Original Article

Cross evaluation of different classes of alpha-adrenergic receptor antagonists to identify overlapping pharmacophoric requirements

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ARTICLE INFO

ABSTRACT

Structurally dispersive classes of drugs targeting identical receptor binding site can serve as a source of information in the design of novel drug candidates. Their comparative cross structural features can be utilized toward optimization of receptor–ligand interactions. Five established alpha-adrenergic receptors antagonists were selected as representative compounds of their respective classes. The selected antagonists are Phenoxybenzamine, Phentolamine, Prazosin, Ergoloid Mesylate and Labetalol. A small library of 1000 molecules, 200 from each class, were submitted to molecular docking in the antagonist binding site of alpha-adrenergic receptor. The present work includes homology modeling of alpha-adrenergic receptor using SPDBV and its structure validation from Procheck. The molecule library was developed using drug likeness filters (Lipinski's rules). Flexible molecular docking was performed using MVD (Molegro Virtual Docker) after receptor and ligand preparation. The conclusive outcome of the present work is identification of antagonist binding sites of the alpha-1 (α1)-adrenergic receptor exclusively as hydrophobic due to presence of the amino acids Val 107, Val 157, Asp 106, Ile 157, Ser 158, Ser 192, Ala 189, Phe 288 and Phe 289.The amino acids identified were found crucial to identify pharmacophoric features for alpha-1 (α1)-adrenergic receptor and antagonists. Results also include identification of new molecule (PubChem ID 10289950) similar to Ergoloid Mesylate with re-rank score −113.571. The present work explains successive workflow of homology modeling, flexible molecular docking, and pharmacophoric features identification.

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1.   Introduction

A physiological condition when blood pressure stands consistently higher than normal magnitudes is referred to as hypertension.[1] This physiological event implies extra performance and also poses serious health risks. Hypertension has been identified and proven to be a major cause of strokes and heart attacks. In addition, higher blood pressure also results into the devastation of coronary arteries, kidneys, brain and eyes.[2,3]

Target identification events have confirmed the cardinal role in regulation of a variety of physiological events, markedly within the cardiovascular system. Recent advances encompass the concerned studies related to physiological events and messenger systems in which the α-adrenergic receptors are involved.[4,5] Literature survey reveals development of agonists and antagonists, highly selective for the various subtypes of α-adrenergic receptors and with possible therapeutic values and lesser side effects.[6–9]

The target site selection in alpha-adrenergic receptor was identified from the literature survey pertaining to current work. The active site residues were found to be Phe 312 and Phe 308, which is the major site of antagonist affinity. This active site is present on the transmembrane domain 7 of the alpha (1a)-adrenergic receptor.[10] Mutation of either Phe 312 or Phe 308 results into a significant loss of affinity for the antagonists Prazosin, Phentolamine, Labetalol, Phenoxybenzamine, with no changes in affinity for agonists compounds such as Phenylephrine, Epinephrine and Methoxamine.[10]

Information retrieved from drug bank (http://www.drugbank.ca/) affirmed that drugs like Phenoxybenzamine, Phentolamine, Labetalol, Ergoloid Mesylate and Prazosin are implied in cardiovascular diseases after binding alpha-adrenergic receptor as antagonists. Phenoxybenzamine (DB00925) is employed to dilate blood vessels leading muscle repose.[11] Phentolamine (DB00692) is prescribed during pheochromocytomectomy to guard patients from paroxysmal
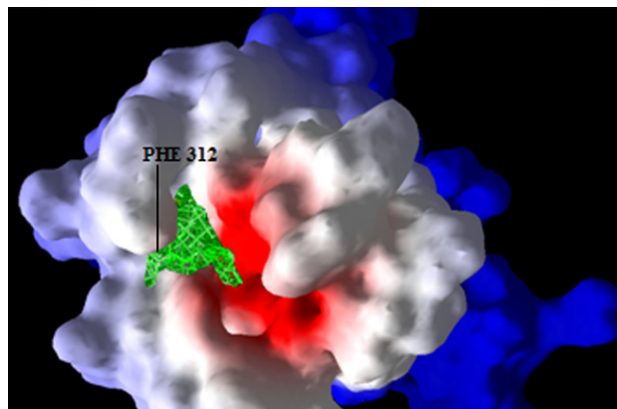

Fig. 2 – Modeled structure of alpha-1A-adrenergic receptor showing antagonist binding site with identified cavity in green color.

hypertension resulted from surgical events. Labetalol (DB00598) particularly antagonizes alpha-adrenergic receptor in hypertension and compatible in angina pectoris. Ergoloid Mesylate (DB01049) has been found significant in dementia causing slow down of the heart rate. Prazosin (DB00457) with even larger profile is employed in symptomatic benign prostatic hyperplasia and severe congestive heart failure along with hypertension.

Molecular docking is a computational technique used in measuring the receptor–ligand interactions on the basis of physico–chemical interactions pertaining to force-field (molecular mechanics). Molecular docking helps to identify pharmacophores, particularly in structure-based drug design.[12] Pharmacophoric atoms, groups and substructures controlling H-bond, electrostatic, hydrophobic, hydrophilic, van der Waals interactions are to be identified as the objective of present investigations. Present work is an overlapping information extraction from structure based drug design and
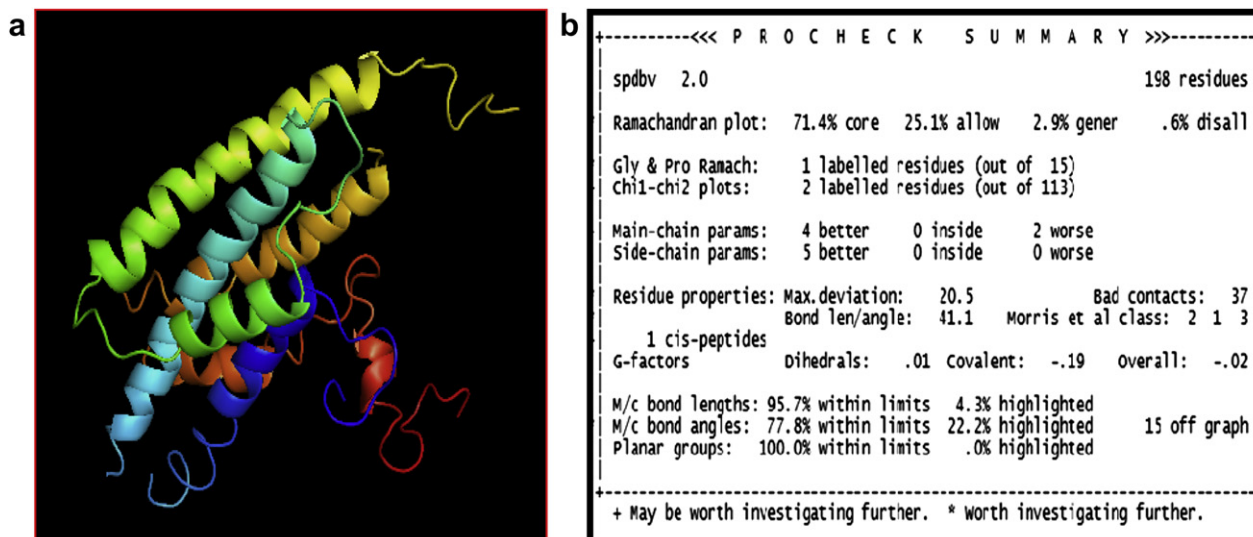

Fig. 1 – a- 3D structure of alpha-1A-adrenergic receptor. b- Quality assessment of modeled 3D structure of alpha-1A-adrenergic receptor using Ramachandran plot.