



Design, Synthesis and Activity Evaluation of N-(pyridin-4-yl) Salicylamides as Antimycobacterial Agents

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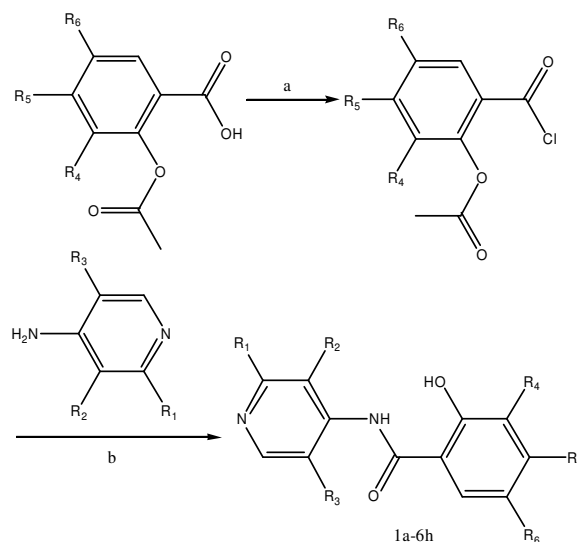
A series of N-(pyridin-4-yl) salicylamides derivatives were prepared through acylation of the corresponding acetylsalicyloyl chlorides with substituted 4-amino-pyridines. These compounds were evaluated *in vitro* for antimycobacterial activities against *Mycobacterium tuberculosis* (TB) and *Mycobacterium avium* (A) by the minimum inhibitory concentrations (MIC) values. Eight of the compounds exhibited lower MIC against A than the one of isoniazide. Meanwhile, four of the compounds exhibited good anti-TB activity compared to isoniazide. Antimycobacterial activities of N-(pyridin-4-yl) salicylamides were influenced by the balance between hydrophobicity and electron withdrawing substituent effects on the phenyl and pyridine ring. These studies show that the compounds might serve as prospective wide-spectrum antimycobacterial substances.

Keywords: *Mycobacterium tuberculosis*, N-(pyridin-4-yl) salicylamides, Activity evaluation, Synthesis.

INTRODUCTION

Searching for new antimycobacterial compounds is one of the most challenging tasks in current medicinal chemistry. Particularly, antimycobacterial properties of salicylanilides^{1,2} inhibiting two-component regulatory systems in mycobacteria, as a known strategic opportunity for design of selective antimycobacterial agents¹⁻⁸, is of great interest. Isosteres of salicylanilides were systematically documented, *i.e.* 3-hydroxypicolinamilides⁹, 2-sulfanylbenzanilides⁹, N-benzylsalicylamides¹⁰ and N-pyridin-2-ylsalicylamides¹¹. However, N-pyridin-4-ylsalicylamides as antimycobacterial agents have rarely been studied systematically in literatures. We thus prepared a series of new N-pyridin-4-yl salicylamide analogues (Fig. 1) to study their antimycobacterial activities by varying the substituents on the heterocyclic and salicylic moieties.

The synthetic route to N-(pyridin-4-yl) salicylamides was shown in Fig. 1. N-(pyridin-4-yl) salicylamides **1a-6h** were prepared by treatment of the corresponding substituted acetylsalicyloyl chlorides with substituted 4-amino-pyridines in chloroform in the presence of triethylamine. After addition of 10 % hydrochloric acid and saturated sodium bicarbonate the products was isolated in more than 85 % yield according to the theoretical value. The structure was fully identified by ¹H NMR, ¹³C NMR and IR spectra.



R₁ = H, Cl, CH₃; R₂ = H, Cl, CF₃; R₃ = R₄ = H, Cl; R₅ = OCH₃; R₆ = H, Cl, Br, CF₃

Reagents and conditions: (a) Pyridine, SOCl₂, 75-100 °C, reflux, 3-5h; (b) CHCl₃, NEt₃, r. t., 24-48 h.

Fig. 1. Synthesis of Compounds **1a-6h** N-(pyridin-4-yl) salicylamides

EXPERIMENTAL

Chemistry. melting points (m.p.) were determined on an YRT-3 digital melting point apparatus and were uncorrected.

Infrared (IR) spectra were measured in KBr pellets on an EQU NOX-55 instrument. ^1H NMR and ^{13}C NMR spectra were recorded in $\text{DMSO-}d_6$ solution on a Bruker DRX-300M spectrometer operating at 300 MHz. Chemical shifts were reported in δ (ppm) units relative to the internal standard tetramethylsilane (TMS) via the solvent signal (2.49 for ^1H or 39.78 for ^{13}C). EI and FAB mass spectra were obtained on a HP-5988 and a HS-ZAB mass spectrometer. Elemental analyses were performed on a CARLOERBA 1106 instrument and the results of elemental analyses for C, H and N were within $\pm 0.4\%$ of the theoretical values. All chemicals and solvents used were of reagent grade purified and dried by standard methods before use. TLC monitoring all the reaction was performed on pre-coated silica gel G plates at 254/365 nm under a UV lamp, with petrol ether/acetone/triethylamine as the mobile phase.

General procedure for the synthesis of compounds of substituted acetylsalicyloyl chlorides: Thionyl chloride (0.1 mol) was added dropwise to the mixture of 0.1 mol substituted acetylsalicylic acid and dried pyridine in minute quantities under stirring in the ice bath. The solution was stirred for 0.5 h at the same temperature, warmed to room temperature and then stirred under 75-90 °C for further 2.5-5 h. The formed faint yellow liquid was used in the next step without further purification.

General procedure for the synthesis of the compounds of series 1a-6h: To a solution of substituted acetylsalicyloyl chlorides (0.022 mol) in anhydrous chloroform (100 mL) was added triethylamine (0.023 mol) at 4 °C. After the mixture was stirred for 5-15 min and then substituted 4-amino pyridine was added portion wise in the ice bath. After warmed to room temperature, the solution was stirred for 24-48 h and then quenched by 1 mL of 1 M hydrochloric acid. The reaction mixture was extracted with 10 % hydrochloric acid (50, 30 and 30 mL) and the combined aqueous was basified to pH 7-9 with cooled saturated sodium bicarbonate solution. The yellow precipitation was filtered producing the crude products. After recrystallized in ethanol, the products were isolated as pure form in more than 85 % yields.

2-Hydroxy-N-(pyridin-4-yl)benzamide (1a): m.p. 233-234 °C (234-236 °C^[1]); m.f. $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_2$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1676; ^1H NMR: δ 10.67 (bs, 1H, NH), 8.53-8.45 (m, 2H, H2', H6'), 7.86 (dd, 1H, $J = 8.10$ Hz, $J = 1.80$ Hz, H6), 7.75-7.73 (m, 2H, H3, H5), 7.47-7.41 (m, 1H, H4), 7.02-6.94 (m, 2H, H3', H5'); ^{13}C NMR: δ 166.8, 157.5, 150.4, 145.4, 133.8, 129.7, 119.3, 118.7, 117.2, 114.3.

N-(3-Chloropyridin-4-yl)-2-hydroxybenzamide (2a): m.p. 187-188 °C; m.f. $\text{C}_{12}\text{H}_9\text{N}_2\text{O}_2\text{Cl}$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1658; ^1H NMR: δ 10.52 (bs, 1H, NH), 8.69 (s, 1H, H2'), 8.58 (d, 1H, $J = 8.93$ Hz, H6'), 7.86 (dd, 1H, $J = 7.92$ Hz, $J = 1.90$ Hz, H6), 7.75-7.73 (m, 2H, H3, H5), 7.47-7.41 (m, 1H, H4), 7.14 (d, 1H, $J = 8.93$ Hz, H5'); ^{13}C NMR: δ 166.6, 157.4, 150.2, 143.2, 142.9, 133.6, 129.5, 123.0, 119.4, 118.9, 117.0, 115.4.

2-Hydroxy-N-[3-(trifluoromethyl)pyridin-4-yl]benzamide (3a): m.p. 174-175 °C; m.f. $\text{C}_{13}\text{H}_9\text{F}_3\text{N}_2\text{O}_2$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1669; ^1H NMR: δ 10.98 (bs, 1H, NH), 8.94-8.85 (m, 2H, H2', H6'), 7.88 (dd, 1H, $J = 7.97$ Hz, $J = 1.84$ Hz, H6), 7.77-7.74 (m, 2H, H3, H5), 7.46-7.42 (m, 1H, H4), 8.27 (d, 1H, $J = 8.98$ Hz, H5'); ^{13}C NMR: δ 165.9, 157.1, 150.6, 144.1,

142.3, 133.8, 128.8, 123.8, 119.2, 118.6, 117.5, 116.8 ($J = 267$ Hz), 114.1.

N-(3-Methylpyridin-4-yl)-2-hydroxybenzamide (4a): m.p. 203-204 °C; m.f. $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1683; ^1H NMR: δ 10.65 (bs, 1H, NH), 9.42 (s, 1H, H2'), 8.88 (d, 1H, $J = 7.52$ Hz, H6'), 7.84 (dd, 1H, $J = 7.20$ Hz, $J = 2.00$ Hz, H6), 7.78-7.75 (m, 2H, H3, H5), 7.49-7.43 (m, 1H, H4), 7.22 (d, 1H, $J = 7.52$ Hz, H5'), 2.41 (s, 3H, -CH₃); ^{13}C NMR: δ 164.9, 157.3, 150.4, 144.7, 141.9, 133.6, 128.3, 123.3, 119.2, 118.7, 117.4, 113.9, 17.7.

N-(2-Chloropyridin-4-yl)-2-hydroxybenzamide (5a): m.p. 220-221 °C; m.f. $\text{C}_{12}\text{H}_9\text{N}_2\text{O}_2\text{Cl}$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1667; ^1H NMR: δ 10.66 (bs, 1H, NH), 8.84 (d, 1H, $J = 8.90$ Hz, H6'), 7.88 (dd, 1H, $J = 7.92$ Hz, $J = 1.73$ Hz, H6), 7.74-7.72 (m, 2H, H3, H5), 7.48-7.43 (m, 1H, H4), 7.26-7.23 (dd, 2H, $J = 8.90$ Hz, $J = 2.60$ Hz, H3', H5'); ^{13}C NMR: δ 169.2, 157.0, 151.1, 144.9, 144.4, 133.8, 129.5, 119.5, 118.7, 117.2, 115.7, 114.3.

N-(3,5-Dichloropyridin-4-yl)-2-hydroxybenzamide (6a): m.p. 230-231 °C; m.f. $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_2\text{Cl}_2$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1652; ^1H NMR: δ 10.69 (bs, 1H, NH), 8.78 (s, 2H, H2', H6'), 7.88 (dd, 1H, $J = 7.79$ Hz, $J = 1.96$ Hz, H6), 7.76-7.73 (m, 2H, H3, H5), 7.45-7.40 (m, 1H, H4); ^{13}C NMR: δ 164.4, 155.7, 150.4, 141.8, 133.6, 129.3, 119.9, 119.3, 118.7, 117.2.

3,5-Dichloro-2-hydroxy-N-(pyridin-4-yl)benzamide (1b): m.p. 334-336 °C; m.f. $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_2\text{Cl}_2$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1679; ^1H NMR: δ 10.87 (bs, 1H, NH), 8.57-8.49 (m, 2H, H2', H6'), 7.77-7.71 (m, 2H, H3', H5'), 7.76 (d, 1H, $J = 2.01$ Hz, H6), 7.45 (d, 1H, $J = 2.01$ Hz, H4); ^{13}C NMR: δ 165.4, 154.2, 151.3, 146.1, 132.3, 127.9, 126.9, 126.2, 121.5, 114.0.

3,5-Dichloro-N-(3-chloropyridin-4-yl)-2-hydroxybenzamide (2b): m.p. 287-288 °C; m.f. $\text{C}_{12}\text{H}_7\text{N}_2\text{O}_2\text{Cl}_3$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1661; ^1H NMR: δ 10.88 (bs, 1H, NH), 8.72 (s, 1H, H2'), 8.54 (d, 1H, $J = 8.94$ Hz, H6'), 7.90 (d, 1H, $J = 8.94$ Hz, H5'), 7.84 (d, 1H, $J = 2.03$, H6), 7.51 (d, 1H, $J = 2.03$, H4); ^{13}C NMR: δ 166.8, 157.5, 150.4, 145.4, 133.8, 129.7, 119.3, 118.7, 117.2, 114.3.

3,5-Dichloro-N-(3-(trifluoromethyl)pyridin-4-yl)-2-hydroxybenzamide (3b): m.p. 363-265 °C; m.f. $\text{C}_{13}\text{H}_7\text{N}_2\text{O}_2\text{Cl}_2\text{F}_3$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1672; ^1H NMR: δ 10.99 (bs, 1H, NH), 9.02-8.94 (m, H2', H6'), 8.19 (d, 1H, $J = 9.02$ Hz, H5'), 7.85 (d, 1H, $J = 2.65$ Hz, H6), 7.45 (d, 1H, $J = 2.65$ Hz, H4); ^{13}C NMR: δ 166.8, 157.5, 150.4, 145.4, 133.8, 129.7, 119.3, 118.7, 117.2 ($J = 268$ Hz), 114.0.

3,5-Dichloro-2-hydroxy-N-(2-methylpyridin-4-yl)benzamide (4b): m.p. 356-358 °C; m.f. $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2\text{Cl}_2$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1686; ^1H NMR: δ 10.79 (bs, 1H, NH), 8.60 (d, 1H, $J = 7.50$ Hz, H6'), 7.76 (d, 1H, $J = 1.99$ Hz, H6), 7.63 (d, 1H, $J = 2.59$ Hz, H3'), 7.52 (dd, 1H, $J = 7.50$ Hz, $J = 2.58$ Hz, H5'), 7.45 (d, 1H, $J = 2.00$ Hz, H4), 2.45 (s, 3H, -CH₃); ^{13}C NMR: δ 166.8, 157.5, 150.4, 145.4, 133.8, 129.7, 119.3, 118.7, 117.2, 114.3.

3,5-Dichloro-N-(2-chloropyridin-4-yl)-2-hydroxybenzamide (5b): m.p. 310-311 °C; m.f. $\text{C}_{12}\text{H}_7\text{N}_2\text{O}_2\text{Cl}_3$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1670; ^1H NMR: δ 10.89 (bs, 1H, NH), 8.72 (d, 1H, $J = 9.01$, H6'), 7.77 (d, 1H, $J = 2.07$ Hz, H6), 7.45 (d, 1H, $J = 2.08$ Hz, H4), 7.06-6.97 (m, 2H, H3', H5'); ^{13}C NMR: δ 166.8, 157.5, 150.4, 145.4, 133.8, 129.7, 119.3, 118.7, 117.2, 114.3.

3,5-Dichloro-N-(3,5-dichloropyridin-4-yl)-2-hydroxybenzamide (6b): m.p. 353-354 °C; m.f. C₁₂H₆N₂O₂Cl₄; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1654; ¹H NMR: δ 10.91 (bs, 1H, NH), 8.81 (s, 2H, H2', H6'), 7.81 (d, 1H, J = 2.06 Hz, H6), 7.46 (d, 1H, J = 2.07 Hz, H4); ¹³C NMR: δ 166.8, 157.5, 150.4, 145.4, 133.8, 129.7, 119.3, 118.7, 117.2, 114.3.

5-Chloro-2-hydroxy-N-(pyridin-4-yl)benzamide (1c): m.p. 313-315 °C (314-316 °C^[1]); m.f. C₁₂H₉N₂O₂Cl; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1677; ¹H NMR: δ 10.83 (bs, 1H, NH), 8.52-8.44 (m, 2H, H2', H6'), 7.82 (d, 1H, J = 2.61 Hz, H6), 7.74-7.68 (m, 2H, H3', H5'), 7.44 (dd, 1H, J = 7.88 Hz, J = 2.60 Hz, H4), 7.01 (d, 1H, J = 7.88 Hz, H3); ¹³C NMR: δ 166.0, 157.1, 150.4, 145.4, 133.6, 129.1, 122.3, 120.7, 119.2, 114.1.

5-Chloro-N-(3-chloropyridin-4-yl)-2-hydroxybenzamide (2c): m.p. 355-357 °C; m.f. C₁₂H₈N₂O₂Cl₂; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1659; ¹H NMR: δ 10.85 (bs, 1H, NH), 8.71 (s, 1H, H2'), 8.53 (d, 1H, J = 9.08 Hz, H6'), 7.93 (d, 1H, J = 9.07 Hz, H5'), 7.82 (d, 1H, J = 1.97 Hz, H6), 7.44 (dd, 1H, J = 7.96 Hz, J = 1.97 Hz, H4), 7.01 (d, 1H, J = 7.96 Hz, H3); ¹³C NMR: δ 164.9, 156.9, 150.2, 144.3, 143.6, 133.3, 129.0, 122.4, 121.7, 120.9, 119.4, 115.4.

5-Chloro-N-(3-(trifluoromethyl)pyridin-4-yl)-2-hydroxybenzamide (3c): m.p. 343-342 °C; m.f. C₁₃H₈N₂O₂ClF₃; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1672; ¹H NMR: δ 10.91 (bs, 1H, NH), 9.00-8.93 (m, 2H, H2', H6'), 8.21 (d, 1H, J = 9.01 Hz, H5'), 7.83 (d, 1H, J = 2.72 Hz, H6), 7.46 (dd, 1H, J = 7.93 Hz, J = 2.72 Hz, H4), 7.01 (d, 1H, J = 7.92 Hz, H3); ¹³C NMR: δ 165.1, 157.0, 150.5, 146.3, 143.3, 133.4, 129.2, 122.3, 120.8, 120.1, 119.3, 117.4 (J = 271 Hz), 113.9.

5-Chloro-2-hydroxy-N-(2-methylpyridin-4-yl)benzamide (4c): m.p. 338-339 °C; m.f. C₁₃H₁₁N₂O₂Cl; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1684; ¹H NMR: δ 10.76 (bs, 1H, NH), 8.59 (d, 1H, J = 7.58 Hz, H6'), 7.79 (d, 1H, J = 2.31 Hz, H6), 7.61-7.49 (m, 2H, H3', H5'), 7.42 (dd, 1H, J = 7.96 Hz, J = 2.31 Hz, H4), 6.99 (d, 1H, J = 7.96 Hz, H3), 2.50 (s, 3H, -CH₃); ¹³C NMR: δ 165.2, 157.3, 157.0, 150.6, 144.8, 133.5, 128.9, 122.1, 121.0, 119.0, 114.5, 112.6, 24.1.

5-Chloro-N-(2-chloropyridin-4-yl)-2-hydroxybenzamide (5c): m.p. 354-356 °C; m.f. C₁₂H₈N₂O₂Cl₂; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1668; ¹H NMR: δ 10.86 (bs, 1H, NH), 8.70 (d, 1H, J = 9.04 Hz, H6'), 8.06-7.97 (m, 2H, H2', H6'), 7.81 (d, 1H, J = 2.63 Hz, H6), 7.74-7.68 (m, 2H, H3', H5'), 7.43 (dd, 1H, J = 7.72 Hz, J = 2.63 Hz, H4), 7.01 (d, 1H, J = 7.71 Hz, H3); ¹³C NMR: δ 166.3, 158.5, 157.4, 145.7, 144.6, 133.4, 129.3, 122.2, 120.7, 119.2, 115.5, 114.4.

5-Chloro-N-(3,5-dichloropyridin-4-yl)-2-hydroxybenzamide (6c): m.p. 391-393 °C; m.f. C₁₂H₇N₂O₂Cl₃; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1653; ¹H NMR: δ 10.89 (bs, 1H, NH), 8.81 (s, 2H, H2', H6'), 7.82 (d, 1H, J = 2.58 Hz, H6), 7.43 (dd, 1H, J = 8.09 Hz, J = 2.58 Hz, H4), 7.01 (d, 1H, J = 8.08 Hz, H3); ¹³C NMR: δ 166.7, 157.5, 149.1, 142.6, 133.6, 129.1, 122.3, 120.7, 120.2, 118.9.

3-Chloro-2-hydroxy-N-(pyridin-4-yl)benzamide (1d): m.p. 296-297 °C; m.f. C₁₂H₉N₂O₂Cl; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1678; ¹H NMR: δ 10.84 (bs, 1H, NH), 8.53-8.45 (m, 2H, H2', H6'), 7.69 (dd, 1H, J = 7.61 Hz, J = 2.58 Hz, H6), 7.76-7.70 (m, 2H, H3', H5'), 7.43 (dd, 1H, J = 7.89 Hz, J = 2.58 Hz, H4), 7.05 (t, 1H, J = 7.89 Hz, J = 7.61 Hz, H5); ¹³C NMR: δ 166.4, 157.7, 150.3, 145.2, 133.1, 127.0, 121.3, 120.9, 119.0, 113.8.

3-Chloro-N-(3-chloropyridin-4-yl)-2-hydroxybenzamide (2d): m.p. 271-273 °C; m.f. C₁₂H₈N₂O₂Cl₂; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1650; ¹H NMR: δ 10.86 (bs, 1H, NH), 8.72 (s, 1H, H2'), 8.58 (d, 1H, J = 9.01 Hz, H6'), 7.91 (d, 1H, J = 9.00 Hz, H5'), 7.67 (dd, 1H, J = 7.58 Hz, J = 2.53 Hz, H6), 7.41 (dd, 1H, J = 7.82 Hz, J = 2.53 Hz, H4), 7.10 (t, 1H, J = 7.81 Hz, J = 7.56 Hz, H5); ¹³C NMR: δ 166.6, 157.5, 150.1, 144.1, 143.8, 133.3, 126.9, 121.1, 120.8, 119.1, 118.4, 114.8.

3-Chloro-N-[3-(trifluoromethyl)pyridin-4-yl]-2-hydroxybenzamide (3d): m.p. 256-257 °C; m.f. C₁₃H₈N₂O₂ClF₃; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1669; ¹H NMR: δ 10.90 (bs, 1H, NH), 8.97-8.92 (m, 2H, H2', H6'), 8.23 (d, 1H, J = 9.09 Hz, H5'), 7.82 (dd, 1H, J = 7.90 Hz, J = 2.69 Hz, H6), 7.45 (dd, 1H, J = 7.97 Hz, J = 2.69 Hz, H4), 7.11 (t, 1H, J = 7.96 Hz, J = 7.90 Hz, H5); ¹³C NMR: δ 166.6, 157.6, 150.5, 146.0, 143.2, 133.2, 127.1, 121.5, 120.6, 119.6, 118.9, 117.7 (J = 266 Hz), 113.4.

3-Chloro-2-hydroxy-N-(2-methylpyridin-4-yl)benzamide (4d): m.p. 268-270 °C; m.f. C₁₃H₁₁N₂O₂Cl; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1685; ¹H NMR: δ 10.74 (bs, 1H, NH), 8.60 (d, 1H, J = 7.52 Hz, H6'), 7.63-7.52 (m, 2H, H3', H5'), 7.66 (dd, 1H, J = 7.53 Hz, J = 2.52 Hz, H6), 7.39 (dd, 1H, J = 7.86 Hz, J = 2.52 Hz, H4), 7.02 (t, 1H, J = 7.85 Hz, J = 7.53 Hz, H5), 2.49 (s, 3H, -CH₃); ¹³C NMR: δ 165.7, 158.3, 157.8, 150.4, 144.5, 133.0, 127.1, 121.4, 120.7, 119.2, 114.2, 112.3, 23.9.

3-Chloro-N-(2-chloropyridin-4-yl)-2-hydroxybenzamide (5d): m.p. 243-246 °C; m.f. C₁₂H₈N₂O₂Cl₂; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1669; ¹H NMR: δ 10.87 (bs, 1H, NH), 8.72 (d, 1H, J = 9.07 Hz, H6'), 8.06-7.97 (m, 2H, H3', H5'), 7.68 (dd, 1H, J = 7.59 Hz, J = 2.53 Hz, H6), 7.42 (dd, 1H, J = 7.86 Hz, J = 2.53 Hz, H4), 7.05 (t, 1H, J = 7.87 Hz, J = 7.59 Hz, H5); ¹³C NMR: δ 166.6, 158.1, 157.3, 145.5, 144.0, 133.0, 127.2, 121.3, 120.7, 118.8, 115.2, 114.1.

3-Chloro-N-(3,5-dichloropyridin-4-yl)-2-hydroxybenzamide (6d): m.p. 287-288 °C; m.f. C₁₂H₇N₂O₂Cl₃; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1654; ¹H NMR: δ 10.90 (bs, 1H, NH), 8.81 (s, 2H, H2', H6'), 7.70 (dd, 1H, J = 7.71 Hz, J = 2.62 Hz, H6), 7.42 (dd, 1H, J = 7.93 Hz, J = 2.62 Hz, H4), 7.05 (t, 1H, J = 7.93 Hz, J = 7.71 Hz, H5); ¹³C NMR: δ 165.5, 157.5, 149.5, 142.4, 129.7, 126.8, 121.0, 120.6, 119.4, 118.5.

5-Bromo-2-hydroxy-N-(pyridin-4-yl)benzamide (1e): m.p. 302-303 °C (304-305 °C^[1]); m.f. C₁₂H₉N₂O₂Br; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1678; ¹H NMR: δ 10.84 (bs, 1H, NH), 8.50-8.44 (m, H2', H6'), 7.93 (d, 1H, J = 2.46 Hz, H6), 7.72-7.68 (m, 2H, H3', H5'), 7.55 (dd, 1H, J = 8.78 Hz, J = 2.47 Hz, H4), 6.97 (d, 1H, J = 8.78 Hz, H3); ¹³C NMR: δ 165.6, 157.1, 150.4, 145.5, 136.3, 131.7, 121.3, 119.7, 114.2, 110.2.

5-Bromo-N-(3-chloropyridin-4-yl)-2-hydroxybenzamide (2e): m.p. 343-345 °C; m.f. C₁₂H₈N₂O₂BrCl; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1659; ¹H NMR: δ 10.85 (bs, 1H, NH), 8.71 (s, 1H, H2'), 8.54 (d, 1H, J = 8.97 Hz, H6'), 7.94 (d, overlapped, 1H, J = 2.46 Hz, H6), 7.92 (d, overlapped, 1H, J = 8.96 Hz, H5'), 7.55 (dd, 1H, J = 8.79 Hz, J = 2.47 Hz, H4), 6.96 (d, 1H, J = 8.79 Hz, H3); ¹³C NMR: δ 165.2, 157.0, 150.2, 144.5, 144.1, 136.2, 131.6, 121.1, 119.6, 118.6, 114.4, 111.5.

5-Bromo-N-(3-[trifluoromethyl]pyridin-4-yl)-2-hydroxybenzamide (3e): m.p. 331-333 °C; m.f. C₁₃H₈N₂O₂BrF₃; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1670; ¹H NMR: δ 10.89 (bs, 1H, NH), 8.89-8.85 (m, H2', H6'), 7.94 (d, 1H, J = 2.48 Hz, H6), 8.22(d,

1H, $J = 9.02$ Hz, $H5'$), 7.55 (dd, 1H, $J = 8.81$ Hz, $J = 2.48$ Hz, $H4$), 6.97 (d, 1H, $J = 8.80$ Hz, $H3$); ^{13}C NMR: δ 165.8, 157.2, 150.6, 146.3, 143.5, 136.2, 131.5, 121.4, 119.9, 119.4, 115.1, 114.9 ($J = 266$ Hz), 110.

5-Bromo-2-hydroxy-N-(2-methylpyridin-4-yl)-benzamide (4e): m.p. 299-301 °C; m.f. $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_2\text{Br}$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1684; ^1H NMR: δ 10.71 (bs, 1H, NH), 8.59 (d, 1H, $J = 7.56$ Hz, $H6'$), 7.62-7.54 (m, 2H, $H3'$, $H5'$), 7.91 (d, 1H, $J = 1.96$ Hz, $H6$), 7.53 (dd, 1H, $J = 8.93$ Hz, $J = 1.96$ Hz, $H4$), 6.94 (d, 1H, $J = 8.93$ Hz, $H3$), 2.45 (s, 3H, $-\text{CH}_3$); ^{13}C NMR: δ 165.9, 158.6, 157.0, 150.6, 146.9, 136.4, 131.6, 121.0, 119.9, 114.4, 110.6, 108.7, 23.9.

5-Bromo-N-(2-chloropyridin-4-yl)-2-hydroxybenzamide (5e): m.p. 274-275 °C; m.f. $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_2\text{BrCl}$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1666; ^1H NMR: δ 10.83 (bs, 1H, NH), 8.70 (d, 1H, $J = 9.04$, $H6'$), 8.05-7.98 (m, 2H, $H3'$, $H5'$), 7.94 (d, 1H, $J = 2.52$ Hz, $H6$), 7.56 (dd, 1H, $J = 8.74$ Hz, $J = 2.51$ Hz, $H4$), 6.96 (d, 1H, $J = 8.75$ Hz, $H3$); ^{13}C NMR: δ 165.6, 156.7, 156.4, 145.8, 144.3, 136.5, 131.4, 121.6, 119.5, 114.1, 111.6, 110.5.

5-Bromo-N-(3, 5-dichloropyridin-4-yl)-2-hydroxybenzamide (6e): m.p. 317-319 °C; m.f. $\text{C}_{12}\text{H}_7\text{N}_2\text{O}_2\text{BrCl}_2$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1653; ^1H NMR: δ 10.88 (bs, 1H, NH), 8.80-8.74 (m, $H2'$, $H6'$), 7.94 (d, 1H, $J = 2.52$ Hz, $H6$), 7.56 (dd, 1H, $J = 8.84$ Hz, $J = 2.52$ Hz, $H4$), 6.96 (d, 1H, $J = 8.84$ Hz, $H3$); ^{13}C NMR: δ 166.8, 157.5, 150.4, 145.4, 133.8, 129.7, 119.3, 118.7, 117.2, 114.3.

5-(Trifluoromethyl)-2-hydroxy-N-(pyridin-4-yl)benzamide (1f): m.p. 261-263 °C; m.f. $\text{C}_{13}\text{H}_9\text{N}_2\text{O}_2\text{F}_3$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1732; ^1H NMR: δ 11.57 (bs, 1H, NH), 8.55-8.48 (m, 2H, $H2'$, $H6'$), 8.28 (d, 1H, $J = 2.30$ Hz, $H6$), 7.81 (dd, 1H, $J = 8.31$ Hz, $J = 2.30$ Hz, $H4$), 7.21 (d, 1H, $J = 8.30$ Hz, $H3$), 7.04-6.97 (m, 2H, $H3'$, $H5'$); ^{13}C NMR: δ 165.3, 161.4, 151.2, 145.7, 130.1, 124.9, 121.6 ($J = 270$ Hz), 120.2, 119.4, 117.8, 110.3.

N-(3-Chloropyridin-4-yl)-5-(trifluoromethyl)-2-hydroxybenzamide (2f): m.p. 232-234 °C; m.f. $\text{C}_{13}\text{H}_8\text{N}_2\text{O}_2\text{ClF}_3$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1714; ^1H NMR: δ 11.56 (bs, 1H, NH), 8.72 (s, 1H, $H2'$), 8.61 (d, 1H, $J = 9.07$ Hz, $H6'$), 8.29 (d, 1H, $J = 2.32$ Hz, $H6$), 7.91 (d, 1H, $J = 9.06$ Hz, $H5'$), 7.81 (dd, 1H, $J = 8.33$ Hz, $J = 2.33$ Hz, $H4$), 7.22 (d, 1H, $J = 8.32$ Hz, $H3$); ^{13}C NMR: δ 165.5, 161.3, 151.4, 144.5, 143.6, 130.0, 124.8, 121.5 ($J = 270$ Hz), 120.3, 119.5, 119.1, 117.7, 111.6.

5-(Trifluoromethyl)-N-(3-(trifluoromethyl)pyridin-4-yl)-2-hydroxybenzamide (3f): m.p. 219-221 °C; m.f. $\text{C}_{14}\text{H}_8\text{N}_2\text{O}_2\text{F}_6$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1725; ^1H NMR: δ 11.62 (bs, 1H, NH), 8.91-8.87 (m, 2H, $H2'$, $H6'$), 8.29 (d, 1H, $J = 2.32$ Hz, $H6$), 8.22 (d, 1H, $J = 9.05$ Hz, $H5'$), 7.81 (dd, 1H, $J = 8.28$ Hz, $J = 2.33$ Hz, $H4$), 7.21 (d, 1H, $J = 8.28$ Hz, $H3$); ^{13}C NMR: δ 166.1, 161.6, 151.4, 146.5, 143.5, 130.2, 124.8, 121.5 ($J = 270$ Hz), 120.3, 119.2, 118.7, 117.8, 117.3 ($J = 266$ Hz), 110.1.

5-(Trifluoromethyl)-2-hydroxy-N-(2-methylpyridin-4-yl)benzamide (4f): m.p. 255-256 °C; m.f. $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_2\text{F}_3$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1739; ^1H NMR: δ 11.44 (bs, 1H, NH), 8.60 (d, 1H, $J = 7.58$ Hz, $H6'$), 8.25 (d, 1H, $J = 1.83$ Hz, $H6$), 7.62-7.53 (m, 2H, $H3'$, $H5'$), 7.77 (dd, 1H, $J = 8.16$ Hz, $J = 1.83$ Hz, $H4$), 7.14 (d, 1H, $J = 8.16$ Hz, $H3$), 2.47 (s, 3H, $-\text{CH}_3$); ^{13}C NMR: δ 165.5, 161.3, 154.6, 151.4, 145.0, 130.2,

124.8, 121.4 ($J = 270$ Hz), 120.2, 119.3, 117.8, 110.7, 108.8, 23.8.

N-(2-Chloropyridin-4-yl)-5-(trifluoromethyl)-2-hydroxybenzamide (5f): m.p. 233-235 °C; m.f. $\text{C}_{13}\text{H}_8\text{N}_2\text{O}_2\text{ClF}_3$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1723; ^1H NMR: δ 11.56 (bs, 1H, NH), 8.72 (d, 1H, $J = 9.06$, $H6'$), 8.05-8.01 (m, 2H, $H3'$, $H5'$), 8.29 (d, 1H, $J = 2.36$ Hz, $H6$), 7.82 (dd, 1H, $J = 8.35$ Hz, $J = 2.37$ Hz, $H4$), 7.23 (d, 1H, $J = 8.35$ Hz, $H3$); ^{13}C NMR: δ 166.3, 161.7, 154.5, 146.0, 145.6, 130.2, 125.1, 121.5 ($J = 270$ Hz), 120.2, 119.3, 117.6, 111.7, 110.6.

N-(3,5-Dichloropyridin-4-yl)-5-(trifluoromethyl)-2-hydroxybenzamide (6f): m.p. 273-275 °C; m.f. $\text{C}_{13}\text{H}_7\text{N}_2\text{O}_2\text{Cl}_2\text{F}_3$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1708; ^1H NMR: δ 11.61 (bs, 1H, NH), 8.81-8.76 (m, $H2'$, $H6'$), 8.29 (d, 1H, $J = 2.37$ Hz, $H6$), 7.82 (dd, 1H, $J = 8.38$ Hz, $J = 2.38$ Hz, $H4$), 7.20 (d, 1H, $J = 8.38$ Hz, $H3$); ^{13}C NMR: δ 165.5, 161.3, 150.8, 142.9, 130.0, 124.7, 121.8 ($J = 270$ Hz), 120.4, 119.2, 118.7, 117.7.

5-Chloro-2-hydroxy-4-methoxy-N-(pyridin-4-yl)-benzamide (1g): m.p. 333-334 °C; m.f. $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_3\text{Cl}$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1678; ^1H NMR: δ 10.80 (bs, 1H, NH), 8.51-8.45 (m, 2H, $H2'$, $H6'$), 7.73-7.69 (m, 2H, $H3'$, $H5'$), 7.71 (s, 1H, $H6$), 6.52 (s, 1H, $H3$), 3.76 (s, 3H, $-\text{CH}_3$); ^{13}C NMR: δ 166.7, 160.2, 156.6, 150.3, 145.0, 130.9, 114.6, 114.1, 113.7, 103.0, 55.5.

5-Chloro-N-(3-chloropyridin-4-yl)-2-hydroxy-4-methoxybenzamide (2g): m.p. 365-367 °C; m.f. $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_3\text{Cl}_2$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1660; ^1H NMR: δ 10.81 (bs, 1H, NH), 8.69 (s, 1H, $H2'$), 8.63 (d, 1H, $J = 9.55$ Hz, $H6'$), 7.94 (d, 1H, $J = 9.56$ Hz, $H5'$), 7.75 (s, 1H, $H6$), 6.54 (s, 1H, $H3$), 3.74 (s, 3H, $-\text{CH}_3$); ^{13}C NMR: δ 166.7, 160.1, 156.7, 150.2, 144.0, 143.6, 130.6, 122.5, 114.6, 114.3, 114.0, 103.0, 55.6.

5-Chloro-N-(3-(trifluoromethyl)pyridin-4-yl)-2-hydroxy-4-methoxybenzamide (3g): m.p. 349-352 °C; m.f. $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_3\text{ClF}_3$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1671; ^1H NMR: δ 10.87 (bs, 1H, NH), 9.02-8.96 (m, 2H, $H2'$, $H6'$), 8.19 (d, 1H, $J = 9.07$ Hz, $H5'$), 7.73 (s, 1H, $H6$), 6.55 (s, 1H, $H3$), 3.73 (s, 3H, $-\text{CH}_3$); ^{13}C NMR: δ 166.3, 159.7, 156.7, 150.5, 144.9, 143.1, 130.9, 122.0, 115.7, 114.9 ($J = 263$ Hz), 113.8, 113.5, 103.1, 55.6.

5-Chloro-2-hydroxy-4-methoxy-N-(2-methylpyridin-4-yl)benzamide (4g): m.p. 346-348 °C; m.f. $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_3\text{Cl}$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1685; ^1H NMR: δ 10.73 (bs, 1H, NH), 8.59 (d, 1H, $J = 7.63$ Hz, $H6'$), 7.63-7.52 (m, 2H, $H3'$, $H5'$), 7.68 (s, 1H, $H6$), 6.47 (s, 1H, $H3$), 3.76 (s, 3H, $-\text{CH}_3$), 2.46 (s, 3H, $-\text{CH}_3$); ^{13}C NMR: δ 165.8, 159.4, 157.9, 156.3, 150.4, 144.3, 130.8, 114.7, 114.3, 113.9, 112.2, 103.2, 55.3, 24.7.

5-Chloro-N-(2-chloropyridin-4-yl)-2-hydroxy-4-methoxybenzamide (5g): m.p. 365-367 °C; m.f. $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_3\text{Cl}_2$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1670; ^1H NMR: δ 10.81 (bs, 1H, NH), 8.72 (d, 1H, $J = 9.38$, $H6'$), 8.06-8.03 (m, 2H, $H3'$, $H5'$), 7.72 (s, 1H, $H6$), 6.54 (s, 1H, $H3$), 3.78 (s, 3H, $-\text{CH}_3$); ^{13}C NMR: δ 165.8, 159.1, 156.3, 156.0, 145.3, 143.8, 131.2, 115.0, 114.3, 113.7, 113.2, 103.0, 55.1.

5-Chloro-N-(3, 5-dichloropyridin-4-yl)-2-hydroxy-4-methoxybenzamide (6g): m.p. 386-388 °C; m.f. $\text{C}_{13}\text{H}_9\text{N}_2\text{O}_3\text{Cl}_3$; IR (KBr, ν_{max} , cm^{-1}): (C=O) 1654; ^1H NMR: δ 10.84 (bs, 1H, NH), 8.79-8.74 (m, $H2'$, $H6'$), 7.70 (s, 1H, $H6$), 6.51 (s, 1H, $H3$), 3.74 (s, 3H, $-\text{CH}_3$); ^{13}C NMR: δ 166.6, 169.4, 156.4, 149.9, 142.3, 130.5, 115.5, 114.9, 114.4, 103.6, 55.3.

2-Hydroxy-4-methoxy-N-(pyridin-4-yl)benzamide (1h): m.p. 279-281 °C; m.f. C₁₃H₁₂N₂O₃; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1683; ¹H NMR: δ 10.89 (bs, 1H, NH), 8.55-8.48 (m, 2H, H2', H6'), 7.83 (d, 1H, *J* = 8.65 Hz, H6), 7.05-6.98 (m, 2H, H3', H5'), 6.60-6.57 (m, 2H, H3, H5), 3.80 (s, 3H, -OCH₃); ¹³C NMR: δ 167.5, 164.1, 160.6, 150.5, 145.5, 131.1, 116.3, 114.5, 111.9, 100.2, 55.6.

N-(3-Chloropyridin-4-yl)-2-hydroxy-4-methoxybenzamide (2h): m.p. 304-306 °C; m.f. C₁₃H₁₁N₂O₃Cl; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1666; ¹H NMR: δ 10.90 (bs, 1H, NH), 8.72 (s, 1H, H2'), 8.61 (d, 1H, *J* = 9.60 Hz, H6'), 7.93 (d, 1H, *J* = 9.61 Hz, H5'), 8.55-8.48 (m, 2H, H2', H6'), 7.83 (d, 1H, *J* = 8.65 Hz, H6), 6.59-6.55 (m, 2H, H3, H5), 3.82 (s, 3H, -OCH₃); ¹³C NMR: δ 167.3, 164.0, 160.4, 150.3, 144.4, 144.0, 131.0, 116.4, 123.4, 115.8, 112.1, 100.3, 55.5.

N-(3-(Trifluoromethyl)pyridin-4-yl)-2-hydroxy-4-methoxybenzamide (3h): m.p. 290-292 °C; m.f. C₁₄H₁₁N₂O₃F₃; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1667; ¹H NMR: δ 10.96 (bs, 1H, NH), 8.97-8.92 (m, 2H, H2', H6'), 8.24 (d, 1H, *J* = 9.65 Hz, H5'), 7.85 (d, 1H, *J* = 9.27 Hz, H6), 7.05-6.98 (m, 2H, H3', H5'), 6.59-6.55 (m, 2H, H3, H5), 3.79 (s, 3H, -OCH₃); ¹³C NMR: δ 167.7, 164.2, 160.7, 150.7, 146.3, 143.5, 131.2, 124.2, 121.5 (*J* = 266 Hz), 116.1, 114.3, 111.8, 100.1, 55.7.

2-Hydroxy-4-methoxy-N-(2-methylpyridin-4-yl)benzamide (4h): m.p. 285-287 °C; m.f. C₁₄H₁₄N₂O₃; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1691; ¹H NMR: δ 10.82 (bs, 1H, NH), 8.59 (d, 1H, *J* = 8.23 Hz, H6'), 7.05-6.97 (m, 2H, H3', H5'), 7.80 (d, 1H, *J* = 8.68 Hz, *J* = 1.77 Hz, H6), 6.65-6.52 (m, 1H, H4), 3.80 (s, 3H, -OCH₃); ¹³C NMR: δ 167.6, 164.2, 160.6, 154.2, 150.6, 144.8, 131.1, 116.1, 114.9, 113.0, 111.8, 100.2, 55.8, 24.2.

N-(2-Chloropyridin-4-yl)-2-hydroxy-4-methoxybenzamide (5h): m.p. 181-183 °C; m.f. C₁₃H₁₁N₂O₃Cl; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1674; ¹H NMR: δ 10.90 (bs, 1H, NH), 8.74 (d, 1H, *J* = 9.45, H6'), 8.08-8.06 (m, 2H, H3', H5'), 7.84 (d, 1H, *J* = 8.57 Hz, H6), 6.62-6.58 (m, 2H, H3, H5), 3.82 (s, 3H, -OCH₃); ¹³C NMR: δ 167.9, 164.3, 160.7, 153.6, 145.8, 144.3, 131.2, 116.2, 115.9, 114.8, 111.7, 100.0, 55.8.

N-(3, 5-Dichloropyridin-4-yl)-2-hydroxy-4-methoxybenzamide (6h): m.p. 224-226 °C; m.f. C₁₃H₁₀N₂O₃Cl₂; IR (KBr, ν_{\max} , cm⁻¹): (C=O) 1659; ¹H NMR: δ 10.93 (bs, 1H, NH), 8.81-8.77 (m, 2H, H2', H6'), 7.82 (d, 1H, *J* = 8.58 Hz, H6), 6.59-6.55 (m, 2H, H3, H5), 3.77 (s, 3H, -OCH₃); ¹³C NMR: δ 167.1, 163.8, 159.7, 149.6, 142.7, 129.7, 124.3, 116.6, 112.1, 100.5, 55.8

Biological Activity: The following strains, obtained from Pulmonary Hospital of Lanzhou, were used for the evaluation of *in vitro* antimycobacterial activity: *Mycobacterium tuberculosis* PHL 474/528 and *Mycobacterium avium* PHL 599/778. Antimycobacterial activity of the compounds against these strains was determined in the Sauton semiliquid medium (with 5 % bovine serum). The Sauton semiliquid medium was routinely used in Pulmonary Hospital of Lanzhou. Each strain was simultaneously inoculated into a Petri dish containing the improved Löwenstein-Jensen medium for the control of the sterility of the inoculums and its growth^{15,16}. The compounds were added to the medium in sodium phosphate buffer solutions with 7.2 of pH value. The final concentrations were 1200, 600, 300, 150, 75, 37.5, 18.8, 9.4, 4.7, 2.3 and 1.2 μ mol L⁻¹. MICs, at which inhibition of the growth of the mycobacteria

occurred, were determined after incubation at 37 °C for 4 weeks (Table-1).

RESULTS AND DISCUSSION

The salicylanilides could inhibit the TCS nonspecifically by a mechanism involving in uncoupling oxidative phosphorylation⁶. With respect to the activities against *M. tuberculosis* (TB), there are two additional major aspects considered: innate resistance, the unique structure and composition of the highly hydrophobic cell wall that must be traversed. It is well known that increasing the lipophilicity improve cell wall permeability¹²⁻¹⁴, which implied that the differences in antimicrobial activities of N-pyridin-4-yl salicylamide analogues arises from the differences in lipophilicity. Furthermore, we studied the influence of the substituent effect on the heterocycle and salicylic moieties. The minimum inhibitory concentrations (MICs) against *M. avium* (A) of the eight substrates (**2c**, **4c**, **5c**, **4e**, **5e**, **2d**, **4f**) are equal to 75 μ mol L⁻¹, which are remarkably lower than 300 μ mol L⁻¹ of the MIC against A of isoniazide. Among them, compounds **4c**, **5c**, **4e** and **5e** exhibit good anti-TB activity compared to isoniazide (Table-1). These results suggest that such compounds might serve as prospective wide-spectrum antimycobacterial substances.

Table-1 showed that when position 2 of the heterocycle, or position 3 or 5 of the salicylic moiety was substituted by chlorine, methyl or bromine, the antimycobacterial activity will be increased. This antimycobacterial value is particularly high against the typical mycobacterial strains A. For example, the compounds **4c**, **5c**, **4e** and **5e** in anti-TB activity are almost the same as INH. However, they exhibit higher anti-A activity than INH. Therefore, it is likely that N-(pyridin-4-yl) salicylamides may constitute a new group of promising compounds bearing potential antimycobacterial activity.

When higher hydrophobicity compounds substituted on position 2 of the heterocyclic moiety were used, the antimycobacterial activity decreased dramatically (*e.g.* **4c**, **5c**, **4e** and **5e**). While introduction of methoxyl group on position 4 of the salicylic moiety, with lower hydrophobicity, led to decreased activity. In general, introduction of higher hydrophobic substituents leads to higher activity towards both anti-TB and anti-A. However, based on our research, the activities were affected not only by hydrophobicity but also structure and electronic requirements. For example, **5c** and **5e** with lg P more than 2.5 resulted in high potency, but **6b** and **6e** with lg P more than 3 gave decreased potency.

The compounds substituted on position 3 and 5 of the heterocyclic moiety and on position 3 of the salicylic moiety exhibited decreased antimycobacterial activity in spite of higher or lower hydrophobicity. These results might be so due to the steric reasons for the substituents can prevent the donor or acceptor of amide and hydroxyl groups from interacting with the corresponding biomacromolecule by hydrogen bond.

Conclusion

Present studies of structure-activity relationship suggests that the introduction of substitutes with some balance between hydrophobicity and electron effects in position 2 of the heterocyclic, or in position 3 or 5 of the salicylic moiety may greatly affect the antimycobacterial activity, which contribute to the

TABLE-1
in vitro ANTIMYCOBACTERIAL ACTIVITY AND IgP OF N-(pyridin-4-yl) SALICYLAMIDES

Compd.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	IgP	MICs (μmol L ⁻¹)	
								<i>M. tuberculosis</i> PHL 474/528 (28 days)	<i>M. avium</i> PHL 599/778 (28 days)
1a	H	H	H	H	H	H	1.11	75	300
2a	H	H	Cl	H	H	H	1.67	75	150
3a	H	H	CF ₃	H	H	H	2.03	300	1200
4a	CH ₃	H	H	H	H	H	1.60	37.5	75
5a	Cl	H	H	H	H	H	2.01	18.8	75
6a	H	Cl	Cl	H	H	H	2.23	75	300
1b	H	H	H	Cl	H	Cl	2.23	150	1200
2b	H	H	Cl	Cl	H	Cl	2.79	75	300
3b	H	H	CF ₃	Cl	H	Cl	3.15	150	600
4b	CH ₃	H	H	Cl	H	Cl	2.93	37.5	300
5b	Cl	H	H	Cl	H	Cl	3.13	18.8	37.5
6b	H	Cl	Cl	Cl	H	Cl	3.35	300	1200
1c	H	H	H	H	H	Cl	1.67	18.8	150
2c	H	H	Cl	H	H	Cl	2.23	9.4	75
3c	H	H	CF ₃	H	H	Cl	2.59	37.5	300
4c	CH ₃	H	H	H	H	Cl	2.38	2.3	9.4
5c	Cl	H	H	H	H	Cl	2.57	1.2	4.7
6c	H	Cl	Cl	H	H	Cl	2.79	37.5	300
1d	H	H	H	Cl	H	H	1.67	37.5	150
2d	H	H	Cl	Cl	H	H	2.23	9.4	75
3d	H	H	CF ₃	Cl	H	H	2.59	75	300
4d	CH ₃	H	H	Cl	H	H	2.38	18.8	150
5d	Cl	H	H	Cl	H	H	2.57	37.5	300
6d	H	Cl	Cl	Cl	H	H	2.79	75	600
1e	H	H	H	H	H	Br	1.94	18.8	150
2e	H	H	Cl	H	H	Br	2.50	18.8	75
3e	H	H	CF ₃	H	H	Br	2.86	75	300
4e	CH ₃	H	H	H	H	Br	2.65	4.7	18.8
5e	Cl	H	H	H	H	Br	2.84	2.3	18.8
6e	H	Cl	Cl	H	H	Br	3.06	150	600
1f	H	H	H	H	H	CF ₃	2.03	37.5	300
2f	H	H	Cl	H	H	CF ₃	2.59	37.5	150
3f	H	H	CF ₃	H	H	CF ₃	2.96	75	300
4f	CH ₃	H	H	H	H	CF ₃	2.74	9.4	75
5f	Cl	H	H	H	H	CF ₃	2.93	9.4	37.5
6f	H	Cl	Cl	H	H	CF ₃	3.15	37.5	150
1g	H	H	H	H	OCH ₃	Cl	1.54	75	300
2g	H	H	Cl	H	OCH ₃	Cl	2.10	75	150
3g	H	H	CF ₃	H	OCH ₃	Cl	2.47	75	300
4g	CH ₃	H	H	H	OCH ₃	Cl	2.25	37.5	300
5g	Cl	H	H	H	OCH ₃	Cl	2.45	18.8	150
6g	H	Cl	Cl	H	OCH ₃	Cl	2.66	150	600
1h	H	H	H	H	OCH ₃	H	0.99	150	1200
2h	H	H	Cl	H	OCH ₃	H	1.54	18.8	600
3h	H	H	CF ₃	H	OCH ₃	H	1.91	75	600
4h	CH ₃	H	H	H	OCH ₃	H	1.69	37.5	150
5h	Cl	H	H	H	OCH ₃	H	1.89	18.8	75
6h	H	Cl	Cl	H	OCH ₃	H	2.10	150	600
INH							-0.6	1.2	300

discovery of a series of prospective wide-spectrum antimycobacterial substances. The applications of these results and further investigations based on such methodology are underway in our laboratory.

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