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Original Article

IN SILICO DESIGN AND MOLECULAR DOCKING STUDIES OF SOME 1, 2-BENZISOXAZOLE DERIVATIVES FOR THEIR ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT

Objective: *In silico* design and molecular docking of 1,2-benzisoxazole derivatives for their analgesic and anti-inflammatory activity using computational methods.

Methods: *In silico* molecular properties of 1,2-benzisoxazole derivatives were predicted using various software's such as Chemsketch, Molinspiration, PASS and Schrodinger to select compounds having optimum drug-likeness, molecular descriptors resembling those of standard drugs and not violating the 'Lipinski rule of 5'. Molecular docking was performed on active site of nicotinic acetylcholine receptor (PDB: 2KSR) for analgesic activity and COX-2 (PDB: 6COX) for anti-inflammatory activity using Schrodinger under maestro molecular modelling environment.

Results: From the results of molecular docking studies of 1,2-benzisoxazole derivatives, all the compounds showed good binding interactions with Nicotinic acetylcholine receptor and COX-2. Compounds 4a and 4c showed highest binding scores (-7.46 and-7.21 respectively) with nicotinic acetylcholine receptor and exhibited maximum analgesic activity. Compound 4a showed highest binding score (-7.8) with COX-2 and exhibited maximum anti-inflammatory activity.

Conclusion: All the derivatives of 1,2-benzisoxazole showed good analgesic and anti-inflammatory activity as predicted using molecular docking on respective receptors.

Keywords: *In silico* design, molecular docking, 1, 2-Benzisoxazole, Analgesic activity, Anti-inflammatory activity.

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INTRODUCTION

Current trends in the drug design are to develop new clinically effective agents through the structural modification of lead molecules. Molecular recognition plays a key role in promoting fundamental biomolecular events like enzyme-substrate interactions. In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation, in turn, may be used to predict the strength of association or binding affinity between two molecules.

An analgesic is any member of the diverse group of drugs used to relieve pain (achieve analgesia). Analgesic drugs act in various ways on the peripheral and central nervous systems; they include paracetamol (acetaminophen), the non-steroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, narcotic drugs such as morphine, synthetic drugs with narcotic properties such as tramadol, and various others.

Inflammation is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a protective attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue. Inflammation is not a synonym for infection. In the absence of inflammation, wounds and infections would never heal and progressive destruction of the tissue would compromise the survival of the organism. However, an inflammation that runs unchecked can also lead to a host of diseases, such as hay fever, atherosclerosis, and rheumatoid arthritis. The cyclooxygenase enzyme inhibited by NSAIDs was discovered to have at least 2 different versions: COX-1 and COX-2. Research suggested that most of the adverse effects of NSAIDs were mediated by blocking the COX1 (constitutive) enzyme, with the analgesic effects being mediated by the COX-2 (inducible) enzyme. The COX-2 inhibitors were thus developed to inhibit only the COX-2 enzyme.

Benzisoxazole is an aromatic organic compound with a molecular formula C_7H_5NO containing a benzene fused isoxazole ring structure. Being a heterocyclic compound, benzisoxazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. Its aromaticity makes it relatively stable, although as a heterocycle, it has reactive sites which allow for functionalization. Molecules with substituted 1, 2-benzisoxazole often exhibit anti-inflammatory, tuberculostatic, sedative, analgesic, neuroleptic and antibacterial activity [1-5].

MATERIALS AND METHODS

In silico molecular studies [6-8]

In silico modeling of the molecules using various software such as, Chemsketch, Molinspiration and Schrodinger to select compounds having optimum drug-likeness, molecular descriptors resembling those of standard drugs and not violating the 'Lipinski rule of 5'.

Molecular descriptors analysis

A descriptor is a number that describes a particular molecular property of a drug molecule. The main properties of a drug that appear to influence its activity are its lipophilicity/hydrophobicity, electronic effects within the molecule, molecular volume, polar surface area of the molecule, number of rotatable bonds (nrob) and steric effects (size and shape of the molecule). The parameters are calculated using Molinspiration software.

Lipinski's rule of five

Lipinski's rule of five provides a method of assessing the likelihood that a given molecule could be orally bioavailable based on a series of physicochemical requirements, not more than one of which should be violated. Molecules violating any of these rules may have problems with bioavailability. The analysis was carried out to find whether the newly proposed analogs obeyed this rule using Molinspiration software.

Drug-likeness

Drug-likeness is the complex balance of various molecular properties and structural features which determine whether a particular molecule is similar to the known drugs. Drug-likeness is calculated by using molinspiration software.

Molecular docking

For analgesic and anti-inflammatory activity structure of synthesized molecules were docked with the molecular targets using Schrodinger software. Crystallographic structures of the targets of interests were obtained from PDB (Protein Data Bank) and saved in standard 3D coordinate format. Entire docking processes were carried out on Schrodinger under maestro molecular modelling environment.

Protein preparation

The procedure starts with a protein and a co-crystallized ligand. Prepare the co-crystallized ligands by correctly defining multiple bonds and adding hydrogens. Normally, proteins are provided without attached hydrogens. When hydrogens are present, all are deleted except those in a peptide bond. Neutralize residues that do not participate in the salt bridges and that are more than a specified distance from nearest ligand atom. The script also sets the tautomeric state which is assumed to be neutral, by considering potential metal ligation and the hydrogen interactions. Preprocess the receptor before grid preparation. This is necessary, as the judgment made by the preparation procedure need not be correct always. The optimization of the protein is carried out by adding hydrogens to the protein, to any cofactors and to any added structural waters and the final step carries out series of restrained minimization on the protein-ligand complex.

Ligand preparation

LigPrep generates energy minimized 3D molecular structures. It is used for the versatile generation of accurate 3D molecular models. **LigPrep** goes far beyond simple 2D to 3D structure conversions by including tautomeric, stereochemical and ionization variations as well as energy minimizations and flexible filters to generate fully customized ligand libraries that are optimized for further computational analyses.

Docking

The generated structures of various conformations of drug-like molecules using Ligprep was then docked into the binding site of receptor after generating a receptor grid around the site using glide. The docking was conducted using XP GLIDE (Extra Precision).

RESULTS AND DISCUSSION

In silico molecular analysis of different analogues of 1, 2 Benzisoxazole were done and are given in table no 1.

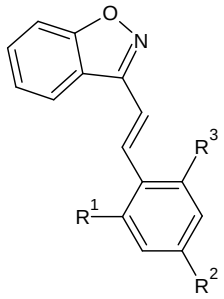

Table 1: Physicochemical descriptors of proposed analogues

Compounds	R	Molecular formula	Molar refractivity (cm^3)	Molar volume (cm^3)	Parachor (cm^3)	Polarizability (cm^3)-[24]	clog P
4a	R^1-H, R^2-H, R^3-H	$C_{15}H_{11}NO$	71.87±0.3	182.7±3.0	493.9±4.0	28.49±0.5	4.347
4b	R^1-Cl, R^2-H, R^3-H	$C_{15}H_{10}ClNO$	76.77±0.3	194.7±3.0	529.7±4.0	30.43±0.5	4.797
4c	R^1-H, R^2-Cl, R^3-Cl	$C_{15}H_9Cl_2NO$	81.67±0.3	206.6±3.0	565.6±4.0	32.37±0.5	4.986
4d	R^1-H, R^2-$N(CH_3)_2$, R^3-H	$C_{17}H_{16}N_2O$	86.19±0.3	220.7±3.0	595.9±4.0	34.16±0.5	4.449
4e	R^1-H, R^2-F, R^3-H	$C_{15}H_{10}FNO$	71.87±0.3	186.9±3.0	501.0±4.0	28.49±0.5	4.51

Analysis of Lipinski's Rule of Five was carried out for the proposed analogs. The results showed that all the analogs obey the rule and are given in table no 2.

Table 2: Analysis of lipinski rule of five

Compound	Log P	Molecular weight	nHDon	nHAcc	nrotb	N violation
4a	4.347	221.259	2	0	2	0
4b	4.797	255.704	2	0	2	0
4c	4.986	290.149	2	0	2	0
4d	4.449	264.328	3	0	3	0
4e	4.51	239.249	2	0	2	0

Drug-likeness analyses of the derivatives showed that the balance of various molecular properties and structural features are similar to the known drugs. The data obtained were shown in table no 3.

Table 3: Drug-likeness analysis of proposed analogues

Compounds	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand
4a	0.41	0.11	-0.70	0.24
4b	0.26	-0.04	-0.78	0.19
4c	0.26	-0.04	-0.72	0.00
4d	0.40	0.06	-0.51	0.39
4e	0.49	0.17	-0.53	0.35

From the results of molecular docking studies of 1,2-benzisoxazole derivatives, all the compounds showed good binding interactions with Nicotinic acetylcholine receptor (PDB: 2KSR) and COX-2(PDB: 6COX). Compounds 4a and 4c showed

highest binding scores (-7.46 and-7.21 respectively) with nicotinic acetylcholine receptor and are showed in table no 4. Compound 4a showed highest binding score (-7.8) with COX-2 and are showed in table no 5.

Table 4: Glide score with nicotinic acetylcholine (PDB: 2KSR) receptor

Compound	Glide g score	Glide h bonds	Glide EVDW
4a	-7.46	-0.62	-4.08
4b	-6.32	-0.7	-4.2
4c	-7.21	-0.7	-4.01
4d	-6.86	-0.7	-4.14
4e	-5.05	-0.7	-3.97

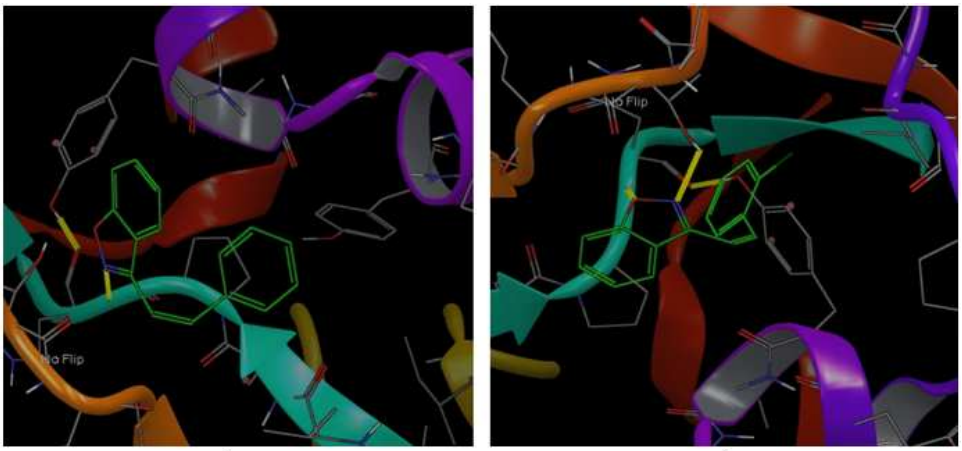

Fig. 1: Images of derivatives with highest glide score docked to nicotinic acetylcholine receptor

Table 5: Glide score with COX-2 (PDB: 6COX) receptor

Compound	Glide gscore	Glide hbonds	Glide Evdw
4a	-7.8	-2.35	-2.45
4b	-6.82	-0.36	-3.04
4c	-5.92	-0.7	-2.66
4d	-5.08	-0.53	-3.16
4e	-5.61	-0.37	-2.86

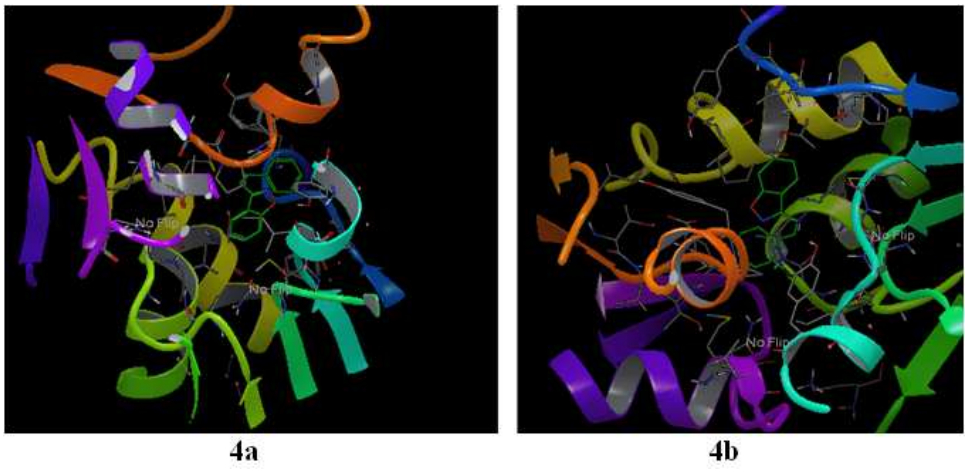

Fig. 2: Images of derivatives with highest glide score docked to COX-2 receptor

CONCLUSION

This research work was focused on design and development of novel 1, 2-benzisoxazole derivatives as an analgesic, and anti-inflammatory drug. *In-silico* molecular modelling of molecules was done by ACD Chemsketch, Molinspiration, PASS online and schrodinger software. The analogues showed good binding affinity with COX-2 and Nicotinic acetylcholine receptors. Compounds 4a and 4c showed highest binding scores (-7.46 and-7.21 respectively) with nicotinic acetylcholine receptor and Compound 4a showed

highest binding score (-7.8) with COX-2. The analogues can be subjected to further detailed studies for consideration as drug candidates.

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CONFLICT OF INTERESTS

Declare none

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