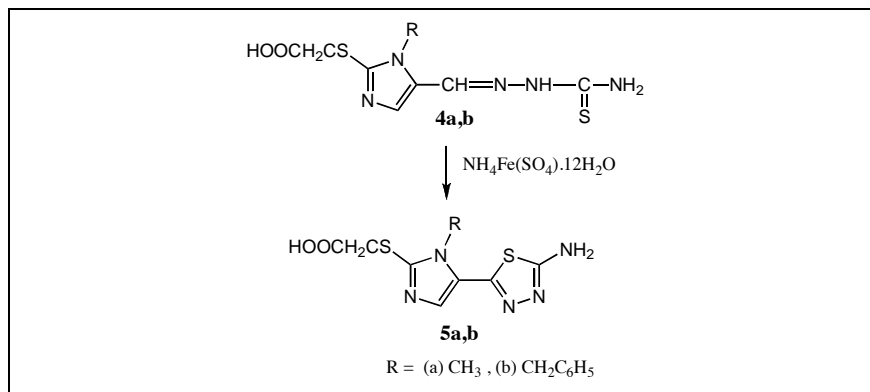


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The paper describes synthesis and antituberculosis activity of α -[5-(5-amino-1,3,4-thiadiazol-2-yl)-imidazol-2-ylthio]acetic acids (**5a,b**). The compounds were tested against *Mycobacterium tuberculosis* strain H37Rv in comparison to rifampicin. Compounds exhibited low activity (MIC ≥ 6.25 $\mu\text{g/ml}$, % inhibition ≤ 24).

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INTRODUCTION

The treatment of mycobacterial infections has become an important and challenging problem because of the emergence of multiple-drug-resistance organisms and because of the acquired immunodeficiency syndrome (AIDS) pandemic [1]. The high rates of drug – resistant tuberculosis currently reported in many countries are alarming, science among this phenomenon rapid drug susceptibility tests are needed and effective chemotherapy regimens with newly developed drugs are urgently being sought [2].

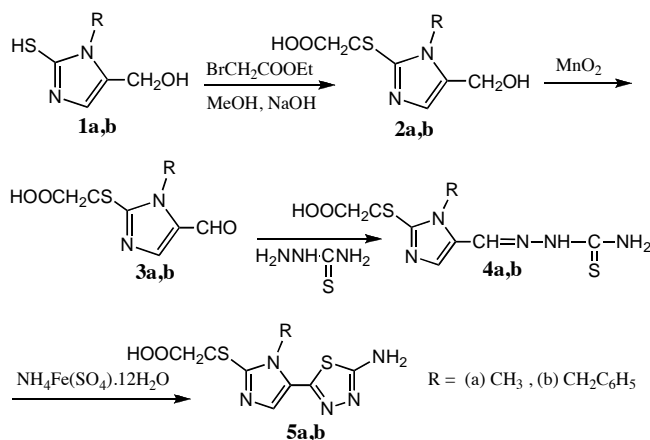
Recently the synthesis of some alkyl α -(5-aryl-1,3,4-thiadiazol-2-ylthio)acetates and 2-(5-nitro-2-furyl)- and 2-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazole derivatives as potential antituberculosis agents has been reported [3,4]. The 1,3,4-thiadiazole ring system have incorporated in many substances with antibacterial, amoebicide, parasiticide and antifungal activity [5,6]. In addition imidazole derivatives are known to possess antimicrobial activity [7,8]. Accordingly we designed and synthesized α -[5-(5-amino-1,3,4-thiadiazol-2-yl)-2-imidazolylthio]acetic acids (**5a,b**). The compounds were tested for antituberculosis activity.

RESULTS AND DISCUSSION

Scheme 1 outline the synthetic sequences employed in our laboratories for preparation of the α -[5-(5-amino-

1,3,4-thiadiazol-2-yl)imidazol-2-ylthio]acetic acids (**5a,b**). 1-Alkyl-2-mercapto-5-hydroxymethylimidazoles (**1a,b**) were synthesized from dihydroxyacetone, potassium thiocyanate and alkylamine hydrochloride as described previously [9]. Treatment of the latter with ethyl bromoacetate gave α -[1-alkyl-5-hydroxymethyl-2-imidazolylthio]acetic acid (**2a,b**).

Scheme 1



Oxidation of **2a,b** with manganese dioxide afforded α -[1-alkyl-5-formyl-2-imidazolylthio]acetic acid (**3a,b**). Condensation of the **3a,b** with thiosemicarbazide gave the

intermediate thiosemicarbazones (**4a,b**). Oxidative ring closure of the latter with iron (III) ammonium sulfate.12H₂O produced α -[5-(5-amino-1,3,4-thiadiazol-2-yl)-1-alkyl-2-imidazolylthio] acetic acid (**5a,b**).

Title compounds **5a,b** were evaluated *in vitro* for anti tuberculosis activity against *Mycobacterium tuberculosis* strain H37Rv in comparison to rifampicin as part of TAACF TB screening program under direction of the U.S. National institute of Health, NIAID division. Compounds exhibited low activity (MIC \geq 6.25 μ g/ml, % inhibition \leq 24)

EXPERIMENTAL

Melting points were determined on Electrothermal Capillary apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer Model 1000. ¹H nmr were obtained on Bruker Ac-80 spectrophotometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Errors of elemental analyses were within \pm 0.4% of theoretical values. Compounds **1a, b** were prepared as described previously [9].

General Procedure for preparation of 2-(5-hydroxymethyl-1-alkyl-2-imidazolylthio)acetic acid (2a,b). To a stirring suspension of compound **1a, b** (22.7 mmoles) in methanol (370 ml) was added dropwise sodium hydroxide (1.0 N, 24 mL) at room temperature. The clear pale yellow suspension was stirred for 10 minutes. Ethyl bromoacetate (66 mmoles, 5.5 mL) was added dropwise and stirring was continued overnight. After evaporation of the methanol, the residue was suspended in water (250 mL) and extracted with chloroform (3 x 100 mL). The solvent was evaporated to give compounds **2a,b**.

2-(5-Hydroxymethyl-1-methyl-2-imidazolylthio)acetic acid (2a). This compound was obtained in 66% yield as an oil; ir (CHCl₃): 3100 (OH), 1650 cm⁻¹ (CO); ¹H nmr (CDCl₃): δ 3.52-3.73 (m, 6H, CH₂S, NCH₃, OH), 4.65 (s, 2H, CH₂O), 7.14 ppm (s, 1H, H-C₄ imidazole); *Anal.* Calcd. for C₇H₁₀N₂O₃S: C, 41.57; H, 4.98; N, 13.85. Found: C, 41.47; H, 4.78; N, 13.96.

2-(5-Hydroxymethyl-1-benzyl-2-imidazolylthio)acetic acid (2b). This compound was obtained in 56% yield; mp 110-111 $^{\circ}$; ir (potassium bromide): 3100 (OH), 1700 cm⁻¹ (CO); ¹H nmr (CDCl₃): δ 3.73 (s, 2H, CH₂S), 4.42 (s, 2H, CH₂O), 5.25 (s, 2H, CH₂N), 6.82-7.31 ppm (m, 6H, arom); *Anal.* Calcd. for C₁₃H₁₄N₂O₃S: C, 56.10; H, 5.07; N, 10.06. Found: C, 56.15; H, 5.17; N, 10.14.

General Procedure for preparation of 2-(5-formyl-1-alkyl-2-imidazolylthio)acetic acid (3a,b). A stirring suspension of compound **2** (12.8 mmoles) and manganese dioxide (82.2 mmoles) in chloroform (50 mL) was refluxed overnight. The reaction mixture was cooled to room temperature and filtered on diatomaceous earth. The chloroform was evaporated to give compound **3a, b**.

2-(5-Formyl-1-methyl-2-imidazolylthio)acetic acid (3a). This compound was obtained in 93% yield as an oil; ir (CHCl₃): 1700 (CO acid), 1655 cm⁻¹ (CO aldehyde); ¹H nmr (CDCl₃): δ 3.73 (s, 2H, CH₂S), 3.92 (s, 3H, NCH₃), 7.84 (s, 1H, H-C₄ imidazole), 9.53 ppm (s, 1H, CHO); *Anal.* Calcd. for C₇H₈N₂O₃S: C, 41.99; H, 4.03; N, 13.99. Found: C, 41.76; H, 3.99; N, 14.20.

2-(5-Formyl-1-benzyl-2-imidazolylthio)acetic acid (3b). This compound was obtained in 95% yield as an oil; ir (CHCl₃): 1700 (CO acid), 1645 cm⁻¹ (CO aldehyde); ¹H nmr (CDCl₃): δ 3.73 (s, 2H, CH₂S), 5.42 (s, 2H, CH₂N), 6.81-7.23 (m, 5H, arom), 7.64 (s, 1H, H-C₄ imidazole), 9.53 ppm (s, 1H, CHO); *Anal.* Calcd. for C₁₃H₁₂N₂O₃S: C, 56.51; H, 4.38; N, 10.14. Found: C, 56.59; H, 4.48; N, 10.23.

General Procedure for preparation of 2-carboxymethylthio-1-alkylimidazol-5-thiosemicarbazone (4a,b). To a stirring mixture of compound **3a, b** (11.95 mmoles) in ethanol (168 mL), conc. hydrochloric acid (0.16 mL) was added. The reaction mixture was heated for 10 minutes and the reaction progress followed by TLC. After cooling, the white precipitate was collected by filtration, washed with H₂O and dried to give compound **4a,b**, which were used directly at the next step.

General Procedure for preparation of α -[5-(5-Amino-1,3,4-thiadiazol-2-yl)-1-alkyl-2-imidazolylthio]acetic acid (5a,b). A stirring solution of compound **4** (1.82 mmoles) and iron (III) ammonium sulfate.12H₂O (1 g, 2.07 mmoles) in distilled water (15 mL) was refluxed for 4 hours. Again iron (III) ammonium sulfate.12H₂O (1 g, 2.07 mmoles) and distilled water (30 mL) was added and the reflux continued for 4 hours. After cooling the precipitate was collected by filtration and washed with distilled water to give compounds **5a, b**.

α -[5-(5-Amino-1,3,4-thiadiazol-2-yl)-1-methyl-2-imidazolylthio]acetic acid (5a). This compound was obtained in 80% yield; as an oil; ¹H nmr (D₂O+CF₃COOH): δ 3.72 (s, 2H, CH₂S), 3.93 (s, 3H, NCH₃), 7.82 (s, 1H, H-C₄ imidazole); *Anal.* Calcd. for C₈H₉N₅O₂S₂: C, 35.41; H, 3.34; N, 25.81. Found: C, 35.29; H, 3.23; N, 25.79.

α -[5-(5-Amino-1,3,4-thiadiazol-2-yl)-1-benzyl-2-imidazolylthio]acetic acid (5b). This compound was obtained in 86% yield; mp 215-214 $^{\circ}$; ir (potassium bromide): 3400 cm⁻¹ (NH). ¹H nmr (DMSO-*d*₆): δ 3.73 (s, 2H, CH₂S), 5.62 (s, 2H, CH₂N), 6.81-7.53 (m, 7H, arom, NH₂), 7.99 (s, 1H, H-C₄ imidazole), 11.33 ppm (br-s, 1H, COOH); *Anal.* Calcd. for C₁₄H₁₃N₅O₂S₂: C, 48.40; H, 3.77; N, 20.16. Found: C, 48.35; H, 3.89; N, 20.29.

Biological assay. The compounds were screened for antituberculosis activity under direction of the US National Institute of Health, NIAID division. All compounds were initially screened against *Mycobacterium tuberculosis* strain H₃₇Rv at single concentration of 6.25 μ g/ml in BACTEC 12B medium using a broth microdilution assay. Compounds demonstrating growth inhibition \geq 90% in the primary screening were considered active. None of the compounds **5a** and **5b** were found to be active. They exhibited only low activity (MIC \geq 6.25 μ g/ml, % inhibition \leq 24). Rifampicin (MIC= 0.025- 0.125 μ g/ml) was used as positive control drug.

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