IJMPR 2018, 2(6), 09-16

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 3.458

A REVIEW ON PHARMACOLOGICAL PROFILE AND FUTURE PERSPECTIVE OF 1, 4-DIHYDROPYRIDINE DERIVATIVES

Asish Bhaumik*[1], S. Chaitanya Kumar[1] and Bilal Ahmed[1]

[1]Department of Pharmaceutical Chemistry, Anurag Pharmacy College, Ananthagiri, Kodad-508206, Suryapet (Dist.), Telangana, India.

Received on: 14/10/2018
Revised on: 04/11/2018
Accepted on: 25/11/2018

***Corresponding Author**
Asish Bhaumik
Department of Pharmaceutical Chemistry, Anurag Pharmacy College, Ananthagiri, Kodad-508206, Suryapet (Dist.), Telangana, India.

ABSTRACT

Dihydropyridine is a pyridine which has had two H atoms added to the ring. As a result it has only two double bonds in the ring rather than three and it is NOT aromatic. The dihydropyridine ring is the basis for making several drugs which are commonly used for treating hypertension and angina. 1, 4-Dihydropyridine (DHP), an important class of calcium antagonist, inhibits the influx of extracellular Ca+2 through L-type voltage-dependent calcium channels. Three-dimensional (3D) structure of calcium channel as a receptor for 1, 4-dihydropyridine is a step in understanding its mode of action. Protein structure prediction and modeling tools are becoming integral parts of the standard toolkit in biological and biomedical research. So, homology modeling (HM) of calcium channel alpha-1C subunit as DHP receptor model was achieved. The 3D structure of potassium channel was used as template for HM process. The resulted dihydropyridine receptor model was checked by different means to assure stereochemical quality and structural integrity of the model. This model was achieved in an attempt to understand the mode of action of DHP calcium channel antagonist and in further computer-aided drug design (CADD) analysis.

KEYWORDS: Dihydropyridine; calcium antagonist; homology modelling; stereochemical etc.

INTRODUCTION

Dihydropyridine is a molecule based upon pyridine, and the parent of a class of molecules that have been semi saturated with two substituent replacing one double bond. They are particularly well known in pharmacology as L-type calcium channel blockers, used in the treatment of hypertension. Compared with certain other L-type calcium channel blockers (for example those of the phenylalkylamine class such as verapamil) that have significant action at the heart, they are relatively vascular selective in their mechanism of action in lowering blood pressure.[1]

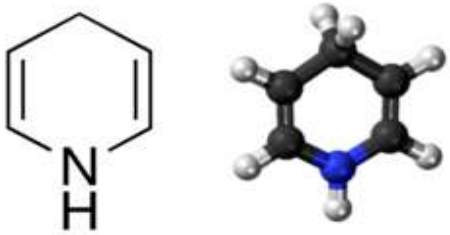
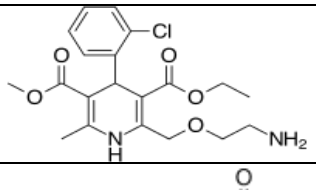
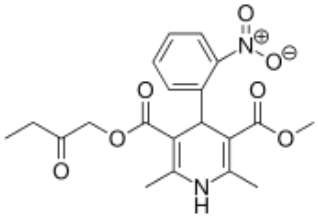
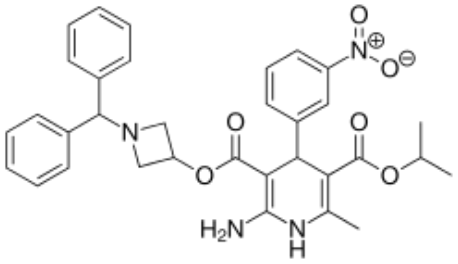
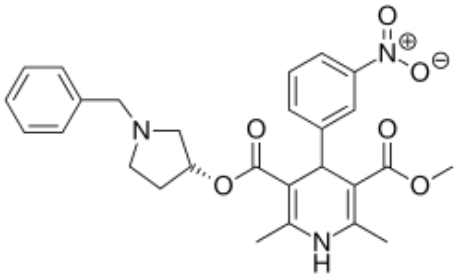
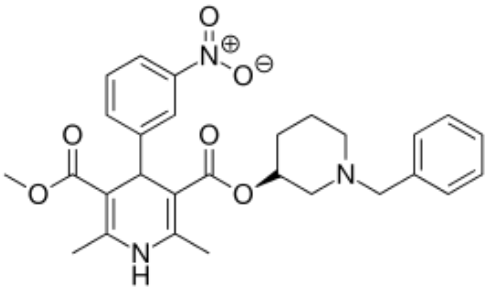
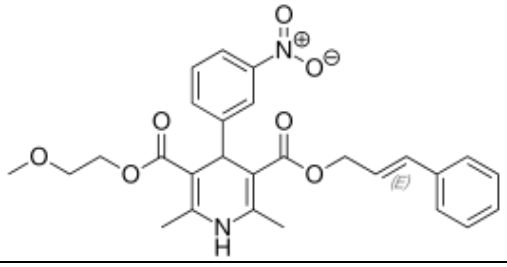
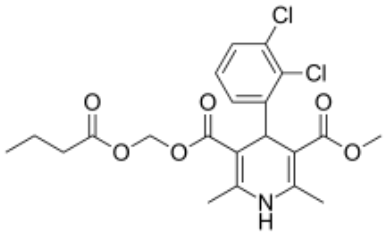
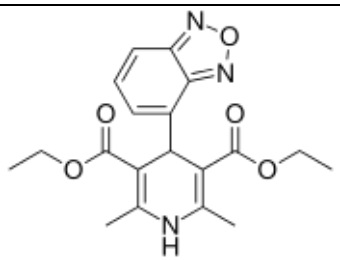
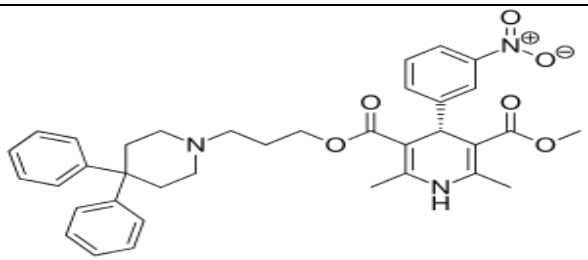
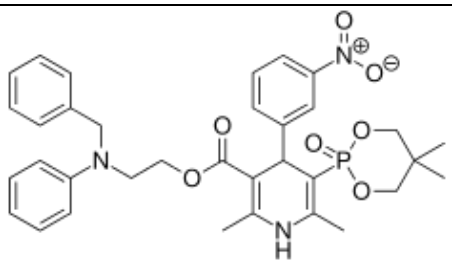
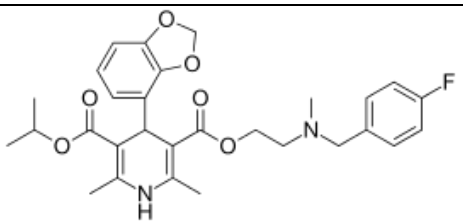
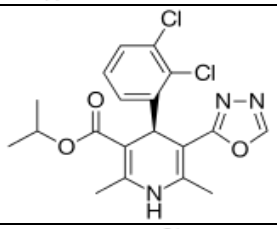
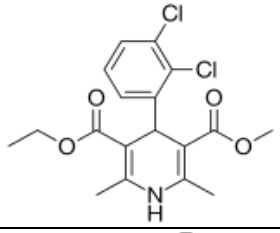
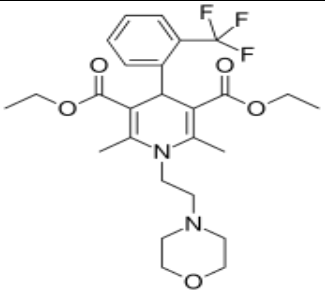
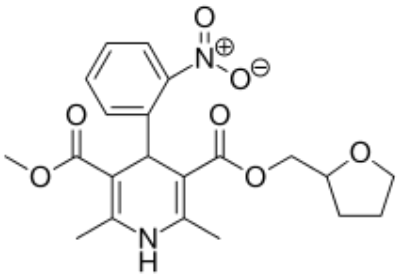
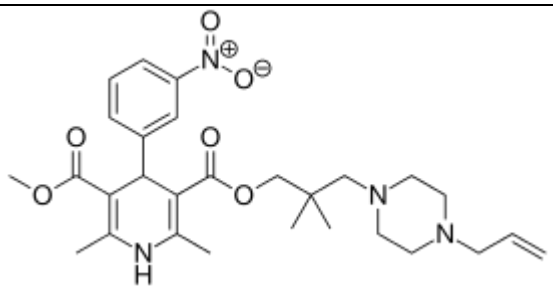


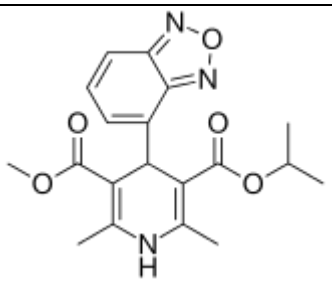
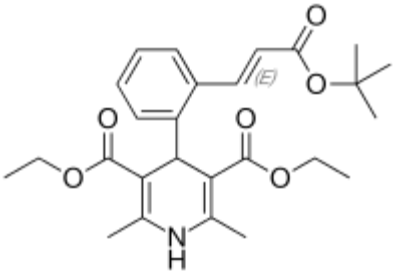
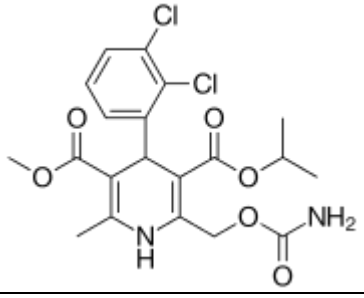
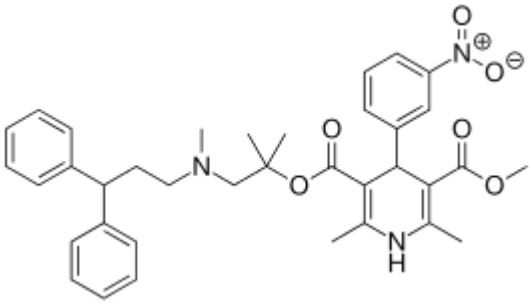
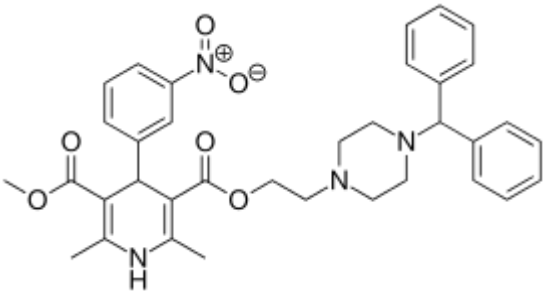
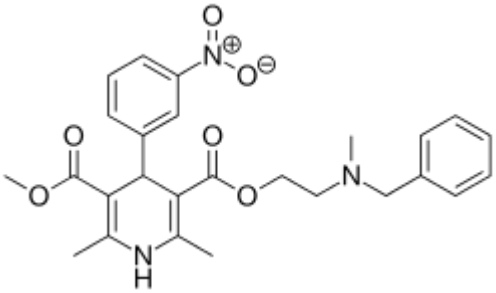
Fig. 1: 4-Dihydropyridine.

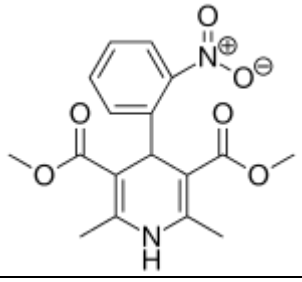
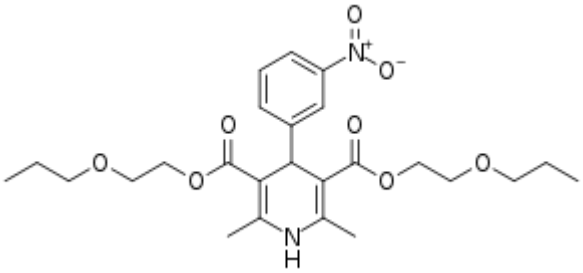
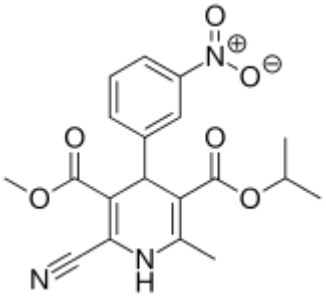
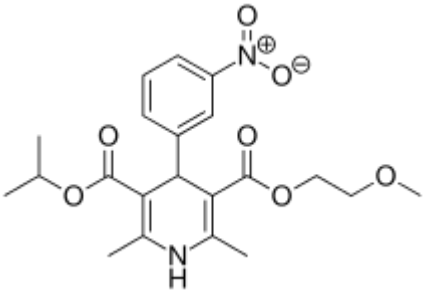
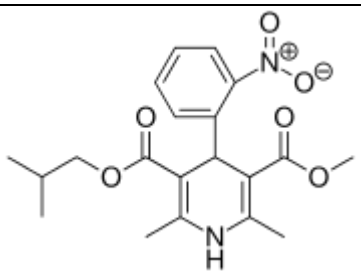
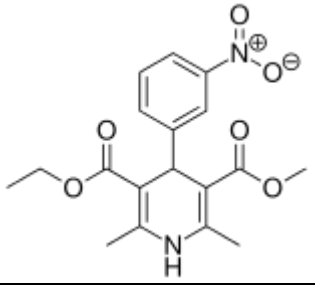
Class members

Name of compounds		Structures
1.	Amlodipine	
2.	Aranidipine	

3.	Azelnidipine	
4.	Barnidipine	
5.	Benidipine	
6.	Cilnidipine	
7.	Clevidipine	
8.	Darodipine	
9.	Dexniguldipine	

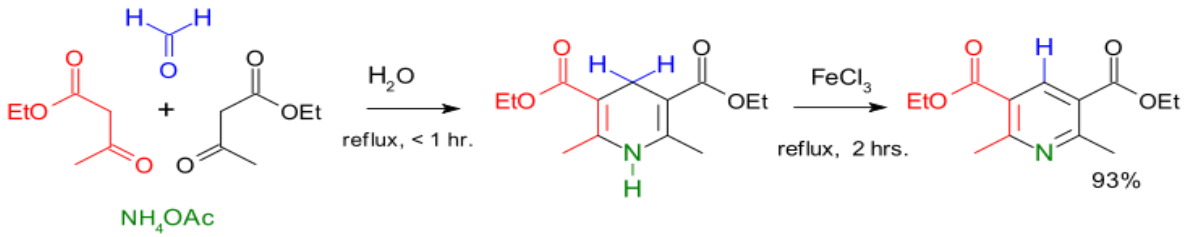
10.	Efonidipine	
11.	Elgodipine	
12.	Elnadipine	
13.	Felodipine	
14.	Flordipine	
15.	Furnidipine	
16.	Iganidipine	

17.	Isradipine	
18.	Lacidipine	
19.	Lemildipine	
20.	Lercanidipine	
21.	Manidipine	
22.	Nicardipine	

23.	Nifedipine	
24.	Niludipine	
25.	Nilvadipine	
26.	Nimodipine	
27.	Nisoldipine	
28.	Nitrendipine	

The Hantzsch pyridine synthesis or Hantzsch dihydropyridine synthesis is a multi-component organic reaction between an aldehyde such as formaldehyde, 2 equivalents of a β-keto ester such as ethyl acetoacetate and a nitrogen donor such as ammonium acetate or ammonia.[2] The initial reaction product is a

dihydropyridine which can be oxidized in a subsequent step to a pyridine. The driving force for this second reaction step is aromatization. This reaction was reported in 1881 by Arthur Rudolf Hantzsch. A 1, 4-dihydropyridine dicarboxylate is also called a 1, 4-DHP compound or a Hantzsch compound. These compounds are an important class of calcium channel blockers and as such commercialized in for instance nifedipine, amlodipine or nimodipine. The reaction has been demonstrated to proceed in water as reaction solvent and with direct aromatization by ferric chloride, Manganese Dioxide or potassium permanganate in a one-pot synthesis.[3]



The Hantzsch dihydropyridine synthesis is found to benefit from microwave chemistry.[4] Calcium channel blockers (CCB), calcium channel antagonists or calcium antagonists.[5] are several medications that disrupt the movement of calcium (Ca2+) through calcium channels.[6] Calcium channel blockers are used as antihypertensive drugs, i.e., as medications to decrease blood pressure in patients with hypertension. CCBs are particularly effective against large vessel stiffness, one of the common causes of elevated systolic blood pressure in elderly patients.[7] Calcium channel blockers are also frequently used to alter heart rate, to prevent cerebral vasospasm, and to reduce chest pain caused by angina pectoris. N-type, L-type, and T-type voltage-dependent calcium channels are present in the zona glomerulosa of the human adrenal, and CCBs can directly influence the biosynthesis of aldosterone in adrenocortical cells, with consequent impact on the clinical treatment of hypertension with these agents.[8]

Ankle oedema appears to occur more frequently in CCBs from the DHP group, although some agents such as lacidipine and lercanidipine may cause it less frequently than nifedipine and amlodipine. Diltiazem, a non-DHP agent, seems to be associated with the lowest incidence of ankle oedema. Common side effects of calcium channel blockers include: headache, constipation, rash, nausea, flushing, edema (fluid accumulation in tissues), drowsiness, low blood pressure.

Pharmacology

This mini review is devoted to the design and pharmacological studies of novel atypical 1, 4-dihydropyridine (DHP) derivatives which differ to a great extent from the traditional DHPs either by lack of neuronal calcium channel blocking activity and/or inability to protect mitochondrial processes. About 100 new DHP derivatives were screened and the mostly active were selected for detailed studies. The compounds of the series of the amino acid ("free" plus "crypto")-containing DHPs and lipophilic di-cyclic DHPs demonstrated long-lasting neuroprotective and/or memory-enhancing action, particularly at low doses (0.005–0.05 mg/kg) in different neurodeficiency rat or mice models, and exerted neurotransmitter-modulating effects. The studies have shown an ability of these atypical DHPs to normalize the expression of neuronal proteins, which participate in the regulation of neurotransmission (particularly of the GABAergic system) and synaptic plasticity that has been impaired in animal models, including Alzheimer's disease transgenic mice. The obtained results indicate that the tested DHP compounds can be considered as candidate molecules either for their further chemical modifications or for the more detailed studies to identify cell targets essential for neuroprotection and memory enhancing.

The 1, 4-dihydropyridine (DHP) class of calcium channel blockers are widely utilized in the treatment of cardiovascular diseases such as hypertension, angina pectoris, and other spastic smooth muscle disorders1. The SAR of calcium channel blockers signifies the presence of ester linkage and electron withdrawing groups like nitro and carbonyl groups. The Pyrimidine nucleus has been showing the various pharmacological activities like calcium channel blockers, anti-cancer, antimicrobial, antiviral. Calcium channel blockers proceed onion conducting cell membrane channels. The1, 4-dihydropyridine moiety is commonly useful as calcium channel blockers and are used most frequently as drugs such as nifedipine, diltiazem, nicardipine, amlodipine (AD), which have been found as potent cardiovascular agents for the treatment of hypertension.[10]

Many 1, 4-dihydropyridines (DHPs) possess redox properties. In this review DHPs are surveyed as protectors against oxidative stress (OS) and related disorders, considering the DHPs as specific group of potential antioxidants with bioprotective capacities. They have several peculiarities related to antioxidant activity (AOA). Several commercially available calcium antagonist, 1,4-DHP drugs, their metabolites, and calcium agonists were shown to express AOA. Synthesis, hydrogen donor properties, AOA, and methods and approaches used to reveal biological activities of various

groups of 1,4-DHPs are presented. Examples of DHPs antioxidant activities and protective effects of DHPs against OS induced damage in low density lipoproteins (LDL), mitochondria, microsomes, isolated cells, and cell cultures are highlighted. Comparison of the AOA of different DHPs and other antioxidants is also given. According to the data presented, the DHPs might be considered as bellwether among synthetic compounds targeting OS and potential pharmacological model compounds targeting oxidative stress important for medicinal chemistry.[11]

The in-vivo Hepatoprotective activity was carried out by using albino rats. The results displayed that the elevated levels of SGOT, SGPT, ALP and Serum bilirubin were mainly due to CCl_4 intoxication, reduced significantly (*P< 0.05) in rats, after treatment with synthe sized compounds. Treatment with a synthesized compound at a dose of 250 mg/kg b.w. decreased the SGOT, SGPT, ALP, Serum bilirubin levels by 6.23% ns (non significantly), 28.96%, 8.81%, and 11.11% ns (non significantly) respectively, while a higher dose of 500 mg/kg b. wt. was more effective, causing a reduction of 25.02%, 47.65%, 24.09% and 27.35%. Silymarin was used as standard drug showed a reduction of 55.09%, 68.98%, 57.46% and 35.04% receiving CCl_4 alone. So depending upon the experimental data it was confirmed that the biochemical parameters of the group treated with compounds were significantly lower than the CCl_4 treated group. Moreover the treatment with the synthesized compounds significantly reduced the previously raised levels of AST, ALT, ALP and bilirubin in hepatotoxic rats. Histopathological investigation displayed that at both doses (250 mg/kg b.w. and 500 mg/kg b.w.) the synthesized compounds were possessed moderate to good hepatoprotective activity, but at 500 mg/kg b.w. executed excellent hepatoprotective activity against CCl_4 induced damaged hepatocytes.[12]

1,4-dihydropyridine compounds executed moderate to good antibacterial activity against tested microorganisms (Gram positive and Gram negative bacteria) with an MIC range of 9-22 µg/ml (gram positive organisms) and with an MIC range of 10-26 µg/ml (gram negative organisms). The MIC of the synthesized compounds (B1, B2, B3, B4, B5 and B6) for different gram positive bacteria were found to be S. aureus (MIC: 9-18 µg /ml), B. subtilis (MIC: 10-21 µg /ml), S. typhi (MIC: 11-22 µg /ml) and S. epidermidis (MIC:12-21 µg /ml). The synthesized compounds (B1, B2, B3, B4, B5 and B6) were active against all the tested gram negative microorganisms with the range of MIC values for P. aeruginosa (MIC: 10-20 µg/ml), P. flurocense (MIC: 12-25 µg/ml) and E. coli (MIC: 11-26 µg/ml) and V. cholerae (MIC: 12-23 µg/ml).[13]

The *in vitro* anticancer activities were carried out against Human small cell lung DMS 114 cell line and Human colon cancer cell line HCC 2998 and MTT assay was used to analyze the cell growth inhibition of the both. The results had been displayed that compound B1-B4 were possessed an excellent anticancer activity (at 25 µg/ml) against both Human small cell lung DMS 114 cancer cell line and Human colon cancer cell line HCC 2998 and doxorubicin (at 10µg/ml) was used as a standard drug for Human small cell lung DMS 114 cancer cell line and 5-Fluro uracil (5-FU) for Human colon cancer cell line HCC 2998. In the present study IC_{50} values below 4 µg/ml were displayed by the compound B1 (IC_{50} of 4.0 µg/ml), B2 (IC_{50} of 3.4 µg/ml), B3 (IC_{50} of 3.2 µg/ml) and B4 (IC_{50} of 3.1 µg/ml) against Human small cell lung DMS 114 cancer cell line and B1(IC_{50} of 3.5 µg/ml), B2 (IC_{50} of 3.2 µg/ml), B3 (IC_{50} of 2.9 µg/ml) and B4 (IC_{50} of 2.9 µg/ml) against Human colon cancer cell line HCC 2998. The IC_{50} values of standard drugs doxorubicin and 5-FU were found to be 1.2 µg/ml and 1.1.[14]

CONCLUSION

Voltage-gated Ca^{2+} channels played an integral role in the entry of calcium ions into excitable cells which are involved in many physiological and pathological calcium-dependent processes. 3D structure model of L-type calcium channel alpha-1 subunit with similar quality to the template has been developed and validated. It can be used in further computer-aided drug design (CADD) for predicting and rationalizing 1, 4-DHPs activity. 1, 4-DHPs calcium channel modulators are used as antihypertensive and antianginal agents. Their structure-activity relationship was reviewed and discussed in detail in an attempt to clear how they modulate calcium channel activity. 1, 4-dihydropyridine derivatives also displayed antibacterial and potential anticancer activity. This review article provided a wide range of therapeutic strategy of 1,4-dihydropyridine derivatives and further molecular simulation and docking prediction with the different target proteins lead to develop potential therapeutic candidates in future for the treatment of various diseases.

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