Supplementary Material

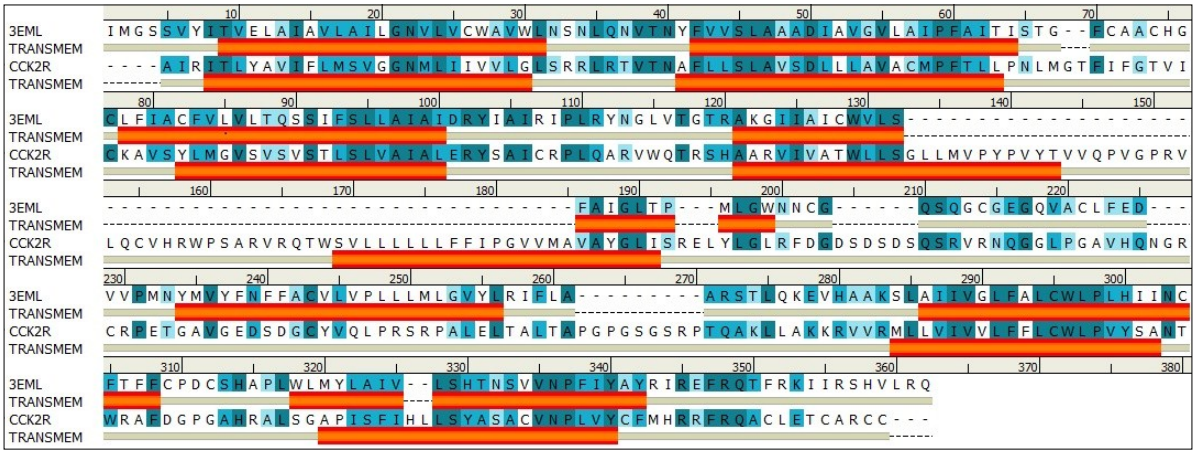


Figure S1: Alignment of CCK-2R with template PDB ID : 3EML. The regions shown in orange represent the trans-membrane regions.

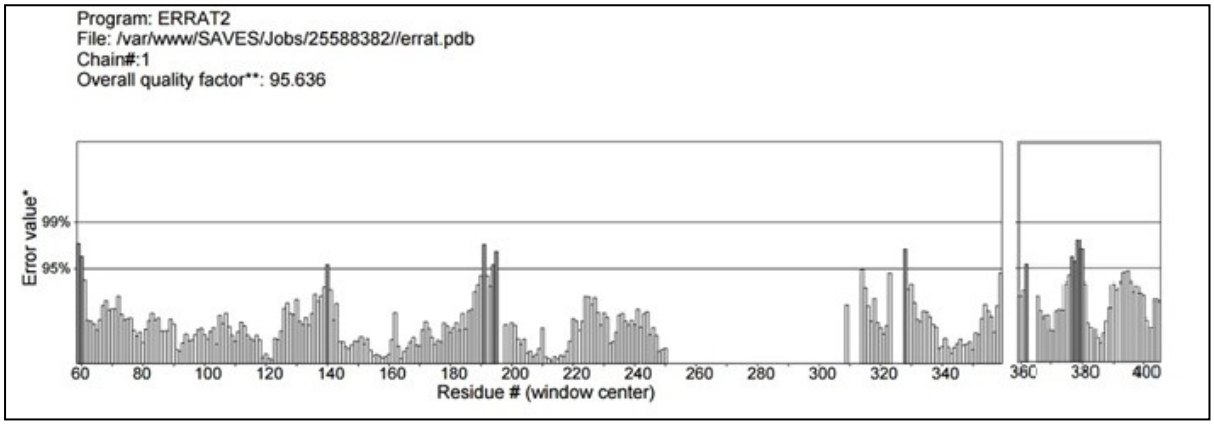
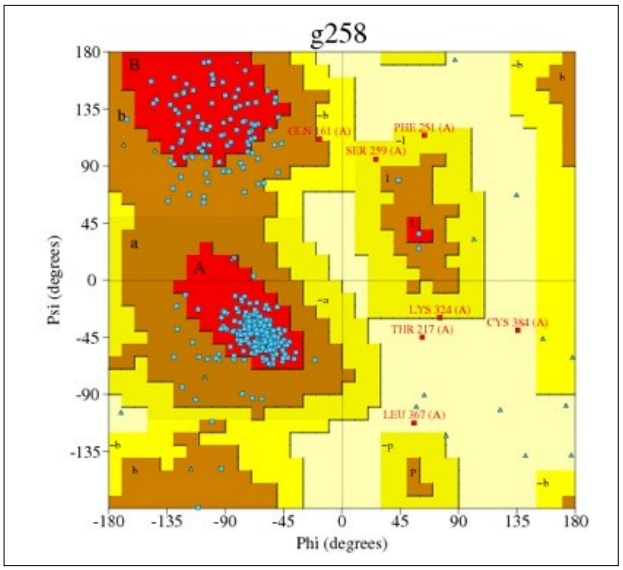


Figure S2: Errat score



FigureS3:**Ramachandran plot of CCK2R homology model showing phi & psi angles in 2D graphical representation.**

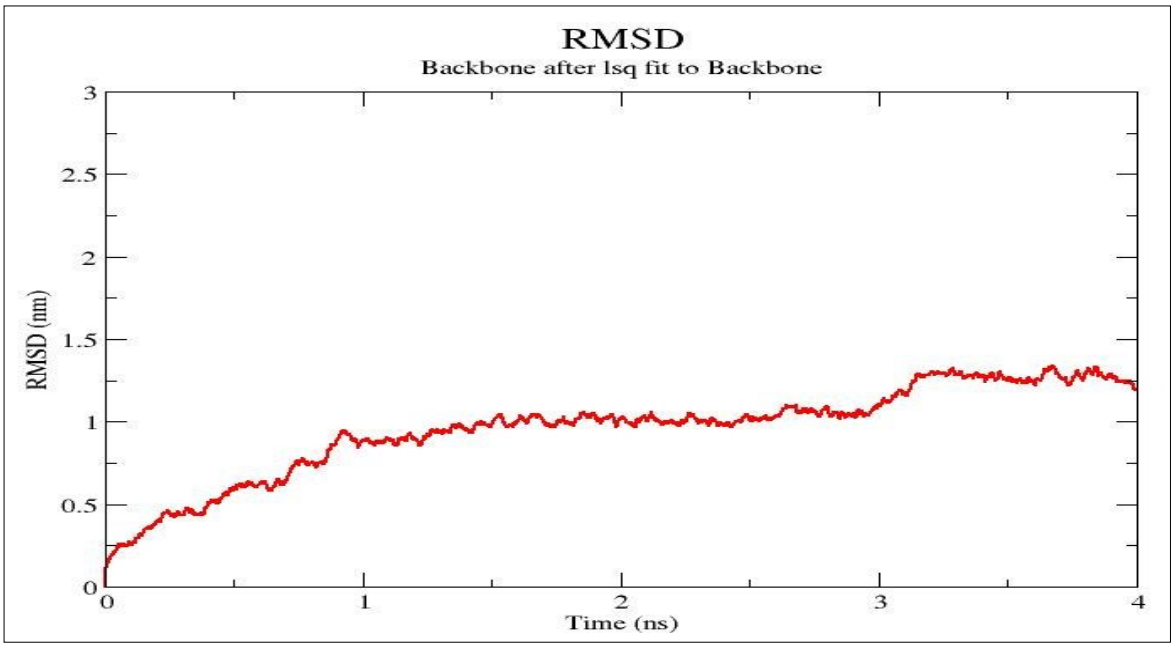


Figure S4: RMSD graph of CCK2R simulation. The X-axis shows the time interval in nanosecond (ns) whereas Y-axis represents backbone deviation in nanometer (nm).

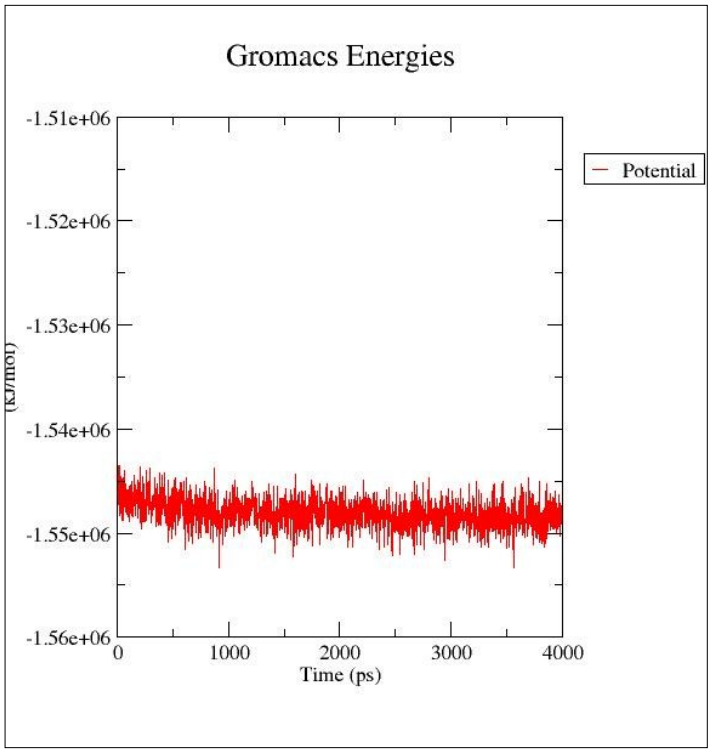


Figure S5: 2D representation of potential energy variation during MD simulation of CCK2R protein. In plot, the x-axis represents the simulation time in picosecond(ps) and y-axis shows potential energy in KJ/mol. The potential energy during simulation is stabilized at approximately –1.546 × 10^6kj/mol.

ADMET PLOT:

The compounds were subjected to ADMET calculations. Parameters such as aqueous solubility, absorption, plasma protein binding, cytochrome P450 2D6 inhibition, and hepatotoxicity were all determined using the ADMET protocol in DS4.0 (Table TS1). Moreover, the toxicity potential (ie, carcinogenicity and mutagenicity) of the compounds was also predicted using the TOPKAT (TOxicity Prediction by Komputer Assisted Technology) protocol in DS4.0 (Table TS2).

1. The **human intestinal absorption model**
   As seen in Fig S6, our all compounds lie within the 95% and 99% confidence ellipses and their predicting value lies in 0-1 range (Table TS1), hence all the compounds showed good absorption.

2. The **blood brain barrier model**
   As seen in Fig S6, our 9 out of 15 compounds are out of outside the 95% and 99% confidence ellipsoids, therefore no prediction can be made for them. For rest of the 6 compounds, BBB values are in 2-4 range (Table TS1) which demarcates them into low penetrants category which indicates that our compounds can be used for tumour regression and will not BBB to give hazardous side-effects.

3. **Aqueous Solubility**

   As seen in Table TS1, our compounds log (Sw) lies in range of 1-2 values, which demarcates all these compounds into low solubility group.

4. The **cytochrome P450 2D6 (CYP2D6)** model predicts CYP2D6 enzyme inhibition using 2D chemical structure as input. CYP2D6 is involved in the metabolism of a wide range of substrates in the liver and its inhibition by a drug constitutes majority cases of drug-drug interaction.The impact of CYP2D6 activity differs on a drug-by-drug basis, depending on whether CYP2D6 is involved in the activation or inactivation of the drug.

5. The **plasma protein binding model** predicts whether a compound is likely to be highly bound (>= 90% bound) to carrier proteins in the blood. Plasma protein binding of drug molecules can affect the efficiency of a drug, because the bound fraction is temporarily shielded from metabolism. On the other hand, only the unbound fraction exhibits pharmacological effects.

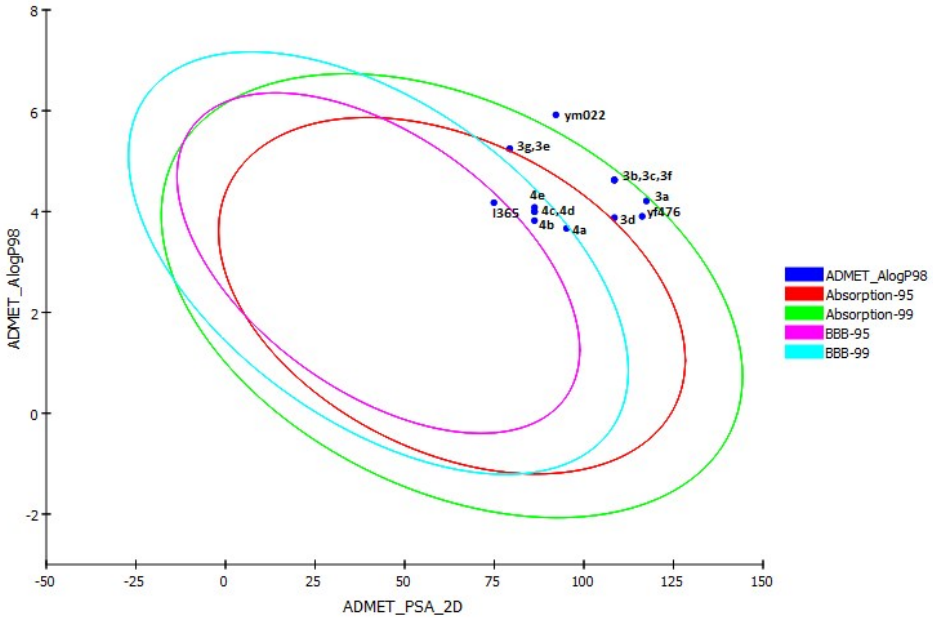


FIG S6: Plot of polar surface area (PSA) versus ALogP for all compounds, showing the 95% and 99% confidence limit ellipses corresponding to the blood brain barrier (BBB) and intestinal absorption.

Compound	AlogP	PSA_2D	Intestinal absorption[a]	CYP2D6 binding[b]	Plasma protein binding[d]	Aqueous solubility	BBB penetration
4b	3.82	86.221	0 (good)	False (non-inhibitor)	True (highly bounded)	2 (low)	2 (medium)
4c	3.998	86.221	0 (good)	False (non-inhibitor)	True (highly bounded)	1 (poor)	2 (medium)
4d	3.998	86.221	0 (good)	False (non-inhibitor)	True (highly bounded)	1 (poor)	2 (medium)
4e	4.082	86.221	0 (good)	False (non-inhibitor)	True (highly bounded)	1 (poor)	2 (medium)
3g	5.245	79.337	1 (moderate)	False (non-inhibitor)	True (highly bounded)	1 (poor)	4 (undefined)
4a	3.666	95.151	0 (good)	False (non-inhibitor)	True (highly bounded)	2 (low)	3 (Poor)
3a	4.21	117.453	1 (moderate)	False (non-inhibitor)	True (highly bounded)	2 (low)	4 (undefined)
3d	3.878	108.523	1 (moderate)	False (non-inhibitor)	True (highly bounded)	2 (low)	4 (undefined)
3c	4.626	108.523	1 (moderate)	False (non-inhibitor)	True (highly bounded)	1 (poor)	4 (undefined)
3e	5.245	79.337	1 (moderate)	False (non-inhibitor)	True (highly bounded)	1 (poor)	4 (undefined)
3f	4.626	108.523	1 (moderate)	False (non-inhibitor)	True (highly bounded)	1 (poor)	4 (undefined)
3b	4.626	108.523	1 (moderate)	False (non-inhibitor)	True (highly bounded)	1 (poor)	4 (undefined)
I365	4.176	74.897	0 (good)	False (non-inhibitor)	True (highly bounded)	2 (low)	2 (medium)
yf476	3.905	116.269	1 (moderate)	False (non-inhibitor)	True (highly bounded)	2 (low)	4 (undefined)
ym022	5.918	92.198	2 (poor)	False (non-inhibitor)	True (highly bounded)	1 (poor)	4 (undefined)

Table TS1: ADMET predicted using ADMET protocol in DS4.0

Notes:

ADMET_Absorption_T2_2D is the Mahalanobis distance for the compound in the ADMET_PSA_2D, ADMET_AlogP98 plane. It is referenced from the center of the region of the chemical space defined by well-absorbed compounds.

[b]The prediction whether a compound is a cytochrome P450 2D6 inhibitor was classified using the cutoff Bayesian score of 0.161 obtained by minimizing the total number of false positives and false negatives.

[c]The prediction whether a compound is hepatotoxic was classified using the cutoff Bayesian score of −4.154 obtained by minimizing the total number of false positives and false negatives.

[d]The prediction whether a compound is highly bound (≥90% bound) to plasma proteins was classified using the cutoff Bayesian score of −2.209 obtained by minimizing the total number of false positives and false negatives.

Abbreviations: ADMET, absorption, distribution, metabolism, excretion, and toxicity; DS4.0, Discovery Studio 4.0.**AlogP**, the logarithm of the partition coefficient between n-octanol and water; **PSA**, polar surface area, **CYP450** cytochrome P450, **PPB** plasma protein binding, **BBB** blood brain barrier.

COMPOUND NAME	TOPKAT_WOE	TOPKAT_AMES	TOPKAT_DTP	TOPKAT SKIN IRRITANCY
4b	Non-Carcinogen	Non-Mutagen	Non-Toxic	Non-Irritant
4c	Non-Carcinogen	Non-Mutagen	Non-Toxic	Non-Irritant
4d	Non-Carcinogen	Non-Mutagen	Non-Toxic	Non-Irritant
4e	Non-Carcinogen	Non-Mutagen	Non-Toxic	Non-Irritant
3g	Non-Carcinogen	Non-Mutagen	Toxic	Non-Irritant
4a	Non-Carcinogen	Non-Mutagen	Toxic	Non-Irritant
3a	Non-Carcinogen	Non-Mutagen	Toxic	Non-Irritant
3d	Non-Carcinogen	Non-Mutagen	Non-Toxic	Non-Irritant
3c	Carcinogen	Non-Mutagen	Non-Toxic	Non-Irritant
3e	Non-Carcinogen	Non-Mutagen	Toxic	Non-Irritant
3f	Carcinogen	Non-Mutagen	Non-Toxic	Non-Irritant
3b	Carcinogen	Non-Mutagen	Non-Toxic	Non-Irritant
l365	Non-Carcinogen	Non-Mutagen	Non-Toxic	Non-Irritant
yf476	Non-Carcinogen	Non-Mutagen	Non-Toxic	Non-Irritant
ym022	Non-Carcinogen	Non-Mutagen	Non-Toxic	Non-Irritant

Table TS2: Toxicity predicted using the TOPKAT DS 4.0