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Short Note

4-Methyl-7-((2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethyl) thio)-coumarin

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Abstract: The novel compound 4-methyl-7-((2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethyl)thio)-coumarin is obtained in good yield via a two-step protocol; that is, initial synthesis of the reagent 2-((2-chloroethyl)thio)-5-methyl-1,3,4-thiadiazole followed by alkylation of 7-mercapto-4-methylcoumarin. The product's structure is assigned by 1D and 2D NMR experiments and is confirmed by single-crystal XRD.

Keywords: coumarin derivative; 1,3,4-thiadiazole unit; NMR; single-crystal XRD

1. Introduction

Coumarin, or 2*H*-chromen-2-one, is a natural bicyclic organic compound isolated from a variety of plants. Its derivatives have found broad applications such as fluorescent probes [1–4], food additives [5–7], in polymer chemistry [8–11], and so on. Numerous representatives have displayed variable bioactivity profiles [12–18], including anticancer [19–24], anti inflammatory [25–27], anti-tuberculosis [28,29], antimicrobial [30], and many others. Several drugs with coumarin skeleton are available on the market, such as immunosuppressant scoparone, anti-inflammatory drug 8-methoxypsoralen, vasodilator carbochromen, anticoagulants warfarin and phenprocoumon, antifungal agent osthole, anti-HIV preparatus calanolide, anticancer drug flavopiridol, antibiotics novobiocin and clorobiocin, and so on; some are shown in Figure 1.

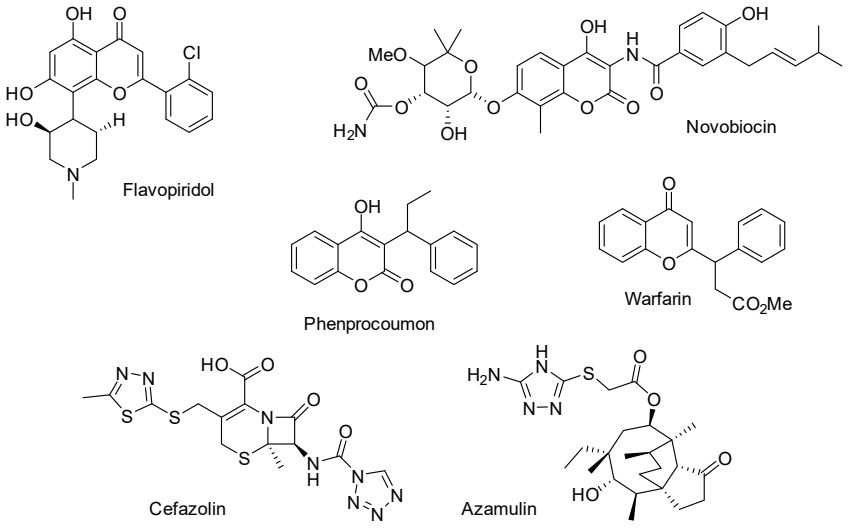

Figure 1. Representatives of clinically used coumarin and thiadiazole derivatives.

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Citation: Kurteva, V.; Rusew, R.; Shivachev, B. 4-Methyl-7-((2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethyl)thio)-coumarin. *Molbank* **2022**, *2022*, M1491. https://doi.org/10.3390/M1491

Academic Editor: Fawaz Aldabbagh

Received: 27 October 2022
Accepted: 8 November 2022
Published: 12 November 2022

1,3,4-thiadiazole is a five-membered heterocyclic compound with three heteroatoms, which exists as a structural subunit in a number of bioactive compounds [31–35]. Molecules possessing thiadiazole fragment have shown anticancer [36–39], antimicrobial [40,41], antiepileptic [42], and many other properties. Among the variety of clinically used representatives, the antibiotics cefazolin and azamulin are shown on Figure 1.

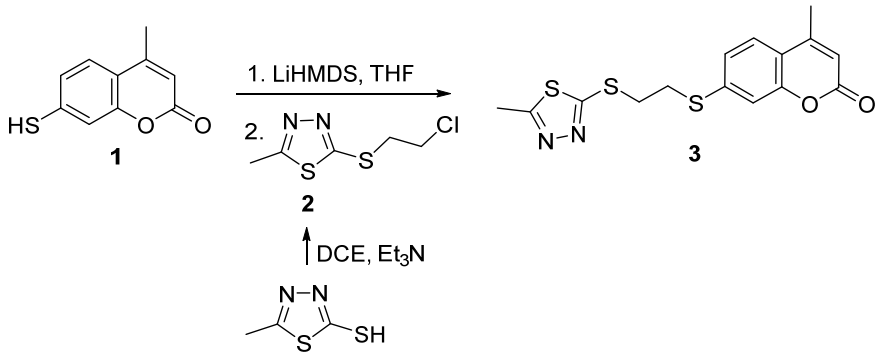
Contrary to coumarin and thiadiazole derivatives, compounds combining both structural subunits in a common molecule are relatively poorly studied. Nevertheless, several examples have shown a wide spectrum of biological activities, including antimicrobial [43], antifungal [44,45], anticancer [46,47], for the treatment of Alzheimer's disease and neurodegenerative disorders [48], suppressing allergic reactions agents [49], and many others.

Herein, we report on the synthesis and characterization of a novel coumarin derivative possessing thiol bridged 2-mercapto-thiadiazole fragment as a substituent.

2. Results and Discussion

2.1. Synthesis

The title compound 4-methyl-7-((2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethyl)thio)-coumarin **3** is obtained via a two-step protocol, shown in Scheme 1. The alkylating reagent 2-((2-chloroethyl)thio)-5-methyl-1,3,4-thiadiazole **2** is prepared in a very simple and efficient procedure. Namely, 2-mercapto-5-methyl-1,3,4-thiadiazole is stirred at room temperature in dichloroethane (DCE) in the presence of triethylamine as a base for 48 h. The reagent is isolated in 98% yield after column chromatography purification, but it can also be used without purification in subsequent steps. It is important to underline that it is crucial to avoid heating when preparing or using chloride **2** in order to avoid HCl elimination.



Scheme 1. Synthesis of 4-methyl-7-((2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethyl)thio)-coumarin **3**.

The reaction conditions for the main reaction, the synthesis of target product **3**, are optimized. Several bases and solvents are tested and the best conversion is achieved using lithium hexamethyldisilazide (LiHMDS) in dry THF at room temperature in an inert atmosphere. Therefore, the starting 7-mercapto-4-methylcoumarin **1** is metallized by LiHMDS and then alkylated with freshly prepared chloride **2** for 3 h. The target product is isolated in 59% yield by column chromatography.

The structure of product **3** is assigned by 1D and 2D NMR spectra (see Supplementary Materials). The ^{1}H spectrum in $CDCl_3$ shows characteristic signals for the aromatic coumarin protons; a doublet with ^{4}J at 6.236 for CH-3, a doublet for CH-5, a doublet of doublets for CH-6, and a doublet with ^{4}J for CH-8; with the latter being overlapped with the signal for chloroform. Both methylene groups give multiplets at a strong field, while a singlet and a doublet with small *J*-constants are observed for the thiadiazole and coumarin methyl groups, respectively. ^{13}C spectrum show two signals each for methyl and methylene groups, four signals for aromatic CH, and seven signals for quaternary carbons. The latter are assigned by analyzing the specific interactions in the HMBC experiment. The ATR IR spectrum of product **3** shows a characteristic band for lactone carbonyl at 1719 cm^{-1}.

2.2. Crystallography

Compound **3** appears as an orange-colored crystal (blocks) obtained by slow-evaporation from acetonitrile. Compound **3** crystallizes in the monoclinic $P2_1/n$ space group with the following cell parameters: a = 13.513 (3) Å, b = 4.189 (1) Å, c = 27.577 Å, and β = 94.12 (2)° (Table S1). The unit cell contains a total of four molecules of **3** (Z = 4, Z′ = 1), occupying a volume of 1557.2 (7) $Å^3$. A close inspection of the molecular features reveals that compound **3** is built up by two main fragments—4-methyl coumarin and 2-methyl-1,3,4-thiadiazole—connected by a –S–CH_2–CH_2–S– bridge (Figure 2). The 4-methyl coumarin and the 2-methyl-1,3,4-thiadiazole fragments are conjugated systems and are expected to be planar with small variations in planarity owing to the presence of methyl groups attached to C13 and C2, respectively. The calculated values for the RMSD of 4-methyl coumarin and the 2-methyl-1,3,4-thiadiazole are 0.028 and 0.011 Å, respectively. The presence of the –S–CH_2–CH_2–S– bridge between the two main fragments results in conformational flexibility of compound **3**, expressed in a relatively high value of the angle between the norms of the mean planes (65.65 (11)°) of the 4-methyl coumarin and 2-methyl-1,3,4-thiadiazole. In addition, the twist and fold angles between the mean planes of the two fragments are 63.40 (12)° and 21.11 (13)°, respectively. The molecular structure of **3** does not have any typical donor and only one C=O acceptor (in the coumarin fragment). Therefore, no typical hydrogen bonding is expected nor detected. Furthermore, no π ... π stacking interactions between the conjugated systems are present. The only possibility for the stabilization of the crystal structure is through short contacts between S ... O=C, C-H_{methyl} ... O, and C-$H_{methylenic}$ ... N, predominantly shorter than the sum of the van der Walls radii and with distances varying between 2.69 Å and 3.314 Å (Figure 3).

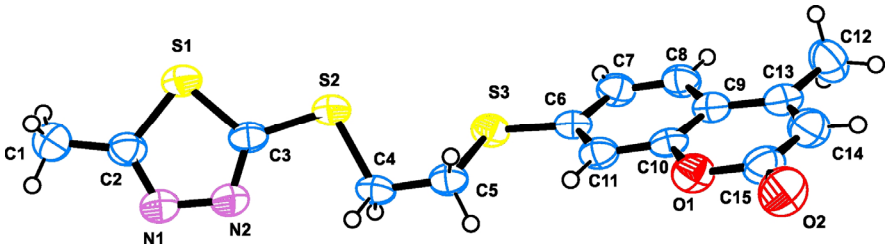


Figure 2. A representation of the molecule present in the asymmetric unit of compound **3** along with the employed numbering scheme; atomic displacement parameters (ADPs) are at 50%, hydrogen atoms are shown as small spheres with arbitrary radii.

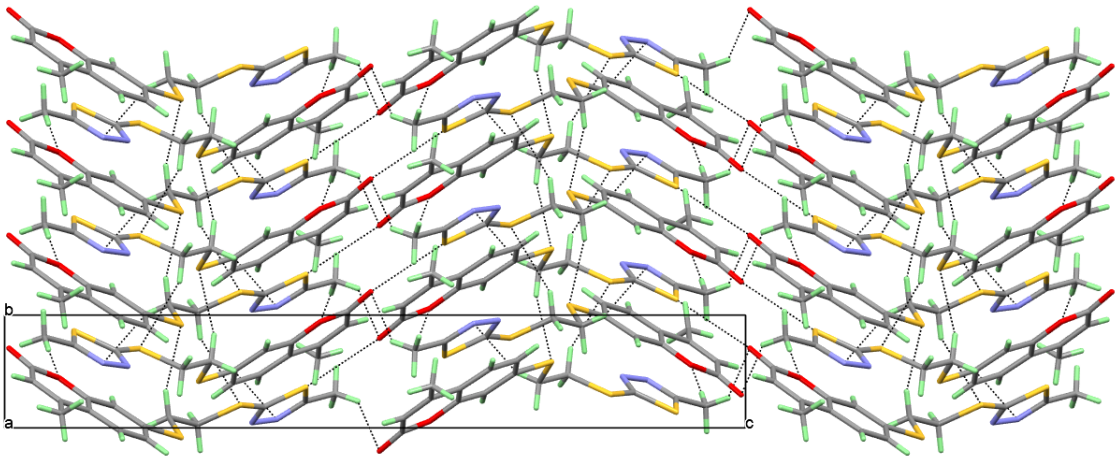


Figure 3. Observed weak C-H_3 ... O, C-H_2, and S ... O=C interactions, stabilizing the crystal packing in **3**.

3. Materials and Methods

3.1. General

All reagents were purchased from Aldrich, Merck, and Fluka and were used without any further purification. The deuterated chloroform was purchased from Deutero GmbH. Fluka silica gel (TLC-cards 60,778 with fluorescent indicator 254 nm) was used for TLC chromatography and R_f-values' determination. Merck Silica gel 60 (0.040–0.063 mm) was used for flash chromatography purification of the products. The melting point was determined in capillary tubes on an SRS MPA100 OptiMelt (Sunnyvale, CA, USA) automated melting point system with a heating rate of 1 °C per min. The NMR spectra were recorded on a Bruker Avance II+ 600 spectrometer (Rheinstetten, Germany) in $CDCl_3$; the chemical shifts were quoted in ppm in δ-values against tetramethylsilane (TMS) as an internal standard and the coupling constants were calculated in Hz. The assignment of the signals is confirmed by applying two-dimensional HSQC and HMBC techniques. The spectra were processed with the Topspin 3.6.3 program. For simplicity, the thiadiazole nuclei are depicted as "thd" and the ethylene bridge groups as "CH_2-S_{cm}" and "CH_2-S_{thd}" for methylene groups connected with the S-atom belonging to coumarin and thiadiazole, respectively. The IR spectra were measured on a Shimadzu IR Spirit FT-IR spectrometer (Shimadzu Corporation, Columbia, SC, USA) using QATR-S as a single-reflection ATR measurement attachment. The mass spectra were recorded in positive mode on a Q Exactive Plus Hybrid Quadrupole-Orbitrap Mass Spectrometer Thermo Scientific (ESI HR-MS). The spectra were processed with Xcalibur Free Style program version 4.5 (Thermo Fisher Scientific Inc., Waltham, MA, USA).

3.2. Synthesis of 2-((2-chloroethyl)thio)-5-methyl-1,3,4-thiadiazole

A solution of 2-mercapto-5-methyl-1,3,4-thiadiazole (10 mmol) and Et_3N (12 mmol) in DCE (20 mL) was stirred at RT for 48 h. The solid phase formed was filtered off and washed with DCE. The organic solution was extracted with water, dried over $MgSO_4$, and evaporated to dryness. The product was purified by column chromatography on silica gel using a mobile phase with a gradient of polarity from DCM to 1% acetone in DCM to obtain the pure compound: 98% yield; R_f 0.67 (2% acetone in DCM); colourless liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.741 (s, 3H, CH_3), 3.648 (t, 2H, J = 7.1 Hz, CH_2-S), 3.901 (t, 2H, J = 7.1 Hz, CH_2-Cl) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.68 (CH_3), 35.36 (CH_2-S), 42.33 (CH_2-Cl), 163.88 (C_q-2), 165.48 (C_q-5) ppm; IR (ATR) 1382, 1187, 1068, 1035, 696, 615 cm^{-1}; HRMS (ESI$^+$) m/z calcd. for $C_5H_8ClN_2S_2^+$ $[M + H]^+$ 194.9812, found 194.9811, $\Delta = -0.1$ mDa.

3.3. Synthesis of 4-Methyl-7-((2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethyl)thio)-coumarin

To a solution of 7-mercapto-4-methylcoumarin (1 mmol) in dry THF (15 mL), LiHMDS (1.1 mmol) was slowly added in argon atmosphere and the mixture was stirred at RT for 30 min. A solution of 2-((2-chloroethyl)thio)-5-methyl-1,3,4-thiadiazole (1 mmol) in dry THF (5 mL) was then added and the mixture was stirred at RT for 3 h. The excess of LiHMDS was quenched with water and the mixture was extracted with DCM. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The product was purified by column chromatography on silica gel using a mobile phase with a gradient of polarity from DCM to 5% acetone in DCM to obtain the pure compound: 59% yield; R_f 0.31 (2% acetone in DCM); m. p. 157.2–157.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.420 (d, 3H, ^4J = 1.1 Hz, CH_3-4), 2.763 (s, 3H, CH_3 thd), 3.499 (m, 2H, CH_2-S_{thd}), 3.554 (m, 2H, CH_2-S_{cm}), 6.236 (d, 1H, ^4J = 1.0 Hz, CH-3), 7.269 (d, 1H, CH-8, overlapped with the signal of chloroform), 7.348 (dd, 1H, ^3J = 8.4 Hz, ^4J = 1.7 Hz, CH-6), 7.542 (d, 1H, ^3J = 8.4 Hz, CH-5) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.76 (CH_3 thd), 18.66 (CH_3-4), 31.69 (CH_2-S_{thd}), 32.64 (CH_2-S_{cm}), 114.24 (CH-3), 115.02 (CH-8), 117.68 (C_q-4a), 123.30 (CH-6), 125.05 (CH-5), 141.25 (C_q-7), 152.14 (C_q-4), 153.84 (C_q-8a), 160.56 (C_q-2=O), 164.23 (C_q-2 thd), 165.50 (C_q-5 thd) ppm; IR (ATR) 1719 ($\nu_{C=O}$), 1600 ($\nu_{C=C}$), 1385, 960, 834, 438 cm^{-1}; HRMS (ESI$^+$) m/z calcd. for $C_{15}H_{15}N_2O_2S_3^+$ $[M + H]^+$ 351.0290, found 351.0287, $\Delta = -0.3$ mDa.

3.4. Crystallography

Orange-colored crystal blocks from compound **3** were obtained by slow evaporation of acetonitrile solution at room temperature under normal pressure. A suitable crystal with appropriate size (0.25 × 0.2 × 0.1 mm^3) was mounted on a nylon loop using cryoprotective Paratone oil. Diffraction data were collected on a Bruker D8 Venture diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) equipped with IμS micro-focus sealed X-ray source (MoKα radiation, λ = 0.71073 Å) and a PHOTON II CPAD detector. Diffraction data were processed in APEX4 software package [50]; peaks were integrated with Bruker SAINT software [51] using the narrow-frame algorithm. Intensities were scaled and the data were corrected for absorption effects using the multi-scan method (SADABS) [51]. The structure was solved with the intrinsic phasing method and refined by the full-matrix least-squares method on F^2 (ShelxT and ShelxL program packages [52,53]) using OLEX–ver. 1.5 software [54]. All non-hydrogen atoms were located successfully from the Fourier map and were refined anisotropically. Hydrogen atoms were placed on calculated positions riding on the parent carbon atoms using the following scheme: Ueq = 1.2 for C-$H_{aromatic}$ = 0.93 Å, C-H_{methyl} = 0.96 Å, and C-$H_{methylenic}$ = 0.97 Å. ORTEP-3v2 software [55] was used to illustrate the molecules of **3** in the asymmetric unit. Three-dimensional packing visualization of the molecules of **3** was made using CCDC Mercury [56]. The most important data collection and crystallographic refinement parameters for **3** are presented in Table S1. Complete crystallographic data for the reported structure have been deposited in the CIF format with the Cambridge Crystallographic Data Center as 2215392. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, deposited on 15 June 2022, (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +441223336033; E-mail: depos-it@ccdc.cam.ac.uk).

4. Conclusions

4-Methyl-7-((2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethyl)thio)-coumarin is obtained in good yield by alkylation of 7-mercapto-4-methylcoumarin with freshly prepared 2-((2-chloroethyl)thio)-5-methyl-1,3,4-thiadiazole. The product is purified by column chromatography on silica gel and characterized by 1D and 2D NMR, IR, and HRMS spectra. The single-crystal XRD reveals that the compound crystallizes in the monoclinic $P2_1/n$ space group.

Supplementary Materials: The following are available online: ^1H, ^{13}C, HSQC and HMBC NMR, HRMS, and IR spectra. Table S1, CIF and checkcif report for the title compound.

Author Contributions: The synthetic experiments and NMR analyses were carried out by V.K. The single-crystal XRD was performed by R.R. and B.S. All authors contributed in the discussion of the results and in the manuscript writing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Acknowledgments: The financial support by the Operational Program "Science and Education for Smart Growth" 2014–2020, co-financed by European Union through the European Structural and Investment Funds, under the Project Centre of Excellence "National centre of mechatronics and clean technologies", project BG05M2OP001-1.001-0008 (for Bruker D8venture XRD equipment), is gratefully acknowledged.

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

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

References

1. 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]
2. Oliveira, E.; Bértolo, E.; Núñez, 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*, 9–52. [CrossRef] [PubMed]
3. Sun, X.; Liu, T.; Sun, J.; Wang, X. Synthesis and application of coumarin fluorescence probes. *RSC Adv.* **2020**, *10*, 10826–10847. [CrossRef] [PubMed]
4. Davis, A.B.; Ihde, M.H.; Busenlehner, A.M.; Davis, D.L.; Mia, R.; Panella, J.; Fronczek, F.R.; Bonizzoni, M.; Wallace, K.J. Structural features of a family of coumarin–enamine fluorescent chemodosimeters for ion pairs. *Inorg. Chem.* **2021**, *60*, 14238–14252. [CrossRef]
5. Ballin, N.Z.; Sørensen, A.T. Coumarin Content in Cinnamon Containing Food Products on the Danish Market. *Food Control* **2014**, *38*, 198–203. [CrossRef]
6. Zhu, J.-J.; Jiang, J.-G. Pharmacological and nutritional effects of natural coumarins and their structure–activity relationships. *Mol. Nutr. Food Res.* **2018**, *62*, 1701073. [CrossRef]
7. Lončar, M.; Jakovljevíc, M.; Šubaríc, D.; Pavlíc, M.; Buzjak Služek, V.; Cindríc, I.; Molnar, M. Coumarins in food and methods of their determination. *Foods* **2020**, *9*, 645. [CrossRef]
8. Abdallah, M.; Hijazi, A.; Graff, B.; Fouassier, J.-P.; Rodeghiero, G.; Gualandi, A.; Dumur, F.; Cozzi, P.G.; Lalevée, J. Coumarin derivatives as versatile photoinitiators for 3D printing, polymerization in water and photocomposite synthesis. *Polym. Chem.* **2019**, *10*, 872–884. [CrossRef]
9. Cazin, I.; Rossegger, E.; de la Cruz, G.G.; Griesser, T.; Schlögl, S. Recent advances in functional polymers containing coumarin chromophores. *Polymers* **2021**, *13*, 56. [CrossRef]
10. Lima, C.; Silva, K.; Nascimento, J.; Rossi, C.; Granato, M.; Oliveira, F. Optimization of the polyester fabric dyeing process using coumarin as a green carrier. *Text. Res. J.* **2022**, *92*, 3875–3888. [CrossRef]
11. Liu, Z.; Dumur, F. Recent advances on visible light coumarin-based oxime esters as initiators of polymerization. *Eur. Polym. J.* **2022**, *177*, 111449. [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. Carneiro, A.; Matos, M.J.; Uriarte, E.; Santana, L. Trending topics on coumarin and its derivatives in 2020. *Molecules* **2021**, *26*, 501. [CrossRef] [PubMed]
14. Agíc, D.; Karnaš, M.; Šubaríc, D.; Lončari'c, M.; Tomíc, S.; Karačíc, Z.; Bešlo, D.; Rastija, V.; Molnar, M.; Popovíc, B.M.; et al. Coumarin derivatives act as novel inhibitors of human dipeptidyl peptidase III: Combined in vitro and in silico study. *Pharmaceuticals* **2021**, *14*, 540. [CrossRef]
15. Tsivileva, O.M.; Koftin, O.V.; Evseeva, N.V. Coumarins as fungal metabolites with potential medicinal properties. *Antibiotics* **2022**, *11*, 1156. [CrossRef]
16. Chaudhary, D.; Bedi, P.; Santra, S.; Pramanik, T. Synthesis and biological properties of coumarin analogue: A brief review. *Lett. Org. Chem.* **2022**, *19*, 362–387. [CrossRef]
17. Nasab, N.H.; Azimian, F.; Kruger, H.G.; Kim, S.J. Coumarin-chalcones generated from 3-acetylcoumarin as a promising agent: Synthesis and pharmacological properties. *ChemistrySelect* **2022**, *7*, e202200238. [CrossRef]
18. 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]
19. Thakur, A.; Singla, R.; Jaitak, V. Coumarins as anticancer agents: A review on synthetic strategies, mechanism of action and SAR studies. *Eur. J. Med. Chem.* **2015**, *101*, 476–495. [CrossRef]
20. Song, X.-F.; Fan, J.; Liu, L.; Liu, X.-F.; Gao, F. Coumarin derivatives with anticancer activities: An update. *Arch. Pharm.* **2020**, *353*, 2000025. [CrossRef]
21. Akkol, E.K.; Genç, Y.; Karpuz, B.; Sobarzo-Sánchez, E.; Capasso, R. Coumarins and coumarin-related compounds in pharmacotherapy of cancer. *Cancers* **2020**, *12*, 1959. [CrossRef]
22. Banikazemi, Z.; Mirazimi, S.M.; Dashti, F.; Mazandaranian, M.R.; Akbari, M.; Morshedi, K.; Aslanbeigi, F.; Rashidian, A.; Chamanara, M.; Hamblin, M.R.; et al. Coumarins and gastrointestinal cancer: A new therapeutic option? *Front. Oncol.* **2021**, *11*, 752784. [CrossRef] [PubMed]
23. Rubab, L.; Afroz, S.; Ahmad, S.; Hussain, S.; Nawaz, I.; Irfan, A.; Batool, F.; Kotwica-Mojzych, K.; Mojzych, M. An update on synthesis of coumarin sulfonamides as enzyme inhibitors and anticancer agents. *Molecules* **2022**, *27*, 1604. [CrossRef] [PubMed]
24. Salinas-Torres, A.; Jiménez, E.; Becerra, D.; Martínez, J.J.; Rojas, H.; Castillo, J.-C.; Macías, M.A. Synthesis, anticancer evaluation, thermal and X-ray crystallographic analysis of 2-oxo-2H-chromen-7-yl 4-chlorobenzoate using a conductively heated sealed-vessel reactor. *J. Mol. Struct.* **2023**, *1274*, 134414. [CrossRef]
25. Kirsch, G.; Abdelwahab, A.B.; Chaimbault, P. Natural and synthetic coumarins with effects on inflammation. *Molecules* **2016**, *21*, 1322. [CrossRef] [PubMed]
26. Di Stasi, L.C. Coumarin derivatives in inflammatory bowel disease. *Molecules* **2021**, *26*, 422. [CrossRef]

27. Rostom, B.; Karaky, R.; Kassab, I.; Veitía, M.S.-I. Coumarins derivatives and inflammation: Review of their effects on the inflammatory signaling pathways. *Eur. J. Pharmacol.* **2022**, *922*, 174867. [CrossRef]
28. Reddy, D.S.; Kongot, M.; Kumar, A. Coumarin hybrid derivatives as promising leads to treat tuberculosis: Recent developments and critical aspects of structural design to exhibit anti-tubercular activity. *Tuberculosis* **2021**, *127*, 102050. [CrossRef]
29. Mujeeb, S.; Singh, K.; Yogi, B.; Ansari, V.; Sinha, S. A review on coumarin derivatives as potent anti-tuberculosis agents. *Mini-Rev. Med. Chem.* **2022**, *22*, 1064–1080. [CrossRef]
30. Cheke, R.S.; Patel, H.M.; Patil, V.M.; Ansari, I.A.; Ambhore, J.P.; Shinde, S.D.; Kadri, A.; Snoussi, M.; Adnan, M.; Kharkar, P.S.; et al. Molecular insights into coumarin analogues as antimicrobial agents: Recent developments in drug discovery. *Antibiotics* **2022**, *11*, 566. [CrossRef]
31. Jain, A.K.; Sharma, S.; Vaidya, A.; Ravichandran, V.; Agrawal, R.K. 1,3,4-Thiadiazole and its derivatives: A review on recent progress in biological activities. *Chem. Biol. Drug Des.* **2013**, *81*, 557–576. [CrossRef] [PubMed]
32. Hu, Y.; Li, C.-Y.; Wang, X.-M.; Yang, Y.-H.; Zhu, H.-L. 1,3,4-Thiadiazole: Synthesis, reactions, and applications in medicinal, agricultural, and materials chemistry. *Chem. Rev.* **2014**, *114*, 5572–5610. [CrossRef] [PubMed]
33. Matysiak, J. Biological and pharmacological activities of 1,3,4-thiadiazole based compounds. *Mini Rev. Med. Chem.* **2015**, *15*, 762–775. [CrossRef]
34. Joseph, L.; George, M.; Mathews, P. A review on various biological activities of 1,3,4- thiadiazole derivatives. *J. Pharm. Chem. Biol. Sci.* **2015**, *3*, 329–345.
35. Schatz, J.; Gogić, K.; Benkert, T. 1,3,4-Thiadiazoles. In *Comprehensive Heterocyclic Chemistry IV*, 4th ed.; Elsevier: Amsterdam, The Netherlands, 2020; Volume 5, Chapter 5.10; pp. 407–447. [CrossRef]
36. Aliabadi, A. 1,3,4-Thiadiazole based anticancer agents. *Anti-Cancer Agents Med. Chem.* **2016**, *16*, 1301–1314. [CrossRef]
37. Raj, V.; Rai, A.; Saha, S. Human Cancer cell line based approach of 1,3,4-thiadiazole and its fused ring: A comprehensive review. *Anti-Cancer Agents Med. Chem.* **2017**, *17*, 500–523. [CrossRef]
38. Janowska, S.; Paneth, A.; Wujec, M. Cytotoxic properties of 1,3,4-Thiadiazole derivatives—A review. *Molecules* **2020**, *25*, 4309. [CrossRef]
39. Obakachi, V.A.; Kushwaha, B.; Kushwaha, N.D.; Mokoena, S.; Ganai, A.M.; Pathan, T.K.; van Zyl, W.E.; Karpoormath, R. Synthetic and anti-cancer activity aspects of 1, 3, 4-thiadiazole containing bioactive molecules: A concise review. *J. Sulfur Chem.* **2021**, *42*, 670–691. [CrossRef]
40. Serban, G.; Stanasel, O.; Serban, E.; Bota, S. 2-Amino-1,3,4-thiadiazole as a potential scaffold for promising antimicrobial agents. *Drug Des. Devel. Ther.* **2018**, *12*, 1545–1566. [CrossRef]
41. Barbosa, G.A.D.; de Aguiar, A.P. Synthesis of 1,3,4-thiadiazole derivatives and microbiological activities: A review. *Rev. Virtual Quim.* **2019**, *11*, 806–848. [CrossRef]
42. Anthwal, T.; Nain, S. 1,3,4-Thiadiazole scaffold: As anti-epileptic agents. *Front. Chem.* **2022**, *9*, 671212. [CrossRef] [PubMed]
43. Karcz, D.; Starzak, K.; Ciszkowicz, E.; Lecka-Szlachta, K.; Kamiński, D.; Creaven, B.; Jenkins, H.; Radomski, P.; Miłoś, A.; Ślusarczyk, L.; et al. Novel coumarin-thiadiazole hybrids and their Cu(II) and Zn(II) complexes as potential antimicrobial agents and acetylcholinesterase. *Int. J. Mol. Sci.* **2021**, *22*, 9709. [CrossRef] [PubMed]
44. Al-Amiery, A.A.; Musa, A.Y.; Kadhum, A.A.H.; Mohamad, A.B. The use of umbelliferone in the synthesis of new heterocyclic compounds. *Molecules* **2011**, *16*, 6833–6843. [CrossRef] [PubMed]
45. Sabt, A.; Abdelrahman, M.T.; Abdelraof, M.; Rashdan, H.R.M. Investigation of novel mucorales fungal inhibitors: Synthesis, in-silico study and anti-fungal potency of novel class of coumarin-6-sulfonamides-thiazole and thiadiazole hybrids. *ChemistrySelect* **2022**, *7*, e202200691. [CrossRef]
46. Morsy, S.A.; Farahat, A.A.; Nasr, M.N.A.; Tantawy, A.S. Synthesis, molecular modeling and anticancer activity of new coumarin containing compounds. *Saudi Pharm. J.* **2017**, *25*, 873–883. [CrossRef] [PubMed]
47. Toan, V.N.; Thanh, N.D.; Tri, N.M. 1,3,4-Thiadiazoline−coumarin hybrid compounds containing D-glucose/D-galactose moieties: Synthesis and evaluation of their antiproliferative activity. *Arabian J. Chem.* **2021**, *14*, 103053. [CrossRef]
48. Ujan, R.; Saeed, A.; Channar, P.A.; Larik, F.A.; Abbas, Q.; Alajmi, M.F.; El-Seedi, H.R.; Rind, M.A.; Hassan, M.; Raza, H.; et al. Drug-1,3,4-thiadiazole conjugates as novel mixed-type inhibitors of acetylcholinesterase: Synthesis, molecular docking, pharmacokinetics, and ADMET evaluation. *Molecules* **2019**, *24*, 860. [CrossRef]
49. Blouin, M.; Grimm, E.L.; Gareau, Y.; Gagnon, M.; Juteau, H.; Laliberte, S.; Mackay, B.; Friesen, R. Thiadiazole substituted Coumarin Derivatives and their Use as Leukotriene Biosynthesis Inhibitor. Patent WO200609, 28 September 2006.
50. Bruker AXS Inc. *APEX 3*; Bruker Advanced X-ray Solutions: Madison, WI, USA, 2016.
51. Bruker AXS Inc. *Saint and SADABS*; Bruker AXS Inc.: Madison, WI, USA, 2009.
52. Sheldrick, G.M. SHELXT–Integrated space-group and crystal-structure determination. *Acta Crystallogr. Sect. A* **2015**, *71*, 3–8. [CrossRef]
53. Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Crystallogr. Sect. C.* **2015**, *71*, 3–8. [CrossRef]
54. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.; Puschmann, H. OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* **2009**, *42*, 339–341. [CrossRef]
55. Farrugia, L.J. WinGX and ORTEP for Windows: An update. *J. Appl. Crystallogr.* **2012**, *45*, 849–854. [CrossRef]
56. Macrae, C.F.; Sovago, I.; Cottrell, S.J.; Galek, P.T.; McCabe, P.; Pidcock, E.; Platings, M.; Shields, G.P.; Stevens, J.S.; Towler, M. Mercury 4.0: From visualization to analysis, design and prediction. *J. Appl. Crystallogr.* **2020**, *53*, 226–235. [CrossRef] [PubMed]