

Review

Insight on Mercapto-Coumarins: Synthesis and Reactivity

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Abstract: Mercapto (or sulfanyl)-coumarins are heterocycles of great interest in the development of valuable active structures in material and biological domains. They represent a highly exploitable class of compounds that open many possibilities for further chemical transformations. The present review aims to draw focus toward the synthetic applicability of various forms of mercapto-coumarins and their representations in pharmaceuticals and industries. This work covers the literature issued from 1970 to 2021.

Keywords: mercapto-coumarins; diazosulfuration; Newman–Kwart; fluorescence; biological activity

1. Introduction

Coumarins (2*H*-1-benzopyran-2-ones) are an elite class of compounds present in various natural products, and they have wide applications, *viz.*, as additives in food [1,2], perfumes [3], cosmetics [4], and pharmaceuticals [5,6], as well as in the preparation of optical brighteners [7], dispersed fluorescent [8–10] and laser dyes [11], and useful medicinal products [12,13]. On the other hand, the carbon–sulfur bond formation plays an important role in organic synthesis [14–17]. The introduction of the thiol group to organic structures has emerged as an important tool in medicinal chemistry and chemical biology [18–21]. It plays a distinguished role in the fabrication of applicable substances in the field of advanced functional materials [22], structural frameworks of natural products [23], and the pharmaceutical industry [24–26]. Therefore, there is an increasing demand to investigate thiol-based coupling reactions focusing on their chemoselectivity and their tolerance of various functional groups in order to provide feasible access to new chemical architectures [27,28].

The incorporation of a thiol functional group into coumarin results in mercapto-coumarins. Although mercapto-coumarins have been relatively less extensively studied [18–21], their chemistry and bioactivity appear to be interesting. This functionalization of coumarin allows a special reactivity due to the implication of the thiol group in different types of organic reactions. This facilitates access to various series of derivatives that may have special applications or biological activities.

By exploring mercapto-coumarin derivatives, we found that four common forms of functional thiol group integrate into the coumarin moiety that occupies different positions, either on the pyrone ring or on the benzene ring. The common four mercapto-coumarins are 3-mercapto-coumarin, 4-mercapto-coumarin, 6-mercapto-coumarin, and 7-mercapto-coumarin (Figure 1).

The present review is concerned with the period from 1970 to 2021 to shed light on the different pathways of mercapto-coumarin synthesis, while also covering their broad applications at both industrial and biological levels. In addition, it is a groundbreaking release on these compounds, to open a platform for researchers to progress the development of this chemistry.



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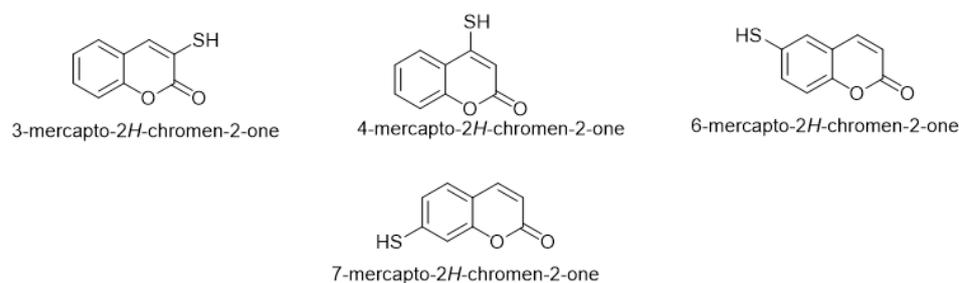
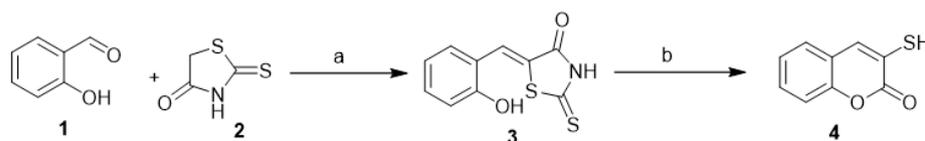


Figure 1. The four common mercapto-coumarin derivatives.

2. 3-Mercapto-Coumarin

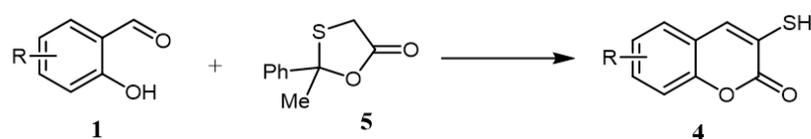
By analyzing the synthesis of 3-mercapto-coumarin, we found that the source of sulfur was a heterocyclic compound not an inorganic reagent. In addition, the coumarin was formed in situ from primary sources, which were salicylaldehydes.

Qiyi et al. reported the synthesis of 3-mercapto-coumarin (**4**) from 2-hydroxybenzylidene nerhodanine (**3**). The latter was produced in situ from salicylaldehyde (**1**) and 2-thioxothiazolidin-4-one (**2**). The reaction proceeded to the final target by refluxing of compound **3** in diluted ethanolic sodium hydroxide solution (Scheme 1) [18].



Scheme 1. The synthesis of 3-mercapto-coumarin (**4**). Reagents and conditions: (a) EtOH, reflux, TEA, 80% yield; (b) EtOH, NaOH, reflux, 88% yield.

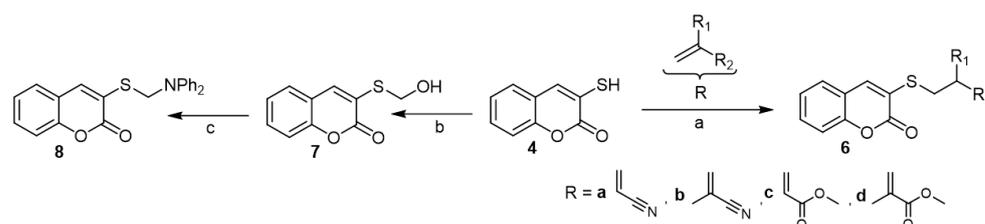
In 2009, a green catalyst-free synthetic protocol for synthesizing varieties of the target 3-mercapto-coumarins was reported. In this protocol, refluxing of 2-methyl-2-phenyl-1,3-oxa-thiolan-5-one (**5**) and salicylaldehyde derivatives in water afforded the formation of corresponding 3-mercapto-coumarins (**4**) in excellent yields (82–97%) (Scheme 2) [22].



Scheme 2. Catalyst-free conditions for the synthesis of 3-mercapto-coumarins (**4**): Reagents and conditions: water; reflux; 8–10 h; 8 outputs with 82–97% yield.

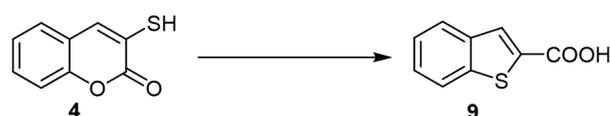
3. Reactivity of 3-Mercapto-Coumarin

3-Mercapto-coumarin (**4**) contributed to the synthesis of many chain and fused compounds. Accordingly, the reaction of 3-mercapto-coumarin (**4**) with some acrylonitriles and acrylates under the Michael addition condition created *S*-acetonitrile **6a**, *S*-propanenitrile **6b**, *S*-ethyl acetate **6c**, and *S*-propanoate **6d** coumarin derivatives, respectively (Scheme 3) [18]. In another publication on the Mannich reaction, 3-mercapto-coumarin (**4**) condensed with formaldehyde and produced 3-hydroxy-methylthio-coumarin (**7**). The latter reacted with diphenylamine to give the corresponding α -aminomethylated thioether (**8**) (Scheme 3) [23].



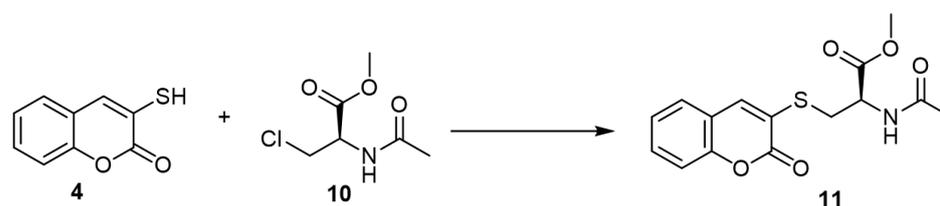
Scheme 3. Michael addition and Mannich reaction of 3-mercapto-coumarins (4). Reagents and conditions: (a) water, NaOH 10%, 50–56 °C, 4–12 h, four outputs with 40–92% yield; (b) formaldehyde, ethanol; (c) diphenyl amine, AcOH.

In a Chinese patent (2016), the author disclosed a method to fabricate benzothiophene-2-carboxylic acid (9) via a phase-transfer catalyst of 3-mercapto-coumarin (4) under high-pressure, 0.8–1.2 MPa (Scheme 4) [24].



Scheme 4. Benzothiophene-2-carboxylic (9) acid via phase-transfer catalyst: Reagents and conditions: high-pressure vessel, 0.8–1.2 MPa; aq. KOH 37%; tetrabutyl ammonium hydroxide; 135 °C, 10 h; conc. HCl; 41.6% yield.

N-Acetyl-S-(3-coumarinyl)cysteine (11), which could be isolated from rat urine [25], was synthesized by the reaction of 3-mercapto-coumarin (3) and *N*-acetyl-3-chloro-*D,L*-alanine methyl ester (10) (Scheme 5) [26].

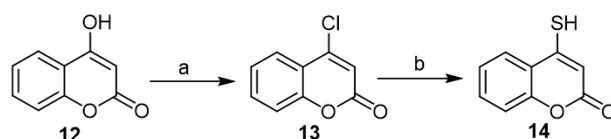


Scheme 5. Synthesis of *N*-acetyl-S-(3-coumarinyl)cysteine. Reagents and conditions: TEA, acetonitrile, N₂, 4 h, stirring, 47% yield.

4. 4-Mercapto-Coumarin

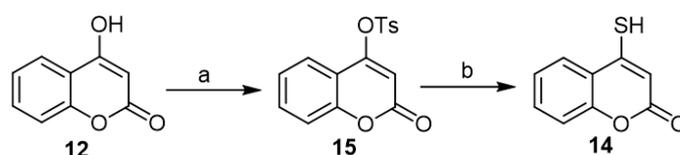
The synthesis of 4-mercapto-coumarin by methods based on 4-hydroxycoumarin has already been discussed [19,27–30].

In 1970, Peinhardt and Reppel allowed 4-hydroxycoumarin (12) to react with phosphorus oxychloride to get 4-chlorocoumarin (13). The latter, under reaction with potassium hydrosulfide in situ prepared from potassium hydroxide with methanol saturated with hydrogen sulfide (H₂S), gave the corresponding 4-mercapto-coumarin (14) in a good yield, 90% (Scheme 6) [27].



Scheme 6. The synthesis of 4-mercapto-coumarin (14). Reagents and conditions: (a) POCl₃, reflux, 2 h, 55% yield; (b) KSH generated from (KOH, MeOH saturated with H₂S), reflux, 90% yield.

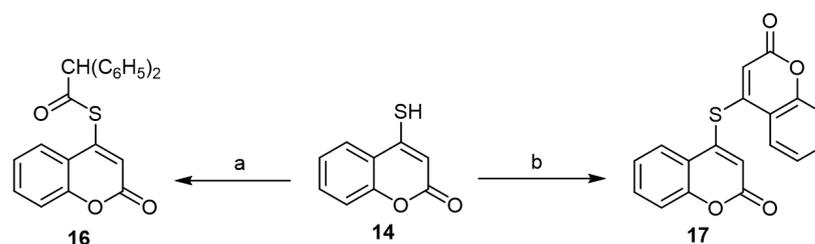
Recently, the synthesis of 4-mercapto-coumarin (**14**) occupied the scope of interest of Ghosh's work as an in situ transformed intermediate to synthesize different coumarin-fused heterocycles via 4-hydroxycoumarin (**12**) [19,28–30]. Dissolving the 4-hydroxycoumarin (**12**) in pyridine followed by the addition of toluene-4-sulfonyl chloride led to the formation of the tosyl derivative (**15**). Treatment of the latter with NaSH in ethanol furnished the corresponding 4-mercapto-coumarin (**14**), which succeeded by transformation to the final product (Scheme 7).



Scheme 7. The synthesis of 4-mercapto-coumarin (**14**) according to Ghosh's work. Reagents and conditions: (a) TsCl, pyridine, 30 min, stirring, 90% yield; (b) NaSH, EtOH, 0–10 °C, 2 h, stirring, no yield was recorded as the product was used in the subsequent reaction without further purification.

5. Reactivity of 4-Mercapto-Coumarin

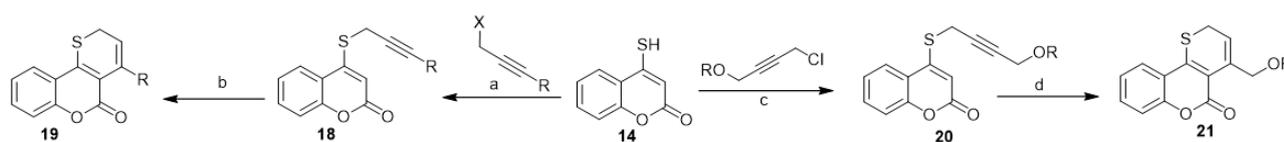
In 1975, Eiden and Zimmermann synthesized diphenylacetyl thioester (**16**) and biscoumarinyl sulfide (**17**) via the reaction of 4-mercapto-coumarin with 2,2-diphenylethen-1-one according to Scheme 8 [31].



Scheme 8. The reaction of 4-mercapto-coumarin (**14**) with 2,2-diphenylethen-1-one. Reagents and conditions: (a) 2,2-diphenylethen-1-one, benzene, 16 h, reflux, 59% yield; (b) 2,2-diphenylethen-1-one, benzene, 5 h, 6.2% yield.

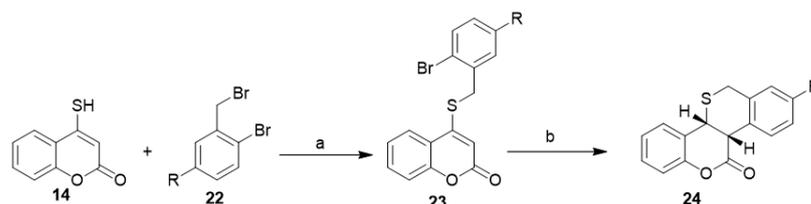
In the previous example of Ghosh's work, 4-mercapto-coumarin served as a transitional compound to produce different coumarin-fused heterocycles employing 4-hydroxycoumarin (**12**) as a starting reactant. As the compound (**14**) was produced, it converted immediately to the final products (Scheme 7).

Accordingly, various 2*H*-thiopyrano[3,2-*c*][1]benzopyran-5-ones (**19**) [28,29] and 4-aryloxymethylthiopyrano[3,2-*c*][1]benzopyran-5(2*H*)-ones (**21**) [19,30] were prepared through the thio-Claisen rearrangement of 4-propargylthio[1]benzopyran-2-ones (**18**) and 4-[4-aryloxybut-2-ynylthio][1]benzopyran-2-ones (**20**) (Scheme 9). Compounds **18** and **20** were prepared based on a two-phase mixture of 4-mercapto-coumarin (**14**) with propargyl halides and 1-chloro-4-aryloxybut-2-yne, respectively (Scheme 9).



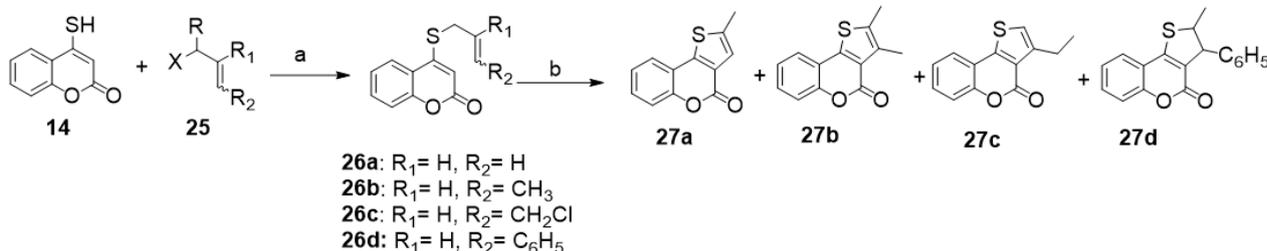
Scheme 9. Utilization of 4-mercapto-coumarin (**14**) in the synthesis of 2*H*-thiopyrano[3,2-*c*][1]benzopyran-5-ones. Reagents and conditions: (a,c) CHCl₃, 1% aqueous NaOH, r.t., stirring, benzyltriethyl ammonium chloride (BTEAC) or tetrabutylammonium bromide (TBAB); (b,d) chlorobenzene, reflux, 30 min–4 h, six derivatives of 79–85% yield.

Regioselective synthesis of coumarin-annulated sulfur heterocycles, *cis*-benzothiopyrano[3,2-*c*]benzopyran-7(2*H*)-ones (**24**), was reported through aryl radical cyclization. The corresponding 4-[(2-bromobenzyl)sulfanyl]-2*H*-chromen-2-ones (**23**) was in situ prepared from a reaction between 4-mercapto-coumarin (**14**) and tributyltin hydride (**22**) in the presence of a radical initiator (AIBN) (Scheme 10) [32].



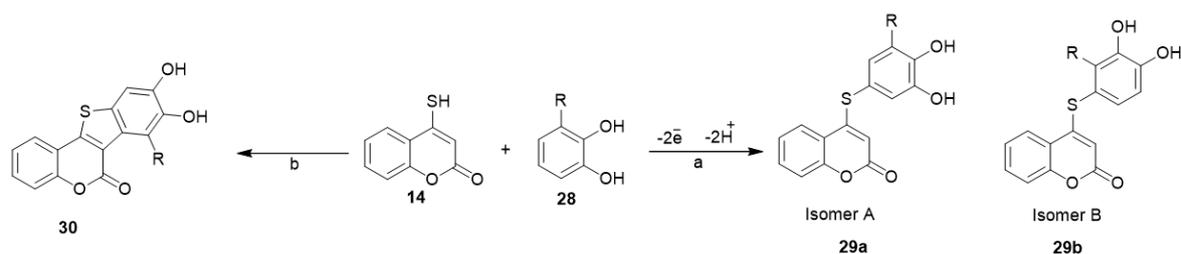
Scheme 10. Regioselective synthesis of coumarin-annulated sulfur heterocycles. Reagent and conditions: (a) 1% aq. NaOH-CHCl₃, benzyltriethyl ammonium chloride (BTEAC), 1 h, r.t., R=H 83% yield, R=OCH₃ 85% yields; (b) Bu₃SnH, AIBN, benzene, N₂, reflux, 1 h, R=H 72% yield, R=OCH₃ 75% yield.

In another publication, some thieno[3,2-*c*][1]benzopyran-4-ones (**27**) were synthesized by thermal thio-Claisen rearrangement of 4-allylthio[1]benzo-pyran-2-ones (**26**) (Scheme 11). Compounds **26** resulted from a basic catalyzed reaction between 4-mercapto-coumarin (**8**) and different allylic halides (**25**). Without being separated from the reaction medium, compounds **26a–d** ended in four different derivatives via phase-transfer-catalyzed alkylation using TBAB or BTEAC as a catalyst. The differentiation of the end products depended on the alkyl substitutions (R₁, R₂) on the allyl halide, which influenced the mechanism of the cyclization during the final step (Scheme 11) [33].



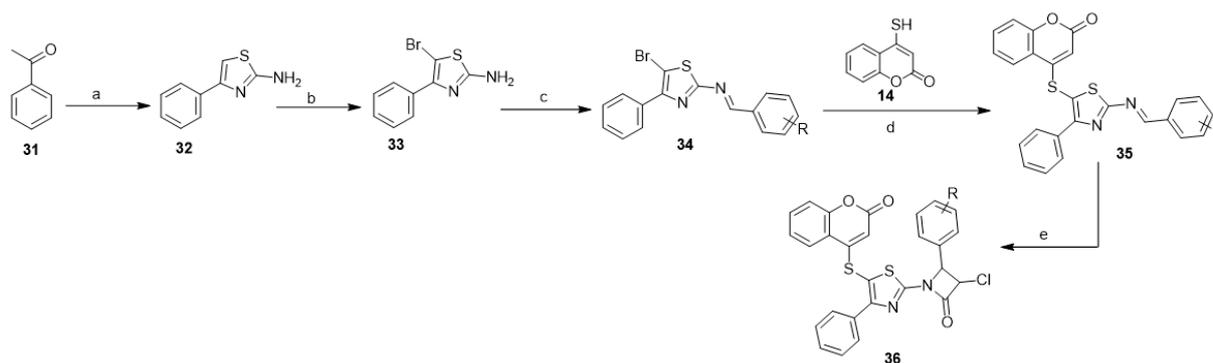
Scheme 11. Regioselective synthesis of thieno[3,2-*c*][1]benzopyran-4-ones (**27**). Reagent and conditions: (a) 1% aq. NaOH-CHCl₃, benzyltriethyl ammonium chloride (BTEAC), stirring, 4 h, r.t., four products, 75–85% yield; (b) reflux, 0.5 h, HCl, four products, 65–80% yield.

Nematollahi et al. investigated the electrochemical oxidation of catechols (**28**) in the presence of 4-mercapto-coumarin (**14**) as the nucleophile in water/acetonitrile (50/50) solution. Through an EC mechanism and in a one-pot process, 4-(dihydroxyphenylthio)-2*H*-chromen-2-one derivatives **29a** and **29b** were afforded (Scheme 12) [34]. In another work of the same group, they explored the reactivity of catechol (**28**) and 4-mercapto-coumarin (**14**) in the presence of potassium ferricyanide as an oxidizing agent (decker oxidation) to develop thieno[3,2-*c*]chromen-6-one derivatives (**30**) (Scheme 12) [35].



Scheme 12. Synthetic pathways for the reaction of catechol with 4-mercapto-coumarin. Reagents and conditions: (a) sodium acetate solution ($c = 0.2 \text{ M}$) in water/acetonitrile (50/50), undivided cell equipped with graphite anode, a large stainless steel gauze cathode, $25 \text{ }^\circ\text{C}$, $\text{R}=\text{CH}_3$ isomer ratio with 52.5%/47.5% yield, $\text{R}=\text{OCH}_3$ isomer ratio with 96.5%/3.5% yield; (b) sodium acetate solution (0.2 M)/acetonitrile (70/30), stirring, r.t., 20–30 min, $\text{R}=\text{CH}_3$ 75% yield, $\text{R}=\text{OCH}_3$ 70% yield.

A series of 3-chloro-1-(5-((2-oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl)-4-substituted phenyl azetidin-2-ones (36) were synthesized in five sequential steps with the participation of 4-mercapto-coumarin (14) in addition to acetophenone (31), thiourea, and chloroacetyl chloride [36] (Scheme 13). The synthesized compounds showed potent antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Aspergillus niger*, *Aspergillus clavatus*, and *Candida albicans* [36].

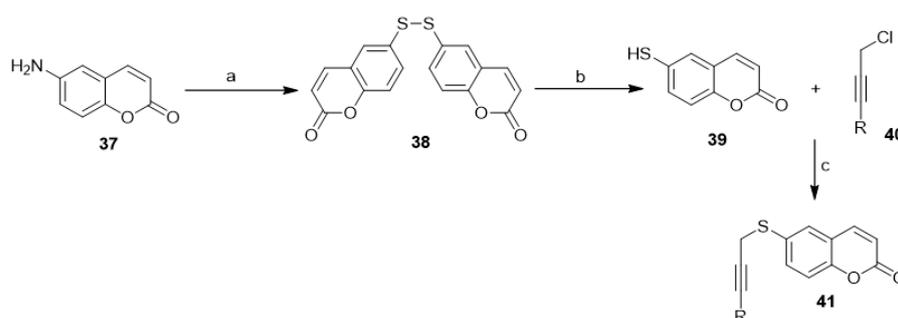


Scheme 13. 4-Mercapto-coumarin in the synthesis 3-chloro-azetidin-2-one derivatives (36). Reagents and conditions: (a) iodine, thiourea, ethanol, 2–3 h; (b) bromine, acetic acid reflux, 2 h; (c) aromatic aldehyde, acetic acid, ethanol, reflux, 6 h; (d) ethanol, reflux, 5 h; (e) chloroacetyl-chloride, triethylamine, 1,4-dioxane, reflux 7 h, 10 outputs 70–78% yields.

6. 6-Mercapto-Coumarin

The structure creation of 6-mercapto-coumarin was performed following the synthesis of 3-SH and 4-SH-coumarin. This 6-SH-coumarin is an unstable compound that reacts directly with halo-compounds to give S-alkyl coumarin derivatives.

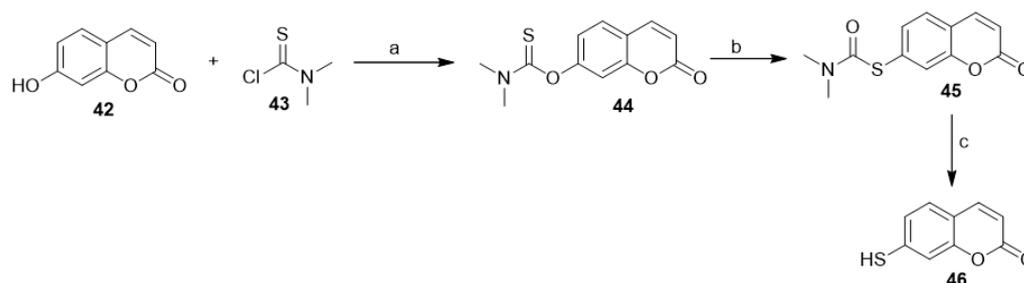
In 1999, Majumdar and Biswas reported 6-mercapto-coumarin (39) as an unstable compound [37]. 6-Mercapto-coumarin (39) was generated in situ from the disulfide (38) (Scheme 14). This reduction was achieved with zinc dust in acetic acid in the presence of 6 N sulfuric acid by heating at $80 \text{ }^\circ\text{C}$ until the solution became clear. 6-Mercapto-coumarin (39) was used without further purification for the synthesis of 6-(4-aryloxybut-2-ynylthio)[1]benzo-pyran-2-ones (41) by its reaction with 1-aryloxy-4-chloro-but-2-yne (40) (Scheme 14) [37].



Scheme 14. The synthesis of 6-mercapto-coumarin (**33**). Reagents and conditions: (a) HCl/NaNO₂; potassium ethyl xanthate, EtOH–KOH, 65% yield; (b) Zn/6 N H₂SO₄, AcOH, no yield was recorded for compound **30** as the product was used in the subsequent reaction without further purification; (c) Me₂CO, K₂CO₃, NaI, 2 h, reflux, five outputs 85–91% yield.

7. 7-Mercapto-Coumarin

To our knowledge, only one article discussed the synthesis of 7-mercapto-coumarin (**46**) [20]. Therein, 7-hydroxycoumarin (**42**) was treated with sodium hydride and subsequently reacted with dimethylthiocarbamoyl chloride (**43**) to yield the 2-oxo-2*H*-chromen-7-yl dimethylcarbamate (**44**). The latter was subjected to a Newman–Kwart-type rearrangement to form *S*-(2-oxo-2*H*-chromen-7-yl) dimethylcarbamothioate (**45**). Cleaving of the carbamate group of **45** afforded 7-mercapto-coumarin (**46**) [20] (Scheme 15).

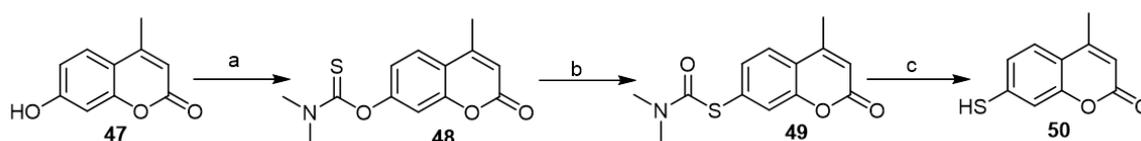


Scheme 15. The synthesis of 7-mercapto-coumarin (**46**). Reagents and conditions: (a) THF, NaH, then (CH₃)₂NCSCl; (b) DMA, MW, 250 W, 260 °C; (c) KOH, MeOH, r.t., 7 h, then HCl, the product was obtained as a viscous mustard liquid, which could not be recrystallized or purified due to its tackiness.

One of the 7-mercapto-coumarin derivatives with the widest applications is 7-mercapto-4-methyl coumarin (MMC). MMC has a wide range of applications in the field of biology and material science. This substrate is considered as a frontier to synthesize varieties of bioactive compounds [38,39]. It is also indicated as a suitable matrix for the analysis of small molecular compounds [40]. The other described incorporation of this highly valuable scaffold is as a reporter molecule [41], reporters for thiol interactions at the nanoparticle surface [42], fluorescent probe [43–45], sugar acceptor [46], Raman reporter [47–56], an excellent substrate for fluorescence spectroscopy [57], photodimerizable and healable reactant [58], fluorescent dye [59,60], and probe molecule on gold-coated silicon nanowires [61].

7.1. Synthesis of 7-Mercapto-4-Methyl Coumarin (MMC)

The general procedure for the synthesis of 7-mercapto-4-methyl coumarin (**50**, MMC) depends on 7-hydroxy-4-methyl coumarin (**47**). The reaction of 7-hydroxy-4-methyl coumarin (**47**) with dimethylthiocarbamoyl chloride, was followed by a thermos-rearrangement that afforded the corresponding *S*-4-methyl-2-oxo-2*H*-chromen-7-yl dimethylcarbamothioates (**49**) (Newman–Kwart-type rearrangement) (Scheme 16). The latter, upon hydrolysis in the presence of NaOCH₃/CH₃OH and acidification by HCl, produced the target 7-mercapto-4-methyl coumarin (**50**, MMC) (Scheme 16) [21,62–66].

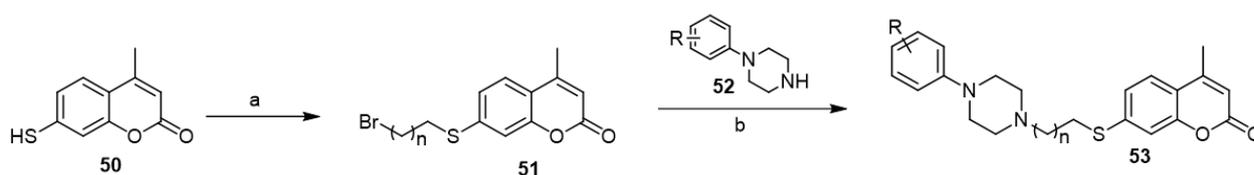


Scheme 16. Synthesis of 7-mercapto-4-coumarin (**50**, MMC). Reagents and conditions: (a) dimethylthiocarbamoyl chloride, DMAP/CH₂Cl₂, 86% yield; (b) heating, 87% yield; (c) (i) NaOCH₃/MeOH, (ii) HCl, 74% yield.

7.2. Reactivity of 7-Mercapto-4-Methyl Coumarin (MMC)

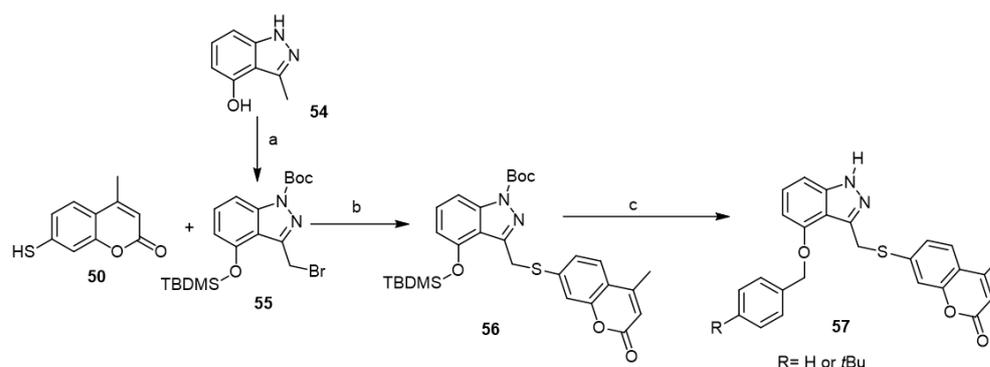
7.2.1. Utilization of 7-Mercapto-4-Methyl Coumarin in the Synthesis of Bioactive Compounds

Novel 7-mercapto-coumarin derivatives (**53**) were designed starting from 7-mercapto-4-methyl coumarin (**50**). Most of compounds in **53** exhibited strong $\alpha 1$ antagonistic activity [65]. In particular, compound **53c** showed excellent activity, which was better than that of the reference compound prazosin [65]. 7-((4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)thio)-4-methyl-2H-chromen-2-one (**53c**) was synthesized via the reaction of 7-mercapto-4-methyl coumarin (**50**) with 1,2-dibromoethane to give **51**, which in turn reacted with 1-(2-methoxyphenyl)piperazine (**52c**) (Scheme 17) [65].



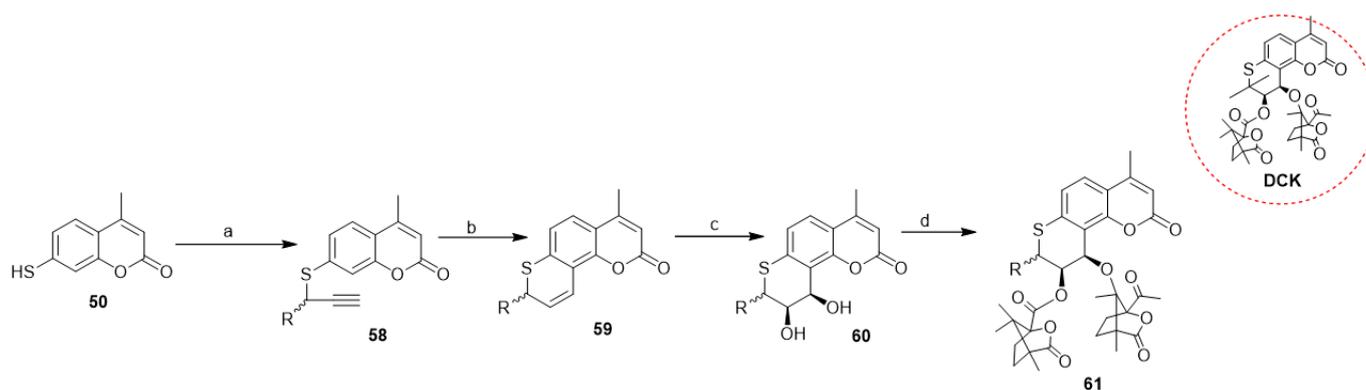
Scheme 17. Synthesis of conjugated coumarin and piperazine derivatives. Reagents and conditions: (a) Br(CH₂)_nBr ($n = 2-4$), K₂CO₃, acetone, 4 h, reflux, five outputs 61–70% yield; (b) CH₃CN, K₂CO₃, 8 h, reflux, five derivatives of 16–42% yield.

In an effort to find inhibitors of the bacterial enzyme DNA gyrase, Miller and his co-workers developed a potential low-molecular-weight inhibitor of 7-[4-(4-tert-butylbenzyloxy)-1H-indazol-3-ylmethylsulfanyl] 4-methylcoumarin (**57**) (Scheme 18) [67]. The protected and brominated product (**56**) was involved in thioether formation with MMC (**50**) by nucleophilic substitution to give **56**. The phenolic protection of **56** was removed and formed ether linkage simultaneously with BnBr or *p*-tBu-BnBr in presence of fluoride ion. The removal of the Boc protection was performed simply in acidic condition to give **57**. Compound **57** was 10 times more potent than the reference drug, novobiocin as a DNA gyrase inhibitor [67].



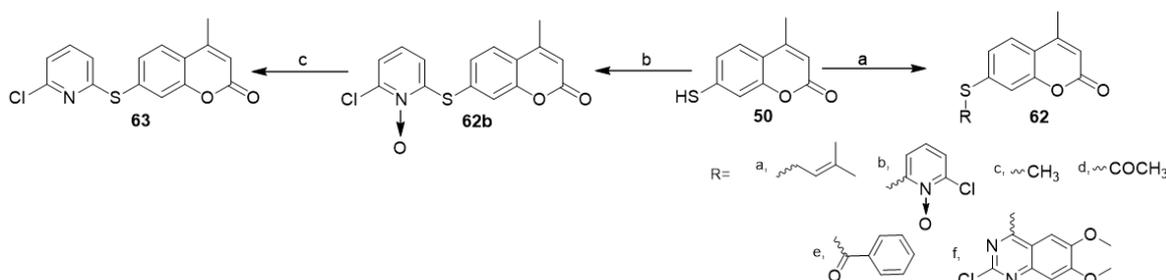
Scheme 18. Synthesis of bacterial enzyme DNA gyrase inhibitor. Reagents and conditions: (a) (i) TBDMSCl, imidazole, DMF, 12 h, r.t.; (ii) (BOC)₂O, Et₃N, DMAP, MeCN, 3 h, r.t.; (iii) NBS, (PhCO₂)₂, CCl₄, 4.5 h, 78 °C, 72% yield; (b) Et₃N, CH₂Cl₂, 4 h, r.t., 90% yield; (c) (i) BnBr or *p*-tBu-BnBr, KF, DMF, 4 h, r.t.; (ii) TFA, CH₂Cl₂, 4 h, r.t., 90% yield.

Lee and his co-workers synthesized analogs of DCK, which was known to be active against HIV. In these new structures (thia-DCK), the sulfur atom was the isosteric equivalent to the oxygen atom in the original structure. These derivatives (**61a** and **61b**) were synthesized by fusing the derivatized thiane ring within the benzene moiety of coumarin through a four-step reaction (Scheme 19) [21,64]. They proved to be potent as an anti-HIV agent with an EC_{50} value of 0.14 and 0.039 μM and a remarkable therapeutic index of 1110 and 1000 for **61a** and **61b**, respectively [21,64].



Scheme 19. Synthesis of anti-AIDS agents. Reagents and conditions: (a) 3-bromo-1-propyne or 3-chloro-1-butyne, K_2CO_3 , KI, acetone, N_2 , **58a**: $R=H$ 89.13%, **58b**: $R=CH_3$ 75% yield; (b) *N,N*-diethylaniline, reflux, **59a**: $R=H$ 77.6%, **59b**: $R=CH_3$ 56% yield; (c) (i) $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, $(DHQ)_2$ -PHAL, K_2CO_3 , (ii) Na_2SO_3 , **60a**: $R=H$ 51.3% yield, **60b**: $R=CH_3$ (*S* configuration) 52% yield; (d) camphanic chloride, DMAP/ CH_2Cl_2 , **61a**: $R=H$ 95%, **61b**: $R=CH_3$ 78% yield.

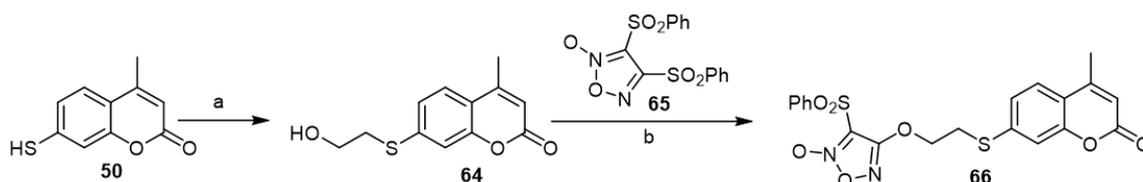
Another 12 antiviral agents of *S*-substituted 7-mercapto-4-methyl coumarin analogs (**62**) were synthesized and evaluated against HBV in HepG2 cells (Scheme 20) [62]. These series of derivatives were prepared from reaction between MMC and halo compounds assisted by K_2CO_3/KI . The IC_{50} of **62a** and **62b** as anti-HBsAg activities was (0.01 $\mu\text{mol/L}$), which was 16-fold more potent than the reference (3TC). Compounds **62c–f** exhibited interesting inhibitory activity toward both HBsAg and HBeAg [62]. Another approach belonging to Chen et al. was to prepare and evaluate the effectiveness of **63** as an antitumor agent [68]. This compound, which afforded by reduction of **62b**, showed a broad spectrum of activity against four tumor cells, as well as remarkably increased cellular apoptosis in a concentration-dependent manner. Furthermore, it induced A549 cell cycle arrest at the G2/M phase [68].



Scheme 20. Synthesis of *S*-substituted 7-mercapto-4-methyl coumarin analogs. Reagents and conditions: (a) halides, K_2CO_3 , KI, acetone/ N_2 ; (b) 2,6-dichloropyridine *N*-oxide, pyridine, r.t., 48% yield; (c) PCl_3 , $CHCl_3$, reflux, 48% yield.

In 2014, Liu et al. aimed to prepare furoxan-based nitric oxide (NO) releasing *S*-coumarin, 4-(2-(4-methyl-2-oxo-2H-chromen-7-ylthio)ethoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole 2-oxide (**66**) (Scheme 21). It was attained by the formation of an ethyl linker be-

tween MMC and the NO-releasing moiety (**65**). This linker was established by the reaction of chloroethanol with MMC in a K_2CO_3 -containing solvent. The resulting intermediate (**64**) reacted with compound **65** in DCM, while DBU acted as a catalyst to deliver compound **66**. This latter showed antiproliferation activity on A549, HeLa, A2780, A2780/CDDP, and HUVEC cell lines with IC_{50} (μM) of 0.12, 0.024, 0.036, 0.14, 0.22, respectively [69].



Scheme 21. Furoxan-based nitric oxide (NO) releasing S-coumarin. Reagents and conditions: (a) chloroethanol, K_2CO_3 , acetone or DMF, reflux, 89% yield; (b) CH_2Cl_2 , DBU, $-15\text{ }^\circ C$, 3 h, 83% yield.

Guo et al. synthesized 4-methyl-7-thiocyanato-2H-chromen-2-one (**67**), which may be used as an inhibitor of monoamine oxidase A or anti-influenza drug [70]. Cutting off the C–S bond through a photocatalysis of inorganic thiocyanates salt delivered the green “CN”, which transformed 7-SH group of 7-mercapto-4-methyl coumarin (**50**) in the presence of a 10 W white light and 1 mol% Rose Bengal to 7-SCN (**67**) (Scheme 22) [70].

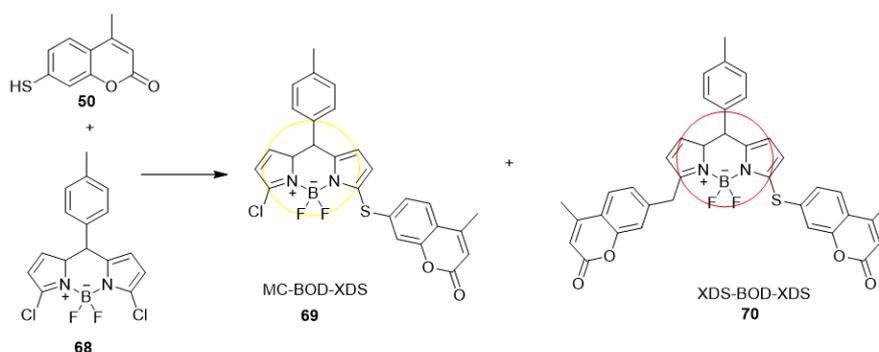


Scheme 22. Direct photocatalytic S–H Bond cyanation with green “CN” source. Reagents and conditions: Rose Bengal (1 mol%), CH_3CN , r.t., 12 h, white light (10 W), 52% yield.

7.2.2. 7-Mercapto-4-Methyl Coumarin as a Fluorophore Probe

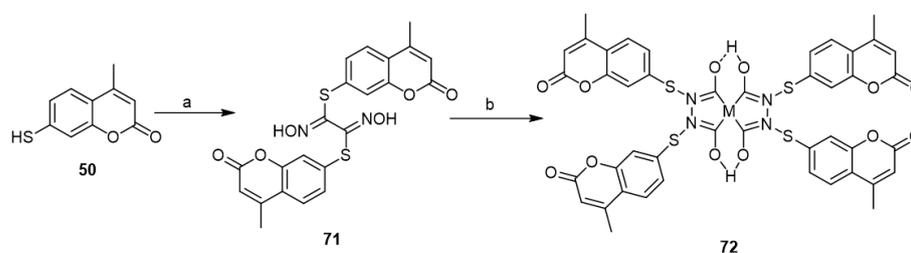
Fluorescent probes based on 7-mercapto-4-methyl coumarin (MMC) are widely reported in the literature [71–74]. In contrary to 7-mercapto-4-methyl coumarin’s poor emission characteristic, its thiol-alkylated analog shows high fluorescence.

A specific fluorescent probe based on monosulfanyl-coumarin-BODIPY for the selective detection of cysteine in living cells and artificial urine has been synthesized via a simple substitution reaction on the 5-position of XDS-BOD-XDS:BODIPY- Cl_2 (**68**) with the thiol group generated from 7-mercapto-4-methyl coumarin (**50**) to yield MC-BOD-XDS (**69**), XDS-BOD-XDS (**70**) (Scheme 23) [75]. The reactivity could be attributed to the free SH-coumarin, which quickly binds to another MC-BOD-XDS and produces strong red fluorescent XDS-BOD-XDS (**70**) [75].



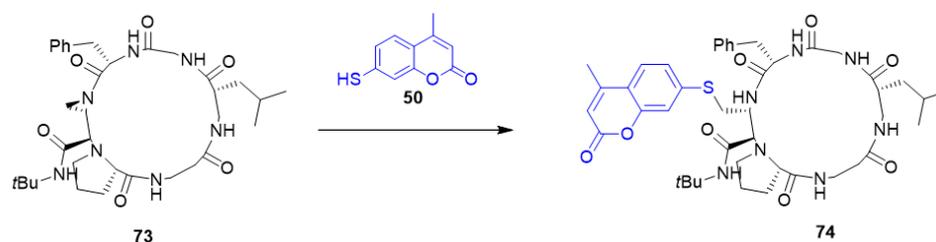
Scheme 23. Synthesis of fluorescent probe based on monosulfanyl-coumarin-BODIPY. BODIPY is the technical common name of a chemical compound with the formula $C_9H_7BN_2F_2$.

Özer et al. presented a new fluorescent chemosensor for some transition metals, which was obtained by conjugating two molecules of 7-mercapto-4-methyl coumarin (**50**) through a glyoxime bridge. This dimer was formed by a refluxing mixture of mercapto-coumarin, (*E,E*)-dichloroglyoxime DCGO, and NaHCO₃ in MeOH. The coumarin collaborates in this conjugate by its fluorophore property while vic-dioxime acts as a metal-chelating moiety. This chelating capability was expressed in the last step of the following scheme to deliver **72** (Scheme 24) [76].



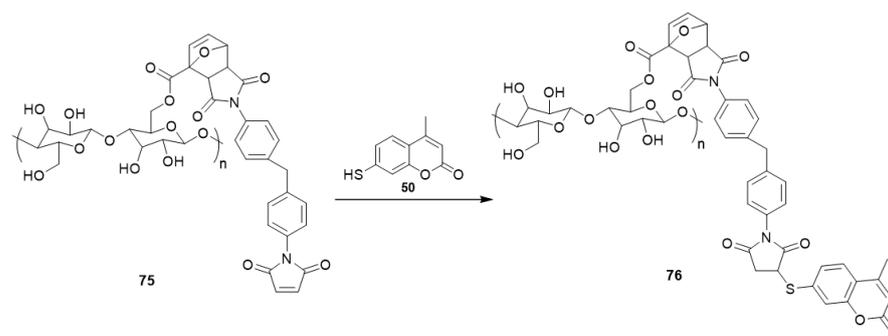
Scheme 24. Synthesis of fluorescent chemosensor for some transition metals. Reagents and conditions: (a) MeOH, (*E,E*)-dichloroglyoxime DCGO, reflux, NaHCO₃, 47% yield; (b) MX₂·6H₂O (M = Ni^{II}, Cu^{II}, Co^{II}, UO₂⁺²). X = NO₃, Et₃N, THF, 28–35% yield.

Hili et al. used the 7-mercapto-4-methyl coumarin (**50**) as a fluorescent tag, to demonstrate the cyclic peptide conjugation strategy through the nucleophilic ring-opening of an aziridine moiety during the macrocyclization of linear peptides enabled by amphoteric molecules (Scheme 25) [77].



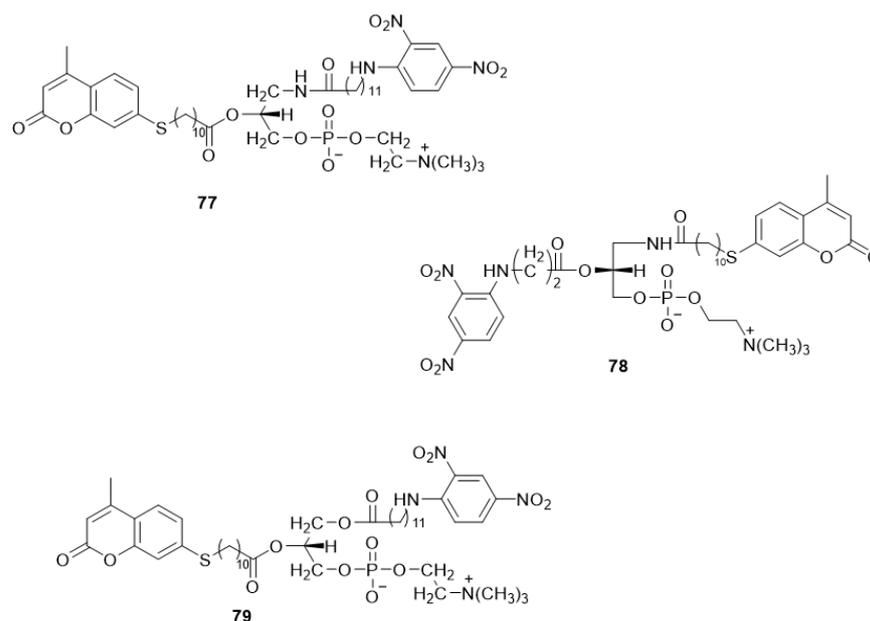
Scheme 25. The fluorescent tag, 7-mercapto-4-methyl coumarin. Reagents and conditions: CHCl₃, NEt₃, r.t., 77% yield.

Navarro et al. labeled the modified cellulose nanofibrils (CNFs) with furan and maleimide moieties by the fluorescent probe, 7-mercapto-4-methyl coumarin, through the thiol-Michael reaction (Scheme 26) [78]. The fluorescein/coumarin labeled cellulose nano-fibrils (FC-CNFs) avoid a dye-to-dye interaction (for the same molecule) with an expected wide biological application such as multimodality molecular imaging [78].



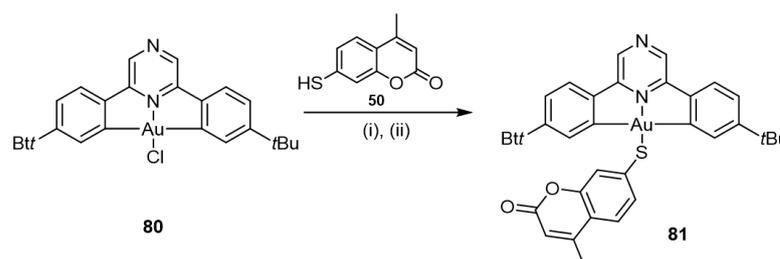
Scheme 26. Thiol-Michael reaction between maleimide-CNF and 7-mercapto-4-methyl coumarin. Reagents and conditions: DMSO, phosphate buffer (pH = 7), stirring, 24 h, r.t.

Hajdu and his co-workers reported the synthesis and enzymological characterization of three fluorogenic phosphatidylcholine analogs PC-1 (**77**), PC-2 (**78**), and PC-3 (**79**), targeting the detection and the quantitative assays of phospholipase A2 (sPLA2) [79]. Each demonstrated molecule contained a 7-mercapto-4-methyl coumarin fluorophore and 2,4-dinitroaniline quencher on both tails (Scheme 27) [79]. The small size of these molecules helps to not disrupt the natural membrane.



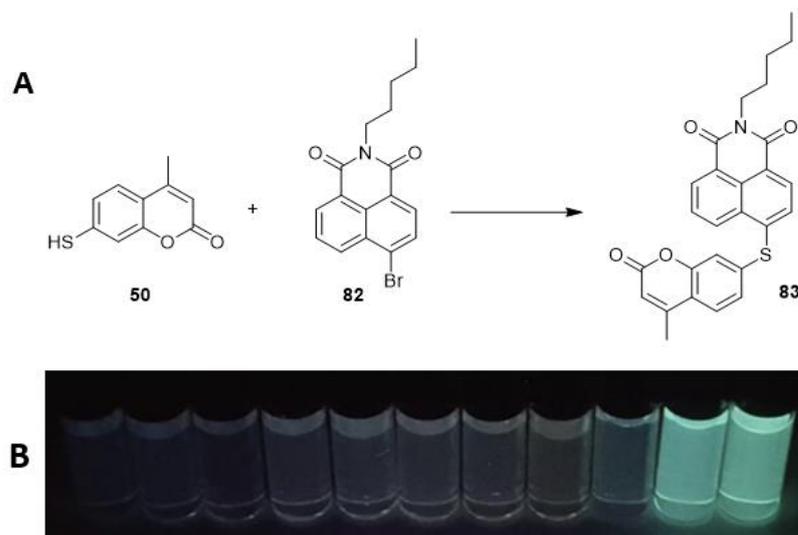
Scheme 27. Structures of fluorogenic phosphatidylcholine analogs.

Gold(III)–thiolato complexes based on cyclometallated pyrazine-centered pincer ligands form a new class of photoluminescent gold compounds. The luminescence behavior of these gold-core compounds depends on the arrangement of supramolecule in the solid and liquid forms [80]. $(C^{\wedge}N^{Pz^{\wedge}}C)AuSR$ (**81**) was prepared by the described method and isolated as a yellow to red solid (Scheme 28) [80]. In this formula, $C^{\wedge}N^{Pz^{\wedge}}C$ represents 2,6-bis(4-ButC₆H₄)pyrazine dianion and R is 7-mercapto-4-methyl coumarin [80].



Scheme 28. Gold(III)–thiolato complex. Reagents and conditions: (i) K₂CO₃, acetone, 18 h; (ii) potassium *t*-butoxide, N₂, dry toluene, 6 h, stirring, 84% yield.

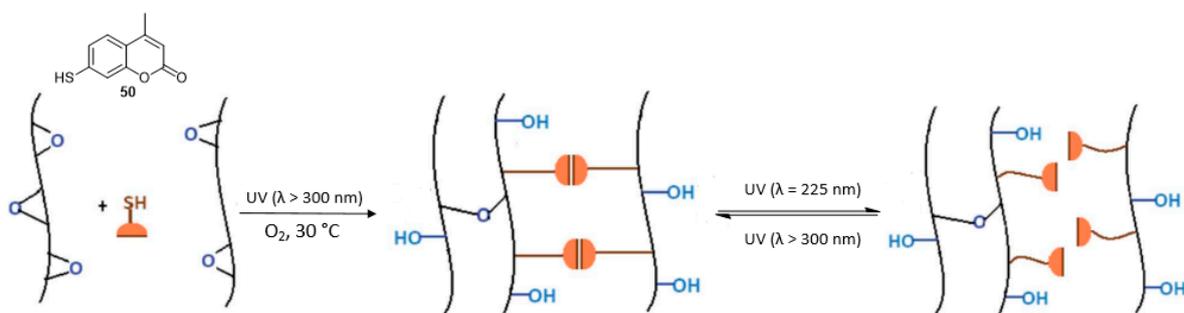
Choi and co-workers developed a naphthalimide–coumarin conjugate (NC) typically through thioether linkage (Scheme 29) [81]. 6-Bromo-2-butyl-benzo[de]isoquinoline-1,3-dione (**82**) reacted with 7-mercapto-4-methyl coumarin (**50**) in the presence of potassium carbonate to give 2-butyl-6-((4-methyl-2-oxo-2H-chromen-7-yl)thio)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**83**) (Scheme 29A) [81]. The molecular flexibility and the aggregation of the nanoparticles of the investigated compound (**83**) enhanced the aggregation-induced emission (Scheme 29B) [81].



Scheme 29. (A). The synthesis of the naphthalimide coumarins (NCs). Reagents and conditions: DMF, K_2CO_3 , N_2 , $90\text{ }^\circ\text{C}$, stirring 3 h, 74% yield. (B). Photographs were taken under 365 nm UV-light in different THF/ H_2O mixtures (50 μM).

7.2.3. 7-Mercapto-4-Methyl Coumarin as Photodimerizable and Healable Reactant

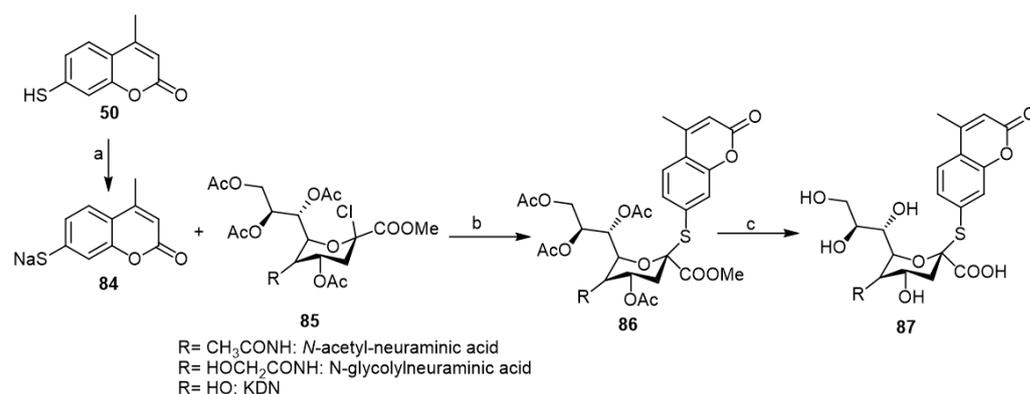
Zhao et al. exploited the photodimerization character of 7-mercapto-coumarin to introduce a novel bio-sourced self-healing technique. The epoxidized cottonseed oil was used as the main reagent, and it was photocrosslinked in the presence of 0.25 equivalents of 7-mercapto-4-methyl coumarin (50) as a photodimerizable and healable reactant. The reaction was initiated with 2 wt.% of a photo-based generator porphobilinogen (PBG) (Scheme 30) [82].



Scheme 30. 7-Mercapto-4-methyl coumarin as a photodimerizable and healable reactant.

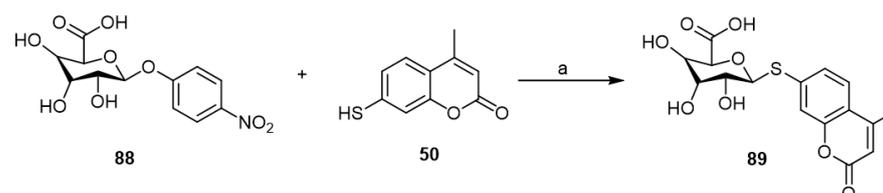
7.2.4. 7-Mercapto-4-Methyl Coumarin for Thioglycosylation Reaction

The reaction of 7-mercapto-4-methyl coumarin with glycosides and their possible applications have been in the scope of many researchers [83,84]. One such group was Tanaka et al., who investigated the synthesis of 4-methyl coumarin-7-yl- α -S-glycosides 87 by Williamson condition starting from *N*-acetyl-neuraminic acid, *N*-glycolylneuraminic acid, or 3-deoxy-*D*-glycero-*D*-galacto-2-non-ulopyranosonic acid (KDN) (85) (Scheme 31). The product is efficient as fluorogenic substrates for tracking and quantitative analysis of the bacterial enzyme neuramidase [85].



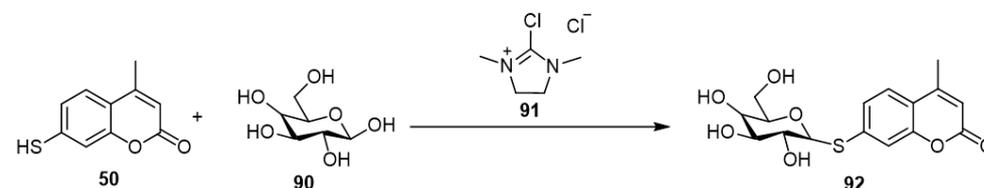
Scheme 31. Synthesis of new fluorogenic substrates for neuramidase. Reagents and conditions: (a) NaOH (1.0 N), MeOH, 60% yield; (b) DMF, overnight, r.t., stirring, three outputs 60–88% yield; (c) NaOH (1.0 N), MeOH, three outputs 90% yield.

Enzymatic synthesis of *S*-glycosides (**89**) from the reaction of 7-mercapto-4-methyl coumarin (**50**) as aromatic thiol acceptors and 4-nitrophenyl- β -D-glucuronide (*p*NP-GlcA) (**88**) as a sugar donor (glucuronide donor) was reported (Scheme 32) [86]. The reaction was efficiently glycosylated by *Dt*GlcA-E396Q (the mutated form of β -D-glucuronidase *Dt*GlcA) as a biocatalyst with a 51% yield in pKa 5.03 [86].



Scheme 32. Enzymatic synthesis of *S*-glycosides. Reagents and conditions: (a) *Dt*GlcA-E396Q, dichlorodiphenyltrichloroethane (DDT), 37 °C, o/n.

Yoshida et al. developed a novel oligosaccharide-labeling with 7-mercapto-4-methyl coumarin (MMC) as the detachable fluorescent tag linked to the anomeric center of unprotected sugar (**92**) (Scheme 33) [87]. The resulting MMC-labeled sugars (**92**) showed a high sensitivity for fluorescence detection and could be used for the quantification of oligosaccharide mixtures [87].

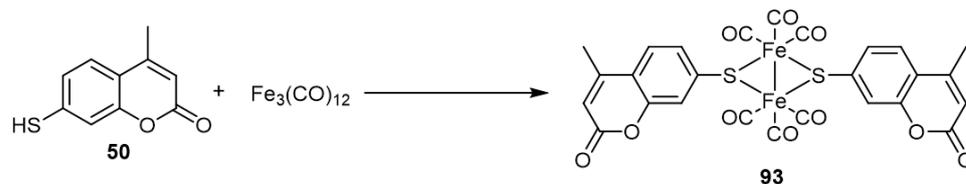


Scheme 33. MMC-labeled sugars. Reagents and conditions: TEA, CH₃CN/H₂O (1/1), 1.5 h, 0 °C, 46% yield.

7.2.5. 7-Mercapto-4-Methyl Coumarin as Metal Chelator (Complex Formation)

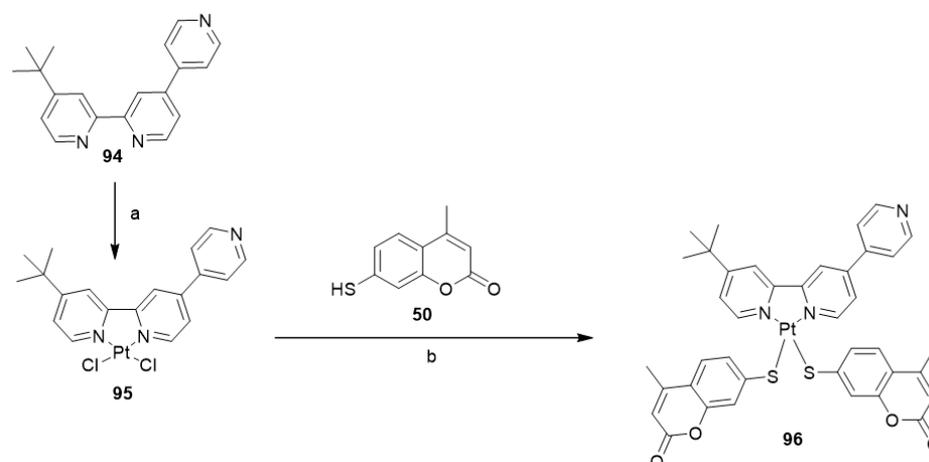
7-Mercapto-4-methyl coumarin (**50**) is characterized by its ability to accept transition metals and form metal chelates that play a prominent role in the development of coordination chemistry [88,89].

A diironhexacarbonyl cluster covalently linked to *S*-4-methyl coumarin (**93**) was synthesized (Scheme 34) [90]. The complex, **93**, is electrochemically unstable and exhibited photoinduced intramolecular electron transfer from coumarin to the iron-carbonyl unit [90].



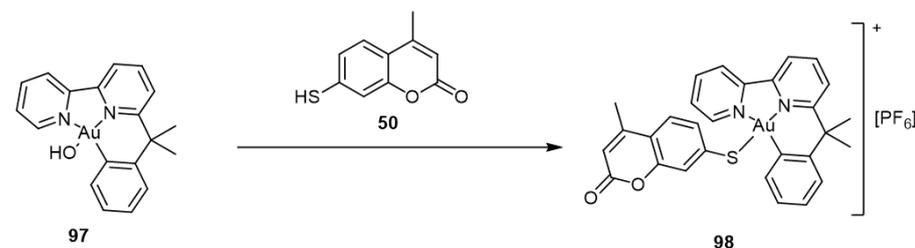
Scheme 34. Diironcarbonyl–coumarin complex. Reagents and conditions: THF, stirring, r.t., overnight, 77.5% yield.

Rank et al. demonstrated a bis(coumarin thiolate) complex (96) to constitute an interesting building block for multimetal structures in a “complexes as ligands” approach [88]. The reaction of the terpyridine ligand, 4-*t*-butyl-4'-(4-pyridinyl)-2,2'-bipyridine (94), with $[\text{PtCl}_2(\text{dmsO})_2]$ yielded the corresponding complex *cis*- $[\text{PtCl}_2(\text{L})]$ (95). The coupling reaction of with 7-mercapto-4-methyl coumarin led to the formation of the bis(coumarin thiolate) complex $[\text{Pt}(4\text{-methyl-coumarin-7-thiolate})_2(4\text{-}t\text{-butyl-4'-(4-pyridinyl)-2,2'-bipyridine})]$ (96) (Scheme 35) [88].



Scheme 35. Bis(coumarin thiolate) complex. Reagents and conditions: (a) DMF, reflux, 20 h, 53% yield; (b) KOH, MeOH, 5 min, stirring, 69% yield.

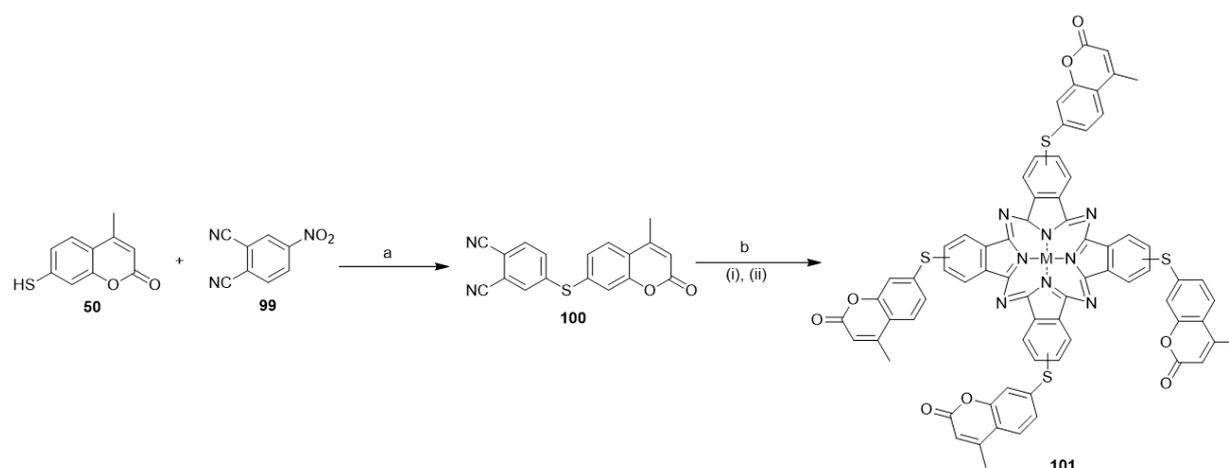
Carboni et al. synthesized novel (C[∞]N[∞]N) cyclometalated Au^{III} complexes with the general formula $[\text{Au}(\text{bipydmb-H})\text{X}][\text{PF}_6]$ (bipydmb-H is C[∞]N[∞]N cyclometalated 6-(1,1-dimethylbenzyl)-2,2'-bipyridine) (Scheme 36) [91]. The $[\text{Au}(\text{bipydmb-H})(\text{MeQS})][\text{PF}_6]$ (3- PF_6) including coumarin expressed distinctive biological activity as an anticancer agent against human lung epithelial cancer (A549) and human ovarian cancer (SKOV-3) cells [91].



Scheme 36. $[\text{Au}(\text{bipydmb-H})(\text{MeQS})][\text{PF}_6]$ (3- PF_6) complex. Reagents and conditions: dichloromethane, stirring, r.t., 24 h, 88% yield.

Novel metal-free and metallophthalocyanines with 7-thioether-4-methyl coumarin were prepared from the reaction of 7-mercapto-4-methyl coumarin (50) with 1,2-dicyano-4-nitrobenzene (99) to give 7-(3,4-dicyanophenylthio)-4-methyl coumarin (100) (Scheme 37) [92].

Cyclotetramerization of this structure under heating with dry 2-*N,N*-dimethylaminoethanol in a sealed tube afforded 2,9,16,23-tetrakis(7-coumarinthio-4-methyl)-phthalocyanine (**101a**). The latter chelated various metals in a reaction with their salts, $\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, CuCl , and $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, and gave the corresponding metallophthalocyanines **101b–e** (Scheme 37) [92].



Scheme 37. Synthesis of metallophthalocyanines. Reagents and conditions: (a) DMF, K_2CO_3 , r.t., 93.3% yield; (b) (i) heat $145\text{ }^\circ\text{C}$, sealed tube, $\text{M} = \text{H}$ (**92a**) with 63% yield; (ii) heat at $195\text{ }^\circ\text{C}$, dry quinolone, sealed tube, stirring, 24 h, $\text{M} = \text{Zn}$ (**92b**) 95.1% yield, $\text{M} = \text{Cu}$ (**92c**) 95.2% yield, $\text{M} = \text{Ni}$ (**92d**) 96% yield, $\text{M} = \text{Co}$ (**92e**) 96% yield.

8. Conclusions

Coumarins are one of the heterocyclic structures of great interest in the development of valuable structures with both biological and industrial applications.

Mercapto (or sulfanyl)-coumarins represent an interesting class of compounds that open many possibilities for further chemical transformations. As a nucleophile, mercapto-coumarin can be used to prepare derivatives with halides, activated halides, and in nucleophilic aromatic substitutions with the appropriate aromatic halides. They can also be used in Michael addition and Mannish reactions. Additionally, they can serve as an intermediate for the synthesis of thiophenes fused to coumarin as well as for the preparation of a thiocoumarin or a thiochromone ring.

Remarkably, 7-mercapto-4-methyl coumarin (MMC) shows the most useful structure for different applications. This substrate is considered as a starting compound to synthesize varieties of bioactive compounds. In addition, it plays an important role in materials science, where it serves as a reporter molecule, fluorescent probe, sugar acceptor, metal chelator (complex formation), and Raman reporter.

Finally, 5 and 8 mercapto-coumarins leave a lot of space for further investigation as there are not described in the literature. Even 8-mercapto-4,6-dimethyl coumarin was claimed to have been obtained [93], no proof of this structure was given.

Author Contributions: E.R.E.-S. and G.K. collected publications and sorted them. E.R.E.-S. analyzed the literature and wrote the first draft. A.B.A. and G.K. developed the concept of the review. E.R.E.-S., A.B.A. and G.K. wrote the final draft and corrected the manuscript. All authors have read and agreed to the published version of the manuscript.

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Sample Availability: Samples of the compounds are not available from the authors.

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