






Supporting Information

Design and synthesis of novel *N*-benzylidene derivatives of 3-amino-4-imino-3,5-dihydro-4*H*-chromeno[2,3-*d*]pyrimidine under microwave, *in silico* ADME predictions, *in vitro* antitumoral activities and *in vivo* toxicity.

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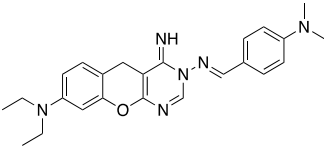
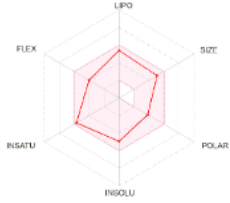
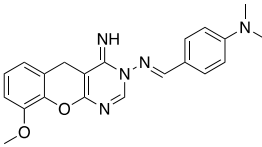

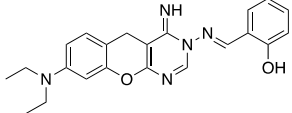
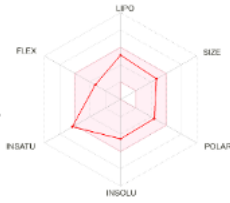
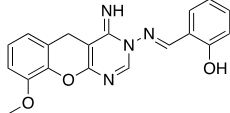

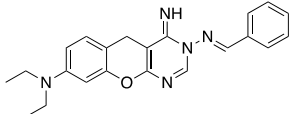

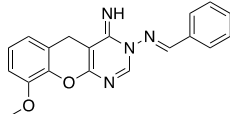

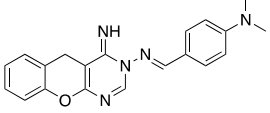

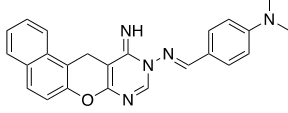
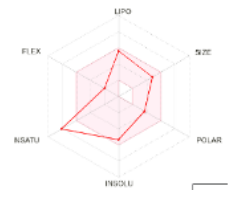
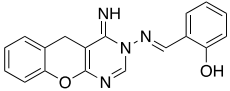

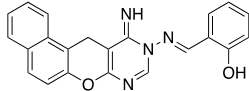

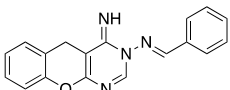

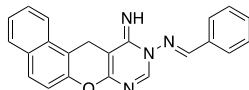

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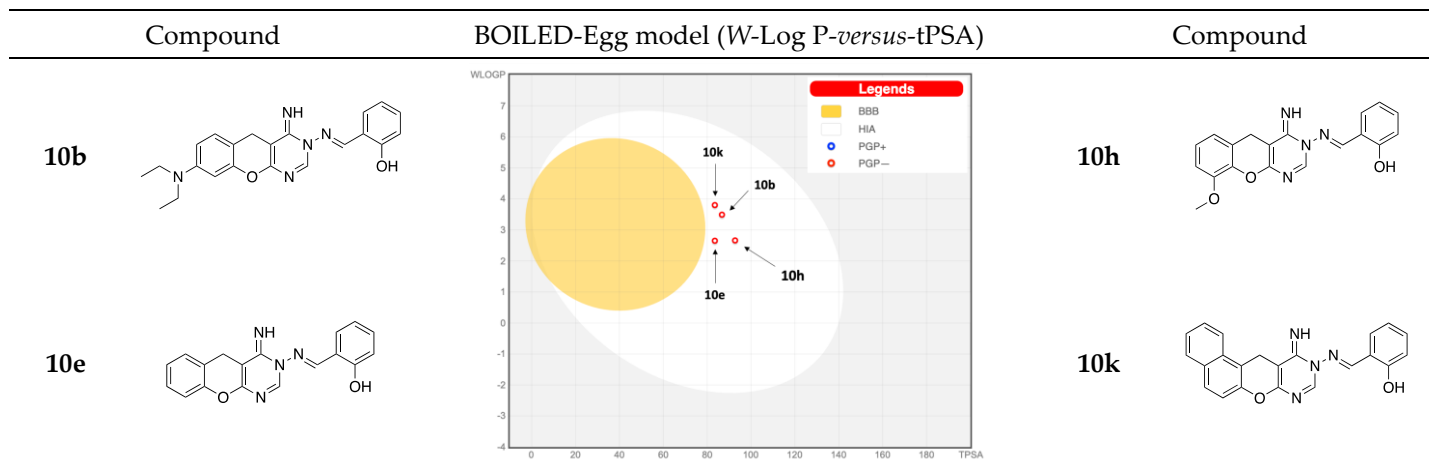
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Table S1: Bioavailability radar related to the physicochemical properties of compounds **10(a-l)** issued from SwissADME server [1-2]. The pink colored zone is the suitable physicochemical space for oral bioavailability. LIPO (Lipophilicity): $-0.7 < \text{Log } P < +5.0$; SIZE: $150 \text{ g/mol} < \text{MW} < 500 \text{ g/mol}$; POLAR (Polarity): $20 \text{ \AA}^2 < t\text{PSA} < 130 \text{ \AA}^2$; INSOLU (Insolubility): $-6 < \text{Log } S < 0$; INSATU (Insaturation): $0.25 < \text{Fraction } C_{sp^3} < 1$; FLEX (Flexibility): $0 < \text{Number rotatable bonds} < 9$.

Compound	Bioavailability radar ^a	Compound	Bioavailability radar ^a
10a 		10g 	
10b 		10h 	
10c 		10i 	
10d 		10j 	
10e 		10k 	
10f 		10l 	

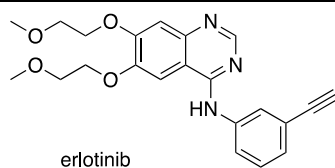
^a %Abs: 55 for all compounds **10(a-l)**.

Figure S1: BOILED-Egg model of compounds **10b**, **10e**, **10h** and **10k** (bearing a hydroxyl group, for comparison ^a) to predict gastrointestinal absorption (HIA-human gastrointestinal absorption) and BBB penetration in function of the position of the molecules in the *W-Log P-versus-tPSA* referential. The “white region” is for high probability of passive absorption by the gastrointestinal tract, and the “yellow region” (yolk) is for high probability of brain penetration. Yolk and white areas are not mutually exclusive. The “gray region” concerned compounds which are predicted not absorbed in gastrointestinal tract and not BBB permeant. PGP⁺ in blue color means substrate of P-glycoprotein; PGP⁻ in red color means non-substrate of P-glycoprotein, issued from SwissADME server [1-2].



^a Compounds **10b**, **10e**, **10h** and **10k** are not predicted to passive BBB penetration and are not effluxed by P-glycoprotein (PGP⁻, red color).

Figure S2: Images ^a of toxicity assays with erlotinib on Zebrafish *danio rerio* eleutheroembryos (according to Fish Embryo Acute Toxicity (FET) Test, OCDE (2013) [3]).



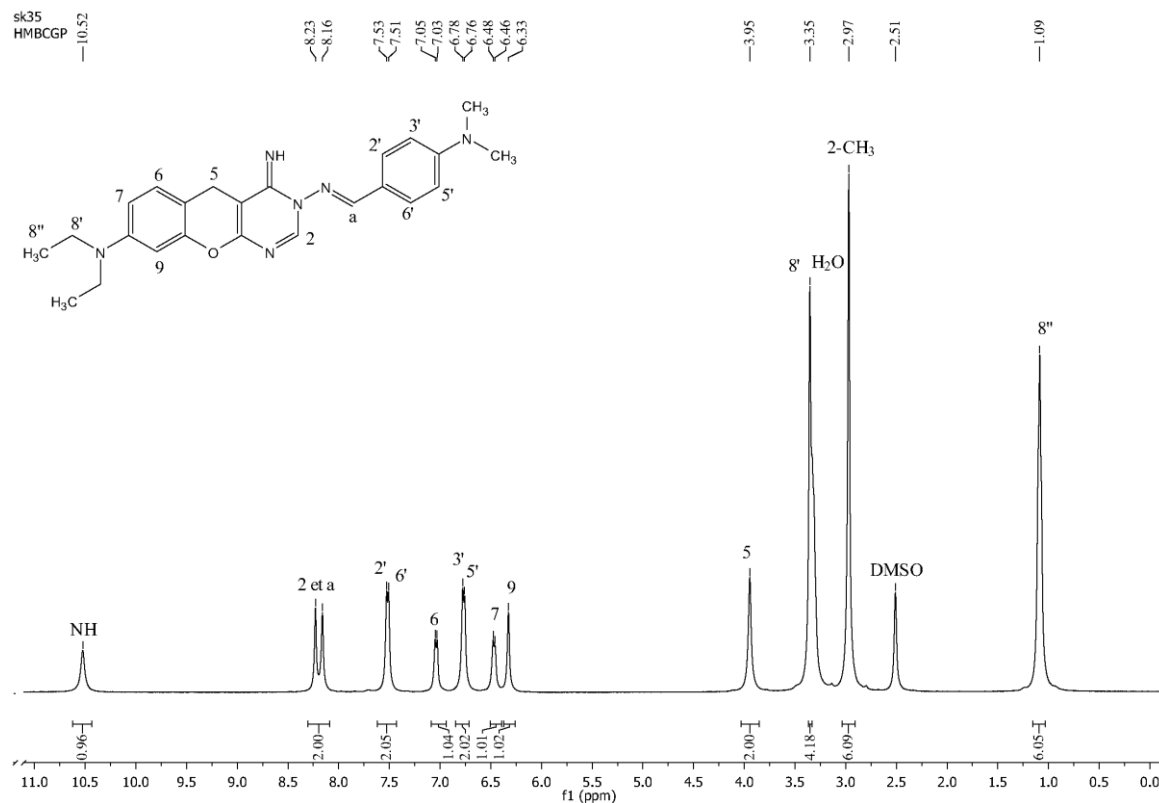
Dose of erlotinib (μM)	0 hpf	24 hpf	48 hpf	72 hpf	Dose of erlotinib (μM)	0 hpf	24 hpf	48 hpf	72 hpf
3					0.03				
1					0.01				
0.33					No treatment				
0.11									

^a magnification: 2.5x

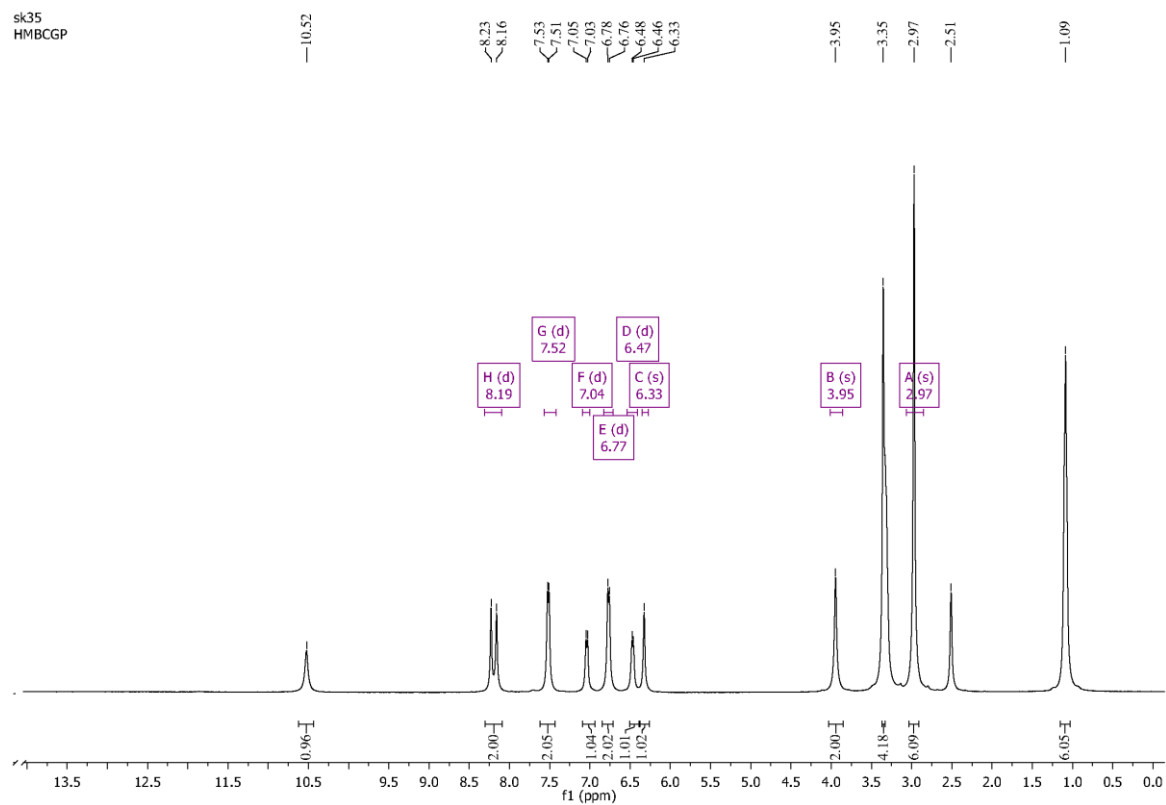
References:

1. Daina, A.; Michielin, O.; Zoete, V. SwissADME: a free web tool to. evaluate pharmacokinetics, druglikeness and medicinal chemistry friendliness of small molecules. *Nature Sc. Rep.* **2017**, *7*, 42717. doi: 10.1038/srep42717
2. Swiss ADME of Swiss Institute of Bioinformatics. Accessed 20 November 2023. <http://www.swissadme.ch/>
3. OECD. Test No. 236: Fish Embryo Acute Toxicity (FET) Test. OECD Guidelines for the testing of chemicals, Section 2. OECD Publishing: Paris, France, 2013.

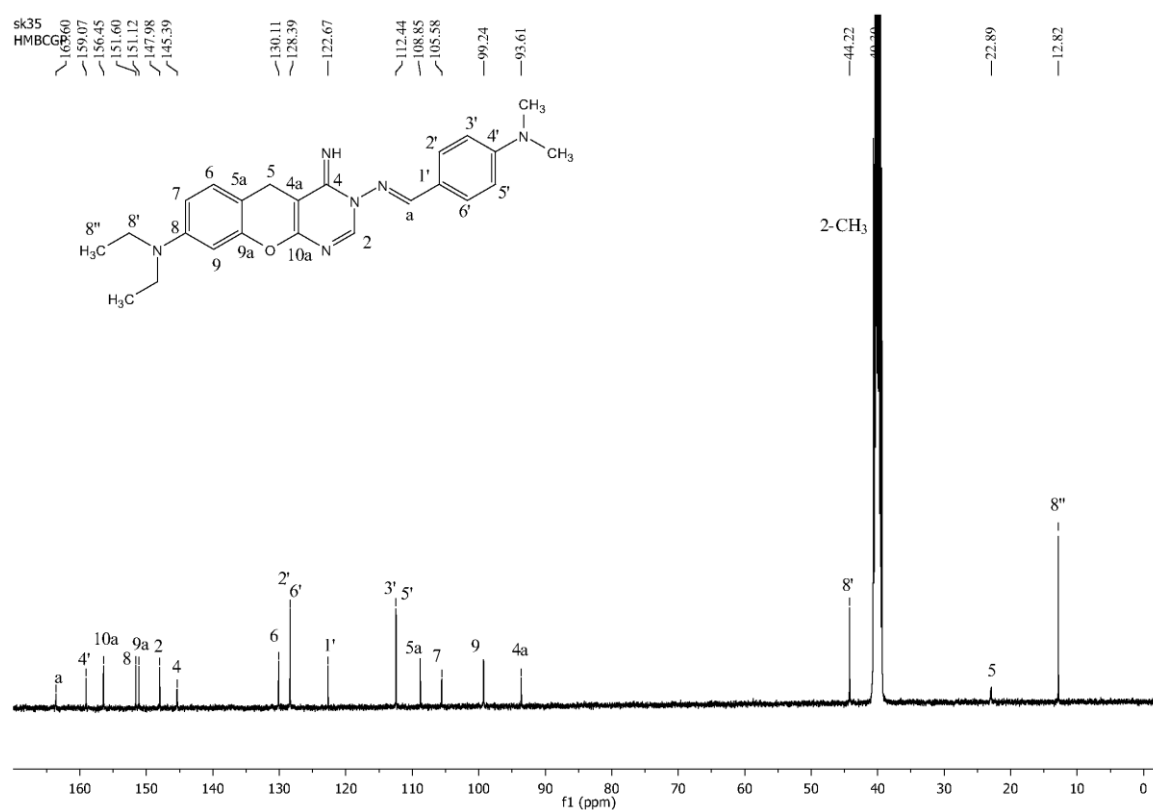
^1H NMR (300 MHz, $\text{DMSO-}d_6$) spectrum of compound (**10a**).



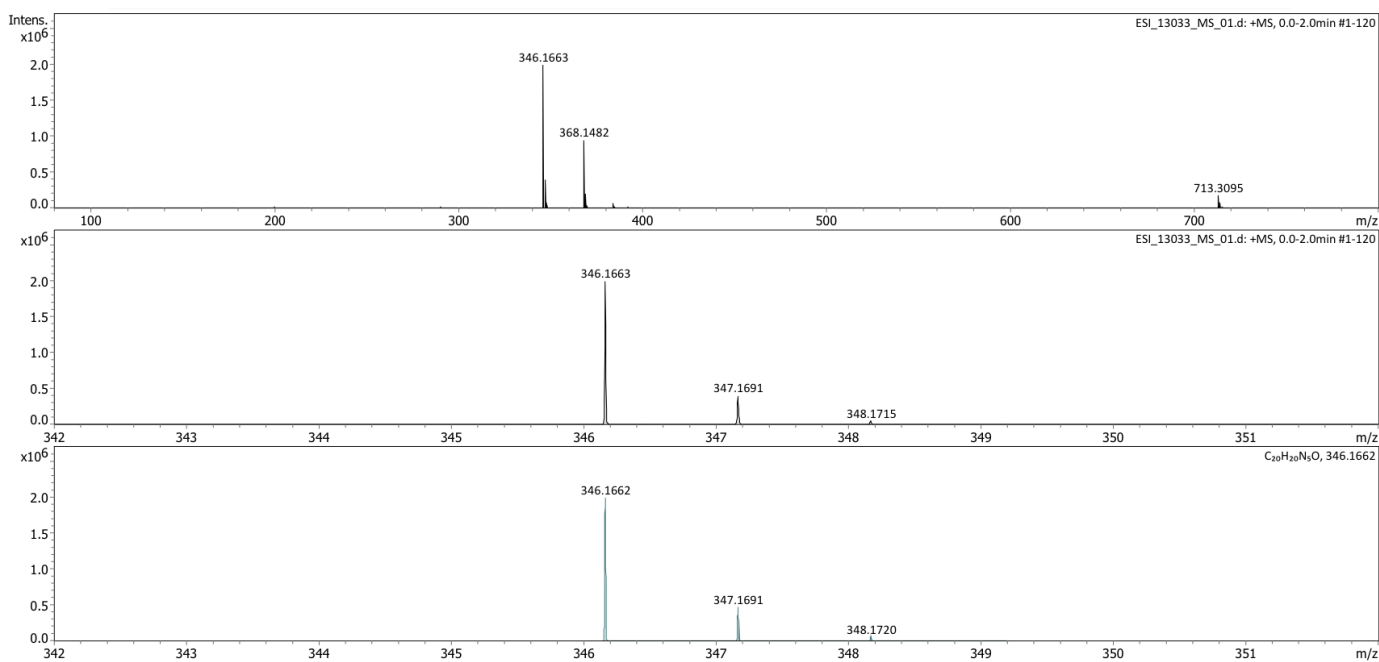
Details on the ^1H NMR (300 MHz, $\text{DMSO-}d_6$) spectrum of compound (**10a**).



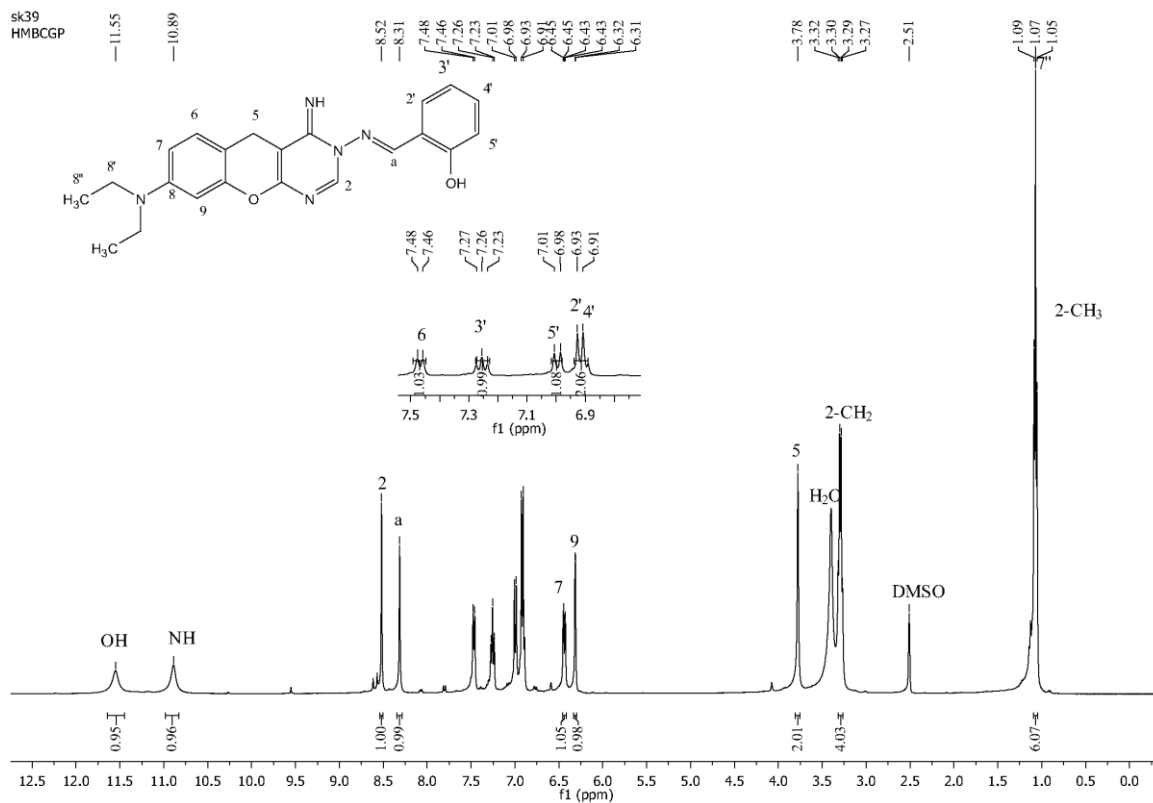
^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) spectrum of compound (10a).



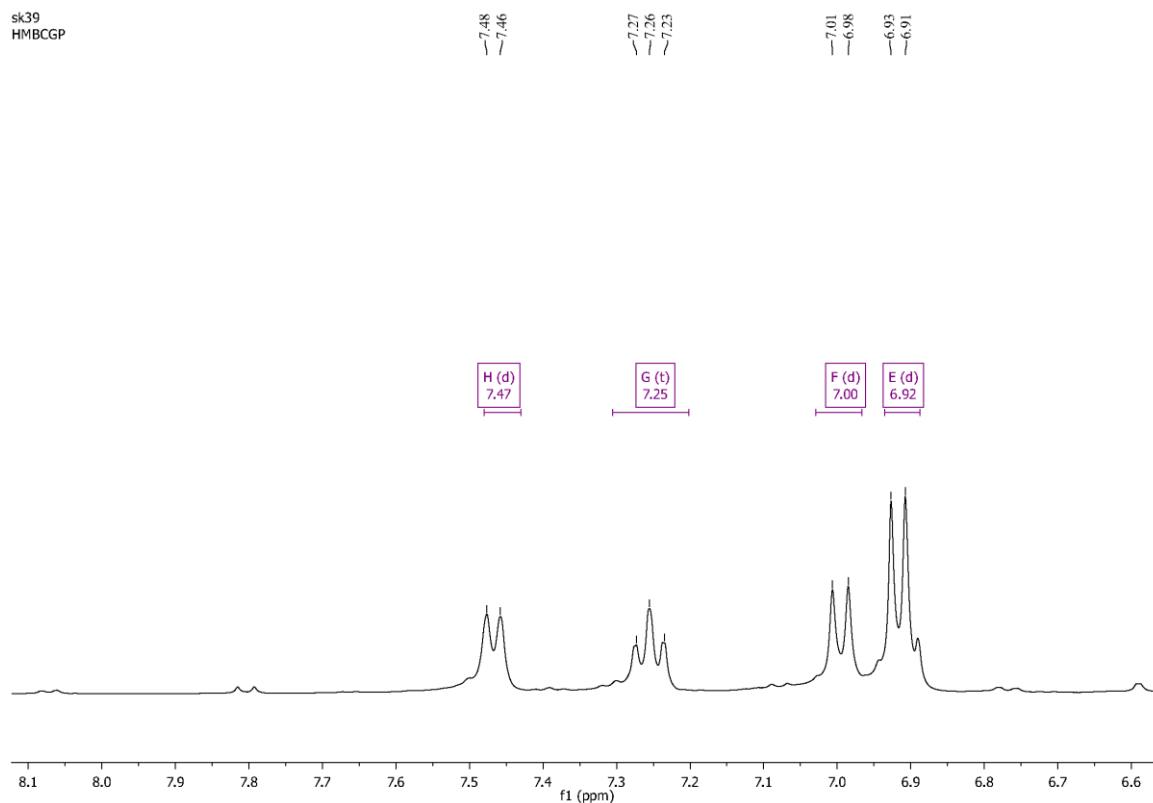
MS spectrum of compound (10a).



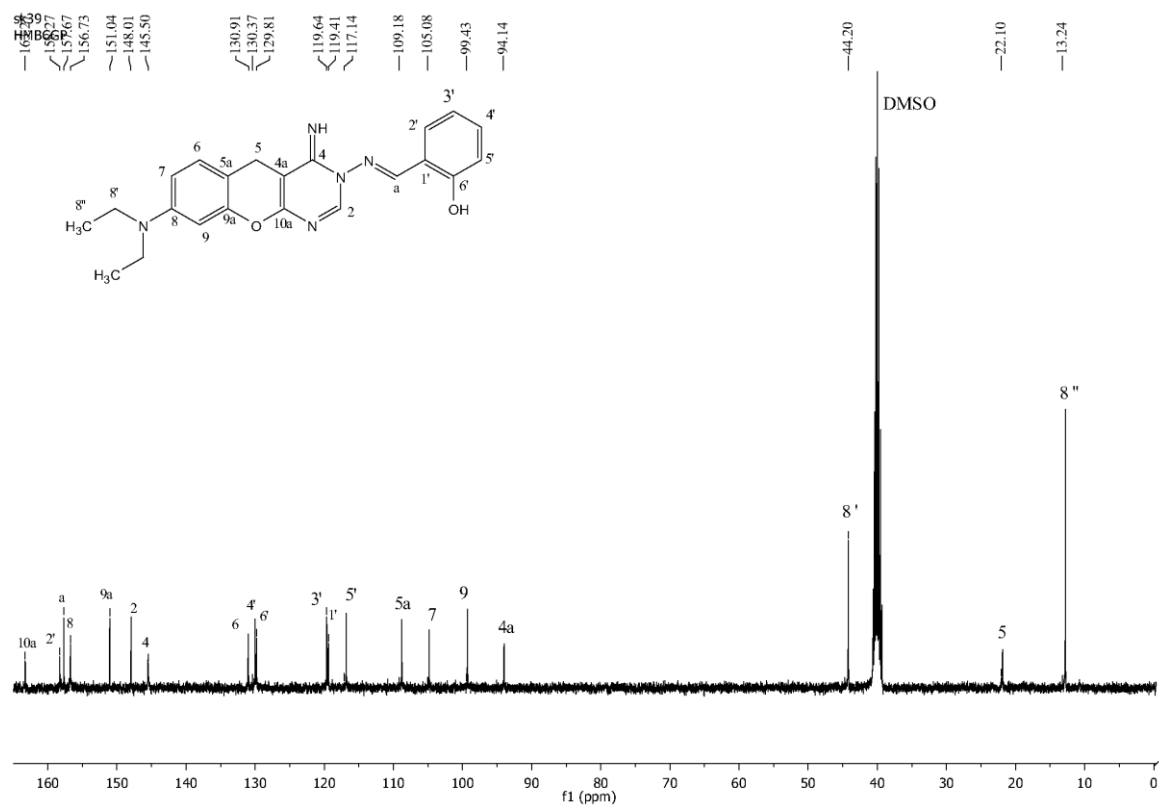
¹H NMR (300 MHz, DMSO-*d*₆) spectrum of compound (**10b**).



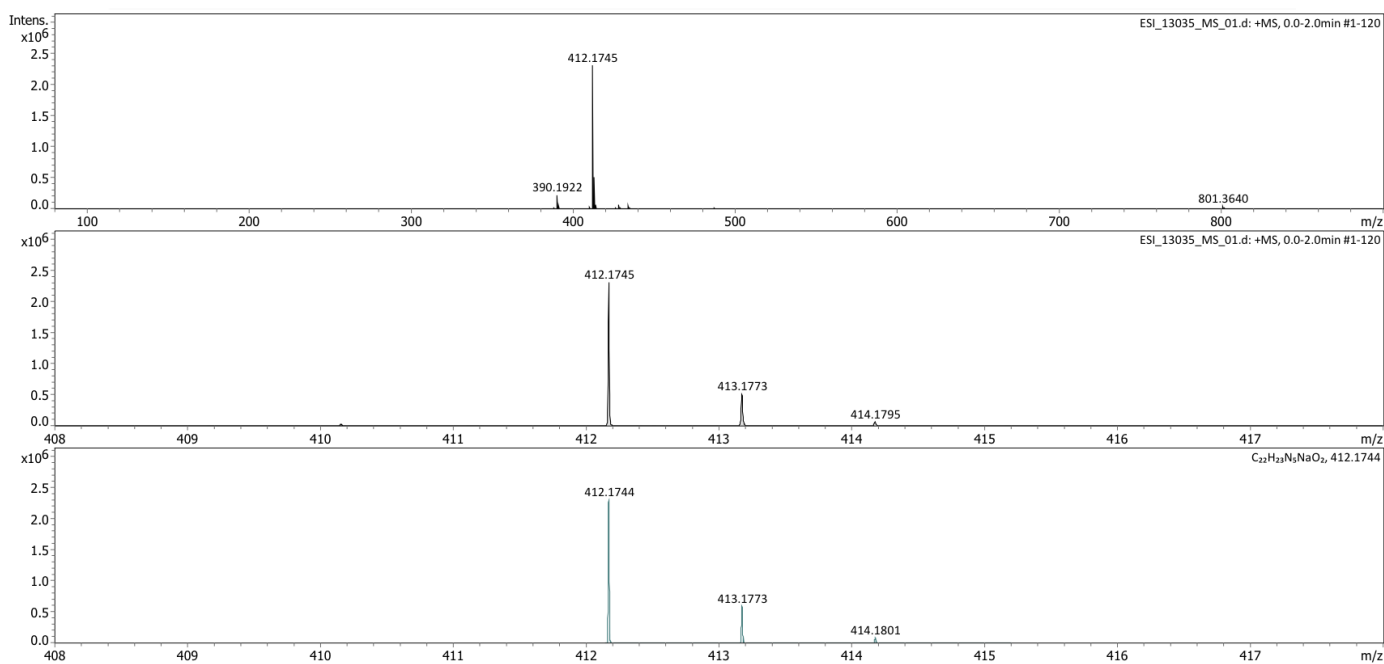
Details on the ^1H NMR (300 MHz, $\text{DMSO-}d_6$) spectrum of compound (**10b**).



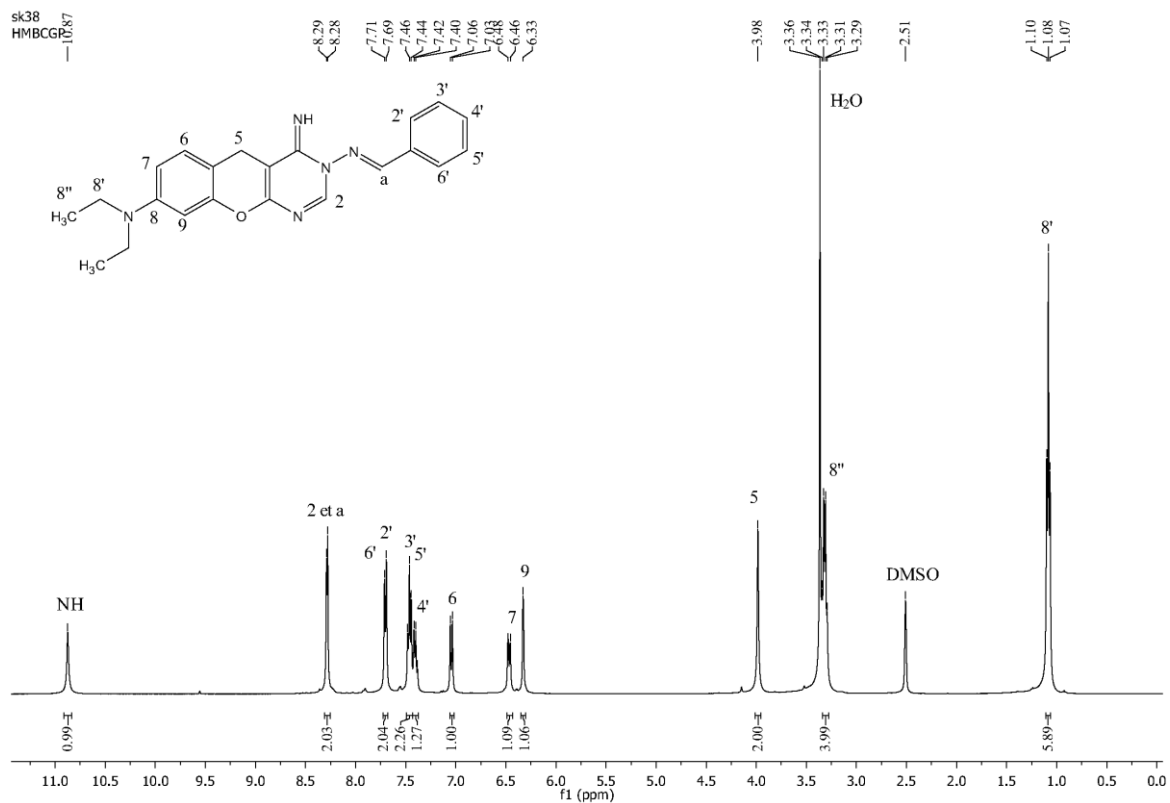
^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10b**).



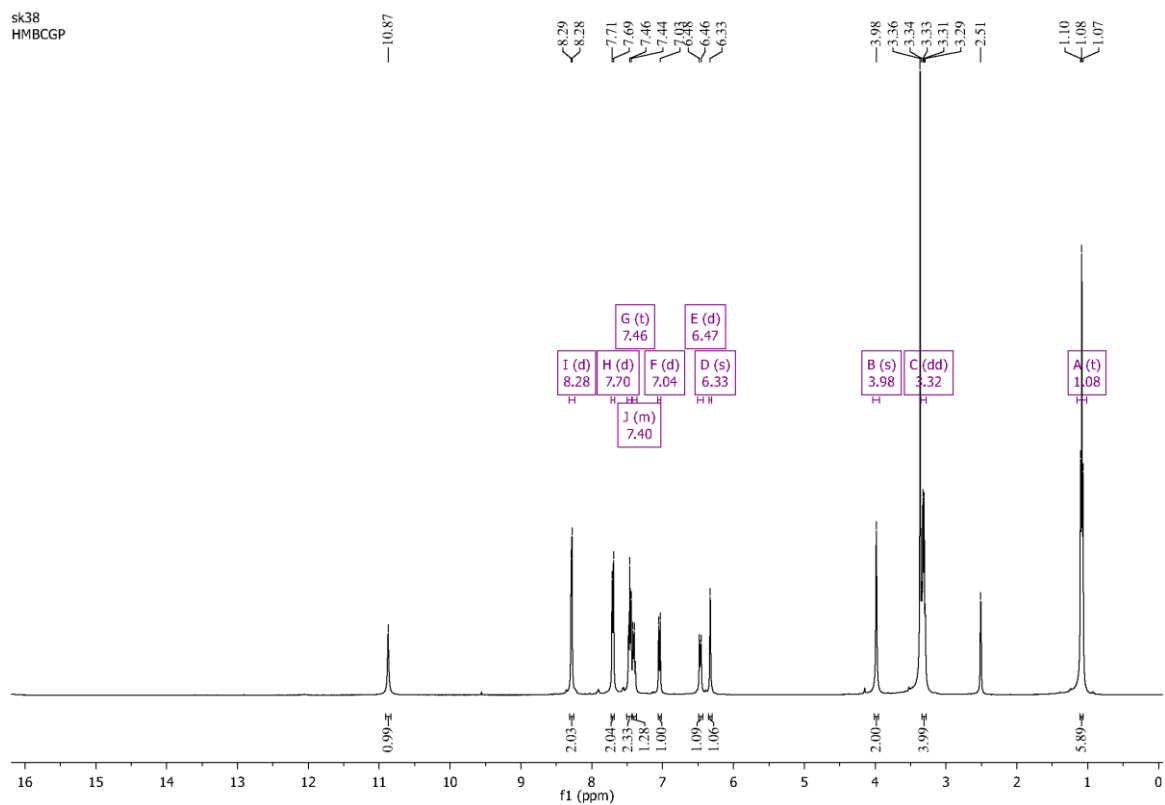
MS spectrum of compound (**10b**).



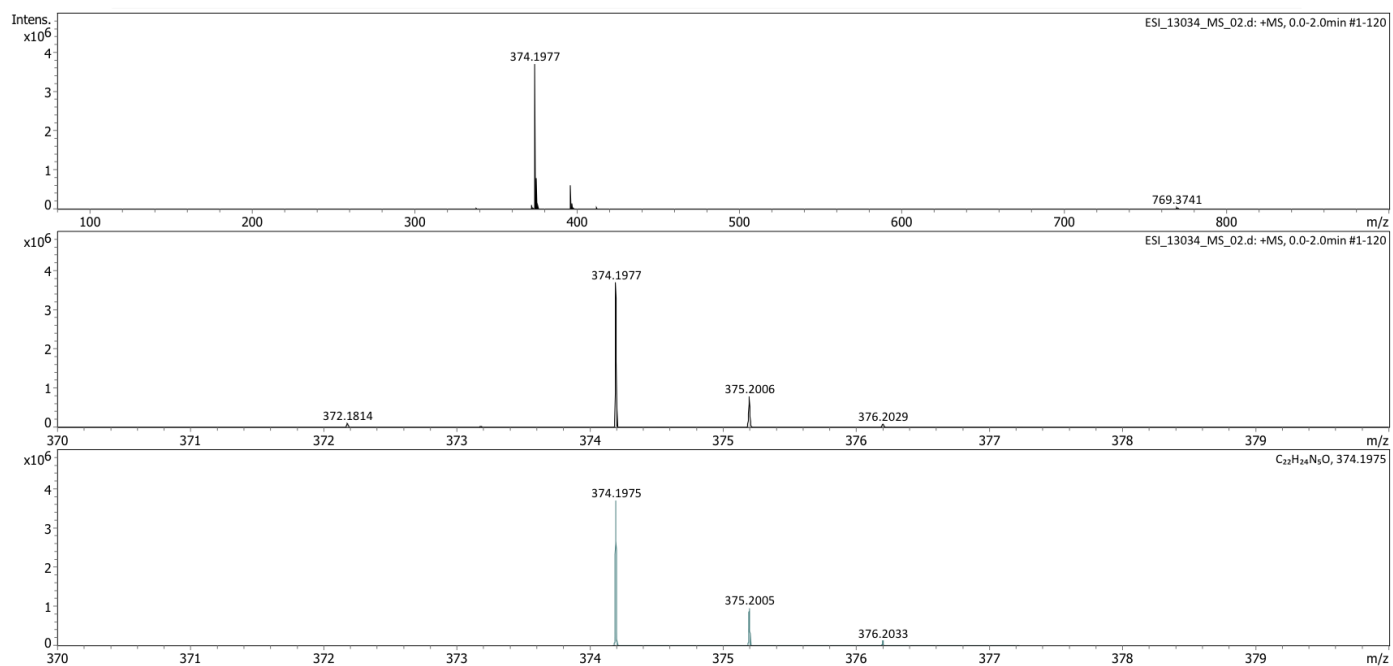
^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10c**).



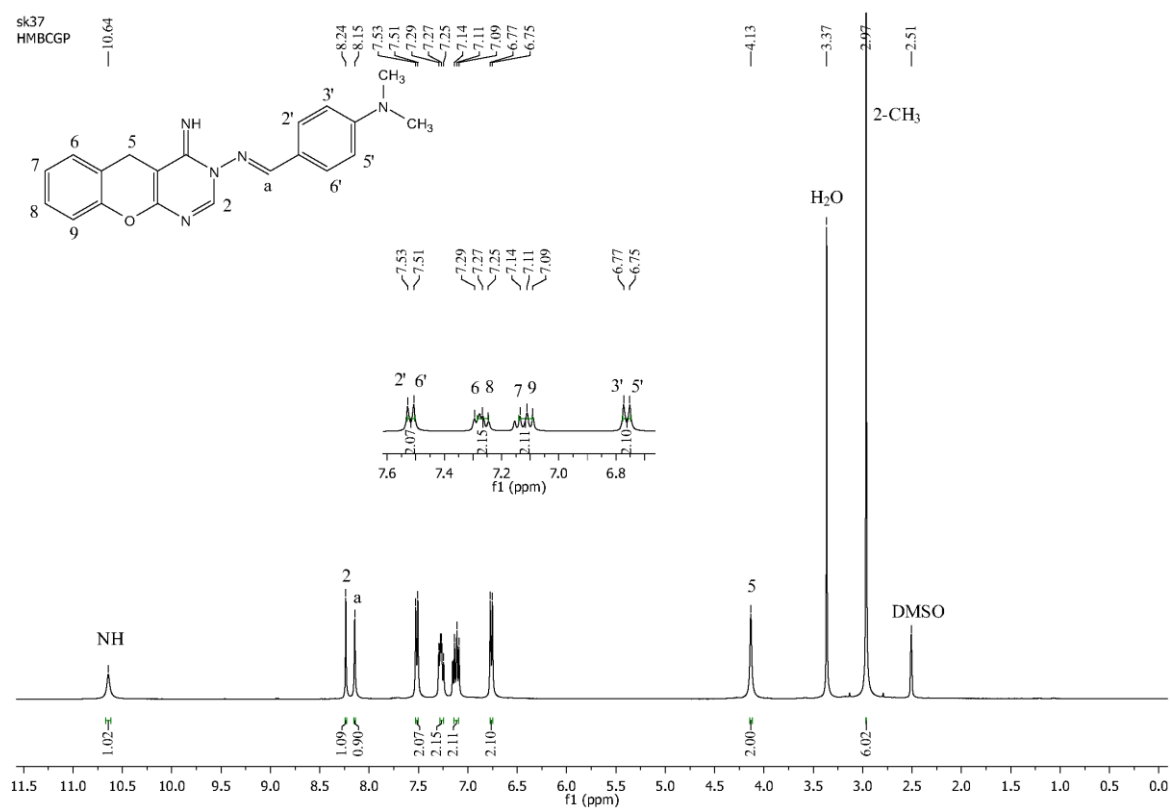
Details on the ^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10c**).



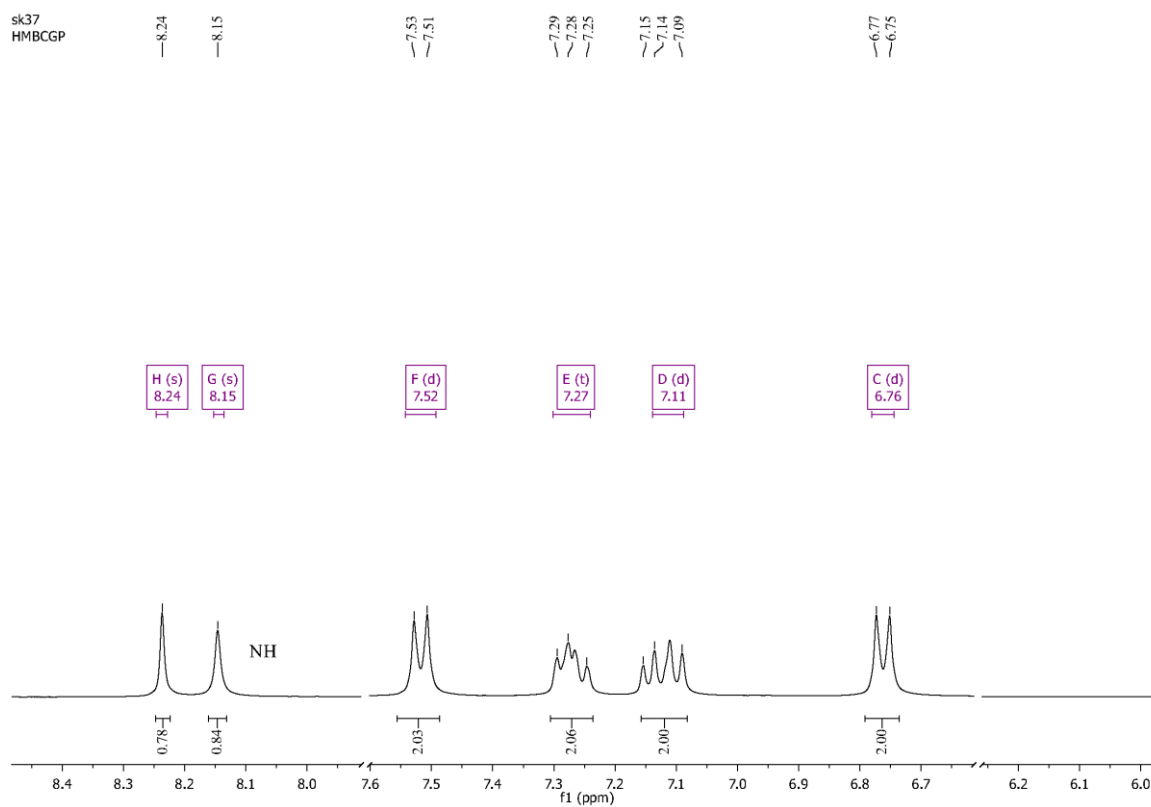
MS spectrum of compound (10c).



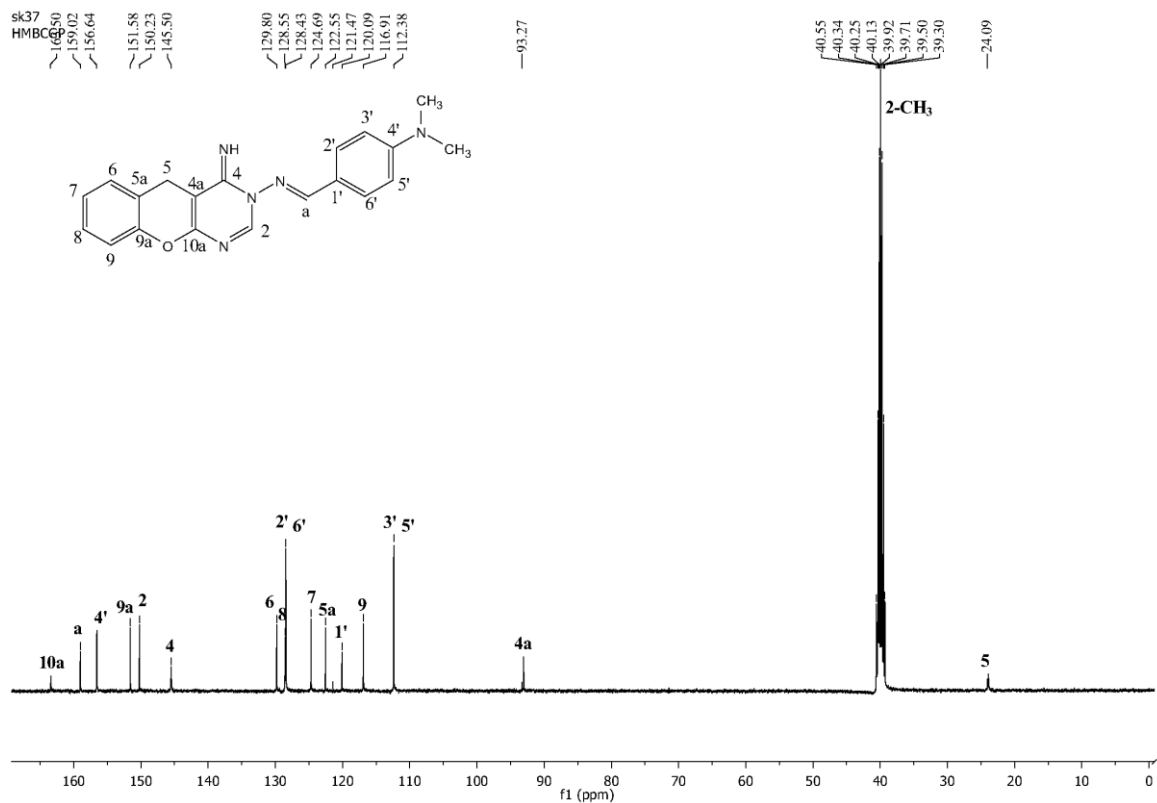
^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10d**).



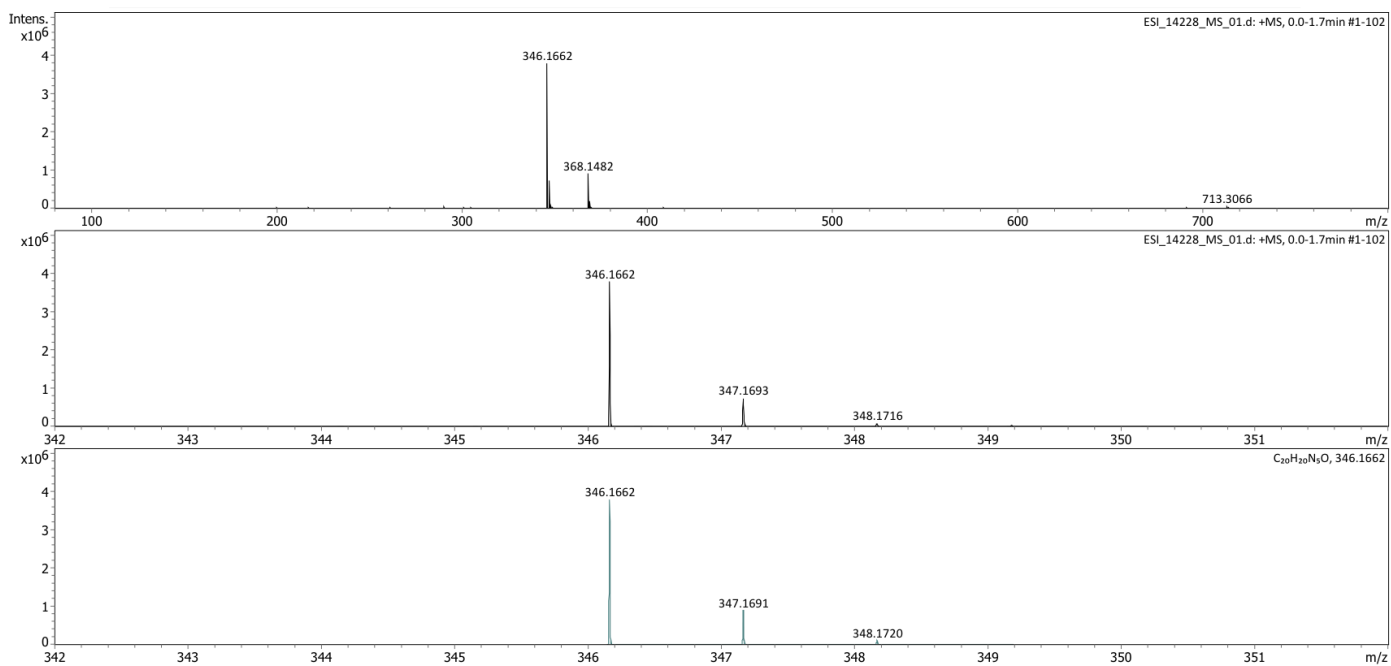
Details on the ^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10d**).



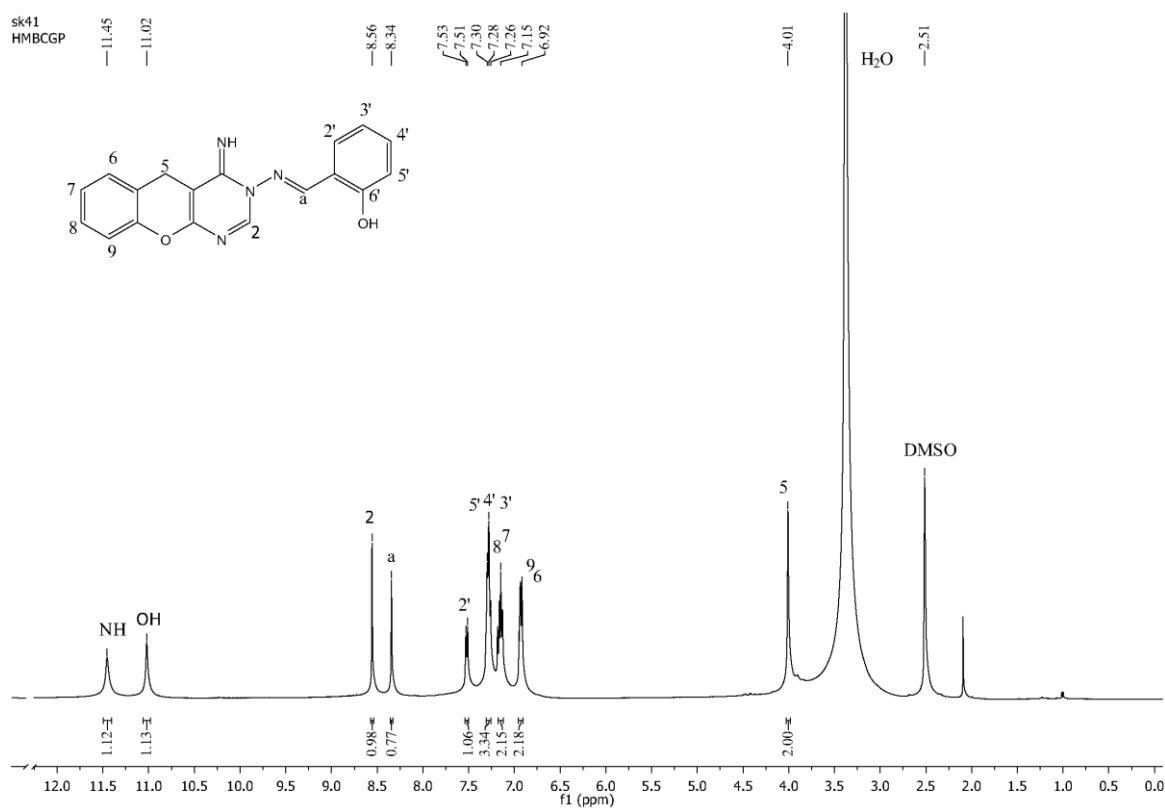
^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10d**).



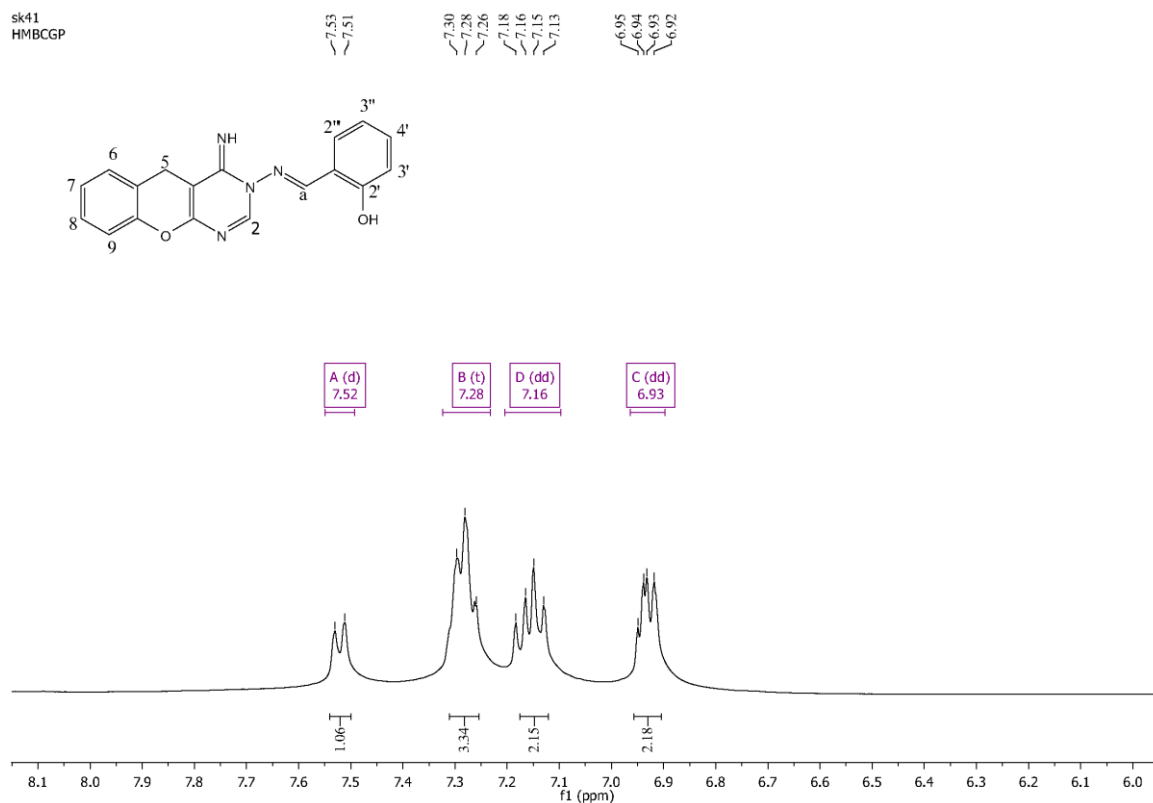
MS spectrum of compound (**10d**).



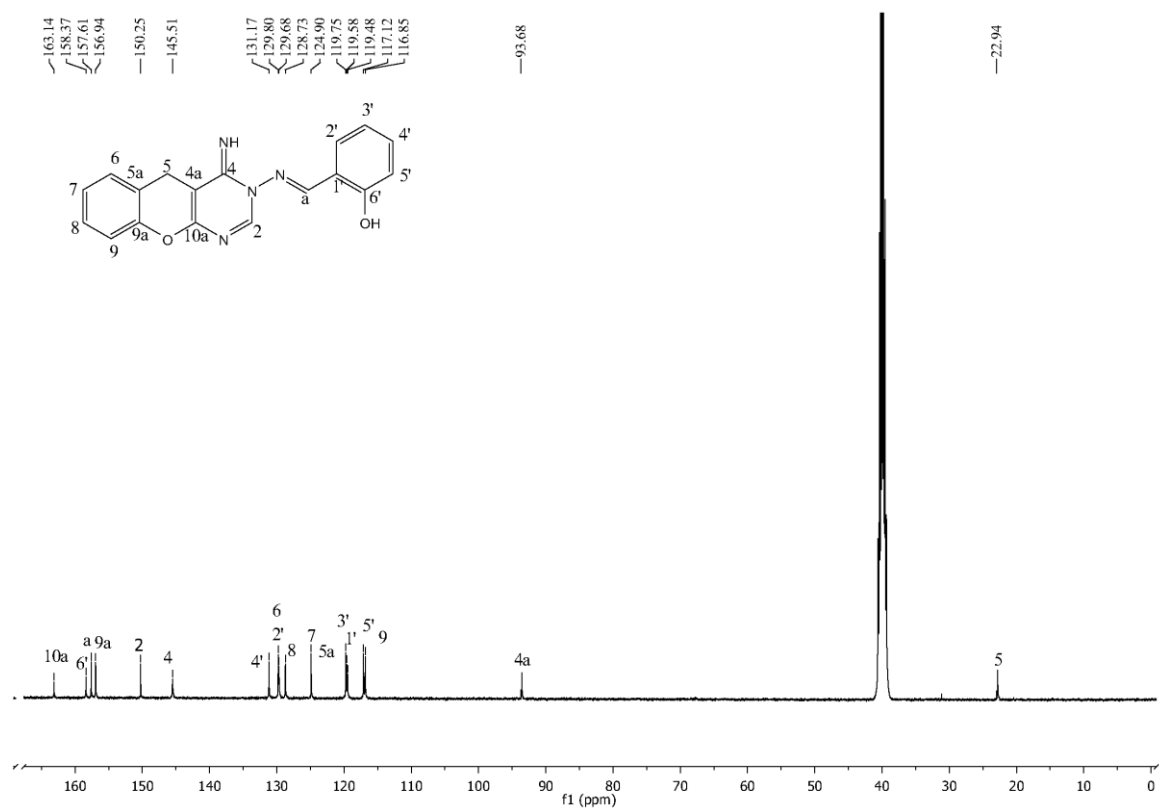
^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10e**).



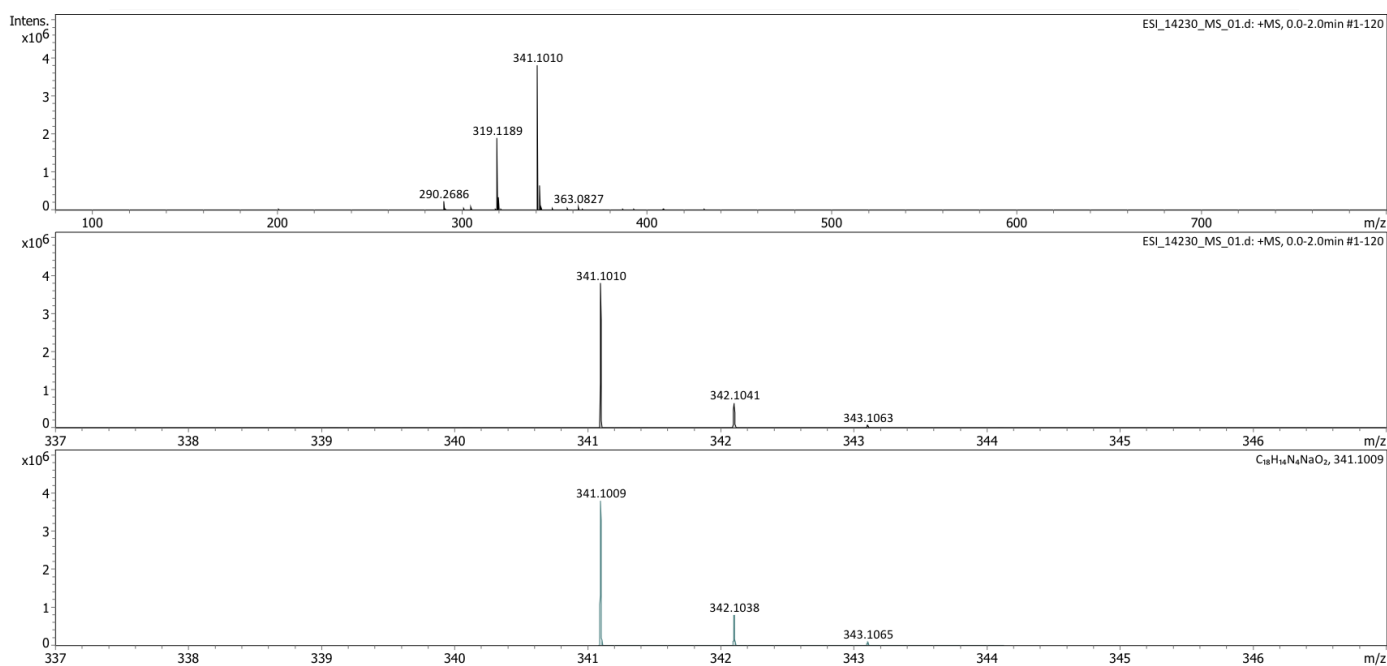
Details on the ^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10e**).



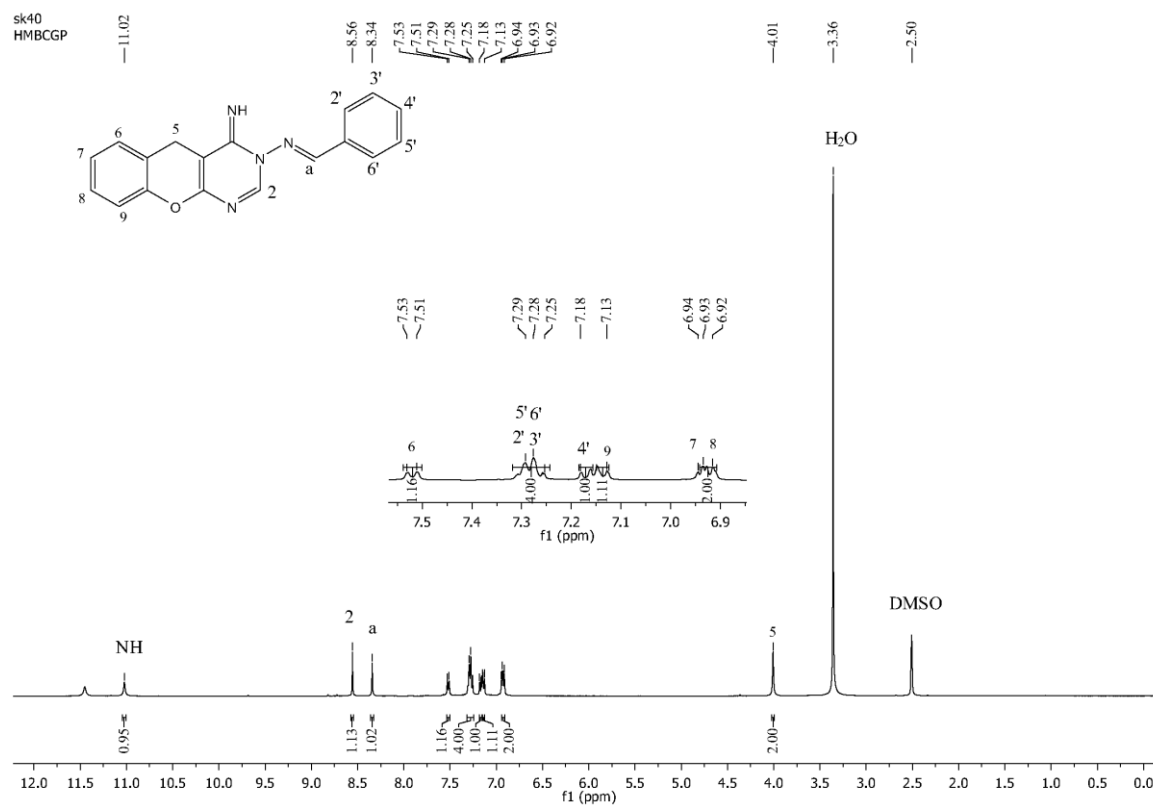
^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10e**).



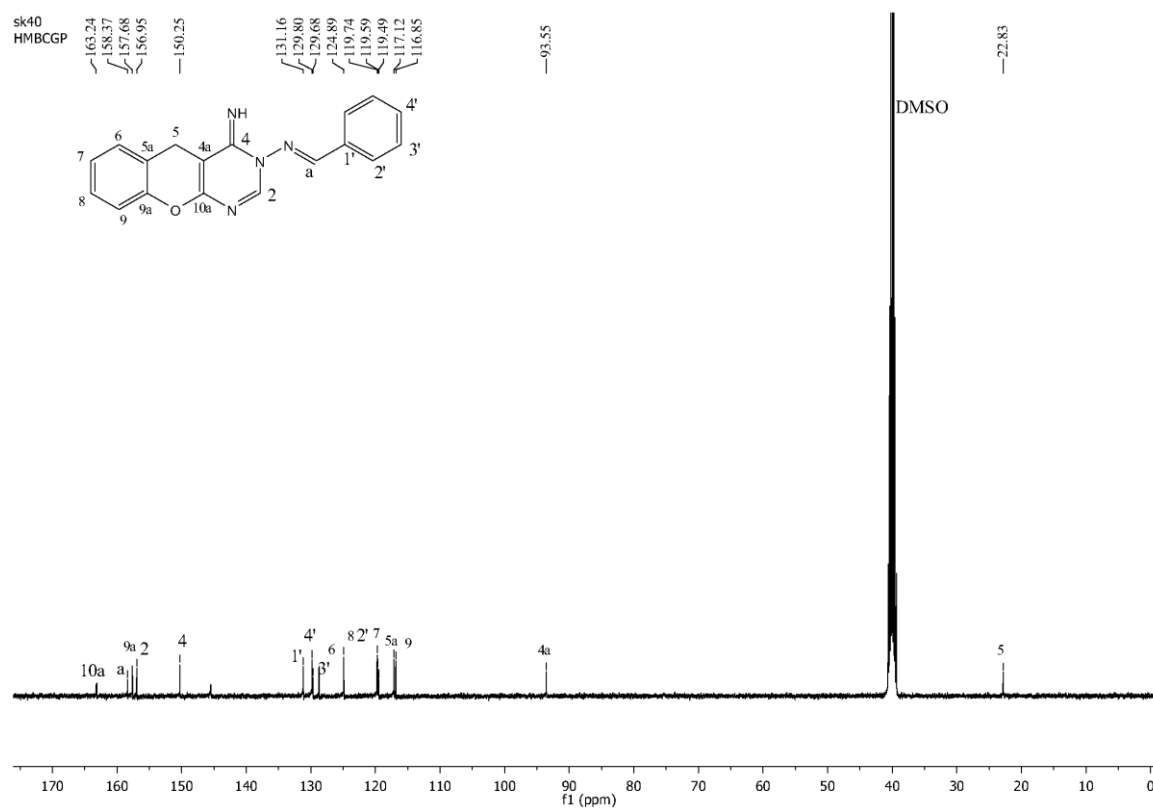
MS spectrum of compound (**10e**).

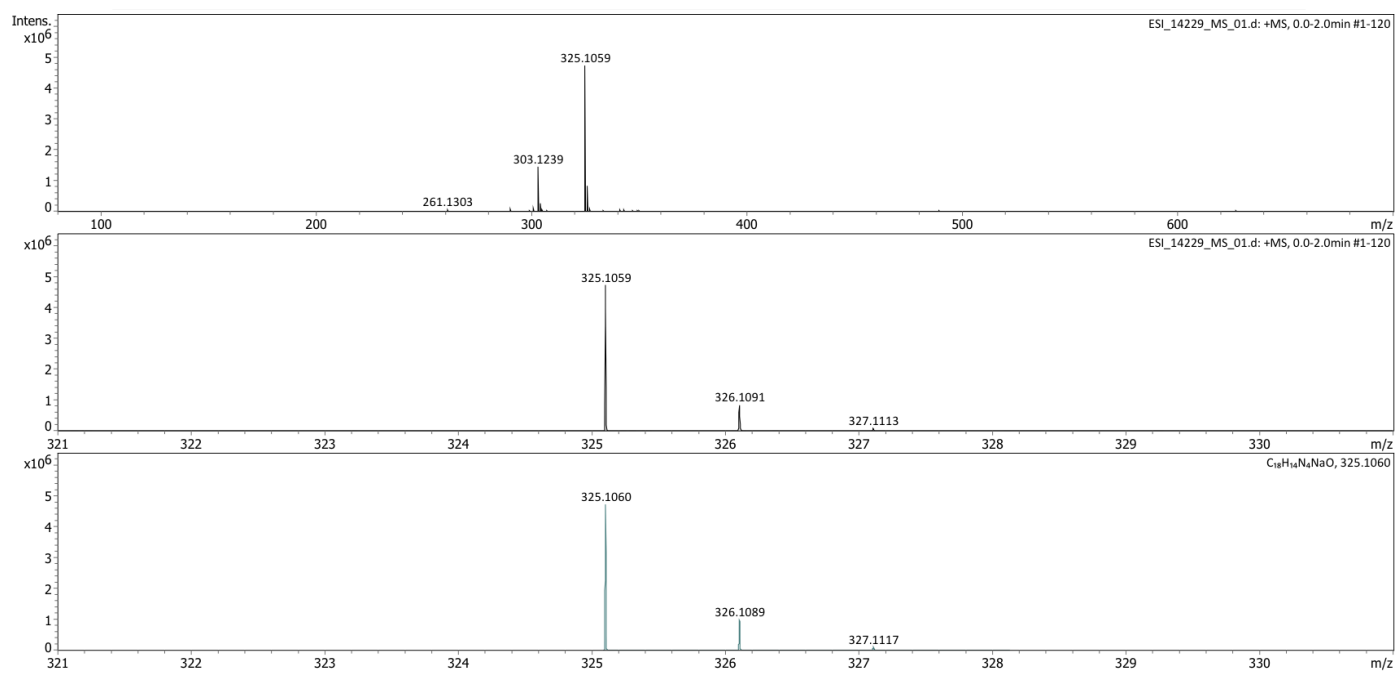


¹H NMR (300 MHz, DMSO-*d*₆) spectrum of compound (**10f**).

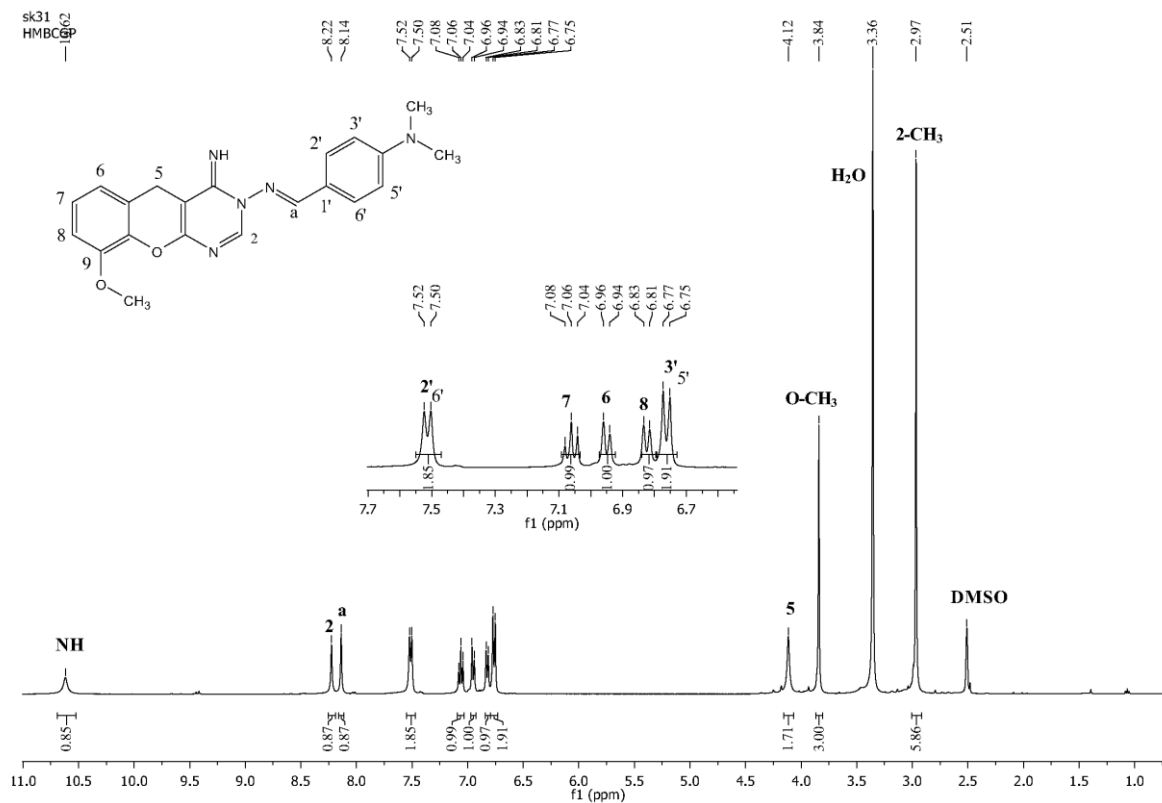


¹³C NMR (75 MHz, DMSO-*d*₆) spectrum of compound (**10f**).

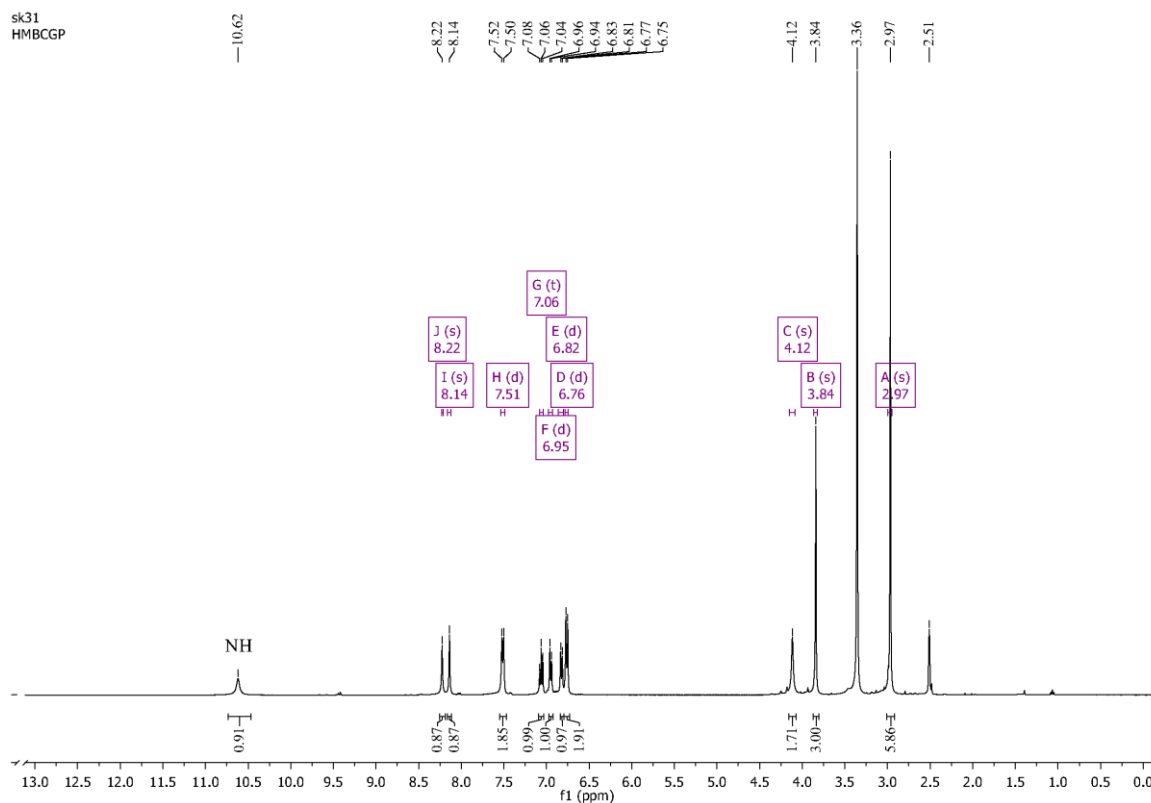


MS spectrum of compound (**10f**).

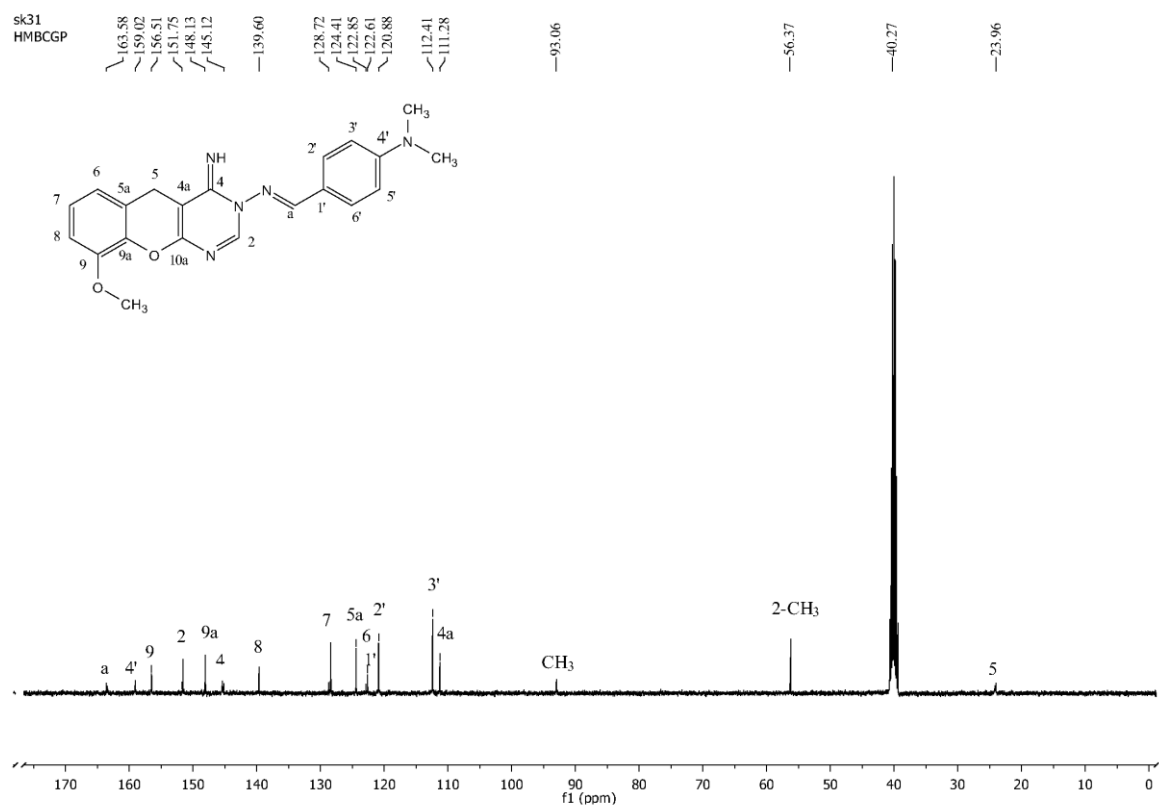
^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10g**).



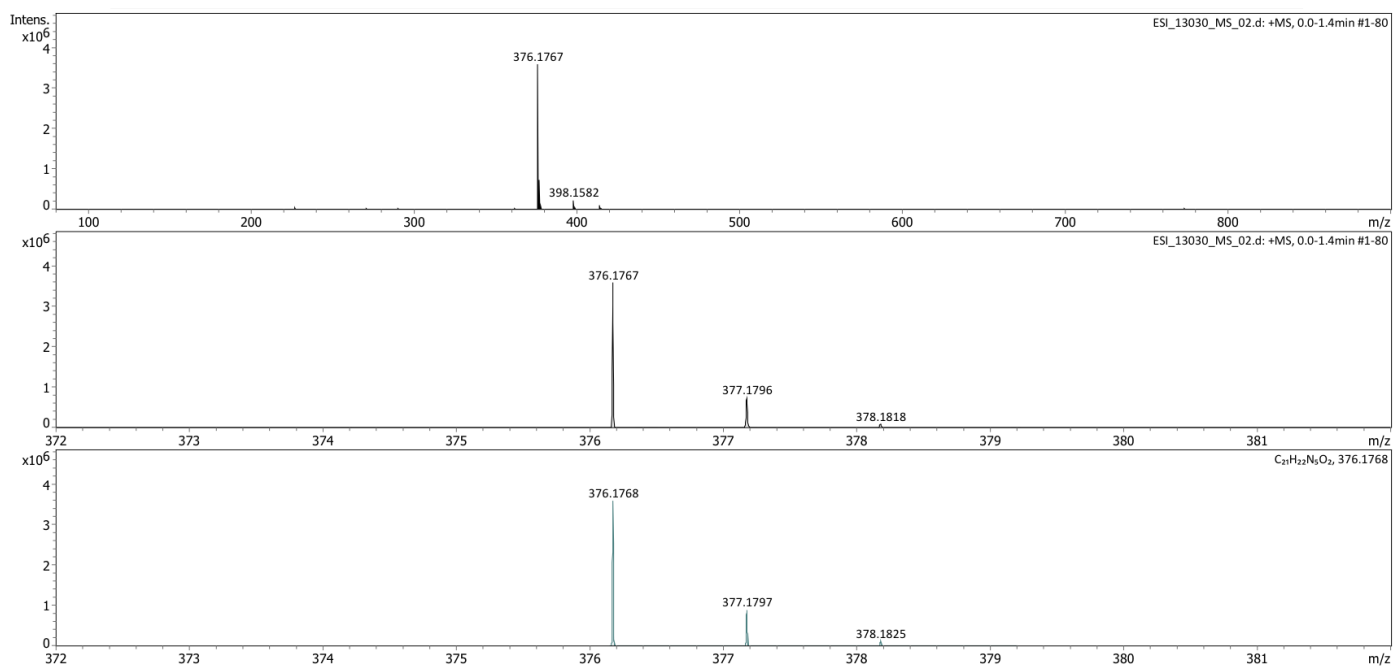
Details on the ^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10g**).



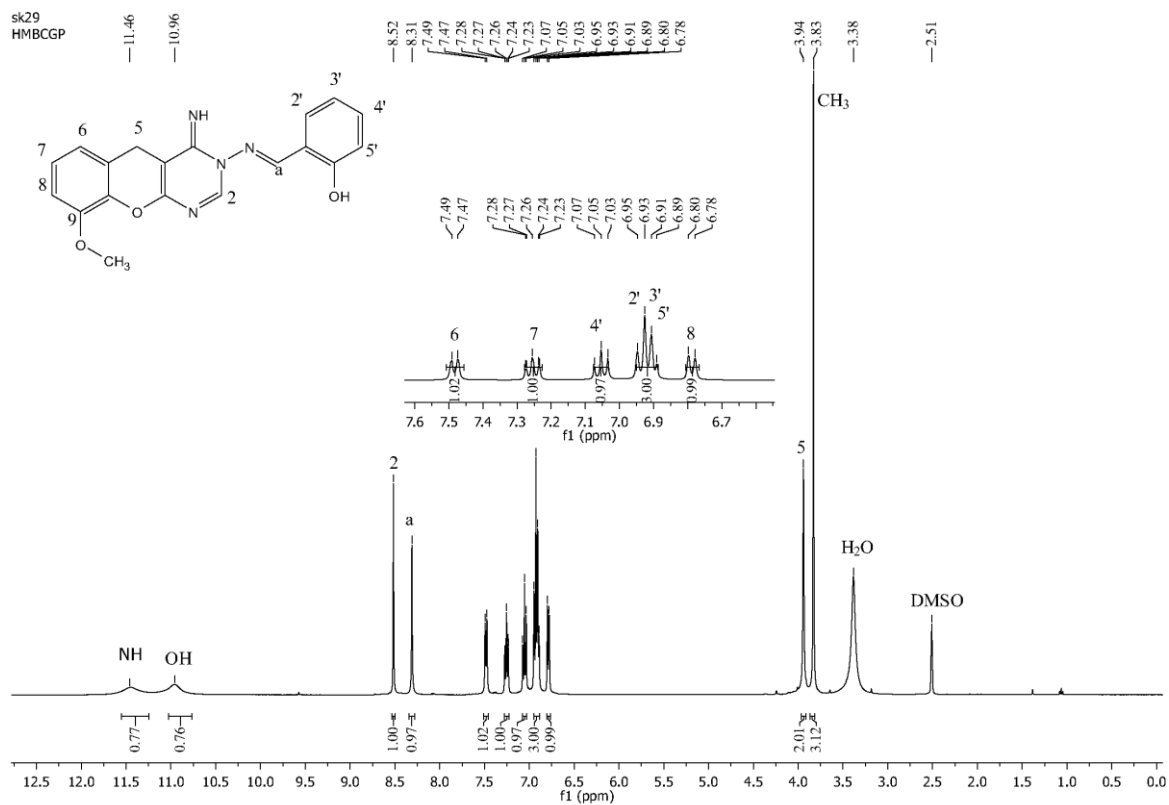
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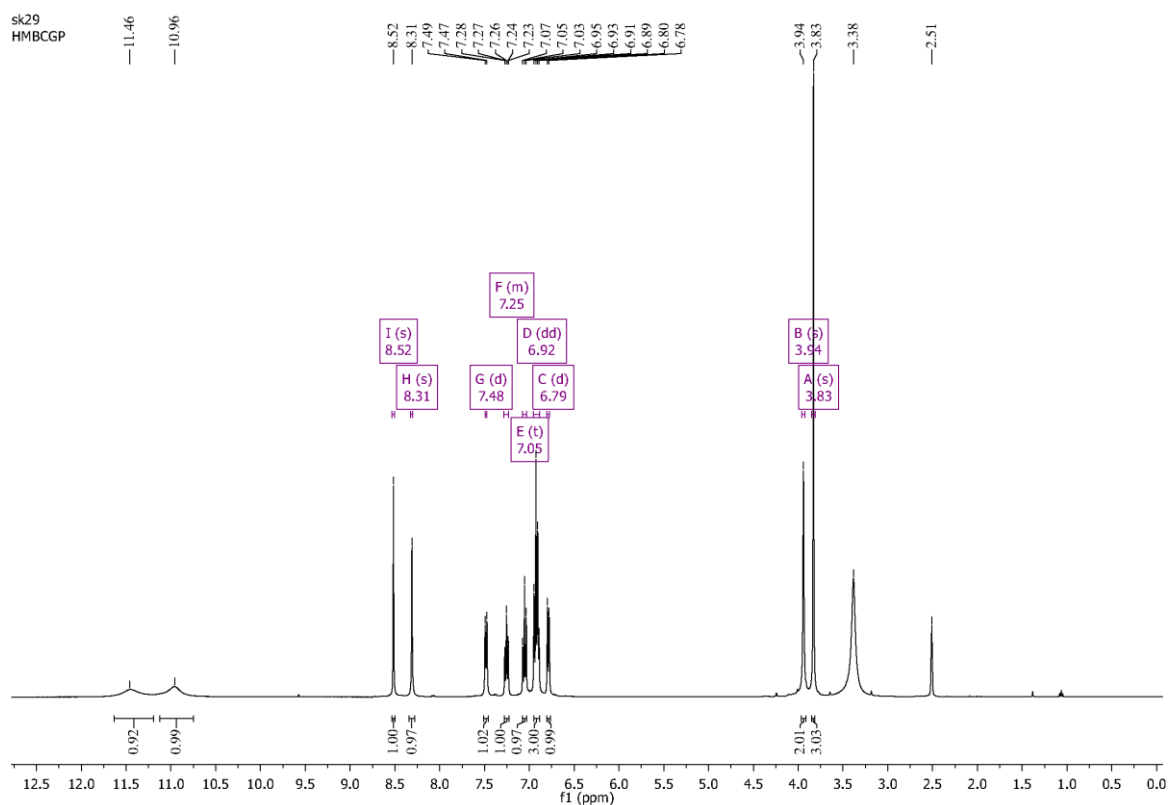
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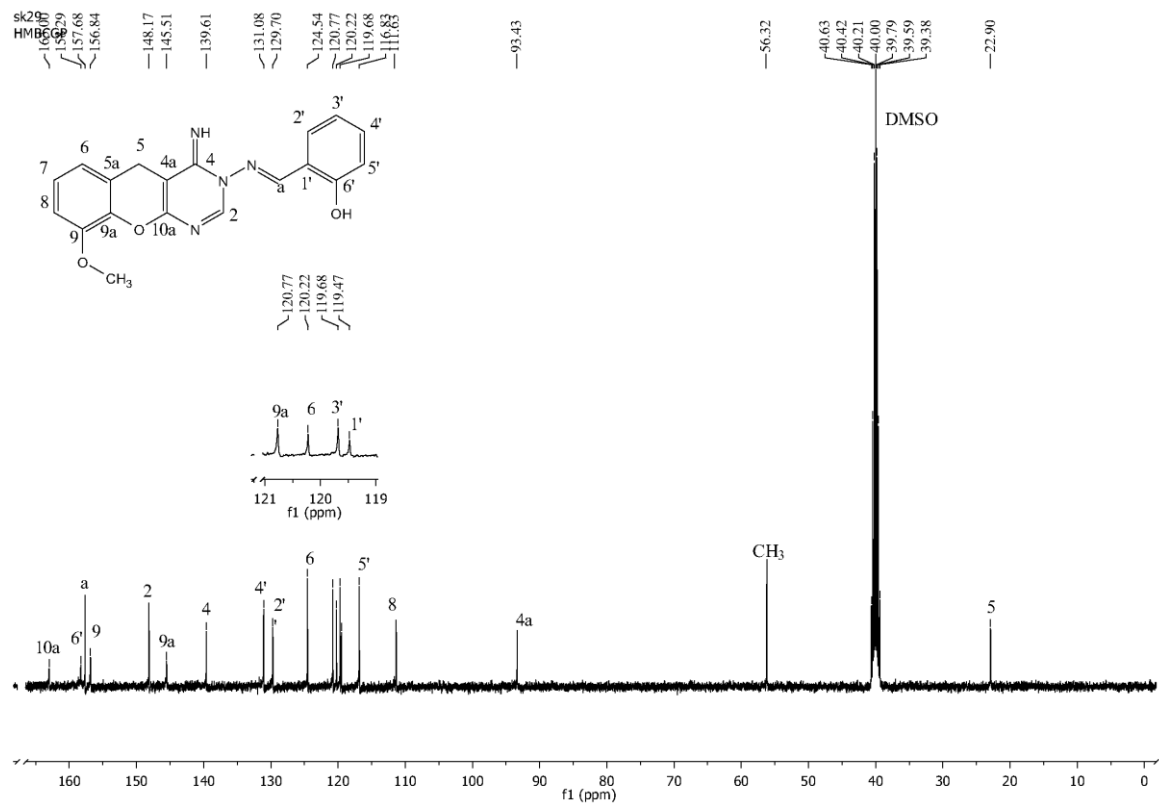
^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (10h).



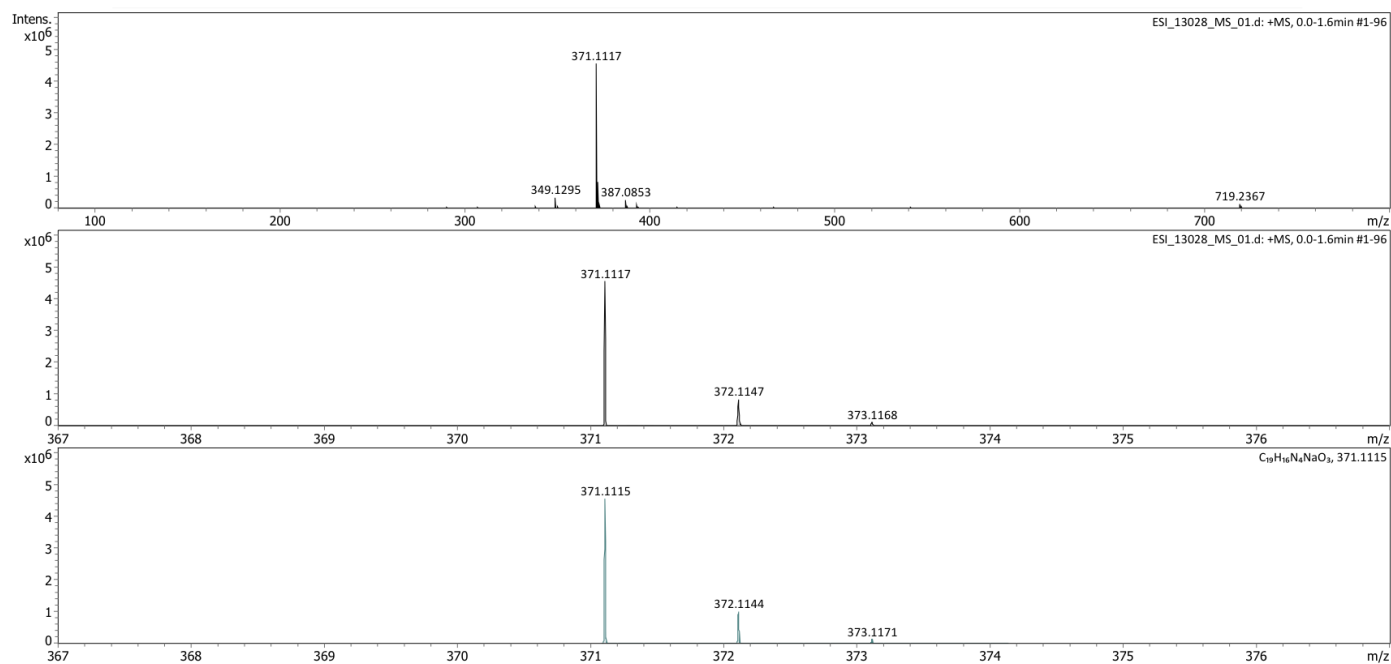
Details on the ^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (10h).



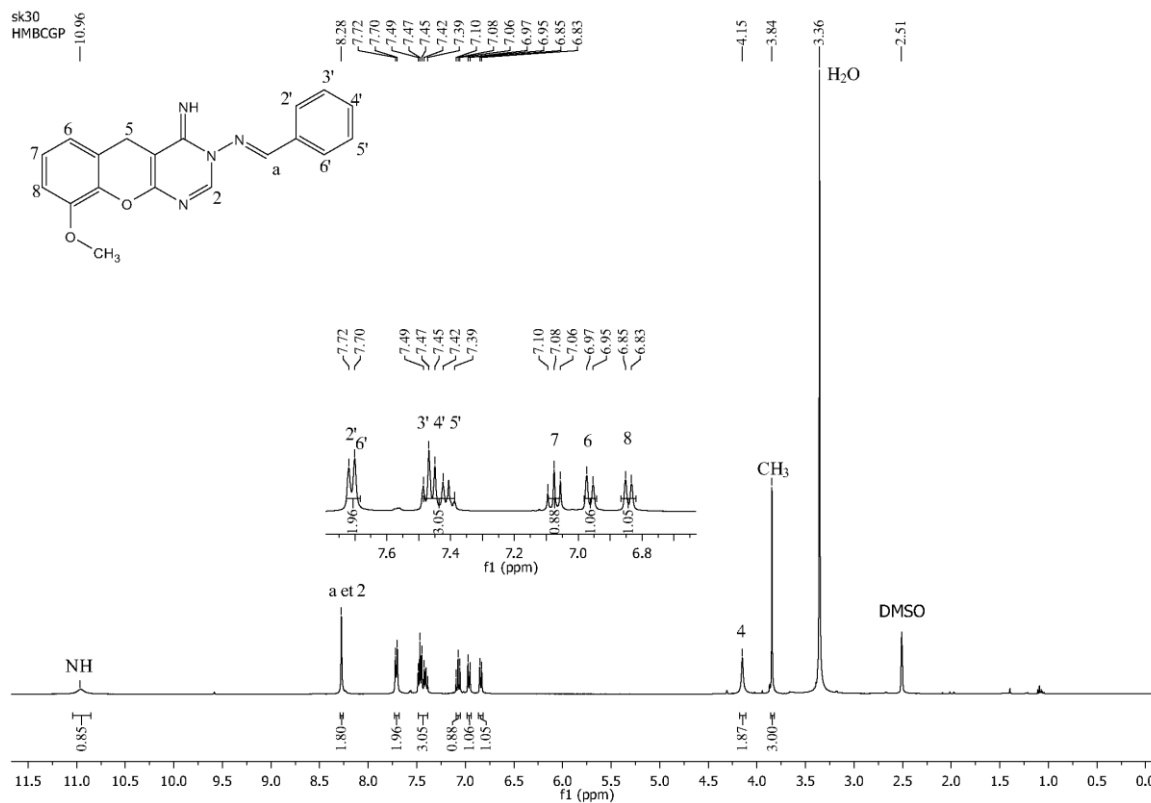
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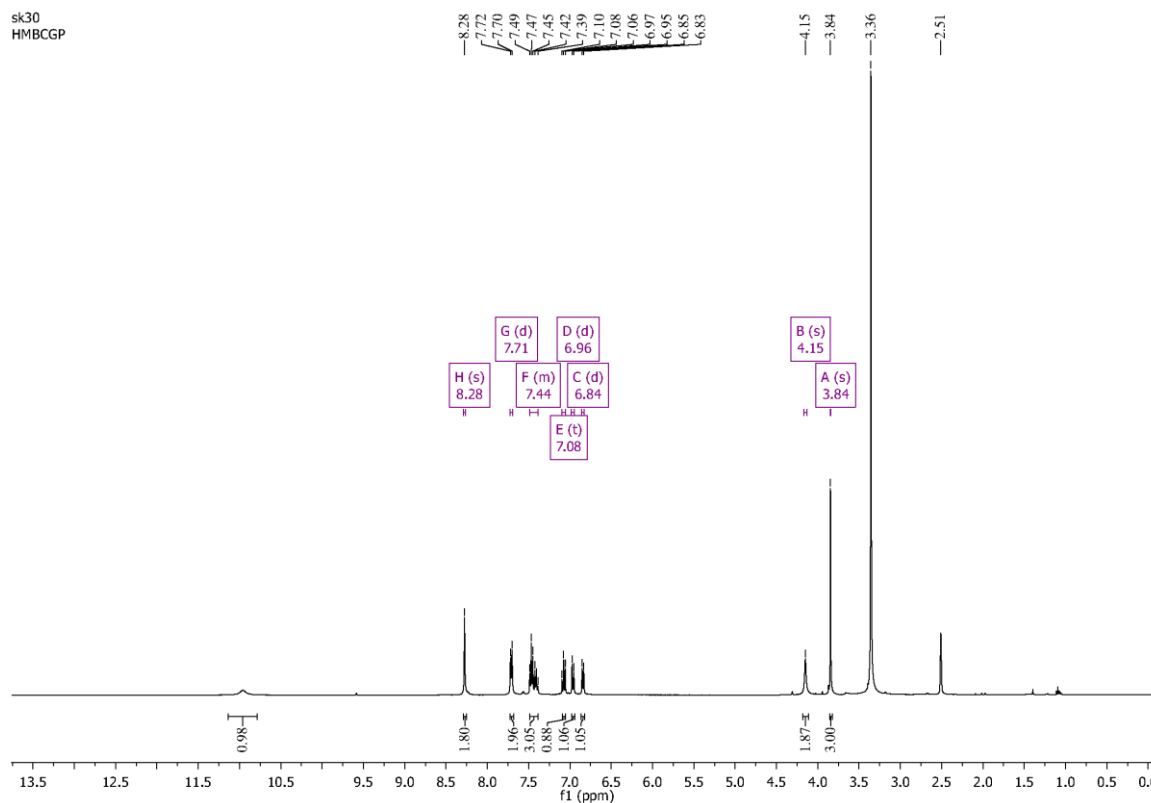
MS spectrum of compound (**10h**).



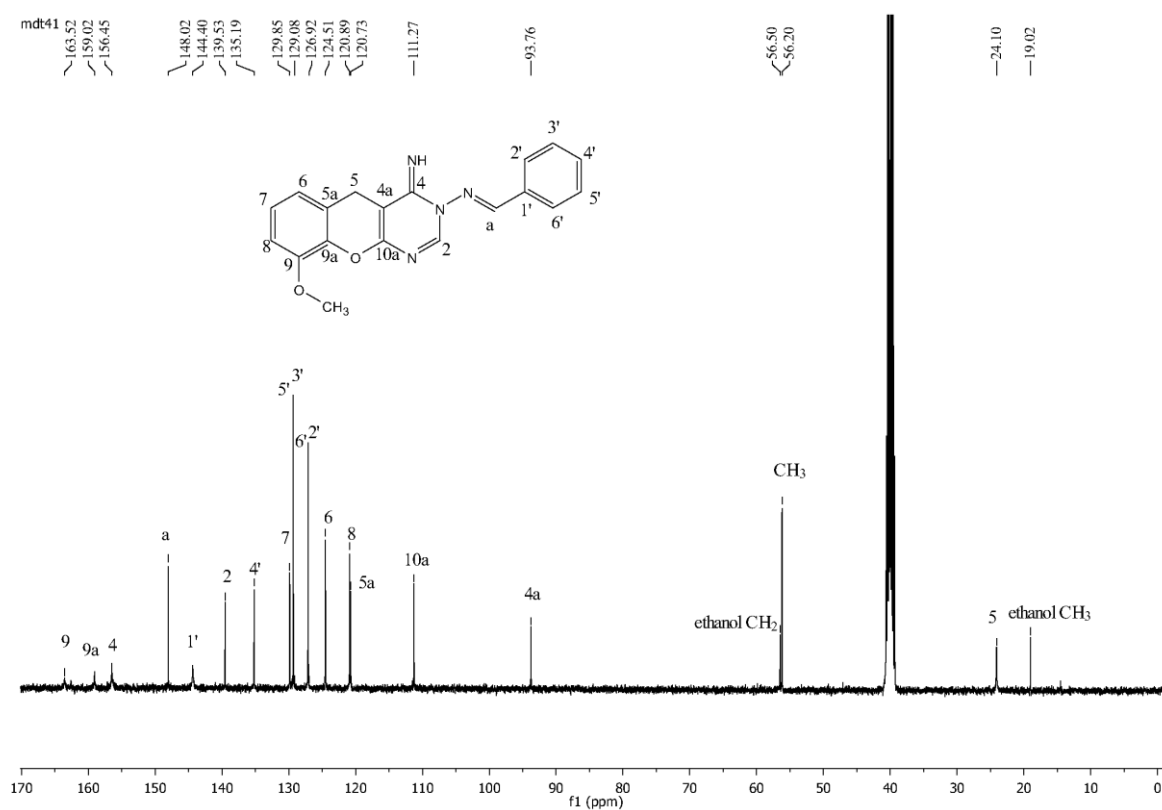
^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10i**).



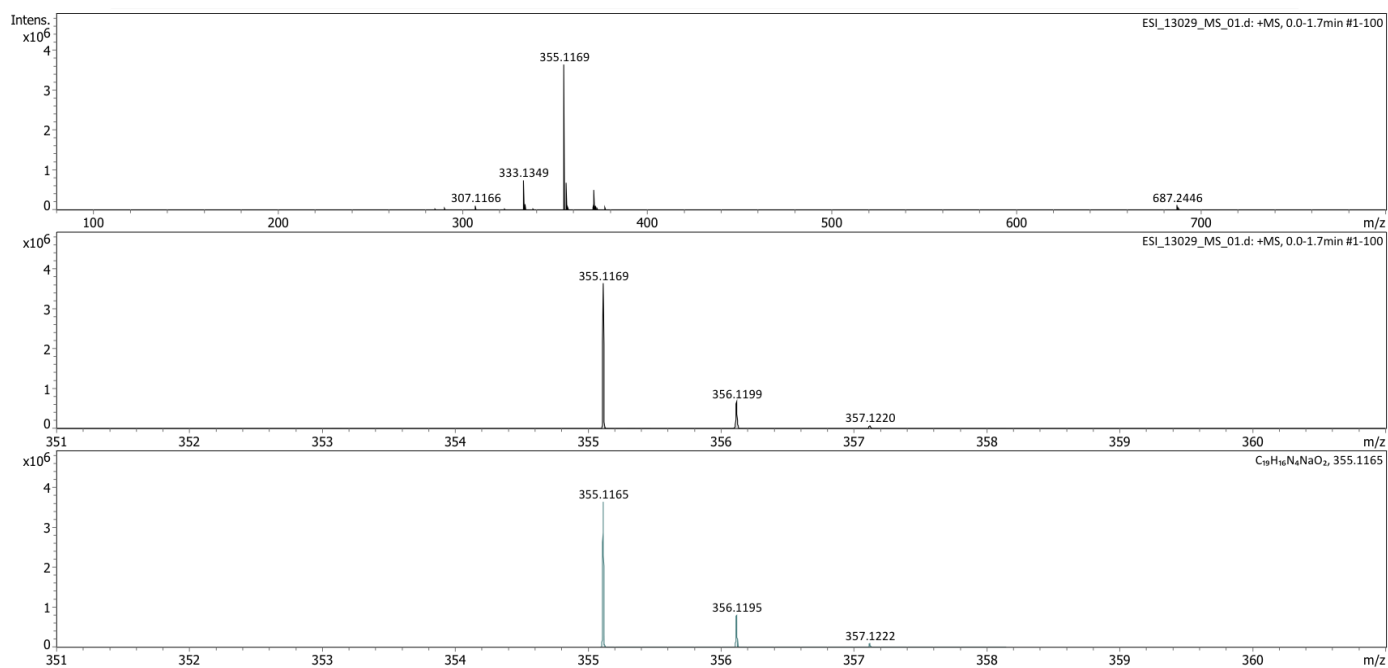
Details on the ^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10i**).



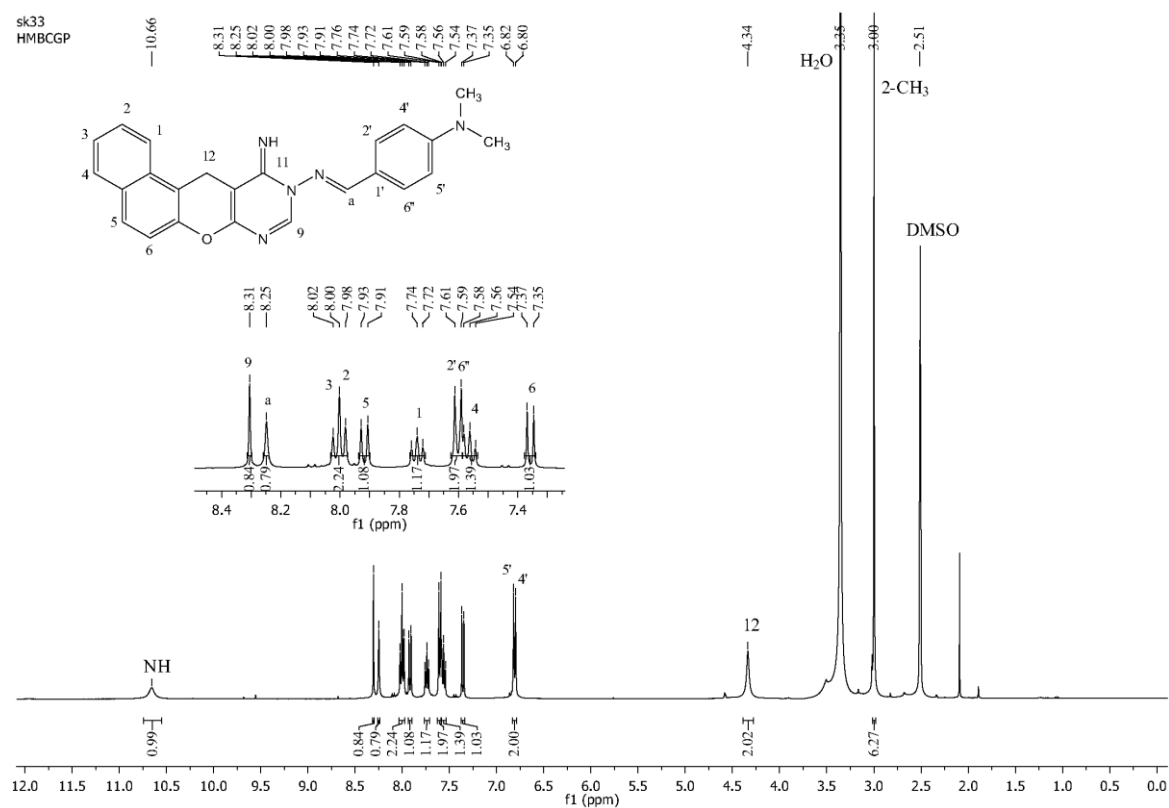
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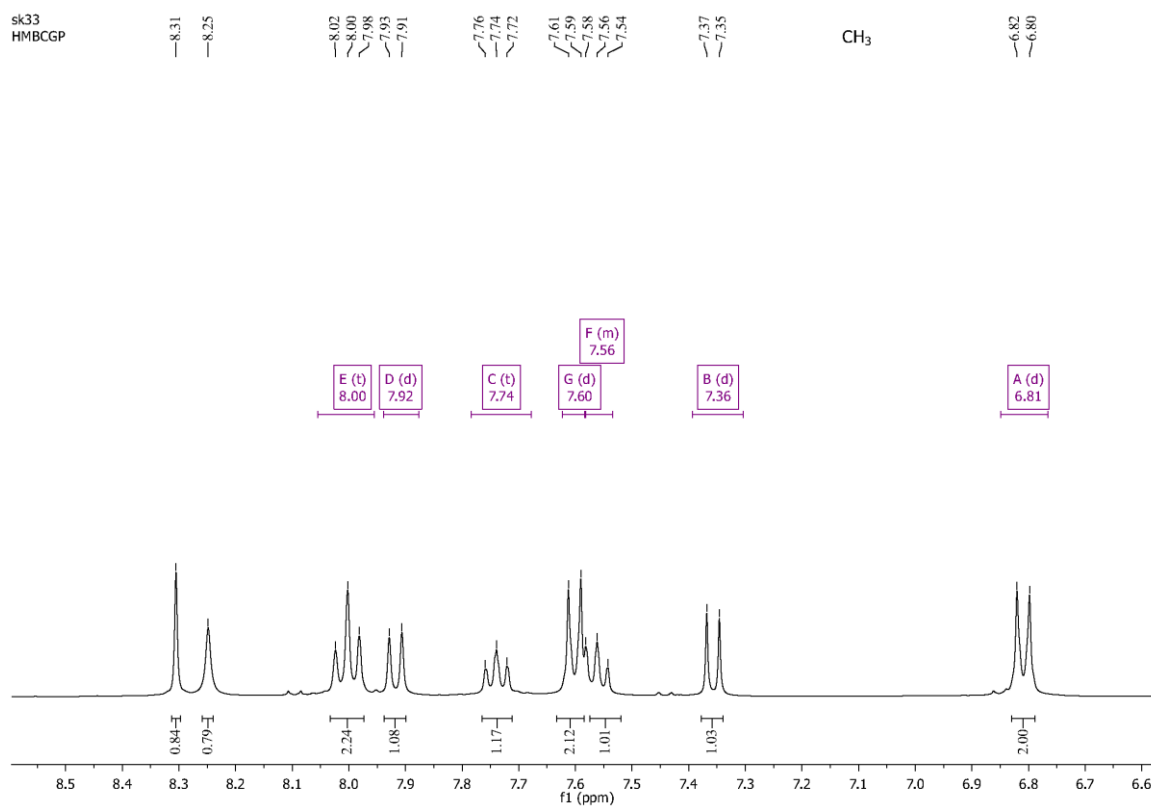
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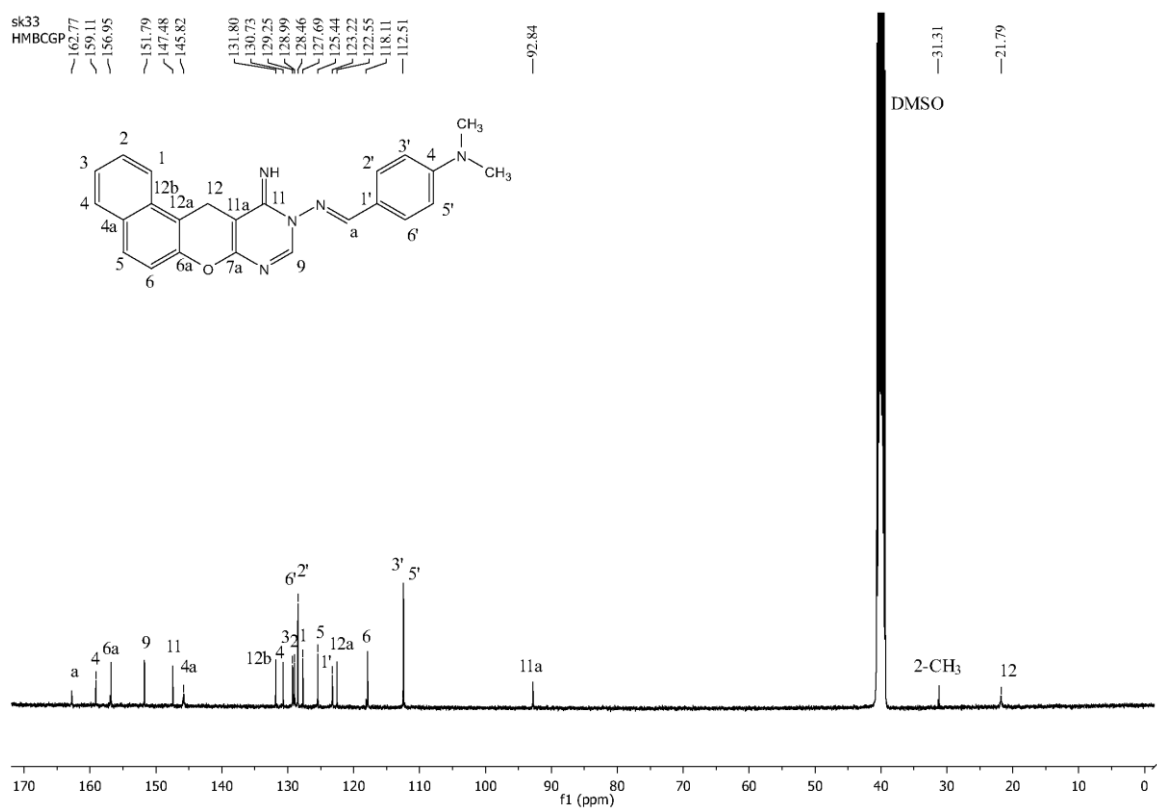
^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10j**).



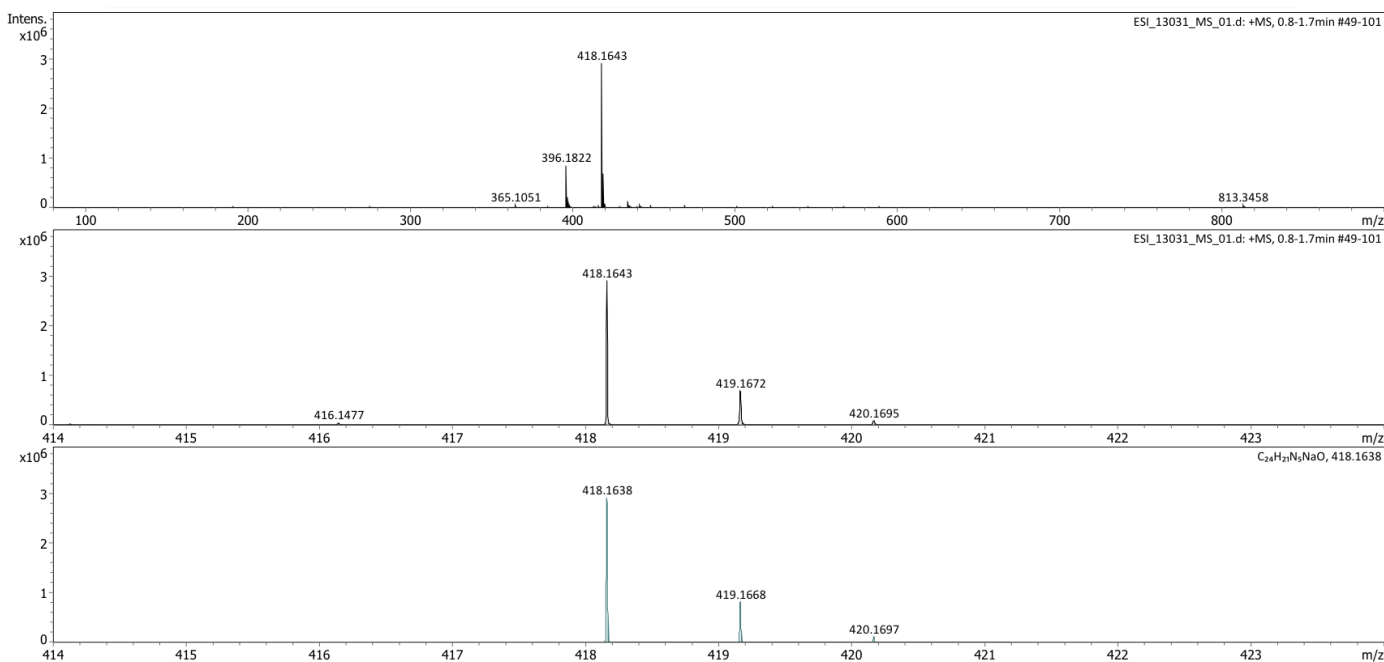
Details on the ^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10j**).



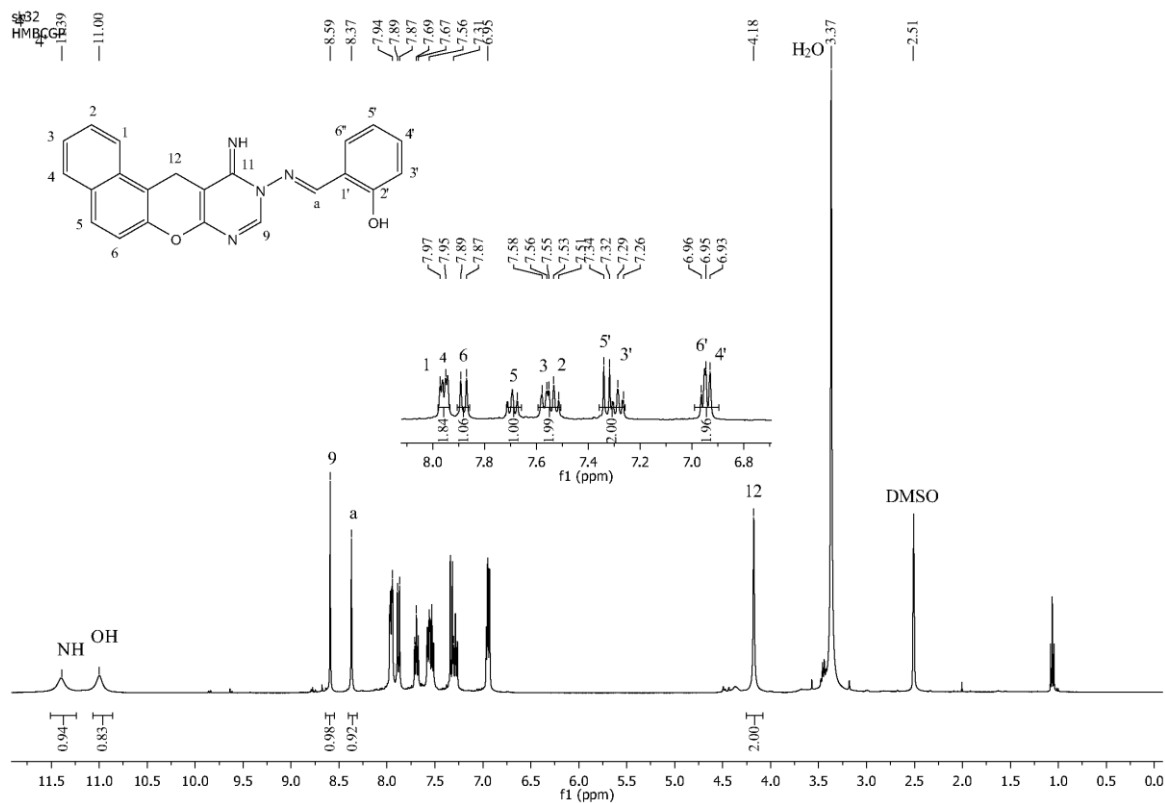
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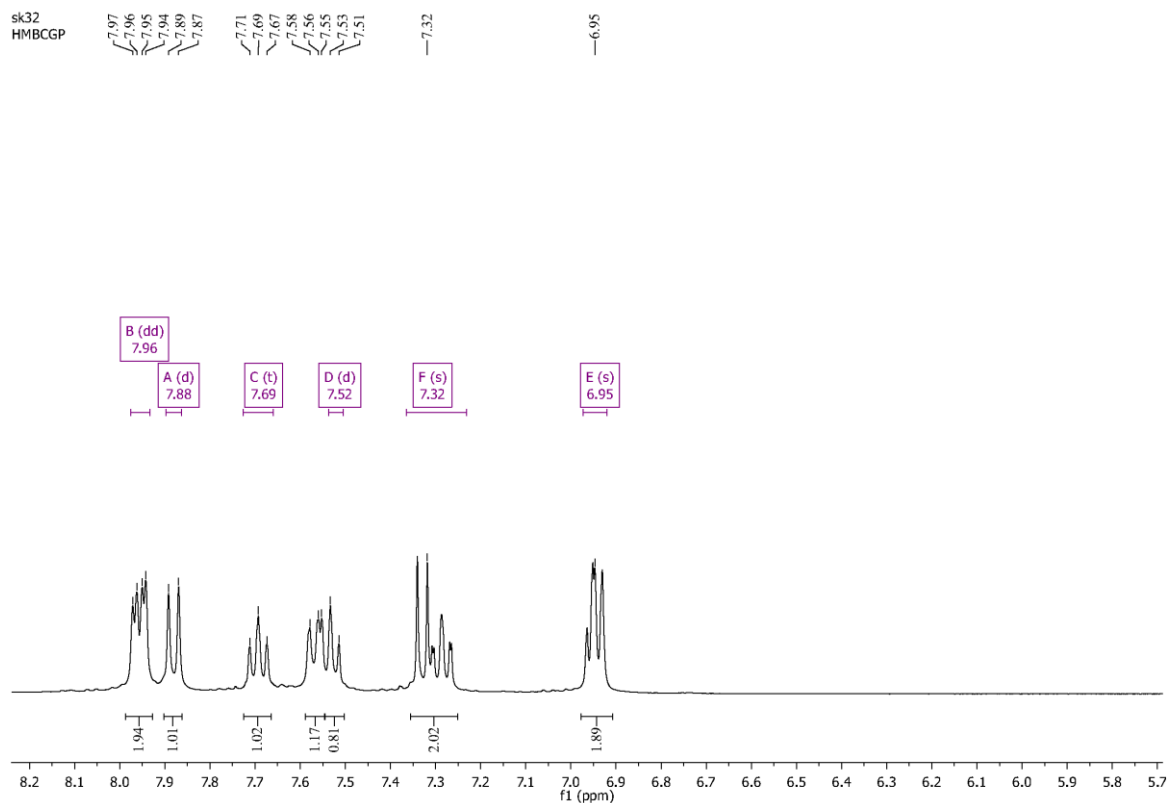
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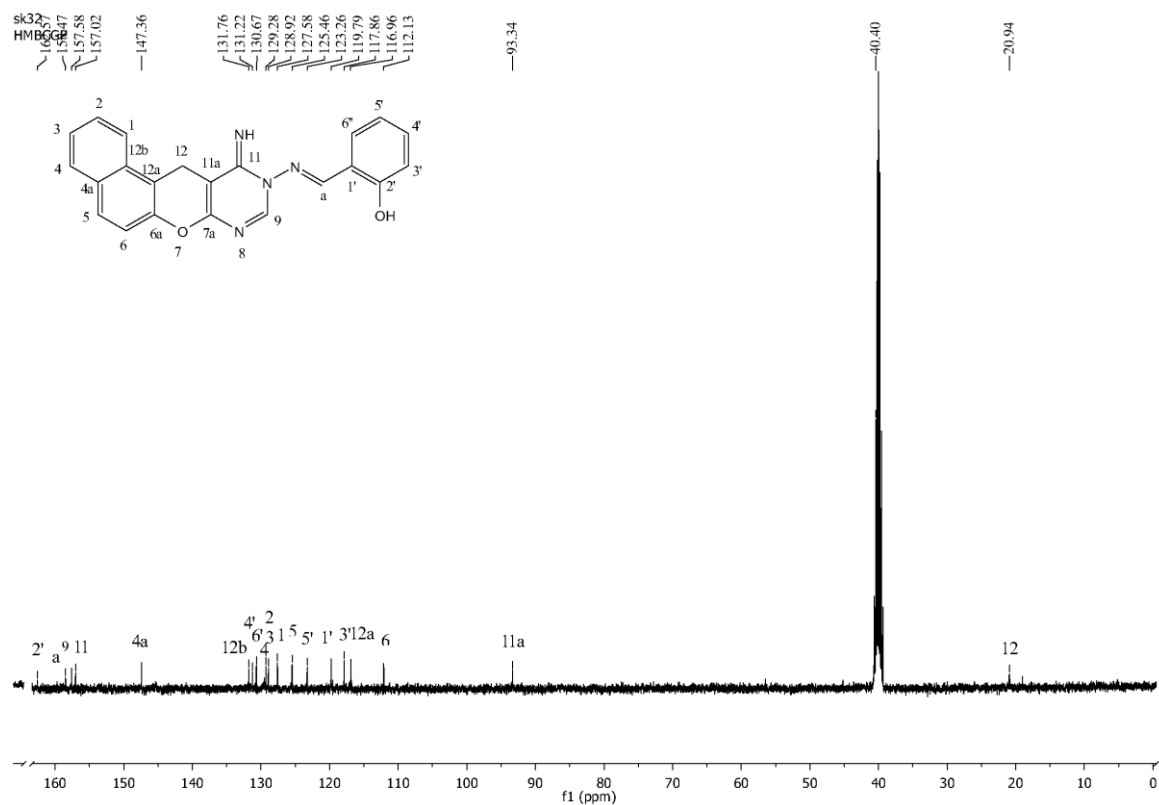
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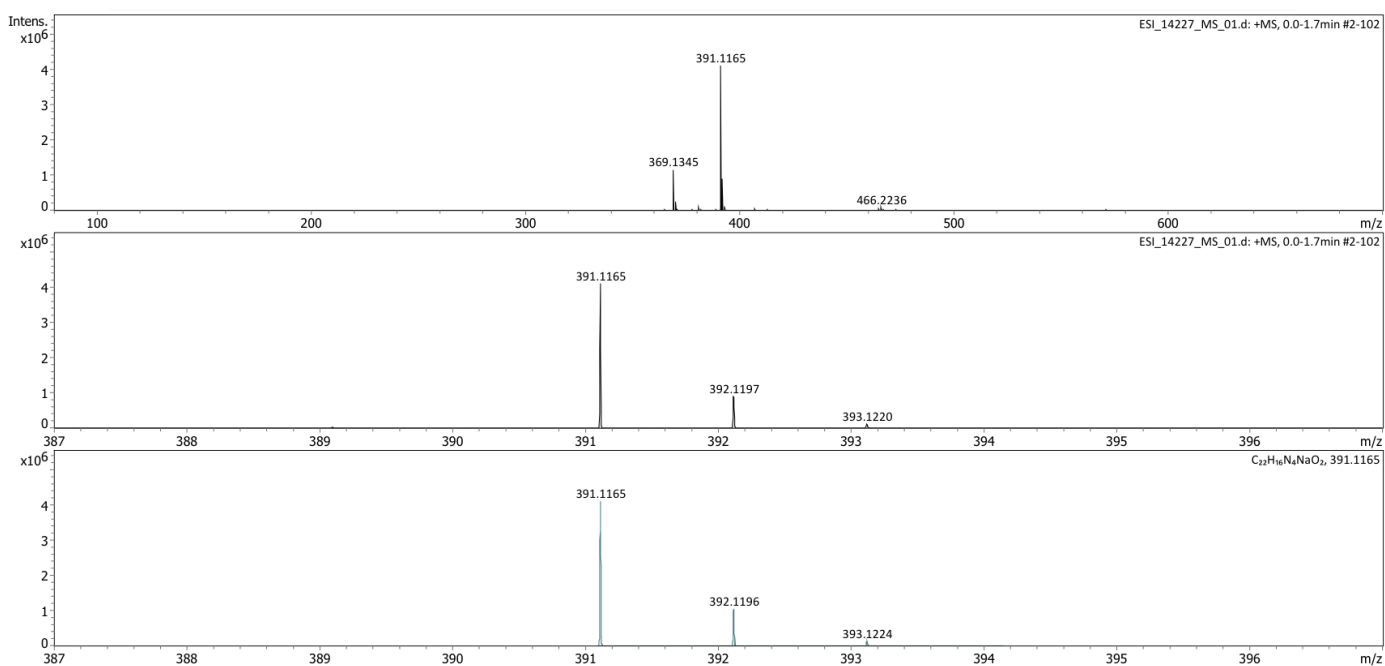
Details on the ^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10k**).



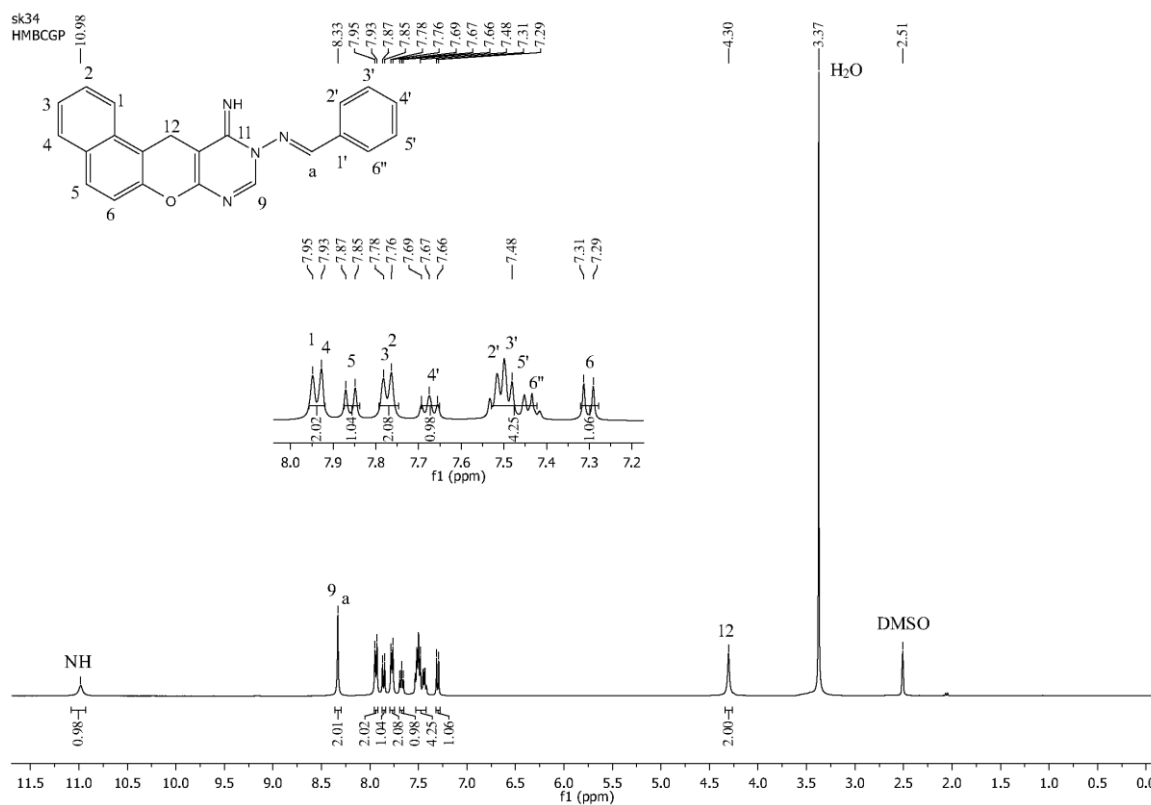
^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10k**).



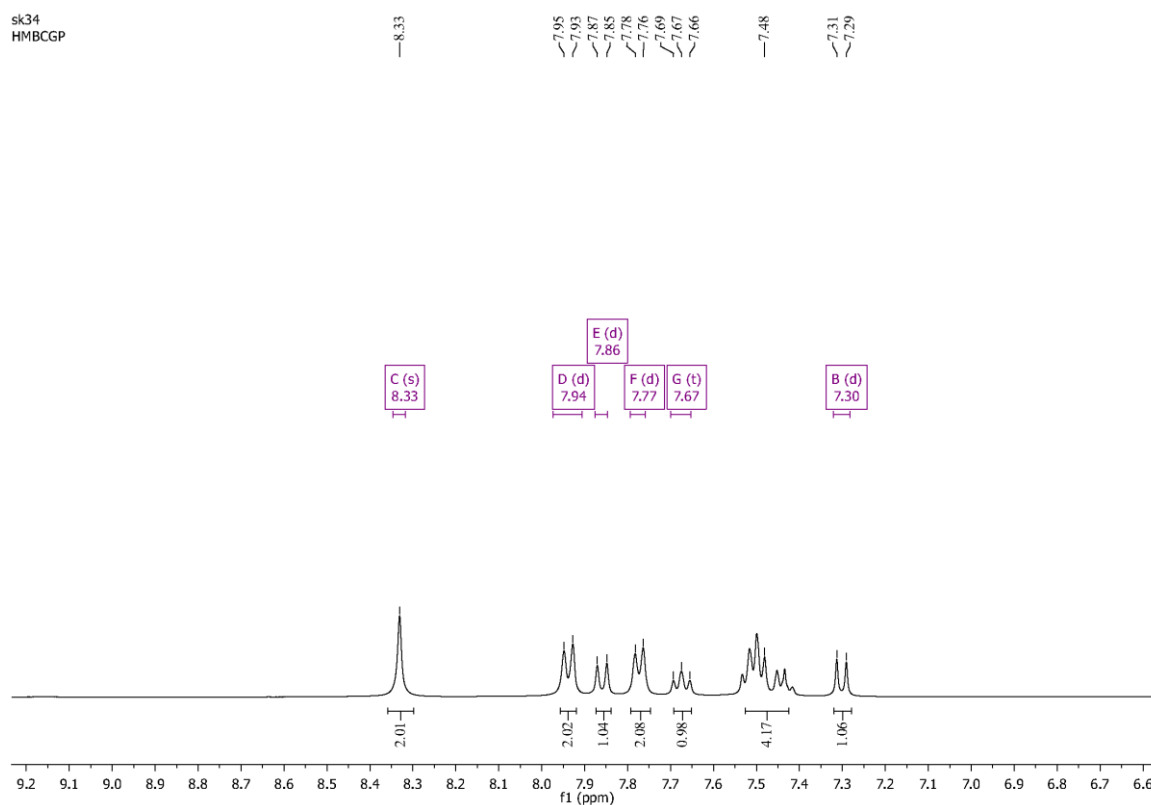
MS spectrum of compound (**10k**).



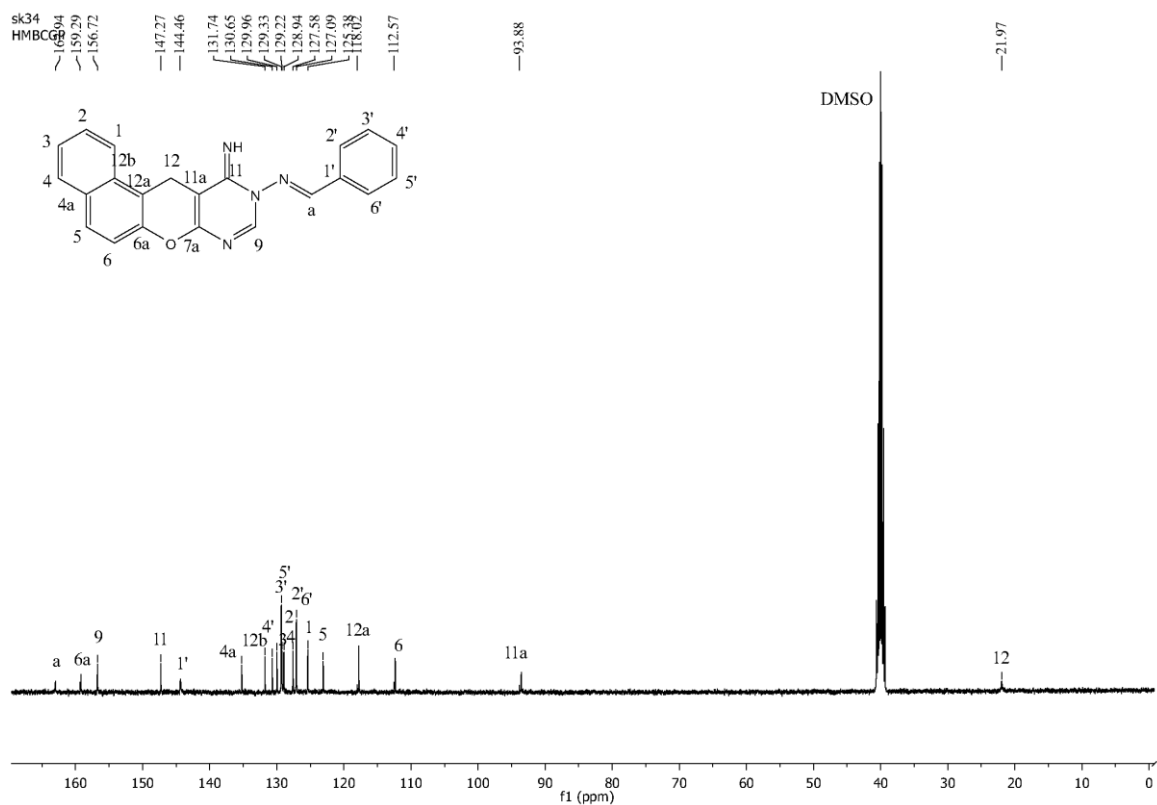
^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10l**).



Details on the ^1H NMR (300 MHz, $\text{DMSO}-d_6$) spectrum of compound (**10l**).



^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) spectrum of compound (**101**).



MS spectrum of compound (**101**).

