

SYNTHESIS OF SOME NEW UNSYMMETRICAL 1,4-DIHYDROPYRIDINE DERIVATIVES AS POTENT ANTITUBERCULAR AGENTS

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ABSTRACT

2,6-dimethyl-3-acetyl-5-carbomethoxy-4-(3'-nitrophenyl)-1,4-dihydropyridine **1** was condensed with aromatic and heterocyclic aldehydes to form chalcone analogs **2a-h** and then cyclised to substituted pyrazolines leading to novel 1,4-dihydropyridine **3a-h**, **4a-h** and **5a-h** which are directly attached to heterocyclic moiety and devoid of the ester function at C₅ (of DHP). All compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* (H₃₇Rv).

INTRODUCTION

The dihydropyridines are the well-known drug moiety for the treatment of antihypertensive and cardiovascular disorders¹. However, it is also associated with antiallergic², antiinflammatory³, treatment of circulating diseases⁴, calcium channel antagonism⁵⁻⁸ etc. About 50 different dihydropyridines are launched as new drugs in last 20 years. The 3-nitrophenyl substituent at C₄ of DHP provides excellent stability and pharmacodynamic properties leading to many drugs like Nicardipine⁷, Pranidipine⁹, Nimodipine⁹, Tiamdipine¹⁰ and Manidipine¹¹. These drugs mainly exhibit calcium channel antagonist activity. The DHPs are still the subject of intensive study, due to recent development on *mdr* reversal in tumor cells which has given a new dimension of application of dihydropyridines¹²⁻¹³.

Our aim was to prepare some interesting new unsymmetrical dihydropyridine derivatives from 2,6-dimethyl-3-acetyl-5-carbomethoxy-4-(3'-nitrophenyl)-1,4-dihydropyridine **1**. Due to active group at 3rd position of DHP ring, the aldehydes were condensed with acetyl group in presence of base catalyst in ethanol to form chalcone analogs **2a-h**. They were refluxed with hydrazine or phenylhydrazine with acetic acid to afford substituted pyrazolines **3a-h**, **4a-h**, **5a-h** linked directly with dihydropyridine nucleus.

Elemental and spectral analysis supported the constitution of the product. The product was screened for their antitubercular activity. The compounds were tested against *M. Tuberculosis* H₃₇Rv. The standard drug used was Rifampicin. Primary screening was conducted at 12.5 µg/ml against *Mycobacterium Tuberculosis* (H₃₇Rv) strain in BACTEC 12B medium using the BACTEC 460-radiometric system¹⁴.

RESULTS AND DISCUSSION

It can be seen from Table-1 that substitution at 4-phenyl ring considerably affects the antitubercular activity and other analogs having 4-N, N-dimethylaminophenyl and 4-methoxyphenyl moieties showed 66% and 45% inhibition respectively. The percentage of inhibition indicated that

chalcone **2a** containing 3-nitrophenyl substitution showed significant activity (85%). The other substitutions did not show good activity. The 1H pyrazoline linked dihydropyridines were found to be almost inactive. The acetyl pyrazoline exhibited very good activity. The unsubstituted 4-phenyl ring of acetylpyrazoline **4f** showed 87% inhibition. The 1'-phenyl derivatives also exhibited significant activity. So far as structure activity relationship is concerned, 3-nitrophenyl group is able to exhibit significant activity.

EXPERIMENTAL

The melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded in NICOLET-MAGNA-IR 550 SERIES II and ¹H NMR recorded on Bruker AC-300 MHz FT NMR using TMS as an internal standard, chemical shift in δ ppm.

The compound 2,6-Dimethyl-3-acetyl-5-carbmethoxy-4-(3''-nitrophenyl)-1,4-dihydropyridine **1** was prepared according to the method described in literature¹⁵⁻¹⁷.

Preparation of 2,6-Dimethyl-5-carbmethoxy-4-(3'-nitrophenyl)-3-[3''-(4''-methoxyphenyl)]propane-1-one]-1,4-dihydropyridine **2a**.

To a well-stirred solution of 2,6-dimethyl-3-acetyl-5-carbmethoxy-4-(3'-nitrophenyl)-1,4-dihydropyridine (3.3 g, 0.01 M) and p-anisaldehyde (1.36 g, 0.01 M) in absolute ethanol, 40% NaOH solution was added till pH reaches to 8.0. Then reaction mixture was stirred for 24 hrs at 25-30°C. The reaction mixture was poured into crushed ice containing little amount of HCl. 10% Sodium bicarbonate solution was added and sticky mass was left overnight for isolation. The product was filtered, dried and recrystallised from ethanol, m.p. 160°C; yield 60%. Calculated for C₂₈H₂₄N₂O₈, C, 66.96; H, 5.36; N, 6.25; Found C, 67.00; H, 5.30; N, 6.29, ¹H NMR (300 MHz, CDCl₃+DMSO-d₆) δ : 3.80 (s, 3H); CH₃, 6.10-6.40 (dd, 2H, COCH=CH); 2.35 (s, 6H 2xCH₃); 3.59 (s, 3H, OCH₃); 5.23 (s, 1H, C₄H). IR (KBr) cm⁻¹: 1703 (C=O ester); 1685 (C=O chalcone); 1535, 1330 cm⁻¹ (C-NO₂).

Similarly other chalcones **2b-h** were prepared. The physical and analytical data were recorded in Table-2

Preparation of 2,6-Dimethyl-4-(3'-nitrophenyl)-5-carbmethoxy-3-[3''-(4''-methoxyphenyl)-2H-pyrazoline-5'-yl]-1,4-dihydropyridine **3a**.

A mixture of **2a** (4.48g, 0.01M) in ethanol, hydrazine hydrate (0.5g, 0.01M) and piperidine (1ml) was refluxed for 8-10 hrs in absolute ethanol. The isolated product was filtered, dried and recrystallised from ethanol to give **3a**, m.p. 144°C, yield 62%. Calculated for C₂₈H₂₈N₄O₅ : C, 64.93; H, 5.62; N, 12.12; Found C, 64.85; H, 5.73; N, 12.01; ¹H NMR (300 MHz CDCl₃+DMSO-d₆) δ : 2.36 (s, 6H, 2xCH₃); 3.56 (s, 3H, OCH₃); 3.64(s, 3H, COOCH₃); 5.10 (s, 1H, C₄H); 2.7-2.8 (t, 1H, CH-CH₂). IR (KBr) cm⁻¹: 3135 (NH); 1530, 1324 (C-NO₂).

Similarly other compounds **3b-h** were prepared. The physical and analytical data were recorded in Table-2.

Preparation of 2,6-Dimethyl-4-(3'-nitrophenyl)-5-carbmethoxy-3-[3'-(4''-methoxyphenyl)-2'-acetylpyrazoline-5'-yl]-1,4-dihydropyridine **4a**.

A mixture of **2a** (4.48g, 0.01 M) in acetic acid (10ml) and hydrazine hydrate (0.5g, 0.01M) was refluxed on constant temperature bath for 8hrs and kept overnight. The product was isolated dried and recrystallised in ethanol to give **4a**, m.p. 130°C, yield 58%. Calculated for C₂₇H₂₈N₄O₆ : C, 64.28; H, 5.52; N,

11.11; found: C, 64.32; H, 5.60; N, 11.00. ¹H NMR (300 MHz CDCl₃+DMSO-d₆) δ : 2.28 (s, 6H, 2xCH₃); 3.62 (s, 3H, OCH₃); 3.76 (s, 3H, COOCH₃); 5.07 (s, 1H >CH); 2.1-2.2 (t, 1H, -CH-CH₂); 3.76-3.81 (d, 2H, CH-CH₂); 1.93 (s, 3H, N-COCH₃). IR (KBr) cm⁻¹: 1701 (C=O-OCH₃); 1635 (N-C=OCH₃); 3227 (NH); 1635 (C=N); 1529,1347(C-NO₂).

Similarly other compounds **4b-h** were prepared. The physical and analytical data were recorded in Table-2.

Preparation of 2,6-Dimethyl-4-(3'-nitrophenyl)-5-carbmethoxy-3-[3'(4"-methoxyphenyl)-2'-phenylpyrazoline-5'-yl]-1,4-dihydropyridine 5a.

A mixture of **2a** (4.48gm, 0.01M) in 20ml of acetic acid and phenyl hydrazine (1.08g, 0.01M) was refluxed for 10-12 hrs on oil bath at 110-15°C. The resulting mixture was concentrated, cooled and poured into ice-cold water containing little HCl. The yellowish colored product was then filtered dried and recrystallized from aqueous ethanol to give **5a**, m.p. 115°C, yield 56%. Calculated for C₃₁H₃₁N₄O₅: C, 69.14; H, 5.57; N, 10.41; found C, 69.02; H, 5.63; N, 10.48. ¹H NMR (300 MHz CDCl₃+ DMSO-d₆) δ 2.33 (s, 6H, 2xCH₃); 3.66 (s, 3H, OCH₃); 3.77 (s, 3H, COOCH₃); 2.55-2.66 (t, 1H, CH-CH₂); 3.75-3.80 (d, 2H, -CH-CH₂); 5.20(s, 1H, C₄H). IR (KBr) cm⁻¹: 1720 (C=O-OCH₃); 1599 (C=N); 1599,1347 (C-NO₂).

Similarly other compounds **5b-h** were prepared. The physical and analytical data were recorded in Table-2

Table-1: Antitubercular screening result of compounds showing good activity against *M. Tuberculosis* (H₃₇Rv strain)

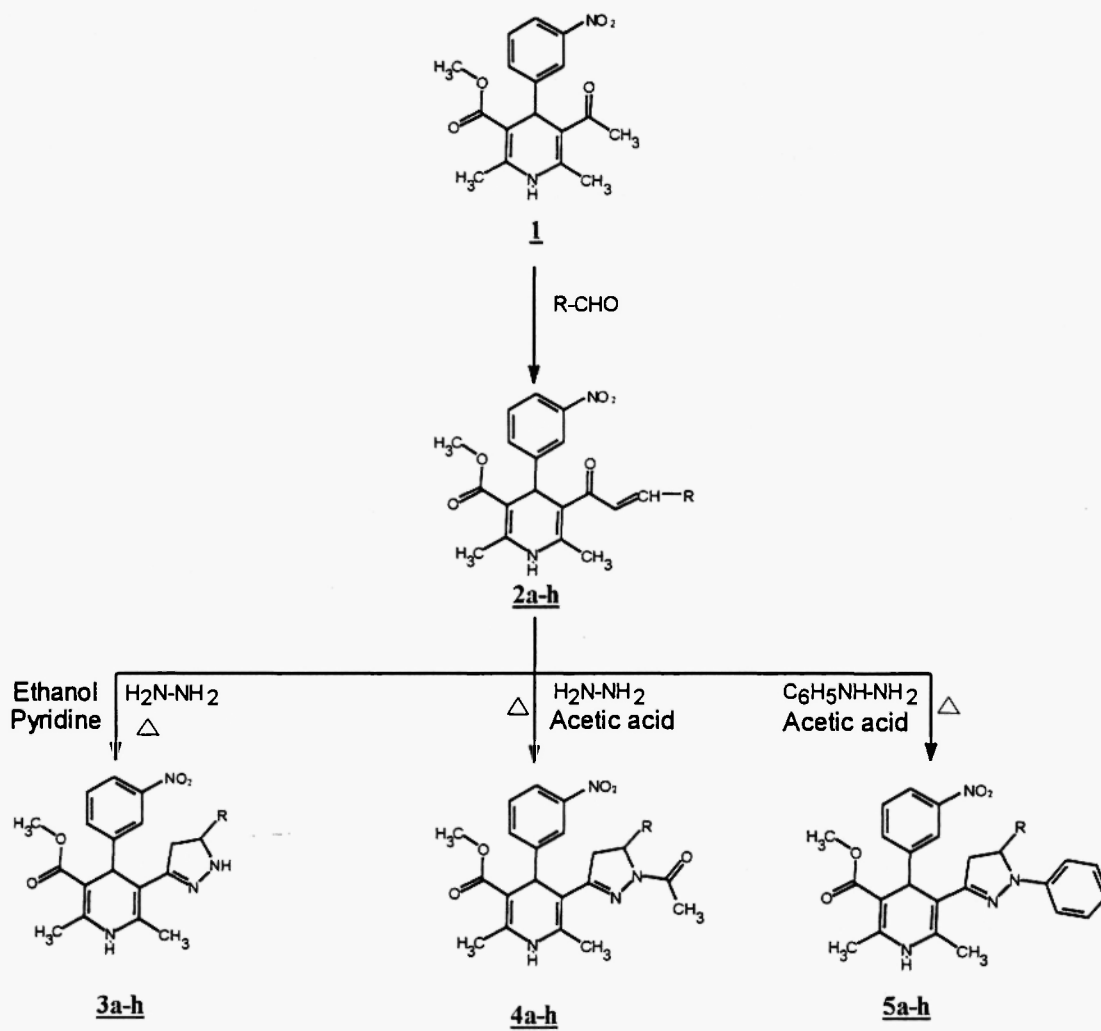
Compd.	MIC (μg/ml)	% Inhibition
4f	>12.5	87
2e	>12.5	85
5c	>12.5	68
5h	>12.5	66
4b	>12.5	63
5g	>12.5	57
4a	>12.5	54
4c	>12.5	52
4d	>12.5	50

*Rifampicin was used as a standard (MIC = 0.25 μg/ml)

Table-2: Physical and Analytical data of 2,6-Dimethyl-4-(3'-nitrophenyl)-5-carbomethoxy-3-substituted 1,4-dihydropyridines.

Compd.	R	Molecular Formula	M.P. (°C)	Yield (%)	% of Nitrogen Calcd.	Found
2a	4-OCH ₃ -C ₆ H ₄	C ₂₅ H ₂₄ N ₂ O ₆	160	52	6.25	6.29
2b	2-OCH ₃ -C ₆ H ₄	C ₂₅ H ₂₄ N ₂ O ₆	145	51	6.25	6.29
2c	2-NO ₂ -C ₆ H ₄	C ₂₄ H ₂₁ N ₃ O ₇	167	53	9.07	8.92
2d	3,4-(Cl) ₂ -C ₆ H ₃	C ₂₄ H ₂₀ N ₂ O ₅ Cl ₂	130	46	5.75	5.65
2e	3-NO ₂ -C ₆ H ₄	C ₂₄ H ₂₁ N ₃ O ₇	165	60	9.07	9.00
2f	C ₆ H ₅	C ₂₄ H ₂₂ N ₂ O ₅	130	49	6.70	6.38
2g	C ₄ H ₃ O(furyl)	C ₂₂ H ₂₀ N ₂ O ₆	194	58	6.86	6.48
2h	4-N,N-(CH ₃) ₂ -C ₆ H ₄	C ₂₆ H ₂₇ N ₃ O ₅	168	57	9.11	9.42
3a	4-OCH ₃ -C ₆ H ₄	C ₂₅ H ₂₈ N ₄ O ₅	144	55	12.12	12.01
3b	2-OCH ₃ -C ₆ H ₄	C ₂₅ H ₂₈ N ₄ O ₅	148	64	12.12	12.03
3c	2-NO ₂ -C ₆ H ₄	C ₂₄ H ₂₃ N ₅ O ₆	195	48	14.67	14.78
3d	3,4-(Cl) ₂ -C ₆ H ₃	C ₂₄ H ₂₂ N ₄ O ₄ Cl ₂	162	58	11.17	11.32
3e	3-NO ₂ -C ₆ H ₄	C ₂₄ H ₂₃ N ₅ O ₆	135	52	14.67	14.80
3f	C ₆ H ₅	C ₂₄ H ₂₄ N ₄ O ₄	140	35	12.96	13.06
3g	C ₄ H ₃ O(furyl)	C ₂₂ H ₂₂ N ₄ O ₅	138	37	13.27	13.42
3h	4-N,N-(CH ₃) ₂ -C ₆ H ₄	C ₂₆ H ₂₈ N ₅ O ₄	172	48	14.73	14.30
4a	4-OCH ₃ -C ₆ H ₄	C ₂₇ H ₂₈ N ₄ O ₆	130	58	11.11	11.00
4b	2-OCH ₃ -C ₆ H ₄	C ₂₇ H ₂₈ N ₄ O ₆	148	55	11.11	11.05
4c	2-NO ₂ -C ₆ H ₄	C ₂₆ H ₂₅ N ₅ O ₇	182	60	13.51	13.54
4d	3,4-(Cl) ₂ -C ₆ H ₃	C ₂₆ H ₂₄ N ₄ O ₅ Cl ₂	120	35	10.31	10.25
4e	3-NO ₂ -C ₆ H ₅	C ₂₆ H ₂₈ N ₅ O ₇	140	40	13.48	13.40
4f	C ₆ H ₅	C ₂₆ H ₂₈ N ₄ O ₅	125	56	11.81	11.70
4g	C ₄ H ₃ O (furyl)	C ₂₄ H ₂₄ N ₄ O ₆	165	62	12.06	12.26
4h	4-N,N-(CH ₃) ₂ -C ₆ H ₄	C ₂₈ H ₃₁ N ₅ O ₅	155	51	13.54	13.50
5a	4-OCH ₃ -C ₆ H ₄	C ₃₁ H ₃₀ N ₄ O ₅	115	56	10.41	10.48
5b	2-OCH ₃ -C ₆ H ₄	C ₃₁ H ₃₀ N ₄ O ₅	110	42	10.41	10.49
5c	2-NO ₂ -C ₆ H ₄	C ₃₀ H ₂₇ N ₅ O ₆	125	53	12.65	12.80
5d	3,4-(Cl) ₂ -C ₆ H ₃	C ₃₀ H ₂₆ N ₄ O ₄ Cl ₂	118	52	9.70	9.75
5e	3-NO ₂ -C ₆ H ₄	C ₃₀ H ₂₇ N ₅ O ₆	125	40	12.65	12.80
5f	C ₆ H ₅	C ₃₀ H ₂₈ N ₄ O ₄	120	61	11.02	11.08
5g	C ₄ H ₃ O(furyl)	C ₂₈ H ₂₆ N ₄ O ₅	104	38	11.24	11.15
5h	4-N,N-(CH ₃) ₂ -C ₆ H ₄	C ₃₂ H ₃₃ N ₅ O ₄	110	43	12.70	12.74

REACTION SCHEME



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