Computational Molecular Docking Analysis Of 5-ethyl pyridin-2-ethanol Derivatives

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Abstract: The present study deals with a systematic approach on synthesis, molecular docking and pharmacological activities associated with 5-ethyl pyridin-2-ethanol derivatives. Pioglitazone is an oral antidiabetic agent that has been developed by the derivatization of title compound. In addition numerous pharmaceutically active compounds of this class were reported timely, which possess diverse biological activities such as antimicrobial, antitumor, anticancer, anti-HIV and antibacterial with least adverse effects. Molecular docking on several reported phenoxy ethyl pyridine substituents are done with 5Y2T obtained from RSCB protein data bank. With reference to the above computational analysis, new moieties of 5-ethyl-2-(2-{4-[(E)-(2-substituted phenyl hydrazinylidene)methyl]phenoxy}ethyl)pyridine are designed and synthesized with characterization. The newly synthesized moieties exhibited promising biological activities in comparison with the selected reported drugs through docking studies**.**

Index Terms **- Computational study, Antidiabetic activity, Molecular docking, Pioglitazone.HCl**

I. INTRODUCTION

Diabetes has become a universal ailment amongst people and sadly among the youth too. World Health Organization (WHO) has reported 422 million diabetics with 1.6 million deaths every year. One in three adults are diabetic and one in six are obese [1]. Diabetes mellitus originated with variations in metabolite and hyperglycemia. Progressively leading to morbidity and mortality if untreated or not supervised well [2]. The disorder falls in to two major classes, type 1 and 2 with later being more widespread. Type 1 characterized by low production of insulin in pancreas and hence insulin-dependent diabetes [3]. Type 2 diabetes (T2D) associated with insulin resistance and pancreatic B cell dysfunction [4]. The patients are also in a high risk of damage to heart, blood vessels, kidneys, nerves and eyes over long time if not provided with apt quality care. The medications include insulin in the case of type 1 and oral medicines with insulin for type 2 for the management of DM. These therapies concentrate on gycemic control without causing hypoglycaemia and cardiovascular diseases along with other side effects like gastrointestinal intolerability, weight gain etc. The present oral pharmacological agents includes biguanides, sulfonyl ureas(SU), glinides, thiazolidinediones(TZD), dipeptidyl peptidase -4 inhibitors(DPP), alpha-glucosidase inhibitors, bile acid sequestrants, bromocriptine quick release, sodium glucose cotransporter-2[5].

TZD class of compounds well known as glitazones in market approved for treatment of diabetes in 1990s [5]. Ciglitazone are the first prototype in early 1980s which was never used for medication due to lower potential action and higher impact on cataract with animal testing for lasting use [6]. Several analogues were later discovered the foremost being troglitazone introduced in 1997 and cell withdrawn due to high risk of hepatic necrosis by 2000[7]. Rosiglitazone and Pioglitazone are the representative agents of TZD class invented later in 1990 and 2008 currently on market with concerns of specific side effects [8-9]. Thiazolidinediones are effective agonists of receptor PPAR (peroxisome proliferator-activated receptor) gamma, a member of PPAR nuclear transcription factors which regulate and metabolize fatty acids. Increased insulin sensitivity with better glucose uptake ensues instantly in adipose, muscle and liver tissues by TZD on activating PPAR [10]. Additional mechanism includes decrease in plasma insulin and lowered triglycerides with improved β cell exhaustion.

In the present inquisition Pioglitazone (Figure.1) is considered as the reference drug with TZD group acting as PPAR gamma agonist [11]. This moiety has great scope for modification and possible novel drug design. Numerous structural substitutes of Pioglitazones are in progress which could result in novel compounds that favour PPAR gamma activity[12] .This background lead us to the idea of replacing TZD with new ring system as projected in Figure .2. Molecular docking study powered by Auto dock was carried out on PPAR gamma to identify the lead compounds. The representative synthesis of these compounds is shown in Scheme .1. The newly designed ligand and protein interaction carried out on the biased compounds.

Figure 1.Structure of Pioglitazone

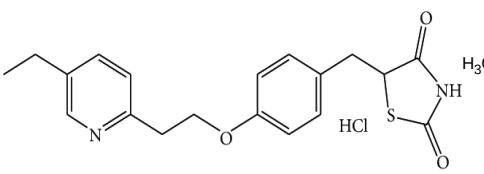
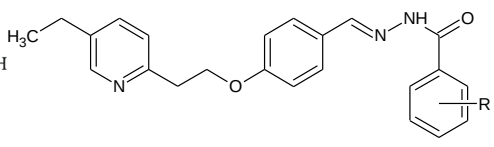


Figure 2.Structure of newly designed drug



II. RESEARCH METHODOLOGY

2.1. Materials and Methods

All chemicals used for synthesis were purchased from Sigma Aldrich and Merck. Melting and boiling points were measured for all synthesized compounds by Thiele tube apparatus. The Infrared spectra were recorded in KBr discs on Win IR FTS 135 instrument. Thin layer chromatography was carried out using silica gel G-coated TLC plates.

2.2. Molecular docking studies

All the structure for modeling are constructed using ACD Chem. Sketch freeware. Molecular docking and 3D structures of PPAR gamma with PDB ID 5Y2T and 5Y2O are carried out with the help of ADT AUTODOCK tools from SCRIPPS.EDU [13]. The extraction of protein structure from complex executed through PYMOL. The docking experiments of newly designed molecules with PPAR gamma were performed with reference to Pioglitazone. The primary work concentrates on the docking score of ligand in to the active site of protein.

2.2.1 Protein Preparation

The 3D crystal structure of PPAR gamma was downloaded from RSCB protein data bank. PPAR gamma complex with PDB ID 5Y2T and 5Y2O were chosen for computational simulation. Using PYMOL the identified protein was extracted by protein alignment and sequence comparison. This extracted protein was prepared by adding hydrogen's, removal of water, adding partial charges, and finally acting as active receptor.

2.2.2 Ligand Preparation

The ligands are sketched in https://www.mn-am.com/online_demos/corina_demo 3D structure and downloaded the .pdb file. Using Auto Dock the torsions are set and energy minimization was done.

2.2.3 Molecular Docking

To study the interactions between the receptor (PPAR gamma) and ligand (synthesized molecules) a search space in 3D were set using grid points in X,Y,Z directions. For the present study the three points are set at 70X70X70 and the center was placed at the center of active pocket. On running AUTOGRID and AUTODOCK programs successively results are visualized. Ligands were then ranked as per binding energy and interactions were analyzed.

2.3. Chemical methods of Synthesis

The compounds 1-3[14] were prepared according to previously reported methods. The title compound 2-(5-ethyl-2-pyridine) ethanol was initially tosylated in presence of a base. This was followed by coupling with 4-hydroxybenzaldehyde.The resulting 4-[2-(5-ethyl-2-pyridinyl)ethoxy]benzaldehyde was condensed with substituted phenylhydrazinesto yield 5-ethyl-2-(2-{4-[(E)-(2-substituted phenyl hydrazinylidene)methyl]phenoxy}ethyl)pyridine. Product confirmation was done by IR and TLC for all obtained products.

2.3.1. Procedure for synthesis of 5-ethyl-2-(2-{[(4-methylphenyl)sulfonyl]methoxy}ethyl)pyridine

20.2ml of 2-(5-ethyl-2-pyridine) ethanol, 20ml methylene dichloride and 27.5ml TEA was taken in a three necked round bottom flask. The mixture was cooled to 100C and was added tosyl chloride drop wise in 80ml MDC. Then the mixture was allowed to reflux for about three hours at 45^0C. After completion of the reaction (checked by TLC) the pH was adjusted to 7-8 by addition of 8% $NaHCO_3$. Then separated the MDC layer and distilled under high vacuum to remove traces of solvent. Weight of the residual liquid was noted and boiling point determined.

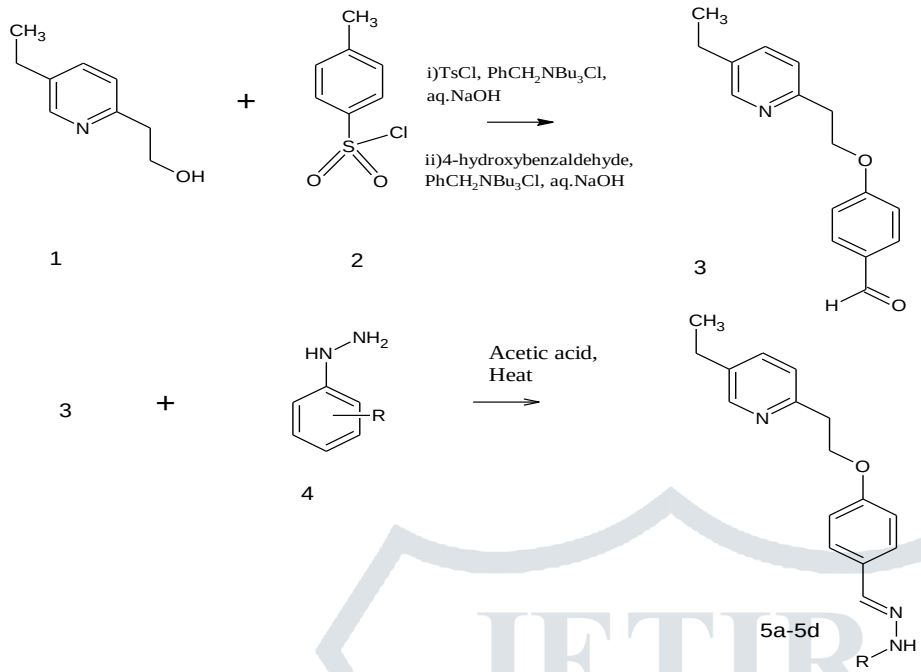
2.3.2. Procedure for synthesis of 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde

5g of 2-(5-ethylpyridine-2yl) ethyl4-methyl benzene sulfonate, 1mole ratio 4-hydroxybenzaldehyde, 2.2528g potassium carbonate and 20ml IPA was taken in a three necked round bottom flask. The mixture was heated for about five hours at80^0C under reflux. After completion of the reaction (monitored by TLC) the reaction mixture was distilled under vacuum at 50^0C.To the resulting mixture added 10ml water stirred for 15 minutes. Then added 17.5ml toluene and stirred for about half an hour. Toluene layer was separated and concentrated under high vacuum to remove traces of solvent.Oil obtained and boiling point.

2.3.3. Procedure for synthesis of 5-ethyl-2-(2-{4-[(E)-(2-substituted phenyl hydrazinylidene)methyl]phenoxy}ethyl)pyridine

Taken 1g of 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde, 1 mole ratio phenyl hydrazine(substituted) and 15ml acetic acid was taken and stirred well. Heat the above mixture for about three hours. Cooled to room temperature and extracted the reaction mixture with ethyl acetate. Separated the organic layer and concentrated under high vacuum at 54^0C.

Scheme 1.Synthesis of 5-ethyl-2-(2-{4-[(E)-(2-substituted phenyl hydrazinylidene)methyl]phenoxy}ethyl)pyridine.



5a: R Phenyl
5b: R(2,4,6-trichlorophenyl)
5c: R Phenone
5d: R1-phthalazine

III. RESULTS AND DISCUSSION

3.1. Docking

The Binding affinity and Inhibition constant computed for the derivatives of 5-ethyl-2-(2-{4-[(*E*)-(2-substituted phenyl hydrazinylidene)methyl]phenoxy}ethyl)pyridineand Pioglitazone as a reference drug. The results in the Table.1 describe the substituted compound, number of torsions set, inhibition constant and binding energy.

Table.1 Results of molecular Docking

Sl.No.	Ligand	Torsions	Inhibition Constant(μM)	Binding Energy(Kcal/mole)
1	Phenyl		32.91	-6.12
2	(2,4,6-trichloro phenyl)	8	65.57	-5.71
3	Phenone	8	20.03	-7.98
4	1-phthalazine	8	56.61	-5.79
5	Pioglitazone	7	0.13	-9.4

The above docking study reveals and proposes a systematic method for the identification of effective drugs. The ligands designed and synthesized in the present study have significant binding affinity in comparison with standard drug Pioglitazone. The hydrazine derivatives effectively bind with the amino acid residues, analogues to reference drug. Among the docked ligand molecules the phenone derivative displays maximum binding energy.

3.2. Chemistry

All the reagents and solvents used were of high quality and used without purification. The IR spectra validated some of the characteristic features of final hydrazine moiety. The stretching frequency of the C=O was observed at 1691cm^{-1}, bending around 1116cm^{-1}and aldehyde C-H stretching of 2966cm^{-1}for4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde. The final molecule (5a-5d) was observed in the range of 3446-3522cm^{-1} for N-H stretch ,1716cm^{-1}for C=N stretch ,1661cm^{-1}for C=O stretch and 1293cm^{-1} for N-H bend.

IV. CONCLUSION

Based on the findings of this study the phenone substituted hydrazinylidene exhibits better scope of developing as an antidiabetic drug. The authors would like to further explore in this field since many more novel drug molecules can be designed and discovered by further derivatization or cyclisation of final compound. The replacement of ethyl pyridine ring in Figure.1with other ring system will evolve a new area of future study, which is under progress.

V. ACKNOWLEDGEMENT

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