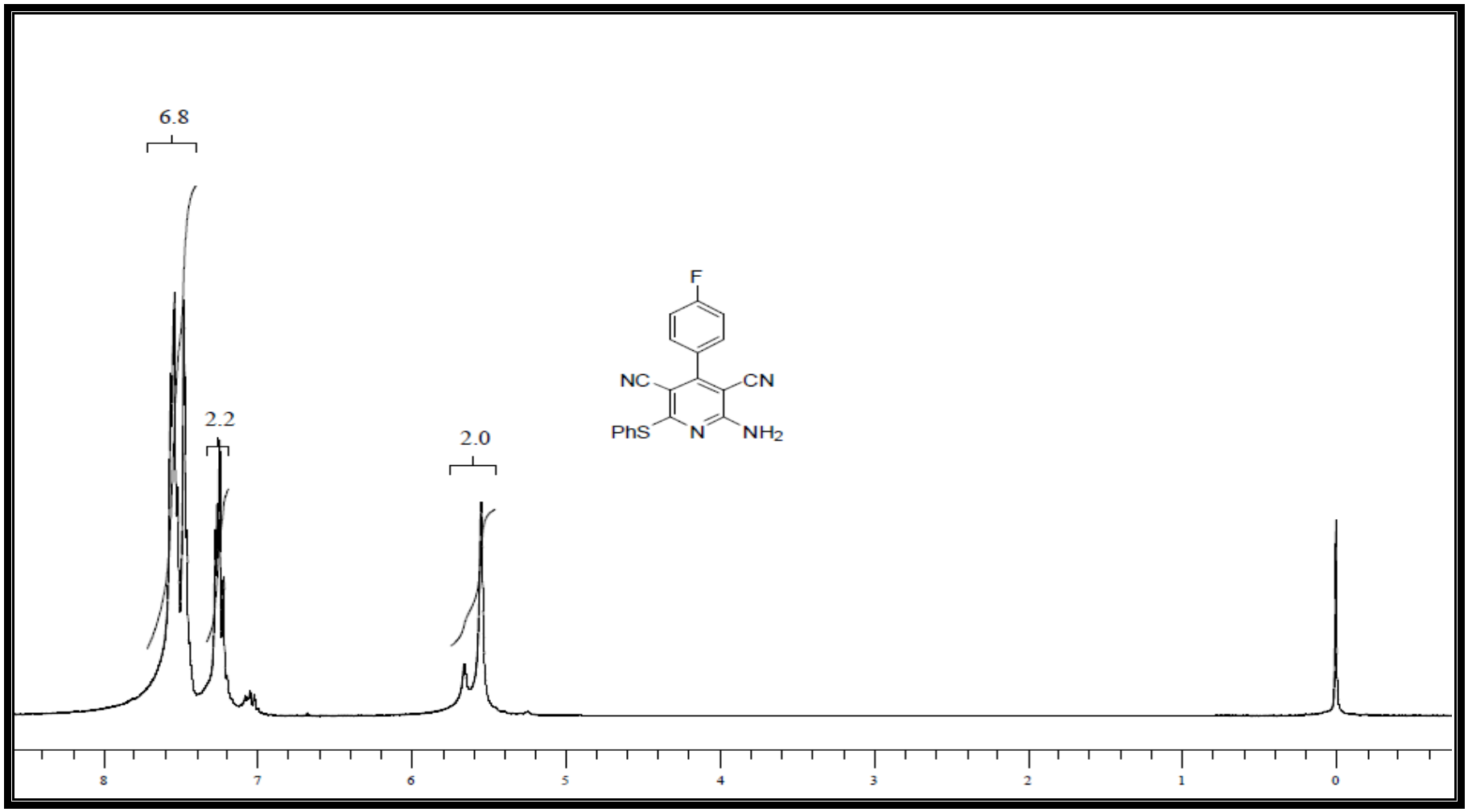
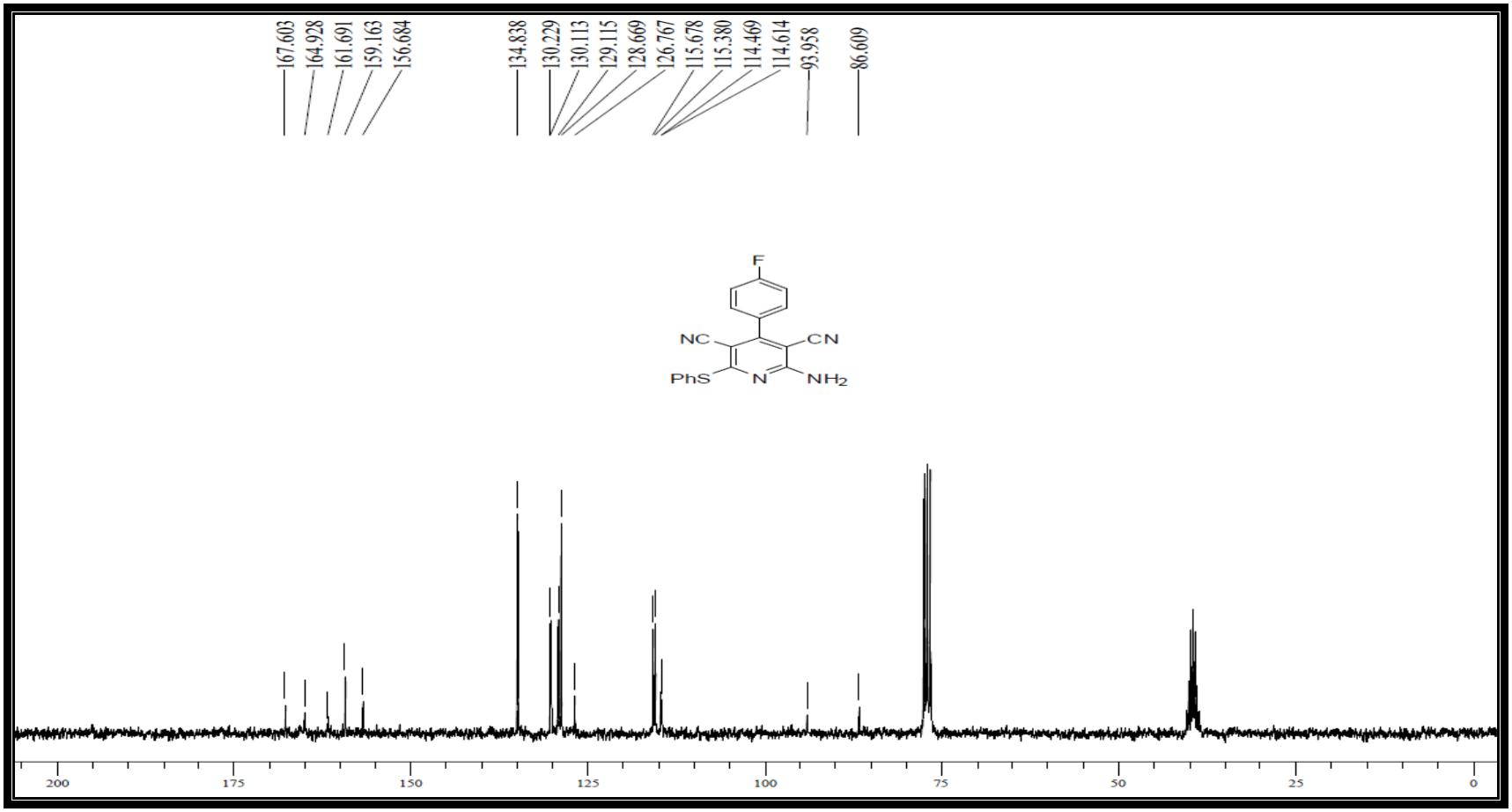
Supporting Information

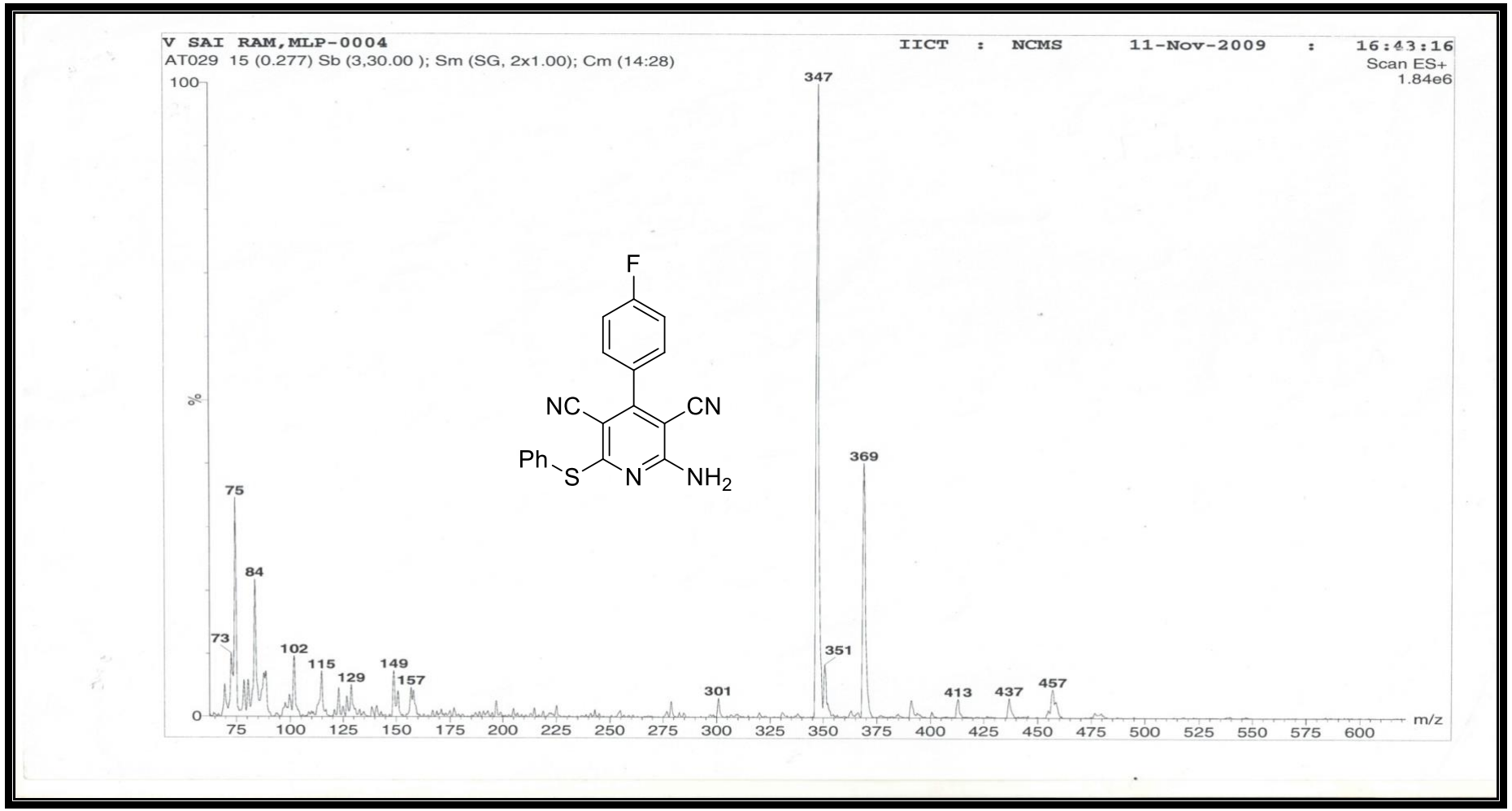
Spectral characterization of compound 4f



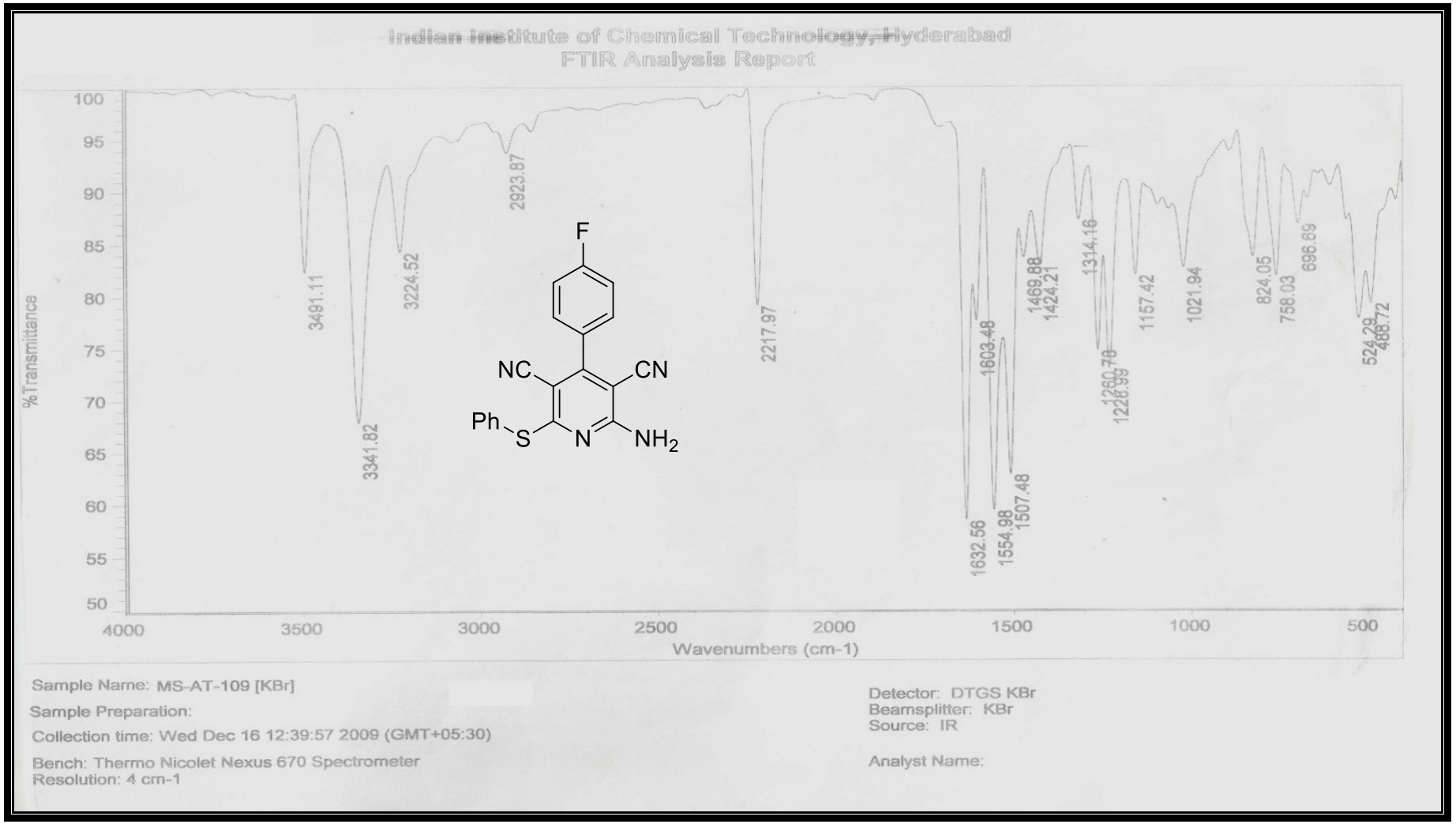
^{1}H NMR Spectrum of compound 4f



^{13}C NMR Spectrum of compound 4f



Mass Spectrum of compound 4f



IR Spectrum of compound 4f

Table S5: Protein-ligand interaction profiles of novel compounds with 2VF5.

Ligands	*ΔG* binding kcal/mol	Hydrogen Bond Interactions			Hydrophobic Interactions		
		AA Residues	Distance (Å)	Angle°	AA Residues	Type	Distance (Å)
4a	**-7.4**	Val605	2.43	153.55	Cys300	Pi-Alkyl	5.45
					Leu484	Pi-Sigma	3.46
					Leu601	Pi-Alkyl	5.46
4b	**-7.3**	Val399	2.05	139.99	Cys300	Pi-Alkyl	5.47
		Gln348	2.98	20.92	Val605	Pi-Alkyl	5.45
		Glu488	2.06	131.33			
		Val605	2.56	149.68			
4c	**-7.0**	Ser303	3.31	114.83	Ala404	Alkyl	3.76
		Thr352	1.91	153.96	Leu601	Pi-Alkyl	4.86
		Ala400	3.77	165.57	Ala602	Sulfur-X	3.30
		Ser401	4.02	40.51			
4d	**-7.6**	Ser303	2.24	132.63	Ala299	4.15	Alkyl
		Ser303	2.39	118.41	Cys300	4.84	Alkyl
		Leu346	3.78	127.13	Ala602	4.99	Alkyl
		Val399	2.22	168.73	Val605	4.82	Alkyl
		Ser401	3.35	110.72			
		Ser401	3.374	84.71			
		Ser401	3.58	90.83			
		Glu488	2.58	97.54			
4e	**-7.1**	Gly301	2.63	110.65	Cys300	4.57	Alkyl
		Thr352	2.56	124.43	Cys300	3.82	Pi-Alkyl
		Ser401	4.09	40.12	Val605	3.76	Alkyl
		Ala602	2.98	93.83	Val605	5.48	Pi-Alkyl
		Ala602	2.27	123.09			
4f	**-7.0**	Ser303	3.16	101.27	Ala404	Alkyl	3.68
		Thr352	2.04	145.27	Leu601	Pi-Sigma	3.74
		Ser401	2.90	93.13			
4h	**-7.1**	Thr302	2.37	133.76	Ala602	Pi-Alkyl	5.05
		Glu488	1.90	158.73	Val605	Alkyl	3.94

		Val605	2.43	146.81	Val605	Pi-Alkyl	4.84
4i	**-8.1**	Thr302	2.94	93.06	Cys300	Pi-Alkyl	4.60
		Gln348	2.23	122.97			
		Gln348	2.38	170.00			
		Ser349	2.14	149.94			
		Thr352	2.98	112.20			
		Ser401	2.96	139.85			
		Glu488	2.48	102.53			
4j	**-7.3**	Thr352	1.93	152.73	Leu601	Pi-Alkyl	4.71
		Ser401	4.01	43.83			
4k	**-6.9**	Thr352	2.05	139.901	Ala404	Alkyl	3.61
		Ala400	3.67	168.12	Leu601	Pi-Sigma	3.81
		Ser401	4.09	41.171			
4l	**-6.8**	Thr302	2.40	128.78	Leu601	Pi-Alkyl	5.48
		Glu488	1.88	163.51	Ala602	Pi-Alkyl	5.13
		Val605	2.49	145.57	Val605	Pi-Alkyl	4.91
***GPL**	**-6.3**	CYS300	3.49037	96.838			
		SER303	1.86703	154.536			
		SER347	2.88629	104.087			
		GLN348	3.10329	42.672			
		SER349	2.07918	125.339			
		SER349	3.09821	18.874			
		THR352	2.77294	110.056			
		VAL399	2.22192	155.545			
		GLU488	2.74896	94.513			
		ALA602	2.93043	98.258			
		LYS603	1.76205	177.673			

Table S6: Protein-ligand interaction profiles of novel compounds with 2POC.

Ligands	*ΔG* binding kcal/mol	Hydrogen Bond Interactions			Hydrophobic Interactions		
		AA Residues	Distance (Å)	Angle°	AA Residues	Type	Distance (Å)
4a	**-7.3**	His492	2.24	153.44	Arg370	Pi-Alkyl	5.42
		Asn494	2.60	29.25			
4b	**-7.9**	Ser484	2.42	107.73	Cys489	Amide-Pi Stacked	4.48
		Thr487	2.48	142.53	His492	Pi-Pi T-shaped	4.56
		Thr487	2.42	107.63	His492	Pi-Alkyl	5.28
		Thr487	2.78	146.65			
		His488	2.80	112.14			
4c	**-7.4**	His492	2.32	153.35			
		Asn494	2.56	117.58			
		Thr381	3.58	125.11			
		Asn494	2.54	31.88			
4d	**-7.7**	His492	3.03	94.44	Lys386	Pi-Alkyl	4.97
					His492	Pi-Alkyl	4.00
4e	**-7.6**	Trp388	2.69	148.69	Trp388	Pi-Sulfur	4.71
		Ser484	2.99	126.42	Trp388	Pi-Sulfur	5.88
		Thr487	2.98	95.35	Val491	Alkyl	4.45
		Thr487	2.81	105.88	His492	Pi-Alkyl	4.94
		His488	3.08	97.97	His492	Pi-Cation	4.96
		His488	2.27	144.82	His492	Pi-Pi T-shaped	4.46
		His492	2.18	152.53			
4f	**-7.8**	-	-	-	His492	Pi-Cation	4.35

					His492	Pi-Pi Stacked	4.52
					His492	Pi-Alkyl	4.54
					Lys386	Pi-Alkyl	4.96
4g	**-7.4**	Arg370	2.52	109.30	Arg370	Pi-Alkyl	5.38
		Gly383	2.42	151.21	His492	Pi-Alkyl	5.10
					His492	Pi-Alkyl	4.89
4h	**-7.6**	Gly383	2.20	152.73	Arg372	Pi-Cation	4.38
		Arg370	2.58	105.97	His492	Pi-Alkyl	4.52
					His492	Pi-Alkyl	4.80
					Arg370	Pi-Alkyl	5.35
4i	**-7.7**	Gly383	2.88	109.77			
		His492	2.23	156.78			
		Asn494	2.60	119.87			
		Asn494	2.64	31.91			
4j	**-7.3**	Gly383	2.88	109.77			
		His492	2.23	156.78			
		Asn494	2.60	119.87			
		Asn494	2.64	31.91			
4k	**-7.4**	Arg370	1.94	154.41	Arg370	Pi-Alkyl	5.38
		Gly383	2.43	153.93	His492	Pi-Alkyl	4.52
4l	**-7.4**	Gly383	2.39	152.85	His492	Pi-Alkyl	4.76
		Arg370	2.24	123.14	Arg370	Pi-Alkyl	5.38
UD1	**-6.1**	Arg372	3.23	114.885			
		Arg372	5.45	Electrostatic			
		Arg372	2.97	146.00			
		Gly383	3.22	131.79			
		Gly384	3.06	112.38			
		Ser484	2.96	121.70			
		Ser484	3.50	91.61			
		Thr487	2.88	104.95			
		Gly490	3.70	117.86			
		His492	2.98	123.36			

		His492	2.85	101.65			
		His492	3.52	111.54			
		His492	4.61	Electrostatic			

Table S7: A quantitative assessment of drug-likeness, RO5 principles and ADMET properties of the lead compounds.

Properties*	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**	**4j**	**4k**	**4l**
Physicochemical properties												
MW	328.39	342.42	358.42	388.44	418.47	372.44	399.51	370.47	373.39	346.38	362.84	407.29
Fraction Csp3	0	0.05	0.05	0.1	0.14	0.1	0.17	0.14	0	0	0	0
ROTB	3	3	4	5	6	5	6	4	4	3	3	3
nHBAs	3	3	4	5	6	4	3	3	5	4	3	3
nHBDa	1	1	1	1	1	1	1	1	1	1	1	1
MR	94.07	99.04	100.56	107.06	113.55	105.37	117.89	108.65	102.89	94.03	99.08	101.77
TPSA	111.79	111.79	121.02	130.25	139.48	121.02	115.03	111.79	157.61	111.79	111.79	111.79
LOGP	2.4	2.63	2.65	2.73	2.97	2.88	3.23	3	1.74	2.55	2.67	2.73
ESOL Class	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble
Absorption												
GIA	High	High	High	Low	Low	Low	Low	Low	Low	High	High	High
Distribution												
BBB permeant	No	No	No	No	No	No	No	No	No	No	No	No
Pgp substrate	No	No	No	No	No	No	No	No	No	No	No	No
Metabolism												
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

CYP2C9 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP2D6 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No
CYP3A4 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
log Kp (cm/s)	-5.09	-4.92	-5.3	-5.5	-5.7	-5.12	-4.92	-4.55	-5.49	-5.13	-4.86	-5.09
Medicinal chemistry properties												
Lipinski violations	0	0	0	0	0	0	0	0	0	0	0	0
Ghose violations	0	0	0	0	0	0	0	0	0	0	0	0
Veber violations	0	0	0	0	0	0	0	0	1	0	0	0
Egan violations	0	0	0	0	1	0	0	0	1	0	0	0
Muegge violations	0	0	0	0	0	0	1	1	1	0	1	1
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55
PAINS #alerts	0	0	0	0	0	0	0	0	0	0	0	0
Brenk alerts	0	0	0	0	0	0	0	0	1	0	0	0
Leadlikeness violations	1	1	2	2	2	2	2	2	2	1	2	2
Synthetic Accessibility	2.97	3.08	3.02	3.23	3.41	3.11	3.37	3.23	3.06	2.99	2.96	2.99
* MW: Molecular Weight; ROTB: Number of rotatable bonds; nHBAs: Number of hydrogen bond acceptors; nHBDa: Number of hydrogen bond donors; MR: Molar refractivity; GIA: Gastrointestinal absorption; BBB permeant: Blood-brain barrier permeability; Pgp substrate: P-glycoprotein substrate; TPSA: Topological polar surface area; LOGP: Logarithm of the partition coefficient												