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.

1. Introduction

Coumarins are one of the most common host heterocyclic systems reported in the literature of organic chemistry. Furthermore, coumarins and their derivatives are seen to be the pivotal components of a plethora of many natural products and pharmaceuticals and synthetic dyes. The pharmacological activities discovered amongst coumarin derivatives include the treatment categories of Alzheimer’s and haematopoietic necrosis (IHN); they have shown potent anticoagulant, antibiotic, antiemolic, antiosidative, and anti-ischemic activities. Among these compounds, 3-(bromoacetyl)coumarin 1 and its derivatives are a prominent structural class in the synthesis of various bioactive heterocyclic scaffolds. They also are important components in drug discovery due to their biological activities such as antiproliferative, antimicrobial activities, and are promising inhibitors of type 2 diabetes mellitus. In addition, numerous chemosensors are based on polyfunctional coumarin platforms used to detect multianalyte detection, such as different bioactive elements and various environmental pollutants. 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 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, 1H NMR, 13C NMR, and Mass) of 3-(bromoacetyl) coumarin. 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⁻¹ (ref. 29) and two carbonyl characteristic peaks at ν 1674 and 1729 cm⁻¹ related to α,β-unsaturated ketonic and lactonic, respectively. 1H NMR spectrum of parent 3-(bromoacetyl)coumarin 1 shows singlet signal of H-4 at δ = 8.63 ppm, while the CH₂ group appears as singlet signal at δ = 4.74 ppm. Also, 13C NMR spectrum of 3-(bromoacetyl)coumarin exhibits characteristic signals at δ = 188.9, 158.9, and 35.6 ppm corresponding to α,β-unsaturated ketonic, lactonic and methylene carbons, respectively. In the same context, HRMS/MS is mentioned as characteristic spectrometric data for 3-(bromoacetyl)coumarin 1 shows m/z 266.9665 (calcd. for C₁₁H₈BrO₃ [M + H]⁺ 266.9657). In 1991, Vasudevan et al. 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 reported a polymorph of 3-(bromoacetyl)coumarin (Fig. 3). Whereas, Chennuru et al.
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 (PhTAPBr₃), N-bromosuccinimide (NBS), and copper(II) bromide (CuBr₂) (Scheme 1).

35–47

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 (CH₂Br) (position 2), lactonic carbonyl group (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 α-bromoacetylcoumarin towards oxygen, nitrogen, and sulphur nucleophiles is discussed in this review.

5. Reactions

5.1. Amination

Sinnur et al.48 reported a short and efficient synthesis for aminomethyl-3-coumarinyl ketone hydrochloride 4 via
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-aminothiazole, 2-aminobenzothiazole, 2-amino-1,3,4-oxadiazole, 2-amino-1,3,4-thiadiazole, and 3-amino-4H-1,2,4-triazole derivatives in DMF to give the corresponding 2H-chromen-2-ones 6 (Scheme 3).\(^{50,51}\)

Selective nucleophilic substitution of 3-(bromoacetyl)coumarin 1 was accomplished through stirring with benzimidazole 9 in acetonitrile at ambient temperature afforded the corresponding imidazole-1-carbonyl-chromenone 10 (Scheme 5).\(^{52}\)

Valadbeigi \textit{et al.}\(^{53}\) reported the synthesis of thiazolidinedione derivatives 12 through heating of 3-(bromoacetyl)coumarin 1...
The reaction of the 3-(bromoacetyl)coumarin derivatives \(1\) with substituted arylamine \(13\) in ethanol in the absence or the presence of sodium bicarbonate \(41,55,56\) or under solvent-free condition using \(K_2CO_3\) (ref. 57) yielded the corresponding 3-(2-(phenylanliino)acetyl)-2\(H\)-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).\(^{54}\)

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).\(^{51,56-62}\)

### 5.2. Azidation

Evans and coworkers\(^{58}\) reported the synthesis of coumarin fluoroaphore 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.\(^{63}\) reported the treatment of 3-(bromoacetyl) coumarin derivatives \(1\) with potassium thiocyanate (\(KSCN\)) \(20\)
Scheme 7  Transformation of 3-(bromoacetyl)coumarins 1 to chromenones 14.

\[
\begin{align*}
\text{Condition A} & \quad \text{Condition B} \\
14aa) R_1 = R_2 = R_3 = R_4 = H & \quad 14ba) R_1 = R_2 = R_3 = R_4 = H \\
14ab) R_1 = \text{OH}, R_2 = R_3 = H, R_4 = \text{CO}_2\text{C}_2\text{H}_5 & \quad 14bb) R_1 = \text{H}, R_2 = \text{Br}, R_3 = R_4 = H \\
14ac) R_1 = \text{OCH}_3, R_2 = R_3 = H, R_4 = \text{CO}_2\text{H} & \quad 14bc) R_1 = R_2 = \text{Br}, R_3 = R_4 = H \\
14ad) R_1 = \text{H}, R_2 = \text{Cl}, R_3 = H, R_4 = \text{CO}_2\text{H} & \quad 14bd) R_1 = \text{H}, R_2 = \text{Br}, R_3 = R_4 = H \\
14ae) R_1 = \text{H}, R_2 = \text{OCH}_3, R_3 = H, R_4 = \text{CO}_2\text{H} & \quad 14be) R_1 = \text{Cl}, R_2 = \text{Cl}, R_3 = R_4 = H \\
14af) R_1 = \text{OCH}_3, R_2 = \text{Cl}, R_3 = H, R_4 = \text{CO}_2\text{H} & \quad 14bf) R_1 = R_2 = H, R_3 = \text{Cl}, R_4 = H \\
14ag) R_1 = \text{OCH}_3, R_2 = \text{CH}_3\text{CH}=\text{CH}_2, R_3 = H, R_4 = \text{CO}_2\text{H} & \quad 14cg) R_1 = \text{H}, R_2 = \text{Br}, R_3 = \text{Cl}, R_4 = \text{H} \\
\end{align*}
\]

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

Scheme 8  Synthesis of imino derivatives 15.

\[
\begin{align*}
1a,15a: R = 6\text{-Br} & \quad 1b,15b: R = 6,8\text{-diBr} \\
1c,15c: R = 3\text{-CH}_3 & \quad 1d,15d: R = 4\text{-CH}_3 \\
1e,15e: R = 2\text{-OCH}_3 & \quad 1e,15e: R = 3\text{-OCH}_3 \\
1f,15f: R = 4\text{-Cl} & \\
\end{align*}
\]

Scheme 8  Synthesis of imino derivatives 15.

Scheme 9  Synthesis of bromoacetylcoumarin oximes 17.

\[
\begin{align*}
1a - c & \quad 17a-g \\
1a - c & \quad 17a-g \\
1a - c & \quad 17a-g \\
\end{align*}
\]

Scheme 9  Synthesis of bromoacetylcoumarin oximes 17.
in ethanol furnished 3-thiocyanatoacyl 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). Furthermore, the reactions of this type were promoted under solvent-free conditions, as reported in literature.

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.
5.5. Coupling reactions

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

5.6. Trifluoromethylation reaction

Novak and co-workers showed that trifluoromethylation of 3-(bromoacetyl)coumarin 1 with CHF₃ 29 derived CuCF₃ at room temperature to give 2-trifluoromethylcoumarin 30 in yield 57% (Scheme 15).

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

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).
5.9. Reaction with active methylene compound

2-Hydroxy-1-(2-oxo-2H-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).79

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-benzy1-N,N,N-triethylammonium chloride (BTEAC) as a phase-transfer catalyst (Scheme 20).77

5.10.2. Synthesis of five-membered rings with one heteroatom

5.10.2.1. Pyroles. 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).78

Pal et al.79 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 acetylacetonate 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–I2) (Scheme 23).80

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).81

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).82
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). 70

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-oxo-2H-chromen-3-yl)oxazol-2-yl)acetyl)-1H-pyrazol-5(4H)-one 57 was carried out without using any

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catalyst through the reaction of 3-(bromoacetyl)coumarin 1 with 3-oxopropanamide 56 in ethanol under heating (Scheme 27). \(^{55} \)

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,
ammonium thiocyanate 58, and phenacyl aniline 59 (Scheme 28).

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).

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-amino-pyrilimidine 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).³⁷

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-5-2H-chromen-2-ones 65 (Scheme 31).

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

Scheme 31 Reaction of bromoacetylcoumarins 1 with thiazole derivatives 5.

Scheme 32 Reaction of 3-(bromoacetyl)coumarin 1 and 1,3,4-thiadiazoles 5.
3-(2-Cyclohexylimidazo[2,1-b][1,3,4]thiadiazol-6-yl)-2H-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).

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).

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).

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).

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Using grindstone chemistry, the synthesis of 3-(7-methylimidazo[1,2-α]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).²³

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).³³

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).⁷⁴

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).⁵⁴,⁹⁴–¹⁰⁹

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 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.

**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)-2H-chromen-2-ones 87a,b.
benzenesulfonamide, ethyl thiooxamate, dihydrophthalazine carbothioamide, and pyrazole carbothiamides) in refluxing ethanol or tetrahydrofuran under alkaline condition (sodium acetate and sodium carbonate) (Scheme 40). \(^{110-116}\)

3-(Bromoacetyl)coumarin 1 was reacted with the appropriate carbothioamides 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). \(^{117}\)

Scheme 42  Synthesis of series of hydrazinyl thiazolyl coumarin derivatives 89–99.
Scheme 43  The synthesis of 2-oxochroman-3-thiazol-2-hydrazono-indolin-2-one 101.

Scheme 44  Formation of bis(thiazole-4,2-diyl)bis(2H-chromen-2-ones) 103 and 104.

Scheme 45  Synthesis of thiazolylicoumarin derivatives 106.

Scheme 46  Synthesis of bis-coumarin–iminothiazole hybrids 108a–m.
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).94,118

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 hydrazincarbothioamide 100 (Scheme 43).94,128

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).130

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

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

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Reflexing of 3-(bromoacetyl)coumarin 1 and coumarinothiosemicarbazides 107a–m in methanol containing drops of
acetic acid as catalyst gave bis-coumarin–nimothiazole hybrids 108a-m in good yields (Scheme 46).131

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).132

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,133,134 pyrazole,134 imidazo[1,2-a]pyridine,135 indole136) 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 thiocarbohydrazide 118 in the presence of a catalytic amount of acetic acid in the microwave for 6–8 min (Scheme 49).137

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.
Three-component condensation of 3-(bromoacetyl)coumarin derivatives 1, thiocarbohydrazide 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). 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).

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).
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).140

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).141

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

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

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thiazolines 131 by the condensation of 3-(bromoacetyl)coumarin derivatives 1, arylisothiocyanates 128, and amine 130 (Scheme 54). 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 thiazol-2H-chromene) 133 (Scheme 55). Microwave irradiation was reported as a green chemistry method for the synthesis of coumarin-3-yl-thiazol-2-arylacrylonitriles 138.

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.

Scheme 61 Synthesis annulated 4-(coumarin-3-yl)thiazoles 144.
5.10.3.5. Thiazolopyrazolones. A mixture of 3-(bromoacetyl)coumarin derivatives 1, acetophenones 139, and thiosemicarbazide 112 were subjected to a one-pot multicomponent Vilsmeier–Haack reaction condition afforded series of substituted thiazolyl-3-aryl-pyrazole-4-carbaldehydes bearing coumarin moiety 140 in moderate yields (Scheme 59).146

4,5-Dihydropyrazolyl–thiazole–coumarin systems 142 were obtained via the reaction of 3-(bromoacetyl)coumarin 1 with numerous aryl/heteryl aldehydes 49 and 2-cyanothioacetamide 137 (Scheme 58).145

triazolin-3-ones 135 by Shaikh et al.144 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).139

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).145

![Scheme 62](image-url)

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

![Scheme 63](image-url)

**Scheme 63** Coumarin bearing pyrazole and thiazole hybrids 148.

![Scheme 64](image-url)

**Scheme 64** Synthesis of binary pyrazol-1-thiazol-4-2H-chromen-2-one derivatives 150a-l.
Scheme 65  Formation of (2H-chromen-5-phenyl-1H-pyrazol-thiazol-4-yl) chromenones 152.

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

Scheme 67  Synthesis of fused thiazolo[3.2-a]pyrimidine derivatives 156.

Scheme 68  Synthesis of phenylindeno[1,2-d]thiazolo[3.2-a]pyrimidin-6(5H)-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.
disubstituted phenyl-4,5-dihydropyrazole-1-carbothioamide 141 in ethanol (Scheme 60). 147

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-thiocarboxamides 143 in ethanol (Scheme 61). 148

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). 149

Series of pyrazoles bearing coumarin moieties 148 were prepared underwent Hantzsch cyclocondensation of 3-(bromoacetyl)coumarin 1, thiosemicarbazide 89, aryl aldehyde 49, and ethyl acetoacetate 145 in refluxing ethanol (Scheme 63). 149

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(2H)-chromene-2(1H)-thiones 155a-g under conventional heating in acetic acid as solvent (Scheme 67). 155, 154

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(5H)-ones 158 in high yields (Scheme 68). 155

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]HSO4 as a mediated ionic liquid catalyst, leading to the formation of a double electrophilic pyrimidine-2(5H)-thione as an intermediate which cyclized directly to furnish the targeting products 160a-d (Scheme 69). 157

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

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(1H)-thiones 155a-g under conventional heating in acetic acid as solvent (Scheme 67). 155, 154

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). 151

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(5H)-ones 158 in high yields (Scheme 68). 155
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 poly(4-vinylpyridinium) hydrogen sulfate [P(4-VPH)HSO4] as Brønsted acid catalyst under neat condition afforded aryl-thiazolo[2,3-b]quinazoline derivatives 162a-j (Scheme 70).

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).

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

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

5.10.6. Synthesis of six-membered rings with one heteroatom

5.10.6.1. Pyran derivatives. Mohareb and MegallyAbdo described the preparation of 2-amino-3-cyano-pyran derivatives.
using three-component reactions of 3-(bromoacetyl)coumarin with malononitrile and aromatic aldehydes 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 in lieu of triethylamine afforded the pyridine systems 169a-d (Scheme 75).

Multicomponent condensation of 3-(bromoacetyl)coumarin, cyanothioacetamide, benzaldehyde derivatives and methyl 4-methyl-3-oxopentanoate led to formation of fused chromeno[3,00,4,00;5,0]pyrido[2,0,3-d]pyridine derivatives 171 (Scheme 76).

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**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 in boiling ethanol containing catalytic drops of trimethylamine (Scheme 74).

Multicomponent condensation of 3-(bromoacetyl)coumarin 1, cyanothioacetamide 137, benzaldehyde derivatives and methyl 4-methyl-3-oxopentanoate led to formation of fused chromeno[3″,4″:5″,6″]pyrido[2′,3′:4,5]thieno[3,2-e]pyridine derivatives 171 (Scheme 76).

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

| Compound | Conditions | Yield |
|----------|------------|-------|
| 1a,193a | K$_2$CO$_3$, MW/400 W, 4-6 min | 72-90% |
| 1b,193b | EtOH, reflux, 4-6 h | 66-82% |
| Structures | Activities | Ref. |
|------------|------------|-----|
| ![Structure 198](image1) | Antibacterial activity against: *(E. coli, S. aureus and P. aeruginosa)*  
Antifungal activity against: *(A. flavus, C. keratinophilum, and C. albicans)*  
Antioxidant activity: (moderate potency in scavenging DPPH radical (approximately 65%)) | 175 |
| ![Structure 199](image2) | Antibacterial activity (zone of inhibition, ZI) against:*S. aureus, ZI = 36.8 ± 0.6 mm*  
• *S. mutans, ZI = 25.4 ± 0.5 mm*  
• *K. pneumoniae, ZI = 27.2 ± 0.5 mm*  
• *E. coli, ZI = 26.3 ± 0.3 mm* | 176 |
| ![Structure 200](image3) | Anti-influenza A virus H1N1: \( IC_{50} = 4.84 \mu g \text{ mL}^{-1} \) in MDCK cells | 108 |
| ![Structure 201](image4) | Antimicrobial agents: *M. tuberculosis* (MIC = 15 \( \mu \text{M} \)) | 177 |
### Table 1 (Contd.)

| Structures | Activities | Ref. |
|------------|------------|------|
| ![Structure 202](image1.png) | Anti-Alzheimer activity: anti-cholinesterases ($IC_{50} = 43$ nM) | 178 |
| ![Structure 135](image2.png) | Anticancer activity against:  - Breast cancer  - Lung cancer  - Leukemia  - Human cervical cancer | 144 |
| ![Structure 168](image3.png) | Anticancer activity against human gastric cancer NUGC:  - $168a$: $Ar = 2$-furyl, $IC_{50} = 29$ nM (against human gastric cancer NUGC)  - $168b$: $Ar = 4$-Cl-C$_6$H$_5$, $IC_{50} = 89$ nM (against MCF) | 70 |
| ![Structure 111](image4.png) | Anticancer activity (against MCF-7, HepG2 and SW480 cells): $IC_{50} = 7.5-16.9$ µg mL$^{-1}$ | 132 |
Table 1 (Contd.)

| Structures | Activities | Ref. |
|------------|------------|-----|
| ![Structure 140](image1.png) | Anticancer activity (against HeLa cell line)  
- \( R = 6,8\text{-dCl}, R_1 = 4\text{-MeC}_6\text{H}_4, IC_{50} = 5.75 \mu\text{M} \)  
- \( R = 6,8\text{-dBr}, R_1 = 4\text{-MeC}_6\text{H}_4, IC_{50} = 6.25 \mu\text{M} \)  | 146 |
| ![Structure 176](image2.png) | Anticancer activity (against Melanoma tumor cell line): 55.75% GI | 99 |
| ![Structure 144](image3.png) | Anti-inflammatory agents: 73–86% of inhibition after 1 h | 148 |
| ![Structure 185](image4.png) | Antiproliferative activity: IC_{50} = 10.364 \pm 0.270 \mu\text{M} | 170 |
| ![Structure 138](image5.png) | Anti-hepatocarcinoma activity: IC_{50} = 2.33 \pm 0.004 \mu\text{M} | 145 |
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-CH₂CPFX) with 3-bromoacetyl coumarins 1 in dimethylformamide, in the presence of NaHCO₃, provide fluoroquinolone derivatives 173 (Scheme 77).⁶⁵

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).¹⁶³-¹⁶⁵

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 thiocarboxydraside 118 as bishydrazide in ethanol and in the presence a catalytic amount of acetic acid afforded 2-hydrazino[1,3,4]thiadiazin-5-5-chromene 178 (Scheme 79).¹⁶⁴

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

5.10.8.3. Triazolof[3,4-b]thiazin derivatives. 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]triazolof[3,4-b][1,3,4]thiadiazine hybrids 181-185 in good to excellent yields (Scheme 81).⁴⁷,¹⁶⁶-¹⁶⁹

Triazolof[3,4-b]thiazine 187 was produced from the treatment of 3-(bromoacetyl) coumarin 1 with 4-amino triazole-3-thiol 186 under both conventional and microwave conditions (Scheme 82).⁷⁷

Bis coumarinyl bis triazolothiadiazinyl ethane derivatives 189 were synthesized through the reaction of ethane-1,2-diyli 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).¹⁶⁵

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 derivatifs 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).⁷⁷

Pavurala and Vedula²⁷ disclosed multi-component one-pot synthesis of pyrazolyl triazolo thidiazinyl 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 Rao²⁷ reported the synthesis of thiadiazinyl-phthalazine-1,4-dione derivatives 195 via one-pot condensation reaction of 3-(bromoacetyl) coumarins 1, thiocarboxydraside 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]thiadiazinof[2,3-b] quinzolinol-6(2H)-ones 197 in high yields through cyclo-condensation of 3-(bromoacetyl) coumarins 1 with 3-amino-2mercapt-3H-quinazolin-4-one 196 under the conventional and microwave conditions in the presence of potassium carbonate (Scheme 87).⁷⁷

Fig. 6 Representative inhibitors of metalloproteinase with significant inhibitory effects.
1. Fluorescent Chemosensors for Anions

1.1. Chemosensors for CN

1.2. Chemosensors for F

1.3. Chemosensors for ClO

2. Fluorescent Chemosensors for Metal Ions

2.1. Chemosensors for Cu²⁺/Cu⁺

2.2. Chemosensors for Hg²⁺

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,\textsuperscript{131} aldose reductase,\textsuperscript{130} alpha-glucosidase,\textsuperscript{91} 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.\textsuperscript{179,180} 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\textsuperscript{181–184} (Fig. 7).

7. Conclusion

This review has illuminated different aspects of 3-bromoacet- ylcoumarin 1 and its derivatives chemistry up to the beginning of 2021. It implies many sections on the synthesis of bromocoumarin derivatives. Besides different chemical reactions of bromoacetylcoumarins 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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