

# Synthesis of 1, 4-Dihydropyridine Derivatives By Schiff And Mannich Base

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**ABSTRACT:** A series of Diethyl 2, 6-dimethyl-4-substituted phenyl-1, 4-dihydropyridine-3, 5 dicarboxylate (1a & 1b) are prepared following Hantzsch pyridine synthesis by condensation of ethyl acetoacetate with different aromatic aldehyde in presence of ammonia (1). Compound 1a-1b on reaction with p-formaldehyde and different secondary amines yields diethyl 2, 6-dimethyl-4-substituted phenyl-1-methyl substituted amine, 4-dihydropyridine-3, 5-dicarboxylate (2a-2g). The structures of the synthesized compounds were elucidated by spectral analysis (IR and <sup>1</sup>HNMR). Investigations of anti-inflammatory activity effects of the synthesized compounds were studied by carrageenan-induced acute rat hind paw edema model and compared with indomethacin as a standard drug. The study indicated that all compounds exhibited good anti-inflammatory activity.

**KEYWORDS:** 1, 4-dihydropyridine, Schiff and mannich base, Antiinflammatory activity.

## I. INTRODUCTION

1, 4-Dihydropyridines (1, 4-DHPs) are important class of compounds in the field of drugs and Pharmaceuticals. Hantzsch 1, 4-dihydropyridines (dialkyl 1, 4-dihydro-2, 6 dimethylpyridine-3, 5-dicarboxylates) are widely used clinically as calcium channel blockers for the treatment of cardiovascular diseases, such as, nifedipine and nitrendipine are used for the treatment of hypertension and angina pectoris<sup>1</sup>. 1, 4-Dihydropyridines (1, 4-DHP's) have a broad range of pharmacological activities and also proven to be very important synthetic intermediates, finding application in the preparation of a large number of nitrogen alkaloids<sup>2</sup>. 1,4 Dihydro pyridines are nitrogen containing heterocyclic compound, possessing broad spectrum of biological and pharmacological activities such as antimicrobial<sup>3,4</sup>, anticonvulsant<sup>5</sup>, antioxidant<sup>6</sup>, antituberculosis<sup>7</sup>, antiulcer<sup>8</sup>.

## II. EXPERIMENTAL

Melting points were determined in open capillary tubes and were found uncorrected. R<sub>f</sub> values were obtained using silica gel thin layer chromatography plates. The infrared spectra of all compounds were recorded on FT-IR spectrometer using KBR disc method.<sup>1</sup>HNMR spectra were recorded on <sup>1</sup>H FT-NMR (Bruker AMX 400MHz) spectrometer in DMSO. The compounds were analyzed for elemental analysis. Pharmacological screening was done in institutional animal ethics committee (IAEC) of bharathi college of pharmacy.

*Method for preparation of diethyl 2, 6-dimethyl-4-substituted phenyl-1, 4-dihydropyridine-3, 5 dicarboxylate (1a-1b)*

The equimolar quantities of different substituted aromatic benzaldehydes (0.2 M) and ethyl acetoacetate (0.2 M) and ammonia (8 ml) in ethanol (30 ml) and reflux for 3 hr then to the resulting mixture add 40 ml warm water and cool filter the product and recrystallized from alcohol. Similarly, compounds (1a-1b) were prepared by condensation of (0.2 M) ethylacetoacetate and ammonium hydroxide with other aromatic aldehyde.

*Method for preparation of diethyl 2, 6-dimethyl-4-substituted phenyl-1-methyl substituted amine, 4-dihydropyridine-3, 5-dicarboxylate (2a-2g)*

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The equimolar quantities of compound (1a-1b) and different secondary amines and *p*-formaldehyde in 20ml of ethanol were added drop wise with vigorous stirring at room temperature for 12 hr. The mixture was cooled followed by refrigeration for 1days, filter the solid mass and dry. Similarly, compounds (2a-g) were prepared by using different secondary amines (morpholine, piperidine, diethyl amine, diphenylamine, piperazine) and *p*-formaldehyde with product (1a-b).

## Biological activity

### Antiinflammatory activity

The inhibitory activity of synthesized compound on carrageenan induced rat paw edema will be determined according to mercury displacement method by using plethismograph. 4 groups of adult male albino rates (130-180 gm) four animals in each will be orally dosed with synthesized compound one hour before carrageenan challenge, hind paw edema will be induced by sub planter injection of 0.05 ml of 1% suspension of carrageenan in saline in to the planter tissue of one hind paw. The equal vol. of saline will be injected serve as a control group. The standard group will receive indomethacin (10 mg/kg) s.c. The mercury displacement will be compared with standard for evaluation of anti-inflammatory activity of synthesized compound., the paw volumes were recorded with in 1hr interval time duration.

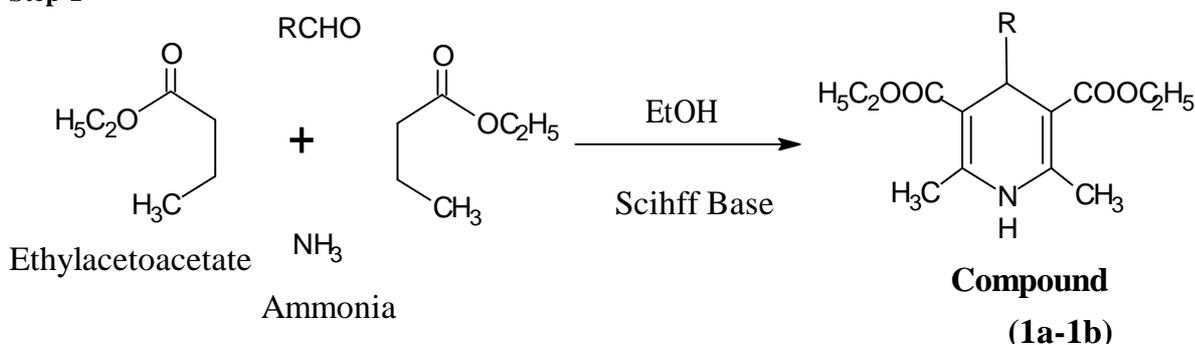
## III. RESULTS AND DISCUSSION

### Chemistry

Substituted 1,4-dihydropyridine was a versatile starting material for the synthesis of number of proposed compounds (Scheme, Table 1). The different diethyl 2, 6-dimethyl-4-substitutedphenyl-1-methylsubstituted amine, 4-dihydropyridine-3, 5-dicarboxylate were prepared by reacting the diethyl 2, 6-dimethyl-4-substituted phenyl-1, 4-dihydropyridine-3, 5 dicarboxylate (Scheme). These synthesized compounds (2a-2g) showed absorption bands ranging from 2900-3000  $\text{cm}^{-1}$  for C-H stretching of aromatic ring (phenyl). For compound (2b), it shows peak at 2399.45  $\text{cm}^{-1}$  for O-CH<sub>3</sub>. For compound (2a, 2d, 2f), it show a peak at 2966.52  $\text{cm}^{-1}$  for aliphatic CH. For compound (2c), it shows peak at 1483.26 for CH<sub>2</sub> group. For compound (2e), it shows peak at 1660.71  $\text{cm}^{-1}$  for C=O group. For compound (2g), it shows peak at 3319.49  $\text{cm}^{-1}$  for NH group. The <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>,  $\delta$  ppm) spectra of all the compounds indicates aromatic multiplet between  $\delta$  7.0-7.4 ppm. For the compound (2a-2g), <sup>1</sup>H-NMR value is  $\delta$  1.14-1.77 (t, 4H) for CH<sub>2</sub> and  $\delta$  3.92-4.05 (m, 6H) for O-CH<sub>3</sub>. For the compound (2b, 2c), <sup>1</sup>H-NMR value is  $\delta$  3.6 (s, 3H) for OCH<sub>3</sub>. MASS spectra showed molecular ion peak at *m/z* [M<sup>+</sup>] 426.54, 427.53 and 388.39 for compounds (2a), (2b) and (2g), respectively, which is in agreement with proposed molecular formula C<sub>25</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>, C<sub>24</sub>H<sub>33</sub>N<sub>3</sub>O<sub>4</sub>, C<sub>24</sub>H<sub>33</sub>N<sub>3</sub>O<sub>4</sub>.

### SCHEME

#### Step-1



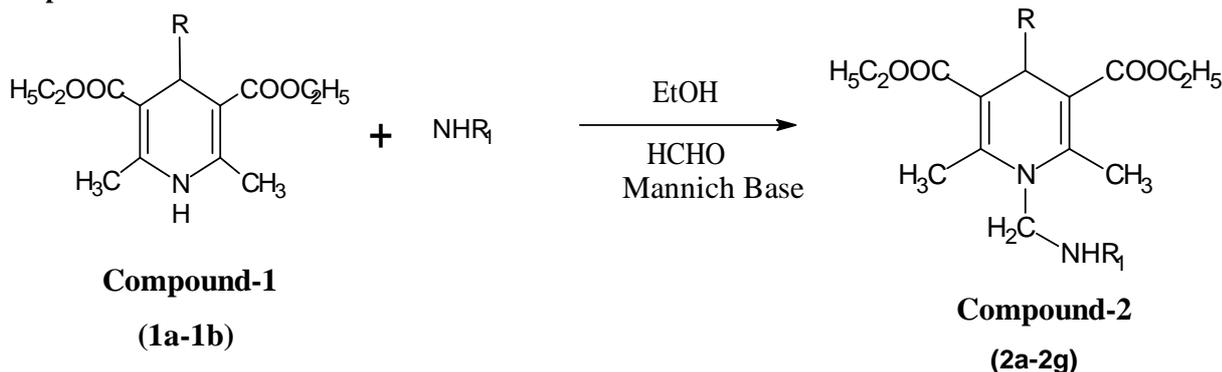
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### Step-2



R = Benzaldehyde, Anisaldehyde

R<sub>1</sub> = Piperidine, Morpholine, Diphenylamine, Dimethylamine, Piperazine

**Table 1:** Physicochemical data of synthesized compounds

Compound	R	R <sub>1</sub>	M.P	Mol.Formula	Mol.Wt	R <sub>f</sub> Value
2a	Benzaldehyde	Piperidine	188-190 °C	C <sub>25</sub> H <sub>34</sub> N <sub>2</sub> O <sub>4</sub>	426.54	0.46
2b	Anisaldehyde	Morpholine	192-193 °C	C <sub>25</sub> H <sub>34</sub> N <sub>2</sub> O <sub>6</sub>	458.54	0.56
2c	Anisaldehyde	Piperidine	188-190 °C	C <sub>26</sub> H <sub>36</sub> N <sub>2</sub> O <sub>5</sub>	456.57	0.72
2d	Benzaldehyde	Morpholine	190-192 °C	C <sub>24</sub> H <sub>32</sub> N <sub>2</sub> O <sub>5</sub>	428.52	0.50
2e	Benzaldehyde	diphenylamine	194-196 °C	C <sub>32</sub> H <sub>34</sub> N <sub>2</sub> O <sub>4</sub>	510.62	0.40
2f	Benzaldehyde	dimethylamine	192-194 °C	C <sub>22</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub>	336.48	0.51
2g	Benzaldehyde	Piperazine	190-192 °C	C <sub>24</sub> H <sub>33</sub> N <sub>3</sub> O <sub>4</sub>	427.53	0.33

**Table 2:** Spectral data of synthesized compounds

Compound	IR (KBr, cm <sup>-1</sup> )	<sup>1</sup> HNMR (δ, ppm)	MS
2a	3076.46 (aromatic C-H Str.), 2966.52 (Str. for aliphatic C-H), 1672.28 (Str. for C=O), 1298.90 (C-N), 1477.47 (Str. for CH <sub>2</sub> )	δ 7.1-7.2 (m, H, Ar-H), δ 1.1-1.4 (t, 4H, 2×CH <sub>2</sub> ester), δ 3.9-4.0 (m, 6H, O-CH <sub>3</sub> ester), δ 2.2 (s, 6H, C-CH <sub>3</sub> ), 4.8 (s, 2H, N-CH <sub>2</sub> ), 3.8 (s, 1H, CH).	426
2b	3089.96 (aromatic C-H Str.), 2399.45 (O-CH <sub>3</sub> ), 2964.59 (Str. for aliphatic C-H), 1664.57 (Str. for C=O), 1024.2 (C-O), 1467.83 (Str. For CH <sub>2</sub> )	δ 3.6 (s, 3H, OCH <sub>3</sub> ), δ 6.74-6.77 (d, ar-CH), 7.03-7.06 (d, Ar-CH), 1.12-1.15 (t, 4H, 2×CH <sub>2</sub> ester), δ 3.9-4.0 (m, 6H, O-CH <sub>3</sub> ester), δ 2.24 (s, 6H, C-CH <sub>3</sub> ), 4.79 (s, 2H, N-CH <sub>2</sub> ), 3.8 (s, 1H, CH).	458
2c	3086.14 (aromatic C-H Str.), 2964.59 (Str. for aliphatic C-H), 1658.78 (Str. For C=O), 1296.16 (C-N), 1483.26 (Str. for CH <sub>2</sub> ).	δ 3.67 (s, 3H, OCH <sub>3</sub> ), δ 6.74-6.77 (d, Ar-CH), 7.03-7.05 (d, Ar-CH), 1.11-1.15 (t, 4H, 2×CH <sub>2</sub> ester), δ 3.92-4.04 (m, 6H,	

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		O-CH <sub>3</sub> ester), $\delta$ 2.24 (s, 6H, C-CH <sub>3</sub> ), 4.79 (s, 2H, N-CH <sub>2</sub> ), 3.8 (s, 1H, CH).	
2d	3078.39 (aromatic C-H Str.), 2966.52 (Str. for aliphatic C-H), 1658.78 (Str. for C=O), 1292.31(C-N), 1477.47 (Str. for CH <sub>2</sub> ).	$\delta$ 7.14-7.21 (m, 5H, Ar-H), $\delta$ 1.11-1.14 (t, 4H, 2 $\times$ CH <sub>2</sub> ester), $\delta$ 3.92-4.05 (m, 6H, O-CH <sub>3</sub> ester), $\delta$ 2.26 (s, 6H, C-CH <sub>3</sub> ), 4.87 (s, 2H, N-CH <sub>2</sub> ), 3.33 (s, 1H, CH <sub>2</sub> ).	
2e	3070.68 (aromatic C-H Str.), 2964.59 (Str. for aliphatic C-H), 1660.71 (Str. for C=O), 1361.74 (C-N), 1481.33 (Str. for CH <sub>2</sub> ).	$\delta$ 7.14-7.22 (m, 5H, Ar-H), $\delta$ 1.1-1.4 (t, 4H, 2 $\times$ CH <sub>2</sub> ester), $\delta$ 3.92-4.04 (m, 6H, O-CH <sub>3</sub> ester), $\delta$ 2.25 (s, 6H, C-CH <sub>3</sub> ), 4.86 (s, 2H, N-CH <sub>2</sub> ), 3.32 (s, 1H, CH), 5.13(s 10H CH).	510
2f	3074.53 (aromatic C-H Str.), 2966.52 (Str. for aliphatic C-H), 1666.5 (Str. for C=O), 1298.09 (C-N), 1483.29 (Str. for CH <sub>2</sub> ).	$\delta$ 7.14-7.21 (m, 5H, Ar-H), $\delta$ 1.11-1.14 (t, 4H, 2 $\times$ CH <sub>2</sub> ester), $\delta$ 3.92-4.05 (m, 6H, O-CH <sub>3</sub> ester), $\delta$ 2.26 (s, 6H, C-CH <sub>3</sub> ), 4.86 (s, 2H, N-CH <sub>2</sub> ), 3.33 (s, 6H, N-CH <sub>3</sub> ).	
2g	3319.49 (NH), 3074.53 (aromatic C-H Str.), 2964.59 (Str. for aliphatic C-H), 1693.5 (Str. for C=O), 1298.09 (C-N), 1462.04 (Str. for CH <sub>2</sub> ).	$\delta$ 7.14-7.21 (m, 5H, Ar-H), $\delta$ 1.11-1.14 (t, 4H, 2 $\times$ CH <sub>2</sub> ester), $\delta$ 3.92-4.05 (m, 6H, O-CH <sub>3</sub> ester), $\delta$ 2.26 (s, 6H, C-CH <sub>3</sub> ), 4.86 (s, 2H, N-CH <sub>2</sub> ), 3.33 (s, 4H, CH <sub>2</sub> ).	427

## IV. BIOLOGICAL ACTIVITY

The anti-inflammatory activity of all the synthesized derivatives substituted at 1<sup>th</sup> position has showed mild to good activity to induced inflammation. Among these morpholine, piperidine, diphenylamine, dimethylamine, piperazine, substituted derivatives were found to show potent anti-inflammatory activity at the end of 180 min (>60%) comparable with the standard indomethacin. The A<sub>2</sub>, A<sub>3</sub>, A<sub>5</sub>, A<sub>6</sub> and A<sub>7</sub> exhibited good anti-inflammatory activity at the end of 180 min (<60%).

Sl. No	Group	0hr	1hr	2hr	3hr
1	Control	2.95 $\pm$ 0.05	0.32 $\pm$ 0.04	0.35 $\pm$ 0.02	0.70 $\pm$ 0.04
2	Standard	2.82 $\pm$ 0.08	0.15 $\pm$ 0.01** (55.55%)	0.17 $\pm$ 0.02** (48.64%)	0.20 $\pm$ 0.01** (71.62%)
3	A <sub>1</sub>	2.88 $\pm$ 0.02	0.23 $\pm$ 0.01* (33.33%)	0.24 $\pm$ 0.03 (27.02%)	0.33 $\pm$ 0.01** (54.05%)
4	A <sub>2</sub>	2.89 $\pm$ 0.04	0.19 $\pm$ 0.01** (44.44%)	0.21 $\pm$ 0.01** (40.54%)	0.24 $\pm$ 0.02** (64.86%)
5	A <sub>3</sub>	2.91 $\pm$ 0.06	0.20 $\pm$ 0.01** (41.66%)	0.23 $\pm$ 0.02** (32.43%)	0.24 $\pm$ 0.01** (66.21%)
6	A <sub>4</sub>	2.88 $\pm$ 0.05	0.20 $\pm$ 0.01 (41.66%)	0.21 $\pm$ 0.04 (32.43%)	0.23 $\pm$ 0.06 (60.81%)
7	A <sub>5</sub>	2.92 $\pm$ 0.07	0.22 $\pm$ 0.01 (36.11%)	0.20 $\pm$ 0.05 (32.43%)	0.19 $\pm$ 0.04 (68.91%)

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8	A <sub>6</sub>	2.90 ± 0.04	0.21 ± 0.02** (36.11%)	0.19 ± 0.01 (45.94%)	0.18 ± 0.03** (71.62%)	<b>Table 3:</b> Anti-inflammatory activity of synthesized compound
9	A <sub>7</sub>	2.87 ± 0.04	0.18 ± 0.01** (47.22%)	0.21 ± 0.01** (40.54%)	0.24 ± 0.02** (64.86%)	

s (1a-1b) by using carageenan-induced rat paw edema model

## V. CONCLUSION

We have prepared seven compounds by reacting substituted diethyl 2, 6-dimethyl-4-substituted phenyl-1, 4-dihydropyridine-3, 5 dicarboxylate and various secondary amines in alcohol in presence of glacial acetic acid. All synthesized compounds were characterized by TLC, MP, and spectral analysis. IR spectrum of all synthesized compounds showed sharp peak at 2900-3000 cm<sup>-1</sup> for C-H stretching of aromatic ring (phenyl). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ ppm) spectra of all the compounds indicates aromatic multiplet between δ 7.0-7.4 ppm. All compounds were screened for anti-inflammatory activity. Compounds A<sub>2</sub>, A<sub>3</sub>, A<sub>5</sub>, A<sub>6</sub> and A<sub>7</sub> exhibited good anti-inflammatory activity comparable with the standard indomethacin at the end of 180 min (>60%).

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