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Designing of next-generation dihydropyridine-based calcium channel blockers: An *in silico* study

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ABSTRACT

Hypertension is a most prevalent problem in this world and it is seen among all races and all social classes. The trend of mortality rate has been increasing day by day. But different drug molecules have been utilised to control hypertension and associated problems. Dihydropyridine (DHP)-based drugs, which are calcium channel blockers (CCBs), are prescribed as a first-line option. It is well documented that minor changes to the core scaffold of an existing medicine can significantly improve its efficacy. The goal of this research was to develop prospective antihypertensive medicines using a 1,4-DHP scaffold and investigate their binding mechanisms with calcium channel proteins having Protein Data Bank IDs 5KLS and 5KLB. The binding efficiency of newly created prospective compounds such as calcium CCBs was predicted using molecular docking and molecular dynamics (MD) simulation analyses in this study. The binding energy of the proteins with the newly created compounds ranged between -6.86 and −10.05 kcal/mol (Autodock 4.2). Compound 10 with the proteins had the lowest binding energies of −10.05 and −9.99 kcal/mol, which were lower than the commonly used drugs, amlodipine and nifedipine. The molecular mechanics/generalized born surface area calculations based on dynamics yielded good results, and MD simulation indicates that the complexes are stable.

INTRODUCTION

Hypertension is a challenging global problem and is increasing day by day in every community (NCD-RisC, 2021). It is reported that the deaths due to hypertension-related diseases are approximately 9.4 million annually (Guwatudde *et al*., 2015). There are different types of antihypertensive medicines to treat this problem. The dihydropyridine (DHP)-based calcium channel blockers (CCBs) are considered frontline agents in hypertension treatment and support cardiovascular benefits (Pitt *et al*., 2000; Whelton *et al*., 2018). These CCBs are safe as they do not require routine electrolyte or kidney function monitoring, nor do they cause diuresis (Caballero-Gonzalez *et al*, 2015; Li *et al*., 2014; Makani *et al*., 2011; Mann and Hilger *et al*., 2019; Whelton *et al*., 2018). Basically, CCBs work on calcium channel proteins. Calcium channel proteins consisting of calcium selective pores are found in different parts of the human plasma membrane, like cardiac muscle neurons, vascular smooth muscles, etc. (Catterall, 2011), and controls various physiological processes including cardiac muscle contraction and neurotransmitter release (Dolphin, 2016). Calcium ion movement through the CaV1.2 channel of hypertensive patients takes place more and CCBs control these movements (Johnson *et al*., 2020). Antihypertensive drugs prevent the entrance of calcium into the cell by blocking calcium channels, thereby exhibiting the antihypertensive effect. CCBs also shows renoprotective effects (Jadhav *et al*., 2021). 1,4-DHPs like amlodipine and nifedipine have been used as antihypertensive drugs successfully for the last several decades (De Luca *et al*., 2019; Karthick *et al*., 2022). Any molecule that can block CaV1.2 could be useful in the treatment of hypertension. It is generally known that DHPs have the ability to block calcium channels, and it has been demonstrated that even little alterations in the structure of the DHP ring can result in significant changes in pharmacological effects. The biological action of DHP calcium channel antagonists has been observed to be affected by substituents at different locations in the DHP ring (Jamalian *et al*., 2011). The 1,8-acridinedione scaffold showed a

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variety of biological activities that were improved (Moallem *et al*., 2015; Xiong *et al*., 2018). Few works reported that acridinedione moiety-based derivatives had lower calcium antagonist activity (Jamalian *et al*., 2011). It is also reported that acridinedione-based derivatives possess the vasorelaxant effect (Imenshahidi *et al*., 2012). Another research group investigated their effects on vascular potassium channels, and the potassium channel in particular has several general features analogous to the calcium channel (Berkan *et al*., 2002). As a matter of fact, the antagonist activity is optimized by different substituents at different locations of the molecule. Therefore, our aim is to modulate the antagonist activity of acridinedione by modifying the scaffold using different substituents. We consider the basic skeleton of amlodipine–nifidipine and the acridinedione structure and use the thiophene as the modifier substituent. Thiophene-based molecules have been used as hypertensive drugs (Ronald *et al*., 1988), and so our interest is to check and modulate the DHP-based scaffolds activity by introducing thiophene moiety. Further tuning was performed by substitution in the thiophene moiety. An "*in silico*" approach is considered to be one of the most demanding methods in modern approach to find the potential molecules for many reasons. This motivates us to work with molecular docking and simulation analysis to search for new effective drugs.

MATERIALS AND METHODS

Proteins and ligands selection

A good quality 3D structure is necessary for the development of calcium CCBs and complete 3D structure of the L-type calcium channel of humans is yet not available. Bacterial voltage-gated Ca^{2+} channels are probably the evolutionary ancestors of human calcium channels (Tang *et al*., 2016). So, in this study, we took the crystal structure of calcium channels of *Arcobacterbutzleri* (CavAb) having Protein Data Bank IDs 5KLB and 5KLS, respectively (https://www.rcsb.org/). As our target is to design novel DHPs having calcium channel blocking ability better than nifedipine and amlodipine, we designed a library of 25 DHP-based derivatives. 2D structures were drawn using ChemSketch (Advanced Chemistry Development, Inc., 2021) and, subsequently, geometrically optimized using MOPAC software (Stewart Computational Chemistry, 2021).

Molecular docking

25 new derivatives along with nifedipine and amlodipine were docked with the 2 CavAb proteins (5KLB and 5KLS) using AutoDock 4.2 programme in order to explore the protein–ligand interactions and to recognize the potent drug for the treatment of diseases. Proteins were prepared using AutoDock tools, downloaded from MGLTools (2021). During the docking simulation, the Lamarckian genetic algorithm was employed. BIOVIA Discovery Studio Visualizer (2021) and Chimera software's were used to visualise docked complexes and also to study the docking interactions.

Molecular dynamic (MD) simulations

MD simulations were executed to investigate the stability of the protein–ligand complexes. Ligand and Receptor Molecular Dynamics (LARMD) server (2018) was used to study the dynamics of the protein–ligand complexes. We have used the default option of LARMD server (2018) to run 1 nanosecond MD simulations. PDB files of the protein–ligand-docked complexes were uploaded on the LARMD server (2018). The explicit water model was chosen to run the simulations. In the LARMD server (2018), AMBER16 program and force field AMBER ff14SB were used. In order to investigate the stability of the protein–ligand complexes, we inspected the following parameters, root mean square deviation (RMSD), root mean square fluctuation (RMSF), and radius of gyration (Rg) of the docked complexes. MM/PB (GB) SA binding energy calculations on the simulated paths were also performed.

Drug-likeness and Absorption, Distribution, Metabolism, Elimination, Toxicity (ADMET) properties

The drug-likeness and ADME properties were calculated using online server SWISSADME (2017) and to check the bioavailability score. Molinspiraton online server (Molinspiraton) was also used.

RESULTS AND DISCUSSION

1,4-DHPs (or acridinedione) act as hydrogen donors and could be potential pharmacophores. In the case of the Hantzsch ester, the partially hydrogenated N-heteroaromatic DHP nucleus or its fragments, i.e., the NH group, act as hydrogen donors, which are required for antioxidaive activity. DHPs have substantial hydrogen donating ability due to the presence of labile hydrogen atoms (mostly at positions 1,4-) in their molecules. DHPs ensure their reductant role by donating electrons and/or hydrogen, resulting in antioxidant activity and antiradical activity. The oxidation of DHPs results in the formation of heteroaromatic pyridine derivatives, which operate as antioxidative and antiradical agents (Velena *et al*., 2016). Antioxidants will protect the cell from oxidative injury by preventing and inhibiting the factors that cause it. An antioxidant's capacity to scavenge free radicals is thought to be linked to its ability to donate hydrogen. Along with its β-blocking ability, Amlodipine besylate (AMB) may easily scavenge free radicals in the biological system. AMB minimises oxidative stress in biological system and hypertension in patients in this way (Safna Hussan *et al*., 2019).

The interaction of newly designed calcium CCBs with the proteins involved has been identified at the atomic level.

Molecular docking and binding mode analysis

Both 5KLB and 5KLS are CavAb proteins consisting of four identical chains forming a homotetramer. Four chains, containing 286 amino acid residues each, are similar to four homologous repeats I, II, III, and IV of mammalian CaV channels. Each chain comprises six transmembrane helices, S1–S6, and supporting helices, P1 and P2, having two functional domains: S1–S4 constitutes the voltage-sensing domain and S5 and S6 along with P1 and P2 constitute the ion-conducting pore domain.

The ion-selective pore is located in the homotetramer of the CavAb channel. The calcium CCBs nifedipine and amlodipine are widely used and hence serve as control molecules in this investigation. DHP is distinguished by its heterocyclic ring, which inhibits the flow of extracellular Ca^{+2} via L-type voltage-dependent calcium channels. The distinctive chemical structure of amlodipine was developed from the DHP (Safna Hussan

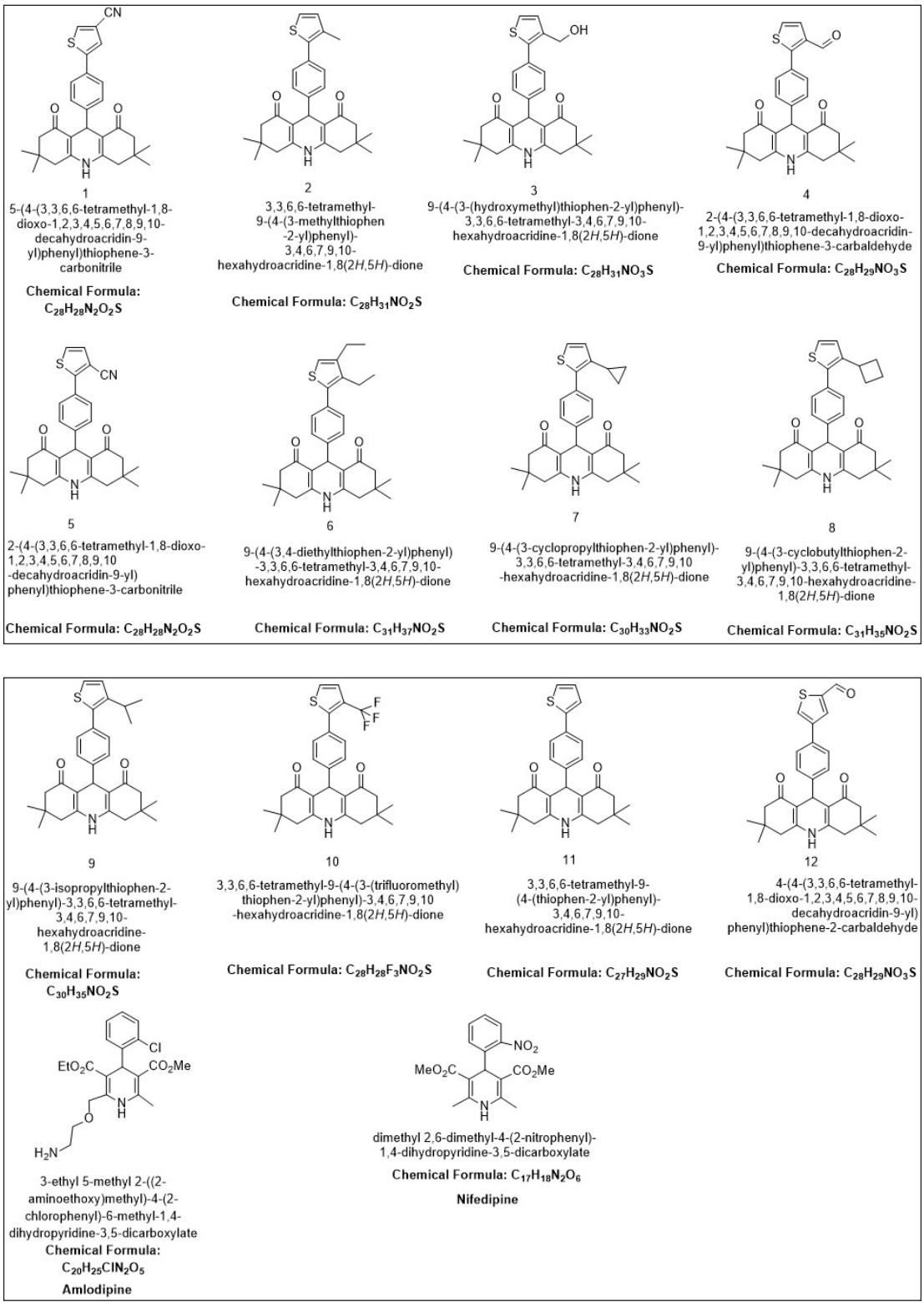

Figure 1. Chemical structures of the thiophene-based derivatives.

et al., 2019). El-Moselhy (2012) employed nifedipine as a calcium antagonist reference. The interaction of various residues has been used to explain the affinity of nifedipine as a reference molecule to the DHP receptor (El-Moselhy, 2012).

Here, we are interested in designing calcium CCBs better than nifedipine and amlodipine. The calcium channel proteins were docked with 25 DHPs, as well as nifedipine and amlodipine. A molecular docking study was carried out on all of the newly

developed DHPs derivatives; however, only 12 of them showed significantly greater binding affinity for the two target proteins (Figure 1 and Table 1) (Shityakov *et al*., 2014). The molecular docking analysis of the selected 12 designed derivatives along with control molecules with the proteins 5KLB and 5KLS showed that the majority of the compounds bind to 5KLB and 5KLS with favourable binding energies ranging between −10.05 and −6.86 kcal/mol. Among the compounds, compound 10 showed the lowest binding energy (−10.05 and −9.99 kcal/mol) with two target CavAb proteins. Safna Hussan *et al*. (2019) showed that the docking result of amlodipine based drug was of −7.2 kcal/mol (Safna Hussan *et al*., 2019). During the docking analysis, the binding pattern of compound 10 with the B-chain of protein 5KLB (Figure 2) showed the formation of three hydrogen bonds: a hydrogen bond between the O atom of keto group of the ligand and NH group of the Val158 with a distance of 2.67 Å and one of the F atoms of CF_3 group formed two hydrogen bonds with the NH groups of both the residues Arg155 and Phe158 with a distance of 2.27 and 2.26 Å, respectively. Safna Hussan *et al*. (2019) reported similar results, and they found that amlodipine-based drugs interact with the active site amino acids of the protein via H-bonding (Safna Hussan *et al*., 2019). El-Moselhy (2012) revealed that the NH group of nifedipine forms a H-bond with the protein residue Tyr and hydrophobic interaction occurs between the aromatic ring and Tyr residue (El-Moselhy, 2012). A halogen (fluorine) interaction with residue Phe156, a *pi*–sigma interaction with Leu74, a *pi*–alkyl interaction with Arg155, and a large number of *pi*–alkyl interactions with residues Phe13, Arg15, Cys46, Pro47,

Table 1. Results of the binding energy of the 12 DHP-based ligands docked with 2 CavAb proteins.

Compounds	Binding energy (kcal/mol)		Compounds	Binding energy (kcal/mol)	
	5KLB	5KLS		5KLB	5KLS
1	−8.47	−8.01	9	−8.18	−8.05
2	−9.62	−8.93	10	−10.05	−9.99
3	−6.86	−7.34	11	−9.86	−9.35
4	−8.57	−7.02	12	−8.87	−9.93
5	−8.87	−7.39	13 (Thiophene only)	−8.50	−9.34
6	−8.94	−7.86	Amlodipine	−4.08	−5.96
7	−7.38	−7.96	Nifidipine	−5.47	−3.65
8	−7.83	−7.75			

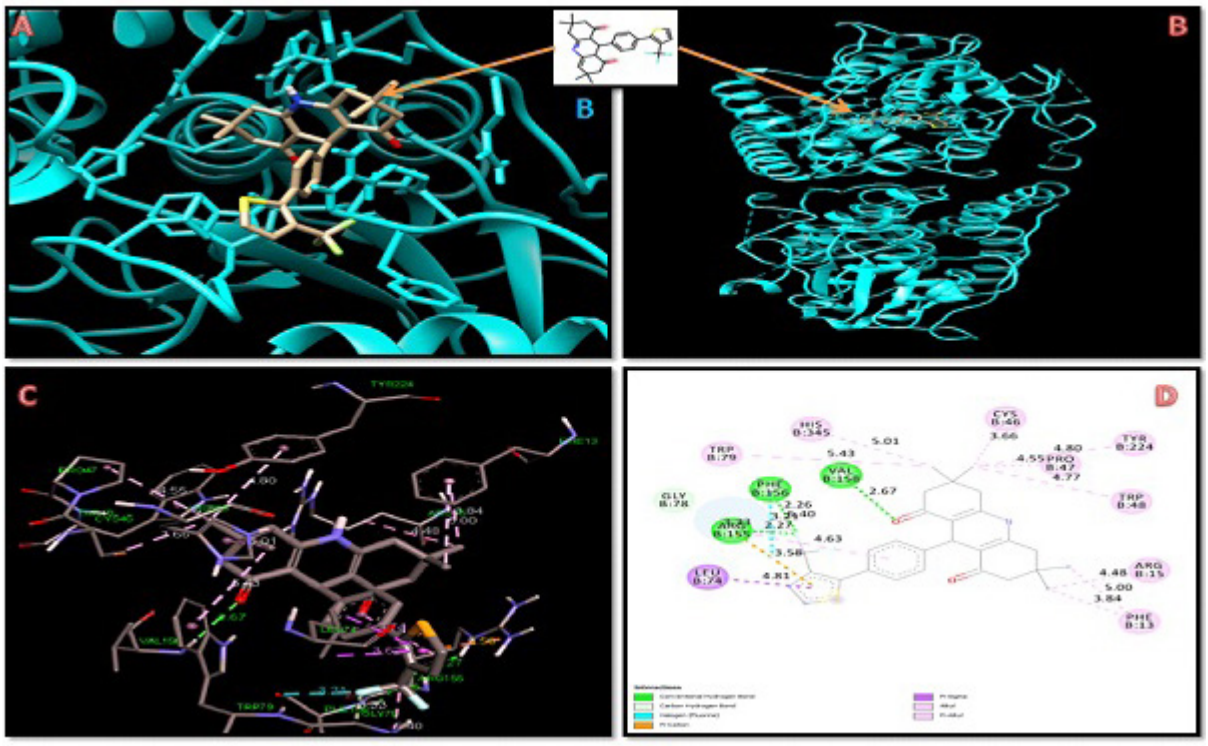

Figure 2. Docking interaction of compound 10 with 5KLB protein.

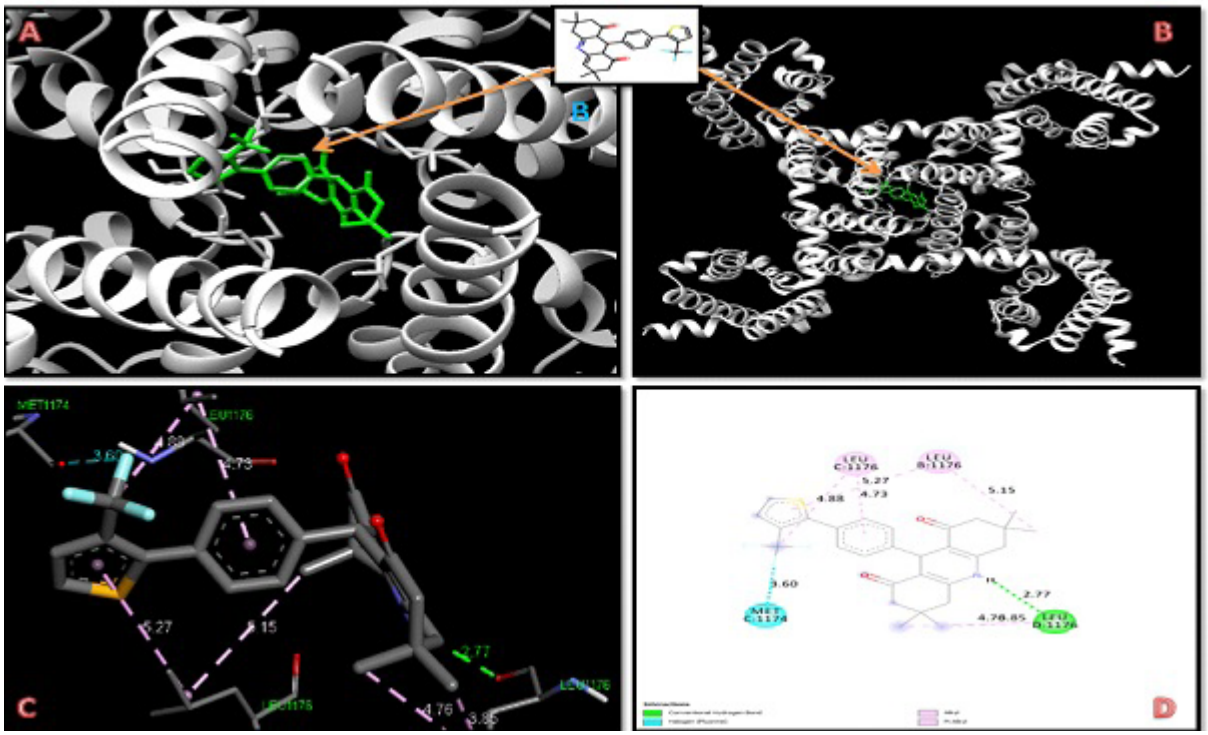

Figure 3. Docking interaction of compound 10 with 5KLS protein.

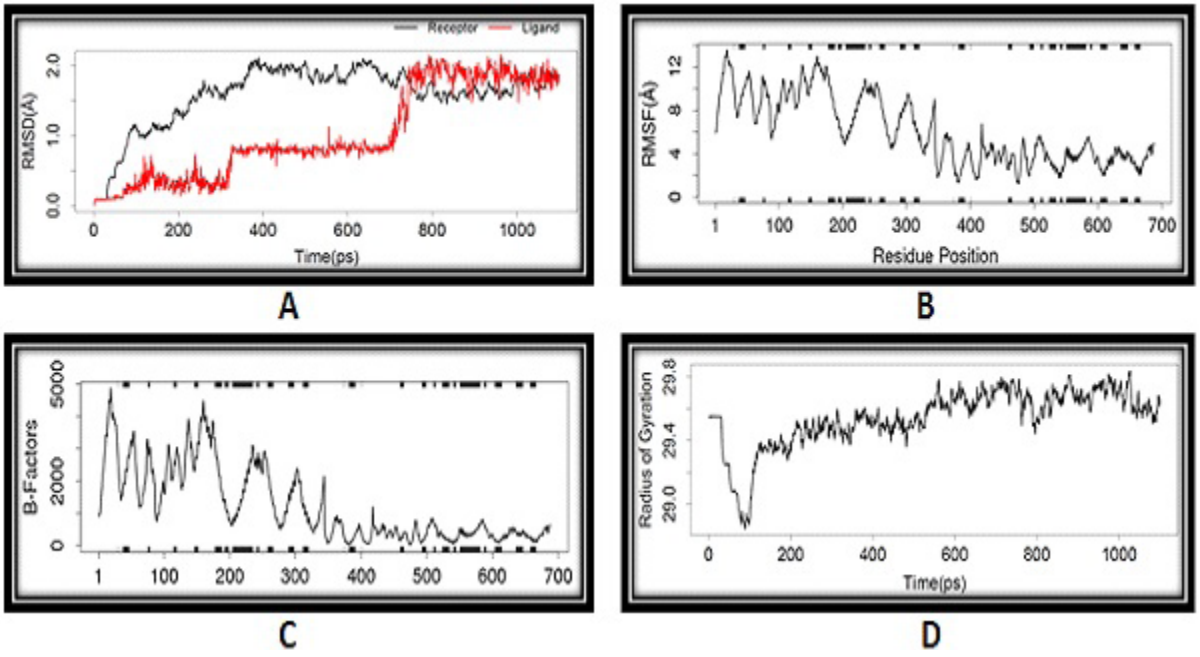

Figure 4. MDs: (A) RMSD, (B) RMSF, (C) B-factor, and (D) Rg of compound 10 with 5KLB.

Trp48, Trp79, Tyr224, His345, and Leu1176 of B-chain of 5KLB were also found. In the complex of compound 10 and protein 5KLS (Figure 3), there was a hydrogen bond in between the H atom of the NH group of the ligand and the O atom of the carbonyl group of Leu1176 (D chain) with a distance of 2.77 Å. Moreover, a halogen (fluorine) interaction with residue Met1174 (C chain), one pi–alkyl interaction with Leu1176 (B chain) and Leu1176 (C chain), three alkyl interactions with Leu1176 (B chain), Leu1176 (C chain), and Leu1176 (D chain), respectively, also existed.

DHP derivatives with a bulky group, like $–CF_3$, displayed a better binding affinity when compared to other substituents.

MD simulations

MD simulation is useful in understanding the conformational stability of docked complexes. Because compound 10 has the highest binding energy, we used MD simulation to investigate the stability of docked complexes with time. The docked complex of compound 10 was subjected to MD simulation utilising the LARMD server to achieve various geometric features such as RMSD, RMSF, Rg, and so on. The RMSD plots of the complexes of compound 10 with 5KLB and 5KLS are shown in Figures 4A and 5A. The higher the RMSD fluctuation of a ligand, the greater its conformational changes in the receptor. RMSD fluctuations of both complexes were found to remain either lesser than or around 2 Å. From the RMSD plots, it was found that the complex of compound 10 and 5KLB showed more favourable complexation compared to the complex of compound 10 and 5KLS. The time evolution plots of RMSF for all C-α atoms of the complexes are shown in Figures 4B and 5B. Compound 10–5KLB and compound 10–5KLS complexes showed regular RMSF fluctuation patterns between 2 and 14 Å and 2 and 20 Å, respectively. Such low fluctuations in the RMSF of both the complexes directed nonstop interactions between the receptor and compound 10. Structural integrity and compactness of protein structure are best understood by Rg. The Rg plots of both complexes are shown in Figures 4D and 5D. The Rg plots revealed that compound 10–5KLB complex showed minor fluctuations (Rg < 29.8 Å) compared to compound 10–5KLS complex (Rg < 33 Å). These results suggest that the compound 10–5KLB complex is more stable than the compound 10–5KLS complex.

Binding free energy calculation through MM [generalized born surface area continuum solvation / Poisson–Boltzmann surface area continuum solvation (GBSA/PBSA)]

The binding free energy was also calculated on the simulated trajectories using both PBSA and GBSA methods in the LARMD server and the results are presented in Table 2. The deltaGB binding energy of the compound 10–5KLB complex was −19.42 kcal/mol and that of compound 10–5KLS was −20.94 kcal/mol. Electrostatic energy (ELE), van der Waals contribution, polar and nonpolar contributions to solvation (PBSOL or GBSOL) and entropy (TS) are taken into account for the estimation of free energy (deltaPB/ deltaGB). Complex of compound 10 with protein 5KLS has higher gas phase energy compared to complex of compound 10 and 5KLB. PBSOL to the binding free energy (deltaPB) of the complex of compound 10 and 5KLB was higher than that of complex of compound 10–5KLS (Table 2). 5KLS has higher deltaPB and deltaGB values when compared to 5KLB protein. Molecular mechanics/generalized born surface area (MM/GBSA)/PBSA calculation suggests that compound 10 is a potential candidate and may replace the first-line drugs.

Table 2. Binding free energy MM (GBSA/PBSA) of the best docked complexes of both the proteins.

Target	ELE	VDW	Total gas phase energy	PBSOL	PBTOT	GBSOL	GBTOT	TS	deltaPB	deltaGB
Compound 10-CavAb (5KLB)	−2.94	−48.87	−51.81	21.12	−30.69	12.38	−39.43	20.01	−10.68	−19.42
compound 10 –CavAb (5KLS)	−6.13	−44.67	−50.81	13.74	−37.06	11.01	−39.80	18.86	−18.20	−20.94

Table 3. a. The ADME properties of compounds obtained from the online server SWISSADME.

Compounds	MW	#Heavy atoms	#Aromatic heavy atoms	Fraction Csp3	#Rotatable bonds	#H-bond acceptors	#H-bond donors
1	456.6	33	11	0.39	2	1	1
2	445.6	32	11	0.43	2	2	1
3	461.6	33	11	0.43	3	3	2
4	4.59.6	33	11	0.39	3	3	1
5	456.60	33	11	0.39	2	3	1
6	487.70	35	11	0.48	4	2	1
7	471.65	34	11	0.47	3	2	1
8	485.68	35	11	0.48	3	2	1
9	473.67	34	11	0.47	3	2	1
10	499.59	35	11	0.43	3	5	1
11	499.59	35	11	0.43	3	5	1
12	459.60	33	11	0.39	3	3	1
Amlodipine	408.88	28	6	0.40	10	6	2
Nifidipine	346.33	25	6	0.29	6	6	1

Table 3. b. The ADME properties of compounds obtained from the online server SWISSADME.

Compounds	MR	TPSA	Consensus Log P	ESOL Log S	GI absorption	BBB permeant	Lipinski's #violation	Bioavailability score
1	136.65	98.20	5.01	−5.96	Low	No	Yes, 0	0.55
2	135.91	74.4	5.53	−6.31	High	No	Yes, 0	0.55
3	137.07	94.64	4.70	−5.55	High	No	Yes, 0	0.55
4	136.33	91.48	4.94	−5.76	High	No	Yes, 0	0.55
5	135.65	98.20	4.99	−5.96	Low	No	Yes, 0	0.55
6	150.49	74.41	6.44	−7.19	Low	No	Yes, 1	0.55
7	143.41	74.41	5.97	−6.73	Low	No	Yes, 1	0.55
8	148.21	74.41	6.28	−7.16	Low	No	Yes, 1	0.55
9	145.52	74.41	6.13	−6.88	Low	No	Yes, 1	0.55
10	135.94	74.41	6.24	−6.88	Low	No	Yes, 1	0.55
11	135.94	74.41	6.24	−6.86	Low	No	Yes, 1	0.55
12	136.33	91.48	5.01	−5.94	High	No	Yes, 0	0.55
Amlodipine	108.93	99.88	2.52	−3.76	High	No	Yes, 0	0.55
Nifidipine	94.52	110.45	1.64	−3.15	High	No	Yes, 0	0.55

Table 4. Bioactivity scores of the designed compounds according to Molinspiraton cheminformatics software.

Molecule	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Compound 10	−0.29	−0.31	−0.81	−0.15	−0.48	−0.31
Amlodipine	−0.23	−0.02	−0.89	−0.41	−0.56	−0.50
Nifidipine	−0.45	−0.13	−1.07	−0.25	−0.73	−0.49

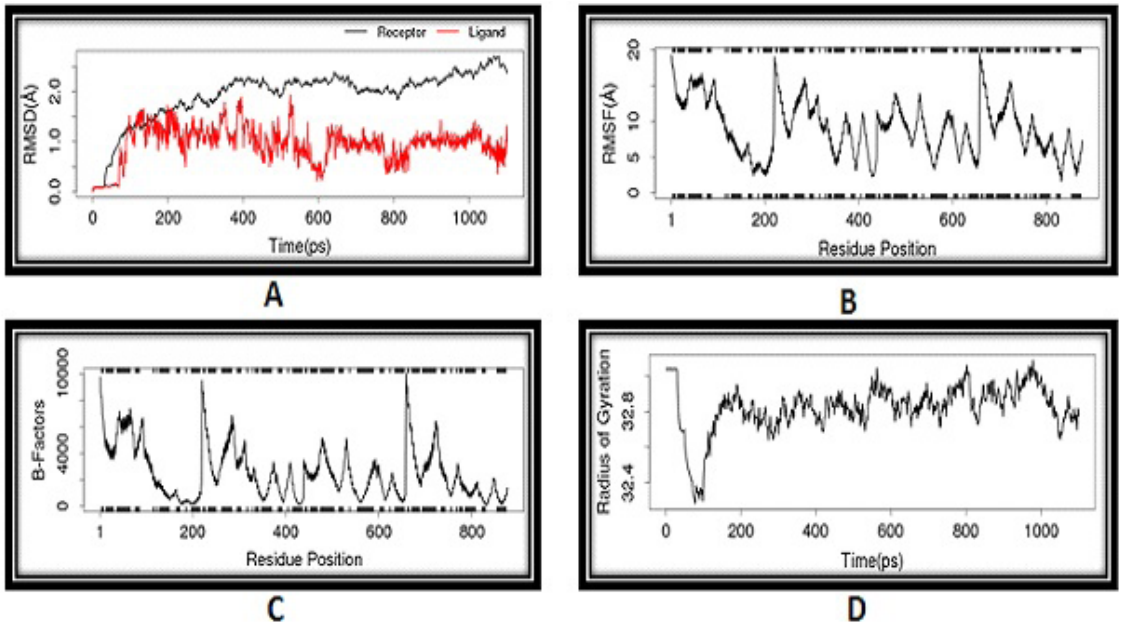

Figure 5. Molecular dynamics: (A) RMSD, (B) RMSF, (C) B-factor and (D) Rg of compound 10 with 5KLS.

ADME properties analysis

The pharmacokinetic profile of a medicine is a critical component, and many therapeutic compounds are unable to enter the market because of their low profile. The features of a proposed therapeutic molecule should be appealing. The SWISSADME server was used to create the Lipinski rule of 5, as well as a few other important parameters (Daina *et al*., 2017). A therapeutic molecule will be active if the limiting value of two or more of these criteria is not breached, according to the Lipinski rule of 5. The profile has been presented in Table 3a and b and compared with the control

molecules. Compound 10 follows the Lipinski rule with only one violation. Bioavailability score is a vital parameter and compound 10 possesses a score value of 0.55, which indicates that it has high-quality pharmacokinetic properties (Table 4). The same value was found in control molecules. The parameter topological polar surface area (TPSA) can be used to predict drug transport qualities. This metric is an excellent indicator of a drug's bioavailability. The considered compounds were found to have TPSA below 140 Å^2. A low TPSA value indicates that compound 10 is better behaved than the control molecules (Imane *et al*., 2021). The number of bonds which can easily rotate indicates the conformational changes of the compounds and ultimately for the binding of receptors or channels, so it is a good parameter (Salma *et al*., 2017). A lower value of this parameter (<10) indicates the low conformational flexibility. Most of the molecules possess a lower range of rotatable bonds except for one of the control molecules. It is seen that all the designed molecules possess molecular weights (MWs) below 500. According to the Lipinski rule of 5, the limiting number of hydrogen bond donors (nOHNH) is less than or equal to 5. All the molecules possess only one hydrogen donor except compound 3 and amlodipine which have two donors. Hydrogen bond acceptors (nON) of all the molecules range from 1 to 6, which is below the limiting value (<10) of the Lipinski rule of 5. The Blood-brain barrier (BBB) parameter showed that the designed molecules have no issues. The absorption percentage (%Ab) was calculated using the following relationship (Husain *et al*., 2016; Zhao *et al*., 2002):

$$\%Ab = 109 - (0.345 \times TPSA).$$

The absorption percentage of compound 10 and control molecules are 83, 71, and 74, respectively, which indicates better oral bioavailability (Husain *et al*., 2016).

As a result of the foregoing findings, compound 10 possesses good therapeutic characteristics that meet the required criteria. So, this compound was thoroughly screened for bioactivity and compared to control molecules. Interaction with the living systems with these compounds were predicted by calculating the activity score toward G protein-coupled receptors (GPCR ligand), calcium CCB, transcription factors, kinase inhibitor, protease inhibitor, and enzyme inhibitor with the assistance of software Molinspiration (2002) score online. The bioactivity of the compounds is presented in Table 4; the drug-likeness score suggests that the compound has potential biological activity. So, the considered compound may be useful as a key compound for CCBs and transcription factors.

CONCLUSION

In this article, computational docking studies for two CavAb channel proteins (5KLB and 5KLS) were performed in order to screen the newly designed potential drugs. The docking results are also compared to the control molecules amlodipine and nifidipine. Compound 10 had the lowest binding energy with both the proteins (5KLS and 5KLB). MD simulations and MM/ (GBSA/ PBSA) calculations of the docked complexes of compound 10 with 5KLS and 5KLB showed that complexes were stable. In addition to that pharmacological *in silico* interpretations suggest that compound 10 may be projected for further *in vivo* and *in vitro* studies.

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CONFLICT OF INTERESTS

No potential conflict of interests was reported by the authors.

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None.

AUTHORS' CONTRIBUTION

All the authors in the manuscript are equally responsible for the technical information communicated to the journal. All the authors discussed the results and contributed to the final manuscript.

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