Synthesis and characterisation of some coumarin-1,2,4-triazol-3-thioether hybrid molecules

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A new series of *N*'-{[(4-methyl/phenyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio]acetyl}-2-oxo-2*H*-chromene-3-carbohydrazides was synthesised *via* the reaction of 2-[(4-methyl/phenyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio]acetohydrazides and 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-ones in good yields.

Keywords: coumarin, 1,2,4-triazol-3-thiol, hybrid molecule, acid hydrazide, benzotriazole

Coumarin and its derivatives are common oxygen-containing heterocyclic compounds that are the subject of many studies. The great interest in these compounds comes from their biological activities against different pathologies, which has motivated researchers to develop several drugs based on these compounds, such as warfarin, acenocoumarol and phenprocoumon. Also, coumarin analogues have shown a broad spectrum of pharmacological activities, such as anticoagulant, antibacterial, antifungal, antimycobacterial, antimutagenic and anti-inflammatory. With these activities, coumarins have been used for preliminary studies in pharmacology.[1–5]

1,2,4-Triazoles have great importance in medicinal chemistry and are known to show diverse biological activities. Ribavirin (antiviral), rizatriptan (antimigraine), alprazolam (anxiolytic), letrozole, vorozole and anastrozole (antitumoral) are some examples of 1,2,4-triazole-containing drugs.[6–9]

The molecular modification method is considered as an effective method for developing new drug members. Molecular hybridisation is included in this method for obtaining new molecules that have better pharmaceutical activities. Recently, this method has become a powerful tool for obtaining more bioactive compounds.[10–12] Considering the promising activity of coumarin and triazole moieties, the use of these heterocycles in a molecule can result in the formation of more bioactive compounds. In the literature, studies on coumarin-1,2,4-triazol-3-thioether derivatives are limited. However, synthesis of these types of molecules is an important research area today. In our previous studies, we have synthesised coumarin-triazol-3-on hybrid molecules as antimicrobial and antilipase agents.[11] In this work, coumarin-1,2,4-triazol-3-thioether hybrid molecules were synthesised as potential bioactive agents. Hence, we decided to use coumarin and 1,2,4-triazol-3-thiol moieties in one molecule to design new potential bioactive compounds

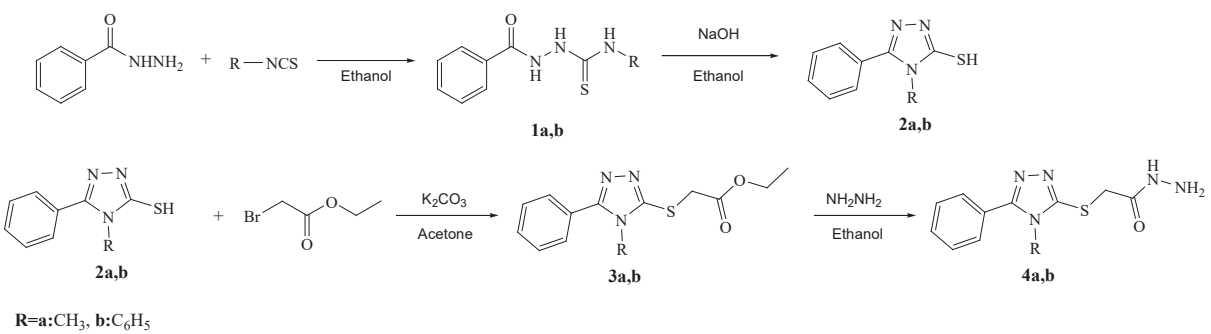
Results and discussion

The primary aim of this study was to synthesise coumarin-1,2,4-triazole hybrid molecules. The synthetic strategy for the intermediate and target compounds was performed according to the reactions outlined in Schemes 1–3. The compounds **1a** and **1b** were obtained by the reaction of phenyl hydrazide and the corresponding isothiocyanate in ethanol. Treatment of compounds **1a** and **1b** with NaOH solution in ethanol gave 1,2,4-triazol-3-thiol derivatives (**2a**, **2b**). The compounds **3a** and **3b** were obtained by simple alkylation of compounds **2a** and **2b** and ethyl bromoacetate in acetone and these compounds were reacted with hydrazine monohydrate in ethanol to prepare compounds **4a** and **4b**, which are the first intermediate[13,14] (Scheme 1).

To synthesise the second intermediate compounds, five different salicylaldehyde derivatives were reacted with 2,2-dimethyl-1,3-dioxane-4,6-dione[15] in ethanol to synthesise coumarin-3-carboxylic acid (**5a**–**e**). Then, the compounds **5a**–**e** were reacted with 1*H*-benzotriazole in dichloromethane in the presence of thionyl chloride to obtain compounds **6a**–**e**[11] (Scheme 2).

The benzotriazole group is an easy leaving group. This group offers many advantages to researchers in synthetic applications.[11,12,15] Treatment of compounds **6a**–**e** with **4a** and **4b** resulted in the synthesis of the target coumarin-1,2,4-triazol-3-thioether hybrid molecules (**7a**–**j**) (Scheme 3). In this reaction, we aimed for the use of organic solvent in minimum quantity in line with principle of environmental chemistry.

Spectral investigations of the hybrid molecules were in accordance with the proposed structures. In the IR spectra, NH and C=O signals were shown at about 3150 and 1700 cm^{-1}, respectively. In the ^1H NMR spectra of these compounds, two NH signals (exchangeable with D_2O) were shown at about 10.70 and 11.20 ppm. The SCH_2 and coumarin–C_3–H signals were observed at about 4.00 and 8.80 ppm, respectively. In the ^{13}C



Scheme 1 Synthesis of compounds **4a** and **4b**.

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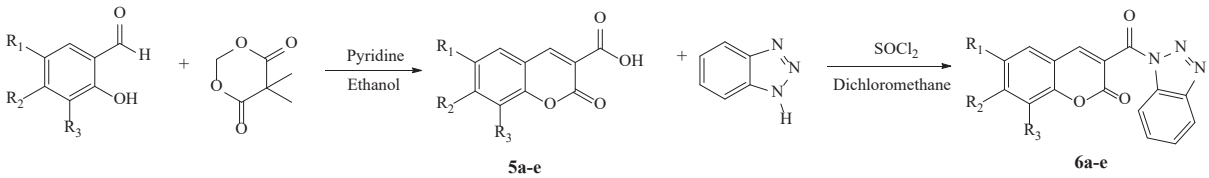
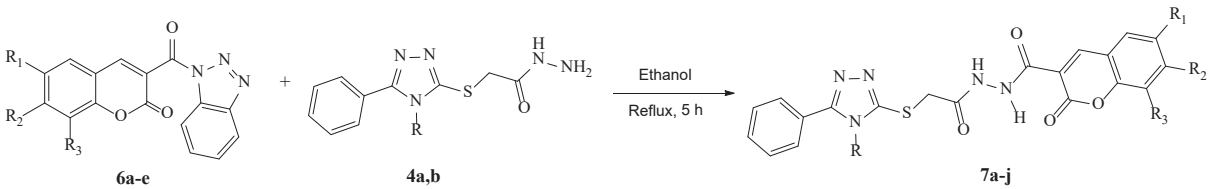


5a-e 6a-e

5, 6	R_1	R_2	R_3
a	H	H	H
b	Cl	H	H
c	Br	H	H
d	Cl	H	Cl
e	H	$N(C_2H_5)_2$	H

Scheme 2 Synthesis of compounds **6a–e**.



6a-e 4a,b 7a-j

Compound	R	R_1	R_2	R_3	Compound	R	R_1	R_2	R_3
7a	CH_3	H	H	H	**7f**	C_6H_5	H	H	H
7b	CH_3	Cl	H	H	**7g**	C_6H_5	Cl	H	H
7c	CH_3	Br	H	H	**7h**	C_6H_5	Br	H	H
7d	CH_3	Cl	H	Cl	**7i**	C_6H_5	Cl	H	Cl
7e	CH_3	H	$N(C_2H_5)_2$	H	**7j**	C_6H_5	H	$N(C_2H_5)_2$	H

Scheme 3 The synthetic route for target compounds.

NMR spectra of these compounds, three C=O signals were observed at about 165.00, 160.00 and 158.00 ppm. The triazole C=N signals were shown at about 156.00 and 154.00 ppm. Also, the numbers of other aromatic carbons in the ^{13}C NMR spectra were in agreement with the proposed structure. In addition, all compounds gave suitable elemental analysis results.

Conclusion

We report here the synthesis of coumarin-1,2,4-triazole hybrid molecules using a simple and practical method. This present method was achieved under catalyst-free conditions and using a low amount of organic solvent (only 10 mL). Therefore, this method is more important than others in terms of green chemistry. This study could be the inspiration for further investigation of potential bioactive heterocyclic compounds.

Experimental

All chemicals were supplied from Merck, Aldrich and Fluka. Melting points were determined in capillary tubes on a Stuart SMP30 melting point apparatus and uncorrected. The IR spectra were recorded for KBr pellets on a PerkinElmer 100 FTIR spectrometer. ^1H NMR and ^{13}C NMR spectra were performed on a Bruker 400 MHz spectrometer in DMSO-d_6 using TMS as an internal standard. The elemental compositions were determined on a Carlo Erba 1106 CHN analyser; the experimental values were in agreement (±0.4%) with the calculated values. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 2.54 0.2 mm thickness). Compounds **4a** and **4b**[13,14] and **6a**-**e**[11] were synthesised according to published methods.

Synthesis of compounds **7a**–**j***; general procedure*

A mixture of compounds **4a** or **4b** (0.01 mol), **6a**–**e** (0.011 mol) and ethanol (10 mL) were placed in a round-bottomed flask and refluxed for 5 h. The end of the reaction was determined by TLC (ethyl acetate:hexane: 4:1) and the product was precipitated by cooling the mixture to room temperature. The product was filtrated off and washed with ethanol to obtain the pure products.

N'-*{[(4-Methyl-5-phenyl-4*H-*1,2,4-triazol-3-yl)thio]acetyl}-2-oxo-2*H-*chromene-3-carbohydrazide* (**7a**): Yield 3.30 g (76%); m.p. 268–269 °C; IR (KBr) (cm^{-1}): 3168, 3110, 1697, 1680, 1193; ^1H NMR: δ (400 MHz, DMSO-d_6): 3.67 (s, 3H), 4.03 (s, 2H), 7.66 (t, *J* = 8.0, 1H), 7.52–7.98 (m, 4H), 7.70–7.74 (m, 2H), 7.78 (t, *J* = 8.0, 1H), 8.01 (d, *J* = 8.0, 1H), 8.89 (s, 1H), 10.72 (s, 1H), 11.15 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 31.80, 34.89, 116.25, 118.00, 118.30, 127.12, 128.38, 128,88, 129.97, 130.35, 134.42, 147.95, 149.99, 153.95, 155.45, 158.42, 159.84, 164.53. Anal. calcd for $C_{21}H_{17}N_5O_4S$: C, 57.92; H, 3.93; N, 16.08; S, 7.36; found; C, 57.87; H, 3.79; N, 15.89; S, 7.28.

*6-Chloro-*N'-*{[(4-methyl-5-phenyl-4*H-*1,2,4-triazol-3-yl)thio]acetyl}-2-oxo-2*H-*chromene-3-carbohydrazide* (**7b**): Yield 3.20 g (68%); m.p. 277–278 °C; IR (KBr) (cm^{-1}): 3153, 1702, 1689, 1186; ^1H NMR (400 MHz, DMSO-d_6): δ 3.65 (s, 3H), 4.02 (s, 2H), 7.56–7.59 (m, 4H), 7.71–7.74 (m, 2H), 7.80 (dd, *J* = 8.8, *J* = 2.4, 1H), 8.16 (d, *J* = 2.4, 1H), 8.84 (s, 1H), 10.70 (s, 1H), 11.14 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 31.75, 35.11, 115.29, 118.03, 118.91, 128.10, 128.25, 128,83, 129.99, 130.81, 135.61, 148.99, 150.99, 154.99, 156.98, 159.92, 160.81, 165.56. Anal. calcd for $C_{21}H_{16}ClN_5O_4S$: C, 53.68; H, 3.43; N, 14.90; S, 6.82; found; C, 53.57; H, 3.39; N, 14.81; S, 6.74.

*6-Bromo-*N'-*{[(4-methyl-5-phenyl-4*H-*1,2,4-triazol-3-yl)thio]acetyl}-2-oxo-2*H-*chromene-3-carbohydrazide* (**7c**): Yield 3.65 g (71%); m.p. 273–274 °C; IR (KBr) (cm^{-1}): 3158, 1703, 1688, 1186; ^1H NMR (400 MHz, DMSO-d_6): δ 3.65 (s, 3H), 4.03 (s, 2H), 7.52 (d, *J* = 9.2, 1H), 7.56–7.58 (m, 3H), 7.71–7.74 (m, 2H), 7.92 (dd, *J* = 8.4, *J* = 2.4, 1H), 8.29 (d, *J* = 2.4, 1H), 8.83 (s, 1H), 10.70 (s, 1H), 11.15 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 31.90, 34.88, 116.72, 118.55, 119.28, 120.16, 127.11, 128,37, 128.89, 129.97, 132.16, 136.52, 146.51, 149.98, 152.98, 155.45, 158.21, 159.32, 164.60. Anal. calcd for $C_{21}H_{16}BrN_5O_4S$: C, 49.04; H, 3.14; N, 13.62; S, 6.23; found; C, 49.00; H, 3.04; N, 13.51; S, 6.11.

*6,8-Dichloro-*N'-*{[(4-methyl-5-phenyl-4*H-*1,2,4-triazol-3-yl)sulfanyl]acetyl}-2-oxo-2*H-*chromene-3-carbohydrazide* (**7d**): Yield

3.69 g (73%), m.p. 292–293 °C; IR (KBr) (cm^{-1}): 3206, 1731, 1699, 1204; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.66 (s, 3H), 4.03 (s, 2H), 7.56–7.58 (m, 3H), 7.71–7.73 (m, 2H), 8.11 (d, *J* = 2.4, 1H), 8.14 (d, *J* = 2.4, 1H), 8.82 (s, 1H), 10.63 (s, 1H), 11.11 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 31.90, 34.88, 99.51, 118.47, 119.59, 120.75, 128.26, 128.37, 129.81, 130.17, 133.10, 137.59, 147.01, 150.62, 153.70, 156.59, 159.19, 160.97, 165.71. Anal. calcd for $C_{21}H_{15}Cl_2N_5O_4S$: C, 50.01; H, 3.00; N, 13.89; S, 6.36; found; C, 49.89; H, 2.91; N, 13.78; S, 6.27.

7-Diethylamino-N'-*{[(4-methyl-5-phenyl-4*H-*1,2,4-triazol-3-yl) thio]acetyl}-2-oxo-2*H-*chromene-3-carbohydrazide* (**7e**): Yield 3.23 g (64%), m.p. 259–260 °C; IR (KBr) (cm^{-1}): 3155, 1699, 1685, 1188; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.15 (t, *J* = 6.8, 6H), 3.50 (q, *J* = 6.8, 4H), 3.66 (s, 3H), 4.02 (s, 2H), 6.42 (d, *J* = 2.0, 1H), 6.82 (dd, *J* = 9.2, *J* = 2.4, 2H), 7.56–7.59 (m, 3H), 7.70–7.74 (m, 3H), 8.69 (s, 1H), 10.62 (s, 1H), 11.08 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 12.30, 31.92, 34.90, 44.40, 99.46, 107.58, 107.69, 110.37, 127.06, 128,38, 128.88, 129.99, 131.80, 148.22, 150.03, 152.85, 155.42, 157.40, 159.48, 161.38, 164.24. Anal. calcd for $C_{25}H_{26}N_6O_4S$: C, 59.27; H, 5.17; N, 16.59; S, 6.33; found; C, 59.18; H, 5.10; N, 16.47; S, 6.25.

N'-*{[(4-Phenyl-5-phenyl-4*H-*1,2,4-triazol-3-yl)thio]acetyl}-2-oxo-2*H-*chromene-3-carbohydrazide* (**7f**): Yield 3.53 g (71%), m.p. 275–276 °C; IR (KBr) (cm^{-1}): 3161, 1716, 1690, 1194; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.11 (s, 2H), 7.30–7.35 (m, 5H), 7.43–7.48 (m, 4H) 7.57 (t, *J* = 8.0, 2H), 7.78 (t, *J* = 8.4, 1H), 8.03 (d, *J* = 8.4, 1H), 8.91 (s, 1H), 10.73 (s, 1H), 11.21 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 33.95, 116.25, 117.95, 118.31, 125.24, 126.58, 127.66, 127.90, 128.56, 129.77, 129.97, 130.11, 130.36, 133.77, 134.43, 147.98, 151.18, 153.95, 154.44, 158.28, 159.89, 164.17. Anal. calcd for $C_{26}H_{19}N_5O_4S$: C, 62.77; H, 3.85; N, 14.08; S, 6.44; found; C, 62.63; H, 3.78; N, 14.01; S, 6.30.

6-Chloro-N'-*{[(4-phenyl-5-phenyl-4*H-*1,2,4-triazol-3-yl)thio] acetyl}-2-oxo-2*H-*chromene-3-carbohydrazide* (**7g**): Yield 3.08 g (58%); m.p. 283–284 °C; IR (KBr) (cm^{-1}): 3174, 3104, 1715, 1694, 1188; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.11 (s, 2H), 7.34–7.45 (m, 7H), 7.55–7.60 (m, 4H), 7.80 (dd, *J* = 8.8, *J* = 2.4, 1H), 8.16 (dd, *J* = 8.8, *J*=2.4, 1H), 8.91 (s, 1H), 10.71 (s, 1H), 11.20 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 33.94, 118.29, 119.27, 119.68, 126.57, 127.66, 127.89, 128.56, 128.91, 129.15, 129.77, 129.97, 130.11, 133.78, 146.62, 151.17, 152.57, 154.44, 158.06, 159.41, 164.22. Anal. calcd for $C_{26}H_{18}ClN_5O_4S$: C, 58.70; H, 3.41; N, 13.16; S, 6.03; found; C, 58.57; H, 3.28; N, 13.09; S, 5.89.

6-Bromo-N'-*{[(4-phenyl-5-phenyl-4*H-*1,2,4-triazol-3-yl)thio] acetyl}-2-oxo-2*H-*chromene-3-carbohydrazide* (**7h**): Yield 3.55 g (63%); m.p. 277–278 °C; IR (KBr) (cm^{-1}): 3159, 1716, 1690, 1188; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.12 (s, 2H), 7.23–7.36 (m, 3H) 7.46–7.58 (m, 4H), 7.62–7.78 (m, 4H), 7.92 (dd, *J* = 8.8, *J* = 2.0, 1H), 8.28 (dd, *J* = 2.0, 1H), 8.84 (s, 1H), 10.71 (s, 1H), 11.20 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 33.95, 113.77, 116.72, 118.53, 119.21, 119.42, 120.17, 127.15, 127.77, 128.56, 129.77, 129.98, 130.11, 132.17, 136.52, 146.55, 151.17, 152.97, 154.43, 158.06, 159.37, 164.23. Anal. calcd for $C_{26}H_{18}BrN_5O_4S$: C, 54.18; H, 3.15; N, 12.15; S, 5.56; found; C, 54.07; H, 3.09; N, 12.04; S, 5.47.

6,8-Dichloro-N'-*{[(4-phenyl-5-phenyl-4*H-*1,2,4-triazol-3-yl) thio]acetyl}-2-oxo-2*H-*chromene-3-carbohydrazide* (**7i**): Yield 3.51 g (62%); m.p. 285–286 °C; IR (KBr) (cm^{-1}): 3153, 1710, 1682, 1196; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.12 (s, 2H), 7.35–7.45 (m, 7H), 7.53–7.58 (m, 3H), 8.11–8.16 (m, 2H), 8.85 (s, 1H), 10.72 (s, 1H), 11.21 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 33.95, 118.29, 119.27, 119.68, 120.25, 120.91, 127.66, 128.26, 128.56, 128.77, 128.91, 129.15, 129.77, 129.98, 130.11, 133.01, 133.76, 146.20, 146.62, 148.38, 151.17, 152.56, 154.44, 158.05, 159.41, 164.22. Anal. calcd for $C_{26}H_{17}Cl_2N_5O_4S$: C, 55.13; H, 3.03; N, 12.36; S, 5.66; found; C, 55.04; H, 2.91; N, 12.28; S, 5.55.

7-Diethylamino-N'-*{[(4-phenyl-5-phenyl-4*H-*1,2,4-triazol-3-yl) thio]acetyl}-2-oxo-2*H-*chromene-3-carbohydrazide* (**7j**): Yield 3.86 g (68%); m.p. 211–212 °C; IR (KBr) (cm^{-1}): 3150, 1709, 1688, 1187; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, *J* = 6.4, 6H), 3.51 (d, *J* = 6.4, 6H), 4.09 (s, 2H), 6.67 (d, *J* = 2.0, 1H), 6.86 (dd, *J* = 9.2, *J* = 2.0, 2H), 7.20–7.63 (m, 6H), 7.71–7.94 (m, 5H), 8.87 (s, 1H), 10.61 (s, 1H), 11.11 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 12.33, 31.90, 35.93, 44.45, 95.98, 96.34, 106.89, 107.71, 110.27, 110.39, 113.71, 120,04, 126.51, 127.61, 128.56, 129.76, 129.96, 130.10, 131.81, 131.93, 145.38, 148.25, 149.55, 153.87, 153.17, 157.87, 159.48, 163.24, 163.92. Anal. calcd for $C_{30}H_{28}N_6O_4S$: C, 63.36; H, 4.96; N, 14.78; S, 5.64; found; C, 63.29; H, 4.84; N, 14.63; S, 5.51.

Electronic Supplementary Information

The ESI is available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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