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ARTICLE

Design and *in silico* Evaluation of Some Pyridine Derivatives for Antihypertensive Activity

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ABSTRACT

A novel series of 2,4,6-trisubstituted 1,4-dihydropyridine derivatives was designed and utilized for the computational studies for predicting absorption, distribution metabolism, elimination (ADME), pharmacological profile, toxicity and molecular docking of these derivatives. Some of the derivatives were found to have significant antihypertensive activity without toxicity.

KEYWORDS

Antihypertensive activity, *in silico* ADME studies, Toxicity, Molecular docking, Calcium channel blocker receptor.

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INTRODUCTION

Heterocyclic compounds play key role in the drug discovery and design due to variety of biological properties [1]. The existence of the pyridine ring system in natural products such as NAD nucleotides, pyridoxal (vitamin B_6), pyridine alkaloids and variety of pharmacologically important molecules has rendered this molecule a prime target for scientific research.

It has a conjugated system of six π-electron accurately as benzene and delocalized over the heterocyclic ring [2]. Pyridine and its simple derivatives are stable and comparatively unreactive liquids, with strong unpleasant penetrating odours [3]. Pyridine molecules possess π-stacking ability, H-bonding capability, they are thermally stable, which makes them suitable molecule for drug design approach [4].

EXPERIMENTAL

Designing of library of compounds

Pass online study: The prediction of activity spectra of substances (PASS) is a tool for online prediction of biological activity/or toxic and side effects of compounds [5,6].

Pharmacokinetics and toxicity study: ADME-Tox play an important role in medicinal application of drug candidate. ADME is well known in pharmacology and drug design and show a significant applications in both toxicology and green chemistry design (uptake and fate of a chemical in the body). ADME when predicted in the drug development process, helps to eliminate the molecules, having poor pharmacokinetics

properties and contributes for significant results in drug development. The safety and efficacy of a drug molecule predicted by *in silico* ADME studies, are important for regulatory approval too. Various software are available to predict the ADMET properties of newly synthesized drugs.

SwissADME is free online software used for prediction of pharmacokinetics, medicinal chemistry friendliness and drug-likeness. Protox-II software used to predicate the toxicity of the compound Protox-II tool predicts acute toxicity, hepatotoxicity, carcinogencity, mutagenicity and immunotoxicity [5,6].

Molecular docking: Computational molecular docking is widely used for the study of protein-ligand interactions and for drug discovery and development. Process includes identification of target, search for the target in PDB database, study of a crystallographic structure of the target, preparation of the target by adding missing groups and extracting the bound complexes, docking predicts the bound conformation and the binding free energy of small molecules to the target. Single docking experiments are useful for exploring the function of the target and virtual screening in which a large library of compounds is docked and ranked may be used to identify new inhibitors for drug development. Molecular docking is performed using V-Life MDS 4.6 MDS software.

Preparation of protein: The PDB structures (www.rcsb.org) were downloaded and energy minimization of the protein complex. All the bound water molecules, ligands and confactors were removed (preprocess) from the proteins which should be taken in PDB format. Incomplete residues were completed and missing residues were added in the protein. The complex obtained was minimized using Merck molecular force field.

Preparation of ligands: Structure of the ligands were sketched using built VLife 2 draw taken in mol format. Converts it into 3D structure and perform a geometry decrease of the ligands Merck Molecular force fields (MMFF) with default settings were used for the ligand minimization.

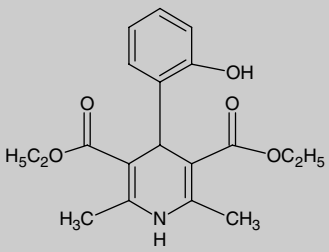
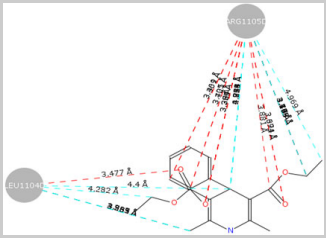
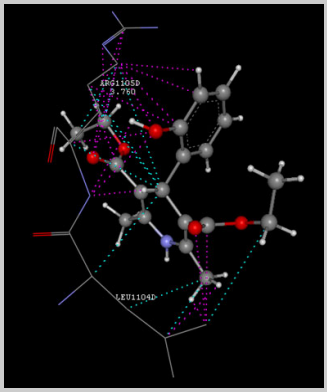
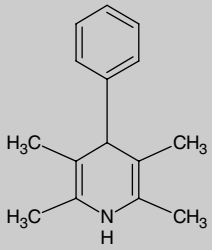
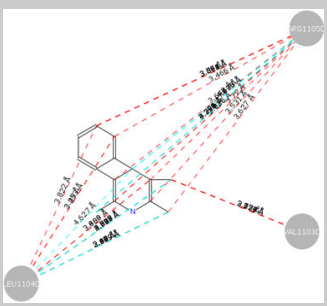
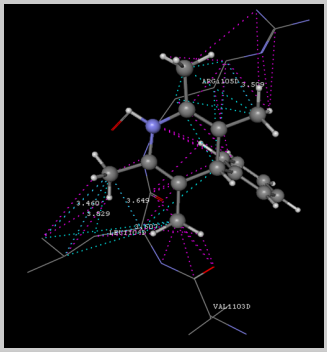
Receptor structure: Molecular docking by using calcium channel blocker receptor was studied whereas the structural basis of Ca^{2+} selectivity of a voltage-gated calcium channel was carried out using PDB ID 4MS2.

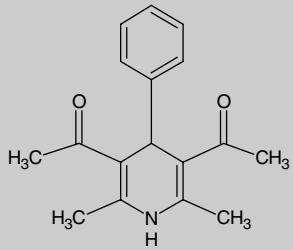
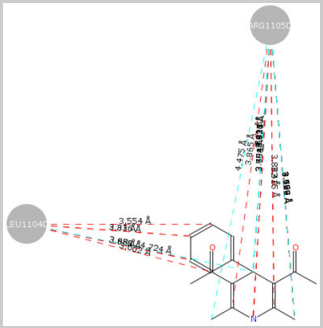
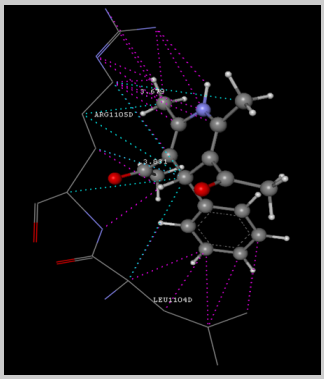
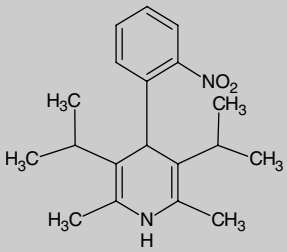
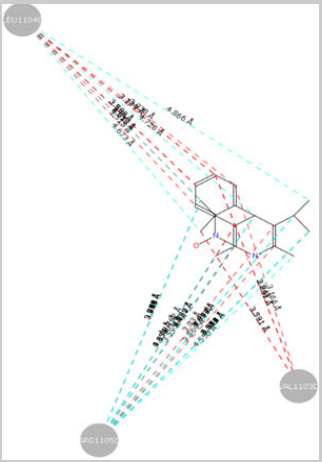
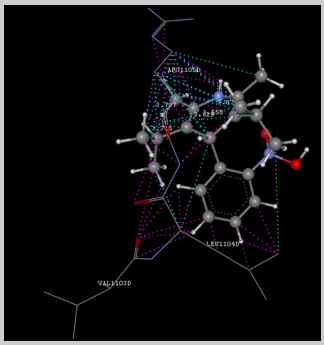
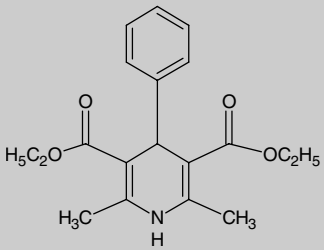
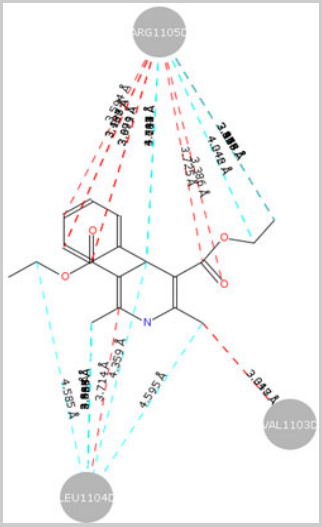
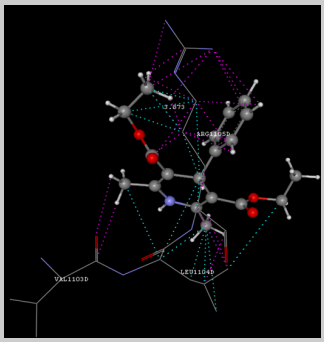
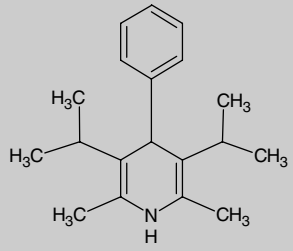
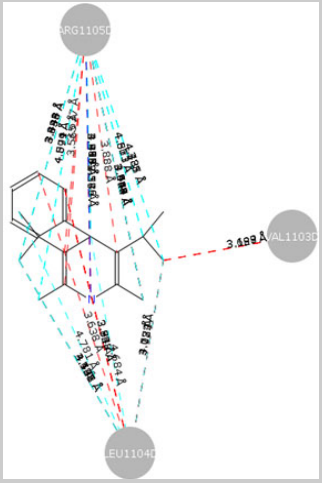
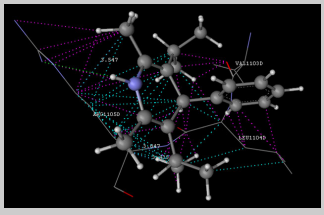
RESULTS AND DISCUSSION

The *in silico* evaluation of pharmacological profile (PASS online) and physico-chemical properties (Swiss ADME) and toxicity prediction by PROTOX-II are summarized in Table-1, which indicated that all the investigated compounds present a high gastrointestinal absorption. The evaluation of pharmacological activity by (passonline) result presence in described (Table-2) indicated that AG7 compound posses high antihypertensive potential than other compounds. From the results obtained using protox-II computational tool only AG5 compound was found to have potential hepatotoxicity and carcinogencity (Table-3). The radar Fig. 1 shows the predicted toxicity in percentage.

Molecular docking: Docking study was performed on Vlife 4.6.08032021. The GRIP-based ligand docking was performed using specific cavity of the receptor. The minimum dock score of the complex were measured by PLP scoring function. Docking studies of the newly design pyridine deri-

TABLE-1
DESIGN OF LIBRARY OF COMPOUNDS

Compd. code	Structure	Antihypertensive		2D structure	3D structure
		Pa	Pi		
AG2		0.852	0.004		
AG3		0.894	0.004		

AG4		0.821	0.004		
AG5		0.922	0.004		
AG7		0.940	0.004		
AG8		0.837	0.004		

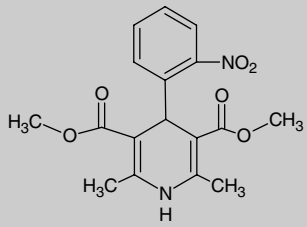
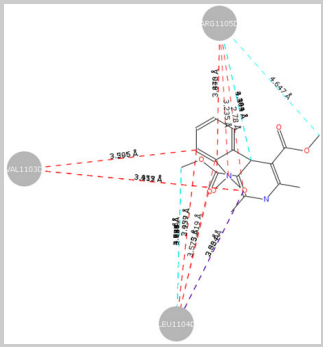
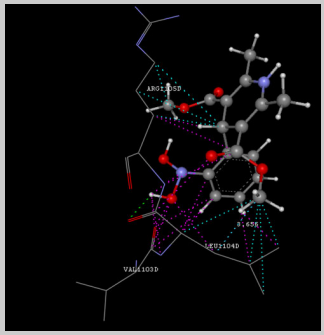
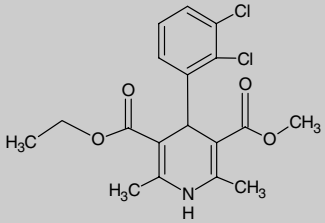
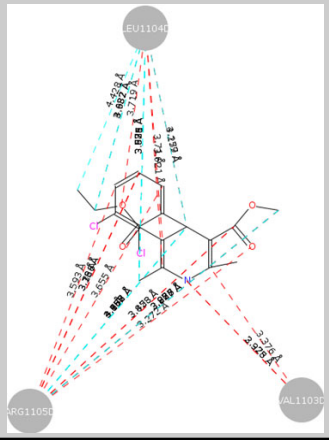
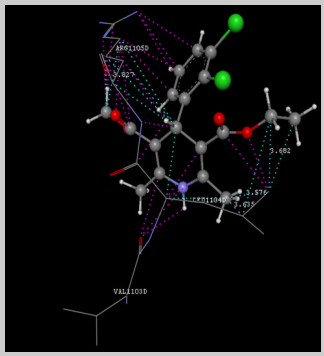
Nifedipine		0.965	0.004		
Felodipine		0.927	0.004		

TABLE-2
ADME PREDICTION OF COMPOUNDS BY SWISS ADME

Compd. No.	m.w. (g/mol)	log P o/w	Water solubility	GI	BBB	Bioavailability score
AG2	345.39	2.54	-3.26	High	No	0.55
AG3	213.32	3.36	-3.42	High	Yes	0.55
AG4	269.34	2.55	-2.93	High	Yes	0.55
AG5	314.42	3.36	-4.61	High	Yes	0.55
AG7	329.39	3.03	-3.76	High	Yes	0.55
AG8	269.42	4.45	-4.53	High	Yes	0.55
Nifedipine	346.33	1.64	-3.15	High	No	0.55
Felodipine	384.25	3.65	-4.44	High	Yes	0.55

TABLE-3
TOXICITY PROFILES OF COMPOUNDS BY PROTOX-II

Compd. code	AG2	AG3	AG4	AG5	AG7	AG8	Nifedipine	Felodipine
Predicted LD_{50} (mg/kg)	3000	1700	3000	202	3000	3000	202	250
Predicted accuracy (%)	70.97	67.38	68.07	67.38	72.9	67.38	70.97	100
Hepatotoxicity	Inactive	Inactive	Inactive	Active	Inactive	Inactive	Active	Inactive
Carcinogenecity	Inactive	Inactive	Inactive	Active	Inactive	Inactive	Inactive	Inactive
Immunotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Mutagenecity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive

vative using the structural basis of Ca^{2+} selectivity of a voltage-gated calcium channel PDB code 4MS2 for antihypertensive activity (Fig. 2). All the ligands showed a similar interaction with three strong hydrogen-bonding between H-N of the pyridine derivative with three amino acids in the side pocket (Table-1) which may explain the increase of high predicted activity of the designed ligands.

The outcomes of compiled data of molecular docking, pharmacological activity and toxicity are summarized in Table-4 and also graphical representation in Fig. 3. All the investigated synthesized compounds a docking score is 38.99 in AG4 compound comparatively other compound docking score is less than AG4 compound. The pharmacological activity in compiled data AG7 compound is maximum anti-hypertensive activity compare with reference felodipine. In toxicity profile, compound AG5 is found to be hepatotoxicity and carcinogenicity. Since, compound AG5 having nitro substitution on phenyl ring show the toxicity compare with reference nifedipine also the nitro substitution on phenyl ring also toxic. This is compiled study of the synthesized compounds.

TABLE-4
DOCKING, PASS ONLINE, TOXICITY DATA FOR DESIGNED COMPOUNDS

Compd. code	AG4	AG5	AG3	AG2	AG7	AG8	Nifedipine	Felodipine
Dock score	-38.99	-33.23	-29.77	-27.84	-23.84	-27.25	-13.965	-43.317
Pass online (Pa)	0.821	0.922	0.894	0.852	0.940	0.837	0.965	0.927
Hepatotoxicity	Inactive	Active	Inactive	Inactive	Inactive	Inactive	Active	Inactive
Carcinogenecity	Inactive	Active	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Immunotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Mutagenecity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive

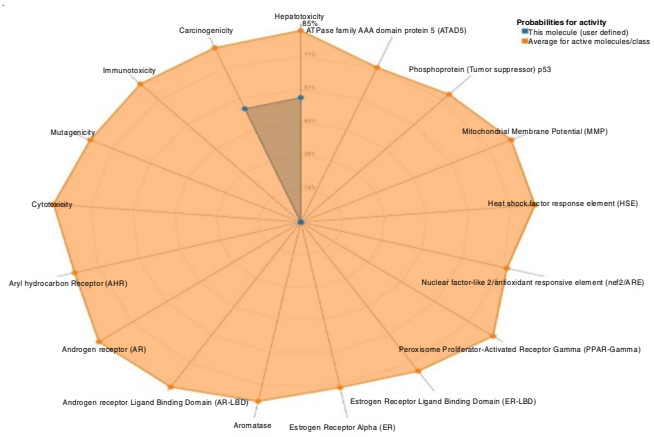


Fig. 1. Radar figure of predicted toxicity of compound AG5

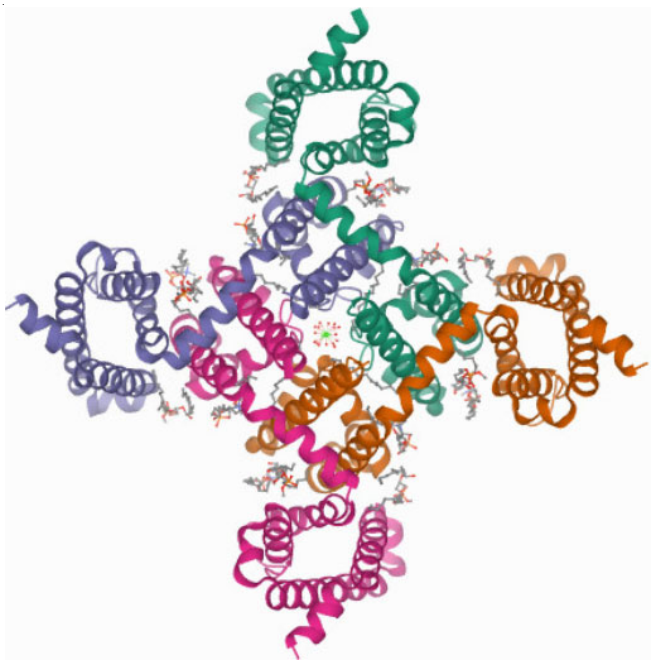


Fig. 2. Structural basis of Ca^{2+} selectivity of a voltage-gated calcium channel (3D) view

Conclusion

In this study, the biological activity, toxicity of some 2,4,6-trisubstituted 1,4-dihydropyridine derivatives were predicted using computationl tools. This confirmed that the designed compounds revealed the good bioavailability andalso high gastrointestinal absorption and only one designed pyridine derivatives AG5 was found to posses hepatoxicity and carcinogencity. Docking scores yield a high activity of compound AG4 compared to reference drug nifedipine. The results obtained

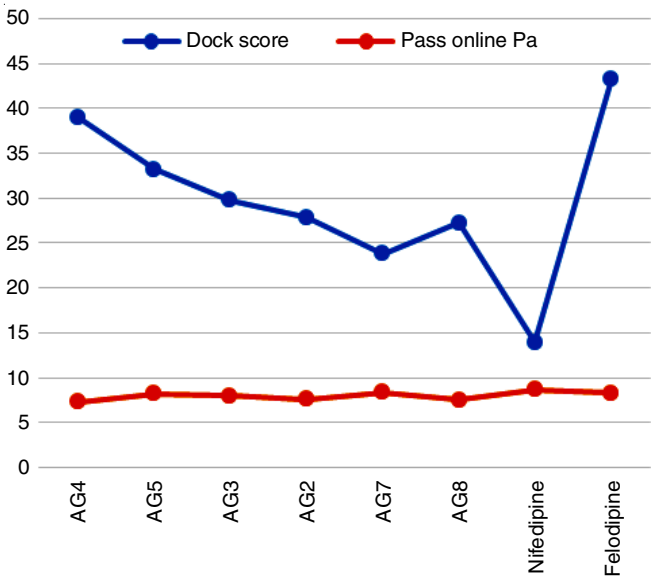


Fig. 3. Compiled data of docking and passonline Pa of compounds

by computational tool can complete the *in silico* toxicity test to improve the predictive toxicity and safety assessment of these pyridine derivatives.

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