Learnovate-International
An International Open-Access Journal Published By Lapain Press Publications [LPP]
Content Available at www.lapinjournals.com E-ISSN: 3049-1592
Research Article Open Access

SYNTHESIS AND CHARACTERIZATION OF FEW 1,4-DIHYDRO PYRIDINES AND THEIR IN SILICO PREDICTION

Sivakumar Peta*[1], Pallepati Kavitha[2]

[*1]Associate Professor, Department of Pharmaceutical Chemistry, Gokula Krishna College of Pharmacy, Sullurupeta, Andhra Pradesh 524121.

[2]Associate Professor, Department of Pharmaceutics, Gokula Krishna College of Pharmacy, Sullurupeta, Andhra Pradesh 524121.

Article History: Received: 22 June 2025, Revised: 11 July 2025, Accepted: 28 July 2025

***Corresponding author**
Sivakumar Peta

Abstract

Heterocyclic compounds form the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. 1,4-Dihydropyridines are an important class of compounds with a wide range of biological activities. Dihydropyridines were reported for their antitumor, calcium channel blokers, antitubercular, analgesic, antithrombotic, anti-inflammatory, acaricidal, insecticidal, bactericidal, anticonvulsant and other pharmacological activities. Keeping this in view, it was proposed to synthesize some new dihydropyridine derivatives by conventional method. All the synthesized compounds were characterized by FT-IR, and^{1}H NMR spectral studies and their structures were established. All the synthesized compounds were predicted for biological properties by using PASS (Prediction of Activity Spectrum of Substances) computer program. The results of these predictions are given in PASS computer program predicts all title compounds. All the title compounds were synthesized, characterized and screened for their antihypertensive activity.

Keywords: Heterocyclic compounds, 1,4-Dihydropyridines, FT-IR, and^{1}H NMR, PASS computer program, antihypertensive activity.

INTRODUCTION

Heterocyclic compounds form the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. One striking structural features inherent to heterocyclic compounds, which are greatly exploited by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three dimensional representations. Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic and approximately half are heterocyclic2. The presence of heterocycles in all kinds of organic compounds of interest in pharmacy, electronics, biology, optics, material sciences is very well known. Among them, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis [1-3]. Heterocyclic synthesis has emerged as a powerful technique for generating new chemical entities useful for drug discovery. Heterocyclic compounds provide scaffolds on which pharmacophores can be arranged to obtain potent and selective drugs. Synthetic heterocycles have widespread therapeutic uses such as antibacterial, antifungal, anti-mycobacterial, trypanocidal, anti-HIV activity, anti-leishmanial agents, genotoxic, anti-tubercular, anti-malarial, herbicidal, analgesic, anti-inflammatory, muscle relaxants anticonvulsant, anticancer and lipid peroxidation inhibitor, hypnotics, antidepressant, antitumor, anthelminthic and insecticidal agents [4-7].

1,4-DIHYDRO PYRIDINE

The first synthesis of a dihydropyridine was performed by Arthur Hantzsch in 1881. The synthesis, which now bears his name, consists of the cyclocondensation of an aldehyde with an active methylene carbonyl compound (e.g., ethyl acetoacetate) and ammonia or a primary amine. 1, 4 dihydropyridines is six membered aromatic ring containing nitrogen at first position which is saturated at first and fourth position.

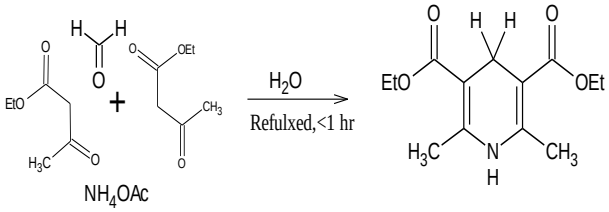
Table 01: Physical properties of 1,4-dihydropyridine

Properties of 1,4-dihydropyridine	
Molecular formula	C5H7N
Molar mass	81.12g/mol
Density	0.9±0.1g/cm3
Flash Point	46.32-68.480C
Boiling Point	152.12-190.000C
Log P	-0.4

1,4-Dihydropyridines are an important class of compounds with a wide range of biological activities. Dihydropyridines were reported for their antitumor, calcium channel blokers, antitubercular, analgesic, antithrombotic, anti-inflammatory, acaricidal, insecticidal, bactericidal, anticonvulsant and other pharmacological activities8-11. Some of the marketed drug preparation containing 1, 4-dihydropyridine moieties are Clindipine (2), Efonidipine (3), etc.

GENERAL METHODS OF SYNTHESIS OF 1,4-DIHYDROPYRIDINE

Hantzsch dihydropyridine synthesis reported the synthesis of some novel 1,4-dihydro pyridine between an aldehyde such as formaldehyde, 2 equivalents of a β-keto ester such as ethyl acetoacetate and a nitrogen donor such as ammoniumacetate or ammonia. 1,4-dihydro pyridine derivatives as an important class of calcium channel blockers. It starts from β-keto ester such as ethyl acetoacetate. by Arthur Rudolf Hantzsch.[Scheme 1]



[Scheme 1]

AIM AND OBJECTIVES

To attempt a very simple and facile procedures for the synthesis of the dihydropyridine derivatives [DHPDs]

- To purify the final compounds by appropriate methods.
- To characterize the newly synthesized compounds by their physical state, TLC, Solubility, FT-IR, 1H NMR and spectral studies.
- To predict the biological activity of the synthesized compounds by a computer program, PASS (Prediction of Activity Spectrum of Substances).
- To identify the compounds for further exploitation.

METHODOLOGY

The following experimental methods were used for the characterization of the synthesized compounds.

- The synthesized compounds were subjected to TLC (pre coated silica gel plates).
- Infrared spectra (υ-cm-1) were recorded on a SHIMADZU FT-IR 4000 using KBr pellet technique.
- 1H NMR spectra were taken on BRUKER AV-III 500 MHz FT-NMR spectrophotometer using TMS as internal standard.

EXPERIMENTAL WORK HAS BEEN DIVIDED INTO THREE PARTS

- Synthetic methodology,
- *In-Silico* methodology,

SYNTHETIC METHODOLOGY

GENERAL PROCEDURE:

SYNTHESIS OF 1,4-DIHYDROPYRIDINE DERIVATIVES

To the solution of substituted benzaldehyde (0.01mol), ethyl acetoacetate (0.02mol) in methanol (20 mL) was treated with (0.01mol) of substituted aniline and refluxed for 8-10 hrs. After completion of the reaction, the mixture was cooled to obtain crude crystals. The solid separated was filtered and washed with aqueous methanol and dried. Recrystallization was done with methanol to obtain synthesized compound was carried out by TLC.

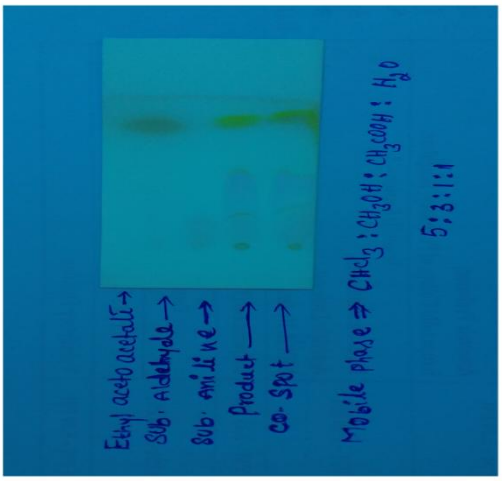


Fig 01: TLC plate

$$R_f \text{ value} = \frac{\text{Distance travelled by the component}}{\text{Distance travelled by the solvent}}$$

Table 02: R_f values of synthesized 1,4-dihydropyridines (GKCP-1 to GKCP-5)

S No	Compound Code	R_f value
1	GKCP-1	0.73
2	GKCP-2	0.58
3	GKCP-3	0.69
4	GKCP-4	0.48
5	GKCP-5	0.77

Table 03: Structural details of synthesized compounds(GKCP-1 TO GKCP-5):

S No	Compound Code	Molecular formula	R	R′	R″	Molecular weight	Density g/cm³	R_fValue	%yield
1	GKCP-1	$C_{25}H_{25}N_3O_8$	H	NO_2	NO_2	495.49	1.316±0.06	0.73	79%w/w
2	GKCP-2	$C_{27}H_{31}N_3O_8$	H	NC_2H_6	NO_2	493.55	1.226±0.06	0.58	73% w/w
3	GKCP-3	$C_{27}H_{30}N_2O_8$	OCH_3	OCH_3	NO_2	510.53	1.237±0.06	0.69	81% w/w
4	GKCP-4	$C_{27}H_{27}N_3O_6$	INDOLE		NO_2	489.51	1.298±0.06	0.48	75% w/w
5	GKCP-5	$C_{27}H_{28}N_2O_6$	2-phenyl Ethene		NO_2	476.52	1.259±0.06	0.77	82% w/w

LEMENTAL ANALYSIS (CALCULATED)

Table 04: Elemental analysis of the synthesized compounds (GKCP-1 to GKCP-5)

S no	Compound Code	Molecular formula	C%	H%	N%	O%
1	GKCP-1	$C_{25}H_{25}N_3O_8$	60.60	5.09	8.48	25.83
2	GKCP-2	$C_{27}H_{31}N_3O_8$	65.71	6.33	8.51	19.45
3	GKCP-3	$C_{27}H_{30}N_2O_8$	63.52	5.92	5.49	25.07
4	GKCP-4	$C_{27}H_{27}N_3O_6$	66.25	5.56	8.58	19.61
5	GKCP-5	$C_{27}H_{28}N_2O_6$	68.05	5.92	5.88	20.15

Table 05: Solubility profile of the synthesized compounds (GKCP-1 to GKCP-5)

S No	Solvent	GKCP-1	GKCP-2	GKCP-3	GKCP-4	GKCP-5
1	Hexane	--	--	--	--	--
2	Cyclohexane	--	--	--	--	--
3	Tolune	++	++	++	++	++
4	Benzene	++	++	++	++	++
5	Ether	++	++	++	++	++
6	Chloroform	++	++	++	++	++
7	Methanol	++	++	++	++	++
8	Acetone	++	++	++	++	++
9	Ethanol	++	++	++	++	++
10	Water	--	--	--	--	--

Table 06: IR and ^{1}H NMR Spectral details of synthesized compound (GKCP-1)

Compound code	IR (KBr pellet method) position of absorption band (cm^{-1})			^{1}H NMR chemical shift δ (ppm)
GKCP-1	Functional Group	Reported	Observed	3.0-3.5 (s,16-^{1}H alkyl) 6.5-8.5 (m,8-^{1}H Aromatic)
	Ar-CO-R	1340-1230 (S)	1289	
		1150-1070 (M)	1066	
	R-(Alkyl)	1480-1400 (S)	1408	
		1400-1340 (M)	1360	
	C=C (Aromatic)	1550-1490 (M)	1580	
	C-H (Ar) (oop)	900-675 (S)	857	
	Ar-NO_2	1550-1350	1514	
		600-550	586	
	C-N-C (Aromatic)	1280-1170 (S)	1178	

IUPAC Name: Diethyl-1 -(4 - Nitro phenyl) -4-(4-N,N-Dimethyl amino phenyl)-2,6-dimethyl -3,5- dioxycarbonyl-1,4 -dihydro Pyridine

Table 07: IR and ^{1}H NMR Spectral details of synthesized compound (GKCP-2)

Compound code	IR (KBr pellet method) position of absorption band (cm^{-1})			^{1}H NMR chemical shift δ (ppm)
GKCP-2	Functional Group	Reported	Observed	3.0-3.5 (s,21-^{1}H alkyl) 6.5-8.5 (m,7-^{1}H Aromatic)
	3^0 amines	1370-1290 (S)	1328	
	Ar-CO-O-R	1340-1230 (S)	1269	
		1150-1070 (M)	1124	
	R-(alkyl)	1480-1400 (S)	1417	

		1400-1340 (M)	1368	
	C=C(Aromatic) C-H(Ar)	1640-1570	1602	
		900-675 (S)	843	
	C-N-C(Aromatic)	1280-1170 (S)	1182	
	Ar-NO_2	1550-1350	1514	
		600-550	568	

IUPAC Name: Diethyl-1-(4-Nitro phenyl) -4 -(3,4 -Dimethoxy phenyl) - 2,6 -dimethyl-3,5- dioxycarbonyl-1,4- dihydro Pyridine.

Table 08: IR and ^{1}H NMR Spectral details of synthesized compound (GKCP-3)

Compound code	IR (KBr Pellet method) position of absorption band (cm^{-1})			^{1}H NMR chemical shift δ (ppm)
GKCP-3	Functional Group	Reported	Observed	3.0-3.5 (s,16-^{1}H methyl) 3.5-4.0 (m,6-^{1}H methoxy) 6.5-8.5 (m,7-^{1}H Aromatic)
	Ar-CO-O-R	1340-1230 (S)	1327	
		1150-1070 (M)	1069	
	Ar-O-R	1300-1180 (S)	1242	
	C=C(Aromatic) C-H(Ar)	1640-1570	1596	
		900-675 (S)	837	
	C-N-C(Aromatic)	1280-1170 (S)	1178	
	R-(alkyl)	1480-1400 (S)	1465	
		1400-1340 (M)	1361	
	Ar-NO_2	1550-1350	1505	
		600-550	594	

IUPAC Name: Diethyl-1-(4-Nitro phenyl)-4-(3- Indole) -2,6- dimethyl-3,5- dioxycarbonyl-1,4-dihydro Pyridine.

Table No 9::IR and ^{1}H NMR Spectral details of synthesized compound (GKCP-4)

Compound code	IR ((KBr Pellet method) position of absorption band (cm^{-1})			^{1}H NMR chemical shift δ (ppm)
GKCP-4	Functional Group	Reported	Observed	3.0-3.5 (s,16-^{1}H alkyl) 6.5-8.5 (m,8-^{1}H Aromatic) 9.5-10.0 (s,1-^{1}H 2^0-NH)
	Ar-CO-O-R	1340-1230 (S)	1278	
		1150-1070 (M)	1069	
	R-(alkyl)	1480-1400 (S)	1442	
	C=C(Aromatic) C-H(Ar)	1640-1570	1654	
		900-675 (S)	802	
	C-N-C(Aromatic)	1280-1160 (S)	1170	
	Ar-NO_2	1550-1350	1514	
		600-550	570	
	2^0 amines	1370-1250 (S)	1361	

IUPAC Name: Diethyl-1-(4-Nitro phenyl -4-(2-phenyl ethene) -2,6-dimethyl-3,5- dioxycarbonyl -1,4-dihydro Pyridine.

Table 10: IR and ^{1}H NMR Spectral details of synthesized compound (GKCP-5)

Compound code	IR ((KBr Pellet method) position of absorption band (cm^{-1})			^{1}H NMR chemical shift δ (ppm)
GKCP-5	Functional Group	Reported	Observed	3.0-3.5 (s,16-^{1}H alkyl) 6.5-8.5 (m,10-^{1}H Aromatic)
	Ar-CO-O-R	1340-1230 (S)	1270	
		1150-1070 (M)	1066	
	R-(alkyl)	1480-1400 (S)	1411	
		1400-1340 (M)	1361	
	C=C(Aromatic) C-H(Ar)	1640-1500(S)	1512	
		900-675 (S)	763	
	C-N-C (Aromatic)	1280-1160 (S)	1178	
	Ar-NO_2	1550-1350	1512	
		600-550	586	
	C=C(Alkene)	1000-950(S)	960	

RESULTS AND DISCUSSION

A facile method has been devised to synthesize the title compounds where the pharmacophores Methyl group at 2nd and 6th position, p-nitro phenyl, N,N-dimethyl phenyl,3,4-di methoxy phenyl,Indole and 2-phenyl ethene at 4th position and Ethyl corboxylate at3rd and 5th position are incorporated into the 1,4-dihydro pyridine nucleus. The methods include mild conditions and the yields were satisfactory. The course of the proposed reaction was confirmed by Thin Layer Chromatography. All the synthesized compounds were characterised by FT-IR, and^{1}H NMR spectral studies and their structures were established. All the synthesized compounds were predicted for biological properties by using PASS (Prediction of Activity Spectrum of Substances) computer program [12-14]. The results of these predictions are given in PASS computer program predicts all title compounds [15].

CONCLUSION

All the title compounds were synthesized, characterized and screened *(IN SILICO)* for their antihypertensive activity[16]. The results of antihypertensive activity revealed that all title compounds predictions are given in PASS computer program. Further studies involves QSAR modelling and docking studies of title compounds GKCP-1, GKCP-2, GKCP-3, GKCP-4 and GKCP-5.

AUTHOR CONTRIBUTIONS

Both authors contributed equally

CONFLICT OF INTEREST

The authors declare no conflict of interest

FUNDING

Nil

REFERENCES

1. Radha Krishna S, Surendra Kumar R, Idhayadhulla A, Abdul Nasser AJ, Selvin J. Synthesis and antimicrobial activity of a new series of 1,4-dihydropyridine derivatives. Chem Soc. 2011;76(1):1–11.
2. Pramesh M, Jayanthi S, Perumal T, Venkatraman BR. Synthesis of a new class of 4-pyrazole substituted 1,4-dihydropyridines by multicomponent reactions. Int J Adv Res. 2015;3(11):1094–1100.
3. Jadhav P, Pujari RR, Chatterjee NR. Green synthesis and antihypertensive activity of some Mannich bases of 1,4-dihydropyridine compounds. Int J Biomed Res. 2012;3(7):1–6.
4. Mohammed R, Samaunnia A, Venkataramana CHS, Madhavan V. Antihypertensive activity of novel 1,4-dihydropyridine derivatives. Int J Biomed Res. 2014;5(5):297–301.
5. Satyanarayana B, Murali Krishna P, Sreenivasareddy B, Ramachandran D. Three-component reaction of 3-nitrobenzaldehyde, isopropyl acetoacetate and 1-benzhydryl-azetidin-3-yl-2-amino-2-iminoacetate in the presence of potassium carbonate: an efficient one-pot synthesis of 1,4-dihydropyridine derivatives. Int Res J Pharm. 2012;3(11):185–188.
6. Samaunnia A, Venkataramana CHS, Madhavan V. Virtual toxicity studies of novel 1,4-dihydropyridine derivatives. Int Res J Pharm. 2013;4(3):186–189.
7. Mathi VN, Suresh AJ, Mathi SCB. Eco-friendly one-pot synthesis and characterization of 1,4-dihydropyridine derivatives. Int J Pharm Sci. 2012;4(3):651–654.
8. Filipan-Litvic M, Litvic M, Cepanec I, Vinkovic V. Synthesis of 2,6-dimethyl-3,5-demethoxycarbonyl-4-(o-methoxyphenyl)-1,4-dihydropyridine: a novel cyclization leading to unusual formation of 1-amino-2-methoxycarbonyl-3,5-bis(o-methoxyphenyl)-4-oxa-cyclohex-1-ene. Molecules. 2007;12:2546–2558.
9. Akbari JD, Tala SD, Dhaduk MF, Joshi HS. Molecular iodine-catalyzed one-pot synthesis of some new Hantzsch 1,4-dihydropyridines at ambient temperature. ARKIVOC. 2008;(i):126–135.
10. Abdoli-Senejani M, Foruzan N, Bahmani M, Isfahani TM, Dustepour S, Abdoli-Senejani M, et al. Oxidative aromatization of some 1,4-dihydropyridine derivatives using $NaBrO_3$. Iran Chem Commun. 2016;4:1–8.
11. Thombal RS, Jadhav VH. One-pot synthesis of 1,4-dihydropyridines under solvent-free conditions using a carbonaceous solid acid catalyst. J Chem Appl Biochem. 2015;2(1):1–6.
12. Bagley MC, Fusillo V, Jenkins RL, Lubina MC, Mason C. One-step synthesis of pyridines and dihydropyridines in a continuous-flow microwave reactor. Beilstein J Org Chem. 2013;9:1957–1968.
13. Mojarrad JS, Zamani Z, Nazemiyeh H, Ghasemi S, Asgari D. Synthesis of novel 1,4-dihydropyridine derivatives bearing biphenyl-2-tetrazole substitution as potential angiotensin II receptor and calcium channel blockers. Adv Pharm Bull. 2011;1(1):1–9.
14. Kaur P, Singh RK. Investigation of various green chemistry approaches for the efficient synthesis of dialkyl-1,4-dihydro-4-(substituted phenyl)-2,6-dimethylpyridine-3,5-dicarboxylates. Chem Sci Trans. 2013;2(1):295–301.
15. Vigante B, Rucins M, Plotniece A, Pajuste K, Luntena I, Cekavicus B, et al. Direct aminolysis of ethoxycarbonyl methyl 1,4-dihydropyridine-3-carboxylates. Molecules. 2015;20:20341–20345.