Synthesis and antitubercular activity of new N,N-diaryl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamides

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Received 5 June 2007; Revised 23 Oct 2007; Accepted 15 Nov 2007

ABSTRACT

Background and the purpose of the study: Dihydropyridines having carboxamides in 3 and 5 positions show anti-tuberculosis activity. The purpose of the present study was to synthesize new DHPs having possible anti-tuberculosis activity.

Methods: 4,5-Dichloroimidazole-2-carboxaldehyde was condensed with N-arylaceto-acetamides and ammonium acetate in methanol to give N,N-diaryl-4-(4,5-dichloroimid-azole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamides. All compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* ($H_{37}Rv$).

Results and major conclusion: Some of the new synthesized compounds exhibited a moderate activity in comparison to rifampicin.

Keywords: Antituberculosis, Dihydropyridine, Dichloroimidazole

INTRODUCTION

The dihydropyridines (DHPs) are well-known drugs for the treatment of hypertension and cardiovascular disorders (1). They also have antiallergic (2), anti-inflammatory (3) and Ca^{2+} channel antagonist activities (4). Recently, the syntheses of DHPs with respect to Multidrug Resistance (MDR) reversal in tumor cell gave a new dimension to their applications (5-6). In addition, 1,4-DHP class of compounds are excellent starting synthons for development of antitubercular agents (7-9). It has been demonstrated that substitution of aryl-amide group for dicarboxylic esters moiety reduces the Ca^{2+} channel blocker activity and increases antitubercular activity (10).

Previous studies have shown a moderate to good antitubercular activity for several aryl six-membered ring at 4-position and aryl-amide side chain in C_3 and C_5 of DHPs against *Mycobacterium tuberculosis* ($H_{37}Rv$) (7-9).

As a part of our ongoing research to design novel dihydropyridines (11-17), in this study the design, synthesis and antitubercular activity of N,N-diaryl-4-(4,5-dichloroimid-azole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine- dicarboxamides **3a-j** are described.

MATERIAL AND METHODS

Chemistry

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. ^{1}HNMR spectra were run on a Bruker FT-80 spectrometer. TMS was used as an internal standard. Mass spectra were measured with a Finnigan TSQ-70 spectrometer at 70 eV. The IR spectra were recorded on a Nicolet FTIR 550 spectro-photometer.

The compounds **3a-j** (Table 1) were synthesized according to Scheme 1, from condensation of 4,5-dichloroimidazole-2-carboxaldehyde **1**, N-aryl-acetoacetamide **2** and ammonium acetate in methanol. 4,5-Dichloroimidazole-2-carboxaldehyd was prepared according to reported method (13).

N-Arylacetoacetamides (**2a-j**) were synthesized according to modified Clemens method (18) by simple condensation of 2,2,6-trimethyl-1,3-di-oxin-4-one with the appropriate arylamine.

*General procedure for the preparation of compounds **3a-j**.*

To 3 mmoles of 4,5-dichloroimidazole-2-carboxaldehyde **1** was added 6 mmoles of N-arylacetoacetamide **2** and 20 mmoles of ammonium acetate in 20 ml of methanol. The mixture was refluxed for 24 h and the solvent was

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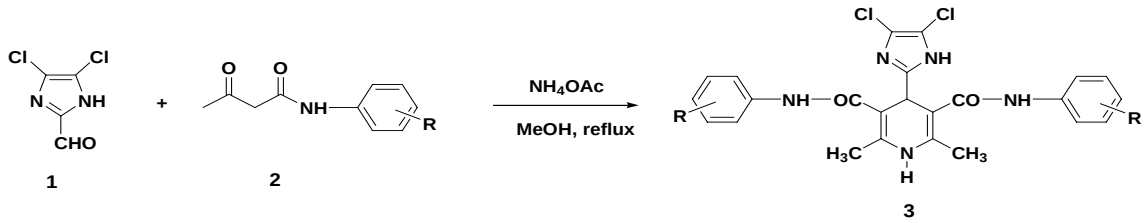


R= (a) H, (b) 3-F, (c) 4-F, (d) 3-Cl, (e) 4-Cl,

(f) 3,4-Cl_2, (g) 3-Br, (h) 4-Br, (i) 3-nitro, (j) 4-nitro.

Scheme 1

removed under reduced pressure. The residue was purified by column chromatography using chloroform/methanol (20:1) as eluent. Crystallization from chloroform & petroleum ether gave pure compounds **3a-j**.

*N,N-Diphenyl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamide (**3a**).*
IR (KBr) ν cm^{-1}: 3277 (NH), 1670 (C=O). ^{1}HNMR (DMSO-d_6) δ: 2.17 (s, 6H, $Me_{2,6}$), 4.80 (s, 1H, H_4), 6.99-7.80 (m, 10H, aromatic), 8.6 (bs, 1H, NH-dihydropyridine), 9.90 (bs, 2H, NH-amide), 12.8 (bs, 1H, NH-imidazole). MS: m/z (%) 391 (M^+, 4), 388 (38), 345 (36), 296 (76), 253 (90), 196 (20), 136 (19), 106 (36), 93 (100).

*N,N-Di-3-fluorophenyl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamide (**3b**).*
IR (KBr) ν cm^{-1}: 3258 (NH), 1673 (C=O). ^{1}HNMR (DMSO-d_6) δ: 2.15 (s, 6H, $Me_{2,6}$), 4.95 (s, 1H, H_4), 6.81-7.15 (m, 2H), 7.38-7.55 (m, 6H), 8.65 (bs, 1H, NH-dihydropyridine), 9.90 (bs, 2H, NH-amide), 12.55 (bs, 1H, NH-imidazole). MS: m/z (%) 518 (M^+, 3), 381 (48), 296 (45), 271 (100), 160 (10), 137 (83), 111(80), 82 (42).

*N,N-Di-4-fluorophenyl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamide (**3c**).*
IR (KBR) ν cm^{-1}: 3245 (NH), 1665 (C=O). ^{1}HNMR (DMSO-d_6) δ: 2.15 (s, 6H, $Me_{2,6}$), 4.98 (s, 1H, H_4), 7.0-7.32 (m, 4H), 6.55-7.65 (m, 4H), 8.60 (bs, 1H, NH-dihydropyridine), 9.95 (bs, 2H, NH-amide), 12.5 (bs, 1H, NH-imidazole). MS: m/z (%) 518 (M^+, 2), 406 (17), 381 (40), 353 (19), 296 (42), 271 (100), 233 (10), 160(15), 137 (83), 111 (88), 109 (78), 82 (38).

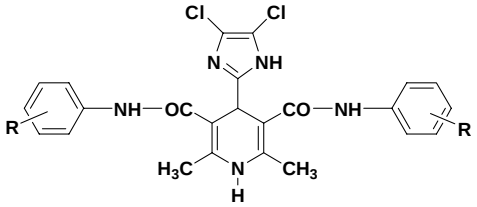
*N,N-Di-3-chlorophenyl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamide (**3d**).*
IR (KBr) ν cm^{-1}: 3266 (NH), 1670 (C=O). ^{1}HNMR (DMSO-d_6) δ: 2.15 (s, 6H, $Me_{2,6}$), 4.90 (s, 1H, H_4), 6.91-7.15 (m, 6H), 7.65-7.75 (m, 2H), 8.65 (bs, 1H, NH-dihydropyridine), 9.90 (bs, 2H, NH-amide), 12.55 (bs, 1H, NH-imidazole). MS: m/z (%) 518 (M^+, 4), 406 (20), 381 (40), 353 (10), 296 (40), 271 (100), 233 (10), 137 (80), 111 (90), 109 (85), 82 (38).

*N,N-Di-4-chlorophenyl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamide (**3e**).*
IR (KBr) ν cm^{-1}: 3244 (NH), 1675 (C=O). ^{1}HNMR (DMSO-d_6) δ: 2.15 (s, 6H, $Me_{2,6}$), 4.95 (s, 1H, H_4), 7.33 (d, J = 8Hz, 4H), 7.75 (d, J = 8Hz, 4H), 8.60 (bs, 1H, NH-dihydropyridine), 9.90 (bs, 2H, NH-amide), 12.40 (bs, 1H, NH-imidazole). MS: m/z (%) 518 (M^+, 10), 406 (15), 381 (38), 296 (28), 271 (71), 137 (85), 111 (100), 109 (83), 83 (42).

*N,N-Di-3,4-dichlorophenyl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamide (**3f**).*
IR (KBr) ν cm^{-1}: 3275 (NH), 1669 (C=O). ^{1}HNMR (DMSO-d_6) δ: 2.10 (s, 6H, $Me_{2,6}$), 4.92 (s, 1H, H_4), 7.36-7.51(m, 4H), 8.05 (s, 2H), 8.40 (bs, 1H, NH-dihydropyridine), 10.26 (bs, 2H, NH-amide), 12.40 (bs, 1H, NH-imidazole). MS: m/z (%) 577 (M^+, 10), 549 (6), 368 (18), 255 (8), 236 (18), 138 (12), 123 (20), 111 (35), 97 (47), 83 (70), 57 (100).

*N,N-Di-3-bromophenyl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamide (**3g**).*
IR (KBr) ν cm^{-1}: 3250 (NH), 1677 (C=O). ^{1}HNMR (DMSO-d_6) δ: 2.20 (s, 6H, $Me_{2,6}$), 4.90

Table 1. Physical data and antitubercular screening results of compounds **3a-j** against *M. Tuberculosis (H$_3$Rv strain)*



Comp. No.	R	Mp (°C)	Yield (%)	Inhibition (%)
3a	H	260-262	45	9
3b	3-F	159-161	30	0
3c	4-F	175-176	27	13
3d	3-Cl	170-172	52	50
3e	4-Cl	168-169	50	12
3f	3,4-Cl_2	254-256	47	34
3g	3-Br	178-180	50	1
3h	4-Br	254-255	49	0
3i	3-NO_2	250-253	48	43
3j	4-NO_2	285-288	50	43
rifampicin				>98

(s, 1H, H_4), 6.90-7.25 (m, 4H), 7.45-7.65 (m, 2H), 8.05 (bs, 1H, NH-dihydropyridine), 9.90 (bs, 2H, NH-amide), 12.55 (bs, 1H, NH-imidazole). MS: m/z (%) 638 (M^+, 2), 503 (8), 415 (5), 331 (100), 269 (23), 197 (42), 173 (30), 106 (29), 63 (18).

*N,N-Di-4-bromophenyl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamide (**3h**).*
IR (KBr) ν cm^{-1}: 3244 (NH), 1675 (C=O). ^{1}HNMR (DMSO-d_6) δ: 2.20 (s, 6H, $Me_{2,6}$), 4.90 (s, 1H, H_4), 7.40 (d, J = 7.8 Hz, 4H), 7.60 (d, J = 7.8 Hz, 4H), 8.40 (bs, 1H, NH-dihydropyridine), 10.18 (bs, 2H, NH-amide), 12.40 (bs, 1H, NH-imidazole). MS: m/z (%) 638 (M^+, 2), 577 (10), 331 (15), 242 (22), 142 (100), 100 (72), 44 (62).

*N,N-Di-3-nitrophenyl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamide (**3i**).*
IR (KBr) ν cm^{-1}: 3245 (NH), 1675 (C=O). ^{1}HNMR (DMSO-d_6) δ: 2.18 (s, 6H, $Me_{2,6}$), 4.95 (s, 1H, H_4), 7.23-7.58 (m, 2H), 7.75-7.85 (m, 4H), 8.50-8.65 (m, 2H), 8.75 (bs, 1H, NH-dihydropyridine), 10.25 (bs, 2H, NH-amide), 12.80 (bs, 1H, NH-imidazole). MS: m/z (%) 572 (M^+, 10), 551 (25), 381 (10), 368 (60), 236 (58), 98 (65), 83 (78), 43 (100).

*N,N-Di-4-nitrophenyl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamide (**3j**).*
IR (KBr) ν cm^{-1}: 3254 (NH), 1670 (C=O). ^{1}HNMR (DMSO-d_6) δ: 2.15 (s, 6H, $Me_{2,6}$), 4.95 (s, 1H, H_4), 7.80 (d, J = 9Hz, 4H), 8.20 (d, J = 9Hz, 4H), 8.85 (bs, 1H, NH-dihydropyridine), 10.40 (bs, 2H, NH-amide), 12.80 (bs, 1H, NH-imidazole). MS: m/z (%) 572 (M^+, 35), 551 (15), 523 (10), 368 (17), 313 (22), 264 (15), 236 (25), 111 (38), 83, (60), 57 (75), 45 (100).

RESULT AND DISCUSSION

All compounds were tested against *M. tuberculosis* H_{37}Rv strain at concentration of 6.25 μg/ml in DMSO. Rifampicin was used as a reference drug. Primary screening was conducted in Bactec 12 B medium using the Bactec 460 radiometric system (19). The antitubercular activity and physical data of compounds **3a-j** are summarized in Table 1. From the Results it appears that substitution of 4,5-dichloroimidazole ring at 4-position of 1,4-DHP affects the antitubercular activity when 3,5-diester group in classic DHP structure was replaced by carboxamide moiety. The results demonstrate that a five member heterocyclic group with electron withdrawing substituent is a suitable bioisoster for nitro phenyl group which was previously reported as antitubercular agent (10).
Comparison of the activities of **3a-j** indicates that the most active compound is **3d** with 3-chlorophenyl group at 3,5 dicarbox-amide position. 3-Nitrophenyl and 4-nitrophenyl substituted compounds were also relatively active, but other substitutions did not show good activity. Compounds **3a-j** could serve as valuable probes to study the structure-function relationships for antitubercular activity.

ACKNOWLEDGMENT

The authors are very thankful to the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF), funded by the National Institute of Allergy and Infectious Diseases, a division of the National Institute of Health, USA, for providing biological screening results. This work was supported by grants from the Research Council of Tehran University of Medical Sciences, INSF (Iran National Science Foundation) and Iran Chapter of TWAS.

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