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EXPLORING BENZOPHENONE DERIVATIVE AS PANCREATIC LIPASE INHIBITORS

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ABSTRACT

Obesity is the imbalance between calories burned and calories expended which leads to increased consumption of energy-dense foods and physical inactivity. Obesity disorder comprises underlying causes and etiological relationships. Overweight or obese individuals can be assessed by Body mass index (BMI) measurement. Metabolic treatments and supplements are often used to prevent or reduce obesity. Lipid absorption by hydrolysis occurs by the Pancreatic lipase enzyme. So inhibition of pancreatic lipase can be suggested as an effective therapy in the treatment of obesity. The benzophenone scaffold is considered a unique structure, because of its presence in several natural and synthetic derivatives having a variety of biological activities, like anticancer, antimicrobial, and antiviral. Researchers are interested in Benzophenone motifs as they are present in pharmacologically relevant natural products. A molecular modeling technique was used to investigate the capacity of morpholino-linked benzophenone derivatives to inhibit human pancreatic lipase. An efficient method for developing novel compounds that inhibit pancreatic lipase is demonstrated by in silico docking studies and MM-GBSA binding free energy calculations. ADME investigations confirmed the similar qualities of drugs.

Keywords: Obesity, Pancreatic Lipase, Benzophenone Derivatives, Molecular Modeling, Anti-Inflammatory.

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INTRODUCTION

While adult malnutrition is still a serious issue, obesity has become a global public health concern. Around the world, there are more and more people who are overweight or obese; since 1975, this number has nearly tripled.[1] Obesity and overweight are related to the energy imbalance between calories burned with calories expended. With the increased sedentary character of occupations modern evolution in transportation, and the urbanization speed, a habit of consuming energy-dense foods which have high fat content and sugar along with an increase in physical inactivity on a global scale.[2] Obesity can lead to diseases and even death.[3,4] According to a recent WHO report from 2009, more than 1 billion individuals worldwide are overweight, and at least 400 million of them are considered obese.[5] The basic approach to preventing or reducing obesity is to maintain a well-balanced diet together with consistent physical activity. However, it can be quite difficult and frequently fails to change one's diet and exercise habits. To lower obesity, it is frequently required to employ metabolic treatments or supplements as supplementary factors.[6] Currently, it is widely accepted that reducing the digestion and absorption of fat is the most efficient strategy to avoid obesity. A major target for absorption is the pancreatic lipase (PL) that is released by the pancreas. Particularly, PL is in charge of hydrolyzing between 50 and 70 percent of dietary fat.[7] The Food and Drug Administration (FDA) has approved orlistat and sibutramine as long-term treatments for obesity. In March 1999, Orlistat (Xenical) was approved for use in treating obesity.[8] A heterocyclic substance with a wide range of demonstrated pharmacological properties is morphine, a six-membered ring with two heteroatoms of nitrogen and oxygen. Analogues of the benzophenone morpholine shown to be antagonistic to the development of cancer. However, there hasn't been a thorough investigation into Pancreatic Lipase inhibition.[9] Weight loss at a dose of 120 mg can be between 7-8%. Only 20% of persons who use orlistat will lose more than 5% of their body weight, and it is not advised to take it for longer than two years.[10] Poor adherence to a low-fat diet while taking the medication may result in unwanted effects such as gastrointestinal distress, fecal urgency, and fecal soiling.[11] In this study, a molecular modeling technique was used to investigate the capacity of morpholino-linked benzophenone derivatives to inhibit human

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pancreatic lipase. It is considered a preliminary investigation. Orlistat, co-crystallized ligand, and morpholino-linked benzophenone derivatives were used in the molecular docking study on the HPL active site. Nearly 10 different compounds have been created and docked into the same domain. The general structure of morphine-linked benzophenone is given in the Fig.-1.

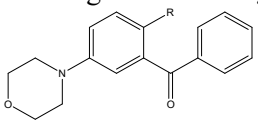

Fig.-1: General Structure of Morpholine Linked Benzophenone

Triacylglycerol acyl hydrolase, or pancreatic lipase, hydrolyzes ingested fat into diglycerides, monoglycerides, and free fatty acids. X-ray crystallography is used to ascertain the structure of human pancreatic lipase in three-dimensional mode, and complementary DNA clone sequencing is used to ascertain the enzyme's main structure. The bigger N-terminal (residues from 1 to 335) and C-terminal (residues from 336 to 449) of HPL, which has a total of 449 amino acids, are related to colipase. Particularly 247 to 258 in the N-terminal region represents an active site with the catalytic triad Ser-152, Asp-176, and His-263 (Figure). This triad identifies the HPL lipolytic site.[12]

EXPERIMENTAL

Pancreatic Lipase: Structure Detailing

The molecular weight of the pure Human Pancreatic Lipase, a glycoprotein, is found as 46000 Dalton. Although the isolation of Human Pancreatic Lipase. has been done, no chemical techniques could be able to clarify the primary structure. By performing the c DNA technique, it was found that HPL comprises 465 amino acids and a molecular weight of 51156 Dalton. The projected sequence was compared with the N-terminal sequence of HPL, and it became evident that HPL was a short signal peptide with only 16 amino acids. The mature HPL was identified as having 449 amino acids and a molecular weight of 49,558 Dalton after the signal peptide was removed by in vitro translation of c DNA in the presence of microsomes. The primary structure was added to the tertiary structure with the aid of radiographic crystallography at 2.8 A^0. A globular N-terminal domain and a narrower C-terminal domain make up pancreatic lipase. A central - -sheet core that extends from amino acids 1-335 represents the N-terminal domain of pancreatic lipase, which has 449 amino acids. A - -sheet sandwich structure represents the C-terminal domain. These short stretches of amino acids, which are strengthened by seven disulfide bonds, have been used to divide the N- and C-terminal portions of the protein from one another. For pancreatic lipase to function, another component is necessary. This substance was recognized as a protein with a low molecular weight originally known as colipase, of which several isoforms with a purification mass of 10,000 Dalton were obtained. Processing of the human procolipase takes place from both the N- and C-termini. There is no connection between the procolipase and the N-terminal domain of the colipase in its tertiary structure, and this does not change the confirmation of pancreatic lipase. Instead, the procolipase connects to the pancreatic lipase through the C-terminal domain. In pancreatic lipase, Ser-His-Asp constitutes a catalytic trio. The Ser-153 in the N-terminal domain of human pancreatic lipase creates a hydrogen bond with His-264, which then forms a hydrogen bond with Asp-177.[13]

Functions of Pancreatic Lipase

The manufacture of enzymes takes place in acinar cells in the pancreas. The duodenum, which also contains proteolytic, lipolytic, and amylolytic enzymes capable of breaking down dietary lipids, receives this pancreatic fluid. The primary function of the enzyme pancreatic lipase is the absorption and breakdown of dietary fat. Preduodenal lipase is predominantly used in the stomach to begin the hydrolysis of dietary fat, which concludes in the proximal small intestine. As the fatty acid enters the duodenum, CCK and gastric inhibitory peptides are released (GIP). Both the release of pancreatic enzyme and bile acid from the gall bladder are triggered by CCK. Carboxylic esterase, often known as pancreatic lipase, is a crucial enzyme that aids in the breakdown of fats. Colipase is a cofactor that pancreatic lipase needs to function. Pancreatic lipase requires colipase, bile salts, Ca^{2+}, and an alkaline pH in order to function. Trypsin and colipase are produced from procolipase, a precursor of colipase that is secreted by the pancreas. By increasing the

surface area of oil-water interfaces, bile salts enhance the lipolytic activity of water-soluble lipase. Despite being secreted in its active form, pancreatic lipase is inert in the absence of bile salts. Bile salts are used in the emulsification of fat. By covering the water-soluble interface, bile salts stop lipase from adhering to triglycerides. Colipase has stopped this by attaching to the micelle's interface and forming the Michaelis-Menten adsorption complex. For lipase to hydrolyze the substrate into monoglycerides, fatty acids, and cholesterol, it must be anchored to the interface. Compared to long-chain triglycerides, short-chain triglycerides have a higher activity. The small intestine is then created from these digesting byproducts.[14] Pancreatic triglyceride lipase (PTL) with its congeners pancreatic lipase-related protein-1 (PNLIPRP-1/ PLRP-1) and protein-2 (PNLIPRP-1/ PLRP-2) are the main lipolytic enzymes.[15]

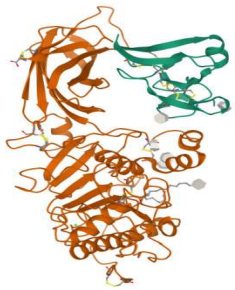

Fig.-2: Tertiary Structure of Human Pancreatic Lipase (1LPB)

RESULTS AND DISCUSSION

Molecular Docking Study

Preparation of the Enzymes

Using Maestro 12.8 for protein preparation (Schrodinger). Protein 1LPB's PDB-formatted crystallographic model was retrieved from the Protein Data Bank at www.rscb.org. The protein has undergone processing that includes bond order assignment, hydrogen addition, formation of zero-order metal bonds, disulfide bonds, conversion of selenomethionines to methionines, deletion of waters from het groups that extend beyond 5A^{o}, and generation of het states using epic pH 7+/-2. The protein has two chains, A and B. A is eliminated, and the B chain is chosen. 1LPB generally contain the metal CA 45, the ligands BOG 96(A), BOG 97(A), BOG 450(B), BOG 451(B), BOG 452(B), and MUP 901(B) (B). The het state is successfully created once the co-crystal MUP (901) is chosen, and additional ligand BOG and metal CA have been eliminated. The OPLS4 force field is then used to minimize energy, assisting in the convergence of heavy atoms to RMSD 0.30 A^{0}.

Preparation of Ligand & Ligand Docking

From the online PubChem database, the 2D structure of orlistat (PubChem CID: 3034010) was obtained. Using the 'Lig Prep' option, this structure was transformed into a minimal 3D structure. Using Maestro 12.8 (Schrodinger), the "Lig prep" option is used to perform ligand preparation. The OPLS4 force field is used for energy minimization. At target pH 7+/- 2.0, the potential ionization state was produced using Epik. At most 32 stereoisomers were produced per ligand when the specified chiralities were preserved. Maestro 12.8 conducted the ligand docking (Schrodinger), and they prepared a gliding grid using the 1LPB option. Xtra precision has been chosen.

Validation of Docking Protocol

By redocking MUP, the co-crystallized inhibitor, into the Human Pancreatic Lipase Inhibitor, the docking process was validated. Through the hydrogen bond interaction of Phe-77, Ser-152, and Leu-153, MUP with HPL is confirmed.

Docking And Mmgbsa Calculation

One significant method for estimating binding energies that can be correlated with experimental values is MMGBSA. Binding-free energies are quickly and accurately estimated using MMGBSA. It is never easy to create new compounds with the right biological value. Different computational tools can be used to

examine the target site's structure and function and forecast how ligand molecules will interact with the target.[16] Predicting the biological activity of a novel designer molecule would be made easier with solid computer analysis. Molecular docking is a key method for computational screening and ranking molecules to the target protein's active site in structure-based drug discovery.

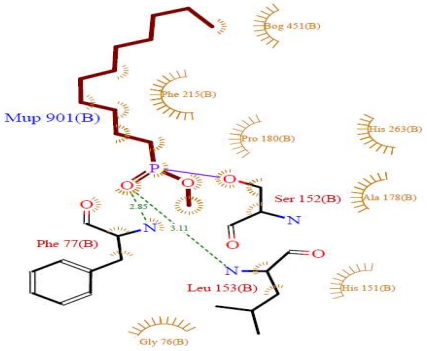

Fig.-3: Interaction of Co-Crystal

Steric and electrostatic complementarities can be measured and quantified in terms of energy scores using docking techniques. These are prioritized by several orders of magnitude using MM-GBSA and MM-PBSA. With MM-GBSA, a single protein-ligand structure is sufficient to predict ligand affinity and can help to ensure the success of docking.[17] EMM is the molecule's molecular mechanical energy, Gpsolv is its polar solvation energy, Gnpsolv is its non-polar solvation energy, T is its absolute temperature, and S is its entropy. EMM is obtained by taking the sum of the result of electrostatic force effects and Van der Waals interactions into the internal energy of molecules. Calculating binding free energy both with and without the entropic term is possible:

$$\Delta G_{bind} = \Delta E_{MM} + \Delta G_{solv}$$

$$\Delta G_{bind} = \Delta E_{MM} + \Delta G_{solv} - T\,\Delta S$$

Docking score and MMGBSA score of derivatives

Table-1: Docking Scores and MMGBSA Values of Designing Molecules

Compound	Docking score	MMGBSA	Binding amino acid residues	Type of bond
A1	-5.183	-39.07	Phe 77 Asp 79 Phe 215	H bond Pi-Pi stacking Pi-Pi stacking
A2	-5.108	-45.94	Ala 259	H bond
A3	-4.986	-49.7	Phe 215	Pi-Pi stacking
A4	-4.951	-48.18	Ala 259	H bond
A5	-4.817	-61.12	Ala 259 Phe 215	H bond Pi-Pi stacking
A6	-4.783	-52.53	Ala 259	H bond
A7	-4.595	-64.13	Ala 259 Phe 215	H bond Pi-Pi stacking
A8	-4.556	-55.81	Ala 259 Phe 215	H bond Pi-Pi stacking
A9	-4.317	-58.98	Ala 259 Phe 215	H bond Pi-Pi stacking
A10	-4.275	-41.68	Asp 79	H bond

Docking was done on ten compounds that were created. When compared to orlistat, all drugs with high docking scores (docking score: -2)

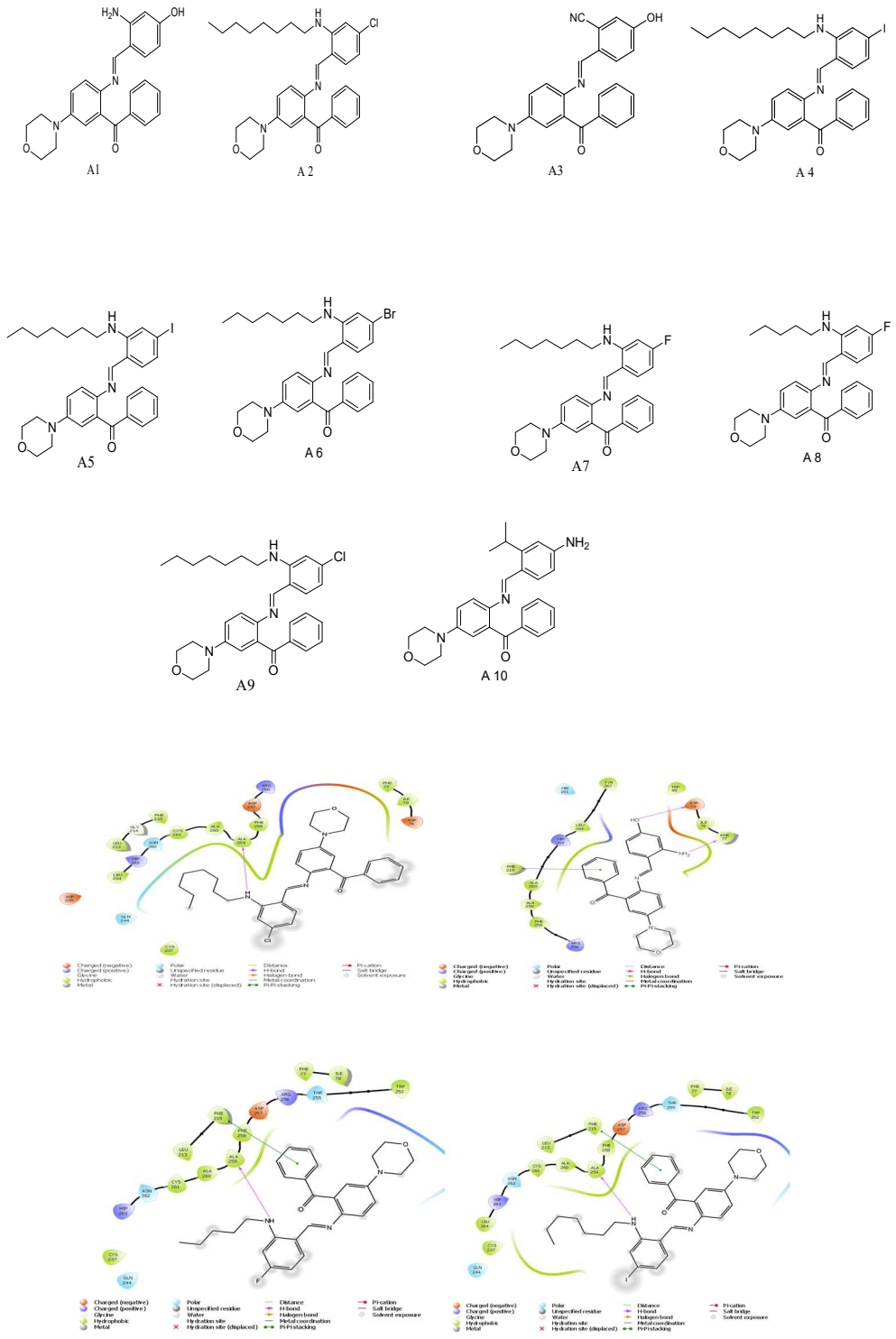

Fig.-4: Structures of the Derivatives and Docking

Admet Properties

Different types of physical descriptors are available in the Maestro 12.8 (Schrodinger) Quick prop tool, which can be used to forecast the ADMET characteristics of connected ligand molecules. A number of properties linked to ADMET are estimated. CNS penetration, the index of cohesion interaction predicted from polarizability, the number of hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), and Caco-2 cell permeability, QP Caco in nm/s; assumed blood/brain barrier partition coefficient, QP log BB; Madin-Darby canine kidney (MDCK) cell permeability, QPPMDCK in nm/s; and the IC50 value calculated

to check blocking HERG K+ channels, QP log HERG Human oral absorption, skin permeability log Kp, QP log Po/w, percent of human oral absorption, and others were anticipated.[18] The Lipinski rule of five is used to determine how similar the molecule is to a drug. All chemicals that adhere to this rule (Table-2). Lipinski suggests five key requirements for druggability. a molecule must have a less than 500 Dalton weight, hydrogen bond donors of less than 5, hydrogen bond acceptors of less than 10, and a log P value should be <5 is essential to have oral activity.[19]

Table-2: Lipinski Rule of Five Predictions for Designing Molecules

S.No.	Compound	donor HB (<5)	accept HB (<5)	QPlog Po/w	QP polrz	QPlog Kp	Human Oral Absorption	Percent Human Oral Absorption
1	A1	2.5	7.45	3.123	40.831	-1.996	3	95.392
2	A2	1	6.7	8.154	61.475	-0.003	1	100
3	A3	1	7.95	3.402	43.459	-1.998	3	95.888
4	A4	1	6.7	7.786	58.814	-0.287	1	100
5	A5	1	6.7	7.667	57.952	0.09	1	100
6	A6	1	6.7	7.404	57.085	-0.273	1	100
7	A7	1	6.7	7.121	55.728	-0.034	1	100
8	A8	1	6.7	6.536	53.253	-0.174	1	100
9	A9	1	6.7	7.463	57.11	0.032	1	100
10	A10	1.5	6.7	4.648	46.976	-1.712	3	100

Jorgensen's rule of 3 suggests that parameters like Caco-2 cell permeability of faster than 22 nm/s, logS (aqueous solubility) > 5.7 and the number of metabolites should be less than 7 and Pharmacokinetic Parameters of Designing Molecules are given in Table-3.

Table-3: Pharmacokinetic Parameters of Designing Molecules

S.No.	CNS	SASA	QP logS	QP log HERG	QPP Caco	QPlogBB	PSA	Rule of Three	QPPMDCK
1	-2	642.931	-4.18	-5.5	634.717	-1.012	85.465	0	302.66
2	-1	995.534	-10.041	-7.818	2873.93	-0.77	56.278	1	3820.56
3	-2	681.847	-5.6	-6.043	548.142	-1.143	88.533	0	258.30
4	-1	942.921	-9.134	-7.089	2692.545	-0.727	56.431	1	4139.26
5	0	926.803	-9.003	-7.25	4105.127	-0.437	56.602	1	6524.89
6	0	915.401	-8.769	-7.084	2903.484	-0.634	58.125	1	4149.10
7	0	891.746	-8.208	-7.083	3458.857	-0.602	57.882	1	3417.77
8	0	846.794	-7.722	-6.958	3594.932	-0.448	58.339	1	3563.38
9	0	909.571	-8.639	-7.413	3778.126	-0.501	56.902	1	5132.72
10	-1	722.867	-5.8	-5.781	1031.426	-0.873	72.059	1	511.53

CONCLUSION

An effective strategy of creating novel compounds as pancreatic lipase inhibitors is shown by *in silico* docking studies and binding free energy calculations using MM-GBSA. The drug similarity qualities were validated by ADME investigations. Anticipating the compounds showed higher pancreatic lipase inhibitory activity.

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CONFLICT OF INTERESTS

There is no conflict of Interest during the study.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID IDs, given below:

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