Synthesis and characterisation of some new hybrid molecules containing thiophene, triazole and coumarin rings under microwave conditions

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In this work, a new series of *N*′-{[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-2-oxo-2*H*-1-benzopyran-3-carbohydrazides (thiophene–triazole–coumarin hybrid molecules) was synthesised from the reaction of 2-[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetohydrazide and 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-ones by using microwave irradiation and conventional heating procedures and their results were compared. The reaction was performed using a very small amount of organic solvent and without using a catalyst.

Keywords: thiophene, triazole, coumarin, hybrid molecule, microwave irradiation, benzotriazole

Sulfur-containing heterocycles (such as the thiophene ring) have an important role in medicinal chemistry. Thiophene derivatives with other bioactive heterocycles have been used extensively in pharmaceutical applications as they have antiallergic,[1] anti-inflammatory[2] and ocular hypotensive[3] activities. Raloxifene, a drug based on thiophene, has been approved by the US Food and Drug Administration for the prevention and treatment of osteoporosis associated with the postmenopause.[4]

1,2,4-Triazole rings are well-known to show powerful antimicrobial,[5] anticonvulsant,[6] antilipase[7] and analgesic[8] activities. Furthermore, synthesis of 1,2,4-triazoles in combination with other heterocyclic rings has attracted wide attention because of their biological applications[6,9–12].

Coumarins are an important class of oxygen-containing heterocycles that are obtained from both natural and synthetic sources. Most coumarin derivatives have been extensively used as key intermediates in the design of synthetic drug candidates due to their pharmacological activities such as anti-microbial,[13] anti-inflammatory,[14] anti-diabatic[15] and anti-HIV.[16]

Molecular hybridisation is a strategy for drug design widely used in medicinal chemistry and aims to combine two or more chemical moieties into a single compound, targeting an increase in biological activity. The presence of prototype heterocyclic systems is of great interest in the design of new drugs. Features such as small molecular weight and the presence of heteroatoms and aromatic structures can mimic endogenous substrates, which may lead to the development of biological activity.[14,16]

Thus, this study describes the production of novel thiophene–triazole–coumarin hybrid molecules through the molecular hybridisation strategy. These new hybrid molecules might serve as interesting bioactive templates.

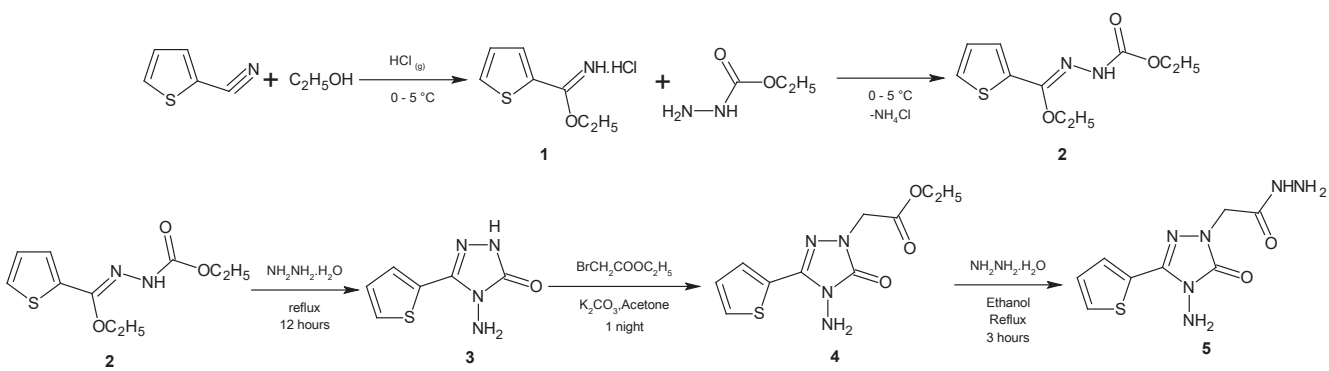
Results and discussion

In this study, a simple procedure was used for the synthesis of hybrid compounds that include thiophene, 1,2,4-triazol-3-one and coumarin moieties. The synthesis of the target compounds was performed by the reaction of 2-[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl] acetohydrazide and 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-one derivatives.

First, ethyl 2-thiophenecarboximidate hydrochloride (**1**) was synthesised according to the literature.[17] Then, compound **1** was converted to ethyl(thiophen-2-yl) etoxycarbonylhydrazone (**2**). The treatment of compound **2** with hydrazine monohydrate in water gave 4-amino-5-(thiophen-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**3**). Ethyl[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetate **4** was prepared from the reaction of 4-amino-5-(thiophen-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**3**) and ethyl bromoacetate in the presence of potassium carbonate in dry acetone. Then, compound **4** was treated with hydrazine hydrate in ethanol to prepare 2-[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetohydrazide (**5**) (Scheme 1).

Coumarin-3-carboxylic acid derivatives (**6a**–**e** and **7**) were obtained from the reaction of the respective salicylic aldehydes and 2,2-dimethyl-1,3-dioxane-4,6-dione in ethanol containing a catalytic amount of pyridine. Then, these compounds were reacted with 1*H*-benzotriazole in the presence of $SOCl_2$ in dichloromethane to prepare 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-ones (**8a**–**e** and **9**) (Scheme 2).

A literature search revealed that benzotriazole is an easy leaving group and this offers many advantages for synthetic applications.[18,19] Therefore, we used compounds **7a**–**f** and **9** for



Scheme 1 Synthetic route for compound **5**.

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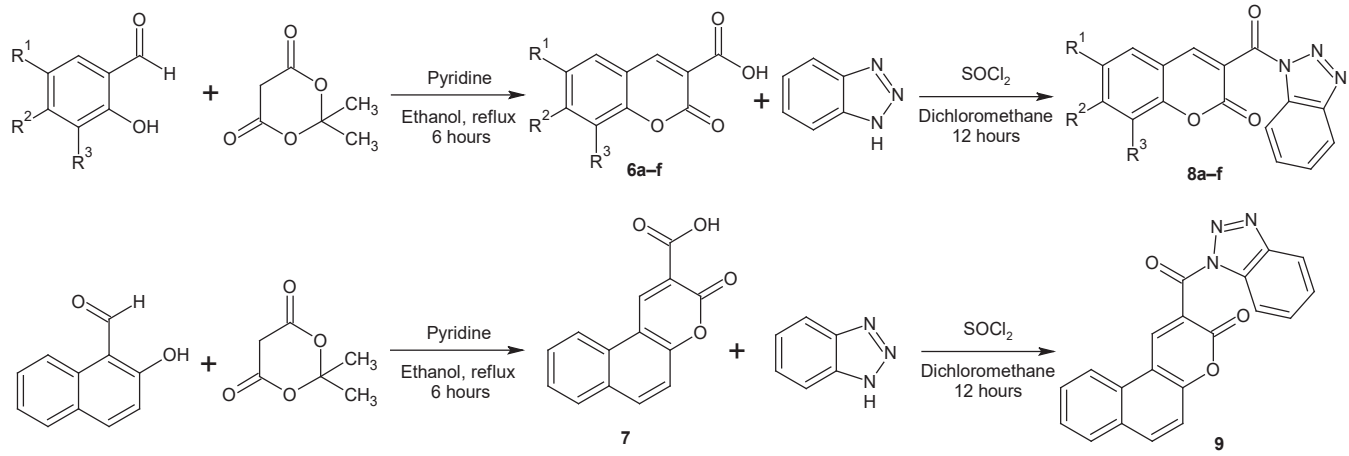
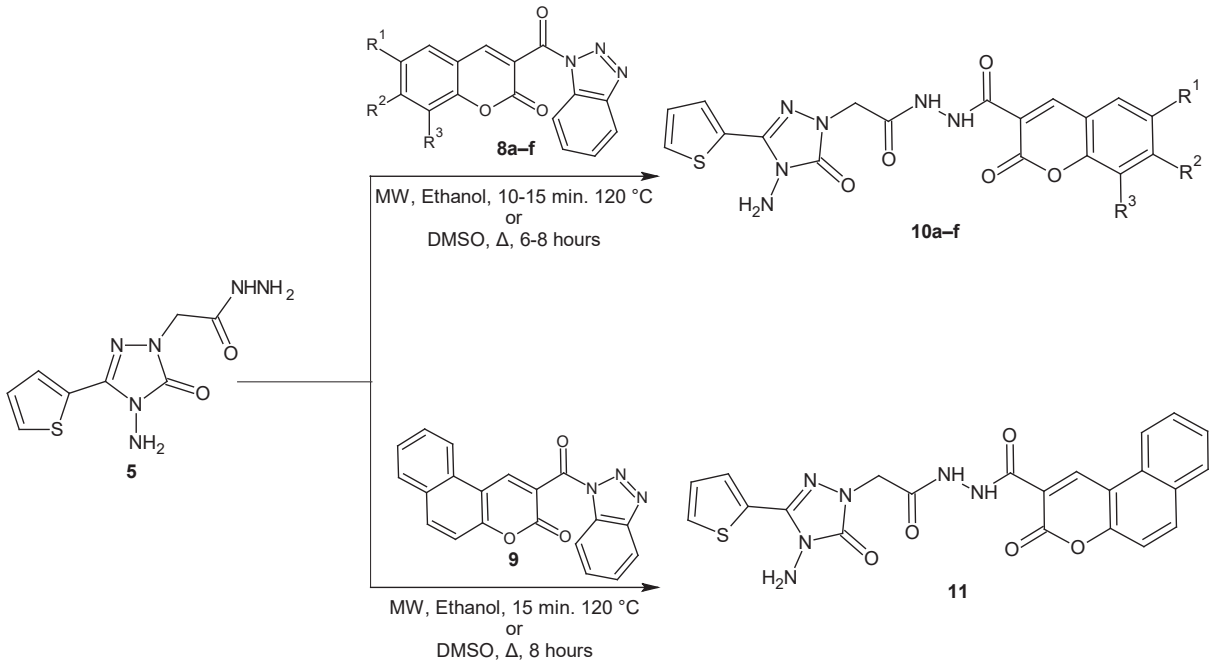


a: R^1: H, R^2:H, R^3: H, **b:** R^1: Cl, R^2:H, R^3: H, **c:** R^1: Br, R^2:H, R^3: H
d: R^1: Cl, R^2:H, R^3: Cl, **e:** R^1: H, R^2:$N(et)_2$, R^3: H, **f:** R^1: H, R^2:H, R^3: OCH_3

Scheme 2 Synthetic route for compounds **8a–f** and **9**.



a: R^1: H, R^2:H, R^3: H, **b:** R^1: Cl, R^2:H, R^3: H, **c:** R^1: Br, R^2:H, R^3: H
d: R^1: Cl, R^2:H, R^3: Cl, **e:** R^1: H, R^2:$N(et)_2$, R^3: H, **f:** R^1: H, R^2:H, R^3: OCH_3

Scheme 3 Synthetic route for compounds **10a–f** and **11**.

the preparation of hybrid molecules (**10a–f** and **11**) (Scheme 3). In some of the literature sources, it can be seen that this reaction can be directly carried out by using coumarin-3-acyl chloride and a hydrazide derivative.[20] However, this approach is not suitable for the microwave irradiation technique in a closed system because of the excess of $HCl_{(g)}$. Therefore, we chose to convert coumarin-3-carboxylic acids to 1*H*-benzotriazole derivatives to allow the use of the microwave irradiation technique. In addition, these reactions were performed with conventional heating and it was shown that microwave heating gives higher yields and faster reaction rates, compared with conventional heating (Table 1).

Table 1 Comparison of microwave and conventional heating procedures for the synthesis of compounds **10a–f** and **11**

Compound	Microwave heating			Conventional heating	
	Temperature (°C)	Time (min)	Yield (%)	Time (h)	Yield (%)
10a	120	10	67	6.0	65
10b	120	15	52	7.5	48
10c	120	15	55	7.5	39
10d	120	15	59	7.0	53
10e	120	10	65	6.0	57
10f	120	15	60	7.0	47
11	120	15	53	8.0	50

The results of spectral investigations of the target compounds are in agreement with the proposed structures. In the ^{1}H NMR spectra of these compounds, two NH signals were shown at about 11.00 and 10.50 ppm and an NH_2 signal was shown at about 5.50 ppm. The NCH_2 signal was observed at about 4.50 ppm. In the ^{13}C NMR spectra of these compounds, four C=O signals were shown at about 165.0 (hydrazide), 160.0 (hydrazide), 159.0 (coumarin C2) and 153.0 (triazole C3) ppm, while the C=N

(triazole C5) signal was observed at about 147.0 ppm. Also, the number of aromatic carbon atoms in the ^{13}C NMR spectra was in agreement with their structures. In addition, all compounds showed the expected elemental analysis results.

Conclusion

We report here the synthesis of thiophene–triazole–coumarin hybrid molecules using a simple method. This present method was achieved using microwave irradiation and conventional heating procedures without using a catalyst. This study could provide inspiration for further investigation of the potential bioactivity of these heterocyclic compounds.

Experimental

All the chemicals were supplied from Merck, Sigma-Aldrich and Fluka. All reaction progress was monitored by TLC on silica gel plates (Merck 60, F_{254}, 0.2 mm). The melting points were determined on capillary tubes on Stuart SMP30 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were obtained using a Varian-Mercury (tetra methyl silane as internal standard): chemical shifts are expressed in δ values (ppm). The elemental compositions were determined on a Carlo Erba 1106 CHN analyser; the experimental values were in agreement (±0.4%) with the calculated ones. A monomode CEM Discover Microwave was used in the standard configuration as delivered, including proprietary software. All experiments were carried out in microwave process vials (30 mL) with temperature control by an infrared sensor. Temperature was monitored by a computer and maintained constant by discrete modulation of the delivered microwave power. After the reaction completion, the vial was cooled to 60 °C *via* air-jet cooling.

Synthesis of ethyl(thiophen-2-yl)acetateetoxycarbonylhydrazone (**2**)

In a round-bottom flask equipped with a magnetic stirrer, ethyl 2-thiophenecarboximidate hydrochloride (**1**) (0.01 mol) was dissolved in absolute ethanol (50 mL) with ice-bath cooling. Then ethyl carbazate (0.01 mol) dissolved in absolute ethanol (20 mL) was then added to this solution. After stirring for 8 h in an ice bath, the mixture was filtered to remove the ammonium chloride, which separated from the solution, and the filtrate was evaporated at 30–35 ºC under reduced pressure. The solid residue, after drying in a desiccator, was extracted with petroleum ether to give compound **2** as a white solid; yield 1.76 g (72%), m.p. 78–79 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.19–1.30 (m, 6H), 4.06–4.13 (m, 4H), 7.13 (br, 1H), 7.63 (d, J = 4.8 Hz, 1H), 7.70 (s, 1H), 10.09 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.98, 15.42, 60.97 + 63.22 (CH_2), 67.44, 128.04, 128.44, 129.15, 134.41, 153.94, 155.61. Anal. calcd for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56; S, 13.23; found: C, 49.43; H, 5.71; N, 11.47; S, 13.15%.

*Synthesis of 4-amino-5-(thiophen-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one* (**3**)

A solution of ethyl(thiophen-2-yl)acetate etoxycarbonylhydrazone (**2**) (0.01 mol) in H_2O (75 mL) was refluxed with hydrazine monohydrate (1.50 mL, 0.03 mol) for 12 h. After the mixture was cooled to room temperature, a white solid appeared. This was filtered, dried and recrystallised from water to give compound **3** as a white solid; yield 1.52 g (83%); m.p. 195–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.46 (s, 2H), 7.14 (s, 1H), 7.67 (d, J = 4.8 Hz, 1H), 7.80 (br, 1H), 11.79 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 127.82, 128.17, 128.44, 128.82, 142.69, 154.95. Anal. calcd for $C_6H_6N_4OS$: C, 39.55; H, 3.32; N, 30.75; S, 17.60; found: C, 39.47; H, 3.24; N, 30.64; S, 17.53%.

*Synthesis of ethyl[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetate* (**4**)

4-Amino-5-(thiophen-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**3**) (0.01 mol) was dissolved in dry acetone (50 mL). Then, potassium carbonate (0.025 mol) was added to this solution and it was stirred for 15 min at room temperature. Then, ethyl bromoacetate (1.84 g, 0.011 mol) was added and the mixture was stirred overnight at room temperature. After the reaction was completed (monitored by TLC, eluent EtOAc–hexane, 3:1), the product was precipitated by the addition of water. The product was filtered off, washed with water and recrystallised from ethanol/water (1:1) to give compound **4** as a white solid; yield 2.47 g (92%); m.p. 116–117 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.91 (t, J = 6.4 Hz, 3H), 4.14 (q, J = 6.4 Hz, 2H), 4.62 (s, 2H), 5.76 (s, 2H), 7.17 (br, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.92 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.46, 47.26, 61.65, 127.53, 127.95, 128.84, 129.52, 142.15, 142.69, 153.66, 168.24. Anal. calcd for $C_{10}H_{12}N_4O_3S$: C, 44.77; H, 4.51; N, 20.88; S 11.95; found: C, 44.68; H, 4.44; N, 20.76; S, 11.78%.

*Synthesis of 2-[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetohydrazide* (**5**)

Hydrazine monohydrate (1.25 mL, 0.025 mol) was added to a solution of ethyl[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetate (**4**) (0.01 mol) in ethanol (25 mL). The mixture was then refluxed for 3 h. After the mixture was cooled, a white solid formed. This crude product was filtered off, and recrystallised from EtOH to give compound **5** as a white solid; yield 2.00 g (80%); m.p. 198–199 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.28 (s, 2H), 4.31 (s, 2H), 5.57 (s, 2H), 7.16 (t, J = 6.4 Hz, 1H), 7.72 (d, J = 5.2 Hz, 1H), 7.90 (br, 1H), 9.24 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 47.13, 127.83, 127.90, 128.61, 129.80, 141.86, 153.77, 166.21. Anal. calcd for $C_8H_{10}N_6O_2S$: C, 37.79; H, 3.96; N, 33.05; S, 12.61; found: C, 37.66; H, 3.88; N, 32.89; S, 12.57%.

Synthesis of compounds **6a–f** *and* **7***; general procedure*

A solution of salicylaldehyde derivatives or 2-hydroxynaphthaldehyde (0.01 mol) and Meldrum's acid (1.58 g, 0.011 mol) in ethanol (50 mL) and pyridine (0.5 mL) was refluxed in a round-bottom flask for 6 h. After the reaction was completed (monitored by TLC, EtOAc–hexane, 4:1), the solvent was evaporated under reduced pressure. The obtained solid was washed with H_2O and recrystallised from a mixture of EtOH–H_2O, 3:2.

*2-Oxo-2*H*-chromene-3-carboxylic acid* (**6a**): White solid; yield 1.39 g (73%); m.p. 189–190 °C (lit.[10] 188 °C).

*6-Chloro-2-oxo-2*H*-chromene-3-carboxylic acid* (**6b**): White solid; yield 2.47 g (76%); m.p. 194–195 °C (lit.[21] 193 °C).

*6-Bromo-2-oxo-2*H*-chromene-3-carboxylic acid* (**6c**): White solid; yield 1.80 g (67%); m.p. 195–196 °C (lit.[10] 194–196 °C).

*6,8-Dichloro-2-oxo-2*H*-chromene-3-carboxylic acid* (**6d**): White solid; yield 1.78 g (69%); m.p. 222–223 °C (lit.[22] 220–224 °C).

*7-Diethylamino-2-oxo-2*H*-chromene-3-carboxylic acid* (**6e**): Yellow solid; yield 1.95 g (75%); m.p. 232–233 °C (lit.[23] 230–232 °C).

*8-Methoxy-2-oxo-2*H*-chromene-3-carboxylic acid* (**6f**): White solid; yield 1.95 g (75%); m.p. 215–216 °C (lit.[24] 214–216 °C).

*3-Oxo-3*H*-naphtho[2,1-*b*]pyran-2-carboxylic acid* (**7**): White solid; yield 1.61 g (67%); m.p. 238–239 °C (lit.[25] 236–237 °C).

Synthesis of compounds **8a–f** *and* **9***; general procedure*

Thionyl chloride (1.78 g, 0.015 mol) was added to a solution of 1*H*-benzotriazole (5.95 g, 0.05 mol) in CH_2Cl_2 (75 mL). The mixture was stirred for 30 min at room temperature. Then the corresponding coumarin-3-carboxylic acid (**6a–f** and **7**) (0.01 mol) was added and the reaction mixture was stirred for 12 h at room temperature. The precipitate was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 (100 mL), and the solution was washed with 10 % Na_2CO_3 solution (50 mL) and 4 N HCl (50 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave compounds **8a–f** and **9**, which were recrystallised from CH_2Cl_2–hexane, 1:1.

*3-(1*H*-Benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-one* (**8a**): White solid; yield 2.12 g (73%); m.p. 179–180 °C (lit.[10] 176–177 °C).

*3-(1*H*-Benzotriazol-1-ylcarbonyl)-6-chloro-2*H*-chromen-2-one* (**8b**): White solid; yield 2.20 g (63%); m.p. 248–249 °C (lit.[16] 248–249 °C). Anal. calcd for $C_{16}H_8ClN_3O_3$: C, 59.00; H, 2.48; N, 12.90; found: C, 58.87; H, 2.39; N, 12.82%.

*3-(1*H*-Benzotriazol-1-ylcarbonyl)-6-bromo-2*H*-chromen-2-one* (**8c**): White solid; yield 2.52 g (68%); m.p. 250–251 °C (lit.[10] 250–251 °C).

*3-(1*H*-Benzotriazol-1-ylcarbonyl)-6,8-dichloro-2*H*-chromen-2-one* (**8d**): White solid; yield 2.34 g (65%); m.p. 263–264 °C (lit.[12] 263–264 °C).

*3-(1*H*-Benzotriazol-1-ylcarbonyl)-7-diethylamino-2*H*-chromen-2-one* (**8e**): Yellow solid; yield 2.46 g (68%); m.p. 210–211 °C (lit.[12] 210–211 °C).

*3-(1*H*-Benzotriazol-1-ylcarbonyl)-8-methoxy-2*H*-chromen-2-one* (**8f**): White solid; yield 2.46 g (68%); m.p. 236–237 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.96 (s, 3H), 7.57 (d, *J*=7.2 Hz, 1H). 7.77 (t, *J*=7.2 Hz, 1H), 7.98 (s, 1H), 7.99–8.11 (m, 3H), 8.29 (s, 1H), 8.74 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 62.14, 114.20, 119.11, 119.35, 120.77, 122.62, 127.56, 129.51, 130.92, 131.78, 134.44, 145.91, 146.92, 153.46, 157.29, 162.75. Anal. calcd for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.08; found: C, 63.47; H, 3.40; N, 13.01%.

*2-(1*H*-Benzotriazole-1-carbonyl)-3*H*-naphtho[2,1-*b*]pyran-3-one* (**9**): CAS Registry Number: 886124-23-8; White solid; yield: 2.47 g (72%); m.p. 267–268 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.64–7.77 (m, 4H), 7.88 (t, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 8.28–8.35 (m, 3H), 8.85 (d, *J* = 8.4 Hz, 1H), 9.96 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 112.44, 114.18, 117.09, 119.98, 120.78, 122.64, 127.09, 127.50, 129.51, 131.07, 131.74, 136.67, 144.66, 145.98, 155.25, 157.21, 163.27. Anal. calcd for $C_{20}H_{11}N_3O_3$: C, 70.38; H, 3.25; N, 12.31; found: C, 70.26; H, 3.18; N, 12.20%.

Synthesis of compounds **10a–f** *and* **11***; general procedure*

Conventional method. A solution of 2-[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetohydrazide (**5**) (0.01 mol) and compounds **8a–f** and **9** (0.012 mol) in dimethyl sulfoxide (10 mL) were placed in a round-bottomed flask. The mixture was refluxed for 6–8 h. After the completion of the reaction (monitored by TLC, eluent EtOAc–hexane, 3:1), the mixture was cooled to room temperature, and the product was precipitated by addition of water. It was filtered and washed with hot water and hot ethanol to obtain the pure product.

Microwave method. A mixture of 2-[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetohydrazide (**5**) (0.01 mol) and compounds **8a–f** and **9** (0.012 mol) in ethanol (5 mL) were transferred to a microwave process vial and irradiated with microwaves at 120 °C for 10–15 min at 300 W maximum power. After the reaction was completed (monitored by TLC, EtOAc–hexane, 3:1), the mixture was poured into a beaker with hot ethanol, and a solid was formed. This crude product was filtered off and washed with hot ethanol to obtain the pure product.

N′*-{[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-2-oxo-2*H*-1-benzopyran-3-carbohydrazide* (**10a**): White solid; m.p. 325–326 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.55 (s, 2H), 5.64 (s, 2H), 7.17 (t, *J* = 4.4 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.71–7.77 (m, 2H), 7.92 (d, *J* = 4.4 Hz, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 8.82 (s, 1H), 10.64 (s, 1H), 11.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.79, 116.70, 118.50, 118.73, 125.68, 127.71, 127.93, 128.72, 129.41, 130.81, 134.88, 142.01, 148.40, 153.86, 154.38, 159.16, 160.25, 164.46. Anal. calcd for $C_{18}H_{14}N_6O_5S$: C, 50.70; H, 3.31; N, 19.71; S, 7.52; found: C, 50.57; H, 3.25; N, 19.63; S, 7.45%.

N′*-{[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-6-chloro-2-oxo-2*H*-1-benzopyran-3-carbohydrazide* (**10b**): White solid; m.p. 343–344 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.44 (s, 2H), 5.30 (s, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.45–7.53 (m, 3H), 7.75 (d, *J* = 8.8 Hz, 1H), 8.10 (s, 1H), 8.80 (s, 1H), 10.62 (s, 1H), 11.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.54, 118.70, 119.69, 120.05, 120.27, 129.36, 129.58, 131.50, 131.69, 134.22, 135.66, 147.01, 147.17, 152.97, 153.88, 158.77, 159.78, 164.59. Anal. calcd for $C_{18}H_{13}ClN_6O_5S$: C, 46.91; H, 2.84; N, 18.24; S, 6.96; found: C, 46.80; H, 2.75; N, 18.18; S, 6.85%.

N′*-{[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-6-bromo-2-oxo-2*H*-1-benzopyran-3-carbohydrazide* (**10c**): White solid; m.p. 331–332 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.55 (s, 2H), 5.64 (s, 2H), 7.17 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 4.4 Hz, 1H), 7.87–7.90 (m, 2H), 8.25 (s, 1H), 8.80 (s, 1H), 10.62 (s, 1H), 11.05 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.79, 117.16, 118.97, 119.97, 120.59, 127.71, 127.92, 128.72, 129.41, 132.60, 136.96, 142.05, 146.97, 153.42, 153.85, 158.95, 159.72, 164.53. Anal. calcd for $C_{18}H_{13}BrN_6O_5S$: C, 42.78; H, 2.59; N, 16.63; S, 6.35; found: C, 42.67; H, 2.47; N, 16.58; S, 6.26%.

N′*-{[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-6,8-dichloro-2-oxo-2*H*-1-benzopyran-3-carbohydrazide* (**10d**): White solid; m.p. 345–346 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.55 (s, 2H), 5.64 (s, 2H), 7.17 (br, 1H), 7.20 (d, *J* = 4.0 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 8.13 (s, 1H), 8.80 (s, 1H), 10.63 (s, 1H), 11.06 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.79, 117.16, 118.97, 119.77, 120.60, 127.70, 127.92, 128.71, 129.42, 132.59, 136.98, 142.01, 146.96, 153.41, 153.87, 158.96, 159.71, 164.55. Anal. calcd for $C_{18}H_{12}Cl_2N_6O_5S$: C, 43.65; H, 2.44; N, 16.97; S, 6.47; found: C, 43.54; H, 2.32; N, 16.83; S, 6.36%.

N′*-{[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-7-diethylamino-2-oxo-2*H*-1-benzopyran-3-carbohydrazide* (**10e**): White solid; m.p. 327–328 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12 (t, *J* = 6.4 Hz, 6H), 3.48 (q, *J* = 6.4 Hz, 4H), 4.71 (s, 2H), 5.48 (s, 2H), 6.62 (s, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 7.47–7.58 (m, 3H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.89–7.93 (m, 1H), 8.70 (s, 1H), 10.34 (s, 1H), 10.85 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.76 ($2CH_3$), 44.85 ($2CH_2$), 46.54, 96.37, 108.04, 110.80, 122.07, 128.36, 130.02, 130.98, 131.90, 132.25, 139.05, 147.00, 148.69, 153.85, 157.85, 160.09, 161.82, 164.28. Anal. calcd for $C_{22}H_{23}N_7O_5S$: C, 53.11; H, 4.66; N, 19.71; S, 6.44; found: C, 53.03; H, 4.53; N, 19.63; S, 6.36%.

N′*-{[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-8-methoxy-2-oxo-2*H*-1-benzopyran-3-carbohydrazide* (**10f**): White solid; m.p. 335–336 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.92 (s, 3H), 4.55 (s, 2H), 5.64 (s, 2H), 7.17 (br, 1H), 7.38 (d, *J* = 6.8 Hz, 1H), 7.44 (d, *J* = 6.8 Hz, 1H), 7.53 (d, *J* = 6.0 Hz, 1H), 7.72 (br, 1H), 7.92 (s, 1H), 8.84 (s, 1H), 10.65 (s, 1H), 11.06 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.78, 56.69, 116.84, 118.62, 119.29, 121.68, 125.63, 127.71, 127.92, 128.72, 129.41, 142.01, 143.71, 146.75, 148.65, 153.85, 159.12, 159.95, 164.46. Anal. calcd for $C_{19}H_{16}N_6O_6S$: C, 50.00; H, 3.53; N, 18.41; S, 7.03; found: C, 49.85; H, 3.41; N, 18.34; S, 6.92%.

N′*-{[4-amino-5-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}-3-oxo-3*H*-naphtho[2,1-*b*]pyran-2-carbohydrazide* (**11**): White solid; m.p. >350 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.48 (s, 2H), 5.37 (s, 2H), 7.15 (br, 1H), 7.25 (d, *J* = 6.4 Hz, 1H), 7.39 (d, *J* = 6.4 Hz, 1H), 7.44–7.57 (m, 3H), 7.65 (br, 1H), 7.70–7.81 (m, 2H), 7.95 (br, 1H), 8.81 (s, 1H), 10.68 (s, 1H), 11.09 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.52, 118.72, 119.73, 120.07, 128.74, 128.76, 129.35, 129.57 (2C), 131.11, 131.79 (2C), 134.27, 135.25, 147.05, 147.22, 149.87, 152.78, 153.88, 158.78, 164.59. Anal. calcd for $C_{22}H_{16}N_6O_5S$: C, 55.46; H, 3.38; N, 17.64; S, 6.73; found: C, 55.39; H, 3.27; N, 17.58; S, 6.61%.

Electronic Supplementary Information

The ESI associated with this paper can be found at:
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