

Computer Aided Screening of Indirubin Analogues Targeting GSK-3 β Protein Using Molecular Docking

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Abbreviations: PDB ID: Protein Data Bank; ADT: Auto Dock Tools; NSCLC: Non-Small-Cell Lung Cancer; SCLC: Small Cell Lung Cancer

ABSTRACT

Objective: To study the inhibition effects of indirubin analogues with GSK-3 β protein using molecular modeling and docking tools.

Materials and Methods: Crystal structure of GSK-3 β was taken from Protein data bank (PDB ID: 1Q41). The construction and optimization of the three-dimensional structure of small molecules was done using ChemDraw and Chem3D version 18.1 (PerkinElmer®). All ligands and protein were prepared for docking using Auto Dock Tools (ADT) 1.5.6. AutoDock 4.2.6 was utilized for the molecular docking simulation.

Results: Overall, amongst 12 indirubin derivatives, 8 analogues appear to inhibit GSK-3 β function based on docking score ranking, the formed hydrogen bonds of topmost compounds share same residues in the binding site as compared to standard indirubin-3'-oxime.

Conclusion: Further *in vitro* and *in vivo* experimentation are needed to confirm the efficacy and potency of potential compounds. This model can be applied for design candidate drug with desired biological properties by chemical modification in functional group at appropriate places.

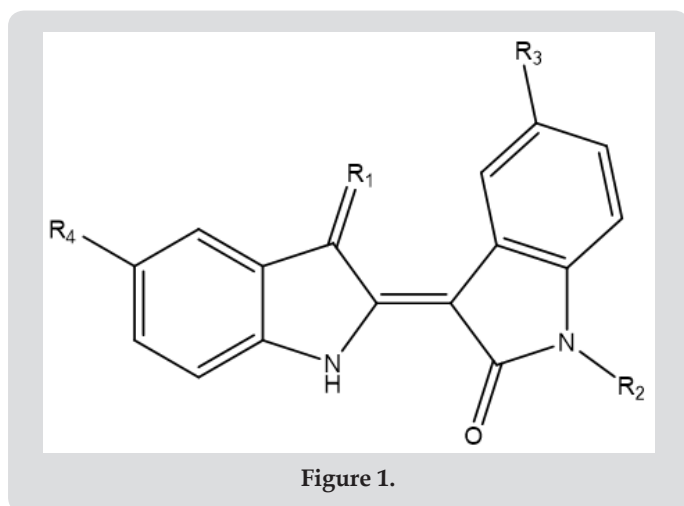
Introduction

Lung cancer is one of the leading causes of cancer-related death worldwide both with men and women, it is responsible for about 1.3 million deaths annually [1,2]. In Vietnam, lung cancer has very high rate of mortality with 24,000 new cases annually in which 90% result in deaths. There are two major types of lung cancer: non-small-cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [3,4]. Non-small cell lung cancer accounts for about 80% of overall lung cancer cases. Despite many efforts have been made in the last 25 years, the treatment drugs for patients remain poor efficacy. Indirubin and its analogues have been well known for their activities against many types of cancer cell line, mainly by inhibition of cell proliferation and induction of cell death [5,6]. These data suggest the development of indirubin derivatives as potential candidates for the treatment of lung cancer. Recent studies have discovered activity of GSK-3 β in cancer and its role in regulating tumor cell proliferation and survival of multiple human malignances. For the purpose of finding novel compounds and new

idea for drug design, 12 analogues of indirubin were allowed to dock with GSK-3 β protein.

Materials and Methods

Crystal structure of GSK-3 β was taken from Protein data bank (PDB ID: 1Q41). The construction and optimization of the three-dimensional structure of small molecules was done using Chem Draw and Chem3D version 18.1 (PerkinElmer®). All ligands and protein were prepared for docking using Auto Dock Tools (ADT) 1.5.6. The ligands and protein were protonated. The default Kollman charges and solvation parameters were allocated to the protein atoms. Gasteiger charges were added to each ligand atom. Grid box was generated around possible ligand-binding site. The pre-calculated binding affinity of each ligand's atom type was prepared using Autogrid. Auto Dock 4.2.6 was utilized for the molecular docking simulation and Accelrys Discovery Studio Visualizer 4.0 was used for docking results visualization (Figure 1) and (Table 1).

**Table 1.**

No	R1	R2	R3	R4
1	O	H	NH ₂	H
2	O	H	NH ₂	Br
3	O	H	NHAc	H
4	O	H	NHAc	Br
5	NOH	H	NH ²	H
6	NOH	H	NH ²	Br
7	NOH	H	NHAc	H
8	NOH	H	NHAc	Br
9	NOH	H	NO ²	Br
10	NOH	CH ₃	NO ²	H
11	NOH	H	NO ²	H
12	NOH	CH ₃	NO ²	Br

Results

In general, 8 derivatives of indirubin showed better docking score to GSK-3 β than the standard indirubin-3'-oxime. Most of the designed derivatives form H-bonds with GSK-3 β when binding in its ATP-binding site. The hydrogen bonds occur mainly with VAL135 and ASP133 in the Hinge region and ARG14 which is the important region for the function of protein. In some of the molecules it also forms H-bonds with GLN185, LEU132, ASP200 and LYS88 amino acids of GSK-3 β (Table 2).

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Table 2.

No.	Docking score (kcal/mol)	No.	Docking Score (kcal/mol)
Compound 1	-8.5300	Compound 8	-9.7500
Compound 2	-8.2500	Compound 9	-12.0100
Compound 3	-7.7200	Compound 10	-11.9500
Compound 4	-7.5600	Compound 11	-11.4300
Compound 5	-11.2400	Compound 12	-11.6500
Compound 6	-11.0700	Indirubin-3'-oxime	-9.5900
Compound 7	-9.9800		

Conclusion

Molecular docking studies were conducted for all the designed molecules against the structure of protein GSK-3 β . There 8 amongst 12 compounds exhibit potential inhibition activity in the ATP-binding site of the protein. Further *in vitro* and *in vivo* experimentation are needed to confirm the efficacy and potency of potential compounds and could be leads compounds for medicine drugs.

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