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Synthesis, characterization and *In-vitro* antioxidant activity of Mannich bases of novel 1, 4-dihydro pyridines derivatives

M Vijey Aanandhi, S Kalvikkarasi*, K Arumuga Navamani, P Shanmugasundaram

Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, VELS University,Chennai - 117.Tamilnadu.INDIA.

ABSTRACT

A series of mannich bases (1a-2e) were synthesized by the reaction of β-Keto ester and formaldehyde and appropriate amines by condensation technique. The procedure afforded various 1,4 – dihydro pyridine derivatives with 70% yield .Structures were characterized by means of spectral data. All the synthesized compounds were subjected to biological evaluation for anti-bacterial, anti-fungal and anti-oxidant activity.

Keywords: 1,4dihydro pyridines, Mannich bases, Anti-bacterial, Anti-fungal, Anti oxidant activity.

Corresponding author
Email: mvaanandhi@gmail.com

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INTRODUCTION

1,4 Dihydro pyridines are nitrogen containing heterocyclic compound, possessing broad spectrum of biological and pharmacological activities such as anti microbial, analgesic, anti convulsant, anti inflammatory and anti ulcer activity. Earlier reports have shown that beneficial to antioxidant, antimicrobial activity. In this regard it was planned to synthesize some 1,4 dihydro pyridine derivatives by different substituted aromatic aldehydes group with aryl amines using mannich reaction.

EXPERIMENT

Melting points were determined in open capillary tubes and were found uncorrected.IR spectra wererecordedonFT-IR spectrometer(Perkin Elmer) using KBR disc method.^{1}HNMR spectra were recorded on ^{1}H FT-NMR (BruckerAMX 400MHz) spectrometer in DMSO.The compounds were analyzed for elemental analysis and the percentage of elements were found to be near that of the calculated values.Physical data of the compounds are recorded in Table-1 and the spectral data are recorded in Table-2.

Procedure

Step I Preparation of the 1,4-dihydropyridine derivatives

General procedure

A mixture of aldehyde (0.2mole), ethylacetoacetate (0.2mole) and concentrated ammonium hydroxide (8 ml) in ethanol (60ml) was heated under reflux for 3 hours. To the resulting mixture, warm water (40 ml) was added and then allowed to cool. The separated product was filtered off, washed with 60% aqueous ethanol and recrystallized from alcohol to give product and it is used for the further reaction. **(compound 1a).**

Similarly, compounds(1a-e) were prepared by condensation of 2moles ethylacetoacetate and ammonium hydroxide with other aromatic aldehyde.

Step II Preparation of 1,4-dihydropyridine derivatives

A mixture of compound (Ia), p- aminobenzoic acid (0.01 mole) and p-formaldehyde (0.02 mole) was taken in 15 ml of rectified spirit and heated under reflux for 4 hours. The reaction mixture was poured on to crushed ice. The product was filtered and recrystallized from aqueous ethanol to give product **(compound 2a).**

Similarly, compounds **(2a-e)** were prepared by condensation of p-aminobenzoic acid and p-formaldehyde with product (1a-e).

Melting point 120° – 155°C

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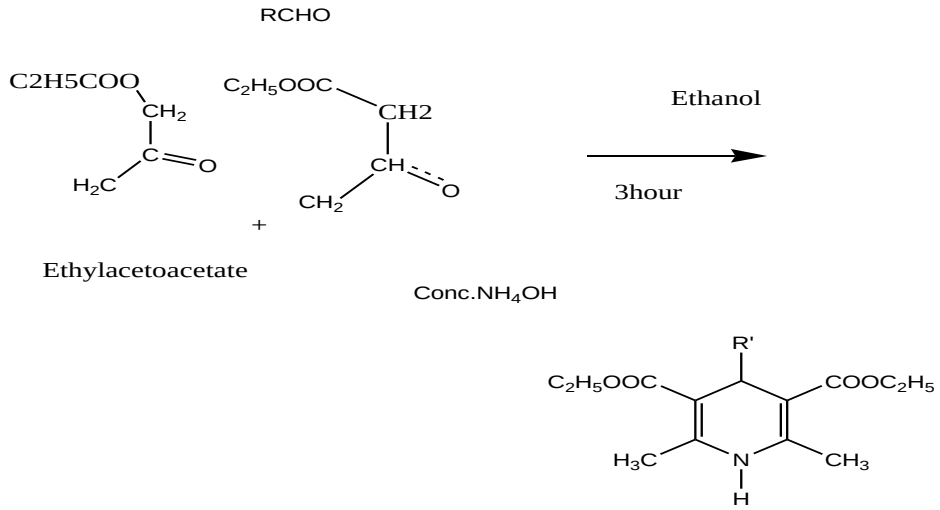
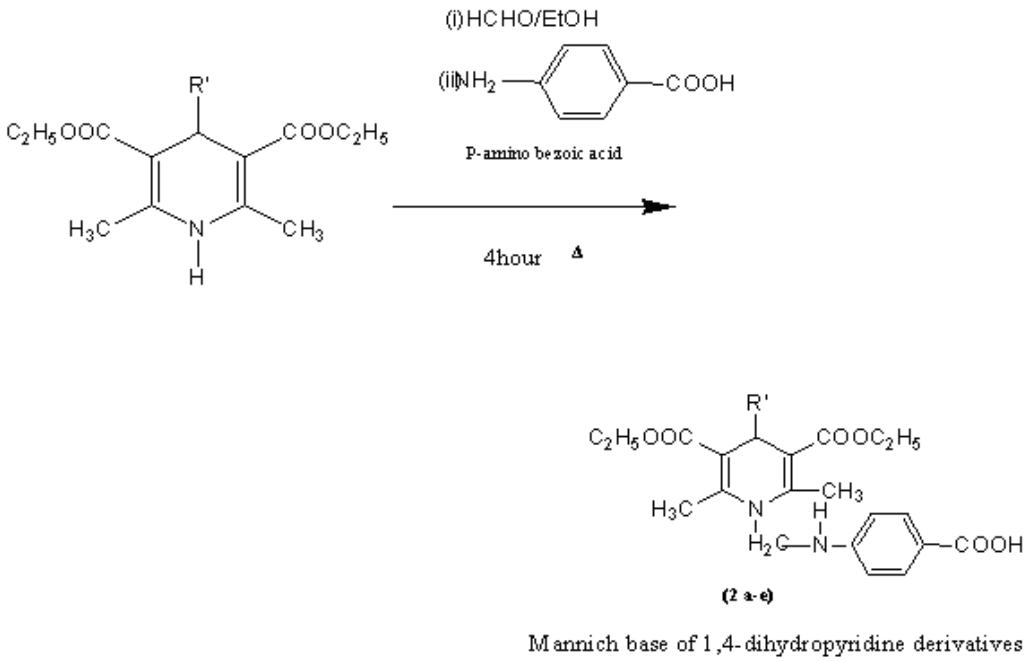
R_f value	0.23-0.71
% yield	70%

SCHEME **STEP – I**



(1 a-e)

STEP II



(2 a-e)

Mannich base of 1,4-dihydropyridine derivatives

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RESULTS AND DISCUSSION

Pharmacological evaluation

Anti- oxidant activity

The synthesized compounds were screened for there *in vitro* antioxidant activity by Nitrous oxide and Hydroxyl radical scavenging activity. The results obtained were tabulated in **Table 4, 5** were given as mean IC_{50}. All the synthesized compounds showed good anti-oxidant activity, out of all the synthesized compounds 1e, 2c, 2d, 2e showed significant anti-oxidant activity, in all the method except the compound 1a is less when compared to that of the standard Butylated hydroxyl Toluene (BHT).

Anti -microbial activity

The synthesized compounds were screened for their anti-microbial activity by Disc diffusion methodusing M.H Agar media and sabouraud's dextrose agar medium for bacteria and fungi respectively. The disc (6mm in diameter), impregnated with test compound 100µg/disc and ciprofloxacin (1000µg/disc) were used as positive reference standards to determine the sensitivity of each microbial species tested. The plates are innoculated at 37°C for 24 hrs and 27°C for 72 hrs for bacterial and fungal strains respectively. Anti microbial activity was evaluated by measuring the diameterof zone of inhibition against test organisms.Based on the results it is refered that synthesis of some 1,4- dihydro pyridine derivatives have significant inhibition effect on the growth of bacteria like *Escherichia coli, Pseudomonas aeruginosa Bacillus cereuves, Staphylococus aureus.*The results were tabulated in **Table 9**. The results showed that the compounds 1d, 2b 2c showedvery good activity when compare to that of the standard (ciprofloxacin).The activity was due to the presence of methoxy group in 3&4th position in compd(2b), compd (2c) presence of chlorine in 2&4th position and presence of methyl group in p-position in compd(1d) [1-17].

CONCLUSION

In summary, 1,4-dihydro pyridines containing methoxy, ester,chlorine substitution showed more anti-microbial activity and compound containing hydroxyl,methoxy,methyl showed more anti-oxidant activity

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Table 1: Physical and analytical data of synthesized compounds

S.No.	Compound	Mol. Formula	Molecular Weight	Yield in percentage (%)
1	1a	$C_{29}H_{32}N_2O_6$	355.43	65
2	1b	$C_{28}H_{32}N_2O_7$	389.44	68
3	1c	$C_{27}H_{28}N_2O_6Cl_2$	361.64	67
4	1d	$C_{28}H_{32}N_2O_6$	343.42	70
5	1e	$C_{29}H_{34}N_2O_9$	450.16	63
6	2a	$C_{29}H_{32}N_2O_6$	504.57	62
7	2b	$C_{28}H_{32}N_2O_7$	508	63
8	2c	$C_{27}H_{28}Cl_2N_2O_6$	510.70	62
9	2d	$C_{28}H_{32}N_2O_6$	492	65
10	**2e**	$C_{29}H_{34}N_2O_9$	554	60

Table 2: Spectral data of synthesized compounds

S.No	I.R	NMR	Mass
1a	3369,1443,1283,1147	7.14-7.30	355.58 M^+
1b	3348,1776,1388,1198	114.1-149.7, 16.3	389.66 M^+
1c	3380,1621,1400,1269	4.43,7.16,1.71	361.64 M^+
1d	3409,1581,1315,1067	4.43-6.94,	343.42 M^+
1e	3667,1744,1694,1645	5.96,1.71	450.16 M^+
2a	3177,1509,1371,1231	6.87-7.30,1.71	504.57 M^+
2b	3335,1651,1475,1360,1167	6.46-8.05, 1.71,3.73	508 M^+
2c	3464,1721,1530,1150,830	6.94-8.05, 1.71	510.70 M^+
2d	3365,1587,1299,724,693	6.87-8.05, 1.7-2.78	492 M^+
2e	3369,1443,1315,1147,694	5.96-8.05, 1.71,5.0,3.73	554 M^+

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Table 3: Antimicrobial activity of synthesized 1,4-dihydropyridine derivatives

S. No.	Compound	Antibacterial activity zone of inhibition (mm)				Antifungal activity zone of inhibition (mm)	
		B.cereus	*S.aureus*	*E.coli*	*P.aeruginosa*	*C.albicans*	*A.niger*
1	**1a**	14	12	13	-	12	18
2	**1b**	17	-	-	14	13	14
3	**1c**	13	15	17	17	15	19
4	**1d**	**20**	16	19	16	16	18
5	**1e**	-	-	17	12	12	17
6	**2a**	13	-	14	-	19	16
7	**2b**	**24**	19	15	20	17	14
8	**2c**	**25**	12	18	18	16	19
9	**2d**	18	-	17	-	14	15
10	**2e**	14	16	-	19	18	17
11	**Ciprofloxacin**	30	30	28	28	-	-
12	**Ketokonazale**	-	-	-	-	31	30

Bold -> showed ↑ activity

Table 4*: In -vitro* Nitric oxide scavenging activity of synthesized compounds

S. No.	Compounds	%RSC				IC_{50}
		25µg/ml	50µg/ml	75µg/ml	100µg/ml	
1	**1a**	7.15±0.07	13.59±0.09	22.61±0.13	39.02±0.01	>100
2	**1b**	18.71±0.25	29.00±0.32	40.19±0.08	51.00±0.001	98.03
3	**1c**	14.86±0.23	28.57±0.09	39.48±0.12	50.30±0.19	99.22
4	**1d**	19.43±0.14	30.22±0.1	43.00±0.37	54.22±0.23	92.21
5	**1e**	26.39±0.12	52.79±0.2	72.28±0.19	82.00±0.09	47.35
6	**2a**	13.28±0.12	27.86±0.09	38.27±0.2	51.82±0.3	96.48
7	**2b**	16.90±0.08	31.00±0.019	44.08±0.13	66.12±0.09	75.62
8	**2c**	31.71±0.07	50.64±0.12	67.95±0.19	81.00±0.24	49.36
9	**2d**	34.00±0.09	59.81±0.21	73.39±0.25	84.56±0.16	41.79
10	**2e**	40.43±0.23	65.28±0.13	78.80±0.09	90.73±0.24	38.29
11	**BHT**	70.25±0.62	75.27±0.41	81.23±1.03	83.77±0.42	16.29

All the readings were expressed as mean ± SD for three values

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Table 5 *: In -vitro* Hydroxyl radical scavenging activity of synthesized compounds

S. No.	Compounds	%RSC				IC_{50}
		25µg/ml	50µg/ml	75µg/ml	100µg/ml	
1	**1a**	10.23±0.12	20.32±0.32	34.19±0.10	49.12±0.01	>100
2	**1b**	17.71±0.21	28.59±0.32	39.19±0.83	50.00±0.83	100
3	**1c**	10.49±0.02	19.96±0.4	33.83±0.09	51.96±0.1	51.66
4	**1d**	16.90±0.28	30.69±0.42	43.18±068	58.12±0.1	86.02
5	**1e**	23.28±0.56	67.86±0.35	79.27±0.81	92.82±0.3	36.84
6	**2a**	18.63±0.25	29.60±0.32	42.00±0.08	51.00±0.001	98.03
7	**2b**	19.43±0.14	31.22±0.1	48.36±0.34	62.22±0.28	80.36
8	**2c**	32.92±0.05	62.83±0.12	73.19±0.10	81.31±0.20	39.78

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