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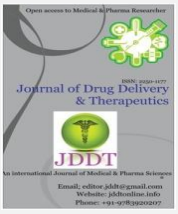

Open Access Research Article

DOCKING STUDIES ON IMIDAZOLIDINE ANALOGUES FOR MANAGEMENT OF DIABETES

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ABSTRACT

Glycogen synthase kinase-3β (GSK-3β) has recently emerged, in the field of medicinal chemistry, as one of the most attractive therapeutic targets for type II diabetes. Phenylmethylene hydantoins (PMHs) forms strong interactions with the hinge region of GSK-3β; carbonyl oxygen at position 2 form a H-bonding with backbone nitrogen of Val135 and the NH at position 3 to the carbonyl oxygen of Asp133. The hydantoin ring was sandwiched between Ala83, on top, and Leu188, on the bottom. The aromatic ring is rotated out of plane from the hydantoin plane, allowing extensive interactions with the nucleotide-binding loop. Furthermore, the substituted benzylidene ring system builds an H-bonding interaction with the guanidine moiety of Arg141. Targeting Arg141 is important to improve the activity in the process of designing new derivatives because it is considered the selectivity residue for GSK-3β.

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INTRODUCTION:

The insulin insensitive form of diabetes, type 2 diabetes mellitus characterized by hyperglycaemia which is also known as elevated blood glucose concentrations, most frequently arises as a consequence of obesity, represents approximately 95% of the overall incidence of diabetes-I. Additionally, diabetes related complications exert a heavy toll on patients with poor metabolic control [1-5]. Most of kinase inhibitors act by competition with either ATP or metal-binding sites that are involved directly in the catalytic process. Over the past 15 years, there have been extensive efforts to understand and reduce the high attrition rates of drug candidates with an increased focus on physicochemical properties. The fruits of this labour have been the generation of numerous efficiency indices, metric-based rules and visualization tools to help guide medicinal chemists in the design of new compounds with more favorable properties. This deluge of information may have had the unintended consequence of further obfuscating molecular optimizations by the inability of these scoring functions, rules and guides to reach a consensus on when a particular transformation is identified as beneficial. In spite of the early discovery of insulin and its subsequent widespread use in the treatment of diabetes mellitus, and later discovery and use of sulfonylureas e.g. chlorpropamide, tolbutamide and biguanides viz. phenformin as oral hypoglycemic agents, the treatment of diabetes mellitus remains less than satisfactory. Insulin can only be administered intravenously due to its chemical nature, and therefore, is troublesome and inconvenient to use. Oral hypoglycemic agents tend to promote side effects such as excessive hypoglycemia or lactic acidosis. Glycogen synthase kinase-3β (GSK-3β) has recently emerged, in the field of medicinal chemistry, as one of the most attractive therapeutic targets for Type II diabetes. The full potential of GSK-3β inhibitors is yet to be realized and the number of drug candidates being developed by both academic centers and pharmaceutical companies has increased exponentially in the last few years. Glycogen synthase kinase-3β (gsk-3β) is a unique multifunctional serine/threonine kinase that is inactivated by phosphorylation in response to insulin binding; PKB/AKT phosphorylates GSK-3β on serine9, which prevents the enzyme from phosphorylating glycogen synthase. Unphosphorylated glycogen synthase is active & able to synthesize glycogen.

Phenylmethylene hydantoins (PMHs) forms strong interactions with the hinge region of GSK-3β; carbonyl oxygen at position 2 form a H-bonding with backbone nitrogen of Val135 and the NH at position 3 to the carbonyl oxygen of Asp133. The hydantoin ring was sandwiched between Ala83, on top, and Leu188, on the bottom. The aromatic ring is rotated out of plane from the hydantoin plane, allowing extensive interactions

with the nucleotide-binding loop. Furthermore, the substituted benzylidene ring system builds an H-bonding interaction with the guanidine moiety of Arg141. Targeting Arg141 is important to improve the activity in the process of designing new derivatives because it is considered the selectivity residue for GSK-3β. Design of potent and selective GSK-3β inhibitors should consider the following important hot spots

- H-bonding interaction with the hinge region of Asp133 and Val135.
- Targeting Arg141 and Gln185 amino acids.
- Filling the Val70, Lys85 and Cys99 hydrophobic pocket. For example, keeping the hydantoin ring and chemical moiety at benzylidene ring system can afford potent and selective GSK-3β inhibitor.

The wide chemical diversity of possible inhibitors and the existence of multiple sites for potential inhibition encourage researcher topursue the development of GSK-3β inhibitors as potential drugs. Therefore it is worthwhile to develop further substituted GSK-3β inhibitors as antidiabetic agents [1-4].

MATERIAL AND METHODS:

Docking of Designed Compounds The molecular docking was performed using Molegro Virtual Docker (MVD) 2006. 1.5 and CS Chem Office version 11.0. The docking scoring function of MolDock that we use is based on a piecewise linear potential (PLP) including new hydrogen bonding and electrostatic terms introduced. Structures of all the compounds were sketched using builder module of the program. The sketched structures were subjected to energy minimization using molecular mechanics (MM2) until the RMS gradient value became smaller than 0.1 kcal/molA°. The energy minimized molecules were subjected to re-optimization via Austin model-1 (AM1) method until the RMS gradient attained a value smaller than 0.01 kcal/mol °A using MOPAC The descriptor values for all the molecules were calculated using "compute properties" module of program. The minimized molecule was saved as MOL file format[5].

Following Steps were used for docking through MVD:

1) Importing and Preparing Molecules

- File Import: - MVD supports PDB, Mol2, SDF, and its own XML-based format,
- MVDML.
- Adding a Molecular Surface
- Predicting the Binding Site

2) Running the Docking Simulation: -

- By selecting **Docking** | **Docking Wizard**
- Choosing Structures
- Defining the Region of Interest

3) Viewing the Results

These designed analogs were docked in the ATP binding site of GSK-3β by Molegro Virtual Docker 2006.1.5.

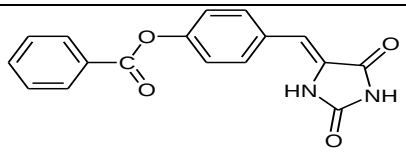
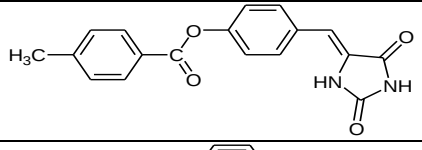
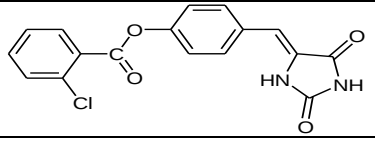
RESULTS AND DISCUSSION:

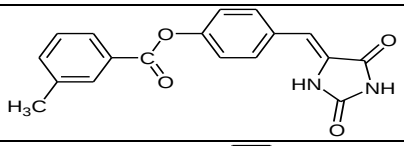
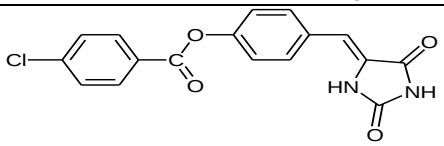
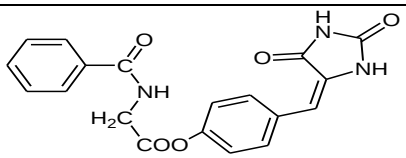
On the basis of literature study hydantoin analogs were designed. These designed analogs were docked in the ATP binding site of GSK-3β by Molegro Virtual Docker 2006.1.5.

Phenylmethylene hydantoins (PMH) forms strong interactions with the hinge region of GSK-3β; carbonyl oxygen at position 2 form a H-bonding with backbone nitrogen of Val135 and the NH at position 3 to the carbonyl oxygen of Asp200.

Furthermore, the substituted benzylidene ring system builds an H-bonding interaction with the guanidine moiety of Arg141. Targeting Arg141 is important to improve the activity in the process of designing new derivatives because it is considered the selectivity residue for GSK-3β. Substitution at benzylidene ring system can afford potent and selective GSK-3β inhibitors as H (a-f).

Table 1: Docking Score of Synthesized compound

Comp. Code	Synthesized Compound	Mol Dock Score (E-Total)	H-Bonds Interactions With Amino Acids
H-a		-113.32	Arg 141 Pro 136 Tyr 134
H-b		-126.06	Asp 200 Lys 183 Asp 200
H-c		-129.62	Tyr 134 Arg 141 Pro 136 Cys 199

H-d		-125.06	Arg 141 Pro 136 Tyr 136 Cys 199
H-e		-127.93	Val 135 Asp 200 Phe 201 Glu 97
H-f		-147.53	Arg 141 Asn 64 Ile 62 Glu 97

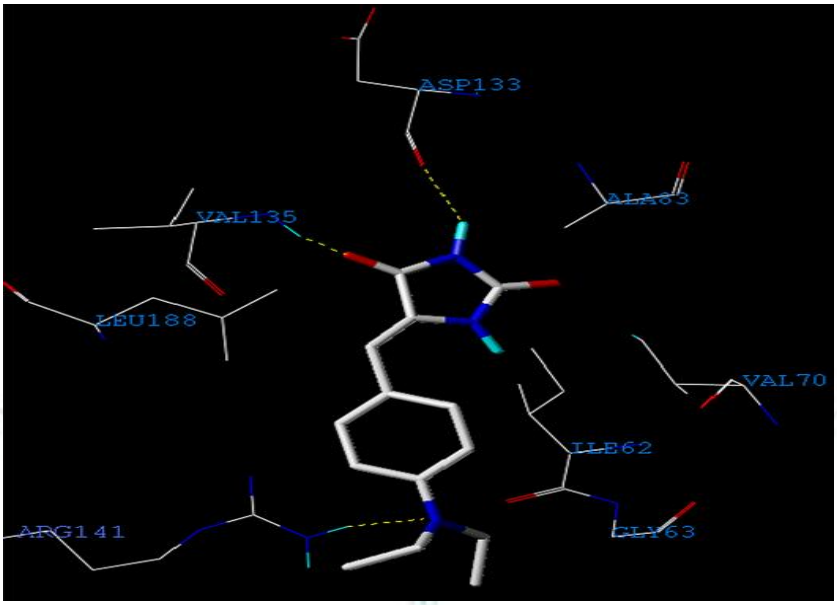


Figure 1: The prototype pose of docked structure of a Hydantoin analogue.

CONCLUSION:

Glycogen synthase kinase-3β (GSK-3β) is a unique multifunctional serine/threonine kinase that is inactivated by phosphorylation in response to insulin binding; PKB/AKT phosphorylates GSK-3β on serine9, which prevents the enzyme from phosphorylating glycogen synthase. Unphosphorylated glycogen synthase is active & able to synthesize glycogen.

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