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

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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[5,6] etc. About 50 different dihydropyridines are launched as new drugs in last 20 years. The 3-nitrophenyl substitution 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 developments with respect to ***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 products were 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-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-MEGNA-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, CH_3); 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, 0.01 M) 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.

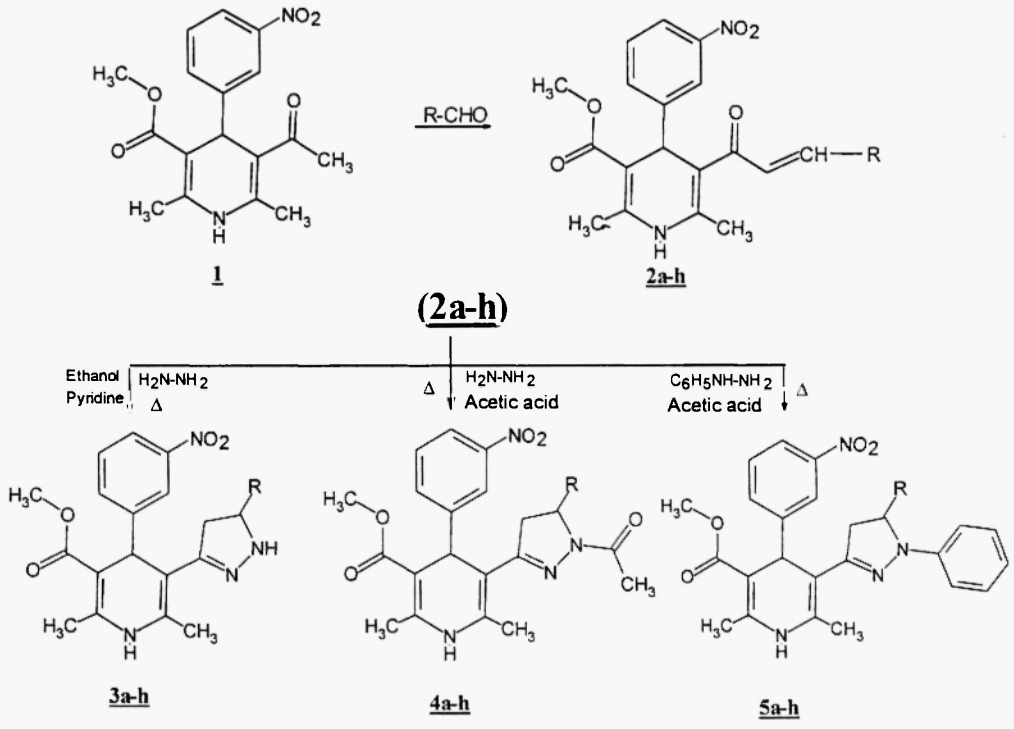
Preparation of 2,6-Dimethyl-4-(3'nitrophenyl)-5-carbmethoxy-3-[3'-(4"-methoxyphenyl)-2'-acetylpyrazoline-5'-yl]-1,4-dihydropyridine 4a.

A mixture of **2a** (4.48g, 0.01M) 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 $C_{27}H_{26}N_4O_6$: C, 64.28; H, 5.52; N, 11.11; Found: C, 64.32; H, 5.60; N, 11.00. ^{1}H NMR (300 MHz $CDCl_3$+DMSO-d_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 ester); 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.

REACTION SCHEME



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 (1.08gm, 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 recrystallised 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 ester); 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

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