

Click to learn, learn to click: Undergraduate Synthetic Organic Chemistry experiments

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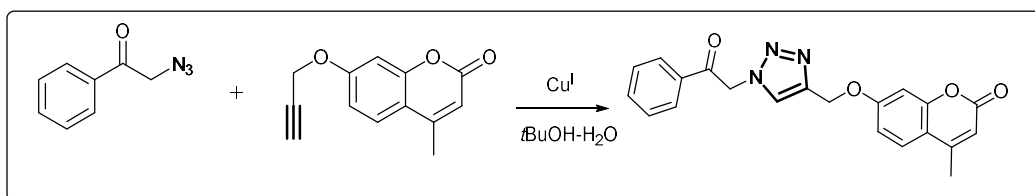
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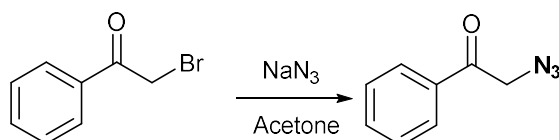
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Click Chemistry: Synthesis of Triazole Coumarin by CuAAC

The Cu(I) catalysed Azide Alkyne Cycloaddition (CuAAC) is a 1,3-dipolar cycloaddition discovered independently by Morten Meldal, and K. Barry Sharpless, recipients of The Nobel Prize in Chemistry (2022). This reaction is the origin and most known example of Click Chemistry. It takes place between a terminal alkyne and an organic azide to form the 1,4-disubstituted triazole in a regioselective process when catalysed by Cu(I) and all atoms in both azide/alkyne are incorporated into the final product. It has found a huge number of applications in many disciplines including material science, drug design and bioconjugation.



1.- Synthesis of 2-Azido-1-phenylethanone:

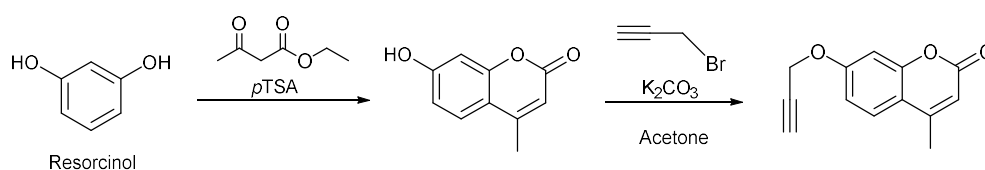


In a 100 mL round bottom flask 2-bromo-1-phenylethanone (760 mg) and NaN_3 (620 mg) in acetone (40 mL) are heated at reflux for 60 min. After that the acetone is evaporated under vacuum. The crude is dissolved in EtOAc (40 mL) and washed with saturated NaHCO_3 (30 mL) and water (30 mL). The organic phase is dried with anhydrous Na_2SO_4 and after filtration the solvent is evaporated under vacuum to obtain the organic azide. Calculate the yield. [Aqueous waste in basic waste, organic solvent in non-halogenated waste]

2.- Synthesis of alkyne-coumarin:

2.1.- Preparation of 7-hydroxy-4-methylcoumarin by Pechmann reaction:

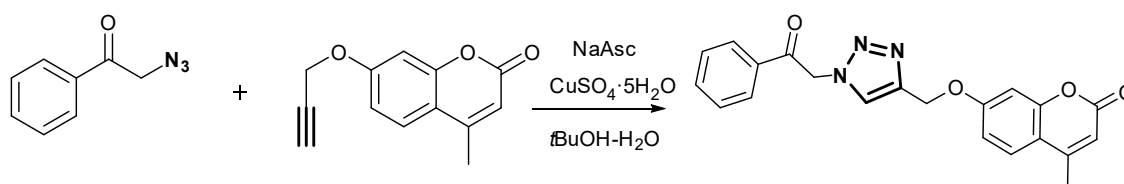
In a 100 mL round bottom flask resorcinol (1.2 g) is added together with ethyl acetoacetate (1.25 mL) and *p*-toluenesulfonic acid (*p*TSA, 90 mg). The reaction is heated at 100°C under magnetic stirring for 10 min. The reaction is allowed to cool until room temperature, followed by the addition of ethanol:water (1:1, 10 mL). The obtained precipitate is filtered under vacuum and kept 24h in a desiccator. The solid is kept in a vial and yield calculated. [Waste from filtration disposed as non-halogenated organic solvents]



2.2.- Synthesis of 4-methyl-7-propargyloxycoumarin by O-alkylation:

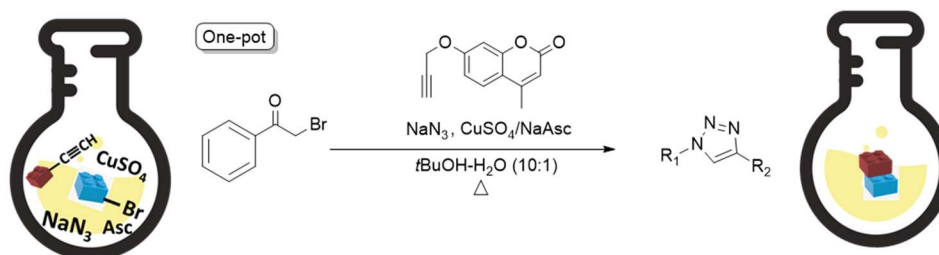
In a 100 mL round bottom flask 7-hydroxy-4-methylcoumarin (1.16 g) is added together with K_2CO_3 (1.16 g) and acetone (30 mL). To the mixture propargyl bromide is slowly added (1 mL). The reaction mixture is heated under reflux for 90 min with magnetic stirring. After allowing to cool, water (30 mL) is added. The acetone is evaporated under vacuum and the remaining aqueous phase is extracted with ethyl acetate (100 mL), washed with water (2×50 mL) and dried with anhydrous sodium sulfate. After filtration, the solvent is eliminated under vacuum. Calculate the yield of the reaction. The compound can be purified by column chromatography (eluent EtOAc:Hexane 1:1). [Aqueous waste, disposed with basic waste. Organic solvent in non-halogenated organic waste]

3.- Click reaction:



In a 100 mL round bottom flask the following reagents are added: alkyne (2.7 mmol), azide (2.7 mmol), sodium ascorbate (NaAsc) (0.27 mmol) and $CuSO_4 \cdot 5H_2O$ (0.135 mmol) dissolving the mixture in *t*BuOH:water (10:1, 20 mL). The reaction is stirred and heated under reflux for 15 min. Once at room temperature, water (30 mL) is added and the reaction crude extracted with EtOAc (2×40 mL). The organic phase is dried with anhydrous Na_2SO_4 , filtered and evaporated under vacuum. Calculate yield. The reaction progress can be monitored by TLC (EtOAc-Hexane 2:1) and UV lamp or potassium permanganate staining.

4.- One-pot method



(Alternative to protocol 2. + 3.): In a 100 mL round bottom flask the following reagents are added: 2.7 mmol of 2-bromoacetophenone, 2.7 mmol of sodium azide, 2.7 mmol of coumarin-alkyne, 0.27 mmol sodium ascorbate and 0.135 mmol of $CuSO_4 \cdot 5H_2O$, in a mixture *t*BuOH:water (10:1, 20 mL). After heating at reflux for 3h, and cooling down to room temperature, water (25 mL) is added and the crude extracted with EtOAc (2×50mL). The organic phase is dried with anhydrous Na_2SO_4 and after filtration the solvent is evaporated under vacuum. The compound can be purified by column chromatography (EtOAc:hexane 1:1→ EtOAc). [Aqueous phase is disposed with basic waste, organic solvent in non-halogenated residues].

Chemical	Mass	MW	mmol	Density	Vol	Purity
Resorcinol						
Ethyl acetoacetate						
Obtained						
Yield						

Spectroscopic Characterization

Figure S1: ¹H-NMR compound **3** in CDCl₃: (aromatic region zoomed below)

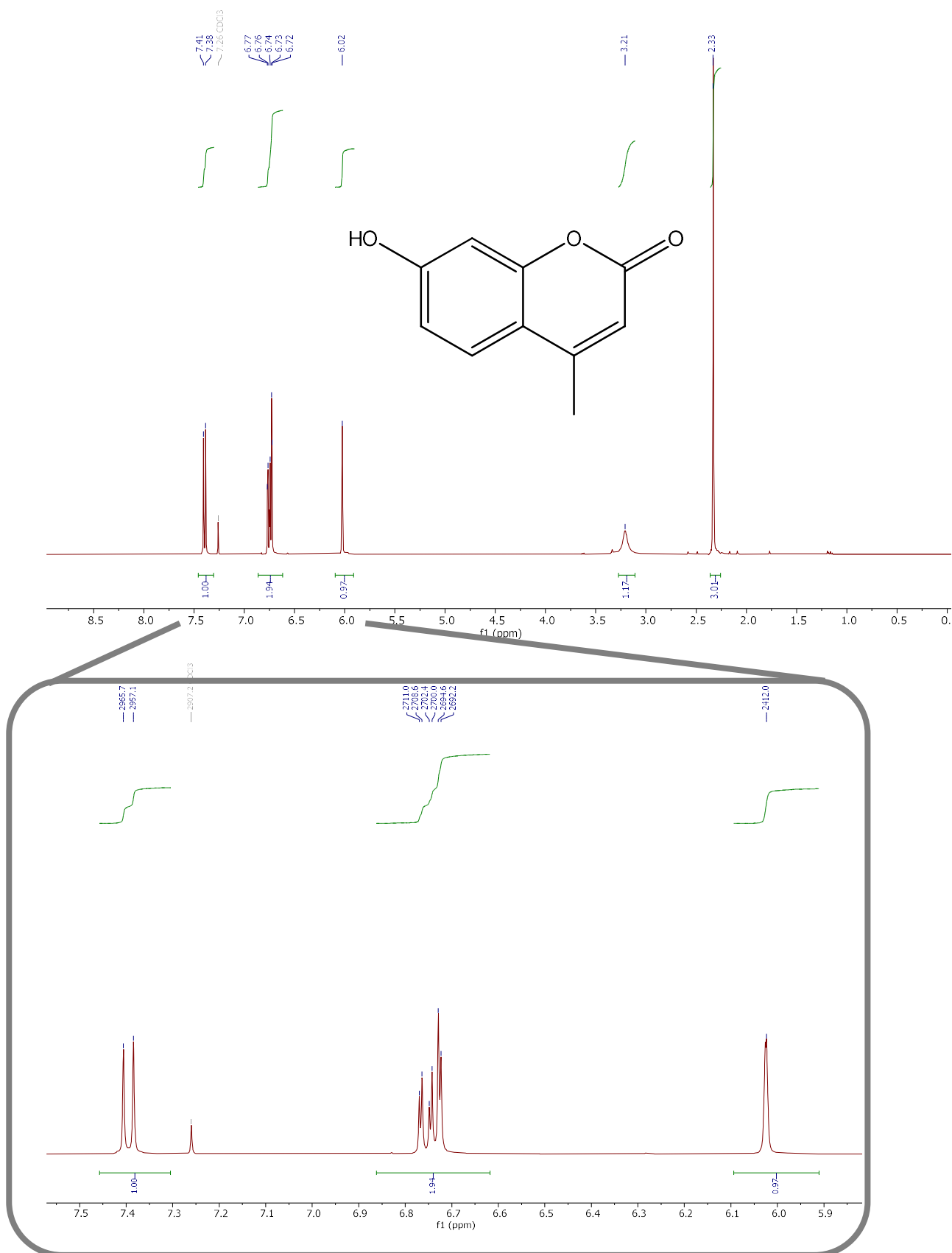


Figure S2: ^{13}C -NMR compound **3** in CDCl_3 :



Figure S3: IR spectrum compound **3**:

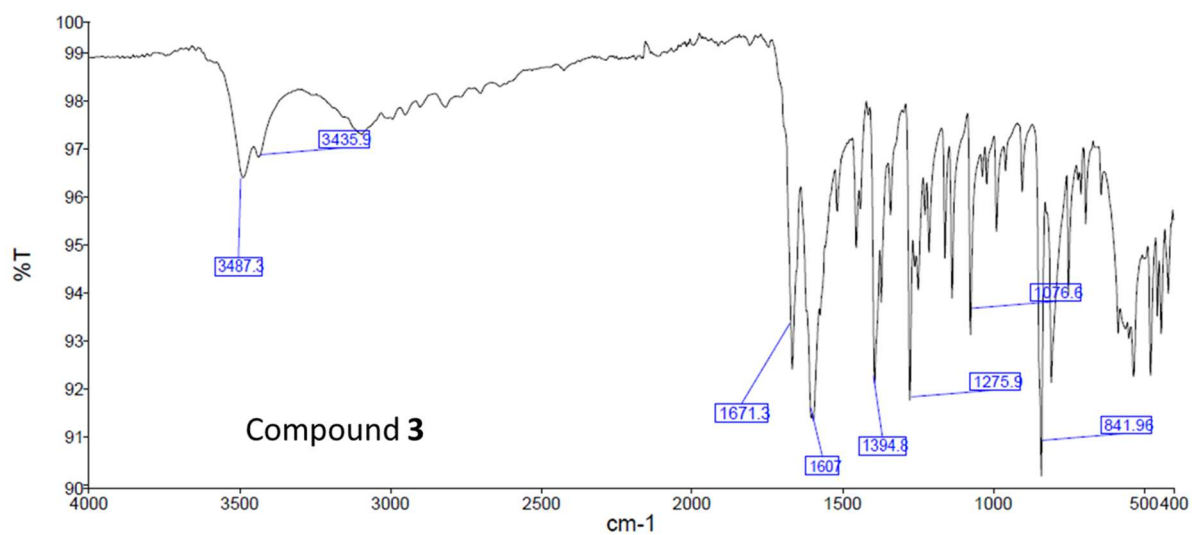


Figure S4: ¹H-NMR compound **5** in CDCl₃: (signals zoomed below)

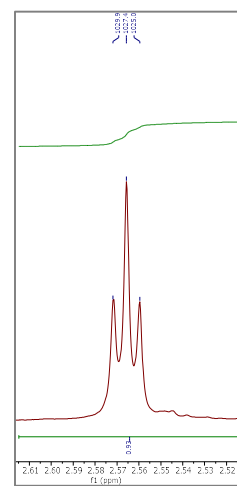
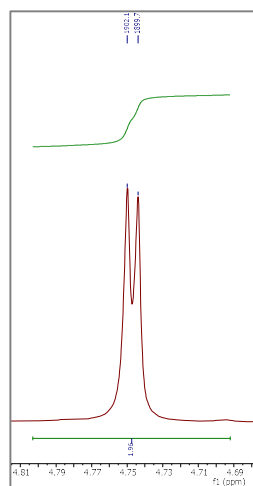
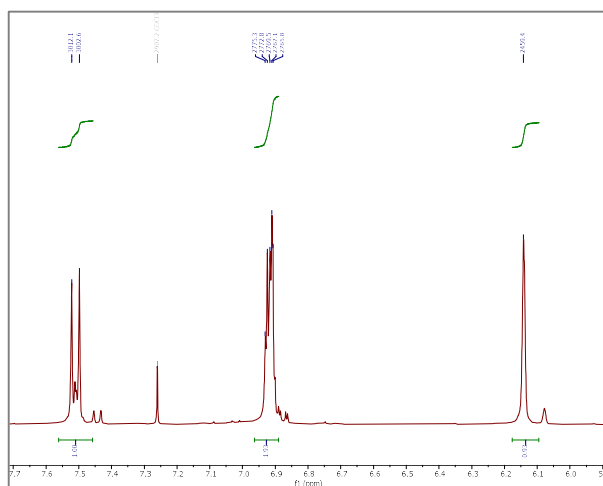
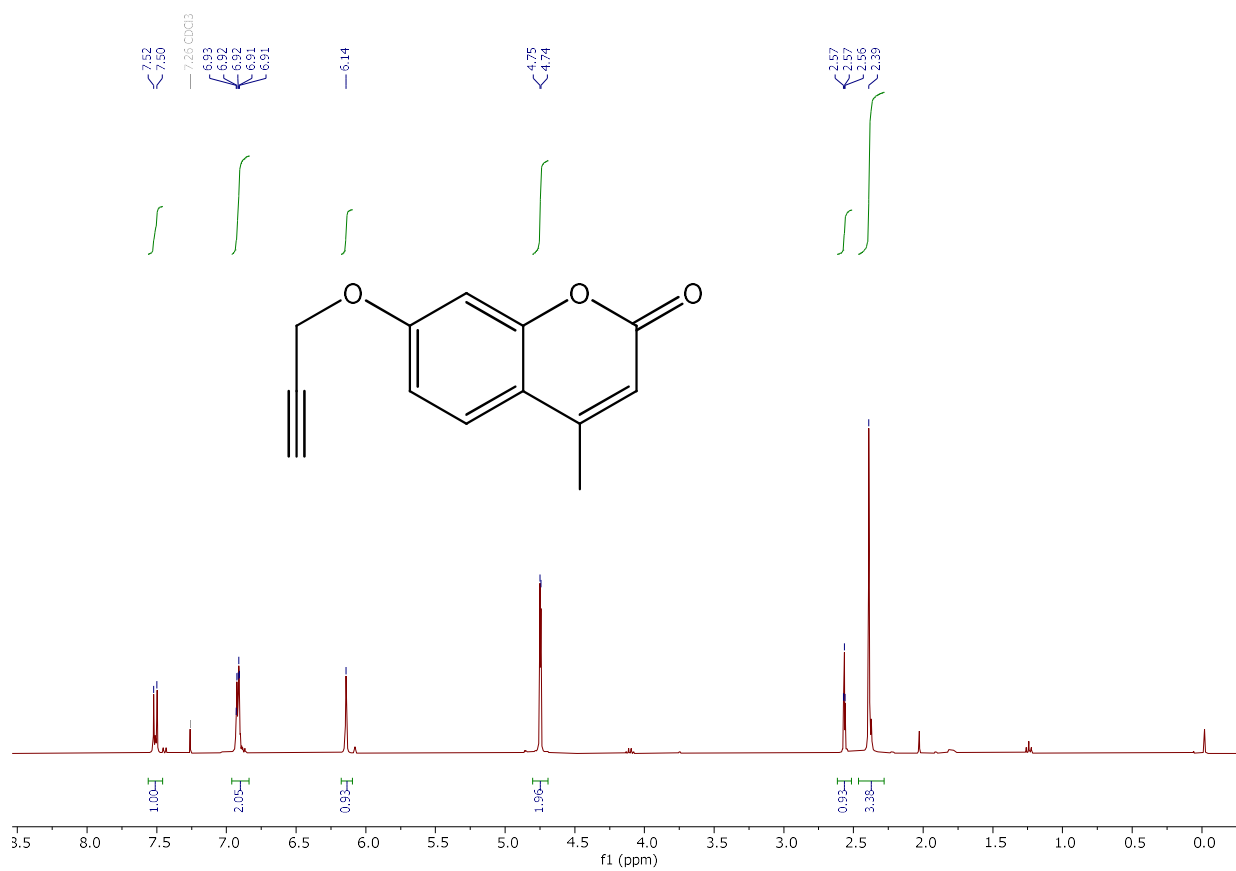


Figure S5: ^{13}C - NMR compound **5** in CDCl_3 :

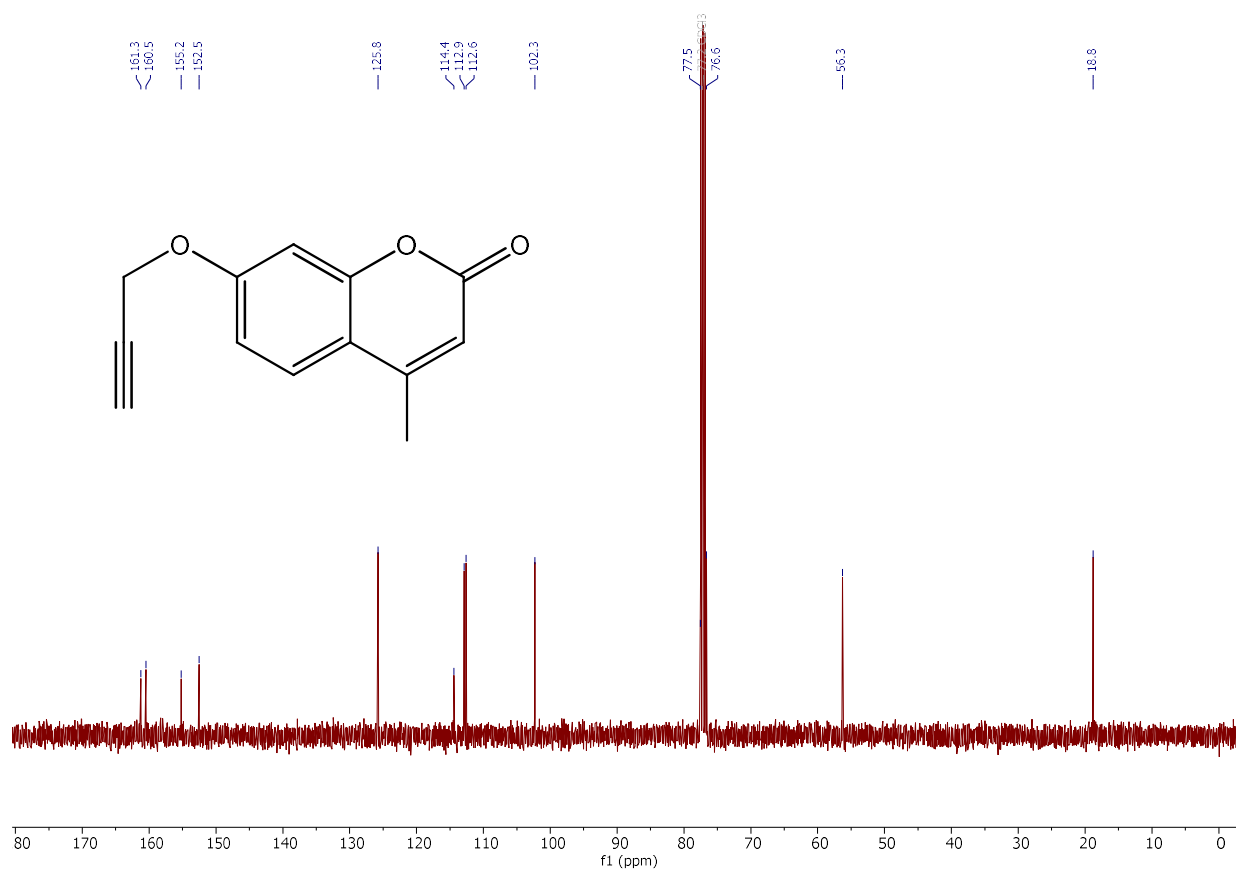


Figure S6: HSQC compound **5** in CDCl₃:

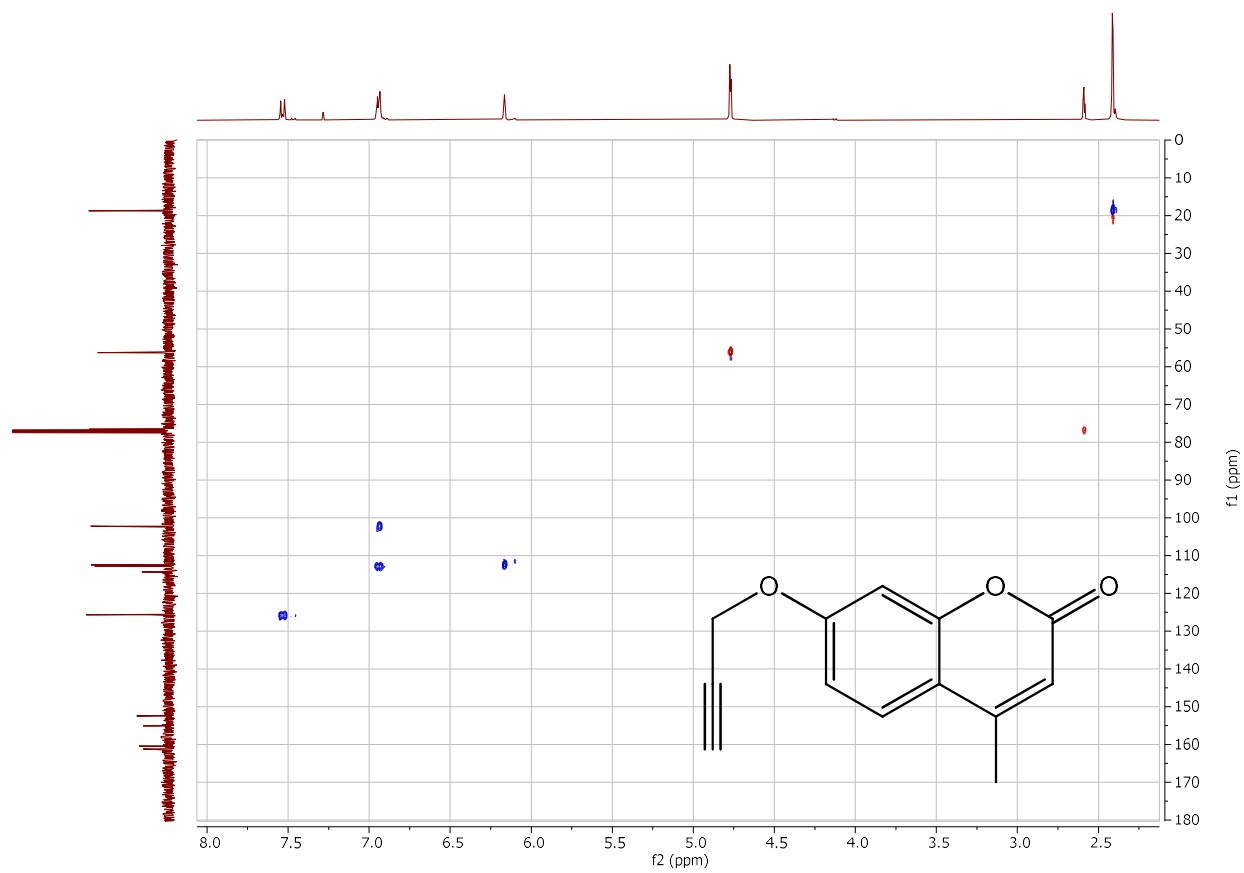


Figure S7: ¹H-NMR compound **7** in CDCl₃:

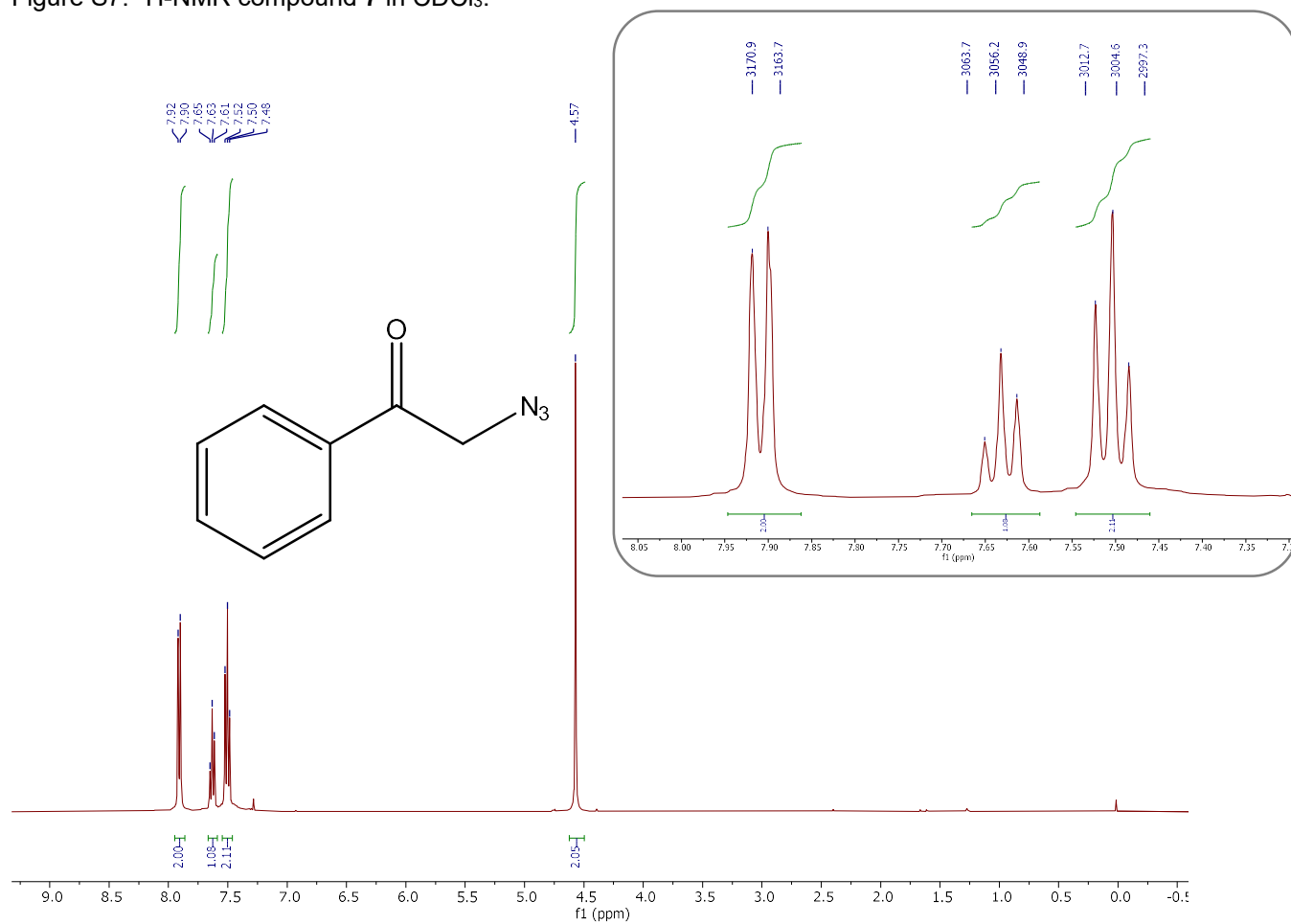


Figure S8: ^{13}C -NMR compound **7** in CDCl_3 :

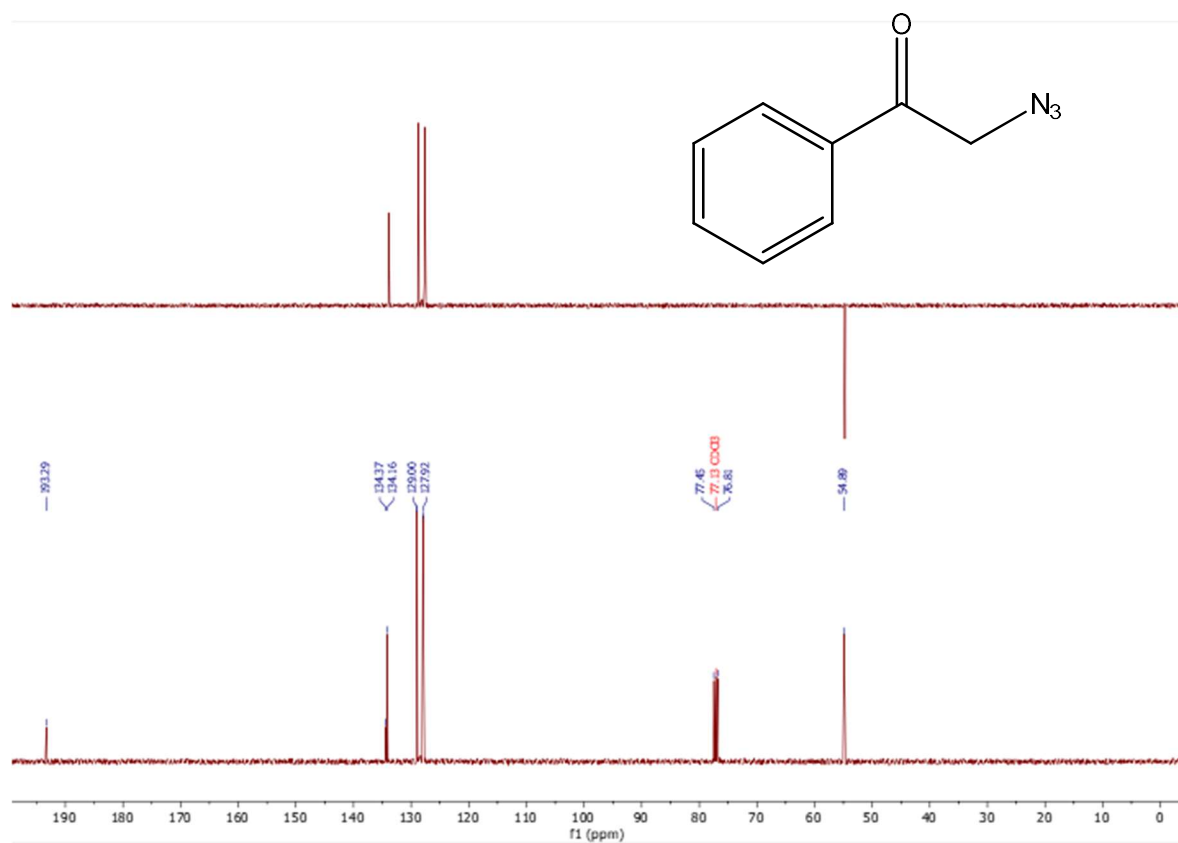


Figure S9: HSQC compound **7** in CDCl_3 :

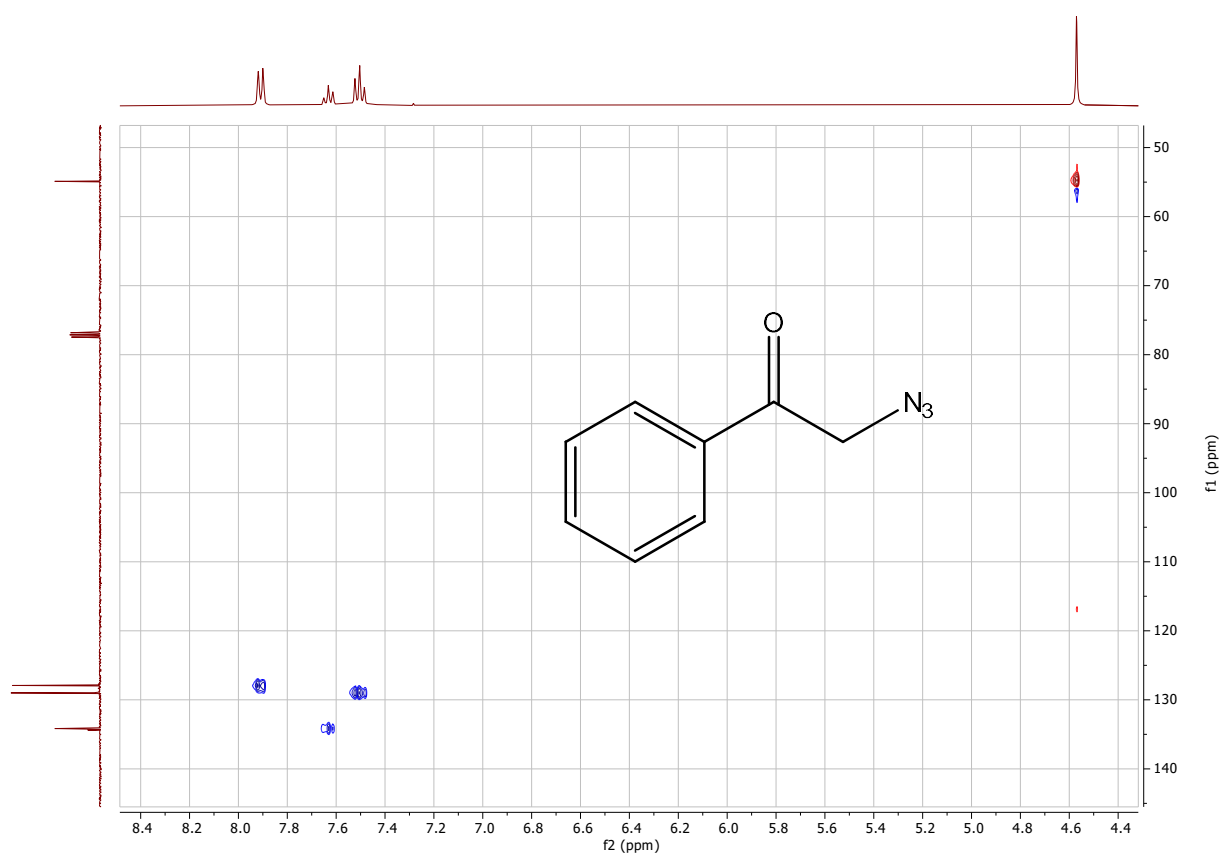


Figure S10: ¹H-NMR compound **8** in DMSO-d₆:

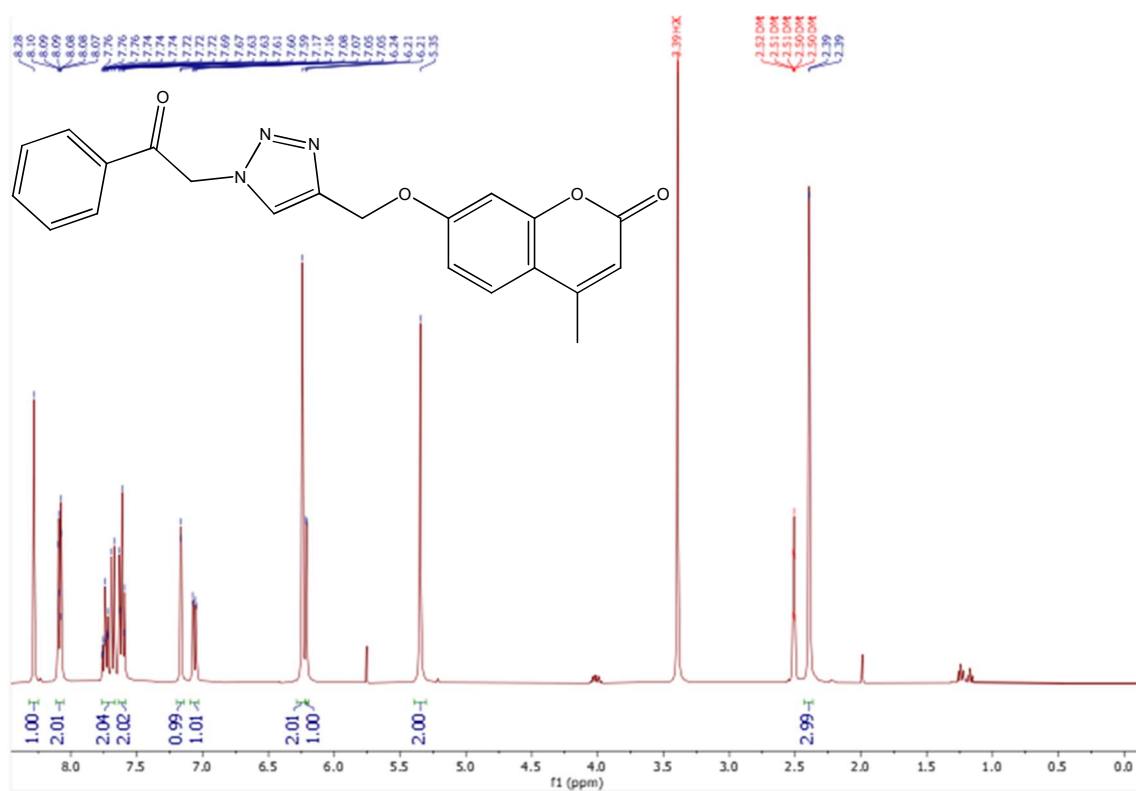


Figure S11: DEPT-135 and ¹³C-NMR compound **8** in DMSO-d₆:

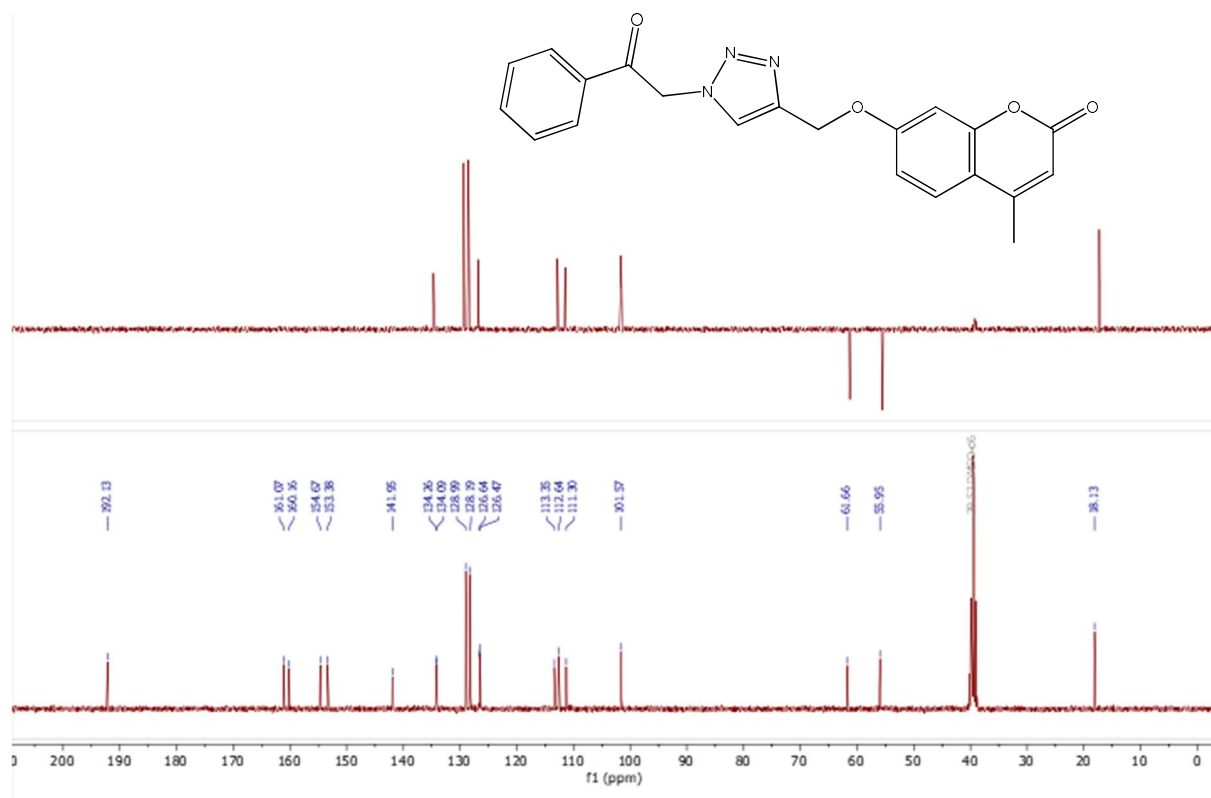


Figure S12: HSQC NMR compound **8** in DMSO-d₆:

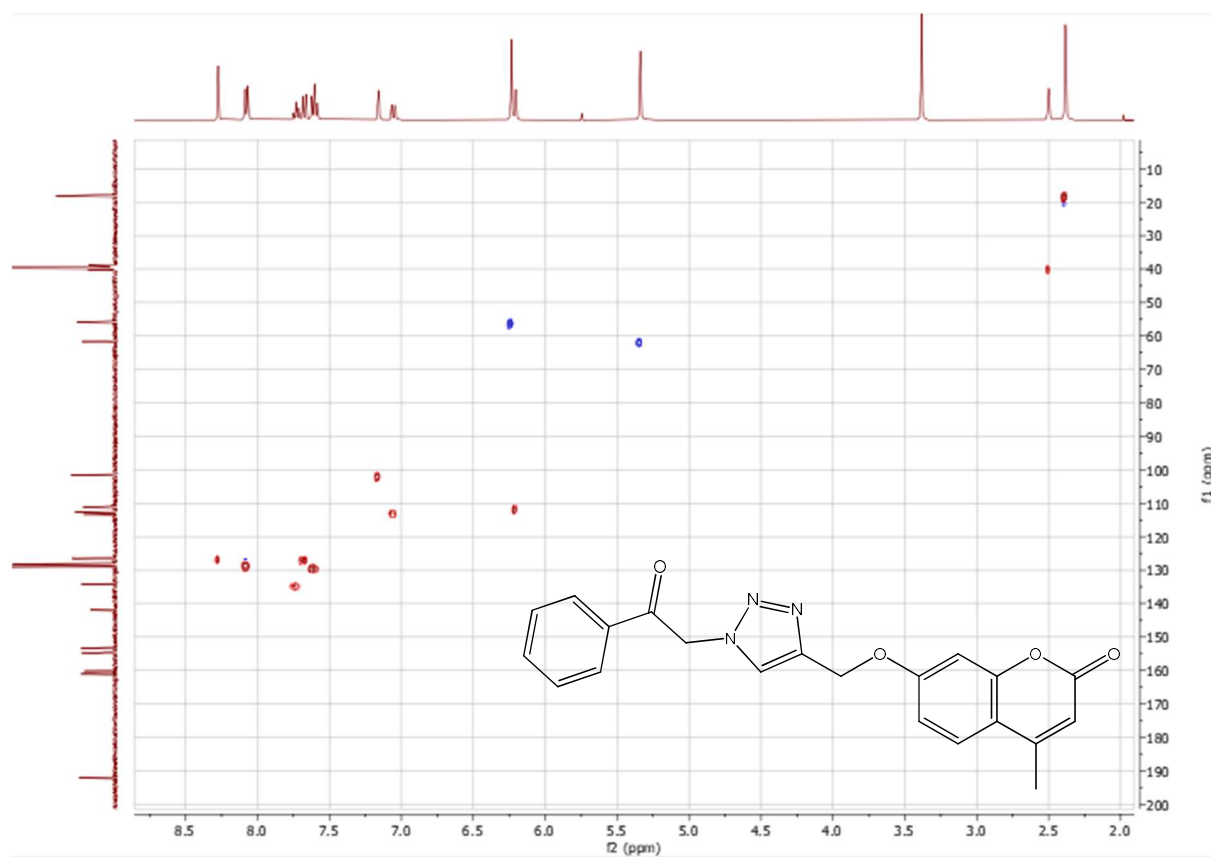


Figure S13: COSY NMR compound **8** in DMSO-d₆:

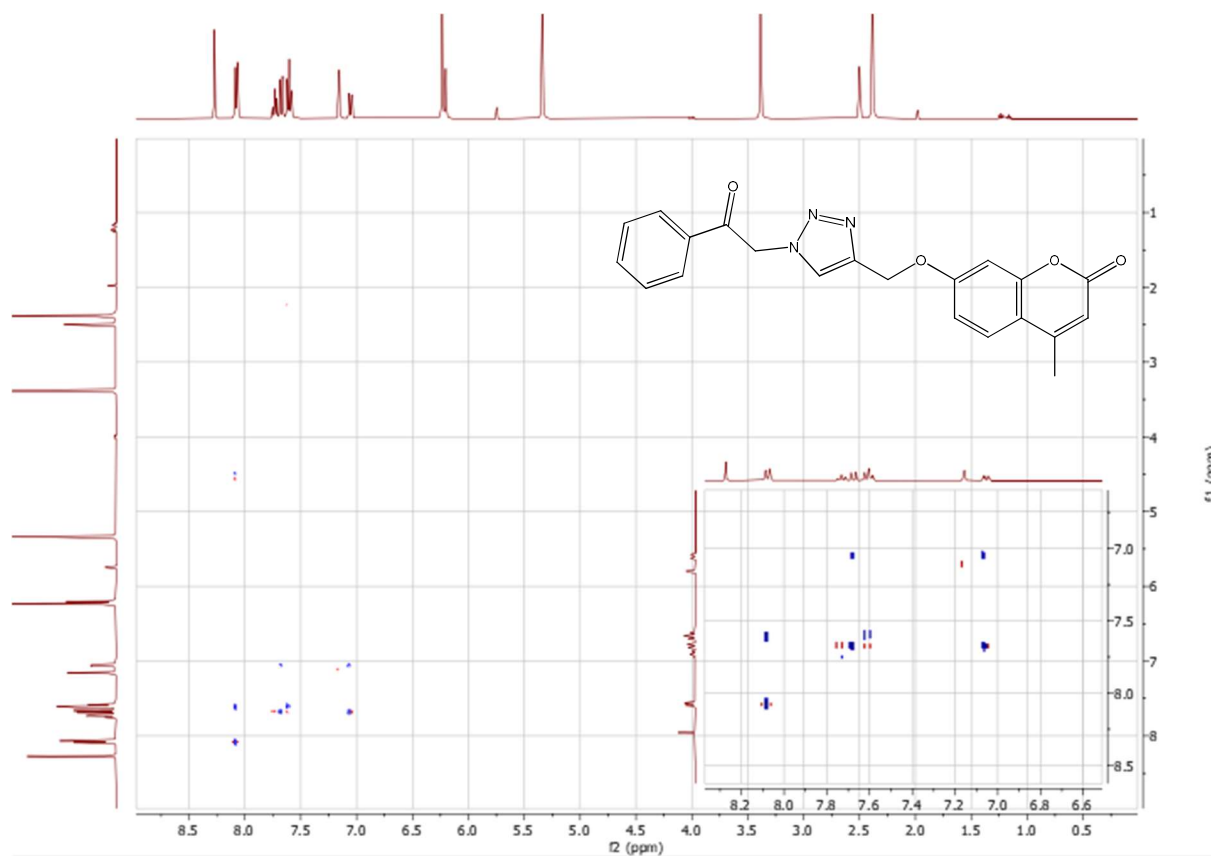


Figure S14: HRMS compound **5**

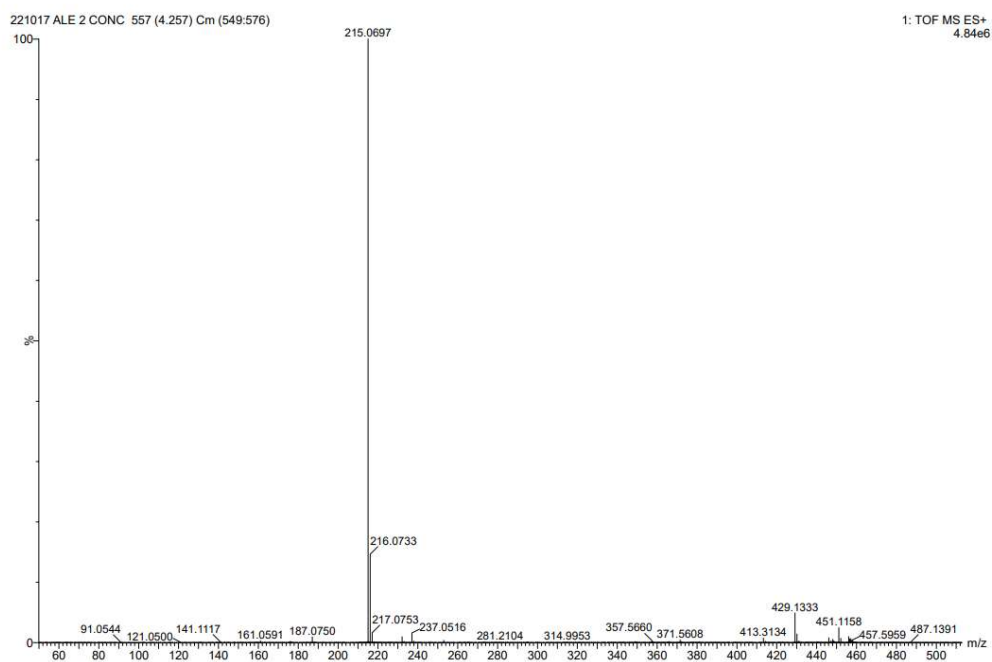


Figure S15: HRMS compound **8**

