Journal of Sciences, Islamic Republic of Iran 19(4): 323-328 (2008) http://jsciences.ut.ac.ir
University of Tehran, ISSN 1016-1104

Synthesis and Antitubercular Activity of N^3,N^5-Diaryl-4-(5-arylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide

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Received: 26 February 2008 / Revised: 29 May 2008 / Accepted: 10 July 2008

Abstract

5-Arylisoxazolyl-3-carboxaldehydes were condensed with *N*-aryl acetoacetamide and ammonium acetate in methanol to give N^3,N^5-diaryl-4-(5-arylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamides. All compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* (H_{37}Rv). The results for new synthesized compounds showed a moderate activity in comparison to rifampicin.

Keywords: Dihydropyridine; 5-Arylisoxazole; Antituberculosis

Introduction

Tuberculosis is the leading cause of death by infectious disease with one-third of the world population infected [1]. Due to multi-drug resistant (MDR) strains of mycobacterium and to a high prevalence of tuberculosis in patients who have acquired human-immunodeficiency syndrome (AIDS) the number of patients infected with the disease is increasing world wide [2]. Compared with the recent rapid advances in the diagnosis of tuberculosis, advances in the treatment of tuberculosis have been quite slow. Because of the global health problems of tuberculosis the increasing rate of MDR tuberculosis and the high rate of a co-infection with HIV, the development of potent new anti-tuberculosis drugs without cross resistance with known anti-mycobacterium agents is urgently needed. Previous studies showed that 1,4-dihydropyridines class of compounds (DHPs) are excellent starting synthon for the development of anti-tubercular agents. We have demonstrated before that substitution of aryl amide group for dicarboxylic esters group reduces the Ca^{2+} channel blocker activity and raises anti-tubercular property [3]. Studies showed a moderate to good activity for several aryl six-membered ring in 4-position and aryl-amide side chain in C_3 and C_5 of DHPs when were screened for their anti-tubercular activity against *Mycobacterium tuberculosis* (H_{37}RV) [4-6].

As a part of our ongoing research to design novel compounds to have calcium channel inhibitory activity or anti-tubercular activity [7-12] herein we report the design and anti-tubercular evaluation of N^3, N^5-diaryl-4-(5-arylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide.

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Materials and Methods

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR spectra was run on a Varian FT-400 unity plus spectrometer. TMS was used as an internal standard. The IR spectra were recorded on a Nicolet FTIR 550 spectrophotometer. The results of the elemental analysis (C, H, N) were within ±0.4 % of the calculated amounts.

5-Phenylisoxazole-3-carboxaldehyde (**5a**) was prepared according to the literature procedures [13].

Synthesis of Ethyl 4-(2,4-dichlorophenyl)-2,4-dioxobutanoate (2b)

0.35 Mole (8.1 g) of sodium was dissolved in 120 ml of dry ethanol. A solution of 0.35 mole (51.1 g) of diethyl oxalate and 0.35 mole (66.57 g) of 2,4-dichloroacetophenone was slowly added to this ice-cooled solution of sodium ethoxide with stirring. The paste formed was permitted to stand at 25 °C for 24 h and warmed at 80 °C on a steam bath for 0.5 h. The pasty mass was cooled and diluted sulfuric acid (10%) was added until pH 2 was obtained. The separated oil was extracted with $CHCl_3$ (3×200 ml). The solvent was dried by anhydrous sodium sulfate and evaporated under reduced pressure. Crystallization from ethanol gave 61 g (60%) of white fluffy crystals m.p. 66-68 °C; IR (KBr): 1740, 1720, 1685 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.87 (d, 1H, J=8.8 Hz, H_6), 7.56 (d, 1H, J=1.6 Hz, H_3), 7.37 (dd, 1H, J=8.8 Hz, J=1.6 Hz, H_5), 6.94 (s, 2H, CH_2), 4.38 (q, 2H, J=7.2 Hz, OCH_2), 1.39 (t, 3H, J=7.2 Hz, CH_3).

Synthesis of Ethyl 5-(2,4-dichlorophenyl)isoxazol-3-carboxylate (3b)

Hydroxylamine hydrochloride (0.04 mole, 3.6 g) was added to a solution of **2b** (0.04 mole, 12.71 g) in ethanol (100 ml). The mixture was refluxed for 2 h. The solvent was removed to ¼ initial volumes and a solution of 10% sodium bicarbonate (200 ml) was added. The extraction was performed by diethyl ether (3×100 ml) and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure. The product was crystallized from ethanol to give **3b**, 7.02 g, (71%); m.p. 97-98 °C, IR (KBr): 1740 (CO) cm^{-1}, ^{1}HNMR ($CDCl_3$) δ: 7.81 (d, 1H, J=8.8 Hz, H_6), 7.50 (d, 1H, J=1.6 Hz, H_3), 7.33 (dd, 1H, J=8.8 Hz, J=1.6 Hz, H_5), 7.31 (s, 1H, H_4-isoxazole), 4.55 (q, 2H, J=7.2 Hz, OCH_2), 1.51 (t, 3H, J=7.2 Hz, CH_3).

Synthesis of 5-(2,4-dichlorophenyl)isoxazol-3-yl methanol (4b)

Sodium brohydride (0.08 mole, 3.13 g) was added portion-wise to an ice-cooled stirred solution of **3b** (0.04 mole, 14.22 g) in dry ethanol (100 ml). The resulting solution was stirred at room temperature for 3 h, carefully acidified with hydrochloric acid (1N) and concentrated in vacuum. The aqueous solution was extracted with diethyl ether (3×100 ml) and concentrated in vacuum to give an oil which was crystallized from ethanol to afford **4b** (10.6 g, 70%). m.p. 78-80 °C, IR (KBr): 3330, (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.87 (d, 1H, J=8.8 Hz, H_6), 7.52 (d, 1H, J=1.6 Hz, H_3), 7.33 (dd, 1H, J=8.8 Hz and J=1.6 Hz, H_5), 7.01 (s, 1H, H_4-isoxazole), 4.82 (s, 2H, CH_2OH).

Synthesis of 5-(2,4-dichlorophenyl)isoxazol-3-carboxaldehyde (5b)

A mixture of **4b** (0.31 mole, 7.63 g) and activated manganese (IV) oxide (33.27 g) in chloroform (100 ml) was refluxed for 7 h. After cooling, the mixture was filtered on diatomaceous earth and the solvent removed under reduced pressure. The product was crystallized from methanol to give **5b** (5.53 g, 73%), m.p. 109-110 °C, IR (KBr): cm^{-1}: 1711 (CO), ^{1}H NMR ($CDCl_3$) δ: 10.21 (s, 1H, CHO), 7.92 (d, 1H, J=8.8 Hz, H_6), 7.55 (d, 1H, J=1.6 Hz, H_3), 7.4 (dd, 1H, J=8.8 Hz, J=1.6 Hz, H_5), 7.29 (s, 1H, H_4-isoxazole).

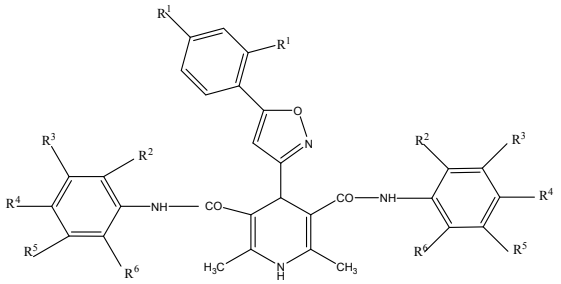
General Procedure for Preparation of Compounds 9a (1-8) and 9b (1-8)

To *N*-aryl acetoacetate **8** (1 mmole) and 1g of ammonium acetate in 10 ml methanol was added 0.5 mmole of **5a** or **5b**. The mixture was refluxed for 24 h and the precipitate was filtered and washed with cooled methanol. It was re-crystallized from methanol-water to give the desired compound. The melting point and the yield are given in Table 1.

Synthesis of 2,6-Dimethyl-N^3,N^5-diphenyl-4-(5-phenylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide (9a-1)

IR (KBr): 1670 (CO), 3242 and 3462 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 9.45 (bs, 2H, NH), 8.40 (bs, 1H, NH), 7.8 (dd, 2H, J=8.0 Hz and J=1.6 Hz), 7.61 (d, 4H, J= 7.6 Hz), 7.49 (m, 3H), 7.24 (t, 4H, J=7.6 Hz), 7.0 (t, 2H, J=7.6 Hz), 6.75 (s, 1H, H_4-isoxazole), 5.2 (s, 1H, H_4), 2.15 (s, 6H, $Me_{2,6}$).

Table 1. Physical constant and inhibition percent of the synthesized compounds



Com.	R^1	R^2	R^3	R^4	R^5	R^6	m.p. (°C)	% yield	% inhibition
9a-1	H	H	H	H	H	H	266-268	68	1
9a-2	H	Cl	H	H	H	H	204-206	62	0
9a-3	H	F	H	H	H	H	191-193	57	0
9a-4	H	H	H	NO_2	H	H	162-164	18	20
9a-5	H	H	Cl	Cl	H	H	213-215	15	17
9a-6	H	Cl	H	H	H	Cl	>250	50	0
9a-7	H	NO_2	H	OCH_3	H	H	190-192	38	62
9a-8	H	Cl	H	Cl	Cl	H	233-235	70	0
9b-1	Cl	H	H	H	H	H	278-279	52	0
9b-2	Cl	Cl	H	H	H	H	170-172	21	0
9b-3	Cl	F	H	H	H	H	157-159	50	0
9b-4	Cl	H	H	NO_2	H	H	133-135	30	41
9b-5	Cl	H	Cl	Cl	H	H	176-178	34	0
9b-6	Cl	Cl	H	H	H	Cl	>250	35	0
9b-7	Cl	NO_2	H	OCH_3	H	H	102-104	20	0
9b-8	Cl	Cl	H	Cl	Cl	H	206-208	62	17

Synthesis of N^3,N^5-bis(2-chorophenyl)-2,6-dimethyl-4-(5-phenylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide (9a-2)

IR (KBr): cm^{-1}: 1670 (CO), 3288 (NH), ^{1}H NMR (DMSO-d_6) δ: 9.0 (bs, 2H, NH), 8.7 (bs, 1H, NH), 7.84 (d, 2H, J=8.0 Hz), 7.78 (d, 2H, J= 8.0 Hz), 7.51 (m, 3H), 7.46 (d, 2H, J= 8.0 Hz), 7.31 (t, 2H, J=8.0 Hz), 7.15 (t, 2H, J=8.0 Hz), 6.84 (s, 1H, H_4-isoxazole), 5.21 (s, 1H, H_4), 2.26 (s, 6H, $Me_{2,6}$).

Synthesis of N^3,N^5-bis(2-flurophenyl)-2,6-dimethyl-4-(5-phenylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide (9a-3)

IR (KBr): 1670 (CO), 3236 and 3457 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 9.23 (bs, 2H, NH), 8.66 (bs, 1H, NH), 7.85 (d, 2H, J=8.0 Hz), 7.73 (m, 2H), 7.51(m, 3H), 7.23 (m, 3H), 7.14 (m, 3H), 6.85 (s, 1H, H4-isoxazole), 5.17 (s, 1H, H_4), 2.22 (s, 6H, $Me_{2,6}$).

Synthesis of 2,6-dimethyl-N^3,N^5-bis(4-nitrophenyl)-4-(5-phenylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide (9a-4)

IR (KBr): 1326, 1541 (NO_2), 1675 (CO), 3308 (NH); 3445 (NH) cm^{-1}, ^{1}H NMR (DMSO-d_6) δ: 10.3 (bs, 2H, NH), 8.8 (bs, 1H, NH), 8.2 (d, 4H, J=8.8 Hz), 7.91 (d, 4H, J= 8.8 Hz), 7.81 (d, 2H, J= 7.6 Hz), 7.5 (m, 3H), 6.87 (s, 1H, H_4-isoxazole), 5.36 (s, 1H, H_4), 2.18 (s, 6H, $Me_{2,6}$).

Synthesis of N^3,N^5-bis-(3,4-dichlorophenyl)-2,6-dimethyl-4-(5-phenylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide (9a-5)

IR (KBr): 1670 (CO), 3297 and 3430 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 9.81 (bs, 2H, NH), 8.62 (bs, 1H, NH), 8.02 (d, 2H, J=2.0 Hz), 7.81 (dd, 2H, J= 8.0 Hz and J= 2.0 Hz), 7.56 (m, 5H), 7.49 (d, 2H, J= 8.0 Hz), 6.75 (s, 1H, H_4-isoxazole), 5.2 (s, 1H, H_4), 2.15 (s, 6H, $Me_{2,6}$).

Synthesis of N^3,N^5-bis-(2,6-dichlorophenyl)-2,6-dimethyl-4-(5-phenylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide (9a-6)

IR (KBr): 1667 (CO), 3290 and 3410 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 9.24 (bs, 2H, NH), 8.47 (bs, 1H, NH), 7.79 (dd, 2H, J=8.8 Hz and J=1.6 Hz), 7.53 (m, 3H), 7.49 (d, 4H, J=8.0 Hz), 7.3 (t, 2H, J=8.0 Hz), 6.79 (s, 1H, H_4-isoxazole), 5.24 (s, 1H, H_4), 2.25 (s, 6H, $Me_{2,6}$).

Synthesis of N^3,N^5-bis-(4-methoxy-2-nitrophenyl)-2,6-dimethyl-4-(5-phenylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide (9a-7)

IR (KBr): cm^{-1}: 1675 (CO), 3363 and 3430 (NH), ^1H NMR (DMSO-d_6) δ: 9.86 (bs, 2H, NH), 8.74 (bs, 1H, NH), 7.81 (d, 2H, J=7.2 Hz), 7.61 (d, 2H, J= 8.8 Hz), 7.50 (m, 3H), 7.46 (d, 2H, J=2.8 Hz), 7.30 (dd, 2H, J = 8.8 Hz, J = 2.8 Hz), 6.75 (s, 1H, H_4-isoxazole), 5.12 (s, 1H, H_4), 3.81 (s, 6H, OCH_3), 2.23 (s, 6H, $Me_{2,6}$).

Synthesis of N^3,N^5-bis-(2,4,6-trichlorophenyl)-2,6-dimethyl-4-(5-phenylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide (9a-8)

IR (KBr): 1670 (CO), 3236 and 3426 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 9.18 (bs, 2H, NH), 8.94 (bs, 1H, NH), 8.17 (s, 2H), 7.90 (s, 2H), 7.85 (dd, 2H, J=8.0 Hz and J=2.4 Hz), 7.50 (m, 3H), 6.85 (s, 1H, H_4-isoxazole), 5.2 (s, 1H, H_4) 2.27 (s, 6H, $Me_{2,6}$).

Synthesis of 4-[5-(2,4-dichlorophenyl)isoxazol-3-yl)-2,6-dimethyl-N^3,N^5-diphenyl-1,4-dichlorophenyl-3,5-dicarboxamide (9b-1)

IR (KBr): 1675 (CO), 3225 and 3295 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 9.56 (bs, 2H, NH), 8.41 (bs, 1H, NH), 7.88 (d, 1H, J=8.8 Hz), 7.82 (s, 1H), 7.51-7.62 (m, 5H), 7.27 (t, 4H, J=7.2 Hz), 7.01 (t, 2H, J=7.2 Hz), 6.87 (s, 1H, H_4-isoxazole), 5.25 (s, 1H, H_4), 2.12 (s, 6H, $Me_{2,6}$).

Synthesis of N^3,N^5-bis-(2-chlorophenyl)-4-[5-(2,4-dichlorophenyl)isoxazol-3-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxamide (9b-2)

IR (KBr): 1670 (CO), 3210 and 3277 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 9.10 (bs, 2H, NH), 8.7 (bs, 1H, NH), 7.90 (d, 1H, J=8.0 Hz), 7.86 (d, 1H, J=2.0 Hz), 7.42 (dd, 2H, J=8.0 Hz and J=1.6 Hz), 7.61(dd, 1H, J=8.0 Hz and J = 2.0 Hz), 7.47(dd, 2H, J = 8.0 Hz and J = 1.6 Hz), 7.31 (m, 2H), 7.16 (m, 2H,), 6.87 (s, 1H, H_4-isoxazole), 5.26 (s, 1H, H_4), 2.25 (s, 6H, $Me_{2,6}$).

Synthesis of 4-[5-(2,4-dichlorophenyl)isoxazol-3-yl]-N^3,N^5-bis-(2-flurophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxamide (9b-3)

IR (KBr): 1670 (CO), 3220 and 3276 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 9.23 (bs, 2H, NH), 8.64 (bs, 1H, NH), 7.92 (d, 1H, J=8.0 Hz), 7.85 (s, 1H), 7.69 (t, 2H, J=9.2 Hz), 7.61 (d, 1H, J=8.4 Hz), 7.17 (m, 6H), 6.92 (s, 1H, H_4-isoxazole), 5.25 (s, 1H, H_4), 2.21 (s, 6H, $Me_{2,6}$).

Synthesis of 4-[5-(2,6-dichlorpphenyl)isoxazol-3-yl)-2,6-dimethyl-N^3,N^5-bis(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxamide (9b-4)

IR (KBr): 1332, 1540 (NO_2), 1680 (CO), 3240 and 3334 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 10.2 (bs, 2H, NH), 8.24 (d, 4H, J=8.8 Hz), 8.01 (bs, 1H, NH), 7.89 (d, 4H, J=8.8 Hz), 7.84 (m, 2H), 7.58 (d, 1H, J=8.4 Hz), 6.86 (s, 1H, H_4-isoxazole), 5.38 (s, 1H, H_4), 2.18 (s, 6H, $Me_{2,6}$).

Synthesis of N^3,N^5-bis-(3,4-dichlorophenyl)-4-[5-(2,4-dichlorophenyl)isoxazol-3-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxamide (9b-5)

IR (KBr): 1680 (CO), 3210 and 3393 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 9.86 (bs, 2H, NH), 8.59 (bs, 1H, NH), 8.02 (d, 2H, J=2 Hz), 7.88 (d, 1H, J=8.0 Hz), 7.83 (d, 1H, J=2.0 Hz), 7.52-7.60 (m, 5H), 6.87 (s, 1H, H_4-isoxazole), 5.31 (s, 1H, H_4), 2.18 (s, 6H, $Me_{2,6}$).

Synthesis of N^3,N^5-bis(2,6-dichlorophenyl-)4-[5-(2,4-dichlorpphenyl)isoxazol-3-yl)-2,6-dimethyl- -1,4-dihydropyridine-3,5-dicarboxamide (9b-6)

IR (KBr): 1680 (CO), 3308 and 3349 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 9.31 (bs, 2H, NH), 8.51 (bs, 1H, NH), 7.62 (d, 1H, J=8.8 Hz), 7.49 (d, 4H, J=8.0 Hz), 7.31 (t, 2H, J=8.0 Hz), 6.95 (s, 1H), 6.87 (s, 1H, H_4-isoxazole), 6.64 (d, 1H, J=8.8 Hz), 5.28 (s, 1H, H_4), 2.26 (s, 6H, $Me_{2,6}$).

Synthesis of 4-[5-(2,4-dichlorophenyl)isoxazol-3-yl)-N^3,N^5-bis(4-methoxy-2-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxamide (9b-7)

IR (KBr): cm^{-1}: 1343, 1536 (NO_2), 1670 (CO), 3305 and 3357 (NH), ^1H NMR (DMSO-d_6) δ: 9.9 (bs, 2H, NH), 8.8 (s, 1H, NH), 7.90 (d, 1H, J=8.4 Hz), 7.85 (d, 1H, J=2.0 Hz), 7.69 (dd, 1H, J=8.4 Hz and J=2.0 Hz), 7.60 (d, 2H, J=8.8 Hz), 7.45 (d, 2H, J=2.8 Hz), 7.29 (dd,

2H, J=8.8 Hz, J=2.8 Hz), 6.93 (s, 1H, H_4-isoxazole), 5.18 (s, 1H, H_4), 5.82 (s, 6H, OCH_3), 2.23 (s, 6H, $Me_{2,6}$).

Synthesis of 4-[5-(2,4-dichlorophenyl)isoxazol-3-yl)-2,6-dimethyl-N^3,N^5-bis(2,4,5-trichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxamide (9b-8)

IR (KBr): cm^{-1}: 1680 (CO), 3180 and 3410 (NH), ^{1}H NMR (DMSO-d_6) δ: 8.93 (bs, 2H, NH), 8.20 (bs, 1H, NH), 8.1 (s, 2H), 7.95 (d, 1H, J=8.4 Hz), 7.85 (s, 2H), 7.86 (d, 1H, J=2.0 Hz), 7.61 (dd, 1H, J=8.4 Hz, J=2.0 Hz), 6.93 (s, 1H, H_4-isoxazole), 5.24 (s, 1H, H_4), 2.26 (s, 6H, $Me_{2,6}$).

Antitubercular Activity

All compounds were tested against *M. tuberculosis* H_{37}RV strain at a concentration of 6.25 μg/ml in DMSO. Rifampicin was used as a standard drug. Primary screening was conducted at 6.25 μg/ml against M. tuberculosis (H_{37}RV) strain in Bactec 12B medium using the Bactec 460 radiometric systems [14]. The antitubercular activity and physical data of compounds **9** are summarized in Table 1.

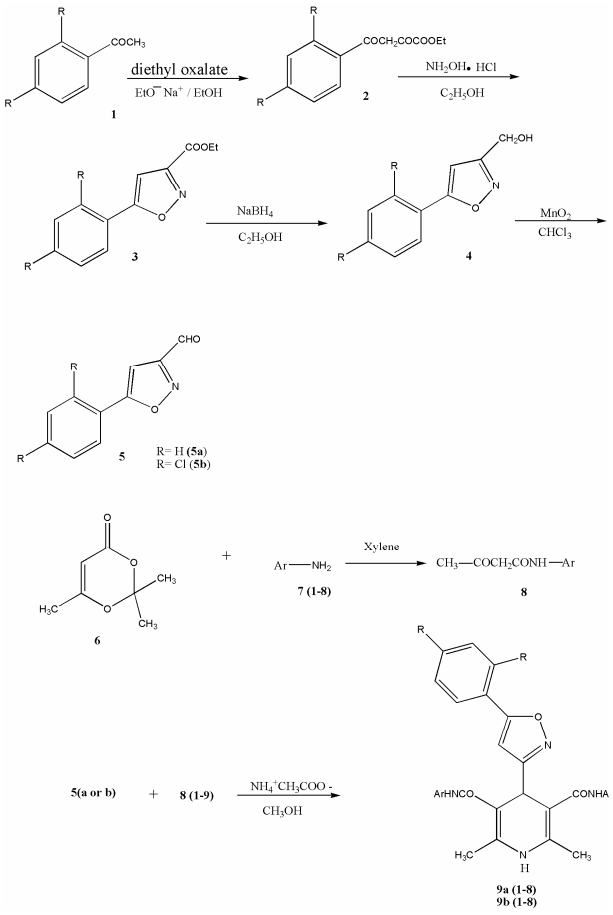
Results and Discussion

The development of a reproducible screening procedure for tuberculosis infection permitted to introduce 1,4-DHPs as a prototype of anti-tuberculosis agents [6]. It could be seen from pervious study [5] that an aryl-amid chain at 3 and 5-position of 1,4-DHP ring affected the anti-tubercular activity. Several aryl six member ring and some aliphatic substitution in 4-position of 3,5-dicarboxamid-1,4-DHP were synthesized. Some of them showed a moderate to good activity against *Mycobacterium tuberculosis* [5]. In view of the important biological properties of 1,4-dihydropyridine it was therefore of our interest to examine further DHP derivatives which possess a linkage between isoxazolyl ring and 1,4-DHPs ring with diaryl carboxamid moiety in 3,5-position.

The synthetic pathway involved construction of the N^3,N^5-Diaryl-4-(5-arylisoxazol-3-yl)-1,4-dihydropyridine-3,5-dicarboxamide (**9**) is outlined in Scheme 1.

Reaction of 2,4-dichloroacetophenone (**1b**) with diethyl oxalate and sodium ethoxide in absolute ethanol afforded ethyl 4-(2,4-dichlorophenyl)-2,4-dixobutanoate (**2b**). Reaction of compound **2b** with hydroxylamine hydrochloride according to the modified method reported previously [15,16] gave the desired compound ethyl 5-(2,4-dichlorophenyl)isoxazole-3-carboxylate (**3b**). The ester group of compound **3** was then transformed into aldehyde function by a two step-procedure, namely, reduction of compound **3b** with sodium borohydride in methanol [15] gave the corresponding alcohol **4b**, and subsequent oxidation of the alcohol **4b** with pyridinium chlorochromate [15] gave the aldehyde **5b** in low yield. However, the aldehyde **5b** was obtained through the manganese (IV) oxide oxidation in chloroform in high yield [13].

Several syntheses of 1,4-dihydropyridines have been reported. Symmetrical 1,4-dihydropyridines were prepared by the well known Hantzch reaction [17]. A one-pot condensation of an aldehyde with alkyl acetoacetate and ammonia either in acetic acid or refluxing in an alcohol was later developed [18]. In addition it has been reported that dihydropyridine may undergo oxidation during synthesis [19,20]. Recently the preparation of 1,4-dihydropyridines under solvent free conditions at 80 °C was reported [21]. Good to excellent yields were obtained by this method for some



Scheme 1.

aliphatic, aromatic and heteroaromatic aldehydes. However, condensation of aldehyde **5**, with *N*-aryl-acetoacetamide **8** under same conditions gave only low yields of the corresponding dihydropyridines. We could prepare the desired compounds **9a** and **9b** through the modified method of Hantzch reaction. Thus the reaction of aldehydes **5** with *N*-aryl-acetoacetamides **8** and ammonium acetate in reluxing methanol in dark conditions and under nitrogen atmosphere afforded the dihydropyridines **9a** and **9b** (Table 1).

Comparison the activities of **9** indicates that 2-nitro-4-methoxyphenyl group in 3,5-dicarboxamide position have the most inhibition percentage. 4-Nitrophenyl and 2,4,5-trichloro phenyl groups substitution were partially active. The other substitution did not show activity. The results demonstrate that a five member heterocyclic group with an aryl group in 5-position of isoxazole ring is a suitable bioisoester for nitrophenyl group which was previously reported as an anti-tubercular agent [3].

Acknowledgment

This work was supported by grants from Research Council of Tehran University of medical Sciences and INSF (Iran National Science Foundation). We are thankful of TAACF (Tuberculosis Antimicrobial Acquisition & Coordination Facility) for carrying out the anti-tuberculosis activity of the compounds.

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