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# Synthesis and exploratory biological evaluation of 3-[(*N*-4-benzyloxyphenyl)iminoethyl]- and 3-(1-hydrazonoethyl)-4-hydroxycoumarins

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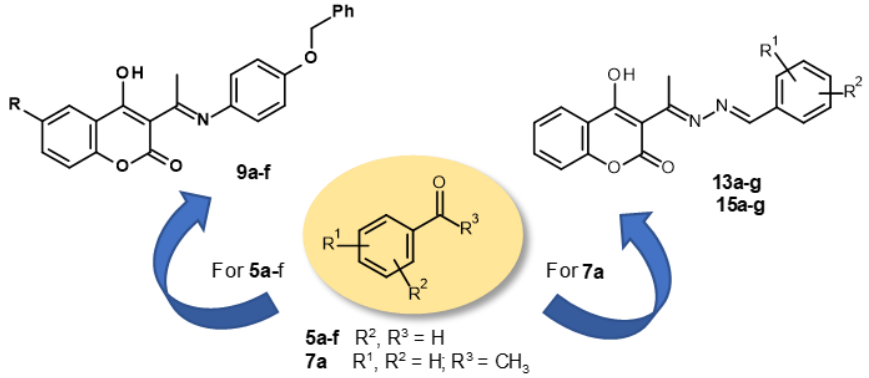
## Abstract

Three series of 4-hydroxycoumarin derivatives, comprising a total of 20 novel compounds have been prepared from 2-hydroxyacetophenones. These include a set of 3-[(*N*-4-benzyloxyphenyl)iminoethyl]-4-hydroxycoumarins, and two differently substituted sets of 3-(1-hydrazonoethyl)-4-hydroxycoumarins. The products were subjected to exploratory biological studies, and some of the compounds exhibited encouraging activity against the trypanosomal parasite *T.b. brucei*, two of them exhibiting $IC_{50}$ values of 0.90 µM and 27.88 µM.




**Keywords:** Synthesis, 4-hydroxycoumarins, imines, hydrazones, bioassay, anti-trypanosomal activity

## Introduction

Naturally occurring and synthetic chromone (2*H*-1-benzopyran-2-one) derivatives comprise an important and extensive class of heterocyclic compounds. Reviewed by Sethna and Shah[1] more than 75 years ago, these compounds continue to enjoy the attention of synthetic and medicinal chemists and remain the subject of ongoing reviews.[2,3] Coumarin derivatives are known to exhibit a broad range of medicinal properties, including anti-coagulant, anti-HIV, anti-cancer and anti-inflammatory activities, and inhibitory activity against important enzymes, such as monoamine oxidase and cyclooxygenase.[4] Synthetic *N*-aryl coumarin-3-carboxamides have been evaluated[5,6] for activity against human lung fibroblasts and breast cancer cell lines, and the most potent compound (with an $IC_{50}$ of 0.166 μM against ErbB-2 kinase) was the 6-chlorocoumarin derivative **1** (Figure 1). Küçükbay *et al*.[7] have reported carbonic anhydrase inhibition by amino acid-coumarin conjugates at sub-micromolar concentrations. A common feature in many biologically active coumarin derivatives is the presence of a 4-hydroxy group, as in the anti-coagulant phenprocoumon **2**;[8] in fact, this appears to be one of the minimum structural requirements for anti-coagulant activity in analogous systems.[9] A series of hybrid coumarin derivatives, including the hydrazine derivative **3**, were shown to exhibit promising anti-HIV activity.[10]

Compounds containing an imino group have exhibited a range of biological activities, including anti-cancer,[11] anti-viral[12] and anti-β-secretase[13] properties, while there appears to be growing interest in the medicinal potential of hydrazone derivatives.[14,15] The alkyne moiety is present in a number of pharmaceuticals, including Efavirenz,[14] an antiretroviral, and the antifungal agent Terbanafine.[16]

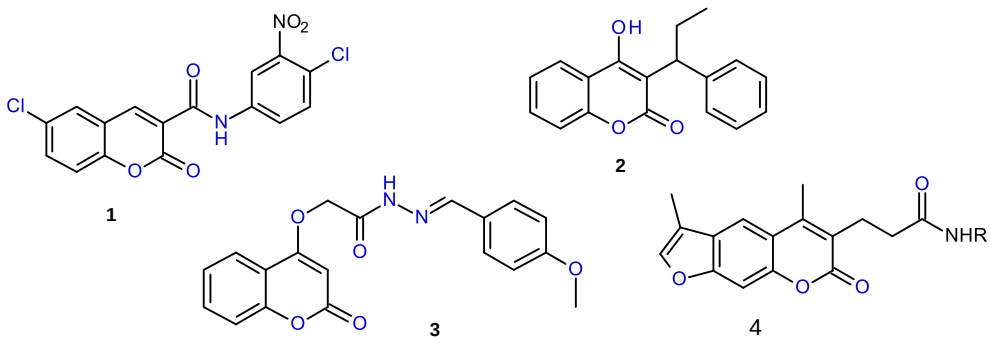



**Figure 1.** Biologically active coumarin derivatives **1**,[5] **2**,[7] **3**,[8] **and 4**.[18]

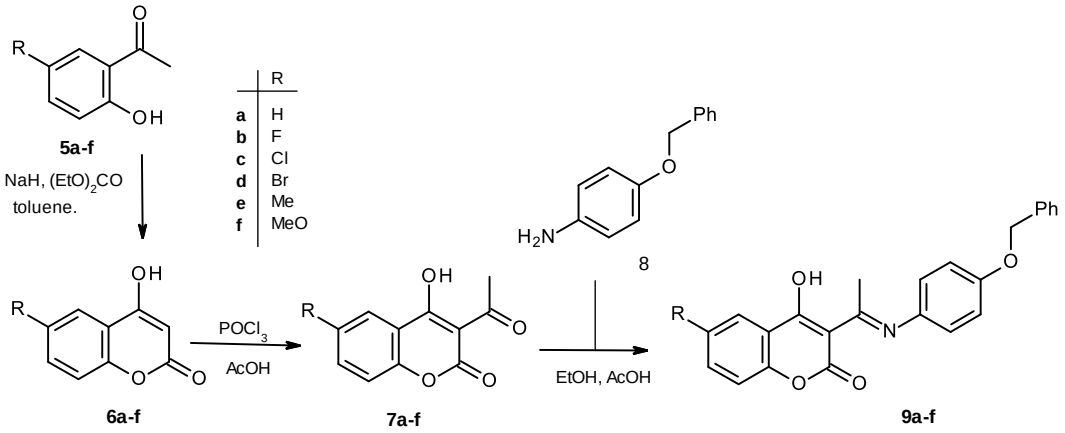
We have a close and ongoing interest in applications of Morita-Baylis-Hillman methodology in the synthesis of benzannulated heterocyclic systems in general[17] and coumarin derivatives[18] in particular. Attention has been given to the synthesis of novel furocoumarins **4** – designed to serve as HIV-1 Integrase inhibitors[19] – and coumarin-AZT conjugates as portmanteau HIV-1 protease and reverse transcriptase inhibitors.[20] Access to 4-hydroxycoumarins, however, has required the application of a different methodology and, in a recent study,[21] we made use of a procedure developed by Zhao *et al*.[22] to access these systems. We now report the preparation and exploratory biological evaluation of three series of compounds containing 4-hydroxycoumarin, iminoethyl , hydrazonoethyl and alkynyl moieties.

## Results and Discussion

### Synthesis of 4-hydroxycoumarin derivatives

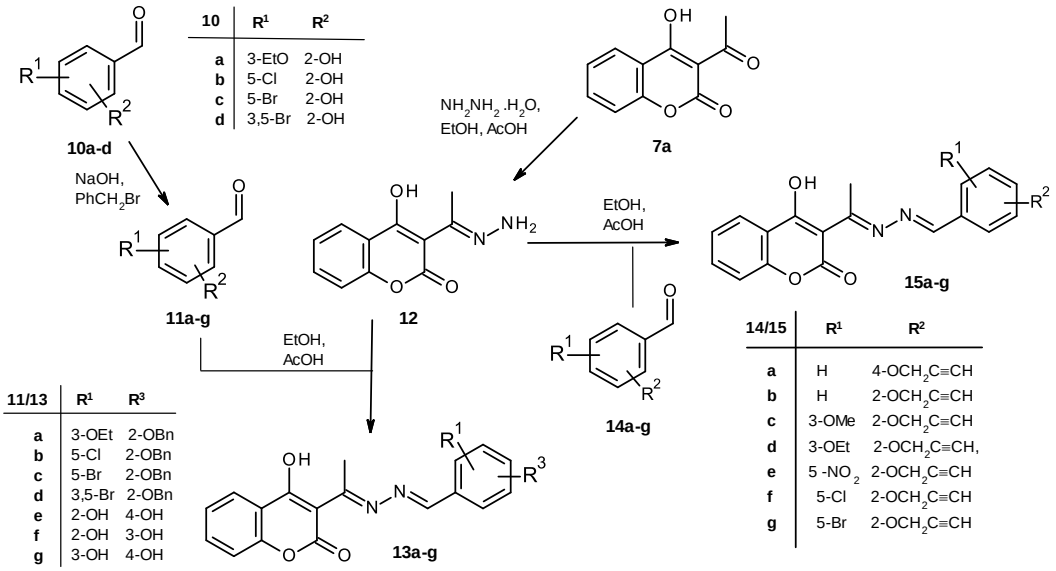
With minor modifications of the method reported by Zhao *et al*.,[22] the 2-hydroxyacetophenones **5a**-**f** were reacted with diethyl or dimethyl carbonate in the presence of sodium hydride to afford the 4-hydroxycoumarins **6a**-**f** in yields of 60-87% (Scheme 1). Adapting a procedure described by Sukdolak *et al*.,[23] the 4-hydroxycoumarins **6a**-**f** were reacted with $POCl_3$ in acetic acid to give the 3-acetylated derivatives **7a-f** in yields ranging from 41% to 90%. Increasing the reaction time to at least 1 hour improved the yield, while washing the resulting precipitates with methanol gave the respective products in high purity thus obviating the need for recrystallisation. Each of the 3-acetyl-4-hydroxycoumarins **7a-f** was condensed with 4-benzyloxyaniline **8** (obtained by prior neutralisation of the hydrochloride salt) in an acetic acid-catalysed reaction in refluxing methanol for at least an hour. The resulting precipitates were filtered off, washed with methanol and dried to give the targeted products **9a-f** in high yield (82 - 94%) and high purity - as confirmed by NMR analysis.




**Scheme 1.** Synthesis of 3-[(*N*-4-benzyloxyphenyl)iminoethyl]-4-hydroxycoumarins **9a-f**.

The 3-acetyl-4-hydroxycoumarin **7a** was reacted with hydrazine hydrate under reflux for 1 hour using ethanol as the solvent and acetic acid as a catalyst to afford the hydrazone derivative **12** in 80% yield (Scheme 2). The deshielding of the OH signal (at 15.53 ppm) in the $^1$H NMR spectrum of this compound is consistent with involvement of the hydrazone $N^1$ atom and the phenolic proton in a six-membered hydrogen-bonded chelate. The hydrazone **12** then provided access to two series of dihydrazone derivatives **13a-g** and **15a-g**. For the first series, the hydrazone **12** was reacted with each of seven disubstituted benzaldehydes **11a-g** in refluxing ethanol (to which a catalytic quantity of 2N-HCl had been added) to yield the novel 3-[1-(benzylidenehydrazono)ethyl]- 4-hydroxycoumarins **13a-g** in moderate to good yields (51-76%)**.** Four of the benzaldehyde precursors **11a-d** had been obtained in 65-75% yields by prior *O*-benzylation of their phenolic precursors **10a-d**; the other three benzaldehyde precursors (**11e-g**) were commercially available. For the second series, the hydrazone **12** was similarly reacted with each of the propargyloxy-substituted benzaldehydes **14a-g** to afford the corresponding 3-[1-(benzylidenehydrazono)ethyl]-4-hydroxycoumarins **15a-g** in good yields (65-80%).




| 10 | R¹ | R² |
|---|---|---|
| a | 3-EtO | 2-OH |
| b | 5-Cl | 2-OH |
| c | 5-Br | 2-OH |
| d | 3,5-Br | 2-OH |

| 11/13 | R¹ | R³ |
|---|---|---|
| a | 3-OEt | 2-OBn |
| b | 5-Cl | 2-OBn |
| c | 5-Br | 2-OBn |
| d | 3,5-Br | 2-OBn |
| e | 2-OH | 4-OH |
| f | 2-OH | 3-OH |
| g | 3-OH | 4-OH |

| 14/15 | R¹ | R² |
|---|---|---|
| a | H | 4-$OCH_2C{\equiv}CH$ |
| b | H | 2-$OCH_2C{\equiv}CH$ |
| c | 3-OMe | 2-$OCH_2C{\equiv}CH$ |
| d | 3-OEt | 2-$OCH_2C{\equiv}CH$, |
| e | 5 -$NO_2$ | 2-$OCH_2C{\equiv}CH$ |
| f | 5-Cl | 2-$OCH_2C{\equiv}CH$ |
| g | 5-Br | 2-$OCH_2C{\equiv}CH$ |

**Scheme 2.** Synthesis of 3-[1-(benzylidenehydrazono)ethyl]-4-hydroxycoumarin analogues (**13**) and (**15**).

All of the novel compounds were fully characterised using HRMS, IR and 1-D and, where appropriate, 2-D NMR analytical data. Use of COSY and HSQC data, as illustrated in **Figures 2** and **3**, respectively, facilitated the assignment of $^{1}$H- and $^{13}$C-NMR signals to the corresponding aromatic nuclei, with different and distinctive proton-proton coupling patterns, in the two benzenoid rings in compound **13f**. Interestingly, Milenko *et al*.[24] have reported the preparation of analogous compounds with very encouraging antimicrobial properties and have used NOE and HMBC experiments to confirm their structural identity. *In vitro* bioassay and molecular docking studies of closely related 3-hydroxycoumarin derivatives have been undertaken by Batran *et al*.[25] to investigate antifungal properties and by Abdel Latif et al.[26] to explore their anti-cancer potential.

**Biological evaluation**

The novel, synthetic products were screened for cytotoxicity against HeLa cells and, variously, for HIV-1 IN and PR enzyme inhibitory potential and for antimalarial, trypanocidal and anti-mycobacterial activity. The bioassay protocols and results for each series of products are provided in the Supporting Information file. The 3-[(*N*-4-benzyloxyphenyl)iminoethyl]-4-hydroxycoumarins **9a-f**, at 20 µM concentration, exhibited little if any significant cytotoxicity (< 50% viability of Hela cells) nor activity against the malaria parasite (pLDH) – patterns generally common to the analogous benzylidenehydrazono series (**13**) and (**15**). Compounds **9a-d**, however, decreased the viability of the *T.b. brucei* parasite to 23.3 – 37.9% with the most active compound **9d** having an $IC_{50}$ value of 27.88 µM. While some of the 3-[1-(benzylidenehydrazono)ethyl]-4-hydroxycoumarins (**13**) exhibited a measure of trypanocidal activity, compound **13g** was notable, decreasing *T.b. brucei* viability to 1.53% and exhibiting an $IC_{50}$ value of 0.90 µM. Compound **13g** was also the only compound observed to exhibit, albeit weakly, anti-mycobacterial (anti-TB) activity with $MIC_{90}$ values of 62.50 µM (visual) and 62.44 µM (calculated).

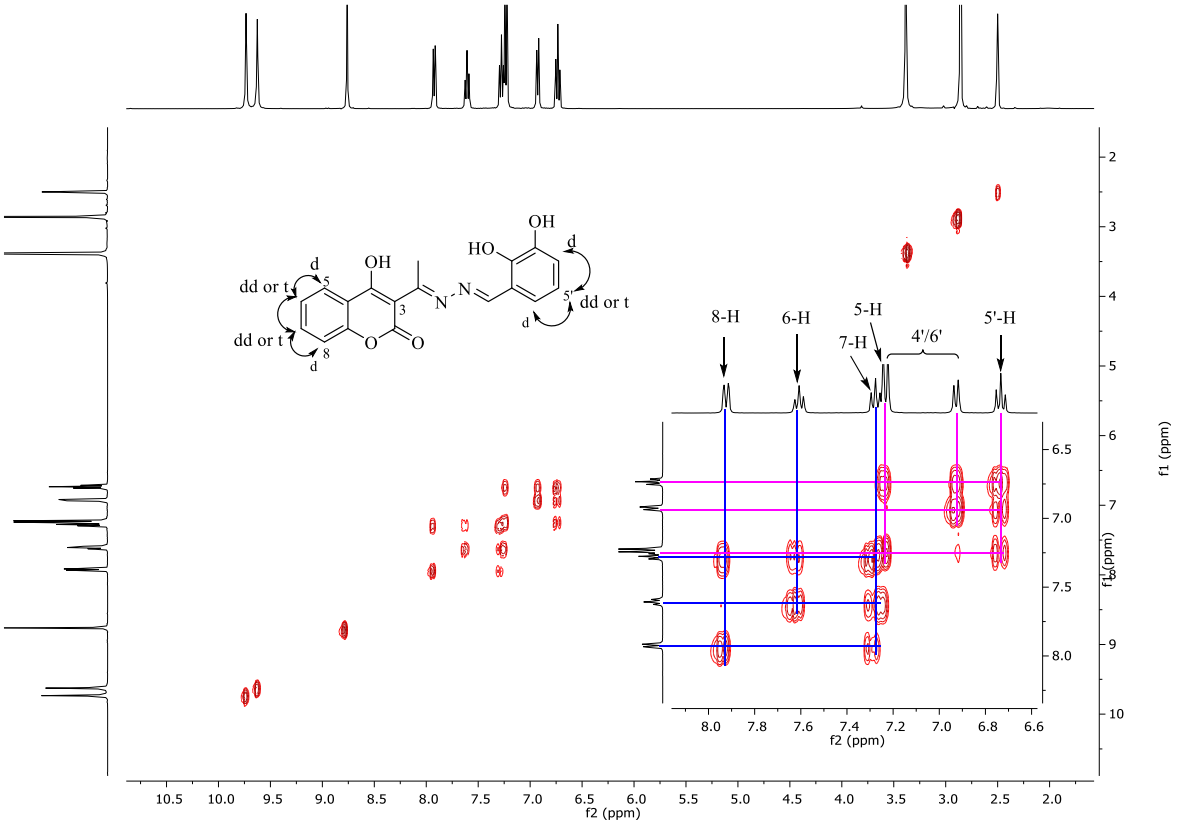



**Figure 2**. 400 MHz COSY NMR spectrum of compound **13f** in DMSO-$d_6$.

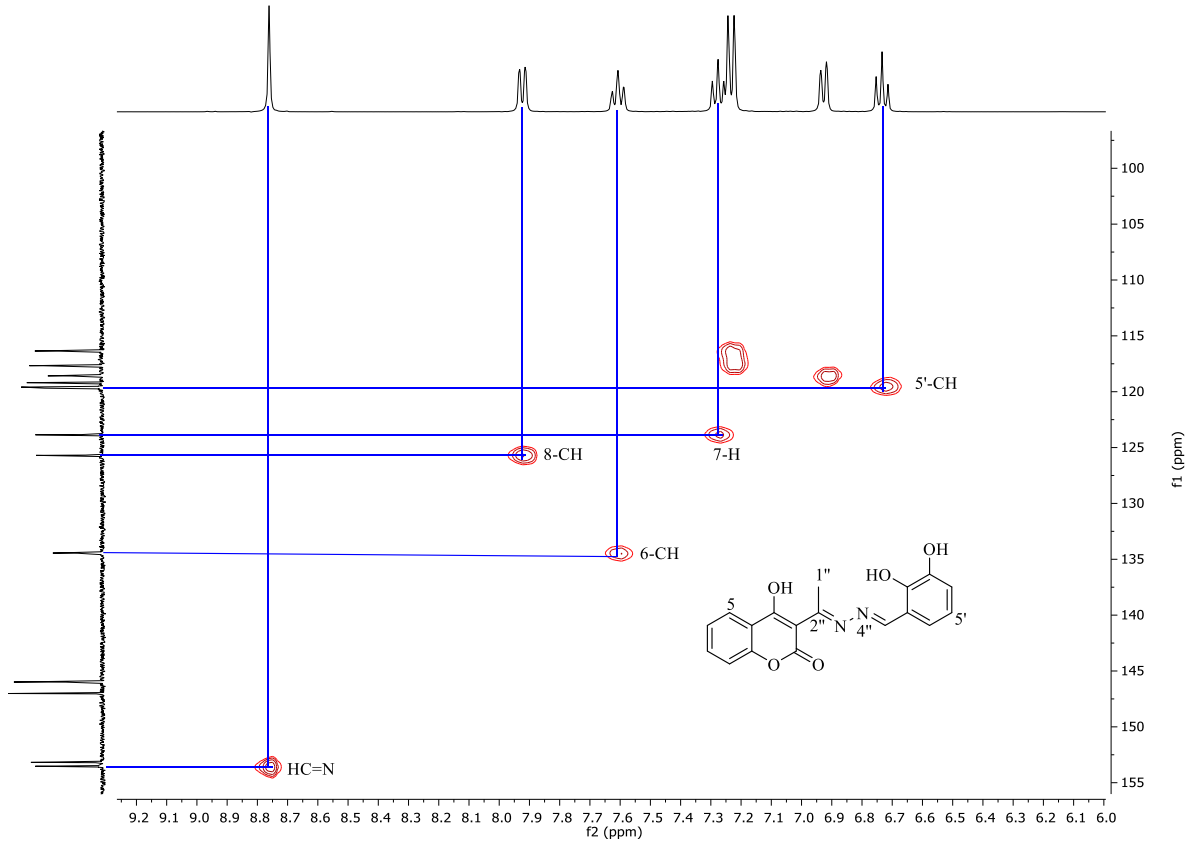



**Figure 3**. Partial HSQC NMR spectrum of compound **13f** in DMSO-$d_6$.

## Conclusions

Convenient synthetic access has been successfully established to three series of novel 4-hydroxycoumarin derivatives from substituted acetophenone and benzaldehyde precursors. The products contain several biologically important motifs, *viz*., 4-hydroxycoumarin, imino, hydrazono and alkynyl moieties. Exploratory bioactivity studies have revealed that some of the products exhibit anti-trypanosomal activity, with one of them having an $IC_{50}$ value as low as of 0.90 µM against the *T.b. brucei* parasite.

## Experimental Section

**General.** Chemicals were purchased from Sigma-Aldrich Chemical Co. and used without further purification. NMR spectra were recorded on Bruker Biospin 600 MHz NMR and AMX 400 MHz spectrometers and chemical shifts were calibrated relative to the residual proton signal in DMSO-$d_6$ (2.5 ppm) and in $CDCl_3$ (7.26 ppm). IR Spectra were recorded on a Perkin Elmer Spectrum 100 FTIR spectrometer with a diamond window. Melting points were determined using a Stuart SMP30 apparatus apparatus and are uncorrected. HRMS analyses were conducted at Rhodes University and by the Central Analytical Facilities Unit at the University of Stellenbosch.

The 3-acetyl-4-hydroxycoumarins **7a**,[22] **7b**,[27] **7c**,[28] **7d**,[29] **7e**,[30] and **7f**,[31] 3-(1-hydrazonoethyl)-4-hydroxycoumarin **12**,[32] the 4-(benzyloxy)benzaldehydes **11a**,[33] **11b**,[34] **11c**,[35] **11d**,[36] and **11e**-**11g** (commercial compounds from Sigma-Aldrich) and the propargyloxy benzaldehydes **14a**,[37] **14b**,[38] **14c**,[39] **14d**,[40] **14e**,[39] **14f**,[41] and **14g**,[42] are known compounds. Synthetic procedures for new compounds are provided below. The Supporting Information File contains NMR spectra for new compounds and *in vitro* bioassay protocols and data.

**The synthesis of the 3-[1-(*N*-4-benzyloxyphenyl)iminoethyl]-4-hydroxycoumarins (9a-f)** is illustrated by the following example.

A mixture of 3-acetyl-4-hydroxycoumarin **7a** (0.10 g, 0.5 mmol) and 4-(benzyloxy)aniline **8** (0.1 g, 0.5 mmol) was dissolved in ethanol (5 mL) and one drop of 2N-HCl was added, after which the mixture was refluxed for at least 1 hour, then cooled and filtered to collect the resulting precipitate which was washed with MeOH and dried to yield **3-[1-(*N*-4-benzyloxyphenyl)iminoethyl]-4-hydroxycoumarin 9a** as a white crystalline product (0.18 g, 93%), m.p. 136-137 °C; [HRMS: *m/z* calculated for $C_{24}H_{20}NO_4$ ($MH^+$) 386.1392. Found 386.1395]; $\nu_{max}/cm^{-1}$ 1710 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.54 (3H, s, $CH_3$), 4.98 (2H, s, $PhCH_2$), 6.90-6.95 (2H, m, ArH), 6.99-7.04 (2H, m, ArH), 7.09-7.16 (2H, m, ArH), 7.24 (1H, m, ArH), 7.27-7.35 (4H, m, ArH), 7.44 (1H, ddd, *J* = 8.7, 7.3, 1.8 Hz, ArH) and 7.95 (1H, dd, *J* = 7.8, 1.8 Hz, ArH); $\delta_C$ (100 MHz; $CDCl_3$) 20.9 ($CH_3$), 70.5 ($PhCH_2$), 98.0 (C-3), 115.8, 116.8, 120.3, 123.7, 126.1, 126.9, 127.6, 128.4, 128.8, 129.2, 134.2, 136.4, 154.0 and 158.6 (Ar-C), 162.6 (C=O), 176.3 (C=N) and 181.9 (C-OH).

**3-[1-(*N*-4-Benzyloxyphenyl)iminoethyl]-6-fluoro-4-hydroxycoumarin 9b** as a white crystalline product (0.19 g, 94%), m.p. 145-147 °C; [HRMS: *m/z* calculated for $C_{24}H_{19}FNO_4$ ($MH^+$) 404.1298. Found 404.1296]; $\nu_{max}/cm^{-1}$ 1702 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.53 (3H, s, $NCH_3$), 4.97 (2H, s, $PhCH_2$), 6.92 (2H, d, *J* = 8.9 Hz, ArH), 7.00 (2H, d, *J* = 8.8 Hz, ArH), 7.06 (1H, dd, *J* = 8.9, 4.3 Hz, ArH), 7.13 (1H, m, ArH), 7.22 (1H, dd, *J* = 8.4, 5.4 Hz, ArH), 7.25-7.34 (4H, m, ArH) and 7.57 (1H, dd, *J* = 8.3, 2.7 Hz, ArH); $\delta_C$ (100 MHz; $CDCl_3$) 20.9 ($CH_3$), 70.5 ($PhCH_2$), 97.8 (C-3), 111.4 (d, $^2J_{CF}$ = 24.2 Hz, C-5), 115.9 and 118.4 (Ar-C), 121.3 (d, $^3J_{CF}$ = 7.8 Hz, C-10), 121.7 (d, $^2J_{CF}$ = 24.4 Hz, C-7), 126.9, 127.6, 128.4, 128.8, 129.1, 136.4, 150.0 and 158.7(Ar-C), 158.8 (d, $^1J_{CF}$ = 243.0 Hz, C-6), 162.3 (C=O), 176.5 (C=N) and 180.8 (C-OH).

**3-[1-(*N*-4-Benzyloxyphenyl)iminoethyl]-6-chloro-4-hydroxycoumarin 9c** as a white crystalline product (0.19 g, 91%), m.p. 162-163 °C; [HRMS: *m/z* calculated for $C_{24}H_{19}ClNO_4$ ($MH^+$) 420.1003. Found 420.1005]; $\nu_{max}/cm^{-1}$ 1695 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.66 (3H, s, $CH_3$), 5.11 (2H, s, $PhCH_2$), 7.04-7.08 (2H, m, ArH), 7.11-7.20 (3H, m, ArH), 7.35-7.51 (6H, m, ArH) and 8.02 (1H, d, *J* = 2.5 Hz, ArH); $\delta_C$ (100 MHz; $CDCl_3$) 21.0 ($CH_3$), 70.4 ($PhCH_2$), 97.8 (C-3), 115.9, 118.4, 121.4, 125.7, 126.9, 127.6, 128.4, 128.8, 129.0, 129.3, 134.1, 136.3, 152.3 and 158.7 (Ar-C), 162.1 (C=O), 176.4 (C=N) and 180.5 (C-OH).

**3-[1-(*N*-4-Benzyloxyphenyl)iminoethyl]-6-bromo-4-hydroxycoumarin 9d** as a white crystalline product (0.20 g, 86%), m.p. 161-162 °C; [HRMS: *m/z* calculated for $C_{24}H_{19}BrNO_4$ ($MH^+$) 464.0497. Found 464.0497]; $\nu_{max}/cm^{-1}$ 1701 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.66 (3H, s, $CH_3$), 5.10 (2H, s, $PhCH_2$), 7.04-7.16 (5H, m, ArH), 7.35 (1H, m, ArH), 7.38-7.46 (4H, m, ArH), 7.62 (1H, dd, *J* = 8.7, 2.5 Hz, ArH) and 8.17 (1H, d, *J* = 2.2 Hz, ArH); $\delta_C$ (100 MHz; $CDCl_3$) 20.9 ($CH_3$), 70.5 ($PhCH_2$), 97.9 (C-3), 115.9, 116.6, 118.7, 121.8, 126.9, 127.6, 128.4, 128.8, 129.0, 136.4, 136.9, 152.8 and 158.7 (Ar-C), 162.0 (C=O), 176.4 (C=N) and 180.4 (C-OH).

**3-[1-(*N*-4-Benzyloxyphenyl)iminoethyl]-4-hydroxy-6-methylcoumarin 9e** as a white crystalline product (0.19 g, 95%), m.p. 142-144 °C; [HRMS: *m/z* calculated for $C_{25}H_{22}NO_5$ ($MH^+$) 400.1549. Found 400.1548]; $\nu_{max}/cm^{-1}$ 1650 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.40 (3H, s, $CH_3$), 2.66 (3H, s, $CH_3C$=N), 5.10 (2H, s, $PhCH_2$), 7.05 (2H, m, ArH), 7.10-7.16 (3H, m, ArH), 7.33-7.38 (2H, m, ArH), 7.38-7.46 (4H, m, ArH) and 7.85 (1H, s, ArH); $\delta_C$ (100 MHz; $CDCl_3$) 20.9 ($CH_3$), 20.9 ($CH_3$C=N), 70.5 ($PhCH_2$), 98.0 (C-3), 115.8, 116.5, 119.9, 125.8, 126.9, 127.6, 128.3, 128.8, 129.3, 133.3, 135.3, 136.4, 152.1 and 158.5 (Ar-C), 162.8 (C=O), 176.2 (C=N) and 182.0 (C-OH).

**3-[1-(*N*-4-Benzyloxyphenyl)iminoethyl]-4-hydroxy-6-methoxycoumarin 9f** as a white crystalline product (0.17 g, 82%), m.p. 136-137 °C; [HRMS: *m/z* calculated for $C_{25}H_{22}NO_5$ ($MH^+$) 416.1498. Found 416.1500; $\nu_{max}/cm^{-1}$ 1691 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.66 (3H, s, $CH_3$), 3.85 (3H, s, $OCH_3$), 5.10 (2H, s, $PhCH_2$), 7.05 (2H, m, ArH), 7.11-7.17 (4H, m, ArH), 7.35 (1H, dd, *J* = 8.3, 5.5 Hz, ArH), 7.38-7.46 (4H, m, ArH) and 7.48 (1H, s, ArH); $\delta_C$ (100 MHz; $CDCl_3$) 20.9 ($CH_3$), 55.9 ($OCH_3$), 70.5 ($PhCH_2$), 97.9 (C-3), 106.8, 115.9, 118.0, 120.5, 123.0, 126.8, 127.6, 128.3, 128.8, 129.3, 136.4, 148.5, 155.9 and 158.6 (Ar-C), 162.7 (C=O), 176.3 (C=N) and 181.6 (C-OH).

**The synthesis of the 3-{[2-(benzyloxy-3-ethoxybenzylidene)hydrazono]ethyl}-4-hydroxycoumarin 13a-g is illustrated by the following example.**

A solution of 3-(1-hydrazonoethyl)-4-hydroxycoumarin **12** (0.11 g, 0.5 mmol), 2-(benzyloxy)-3-ethoxybenzaldehyde **11a** (0.13 g, 0.5 mmol) and one drop of 2N HCl in ethanol (5 mL) was refluxed for at least one hour and then cooled to room temperature. The resulting precipitate was filtered off, washed with methanol and air dried to afford **3-{[2-(benzyloxy-3-ethoxybenzylidene)hydrazono]ethyl}-4-hydroxycoumarin 13a** as a yellow solid (0.20 g, 88%) m.p. 190-192 °C; [HRMS: *m/z* calculated for $C_{27}H_{25}N_2O_5$ ($MH^+$) 457.1763. Found 457.1766]; $\nu_{max}/cm^{-1}$ 1738 (C=O); $\delta_H$ (600 MHz; $CDCl_3$) 1.31 (3H, t, *J* = 7.0 Hz, $CH_3CH_2$), 2.98 (3H, s, $CH_3C$=N), 3.93 (2H, q, *J* = 6.9 Hz, $CH_3CH_2$), 4.94 (2H, s, $PhCH_2$), 6.84 (1H, d, *J* = 7.5 Hz, ArH), 6.90 (1H, t, *J* = 8.0 Hz, ArH), 7.03 (1H, d, *J* = 8.2 Hz, ArH), 7.07 (1H, t, *J* = 7.5 Hz, ArH), 7.12 (1H, t, *J* = 7.2 Hz, ArH), 7.18 (2H, t, *J* = 7.5 Hz, ArH), 7.22 (2H, d, *J* = 7.2 Hz, ArH), 7.31 (1H, d, *J* = 7.5 Hz, ArH), 7.36 (1H, t, *J* = 7.7 Hz, ArH) 7.89 (1H,d, *J* = 7.7 Hz, ArH) and 8.24 (1H s, CH=N); $\delta_C$ (150 MHz; $CDCl_3$) 15.0 and 17.7 (2x$CH_3$), 64.5 ($CH_3CH_2$), 76.0 ($PhCH_2$), 96.5 (C-3), 116.3, 116.8, 118.1, 120.2, 123.8, 124.6, 126.1, 127.3, 128.6, 128.7, 129.0, 134.3, 136.5 and 148.1 (Ar-C), 151.2 (ArC=N), 152.3 and 153.9 (Ar-C), 162.4 (C=O), 173.1 ($CH_3C$=N) and 181.6 (C-4).

**3-{[2-(Benzyloxy-5-chlorobenzylidene)hydrazono]ethyl}-4-hydroxycoumarin 13b** as a yellow solid (0.19 g, 85%), m.p. 230-232 °C; [HRMS: *m/z* calculated for $C_{25}H_{20}ClN_2O_4$ ($MH^+$) 447.1112. Found 447.1111]; $\nu_{max}/cm^{-1}$ 1694 (C=O); $\delta_H$ (600 MHz; $CDCl_3$) 2.98 (3H, s, $CH_3$) 5.08 (2H, s, $PhCH_2$), 6.83 (1H, d, *J* = 8.9 Hz, ArH), 7.14 (1H, m, ArH), 7.17 (1H, d, *J* = 7.6 Hz, ArH), 7.25 (1H, dd, *J* = 8.9, 2.6 Hz, ArH), 7.28-7.37 (5H, m, ArH), 7.48 (1H, t, *J* = 7.7 Hz, ArH) 7.88 (1H, d, *J* = 2.6 Hz, ArH), 7.94 (1H, d, *J* = 7.8 Hz, ArH) and 8.64 (1H s, CH=N); $\delta_C$ (150 MHz; $CDCl_3$)

17.9 ($CH_3$), 71.1 ($PhCH_2$), 96.8 (C-3), 114.4, 116.8, 120.1, 122.9, 123.9, 126.0, 126.7, 126.8, 127.7, 128.7, 129.0, 133.0, 134.5, 135.7 (Ar-C), 149.3 (ArC=N), 154.0 and 156.7 (Ar-C), 162.3 (C=O), 173.7 ($CH_3$*C*=N) and 181.9 (C-4).

**3-{[2-(Benzyloxy-5-bromobenzylidene)hydrazono]ethyl}-4-hydroxycoumarin 13c** as a yellow solid ( 0.19 g, 77%), m.p. 232-234 °C; [HRMS: *m/z* calculated for $C_{25}H_{20}BrN_2O_4$ ($MH^+$) 491.0606. Found 491.0608]; $\nu_{max}/cm^{-1}$ 1686 (C=N); $\delta_H$ (600 MHz; $CDCl_3$) 2.98 (3H, s, $CH_3$) 5.09 (2H, s, $PhCH_2$), 6.79 (1H, d, *J* = 8.9 Hz, ArH), 7.13-7.19 (2H, m, ArH), 7.28-7.36 (5H, m, ArH), 7.39 (1H, dd, *J* = 8.8, 2.3 Hz, ArH), 7.48 (1H, t, *J* = 7.7 Hz, ArH) 7.95 (1H, d, *J* = 7.5 Hz, ArH), 8.02 (1H, d, *J* = 2.2 Hz, ArH) and 8.64 (1H s, CH=N); $\delta_C$ (150 MHz; $CDCl_3$) 17.9 ($CH_3$), 71.1 ($PhCH_2$), 96.8 (C-3), 114.0, 114.8, 116.9, 120.1, 123.5, 123.9, 126.1, 126.7, 128.7, 129.1, 129.8, 134.5, 135.7 and 135.8 (Ar-C), 149.2 (ArC=N), 154.0 and 157.2 (Ar-C), 162.2 (C=O), 173.7 ($CH_3$*C*=N) and 181.9 (C-4).

**3-{[2-(Benzyloxy-3,5-dibromobenzylidene)hydrazono]ethyl}-4-hydroxycoumarin 13d** as a yellow solid (0.22 g, 77%), m.p. 219-221 °C; [HRMS: *m/z* calculated for $C_{25}H_{19}Br_2N_2O_4$ ($MH^+$) 568.9712. Found 568.9719]; $\nu_{max}/cm^{-1}$ 1694 (C=O); $\delta_H$ (600 MHz; $CDCl_3$) 2.84 (3H, s, $CH_3$) 4.95 (2H, s, $PhCH_2$), 7.10-7.17 (2H, m, ArH), 7.20 (1H, m, ArH), 7.24-7.29 (4H, m, ArH), 7.46 (1H, t, *J* = 7.1 Hz, ArH), 7.73 (1H, s ArH), 7.83 (1H, s ArH), 7.95 (1H, s, CH=N) and 7.96 (1H, s, ArH); $\delta_C$ (150 MHz; $CDCl_3$) 17.8 ($CH_3$), 77.5 ($PhCH_2$), 96.9 (C-3), 116.9, 118.3, 119.3, 120.0, 123.9, 126.2, 128.8, 129.1, 129.2, 129.4, 130.4, 134.6, 134.8 and 138.9 (Ar-C), 148.5 (ArC=N), 154.0 and 154.4 (Ar-C), 162.2 (C=O), 173.8 ($CH_3$*C*=N) and 181.9 (C-4).

**3-{[2,4-(Dihydroxybenzylidene)hydrazono]ethyl}-4-hydroxycoumarin 13e** as a yellow solid (0.15 g, 87%), m.p. 238-240 °C; [HRMS: *m/z* calculated for $C_{18}H_{15}N_2O_5$ ($MH^+$) 339.0981. Found 339.0981]; $\nu_{max}/cm^{-1}$ 3206 (O-H) and 1669 (C=N); $\delta_H$ (600 MHz; DMSO-$d_6$) 2.81 (3H, s, $CH_3$) 6.36 (2H, dd, *J* = 4.3, 2.3 Hz, ArH), 7.20 (1H, d, *J* = 8.2 Hz, ArH), 7.25 (1H, t, *J* = 7.5 Hz, ArH), 7.56-7.60 (2H, m, ArH), 7.90 (1H, d, *J* = 6.6 Hz, ArH), 8.59 (1H s, CH=N), 10.24 and 10.37 (2H, 2xs, 2xOH); $\delta_C$ (150 MHz; DMSO-$d_6$) 17.1 ($CH_3$), 95.2 (C-3), 102.4, 116.4, 108.7, 110.4, 116.3, 119.7, 123.7, 125.6, 129.5, 134.2 and 153.1 (Ar-C), 153.2 (ArC=N), 161.4 (Ar-C), 162.9 (C=O), 169.9 ($CH_3$*C*=N) and 179.6 (C-4).

**3-{[2,3-(Dihydroxybenzylidene)hydrazono]ethyl}-4-hydroxycoumarin 13f** as a yellow solid (0,12 g, 71%), m.p. 260-261 °C; [HRMS: *m/z* calculated for $C_{18}H_{15}N_2O_5$ ($MH^+$) 339.0981. Found 339.0983]; $\nu_{max}/cm^{-1}$ 3412 (O-H) and 1701 (C=O); $\delta_H$ (400 MHz; DMSO-$d_6$) 2.86 (3H, s, $CH_3$) 6.73 (1H, t, *J* = 7.8 Hz, ArH), 6.93 (1H, d, *J* = 7.5 Hz, ArH), 7.23 (2H, 2 coinciding doublets, *J* = 8.2 Hz, ArH), 7.28 (1H, t, *J* = 7.6 Hz, ArH), 7.61 (1H, t, *J* = 7.7 Hz, ArH) 7.92 (1H, d, *J* = 7.2 Hz, ArH), 8.76 (1H s, CH=N), 9.63 and 9.73 (2H, 2xs, 2xOH); $\delta_C$ (100 MHz; DMSO-$d_6$) 17.3 ($CH_3$), 95.5 (C-3), 116.4, 117.7, 118.6, 119.2, 119.6, 119.7, 123.9, 125.7, 134.4, 146.0, 147.0 and 153.2 (Ar-C), 153.5 (ArC=N), 161.3 (C=O), 171.2 ($CH_3$*C*=N) and 179.9 (C-4).

**3-{[3,4-(Dihydroxybenzylidene)hydrazono]ethyl}-4-hydroxycoumarin 13g** as yellow solid (0.14 g, 83%), m.p. 285-286 °C; [HRMS: *m/z* calculated for $C_{18}H_{15}N_2O_5$ ($MH^+$) 339.0981. Found 339.0987]; $\nu_{max}/cm^{-1}$ 3333 (O-H) and 1684 (C=N); $\delta_H$ (400 MHz; DMSO-$d_6$) 2.88 (3H, s, $CH_3$) 6.86 (1H, d, *J* = 8.1 Hz, ArH), 7.15 (1H, dd, *J* = 8.2, 1.8 Hz, ArH), 7.25 (1H, d, *J* = 8.2 Hz, ArH), 7.29 (1H, t, *J* = 7.5 Hz, ArH), 7.33 (1H, d, *J* = 1.8 Hz, ArH), 7.62 (1H, t, *J* = 7.1 Hz, ArH) 7.93 (d, *J* = 6.7 Hz, ArH), 8.48 (1H s, CH=N), 9.50 and 9.89 (2H, 2xs, 2xOH); $\delta_C$ (100 MHz; DMSO-$d_6$) 17.7 ($CH_3$), 95.7 (C-3), 114.2, 116.2, 116.8, 120.2, 123.3, 124.2, 124.5, 126.1, 134.7, 146.3, 150.5 and 153.6 (Ar-C), 157.1 (ArC=N), 161.8 (C=O), 171.2 ($CH_3$*C*=N) and 180.2 (C-4).

**The synthesis of 3-{1-[(propargyloxybenzylidene)hydrazono]ethyl}-4-hydroxycoumarins 15a-g** is illustrated by the following example.

A solution of 3-(1-hydrazonoethyl)-4-hydroxycoumarin **12** (0.22 g, 1 mmol), 4-(propargyloxy)benzaldehyde **14a** (0.17 g, 1.1 mmol) and one drop of 2N-HCl in ethanol (5 mL) was refluxed for at least one hour and then cooled to room temperature. The mixture was filtered to remove the resulting precipitate which was then washed with methanol and dried to afford 4-hydroxy-3-{1-[(4-propargyloxybenzylidene)hydrazono]ethyl}coumarin **15a** as a yellow solid (0.4 g, 83%) m.p. 209-211 °C; [HRMS: *m/z* calculated for $C_{21}H_{17}N_2O_4$

($MH^+$) 361.1188. Found 361.1191]; $\nu_{max}/cm^{-1}$ 1695 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.57 (1H, t, *J* = 2.4 Hz, C≡CH) 3.06 (3H, s, $CH_3$), 4.76 (2H, d, *J* = 2.4 Hz, $CH_2$) 7.06 (2H, d, *J* = 8.8 Hz, ArH), 7.21-7.28 (2H, m, ArH), 7.56 (1H, t, *J* = 8.5 Hz, ArH), 7.75 (2H, d, *J* = 8.8 Hz, ArH), 8.05 (1H, d, *J* = 9.0 Hz, ArH) and 8.31 (1H, s, CH=N); $\delta_C$ (100 MHz; $CDCl_3$) 17.8 ($CH_3$), 56.1 ($CH_2$), 76.4 (C≡*C*H). 77.9 (*C*≡CH), 95.6 (C-3), 115.6, 116.9, 120.2, 123.8, 126.1, 126.2, 130.4, 134.3 and 154.0 (Ar-C), 154.4 (ArC=N), 160.8 (Ar-C), 162.4 (C=O), 173.1 ($CH_3$*C*=N) and 181.7 (C-4).

4-Hydroxy-3-{1-[(2-propargyloxy)benzylidene)hydrazono]ethyl}coumarin **15b** as a pale yellow solid (0.32 g, 89%), m.p. 188-190 °C; [HRMS: *m/z* calculated for $C_{21}H_{17}N_2O_4$ ($MH^+$) 361.1188. Found 361.1190]; $\nu_{max}/cm^{-1}$ 1695 (C=O); $\delta_H$ (300 MHz; $CDCl_3$) 2.48 (1H, t, *J* = 2.4 Hz, C≡CH) 2.96 (3H, s, $CH_3$), 4.70 (2H, d, *J* = 2.4 Hz, $CH_2$) 6,90-7.01 (2H, m, ArH), 7.21-7.28 (2H, m, ArH), 7.36 (1H, t, *J* = 7.9 Hz, ArH), 7.45 (1H, t, *J* = 7.7 Hz, ArH), 7.94 (2H, t, *J* = 7.5 Hz, ArH) and 8.70 (1H, s, CH=N); $\delta_C$ (75 MHz; $CDCl_3$) 17.8 ($CH_3$), 56.4 ($CH_2$), 76.6 (C≡*C*H). 77.9 (*C*≡CH), 96.6 (C-3), 113.0, 116.8, 120.2, 121.9, 122.1, 123.8, 126.1, 127.4, 130.4, 133.4 and 134.3 (Ar-C), 150.8 (ArC=N), 154.0, 157.1 (Ar-C), 162.3 (C=O), 173.3 ($CH_3$*C*=N) and 181.7 (C-4).

**4-Hydroxy-3-{1-[(3-methoxy-2-propargyloxybenzylidene)hydrazono]ethyl}coumarin 15c** as a pale yellow solid (0.35 g, 90%), m.p. 192-194 °C; [HRMS: *m/z* calculated for $C_{22}H_{19}N_2O_5$ ($MH^+$) 391.1294. Found 391.1295]; $\nu_{max}/cm^{-1}$ 1713 (C=O); $\delta_H$ (300 MHz; $CDCl_3$) 2.52 (1H, t, *J* = 2.4 Hz, C≡CH) 3.08 (3H, s, $CH_3$), 3.91 (3H, s, $CH_3O$), 4.87 (2H, d, *J* = 2.4 Hz, $CH_2$) 7.04 (1H, d, *J* = 9.4 Hz, ArH), 7.17 (1H, t, *J* = 8.0 Hz, ArH), 7.21-7.29 (2H, m, ArH), 7.57 (1H, t, *J* = 8.5 Hz, ArH), 7.65 (1H, d, *J* = 9.1 Hz, ArH), 8.08 (1H, d, *J* = 8.9 Hz, ArH) and 8.85 (1H, s, CH=N); $\delta_C$ (75 MHz; $CDCl_3$) 17.9 ($CH_3$), 56.1 ($CH_3O$), 60.7 ($CH_2$), 77.0 (C≡*C*H). 78.6 (*C*≡CH), 96.7 (C-3), 115.4, 116.8, 118.4, 120.2, 123.9, 125.2, 126.2, 127.9, 134.4 and 146.9 (Ar-C), 151.7 (ArC=N), 152.9, 154.1 (Ar-C), 162.4 (C=O), 173.5 ($CH_3$*C*=N) and 181.9 (C-4).

**3-{1-[(3-Ethoxy-2-propargyloxybenzylidene)hydrazono]ethyl}-4-hydroxycoumarin 15d** as a pale yellow solid (0.37 g, 91%), m.p. 202-204 °C; [HRMS: *m/z* calculated for $C_{23}H_{21}N_2O_5$ ($MH^+$) 405.1450. Found 405.1457]; $\nu_{max}/cm^{-1}$ 1705 (C=O); $\delta_H$ (600 MHz; $CDCl_3$) 1.30 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$) 2.34 (1H, s, C≡CH) 2.88 (3H, s, $CH_3$), 3.91 (2H, q, *J* = 6.9 Hz, $CH_3$C*H*$_2$), 4.72 (2H, d, *J* = 1.8 Hz, $CH_2$) 6.83 (1H, d, *J* = 8.0 Hz, ArH), 6.95 (1H, t, *J* = 8.0 Hz, ArH), 7.03-7.09 (2H, m, ArH), 7.38 (1H, t, *J* = 7.7 Hz, ArH), 7.44 (1H, d, *J* = 7.9 Hz, ArH), 7.88 (1H, d, *J* = 7.8 Hz, ArH) and 8.65 (1H, s, CH=N); $\delta_C$ (150 MHz; $CDCl_3$) 14.9 and 17.9 2x$CH_3$, 60.5 ($CH_2$), 64.5 (*C*H$_2$CH$_3$), 76.9 (C≡*C*H). 78.7 (*C*≡CH), 96.6 (C-3), 116.2, 116.8, 118.1, 120.1, 123.8, 125.1, 126.1, 127.8, 134.3, 146.8 (Ar-C), 151.7 (ArC=N), 152.1, 153.9 (Ar-C) and 162.4 (C=O), 173.4 ($CH_3$*C*=N) and 181.8 (C-4).

**4-Hydroxy-3-{1-[(5-nitro-2-propargyloxybenzylidene)hydrazono]ethyl}coumarin 15e** as a pale yellow solid (0.35 g, 86%), m.p. 222-224 °C; [HRMS: *m/z* calculated for $C_{21}H_{16}N_3O_6$ ($MH^+$) 406.1039. Found 406.1035]; $\nu_{max}/cm^{-1}$ 1688 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.64 (1H, s, C≡CH) 3.09 (3H, s, $CH_3$), 4.92 (2H, s, $CH_2$) 7.15-7.24 (3H, m, ArH), 7.56 (1H, t, *J* = 6.7 Hz, ArH), 8.02 (1H, d, *J* = 7.4 Hz, ArH), 8.33 (1H, d, *J* = 8.5 Hz, ArH), 8.73 (1H, s, CH=N) and 8.86 (1H, s, ArH); $\delta_C$ (100 MHz; $CDCl_3$) 17.9 ($CH_3$), 57.2 ($CH_2$), 76.4 (C≡*C*H). 78.0 (*C*≡CH), 97.2 (C-3), 113.1, 117.0, 120.0, 122.7, 123.1, 124.0, 126.1, 128.1, 134.7 and 142.5 (Ar-C), 148.2 (ArC=N), 154.1, 160.7 (Ar-C), 162.1 (C=O), 174.4 ($CH_3$*C*=N) and 182.2 (C-4).

**3-{1-[(5-Chloro-2-propargyloxybenzylidene)hydrazono]ethyl}-4-hydroxycoumarin 15f** as a pale yellow solid (0.36 g, 91%), m.p. 232-234 °C; [HRMS: *m/z* calculated for $C_{21}H_{16}ClN_2O_4$ ($MH^+$) 395.0799. Found 395.0793]; $\nu_{max}/cm^{-1}$ 1694 (C=O); $\delta_H$ (600 MHz; $CDCl_3$) 2.55 (1H, t, *J* = 2.4 Hz, C≡CH) 3.04 (3H, s, $CH_3$), 4.77 (2H, d, *J* = 2.3 Hz, $CH_2$) 7.00 (1H, d, *J* = 8.9 Hz, ArH), 7.18-7.24 (2H, m, ArH), 7.37 (1H, dd, *J* = 8.9, 2.6 Hz, ArH), 7.54 (1H, t, *J* = 8.5 Hz, ArH), 7.95 (1H, d, *J* = 2.6 Hz, ArH), 8.01 (1H, d, *J* = 7.8 Hz, ArH) and 8.69 (1H, s, CH=N); $\delta_C$ (150 MHz; $CDCl_3$) 17.9 ($CH_3$), 56.8 ($CH_2$), 77.0 (C≡*C*H). 77.4 (*C*≡CH), 96.9 (C-3), 114.5, 116.9, 120.1, 123.4, 123.9, 126.1, 126.8, 127.6, 132.9, 134.5, (Ar-C), 149.3 (ArC=N), 154.1 and 155.5 (Ar-C), 162.3 (C=O), 173.8 ($CH_3$*C*=N) and 182.0 (C-4).

**3-{1-[(5-Bromo-2-propargyloxybenzylidene)hydrazono]ethyl}-4-hydroxycoumarin 15g** as a pale yellow solid (0.39 g, 89%), m.p. 234-235 °C; [HRMS: *m/z* calculated for $C_{21}H_{16}BrN_2O_4$ ($MH^+$) 439.0293. Found 439.0298]; $\nu_{max}/cm^{-1}$ 1695 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.56 (1H, t, *J* = 2.2 Hz, C≡CH) 3.05 (3H, s, $CH_3$), 4.77 (2H, d, *J* = 2.2 Hz, $CH_2$) 6.96 (1H, d, *J* = 8.9 Hz, ArH), 7.17-7.27 (2H, m, ArH), 7.50-7.57 (2H, m, ArH), 8.03 (1H, d, *J* = 7.1 Hz, ArH), 8.10 (1H, d, *J* = 2.3 Hz, ArH) and 8.68 (1H, s, CH=N); $\delta_C$ (100 MHz; $CDCl_3$) 17.9 ($CH_3$), 56.7 ($CH_2$), 77.1 (C≡*C*H). 77.4 (*C*≡CH), 96.9 (C-3), 114.8, 114.9, 116.9, 120.1, 123.8, 123.9, 126.1, 129.8, 134.5 and 135.8 (Ar-C), 149.2 (ArC=N), 154.1, 156.0 (Ar-C), 162.3 (C=O), 173.8 ($CH_3$*C*=N) and 182.0 (C-4).

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## Supplementary Material

NMR spectra for all new compounds and bioassay protocols and data are provided in the Supporting Information file.

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