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Pharmacophore & Docking based combined Insilico study of Kappa Opioid Receptor Agonists

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Abstract: The purpose of the study was to compare the binding energy of pharmacophores of different classes targeting to kappa opioid receptor (KOR) with ketazocine and pentazocine which are having good activity on the KOR. The 3D structure of KOR receptor was built by Homology modeling; pharmacophores were characterized by using Ligand scout. Docking studies for the KOR agonists were performed in Autodock4.0. It was observed that 2-(3,4-Dichloro-2-methylphenyl)-*N*-methyl-*N*-[(5*R*,7*S*,8*S*)-7-(pyrrolidin-1-yl)-1-oxaspiro[4.5]dec-8-yl]acetamide and 6-(2-{2-(Dimethylamino) methyl] piperidin-1-yl}-2-oxoethyl)-3,4-dihydronaphthalen-1(2*H*)-one compounds may exhibit better activity than ketazocine. This study states the importance of pharmacophoric groups and their use to enhance drug discovery process prior synthesis.
Keywords: Homology modeling, pharmacophore, docking, kappa opioid receptor, Ligand scout, Autodock4.0.

Introduction:

The κ-opioid receptor (KOR) is a G-protein coupled receptor to which the endogenous opioid peptide dynorphin binds as a ligand. Based on receptor binding studies, three subtypes of kappa opioid receptors κ1, κ2, κ3, have been characterized [1] .Only one cDNA clone was identified for these subtypes, hence these receptor subtypes likely arise from interaction of the κ-opioid receptor protein with other membrane associated proteins. Activation of κ-opioid receptor antagonizes the effects of μ-opioid receptor agonists. Ketazocine is a potent and selective KOR agonist also known as ketocyclazocine which is a benzomorphan derivative, an exogenous opioid. The best pharmacophore hypothesis consists of five chemical features (one hydrogen-bond acceptor, one hydrogen-bond donor, two ring aromatic and one positive ionizable feature).

The increasing knowledge of the KOR structure, activity and the mode of interaction between receptor and agonists, is giving momentum to the development of computational models, Pharmacophore modeling has been one of the important and successful ligand based approaches for new drug discovery in the last few years [2-5]. A pharmacophore hypothesis collects common features distributed in three-dimensional space representing groups in a molecule that participate in important interactions between drug and active site [6].

RESULTS & DISCUSSION

The 3-D structure of KOR was modeled by homology modeling. The sequence of kappa opioid receptor obtained from NCBI consists of 380 amino acids and the modeled structure was shown in fig1.

The energy minimized model of KOR was evaluated using Ramachandran plot (fig2), PROSA-web, PROCHECK, WHAT IF.

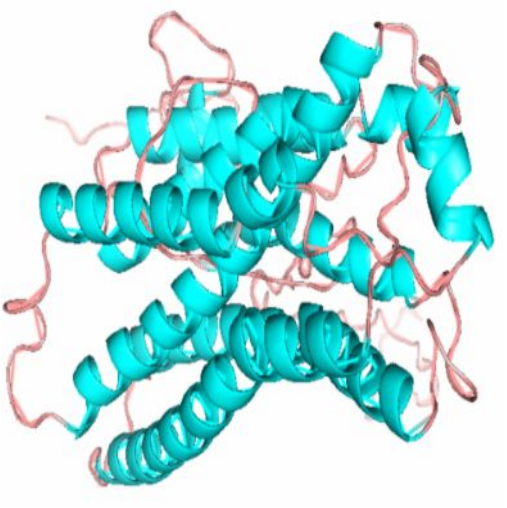

Fig. 1. Structure of KOR
The built 3D model of KOR showing different secondary structure conformations. The α-helix is represented in red, β-turns in cyan.

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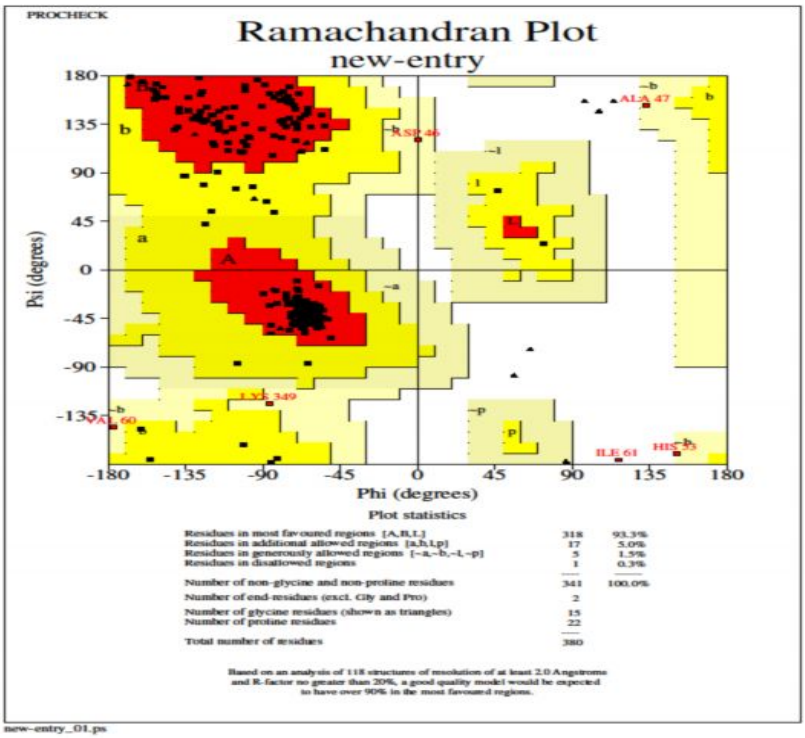


Fig. 2. Ramachandran plot of KOR model

For the energy minimized structure of KOR the residues in the most favored region was found to be 93.3% and the residues in the disallowed region was 0.3% and hence it can be considered to be the best.

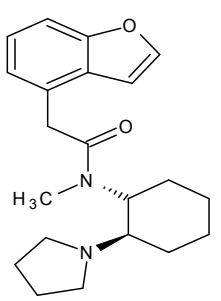
The Z-score value of KOR in the PROSA-web was found to be -2.83 which were in the range of native conformations. The WHAT IF analysis for the KOR have shown that RMS Z score average packing of the protein 1.093, back bone conformation is -1.810 which was with in the range, bond length 0.980 and bond angle 1.321 has shown that this model is having good quality.

PROCHECK analysis for the KOR gives the main chain parameters, side chain parameters, geometrical properties of all the amino acid residues of KOR. The main chain parameters have the overall G-value with in the range.

The active site for the KOR was predicted by using CASTp server and the active site aminoacids were Glu-45, Asp-46, Gln-48, Ser-67, Phe-70, Tyr-111, Pro-113, Gln-115, Ser-116, Lys-132, Ile-133, Ser-136, Tyr-139, Ile-194, Glu-203, Asp-204, Ser-211, Leu-212, Gln-213, Phe-214, Asp-217,Val-230, Tyr-312, Ile-316.

Based on the published literature, we selected a series of potent and selective KOR agonists (Fig 3) to generate a pharmacophore model in ligand scout. These compounds were taken from different literature sources [7-10], and docking studies were performed using Auto dock 4. The maximum number of genetic algorithm runs was set to 30 for each compound and the results for the more active compounds were shown below along with the pharmacophoric groups generated in the ligand scout and the lowest docking energy.

The interactions of active compounds with KOR and their pharmacophores were shown in Fig 4 & 5 and the ketazocine interaction with KOR was given in Fig 6.IUPAC names for the compounds were given in table1.



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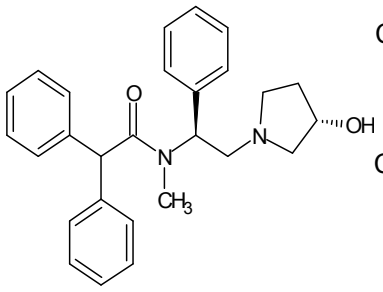

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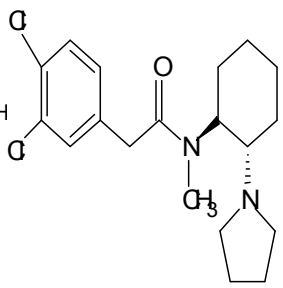

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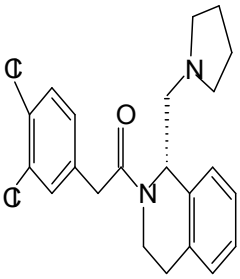

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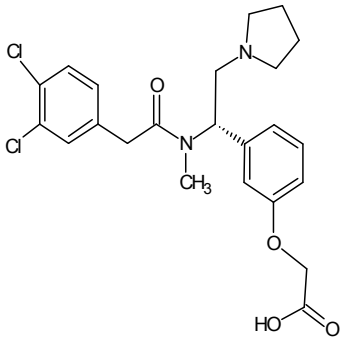

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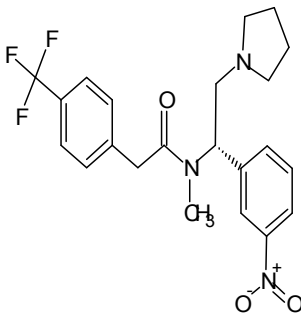

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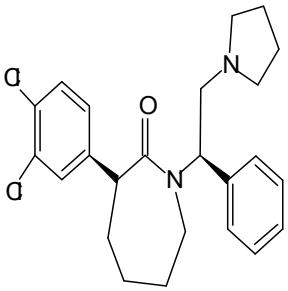

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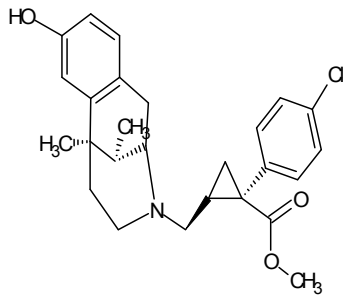

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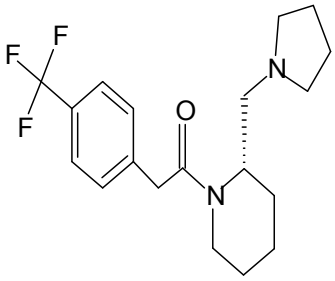

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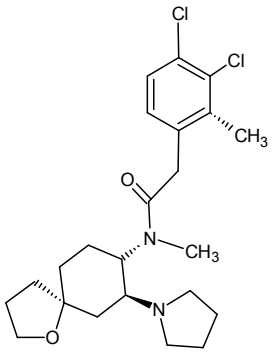

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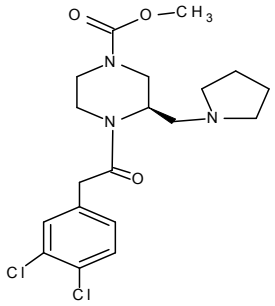

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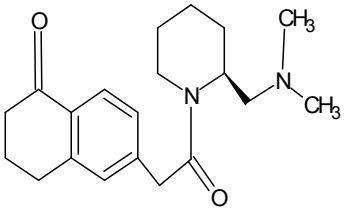

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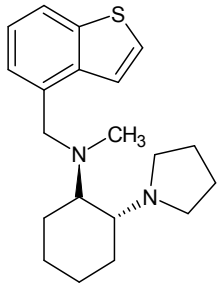
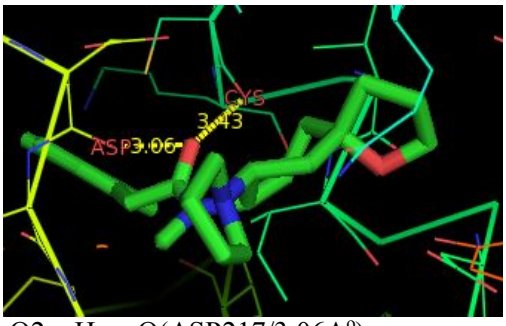
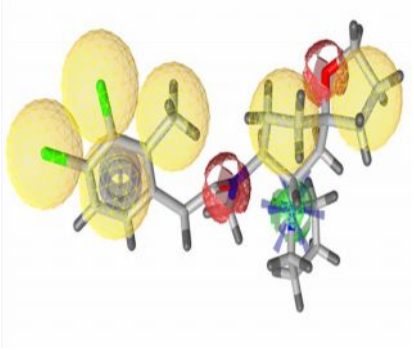


(13)

Table1: IUPAC names for the structures

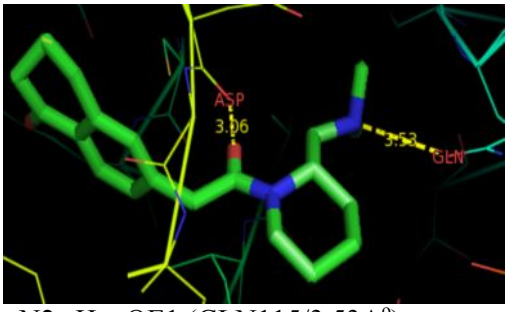
Compound No	IUPAC name
1	2-(1-Benzofuran-4-yl)-*N*-methyl-*N*-[(1*R*,2*R*)-2-(pyrrolidin-1-yl)cyclohexyl]acetamide
2	*N*-{(1*S*)-2-[(3*S*)-3-Hydroxypyrrolidin-1-yl]-1-phenylethyl}-*N*-methyl-2,2-
3	2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*S*,2*S*)-2-(pyrrolidin-1-
4	2-(3,4-Dichlorophenyl)-1-[(1*S*)-1-(pyrrolidin-1-ylmethyl)-3,4-
5	{3-[(1*S*)-1-{[(3,4-Dichlorophenyl)acetyl](methyl)amino}-2-(pyrrolidin-1-
6	*N*-Methyl-*N*-[(1*S*)-1-(3-nitrophenyl)-2-(pyrrolidin-1-yl)ethyl]-2-[4-
7	(3*S*)-3-(3,4-Dichlorophenyl)-1-[(1*R*)-1-phenyl-2-(pyrrolidin-1-
8	Methyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-{[(1*R*,13*R*)-4-hydroxy-1,13-dimethyl-10-azatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-10-
9	Methyl (2-{methyl[(1*S*)-1-phenyl-2-(pyrrolidin-1-yl)ethyl]amino}-2-oxo-
10	2-(3,4-Dichloro-2-methylphenyl)-*N*-methyl-*N*-[(5*R*,7*S*,8*S*)-7-(pyrrolidin-1-
11	2-(3,4-Dichlorophenyl)-1-[(2*R*)-4-[hydroxy(methoxy)methyl]-2-
12	6-(2-{2-[(Dimethylamino)methyl]piperidin-1-yl}-2-oxoethyl)-3,4-
13	(1*R*,2*R*)-*N*-(1-Benzothiophen-4-ylmethyl)-*N*-methyl-2-(pyrrolidin-1-yl)cyclohexanamine

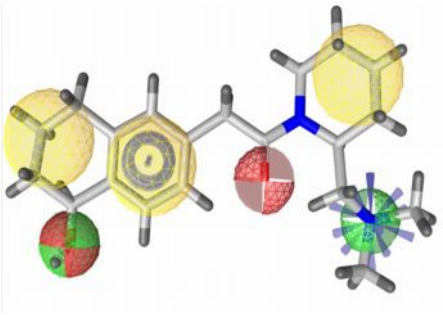




O2---H──O(ASP217/3.06A^{o})
O2---H──O (CYS131/3.43A^{o})
Compound 10 with docking energy -13.21

Fig. 4. Interaction of compound with KOR and its pharmacophores.





N2─H---OE1 (GLN115/3.53A^{o})
O2---H──O (ASP217/3.06A^{o})
Compound12 with docking energy -13.11

Fig. 5. Interactions of compound with KOR and its pharmacophores.

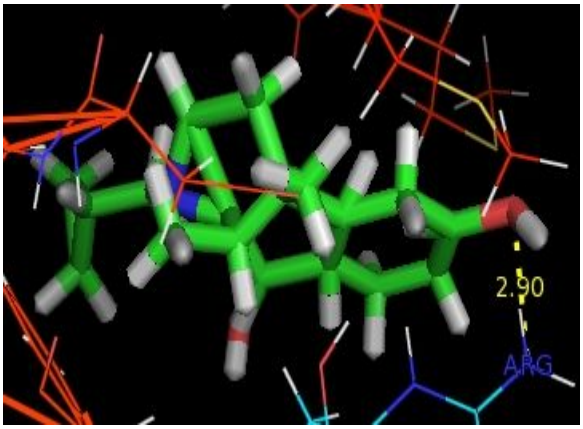


Fig 6 Interaction of ketazocine with the KOR

The interaction of ketazocine with the kappa opioid receptor was observed with Arginine. O1─ H --- N (Arg202/2.90A^{0}). The docking energy was found to be -13.08 KJ/mol.

Conclusion:

From this study, we conclude that most of the hydrogen bonding interactions shown was by the pharmacophoric groups (HBAs, HBDs, Hydrophobic groups, Positive ionisable area) identified in the ligand scout. By the above study it was observed that CONH functional group was involved in the biological interaction.

Compounds **27** (-13.21) KJ/mol, **31**(-13.11) KJ/mol were found to have highest docking energy when compared to ketazocine (-13.08) KJ/mol which was a highly selective kappa opioid agonist. These compounds were predicted to be having oral bioavailability of about 30-70%. Hence they may show better activity than ketazocine among all the analogues.

This study states the importance of pharmacophoric groups and their use to enhance drug discovery process prior synthesis. Further, work can be extended to develop new analogues of the kappa opioid receptor agonists based on the pharmacophoric groups involved in the biological activity and can go for structure based virtual screening.

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