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MOLECULAR DOCKING OF NOVEL BENZOPYRAN ANALOGUES AND INHIBITION PROPERTIES OF ANTIDIABETIC AGENTS AGAINST *α-AMYLASE* AND *α-GLUCOSIDASE*

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ABSTRACT
Alpha amylase and alpha-glucosidase inhibitors play a key role in treating diabetes mellitus. Based on this idea the present study aimed in designing different benzopyran analogs and investigate the binding interaction with protein PDB: 1HNY and PDB:5NN3 through molecular docking by autodockpyrx. The results evaluated by docking studies found that different substituted derivatives of 4-Hydroxycoumarine, 3-acetyl 4-hydroxy coumarin, 8 hydroxycoumarine, 7-hydroxycoumarine, 4-hydroxy, 5-methoxycoumarine compounds and compared with standard quercetin which is the target protein. The compound showing the best score for 1HNY is hydroxyl substituent with dicyandiamide,4-methyl carbothioamide, 3-methoxy formamide, 3-methoxycarbothioamide and for 5NN3 is 4-methyl formamide,4-Fluro carbohioamide. Totally 107 compounds were subjected to docking and the selected fifteen potent compounds were subjected to predict the molecular property, drug-likeness, absorption, distribution, and metabolism analysis by using online free software Molinspiration and Swiss ADME, which were satisfied with the Lipinski rule of 5 which plays an important role in filtering the protocol. The filtered compounds showed 0 violations for the physiochemical properties of the molecule**.**
Keywords: Benzopyran, molinspiration, quercetin, Lipinskirule,Swiss ADME.
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INTRODUCTION

Insulin Dependent and Non-Insulin dependent diabetes is a metabolic disorder characterized by increased blood sugar level[1] if remains untreated leading to retinopathy, neuropathy, nephropathy, and premature atherosclerosis.[2]Hence during the early stage of diabetes the proper blood glucose level should be maintained. Many drugs such as Thiazolidinedione, Ciglitazone, Troglitazone[3], Piglitazone[4], and Rosiglitazone[5]and the major side effect is it produces hepatic toxicity. The researcher has focused on insulin sensitizerS in recent years. Benzopyran is the classic nucleus in flavonoid present naturally in plants. The research review on benzopyran skeleton gleaned to design a new series of derivatives for insilico alpha- amylase and alpha-glucosidase inhibitor activity.[5]NN3 a crystal structure of humanlysosomal alpha- glucosidase and 1HNY is the structure of human pancreatic alpha-amylase which is used for the docking study using auto dock vina with the quercetin as standard. In order to understand pharmacokinetic properties, it is in need of studying the ADME and also to predict bioavailability studies.[6]Molinspiration is cheminformatics software that helps in molecular manipulation and processing using SMILES and also the calculation of various molecular properties which are widely used in QSAR. It is a free online service for predicting bioactive score and calculating the molecular properties such as the number of hydrogen bond acceptors and donors, the log P value, and total polar surface area as a result it produces high eminence of scientific outcomes.[7] Different novelbenzopyran derivatives were drawn and translated to smiles notation which was further used for predicting the molecular properties by using molinspiration. The docking study was done by using Autodock VINA 4.2. The biological database

such as Protein Data Bank was obtained from the proper target protein through RCSB and ACD/Chem Sketch for drawing various structures and helps in calculating the chemical properties and proposal of skillful reports and performance. The structure-based analog drug design is done in order to calculate molecular properties and drug likeness[8] which determines the oral bioavailability and pharmacokinetic property. The pink area empowers the oral bioavailability such as lipophilicity, polarity, insolubility, unsaturation, and flexibility respectively. Lipophilicity:XLOGP3 (1.54 to 5.37), Polarity: TPSA (125 o 137 A2), SP_3 hybridization, Flexibility: not more than 9 rotatable bonds.

EXPERIMENTAL

Preparation of α-amylase and α-glucosidase

The crystal structure of the protein alpha-amylase 1HNY and alpha-glycosidase 5NN3macromolecule used in this study was regained from the protein data bank.[9]All the PDB files were energy minimized and the PDBQT protein was further used for docking.

Ligand Preparation

The different derivatives of benzopyran analogs have been designed and the structures are drawn and the smiles notation has been generated from the drawn structures.

Molecular Docking Studies

The different benzopyran derivative was docked against alpha-glycosidase and alpha-amylase to study protein-ligand interaction by using Auto dock of pyrex virtual screening software. The structure-based docking study was carried out using PDB id: 5NN3 and 1HNY which was downloaded from (www.rcsb.com).[10] The protein was pre-processed by deleting the substrate co-factor and the water molecule. Finally, the prepared ligand was docked with protein and the docking score is mentioned.

Swiss ADME

The Prediction of ADME is done by determining the physiochemical properties and pharmacokinetic properties by the swiss ADME online software.[11] In order to avoid wastage of time this is one of the quick methods which gives a detailed study about the absorption of the drug, which depends upon the membrane permeability; the distribution depends on factors that include the blood-brain barrier, the volume of distribution, and CNS permeability.[12] The smiles notation is generated from the structure drawn by using Chem sketch and pasted in the right-hand side provided space of the Swiss ADME as per the protocol and the properties have been generated and the results have been tabulated in excel sheet for each individual compound and contain detailed information. The fifteen benzopyran derivatives were compared with quercetin and the result were analyzed.The predicted value represents that all fifteen compounds follow the Lipinski rule of five. The number of heavy atoms, number of rotatable bonds, number of hydrogen bond donors, and TPSA are within the range. The hydrogen bond donors are less than 5, the hydrogen bond acceptor is less than 10, and the number of rotatable bonds is less than 10 shows the best criteria for the selection of compounds for synthesis. The lipophilicity and hydrophilicity are best predicted by the Log P value which is the measure of the concentration of drug between two solvents in unionized form. The Bioavailability Radar (Fig.-3) explains the drug-likeness property of molecules under study[13]and also empowers oral bioavailability such as lipophilicity, polarity, insolubility, unsaturation, and flexibility respectively. Lipophilicity:XLOGP3 (1.54 to 5.37), Polarity: TPSA (125 o 137 A^2), SP_3hybridization, Flexibility: not more than 9 rotatable bonds.

RESULTS AND DISCUSSION

Docking studies were performed using autodock pyrex and the crystal structure is prepared by removing water molecules and other coordinates which are repeated. By using Kollam united atoms force field the hydrogen atom and charge are allotted to the protein structure. 4-Hydroxy coumarin, 3-acetyl4-hydroxy coumarin, 8-hydroxycoumarin, 7-hydroxycoumarin, 4-hydroxy 5-methoxycoumarin show binding affinity ranging from -8.3 to-9.9 Kcal/mol. The binding score was compared with the quercetin (-8.7 Kcal/mol) for 1HNY and (-9.5 Kcal/mol) for $5NN_3$.Based on the docking calculation the 7 hydroxycoumarine substituted with 4- phenyl carbothioamide showed better inhibition of *α-amylase* (-9.9 Kcal/mol) compared to *α-glucosidase*.The residues GLN A:8,HR A:6,PHE A:335 with -SO- and PRO

A:332 and ASP A:398(Phenyl),THR A:21(-NH-),GLY A: 334(Aromatic phenyl ring) showed the interaction for α-amylase and PRO A:816,ASP A:802 (-NH-),VAL A:548,ARG A:136,PRO A:543 (Aromatic phenyl),PRO A:315,ARG A:316,ALA A:135(Phenyl),THR A:665, LEU A:668(Coumarine) showed interaction with α-glucosidase. The docking score alone is not feasible for predicting the potent drug. The discovery of a drug along ADME and drug-likeness helps to decide whether it is good for the biological system. The main target for the molecular physiochemical property is the 0 violation that was observed in all the compounds. The bioavailability score is not above 0.55 which predicts how much amount of the drug reaches the systemic circulation. The Bioavailability radar (Fig.-4)explains the oral bioavailability and the prediction is based upon the pink area. It predicts oral bioavailability Saturation of the fraction of Csp3 is not less than 0.04,Flexibility not more than 8 rotatable bonds, Liphophilicity characters shows that (XLOGP3 between +1.54 to + 5.37),Polarity(TPSA between 121 to 140). It predicts the drug-likenessproperty,the pharmacokinetic property reveals that 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H–Chromen-4-One and 1-(4-methylphenyl)-3-{4-[(2-oxo-3,4-dihydro-2H-1-benzopyran-3-yl)amino]benzenesulfonyl}urea showed high gastrointestinal absorption.

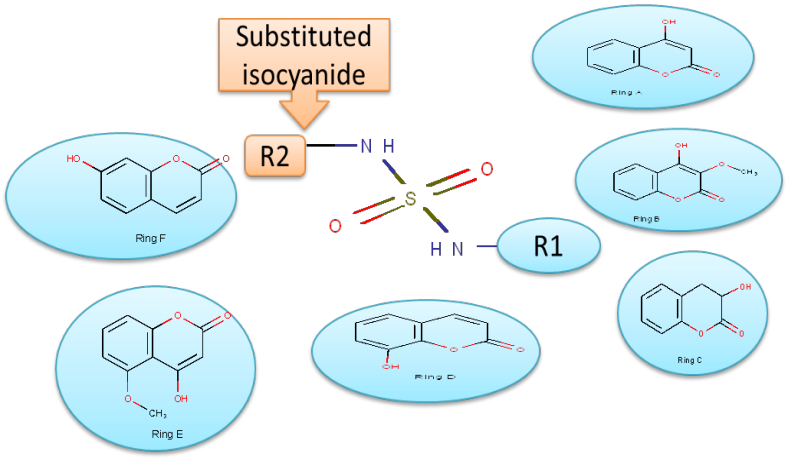


Fig.-1: Schematic Representation of Scheme

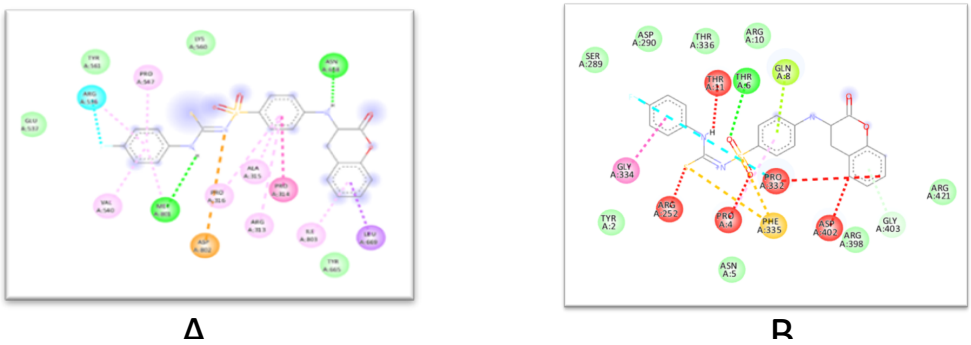


Fig.-2: Molecular Docking Interaction with the Active Site (PDB:1HNY) a-2D representation (comp-8) b. (PDB: 5NN3) 2D representation (comp-11)

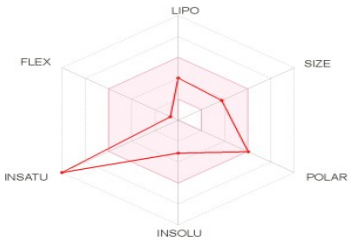
CONCLUSION

The present study evaluates the binding affinities of lead moiety with the protein human lysosomal alpha-glucosidase and human pancreatic alpha-amylase recognize the potency of the selected compound and the physicochemical properties were done by using SWISS dock online software. The docking score reveals the tight binding affinity with the targeted enzyme, while comparing with 107 compounds the 7-hydroxycoumarine with 4-phenyl formamide and 3-dihydro, 3-hydroxycoumarine with 4-Fluro phenyl carbothioamide derivatives showed better binding energy of -9.9 Kcal/mol for alpha-amylase inhibition.

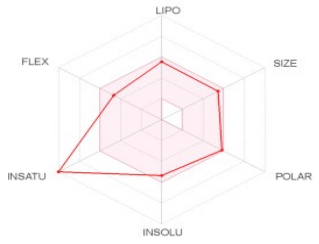
The ADME and drug-likeness revealed that the selected 15 compounds showed good pharmacokinetic properties and predictions about oral bioavailability. Further research work is in progress to synthesize and evaluates in vivo anti-diabetic activity of active compounds of benzopyran derivatives.

Table-1: Physiochemical Properties and Docking Score for Selected Compounds

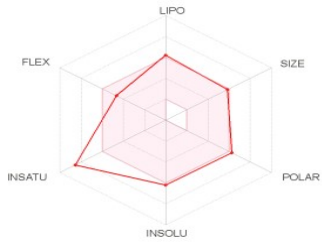
Comp. Code	RING	X	R2	1HNY	5NN3	iLOGP	Fraction Csp3	Number of Rotatable bonds	Number of H-bond acceptor	Number of H-bond donor	Molar refractivity	TPSA
1	Ring-A	S	Phenyl	-8.5	-8.8	1.63	0.00	8	7	6	111.91	191.77A²
2		S	4-methylphenyl	-8.7	-8.0	2.39	0.00	7	6	3	117.30	125.89A²
3		O	Phenyl	-8.6	-8.8	2.70	0.09	7	4	3	127.14	137.00A²
4		O	3-methoxy phenyl	-8.5	-9.1	2.64	0.04	7	5	3	122.31	125.89A²
5		O	4-flurophenyl	-9.3	-9.0	2.74	0.13	7	4	3	127.10	137.00A²
6	Ring-B	S	Phenyl	-9.0	-9.6	2.68	0.00	7	5	3	117.34	125.89A²
7	Ring-C	S	4-methyl phenyl	-8.8	-9.3	2.88	0.04	7	4	3	129.51	140.91A²
8		S	4-flurophenyl	-9.9	-9.6	2.39	0.13	7	5	3	119.90	121.98 Å²
9	Ring-D		2-cyano guanidine	-9.1	-8.8	2.54	0.13	8	6	3	121.42	131.21 Å²
10	Ring-E		2-cyano guanidine	-9.4	-9.7	2.74	0.00	7	5	3	117.34	125.89 Å²
11	Ring-F	S	3-methoxy phenyl	-8.9	-9.8	3.10	0.00	7	4	3	124.54	140.91 Å²
12		O	Phenyl	-9.9	-8.7	2.63	0.04	8	6	3	123.83	135.12 Å
13		O	3-methoxy phenyl	-9.8	-8.8	2.80	0.09	7	5	3	122.09	137.0 Å²
14		O	4-methyl phenyl	-8.3	-9.0	3.27	0.00	7	4	3	129.55	140.91 Å²
15	Ring-D	S	3-methoxy phenyl	-9.2	-8.1	3.20	0.04	8	5	3	131.03	150.14 Å²
	Quercetin			-7.7	-9.5	1.63	0	1	7	5	78.04	131.36 Å²



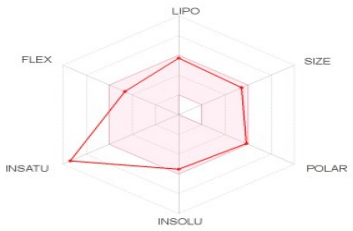
C-1



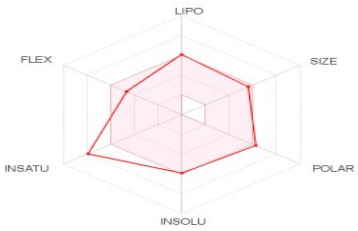
C-2



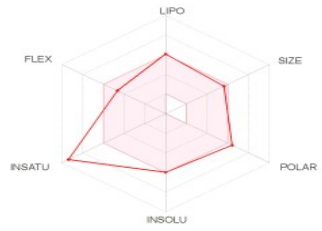
C-3



C-4



C-5



C-6

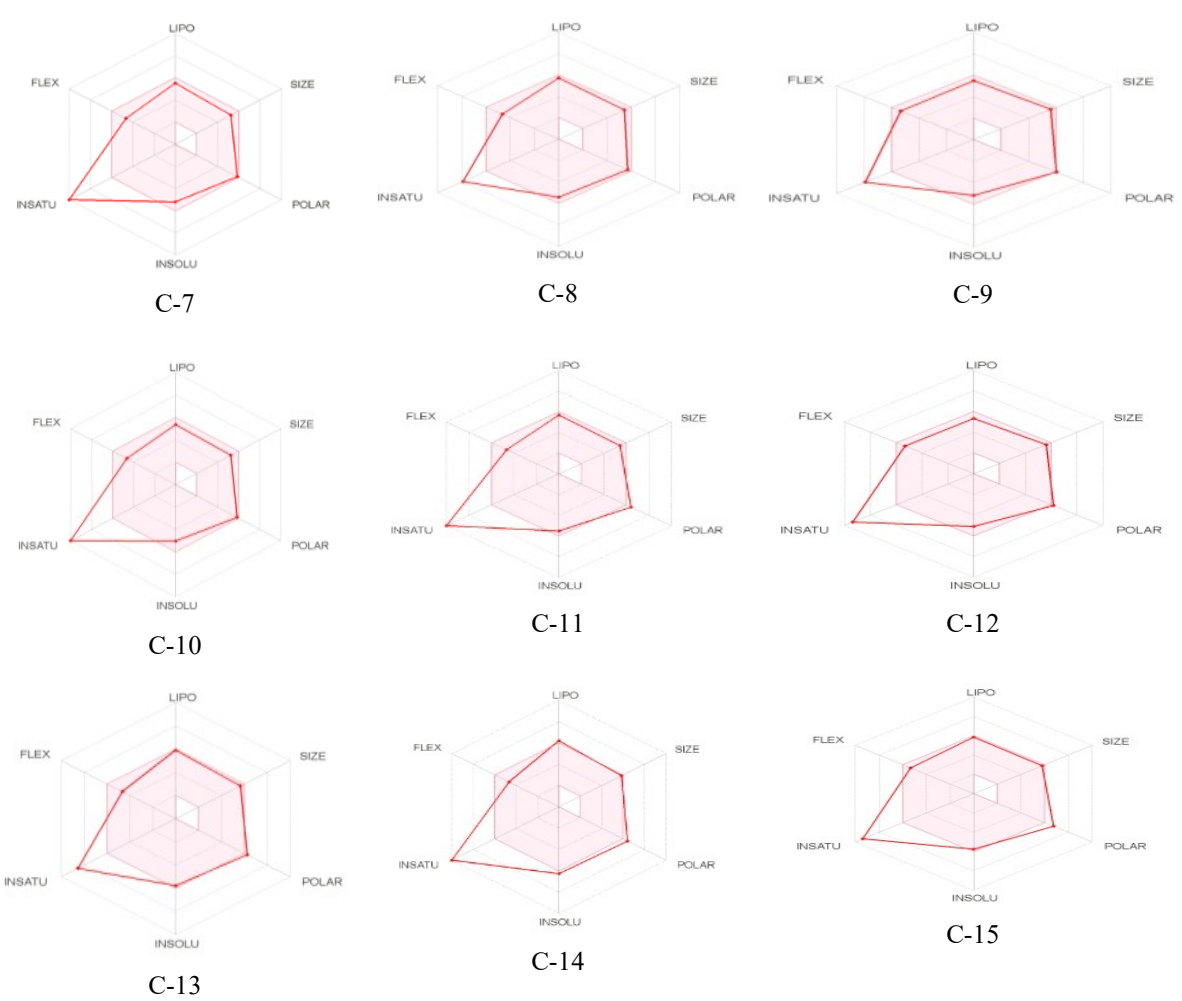


Fig-3: The Bioavailability Radar Explains about the Optimal Range of the Liphophilicity, TPSA, Polarity, SP^3hybridization

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