Electronic Supplementary Material (ESI) for New Journal of Chemistry.

1,2,4-Triazolo[4,3-*c*]quinazolines: A bioisosterism-guided approach towards the development of novel PCAF inhibitors with potential anticancer activity

Mohamed H. El-Shershaby[a], Adel Ghiaty[a], Ashraf H. Bayoumi[a], Hany E. A. Ahmed[a,b], Mona S. El-Zoghbi[c], Khaled El-Adl[d,e], Hamada S. Abulkhair[a,f*]

Supporting Information

Contents

Docking Files

Summary of docking results

Table 1: Results of in silico docking scores for new compounds and the co-crystallized ligand (L-45) with the binding site of histone acetyltransferase GCN5

Comp.	ΔG	RMSD	Ligand	Receptor	H-bonding interactions		Hydrophobic interactions	
	(kcal/mol)	(Å)			Residue	Distance (Å)	Residue	Distance (Å)
L-45	-11.52	0.81	C 15	OE2	GLU 1389	3.47		
			N 19	OE1	GLU 1389	2.82		
			N 13	ND2	ASN 1436	3.40		
			6-ring	6-ring			TYR 1442	3.63
21	-10.15	0.98	N 13	ND2	ASN 1436	3.31		
			6-ring	6-ring			TYR 1442	3.62
22	-10.12	1.19	6-ring	CZ3			TRP 1379	4.10
			6-ring	CZ3			TRP 1379	4.34
			6-ring	CG2			VAL 1385	3.60
			6-ring	6-ring			TYR 1442	3.77
23	-10.98	1.00	N 7	OE1	GLU 1389	3.09		
			CL 21	O	THR 1401	3.24		
			N 12	ND2	ASN 1436	2.84		
			5-ring	6-ring			TYR 1442	3.85
			6-ring	6-ring			TYR 1442	3.84
24	-10.26	1.20	CL 14	O	PRO 1380	3.20		

Comp.	ΔG	RMSD	Ligand	Receptor	H-bonding interactions		Hydrophobic interactions	
	(kcal/mol)	(Å)			Residue	Distance (Å)	Residue	Distance (Å)
			N 13	ND2	ASN 1436	2.98		
			6-ring	CB			ALA 1390	4.52
			6-ring	6-ring			TYR 1442	3.65
25	-10.10	0.73	N 12	ND2	ASN 1436	2.99		
			5-ring	6-ring			TYR 1442	3.94
			6-ring	6-ring			TYR 1442	3.90
26	-10.74	1.11	CL 21	O	THR 1401	3.42		
			N 12	ND2	ASN 1436	2.84		
			5-ring	6-ring			TYR 1442	3.90
			6-ring	6-ring			TYR 1442	3.80
27	-10.07	0.92	N 12	ND2	ASN 1436	3.45		
			5-ring	6-ring			TYR 1442	3.84
			6-ring	6-ring			TYR 1442	3.78
28	-9.79	0.80	C 15	SG	CYS 1432	3.76		
			N 17	ND2	ASN 1436	2.71		
29	-11.556	1.162	N 12	ND2	ASN 1436	3.11		
			6-ring	6-ring			TYR 1442	3.98
30	-10.02	1.20	C 20	6-ring			TYR 1442	3.74
				6-ring			TRP 1379	4.15
31	-9.53	1.06	N 12	ND2	ASN 1436	2.93		
			5-ring	6-ring			TYR 1442	3.76
			6-ring	6-ring			TYR 1442	3.75
32	-9.55	0.89	CL 23	O	THR 1401	3.44		

Comp.	ΔG	RMSD	Ligand	Receptor	H-bonding interactions		Hydrophobic interactions	
	(kcal/mol)	(Å)			Residue	Distance (Å)	Residue	Distance (Å)
			N 12	ND2	ASN 1436	2.85		
			5-ring	6-ring			TYR 1442	3.91
			6-ring	6-ring			TYR 1442	3.79
33	-10.80	0.99	N 12	ND2	ASN 1436	2.85		
			5-ring	6-ring			TYR 1442	3.96
			6-ring	6-ring			TYR 1442	3.75
34	-9.78	1.16	CL 23	O	THR 1401	3.42		
			N 12	ND2	ASN 1436	2.87		
			5-ring	6-ring			TYR 1442	3.95
			6-ring	6-ring			TYR 1442	3.75
35	-9.89	1.10	N 14	OE1	GLU 1389	2.97		
36	-9.92	1.19	6-ring	6-ring			TYR 1442	3.93

Predicted binding mode of l-45 redocked

Score -11.5259777

RMSD 0.957672298

Ligand Interactions Report

5TPX: TRANSFERASE / 5TPX: TRANSFERASE

Ligand Receptor Interaction Distance E (kcal/mol)

C14 1 O PRO 1384 (A) H-donor 3.38 -0.7

N5 5 OE1 GLU 1389 (A) H-donor 3.32 -0.9

N5 5 OE2 GLU 1389 (A) H-donor 2.72 -16.6

N4 45 ND2 ASN 1436 (A) H-acceptor 2.88 -2.5

N5 5 OE1 GLU 1389 (A) ionic 3.32 -2.6

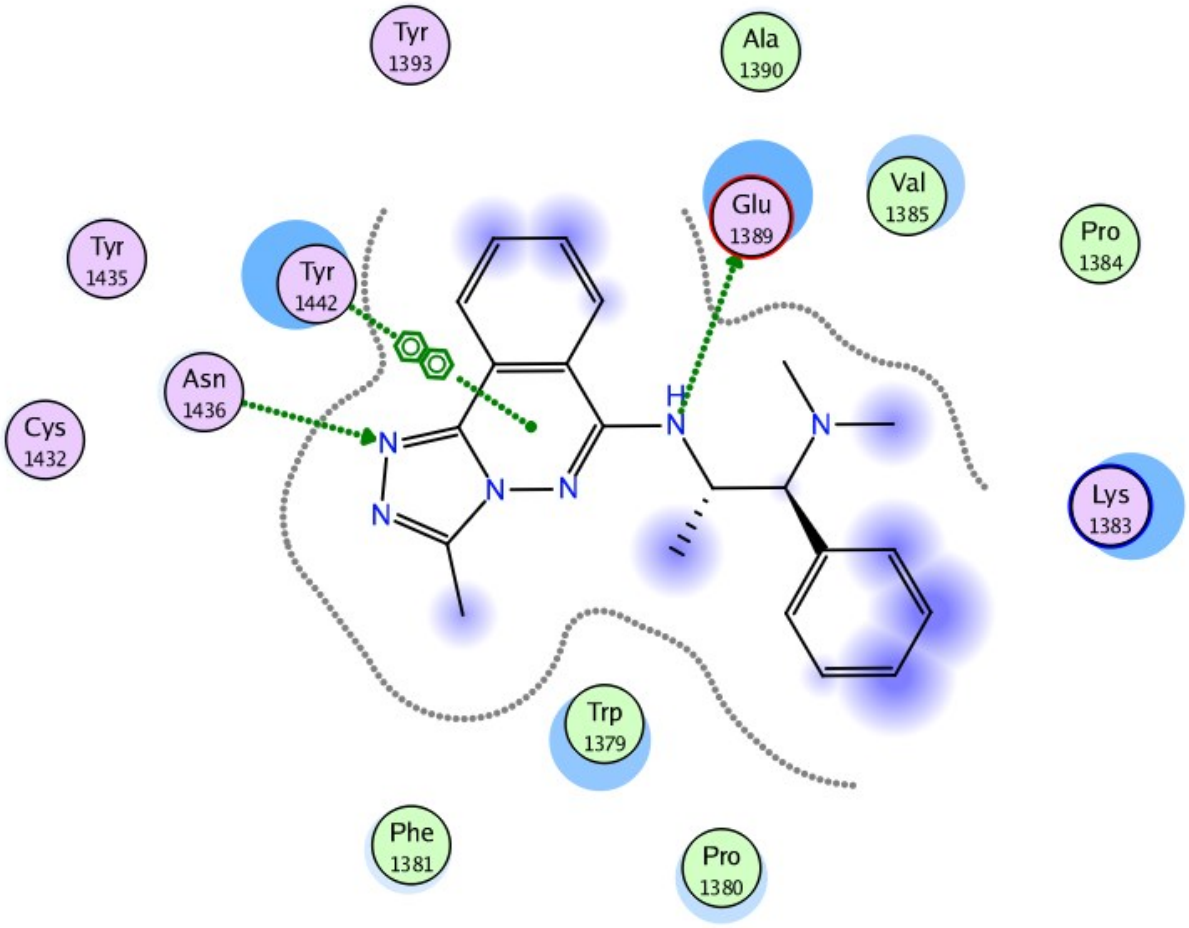
N5 5 OE2 GLU 1389 (A) ionic 2.72 -6.6

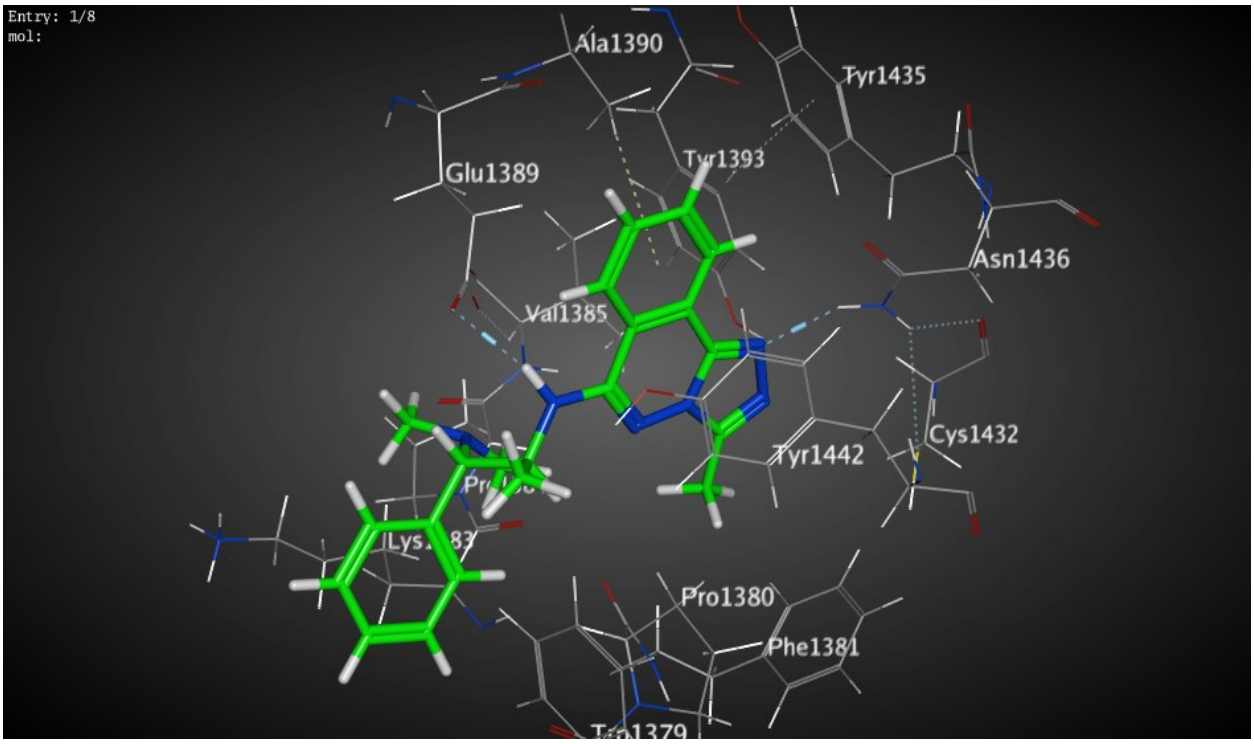
6-ring 6-ring TYR 1442 (A) pi-pi 3.67 -0.0

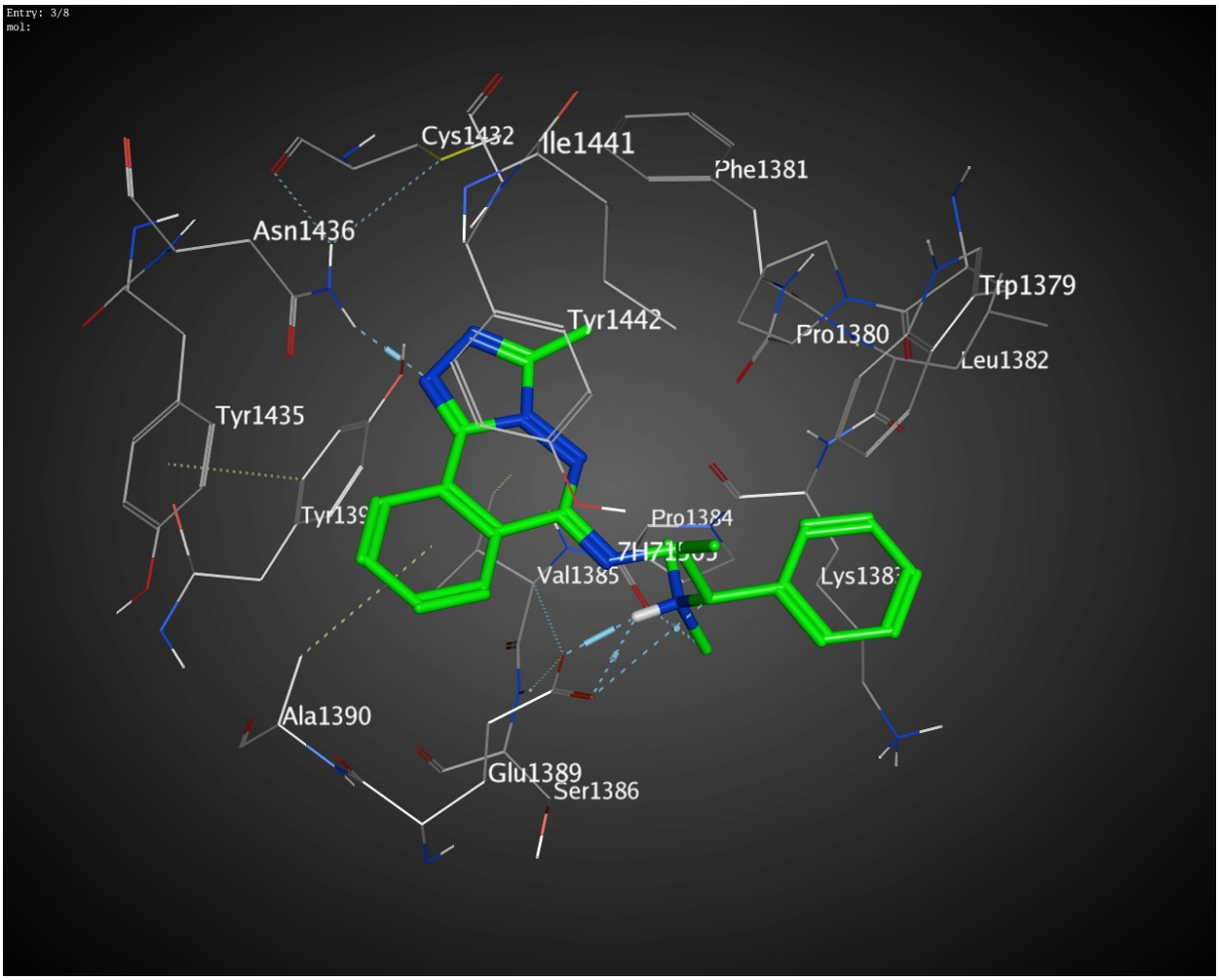
5TPX: TRANSFERASE / 5TPX

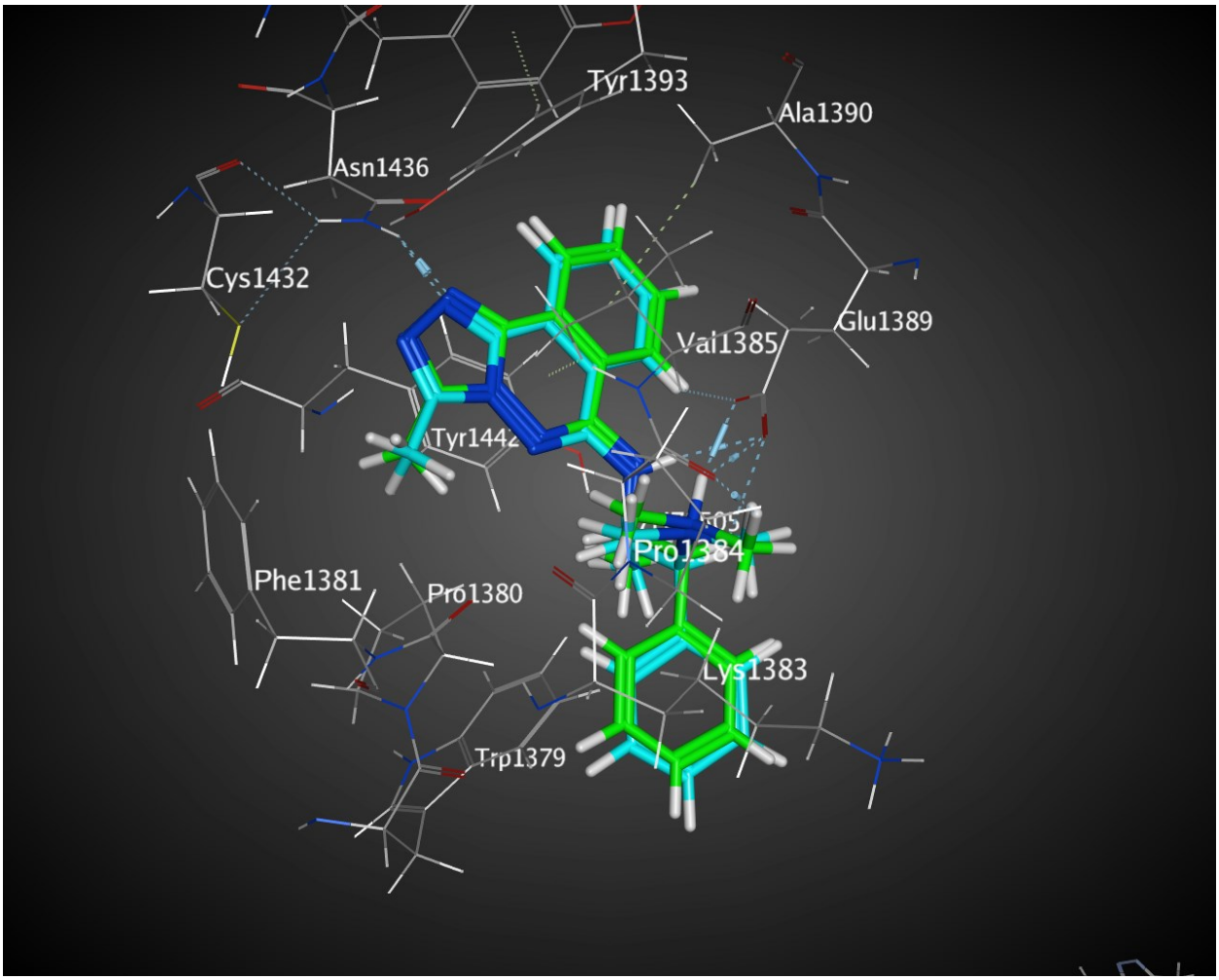
Ligand Receptor Interaction Distance E (kcal/mol)

6-ring 6-ring TYR 1442 (A) pi-pi 3.84 -0.0


Tyr
1393
Ala
1390
Glu
1389
Val
1385
Pro
1384
Tyr
1435
Tyr
1442
Asn
1436
Cys
1432
H
N
N
N
N
N
Lys
1383
Trp
1379
Phe
1381
Pro
1380


Entry: 1/8
mol:
Ala1390
Tyr1435
Glu1389
Tyr1393
Asn1436
Val1385
Cys1432
Tyr1442
Pro1380
Phe1381


Entry: 3/8
mol:
Cys1432
Ile1441
Phe1381
Asn1436
Trp1379
Tyr1442
Pro1380
Leu1382
Tyr1435
Pro1384
Val1385
Ala1390
Glu1389
Ser1386



Superimposition of the co-crystallized ligand and L-45 redocked

Predicted binding mode of 21

Score -10.15808037 RMSD 0.980336607

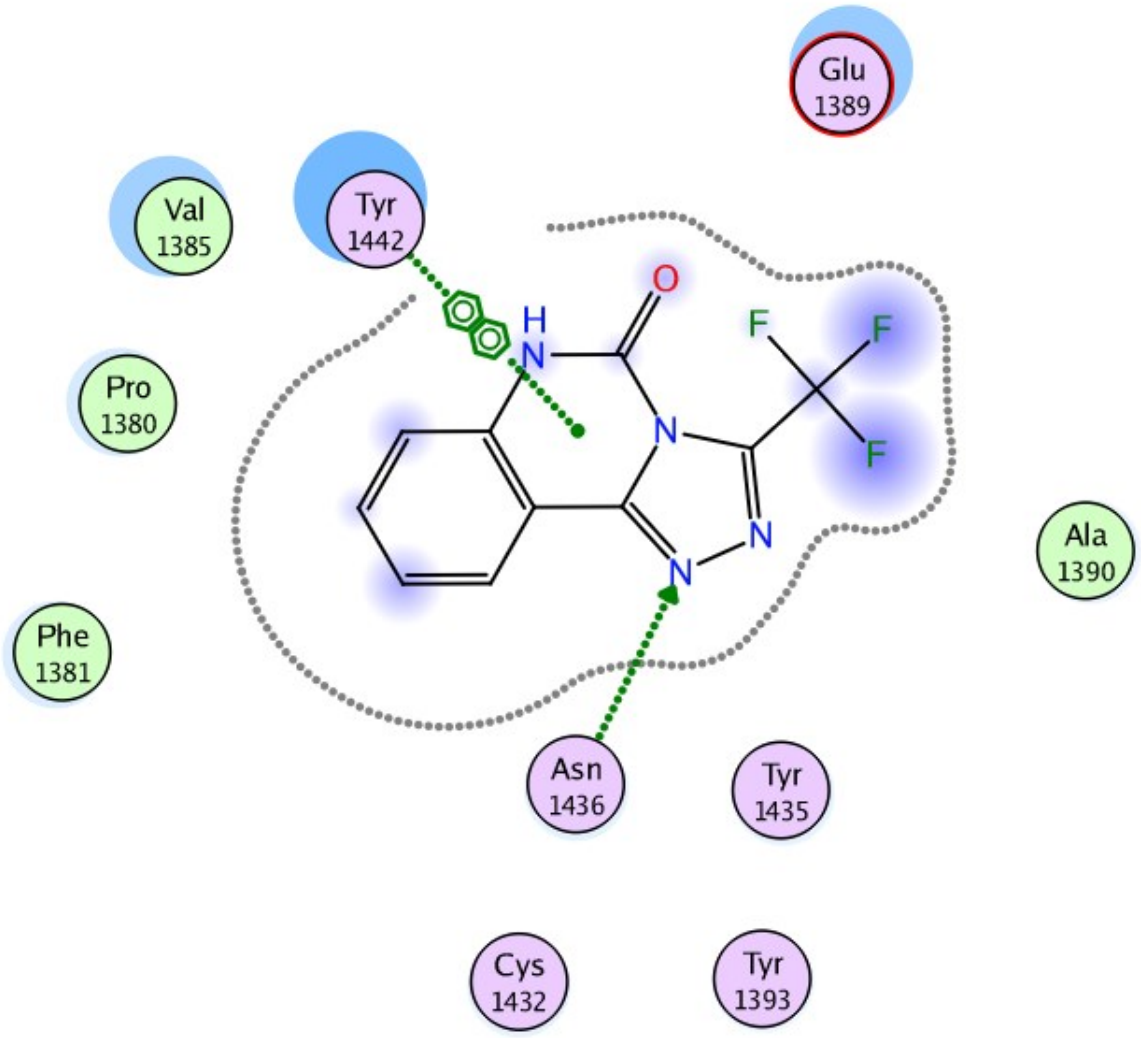
Ligand Interactions Report

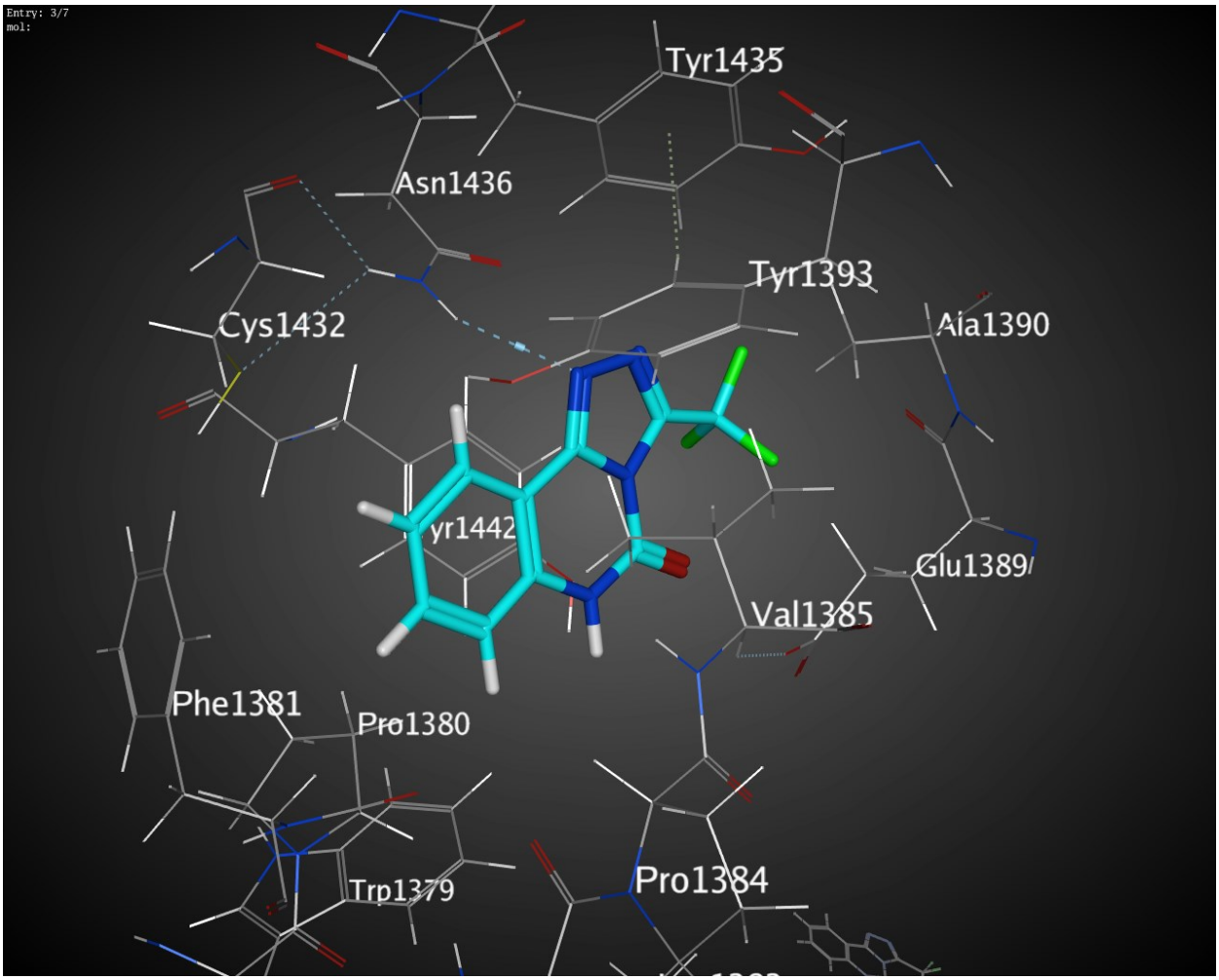
5TPX: TRANSFERASE / 5TPX

Ligand Receptor Interaction Distance E (kcal/mol)

N 13 ND2 ASN 1436 (A) H-acceptor 3.31 -0.8

6-ring 6-ring TYR 1442 (A) pi-pi 3.62 -0.0




Entry: 3/7
mol:
Tyr1435
Asn1436
Tyr1393
Cys1432
Ala1390
yr1442
Glu1389
Val1385
Phe1381
Pro1380
Trp1379
Pro1384

Predicted binding mode of 22

Score -10.1240214 RMSD 1.19

Ligand Interactions Report

5TPX: TRANSFERASE / 5TPX

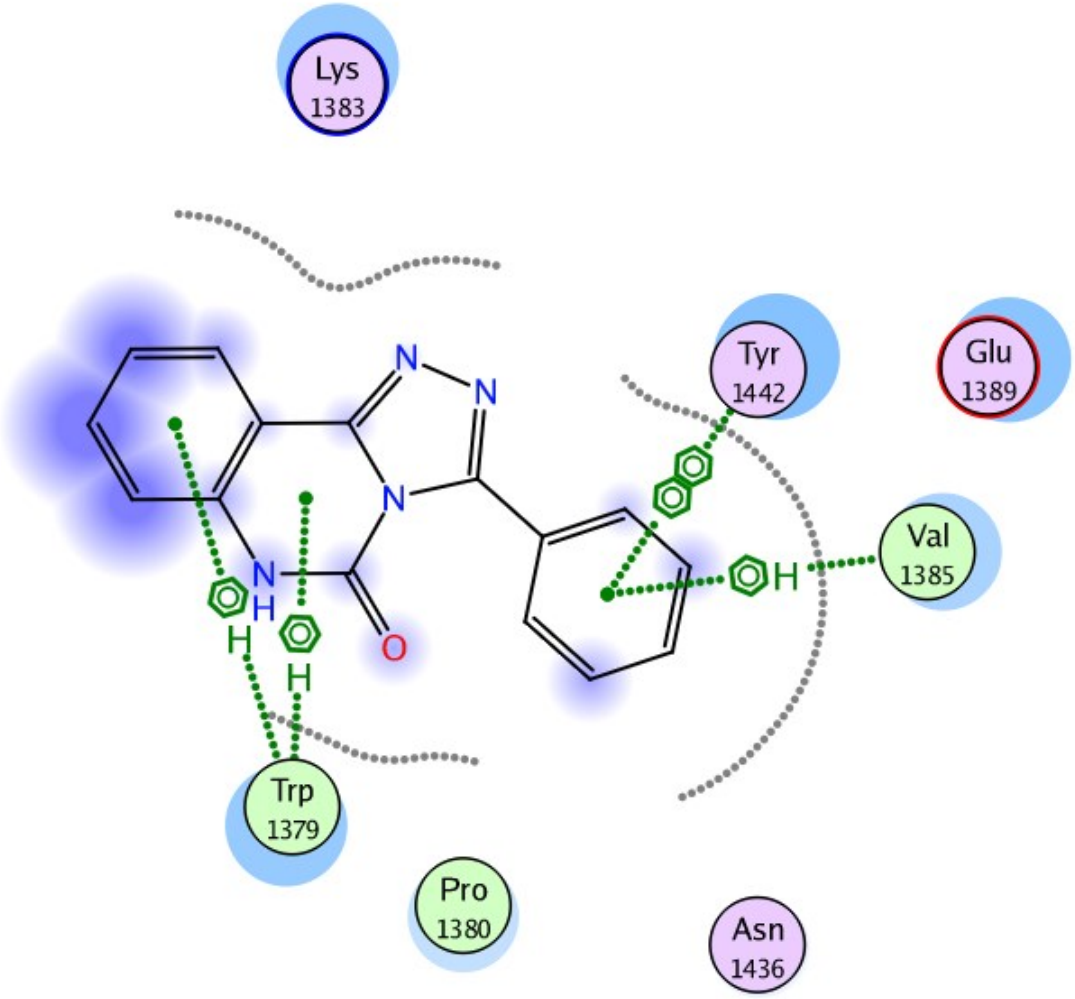
Ligand Receptor Interaction Distance E (kcal/mol)

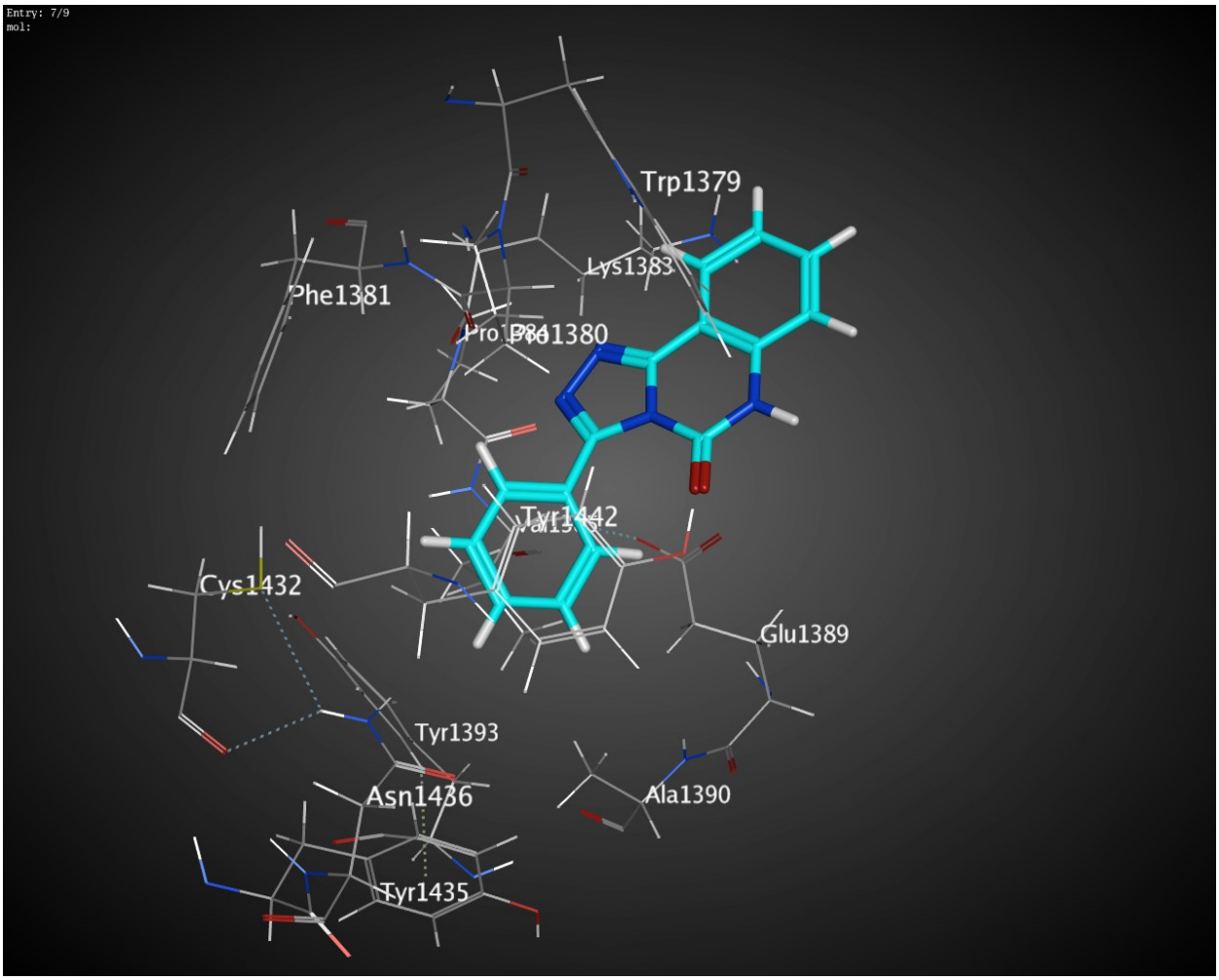
6-ring CZ3 TRP 1379 (A) pi-H 4.10 -0.7

6-ring CZ3 TRP 1379 (A) pi-H 4.34 -0.7

6-ring CG2 VAL 1385 (A) pi-H 3.60 -0.6

6-ring 6-ring TYR 1442 (A) pi-pi 3.77 -0.0




Entry: 7/9
mol:
Trp1379
Lys1383
Phe1381
Pro1384
Phe1380
Tyr1442
Cys1432
Glu1389
Tyr1393
Asn1436
Ala1390
Tyr1435

Predicted binding mode of 23

Score -10.9885861 RMSD 1.00

Ligand Interactions Report

5TPX: TRANSFERASE / 5TPX

Ligand Receptor Interaction Distance E (kcal/mol)

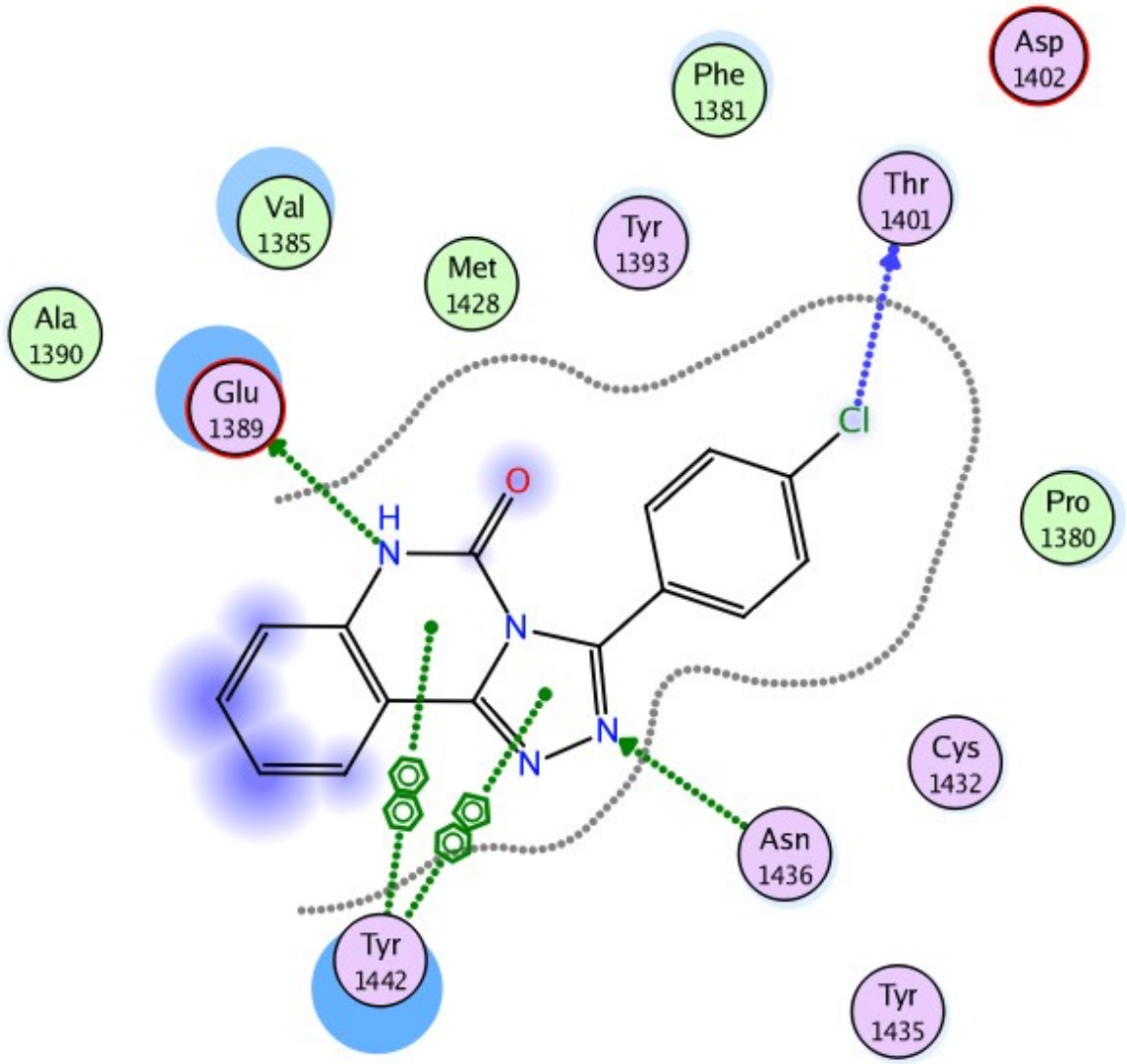
N 7 OE1 GLU 1389 (A) H-donor 3.09 -0.8

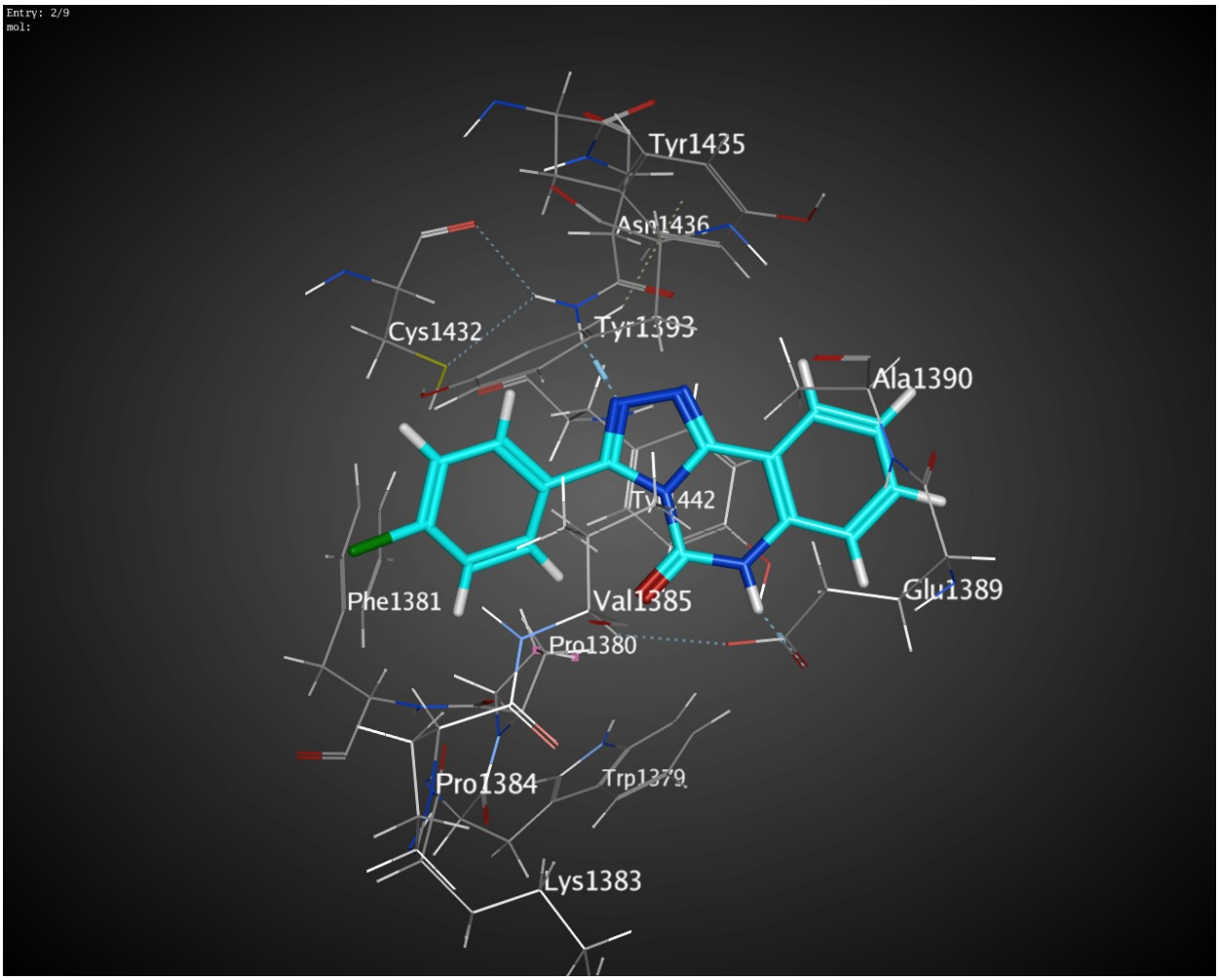
CL 21 O THR 1401 (A) H-donor 3.24 -0.9

N 12 ND2 ASN 1436 (A) H-acceptor 2.84 -2.7

5-ring 6-ring TYR 1442 (A) pi-pi 3.85 -0.0

6-ring 6-ring TYR 1442 (A) pi-pi 3.84 -0.0


Asp
1402
Phe
1381
Thr
1401
Val
1385
Tyr
1393
Met
1428
Ala
1390
Glu
1389
Cl
O
H
N
Pro
1380
N
N
N
Cys
1432
Asn
1436
Tyr
1442
Tyr
1435


Entry: 2/9
mol:
Tyr1435
Asn1436
Cys1432
Tyr1393
Ala1390
Tyr1442
Phe1381
Val1385
Glu1389
Pro1380
Pro1384
Trp1379
Lys1383

Predicted binding mode of 24

Score -10.2610031 RMSD 1.20

Ligand Interactions Report

5TPX: TRANSFERASE / 5TPX

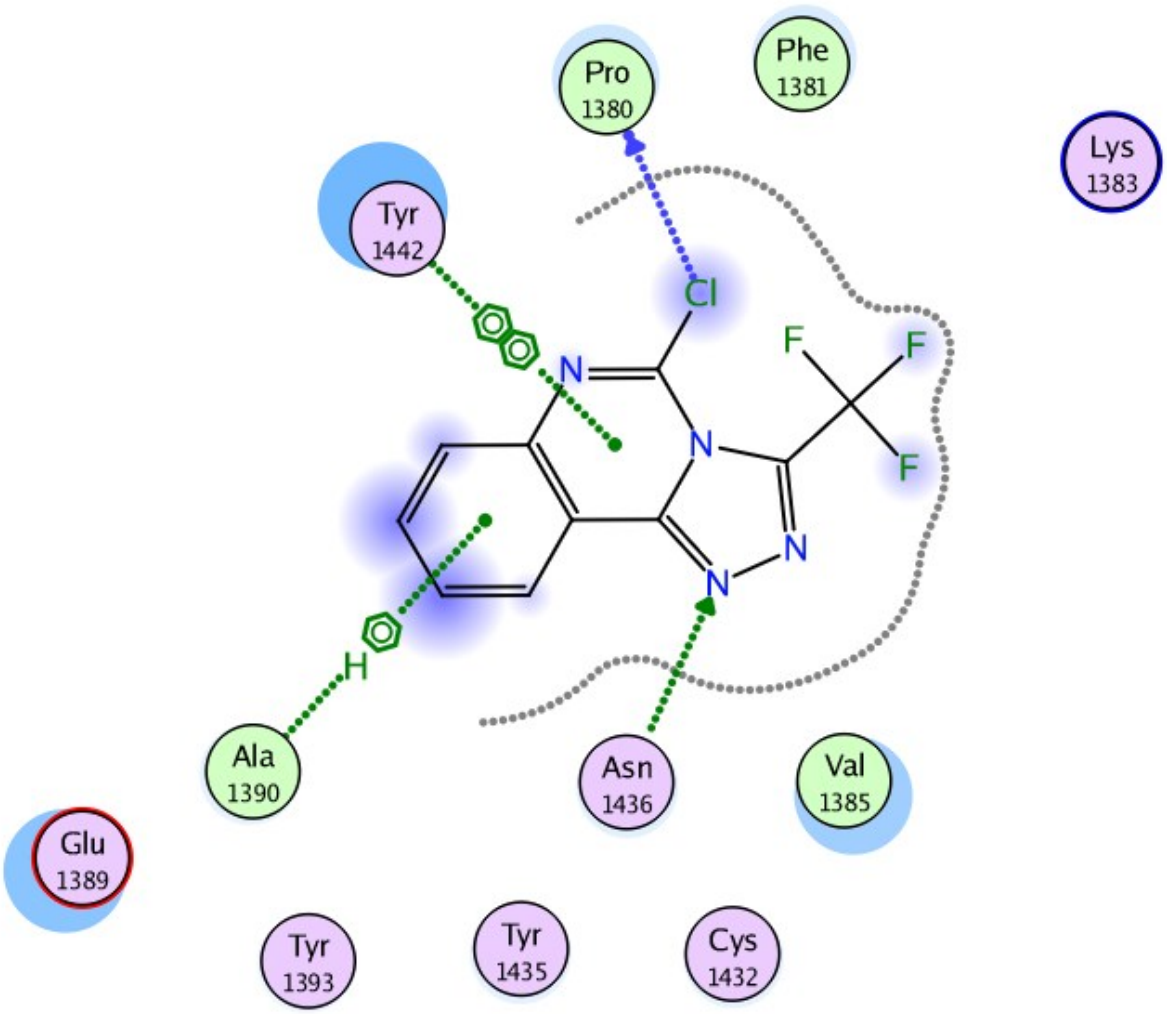
Ligand Receptor Interaction Distance E (kcal/mol)

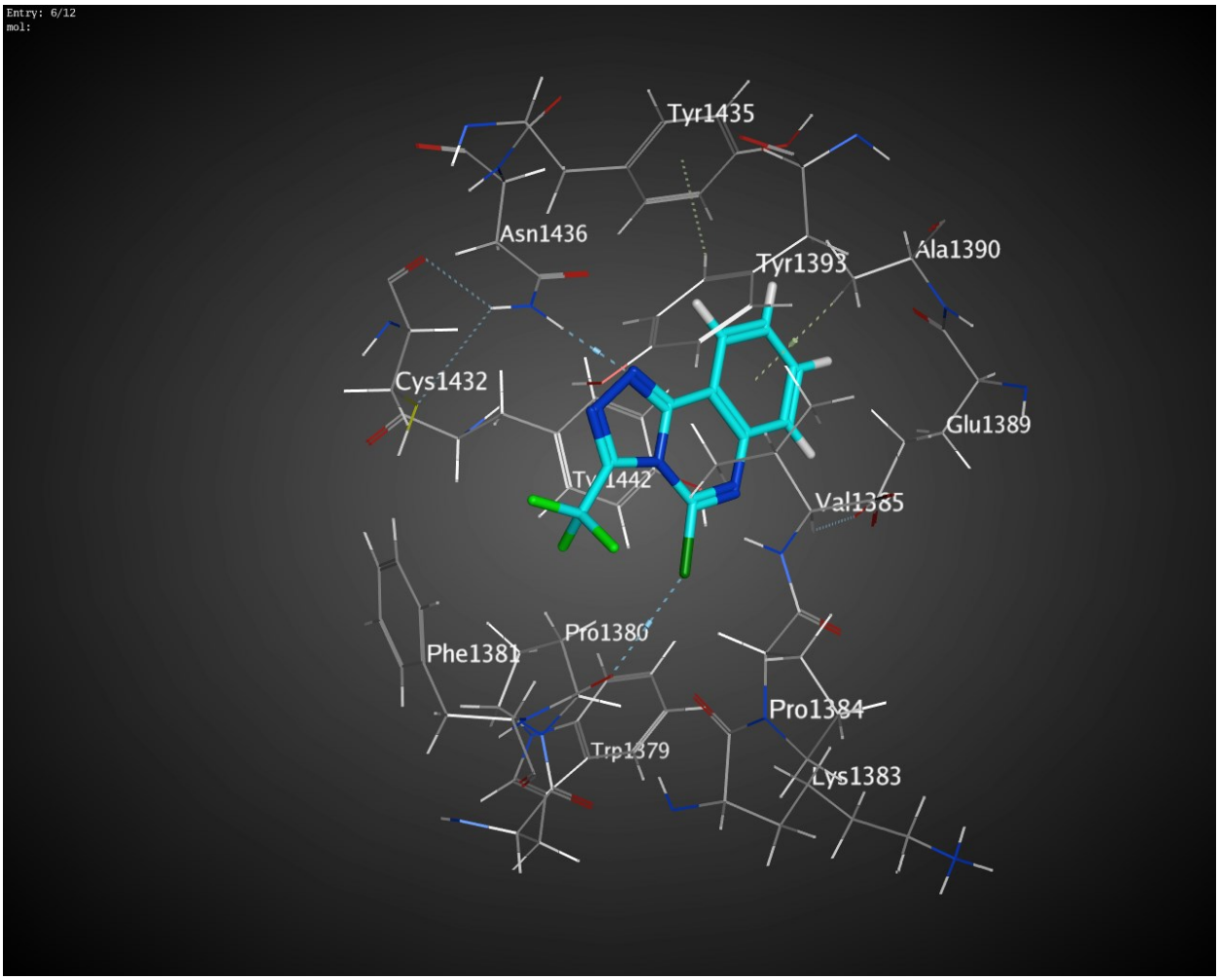
CL 14 O PRO 1380 (A) H-donor 3.20 -1.0

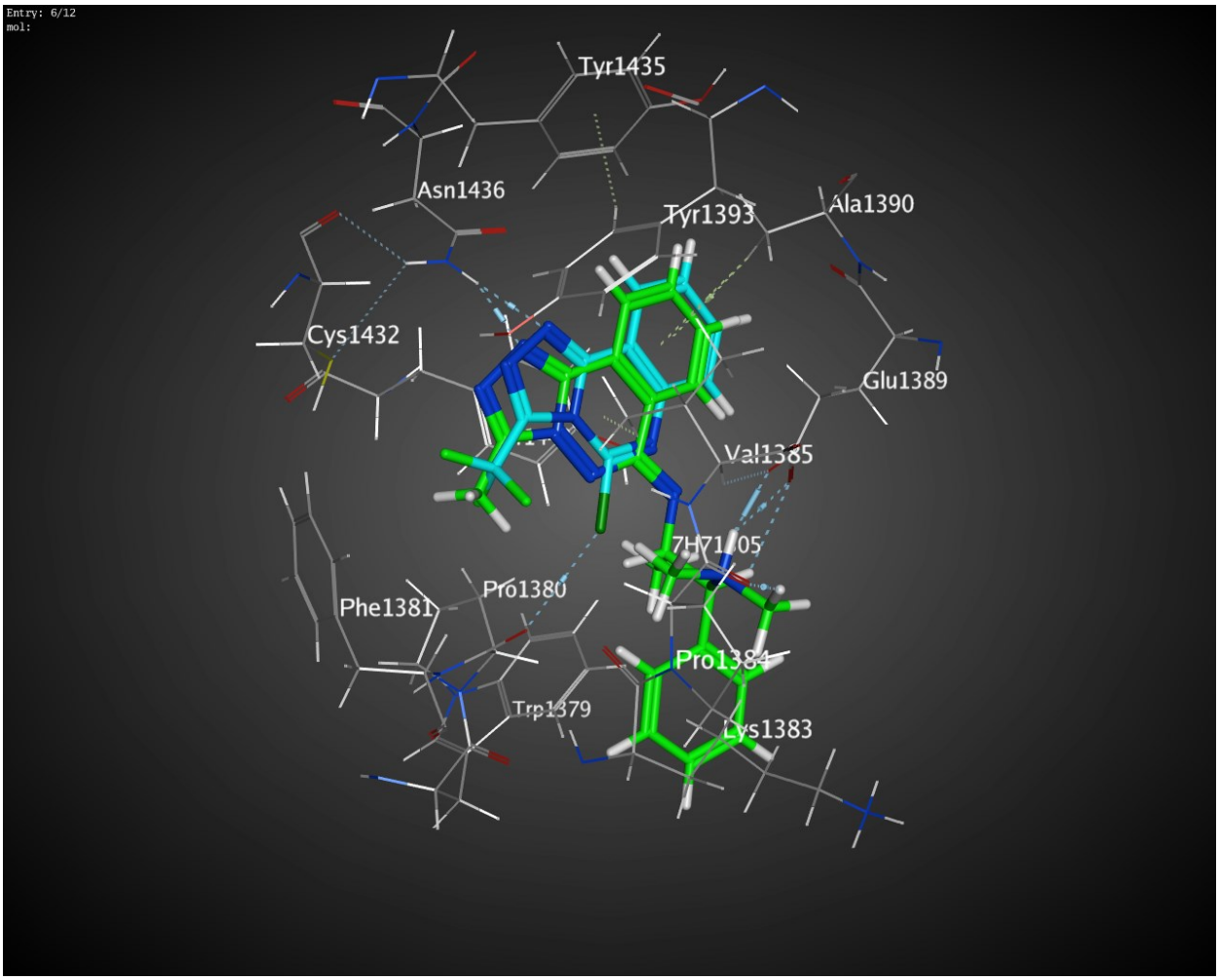
N 13 ND2 ASN 1436 (A) H-acceptor 2.98 -1.2

6-ring CB ALA 1390 (A) pi-H 4.52 -0.6

6-ring 6-ring TYR 1442 (A) pi-pi 3.65 -0.0




Entry: 6/12
mol:
Tyr1435
Asn1436
Tyr1393
Ala1390
Cys1432
Glu1389
Tyr1442
Val1385
Pro1380
Phe1381
Pro1384
Trp1379
Lys1383



superimposition of l-45 and 24

Predicted binding mode of 25

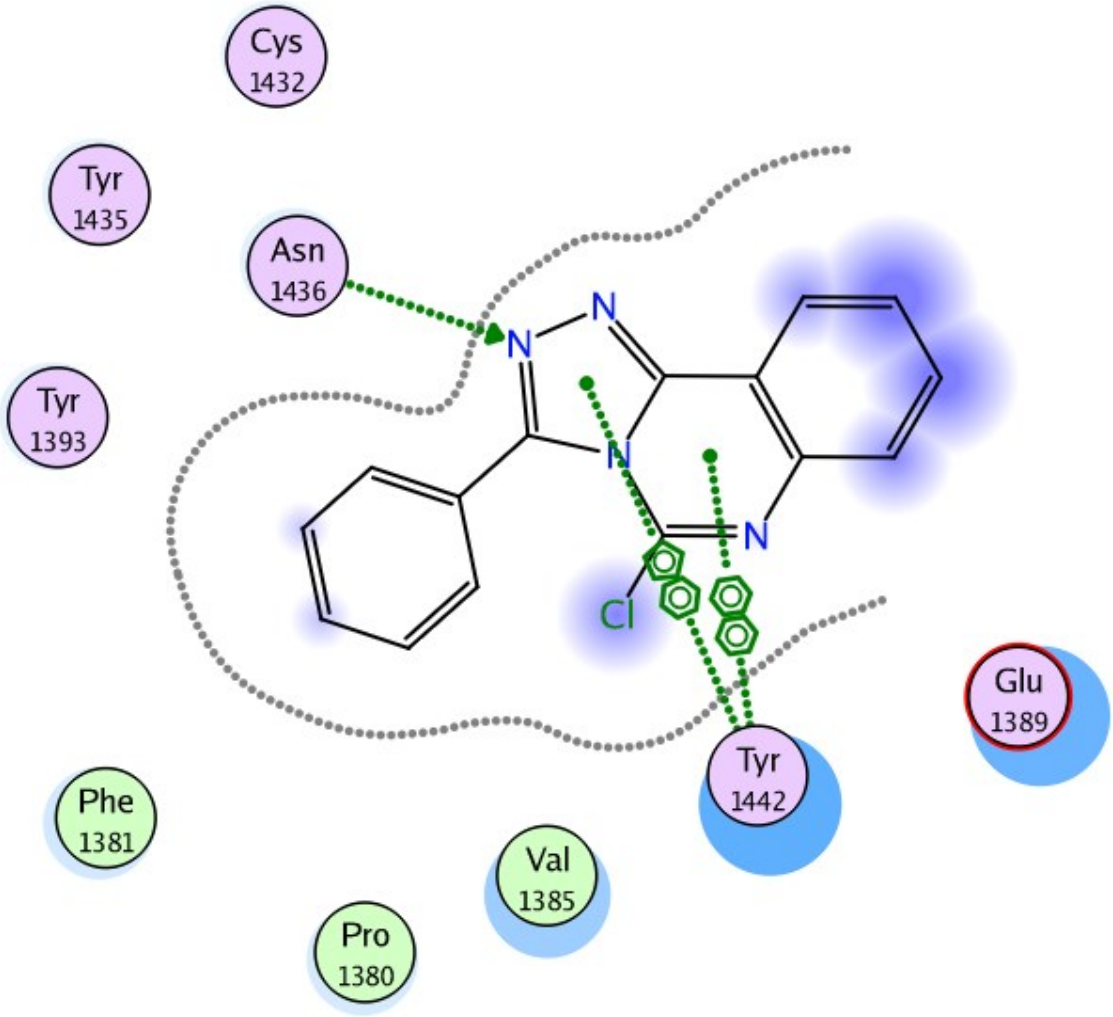
Score -10.1086307 RMSD 0.7342

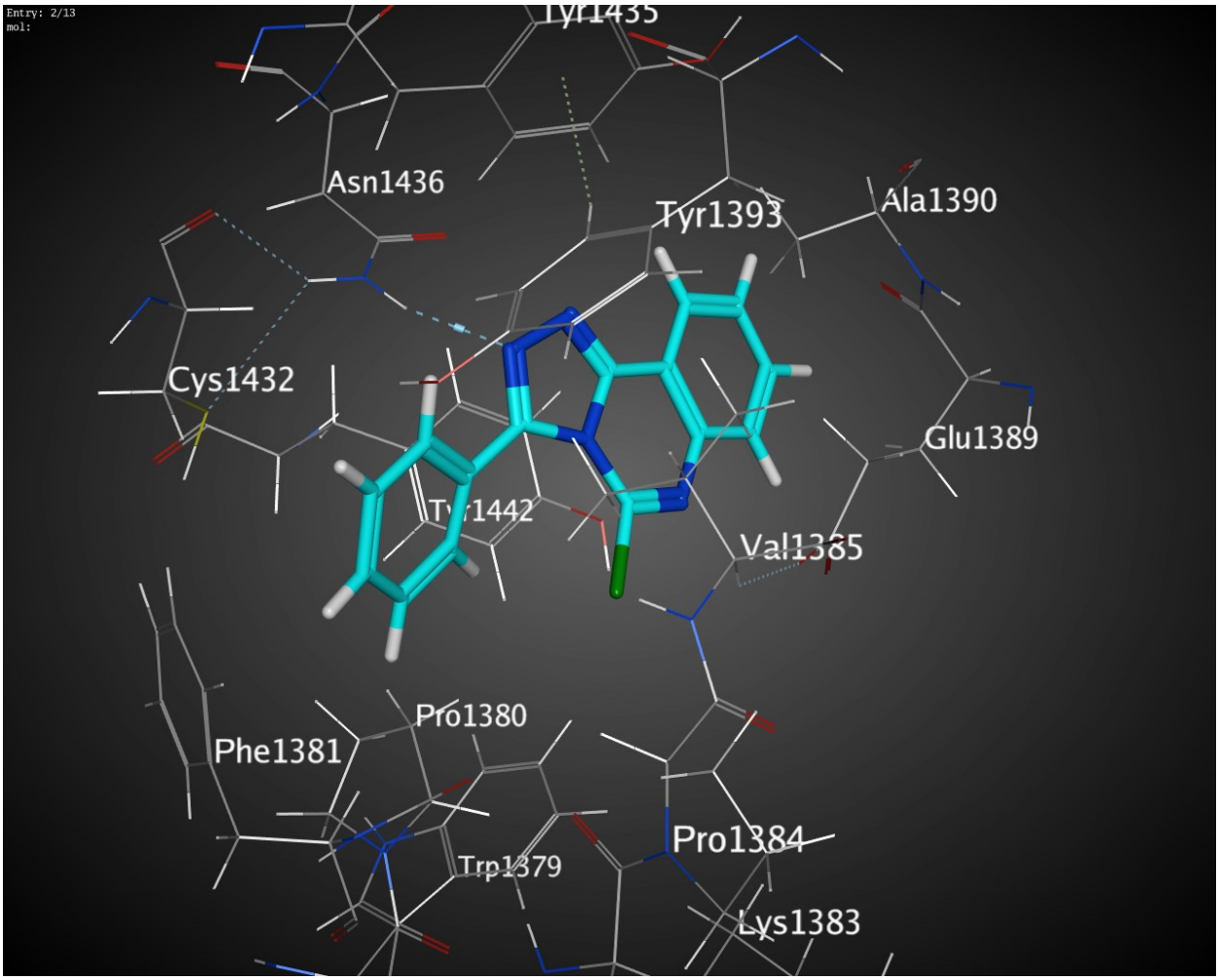
Ligand Receptor Interaction Distance E (kcal/mol)

N 12 ND2 ASN 1436 (A) H-acceptor 2.99 -1.6

5-ring 6-ring TYR 1442 (A) pi-pi 3.94 -0.0

6-ring 6-ring TYR 1442 (A) pi-pi 3.90 -0.0




Entry: 2/13
mol:
Tyr1435
Asn1436
Tyr1393
Ala1390
Cys1432
Glu1389
Tyr1442
Val1385
Pro1380
Phe1381
Pro1384
Trp1379
Lys1383

Predicted binding mode of 26

Score -10.7440429 RMSD 1.118343

Ligand Interactions Report

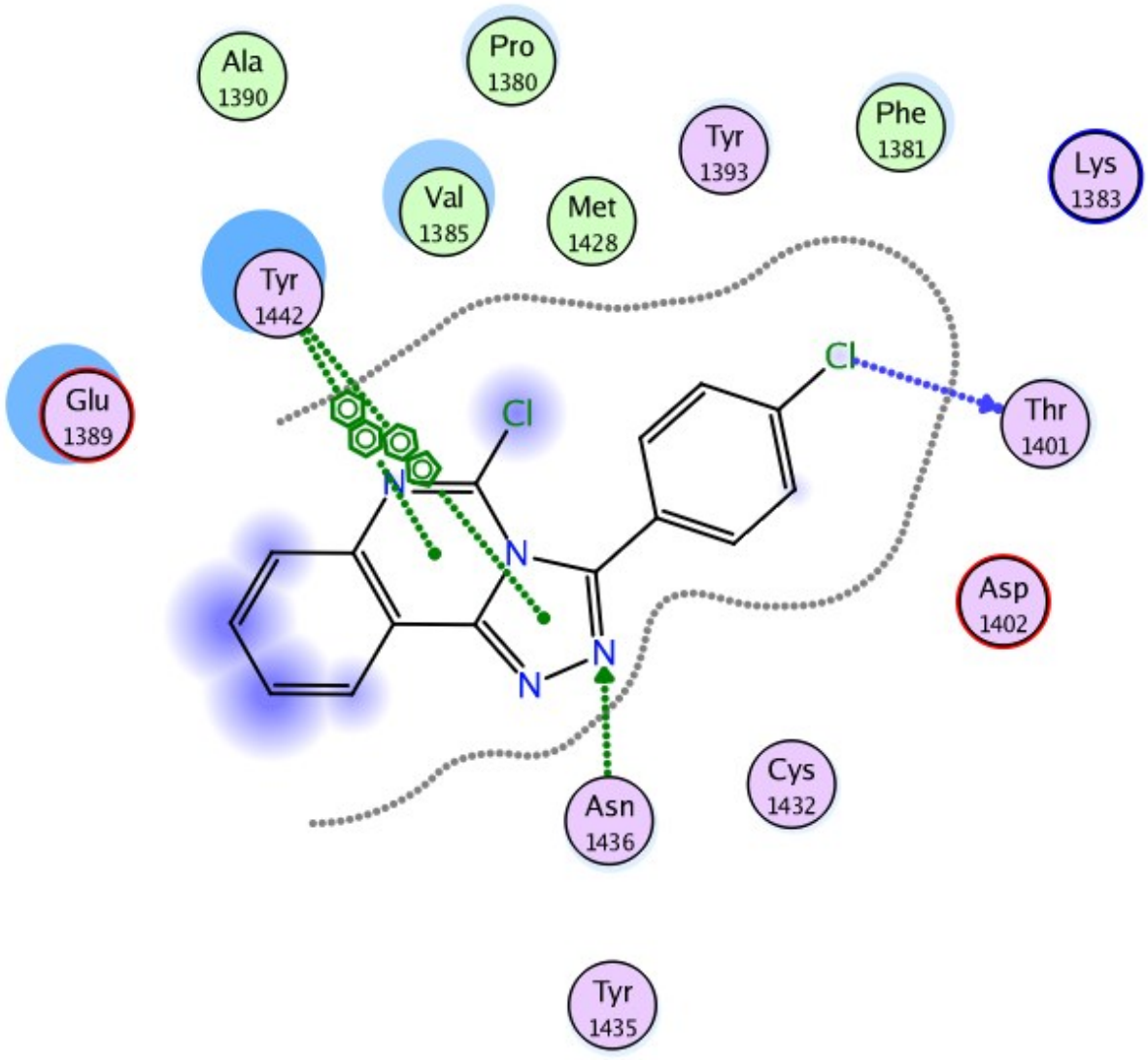
Ligand Receptor Interaction Distance E (kcal/mol)

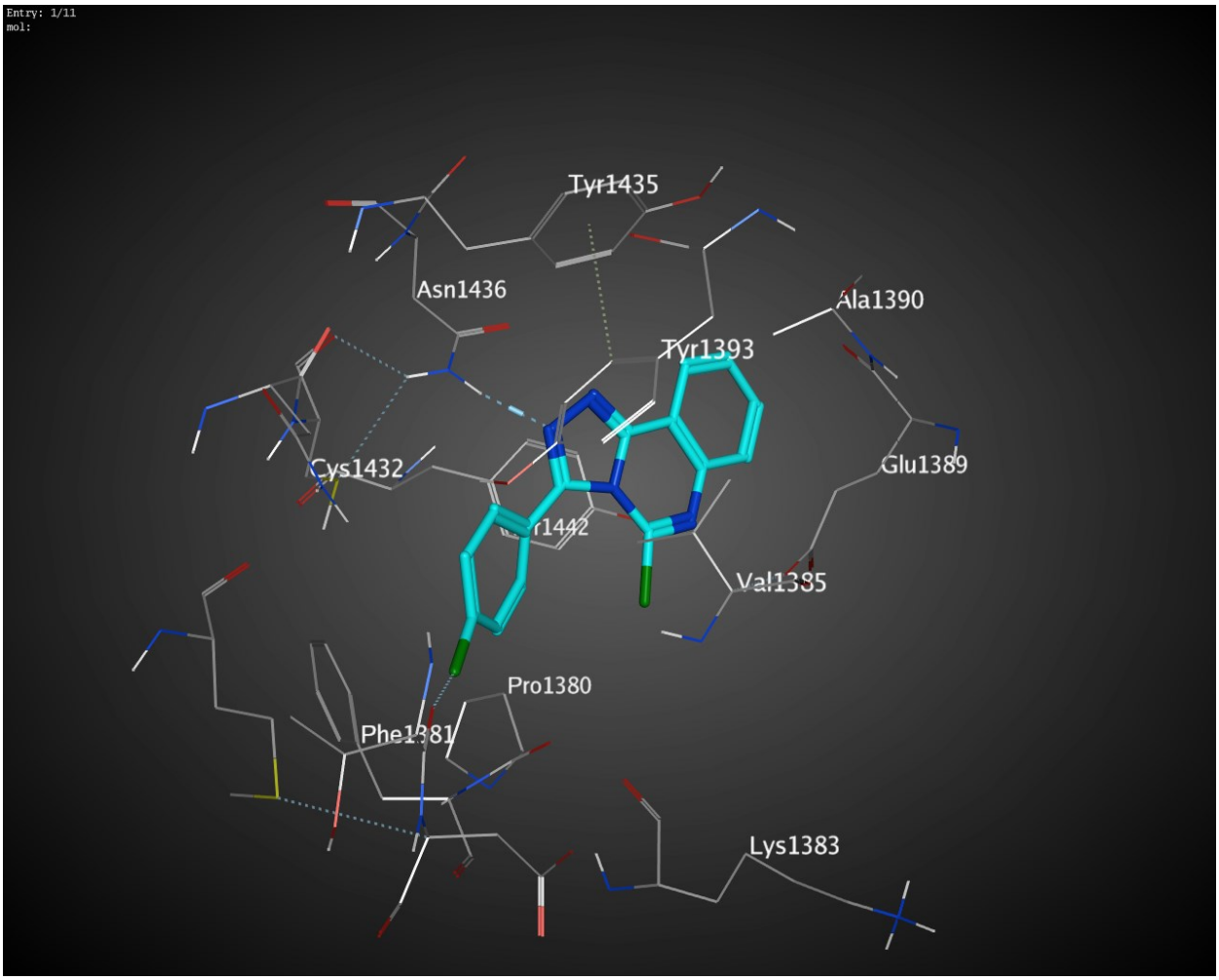
CL 21 O THR 1401 (A) H-donor 3.42 -0.5

N 12 ND2 ASN 1436 (A) H-acceptor 2.84 -1.8

5-ring 6-ring TYR 1442 (A) pi-pi 3.90 -0.0

6-ring 6-ring TYR 1442 (A) pi-pi 3.80 -0.0




Entry: 1/11
mol:
Tyr1435
Asn1436
Ala1390
Tyr1393
Cys1432
Glu1389
Val1385
Pro1380
Phe1381
Lys1383

Predicted binding mode of 27

Score -10.0714397 RMSD 0.9232

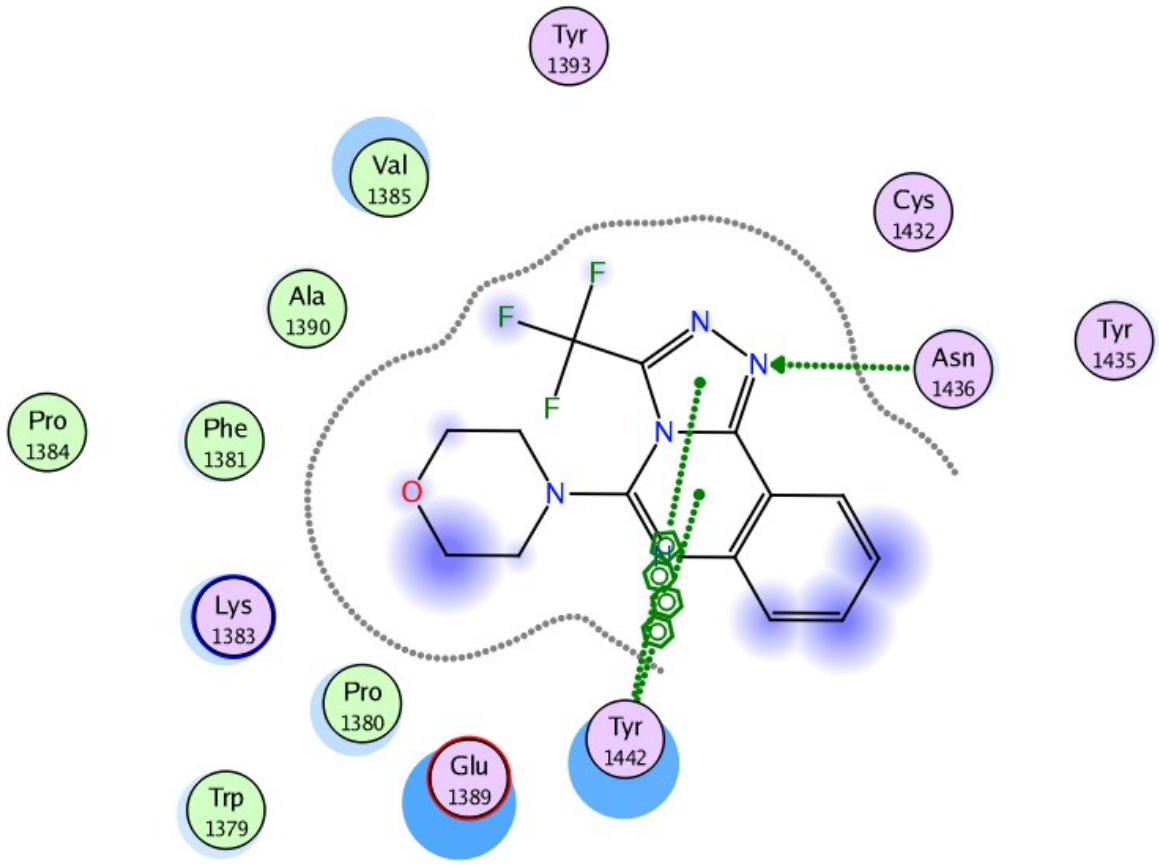
Ligand Interactions Report

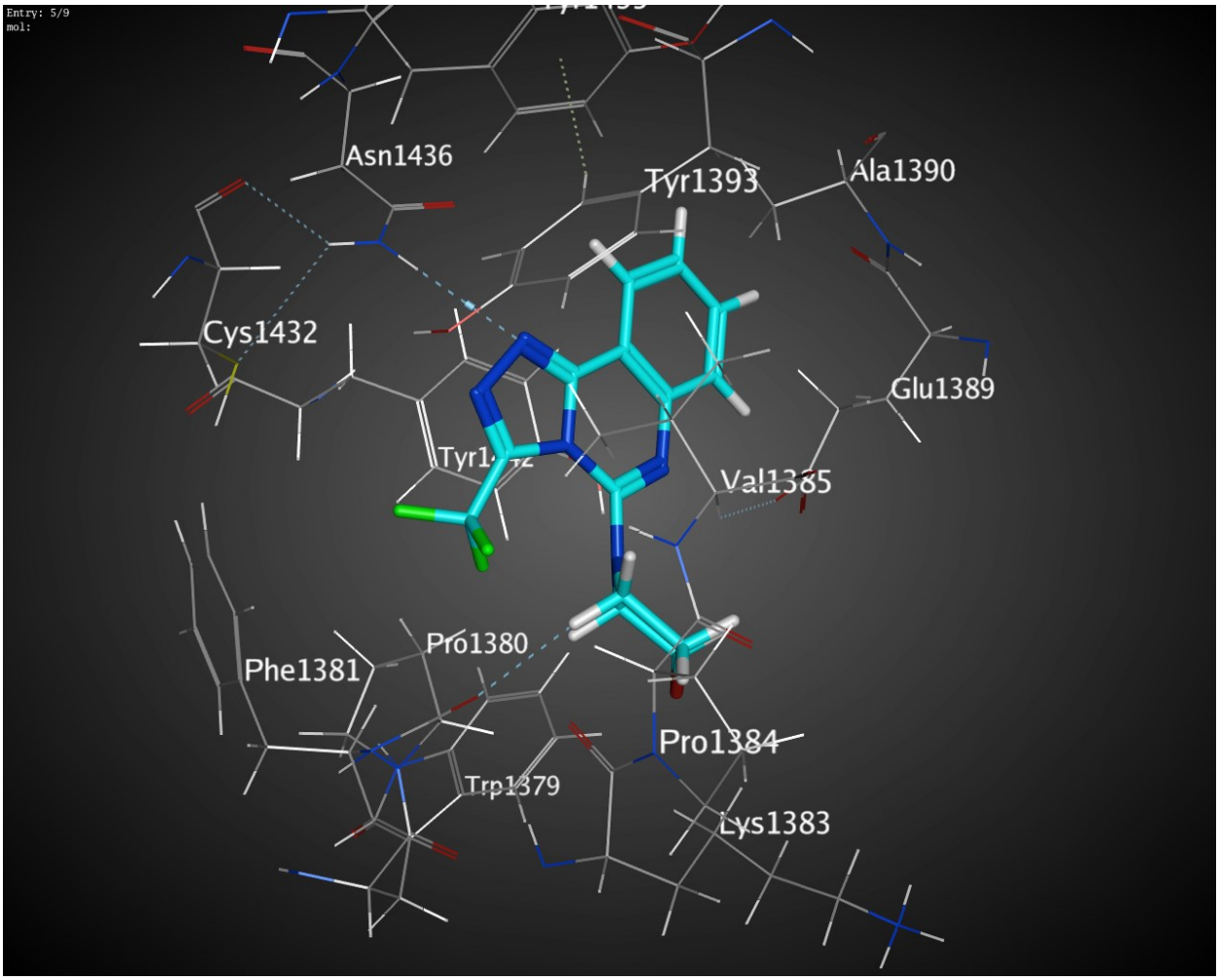
Ligand Receptor Interaction Distance E (kcal/mol)

N 13 ND2 ASN 1436 (A) H-acceptor 3.45 -0.8

5-ring 6-ring TYR 1442 (A) pi-pi 3.84 -0.0

6-ring 6-ring TYR 1442 (A) pi-pi 3.78 -0.0




Entry: 5/9
mol:
Asn1436
Tyr1393
Ala1390
Cys1432
Glu1389
Val1385
Pro1380
Phe1381
Pro1384
Trp1379
Lys1383

Predicted binding mode of 28

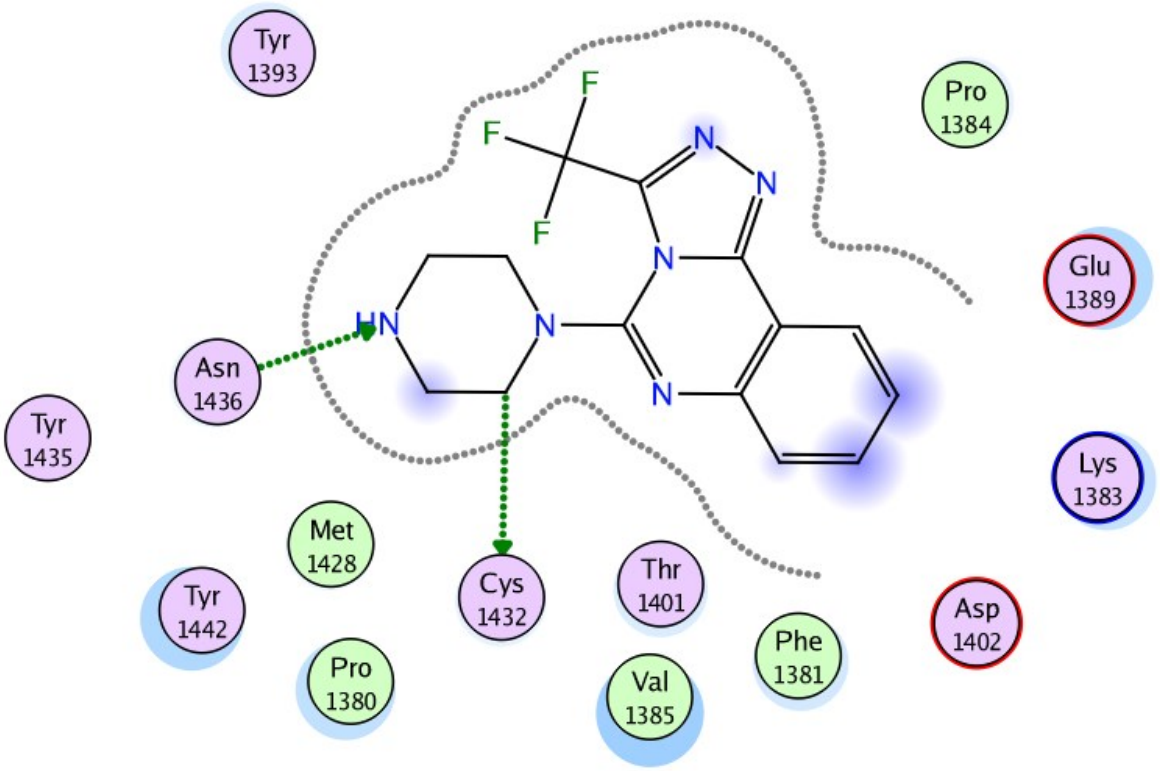
Score -9.7896881 RMSD 0.8089

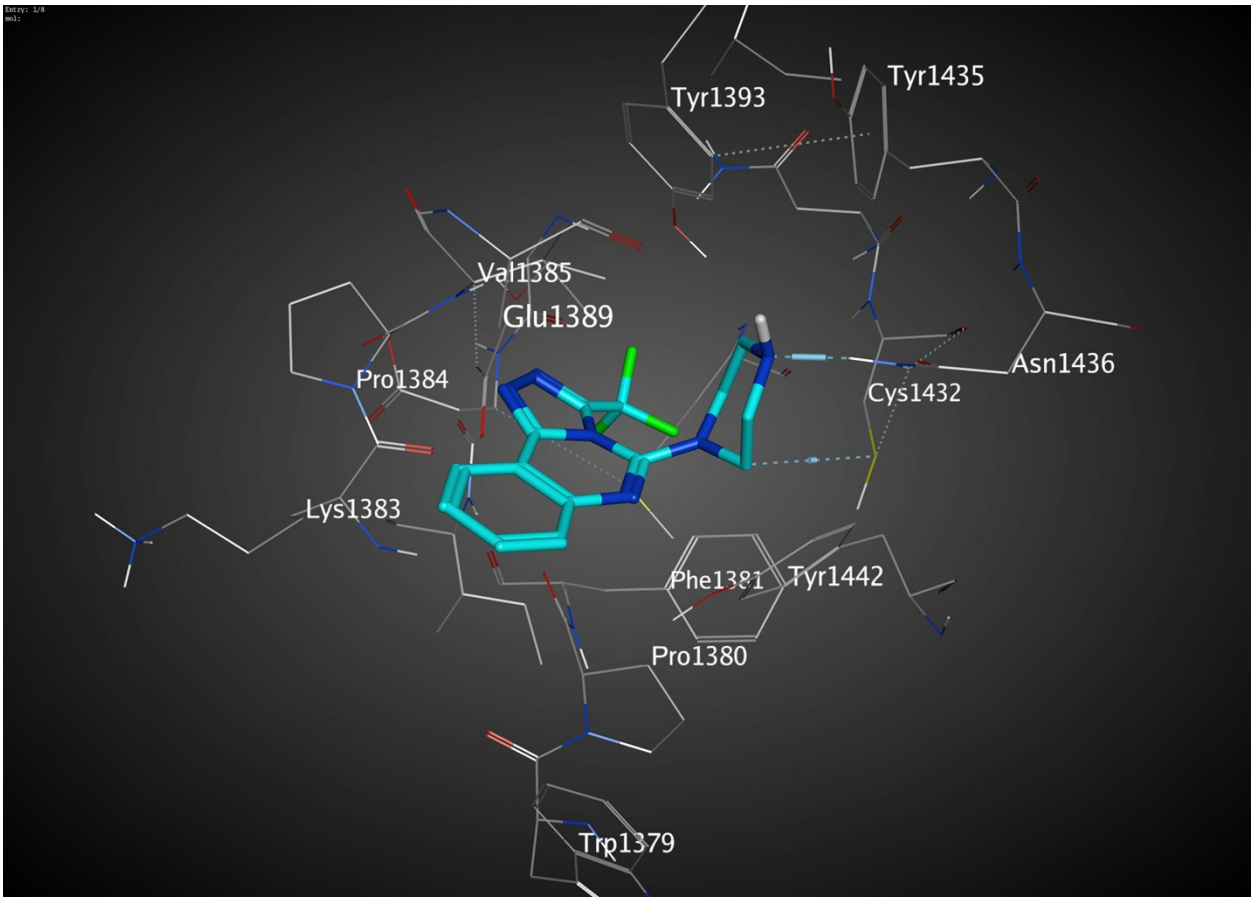
Ligand Interactions Report

Ligand Receptor Interaction Distance E (kcal/mol)

C 15 SG CYS 1432 (A) H-donor 3.76 -0.7

N 17 ND2 ASN 1436 (A) H-acceptor 2.71 -3.9




Tyr1393
Tyr1435
Val1385
Glu1389
Pro1384
Asn1436
Cys1432
Lys1383
Phe1381
Tyr1442
Pro1380
Trp1379

Predicted binding mode of 29

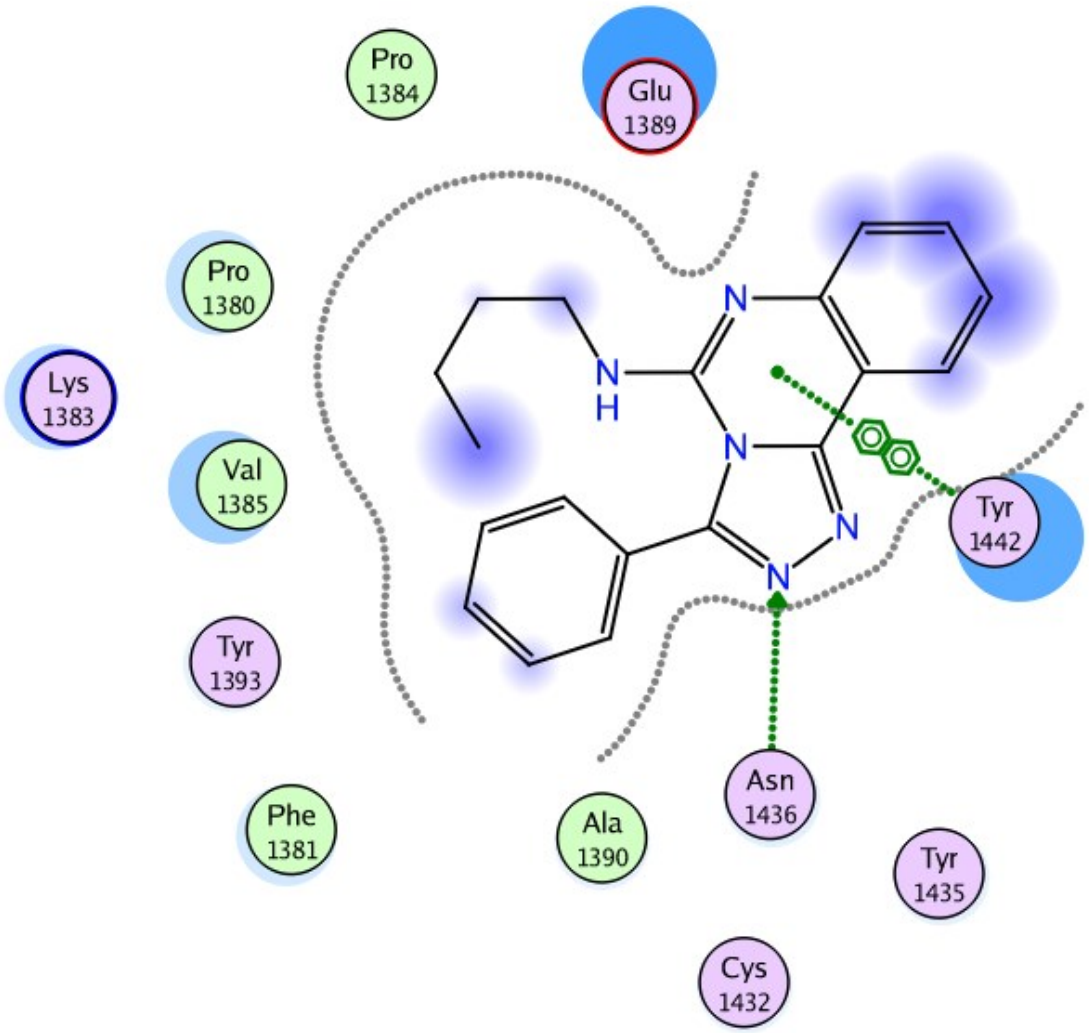
Score -11.5561466 RMSD 1.1623

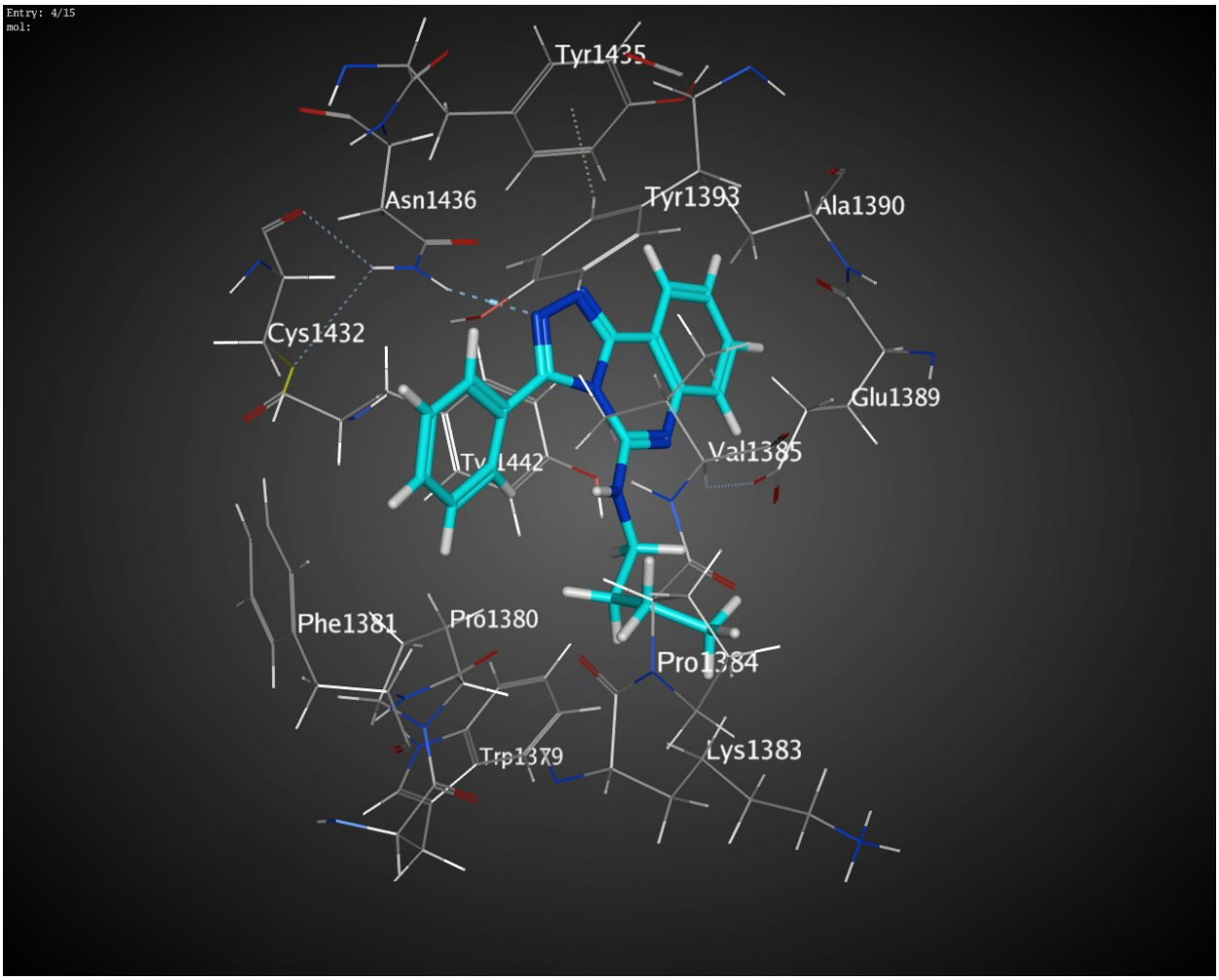
Ligand Interactions Report

Ligand Receptor Interaction Distance E (kcal/mol)

N 12 ND2 ASN 1436 (A) H-acceptor 3.11 -1.0

6-ring 6-ring TYR 1442 (A) pi-pi 3.98 -0.0




Entry: 4/15
mol:
Tyr1435
Asn1436
Tyr1393
Ala1390
Cys1432
Glu1389
Val1385
Phe1381
Pro1380
Pro1384
Trp1379
Lys1383

Predicted binding mode of 30

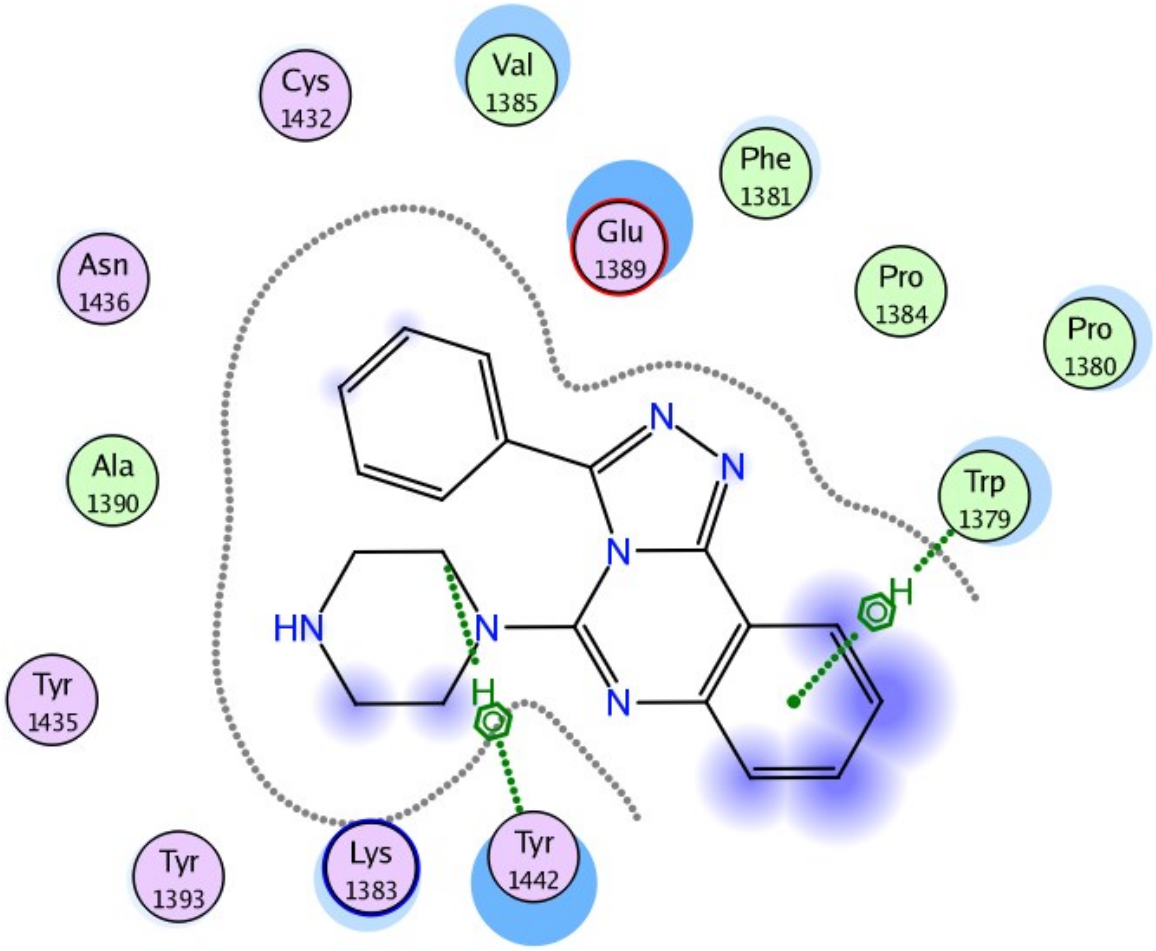
Score -10.0245259 RMSD 1.2001

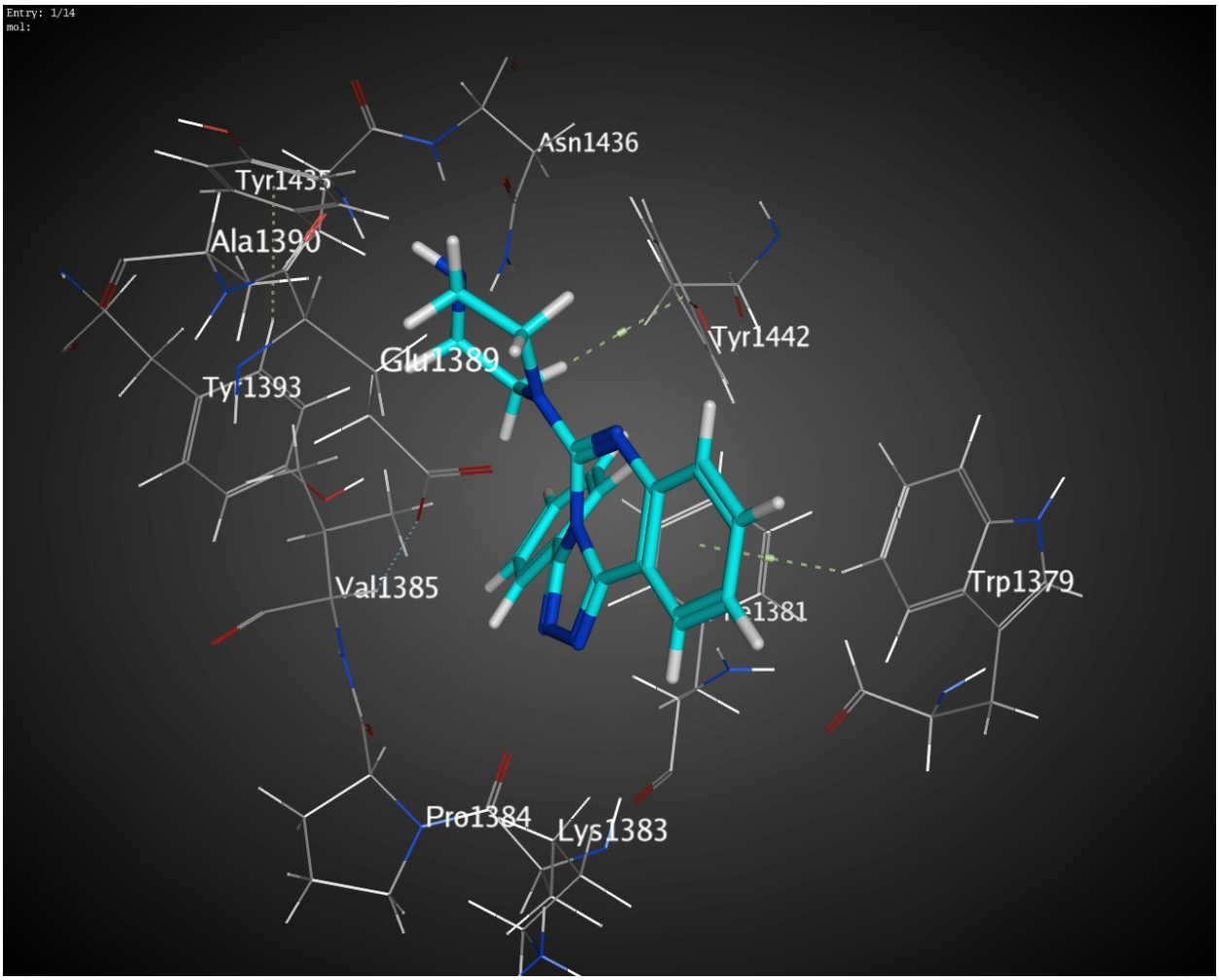
Ligand Interactions Report

Ligand Receptor Interaction Distance E (kcal/mol)

C 20 6-ring TYR 1442 (A) H-pi 3.74 -0.9

6-ring CZ3 TRP 1379 (A) pi-H 4.15 -0.7




Entry: 1/14
mol:
Asn1436
Tyr1435
Ala1390
Glu1389
Tyr1442
Tyr1393
Val1385
Trp1379
Pro1384
Lys1383

Predicted binding mode of 31

Score -9.5325899 RMSD 1.0643

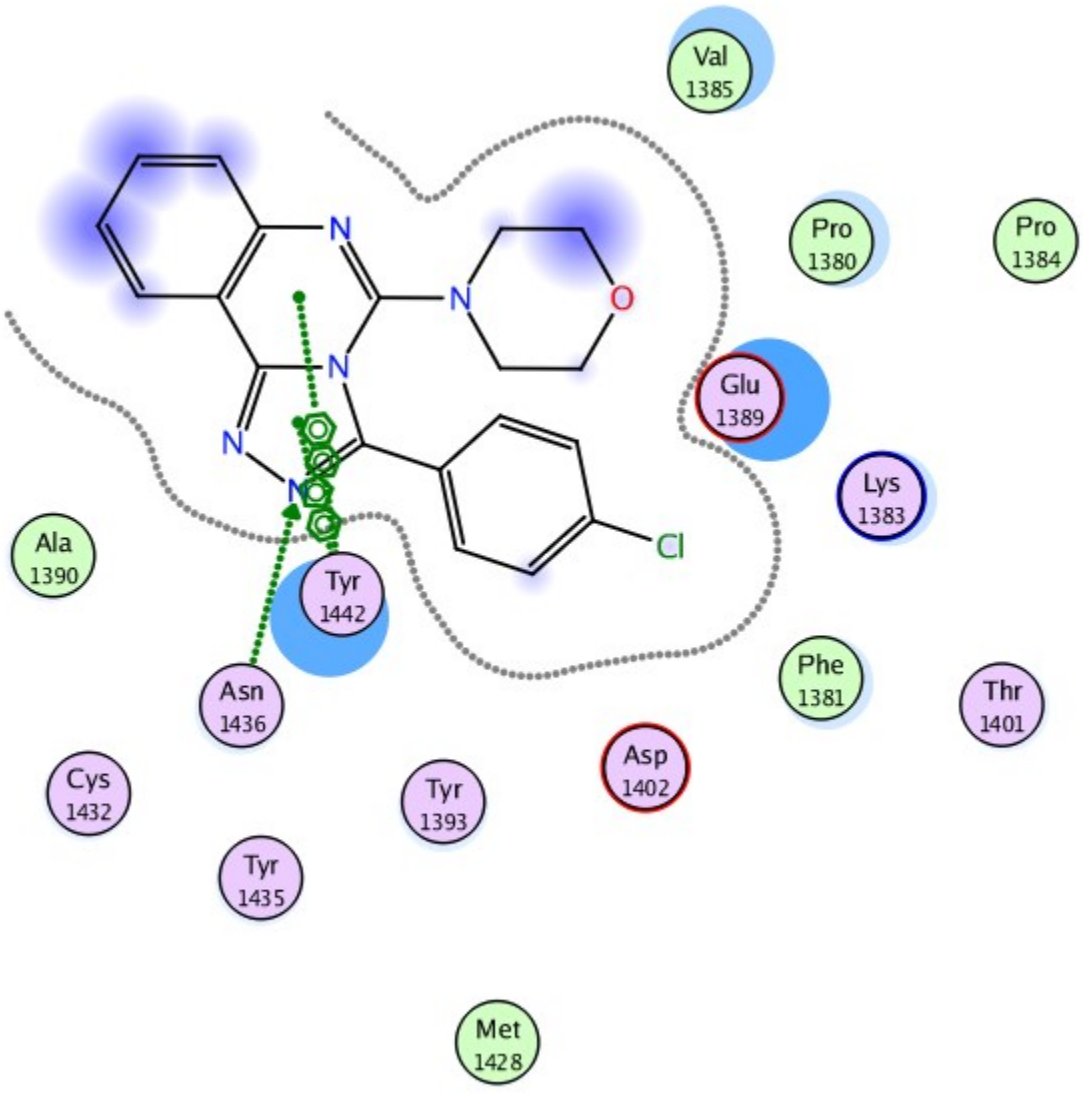
Ligand Interactions Report

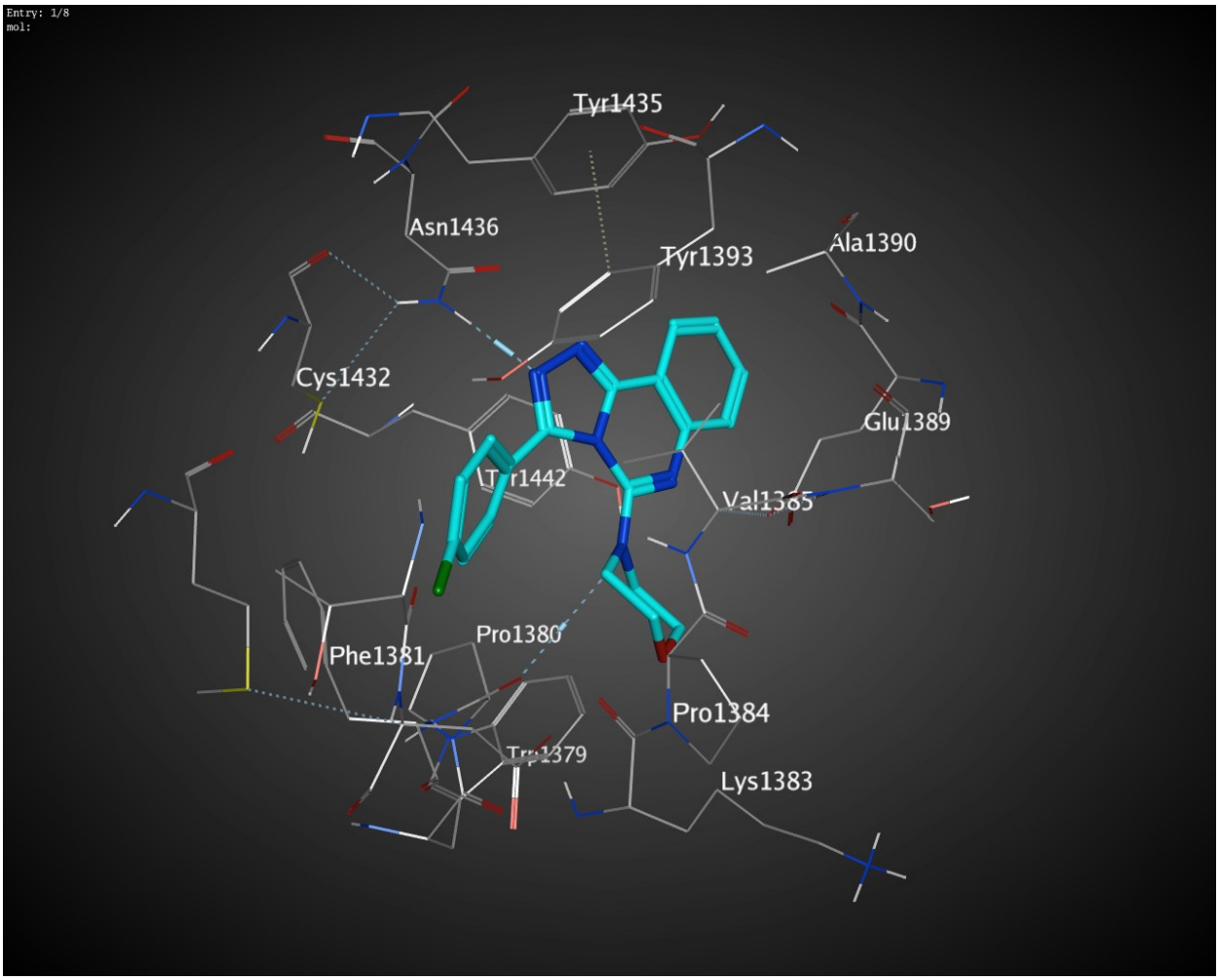
Ligand Receptor Interaction Distance E (kcal/mol)

N 12 ND2 ASN 1436 (A) H-acceptor 2.93 -3.3

5-ring 6-ring TYR 1442 (A) pi-pi 3.76 -0.0

6-ring 6-ring TYR 1442 (A) pi-pi 3.75 -0.0




Entry: 1/8
mol:
Tyr1435
Asn1436
Tyr1393
Ala1390
Cys1432
Glu1389
Tyr1442
Val1385
Pro1380
Phe1381
Pro1384
Trp1379
Lys1383

Predicted binding mode of 32

Score -9.55867863 RMSD 0.8899

Ligand Interactions Report

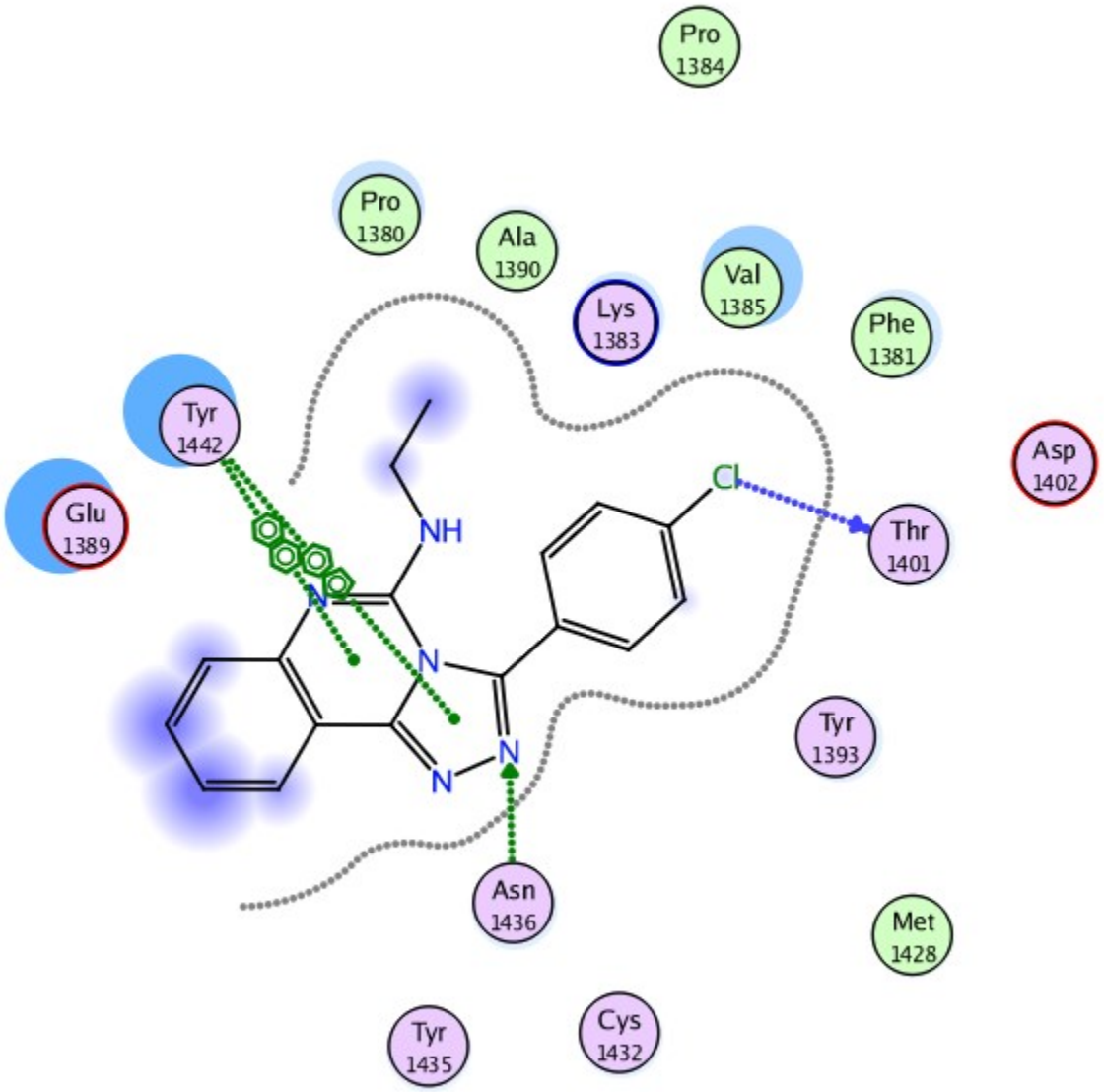
Ligand Receptor Interaction Distance E (kcal/mol)

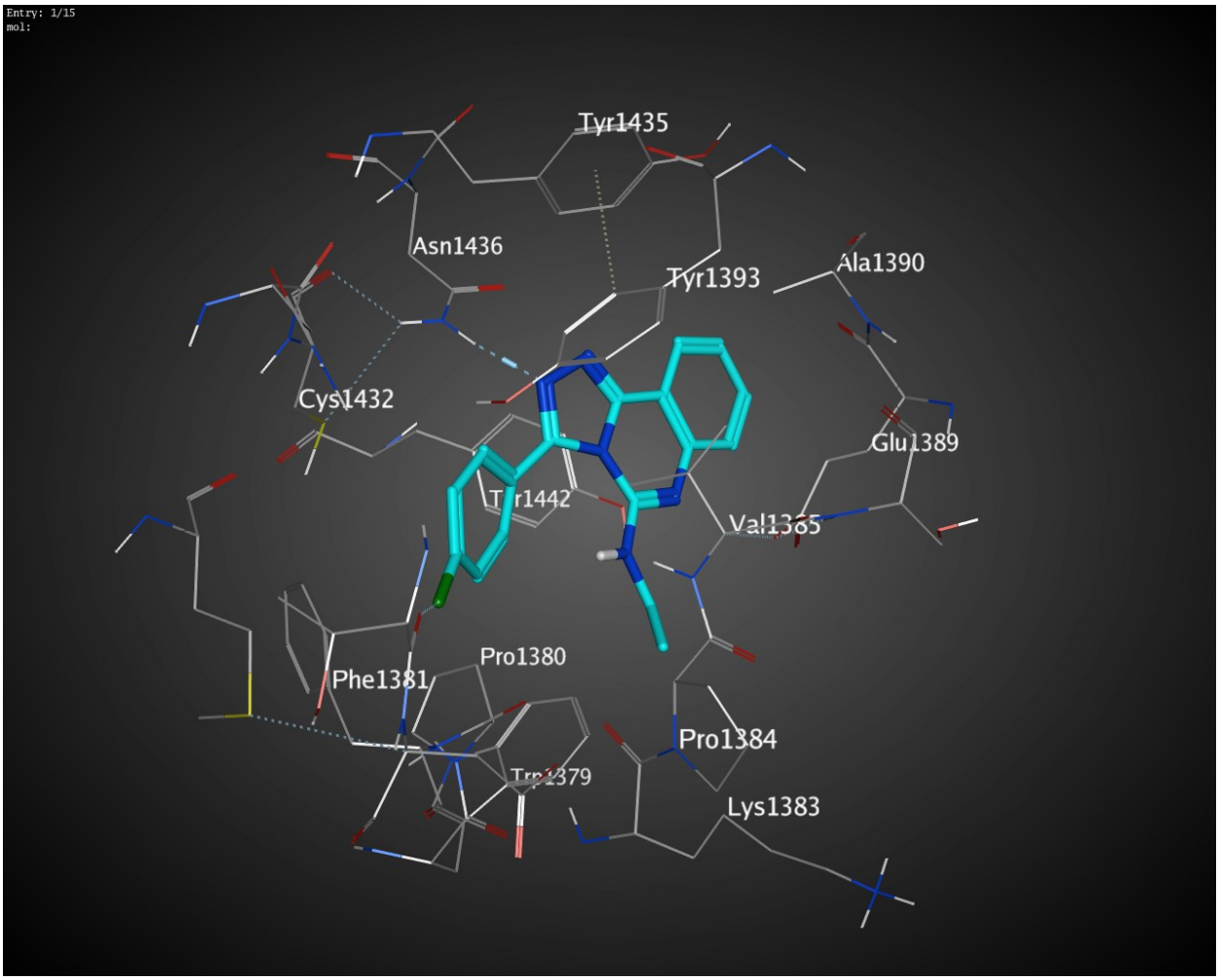
CL 23 O THR 1401 (A) H-donor 3.44 -0.5

N 12 ND2 ASN 1436 (A) H-acceptor 2.85 -1.7

5-ring 6-ring TYR 1442 (A) pi-pi 3.91 -0.0

6-ring 6-ring TYR 1442 (A) pi-pi 3.79 -0.0




Entry: 1/15
mol:
Tyr1435
Asn1436
Tyr1393
Ala1390
Cys1432
Glu1389
Tyr1442
Val1385
Pro1380
Phe1381
Pro1384
Trp1379
Lys1383

Predicted binding mode of 33

Score -10.8010445 RMSD 0.9960

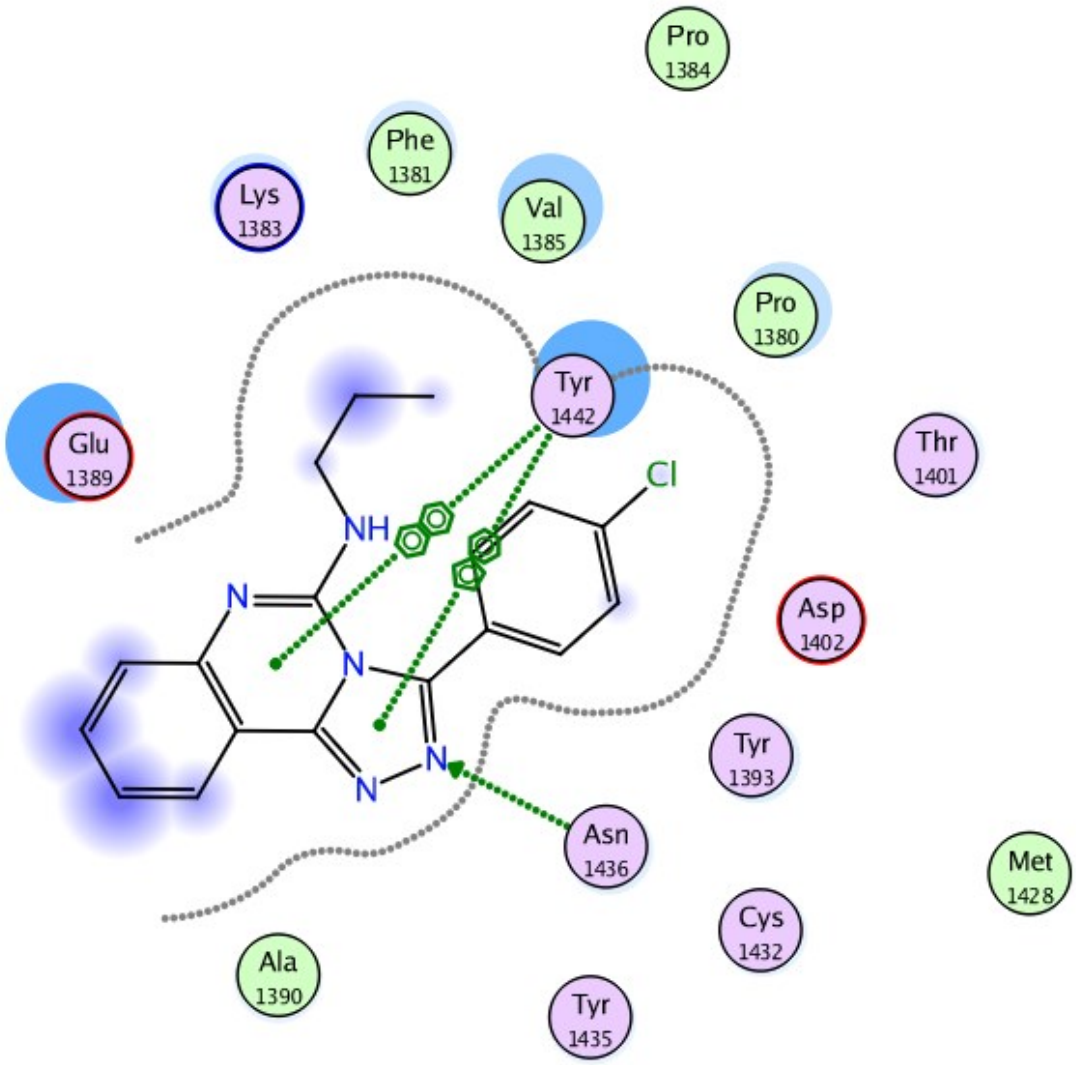
Ligand Interactions Report

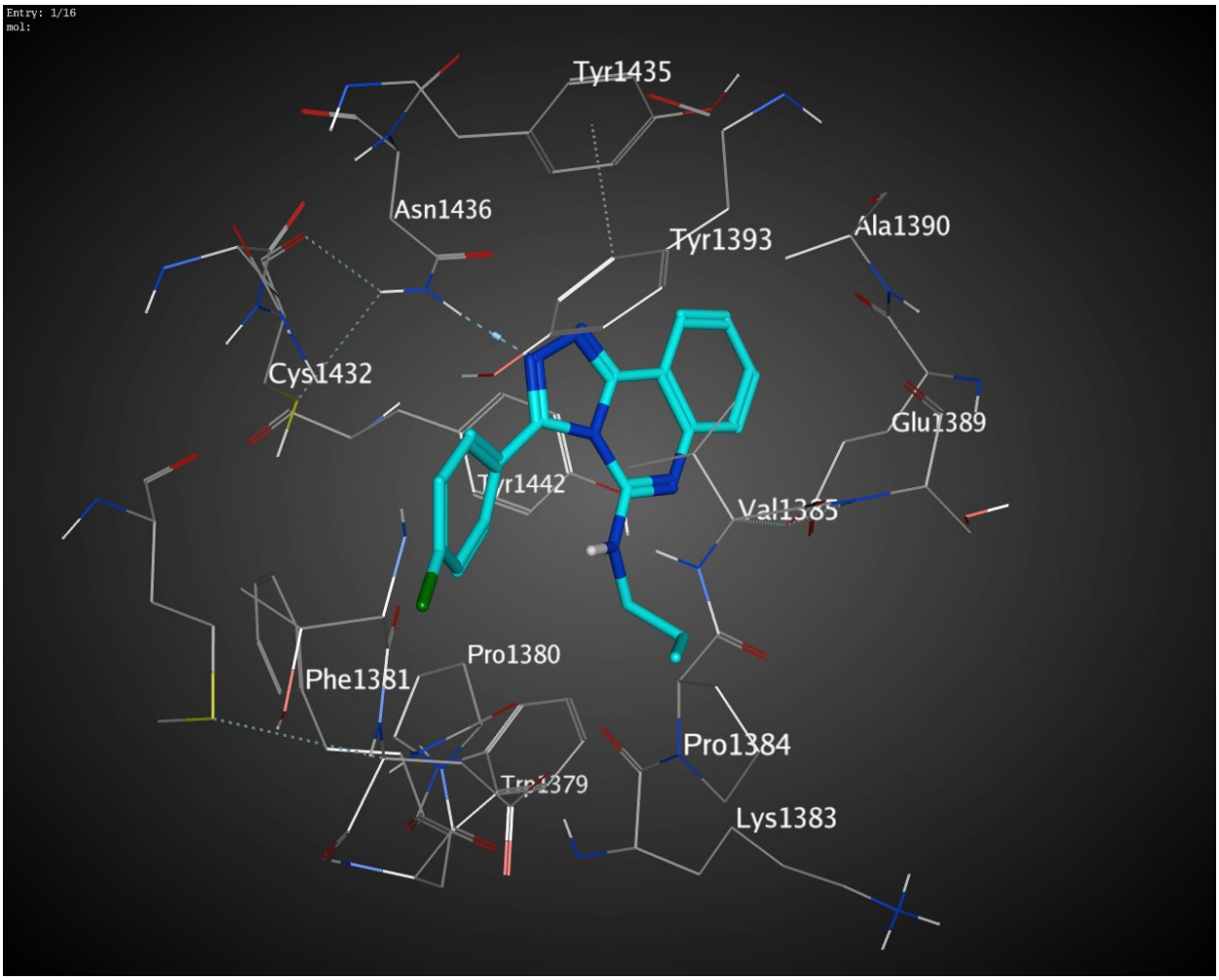
Ligand Receptor Interaction Distance E (kcal/mol)

N 12 ND2 ASN 1436 (A) H-acceptor 2.85 -1.2

5-ring 6-ring TYR 1442 (A) pi-pi 3.96 -0.0

6-ring 6-ring TYR 1442 (A) pi-pi 3.75 -0.0




Entry: 1/16
mol:
Tyr1435
Asn1436
Tyr1393
Ala1390
Cys1432
Glu1389
Tyr1442
Val1385
Pro1380
Phe1381
Pro1384
Trp1379
Lys1383

Predicted binding mode of 34

Score -9.7841425 RMSD 1.1640

Ligand Interactions Report

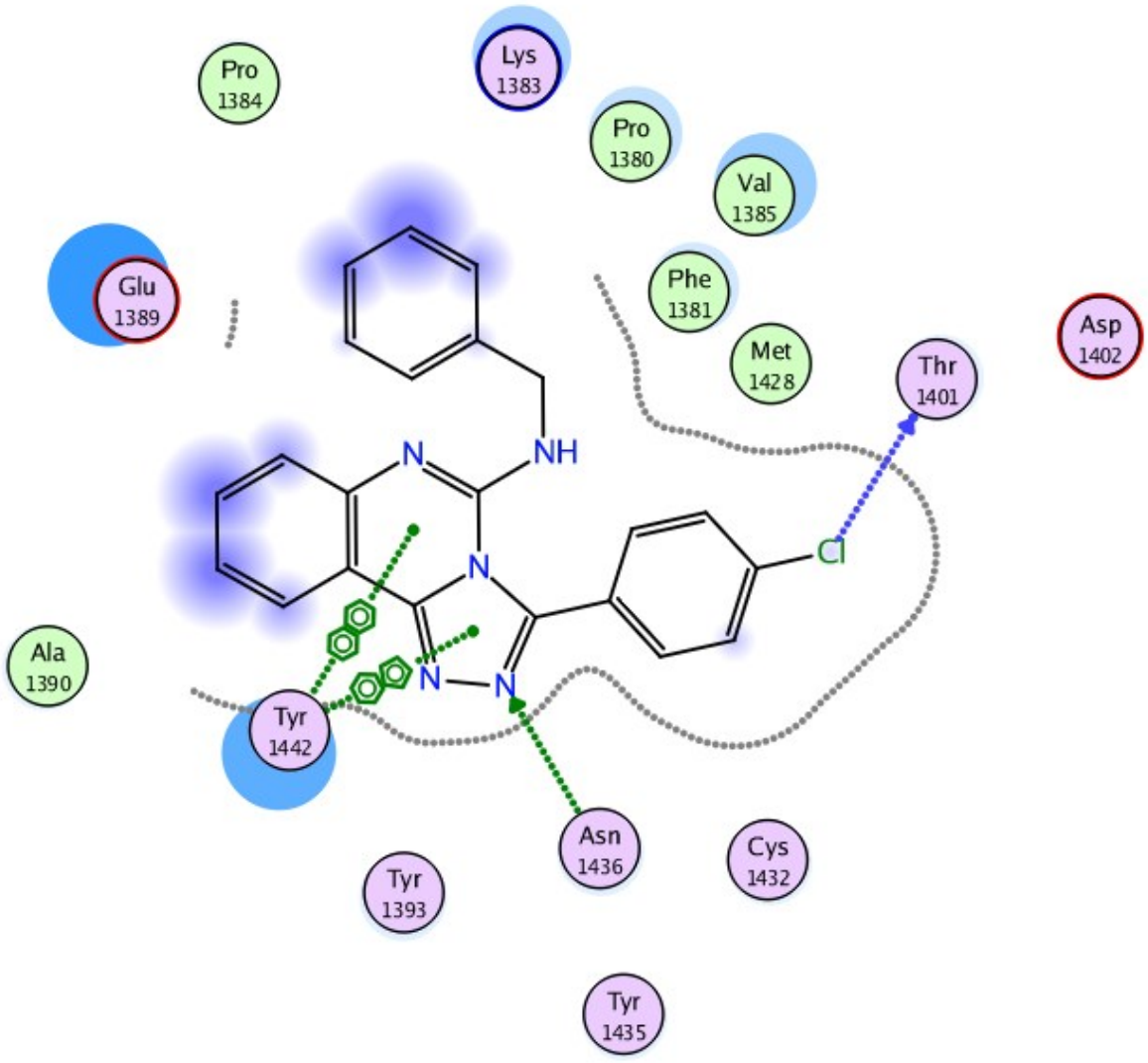
Ligand Receptor Interaction Distance E (kcal/mol)

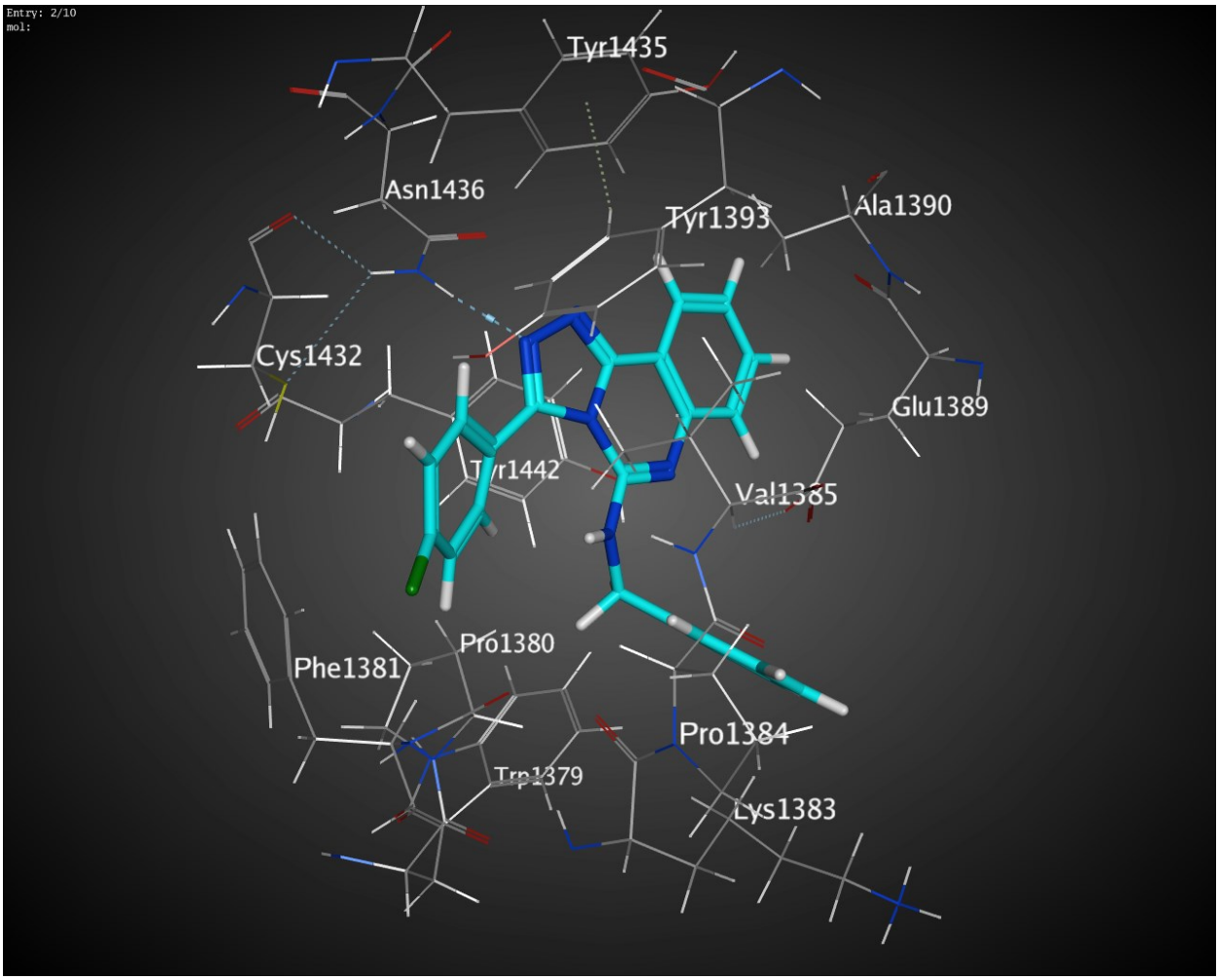
CL 23 O THR 1401 (A) H-donor 3.42 -0.3

N 12 ND2 ASN 1436 (A) H-acceptor 2.87 -1.4

5-ring 6-ring TYR 1442 (A) pi-pi 3.95 -0.0

6-ring 6-ring TYR 1442 (A) pi-pi 3.75 -0.0




Entry: 2/10
mol:
Tyr1435
Asn1436
Tyr1393
Ala1390
Cys1432
Glu1389
Tyr1442
Val1385
Pro1380
Phe1381
Pro1384
Trp1379
Lys1383

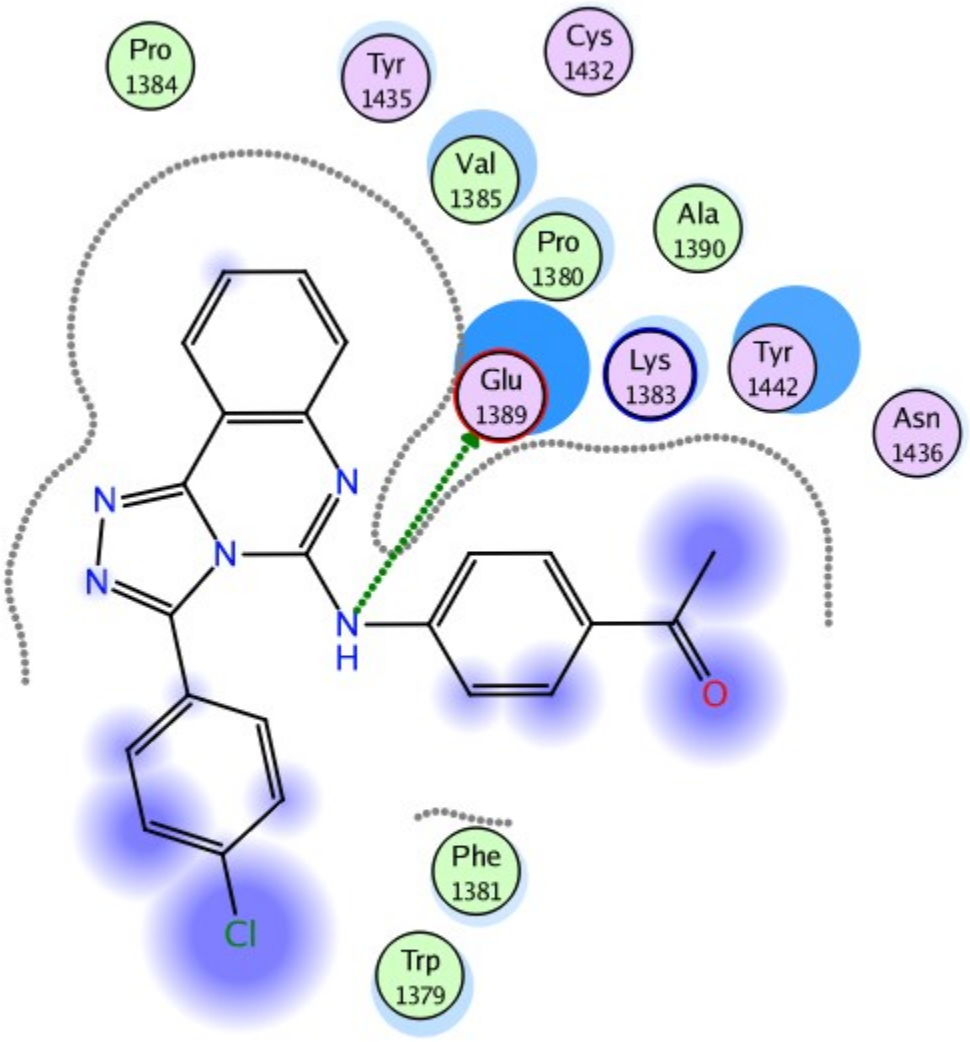
Predicted binding mode of 35

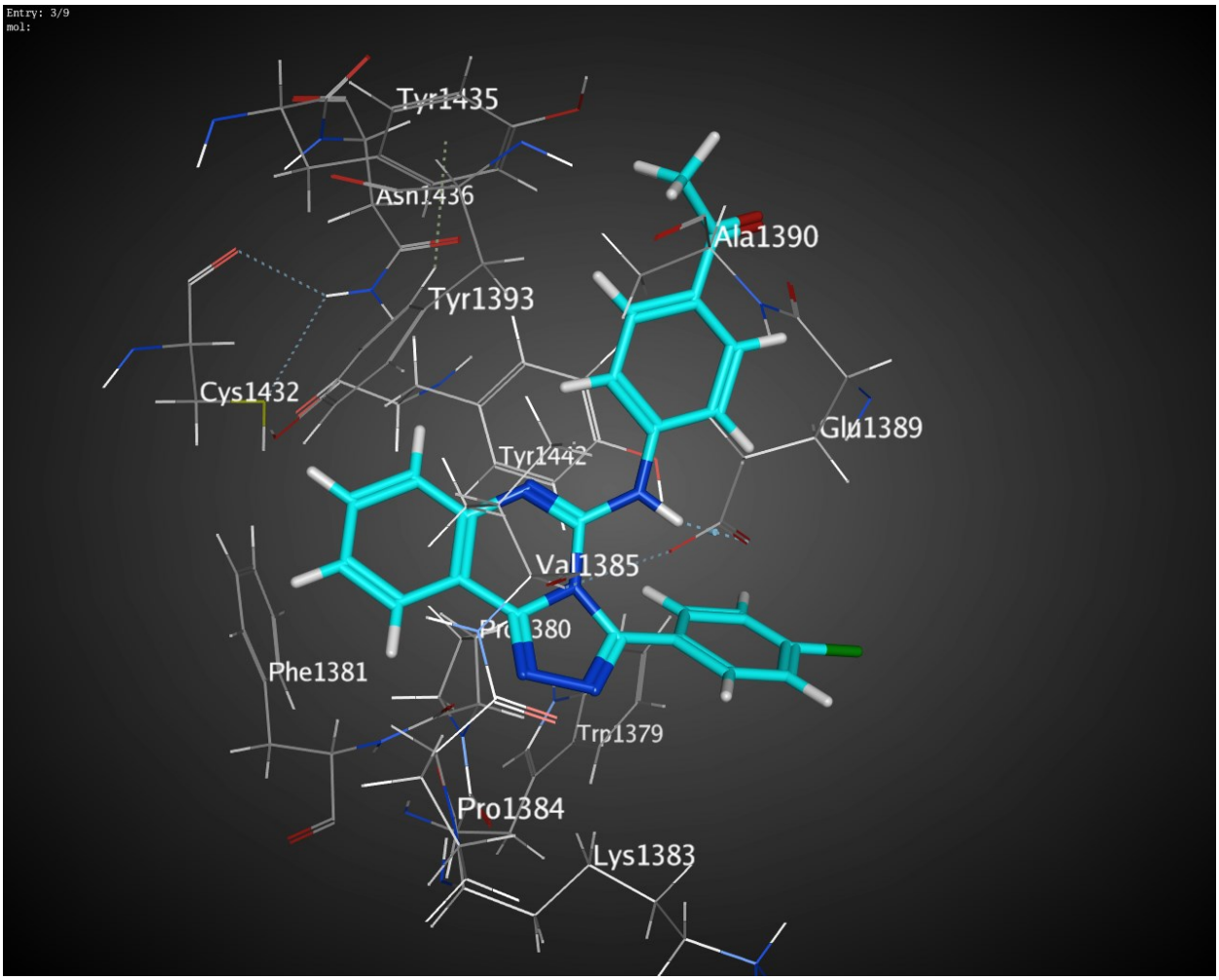
Score -9.899581 RMSD 1.1064

Ligand Interactions Report

Ligand Receptor Interaction Distance E (kcal/mol)

N 14 OE1 GLU 1389 (A) H-donor 2.97 -1.2




Entry: 3/9
mol:
Tyr1435
Asn1436
Ala1390
Tyr1393
Cys1432
Glu1389
Tyr1442
Val1385
Phe1381
Trp1379
Pro1384
Lys1383

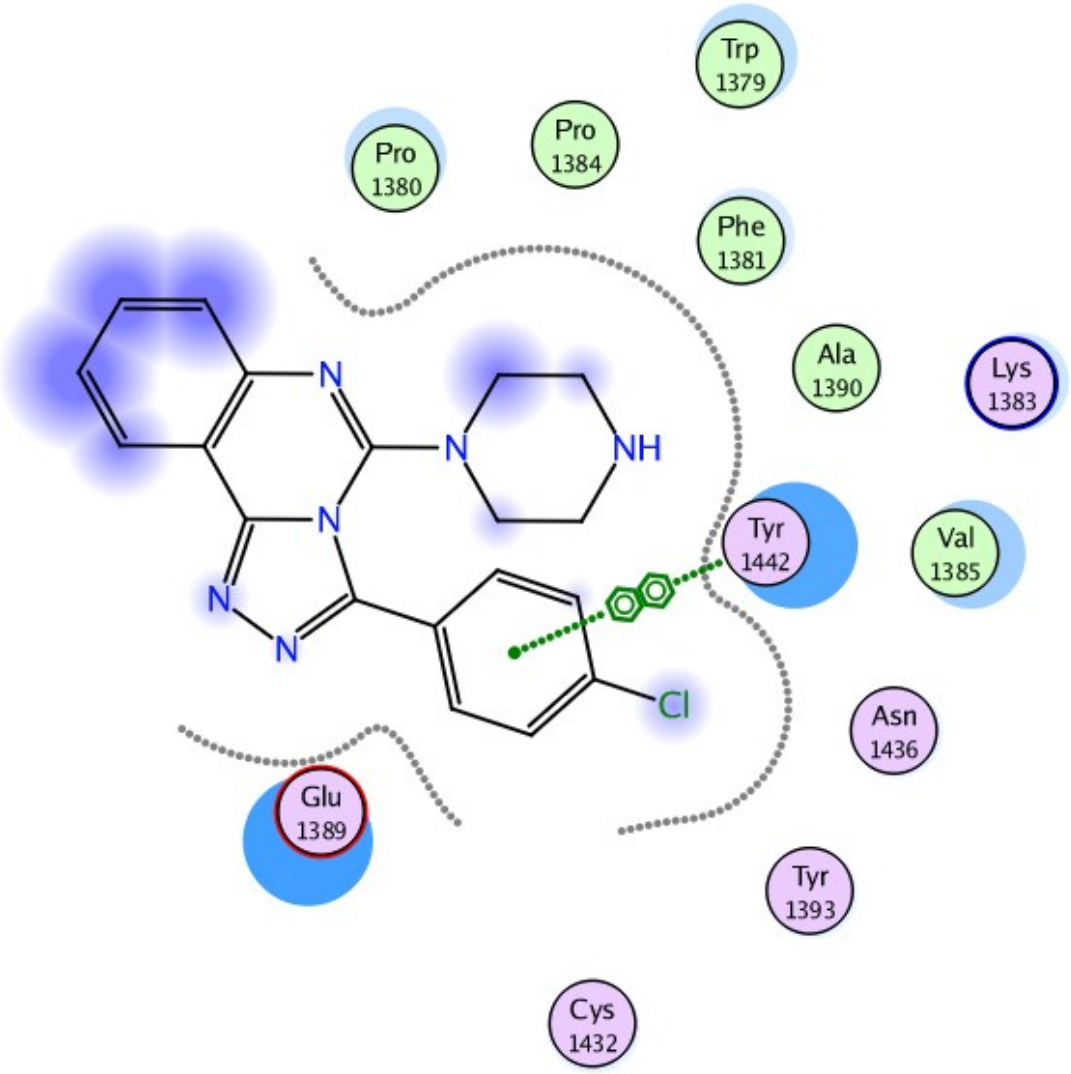
Predicted binding mode of 36

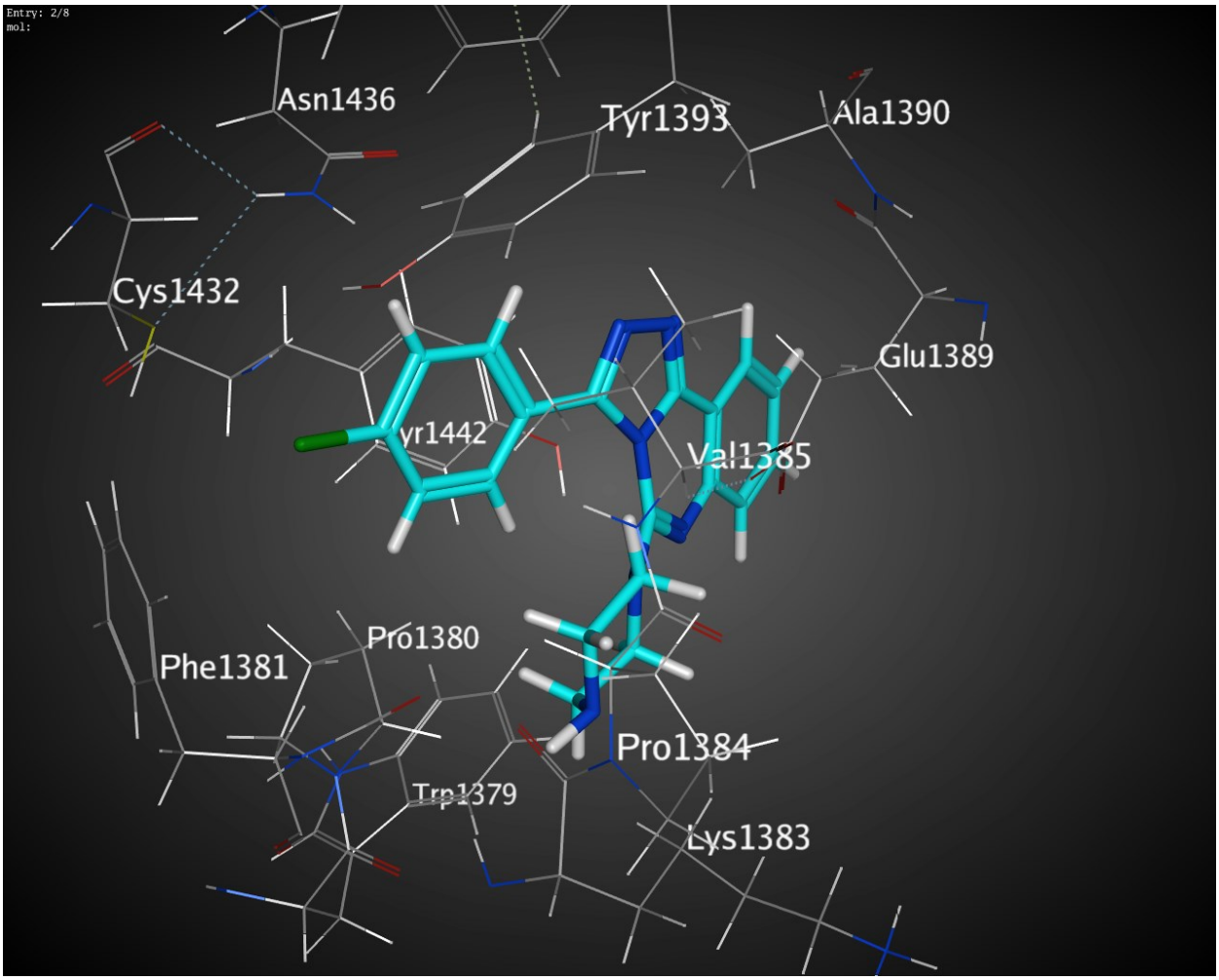
Score -9.9297094 RMSD 1.1946

Ligand Interactions Report

Ligand Receptor Interaction Distance E (kcal/mol)

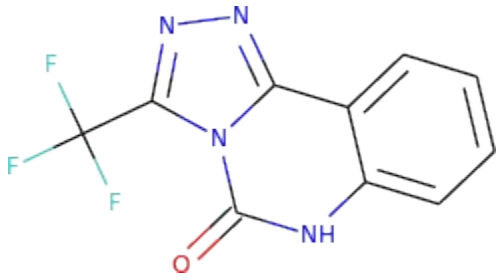
6-ring 6-ring TYR 1442 (A) pi-pi 3.93 -0.0




Entry: 2/8
mol:
Asn1436
Tyr1393
Ala1390
Cys1432
Glu1389
yr1442
Val1385
Pro1380
Phe1381
Pro1384
Trp1379
Lys1383

In silico Pharmacokinetic Studies

Pharmacokinetic Properties of 21



Molecule properties:

Descriptor	Value
Molecular Weight	254.171
LogP	1.5896
#Rotatable Bonds	0
#Acceptors	4
#Donors	1
Surface Area	96.882

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	**-4.042**	Numeric (log mol/L)
Absorption	Caco2 permeability	**0.523**	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption	92.599	Numeric (% Absorbed)

Descriptor	Value		
	(human)		
Absorption	Skin Permeability	-3.032	Numeric (log Kp)
Absorption	P-glycoprotein substrate	No	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	No	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	No	Categorical (Yes/No)
Distribution	VDss (human)	-0.378	Numeric (log L/kg)
Distribution	Fraction unbound (human)	0.321	Numeric (Fu)
Distribution	BBB permeability	0.449	Numeric (log BB)
Distribution	CNS permeability	-2.28	Numeric (log PS)
Metabolism	CYP2D6 substrate	No	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	No	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	Yes	Categorical (Yes/No)

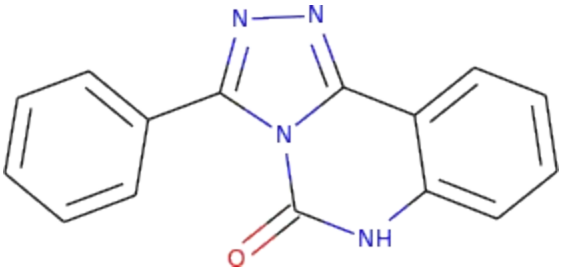
Descriptor	Value		
Metabolism	CYP2C19 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitior	No	Categorical (Yes/No)
Excretion	Total Clearance	0.27	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	No	Categorical (Yes/No)
Toxicity	AMES toxicity	Yes	Categorical (Yes/No)
Toxicity	Max. tolerated dose (human)	-0.2	Numeric (log mg/kg/day)
Toxicity	hERG I inhibitor	No	Categorical (Yes/No)
Toxicity	hERG II inhibitor	No	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	2.613	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	1.367	Numeric (log mg/kg_bw/day)

Descriptor	Value		
Toxicity	Hepatotoxicity	Yes	Categorical (Yes/No)
Toxicity	Skin Sensitisation	No	Categorical (Yes/No)
Toxicity	T.Pyriformis toxicity	0.606	Numeric (log ug/L)
Toxicity	Minnow toxicity	1.661	Numeric (log mM)

Top of Form

Bottom of Form

Pharmacokinetic Properties of 22



Molecule properties:

Descriptor	Value
Molecular Weight	262.272
LogP	2.2378
#Rotatable Bonds	1
#Acceptors	4

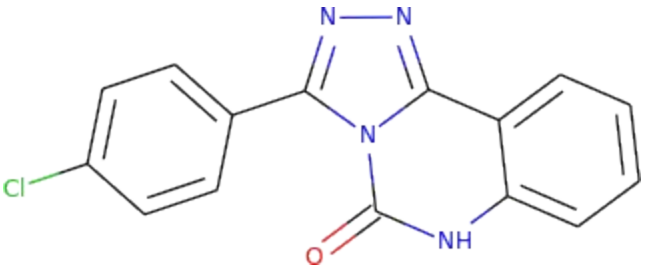
Descriptor	Value
#Donors	1
Surface Area	113.077

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	-3.398	Numeric (log mol/L)
Absorption	Caco2 permeability	0.734	Numeric (log Papp in 10-6 cm/s)
Absorption	Intestinal absorption (human)	96.169	Numeric (% Absorbed)
Absorption	Skin Permeability	-2.753	Numeric (log Kp)
Absorption	P-glycoprotein substrate	Yes	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	No	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	No	Categorical (Yes/No)
Distribution	VDss (human)	-0.2	Numeric (log L/kg)
Distribution	Fraction unbound (human)	0.133	Numeric (Fu)

Descriptor	Value		
Distribution	BBB permeability	0.58	Numeric (log BB)
Distribution	CNS permeability	-2.097	Numeric (log PS)
Metabolism	CYP2D6 substrate	No	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	Yes	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP2C19 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitior	Yes	Categorical (Yes/No)
Excretion	Total Clearance	0.784	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	No	Categorical (Yes/No)
Toxicity	AMES toxicity	Yes	Categorical (Yes/No)

Descriptor	Value		
Toxicity	Max. tolerated dose (human)	0.407	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)	2.749	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	1.368	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	Yes	Categorical (Yes/No)
Toxicity	Skin Sensitisation	No	Categorical (Yes/No)
Toxicity	T.Pyriformis toxicity	0.31	Numeric (log ug/L)
Toxicity	Minnow toxicity	0.618	Numeric (log mM)

Pharmacokinetic Properties of 23



Molecule properties:

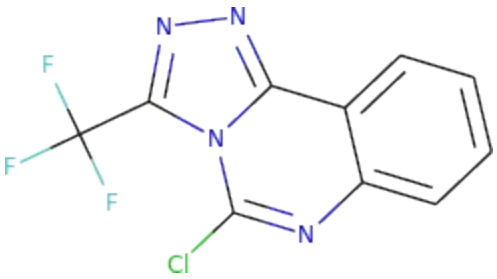
Descriptor	Value
Molecular Weight	296.717
LogP	2.8912
#Rotatable Bonds	1
#Acceptors	4
#Donors	1
Surface Area	123.381

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	-3.509	Numeric (log mol/L)
Absorption	Caco2 permeability	0.829	Numeric (log Papp in 10-6 cm/s)
Absorption	Intestinal absorption (human)	94.648	Numeric (% Absorbed)
Absorption	Skin Permeability	-2.757	Numeric (log Kp)
Absorption	P-glycoprotein substrate	Yes	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	No	Categorical (Yes/No)

Descriptor	Value		
Absorption	P-glycoprotein II inhibitor	No	Categorical (Yes/No)
Distribution	VDss (human)	-0.116	Numeric (log L/kg)
Distribution	Fraction unbound (human)	0.144	Numeric (Fu)
Distribution	BBB permeability	0.535	Numeric (log BB)
Distribution	CNS permeability	-1.98	Numeric (log PS)
Metabolism	CYP2D6 substrate	No	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	Yes	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP2C19 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitior	Yes	Categorical (Yes/No)

Descriptor	Value		
Excretion	Total Clearance	-0.038	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	No	Categorical (Yes/No)
Toxicity	AMES toxicity	Yes	Categorical (Yes/No)
Toxicity	Max. tolerated dose (human)	0.389	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)	2.753	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	1.308	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	Yes	Categorical (Yes/No)
Toxicity	Skin Sensitisation	No	Categorical (Yes/No)
Toxicity	T.Pyriformis toxicity	0.315	Numeric (log ug/L)
Toxicity	Minnow toxicity	0.143	Numeric (log mM)

Pharmacokinetic Properties of 24



Molecule properties:

Descriptor	Value
Molecular Weight	272.617
LogP	2.9497
#Rotatable Bonds	0
#Acceptors	4
#Donors	0
Surface Area	103.023

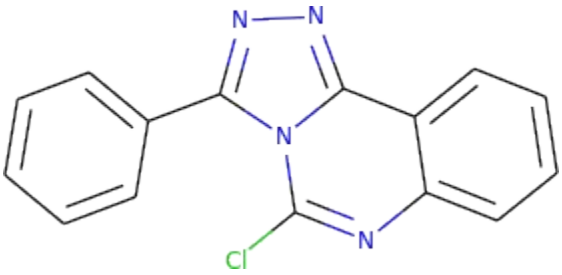
Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	-3.711	Numeric (log mol/L)
Absorption	Caco2 permeability	1.751	Numeric (log Papp in 10-6 cm/s)
Absorption	Intestinal absorption	93.989	Numeric (%

Descriptor	Value		
	(human)		Absorbed)
Absorption	Skin Permeability	-2.582	Numeric (log Kp)
Absorption	P-glycoprotein substrate	No	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	No	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	No	Categorical (Yes/No)
Distribution	VDss (human)	-0.304	Numeric (log L/kg)
Distribution	Fraction unbound (human)	0.223	Numeric (Fu)
Distribution	BBB permeability	0.918	Numeric (log BB)
Distribution	CNS permeability	-1.664	Numeric (log PS)
Metabolism	CYP2D6 substrate	No	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	Yes	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	Yes	Categorical (Yes/No)

Descriptor	Value		
Metabolism	CYP2C19 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitior	No	Categorical (Yes/No)
Excretion	Total Clearance	0.133	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	No	Categorical (Yes/No)
Toxicity	AMES toxicity	Yes	Categorical (Yes/No)
Toxicity	Max. tolerated dose (human)	-0.079	Numeric (log mg/kg/day)
Toxicity	hERG I inhibitor	No	Categorical (Yes/No)
Toxicity	hERG II inhibitor	No	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	2.713	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	1.642	Numeric (log mg/kg_bw/day)

Descriptor	Value		
Toxicity	Hepatotoxicity	Yes	Categorical (Yes/No)
Toxicity	Skin Sensitisation	No	Categorical (Yes/No)
Toxicity	T.Pyriformis toxicity	0.5	Numeric (log ug/L)
Toxicity	Minnow toxicity	0.693	Numeric (log mM)

Pharmacokinetic Properties



Molecule properties:

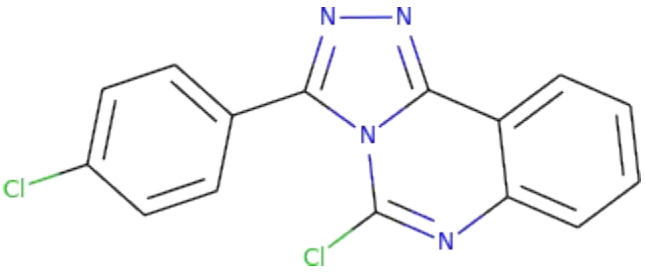
Descriptor	Value
Molecular Weight	280.718
LogP	3.5979
#Rotatable Bonds	1
#Acceptors	4
#Donors	0
Surface Area	119.219

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	-3.458	Numeric (log mol/L)
Absorption	Caco2 permeability	1.607	Numeric (log Papp in 10-6 cm/s)
Absorption	Intestinal absorption (human)	97.685	Numeric (% Absorbed)
Absorption	Skin Permeability	-2.731	Numeric (log Kp)
Absorption	P-glycoprotein substrate	No	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	No	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	Yes	Categorical (Yes/No)
Distribution	VDss (human)	0.095	Numeric (log L/kg)
Distribution	Fraction unbound (human)	0.248	Numeric (Fu)
Distribution	BBB permeability	1.011	Numeric (log BB)
Distribution	CNS permeability	-1.4	Numeric (log PS)

Descriptor	Value		
Metabolism	CYP2D6 substrate	No	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	Yes	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP2C19 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitior	No	Categorical (Yes/No)
Excretion	Total Clearance	0.215	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	No	Categorical (Yes/No)
Toxicity	AMES toxicity	Yes	Categorical (Yes/No)
Toxicity	Max. tolerated dose (human)	0.535	Numeric (log mg/kg/day)
Toxicity	hERG I inhibitor	No	Categorical (Yes/No)

Descriptor	Value		
Toxicity	hERG II inhibitor	No	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	2.436	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	0.853	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	Yes	Categorical (Yes/No)
Toxicity	Skin Sensitisation	No	Categorical (Yes/No)
Toxicity	T.Pyriformis toxicity	0.293	Numeric (log ug/L)
Toxicity	Minnow toxicity	-0.048	Numeric (log mM)

Pharmacokinetic Properties of 26



Molecule properties:

Descriptor	Value
Molecular Weight	315.163

Descriptor	Value
LogP	4.2513
#Rotatable Bonds	1
#Acceptors	4
#Donors	0
Surface Area	129.522

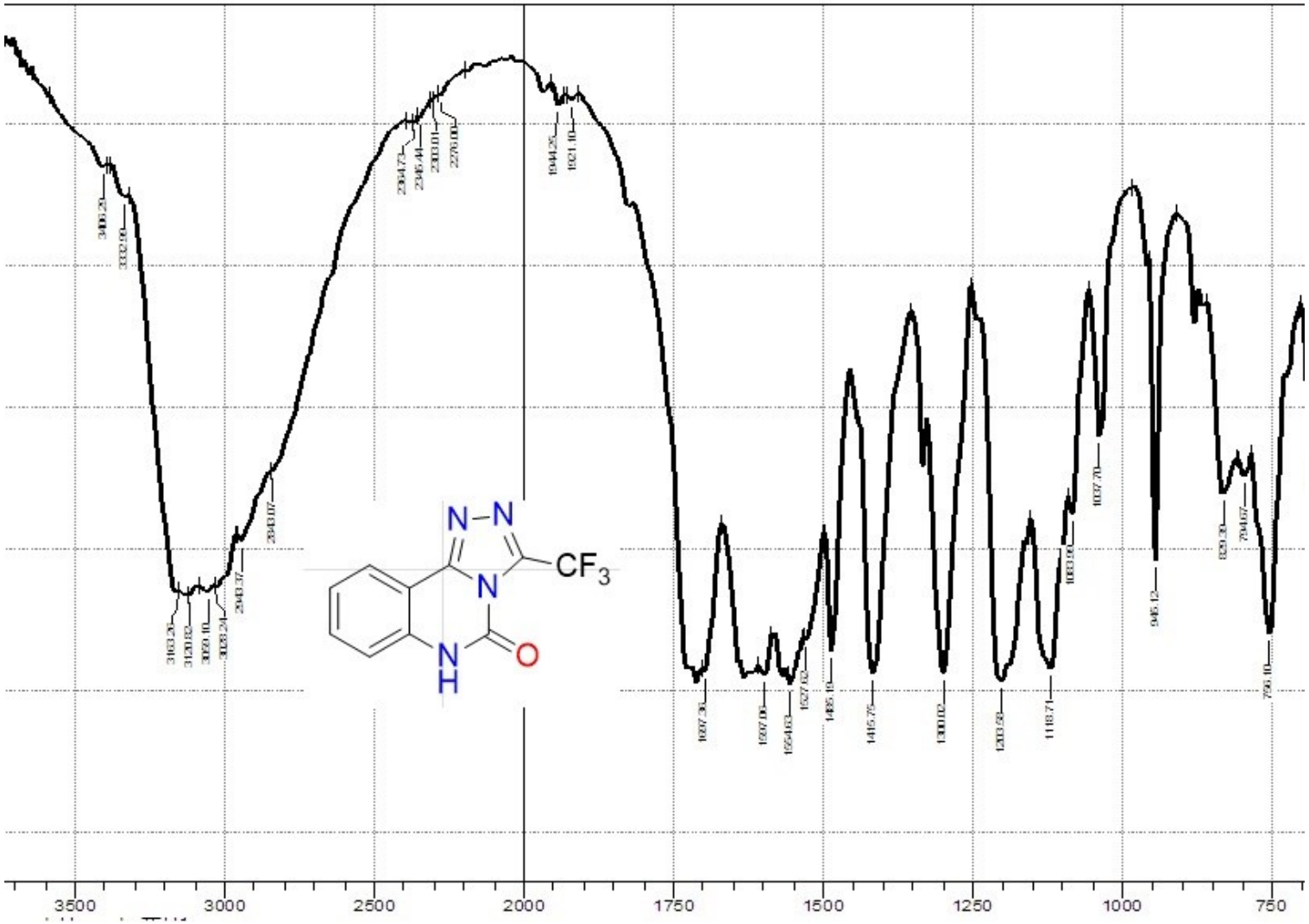
Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	-3.611	Numeric (log mol/L)
Absorption	Caco2 permeability	1.458	Numeric (log Papp in 10-6 cm/s)
Absorption	Intestinal absorption (human)	96.101	Numeric (% Absorbed)
Absorption	Skin Permeability	-2.729	Numeric (log Kp)
Absorption	P-glycoprotein substrate	No	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	No	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	Yes	Categorical (Yes/No)

Descriptor	Value		
Distribution	VDss (human)	0.187	Numeric (log L/kg)
Distribution	Fraction unbound (human)	0.26	Numeric (Fu)
Distribution	BBB permeability	0.965	Numeric (log BB)
Distribution	CNS permeability	-1.396	Numeric (log PS)
Metabolism	CYP2D6 substrate	No	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	Yes	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP2C19 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitior	No	Categorical (Yes/No)
Excretion	Total Clearance	-0.035	Numeric (log ml/min/kg)

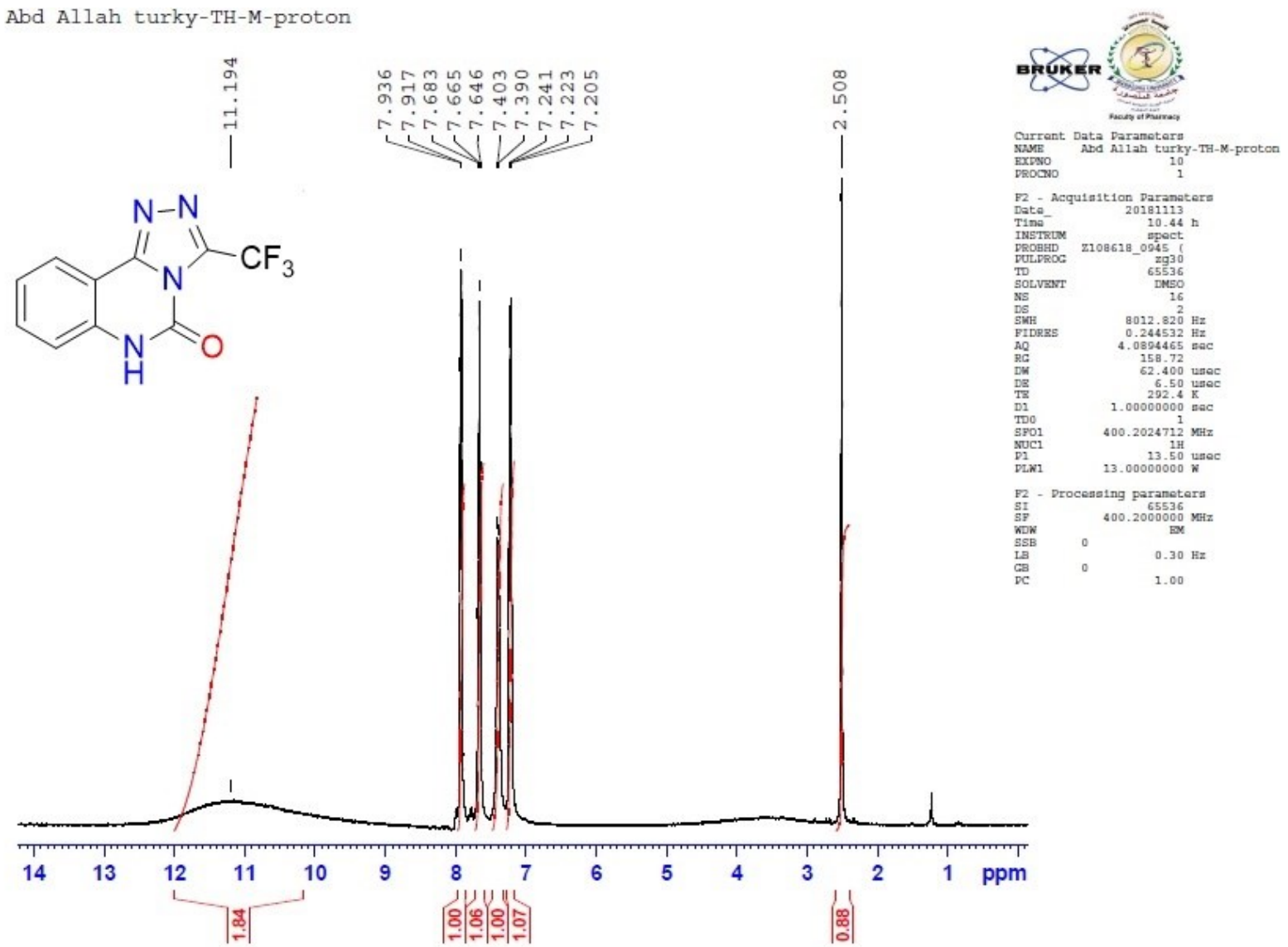
Descriptor	Value		
Excretion	Renal OCT2 substrate	No	Categorical (Yes/No)
Toxicity	AMES toxicity	No	Categorical (Yes/No)
Toxicity	Max. tolerated dose (human)	0.442	Numeric (log mg/kg/day)
Toxicity	hERG I inhibitor	No	Categorical (Yes/No)
Toxicity	hERG II inhibitor	No	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	2.458	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	0.675	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	Yes	Categorical (Yes/No)
Toxicity	Skin Sensitisation	No	Categorical (Yes/No)
Toxicity	T.Pyriformis toxicity	0.296	Numeric (log ug/L)
Toxicity	Minnow toxicity	-0.914	Numeric (log mM)

Spectral Date of New Compounds

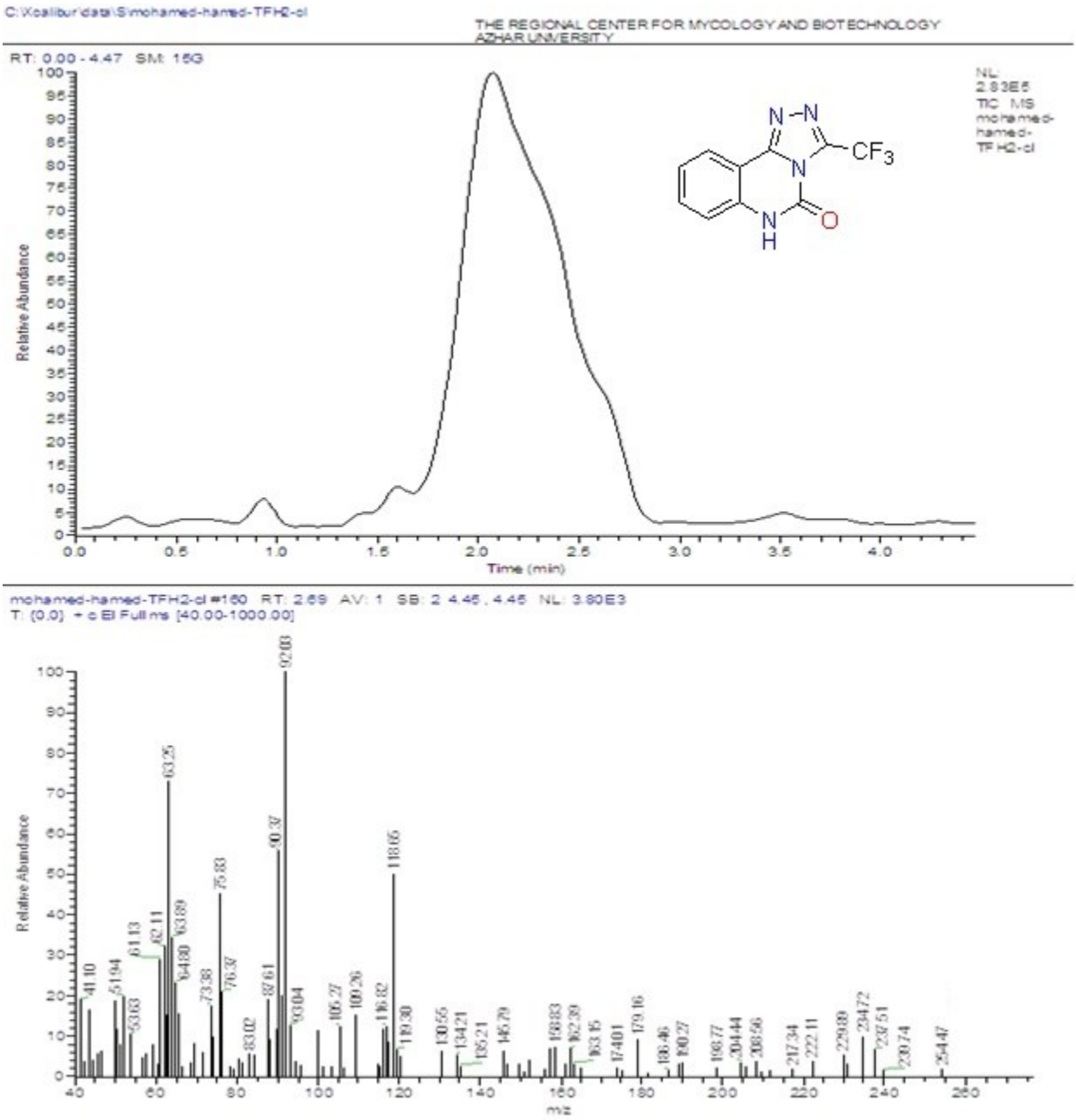
IR spectrum of compound 21



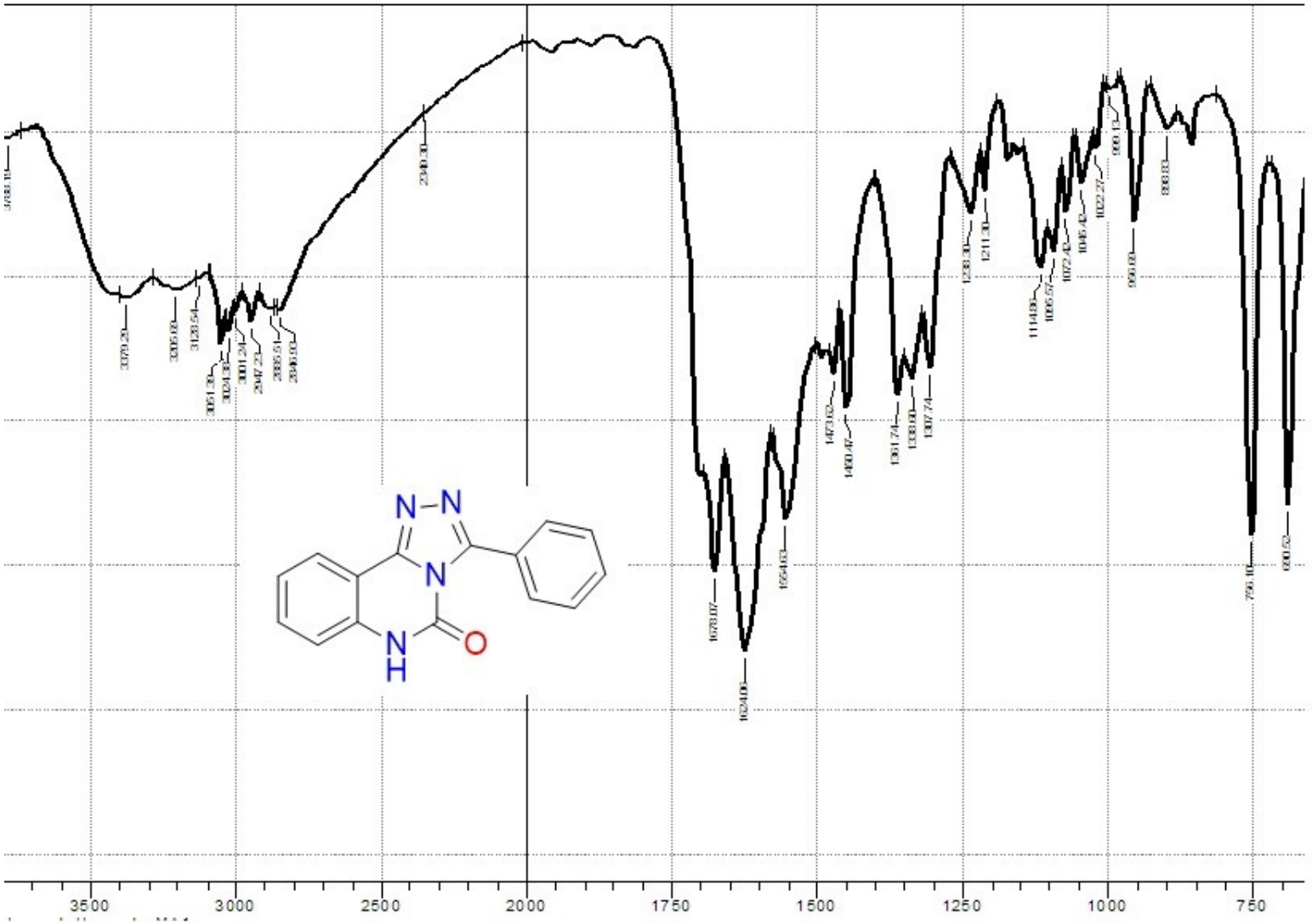
^{1}H NMR Spectrum of compound 21



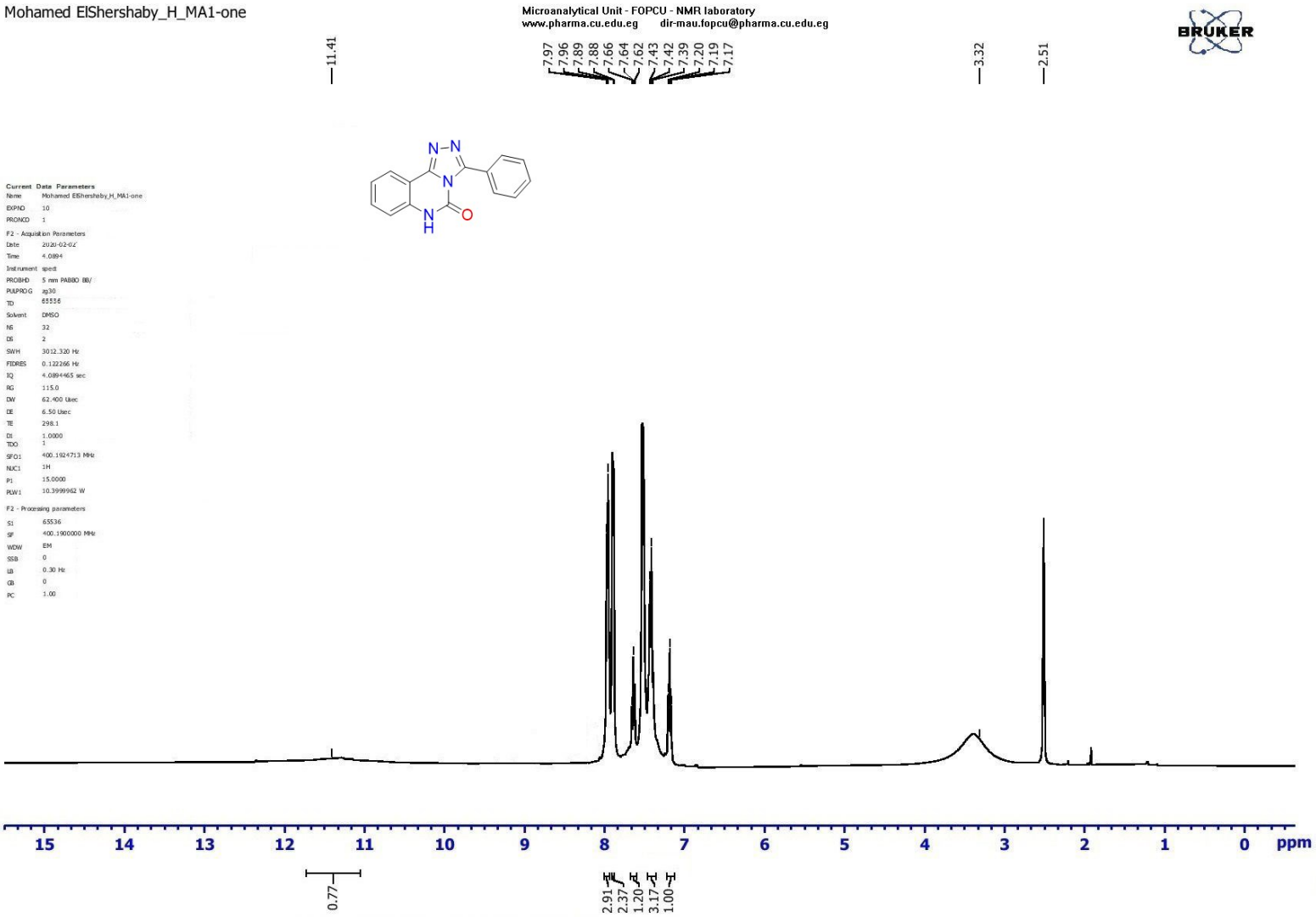
Mass spectrum of compound 21



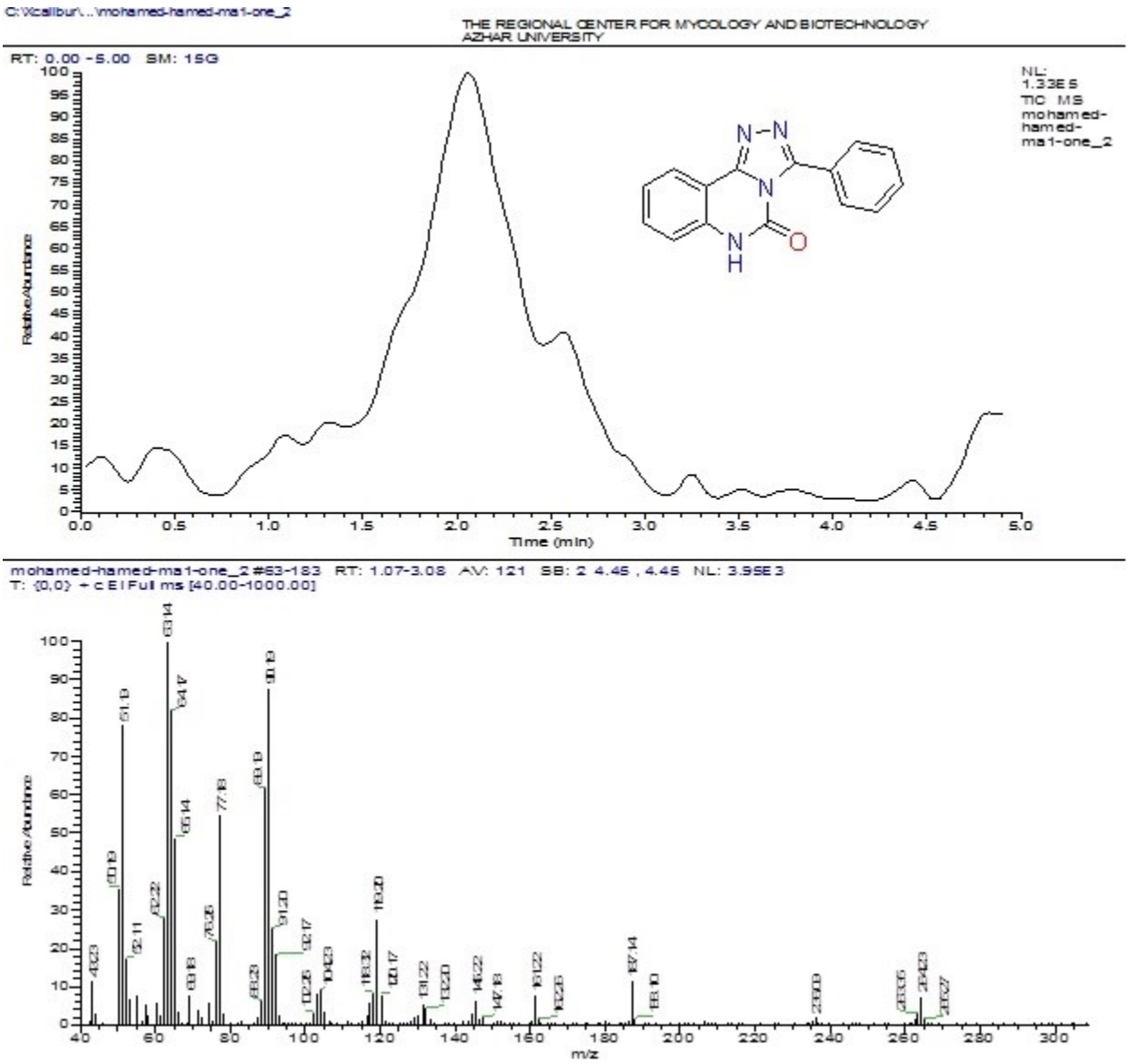
IR spectrum of compound 22



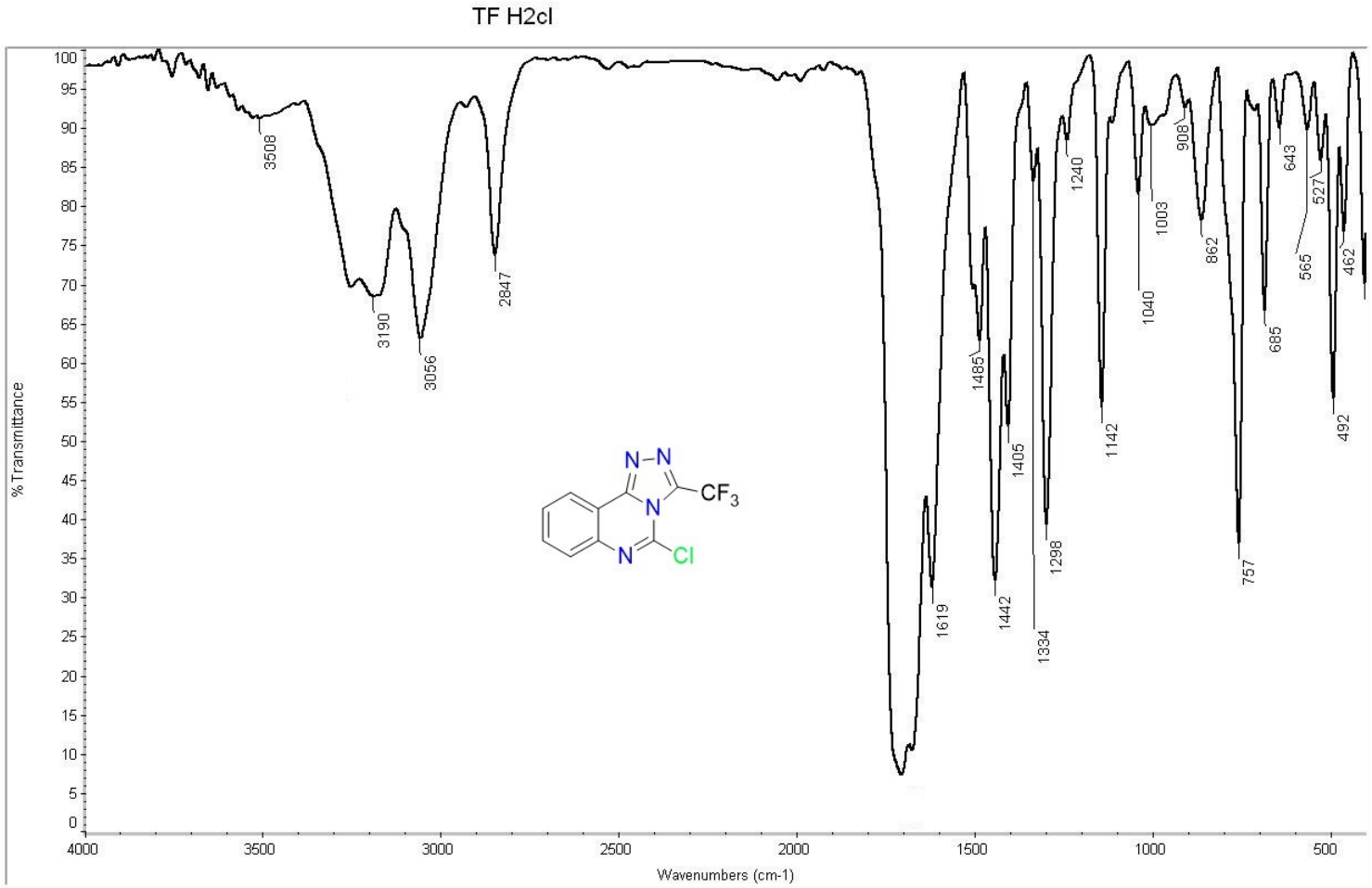
^{1}H NMR Spectrum of compound 22



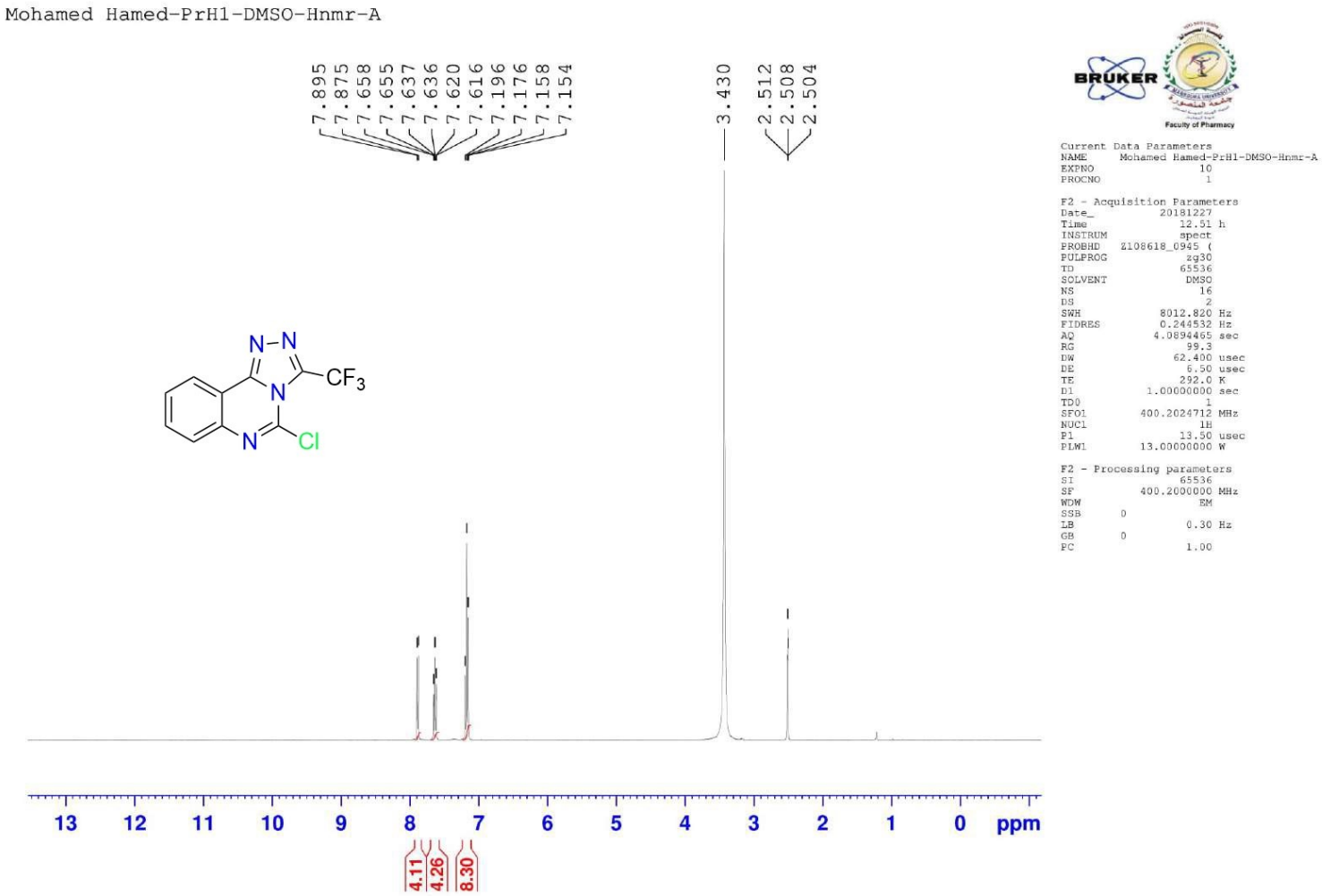
Mass spectrum of compound 22



IR spectrum of compound 24



^{1}H NMR Spectrum of compound 24

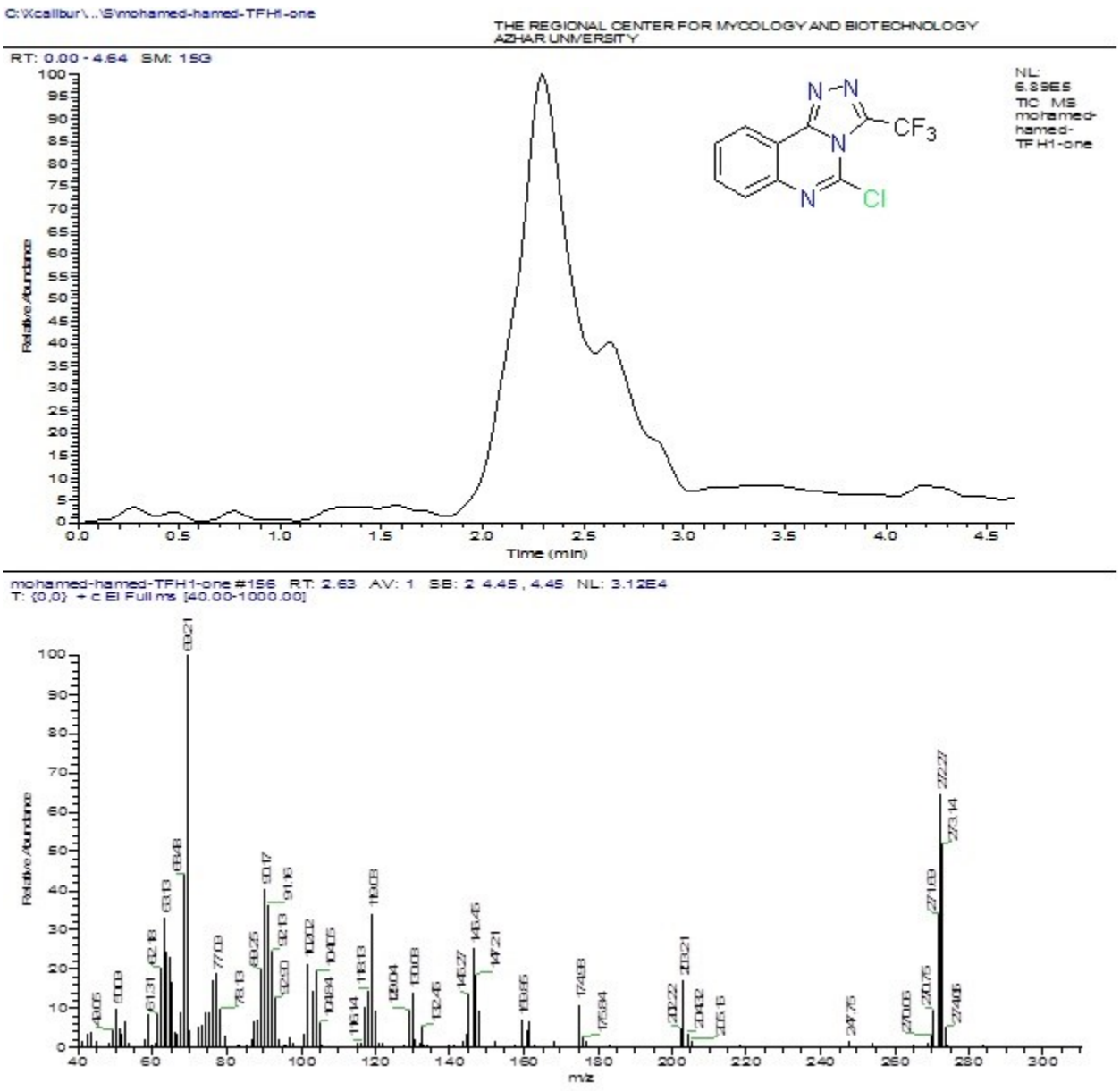


BRUKER

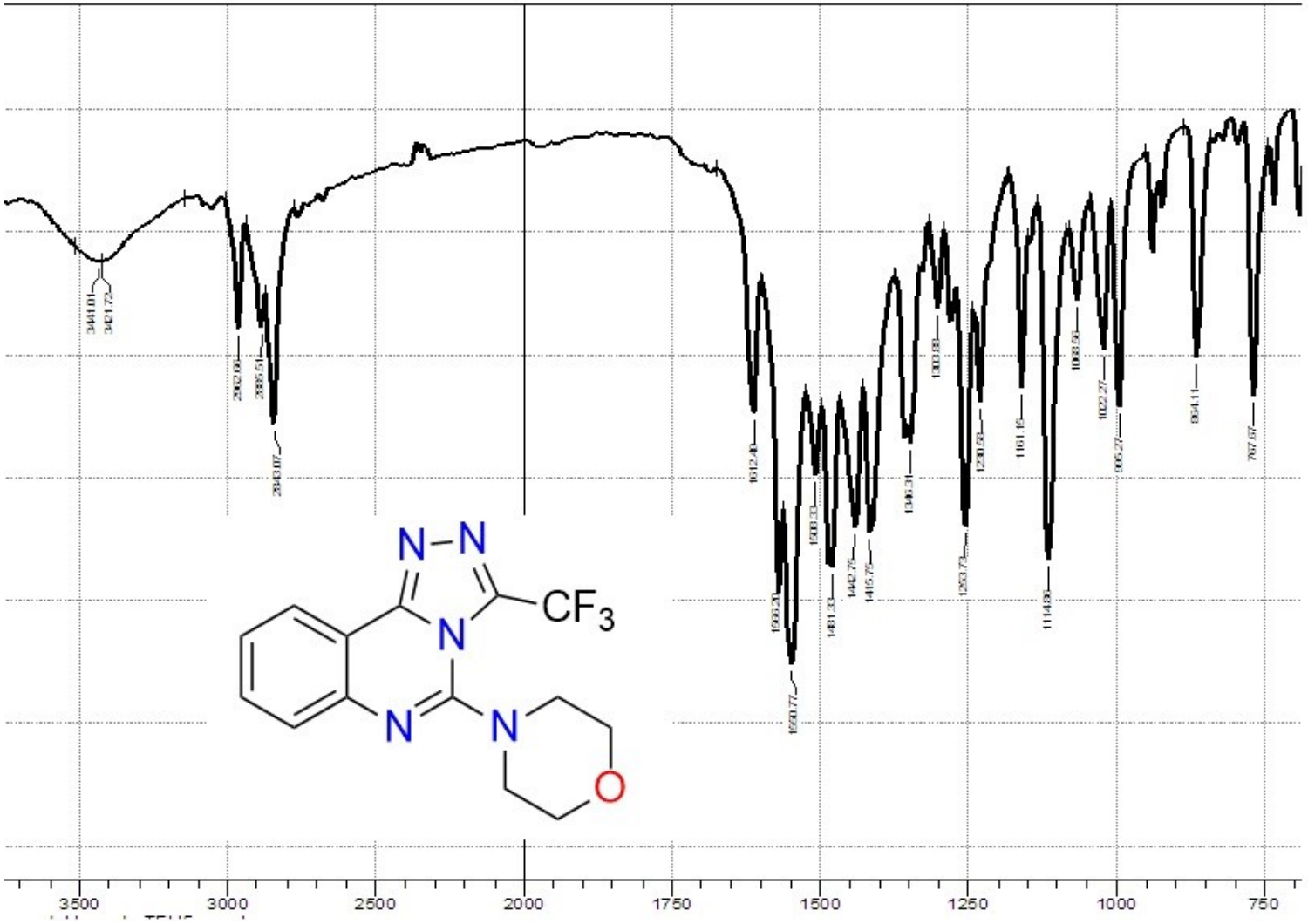
Faculty of Pharmacy

```
Current Data Parameters
NAME      Mohamed Hamed-PrH1-DMSO-Hnmr-A
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20181227
Time              12.51 h
INSTRUM             spect
PROBHD   Z108618_0945 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH            8012.820 Hz
FIDRES         0.244532 Hz
AQ             4.0894465 sec
RG                  99.3
DW                62.400 usec
DE                 6.50 usec
TE                292.0 K
D1             1.00000000 sec
TD0                    1
SFO1         400.2024712 MHz
NUC1                  1H
P1                 13.50 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
SF           400.2000000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

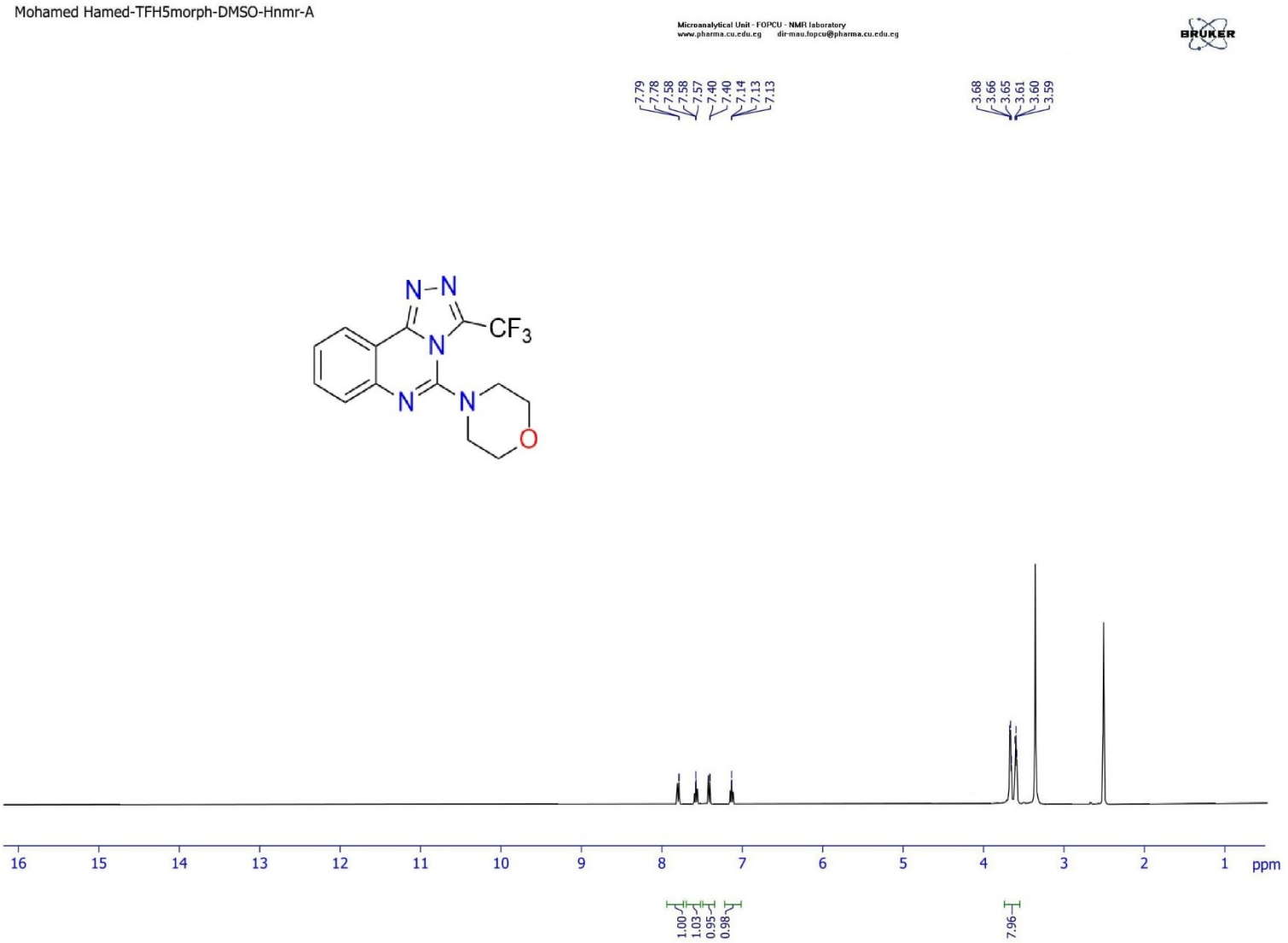
Mass Spectrum of Compound 24



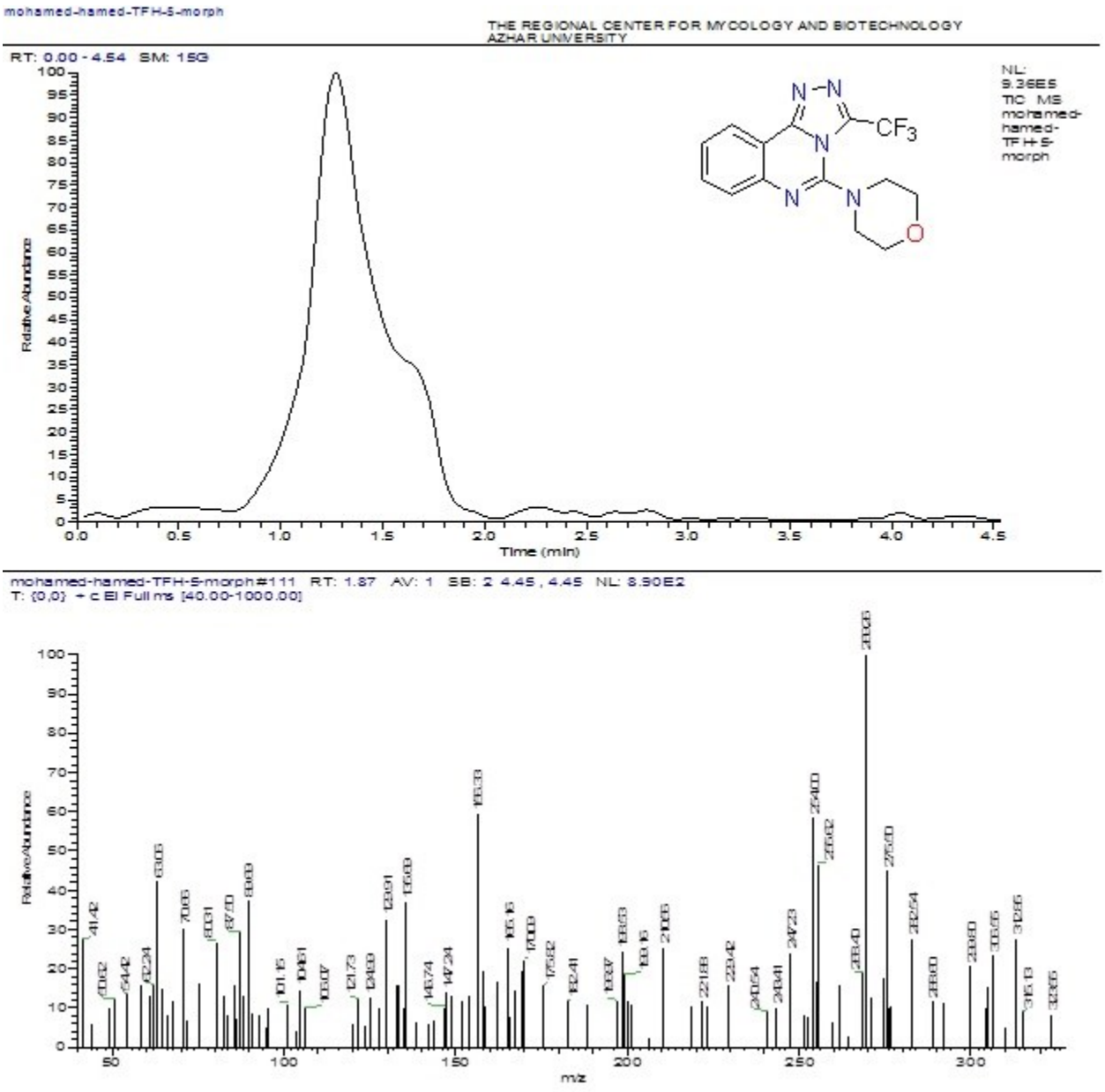
IR spectrum of compound 27



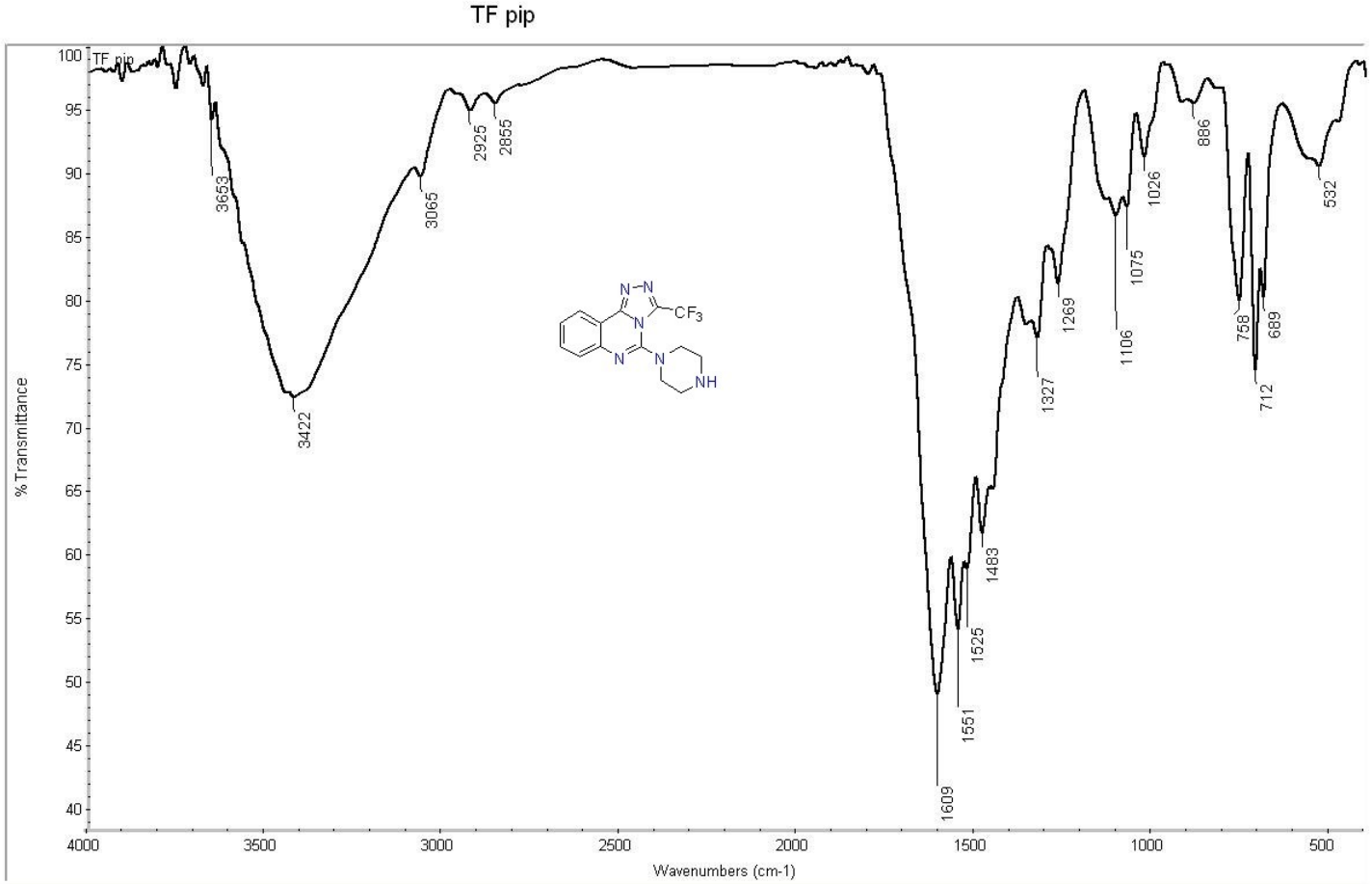
^{1}H NMR Spectrum of compound 27



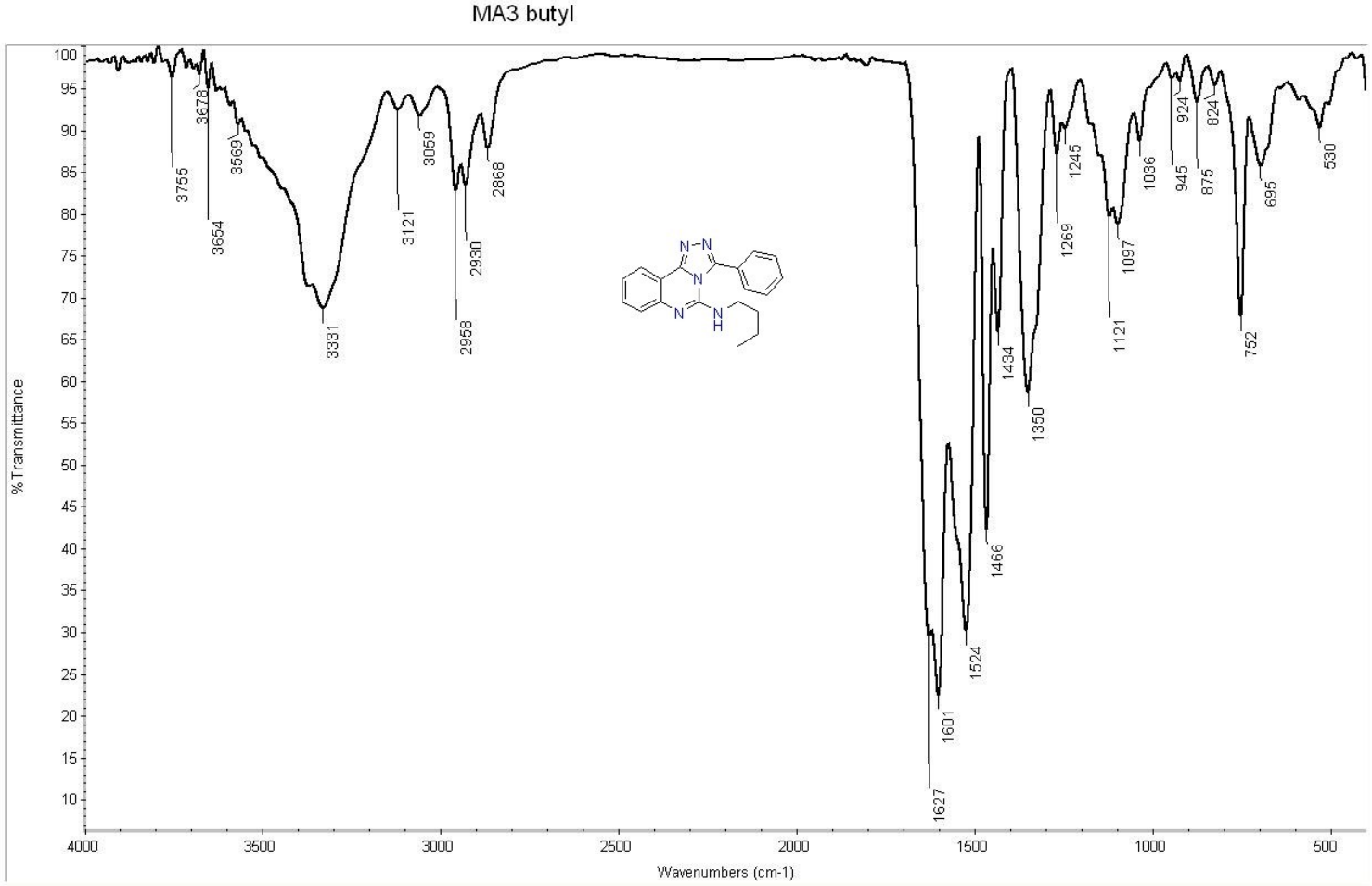
Mass Spectrum of Compound 27



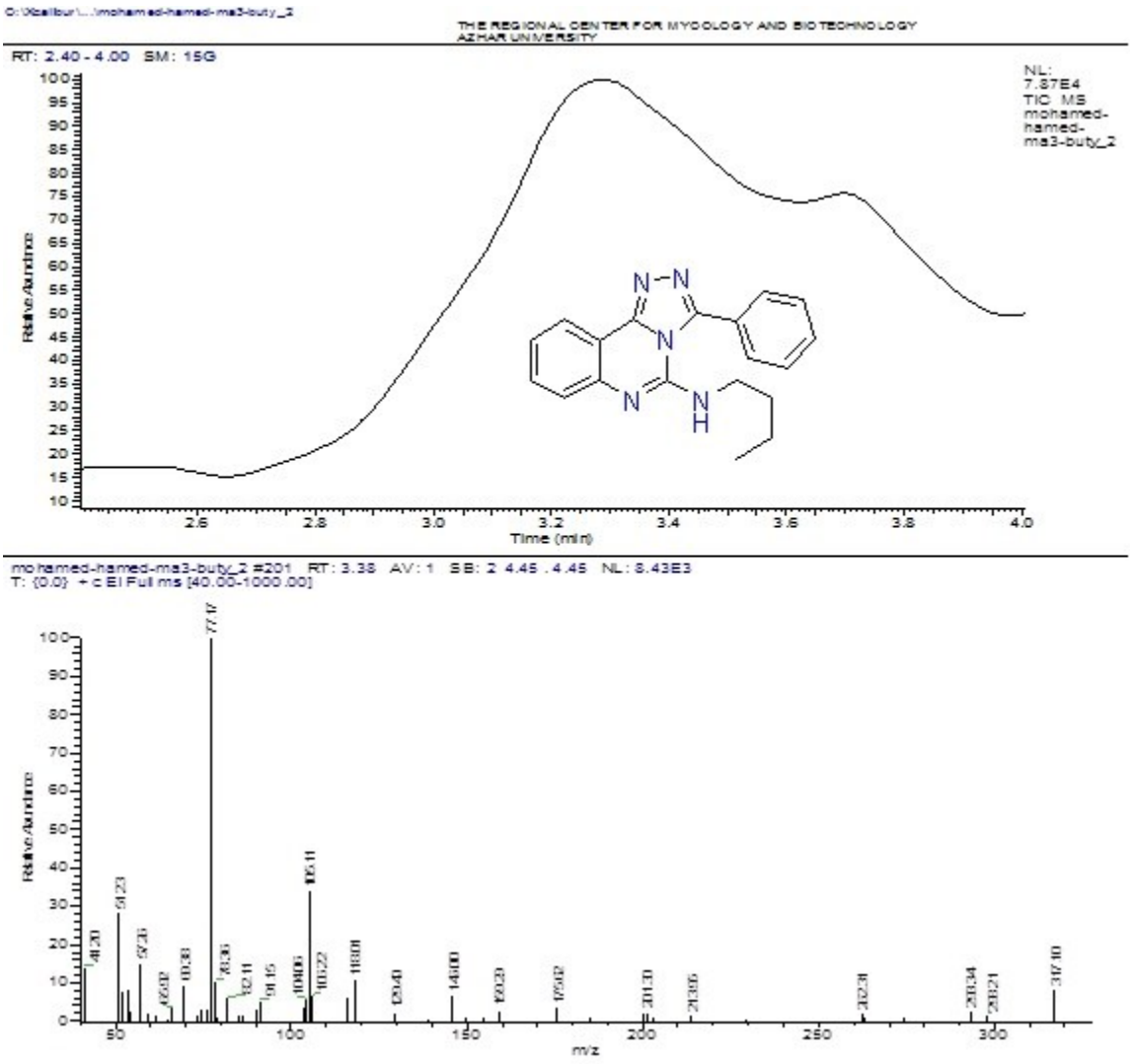
IR spectrum of compound 28



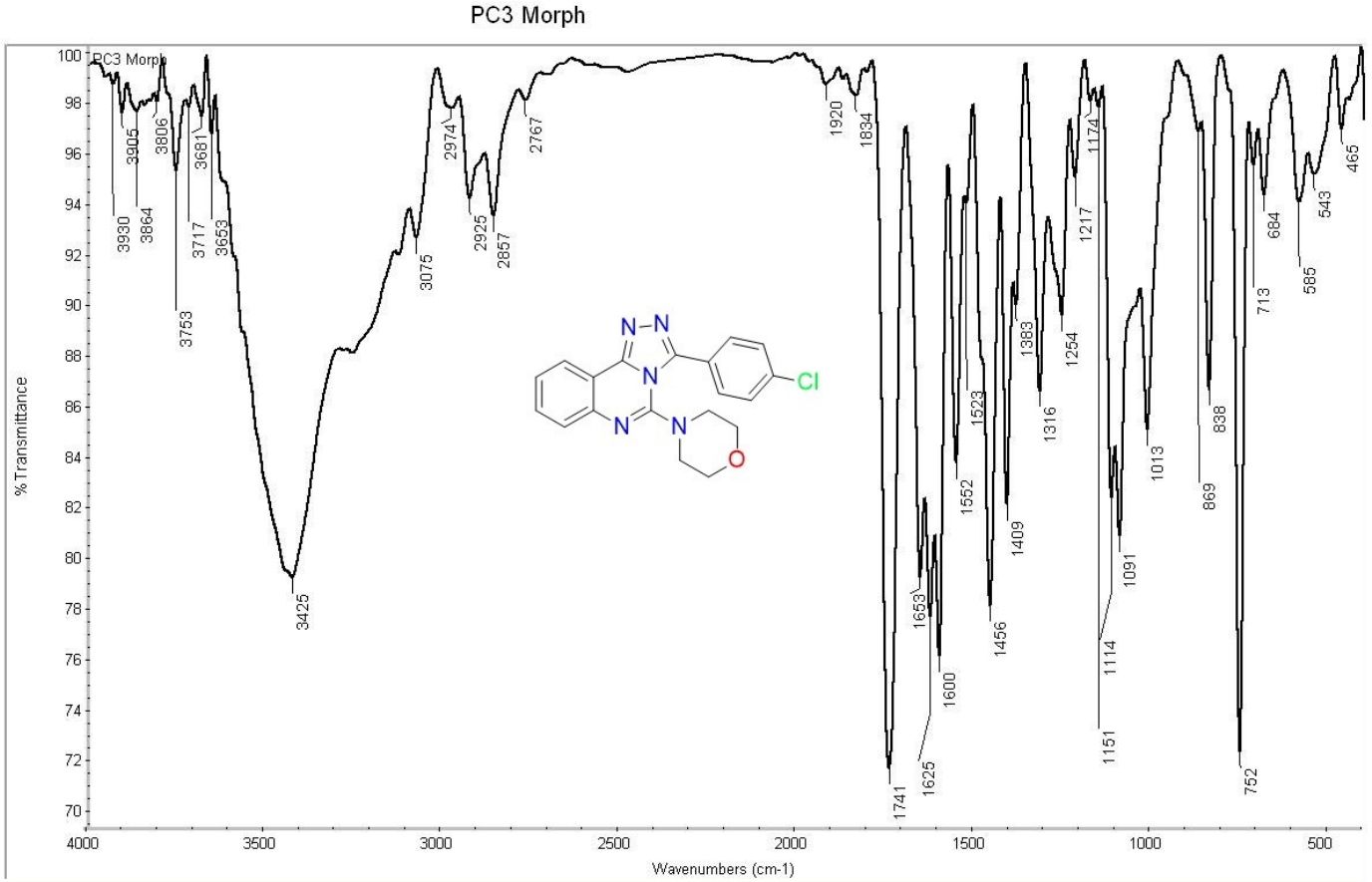
IR spectrum of compound 29



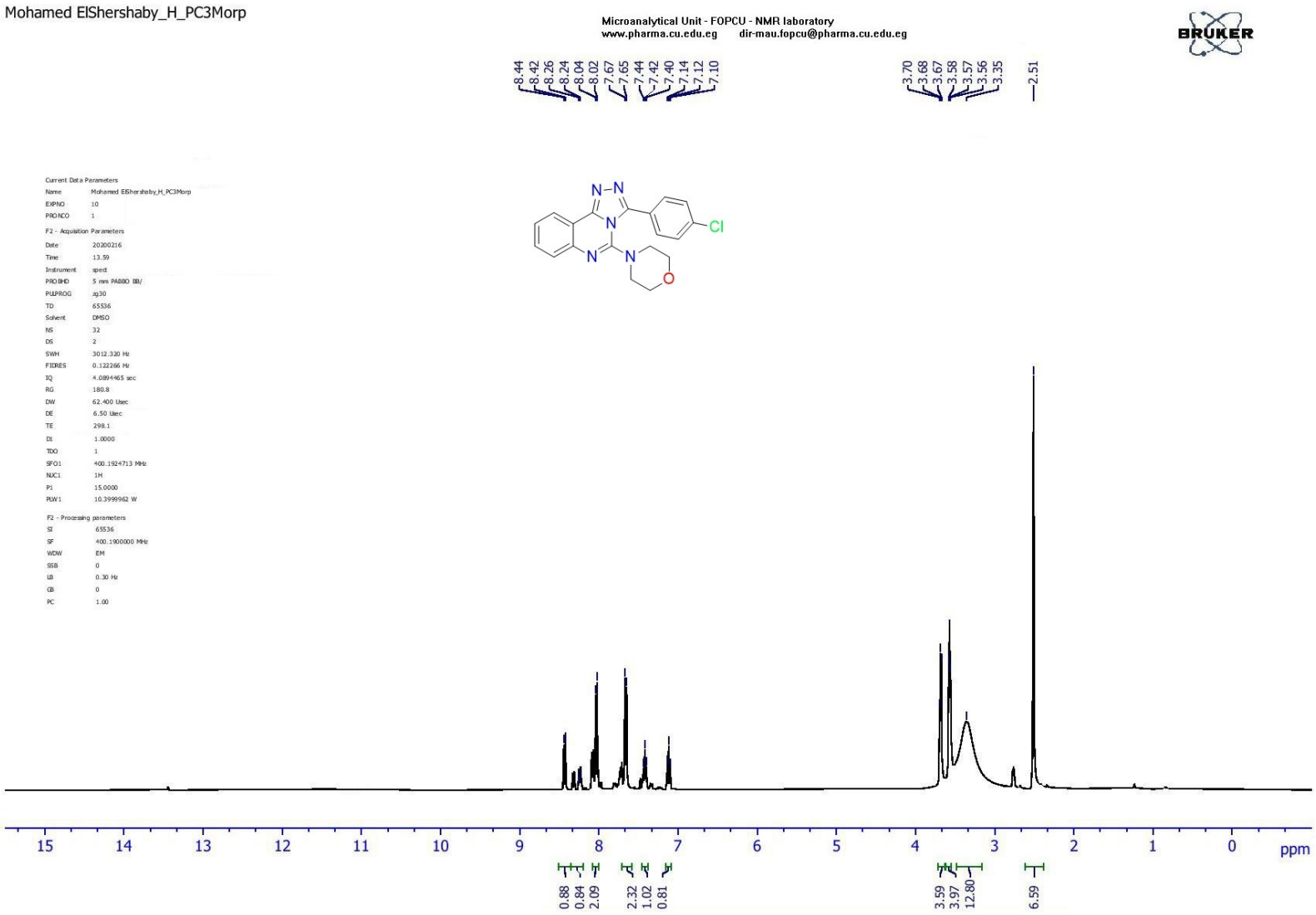
Mass Spectrum of Compound 29



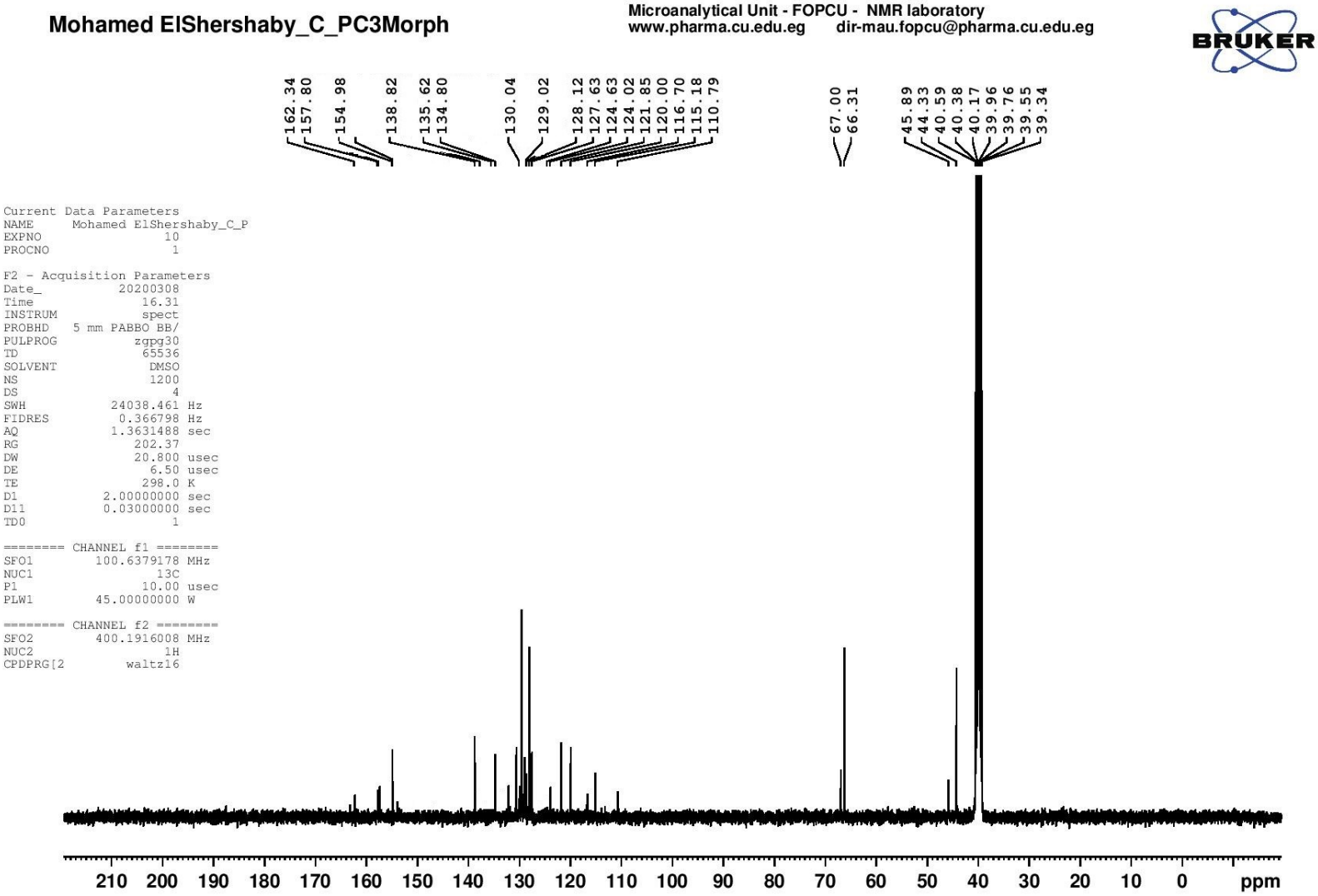
IR spectrum of compound 31



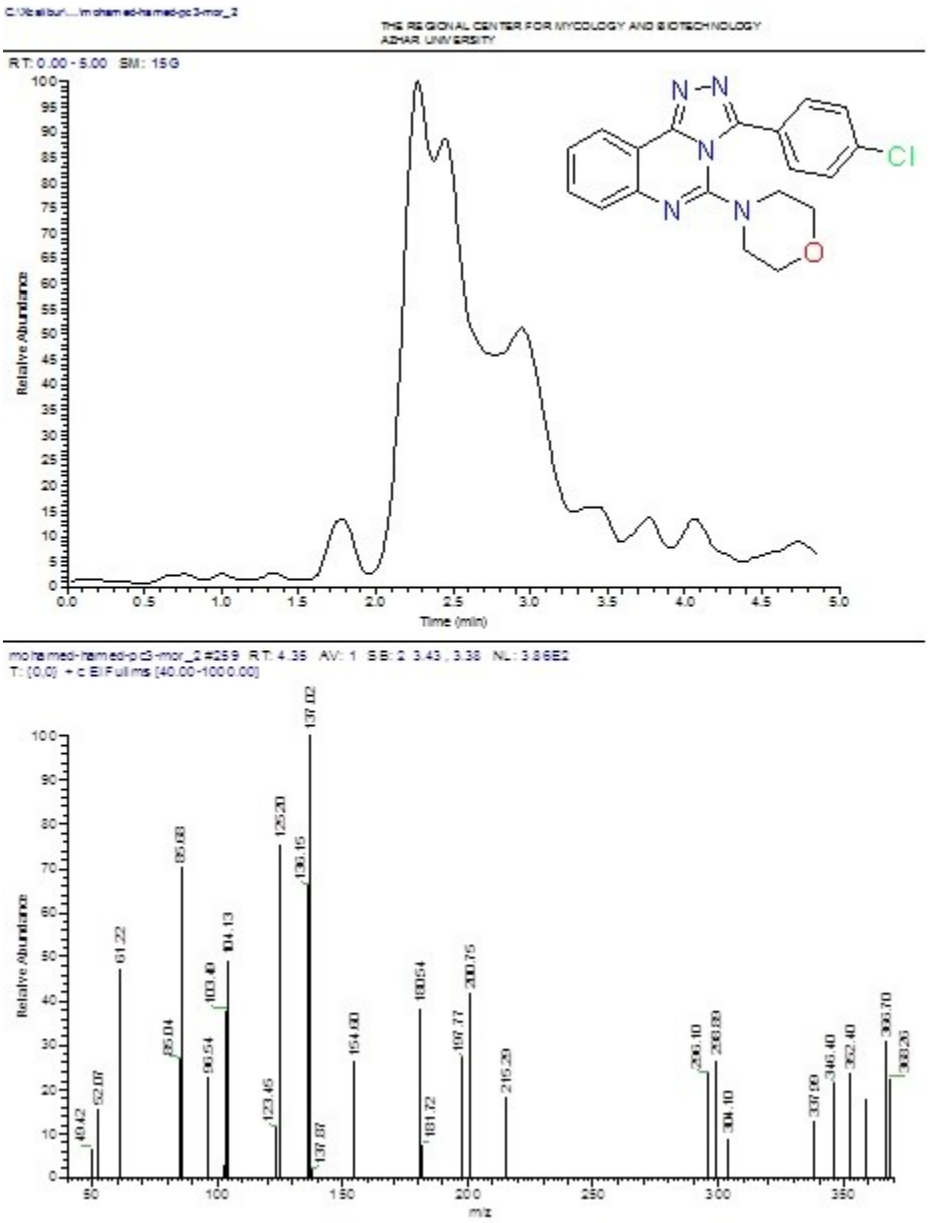
^{1}H NMR Spectrum of compound 31



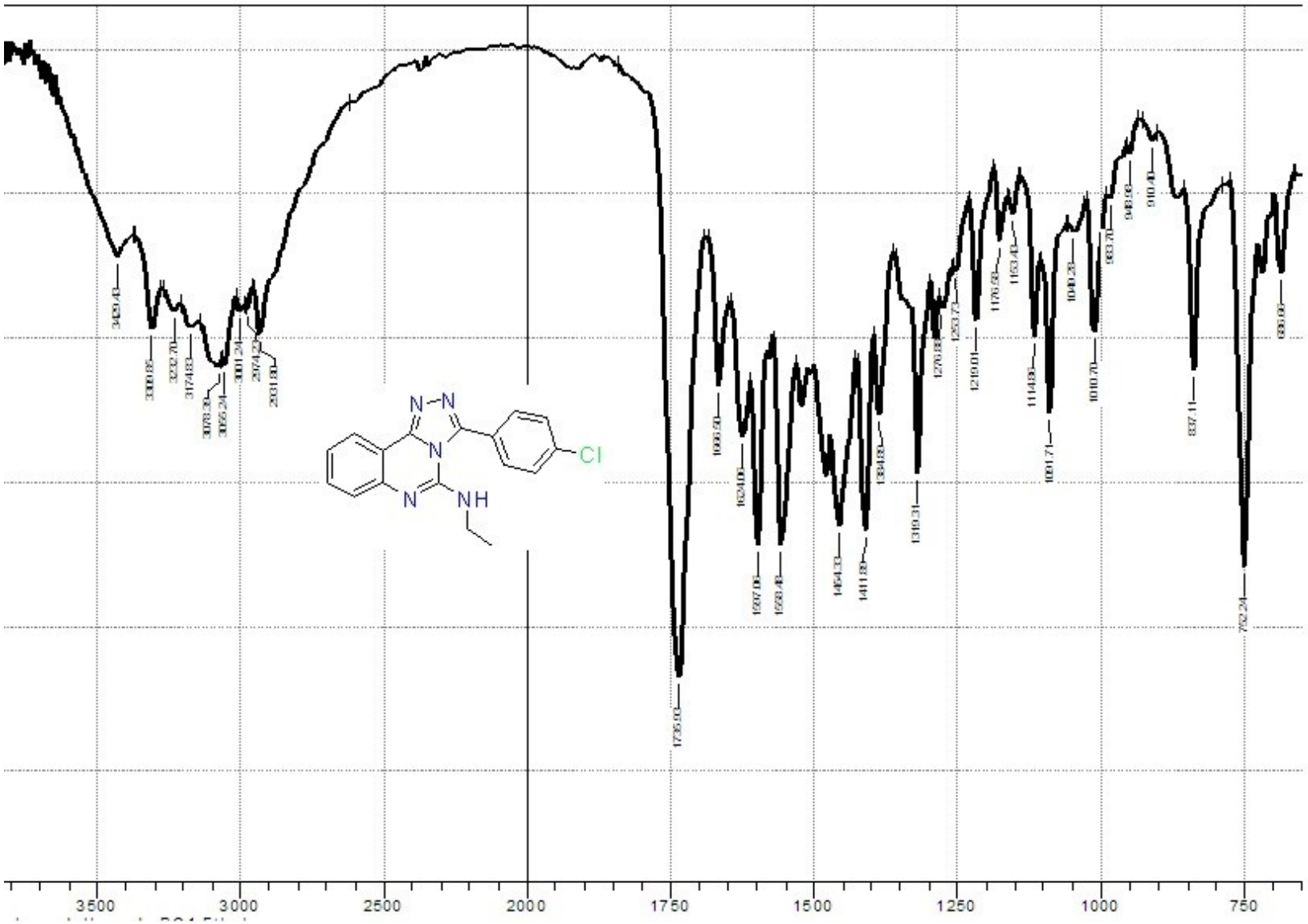
^{13}C NMR Spectrum of compound 31



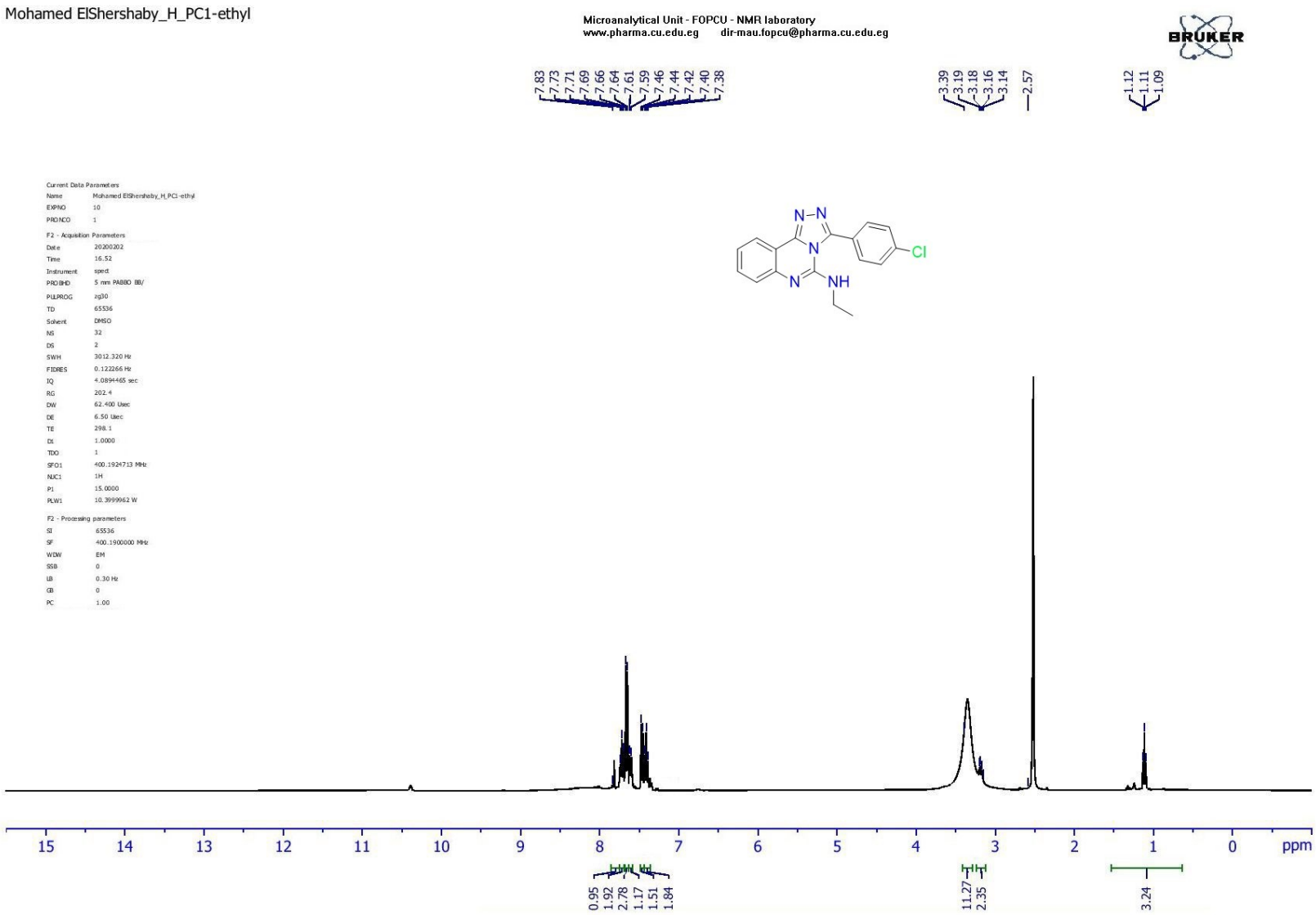
Mass Spectrum of Compound 31



IR spectrum of compound 32

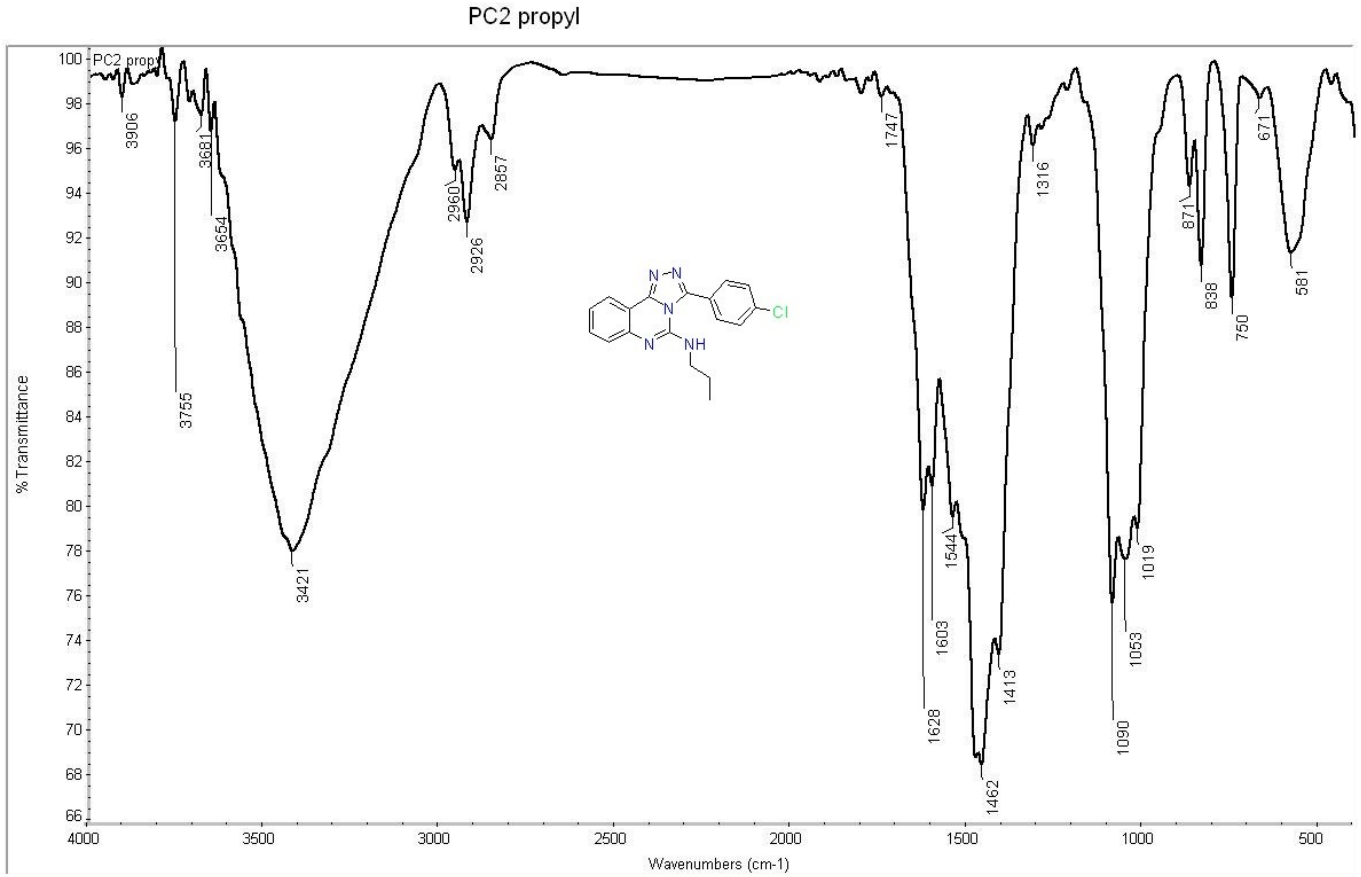


^{1}H NMR Spectrum of compound 32

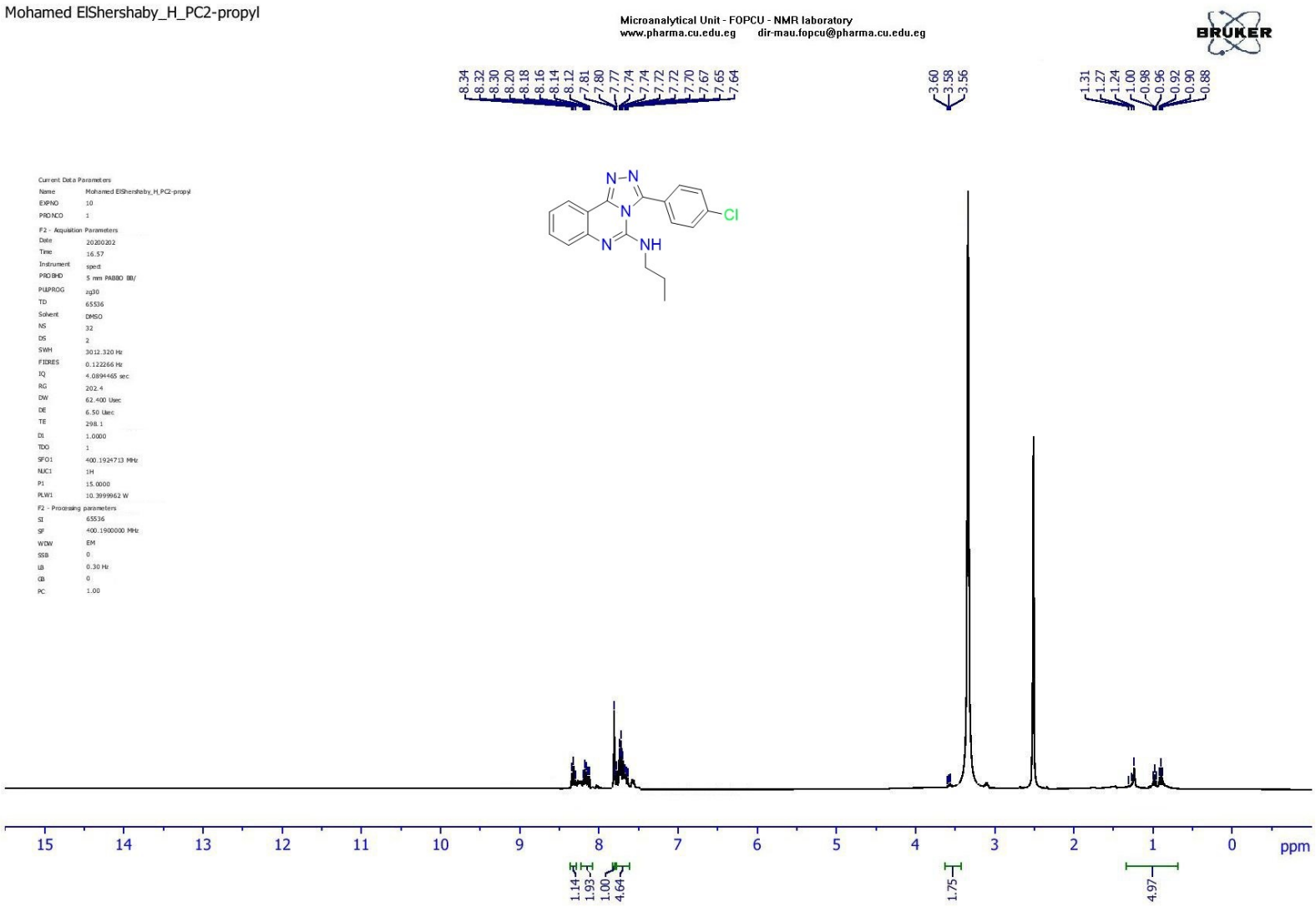


Mass Spectrum of Compound 32

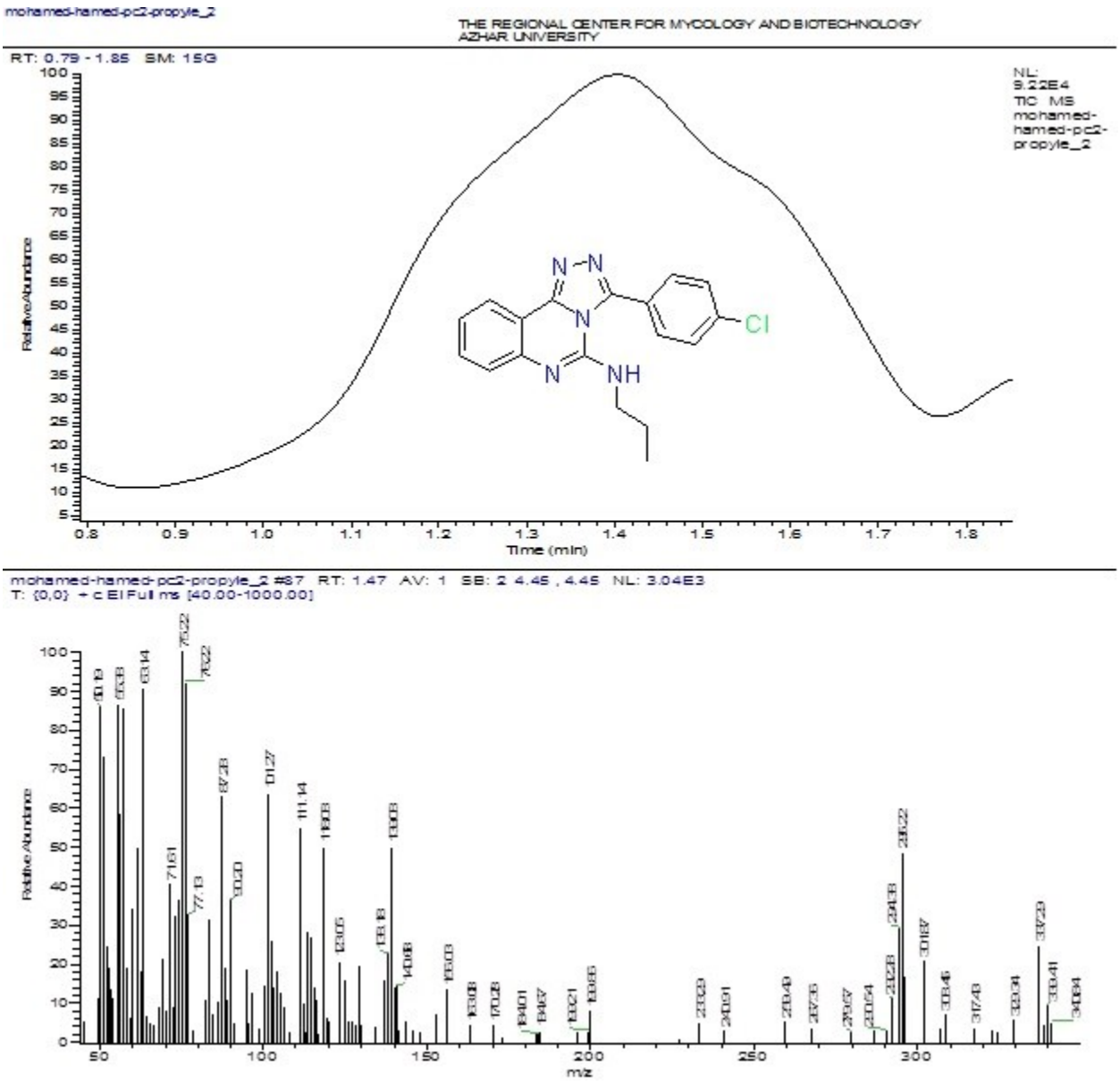
IR spectrum of compound 33



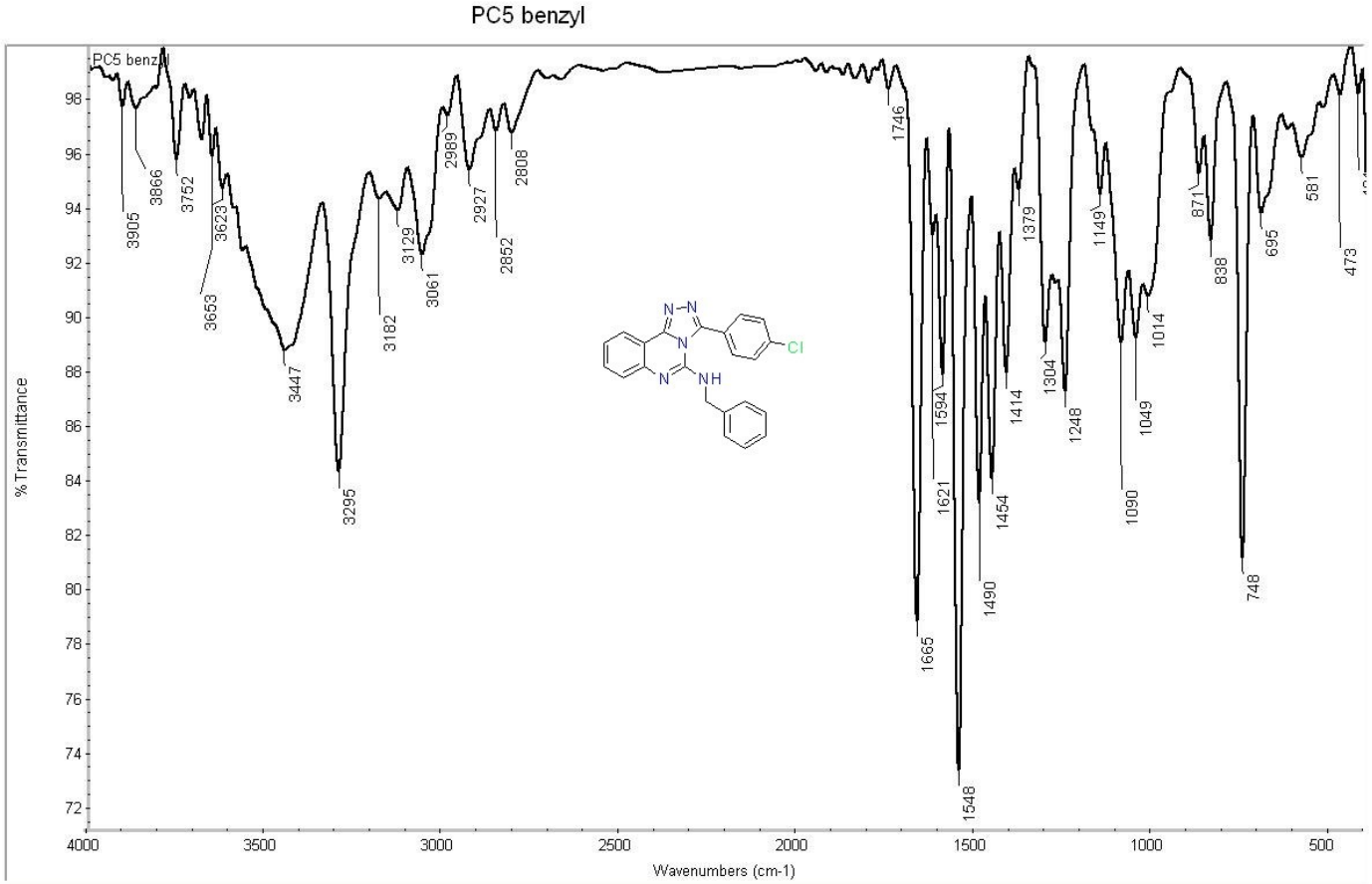
^{1}H NMR Spectrum of compound 33



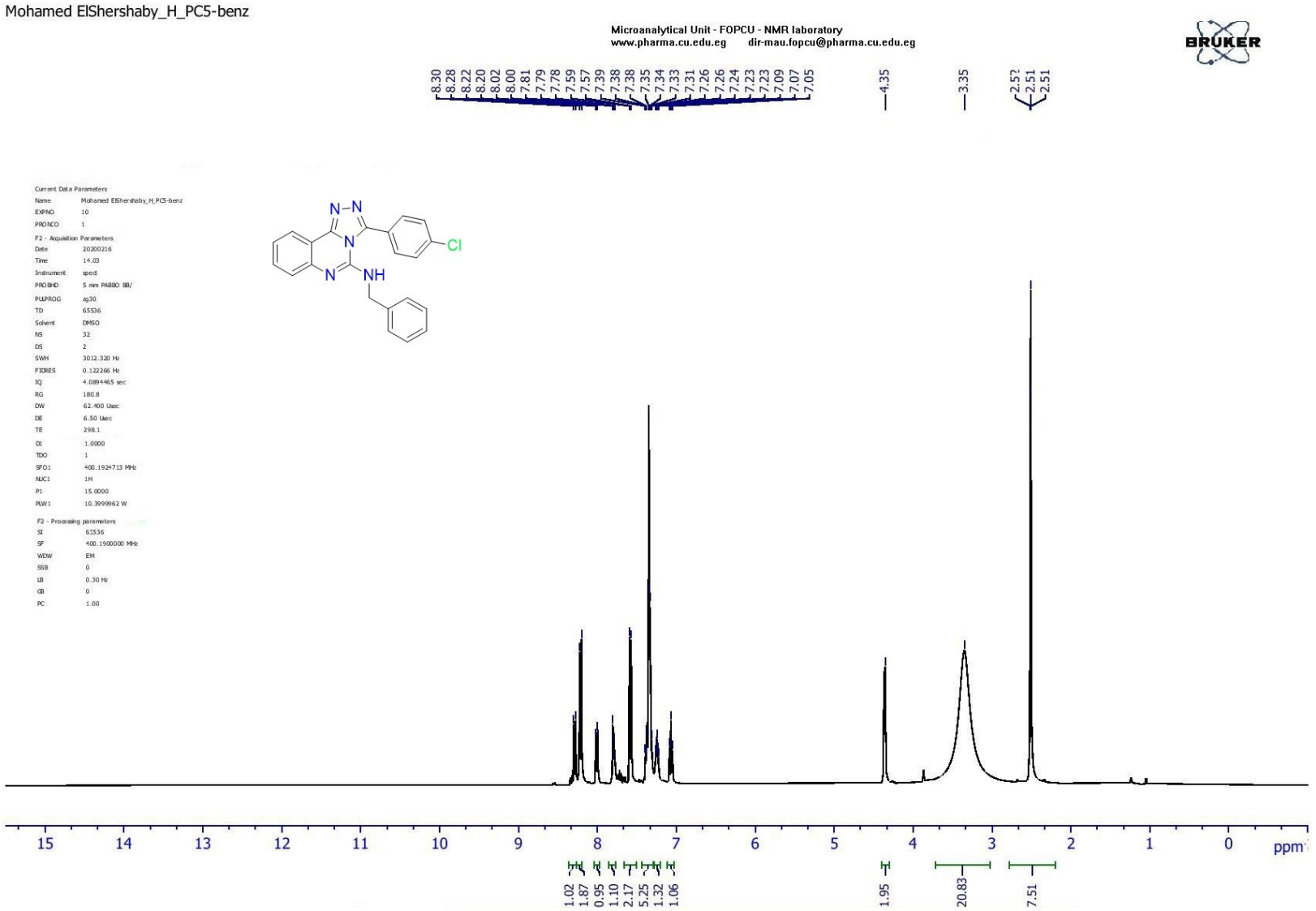
Mass Spectrum of Compound 33



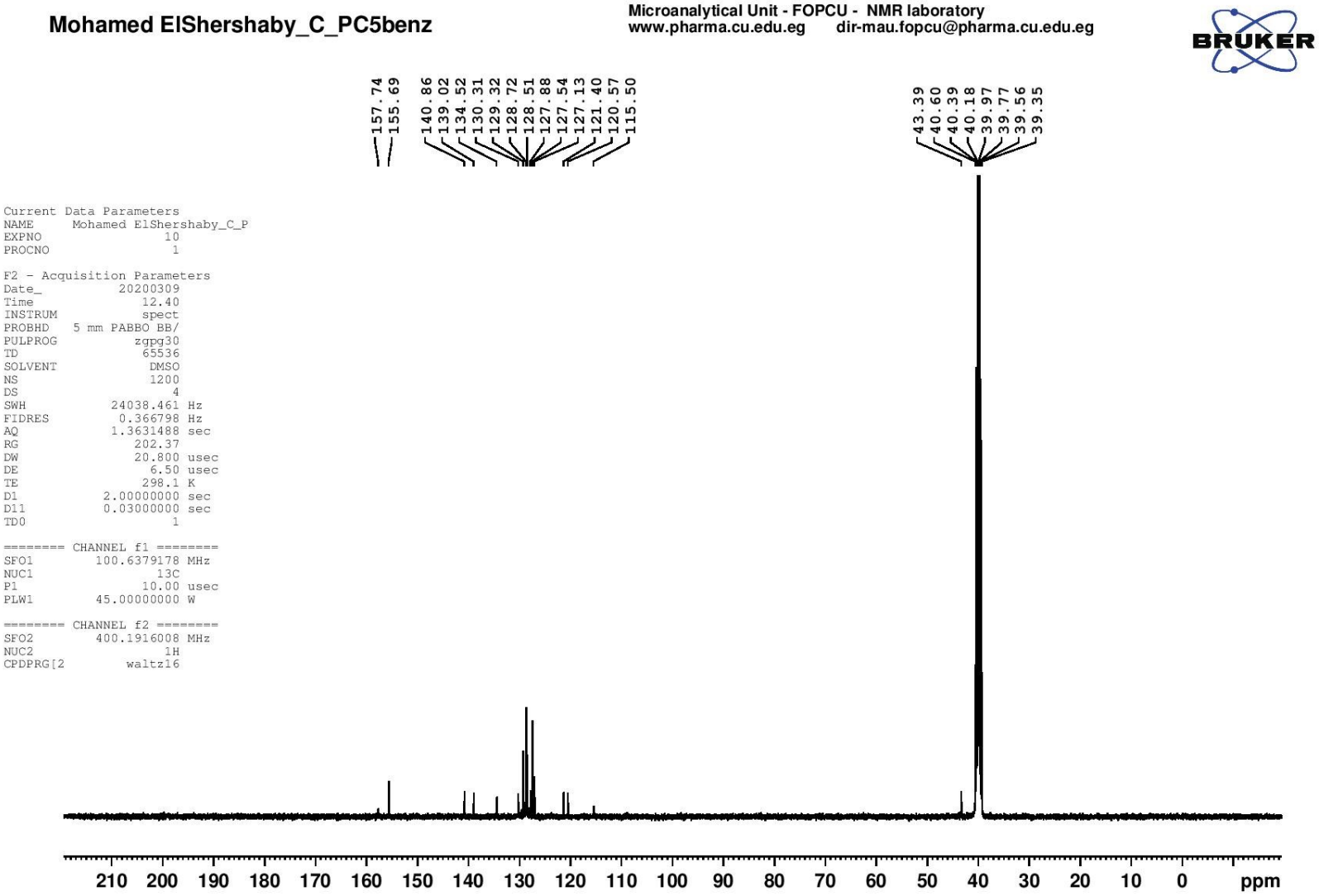
IR spectrum of compound 34



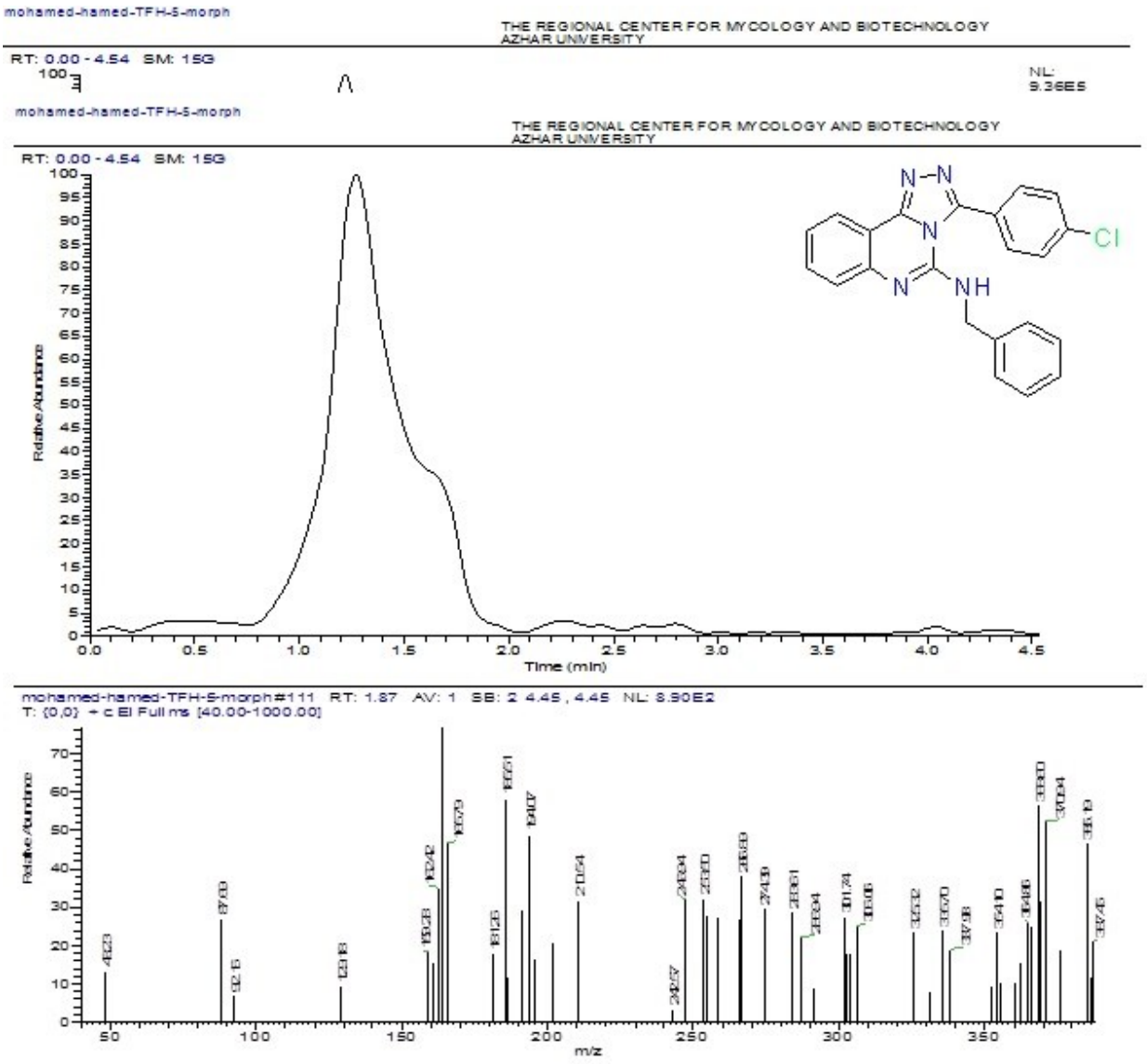
^{1}H NMR Spectrum of compound 34



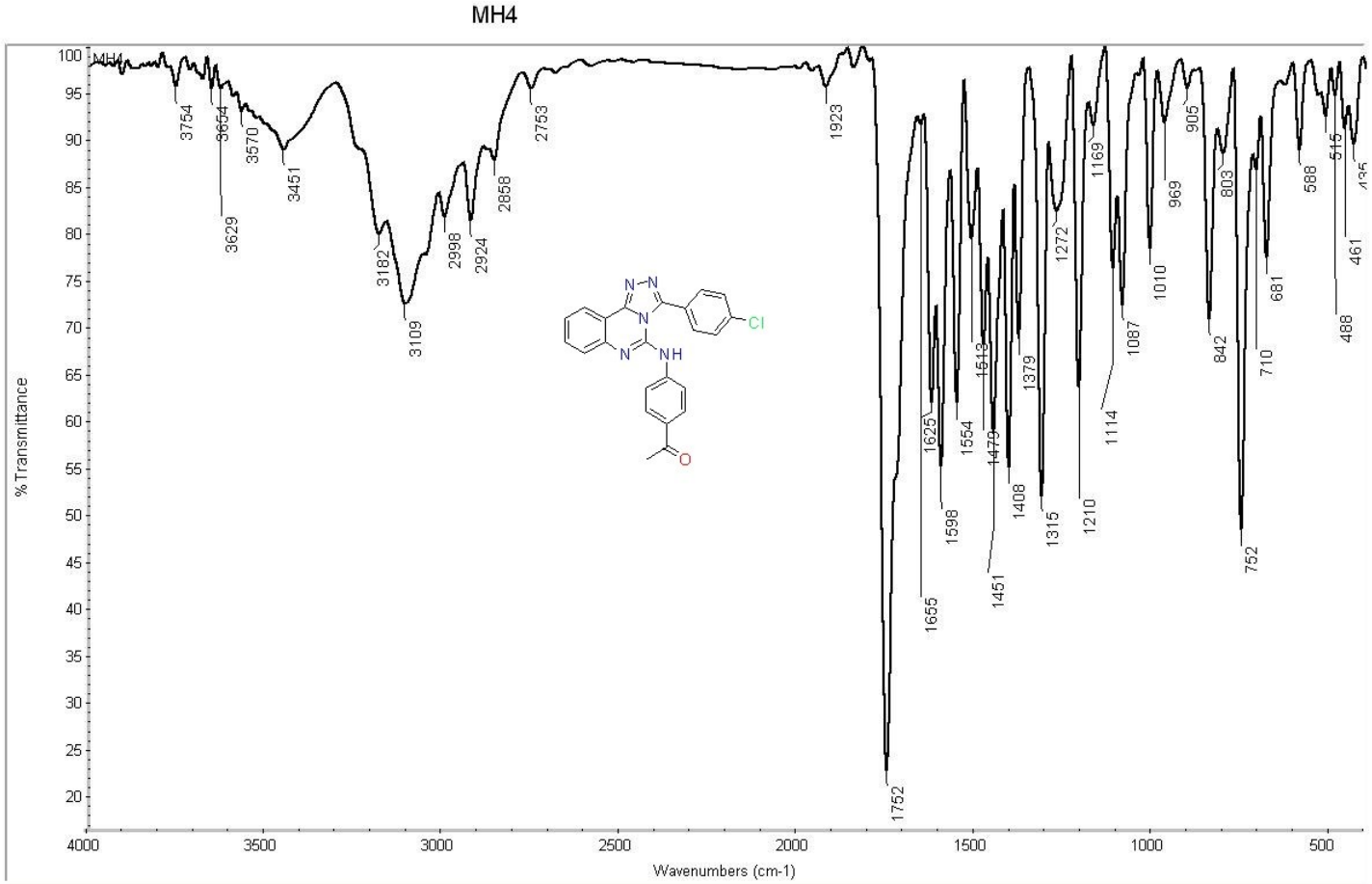
^{13}C NMR Spectrum of compound 34



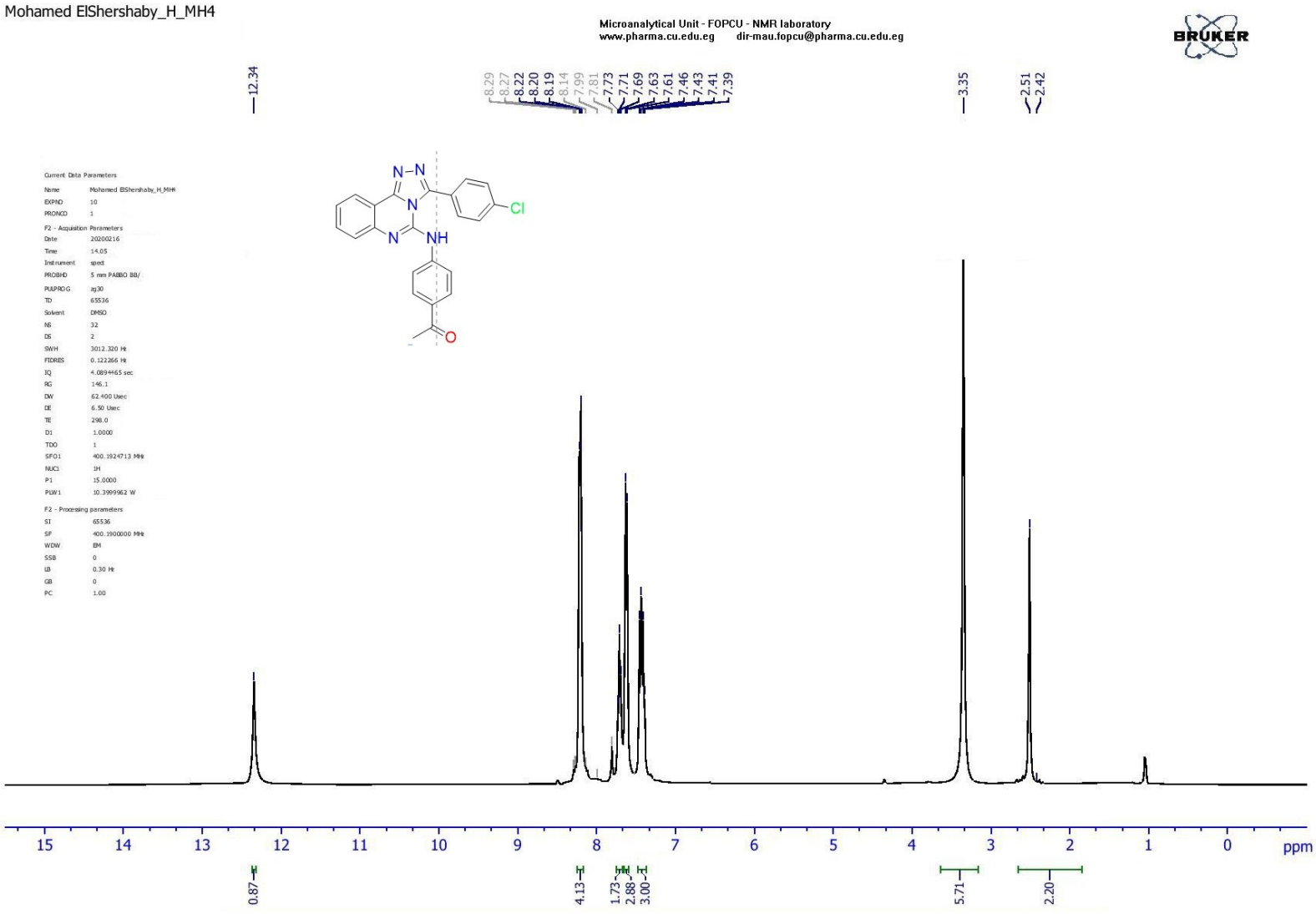
Mass Spectrum of Compound 34



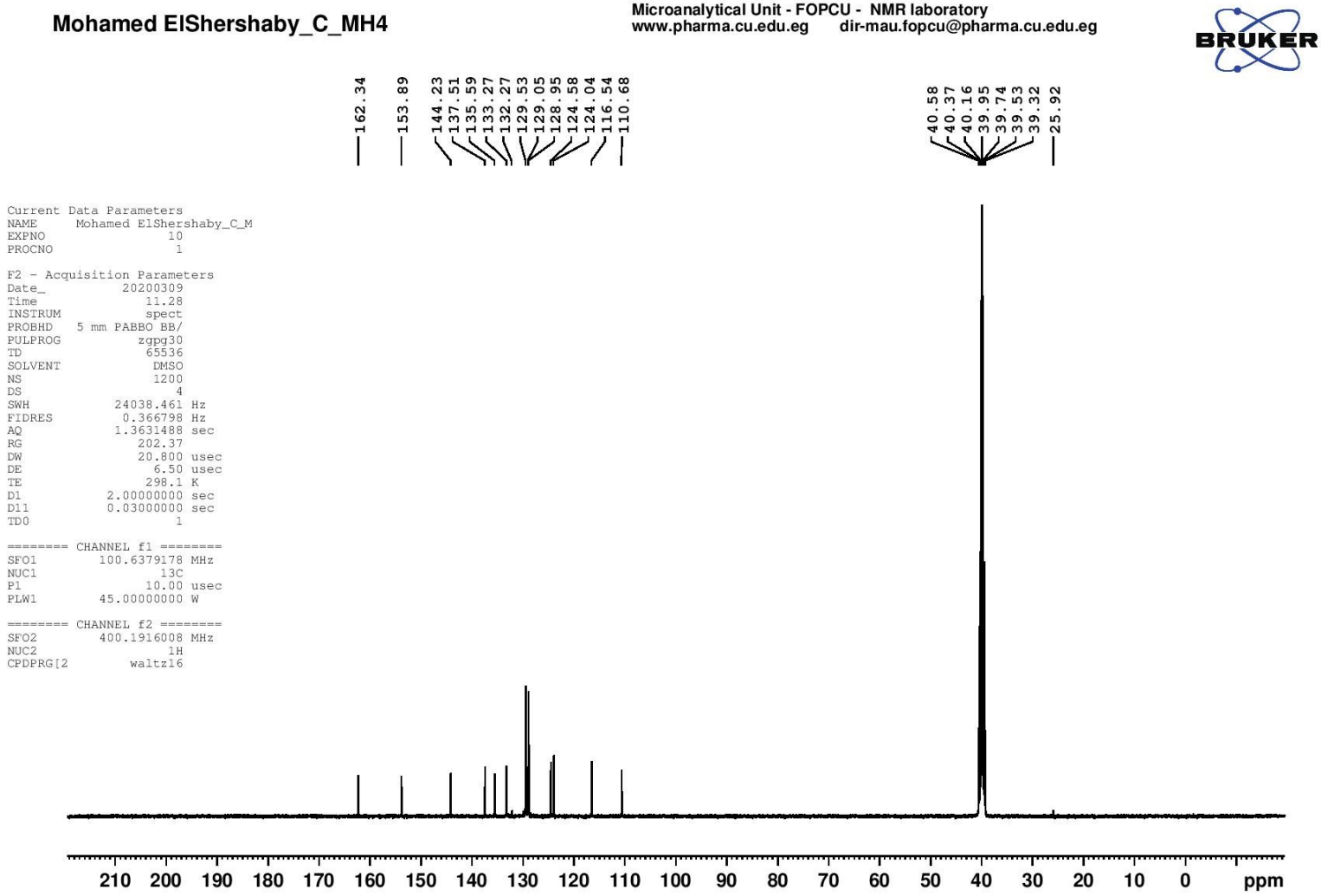
IR spectrum of compound 35



^{1}H NMR Spectrum of compound 35



^{13}C NMR Spectrum of compound 35



Mass Spectrum of Compound 35