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1,4-Dihydropyridines: A Multtifunctional Molecule- A Review

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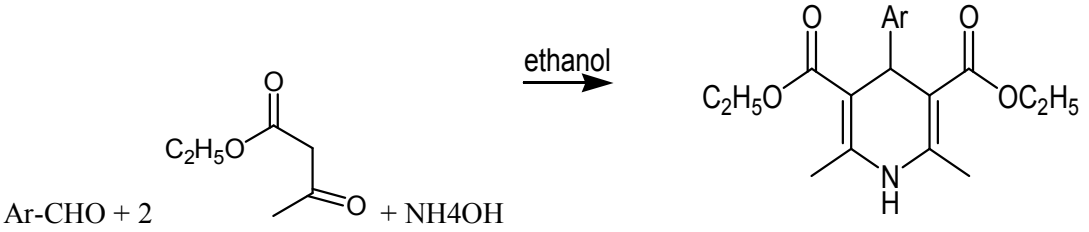
Abstract: 1,4-dihydropyridine is the most feasible heterocyclic ring with various substitutions at several positions. This molecule binds to the L-type calcium channel and act as a multifunctional lead molecule for the various Cardiovascular activities which include Antihypertensive, Antianginal, vasodilator and cardiac depressants activities. Apart from the CVS activities it also exhibit antitubercular ,anticonvulsant, antitumour ,analgesic, anti-inflammatory , stress protective activities. The present review highlights the various synthetic routes with specified structural activity features with corresponding pharmacological activities.
Keywords: 1,4-dihydropyridines, cvs activitites, other activities.

Introduction:

1,4-dihydropyridine is a six membered aromatic ring containing N at 1st postion ,which is saturated at1 and 4th position are 1,4-DHP . the most feasible position for substitution is 4th which exhibit various activities i.e., as the calcium channel antagonists [1] and the heterocyclic ring is the common feature for various pharmacological activities such as antihypertensive , antianginal [2-4],antitumor [5],anti-inflammatory activity [6,7], antitubercular activity[8],analgesic activity [9], antithrombotic [10,11]. It binds to L-type channel and also shows action by binding to N-type channel also [12].other activities like vasodilation [13], anticonvulsant [14].stress protective effect [15], cardio depressant activity [16]. Biological activity of various 1, 4-dihydropyridines derivatives have been published in various papers and their brief review is given in this paper.

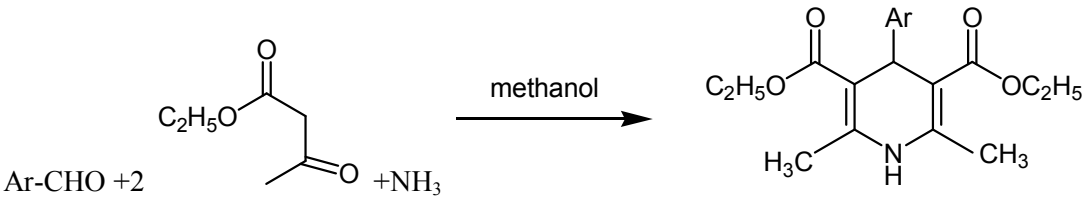
Chemistry:

Various methods have been proposed by various scientists for the synthesis of 1,4-dihydropyridine.
Synthesis of 1,4-dihydropyridines was first reported by Hantzsch by refluxing of aldehyde, β-ketoester and ammonia or ammonium salts in ethanol**.(scheme-1)[**17]



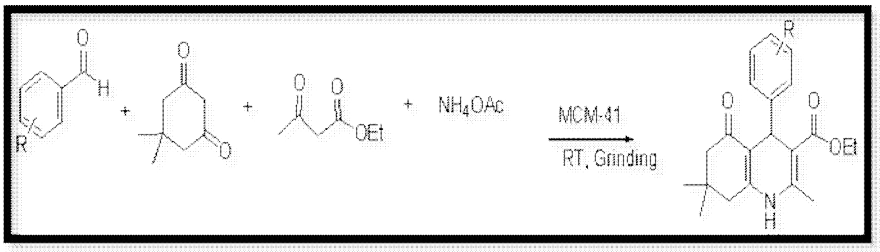
Scheme-1

Some other have reported the one-pot synthesis of 1,4-DHP with 3-component (aldehyde,alkylacetoacetate,ammonia) by refluxing with methanol gives good yield**(scheme-2**)[18].



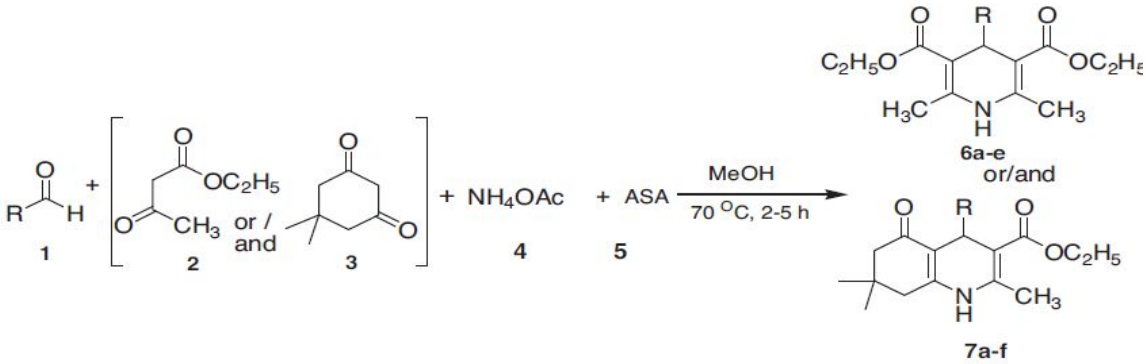
Scheme-2

An efficient one- pot synthesis of polyhydroquinolines by reaction of aldehyde , ethylacetoacetate, dimedone, ammonium acetate, in presence of the MCM-41 as catalyst by using grinding method have been reported(scheme-3)[19].



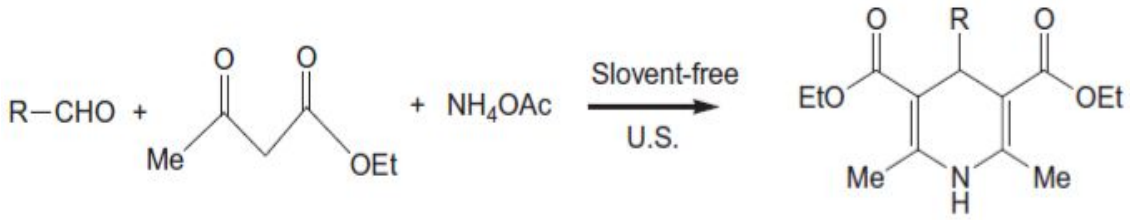
Scheme-3

Some other authours have reported the preparation of 1,4-dihydropyridines using catalyst alumina sulphuric acid by condensing aldehydes, 1,3-dicarbonyl compounds, and ammonium acetate(scheme-4)[20].



Scheme-4

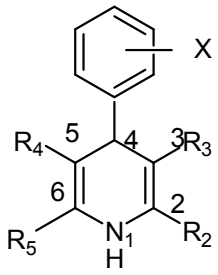
A new synthesis have reportd for 1,4-DHP under ultrasound irridation with out solvent and catalyst and get higher yield at shorter time(scheme-5)[21].



Scheme-5

Structure Activity Relationship(SAR):

The detail study on the structural features of 1,4-DHP as lead compound have been described[22,23].



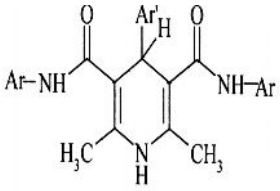
Structure of 1, 4-Dihydropyridine.

1. The 1,4 DHP ring is essential for activity.
2. The unsaturation of the basic ring will decrease the activity.
3. Substitution at N_1 Position or the oxidized (Piperidine) or reduced (pyridine) ring system greatly decreases or abolishes the activity .
4. The 2,6 –Substituents of 1,4-DHP rimd should be Lower, alkyl, and one NH_2 group is tolerated.
5. Ester groups at C_3 and C_5 position shows optimum activity .The presence of electron withdrawing groups shows decreased antagonistic activity and may even shows agonist activity .
   EX: Isradipine
   Removal or replacement by COMe orCN greatly reduces activity
6. Ester substitution larger than COOMe greatly maintain or even increases the activity because of bulk tolerance in the site of 1,4-DHP
   Ex: Amlodipine. C_3-methyl, c_5 ethyl.
7. Ester at C3 andC5 are non identical ,the C4 carbon becomes chiral and stereo selectivity between the enantiomers is observed.
8. Substitution of phenyl ring at C_4 position has optimum activity.
9. Substitution of small non planar alkyl or cyclo alkyl group shows decreased activity .
10. Compound with ortho or meta substitution posses optimum activity,while unsubstituted or a para substitution show decrease in activity according to their electronic and steric effect.

Pharmacological Activities:

Antituberculosis activity:

Antituberculosis activity of some 4-substituted-2,6-dimethyl-3,5-bis-N-(heteroaryl)-carbamoyl-1,4-dihydropyridines have studied and the compound with 2-Pyridyl at 4th position and 6-methylpyridin-2-yl at 3 & 5th position 1a (IC_{50} = 12.5 µg/mL) is more potent than control pyrazinamide (IC_{50} = 32 µg/mL) and 2-Imidazolyl at 4th position and 5-chloropyridin-2-yl at 3 & 5th position 1b (IC50= 25 lg/mL) exhibit good activity and almost equipotent to pyrazinamide (IC_{50} = 32 µg/mL) [24].(scheme:6)



	Ar	Ar ‘
1a	5-Chloropyridin-2-yl	2-imidazolyl
1b	6-Methylpyridin-2-yl	2-Pyridyl

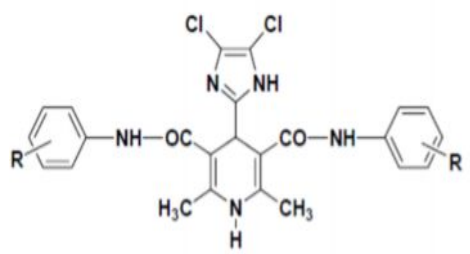
Scheme-6

A series of symmetrical , asymmetrical & unsubstituted 1,4-dihydropyridines have studied for antituberculosis activity (against mycobacterium tuberculosis H_{37} strians.The highest activity was observed for the 4-(4-(Dimethylamino)phenyl)-1,4-dihydro-N^3,N^5-bis(2-methoxyphenyl)- 2,6-dimethylpyridine-3,5-dicarboxamide shows 93% & 4-(2-Hydroxyphenyl)- 1,4-dihydro- N^3,N^5-bis(3-nitro-phenyl)- 2,6-dimethylpyridine-3,5-dicarboxamide shows 92% of inhibition because of the presence of 2-methoxy and 3-nitro groups on the carbonyl moiety and 4 $N(CH_3)_2$ and 2-OH on the aryl ring. The other compounds like 4-(4-Chlorophenyl)-1,4-dihydro-N^3,N^5-bis(3-chloro-4-fluorophenyl)-2,6-dimethylpyridine-3,5-dicarboxamide shows 88% of inhibition because of 3-chloro and 4-fluro substitiution in the carbmoyl sidechian and m-chloro on phenyl ring and 4-(4-Chlorophenyl)-1,4-dihydro-N^3,N^5-bis(3-chloro-phenyl)-2,6-dimethylpyridine

3,5dicarboxamide shows 85% because of 2-chloro substitution in carbomoyl side chain 4-chloro in phenyl ring[25].similar studies have been performed for series of 4-Substituted Phenyl-2,6-dimethyl-3,5-Bis-N-(substituted Phenyl)carbamoyl-1,4-dihydropyridines. The compounds substituted with NO2 group or 2-Cl or OCH_3 at 3 and 4 position of phenyl carbamoyl ring exhibit >90% of inhibition against H_{37} RV in comparision with rifampicin **[**26].

Some of the novel 4-substituted imidazolyl-2,6-dimethyl-N^3,N^5-bisaryl-1,4-dihydropyridine-3,5-dicarboxamides have studied for the antituberculosis activity against M.tuberculosis H_{37}RV strain .The compound 4-(1-Benzyl-2-(methylthio)-1H-imidazol-5-yl)-2,6-dimethyl-N^3,N^5-bis(4-chlorophenyl) -1,4dihydropyridine-3,5-dicarboxamide is as potent as rifampicin and 4-(1-Benzyl-2-(methylthio)-1H-imidazol-5-yl)-2,6-dimethyl-N^3,N^5-bis(pyridin-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide shows potent activity (MIC-2µg/ml) [27].

In the same way a new series of N^3,N^5-diaryl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamides have screened for the antituberculosis activity against m.tuberculosis (H_{37}Rv) and the compound with 3-chlorophenyl group at 3,5 dicarbox-amide position was the most active compound & the compounds with 3-Nitrophenyl and 4-nitrophenyl compound are relatively active compared to rifampicin [28](scheme-7).



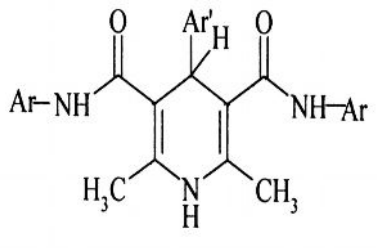
	R
7a.	3-chloro
7b.	3-nitro
7c.	4-nitro

Scheme-7

A series of N^3, N^5-Diaryl-4-(5-arylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide have tested for same activity and the compound N^3,N^5-bis-(4-methoxy-2-nitrophenyl)-2,6-dimethyl-4-(5-phenylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide exhibit good activity [29].

Antimicrobial activity :

The antimicrobial activity was performed against various bacteria, fungi, other microorganism by paper disc method & cup and plate method. Agar was used to culture the test bacteria and Potato Dextrose Agar was used to culture fungi. The microbial culture were grown at 37°C for 8 hours and then appropriately diluted with sterile 0.8% saline solution.The concentration of test drugs was kept 200 µg/ml in DMF. Standard drugs Novobiocine, Gentamycin, Kanamycin, Amikacin (for antibacterial) and Ampicilline (for antifungal) were used for comparison. The Antimicrobial activity was evaluated by measuring the zone of growth inhibition around disc of test organism. A new series 4-substituted-2,6-dimethyl-3,5-bis-N-(heteroaryl)-carbamoyl-1,4-dihydropyridines have been screened for the antibacterial activity gram +ve bacteria (Bacillus subtilis and Staphylococcus aureus) and gram – ve bacteria (Escherichia coli and Proteus vulgaris). 4-(2-Pyridyl)-2,6-dimethyl-3,5-bis-N-(6-methylpyridin-2-yl)-carbamoyl-1,4-dihydropyridine(8a) exhibit almost equal activity to streptomycin against gram negative bacteria and the compound 4-(2-Imidazolyl)-2,6-dimethyl-3,5-bis-N-(2-methyl-4-oxo-3H-quinazolin-3-yl)-carbamoyl-1,4-dihydropyridine (8b) exhibit more potent activity against Bacillus subtilis **(scheme -8)[**24].

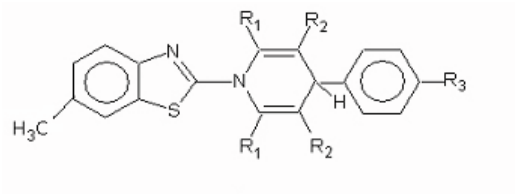


	Ar	**Ar**
2a.	6-Methylpyridin-2-yl	2-Pyridyl
2b.	2-Methyl-4-oxo-3H-quinazolin-3-yl	2-Imidazolyl

Scheme:8

Some other 4-substituted 3-(4,4-dimcthyloxazolin-2-yl)-I,4-dihydropyridylacetic acids derivatives have been screened against Gram-Prositive bacteria and only few analogs shows moderate antibacterial activity [30].

A series of N-(6-methylbenzothiazolyl)- 2 , 3 , 5 , 6-tetrasubstituted-4-(aryl)-1,4-dihydropyridines have been evaluated for antibacterial , antifungal ,and Entomological activity . The compounds N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-dimethyl-4-(m-nitrophenyl)-1,4-dihydropyridine 9a , N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-diethoxy-4-(m-nitrophenyl)-1,4 dihydropyridine 9b, N-(6-methylbenzothiazolyl)-3,5-diacetyl-2,6-dimethyl-4-(m-nitrophenyl)-1,4-dihydropyridine 9c exhibit highest activity againt various bacterial strains like lactobacillus sps, Pseudomonas aeruginosa, Micrococcus lutius and Kocuria rosea when compared to standard drug like kanamycin ,gentamycin ,novobiocin.. and also shows potent activity against fungal sps like Aspergillus niger and Aspergillus candidus compared to standard Ampicillin drug. The other compounds like N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-dimethy l - 4 - (p - m e t hoxypheny l) - 1 , 4 –dihydropyridine 9d ,N-(6-methylbenzothiazolyl)-3,5-diacetyl-2,6-dimethyl-4-(p-methoxyphenyl)-1,4-dihydropyridine 9e, N-(6-Methyl-benzothiazolyl)-3,5-dicarbethoxy-2 , 6 - d iethox y - 4 - (p - m e t hoxypheny l) - 1 , 4 –dihydropyridine 9f ,N-(6-methylbenzothiazolyl)-3,5-diacetyl-2,6-dimethyl-4-(m-nitrophenyl)-1,4-dihydropyridine 9g exhibit highest antifeedent activity fourth instars larvae of spodoptera litura .The compoundN-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2 , 6 - diethoxy - 4 - (p - hydroxy phenyl) - 1 , 4-dihydropyridine shows highest acaricidal activity against Tetranychus urticae of mites **(scheme-9) [**31].



Scheme-9

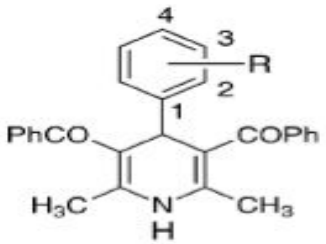
	R_1	R_2	R_3
9a.	Me	O=COEt	m-NO_2
9b.	Oet	O=COEt	m-NO_2
9c.	Me	COMe	m-NO_2
9d.	Me	O=COEt	p-OMe
9e	Me	COMe	p-OMe
9f	Me	COMe	p-OH
9g.	Me	COMe	m-NO2

Some other scientist have studied the antifungal activity of dihydropyridine derivatives against aspergillus fumigates ,candida albicans .The compound diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridin-3,5-dicarboxylate exhibit significant and appreciable activity against A.fumigatus and the compound dimethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridin-3,5-dicarboxylate significant activity against A.fumigatus in disc diffusion, microbroth dilution and percent spore germination inhibition assay but these are less potent when compared to standard drug Amphotericin B [32]. The compound 2.6-dimethyl-4-phenyl-pyridine-3,5-dicarboxylic acid diethylester has been isolated from natural source jatropha elliptica belongs to family euphorbiacea.This compound have screened for antibacterial activity and it shows enhancing antibacterial activity against Staphylococcus aureus possessing the MsrA and NorA resistance efflux mechanisms [29]. Similar studies have performed for 4-[5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl]-1,4-dihydropyridines in various bacterial strains that is Proteaus valgaris , P.aeurginosia , E.coli. The compound 4-[5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3-ethyl-5-methyl dicarboxylate shows good activity with reference to gentamycin[33].

Anticancer activity:

The anticancer activity of 4-substituted-2,6-dimethyl-3,5-bis-N-(heteroaryl)-carbamoyl-1,4-dihydropyridines have been studied and the compound 4-Chlorophenyl at c_4 position and 2-methyl-4-oxo-3H-quinazolin-3-yl substitution at c_3 & c_5 position of 1,4-dihydropyridine have shown the equipotent activity compared to methotrexate drug against MCF-7 and HT-29 cell lines [24].

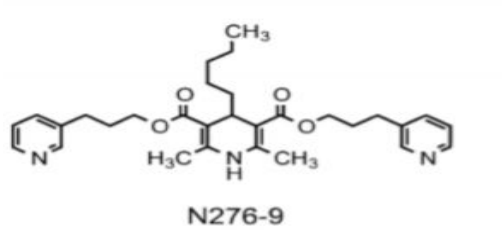
A new 3,5-Dibenzoyl-4-(3-phenoxyphenyl)-1,4-dihydro-2,6-dimethylpyridine (DP-7) ,which is a novel multidrug resistance inhibitor, and it is investigated in lagendorff-perfused rat heart and compared with that of nifedipine .The result showed that DP7 is a lead compound foe the design of novel ,safe ,potent MDR chemosensitizer [34]. Other authours have studied the substituted 4-phenyl-3,5-dibenzoyl-1,4-dihydropyridines derivatives for the cytotoxic activity and MDR-reversing activity .The results showed that the compounds with 2'-trifluoromethylphenyl 10a, 2' -chlorophenyl (IC_{50}=7.0µm) 10b,3 -chlorophenyl (IC_{50}=7.0µm) 10c at c_4 position, have shown the highest cytotoxic activity against HSC-2 cell lines. The compound 10c also shows the high MDR-modulating activity and tumour –specific cytotoxicity, so it is recommended as new drug for cancer treatment **(scheme-10)** [35].



	R
10a	2-cf3
10b	2-cl
10c	3-cl

Scheme-10

The antitumour activity of several newly synthesized 1,4-dihydropyridines have been screened by using mice carrying P388 leukemia cells invivo. The results shows that the compound N276-9 , N276-16 was found to be the active compound to overcome the multidrug resistance because of the presence of 3-pyridylpropyrlesters (scheme-11)[36].



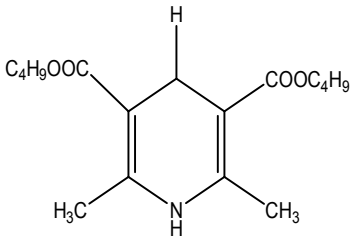
N276-9

Scheme-11

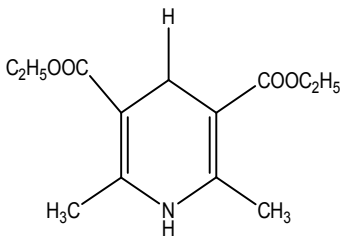
Some of the scientists have studied the β-carbonyl-1, 4-dihydropyridine series (AV-153 or sodium 3, 5-bis-ethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate) with high genoprotective activity in order to determine DNA repair and apoptosis. The results indicate that AV-153 have high efficiency in stimulating DNA repair and also modulate apoptosis in human cells .In this peripheral blood lymphocytes of healthy donors are used instead of cell lines [37]. The compound 2.6-dimethyl-4-phenyl-pyridine-3,5-dicarboxylic acid diethyl ester has been isolated from natural source jatropha elliptica belongs to family euphorbiacea.This compound have screened for cancer activity and it shows enhancing anticancer activity[38].

Antioxidant activity:

The antioxidant activity of a series of 2,6-dimethyl-3,5-dialkoxycarbonyl-1,4-dihydropyridines possessing various side chain length alkyls (CH_3 - $C_{16}H_{33}$) in ester moiety were evaluated in transition metal-ion catalysed liposome peroxidation .The compounds 2,6-dimethyl-3,5-diethyloxycarbonyl-1,4-dihydropyridines 12a and 2,6-dimethyl-3,5-dibutyloxycarbonyl-1,4-dihydropyridines 12b exhibit high activity when compare with antioxidant activity of Trolox and probucol (scheme-12)[39].



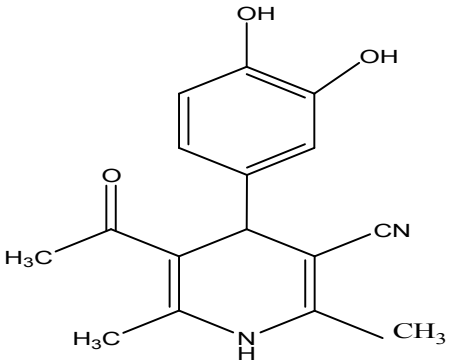
12b



12a

Scheme-12

Similar studies have been studied in a series of novel 5-acetyl-2-alkylthio-4-aryl-6-methyl-1,4-dihydropyridine-3-carboxylic acid nitriles .The results conclude that the compound 3,4-dihydrophenyl at 4^{th} position is the most active compound compared with the standard antioxidant activity of trolox because of the presence of dihydroxy phenyl substitution at 4-position (scheme-13)[40].



Scheme-13

Another scientists have studied the antioxidant activity of N-aryl-1, 4-dihydropyridines. The compounds 2-Methyl-1,4-diphenyl-1,4-dihydro-pyridine-3-carboxylic acid tert-butyl ester and 1-(4-Chlorophenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylic acid tert-butyl ester shows significant antioxidant activity because of the presence of teritiary buyl ester group[41].

Cardiovascular activity:

The antihypertensive activity of new 1,4-dihydropyridine derivatives containing nitrooxyalkylester moieties at the 3- and 5- position are studied and the compound 2-nitrooxypropyl 3-nitrooxypropyl -2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (CD-349) was more potent antihypertensive activity when campared to nifedipine[42].The same activity is done on some new nitroxyalkyl 1,4-dihydropyridine derivatives in rat Model of Two-Kidney ,One-Clip Hypertension and the results showed that the compound containing two nitroxy groups had poor effect of decreasing in Men Arterial pressure compared to nifedipine [43].

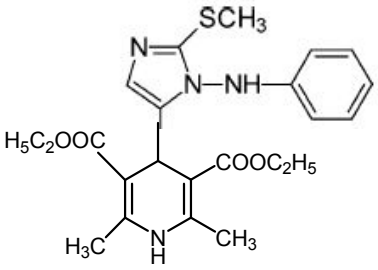
A series of novel 4-[1-(4-x-benzyl)-5-imidazolyl] dihydropyridines have been screened for the antihypertensive activity in desoxycortisone acetate induced in hypertension in rats. The compound 1, 4 – dihydro – 2 , 6 – dimethyl – 4 - [1-(4-fluro-benzyl)-5-imidazolyl] – 3 , 5-pyridinedicarboxylate shows most active activity than that of amlodipine because of presence of electron withdrawing groups at Para position of benzyl ring [44]. Some authours have reported the antihypertensive effect 3-(4-Allyl-l-piperazinyl)-2, 2-dimethylpropyl methyl 1, 4-dihydro-2, 6-dimethyl-4-(3-nitrophenyl)-3, 5-pyridinedicarboxylate dihydrochloride (NKY- 722) which is a new water- soluble 1,4-dihydropyridine derivative produces a dose dependent activity in conscious spontaneously hypertensive rats (SHR). After administration of NKY-722, at a dose of 3 mg/kg, the peak decrease in blood pressure recorded was 50±8mmHg (n=5),while the nifedipine was only 18±3mmHg (n=5) and it shows prolonged action 8hr at 1 and 3 mg/kg [45].

Similar activities are performed for stereo isomers of 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine-dicarboxylic acid methyl 1-(phenylmethyl)-3-piperidinyl ester which is a highly potent calcium antagonist, the compounds are separated in to stereo and optical isomers and their antihypertensive activity are screened , the results showed the alpha isomer is more potent than beta isomer , the hypotensive effect of (+)-alpha, namely (S)-(S)-1, was 30 to 100 times stronger than that of (-)-alpha in intravenously administered spontaneously hypertensive rats [46].

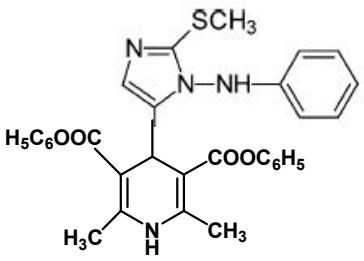
In the same way antihypertensive activity of novel 1,4-dihydropyridine derivatives bearing 3-[4-(substituted amino) phenylalkyl]ester derivatives have been studied . The results showed that most compound are potent and a longer duration of action . 2-[4-(4-benzhydryl -1-piperazinyl) phenyl]ethyl methyl 1,4-dihydro -2,6-dimethyl -4-(3-nitrophenyl)-3,5-pyridinedicarboxylate ,its analogs 4-(4-cyno-2-pyridyl) , 3-[4-(4-benzhydryl -1-piperazinyl)phenyl]propyl ester analogue , 2-[4-(4-benhydryl-1- piperidinyl)phenyl]ethyl ester analogue , 2-[4-(1-benzhydryl-4-piperidinyl)phenyl]ethyl ester analogue shows good activity and these are used for further pharmacological investigations[47]. A series of new 1,4-dihydropyridne derivatives with 4-(disubstituted phenyl and an amino ethyl ester or an amino -2,2-dimethyl –propyl ester groups are evaluated for antihypertensive activity

in normotensive rats and spontaneously hypertensive rats. Most of the compounds showed a more potent activity and longer duration of action than nifedipine . The compound TC -81 showed highly potent and long lasting activity [48]. A novel 2-amino-1,4-dihydropyridine derivatives with nitroxy-alkoxycarbonyl groups at 3-and /or 5-position were screened for antihypertensive activity in spontaneously hypertensive rats.the compound with tertiary amino group at either side of an ester chain shows potent and prolonged duration of action [49]. Symmetrical and unsymmetrical substitution of 1,4-dihydropyridine derivatives have studied for calcium channel blocking activity i.e., antihypertensive activity .the compound with 4-trimethoxy phenyl, 4- [3-methoxy,4-benzyloxy phenyl], 4-[3-methoxy,4-hydroxy phenyl] at c_4 position have shown the good activity compared with standard felodipine [50]
Calcium antagonistic activity of 1,4-dihydro-2,6-dimethyl-4-(5-phenylisoxazol-3-yl) pyridine-3,5-dicarboxylate were studied using the high k+ concentration of guinea–pig ileum longitudinal smooth muscle assay . The results indicates that synthesized compounds exhibit less potent activity (10^{-5}-10^{-7}) compared to nifedipine (IC_{50}=1.10±0.40 X 10^{-8}) [51]. Similar activites have been studied in lipophilic nitroimidazolyl-1,4-dihydropyridines . It states that the lipophilic aromatic substitution at the c-6 position of dihydropyridine ring are supposed to improve penetration in to the organs ,but substitution of aromatic ring at both c-2 and c-6 position of DHP by replacing bith methyl groups shows lower calcium antagonistic acitivity , due to increased steric hindrance. It also showed that the compound 5-ethyl-3-n-propyl-1,4-dihyro-2-methyl-6-phenyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5pyridine dicarboxylate , 5-ethyl-3-n-butyl -1,4-dihyro-2-methyl-6-phenyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5pyridine Dicarboxylate, 5-ethyl-3-isobutyl-1,4-dihyro-2-methyl-6-phenyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5pyridine dicarboxylate exhibit higher activity , due to increased alkyl chain at c-3-position(scheme-10) [52]. Similar activity is studied in Isobutyl Methyl 2,6-Dimethyl-4-(substituted phenyl)-1,4-dihydropyridine-3,5-dicarboxylate(Nisoldipine) Series , it also studied the radio ligand bioassay.
The results showed that the compounds are approximately 10-fold more active in the radio ligand bioassay than the pharmacological assay , and also the pharmacological action increases with increasing ring planarity [53].

Some of the authors have studied the 1,4-dihydropyridines containing phenylaminoimidazolyl substituents for their calcium antagonist activity . some of the compounds with Diethyl 14a and diphenyl 14b at 3 & 5th carbon and 2-methylthio-1-phenylamino-5-imidazolyl at 4th carbon were more active than nifedipine It concluded that the increasing the alkyl ester chain at c-3 and c-5 position with more than two alkyl groups decrease the activity (scheme-14)[54].



14a

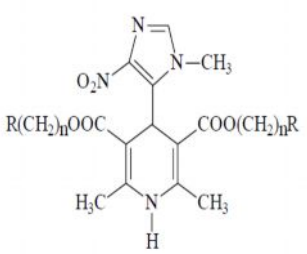


14b

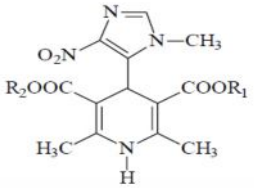
Scheme-14

Anticonvulsant activity :

A new series of 1,4-dihydropyridines have been screened for the anticonvulsant activity by Maximal Electroshock Induced convulsions in Rats, PTZ induced convulsions in Rats, and Strychnine induced Convulsions in Rats methods. All the synthesised compounds have been found to exhibit good anticonvulsant activity [55].
Anticonvulsant activity of Alkyl, cycloalkyl and aryl alkyl ester analogues of nifedipine in which the ortho-nitro phenyl group at position 4 is replaced by 1-methyl-4-nitro-5-imidazolyl substituent have seen determined against pentylenetetrazole-induced convulsions in mice. The results showed that most of the compound were more potent than nifedipine [56].



No.	R	N
a	CH_3	0
b	CH3	1
c	C_6H_5	1
d	C_6H_5	2

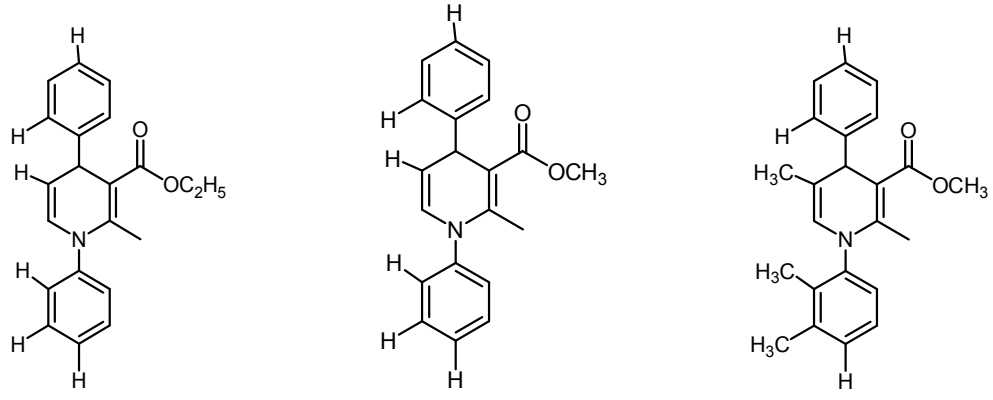


NO	R_1	R_2
a	$CH_2CH_2CH_2C_6H_5$	CH_3
b	$CH_2CH_2CH_2C_6H_5$	CH_2CH_3
c	$CH_2C_6H_{11}$(Cyclohexyl)	CH_3
d	$CH_2CH_2C_6H_{11}$(Cyclohexyl)	CH_3

Other activities:

Antidyslipidemic activity:

The antidyslipidemic activity of N-aryl-1,4-dihydropyridines have been studied and the compounds 2-Methyl-1,4-diphenyl-1,4-dihydro-pyridine-3-carboxylicacid ethyl ester 15a, 2-Methyl-1,4-diphenyl-1,4-dihydro-pyridine-3-carboxylic acid methyl ester 15b , and 1-(2,3-Dimethyl-phenyl)-2,5-dimethyl-4-phenyl-1,4-dihydro-pyridine-3-carboxylic acid methyl ester have exhibit the good lipid and TG lowering activity (scheme-15)[41].

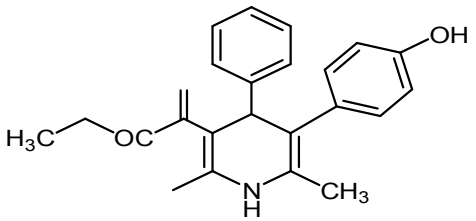


15a **15b** **15c**

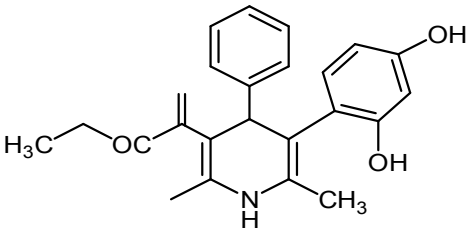
Scheme-15

Analgesic & Anti-inflammatory activity:

Some other 1,4-dihydropyridine derivatives were found to posses analgesic and antiinflammatory activity and the compounds have almost equipotent activity compared to piroxicam at a dose of 70mg/kg body wt(scheme-16)[57].



16a

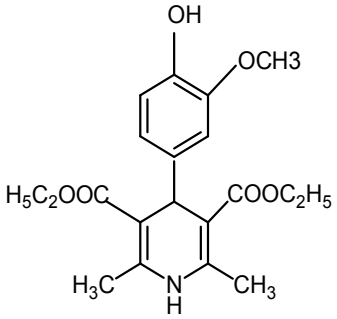


16b

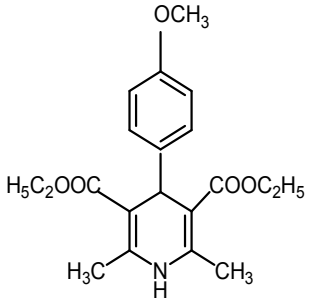
Scheme-16

Antiulcer activity:

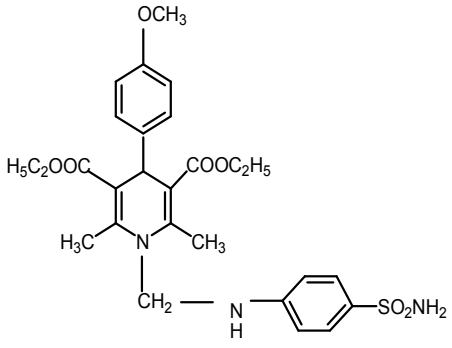
A novel 1,4-dihydropyridines and their mannich bases with sulfanilamide are studied for antiulcer activity and the compound containing methoxy substitution at c-4 position shows good antiulcer activity(scheme-17)[58].



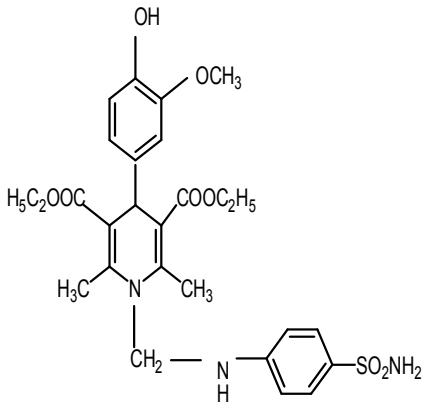
17a



17b



17c



17d

Scheme-17

Conclusion:

The present review concludes that 1,4-DHP as a Multifunctional potent lead Molecule, which has various feasible positions for substitution and exhibit several pharmacological activities such as calcium channel antagonist activity, antihypertensive activity, vasodilator activity, antianginal activity and apart from CVS activities it also exhibit other pharmacological activities such as antitubercular activity ,antibacterial activity, anti-inflammatory activity, anticonvulsant activity,antiulcer activity and soon.

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