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SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL 1, 4-DIHYDROPYRIDINE DERIVATIVES

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Abstract:
A new series of new1, 4-dihydropyridine and their derivatives have been synthesized and the structures of the compounds have been confirmed by IR and NMR. Representative compounds were screened for their anti-microbial activity against gram-negative bacteria, *E coli* and *P.aeruginosa* and gram-positive bacteria, *S aureus*, and *C diphtheriae* using disc diffusion method. Some of these compounds have been found to exhibit excellent antibacterial activity.

Keywords : 1,4- Dihydropyridine, Indandione, aromatic aldehydes

INTRODUCTION:

1,4-Dihydropyridines [1,2] are well known as calcium channel blockers and have emerged as one of the important classes of drugs for the treatment of hypertension[3].1,4-Dihydropyridines plays a significant role in the world of medicine because of their effectiveness as calcium channel blockers. Among 1,4-dihydropyridines,4-aryl-1,4-Dihydropyridine dicarboxylic diester of nifedipine have been used in the cardiovascular diseases. Due to their vasodilator [4] properties in the angima and hypertension. The dihydropyridine heterocyclic ring is the common feature of various bioactive compounds such as vasodilator [5], antitumour and antidiabetic[1].
Recently reported studies have shown that compounds possessing 1,4-dihydropyridine nucleus possess variety of biological activities including antimicrobial agents[6-8],myocardial infarction, peripheral vascular disorders4,antitubercular,anti-inflammatory agents. The studies have revealed that 1,4 DHP's exhibit several other medicinal applications, which include neuroprotectant and platelet antiaggregatory activity, in addition to acting as a cerebral antiischemic agent in the treatment of Alzheimer's diseases and chemosensitiser[9] in the therapy. The examples clearly demonstrated the potential of novel DHP derivatives as a source of valuable drug candidate.

Dihydropridine appears to be a privileged structure in medicinal chemistry and pharmacology. They display the affinity for many diverse binding sites. This adaptability has been utilized to optimize the affinity in binding to many receptors. Thus by careful structural modification, regioselectivity has been possible at sites other than Ca^{+2} channels[10].

A recent computational analysis of compressive medicinal chemistry database found the DHP framework to be among the most profilic chemo-type found. Thus the synthesis of this heterocyclic nucleus is of continuing interest. The success of these calcium antagonists has led to the development of novel synthetic strategies to improve their classical methods of preparation. In view of the above facts, six new derivatives of 1, 4-Dihydropryridine has been synthesized, characterized and evaluated for their antibacterial activity.

RESULTS AND DISCUSSION

The original protocol for the preparation of 1,4-Dihydropyridine consisted of heating a mixture of the three components β-keto-ester, aromatic aldehyde, and Ammonium acetate (3) in ethanol, using Ammonium Acetate itself as a catalyst.This procedure leads in one-step one pot to the desired 1,4-dihydropyridine.

The target molecules 1, 4 dihydro-4-(Substituted phenyl) - 2(3)-5(6)-di-indino-pyridine **4a-f** were synthesized in good yield by the one pot reaction of Aromatic aldehydes **1**, Indandione **2**, and Ammonium Acetates **3** in refluxing ethanol using Ammonium Acetate itself as a catalyst **(Scheme I)**. Further, the newly synthesized compounds were screened for their antibacterial activity against gram negative as well as gram positive bacteria, which shows promising activity against both.

The spectral analysis of representative compounds will be as follows:

*1, 4 dihydro-4- pheny)-2(3)-5(6)-di-indino-pyridine (**4a**)*
Yield: 84%; m.p.=190-192°C ;
Anal.Calcd for $C_{25}H_{15}O_2N$: C,83.10;H,4.16;N,3.88%.Found: C,83.05;H,4.12,N,4.11%.
IR (cm^{-1}): 1670 (C=O), 3330(NH)**,**
^{1}H NMR(DMSO-d_6,δ /ppm): 6.85(1H,s,CH),7.05-7.46 (13H, m, Ar- H), 9.26 (1H,s,NH).

*1, 4 dihydro-4- (4'-chloropheny)-2(3)-5(6)-di-indino-pyridine (**4b**)*
Yield: 86%; m.p.=220-222°C ;
Anal.Calcd for $C_{25}H_{14}O_2NCl$: C,75.86;H,3.54;N,3.54%.Found: C,75.83;H,3.51,N,3.51%.
IR (cm^{-1}): 1685 (C=O), 3321(NH)

1, 4 dihydro-4-(4'-methoxy- phenyl)-2(3)-5(6)-di-indino-pyridine **(4c)**
Yield: 88%; m.p.=185-188°C ;
Anal.Calcd for $C_{26}H_{17}O_3N$: C,79.80;H,4.35;N,3.58%.Found: C,79.75;H,4.32,N,3.54%.
IR (cm^{-1}): 1692 (C=O), 3310(NH)**,**
^{1}H NMR(DMSO-d_6,δ/ppm): 3.89(3H,s,OCH_3), 6.62 (1H,s,CH), 6.93-7.90 (12H,m,Ar- H), 8.81 (1H,s, NH),
^{13}C NMR(DMSO-d_6,δ/ ppm): 55.38(OCH_3), 115.28 (CH), 122.63-147.02 (C=C,Ar-C), 182.7 (C=O).

1, 4 dihydro-4-(2'-hydroxy- phenyl)-2(3)-5(6)-di-indino-pyridine **(4d)**
Yield: 83%; m.p.=193-196°C ;
Anal.Calcd for $C_{25}H_{15}O_3N$: C,79.58; H,3.98; N,3.71%. Found: C,79.54; H,3.98, N,3.68%
IR (cm^{-1}): 1750(C=O), 3290(NH)**,**

1, 4 dihydro-4-(2'-hydroxy-4'-methoxy- phenyl)-2(3)-5(6)-di-indino-pyridine (**4e)**
Yield: 87%; m.p.=201-203°C ;
Anal.Calcd for $C_{26}H_{17}O_4N$: C,76.66; H,4.18; N,3.44%. Found: C,76.62; H,4.12, N,3.48%.
IR (cm^{-1}): 1750(C=O), 3290(NH)**,**
^1H NMR(DMSO-d_6,δ /ppm): 3.56 (3H,s,OCH_3), 5.24 (1H,s,OH),6.63 (1H,s,CH),7.4-7.9 (11H,m,Ar- H), 8.8 (1H,s, NH).
^{13}C NMR(DMSO-d_6,δ/ ppm): 55.65(OCH_3), 114.29 (CH), 120.56-139.8 (C=C,Ar-C), 182.7 (C=O).

1, 4 dihydro-4-(4'-hydroxy- phenyl)-2(3)-5(6)-di-indino-pyridine (**4f)**
Yield: 82%; m.p.=204-206°C ;
Anal.Calcd for $C_{25}H_{15}O_3N$: C,79.58; H,3.98; N,3.71%. Found: C,79.55; H,3.94, N,3.69%.
IR (cm^{-1}): 1758(C=O), 3305(NH)**,**

EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. 1H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using CDCl3/DMSO-d6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

SYNTHESIS OF 1, 4-DIHYDROPYRIDINE:

General Procedure.
Aromatic aldehydes **1**(0.05 mol), Indandione **2** (0.05 mol) and Ammonium Acetate **3** (0.1 mol) was refluxed on a water bath in ethanol using Ammonium Acetate itself as a catalyst. The progress of the reaction was monitored by TLC. After completion of the reaction, the concentrated reaction mixture was cooled and poured onto ice-cold water. The solid that separated was filtered off, dried, and recrystallized from absolute alcohol to obtain pure compound (**4**)
The physical characterization of synthesized compound was given in **Table I**.

Antimicrobial and antifungal activities

All the newly synthesized compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method[11, 12]. The zone of inhibition was measured in mm and the activity was compared with standard drug. The antimicrobial data was given in **Table II**.

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TABLE I: Physical data of Compounds 4

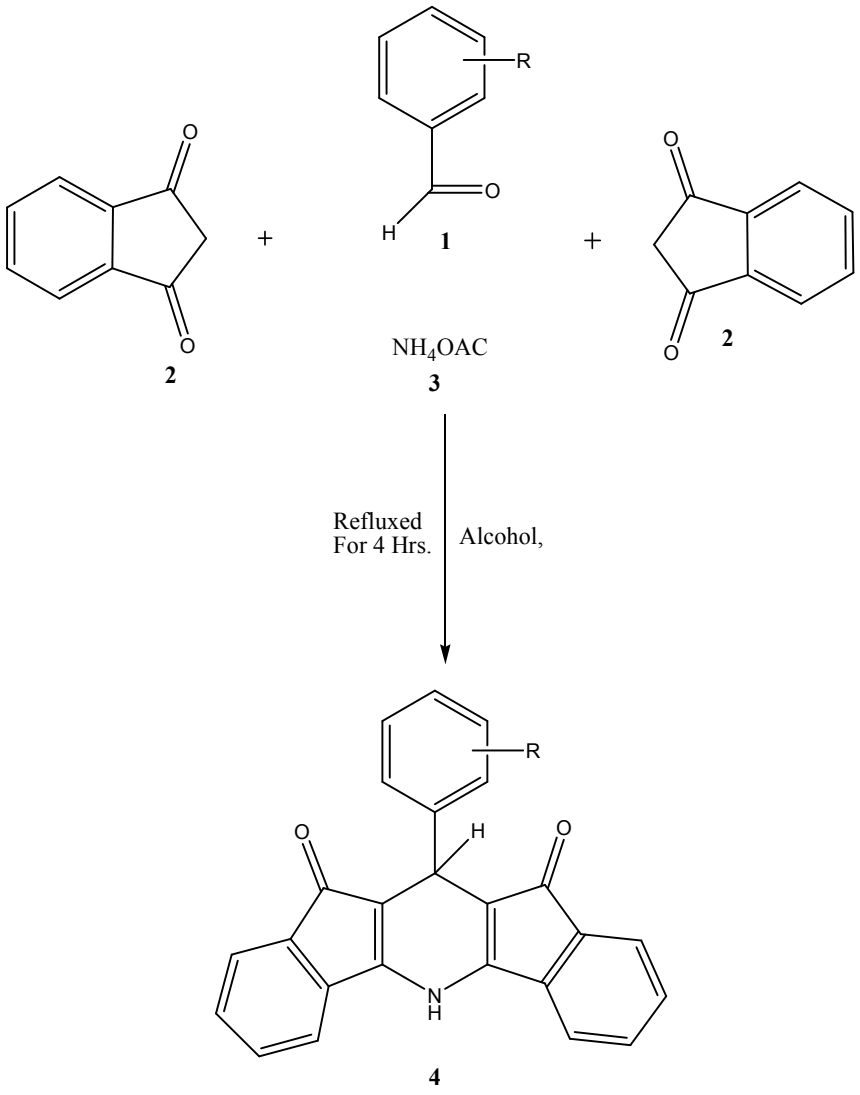
Compounds	R	Mol. Formula	m.p. (°C)	Yield (%)
4a	H	$C_{25}H_{15}O_2N$	190-192	84
4b	4-Cl	$C_{25}H_{14}O_2NCl$	220-222	86
4c	4-OCH_3	$C_{26}H_{17}O_3N$	185-188	88
4d	2-OH	$C_{25}H_{15}O_3N$	193-196	83
4e	4-OCH_3,2-OH	$C_{26}H_{17}O_4N$	201-203	87
4f	4-OH	$C_{25}H_{15}O_3N$	204-206	82

TABLE II: Antibacterial Activity of compound 4

Antibacterial Activity of compound 4				
Comp.	**Zone of inhibition (in mm)**			
	Gram Positive		**Gram negative**	
	S.aureus	**C.diphtheria**	**P.aeruginosa**	**E.coli**
4b	22	20	21	19
4c	21	18	20	18
4d	18	19	18	14
4e	16	18	17	18
4f	21	22	16	17
Amphicilin trihydrate	26	28	24	21
DMSO	0	0	0	0

* Diameter of the disc was 6mm;
Concentration of the compounds taken was about 100 μg/mL.

Scheme I



Scheme I : Pathway of Synthesis of 4(a-f)