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RESEARCH ARTICLE OPEN ACCESS

"Design and Synthesis of Tetra hydro Benzpyrimidine analogs as potential Calcium channel Blocker"

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ABSTRACT:
To further elucidate the chemical mechanism behind the activity seen, further research is warranted into the exceptional features of this novel family of antihypertensive drugs. A thorough investigation is also necessary to identify new physiochemical and biological characteristics in order to enhance the performance of a series of molecules and gain a deeper understanding of the relationship between structure and activity. It is possible that some of the newer compounds with antihypertensive activity that showed promise can be further developed to have more potency than the conventional medications. Therefore, the freshly formed Tetrahydro Benzpyrimidine Heterocyclic Derivatives may offer useful leads for creating new antihypertensive drugs. Our goal is to create Tetrahydro Benzpyrimidine derivatives that are more effective at lowering blood pressure than currently available derivatives. Results revealed that every final product was a stable, pure chemical. They were lipophilic substances, like other nifedipine analogues. Nifedipine (10 mg/kg, i.p.) and D3 to D6 (10 mg/kg, i.p.) shown that all substances decreased mean arterial blood pressure. We came to the conclusion that molecular docking, the foundation upon which we constructed molecules, has shown to be promising, at least in these initial in vivo pharmacological screening models, after thoroughly analyzing the pharmacological activities of generated compounds. These substances considerably lowered the mean arterial blood pressure in rats, but had no effect on heart rate. To offer a thorough profile of these compounds for their potential application in medication therapy, additional pharmacological and toxicological research is necessary.

Keywords: Tetrahydro Benzpyrimidine, Nifedipine,

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I. INTRODUCTION

Hypertension, also known as high or raised blood pressure, is a condition in which the blood vessels have persistently raised pressure. Blood is carried from the heart to all parts of the body in the vessels. Each time the heart beats, it pumps blood into the vessels. Blood pressure is created by the force of blood pushing against the walls of blood vessels (arteries) as it is pumped by the heart. The higher the pressure, the harder the heart has to pump. Hypertension is a serious medical condition and can increase the risk of heart, brain, kidney and other diseases. It is a major cause of premature death worldwide, with upwards of 1 in 4 men and 1 in 5 women – over a billion people – having the condition. The burden of hypertension is felt disproportionately in low- and middle-income countries, where two thirds of cases are found, largely due to increased risk factors in those populations in recent decades.[1]

Hypertension, elevated blood pressure, is a noteworthy public health concern worldwide due to its significant contribution to the global health burden and its role as a prominent risk factor for the development of a number of disease processes. In the year 2001, high blood pressure accounted for 54% of stroke, 47% of ischemic heart disease, 75% of hypertensive disease, and 25% of other cardiovascular disease worldwide" (Lawes, Hoorn, & Rodgers, 2008). The negative impact of hypertension on health status is clear, especially taking into account the disability, decreased quality of life, and mortality associated with stroke and cardiovascular disease. In 2001, 7.6 million deaths (13.5% of all deaths) and 92 million disability life-years (6% of total) were attributable to systolic blood pressure greater than 115mmHg. It is saddening to note that such pervasive negative effects are related to such a modifiable cause.[1]

Molecular Modeling
MolecularModelingandComputationalChemistry :

Medicinal chemists today are facing many complicated challenges. The most demanding and perhaps the most rewarding one is the rational design of new therapeutic agents for treating human diseases.

The definition currently accepted of what molecular modeling can be stated as "molecular modeling is anything that requires the use of a computer to paint, describe or evaluate any aspect of the properties of the structure of a molecule". Methods used in the molecular modeling are regarding automatic structure generation, analysis of three-dimensional (3D) databases and construction of protein models by techniques based on sequence homology, diversity analysis, docking of ligand. Molecular modeling has widened the horizons of pharmaceutical research by providing tools for finding new leads.

Target structure:
The structure of target was obtained from the protein databank

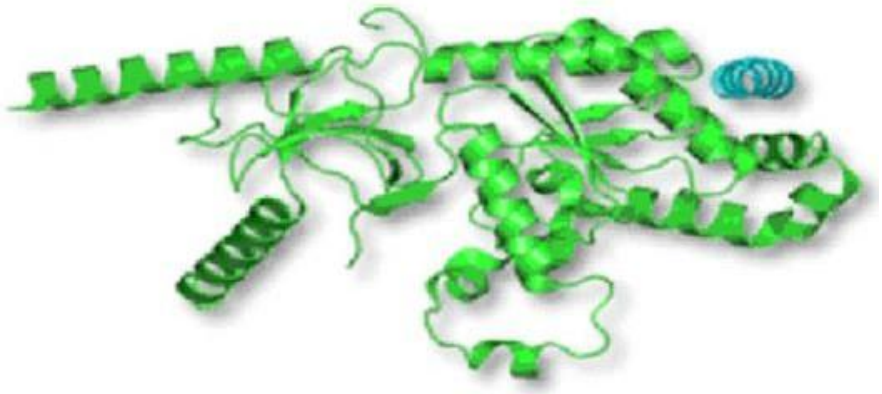


Figure1: AID-b complex of L-type calcium channel(PDB code1T3

II. Methodology:

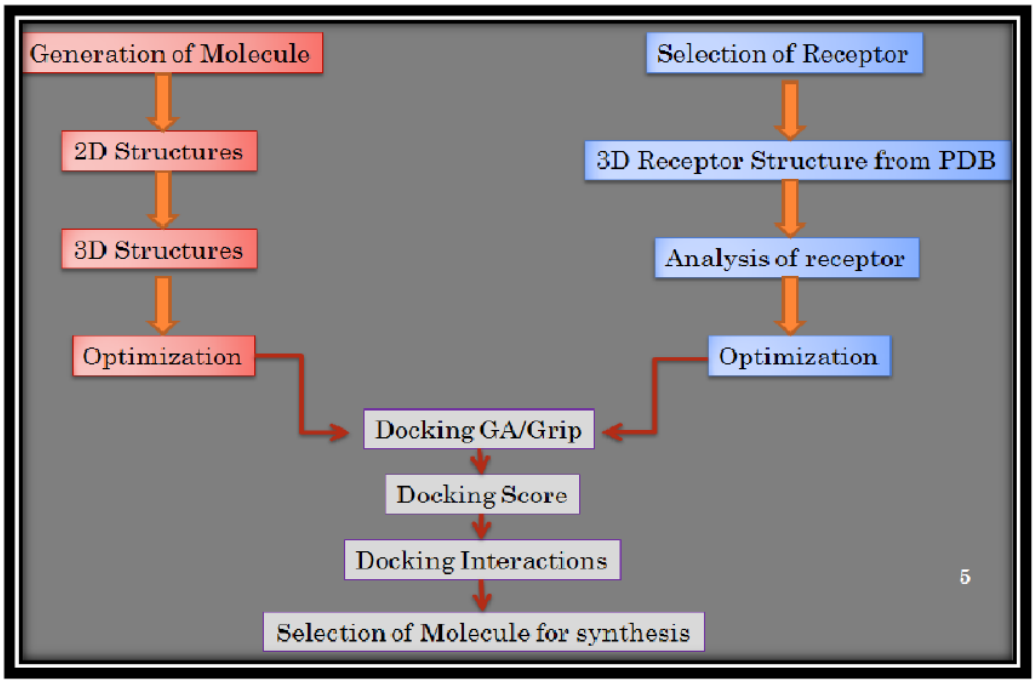


Figure2: Docking methodology

Molecular docking study of designed Tetrahydro Benzpyrimidine derivativesdockingcomponent

Docking studies were carried out by using the program AUTODOCK VINA. Thisprogram starts with a ligand molecule in an arbitrary conformation, orientation, andposition and finds favorable dockings in a protein-binding site using both simulatingannealing and genetic algorithms. The program Auto Dock Tools Vina (ADT), which has been released as an extension suite to the Python Molecular Viewer, was used toprepare the protein and the ligand.

For the macromolecule (L-type calcium channel, that was generated by resorting to multi body molecular ynamics simulations, was downloading from the PDB bank server [PDB entry 1T3L]), polar hydrogens were added, and then Kollman United Atom charges and atomic solvation parameters were assigned. The grid maps of docking studies were computed using the AutoGrid Vina included in the Autodock (x = -46.850081, y = 39.302763, z = 20.640561) distribution. Grid center was centered on the active site was obtained by trial and error and previous study 60x60x60 points with grid spacing of 0.375 were calculated. The GA-LS method was adopted to perform the molecular docking. The parameters for GA were defined as follows: a maximum number of 250,000 energy evaluations; a maximum number of generations of 27,000; mutation and crossover rates of 0.02 and 0.8, respectively. Pseudo-Solis & Wets parameters were used for local search and 300 iterations of Solis & Wets local search were imposed. The number of docking runs was set to 9. Both Autogrid and Autodock computations were performed on Cygwin. After docking, all structures generated were assigned to clusters based on a tolerance of 1A ° all-atom RMSD from the lowest-energy structure. Hydrogen bonding and hydrophobic interactions between docked potent agents and macromolecule were analyzed using ADTV [10]

Molecular docking Results:

Table3:Dockingstudy ofthedesignedTetrahydroBenzpyrimidine derivatives

Compound	BindingAffinity	LigandEnergy (kcal/mol)	Interactingaminoacids	
			HydrogenBond/Hydrophobic	Distance
D1	-6.3	31.4193 kcal/mol	ARG228ARG228:HH2TYR402LEU109	2.05977 2.40696 2.62192 5.0252
D2	-6.2	30.4067 kcal/mol	ARG228VAL110ARG228 PHE93	2.54679 2.88252 2.82211 5.01931
D3	-6.3	32.6675 kcal/mol	ARG228VAL110ARG228 PHE93	2.46058 2.84226 2.73216 4.91986
D4	-6.2	31.5246 kcal/mol	ARG228ARG228	1.94915 2.64758
D5	-6.2	25.9822 kcal/mol	ARG228TYR402ARG228PHE93	2.51129 3.07524 2.88967 4.99747
D6	-6.3	27.7993 kcal/mol	ARG228ARG228GLU381PRO327 LEU330, SER331PRO337	2.18269 2.15822 1.91846 1.95871 4.93232 5.44834

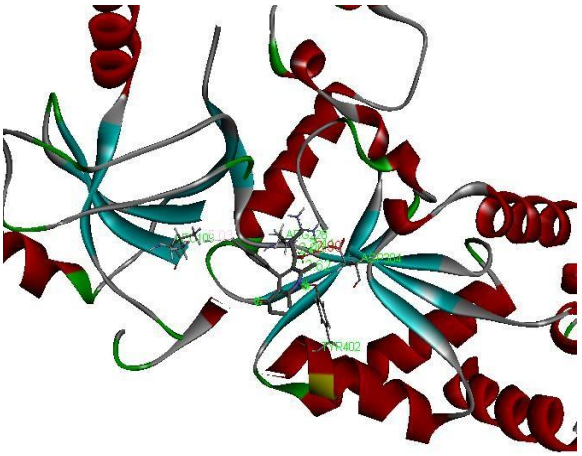


Figure3:Binding interactionofD1with1T3Lprotein

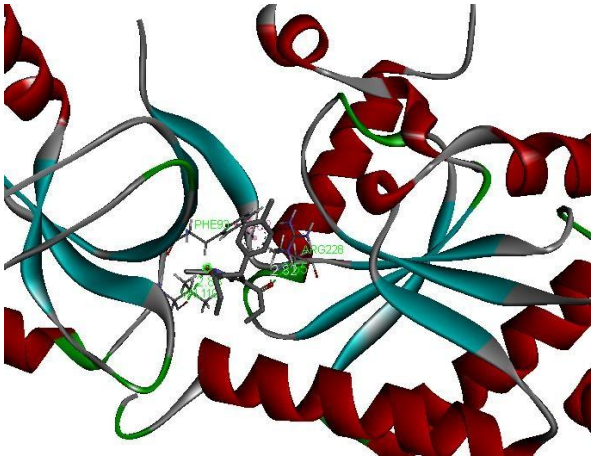


Figure4: Binding interactionofD2 with 1T3Lprotein

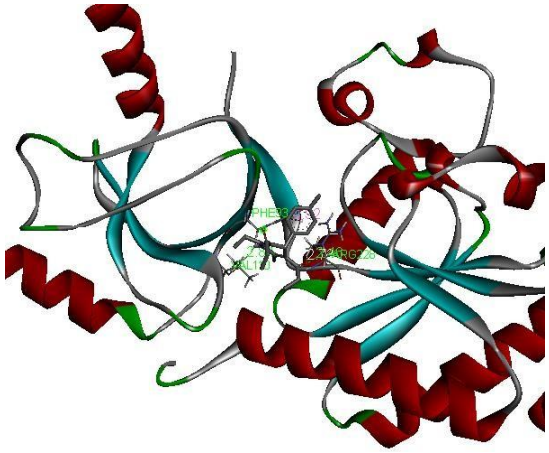


Figure5: Binding interactionofD3 with 1T3Lprotein

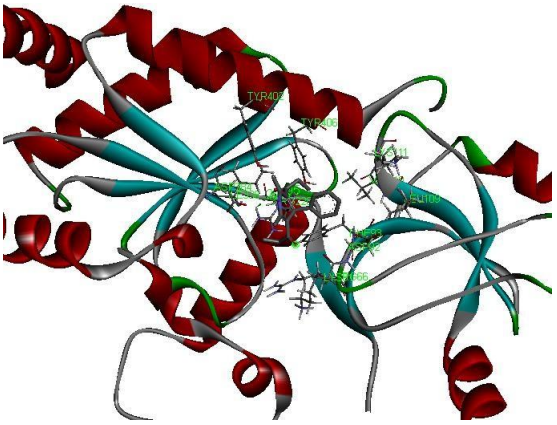


Figure6: Binding interactionofD4 with 1T3Lprotein

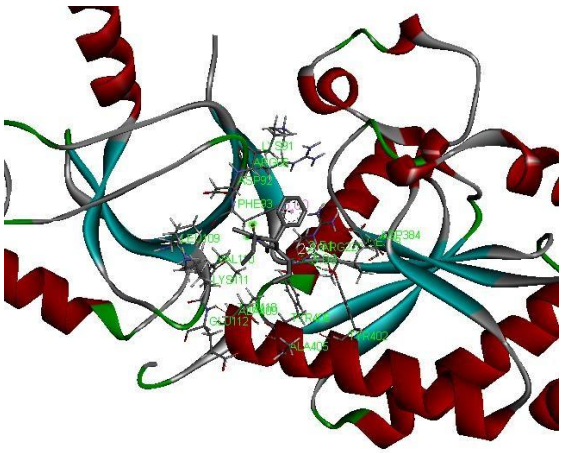


Figure7: Binding interactionofD5 with 1T3Lprotein

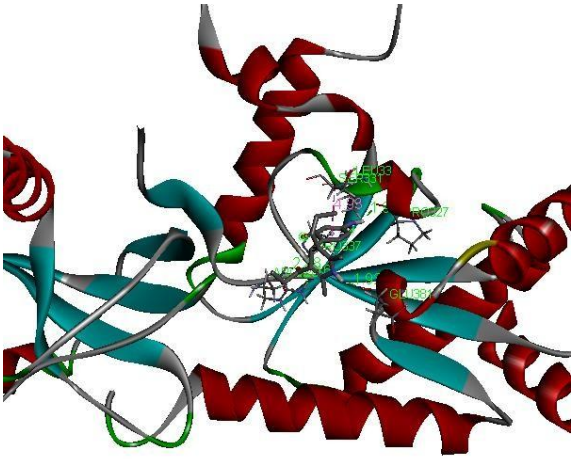


Figure8: Binding interactionofD6 with 1T3Lprotein

Design of Scheme

Synthesis of 2,7,7-trimethyl-4-phenyl-2,6,7,8-tetrahydroquinazolin-5(1H)-one

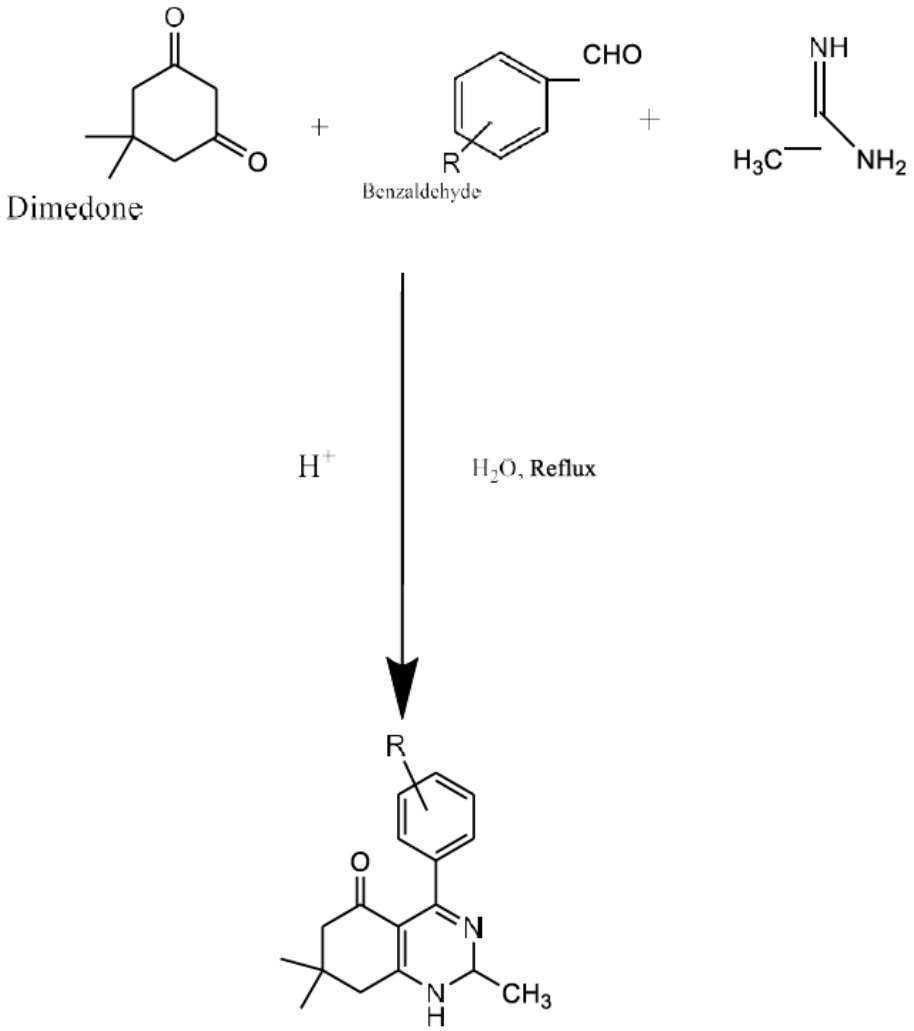


Figure9: Scheme of synthesis

SynthesisofCompounds
Synthesis of 2,7,7-trimethyl-4-phenyl-2,6,7,8-tetrahydroquinazolin-5(1H)-one

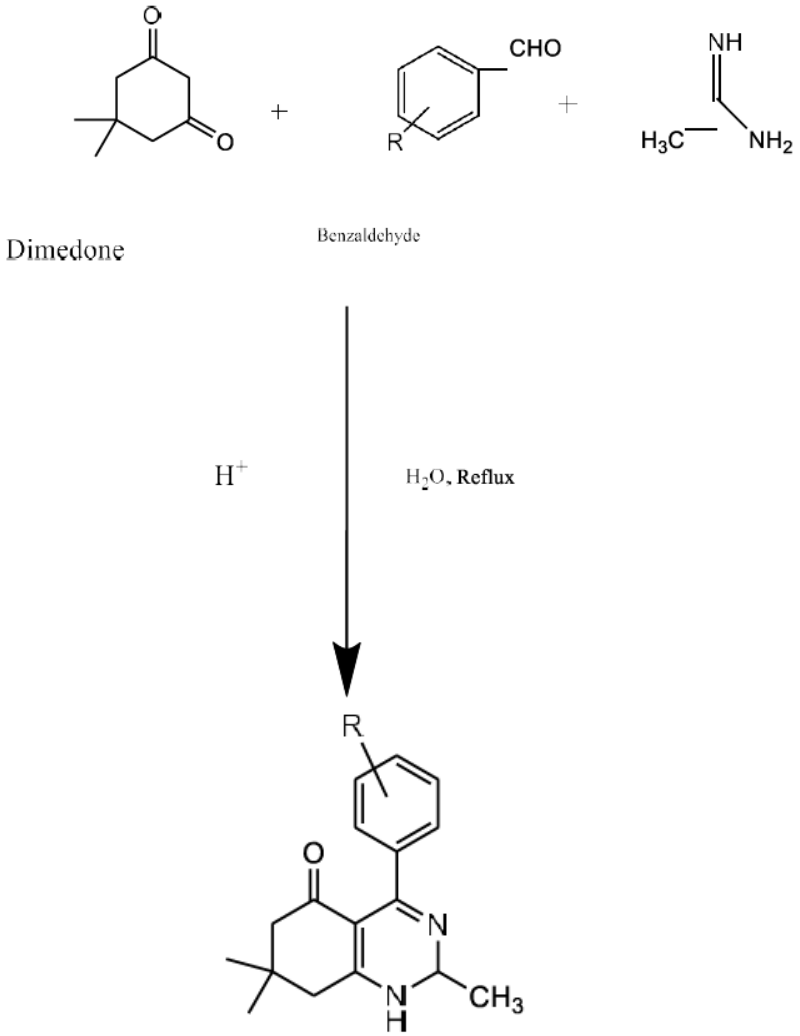


Figure10: Scheme of synthesis

Table4:Derivatives of Tetrahydro Benzpyrimidine.

Sr.No.	Derivatives/Label	R
1	D1	-CH_3
2	D2	-Cl
3	D3	-C_2H_5
4	D4	-OCH_3
5	D5	-H
6	D6	-NH_2

General procedure.
1. The amount of equimolar substituted Benzaldehyde dimedone and Amidine were refluxed for 2-3 hrs in aqueous acid medium
2. After 2-3 hrs the reaction completion was monitored by thin layer chromatography (TLC).
3. After cooling precipitate was form, filter the precipitate and recrystallized with ethanol.

Procedure for synthesis of 2,7,7-trimethyl-4-(p-tolyl)-2,6,7,8-tetrahydroquinazolin-5(1H)-one-D1

4-Methyl benzaldehyde (0.01 mol) with same quantity of (0.01 mol) dimedone ad(0.01 mol) Amidine was taken in round bottom flask to this add H_2O and drop of$Conc^nHCl$, reflux for 3hours, filter& recrystallized withethanol.Meltingpoint:172-175^oc,%Yield-75.30

Procedure for synthesis of 4-(4-chlorophenyl)-2,7,7-trimethyl-2,6,7,8-tetrahydroquinazolin-5(1H)-one-D2

4-Chloro benzaldehyde (0.01 mol) with same quantity of (0.01 mol) dimedone ad(0.01 mol) Amidine was taken in round bottom flask to this add H_2O and drop of$Conc^nHCl$, reflux for 3 hours, filter&recrystallizedwith ethanol.Meltingpoint:172-174^oC, %Yield-70.46

Procedure for synthesis of 4-(4-ethylphenyl)-2,7,7-trimethyl-2,6,7,8-tetrahydroquinazolin-5(1H)-one-D3

4-Ethyl benzaldehyde (0.01 mol) with same quantity of (0.01 mol) dimedone ad(0.01 mol) Amidine was taken in round bottom flask to this add H_2O and drop of$Conc^nHCl$, reflux for 3 hours, filter& recrystallized withethanol.Meltingpoint:170-173^oc,%Yield-65.38

Procedure for synthesis of methyl -(4-methoxyphenyl)-2,7,7-trimethyl-2,6,7,8-tetrahydroquinazolin-5(1H)-one-D4

4-Methoxy benzaldehyde (0.01 mol) with same quantity of (0.01 mol) dimedone ad(0.01 mol) Amidine was taken in round bottom flask to this add H_2O and drop of$Conc^nHCl$, reflux for 3 hours, filter&recrystallizedwith ethanol.Meltingpoint:173-175^oC, %Yield-73.76

Procedureforsynthesisof1-(6-amino-5-((aminooxy)carbonyl)-2-methyl-4-phenyl-1,4-dihydropyridin-3-yl)propan-1-one-D5

A benzaldehyde (0.01 mol) with same quantity of (0.01 mol) 5-(aminooxy)-3,5-dioxopentanimidamide& (0.01 mol) of ammonia was taken in round bottom flaskto this add H_2O and drop of $Conc^nHCl$, reflux for 3 hours, filter & recrystallizedwith ethanol.Meltingpoint:170-173^oC,%Yield-80.13

Procedure for synthesis of 4-(4-aminophenyl)-2,7,7-trimethyl-2,6,7,8-tetrahydroquinazolin-5(1H)-one-D6

4-Amino benzaldehyde (0.01 mol) with same quantity of (0.01 mol) dimedone ad(0.01 mol) Amidine was taken in round bottom flask to this add H_2O and reflux for3hours, filter & recrystallizedwith ethanol.Meltingpoint:171-176^oC, %Yield-68.25

Merck index table:

Table5: Merckindex table

Merk Index No	Name (M.F.)	Mol.Wt.	Density	Physical Constant		Solubility	Caution
				M.P	B.P		
1057	Benzaldehyde	106.12	1.050	-	179	Miscible in Alcohol, ether.	Narcotic in high conc. May cause contact dermatitis
6620	p-Nitro benzaldehyde	151%	-	108-110	-	Alcohol, ether.	-
2319	P-Chlorobenzaldehyde	132.16	-	-	176	Miscible with alcohol, ether	-
3760	Ethanol C_2H_5OH	46.07	0.789	-114.1	78.5	Miscible in water and various organic	Irritation of eye, skin, nose
4836	4-Methyl Benzaldehyde`	122.12	-	116	-	Sparingly soluble in cold water, more soluble in hot water	-
3546	Ammonia	17.031	0.73 kg/m³	-	-33.34	solubility of ammonia gas in water	-
4837	4-ethyl Benzaldehyde`	185.03	-	-	123 °C	Sparingly soluble in cold water, more soluble in hot water	-

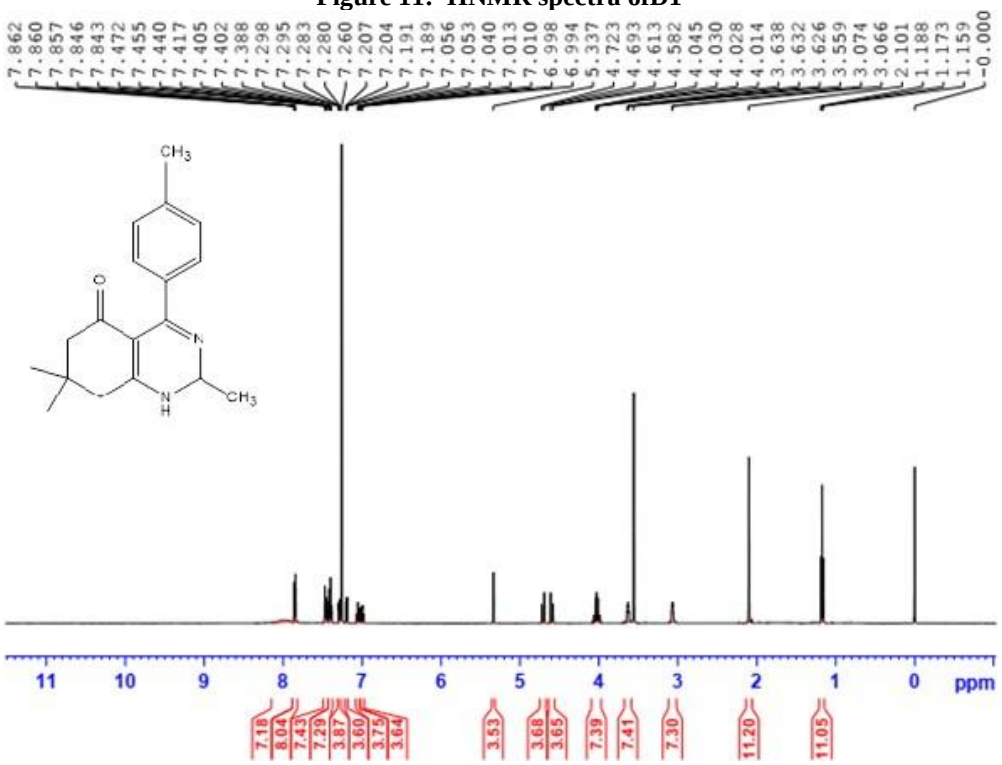
Elemental Analysis of Title Compounds:

TableNo.7:Elemental Analysisof Title Compounds(Calculated)

Compound	Elements				
	C	H	N	O	Cl
D1	68.77	6.68	4.22	9.64	10.68
D2	61.38	5.44	3.98	3.08	20.13
D3	77.50	8.36	4.30	9.83	-
D4	60.65	5.89	3.72	8.50	-
D5	72.46	7.43	9.39	10.72	-
D6	73.05	7.74	8.97	10.24	-

^{1}H NMR data of respected compounds

Figure 11:^{1}HNMR spectra ofD1



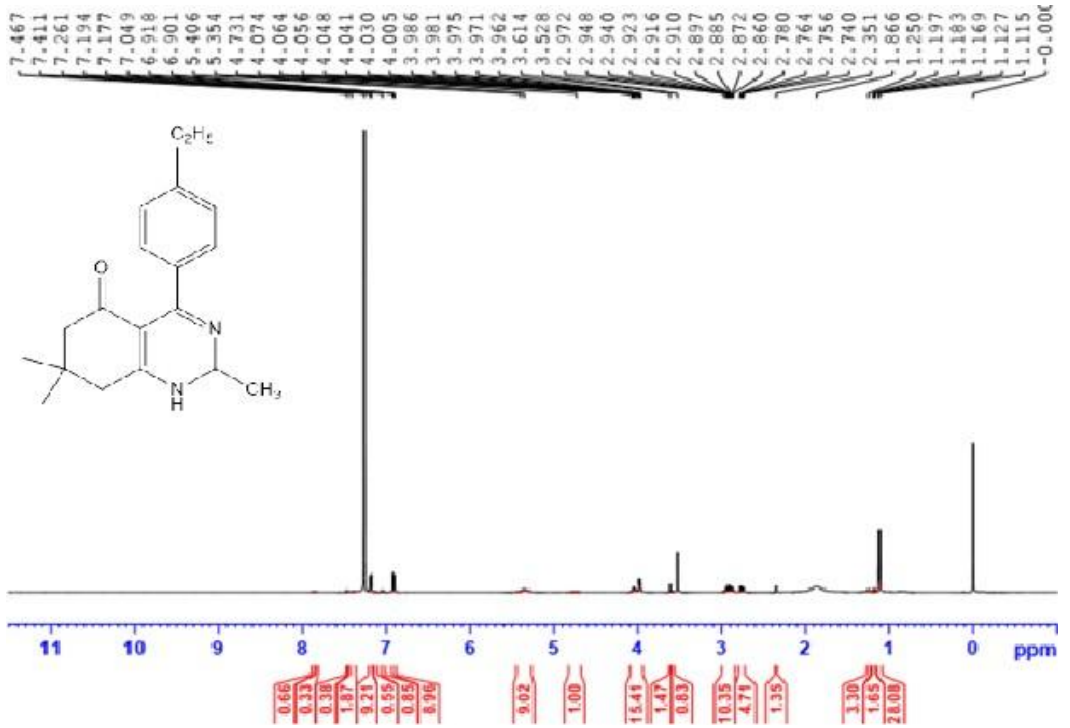


Figure 12:[1]HNMR spectra of D3

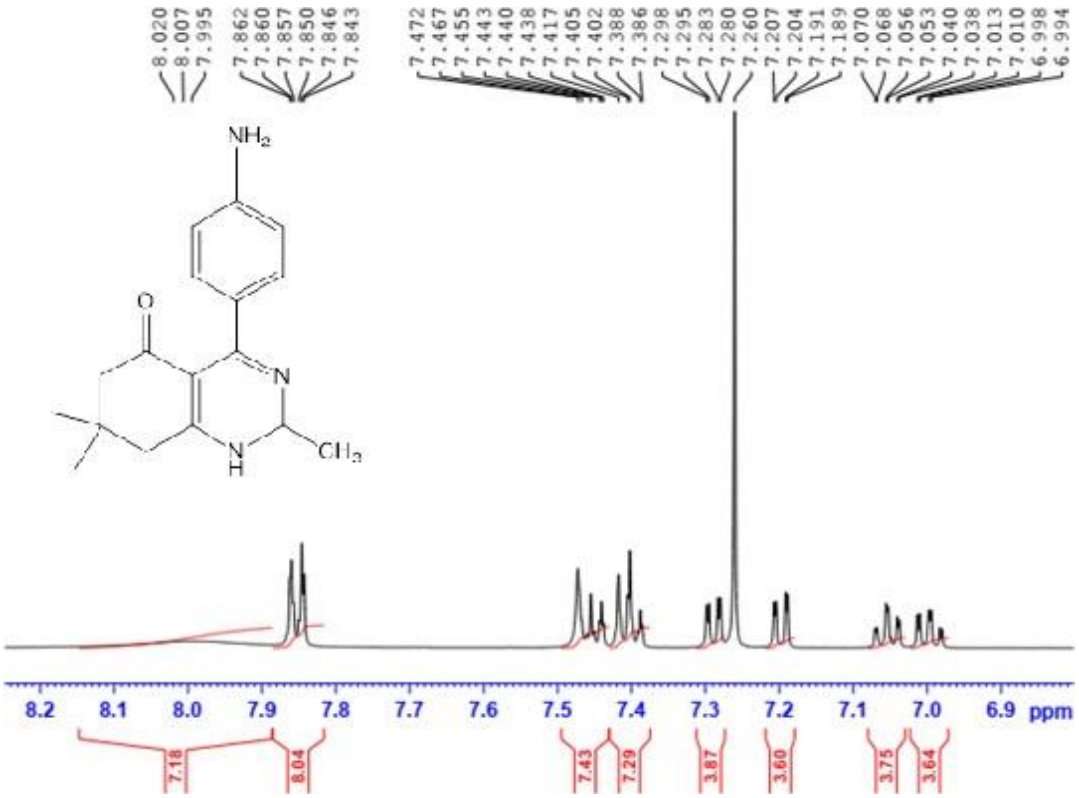


Figure 13:[1]HNMRspectra of D6

IR data of respected compounds

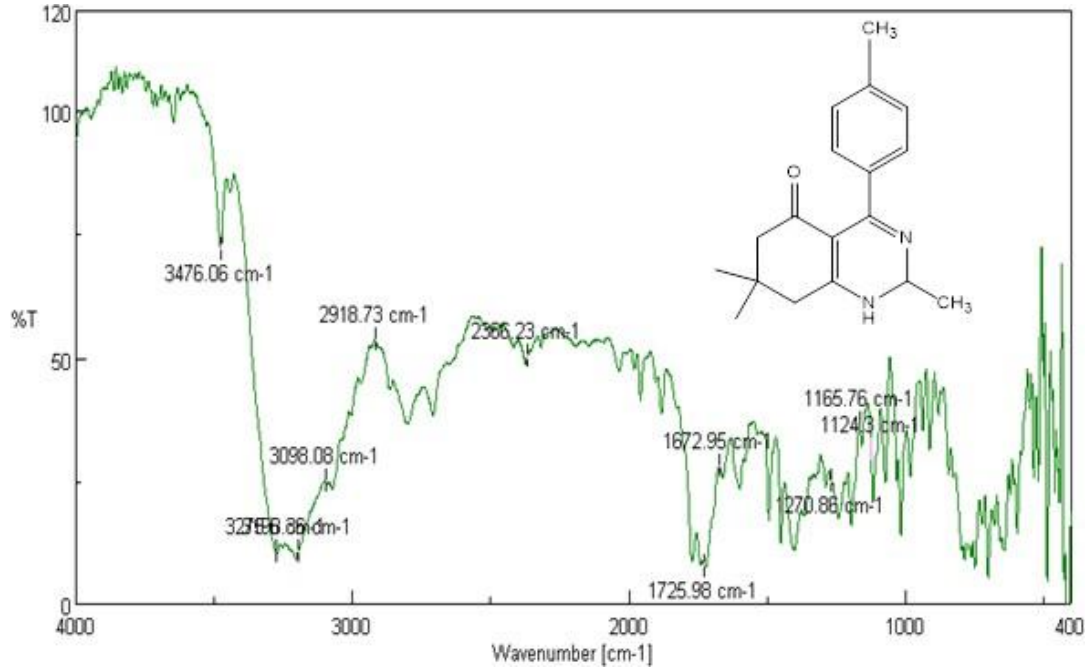


Figure14:IR spectra of D1

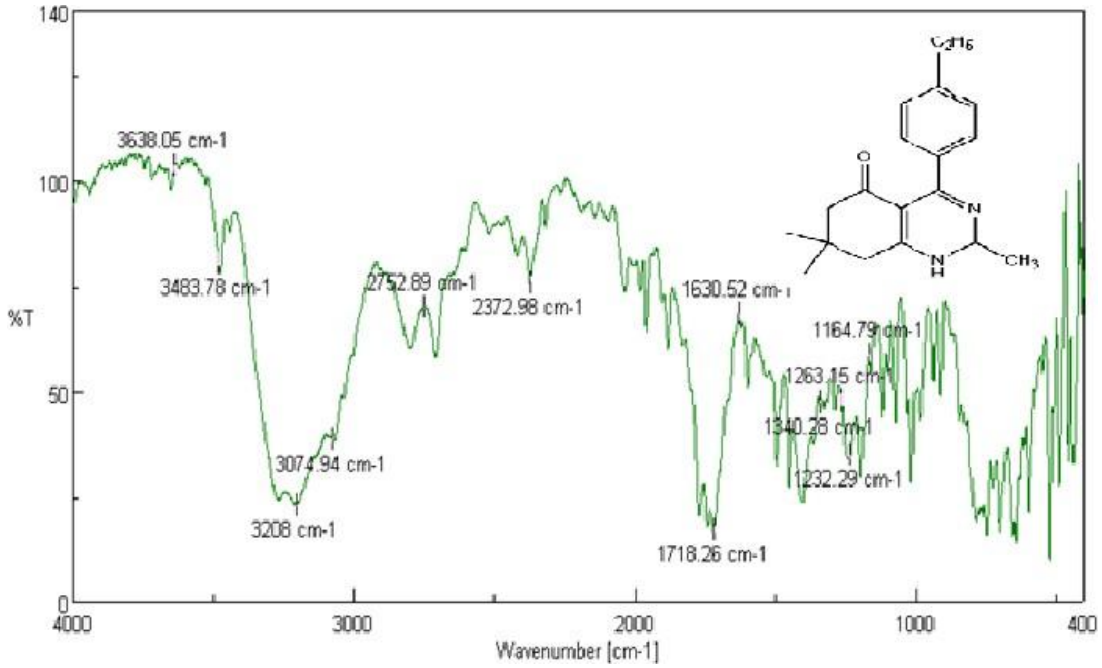


Figure15:IR spectra of D3

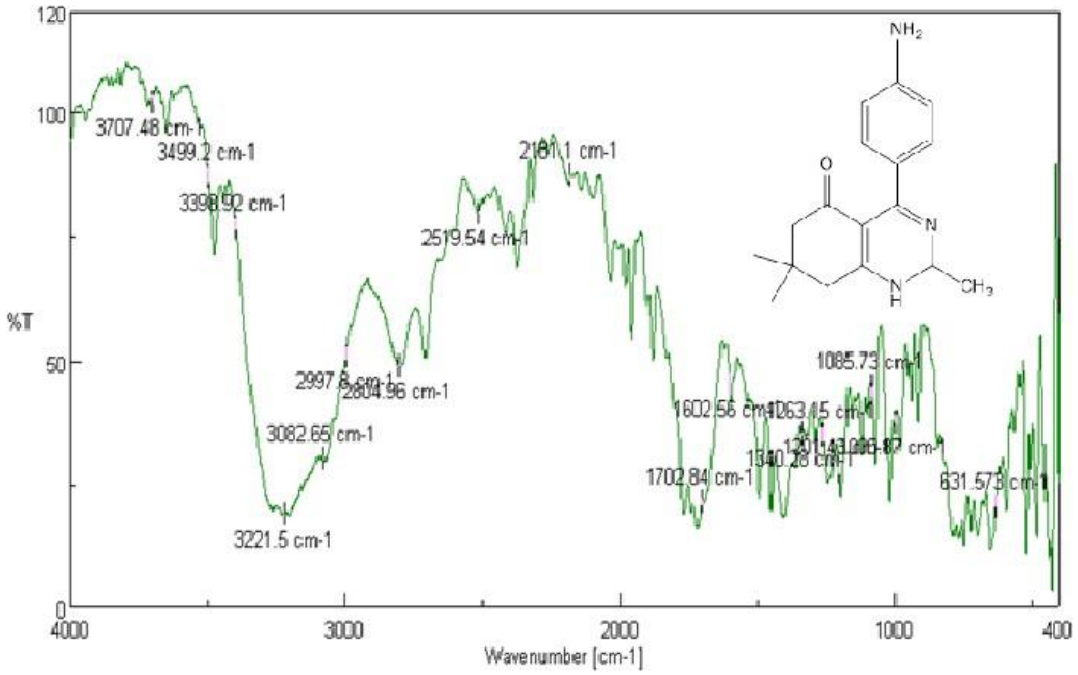


Figure16:IR spectra of D6

Biological Screening

Calcium channel blocker activity:

The term cardioprotection refer to the technique used to prevent or to delay the development of myocardial injury, particularly during ischemia. This is a crucial issue in the context of cardiac surgery where the development of appropriate cardiacprotection procedure has allowed substantial improvement in patient care. Cardiovascular diseases (CVDs) are the major health problem of advanced as well as developing countries of the world and are the secondary causes of death in many parts of the world. Hypertension is the common cardiac disease followed by ischemic heart disease (IHD). In 2002, the WHO estimated that 12.6% of death worldwide was from IHD. Catecholamine's in large doses produce myocardial necrosis. Since catecholamine readily undergoes oxidation and the oxidation product of catecholamine are responsible for myocardial damage. Catecholamines have been show to enhance myocardial oxygen consumption [1-3].

Material and methods for Rat Ileum:

1. Chemicals and reagent

Nifedipine (sigma Aldrich) was purchased from market and Tetrahydro Benzpyrimidine derivative are synthesized from lab scale. (Comp. no: 3j-4r)

2. Apparatus:

Shearing tons rotating drum, tissue organ bath, water bath, lever, clay, tread, scissor, needle, syringes, IV set, aerator, aeration tube, sketch pen tip.

3. Animals:

The adult albino rats aged between 2-3 months of both sexes, weighing between 200 and 220 g were used.

All the animals were obtained from animal house. They were kept in medium sized plastic cages. They were allowed to live at room temperature, fed on standard pellets of rat's food and allowed to drink water ad libitum. All the protocols of animal experiments were approved by the Institutional Animal Ethics Committee in accordance to the guideline of committee for the purpose of Control and Supervision of experiments on Animals (CPCSEA Registration

No:1670/PO/ReBiBt/S/12/CPCSEA), ministry of Social Justice and Empowerment, Government of India, New Delhi.

Experimental Design:

Procedure [4-6]]:

1. Male & female albino rats weighing between 200 & 220g were used in this study.
2. Animals entered the test having fasted overnight.
3. After the animals had been scarified by cervical dislocation, the ileum (10-15cm terminal portion) was immediately removed, discarding the 5-8 cm segment proximal to the ilio-caecal junction.
4. Segment 1-1.5 cm long were mounted vertically in 10ml organ bath containing tyrode solution of the following composition (mm): NaCl,136.87;

KCl,2.68; CaCl2, 1.80; MgSO4, 0.81; NaH2PO4 ,4.16; NaHCO3, 11.9; glucose 11.1.
5. The bath contents were maintained at 37c & aerated by 95% O2 & CO2.
6. A tension of 2gm was applied to frontal lever & recording was done using a frontal lever.
7. Responses were recorded with following 5 min cycle.
8. The preparations were allowed to equilibrate for 60 min with regular washes every 15 min.
9. In order to check antagonistic effects, contraction was induced with barium chloride.
10. After thorough washing out, this process was repeated until the amplitude of the concentration become constant.
11. The substances to be tested were investigated using the single dose technique.
12. Barium chloride concentration were induced after addition of test substances at different concentration (10, 50,100 ug\ml) & 1.30 min exposure time.
13. Only one compound was tested in each preparation.
14. Because of solubility problem, the compounds were dissolved in dimethylsulfoxide (DMSO) & control responses were taken after the addition of 0.1 ml DMSO.
15. Results were expressed as the percentage of maximum relaxation of the concentration of the compounds.
16. The responses of compounds were compared to those of nifedipine.
The data as expressed as means + SD. Student's test (Paired-t test) was used for statistical analysis. P values less than 0.05 were consider to be statistical significant

Caution:
1. Syringe should not contain air bubble.
2. Balance should be calibrated.
3. Instrument should be well magnifying.
4. Tying should be proper.
5. Tissue should be clean properly.
6. Level of tyrode solution should be maintained.
7. Aeration and Temp. Should be maintaining in organ bath.

Cardioprotective activity (Measurement of ECG)- Chemical and reagents
Adrenaline (Sigma-Aldrich) was purchased from market and synthesized derivatives of Tetrahydro Benzpyrimidine on lab scale.

Animals
Adult rats of Sprague–dawley strain were aged between 2 and 3 months of both sexes, weighing between 180 and 220 g. All the animals were obtained from animal house. They were kept in medium-sized plastic cages. They were allowed to live at room temperature, fed on standard pellets of rat's food and allowed to drink water ad libitum. All the protocols of animal experiments were approved by the Institutional Animal Ethics Committee in accordance with the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals, Ministry of Social Justice and Empowerment, Government of India, New Delhi. Experimental design Adrenaline- induced cardiac hypertrophy and cardiotoxicity the experimental rats were divided into six groups (n = 6 in each group) and treated as follows [7]:
Group 1: Normal control rats treated with distilled water.
Group 2: Rats treated with nifedipine (5 mg/kg body weight/day orally 15 days) **Group 3:** Rats treated with test compounds (5 mg/kg body weight/day orally for 15 days).
Group 4: Rats pretreated with test compounds (5 mg/kg body weight/day orally for 15 days)
At the end of experimental period in the present study, the following pharmacological tests were carried out to assess the effect on normal electrocardiogram (ECG), hypotensive and effect on the heart rate of synthesized compounds. All compounds were administered at a dose of 10 mg/kg i.p. per compound. Power lab instrument was used for data acquisition. Body temperature was recorded using a rectal thermostat probe and was maintained at 37 ± 0.5 C using an incandescent lamp placed over the abdomen. After stabilization, arterial blood pressure (systolic, diastolic and mean), and heart rate were recorded.

Table 8: Responses (Mean Arterial Blood Pressure) versus time (min), following the administration of the compounds (10 mg/kgi.p.).

CompoundCode	**Meanblood pressures[mmHg]**				
	0	**15**	**30**	**45**	**60**
NormalControl	63.22	63.11	62.87	62.44	62.45
Nifedipine	66.28	64.78	63	62.89	60.11

D3	66.81	64.45	62.34	62	60
D6	69	68	68.25	67.99	67.44

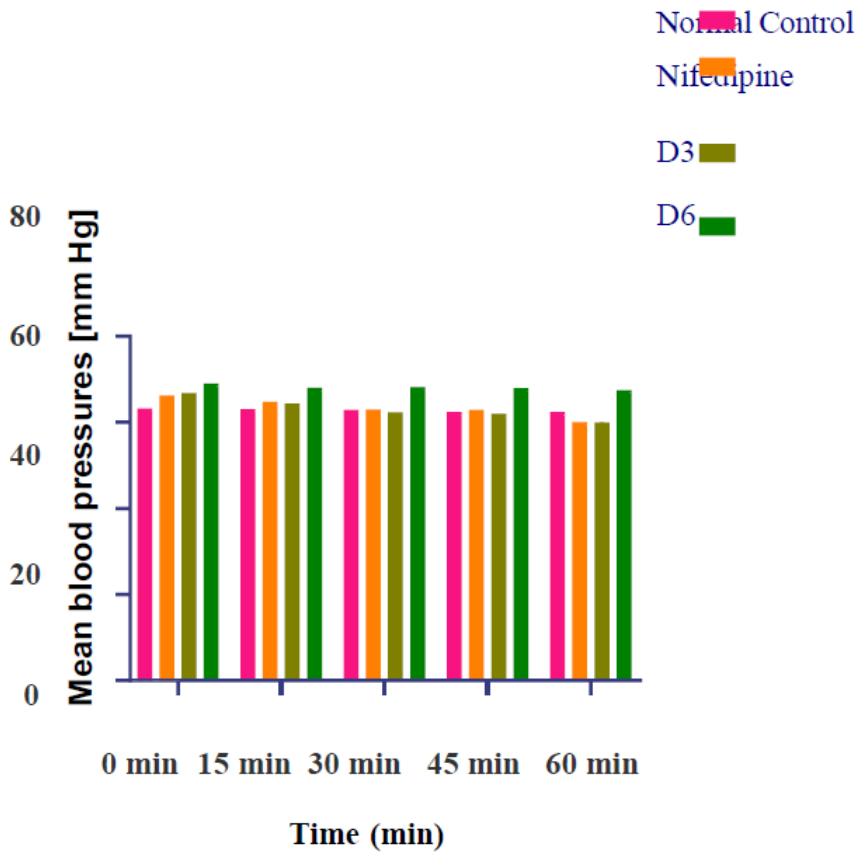


Figure 17: Graph – Hypotensive activity of compounds D3, D3, nifedipine andnormal control tested after i.p. administration in anaesthetized normotensiverats.

Table 9: Effects of an intraperitoneal injection of the investigated compounds (10 mg/kg i.p.) on heart rate in anaesthetized Wistar rats.

CompoundCode	**HeartRate(beats permin)**				
	0	**15**	**30**	**45**	**60**
NormalControl	326.7	320.422	320.35	322.32	320.31
Nifedipine	392.001	392.453	307.543	297.444	311.356
D3	372.026	372.07	370.017	367.013	363.012
D6	284.457	265.556	256.442	269.112	278.098

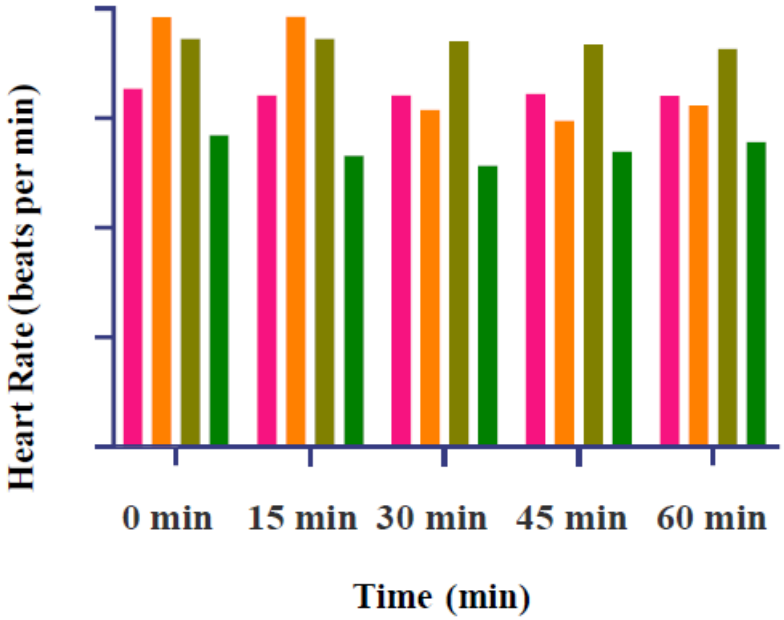


Figure 30: Graph – Effects of an intraperitoneal injection of the investigated compounds (10 mg/kg i.p.) on heart rate in anaesthetized Wistar rats

Table 10: Effects of an intraperitoneal injection of the investigated compounds (10 mg/kg i.p.) on ECG intervals in anaesthetized Wistar rats.

CompoundCode	Parameter	Timeof observation inmin				
		0	15	30	45	60
D3	RR	0.1663	0.1658	0.1610	0.1506	0.1637
	QRS	0.0118	0.0118	0.0116	0.0114	0.0119
	QT	0.0118	0.0960	0.0931	0.0938	0.0951
D6	RR	0.5526	0.2326	0.2327	0.2216	0.2211
	QRS	0.1911	0.0110	0.0110	0.0110	0.0110
	QT	0.0964	0.0968	0.0951	0.0958	0.0958

III. Discussion

Synthetic work and molecular docking

Molecular docking is a method for predicting the major binding mode of a ligand with a target protein of known 3D structure, which is an important tool in structure-based computer assisted drug design. The designed Tetrahydro Benzpyrimidine derivatives are docked well into the active site of the target protein (PDB code: 1TL3) using autodock Vina software. The entire designed compound shows appropriate binding to the target protein by hydrogen bond and hydrophobic interaction. Among them, D2, D3 and D6 from show other (Pi-Pi) type of interaction. (Table 7). Almost all the compounds were active and the most active compounds are D1, D2 and D4 with minimum binding affinity are selected as potent inhibitors. Hydrophobic interaction of D1, D2, and D6 with LEU109, PHE93, LEU330, SER331 and PRO337 are

Distinguished. There is also the formation of the hydrogen bonds between molecules ARG228, TYR402, VAL110 TYR402 GLU381 and PRO327are fully recognized as indicated which have observed in (Table 7).

Docking studies revealed that it shows binding mode of the most active compounds with designed compound and target protein. According to

the mol log P, compounds D1, D3, D3 and D6 are lipophilic hence they form hydrophobic interaction. This was taken because it has the structural similarity of nucleus with the designed compound. The Tetrahydro Benzpyrimidine nucleus is a basic ring i.e., D2, D3 and D6 designed compound for inhibitor activity. all the designed compounds have the lowest binding efficacy than standard, it seems that designed compounds are more potent inhibitors than standard.

Here in we reported simple method for the synthesis of substituted analogues. The reaction between substituted benzaldehyde, acetamidine and ammonia in presence of acidic condition yielded gives final substituted Tetrahydro Benzpyrimidine. Structures of the synthesized compounds were characterized by melting point, TLC, IR spectroscopy, NMR spectroscopy.

Biological Screening:

The title compounds (D3 and D6) (10 mg/kg, i.p.) produced blood pressure lowering effect (Table 8, Figure 29) and the heart rate is constant in urethane-anesthetized normotensive Wistar rats. (Table 9, Figure 30). There were no significant differences between the mean blood pressures before and after Control (DMSO) administration. Nifedipine was taken as standard, at a dose of 10 mg/kg produced significant reduction in blood pressure after dosing. Only ortho Nitro and Methyl derivative and substituted phenyl analogues (Nitro and methyl) were effective antihypertensive agents. D3 and D6 did not show much variation in ECG records (Table 9 and 10; Figure 30).

Compounds D3 and D6 showed increase in the heart rate initially due to reflex action, compared to Control (DMSO). This effect could be the result of vasodilatory effects of test compounds. The reflex tachycardia has been previously reported (Valdivielso et al., 1997; Nekooeian et al., 2009) for classic Tetrahydro Benzpyrimidine compounds like nifedipine.

IV. Conclusion

The outstanding properties of this new class of antihypertensive substances deserve further investigation in order to clarify the mode of action at molecular level responsible for the activity observed. An extensive study is also warranted to determine additional physiochemical and biological parameters to have a deeper insight into its structure– activity relationship and to optimize the effectiveness of series of molecules. Among the newer derivatives, it is conceivable that some of the derivatives that displayed promising antihypertensive activity can be further modeled to exhibit better potency than the standard drugs. Thus, the new synthesized Tetrahydro Benzpyrimidine heterocyclic derivatives may provide valuable leads for developing new antihypertensive agents. Our aim is to synthesize the Tetrahydro Benzpyrimidine derivatives which will have the better antihypertensive activity than the existing derivatives.

1. The Tetrahydro Benzpyrimidine analogs were synthesized according to scheme.
2. The purity of all compounds' was achieved by determining the melting point, Rf value.
3. Structure of title compounds were confirmed by 1HNMR and IR

Results showed that all final products were pure and stable compounds. Similar to other analogues of nifedipine, they were lipophilic compounds. D3 to D6 (10 mg/kg, i.p.) with nifedipine (10 mg/kg, i.p.) showed that all compounds reduced the mean arterial blood pressure. From the detailed analysis of pharmacological activities of synthesized compounds, we concluded that the Molecular docking based on which we have designed molecules, has proven to be promising at least in these preliminary in vivo pharmacological screening models. These compounds decreased mean arterial blood pressure significantly, while no effect on the heart rate in rats. Further pharmacological and toxicological studies are required to provide a comprehensive profile of these compounds for their prospective use in drug therapy.

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