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Molecular modeling studies and structure based virtual screening for identification of potent ligands for Cb2 receptor

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Abstract
The CB2 receptor is an attractive drug target for treatment of pain and inflammation. CB2 receptor is member of rhodopsin-like family of seven-transmembrane G-protein-coupled receptor. In this work, three dimensional structure model of CB2 receptor in Homo sapiens was determined based on template sequence (PDB code: 2KS9) by comparative homology modeling program MODELLER9v10. Selection of template was done through mGenTHREADER tool in MODELLER, which has 13.1% sequence identity with CB2 receptor. The computed model's energy was minimized and validated using PROCHECK and ERRAT to obtain a stable model structure. Stable model was further used for virtual screening against N-1 alkyl chain length of cannabimimetic indoles through molecular docking studies using AutoDock 3.05. The docked complexes were validated and enumerated based on the AutoDock Scoring function to pick out the best agonist based on docked Energy. Thus from the entire 30 compounds which were Docked, we got best 3 of them with optimal docked energy as JHW-156 (Docking Energy -13.26 kcal/mol), JWH-122(Docking Energy:-12.53 kcal/mol) and JWH-146 (Docking Energy: -12.46 kcal/mol). Further the three best-docked complexes were analyzed through Python Molecular Viewer software for their interaction studies. Thus from the Complex scoring and binding ability its deciphered that these ligands could be used as interesting leads for the development of new active CB2 ligands. QSAR Properties of all these compounds were calculated, which shows these compounds could be used as interesting leads for development of new active CB2 ligands

Keywords: CB2 receptor, mGenTHREADER, PROCHECK, AutoDock, cannabimimetic indoles

1. Introduction
Marijuana, or cannabis (*Cannabis sativa)*, one of the oldest and most widely abused drugs, has also been used for medicinal purposes by various cultures. The primary psychoactive constituent of marijuana is a cannabinoid compound, Δ9-tetrahydrocannabinol (Δ9-THC). The ability of extracts of the hemp plant (*Cannabis sativa*) to cause a variety of medicinal effects unrelated to its psychoactive properties had been recognized as early as the third millennium BC, when Chinese texts described its usefulness in the relief of pain and cramps (Pal pacher *et al*., 2006, Mechoulam, 1986 [2]). In ancient India, the anxiety-relieving effect of bhang (the Indian term for marijuana ingested as food) had been recorded more than 3000 years ago.
Cannabinoid receptors are members of the rhodopsin-like family of seven transmembrane (7TM) G-protein-coupled receptors (GPCRs). The G-protein coupled receptor (GPCR) superfamily is comprised of estimated 600–1,000 members and is the largest known class of molecular targets with proven therapeutic value. They are ubiquitous in our body, being involved in regulation of every major mammalian physiological system (Laurent Jacob *et al*., 2008, Bockaert and Pin., 1999) [5, 4] and There are two distinct cannabinoid receptors, CB1 and CB2, have been identified in mammalian tissues and cloned (Matsuda *et al*., 1990, Munro *et al*., 1993, Poso and Huffman., 2008) [6, 7, 8]. The CB2 receptor is localized primarily in the spleen, tonsils, and immune cells (Tuccinardi *et al*., 2006 and Martin, 1986) [9, 10], but recently were found to be present in the brain (Van Sickle *et al*., 2005; Gong *et al*., 2006) [21, 22], in nonparenchymal cells of the cirrhotic liver (Julien *et al*., 2005) [23], in the endocrine pancreas (Juan-Pico *et al*., 2005) [24], and in bone (Karsak *et al*., 2004; Idris *et al*., 2005; Ofek *et al*., 2006) [25, 26, 63] and it is an attractive target for drug development for the treatment of pain, inflammation, osteoporosis, growth of malignant gliomas and tumors of immune origin, and immunological disorders (Tuccinardi *et al*., 2006 and Raitio *et al*., 2005) [12, 11]. We have established a structure-based virtual screening protocol to search for CB2 bioactive antagonists based on the 3D CB2 homology structure model.

2.0 Materials and methods

2.1. Retrieval of the target protein sequence and alignment with template sequence

The amino acid sequences of CB2 receptor in *Homo sapiens* was retrieved through Swiss-Prot (Id: P34972) (*http://www.expasy.ch*). Selection of template has done through GenTHREADER of target sequence. GenTHREADER is a method for structure prediction on a genomic scale. The method combines profile–profile alignments with secondary-structure specific gap-penalties, classic pair-and solvation potentials using a linear combination optimized with a regression SVM model. The templates of CB2 was downloaded from protein databank (www.rcsb.org/pdb) with PDB ID 2KS9-A. The sequence alignment of targets with corresponding templates was performed by using dynamics programming based align2d module in Modeller (Sali *et al*., 1993) [72].

2.2. Homology modeling of CB2 receptor

Homology model of CB2 receptor was constructed using program Modeller9v10. Modeller is simply an implementation of automated approach to comparative modeling by satisfaction of the spatial restraints. After aligning query CB2 receptor with template 2KS9-A using align2d script were used as input in Modeller program and five comparative models were generated for each target, respectively. The model of CB2 receptor was validated with the help of modeller objective function and DOPE score, which are the statistical parameter for the assessment of model using the standard modeller energy function. The validated CB2 model was chosen for further studies and refinement.

2.3 Modeling and structure refinement

Models were further checked with ERRAT (Colovos and Yeates, 1993) [73] and Ramachandran plot at PROCHECK (Laskowski *et al*., 1993) [74]. The model constructed was solvated and subjected to constraint energy minimization with a harmonic constraint of 100 kJ/mol/Å, applied for all protein atoms, using the steepest descent and conjugate gradient method. Computations were carried out in vacuo with the GROMOS96 43B1 parameters set using SWISS-pdbVIEWER (Guex and Peitsch, 1997) [75].

2.4 Model validation

The constructed model of CB2 receptor was examined for validation using different criteria. Backbone conformation and non-GLY residues at the disallowed regions were evaluated by the inspection of the Psi/Phi Ramachandran plot obtained from PROCHECK analysis. The Swiss-PdbViewer energy minimization test was applied to check for energy criteria in comparison with the potential of mean force derived from a large set of known protein structures. Packing quality of the refined structure was investigated by the calculation of PROCHECK Quality Control value.

2.5. Database screening

Thirteen N-1 alkyl chain length of cannabimimetic indoles were retrieve from the literature (Anug *et al*., 2000).

2.6. Virtual screening

Docking of N-1 alkyl chain lengths of cannabimimetic indoles against CB2 was performed with molecular docking program AutoDock 3.0.5. Gasteiger charges are added to the ligand and maximum 6 numbers of active torsions are given to the lead compounds using AutoDock Tool (http://autodock.scripps.edu/resources/adt). Kollman charges and the solvation term were then added to the protein structure using the same. We have made the grid and adjusted the number of points in X, Y, Z axis, so that it covers the entire active site of the CB2 receptor. The default value is 0.375 Å between grid points, which is about a quarter of the length of a carbon-carbon single bond. The spacing between grid points can be adjusted with another thumbwheel. Grid spacing values of up to 1.0 Å can be used when a large volume is to be investigated in this work it was increased to 0.542Å.The Lamarckian genetic algorithm implemented in Autodock was used. Docking parameters were as follows: 30 docking trials, population size of 150, maximum number of energy evaluation ranges of 25,0000, maximum number of generations is 27,000, mutation rate of 0.02, cross-over rate of 0.8, Other docking parameters were set to the software's default values. After docking, the ligands were ranked according to their docked energy as implemented in the AutoDock program.

2.7 QSAR Properties Calculation

2.7.1 Lipinski's rule-of-five analysis

Christopher Lipinski's rule-of-five (Lipinski *et al*., 2001) [79] analysis helped to raise awareness about properties and structural features that make molecules more or less drug-like. The guidelines were quickly adopted by the pharmaceutical industry as it helped apply ADME considerations early in preclinical development and could help avoid costly late-stage preclinical and clinical failures.

2.7.2 Topology analysis

The topology analysis is important because it provides characteristic values related to the topological structure of a molecule which is helpful in launching a compound to be a drug candidate. Atom count which is number of atoms in the molecule including hydrogens, Bond count which is number of bonds in the molecule including hydrogens, Formal charge which is net charge positive or negative occupied by a compound and Polar surface area are some important parameter for drug designing.

2.7.3 Rotatable bond count

Rotatable bond count is defined as number of rotatable bonds in the molecule. Those single bonds are considered rotatable, which are not connected to hydrogens, nor to terminal atoms (atoms having maximum one non-hydrogen adjacent). Amides, sulphonamides and single bonds connecting two hindered aromatic rings (having at least three ortho substituents) are also considered non-rotatable.

2.7.4 Polar surface area

Polar surface area (PSA) is formed by the polar atoms of a molecule. This descriptor was shown to correlate well with passive molecular transport through membranes and therefore allows prediction of transport properties of drugs and has been linked to drug bioavailability. Generally, passively absorbed molecules with a PSA $\geq$ 140 $Å^2$ are thought to have low oral bioavailability (Ertl *et al*., 2000) [81].

3. Results and discussion

4.1 Homology modeling of CB2 receptor

A search for potentially related sequences of known structure was performed by the mGenTHREADER (Lobley *et al*., 2009) [82] sited at CSB institute, which is a fold recognition method use profiles and predicted secondary structures. To do this, we put the target CB2 sequence in plain format in to the text box of

mGenTHREADER. Result of mGenTHREADER was shown in table 1. The sequence identity was 13.1% with template sequence (fig.1). The sequence alignment of the query CB2 receptor sequence of Homo sapiens with template (PDB Code: 2KS9-A) was shown in fig.2.

Table 1: Result of mGenTHREADER program. Numbers in red indicates possibly low quality or incorrect models.

Conf.	Net Score	p-value	PairE	SolvE	Aln Score	Aln Len	Str Len	Seq Len	Alignment
CERT	60.640	4e-05	-310.2	-5.8	207.0	271	297	605	1q0rA0
CERT	60.296	4e-05	-330.2	-10.9	193.0	262	275	605	1zoiA0
CERT	57.432	8e-05	-301.0	-9.1	188.0	234	242	605	1tqhA0
CERT	57.123	9e-05	-415.2	-9.0	152.0	269	277	605	3fobA0
HIGH	55.752	0.0001	-330.7	-6.9	167.0	268	277	605	1brtA0
HIGH	55.240	0.0001	-330.8	-7.0	164.0	263	283	605	2rhwA0
HIGH	54.090	0.0002	-349.7	1.1	165.0	260	271	605	1uk8A0
HIGH	53.826	0.0002	-322.2	-4.0	167.0	228	255	605	3bf7A0
HIGH	53.753	0.0002	-330.9	-10.4	158.0	204	218	605	2fukA0
HIGH	53.667	0.0002	-322.1	-4.6	158.0	269	279	605	1hkhA0
HIGH	53.416	0.0002	-369.1	-13.5	135.0	241	278	605	2qmqA0
HIGH	52.906	0.0002	-372.0	-6.9	138.0	262	272	605	2qruA0
HIGH	52.826	0.0002	-349.4	-10.1	141.0	244	256	605	1m33A0
HIGH	52.354	0.0003	-367.5	-10.0	131.0	257	318	605	1l7aA0
HIGH	51.718	0.0003	-350.5	-12.5	128.0	251	294	605	1y37A0
HIGH	51.351	0.0003	-282.9	-3.8	152.0	274	310	605	1b6gA0
HIGH	50.705	0.0004	-307.7	-4.6	137.0	295	305	605	2psdA0
HIGH	49.980	0.0005	-342.0	-8.4	130.0	217	245	605	3e0xA0
HIGH	49.858	0.0005	-315.0	-1.3	148.0	213	256	605	3c70A0
HIGH	49.745	0.0005	-386.7	-3.7	123.0	229	258	605	3bxpA0
HIGH	48.222	0.0007	-335.6	-10.1	118.0	206	241	605	3dkrA0
HIGH	47.534	0.0008	-342.6	-13.1	97.0	266	307	605	2o7rA0
HIGH	47.387	0.0008	-381.9	-9.5	89.0	286	317	605	1lzlA0
HIGH	47.335	0.0008	-286.9	-0.1	133.0	250	285	605	3bwxA0
HIGH	46.757	0.001	-344.4	-8.5	96.0	283	298	605	1mj5A0
MEDIUM	46.476	0.001	-326.0	-0.6	116.0	254	288	605	3icvA0
MEDIUM	46.349	0.001	-241.6	0.8	151.0	175	316	605	1cvlA0
MEDIUM	46.079	0.001	-278.4	-7.1	112.0	269	357	605	2b61A0
MEDIUM	45.908	0.001	-332.0	-9.4	91.0	289	296	605	2qvbA0
MEDIUM	45.644	0.001	-380.3	-6.9	85.0	264	308	605	3ga7A0

```
 10 20 30 40 50
 --CCCCCCCCCCCCCCCCCCCCCCCCCCCCHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHH
2ks9A0 --DNVLPVDSDLSPNISTNTSEPNQFVQPAWQIVLWAAAYTVIVVTSVVGNVVVMWIILA
Query MEECWVTEIANGSKDGLDSNPMKDYMILSGPQKTAVAVLCTLLGLLSALENVAVLYLILS
 CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHH
 10 20 30 40 50 60

 70 80 90 100 110
        HHHHHHHHHHHHHHHHHHCHHHHHHHHHHHCCCCCCHHHHHHHHHHHHHHHHHH
2ks9A0 HKRMR-TVTNYFLVNLAFAEASMAAFNTVVNFTYAVHNEWYYGLFYCKFHNFFPIAAVFA
Query SHQLRRKPSYLFIGSLAGADFLASVVFACSFVNFHVFHGVD-SKAVFLLKIGSVTMTFTA
        HHHHHHHHHHHHHHHHHHHHHHHHHHHHHHCCCCC- HHHHHHHHHHHHHHHHHH
 70 80 90 100 110

 120 130 140 150 160 170
 HHHHHHHHHHHHHHHHHCCCCCCCCHHHHHHHHHHHHHHHHHHCCCCCCCCCCCCCCCC
2ks9A0 SIYSMTAVAFDRYMAIIHPLQPRLSATATKVVICVIWVLALLLAFPQGYYSTTETMPSRV
Query SVGSLLLTAIDRYLCLRYPPSYKALLTRGRALVTLGIMWVLSALVS----YLPLMGWTCC
 HHHHHHHHHHHCCEEEEECCCCCCCCCCEEEEEEEHHHHHHHHHH----CCCCCCCCCC
 130 140 150 160 170

 180 190 200 210 220 230
```

```
 CCCCCCCCCCCCCCHHHHHHHHHHHH HHHHHHHHHHHHHHHHCCCCCCCCCCCCCCCCH
2ks9A0 VCMIEWPEHPNKIYEKVYHICVTVLIYFLPLLVIGYAYTVVGITLWASEIPGDSSDRYHE
Query PRPCSELFPLIPNDYLLSWLLFIAFLFSGIIYTYGHVLWKAHQHVASLSGHQDRQVPGMA
  CCCCCCCCCCCCCCHHHHHHHHHHHCEEEEEEEEEEECCCCCCCCCCCCCCCCCCCCCC
 180 190 200 210 220 230

 240 250 260 270 280 290
 HHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHCCCCCCCCCCHHHHHHHHHHHHHH
2ks9A0 QVSAKRKVVKMMIVVVCTFAICWLPFHIFFLLPYINPDLYLKKFIQQVYLAIMWLAMSST
Query RMRLDVRLAKTLGLVLAVLLICWFPVLALMAHSLATTLSDQVK---KAFAFCSMLCLINS
 CCCCCCCCCCEEEEEEEEEEEECCCEEEECCCCCCCCCCHHH---HHHCCEEEEEECCC
 240 250 260 270 280 290

 300 310 320 330 340 350
 HHHHHHHHHH HHHHHHHHHHCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
2ks9A0 MYNPIIYCCLNDRFRLGFKHAFRCCPFISAGDYEGLEMKSTRYLQTQGSVYKVSRLETTI
Query MVNPVIYALRSGEIRSSAHHCLAHWKKCVRG------LGSEAKEEAPRSSVTETEADGKI
    HHHHH   HHHHHHHHHHCCCCCCCCC------CCCCCCCCCCCCCCCCCCCCCC
 300 310 320 330

 360
 CCCCCC--------
2ks9A0 STVVGA--------
Query TPWPDSRDLDLSDC
 CCCCCCCCCCCCCC
 350 360

Percentage Identity = 13.1%
```

Fig 1: Secondary Structure of CB2 receptor

```
 >P1;2ks9A
 structureX:2ks9::A::::::
 --DNVLPVDSDLSPNISTNTSEPNQFVQPAWQIVLWAAAYTVIVVTSVVGNVVVMWIILA
 HKRMR-TVTNYFLVNLAFAEASMAAFNTVVNFTYAVHNEWYYGLFYCKFHNFFPIAAVFA
 SIYSMTAVAFDRYMAIIHPLQPRLSATATKVVICVIWVLALLLAFPQGYYSTTETMPSRV
 VCMIEWPEHPNKIYEKVYHICVTVLIYFLPLLVIGYAYTVVGITLWASEIPGDSSDRYHE
 QVSAKRKVVKMMIVVVCTFAICWLPFHIFFLLPYINPDLYLKKFIQQVYLAIMWLAMSST
 MYNPIIYCCLNDRFRLGFKHAFRCCPFISAGDYEGLEMKSTRYLQTQGSVYKVSRLETTI
 STVVGA--------*
 >P1; Query
 sequence:::::::::
 MEECWVTEIANGSKDGLDSNPMKDYMILSGPQKTAVAVLCTLLGLLSALENVAVLYLILS
 SHQLRRKPSYLFIGSLAGADFLASVVFACSFVNFHVFHGVD-SKAVFLLKIGSVTMTFTA
 SVGSLLLTAIDRYLCLRYPPSYKALLTRGRALVTLGIMWVLSALVS----YLPLMGWTCC
 PRPCSELFPLIPNDYLLSWLLFIAFLFSGIIYTYGHVLWKAHQHVASLSGHQDRQVPGMA
 RMRLDVRLAKTLGLVLAVLLICWFPVLALMAHSLATTLSDQVK---KAFAFCSMLCLINS
 MVNPVIYALRSGEIRSSAHHCLAHWKKCVRG------LGSEAKEEAPRSSVTETEADGKI
 TPWPDSRDLDLSDC*
```

Fig 2: Alignment between the P34972 sequence and the 2ks9-A

The result of alignment was employed to build new homology model. Reliability of new homology model for CB2 was identified by Ramachandran plot. After the optimization and energy minimization process, the best model was selected among five 3D models generated for CB2 receptor on the basis of modeller scores. Energy minimization of 3D structure is vital for providing the maximum stability to the protein. Ramachandran plot drawn through PROCHECK (Laskowski *et al*., 1993) [74] program validated along with and ERRAT, the model with 90.0% of the total residues in most favoured region and residues in additional allowed regions was 8.7% and .9% in the generously allowed region (Fig.3 & 4). This stipulates that protein backbone dihedral angles phi (φ) and psi (ψ) occupied reasonably accurate positions in the selected 3D model. Computationally modeled 3D structure of CB2 receptor is shown in fig.5.

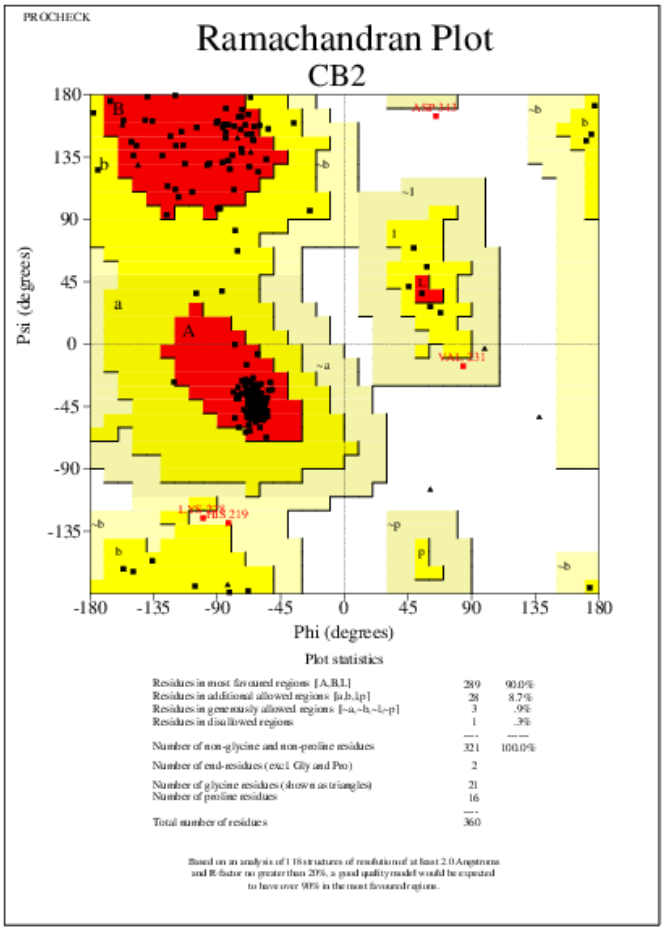


Fig 3: Ramachandran plot of CB2 receptor model.

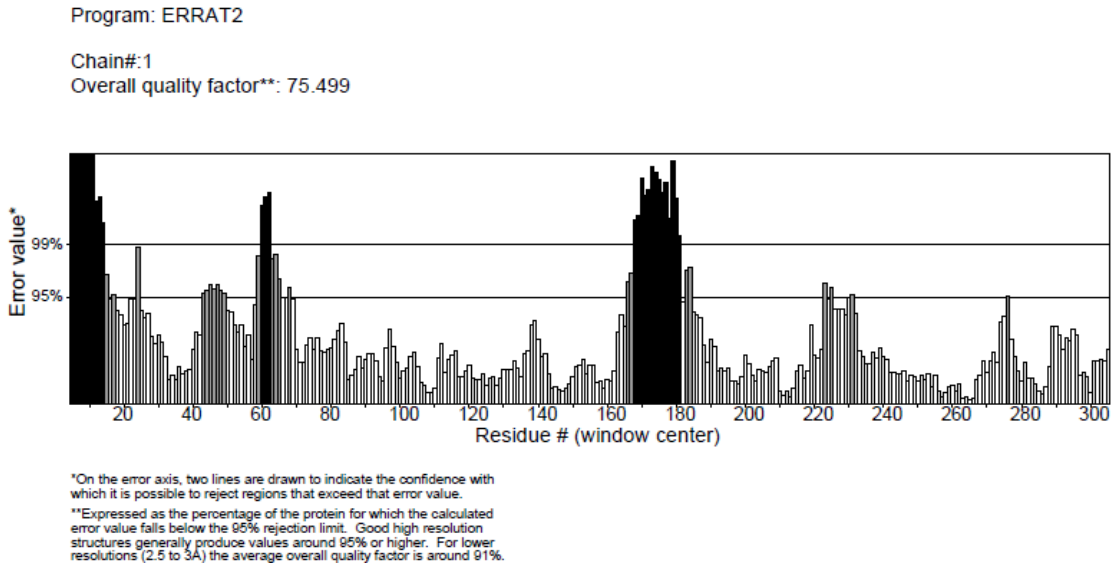


Fig 4: ERRAT plot of CB2 receptor model.

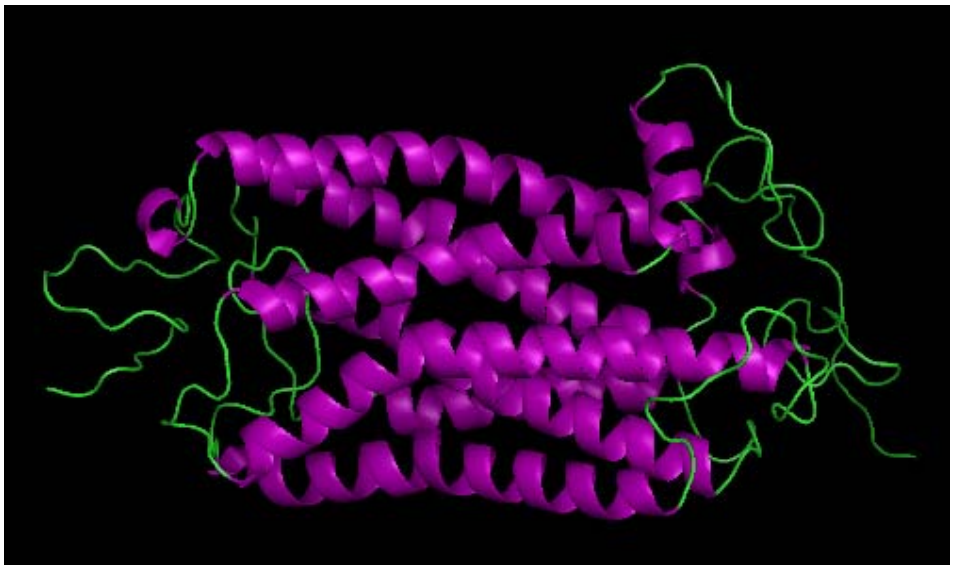
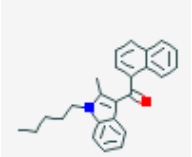
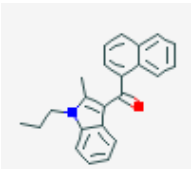
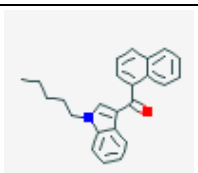
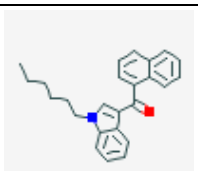


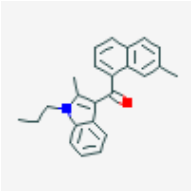
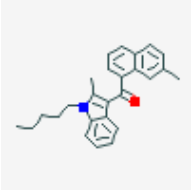
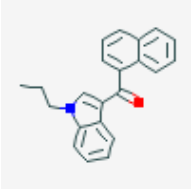
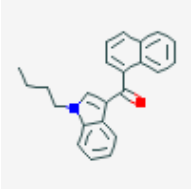
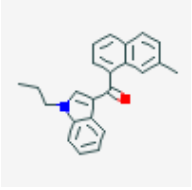
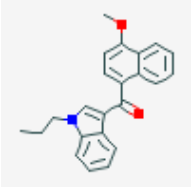
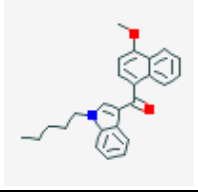
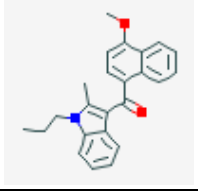
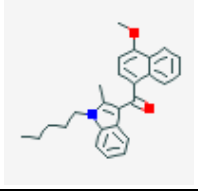
Fig 5: Computationally modeled 3D structure of CB2 receptor obtained from Modeller

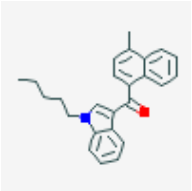
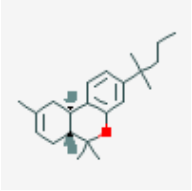
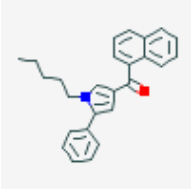
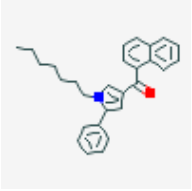
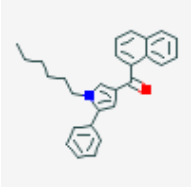
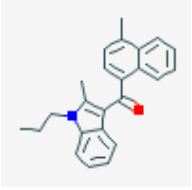
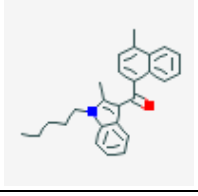
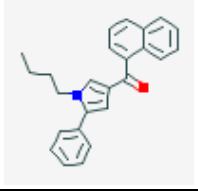
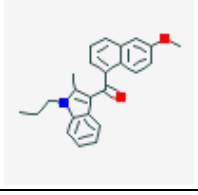
3.2 Results of virtual screening

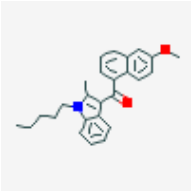
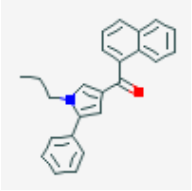
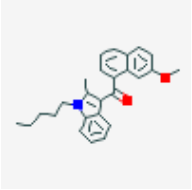
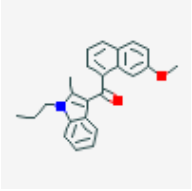
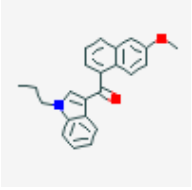
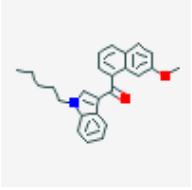
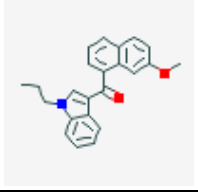
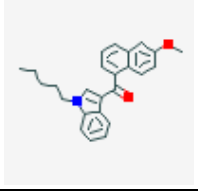
Docking studies predicted the interaction of ligands with protein. For such interaction studies, the most important requirement was the proper orientation and conformation of ligand which fitted to the protein binding site appropriately and formed protein-ligand complex. Therefore, optimal interactions and the best autodock score were used as criteria to interpret the best conformation among the 30 conformations, generated by AutoDock program. Docking of 30 CB2 Agonists derived compound against Cannabinoid CB2 receptor structure was performed with molecular docking program AutoDock 3.0.5 shown in table 2.

Table 2: Docking results of thirty agonist of CB2 screened from literature

Sl. No	CID Code	Structure	MWT (g/mol)	XlogP	HBD	HBA	Docking energy (kcal/mol)	Ref RMS Value
1	10360860		355.4721	6.7	0	1	-11.06	24.61
2	4273754		327.41894	5.8	0	1	-9.9	23.71
3	10382701		341.44552	6.3	0	1	-10.45	25.36
4	52224389		355.4721	6.9	0	1	-10.67	19.29

5	11473309		341.44552	6.2	0	1	-10.27	21.95
6	11280135		369.49868	7.1	0	1	-11.38	24.88
7	45271208		313.39236	5.4	0	1	-12.1	19.95
8	10471670		327.41894	5.8	0	1	-11.53	9.59
9	45270383		327.41894	5.8	0	1	-7.43	17.67
10	10831231		343.41834	5.4	0	2	-5.36	9.47
11	10547208		371.4715	6.3	0	2	-9.05	21.56
12	45272115		357.44492	5.8	0	2	-7.57	24.71
13	45272116		385.49808	6.7	0	2	-7.85	20.43

14	44466638		355.4721	6.7	0	1	-12.53	19.82
15	6918505		312.48888	6.4	0	1	-6.67	18.39
16	44418304		367.4828	6.6	0	1	-11.11	22.27
17	44418308		395.53596	7.7	0	1	-12.46	15.54
18	44418307		381.50938	7.2	0	1	-11.29	12.5
19	45267819		341.44552	6.2	0	1	-10.3	24.94
20	45267820		369.49868	7.1	0	1	-11.77	24.19
21	44418303		353.45622	6.1	0	1	-11.67	14.92
22	11233636		357.44492	5.8	0	2	-9.31	22.15

23	11176619		385.49808	6.7	0	2	-9.45	22.23
24	44418301		339.42964	5.7	0	1	-13.26	11.11
25	45272119		385.49808	6.7	0	2	-8.3	21.44
26	45267825		357.44492	5.8	0	2	-8.0	16.57
27	11313905		343.41834	5.4	0	2	-6.52	17.67
28	45271217		371.4715	6.3	0	2	-10.36	22.64
29	45271218		343.41834	5.4	0	2	-7.53	10.18
30	11372171		371.4715	6.3	0	2	-8.55	17.33

MWT: molecular weight; ref RMS: ref root mean square deviation; HBD: hydrogen bond donar; HBA: hydrogen bond acceptor.

Among the above docked compounds there were three JWH-156, JWH-122 and JWH-146 best docked agonists. A close view of the binding interactions of CB2 receptor with JWH-156, JWH-122 and JWH-146 CB2 Agonists compounds were analyzed through Python Molecular viewer and shown below in Figure 6, 7, 8, respectively. Ligand is coloured in brown (in stick drawing) whereas amino acids involved in hydrogen bonds color by atom type.

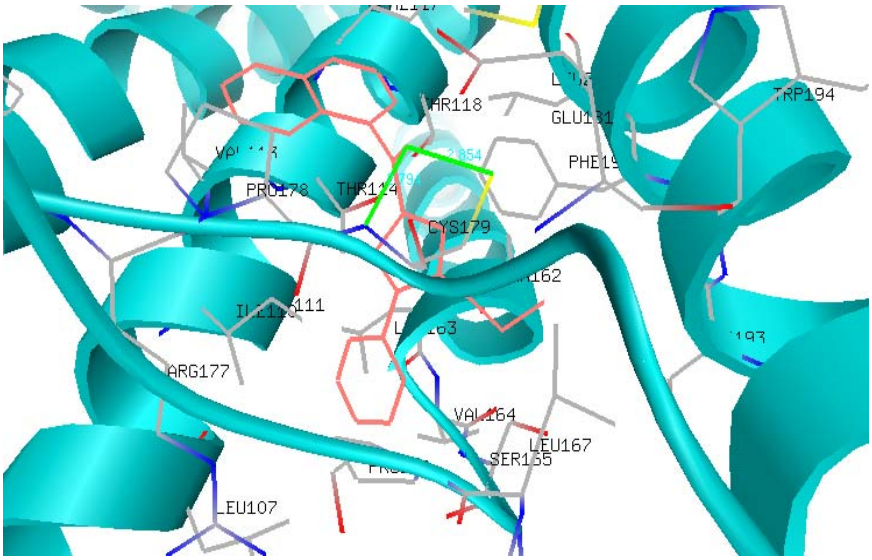


Fig 6: Two H-bonds is formed between amino acid CYS179 (N), CYS179 (SG) of CB2 receptor and compound JWH-156 with bond length 2.854 Å and 2.794 Å

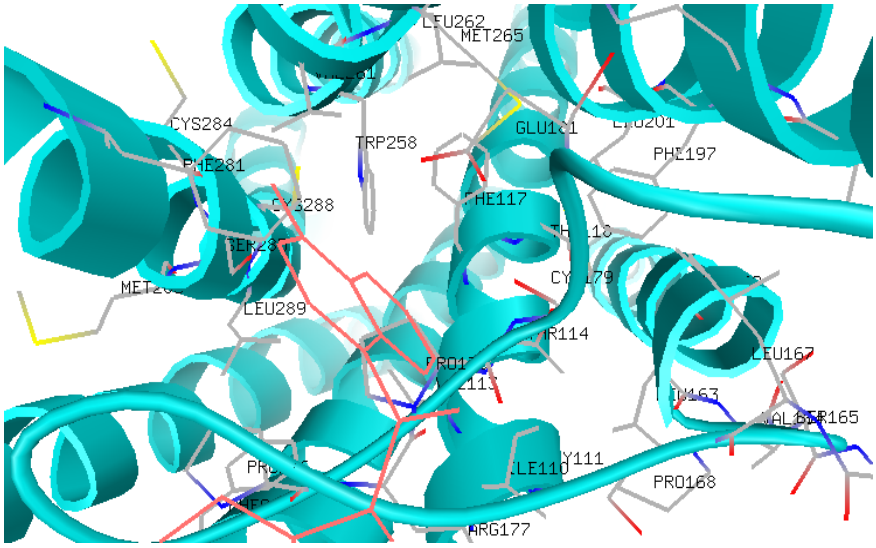


Fig 7: Interaction between active site amino acid of CB2 receptor and JWH-122

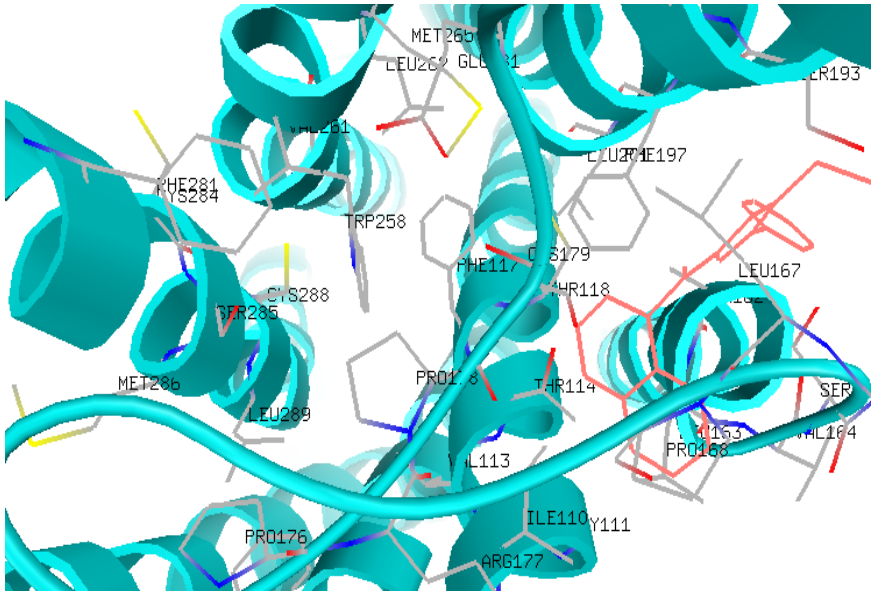


Fig 8: Interaction between active site amino acid of CB2 receptor compound JWH-146

3.5 QSAR Result

All the compounds were subjected to Lipenski's Rule of Five to evaluate their absorption and permeability. All best docked Compounds satisfy the criteria (having molecular weight <500; hydrogen bond donor < 5; hydrogen bond acceptor <10) therefore have better prospects of acting as drugs due to their high drug likeness (table 3). Topological Polar Surface Area (TPSA) of all compounds correlate with the prediction of transport properties of drugs and has been linked to drug bioavailability, selected compound shows a low TPSA (< 140 value) resulting these compounds to have high bioavailability as a drug candidate.

Table 3: QSAR Parameter for best docked compound

Sl. No.	CID No	IUPAC Name	MWT (g/mol)	XLogP	HBD	HBA	RBC	TPSA	HAC	FC
1	44418301	naphthalen-1-yl-(5-phenyl-1-propylpyrrol-3-yl)methanone	339.42964	5.7	0	1	5	22	26	0
2	44466638	(4-methylnaphthalen-1-yl)-(1-pentylindol-3-yl)methanone	355.4721	6.7	0	1	6	22	27	0
3	44418308	(1-heptyl-5-phenylpyrrol-3-yl)-naphthalen-1-ylmethanone	395.53596	7.7	0	1	9	22	30	0

MWT: Molecular Weight; HBD: H-Bond Donor; HBA: H-Bond Acceptor; RBC: Rotatable Bond Count; TPSA: Topological Polar Surface Area; HAC: Heavy Atom Count; FC: Formal Charge.

4. Conclusion

The CB2 receptor is a widely abused drug target for treatment of pain, inflammation, and Immunosuppressive that underlie the biology of Homo sapiens. CB2 receptor is member of rhodopsin-like family of seven-transmembrane G-protein-coupled receptor. In this work, we have constructed a 3D model of CB2 receptor, using the MODELLER software and obtained a refined model after energy minimization. The final refined model was further assessed by PROCHECK program, and the results show that the model was stable and reliable. The stable model was further used to identify some potent agonists for CB2 receptor in Homo sapiens. Flexible docking of ligand from chemical database to receptor is an emerging approach and is extensively used to reduce cost and time in drug discovery. The approach utilized in this study is successful in finding three potent CB2 agonists as JHW-156 (Docking Energy -13.26 kcal/mol), JWH-122(Docking Energy:-12.53 kcal/mol) and JWH-146 (Docking Energy: -12.46 kcal/mol). Further the three best-docked complexes were analyzed through Python Molecular Viewer software for their interaction studies. Thus from the Complex scoring and binding ability its deciphered that these ligands could be used as interesting leads for the development of new active CB2 ligands. QSAR Properties of all these compounds were calculated. The results shows that all best docked compounds satisfy the criteria (molecular weight <500, hydrogen bond donor < 5; hydrogen bond acceptor <10) and shows a low Topological Polar Surface Area (<140 value) resulting these compounds could be used as interesting leads for development of new active CB2 ligands.

5. References

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