Supplementary Materials

Dihydro-2H-thiopyran-3(4H)-one-1,1-dioxide - a versatile building block for the synthesis of new thiopyran-based heterocyclic systems

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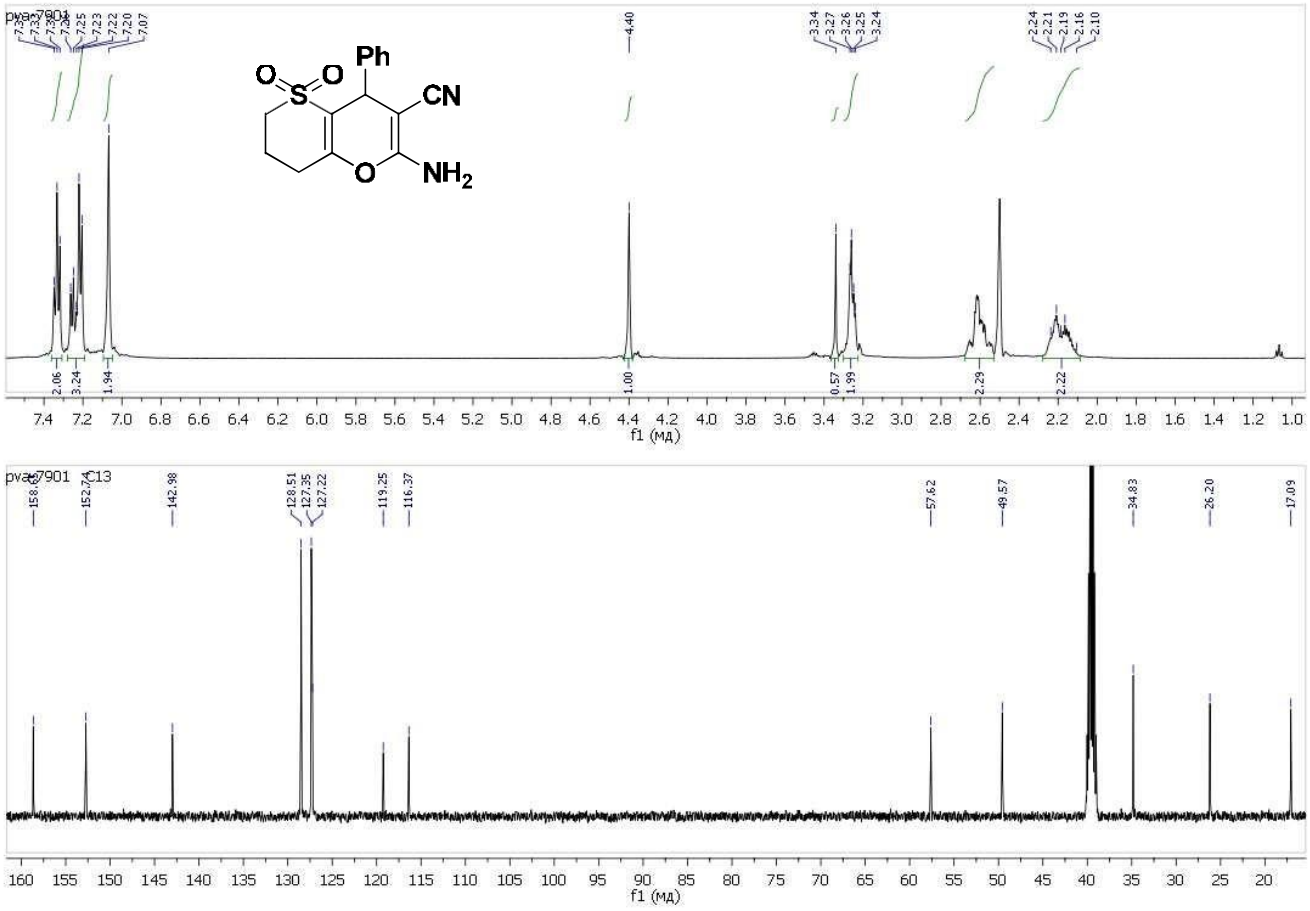

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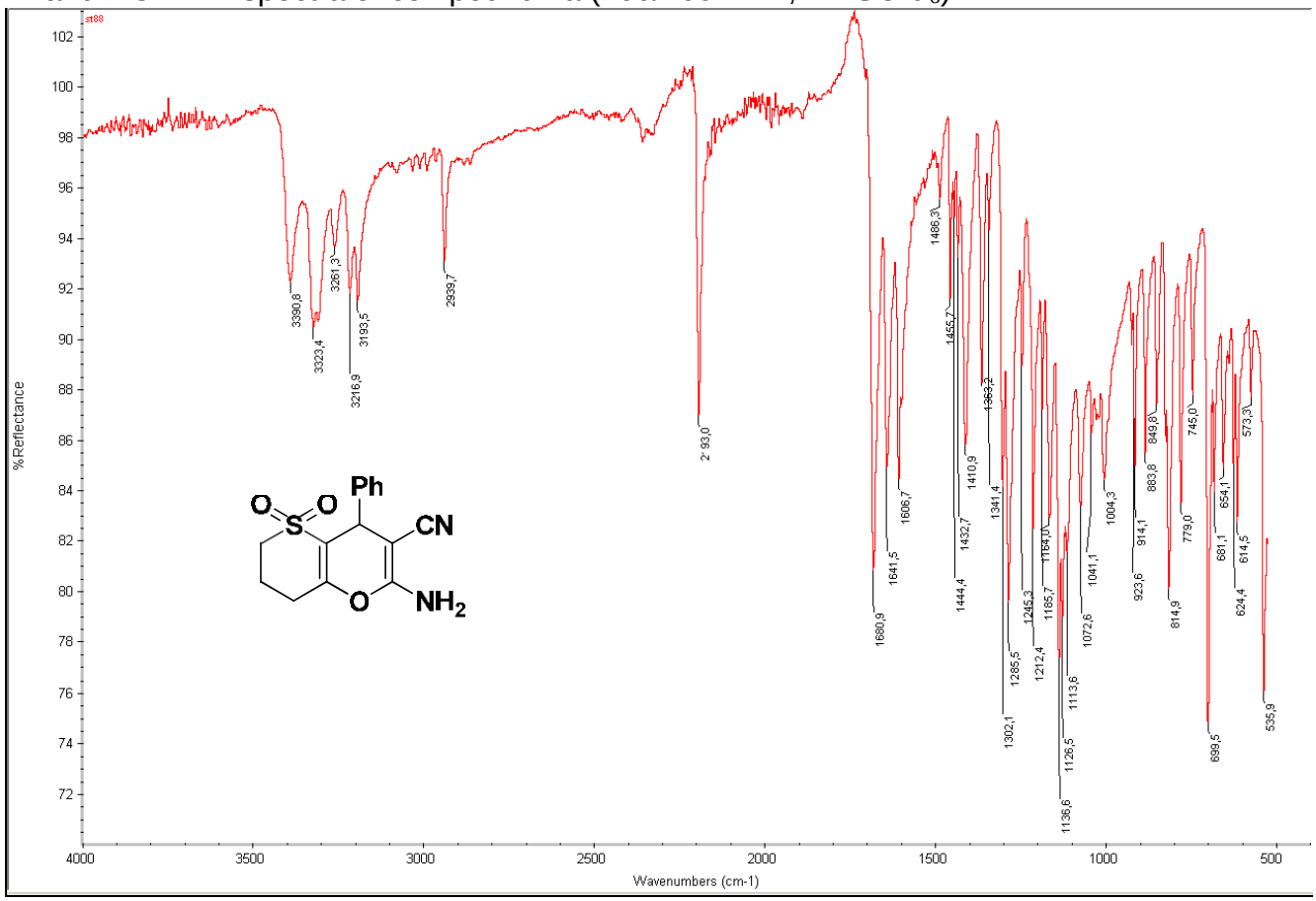

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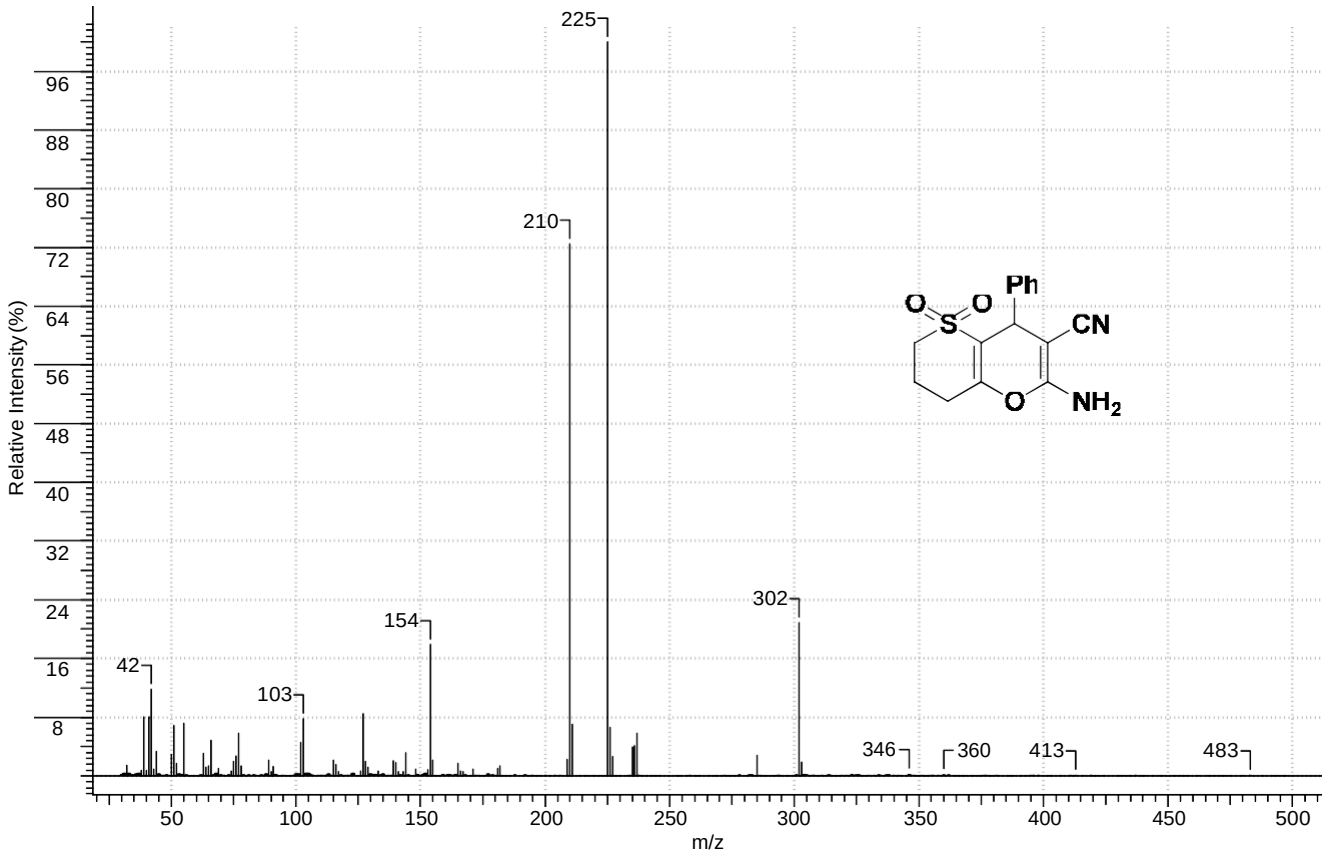

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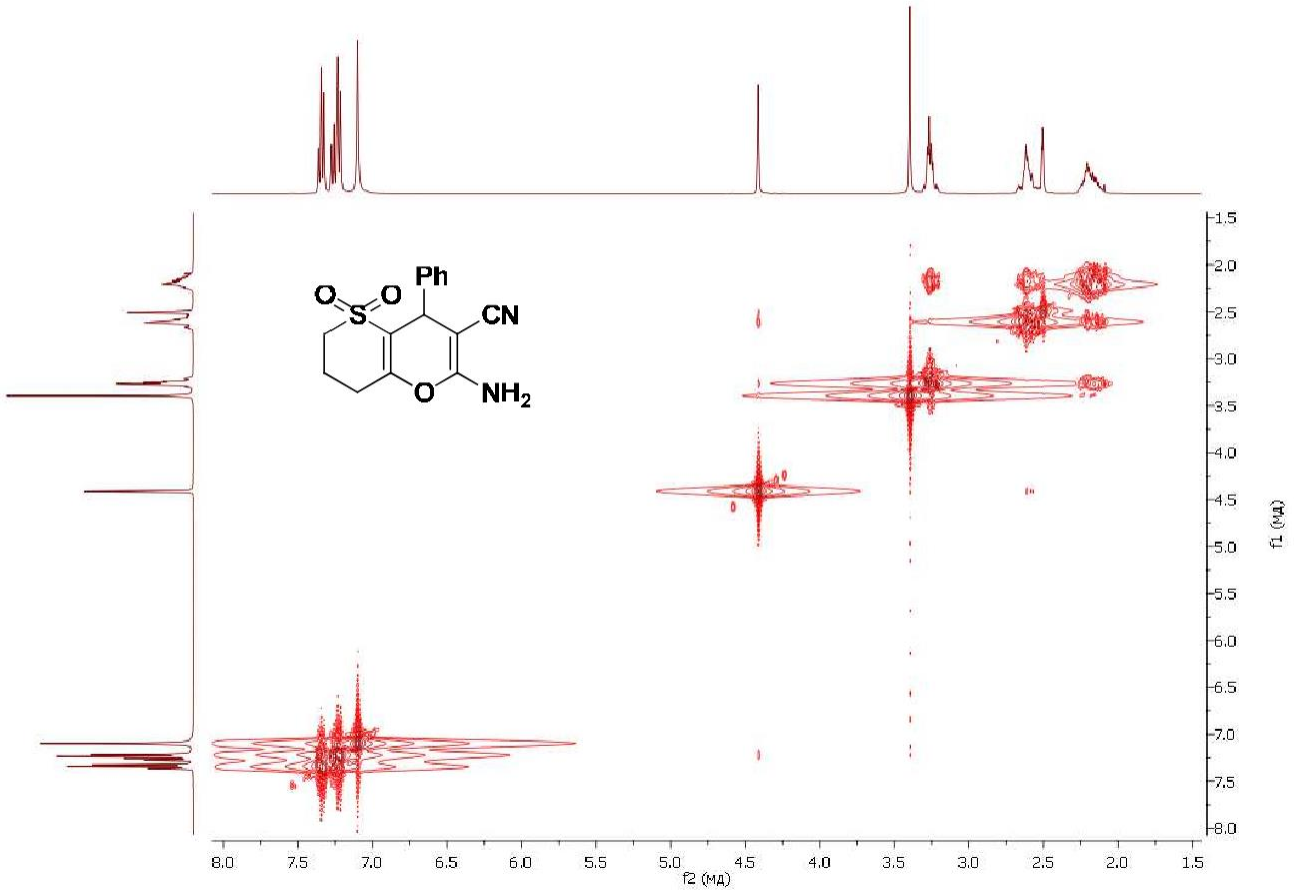

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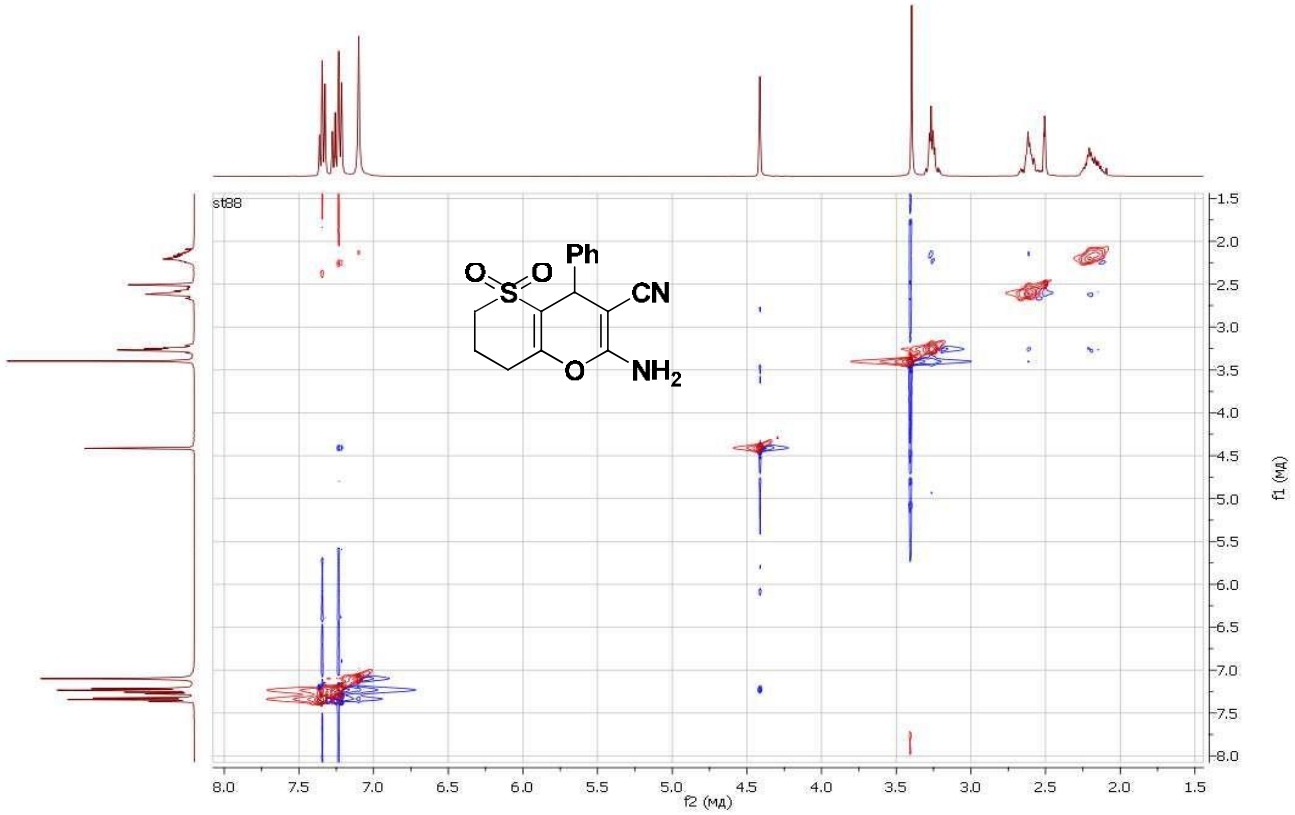

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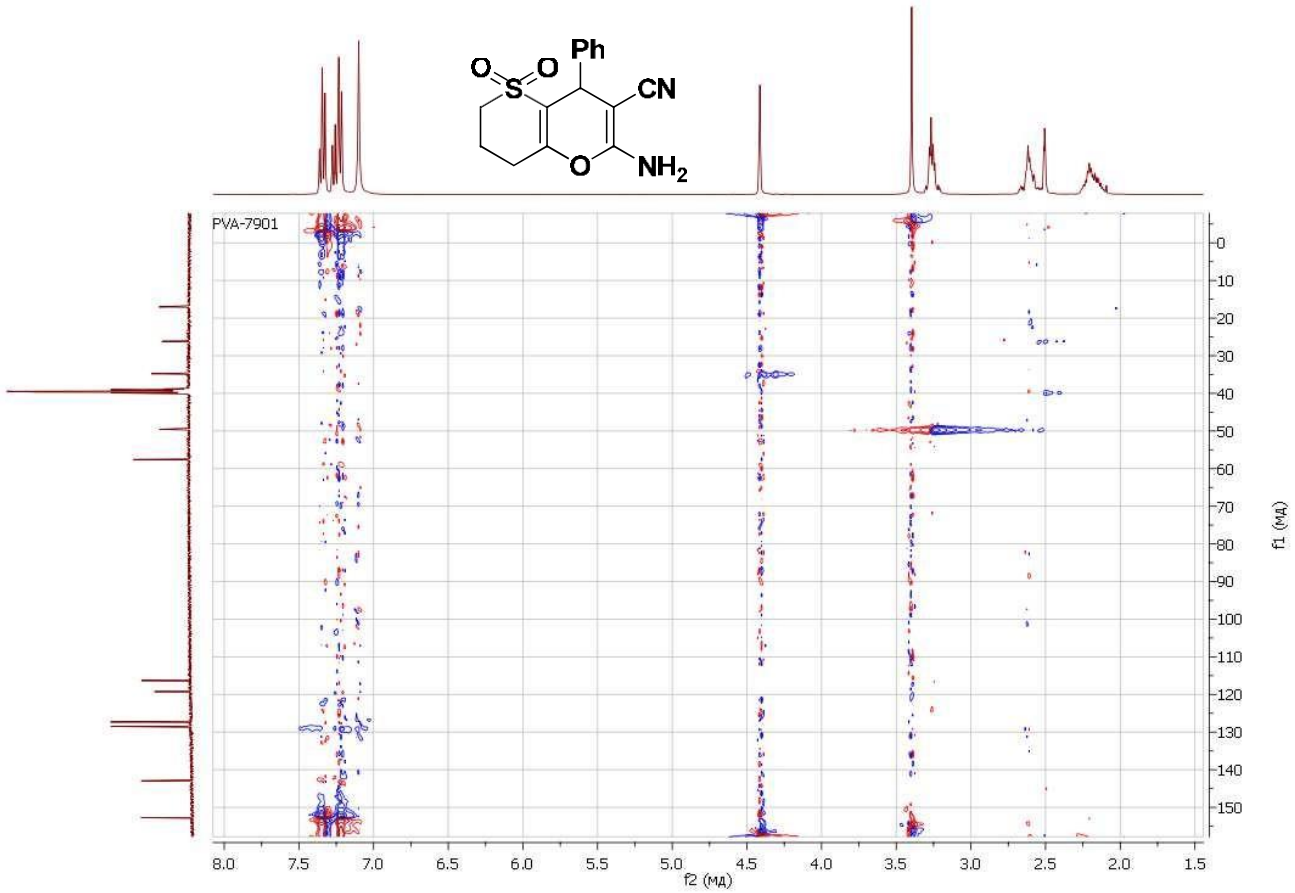

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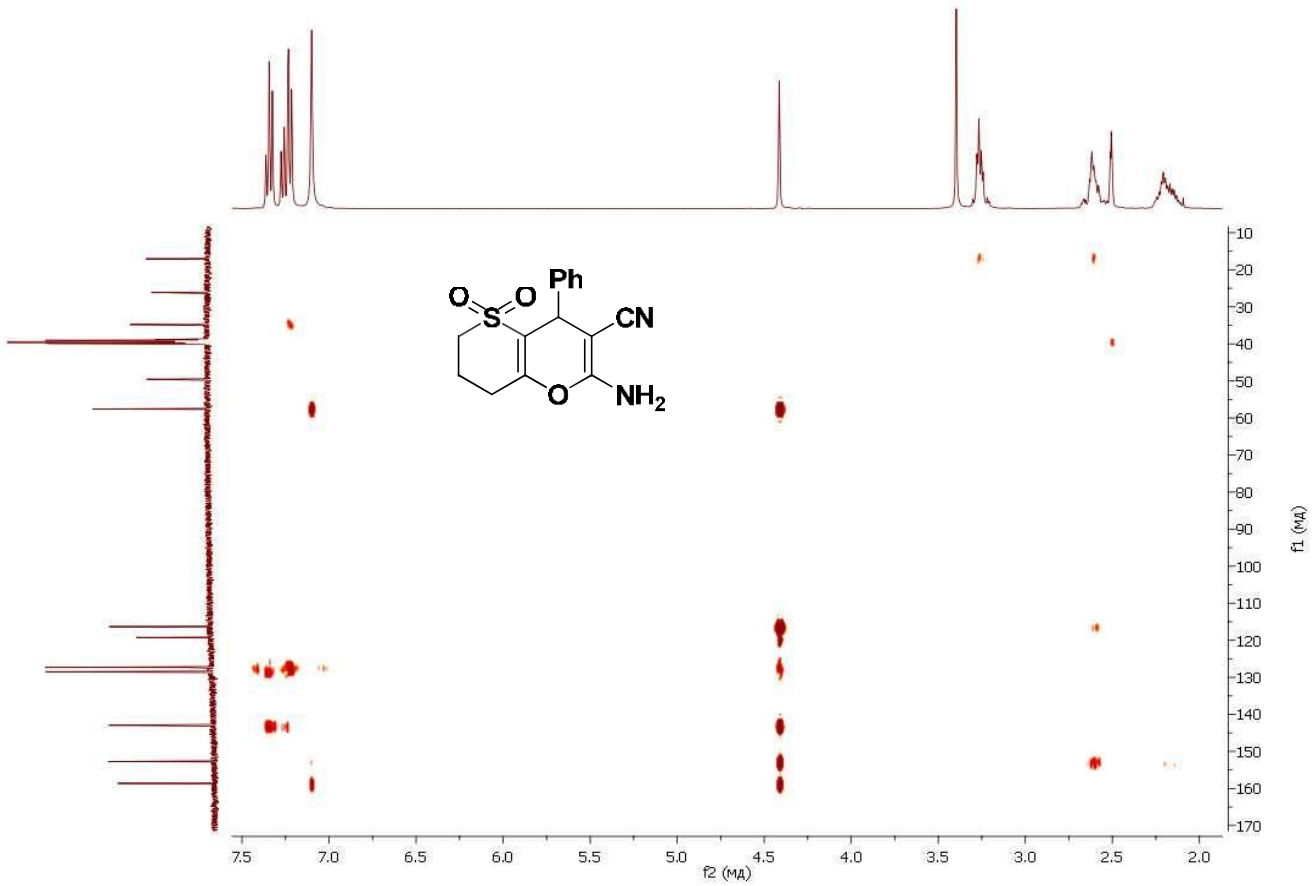

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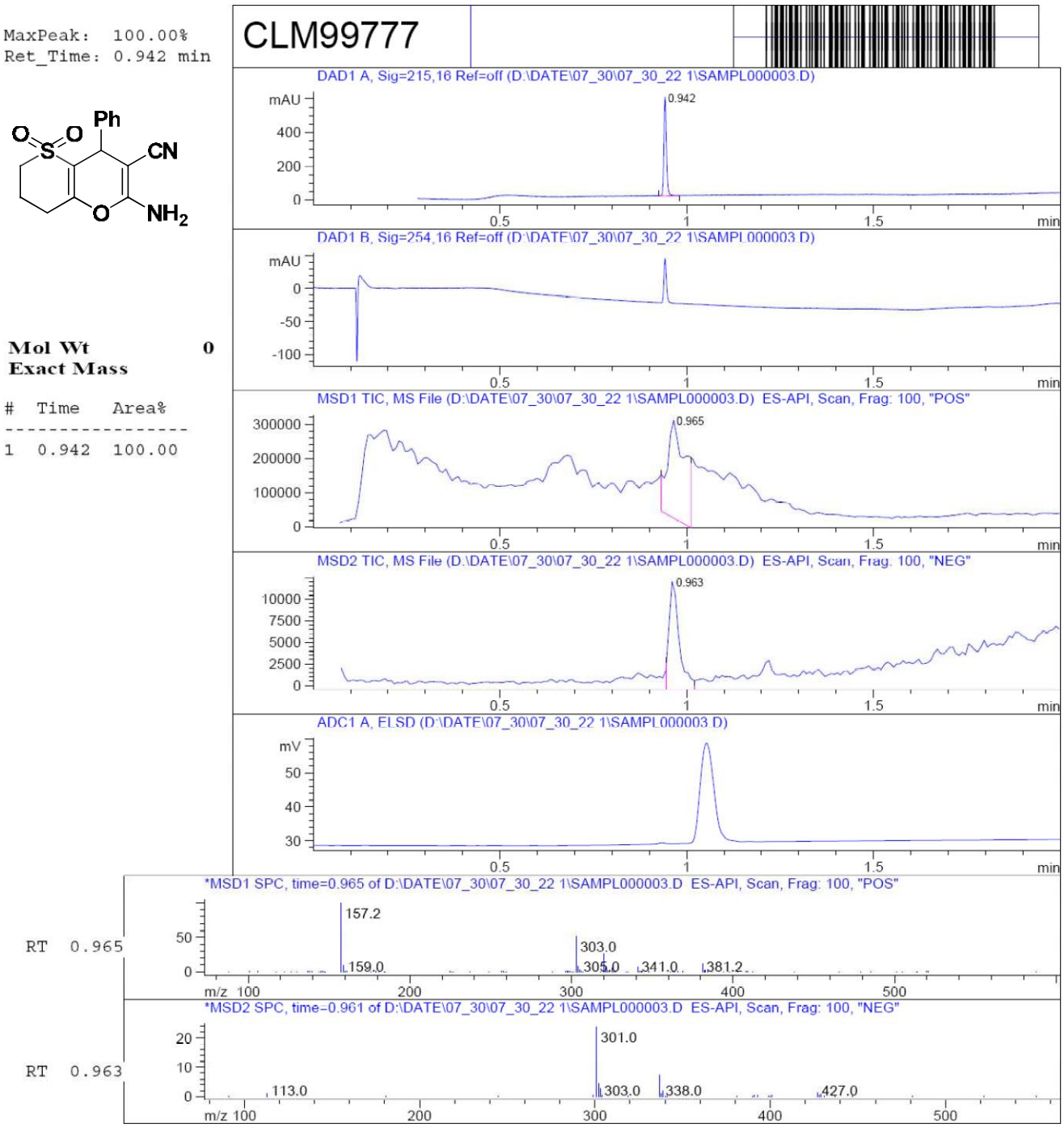
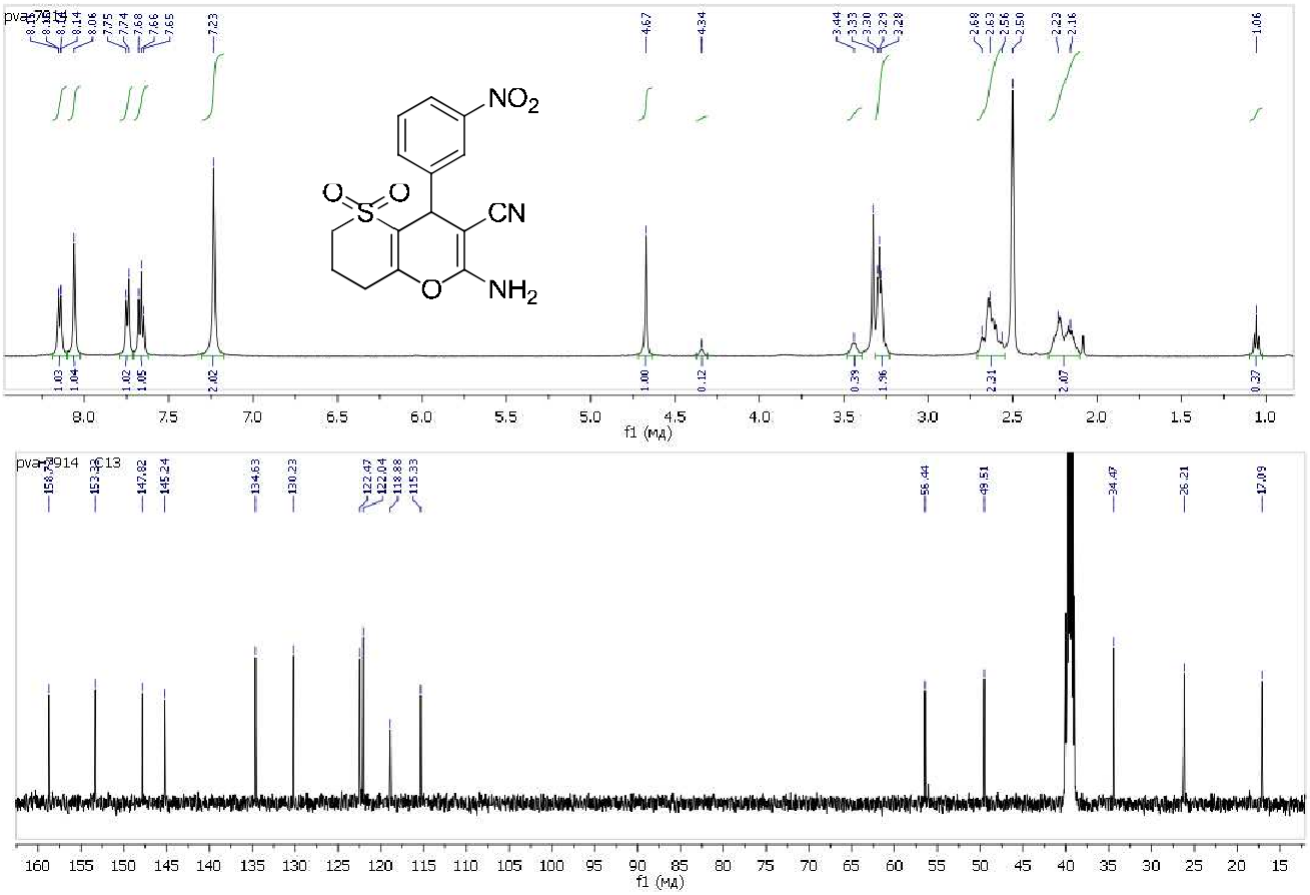
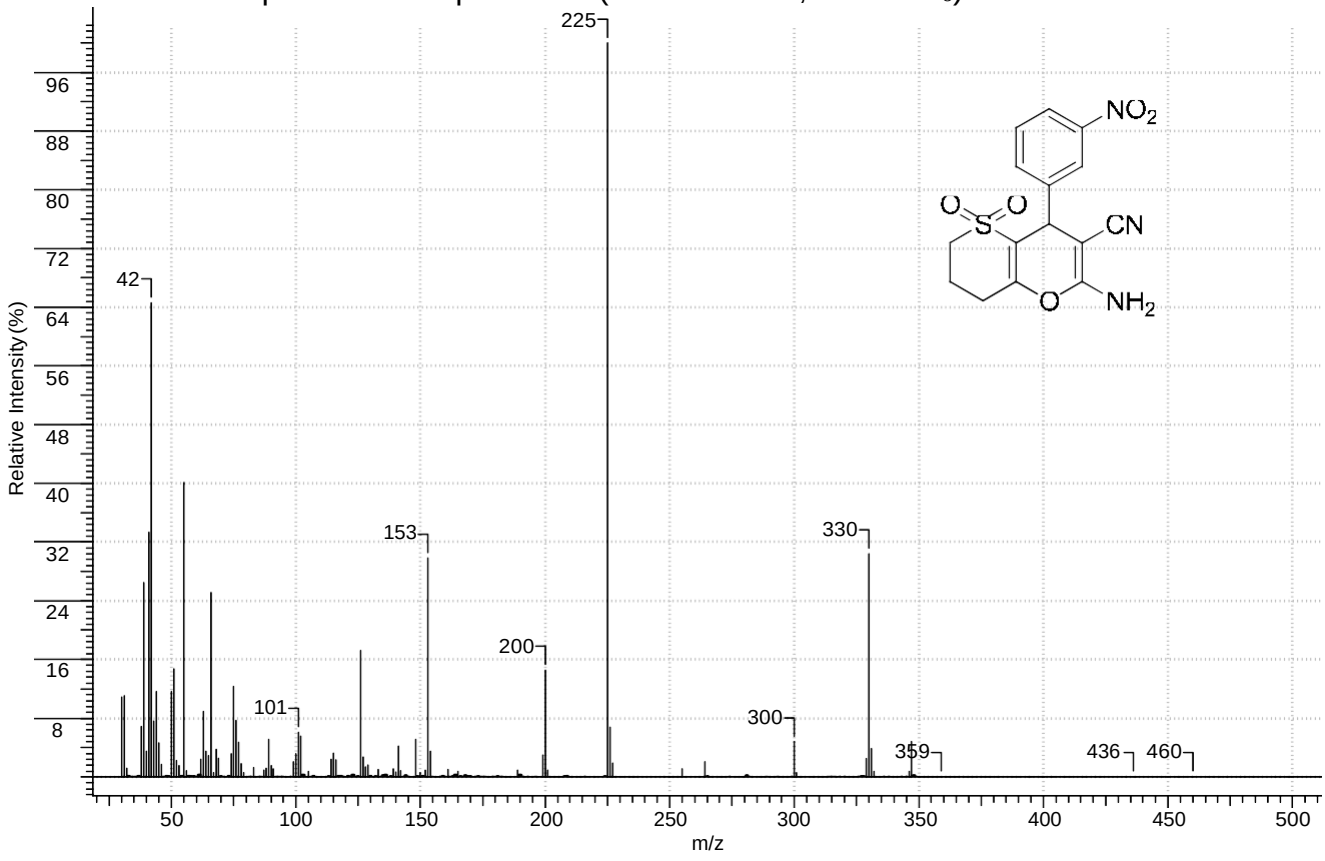


LC-MS data for compound 2a



^{1}H and ^{13}C NMR spectra of compound 2b (500/126 MHz, DMSO-d_6)



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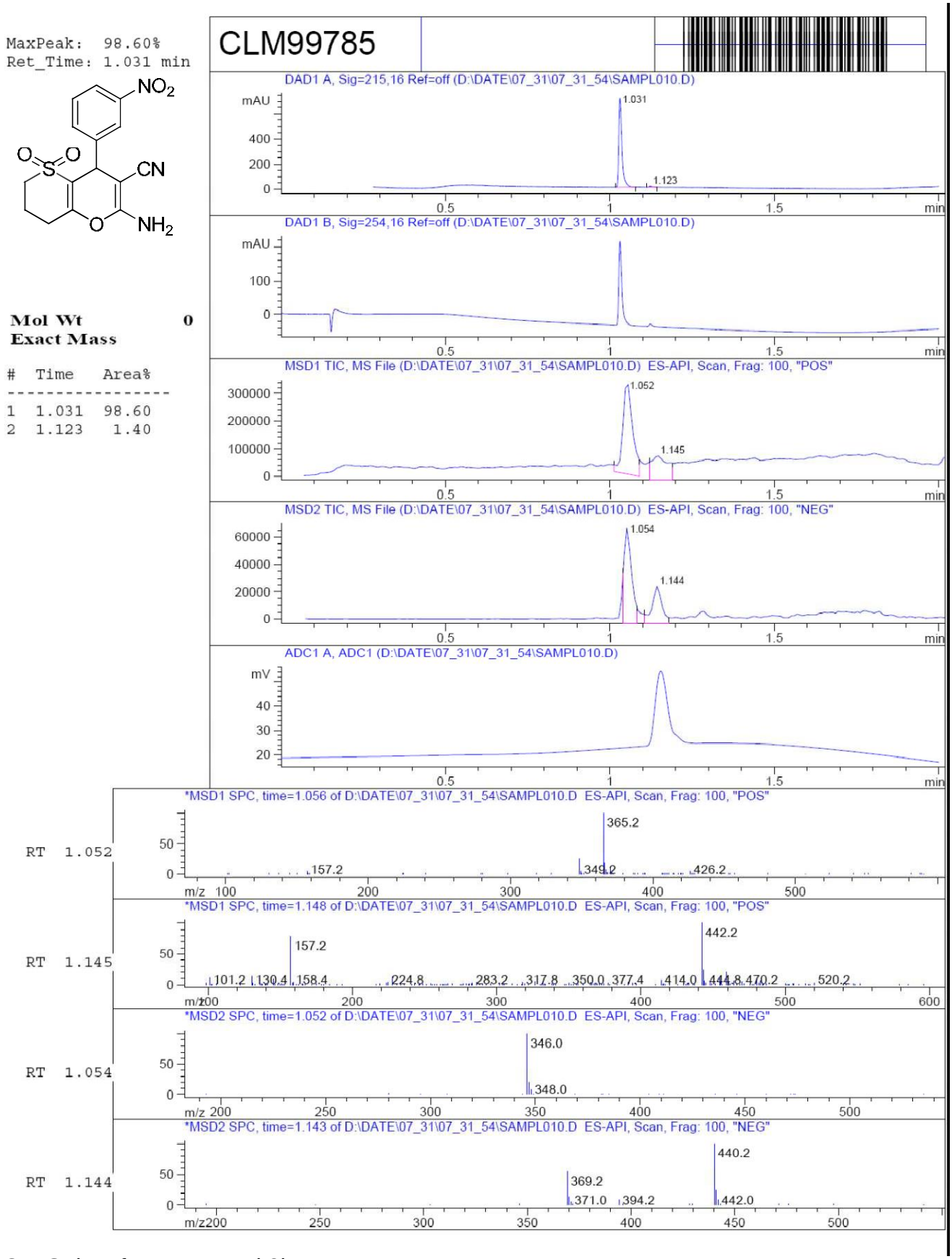
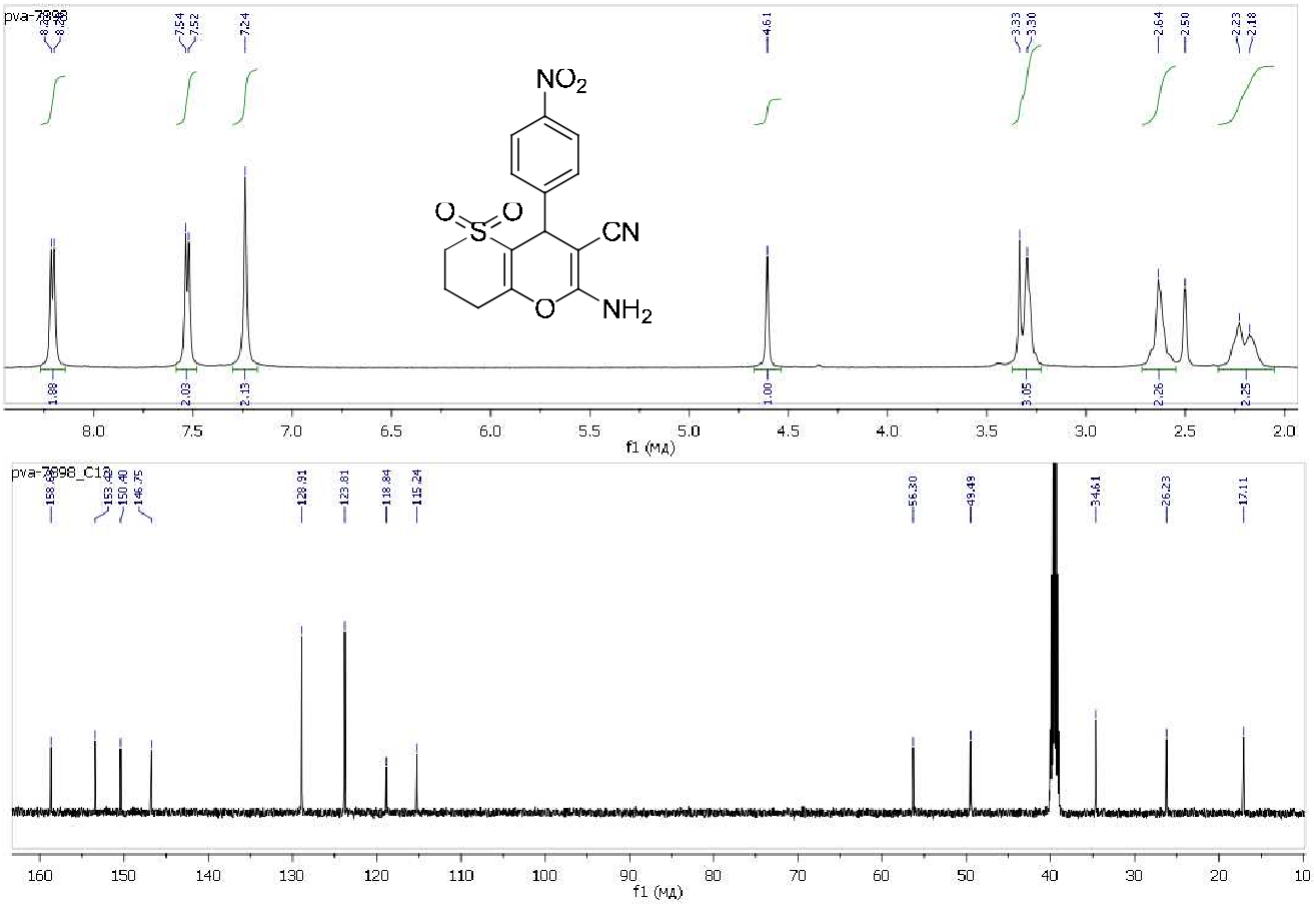
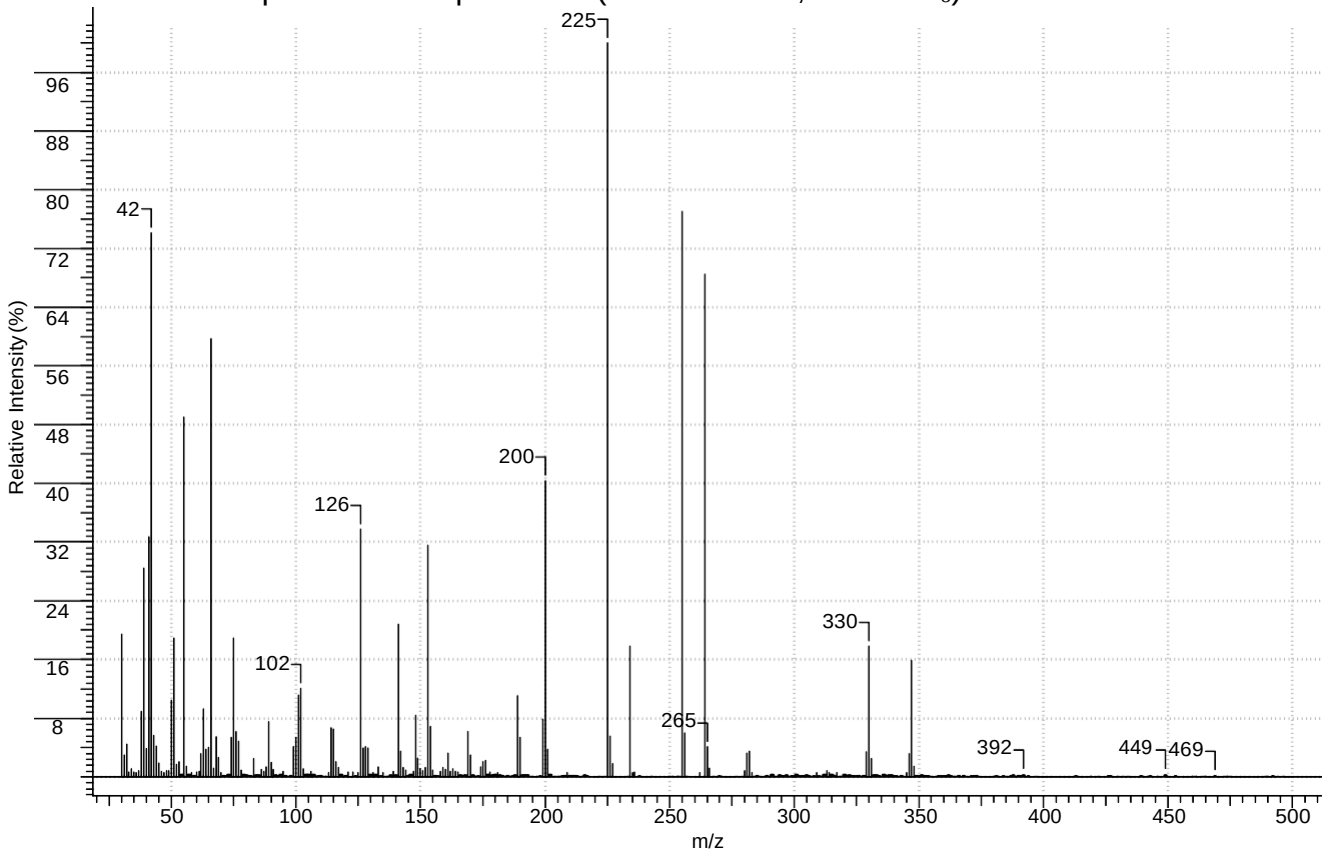


LC-MS data for compound 2b



^{1}H and ^{13}C NMR spectra of compound 2c (500/126 MHz, DMSO-d_6)



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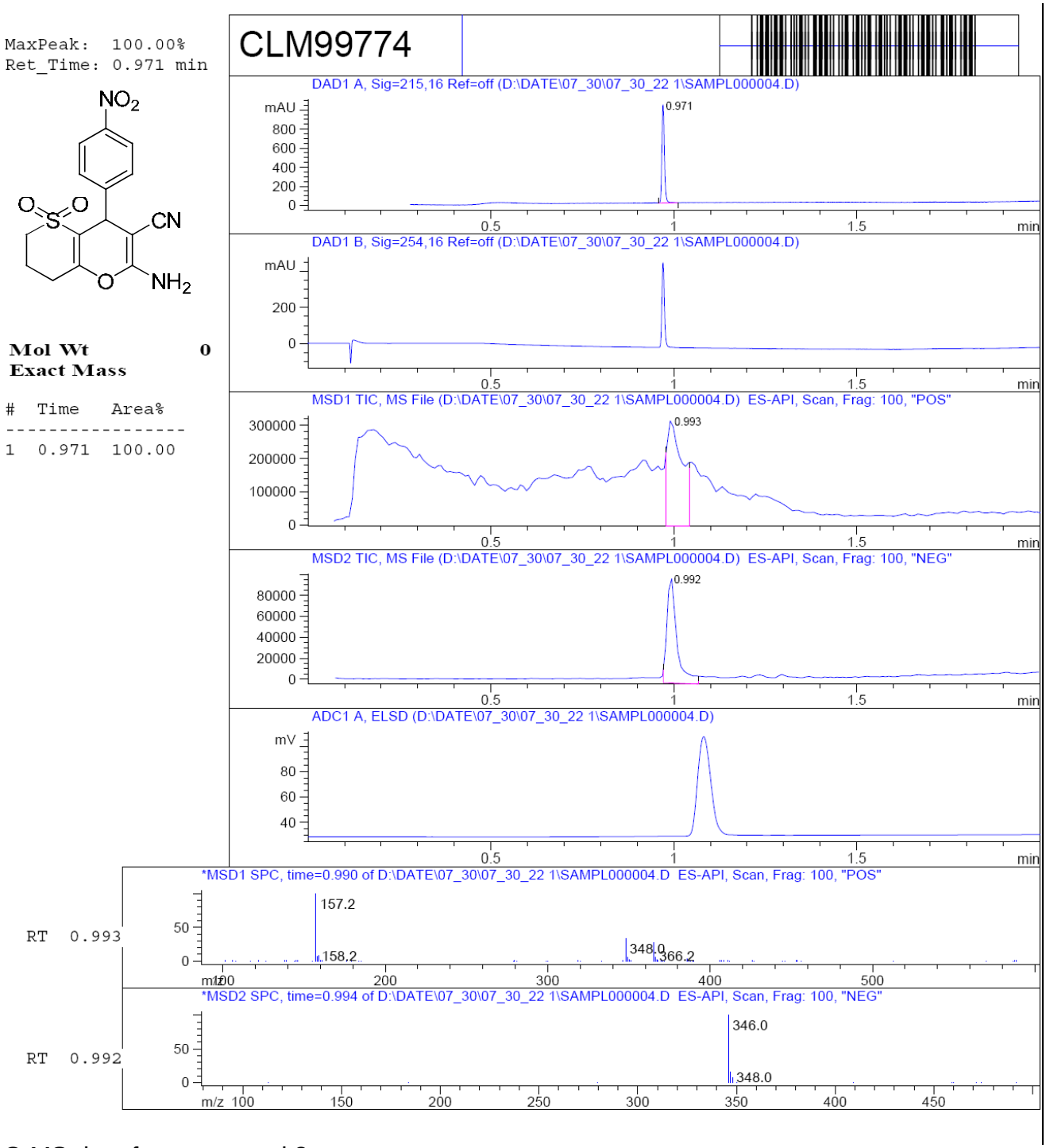

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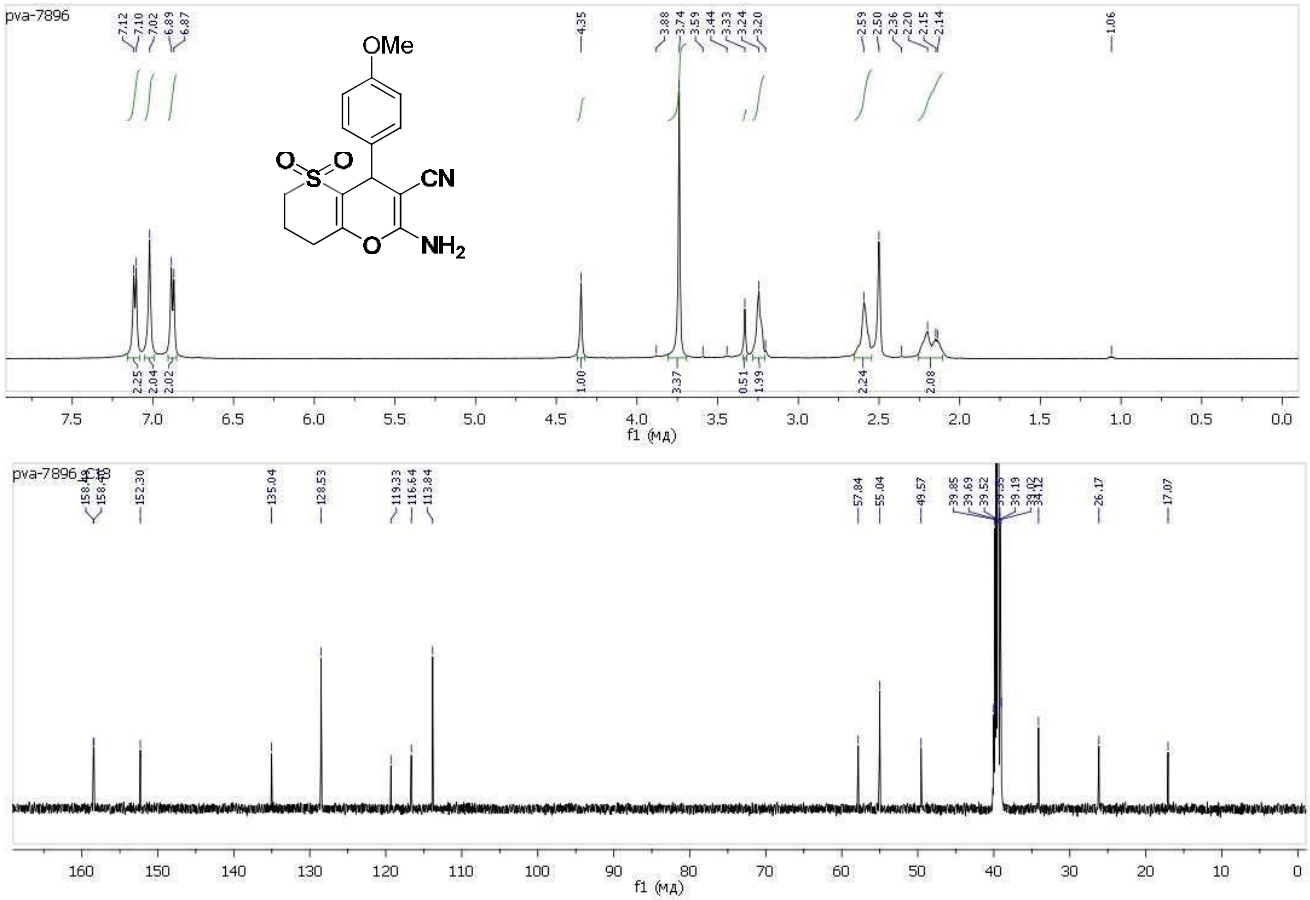
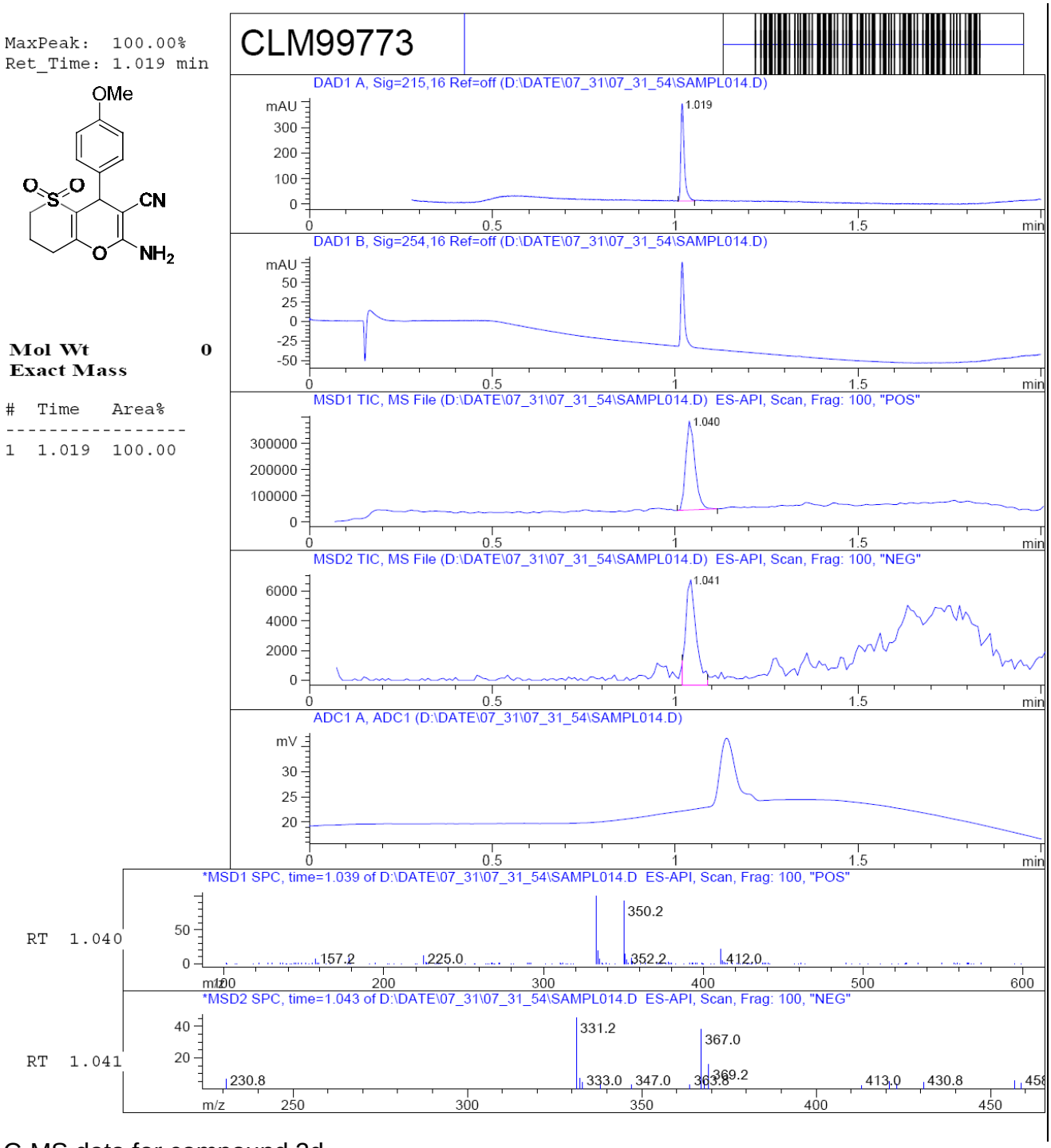


^{1}H and ^{13}C NMR spectra of compound 2d (500/126 MHz, DMSO-d_6)



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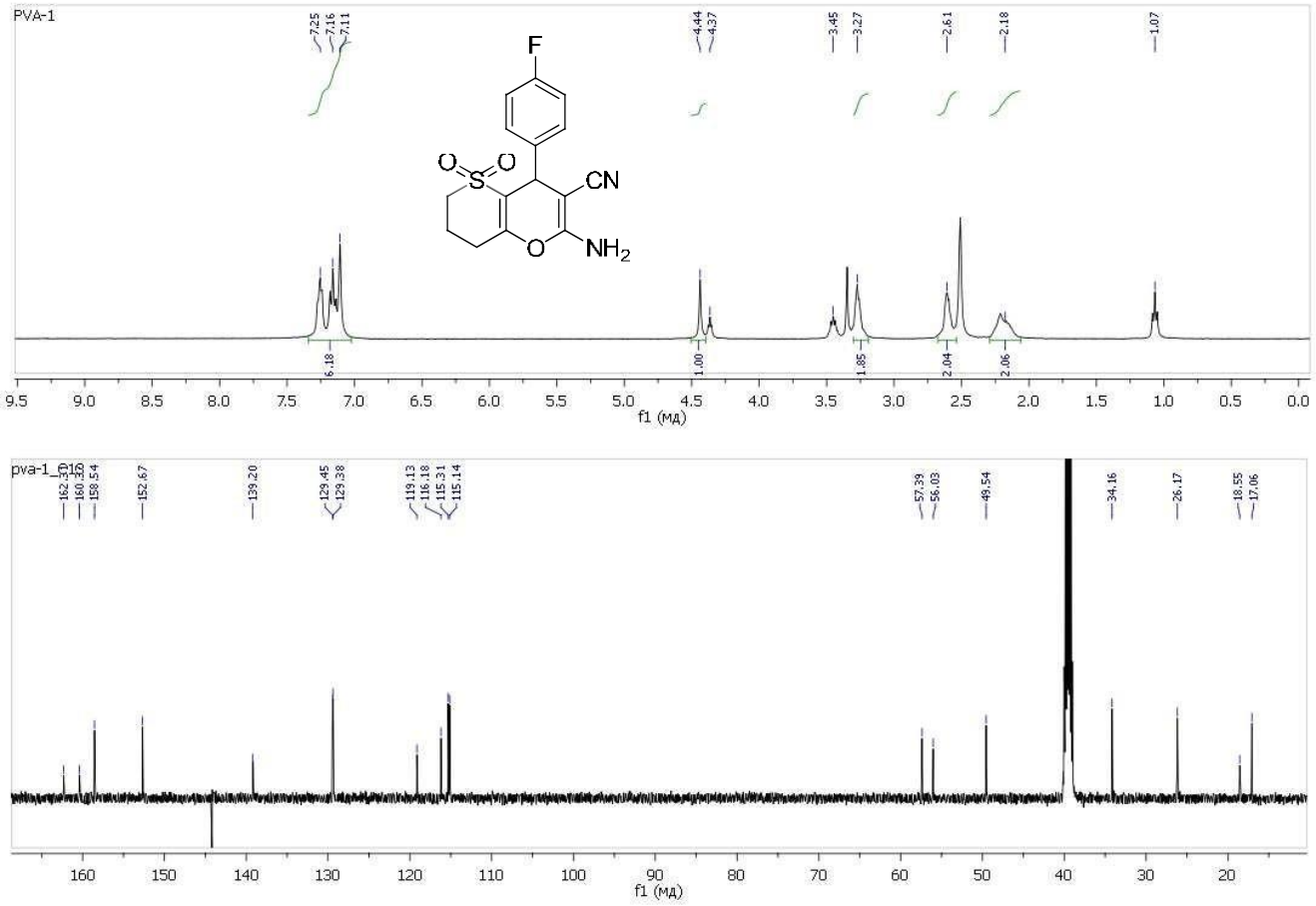
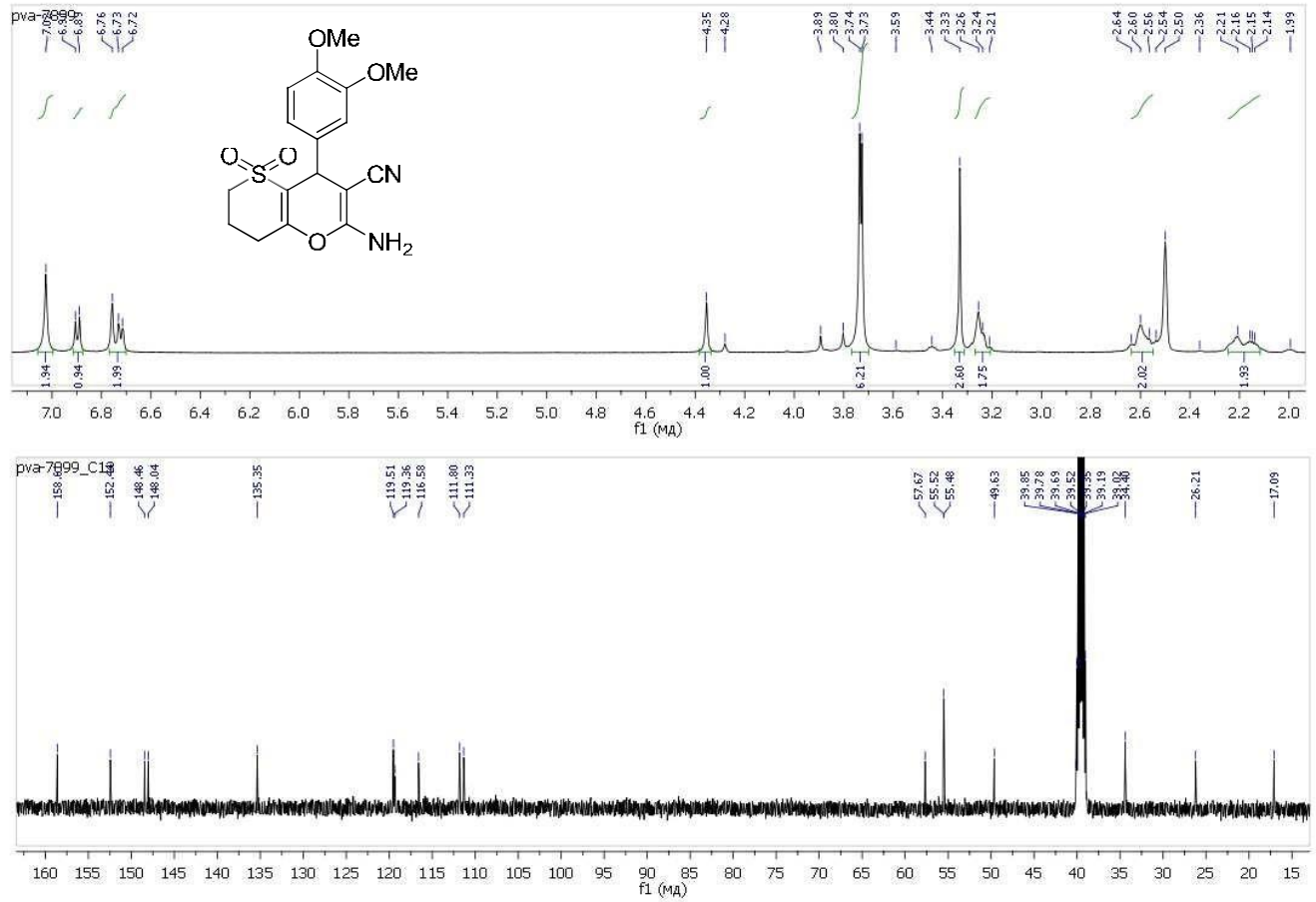
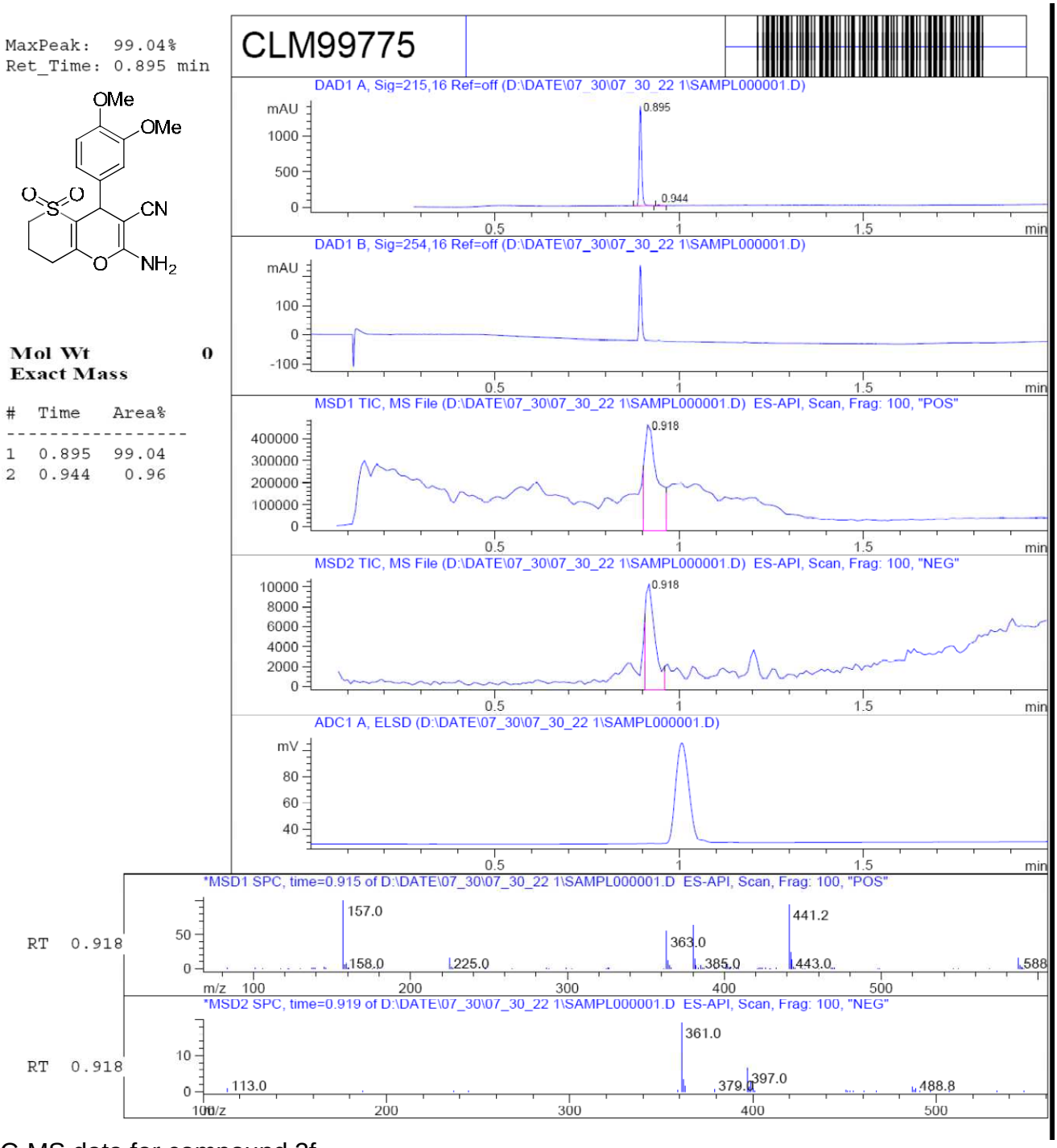


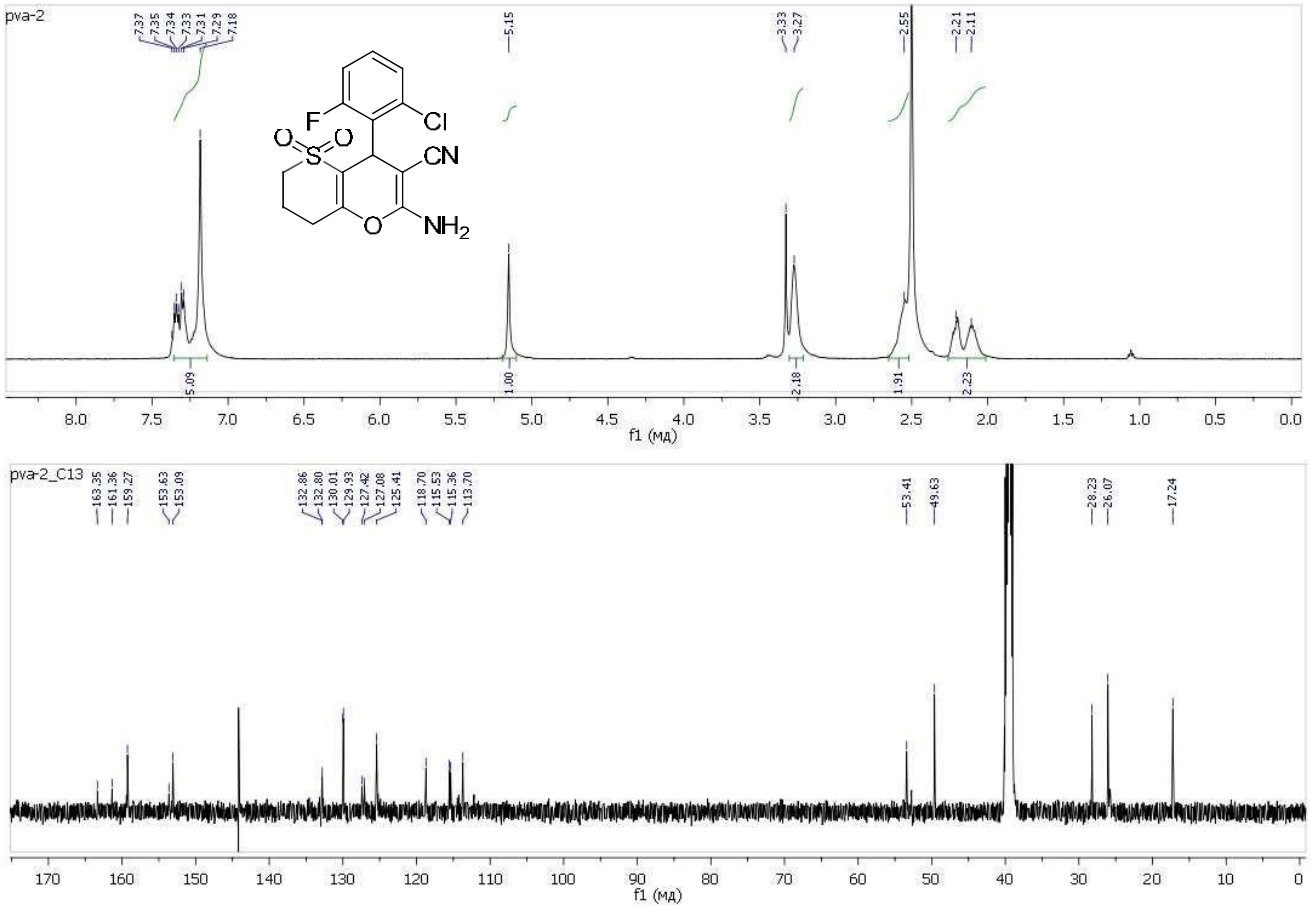
^{1}H and ^{13}C NMR spectra of compound 2e (500/126 MHz, DMSO-d_6)



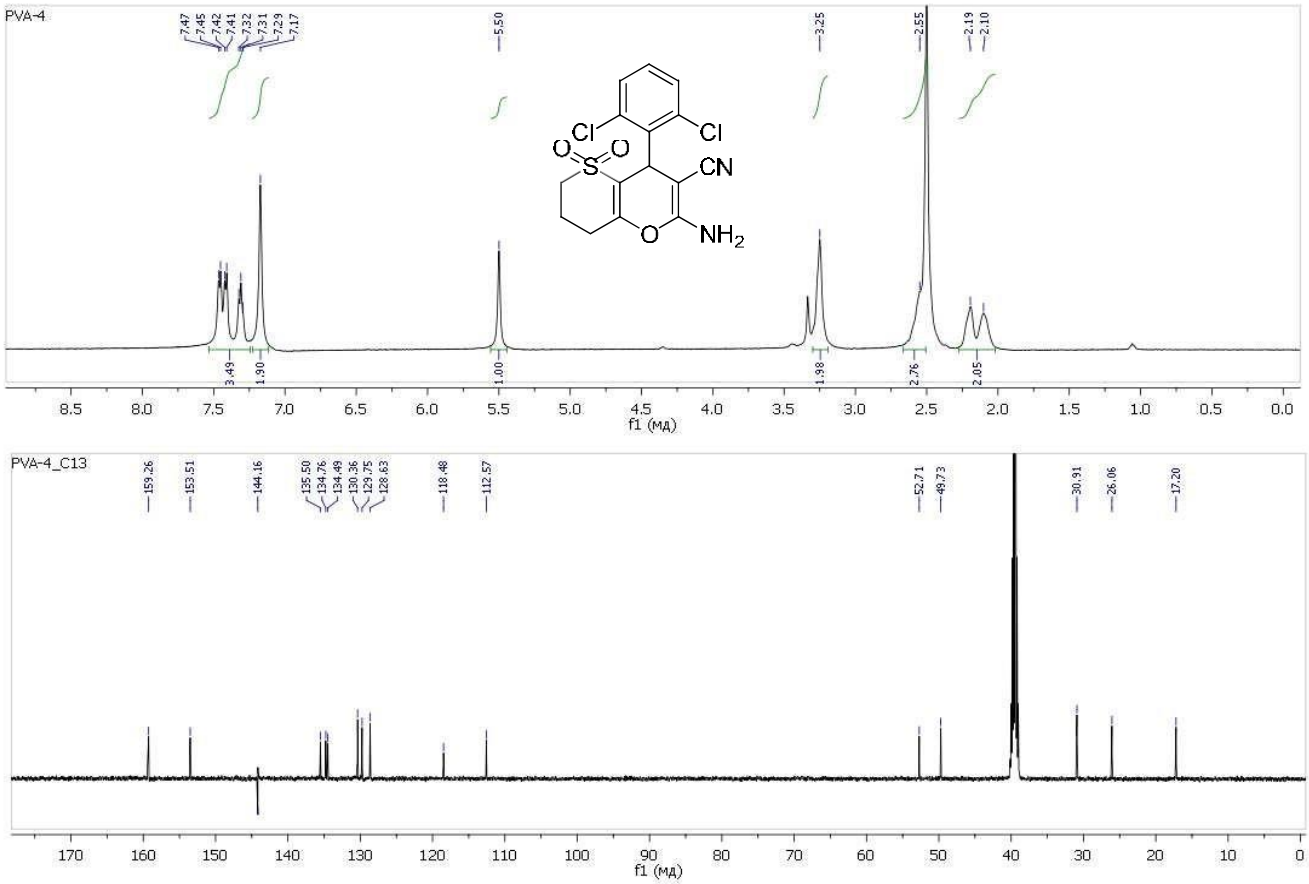
^{1}H and ^{13}C NMR spectra of compound 2f (500/126 MHz, DMSO-d_6)



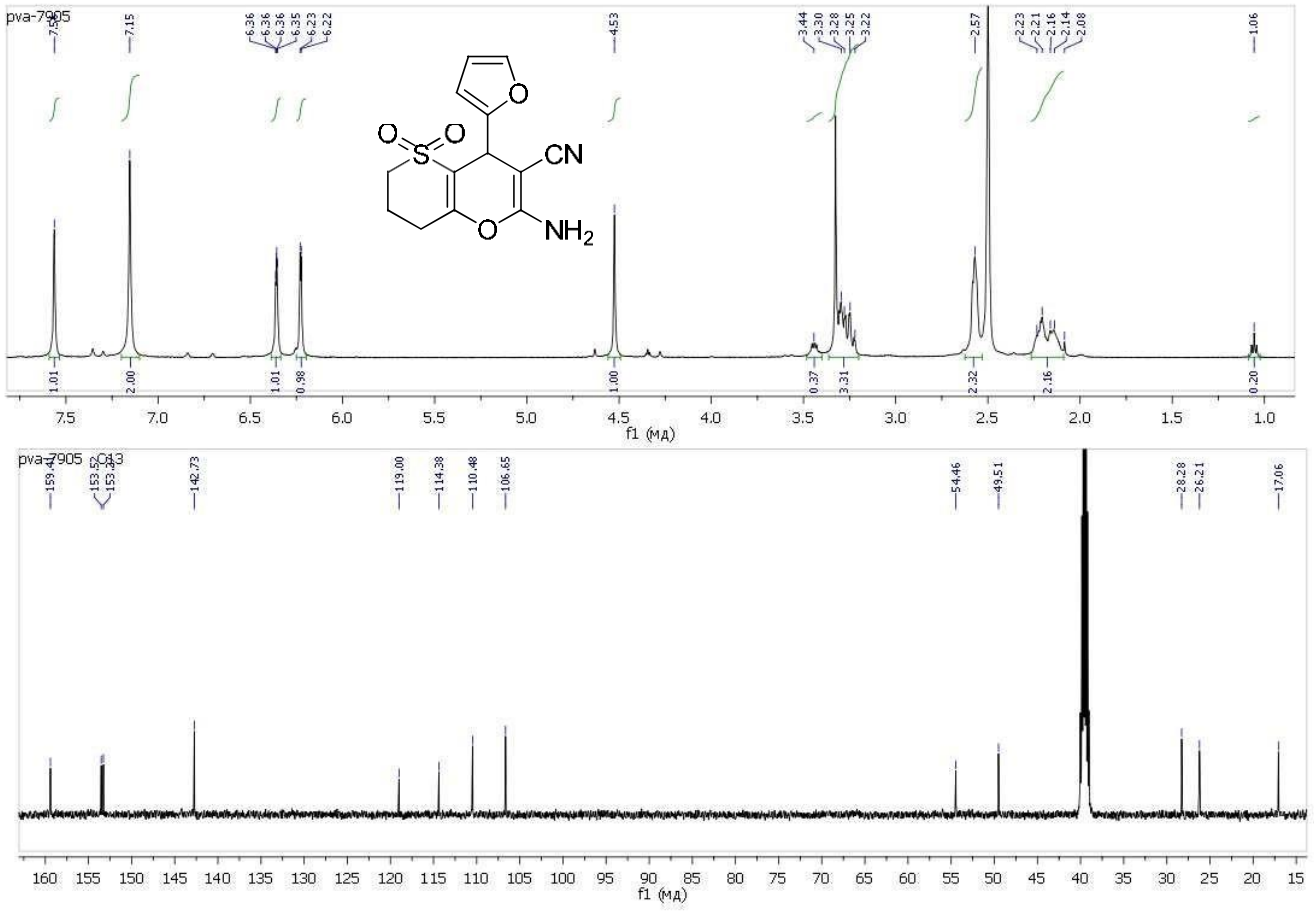
LC-MS data for compound 2f



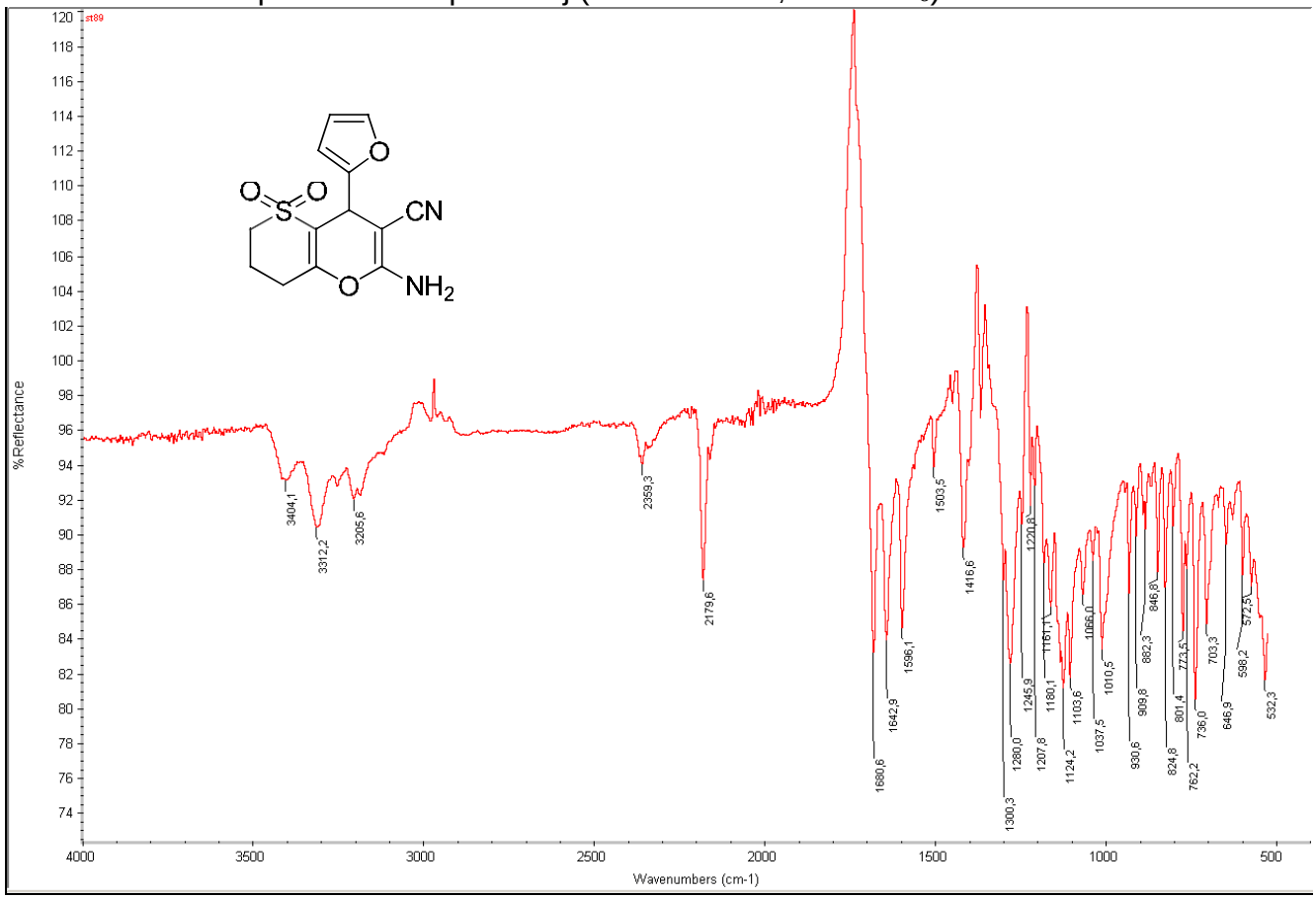
^{1}H and ^{13}C NMR spectra of compound 2g (500/126 MHz, DMSO-d_6)



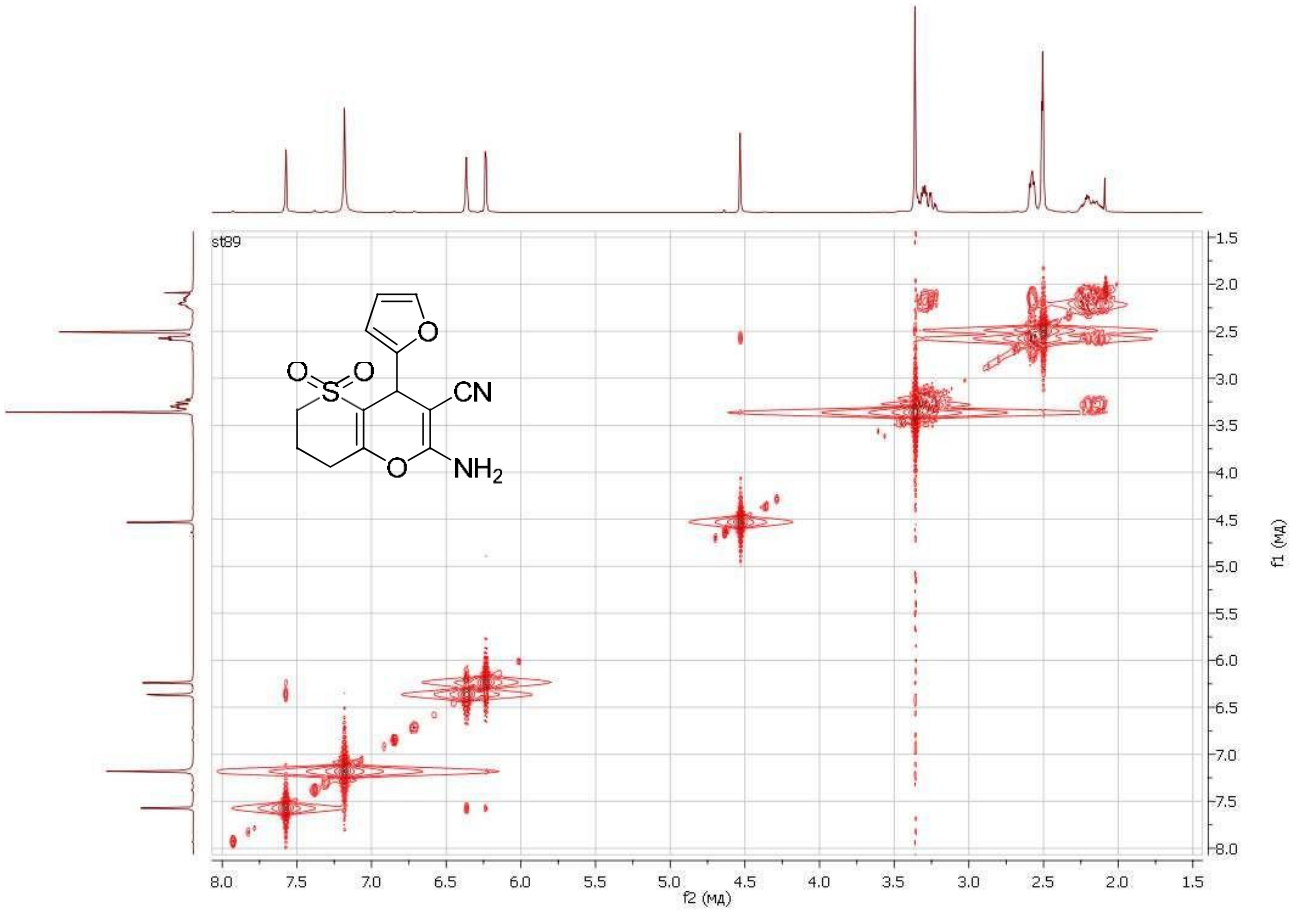
^{1}H and ^{13}C NMR spectra of compound 2h (500/126 MHz, DMSO-d_6)



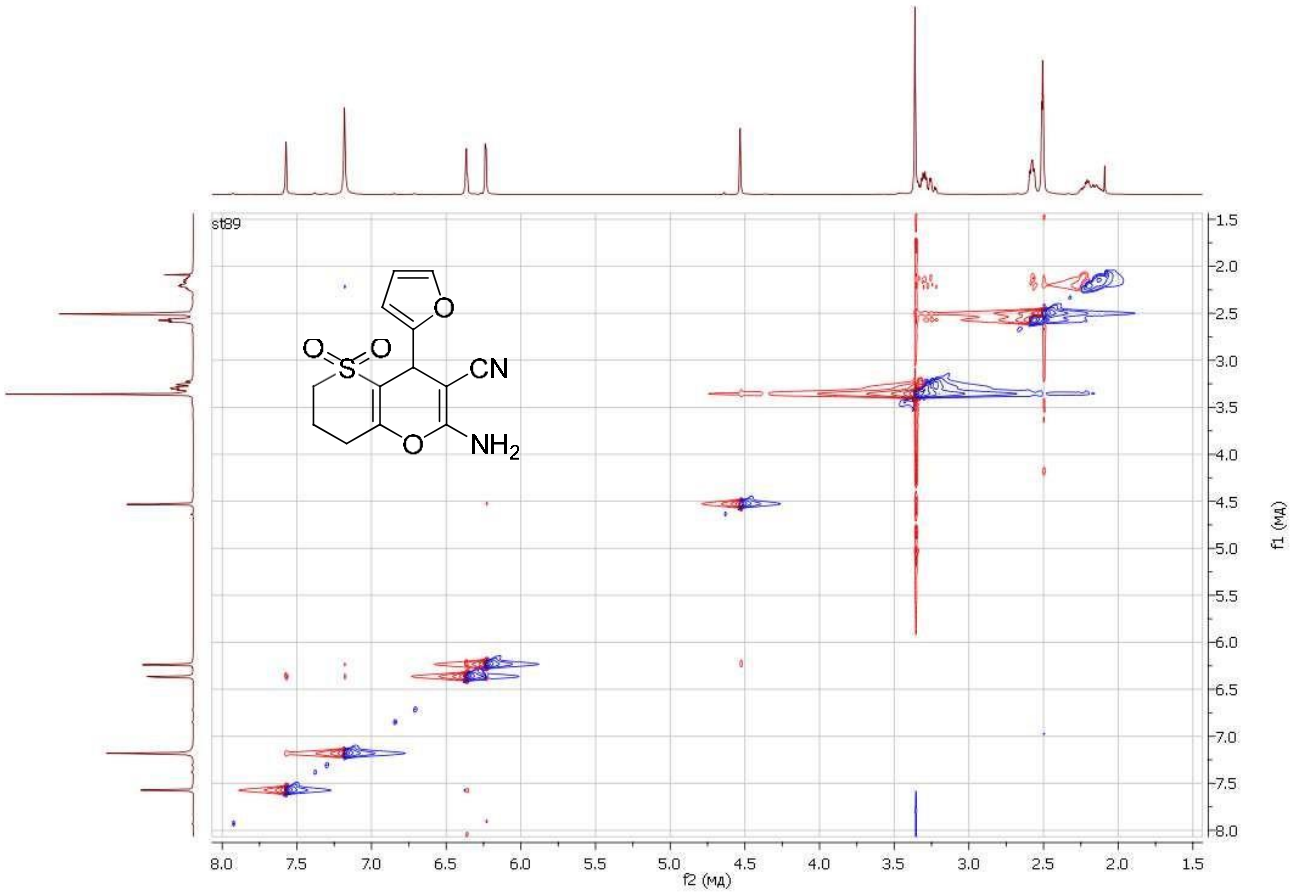
^{1}H and ^{13}C NMR spectra of compound 2j (400/100 MHz, DMSO-d_6)



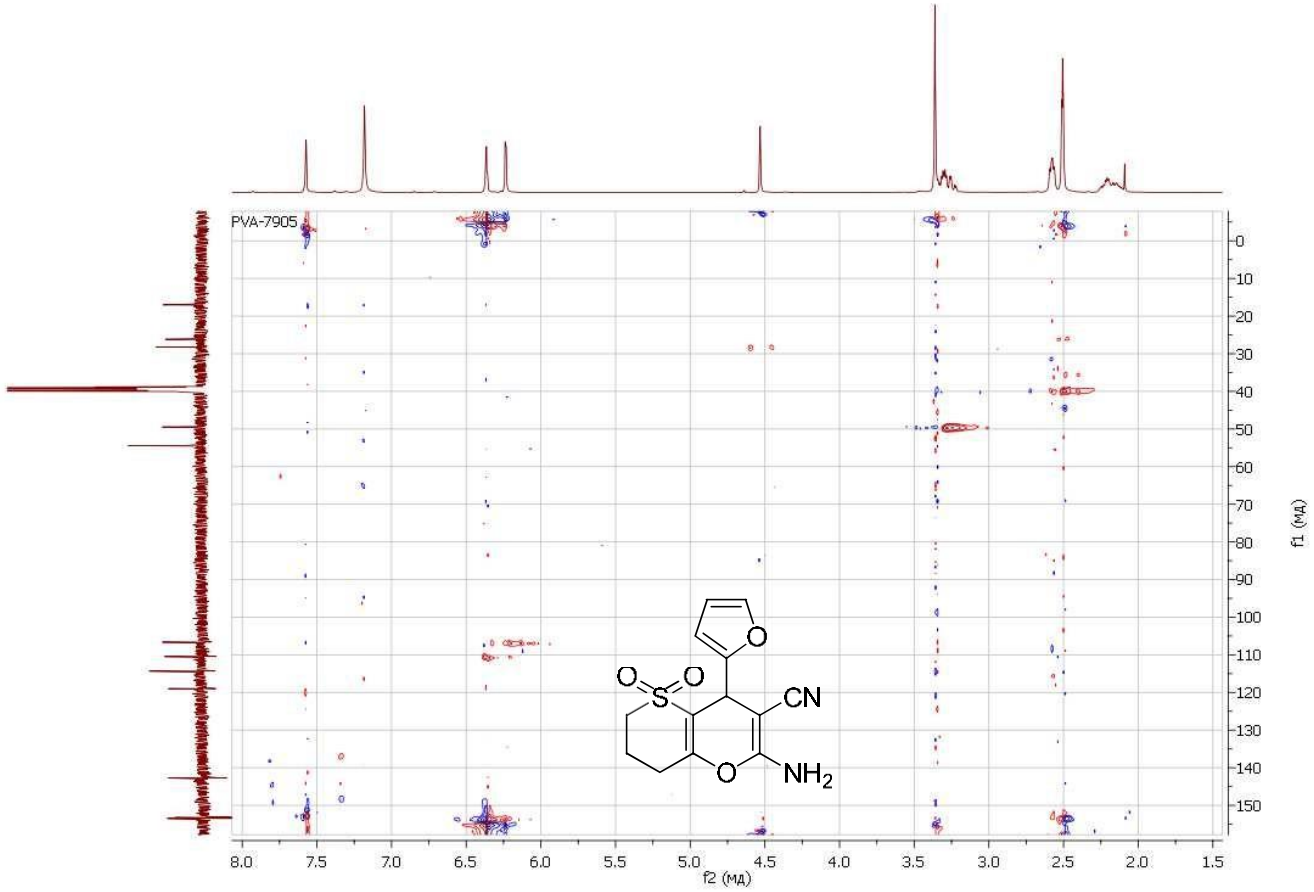
IR spectrum of compound 2j



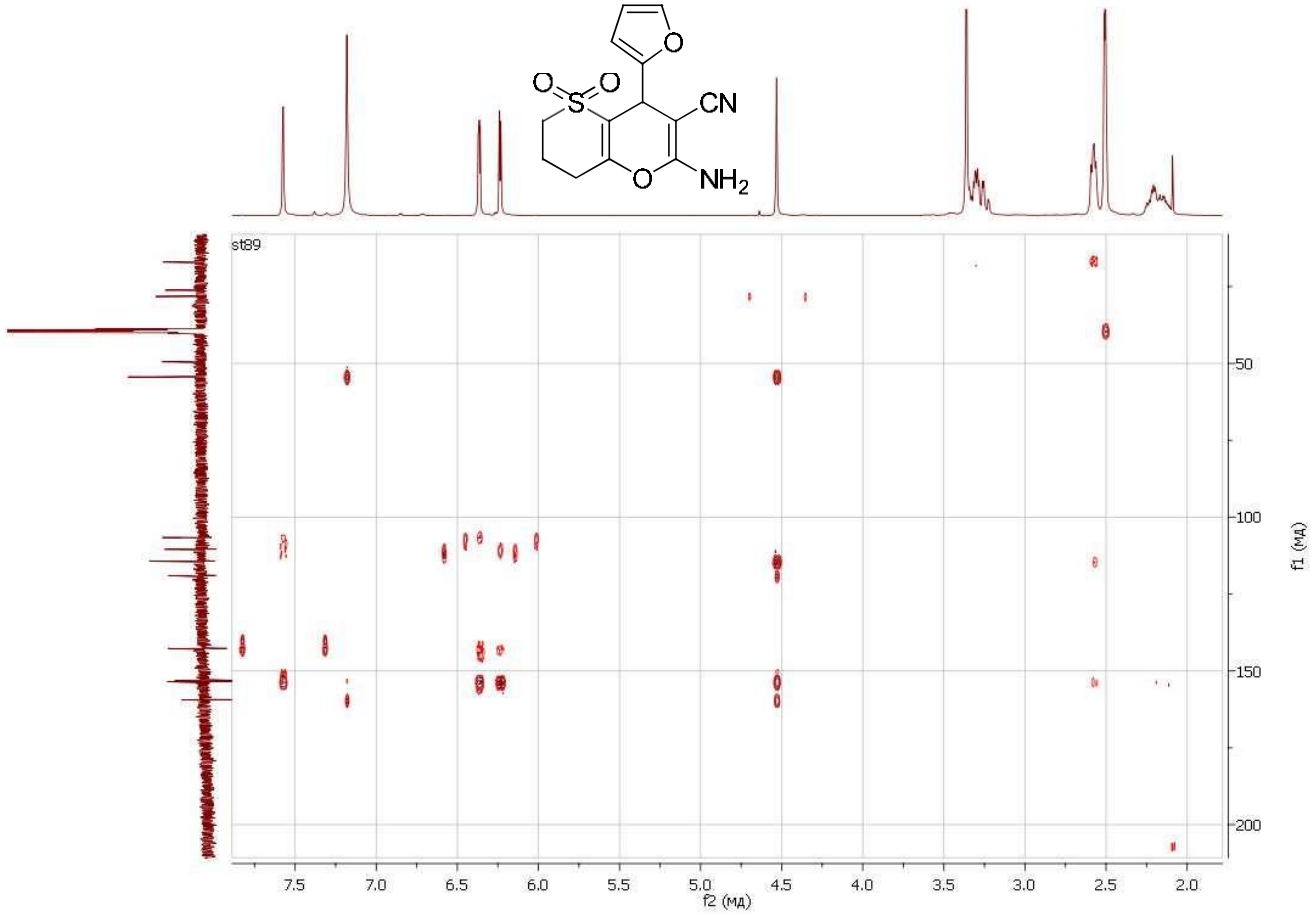
^{1}H-^{1}H COSY spectrum of compound 2j (400 MHz, DMSO-d_6)



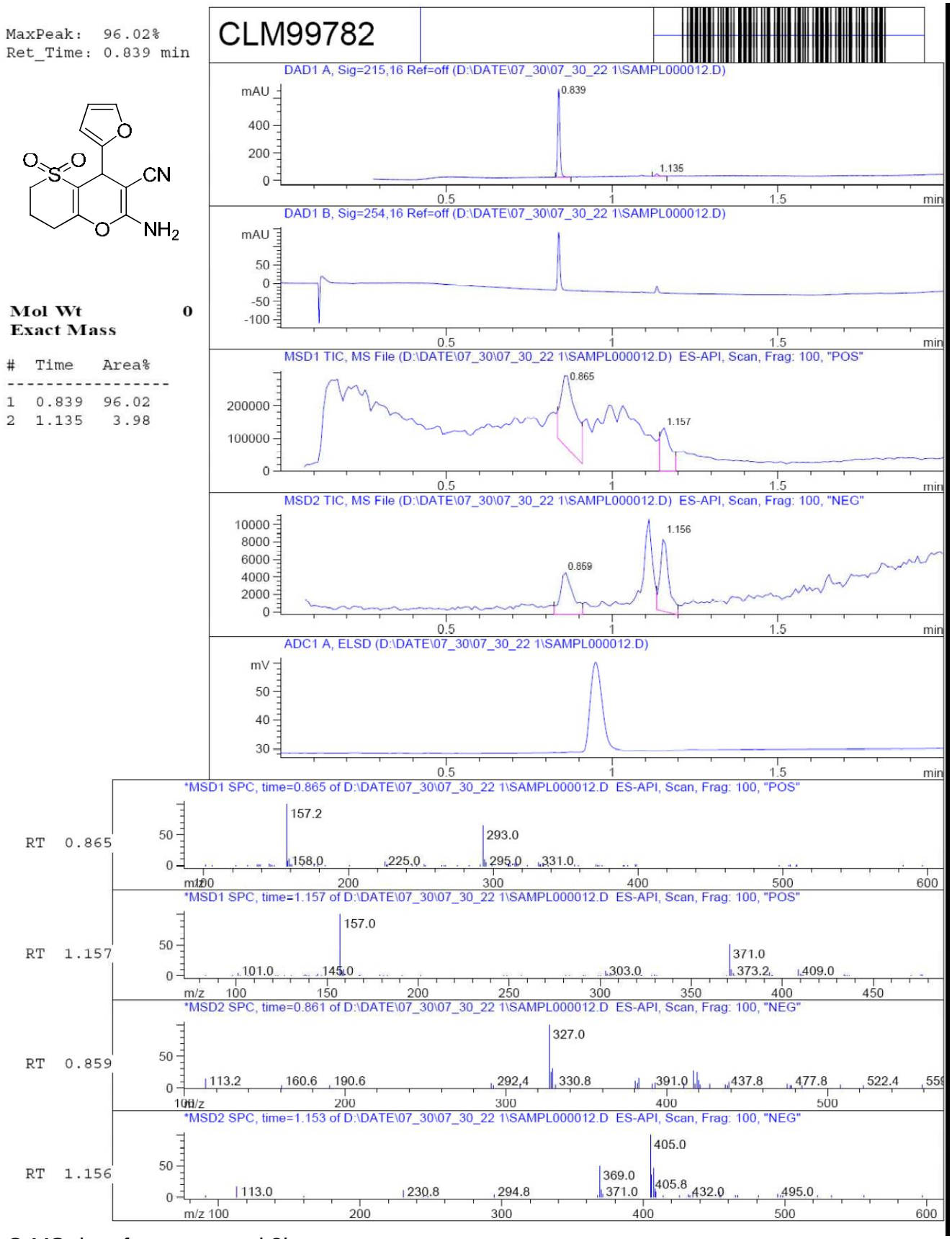
NOESY spectrum of compound 2j (400 MHz, DMSO-d_6)



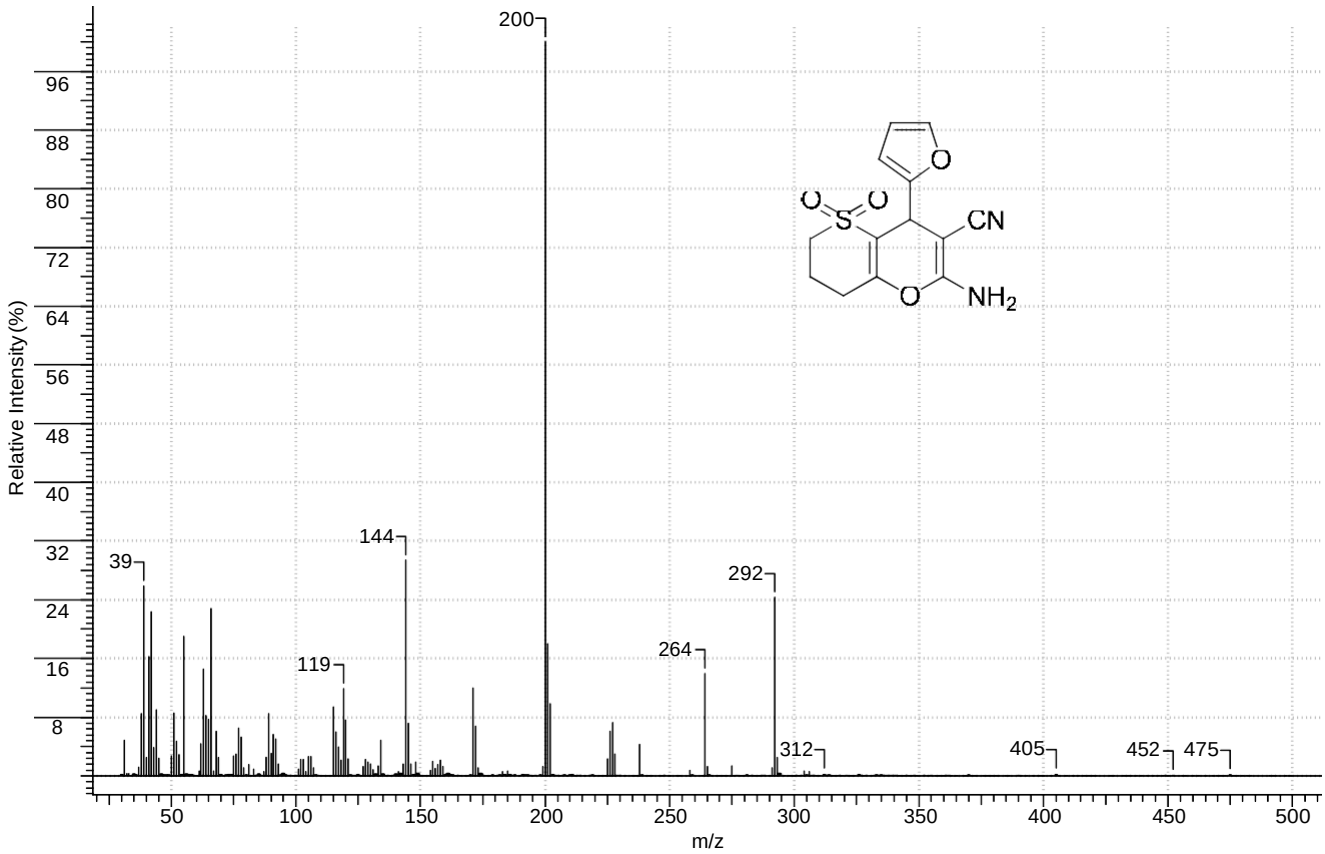
^{1}H-^{13}C HSQC spectrum of compound 2j (400/100 MHz, DMSO-d_6)



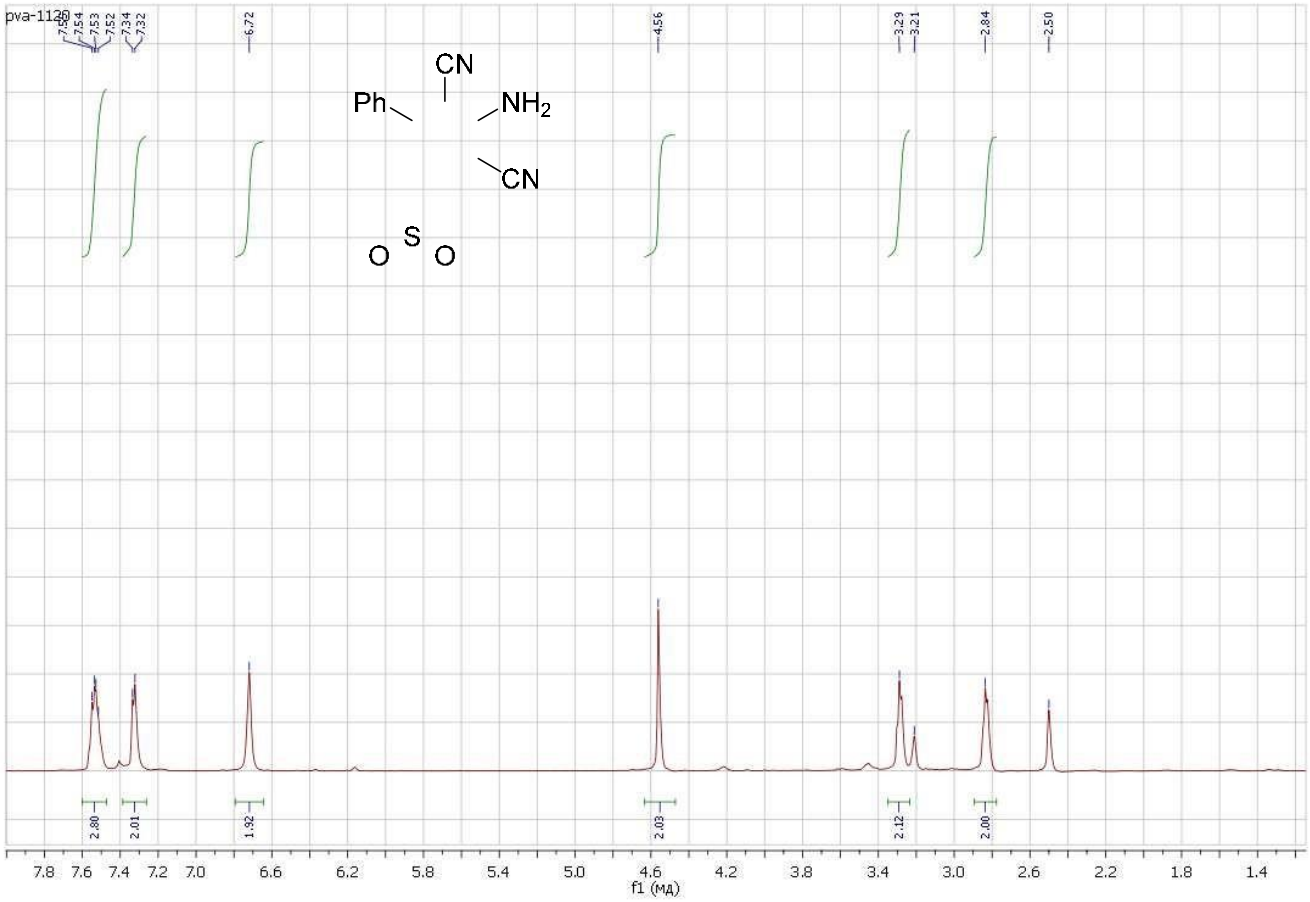
^{1}H-^{13}C HMBC spectrum of compound 2j (400/100 MHz, DMSO-d_6)



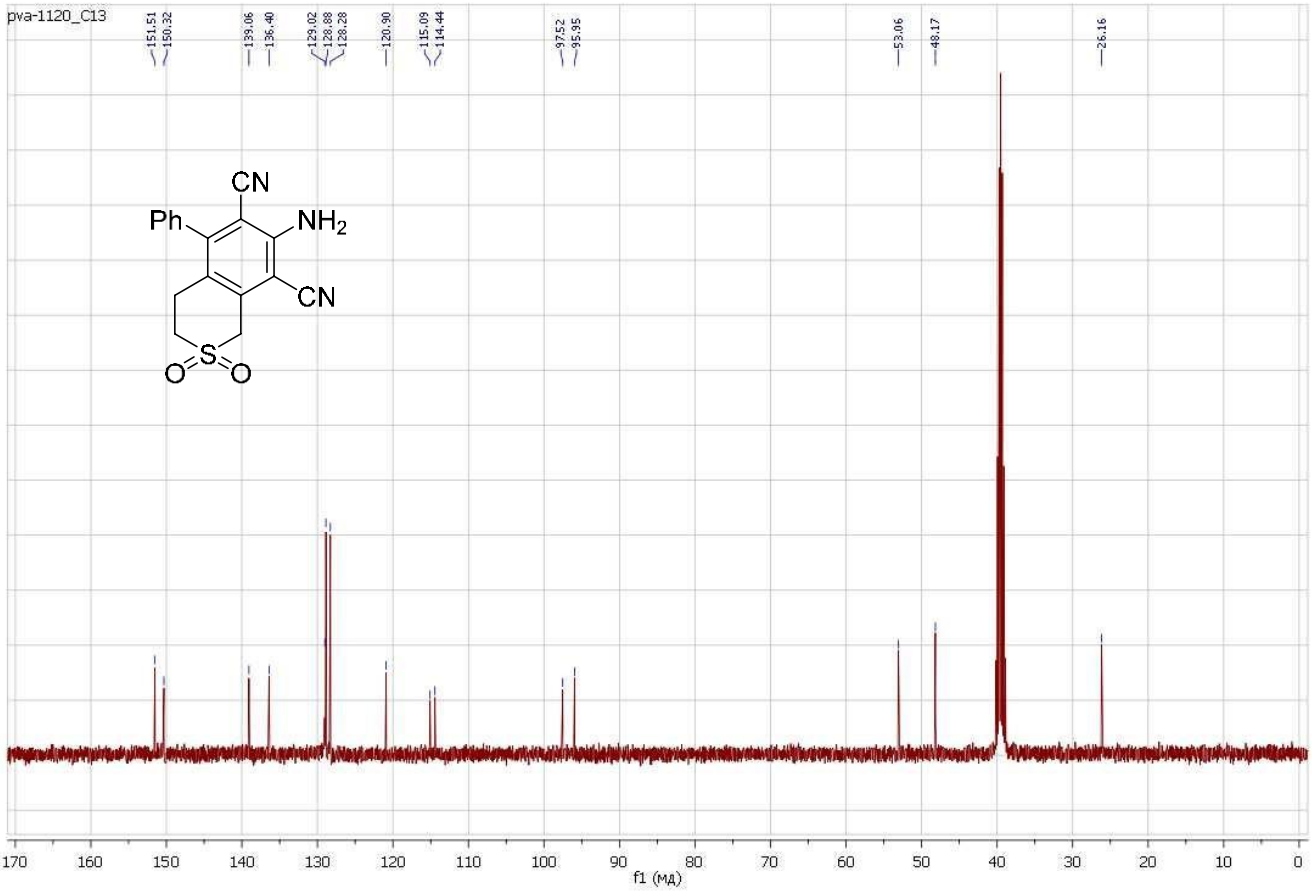
LC-MS data for compound 2j



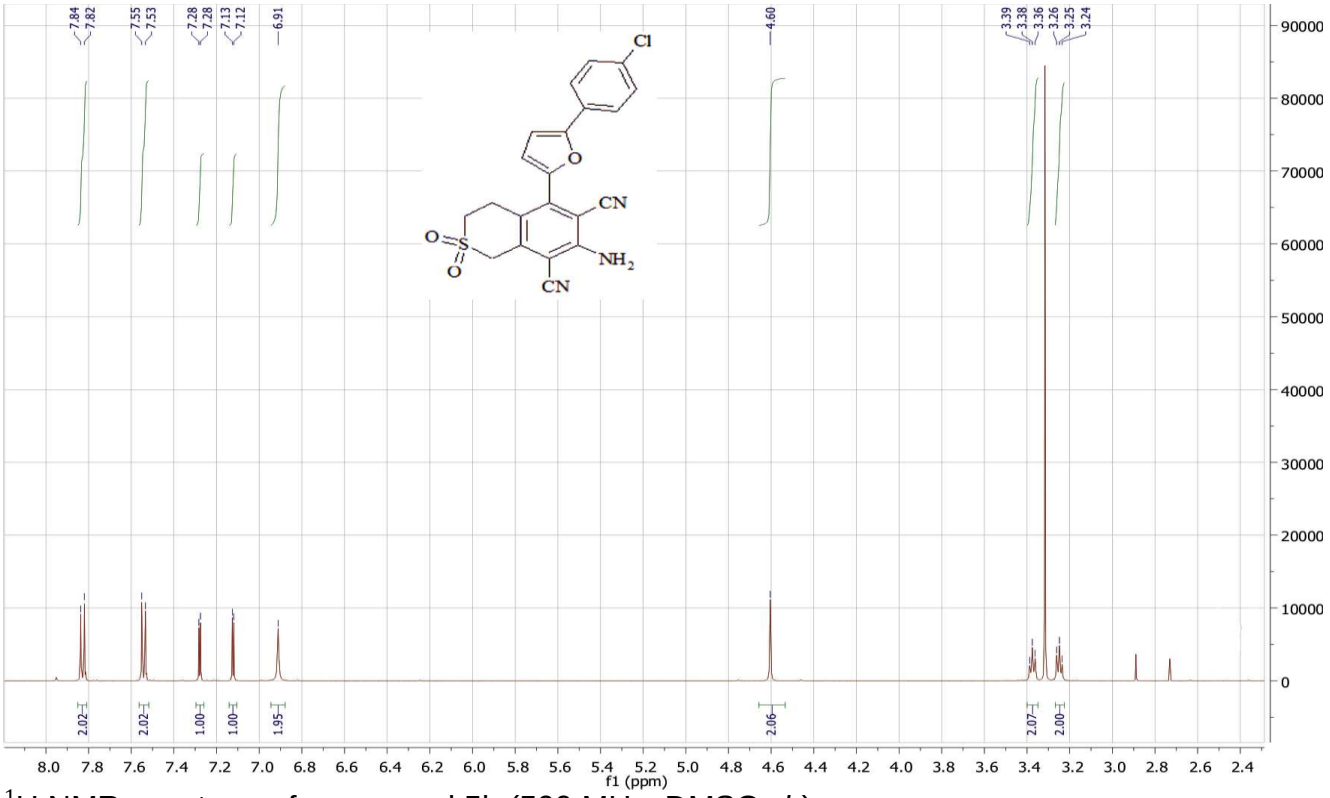
Mass spectrum (EI) of compound 2j



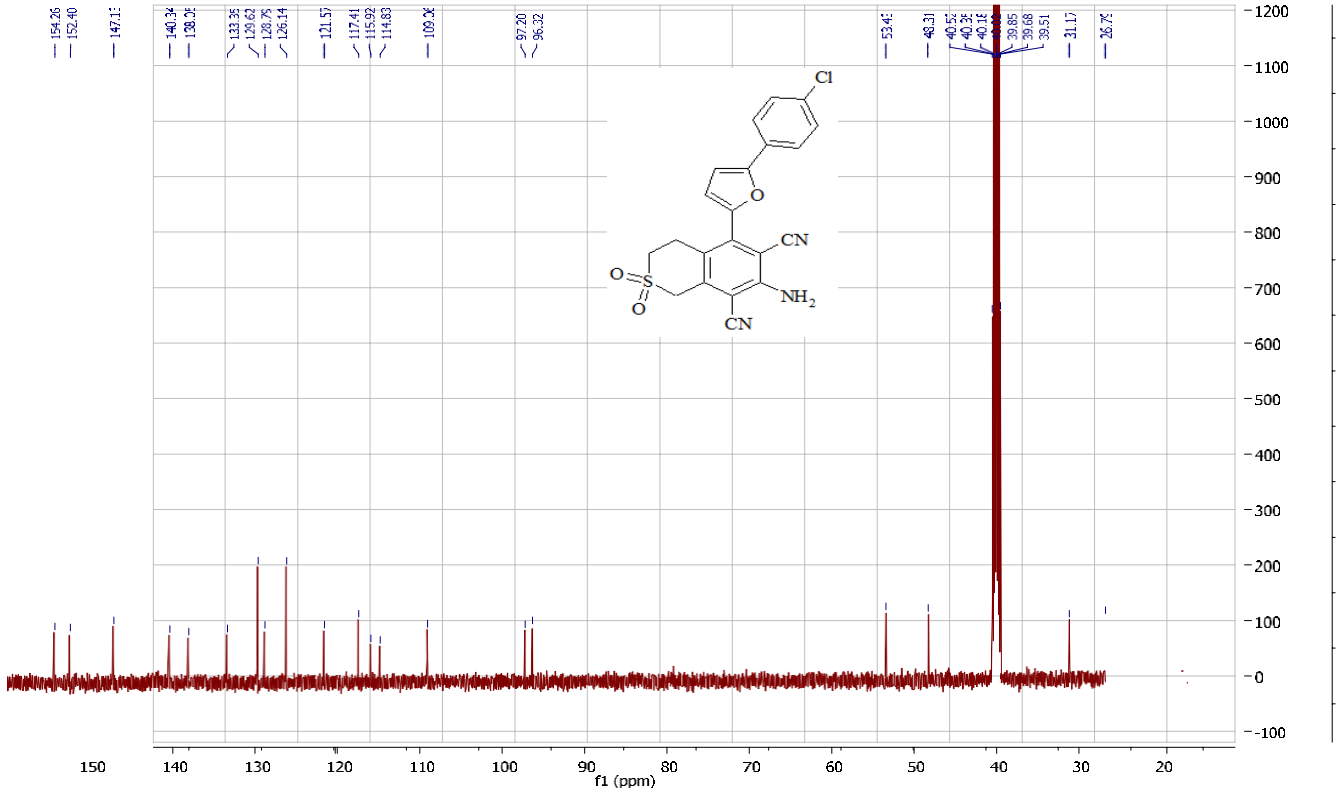
^{1}H NMR spectrum of compound 5a (500 MHz, DMSO-d_6)



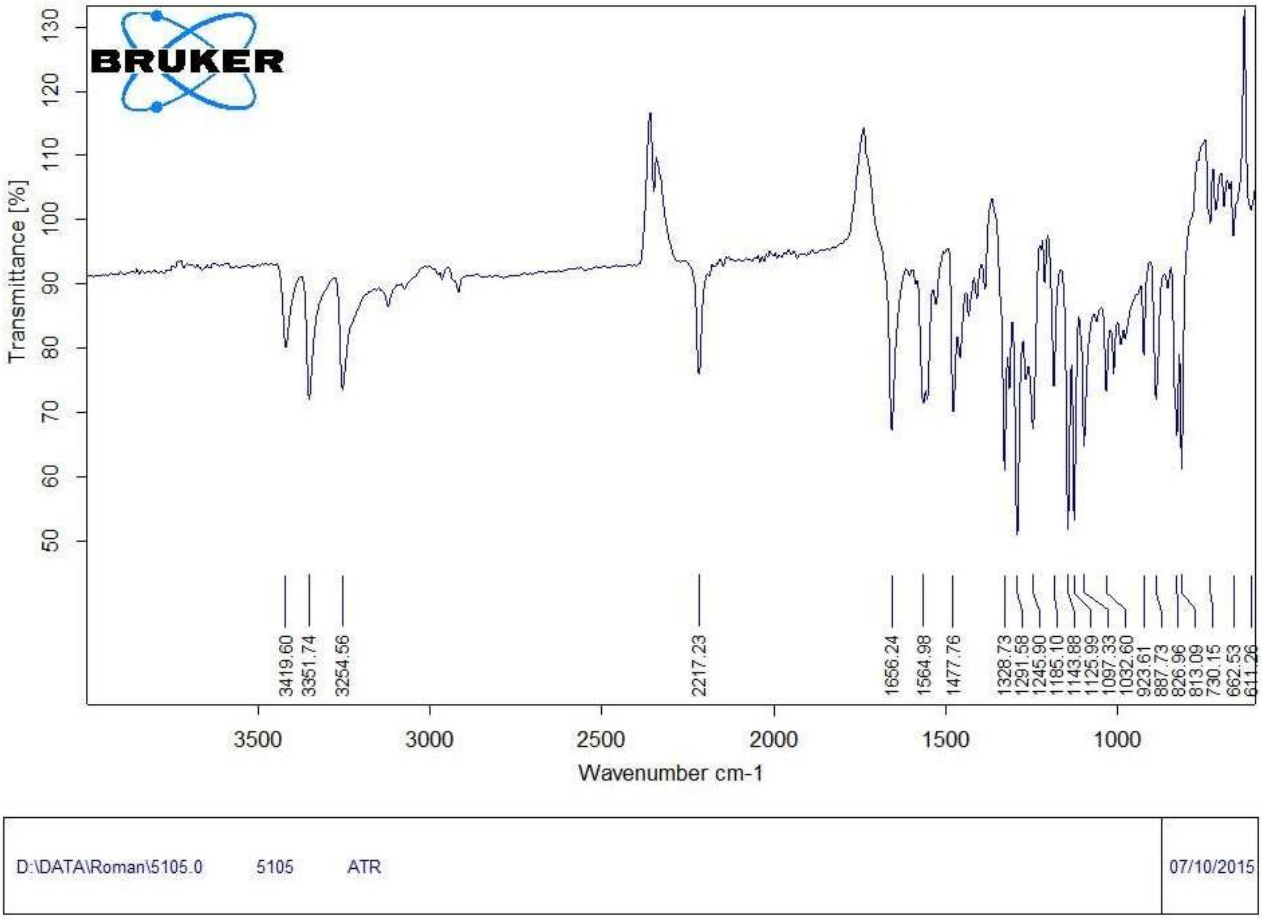
^{13}C NMR spectrum of compound 5a (126 MHz, DMSO-d_6)



^{1}H NMR spectrum of compound 5b (500 MHz, DMSO-d_6)



^{13}C NMR spectrum of compound 5b (126 MHz, DMSO-d_6)



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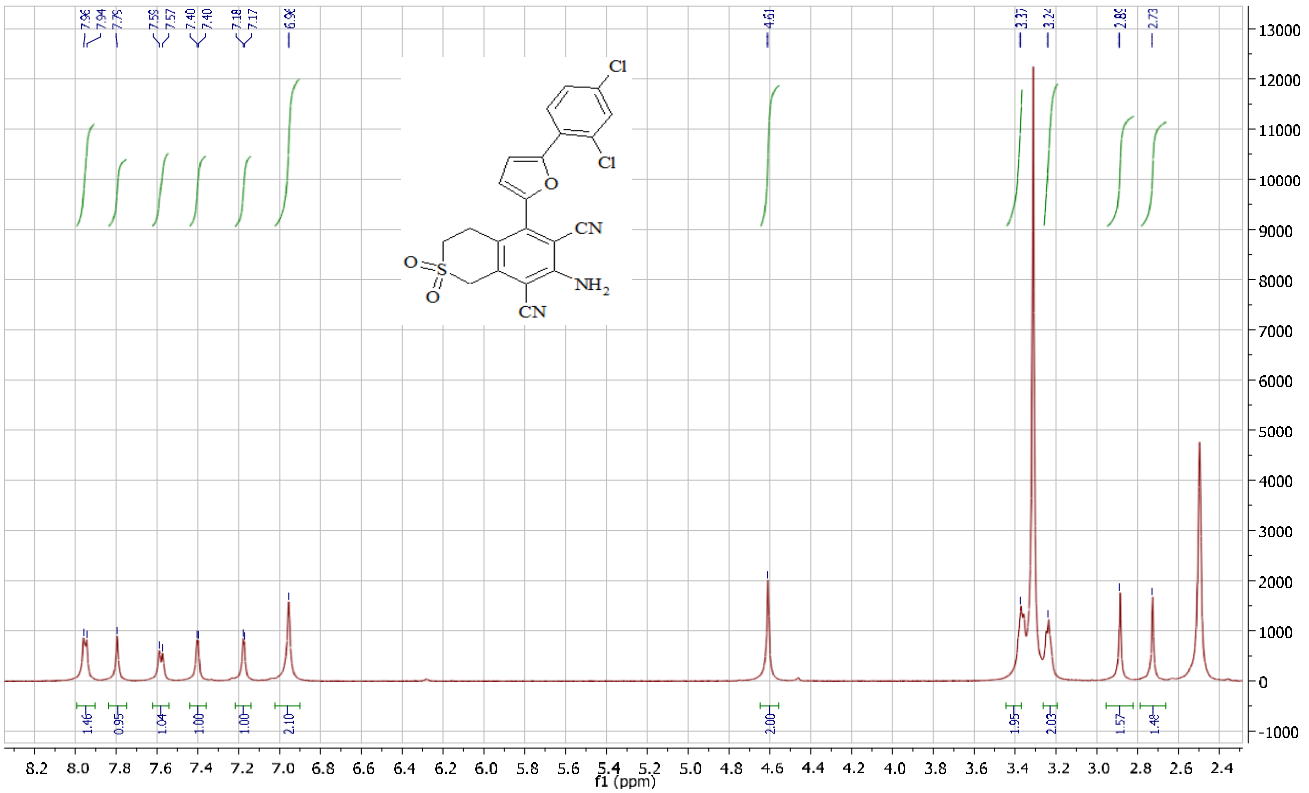
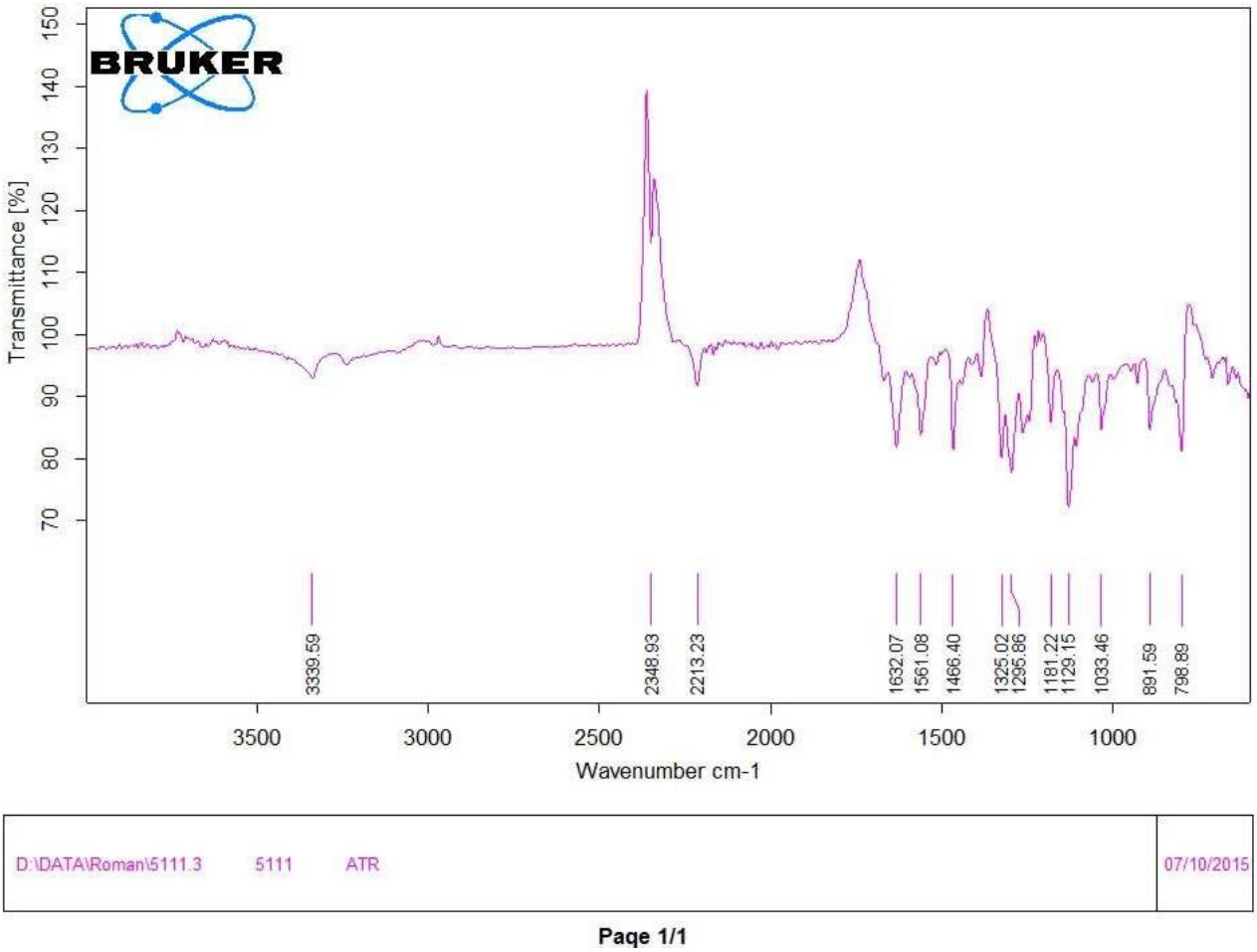
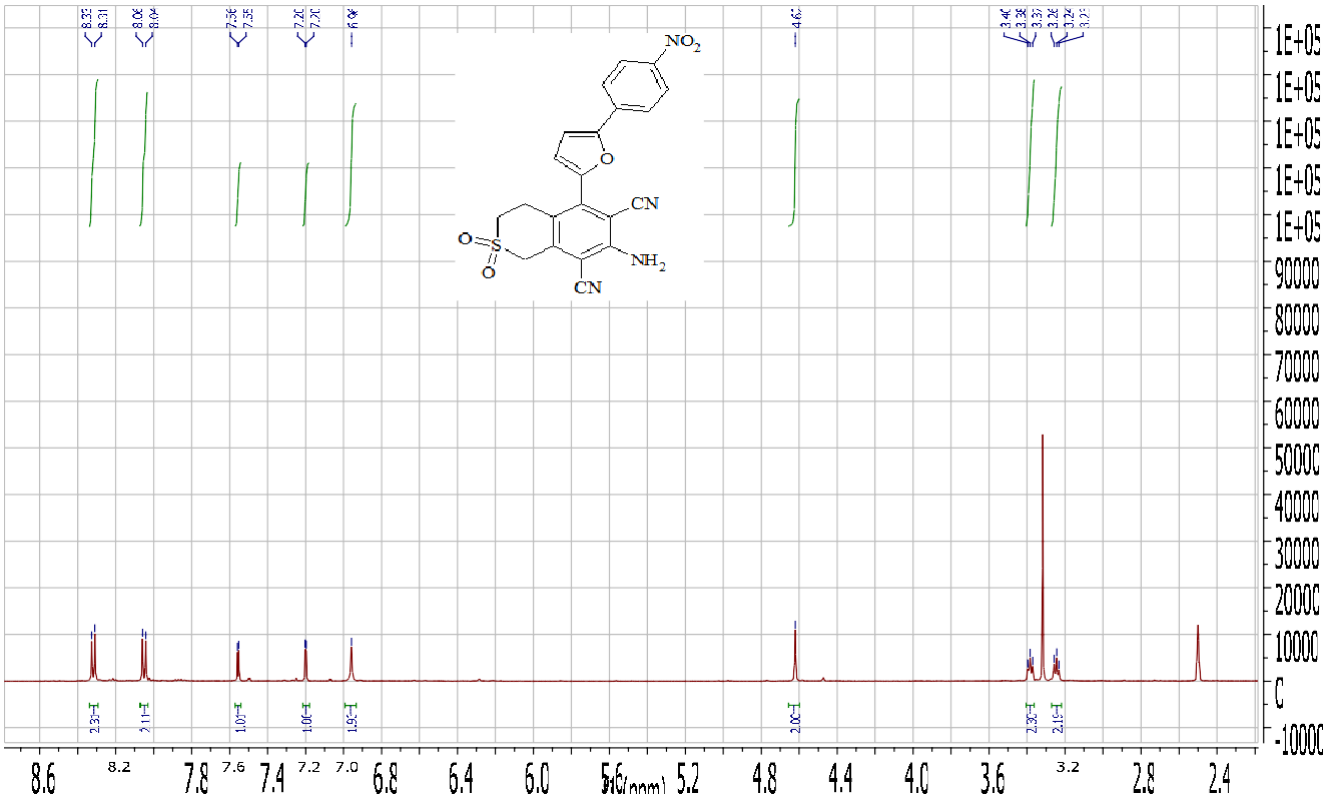
IR spectrum of compound 5b



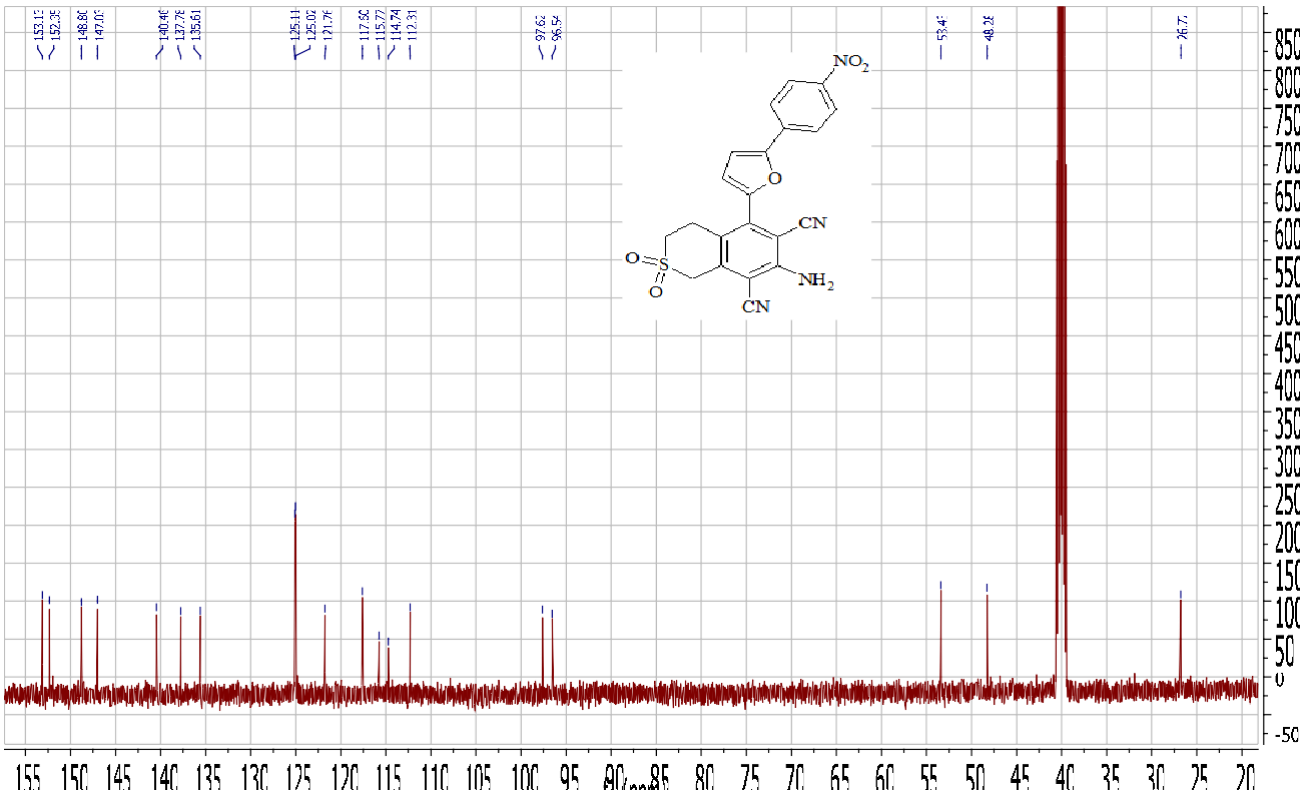
^{1}H NMR spectrum of compound 5c (500 MHz, DMSO-d_6)



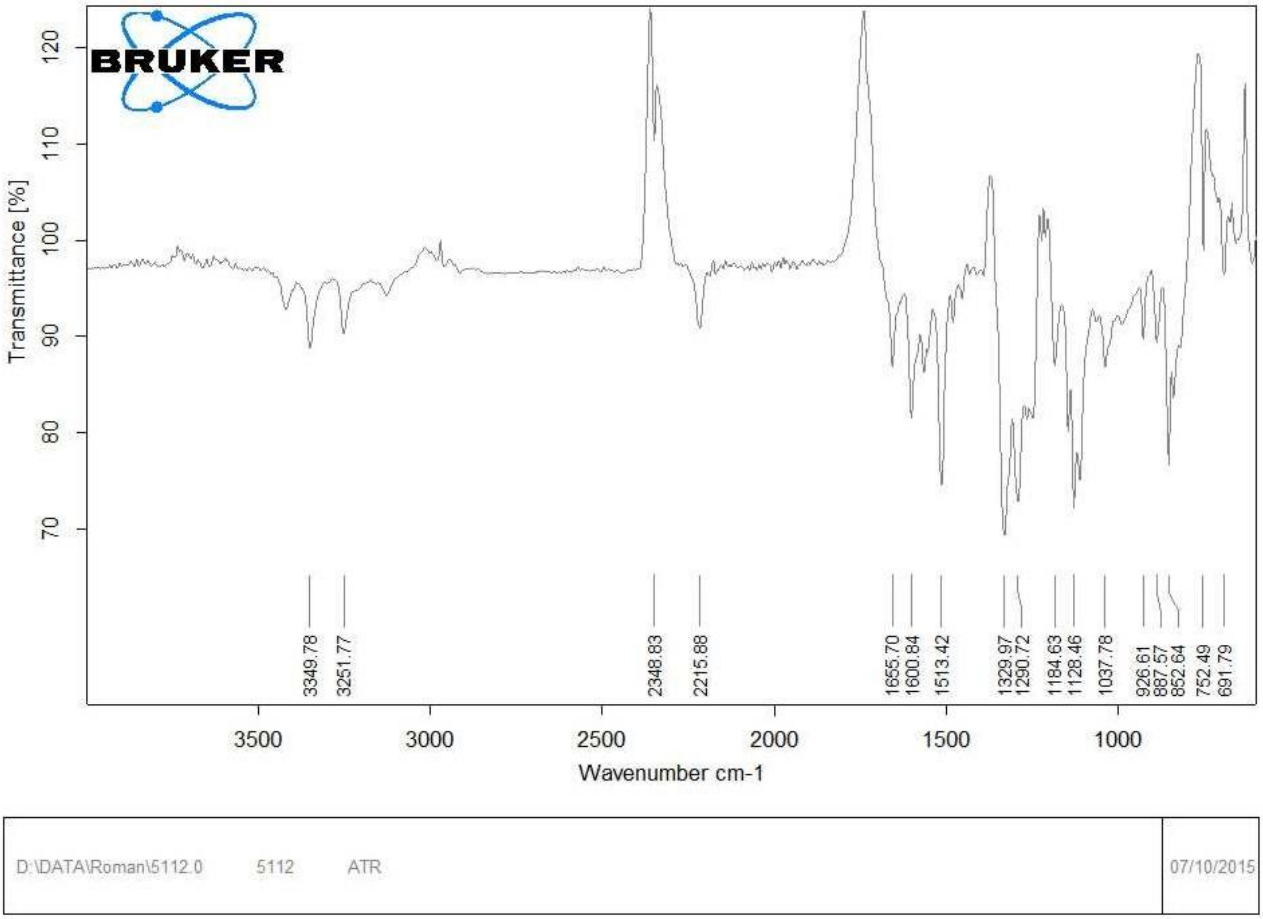
IR spectrum of compound 5c



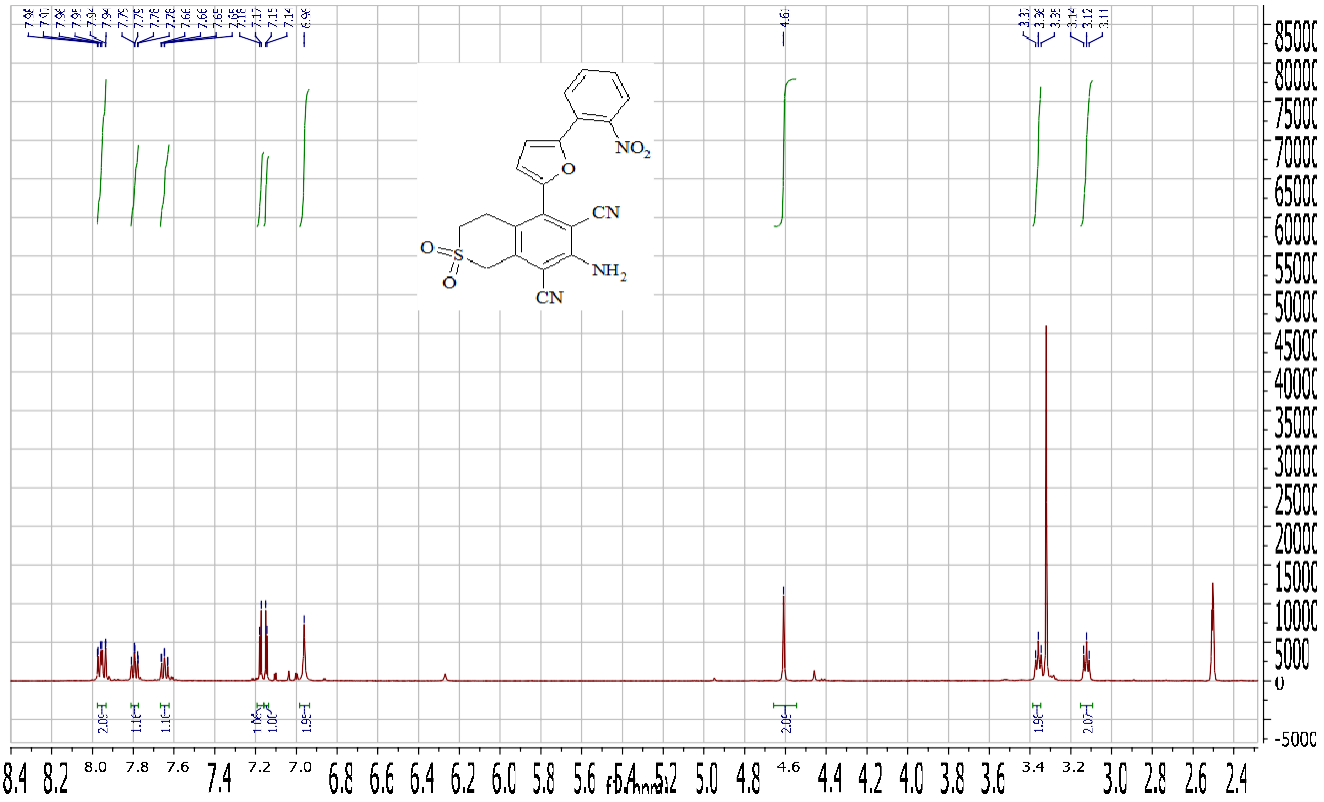
^{1}H NMR spectrum of compound 5d (500 MHz, DMSO-d_6)



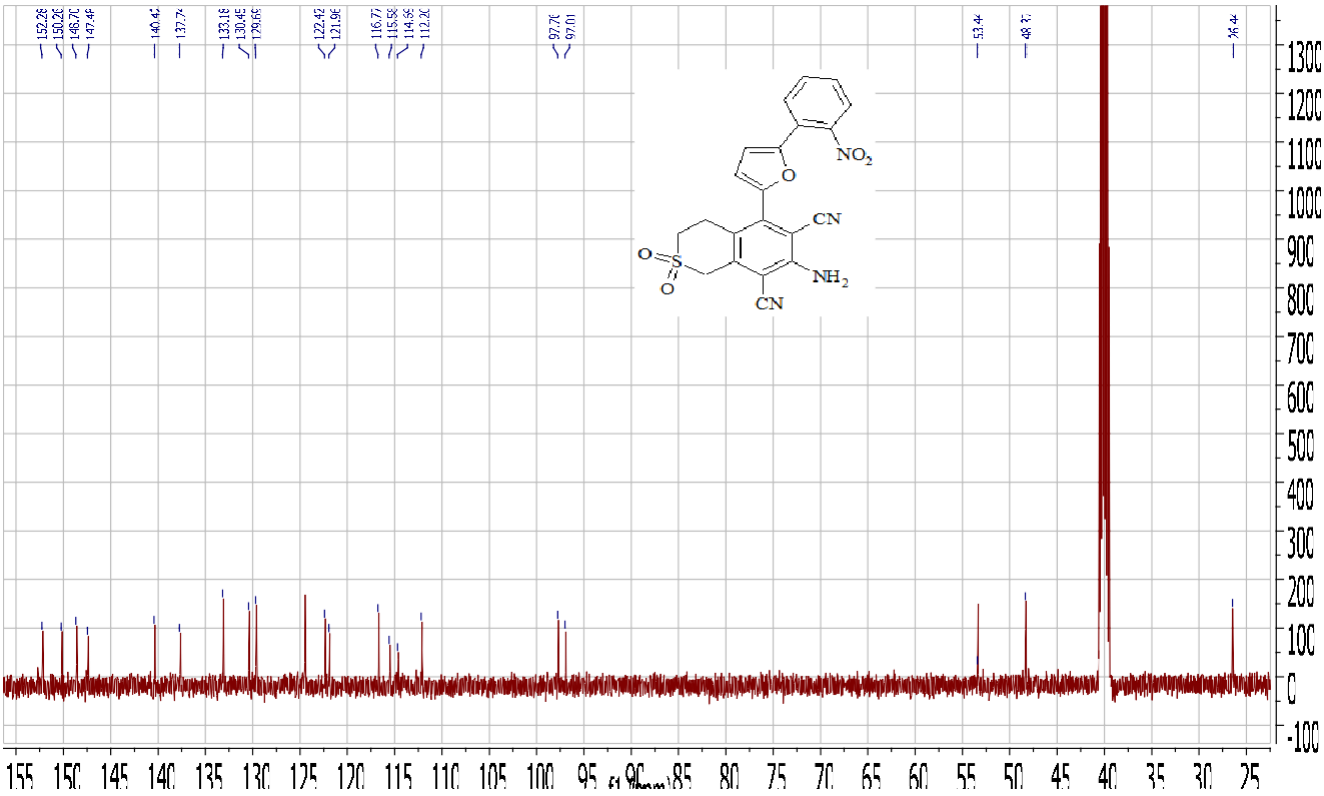
^{13}C NMR spectrum of compound 5d (126 MHz, DMSO-d_6)



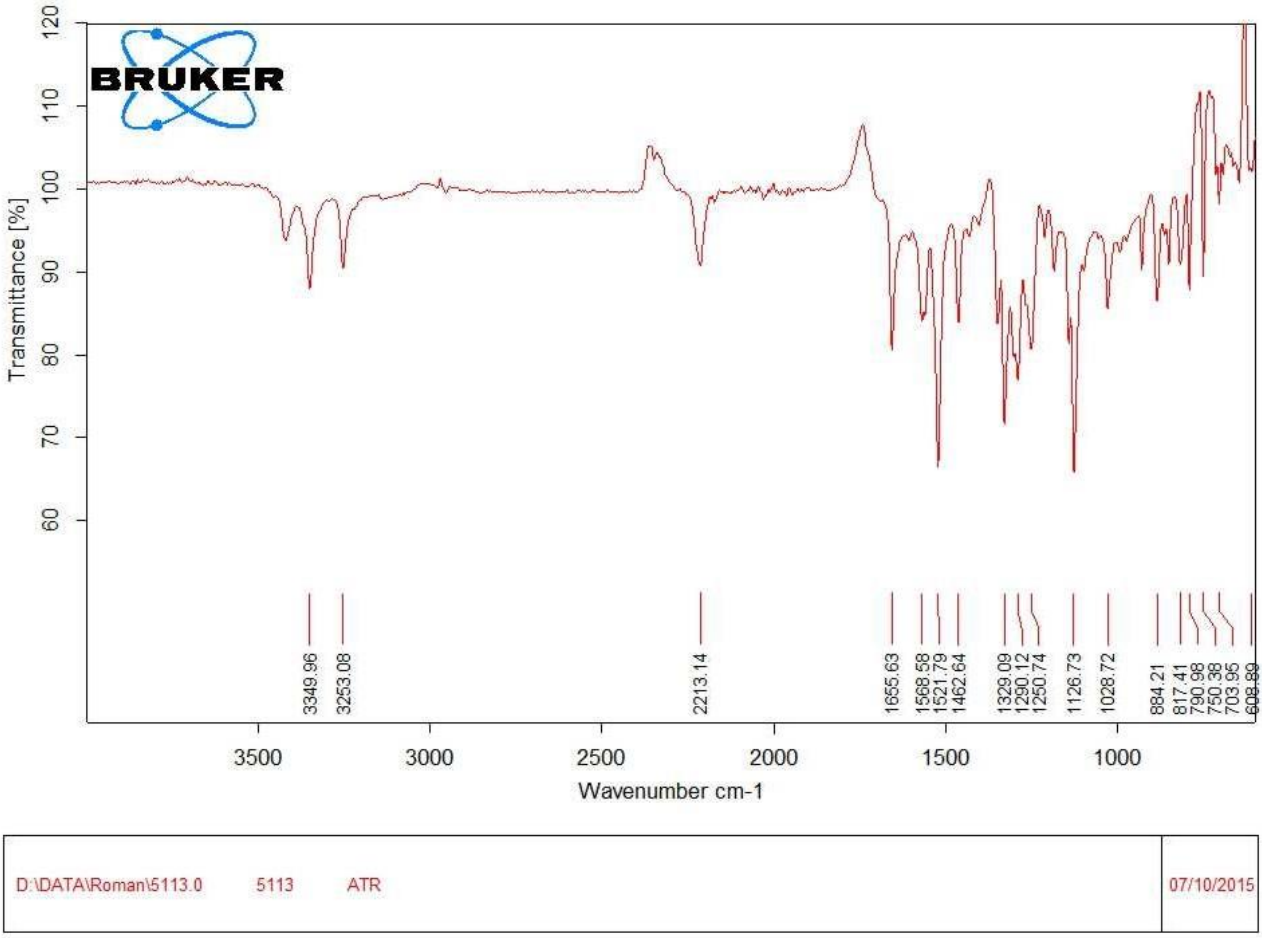
IR spectrum of compound 5d



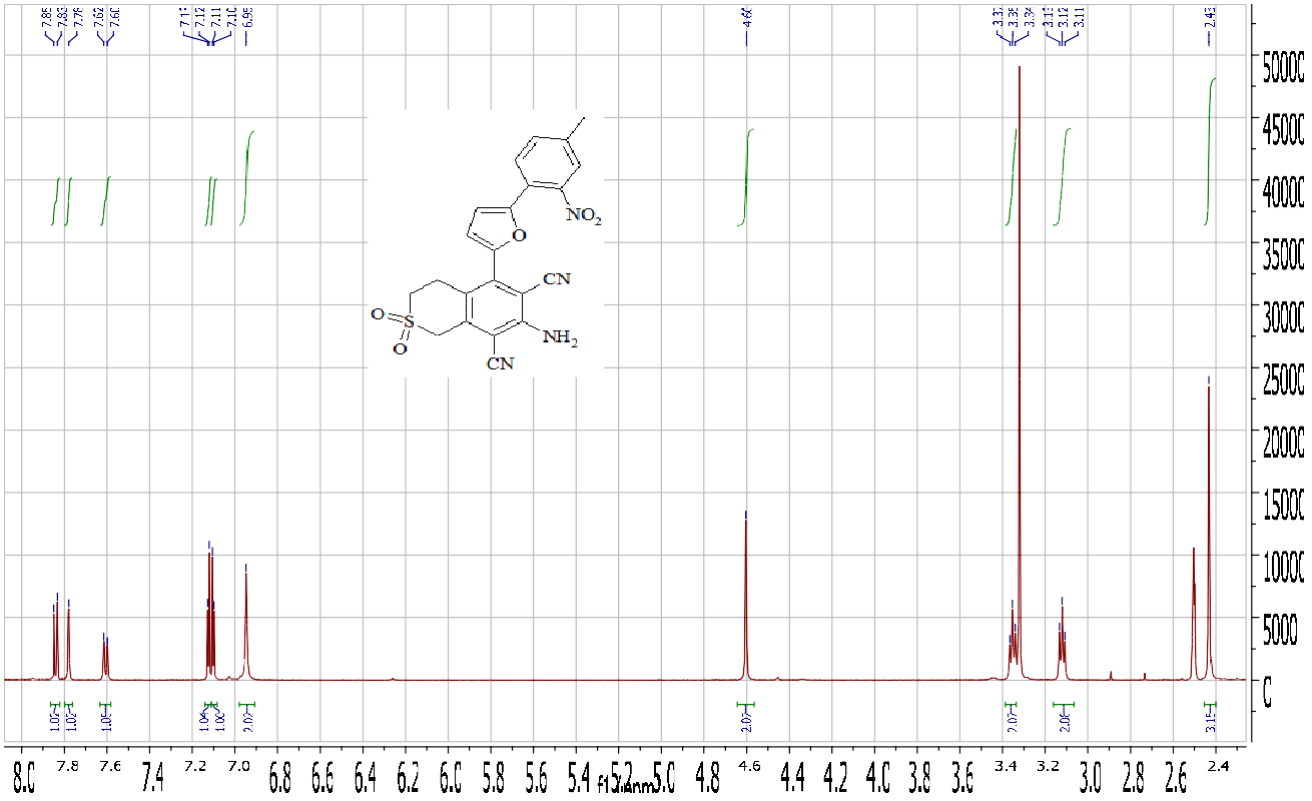
^{1}H NMR spectrum of compound 5e (500 MHz, DMSO-d_6)



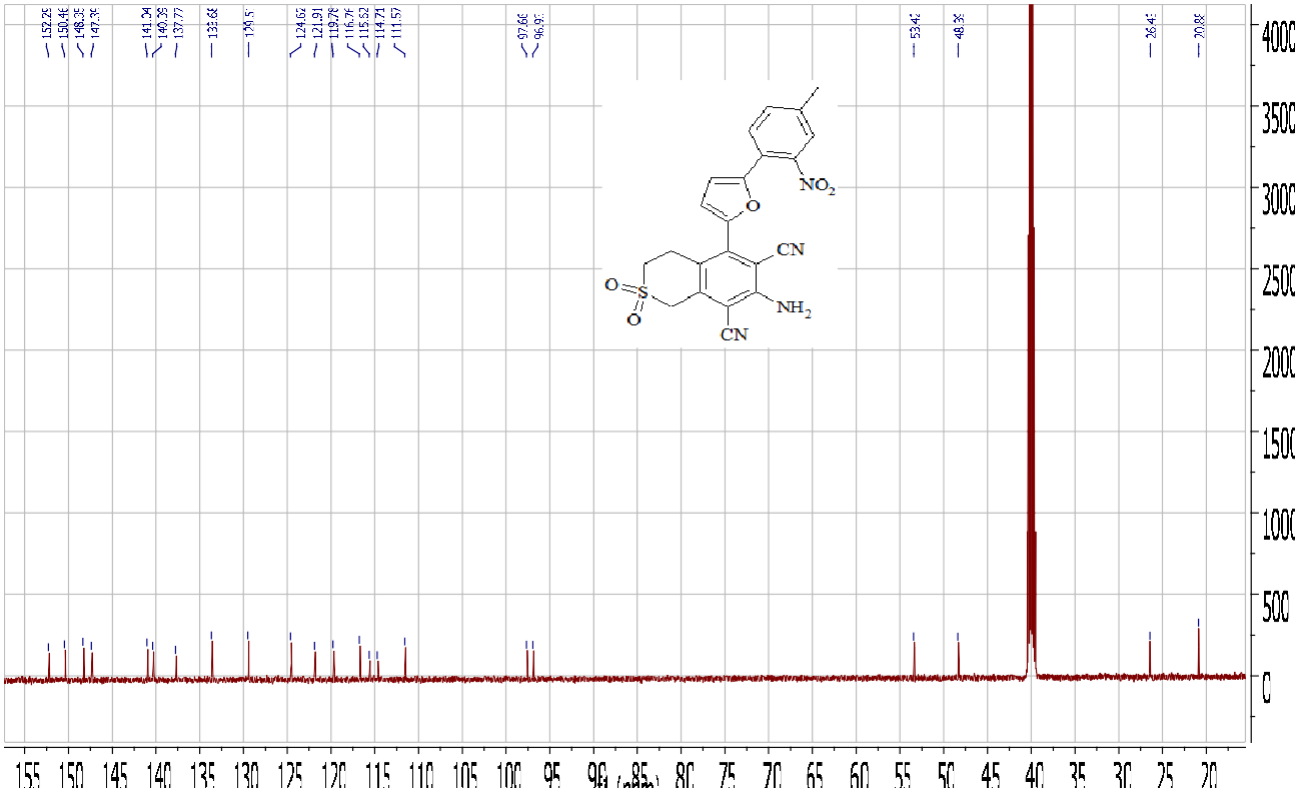
^{13}C NMR spectrum of compound 5e (126 MHz, DMSO-d_6)



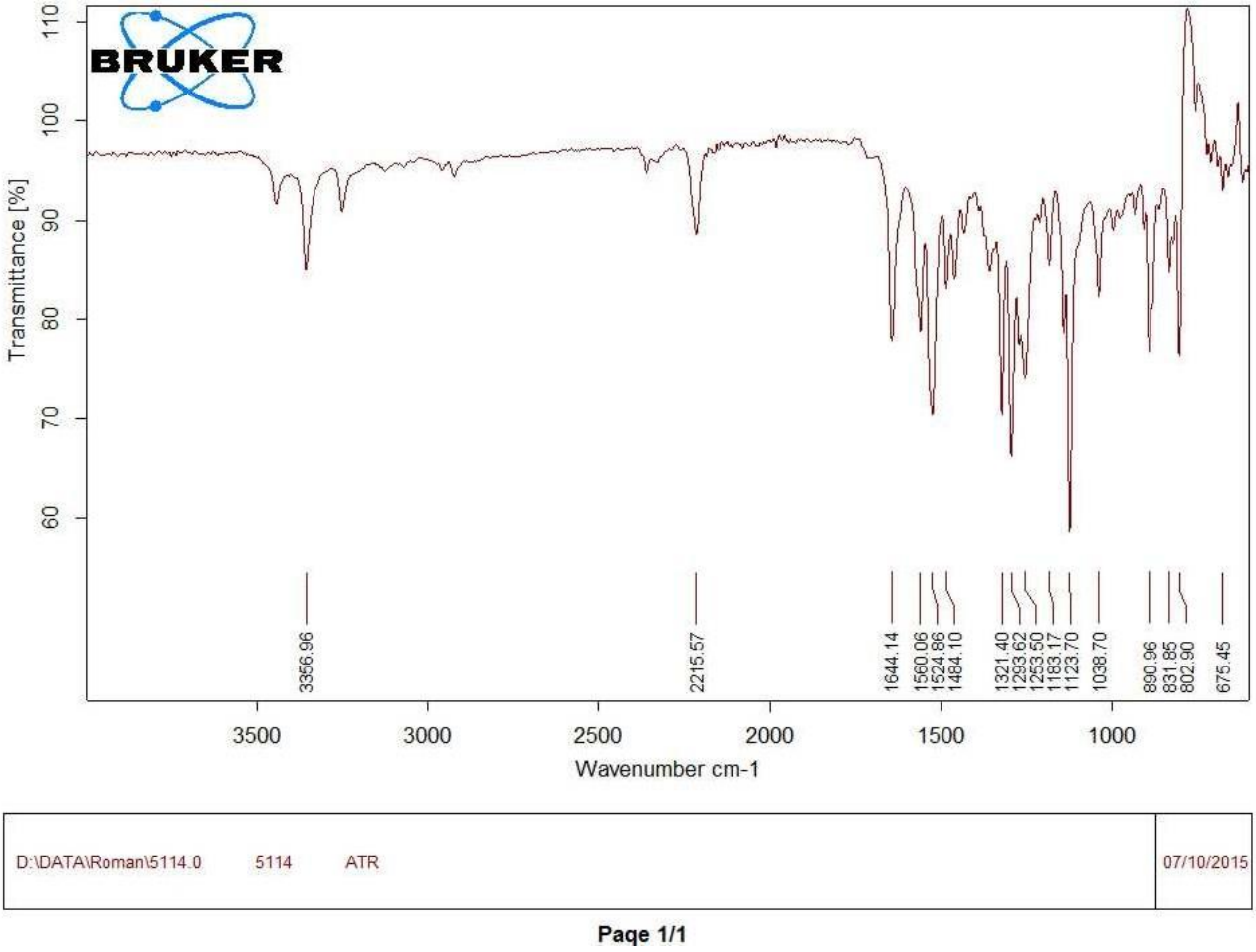
IR spectrum of compound 5e



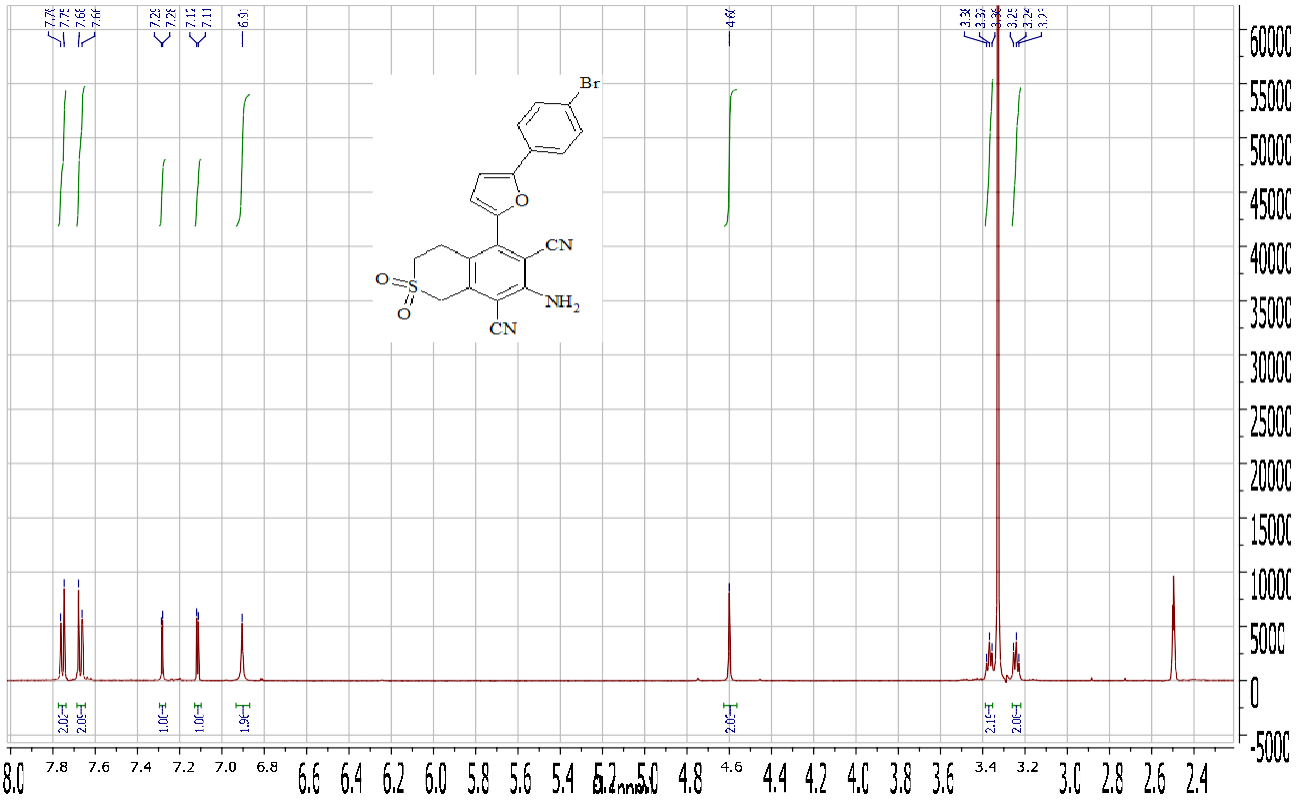
^{1}H NMR spectrum of compound 5f (500 MHz, DMSO-d_6)



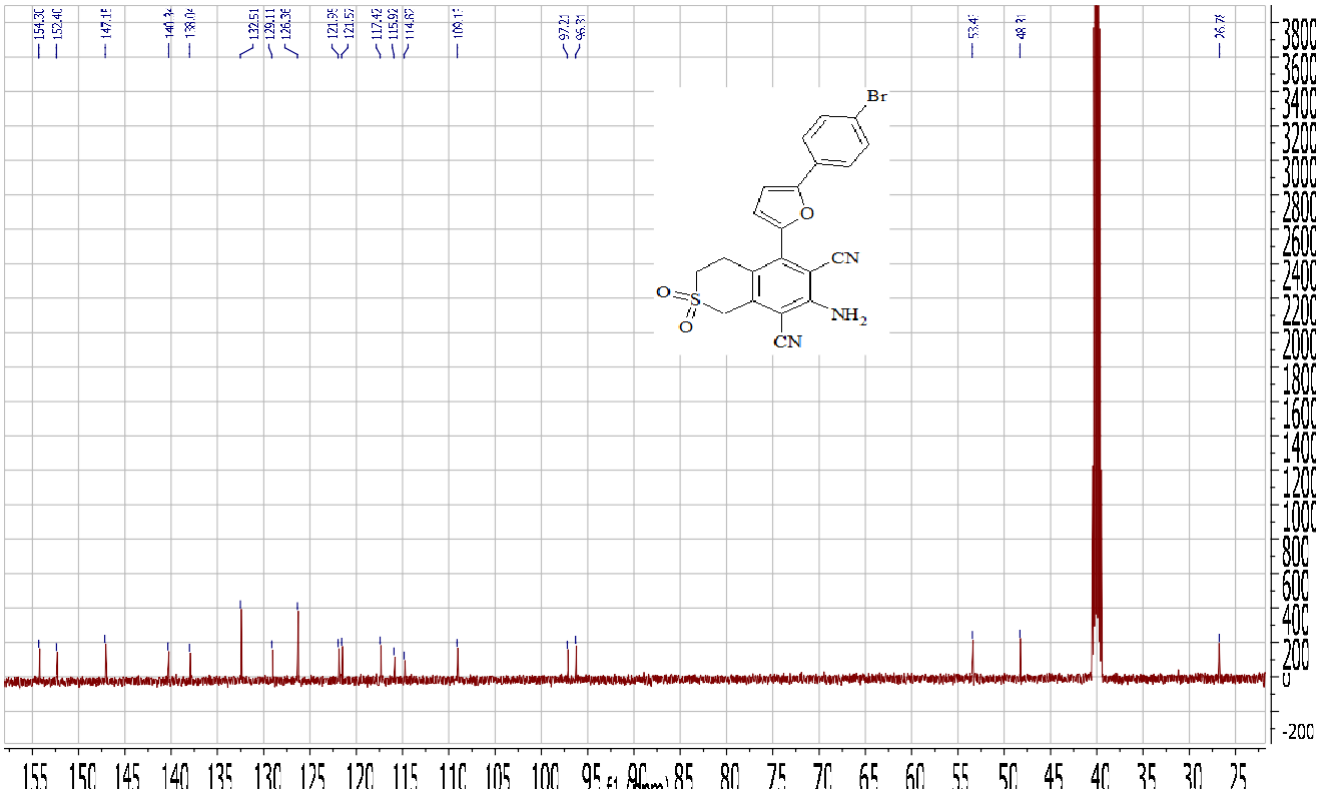
^{13}C NMR spectrum of compound 5f (126 MHz, DMSO-d_6)



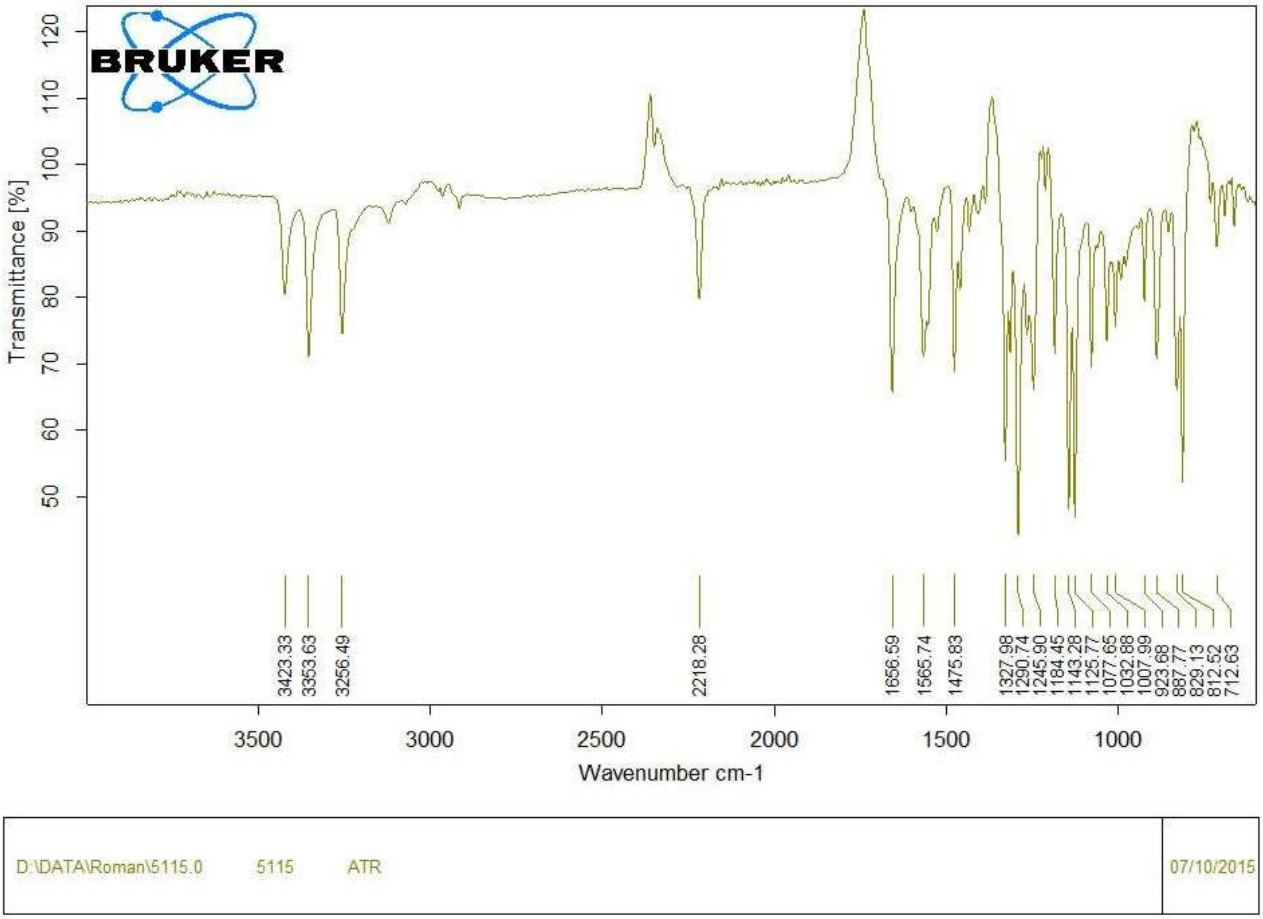
IR spectrum of compound 5f



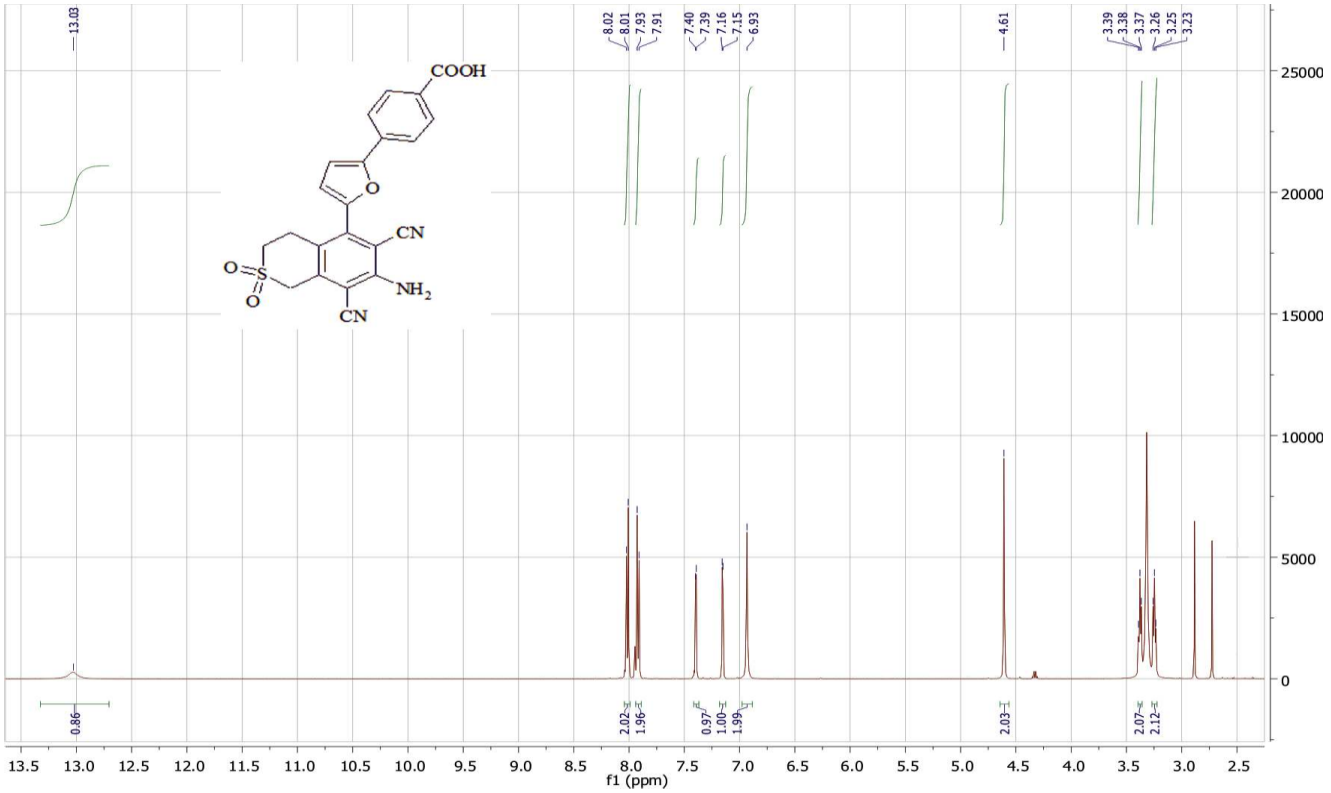
^{1}H NMR spectrum of compound 5g (500 MHz, DMSO-d_6)



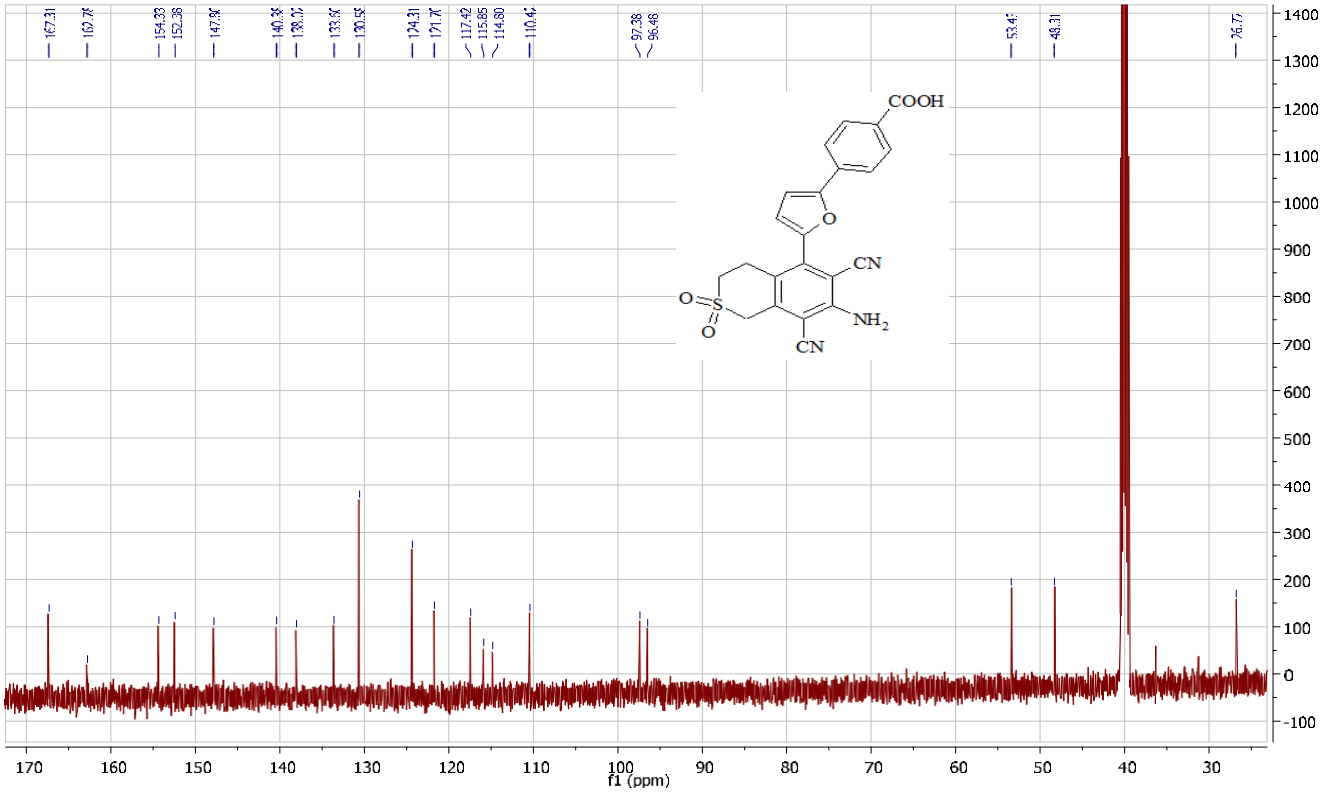
^{13}C NMR spectrum of compound 5g (126 MHz, DMSO-d_6)



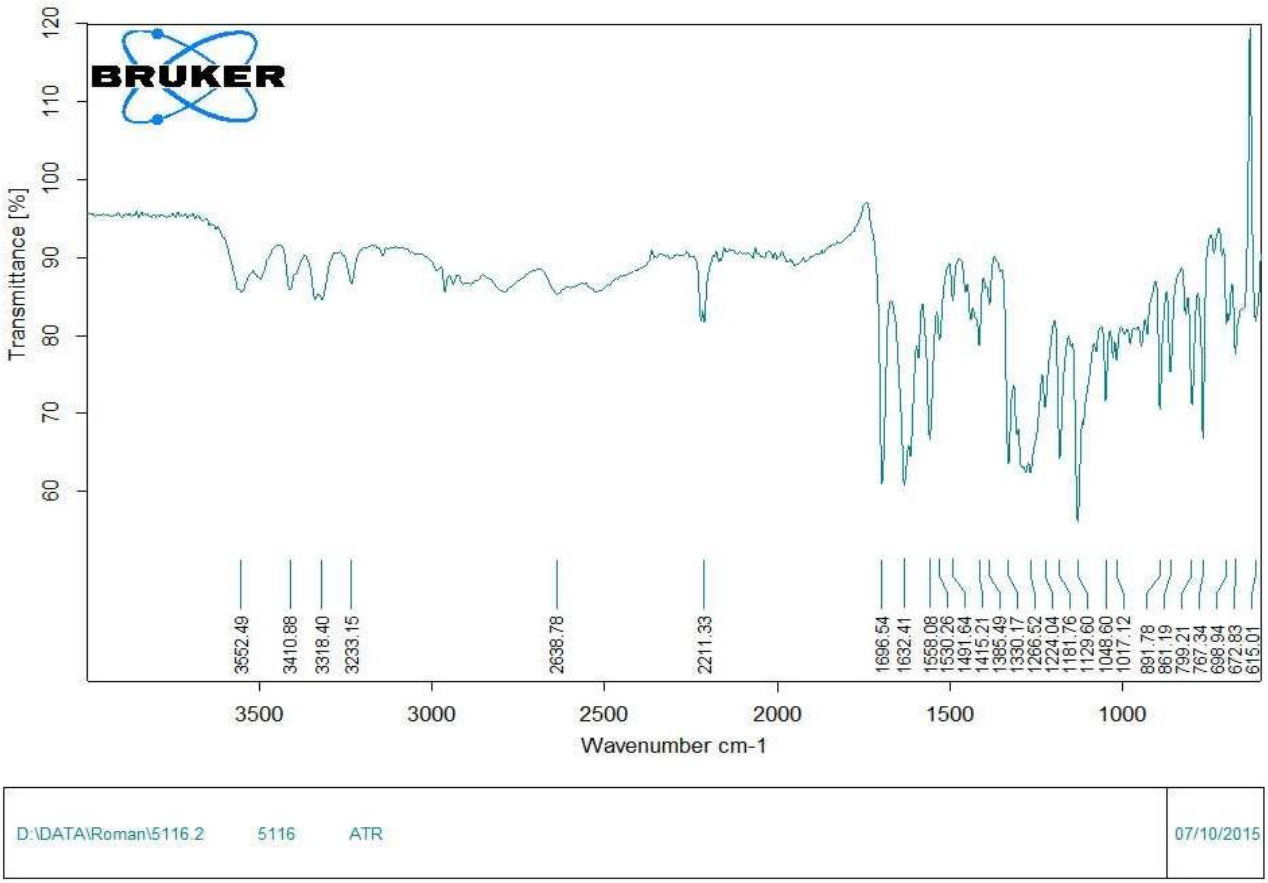
IR spectrum of compound 5g



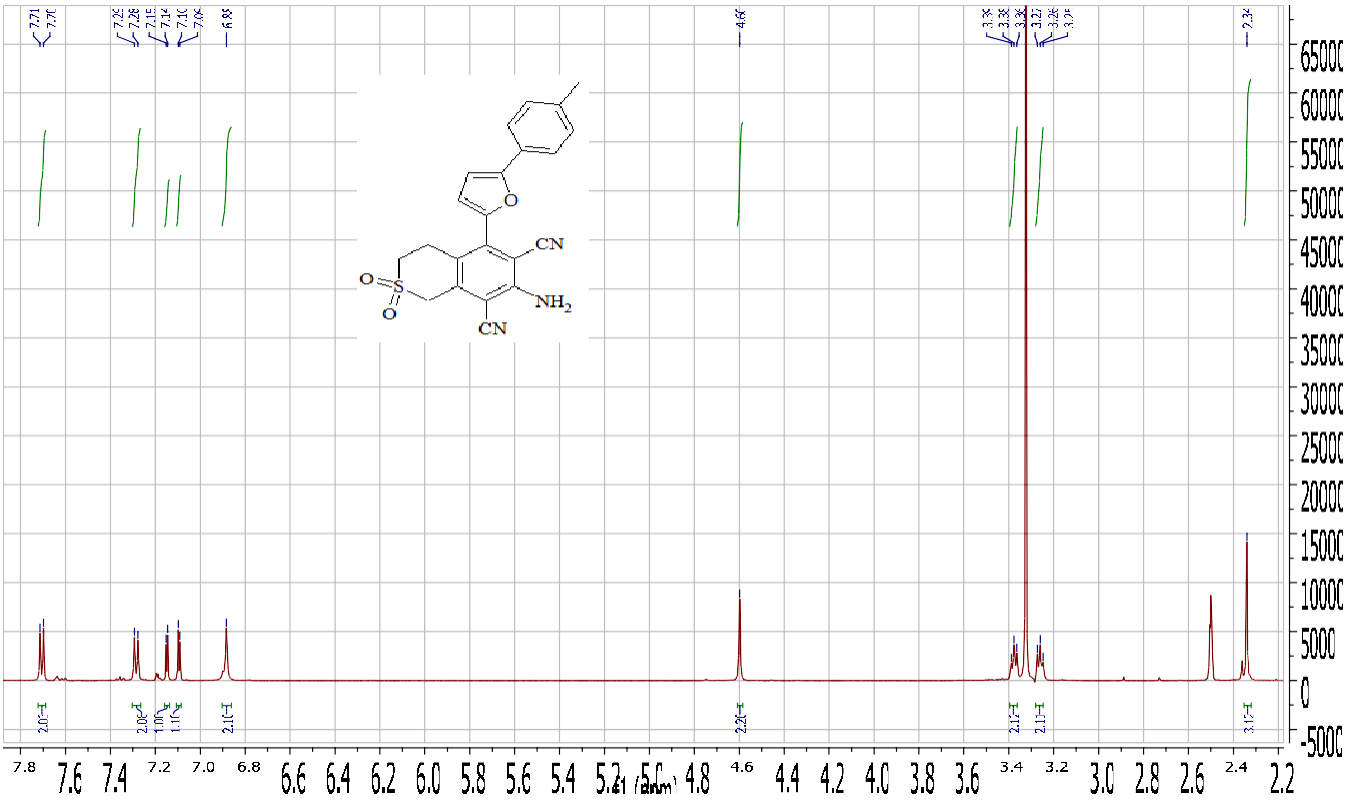
^{1}H NMR spectrum of compound 5h (500 MHz, DMSO-d_6)



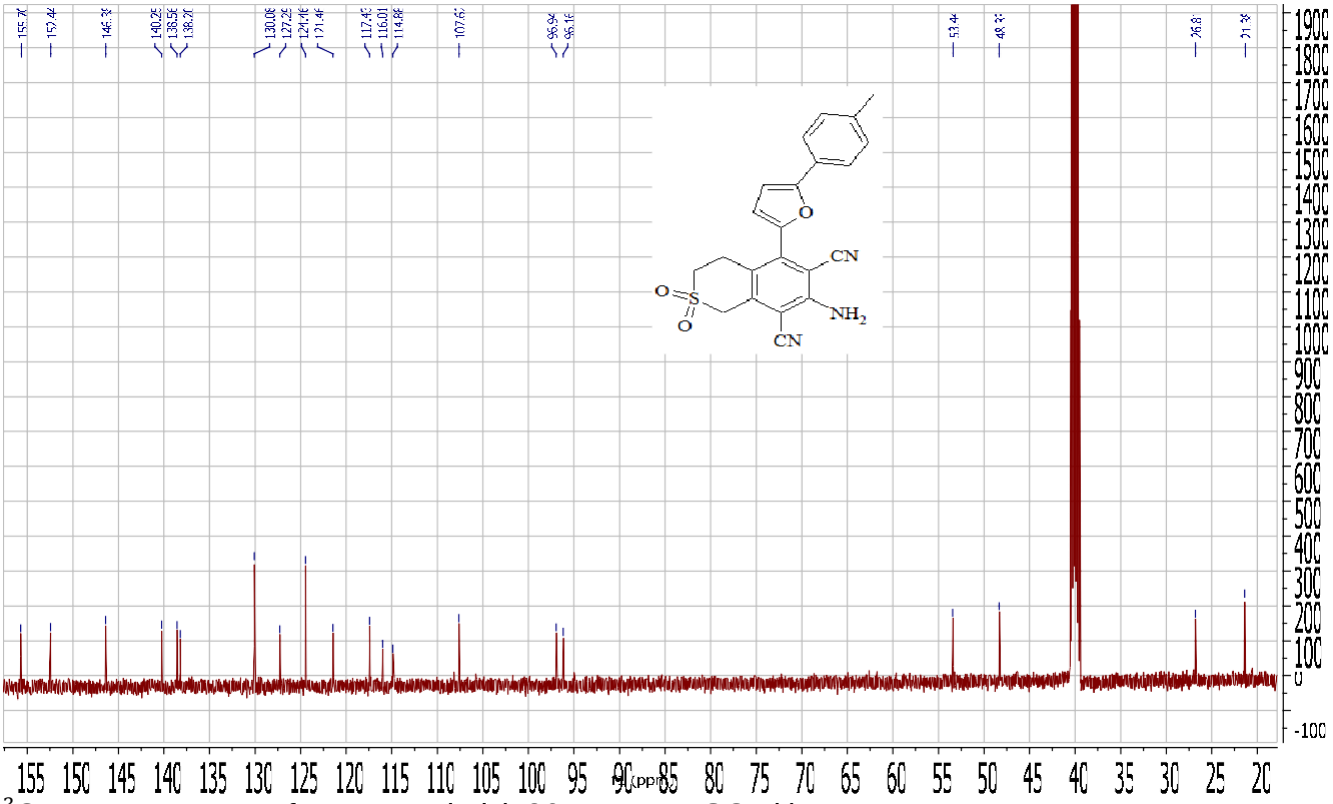
^{13}C NMR spectrum of compound 5h (126 MHz, DMSO-d_6)



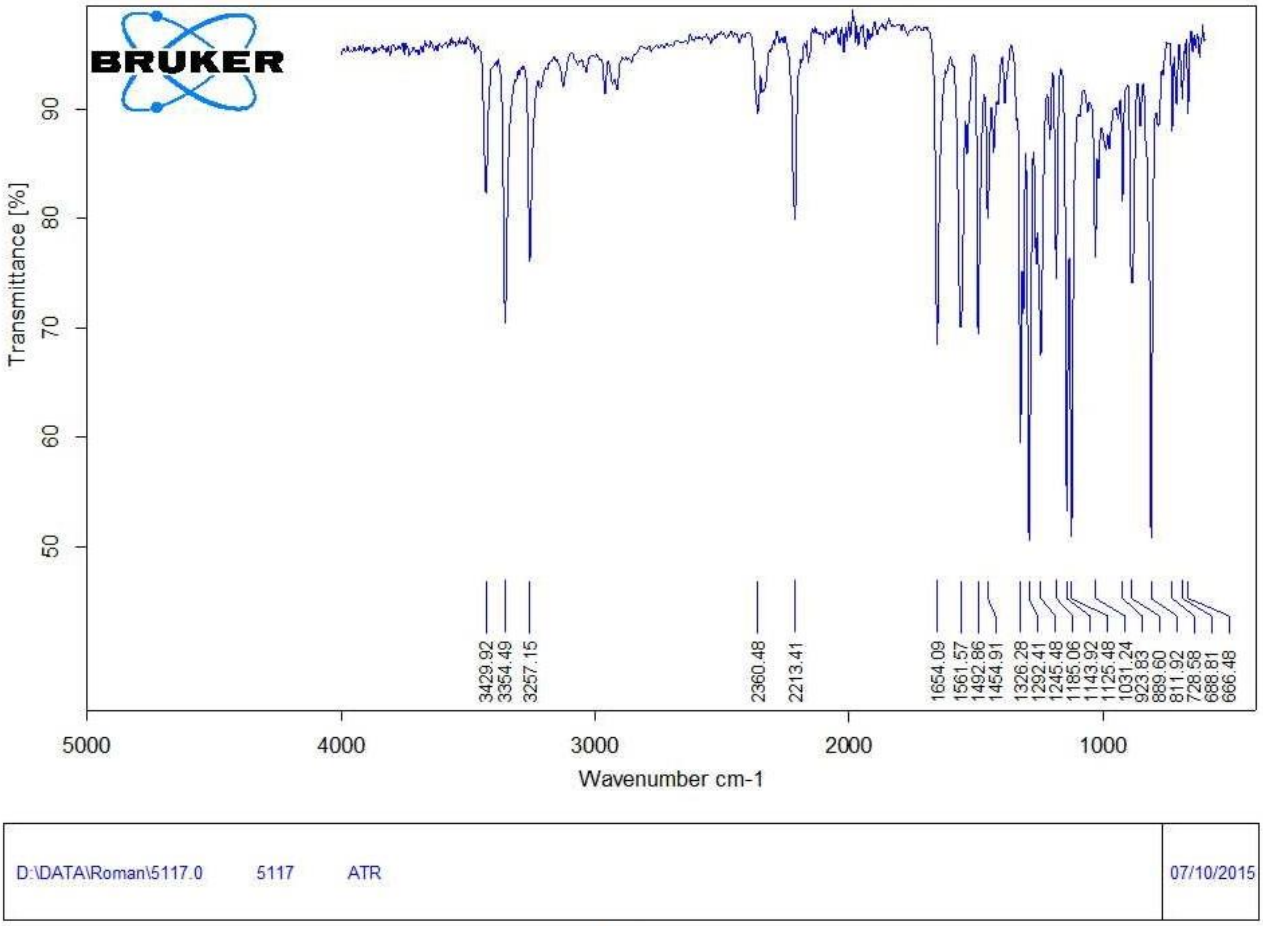
IR spectrum of compound 5h



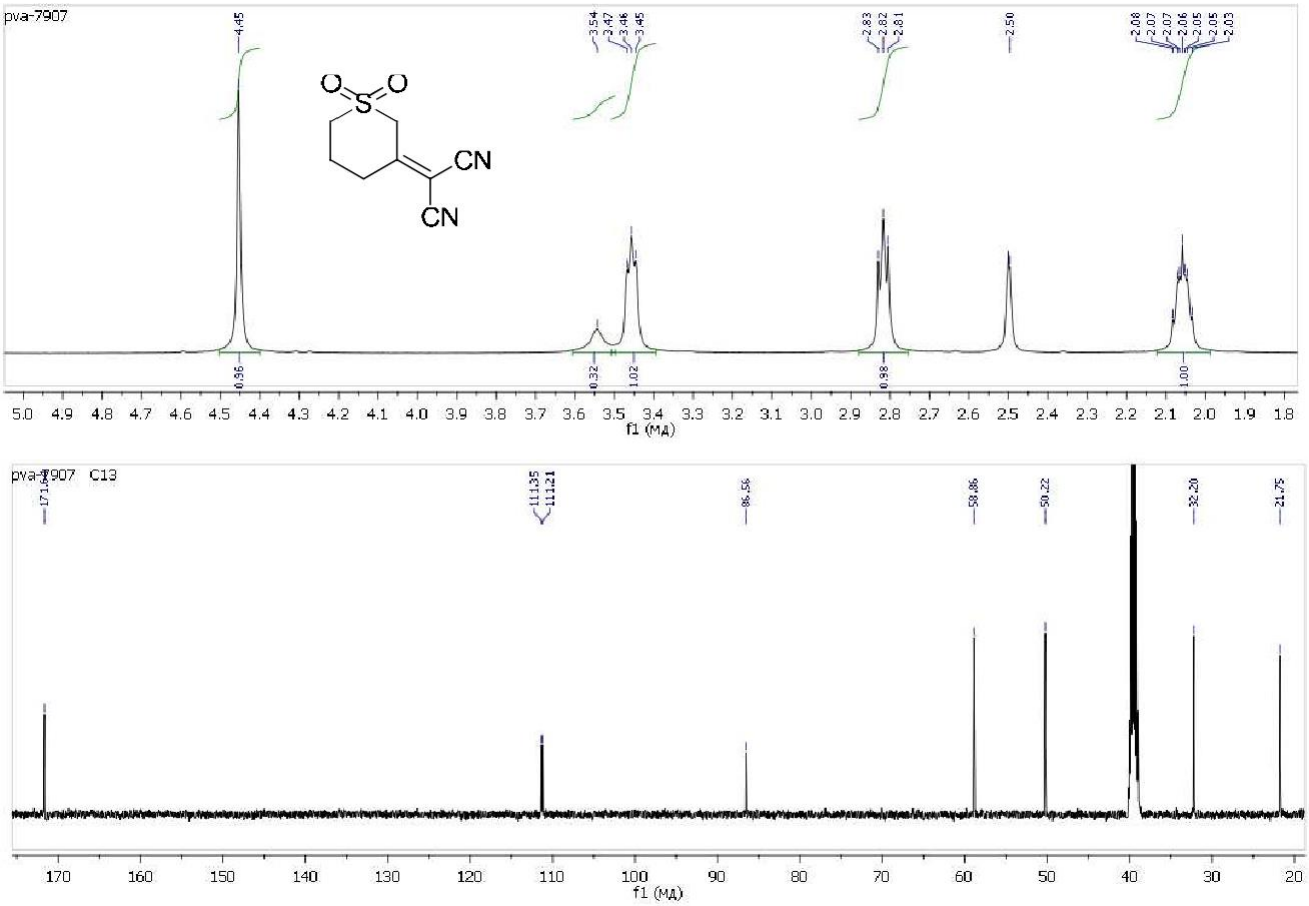
^{1}H NMR spectrum of compound 5i (500 MHz, DMSO-d_6)



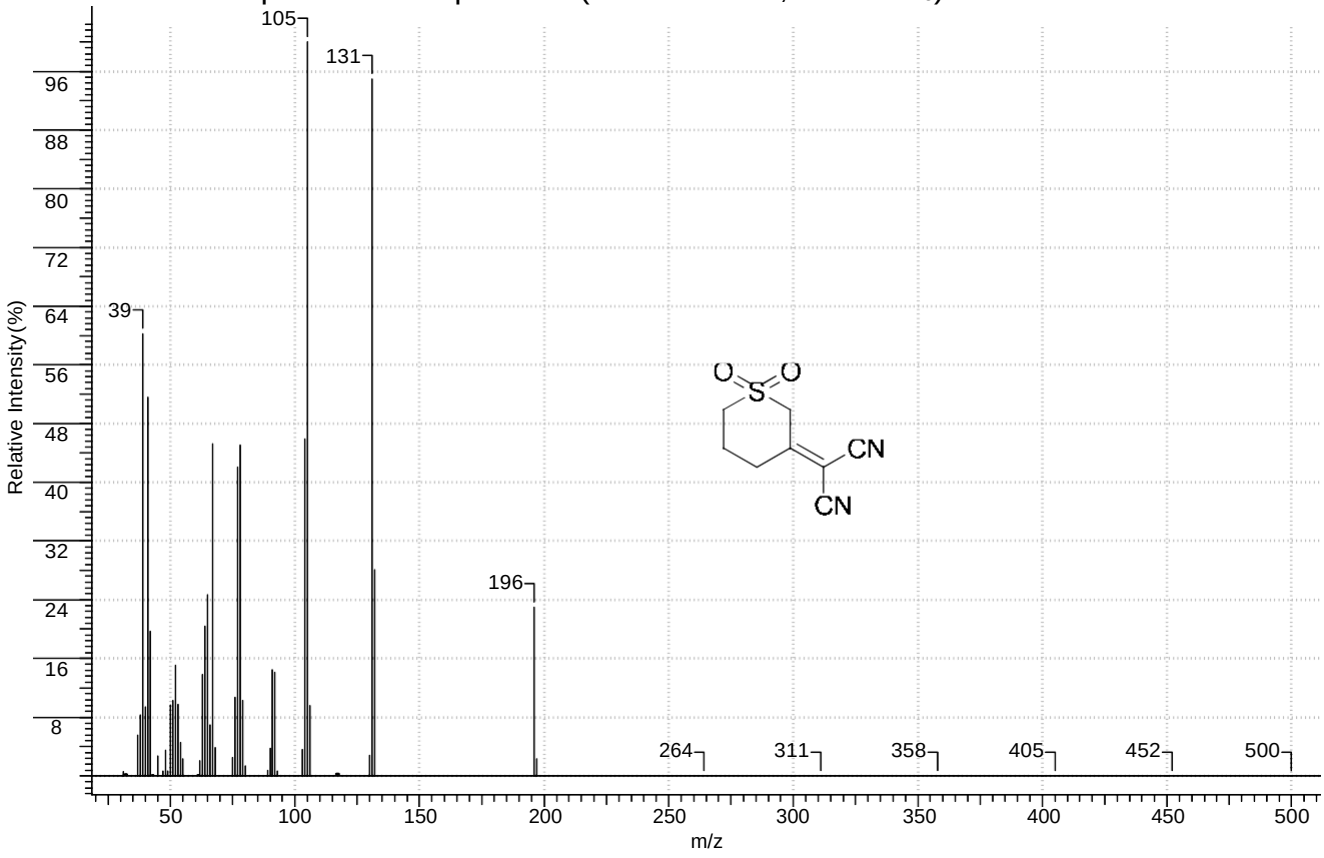
^{13}C NMR spectrum of compound 5i (126 MHz, DMSO-d_6)



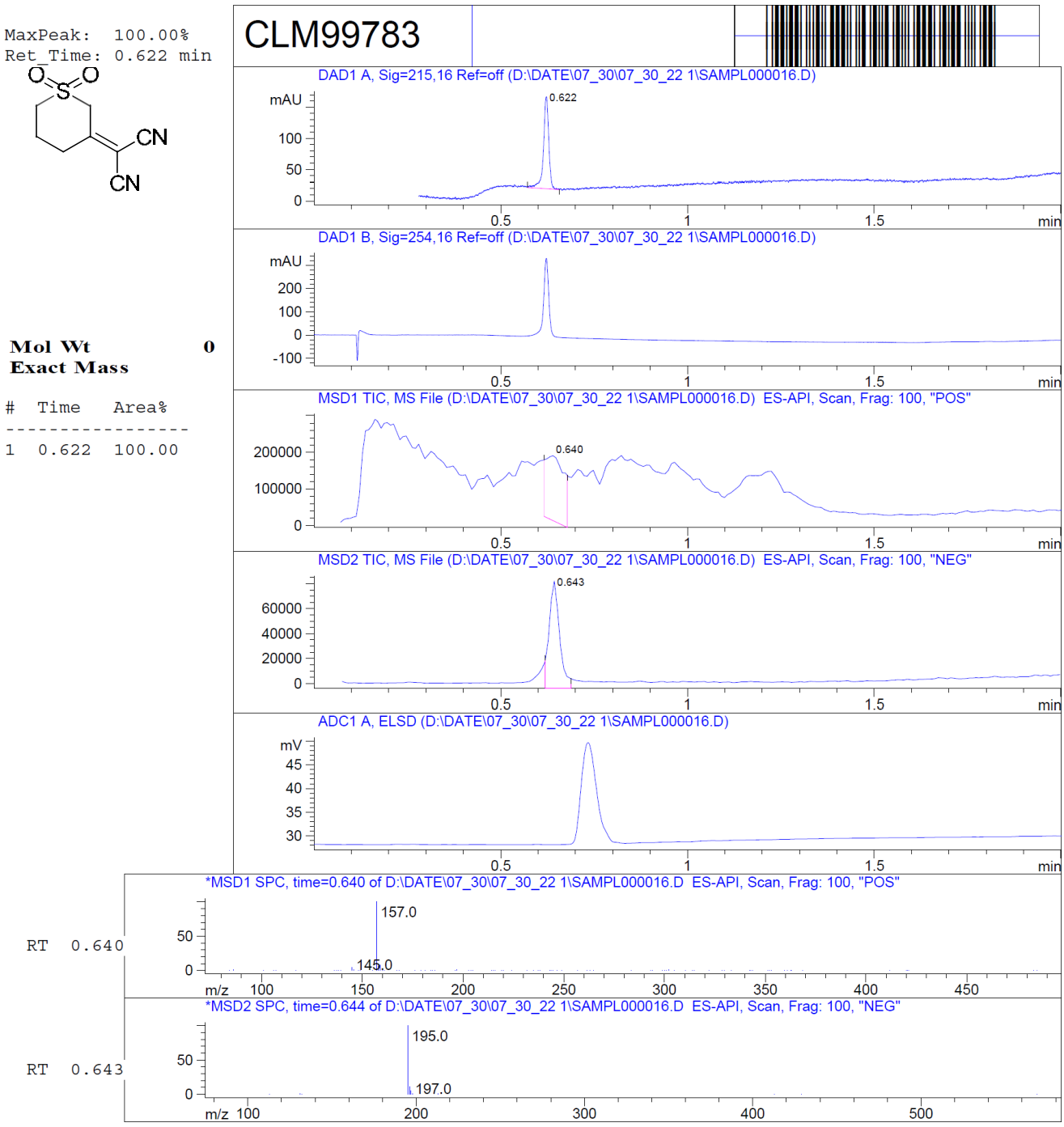
IR spectrum of compound 5i



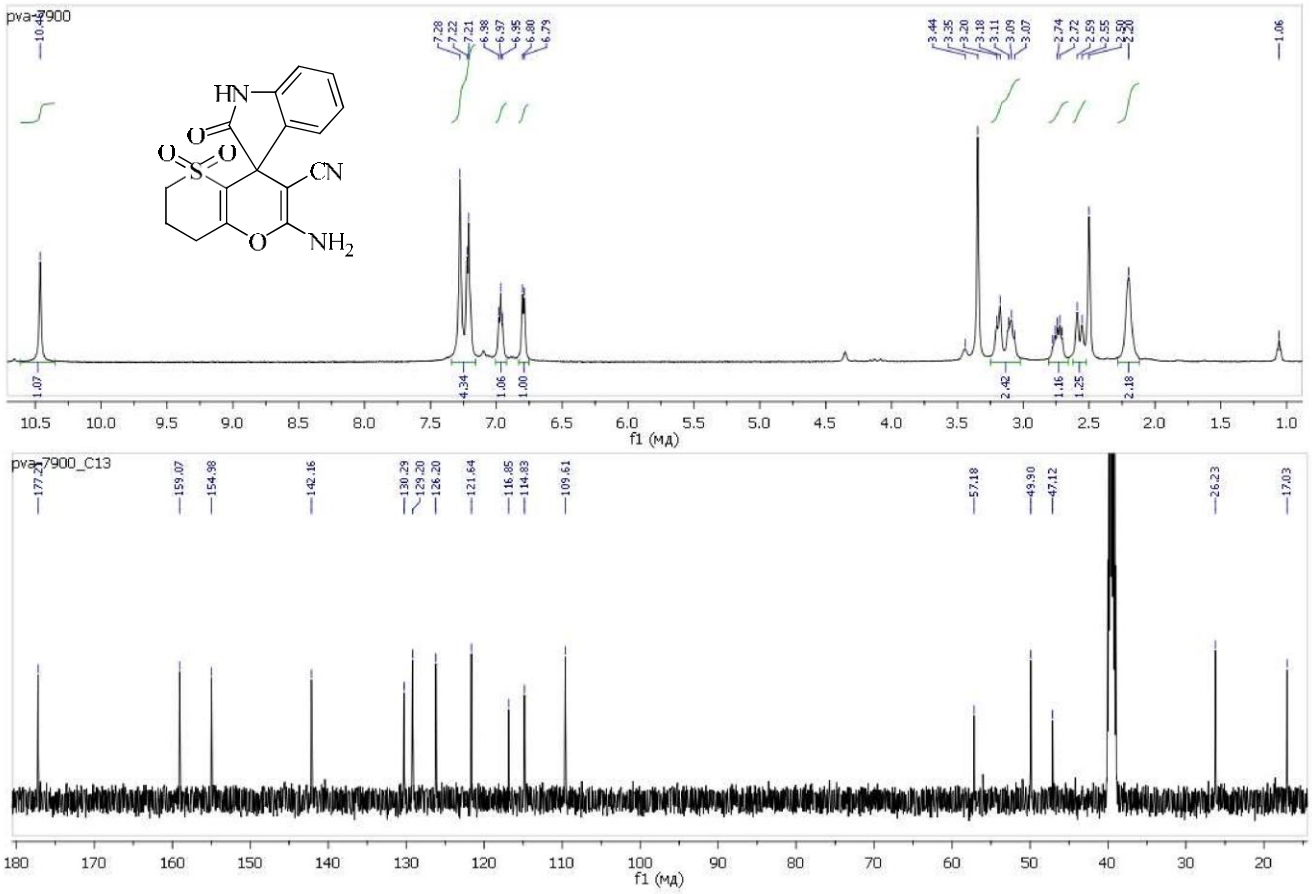
^{1}H and ^{13}C NMR spectra of compound 6 (500/126 MHz, DMSO-d_6)



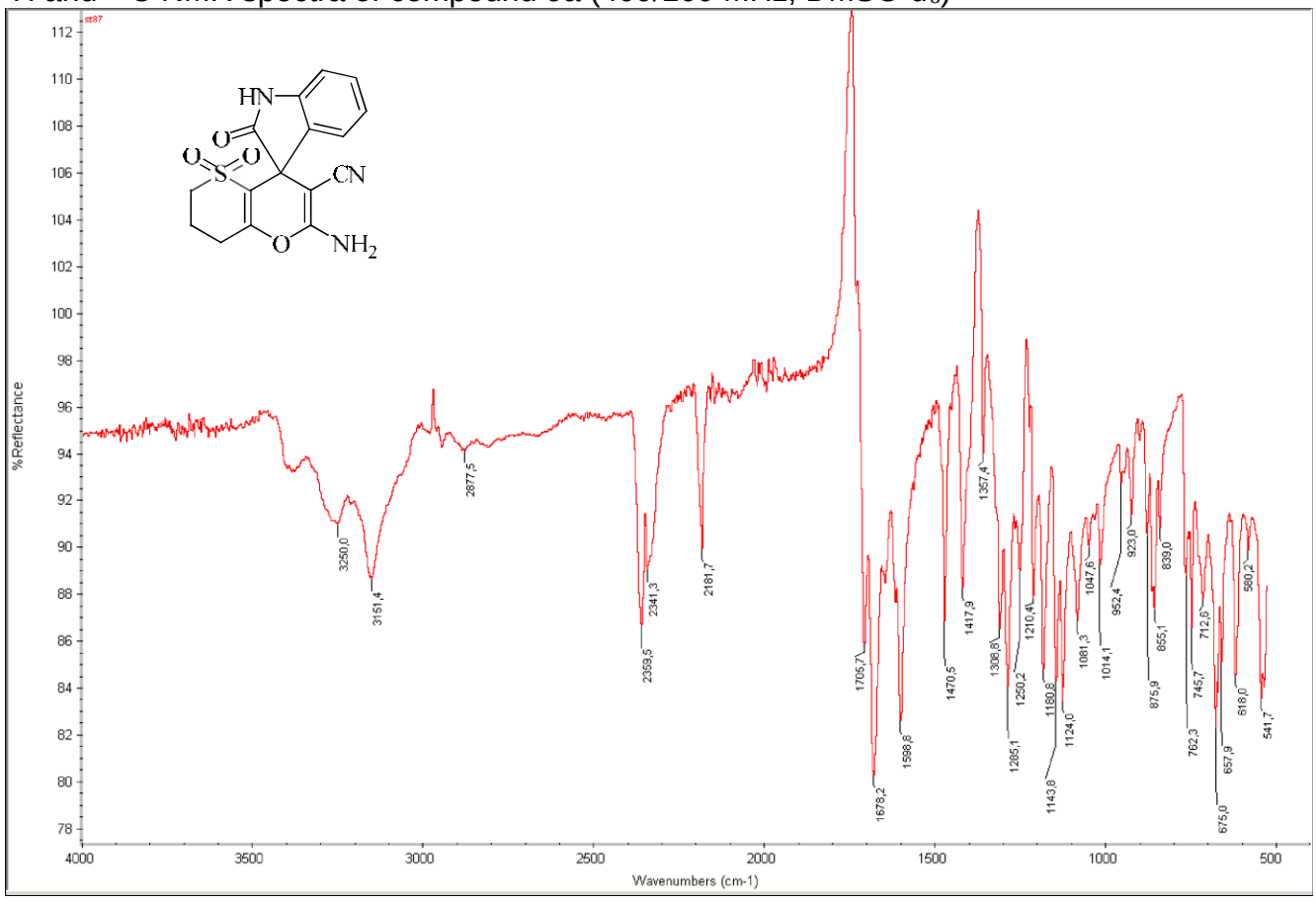
Mass spectrum (EI) of compound 6



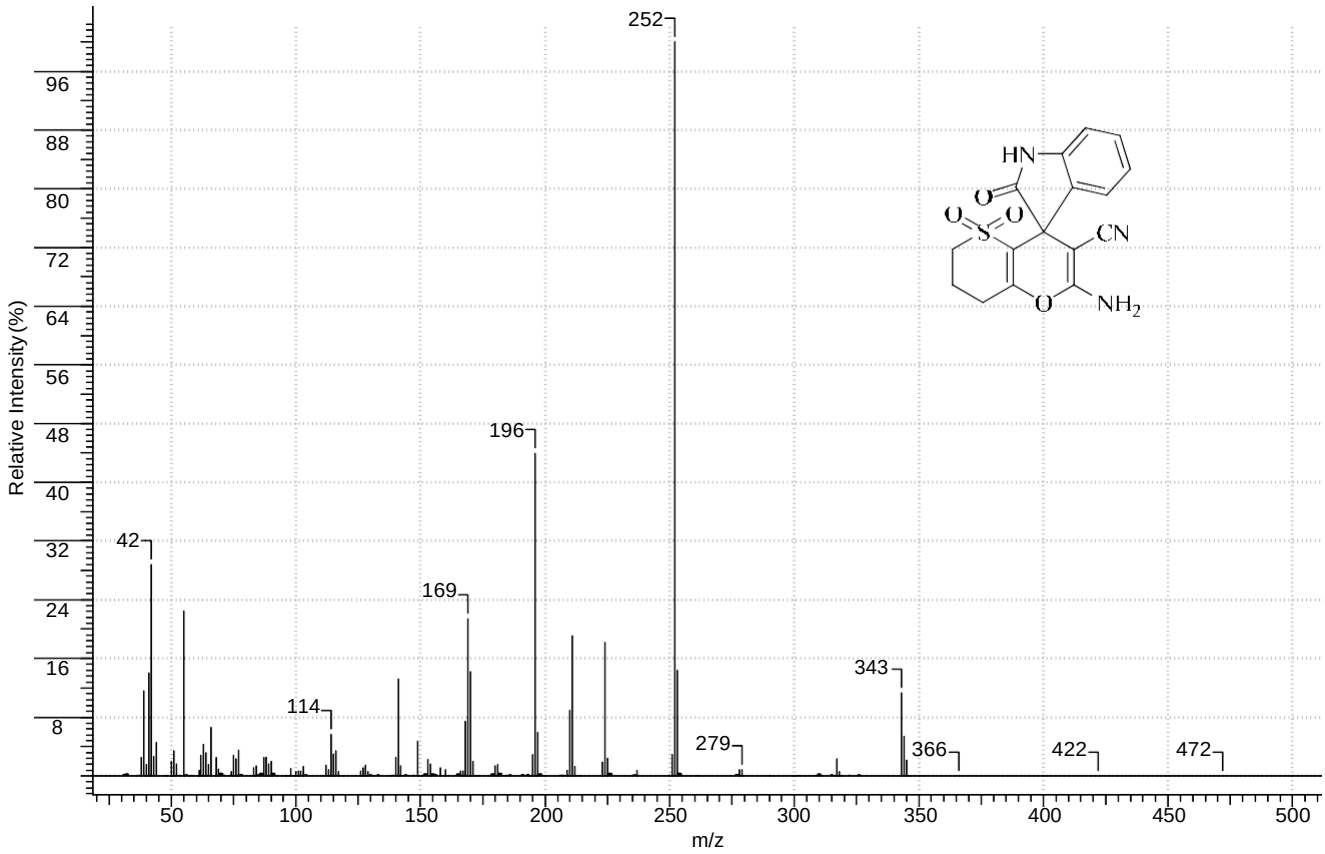
LC-MS data for compound 6



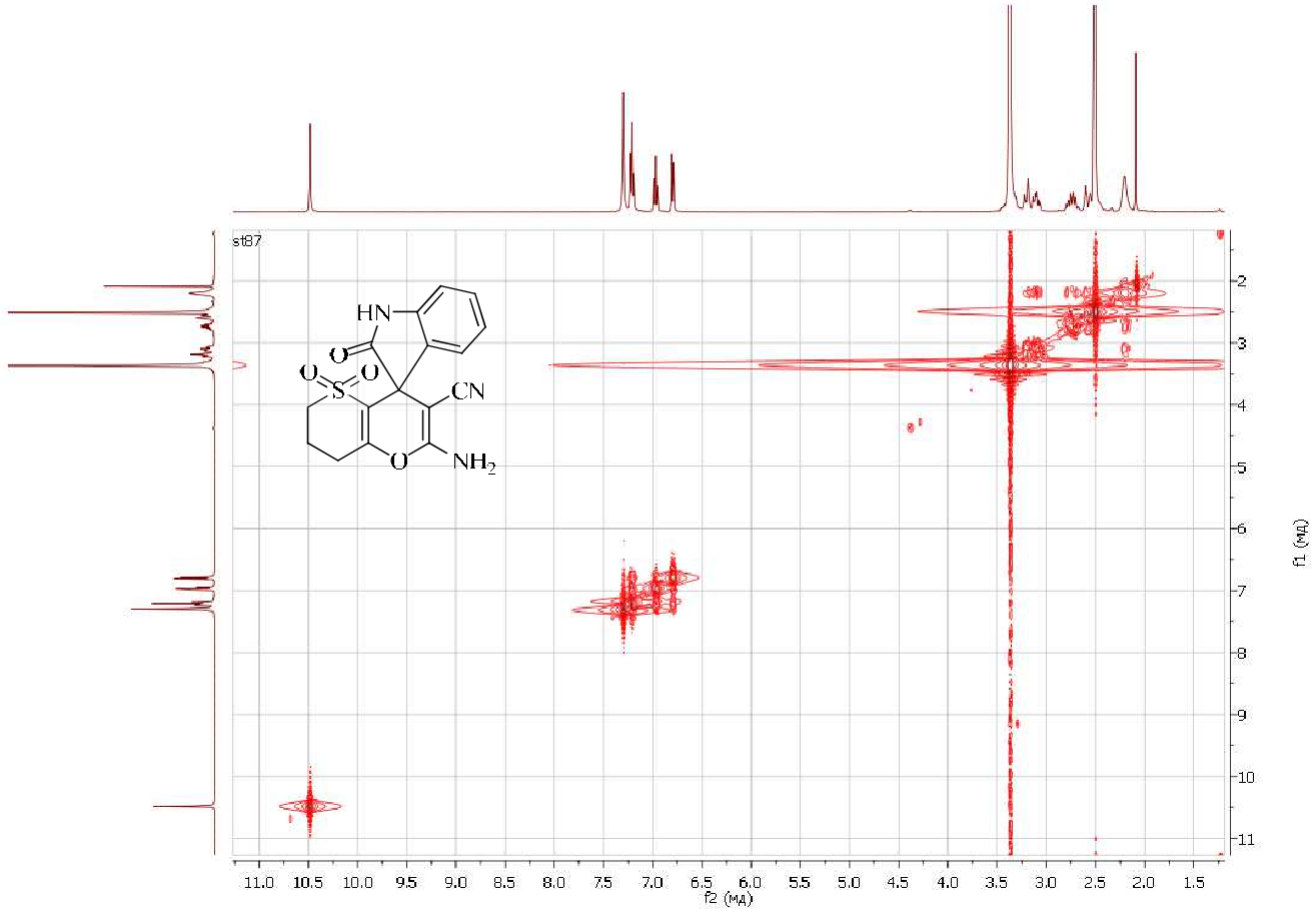
^{1}H and ^{13}C NMR spectra of compound 9a (400/100 MHz, DMSO-d_6)



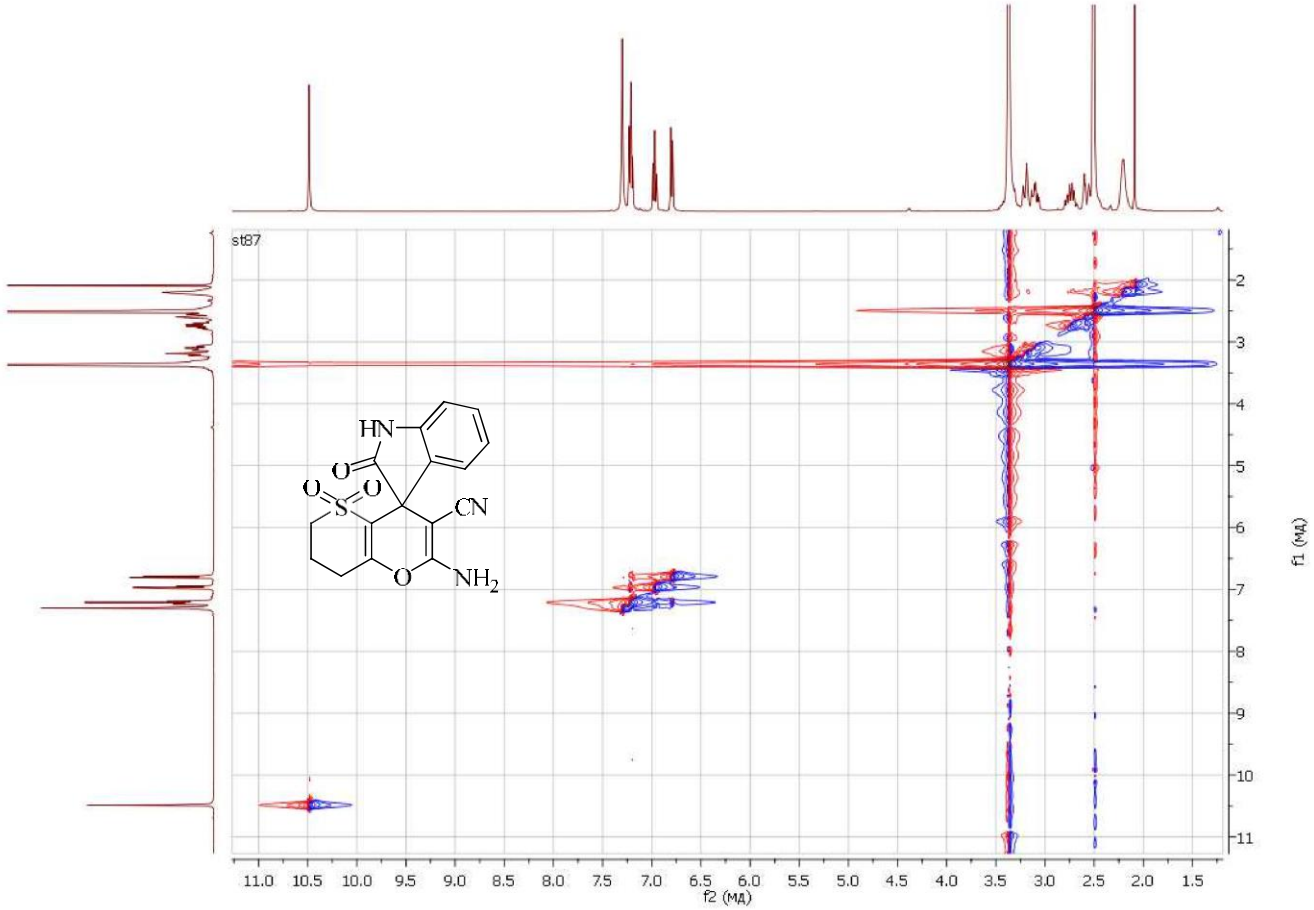
IR spectrum of compound 9a



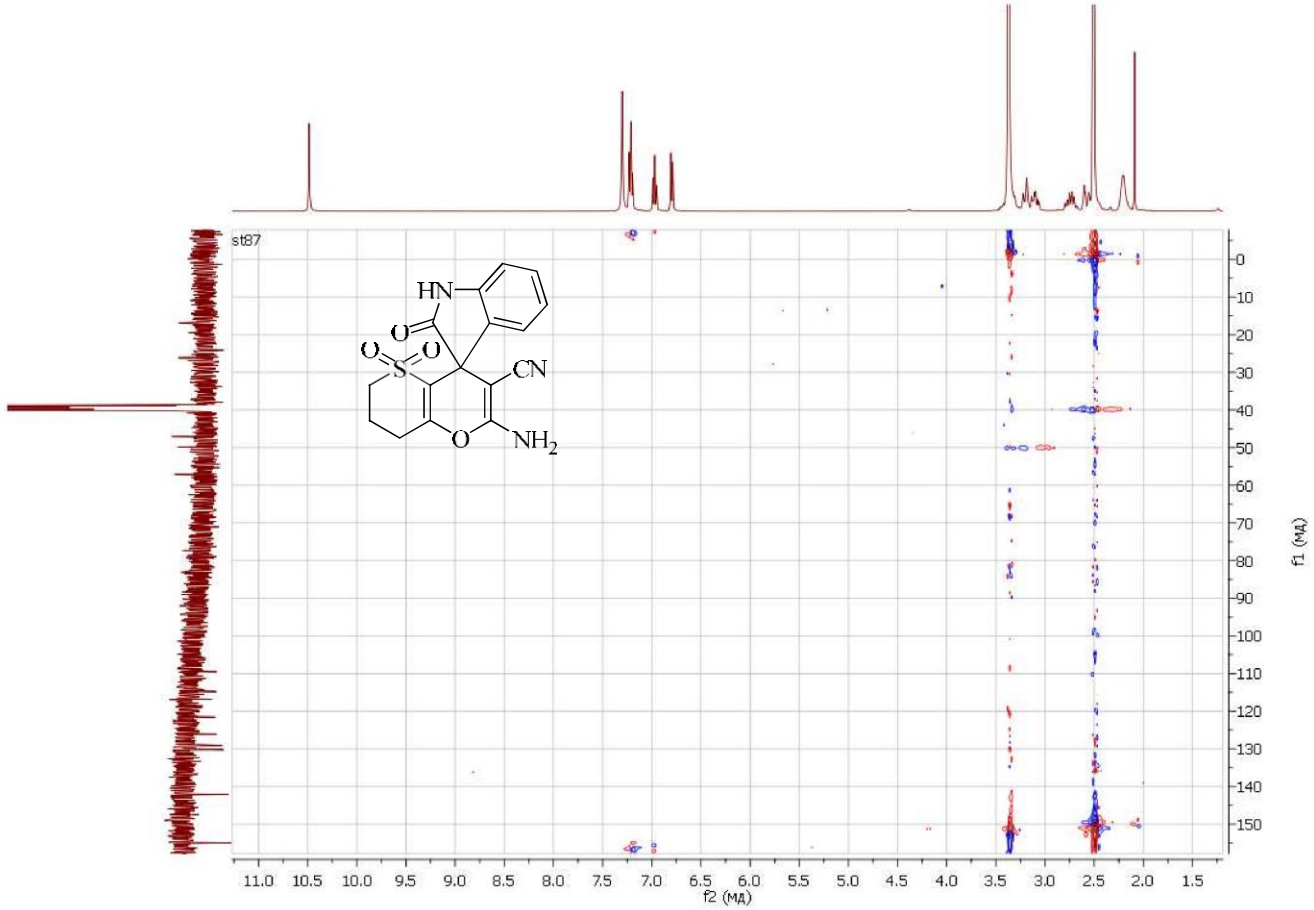
Mass spectrum (EI) of compound 9a



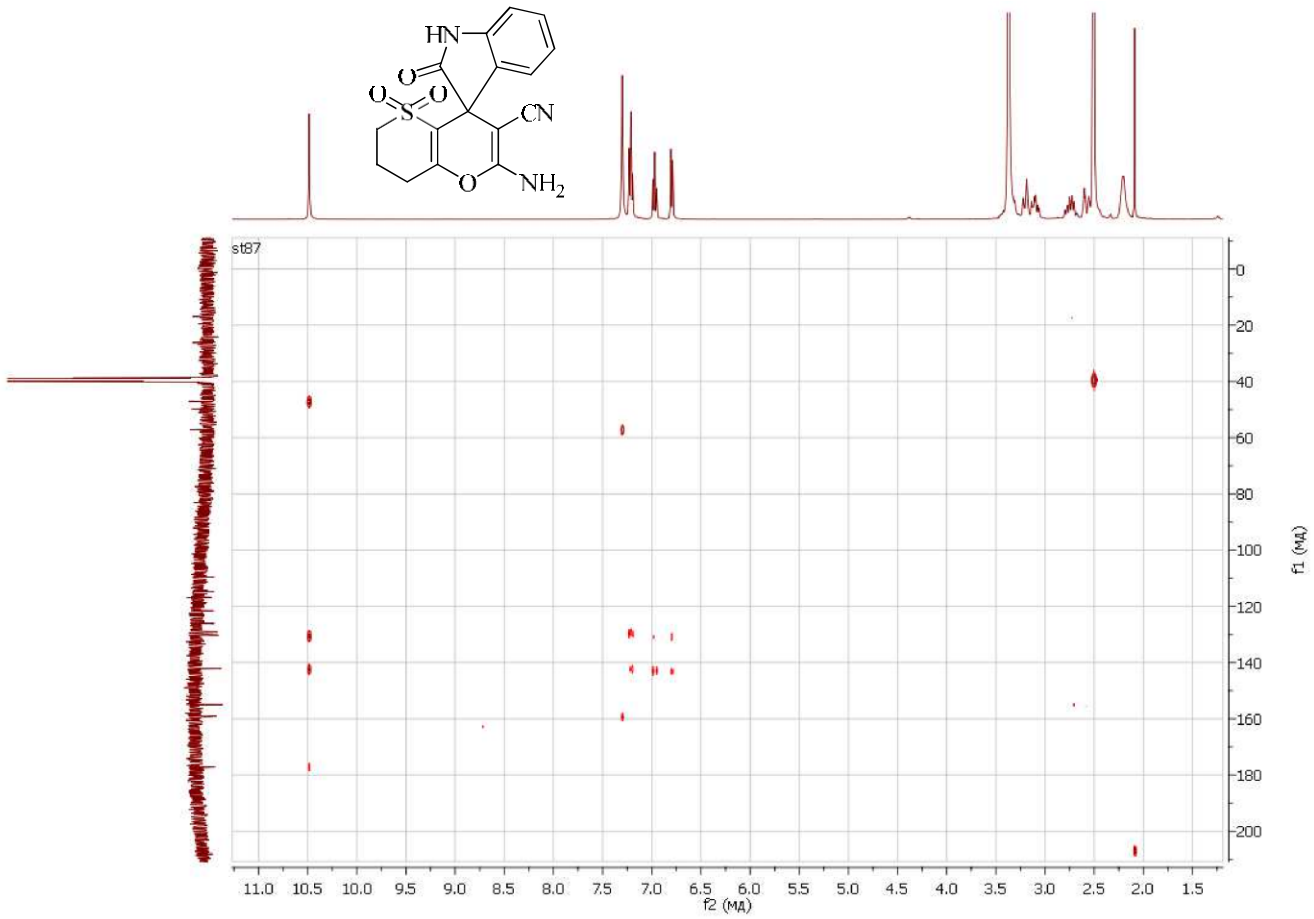
^{1}H-^{1}H COSY spectrum of compound 9a (400 MHz, DMSO-d_6)



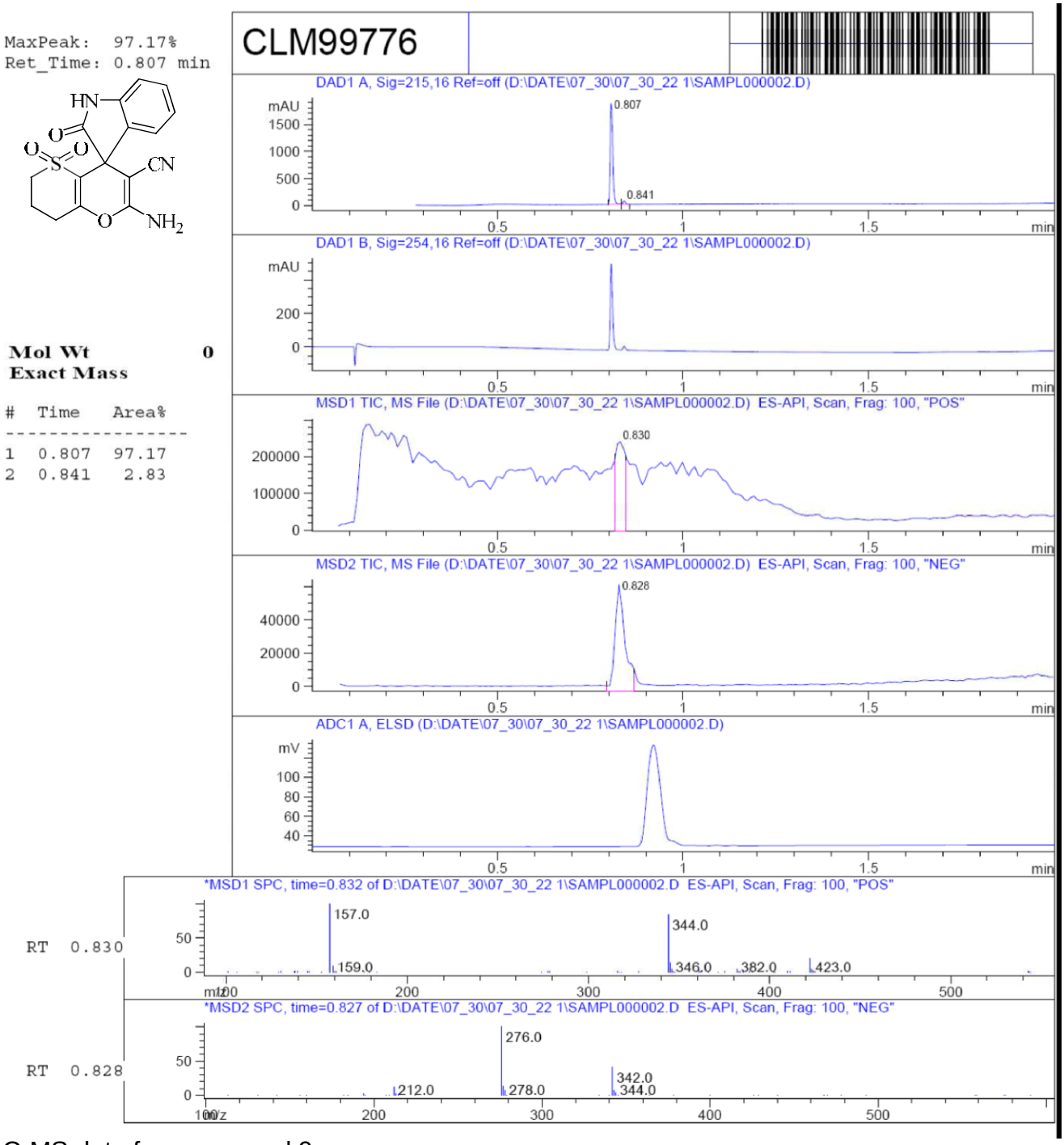
NOESY spectrum of compound 9a (400 MHz, DMSO-d_6)



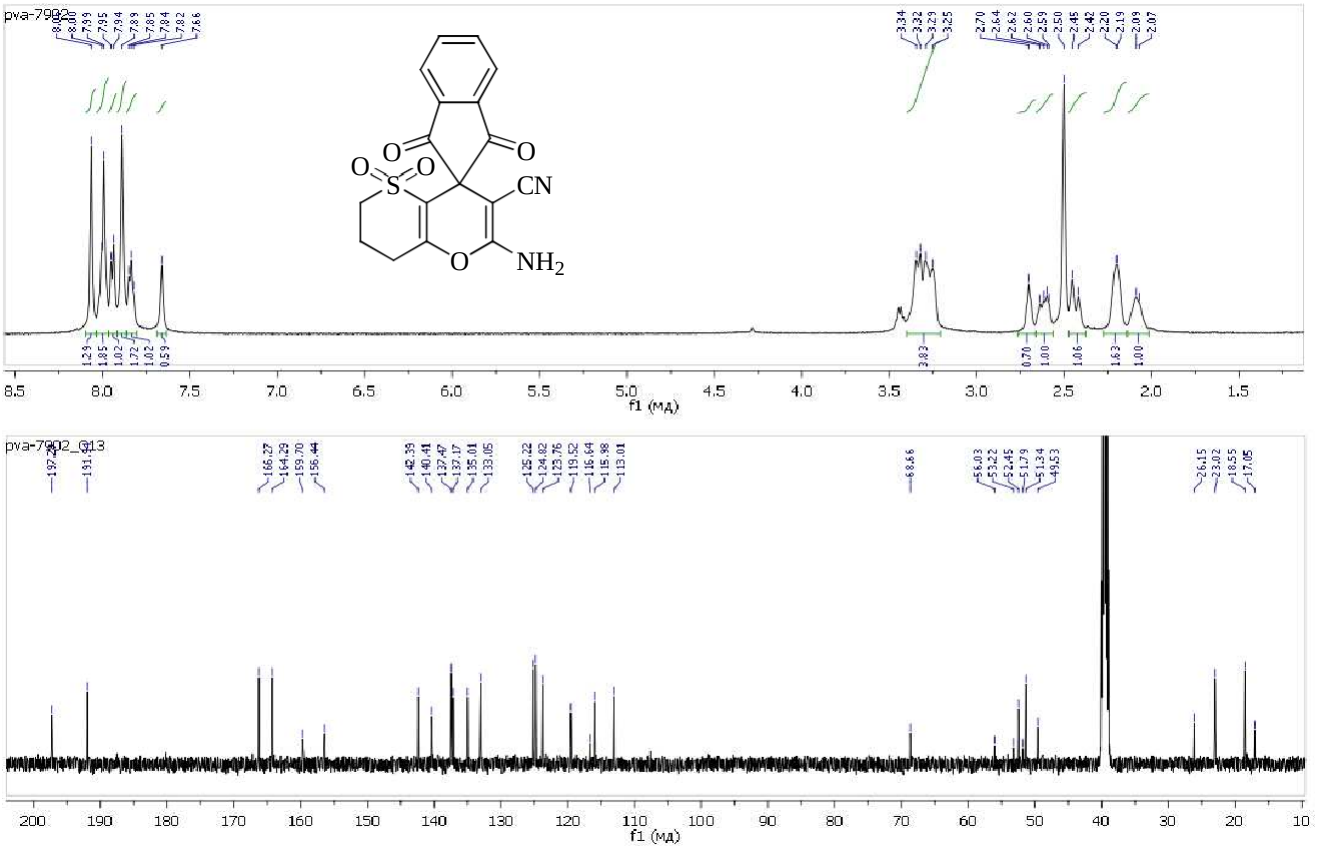
^{1}H-^{13}C HSQC spectrum of compound 9a (400/100 MHz, DMSO-d_6)



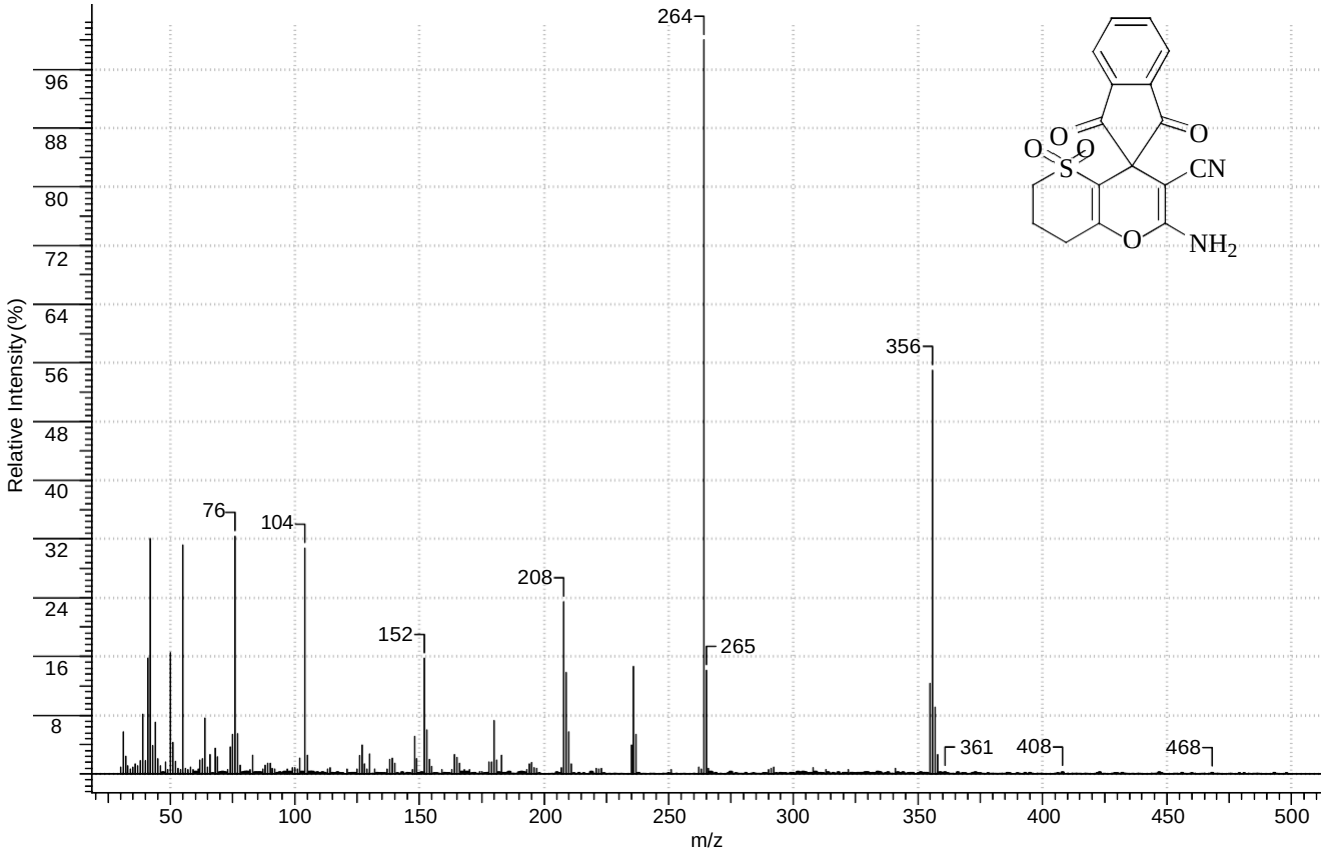
^{1}H-^{13}C HMBC spectrum of compound 9a (400/100 MHz, DMSO-d_6)



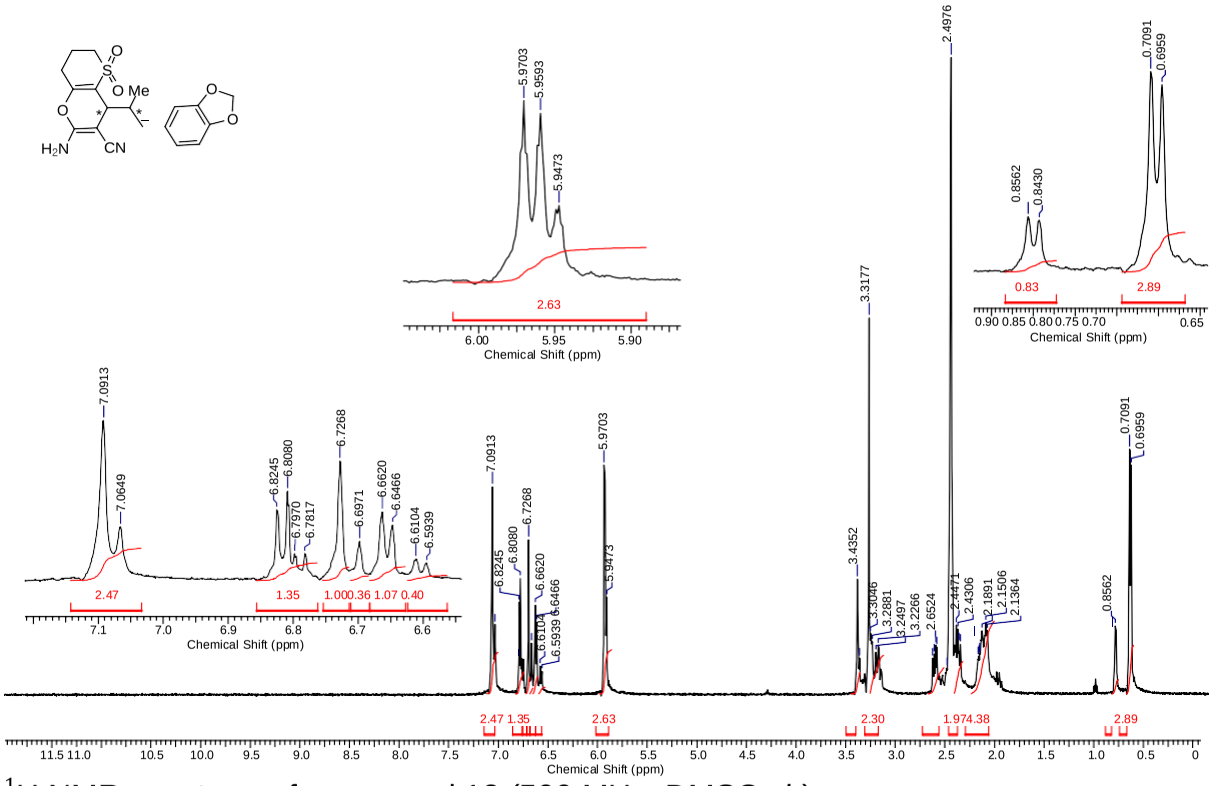
LC-MS data for compound 9a



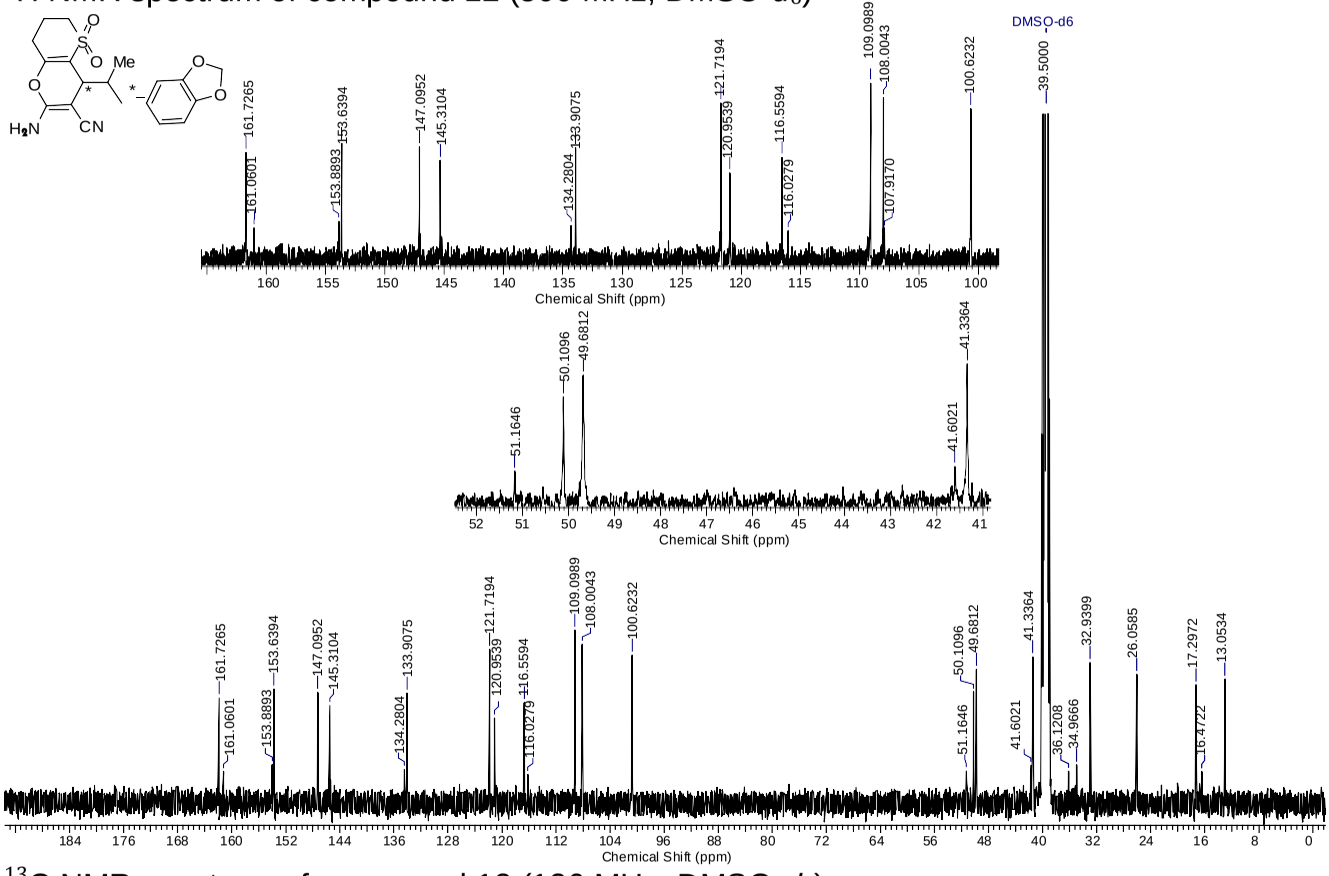
^{1}H and ^{13}C NMR spectra of compound 10 (500/126 MHz, DMSO-d_6)



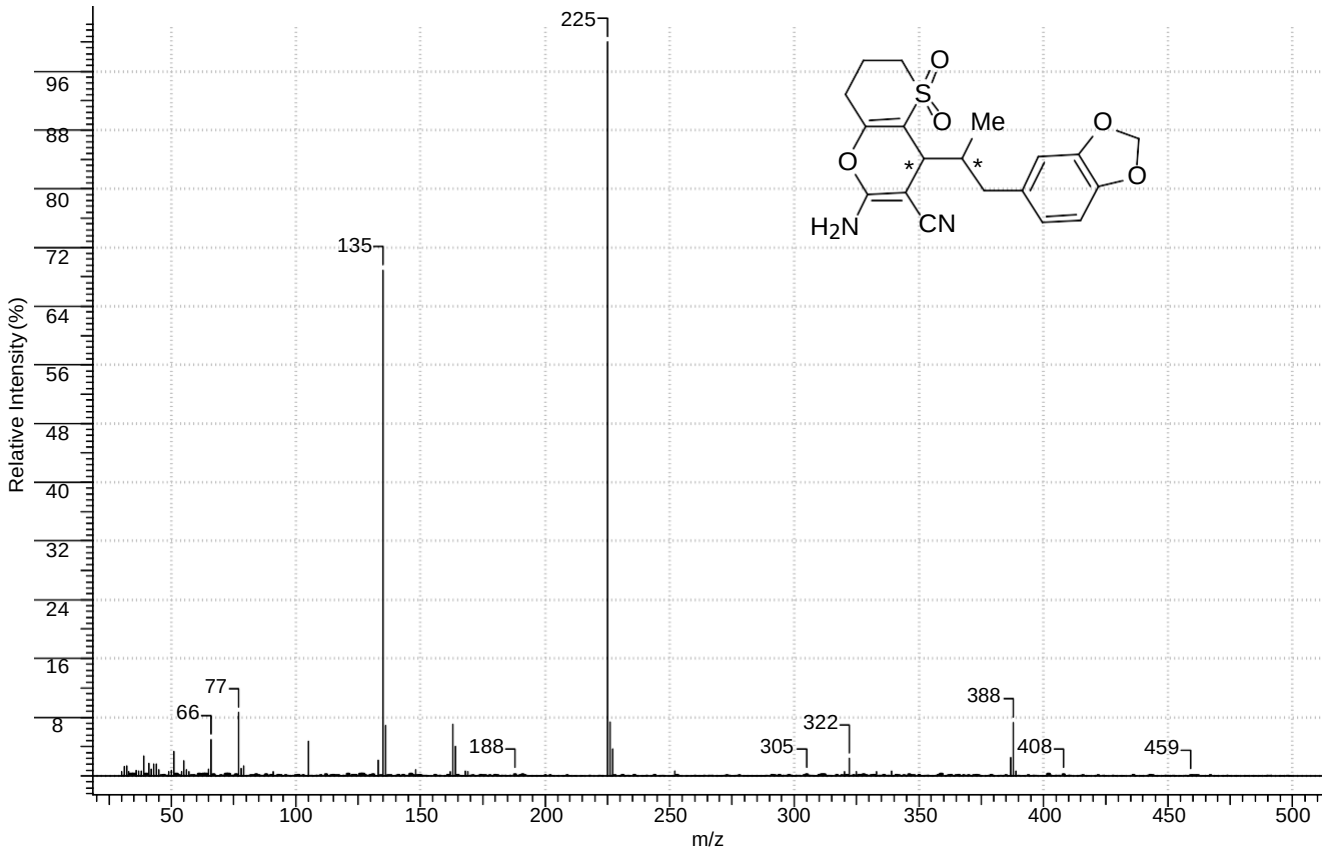
Mass spectrum (EI) of compound 10



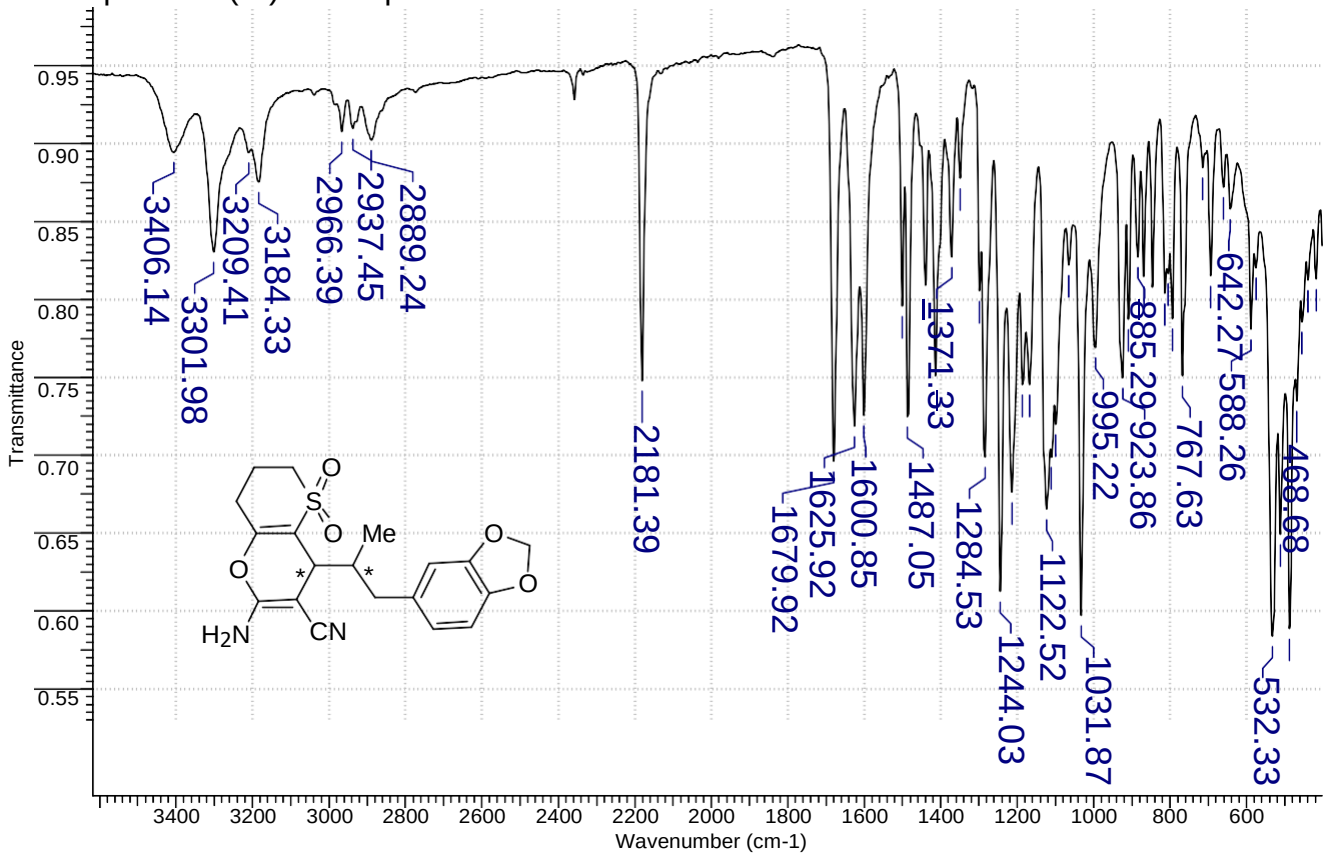
^{1}H NMR spectrum of compound 12 (500 MHz, DMSO-d_6)



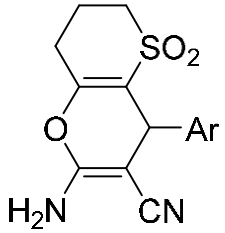
^{13}C NMR spectrum of compound 12 (126 MHz, DMSO-d_6)



Mass spectrum (EI) of compound 12



IR spectrum of compound 12



2a-j

Entry	Compound	Ar
1	2a	Ph
2	2b	3-$NO_2C_6H_4$
3	2c	4-$NO_2C_6H_4$
4	2d	4-$MeOC_6H_4$
5	2e	4-FC_6H_4
6	2f	3,4-$(MeO)_2C_6H_3$
7	2g	2-Cl-6-FC_6H_3
8	2h	2,6-$Cl_2C_6H_3$
9	2i	2,6-$F_2C_6H_3$
10	2j	2-furyl

In silico predicted results for compound 2a

☐ All ☐ Pa>Pi ☒ Pa>0,3 ☐ Pa>0,7

0,752	0,002	Cystinyl aminopeptidase inhibitor
0,739	0,011	Antiinflammatory
0,690	0,009	Antiasthmatic
0,689	0,013	Neurotransmitter uptake inhibitor
0,676	0,002	Catalase stimulant
0,640	0,002	I kappa B kinase 2 inhibitor

0,649	0,022	Antiarthritic
0,637	0,013	Antiallergic
0,606	0,002	Potassium channel large-conductance Ca-activated activator
0,573	0,005	Urologic disorders treatment
0,563	0,005	Urinary incontinence treatment
0,489	0,055	Alopecia treatment
0,431	0,005	Systemic lupus erythematosus treatment
0,437	0,057	Apoptosis agonist
0,372	0,001	Excitatory amino acid transporter 1 inhibitor
0,366	0,044	Cognition disorders treatment
0,344	0,034	Antiischemic
0,304	0,010	Dual specificity phosphatase 1 inhibitor
0,307	0,067	Albendazole monooxygenase inhibitor
0,337	0,110	Chemosensitizer
0,408	0,200	Membrane permeability inhibitor
0,308	0,168	Thioredoxin inhibitor
0,310	0,260	Aspulvinone dimethylallyltransferase inhibitor
0,309	0,293	Phosphatase inhibitor
0,305	0,291	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
0,316	0,307	Phobic disorders treatment

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)

0,116 in AD	-0,524 in AD	-0,008 out of AD	-0,395 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
394,600 in AD	90,460 in AD	296,800 out of AD	121,700 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 in AD	Class 4 in AD	Class 3 out of AD	Class 3 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
out of AD - compound is out of applicability domain of models
http://www.pharmaexpert.ru/GUSAR/AcuToxPredict/

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In silico predicted results for compound 2b

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,692	0,003	Cystinyl aminopeptidase inhibitor
0,646	0,002	Catalase stimulant

0,611	0,029	Antiinflammatory
0,558	0,003	I kappa B kinase 2 inhibitor
0,588	0,033	Neurotransmitter uptake inhibitor
0,550	0,021	Antiasthmatic
0,503	0,003	Potassium channel large-conductance Ca-activated activator
0,508	0,027	Antiallergic
0,461	0,007	Urologic disorders treatment
0,455	0,007	Urinary incontinence treatment
0,495	0,049	Antiarthritic
0,435	0,037	Chemosensitizer
0,397	0,003	Potassium channel activator
0,374	0,005	Calcium channel blocker
0,389	0,024	Antiischemic
0,346	0,014	Systemic lupus erythematosus treatment
0,403	0,072	Apoptosis agonist
0,338	0,019	Mcl-1 antagonist
0,371	0,060	UGT2B12 substrate
0,374	0,064	HMGCS2 expression enhancer
0,326	0,065	Antihypertensive
0,360	0,138	Alopecia treatment
0,317	0,117	Alcohol O-acetyltransferase inhibitor
0,366	0,219	Membrane permeability inhibitor

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,355 out of AD	-0,574 in AD	-0,212 out of AD	-0,400 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
785,900 out of AD	92,630 in AD	213,200 out of AD	138,300 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 out of AD	Class 4 in AD	Class 3 out of AD	Class 3 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
out of AD - compound is out of applicability domain of models
http://www.pharmaexpert.ru/GUSAR/AcuToxPredict/
GUSAR - Prediction of Values for Substances Copyright (C) 2010 A. Zakharov, V. Poroikov & Associates

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In silico predicted results for compound 2c

☐ All ☐ Pa>Pi ☉ Pa>0,3 ☐ Pa>0,7

0,710	0,003	Cystinyl aminopeptidase inhibitor
0,658	0,002	Catalase stimulant
0,638	0,025	Antiinflammatory
0,592	0,032	Neurotransmitter uptake inhibitor
0,577	0,003	I kappa B kinase 2 inhibitor
0,573	0,018	Antiasthmatic
0,531	0,023	Antiallergic
0,524	0,003	Potassium channel large-conductance Ca-activated activator
0,518	0,044	Antiarthritic
0,474	0,006	Urologic disorders treatment
0,466	0,006	Urinary incontinence treatment
0,444	0,033	Chemosensitizer
0,412	0,068	Apoptosis agonist
0,390	0,208	Membrane permeability inhibitor
0,389	0,024	Antiischemic
0,385	0,117	Alopecia treatment
0,380	0,003	Potassium channel activator
0,375	0,058	UGT2B12 substrate
0,354	0,013	Systemic lupus erythematosus treatment
0,346	0,018	Mcl-1 antagonist
0,345	0,007	Calcium channel blocker
0,344	0,100	Alcohol O-acetyltransferase inhibitor
0,341	0,081	HMGCS2 expression enhancer
0,328	0,233	Fusarinine-C ornithinesterase inhibitor
0,323	0,220	Acrocylindropepsin inhibitor

0,323	0,220	Chymosin inhibitor
0,323	0,220	Saccharopepsin inhibitor
0,314	0,070	Antihypertensive
0,301	0,269	Polyporopepsin inhibitor

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,309 out of AD	-0,536 in AD	-0,205 out of AD	-0,198 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
707,200 out of AD	101,200 in AD	216,600 out of AD	220,400 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 out of AD	Class 4 in AD	Class 3 out of AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
out of AD - compound is out of applicability domain of models
http://www.pharmaexpert.ru/GUSAR/AcuToxPredict/

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In silico predicted results for compound 2d

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,709	0,003	Cystinyl aminopeptidase inhibitor
0,707	0,015	Antiinflammatory
0,684	0,009	Antiasthmatic
0,662	0,002	Catalase stimulant
0,644	0,012	Antiallergic
0,628	0,025	Antiarthritic
0,598	0,003	I kappa B kinase 2 inhibitor
0,605	0,029	Neurotransmitter uptake inhibitor
0,556	0,003	Potassium channel large-conductance Ca-activated activator
0,501	0,005	Urologic disorders treatment
0,491	0,005	Urinary incontinence treatment
0,458	0,050	Apoptosis agonist
0,399	0,006	Systemic lupus erythematosus treatment
0,352	0,032	Antiischemic
0,314	0,061	Antiinflammatory, intestinal
0,314	0,065	Cognition disorders treatment
0,421	0,178	Aspulvinone dimethylallyltransferase inhibitor
0,341	0,105	Chemosensitizer
0,348	0,149	Alopecia treatment
0,354	0,202	Nicotinic alpha4beta4 receptor agonist

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,046 out of AD	-0,398 in AD	0,201 out of AD	0,307 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
369,400 out of AD	132,900 in AD	528,300 out of AD	674,500 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 out of AD	Class 4 in AD	Class 4 out of AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
out of AD - compound is out of applicability domain of models
http://www.pharmaexpert.ru/GUSAR/AcuToxPredict/
GUSAR - Prediction of Values for Substances Copyright (C) 2010 A. Zakharov, V. Poroikov & Associates

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In silico predicted results for compound 2e

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,729	0,012	Antiinflammatory
0,704	0,003	Cystinyl aminopeptidase inhibitor
0,683	0,018	Antiarthritic
0,661	0,011	Antiasthmatic
0,636	0,002	Catalase stimulant
0,614	0,003	I kappa B kinase 2 inhibitor
0,611	0,014	Antiallergic
0,618	0,026	Neurotransmitter uptake inhibitor
0,578	0,002	Potassium channel large-conductance Ca-activated activator
0,561	0,005	Urologic disorders treatment
0,552	0,005	Urinary incontinence treatment
0,399	0,006	Systemic lupus erythematosus treatment
0,371	0,043	Cognition disorders treatment
0,340	0,035	Antiischemic
0,382	0,081	Apoptosis agonist
0,328	0,109	Dementia treatment
0,351	0,146	Alopecia treatment
0,358	0,222	Membrane permeability inhibitor

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,046 out of AD	-0,438 in AD	-0,038 out of AD	0,038 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)

355,900 out of AD	116,900 in AD	293,300 out of AD	349,800 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 out of AD	Class 4 in AD	Class 3 out of AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
out of AD - compound is out of applicability domain of models
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In silico predicted results for compound 2f

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,707	0,008	Antiasthmatic
0,699	0,003	Cystinyl aminopeptidase inhibitor
0,710	0,014	Antiinflammatory
0,668	0,010	Antiallergic
0,652	0,002	Catalase stimulant

0,627	0,025	Antiarthritic
0,582	0,003	I kappa B kinase 2 inhibitor
0,592	0,032	Neurotransmitter uptake inhibitor
0,531	0,003	Potassium channel large-conductance Ca-activated activator
0,486	0,006	Urologic disorders treatment
0,476	0,006	Urinary incontinence treatment
0,474	0,045	Apoptosis agonist
0,398	0,006	Systemic lupus erythematosus treatment
0,346	0,034	Antiischemic
0,349	0,097	Chemosensitizer
0,429	0,189	Membrane permeability inhibitor
0,361	0,137	Alopecia treatment
0,314	0,144	Antineoplastic
0,341	0,218	Nicotinic alpha4beta4 receptor agonist
0,324	0,248	Aspulvinone dimethylallyltransferase inhibitor

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,067 out of AD	-0,552 in AD	0,173 in AD	0,382 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
423,000 out of AD	101,800 in AD	540,000 in AD	874,300 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 out of AD	Class 4 in AD	Class 4 in AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
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In silico predicted results for compound 2g

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,752	0,006	Antiasthmatic
0,704	0,008	Antiallergic
0,655	0,003	Cystinyl aminopeptidase inhibitor
0,665	0,020	Antiinflammatory
0,595	0,002	Catalase stimulant
0,589	0,030	Antiarthritic
0,558	0,003	Potassium channel large-conductance Ca-activated activator
0,541	0,003	I kappa B kinase 2 inhibitor
0,467	0,007	Urologic disorders treatment

0,461	0,006	Urinary incontinence treatment
0,488	0,066	Neurotransmitter uptake inhibitor
0,382	0,008	Systemic lupus erythematosus treatment
0,311	0,066	Cognition disorders treatment
0,302	0,126	Apoptosis agonist

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,337 out of AD	-0,354 in AD	-0,039 out of AD	-0,024 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
770,300 out of AD	157,000 in AD	324,700 out of AD	335,400 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 out of AD	Class 4 in AD	Class 4 out of AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
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In silico predicted results for compound 2h

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,827	0,005	Antiasthmatic
0,798	0,005	Antiallergic
0,768	0,009	Antiinflammatory
0,713	0,003	Cystinyl aminopeptidase inhibitor
0,724	0,014	Antiarthritic
0,645	0,002	Catalase stimulant
0,607	0,003	I kappa B kinase 2 inhibitor
0,582	0,002	Potassium channel large-conductance Ca-activated activator
0,552	0,043	Neurotransmitter uptake inhibitor
0,476	0,006	Urologic disorders treatment
0,468	0,006	Urinary incontinence treatment
0,408	0,005	Systemic lupus erythematosus treatment
0,364	0,090	Apoptosis agonist
0,345	0,152	Alopecia treatment
0,364	0,220	Membrane permeability inhibitor
0,356	0,236	Phosphatase inhibitor
0,315	0,257	Nicotinic alpha4beta4 receptor agonist

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,321 out of AD	-0,496 in AD	0,363 out of AD	0,127 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
777,300 out of AD	118,400 in AD	856,600 out of AD	497,200 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 out of AD	Class 4 in AD	Class 4 out of AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
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In silico predicted results for compound 2i

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,707	0,008	Antiasthmatic
0,695	0,003	Cystinyl aminopeptidase inhibitor
0,703	0,015	Antiinflammatory

0,625	0,002	Catalase stimulant
0,630	0,013	Antiallergic
0,607	0,003	I kappa B kinase 2 inhibitor
0,622	0,026	Antiarthritic
0,573	0,003	Potassium channel large-conductance Ca-activated activator
0,552	0,043	Neurotransmitter uptake inhibitor
0,512	0,005	Urologic disorders treatment
0,504	0,005	Urinary incontinence treatment
0,394	0,007	Systemic lupus erythematosus treatment
0,404	0,022	Antiischemic
0,338	0,055	Cognition disorders treatment
0,340	0,060	Antihypertensive
0,355	0,095	Apoptosis agonist
0,323	0,114	Dementia treatment
0,345	0,152	Alopecia treatment

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,420 out of AD	-0,252 in AD	0,053 out of AD	-0,003 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
889,800 out of AD	189,400 in AD	382,700 out of AD	335,600 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 out of AD	Class 4 in AD	Class 4 out of AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
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out of AD - compound is out of applicability domain of models
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In silico predicted results for compound 2j

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,724	0,013	Antiinflammatory
0,702	0,003	Cystinyl aminopeptidase inhibitor
0,668	0,002	Catalase stimulant
0,615	0,003	I kappa B kinase 2 inhibitor
0,594	0,030	Antiarthritic
0,587	0,033	Neurotransmitter uptake inhibitor
0,537	0,003	Potassium channel large-conductance Ca-activated activator
0,512	0,005	Amyloid beta precursor protein antagonist
0,510	0,005	Urologic disorders treatment

0,502	0,005	Urinary incontinence treatment
0,488	0,008	Mcl-1 antagonist
0,467	0,020	Cognition disorders treatment
0,526	0,091	Phosphatase inhibitor
0,465	0,041	Neurodegenerative diseases treatment
0,442	0,055	Apoptosis agonist
0,416	0,048	HMGCS2 expression enhancer
0,375	0,009	Systemic lupus erythematosus treatment
0,412	0,049	Antiallergic
0,379	0,054	Antiasthmatic
0,351	0,034	NF-E2-related factor 2 stimulant
0,324	0,009	HCV NS3-helicase inhibitor
0,344	0,034	Antiischemic
0,316	0,009	Dual specificity phosphatase 1 inhibitor
0,341	0,053	Focal adhesion kinase 2 inhibitor
0,429	0,162	Antiischemic, cerebral
0,306	0,047	Hepatic disorders treatment
0,343	0,154	Alopecia treatment

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,324 out of AD	-0,630 in AD	-0,257 out of AD	-0,518 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)

616,800 out of AD	68,560 in AD	161,800 out of AD	88,620 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 out of AD	Class 4 in AD	Class 3 out of AD	Class 3 out of AD

IP - Intraperitoneal route of administration
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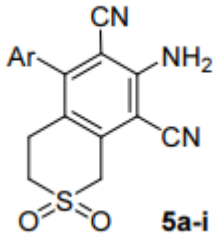

5a-i

Entry	Compound	Ar
1	5a	Ph
2	5b	5-(4-ClC_6H_4)furan-2-yl
3	5c	5-(2,4-$Cl_2C_6H_3$)furan-2-yl
4	5d	5-(4-$NO_2C_6H_4$)furan-2-yl
5	5e	5-(2-$NO_2C_6H_4$)furan-2-yl
6	5f	5-(2-NO_2-4-MeC_6H_3)furan-2-yl
7	5g	5-(4-BrC_6H_4)furan-2-yl
8	5h	5-(4-$HOOCC_6H_4$)furan-2-yl
9	5i	5-(4-MeC_6H_4)furan-2-yl

In silico predicted results for compound 5a

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,603	0,029	Neurotransmitter uptake inhibitor
0,593	0,022	Alopecia treatment
0,448	0,016	Antiischemic
0,524	0,133	Membrane permeability inhibitor
0,423	0,090	Thioredoxin inhibitor
0,391	0,097	Octopamine antagonist
0,342	0,052	Focal adhesion kinase 2 inhibitor
0,333	0,049	Antiinflammatory, intestinal

0,397	0,144	Platelet aggregation stimulant
0,302	0,070	Albendazole monooxygenase inhibitor
0,409	0,185	Aspulvinone dimethylallyltransferase inhibitor
0,313	0,164	Leukopoiesis stimulant
0,303	0,163	Venombin AB inhibitor
0,326	0,188	Complement factor D inhibitor
0,359	0,222	Calcium channel (voltage-sensitive) activator
0,305	0,174	Oxygen scavenger
0,315	0,204	Antiviral (Picornavirus)
0,327	0,226	Glutamyl endopeptidase II inhibitor
0,359	0,259	Nootropic
0,306	0,217	Phthalate 4,5-dioxygenase inhibitor

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,484 out of AD	-0,591 in AD	0,251 in AD	0,245 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
985,600 out of AD	82,980 in AD	576,200 in AD	569,000 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 out of AD	Class 4 in AD	Class 4 in AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
out of AD - compound is out of applicability domain of models
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In silico predicted results for compound 5b

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,612	0,081	Membrane permeability inhibitor
0,526	0,051	Neurotransmitter uptake inhibitor
0,426	0,019	Antiischemic
0,387	0,005	Allergic rhinitis treatment
0,420	0,057	Kinase inhibitor
0,373	0,062	Rhinitis treatment
0,332	0,037	CYP2A11 substrate
0,340	0,081	HMGCS2 expression enhancer
0,372	0,125	Anaphylatoxin receptor antagonist
0,324	0,080	CYP1A substrate
0,324	0,084	CYP3A4 inducer

0,304	0,077	Focal adhesion kinase 2 inhibitor
0,305	0,092	CYP1A2 substrate
0,367	0,216	Antiischemic, cerebral
0,306	0,192	Alopecia treatment
0,344	0,249	Phosphatase inhibitor
0,311	0,238	5 Hydroxytryptamine uptake stimulant

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
-0,029 out of AD	-0,703 in AD	0,263 in AD	0,551 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
396,100 out of AD	84,050 in AD	776,200 in AD	1508,000 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 out of AD	Class 4 in AD	Class 4 in AD	Class 5 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration

in AD - compound falls in applicability domain of models
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In silico predicted results for compound 5c

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,603	0,020	Kinase inhibitor
0,499	0,061	Neurotransmitter uptake inhibitor
0,419	0,020	Antiischemic
0,361	0,006	Allergic rhinitis treatment
0,493	0,153	Membrane permeability inhibitor
0,320	0,090	Rhinitis treatment
0,358	0,134	Trans-acenaphthene-1,2-diol dehydrogenase inhibitor
0,305	0,108	HMGCS2 expression enhancer
0,313	0,281	Antiischemic, cerebral
0,309	0,293	Phosphatase inhibitor

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,207 out of AD	-0,731 in AD	0,490 out of AD	0,504 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
738,000 out of AD	85,180 in AD	1415,000 out of AD	1461,000 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 out of AD	Class 4 in AD	Class 4 out of AD	Class 5 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
out of AD - compound is out of applicability domain of models
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In silico predicted results for compound 5d

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,589	0,094	Membrane permeability inhibitor
0,481	0,013	Antiischemic
0,512	0,056	Neurotransmitter uptake inhibitor

0,446	0,040	HMGCS2 expression enhancer
0,342	0,007	Allergic rhinitis treatment
0,379	0,055	CYP1A substrate
0,374	0,057	CYP1A2 substrate
0,366	0,062	UGT2B12 substrate
0,346	0,050	Focal adhesion kinase 2 inhibitor
0,305	0,014	Myocardial ischemia treatment
0,320	0,040	CYP2A11 substrate
0,316	0,089	CYP19A1 expression inhibitor
0,327	0,116	Kinase inhibitor
0,353	0,145	Alopecia treatment
0,319	0,245	Fusarinine-C ornithinesterase inhibitor
0,302	0,294	Antiischemic, cerebral

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
-0,003 in AD	-0,843 in AD	0,083 out of AD	0,210 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
431,300 in AD	62,390 in AD	526,500 out of AD	705,400 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 in AD	Class 4 in AD	Class 4 out of AD	Class 4 out of AD

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IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
out of AD - compound is out of applicability domain of models
http://www.pharmaexpert.ru/GUSAR/AcuToxPredict/

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In silico predicted results for compound 5e

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,524	0,052	Neurotransmitter uptake inhibitor
0,502	0,034	Kinase inhibitor
0,473	0,013	Antiischemic
0,313	0,008	Allergic rhinitis treatment
0,333	0,034	Stroke treatment
0,339	0,072	CYP1A substrate
0,337	0,076	CYP1A2 substrate

0,328	0,089	HMGCS2 expression enhancer
0,354	0,144	Alopecia treatment
0,391	0,208	Membrane permeability inhibitor
0,308	0,127	Interleukin 2 agonist
0,314	0,165	HIF1A expression inhibitor

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
-0,093 in AD	-0,831 in AD	0,197 in AD	0,254 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
350,900 in AD	64,090 in AD	683,100 in AD	779,100 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 in AD	Class 4 in AD	Class 4 in AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
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http://www.pharmaexpert.ru/GUSAR/AcuToxPredict/

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In silico predicted results for compound 5f

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,477	0,039	Kinase inhibitor
0,448	0,016	Antiischemic
0,462	0,078	Neurotransmitter uptake inhibitor
0,315	0,008	Allergic rhinitis treatment
0,452	0,176	Membrane permeability inhibitor
0,323	0,081	CYP1A substrate
0,302	0,094	CYP1A2 substrate
0,301	0,178	HIF1A expression inhibitor

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,215 out of AD	-0,949 in AD	0,043 out of AD	-0,106 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
736,500 out of AD	50,400 in AD	495,300 out of AD	351,100 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 out of AD	Class 4 in AD	Class 4 out of AD	Class 4 out of AD

IP - Intraperitoneal route of administration
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Oral - Oral route of administration
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In silico predicted results for compound 5g

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,538	0,024	HMGCS2 expression enhancer
0,526	0,051	Neurotransmitter uptake inhibitor
0,381	0,005	Allergic rhinitis treatment
0,385	0,025	Antiischemic
0,314	0,012	Protein phosphatase inhibitor
0,311	0,010	Protein-tyrosine phosphatase inhibitor
0,318	0,020	Retinoprotector
0,332	0,037	CYP2A11 substrate
0,343	0,102	Kinase inhibitor

0,317	0,106	Centromere associated protein inhibitor
0,306	0,192	Alopecia treatment

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,169 out of AD	-0,657 in AD	0,193 out of AD	0,439 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
690,600 out of AD	103,100 in AD	730,300 out of AD	1287,000 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 out of AD	Class 4 in AD	Class 4 out of AD	Class 5 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
out of AD - compound is out of applicability domain of models
http://www.pharmaexpert.ru/GUSAR/AcuToxPredict/

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In silico predicted results for compound 5h

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,602	0,086	Membrane permeability inhibitor
0,552	0,049	Glutamate-5-semialdehyde dehydrogenase inhibitor
0,489	0,065	Neurotransmitter uptake inhibitor
0,486	0,068	Anaphylatoxin receptor antagonist
0,455	0,048	Aspartyltransferase inhibitor
0,400	0,023	Antiinflammatory, intestinal
0,395	0,030	Cholestanetriol 26-monooxygenase inhibitor
0,433	0,072	Benzoate-CoA ligase inhibitor
0,360	0,008	Protein phosphatase inhibitor
0,428	0,076	Trans-acenaphthene-1,2-diol dehydrogenase inhibitor
0,357	0,006	Allergic rhinitis treatment
0,377	0,026	Antiischemic
0,351	0,007	Protein-tyrosine phosphatase inhibitor
0,346	0,035	CYP2A11 substrate
0,311	0,005	Protein-tyrosine phosphatase 1B inhibitor
0,404	0,109	Chlordecone reductase inhibitor
0,368	0,084	Kinase inhibitor
0,374	0,091	4-Nitrophenol 2-monooxygenase inhibitor
0,318	0,052	3'-Demethylstaurosporine O-methyltransferase inhibitor
0,320	0,072	Leukotriene-B4 20-monooxygenase inhibitor
0,326	0,082	CYP3A4 inducer
0,356	0,113	2-Dehydropantoate 2-reductase inhibitor

0,321	0,103	Centromere associated protein inhibitor
0,305	0,090	CYP3A inducer
0,352	0,145	Alopecia treatment
0,325	0,118	Hydrogen dehydrogenase inhibitor
0,306	0,100	CDP-diacylglycerol-serine O-phosphatidyltransferase inhibitor
0,306	0,101	Muscular dystrophy treatment
0,320	0,115	Alcohol O-acetyltransferase inhibitor
0,379	0,174	Glutamyl endopeptidase II inhibitor
0,351	0,151	Sugar-phosphatase inhibitor
0,350	0,159	Antiviral (Rhinovirus)
0,329	0,144	UDP-N-acetylglucosamine 4-epimerase inhibitor
0,314	0,138	Lysine 2,3-aminomutase inhibitor
0,314	0,152	Oxidoreductase inhibitor
0,376	0,215	Phosphatase inhibitor
0,343	0,188	5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
0,356	0,202	Fusarinine-C ornithinesterase inhibitor
0,322	0,172	NADPH-cytochrome-c2 reductase inhibitor
0,313	0,164	Phosphatidylcholine-retinol O-acyltransferase inhibitor
0,313	0,171	Cytoprotectant
0,344	0,222	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
0,321	0,199	Ribulose-phosphate 3-epimerase inhibitor
0,308	0,202	Electron-transferring-flavoprotein dehydrogenase inhibitor
0,340	0,248	Antiischemic, cerebral

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
-0,091 out of AD	-0,132 in AD	0,215 out of AD	0,327 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
351,400 out of AD	319,700 in AD	710,700 out of AD	919,800 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 out of AD	Class 5 in AD	Class 4 out of AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
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In silico predicted results for compound 5i

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,604	0,085	Membrane permeability inhibitor

0,541	0,047	Neurotransmitter uptake inhibitor
0,426	0,019	Antiischemic
0,395	0,005	Allergic rhinitis treatment
0,422	0,057	Kinase inhibitor
0,388	0,056	Rhinitis treatment
0,360	0,032	CYP2A11 substrate
0,313	0,048	NF-E2-related factor 2 stimulant
0,325	0,083	CYP3A4 inducer
0,370	0,130	Alopecia treatment
0,302	0,078	Focal adhesion kinase 2 inhibitor
0,304	0,090	CYP3A inducer
0,301	0,178	Oxygen scavenger
0,349	0,244	Phosphatase inhibitor

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,042 in AD	-0,686 in AD	0,060 in AD	0,339 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
444,800 in AD	83,120 in AD	463,400 in AD	880,300 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification

Class 4 in AD	Class 4 in AD	Class 4 in AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
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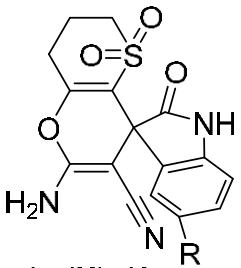
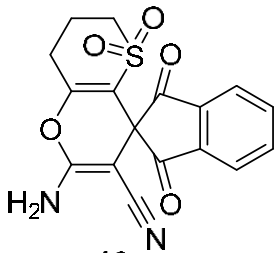


9a (H), 9b (Me)



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In silico predicted results for compound 9a

☐ All ☐ Pa>Pi ☒ Pa>0,3 ☐ Pa>0,7

0,718	0,014	Antiinflammatory
0,590	0,003	I kappa B kinase 2 inhibitor
0,549	0,004	Cystinyl aminopeptidase inhibitor

0,528	0,003	Potassium channel large-conductance Ca-activated activator
0,537	0,048	Neurotransmitter uptake inhibitor
0,442	0,008	Urologic disorders treatment
0,436	0,008	Urinary incontinence treatment
0,363	0,004	Catalase stimulant
0,406	0,077	Antiarthritic
0,301	0,011	Dual specificity phosphatase 1 inhibitor
0,307	0,030	Systemic lupus erythematosus treatment
0,357	0,130	Thioredoxin inhibitor
0,332	0,116	Chemosensitizer
0,325	0,113	Apoptosis agonist
0,343	0,154	Alopecia treatment
0,306	0,149	Antineoplastic

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
-0,006 out of AD	-0,486 in AD	-0,036 out of AD	0,071 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
338,500 out of AD	112,300 in AD	316,100 out of AD	404,100 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification

Class 4 out of AD	Class 4 in AD	Class 4 out of AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
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http://www.pharmaexpert.ru/GUSAR/AcuToxPredict/

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In silico predicted results for compound 9b

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,705	0,015	Antiinflammatory
0,536	0,003	I kappa B kinase 2 inhibitor
0,503	0,005	Cystinyl aminopeptidase inhibitor
0,493	0,003	Potassium channel large-conductance Ca-activated activator
0,490	0,065	Neurotransmitter uptake inhibitor
0,415	0,010	Urologic disorders treatment
0,408	0,009	Urinary incontinence treatment
0,347	0,004	Catalase stimulant
0,384	0,085	Antiarthritic
0,325	0,112	Apoptosis agonist
0,326	0,123	Chemosensitizer

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,307 out of AD	-0,626 in AD	0,000 out of AD	-0,091 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
724,200 out of AD	84,600 in AD	357,300 out of AD	290,100 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 out of AD	Class 4 in AD	Class 4 out of AD	Class 4 out of AD

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In silico predicted results for compound 10

☐ All ☐ Pa>Pi ☉ Pa>0,3 ☐ Pa>0,7

0,761	0,009	Antiinflammatory
0,710	0,010	Neurotransmitter uptake inhibitor
0,636	0,002	I kappa B kinase 2 inhibitor
0,623	0,003	Cystinyl aminopeptidase inhibitor
0,600	0,002	Potassium channel large-conductance Ca-activated activator
0,518	0,005	Urologic disorders treatment
0,510	0,005	Urinary incontinence treatment
0,527	0,040	Alopecia treatment
0,495	0,050	Antiarthritic
0,445	0,003	Catalase stimulant
0,353	0,006	Dual specificity phosphatase 1 inhibitor
0,371	0,062	Antiallergic
0,323	0,022	Systemic lupus erythematosus treatment
0,305	0,052	NF-E2-related factor 2 stimulant
0,372	0,119	Thioredoxin inhibitor
0,321	0,077	Antiasthmatic
0,340	0,106	Chemosensitizer
0,320	0,116	Apoptosis agonist
0,306	0,124	3-Hydroxybenzoate 6-monooxygenase inhibitor
0,389	0,209	Membrane permeability inhibitor
0,369	0,213	Antiischemic, cerebral
0,302	0,152	CYP2C12 substrate
0,305	0,266	Aspulvinone dimethylallyltransferase inhibitor
0,309	0,293	Phosphatase inhibitor

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
-0,137 in AD	-0,463 in AD	0,119 out of AD	0,119 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
259,800 in AD	122,600 in AD	468,200 out of AD	468,300 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 in AD	Class 4 in AD	Class 4 out of AD	Class 4 out of AD

IP - Intraperitoneal route of administration
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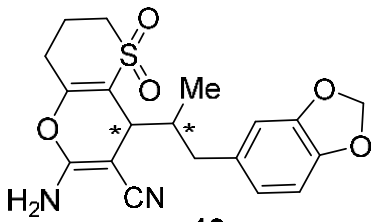

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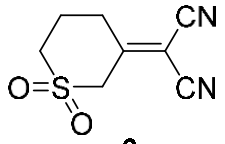

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In silico predicted results for compound 12

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,768	0,005	Neurotransmitter uptake inhibitor
0,764	0,001	Excitatory amino acid transporter 1 inhibitor
0,770	0,025	Antieczematic
0,623	0,027	Antiinflammatory
0,478	0,005	Cystinyl aminopeptidase inhibitor
0,433	0,003	Potassium channel large-conductance Ca-activated activator
0,425	0,004	I kappa B kinase 2 inhibitor
0,413	0,010	Urologic disorders treatment
0,407	0,009	Urinary incontinence treatment
0,364	0,033	Carminative
0,331	0,004	Catalase stimulant
0,329	0,020	Systemic lupus erythematosus treatment
0,384	0,085	Antiarthritic
0,318	0,079	Antiasthmatic
0,315	0,095	Calcium regulator
0,341	0,253	Phosphatase inhibitor

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
-0,217 out of AD	-0,864 in AD	0,089 in AD	-0,072 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
235,800 out of AD	53,160 in AD	476,800 in AD	329,000 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 out of AD	Class 4 in AD	Class 4 in AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
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In silico predicted results for compound 6

☐ All ☐ Pa>Pi ☉ Pa>0,3 ☐ Pa>0,7

0,704	0,037	Membrane permeability inhibitor
0,702	0,063	Aspulvinone dimethylallyltransferase inhibitor
0,650	0,019	Thioredoxin inhibitor
0,645	0,022	Phosphatidylcholine-retinol O-acyltransferase inhibitor
0,641	0,023	Antiarthritic
0,646	0,044	Sugar-phosphatase inhibitor
0,599	0,018	All-trans-retinyl-palmitate hydrolase inhibitor
0,583	0,005	Tumour necrosis factor alpha release inhibitor
0,604	0,029	Neurotransmitter uptake inhibitor
0,611	0,050	Glutamyl endopeptidase II inhibitor
0,637	0,077	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
0,573	0,012	Glucan 1,4-alpha-maltotetraohydrolase inhibitor
0,577	0,020	Glucan 1,4-alpha-maltotriohydrolase inhibitor
0,574	0,032	Gastrin inhibitor
0,570	0,040	Alkylacetylglycerophosphatase inhibitor
0,544	0,022	Antiasthmatic
0,561	0,042	Electron-transferring-flavoprotein dehydrogenase inhibitor
0,571	0,056	5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
0,559	0,051	Acylcarnitine hydrolase inhibitor
0,596	0,089	CYP2J substrate
0,554	0,055	NADPH peroxidase inhibitor
0,536	0,037	Alopecia treatment
0,548	0,056	Ribulose-phosphate 3-epimerase inhibitor
0,569	0,084	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
0,494	0,024	Antipsoriatic

0,521	0,053	Carboxypeptidase Taq inhibitor
0,515	0,051	Venombin AB inhibitor
0,545	0,083	Glycosylphosphatidylinositol phospholipase D inhibitor
0,493	0,039	L-glutamate oxidase inhibitor
0,504	0,051	Chloride peroxidase inhibitor
0,483	0,031	Antiallergic
0,510	0,059	Alkenylglycerophosphocholine hydrolase inhibitor
0,515	0,065	Complement factor D inhibitor
0,458	0,008	Antineoplastic (pancreatic cancer)
0,530	0,084	CYP2C12 substrate
0,511	0,068	Phthalate 4,5-dioxygenase inhibitor
0,465	0,032	N-formylmethionyl-peptidase inhibitor
0,470	0,038	Mannan endo-1,4-beta-mannosidase inhibitor
0,503	0,077	Omptin inhibitor
0,469	0,045	Gluconate 5-dehydrogenase inhibitor
0,469	0,051	Hydrogen dehydrogenase inhibitor
0,428	0,014	NF-E2-related factor 2 stimulant
0,469	0,060	Glucan endo-1,6-beta-glucosidase inhibitor
0,429	0,023	Xylan endo-1,3-beta-xylosidase inhibitor
0,444	0,039	Glyoxylate reductase inhibitor
0,450	0,048	3-Hydroxybenzoate 6-monooxygenase inhibitor
0,474	0,072	Phospholipid-translocating ATPase inhibitor
0,439	0,038	Pullulanase inhibitor
0,461	0,062	Lysine 2,3-aminomutase inhibitor
0,444	0,046	(S)-6-hydroxynicotine oxidase inhibitor

0,546	0,149	Phobic disorders treatment
0,397	0,004	Antiemphysemic
0,487	0,098	Fusarinine-C ornithinesterase inhibitor
0,444	0,057	Feruloyl esterase inhibitor
0,397	0,010	Septic shock treatment
0,498	0,113	Acrocylindropepsin inhibitor
0,498	0,113	Chymosin inhibitor
0,498	0,113	Saccharopepsin inhibitor
0,395	0,010	Amyloid beta precursor protein antagonist
0,387	0,006	Antineoplastic (renal cancer)
0,450	0,070	Oxygen scavenger
0,404	0,029	Cyclohexyl-isocyanide hydratase inhibitor
0,407	0,032	Poly(beta-D-mannuronate) lyase inhibitor
0,405	0,034	2-Haloacid dehalogenase inhibitor
0,400	0,031	Glyoxylate oxidase inhibitor
0,415	0,047	Cyclohexanone monooxygenase inhibitor
0,396	0,031	Glycolate dehydrogenase inhibitor
0,381	0,022	Polyneuridine-aldehyde esterase inhibitor
0,448	0,089	Macrophage colony stimulating factor agonist
0,431	0,073	Aminobutyraldehyde dehydrogenase inhibitor
0,418	0,060	Exoribonuclease II inhibitor
0,384	0,027	Yeast ribonuclease inhibitor
0,437	0,081	Limulus clotting factor B inhibitor
0,480	0,125	Polyporopepsin inhibitor
0,438	0,084	Glucan endo-1,3-beta-D-glucosidase inhibitor

0,374	0,024	Pediculicide
0,386	0,040	Albendazole monooxygenase inhibitor
0,411	0,067	Biotinidase inhibitor
0,407	0,063	Adenomatous polyposis treatment
0,344	0,002	Interleukin 1 beta converting enzyme inhibitor
0,433	0,094	NADPH-cytochrome-c2 reductase inhibitor
0,423	0,086	UDP-N-acetylglucosamine 4-epimerase inhibitor
0,395	0,059	Alkenylglycerophosphoethanolamine hydrolase inhibitor
0,363	0,032	Shikimate O-hydroxycinnamoyltransferase inhibitor
0,408	0,078	Pterin deaminase inhibitor
0,393	0,065	Acetylgalactosaminyl-O-glycosyl-glycoprotein beta-1,3-N-acetylglucosaminyltransferase inhibitor
0,410	0,083	(R)-6-hydroxynicotine oxidase inhibitor
0,453	0,128	CYP2J2 substrate
0,328	0,005	Beta lactamase inhibitor
0,350	0,029	Myeloblastin inhibitor
0,406	0,089	Leukopoiesis stimulant
0,432	0,115	Platelet aggregation stimulant
0,388	0,072	Polyamine-transporting ATPase inhibitor
0,448	0,133	Kidney function stimulant
0,385	0,073	Cl--transporting ATPase inhibitor
0,379	0,068	Centromere associated protein inhibitor
0,401	0,092	1,4-Lactonase inhibitor
0,375	0,065	N-acetylneuraminate 7-O(or 9-O)-acetyltransferase inhibitor
0,355	0,046	Sulfite oxidase inhibitor
0,383	0,075	Endopeptidase So inhibitor

0,368	0,061	Dermatologic
0,374	0,069	Dementia treatment
0,415	0,112	Nicotinic alpha2beta2 receptor antagonist
0,393	0,089	GST A substrate
0,325	0,023	Analgesic stimulant
0,325	0,025	Dihydroorotase inhibitor
0,383	0,083	CYP2D16 substrate
0,413	0,115	Protein-disulfide reductase (glutathione) inhibitor
0,343	0,046	Cyclomaltodextrinase inhibitor
0,400	0,106	27-Hydroxycholesterol 7alpha-monooxygenase inhibitor
0,377	0,084	Fatty-acyl-CoA synthase inhibitor
0,331	0,039	Cutinase inhibitor
0,406	0,116	Ovulation inhibitor
0,362	0,074	CYP2A8 substrate
0,375	0,088	Dimethylargininase inhibitor
0,343	0,057	Chitosanase inhibitor
0,353	0,068	Acetylesterase inhibitor
0,345	0,064	Dolichyl-diphosphooligosaccharide-protein glycotransferase inhibitor
0,331	0,051	2-Hydroxymuconate-semialdehyde hydrolase inhibitor
0,348	0,068	Calcium regulator
0,340	0,062	Creatininase inhibitor
0,366	0,088	Nitrate reductase (cytochrome) inhibitor
0,372	0,096	Trimethylamine-oxide aldolase inhibitor
0,331	0,058	Mannose isomerase inhibitor
0,421	0,147	Pseudolysin inhibitor

0,431	0,159	Mucomembranous protector
0,331	0,061	IgA-specific serine endopeptidase inhibitor
0,346	0,076	Tpr proteinase (Porphyromonas gingivalis) inhibitor
0,342	0,073	CYP2C18 substrate
0,326	0,057	N-benzyloxycarbonylglycine hydrolase inhibitor
0,320	0,052	S-alkylcysteine lyase inhibitor
0,351	0,084	Na+-transporting two-sector ATPase inhibitor
0,359	0,095	Fragilysin inhibitor
0,344	0,080	Peptidoglycan glycosyltransferase inhibitor
0,351	0,088	Dehydro-L-gulonate decarboxylase inhibitor
0,329	0,067	Glutamine-phenylpyruvate transaminase inhibitor
0,302	0,040	Oryzin inhibitor
0,325	0,063	Methylumbelliferyl-acetate deacetylase inhibitor
0,336	0,076	Mucinaminylserine mucinaminidase inhibitor
0,324	0,065	Nitrite reductase (NO-forming) inhibitor
0,341	0,085	Phenol O-methyltransferase inhibitor
0,302	0,046	2,3,4,5-Tetrahydropyridine-2,6-dicarboxylate N-succinyltransferase inhibitor
0,363	0,107	Sulfur reductase inhibitor
0,345	0,089	S-formylglutathione hydrolase inhibitor
0,436	0,181	Ubiquinol-cytochrome-c reductase inhibitor
0,338	0,085	CYP2A4 substrate
0,333	0,080	CYP2B5 substrate
0,349	0,099	Arginine 2-monooxygenase inhibitor
0,355	0,106	JAK2 expression inhibitor
0,340	0,095	Aspartate-phenylpyruvate transaminase inhibitor

0,352	0,106	Fibrolase inhibitor
0,308	0,064	Antiinflammatory, intestinal
0,325	0,082	Methylamine-glutamate N-methyltransferase inhibitor
0,331	0,091	Hydroxylamine oxidase inhibitor
0,378	0,139	5 Hydroxytryptamine uptake stimulant
0,338	0,100	Antimyopathies
0,314	0,079	Chenodeoxycholoyltaurine hydrolase inhibitor
0,310	0,075	3-Cyanoalanine hydratase inhibitor
0,316	0,083	Fucosterol-epoxide lyase inhibitor
0,307	0,078	Peptide-N4-(N-acetyl-beta-glucosaminyl)asparagine amidase inhibitor
0,306	0,078	Adenylyl-sulfate reductase inhibitor
0,302	0,077	Phosphopantothenoylcysteine decarboxylase inhibitor
0,319	0,095	Histidine N-acetyltransferase inhibitor
0,323	0,100	Thymidylate 5'-phosphatase inhibitor
0,333	0,114	Pancreatic elastase inhibitor
0,350	0,132	Cytoprotectant
0,326	0,108	CYP4A11 substrate
0,304	0,086	Phosphoinositide 5-phosphatase inhibitor
0,315	0,098	Formaldehyde transketolase inhibitor
0,333	0,117	Nicotine dehydrogenase inhibitor
0,306	0,091	HMOX1 expression enhancer
0,347	0,135	MAP kinase stimulant
0,321	0,110	Glycerol-3-phosphate oxidase inhibitor
0,310	0,100	Gamma-guanidinobutyraldehyde dehydrogenase inhibitor
0,311	0,103	Manganese peroxidase inhibitor

0,336	0,132	Pin1 inhibitor
0,343	0,139	Neurotransmitter antagonist
0,336	0,134	Apyrase inhibitor
0,307	0,105	Malate oxidase inhibitor
0,338	0,136	CYP2D15 substrate
0,335	0,141	2-Hydroxyquinoline 8-monooxygenase inhibitor
0,314	0,127	Fibrinogen receptor antagonist
0,341	0,155	Octopamine antagonist
0,317	0,137	4-Nitrophenol 2-monooxygenase inhibitor
0,334	0,156	Fructose 5-dehydrogenase inhibitor
0,305	0,127	EIF4E expression inhibitor
0,326	0,151	Erythropoiesis stimulant
0,314	0,146	Chlordecone reductase inhibitor
0,323	0,206	CYP3A2 substrate
0,307	0,215	Antiviral (Picornavirus)
0,339	0,249	Calcium channel (voltage-sensitive) activator

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,064 in AD	-0,345 in AD	0,516 in AD	-0,076 in AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
227,500 in AD	88,680 in AD	644,000 in AD	164,700 in AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 in AD	Class 4 in AD	Class 4 in AD	Class 4 in AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
Oral - Oral route of administration
SC - Subcutaneous route of administration
in AD - compound falls in applicability domain of models
out of AD - compound is out of applicability domain of models
http://www.pharmaexpert.ru/GUSAR/AcuToxPredict/
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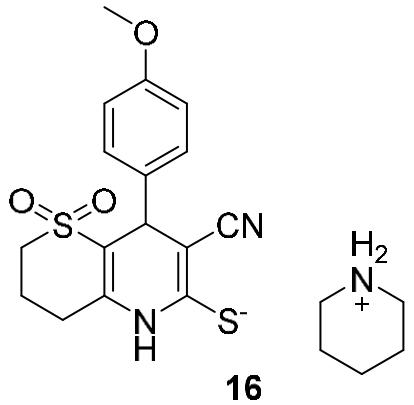

16

In silico predicted results for compound 16

☐ All ☐ Pa>Pi ◉ Pa>0,3 ☐ Pa>0,7

0,685	0,006	Antihypertensive
0,664	0,010	Antiasthmatic
0,563	0,003	Calcium channel blocker
0,542	0,022	Antiallergic
0,554	0,042	Neurotransmitter uptake inhibitor
0,506	0,011	Antiischemic
0,442	0,027	Cardiotonic
0,398	0,009	Myocardial ischemia treatment
0,374	0,013	Urologic disorders treatment
0,349	0,014	Urinary incontinence treatment
0,335	0,004	Falcipain 2 inhibitor
0,335	0,004	Falcipain inhibitor
0,331	0,233	Nicotinic alpha4beta4 receptor agonist

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,135 in AD	-0,353 in AD	0,344 in AD	0,259 out of AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
475,100 in AD	154,700 in AD	769,600 in AD	632,800 out of AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 4 in AD	Class 4 in AD	Class 4 in AD	Class 4 out of AD

IP - Intraperitoneal route of administration
IV - Intravenous route of administration
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