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Research Article

Molecular Docking Analysis of Piperonal and its Analogues as Promising Cancer Therapeutics by Modulating Angiogenesis

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Abstract

Cancer is an emerging disease that pose severe public health problem that has a poor prognosis at early stage encompassing small number of effective therapies leading to high mortality rate at an alarming rate. The cancer cell multiplication and growth can be arrested at an early metastasis stage by inhibiting VEGF involved in angiogenesis. Hence in the present study, insilico approach is followed to screen piperonal and its significant analogues for inhibitory role against VEGF. The molecular properties were analysed using Molinspiration and molecular docking analysis was performed using Glide Schrodinnger. The compounds tenamfetamine and midomafetamine showed better binding strength when compared with Sorafenib.

Keywords: Piperonal, Structural Analogues, Angiogenesis, Metastasis, VEGF, Molecular docking, Autodock.

INTRODUCTION

Cancer is the most common reason for fatal end to both men and women in India. The disease needs early diagnosis and therapy that may prolong the life of any affected individual. The routine therapy for chronic cancer leads to emotional and physical stress. Cancers still account for significant morbidity and mortality globally despite remarkable advances in the management of cancers [1]. Cancers are characterised by alterations in vascular architecture and unregulated angiogenesis [2]. Angiogenesis involves complex regulatory system comprising both proangiogenic and antiangiogenic proteins after a tissue undergoes inflammation and deregulating the process of angiogenesis leads to an aberrant microenvironment and promotes tumor progression [3,4,5]. The pathway of angiogenesis plays a fundamental role in various physiological and pathological conditions, including wound healing and bone repair and regeneration, by reestablishing the normal blood flow and consequently the efflux of gases, nutrients, and growth factors [6,7,8].

The recent literature cited the proteins and signaling pathways associated with tumor angiogenesis as promising targets for therapeutic strategies in different tumor types [9]. The process of angiogenesis is initiated by the binding actions of vascular endothelial growth factor (VEGF) and fibroblast growth factors (FGF1/2) [10]. Thus, VEGF and the resulting tumor angiogenesis present an attractive therapeutic target in the treatment of cancer. The potential Inhibitors of VEGF/angiogenesis have been gaining attention and studied for their therapeutic application in most solid tumors [11, 12]. Further, preclinical studies have demonstrated that anti-VEGF compounds increase the efficacy of ensuing antitumor treatment, although the mechanism of this effect is unclear [13].

Piperonal, an important aromatic aldehyde containing the benzene ring fused to 1, 3- dioxolane moiety. Piperonal derivatives have shown a wide spectrum of pharmacological and therapeutic application. Pyrazoline and Thiazepine and subsequent derivatives have found to possess anti-cancer, anti-oxidant, anti-bacterial, anti-malarial and anti-mycobacterial activities. The structure of piperonal forms the basis for the synthesis of various chalcones and flavonoids. The study reported potent antioxidant free radical scavenging potential of piperonal and EDP schiffs base linked piperonal [14]. However, the piperonal and its structural analogues were not explored for the down regulation of VEGFR targeting angiogenesis. Hence, the current study aimed to investigate

the potential of Piperonal and its analogues to modulate VEGF mediated angiogenesis targeting cancer therapy.

MATERIALS AND METHODS

Retrieval of Ligands

A set of 7 compounds (Table 1) constituting piperonal and their structural analogue with similar parent connectivity was chosen from PUBCHEM database and the ligands were downloaded in SDF format[15]. The standard VEGF inhibitor sorafenib was also downloaded and compared with the set of test ligands.

Protein preparation

The X-ray crystal structure of VEGF (PDB code: 1FLT) was downloaded from the protein structure database, Brookhaven Protein Data Bank (www.rcsb.org/pdb).

Structural Properties and Bioactivity Prediction

The pharmacokinetic properties of the test ligands and bioactivity scores were calculated by the Molinspiration tool [Molinspiration Cheminformatics 2001].

Molecular Docking

The proteins and ligands were prepared for molecular docking using the inbuilt suite of MAESTRO software of Schrodinger. The Protein Preparation Wizard, Schrodinger, LLC, NY 2021 was used to prepare the retrieved protein structure with default parameters included assigning the proper bond order, adding hydrogen atoms, deleting crystalline waters and filling in the missing loops. Energy minimization and optimization was done by using OPLS-2005 force field [16].

All of the compounds were taken into the Ligprep module of Schrodinger, LLC, NY 2021 for 2D to 3D conversion, charge neutralization, stereoisomer generation, and ionization state at pH 7.2 ± 0.2 by using force field OPLS-2005. Glide XP Glide module of Schrodinger was used to predict the binding efficacy, mode of binding and interacting residues of the ligands against VEGFR. The highest binding energy (most negative) is considered as a ligand with high binding affinity. The docking poses collected for each compound have been rated according to their dock score generated by the software.

RESULTS AND DISCUSSION

The physical properties of the test compounds namely Piperonal, Veratraldehyde, Tenamfetamine, Midomafetamine, Myristicin and Safrole with their corresponding PUBCHEM ID was provided in Table 1. The 3D structures were depicted in Figure 1.

The 3-dimensional structural coordinates of VEGFR with PDB ID: 1FLT was downloaded in .pdb format and shown in Figure 2.

Figure 1: The 3D structure of Ligands.

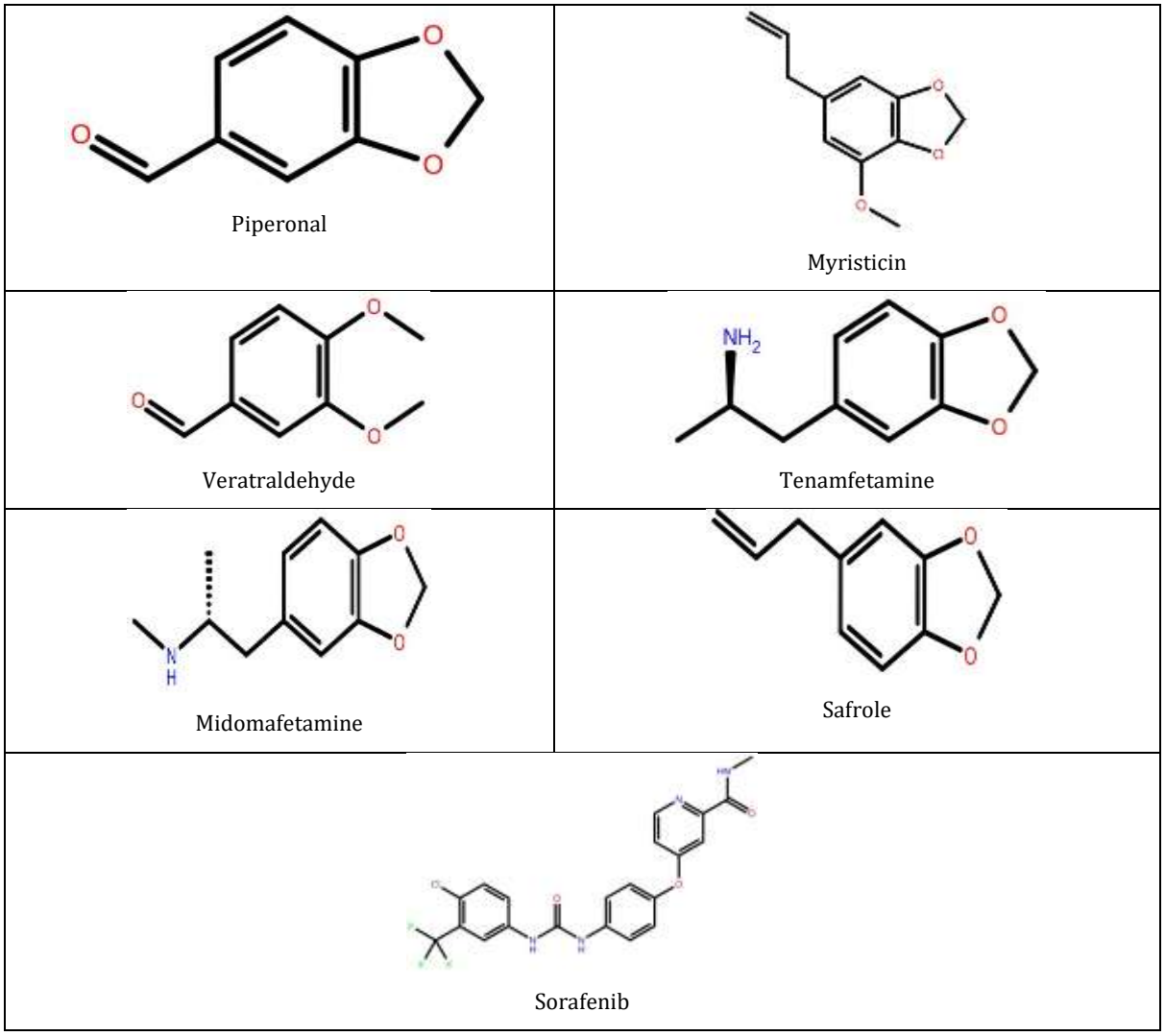


Table 1: The set of Ligands with PubChem CID.

S.No	Name of the Compound	Pubchem ID	Molecular Weight g/mol	Molecular Formula	SMILES
1	Piperonal	8438	150.13	$C_8H_6O_3$	C1OC2=C(O1)C=C(C=C2)C=O
2	Veratraldehyde	8419	166.17	$C_9H_{10}O_3$	COC1=C(C=C(C=C1)C=O)OC
3	Tenamfetamine	1614	179.22	$C_{10}H_{13}NO_2$	CC(CC1=CC2=C(C=C1)OCO2)N
4	Midomafetamine	1615	193.24	$C_{11}H_{15}NO_2$	CC(CC1=CC2=C(C=C1)OCO2)NC
5	Myristicin	4276	192.21	$C_{11}H_{12}O_3$	COC1=CC(=CC2=C1OCO2)CC=C
6	Safrole	5144	162.18	$C_{10}H_{10}O_2$	C=CCC1=CC2=C(C=C1)OCO2
7	Sorafenib	216239	464.8	$C_{21}H_{16}ClF_3N_4O_3$	CNC(=O)C1=NC=CC(=C1)OC2=CC=C(C=C2)NC(=O)NC3=CC(=C(C=C3)Cl)C(F)(F)F

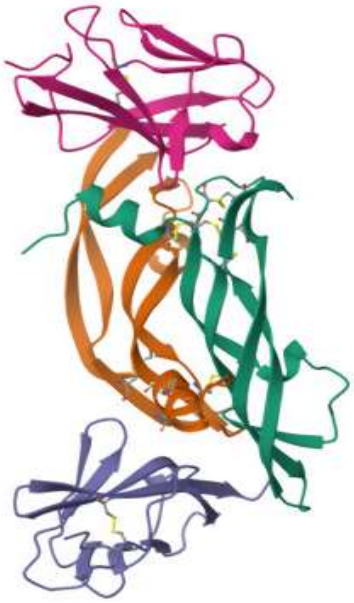


Figure 2: 3D structure of 1FLT retrieved from www.rcsb.org.

Table 2: The Physico chemical Properties predicted by Molinspiration

S.No	Name of the Compound	miLogP	TPSA	N atoms	nON	nOHON	Nvio	Nrotb	volume
1	Piperonal	1.62	35.54	11	3	0	0	1	126.96
2	Veratraldehyde	1.37	35.54	12	3	0	0	3	154.12
3	Tenamfetamine	1.21	44.49	13	3	2	0	2	169.45
4	Midomafetamine	2.12	30.50	14	3	1	0	3	187.13
5	Myristicin	2.44	27.70	14	3	0	0	3	178.05
6	Safrole	2.65	18.47	12	2	0	0	2	152.51
7	Sorafenib	4.76	92.35	32	7	3	0	6	368.26

The physico chemical properties and bioactivity scores of all the ligands were predicted by using Molinspiration Cheminformatics online server [Table 2]. These properties were computed to check the violations of the test ligands from Lipinski,s rule of 5. The Log P value ranges from 1.21 to 2.44. PSA ranges from 18.47 by Safrole to 92.35 for Sorafenib which is characterised for bioabsorption and oral bioavailability. The other values are used to predict the deviations from Lipinski,s rule of 5. Sorafenib showed highest number of rotatable bonds and volume when compared with test ligands.

The druglikeness score towards GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors and other enzyme targets has been computed and showed in Table 3. The bioactivity score typically ranges between -3 to 3 and the molecule showing highest score will be highly active. Piperonal, veratraldehyde, midomafetamine and safrole showed highest score for ion channel modulator whereas Tenamfetamine and Myristicin showed highest score for enzyme inhibitors.

Table 3: The Bioactivity score predicted by Molinspiration

Bioactivity	Piperonal	Veratraldehyde	Tenamfetamine	Midomafetamine	Myristicin	Safrole	Sorafenib
GPCR ligand	-1.17	-1.12	-0.22	-0.20	-0.71	-0.84	0.18
Ion channel modulator	-0.65	-0.54	-0.18	-0.09	-0.42	-0.46	0.00
Kinase inhibitor	-1.27	-1.05	-0.59	-0.71	-1.12	-1.27	0.44
Nuclear receptor ligand	-1.16	-0.93	-0.95	-1.05	-0.90	-1.01	-0.07
Protease Inhibitor	-1.59	-1.48	-0.45	-0.49	-1.10	-1.24	0.11
Enzyme inhibitor	-0.72	-0.65	-0.13	-0.21	-0.43	-0.49	0.08

Molecular Docking

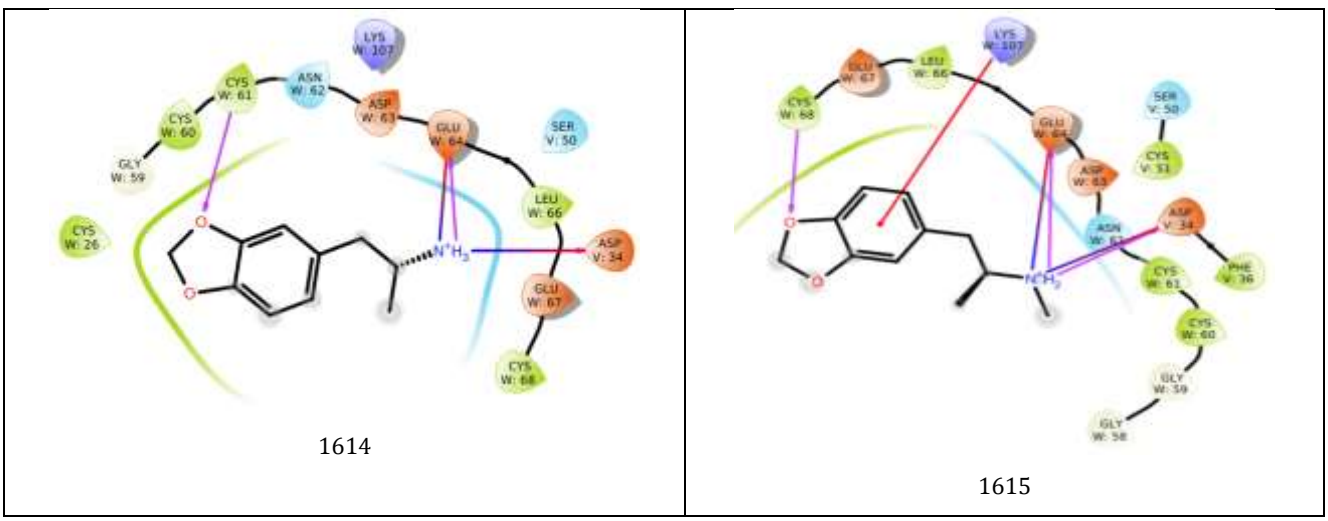
The docking score was represented in Table 4 and the binding interaction diagram of the chosen ligands with the target protein was depicted in Figure 3. The binding affinity was assessed by the Glide score and least score showed the compound with high binding affinity towards the active site of the protein. The docking score revealed that though piperonal showed energy values nearing to Sorafenib, its analogues tenamfetamine and midomafetamine showed higher values of docking energy score.

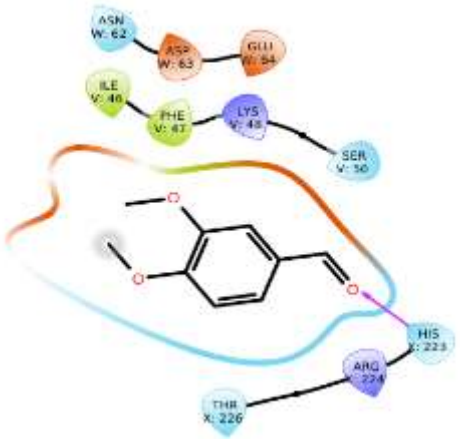
The best docked complexes was analysed by number of hydrogen bonds and interacting aminoacid residues in close proximity to the active site of the target protein. The mode of interaction is shown in figure 3 which showed that the selected compounds interact with VEGF protein via H bond interactions. These compounds showed the strong interaction with active site residues. The presence of the H-bond interactions enabled the complex to attain the specified configuration of the complex structure.

Table 4: Docking Score shown by the ligands against the target protein 1FLT.

S.No	Compound Name	Docking Score kcal/mol	Glide Energy kcal/mol	Glide model kcal/mol
1	Tenamfetamine	-5.035	-27.427	-32.349
2	Midomafetamine	-4.599	-31.099	-36.207
3	Veratraldehyde	-3.378	-19.521	-21.067
4	Piperonal	-3.274	-19.783	-24.003
5	Safrole	-3.115	-20.181	-24.323
6	Myristicin	-2.534	-24.410	-27.682
7	Sorafenib	-3.556	-39.104	-59.918

Figure 3: 3D Interaction diagram of docked Poses.





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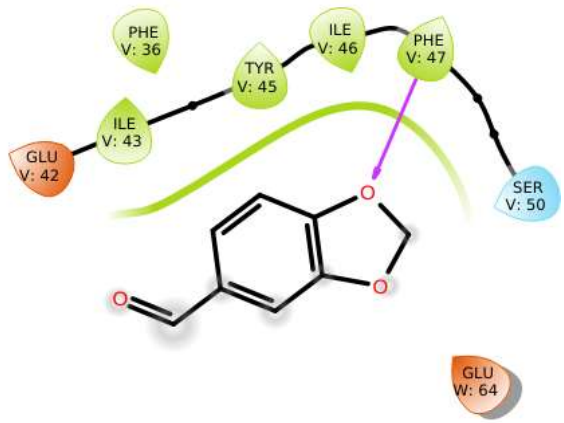

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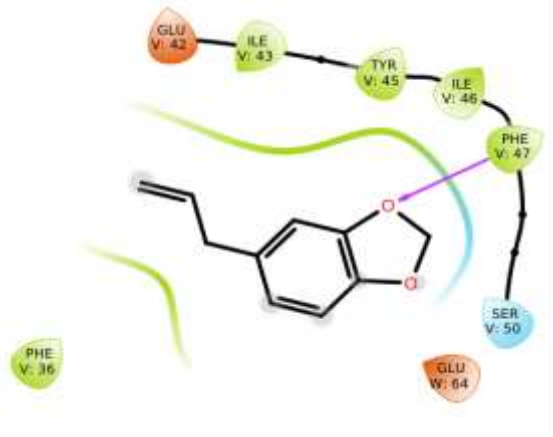

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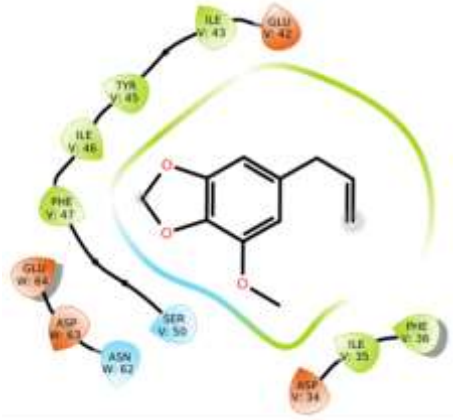

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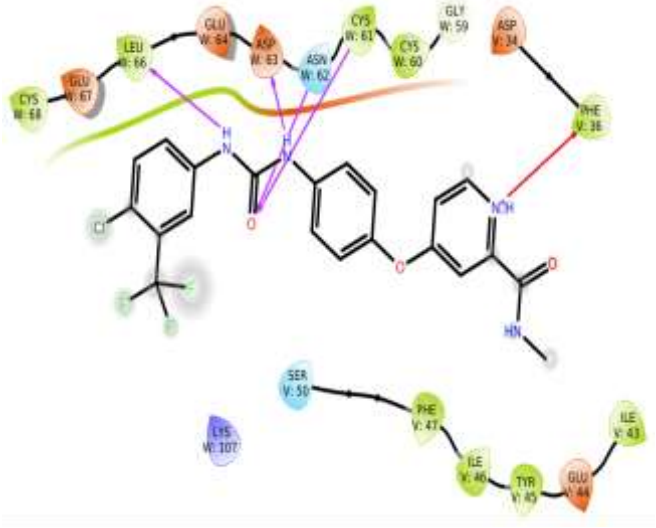

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CONCLUSION

The insilico methods paved way to analyse the structural parameters and binding mode in less time and can be performed with he set of ligands targeting multiple ligands. It also helps us in understanding the behaviour of lead molecules in various biophysical environments. In the current study the binding potential of piperonal and its analogues were compared with sorafenib as known inhibitor of VEGFR. Hence, the test compounds can be explored as novel antiangiognenesis drugs. However, the drugs targeting angiogenesis by downregulation of VEGF receptors would further analused by clinical studies.

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Conflict of Interest

The authors declare no conflict of interest.

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