Electronic Supplementary Material (ESI) for Molecular BioSystems.

Identification of novel inhibitors of the translationally controlled tumor protein (TCTP): insights from molecular dynamics

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All authors approved the final manuscript before submission.

There is no conflict of interest.

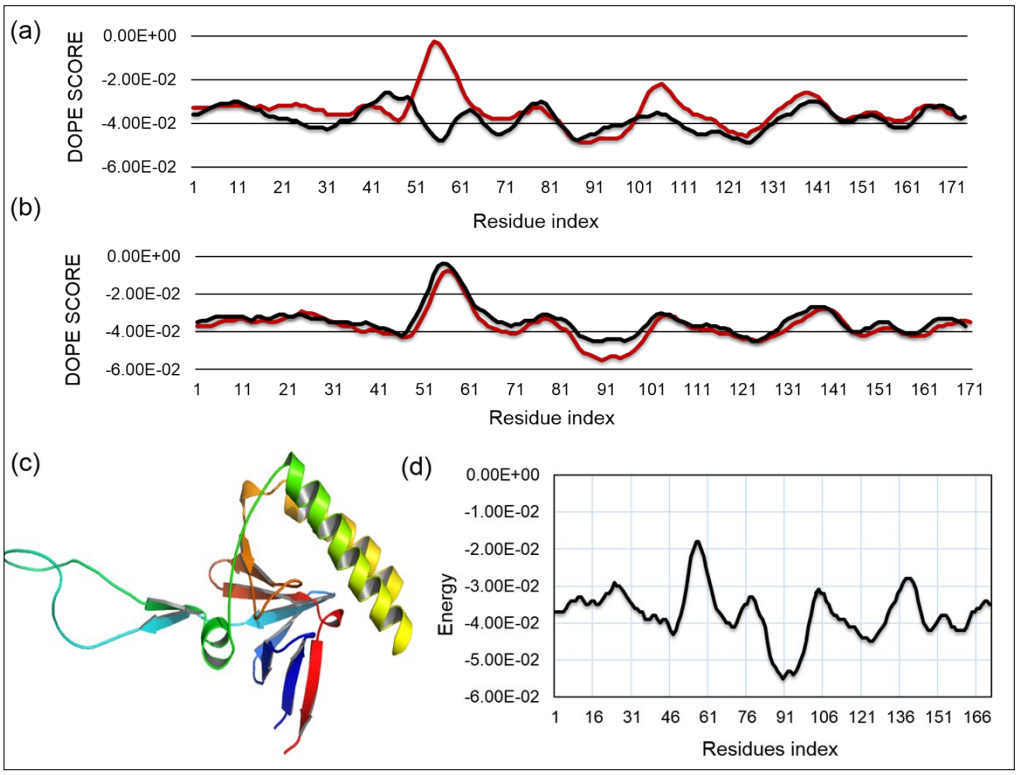
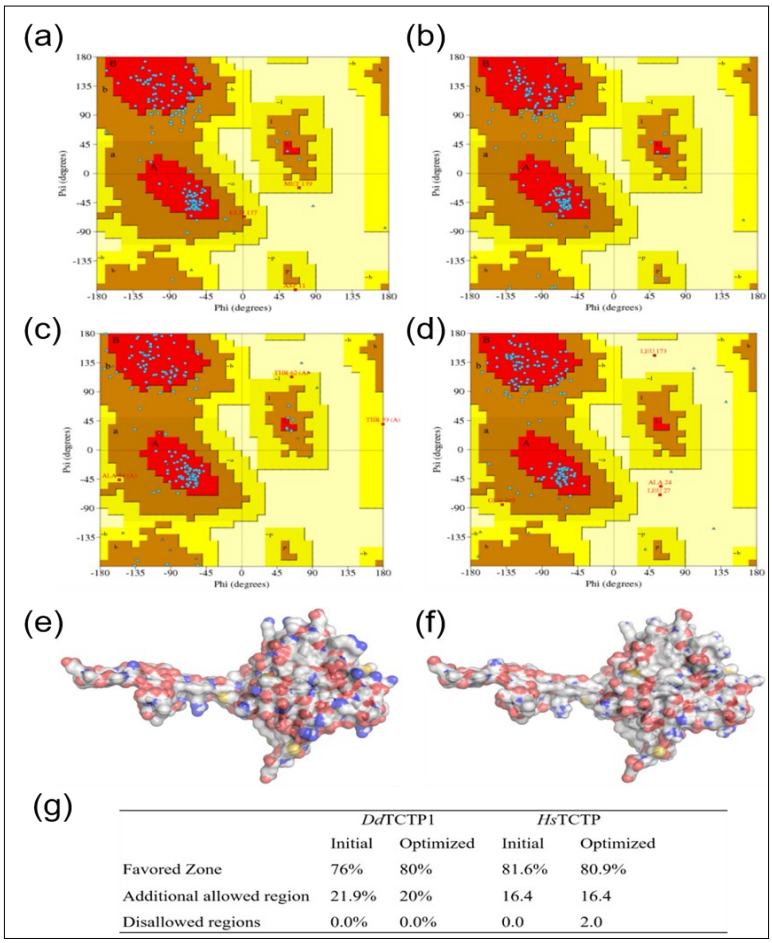


Fig. S1. **Energy profiles of the models generated.** (a) Energy profile of b3.pdb model of *Dd*TCTP. (b) Energy profile of b3.pdb model of *Dd*TCTP. Template is shown in black. (c) General overview of the structure of *Dd*TCTP (final model) generated in PyMol and shown in publication cartoon. (d) Energy profile of final model (BL2.pdb).



	*Dd*TCTP1		*Hs*TCTP	
	Initial	Optimized	Initial	Optimized
Favored Zone	76%	80%	81.6%	80.9%
Additional allowed region	21.9%	20%	16.4	16.4
Disallowed regions	0.0%	0.0%	0.0	2.0

Fig. S2. The Ramachandran plots of (a) *Dd*TCTP initial model. (b) *Dd*TCTP optimized model. (c) *Hs*TCTP initial model. (d) *Hs*TCTP optimized model. (e) *Hs*TCTP initial structure. (f) *Hs*TCTP optimized structure. (g) Statistics of Ramachandran plots. It provides the visualization of protein backbone through phi and psi angle. Each point in the plot is an amino acid residue. The triangle represents glycine. Tertiary structures are shown in transparent cartoon surface rendered in PyMol.

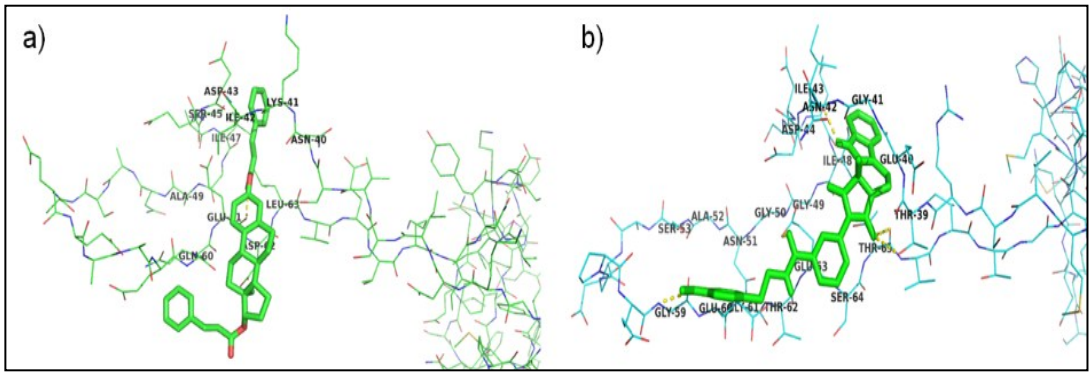


Fig. S3. Binding pose of top protein-ligand complex structure. a) *Dd*TCTP-ZINC12863423 and b) *Hs*TCTP-ZINC12863423. Receptors and ligands are display in lines and stick model respectively. Hydrogen bonds are shown in yellow dotted lines.

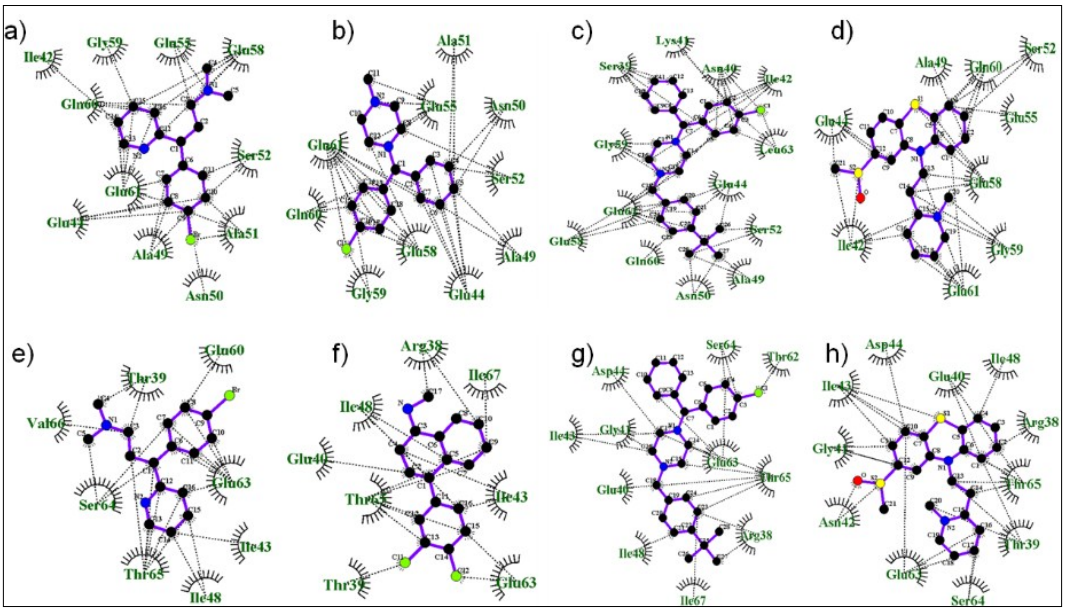


Fig. S4. 2D interaction plots of protein-ligand complexes of known and analog compounds. (a) *Dd*TCTP-ZINC00896455. (b) *Dd*TCTP-ZINC01853550. (c) *Dd*TCTP-ZINC19364226. (d) *Dd*TCTP-ZINC19361042. (e) *Hs*TCTP-ZINC00896455. (f) *Hs*TCTP-ZINC01853550. (g) *Hs*TCTP-ZINC19364226. (h) *Hs*TCTP-ZINC19361042. Hydrophobic contacts are indicated by green arc with black spokes radiating towards the ligand atoms they contact. Hydrophilic interactions are shown black in color.

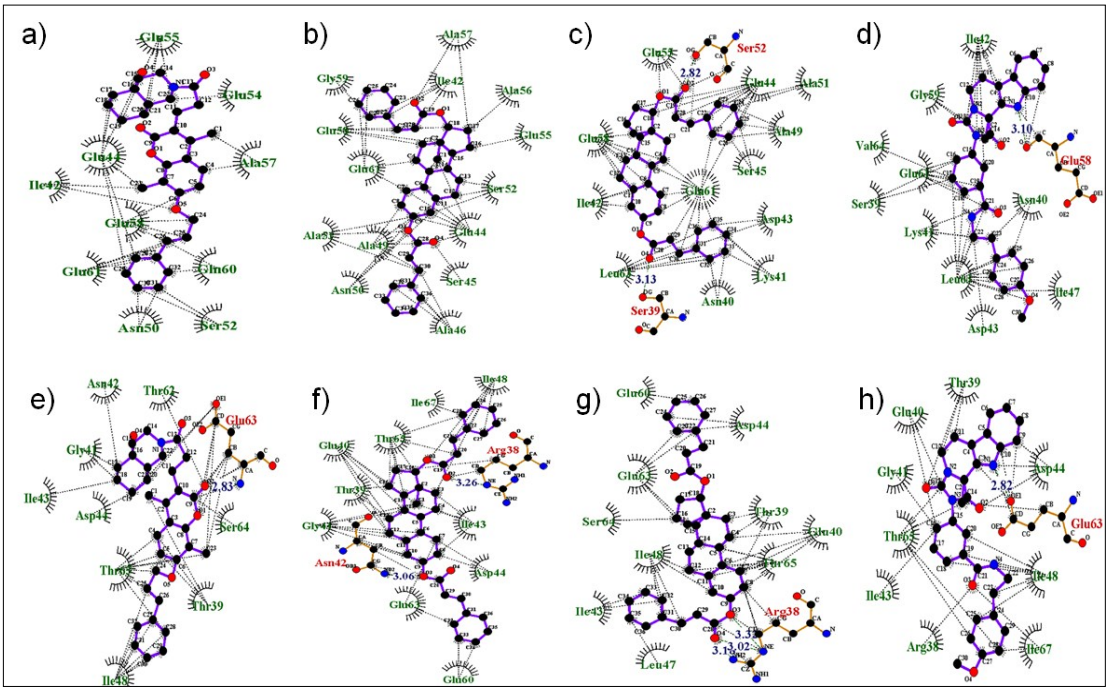


Fig. S5. 2D interaction plots of protein-ligand complexes with novel compounds. (a) *Dd*TCTP-ZINC19361042. (b) *Dd*TCTP-ZINC12657071. (c) *Dd*TCTP-ZINC12657067. (d) *Dd*TCTP-ZINC12863423. (e) *Hs*TCTP-ZINC19361042. (f) *Hs*TCTP-ZINC12657071. (g) *Hs*TCTP-ZINC12657067. (h) *Hs*TCTP-ZINC12863423. Hydrophobic contacts are

indicated by green arc with black spokes radiating towards the ligand atoms they contact. Hydrophilic interactions are shown black in color.

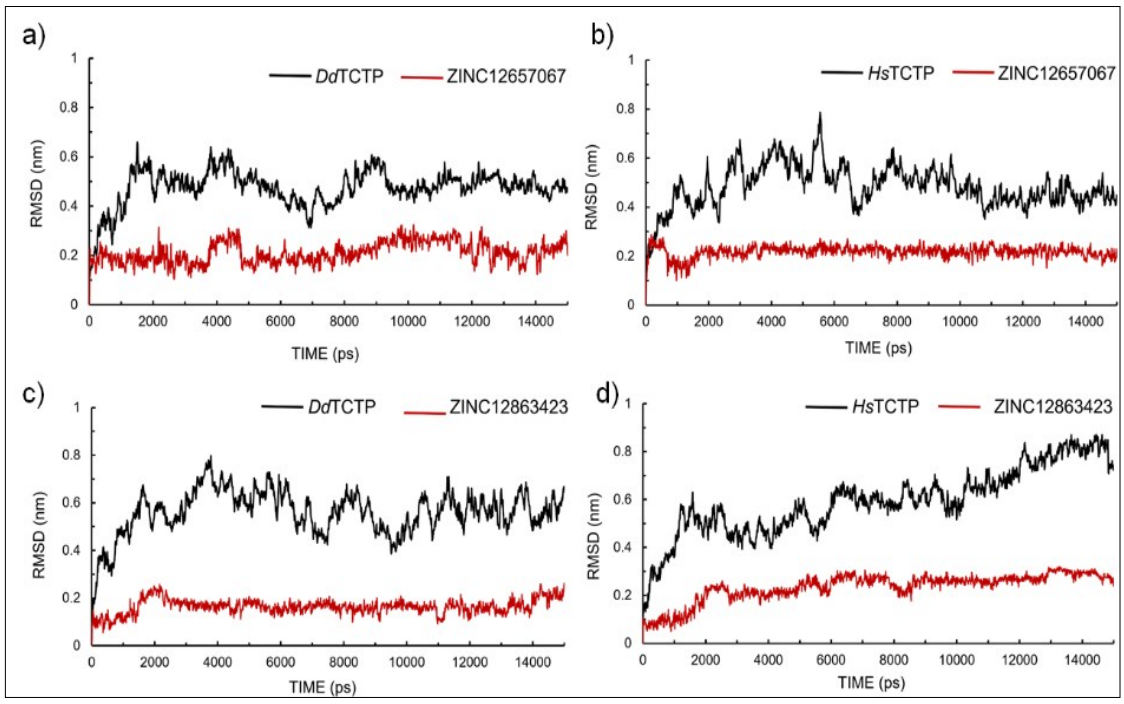


Fig S6. Root mean square deviation versus time period of a) *Dd*TCTP- ZINC12657067 b) *Hs*TCTP- ZINC12657067 c) *Dd*TCTP- ZINC12863423 and d) *Hs*TCTP- ZINC12863423.

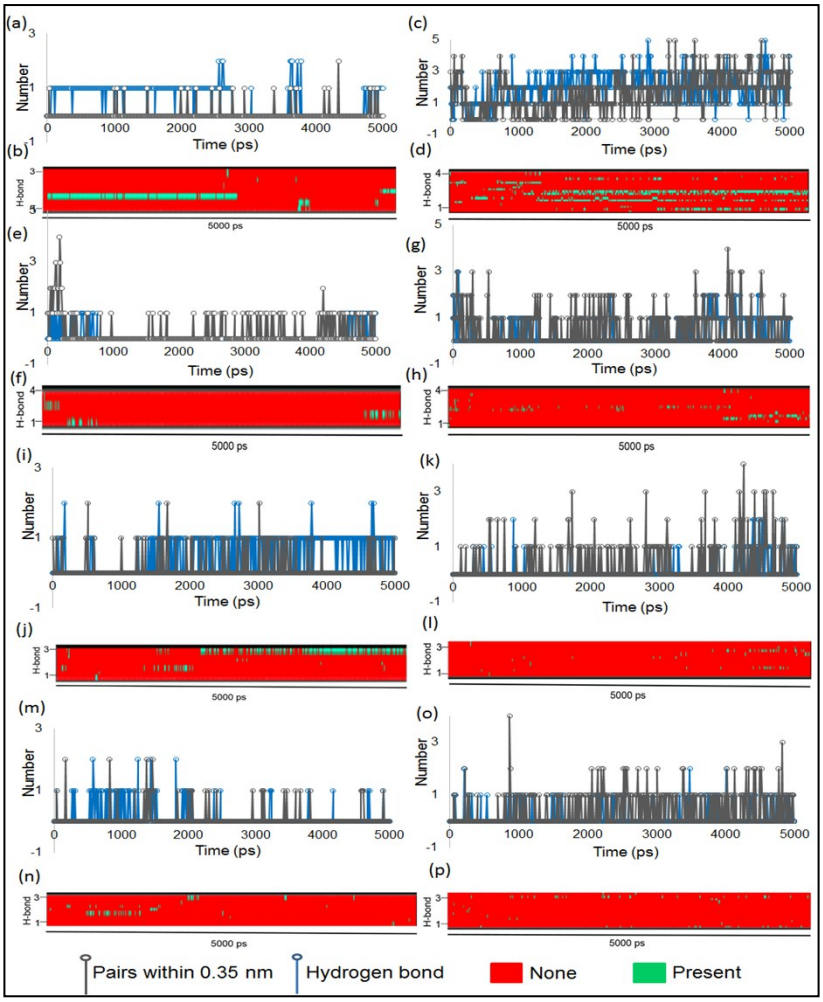


Fig. S7. **Total number of inter-molecular H-bond.** (a) Graph showing H-bond between *Dd*TCTP and ZINC08918508. (b) H-bond existence map of *Dd*TCTP and ZINC08918508 (c) Graph showing H-bond between *Hs*TCTP and ZINC08918508. (d) H-bond existence map of *Hs*TCTP and ZINC08918508. (e) Graph showing H-bond between *Dd*TCTP and ZINC12657067. (f) H-bond existence map of *Dd*TCTP and ZINC12657067. (g) Graph showing H-bond between *Hs*TCTP and ZINC12657067. (h) H-bond existence map of *Hs*TCTP and ZINC12657067. (i) Graph showing H-bond between *Dd*TCTP and ZINC12657071. (j) H-bond existence map of *Dd*TCTP and ZINC12657071. (k) Graph showing H-bond between *Hs*TCTP and ZINC12657071. (l) H-bond existence map of *Hs*TCTP and ZINC12657071. (m) Graph showing H-bond between *Dd*TCTP and ZINC19361042. (n) H-bond existence map of *Dd*TCTP and ZINC19361042. (o) Graph showing H-bond between *Hs*TCTP and ZINC19361042. (p) H-bond existence map of *Hs*TCTP and ZINC19361042.

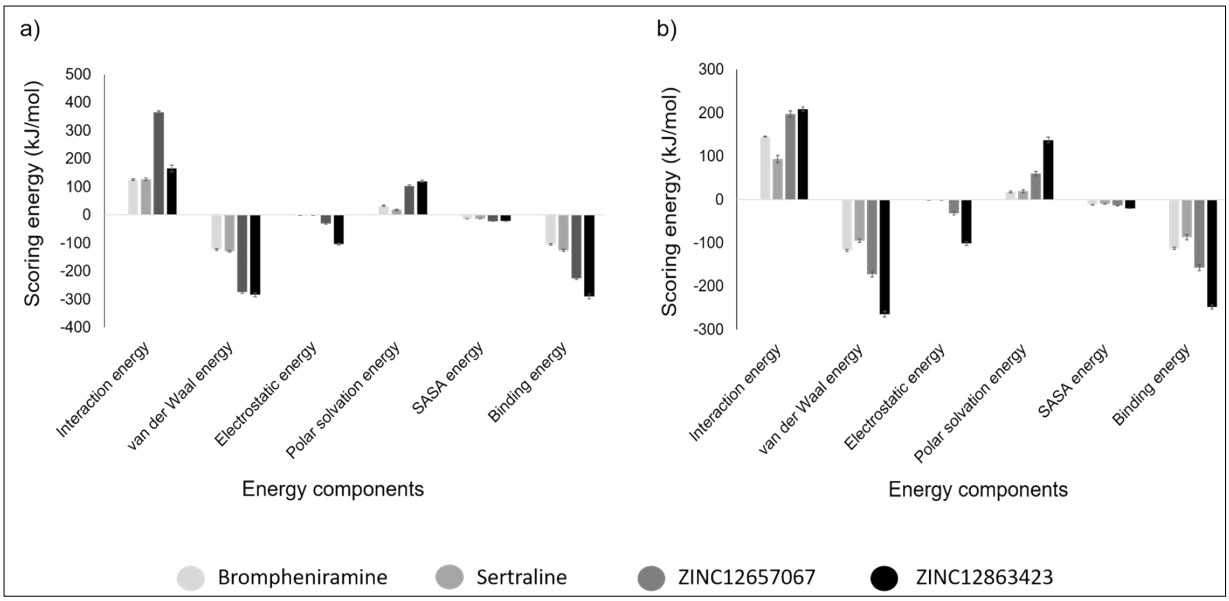


Fig. S8. Calculated binding free energy components of a) *Dd*TCTP and b) *Hs*TCTP with known and novel drugs (All in kJ/mol).

Table S1. 10 models generated after of loop refinement method.

Model	DOPE score
qseq1.BL00010001.pdb	-17578.64453
qseq1.BL00020001.pdb	**-17594.81836**
qseq1.BL00030001.pdb	-17514.93945
qseq1.BL00040001.pdb	-17357.62891
qseq1.BL00050001.pdb	-17519.33984
qseq1.BL00060001.pdb	-17551.38867
qseq1.BL00070001.pdb	-17586.92773
qseq1.BL00080001.pdb	-17530.12109
qseq1.BL00090001.pdb	-17263.0625
qseq1.BL00100001.pdb	-17553.16016

Table S2. Quality assessment results

	Dd TCTP		*Hs*TCTP	
Tools	**Initial Model**	**Optimized model**	**Initial Model**	**Optimized model**
ERRAT	Overall quality factor = 71.14	Overall quality factor = 88.09	Overall quality factor = 73.10	Overall quality factor = 89.55
Verify 3D	Fail	Pass	Pass	Pass
ProSA	Z- Score = -4.63	Z- Score = -5.13	Z- Score = -5.08	Z- Score = -5.03
QMEAN	Q Score = 0.68 Z Score = -0.88	Q Score = 0.52 Z Score = -2.48	Q Score = 0.76 Z Score = -0.00	Q Score = 0.41 Z Score = -3.58

Table S3. Hydrophobic and hydrophilic residues in top scoring active sites in (a) *Dd*TCTP, (b) *Hs*TCTP active sites.

a)

Active sites	**Hydrophobic Residues**	**Polar Residues**	**Charged Residues**	**Z-score**
Active site 1	Gly41, Ile48, Val66, Ile43, Gly59, Gly49, Ile67, Gly61, Gly50, Ala52	Asn51, Ser64, Asn42, Ser53, Thr39, Thr62, Ser46, Thr65	Asp45, Glu40, Asp44, Arg38, Glu63, Glu60	15.74
Acitve site 2	Leu29, Leu103, Gly26, Leu27, Leu167, Ile23,Leu7, Ile20	Met169, Gln106, Tyr4	Glu168, Arg107, Glu109, Lys102, Lys164, Arg110, Asp165, Glu22, Arg21	10.64
Active site 3	Leu27, Leu29			1.27

b)

Active sites	**Hydrophobic Residues**	**Polar Residues**	**Charged Residues**	**Z-score**
Active site 1	Ala56, Gly59, Ala49, Gly48, Ile42, Leu63, Ala53, Ala57, Ala51, Ala46, Ile47	Asn40, Ser52, Gln60, Ser45, Val64, Asn50, Ser39	Glu44, Glu61, Lys41, Glu58, Glu54, Asp62, Glu55, Asp43	14.54
Acitve site 2	Phe28, Gly120, Ala117, Ile145, Val124, Ala118, Leu147, Ile90, Leu98, Val162, Val121, Ile94, Phe86, Phe113, Leu125	Gln87, Tyr93, Thr119, Trp160, Trp131	Arg116, Lys95, Lys122, Lys114, Lys24, Lys91	11.22
Active site 3	Gly165, Ala109, Ile166, Phe27, Ile167, Ile101, Ala168, Leu97		Lys163, Asp26, Lys105, Glu25, Glu108, Lys7, Glu112, Asp164, Glu104	7.78

Table S4. Top scoring docking complexes of *Dd*TCTP and *Hs*TCTP

		*Dd*TCTP			*Hs*TCTP	
Solution no.	Score	Area	ACE	Score	Area	ACE
1	6070	811.6	-288.9	5610	688.9	-320.67
2	6052	774.1	-267.6	5416	685.3	-364.36
3	5940	898.1	-219.03	5346	657.2	-295.03
4	5680	808.7	-316.8	5150	699.2	-235.63
5	5632	761.6	-218.5	5122	596.5	-94.61
6	5596	712.1	-311.47	5102	615.6	-142.78
7	5484	718.8	-212.9	5102	689.3	-257.68
8	5356	649.2	-209.2	5030	606.3	-222.95
9	5338	852.6	-393.3	4978	611.9	-89.4
10	5314	744.4	-218.3	4964	556.9	-34.58

Table S5. Physico-chemical properties of the lead compounds

ZINC ID	**IUPAC Convention or popular name**	**Molecular weight(g/mol)**	**H-Bond donor**	**H-Bond Acceptor**	**Rotatable bonds**	**xlogP**
ZINC12863423	N-[2-(4-methoxyphenyl)ethyl]-3-(methyl-dioxo-BLAHyl)benzamide	508.578	2	8	6	4.61
ZINC12657071	[(8S,9S,13S,14S,17S)-13-methyl-3-[(E)-3-phenylprop-2-enoyl]oxy-6,7,8,9,11,12,14,15,16,17-decahydrocy	532.68	0	4	8	8.37
ZINC12657067	[(8R,9S,13S,14S,17S)-13-methyl-3-[(E)-3-phenylprop-2-enoyl]oxy-6,7,8,9,11,12,14,15,16,17-decahydrocy	532.68	0	4	8	8.37
ZINC00896455	Brompheniramine maleate	319.239	0	2	5	3.75
ZINC01853550	Sertraline hydrochloride	306.23	1	1	2	5.06
ZINC19364226	1-(4-(tert-Butyl)benzyl)-4-((4-chlorophenyl)(phenyl)methyl)piperazine dihydrochloride	433.023	0	2	6	6.1
ZINC03831041	Mesoridazine besylate	386.574	0	3	4	3.83
ZINC19361042	Meclizine hydrochloride	391.966	1	2	5	5.91