

In Silico ADMET, Network Pharmacology, and Docking Analysis of Green-Synthesized Tetrahydropyrimidine Derivatives

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Pyrimidine derivatives are significant heterocyclic frameworks exhibiting several pharmacological actions, including antihypertensive properties. In this research, two new tetrahydropyrimidine derivatives were synthesized using an environmentally friendly Biginelli reaction that was sped up by onion peel powder, which is a bio-waste material that can be reused. IR and mass spectrometry was used to establish the structures of the synthesised compounds, and computer modeling was performed to see how well they may work as antihypertensive drugs. SwissADME, pkCSM, and ProTox-II tools were used to check the ADMET properties. Network pharmacology analysis, protein-protein interaction, Gene Ontology, and KEGG pathway enrichment analyses were used to find the common targets between genes linked to hypertension and targets linked to compounds. Molecular docking using AutoDock was performed on five important antihypertensive targets: Src kinase, MMP-2, GSK3 β , ROCK1, and PKCa. We then compared the results to those of the reference medication nifedipine. Both compounds had good drug-like and pharmacokinetic qualities, while Compound 1 had the best balance of ADME and safety. Docking findings showed that the synthesized compounds, especially Compound 1, had similar or stronger binding affinities to important targets than nifedipine. In general, these results indicate that the tetrahydropyrimidine derivatives are excellent candidates for further testing as antihypertensive medicines.

Keywords: ADMET Profiling; Biginelli Reaction; Green Synthesis; Molecular Docking; Network Pharmacology; Tetrahydropyrimidine.

The pyrimidine derivatives have turned out to be important heterocyclic rings in medicinal chemistry due to their broad spectrum of biological functions, such as anticancer, antibacterial, anti-inflammatory, and most specifically antihypertensive properties.¹⁻⁴ They are attractive targets of new drug development due to their structural diversity, which allows the formation of compounds that effectively bind several biological targets, such as angiotensin-converting enzyme

(ACE) and calcium channels.⁵⁻⁹ The Biginelli reaction, a classical multicomponent condensation reaction involving an aldehyde, a ketone (or a ketoester), and urea or thiourea, is a simple and effective process to prepare 3,4-dihydropyrimidin-2(1H)-ones/thiones.^{10,11} Heterocyclic compounds possess varied pharmacological characteristics, and the Biginelli reaction provides an exceptional method for producing molecular diversity in a single step.¹² In the past, the reaction required

intense acidic conditions and extended periods of time, but in recent times there has been a focus on enhancing its efficiency and sustainability.

The “one-drug-one-target-one-disease” model used in traditional drug discovery doesn’t work for disorders like hypertension that have several causes and involve complicated signaling networks. Network pharmacology signifies a paradigm shift, pinpointing principal hub targets using pathway enrichment analysis and an extensive investigation of GO/KEGG pathways to clarify multi-target processes.¹³⁻¹⁷

Every month, humankind generates millions of tons of bio-waste, most of which is generated through households, food stalls, restaurants, and food processing plants. Over the years, most of the biological waste has been disposed of in landfills, and the residue could cause harmful effects to our ecosystem, wildlife, and human health. Onion (*Allium Cepa* L.) is one of the most widely cultivated crops in the world, which is appreciated because of its medicinal, nutritional, and other functional qualities, and their by-products. Biological waste is produced annually, and it is the onion peel. According to surveys, food processing companies and human consumption in some countries, such as the US and European ones, generate over 100,000 tons of onion waste annually. Against this background of the rising need to have a simple, cost-efficient, and environmentally friendly approach to the synthesis of various heterocyclic privileged compounds, hereby, we report the use of onion peel as a natural catalyst in the synthesis of a major privileged structure in the pharmaceutical industry.¹⁸⁻²³ Previous studies have reported two uses: the water extract of burnt ash from onion peel waste (ash-water extract) in the synthesis of bisenols, and the water extract of onion peel in the synthesis of bisindolylmethanes.²⁴⁻²⁶ The current work is focusing on the synthesis and characterization of two new tetrahydropyrimidine derivatives using the environmentally friendly Biginelli reaction. They were assessed *in silico* for their potential antihypertensive effects using molecular docking against key network pharmacology targets (Src kinase [2SRC], MMP-2 [1M17], GSK3 α [1Q5K], ROCK1 [5IKR], PKC α [1GKC]) and through ADMET profiling. The results were also compared

to those of nifedipine, the standard calcium channel blocker, to see how effective and drug-like the synthetic compounds were.

MATERIALS AND METHODS

All the chemicals and solvents (technical grade) utilized in this experiment were purchased from Southern India Scientific Corporation (Chennai) and were used without further purification unless stated.

Onion Peel powder preparation

A local restaurant was used to collect onion trash to use for the study. The onion skin was stripped off from the bulb and wiped with distilled water. The peeled onions were dried in the air after four days. The dried onion peel was cut into little pieces and ground into a fine powder using a mortar and pestle.²⁷

Procedure for Green Synthesis

The onion peel powder was transferred into a round-bottom flask containing benzaldehyde (1.00 mmol), thiourea (1.00 mmol), and ethyl acetoacetate (1.00 mmol) and ethanol under solvent-free conditions. Magnetic stirring was then performed on the mixture, and it was heated to 120°C. Thin Layer Chromatography (TLC) was used to determine the progress of the reaction by using ethyl acetate and n-hexane (2:8) as the mobile phase. Recrystallized using ethanol and characterized using IR and MS.

Ligand Designing

Each of the molecules suggested was drawn with ChemDraw 16.0 and saved as a .mol2 file. The Avogadro program was used to construct the structures of the ligands and optimize them using the MMFF94 force field. *In silico* ADMET and molecular modelling ligand generation were also predicted by the conformations of the ligand that were designed and used.²⁸

ADMET Profiling

Canonical SMILES of the tetrahydropyrimidine derivatives were produced using ChemSketch, and subsequently these were inputted into Swiss ADME, Molinspiration, and pkCSM programs to estimate *in silico* ADME and other molecular characteristics. Protox-II was used to predict toxicological endpoints and organ toxicity.²⁹⁻³¹

Network Pharmacology Analysis

Disease and Compound Target Identification

We got 14,362 genes that are linked to hypertension from disease databases like DisGeNET and GeneCards. Using SwissTargetPredictions, we predicted 232 compound-related genes for the tetrahydropyrimidine derivatives. Using Venny 2.0³², we found 131 common target genes by crossing disease and compound gene sets.

PPI Network Construction

The 131 frequent target genes were imported into Cytoscape 3.9.1 to build a protein-protein interaction (PPI) network using the STRING database (medium confidence score > 0.4). Based on degree centrality (>15), betweenness centrality, and closeness centrality, network topology analysis found the top 10 hub targets: Src kinase (2SRC), MMP-2 (1M17), GSK3 α (1Q5K), ROCK1 (5IKR), PKC α (1GKC), and five more high-degree nodes.

Functional Enrichment Analysis

The top 10 hub targets were sent to DAVID 6.8 Bioinformatics Resources³³ (<https://david.ncifcrf.gov>) for functional annotation. We did Gene Ontology (GO) enrichment analysis in three areas: biological process (BP), cellular component (CC), and molecular function (MF).

KEGG Pathway Enrichment Analysis

Using the SangerBox (srplot) web platform (<http://www.bioinformatics.com.cn/srplot>)³⁴, we did a KEGG pathway analysis. Pathways that were significantly enriched (q -value < 0.05) are listed below in order of enrichment factor and gene count. The results were shown as bubble plots, with the size of the dots showing the number of genes and the color intensity showing $-\log_{10} p$.

In Silico Molecular Modelling

The hub targets chosen for molecular docking (Src kinase, MMP-2, GSK3 α , ROCK1, and PKC α) were determined by degree centrality analysis of the protein-protein interaction network utilizing the CytoHubba plugin. These proteins exhibited significant connectivity and are extensively recognized for their critical roles in the control of vascular tone, smooth muscle contraction, endothelial function, and intracellular signaling pathways associated with hypertension.

We used AutoDock to undertake molecular docking with the default genetic algorithm settings.

These settings are well-known and make sure that ligand-protein interaction predictions are accurate. To build protein structures, water molecules were taken out and polar hydrogens were added. Ligand geometries were energy-minimized before docking. We set the dimensions of the grid boxes to include the active binding sites of each target protein, which gave them enough room to change shape during docking.

RESULTS

Two new tetrahydropyrimidine derivatives were successfully made using a green Biginelli reaction with onion peel powder as a catalyst made from bio-waste. The yield for Compound 1 was 82%, and the yield for Compound 2 was 88%.

The IR spectrum of Compound 1 had distinct absorption bands at 3056 cm^{-1} , indicative of aromatic C–H stretching, and bands at 2915–2850 cm^{-1} , associated with aliphatic C–H stretching. The strong band at 1680 cm^{-1} showed that there was an ester carbonyl (C=O) group. The C=C stretching vibrations in aromatic compounds were seen at 1592, 1566, and 1553 cm^{-1} . The C–N and C=S stretching vibrations were seen at 1342 and 1324 cm^{-1} , respectively. More bands linked to C–O, C–N stretching, and aromatic C–H out-of-plane bending backed up the suggested structure even more. Mass spectrometry found a molecular ion peak at m/z 322 [M]⁺, which was in line with the projected molecular weight. The IR analysis of Compound 2 showed an N–H stretching vibration at 3371 cm^{-1} and an aromatic/aliphatic C–H stretching vibration between 3006 and 2930 cm^{-1} . Absorption bands at 1741 cm^{-1} and 1675 cm^{-1} , respectively, proved the presence of ester and amide carbonyl groups. The bands at 1595 and 1553 cm^{-1} were for aromatic C=C stretching and amide II stretching. The bands between 1248 and 1067 cm^{-1} were for C–O and C–N stretching, and C–S stretching and aromatic C–H bending vibrations were also seen. The molecular ion peak at m/z 319 [M]⁺ was the same as the estimated molecular mass. NMR analysis was not concentrated in this study, as the primary emphasis was on illustrating the viability of green synthesis utilizing onion peel extract and assessing the biological potential through in silico methodologies. In future studies, NMR characterization will be performed.

Drug likeness and Pharmacokinetic Profile

The physicochemical and pharmacokinetic properties of the synthesized compounds and the reference drug nifedipine were evaluated using

SwissADME and pkCSM (Tables 1 and 2). Both compounds complied fully with Lipinski's rule of five and showed favorable molecular weights, lipophilicity, and molecular complexity.

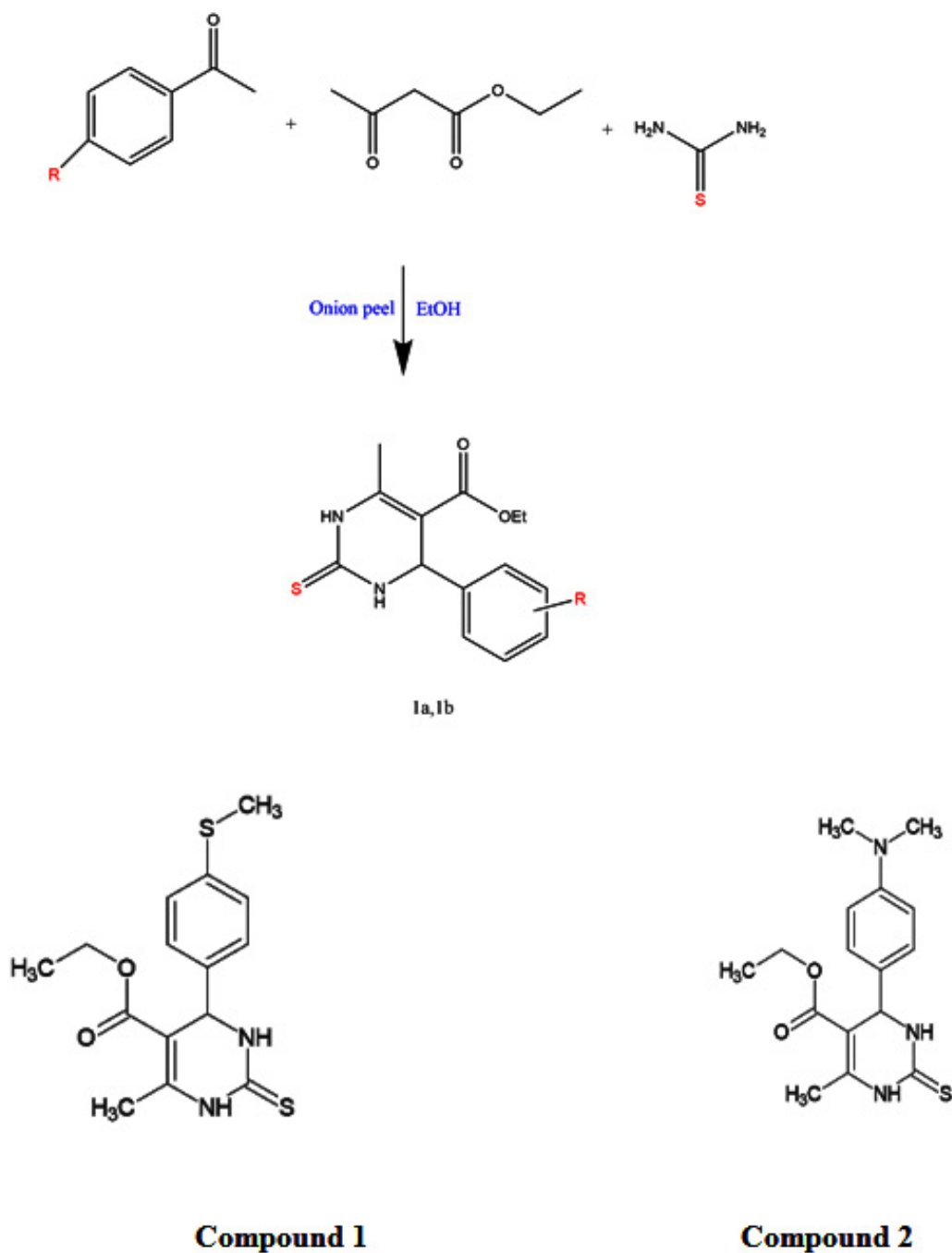


Fig. 1. Green synthesis of tetrahydropyrimidine derivatives (Compound 1 and Compound 2) via the Biginelli reaction using onion peel powder as a bio-waste catalyst

Compound 1 exhibited optimal drug-likeness with no Lipinski, Ghose, Veber, Egan, or Muegge violations. It showed a bioavailability score of 0.55 and good synthetic accessibility (3.67). The compound displayed high gastrointestinal absorption, excellent Caco-2 permeability, and no predicted P-glycoprotein substrate liability. No major CYP450-related metabolic risks were identified, suggesting metabolic stability.

Compound 2 also demonstrated acceptable drug-likeness and a similar bioavailability score (0.55). Gastrointestinal absorption and Caco-2 permeability were high, and no P-glycoprotein substrate activity was predicted. However, Compound 2 showed one PAINS alert and a predicted CYP3A4 substrate liability, indicating a potential risk for metabolic interactions.

Nifedipine exhibited favorable pharmacokinetic properties with high gastrointestinal absorption and moderate synthetic accessibility (3.81). However, it displayed multiple Brenk structural alerts, suggesting a comparatively higher likelihood of long-term structural liabilities.

ProTox-II's toxicological profiling showed that both produced compounds have moderate acute oral toxicity (Class III; LD₅₀ € : 500–2000 mg/kg) (Table 3). Compound 1 exhibited minimal hERG inhibition, absence of Ames mutagenicity, lack of carcinogenicity, and a low risk of hepatotoxicity.

Compound 2 had a comparable acute toxicity classification and minimal hERG inhibition; nevertheless, it was anticipated to be carcinogenic, thus posing a constraint for

Table 1. Physiochemical Properties of the synthesised compounds

Property	Compound 1	Compound 2	Nifedipine
Formula	C ₁₅ H ₁₈ N ₂ O ₂ S ₂	C ₁₆ H ₂₁ N ₃ O ₂ S	C ₁₇ H ₁₈ N ₂ O ₆
MW (g/mol)	322.45	319.42	346.33
Heavy Atoms	21	22	25
Aromatic Heavy Atoms	6	6	6
Fraction Csp ³	0.33	0.38	0.29
Rotatable Bonds	5	5	6
H-bond Acceptors	2	2	6
H-bond Donors	2	2	1
MR (Molecular Refractivity)	96.7	99.19	94.52
TPSA (Å ²)	107.75	85.69	110.45
Synthetic Accessibility	3.67	3.77	3.81

Table 2. ADME Results

Property	Compound 1	Compound 2	Nifedipine
GI absorption	High	High	High
BBB permeant	No	No	No
Pgp substrate	No	No	Yes
CYP1A2 inhibitor	Yes	Yes	Yes
CYP2C19 inhibitor	Yes	Yes	Yes
CYP2C9 inhibitor	Yes	Yes	Yes
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	Yes	No	No
Bioavailability Score	0.55	0.55	0.55
Lipinski violations	0	0	0
Ghose violations	0	0	0
Veber violations	0	0	0
Egan violations	0	0	0
Muegge violations	0	0	0

subsequent development. Nifedipine had a similar toxicity classification, characterized by mild hERG inhibition and an absence of carcinogenic indications.

Network Pharmacology analysis

Targets of Tetrahydropyrimidine Derivatives and Hypertension: The SwissTargetPrediction algorithm was able to successfully predict target genes for the two produced tetrahydropyrimidine derivatives, finding 232 probable target genes. We searched the DisGeNET and GeneCards databases for genes linked to high blood pressure. We found a total of 14,362 genes that are linked to high blood pressure. Venny 2.0 was used to compare the gene sets connected to compounds and diseases in order to find the possible molecular targets of tetrahydropyrimidine derivatives against hypertension. The Venn diagram analysis identified 131 overlapping genes (Fig. 1), indicating shared targets between the produced chemicals and hypertension pathogenesis.

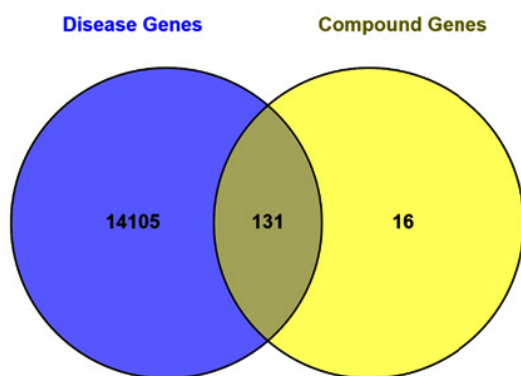


Fig. 2. Venn diagram showing the overlap between predicted targets of tetrahydropyrimidine derivatives and hypertension-associated genes, identifying 131 common targets

Building PPI networks and finding the main targets: The STRING database (medium confidence >0.4) was used to upload the list of 131 overlapping genes and look for protein-protein interactions (Fig. 2). The proteins have a higher degree of centrality if the node size is bigger and the color is darker. Using the Degree technique of the CytoHubba plug-in in Cytoscape 3.9.1, we found the top 10 hub proteins.

Perform Enrichment Analyses Using GO and KEGG Databases: A KEGG pathway enrichment analysis of the projected targets of the antihypertensive drugs showed that they were involved in many pathways linked to diseases and signalling. The most significantly enriched route was endocrine resistance (count = 7, $p = 9.03 \times 10^{-11}$), which means that hormone-regulated signalling pathways that are strongly related to blood pressure control, vascular tone, and metabolic balance were changed. Proteoglycans in cancer (count = 7, $p = 7.27 \times 10^{-9}$) and pathways in cancer (count = 7, $p = 2.21 \times 10^{-6}$) indicate the involvement of extracellular matrix remodeling, cell proliferation, and receptor-mediated signalling, which are also known to contribute to vascular stiffness and endothelial dysfunction in hypertension. Bladder cancer was identified as a highly significant pathway (count = 6, $p = 1.45 \times 10^{-6}$), indicating shared molecular targets implicated in smooth muscle contraction, growth factor signalling, and angiogenesis, activities pertinent to vascular control. The enrichment of pathways related to human cytomegalovirus infection (count = 6, $p = 8.71 \times 10^{-6}$) and Kaposi sarcoma-associated herpesvirus infection (count = 5, $p = 2.05 \times 10^{-5}$) shows how inflammatory and immune-mediated signalling can affect the heart, which supports the idea that inflammation plays a role in the progression of high blood pressure. Additionally, pathways directly associated with vascular and

Table 3. Toxicity Profile for the synthesised compounds

Molecule	AT	CT	Hi	AOT (LD50, mg/kg)	HT
Compound 1	-	-	Weak	500 – 2000 (Class III)	Low
Compound 2	-	+	Weak	500 – 2000 (Class III)	Moderate
Nifedipine	-	-	Weak	500 – 2000 (Class III)	Low

AT- Ames Mutagenicity, CT- Carcinogenicity, HI - hERG Inhibition, AOT- Acute Oral Toxicity, HT – Hepatotoxicity, (-) Negative, (+) Positive

therapeutic response mechanisms, such as EGFR tyrosine kinase inhibitor resistance (count = 5, $p = 5.7 \times 10^{-6}$), the relaxin signalling pathway (count = 5, $p = 4.01 \times 10^{-6}$), and fluid shear stress and atherosclerosis (count = 5, $p = 5.7 \times 10^{-6}$), were significantly enriched. These pathways are tightly linked to endothelial function, vasodilation, vascular remodeling, and anti-atherosclerotic actions, which strongly supports the idea that the chemicals investigated could lower blood pressure.

The KEGG enrichment results indicate that antihypertensive drugs operate via the multitarget modulation of endocrine signalling, vascular smooth muscle function, endothelial shear stress response, and inflammatory pathways, establishing a mechanistic foundation for their blood pressure-lowering and vasoprotective effects.

A Gene Ontology enrichment study of the projected targets of the antihypertensive drugs indicated substantial participation in biological

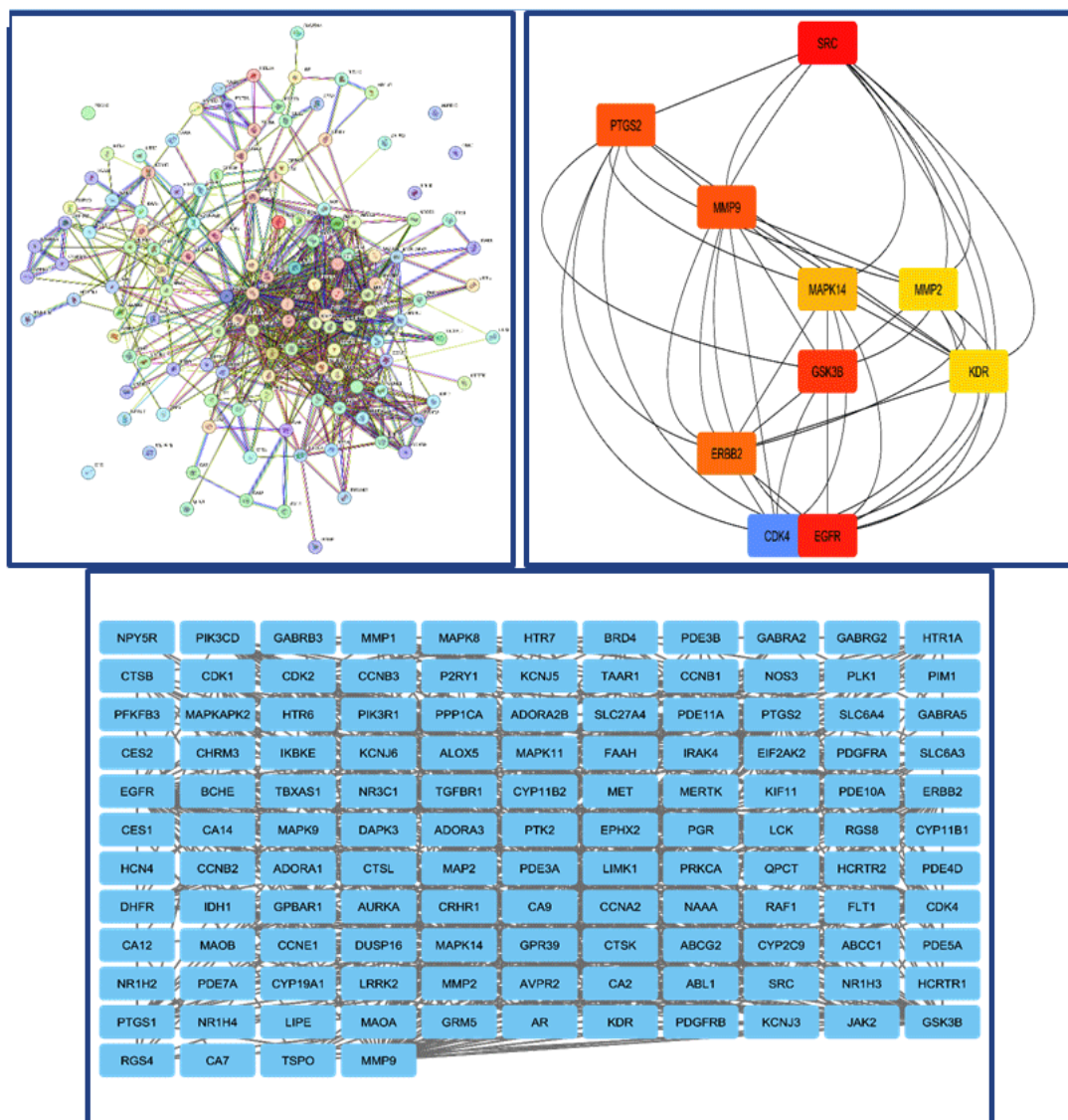


Fig. 3. Network pharmacology analysis of tetrahydropyrimidine derivatives against hypertension: (A) Protein–protein interaction (PPI) network of overlapping targets, (B) Top 10 hub proteins identified using CytoHubba, (C) Compound–gene–pathway interaction network.

processes, cellular components, and molecular functions related to vascular control and signal transduction. The most important biological processes were signal transduction (48) and the G protein-coupled receptor signalling pathway (23), which shows that receptor-mediated mechanisms are very important for controlling blood pressure. Processes associated with protein phosphorylation (count = 20), intracellular signal transduction (count = 15), protein autophosphorylation (count = 14), and lipid metabolic processes (count = 20) further indicate the modulation of kinase-driven signalling and metabolic pathways. Regulatory mechanisms, including the positive regulation of gene expression and transcription by RNA polymerase II, as well as the negative regulation of apoptosis and cell proliferation, suggest protective and adaptive effects on vascular cells. The enhancement of the MAPK cascade, ERK1/ERK2 cascade, and PI3K/Akt signalling regulation underscores critical pathways implicated in

endothelial function, vasodilation, and cellular survival.

The examination of cellular components revealed that the targets were predominantly situated in the membrane, plasma membrane, cytoplasm, and cytosol, indicating the participation of membrane-bound receptors and intracellular signalling proteins. The enhancement of receptor complexes, membrane rafts, and the basolateral plasma membrane signifies the presence of active signalling microdomains pertinent to vascular physiology. The presence of synaptic and neuronal components, such as synapse, postsynapse, glutamatergic synapse, and GABA-A receptor complex, indicates a possible neuromodulatory role in antihypertensive effects, while nucleoplasm location signifies transcriptional control. Kinase-related activities, such as kinase activity, protein kinase activity, and protein serine/threonine kinase activity, as well as ATP and nucleotide binding, were used to define molecular function enrichment.

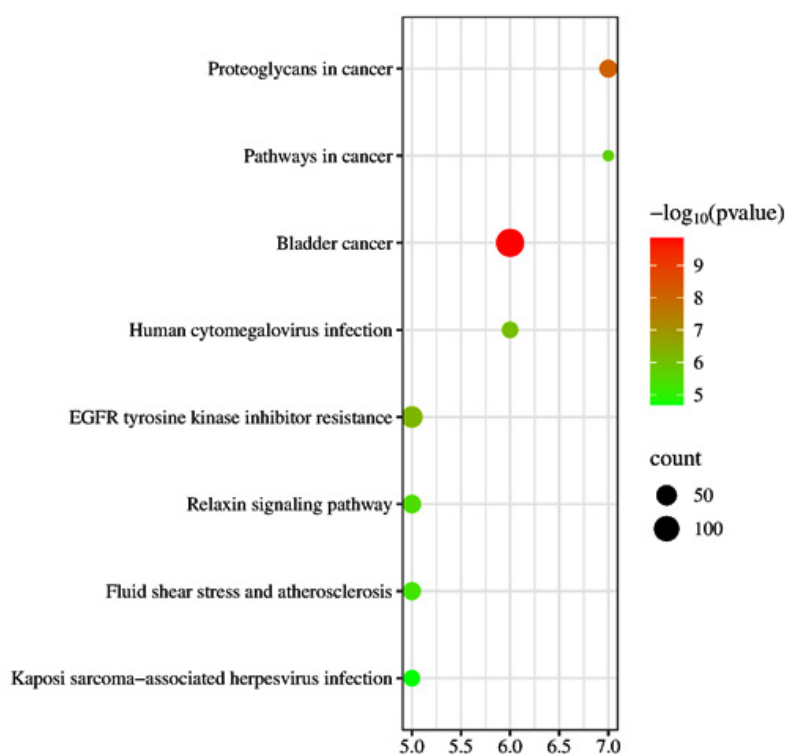


Fig. 4. KEGG pathway enrichment analysis of overlapping targets, highlighting key signalling pathways related to hypertension.

This suggests that phosphorylation-dependent signalling is widespread. The increase in protein tyrosine kinase activity, transmembrane receptor protein tyrosine kinase activity, and MAP kinase activity helps control vascular signalling that is caused by growth factors. Cyclic nucleotide phosphodiesterase activities (cAMP and cGMP), metal ion binding, heme binding, and nuclear receptor activity indicate the modulation of nitric oxide signalling, vascular relaxation, and hormone-dependent mechanisms. In general, these studies show that antihypertensive medicines work by coordinating the regulation of receptor signalling, kinase-mediated pathways, cyclic nucleotide

metabolism, and mechanisms that protect blood vessels.

Docking Results

The binding affinities of Compound 1, Compound 2, and the reference medication nifedipine against the chosen protein targets (1GKC, 5IKR, 1M17, 1Q5K, and 2SRC) were assessed using molecular docking analysis using AutoDock. Both developed compounds showed favorable binding in comparison to nifedipine across the majority of targets, according to the expected binding energies. Compound 1 had the highest binding affinity of all of them, especially against 1GKC (−8.1 kcal/mol) and 5IKR (−7.2 kcal/

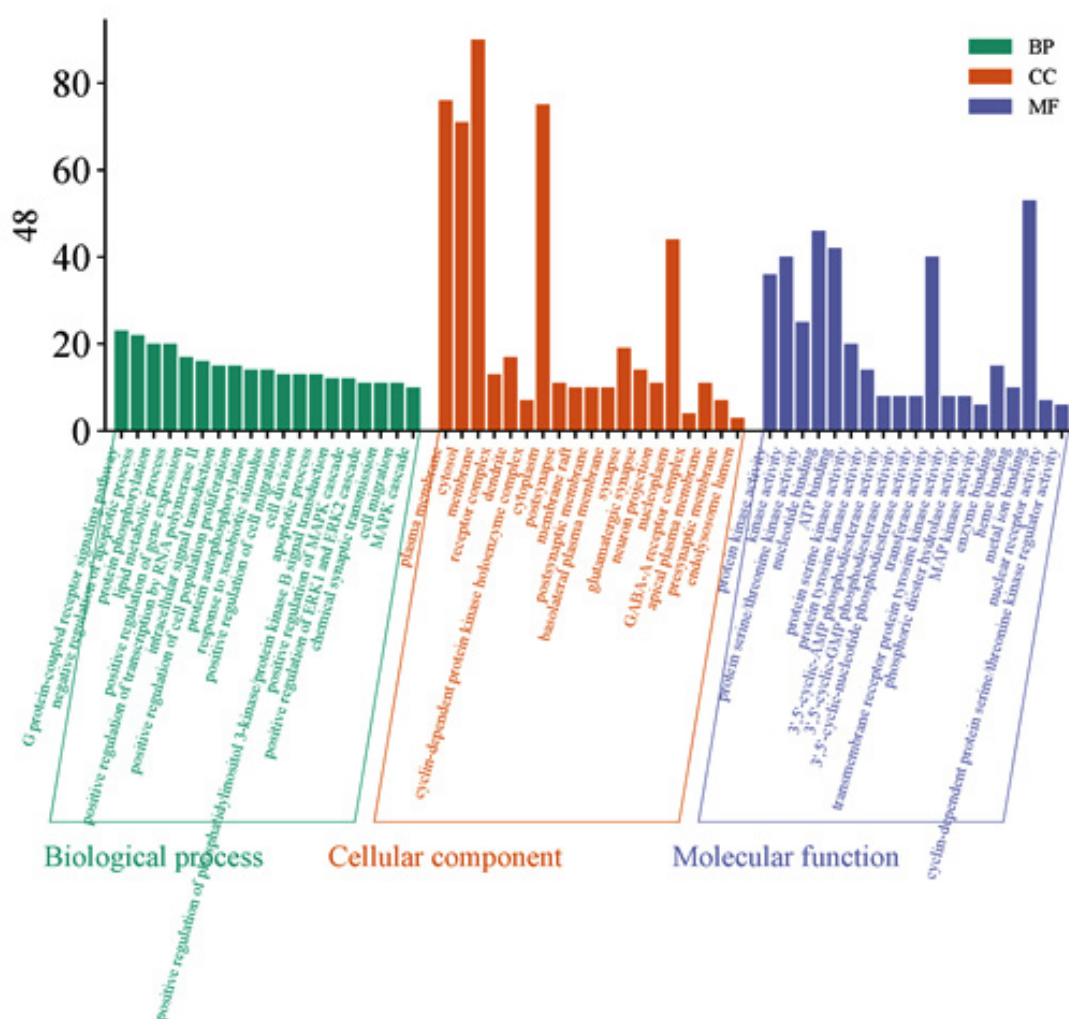


Fig. 5. Gene Ontology (GO) enrichment analysis showing major Biological Processes, Cellular Components, and Molecular Functions associated with the overlapping targets.

mol), while Compound 2 interacted best with 5IKR (−7.5 kcal/mol). With binding energies ranging from −5.9 to −7.0 kcal/mol, nifedipine showed relatively lower or target-dependent binding energies. Compound 2's binding mechanism at the 5IKR active site demonstrated a persistent ligand–protein complex backed by several non-covalent interactions. In addition to hydrophobic and δ -alkyl interactions with LEU188, VAL398, and LEU418, the ligand created a hydrogen bond with GLY186. Van der Waals interactions with residues including MET422, ALA189, HIS405, and TYR420 added

additional stability and helped to achieve the good docking score. In line with its higher binding energy, Compound 1 also demonstrated a distinct interaction profile inside the 1GKC binding pocket. While δ -alkyl interactions were seen with TYR136 and PRO156, the ligand formed hydrogen bonding interactions with GLN327 and ASN34. By means of van der Waals interactions, a number of residues—including MET48, SER49, HIS39, PRO153, and PRO154—contributed, leading to a compact and energetically advantageous binding conformation. Nifedipine, on the other hand,

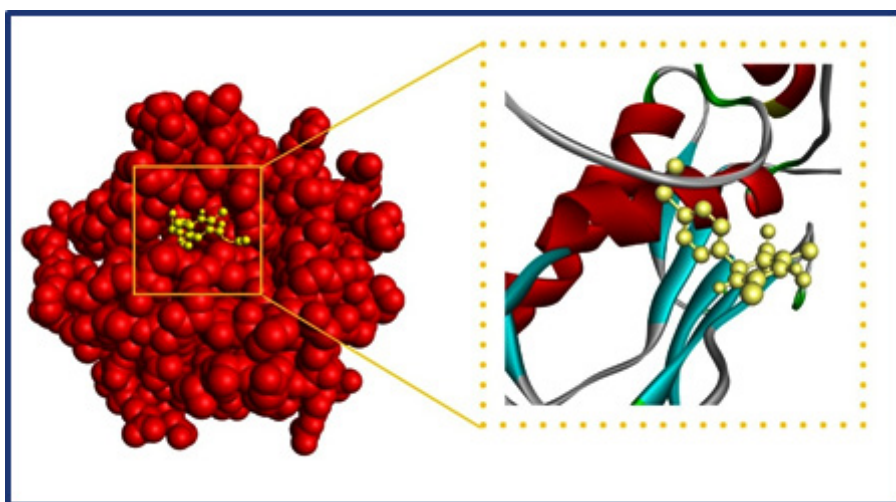


Fig. 6. Molecular docking pose of Compound 1 within the active site of target protein 1GKC, showing key ligand–protein interactions.

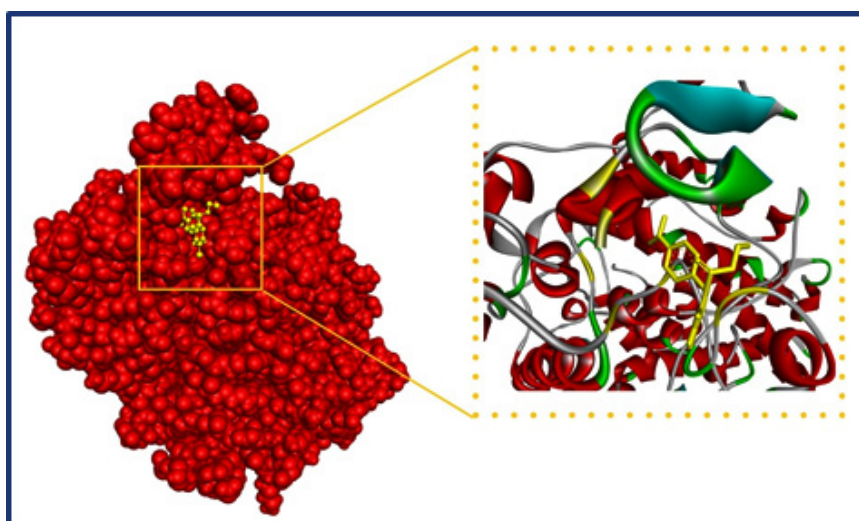


Fig. 7. Molecular docking pose of Compound 2 within the active site of target protein 5IKR, highlighting important binding interactions.

Table 4. Predicted binding energies (kcal/mol) of Compound 1, Compound 2, and nifedipine against selected protein targets obtained using AutoDock

Compounds	Targets	Binding Energy (kcal/mol)
Compound 1	1GKC	-8.1
	5IKR	-7.2
	1M17	-6.0
	1Q5K	-6.5
	2SRC	-6.1
Compound 2	1GKC	-5.9
	5IKR	-7.5
	1M17	-6.0
	1Q5K	-6.7
	2SRC	-6.3
Nifedipine	1GKC	-5.9
	5IKR	-6.8
	1M17	-6.3
	1Q5K	-6.0
	2SRC	-7.0

displayed poorer networks of interactions within the binding sites, exhibiting somewhat lower binding energies and fewer stabilizing connections. Compared to Compounds 1 and 2, nifedipine's overall interaction pattern was less extensive, despite its ability to create hydrogen bonds and aromatic interactions with certain residues. Overall, the docking data show that compared to nifedipine, the newly developed compounds—especially Compound 1—show improved binding affinity and more stable interaction networks. These compounds are excellent candidates for additional experimental validation because the existence of numerous hydrogen bonds, hydrophobic contacts, and van der Waals interactions suggests greater accommodation within the target proteins' active regions.

DISCUSSION

The current study shows that two new tetrahydropyrimidine derivatives can be successfully made utilizing a Biginelli reaction that is safe for the environment by using onion peel powder as a catalyst. This work shows how useful and sustainable agricultural bio-waste may be. The production of the target molecules was validated by spectral analysis, which showed that the synthetic

technique worked. In silico ADMET testing showed that both compounds had excellent drug-like characteristics and pharmacokinetic profiles that are acceptable. Compound 1 had the best balanced profile of the two. It had good absorption in the gastrointestinal tract, no P-glycoprotein substrate liability, low CYP-related hazards, and a good toxicity profile. Even though Compound 2 had excellent absorption and permeability, the fact that it had a PAINS alert and was projected to cause cancer means that it needs more structural optimization before it can move forward. The idea that the synthesized drugs lower blood pressure by modulating multiple targets instead of just one was supported by network pharmacology analysis. Finding 131 common targets between genes related to compounds and genes related to high blood pressure shows how these genes could control complicated biological networks. The hub proteins that were found—Src kinase, MMP-2, GSK3 α , ROCK1, and PKC α —are well-known for controlling the contraction of vascular smooth muscle, the function of endothelial cells, and intracellular signaling. All of these are important for understanding how high blood pressure works. Further GO and KEGG enrichment studies showed that these targets are involved in signaling in the endocrine system, pathways regulated by kinases, inflammatory responses, and processes that change the structure of blood vessels. The pathways that are more active in shear stress, atherosclerosis, and relaxin signaling clearly suggest a system that protects blood vessels and lowers blood pressure. The results of molecular docking backed up the network pharmacology findings by showing that the synthesized drugs interacted strongly and stably with major antihypertensive targets. For instance, compound 1 had a stronger binding affinity and more extensive interaction networks than nifedipine. This suggests that it fits better in the active regions of target proteins. The combination of hydrogen bonds, hydrophobic interactions, and van der Waals forces probably makes the binding more stable and may make it more effective in living things. The results of the integrated green synthesis, in silico pharmacokinetic profiling, network pharmacology, and molecular docking show that these tetrahydropyrimidine derivatives, especially Compound 1, are good candidates for

further testing as antihypertensive agents *in vitro* and *in vivo*.

Limitations of the Study and Future Perspectives

This study has certain drawbacks. All biological interpretations, encompassing target prediction, pharmacokinetic parameters, toxicity evaluation, and molecular docking outcomes, are exclusively derived from *in silico* analyses. Neither *in vitro* nor *in vivo* tests were conducted to empirically evaluate the antihypertensive efficacy or safety of the produced drugs. Furthermore, structural characterization was confined to infrared spectroscopy and mass spectrometry. Subsequent investigations will entail comprehensive NMR characterization, succeeded by *in vitro* biological experiments and *in vivo* evaluations to validate the anticipated antihypertensive efficacy, pharmacokinetic properties, and toxicity profiles of these compounds.

CONCLUSION

The current study illustrates the effective synthesis of two new tetrahydropyrimidine derivatives using an environmentally friendly Biginelli reaction catalyzed by onion peel powder, emphasizing the sustainability and efficacy of agricultural bio-waste utilization. Spectral analysis indicated that the target compounds had been successfully made, which proved the synthetic strategy. *In silico* ADMET testing showed that both compounds have good drug-like characteristics and pharmacokinetic profiles. Compound 1 had the better profile of the two. It had good gastrointestinal absorption, no P-glycoprotein substrate liability, low CYP-related hazards, and a good toxicity profile. Even though Compound 2 exhibited good absorption and permeability, the fact that it had a PAINS alarm and was thought to be carcinogenic means that more structural optimization is needed before moving forward. A network pharmacology study corroborated the idea that the synthesized drugs have antihypertensive effects via multi-target modulation rather than single-target suppression. The discovery of 131 common targets between compound-related and hypertension-associated genes highlights their capacity to modulate intricate biological networks. The hub proteins that were found—Src kinase, MMP-2, GSK3 α , ROCK1, and PKC α —are well-known for controlling the

contraction of vascular smooth muscle, the function of endothelial cells, and signalling inside cells. All of these are very important in the development of hypertension. GO and KEGG enrichment analysis further confirmed that these targets are implicated in endocrine signalling, kinase-mediated pathways, inflammatory responses, and vascular remodeling processes. The enhancement of pathways associated with shear stress, atherosclerosis, and relaxin signalling robustly indicates a vasoprotective and blood pressure-regulating mechanism. The results of molecular docking confirmed the findings of network pharmacology by showing that the synthesized drugs had strong and stable interactions with important antihypertensive targets. Compound 1 exhibited greater binding affinity and more extended interaction networks compared to nifedipine, indicating enhanced accommodation inside the active regions of target proteins. The interplay of hydrogen bonding, hydrophobic contacts, and van der Waals forces probably leads to greater binding stability and possible biological effectiveness. The combined results of green synthesis, *in silico* pharmacokinetic profiling, network pharmacology, and molecular docking show that these tetrahydropyrimidine derivatives, especially Compound 1, are good candidates for further testing as antihypertensive agents *in vitro* and *in vivo*.

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Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human

participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials

Permission to reproduce material from other sources

Not Applicable.

Author Contributions

Fariya Mohideen: Conducted the initial experimental investigations, pertaining to synthesis and characterisation; Sakthi Periyasamy: Conducted network pharmacology analysis; Priya Deivasigamani: Formal analysis, Writing-review & editing.

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