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

Harsukh Gaveriya, Bhavik Desai, Vipul Vora and Anamik Shah*
Department of Chemistry, Saurashtra University, Rajkot-360005, Gujarat (India)

ABSTRACT

2,6-dimethyl-3-acetyl-5-carbmethoxy-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 C_3 (of DHP). All compounds were screened for their antitubercular activity against ***Mycobacterium tuberculosis*** ($H_{37}Rv$).

INTRODUCTION

The dihydropyridines are the well-known drug moiety for the treatment of antihypertensive and cardiovascular disorders[1]. However, it is also associated with antiallergic[2], antiinflammatory[3], treatment of circulating diseases[4], calcium channel antagonism[5-8] etc. About 50 different dihydropyridines are launched as new drugs in last 20 years. The 3-nitrophenyl substituent at C_4 of DHP provides excellent stability and pharmacodynamic properties leading to many drugs like Nicardipine[7], Pranidine[8], Nimodipine[9], Tiamdipine[10] and Manidipine[11]. These drugs mainly exhibits 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 dihydropyridines[12-13].

Our aim was to prepare some interesting new unsymmetrical dihydropyridine derivatives from 2,6-dimethyl-3-acetyl-5-carbmethoxy-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*** $H_{37}Rv$. The standard drug used was Rifampicin. Primary screening was conducted at 12.5 μg/ml against ***Mycobacterium Tuberculosis*** ($H_{37}Rv$) strain in BACTEC 12B medium using the BACTEC 460-radiometric system[14].

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 ***2e*** containing 3-nitophenyl 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 ^{1}H 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 literature[15-17].

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 $C_{25}H_{24}N_2O_6$, C, 66.96; H. 5.36; N. 6.25; Found C, 67.00; H, 5.30; N, 6.29, ^{1}H NMR (300 MHz,$CDCl_3$+DMSO-d_6) δ : 3.80 (S, 3H); CH3, 6.10-6.40 (dd, 2H, COCH=CH); 2.35 (S, 6H 2xCH_3); 3.59 (S, 3H, OCH_3); 5.23 (S, 1H, C_4H). IR (KBr) cm^{-1}: 1703 (C=O ester); 1685 (C=O chalcone); 1535, 1330 cm^{-1} (C-NO_2).

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 $C_{25}H_{26}N_4O_5$: C, 64.93; H, 5.62; N, 12.12; Found C, 64.85; H, 5.73; N, 12.01; ^{1}H NMR (300 MHz $CDCl_3$+DMSO-d_6) δ : 2.36 (s, 6H, 2xCH_3); 3.56 (s, 3H, OCH_3); 3.64(s, 3H, $COOCH_3$); 5.10 (s, 1H, C_4H); 2.7-2.8 (t, 1H, CH-CH_2). IR (KBr) cm^{-1}: 3135 (NH); 1530, 1324 (C-NO_2).

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 $C_{27}H_{28}N_4O_6$: C, 64.28; H, 5.52; N,

11.11; found: C, 64.32; H, 5.60; N, 11.00. ^{1}H NMR (300 MHz $CDCl_3$+$DMSOd_6$) δ : 2.28 (s, 6H, 2xCH_3); 3.62 (s, 3H, OCH_3); 3.76 (s, 3H, $COOCH_3$); 5.07 (s, 1H >CH); 2.1-2.2 (t, 1H, -CH-CH_2); 3.76-3.81 (d, 2H, CH-CH_2); 1.93 (s, 3H, N-$COCH_3$). IR (KBr) cm^{-1} : 1701 (C=O-OCH_3); 1635 (N-C=OCH_3); 3227 (NH); 1635 (C=N); 1529,1347(C-NO_2).

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 $C_{31}H_{31}N_4O_5$: C, 69.14; H, 5.57; N, 10.41; found C, 69.02; H, 5.63; N, 10.48. ^{1}H NMR (300 MHz $CDCl_3$+ DMSO-d_6) δ 2.33 (s, 6H, 2xCH_3); 3.66 (s, 3H, OCH_3); 3.77 (s, 3H, $COOCH_3$); 2.55-2.66 (t, 1H, CH-CH_2); 3.75-3.80 (d, 2H, -CH-CH_2); 5.20(s, 1H, C_4H). IR (KBr) cm^{-1} : 1720 (C=O-OCH_3); 1599 (C=N); 1599,1347 (C-NO_2).

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* (H_{37}Rv strain)

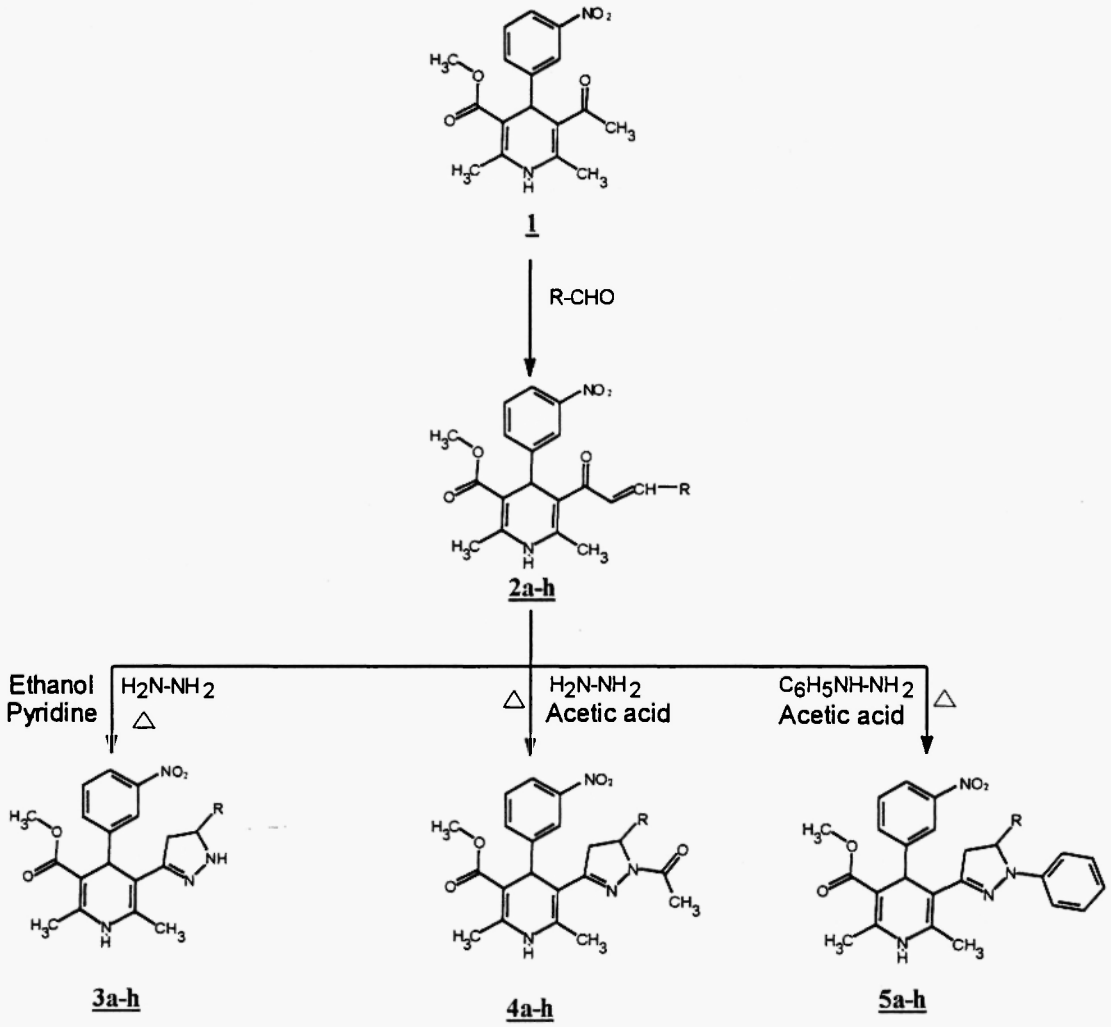
Compd.	MIC (μg/ml)	% Inhibition
4f	>12.5	87
2e	>12.5	85
5c	>12.5	68
5h	>12.5	66
4b	>12.5	63
5g	>12.5	57
4a	>12.5	54
4c	>12.5	52
4d	>12.5	50

*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-carbmethoxy3-substituted 1,4-dihydropyridines.

Compd.	R	Molecular Formula	M.P. (°C)	Yield (%)	% of Nitrogen Calcd.	Found
2a	4-OCH_3-C_6H_4	$C_{25}H_{24}N_2O_6$	160	52	6.25	6.29
2b	2-OCH_3-C_6H_4	$C_{25}H_{24}N_2O_6$	145	51	6.25	6.29
2c	2-NO_2-C_6H_4	$C_{24}H_{21}N_3O_7$	167	53	9.07	8.92
2d	3,4-$(Cl)_2$-C_6H_3	$C_{24}H_{20}N_2O_5Cl_2$	130	46	5.75	5.65
2e	3-NO_2-C_6H_4	$C_{24}H_{21}N_3O_7$	165	60	9.07	9.00
2f	C_6H_5	$C_{24}H_{22}N_2O_5$	130	49	6.70	6.38
2g	C_4H_3O(furyl)	$C_{22}H_{20}N_2O_6$	194	58	6.86	6.48
2h	4-N,N-$(CH_3)_2$-C_6H_4	$C_{26}H_{27}N_3O_5$	168	57	9.11	9.42
3a	4-OCH_3-C_6H_4	$C_{25}H_{28}N_4O_5$	144	55	12.12	12.01
3b	2-OCH_3-C_6H_4	$C_{25}H_{28}N_4O_5$	148	64	12.12	12.03
3c	2-NO_2-C_6H_4	$C_{24}H_{23}N_5O_6$	195	48	14.67	14.78
3d	3,4-$(Cl)_2$-C_6H_3	$C_{24}H_{22}N_4O_4Cl_2$	162	58	11.17	11.32
3e	3-NO_2-C_6H_4	$C_{24}H_{23}N_5O_6$	135	52	14.67	14.80
3f	C_6H_5	$C_{24}H_{24}N_4O_4$	140	35	12.96	13.06
3g	C_4H_3O(furyl)	$C_{22}H_{22}N_4O_5$	138	37	13.27	13.42
3h	4-N,N-$(CH_3)_2$-C_6H_4	$C_{26}H_{28}N_5O_4$	172	48	14.73	14.30
4a	4-OCH_3-C_6H_4	$C_{27}H_{28}N_4O_6$	130	58	11.11	11.00
4b	2-OCH_3-C_6H_4	$C_{27}H_{28}N_4O_6$	148	55	11.11	11.05
4c	2-NO_2-C_6H_4	$C_{26}H_{25}N_5O_7$	182	60	13.51	13.54
4d	3,4-$(Cl)_2$-C_6H_3	$C_{26}H_{24}N_4O_5Cl_2$	120	35	10.31	10.25
4e	3-NO_2-C_6H_5	$C_{26}H_{28}N_5O_7$	140	40	13.48	13.40
4f	C_6H_5	$C_{26}H_{28}N_4O_5$	125	56	11.81	11.70
4g	C_4H_3O (furyl)	$C_{24}H_{24}N_4O_6$	165	62	12.06	12.26
4h	4-N,N-$(CH_3)_2$-C_6H_4	$C_{28}H_{31}N_5O_5$	155	51	13.54	13.50
5a	4-OCH_3-C_6H_4	$C_{31}H_{30}N_4O_5$	115	56	10.41	10.48
5b	2-OCH_3-C_6H_4	$C_{31}H_{30}N_4O_5$	110	42	10.41	10.49
5c	2-NO_2-C_6H_4	$C_{30}H_{27}N_5O_6$	125	53	12.65	12.80
5d	3,4-$(Cl)_2$-C_6H_3	$C_{30}H_{26}N_4O_4Cl_2$	118	52	9.70	9.75
5e	3-NO_2-C_6H_4	$C_{30}H_{27}N_5O_6$	125	40	12.65	12.80
5f	C_6H_5	$C_{30}H_{28}N_4O_4$	120	61	11.02	11.08
5g	C_4H_3O(furyl)	$C_{28}H_{26}N_4O_5$	104	38	11.24	11.15
5h	4-N,N-$(CH_3)_2$-C_6H_4	$C_{32}H_{33}N_5O_4$	110	43	12.70	12.74

REACTION SCHEME



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