J. Chosun Natural Sci.
Vol. 10, No. 2 (2017) pp. 105 – 109
https://doi.org/10.13160/ricns.2017.10.2.105

Molecular Docking Study of Urotension-2 Receptor (UTS2R)

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Abstract

Urotensin-2 receptor (UTS2R) is the most potent vasoconstrictor and plays a major role in the pathophysiology of various cardiovascular diseases and becomes a potential target for human pharmacotherapy. Hence, we have performed molecular docking of six antagonists with different inhibitory activity against UTS2R into its binding site. The binding mode of these antagonists was obtained using Surflex dock program interfaced in Sybyl-X2.0. The residues such as GLN278, THR304, TYR305, THR300, LEU299, CYS302, ASP47, TYR100 and THR304 are found in interaction between UTS2R and its antagonists. This study could be useful for identifying and analyzing the important residues involved in binding site of UTS2R receptor.

Keywords: UTS2R; Molecular Docking

1. Introduction

Human urotensin II (UTS2R) is a cyclic peptide first isolated from the fish spinal cord and has been recognized as a hormone in the neurosecretory system of teleost fish. UTS2R is generated by proteolytic cleavage from a precursor prohormone. UTS2R has been identified as an endogenous ligand of the G protein-coupled receptor (GPR)-14[1-3]. UTS2R is a highly conserved undecapeptide which is well represented in the nervous system, heart and kidney and was initially seen as a vasoconstrictor/cardiodepressant compound and implicated in myocardial and renal dysfunction[4-6]. UTS2R mediates vascular tone and increased contractile force in human atrium and ventricle and the effects of UTS2R are mediated by binding to the urotension receptor[7,8]. UTS2R provokes trophic and/or mitogenic actions in vascular smooth muscle cells, cardiac myocytes and cardiac fibroblasts[9]. Urotension II treatment increased collagen mRNA and protein levels in cardiac fibroblasts and augmented cardiac hypertrophy in cultured neonatal cardiomyocytes after transfection with recombinant urotension II receptor. Urotension receptor expression is increased in cardiac myocytes, endothelial cells and fibroblasts in the rat heart after coronary artery ligation and plays a role in the physiology and pathophysiology of the cardiovascular system. Mammalian UTS2R is the most potent endogenous cardiostimulatory peptide identified and emerging evidence in experimental models and in humans indicates that urotensin II may play a cardioprotective role in coronary heart disease and in chronic renal failure[10,11]. Evidence has been also provided that UTS2R and UT-R are expressed in the adrenal gland and adrenal tumors[12,13]. Plasma levels of urotension II have been found to be elevated in patients with heart failure, systemic hypertension, diabetes mellitus, and renal failure[14,15]. With iontophoresis of urotension II into the skin, urotension II mediated a dose-dependent vasodilator response in normal subjects but a dose-dependent vasoconstrictor response in patients with heart failure, suggesting that urotension II may contribute to the increased peripheral vascular tone that occurs in heart failure. UTS2R is a neuropeptide and may play a role in tumor development. The development of antagonists may provide novel treatment for cardiovascular diseases.

In the present study, the identification of the binding site was performed through in silico approach, molecular docking. The three dimensional structure of UTS2R was taken from our previous study[16]. The antagonist molecules were docked into its binding site and its score and binding mode was obtained using Sur-

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(Received : May 8, 2017, Revised : June 16, 2017, Accepted : June 25, 2017)

flex dock module of SYBYL[17]. The antagonist molecules showed good docking score and also had H-bond interactions with active site residues.

2. Materials and Methods

2.1. Ligand Preparation

The UTS2R antagonist (six molecules) was taken from different literatures[18-23]. The ligand molecules were sketched using sketch molecule function in SYBYL. The energy minimization of the molecules was performed using Tripos force field and atomic charges were assigned using Gasteiger Huckel method. The structure of all molecules is shown in Fig. 1.

2.2. Protein Preparation

The protein structure for docking was prepared using protein preparation tool in biopolymer module of SYBYL. The 3D structure of human UTS2R modelled using homology modelling and threading approach was taken. The hydrogen molecules and Gasteiger Huckel charge was added to the protein structure during preparation. The energy minimization was performed for 100 steps utilizing Tripos force field, Gasteiger Huckel charge and Powell method.

2.3. Molecular Docking

Molecular docking was performed utilizing Surflex dock module of SYBYL. Six UTS2R antagonists taken from different literatures were docked into the binding site of human UTS2R protein. The docking algorithm in surflex dock uses an idealized active site called protomol[24]. The protomol is the representation of intended binding site to which the ligand molecules were docked. Two parameters, such as threshold and bloat, determine the extent of a protomol. The automatic mode of protomol generation was followed to identify the active site. Surflex dock uses an empirical scoring function to score the docked ligand conformation which takes into account several terms, including hydrophobic, polar, repulsive, entropic and solvation[25-27]. To evaluate the docking results, the docking scores are expressed in terms of -log10K_d units, where K_d represents a dissociation constant of a ligand.

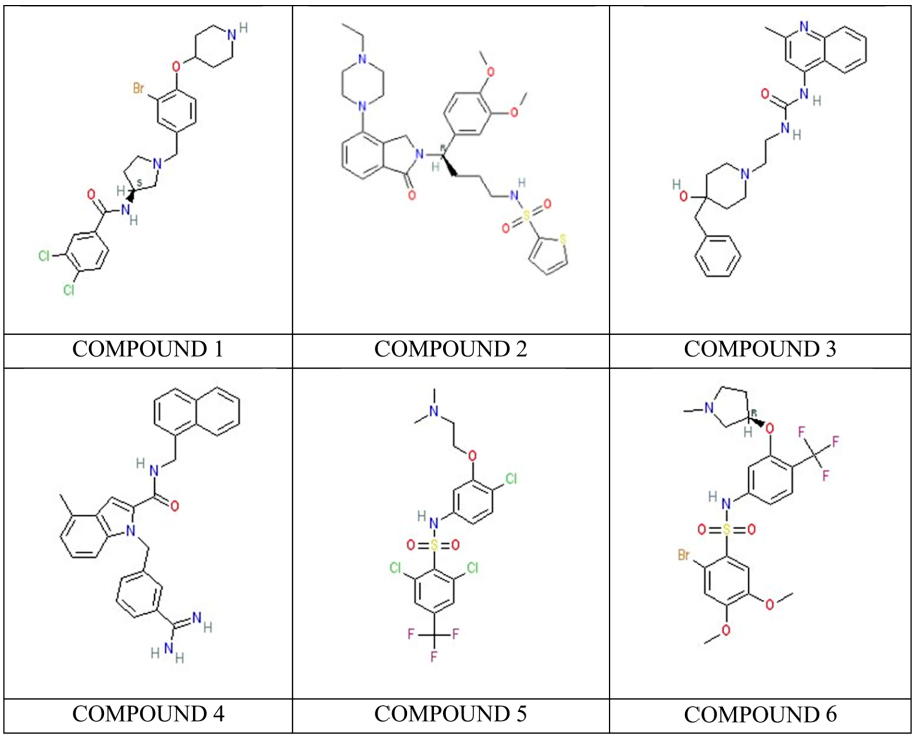

Fig. 1. Chemical structure of UTS2R antagonists.

3. Results and Discussion

3.1. Molecular Docking

Molecular docking was performed for six UTS2R antagonists and 20 different conformations was generated for each molecule and the best conformation was chosen based on surflex score and better interaction with active site residues. The surflex docking score and H-bond interactions for all the molecules are tabulated in Table 1. We found all the molecules possess good

Table 1. Docking scores and H-bond interactions formed between human UTS2R and its antagonist

Compound	Surflex Score	Total no. of H-bonds	Residues involved in forming H-bond
1	5.42	1	GLN278
2	8.26	1	THR304
3	6.25	1	TYR305
4	7.48	4	THR300, LEU299, CYC302
5	5.04	1	ASP47
6	5.68	3	TYR100, THR304

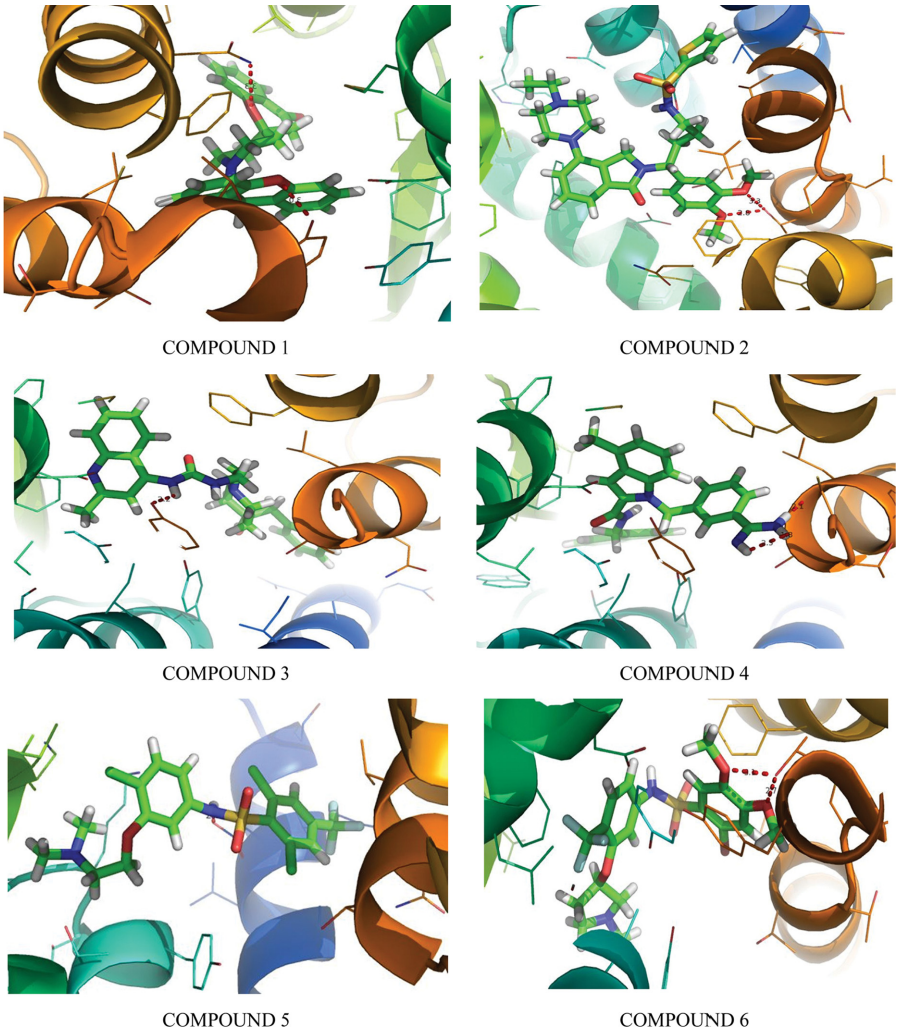

Fig. 2. Docking intercation between UTS2R and its antagonist.

surflex docking scores. Compound 02 obtained higher docking score of 8.26 and forms H-bond interaction with THR304. Compound 03 and compound 04 also possess good docking score of 6.25 and 7.48 respectively. The residues such as GLN278, THR304, TYR305, THR300, LEU299, CYS302, ASP47, TYR100 and THR304 are found in interaction between UTS2R and its antagonists. The interactions of the antagonists with the UTS2R protein are shown in Fig. 2.

4. Conclusion

In this study the docked pose of six UTS2R antagonists was obtained through molecular docking approach. These antagonists bind well within the binding site of UTS2R with higher docking score and shows strong H-bond interaction with the residues such as GLN278, THR304, TYR305, THR300, LEU299, CYC302, ASP47, TYR100 and THR304.

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