

Facile one-pot synthesis of coumarins linked to 1,2,3-triazoles by combining Sonogashira and CuAAC reaction

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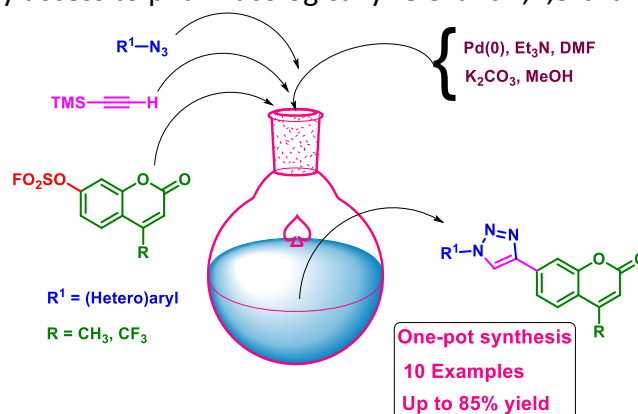
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Abstract

A facile, one-pot, atom economic approach has been developed for the synthesis of 1-(hetero)aryl-1,2,3-triazoles linked to coumarins under mild conditions. The reaction initially proceeds by the palladium-catalyzed Sonogashira cross-coupling reaction of coumarin fluorosulfates with trimethylsilylacetylene (TMS acetylene), followed by the deprotection of TMS group and subsequent copper-catalyzed azide-alkyne cycloaddition (CuAAC) reactions. The salient features of this developed methodology are: step-economic one-pot synthetic approach, utilization of coumarin fluorosulfate as an atom-economical electrophilic coupling partner for Sonogashira coupling, and easy access to pharmacologically relevant 1,2,3-triazole derivatives.



Keywords: Coumarin, Sonogashira coupling, aryl fluorosulfate, CuAAC

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Introduction

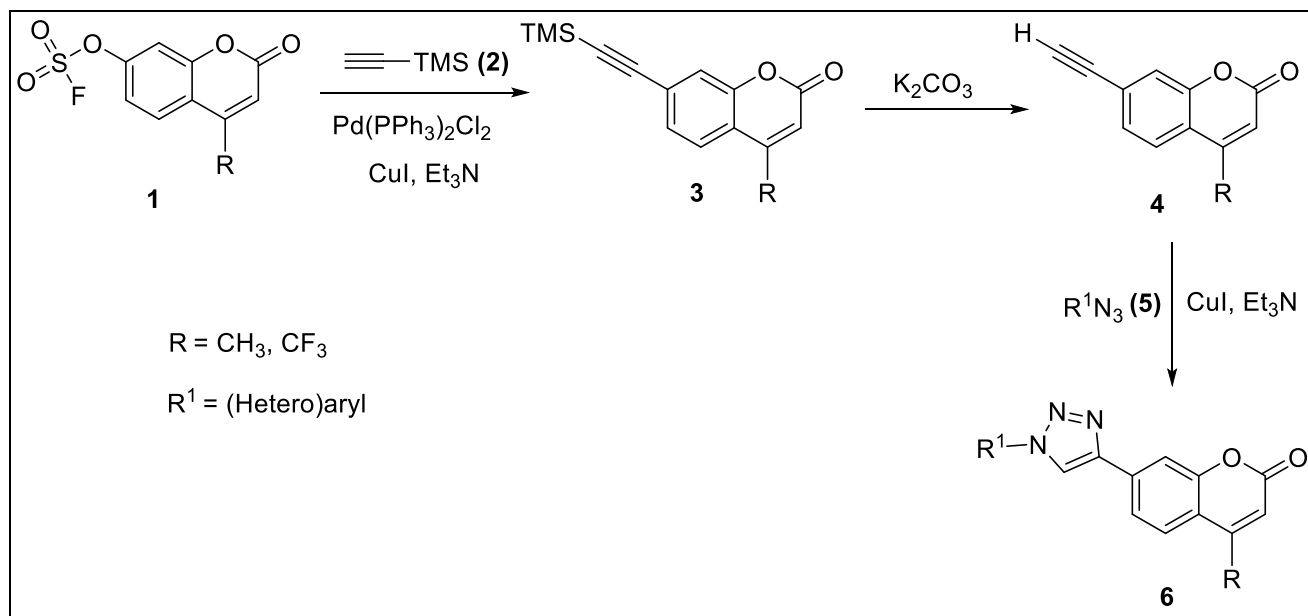
Coumarins, first isolated from green plants, are an important class of oxygen-containing heterocyclic biomolecule belonging to the benzopyrone family.¹ The naturally occurring coumarins and their synthesized derivatives are known to possess various biological activities such as antibacterial, anticancer, anti-inflammatory and antitubercular activities.²⁻⁵ Coumarin derivatives are also reported to possess good photophysical properties and the anticoagulant property of coumarins has been extensively studied worldwide.⁶⁻⁹ On the other hand, the 1,2,3-triazole motif linearly connected to other pharmacologically relevant heterocycles were found to possess good antiviral, anticancer and antibacterial properties.¹⁰⁻¹³ The presence of 1,2,3-triazole nucleus in many marketed drugs further highlights its significance as an important nitrogen-containing heterocyclic molecule.¹⁴ In view of these observations, the synthesis of new molecules containing coumarin and 1,2,3-triazole molecule is highly important in medicinal chemistry, especially in drug-discovery research.

In the last four decades, the palladium-catalyzed cross-coupling reactions of organic halides/pseudohalides with different coupling partners like boronic acids, alkenes, terminal acetylenes etc. have emerged as an essential tool in organic synthesis.¹⁵⁻²⁰ Among these, Sonogashira cross-coupling reaction between halides/pseudohalides and terminal acetylenes has been utilized by various researchers throughout the world for the construction of highly challenging molecules containing alkynes.²¹⁻²⁴ Different aryl halide surrogates such as arenediazonium salts and various pseudohalide leaving groups such as aryl nonaflates, triflates, fluorosulfates etc., have been successfully employed as electrophilic cross-coupling partners by various research groups in Sonogashira coupling reactions under mild or copper-free conditions.^{25,26} Even though the palladium-copper bimetallic catalytic systems are generally used in Sonogashira coupling because of the low-cost and availability of copper, several researchers have successfully employed gold and silver catalysts instead of copper nowadays.²⁷⁻³⁰ On the other hand, the copper-catalyzed cycloaddition reaction of azides and terminal alkynes (CuAAC) has emerged as an important tool for the synthesis of 1,2,3-triazole molecules with excellent regioselectivity and high yields.³¹⁻³⁴ Furthermore, the coumarins linked to 1,2,3-triazoles have been reported to possess various pharmacological properties such as anticancer, anti-inflammatory and antitubercular activities.^{35,36}

In the modern arena of synthetic chemistry, the need for developing atom and step-economic synthetic approaches is highly significant owing to the global environmental hazards and climate change. The development of one-pot synthetic protocol as an alternative for multi-step synthesis is an important step for this vision of waste minimization and environmental friendliness.³⁷⁻³⁹ Recently, we reported the synthesis of various 4-methyl-7-alkynyl coumarin derivatives by employing the copper-free Sonogashira cross-coupling of coumarin fluorosulfate with different terminal alkynes in water.⁴⁰ We also reported the facile CuAAC methodology for synthesizing diverse coumarins linked to 1-(hetero)aryl-1,2,3-triazoles connected via -OCH₂ linker recently.^{41,42} The success of these reactions encouraged us to develop a protocol for the synthesis of some pharmacologically relevant coumarin derivatives directly connected to 1,2,3-triazoles. As a continuation of our ongoing research work in the synthesis of novel pharmacologically relevant coumarin derivatives,⁴³⁻⁴⁵ we herein report our successful one-pot, atom-economic methodology for the synthesis of coumarins linked to 1,2,3-triazoles.

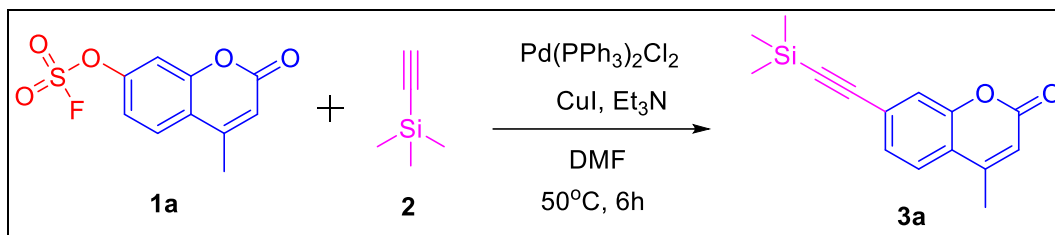
Results and Discussion

We started our synthetic plan by optimizing the multi-step synthesis of target compounds **6** as detailed in Scheme 1. The synthesis of coumarin fluorosulfate intermediate **1** was carried out according to our previously reported methodology.⁴⁰ This fluorosulfate **1** was initially subjected to palladium-catalyzed Sonogashira cross-coupling reaction with trimethylsilylacetylene (TMS acetylene) **2** to obtain intermediate **3**, which was then deprotected to obtain the terminal acetylene **4**. This acetylene intermediate was planned to react with different (hetero)aryl azides **5** to obtain the target compounds **6**.



Scheme 1. Initial optimization plan for synthesizing coumarins linked to 1,2,3-triazoles **6**.

The optimization of Sonogashira coupling reaction was initially carried out between coumarin fluorosulfate intermediate **1a** and TMS acetylene **2** by employing our previously reported copper-free protocol in water.⁴⁰ However, we didn't obtain the desired product **3a** in our reaction conditions (Table 1, entry 2). Later, a series of catalysts, bases and solvents were screened to identify the optimal reaction conditions for the formation of **3a** (Table 1). Gratifyingly, we got the expected product **3a** in 65% isolated yield when the reaction was performed at 50°C in Pd(PPh₃)₂Cl₂ and copper iodide (CuI) catalysts, triethylamine (Et₃N) base and DMF solvent (Table 1, entry 1). The reaction didn't proceed in the absence of CuI (Table 1, entry 3). The utilization of other bases and solvents rendered the desired product in lower or negligible yield (Table 1, entries 4-7). After careful screening of the time taken for product formation, the reaction time was affixed to 6 hours (Table 1, entries 8,9). The employment of 5 mol % catalyst delivered the expected product in comparable yield whereas the lower catalyst loadings led to detrimental results (Table 1, entries 10-12).

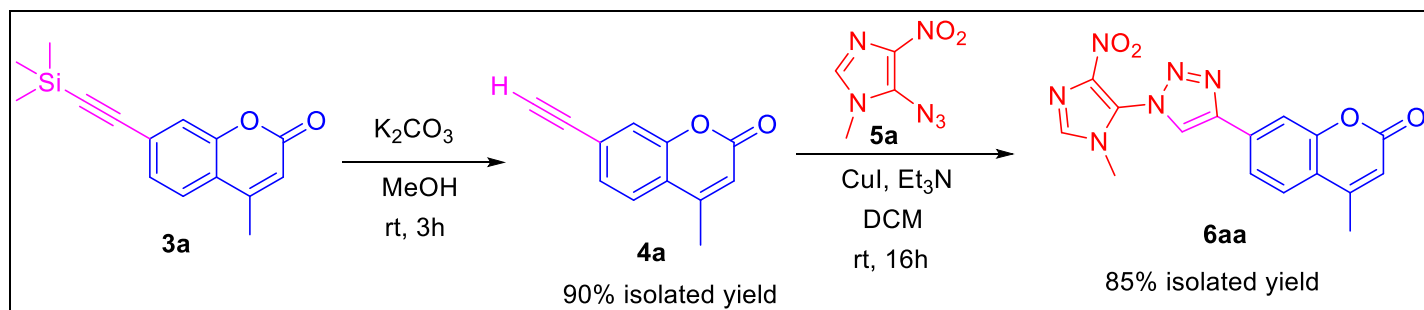
Table 1. Optimization of reaction conditions for Sonogashira coupling^a

Entry	Deviation from standard conditions	Yield ^b 3a (%)
1	None	65
2	Without CuI and H ₂ O instead of DMF	Nil
3	Without CuI	20
4	H ₂ O instead of DMF	trace
5	Dioxane instead of DMF	30
6	Na ₂ CO ₃ instead of Et ₃ N	trace
7	DBU instead of Et ₃ N	20
8	Reaction carried out for 3h	45
9	Reaction carried out for 10h	60
10	5 mol % Pd(PPh ₃) ₂ Cl ₂ instead of 10 mol %	60
11	2 mol % Pd(PPh ₃) ₂ Cl ₂ instead of 10 mol %	35
12	1 mol % Pd(PPh ₃) ₂ Cl ₂ instead of 10 mol %	20

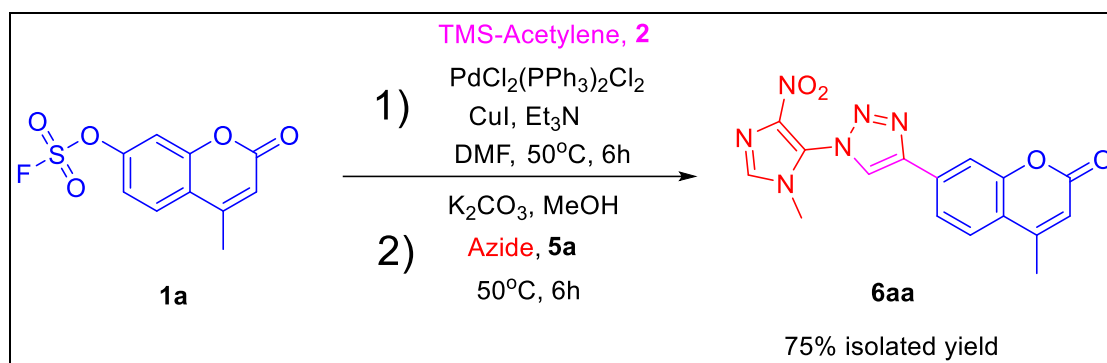
^aReaction conditions: coumarin fluorosulfate **1a** (1 mmol), TMS acetylene **2** (1.1 mmol), Pd(PPh₃)₂Cl₂ (10 mol%), CuI (10 mol %), base (3 mmol), solvent (3 mL).

^bIsolated yield.

After optimizing the Sonogashira cross-coupling reaction, the deprotection of TMS group from **3a** was easily achieved by performing a previously reported protocol.⁴⁶ The reaction was carried out in excess potassium carbonate at room temperature in methanol (MeOH) solvent to obtain the terminal acetylene **4a** in 90% isolated yield (Scheme 2). The CuAAC reaction of **4a** with 5-azido-1-methyl-4-nitro-1*H*-imidazole **5a** was then carried out in presence of CuI and Et₃N to obtain the coumarin linked to 1,2,3-triazole **6aa** in 85% isolated yield in DCM solvent at room temperature (Scheme 2).

**Scheme 2.** Deprotection of TMS group and subsequent CuAAC reaction.

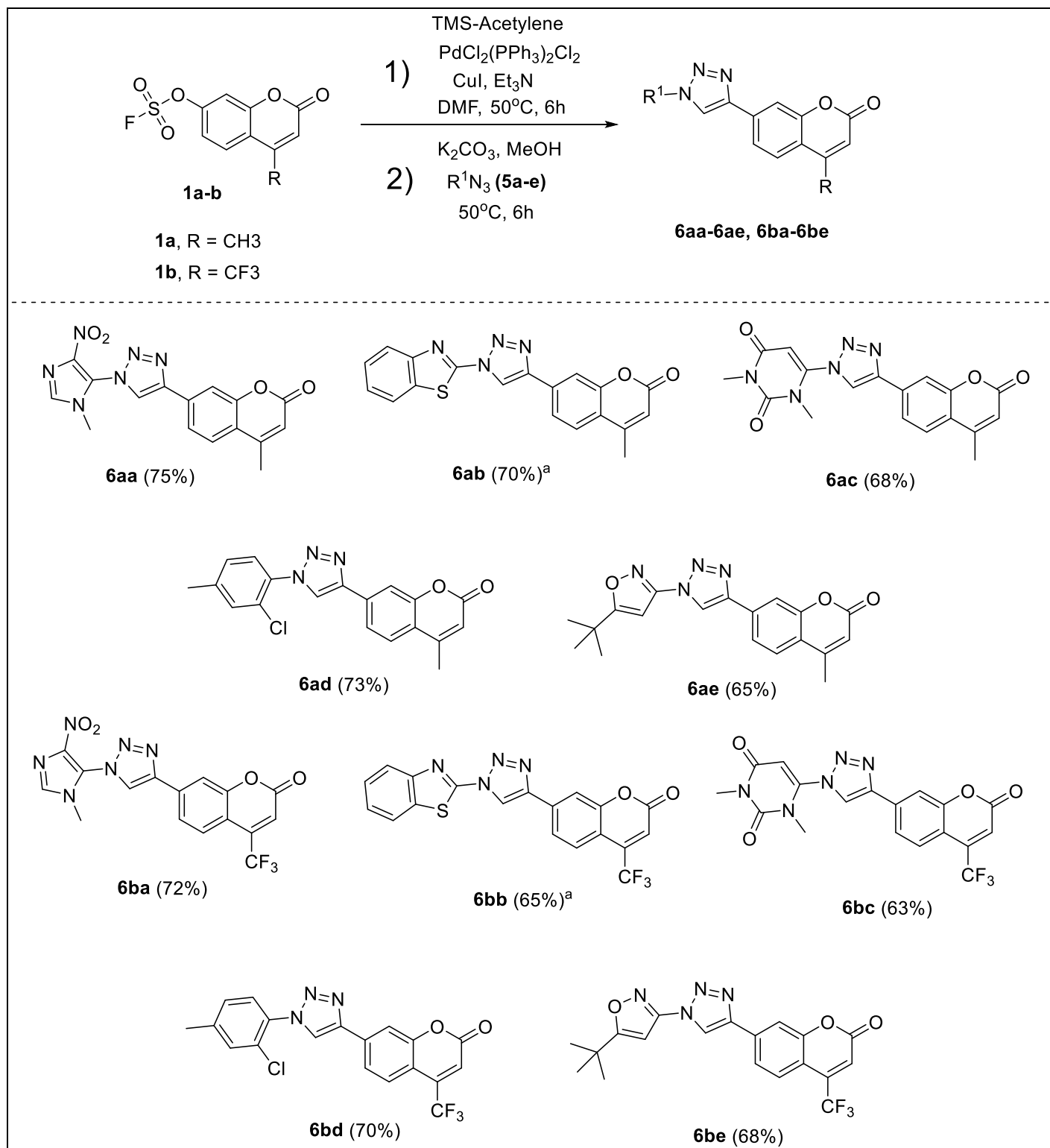
After obtaining the desired target compound **6aa** in hand, our next attention was to evaluate the possibility of synthesizing **6aa** in one-pot. Keeping this in mind, we initially performed the Sonogashira coupling reaction according to the previously optimized protocol. After that, we added potassium carbonate, methanol and azide **5a** to the same reaction vessel and continued the reaction at 50°C for 6 hours (Scheme 3). To our delight, we obtained the desired product **6aa** in 75% isolated yield. It is worth noting that the stoichiometry of azide **5a** is reduced to 0.7 equivalence, taking into consideration the lower yield in the first step (Sonogashira coupling) of the overall reaction.



Scheme 3. One-pot synthesis of **6aa**.

Reaction conditions: (1) coumarin fluorosulfate **1a** (1 mmol), TMS-acetylene (1.1 mmol), Pd(PPh₃)₂Cl₂ (10 mol %), CuI (10 mol %), Et₃N (3 mmol), 2 mL DMF, 50°C for 6h; (2) K₂CO₃ (3 mmol), azide **5a** (0.7 mmol), 1 mL MeOH, 50 °C for 6 h.

After optimizing the one-pot protocol for the synthesis of coumarin linked to 1,2,3-triazole, we directed our attention to evaluate the substrate scope of this methodology. Keeping this in mind, the coumarin fluorosulfates **1a-b** and different (hetero)aryl azides **5a-e** were reacted in one-pot according to our optimized reaction conditions (Scheme 4). To our delight, we obtained the desired triazole products **6aa-6ae** and **6ba-6be** in good to acceptable yields. The aryl azide **5d** reacted with coumarin fluorosulfates **1a** and **1b** to render the expected products **6ad** and **6bd** in 68% and 70% isolated yields. Other heteroaryl azides furnished the required products in good to moderate yields (Scheme 4).



Scheme 4. Substrate scope of the optimized methodology.

Reaction conditions: (1) coumarin fluorosulfate **1a-b** (1 mmol), TMS-acetylene (1.1 mmol), Pd(PPh₃)₂Cl₂ (10 mol %), Cul (10 mol %), Et₃N (3 mmol), 2 mL DMF, 50°C for 6h; (2) K₂CO₃ (3 mmol), azide **5a-e** (0.7 mmol), 1 mL MeOH, 50°C for 6h. Isolated yield in parenthesis.

^a1 equivalence of Cul used in second step because of the possible existence of 2-azido-1-benzothiophene in its tetrazole form.

Conclusions

We successfully achieved the synthesis of some 1-(hetero)aryl-1,2,3-triazoles linked to coumarins by employing a one-pot, atom economic methodology in mild conditions. The utilization of coumarin fluorosulfate as a key electrophilic cross-coupling partner in Sonogashira cross-coupling reaction and the facile in situ deprotection of TMS group followed by its reaction with azides in same reaction vessel was the key for success of our developed protocol. This methodology can be adopted for the facile, step economic synthesis of other complex heterocyclic molecules linked to 1,2,3-triazole derivatives in future.

Experimental Section

General. All chemicals were purchased from commercial suppliers and used as delivered. ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at 400, 100 and 376 MHz or 600, 150 and 565 MHz respectively. Chemical shifts are reported in parts per million (ppm) and coupling constants in Hertz (Hz). Tetramethylsilane (TMS) ($\delta = 0.00$ ppm) or residual solvent peak in $\text{DMSO}-d_6$ ($\delta = 2.50$ ppm) and CDCl_3 ($\delta = 7.26$ ppm) served as internal standard for recording.⁴⁷ Molecular weights of unknown compounds were determined by GCMS-QP2010 Ultra gas chromatograph operating at an ionization potential of 70 eV (EI) or Thermo Finnigan LCQ Advantage apparatus (ESI). Microanalyses were performed on PerkinElmer Series II CHNS/O 2400 elemental analyzer. Melting points were determined using a Stuart SMP 3 apparatus. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F₂₅₄ TLC plates.

Procedure for the synthesis of coumarin fluorosulfates 1a-b

The synthesis of coumarin fluorosulfates **1a-b** was carried out according to a previously reported procedure by us.⁴⁰

Procedure for the one-pot synthesis of triazoles by combining Sonogashira coupling and CuAAC

In a sealed tube with screw cap, coumarin fluorosulfates **1a-b** (1 mmol, 1 equiv.), trimethylsilylacetylene **2** (1.1 mmol, 1.1 equiv.), CuI (0.1 mmol, 0.1 equiv.), Et_3N (3 mmol, 3 equiv.) and DMF (2 mL) was added. The reaction mixture was degassed for 10 min. under N_2 atmosphere and then $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.1 mmol, 0.1 equiv.) was added. The reaction mixture was heated at 50°C for 6 hours. After the completion of reaction monitored by TLC, K_2CO_3 (3 mmol, 3 equiv.), azides **5a-e** (0.7 mmol, 0.7 equiv.) and MeOH (1 mL) was added to the reaction mixture. The reaction mixture was heated at 50°C for 6 hours. After the specified time, the reaction mixture was filtered through celite and distilled under reduced pressure to obtain the crude product. The crude was purified by column chromatography in hexane-ethyl acetate in varying polarities to obtain the titled products **6aa-6ae** and **6ba-6be** in varying yields.

4-Methyl-7-(1-(1-methyl-4-nitro-1H-imidazol-5-yl)-1H-1,2,3-triazol-4-yl)-2H-chromen-2-one (6aa). Yield: 75% (264 mg); light brown solid; mp $201-204^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 2.48$ (d, $J = 1.6$ Hz, 3H, CH_3), 3.65 (s, 3H, NCH_3), 6.45 (d, $J = 1.2$ Hz, 1H, ArH), 7.93-7.99 (m, 3H, ArH), 8.19 (s, 1H, ArH), 9.35 (s, 1H, ArH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): $\delta = 18.5, 33.0, 113.3, 115.0, 120.2, 121.8, 123.7, 127.0, 127.3, 133.3, 136.9, 139.4, 145.8, 153.5, 154.0, 160.1$; MS (EI): m/z (%) = 352 (1) $[\text{M}]^+$, 187 (100); Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{N}_6\text{O}_4$: C, 54.55; H, 3.43.14; N, 23.85%; Found: C, 54.60; H, 3.81; N, 23.73%.

7-(1-(Benzo[d]thiazol-2-yl)-1H-1,2,3-triazol-4-yl)-4-methyl-2H-chromen-2-one (6ab). Yield: 70% (252 mg); off white solid; mp $220-223^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 2.42$ (s, 3H, CH_3), 6.34 (s, 1H, ArH), 7.52-7.60 (m, 2H, ArH), 7.81 (d, $J = 8.4$ Hz, 1H, ArH), 7.95 (s, 1H, ArH), 8.00 (d, $J = 7.6$ Hz, 2H, ArH), 8.17 (d, $J = 7.6$ Hz, 1H,

ArH), 9.67 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 18.4, 113.6, 115.0, 120.3, 120.9, 122.0, 123.3, 126.6 (2 peaks), 126.8, 127.8, 133.0, 133.3, 147.0, 150.1, 153.2, 153.9, 156.6, 160.0.

MS (EI): m/z (%) = 360 (1) $[\text{M}]^+$, 332 (100); Anal. Calcd for $\text{C}_{19}\text{H}_{12}\text{N}_4\text{O}_2\text{S}$: C, 63.32; H, 3.36; N, 15.55; S, 8.90%; Found: C, 63.54; H, 3.10; N, 15.43; S, 9.10%.

1,3-Dimethyl-6-(4-(4-methyl-2-oxo-2H-chromen-7-yl)-1H-1,2,3-triazol-1-yl)pyrimidine-2,4(1H,3H)-dione (6ac).

Yield: 68% (248 mg); off white solid; mp 282–285 °C; ^1H NMR (400 MHz, DMSO- d_6): δ = 2.48 (d, J = 1.6 Hz, 3H, CH_3), 3.16 (s, 3H, NCH_3), 3.26 (s, 3H, NCH_3), 6.26 (s, 1H, ArH), 6.45 (d, J = 1.6 Hz, 1H, ArH), 7.92–7.99 (m, 3H, ArH), 9.26 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 18.5, 28.6, 32.9, 99.1, 113.4, 115.1, 120.2, 121.9, 125.6, 126.9, 133.2, 145.3, 145.9, 151.6, 153.5, 154.0, 160.1, 161.7; MS (EI): m/z (%) = 365 (1) $[\text{M}]^+$, 337 (100); Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_5\text{O}_4$: C, 59.18; H, 4.14; N, 19.17%; Found: C, 59.21; H, 4.39; N, 19.21%.

7-(1-(2-Chloro-4-methylphenyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2H-chromen-2-one (6ad). Yield: 73% (256 mg); light yellow solid; mp 233–236 °C; ^1H NMR (400 MHz, DMSO- d_6): δ = 2.31 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.28 (s, 1H, ArH), 7.29 (d, J = 7.2 Hz, 1H, ArH), 7.44–7.46 (m, 3H, ArH), 7.56–7.59 (m, 2H, ArH), 9.21 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 14.1, 18.5, 115.5, 119.8, 120.0, 121.2, 124.5, 127.1, 127.3, 127.8, 128.4, 129.9, 131.2, 133.3, 140.3, 141.9, 151.7, 153.5, 160.2; MS (EI): m/z (%) = 351 (2) $[\text{M}]^+$, 323 (100); Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{ClN}_3\text{O}_2$: C, 64.87; H, 4.01; Cl, 10.08; N, 11.94%; Found: C, 64.72; H, 4.18; Cl, 9.73; N, 12.18%.

7-(1-(5-(Tert-butyl)isoxazol-3-yl)-1H-1,2,3-triazol-4-yl)-4-methyl-2H-chromen-2-one (6ae). Yield: 65% (228 mg); off white solid; mp 215–218 °C; ^1H NMR (400 MHz, DMSO- d_6): δ = 1.40 (s, 9H, 3 CH_3), 2.47 (d, J = 1.2 Hz, 3H, CH_3), 6.43 (d, J = 1.6 Hz, 1H, ArH), 7.06 (s, 1H, ArH), 7.90 (d, J = 8.4 Hz, 1H, ArH), 7.98–8.04 (m, 2H, ArH), 9.53 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 19.0, 28.7, 33.6, 93.8, 113.5, 115.0, 120.2, 121.7, 121.9, 126.8, 133.3, 146.6, 153.4, 154.0, 157.6, 160.2, 184.6; MS (EI): m/z (%) = 350 (1) $[\text{M}]^+$, 322 (100); Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_3$: C, 65.13; H, 5.18; N, 15.99%; Found: C, 65.53; H, 5.55; N, 15.71%.

7-(1-(1-Methyl-4-nitro-1H-imidazol-5-yl)-1H-1,2,3-triazol-4-yl)-(4-(trifluoromethyl)-2H-chromen-2-one (6ba). Yield: 72% (292 mg); light yellow solid; mp 252–255 °C; ^1H NMR (600 MHz, DMSO- d_6): δ = 3.63 (s, 3H, NCH_3), 7.08 (s, 1H, ArH), 7.85 (d, J = 7.8 Hz, 1H, ArH), 8.03 (s, 2H, ArH), 8.18 (s, 1H, ArH), 9.36 (s, 1H, ArH); ^{13}C NMR (150 MHz, DMSO- d_6): δ = 33.1, 113.6, 114.1, 117.8, 122.1 (q, J = 273 Hz), 122.5, 123.6, 126.3, 127.8, 134.3, 136.9, 139.1 (q, J = 33 Hz), 139.4, 145.2, 154.9, 158.7; ^{19}F NMR (565 MHz, DMSO- d_6): δ = -63.6; MS (EI): m/z (%) = 406 (1) $[\text{M}]^+$, 241 (100); Anal. Calcd for $\text{C}_{16}\text{H}_9\text{F}_3\text{N}_6\text{O}_4$: C, 47.30; H, 2.23; N, 20.69%; Found: C, 47.29; H, 2.10; N, 20.50%.

7-(1-(Benzo[d]thiazol-2-yl)-1H-1,2,3-triazol-4-yl)-(4-(trifluoromethyl)-2H-chromen-2-one (6bb). Yield: 65% (269 mg); off white solid; mp 265–267 °C; ^1H NMR (600 MHz, CDCl_3 +DMSO- d_6): δ = 6.91 (s, 1H, ArH), 7.47–7.57 (m, 2H, ArH), 7.78 (d, J = 8.4 Hz, 1H, ArH), 7.98 (d, J = 8.4 Hz, 1H, ArH), 8.06–8.14 (m, 3H, ArH), 9.77 (s, 1H, ArH); ^{13}C NMR (150 MHz, CDCl_3 +DMSO- d_6): δ = 112.8, 113.8, 116.2 (q, J = 5 Hz), 120.4, 121.1 (q, J = 273 Hz), 122.1, 122.2, 125.3, 125.9, 126.8, 132.5, 133.8, 139.5 (q, J = 32 Hz), 145.9, 149.4, 154.1, 155.6, 157.8; ^{19}F NMR (565 MHz, DMSO- d_6): δ = -64.0; MS (EI): m/z (%) = 414 (1) $[\text{M}]^+$, 386 (100); Anal. Calcd for $\text{C}_{19}\text{H}_9\text{F}_3\text{N}_4\text{O}_2\text{S}$: C, 55.07; H, 2.19; N, 13.52; S, 7.74%; Found: C, 54.86; H, 2.46; N, 13.67; S, 8.14%.

1,3-Dimethyl-6-(4-(2-oxo-4-(trifluoromethyl)-2H-chromen-7-yl)-1H-1,2,3-triazol-1-yl)pyrimidine-2,4(1H,3H)-dione (6bc). Yield: 63% (264 mg); off white solid; mp 278–281 °C; ^1H NMR (400 MHz, DMSO- d_6): δ = 3.36 (s, 3H, NCH_3), 3.71 (s, 3H, NCH_3), 7.04 (s, 1H, ArH), 7.15 (s, 1H, ArH), 8.04–8.07 (m, 3H, ArH), 9.43 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 28.8, 33.0, 99.5, 113.5, 115.2, 120.3, 122.1 (q, J = 274 Hz), 125.8, 127.1, 133.3, 138.6 (q, J = 32 Hz), 145.4, 145.9, 151.7, 153.6, 154.1, 160.2, 161.8; MS (EI): m/z (%) = 419 (100) $[\text{M}]^+$, 391 (100); Anal. Calcd for $\text{C}_{18}\text{H}_{12}\text{F}_3\text{N}_5\text{O}_4$: C, 51.56; H, 2.88; N, 16.70%; Found: C, 51.67; H, 2.64; N, 16.62%.

7-(1-(2-Chloro-4-methylphenyl)-1H-1,2,3-triazol-4-yl)-4-(trifluoromethyl)-2H-chromen-2-one (6bd). Yield: 70% (284 mg); off white solid; mp 240–243 °C; ^1H NMR (400 MHz, DMSO- d_6): δ = 2.33 (s, 3H, CH_3), 7.03 (s, 1H, ArH), 7.33 (d, J = 7.2 Hz, 1H, ArH), 7.45–7.49 (m, 3H, ArH), 7.57–7.60 (m, 2H, ArH), 9.38 (s, 1H, ArH); ^{13}C NMR (100

MHz, DMSO-*d*₆): δ = 14.1, 115.6, 119.9, 120.1, 121.0, 122.3 (q, *J* = 272 Hz), 124.4, 127.0, 127.3, 127.9, 128.4, 129.9, 131.1, 133.2, 137.8 (q, *J* = 33 Hz), 141.9, 151.8, 153.6, 160.1; MS (EI): *m/z* (%) = 405 (100) [M]⁺, 377 (100); Anal. Calcd for C₁₉H₁₁ClF₃N₃O₂: C, 56.24; H, 2.73; Cl, 8.74; N, 10.36%; Found: C, 56.07; H, 3.09; Cl, 8.61; N, 10.32%. **7-(1-(5-(*tert*-Butyl)isoxazol-3-yl)-1*H*-1,2,3-triazol-4-yl)-4-(trifluoromethyl)-2*H*-chromen-2-one (6be)**. Yield: 68% (275 mg); light yellow solid; mp 198-202 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 1.40 (s, 9H, 3CH₃), 7.05 (s, 1H, ArH), 7.37 (d, *J* = 7.2 Hz, 1H, ArH), 7.48-7.52 (m, 3H, ArH), 9.46 (s, 1H, ArH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 18.7, 28.8, 33.6, 113.2, 115.2, 120.5, 121.9 (q, *J* = 274 Hz), 123.9, 127.0, 127.2, 133.3, 136.9, 139.6 (q, *J* = 34 Hz), 145.9, 153.7, 154.2, 160.2; MS (EI): *m/z* (%) = 404 (100) [M]⁺, 376 (100); Anal. Calcd for C₁₉H₁₅F₃N₄O₃: C, 56.44; H, 3.74; N, 13.86%; Found: C, 56.37; H, 3.38; N, 13.93%.

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