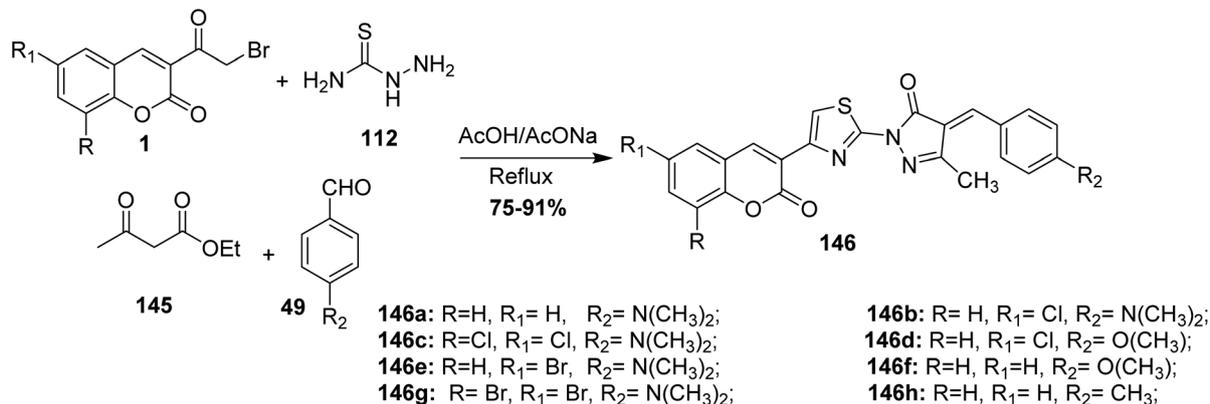
isothiocyanates **128**, and *p*-phenylenediamine **132** in refluxing DMF have been carried out for getting the new series of bis (phenylimino dihydro thiazolyl-2*H*-chromene) **133** (Scheme 55).<sup>143</sup>

Microwave irradiation was reported as a green chemistry method for the synthesis of coumarin-3-yl-thiazol-3-yl-1,2,4-

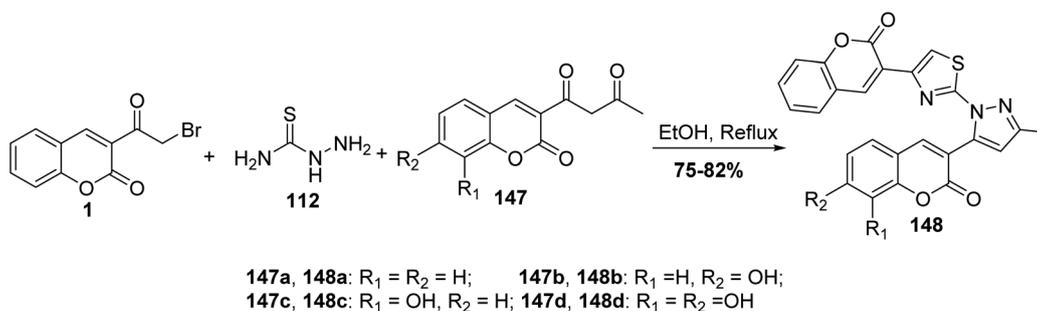


Scheme 61 Synthesis annulated 4-(coumarin-3-yl)thiazoles 144.





Scheme 62 Synthesis of coumarin bearing thiazol-pyrazolone moieties 146.



Scheme 63 Coumarin bearing pyrazole and thiazole hybrids 148.

triazolin-3-ones **135** by Shaikh *et al.*<sup>144</sup> via mixing of 3-(bromoacetyl)coumarin derivatives **1**, 1,2,4-triazolone, **134** and aryl isothiocyanate **128** in DMF without using a catalyst (Scheme 56).

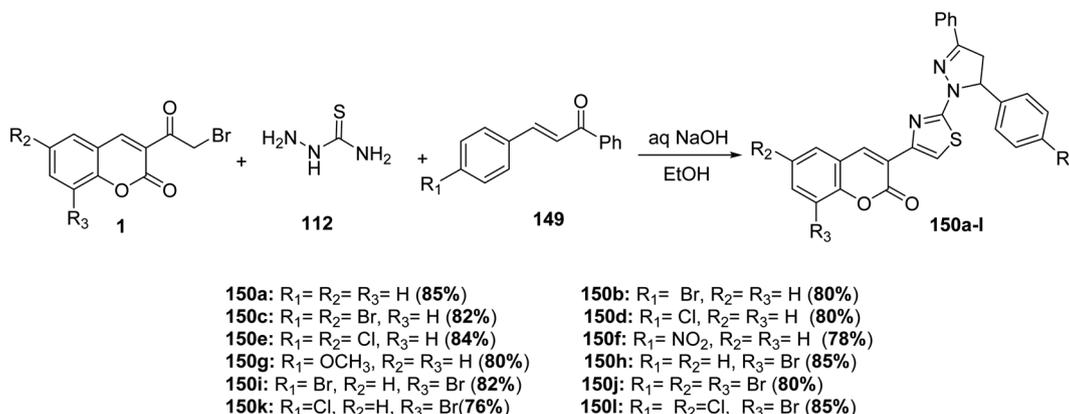
An efficient synthesis of 3-[2-(arylamino)thiazol-4-yl] coumarins **136a-k** via grinding of 3-(bromoacetyl)coumarin derivatives **1**, arylamines, **13** and potassium thiocyanate **20** in the least amount of ethanol as solvent under free catalyst and neat condition (Scheme 57).<sup>109</sup>

L-Proline catalyzed efficient one-pot three-component route for the synthesis of (2-oxo-2H-chromen-3-yl-thiazol-2-yl)-3-arylacrylonitriles **138a-h** via treating 3-(bromoacetyl)coumarin

**1** with numerous aryl/heteryl aldehydes **49** and 2-cyanothioacetamide **137** (Scheme 58).<sup>145</sup>

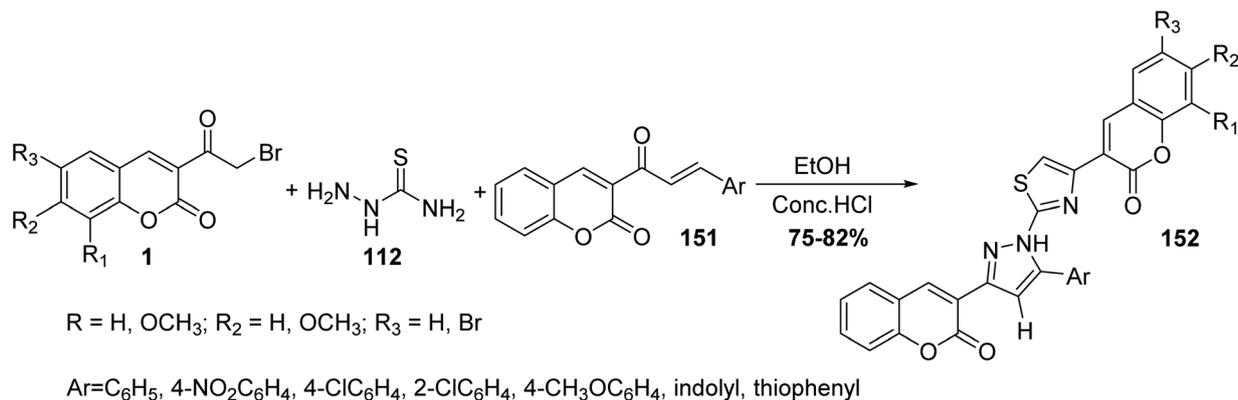
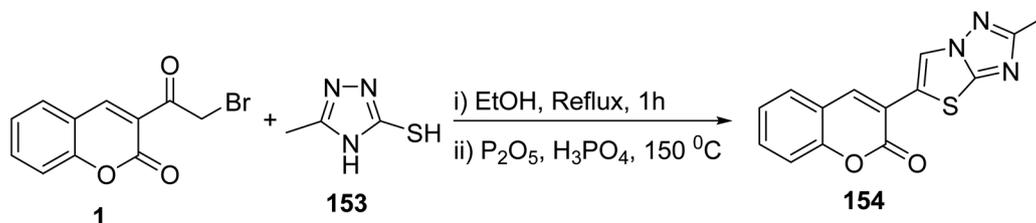
**5.10.3.5. Thiazolopyrazolones.** A mixture of 3-(bromoacetyl) coumarin derivatives **1**, acetophenones **139**, and thiosemicarbazide **112** were subjected to a one-pot multi-component Vilsmeier-Haack reaction condition afforded series of substituted thiazolyl-3-aryl-pyrazole-4-carbaldehydes bearing coumarin moiety **140** in moderate yields (Scheme 59).<sup>146</sup>

4,5-Dihydropyrazolyl-thiazole-coumarin systems **142** were obtained via the reaction of 3-(bromoacetyl)coumarin **1** and 3,5-

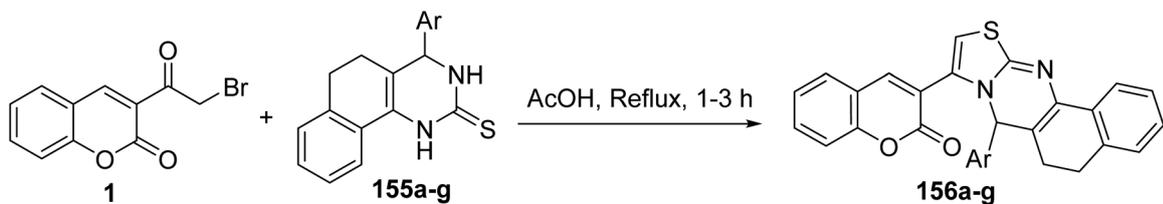
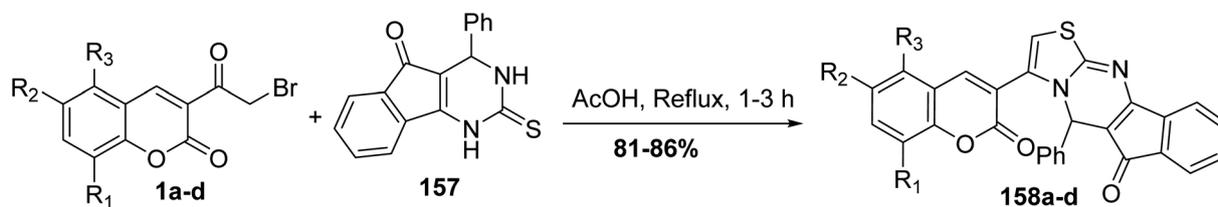


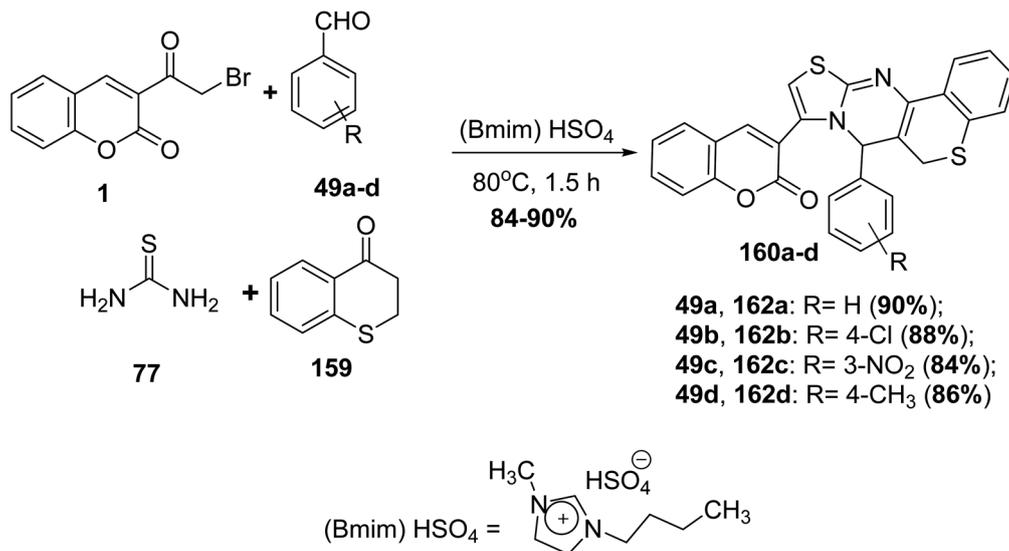
Scheme 64 Synthesis of binary pyrazol-1-thiazol-4-2H-chromen-2-one derivatives 150a-l.



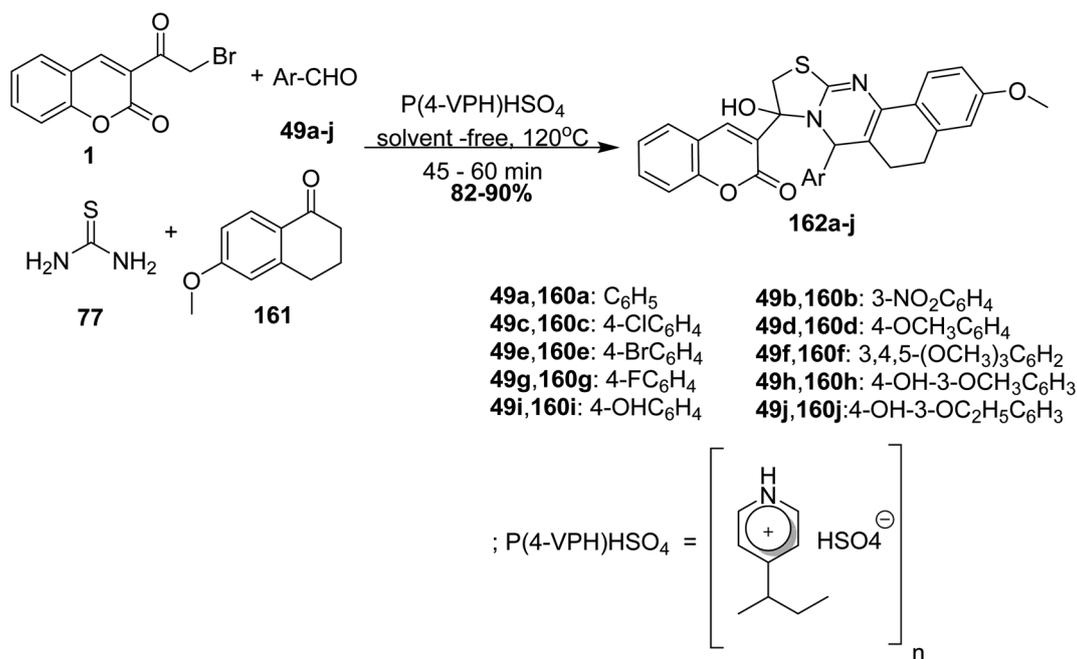
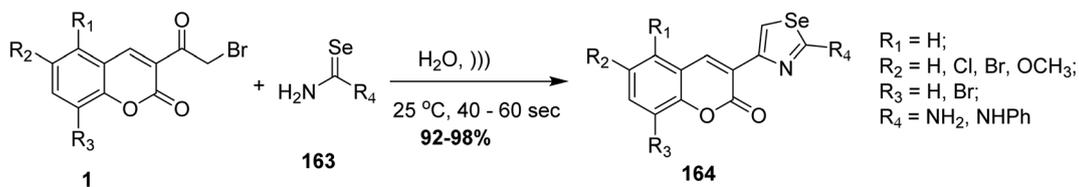
Scheme 65 Formation of (2*H*-chromen-5-phenyl-1*H*-pyrazol-thiazol-4-yl) chromenones 152.

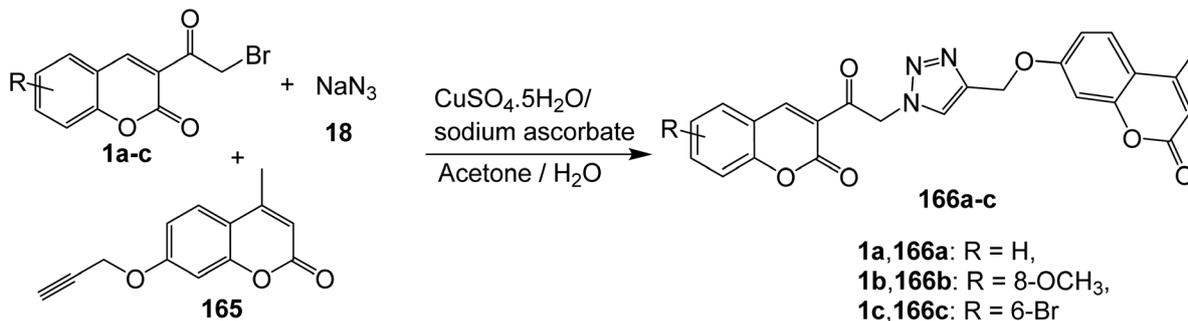
Scheme 66 Treatment of 3-(bromoacetyl)coumarin 1 with 5-phenyl-1,2,4-triazole-3-thiol 154.

**155a, 156a:** Ar = C<sub>6</sub>H<sub>5</sub> (88%)**155c, 156c:** Ar = 4-FC<sub>6</sub>H<sub>4</sub> (80%)**155e, 156e:** Ar = 3,4-(OCH<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub> (89%)**155g, 156g:** Ar = 4-ClC<sub>6</sub>H<sub>4</sub> (83%)**155b, 156b:** Ar = 4-OHC<sub>6</sub>H<sub>4</sub> (82%)**155d, 156d:** Ar = 4-OCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> (87%)**155f, 156f:** Ar = 4-OH-3-OCH<sub>3</sub>C<sub>6</sub>H<sub>3</sub> (88%)Scheme 67 Synthesis of fused thiazolo[3.2-*a*]pyrimidine derivatives 156.**1a, 158a:** R<sub>1</sub> = H, R<sub>2</sub> = H, R<sub>3</sub> = H**1b, 158b:** R<sub>1</sub> = OCH<sub>3</sub>, R<sub>2</sub> = Br, R<sub>3</sub> = H**1c, 158c:** R<sub>1</sub> = OCH<sub>3</sub>, R<sub>2</sub> = H, R<sub>3</sub> = H**1d, 158d:** R<sub>1</sub> = NO<sub>2</sub>, R<sub>2</sub> = NO<sub>2</sub>, R<sub>3</sub> = HScheme 68 Synthesis of phenylindeno[1,2-*d*]thiazolo[3,2-*a*]pyrimidin-6(5*H*)-ones 158.

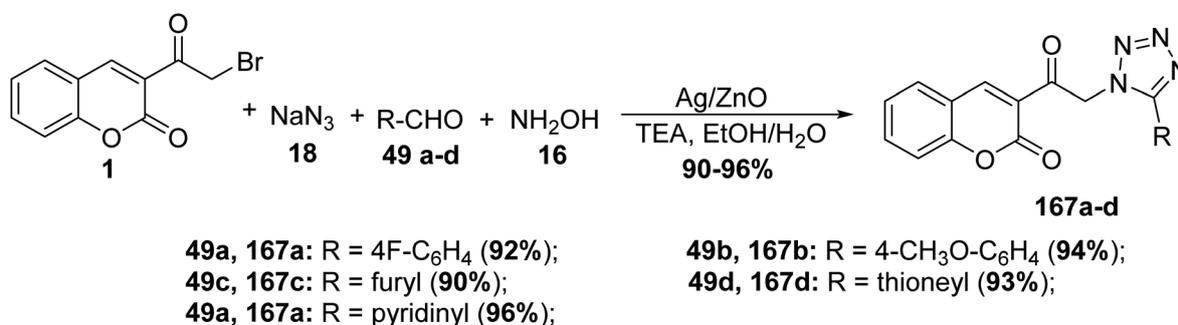


Scheme 69 One-pot four-component Biginelli reaction.

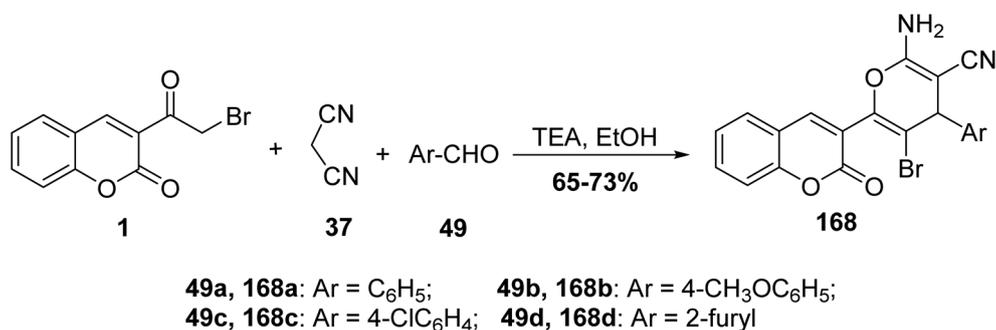
Scheme 70 Synthesis of fused thiazolo[2,3-*b*]quinazoline derivatives **162a-j**.Scheme 71 Formation of 2,4-disubstituted selenazoles **164**.



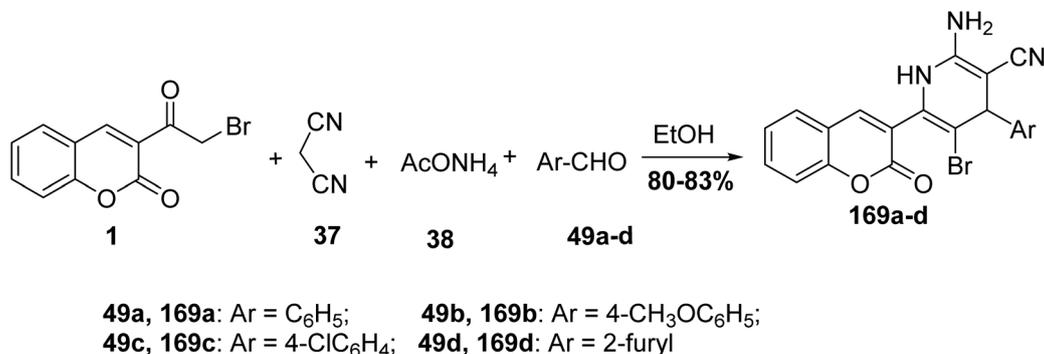
Scheme 72 Click cycloaddition reaction of 3-(bromoacetyl)coumarins 1a-c.



Scheme 73 Preparation of 1,5-disubstituted tetrazole 167.

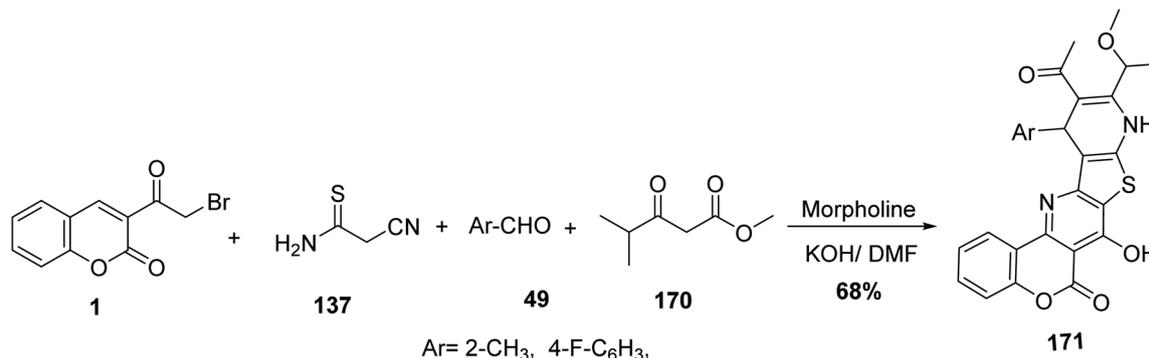


Scheme 74 Synthesis of 3-cyano-pyran derivatives 168.

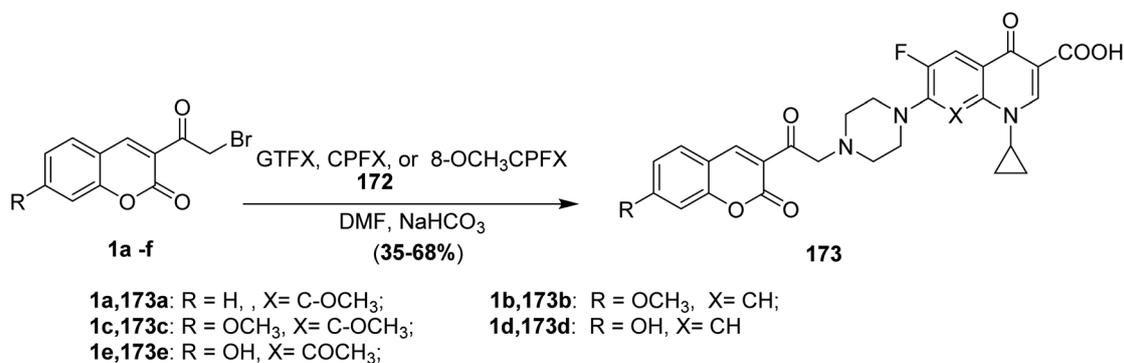


Scheme 75 Formation of pyridine derivatives 169a-d.





Scheme 76 Synthesis of pyridines 171.



Scheme 77 Formation of various fluoroquinolone derivatives 173.

disubstituted phenyl-4,5-dihydropyrazole-1-carbothioamide **141** in ethanol (Scheme 60).<sup>147</sup>

5-Hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-4-(coumarin-3-yl)thiazoles **144** were obtained by refluxing of 3-(bromoacetyl)coumarin derivatives **1** with 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-thiocarbonyl amides **143** in ethanol (Scheme 61).<sup>148</sup>

Synthesis of coumarin-substituted thiazolyl-pyrazolone derivatives **146** was reported by Pavurala *et al.* via a one-pot reaction of 3-(bromoacetyl)coumarin derivatives **1**, thiosemicarbazide **89**, aryl aldehyde **49**, and ethyl acetoacetate **145** in boiling acetic acid (Scheme 62).<sup>149</sup>

Series of pyrazoles bearing coumarin moieties **148** were prepared underwent Hantzsch cyclocondensation of 3-(bromoacetyl)coumarin **1**, thiosemicarbazide **112** and various 3-(acetoacetyl) coumarins **147** in refluxing ethanol (Scheme 63).<sup>150</sup>

One pot, three-component reaction of chalcones **149**, thiosemicarbazide **112**, and different substituted 3-(bromoacetyl) coumarin derivatives **1** in refluxing ethanol containing catalytic amount of aqueous sodium hydroxide was achieved as an effective route for the synthesis of 4,5-dihydro-3,5-diphenylpyrazol-1-thiazol-4-2*H*-chromen-2-one derivatives **150a-l** in one step (Scheme 64).<sup>149</sup>

In the same fashion, Ghodsi *et al.* have been reported the synthesis of fused substituted thiazolyl-pyrazole-biscoumarin **152** through cyclocondensation of different coumarin chalcones **151**, thiosemicarbazide **112**, and 3-(bromoacetyl)

coumarin derivatives **1** in ethanol in the presence of hydrochloric acid (Scheme 65).<sup>151</sup>

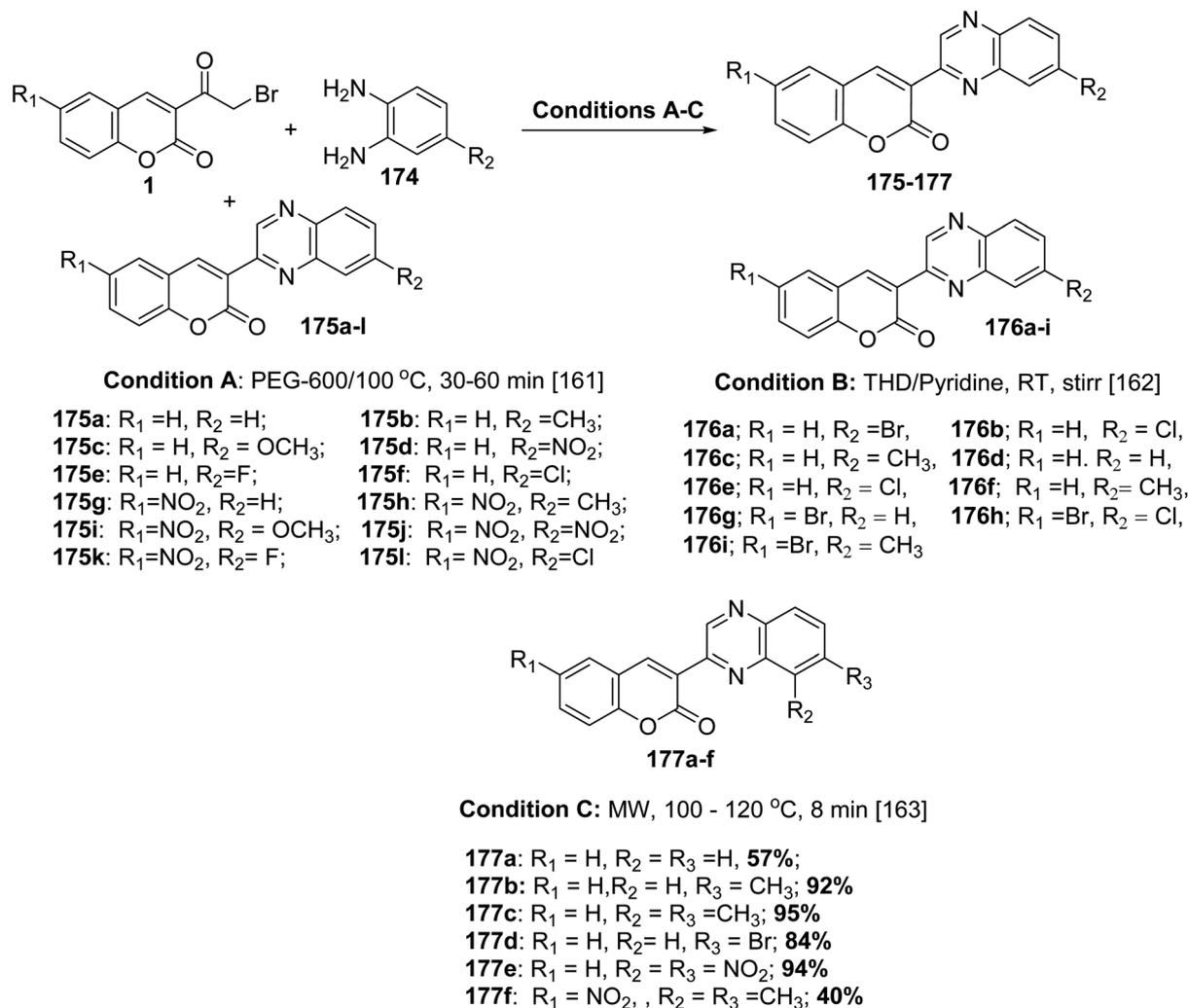
**5.10.3.6. Thiazolotriazoles.** On the other hand, the reaction of 3-(bromoacetyl)coumarin **1** with 5-phenyl-4*H*-1,2,4-triazole-3-thiol **153** gave fused thiazolo[3,2-*b*] [1,2,4]triazol-5-chromenone **154** (Scheme 66).<sup>152</sup>

**5.10.3.7. Thiazolopyrimidines.** Novel fused thiazolo[3,2-*a*] pyrimidines **156a-g** have been obtained in good yields by treatment of 3-(bromoacetyl)coumarin **1** with aryl-3,4-dihydropyrimidin-2(1*H*)-thiones **155a-g** under conventional heating in acetic acid as solvent (Scheme 67).<sup>153,154</sup>

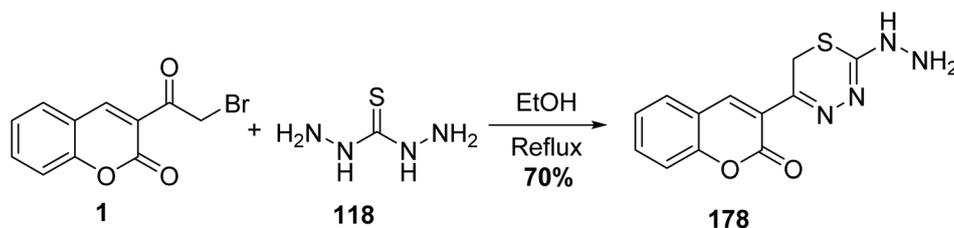
The cyclocondensation reaction of 3-(bromoacetyl)coumarin derivatives **1** with 4-phenyl-2-thioxo-indeno[1,2-*d*]pyrimidinone **157** in boiling acetic acid furnished phenylindeno[1,2-*d*]thiazolo[3,2-*a*]pyrimidin-6(5*H*)-ones **158** in high yields (Scheme 68).<sup>155</sup>

A new version of the Biginelli reaction using new variants was applied for the synthesis of substituted thiazolo[3,2-*a*]thiochromeno[4,3-*d*]pyrimidine **160a-d** through mixing an equimolar ratio of 3-(bromoacetyl)coumarin **1**, thiochromanone **159**, substituted benzaldehyde **49a-d** and thiourea **77** in one-pot reaction in the presence of [Bmim]HSO<sub>4</sub> as a mediated ionic liquid catalyst, leading to the formation of a double electrophilic pyrimidine-2(5*H*)-thione as an intermediate which cyclized directly to furnish the targeting products **160a-d** (Scheme 69).<sup>157</sup>





Scheme 78 Synthesis of 3-(quinoxalin-2-yl)-2H-chromen-2-ones 175–177.



Scheme 79 Formation of 3-(2-hydrazino-6H-[1,3,4]thiadiazin-5-yl)-chromen-2-one 178.

**5.10.3.8. Thiazoloquinazolines.** Biginelli reaction of 3-(bromoacetyl)coumarin **1**, aryl aldehyde **49a-j**, thiourea **77** and 6-methoxy-1-tetralone **161** in the presence of in poly(4-vinylpyridinium)hydrogen sulfate [P(4-VPH)H<sub>2</sub>SO<sub>4</sub>] as Brønsted acid catalyst under neat condition afforded aryl-thiazolo[2,3-*b*]quinazoline derivatives **162a-j** (Scheme 70).<sup>156</sup>

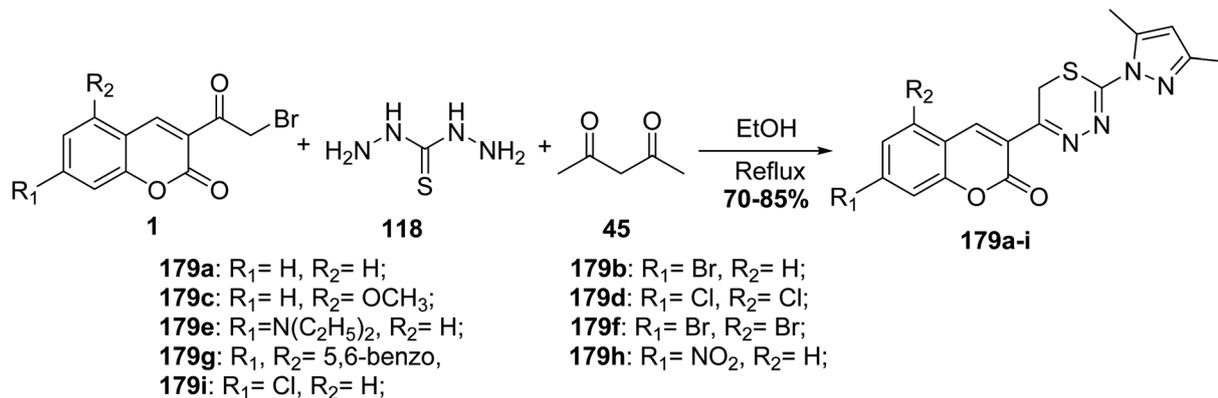
**5.10.3.9. Selenazoles.** An efficient synthesis of functionalized selenazoles **164** was achieved *via* ultrasonic irradiation of 3-(bromoacetyl)coumarin **1** with selenourea **163** at ambient

temperature an aqueous medium under ultrasonic irradiation (Scheme 71).<sup>99</sup>

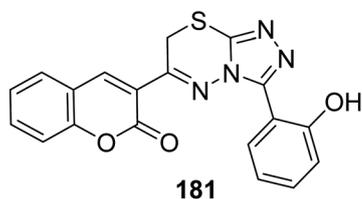
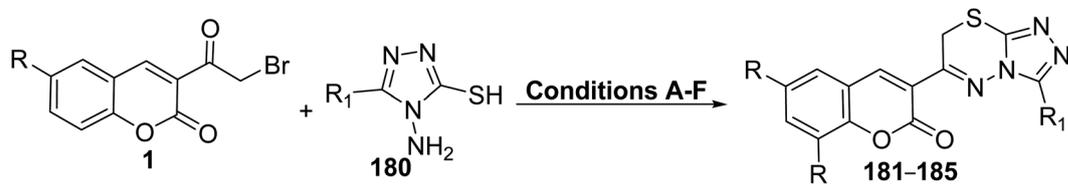
#### 5.10.4. Synthesis of five-membered rings with three heteroatoms

**5.10.4.1. Triazoles.** Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction of 3-(bromoacetyl)coumarin derivatives **1**, sodium azide **18**, and coumarin propargyl ethers **165** has been employed for the construction of bis-coumarinyl triazoles **166** (Scheme 72).<sup>158</sup>

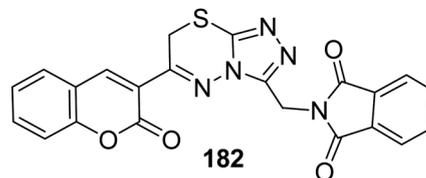




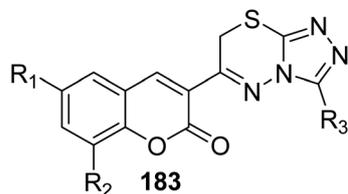
Scheme 80 Synthesis of pyrazolyl-thiadiazinyl-2H-chromenone derivatives 179a–i.



**Condition A:** AcOH/ EtOH, Reflux, 2h [166]



**Condition B:** EtOH, Et<sub>3</sub>N, Reflux [167]



**Condition C:** EtOH, Reflux [168]

**183a:**  $R_1, R_2 = \text{H}; R_3 = \text{C}_2\text{H}_4\text{SH}$ , **82%**

**183b:**  $R_1 = \text{H}; R_2 = \text{OCH}_3; R_3 = \text{C}_2\text{H}_4\text{SH}$ , **80%**

**183c:**  $R_1 = \text{Br}; R_2 = \text{H}; R_3 = \text{C}_2\text{H}_4\text{SH}$ , **90%**

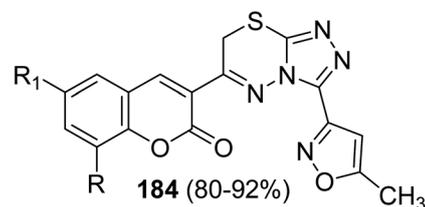
**183d:**  $R_1, R_2 = \text{Br}; R_3 = \text{C}_2\text{H}_4\text{SH}$ , **92%**

**183e:**  $R_1, R_2 = \text{H}, R_3 = \text{CH}_2\text{CH}(\text{CH}_3)\text{SH}$  **86%**

**183f:**  $R_1 = \text{H}; R_2 = \text{OMe}; R_3 = \text{CH}_2\text{CH}(\text{CH}_3)\text{SH}$  **85%**

**183g:**  $R_1 = \text{Br}; R_2 = \text{H}; R_3 = \text{CH}_2\text{CH}(\text{CH}_3)\text{SH}$  **89%**

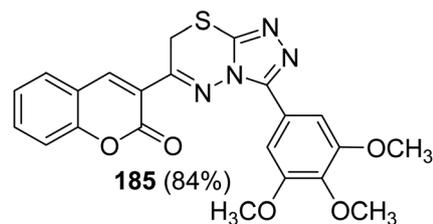
**183h:**  $R_1, R_2 = \text{Br}, R_3 = \text{CH}_2\text{CH}(\text{CH}_3)\text{SH}$  **92%**



**Condition E:** EtOH, Reflux [169]

$R = \text{H}, \text{Br}, \text{Cl}, \text{OCH}_3, \text{NO}_2, \text{C}(\text{CH}_3)_3$

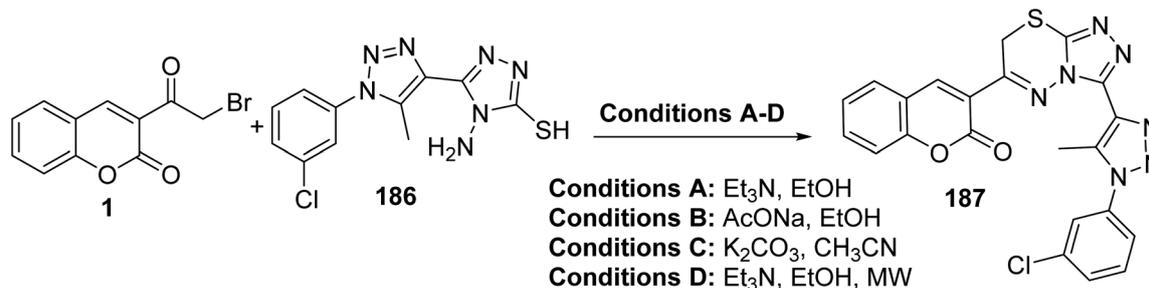
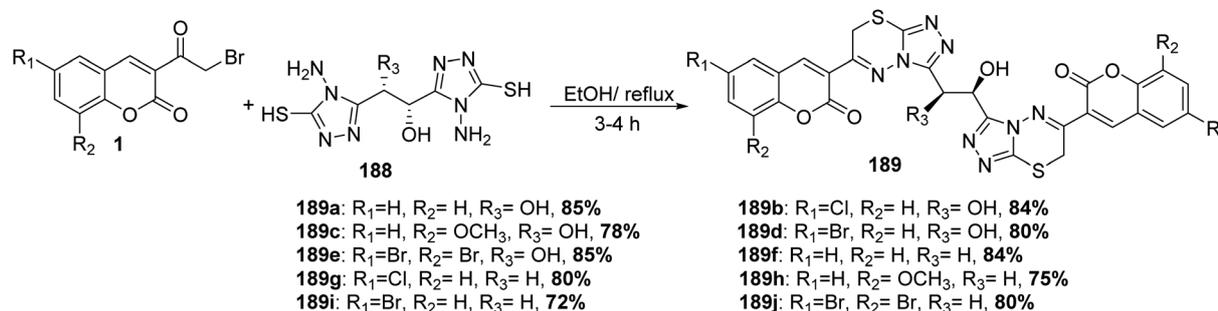
$R_1 = \text{H}, \text{Br}, \text{Cl}, \text{OCH}_3, \text{NO}_2, \text{C}(\text{CH}_3)_3$



**Condition F:** EtOH/ Reflux [47]

Scheme 81 Synthesis of coumarin[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine hybrids 181–185.



Scheme 82 Formation of triazolo[3,4-*b*]thiadiazines 187.

Scheme 83 Synthesis of bis coumarinyl bis triazolothiadiazinyl ethane derivatives 189.

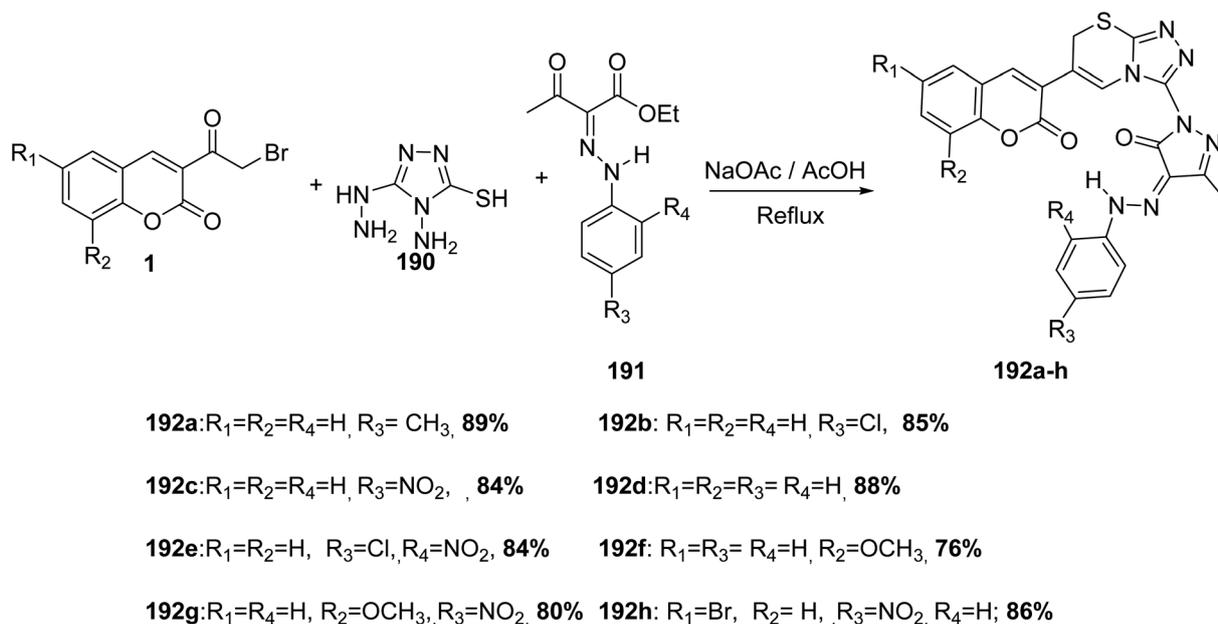
### 5.10.5. Synthesis of five-membered rings with four heteroatoms

**5.10.5.1. Tetrazoles.** 1,5-Disubstituted tetrazole based chromone derivatives **167a-d** were synthesized employing four-component condensation of 3-(bromoacetyl)coumarin **1**, aldehyde derivatives **49a-d**, sodium azide **18**, and hydroxylamine **16** in ethanol containing catalytic drops of trimethylamine, the

reaction was supported by nanorods of zinc oxide (NRs) and Ag-doped ZnO nanocomposites (NCs) as photocatalysts (Scheme 73).<sup>159</sup>

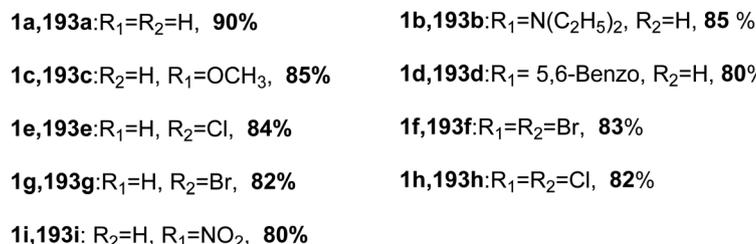
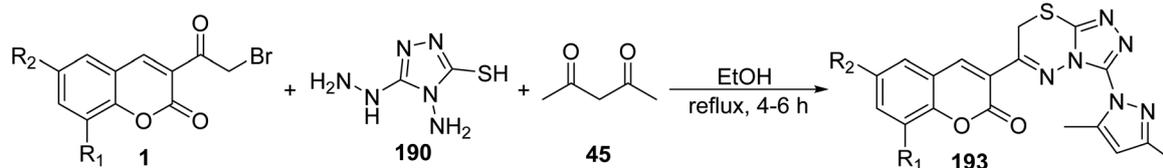
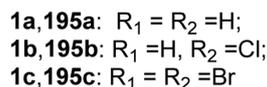
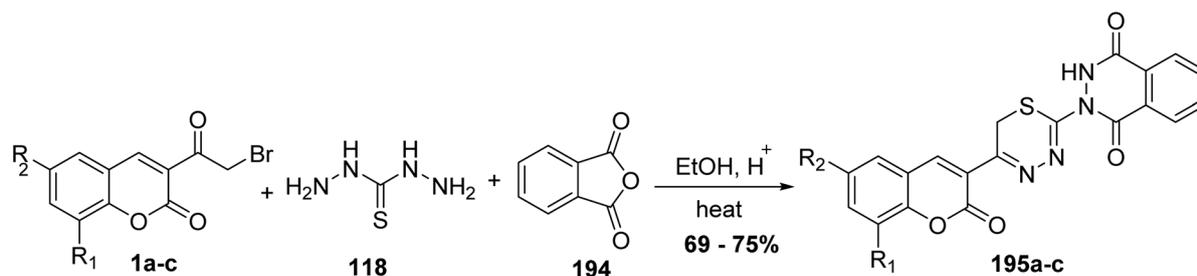
### 5.10.6. Synthesis of six-membered rings with one heteroatom

**5.10.6.1. Pyran derivatives.** Mohareb and MegallyAbdo<sup>70</sup> described the preparation of 2-amino-3-cyano-pyran derivatives



Scheme 84 Synthesis of triazolothiadiazinyl-pyrazolone 192a-h.



Scheme 85 One-pot synthesis of series of fused pyrazolyl triazolo thiadiazinyl chromenones **193**.Scheme 86 Multi-component reaction for the synthesis of thiadiazinyl-phthalazine-1,4-diones **195**.

**168** using three-component reactions of 3-(bromoacetyl) coumarin **1** with malononitrile **37** and aromatic aldehydes **49** in boiling ethanol containing catalytic drops of trimethylamine (Scheme 74).

5.10.6.2. *Pyridines*. On the other hand, repeating the previous reaction using a catalytic amount of ammonium

acetate **38** *in lieu* of triethylamine afforded the pyridine systems **169a-d** (Scheme 75).<sup>70</sup>

Multicomponent condensation of 3-(bromoacetyl)coumarin **1**, cyanothioacetamide **137**, benzaldehyde derivatives **49** and methyl 4-methyl-3-oxopentanoate **170** led to formation of fused chromeno[3'':4'':5',6']pyrido[2':3':4,5]thieno[3,2-e]pyridine derivatives **171** (Scheme 76).<sup>160</sup>

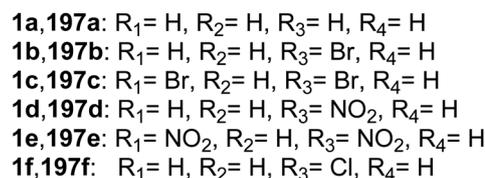
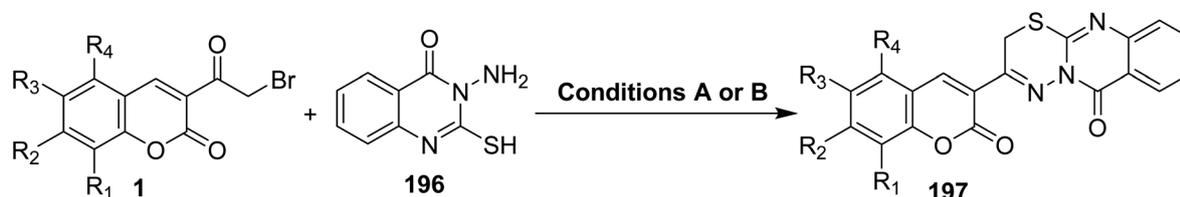
Scheme 87 Synthesis of chromenothiadiazino[2,3-b]quinazolin-6-ones **197**.



Table 1 Examples of a vast array of biologically active molecules towards some diseases

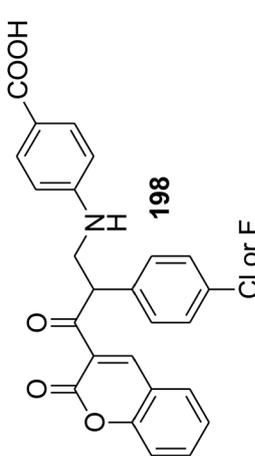
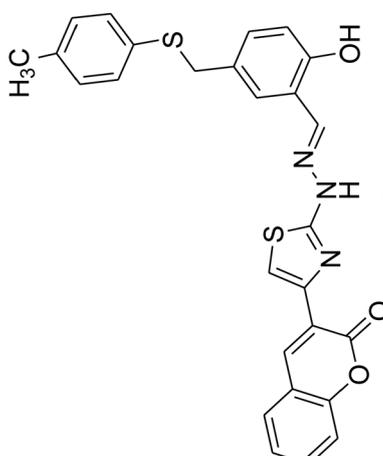
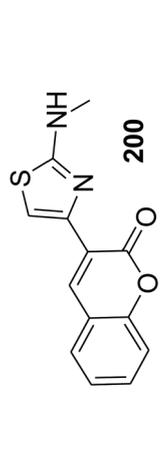
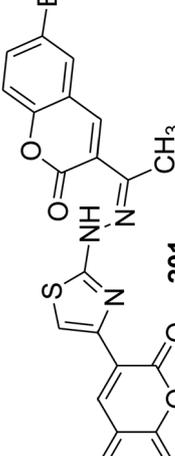
Structures	Activities	Ref.
 198	Antibacterial activity against: ( <i>E. coli</i> , <i>S. aureus</i> and <i>P. aeruginosa</i> ) Antifungal activity against: ( <i>A. flavus</i> , <i>C. keratinophilum</i> , and <i>C. albicans</i> ) Antioxidant activity: (moderate potency in scavenging DPPH radical (approximately 65%))	175
 199	Antibacterial activity (zone of inhibition, ZI) against: <i>S. aureus</i> , ZI = 36.8 ± 0.6 mm • <i>S. mutans</i> , ZI = 25.4 ± 0.5 mm • <i>K. pneumoniae</i> , ZI = 27.2 ± 0.5 mm • <i>E. coli</i> , ZI = 26.3 ± 0.5 mm	176
 200	Anti-influenza A virus H1N1: IC <sub>50</sub> = 4.84 µg mL <sup>-1</sup> in MDCK cells	108
 201	Antimicrobial agents: <i>M. tuberculosis</i> (MIC = 15 µM)	177



Table 1 (Contd.)

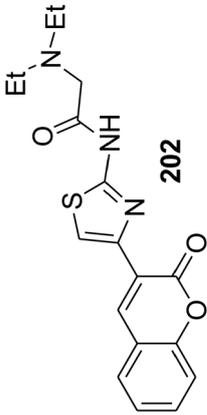
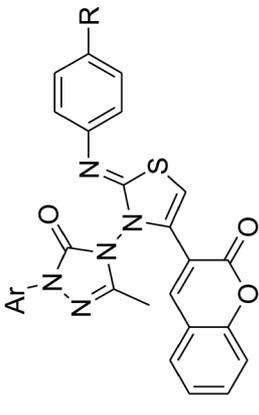
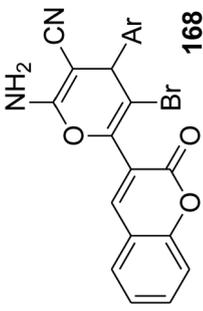
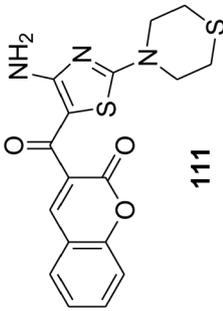
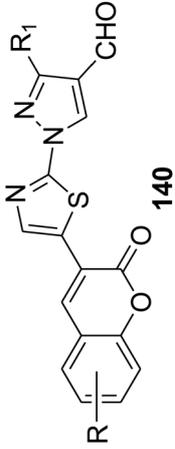
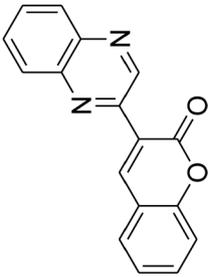
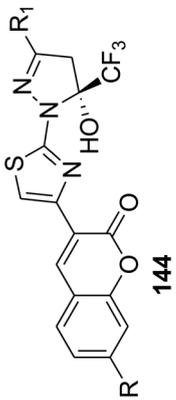
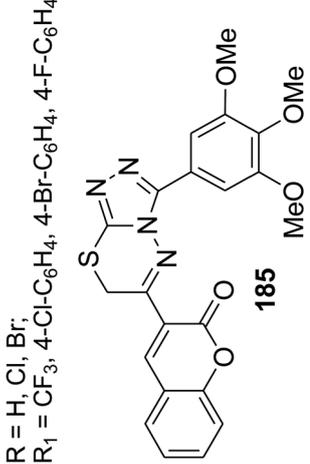
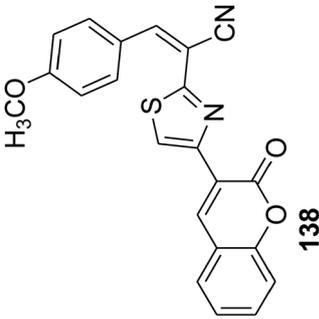
Structures	Activities	Ref.
 <p><b>202</b></p>	<p>Anti-Alzheimeractivity: anti-cholinesterases (IC<sub>50</sub> = 43 nM)</p> <p>Anticancer activity against</p> <ul style="list-style-type: none"> <li>• Breast cancer</li> <li>• Lung cancer</li> <li>• Leukemia</li> <li>• Human cervical cancer</li> </ul>	178
 <p><b>135</b></p> <p>Ar = Ph, 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub></p> <p>R = H, 4-CH<sub>3</sub>O, 4-Br, 4-CH<sub>3</sub></p>	<p>Anticancer activity against human gastric cancer NUGC</p> <ul style="list-style-type: none"> <li>• 168a: Ar = 2-furyl, IC<sub>50</sub> = 29 nM (against human gastric cancer NUGC)</li> <li>• 168b: Ar = 4-Cl-C<sub>6</sub>H<sub>4</sub>, IC<sub>50</sub> = 89 nM (against MCF)</li> </ul>	70
 <p><b>168</b></p>	<p>Anticancer activity (against MCF-7, HepG2 and SW480 cells); IC<sub>50</sub> = 7.5–16.9 μg mL<sup>-1</sup></p>	132
 <p><b>111</b></p>		

Table 1 (Contd.)

Structures	Activities	Ref.
 <p style="text-align: center;"><b>140</b></p>	<p>Anticancer activity (against HeLa cell line)</p> <ul style="list-style-type: none"> <li>• <math>R = 6,8\text{-diCl}</math>, <math>R_1 = 4\text{-MeC}_6\text{H}_4</math>, <math>\text{IC}_{50} = 5.75 \mu\text{M}</math></li> <li>• <math>R = 6,8\text{-diBr}</math>, <math>R_1 = 4\text{-MeC}_6\text{H}_4</math>, <math>\text{IC}_{50} = 6.25 \mu\text{M}</math></li> </ul>	146
 <p style="text-align: center;"><b>176</b></p>	Anticancer activity (against Melanoma tumor cell line): 55.75% GI	99
 <p style="text-align: center;"><b>144</b></p>	Anti-inflammatory agents: 73–86% of inhibition after 1 h	148
 <p style="text-align: center;"><b>185</b></p>	Antiproliferative activity: $\text{IC}_{50} = 10.364 \pm 0.270 \mu\text{M}$	170
 <p style="text-align: center;"><b>138</b></p>	Anti-hepatocarcinoma activity: $\text{IC}_{50} = 2.33 \pm 0.004 \mu\text{M}$	145

$R = \text{H, Cl, Br};$   
 $R_1 = \text{CF}_3, 4\text{-Cl-C}_6\text{H}_4, 4\text{-Br-C}_6\text{H}_4, 4\text{-F-C}_6\text{H}_4$



### 5.10.7. Synthesis of six-membered rings with two heteroatoms

**5.10.7.1. Fluoroquinolone derivatives.** Nucleophilic substitution reactions of fluoroquinolones **172** (GTFX, CPFX, and 8-OCH<sub>3</sub>CPF<sub>X</sub>) with 3-(bromoacetyl)coumarin derivatives **1** in dimethylformamide, in the presence of NaHCO<sub>3</sub>, provide fluoroquinolone derivatives **173** (Scheme 77).<sup>62</sup>

**5.10.7.2. 3-(Quinoxalin-2-yl)-2H-chromen-2-ones.** 3-(Quinoxalin-2-yl)-2H-chromen-2-ones **175-177** have been synthesized *via* substituted 3-(bromoacetyl)coumarins **1** and substituted *o*-phenylenediamines **174** in the presence of a catalyst such as PEG-600 or pyridine or without catalyst through microwave irradiation (Scheme 78).<sup>161-163</sup>

### 5.10.8. Synthesis of six-membered rings with three heteroatoms

**5.10.8.1. Thiadiazin derivatives.** One-pot condensation reaction between 3-(bromoacetyl)coumarin **1** and thiocarbohydrazide **118** as bishydrazide in ethanol and in the presence a catalytic amount of acetic acid afforded 2-hydrazino[1,3,4]thiadiazin-5-chromenone **178** (Scheme 79).<sup>164</sup>

**5.10.8.2. Pyrazolyl-thiadiazine derivatives.** Refluxing of an equimolar mixture of substituted 3-(bromoacetyl)coumarins **1**, acetylacetone **45**, and thiocarbohydrazide **118** in ethanol furnished pyrazolyl-thiadiazinyl-2H-chromenones **179a-i** (Scheme 80).<sup>165</sup>

**5.10.8.3. Triazolol[3,4-*b*]thiadiazines.** Series of functionalized 4-amino-4H-1,2,4-triazole-3-thiols **180** on reaction with substituted 3-(bromoacetyl)coumarins **1** under simple reaction conditions formed the title products coumarin-substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine hybrids **181-185** in good to excellent yields (Scheme 81).<sup>47,166-169</sup>

Triazolol[3,4-*b*]thiadiazine **187** was produced from the treatment of 3-(bromoacetyl)coumarin **1** with 4-aminotriazole-3-

thiol **186** under both conventional and microwave conditions (Scheme 82).<sup>170</sup>

Bis coumarinyl bis triazolothiadiazinyl ethane derivatives **189** were synthesized through the reaction of ethane-1,2-diyl bis-4-amino-4H-1,2,4-triazole-3-thiols **188** with different substituted 3-(bromoacetyl)coumarin derivatives **1** in the presence of ethanol solvent (Scheme 83).<sup>165</sup>

A one-pot, multi-component reaction of 3-(bromoacetyl)coumarins **1**, 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol **190** and various ethyl 2-(2-(aryl)hydrazono)-3-oxobutanoate derivatives **191** in acetic acid in the presence of sodium acetate provide a direct route for the synthesis of corresponding triazolothiadiazinyl-pyrazolone **192a-h** (Scheme 84).<sup>171</sup>

Pavurala and Vedula<sup>172</sup> disclosed multi-component one-pot synthesis of pyrazolyl triazolo thiadiazinyl chromen-2-ones **193** was achieved *via* the multi-component reaction of 3-(bromoacetyl)coumarins **1**, 4-amino-5-hydrazino-4H-[1,2,4]triazole-3-thiol **190** and acetylacetone **45** in absolute ethanol (Scheme 85).

**5.10.8.4. Thiadiazinyl-phthalazine-1,4-diones.** Rao Chunduru and Rao<sup>173</sup> reported the synthesis of thiadiazinyl-phthalazine-1,4-dione derivatives **195** *via* one-pot condensation reaction of 3-(bromoacetyl)coumarins **1**, thiocarbohydrazide **118**, and phthalic anhydride **194** in ethanol containing a catalytic amount of acetic acid (Scheme 86).

**5.10.8.5. Thiadiazino[2,3-*b*]quinazolin-6(2H)-ones.** An efficient one-pot synthesis of chromenyl[1,3,4]thiadiazino[2,3-*b*]quinazolin-6(2H)-ones **197** in high yields through cyclocondensation of 3-(bromoacetyl)coumarins **1** with 3-amino-2mercapto-3H-quinazolin-4-one **196** under the conventional and microwave conditions in the presence of potassium carbonate (Scheme 87).<sup>174</sup>

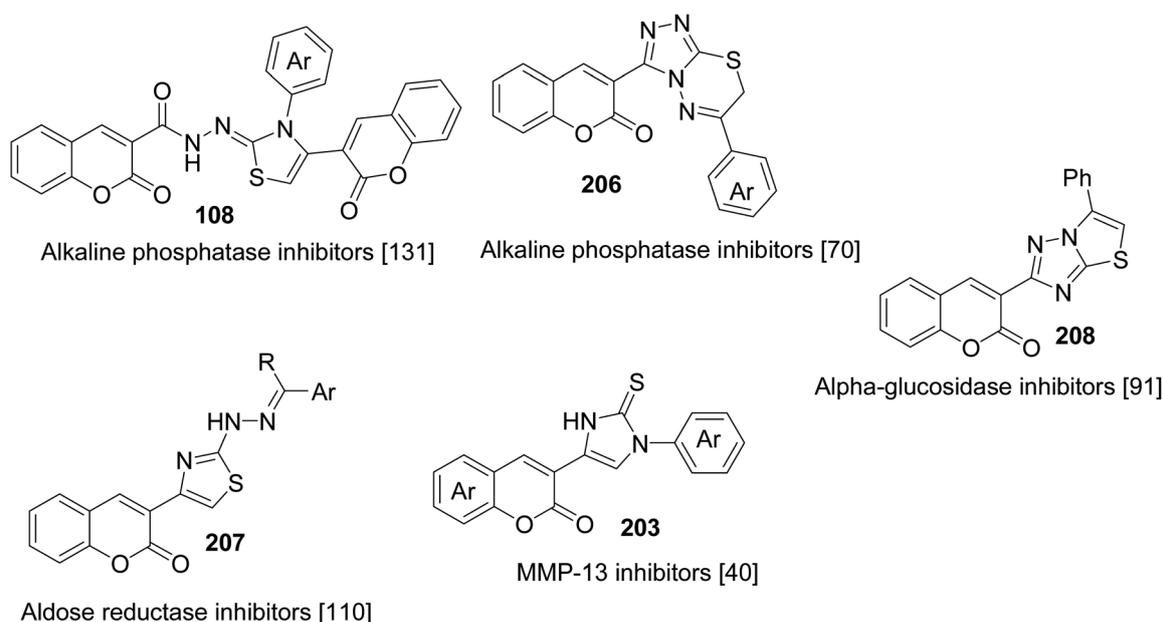
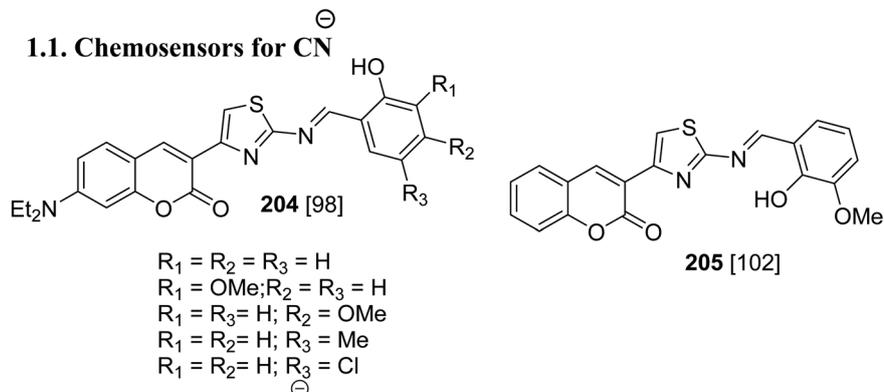


Fig. 6 Representative inhibitors of metalloproteinase with significant inhibitory effects.

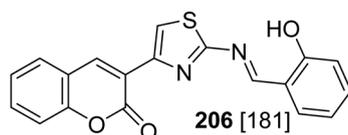


## 1. Fluorescent Chemosensors for Anions

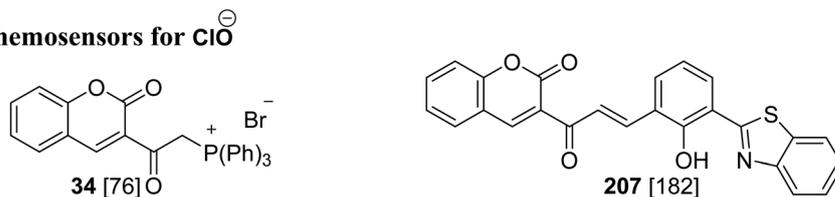
### 1.1. Chemosensors for CN<sup>⊖</sup>



### 1.2. Chemosensors for F<sup>⊖</sup>

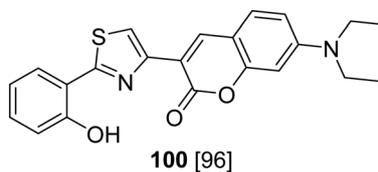


### 1.3. Chemosensors for ClO<sup>⊖</sup>

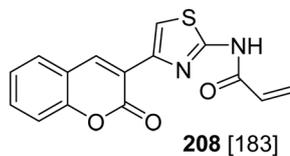


## 2. Fluorescent Chemosensors for Metal Ions

### 2.1. Chemosensors for Cu<sup>2+</sup>/Cu<sup>+</sup>



### 2.2. Chemosensors for Hg<sup>2+</sup>



## 3. Fluorescent Chemosensors for Biological Thiols

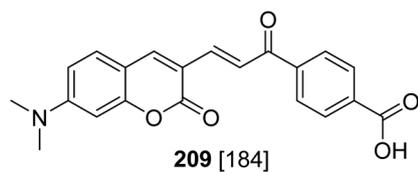


Fig. 7 Fluorescent chemosensors towards metal cations, anions, and biomolecules.



## 6. Applications

### 6.1. Biological activities

3-(Bromoacetyl)coumarins are being employed as privileged building blocks for the production of several bioactive heterocyclic compounds with a broad spectrum of medicinal agents including antibacterial, antifungal, antioxidant, anticancer, anti-inflammatory, anti-hepatocarcinoma, and antiproliferative agents (Table 1). Moreover, many approaches have also been explored for the construction and synthesis of a diverse range of inhibitors of metalloproteinase with significant inhibitory effects. These as a versatile scaffold include, for example, alkaline phosphatase,<sup>131</sup> aldose reductase,<sup>110</sup> alpha-glucosidase,<sup>91</sup> and MMP-13 (ref. 40) inhibitors (Fig. 6).

### 6.2. Analytical applications

3-(Bromoacetyl)coumarin and 3-bromoacetyl-7-methoxycoumarin were used for the analysis of an emerging contaminant, perfluorinated substances.<sup>179,180</sup> 3-(Bromoacetyl)coumarins are versatile scaffolds with pivotal templates which have a vast array of applications in the field of fluorescent chemosensors towards metal cations, anions, and biomolecules<sup>181–184</sup> (Fig. 7).

## 7. Conclusion

This review has illuminated different aspects of 3-bromoacetyl coumarin **1** and its derivatives chemistry up to the beginning of 2021. It implies many sections on the synthesis of bromoacetyl coumarin derivatives. Besides different chemical reactions of bromoacetyl coumarins with various reagents, their biological evaluations and analytical application have been presented. Eventually, we hope that showcasing information accumulated over the years in developing 3-(bromoacetyl)coumarins core ranging from chemistry to applications will supplement the ongoing and forthcoming efforts towards the advancement of new functional molecular materials in the industry, biochemistry, and the environment.

## Conflicts of interest

There are no conflicts to declare.

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