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# Green Synthesis, Characterization, In Silico ADMET Profiling, Molecular Docking Studies of 3, 4-Dihydropyrimidin-2-(1H)-ones Against Voltage-Gated Calcium Channel (4MS2) Receptor

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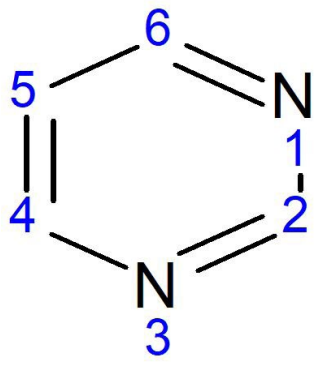
**Abstract**

*The present work involves design, synthesis and evaluation of derivatives of 3,4-dihydropyrimidine 2 one. Using pyrimidine as a core structure for design of novel pyrimidine derivatives which are calcium channel blocker, Derivatives of 3,4-dihydropyrinidine-2-one was synthesized by microwave assisted synthesis method. There are ten derivatives are synthesized by microwave assisted synthesis in laboratory. The entire synthesized compound was tested using Insilco parameters like Pass online data, SwissADME parameters and toxicity parameters by using protox II. All the synthesized compound tested by pass online software for its biological activity. All the synthesized compounds reflelects various activities like antihypertensive, antianginal, antiviral, antifungal and all of them are calcium channel blockers.*

## Introduction

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. Heterocycles make up an exceedingly important class of compounds. In fact, more than half of all known organic compounds are heterocycles [1].

There are numerous biologically active molecules with six-membered rings, containing two hetero atoms. Pyrimidine is a heterocyclic aromatic organic compound similar to benzene and pyridine, containing two nitrogen atoms at positions 1 and 3 of the six-member ring. It is isomeric with two other forms of diazine [1, 2].




**Pyrimidine Ring**

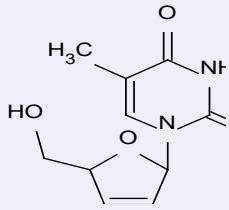
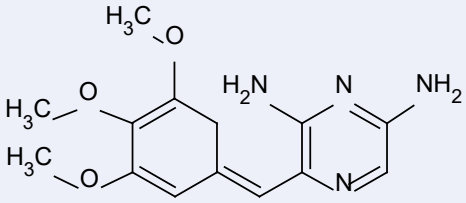
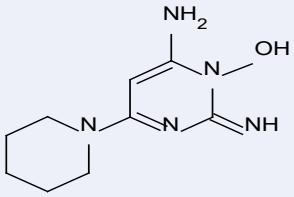
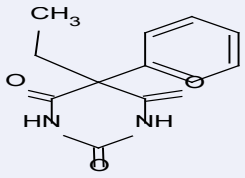
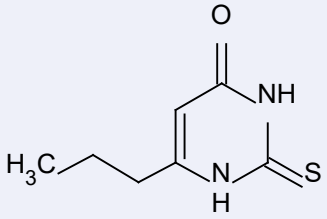
Pyrimidines are 6-membered heterocyclic ring compounds composed of nitrogen and carbon. They are present throughout nature in various forms and are the building blocks of numerous natural compounds from antibiotics to vitamins and liposacharides. The origin of the term pyrimidine dates back to 1884 when Pinner coined the term from a combination of the words pyridine and amidine because of the structural similarity to those compounds [3].

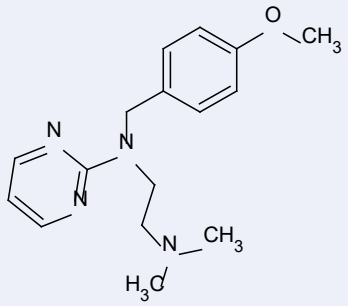
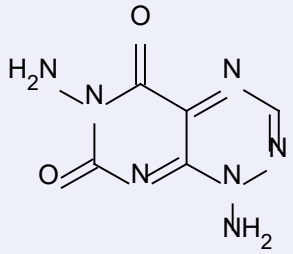
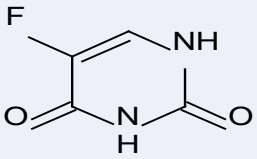
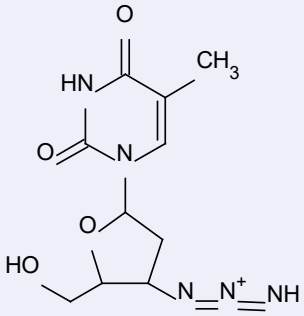
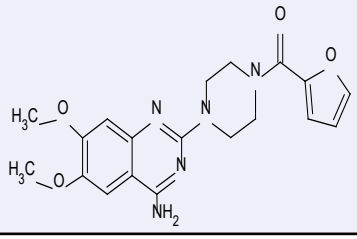
One method is the classic Biginelli reaction. The Biginelli reaction is a multiple-component chemical reaction that creates 3,4-dihydropyrimidin-2(1H)- ones from ethyl acetoacetate, an aryl aldehyde (such as benzaldehyde), and urea Fig 2. The combination of an aldehyde 1, β-keto ester 2, and urea 3 under acid catalysis to give a dihydropyrimidine 4 (Scheme 1) was first reported by Pietro Biginelli in 1893 referred to as the Biginelli reaction [4]. A large number of Biginelli products can be synthesized by a combination of a relatively small number of individual building blocks. The product of this onepot condensation reaction was obtained by considering three building blocks, i.e., an aldehyde, a urea (thiourea), and a 1,3-dicarbonyl compound [5]. The first mechanistic studies of the Biginelli reaction were conducted by Folkers and Johnson forty years after Biginelli's initial report [5]. The literature survey specify that a wide range of pharmacological activities are exhibited by the compounds encircle within pyrimidines nucleus. In ad-

dition to this, various analogs of pyrimidines have been found to posses antibacterial, antifungal, antileishmanial, anti-inflammatory, analgesic, antihypertensive, antipyretic, antiviral, antidiabetic, antiallerggic, anticonvulsant, antioxidant, antihistaminic, herbicidal, and anticanceractivities and many of pyrimidines derivatives are reported to possess potential central nervous system (CNS) depressant properties and also act as calcium channel blockers.

Precise regulation of calcium homeostasis is crucial for many physiological functions [6]. Divergent types of calcium channels and pumps can control the influx of calcium ions into cells [7, 8]. Consequently, targeting calcium channels is advantageously beneficial to yield useful drugs. CaV1.2 blockers can be roughly categorized into three different chemical classes: 3,4-dihydropyrimidine-2-one (DHP) derivatives, phenylalkylamine derivatives and benzothiazepine derivatives. Calcium antagonists have a versatile pharmacological activity such as antihypertensive and antianginal, antitumor, anti-inflammatory, antitubercular, anticonvulsant and antithrombotic [9-19].

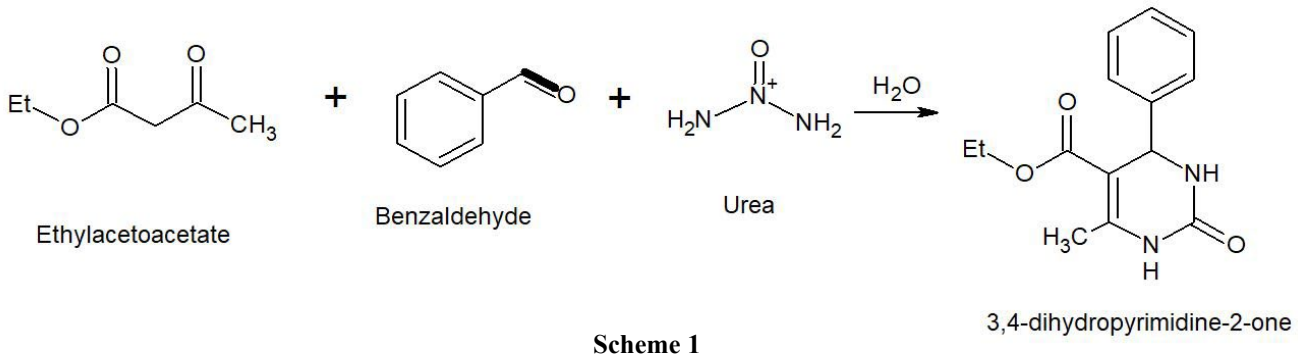
**Table 1: Chemical Structure and Physical Data of 3,4-dihydropyrimidine-2-one Derivatives**

| | | | |
|---|---|---|---|
| 1 | Trifluridine |  | Antiviral |
| 2 | Stavudine |  | Anti-HIV |
| 3 | Trimethoprim |  | Antibacterial |
| 4 | Minoxidil |  | Antihypertensive |
| 5 | Phenobarbitone |  | Sedative & hypnotic |
| 6 | Propylthiouracil |  | Antithyroid |

| | | | |
|---|---|---|---|
| 7 | Thionzylamine |  | H1-antihistaminic |
| 8 | Toxaflavin |  | Antibiotic |
| 9 | 5-flurouracil |  | Anticancer |
| 10 | Idoxuridine |  | Antiviral |
| 11 | Zidovudine |  | Anti-HIV |
| 12 | Prazosin |  | Antihypertensive |

## Chemistry

3,4-dihydropyrimidine-2-one derivatives, D1-D10 were prepared by the method summarized in Scheme 1. The target key intermediate 3,4-dihydropyrimidine-2-one was synthesized according to the reported procedure. Compounds was reacted with water and the reaction mass was irradiated in microwave for 10-20 min according on the reaction material at 450 watts. The obtained solid was crushed and added into water [20]. The crude product was isolated by filtration that further purifird by recrystalization with ethanol to afford pure 3,4-DHMPs.7 The synthesized derivatives yields 70–78%. These synthesized compounds were characterized by different in sillico mwthods and IR with physical analysis. The chemical structures, physical data and purity of all the synthesized compounds are given in Table 1.




**Scheme 1**

## Experimental

### General Procedure for Synthesis of 3,4 dihydropyrimidine-2-one Derivatives

A 25 ml round bottomed flask was charged with aldehyde (2 mmol), urea (2 mmol), b-dicarbonyl compound (2 mmol), and 3-4 drops of water. The resulting suspension was microwave irradiation (450 W, 2 min). The mixture became solid at the end of the reaction, which was crushed and added into the water. The crude product was isolated by filtration that further purified by recrystallization with ethanol to afford pure 3,4-DHMPs [21].

### Synthesis of Ethyl 4-methyl-2-oxo-6-phenylhexahydropyrimidine-5-carboxylate D1

The general procedure for synthesis of 3,4-dihydropyrmidine-2-one was discuss in above section. benzaldehyde, ethylacetoacetate and urea was used in synthesis of this derivative. suspention was microwave irradiated at 450 W for 12 min. Recrystallization from ethanol afforded (70.00%), FT-IR (KBr, $cm^{-1}$) m: 3232 (N-H), 3105 ($CH_3$), 2980 (C-H), 1693 (C=O), 1452 (C=C), 1379 (C-N), 759 (C-O).

### Synthesis of ethyl 4-(2-hydroxyphenyl)-6-methyl-2-oxohexahydropyrimidine-5-carboxylate D2

The general procedure for synthesis of 3,4-dihydropyrmidine-2-one was discuss in above section. salicyldehyde, ethylacetoacetate and urea was used in synthesis of this derivative. suspention was microwave irradiated at 450 W for 15 min. Recrystallization from ethanol afforded (65.41%). FT-IR (KBr, $cm^{-1}$); 3462 (O-H), 3217 (N-H), 2924 (C-H), 1680 (C=O), 1450 (C=C), 1226 (C-N), 752 (C-O).

### Synthesis of ethyl 4-(2-hydroxyphenyl)-6-methyl-oxohexahydropyrimidine-5-carboxylate D3

The general procedure for synthesis of 3,4-dihydropyrmidine-2-one was discuss in above section salicyldehyde, ethylacetoacetate and thiourea was used in synthesis of this derivative. suspention was microwave irradiated at 450 W for 15 min. Recrystallization from ethanol afforded (58.75%).

### Synthesis ofethyl 4-methyl-6-phenyl-2-thioxohexahydropyrimidine-5-carboxylate D4

The general procedure for synthesis of 3,4-dihydropyrmidine-2-one was discuss in above section. benzaldehyde, ethylacetoacetate and thiourea was used in synthesis of this derivative. suspention was microwave irradiated at 450 W for 12 min. Recrystallization from ethanol afforded (53.40%), FT-IR (KBr, $cm^{-1}$); 3305 (O-H), 3169 (N-H), 3061 (C-H),2824 ($CH_3$), 1637 (C=O), (C=S), 759 (C-O).

### Synthesis of ethyl 4-methyl-6-(2-nitrophenyl)-2-oxohexahydropyrimidine-5-carboxylate D5

The general procedure for synthesis of 3,4-dihydropyrmidine-2-one was discuss in above section .2-nitrobenzaldehyde, ethylacetoacetate and urea was used in synthesis of this derivative. suspention was microwave irradiated at 450 W for 15 min. Recrystallization from ethanol afforded (60.59%) FT-IR (KBr, $cm^{-1}$); 3182 (N-H), 3072 (C-H), 2983 ($CH_3$), 1658 (C=O), 1521 ($NO_2$), 1232 (C-O).

### Synthesis of ethyl 4-methyl-6-(2-nitrophenyl)-2-thioxohexahydropyrimidine-5-carboxylate D6

The general procedure for synthesis of 3,4-dihydropyrmidine-2-one was discuss in above section. 2-nitrobenzaldehyde, ethyl acetoacetate and thiourea was used in synthesis of this derivative. suspention was microwave irradiated at 450 W for 15 min. Recrystallization from methanol afforded (65.32%).

### Synthesis of ethyl 4-methyl-6-(2-nitrophenyl)-2thioxo-hexahydropyrimidine-5-carboxylate D7

The general procedure for synthesis of 3,4-dihydropyrmidine-2-one was discuss in above section. benzaldehyde, ethylcynoacetate and urea was used in synthesis of this derivative. suspention was microwave irradiated at 450 W for 17 min. Recrystallization from ethanol afforded (58.90%).

### Synthesis of ethyl 4-cyano-6-phenyl-2-thioxohexahydro-pyrimidine-5-carboxylate D8

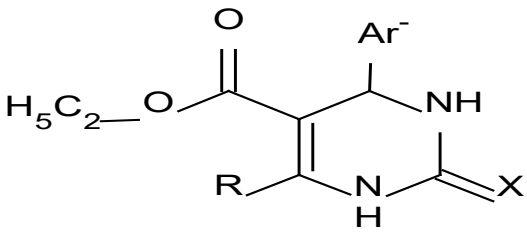
The general procedure for synthesis of 3,4-dihydropyrmidine-2-one was discuss in above section. benzaldehyde, ethylcynoacetate and thiourea was used in synthesis of this derivative. suspention was microwave irradiated at 450 W for 19 min. Recrystallization from ethanol afforded (61.67%).

### Synthesis of ethyl 4-cyano-6-(2-hydroxyphenyl)-2-oxo-hexahydropyrimidine-5-carboxylate D9

The general procedure for synthesis of 3,4-dihydropyrmidine-2-one was discuss in above section. salicyldehyde, ethylcynoacetate and urea was used in synthesis of this derivative. suspention was microwave irradiated at 450 W for 17 min. Recrystallization from ethanol afforded (59.11%) FT-IR (KBr, $cm^{-1}$); 3462 (N-H $1^0$), 3360 (N-H $2^0$), 3207 (O-H), 3062 ($CH_3$), 2839 (C-H), 1701 (C=O), 1602 (Cyno), 756 (C-O).

### Synthesis of ethyl 4-cyano-6-(2-hydroxyphenyl)-2-thiox-ohexahydropyrimidine-5 carboxylate D10

The general procedure for synthesis of 3,4-dihydropyrmidine-2-one was discuss in above section. salicyldehyde, ethylcynoacetate and thiourea was used in synthesis of this derivative. suspention was microwave irradiated at 450 W for 18 min. Recrystallization from ethanol afforded (54.67%).




3,4-dihydropyrimidine-2-one

**Table 1: Chemical Structure and Physical Data of 3,4-dihydropyrimidine-2-one Derivatives**

| Comp.code | Ar | R | X | Yelid % | Melting point (0C) | Mol. Formula | Reaction time(min) |
|---|---|---|---|---|---|---|---|
| D1 | C6H6O | CH3 | O | 88.00 | 196-200 | C14H16N O3 | 12 |
| D2 | Ar-O-OH | CH3 | O | 81.41 | 207-209 | C14H16N2O4 | 15 |
| D3 | Ar-O-OH | CH3 | S | 70.75 | 196-198 | C14H16N2O3S | 15 |
| D4 | C6H6O | CH3 | S | 68.40 | 174-176 | C14H16N2O2S | 12 |
| D5 | Ar-O-NO2 | CH3 | O | 85.59 | 196-198 | C14H16N3O5 | 15 |
| D6 | Ar-O-NO2 | CH3 | S | 87.14 | 199-201 | C14H16N3O4S | 15 |
| D7 | C6H6O | CN | O | 73.26 | 212-214 | C14H13N3O3 | 17 |
| D8 | C6H6O | CN | S | 78.00 | 230-232 | C14H13N3O2S | 19 |
| D9 | Ar-O-OH | CN | O | 72.48 | 214-216 | C14H13N3O4 | 17 |
| D10 | Ar-O-OH | CN | S | 62.50 | 226-228 | C14H13N3O3S | 18 |

## Molecular Docking

Herewith, we have sequence of the target protein and the 3D structure is available, and then its similarity with protein sequences in database(s) is analyzed. Consequently, suitable coordinates of the DHP receptor model were used [22]. All ligands were drawn into VLIFE MDS 4.6.08032021 [23]. The most energetically favored conformer was saved as (*. mol2) file format for docking. The optimal geometry of the ligands was determined during the docking process. The Molecular docking study was performed on selected molecules along with the reference molecule (nifedipine) into the DHPs receptor model active site using VLIFE MDS 4.6.08032021. Docking results were visualized the same software. The docking parameters are saved in a configuration file which is provided as an example in the supporting data.

## ADMET Prediction

The computational approach, also known as in silico approach, is one of the modern and fastest developing techniques being used today in drug discovery to assess the pharmacokinetics, ADME (absorption, distribution, metabolism, and excretion), and toxicity predictions. The application of computational technology during drug discovery and development offers considerable potential for reducing the number of experimental studies required for compound selection and development and for improving the success rate [24]. This early prediction of ADMET properties will help researchers to select the best candidates for drug development, as well as to reject those with a low probability of success. The ultimate goal of the in silico ADMET properties is the prediction of the in vivo pharmacokinetics of a potential drug molecule in man, while it exists as only a virtual structure [25].

With the intention of find out the drug-like properties for the synthesized compounds, ADME calculation was performed by ADMET predictor of Simulation Plus [26, 27]. We have predicted various ADMET properties of these compounds, among which were aq. solubility, human intestinal absorption, plasma protein binding (PPB), blood–brain barrier (BBB) penetration, cytochrome P450 inhibition, and hepatotoxicity levels [28].

## Result and Discussion

### Molecular Docking

Computational molecular docking is widely used for the study of protein–ligand interactions and for drug discovery and development. Typically, the process starts with a target of known structure, such as a crystallographic structure of an enzyme of medicinal interest or a homology model. Docking is then used to predict the bound conformation and the binding free energy of small molecules to the target. Single docking experiments are useful for exploring the function of the target, and virtual screening- in which a large library of compounds is docked and ranked-may be used to identify new inhibitors for drug development.

To our knowledge, several theoretical models of CaV1.2- DHPs have been reported. In 2001, Zhorov et al. built two models of the pore region of CaV1.2 from rabbit cardiac muscle, and docked nifedipine into the active site to explore the interactions of agonists and antagonists [29].

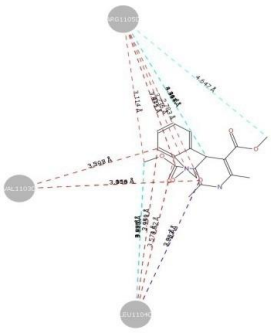
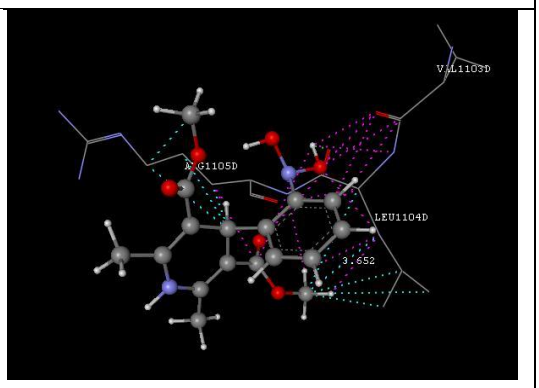
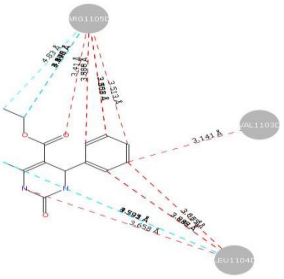
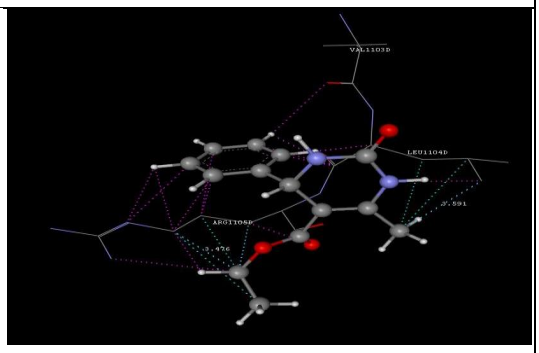
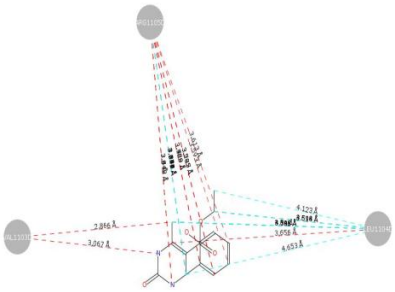
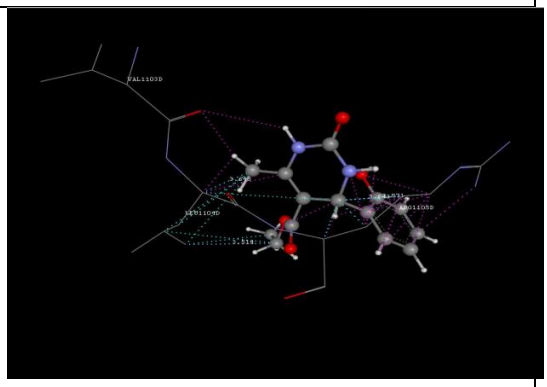
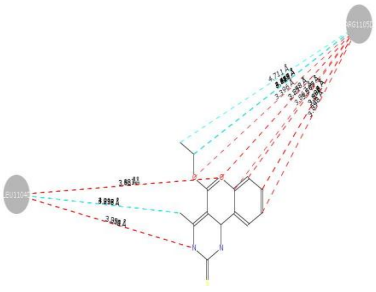
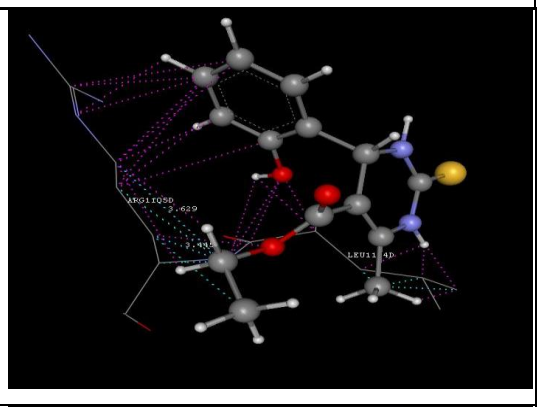
In 2003, Lipkind and Fozzard constructed the inner pore structure of CaV1.2 and predicted the binding conformations of nifedipine, phenylalkylamine and agonist Bay K8644 by using the molecular-docking approach [30]. In 2007, Cosconati et al. constructed the central pore of CaV1.2 and explored the binding modes of nine different DHPs [31]. In 2009, Tikhonov and Zhorov constructed two structural models of CaV1.2 in open and closed states, and explored the possible binding structures of (S)-nimodipine the crystal structure of the voltage-gated calcium channel from bacterium Arcobacter butzleri (CaVAb) was reported (**PDB entry: 4MS2**) [32].

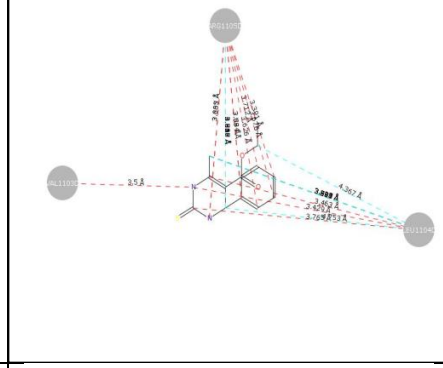
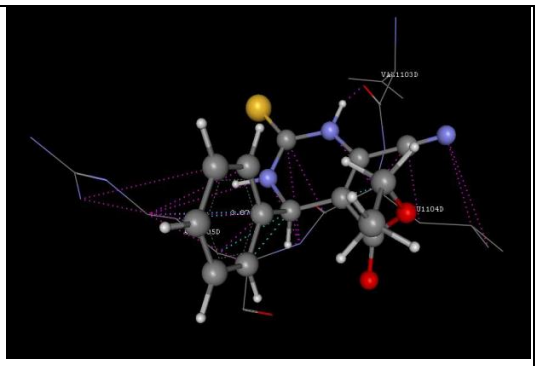
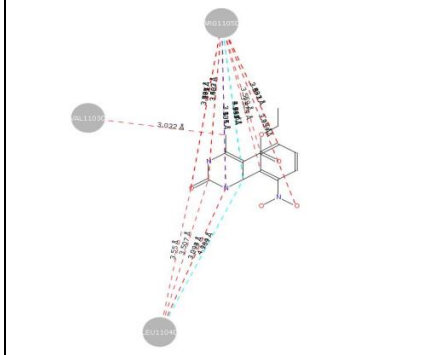
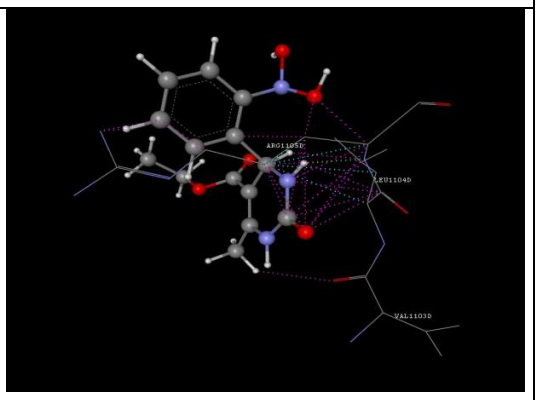
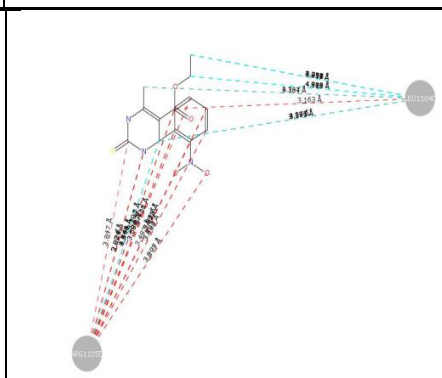
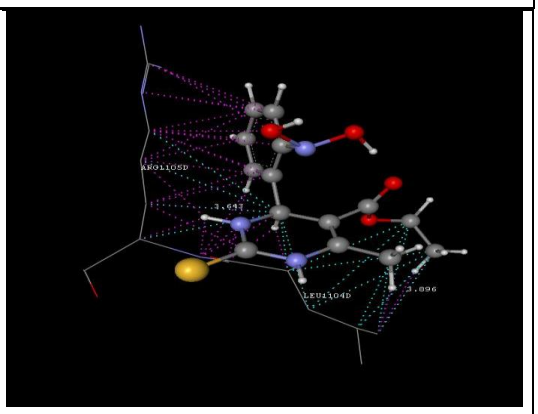
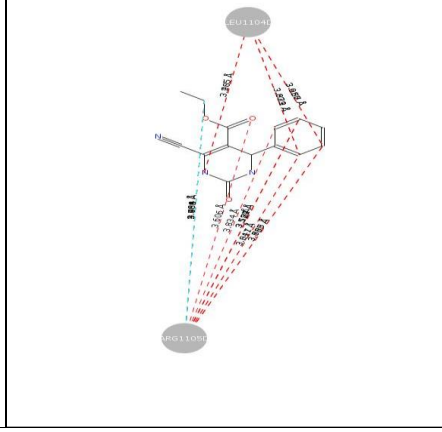
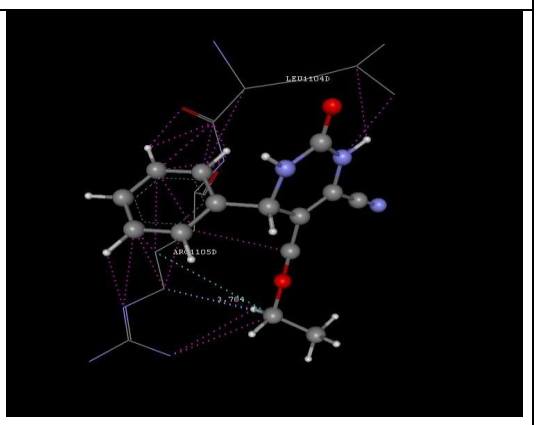
In our research paper, we use the nifedipine as a standard drug or ligand which shows anthihypertensive activity and the protein or receptorwe used is a voltage-gated calcium channel from bacterium Arcobacter butzleri (CaVAb), (**PDB entry: 4MS2**). The further docking result we can compare in next table.

**Table 2: Docking Score of Synthesized Derivatives with Standard Ligand Score**

| Ligand | Docking score (kcal/mol) |
|---|---|
| Nifedipine (std) | -14.2417 |
| D1 | -33.8668 |
| D2 | -34.6152 |
| D3 | -32.3780 |
| D4 | -37.9724 |
| D5 | -35.1175 |
| D6 | -39.6089 |
| D7 | -37.6426 |
| D8 | -38.7153 |
| D9 | -35.4055 |
| D10 | -38.3155 |

In the molecular docking 2D and 3D interaction of ligand either receptors are play important role. All the 2D and 3D interaction of synthesized compound/derivative sof 3,4-dihydropyrimidine-2-one with the selected protein/receptor was tabulated in following table.

| Comp. no | 2D interaction | 3D interaction |
|---|---|---|
| Std. nifedpine |  |   |
| D1 |  |  |
| D2 |  |  |
| D3 |  |  |

| | | |
|---|---|---|
| D4 |  |  |
| D5 |  |  |
| D6 |  |  |
| D7 |  |  |

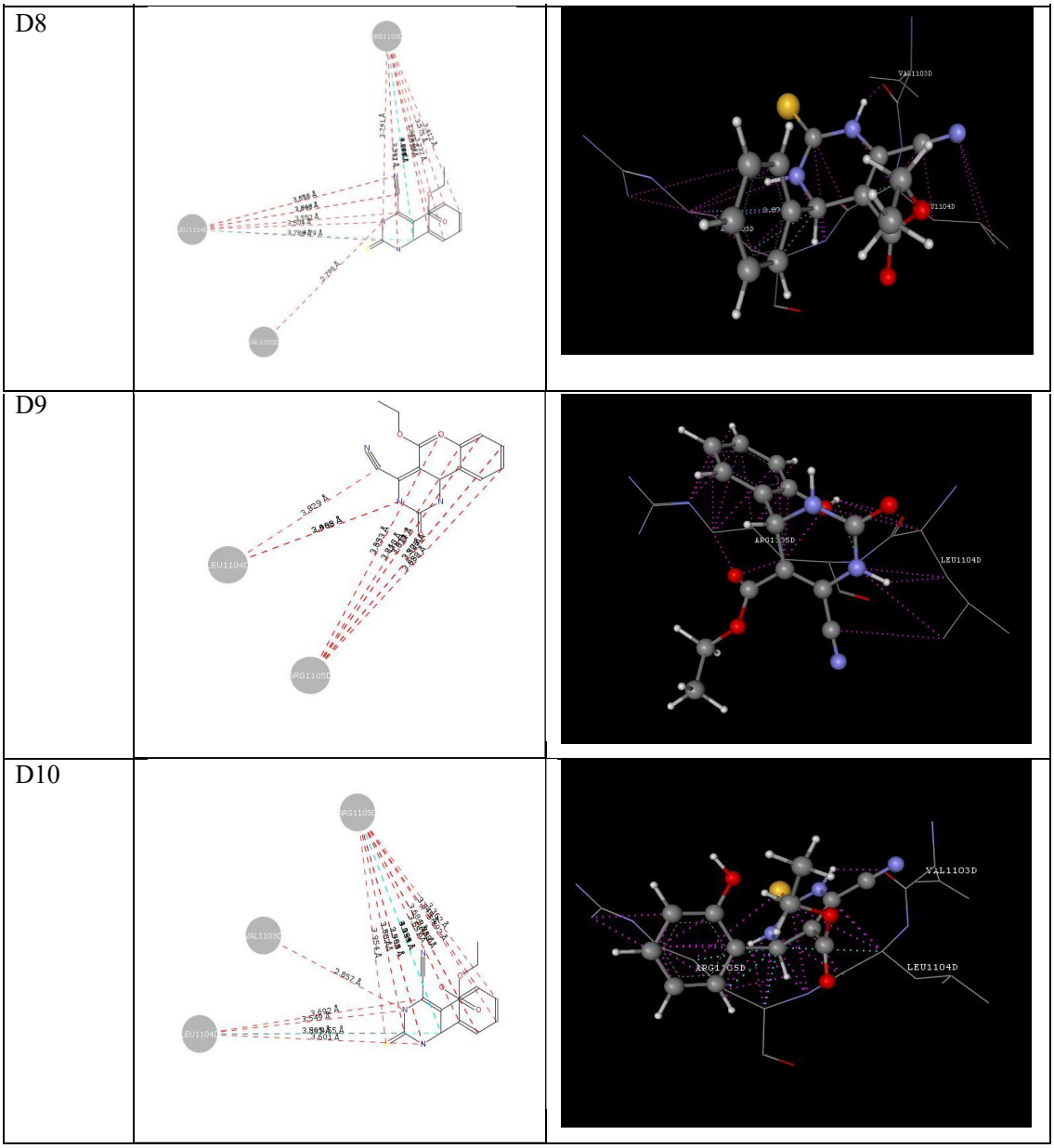



**Figure 1:** 2D and 3D Interaction of Synthesizes 3,4-dihydopyrimidine-2-one derivatives(D1-D10)

In docking studies, we can conclude that, std drug nifedipine shows the docking score -14.2417, and remaning synthesized ligand shows the docking scores are higher than standard drug which means the antihypertensive activity shown by synthesized deriavaties (D1-D10), is better than the std drug. The derivative no D6 have more higher score in the all of derivatives which shows better hypertensive activity in all derivatives and than standard one.

## ADMET Prediction

A large variety of *in silico* methods share the objective of predicting ADME parameters from molecular structure [33]. Noteworthy, the pioneer work of Lipinski *et al.* examined orally active compounds to define physicochemical ranges for high probability to be an oral drug (i.e. the drug-likeness) [34]. This so-called *Rule-of-five* delineated the relationship between pharmacokinetic and physicochemical parameters. Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery process, at a stage when considered compounds are numerous but access to the physical samples is limited.

ADME was performed in software, Swiss ADME which is open access software. SwissADME web tool that gives free access to a pool of fast yet robust predictive models for physicochemical properties, pharmacokinetics, drug-likeness and medicinal chem-

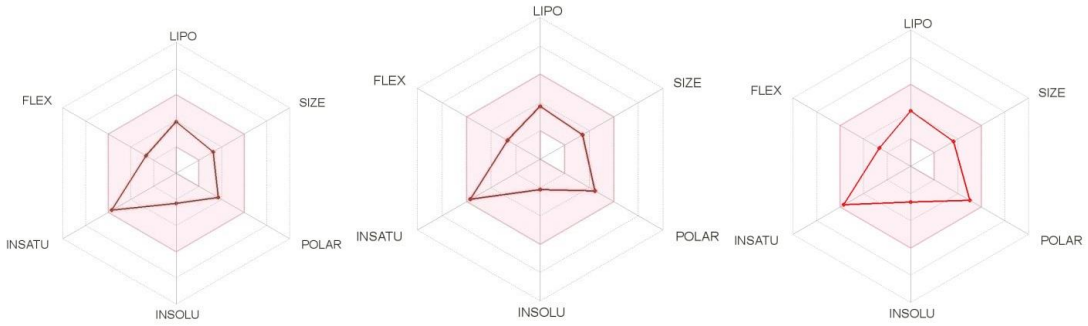
istry friendliness, among which in-house proficient methods such as the BOILED-Egg, iLOGP and Bioavailability [35].

Molecular descriptors of synthesized compounds were calculated. An inspection of the data given in Table 3.

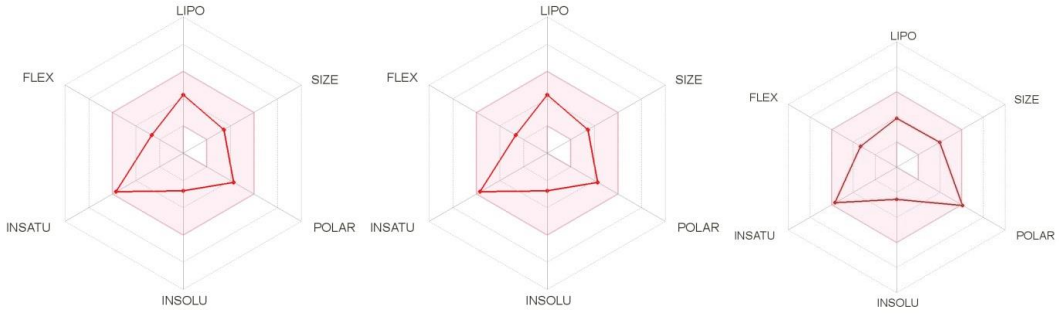
Molecular descriptors such as logP, molecular weight, Pka, and logBBB have been proven to be useful in modeling distribution [36]. Volume of distribution (Vd), an important parameter, relates the amount of a drug in body to the measured concentration in a relevant biological fluid. ADME parameters of compounds are tabulated in Table 3.

**Table 3: ADME Prediction of Synthesized Derivatives of 3,4-dihydropyrimidine-2-one**

| Comp. No | Lipophilicity | Molar refractivity | Topological polar surface area TPSA $A^0$ | i LOG P | X LOG P3 | Synthetic accessibility | Bioavillabity score | GI absorption | BBB | Skin penetration(cm/s) |
|---|---|---|---|---|---|---|---|---|---|---|
| D1 | 2.34 | 77.78 | 67.43 | 2.34 | 1.38 | 3.60 | 0.55 | High | No | -6.91 |
| D2 | 1.97 | 79.80 | 87.66 | 1.97 | 1.02 | 368 | 0.55 | High | No | -7.26 |
| D3 | 2.32 | 87.00 | 102.68 | 2.32 | 1.62 | 3.64 | 0.55 | High | No | -6.93 |
| D4 | 2.70 | 84.98 | 82.45 | 2.70 | 1.9 | 3.58 | 0.55 | High | No | -6.68 |
| D5 | -4.51 | 85.02 | 117.09 | -4.51 | 0.74 | 3.77 | 0.55 | High | No | -7.64 |
| D6 | -2.91 | 92.22 | 132.11 | -2.91 | 1.34 | 3.76 | 0.55 | High | No | -7.31 |
| D7 | 1.88 | 77.53 | 91.22 | 1.88 | 0.93 | 3.65 | 0.55 | High | No | -7.29 |
| D8 | 2.21 | 84.73 | 106.24 | 2.21 | 1.53 | 3.63 | 0.55 | High | No | -6.97 |
| D9 | 1.74 | 79.55 | 111.45 | 1.74 | 0.58 | 3.72 | 0.55 | High | No | -7.64 |
| D10 | 1.91 | 86.75 | 126.47 | 1.91 | 1.18 | 3.68 | 0.55 | High | No | -7.31 |




**D1** **D2** **D3**




**D4** **D5** **D6**

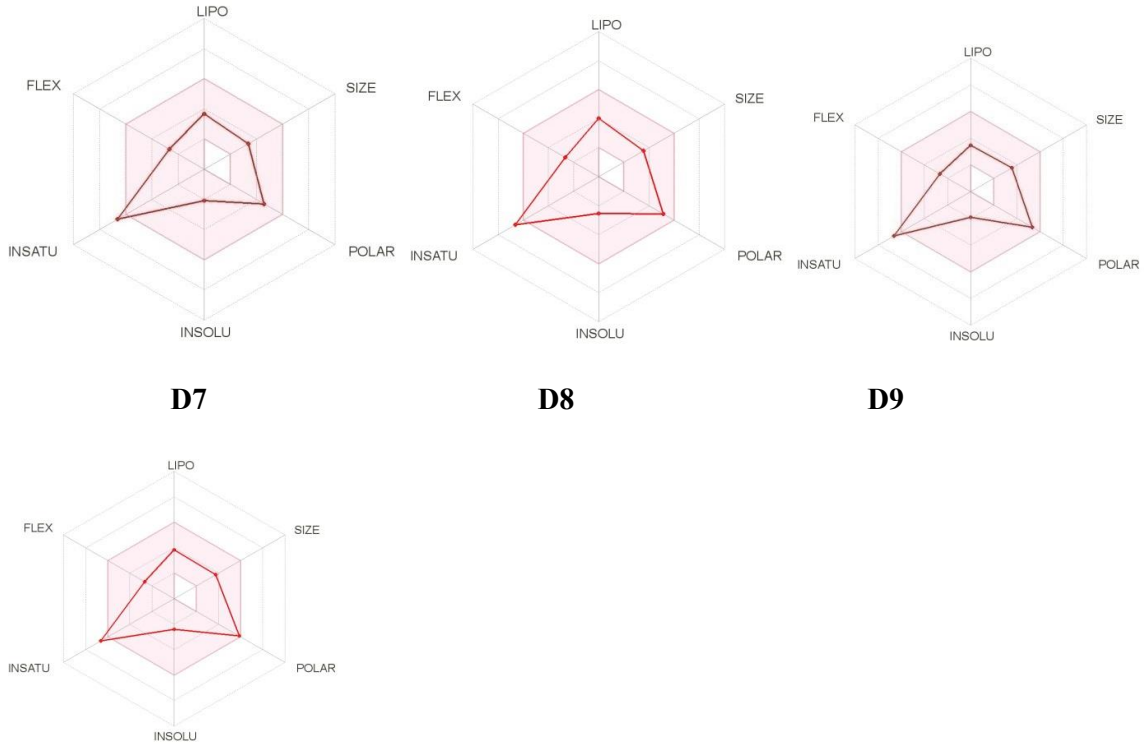



**Figure 2:** The Bioavailability Radar enables a first glance at the drug-likeness of a molecule. The pink area represents the optimal range for each properties (lipophilicity: XLOGP3 between − 0.7 and + 5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 A2, solubility: log S not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds. In this example, the compound is predicted orally bioavailable, because it is not flexible and nor polar.

Toxicity is currently the major reason for drug candidate failure in clinical trials. Therefore, there is a considerable interest of drug designing researchers in developing predictive in silico models. we present ProTox-II that incorporates molecular similarity, pharmacophores, fragment propensities and machine-learning models for the prediction of various toxicity endpoints; such as acute toxicity, hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity, immunotoxicity, adverse outcomes pathways (Tox21) and toxicity targets. The predictive models are built on data from both in vitro assays (e.g. Tox21 assays, Ames bacterial mutation assays, hepG2 cytotoxicity assays, Immunotoxicity assays) and in vivo cases (e.g. carcinogenicity, hepatotoxicity). The models have been validated on independent external sets and have shown strong performance [37-39]. Toxicity predictions of synthesized compounds are tabulated in table no 4.

**Table 4: Toxicity Profile of Synthesized Derivatives of 3,4-dihdropyrimidine-2-one.**

| Comp. code | Predicted LD50(mg/kg | Prediction accuracy | Hepatotoxicity | Carcinogenicity | Immunotoxicity | Mutagenicity | Cytotoxicity |
|---|---|---|---|---|---|---|---|
| D1 | 2495 | 67.38 | Inactive | Active | Inactive | Inactive | Inactive |
| D2 | 2495 | 54.26 | Inactive | Inactive | Inactive | Inactive | Inactive |
| D3 | 150 | 54.26 | active | Active | Inactive | Inactive | Inactive |
| D4 | 785 | 54.26 | Inactive | Active | Inactive | Inactive | Inactive |
| D5 | 50 | 67.38 | active | Active | Inactive | Inactive | Inactive |
| D6 | 50 | 67.38 | active | Active | Inactive | Inactive | Inactive |
| D7 | 2495 | 54.26 | Inactive | Active | Inactive | Inactive | Inactive |
| D8 | 785 | 54.26 | active | Active | Inactive | Inactive | Inactive |
| D9 | 3000 | 54.26 | Inactive | Inactive | Inactive | Inactive | Inactive |
| D10 | 150 | 54.26 | active | Inactive | Inactive | Inactive | Inactive |

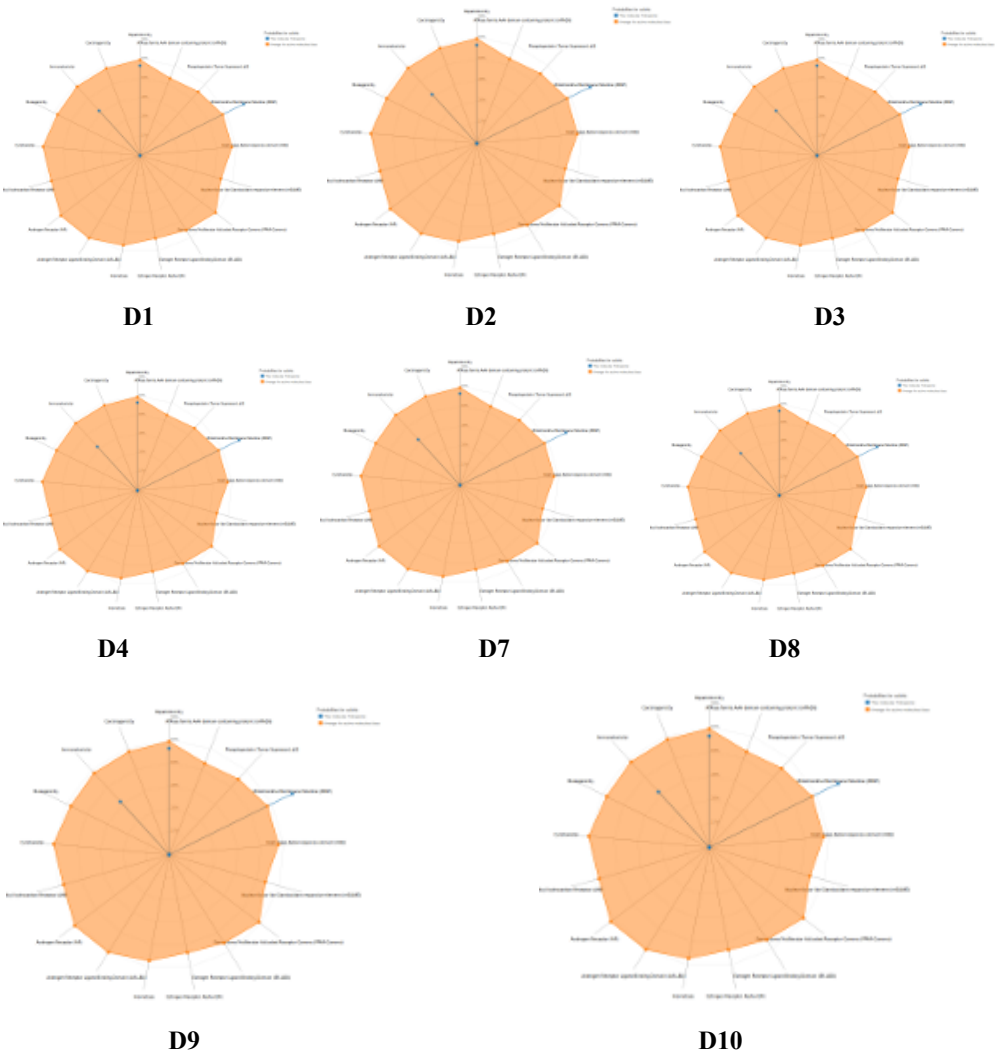



**Figure 3:** Toxicity Profile of Synthesized Derivatives of 3,4-dihdropyrimidine-2-one

## Conclusion

In conclusion, a series of novel 3,4-dihydropyrimidine-2-one derivatives, D1-D10 was synthesized and their antihypertensive activity is shown. Molecular docking study was carried out to understand the binding modes of these newly synthesized compounds. From the molecular docking study, it was confirmed that these compounds might be act as a potential candidate for calcium channel inhibitor. Further lead optimization of drug-like properties was evaluated through in silico predictions using ADMET predictor software. The BBB penetration for all the synthesized compounds is predicted to neligible. The GI qbsorbtion of all synthesized compound are predicted to be high.

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