Synthesis of new coumarin containing benzimidazole derivatives

Emre Menteşe[a*], Fatih Yılmaz[a], Fatih Mutlu[a] and Bahittin Kahveci[b]

[a]*Department of Chemistry, Art and Science Faculty, Recep Tayyip Erdoğan University 53100-Rize, Turkey*
[b]*Department of Nutrition and Dietetics, Faculty of Health Sciences, Karadeniz Technical University 61100-Trabzon, Turkey*

This study describes the synthesis of a new series of benzimidazoles that contain a coumarin moiety. The high yielding synthetic reaction was between hydrazide derivatives of benzimidazoles and 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-one. The reaction was performed using a very small amount of the organic solvent and without the use of a catalyst.

Keywords: coumarins, benzimidazoles, Meldrum's acid, benzotriazoles

Coumarins are an important class of natural compounds with a wide range of biological activities.[1-4] Coumarin derivatives have significant therapeutic potential and are a good source of potential drug candidates with regards to their safety and efficacy.[5] They are also commonly used as additives in fragrances, agrochemicals, insecticides and in food and cosmetics.[6] Futhermore, they have found applications as photosensitisers, laser dyes, fluorescent indicators and optical brighteners.[7, 8]

Benzimidazoles constitute an important class of molecules in medicinal chemistry. They have anticancer,[9] antiviral,[10] anti-inflammatory,[11] antioxidant[12] and anticoagulant properties.[13] Many benzimidazole drugs such as mebendazole/thiabendazole/albendazole, norastemizole/ mizolastine, and telmisartan have been successfully used clinically as antiparasitic, antihistaminic and antihypertensive drugs. This has prompted the investigation of other benzimidazole derivatives as potential clinical therapeutics. Recently, there have been major efforts to develop structurally novel benzimidazole compounds as antimicrobial agents.

With a goal of developing molecules as new therapeutic agents, we have established a protocol for the synthesis of some coumarin containing benzimidazoles. Our study demonstrated that this is an efficient and environmentally safe protocol that leads to an easy synthesis in high yield.

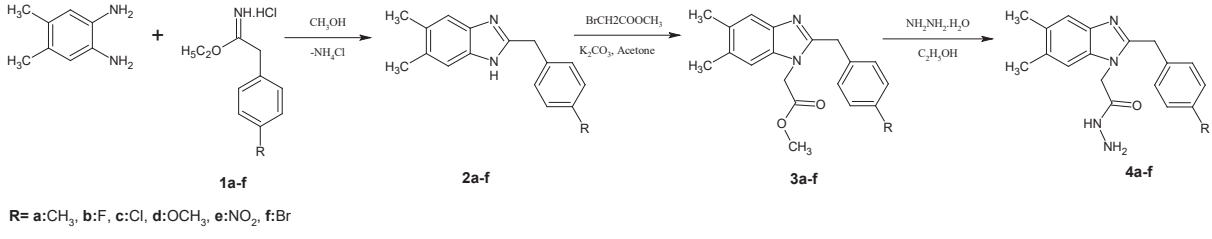
Results and discussion

First, iminoester hydrochlorides (**1a–f**) were synthesised according to the literature.[14] Treatment of compounds **1a–f** with 4,5-dimethyl-*o*-phenylenediamine in methanol gave benzimidazole derivatives (**2a–f**) and the compounds **2a–f** were treated with methyl bromoacetate to synthesise methyl acetate derivatives (**3a–f**). Finally, treatment of compounds **3a–f** with hydrazine monohydrate in ethanol gave hydrazide derivatives (**4a–f**) which are the first intermediate compounds (Scheme 1).

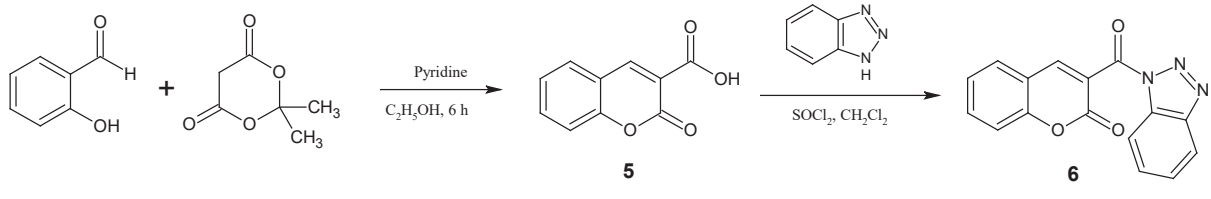
To synthesise the second intermediate, 3-(1H-benzotriazol-1-yl carbonyl)-2H-chromen-2-one (**6**), salicylaldehyde was reacted with 2, 2-dimethyl-1, 3-dioxane-4, 6-dione (Meldrum's acid), which was prepared according to the literature,[15] in ethanol to synthesise coumarin-3-carboxylic acid (**5**). Then, the compound **5** was treated with 1*H*-benzotriazole in dichloromethane in the presence of thionyl chloride to yield 3-(1H-benzotriazol-1-yl carbonyl)-2H-chromen-2-one (**6**) (Scheme 2).

The benzotriazole group offers many advantages for synthetic applications.[16] Treatment of compounds **4a–f** with compound **6** resulted in the synthesis of the target coumarin containing benzimidazole derivatives (**7a–f**), using a low amount of ethanol (10 mL) in 6 h of reflux (Scheme 3).

Spectral investigations of the newly synthesised compounds are in accord with the proposed structures. Two NH signals (exchangeable with D_2O) were shown at about 11.20 and 10.65 ppm in the ^{1}H NMR spectra for the compounds **7a–f**. N–$CH_2$and CH_2 signals were shown at about 4.90 and 4.20 ppm, respectively. The signals of the aromatic protons of these compounds were found to fit the proposed structure by calculation of the *J* constant. In the ^{13}C NMR spectra of these compounds, two hydrazide carbonyl carbons were shown at about 160 and 165 ppm. The coumarin carbonyl (coumarin C-2) was shown at about 159 ppm. The C=N signal associated with the benzimidazole ring was shown at about 154 ppm. The

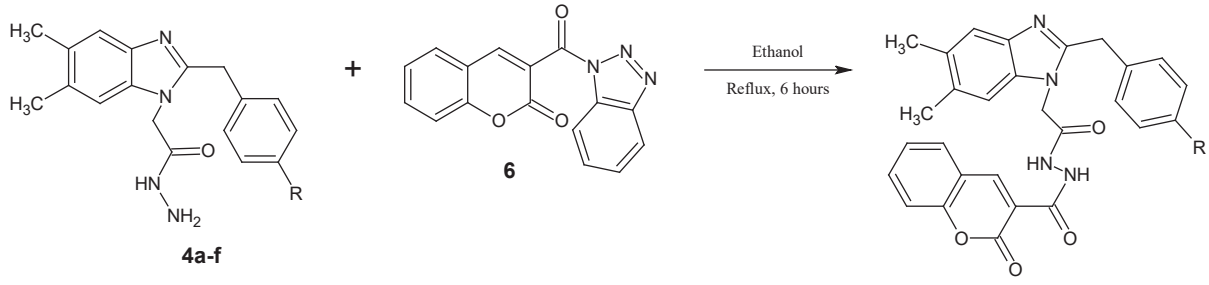


Scheme 1 Synthesis of compounds **4a–f**.



Scheme 2 Synthesis of compound **6**.

* Correspondent. E-mail: emre.mentese@erdogan.edu.tr



4a-f **6** **7a-f**

R= a:CH_3, **b:**F, **c:**Cl, **d:**OCH_3, **e:**NO_2, **f:**Br

Scheme 3 Synthesis of the compounds **7a–f**.

coumarin C-3 and C-4 signals were shown at about 153 and 148 ppm, respectively. These compounds are characterised by the anticipated number of aromatic signals in the ^{13}C NMR spectra and the appropriate ion peaks in their LC–MS spectra.

We report here a new protocol for the synthesis of coumarin-containing benzimidazole derivatives. This protocol offers shorter reaction times, simple workup procedure while using the organic solvent in low amounts and without a need for a catalyst.

Experimental

All the chemicals were supplied from Merck, Aldrich and Fluka. Melting points were determined in capillary tubes on a Buchi oil heating melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were performed on a Varian- Mercury 400 MHz spectrometer in DMSO-d_6 using TMS as internal standard. The mass spectra were recorded on an Agilent 1260 Infinity series Accurate-Mass Time-of-Flight (TOF) LC/MS spectrometer. The elemental compositions were determined on a Carlo Erba 1106 CHN analyser; the experimental values were in agreement (±0.4%) with calculated ones.All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 2.54 0.2 mm thickness).

Synthesis of **2a–f**

These compounds were synthesised according to the literature procedure.[17]

*5,6-Dimethyl-2-(4-methylbenzyl)-1*H*-benzimidazole* (**2a**): Yield 2.22 g (89%); m.p. 200–201°C (lit.[18] 200 °C).

*5,6-Dimethyl-2-(4-fluorobenzyl)-1*H*-benzimidazole* (**2b**): Cas No:1176128-02-1; yield 1.93 g (76%); m.p. 178–179 °C; ^1H NMR (DMSO-d_6, 400 MHz): 4.09 (s, 2H), 7.109–7.13 (m, 2H), 7.21 (s, 2H), 7.30–7.33 (m, 2H), 11.97 (s, 1H). Anal calcd for $C_{16}H_{15}FN_2$: C, 75.57; H, 5.95; N, 11.02; found: C, 75.48; H, 5.90; N, 10.97%. LC-MS:255.23, 256.21 [M+1].

*5,6-Dimethyl-2-(4-chlorobenzyl)-1*H*-benzimidazole* (**2c**): Yield 2.22 g (89%); m.p. 200–201°C (lit.[19] 199–200°C).

*5,6-Dimethyl-2-(4-methoxybenzyl)-1*H*-benzimidazole* (**2d**): Cas No:1175987-50-4; yield 2.21 g (83%); m.p. 195–196 °C; ^1H NMR (DMSO-d_6, 400 MHz):4.04 (s, 2H), 6.85 (d, *J*=8.8, 2H), 7.19–7.22 (m, 4H). Anal calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52; found: C, 76.61; H, 6.74; N, 10.47%. LC-MS:267.34 [M+1].

*5,6-Dimethyl-2-(4-nitrobenzyl)-1*H*-benzimidazole* (**2e**): Yield 2.13 g (76%); m.p. 210–211 °C (lit.[20] 208–210 °C).

*5,6-Dimethyl-2-(4-bromobenzyl)-1*H*-benzimidazole* (**2f**): Cas No:1272924-42-1; yield 2.46 g (78%); m.p. 215–216 °C; ^1H NMR (DMSO-d_6, 400 MHz):4.08 (s, 2H), 7.21–7.25 (m, 4H), 7.46 (d, *J*=8.4, 2H), 12.00 (s, 1H). Anal calcd for $C_{16}H_{15}BrN_2$: C, 60.97; H, 4.80; N, 8.89; found: C, 60.92; H, 4.72; N, 8.83. LC-MS:315.22, 317.25 [M+1].

Synthesis of **3a–f**

A mixture of compounds **2a–f** (0.01 mol) in acetone (25 mL) and dry K_2CO_3 (0.025 mol) was stirred for 10 min and then, methyl bromoacetate (0.011 mol) was added. The mixture was stirred at room temperature for 6 h. After the reaction was complete (monitored by TLC, ethyl acetate/hexane, 3/1), the product precipitated by addition of water. It was filtrated, dried and recrystallised from ethanol:water (1:2).

*Methyl [5,6-dimethyl-2-(4-methylbenzyl)-1*H*-benzimidazol-1-yl]acetate* (**3a**): Yield 2.64 g (82%); m.p. 134–135 °C; ^1H NMR (DMSO-d_6, 400 MHz): 2.23 (s, 6H), 2.27 (s, 3H), 3.49 (s, 3H), 4.13 (s, 2H), 5.03 (s, 2H), 7.07 (d, *J*=8.0, 2H), 7.09 (d, *J*=8.0, 2H), 7.18 (s, 1H), 7.33 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.26, 20.48, 21.04 (CH_3), 32.91 (CH_2), 44.77 (NCH_2), 52.54 (OCH_3), 110.56, 119.20, 129.09 (2C), 129.36 (2C), 130.18, 130.84, 133.95, 134.66, 135.94, 141.18 (ArC), 153.33 (C=N), 168.75 (C=O). Anal calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69; found: C, 74.44; H, 6.82; N, 8.63%. LC-MS: 323.34 [M+1].

*Methyl [5,6-dimethyl-2-(4-fluorobenzyl)-1*H*-benzimidazol-1-yl]acetate* (**3b**): Yield 2.41 g (74%); m.p. 147–148 °C; ^1H NMR (DMSO-d_6, 400 MHz): 2.27 (s, 6H), 3.32 (s, 3H), 4.17 (s, 2H), 5.09 (s, 2H), 7.06–7.11 (m, 2H), 7.18 (s, 1H), 7.25–7.29 (m, 2H), 7.32 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz):20.25, 20.48 (CH_3), 32.32 (CH_2), 44.74 (NCH_2), 52.56 (OCH_3), 110.59, 115.37, 115.58, 119.21, 130.25, 130.92, 131.07, 133.26, 134.63, 141.13, 153.08 (C=N), 161.45 (C-F, $J_{C\text{-}F}$=240.5 Hz), 168.28 (C=O). Anal calcd for $C_{19}H_{19}FN_2O_2$: C, 69.92; H, 5.87; N, 8.58; found: C, 69.85; H, 5.81; N, 8.53%. LC-MS: 327.40 [M+1].

*Methyl [5,6-dimethyl-2-(4-chlorobenzyl)-1*H*-benzimidazol-1-yl]acetate* (**3c**): Yield 2.90 g (85%); m.p. 140–141°C; ^1H NMR (DMSO-d_6, 400 MHz): 2.27 (s, 6H), 3.32 (s, 3H), 4.18 (s, 2H), 5.09 (s, 2H), 7.19 (s, 1H), 7.24–7.30 (m, 2H), 7.31–7.34 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.25, 20.48 (CH_3), 32.42 (CH_2), 44.74 (NCH_2), 52.57 (OCH_3), 110.60, 119.22, 128.70 (2C), 130.33, 131.05, 131.61 (2C), 134.58, 136.14, 141.09 (ArC), 152.85 (C=N), 168.79 (C=O). Anal calcd for $C_{19}H_{19}ClN_2O_2$: C, 66.57; H, 5.59; N, 8.17; found: C, 66.50; H, 5.51; N, 8.14%. LC-MS: 343.29, 345.32 [M+1].

*Methyl [5,6-dimethyl-2-(4-methoxybenzyl)-1*H*-benzimidazol-1-yl] acetate* (**3d**): Yield 2.84 g (84%); m.p. 121–122 °C; ^1H NMR (DMSO-d_6, 400 MHz): 2.25 (s, 6H), 3.51 (s, 3H), 3.74 (s, 3H), 4.13 (s, 2H), 5.03 (s, 2H), 7.81 (d, *J*=8.0, 2H), 7.12 (d, *J*=8.0, 2H), 7.18 (s, 1H), 7.36 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.26, 20.49 (CH_3), 32.41 (CH_2), 44.75 (NCH_2), 52.57, 55.48 (OCH_3), 110.54, 114.23, 119.17, 128.87 (2C), 130.17, 130.23, 130.84 (2C), 134.65, 141.13, 153.52 (ArC), 158.37 (C=N), 168.77 (C=O). Anal calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28; found: C, 70.93; H, 6.48; N, 8.23%. LC-MS: 339.37 [M+1].

*Methyl [5,6-dimethyl-2-(4-nitrobenzyl)-1*H*-benzimidazol-1-yl]acetate* (**3e**): Yield 2.44 g (69%); m.p. 148–149 °C; ^1H NMR (DMSO-d_6, 400 MHz): 2.24 (s, 6H), 3.56 (s, 3H), 4.36 (s, 2H), 5.12 (s, 2H), 7.21 (s, 1H), 7.35 (s, 1H), 7.54 (d, *J*=8.0, 2H), 8.17 (d, *J*=8.0, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.25, 20.35 (CH_3), 32.78 (CH_2), 44.76 (NCH_2), 52.64 (OCH_3), 110.62, 119.26, 123.85 (2C), 130.45, 130.73 (2C), 131.78, 134.49, 141.11, 145.35, 146.72 (ArC), 152.19 (C=N), 168.85 (C=O). Anal calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89; found: C, 64.52; H, 5.37; N, 11.83%. LC-MS: 354.35 [M+1].

*Methyl [5,6-dimethyl-2-(4-bromobenzyl)-1*H*-benzimidazol-1-yl]acetate* (**3f**): Yield 2.94 g (76%); m.p. 139–140 °C; ^1H NMR (DMSO-d_6, 400 MHz): ^1H NMR (DMSO-d_6, 400 MHz): 2.26 (s, 6H), 3.51 (s, 3H), 4.16 (s, 2H), 5.09 (s, 2H), 7.18–7.21 (m, 3H), 7.32 (s, 1H), 7.45 (d, *J*=8.0, 2H).

^{13}C NMR (DMSO-d_6, 100 MHz):20.26, 20.49 (CH_3), 32.49 (CH_2), 44.74 (NCH_2), 52.58 (OCH_3), 110.60, 119.21, 120.10, 130.32, 131.02, 131.57 (2C), 131.63 (2C), 134.57, 136.58, 141.09 (ArC), 152.78 (C=N), 168.78 (C=O). Anal calcd for $C_{19}H_{19}BrN_2O_2$: C, 58.93; H, 4.95; N, 7.23; found: C, 58.85; H, 4.90; N, 7.18%. LC-MS: 387.32, 389.28 [M+1].

Synthesis of **4a–f**

Hydrazine monohydrate (0.05 mol) was added to the solution of compounds **3a–f** (0.01 mol) in ethanol (15 mL). The mixture was stirred for 5 hours at room temperature. After the reaction was completed (monitored by TLC, ethyl acetate/hexane, 3/1), the precipitated product was filtered off, washed with cold ethanol and recrystallized from ethanol.

*2-[5,6-Dimethyl-2-(4-methylbenzyl)-1*H*-benzimidazol-1-yl] acetohydrazide* (**4a**): Yield 2.32 g (72%); m.p. 200–201 °C; ^{1}H NMR (DMSO-d_6, 400 MHz):2.24 (s, 3H), 2.27 (s, 6H), 4.14 (s, 2H), 4.29 (s, 2H), 4.66 (s, 2H), 7.07–7.15 (m, 5H), 7.29 (s, 1H), 9.42 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.28, 20.54, 21.06 (CH_3), 32.98 (CH_2), 44.82 (NCH_2), 110.54, 119.13, 129.03 (2C), 129.10 (2C), 129.41, 130.55, 134.34, 134.59, 135.90, 141.25 (ArC), 153.66 (C=N), 166.47 (C=O). Anal calcd for $C_{19}H_{22}N_4O$: C, 70.78; H, 6.88; N, 17.38; found: C, 70.71; H, 6.82; N, 17.33%. LC-MS: 323.34 [M+1].

*2-[5,6-Dimethyl-2-(4-fluorobenzyl)-1*H*-benzimidazol-1-yl] acetohydrazide* (**4b**): Yield 2.54 g (78%); m.p. 220–221 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 2.26 (s, 3H), 2.27 (s, 3H), 4.19 (s, 4H, CH_2 + NH_2), 4.72 (s, 2H), 7.12–7.38 (s, 6H), 9.47 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.28, 20.54 (CH_3), 32.42 (CH_2), 44.85 (NCH_2), 110.56, 115.37 (2C), 119.16, 130.06, 130.66, 131.16 (2C), 133.63, 134.53, 141.26 (ArC), 153.48 (C=N), 161.44 (C-F, $J_{C\text{-}F}$=240.5 Hz), 166.48 (C=O). Anal calcd for $C_{18}H_{19}FN_4O$: C, 66.24; H, 5.87; N, 17.17; found: C, 66.18; H, 5.81; N, 17.13%. LC-MS: 327.42 [M+1].

*2-[5,6-Dimethyl-2-(4-chlorobenzyl)-1*H*-benzimidazol-1-yl] acetohydrazide* (**4c**): Yield 2.53 g (74%); m.p. 190–191 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 2.28 (s, 3H), 2.29 (s, 3H), 4.19 (s, 2H), 4.24 (s, 2H), 4.75 (s, 2H), 7.11 (s, 1H), 7.21–7.38 (m, 5H), 9.44 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.28, 20.25 (CH_3), 32.55 (CH_2), 44.86 (NCH_2), 110.57, 119.16, 128.70 (2C), 130.08, 130.69, 131.19 (2C), 131.25, 134.51, 136.57, 141.22 (ArC), 153.20 (C=N), 166.45 (C=O). Anal calcd for $C_{18}H_{19}ClN_4O$: C, 63.06; H, 5.59; N, 16.34; found: C, 63.01; H, 5.51; N, 16.26%. LC-MS: 343.40, 345.36 [M+1].

*2-[5,6-Dimethyl-2-(4-methoxybenzyl)-1*H*-benzimidazol-1-yl] acetohydrazide* (**4d**): Yield 2.47 g (73%); m.p. 179–180 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 2.13 (s, 3H), 2.14 (s, 3H), 3.75 (s, 3H), 4.03 (s, 2H), 4.37 (s, 2H), 4.65 (s, 2H), 6.75–6.89 (m, 2H), 7.11–7.23 (m, 3H), 7.31 (s, 1H), 9.41 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.29, 20.54 (CH_3), 32.51 (CH_2), 44.81 (NCH_2), 55.46 (OCH_3), 110.52, 114.26 (2C), 119.12, 129.27, 129.94, 130.25 (2C), 130.53, 134.59, 144.24 (ArC), 153.86 (C=N), 158.35 (C-O, ArC), 166.49 (C=O). Anal calcd for $C_{19}H_{22}N_4O_2$: C, 67.44; H, 6.55; N, 16.56; found: C, 67.37; H, 6.48; N, 16.51%. LC-MS: 339.46 [M+1].

*2-[5,6-Dimethyl-2-(4-nitrobenzyl)-1*H*-benzimidazol-1-yl] acetohydrazide* (**4e**): Yield 2.50 g (71%); m.p. 253–254 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 2.11 (s, 3H), 2.13 (s, 3H), 4.23 (s, 4H, CH_2+NH_2), 4.78 (s, 2H), 7.18 (s, 1H), 7.25 (s, 1H), 7.56 (d, *J*=8.0, 2H), 8.16 (d, *J*=8.0, 2H), 9.42 (s ,1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.28, 20.55 (CH_3), 32.99 (CH_2), 44.90 (NCH_2), 110.58, 119.21, 123.84 (2C), 130.22, 130.83 (2C), 130.87, 134.45, 141.21, 145.76, 146.71 (ArC), 152.56 (C=N), 166.40 (C=O). Anal calcd for $C_{18}H_{19}N_5O_3$: C, 61.18; H, 5.42; N, 19.82; found: C, 61.09; H, 5.37; N, 19.74%. LC-MS: 354.42, 355.33 [M+1].

*2-[5,6-Dimethyl-2-(4-bromobenzyl)-1*H*-benzimidazol-1-yl] acetohydrazide* (**4f**): Yield 3.09 g (80%); m.p. 192–193 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 2.23 (s, 3H), 2.27 (s, 3H), 4.18 (s, 2H), 4.34 (s, 2H), 4.71 (s, 2H), 7.15 (s, 1H), 7. 22 (d, *J*=7.8, 2H), 7.21 (s, 1H), 7.45 (d, *J*=7.8, 2H), 9.42 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.28, 20.56 (CH_3), 32.63 (CH_2), 44.86 (NCH_2), 110.56, 119.17, 120.04, 130.09, 131.58, 131.63 (2C), 131.66 (2C), 134.51, 137.00, 141.21 (ArC), 153.14 (C=N), 166.45 (C=O). Anal calcd for $C_{18}H_{19}BrN_4O$: C, 55.82; H, 4.95; N, 14.47; found: C, 55.73; H, 4.88; N, 14.41%. LC-MS: 387.32, 389.28 [M+1].

*Synthesis of 2-oxo-2*H*-chromene-3-carboxylic acid* (**5**)

Synthesised according to the literature procedure.[21] Yield 1.63 g (86%); m.p. 190–191 °C (lit.[21] 190 °C).

*Synthesis of 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-one* (**6**)

Synthesised according to the literature procedure.[22] Yield 2.21 g (76%); m.p. 185–186 °C (lit.[22] 186–187 °C).

Synthesis of **7a–f**

A solution of compounds **4a–f** (0.01 mol) in ethanol (15 mL) and compound **6** (0.012 mol) was placed in a round-bottomed flask. The mixture was refluxed for 6 h. After the completion of the reaction (monitored by TLC, ethyl acetate:hexane: 3/1), the mixture was cooled to room temperature and a solid appeared. This crude product was filtered and washed with ethanol to obtain the pure product.

*2-(4-Methylbenzyl)-5,6-dimethyl-N'-[(2-oxo-2*H*-chromen-3-yl) carbonyl]-1*H*-benzimidazole-1-carbohydrazide* (**7a**): Yield 3.06 g (62%); m.p. 215–216 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 2.23 (s, 3H), 2.27 (s, 3H), 2.29 (s, 3H), 4.16 (s, 2H), 4.91 (s, 2H), 7.07 (d, *J*=8.0, 2H), 7.14 (d, *J*=8.0, 2H), 7.24 (s, 1H), 7.31 (s, 1H), 7.43 (t, *J*=7.2, 1H), 7.48 (d, *J*=8.8, 1H), 7.75 (t, *J*=8.0, 1H), 7.99 (dd, *J*=8.0, *J*=1.6, 1H), 8.98 (s, 1H), 10.63 (s, 1H), 11.22 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.28, 20.55, 21.06 (CH_3), 32.98 (CH_2), 44.50 (NCH_2), 110.63, 116.70, 118.31, 119.15, 125.69, 129.14, 129.43, 130.06, 130.71, 130.83, 134.22, 134.71, 134.93, 135.95, 141.21 (ArC), 148.59 ($CH_{coumarin\text{-}C4}$), 153.64 (C=N), 154.40 ($C_{coumarin\text{-}C3}$), 159.21 ($C{=}O_{coumarin\text{-}C2}$), 160.29, 164.74 (C=O). Anal calcd for $C_{29}H_{26}N_4O_4$: C, 70.43; H, 5.30; N, 11.33; found: C, 70.35; H, 5.26; N, 11.26%. LC-MS: 495.23 [M+1].

*2-(4-Fluorobenzyl)-5,6-dimethyl-N'-[(2-oxo-2*H*-chromen-3-yl) carbonyl]-1*H*-benzimidazole-1-carbohydrazide* (**7b**): Yield 2.64 g (53%); m.p. 273–274 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 2.23 (s, 3H), 2.29 (s, 3H), 4.21 (s, 2H), 4.96 (s, 2H) 7.06–7.13 (m, 2H), 7.25 (s, 1H), 7.28–7.7.35 (m, 3H), 7.43 (t, *J*=8.0, 1H), 7.49 (d, *J*=8.0, 1H), 7.75 (t, *J*=8.0, 1H), 8.00 (d, *J*=8.0, 1H), 8.90 (s, 1H), 10.65 (s, 1H), 11.25 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.28, 20.56 (CH_3), 32.40 (CH_2), 44.52 (NCH_2), 110.64, 115.40, 115.62, 118.35, 118.75, 119.19, 125.70, 130.13, 130.78, 131.18, 131.26, 133.55, 134.65, 134.93, 141.22 (ArC), 148.58 ($CH_{coumarin\text{-}C4}$), 153.45 (C=N), 154.41 ($C_{coumarin\text{-}C3}$), 159.22 ($C{=}O_{coumarin\text{-}C2}$), 160.28 (C=O), 161.46 (C-F, $J_{C\text{-}F}$=241.2 Hz), 164.75 (C=O). Anal calcd for $C_{28}H_{23}FN_4O_4$: C, 67.46; H, 4.65; N, 11.24; found: C, 67.40; H, 4.57; N, 11.16%. LC-MS: 499.20, 500.19 [M+1].

*2-(4-Chlorobenzyl)-5,6-dimethyl-N'-[(2-oxo-2*H*-chromen-3-yl) carbonyl]-1*H*-benzimidazole-1-carbohydrazide* (**7c**): Yield 3.16 g (61%); m.p. 261–261 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 2.26 (s, 3H), 2.29 (s, 3H), 4.22 (s, 2H), 4.95 (s, 2H), 7.26 (s, 1H), 7.27–7.33 (m, 5H), 7.44 (t, *J*=8.0, 1H), 7.50 (d, *J*=8.0, 1H), 7.75 (t, *J*=8.0, 1H), 8.00 (d, *J*=8.0, 1H), 8.90 (s, 1H), 10.66 (s, 1H), 11.26 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.29, 20.56 (CH_3), 32.55 (CH_2), 44.53 (NCH_2), 110.66, 116.71, 118.34, 118.75, 119.19, 125.70, 128.73 (2C), 130.17, 130.85, 131.27 (2C), 131.61, 134.65, 134.93, 136.45, 141.20 (ArC), 148.58 ($CH_{coumarin\text{-}C4}$), 153.16 (C=N), 154.41 ($C_{coumarin\text{-}C3}$), 159.17 ($C{=}O_{coumarin\text{-}C2}$), 160.28 (C=O), 164.70 (C=O). Anal calcd for $C_{28}H_{23}ClN_4O_4$: C, 65.31; H, 4.50; N, 10.88; found: C, 65.23; H, 4.41; N, 10.82%. LC-MS: 515.17, 517.16 [M+1].

*2-(4-Methoxybenzyl)-5,6-dimethyl-N'-[(2-oxo-2*H*-chromen-3-yl) carbonyl]-1*H*-benzimidazole-1-carbohydrazide* (**7d**): Yield 2.96 g (2.96%); m.p. 228–229 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 2.26 (s, 3H), 2.29 (s, 3H), 3.69 (s, 3H), 4.13 (s, 2H), 4.91 (s, 2H), 6.83 (dd, *J*=6.8, *J*=2.0, 2H), 7.20 (d, *J*=8.2, 2H), 7.23 (s, 1H), 7.31 (s, 1H), 7.46 (t, *J*=8.2, 1H), 7.50 (d, *J*=8.0, 1H), 7.76 (t, *J*=8.2, 1H), 8.00 (dd, *J*=6.8, *J*=2.0, 1H), 8.90 (s, 1H), 10.64 (s, 1H), 11.22 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.29, 20.56 (CH_3), 32.51 (CH_2), 44.48 (NCH_2), 55.44 (OCH_3), 110.62, 114.28 (2C), 116.71, 118.35, 118.75, 119.15, 125.70, 129.15, 130.03, 130.29 (2C), 130.67, 130.84, 134.72, 134.93, 141.23 (ArC), 148.57 ($CH_{coumarin\text{-}C4}$), 153.82 (C=N), 154.41

($C_{coumarin\text{-}C3}$), 158.37 (ArC, C-O), 159.18 ($C{=}O_{coumarin\text{-}C2}$), 160.29 (C=O), 164.74 (C=O). Anal calcd for $C_{29}H_{26}N_4O_5$: C, 68.22; H, 5.13; N, 10.97; found: C, 68.15; H, 5.06; N, 10.91%. LC-MS: 511.22, 512.21 [M+1].

*2-(4-Nitrobenzyl)-5,6-dimethyl-N'-[(2-oxo-2*H*-chromen-3-yl) carbonyl]-1*H*-benzimidazole-1-carbohydrazide* (**7e**): Yield 2.57 g (49%); m.p. 294–295 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 2.26 (s, 3H), 2.29 (s, 3H), 4.39 (s, 2H), 5.01 (s, 2H), 7.28 (s, 1H), 7.31 (s, 1H), 7.44 (t, *J*=8.0, 1H), 7.51 (d, *J*=8.2, 1H), 7.57 (d, *J*=8.2, 2H), 7.75 (t, *J*=8.0, 1H), 8.00 (d, *J*=8.0, 1H), 8.15 (d, *J*=8.0, 2H), 8.89 (s, 1H), 10.64 (s, 1H), 11.28 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.28, 20.58 (CH_3), 30.01 (CH_2), 44.57 (NCH_2), 110.70, 116.71, 118.27, 118.74, 119.22, 123.86, 125.71, 130.32, 130.83, 131.03, 134.62, 134.95, 141.14, 145.56, 146.73 (ArC), 148.58 ($CH_{coumarin\text{-}C4}$), 152.47 (C=N), 154.41 ($C_{coumarin\text{-}C3}$), 159.09 ($C{=}O_{coumarin\text{-}C2}$), 160.28 (C=O), 164.60 (C=O). Anal calcd for $C_{28}H_{23}N_5O_6$: C, 63.99; H, 4.41; N, 13.33; found: C, 63.91; H, 4.36; N, 13.26%. LC-MS: 526.19 [M+1].

*2-(4-Bromobenzyl)-5,6-dimethyl-N'-[(2-oxo-2*H*-chromen-3-yl) carbonyl]-1*H*-benzimidazole-1-carbohydrazide* (**7f**): Yield 3.74 g (67%); m.p. 260–261 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 2.26 (s, 3H), 2.29 (s, 3H), 4.20 (s, 2H), 4.96 (s, 2H), 7.21–7.26 (m, 3H), 7.30 (s, 1H), 7.41–7.53 (m, 4H), 7.75 (t, *J*=8.2, 1H), 8.00 (dd, *J*=8.2, *J*=1.2, 1H), 8.90 (s, 1H), 10.66 (s, 1H), 11.26 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): 20.29, 20.58 (CH_3), 32.62 (CH_2), 44.53 (NCH_2), 110.65, 116.70, 118.334, 118.75, 119.19, 120.10, 125.70, 130.17, 130.85, 131.66, 134.66, 134.94, 136.88, 141.20 (ArC), 148.57 ($CH_{coumarin\text{-}C4}$), 153.09 (C=N), 154.41 ($C_{coumarin\text{-}C3}$), 159.15 ($C{=}O_{coumarin\text{-}C2}$), 160.28 (C=O), 164.69 (C=O). Anal calcd for $C_{28}H_{23}BrN_4O_4$: C, 60.12; H, 4.14; N, 10.02; found: C, 60.04; H, 4.07; N, 9.94%. LC-MS: 559.11, 561.11 [M+1].

This work was supported by The Scientific and Technological Research Council of Turkey (TUBİTAK, project no. 115Z047) and Recep Tayyip Erdogan University Scientific Research Project Unit (BAP, project no. 2014.102.02.05). The authors thank TUBITAK and Recep Tayyip Erdogan University for their support.

Received 10 August 2015; accepted 3 October 2015
Paper 1503537 doi: 10.3184/174751915X14449030550960
Published online: 1 November 2015

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