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ORIGINAL ARTICLE

Molecular Docking and *In Silico* Admet Studies of Potential Ingredients of *Zingiber officinale* Extract as an Anti-Migraine Compounds

Prachi Farande*, Vaibhav Vaidya, Mohit Mahajan, Abhishek Galgate, Shrutika Bhagde, Rohit Jadhav
Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi, Dr. D. Y. Patil Educational Complex, Pune 411044, Maharashtra, India.

ABSTRACT
The peptide known as calcitonin gene-related peptide (CGRP) is a migraine initiator. In the current research. We assessed the CGRP receptor crystal structure binding of our active ligands found in ginger extract using the molecular docking approach and compared their binding energy and affinity with other reference anti-migraine medications/ligands available on the market. Four bioactive chemicals found in ginger have been shown to lower nitric oxide synthase (NOS), which in turn inhibits the production of nitric oxide (NO), which has been linked to a reduction in migraine discomfort. Nitric oxide is inhibited, which causes the intracranial blood vessels to vasoconstrict and lessen migraine pain. a high-throughput screening that includes molecular docking, predictions for absorption, distribution, metabolism, excretion, toxicity, log P values, and the percentage of oral absorption in humans.
Keywords: *Migraine; Calcitonin gene-related peptide; Ginger Extract; In silico studies; ADMET.*

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INTRODUCTION

A neurological disorder called migraine is distinguished by the overexcitation of several active proteins, which causes inflammatory pain in particular parts of the brain. Women are three times as likely than men to have it. Claims that a brain malfunction that activates and sensitizes the trigeminovascular system, notably the trigeminal nociceptive afferents innervating (meninges) and causing headache, is the cause of migraine. [1] The dysfunction in the central nervous system that results in migraine is associated with the release of inflammatory mediators such as calcitonin gene-related peptide (CGRP), substance p, and neurokinin a that mediate vasodilation and mast cell degranulation which further leads to the release of pro-inflammatory agents. These pro-inflammatory agents mediate sensitization and excitation of trigeminal nerves that promote neurogenic inflammation and generation of painful stimuli. [2] In 1938, Harold wolf established the first migraine proposition known as the vascular proposition. Wolff set up that cases with migraines had extracranial vasodilation that could be treated by using vasoconstrictors. Wolff concluded that vasodilation results in migraine pain and vasoconstriction could be used to palliate the pain. [3] after this finding, DeVries suggested that vascular palpitation leads to the activation of stretch receptors causing the release of neuropeptides similar to calcitonin gene-related peptide (CGRP) from perivascular jitters. Strong vasodilators like CGRP can cause migraine discomfort. [4] Numerous studies have demonstrated that ginger can reduce migraine discomfort by inhibiting NO. Additionally, ginger has been shown to operate as a partial 5-HT_{1A} agonist, which inhibits chemicals (CGRP, substance P, and NO) from the trigeminal nerve and causes redistribution of blood flow, reducing inflammation and alleviating migraine discomfort.[5]. Both fresh and dried ginger have been found to have at least 115 different components. [6] at least 14 different bioactive chemicals can be extracted from ginger., including 6 paradol, 14 shogaol, 6 shogaol, 8 gingerol, 8-gingerol, 10-gingerol, 8-gingerol, and 1-dehydro- 1,7-bis-(4′

hydroxyl-3′ methoxyphenyl)-5-methoxyhepthan-3-one, and methoxy [10]-gingerdione, [10]-gingerdione, hexahydrocurcumin, tetrahydrocurcumin, gingerenone a, and methoxy-10-gingerol. [7]

MATERIAL AND METHODS

Compounds used for study

In this study, we used the active compounds of the ginger extract. Both fresh and dried ginger have been found to have at least 115 different components. [7] The bioactive substances listed below have been found to behave as strong antioxidants with reference to migraines. [8]

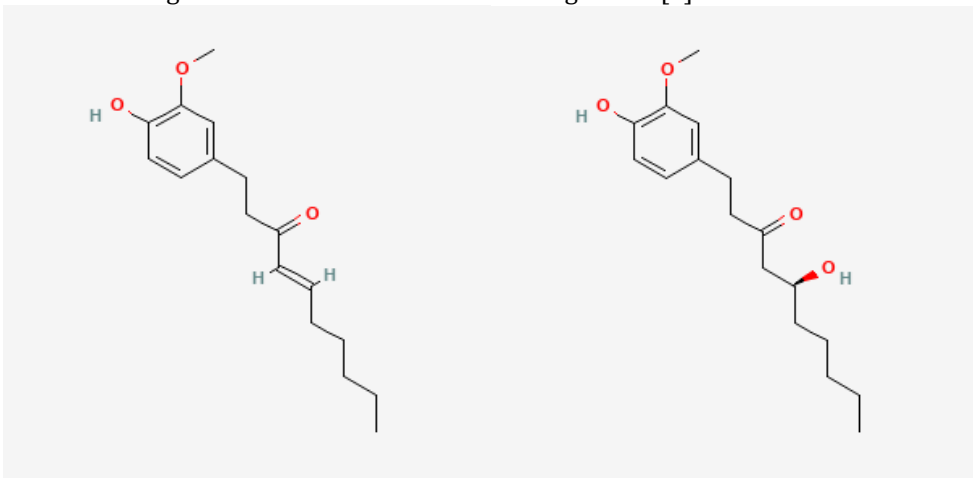

Figure 1: structure of [6] -shogaol **figure 2: structure of [6] -gingerol**

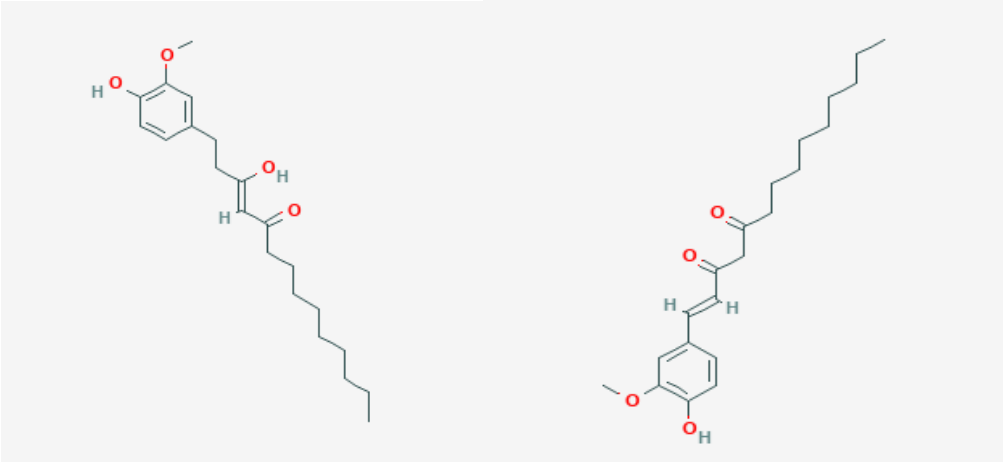

Figure 3: structure of [10]-gingerdion figure 4: 1dehydro-[10]-gingerdione

Preparation of receptor

A class-b GPCR receptor's three-dimensional structure (PDB id: 3n7s) was obtained from the protein data bank (www.rcsb.org). There are four chains in the class-b GPCR receptor's pdb file (PDB id: 3n7s): a, b, c, and d. For the docking investigation, chain a (94 amino acid residues) was utilised. Separate proteins underwent pre-processing that improved hydrogen bonding by removing the substrate cofactor and crystallographically detected water molecules (water devoid of h bonds). [9]

Ligands preparation

The national centre for biotechnology information's (NCBI) Pub chem compound database was utilised to retrieve the structure of the active ingredient in ginger that was used to make the product (http://pubchem.ncbi.nlm.nih.gov). The 3-dimensional conformer SDF file structures of 6-shogaol, 6-gingerol, 10-gingeridone 1-dehydro-10-gingeridone were downloaded from the Pub chem database. [9]

Docking study

A prepared protein molecule for the receptor was transformed in Pyrex software to pdbqt format. Four ligand molecules were subjected to energy minimization and conversion into pdbqt format using open babel and vina vizard. Using Pyrex software, a docking analysis of the receptor protein and the ready ligand was performed. The interaction between ligands and proteins was then performed utilising bio via discovery studio, and the resulting 2D structure was examined. And the results are compared with standard drug sumatriptan succinate.

ADMET prediction

For all four constituents in the ginger extract, an *In silico* pharmacokinetics research was conducted using the Admet sar and SWISS-MODEL tools, and their levels of absorption were assessed.[10]

RESULT AND DISCUSSION

It is generally known how important natural inhibitors are in the fight against numerous diseases. Therefore, it was crucial to investigate how these inhibitors interacted with our target protein. The active components of ginger were the ones we chose for the current investigation. To assess the relationship between individual active ingredients in ginger extract and receptors, we used docking methods, Pyrex, and bio via discovery studio to evaluate the interaction of receptors and individual active compounds in ginger extract. The comparative studies of docking results are shown in table 1. Among all the natural inhibitors docked within the active site of the CGRP receptor, 6- shogaol was found to bind with the best efficacy to the CGRP receptor, 6- gingerol, 10-gingeridone, 1-dehydro 10-gingeridone were also effective. Among all compounds ligand S-1, G-1, G-1, D-1 of 6- shogaol, 6- gingerol, 10-gingeridone, 1-dehydro 10-gingeridone shows better results respectively. These substances have higher binding energies than other substances. Based on dock scores derived by Pyrex software, all comparisons were conducted. As reference medications, these compounds demonstrated superior docking.

Table no. 1: comparative studies of docking results of four active ingredients of ginger and sumatriptan

Sumatriptan		**6- shogaol**		**6-gingeridone**		**10-gingeridone**		**1 Dehyro 10-gingerigone**	
Ligand	Binding affinity	Ligand	Binding Affinity	Ligand	Binding Affinity	Ligands	Binding affinity	Ligand	Binding affinity
S-1	-6.2	S-1	-6.2	G-1	-5.9	G-1	-5.9	D-1	-5.9
S-2	-6	S-2	-6	G-2	-5.7	G-2	-5.9	D-2	-5.8
S-3	-6	S-3	-5.7	G-3	-5.7	G-3	-5.8	D-3	-5.5
S-4	-5.9	S-4	-5.6	G-4	-5.5	G-4	-5.7	D-4	-5.4
S-5	-5.8	S-5	-5.6	G-5	-5.4	G-5	-5.7	D-5	-5.4
S-6	-5.7	S-6	-5.5	G-6	-5.4	G-6	-5.7	D-6	-5.4
S-7	-5.7	S-7	-5.4	G-7	-5.4	G-7	-5.7	D-7	-5.4
S-8	-5.4	S-8	-5.4	G-8	-5.4	G-8	-5.6	D-8	-5.3
S-9	-5.4	S-9	-5.3	G-9	-5.3	G-9	-5.6	D-9	-5.3

Figure 5 to figure 9 represents a two-dimensional interaction diagram with the CGRP receptor. It also shows the CGRP receptor's hydrogen bond interactions with the molecules 6-shogaol, 6- gingerol, and 1-dehydro-10-gingeridone. It was discovered that certain amino acid residues were crucial for the binding of inhibitors to the CGRP receptor's active site. The CGRP receptor's TYR 124, TRP 72, AND ARG 119 are thought to be important actors since they were generally implicated in creating hydrophobic interactions with the active components of ginger extract.

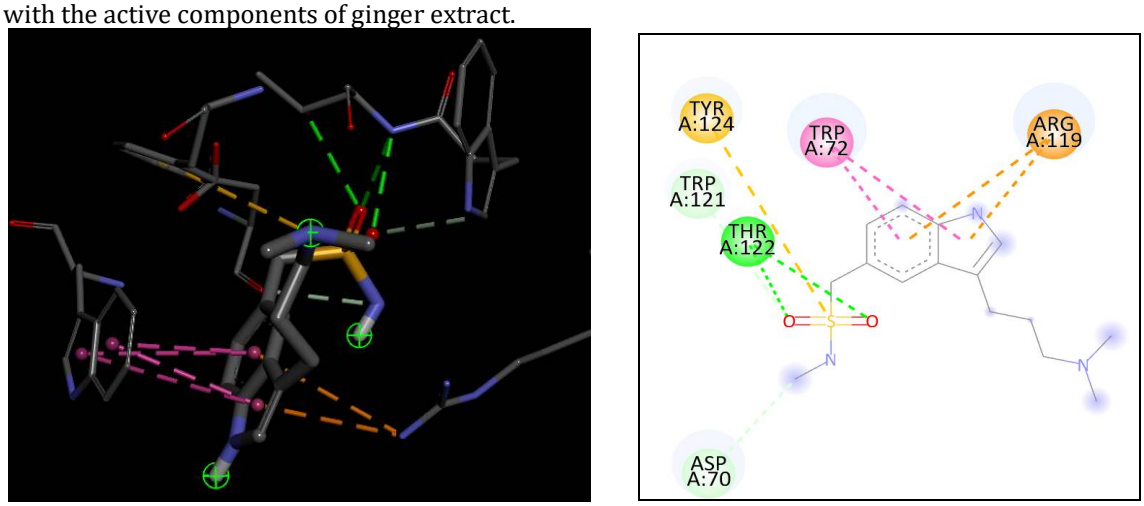

Figure 5: 2d structure of sumatriptan interacts with CGRP receptor

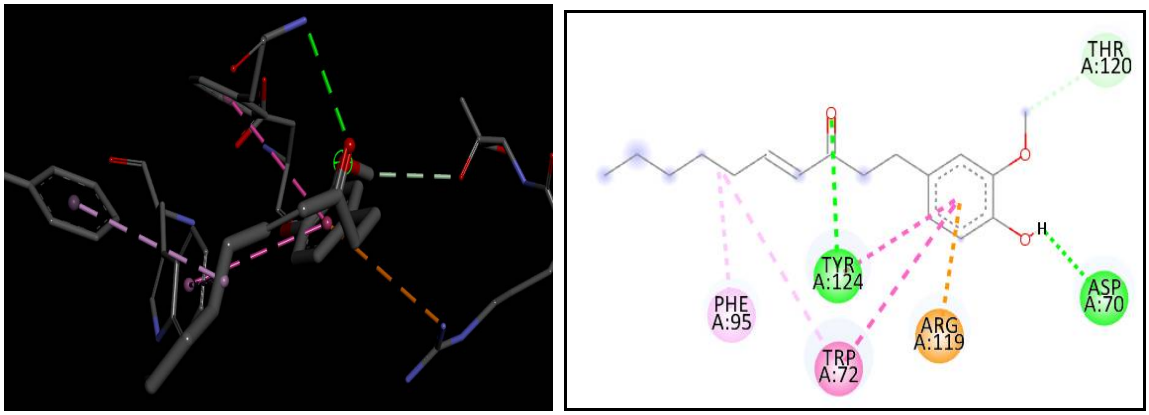

Figure 6: 2d structure of 6-shogaol interacts with CGRP receptor

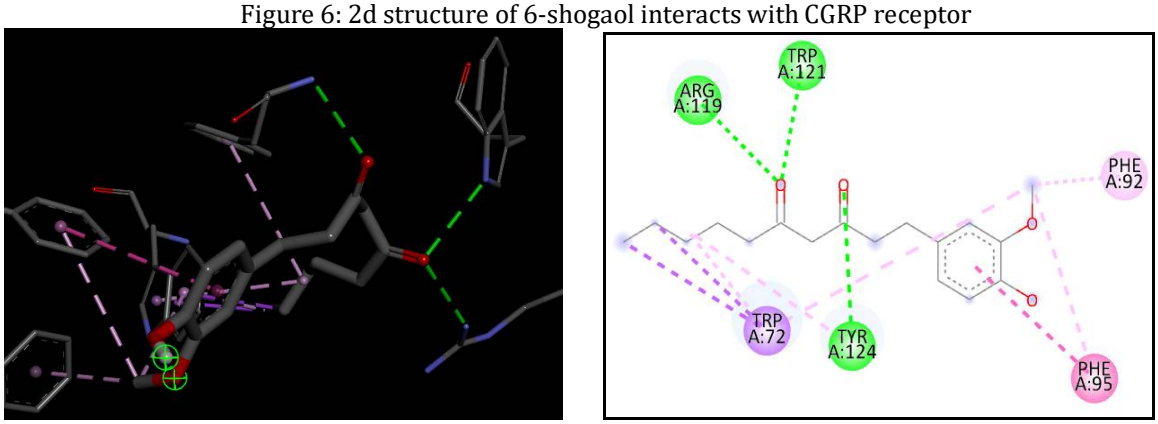

Figure 6: 2d structure of 6- gingerol interacts with CGRP receptor

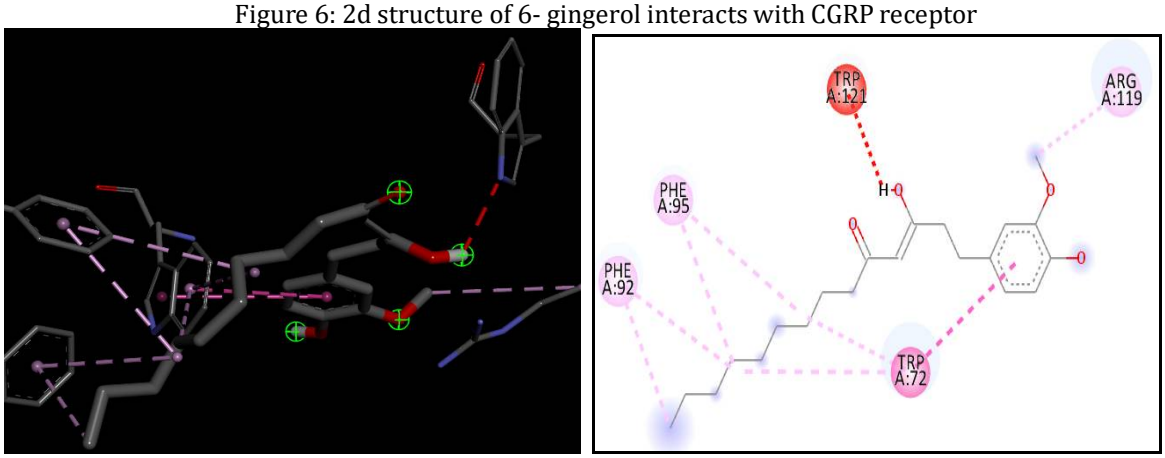

Figure 7: 2d structure of 10- gingeridone interacts with CGRP receptor

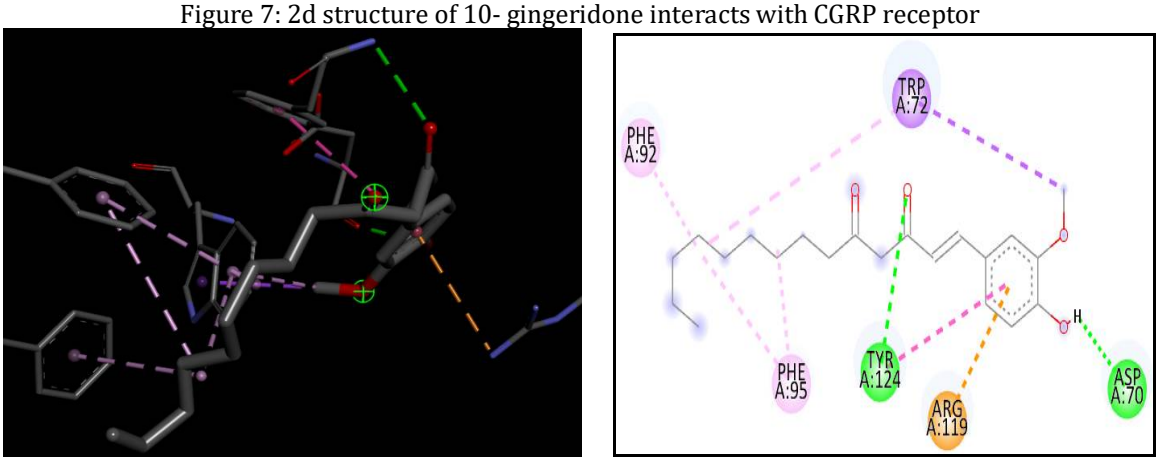

Figure 7: 2d structure of 1-dehydro 10- gingeridone interacts with CGRP receptor

Above diagram illustrating interaction of CGRP protein with sumatriptan and the four ginger active components, 6-shogal, 6-gingeridone, 10-gingeridone, and 1-dehydro-10-gingeridone, as well as their hydrogen bonds. These interactions' findings demonstrated that the CGRP active sites TYR 124, TRP 72, ARG 119, and asp 70 all contain common amino acid residues that the combination of sumatriptan and 6-shogal binds to. The common amino acid residues in CGRP active sites like TYR 124, TRP 72, ARG 119, and TRP 121 are where sumatriptan and 6- gingerol binds. The common amino acid residue in CGRP active sites like TRP 72, ARG 119, and TRP 121 is where sumatriptan and 10 gingeridone bind. Common amino acid residues in CGRP active sites, such as TYR 124 and TRP 72, ARG 119, ASP 70, are what sumatriptan and 1-dehydro-10-gingeridone bind to.
Table 2 shows the oral absorption of all four components was the highest. Additionally, it is able to pass the blood-brain barrier, which enables it to exert direct CNS action by blocking the activation of CGRP receptor signalling.

Table 2: ADMET prediction using SWISS-MODEL

Molecules	**Formula**	**MW**	**Log p**	**GI absorption**	**BBB permeant**
6-shagol	C17h24o3	276.37	3.76	High	Yes
6-gingerol	C17h26o4	294.39	3.13	High	Yes
10-gingeridone	C21h32o4	348.48	4.58	High	Yes
1-dehydro10-gingeridone	C21h30o4	346.46	4.61	High	Yes

When compared to sumatriptan, the 6-shogaol medication showed a higher human intestinal absorption (HIA) score according to ADMET characteristics retrieved from the Admet sar server. The closest readings were for 6-gingeridone and 1-dehydro-10-gingeridone. Greater HIA indicates that, when administered orally, the substance may be more absorbed from the intestinal system. All three chemicals, with the exception of 6-gingeridol, showed the best blood-brain barrier (BBB) penetration, which was also much higher than sumatriptan. To determine whether a chemical is mutagenic or not, a mesa toxicity test is used. All of the test ligands showed negative results in the AMES toxicity test, just like sumatriptan did, indicating that they are not mutagenic. The carcinogenic profile also revealed that the ligands were noncarcinogenic similar to the standard molecule. Important information obtained from the Admet sar server was the computed Ld50 dose in a rat model. Comparing the Ld50 doses. From our observation, we found that sumatriptan had higher Ld50, compared to the other compounds.

Compound	**HIA**	**BBB**	**CYP inhibition/substrate**	**AMES toxicity**	**Carcinogenicity**	**Ld50 in rats**
Sumitriptan	0.9956	0.7339	Substrate/noninhibitor	Nontoxic	Noncarcinogenic	2.5125
6-shagol	1.000	0.8414	Substrate/noninhibitor	Nontoxic	Noncarcinogenic	1.7164
6 gingerone	0.9805	0.6072	Substrate/noninhibitor	Nontoxic	Noncarcinogenic	2.4106
10 gingeridone	0.9758	0.8633	Substrate/noninhibitor	Nontoxic	Noncarcinogenic	2.1731
1-dehydro 10gingeridone	0.9881	0.8621	Substrate/noninhibitor	Nontoxic	Noncarcinogenic	2.1882

Table 3: ADMET prediction using the Admet sar tool

CONCLUSION

Both the pharmacokinetics investigation and the in silico molecular docking analysis found that the active components of ginger extract interacted favorably with the CGRP receptor. similar to reference medications in terms of hydrogen bonding and ligand-protein interaction. The docked compounds are in the acceptable range of several pharmacological parameters, and they behave better in terms of health consequences, according to the ADME-Toxicity prediction. They also demonstrated a brand-new formulation with strong anti-migraine properties that can pass the blood-brain barrier, operate directly on the central nervous system, and prevent the activation of CGRP receptor signalling. This study offers compelling evidence that the active components in ginger extract can function as CGRP receptor antagonists. So, we draw the conclusion that ginger can be a effective treatment in migraine.
We confirm that neither the manuscript nor any parts of its content are currently under consideration or published in another journal.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

ACKNOWLEDGMENTS:
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SIGNIFICANCE OF WORK
To prove that the pharmacokinetics study and the *In silico* molecular docking analysis supported the positive interactions of the active ingredients in ginger extract with the CGRP receptor. in terms of hydrogen bonding and ligand-protein interaction, comparable to reference drugs

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