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ISSN 0975-413X CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(10):221-229 (http://derpharmachemica.com/archive.html)

# Structure activity relationship of Atropine analogues with muscarinic acetyl choline M1 receptor: A molecular docking based approach

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# ABSTRACT

Anticholinergics are used in the treatment of a variety of conditions. Some of the important conditions are: chronic obstructive pulmonary disease (COPD), asthma, motion sickness, dizziness, toxicity by organophosphorus insecticides or compounds like muscarine, conditions inducing high blood pressure and symptoms due to Parkinsonism. Atropine, falling under anticholinergic class of drug consists of l- as well as d- forms of hyoscyamine. The action of which is solely due to its levo form. Atropine counteracts the actions of acetylcholine and other esters of choline, thus is also termed as antimuscarinic agent. Due to the immense use of atropine, it was thought to design novel atropine congeners and to compare their binding affinities with the standard drug Tiotropium for binding at the active site of acetyl choline esterase. The results showed that none of the analogues processed dock scores comparable to Tiotropium. But the study gave us insight about the binding modes of anticholinergics. So, in future studies, more effective analogues will be designed and will be taken for in vitro studies.

Key words: Docking, Extra precision, Glide, Ligprep.

# INTRODUCTION

Atropine, a naturally occurring alkaloid belonging to the family *Solanaceae* is present in plants such as *Atropa belladonna* and Datura Stromonium. Atropine, falling under anticholinergic class of drug consists of 1- as well as d-forms of hyoscyamine. The action of which is solely due to its levo form. Atropine serves as a drug of choice in conditions such as respiratory disorders, chronic obstructive pulmonary disease (COPD), motion sickness, dizziness, toxicity by organophosphorus insecticides or compounds like muscarine, conditions inducing high blood pressure and symptoms due to Parkinsonism. Atropine, falling under anticholinergic class of drug consists of 1- as well as d-forms of hyoscyamine which antagonizes the muscarine-like actions of acetylcholine and other choline esters, thus is also termed as antimuscarinic agent [1]. Suitable doses of atropine has found to obliterate numerous types of reflex vagal cardiac slowing process. Atropine has also been found to also prevent bradycardia due to injection of anticholinesterase agents, choline esters and such agents[2]. When vagal activity is an etiologic factor, atropine may reduce the risk of partial heart block. In clinical doses, atropine can counteract sudden decrease in blood pressure and peripheral dilatation [3]. When atropine binds to muscarinic acetylcholine receptors, it can inhibit them thus eliciting a wide range of anticholinergic effects. The present study gives insights on the binding modes of novel

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atropine analogues. Such studies can be a tool in designing atropine analogues with improved and selective inhibition of choline esterase.

## MATERIALS AND METHODS

**Materials:** The simulation was run in windows xp (2010) with Maestro interface. Schrodinger 2015 was used for docking simulations [4]

### Methods:

# **Protein preparation:**

The present study utilized X-ray crystallographic structure of human M1 muscarinic acetyl choline receptor which was co-crystallized with Tiotropium (PDB ID: 5CXV). These were acquired from Protein Data Bank [5]. The receptor complex was eventually processed using preparation wizard available with Glide 2015 version.

The preparation component adds hydrogens, minimizes the structure and deletes waters beyond 5 angstroms. The preparation process has several steps including refinement and minimizations.

#### Ligand preparation

The target compounds were built through fragment library from Maestro 10.4.Low energy conformer of analogues were generated through optimization with the help of OPLS-2005 force field. The Ligprep ligands were aligned using flexible ligand alignment option available with Schrodinger 2015 version.

#### **Docking simulation studies**

The docking parameters were tested by docking the compounds to be analyzed in the binding site of the muscarinic acetylcholine receptor (PDB ID: 5CXV). The docking studies were conducted using Grid-Based Ligand Docking With Energetics (Glide) software from Schrodinger.

A grid box was created at the middle of the target site for docking. The force field namely, OPLS-2005 (Optimized Potential for Liquid Simulations) was used for this purpose[6]. The best docked analog was then selected using Glide score function, energy and Emodel energy. The minimum energy docked complex was ultimately selected for future studies.

# **RESULTS AND DISCUSSION**

# Analysis of binding site of M1 muscarinic acetyl choline receptor

The 2D interaction diagram of tiotropium with the active site showed significant binding interactions. The basic nitrogen of tropinone ring showed cation-pi interaction with amino acids Tyrosine 106, Tyrosine 404, tryptophan 378, Tyrosine 381 as shown in the figure 1. It was also found that the carbonyl oxygen and ethanolic hydroxyl has interaction with Asparagine 382 and thiophene ring of Tiotropium interacted with Tryptophan 157 at the active site.



Figure 1: 2D interaction diagram of tiotropium binding to the active site

# Binding analysis of designed analogues

Binding site analysis of Atropine R

The 2D interaction diagram of Atropine R isomer showed binding interaction with asparagine 382. (Figure 2)



Figure 2:2D interaction diagram of Atropine R binding to the active site

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#### **Binding Site analysis of Atropine S**

The 2D interaction diagram of Atropine R isomer showed binding interaction with asparagine 382. (Figure 3).

The binding site analysis of both the R and S forms showed interaction with asparagine 382. However, from the docking score, it was found that the binding affinity for S isomer (-6. 999) was significantly greater than the R isomer (-4.688). This could basically be attributed to the spatial arrangement of carbonyl group in Atropine R and S isomers from asparagine 382, resulting in significant difference in docking scores.



Figure 3: 2D interaction diagram of Atropine S binding to the active site

Binding site analysis of Atropa 1



Figure 4:2D interaction diagram of Atropa 1 binding to the active site

The 2D interaction diagram of Atropa 1 showed binding interaction with asparagine 382. (Figure 4).

#### Binding site analysis of Atropa 2



Figure 5:2D interaction diagram of Atropa 2 binding to the active site

The 2D interaction diagram of Atropa 2 showed hydrogen bonding interactions with Asparagine 382. Anilino moiety of Atropa2 showed pi cat interaction with amino acids Tryptophan 157 and Tyrosine 106. The protonated nitrogen of tropinone ring showed pi cat interactions with amino acids Tyrosine 106, Tyrosine 381, Tyrosine 404.

# Binding site analysis of Atropa 3

The 2D interaction diagram of Atropa 3 showed hydrogen bonding interactions with Asparagine 382 and Tyrosine 106



Figuure 6: 2D interaction diagram of Atropa 3 binding to the active site



Figure 7: 2D interaction diagram of Atropa 4 binding to the active site

The 2D interaction diagram of Atropa 4 showed hydrogen bonding interactions with Threonine 190 and Alanine 196.

#### Binding site analysis of Atropa 5



Figure 7: 2D interaction diagram of Atropa 5 binding to the active site

The 2D interaction diagram of Atropa 5 showed hydrogen bonding interactions with asparagine 382. The phenolic moiety of Atropa 5 showed pi cat interactions with Tryptophan 378. Protonated nitrogen of Tropinone moiety showed pi cat interaction with amino acids Tyrosine 404 and Tryptophan 378.

## **Docking results**

None of the analogues showed docking score comparable to the standard ligand Tiotropium (docking score -13.089. (Table1). Atropa 2, Atropa 5 and Atropine S showed significant docking scores (-7.419,-7.621 and -6.999

respectively). The scores may be attributed to the formation of pi cat interaction on the nitrogen of tropinone part in Atropa 2 and Atropa 5, which is not possible in other analogues. Also Atropa 2 and Atropa 5 showed Glide scores comparable to Tiotropium (Table 1).



Figure 8: Pi cat interaction of crystal ligand Tiotropium



Figure 9: Binding surface of Crystal ligand

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Compound Code	Structure	Docking score	Glide score	Glide evdw	GlideE model
5 Cvx ligand	O H N+ S	-13.089	-13.089	-53.898	-105.6
Atropa 1		-3.692	-7.169	-34.841	-65.364
Atropa 2	HN+ O NH3+	-7.419	-11.666	-35.637	-76.559
Atropa 3	OF OH	-6.194	-9.400	-26.687	-51.283
Atropa 4	N O O O O O O O O O O O O O O O O O O O	-4.578	-7.784	-38.873	-61.932
Atropa 5		-7.621	-11.472	-30.785	-66.020
Atropine R	HO	-4.658	-7.685	-39.226	-66.082
Atropine S	HOTO	-6.999	-10.206	-38.070	-67.214

Table 1: Docking results of Atropine analogues



Figure 10: Ramachandran plot

### CONCLUSION

The docking results gave us insight about the structural and stereo chemical features required for binding at the active site of M1 muscarinic acetyl choline receptor. In our future studies attempts will be made to design more potent analogues with less toxicity profiles. The *in vitro* studies will be undertaken in order to authenticate the simulation experiments.

# Acknowledgements

We are thankful to Manipal University and Schrodinger Inc for their valuable support.

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