

A Systematic Review on 1, 4-Dihydropyridines and its Analogues: An Elite Scaffold

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Abstract: 1,4-Dihydropyridines are a group of pyridine-based molecules possessing a magnificent set of biological and therapeutic potentials. Belonging to the class of calcium channel blockers, they are known to be effective in the conditions, angina, hypertension, myocardial infarction and show vasodilatory and cardiac depressant effects. Hypotensive, antimicrobial, anticancer, anticoagulant, antioxidant, anticonvulsant, antimalarial, antiulcer, and neuroprotective effects have been reported with their rational use. The effects are precipitated in response to inhibition of calcium channels, gradually restricting calcium influx. Drugs like nifedipine, felodipine, and amlodipine are commonly used clinically. Several other drugs belonging to this class have been under clinical trials. The present review focuses on the various 1,4-dihydropyridine derivatives and their pharmacological actions.

Keywords: 1,4-Dihydropyridines; calcium channel blockers; 1,4-Dihydropyridine derivatives; antihypertensives; anticancer agents.

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1. Introduction

Dihydropyridines are a group of pyridine-based molecules. Chemically, it is a family of hydrogenated N-hetero-aromatic members. Various derivatives with different substituents are known to exist with them positioned at 2,6,3,5, and 1,4, which can be synthesized via cyclic condensation type reaction, Hantzsch pyridine synthesis [1].

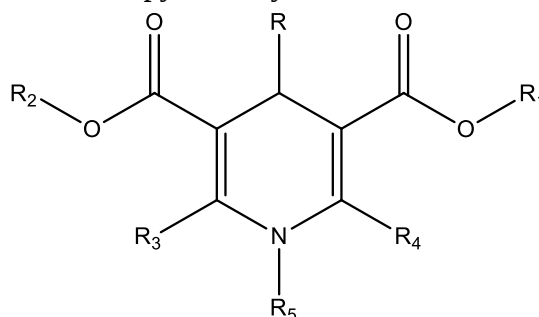


Figure 1. General Structure of 1, 4-dihydropyridines (1).

The implications of 1,4- Dihydropyridines (DHPs) (**1**) are known to be evident and satisfactory for more than four decades now, and newer studies and theories still persist [2]. DHPs' analogy with 1,4-dihydronicotinamide has theorized its possible use in studying the molecular mechanisms as model compounds. They are postulated for providing the base for newer cardiovascular drugs' development [3,4]. A number of drugs commonly used in present

times bear the 1,4-DHP ring-like calcium channel blockers [5-7]. Calcium channel blockers (CCBs) are chiefly accountable for vasodilatory action and are majorly known for their wide acceptance clinically in the treatment regimens for angina pectoris. This class of drugs is known to own a variety of effects which in turn are responsible for the peripheral and cerebral circulation of blood, mainly the heart. Other than the above-mentioned effects, CCBs are effective in the mainstream of all types of headaches, ulcers, tuberculosis, antioxidants, cystic fibrosis, and different tumor forms. These additional effects have broadened the application of these in the therapeutic field, which has further led to the inclusion of new drugs into this class. The administration of these drugs is mostly carried out through oral or intravenous routes. They are engrossed well orally, but few of them have low bioavailability due to the action of the CYP3A4 enzyme in hepatic pre-systemic metabolism. They are heavily protein-bound and have a massive concentration of delivery, according to reports (V_D). It has been documented that liver enzymes are responsible for saturated and decreased first-pass metabolism in overdose cases. This, in turn, augments the absorption of active pharmaceutical ingredients. Modifications in the formulations have led to variations in the half-life of these drugs. These drugs are generally excreted through the kidneys after metabolism. The enzyme CYP3A4, responsible for the metabolism of CCBs are also accountable for the metabolism of various xenobiotics, consequently creating a possibility for drug-drug interactions [8,9].

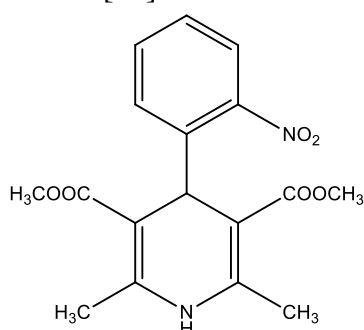
Calcium channel antagonists work by binding to voltage-gated Ca^{2+} channels of the L-type, which are present in the nucleus, pancreas, and vascular smooth muscles, to restrict the influx of Ca^{2+} ions. Considering the primary physiological effects, these drugs are divided majorly into two classes, Non-dihydropyridines and Dihydropyridines. Drugs of the first type have an impeding effect on both the nodes sinoatrial (SA) and atrioventricular (AV), leading to a decelerating effect on the contraction and conduction of heart muscles, which is used in the treatment of hypertension, hypoxia and in controlling arrhythmias. The evidence for the latter shows that, while minor, they directly affect the myocardium and other peripheral vasodilators, which are useful in hypertension, migraines, and post-intracranial hemorrhage [8].

A DHP skeleton is identified as a novel scaffold and its capability to exhibit pleiotropy [10]. Certain DHP derivatives and DHP encompassing formulations are observed to depict antioxidant action [11–13], contributing to their notable pleiotropic effects precipitating into antiaging activity, neuroprotective effect, anticancer movement, antibacterial action [14], among others. When exposed to certain chemical, biological and electrochemical processes, these derivatives tend to release free radicals. It is notable that hydrogen donors like phenol, amine, etc., tend to have an anticancer capacity basically via restricting oxidation and free radical processes. 1,4-dihydropyridines being a significant H-donor initiates similar actions. It further supports their use in cancer conditions. Additionally, synergistic effects might be witnessed on their concomitant use with antioxidants [15]. Likewise, they are associated with the regulation of redox homeostasis of calcium channels [16]. Gradually, calcium imbalance correlates with ROS increment and consequent oxidative stress. DHP mediated calcium antagonism generates secondary relief from oxidative stress, giving elaborative benefits. Optimum intracellular calcium levels and restricted oxidative stress generation collectively contribute well enough in controlling neuronal death. Moreover, their usage as novel antioxidants has also gained popularity now. The derivatives of 1,4-dihydropyridines can be formed by substituting all the 6 atoms with one or more atoms. Theoretically, there are five isomers possible for the dihydropyridine compound. The two derivatives, i.e., -1,2-dihydro

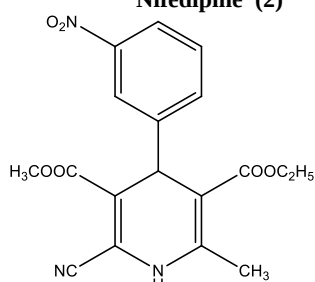
substituted and 1,4-dihydro substituted scaffolds, are well known and are frequently used. They have the most elevated number of the sp^2 -hybridized nucleus. Around the 1930s, hydrogen-transferring coenzyme was identified as a reduced derivative of niacinamide or nicotinic acid amide or famously known- 'nicotinamide' which further initiated work over DHPs, more common of all-over the N-substituted dihydronicotinamides. [17].

Non-dihydropyridine has reported adverse effects which include, bradycardia, reduced cardiac output, and constipation. While, Dihydropyridines cause flushing, headaches, edema, and light-headedness. Both types of drugs have reported the adverse effects of gingival hyperplasia. This drug is not advised to be used in patients who are known to have a hypersensitivity reaction to specifically the drug or any of its components. It is also contraindicated in patients with sick sinus syndrome, where patients with an implanted pacemaker, acute myocardial infarction, respiratory obstruction, and extreme hypotension are excluded. There have been reports of allergic skin reactions and hypotension. Also, peripheral edema is reported when used over the period of 2-3 weeks. In the case of renal and hepatic diseases, the patients have been advised a lower dose of medication. Non-dihydropyridines are not recommended in patients with heart failure and a poor ejection fraction, as well as 2nd and 3rd degree AV blockage, because they have been linked to bradycardia and decreased cardiac activity [18].

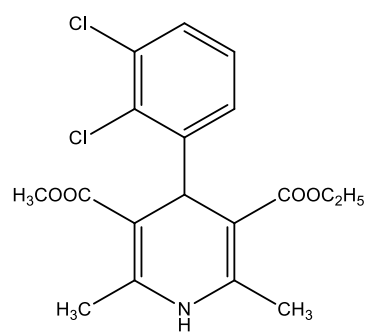
A variety of DHP model compounds have been used in clinical trials in recent decades (2-10) due to their impressive range of pharmacological activities. Hypotensive, antimicrobial, anticoagulant, antioxidant, antitubercular, anticonvulsant, antiulcer, neuroprotective and antimalarial effects have been reported, among others as well [17]. Isradipine, a calcium channel blocker, is used as a supplement to every thiazide or also as a stand-alone treatment for hypertension [19]. Nisoldipine is indicated in cases of angina pectoris, strokes, and certain kidney problems [20]. Nicardipine, administered by the peroral or I.V. route, is a short-term treatment agent for controlling blood pressure and in cases of angina [21]. Nimodipine is indicated in subarachnoid hemorrhage conditions along with certain other brain injuries and is observed to manage vasospasm. It precipitates its effects by an increased blood flow in the cerebral region via dilating the vessels. In the elderly group, it is witnessed to improve cognitive deficit conditions [22].



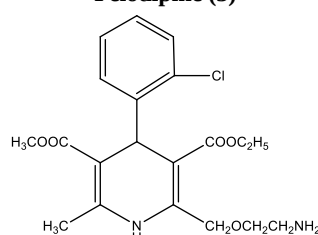
Nifedipine (2)



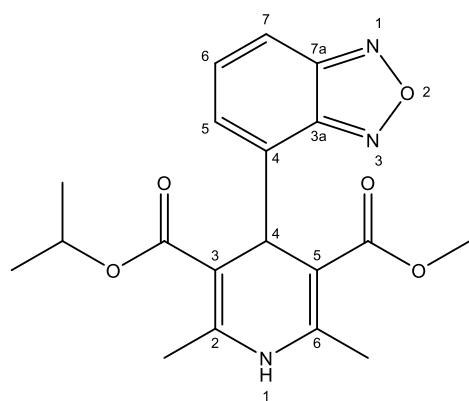
Nilvadipine (4)



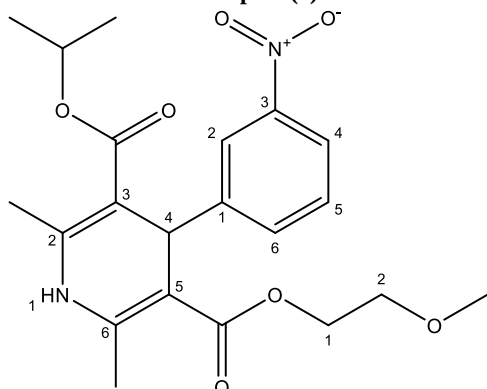
Felodipine (3)



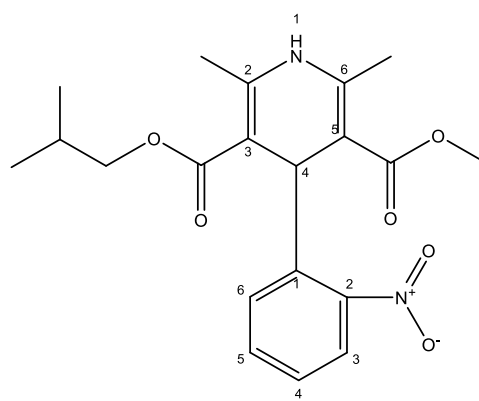
Amlodipine (5)



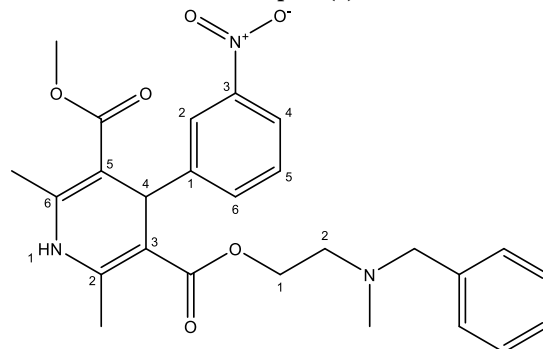
Isradipine (6)



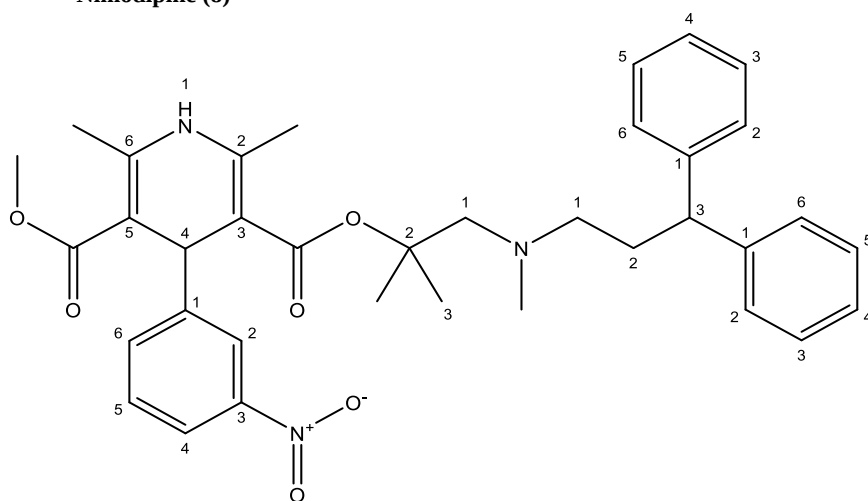
Nimodipine (8)



Nisoldipine (7)



Nicardipine (9)



Lercanidipine (10)

2. Pharmacological Actions

The major pharmacological actions of 1,4-Dihydropyridine analogs are:

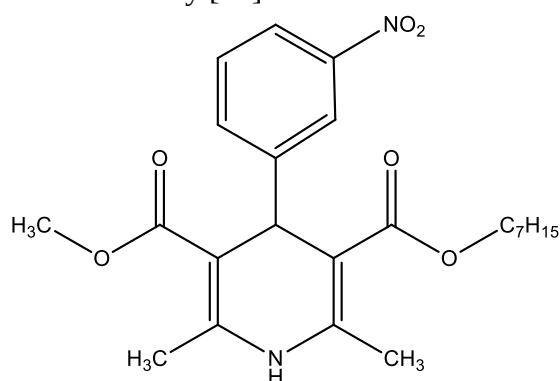
2.1. Antihypertensive agents.

Hypertension (HTN) is also known as the ‘silent killer’ as the condition does not often precipitate major identifiable symptoms. Generally, human beings do not identify and understand blood pressure (BP) elevation until it gets detected by the physician. Malignant hypertension remains an exception as it can eventually cause migraine, congestive cardiovascular breakdown, stroke, seizure, renal disappointment, and anuria [23]. HTN is known to be one of the prominent causes of initiating any kind of Cardiovascular disease (CVD) or coronary artery disease and remains to be a quite significant risk factor in Cerebrovascular diseases [24]. Over the globe, about 20% population experiences HTN; out of

which one-third bear severe HTN while the rest have mild HTN [25]. Owing to all this, it is a primary health care objective now. Every year, about 3-5% of the older hypertensive population is observed to develop CVD, while in the hypertensive youth population, 1 in every 1000 tends to develop despite none of any risk factors other than HTN. Antihypertensive therapy, on the other hand, has shown to be successful in lowering the risk.

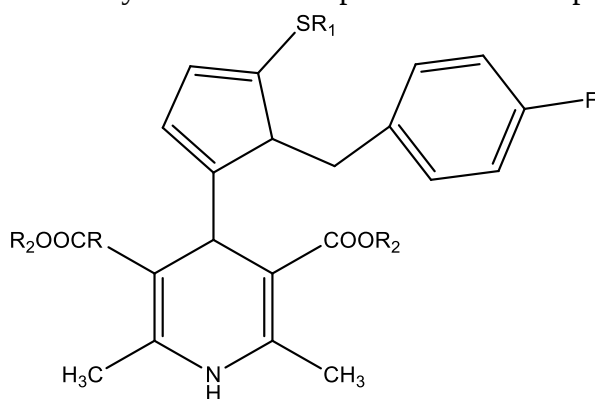
Being Calcium channel antagonists, DHPs exhibit vasodilatory action along with cardio-depressant action to a certain extent. These agents work through the L-type channels by restricting calcium ions' influx and eventually relaxing cardiac, smooth vascular muscles, making them apt candidates for CVD management and condition of HTN and angina [2].

A number of experiments have shown mixed findings, indicating that the application of DHPs is beneficial. In a study by Kai Zhou *et al.*, Nitrendipine and seven of its analogs were prepared. The results concluded that lengthening of nitrendipine analogs at 3rd or 5th positions with an alkyl chain could elaborate their hypotensive activity. Compound (11) was seen to generate significant hypotensive activity [26].



(11)

In another work, DHPs based compounds were prepared (12) and analyzed with a substitution at the 4th position with 1-(4-fluorobenzyl)-5-imidazolyl in rat subjects witnessing abridged antihypertensive activity with these compounds when compared to nifedipine [27].

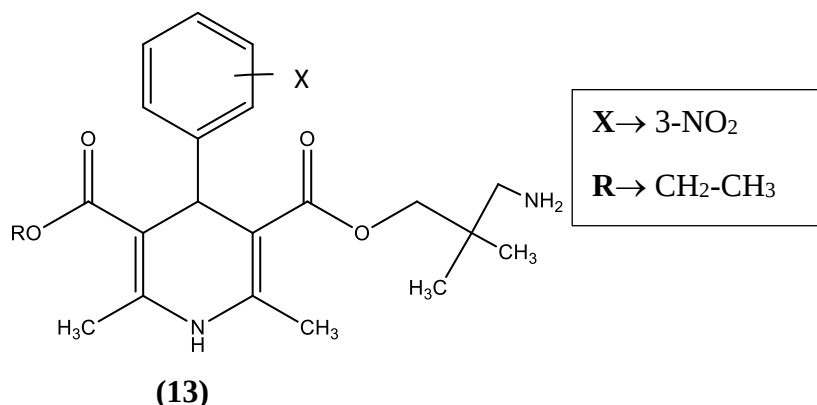


(12)

Table 1. Different substituents at R₁ and R₂ positions in derivative (12).

Serial No.	Compound	R ₁	R ₂
1	12 (a)	-CH ₃	-CH ₃
2	12 (b)	-CH ₃	-CH ₂ -CH ₃
3	12 (c)	-CH ₂ -CH ₃	-CH ₃
4	12 (d)	-CH ₂ -CH ₃	-CH ₂ -CH ₃

Balaev *et al.* synthesized derivatives of 1,4-dihydropyridines with 3-dialkylamino-2,2-dimethylpropyl chains (**13**). In comparison with nifedipine, all those products exhibited a better antihypertensive effect [28].



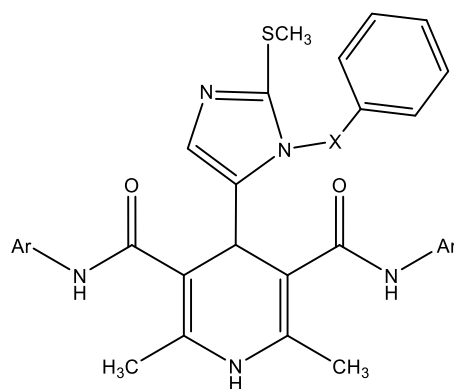
Novel derivatives of nitroxyalkyl DHP were appraised in two-kidney, one-clip HTN rat models. According to this study, a hypotensive effect was largely impacted with the 5th - position in the derivatives [29]. Evaluation of the DHP derivatives by Shashikant *et al.*, concluded positive results, while in another study, results were not supportive to the theory [30-32].

Another study involved preparation of derivatives with the 4th - positioned substitution with 1-(4-Nitrobenzyl)-5-imidazolyl or 2-methylthio-1-(4-Nitrobenzyl)-5-imidazolyl replacing the ortho-nitrophenyl part. Their effectiveness, in comparison to nifedipine, was though found to be lesser but definitely brought a reduction in systolic BP [33].

2.2. Antitubercular agents.

Tuberculosis is an infectious disease that is currently one of the major causes of death worldwide. It is caused by the bacterium *Mycobacterium tuberculosis*, which has developed mutations and gradually developed resistance to treatment regimens, resulting in the need for newer medications [34,35]. In addition to being multifunctional, DHPs with lipophilic groups have been discovered to have a high potential as an antitubercular lead compound. It has been documented that replacing dicarboxylic esters on the skeleton with an aryl amide group reduces calcium channel antagonism and increases antitubercular activity. The dicarboximide group on DHP continues to undergo enzymatic hydrolysis after penetration into the cell wall of mycobacterium, resulting in carboxylate anions, which serve as a precursor for action [36]. Developers synthesized and screened a series of 4-substituted imidazolyl-2,6-dimethyl-N3,

N5-bisaryl-1,4-dihydropyridine-3,5-dicarboxamides compounds. Minimum inhibitory concentration tests revealed the compound is the most potent of all the others. It was shown to be as effective as rifampicin against *M. tuberculosis* bacterial strain H37RV [17,37]. When used to treat *Mycobacterium tuberculosis*, felodipine, a dihydropyridine drug, was found to be as effective as rifampicin. When a 4-chlorophenyl group was substituted at both the C-3 and C-5 positions of the compound (**14**), the derivative was found to be much more efficient than the others. Acts against the mycobacterium were detected when the substitution was repeated in the same position with the pyridyl group [37].



(14)

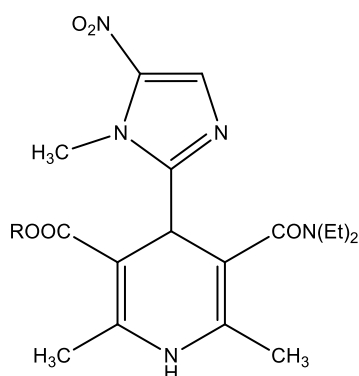
Table 2. Different substitutions at Ar and X in compound (14).

Serial No.	Compound	Ar	X
1	14 (a)	2-chlorophenyl	NH
2	14 (b)	3-chlorophenyl	NH
3	14 (c)	4-chlorophenyl	NH
4	14 (d)	4-bromophenyl	NH
5	14 (e)	2-pyridyl	NH
6	14 (f)	3-pyridyl	NH
7	14 (g)	2-chlorophenyl	CH ₂
8	14 (h)	3-chlorophenyl	CH ₂
9	14 (i)	4-chlorophenyl	CH ₂
10	14 (j)	4-bromophenyl	CH ₂
11	14 (k)	2-pyridyl	CH ₂
12	14 (l)	3-pyridyl	CH ₂

‘Ar’ can be replaced with two distinct groups, all of which are called antitubercular. 4-chlorophenyl and 2-pyridyl are the substituents in concern.

New derivatives of different diethyl carbamoyl groups and alkyl and aryl esters substituents were synthesized at C-3 and C-5 of the DHP ring. The nitroimidazole ring was substituted at the C-4 spot. An updated Hantzsch reaction protocol was used to create these asymmetric analogs. Antitubercular drugs containing aromatic esters were shown to be more effective than alkyl antitubercular drugs in vitro. The most powerful aromatic compound (15), demonstrated equivalent antitubercular behavior compared to the reference compound isoniazid [38].

Lee *et al.* released a recent report that concentrated on iron shortages induced by the concurrent use of CCB’s. Intercellular bacteria such as *Mycobacterium tuberculosis* flourish in the presence of iron. This results in an infection that last longer grows, replicates, or even kills you. The findings favor the use of dihydropyridines in reducing tuberculosis risk [39].



R= 3-phenylpropyl

(15)

2.3. Antioxidant agents.

Previous research has shown that various DHPs can affect cell growth and differentiation by modulating cellular responses to oxidative stress. Their derivatives have been discovered to modulate cellular responses in response to an increase in ROS and oxidative stress generation. ROS amounts are evidently reduced, indicating their ability to scavenge radicals such as hydrogen peroxide. Certain derivatives have antioxidant activity and a cellular-protective effect over time. It is also believed that oxidative imbalance has caused harm [40].

A new series of Hantzsh 1,4-dihydropyridine derivatives (16) with substituted pyrazole moiety was obtained by reacting 3-aryl-1H-pyrazole-4-carbaldehydes with 1,3-dicarbonyl compounds (ethyl acetoacetate and methyl acetoacetate) and ammonium acetate. The DPPH radical scavenging assay was used to assess the antioxidant activity of the synthesized compounds. The most active antibacterial and antioxidant agents were found to be compounds **16** (a), **16** (b), and **16** (c) [11].

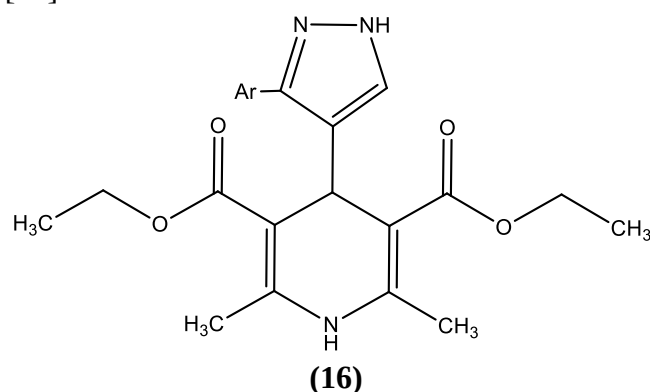


Table 3. Different substituents at Ar of derivative **(16)**.

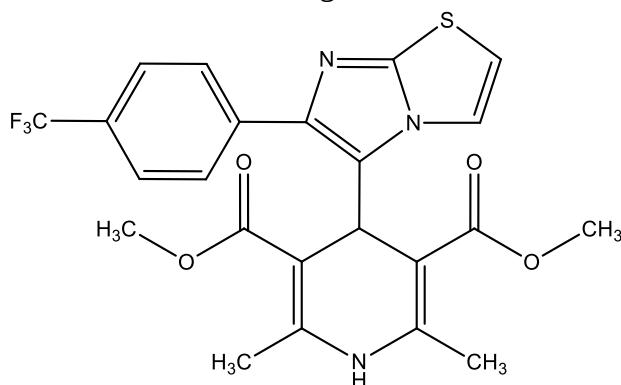
Serial No.	Compound	Ar
1	16 (a)	4-thioanisyl
2	16 (b)	biphenyl
3	16 (c)	4-chlorophenyl

The process of neurodegeneration, which leads to multiple neurodegenerative disorders such as Alzheimer's disease, is aided by oxidative stress (AD). Excessive ROS production induces an imbalance, which speeds up aggregation and causes signs of Alzheimer's disease in patients [41]. The antioxidant activity of DHP derivatives, as well as their anti-inflammatory action against the neuroinflammation they trigger, modulates these factors [42].

2.4. Cystic fibrosis transmembrane conductance regulator action.

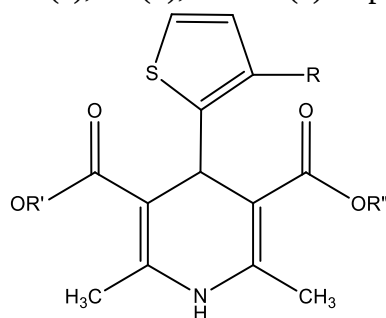
Mutations in the CF transmembrane conductance regulator (CFTR) chloride receptor, which is involved in fluid and salt transport through the ducts of various epithelial organs such as lungs, pancreas, and gastrointestinal tract, cause cystic fibrosis. Patients with CFTR dysfunction suffer epithelial ion and water flow disruption, affecting multiple organs [43]. The advancement of novel treatments for diseases triggered by malfunctions in the pharmacology of the cystic fibrosis transmembrane conductance regulator relies heavily on chlorine channels (CFTR). Cystic fibrosis is a condition caused by mutations that deplete the functions of the CFTR gene (CF). The key factor causing CF is the exhaustion of phenylalanine 508 (F508) in the CFTR chloride pathway. Some antihypertensive medications, such as felodipine, nifedipine, and others that hinder L-type calcium channels, are also potent CFTR gating potentiators, helping them correct F508 and other CFTR anomalies [44,45]. Thus, the

evaluation of recently combined 4-imidazo [2,1-b] thiazoles-1,4 dihydropyridines (**17**) without “inotropy” cardiovascular impact increases F508-CFTR movement. According to research, compound (**17**) is 1, 4-DHPs with a diverse range of activities [48].



(17)

The gating of the CFTR chloride channel was confirmed to be the primary cause of CF. CFTR potentiators, which are small atoms with a thiophen-2-yl and furanyl ring at the 4-position of the middle and a thiophen-2-yl and furanyl ring at the 4-position of the core, could correct the gating defect. The DHPs (**18**) operation to upgrade the motion of the rescued F508-CFTR was evaluated using a halide-sensitive yellow fluorescent protein-based assay. The bulk of the dihydropyridines displayed greater potency than genistein, the reference drug. Within half concentration, compounds like **18** (a), **18** (b), and **18** (c) display great potency [47].



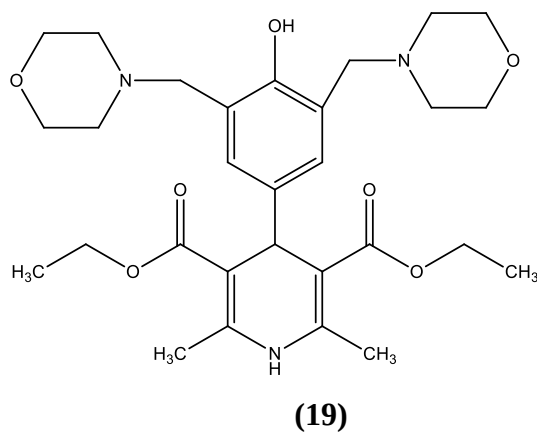
(18)

Table 4. Different substitutions at R, R', R'' in analog (**18**).

Serial No.	Compound	R	R'	R''
1	18 (a)	-CH ₃	Allyl	-C ₂ H ₅
2	18 (b)	-CH ₃	Benzyl	-C ₂ H ₅
3	18 (c)	-SCH ₂ COOCH ₃	Allyl	-C ₂ H ₅

2.5. Antiarrhythmic agents.

The stimulation of CCBs inhibits myocardium contraction, triggers a minute impulse in the conduction system, and induces vasodilation by hindering Ca²⁺ channels in the myocardium or vascular smooth muscle cells [48]. It was stated that a new compound containing para-hydroxy [bis (ortho-morpholinyl methyl)] phenyl-1,4-DHP containing antihypertensive properties and 4-(4-hydroxy-3,5-bis (morpholin-4-ylmethyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl esters (**19**) with antiarrhythmic properties were synthesized and were effective at low doses [49].



2.6. Anticancer agents.

The development of immunity to the effects of different medications is a significant clinical problem in cancer chemotherapy. Multidrug resistance prevention is, therefore, a crucial factor in developing cancer chemotherapy. Verapamil, nifedipine, and other calcium channel antagonists have been shown to resolve opioid resistance both in vivo and in vitro successfully. [50]. A series of thiosemicarbazide and semicarbazide derivatives containing 1, 4-dihydropyridine derivatives were produced whose anticancer behavior was tested (**20**). Three cancer cell lines were shown to be active against certain compounds. Compound **20** (a) was found to be highly effective against HepG2 (liver), MCF7 (breast), and Hela (cervical) [51]. Compound **20** (b) was discovered to be extremely successful against HepG2 (liver) and MCF7 (breast).

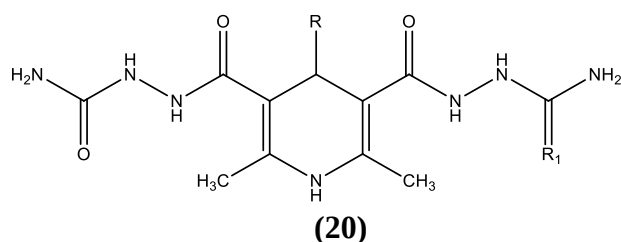
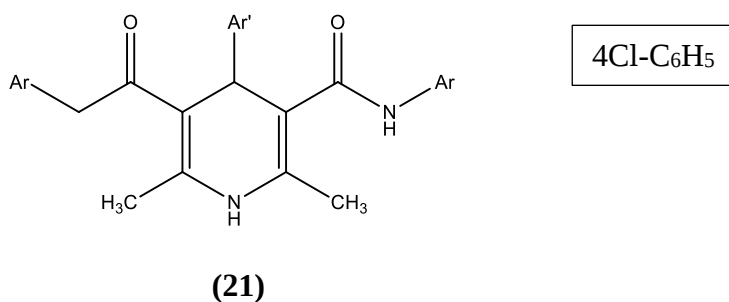


Table 5. Different substitutions at R, R₁ in analog (**20**).

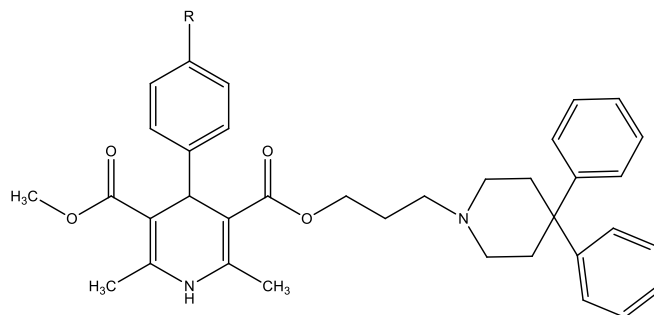
Serial No.	Compound	R	R ₁
1	20 (a)	4-OH-3-OCH ₃ -Ph	O
2	20 (b)	4-OH-3-OCH ₃ -Ph	S

The synthesized compound 4-substituted-2,6-dimethyl-3,5-bis-N-(heteroaryl)-carbamoyl-1,4-dihydropyridine was also found to have anticancer, antitubercular, and antibacterial activities in vitro (**21**). Derivative (**21**) was discovered to be incredibly successful in the fight against cancer [52].



2-Methyl-4-oxo-3H-quinazoline-3-yl

A series of 4-aryl-1,4-dihydropyridines (22) was synthesized to limit calcium channel binding, based on the structural modification of nifedipine to improve multidrug obstruction inversion function. Thirty new aggravates are being discovered. Vinblastine accumulated in the adenocarcinoma cell line MCF-7/adr, which expresses P-glycoprotein, 15 out of 18 4-aryl-1,4-dihydropyridines and each of the 4-aryl pyridines at concentrations of 3 μ M, according to vinblastine accumulation reports. Compounds like 22 (a) and 22 (b) improved their potency by around 15-fold [53].



(22)

Table 6. Different substitutions at R in analogue (22).

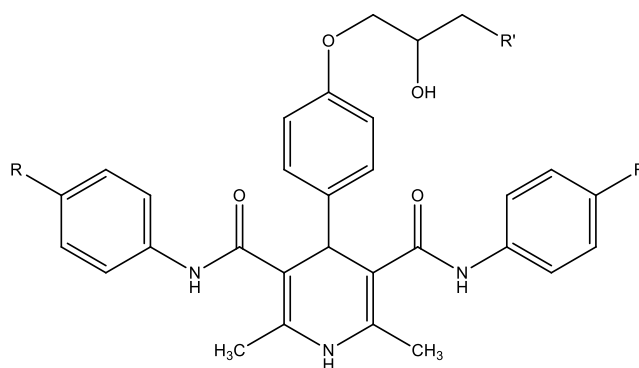
Serial No.	Compound	R
1	22 (a)	4-oxypropyl
2	22 (b)	4-oxybutyl

2.7. Antiepileptic agents.

The term epilepsy comes from the Greek word Epilepsia, which means "to grab hold of, epilepsy." An elliptical seizure results in a brief burst of unimpeded neuronal discharges. Epilepsy is the second most common neurologic disease after stroke, affecting around 1% of the general population. [54].

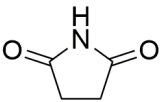
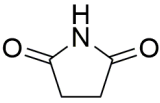
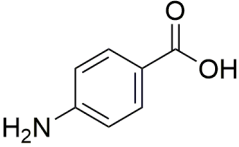
In a series of alkyl, cycloalkyl, and aryl esters of nifedipine, the o-nitrophenyl group at position-4 was substituted by 2-(4-chlorophenyl)-4-thiazolyl; substituents were synthesized and assessed for the anticonvulsant role of the study compounds. Both compounds exhibited remarkable anticonvulsant effectiveness when studied in a pentylenetetrazole (PTZ)-induced seizure procedure [55].

The 1,4-dihydro-2,6-dimethyl-4-(4-(3-(piperidine/morpholine/2-aminopyrazine/1-amino-4-methylpiperazine)-2-hydroxypropoxyl)-phenyl)-pyridine-3-5-carbamoyl)-pyridine-3-5-carbamoyl)-pyridine-3-5-carbamoyl)-pyridine-3-5-carbamoyl compounds 23 (a,b,c) had higher activity than normal medications, when tested using the Maximal Electroshock Method [55].



(23)

Table 7. Different substitutions at R, R' in scaffold (23).

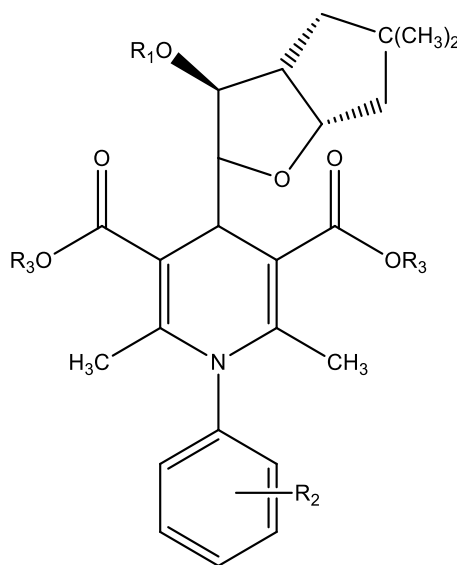
Serial No.	Compound	R	R'
1	23 (a)	p-NO ₂	
2	23 (b)	m-NO ₂	
3	23 (c)	p-NO ₂	

2.8. Antileishmanial agents.

The antileishmanial action of the drug nimodipine was researched, and the structural damage to parasites caused by these medications. This medication was found to be particularly selective against leishmania chagasi promastigotes and intracellular amastigotes, with 50% inhibitory concentrations of 81.3 and 21.6 M, respectively. Calcium channel blockers have shown to be an effective antileishmanial compound in vitro [56].

A sequence of 1-phenyl-4-glycosyl-dihydropyridine derivatives was synthesized and tested for antileishmanial activity in vitro and in vivo. The compounds formed resulted from a reaction carried out in the presence of a catalyst TBAHS between β -Keto compounds, aniline, or substituted aniline and glycosyl aldehyde.

Most of the compounds were reported to exhibit moderate action against promastigotes and amastigotes of *Leishmania Donovanii*. The hybrids **24** (a), **24** (b) **24** (c) and **24** (d) were highly effective with selectivity index estimated to be 7.44-18.94 [57].



(24)

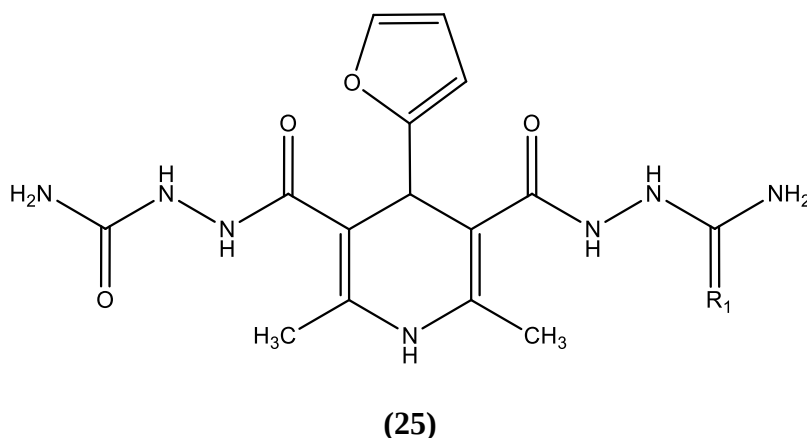
Table 8. Different substitutions at R₁, R₂, R₃ in analog (24).

Serial No.	Compound	R ₁	R ₂	R ₃
1	24 (a)	CH ₂ Ph	4-F	CH ₃
2	24 (b)	CH ₃	4-OCH ₃	CH ₃
3	24 (c)	CH ₃	4-Cl	CH ₃
4	24 (d)	CH ₃	4-CH ₃	CH ₃

2.9. Anticoagulant activity.

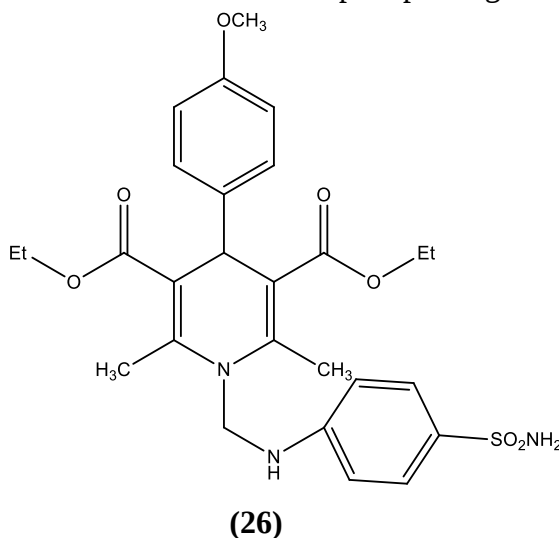
DHPs exhibit effective anticoagulant action by restricting calcium currents with high potency via calcium channels. They were explored in this area owing to their therapeutic use as hypotensive, anti-inflammatory, and anti-ischemic agents [58]. Recent studies showed the effectiveness of a non-dihydropyridine drug, verapamil, precipitating antiplatelet effects. In *in-vitro* trials, the tablet was administered for 4 weeks, and the results showed a decline in platelet agreeability. [59].

1,4-dihydropyridines were fabricated by substituting phenyl-1,4-dihydropyridine-3,5-dicarboxylate derivatives into the base structure 2,6-dimethyl-4. When allowed to react with thiosemicarbazide, the derivatives of the resulting medication form 2,20-(4-(substituted phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl) dicarbonyl) dihydrazinecarbothioamide compounds. The levels of anticoagulant activity were found to be higher with Hybrid (25) than with any other compound studied. At a concentration of 31 mg/m, the time was 720.36 seconds. [58].



2.10. Antiulcer activity.

CCBs have an inhibitory action on histamine, gastrin, carbachol, and cyclic AMP-induced gastric acid stimulation. This, in turn, provides a protective action against gastric ulcers [60]. Compound **(26)**, i.e., 3,5-diethoxycarbonyl-1,4-dihydro-2,6-dimethyl-4-(methoxyphenyl) pyridine on conjugation with a sulfanilamide group and its replacement with the methoxy group have shown to be most effective in precipitating antiulcer activity [61].



A pharmacological study conducted by Patil *et al.*, demonstrated the use on Amlodipine to study its anti-ulcerative properties in rats, and the conclusion was recorded that this drug showed significant antiulcer action in 3 models. There has been an increase in the volume of gastric secretions [62].

2.11. Anti-inflammatory activity.

Certain factors, such as pathogens, microorganisms, heat, chemicals, and others, induce severe injuries, and the body's immune system replies by activating an inflammatory response as a defensive [63]. Vascular inflammation plays an important role in the expansion of multiple heart diseases. Azelnidipine, a DHP-based calcium channel blocker, was shown to have effective anti-inflammatory properties in research by Komoda *et al.* IL-6, IL-8, and some other cytokines were found to be substantially reduced within the first four weeks of use. Whereas antihypertensive potential was seen to have an effect upon 16 weeks of treatment, highlighting the drug's significant potential against endothelial inflammation [64].

Another well-known drug, amlodipine, has often been used as an anti-inflammatory remedy that serves by increasing the synthesis of nitric oxide. The drug reacted with the acyl group, inducing anoxic cell aggregation, which was counteracted by the antioxidant activity. The study was conducted in a total of fifty female adult albino rats, which were divided into 5 groups. The effect of the drug amlodipine was assessed in rats where ovariectomy was done to induce osteoporosis. The observations point to the fact that this compound protects the rats under investigation. [65].

3. Conclusions

This review concludes that 1,4-dihydropyridines are a genus of pharmacologically active molecules that serve as multifunctional potent leads and can be substituted in a variety of positions. Substantial evidence has reported using these drugs to treat several conditions, as they precipitate actions such as calcium channel antagonism, antihypertensive activity, antitubercular activity, anticonvulsant activity, antiulcer activity, anticancer, anti-leishmanial agents, anticoagulant activity, CFTR, and many more. The potential uses of these derivatives account to be significantly capable of combatting the varying pathological impairments in future times.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Kreutzer, D.; Ritter, C.A.; Hilgeroth, A. Novel Nonsymmetrical 1,4-Dihydropyridines as Inhibitors of Nonsymmetrical MRP-Efflux Pumps for Anticancer Therapy. *Pharmaceuticals* **2020**, *13*, <https://doi.org/10.3390/ph13070146>.
2. Cataldi, M.; Bruno, F. 1,4-dihydropyridines: the multiple personalities of a blockbuster drug family. *Translational medicine @ UniSa* **2012**, *4*, 12-26.
3. Pajuste, K.; Rucins, M.; Domracheva, I.; Sobolev, A.; Pikun, N.; Plotniece, M.; Duburs, G.; Pajuste, K.; Plotniece, A. Data for the cytotoxicity, self-assembling properties and synthesis of 4-pyridinium-1,4-dihydropyridines. *Data in Brief* **2020**, *33*, 106545, <https://doi.org/10.1016/j.dib.2020.106545>.
4. Rucins, M.; Plotniece, A.; Bernotiene, E.; Tsai, W.-B.; Sobolev, A. Recent Approaches to Chiral 1,4-Dihydropyridines and their Fused Analogues. *Catalysts* **2020**, *10*, <https://doi.org/10.3390/catal10091019>.
5. van der Vossen, A.C.; Cransberg, K.; de Winter, B.C.M.; Schreuder, M.F.; van Rooij-Kouwenhoven, R.W.G.; Vulto, A.G.; Hanff, L.M. Use of amlodipine oral solution for the treatment of hypertension in children. *Int. J. Clin. Pharm.* **2020**, *42*, 848-852, <https://doi.org/10.1007/s11096-020-01000-9>.
6. Palatnick, W.; Jelic, T. Calcium channel blocker and beta blocker overdose, and digoxin toxicity management. *Emerg. Med. Pract.* **2020**, *22*, 1-42.
7. Velena, A.; Zarkovic, N.; Gall Troselj, K.; Bisenieks, E.; Krauze, A.; Poikans, J.; Duburs, G. 1, 4-dihydropyridine derivatives: dihydronicotinamide analogues—model compounds targeting oxidative stress. *Oxid. Med. Cell. Longev.* **2016**, *2016*, <https://doi.org/10.1155/2016/1892412>.
8. Lin, Y.; Ma, L. Blood pressure lowering effect of calcium channel blockers on perioperative hypertension: A systematic review and meta-analysis. *Medicine* **2018**, *97*, e13152-e13152, <https://doi.org/10.1097/MD.00000000000013152>.
9. Pavasini, R.; Camici, P.G.; Crea, F.; Danchin, N.; Fox, K.; Manolis, A.J.; Marzilli, M.; Rosano, G.M.C.; Lopez-Sendon, J.L.; Pinto, F. Anti-anginal drugs: Systematic review and clinical implications. *Int. J. Cardiol.* **2019**, *283*, 55-63, <https://doi.org/10.1016/j.ijcard.2018.12.008>.
10. Zhou, L.-M.; Qu, R.-Y.; Yang, G.-F. An overview of spirooxindole as a promising scaffold for novel drug discovery. *Expert Opinion on Drug Discovery* **2020**, *15*, 603-625, <https://doi.org/10.1080/17460441.2020.1733526>.
11. Vijesh, A.M.; Isloor, A.M.; Peethambar, S.K.; Shivananda, K.N.; Arulmoli, T.; Isloor, N.A. Hantzsch reaction: Synthesis and characterization of some new 1,4-dihydropyridine derivatives as potent antimicrobial and antioxidant agents. *Eur. J. Med. Chem.* **2011**, *46*, 5591-5597, <https://doi.org/10.1016/j.ejmech.2011.09.026>.
12. Mehta, P.; Verma, P. Antimicrobial activity of some derivatives of 1, 4-dihydropyridines. *Journal of Chemistry* **2013**, *2013*, <https://doi.org/10.1155/2013/865128>.
13. Olejníková, P.; ŠVORC, L.; Olšovská, D.; Panáková, A.; Vihonská, Z.; Kovaryová, K.; Marchalín, Š. Antimicrobial Activity of Novel C2-Substituted 1,4-Dihydropyridine Analogues. *Sci. Pharm.* **2014**, *82*, <https://doi.org/10.3797/scipharm.1311-04>.
14. Sepehri, S.; Sanchez, H.P.; Fassihi, A. Hantzsch-Type Dihydropyridines and Biginelli-Type Tetrahydropyrimidines: A Review of their Chemotherapeutic Activities. *Journal of Pharmacy & Pharmaceutical Sciences* **2015**, *18*, 1-52, <https://doi.org/10.18433/J3Q01V>.
15. Tirzit, G.D.; Dubur, G.Y. 1,4-Dihydropyridines as inhibitors of free-radical reactions. *Chemistry of Heterocyclic Compounds* **1972**, *8*, 126-127, <https://doi.org/10.1007/BF00478512>.
16. Tikhonov, D.B.; Lin, L.; Yang, D.S.C.; Yuchi, Z.; Zhorov, B.S. Phenylalkylamines in calcium channels: computational analysis of experimental structures. *J. Comput.-Aided Mol. Des.* **2020**, *34*, 1157-1169, <https://doi.org/10.1007/s10822-020-00330-0>.
17. Khedkar, S.A.; Auti, P.B. 1, 4-Dihydropyridines: a class of pharmacologically important molecules. *Mini Rev. Med. Chem.* **2014**, *14*, 282-290, <https://pubmed.ncbi.nlm.nih.gov/24251802/>.
18. McKeever, R.G.; Hamilton, R.J. Calcium channel blockers. **2018**, <https://www.ncbi.nlm.nih.gov/books/NBK482473/>.
19. Nagasamy Venkatesh, D.; Meyyanathan, S.N.; Shanmugam, R.; Kamatham, S.S.; Campos, J.R.; Dias-Ferreira, J.; Sanchez-Lopez, E.; Cardoso, J.C.; Severino, P.; Souto, E.B. Physicochemical, pharmacokinetic, and pharmacodynamic characterization of isradipine tablets for controlled release. *Pharm. Dev. Technol.* **2021**, *26*, 92-100, <https://doi.org/10.1080/10837450.2020.1839495>.
20. Chavan, R.B.; Lodagekar, A.; Yadav, B.; Shastri, N.R. Amorphous solid dispersion of nisoldipine by solvent evaporation technique: preparation, characterization, in vitro, in vivo evaluation, and scale up feasibility study. *Drug Delivery and Translational Research* **2020**, *10*, 903-918, <https://doi.org/10.1007/s13346-020-00775-8>.

21. Sadler, W.D.; Hunt, N.; Nelson, K.; Adelmann, E.; Mazurek, P.; Bassin, B.S. Calcium Channel Blocker Intoxication: A Critical Care Transport Perspective. *Air Med. J.* **2021**, *40*, 69-72, <https://doi.org/10.1016/j.amj.2020.11.004>.
22. Grewal, A.K.; Singh, T.G.; Singh, N. Potential herbal drugs for ischemic stroke: a review. *Plant Arch*, **2020**, *20*, 3772-3783.
23. Desai, A.N. High Blood Pressure. *JAMA* **2020**, *324*, 1254-1255, <https://doi.org/10.1001/jama.2020.11289>.
24. Arguedas, J.A.; Leiva, V.; Wright, J.M. Blood pressure targets in adults with hypertension. *Cochrane Database Syst. Rev.* **2020**, <https://doi.org/10.1002/14651858.CD004349.pub3>.
25. Deepika, S.A.; Kaur, R.; Singh, T.G.; Singh, M.; Satija, S.; Singh, R. Prescribing Pattern Of Antihypertensive Drugs In A Tertiary Care Hospital: A Review. *Plant Archives*, **2019**, *19*, 1311-1316.
26. Zhou, K.; Wang, X.Y.; Zhao, Y.; Cao, Q.F.; Zhang S. Synthesis and antihypertensive activity evaluation in spontaneously hypertensive rats of nitrendipine analogs. *Med. Chem. Res.* **2011**; *20*, 1325-1330, <https://doi.org/10.1007/s00044-010-9477-0>.
27. Mohajeri, S.A.; Hosseinzadeh, H.; Salami, S.; Motamedshariaty, V.; Seifi, M.; Hadizadeh, F. Synthesis of Novel 4-[1-(4-fluorobenzyl)-5-imidazolyl] Dihydropyridines and Studying their Effects on Rat Blood Pressure. *Iran J Basic Med Sci* **2011**, *14*, 451-457, <https://doi.org/10.1016/j.bjp.2016.05.012>.
28. Balaev, A.N.; Eleev, A.F.; Eremin, O.G.; Fedorov, V.E. Synthesis and antihypertensive activity of 1, 4-dihydropyridines containing 3- dialkylamino-2, 2- dimethylpropyl fragments. *Pharm. Chem. J.* **2010**; *44*, 8-9, <https://doi.org/10.1007/s11094-010-0396-7>.
29. Nekooian, A.; Khalili, A.; Javidnia, K.; Mehdipour, A.R. Antihypertensive effects of some new nitroxyalkyl 1, 4-dihydropyridine derivatives in rat model of two-kidney, one-clip hypertension. *Iranian Journal of Pharmaceutical Research* **2009**, *8*, 193-199.
30. Mishra, A.P.; Bajpai, A.; Rai, A.K. 1,4-Dihydropyridine: A Dependable Heterocyclic Ring with the Promising and the Most Anticipable Therapeutic Effects. *Mini. Rev. Med. Chem.* **2019**, *19*, 1219-1254, <https://doi.org/10.2174/1389557519666190425184749>.
31. Ozer, E.K.; Gunduz, M.G.; El-Khouly, A.; Sara, Y.; Simsek, R.; Iskit, A.B.; Safak, C. Synthesis of fused 1, 4-dihydropyridines as potential calcium channel blockers. *Turkish J. Biochem.* **2018**, *43*, 578-586, <https://doi.org/10.1515/tjb-2016-0247>.
32. Liang, J.-C.; Yeh, J.-L.; Wang, C.-S.; Liou, S.-F.; Tsai, C.-H.; Chen, I.-J. The new generation dihydropyridine type calcium blockers, bearing 4-phenyl oxypropanolamine, display α -/ β -Adrenoceptor antagonist and long-Acting antihypertensive activities. *Biorg. Med. Chem.* **2002**, *10*, 719-730, [https://doi.org/10.1016/S0968-0896\(01\)00318-2](https://doi.org/10.1016/S0968-0896(01)00318-2).
33. Jamil, S.; Sengupta, M.; Saha, C.; Bandhya, D.; De, R.; Mitra, M.; Ghosh, D. Oral Nifedipine versus Intravenous Labetalol in Hypertensive Emergencies of Pregnancy- A Randomised Trial. *J. Evol. Med. Dent. Sci.* **2019**, *8*, 3588-3593, <https://doi.org/10.14260/jemds/2019/775>.
34. Singh, R.; Dwivedi, S.P.; Gaharwar, U.S.; Meena, R.; Rajamani, P.; Prasad, T. Recent updates on drug resistance in Mycobacterium tuberculosis. *J Appl Microbiol.* **2020**, *128*, 1547-1567, <https://doi.org/10.1111/jam.14478>.
35. Shah, I.; Poojari, V.; Meshram, H. Multi-Drug Resistant and Extensively-Drug Resistant Tuberculosis. *Indian J. Pediatr.* **2020**, *87*, 833-839, <https://doi.org/10.1007/s12098-020-03230-1>.
36. Lentz, F.; Reiling, N.; Spengler, G.; Kincses, A.; Csonka, A.; Molnár, J.; Hilgeroth, A. Dually acting nonclassical 1, 4-dihydropyridines promote the anti-tuberculosis (Tb) activities of clofazimine. *Molecules* **2019**, *24*, 2873. <https://dx.doi.org/10.3390%2Fmolecules24162873>.
37. Fassihi, A.; Azadpour, Z.; Delbari, N.; Saghaie, L.; Memarian, H.R.; Stabet, R.; Alborzi, A.; Miri, R.; Pourabbas, B.; Mardaneh, J.; Mousavi, P.; Moeinifard, B.; Sadeghi, H. Synthesis and antitubercular activity of novel 4-substituted imidazolyl- 2, 6-dimethyl-N3, N5-bisaryl-1, 4-dihydropyridine-3, 5- dicarboxamides. *Eur. J. Med. Chem.* **2009**, *44*, 3253-3258, <https://doi.org/10.1016/j.ejmech.2009.03.027>.
38. Khoshneviszadeh, M.; Edraki, N.; Javidnia, K.; Alborzi, A.; Pourabbas, B.; Mardaneh, J.; Miri, R. Synthesis and biological evaluation of some new 1,4-dihydropyridines containing different ester substitute and diethyl carbamoyl group as antitubercular agents. *Bioorg. Med. Chem.* **2009**, *17*, 1579-1586, <https://doi.org/10.1016/j.bmc.2008.12.070>.
39. Singh, R.; Dwivedi, S.P.; Gaharwar, U.S.; Meena, R.; Rajamani, P.; Prasad, T. Recent updates on drug resistance in Mycobacterium tuberculosis. *J. Appl. Microbiol.* **2020**, *128*, 1547-1567, <https://doi.org/10.1111/jam.14478>.
40. Milkovic, L.; Vukovic, T.; Zarkovic, N.; Tatzber, F.; Bisenieks, E.; Kalme, Z.; Bruvere, I.; Ogle, Z.; Poikans, J.; Velena, A.; Duburs, G. Antioxidative 1,4-Dihydropyridine Derivatives Modulate Oxidative Stress and Growth of Human Osteoblast-Like Cells In Vitro. *Antioxidants (Basel)* **2018**, *7*, 123, <https://doi.org/10.3390/antiox7090123>.

41. Sharma, V.; Kaur, A.; Singh, T.G. Counteracting role of nuclear factor erythroid 2-related factor 2 pathway in Alzheimer's disease. *Biomed. Pharmacother.* **2020**, *129*, 110373, <https://doi.org/10.1016/j.biopha.2020.110373>.
42. Michalska, P.; Mayo, P.; Fernández-Mendivil, C.; Tenti, G.; Duarte, P.; Buendia, I.; Ramos, M.T.; López, M.G.; Menéndez, J.C.; León, R. Antioxidant, Anti-inflammatory and Neuroprotective Profiles of Novel 1,4-Dihydropyridine Derivatives for the Treatment of Alzheimer's Disease. *Antioxidants (Basel)* **2020**, *9*, 650, <https://doi.org/10.3390/antiox9080650>.
43. Balázs, A.; Mall M.A. Role of the SLC26A9 chloride channel as disease modifier and potential therapeutic target in cystic fibrosis. *Front Pharmacol* **2018**, *9*, 1112, <https://doi.org/10.3389/fphar.2018.01112>.
44. Cabrera, D.D.C.; Santa-Helena, E.; Leal, H.P.; Moura, R.R.; Nery, L.E.M.; Gonçalves, C.A.N., Russowsky, D.; D'Oca, M.G.M. Synthesis and antioxidant activity of new lipophilic dihydropyridines. *Bioorg. Chem.* **2019**, *84*, 1-16, <https://doi.org/10.1016/j.bioorg.2018.11.009>.
45. Pedemonte, N.; Diena, T.; Caci, E.; Nieddu, E.; Mazzei, M.; Ravazzlo, R.; Zegarra-Moran, O.; Galietta, L.J.V. Antihypertensive 1,4-Dihydropyridines as Correctors of the Cystic Fibrosis Transmembrane Conductance Regulator Channel Gating Defect Caused by Cystic Fibrosis Mutations. *Mol. Pharmacol.* **2005**, *68*, 1736-1742, <https://doi.org/10.1124/mol.105.015149>.
46. Budriesi, R.; Loan, P.; Leoni, A.; Pedemonte, N.; Locatelli, A.; Micucci, M.; Chiarini, A.; Galieeta, L.J.V. Cystic Fibrosis: A New Target for 4-Imidazo [2, 1-b] thiazole-1,4-Dihydropyridines. *J. Med. Chem.* **2011**, *54*, 3885-3894, <https://doi.org/10.1021/jm200199r>.
47. Cateni, F.; Zacchigna, M.; Pedemonte, N.; Galietta, L.J.V.; Mazzei, M.T.; Fossa, P.; Giampieri, M.; Mazzei, M. Synthesis of 4- thiophen-20-yl-1, 4-dihydropyridines as potentiators of the CFTR chloride channel. *Bioorg. Med. Chem.* **2009**, *17*, 7894-7903. <https://doi.org/10.1016/j.bmc.2009.10.028>.
48. Sueta, D.; Tabata, N.; Hokimoto, S. Clinical roles of calcium channel blockers in ischemic heart diseases. *Hypertens. Res.* **2017**, *40*, 423-428, <https://doi.org/10.1038/hr.2016.183>.
49. Abrego, V.H.; M-Perez, B.; Torres, L.A.; Angeles, E.; Martinez, L.; Marroquin-Pascual, J.L.; Moya-Hernandez, R.; Amaro-Recillas, H.A.; Rueda-Jackson, J.C.; Rodriguez-Barrientos, D.; Rojas-Hernandez, A. Antihypertensive and antiarrhythmic properties of a parahydroxy[bis(ortho morpholinylmethyl)] phenyl1,4-DHP compound: Comparison with other compounds of the same kind and relationship with log P values. *Eur. J. Med. Chem.* **2010**, *45*, 4622-4630, <https://doi.org/10.1016/j.ejmech.2010.07.027>.
50. Gupta, A.; Shah, K.; Oza, M.J.; Behl, T. Reactivation of p53 gene by MDM2 inhibitors: A novel therapy for cancer treatment. *Biomedicine and Pharmacotherapy.* **2019**, *109*, 484-492, <https://doi.org/10.1016/j.biopha.2018.10.155>.
51. Naik, T.R.R. Therapeutic Significance of 1, 4-Dihydropyridine Compounds as Potential Anticancer Agents. *Organic Synthesis: A Nascent Relook.* **2020**, 217, <https://doi.org/10.5772/intechopen.89860>.
52. Sirisha, K.; Achaiah, G.; Reddy, V.M. Facile Synthesis and Antibacterial, Antitubercular, and Anticancer Activities of Novel 1, 4-Dihydropyridines. *Arch. Pharm.* **2010**, *343*, 342-352, <https://doi.org/10.1002/ardp.200900243>.
53. Zhou, X.; Zhang, L.; Tseng, E.; Scott-Ramsay, E.; Schentag, J.J.; Coburn, R.A.; Morris, M.E. New 4-Aryl-1, 4-Dihydropyridines and 4-Arylpyridines as P-Glycoprotein Inhibitors. *Drug. Metab. Dispos.* **2005**, *33*, 321-328, <https://doi.org/10.1124/dmd.104.002089>.
54. Chawla, A.; Kaur, R.; Goyal, A. Importance of microwave reactions in the synthesis of Novel benzimidazole derivatives: A review. *J. Chem. Pharm. Res.* **2011**, *3*, 925-944.
55. Samzadeh-Kermani, A.; Shafaroodi, H.; Miri, R.; Mirkhani, H.; Vosooghi, M.; Shafiee, A. Lipophilic 2-(4-chlorophenyl)-4-thiazolyl-1,4-dihydropyridines: synthesis, calcium channel antagonist activity, and protection against pentylenetetrazole-induced seizure. *Med. Chem. Res.* **2009**, *18*, 112-126, <https://doi.org/10.1007/s00044-008-9112-5>.
56. Tempone, A.G.; Taniwaki, N.N.; Reimao, J.Q. Antileishmanial activity and ultra-structural alterations of Leishmania (L.) Chagasi treated with the calcium channel blocker Nimodipine. *Parasitol. Res.* **2009**, *105*, 499-505, <https://doi.org/10.1007/s00436-009-1427-8>.
57. Pandey, V.P.; Bisht, S.S.; Mishra, M.; Kumar, A.; Siddiqi, M.I.; Verma, A.; Mittal, M.; Sane, S.A.; Gupta, S.; Tripathi, R.P. Synthesis and molecular docking studies of 1-phenyl-4-glycosylDihydropyridines as potent antileishmanial agents. *Eur. J. Med. Chem.* **2010**, *45*, 2381-2388, <https://doi.org/10.1016/j.ejmech.2010.02.018>.
58. Kumar, R.S.; Idhayadhulla, A.; Nasser A.J.A.; Selvin, J. Synthesis and anticoagulant activity of a new series of 1,4-dihydropyridine derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 804-810, <https://doi.org/10.1016/j.ejmech.2010.12.006>.
59. Moschonis, G.; Karatzi, K. Novel Dietary Approaches for Controlling High Blood Pressure. *Nutrients* **2020**, *12*, 3902, <https://doi.org/10.3390/nu12123902>.

60. Bhavé, A.L.; Bhatt, J.D.; Hemavathi, K.G. Antiulcer effect of Amlodipine and its interaction with H₂ blocker and proton pump inhibitor in pylorus ligated rats. *Indian. J. Pharmacol.* **2006**, *38*, 403–407, <https://doi.org/10.4103/0253-7613.28206>.
61. Ahmad Bhat, M.; Al-Omar, M.A.; Naglah, A.M. Synthesis and in vivo antiulcer evaluation of some novel piperidine linked dihydropyrimidinone derivatives. *J. Enzyme. Inhib. Med. Chem.* **2018**, *33*, 978–988, <https://doi.org/10.1080/14756366.2018.1474212>.
62. Patil, A.N.; Advani, M.G.; Mali, S.N.; Pawar, S.; Raut, S.B. Evaluation of antiulcer effect of amlodipine in gastric ulcer models in rats. *Indian. J. Pharmacol.* **2012**, *44*, 387–389, <https://doi.org/10.4103/0253-7613.96344>.
63. Singh, S.; Singh, T.G. Role of Nuclear Factor Kappa B (NF-κB) Signalling in Neurodegenerative Diseases: A Mechanistic Approach. *Current neuropharmacology* **2020**, *18*, 918–935, <https://doi.org/10.2174/1570159X18666200207120949>.
64. Komoda, H.; Inoue, T.; Node, K. Anti-inflammatory properties of azelnidipine, a dihydropyridine-based calcium channel blocker. *Clin Exp Hypertens* **2010**, *32*, 121–128, <https://doi.org/10.3109/10641960903254414>.
65. Annouf, Y.; Al-Lahamm, S.H.A.Z.A.; Al-Shatti, E.Y.A.D. Effect of Amlodipine on Enteropathy induced by Indomethacin in Rats. *Int. J. Curr. Pharm. Res.* **2020**, *12*, 144–150, <http://dx.doi.org/10.22159/ijcpr.2020v12i3.38229>.