

Supporting Information

Sugar Mimics and their Probable Binding Site: Design and Synthesis of Thiazole Linked Coumarin-Piperazine Hybrids as Galectin-1 Inhibitors

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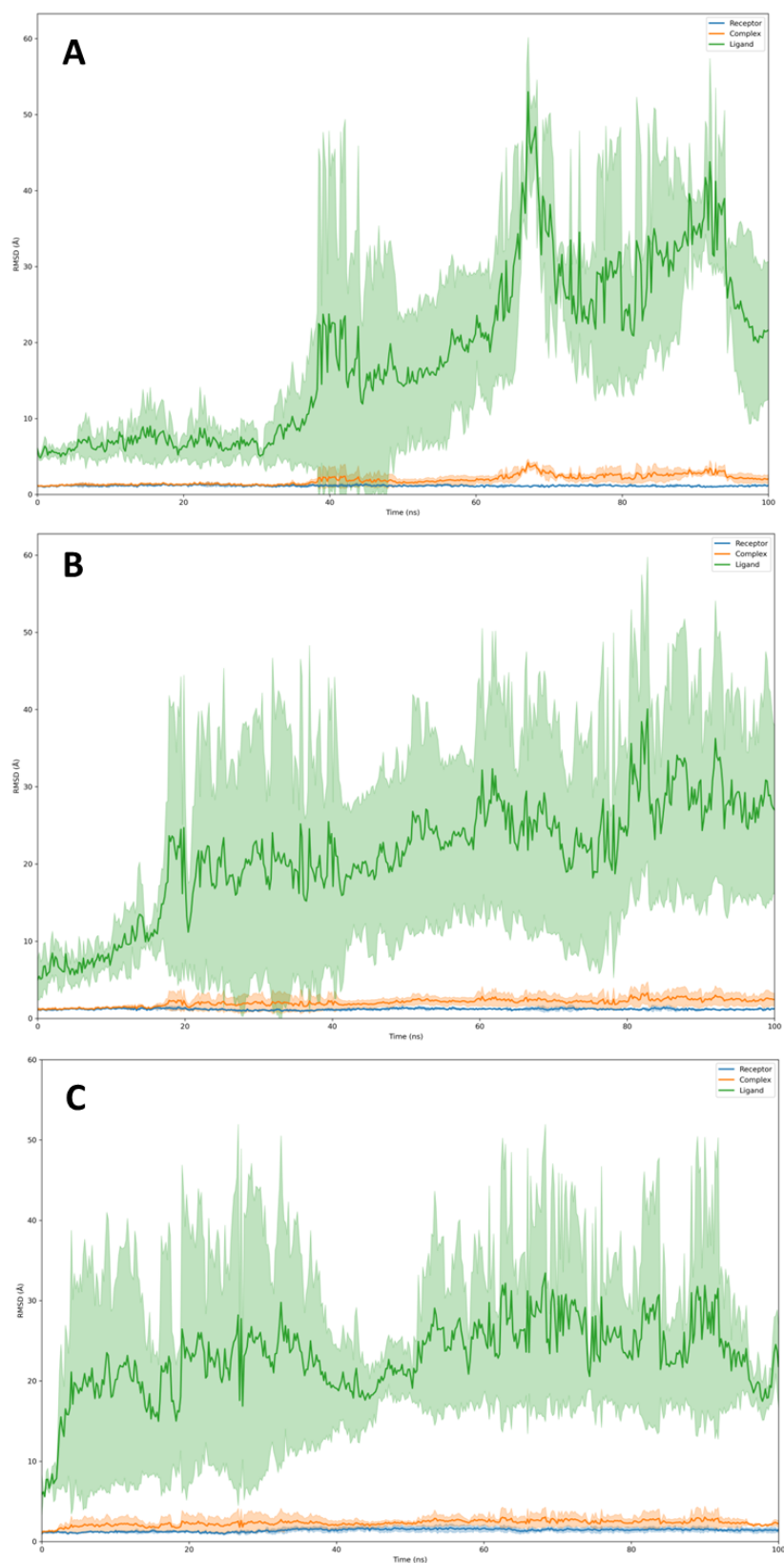


Figure S1 RMSD of ligand i.e. compound 10g (green), complex (orange) and the receptor (blue) for Pose 1 (A), pose 3 (B) and pose 15 (C) over the course of the simulation. The shaded regions represent the standard deviation of the RMSD values.

COc1ccccc1N(CCN(C(=O)Nc2nc(-c3cc4ccccc4oc3=O)cs2)CC1
[Radar view](#)
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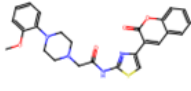
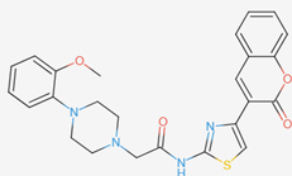
STRUCTURE			ABSORPTION			TOXICITY		
			Caco-2 Permeability	-4.884	● ●	HERG Blockers	0.941	● ●
			MDCK Permeability	0.0	● ●	HERG Blockers (10um)	0.687	● ●
			PAMPA	--	● ●	DLI	0.946	● ●
			Pgp inhibitor	---	● ●	AMES Toxicity	0.352	● ●
			Pgp substrate	---	● ●	Rat Oral Acute Toxicity	0.826	● ●
			HIA	---	● ●	FDAMDD	0.801	● ●
			F20%	--	● ●	Skin Sensitization	0.319	● ●
			F30%	---	● ●	Carcinogenicity	0.825	● ●
			F50%	-	● ●	Eye Corrosion	0.0	● ●
			DISTRIBUTION			Eye Irritation	0.002	● ●
			PPB	97.8%	● ●	Respiratory	0.976	● ●
			VDss	1.408	● ●	Human Hepatotoxicity	0.767	● ●
			BBB	-	● ●	Drug-induced Nephrotoxicity	0.853	● ●
			Fu	1.9%	● ●	Drug-induced Neurotoxicity	0.863	● ●
			OATP1B1 inhibitor	++	● ●	Ototoxicity	0.285	● ●
			OATP1B3 inhibitor	+++	● ●	Hematotoxicity	0.146	● ●
			BCRP inhibitor	---	● ●	Genotoxicity	1.0	● ●
			MRPI inhibitor	+++	● ●	RPMI-8226 Immunotoxicity	0.121	● ●
			BSEP inhibitor	+++	● ●	A549 Cytotoxicity	0.128	● ●
			METABOLISM			Hek293 Cytotoxicity	0.633	● ●
			CYP1A2 inhibitor	+++	● ●	BCF	1.115	● ●
			CYP1A2 substrate	---	● ●	IGC50	4.103	● ●
			CYP2C19 inhibitor	+++	● ●	LC50DM	5.067	● ●
			CYP2C19 substrate	+++	● ●	LC50FM	4.848	● ●
			CYP2C9 inhibitor	+++	● ●	TOX21 PATHWAY		
			CYP2C9 substrate	+++	● ●	NR-AhR	++	● ●
			CYP2D6 inhibitor	---	● ●	NR-AR	--	● ●
			CYP2D6 substrate	+	● ●	NR-AR-LBD	-	● ●
			CYP3A4 inhibitor	+++	● ●	NR-Aromatase	--	● ●
			CYP3A4 substrate	+	● ●	NR-ER	-	● ●
			CYP2B6 inhibitor	+++	● ●	NR-ER-LBD	---	● ●
			CYP2B6 substrate	---	● ●	NR-PPAR-gamma	--	● ●
			CYP2C8 inhibitor	+++	● ●	SR-ARE	+++	● ●
			HLM Stability	+++	● ●	SR-ATAD5	+	● ●
			EXCRETION			SR-HSE	--	● ●
			CL _{plasma}	4.228	● ●	SR-MMP	--	● ●
			T1/2	0.423	● ●	SR-p53	+	● ●
			TOXICOPHORE RULES			<p>ⓘ Tips:</p> <ul style="list-style-type: none"> For the classification endpoints, the prediction probability values are transformed into six symbols: 0-0.1 (---), 0.1-0.3 (--), 0.3-0.5 (-), 0.5-0.7 (+), 0.7-0.9 (++), and 0.9-1.0 (+++). Additionally, the corresponding relationships of the three labels are as follows: ● excellent; ● medium; ● poor; <p>ⓘ Disclaimer:</p> <ul style="list-style-type: none"> These resources are free to use but should not be used for medical or professional advice. 		
			Acute Aquatic Toxicity Rule	0	● ●			
			Genotoxic Carcinogenicity Mutagenicity Rule	2	▲ ●			
			NonGenotoxic Carcinogenicity Rule	0	● ●			
			Skin Sensitization Rule	4	▲ ●			
			Aquatic Toxicity Rule	1	▲ ●			
			NonBiodegradable	0	● ●			
			SureChEMBL Rule	1	▲ ●			
			FAF-Drugs4 Rule	4	▲ ●			
			FAF-Drugs4 Rule	4	▲ ●			
			FAF-Drugs4 Rule	4	▲ ●			

Figure S2 Predicted ADMET values for compound 10g using ADMETLab 3.0.

Molecule Depiction



SMILES

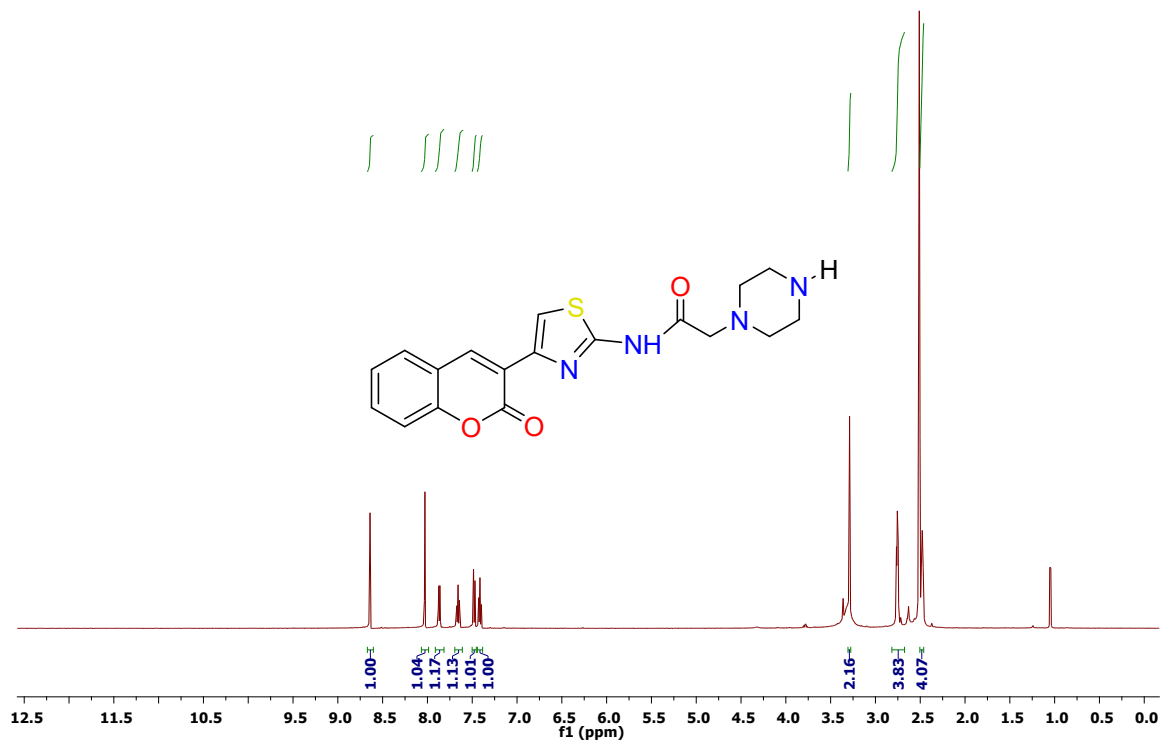
Molecule properties:

Descriptor	Value
Molecular Weight	476.558
LogP	3.6858
#Rotatable Bonds	6
#Acceptors	8
#Donors	1
Surface Area	199.947

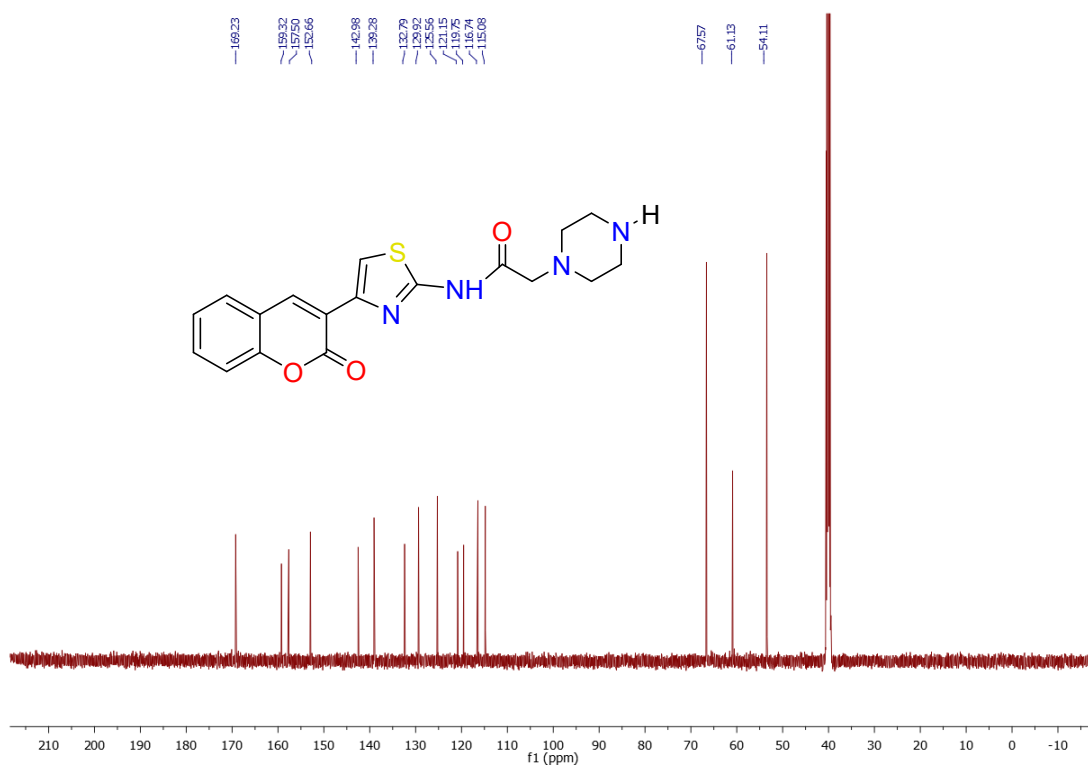
Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	-4.23	Numeric (log mol/L)
Absorption	Caco2 permeability	1.035	Numeric (log Papp in 10 ⁻⁶ cm/s)
Absorption	Intestinal absorption (human)	94.154	Numeric (% Absorbed)
Absorption	Skin Permeability	-2.74	Numeric (log Kp)
Absorption	P-glycoprotein substrate	Yes	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	Yes	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	Yes	Categorical (Yes/No)
Distribution	VDss (human)	0.626	Numeric (log L/kg)
Distribution	Fraction unbound (human)	0.09	Numeric (Fu)
Distribution	BBB permeability	-1.119	Numeric (log BB)
Distribution	CNS permeability	-2.238	Numeric (log PS)
Metabolism	CYP2D6 substrate	Yes	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	Yes	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitor	No	Categorical (Yes/No)
Metabolism	CYP2C19 inhibitor	No	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitor	No	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitor	No	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitor	Yes	Categorical (Yes/No)
Excretion	Total Clearance	0.639	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	Yes	Categorical (Yes/No)
Toxicity	AMES toxicity	No	Categorical (Yes/No)
Toxicity	Max. tolerated dose (human)	0.241	Numeric (log mg/kg/day)
Toxicity	hERG I inhibitor	No	Categorical (Yes/No)
Toxicity	hERG II inhibitor	Yes	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	2.4	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	1.034	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	Yes	Categorical (Yes/No)
Toxicity	Skin Sensitisation	No	Categorical (Yes/No)
Toxicity	<i>T.Pyriformis</i> toxicity	0.315	Numeric (log ug/L)
Toxicity	Minnow toxicity	2.103	Numeric (log mM)

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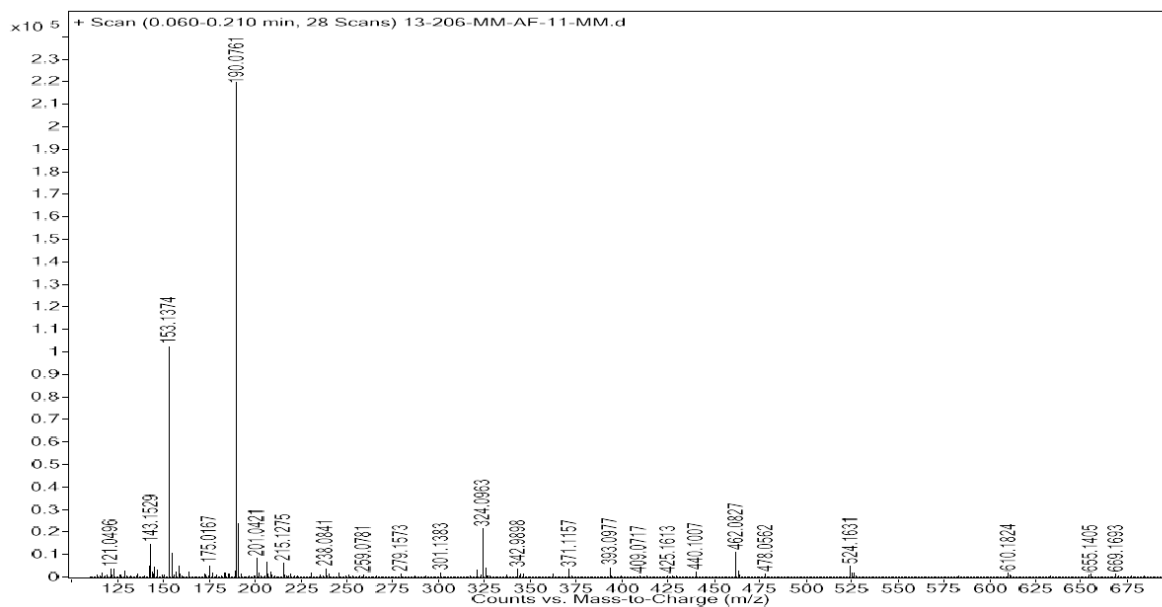
Figure S3 Predicted ADMET values for compound 10g using pkCSM.



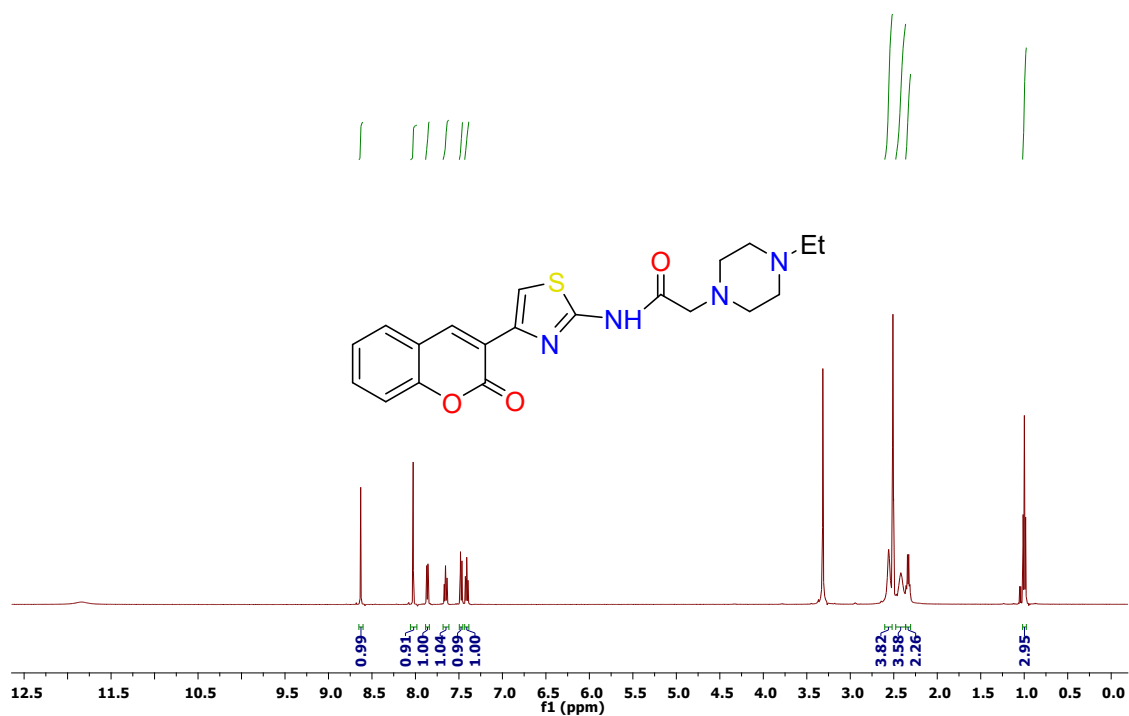
$^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$) spectrum of compound 10a



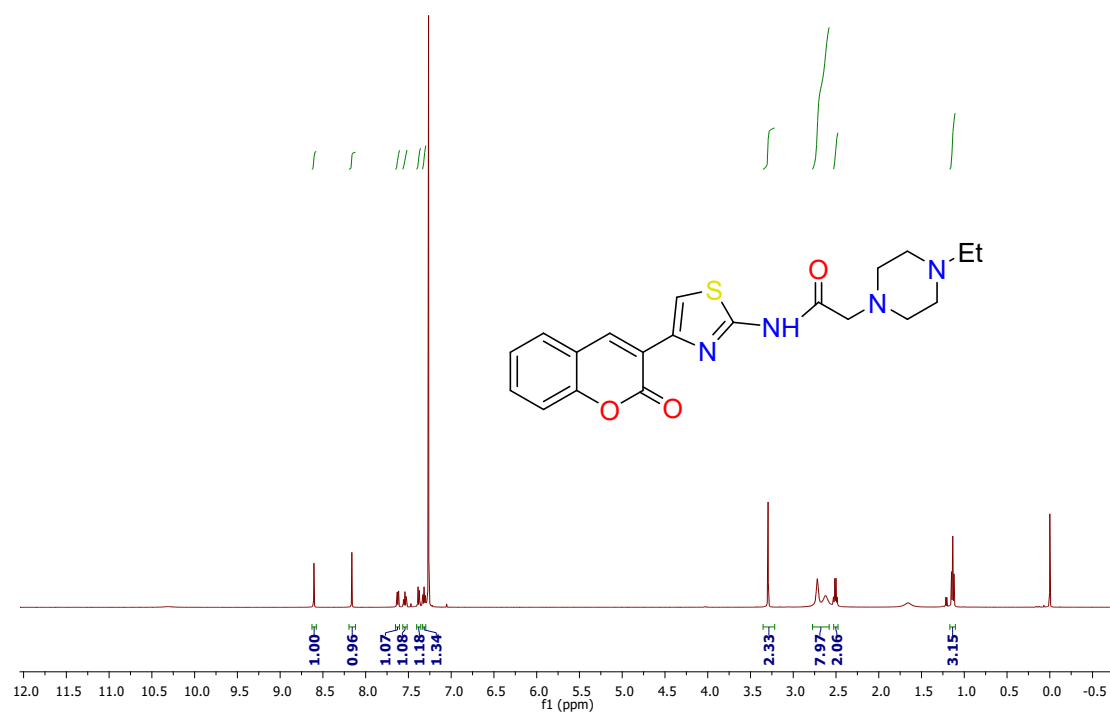
$^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d_6$) spectrum of compound 10a



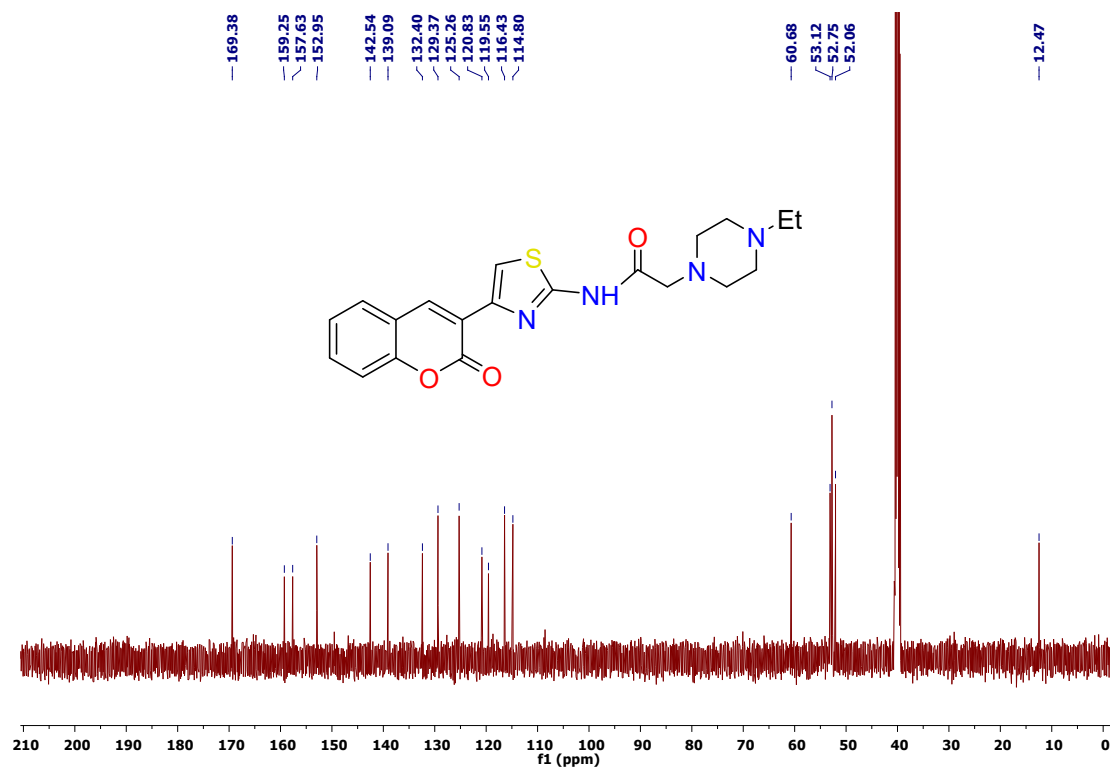
HRMS of compound 10a



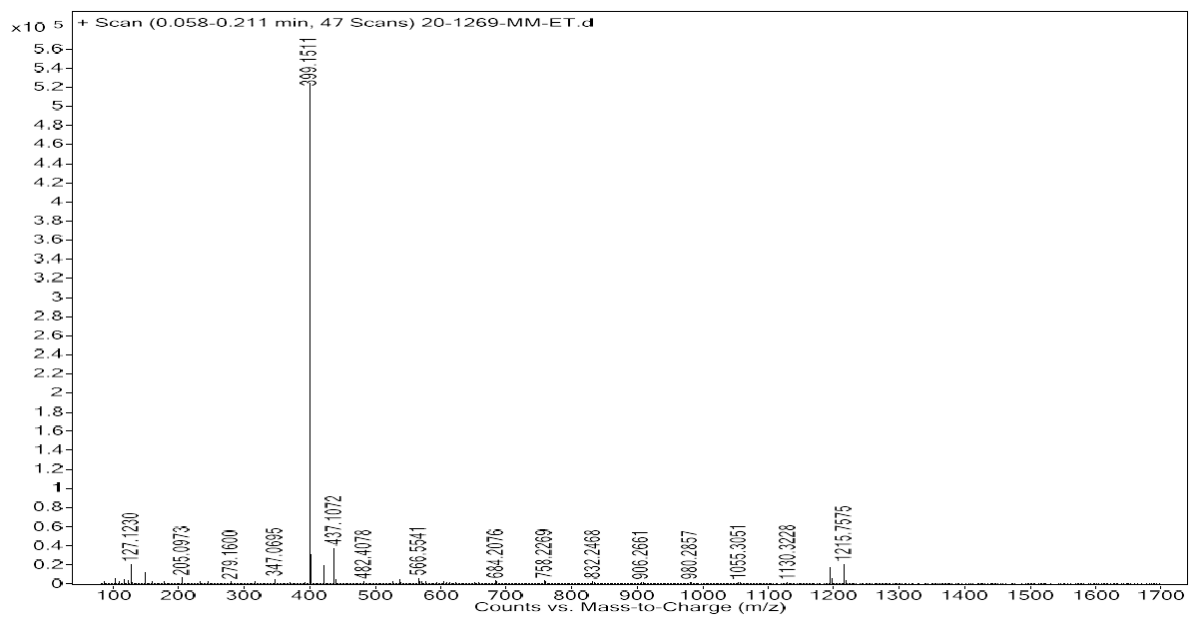
^1H NMR (500 MHz, $\text{DMSO-}d_6$) spectrum of compound 10b



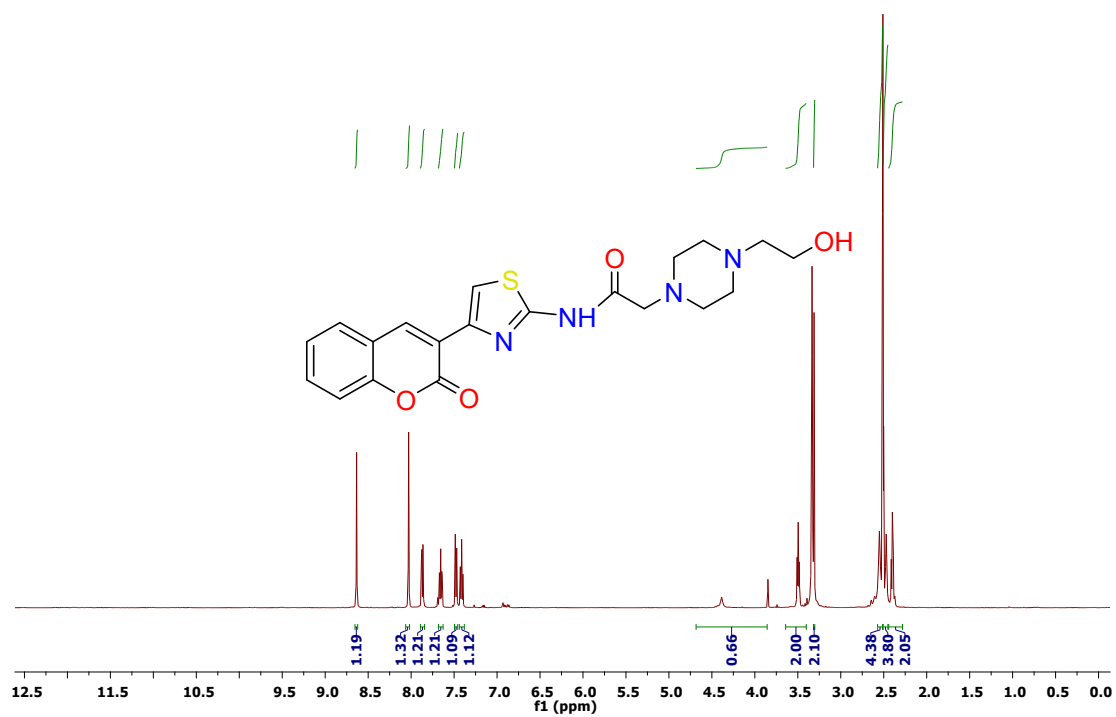
¹H NMR (500 MHz, CDCl₃) spectrum of compound **10b** - Carried out to identify missing CH₂ protons which had overlapped with moisture peak (δ 3.33) in DMSO solvent



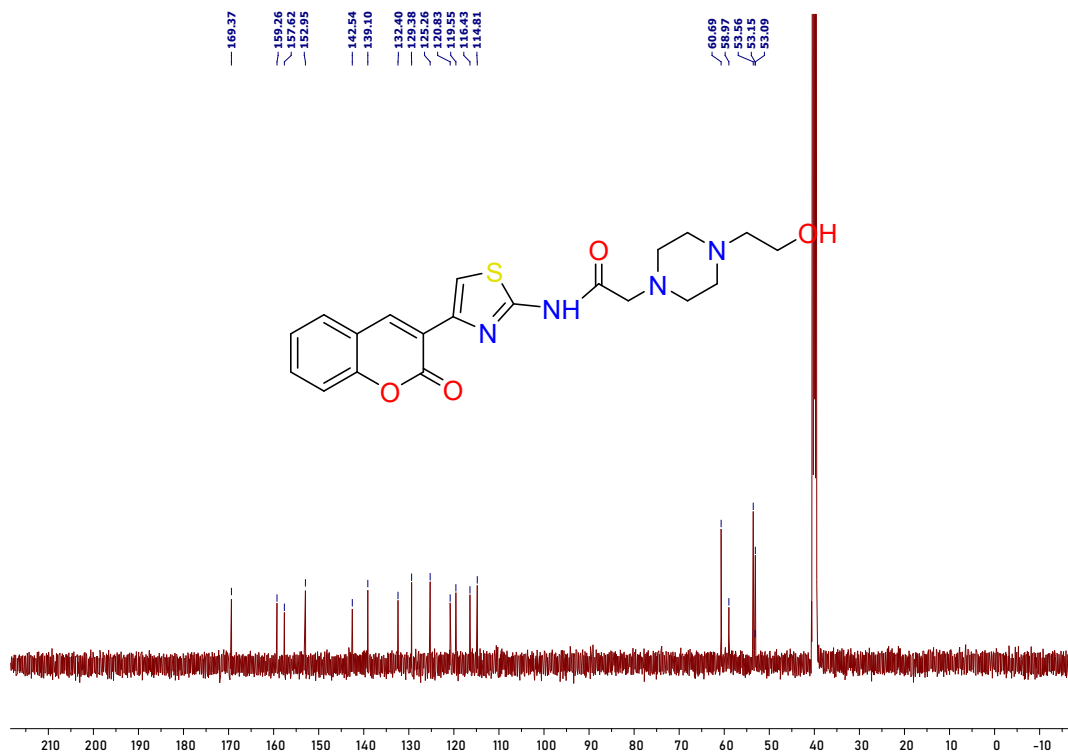
¹³C NMR (125 MHz, DMSO-*d*₆) spectrum of compound **10b**



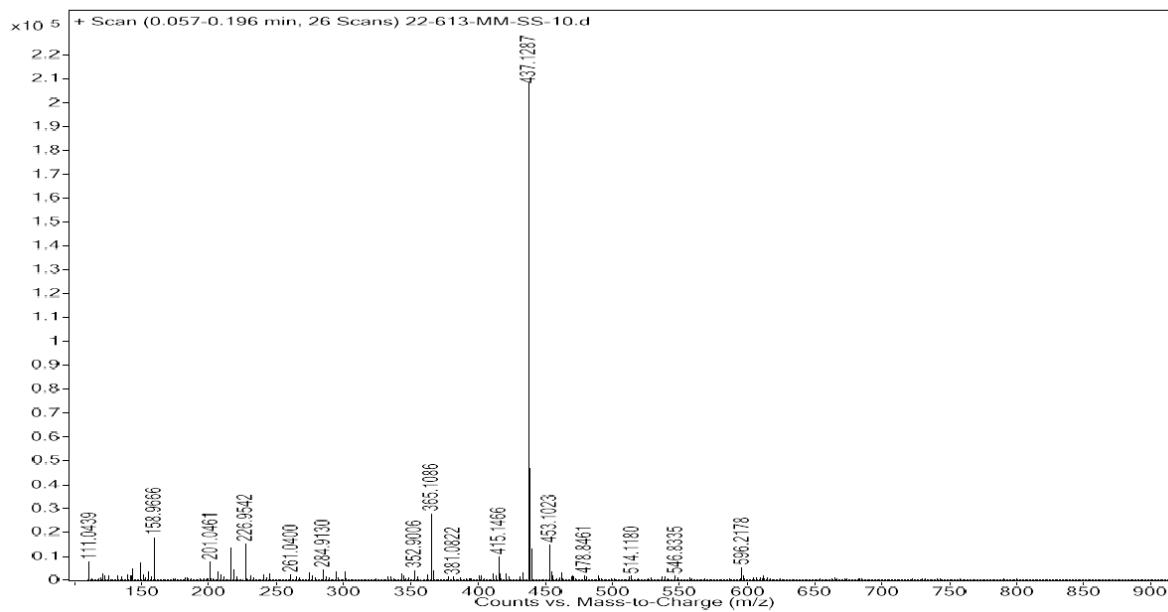
HRMS of compound **10b**



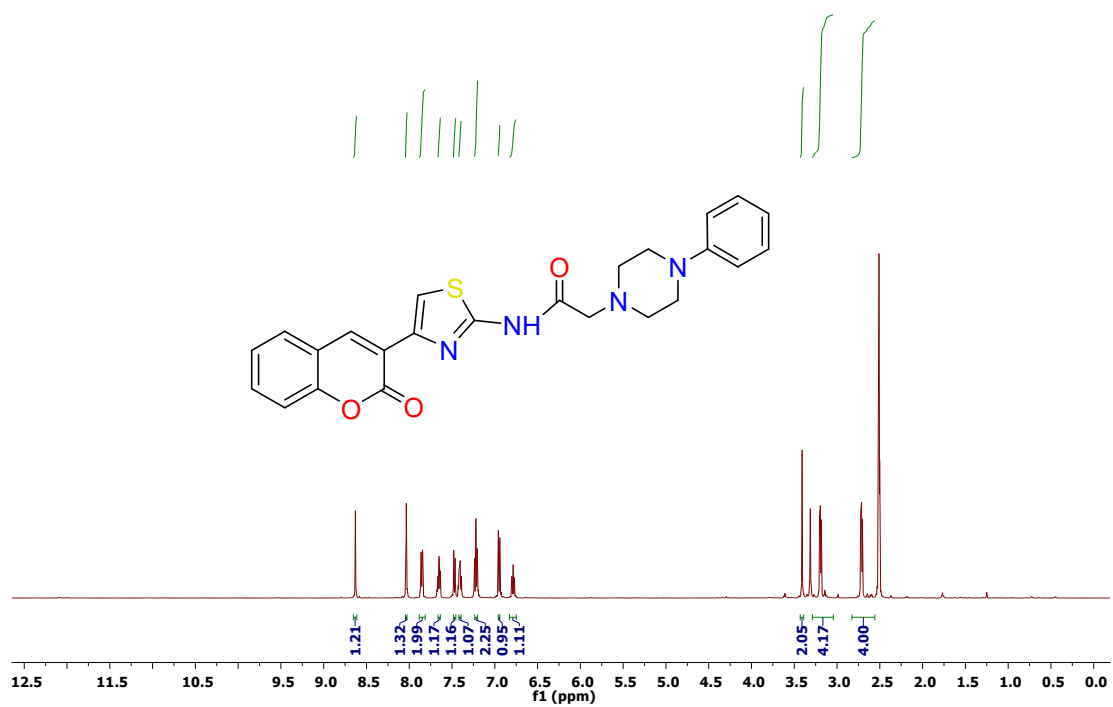
¹H NMR (500 MHz, DMSO-*d*₆) spectrum of compound **10c**



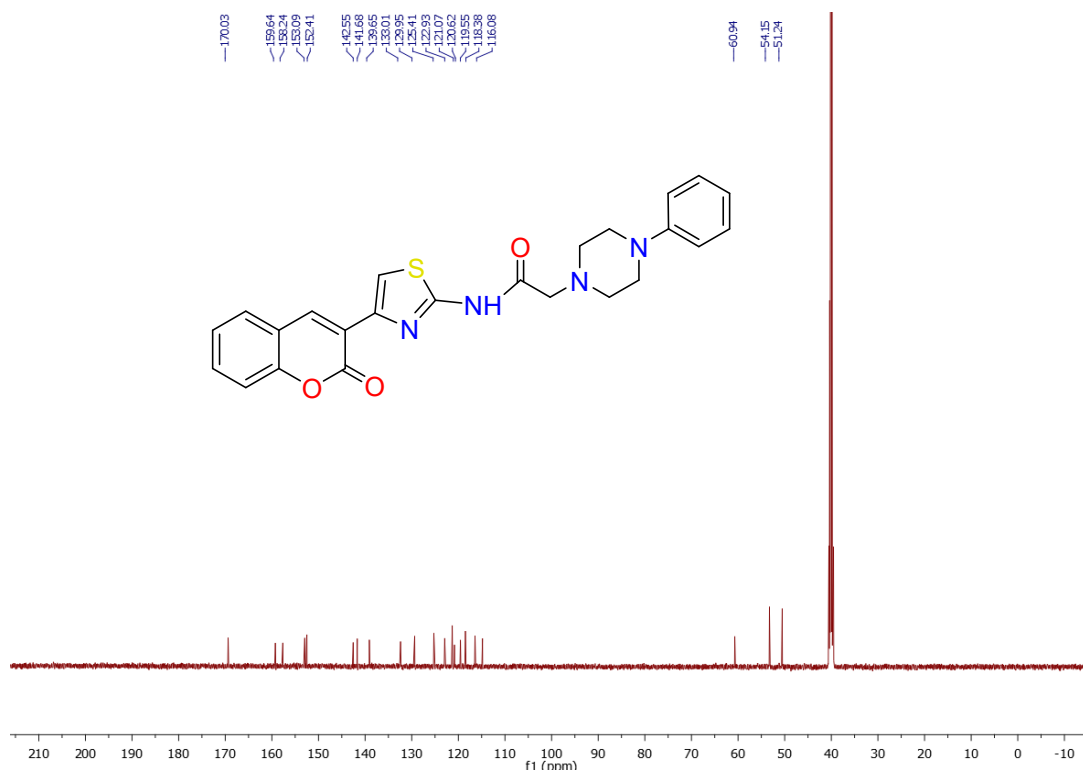
¹³C NMR (125 MHz, DMSO-*d*₆) spectrum of compound 10c



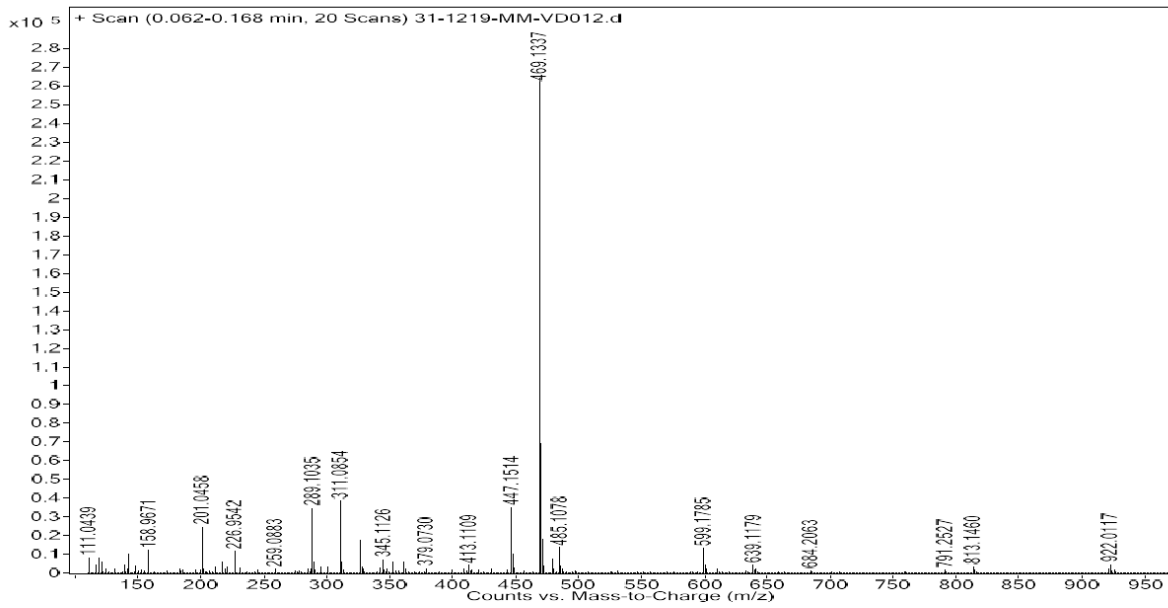
HRMS of compound 10c



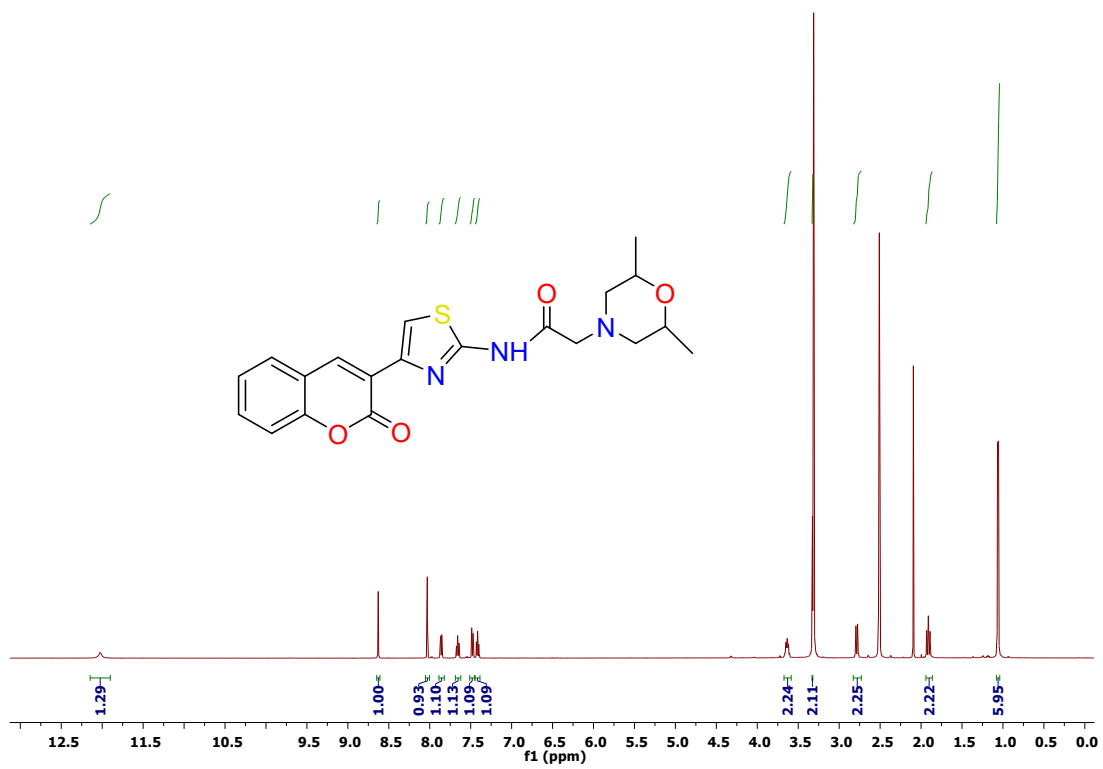
¹H NMR (500 MHz, DMSO-*d*₆) spectrum of compound 10d



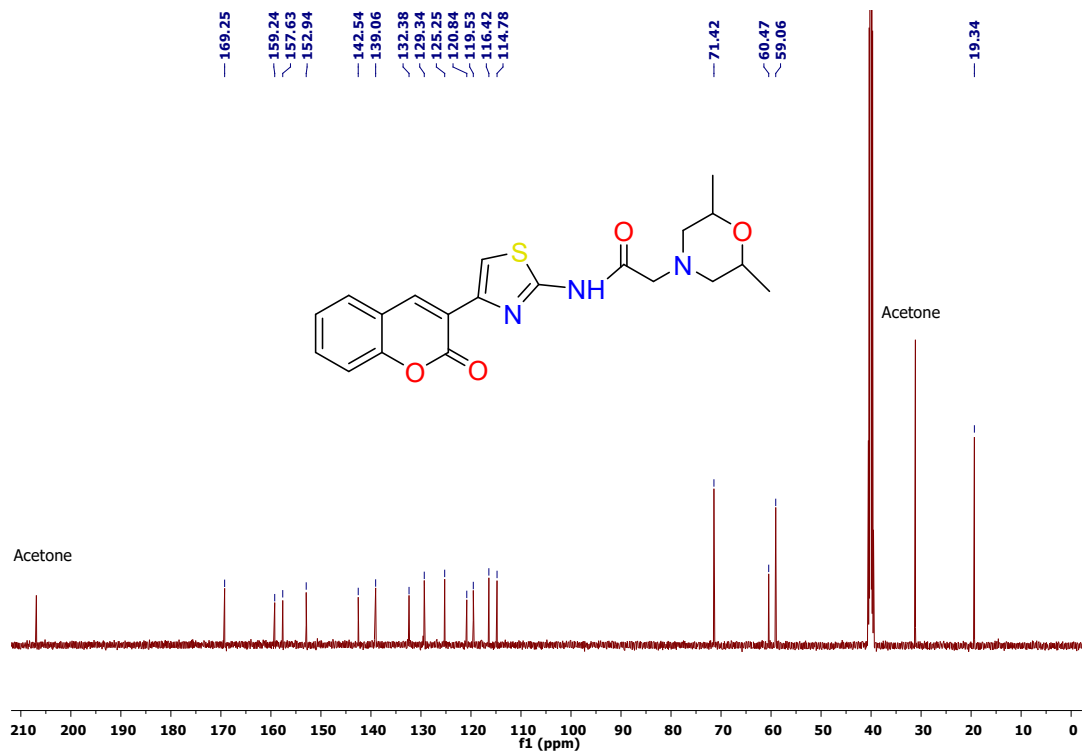
¹³C NMR (125 MHz, DMSO-*d*₆) spectrum of compound 10d



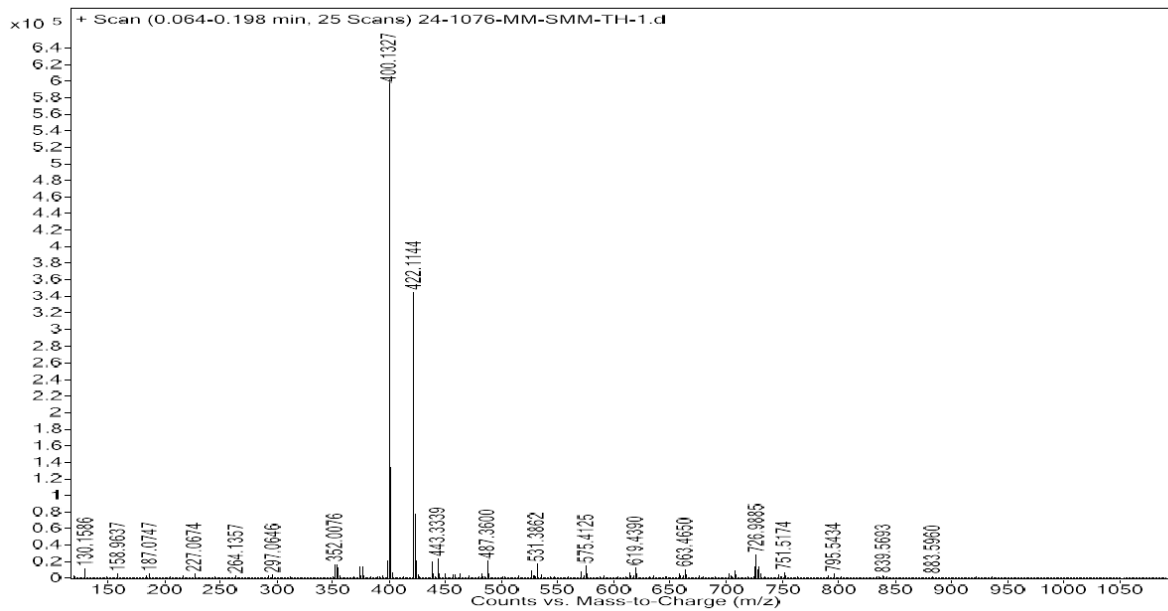
HRMS of compound **10d**



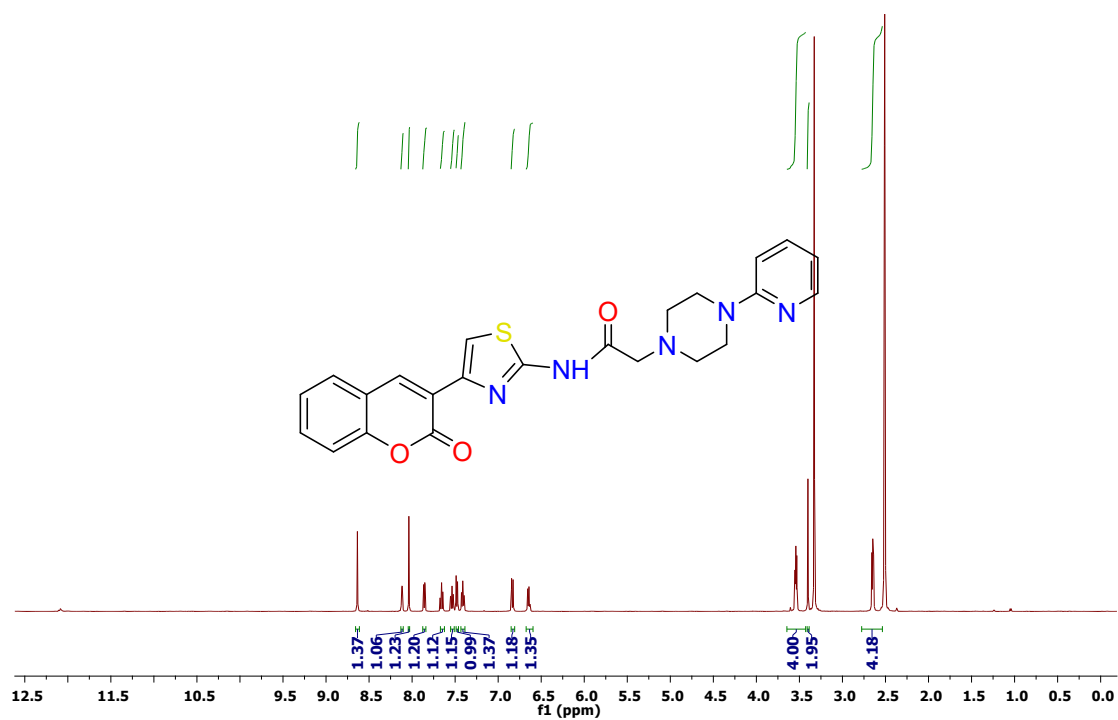
¹H NMR (500 MHz, DMSO-*d*₆) spectrum of compound **10e**



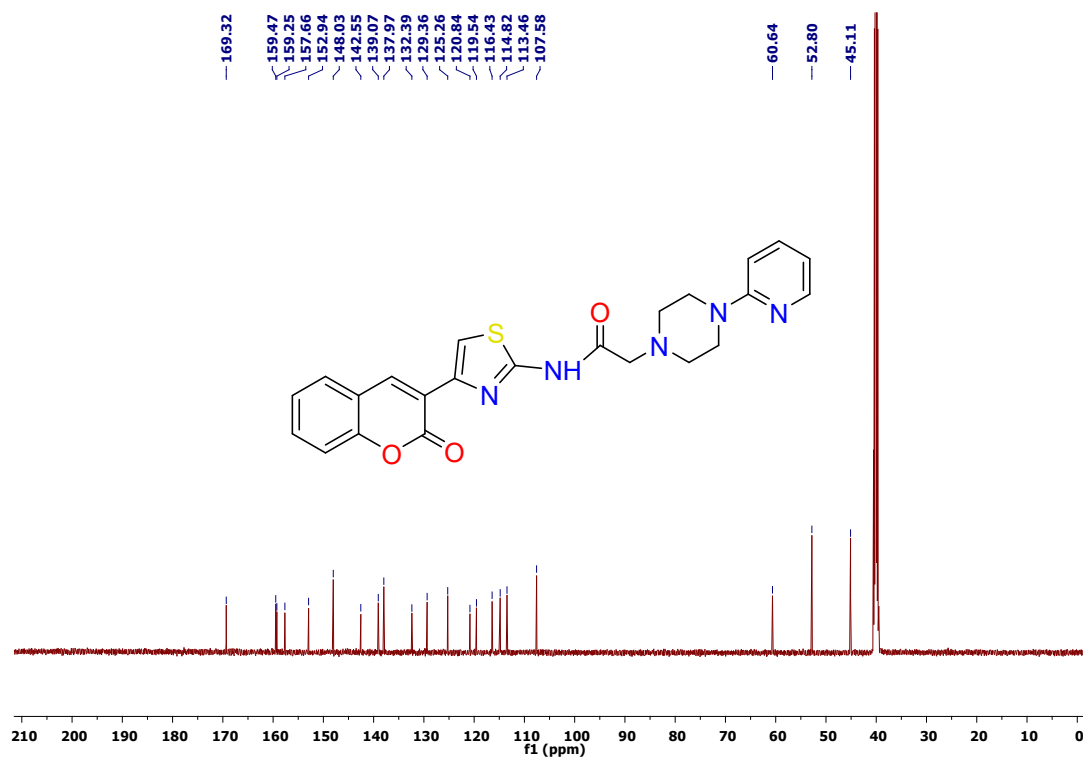
¹³C NMR (125 MHz, DMSO-*d*₆) spectrum of compound 10e



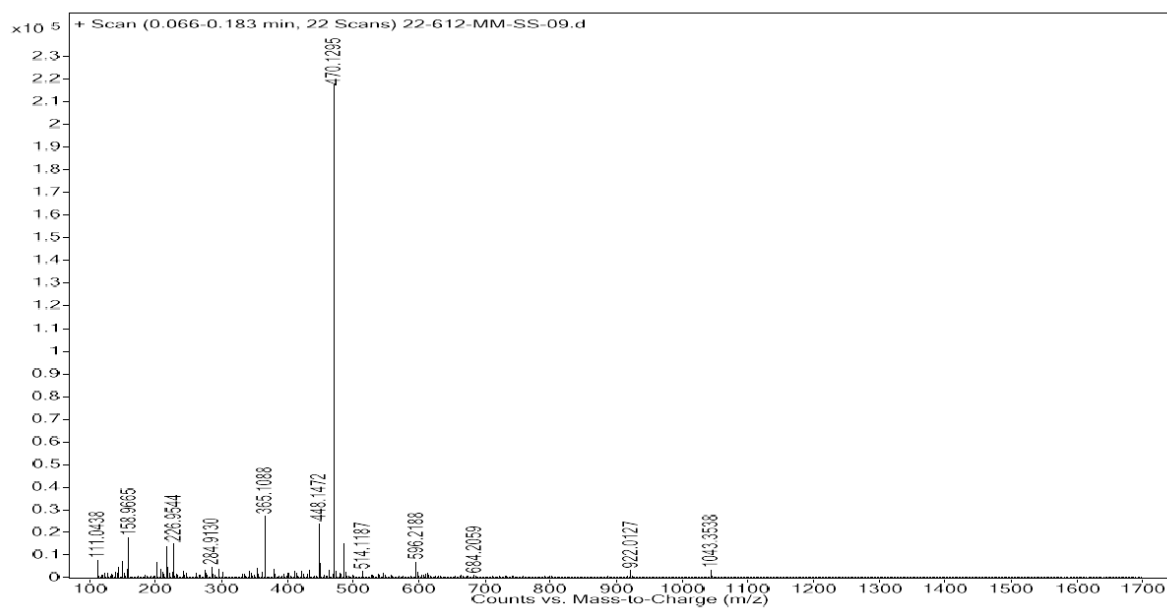
HRMS of compound 10e



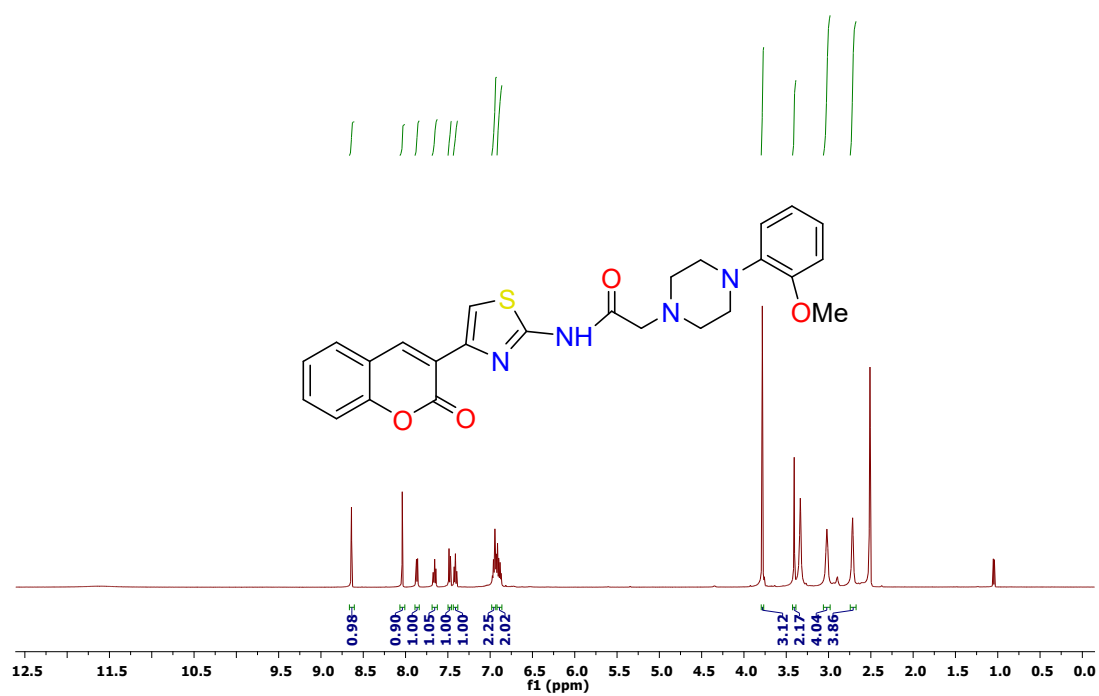
¹H NMR (500 MHz, DMSO-*d*₆) spectrum of compound **10f**



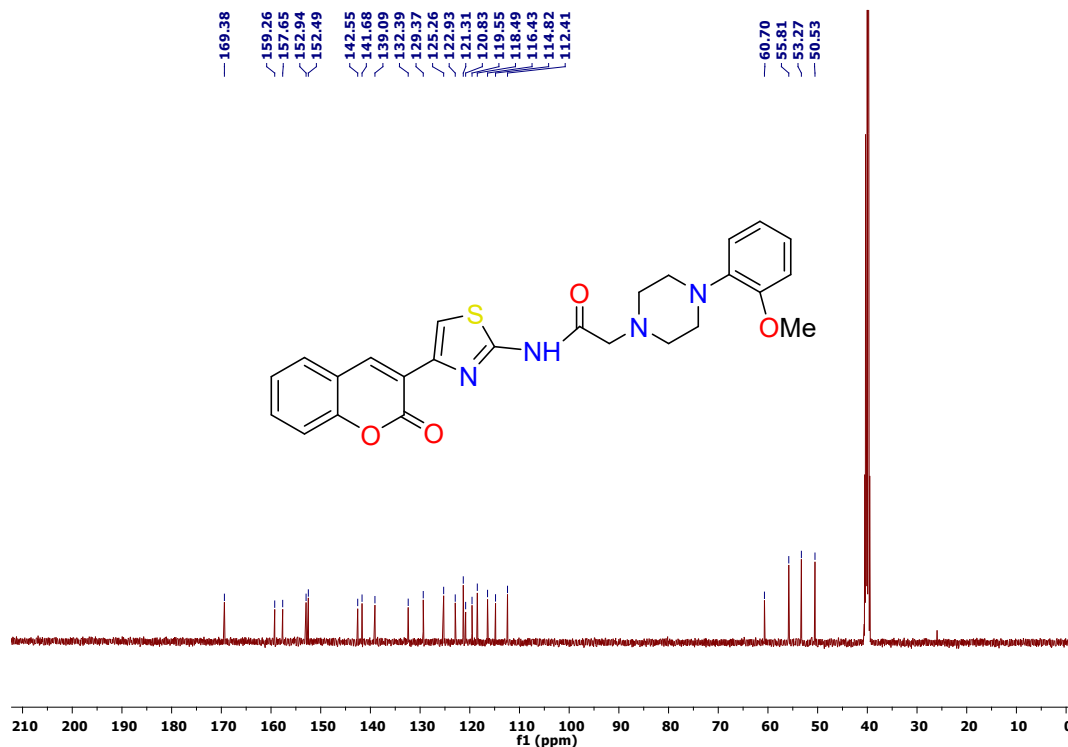
¹³C NMR (125 MHz, DMSO-*d*₆) spectrum of compound **10f**



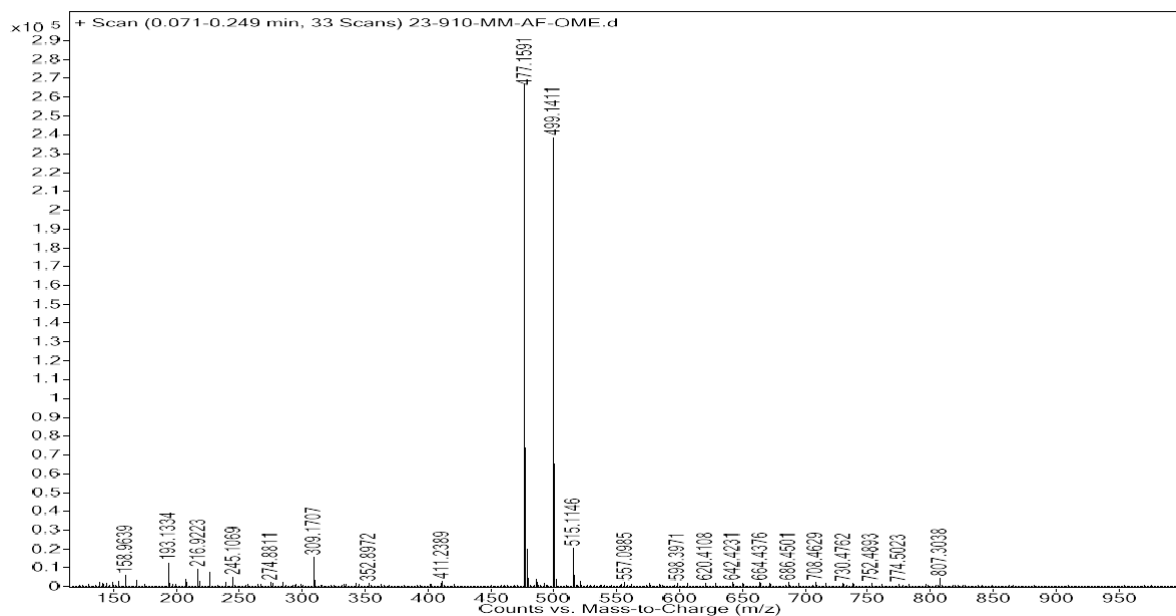
HRMS of compound **10f**



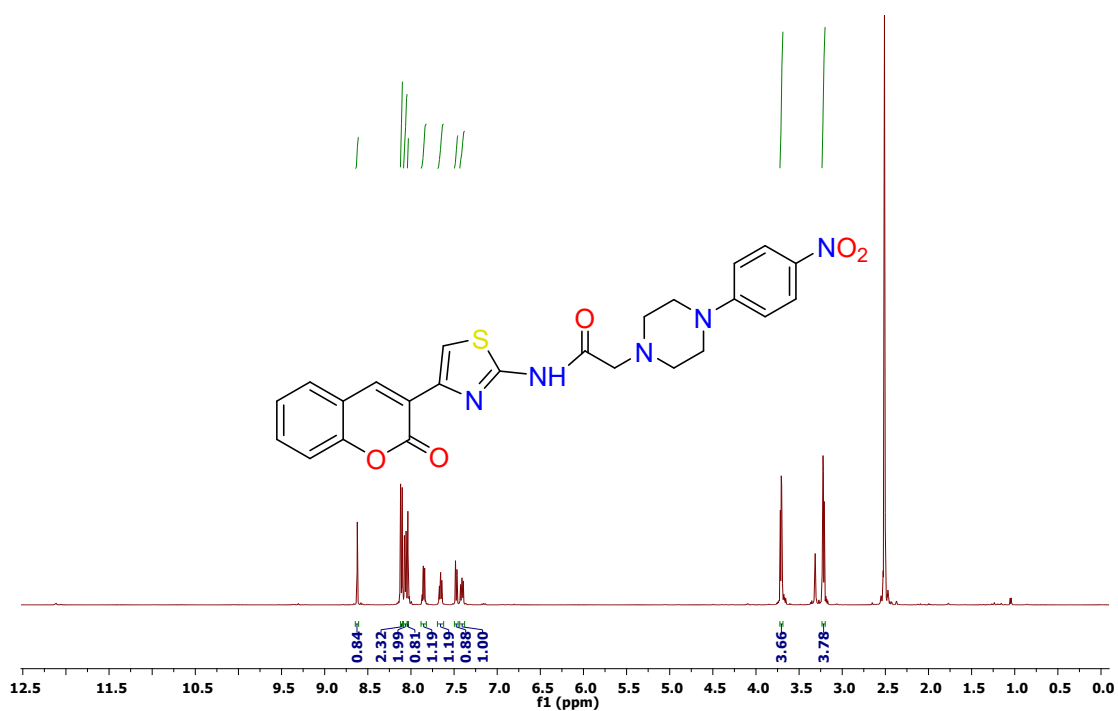
¹H NMR (500 MHz, DMSO-*d*₆) spectrum of compound **10g**



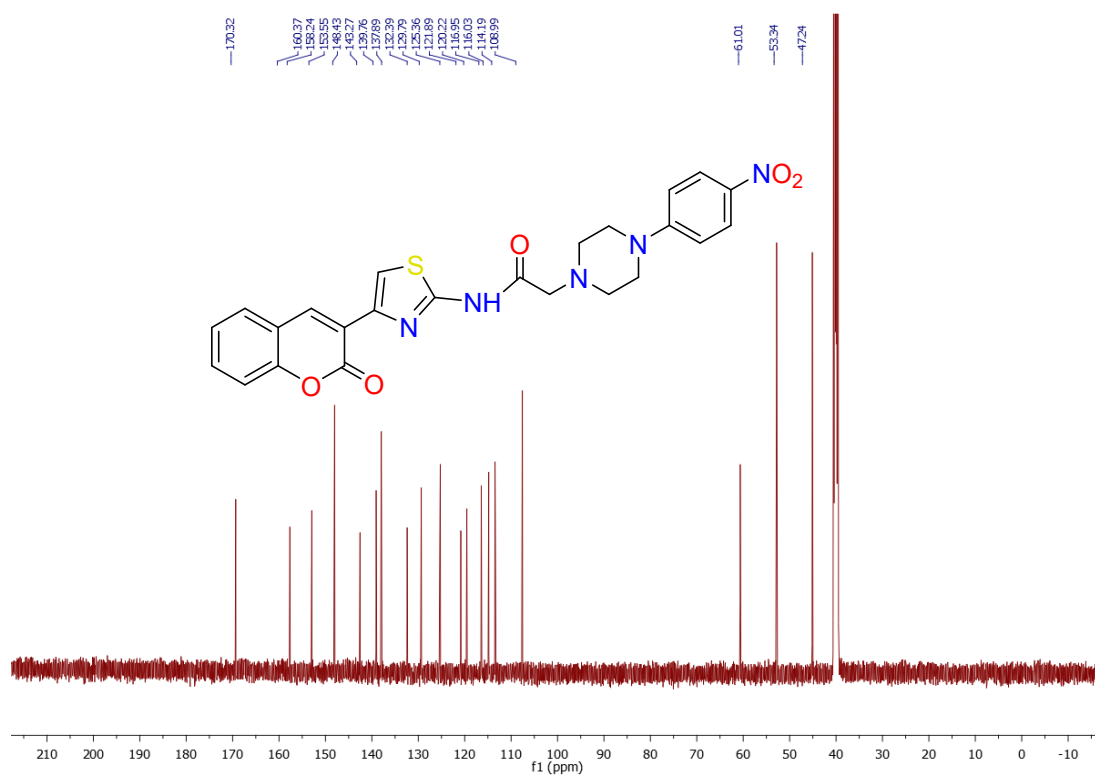
¹³C NMR (125 MHz, DMSO-*d*₆) spectrum of compound 10g



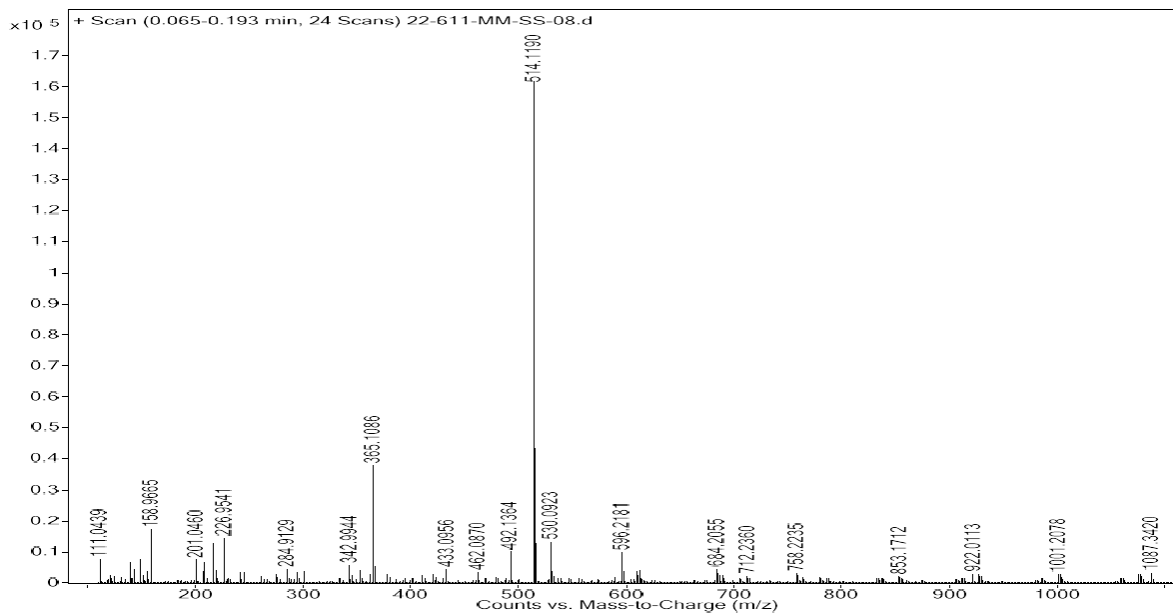
HRMS of compound 10g



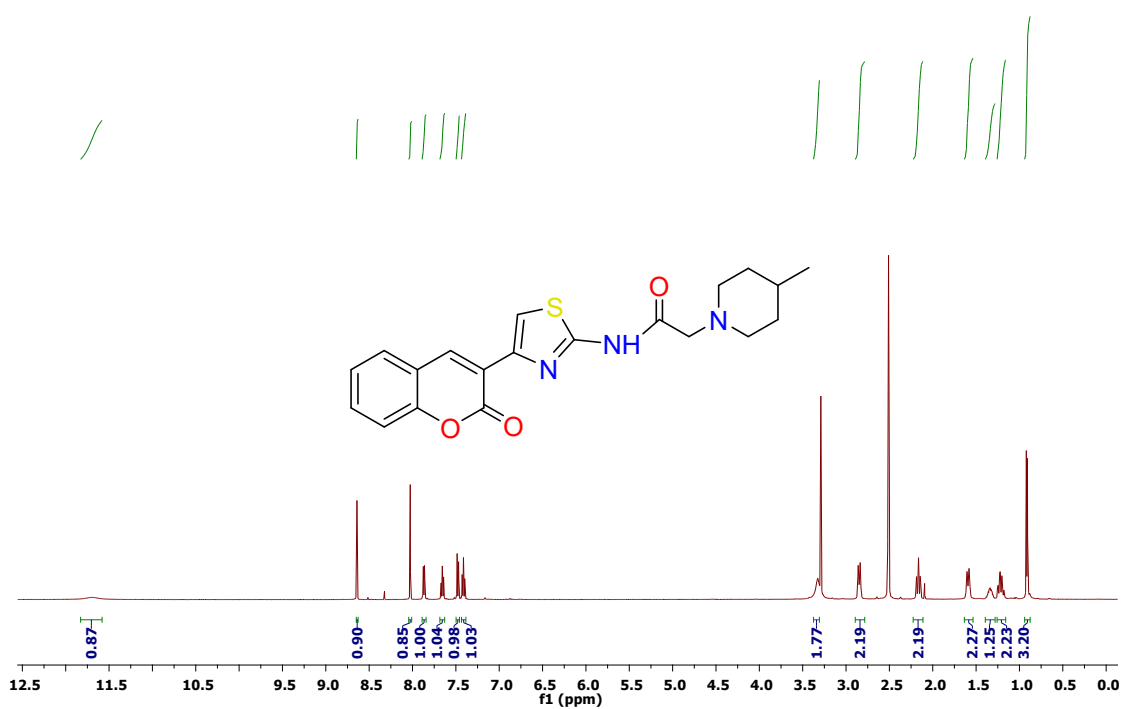
¹H NMR (500 MHz, DMSO-*d*₆) spectrum of compound 10h



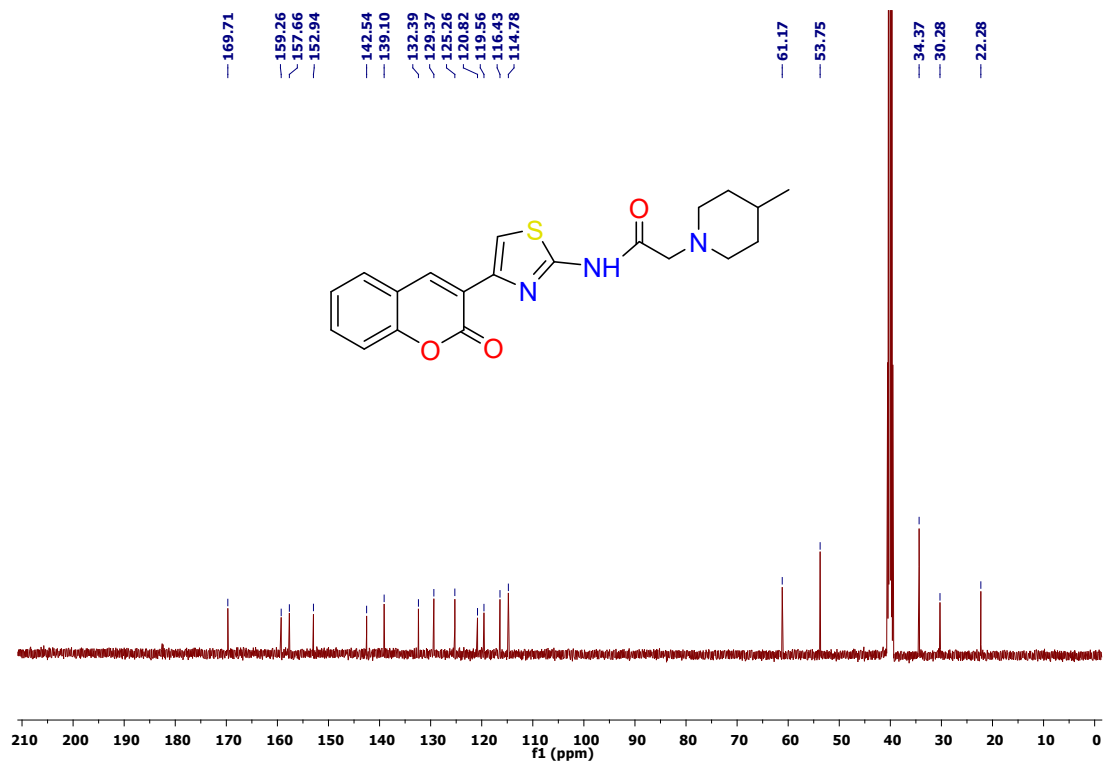
¹³C NMR (125 MHz, DMSO-*d*₆) spectrum of compound 10h



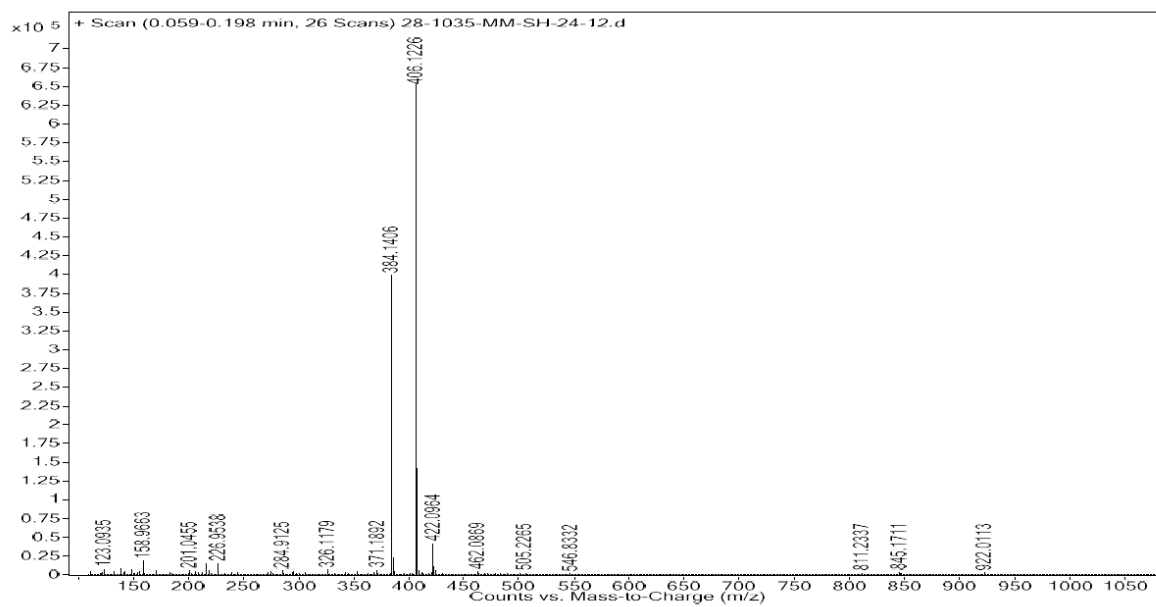
HRMS of compound 10h



¹H NMR (500 MHz, DMSO-*d*₆) spectrum of compound 10i



¹³C NMR (125 MHz, DMSO-*d*₆) spectrum of compound 10i



HRMS of compound 10i