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Inhibitory Perspective of New Synthesized Compounds against Angiotensin Receptor: Schrodinger-based Induced-Fit Molecular Docking

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Authors' contributions

This work was carried out in collaboration among all authors. Author SS designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Author DN helped in performing the docking studies and proof reading and author GA did the proof reading. All authors read and approved the final manuscript.

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ABSTRACT

Angiotensin is a hormone that plays a key role in the development of hypertension. Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) are now the most often prescribed drugs to treat hypertension. The present *in silico* study involves exploring the antihypertensive potentials of substituted benzimidazoles and indazole compounds ARC 36, ARC 38, ARC 45, ARC 76, and ARC 77 against the most prominent molecular target Angiotensin Receptor (PDB ID: 4YAY, XFEL structure of Human Angiotensin Receptor)using the software Schrodinger Maestro .Based on glide score, ARC 45, ARC 76 and ARC77 were having the docking score of -7.461 Kcal/mol, -7.947 Kcal/mol and -6.683 Kcal/mol which is comparable to the standard drug (Telmisartan) -5.036.The compounds were further screened for Lipinski's rule for drug-likeliness, and ADME properties. In this study we reported compounds ARC 76 and ARC38had comparable *in silico* parameters to the standard dug Telmisartan and hence necessitating further *in vitro* and *in vivo* studies.

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1. INTRODUCTION

People all around the globe suffer from hypertension, which is a common and deadly ailment. About 30% of the world's population suffers from hypertension [1]. Angiotensin (Ang) is a hormone that plays a key role in the development of hypertension. Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) are now the most often prescribed drugs to treat hypertension [2]. ARBs are responsible to prevent the binding of Angiotensin-II (Ang-II) to the Angiotensin type-1 (AT1) receptor. Although peptide-based Ang-II antagonists have been used in the past, non-peptide AT1 receptor antagonists (NPAT1RA) have gradually superseded the GPCR superfamily owing to their poor oral bioavailability, short period of action, and partial agonistic effect [3]. AT1 receptors are found in the heart, kidneys, brain, adrenal glands, brain, and liver, and NPAT1RAs have a 10,000-to-30,000-fold greater affinity for AT1 receptors than AT2 receptors. Furthermore, NPAT1RAs are highly selective for ARBs, preventing detrimental effects of Ang-II such as vasoconstriction, aldosterone release, salt and water retention, sympathetic nerve activity, and cell proliferation. The renin-angiotensin system (RAS)'s effector peptide, Ang-II, is the major cause of hypertension [4,5]. The action of Ang-II is mediated by unique diverse communities of Ang-II receptors. Losartan, Candesartan, and Irbesartan bind to the biphenylimidazoles with high affinity, but tetrahydroimidazolpyridines like PD123319 and PD123177 are generally resistant to AT1 receptors [6]. The AT1 receptor is a GPCR whose gene may be located on human chromosome 3. Two AT1 receptor isoforms, AT1A and AT1B, have been found in rats, with a 94% identity [7,8]. AT1 receptors are involved in blood pressure regulation, as well as fluid and electrolyte balance. The AT2 receptor is a member of the GPCR superfamily that binds to Ang II with a similar affinity to the AT1 receptor and has a 34 percent sequence similarity to the AT1 receptor [9]. The AT2 receptor is highly expressed throughout embryonic development, although it rapidly declines after birth. Adults have AT2 receptors in their brains, heart, adrenal medulla, kidney, and reproductive organs [10]. There is growing evidence that there are more Ang receptors that are pharmacologically unique from AT1 and AT2. The AT4 receptor is a new binding site with great selectivity and affinity for Ang-IV but poor affinity for Ang-II, which was recently discovered [11].

Angiotensinogen and Ang-I are inert peptides without a known function. Other than Ang-II, angiotensins (Ang-III, Ang-IV, Ang (1-7)) are active peptides that are produced in small amounts and whose physiological relevance is unclear [12]. As a consequence, the RAS' physiologic functions are assumed to be mediated mostly by the highly active peptide Ang II. The primary hormone of the RAS, Ang-II, is involved in both artery width regulation and Na+/water reabsorption, and so plays a crucial role in blood pressure control [13]. Ang-II has been found to constrict arterioles by directly activating AT1 receptors on vascular smooth muscle cells. Peptidase cleavage of Ang-I, Ang 1-9, or Ang-II leads in the formation of Ang 1-7. Peptases such as the ACE homolog ACE-2, neprilysin (NEP), smooth muscle thimetoligopeptidase, and vascular endothelium prolylendopeptidase may all generate Ang 1-7. Losartan was the first orally active non-peptide angiotensin-II receptor antagonist which was developed as a consequence of groundbreaking RAS research (DUP753). Following this discovery, similar non-peptide ARBs were commercialized for the treatment of hypertension, ushering in a new class of anti-hypertensives [14]. Nowadays there are many non peptide ARBs available in the market and it has been seen that the substituted Benzimidazole compounds are more potent than other compounds. Candesartan and Telmisartan are the two drugs which are widely used and have more potency and side effects as compared to other ARBs.

The present *in silico* study involves exploring the angiotensin II receptor blocking potentials of substituted benzimidazole and indazoles i.e., ARC36[4-(1-((2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1*H*-benzo[d]imidazol-2-zl)thiazo le,ARC384'-((2-(thiazol-4-yl)-1*H*-benzo[d]imidazol-1-yl)met hyl)-[1,1'-biphenyl]-2-carboxylic acid, ARC 451-((2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)m e thyl)-2-phenyl-1*H*-benzo[d]imidazole, ARC761-((2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3-phenyl-1*H*-indazole and ARC774'-((3-phenyl-1*H*-indazol-1-yl)methyl)-[1,1'-biphenyl]-2-carbox ylic acid against the most prominent molecular target Angiotensin Receptor (PDB ID: 4YAY,

XFEL structure of Human Angiotensin Receptor) through induced-fit molecular docking approach by applying the software Schrodinger Maestro.

2. MATERIALS AND METHODS

2.1 Preparation of Ligand

Chemdraw® Ultra software was used to create the structures into original 2D form. The Maestro 9.1 software's LigPrep tool was used to prepare the ligands for molecular docking studies, with 20 stereochemical structures per ligand created with proper protonation states at a target pH of 7.0 sing the Epik ionizer. The OPLS 2005 force field was used to build tautomerized, desalted ligands while maintaining the required chiralities of the input files, and an optimized low energy 3D ligand was created [15].

2.2 Preparation of Protein

The receptor co-crystal structures of XFEL structure of human Angiotensin Receptor (PDB ID: 4YAY) was obtained from the RCSB Protein Data Bank. Maestro 9.1's Protein Preparation Wizard was used to create the protein structures. While preparing the biological target, the pre-processed and examined structures were taken. The disulfide bonds, bond ordering, and formal charges were assigned using the Protein Preparation Wizard module of the Schrodinger Maestro 9.1 to get the correct shape. Co-factors, metal ions, water molecules beyond a distance of $5A^0$ in crystal formations, and the hetero group were all eliminated. The Impref utility tool was used to optimize hydrogen atoms by retaining all heavy atoms *in situ*, while the "H-bond assignment" tool was used to optimize the hydrogen-bonding network. The receptor grids for the protein structure were defined by molecular docking such that a range of ligand poses might bind at the expected active site. Grids were constructed and positioned at the ligand's centroid in such a manner that they covered the whole ligand in a cubic box of definite measurement with the following attributes: 1.00 Van der Waals scale factor and 0.25 charge cut off. The docking was done in XP mode, and the final scoring was done only on the energy-minimized postures, which was stated as a Glide score. The highest-scoring ligands were then docked, and the best-docked posture with the lowest Glide score value for each ligand was taken into consideration [15].

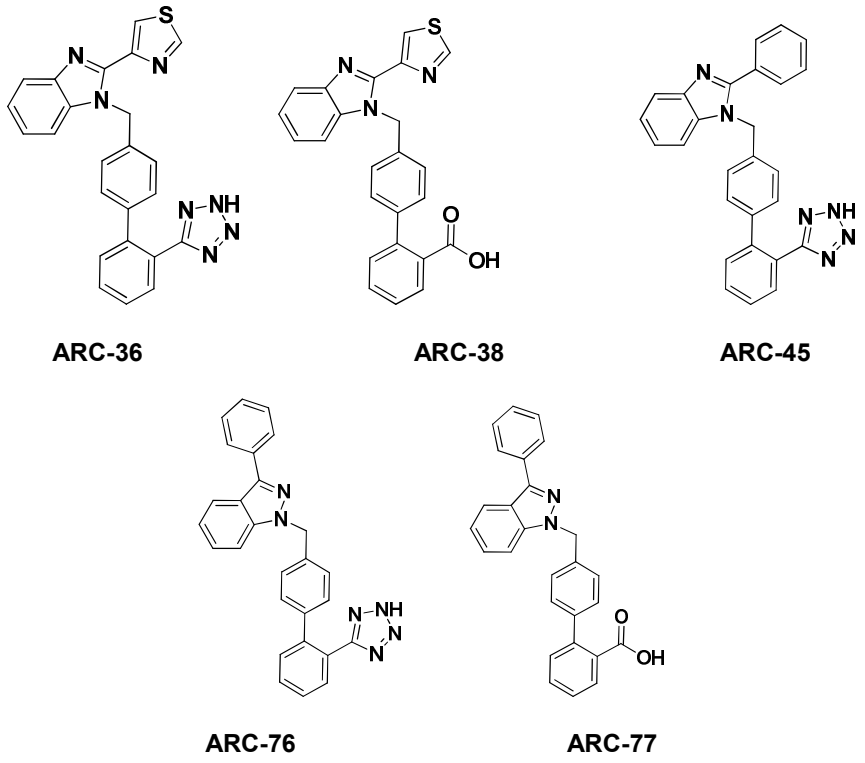


Fig. 1. Chemical structures for induced-fit molecular docking

2.3 Induced-Fit Molecular Docking (IFD)

When the structure of the target protein is known, the structure-based drug design approach is resumed. The stiff receptor was docked with the low-energy ligands, and the quality of the fit into the active site, as well as the expected binding mode, were measured. The ligand interacting with the macromolecule protein (receptor) was represented using a molecular docking methodology in receptor-based computational approaches. IFD expected that the ligand would have an adequate interaction with the target with low energy values. The approach aids in the discovery of low-free-energy conformations and the full eradication of steric conflicts. The maximum number of poses for each ligand remained at 20, with 0.7 Van der Waals scaling for the receptor and 0.5 Van der Waals scaling for the ligand, side chains being reduced, and a 0.18 RMSD value cut off. The compounds were rated based on the information gathered, and a subset was examined experimentally for biological activity. For each ligand, the Glide Score was calculated [15].

2.4 ADME Profiling (Pharmacokinetics)

The Qik Prop module was utilized for determining the imperative PK parameters influencing the processes like absorption, distribution, metabolism and elimination (ADME). The computer-assisted pharmaceutically relevant properties prediction based on physical descriptors involved studies on following parameters: Molecular weight of the compound; Number of Rotatable Bonds; Compound as Donor - Hydrogen Bonds; Compound as Acceptor - Hydrogen Bond; Lipinski Rule of 5 Violations; QP Log K has Serum Protein Binding; QP log P for Octanol/Water; and % Oral human absorption in GIT.

3. RESULTS AND DISCUSSION

3.1 Molecular Docking

The current bioinformatics study revealed that the designed compounds ARC36, ARC38, and ARC45, and ARC 77had a strong interaction with the target by forming hydrogen bonds with the active site residues ARG167 (-5.742 Kcal/mol), ARG167(-6.812 Kcal/mol), ARG167, LYS199 (-7.446 Kcal/mol), and ARG167 (-6.683 Kcal/mol)as well as weak Van der Waals forces with the amino acid residues (Fig. 2). The top candidates have been identified as inhibitor ARC76 (-7.947 Kcal/mol), as shown by their highest docking score (Table 1) by forming hydrogen bonds with the active site residues TYR35. The –OH (hydroxyl) component present in the carboxylic group, as well as the heterocyclic components (thiazole and tetrazole), have been demonstrated to have a vital role in mediating interactions between the chemical molecule and the biological target. The π-π interaction of the amino acids with the aromatic ring present in both molecules is primarily responsible for the binding mode's active force. Hydrophobic interaction due to non-polar residue interaction at the active site of the biological target, as well as water-mediated hydrogen bonding, electrostatic forces, Van der Waals forces, and hydrophobic interaction due to non-polar residue interaction at the active site of the biological target, all interact with the ligands to provide stability to the enzyme-inhibitor complex. As a result, the docking experiments have broadened the possibilities of generating a new class of anti-hypertensive medicines. According to the findings, all the experimental compounds showed better efficacy (ARC 36, ARC 38, ARC 45, ARC 76, and ARC 77).

3.2 Drug Likeliness Property of the Compounds

Molecular properties of the selected compounds are read from this software to satisfy lipinski's rule of five, which is essential for rational drug design. All the compounds showed no violation of all the five rules; not more than 5 hydrogen bond donors, not more than 10 hydrogen bond acceptors, molecular weight of compounds less than 500, partition coefficient (log P) less than 5, rotatable bonds less than 10. In the current study, all the compounds showed good binding affinity, also exhibited drug like characteristics based on Lipinski's rule of 5 that determines if the compound, has certain pharmacological or biological activity to make it an orally active drug in humans [16]. The molecular weights of all the compounds are below 500 Daltons, with less than 5 hydrogen bond donors and 10 hydrogen bond acceptors.

3.3 Pharmacokinetic Predictions

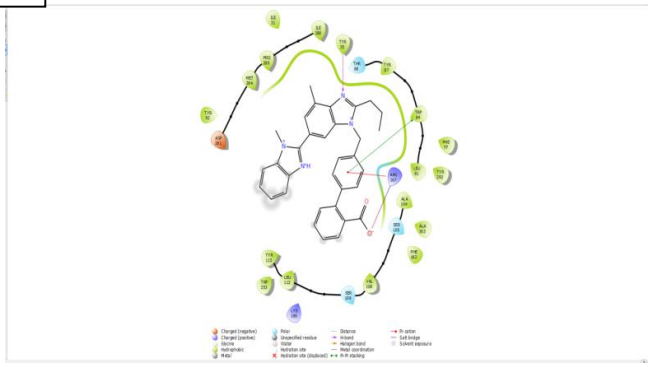
From the predicted pharmacokinetic parameters, the observed values of the drug candidates lay within the prescribed limits. The predicted oral absorption was found to be noteworthy (85-100%) which can be correlated with the oral bioavailability (OB), an imperative parameter for

drug development (Table 2). Higher OB is often associated with the reduction of the dose which invariably decreases the risks of side-effects and toxicity. On the contrary, poor OB leads to high variability in the mediation of pharmacological responses.

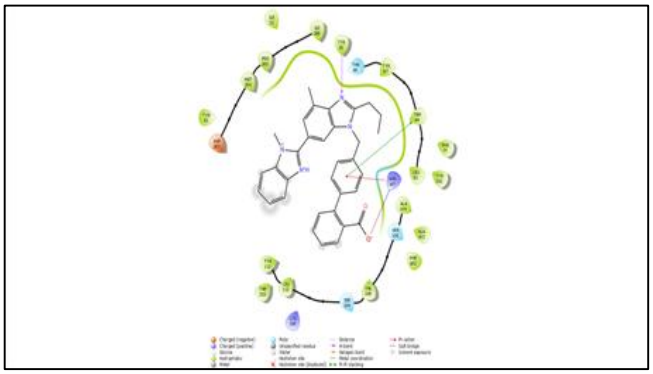
Table 1. Interaction of novel compounds with the Angiotensin Receptor

	Energy (Kcal/mol)	Number of Hydrogen Bonds	Interaction residues
ARC 76	-7.947	1	TYR35,ARG167
ARC 38	-6.812	1	ARG167, LYS199,
ARC 45	-7.446	0	ARG167, LYS199
ARC 36	-5.742	0	ARG167
ARC 77	-6.683	1	ARG167, LYS199
Telmisartan	-5.036	1	TYR35,ARG167

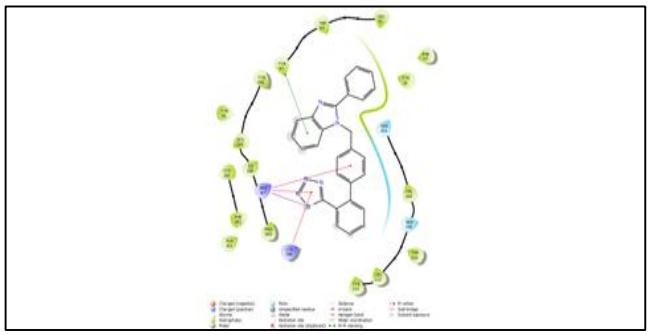
Telmisartan



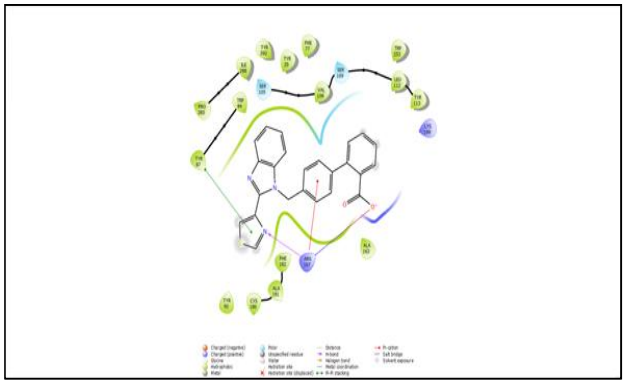
ARC-76



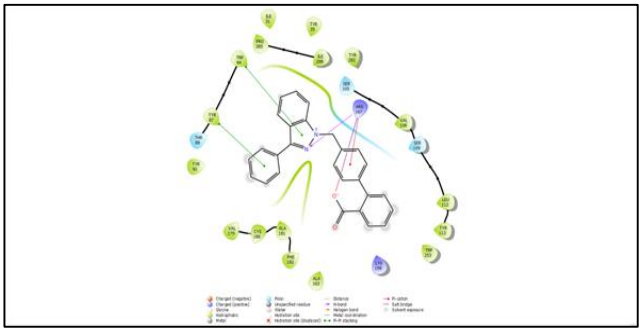
ARC-45



ARC-38



ARC77



ARC36

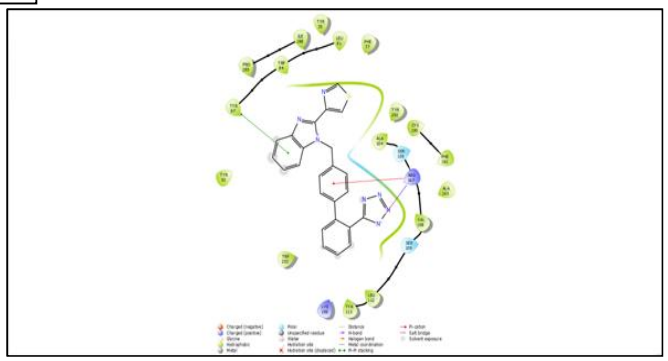


Fig. 2. Molecular docking poses of the compounds

The compound ARC 36expressed log P value of 4.51 which signifies better pharmacological activity owing to a better crossing of biological membranes. However, the predicted lipophilicity profile was suggested to be lower than 5 which confirms with the universal law “Lipinski's rule of five”. A very high lipophilicity results in several troublesome phenomena like low aqueous solubility, noticeably high affinity for the metabolizing enzymes and serum protein binding, etc. Similarly, molecular weight of less than 500, optimized Donor – Hydrogen Bonds of maximum 5, and Acceptor– Hydrogen Bond of maximum 5 played additional benefits to the pharmacological activity as it complied with the “Lipinski's rule of five”.

A significantly high human intestinal absorption was perceived from the fact that the values of molecular weight <500 in case of all the

Table 2. Interaction of novel compounds with the Angiotensin Receptor

Ligand	Glide G score	Glide Energy	XP HBond	XP PhobEn	XP Electro	XP Lipophilic EvdW
ARC76	-7.947	-48.95	1	-2.22	-0.35	-5.213
ARC45	-7.446	-49.279	0	-2.099	-0.359	-4.852
ARC38	-6.812	-44.973	-0.677	-1.4	-0.484	-4.079
ARC77	-6.683	-45.83	-1.148	-1.35	-0.438	-3.782
ARC36	-5.742	-56.324	-0.444	-0.307	-0.524	-4.333
Telmisartan	-5.036	-58.671	-0.473	-1.447	-0.445	-5.398

Table 3. Pharmacokinetic Profile of novel compounds

Parameters	ARC 76	ARC 45	ARC 77	ARC 38	ARC36	Telmisartan
Molecular weight	430.511	428.49	404.467	411.477	435.505	514.626
No. of Rotatable Bonds	3	4	4	4	4	6
Compound as Donor – Hydrogen Bonds	1	1	1	1	1	1
Compound as Acceptor– Hydrogen Bond	5	5	3	5	6	5
Lipinski Rule of 5 Violations	1	1	1	1	0	2
QP Log K Serum Protein Binding	1.053	0.923	1.202	0.654	0.768	1.694
QP log P for Octanol/Water	5.083	5.129	6.667	5.310	4.510	7.744
% Oral human absorption in GIT	94	100	100	85	100	88

molecules, which directly influence OB. The serum protein binding was found to be quite substantial in the case of compounds having value greater than 0.5 represented adequate binding and will serve as a depot. In contrast, the compound having lower values less than 0.5 and the majority of the drug will be in circulation. An optimized binding with the serum protein is reasonably needed for expression of time-bound activity and exhibit better access to the target site. Physiochemical properties and ADME parameters of these ligands, confirms that they can be considered as drug candidates for further studies. In addition, analysis of pharmacokinetic properties such as the partition coefficient and water solubility (QP logS) of the evaluated compounds are within the range. All the pharmacokinetic parameters are within the acceptable range defined for human use, which collectively indicated that the screened compounds could be taken forward, for further analysis.

All the selected 5 ligands showed good docking scores reflecting drug-binding affinities with 4YAY. All the selected ligands showed favorable molecular properties by satisfying Lipinski's rule of 5 and ADME profile. We speculate that the activity of ARC 76, ARC 45, and ARC 38causes the inhibition of the AT_1 receptors from our current *in silico* study.

4. CONCLUSION

In this study, we described docking studies to know that the synthesized substituted benzimidazole and indazole compounds are inhibitors of AT1 receptor and for this these compounds are docked with 4YAY. Three compounds ARC38 4'-((2-(thiazol-4-yl)-1*H*-benzo[d]imidazol-1-yl)methyl)-[1,1'-biphenyl]-2-carboxylic acid, ARC45 1-((2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-phenyl-1*H*-benzo[d]imidazole, ARC76 1-((2'-(2*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-3-phenyl-1*H*-indazole showed good binding affinity and better ADME properties. By leading medicinal chemists in the direction of generating novel heterocycle-based inhibitors that selectively suppress angiotensin receptors, this *in silico* work cleared the path for new anti-hypertensive drug development. These inhibitors form hydrogen bonds, which offer direction for deeper penetration into the active site cavity of the target. These answers to the never-ending hunt for better hypotensive activity in synthetic substances would open doors for academics, contemporary scientists, and scholars, as well as extend pharmacotherapeutic options.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Han XF, He X, Wang M, Xu D, Hao LP, Liang AH, Zhang J, Zhou ZM. Discovery of novel, potent and low-toxicity angiotensin II receptor type 1 (AT1) blockers: Design, synthesis and biological evaluation of 6-substituted aminocarbony lbenzimidazoles with a chiral center. Eur J Med Chem. 2015; 103:473-87.
2. Siragy H. Angiotensin II receptor blockers: review of the binding characteristics. The Am J Cardiol. 1999; 84(10):3-8.
3. Dzau VJ, Sasamura H, Hein L. Heterogeneity of angiotensin synthetic pathways and receptor subtypes: physiological and pharmacological implications. J Hypertens. 1993;11 (3):S13-8.

4. Wan Y, Wallinder C, Plouffe B, Beaudry H, Mahalingam AK, Wu X, Johansson B, Holm M, Botoros M, Karlén A, Pettersson A. Design, synthesis, and biological evaluation of the first selective non peptide
AT2 receptor agonist. J Med Chem. 2004;47(24):5995-6008.
5. Bali A, Bansal Y, Sugumaran M, Saggu JS, Balakumar P, Kaur G, Bansal G, Sharma A, Singh M. Design, synthesis, and evaluation of novelly substituted benzimidazole compounds as angiotensin II receptor antagonists. Bioorg Med Chem Lett. 2005;15 (17):3962-5.
6. Shah DI, Sharma M, Bansal Y, Bansal G, Singh M. Angiotensin II–AT1 receptor antagonists: Design, synthesis and evaluation of substituted carboxamido benzimidazole derivatives. EurJMed Chem. 2008;43(9):1808-12.
7. Cappelli A, Pericot Mohr GL, Gallelli A, Rizzo M, Anzini M, Vomero S, Mennuni L, Ferrari F, Makovec F, Menziani MC, De Benedetti PG. Design, synthesis, structural studies, biological evaluation, and computational simulations of novel potent AT1 angiotensin II receptor antagonists based on the 4-phenylquinoline structure. J Med Chem. 2004;47(10):2574-86.
8. Rosenström U, Sköld C, Lindeberg G, Botros M, Nyberg F, Karlén A, Hallberg A. Design, synthesis, and incorporation of a β-turn mimetic in angiotensin II forming novel pseudopeptides with affinity for AT1 and AT2 receptors. J Med Chem. 2006;49(20):6133-7.
9. Kaur N, Kaur A, Bansal Y, Shah DI, Bansal G, Singh M. Design, synthesis, and evaluation of 5-sulfamoyl benzimidazole derivatives as novel angiotensin II receptor antagonists. Bioorg Med Chem. 2008;16(24):10210-5.
10. Wang JL, Zhang J, Zhou ZM, Li ZH, Xue WZ, Xu D, Hao LP, Han XF, Fei F, Liu T, Liang AH. Design, synthesis and biological evaluation of 6-substituted aminocarbonyl benzimidazole derivatives as nonpeptidic angiotensin II AT1 receptor antagonists. Eur J Med Chem. 2012;49:183-90.
11. Bao X, Zhu W, Yuan W, Zhu X, Yan Y, Tang H, Chen Z. Design, synthesis and evaluation of novel potent angiotensin II receptor 1 antagonists. Eur J Med Chem. 2016;123:115-27.
12. Dhanoa DS, Bagley SW, Chang RS, Lotti VJ, Chen TB, Kivlighn SD, Zingaro GJ, Siegl PK, Patchett AA, Greenlee WJ. Non-peptide angiotensin II receptor antagonists. 1. Design, synthesis, and biological activity of N-substituted indoles and dihydroindoles. J Med Chem. 1993;36(26):4230-8.
13. Zhang J, Wang JL, Zhou ZM, Li ZH, Xue WZ, Xu D, Hao LP, Han XF, Fei F, Liu T, Liang AH. Design, synthesis and biological activity of 6-substituted carbamoyl benzimidazoles as new non peptidic angiotensin II AT1 receptor antagonists. Bioorg MedChem. 2012;20 (14):4208-16.
14. Dhanoa DS, Bagley SW, Chang RS, Lotti VJ, Chen TB, Kivlighn SD, Zingaro GJ, Siegl PK, Patchett AA, Greenlee WJ. Design, synthesis, and biological activity of N-substituted (phenyl amino) phenyl acetic acids and acyl sulfonamides. J Med Chem. 1993;36 (26):4239-49.
15. Joseph TM, Mahapatra DK. Bacterial DNA Gyrase (Topoisomerase) Inhibitory Potentials of Heterocyclic Natural Products: Investigations through Induced-Fit Molecular Docking Approach. Res Rev J Drug Design Discov. 2018;5(2):7-9.
16. Lipinski C A, et al. Adv Drug Deliv Rev. 2001;46:3.

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