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DESIGN, SYNTHESIS, AND IN SILICO EVALUATION OF 1,4 DIHYDROPYRIDINE AND 3,4 DIHYDROPYRIMIDINE 2(1H)-ONES/THIONE DERIVATIVES

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ABSTRACT
Background: Pyridine and pyrimidine derivatives occupy a central position in medicinal chemistry owing to their broad pharmacological significance. In particular, 1,4-dihydropyridines and 3,4-dihydropyrimidines are known for their anti-hypertensive and anti-anginal activities, encouraging further exploration of their chemical space. **Methodology:** This study aimed to design and synthesize a novel series of nineteen derivatives (PS-1 to PS-19) based on 1,4-dihydropyridine and 3,4-dihydropyrimidine-2(1H)-ones/thiones, employing a green synthetic strategy. The pharmacological viability of these compounds was assessed through in silico profiling. A catalyst-free "on-water" approach was used for synthesis, aligning with green chemistry principles to ensure eco-friendliness, operational simplicity, and high yield. Structural elucidation of the synthesized compounds was performed using infrared (IR) and proton nuclear magnetic resonance (^1H NMR) spectroscopy. Purity was assessed via thin-layer chromatography (TLC). Pharmacological activity, physicochemical properties, and toxicity profiles were evaluated using PASS Online, Swiss ADME, and Protox-II. **Results and Discussion**: Among the compounds screened, PS-4 demonstrated the most favorable docking affinity (−49.20), outperforming benchmark calcium channel blockers such as Nifedipine and Felodipine. The developed green synthetic method successfully yielded 19 target compounds with desirable purity and structural fidelity. Three compounds out of 19 showed a strong docking score towards the receptor protein. **Conclusion:** In silico results revealed favorable pharmacological potential and acceptable toxicity margins for several derivatives, suggesting they are promising candidates for further pharmacodynamic and therapeutic investigations.

INTRODUCTION

In drug discovery and design, heterocyclic derivatives are like versatile tools with special properties [1]. Among these, pyridine and pyrimidine are significant nitrogen-containing compounds with six-membered rings. They're found naturally in important substances like NAD nucleotides, vitamin B6 (pyridoxal), and

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various alkaloids. Pyridine shares many similarities with benzene, particularly in having six π-electrons distributed across its ring [2]. Despite their stability, pyridine and its derivatives have a distinct, quite strong, and unpleasant smell. However, this stability, along with their ability to stack on top of each other (π-stacking), form hydrogen bonds, and resist high temperatures, makes them ideal for designing new drugs [3].

Pyrimidine, on the other hand, is crucial as it forms the building blocks of nucleic acids, including thymine, uracil, and cytosine. Many important medicinal compounds, such as 5-fluorouracil, prazosin, buspirone & stavudine, contain the pyrimidine nucleus [4]. Understanding the characteristics of these compounds is essential for discovering new drugs and designing effective treatments. This paper will explore the significance of pyridine and pyrimidine derivatives in drug research and development.

The 1,4-dihydropyridine (1,4-DHP) and 3,4-dihydropyrimidine (DHPM) -2(1H)-one/thione scaffolds are pharmacologically privileged moieties with broad therapeutic relevance. 1,4-DHPs are established calcium channel blockers used in antihypertensive and antianginal therapy, with additional antioxidant, neuroprotective, and anticancer properties. Their synthetic accessibility via the Hantzsch reaction supports structural diversification. DHPMs, typically obtained via the Biginelli reaction, also exhibit calcium-channel-blocking activity, as well as antimicrobial, antioxidant, anticancer, and antiviral effects. Their modifiable structure and compatibility with green synthetic methods make them attractive candidates for sustainable drug development [5].

MATERIALS AND METHODS

Designing a library of compounds

A total of nineteen (PS 1 to PS 19) compounds were designed containing derivatives of 1,4-DHP and 3,4-DHPM- 2(1H)-one/thione.

Pharmacological Evaluation, ADMET Study, Toxicity Analysis, and Molecular Docking Study

The pharmacological potential of the synthesized derivatives was evaluated in silico using the Prediction of Activity Spectra for Substances (PASS) online platform [6], which estimates biological activities from compound molecular structures. To further characterize the drug-like behavior of these candidates, Swiss ADME was employed to predict key pharmacokinetic parameters, assess medicinal chemistry feasibility, and determine drug-likeness profiles [7, 8]. Toxicological assessments were carried out using the Protox-II web server, which provides comprehensive predictions regarding acute toxicity, hepatotoxicity, carcinogenicity, mutagenicity, and immunotoxicity [9]. These evaluations are pivotal for establishing the safety and therapeutic viability of the compounds, thereby supporting their progression toward regulatory approval in the drug development pipeline.

Computational molecular docking is a valuable tool for studying protein-ligand interactions and is widely used in drug discovery and development. Ligands are prepared by sketching their structures, converting them into three-dimensional (3D) representations, and then performing energy minimization. Molecular docking predicts the binding conformation & binding free energy of small molecules to the target protein [10]. In this study, molecular docking was performed using V-Life MDS 4.6 software.

Protein Preparation

The Protein Data Bank provided the crystal structure of the target protein, an L-type calcium channel blocker with voltage-gated calcium channel Ca2+ selectivity (PDB ID: 4MS2). The VLifeMDS suite was used to prepare the proteins. To prevent interference with docking analysis, all non-essential heteroatoms and crystallographic water molecules were eliminated. To guarantee proper protonation states, hydrogen atoms were included in the protein structure. Bond orders were adjusted, and the model's structural integrity was confirmed. To eliminate steric conflicts and produce a stable conformation suitable for molecular docking, the protein structure was then energy-minimized using the force field built into VLife [11].

Ligand Preparation

Ligand molecules were either sketched using the built-in molecule builder in VLifeMDS or imported from standard molecular file formats such as MOL or SDF (Figure 1). Each ligand was converted to its three-dimensional representation, and the correct stereochemistry was ensured. Hydrogen atoms were added, and geometrical optimization was performed using molecular mechanics protocols available within the software.

The finalized ligand structures were saved in a docking-compatible format (e.g., MOL2 or PDB) for use in downstream molecular docking studies [12]. Calcium-channel blockers like Nifedipine (NFD) & Felodipine (FLD) served as references.

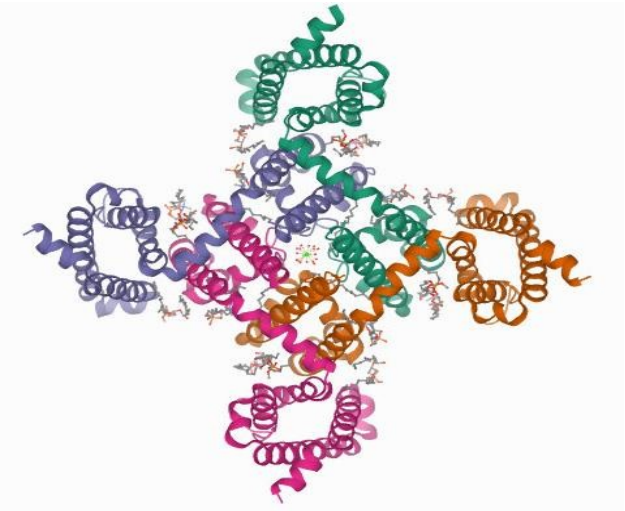


Figure 1: Structural basis of Ca2+ selectivity of a voltage-gated calcium channel (4MS2)

1,4-DHPs are recognized for their diverse pharmacological activities, notably as calcium channel antagonists. The common heterocyclic ring structure among these compounds underlies their varied therapeutic effects, encompassing anti-hypertensive, anti-anginal, anti-tumor, anti-inflammatory, anti-tubercular, analgesic, and anti-thrombotic properties. In this study, we elucidate the design, synthesis, and hypotensive evaluation of 1,4-DHP [3,13].

In Scheme I (Figure 2), a mixture containing aldehyde (2 mmol), ethyl acetoacetate (2.26 mL), and Ammonium acetate (1 mmol) was dissolved in ethanol or Water (2–3 mL) at 70-80°C for a certain period, typically 1 to 10 hours. After the reaction was completed, confirmed by TLC, the mixture was poured into ice-cold water and then extracted with ethyl acetate. The organic layer was treated with sodium thiosulfate and water, then dried and concentrated under vacuum. The resulting crude products were purified by recrystallization to obtain the final product [14]. This protocol was effectively adapted to a variety of carbonyl substrates, including furfuraldehyde, ethyl acetoacetate, formaldehyde, acetylacetone, isobutyl methyl ketone, and ethyl methyl ketone, each yielding well-defined condensation products with satisfactory purity and yield.

Synthetic Scheme: ***Synthesis of 1,4-DHP derivatives***

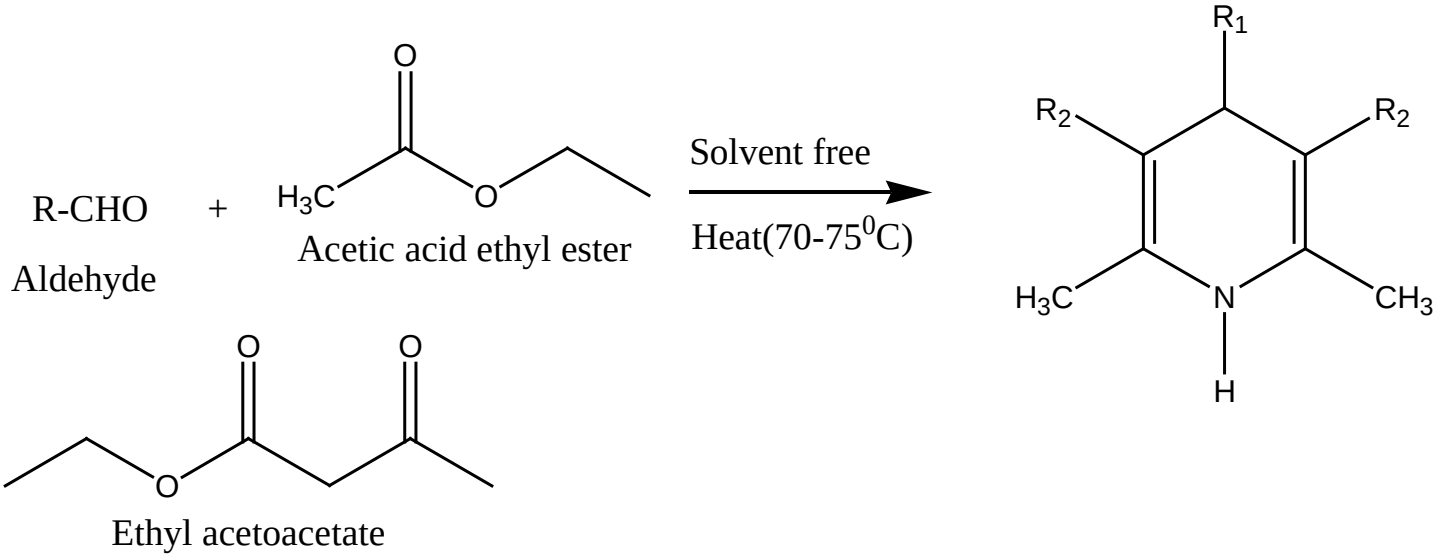


Figure 2: Scheme I - Synthesis of 1,4-DHP derivatives

In Scheme II (Figure 3), a three-component reaction involving aldehyde, ethyl acetate, and urea as a model system [15], [16]. A series of 1,2,3,4-tetrahydropyrimidine derivatives was synthesized via a one-pot multicomponent reaction. In a typical procedure, a mixture of the respective aldehyde (2 mmol), ketone (2.26 ml), urea (1 mmol), and/or thiourea (1 mmol) was refluxed in 2–3 ml of distilled water at 70–75 °C for 3 hours. Reaction progress was monitored by TLC using suitable solvent systems. Upon completion, the reaction mixture was cooled to ambient temp., and the resulting precipitate was collected by filtration. Crude products were purified by recrystallization from ethanol to afford the final compounds in analytically pure form [17,18].

This protocol was employed using a variety of substrates, including furfuraldehyde, ethyl acetoacetate, formaldehyde, acetylacetone, isobutyl ketone, and ethyl methyl ketone, yielding the well-defined products with satisfactory purity and yield.

Scheme - II Synthesis of 3,4-DHPM derivatives

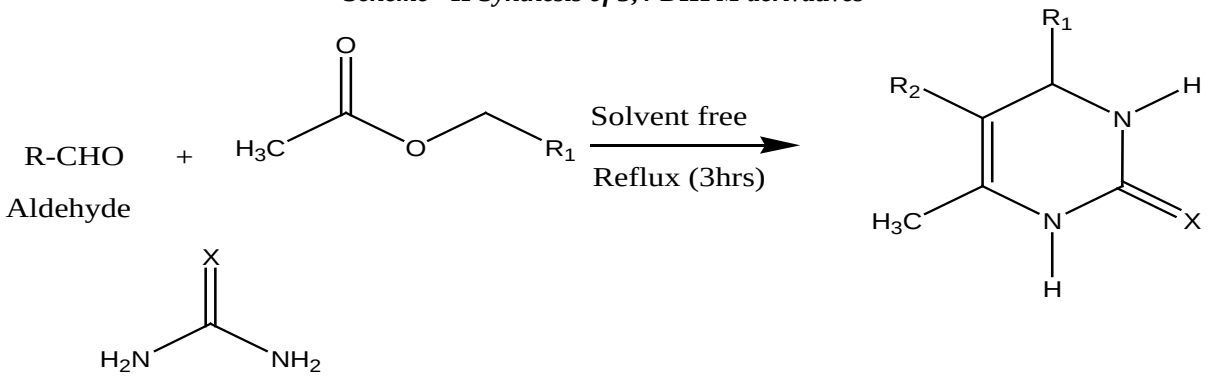


Figure 3: Scheme - II Synthesis of 3,4DHPM- 2(1H)-ones/thiones derivatives

RESULT AND DISCUSSION

Molecular Docking scores of the designed compounds were evaluated using the VLife MDS software and compared with those of the standard drugs Nifedipine and Felodipine. 2D image and 3D image of molecular docking of nifedipine with protein 4MS2 are shown in Figures 4a and 4b, respectively.

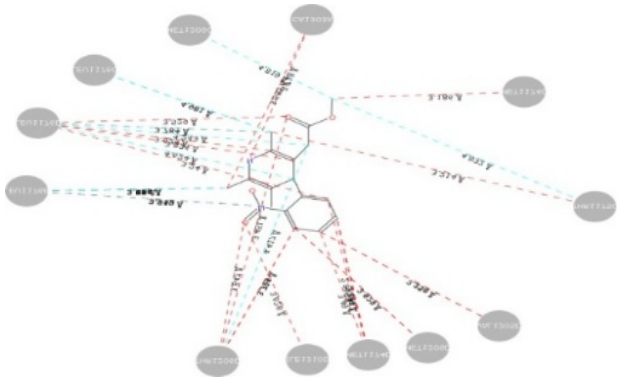


Fig.4a: 2D images of molecular docking of nifedipine with protein 4MS2

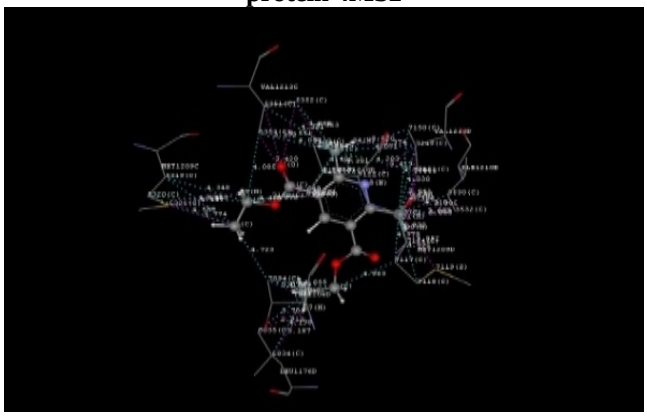


Fig 4b: 3D images of molecular docking of nifedipine with protein 4MS2

Docking scores and evaluation of the antihypertensive and antianginal activity of compounds (PS-1 to PS-19), Pa (probability to be active), and Pi (probability to be inactive), along with standard drugs, were summarized in Table 1

In-silico evaluation of physicochemical properties of designed molecules

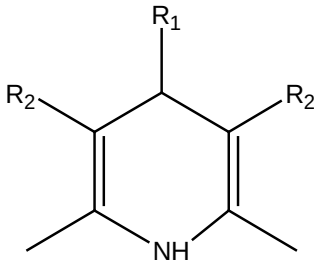
In this study, the pharmacokinetic properties of compounds (PS-1 to PS-19) were evaluated, and the Lipinski rule of five, Water solubility, GI absorption, and blood-brain barrier permeability were evaluated along with Bioavailability (Table 2).

Evaluation of Toxicological Parameters of design compounds by using (Protox-II)

Selected compounds from the docking and pharmacological activity studies were evaluated for their toxicity profiles using Protox II software, as summarized in Table 3.

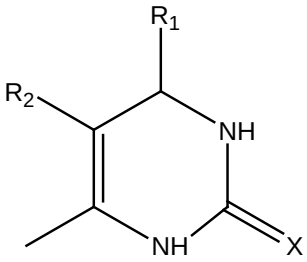
Synthetic scheme

From the above study, PS-1, PS-4, PS-5, PS-9 as Series –A and PS-15, PS-16, PS-18 as Series-B compounds have been selected for synthesis.



(Series - A)Four derivatives of 1,4-dihydropyridine (Series A) were synthesized using scheme I. Physiochemical properties, yield, and M.P. of selected compounds of 1,4-dihydropyridine derivatives are summarized in Table 4.

1. 3,5-diethyl, 2,6-dimethyl- 1,4-dihydropyridine-3, 5-dicarboxylate (PS-1).
2. 3,5-diethyl-1,4(furan-2-yl)-2,6-dimethyl1,4-dihydropyridine-3,5-dicarboxylate (PS-4).
3. 1-[5-acetyl-4-(furan-2-yl)-2,6-dimethyl1,4-dihydropyridine-3-yl] ethan-1-one (PS- 5).
4. 2,3,5,6-tetramethyl-4-phenyl-1,4-dihydropyridine (PS-9).



X = O , S

(Series - B) Three derivatives of 3,4-DHPM (Series B) were synthesized using scheme II.

Physiochemical properties, yield, and M.P. of selected compounds of 3,4-DHPM derivatives (Table 4).

1. Ethyl-6-methyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine-5-carboxylate (PS-15).
2. 1-(6-Methyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidin-5-yl) ethan-1-one (PS-16).
3. 5,6-Dimethyl-1,2,3,4-tetrahydropyrimidin-2-thione (PS-18).

Table 1: Molecular Docking score and pharmacological activity of designed molecules

Ligands	Dock score	Antihypertensive Activity		Antianginal Activity	
		Pa	Pi	Pa	Pi
NFD	-42. 97	0,965	0,004	0,809	0,005
FLD	-38. 39	0,927	0,004	0,763	0,005
PS-1	-38. 20	0,854	0,004	0,658	0,014
PS-2	-26. 84	0,824	0,004	0,642	0,015
PS-3	-33. 65	0,749	0,004	0,602	0,021
PS-4	**-49.20**	0,735	0,004	0,672	0,012
PS-5	-38. 17	0,537	0,004	0,502	0,004
PS-6	-41. 28	0,940	0,004	0,790	0,005
PS-7	-34. 75	0,821	0,005	0,624	0,017
PS-8	-34. 51	0,837	0,004	0,707	0,009
PS-9	-38.94	0,894	0,004	0,738	0,007
PS-10	**-46. 88**	0,865	0,004	0,739	0,007
PS-11	-39. 26	0,805	0,005	0,615	0,019
PS-12	-35. 03	0,724	0,005	0,635	0,006
PS-13	**-47. 58**	0,752	0,005	0,650	0,015
PS-14	**-46. 79**	0,805	0,005	0,715	0,008
PS-16	-28. 70	0,320	0,320	0,623	0,018
PS-17	-29. 38	0,451	0,451	0,691	0,070
PS-18	-25. 15	0,470	0,470	0,725	0,007
PS-19	-37. 09	0,627	0,627	0,627	0,018

Pa: probability to be active, Pi: probability to be inactive

Table 2: ADME prediction of compounds by SWISS ADME

Compound code	Mol. Wt (gm/mol)	LogP o/w	Water solubility	GI	BBB	Bioavailability score
NFD	346.33	2.87	-3.15	High	No	0.55
FLD	384.25	3.46	-4.44	High	Yes	0.55
PS-1	253.29	1.85	-3.00	High	yes	0.55
PS-2	137.22	1.85	-2.78	High	Yes	0.55
PS-3	193.33	3.30	-3.78	High	Yes	0.55
PS-4	319.35	2.34	-3.68	High	No	0.55
PS-5	259.30	1.86	-4.21	High	Yes	0.55
PS-6	329.39	3.30	-5.26	High	Yes	0.55
PS-7	269.34	2.54	-4.11	High	Yes	0.55

Compound code	Mol. Wt (gm/mol)	LogP o/w	Water solubility	GI	BBB	Bioavailability score
PS-8	269.42	3.36	-5.97	High	Yes	0.55
PS-9	213.32	3.30	-5.10	High	Yes	0.55
PS-10	371.43	2.53	-5.51	High	No	0.55
PS-11	311.37	4.43	-5.31	High	Yes	0.55
PS-12	311.37	2.62	-6.29	High	yes	0.55
PS-13	255.35	3.32	-5.44	High	Yes	0.55
PS-14	376.32	2.62	-4.78	High	No	0.55
PS-15	200.06	1.76	-2.55	High	Yes	0.55
PS-16	329.39	1.76	-2.55	High	yes	0.55
PS-17	170.28	1.50	-2.36	High	Yes	0.55
PS-18	142.22	0.92	-1.90	High	No	0.55
PS-19	214.28	1.05	-2.19	High	No	0.55

Table 3: Toxicity profile of selected molecules using Protox II

Compound Code	Predicted LD50	Predicted Accuracy	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
NFD	202	70.79%	Active	Inactive	Inactive	Inactive	Inactive
FLD	250	100%	Inactive	Inactive	Inactive	Inactive	Inactive
PS-1	2000	69.26%	Inactive	Inactive	Inactive	Inactive	Inactive
PS-4	3000	54.20%	Inactive	Inactive	Inactive	Inactive	Inactive
PS-5	1200	57.20%	Inactive	Inactive	Inactive	Inactive	Inactive
PS-9	1700	67.38%-	Inactive	Inactive	Inactive	Inactive	Inactive
PS-15	1353	67.38%	Active	Inactive	Inactive	Inactive	Inactive
PS-16	1000	54.26%	Inactive	Inactive	Inactive	Inactive	Inactive
PS-18	1000	54.26%	Inactive	Inactive	Inactive	Inactive	Inactive

Table 4: Physicochemical properties of synthesized 1,4- DHP and 3,4-DHPM compounds

Compound Code	R_1	R_2	X	Yield (%)	R_f value	Mol. Wt. g/mol	M. P (°C)
PS-1	H	$COOC_2H_5$	-	69 .26%	0.6	253.29	158°C
PS-4	Furfural	$COOC_2H_5$	-	39%	0.5	319.35	150°C
PS-5	Furfural	$COCH_3$	-	65.41%	0.8	259.30	165°c
PS-9	Phenyl	CH_3	-	45.36%	0.9	213.32	170°C
PS -15	H	$COOC_2H_5$	S	85 13%	0.8	200.06	212°C
PS - 16	H	$COCH_3$	S	78.65%	0.4	165.23	231°C
PS - 18	H	CH_3	S	69%	0.6	142.22	224°C

(Mobile Phase: Toluene: Ethyl acetate used for TLC)

Spectral characterization of synthesized derivatives

(PS-1) Molecular Formula: $C_{13}H_{19}NO_4$; Formula Weight: 253.298; It was obtained as a white crystalline solid. Melting Point- 158 ℃; IR(KBr)- 3344 cm^{-1} (N-H stretch) 1485 cm^{-1} (C==C), 1730 cm^{-1} (C==O ester), 3096 cm^{-1} (Aromatic C-H), 2981 cm^{-1} (Aliphatic C-H)

^{1}H NMR: δ 1.18-4.269 (10H, t, q), 2.452 (6H, s), 2.9619 (2H, d), 3.85 (N, s).

(PS-4) Molecular Formula: $C_{17}H_{21}NO_5$; Formula Weight: 319.357; It was obtained as a white solid. Melting Point- 150 ℃; IR(KBr)- 3363 cm^{-1} (N-H stretch), 1289 cm^{-1} (C-H), 1690 cm^{-1} (C=C), 3247 cm^{-1} (Aromatic C-H), 3010 cm^{-1} (Aliphatic C-H).

^{1}H NMR: δ 1.24-4.162 (10H t, q), 2.4759 (6Hs), 6.19-7.379 (3Hd), 4.323 (1Hs), 3.85 (Ns).

(PS- 5) Molecular Formula: $C_{15}H_{17}NO_3$; Formula Weight: 259.305; It was obtained as a brown crystalline solid. Melting Point- 165 ℃ ; IR(KBr)- 3342 cm^{-1} (N-H stretch), 1366 cm^{-1} (C-H), 1700 cm^{-1} (C=C), 3117 cm^{-1} (Aromatic C-H), 2981 cm^{-1} (Aliphatic C-H).

^{1}H NMR: δ 2.28 (6H, s), 2.481 (6H, s), 6.179-7.376 (3Hd), 4.353 (1Hs), 3.85 (Ns),

(PS-9) Molecular Formula: $C_{15}H_{19}N$; Formula Weight: 213.324. It was obtained as a yellow solid. Melting Point- 170℃ ; IR(KBr)- 3448 cm^{-1} (N-H stretch), 3089 cm^{-1} (Aromatic C-H), 2989 cm^{-1} (Aliphatic C-H), 1700 cm^{-1} (C=C).

^{1}H NMR: 1.6524 (6H, s), 2.09 (6H, s), 7.186-7.310 (5H, t, d), 3.807 (1H, s).

(PS-15) Molecular Formula: $C_8H_{12}N_2O_2S$; Formula Weight: 200.256; It was obtained as a white crystalline solid. Melting Point- 212 ℃ ; IR(KBr)- 3397 cm^{-1} (N-H stretch), 1545 cm^{-1} (C=C), 2687 cm^{-1} (C=S), 3058 cm^{-1} (Aromatic C-H), 1253 cm^{-1} (C-N), 1690 cm^{-1} (C=O),

^{1}H NMR: δ 1.163 (3H, t), 4.25 (2H, q), 2.451 (3H, s), 4.37-4.378 (2H, d), 3.80 (N, s).

(PS-16) Molecular Formula: $C_7H_{10}N_2OS$; Formula Weight: 170.23; It was obtained as a red solid. Melting Point- 231 ℃ ; IR(KBr)- 3463 cm^{-1} (N-H stretch), 1590 cm^{-1} (C=C), 2680 cm^{-1} (C=S), 3052 cm^{-1} (Aromatic C-H), 1253 cm^{-1} (C-N), 1710 cm^{-1} (C=O),

^{1}H NMR: 2.269 (3H, s), 2.435 (3H, s), 3.98-4.13 (2H, d). 4.06 (1H, d), 3.80 (N, s).

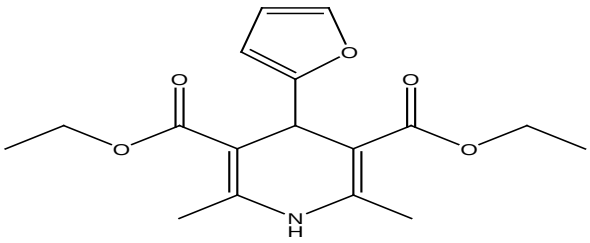
(PS-18) Molecular Formula: $C_6H_{10}N_2S$; Formula Weight: 142.22; It was obtained as a green solid. Melting Point- 224 ℃ ; IR(KBr)- 3455 cm^{-1} (N-H stretch), 1590 cm^{-1} (C=C), 2680 cm^{-1} (C=S), 3052 cm^{-1} (Aromatic C-H), 1253 cm^{-1} (C-N).

^{1}H NMR: 1.627 (3H, s), 1.93 (3H, s), 3.87-4.0 (2H, d), 3.94 (1H, d), 3.85 (N, s).

The Outcomes of compiled data of molecular docking, pharmacological activity, and toxicity profile were summarized in Table 5. Structures of optimized compounds after in silico evaluations are shown in Figure 4a and 4b.

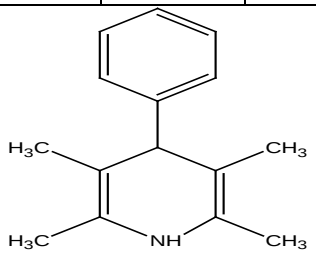
Table 5: Compiled data of docking, pass-online, and toxicity data for the synthesized compound

Compound	Dock score	Pass online Anti-hypertensive(Pa)	Pass online Antianginal(Pa)	Hepato-toxicity	Carcino-genicity	Immuno-toxicity	Mutage-nicity	Cytoto-xicity
NFD	-42.97	0,965	0,901	-	-	-	-	-
FLD	-38.94	0,894	0,738	-	-	-	-	
PS - 4	**-49.20**	0,737	0,672	-	-	-	-	-
PS - 9	**-38.94**	**0,894**	0,738	-	-		-	-
PS - 1	-38.20	0,854	0,658	-	-	-	-	-
PS -5	-38.17	0,537	0,502	-	-	-	-	-
PS -16	-25. 70	0,320	0,625	-	-	-	-	-
PS -18	-25.15	0,470	0,725	-	-	-	-	-
PS -15	-	0,791	0,540	**Active**		-	-	-



PS-4

Figure 5a: Chemical structure of PS 4



PS-9

Figure 5 b: Chemical structure of PS -9

According to the Molecular Docking results, Compound PS-4 (Figure 5a) has a higher docking score of -49.20, surpassing the standard drugs NFD (-42.97) and FLD (-38.39). The molecular docking analysis of PDB ID 4MS2 reveals consistent interactions with amino acid residues THR1206, MET1209, ILE1210, LEU1176, and VAL1213, indicating their critical role in stabilizing dihydropyridine binding. Ligands such as NFD and analogs (PS-4, PS-13, PS-14) exhibited strong affinity, suggesting that these residues are vital to the active site and modulate calcium channel function, thereby contributing to antihypertensive activity.

Toxicity profile the compound PS-1, PS-4, PS-5, PS-9, PS-15, PS-16, PS-18 showed better LD_{50} than NFD and FLD. These compounds were synthesized and evaluated for their spectral characteristics and purity.

Compound PS-4(Figure 5a) exhibited the highest docking score of –49.20 among the synthesized series, outperforming standard reference drugs NFD and FLD.

Compound PS-9(Figure 5b) demonstrated the highest predicted pharmacological activity, with anti-hypertensive and anti-anginal scores of 0.894 and 0.738, respectively, as determined by PASS online analysis.

In the series of synthesized compounds, Compound PS-15 was found to possess Hepatotoxicity as per the Protox II software. The 3,4 DHPM-2(1H) thione derivatives are found to be more toxic than the reference NFD and FLD.

CONCLUSION

In this study, a comprehensive in silico evaluation of 19 novel derivatives of 1,4-DHP and 3,4-DHPM-2(1H)-thione was undertaken to elucidate their pharmacodynamic potential and toxicity profiles. Utilizing PASS Online and Protox-II platforms, we identified promising leads with favorable therapeutic indices and mechanistic plausibility. Among the compounds screened, PS-4 demonstrated the most favorable docking affinity (−49.20), outperforming benchmark calcium channel blockers such as NFD and FLD, thereby positioning itself as a compelling candidate for further investigation. Additionally, PS-9 exhibited pronounced anti-hypertensive and anti-anginal properties, with predictive activity scores of 0.894 and 0.738, respectively, underscoring its potential for cardiovascular intervention.

Conversely, compounds such as PS-15 displayed hepatotoxic tendency based on Protox-II predictions. Notably, compounds PS-1, PS-4, PS-5, PS-9, PS-16, and PS-18 showed no detectable toxicity, highlighting their viability for progression in the drug development pipeline. The comparative toxicity analysis revealed that 3,4-DHPM-2(1H)-thione derivatives exhibited greater predicted toxicological liabilities than their 1,4-DHP counterparts. Structure-activity relationship trends indicated that substitution at the 3rd and 5th positions in the dihydropyridine scaffold, and the 5th position in the Dihydropyrimidine nucleus, favored anti-hypertensive and anti-anginal activity.

Overall, this study reaffirms the utility of computational methodologies in early-phase drug discovery, providing a rational framework for prioritizing lead candidates. Further experimental validation, including in vitro and in vivo pharmacological assays, is warranted to confirm efficacy and safety profiles, potentially contributing to the development of next-generation therapeutics for cardiovascular disorders.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Suvarna Katti contributed to conceptualization, Visualization, and methodology. Manisha Tayde contributed to data Collection, writing, and editing of the manuscript. Anuja Bhosale contributed to the manuscript's overall visualization and editing.

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