WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 12, 738-749. Review Article SSN 2277– 7105

SYNTHESIS AND SIGNIFICATION OF 1,4-DIHYDROPYRIDINES ANALOGS IN DIFFERENT PHARMACEUTICAL DRUG.

Ajit. K. Nangare[1*], Sudarshan B. Kakad[2], Amit. N. Chavan[3] and Sandesh S. Bole[4].

[1*]Department of Pharmaceutical Chemistry, Padmashri Dr. Vithalrao Vikhe Patil Foundation's College of Pharmacy, Vilad Ghat, Ahmednagar, (MS), India, 414111.

[2]Department of Pharmaceutical Analytical Chemistry, Padmashri Dr.Vithalrao Vikhe Patil Foundation's College of Pharmacy, Vilad Ghat, Ahmednagar, (MS), India, 414111.

[3,4]Padmashri Dr. Vithalrao Vikhe Patil Foundation's College of Pharmacy, Vilad Ghat, Ahmednagar, (MS), India, 414111.

Article Received on
08 Oct 2015,

Revised on 31 Oct 2015,
Accepted on 24 Nov 2015

***Correspondence for Author**
Ajit. K. Nangare
Department of Pharmaceutical Chemistry, Padmashri Dr. Vithalrao Vikhe Patil Foundation's College of Pharmacy, Vilad Ghat, Ahmednagar, (MS), India, 414111.

ABSTRACT

In the recent past year, The 1,4-dihydropyridines derivatives have been covering a large area of studding because of their synthetic possibility, different chemical behavior, there biological activities and different applications in the pharmaceutical drug. The 1,4-benzothiazine forms an important class of heterocyclic system, it include the N and Smolecules in the ring. The novel 1,4-benzothiazine derivatives occupancy several biological activities such as anti-inflammatory, anti-rheumatic, antimicrobial, antioxidant, anti-hypertensive, anti-HIV, cardiovascular , ATP-sensitive potassium channel opener, ant malarial, cytotoxic, immunomodulation, neuroprotective and aldose reeducates inhibitor etc.

KEYWORDS: antitumor, anti-inflammatory, 1, 4-dihydropyridines, anticonvulsant, synthesized.

INTRODUCTION

1,4-dihydropyridine is the six membered contain aromatic ring compound which has taken the important place from different organic compound from is biological activities. 1,4-dihydropyridine derivatives variety has been explored developing wide novel pharmaceutical molecules. 1,4-dihydropyridine derivatives has been synthesized by the different methods.[1-5] 1,4-dihydropyridinederivatives are know because for their amazing biological activity

which has been seen such as antifungal, anti-hypertensive, central nervousas the calcium channel antagonists[15] antihypertensive, antianginal[16-18], antitumor[19],anti-inflammatory activity[20,21], ant tubercular activity[22],analgesic activity[23], antithrombotic.[24,25] Vasodilation[26], anticonvulsant[27], stress protective effect[28], cardio depressant activity.[29] The brief review of various 1, 4-dihydropyridines derivativeshave been show in this paper which has been published in different research papers.

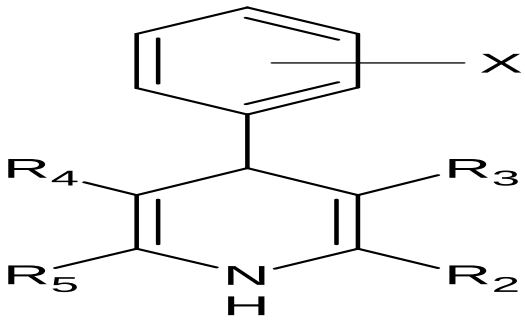


Figure.1: Skeletal formula of 1,4-Benzothiazine Molecule.

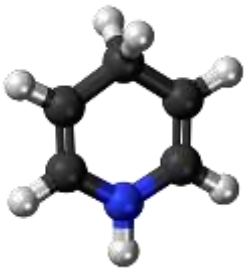


Figure.2: Spacing Model of the 1,4-Dihydropyridine Molecule.

Laboratory synthesis of 1,4-Dihydropyridine

There are different type of method to synthesis the 1,4-dihydropyridines as follow.

1. Different type of method has been proposed by various scientists for the synthesis of 1, 4-dihydropyridine. Hantzsch is the scientists which first synthesis of 1,4-dihydropyridines by refluxing of aldehyde, β-ketoester and ammonia or ammonium salts in ethanol (Figure.3)[1]

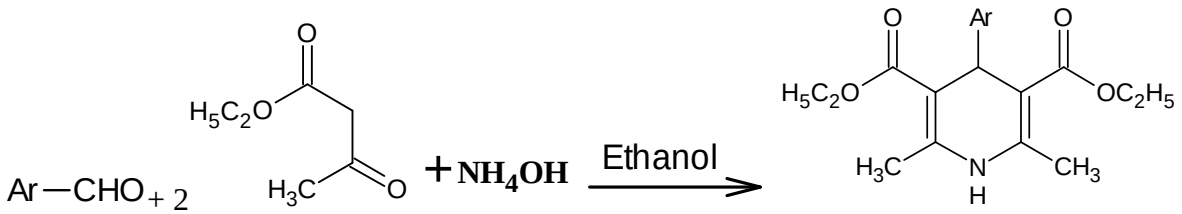


Figure.3: Synthesis of ring from aldehyde, β-ketoester and ammonia or ammonium salts in ethanol.

2. Some otherscientists have reported the one step synthesis of 1,4-dihydropyridines with aldehyde,alkyl acetoacetate, ammonia by refluxing them for some time with methanol shows good yield(Figure.4).[2]

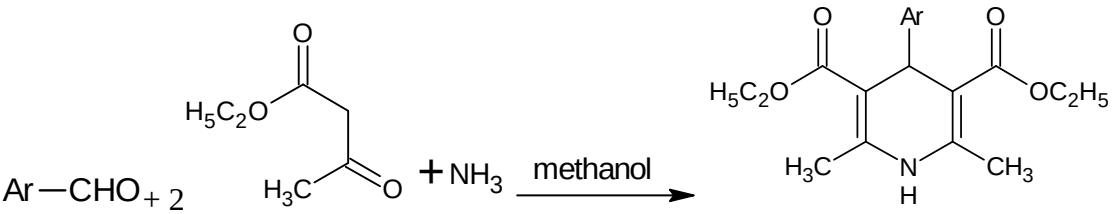


Figure.4: Synthesis of ring from aldehyde,alkyl acetoacetate& ammonia.

3. By using grinding method in presence of the MCM-41 catalyst, one step synthesis has been carried out of polyhydroquinolines. By mixing aldehyde, ethyl acetoacetate, dimedone, ammonium acetate with each other. (Figure.5).[3]

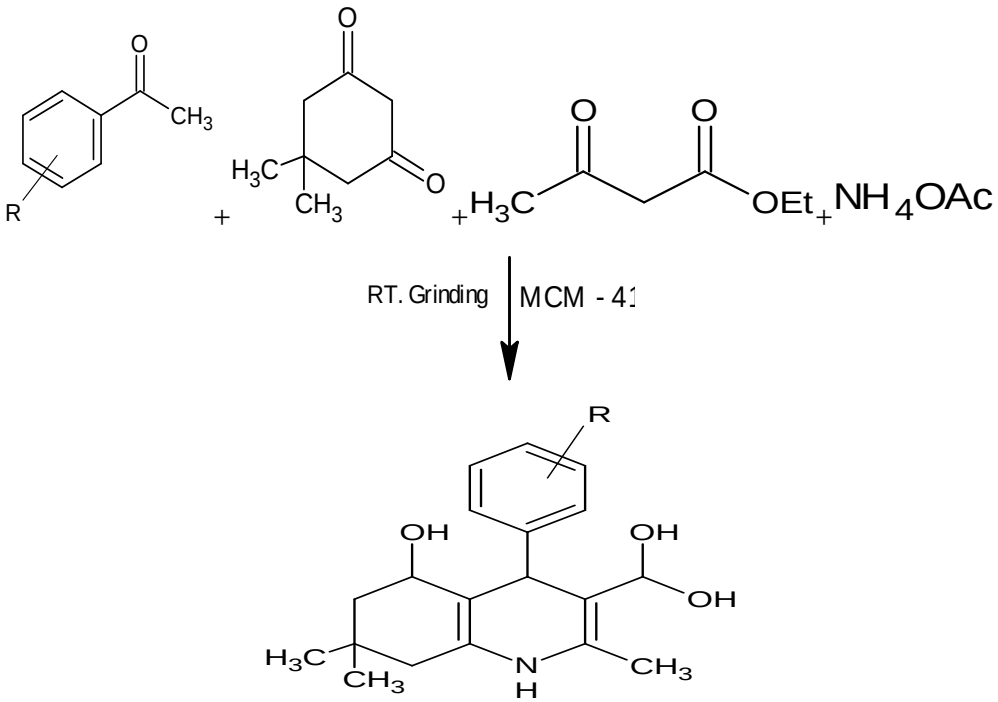


Figure.5: Synthesis of ring from aldehyde, ethyl acetoacetate, dimedone, ammonium acetate with using MCM-41 catalyst.

4. By condensing aldehydes, 1, 3-dicarbonyl compounds, and ammonium acetate,some other have reported the synthesis of 1,4-dihydropyridines,in presence of catalyst alumina sulphuric acid (Figure.6).[4]

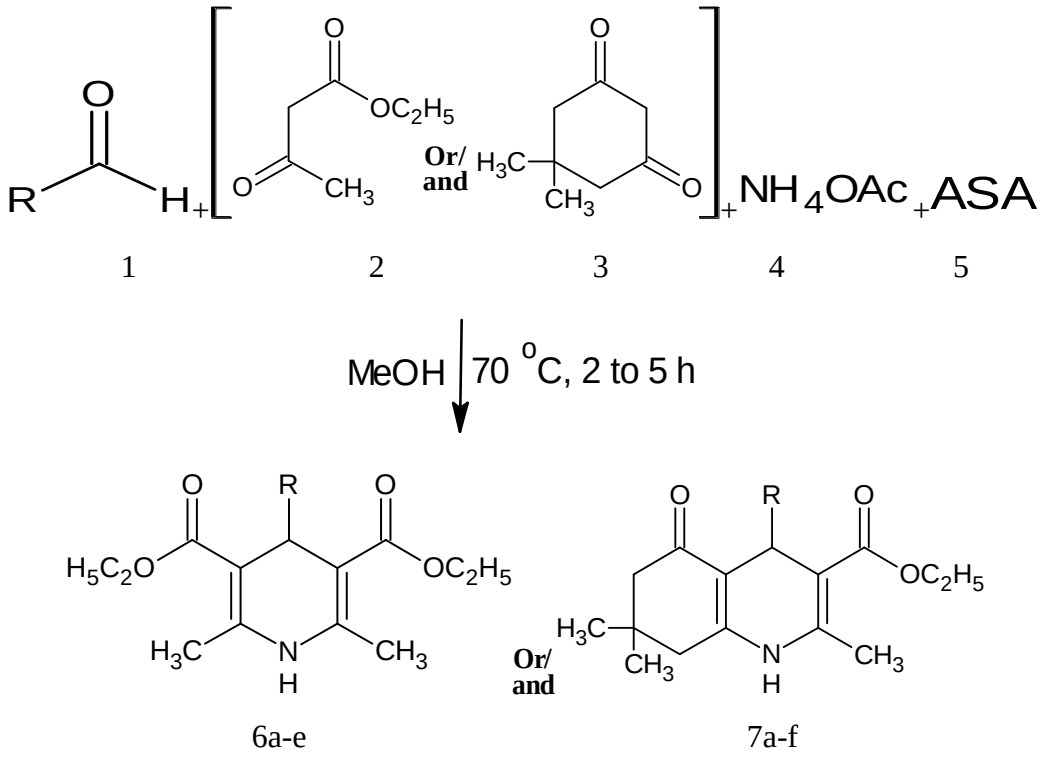


Figure.6: Synthesis of ring from aldehydes, 1, 3-dicarbonyl compounds, and ammonium acetate

5. In shorter time we can get the higher yield by synthesizing the 1,4-dihydropyridines withultrasoundirridationwithout using solvent and catalyst.(Figure.7).[5]

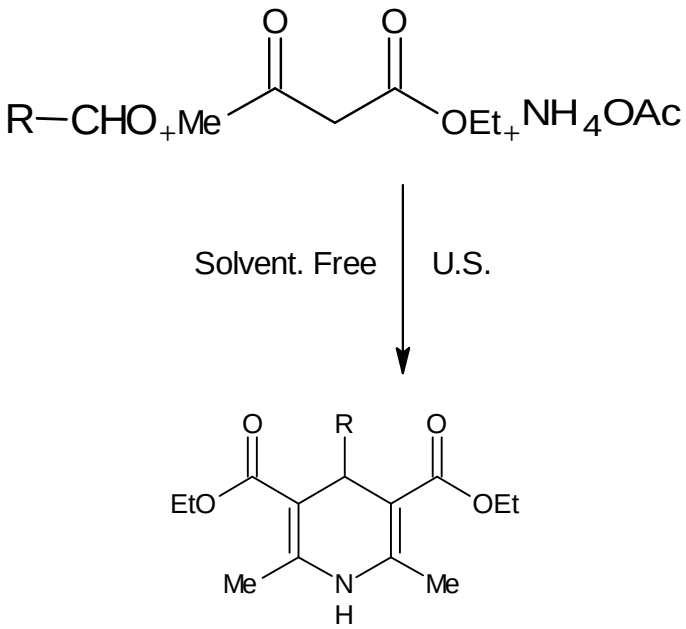
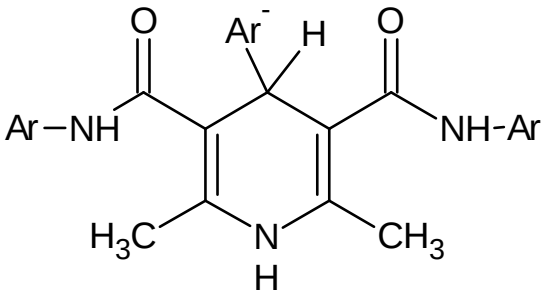


Figure.7: Synthesis of 1, 4-dihydropyridines ring with ultrasound irridation without using solvent and catalyst

Application of the 1,4-dihydropyridine ring system in Drug synthesis

1. Ant tuberculosis/ Anticancer activity

1.1 KalamSirishaandCo-workers[6]: synthesized a novel series of 1,4-Dihydropyridines(Figure.8), which is further tested for antituberculosis activity. From it 4-substituted-2,6-dimethyl-3,5-bis-N-(heteroaryl)-carbamoyl-1,4- dihydropyridines has been studied. From that control pyrazinamide (IC=32 µg/mL) is less potent thanthe compound having 6-methylpyridin-2-yl at 3 & 5th position (at Ar)1b (IC50 = 12.5 µg/mL) and 5-chloropyridin-2-yl at 3 & 5th position (at Ar) 1a (IC50= 25 µg/mL) exhibit good activity.



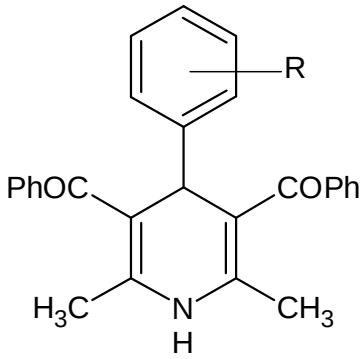
1,4- dihydropyridinesDerivatives (1a-1b)

	Ar	Ar'
1a	5-Chloropyridin-2-yl	2-Imidazolyl
1b	6-Methylpyridin-2-yl	2-Pyridyl

Figure.8: Structure of compound 1a to 1b

1.2 Masami Kawaseand Co-workers[7,8]

Synthesized novel derivatives of3,5-Dibenzoyl-4-(3-phenoxyphenyl)-1,4-dihydro-2,6-dimethylpyridine(DP-7) (Figure.9) , it is a novel multidrug resistance inhibitor, and it has been tested on rat heart in lagendorff- perfused and result is compared with the nifedipine. The result showed that compound DP7 is safe and potent MDR chemosensitizer. Different author have studied the replacement of 4-phenyl-3,5-dibenzoyl-1,4-dihydropyridines derivatives for the looking the cytotoxic activity and MDR- reversing activity. It show that the compounds with 2'-trifluormethylphenyl (10a), 2'-chlorophenyl (10b), 3- chlorophenyl (10c) at c4 position show the maximum activity against HSC-2 cell lines. The 10c compound shows the maximum activity in MDR-modulating and tumour-specific cytotoxicity, it is seen as the new drug in the treatment of cancer.



1,4- dihydropyridinesDerivatives (10a-10c)

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

Figure.9: Structure of compound 10a to 10c

1.3 Shigeyuki Tasakaand Co-workers[9]

Synthesized a new series 1,4-dihydropyridines derivatives (Figure.10).All the synthesized derivatives were investigated for their antitumor activities. The screened is done by using the mice having P388 leukemia cells. 3-pyridylpyrlesters contain compound N276-9 and N276-16 are found to be active.

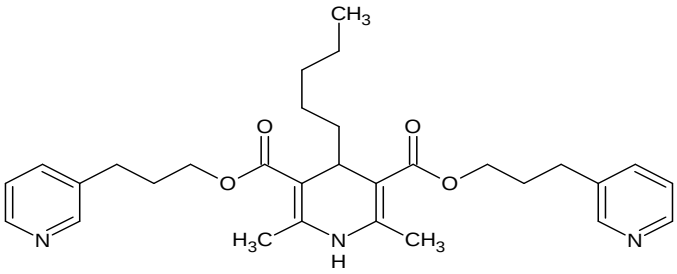


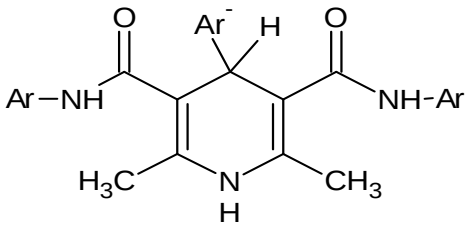
Figure.10: 1,4- dihydropyridinesDerivatives.

2. Antimicrobial activity

2.1 KalamSirishaandCo-workers[6]

Synthesized a new series 4-substituted-2,6-dimethyl-3,5-bis-N-(heteroaryl)-carbamoyl-1,4-dihydropyridines derivatives (Figure.11).All the synthesized derivatives were investigated for their antibacterial and antifungal activities. They tested for in vitro antimicrobial activity against Gram positive and Gram negative bacteria. The activity seen against Gram positive Bacillus subtilis and Staphylococcus aureus, Gram negative Escherichia coli and Proteus vulgaris.8a &8b show good result against the gram positive bacteria,8aderivativeshow almost

same activity to streptomycin against gram negative bacteria and 8b derivativeshow potent activity against Bacillus subtilis. The reference drug was taken Novobiocine, Gentamycin, Kanamycin, Amikacin (form antibacterial) and Ampicillin (For antifungal).



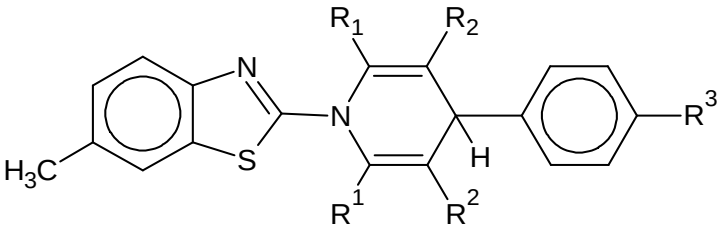
1,4- dihydropyridinesDerivatives (8a-8b)

	Ar	**Ar'**
8a	6-Methylpyridin-2-yl	2-Pyridyl
8b	2-Methyl-4-oxo-	2-Imidazolyl
	3H-quinazolin-3-yl	

Figure.11: Structure of compound 8a to 8b.

2.2 Sushil.K.Dubey and Co-workers[10]

Synthesized a new series N-(6-methylbenzothiazolyl) - 2, 3, 5, 6-tetrasubstituted-4-(aryl)-1,4-dihydropyridines derivatives(9a-9g) (Figure.12).All the synthesized derivatives were investigated for their antibacterial, antifungal and entomological activities.The activity seen against lactobacillus sps, Pseudomonas aeruginosa, Micrococcus lutius and Kocuria rosea.9a, 8b & 9c show good result against bacteria when compared to stranded drugs.Thecompound 9d, 9e, 9f, 9g shows the good antifungal activity. The reference drug was taken kanamycin, gentamycin, Novobiocine (form antibacterial).



1,4- dihydropyridinesDerivatives (9a-9g)

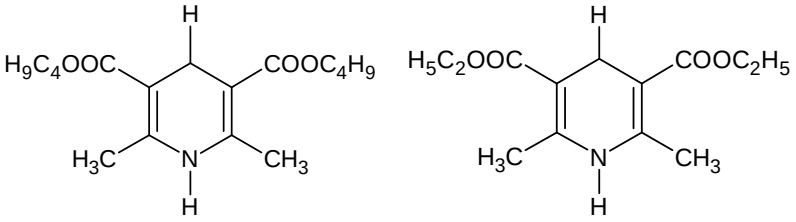
	R_1	**R_2**	**R_3**
9a	Me	O=COEt	m-NO_2
9b	Oet	O=COEt	m-NO_2
9c	Me	COME	m-NO_2
9d	Me	O=COEt	p-OMe
9e	Me	COME	p-OMe
9f	Me	COME	p-OH
9g	Me	COME	m-NO_2

Figure.12: Structure of compound 9a to 9g.

3. Antioxidant activity

3.1 GunarsTirzitisand Co-workers[11]

Synthesized a new series 2, 6-dimethyl-3,5-dialkoxycarbonyl-1,4-dihydropyridines derivatives (Figure.13).All the synthesized derivatives were investigated for their antioxidant activity. The compounds 2,6-dimethyl-3,5-diethyloxycarbonyl-1,4-dihydropyridines (12a) and 2,6-dimethyl- 3,5-dibutyloxycarbonyl-1,4-dihydropyridines (12b) show the maximum activity against when compare with Trolox and probucol.



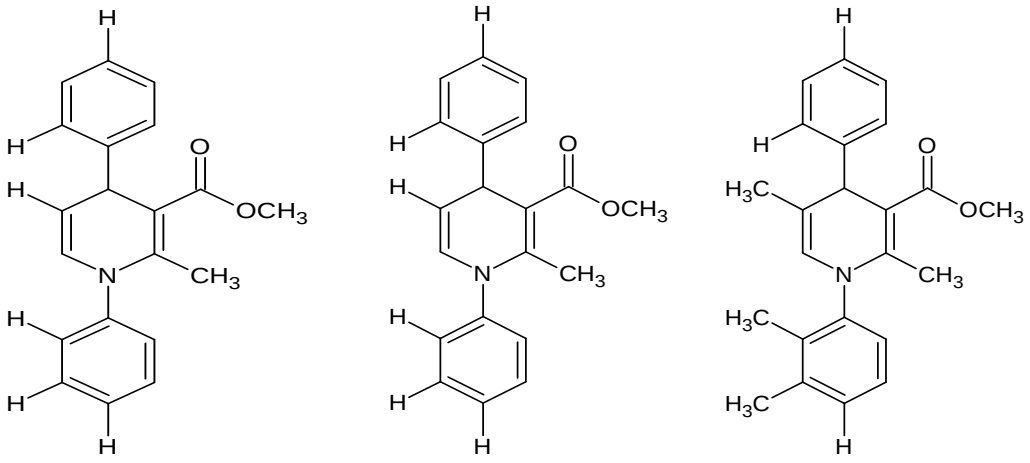
(12b) **(12a)**

Figure.13:1,4- dihydropyridines (12a -12b).

4. Antidyslipidemic activity

4.1 Atul Kumar and Co-workers[12]

Synthesized a new series N-aryl-1,4-dihydropyridines (Figure.14).All the synthesized derivatives were investigated for their antidyslipidemic activity. The compound 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 has been study further. The selected compounds show the nice TG and lipid lowering activity.



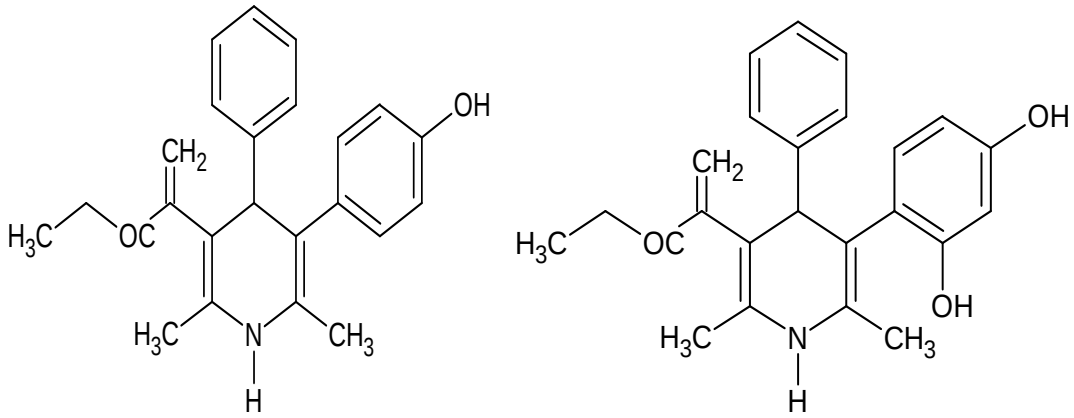
(15a) **(15b)** **(15c)**

Figure.14: 1,4- dihydropyridinesDerivatives (15a-15c).

5. Analgesic & Anti-inflammatory activity

5.1 BrijeshkunvarMishraand Co-workers[13]

Anew synthesized 1,4-dihydropyridine derivatives(Figure.15). The derivative has been check for the analgesic and anti-inflammatory activity. The compound shows the same amount of activity when compared with the ptroxicam at adose of 70 mg/ kg of body w.t.



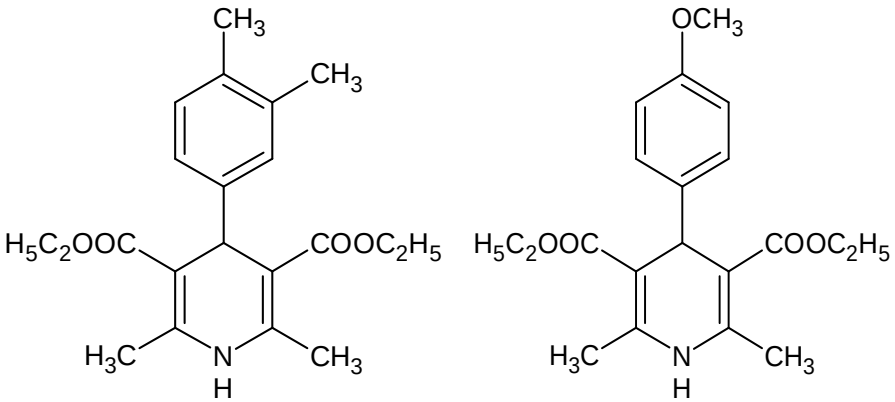
(16a) **(16b)**

Figure.15: 1,4- dihydropyridinesDerivatives (16a-16b).

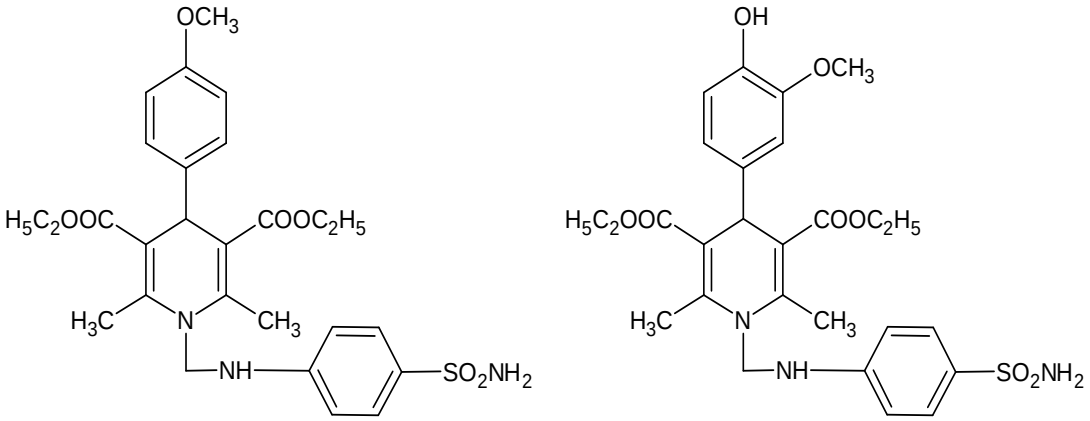
6. Antiulcer activity

6.1 B BSubudhiand Co-workers[14]

A novelsynthesized1,4-dihydropyridines derivatives(Figure.16). The compound where tested for antiulcer activity. The compound containing methoxy at c4 position shows great antiulcer activity.



(17a) **(17b)**



(17c) **(17d)**

Figure.16: 1,4- dihydropyridinesDerivatives (17a-17d).

CONCLUSIONS

This review gives an overview of the broad spectrum of pharmacological activities displayed by 1,4-dihydropyridines. The pharmacological activities of 1,4-dihydropyridines derivatives have attracted considerable attention giving to the use full of this moiety in the field of medicinal chemistry. Further development can be carried out by making slight change leading to severe changes to yield better drug. The 1,4-dihydropyridines importance of moiety can be seen by carrying out further studies on its possible substitution. Thus this paper proves to be significant for further research work on the bioactive 1,4-dihydropyridines ring and biological profiles of these new generations of 1,4-dihydropyridines would represent a successful matrix for further circumstances of better medicinal agents.

REFERENCES

1. Hantsch .A et.al. Hantzsch pyridine synthesis. Ann Chem., 1882; 215: 1-81.
2. D .R.Harishkumar, Nayeem Naira et.al. Synthesis and invitro calcium channel blocking activity of symmetrical and unsymmetrical substituted 1,4- dihydropyridines. Asian journal of Chemistry, 2009; 6(21): 4357-4365.
3. V. M. Markhele, S.A. Sadaphal and M. S. Shingare. An Efficient One-Pot Synthesis of Polyhydroquinolines at RoomTemperature Using MCM-41 catalyst under solvent-freeconditions. Bulletin of the Catalysis Society of India, 2007; 6: 125-131.
4. Mustafa Arslan et.al. An efficient one pot synthesis of 1,4-dihydropyridines using alumina sulfuric acid (ASA) catalyst. Turk J Chem., 2009; 33: 769 – 774.

5. Shu-Xiang Wang, Zhi-Yan Li, Jin-Chao Zhang, Ji-Tai Li. The solvent-free synthesis of 1,4-dihydropyridines under ultrasound irradiation without catalyst. UltrasonicsSonochemistry., 2008; 15: 677–680.
6. KalamSirisha ,GarlapatiAchaiah, and VangaMalla Reddy. Facile Synthesis and Antibacterial, Antitubercular, and Anticancer Activities of Novel 1,4-Dihydropyridines. Arch. Pharm. Chem. Life Sci., 2010; 343: 342 – 352.
7. SimonaSaponara ,Antonella Ferrara , Beatrice Gorelli , Anamik Shah .3,5- Dibenzoyl-4-(3-phenoxyphenyl)-1,4-dihydro- 2,6-dimethylpyridine(DP7): A new multidrug resistance inhibitor devoid of effects on Langendorff-perfused rat heart. European Journal of Pharmacology., 2007; 563: 160–163.
8. Masami Kawase, Anamik Shah, HarsukhGaveriya, Noboru Motohashi, Hiroshi Sakagami, Andreas Vargae and Joseph Molna R. 3,5-Dibenzoyl-1,4-dihydropyridines: Synthesis and MDR Reversal in Tumor Cells, Bioorganic &Medicinal Chemistry, 2002; 10: 1051–1055.
9. Shigeyuki Tasaka, HiromasaOhmori, NoriakiGomi, Mayumi Iino,Tosiki Machida, Akira Kiue, Seiji Naito and Michihiko Kuwanoc. Synthesis and Structure Activity Analysis of Novel Dihydropyridine Derivatives to Overcome Multidrug Résistance. Bioorganic & Medicinal Chemistry Letters, 2001; 11: 275-277.
10. Mithlesh, Pawan.K. Pareek, Ravi Kant, Sanjeev .K. Shukla, Krishan G. Ojha.Rapid synthesis and biological evaluation of 1, 4- dihydropyridine derivatives containing a benzothiazolylmoiety.Cent. Eur. J. Chem, 2010; 8(1): 163–173.
11. GunarsTirzitis ,DaceTirzitis and ZhannaHyonen. Antioxidant activity of 2,6-dimethyl-3,5-dialkyloxycarbonyl-1,4-dihydropyridines in metal ion catalysed lipid peroxidation, Czech.J.FoodSci, 2001; 19(3): 81-84.
12. Atul Kumar, Ram AwatarMaurya, Siddharth Sharma, Mukesh Kumar, Gitika Bhatia. Synthesis and biological evaluation of N-aryl- 1, 4-dihydropyridinesas novel antidyslipidemic and antioxidant agents, European Journal of Medicinal Chemistry, 2010; 45: 501–509.
13. Brijeshkunvar Mishra and Richa Mishra.Synthesis of some 1, 4-dihydropyridine derivatives for anti-inflammatory activity, The Pharmacist, 2007; 2(1): 13-16.
14. B BSubudhi and P K Panda. Synthesis antiulcer activity of 1,4-dihydropyridines and their mannich bases with sulfanilamide. Indian Journal Of Chemistry, 2009; 48B: 725-728.
15. David J. Triggle. Calcium channel antagonists: Clinical uses—Past, present and future. Biochemical Pharmacology, 2007; 74: 1-9.

16. Love. B, Goodman. M, Snader. K, Tedeschi. R, Macko. E. Hantzsch-type dihydropyridine hypertensive agent., J. Med. Chem., 1974; 17: 956-965.
17. Bossert. F, Meyer .H, Wehinger. E. 4- Aryldihydropyridines, a new class of highly active calcium antagonists. Angew. Chem. Int. Ed. Engl., 1981; 20: 762-769.
18. Breitenbucher. J.G., Figliozz . G. Solid-phase synthesis of 4-aryl-1,4-dihydropyridines via the Hantzsch three component condensation. Tetrahedron Lett., 2000; 41: 4311-4315.
19. Boer. R &Gekeler .V. chemosensitiser in tumour therapy: new compounds promise better efficacy, Drugs Fut, 1995; 20: 499-509.
20. Briukhanov .V .M. The effect of Ca antagonist on the development of inflammatory edema in rats. Exp .clin .pharmocology, 1994; 57: 47- 49.
21. BahekarSushilkumar, ShindeDevanand. Synthesis and anti-inflammatory activity of 1, 4-dihydropyridines. Acta pharmaceutica (Zagreb) A., 2002; 52(4): 281-287.
22. Wachter. G. A, Davis M.C. Antimycobacterial activity of substituted isosters of pyridines and pyrazine carboxylic acids. J med chem., 1998; 41: 2436-2438.
23. S.Gullapalli, P.Ramarao. L-type Ca2+ channel modulation by dihydropyridines potentiates- κ-opioid receptor agonist induced acute analgesia and inhibits development of tolerance in rats. Neuropharmacology, 2002; 42: 467–475.
24. Sunkel. C.E, De casa Juana.M.F, Santos.L. 4- alkyl-1,4-dihydropyridines as specific PAF- acether antagonists . J med chem., 1990; 33: 3205-3210.
25. Ono Handkinura. M. Effect of Ca+2antagonist, vasodilators, diltizem, nifedipine, perhexiline and verapamil on platelet aggregation invitro. Arzneim-forsch Drug Res, 1981; 3: 1131- 1134.
26. Wilson and Giswold., Text Book Of Organic medicinal and Pharmaceutical Chemistry,11th Edition, 628.
27. Tusell J.M, Barron.s and Seratosa .J. Anticonvulsant activity of -HCH, calcium channel blockers and calmodulin antagonists in seizures induced by lindane and other convulsant drug. Brain Res, 1993; 622: 99- 104.
28. L. M. Tarasenko, K. S. Neporada, and V. Klusha. Stress-Protective Effect of GlutapyroneBelongingto a New Type of Amino Acid-Containing 1,4-Dihyropyridines on Periodontal Tissuesand Stomach in Rats with Different Resistance to Stress. Bulletin of Experimental Biology and Medicine, 2002; 133(4): 426-428.
29. Roberta Budriesi, PierfrancoIoan, Alessandra Locatelli .Imidazo[2,1-b]thiazole System: A Scaffold Endowing Dihydropyridines with Selective Cardiodepressant Activity. J. Med. Chem., 2008; 51: 1592–1600.