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Current development on catalytic synthesis and pharmacological applications of 1,4-dihydropyridines

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ABSTRACT

1,4-Dihydropyridines (1,4-DHPs) are recognized as one of the most versatile pharmacophores present as central core in many pharmaceuticals. Low yield and harsh reaction conditions prompted the researchers for the development of new environmental-friendly methods for the synthesis of 1,4-DHPs. This review explored the development of various green chemistry approaches using new catalysts developed for constructing novel 1,4-dihydropyridine and its derivatives. The present review also encompasses the synthesis of some novel 1, 4-DHPs derivatives with novel pharmacological actions. We have restricted our review of synthesis and pharmacological actions of 1,4-DHPs from 2006 onwards.

***Keywords**: 1,4-Dihydropyridines; Green Chemistry; Pharmacological actions; Synthesis.*

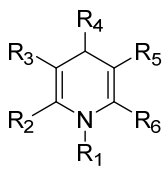
1. Introduction

1,4-Dihydropyridines (1,4-DHPs) (1) comprise a fundamental class of heterocyclic compounds that continue to be at the forefront of research efforts due to its significant biological activities and interesting chemical features. It is one of the most versatile pharmacophores in medicinal chemistry since large number of natural products and drugs contain this heterocyclic unit. Numerous biochemical properties of dihydropyridines have been investigated since it discovery in 1930s when it was found that this nucleus has important role in biological system as "hydrogen transferring coenzyme" [1].

The basic skeleton of 1,4-DHP is a double unsaturated six membered cyclic systems with one heteroatom and two double bonds. The presence of double bond and the lone pair of electrons on the N-atom make the 1,4-DHP skeleton prone to react with electrophilic reagents. The lone pair on N-atom affords basicity to the compounds containing this skeleton.

The potency and activity of 1, 4-DHP is connected to its structure. It is possible that the basicity of the N-atom in 1, 4-DHP is critical to the function of 1,4-DHP based drugs in their ability to bind to calcium channels [2].

Thus, 1,4-DHPs have attracted the attention of several chemists and pharmacologists. As a result of it, several derivatives of 1,4-DHP have been synthesized and screened for their effectiveness. Most of them vary in their nature of substituents at 3, 4 and 5 positions. Further, studies and investigations by several scientists have reviewed these 1, 4-dihydropyridine derivatives which have become drugs of medicinal importance [3-6].



1,4-dihydropyridine
(1)

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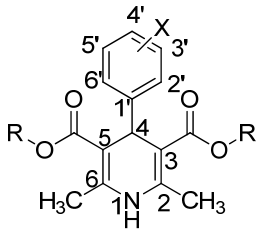
1.1. SAR of 1, 4-Dihydropyridines



(2)

For the optimal activities, the following structure requirements are desired which are summarized as [4-12]:

a) 1, 4-DHP ring is very important as the activity is abolished by removing pyridine ring by oxidation.

b) To optimize the activity, NH group of 1,4-DHP ring must be unsubstituted. Activity is abolishing or decrease by substituting N1 position.

c) The lower alkyl group at 2 and 6-position of pyridine ring optimizes the activity

d) The 3 and 6-positions of pyridine ring should be substituted with ester groups for optimum activity.

e) Substitution of an aryl group at 4-position increases activity.

f) The substituents and its positions are very critical in the phenyl ring. Decrease in activity observed with *para* substitution whereas *ortho* or *meta* substituents generally increases activity due to electronic and steric effects. An increase in substituent size decreases activity especially at the *para* and *meta* positions.

g) Some 1,4-DHPs having diphenylpropyl and diphenylmethyl-azetidine groups at C-4 of the 1,4-dihydropyridine ring showed promising activity against *Leishmania* and *Trypanosoma* parasites.

h) Substitution by carboxylate ester with carboxamide group decreases calcium channel blocking activity, but at the same time provides them significant antimicrobial properties.

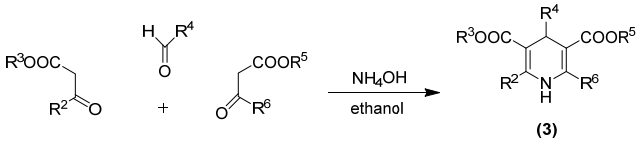
i) Potent antimicrobial activity was observed with 1,4-DHPs having diethyl carbamoyl and ester substituents at 3 and 5 positions and substituted aryl on 4th position of pyridine ring.

j) 1,4-dihydropyridine having dicarbamoyl groups at 3 and 5 positions have considerable activity against *M. tuberculosis* H37Rv and found to be an effective anti-tubercular agent. An important anti-tubercular activity was also demonstrated for unsymmetrical 1,4-dihydropyridines alkyl or aryl esters substituted in C-3 and containing a diethyl carbamoyl group at the C-5.

k) A new series of thiosemicarbazide substituted 1,4-DHPs were developed as anticoagulant agents.

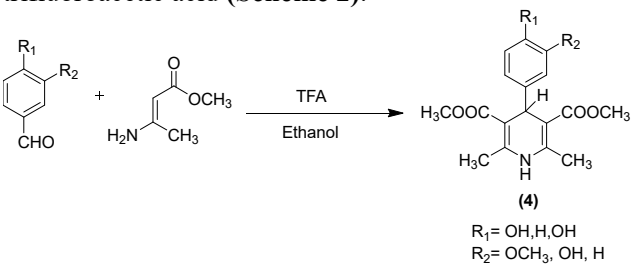
1.2. Catalytic synthesis of dihydropyridines

Dihydropyridine chemistry began in 1882 when Arthur Hantzsch published the synthesis of 1,4-dihydropyridines **(3)** from condensation reaction of an aldehyde, a β-keto ester and aqueous ammonium hydroxide in ethanol **(Scheme 1)** [13].



Scheme 1.

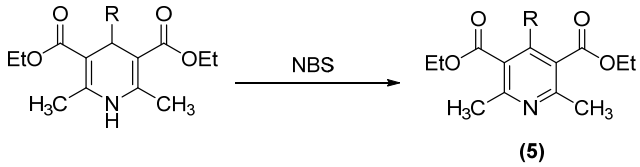
Low yield and harsh reaction conditions encouraged the researchers for the development of new environmental-friendly technology for the synthesis of 1,4-DHPs and its derivatives. We have restricted our study for the synthesis of 1,4-DHPs from 2006 onwards. Jindal *et al.*, 2006, synthesized a new series of 4-aryl-1,4-dihydropyridines **(4)** using modified Hantzsch condensation of various aldehydes with methyl 3-aminocrotonate using catalytic amount of trifluoroacetic acid **(Scheme 2)**.



Scheme 2.

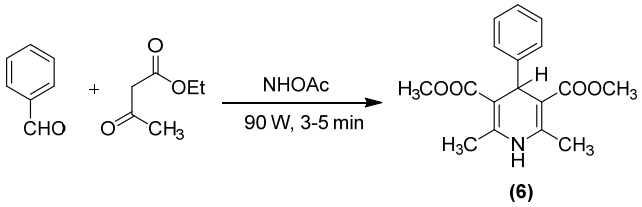
The compounds were subsequently alkylated with various hydrochlorides of dialkylaminoalkyl chlorides, possessing potential calcium channel blocking activity along with good vasodilator activity [14].

Nagrajan *et al.*, 2006, described a new faster method for the oxidation of Hantzsch 1, 4-dihydropyridine to give the aromatic pyridine derivatives **(5)** using easily available *N*-bromosuccinamide (NBS) in methanol at ambient temperature within five minutes & provided good yields **(Scheme 3)** [15].



Scheme 3.

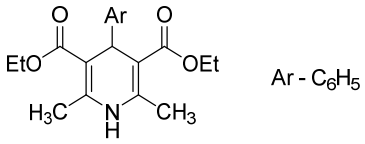
Kotharkar and Shinde, 2006, introduced the eco-friendly, cost effective and solvent free synthesis of 1,4- Dihydropyridines **(6)** by condensing ethyl acetoacetate, aldehyde and ammonium acetate under domestic microwave oven **(Scheme 4)** [16].



(6)

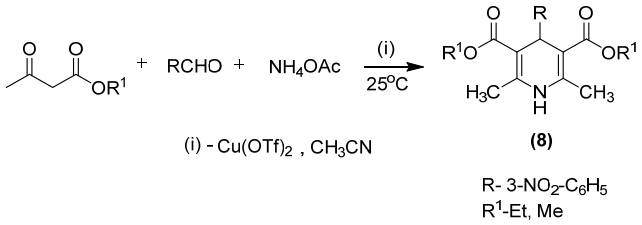
Scheme 4.

Chatterjee *et al.*, 2007, reported the synthesis of 1,4-dihydropyridine derivatives **(7)** using silica gel as catalyst in three component coupling reactions under ultrasonic irradiation. This method is cheap and low energy consumption and high yield [17].



(7)

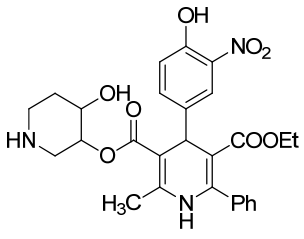
Paraskar and Sudalai, 2007, reported the synthesis of Hantzsch 1,4-dihydropyridines **(8)** by modified Hantzsch method using $Cu(OTf)_2$ as catalyst in CH_3CN at ambient temperature **(Scheme 5)** [18].



(8)

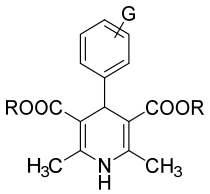
Scheme 5.

Breitenbucher *et al.*, 2007, reported the novel method for synthesis of 1,4-dihydropyridines **(9)** free from any side products. They used **s**olid support for the Hantzsch synthesis in which unwanted reactive impurities were removed from the desired products, by selective cleavage from solid [19].



(9)

Gomez-Pliego *et al.*, 2007, produced Hantzsch esters in a water-bound biphasic medium, using infrared irradiations as the activating source. The reaction conditions were simple and the corresponding yields were good **(10,11)**. This is a contribution of the green chemistry protocol [20].



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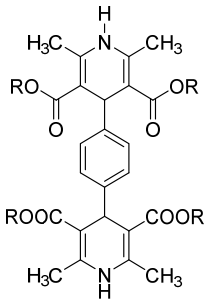
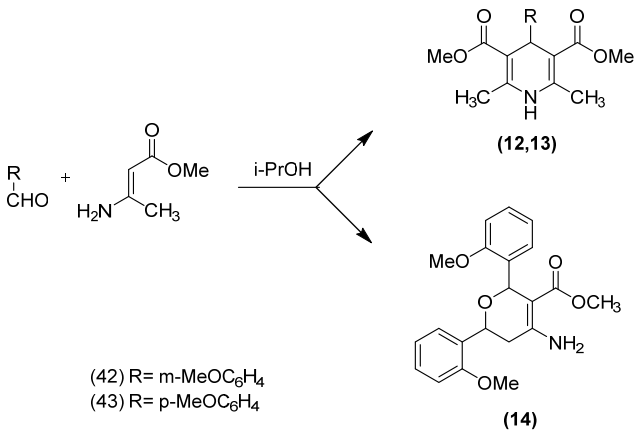


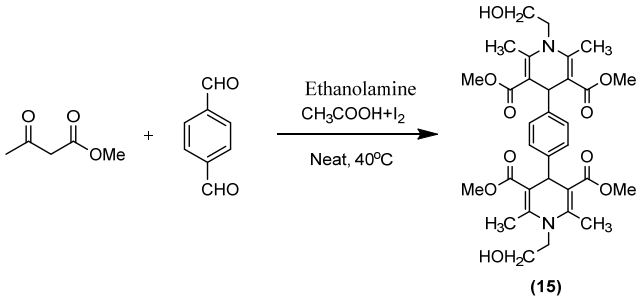
(11)

Litvie and co-workers, 2007 described Hantzsch condensation reaction of two equivalents of methyl-1,3-aminocrotonate with (*m* and *p*)-methoxy benzaldehyde which resulted in formation of the expected products 2,6-dimethyl-3,5-dimethoxy carbonyl 1-4-(*m*-methoxyphenyl)-1,4- dihydropyridine **(12)** and 2,6- dimethyl-3,5- dimethoxycarbonyl 1-4-(*p*-methoxyphenyl)-1,4-dihydropyridine **(13)**, whereas *o*-methoxybenzaldehyde produced 1-amino-2-methoxycarbonyl- 3,5- bis (*o*-methoxyphenyl)- 4- oxa-cyclohexan-1-ene **(14)** (**Scheme 6)** [21].



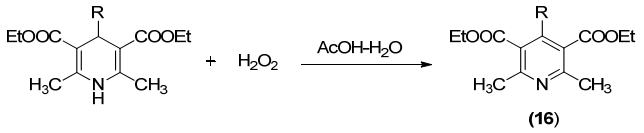
Scheme 6.

Zolfigol *et al.*, 2007, reported the method for the synthesis of novel 1,4-DHP derivatives by substituting pyridine nitrogen. They used the mixture of ethanolamine and acetic acid as ethanolammonium acetate and various aldehydes in the presence of methyl acetoacetate to form *N*-hydroxyethyl 1,4-dihydropyridines **(15)** under mild and solvent free conditions both in the presence or absence of molecular iodine **(Scheme 7)** [22].



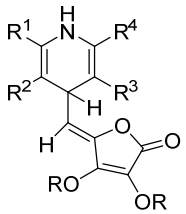
Scheme 7

Chen and Zhang, 2007, reported oxidative aromatization of Hantzsch 1, 4-dihydropyridines **(16)** by aqueous hydrogen peroxide–acetic acid. Hydrogen peroxide had considered being an eco-friendly oxidant because it is relatively non-toxic and easily degradable to non-toxic by-products **(Scheme 8)** [23].



Scheme 8.

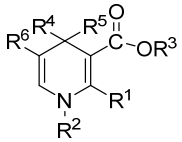
Tripathi *et al*, 2007 in the same year reported a facile synthesis of 4-(butenolide-5-methylidenyl)-1,4-dihydropyridines **(17a-b)** utilizing ascorbic acid in presence of tetrabutyl-ammonium hydrogen sulfate in ethylene glycol [24].



(17 a-b)

	17a	17b
R	CH_3	CH_3
R^1	CH_3	CH_3
R^2	$COOCH_3$	$COCH_3$
R^3	$COOCH_3$	$COCH_3$
R^4	CH_3	CH_3

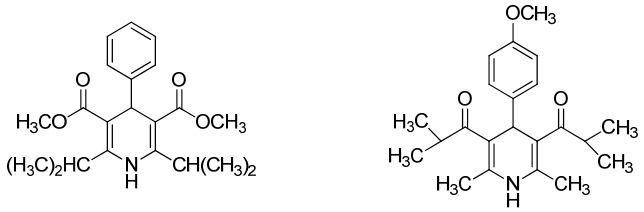
Renaud *et al.,* 2007, described the use of Bronsted acid to catalyze the addition reaction of *β*-enaminoacrylates to *α, β*-unsaturated aldehydes under mild condition leading to substituted dihydropyridines **(18 a-c)** [25].



(18 a-c)

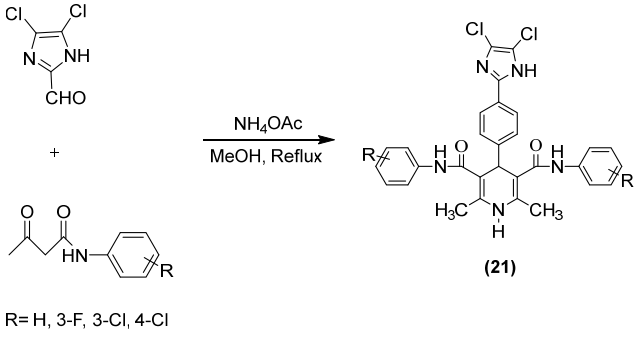
	R^1	R^2	R^3	R^4	R^5	R^6
18a	CH_3	Bn	tBu	CH_3	CH_3	H
18b	CH_3	Bn	Et	CH_3	H	CH_3
18c	Ph	Bn	tBu	Ph	H	H

Akbari *et al.,* 2008, described an efficient and simple one-pot synthesis of some symmetrical **(19)**, unsymmetrical **(20)** and *N*-substituted Hantzsch 1,4-DHPs utilizing molecular iodine as catalyst in ethanol [26].



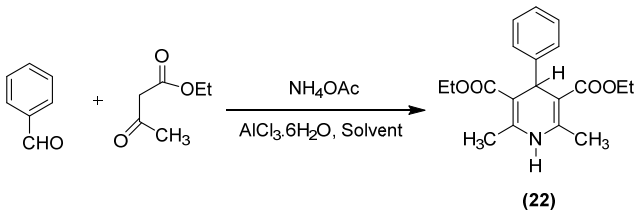
(19) **(20)**

Amini *et al.*, 2008, synthesized new dihydropyridines **(21)** having possible antitubercular activity. They demonstrated that a five-member heterocyclic group with electron withdrawing substituent is an appropriate bioisostere for nitro phenyl group which was described as antitubercular agent **(Scheme 9)** [27].



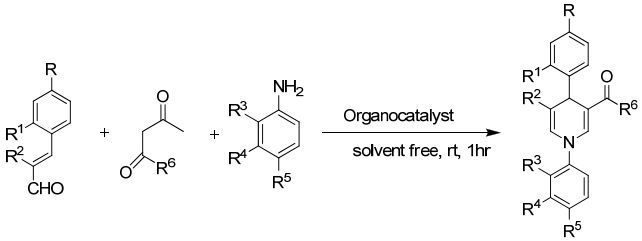
Scheme 9.

Konwar *et al.*, 2008, described the solvent free one-pot four-component synthesis of 1,4-dihydropyridines **(22)** promoted by $AlCl_3.6H_2O$ as a mild and efficient catalyst at 60°C in high yields **(Scheme 10)** [28].



Scheme 10.

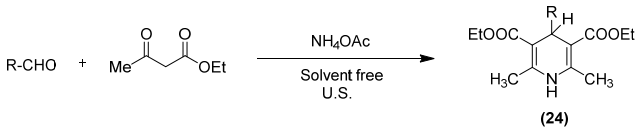
Kumar and Maurya, 2008, described an organocatalyzed one pot three component domino synthesis of 1,4-dihydropyridines **(23 a-d)** under neat conditions **(Scheme 11)** [29].



	R	R^1	R^2	R^3	R^4	R^5	R^6
23a	H	H	H	H	H	H	OC_2H_5
23b	H	HH	H	H	H	CH_3	OC_2H_5
23c	H	H	H	H	H	F	OC_2H_5
23d	H	HH	H	H	H	Cl	OC_2H_5

Scheme 11.

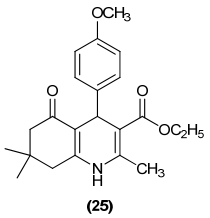
Wang *et al.,* 2008, described the ultrasound irradiation techniques for the synthesis of 1,4-dihydropyridines **(24)** under solvent-free conditions. The reactions were proceeding rapidly under mild condition with high yield without any catalyst **(Scheme 12)** [30].



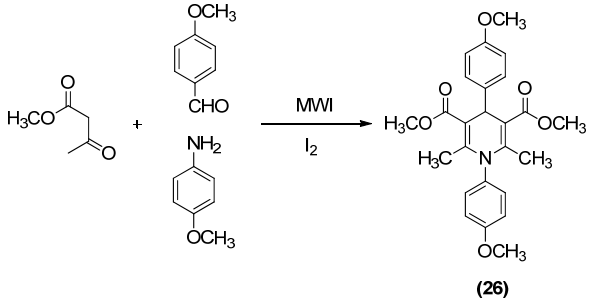
Scheme 12.

Nikpasand *et al.,* 2009, developed a facile and easy protocol for the fast and high yielding synthesis of fused 1,4-dihydropyridines from dimedone in the presence of HY-zeolite as an efficient and reusable heterogeneous catalyst [31].

Arslan and Zengin, 2009, introduced a simple method for the synthesis of 1,4-dihydropyridines **(25)** by using alumina sulfuric acid as a solid acid catalyst, which has many advantages such as easy preparation, non-hazardous, recyclable and environment-friendly catalysts. The method offers high yield with short reaction times [32].



Zhang *et al.*, 2009, synthesized dimethyl-1,4-dihydro-2,6- dimethyl- 1- (4- methylphenyl)- 4- (4- methoxyl phenyl)-pyridine-3, 5-dicarboxylate **(26)** *via* Hantzsch condensation reaction of p-methoxybenzaldehyde, methyl acetoacetate and p-toluidine under microwave irradiation (MWI) in the presence of iodine under solvent-free conditions **(Scheme 13)** [33].

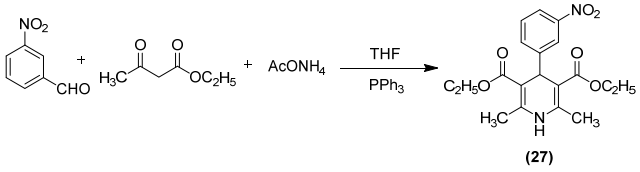


Scheme 13.

Moghaddam *et al.*, 2009, describedthe role of ZnO as reusable and non-toxic catalyst for an efficient of polyhydroquinoline and 1,4-dihydropyridine derivatives.

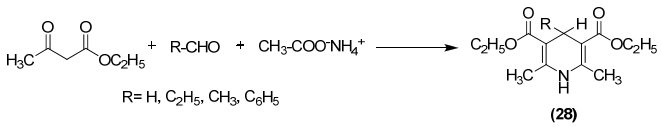
The main benefit of this method was that the products could be obtained in sufficient purity without chromatography [34].

Debache *et al.*, 2009, described the use of triphenylphosphine as a highly efficient catalyst for the synthesis of 4-substituted-1,4-dihydropyridines **(27)** using three component condensation of aldehyde, ethylacetoacetate and ammonium acetate in one pot, providing good to excellent yields **(Scheme 14)** [35].



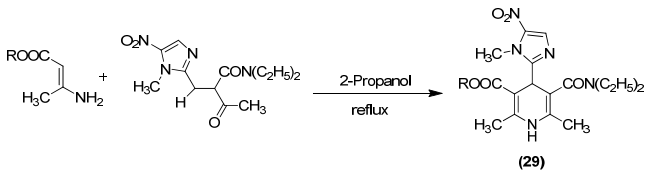
Scheme 14.

Nayak and Reddy, 2009, synthesized different 4-alkyl/aryl-3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydro pyridines **(28)** by conventional and microwave irradiation method **(Scheme 15)** [36].



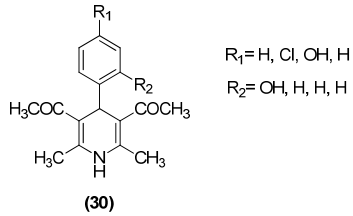
Scheme 15.

Miri *et al.*, 2009, synthesized some new 1,4-dihydropyridines **(29)** comprising different ester substituents and diethyl carbamoyl group which was reported as antitubercular agent **(Scheme 16)** [37].

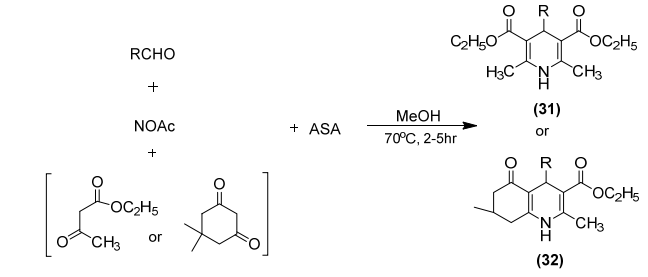


Scheme 16.

Dabholkar and Ansari, 2009, reported that 1,4-dihydropyridines **(30)** were obtained in remarkable yield by using microwave and sonication technique by condensation of aromatic aldehydes with β-diketo derivatives using ammonium acetate [38].

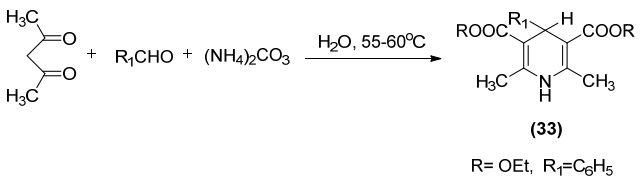


Mustafa *et al.*, 2009, synthesized various 1,4-dihydropyridines **(31-32)** using alumina sulfuric acid (ASA) as an acid catalyst by condensing β-ketoester with ammonium acetate and various aromatic aldehydes in methanol at reflux temperature. ASA was found to be stable catalyst in presence of water which was easily recoverable. **(Scheme 17)** [39].



Scheme 17.

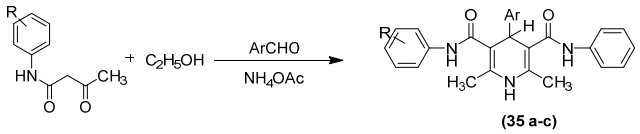
Tamaddon *et al.*, 2010 prepared a variety of known and new 1,4-dihydropyridines **(33)** and 3,4-dihydropyrimidin-2(1*H*)-ones in water *via* Biginelli and Hantzsch reaction using ammonium carbonate as a solid ammonia source and provide high yield products **(Scheme 18)** [40].



Scheme 18.

Kumar *et al.,* 2010, reported that N-aryl-1,4-dihydro pyridines were synthesized *via* iodine catalyzed three component reaction of cinnamaldehydes, anilines and 2-ketoesters in methanol. The synthesized compounds were reported as antidyslipidemic and antioxidants **(Scheme 18)** [41].

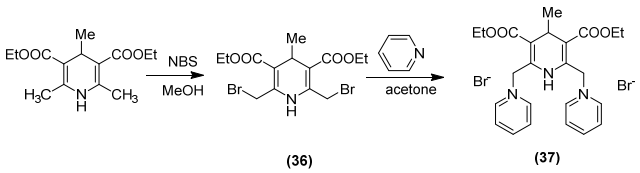
Achaiah *et al.,* 2011, synthesized some new 4-aryl/ heteroaryl-2,6- dimethyl-3,5 -bis-*N*- (aryl)- carbamoyl-1,4- dihydropyridines **(35a-c)** by means of modified Hantzsch condensation reaction of *N*-arylacetoacetamides, aryl or heteroaryl aldehyde and ammonium acetate which were reported as antibacterial and antimycobacterial agents **(Scheme 19)** [42].



	R	Ar
35a	H	2-Furyl
35b	4-CH_3	2-Pyridyl
35c	2-CH_3	2-Thiophenyl

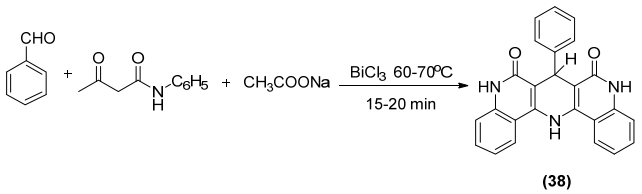
Scheme 19

Petrova *et al.*, 2011, synthesized 1,4-dihydropyridine derivatives **(36)** containing substituents at 2, 6-pyridine carbon. The reaction is initiated with bromination of the methyl groups with *N*-Bromosuccinamide and followed by nucleophilic substitution of bromine by pyridine giving the target compound **37 (Scheme 20)** [43].



Scheme 20.

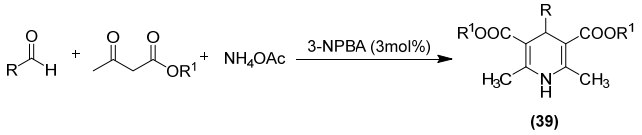
Rao *et al.,* 2012, synthesized 1,4-dihydropyridine derivatives **(38)** using $BiCl_3$ as a Lewis acid catalyst. The $BiCl_3$was found to be good promoter and non-toxic agent for the synthesis of 1, 4-dihydropyridines. The reaction was performed at 60-70°C under neat condition without solvent and 1,4-DHPs were obtained in excellent yield ranging from 85-95% within 15-20 minutes **(Scheme 21)** [44].



(38)

Scheme 21.

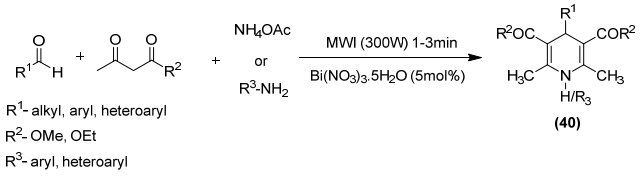
Adude *et al.,* 2012, synthesized 1,4-DHPs **(39)** by reacting aldehyde, β-keto ester and ammonium acetate in acetonitrile in the presence of 3-nitrophenylboronic acid (NPBA). The resulting mixture was stirred at room temperature for 5 h **(Scheme 22)** [45].



(39)

Scheme 22.

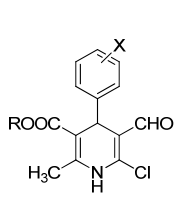
Banik *et al.*, 2012, synthesized 1,4-dihydropyridines **(40)** by one-pot, three component using bismuth nitrate as catalyst (5 mol%) without solvent by microwave technique. Because of the stability of the bismuth nitrate to moisture and oxygen, it was very convenient to conduct reactions. Moreover, the reactions were completed rapidly within 1–3 min with excellent yield **(Scheme 23)** [46].



(40)

Scheme 23.

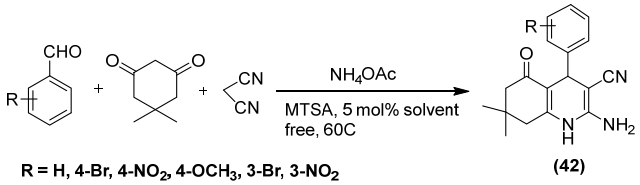
Ruiz *et al.,* 2012, synthesized 6-chloro-5-formyl-1,4-dihydropyridine derivatives **(41 a-f)** with Vilsmeier-Haack reagent under ultrasound mediated reaction. This method offered several practical advantages including faster reaction, higher purity as well as higher yields when compared with the conventional thermal methods [47].



(41 a-f)

	X	R
41a	H	CH_3, CH_2CH_3
41b	2-NO_2	CH_3, CH_2CH_3
41c	3-NO_2	CH_3, CH_2CH_3
41d	4-NO_2	CH_3, CH_2CH_3
41e	2-Cl	CH_3, CH_2CH_3
41f	3-Pyridyl	CH_3, CH_2CH_3

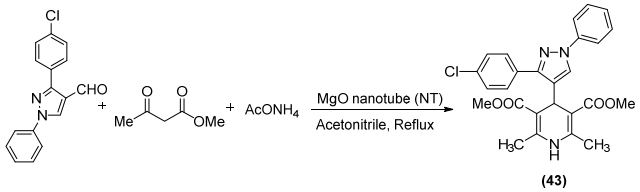
Aswin et al., 2012, introduced an easy and efficient method to prepare a variety of 2-amino-4-phenyl-3-cyano-7,7- dimethyl-5- oxo-1, 4, 5, 6, 7, 8-hexahydroquinolinederivatives **(42)** from the reaction of different aryl aldehydes, dimedone, malononitrile and ammonium acetate using catalytic amount of melamine trisulfonic acid (MTSA) at 60°C under solvent free conditions and products were obtained in good to excellent yields **(Scheme 24)** [48].



(42)

Scheme 24.

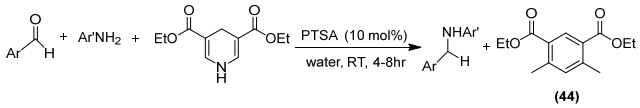
Murugam *et al.*, 2012, synthesized pyrazolyl 1,4-dihydropyridines **(43)** using various amount of MgO nanotubes (NT) as catalyst under proposed operating conditions. The results showed that these catalysts exhibited high activity and good recyclability in DHP synthesis **(Scheme 25)** [49].



(43)

Scheme 25.

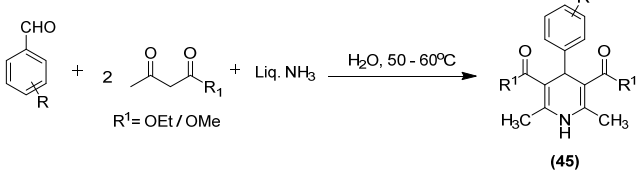
Ghafuri *et al.,* in 2012, reported the utility of dihydropyridine for an efficient, highly chemoselective and simple synthesis of secondary amine via reductive amination. Aldehydes, aromatic amines and inexpensive and easily accessible diethyl 2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylate (DHP)(44) were reacted in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTSA) in water to convert primary amines to secondary amines in good to excellent yields **(Scheme 26)** [50].



(44)

Scheme 26.

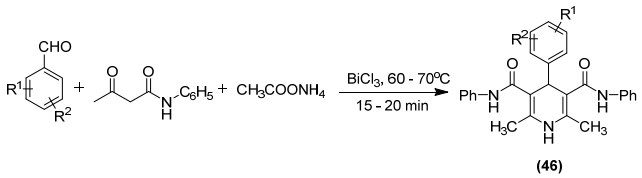
Makone *et al.,* 2012, developed the catalyst-free green synthesis of 1,4-DHP derivative **(45)** using water as solvent under reflux conditions. High yields, environmentally benign solvent and simple work up process were some of the merits of this technique **(Scheme 27)** [51].



(45)

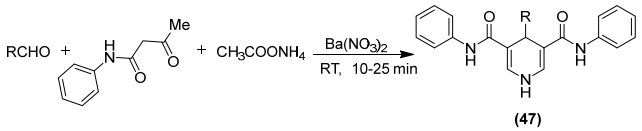
Scheme 27.

Rao *et al.,* 2012, synthesized 1,4-DHPs **(46)** by condensing acetoacetanilide, aromatic aldehydes and ammonium acetate in the presence of bismuth trichloride ($BiCl_3$) as catalyst under solvent free condition. Excellent yields (83% to 96%) with less reaction time (15 to 20 min) and easy workup were some of the merits of this reaction **(Scheme 28)** [52].



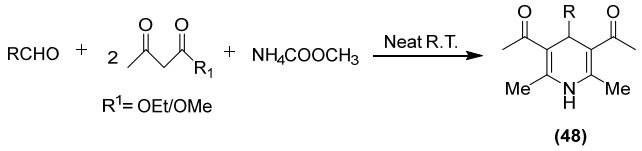
Scheme 28.

Rao *et al.*, 2012, synthesized 1,4–DHPs **(47)** by the condensation of acetoacetanilide with aldehyde and ammonium acetate in the presence of barium nitrate ($BaNO_3$) as catalyst under neat condition with an excellent yield in less time **(Scheme 29)** [53].



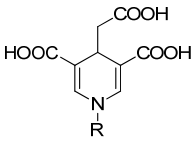
Scheme 29.

Naraimathi *et al.,* 2012 adopted a green chemistry approach for the 1,4-DHP **(48)** synthesis. This procedure has the advantages of high efficiency, safe, less time consuming and could be performed at room temperature **(Scheme 30)** [54].



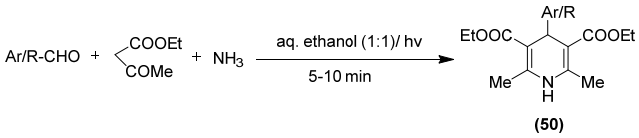
Scheme 30

Homrarven *et al.*, 2013 reported a new fluorescent 1,4-dihydropyridines **(49)** which can be used as a selective chemodosimeter for Hg^{2+} concentration with high quenching efficiency [55].



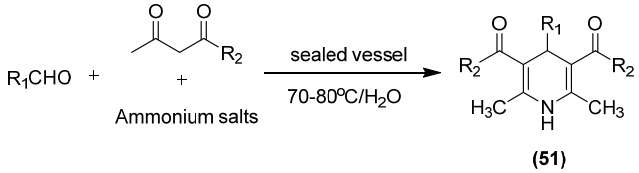
R = Ph, *p*-MeO-Ph, *p*-I-Ph, Benzyl, n-Bu

Ghosh *et al.,* 2013, developed an approach for the synthesis of 1,4-dihydropyridine **(50)** explored the utility of visible light for the synthesis of 1,4-DHPs in aqueous ethanol. The various types of aliphatic and aromatic aldehydes were reacted and gave product in high yield **(Scheme 31)** [56].



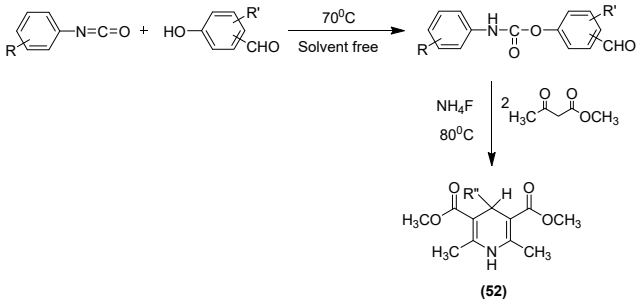
Scheme 31.

Yang *et al.*, 2013, designed a novel, clean, and efficient procedure for synthesis of 1,4-dihydropyridines **(51)** *via* one-pot Hantzsch reactions with satisfactory yields of 86–96%. The catalyst-free, organic solvent-free and condenser-free clean and high efficiency procedure was accomplished smoothly in the sealed system (**Scheme 32)** [57].



Scheme 32.

Habibi *et al.,* 2013 produced a series of 1,4-dihydropyridines **(52)** bearing a carbamate moiety on the 4-position from the primary reaction of different hydroxyl aldehydes with phenyl isocyanates and the subsequent reaction of the obtained carbamates with methyl acetoacetate in the presence of ammonium fluoride **(Scheme 33)** [58].

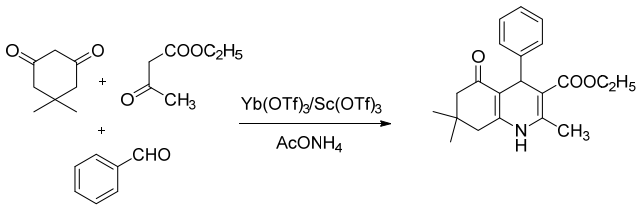


Scheme 33.

Our research group developed various green chemistry approaches for one-pot multicomponent synthesis of 1,4-dihydropyridine derivatives by reacting an aldehyde, β-ketoester and ammonium bicarbonate without catalyst in short reaction time in good yields [59,60].

Vijayakumar, 2013, developed the green method for an efficient synthesis of 1,4-DHPs in microwave oven without catalyst under solvent-free conditions [61].

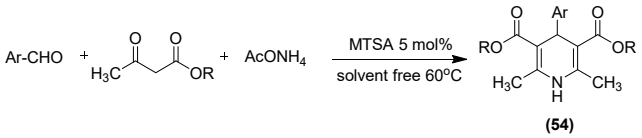
Sabakshi, 2013, explored the catalytic activity of rare earth metal triflates especially $Yb(OTf)_3$ and $Sc(OTf)_3$ for the synthesis of 1,4-dihydropyridine derivatives **(53)** by simply condensing aldehyde, ethyl acetoacetate, dimedone and ammonium acetate **(Scheme 34)** [62].



Scheme 34.

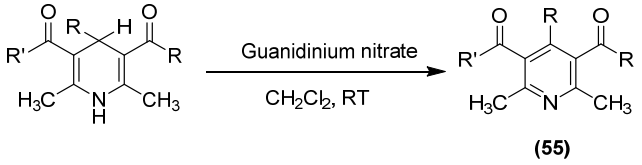
Makone and Vyawahare, 2013, reported the synthesis of 1,4-DHPs using sodium perchlorate with good yield [63].

Mansoor *et al.*, 2013, described a facile synthesis of 1,4-dihydropyridine derivatives (1,4- DHPs) **(54)** using environmentally benign melamine trisulfonic acid (MTSA) as a catalyst in solvent free condition at 60°C **(Scheme 35)** [64].



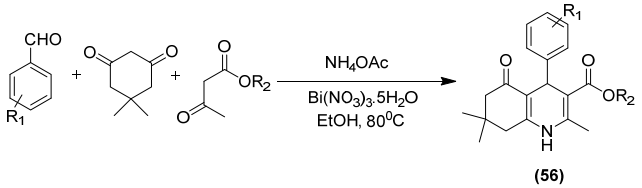
Scheme 35.

Nikoorazm, 2014, introduced a new and convenient method for the oxidation of a variety of Hantzsch 1,4-dihydropyridine derivatives to their corresponding pyridine compounds **(55)** using guanidinium nitrate and silica sulfuric acid. The reactions were performed at room temperature in dichloromethane and the products were obtained in high to excellent yield **(Scheme 36)** [65].



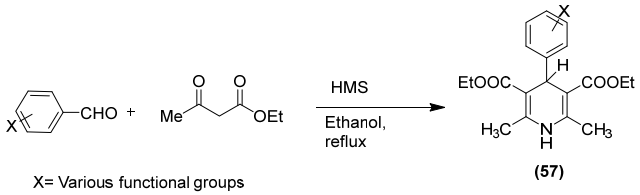
Scheme 36.

Mansoor *et al.,* 2014, developed $Bi(NO_3)_3.5H_2O$ as an efficient catalyst for the synthesis of wide variety of 1,4-dihydropyridine derivatives **(56)** at 75-80°C. $Bi(NO_3)_3$ can be recycled many times and has other benefits of economic viability and good selectivity **(Scheme 37)** [66].



Scheme 37.

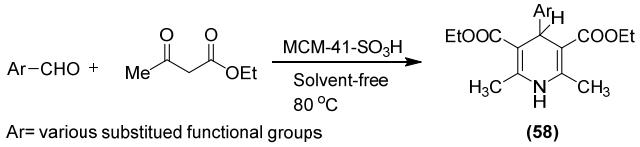
Farhadi *et al.*, 2015, explored the catalytic potential of hexagonal mesoporous silicate (HMS) for one-pot synthesis of 1,4-dihydropyridine derivatives **(57)** by condensing ethyl acetoacetate with various aryl aldehydes and ammonium acetate using EtOH as a solvent under reflux conditions with good to excellent yields. Operational simplicity, short reaction time, high yields of products and use of relatively non-toxic solvents are some of the merits of this method. It was demonstrated that reactivity is related to the number of pores in the HMS catalyst **(Scheme 38)** [67].



Scheme 38.

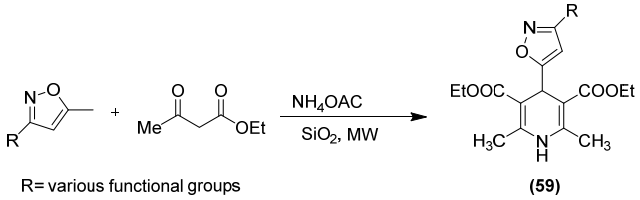
Cao *et al.,* 2015, developed the lactic acid as a green catalyst for formation of diverse 1,4-dihydropyridines using aldehydes, enaminones and amines in water with moderate the excellent yields [68].

Fatholahi *et al.,* 2016, developed an efficient and eco-friendly protocol for the one-step synthesis of 1,4-dihydropyridines **(58)** using the nano sized MCM- 41-SO_3H -catalyzed Hantzsch three-component reaction of an aromatic aldehyde, ethyl acetoacetate, and ammonium acetate under solvent free conditions. The present method offers several other advantages such as simple work up, a remarkable reusability of the catalyst, and short reaction time **(Scheme 39)** [69].



Scheme 39.

Zhang *et al.,* 2016, utilized support SiO_2 as catalyst for the condensation reaction of various 3-substituted isoxazolyl-5-carbaldehydes, ethyl acetoacetate, and ammonium acetate under microwave irradiation and solvent-free conditions leading to the formation of 1,4-dihydropyridines **(59)**. The merits of the method included the environmental friendly reaction conditions, simple operation, extensive substrates, good yields and reuse of the SiO_2 **Scheme 40** [70].



Scheme 40.

2.2. Pharmacological activities

Hantzsch 1,4-DHPs are known to be associated with a wide variety of biological and pharmacological properties. They are most extensively studied for their effective calcium-channel blocking activity and hence antihypertensive action. They are also known to be associated with several other useful and beneficial pharmacological properties (**Fig 1**). We will restrict our study to the latest development in the pharmacological activity of 1,4-DHPs and its derivates.

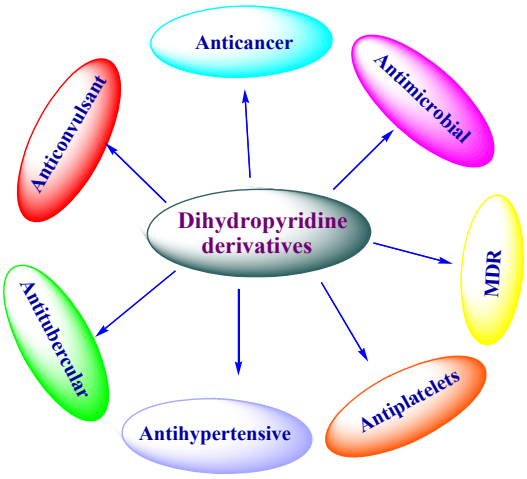
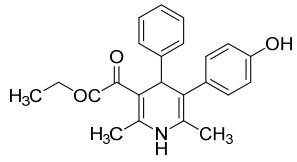


Fig. 1. Various novel pharmacological actions of 1,4-DHPs.

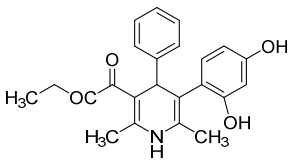
2.2.1. 1,4-DHPs as Analgesic and Anti-inflammatory Agents

It has been known for several years that the blocking of a voltage-gated calcium channel results in ant nociception. Hence, several studies have been carried out to explore the role of 1, 4-DHPs as non- steroidal anti-inflammatory drugs (NSAIDs).

Mishra *et al.,* 2007, synthesized 1,4-dihydropyridine derivatives which were found to possess analgesic and anti-inflammatory activity and the compounds **(60a, 60b)** have almost equipotent activity compared to piroxicam at a dose of 70 mg/kg body wt. [71].



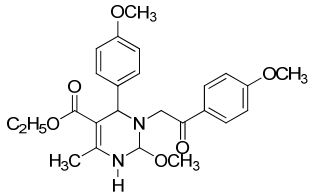
(60a)



(60b)

Ozbakis and Akpinar, 2007, studied the anti-inflammatory effects of nicardipiine as L-type calcium channel blocker on acute and chronic inflammation models in rats and also tested its effect on capillary vascular permeability in rabbits [72].

Chikhale *et al.,* 2009, synthesized 3- (substituted-1-phenylethanone)- 4- (substituted phenyl)- 1, 2, 3, 4-tetrahydropyrimidine- 5- carboxylates **(61)**. The compounds were evaluated for antihypertensive activity by non-invasive tail-cuff method and determined the diastolic blood pressure by carotid artery cannulation method. Carrageenan induced rat-paw edema method was used to check the anti-inflammatory activity [73].

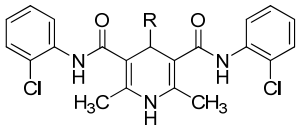


(61)

2.2.2. 1,4-DHPs as anti-tumor agents

After recognizing that the calcium antagonist Verapamil has a strong chemo sensitizing property, plenty of research was undergone to examine the chemo sensitizing properties of calcium antagonists with DHP structure. The high cardiovascular activity of most racemic compounds limits their use as chemo sensitizing agents in humans. Variation in the DHP structure and synthesis of distomers (enantiomers with lower activity) concerning cardiovascular activity resulted in sterically pure racemic DHPs with lower hypotensive properties, but high chemo sensitizing potency. Another strategy employed to lower the cardiovascular activity of DHPs was the use of oxidized DHPs i.e., pyridine.

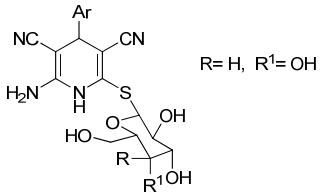
Kumar *et al.*, 2008, synthesized some novel 1,4-dihydropyridines **(62)** by adopting Hantzsch method and screened for their anticancer activities. Compounds exhibited significant anticancer activity with CTC_{50} values at less than 31.25 µg/ml concentration [74].



(62)

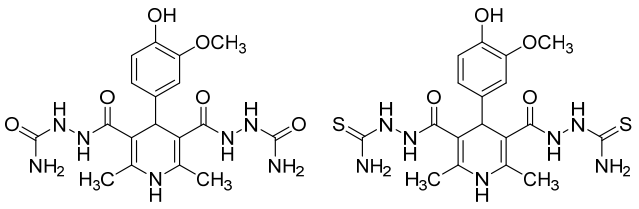
Abbas et al., 2010 describe the synthesis of dihydropyridines thio gylcosides by reacting piperidinium salts of dihydropyridine thiolates with 2, 3, 4, 6-tetra-O-acetyl-α-D-gluco or galacto pyranoyl

bromides having antitumor activity. Activity was evaluated on two different human cell lines (HEPG2 and HELA), in which most active one is compound **(63)** with free glucopyranosylthio and *p*-methoxy phenyl groups [75].



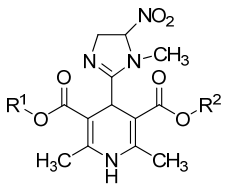
(63)

Kumar *et al.*, 2011, synthesized various 1,4-dihydro pyridine derivatives which were found to be effective against three cancer cell lines. The compound **(64a)** was highly active against HepG2 (Liver), MCF-7 (Breast) and compound **(64b)** is highly active against Hela (cervical) [76].



(64a) **(64b)**

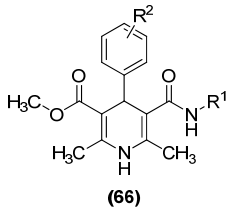
Miri *et al.*, 2011, studied about the intrinsic cytotoxicity of some DHP derivatives **(65 a-f)** which were bearing a nitroimidazole group on the C4 position. Cytotoxic activity of DHP derivatives was evaluated on four different cancer cell lines. Asymmetric derivatives showed good cytotoxicity while symmetric ones were less potent. In addition, QSAR studies revealed the significance of N atom and nitroimidazole group in cytotoxic activity [77].



(65 a-f)

COMPD	R^1	R^2
65a	CH_3	CH_3
65b	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$
65c	$CH_2CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_3$
65d	$CH_2CH_2(CH_3)_2$	$CH_2CH_2(CH_3)_2$
65	CH_2-cyclopropyl	CH_2-cyclopropyl
65f	CH_3	$CH(CH_2ONO_2)_2$

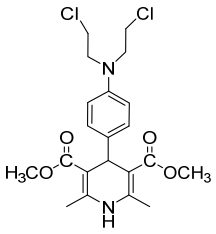
Morusciag *et al.*, 2013, synthesized 7 new compounds, methyl 5- alkyl/ aryl carbamoyl-2, 6- dimethyl-4-(substituted-phenyl)-1,4-dihydropyridine-3-carboxylate derivatives **(66)**. The compounds are presently under evaluation for antitumor activity [78].



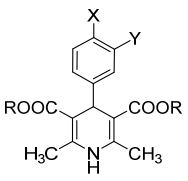
(66)

R^1= NH_2, $C_6H_4(CH_3)_2$, C_5H_5N
R^2= C_6H_4CHO, C_3H_7OH, $C_5H_{11}N$, C_6H_5COOH

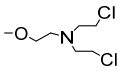
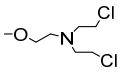
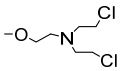
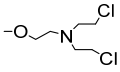
Singh *et al.,* 2014, synthesized twelve substituted 1,4-DHP containing nitrogen mustard pharmacophore to form hybrids without spacer and with ethyl spacer. All compounds were evaluated for *in silico* physicochemical ADME study, 4-(4-nitrobenzyl) pyridine assay and *in vitro* anti proliferative study. Most of the obtained compounds exhibited potent anti-proliferative activity comparable to that of chlorambucil and docetaxel. The promising anti-proliferative activities were displayed by **DHP-M (67)** and **DHP-L-M (68a-d)** [79].



(67)



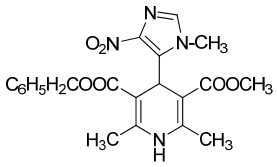
(68)

	X	Y	R
68a		H	CH_3
68b	H		CH_3
68c		-OCH_3	CH_3
68d	-OCH_3		CH_3

2.2.3. 1,4-Dihydropyridine as anticonvulsants

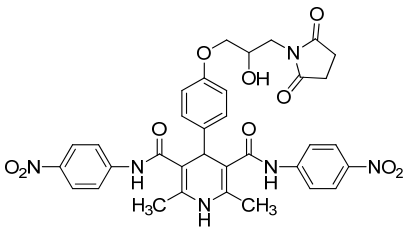
The calcium ions play a fundamental role in vesicular exocytosis, synaptic transmission and release of neurotransmitter at the nerve ending, neurotoxicity and neuronal death. DHPs reduce voltage-sensitive calcium movement in the nerve ending, which likely leads to inhibition of neurotransmitter release at nerve ending, hence may act as anticonvulsants.

Shafiee *et al.,* 2004, report the anticonvulsant activities of new 1,4-dihydropyridines bearing 4-nitroimidazolyl substituents at C-4 position. Anticonvulsant activity of the compound **(69)** wassuperior to reference drug Nifedipine [80].



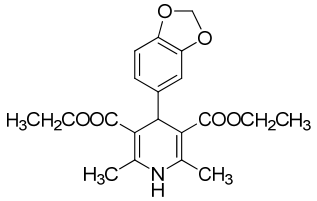
(69)

Pattan *et al.*, 2008, synthesized a new series of 1,4-dihydropyridines and compounds are evaluated for anticonvulsant activity by maximal electroshock method. Among these, compound **(70)** was found to be most potent [81].



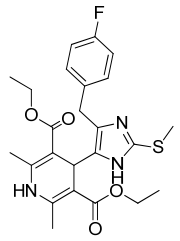
(70)

Later, some scientists in 2013 synthesized fifteen new derivatives that were tested for their anticonvulsant activity. Among these, comp **(71)** showed good anticonvulsant effect comparable to phenytoin. For good anticonvulsant and antioxidant activities, it was found that presence of free NH group of 1,4-DHP, 4-aryl substitution and size of the alkyl group of the ester functionality at positions 3 and 5 are desirable [82,83].

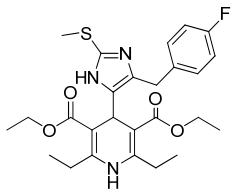


(71)

Hadizadeh et al., 2013 reported that two novel dihydropyridine derivatives, both **(72a)** and **(72b)** have promising anticonvulsant activity in the PTZ-induced seizure model and the Maximal electroshock seizure (MES) test. These compounds were considered useful inpetitmal and grandmal epilepsy [84].



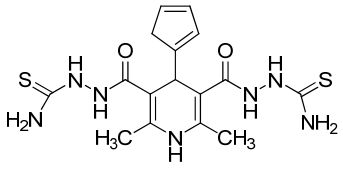
(72a)



(72b)

2.2.4. 1,4-DHPs as platelet aggregation inhibitors-antithrombotic

Kumar *et al.,* 2011, synthesized a new series of 1,4-dihydropyridine derivatives and screened for anticoagulant activity. Among these, compound **(73)** was shown to have promising anticoagulation action (time 720.35 s) at a concentration of 30 mg/mL compared with the other compounds [85].

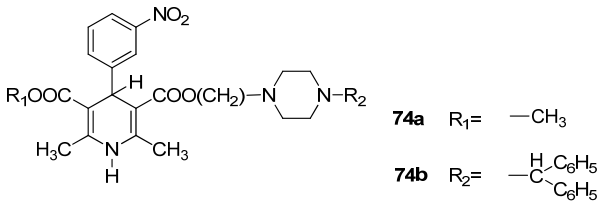


(73)

2.2.5. 1,4-DHPs as potent calcium channel blockers (CCBs)

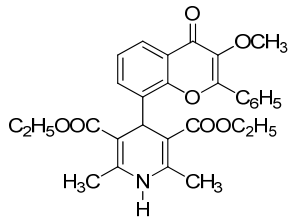
DHPs are a renowned for their potent calcium antagonistic activity and some of these classes of drugs have frequently been used for the treatment of cardiovascular diseases.

Fogari *et al.,* 2005, studied the role of Manidipine or Lisinopril **(74)** in successfully controlling the hypertension diabetic hypertensive patients with microalbuminuria [86].



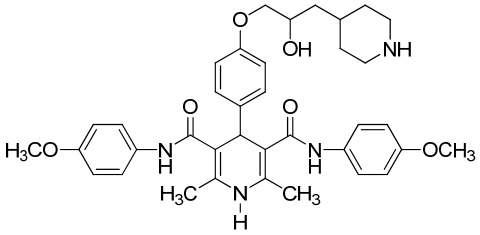
(74 a-b)

In the same year, Budiriesi *et al.*, designed a series of 1,4-dihydropyridines containing 3-methoxyflavone ring in 4th-position **(75).** The most of the new compounds showed a selective bradycardiac activity in the guinea pig isolated right atria [87].



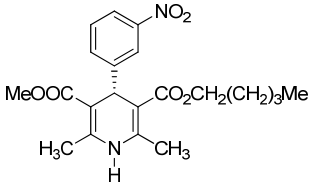
(75)

Pattan *et al.,* 2008, synthesized a new series of 1,4-dihydropyridine derivatives, among which, compound **(76)** was found to be most potent antihypertensive agent checked by tail-cuff method [88].



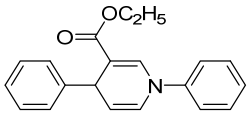
(76)

Zhang *et al.*, 2010, reported the efficient process to synthesized MN9202 **(77)** in high optical purities and investigated the effect of chirality in MN9202. The dihydropyridine receptor binding assay revealed the importance of stereochemistry at C-4 position. The (S)-enantiomer was more active then (R)-enantiomer in rat cardiac and cerebral cortex membrane [89].



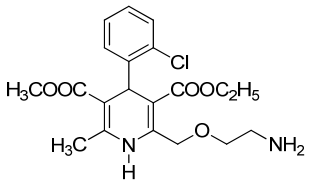
(77) MN9202(+)-(S)

Kumar *et al.,* 2010 synthesized *N*-aryl-1,4-dihydropyridines *via* iodine catalyzed three component reactions of cinnamaldehyde, anilines and 2-ketoesters in methanol having their antilipidemic and antioxidant activity *in vivo* & *in vitro*. Compounds **(78)** having methyl/ethyl ester group have shown promising antidyslipidemic activity whereas compounds with tertiary butyl ester functionality have shown potent antioxidant activity [90].



(78)

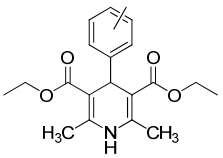
Vitolina *et al.*, 2010, synthesized 1,4-dihydropyridine derivatives with prolonged duration of the antihypertensive action, especially blocking L-type Ca^{2+} ion channels. It promotes beneficial therapeutic effect by coronary and other blood vessel diseases and thus delays development of the atherosclerosis. It has several known trade names; the most mentioned is Norvasc **(79)**. Amlodipine also influences the NO-dependent metabolic processes, stimulates NO synthesis and prolongs NO action duration [91].



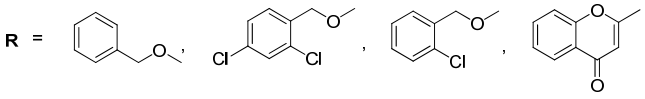
(79)

Shahrisa *et al.,* 2012, synthesized a new 1,4-dihydropyridine derivatives by substituting 4-pyrone ring systems at the 4-position of the pyridine ring and showed weak effect when evaluated for the calcium channel blocking activity [92].

Datar and Auti, 2013 synthesized a series of novel 1,4-dihydropyridine calcium channel blockers and tested for hypotensive activity, including electrocardiographic and effect on heart rate. Compound **(80a)** and comp **(80c)** were the most potent among the series [93].



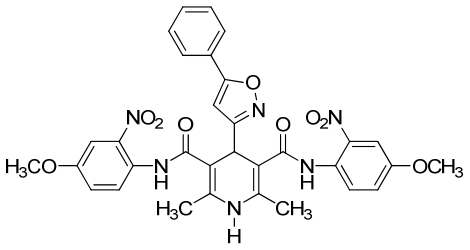
(80 a-d)



(80a) **(80b)** **(80c)** **(80d)**

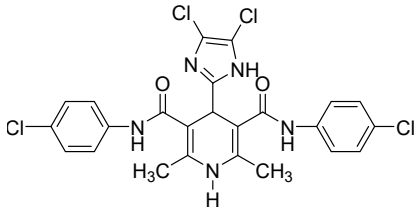
2.2.6. 1,4-DHPs as potential antitubercular agents

Shafii *et al*, 2008 synthesized N^3,N^5-diaryl-4- (5- arylisoxazol- 3- yl)- 1,4- dihydropyridine-3,5- dicarboxamide and evaluated for antitubercular activity against Mycobacterium tuberculosis (H37Rv). The compound **(81)** showed a moderate activity in comparison to rifampicin [94].



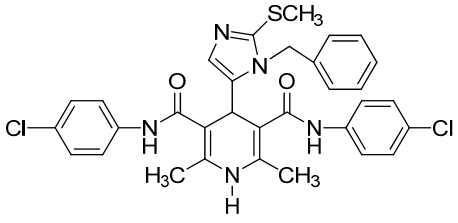
(81)

Amini *et al.,* 2008, synthesized new dihydropyridines having possible antitubercular activity. All compounds were tested against M. tuberculosis $H_{37}Rv$ strain at concentration of 6.25 µg/ml in DMSO. They demonstrated that a five-member heterocyclic group with electron withdrawing substituent is an appropriate bioisoster for nitro aryl group **(82)** which was examined as antitubercular agent [95].



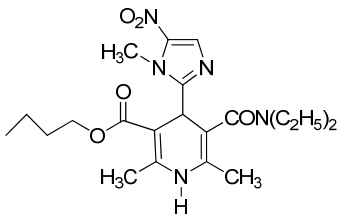
(82)

Fassihi *et al.*, 2009, worked on the series of 4-substituted imidazolyl-2,6-dimethyl-N^3,N^5-bisaryl-1, 4-dihydropyridine-3,5-dicarboxamide. These compounds were tested for antitubercular agents against Mycobacterium tuberculosis $H_{37}Rv$. Compound 1-bisaryl-2-methylthio-1*H*-imidazole-5-yl substituent at C-4 position and 4-chlorophenyl functionality at C-3 and C-5 position of the 1, 4-DHP **(83)** was found to be as potent as rifampicin against M. tuberculosis $H_{37}Rv$. Other compound with substitution 3-pyridyl group at C-3 and C-5 position of the pyridine ring also was an active antitubercular agent. Both compounds were active with MIC=2µg/ml [96].



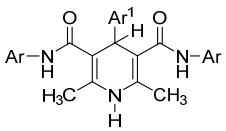
(83)

Khoshneviszadeh *et al.*, 2009, synthesized various unsymmetrical 1,4-DHPs bearing different ester substituents and diethyl carbamoyl derivatives with lipophilic groups at C-3 and C-5 position. Compound **(84)** was the most active one for anti-tubercular activity (MIC=1µM) [97].



(84)

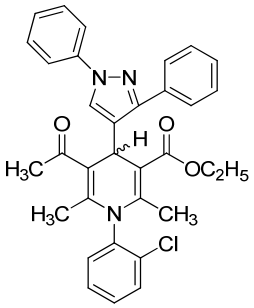
Sirisha *et al.,* 2010, studied some 4-substituted-2,6- dimethyl-3,5- bis-N- (heteroaryl)- carbamoyl-1,4-dihydropyridines **(85 a-b)** and the compound with 2-pyridyl at 4th position and 6-methylpyridin-2-yl at 3rd & 5th position **(85a)** (IC_{50} = 12.5 µg/mL) were more potent than control pyrazinamide (IC_{50} = 32 µg/mL) and 2-Imidazolyl at 4th position and 5-chloropyridin-2-yl at 3rd & 5th position **(85b)** (IC_{50}= 25µg/mL) exhibit good activity and almost equipotent to pyrazinamide (IC_{50} = 32 µg/mL) [98].



(85a) Ar= 5-Chloropyridin-2-yl, Ar^1= 2-imidazolyl
(85b) Ar= 6-Methylpyridin-2-yl, Ar^1= 2-Pyridyl

(85)

Trivedi *et al.*, 2011, synthesized new *N*-aryl-1,4-dihydropyridines having carbethoxy and acetyl group at C-3 and C-5 position and 1H-pyrazole ring at C-4 position of the DHP ring. The compound **(86)** was found to be more potent than first line antitubercular drug isoniazid having lowest minimum inhibitory concentration value of 0.02 µg/mL [99].

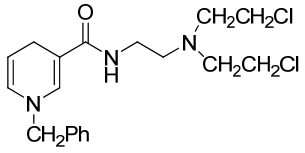


(86)

2.2.7. 1,4-DHPs as carriers in drug targeting

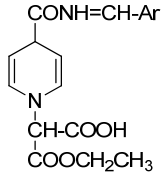
A novel approach for delivery of drugs to brain is the use of dihydropyridine-pyridinium system.

Sherbany *et al.* and Sheha *et al.*, 2003, reported *in vivo* and *in vitro* evaluation of 1,4-DHP↔pyridinium system for targeting anticancer drugs to the brain. The compound **(87)** was found in detectable concentrations in brain when examined by *in vivo* studies and can serve as good carrier [100,101].



(87)

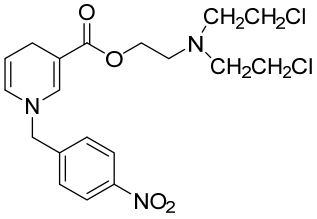
Hassan *et al.,* 2009, synthesized a group of 1-malonyl-1,4-dihydropyridine derivatives **(88)** as new carrier systems for targeted drug delivery to the brain. Compounds (**88a)** and (**88b)** exhibited good antidepressant activity comparable to drug Imipramine [102].



88a Ar= 2-Hydroxyphenyl
88b Ar= 4-Methoxyphenyl

(88)

Singh *et al.* 2013, studied the *in vivo/in vitro* evaluation and ADME studies of 1,4-DHP↔pyridinium reversible redox system for targeting bis(2-chloroethylamino) moiety as alkylating agent to the brain [103,104]. But the final compounds were not stable enough to be explored further. To enhance the stability of the mustard, it was linked to nicotinic acid through ester linker by incorporating various alkyl/aryl groups to pyridine nitrogen. The compound **(89)** was found to be stable enough and explored further for *in vivo* study on rats with promising results [105,106].

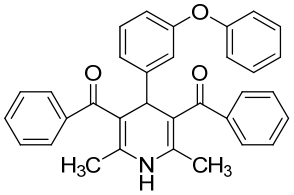


(89)

2.2.8. 1,4-Dihydropyridines as novel multidrug resistance reversers and modifiers

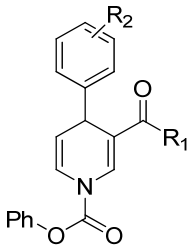
Dihydropyridines can play a vital role in cancer chemotherapy along with clinically used drugs. These compounds have shown to be potent inhibitors of P-glycoproteins (P-gp), which are the important causes of the efflux of toxins outside the cell.

Fusi *et al.* 2006, studied the role of novel dihydropyridine derivatives as MDR reversal agents. The compound DP7 **(90)** found to be lead compound for further design of new DHPs which retain the activity towards ABS-efflux transport and do not affect Cytochrome-P (CYP) [107].



(90)

Voigt *et al.*, 2007, synthesized a series of novel *N*-acyloxy-1,4-DHPs **(91a-f)** and evaluated as P-gp inhibiting activity. The methoxy function within the phenyl ring (**91c & 91f**) have shown highest activity ratios and gave remarkable regiospecific effect on the observed activities showing the interaction between P-gp inhibitor function and P-gp binding region [108].

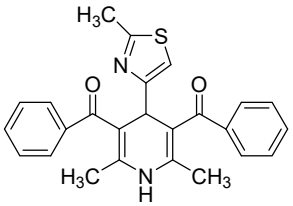


(91)

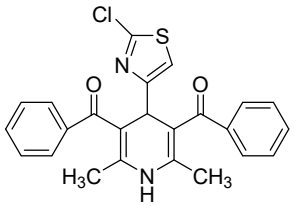
	R_1	R_2
91a	CH_3	4'-CH_3
91b	CH_3	2'-OCH_3
91c	CH_3	4'-OCH_3
91d	OCH_2CH_3	4'-CH_3
91e	OCH_2CH_3	2'-OCH_3
91f	OCH_2CH_3	4'-OCH_3

Miri and Mehdipour, 2008, evaluated potential class of 1,4-dihydropyridines agents which simultaneously effective on both typical and atypical MDR [109].

Bazargan *et al.,* 2008, synthesized a new series of DHPs bearing substituted 1,3-thiazole moiety at C-4 position of DHP ring. Among all compounds (**92a)** and **(92b)** have shown promise as potential new MDR1 reversal agents [110].

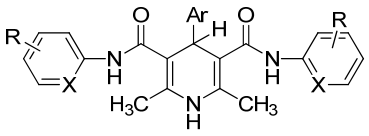


(92a)



(92b)

Sirisha *et al.*, 2011, synthesized the 48 DHP derivatives and molecular docking studies were done with the crystal structure of MRP1. Amongst the compounds tested, compounds **(93a) and (93b)** have shown potent MRP1 inhibitory action with IC_{50} values of 20 ± 4 and 14 ± 2 μM (mean ± SD), respectively as compared to benzbromarone (IC_{50} = 4 μM) [111].

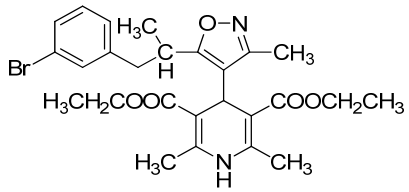


(93)

(93a) X= -CH- R=H Ar= 2-furyl

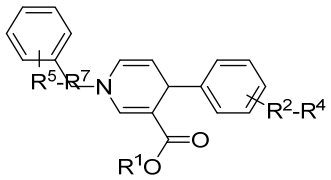
(93b) X= -N- R=H Ar= 2-furyl

Hulubei *et al.*, 2012, synthesized 4-isoxazolyl-dihydropyridines (IDHPs) as multidrug-resistance transporter (MDR-1) inhibitors. SAR study revealed that branching at C-5 of the isoxazole increases the activity. The compound **(94)** was found to most active one [112].



(94)

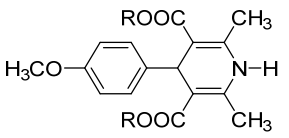
Baumert *et al.*, 2013 prepared a novel series of *N*-benzyl 1,4-dihydropyridines **(95)** and the resulting compounds were examined for P-glycoprotein (P-gp) inhibitory activity. Introduction of 3-ester functionality and *N*-benzyl residue increases the biological activity [113].



(95)

2.2.9. 1,4-Dihydropyridines as antimicrobial agents

Chhillar et al., 2006, synthesized 4-aryl-1,4-dihydropyridines and three 4-aryl-1,2,3,4-tetrahydropyrimidin-2-one derivatives and evaluated their activity against pathogenic strains of *Aspergillus fumigatus* and *Candida albicans.* Two of the compounds **(96a, 96b)** have shown significant activity against *A. fumigates* [114].



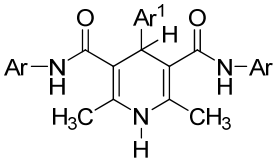
96a R=CH_3

96b R=CH_2CH_3

(96)

Kumar *et al.*, 2009 reported the synthesis of dihydropyridines anddihydropyrimidin-2(*1H*)-ones, having a 5-chloro pyrazole unit at 4-position of dihydropyridine or dihydropyrimidine ring with antimicrobial activity [115]. In the same year, Nayak *et al.*synthesized various 1, 4-dihydropyridines by microwave irradiation and by conventional methods using three component alkyl acetoacetate, aliphatic/aromatic aldehyde and ammonium acetate and synthesized compound screened for their antimicrobial activity [116].

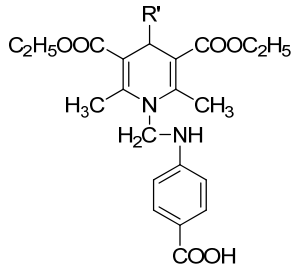
Sirisha *et al.*, 2010, synthesized 4-(2-pyridyl)-2,6-dimethyl-3,5-bis-*N*-(6-methylpyridin-2-yl)-carbamoyl-1,4-dihydropyridine **(97a)** exhibited almost equal activity to streptomycin against gram negative bacteria and the compound 4-(2-imidazolyl)-2,6-dimethyl-3,5-bis-*N*-(2-methyl-4-oxo-3H-quinazolin-3-yl)-carbamoyl-1,4-dihydropyridine **(97b)** exhibited more potent activity against *Bacillus subtilis* [117].



(97)

	Ar	Ar^1
97a	6-Methylpyridin-2-yl	2-Pyridyl
97b	2-Methyl-4-oxo-3H-quinazolin-3-yl	2-Imidazolyl

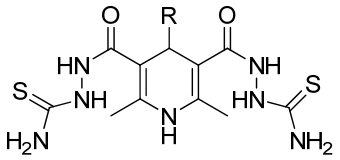
Aanandhi et al., 2010 synthesized a series of Mannich bases **(98)** by reacting β-keto ester and formaldehyde and appropriate amines by condensation technique which leads to formation of various 1,4-dihydropyridine derivatives with 70% yield. All the synthesized compounds were subjected to biological evaluation for anti-bacterial, anti-fungal and anti-oxidant activity [118].



(98)

Kumar *et al.,* 2011 synthesized a new series of 1,4-dihydropyridine derivatives. The synthesized compounds were tested for their antimicrobial activity.

The compounds (**99a & 99b)** were shown to have promising antibacterial and antifungal activities respectively higher than their standards [119].

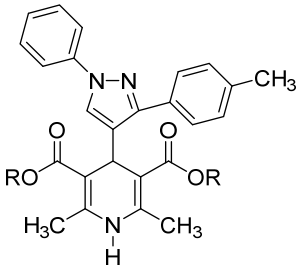


(99)

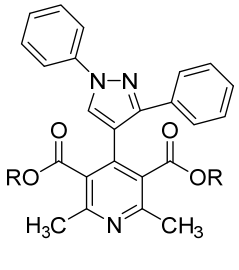
(99a), R= 4-Cl-C_6H_4

(99b), R= 4-OH-C_6H_4

In the same year, some scientist synthesized a series of 1,4-dihydro-4-pyrazolylpyridines and 4-pyrazolyl pyridines in the hope to discover some new structure leads. Compounds **(100a)** and **(100b)** were found to be most effective against *S. aureus* showing lowest MIC value. However, none of the compounds were found superior over the reference drug [120].

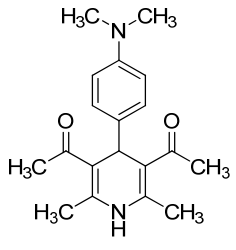


100a)

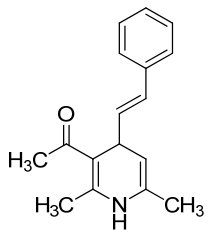


(100b)

Niraimathi *et al.*, 2012, synthesized a series of aryl 1,4-DHP derivatives which were tested for their antibacterial and antifungal activity. The compound with *p*-dimethyl amino group **(101)** at 4th position showed the highest antibacterial activity the compound **(102)** with vinyl substitution has shown prominent activity against *Aspergillus flavus* and *Aspergillus niger* [121].

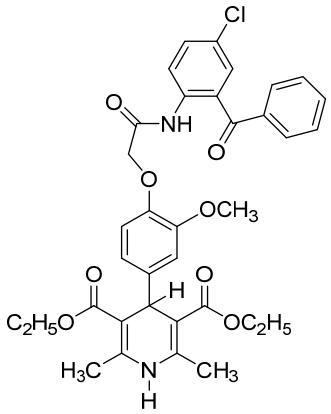


(101)



(102)

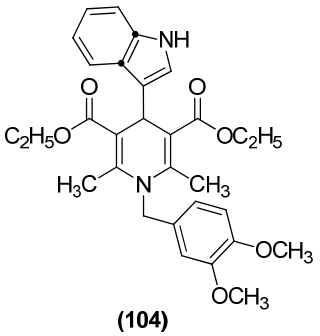
Li *et al.,* 2014, designed novel 1,4-dihydropyridines (1,4-DHPs) linked to 2-aminobenzophenone moiety with the hope of discovering new antibacterial agents. Among all the compounds synthesized, compound **(103)** has shown the maximum activity in their groups [122].



(103)

2.2.10. Miscellaneous

Poondra *et al.,* 2013, synthesized substituted dihydropyridine-based compounds **(104)** as a novel series of PDE4 inhibitors. The synthesized compounds were tested for their inhibitory potency against PDE4B and PDE4D using recombinant isoenzymes at fixed concentration (30 μm). The SAR was discussed and it found that the dihydropyridine core, with indole moiety and 3,4-dimethoxybenzyl group, **(104)** is a potent analogue for PDE4 inhibition [123].



(104)

3. Conclusions

1,4-DHPs are widely known heterocyclic moiety having remarkable biological and pharmacological properties. Because of their important therapeutic value, better search of reagent, catalysts and routes are continually being developed for their efficient synthesis. In this review, we have focused on green catalytic approaches for an environment-friendly synthesis of 1,4-DHPs and its derivatives. Our knowledge of exploring novel catalysts should aid in future research to synthesize various other derivatives having diverse pharmacological actions.

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