Rationale Design, Synthesis, Cytotoxicity Evaluation, and In silico Mechanistic Studies of Novel 1,2,3-Triazoles with Potential Anticancer Activity

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Supporting Information

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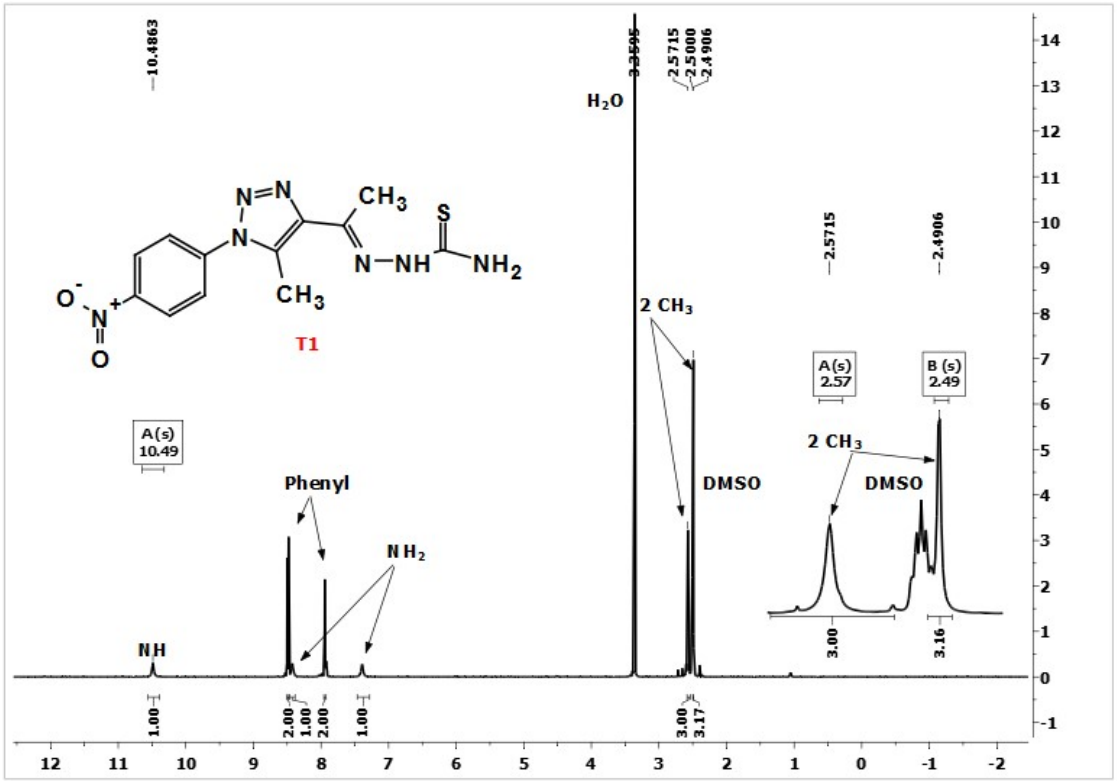
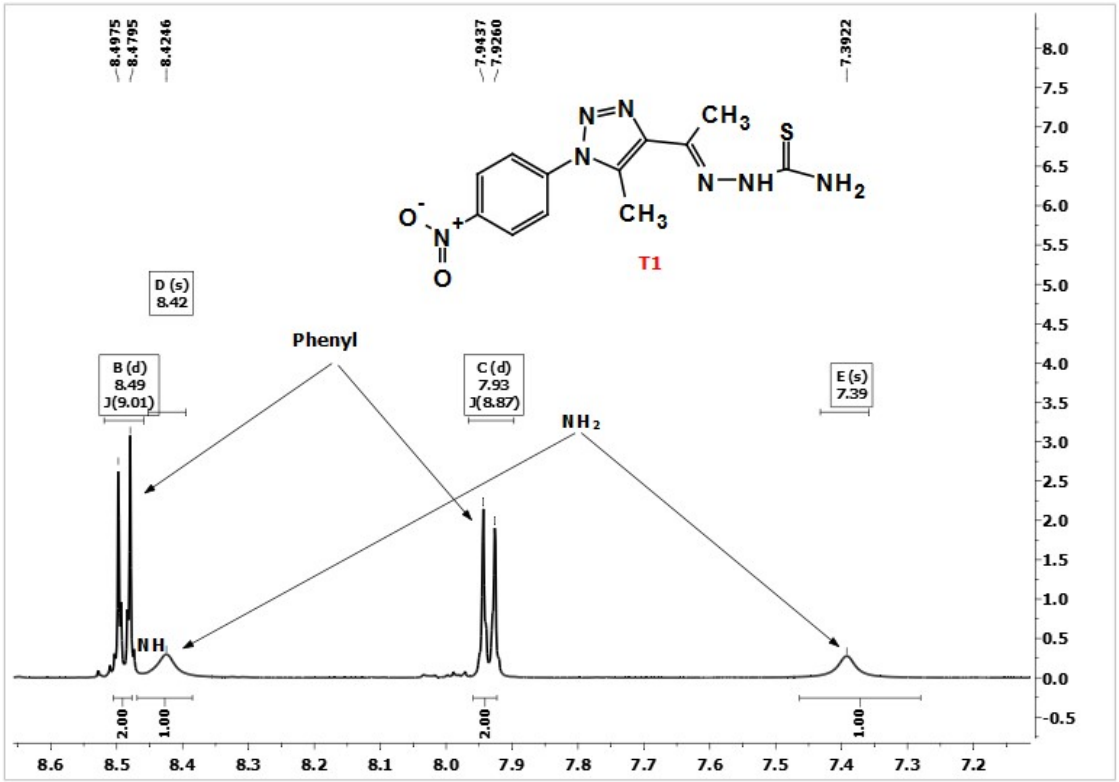
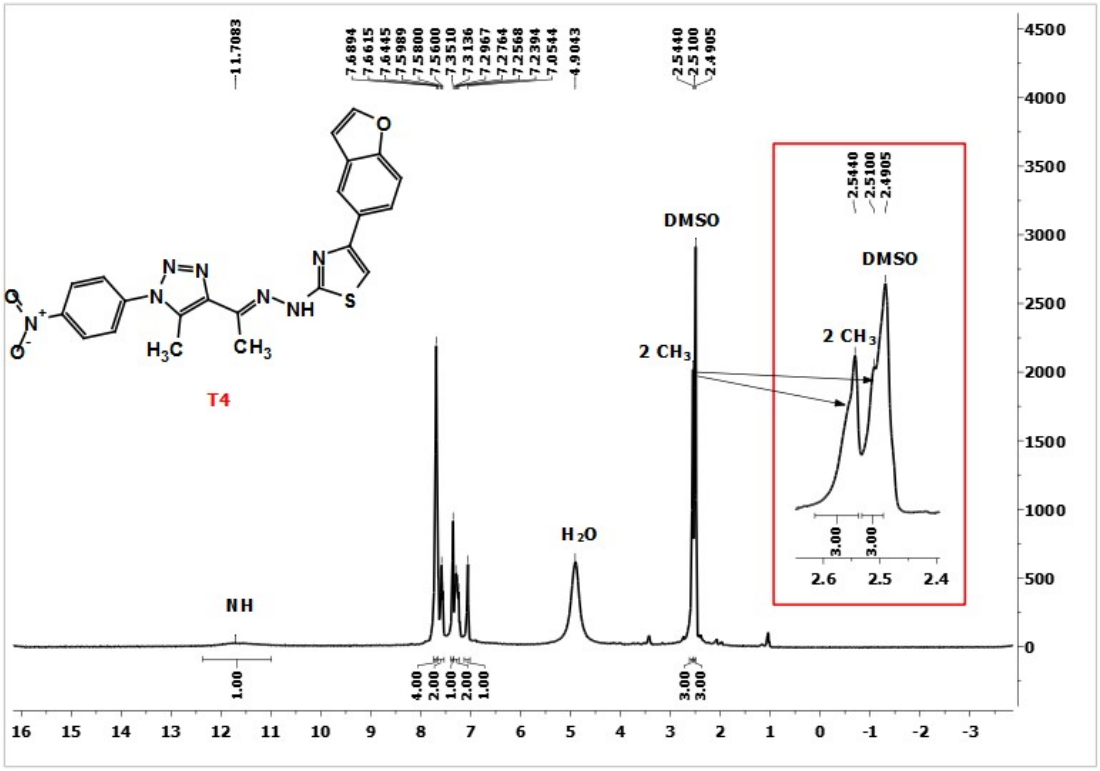
1 Spectral Data of New Compounds

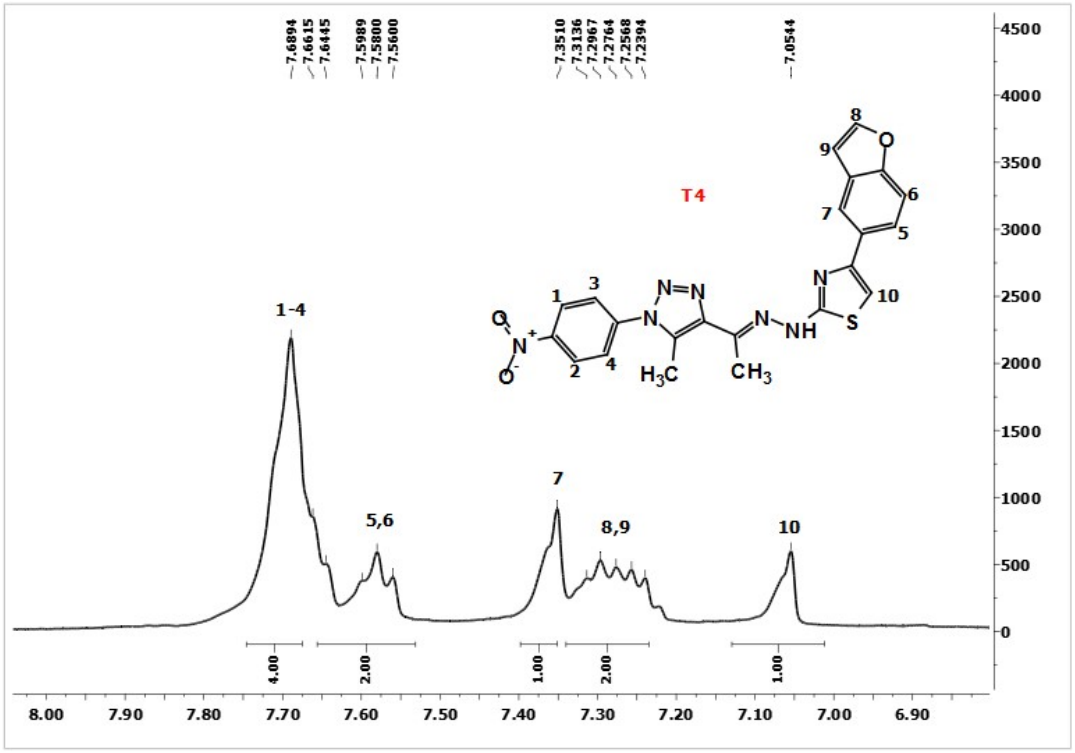
1.1 Spectral Data of 14



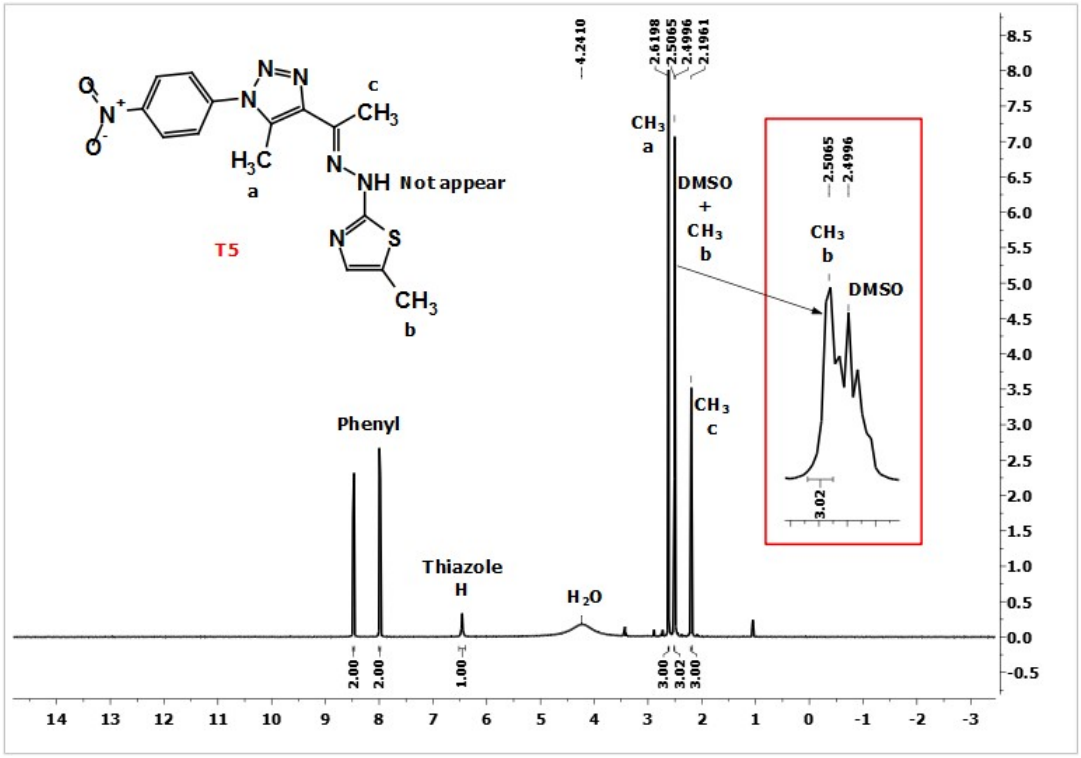


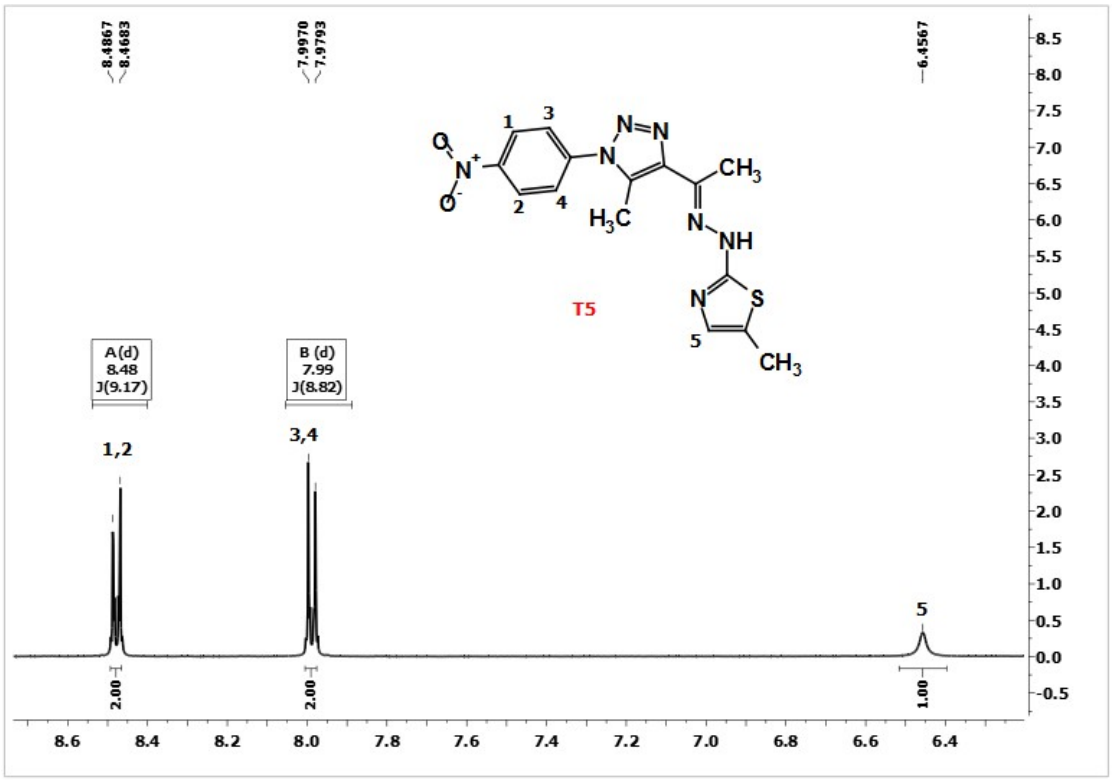
1.2 Spectral Data of 16



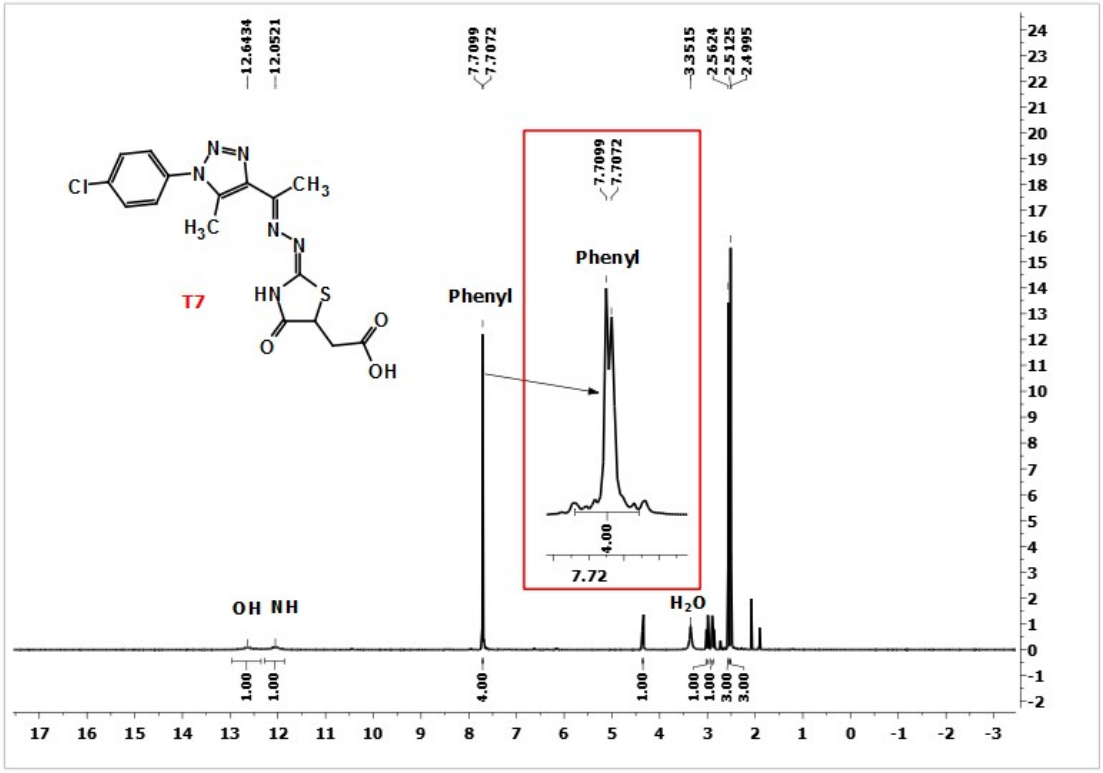


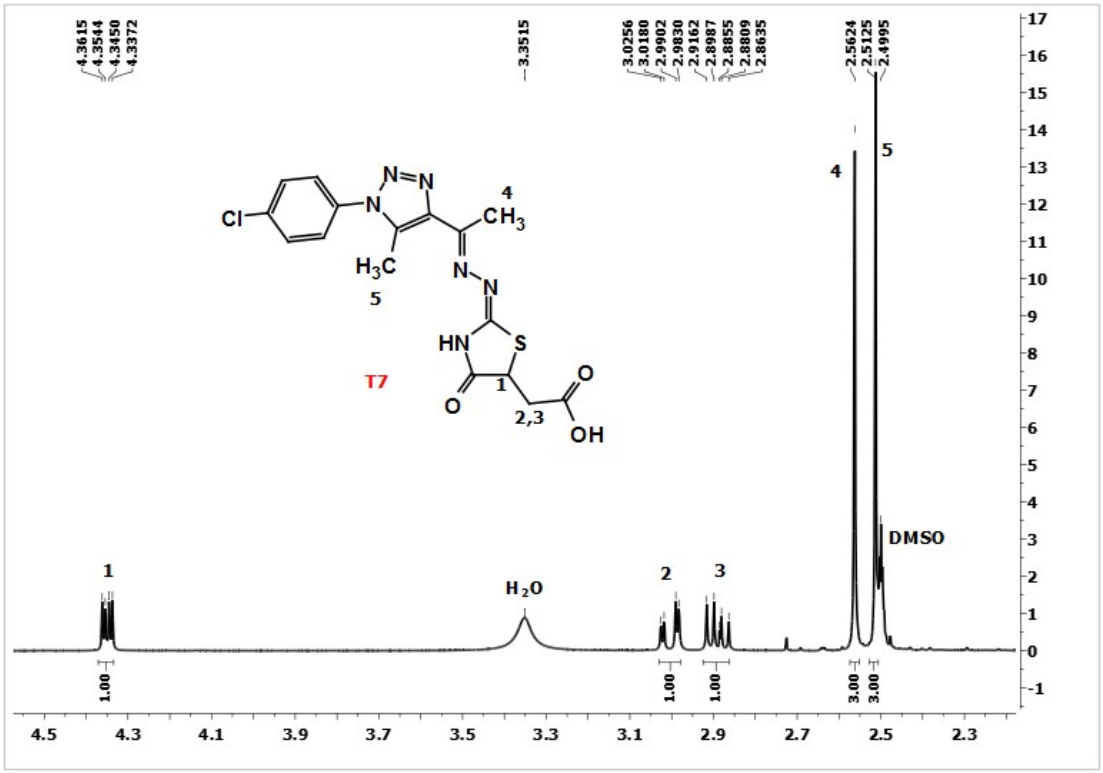
1.3 Spectral Data of 17



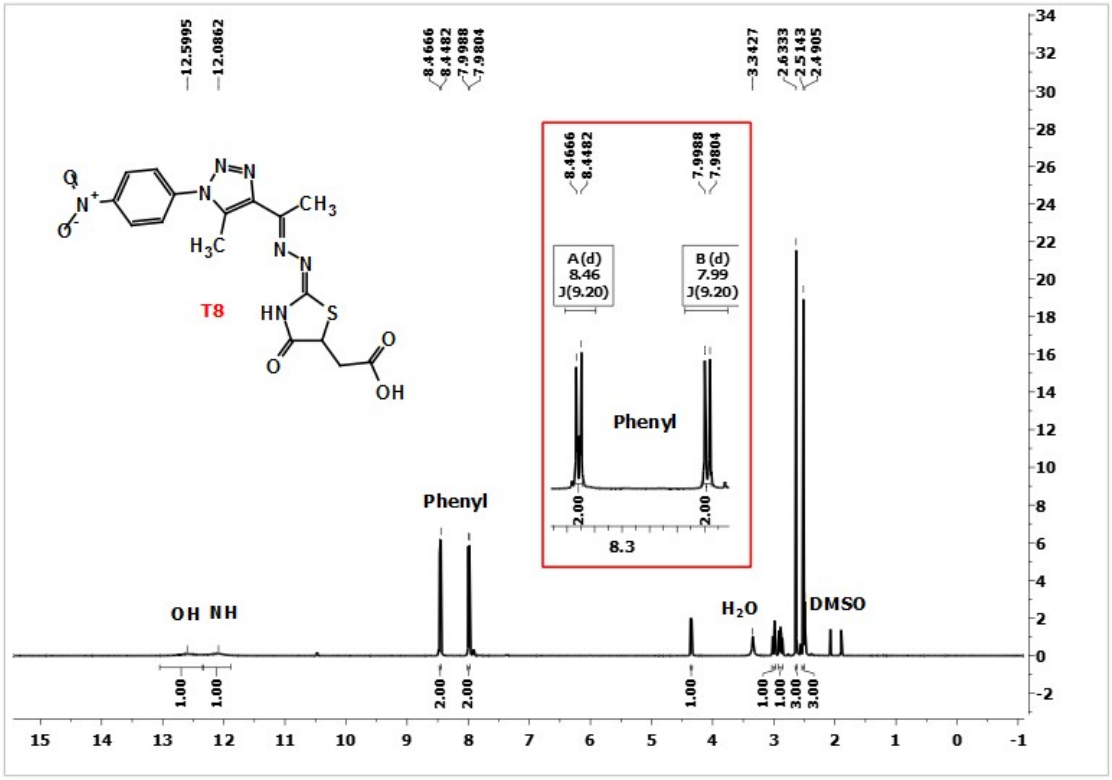


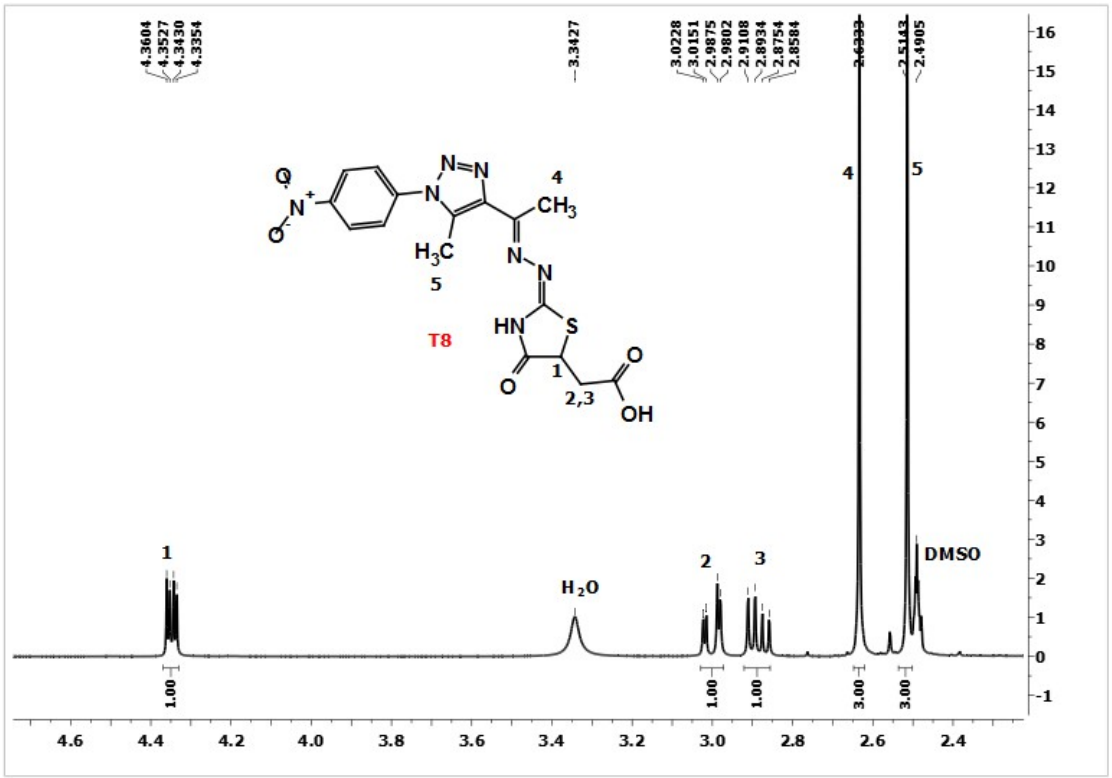
1.4 Spectral Data of 20



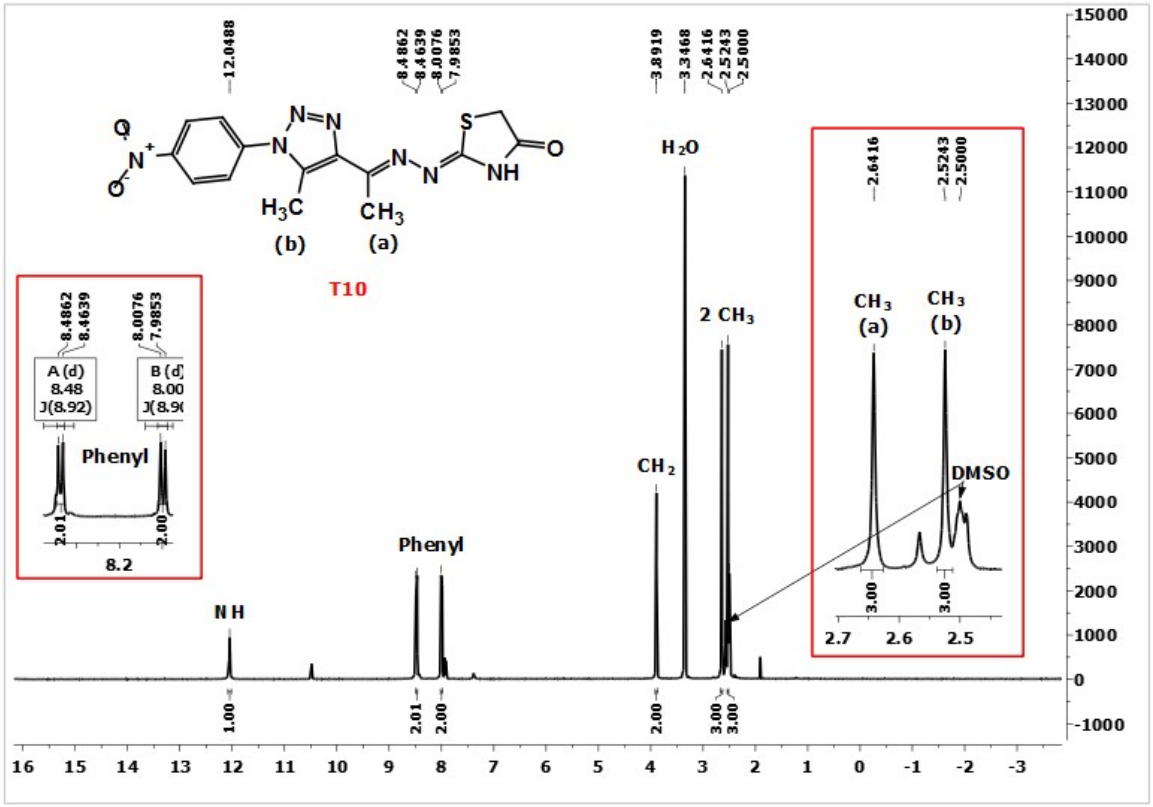


1.5 Spectral Data of 21





1.6 Spectral Data of 22



2 Docking Study

2.1 Sorafenib Re-docked

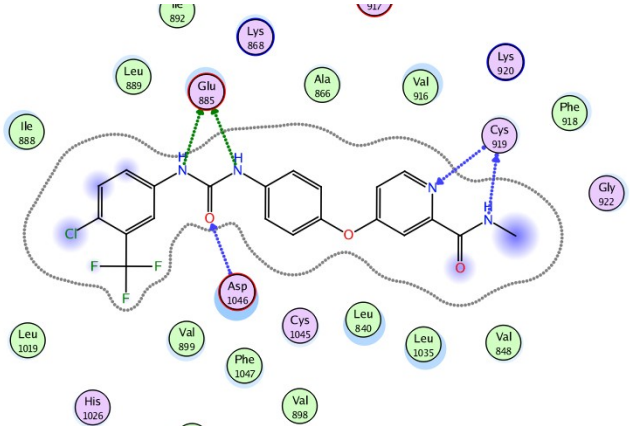
Score -7.47373486 RMSD 1.41946948

Ligand Interactions Report

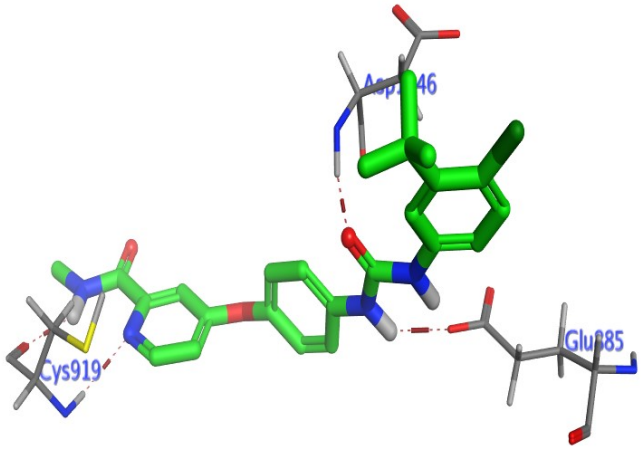
3WZE: TRANSFERASE/TRANSFERASE INHIBITOR / 3WZE: TRANSFERASE/TRANSFERASE INHIBITOR

Ligand Receptor Interaction Distance E (kcal/mol)

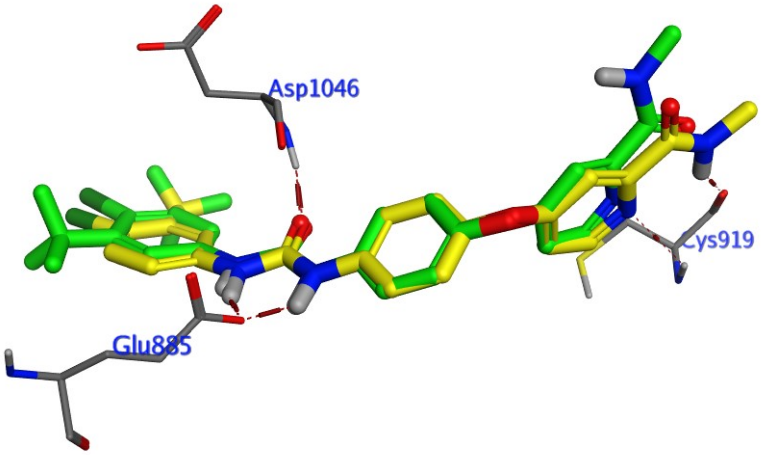
N30	27	O	Cys	919	(A)	H-donor	2.84	-3.0
N12	40	OE2	Glu	885	(A)	H-donor	2.43	13.5
N14	42	OE2	Glu	885	(A)	H-donor	2.89	-4.4
O15	44	N	Asp	1046	(A)	H-acceptor	2.55	-0.2
N26	46	N	Cys	919	(A)	H-acceptor	3.18	-2.2



2D interaction of Sorafenib with the binding pocket of VEGFR-2



3D interaction pattern of Sorafenib with VEGFR-2



Superimposition of the co-crystallized ligand (green) and sorafenib re-docked (yellow) with RMSD value of 1.41

2.2 Results of docking experiment of 14 with VEGFR-2

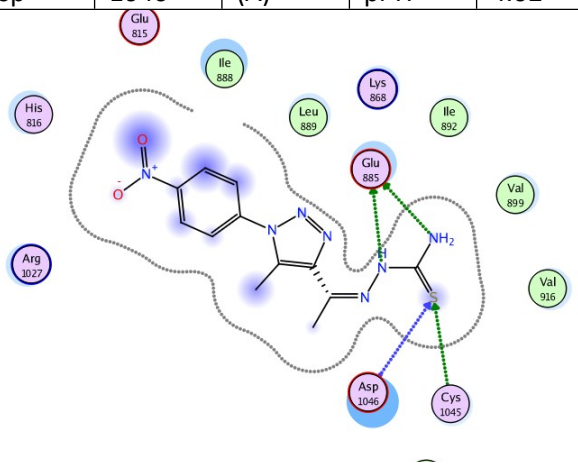
Score -6.73188953 RMSD 2.00392371

Ligand Interactions Report

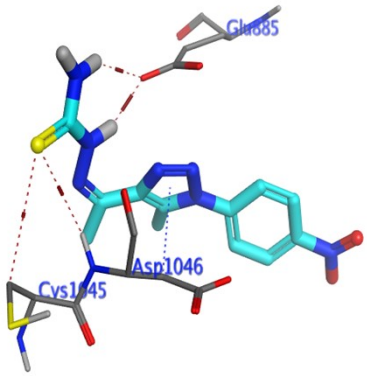
3WZE: TRANSFERASE/TRANSFERASE INHIBITOR / 3WZE

Ligand Receptor Interaction Distance E (kcal/mol)

N	4	OE2	Glu	885	(A)	H-donor	2.84	-4.9
N	6	OE2	Glu	885	(A)	H-donor	2.89	-2.5
S	7	CB	Cys	1045	(A)	H-acceptor	4.14	-0.7
S	7	N	Asp	1046	(A)	H-acceptor	4.10	-1.9
5-ring		Asp	1046	(A)	pi-H	4.02	-0.8	



2D interaction of **14** with the binding pocket of VEGFR-2



3D interaction of **14** with the binding pocket of VEGFR-2

2.3 Results of docking experiment of 15 with VEGFR-2

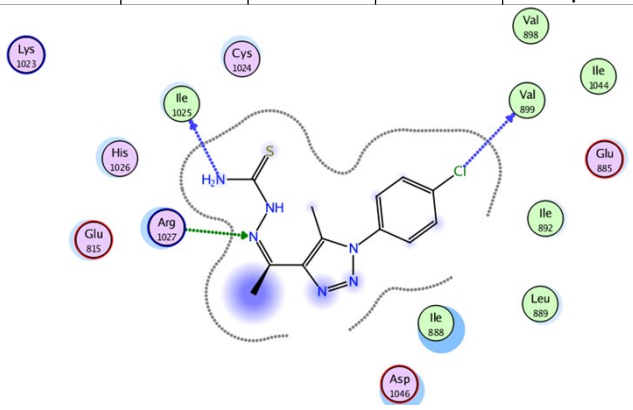
Score -5.13457108 RMSD 1.7709043

Ligand Interactions Report

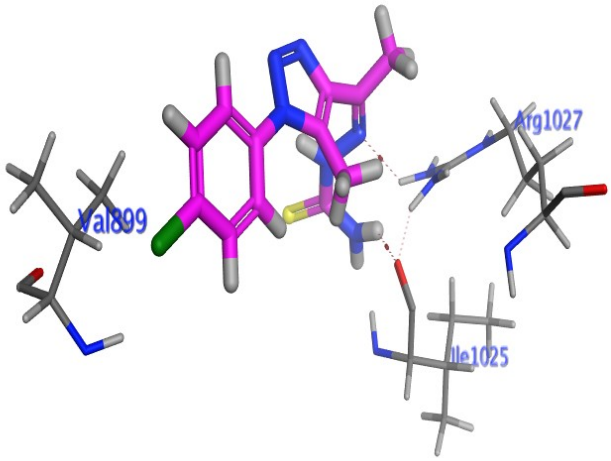
3WZE: TRANSFERASE/TRANSFERASE INHIBITOR / 3WZE

Ligand Receptor Interaction Distance E (kcal/mol)

N	6	O	Ile	1025	(A)	H-donor	3.18	-1.3
CL	19	O	Val	899	(A)	H-donor	3.86	-0.4
N	2	NH2	Arg	1027	(A)	H-acceptor	3.08	-0.9



2D interaction of **15** with the binding pocket of VEGFR-2



3D interaction of **15** with the binding pocket of VEGFR-2

2.4 Results of docking experiment of 16 with VEGFR-2

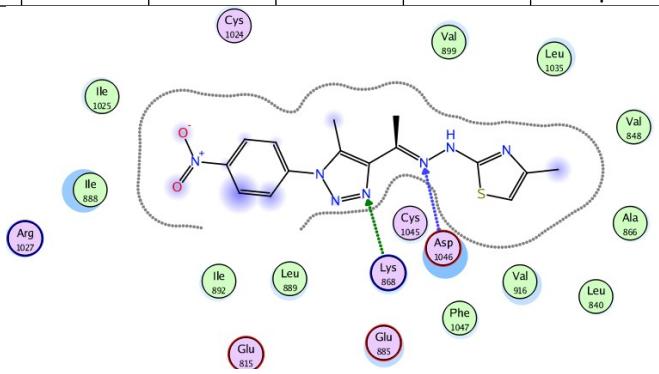
Score -5.94442511 RMSD 1.91050339

Ligand Interactions Report

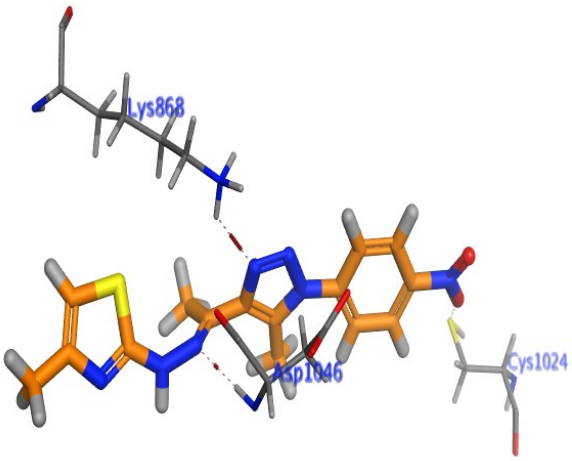
3WZE: TRANSFERASE/TRANSFERASE INHIBITOR / 3WZE

Ligand Receptor Interaction Distance E (kcal/mol)

N	7	N	Asp	1046	(A)	H-acceptor	2.98	-1.4
N	12	NZ	Lys	868	(A)	H-acceptor	2.98	-4.7



2D interaction of **16** with the binding pocket of VEGFR-2



3D interaction of **16** with the binding pocket of VEGFR-2

2.5 Results of docking experiment of 17 with VEGFR-2

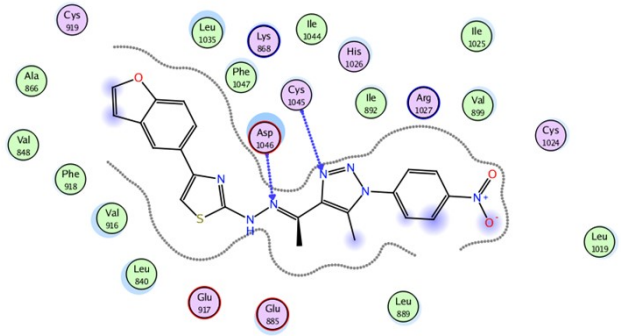
Score -6.68845892 RMSD 1.39521158

Ligand Interactions Report

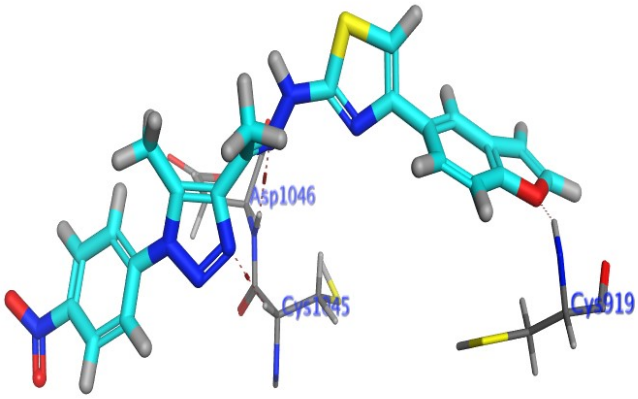
3WZE: TRANSFERASE/TRANSFERASE INHIBITOR / 3WZE

Ligand Receptor Interaction Distance E (kcal/mol)

N	7	N	Asp	1046	(A)	H-acceptor	3.41	-2.4
N	12	CA	Cys	1045	(A)	H-acceptor	3.09	-0.9



2D interaction of **17** with the binding pocket of VEGFR-2



3D interaction of **17** with the binding pocket of VEGFR-2

2.6 Results of docking experiment of 20 with VEGFR-2

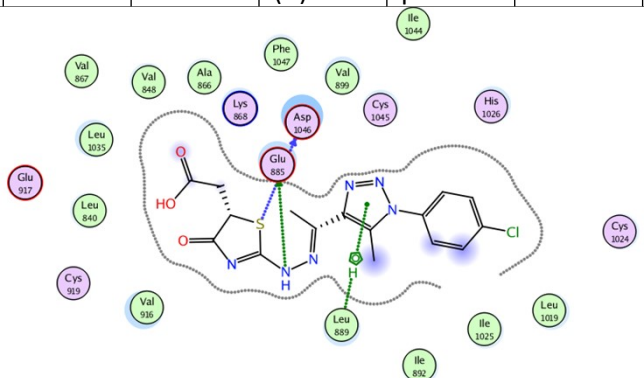
Score -6.85575104 RMSD 2.08517456

Ligand Interactions Report

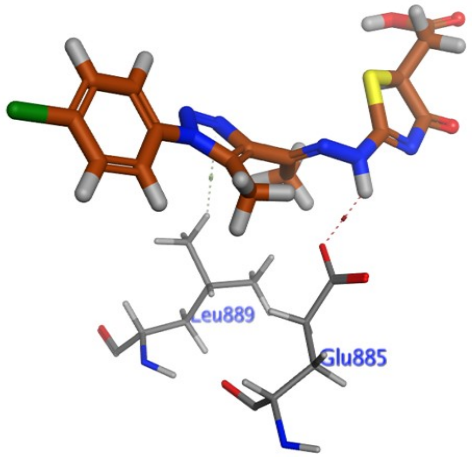
3WZE: TRANSFERASE/TRANSFERASE INHIBITOR / 3WZE

Ligand Receptor Interaction Distance E (kcal/mol)

S	2	O	ASP	1046	(A)	H-donor	3.53	-0.3
N	8	OE2	Glu	885	(A)	H-donor	3.05	-1.5
5-ring	CD2	Leu	889	(A)	pi-H	4.14	-0.8	



2D interaction of **20** with the binding pocket of VEGFR-2



3D interaction of **20** with the binding pocket of VEGFR-2

2.7 Results of docking experiment of 21 with VEGFR-2

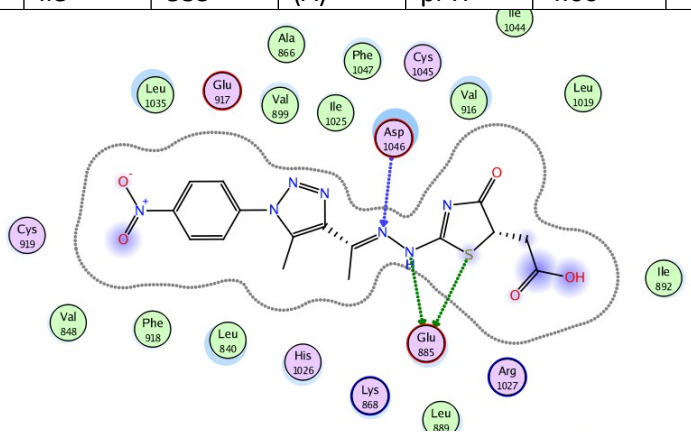
Score -7.00780106 RMSD 1.88689959

Ligand Interactions Report

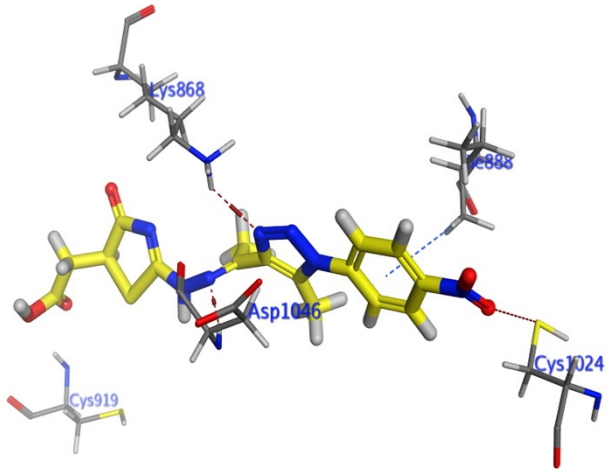
3WZE: TRANSFERASE/TRANSFERASE INHIBITOR / 3WZE

Ligand Receptor Interaction Distance E (kcal/mol)

S	2	OE2	Cys	1024	(A)	H-donor	3.77	-1.0
N	8	OE2	Lys	868	(A)	H-donor	2.94	-6.3
N	9	N	Asp	1046	(A)	H-acceptor	3.26	-2.4
6-ring	CD2	Ile	888	(A)	pi-H	4.00	-0.8	



2D interaction of **21** with the binding pocket of VEGFR-2



2D interaction of **21** with the binding pocket of VEGFR-2

2.8 Results of docking experiment of 22 with VEGFR-2

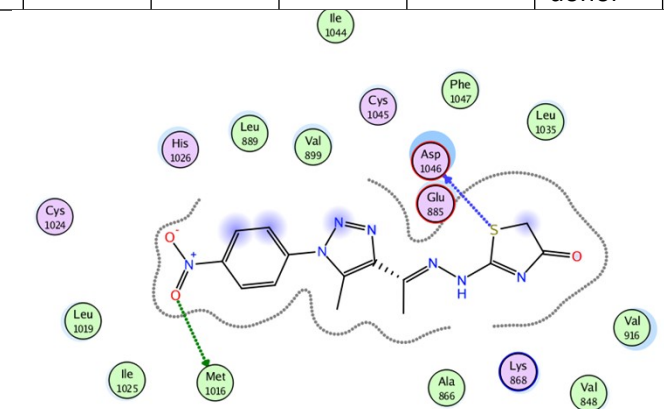
Score -6.31921005 RMSD 1.88676536

Ligand Interactions Report

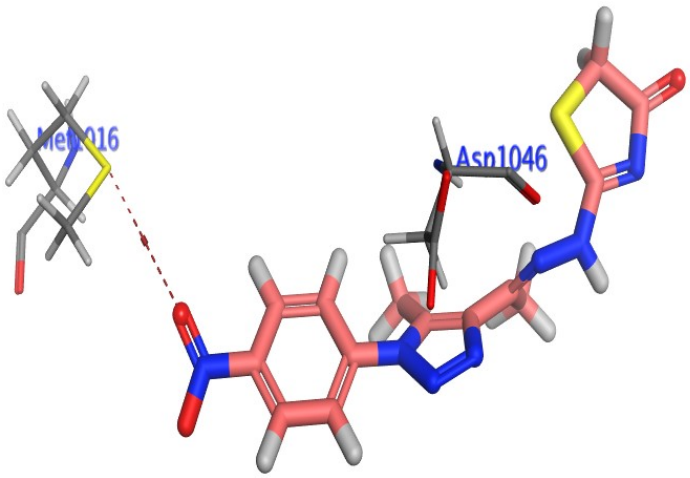
3WZE: TRANSFERASE/TRANSFERASE INHIBITOR / 3WZE

Ligand Receptor Interaction Distance E (kcal/mol)

S	1	O	Asp	1046	(A)	H-donor	3.48	-0.1
O	23	SD	Met	1016	(A)	H-donor	3.68	-1.1



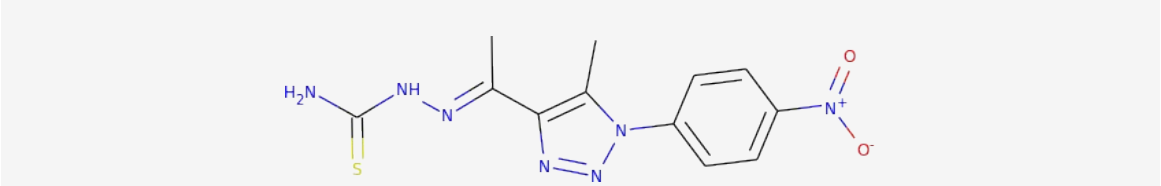
2D interaction of **22** with the binding pocket of VEGFR-2



2D interaction of **22** with the binding pocket of VEGFR-2

3 ADMET Profiling Study

3.1 ADMET Profile of 14



Molecule properties:

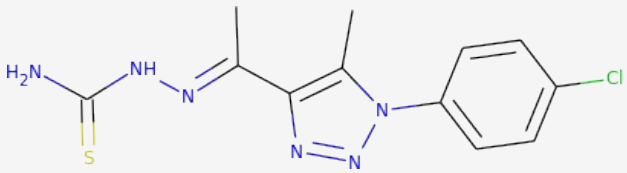
Descriptor	Value
Molecular Weight	319.35
LogP	1.04112
#Rotatable Bonds	4
#Acceptors	7
#Donors	2
Surface Area	130.511

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	**-2.982**	Numeric (log mol/L)
Absorption	Caco2 permeability	**-0.061**	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	**74.97**	Numeric (% Absorbed)
Absorption	Skin Permeability	**-2.763**	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)	**-0.212**	Numeric (log L/kg)
Distribution	Fraction unbound (human)	**0.161**	Numeric (Fu)

Descriptor	Value		
Distribution	BBB permeability	**-1.117**	Numeric (log BB)
Distribution	CNS permeability	**-2.917**	Numeric (log PS)
Metabolism	CYP2D6 substrate	**No**	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	**No**	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	**No**	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	**No**	Categorical (Yes/No)
Excretion	Total Clearance	**-0.017**	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)	**0.531**	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)	**2.256**	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	**2.522**	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	**No**	Categorical (Yes/No)
Toxicity	Skin Sensitisation	**No**	Categorical (Yes/No)
Toxicity	*T.Pyriformis* toxicity	**0.48**	Numeric (log ug/L)
Toxicity	Minnow toxicity	**0.209**	Numeric (log mM)

3.2 ADMET Profile of 15

Molecule Depiction



Molecule properties:

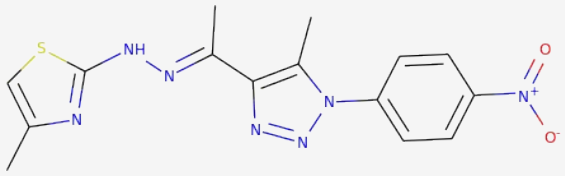
Descriptor	Value
Molecular Weight	308.798
LogP	1.78632
#Rotatable Bonds	3
#Acceptors	5
#Donors	2
Surface Area	126.161

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	**-3.27**	Numeric (log mol/L)
Absorption	Caco2 permeability	**1.315**	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	**92.584**	Numeric (% Absorbed)
Absorption	Skin Permeability	**-2.857**	Numeric (log Kp)
Absorption	P-glycoprotein	**No**	Categorical (Yes/No)

Descriptor	Value		
	substrate		
Absorption	P-glycoprotein I inhibitor	**No**	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	**No**	Categorical (Yes/No)
Distribution	VDss (human)	**-0.105**	Numeric (log L/kg)
Distribution	Fraction unbound (human)	**0.282**	Numeric (Fu)
Distribution	BBB permeability	**-0.78**	Numeric (log BB)
Distribution	CNS permeability	**-3.379**	Numeric (log PS)
Metabolism	CYP2D6 substrate	**No**	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	**No**	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	**No**	Categorical (Yes/No)
Excretion	Total Clearance	**-0.165**	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	**No**	Categorical (Yes/No)
Toxicity	AMES toxicity	**No**	Categorical (Yes/No)

Descriptor	Value		
Toxicity	Max. tolerated dose (human)	**0.686**	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)	**2.345**	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	**1.894**	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	**No**	Categorical (Yes/No)
Toxicity	Skin Sensitisation	**No**	Categorical (Yes/No)
Toxicity	*T.Pyriformis* toxicity	**0.586**	Numeric (log ug/L)
Toxicity	Minnow toxicity	**0.905**	Numeric (log mM)

3.3 ADMET Profile of 16



Molecule properties:

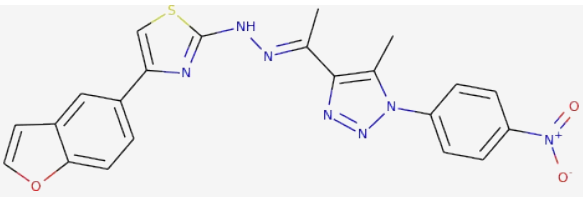
Descriptor	Value
Molecular Weight	357.399
LogP	3.08494
#Rotatable Bonds	5
#Acceptors	9
#Donors	1
Surface Area	146.729

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	**-4.39**	Numeric (log mol/L)
Absorption	Caco2 permeability	**0.023**	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	**93.226**	Numeric (% Absorbed)
Absorption	Skin Permeability	**-2.763**	Numeric (log Kp)
Absorption	P-glycoprotein substrate	**Yes**	Categorical (Yes/No)

Descriptor	Value		
Absorption	P-glycoprotein I inhibitor	**Yes**	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	**No**	Categorical (Yes/No)
Distribution	VDss (human)	**-0.206**	Numeric (log L/kg)
Distribution	Fraction unbound (human)	**0.187**	Numeric (Fu)
Distribution	BBB permeability	**-1.307**	Numeric (log BB)
Distribution	CNS permeability	**-2.501**	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	**0.302**	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	**No**	Categorical (Yes/No)
Toxicity	AMES toxicity	**Yes**	Categorical (Yes/No)
Toxicity	Max. tolerated dose	**-0.279**	Numeric (log mg/kg/day)

Descriptor	Value		
	(human)		
Toxicity	hERG I inhibitor	**No**	Categorical (Yes/No)
Toxicity	hERG II inhibitor	**No**	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	**2.961**	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	**1.127**	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	**Yes**	Categorical (Yes/No)
Toxicity	Skin Sensitisation	**No**	Categorical (Yes/No)
Toxicity	*T.Pyriformis* toxicity	**0.61**	Numeric (log ug/L)
Toxicity	Minnow toxicity	**0.922**	Numeric (log mM)

3.4 ADMET Profile of 17



Molecule properties:

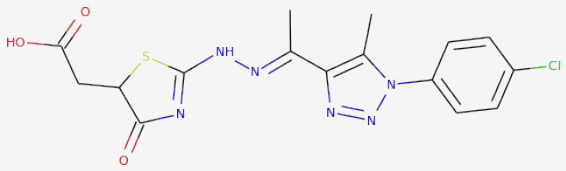
Descriptor	Value
Molecular Weight	459.491
LogP	5.18972
#Rotatable Bonds	6
#Acceptors	10
#Donors	1
Surface Area	190.897

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	**-4.785**	Numeric (log mol/L)
Absorption	Caco2 permeability	**-0.142**	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	**100**	Numeric (% Absorbed)
Absorption	Skin Permeability	**-2.732**	Numeric (log Kp)
Absorption	P-glycoprotein substrate	**Yes**	Categorical (Yes/No)
Absorption	P-glycoprotein I	**Yes**	Categorical (Yes/No)

Descriptor	Value		
	inhibitor		
Absorption	P-glycoprotein II inhibitor	**Yes**	Categorical (Yes/No)
Distribution	VDss (human)	**0.268**	Numeric (log L/kg)
Distribution	Fraction unbound (human)	**0.175**	Numeric (Fu)
Distribution	BBB permeability	**-1.478**	Numeric (log BB)
Distribution	CNS permeability	**-2.065**	Numeric (log PS)
Metabolism	CYP2D6 substrate	**No**	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	**Yes**	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	**No**	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)
Excretion	Total Clearance	**0.323**	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)	**0.288**	Numeric (log mg/kg/day)

Descriptor	Value		
Toxicity	hERG I inhibitor	**No**	Categorical (Yes/No)
Toxicity	hERG II inhibitor	**No**	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	**3.204**	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	**0.419**	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	**Yes**	Categorical (Yes/No)
Toxicity	Skin Sensitisation	**No**	Categorical (Yes/No)
Toxicity	*T.Pyriformis* toxicity	**0.286**	Numeric (log ug/L)
Toxicity	Minnow toxicity	**-1.502**	Numeric (log mM)

3.5 ADMET Profile of 20



Molecule properties:

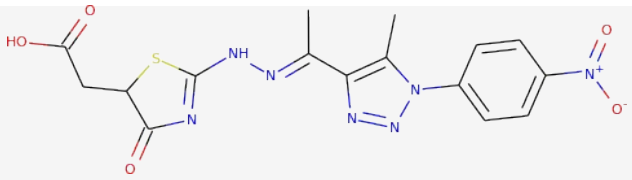
Descriptor	Value
Molecular Weight	406.855
LogP	2.01542
#Rotatable Bonds	5
#Acceptors	8
#Donors	2
Surface Area	163.052

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	**-3.338**	Numeric (log mol/L)
Absorption	Caco2 permeability	**0.67**	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	**58.477**	Numeric (% Absorbed)
Absorption	Skin Permeability	**-2.735**	Numeric (log Kp)
Absorption	P-glycoprotein substrate	**Yes**	Categorical (Yes/No)

Descriptor	Value		
Absorption	P-glycoprotein I inhibitor	**No**	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	**No**	Categorical (Yes/No)
Distribution	VDss (human)	**-1.89**	Numeric (log L/kg)
Distribution	Fraction unbound (human)	**0.318**	Numeric (Fu)
Distribution	BBB permeability	**-1.476**	Numeric (log BB)
Distribution	CNS permeability	**-2.76**	Numeric (log PS)
Metabolism	CYP2D6 substrate	**Yes**	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	**Yes**	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	**No**	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	**No**	Categorical (Yes/No)
Excretion	Total Clearance	**0.119**	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	**No**	Categorical (Yes/No)
Toxicity	AMES toxicity	**No**	Categorical (Yes/No)
Toxicity	Max. tolerated dose	**0.322**	Numeric (log mg/kg/day)

Descriptor	Value		
	(human)		
Toxicity	hERG I inhibitor	**No**	Categorical (Yes/No)
Toxicity	hERG II inhibitor	**No**	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	**2.174**	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	**1.827**	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	**Yes**	Categorical (Yes/No)
Toxicity	Skin Sensitisation	**No**	Categorical (Yes/No)
Toxicity	*T.Pyriformis* toxicity	**0.285**	Numeric (log ug/L)
Toxicity	Minnow toxicity	**1.521**	Numeric (log mM)

3.6 ADMET Profile of 21



Molecule properties:

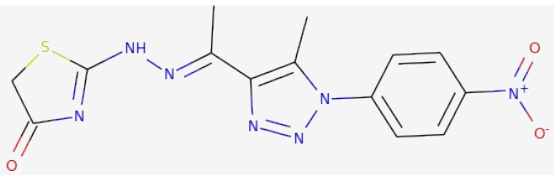
Descriptor	Value
Molecular Weight	417.407
LogP	1.27022
#Rotatable Bonds	6
#Acceptors	10
#Donors	2
Surface Area	167.402

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	**-3.489**	Numeric (log mol/L)
Absorption	Caco2 permeability	**-0.59**	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	**54.111**	Numeric (% Absorbed)
Absorption	Skin Permeability	**-2.735**	Numeric (log Kp)
Absorption	P-glycoprotein substrate	**Yes**	Categorical (Yes/No)
Absorption	P-glycoprotein I	**No**	Categorical (Yes/No)

Descriptor	Value		
	inhibitor		
Absorption	P-glycoprotein II inhibitor	**No**	Categorical (Yes/No)
Distribution	VDss (human)	**-1.916**	Numeric (log L/kg)
Distribution	Fraction unbound (human)	**0.253**	Numeric (Fu)
Distribution	BBB permeability	**-1.803**	Numeric (log BB)
Distribution	CNS permeability	**-3.099**	Numeric (log PS)
Metabolism	CYP2D6 substrate	**Yes**	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	**Yes**	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	**No**	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	**No**	Categorical (Yes/No)
Excretion	Total Clearance	**0.269**	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	**No**	Categorical (Yes/No)
Toxicity	AMES toxicity	**No**	Categorical (Yes/No)
Toxicity	Max. tolerated dose (human)	**-0.177**	Numeric (log mg/kg/day)

Descriptor	Value		
Toxicity	hERG I inhibitor	**No**	Categorical (Yes/No)
Toxicity	hERG II inhibitor	**No**	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	**1.981**	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	**2.463**	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	**Yes**	Categorical (Yes/No)
Toxicity	Skin Sensitisation	**No**	Categorical (Yes/No)
Toxicity	*T.Pyriformis* toxicity	**0.285**	Numeric (log ug/L)
Toxicity	Minnow toxicity	**1.913**	Numeric (log mM)

3.7 ADMET Profile of 22



Molecule properties:

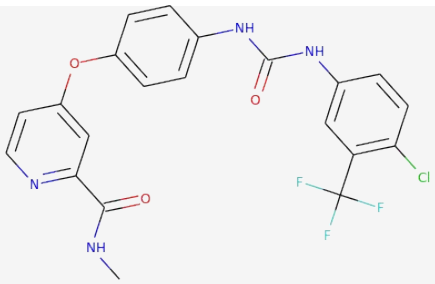
Descriptor	Value
Molecular Weight	359.371
LogP	1.42692
#Rotatable Bonds	4
#Acceptors	9
#Donors	1
Surface Area	145.716

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	**-3.895**	Numeric (log mol/L)
Absorption	Caco2 permeability	**-0.061**	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	**82.65**	Numeric (% Absorbed)
Absorption	Skin Permeability	**-2.759**	Numeric (log Kp)
Absorption	P-glycoprotein substrate	**Yes**	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	**Yes**	Categorical (Yes/No)

Descriptor	Value		
Absorption	P-glycoprotein II inhibitor	**No**	Categorical (Yes/No)
Distribution	VDss (human)	**-0.439**	Numeric (log L/kg)
Distribution	Fraction unbound (human)	**0.24**	Numeric (Fu)
Distribution	BBB permeability	**-1.357**	Numeric (log BB)
Distribution	CNS permeability	**-2.746**	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	**No**	Categorical (Yes/No)
Excretion	Total Clearance	**0.279**	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)	**-0.636**	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)	**2.706**	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	**1.237**	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	**Yes**	Categorical (Yes/No)
Toxicity	Skin Sensitisation	**No**	Categorical (Yes/No)
Toxicity	*T.Pyriformis* toxicity	**1.039**	Numeric (log ug/L)
Toxicity	Minnow toxicity	**2.615**	Numeric (log mM)

3.8 ADMET Profile of Sorafenib



Molecule properties:

Descriptor	Value
Molecular Weight	464.831
LogP	5.5497
#Rotatable Bonds	5
#Acceptors	4
#Donors	3
Surface Area	185.111

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	**-4.888**	Numeric (log mol/L)
Absorption	Caco2 permeability	**0.613**	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	**84.731**	Numeric (% Absorbed)
Absorption	Skin Permeability	**-2.776**	Numeric (log Kp)

Descriptor	Value		
Absorption	P-glycoprotein substrate	**Yes**	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	**Yes**	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	**Yes**	Categorical (Yes/No)
Distribution	VDss (human)	**-0.233**	Numeric (log L/kg)
Distribution	Fraction unbound (human)	**0.058**	Numeric (Fu)
Distribution	BBB permeability	**-1.682**	Numeric (log BB)
Distribution	CNS permeability	**-1.995**	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)

Descriptor	Value		
Metabolism	CYP3A4 inhibitior	**Yes**	Categorical (Yes/No)
Excretion	Total Clearance	**-0.212**	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	**No**	Categorical (Yes/No)
Toxicity	AMES toxicity	**No**	Categorical (Yes/No)
Toxicity	Max. tolerated dose (human)	**0.677**	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)	**2.595**	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	**1.054**	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	**Yes**	Categorical (Yes/No)
Toxicity	Skin Sensitisation	**No**	Categorical (Yes/No)
Toxicity	*T.Pyriformis* toxicity	**0.349**	Numeric (log ug/L)
Toxicity	Minnow toxicity	**-0.421**	Numeric (log mM)