Research article Available online www.ijrpsonline.com ISSN: 2249–3522

International Journal of Research in Pharmacy and Science

Pharmacophore Mapping and Docking on Triazepane Derivatives as DPP-IV Inhibitors

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ABSTRACT

The molecule is inserted on the workspace of the Ligand scout 3.30b trial version. Energy was minimized by **MMFF94** and pharmacophore part of compound is created which shows the hydrogen bonding, hydrophobic bonding and aromatic environment. Pharmacophore mapping shows hydrogen bond, hydrophobic bonding and aromatic hydrogen. The pdb (2OLE) of protein, ligand and reference (vildagliptin) is inserted on the workspace of the Molegro virtual docker 5.0 trial. Preparation of protein as well as ligand done, create surface area of protein, detection of cavity. The reference compound taken in docking is vildagliptin. The parameter selected in the docking studies were moldock optimizer, number of runs 10, population size 50, cross over rate 0.90 and max iteration 2000 and cavity selected is user define. Docking studies help in checking the interaction between protein and the ligand, interaction shows in docking are Glu 205, Arg 125, Gly 741, Trp 629, Ala 654, Asn 710, Asp 708, Val 711, His 740. The derivatives prepared by after docking and pharmacophore mapping helps in creating a most potent compound.

KEYWORDS: Pharmacophore, Vildagliptin, Moldock, Molegro virtual docker, Docking

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INTRODUCTION

Due to type 2 diabetics several forms of neuropathy and peripheral neuropathy in diabetes has been known to approach 70%. DPP-4 preferentially cleaves incretin hormones, GLP-1 and GIP peptides with the amino acid alanine or proline in position 2 of the N-terminus of the peptide chain. Active GLP-1(7–36) amide was cut by DPP-4 to yield a dipeptide (His-Ala) and GLP-1(9–36)amide.[1-3] According to previous studies,[4-7] effective glucose control, diverse antioxidants, and several neurotropic agents can help reduce diabetic polyneuropathy. Type 2 diabetes mellitus (T2DM) disease is characterized by several pathophysiologic defects including insulin resistance, excess hepatic glucose production and progressive pancreatic β cell dysfunction.[8] It creates propblem such as peripheral vascular insufficiencies, neuropathy and retinopathy end stage renal disease. Instead lifestyle interference, treatment of T2DM consists of oral antihyperglycaemic drugs and insulin.[9] Suppress the various possible targets, the development of dipeptidyl peptidase IV inhibitors can prevent the degradation of the incretin hormones appears to be one of the most attractive, rational agents for the treatment of T2DM.[10] Dipeptidyl peptidase IV also known as T-cell antigen CD26[11-12] is present in group of class of serine protease family that selectively cleaves dipeptide from polypeptides, including proline or alanine at the N-terminal penultimate position.[13-14]

MATERIAL AND METHOD

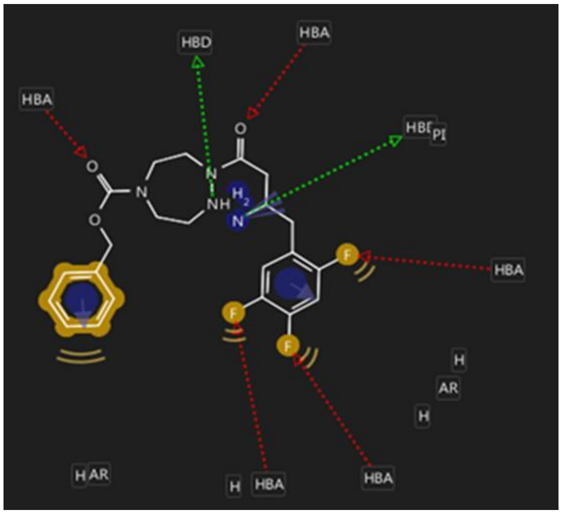
Study data set of Triazepane derivatives (22 molecules) has been taken from the literature. [15]

Pharmacophore mapping

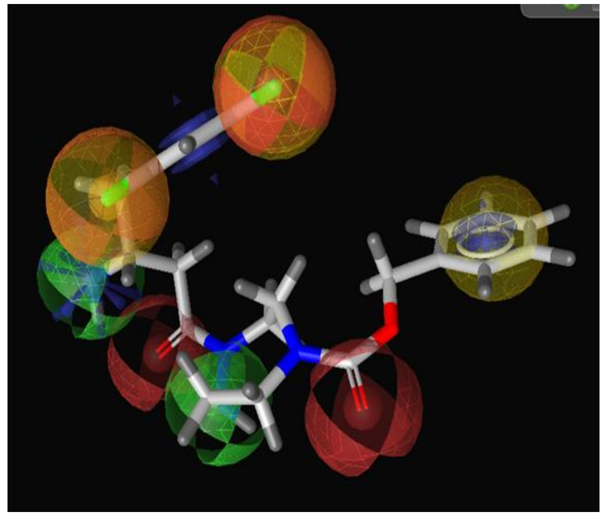
The molecule is inserted on the workspace of the Ligand scout 3.30b trial version. Energy was minimized by **MMFF94** and pharmacophore part of compound is created which shows the hydrogen bonding, hydrophobic bonding and aromatic environment. It was helpful in detection of the atom nature fig 1.

Docking studies

The pdb (2OLE) of protein, ligand and reference is inserted on the workspace of the Molegro virtual docker 5.0 trial. Preparation of protein as well as ligand, create surface area of protein, detection of cavity is done. The reference compound taken in docking is Vildagliptin. The parameter selected in the docking studies were moldock optimizer, number of runs 10, population size 50, cross over rate 0.90 and max iteration 2000 and cavity selectedwas user defined. The **hydrogen bond** interaction and hydrophobic bond interaction is shown in the fig 2. The receptor and ligand interaction is shown in the fig 3. The docking score of the compound is shown in the table 1.



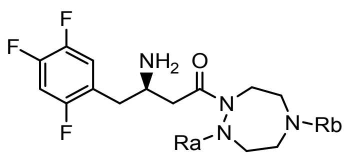
A



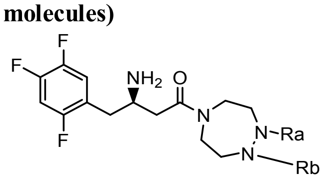
B

Fig 1: The nature of the atom is shown in A, B picture and color line shows the bonding.

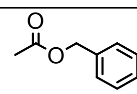
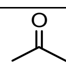
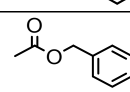
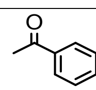
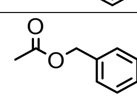
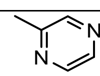
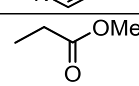
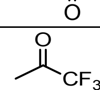
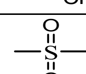
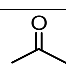
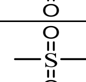
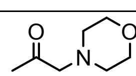
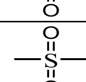
Table 1: General structure of the compounds of cyanopyrrolidine derivatives and their biological activities (data set of 22 molecules)

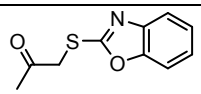
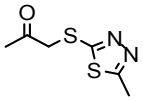
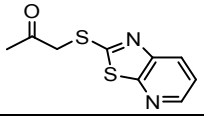
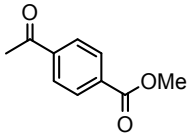
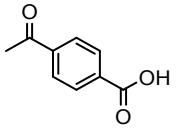
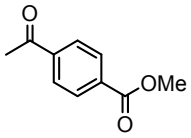
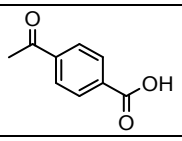
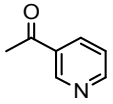
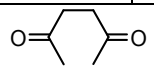


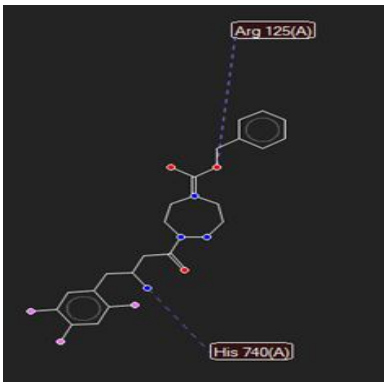
7-13p



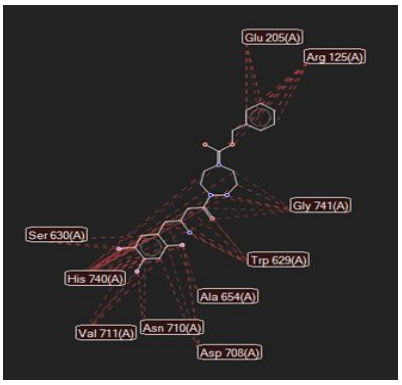
17a-17e

S. No.	Compound	Ra	Rb	IC50 (nM)	log(1/IC50)
1	7	H	H	9800	5
2	13a	H		859	6.06
3	13b			578	6.23
4	13c			1200	5.92
5	13d	H		2500	5.6
6	13e	H		2900	5.53
7	13f	H		681	6.16
8	13g	H		609	6.21
9	13h			1800	5.74
10	13i			700	6.15

11	13j			401	6.39
12	13k			591	6.22
13	13l			151	6.82
14	13m	H		439	6.35
15	13n	H		216	6.66
16	13o			213	6.67
17	13p			98	7
18	17a	H	H	4500	5.34
19	17b		H	3300	5.48
20	17c			1600	5.79
21	17d			660	6.18
22	17e			853	6.06

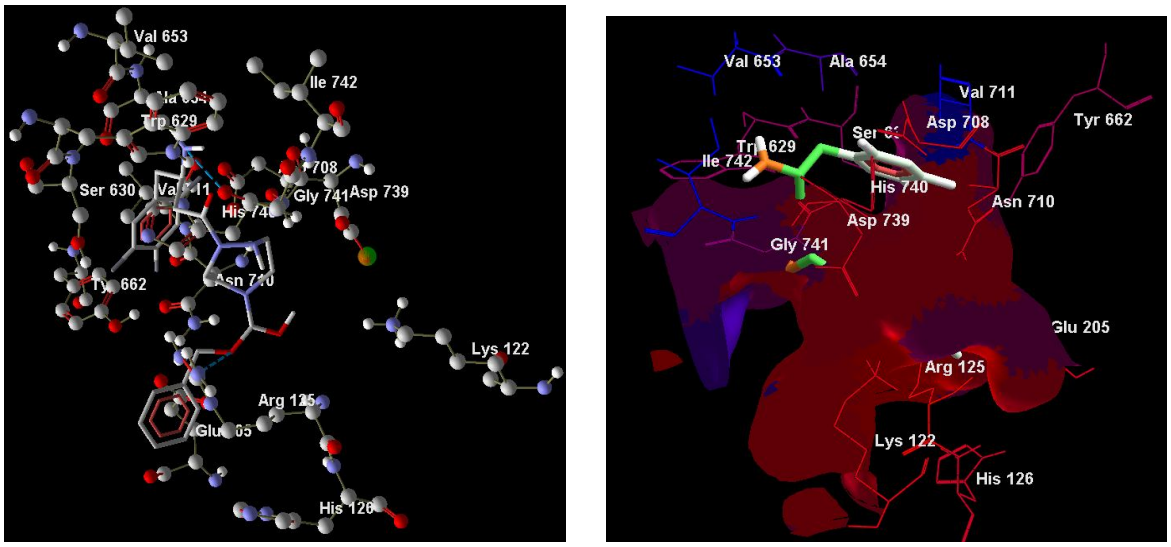


A



B

Fig2. The Diagram A shows hydrogen bond interaction with His 740 and hydrophobic interaction with the receptor.



A B

Fig 3: The Diagram A shows hydrogen bond interaction and B shows hydrophobic interaction with the receptor.

Table 2: The docking score of compound

Ligand	MolDock Score	Rerank Score	HBond
01	-67.7121	-34.8536	-2.399
02	27.058	494.955	0
03	50.3771	573.978	-0.338762
04	88.2865	1082.55	-0.524351
05	-73.4308	-43.7975	0.807523
06	-85.7064	7.265	-5.62086
07	-69.5396	-50.5174	-1.3724
08	-69.2886	-1.95484	0
09	-49.5066	55.8547	-0.798079
10	33.732	496.633	-0.986028
11	49.7545	584.274	0
12	-18.1281	567.026	-7.95629
13	-40.8473	500.308	0.149433
14	-48.8332	171.644	0.500079
15	-48.5538	156.765	-0.632443
16	-78.052	138.233	-3.70352
17	-55.9765	88.0899	-3.55236
18	-78.2862	28.664	-1.68366
19	-69.3886	-17.3276	-1.17221
20	-59.7999	-20.2719	-0.44184
21	-6.64839	702.189	-3.02646
22	-46.2925	-25.8067	3.55661
vildagliptin	-67.9615	33.8519	-3.69553

RESULT AND DISCUSSION

In pharmacophore modeling it is found out that C=O, F group shows the hydrogen bond acceptor nature while NH and NH_2 show the hydrogen bond donor nature. The hydrogen bonding of Arg 125 with Oxygen atom and His 740 with NH_2 is shown in the figure. The hydrophobic interaction between protein and ligand is found at Glu 205, Arg 125, Gly 741, Trp 629, Ala 654, Asn 710, Asp 708, Val 711, His 740. The derivatives prepared by after docking and pharmacophore mappin helps in creating a most potent compound. If in the compound steric interaction is more than compound is fitted in cavity accurately which is required for designing of structural based compound.

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