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MOLECULAR DOCKING STUDY OF ANTI THYROID DRUG AS AN ANTI-HYPERTENSIVE AGENT

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ABSTRACT

AIM: To determine and compare the binding efficiency of anti-thyroid drug (Carbimazole and Methimazole) with standard anti-hypertensive drug(Clonidine) by using docking studies.

MATERIALS AND METHODS: Chem draw Ultra 12.0 software, Argus software, Autodock 4.2 Version, Discovery studio 4.2 visualizer.

RESULTS: Molecular docking studies of Carbimazole and Methimazole were carried out and the docking scores are in the range of **-3.3** on α2B **-3.45** on α2C and shows better binding energy compared to the standrard durg clonidine.

CONCLUSION: The molecular docking studies of anti thyroid drugs namely Carbimazole and Methimazole have shown an excellent binding efficiency results on α2-Adrenergic receptor as anti hypertensive agents. It is observed that Methimazole showed significant binding energy-**3.3** on α2B **-3.45**on α2C at lower concentrations when compared with standard Clonidine **-6.09** α2B **-4.79** α2C.

INTRODUCTION:

The most fundamental goal in drug design is to predict whether a given molecule will bind to a target and if so how strongly. Molecular mechanics or molecular dynamics is most often used to estimate the strength of the intermolecular interaction between the small molecule and its biological target. These methods are also used to predict the confirmation of small molecule and to model conformational changes in the target that may occur when the small molecule binds to it. Semi-empirical, ab initio quantum chemistry methods, or density functional theory are often used to provide optimized parameters for the molecular mechanics calculations and also provide an estimate of the electronic properties of the drug candidate that will influence binding affinity.

Molecular mechanics methods may also be used to provide semi-quantitative prediction of the binding affinity. Also, knowledge based scoring function may be used to provide binding affinity estimates. These methods used linear regression, machine learning, Neural nets or other statistical techniques to derive predictive binding affinity equations by fitting experimental affinities to computationally derived interaction energies between the small molecule and the target.

Ideally, the computational method will be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized, saving enormous time and cost. The reality is that present computational methods are imperfect and provide, at best, only qualitatively accurate estimates of affinity. In practice it still takes several iterations of design, synthesis, and testing before an optimal drug is discovered. Computational methods have accelerated discovery by reducing the number of iterations required and have often provided novel structures

Drug design with the help of computers may be used at any of the following stages of drug discovery:

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1.Hit identification using virtual screening(structure or ligand based design)

2.Hit-to-lead optimization if affinity and selectivity (structure-based design, QSAR, etc.)

3. Lead optimization of other pharmaceutical properties while maintaining affinity.

The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites (usually referred to as pose) and assessment of the binding affinity. These two steps are related to sampling methods and scoring schemes, respectively.

In general prodrugs are derivatives of active drug moities, designed to undergo conversion in the body and to overcome undesirable drug properties. The chemical modifications of the drugs are designed to be activated to produce the active parent drug after an enzymatic or chemical reaction once they have been administered into the body.

METHODOLOGY

Softwares used for docking

1. Chem draw Ultra 12.0 software.
2. Argus software.
3. Autodock 4.2 Version.
4. Discovery studio 4.2 visualizer.

MOLECULAR DOCKING STUDIES

Protien- ligand docking studies of carbimazole and methimazole was evaluated in order to investigate the interaction between the active site of α2-Adrenergic receptor and the ligands on argus software and discovery studio software.

(A) Ligands preparation for docking

The 2D structure of the compound (carbimazole and methimazole) was drawn using Chem Draw Ultra 12.0 software, where later converted to 3D structures of geometry optimization of the compounds. Carbimazole, Methimazole and Clonidine shown in fig.1

(B) Preparation of receptor

The structure of α2-Adrenergic receptor, with PDB codes of p08913 for α2A,p18089 for α2B, p18825 for α2C receptors, was downloaded form protein data bank(PDB). The 3D structure receptor was prepared by discarding water molecules and cofactors using Discovery Studio software and save as PDB. α receptors shown in fig.2

Docking of the ligands with the receptor using Argus software:

The docking of the ligands (Carbimazole and Methimazole) and the receptor (α2-Adrenergic)was performed using Autodock 4.2 Version. From the DLG file we can see the binding energy and inhibition constant. The complexes were visualized to view their interaction using discovery studio 4.2 visualize.

RESULTS

Results were shown in table.1

Discussion:

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- The tested anti thyroid drugs have shown significant activity as anti-hypertensive activity when compared with clonidine.
- Hence it is concluded that Carbimazole and Methimazole can act as anti-hypertensive agent.
- So prescribing anti thyroid drug (Carbimazole and Methimazole) for hypertensive patients should be carefully monitored.
- The molecular docking studies of anti thyroid drugs namely Carbimazole and Methimazole have shown an excellent binding efficiency results on α2-Adrenergic receptor as anti hypertensive agents. It is observed that Methimazole showed significant binding energy**-3.3** on α2B **-3.45**on α2C at lower concentrations when compared with standard Clonidine **-6.09** α2B **-4.79** α2C.

Conclusion:

- Molecular docking is an inexpensive safe and easy to use tool held in investigating interpreting explaining and identification of molecular properties using three-dimensional structures.
- Since different models yield different results it is necessary to have a small number of standard models which are applicable to very large systems.
- Molecular docking used to predict the structural inter molecular complexes formed between two or more constitution molecules. The technique are used in the field of computational chemistry, computerized biology material used for molecular system ranging from small molecules to large biological molecules and material assemblies
- Most of the docking presently being studied the binding of a flexible ligand to a biological receptor.
- Finally, It is concluded that the molecular docking studies of carbimazole and methimazole showed an excellent anti hypertensive activity on α2-Adrenergic receptor

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest in publishing this research paper.

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FIGURES:

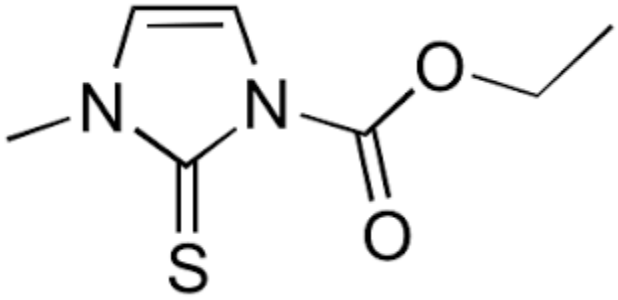

Fig.1.1 Carbimazole IUPAC name: ethyl 3-methyl-2-sulfanylidene-2,3-dihydro-1H-imidazole-1-carboxylate

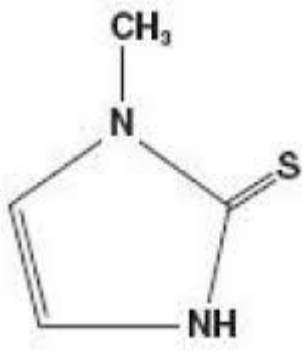

Fig.1.2 Methimazole IUPAC name: 1-methyl-2,3-dihydro-1H-imidazole-2-thione

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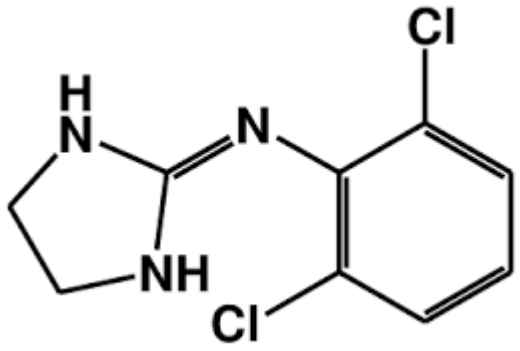

Fig.1.3 Clonidine IUPAC name: N-(2,6-dicholorophenyl)-4,5-dihydro-1H-imidazole-2-amine.

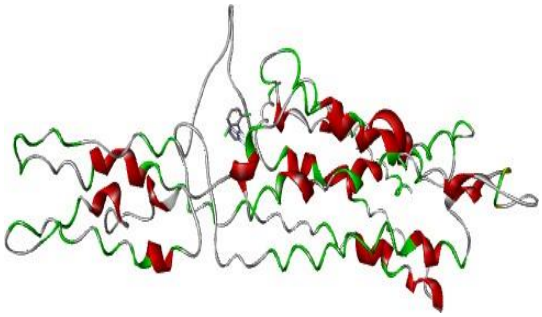

Fig. 2(A) α 2A-Adrenergic recptor

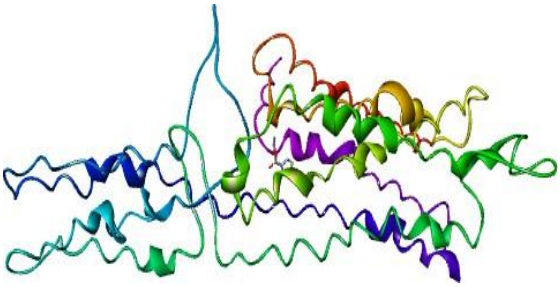

Fig.2(B) α 2B-Adrenergic receptor

Fig.2(C) α 2C- Adrenergic receptor

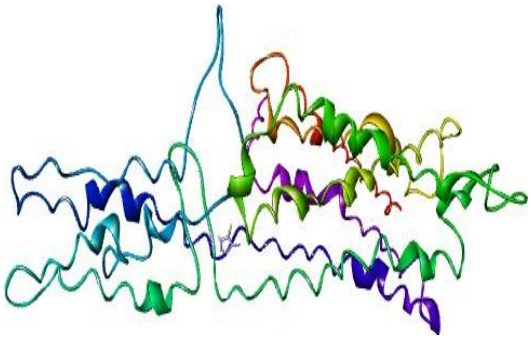

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Table 1

The following are the binding energy values and concentration of drugs used

Receptor		Clonidine	Carbimazole	Methimazole
α2A	Binding energy(kcal/mol)	-6.52	-5.48	-4.09
	Ki (μM)	16.66	96.39	999.36
α2B	Binding energy(kcal/mol)	-6.09	-4.57	-3.3
	Ki (μM)	34.16	444.74	3.84mM
α2C	Binding energy(kcal/mol)	-4.79	-4.76	-3.45
	Ki (μM)	306.9	323.66	2.96Mm