EXPLORING ARYL THIAZOLIDINE CARBOXAMIDES AS A NEW CLASS OF ANTIMYCOBACTERIALS

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Summary

Sixty four 2-(sub aryl)-*N*-(sub)thiazolidine-4-carboxamides were synthesized and evaluated for their *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB), and *Mycobacterium smegmatis* (MC^2).These compounds inhibited MTB with MICs of 0.12-20 µM and MC^2 with MICs of 1.23-29.80 µM. Among the synthesized compounds, compound (4-benzylpiperazin-1-yl)(2-(4-fluorophenyl)thiazolidin-4-yl)methanone **9b** was found to be more potent with MIC of 0.12 µM against MTB and it was 5.5 and 1.9 times more potent than isoniazid and rifampicin respectively.

Keywords: Tuberculosis; antimycobacterial; antitubercular; thiazolidine carboxamide

Introduction

Tuberculosis (TB) is a common, chronic bacterial infection caused by *Mycobacterium tuberculosis* (MTB) harbour the bacterium without symptoms (latent TB), but some develop into active TB disease.[1] TB is a worldwide pandemic[2] and still remains one of the foremost among infectious diseases in the world causing the maximum number of deaths due to the spread of a single microorganism.[3] The World Health Organization (WHO) thus declared it as a global emergency. Of the new TB cases reported, 95 % occur in developing countries every year. Currently, among the infected individuals, approximately eight million develop active TB, and almost two million die from this disease.[4] Currently, the recommended standard chemotherapeutic regimen for TB treatment is prescribed under DOTS. The chemotherapeutic regimen consists of an initial 2-month phase of treatment with isoniazid (INH), rifampicin (RIF), pyrazinamide (PYR), and ethambutol (ETH) followed by a continuation phase of treatment lasting 4 months with isoniazid and rifampicin. Poor patient compliance

can promote the emergence of drug resistance, and this is particularly true in TB chemotherapy.[5] The standard TB therapy is ineffective in controlling multi-drug resistant TB (MDR-TB) in high MDR-TB incidence areas. The need for new drugs to extend the range of TB treatment options is acute. New chemical entities with novel mechanisms of action will most likely possess activity against MDR-TB. However, these alone will not provide the breakthrough that is needed. The key to improving therapy is to develop new agents with potent sterilizing activity that will lead to a shortening of the duration of chemotherapy.[4] Until now, progress in TB drug development has been impeded by two major factors: (a) the belief that there was little need for new agents, and (b) the high cost of development coupled with the perception that the potential global market was insufficient to guarantee return on investment. Recently WHO recommended third-line regimen for the treatment of TB which includes quinolone antibacterial ofloxacin.[4] However, in the last 40 years, only a few drugs have been approved by the Food and Drug Administration (FDA) to treat TB, reflecting the inherent difficulties in discovery and clinical testing of new agents and the lack of pharmaceutical industry research in the area. In particular, in addition to the current drugs approved by the FDA for the treatment of TB and the drugs that commonly are recommended for the treatment of TB but are not FDA approved, a variety of other compounds or classes of compounds are under investigation as potential antimycobacterial drugs.[6] A new TB treatment should offer at least one of three improvements over the existing regimens: (a) shorten the total duration of effective treatment and/or significantly reduce the total number of doses needed to be taken under DOTS supervision; (b) improve the treatment of MDR-TB, which cannot be treated with INH and RIF and/or (c) provide more effective treatment of latent/dormant TB infection, which is essential for eliminating TB.[7]
In an effort to discover new and effective chemotherapeutic agents for the treatment of TB, we recently reported the antimycobacterial activity of various phthalazin-4-ylacetamides, thiazolylthiosemicarbazones, chromeno[3,2-*c*]pyridin-3-yl derivatives, [1,4]-thiazines, thieno-[2,3-*b*]thiophenes, spiro-cyclohexanones, thieno[3,2-*b*]indoles, and furan-2-yl derivatives[8-15]. In the course of screening to discover new compounds employed in the chemotherapy of tuberculosis, we identified 2-(sub aryl)-*N*-(sub)thiazolidine-4-carboxamides to be novel class of compounds having potent antimycobacterial activity.

Materials and methods

Chemistry: Melting points were taken on an electrothermal melting point apparatus (Buchi BM530) in open capillary tubes and are uncorrected. Infrared spectra (KBr disc) were run on Jasco IR Report 100 spectrometer. ^{1}H NMR spectra were scanned on a JEOL Fx300 MHz NMR spectrometer using DMSO-d_6 as a solvent. Chemical shifts are expressed in δ (ppm) relative to tetramethylsilane. ^{13}C NMR spectra were recorded on Bruker AC 200/DPX 400 MHz. Elemental analyses (C, H and N) were performed on Perkin-Elmer model 240 C analuzer and the data were within ±0.4 % of the theoretical values.

General procedure for synthesis of 2-(sub aryl)-*N*-(sub)thiazolidine-4-carboxylic acid iii a-d: To a solution of L-cysteine hydrochloride (**i**, 2g, 1 equiv) in water (17.2 ml), added potassium acetate (1.32g, 1 equiv). To this homogenous mixture, added ethanol (17.2 ml) and appropriate aldehyde (**ii**, 0.5 equiv). The

reaction was stirred below 25 °C for 6h. The solid precipitated was filtered and washed with cold ethanol and dried to afford **iii a-d**.

General procedure for the preparation of 2-(sub aryl)-*N*-(sub)thiazolidine-4-carboxamides 1(a-d)-16(a-d): A mixture of appropriate carboxylic acid (**iii a-d**, 0.2 g, 1 equiv) and DCC (2 equiv) in dichloromethane (20 ml) was stirred for 10 min at 0 °C. To this mixture, appropriate primary or secondary amine was added and stirred for 8 h. The solid urea separated was filtered off and the organic layer was washed with water (2x25 ml), dried over sodium sulphate and distilled under reduced pressure to yield the desired product.

Physical and spectral data's for some representative compounds:

N,2-Diphenylthiazolidine-4-carboxamide (1a): Yield: 57 %; m.p.: 197 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.84 (q, 1H, -CH of thiazolidinone ring), 6.35 (s, 1H, -CH of thiazolidine ring), 7.19-7.43 (m, 10H, Ar-H), 7.56 (s, 1H, -NHC=O, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 172.7, 139.6, 138.5, 128.9, 128.0, 127.1, 126.9, 121.6, 72.2, 71.1, 36.1; Anal ($C_{16}H_{16}N_2OS$) C, H, N.

2-(4-Fluorophenyl)-N-p-tolylthiazolidine-4-carboxamide (2b): Yield: 50 %; m.p.: 219 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.34 (s, 3H, CH_3), 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.84 (q, 1H, -CH of thiazolidinone ring), 6.35 (s, 1H, -CH of thiazolidine ring), 7.11-7.56 (m, 8H, Ar-H), 7.56 (s, 1H, -NHC=O, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 172.7, 161.3, 139.6, 138.5, 136.8, 134.8, 130.3, 128.9, 121.6, 72.2, 71.1, 36.1, 21.3; Anal ($C_{17}H_{17}FN_2OS$) C, H, N.

N-(4-Chlorophenyl)-2-(4-nitrophenyl)thiazolidine-4-carboxamide (3c): Yield: 92 %; m.p.: 122 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.84 (q, 1H, -CH of thiazolidinone ring), 6.35 (s, 1H, -CH of thiazolidine ring), 7.47-8.14 (m, 8H, Ar-H), 7.56 (s, 1H, -NHC=O, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 172.7, 146.3, 145.3, 136.6, 133.3, 129.9, 129.0, 123.8, 120.6, 71.1, 70.6, 36.1; Anal ($C_{16}H_{14}ClN_3O_3S$) C, H, N.

N-(5-Fluoro-2-methylphenyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidine-4-carboxamide (4d): Yield: 73 %; m.p.: 156 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.12 (s, 3H, -CH_3), 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.82 (s, 3H, OCH_3), 3.84 (q, 1H, -CH of thiazolidinone ring), 5.35 (s, 1H, OH, D_2O exchangeable), 6.35 (s, 1H, -CH of thiazolidine ring), 6.72-7.63 (m, 6H, Ar-H), 7.26 (s, 1H, -NHC=O, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 172.7, 160.1, 147.1, 138.5, 132.8, 130.9, 127.1, 122.4, 115.5, 114.2, 111.0, 110.0, 71.1, 56.1, 36.1, 17.3; Anal ($C_{18}H_{19}FN_2O_3S$) C, H, N.

N-(2,4-Dinitrophenyl)-2-phenylthiazolidine-4-carboxamide (5a): Yield: 85 %; m.p.: 141 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.84 (q, 1H, -CH of thiazolidinone ring), 6.35 (s, 1H, -CH of thiazolidine ring), 7.26-8.82 (m, 8H, Ar-H), 7.56 (s, 1H, -NHC=O, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 172.7, 144.4, 143.4, 139.6, 138.5, 137.4, 130.2, 127.1, 126.9, 123.4, 120.3, 72.2, 71.1, 36.1; Anal ($C_{16}H_{14}N_4O_5S$) C, H, N.

2-(4-Fluorophenyl)-N-(5-methylpyridin-2-yl)thiazolidine-4-carboxamide (6b): Yield: 36 %; m.p.: 203 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.34 (s, 3H, CH_3), 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.84 (q, 1H, -CH of thiazolidinone ring), 6.35 (s, 1H, -CH of thiazolidine ring), 7.12-8.66 (m, 7H, Ar-H), 9.56 (s, 1H, -NHC=O, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 172.7, 161.3, 151.1, 149.9, 139.6, 137.7, 134.8, 130.3, 129.6, 115.1, 71.1, 70.8, 36.1, 18.0; Anal ($C_{16}H_{16}FN_3OS$) C, H, N.

N-(6-Methylpyridin-2-yl)-2-(4-nitrophenyl)thiazolidine-4-carboxamide (7c): Yield: 91 %; m.p.: 193 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.54 (s, 3H, CH_3), 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.84 (q, 1H, -CH of thiazolidinone ring), 6.35 (s, 1H, -CH of thiazolidine ring), 7.45-8.15 (m, 7H, Ar-H), 9.56 (s, 1H, -NHC=O, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 172.7, 151.1, 149.9, 146.3, 145.3, 129.6, 125.4, 123.8, 112.8, 71.1, 70.8, 36.1, 23.9; Anal ($C_{16}H_{16}N_4O_3S$) C, H, N.

N-(4-Chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidine-4-carboxamide (8d): Yield: 80 %; m.p.: 204 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 2.92 (2H, d, -CH_2 of thiazolidine ring), 3.82 (s, 3H, OCH_3), 3.84 (q, 1H, -CH of thiazolidinone ring), 5.35 (s, 1H, OH, D_2O exchangeable), 6.35 (s, 1H, -CH of thiazolidine ring), 6.72-8.40 (m, 6H, Ar-H), 9.26 (s, 1H, -NHC=O, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ (ppm): 172.7, 151.1, 148.1, 147.1, 143.7, 132.8, 122.4, 115.1, 114.2, 71.1, 56.1, 36.1; Anal ($C_{16}H_{16}ClN_3O_3S$) C, H, N.

***(4-Benzylpiperazin-1-yl)(2-phenylthiazolidin-4-yl)methanone (9a*)**: Yield: 51 %; m.p.: 260 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.51 (dd, 4H, -CH_2 of piperazine), 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.31 (dd, 4H, -CH_2 of piperazine), 3.65 (s, 2H, -CH_2), 3.84 (q, 1H, -CH of thiazolidinone ring), 6.35 (s, 1H, -CH of thiazolidine ring), 7.25-7.36 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 169.7, 139.6, 137.7, 129.6, 128.6, 127.1, 126.9, 71.1, 69.5, 64.8, 54.5, 49.9, 36.1; Anal ($C_{21}H_{25}N_3OS$) C, H, N.

(2-(4-Fluorophenyl)thiazolidin-4-yl)(4-phenylpiperazin-1-yl)methanone (10b): Yield: 63 %; m.p.: 171 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.31 (dd, 4H, -CH_2 of piperazine), 3.41 (dd, 4H, -CH_2 of piperazine), 3.84 (q, 1H, -CH of thiazolidinone ring), 6.35 (s, 1H, -CH of thiazolidine ring), 6.95-7.29 (m, 9H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 169.7, 161.3, 149.6, 134.8, 130.4, 129.6, 121.4, 115.3, 114.4, 70.8, 69.5, 54.5, 46.5, 36.1; Anal ($C_{20}H_{22}FN_3OS$) C, H, N.

(4-(4-Chlorophenyl)piperazin-1-yl)(2-(4-nitrophenyl)thiazolidin-4-yl)methanone (11c): Yield: 70 %; m.p.: 210 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.31 (dd, 4H, -CH_2 of piperazine), 3.41 (dd, 4H, -CH_2 of piperazine), 3.84 (q, 1H, -CH of thiazolidinone ring), 6.35 (s, 1H, -CH of thiazolidine ring), 6.70-8.13 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 169.7, 145.3, 146.3, 129.6, 127.1, 123.8, 115.4, 70.8, 69.5, 53.5, 46.5, 36.1; Anal ($C_{20}H_{21}ClN_4O_3S$) C, H, N.

1-Cyclopropyl-6-fluoro-7-(4-(2-(4-nitropheny)lthiazolidine-4-carbonyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (12d): Yield: 89 %; m.p.: 175 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.05 (d, 2H, CH of

cyclopropyl), 1.35 (d, 2H, CH of cyclopropyl), 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.31 (dd, 4H, -CH_2 of piperazine), 3.41 (dd, 4H, -CH_2 of piperazine), 3.82 (s, 3H, OCH_3), 3.84 (q, 1H, -CH of thiazolidinone ring), 4.13 (m, 1H, CH of cyclopropyl), 5.35 (s, 1H, OH, D_2O exchangeable), 6.35 (s, 1H, -CH of thiazolidine ring), 6.04-8.03 (m, 5H, Ar-H), 8.67 (s, 1H, CH of quinolone ring), 14.0 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 176.9, 169.7, 166.3, 152.5, 147.6, 147.1, 146.9, 134.5, 132.8, 122.4, 115.4, 114.2, 112.4, 109.3, 102.5, 71.1, 69.5, 56.1, 53.5, 46.5, 36.1, 35.9, 7.7; Anal ($C_{28}H_{29}FN_4O_6S$) C, H, N.

1-Ethyl-6-fluoro-4-oxo-7-(4-(2-phenylthiazolidine-4-carbonyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (13a): Yield: 92 %; m.p.: 179 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.35 (d, 2H, CH of ethyl), 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.31 (dd, 4H, -CH_2 of piperazine), 3.41 (dd, 4H, -CH_2 of piperazine), 3.84 (q, 1H, -CH of thiazolidinone ring), 4.63 (m, 2H, CH_2 of ethyl), 6.35 (s, 1H, -CH of thiazolidine ring), 7.27-8.03 (m, 7H, Ar-H), 9.07 (s, 1H, CH of quinolone ring), 14.0 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 176.9, 169.7, 166.3, 152.5, 147.6, 139.6, 134.5, 128.6, 127.1, 126.9, 114.4, 109.3, 102.5, 71.1, 69.5, 54.5, 51.9, 49.9, 36.1, 14.4; Anal ($C_{26}H_{27}FN_4O_4S$) C, H, N.

1-Ethyl-6,8-difluoro-7-(4-(2-(4-fluorophenyl)thiazolidine-4-carbonyl)-3-methylperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (14b): Yield: 53 %; m.p.: 143 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.31 (3H, CH_3), 1.35 (d, 2H, CH of ethyl), 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.31 (dd, 4H, -CH_2 of piperazine), 3.41 (dd, 4H, -CH_2 of piperazine), 3.84 (q, 1H, -CH of thiazolidinone ring), 4.63 (m, 2H, CH_2 of ethyl), 6.35 (s, 1H, -CH of thiazolidine ring), 7.12-7.77 (m, 5H, Ar-H), 9.07 (s, 1H, CH of quinolone ring), 14.0 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 176.9, 169.7, 166.3, 161.3, 152.5, 149.1, 146.4, 134.8, 134.5, 131.6, 130.3, 126.9, 119.8, 115.4, 109.3, 107.8, 70.9, 69.5, 56.9, 53.6, 49.9, 36.1, 18.5, 14.4; Anal ($C_{27}H_{27}F_3N_4O_4S$) C, H, N.

1-Cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl-4-(2-(4-nitrophenyl)thiazolidine-4-carbonyl)-piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (15c): Yield: 74 %; m.p.: 205 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.05 (d, 2H, CH of cyclopropyl), 1.35 (d, 2H, CH of cyclopropyl), 2.87 (broad, 1H, NH of thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.31 (dd, 4H, -CH_2 of piperazine), 3.41 (dd, 4H, -CH_2 of piperazine), 3.82 (s, 3H, OCH_3), 3.84 (q, 1H, -CH of thiazolidinone ring), 4.13 (m, 1H, CH of cyclopropyl), 6.35 (s, 1H, -CH of thiazolidine ring), 7.49-8.47 (m, 5H, Ar-H), 8.67 (s, 1H, CH of quinolone ring), 14.0 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 176.9, 169.7, 166.3, 158.6, 146.6, 146.3, 145.3, 132.5, 129.6, 125.9, 123.8, 109.3, 104.5, 70.8, 69.5, 56.9, 55.8, 53.9, 52.8, 47.0, 36.1, 18.5, 7.7; Anal ($C_{29}H_{30}FN_5O_7S$) C, H, N.

1-Cyclopropyl-6-fluoro-7-(1-(2-(4-hydroxy-3-methoxyphenyl)thiazolidine-4-carbonyl)tetrahydro-1H-pyrrolo[3,4-b]pyridin-6(2H,7H,7aH)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (16d): Yield: 62 %; m.p.: 202 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.05 (d, 2H, CH of cyclopropyl), 1.33 (1H, CH of pyrrolo pyridine ring), 1.35 (d, 2H, CH of cyclopropyl), 1.43 (1H, CH of pyrrolo pyridine ring), 1.53 (1H, CH of pyrrolo pyridine ring), 1.59 (1H, CH of pyrrolo pyridine ring), 2.65 (1H, CH of pyrrolo pyridine ring), 2.80 (1H, CH of pyrrolo pyridine ring), 2.81 (1H, CH of pyrrolo pyridine ring), 2.87 (broad, 1H, NH of

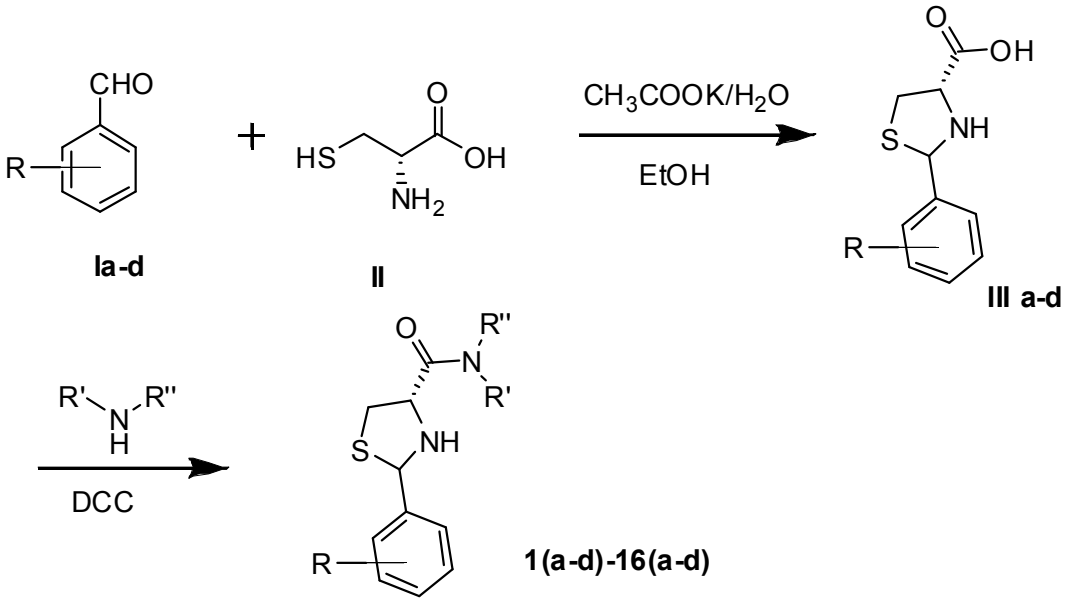
thiazolidine ring, D_2O exchangeable), 3.02 (2H, d, -CH_2 of thiazolidine ring), 3.12 (1H, CH of pyrrolo pyridine ring), 3.68 (1H, CH of pyrrolo pyridine ring), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.84 (q, 1H, -CH of thiazolidinone ring), 4.13 (m, 1H, CH of cyclopropyl), 5.35 (s, 1H, OH, D_2O exchangeable), 6.35 (s, 1H, -CH of thiazolidine ring), 6.72-7.57 (m, 4H, Ar-H), 8.67 (s, 1H, CH of quinolone ring), 14.0 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 176.9, 173.4, 166.3, 158.6, 147.3, 146.9, 146.3, 132.5, 125.7, 123.3, 122.4, 115.5, 114.2, 109.3, 104.5, 71.1, 69.5, 59.5, 55.8, 56.1, 53.3, 42.5, 36.4, 26.5, 23.2, 7.7; Anal ($C_{32}H_{35}FN_4O_7S$) C, H, N.

Antimycobacterial activity*:* All compounds were screened in triplicate for their *in vitro*antimycobacterial activity against log-phase cultures of MTB and *Mycobacterium smegmatis* ATCC 14468 (MC2) in Middlebrook 7H11agar medium supplemented with OADC (albumin– dextrose–sodium chloride) by the agar dilution method, similar to that recommended by the National Committee for Clinical Laboratory Standards, for the determination of MIC[16]. The MIC is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth.

Results and Discussion

Synthesis

Sixty four various new 2-aryl thiazolidine-4-carboxamides were synthesized from L-cysteine according to the literature method (Scheme:1).[17] Briefly, Compounds **i** and **ii** were reacted in ethanol to obtain the thizolidine carboxylic acids (**iii a-d**). Compound **iii (a-d)** were treated with various primary and secondary amine in presence of N,N'-dicyclohexylcarbodiimide (DCC) and dichloromethane (DCM) as solvent to form 2-(aryl substituted)-*N*-(substituted)thiazolidine-4-carboxamides (**iv a-d 1-16**).



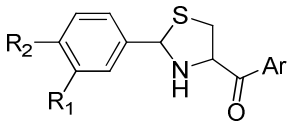
Scheme:1 Synthetic protocol of compounds

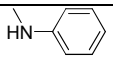
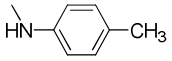
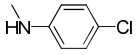
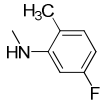
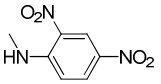
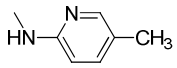
The purity of the synthesized compounds were monitored by thin-layer chromatography (TLC) and elemental analyses and the structures were identified by spectral data.

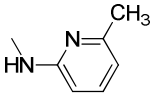
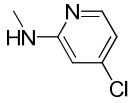
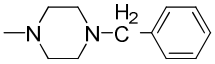
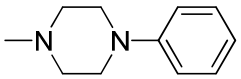
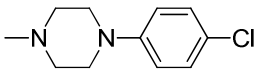
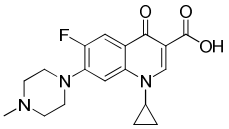
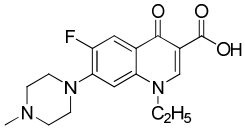
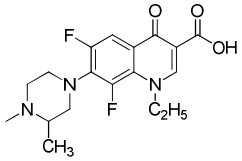
Antimycobacterial activity

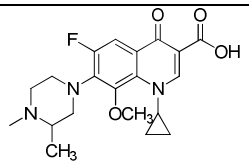
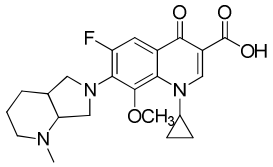
The compounds were screened for their in vitro antimycobacterial activity against MTB and *Mycobacterium smegmatis* ATCC 14468 (MC2) by agar dilution method for the determination of MIC in duplicate. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of the compound required to give complete inhibition of bacterial growth and MICs of the synthesized compounds along with the standard drugs for comparison are presented in Table 1.

Table 1. Physical constants, *in vitro* antimycobacterial activities



Compd No.	Ar	R_1	R_2	M. P. (°C)	Yield (%)	MIC (µM)	
						MTB	MC^2
1a		H	H	197	57	11.00	11.00
1b	-do-	H	F	201	53	5.15	5.19
1c	-do-	H	NO_2	260	83	20.94	20.94
1d	-do-	OCH_3	OH	89	83	18.91	9.47
2a		H	H	125	85	1.34	2.64
2b	-do-	H	F	219	50	4.93	39.50
2c	-do-	H	NO_2	189	70	10.01	5.02
2d	-do-	OCH_3	OH	196	54	0.58	2.29
3a		H	H	159	73	9.81	19.60
3b	-do-	H	F	171	74	0.59	2.34
3c	-do-	H	NO_2	122	92	8.60	17.17
3d	-do-	OCH_3	OH	139	73	1.09	4.30
4a		H	H	142	87	4.93	19.75
4b	-do-	H	F	197	89	4.66	9.36
4c	-do-	H	NO_2	125	82	9.47	18.91
4d	-do-	OCH_3	OH	156	73	2.15	8.63
5a		H	H	141	85	0.53	2.08
5b	-do-	H	F	161	76	1.01	7.97
5c	-do-	H	NO_2	260	88	7.46	29.80
5d	-do-	OCH_3	OH	272	92	0.47	1.87
6a		H	H	203	36	20.87	20.87
6b	-do-	H	F	167	53	0.63	2.48
6c	-do-	H	NO_2	250	85	9.08	18.14
6d	-do-	OCH_3	OH	147	82	1.15	2.28

7a		H	H	153	63	20.87	10.45
7b	-do-	H	F	171	86	0.63	2.48
7c	-do-	H	NO_2	193	91	4.52	18.14
7d	-do-	OCH_3	OH	136	86	4.51	4.51
8a		H	H	189	60	9.78	4.87
8b	-do-	H	F	165	90	1.18	4.64
8c	-do-	H	NO_2	232	57	4.27	17.13
8d	-do-	OCH_3	OH	204	80	4.26	4.26
9a		H	H	260 dec	51	4.24	2.14
9b	-do-	H	F	170 dec	58	0.12	2.04
9c	-do-	H	NO_2	216	73	3.78	15.15
9d	-do-	OCH_3	OH	213	53	1.88	1.88
10a		H	H	155	61	17.68	35.36
10b	-do-	H	F	171	63	1.07	2.12
10c	-do-	H	NO_2	159	81	7.85	15.68
10d	-do-	OCH_3	OH	164	65	7.83	18.09
11a		H	H	197	57	16.11	8.06
11b	-do-	H	F	169	72	0.49	1.94
11c	-do-	H	NO_2	210	70	1.80	3.62
11d	-do-	OCH_3	OH	176	72	0.92	1.82
12a		H	H	205	88	0.76	1.51
12b	-do-	H	F	146	61	1.44	5.79
12c	-do-	H	NO_2	175	89	5.51	11.01
12d	-do-	OCH_3	OH	112	61	0.35	1.38
13a		H	H	179	92	0.78	1.54
13b	-do-	H	F	217	59	2.95	2.97
13c	-do-	H	NO_2	125	92	5.63	5.63
13d	-do-	OCH_3	OH	109	59	0.17	1.41
14a		H	H	201	81	2.88	11.56
14b	-do-	H	F	143	53	2.79	5.60
14c	-do-	H	NO_2	158	81	5.34	10.67
14d	-do-	OCH_3	OH	121	58	1.32	5.33

15a		H	H	209	95	2.75	11.02
15b	-do-	H	F	219	83	0.34	1.35
15c	-do-	H	NO_2	205	74	2.55	5.11
15d	-do-	OCH_3	OH	137	55	1.27	5.10
16a		H	H	194	61	0.67	1.23
16b	-do-	H	F	204	72	0.32	1.23
16c	-do-	H	NO_2	198	54	2.44	1.23
16d	-do-	OCH_3	OH	202	62	0.15	2.45
	INH					0.66	>123.0
	Rifampicin					0.23	45.57
	Ciprofloxacin					4.71	2.35

In the first phase of screening against MTB, all the compounds showed excellent *in vitro* activity against MTB with MICs ranging from 0.12-20.94 µM. Seventeen compounds (**5a**, **12a**, **13a**, **16a**, **3b**, **6b**, **7b**, **9b**, **11b**, **15b**, **16b**, **2d**, **5d**, **11d**, **12d**, **13d**, and **16d**) inhibited MTB with MIC of less than 1 µM. When compared to isoniazid (MIC: 0.66 µM), thirteen compounds (**5a**, **3b**, **6b**, **7b**, **9b**, **11b**, **15b**, **16b**, **2d**, **5d**, **12d**, **13d**, and **16d**) were found to be more active against MTB. Three compounds (**9b, 13d**, and **16d**) were found to be more potent than another first line anti-Tb drug rifampicin (MIC: 0.23 µM), forty two compounds were more potent than fluoroquinolone antibacterial ciprofloxacin (MIC: 4.71 µM). Compound (4-benzylpiperazin-1-yl)(2-(4-fluorophenyl)thiazolidin-4-yl)methanone (**9b**) was found to be the most active compound *in vitro* with MIC of 0.12 µM against MTB and it was 5.5 and 1.9 times more potent than isoniazid and rifampicin respectively.

With respect to structure-anti-TB activity, in the carboxamide end we prepared various phenyl (**1-5**), pyridyl (**7-8**), aryl piperazine (**9-11**) and fluoroquinolone (**12-16**) side chain. Among them the order of activity is fluoro quinolone>aryl piperazine>pyridyl>phenyl side chain. Among the phenyl ring dinitro substituent showed excellent activity, and the order of activity is 2,4-$(NO_2)_2$>4-Cl>4-CH_3>4-CF_3, 6-CH_3>H. In the case of pyridyl ring halogen showed good activity, and the order of activity as follows 4-Cl>5-CH_3>4-CH_3. In aryl ring of piperazine derivatives benzyl group showed promising activity, and the order of activity is benzyl>4-chlorophenyl>phenyl. Among the fluoroquinolones the order of activity is moxifloxacin>gatifloxacin>ciprofloxacin>norfloxacin>lomefloxacin.

The compounds were also evaluated against MC^2 in which all the compounds inhibited MC^2 with MIC values ranging from 1.23 to 39.50 µM. All the sixty four compounds were found to be more potent than standard drugs isoniazid (MIC: >123 µM) and rifampicin(MIC: 45.57 µM). Eighteen compounds were found to be more potent than ciprofloxacin (MIC: 2.35 µM) against MC^2.

Acknowledgements

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