Review

Insight on Mercapto-Coumarins: Synthesis and Reactivity

Eslam Reda El-Sawy 1,* , Ahmed Bakr Abdelwahab 2* and Gilbert Kirsch 3,*

1 National Research Centre, Chemistry of Natural Compounds Department, Dokki, Cairo 12622, Egypt
2 Plant Advanced Technologies (PAT), 54500 Vandœuvre-lès-Nancy, France; ahm@plantadvanced.com
3 Laboratoire Lorrain de Chimie Moléculaire (L2CM), Université de Lorraine, 57050 Metz, France
* Correspondence: eslamelsawy@gmail.com (E.R.E.-S.); gilbert.kirsch@univ-lorraine.fr (G.K.);
Tel.: +33-03-72-74-92-00 (G.K.); Fax: +33-03-72-74-91-87 (G.K.)

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 (2H-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.
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].
The synthesis of 4-mercapto-coumarin (14) was achieved by reacting 3-mercapto-coumarin (4) with propargyl halides and 1-chloro-4-aryloxybut-2-yne, respectively (Scheme 9).

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 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: 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 2H-thiopyrano[3,2-c][1]benzopyran-5-ones (19) [28,29] and 4-aryloxymethylthiopyrano[3,2-c][1]benzopyran-5(2H)-ones (21) [19,30] were prepared through the thio-Claisen rearrangement of 4-propargylothio[1]benzopyran-2-ones (18) and 4-[4-aryloxylbut-2-ynythio][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 2H-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(2H)-ones (24), was reported through aryl radical cyclization. The corresponding 4-[(2-bromobenzyl)sulfanyl]-2H-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].

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)-2H-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 M) in water/acetonitrile (50/50), undivided cell equipped with graphite anode, a large stainless steel gauze cathode, 25 °C, R=CH₃ isomer ratio with 52.5%/47.5% yield, R=OCH₃ isomer ratio with 96.5%/3.5% yield; (b) sodium acetate solution (0.2 M)/acetonitrile (70/30), stirring, r.t., 20–30 min, R=CH₃ 75% yield, R=OCH₃ 70% yield.

A series of 3-chloro-1-(5-((2-oxo-2H-chromen-4-yl)thio)-4-phenyl thiazol-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-mercaptop-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-mercaptop-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 °C until the solution became clear. 6-Mercapto-coumarin (39) was used without further purification for the synthesis of 6-(4-aryloxybut-2-yynythio)[1]benzo-pyran-2-ones (41) by its reaction with l-aryloxy-4-chloro-but-2-ynes (40) (Scheme 14) [37].
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-hydroxy-coumarin (42) was treated with sodium hydride and subsequently reacted with dimethylthiocarbamoyl chloride (43) to yield the 2-oxo-2H-chromen-7-yl dimethylcarbamate (44). The latter was subjected to a Newman–Kwart-type rearrangement to form S-(2-oxo-2H-chromen-7-yl) dimethylcarbamothioate (45). Cleaving of the carbamate group of 45 afforded 7-mercapto-coumarin (46) [20] (Scheme 15).

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.

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-2H-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/CH$_2$Cl$_2$, 86% yield; (b) heating, 87% yield; (c) (i) NaOCH$_3$/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 α1 antagonistic activity [65]. In particular, compound 53c showed excellent activity, which was better than that of the reference compound prazosin [65]. 7-((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(CH$_2$)$_n$Br (n = 2–4), K$_2$CO$_3$, acetone, 4 h, reflux, five outputs 61–70% yield; (b) CH$_3$CN, K$_2$CO$_3$, 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-butylbenzoyloxy)-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 BrBr 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) TBDMS-Cl, imidazole, DMF, 12 h, r.t.; (ii) (BOC)$_2$O, Et$_3$N, DMAP, MeCN, 3 h, r.t.; (iii) NBS, (PhCO$_2$)$_2$, CCl$_4$, 4.5 h, 78 °C, 72% yield; (b) Et$_3$N, CH$_2$Cl$_2$, 4 h, r.t., 90% yield; (c) (i) BrBr or p-tBu-BnBr, KF, DMF, 4 h, r.t.; (ii) TFA, CH$_2$Cl$_2$, 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].

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 K₂CO₃/KI. The IC₅₀ of 62a and 62b as anti-HBsAg activities was (0.01 µmol/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 19. Synthesis of anti-AIDS agents. Reagents and conditions: (a) 3-bromo-1-propyne or 3-chloro-1-butene, K₂CO₃, KI, acetone, N₂, 58a: R=H 89.13%, 58b: R=CH₃ 75% yield; (b) N,N-diethylaniline, reflux, 59a: R=H 77.6%, 59b: R=CH₃ 56% yield; (c) (i) K₂OsO₄(OH)₄, K₃Fe(CN)₆, (DHQ)₂–PHAL, K₂CO₃, (ii) Na₂SO₃, 60a: R=H 51.3% yield, 60b: R=CH₃ (S configuration) 52% yield; (d) camphanic chloride, DMAP/CH₂Cl₂, 61a: R=H 95%, 61b: R=CH₃ 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 K₂CO₃/KI. The IC₅₀ of 62a and 62b as anti-HBsAg activities was (0.01 µmol/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, K₂CO₃, KI, acetone/N₂; (b) 2,6-dichloropyridine N-oxide, pyridine, r.t., 48% yield; (c) PCl₃, CHCl₃, 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)ethanoyl)-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 K₂CO₃-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 IC₅₀ (µM) of 0.12, 0.024, 0.036, 0.14, 0.22, respectively [69].

![Scheme 21](image1.png)

Scheme 21. Furoxan-based nitric oxide (NO) releasing S-coumarin. Reagents and conditions: (a) chloroethanol, K₂CO₃, acetone or DMF, reflux, 89% yield; (b) CH₂Cl₂, DBU, −15 °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](image2.png)

Scheme 22. Direct photocatalytic S–H Bond cyanation with green “CN” source. Reagents and conditions: Rose Bengal (1 mol%), CH₃CN, 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-Cl₂ (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](image3.png)

Scheme 23. Synthesis of fluorescent probe based on monosulfanyl-coumarin-BODIPY. BODIPY is the technical common name of a chemical compound with the formula C₃H₇BN₂F₂.
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 = NiII, CuII, CoII, UO₂²⁺), X = NO₃, Et₃N, THF, 28–35% yield.](image)

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.](image)

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.](image)
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-dinitroanaline 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’Npz)AuSR (81) was prepared by the described method and isolated as a yellow to red solid (Scheme 28) [80]. In this formula, C’Npz-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-mercaptop-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].
The product is efficient as fluorogenic substrates for tracking and quantitative analysis of the bacterial enzyme neuramidase [85].

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].

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-glycolyneuraminic acid, or 3-deoxy-D-glycero-D-galacto-2-non-ulpopyranosonic 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 (pNP-GlcA) (88) as a sugar donor (glucuronide donor) was reported (Scheme 32) [86]. The reaction was efficiently glycosylated by DtGlcA-E396Q (the mutated form of β-D-glucuronidase DtGlcA) as a biocatalyst with a 51% yield in pKa 5.03 [86].

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

Yoshida et al. developed a novel oligosaccharide-labeling with, 7-mercaptop-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, CH$_3$CN/H$_2$O (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′-butyl-4′-(4-pyridinyl)-2,2′-bipyridine (94), with [PtCl2(dmso)] yielded the corresponding complex cis-[PtCl2(L)] (95). The coupling reaction of with 7-mercapto-4-methyl coumarin led to the formation of the bis(coumarin thiolate) complex [Pt(4-methyl-coumarin-7-thiolate)2(4′-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 AuIII complexes with the general formula [Au(bipydmb-H)X][PF6] (bipydmb-H is C’N’N cyclometalated 6-(1,1-dimethylbenzyl)-2,2′-bipyridine) (Scheme 36) [91]. The [Au(bipydmb-H)(MeQS)][PF6] (3-PF6) 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. [Au(bipydmb-H)(MeQS)][PF6] (3-PF6) 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, Zn(CH\textsubscript{3}COO)\textsubscript{2}.2H\textsubscript{2}O, NiCl\textsubscript{2}.6H\textsubscript{2}O, CuCl, and CoCl\textsubscript{2}.6H\textsubscript{2}O, and gave the corresponding metallophthalocyanines 101b–e (Scheme 37) [92].

Scheme 37. Synthesis of metallophthalocyanines. Reagents and conditions: (a) DMF, K\textsubscript{2}CO\textsubscript{3}, r.t., 93.3% yield; (b) (i) heat 145 °C, sealed tube, M = H (92a) with 63% yield; (ii) heat at 195 °C, dry quinolone, sealed tube, stirring, 24 h, M = Zn (92b) 95.1% yield, M = Cu (92c) 95.2% yield, M = Ni (92d) 96% yield, M = 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.

Funding: The APC was funded by MDPI.

Conflicts of Interest: The authors declare no conflict of interest.

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

1. Lončar, M.; Jakovljević, M.; Šubarić, D.; Pavlić, M.; Buzjak Služek, V.; Cindrić, I.; Molnar, M. Coumarins in Food and Methods of Their Determination. *Foods* **2020**, *9*, 645. [CrossRef] [PubMed]

2. Ballin, N.Z.; Sørensen, A.T. Coumarin Content in Cinnamon Containing Food Products on the Danish Market. *Food Control* **2014**, *38*, 198–203. [CrossRef]

3. Coumarin Perfume Ingredient, Coumarin Fragrance and Essential Oils Benzopyrone. Available online: https://www.fragrantica.com/notes/Coumarin-259.html (accessed on 25 February 2022).

4. Stiefel, C.; Schubert, T.; Morlock, G.E. Bioprofiling of Cosmetics with Focus on Streamlined Coumarin Analysis. *ACS Omega* **2017**, *2*, 5242–5250. [CrossRef] [PubMed]

5. Agić, D.; Karnaš, M.; Šubarić, D.; Lončar, M.; Jakovljević, M.; Pavlić, M.; Buzjak Služek, V.; Cindrić, I.; Molnar, M. Coumarins in Food and Methods of Their Determination. *Foods* **2017**, 7, 43. [CrossRef] [PubMed]

6. Patil, S.; Jalde, S.; Patil, G. Medicinal Significance of Novel Coumarins: A Review. *Int. J. Curr. Pharm. Res.*** 2021, *13*, 1–5. [CrossRef]

7. Zhang, G.; Zheng, H.; Guo, M.; Du, L.; Liu, G. Wang, P. Synthesis of Polymeric Fluorescent Brightener Based on Coumarin and Its Performances on Paper as Light Stabilizer, Fluorescent Brightener and Surface Sizing Agent. *Appl. Surf. Sci.* **2016**, *367*, 167–173. [CrossRef]

8. Davis, A.B.; Ihde, M.H.; Busenlehner, A.M.; Davis, D.L.; Mia, R.; Panella, J.; Fronzcek, F.R.; Bonizzoni, M.; Wallace, K.J. Structural Features of a Family of Coumarin–Ename Fluorescent Chemodosimeters for Ion Pairs. *Inorg. Chem.* **2021**, *60*, 14238–14252. [CrossRef]

9. Sun, X.; Liu, T.; Sun, J.; Wang, X. Synthesis and Application of Coumarin Fluorescence Probes. *RSC Adv.* **2020**, *10*, 10826–10847. [CrossRef]

10. Oliveira, E.; Bertolo, E.; Nuñez, C.; Pilla, V.; Santos, H.M.; Fernández-Lodeiro, J.; Fernández-Lodeiro, A.; Djafari, J.; Capelo, J.L.; Lodeiro, C. Green and Red Fluorescent Dyes for Translational Applications in Imaging and Sensing Analytes: A Dual-Color Flag. *ChemistryOpen* **2017**, 7, 3. [CrossRef]

11. Bakhhtiari, G.; Dehaghi, S.; Soltanali, S. A Novel Method for the Synthesis of Coumarin Laser Dyes Derived from 3-(1H-Benzimidazol-2-yl) Coumarin-2-One under Microwave Irradiation. *Arab. J. Chem.* **2011**, 7, 972–975. [CrossRef]

12. Pereira, T.M.; Franco, D.P.; Vitorio, F.; Kummerle, A.E. Coumarin Compounds in Medicinal Chemistry: Some Important Examples from the Last Years. *Curr. Top. Med. Chem.* **2018**, *18*, 124–148. [CrossRef] [PubMed]

13. Arya, C.G.; Gondru, R.; Li, Y.; Banothu, J.; Coumarin–Benzimidazole Hybrids: A Review of Developments in Medicinal Chemistry. *Eur. J. Med. Chem.* **2022**, 227, 113921. [CrossRef]

14. Qiao, Z.; Jiang, X. Recent Developments in Sulfor–Carbon Bond Formation Reaction Involving Thiosulfates. *Org. Biomol. Chem.* **2017**, 15, 1942–1946. [CrossRef] [PubMed]

15. Wimmer, A.; König, B. Photocatalytic Formation of Carbon–Sulfur Bonds. *Beilstein J. Org. Chem.* **2018**, 14, 54–83. [CrossRef] [PubMed]

16. Yang, D.; Yan, Q.; Zhu, E.; Lv, J.; He, W.-M. Carbon–Sulfur Bond Formation via Photochemical Strategies: An Efficient Method for the Synthesis of Sulfur-Containing Compounds. *Chim. Chim. Acta* **2021**, in press. [CrossRef]

17. Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T.S.A.; Liu, X. Recent Advances in C–S Bond Formation via C–H Bond Functionalization and Decarboxylation. *Chem. Soc. Rev.* **2014**, 44, 291–314. [CrossRef]

18. Qiyi, X.; Wenjiang, W.; Dayan, H. 3-Thiolcoumarin and Its Derivatives. *Acta Chim. Sin.* **1987**, 45, 344. [PubMed]

19. Ghosh, S.K. Studies on Thio-Claisen Rearrangement of Propargyl Vinyl Sulphide Moiety in Presence of Aryl Propargyl Ether Segment to Give 4-Aryloxymethyl-2H-Thiopyrano[3,2-c][1]Benzopyran-5(2H)-Ones. *IÖSR J. Appl. Chem.* (IÖSR-JAC) **2015**, 8, 55–59.

20. van Rensburg, C.J.; Robinson, R.S. Synthesis of Oxo- and Thio-Analogues of 2-Oxo-2H-Chromen-7-Yl Dimethylcarbamates: Research Article. *S. Afr. J. Chem.* **2009**, 62, 143–148. [CrossRef]

21. Chen, Y.; Zhang, Q.; Zhang, B.; Xia, P.; Xia, Y.; Yang, Z.-Y.; Kilgore, N.; Wild, C.; Eisenbrand, G. Coumarin Mercapturic Acid Isolated from Rat Urine Indicates Metabolic Formation of Coumarin 3,4-Epoxide. *Chem. Res. Toxicol.* **1991**, 4, 586–590. [CrossRef] [PubMed]

22. Yadav, L.D.; Singha, M.; Rai, V.K. Catalyst-Free, Step and Pot Economic, Efficient Mercurioaetylative Cyclisation in H2O: Synthesis of 3-Mercaptocoumarins. *Green Chem.* **2009**, 11, 878–882. [CrossRef]

23. Da-Yan, H.; Qi-Yi, X.; Sheng, J.; Mu-Jian, L. Kinetic Study of The Mannich Reaction of 3-Thiolcoumarin With Diphenylamine. *Acta Phys. Chim. Sin.* **1990**, 6, 699–705. [CrossRef]

24. Fan, B.; Gao, W.; Lv, X.; Tao, M.; Chen, Y.; Li, G. Process for the Preparation of Benzothiophene-2-Carboxylic Acid from 3-Mercaptocoumarin. 2016. Available online: https://patents.google.com/patent/US20170254611A1/en (accessed on 1 March 2022).

25. Huwer, T.; Altmann, H.J.; Grunow, W.; Lenhardt, S.; Przybylski, M.; Eisenbrand, G. Culmoforin Mercuric Acid Isolated from Rat Urine Indicates Metabolic Formation of Coumarin 3,4-Epoxide. *Chem. Res. Toxicol.* **1991**, 4, 586–590. [CrossRef] [PubMed]

26. Eisenbrand, G.; Otteneder, M.; Tang, W. Synthesis of N-Acetyl-S-(3-Coumarinyl)-Cystine Methyl Ester and HPLC Analysis of Urinary Coumarin Metabolites. *Toxicology* **2003**, 190, 249–258. [CrossRef]

27. Peinhardt, G.; Reppel, L. Contributions to the Knowledge of the Coumarins. Communication: Representation of 4-Mercurioacoumarin and the Thioethers Derived from It. *Pharmazie* **1970**, 25, 68–69. [PubMed]
28. Majumdar, K.C.; Ghosh, S.K. Studies of Bioactive Heterocycles: Facile Thiio-Claissen Rearrangement of Propargylthio[1]Benzopyran-2-Ones. Tetrahedron Lett. 2002, 43, 2115–2117. [CrossRef]

29. Ghosh, S.K. Thioclaissen Rearrangement: An Expedient Avenue for the Synthesis of 2H-Thiopyrano[3,2-c][1]Benzopyran-5-Ones. IOSR J. Appl. Chem. (IOSR-JAC) 2015, 8, 60–63.

30. Majumdar, K.C.; Kundu, U.K.; Ghosh, S.K. Studies in Sigmatropic Rearrangement: Synthesis of a [6,6]Pyranothiopyrano Ring System by Sequential Claissen Rearrangement and Pyridine Hydrotrithiolomide Mediated Regioselective “6-Endo” Cyclization. Org. Lett. 2002, 4, 2629–2631. [CrossRef]

31. Eiden, F.; Zimmermann, E. The reaction of 4-hydroxycoumarin, 4-hydroxy-1-thiocoumarin and 4-mercaptocoumarin with diphenylketene. Arch. Pharm. 1976, 309, 619–624. [CrossRef]

32. Majumdar, K.C.; Biswas, A.; Mukhopadhyay, P. Carbon-Carbon Bond Formation by Radical Cyclisation: Regioselective Synthesis of Coumarin-Annulated Sulfur Heterocycles. Synthesis 2003, 15, 2385–2389. [CrossRef]

33. Majumdar, K.C.; Biswas, A. Regioselective Synthesis of Thieno[3,2-c][1]Benzopyran-4-Ones by Thio-Claissen Rearrangement. Mon. Chem. 2004, 135, 1001–1007. [CrossRef]

34. Nematollahi, D.; Azizian, J.; Sargordan-Arani, M.; Hesari, M.; Jameh-Bozorgi, S.; Alizadeh, A.; Fotouhi, L.; Mirza, B. Electrochemical Synthesis of 4-(Dihydroxyphenylthio)-2H-Chromen-2-One Derivatives. Chem. Pharm. Bull. 2008, 56, 1562–1566.

35. Nematollahi, D.; Azizian, J.; Arani, M.; Hesari, M.; Mirza, B. A Facile Method for the Synthesis of Thioucousmaten Derivatives. J. Heterocycl. Chem. 2009, 46, 1000–1002. [CrossRef]

36. Subramaniam, R.; Rao, G.K.; Pai, S.; Ranjan, A. Design, Synthesis, Antibacterial and Invitro Antioxidant Activity of Substituted 2benzopyran-2-One Derivatives. Int. J. ChemTech Res. 2011, 3, 555–559.

37. Majumdar, K.C.; Biswas, P. Synthesis of Bioactive Heterocycles One Pot Regioselective Synthesis of Pyrano Benzo Thiophene Derivatives. Tetrahedron 1999, 55, 1449–1456. [CrossRef]

38. Ibis, C.; Ayla, S.S.; Bahar, H.; Stasevyych, M.V.; Komarovska-Porokhnyavets, O.; Novikov, V. Synthesis, Characterization, and Biological Properties of Novel Piperidinyl-, Piperidinyl-, and Piperazinyl-Substituted Naphthoquinone Compounds and Their Reactions with Some Thiols. Phosphorus Sulfur Silicon Relat. Elem. 2015, 190, 1422–1433. [CrossRef]

39. Ibis, C.; Ayla, S.S.; Ozkok, F.; Bahar, H. Synthesis of New Piperazinyl and Piperidinyl Substituted P-Chloranil Derivatives and Their Reactions with Thiols. Phosphorus Sulfur Silicon Relat. Elem. 2015, 190, 2273–2282. [CrossRef]

40. Feng, C.-H.; Lu, C.-Y. A New Matrix for Analyzing Low Molecular Mass Compounds and Its Application for Determination of Carcinogenic Areca Alkaloids by Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry. Anal. Chim. Acta 2009, 649, 230–235. [CrossRef]

41. Koktan, J.; Královec, K.; Havelek, R.; Kuličková, J.; Řezanka, P.; Kaman, O. Magnetic Oxide Particles with Gold Nanoshells: Synthesis, Properties and Cytotoxic Effects. Colloids Surf. A Physicochem. Eng. Asp. 2017, 520, 922–932. [CrossRef]

42. Gonzalez-Bejar, M.; Frenette, M.; Jorge, L.; Scaino, J.C. 7-Mercapto-4-Methylcoumarin as a Reporter of Thiol Binding to the CdSe Quantum Dot Surface. Chem. Commun. 2009, 3202–3204. [CrossRef]

43. Galardon, E.; Tomas, A.; Roussel, P.; Artaud, I. New Fluorescent Zinc Complexes: Towards Specific Sensors for Hydrogen Sulfide in Solution. Dalton Trans. 2009, 9126–9130. [CrossRef]

44. Ge, C.; Wang, H.; Zhang, B.; Yao, J.; Li, X.; Feng, W.; Zhou, P.; Wang, Y.; Fang, J. A Thiol–Thiosulfonate Reaction Providing a Novel Strategy for Turn-on Thiol Sensing. Chem. Commun. 2015, 51, 14913–14916. [CrossRef] [PubMed]

45. Varandas, P.A.M.M.; Cobb, A.J.A.; Segundo, M.A.; Silva, E.M.P. Emergent Glycerothiophospholipid Fluorescent Probes: Synthesis and Applications. Bioconjug. Chem. 2020, 31, 417–435. [CrossRef] [PubMed]

46. Chiu, H.-H.; Shen, M.-Y.; Liu, Y.-T.; Fu, Y.-L.; Chiu, Y.-A.; Chen, Y.-H.; Huang, C.-P.; Li, Y.-K. Diversity of Sugar Acceptor of Glycosyltransferase 1 from Bacillus Cereus and Its Application for Glucoside Synthesis. Appl. Microbiol. Biotechnol. 2016, 100, 4459–4471. [CrossRef]

47. Kamil Reza, K.; Wang, J.; Vaidyanathan, R.; Dey, S.; Wang, Y.; Trau, M. Electrohydrodynamic-Induced SERS Immunoassay for Extensive Multiplexed Biomarker Sensing. Small 2017, 13, 1602902. [CrossRef]

48. Cara, E.; Mandrile, L.; Ferrarese L, F.; Giovannozzi, A.M.; Dialameh, M.; Portesi, C.; Sparnacci, K.; De Leo, N.; Rossi, A.M.; Boarino, L. Influence of the Long-Range Ordering of Gold-Coated Si Nanowires on SERS. Sci. Rep. 2018, 8, 11305. [CrossRef]

49. Sacco, A.; Mangino, S.; Portesi, C.; Vittone, E.; Rossi, A.M. Novel Approaches in Tip-Enhanced Raman Spectroscopy: Accurate Measurement of Enhancement Factors and Pesticide Detection in Tip Dimer Configuration. J. Phys. Chem. C 2019, 123, 24723–24730. [CrossRef] [PubMed]

50. Reza, K.K.; Dey, S.; Wuethrich, B.; Kim, K.-H.; Deep, A. Advanced Functional Structure-Based Sensing and Imaging Strategies for Cancer Detection: Possibilities, Opportunities, Challenges, and Prospects. Adv. Funct. Mater. 2019, 29, 1807859. [CrossRef]

51. Mandrile, L.; Giovannozzi, A.M.; Sacco, A.; Martra, G.; Rossi, A.M. Flexible and Transparent Substrates Based on Gold Nanoparticles and TiO$_2$ for in Situ Bioanalysis by Surface-Enhanced Raman Spectroscopy. Biosensors 2019, 9, 145. [CrossRef] [PubMed]
54. Stepula, E.; König, M.; Wang, X.-P.; Levermann, J.; Schimming, T.; Kasimir-Bauer, S.; Schilling, B.; Schlücker, S. Localization of PD-L1 on Single Cancer Cells by ISERS Microscopy with Au/Au Core/Satellite Nanoparticles. *J. Biophotonics* **2020**, *13*, e201960034. [CrossRef] [PubMed]

55. D’Agostino, A.; Giovannozzi, A.M.; Mandrile, L.; Sacco, A.; Rossi, A.M.; Taglietti, A. In Situ Seed-Growth Synthesis of Silver Nanoplates on Glass for the Detection of Food Contaminants by Surface Enhanced Raman Scattering. *Talanta* **2020**, *216*, 120936. [CrossRef] [PubMed]

56. Fu, K.; Wang, X.; Yuan, X.; Wang, D.; Mi, X.; Tan, X.; Zhang, Y. Size-Dependent Penetration of Gold Nanoprobe into Fixed Cells. *ACS Omega* **2021**, *6*, 3791–3799. [CrossRef]

57. Bard, A.; Rondon, R.; Marquez, D.T.; Lanterna, A.E.; Scaiano, J.C. How Fast Can Thiols Bind to the Gold Nanoparticle Surface? *Photochem. Photobiol. Sci.* **2018**, *9*, 1109–1115. [CrossRef]

58. Reddy, K.R.; El-Zein, A.; Airey, D.W.; Alonso-Marroquin, F.; Schubel, P.; Manalo, A. Self-Healing Polymers: Synthesis Methods and Applications. *Nano-Struct. Nano-Objects* **2020**, *23*, 100500. [CrossRef]

59. Gulyuz, S.; Bayram, D.; Ozkose, U.U.; Bolat, Z.B.; Kocak, P.; Saka, O.M.; Devrim, B.; Parlak Khalili, M.; Telci, D.; Sahin, F.; et al. Synthesis, Biocompatibility and Gene Encapsulation of Poly(2-Ethyl 2-Oxazine)-Dioleoyl Phosphatidylethanolamine (PEtOx-DOPE) and Post-Modifications with Peptides and Fluorescent Dye Coumarin. *Int. J. Polym. Mater. Polym. Biomater.* **2021**, *70*, 981–993. [CrossRef]

60. Gospodova, T.; Rashkova, J.; Ivanova, D.; Viteva, L.; Duprat, C.; Marie-Rose, M.; Bakalova, S.; Kaneti, J. Synthetic Potentials of Thiophtalimide Mercocyanine Dyes Containing an Active Chlorine Atom: Reactivity towards Nucleophiles. *Eur. J. Org. Chem.* **2009**, *2009*, 5063–5071. [CrossRef]

61. Cara, E.; Mandrile, L.; Sacco, A.; Giovannozzi, A.M.; Rossi, A.M.; Celegato, F.; Leo, N.D.; Hönnicke, P.; Kayser, Y.; Beckhoff, B.; et al. Towards a Traceable Enhancement Factor in Surface-Enhanced Raman Spectroscopy. *J. Mater. Chem. C* **2020**, *8*, 16513–16519. [CrossRef]

62. Chen, Y.; Zhou, J.; Wang, H.; Xia, Y.; Yang, Z.Y.; Xia, P. Synthesis and Anti-HBV Activity of S-Substituted 7-Mercapto-4-Methylcoumarin Analogs. *Chin. Chem. Lett.* **2008**, *19*, 925–927. [CrossRef]

63. Newman, M.S.; Karnes, H.A. The Conversion of Phenols to Thiophenols via Dialkythiocarbamates. *J. Org. Chem.* **1966**, *12*, 3980–3984. [CrossRef]

64. Xu, S.-Q.; Yan, X.; Chen, Y.; Xia, P.; Qian, K.; Yu, D.; Xia, Y.; Yang, Z.-Y.; Morris-Natschke, S.L.; Lee, K.-H. Anti-AIDS Agents 84. Synthesis and Anti-Human Immunodeficiency Virus (HIV) Activity of 2′-Monomethyl-4-Methyl- and 1′-Thia-4-Methyl-(3′,R,4′,R)-3′,4′-Di-O-(S)-Camphanoyl-(+)-Cis-Khellactone (DCK) Analogs. *Bioorg. Med. Chem.* **2010**, *18*, 7203–7211. [CrossRef] [PubMed]

65. Xie, S.-S.; Wang, X.-B.; Liu, J.-Y.; Kong, L.-Y. Design, Synthesis and Biological Evaluation of Novel 7-Mercaptocoumarin Derivatives as A1-Adenosine Receptor Antagonists. *Chem. Pharm. Bull.* **2013**, *61*, 16–24. [CrossRef]

66. Rodighiero, P.; Pastorni, G.; Chilin, A.; Marotto, A. Synthesis of Methyl Derivatives of Linear and Angular Thienochromins and Thiopyranocoumarins. *J. Heterocycl. Chem.* **1998**, *35*, 847–852. [CrossRef]

67. Boehm, H.-J.; Boehringer, M.; Bur, D.; Gmuender, H.; Huber, W.; Klaus, W.; Kostrewa, D.; Kuehne, H.; Luebbers, T.; Meunier-Keller, N.; et al. Novel Inhibitors of DNA Gyrase: 3D Structure Based Biased Needle Screening, Hit Validation by Biophysical Methods, and 3D Guided Optimization. A Promising Alternative to Random Screening. *J. Med. Chem.* **2000**, *43*, 2664–2674. [CrossRef] [PubMed]

68. Chen, Y.; Liu, H.-R.; Liu, H.-S.; Cheng, M.; Xia, P.; Qian, K.; Wu, P.-C.; Lai, C.-Y.; Xia, Y.; Yang, Z.-Y.; et al. Antitumor Agents 292. Design, Synthesis and Pharmacological Study of S- and O-Substituted 7-Mercapto- or Hydroxy-Coumarins and Chromones as Potent Cytotoxic Agents. *Eur. J. Med. Chem.* **2012**, *49*, 74–85. [CrossRef] [PubMed]

69. Liu, M.-M.; Chiri, Y.; Yuan, X.; Zhang, Y.; Yu, D.; Xia, Y.; Yang, Z.-Y.; Xia, P.; Qian, K.; et al. Synthesis and Anti-HIV Activity of S-Substituted 7-Mercapto- or Hydroxy-Coumarins and Chromones as Potent Antitumor Agents. *J. Med. Chem.* **2013**, *57*, 9343–9356. [CrossRef] [PubMed]

70. Guo, W.; Tan, W.; Zhao, M.; Zheng, L.; Tao, K.; Chen, D.; Fan, X. Direct Photocatalytic S-H Bond Cyanation with Green “CN” Source. *J. Org. Chem.* **2018**, *83*, 6580–6588. [CrossRef]

71. Lanterna, A.E.; Gonzalez-Bajar, M.; Frenette, M.; Sciano, J.C. Photophysics of 7-Mercapto-4-Methylcoumarin and Derivatives: Complementary Fluorescence Behaviour to 7-Hydroxycoumarins. *Photochem. Photobiol. Sci.* **2017**, *16*, 1284–1289. [CrossRef]

72. Bae, J.; Choi, J.; Park, T.J.; Chang, S.-K. Reaction-Based Colorimetric and Fluorogenic Signaling of Hydrogen Sulfide Using a 7-Nitro-2,1,3-Benzoxadiazole–Coumarin Conjugate. *Tetrahedron Lett.* **2014**, *55*, 1171–1174. [CrossRef]

73. Brogan, A.P.; Widger, W.R.; Kohn, H. Bicyclomycin Fluorescent Probes: Synthesis and Biochemical, Biophysical, and Biological Properties. *J. Org. Chem.* **2003**, *68*, 5575–5587. [CrossRef] [PubMed]

74. Mukherjee, S.; Brooks, W.L.A.; Dai, Y.; Sumerlin, B.S. Doubly-Dynamic-Covalent Polymers Composed of Oxime and Oxanorbornene Links. *Polym. Chem.* **2016**, *7*, 1971–1978. [CrossRef]

75. Liu, X.; Wei, H.; Yan, M.; Hai, G.; Li, Q.; Yan, R.; Zhao, S.; Zhao, X.; Sun, X.; Zhang, T. The Two-Steps Reaction Fluorescent Probe for the Selective Detection of Cysteine and Its Applications. *Chem. Biodivers.* **2021**, *19*, e202100862. [CrossRef] [PubMed]

76. Özer, M.; Kandaz, M.; Ozkaya, A.; Bulut, M.; Güney, O. Fluorescent Vic-Dioxime-Type Ligand and Its Mono- and Dinuclear Complexes: The Preparation, Spectroscopy, and Electrochemistry of Its Various Complexes. *Dye. Pigment.* **2008**, *76*, 125–132. [CrossRef]
77. Hili, R.; Rai, V.; Yudin, A.K. Macrocyclization of Linear Peptides Enabled by Amphoteric Molecules. *J. Am. Chem. Soc.* 2010, 132, 2889–2891. [CrossRef]

78. Navarro, J.R.G.; Conzatti, G.; Yu, Y.; Fall, A.B.; Mathew, R.; Edén, M.; Bergström, L. Multicolor Fluorescent Labeling of Cellulose Nanofibrils by Click Chemistry. *Biomacromolecules* 2015, 16, 1293–1300. [CrossRef]

79. Keshavarz, A.; Zelaya, L.; Singh, J.; Ranganathan, R.; Hajdu, J. Activity-Based Targeting of Secretory Phospholipase A2 Enzymes: A Fatty-Acid-Binding-Inhibitor Assisted Approach. *Chem. Phys. Lipids* 2017, 202, 36–48. [CrossRef]

80. Currie, L.; Fernandez-Cestau, J.; Rocchigiani, L.; Bertrand, B.; Lancaster, S.J.; Hughes, D.L.; Duckworth, H.; Jones, S.T.E.; Credgington, D.; Penfold, T.; et al. Luminescent Gold(III) Thiolates: Supramolecular Interactions Trigger and Control Switchable Photoemissions from Bimolecular Excited States. *Chem. Eur. J.* 2017, 23, 105–113. [CrossRef]

81. Zhao, Y.H.; Vuluga, D.; Lecamp, L.; Burel, F. Photoinitiated Thiol–Epoxy Addition for the Preparation of Photoinduced Self-Healing Coatings. *RSC Adv.* 2016, 6, 32098–32105. [CrossRef]

82. Stubbs, K.A.; Macauley, M.S.; Voca, D.J. A Highly Concise Preparation of O-Deacetylated Arylthioglycosides of N-Acetyl-D-Glucosamine from 2-Acetamido-3,4,6-Tri-O-Acetyl-2-Deoxy-Alpha-D-Glucopyranosyl Chloride and Aryl Thiol or Disulfides. *Carbohydr. Res.* 2006, 341, 1764–1769. [CrossRef] [PubMed]

83. Rodrigue, J.; Ganne, G.; Blanchard, B.; Sauzier, C.; Giguère, D.; Shia, T.C.; Varrot, A.; Imbert, A.; Roy, R. Aromatic Thioglycoside Inhibitors against the Virulence Factor LecA from Pseudomonas Aeruginosa. *Org. Biomol. Chem.* 2013, 11, 6906–6918. [CrossRef]

84. Tanaka, M.; Kai, T.; Sun, X.-L.; Takayanagi, H.; Uda, Y.; Furuhata, K. Synthesis of Fluorescent 4-Methyl-7-Thiocoumaryl S-Glycosides of Sialic Acid. *Chem. Pharm. Bull.* 1995, 43, 1844–1848. [CrossRef]

85. Kurdi, M.; Kopeć, M.; Páris, A.; Lewinski, K.; Lafite, P.; Daniellou, R. Thioglycoligation of Aromatic Thiols Using a Natural Glucuronic Acid Donor. *Org. Biomol. Chem.* 2020, 18, 5582–5585. [CrossRef] [PubMed]

86. Yoshida, N.; Fujieda, T.; Kobayashi, A.; Ishihara, M.; Noguchi, M.; Shoda, S. Direct Introduction of Detachable Fluorescent Tag into Oligosaccharides. *Chem. Lett.* 2013, 42, 1038–1039. [CrossRef]

87. Rack, M.; Zabel, M.; Winter, R.F. Pyridine vs. Bipyridine Coordination in PtCl2 Complexes of 4-TButyl-4’-(4-Pyridinyl)-2,2’-Bipyridine. *Z. Anorg. Allg. Chem.* 2013, 639, 2565–2574. [CrossRef]

88. Giannini, F.; Paul, L.E.H.; Furrer, J.; Therrien, B.; Süss-Fink, G. Highly Cytotoxic Diruthenium Trithiolato Complexes of the Type [[H6-p-MeC6H4Pri]2Ru2(M2-SR)3]+: Synthesis, Characterization, Molecular Structure and in Vitro Anticancer Activity. *New J. Chem.* 2013, 37, 3503–3511. [CrossRef]

89. Mebi, C.; Trujillo, J.; Bhiuiyan, A. Diironcarbonyl-Coumarin Complex: Preparation, Intramolecular Electron Transfer, and Electrogen-Generating Hydrogen. *Open Chem.* 2012, 10, 1218–1222. [CrossRef]

90. Aslı Esenpınar, A.; Bulut, M. Synthesis and Characterization of Metal-Free and Metallo-Phthalocyanines with Four Pendant Coumarin/Phospholpyranones with Four Pendant Coumarin/Oxy-Substituents. *Dyes. Pigment.* 2008, 76, 249–255. [CrossRef]

91. der Versuche, B. 4,7-Dimethyl-Coumarin-6-Sulfonsaure. *Krueger Chem. Ber.* 1923, 56, 481–488.