Design, Synthesis, and Computational Studies with ADMET of Novel Cardiovascular Hybrid Drugs

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Abstract: Recently the drug discovery trend has been to design hybrid drug molecules consisting of different pharmacophore groups linked together via spacers. Calcium channel blockers have an important role in the treatment of several cardiovascular diseases. The objective of the present research work is to encompass the strategic design, synthesis, and computational assessment of novel 1,4- dihydropyridine containing calcium channel blocker hybrid containing beta blocker side chain along with NO group as promoting cardiovascular agents as a viable alternative to well-established drugs like Amlodipine, Nifedipine, Felodipine, etc. In this research, we synthesized new 18 cardiovascular hybrid compounds based on structure-activity relationship properties. The 3D crystallographic structure of the calcium channel receptor (6M7H) was obtained from PDB. RCSB and used for docking study. The molecular docking studies were carried out by using the standard option Glide 5.5 in Maestro. *In silico* molecular docking analysis of all the synthesized compounds, AE1 to AE18, showed good docking scores and remarkable interactions with the essential amino acid residues located within the receptor's binding pocket of 6M7H. In comparison to amlodipine, AE12, AE6, AE8, AE11, AE5, AE16, and AE14 exhibit good scores as well as good binding patterns. AE12 exhibits the highest docking score of -8.455 kcal mol^{-1}. Extensive ADMET profiling and structure–activity relationship (SAR) elucidated favorable pharmacokinetic properties and essential structural modifications influencing antihypertensive effectiveness.

Keywords: Cardiovascular hybrid drugs, dihydropyridine, docking study, ADMET

1. Introduction:

Hypertension, most commonly referred to as "high blood pressure", is a medical condition in which the blood pressure is chronically elevated. It was previously referred to as arterial hypertension. High blood pressure is called "the silent killer" because it usually has no symptoms. [1-2] Hypertension is considered to be present when a person's systolic blood pressure is consistently 140 mm Hg or greater, and/or their diastolic blood pressure is consistently 90 mm Hg or greater. Recently, as of 2003, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has defined blood pressure 120/80 mmHg to 139/89 mm Hg as "prehypertension." Prehypertension is not a disease category; rather, it is a designation chosen to identify individuals at high risk of developing hypertension. There are usually no symptoms or signs of hypertension. [3-4]
Monotherapy of hypertension i.e. treatment with a single drug has become more popular because compliance is likely to be better and with some drugs adverse effects are fewer. As with other conventional drug molecules, anti-hypertensive drugs also have their own set of side effects associated with them. [5-6]
A variety of mediators can be involved in the pathophysiological process leading to a disease, in many instances; treatment with a single drug cannot adequately control the illness. Sometimes, the use of a therapeutic agent alone in the treatment of a disease may be limited by side effects caused by its action. Then combinations of drugs with different pharmaco-therapeutic effects are feasible. [7]
Combination drug therapy can be applied either to overcome the side effects of the single drug or to add beneficial effects [8]. The principle of combination drug therapy can be achieved by either using concomitant administration of two or more single active drugs or by drugs in which the single active agents are combined in one molecule, so-called hybrid molecules. As blood pressure is maintained by several interrelated factors, an attempt to block one of them tends to increase the compensatory activity of the others. [9-10] It is rational in such cases to combine drugs with different mechanisms of action or different patterns of hemodynamic effects. For example, when a diuretic is used for initial therapy, compensatory sympathetic activation often follows; conversely, sympatholytic leads to subsequent sodium and water retention. [11]
Combination therapy is more effective in achieving target blood pressure, and some combinations have a more favorable tolerability profile than monotherapy, either because the individual drugs have few adverse effects or

because lower doses of each drug can be used. For example, complementary antihypertensive effects can be achieved using either an ACE inhibitor or an ARB in combination with a diuretic, because the combination provides a higher treatment response rate at lower doses of each drug. [12-13] The principle of combination drug therapy can be achieved by either using concomitant administration of two or more single active drugs or by drugs in which the single active agents are combined in one molecule, so-called hybrid molecules. These hybrid molecules often consist of different pharmacophore groups which are linked to each other via spacers. [14]

1,4-Dihydropyridine-based drugs such as amlodipine are the Ca^{2+} antagonists that are widely used in the treatment of cardiovascular disorders.1,4-dihydropyridines are primarily used to treat hypertension and are considered to act as allosteric modulators that influence L-type voltage-dependent Ca^{2+} channels activation. The binding of 1,4- dihydropyridines to receptors in the L-type voltage-dependent Ca^{2+} channel inhibits the entry of Ca^{2+} ions through voltage-gated Ca^{2+} channels into both the cardiac and vascular smooth muscles. The target proteins CavAb complex and calmodulin were procured from the X-ray crystallographic data to successfully establish the *in silico* efficiency of our candidates as promising anti-hypertensive agents. [15-35]

The present study undertakes a comprehensive exploration of newer 1,4-dihydropyridine-based amlodipine compounds incorporating molecular design, synthetic methodologies, and advanced computational analysis. [23-24] In particular, the *in silico* evaluation, the fundamental aspect of this study plays a pivotal role in analyzing the critical features of the synthesized hybrids, including their binding interactions with target proteins, pharmacokinetic characteristics, and potential therapeutic efficacy. This approach not only accelerates the drug discovery process but also reduces the risks and resource expenditures involved with traditional trial-and-error methods. [16]

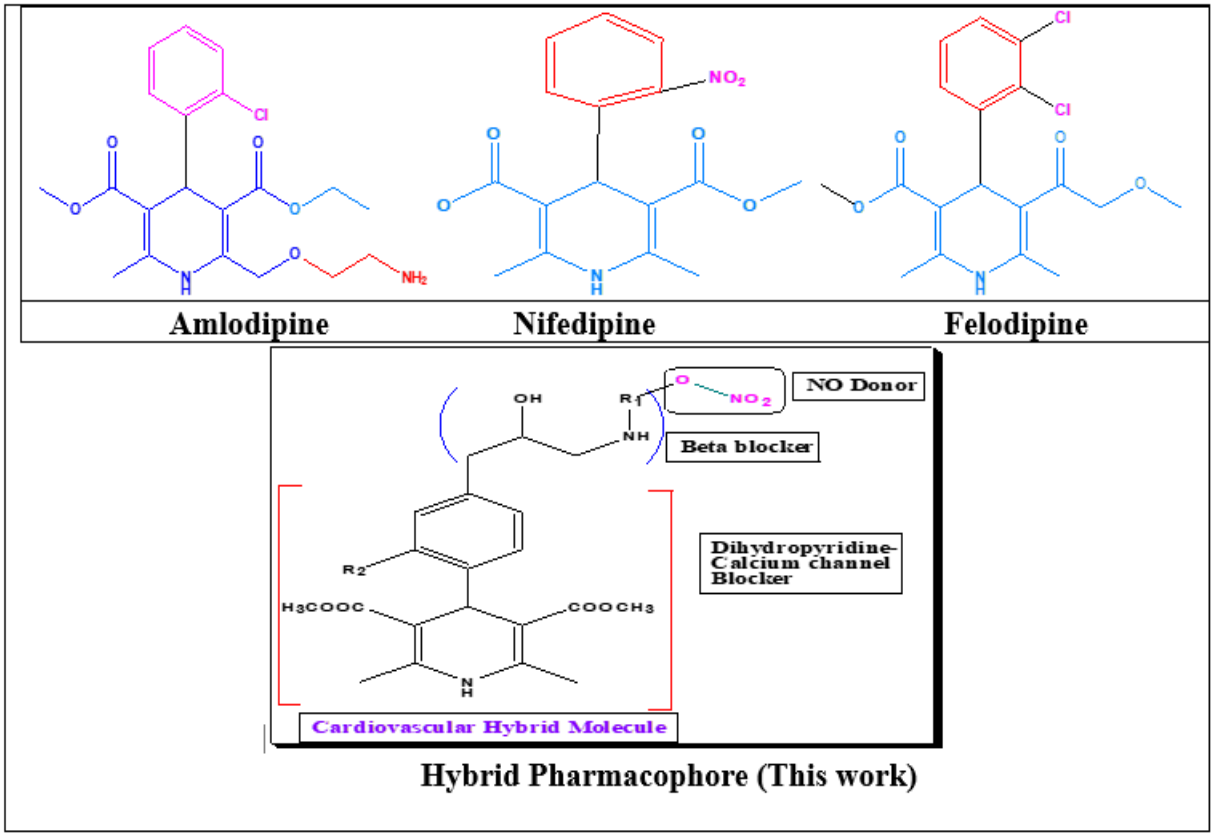


Fig. 1. Chemical structures of well-established 1,4-dihydropyridines as antihypertensive drugs and the framework of hybrid drugs synthesized in this work.

METHODOLOGY

Materials and Methods

All the reagents and solvents (analytical grade) were procured from Pallav chemicals and employed directly for the synthesis without any further purifications. Thin layer chromatographic (TLC) plates precoated with silica gel were used to monitor the reaction optimizations. Melting points were

determined using the Veego VMP-D Digital instrument. KBr disks were utilized to record “JASCO FT-IR 4100 using infrared spectra on a spectrophotometer. FTNMR VARIAN MERCURY YH-300” Spectrometer at 300 MHz Frequency in $CDCl_3$ using TMS as internal standard. [25-26].

General procedure:

Step I) In a 100 mL RBF fitted with a reflux condenser. Aromatic aldehyde (0.02M), epichlorohydrin (0.04M) and anhydrous sodium hydroxide 0.8 g taken in 20 mL of ethanol were refluxed for 45 hours with intermittent stirring. It was then shaken with water and the organic layer was separated using a separating funnel as AA1-AA3. [17]

Step II) The organic layer of AA1-AA3 was added to a solution of primary amines (0.02 M) dissolved in 10 mL of ethanol and refluxed for 50 hours. The product AB1-AB18 was obtained by concentrating the reaction mixture. [18]

Step III) AB1-AB18 Was taken and Hantzsch synthesis was carried out to obtain AC1-AC18 dihydropyridine structures. [7-19]

Step IV) AC1-AC18 in 10 ml of glacial acetic acid in 100 ml conical flask, warmed gently on a water bath until a clear solution results, then cooled as far as possible without the formation of crystals. To this solution added (0.015 M) of liquid bromine temperature was maintained below 45°C during the addition. The brominated product AD1-AD18 separated from the solution when about 3 quarters of bromine had been added. Kept it overnight in the freezer and then filtered the product. [20]

Step V) A solution of the appropriate bromo derivative AD1-AD18, (0.007 M) in dry acetonitrile (2-4 mL) was treated portion wise with a solution of $AgNO_3$ (0.01 M) in dry acetonitrile (5-10 mL) and the whole mixture was stirred at room temperature for 2.5-3.5 hours. The mixture was then filtered, and evaporated to dryness (AE1-AE18) obtained. [21-22].

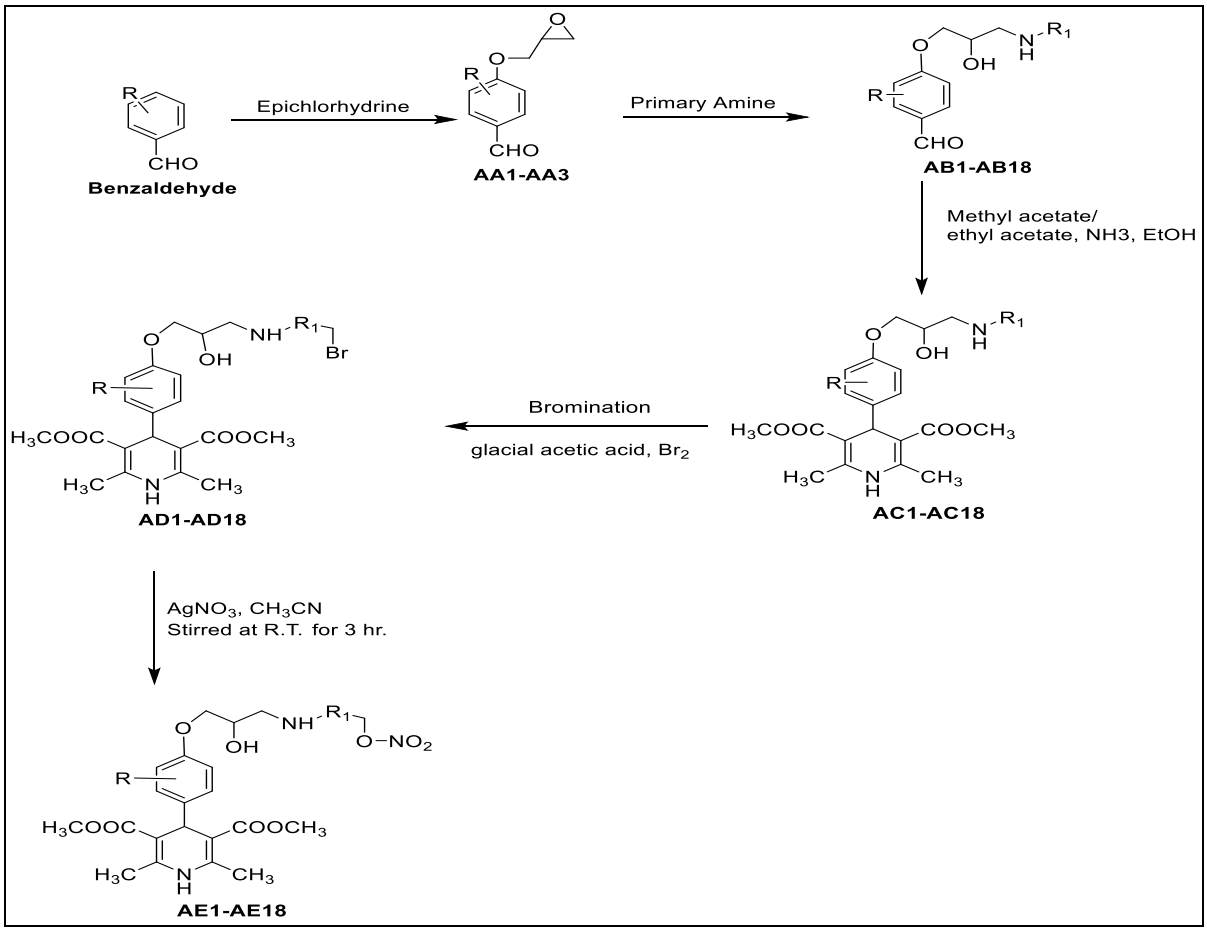


Fig. 2. Scheme for the synthesis of novel cardiovascular hybrids

2.3 Ligand and protein preparation

To fulfill the minimal requirements for additional computational calculations, it was imperative to prepare all target proteins and studied ligands. For ligand preparation, the LigPrep tool, which interfaced with the Schrodinger suite's Maestro module, was utilized. Using the optimized potential liquid simulations (OPLS3e) force field, 3D structures containing all potential tautomers and ionization states at pH 7.0 ± 2.0 of all ligands and reference compounds were created and geometrically minimized. For protein preparations, Schrodinger's multi-step Protein Preparation Wizard was employed. First, the RCSB Protein Data Bank was searched for high-resolution protein crystal structures of the enzyme (PDB ID:6M7H) complexed with a native ligand[37]. Following the assignment of charges and bond orders, heavy atoms were given hydrogens, and all water molecules and heteroatoms were eliminated while maintaining native ligands and metals in the active site. To prevent steric clashes between atoms, final structures were optimized and then minimized using the OPLS3e force field.

2.4. Molecular docking

Molecular docking was done using Schrodinger using Maestro Glide to examine the chosen compounds' mechanism of action, binding affinity, binding mode, and molecular interactions. Maestro build panels were utilized to construct all compounds, and Ligprep (Schrodinger, LLC) was employed to optimize them for lower energy conformers. Protein X-ray crystal structure (PDB ID:6M7H) was acquired from the protein data bank and docking ready with the aid of protein preparation wizards [36]. Next, by utilizing the default box size and centered on the ligand, grids were refined and minimized around the structures. Final docking studies were carried out on a generated protein structure grid using the extra-precision (XP) docking mode for all screened compounds [37-38].

2.5. Calculation of physicochemical and ADMET properties

Several common molecular descriptors, including the dipole moment, the logarithm of the octanol-water partition coefficient (QPlogPo/w), the percentage of oral absorption by humans, the polar surface area (PSA), violations of Lipinski's rule of five, and violations of Jorgensen's rule of three, were used to calculate the ADMET properties [39].

3. RESULTS AND DISCUSSION

3.1 Chemistry

The methodology for the development of novel 1,4-dihydropyridine AE1–AE18 was established in five steps. The structures of the synthesized compounds were substantiated by various spectroscopic techniques, including Nuclear Magnetic Resonance (^{1}H NMR) and Fourier-transform infrared spectroscopy. [40]

Evaluation of ^{1}H NMR of P1 revealed the characteristic peaks at d 8.71 as singlets for one proton each signifying the existence of –NH of 1,4-dihydropyrindine ring. A prominent singlet peak of 1 proton at d 5.29 ppm corresponds to the –CH of the chiral centre of 1,4- dihydropyridine at 4-position. Further, the presence of two ester groups at 1,4- dihydropyridine ring is confirmed by the prominent characteristic peaks at d 167.60 and d 166.72 ppm. Additionally, the MS data of AE11 demonstrated the calculated mass ion $(M + H)^+$as 620.8344, satisfying the observed mass of 620.1228.

Molecular docking evaluation:

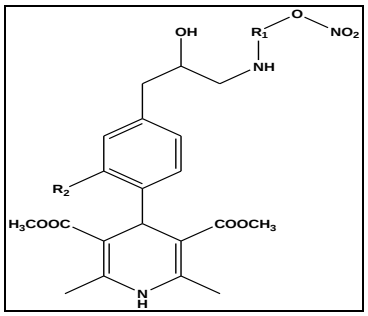


Fig. 3. Novel hybrid Molecule

Table no. 1. Physiochemical properties of hybrid molecules AE1-AE18

Comp Code	R1	R	Mol. formula	Mol. Wt	m.p. (^{0}C)*	% Yield	Mobile phase	R_f Value
AE1	--CH_2	-H	$C_{21}H_{27}N_3O_9$	465.459	173-179	68.96	Benzene:Methanol (2:3)	0.86
AE2	-CH_2-CH_2	-H	$C_{22}H_{29}N_3O_9$	479.486	191-198	55.44	Bnzene:Methanol (2:3)	0.87
AE3	-CH_2-CH_2-CH_2-	-H	$C_{23}H_{31}N_3O_9$	493.513	222-230	40.00	Ethylacetate: Benzene (1:1)	0.89
AE4	-CH_2-CH-CH_3-	-H	$C_{23}H_{31}N_3O_9$	479.486	227-235	71.42	Chloroform:Methanol (3:2)	0.91
AE5	CH_2-CH_2-CH_2-CH_2-	-H	$C_{24}H_{34}N_3O_9$	507.539	230-239	40.81	n-hexane:Methanol (3:2)	0.90
AE6	CH_2-CH-CH_2-CH_3	-H	$C_{24}H_{34}N_3O_9$	404.462	235-242	52.63	Benzene: Methanol (4:1)	0.90
AE7	--CH_2	-H	$C_{21}H_{27}N_3O_9$	409.395	175-183	63.21	Benzene:Methanol (3:2)	0.94
AE8	-CH_2-CH_2	-H	$C_{22}H_{29}N_3O_9$	423.422	190-196	95.83	Ethylacetate: nhexane (3:2)	0.85
AE9	-CH_2-CH_2-CH_2-	-H	$C_{23}H_{31}N_3O_9$	422.434	220-226	60.34	Benzene: Methanol (4:1)	0.88
AE10	-CH_2-CH-CH_3-	-H	$C_{23}H_{31}N_3O_9$	409.395	226-230	65.55	Benzene: Methanol (4:1)	0.89
AE11	CH_2-CH_2-CH_2-CH_2-	-H	$C_{24}H_{34}N_3O_9$	451.475	236-246	45.90	Benzene:Methanol (3:2)	0.90
AE12	CH_2-CH-CH_2-CH_3	-H	$C_{24}H_{34}N_3O_9$	437.449	240-249	70.85	Ethylacetate: nhexane (3:2)	0.87
AE13	--CH_2	-OCH_3	$C_{22}H_{31}N_3O_{10}$	481.458	183-189	58.88	Benzene: Methanol (4:1)	0.91
AE14	-CH_2-CH_2	-OCH_3	$C_{23}H_{33}N_3O_{10}$	495.485	205-211	63.90	Benzene:Methanol (2:3)	0.85
AE15	-CH_2-CH_2-CH_2-	-OCH_3	$C_{24}H_{35}N_3O_{10}$	523.539	252-262	70.10	Bnzene:Methanol (2:3)	0.88
AE16	-CH_2-CH-CH_3-	-OCH_3	$C_{24}H_{35}N_3O_{10}$	509.512	250-255	62.59	Ethylacetate: Benzene (1:1)	0.91
AE17	CH_2-CH_2-CH_2-CH_2-	-OCH_3	$C_{25}H_{37}N_3O_{10}$	537.566	265-271	49.55	Chloroform:Methanol (3:2)	0.90
AE18	CH_2-CH-CH_2-CH_3	-OCH_3	$C_{25}H_{37}N_3O_{10}$	523.539	260-267	71.66	Benzene:Methanol (2:3)	0.87

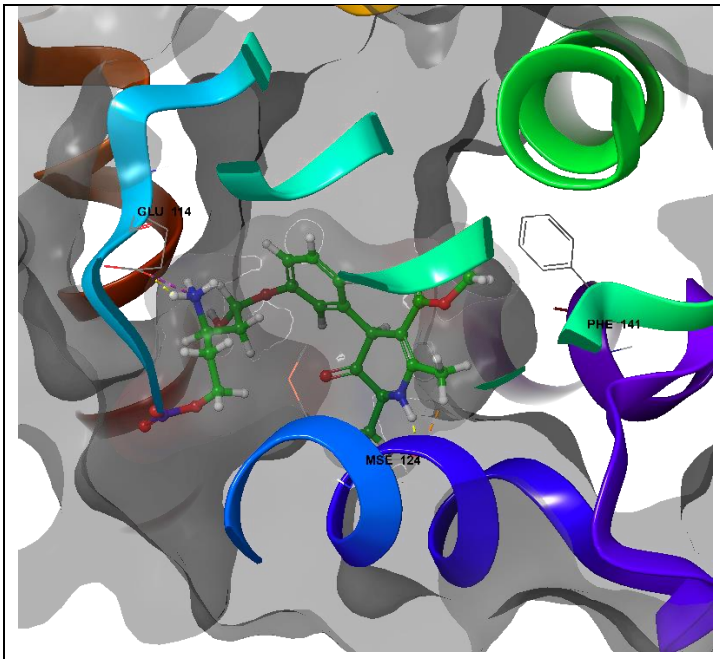
3.2. Molecular docking studies

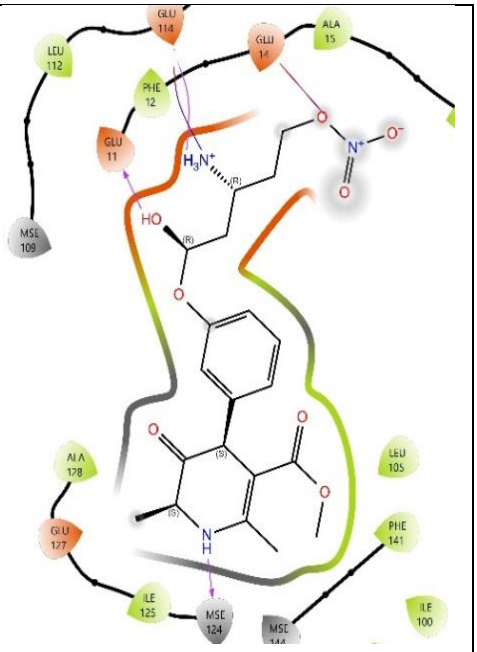
To identify the primary pharmacophores in charge of the anti-hypertensive or calcium channel blocker activities, molecular docking studies were carried out. This study looked at how a group of ligands (amlodipine bioisosteres) interacted with the corresponding protein targets 6M7H. In comparison to the standard amlodipine, as indicated in Table 1, the molecular docking analysis of all the synthesized compounds, AE1 to AE18, showed good docking scores and remarkable interactions with the essential amino acid residues located within the receptor's binding pocket of 6M7H. In comparison to amlodipine, AE12, AE6, AE8, AE11, AE5, AE16, and AE14 exhibit good scores as well as good binding patterns. AE12 exhibits the highest docking score of **-8.455** kcal mol^{-1} across all molecules, and it binds with the residues GLU11, GLU14, MSE124, and GLU114 as indicated in fig.1 as compered by amlodipine which show comparable low docking score **-6.211** kcal mol^{-1} and binds with GLU11, MSE124 by hydrogen bonding and salt bridge.

Table 2. A comparison between the compounds and standard Amlodipine in terms of docking score, binding energy, and interacting residues.

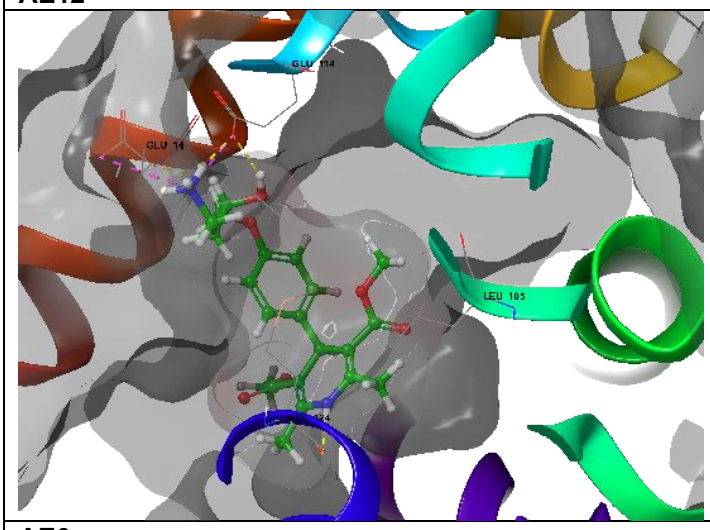
Sr. No.	COMP	DOCKING SCORE (kcal mol^{-1})	BINDING Emodel (kcal mol^{-1})	RESIDUES
1.	AE1	-4.502	-52.471	GLU11 MSE144
2.	AE2	-5.481	-64.729	GLU11
3.	AE3	-4.930	-69.059	GLU11 GLU114
4.	AE4	-5.350	-63.360	GLU11
5.	AE5	-6.960	-86.128	ASP80 MSE145
6.	AE6	-8.032	-58.552	GLU14 MSE124 GLU114
7.	AE7	-4.635	-51.199	GLU11 GLU127
8.	AE8	-7.248	-69.800	MSE144 MSE145 ASP80 MSE124
9.	AE9	-4.758	-52.490	GLU11 GLU127
10.	AE10	-5.356	-45.786	GLU11 MSE124 MSE144 ALA147
11.	AE11	-7.151	-62.790	GLU14 MSE124 GLU114
12.	**AE12**	**-8.455**	**-64.887**	**GLU11 GLU14 MSE124 GLU114**
13.	AE13	-4.124	-55.910	MSE145
14.	AE14	-6.503	-70.996	GLU14 GLU115 GLU114
15.	AE15	-5.713	-71.126	GLU14 GLU120 GLU114 MSE144
16.	AE16	-6.656	-57.695	GLU14 GLU120 GLU114
17.	AE17	-5.179	-71.057	GLU11 GLU127
18.	AE18	-5.203	-69.117	GLU11 GLU127
19.	Amlodipine	-6.211	-57.644	GLU11

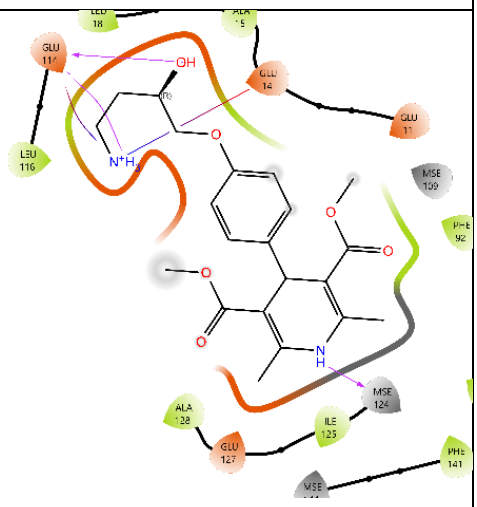
				MSE124



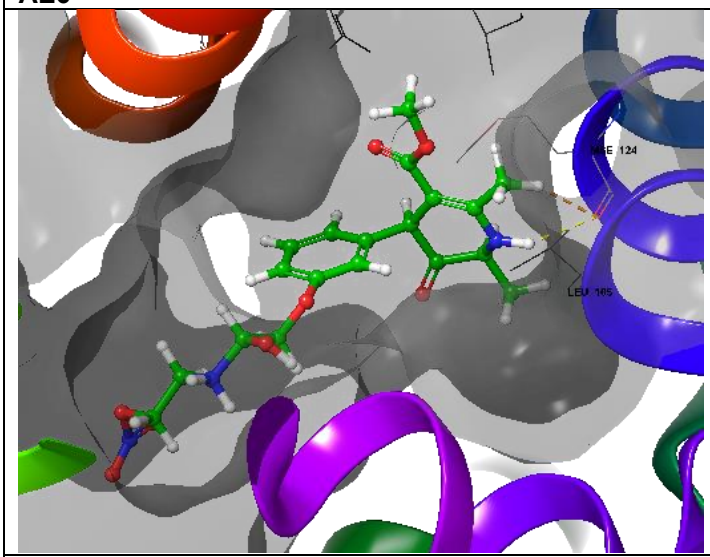


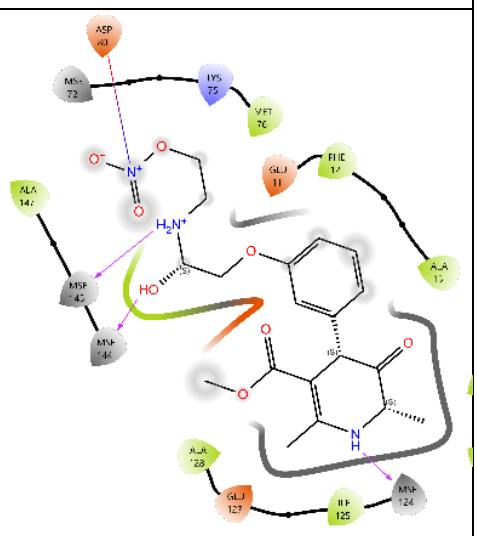
AE12





AE6





AE8

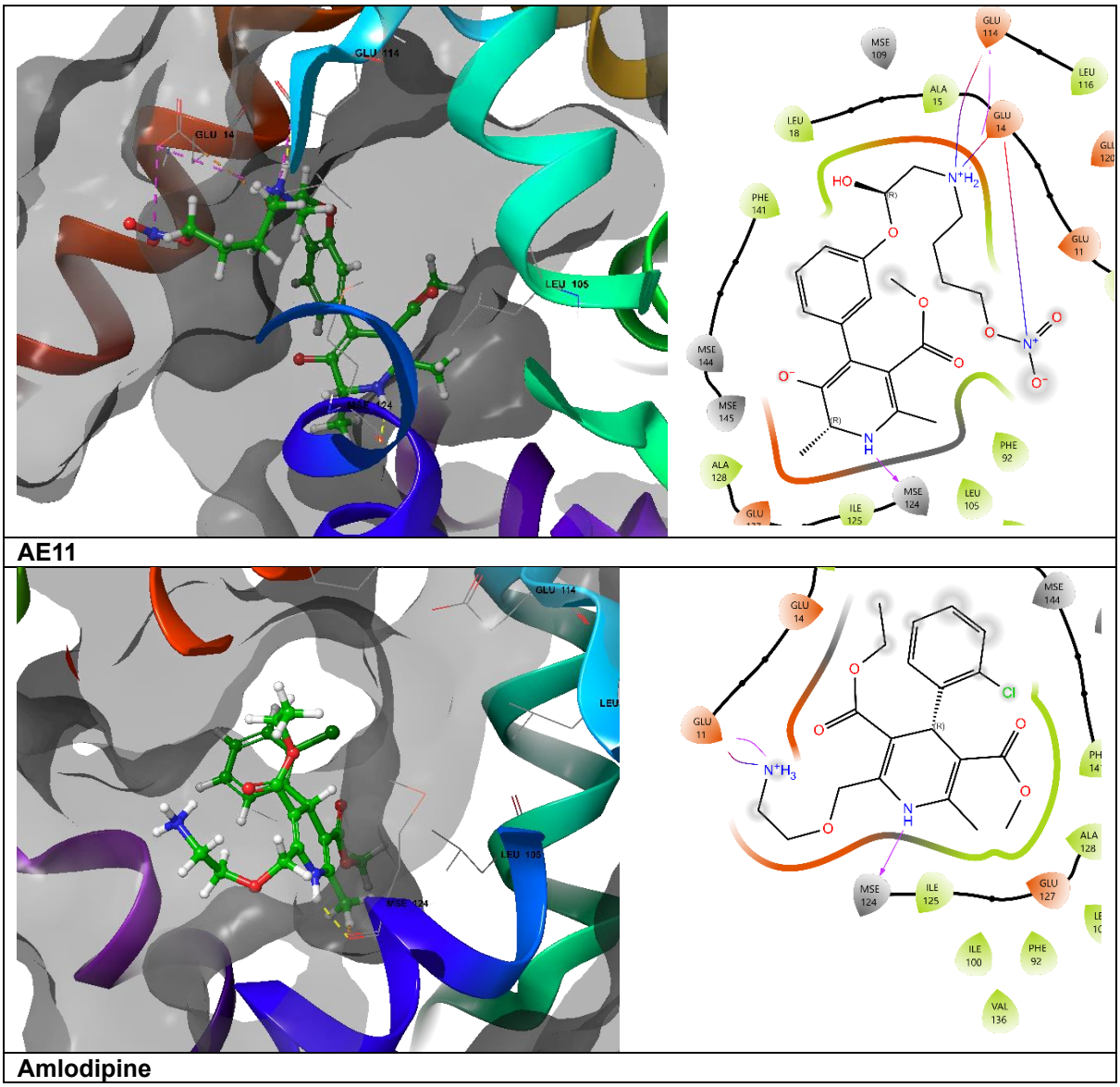


Fig.4. Docked images of the top 4 compounds and standard amlodipine in a 2D and 3D interacting diagram for in protein (PDB ID: 6M7H).

3.3. Drug-likeliness (Lipinski's rule of five) and in silico pharmacokinetic studies

The idea of drug-likeliness is crucial to the safety and effectiveness of pharmaceuticals. The definition of drug likeliness is that the drug under investigation should be similar to an acceptable standard drug. A strong ADMET profile is required. The ADMET study of 18 compounds' pharmacokinetic parameters are displayed in Table 2. Molecular weight, percentage of human oral absorption, polar surface area (PSA), predicted apparent MDCK cell permeability (QPPMDCK in nm/sec), predicted aqueous solubility (S in mol/L), and predicted octanol/water partition coefficient (log p) were the pharmacokinetic parameters that were assessed sequentially. Every one of these ADMET property values had to be within the acceptable range for human use. Their worth implies that they might have therapeutic qualities. [40]

Table 3. Pharmacokinetic characteristics of the 18 synthesized compounds.

Comp.	M. W[a]	QPlogPo/w[b]	QPlogS[c]	QPPCaco[d]	QPPMDCK[e]	Percent Human Oral Absorption[f]	PSA[g]	Rule of Five	Rule of three
AE1	465.459	1.936	-4.334	10.426	3.945	43.543	172.289	1	2
AE2	479.486	2.349	-4.936	9.002	3.366	44.822	173.109	1	2
AE3	493.513	2.624	-5.227	8.028	2.974	45.544	174.364	1	2
AE4	479.486	2.077	-4.743	4.977	1.774	38.626	182.503	1	2
AE5	507.539	3.051	-5.669	8.937	3.34	35.915	173.432	2	2
AE6	404.462	2.796	-4.453	45.804	19.536	73.045	128.467	0	1

AE7	409.395	0.497	-2.842	7.345	2.702	32.398	169.237	1	2
AE8	423.422	0.897	-3.181	8.791	3.281	36.136	167.94	1	2
AE9	422.434	2.3	-4.862	47.556	18.389	70.432	154.191	0	1
AE10	409.395	0.457	-2.044	10.814	4.104	35.17	173.52	1	2
AE11	451.475	2.174	-4.304	12.264	4.702	46.2	158.563	1	1
AE12	437.449	0.88	-3.187	3.14	1.078	28.032	180.584	1	2
AE13	481.458	1.687	-3.967	9.257	3.469	41.162	178.51	1	2
AE14	495.485	2.11	-4.513	10.217	3.86	44.404	177.778	1	2
AE15	523.539	2.669	-5.236	6.99	2.561	31.769	180.173	2	2
AE16	509.512	2.231	-4.644	5.617	2.022	27.508	187.96	2	2
AE17	537.566	3.246	-5.655	11.467	4.372	38.999	176.757	2	2
AE18	523.539	2.505	-4.717	7.266	2.67	31.111	185.423	2	2
Amlodipine	408.881	3	-4.109	194.977	130.228	85.498	105.225	0	1

[a] M.W.: Molecular weight < 500 are acceptable.

[b] QPlogPo/w: Coefficient of partition between octanol and water predicted. Values between -2.0 and 6.5 are acceptable.

[c] QPlogS: Predicted aqueous solubility. Values between –6.5 – 0.5 are acceptable.

[d] QPPCaco: Predicted apparent Caco-2 cell permeability expressed in nm/sec. Recommended values <25 poor, >500 great.

[e] QPPMDCK: Predicted apparent MDCK cell permeability

[f] % Human Oral Absorption: Percent Human Oral Absorption. 80% is considered high while less than 25% is considered poor.

[g] PSA: Polar Surface Area

[h] Rule of five: Lipinski's rule

[i] Rule of three: Jorgensen's rule

CONCLUSION

In conclusion, this study represents a significant advancement in the quest for innovative antihypertensive medicines. A promising series of 1,4-dihydropyridine-based hybrids with No donor was developed as prospective replacements to amlodipine through a novel approach encompassing strategic design, synthesis, and extensive *in silico* evaluation. This comprehensive study involved the use of crystallography, molecular docking, and ADMET profiling. The examination of crystal structure provided valuable structural insights, laying the foundation for subsequent computational evaluations. The existence of the butyl group was substantiated by the better molecular docking results with the concerned calcium channels as compared to amlodipine. ADMET and SAR evaluation uncovered pivotal insights for the future refinement of antihypertensive activity. Furthermore, excellent binding affinity, high GI absorption, no BBB permeability, and the drug likeliness nature of the synthesized hybrids established from the *in silico* ADMET assessments, suggest their suitability for further development. In particular, AE12 showcased extraordinary *in silico* profiling and its crystal structure manifests the molecular interactions with biological systems. This collective effort establishes a robust foundation for the progression and potential clinical applications of these candidates in antihypertensive drug discovery. In essence, this research significantly contributes to the growing scenario of innovative therapeutics by offering prospective solutions for hypertension management and underscoring the importance of exploring novel hybrids in drug design and development.

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Declaration of interest The authors report no conflicts of interest.

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