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1, 4-Dihydropyridines: A Class of Pharmacologically Important Molecules

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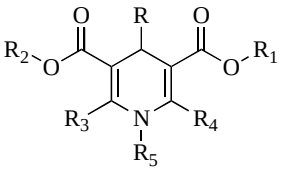
Abstract: The 1, 4-dihydropyridines (DHPs), a class of drugs possess a wide variety of biological and pharmacological actions. It represents one of the most important groups of calcium-channel modulating agents and has experienced widespread use in the treatment of cardiovascular disease which includes antihypertensive, antianginal, vasodilator and cardiac depressants activities. It also shows antibacterial, anticancer, antileishmanial, anticoagulant, anticonvulsant, antitubercular, antioxidant, antiulcer, CFTR, antimalarials, neuroprotection properties, HIV-1 protease inhibitors, antifertility activities and many more. There are many drugs available in market which contains 1, 4-dihydropyridines ring as basic scaffold. Basic motive of this review is to disclose various therapeutic applications of 1, 4-dihydropyridine derivatives reported by other researchers during their research work in 2001 to 2011.

Keywords: Antihypertensive, biological and pharmacological action, calcium channel modulating agents, cardiovascular disease, 1,4-dihydropyridine, therapeutic application.

INTRODUCTION

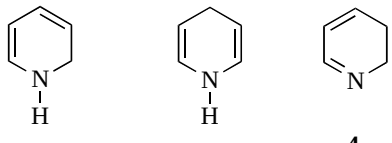
Arthur Hantzsch described the preparation of 1, 4-dihydropyridines compound 1 more than century ago [1, 2]. Dihydropyridines (DHPs) represent a group of small organic compounds based on a pyridine core.



1

The main feature of 1, 4-dihydropyridine derivatives is that one or more of the 6 atoms can be substituted to have different derivatives. Theoretically five isomeric dihydropyridine compounds from 2 to 6 are capable of existence. But the 1, 2-dihydro compound 2 or the 1, 4-Dihydro compound 3 in the dihydropyridines are well known. The reason why compounds 4 and 5 are more common than 5 and 6 is presumably the involvement of the nitrogen lone pair in the π electron system of the former. The isomers compounds 2 and 3 have the highest number of sp^2-hybridized centers.

In 1930's, it was discovered that a "hydrogen-transferring coenzyme" is a reduced nicotinamide derivative which stimulated work on model dihydropyridines, generally N substituted dihydronicotinamides. While the gross structure of the coenzyme NADH compound 7 (reduced Nicotinamide Adenine Dinucleotide the oxidized pyridinium form is known as NAD) was established relatively earlier. The fine structure was not recognized until the late 1950's. Early workers believed that NADH was a 1, 2-dihydronicotinamide derivative and considerable confusion ensued as a result. Eventually, it was proved unambiguously that NADH was the 1, 4-Dihydronicotinamide [3].



2 **3** **4**

5 **6**

BIOLOGICAL ACTIVITY AND USES OF DIHYDROPYRIDINES

In recent years, several Dihydropyridines scaffolds have been in clinical use as compounds 8, 9, 10, and 11. Dihydropyridine posses many pharmacological activities such as antibacterial, anticancer, antileishmanial agents, anticoagulant activity, anticonvulsant agents, antihypertensive activity, antimicrobial activity, antitubercular activity, antioxidant activity, antiulcer, arrhythmia, cardio depressant activity, CFTR, antimalarials, neuroprotection properties, HIV-1 protease inhibitors and many more. The work

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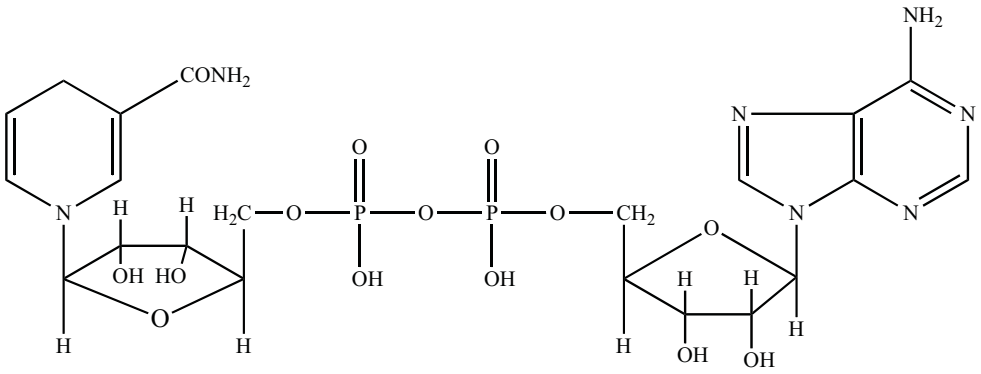

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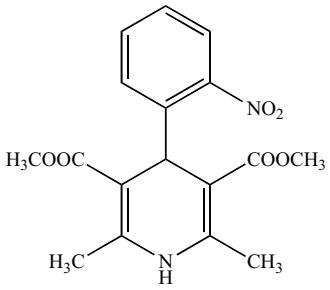
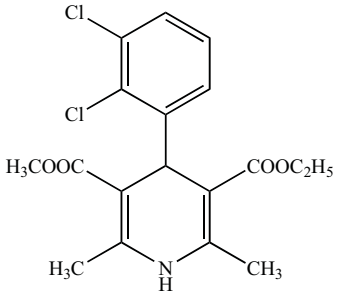
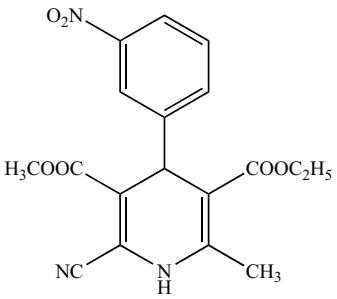


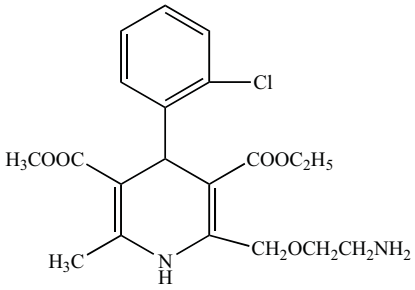
Nifedipine
(Adalat)
8



Felodipine
(Plendil, 1988)
9



Nilvadipine
(Nivaldil, 1989)
10



Amlodipine
11

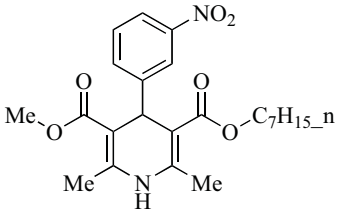
reported worldwide related to dihydropyridines derivatives has been discussed in detail below.

ANTIHYPERTENSIVE AGENT

There are usually no symptoms or signs of hypertension and hence it is called the "silent killer". The increase in blood pressure cannot be understood by human beings until it is checked and detected. The exception is malignant hypertension, which can cause headache, congestive heart failure, stroke, seizure, papilledema, renal failure and anuria [4].

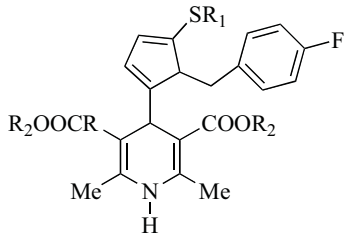
Hypertension is one of the major risk factors for coronary heart disease and the most important risk factor for cerebrovascular diseases [5]. In most countries, almost 20% of the population has high blood pressure levels; two-thirds of those have mild hypertension and the remaining have a more severe disease [6]. It is clear, therefore, that the treatment of hypertension is a primary public health care objective. Both mortality and morbidity appear to be directly related to the degree of hypertension, even if substantial differences can be detected in relation to the severity of the disease. In fact, each year 3% to 5% of the elderly hypertensive patients with a history of cardiovascular disease develop a serious cardiovascular accident and one out of 1000 young hypertensive patients without any other risk factor also develops a serious event every year. Furthermore, it has been clearly demonstrated that antihypertensive treatment decreases the risk in both groups [7].

Kai Zhou *et al.* [8] have reported a series of compounds based on nitrendipine analogs, the antihypertensive activity of nitrendipine analogs can be improved by properly lengthening its alkyl chain in 3- or 5-position. Nitrendipine and its seven analogs were synthesized, and their antihypertensive activities in spontaneously hypertensive rats (SHR) were evaluated by I. P. administration. The antihypertensive activity of nitrendipine analogs can be improved by properly lengthening its alkyl chain in 3- or 5-position. Compound 12 exhibited a significant antihypertensive activity.



12

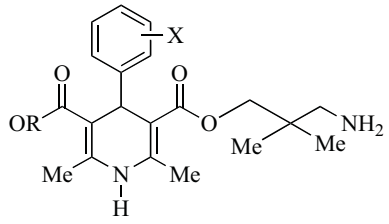
S.A. Mohajeri *et al.* [9] have reported a series of compounds based on 1,4-dihydropyridines bearing 1-(4-fluorobenzyl)-5-imidazolyl substituent at 4-position were synthesized and tested for hypotensive activity in male rats (compound 13). The hypotensive effects of all compounds were less than that of nifedipine.



R_1	R_2
Me	Me
Me	Et
Et	Me
Et	Et

13

A.N. Balaev *et al.* [10] synthesized new 1,4-dihydropyridines containing 3-dialkylamino-2,2-dimethylpropyl fragments; they show that compounds synthesized here had greater hypotensive activity than nifedipine (compound 14).



X	R
3-NO_2	Et

14

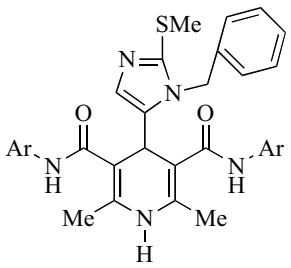
Ali Akbar Nekooeian *et al.* [11], reported antihypertensive effects of some new nitroxyalkyl 1,4-dihydropyridine derivatives in rat model of two-kidney, one-clip hypertension. They concluded that 5 position had a great impact on antihypertensive ability of these DHP derivatives and also the possible interaction with Calcium channels.

Shashikant R. Pathan *et al.* [12] reported synthesis and evaluation of some 1,4-dihydropyridines and their derivatives as antihypertensive agents. The results indicate that all compounds were found to be significantly antihypertensive as compared to nifedipine. F. Hadizadeh *et al.* [13] reported synthesis and antihypertensive activity of new 1,4-dihydropyridines. They synthesized a series of compounds bearing dimethylamino or 1H-imidazol-1-yl as side chain in the position have been tested for antihypertensive activity in DOCA induced hypertensive rat. All compounds were found to be less effective than nifedipine. Jhy-Chong Liang *et al.* [14] in the year 2002 reported synthesis of The New Generation Dihydropyridine Type Calcium Blockers, Bear 4-Phenyl oxypropanolamine, display α-/β-adrenoceptor antagonist and long-acting Antihypertensive Activities. A new series of dihydropyridine derivatives, bearing oxypropanolamine moiety on phenyl ring at the 4-position of the dihydropyridine base, were prepared. Masoumeh Jorjania *et al.* [15] in the year 2002 reported synthesis and biological evaluation of new 1, 4-dihydropyridines as antihypertensive agents in rats, new analogs of nifedipine, as a known calcium channel blocker, were synthesized by replacing the orthonitrophenyl group on position 4 with 1-(4-Nitrobenzyl)-5-imidazolyl or 2- methylthio-1-(4-Nitrobenzyl)-5-imidazolyl substituent. The results indicate that all compounds reduce mean systolic blood pressure but their effectiveness is less than nifedipine.

ANTITUBERCULAR ACTIVITY

Tuberculosis is a leading infectious cause of death worldwide. Because of the concern of the resistance to most of the commonly used drugs displayed by the considered mycobacteria, most efforts have been done to introduce new anti-tubercular agents [16, 17].

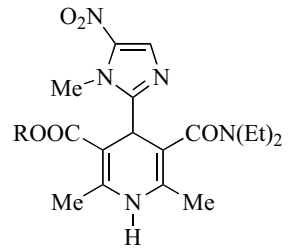
Afshin Fassihi *et al.* [18] reported a prepration of series of 4-substituted imidazolyl-2,6-dimethyl-N3,N5-bisaryl-1,4-dihydropyridine-3,5-dicarboxamides. They were screened as antitubercular agents against Mycobacterium tuberculosis H37Rv. Minimum inhibitory concentrations (MICs) were determined using agar proportion method, compound 9 with 1-benzyl-2-methylthio-1H-imidazole-5-yl substituent at C-4 position and 4-chloromophenyl group at C-3 and C-5 positions of the 1,4-dihydropyridine ring was the most potent one among the tested compounds. It was as potent as rifampicin against M. tuberculosis H37RV. Compound 15 also was an active antitubercular agent with the same substituent as compound 16 at the C-4 position and pyridyl group at C-3 and C-5 positions of the 1,4-dihydropyridine ring.



	Ar
15	4-chlorophenyl
16	2-pyridyl

15, 16

Mehdi Khoshneviszadeh *et al.* [19] synthesized new derivatives of 1,4-dihydropyridines in which different alkyl and aryl esters and diethyl carbamoyl are substituted in C-3 and C-5 of the DHP ring. In addition, nitroimidazole ring is a substitute at C-4 position. These asymmetric analogs were synthesized by a modified Hantzsh reaction using procedure reported by Meyer. The *in vitro* anti-tubercular activity of compounds against Mycobacterium tuberculosis was evaluated. The results indicate that compounds containing aromatic esters are more potent than alkyl ones. The most potent aromatic compound 17 exhibits comparable anti-tubercular activity (MIC = 1 lmol/ml) with reference compound isoniazid (MIC = 1 mol/ml).

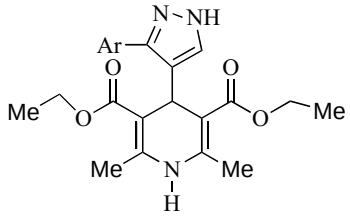


R = 3-phenylpropyl

17

ANTIOXIDANT ACTIVITY

Vijesha *et al.* [20] reported new series of Hantzsch 1,4-dihydropyridine derivatives (1,4-DHPs) containing substituted pyrazole moiety were synthesized by the reaction of 3-aryl-1H-pyrazole-4- carbaldehydes with 1,3-dicarbonylcompounds (ethylacetoacetate and methylacetoacetate) and ammonium acetate. Antioxidant studies of the synthesized compounds were also performed by measuring the DPPH radical scavenging assay. Compounds 18, 19 and 20 were found to be potent antibacterial and antioxidant agents.



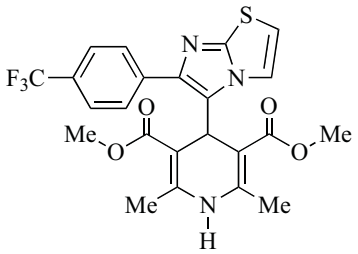
	Ar
18	4-Thioanisyl
19	Biphenyl
20	4-Chlorophenyl

18-20

S. Kalvikkarasi *et al.* [21] also synthesized some Mannich bases of novel 1,4-dihydro pyridines derivatives which were found to be active.

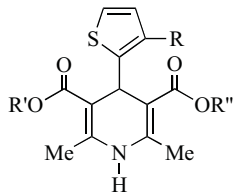
CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR ACTIVITY

The pharmacology of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl channel has attracted significant interest in recent years with the aim to search for rational new therapies for diseases caused by CFTR malfunction. Mutations that abolish the function of CFTR cause the life-threatening genetic disease cystic fibrosis (CF). The most common cause of CF is the deletion of phenylalanine 508 (ΔF508) in the CFTR chloride channel. Felodipine, nifedipine, and other antihypertensive 1,4-dihydropyridines (1,4-DHPs) that block L-type Ca2.1 channels are also effective potentiators of CFTR gating, able to correct the defective activity of ΔF508 and other CFTR mutants [22]. For this purpose, evaluation of the ability of the newly synthesized 4-imidazo[2,1-b]thiazoles-1,4-dihydropyridines without vascular activity and inotropic and/or *chronotropic cardiac effects* [23] enhances the activity of ΔF508-CFTR. Our studies indicate compounds 21 as 1,4-DHPs with an interesting profile of activity.



21

Francesca Cateni *et al.* [24] reported the gating of the CFTR chloride channel which is altered by a group of mutations that cause cystic fibrosis. This gating defect may be corrected by small molecules called potentiators. Some 1,4-dihydropyridine (DHP) derivatives, bearing a thiophen-2-yl and a furanyl ring at the 4-position of the nucleus, were prepared and tested as CFTR potentiators. In particular, we evaluated the ability of novel DHPs to enhance the activity of the rescued DF508-CFTR as measured with a functional assay based on the halide-sensitive yellow fluorescent protein. Most DHPs showed an effect comparable to or better than that of the reference compound genistein. The potency was instead significantly improved, with some compounds, such as 22, 23 and 24 having a half effective concentration in the submicromolar range.

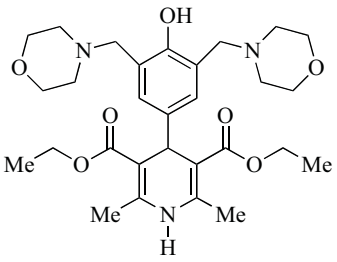


	R	R'	R"
22	Me	allyl	Et
23	Me	benzyl	Et
24	SCH2COOCH3	allyl	Et

22-24

ANTIARRHYTHMIC ACTIVITY

Victor H. Abrego *et al.* [25] reported a new para-hydroxy[bis(ortho-morpholinylmethyl)]phenyl-1,4-DHP substituted compound, (4-(4-hydroxy-3,5-bis(morpholin-4-ylmethyl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester), with antihypertensive and antiarrhythmic properties, which has been synthesized. Compound 25 has good antiarrhythmic effect for low doses.

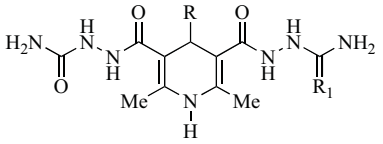


25

ANTICANCER

Development of multidrug resistance is a major therapeutic obstacle in chemotherapy of cancer. Circumvention of the multidrug resistance is thus a critical step to improve cancer chemotherapy. Calcium channel blockers like verapamil, nicardipine and others have been reported to successfully overcome the drug resistance *in vitro* and *in vivo* [26].

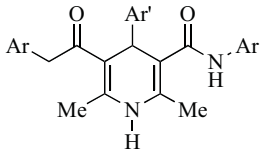
P. Surendra Kumar *et al.* [27] reported a series on the basis of thiosemicarbazide and semicarbazide containing 1,4-dihydropyridine derivatives and tested it against anticancer activity *in vivo*. They found compounds which were active against three cancer cell lines, compound 26 was found to be highly active against HepG2 (liver) MCF7 (Breast), and compound 27 was found to be highly active against Hela (cervical).



	R	R_1
26	4-OH-3-OCH3-Ph	O
27	4-OH-3-OCH3-Ph	S

26, 27

Kalam Sirisha *et al.* [28] also reported an anticancer activity by synthesizing 4-substituted-2,6-dimethyl-3,5-bis-N-(heteroaryl)-carbamoyl-1,4-dihydropyridine and evaluated for their in-vitro anticancer, antibacterial, and antitubercular activities amongst the compounds tested, compound 28 exhibited the highest anticancer activity.

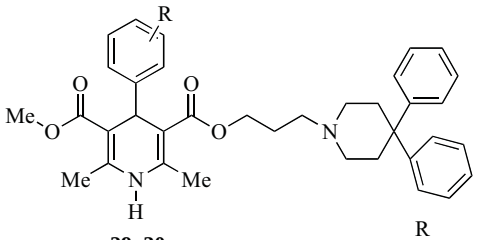


Ar = 2-Methyl-4-oxo-3H-quinazoline-3-yl

Ar' = 4Cl-C6H5

28

X. Zhou *et al.* [29], synthesized a series of 4-aryl-1,4-dihydropyridines and corresponding aromatized 4-arylpyridines which have been synthesized on the basis of structure modifications of niguldipine to enhance multidrug resistance reversal activity, while minimizing calcium channel binding. Thirty new compounds were characterized. [^{3}H]. Vinblastine accumulation studies indicated that at a concentration level of 3 μM, 15 of 18 4-aryl-1,4-dihydropyridines and all 4 arylpyridines can successfully restore intracellular accumulation of vinblastine in a resistant human breast adenocarcinoma cell line, MCF-7/adr, which over expresses P-glycoprotein. The compounds in series that appeared to have the most potent effects are compounds 29 and 30, leading the series with an approximately 15-fold increase.



	R
29	4-oxypropyl
30	4-oxybutyl

29, 30

ANTICONVULSANT AGENTS

The word “Epilepsy” is derived from the Greek, meaning ‘to take hold of, seizure’. An epileptic seizure is a transient paroxysm of uncontrolled discharges of neurons causing an event that is discernible by the person experiencing the seizure and/or by the observer. Epilepsy affects approximately 1% of the whole worldwide population and is the second most common neurologic disorder after stroke [30].

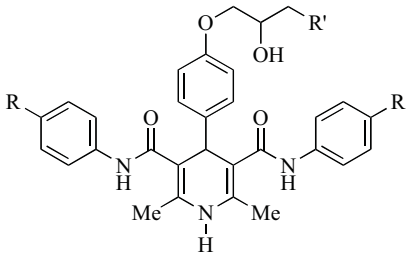
Samzadeh-Kermani *et al.* [31] has developed a series of alkyl, cycloalkyl and aryl esters of nifedipine in which the o-nitrophenyl group at position-4 was replaced by 2-(4-chlorophenyl)-4-thiazolyl, substituents were synthesized and evaluated for the anticonvulsant activity of the test drugs. It was also assessed in pentylenetetrazole (PTZ)-induced seizure where all compounds were shown to have considerable anticonvulsant activity.

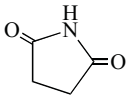
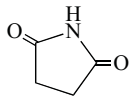
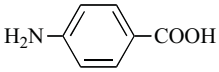
S.R. Pathan *et al.* [32] reported a series of compounds based on 1,4–dihydro 2,6 dimethyl-4-{4-(3-(piperidine/ morpholine/2-aminopyrazine/1-amino-4-methlpiperazine)-2-hydroxypropoxyl)-phenyl}-pyridine 3-5-carbamoyl. They evaluated these compounds for anticonvulsant activity by Maximal Electroshock Method. Test compounds 31, 32 and 33 have shown more activity when compared with standard drugs.

ANTILEISHMANIAL AGENTS

Tempone *et al.,* in his search for new antileishmanial drugs investigated the activity of the calcium channel blocker nimodipine against Leishmania spp and explored the ultra structural damages of parasites induced by nimodipine after a short period of incubation. Nimodipine was highly effective against promastigotes and intracellular amastigotes of Leishmania chagasi with 50% inhibitory concentration values of 81.2 and 21.5 μM, respectively. Calcium channel blocker is an effective *in vitro* antileishmanial compound and if adequately studied could be used as a novel drug candidate or as a novel drug lead compound for drug design studies against leishmaniasis [33].

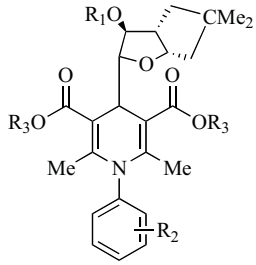
A series of 1-phenyl-4-glycosyl-dihydropyridines was prepared by the one pot multi component reaction of giycosyl aldehyde, β-keto compounds and aniline or substituted aniline in the presence of TBAHS as catalyst.



	R	R'
31	p-NO2	
32	m-NO2	
33	p-NO2	

31-33

The compounds were screened *in vitro* and *in vivo* for their antileishmanial activities. Most of the compounds have exhibited moderate to good activity against amastigotes and promastigotes of Leishmania donovani. The compounds 34, 35, 36 and 37 exhibited potent *in vivo* activity with selectivity index (SI) values ranged from 7.43-18.93 [34].



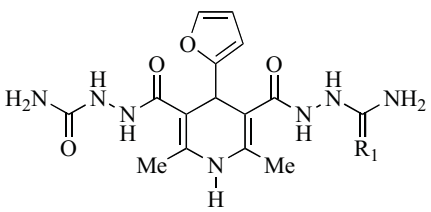
	R_1	R_2	R_3
34	CH2Ph	4-F	Me
35	Me	4-OMe	Me
36	Me	4-Cl	Me
37	Me	4-Me	Me

34-37

ANTICOAGULANT ACTIVITY

A recent placebo-controlled cross-over study in hypertensive patients lends further support to the idea that verapamil has antiplatelet effects as attenuation of platelet agreeability *in vitro* was found after 4 weeks treatment with verapamil [35].

R. Surendra Kumar [36] has synthesized a new series of 1,4-dihydropyridine derivatives on the basis of the 2,6-dimethyl-4-substituted phenyl-1,4-dihydropyridine- 3,5-dicarboxylate derivatives which were reacted with thiosemicarbazide to give 2,20-{[4-(4-substitutedphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl} dihydrazinecarbothioamide compounds. The synthesized compounds were screened for anticoagulant activity. Among these compounds 'Compound 38' was found to have high response on anticoagulation action (time 720.35 s) at a concentration of 30 mg/mL when compared with other compounds.



38

CARDIODEPRESSANT ACTIVITY

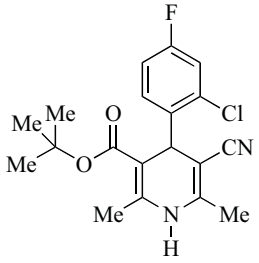
Roberta Budriesi *et al.* [37] reported a synthesis and functional *in vitro* assays in cardiac tissues and smooth muscle (vascular and nonvascular) of a number of 4-imidazo [2,1-*b*]thiazole-1,4-dihydropyridines. The imidazo[2,1-*b*]thiazole system has found to confer to the dihydropyridine scaffold an inotropic and/or chronotropic cardiovascular activity with a high selectivity towards the nonvascular tissue.

Emanuele Carosati *et al.* [38] has reported that N-[2-(dimethylamino)ethyl]-3-hydroxy-2-naphthamide, N,N-dimethyl-N′-(2-pyridin-3-ylquinolin-4-yl)ethane-1,2-diamine, 2-[(4-chlorophenyl)(pyridin-2-yl)methoxy]-N,N-dimethylethanamine (carbinoxamine) and 7-[2-(diethylamino)ethoxy]-2H-chromen-2-one revealed interesting activity and binding to the benzothiazepine site.

MINERALOCORTICOID RECEPTOR ANTAGONISTS

Graciela B. Arhancet *et al.* [39, 40] a number of known 1,4-dihydropyridine CCBs were identified as having comparable potency to the steroidal MR antagonist eplerenone. Study has demonstrated that the stereochemical configuration of asymmetric 1,4-DHPs is critical for their CCB or MR antagonist activity. Replacement of the ester group at the C3 position by a cyano group led to a series of very active MR antagonists with no CCB activity.

A new 1,4-dihydropyridine compound 39 containing a cyano group at the C3 position was recently reported to possess excellent mineralocorticoid receptor (MR) antagonist *in vitro* potency and no calcium channel-blocker (CCB) activity.

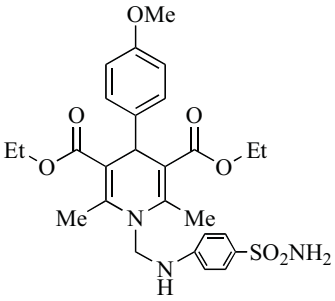


39

ANTIULCER ACTIVITY

B. B. Subudhi *et al.* [41] reported a series based on 3,5-diethoxycarbonyl-1,4-dihydro-26-dimethyl-4-(substituted) pyridine compound 40 and tested for antiulcer activity which

enhanced significantly on conjugation with sulphanilamide substitution of methoxy group which increased the antiulcer activity of the compounds.

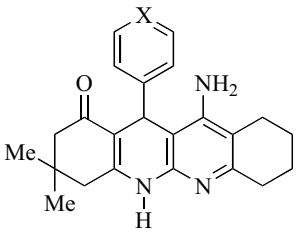


40

ALZHEIMER ACTIVITY

Alzheimer's disease (AD) is an age-related neurodegenerative process characterized by progressive memory loss, decline in language skills and other cognitive impairments [42].

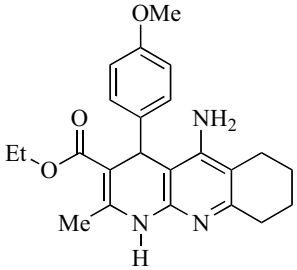
Rafael León *et al.* [43] describe the synthesis and biological evaluation of tacripyrimedones 41-45, a series of new tacrine-1,4-dihydropyridine hybrids bearing the general structure of 11-amino 12-aryl- 3,3-dimethyl-3,4,5,7,8,9,10, 12-octahydrodibenzo[b,g][1,8]naphthyridine-1(2H)-one. They represent a new family of molecules with potential therapeutic application for the treatment of Alzheimer's disease.



41-45

	X
41	C-H
42	C-F
43	C-Me
44	C-OMe
45	N

Jose Marco-Contelles *et al.* [44] have synthesized and evaluated a series of tacrine-DHP hybrids, named tacripyrines, which were potent and selective inhibitors of AChE and showed potent neuroprotection activity. Compound 46, one of the most potent derivatives, was associated to a 30.7 (8.6% inhibition of the proaggregating action of AChE on the β amyloid peptide).



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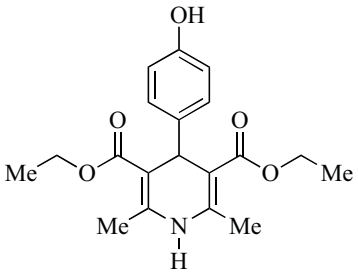
HIV

The discovery of HIV-1 protease as a novel target enzyme for the development of HIV-1 protease inhibitors, certain peptidic PIs have been established in HIV-therapy combined with nucleoside analogs or reverse transcriptase inhibitors. Andreas Hilgeroth *et al.* synthesised a series of novel *N*-alkyl substituted *syn* dimeric 4-aryl-1,4-dihydropyridines and evaluated as HIV-1 protease inhibitors in *in vitro* assays. While the *N*-methyl derivatives were almost inactive with IC_{50}-values of about 225 μM, all the *N*-benzyl compounds with varied ester groups exhibited stronger activities with IC^{50}-values of 11–12 μM for the currently best compounds with ethyl ester functions [45].

Andreas Hilgeroth *et al.* a first series of novel bishydroxymethyl-substituted cage dimeric 4-aryl-1,4-dihydropyridines 5/8 synthesized and evaluated as HIV-1 protease and HIV-inhibitors *in vitro* assays. Moderate activity data of protease inhibition have been found for of the N-Boc substituted compound [46].

ANTIFERTILITY AGENT

In search of non-hormonal male contraceptives, analogs of nifedipine which cause reversible infertility have been synthesized and their interaction at molecular level with model membrane has been probed. Analogs act differently with respect to their antifertility action. This is achieved by altering the cell metabolism thereby directly affecting the motility which is responsible for fertility compound 47 [47].



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CONCLUSION

The present review concludes that 1,4-dihydropyridines are a class of pharmacologically important molecules. 1,4-DHP as a Multifunctional potent lead molecule has various positions for substitution and show several pharmacological activities such as calcium channel antagonist activity, antihypertensive activity, vasodilator activity, antianginal activity. Also, not only the CVS activities but also other pharmacological activities such as antitubercular activity, antibacterial activity, anti-inflammatory activity, anticonvulsant activity, antiulcer activity, anticancer, antileishmanial agents, anticoagulant activity, CFTR, antimalarials, neuroprotection properties, HIV-1 protease inhibitors, antifertility agent and many more have been exhibited.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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