

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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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-arylacetoacetamides and ammonium acetate in methanol to give N,N-diaryl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamides. All compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* (H₃₇Rv).

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 Ca²⁺ 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 Ca²⁺ 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 C₃ and C₅ of DHPs against *Mycobacterium tuberculosis* (H₃₇Rv) (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-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxamides **3a-j** are described.

MATERIAL AND METHODS

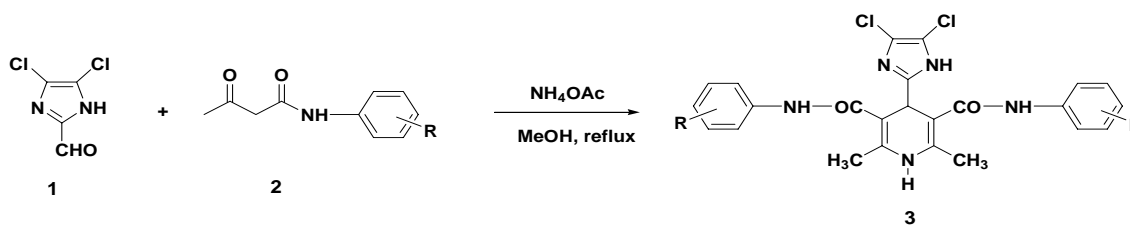
Chemistry

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. ¹HNMR 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 spectrophotometer.

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-carboxaldehyde 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-dioxin-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



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

(f) 3,4-Cl₂, (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). ¹HNMR (DMSO-d₆) δ : 2.17 (s, 6H, Me_{2,6}), 4.80 (s, 1H, H₄), 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). ¹HNMR (DMSO-d₆) δ : 2.15 (s, 6H, Me_{2,6}), 4.95 (s, 1H, H₄), 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). ¹HNMR (DMSO-d₆) δ : 2.15 (s, 6H, Me_{2,6}), 4.98 (s, 1H, H₄), 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). ¹HNMR (DMSO-d₆) δ : 2.15 (s, 6H, Me_{2,6}), 4.90 (s, 1H, H₄), 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**).

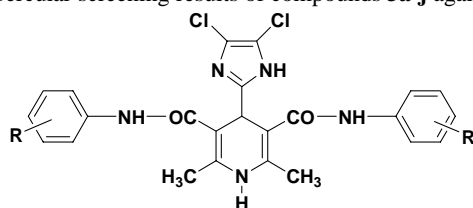
IR (KBr) ν cm⁻¹: 3244 (NH), 1675 (C=O). ¹HNMR (DMSO-d₆) δ : 2.15 (s, 6H, Me_{2,6}), 4.95 (s, 1H, H₄), 7.33 (d, J = 8Hz, 4H), 7.75 (d, J = 8Hz, 4H), 8.60 (bs, 1H, NH-dihydropyridine), 9.90 (bs, 2H, NH-amide), 12.40 (bs, 1H, NH-imidazole). MS: m/z (%) 518 (M⁺, 10), 406 (15), 381 (38), 296 (28), 271 (71), 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). ¹HNMR (DMSO-d₆) δ : 2.10 (s, 6H, Me_{2,6}), 4.92 (s, 1H, H₄), 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). ¹HNMR (DMSO-d₆) 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* (*H₃Rv* 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, H₄), 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). ¹HNMR (DMSO-d₆) δ : 2.20 (s, 6H, Me_{2,6}), 4.90 (s, 1H, H₄), 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). ¹HNMR (DMSO-d₆) δ : 2.18 (s, 6H, Me_{2,6}), 4.95 (s, 1H, H₄), 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). ¹HNMR (DMSO-d₆) δ : 2.15 (s, 6H, Me_{2,6}), 4.95

(s, 1H, H₄), 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* H₃₇Rv strain at concentration of 6.25 μ g/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.

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