

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 antagonism^{5,6} etc. About 50 different dihydropyridines are launched as new drugs in last 20 years. The 3-nitrophenyl substitution at C₄ of DHP provides excellent stability and pharmacodynamic properties leading to many drugs like Nicardipine⁷, Pranidipine⁸, Nimodipine⁹, Tiamdipine¹⁰ and Manidipine¹¹. These drugs mainly exhibit 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-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 products were 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 **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 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 C₂₅H₂₄N₂O₆, 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, 0.01 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 C₂₅H₂₆N₄O₅: 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.

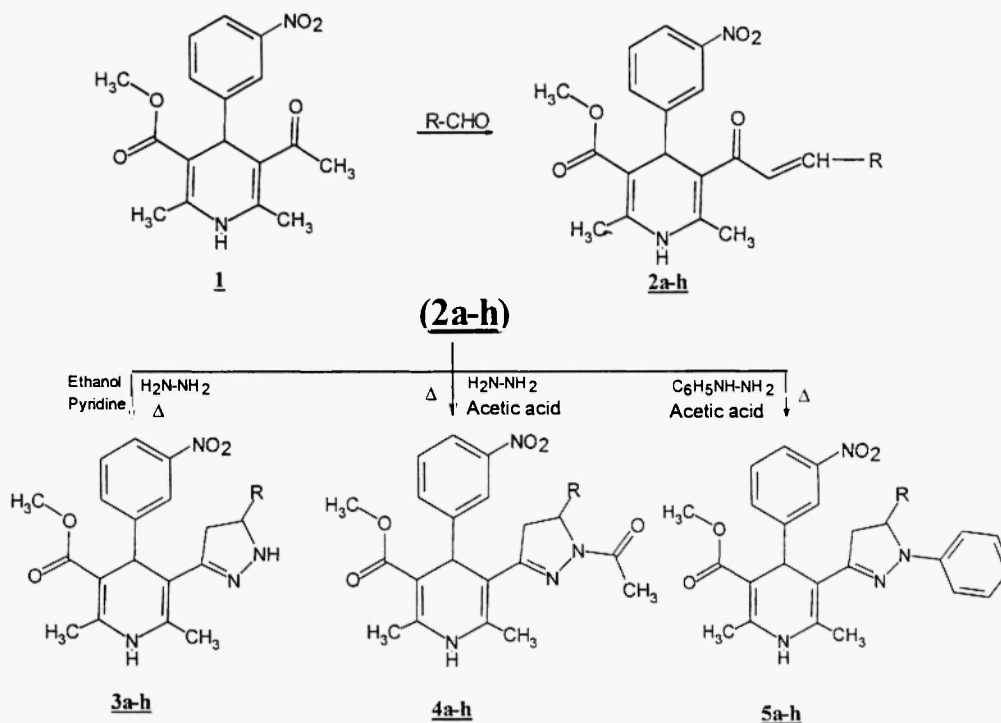
Preparation of 2,6-Dimethyl-4-(3'-nitrophenyl)-5-carbmethoxy-3-[3'-(4''-methoxyphenyl)-2'-acetylpyrazoline-5'-yl]-1,4-dihydropyridine **4a**.

A mixture of **2a** (4.48g, 0.01M) 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 $C_{27}H_{28}N_4O_6$: C, 64.28; H, 5.52; N, 11.11; Found: C, 64.32; H, 5.60; N, 11.00. 1H NMR (300 MHz $CDCl_3$ +DMSO- d_6) δ : 2.28 (s, 6H, $2 \times CH_3$); 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-carbomethoxy-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 $C_{31}H_{31}N_4O_6$: C, 69.14; H, 5.57; N, 10.41; Found C, 69.02; H, 5.63; N, 10.48. 1H NMR (300 MHz $CDCl_3$ +DMSO- d_6) δ : 2.33 (s, 6H, $2 \times CH_3$); 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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REFERENCES

- (1) R. Mannhold, *Drugs Today*, **30**, 103, (1994)
- (2) K. Cooper and F. Michael Johnathan, *Eur. Pat. Appl. Ep.* 294 074, *Chem. Abstr.* **110**, 231441 (1989)
- (3) R.C. Johnson, D. J. Taylor, V. Hann Kenneth and Cheng, Soan, *U.S. Pat.* 4, 758, 669, *Chem. Abstr.*, **109**, 149366 (1988)
- (4) M.H. Kurono, U. Toshinao and T. Suzuki, *Kagaku Kenkyusho Co. Ltd.*, *Eur. Pat.* 220, 917, *Chem. Abstr.*, **107**, 39637 (1987)
- (5) A. Hantzsch, *Liebigs. Ann. Chem.* **1**, 215, (1882)
- (6) T. Godfraind, R. Miller and M. Wimbo, *Pharmaco. Rev.* **38**, 321, (1986)
- (7) T. Takenaka, S. Usuda and T. Nomura, *Arzneim-Forsch.* **26**, 2176-78, (1976)
- (8) N. Nakayama, K. Ikezono, T. Mori and S. Yamashita, *J. Cardiovasc. Pharmacol.* **15**, 836-844, (1990)
- (9) S. Kazda, V. Neaser and K. Schlojbmman, *Arch. Pharmacol. Suppl.* **29s**, R16, (1976)
- (10) A.C. Gandolfi, M. Figerio, S. Spinelli, O. Tofanetti and S. Tognella, *PTC/EP* 86/00445, (1987)
- (11) K. Meguro et al. *Chem. Pharm. Bull.* **33**, 3787, (1985)
- (12) K. Ohsumi, K. Oshishi, Y. Moringa and T. Tsuruo, *Chem. Pharm. Bull.*, **43(5)**, 818-828 (1995)
- (13) A. Shah, H. Gaveriya, N. Motohashi, M. Kawase, S. Saito, H. Sakagami, K. Satoh, Y. Tada, A. Solymosi, K. Walfard and J. Molnar, *Anticancer Research.*, **20**, 373-8 (2000)
- (14) L. Collins and S. G. Franzblau, *Microplate alamar blue assay versus BACTEC-460 system for high throughput screening of compounds against Mycobacterium Tuberculosis and Mycobacterium avium. Antimicrob Agents Chemother* **41**, 1004-1009, (1997)
- (15) J. A. Berson and E. Brown, *J. Am. Chem. Soc.*, **77**, 444-7 (1955), *Chem. Abstr.*, **50**, 983 (1956)
- (16) A. P. Phillips, *J. Am. Chem. Soc.*, **73**, 3522-3 (1951), *Chem. Abstr.*, **46**, 2542 (1952)
- (17) A Courts and V. Petrow, *J. Chem. Soc.*, 1-5 (1951), *Chem. Abstr.*, **45**, 9016 (1952)

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