

FUSED HETEROCYCLES : SYNTHESIS OF SOME NEW IMIDAZOTHIAZOLES

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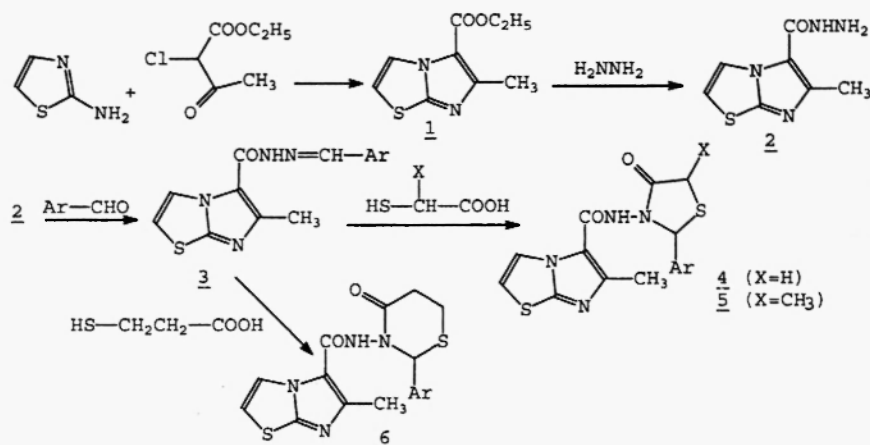
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Abstract- Reaction of aldehyde-hydrazones or semicarbazones bearing an imidazo[2,1-*b*] [1,3]thiazole ring system with mercaptoalkanoic acids were investigated. Antimycobacterial activities of compounds thus obtained were evaluated against *Mycobacterium tuberculosis* H₃₇R_v using rifampine as standard.

Treatment of tuberculosis is still one of the major problems due to the rise of multidrug resistant tuberculosis in clinical practice. Since many years, isonicotinic acid hydrazide (isoniazide) has been used as a principal drug for the treatment of the disease. The effects of substituents and bioisosteric replacements on its antituberculous activity are still under investigation (1).

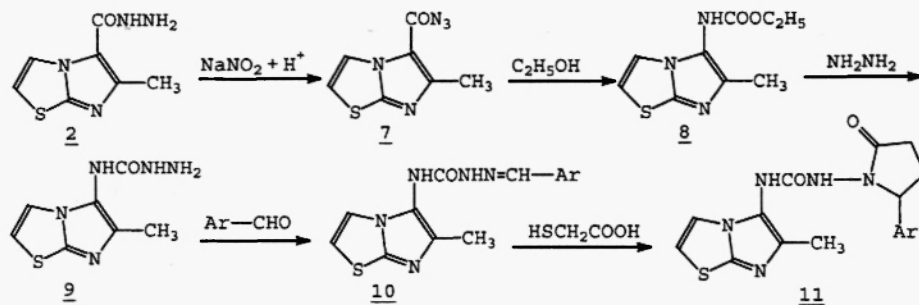
This prompted us to synthesize 6-methylimidazo[2,1-*b*] [1,3]thiazole-5-carbohydrazide **2**, a structural analog of isoniazide, and its hitherto unreported derivatives to screen their antituberculous properties.



Ar: a, C₆H₅; b, C₆H₄F (4); c, C₆H₄Cl (4); d, C₆H₄Br (4);
e, C₆H₄CH₃ (4); f, C₆H₄OCH₃ (4); g, C₆H₄NO₂ (2)

6-Methylimidazo[2,1-*b*] [1,3]thiazole-5-carbohydrazide was synthesized by the reaction of hydrazine with ethyl 6-methylimidazo[2,1-*b*] [1,3]thiazole-5-carboxylate (2). **2** reacted with aromatic aldehydes to afford hydrazide-hydrazones **3** which furnished N-(2-aryl-

4-oxo-1,3-thiazolidin-3-yl)-6-methylimidazo[2,1-b][1,3]thiazole-5-carboxamide 4,5 on cyclodehydration with mercaptoacetic acids. Reacting hydrazide-hydrazones with 3-mercaptopropanoic acid, 4-oxo-1,3-thiazinanes 6 were also obtained. On the other hand 6-methylimidazo[2,1-b][1,3]thiazole-5-carbohydrazide on treatment with sodium nitrite gave 6-methylimidazo[2,1-b][1,3]thiazole-5-carbonyl azide 7 (3) which on refluxing with ethanol was converted into the corresponding carbamate, 8.



Ar: a, C₆H₅; b, C₆H₄F(4)

The carbamate 8 on reaction with hydrazine in ethanol yielded the respective hydrazinecarboxamide 9. Similarly, 9 was also converted into the corresponding semicarbazones 10 and 4-oxo-1,3-thiazolidines 11 by the above sequenced reaction. The compounds 2-11 were found to be inactive against *Mycobacterium tuberculosis* H₃₇R_v.

EXPERIMENTAL

Chemistry

Melting points were determined on a Büchi 530 apparatus in open capillary tubes and are uncorrected. IR spectra were recorded on KBr discs, using a Perkin Elmer 1600 FT-IR spectrophotometer. ¹H NMR spectra were obtained in DMSO-d₆ on a Bruker AC 200 or Varian LX-300 spectrophotometer using TMS as the internal standard. EIMS were performed on a VG Zab Spec(70 eV) instrument. CIMS(CH₄) were run at Sittingbourne Research Center, UK. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. All new compounds gave satisfactory elemental analysis. The starting materials were either commercially available or synthesized according to the references cited.

Ethyl 6-methylimidazo[2,1-b][1,3]thiazole-5-carboxylate 1: 1 was obtained according to the literature method (4) and used without any purification. mp 98°C; yield: 35%.

6-Methylimidazo[2,1-b][1,3]thiazole-5-carbohydrazide 2: 2 was prepared by the reaction of 1 with hydrazine according to the literature method (2) and recrystallized from C₂H₅OH(96%). mp 183-185°C; yield: 80%.

Benzylidene 6-methylimidazo[2,1-b][1,3]thiazole-5-carboxylic acid hydrazides 3:

General procedure

A solution of 0.005 mol 2 in C₂H₅OH(96%)(25 ml) and 0.0055 mol of an appropriate aromatic aldehyde was heated under reflux for one hour. The precipitate obtained was recrystallized from C₂H₅OH(96%).

6-Methyl-N-(phenylmethylidene)imidazo[2,1-b][1,3]thiazole-5-carbohydrazide 3a: (C₁₄H₁₂N₄OS) (284.33); mp 237-239 °C; yield: 31%; IR, ν: 3225, 3096 (NH), 1641 (CO) cm⁻¹; ¹H NMR, δ: 11.32 (1H, s, NH), 8.30 (1H, d, 3-H), 8.00 (1H, d, 2-H), 7.66-7.34(6H, m, N=CH and C₆H₅), 2.49 (3H, s, 6-CH₃) ppm; CIMS(CH₄)(m/z) = 285 (M+H, 100).

6-Methyl-N-[(4-fluorophenyl)methylidene]imidazo[2,1-b][1,3]thiazole-5-carbohydrazide 3b: (C₁₄H₁₁FN₄OS.H₂O) (320.34); mp 252-254 °C; yield: 83%; IR, ν: 3196, 3115(NH), 1634 (CO) cm⁻¹; ¹H NMR, δ: 11.36 (1H, s, NH), 8.33 (1H, s, N=CH), 8.03 (1H, d, 3-H), 7.76 (2H, t, H-3,5), 7.38 (1H, d, 2-H), 7.30 (2H, t, H-2,6), 2.51 (3H, s, 6-CH₃) ppm.

- 6-Methyl-N-[(4-chlorophenyl)methylidene]imidazo[2,1-b][1,3]thiazole-5-carbohydrazide **3c**: ($C_{14}H_{11}ClN_4OS$) (318.77); mp 261-263 °C; yield: 98%; IR, ν : 3191, 3112 (NH), 1635 (CO) cm^{-1} ; 1H NMR, δ : 11.43 (1H, s, NH), 8.32 (1H, s, N=CH), 8.02 (1H, d, 3-H), 7.72 (2H, d, H-3,5), 7.52 (2H, d, H-2,6), 7.37 (1H, d, 2-H), 2.51 (3H, s, 6-CH₃) ppm; CIMS(CH_4) (m/z) = 319 (M+H, 74).
- 6-Methyl-N-[(4-bromophenyl)methylidene]imidazo[2,1-b][1,3]thiazole-5-carbohydrazide **3d**: ($C_{14}H_{11}BrN_4OS$) (363.22); mp 256-258 °C; yield: 95%; IR, ν : 3191, 3113 (NH), 1631 (CO) cm^{-1} ; 1H NMR, δ : 11.40 (1H, s, NH), 8.30 (1H, s, N=CH), 8.01 (1H, d, 3-H), 7.66 (4H, m, H-2,3,5,6), 7.36 (1H, d, 2-H), 2.50 (3H, s, 6-CH₃) ppm.
- 6-Methyl-N-[(4-methylphenyl)methylidene]imidazo[2,1-b][1,3]thiazole-5-carbohydrazide **3e**: ($C_{15}H_{14}N_4OS$) (298.35); mp 222-224 °C; yield: 84%; IR, ν : 3151, 3115 (NH), 1635 (CO) cm^{-1} ; 1H NMR, δ : 11.25 (1H, s, NH), 8.26 (1H, s, N=CH), 7.98 (1H, d, 3-H), 7.56 (2H, d, H-2,6), 7.35 (1H, d, 2-H), 7.25 (2H, d, H-3,5), 2.49 (3H, s, 6-CH₃), 2.32 (3H, s, CH₃) ppm.
- 6-Methyl-N-[(4-methoxyphenyl)methylidene]imidazo[2,1-b][1,3]thiazole-5-carbohydrazide **3f**: ($C_{15}H_{14}N_4O_2S$) (368.40); mp 190-192 °C; yield: 98%; IR, ν : 3151, 3115 (NH), 1641 (CO) cm^{-1} ; 1H NMR, δ : 11.25 (1H, s, NH), 8.28 (1H, s, N=CH), 8.03 (1H, d, 3-H), 7.65 (2H, d, H-2,6), 7.38 (1H, d, 2-H), 7.02 (2H, d, H-3,5), 3.32 (3H, s, OCH₃), 2.50 (3H, s, 6-CH₃) ppm; CIMS(CH_4) (m/z) = 315 (M+H, 52).
- 6-Methyl-N-[(2-nitrophenyl)methylidene]imidazo[2,1-b][1,3]thiazole-5-carbohydrazide **3g**: ($C_{15}H_{11}N_5O_3S$) (347.35); mp 241-243 °C; yield: 92%; IR, ν : 3345, 3134 (NH), 1680 (CO) cm^{-1} ; 1H NMR, δ : 11.22 (1H, s, NH), 8.75 (1H, s, N=CH), 8.10 (2H, d, H-3,6), 8.03 (1H, d, 3-H), 7.81 (1H, t, H-5), 7.69 (1H, t, H-4), 7.40 (1H, d, 2-H), 2.50 (3H, s, 6-CH₃) ppm; CIMS (CH_4) (m/z) = 330 (M+H, 50).

N-(2-Aryl-4-oxo-1,3-thiazolidin-3-yl)-6-methylimidazo[2,1-b][1,3]thiazole-5-carboxamide **4**
 5; N-(2-Aryl-4-oxo-1,3-thiazinan-3-yl)-6-methylimidazo[2,1-b][1,3]thiazole-5-carboxamide **6**
 General procedure

A mixture of hydrazide-hydrazone **3** (0.005 mol) and mercaptoalkanoic acid (30 ml) (mercaptoacetic acid, 2-mercaptopropanoic acid or 3-mercaptopropanoic acid) was refluxed in 30 ml dry benzene using a Dean-Stark water trap. Excess benzene was evaporated in vacuo. The residue was triturated with saturated NaHCO₃ aqueous solution until CO₂ evolution ceased and was allowed to stand overnight. The solid thus obtained was washed with water and recrystallized from C₂H₅OH-H₂O. In the case of **4b** and **4c** which could not be solidified by NaHCO₃, the crude products were converted into their HCl salts by passing dry HCl through their ethanolic-aetheral solution. The salts thus obtained were recrystallized from C₂H₅OH (96%).

- N-(2-Phenyl-4-oxo-1,3-thiazolidin-3-yl)-6-methylimidazo[2,1-b][1,3]thiazole-5-carboxamide **4a**: ($C_{16}H_{14}N_4O_2S_2 \cdot 0.5 H_2O$) (367.35); mp 111-116 °C; yield: 84%; IR, ν : 3280, 3095, 3050 (NH), 1680 (CO, thiazolidine), 1640 (CO) cm^{-1} ; 1H NMR (CDCl₃), δ : 8.06 (1H, d, 3-H), 7.68 (1H, s, NH), 7.45-7.36 (5H, m, C₆H₅), 6.87 (1H, d, 2-H), 5.96 (1H, s, N-CH-S), 3.97, 3.75 (1H, 1H, 2d, J=16 Hz, CH₂-S), 2.18 (3H, s, 6-CH₃) ppm; EIMS (70 eV) (m/z) = 358 (M⁺, 80).
- N-[2-(4-Fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-methylimidazo[2,1-b][1,3]thiazole-5-carboxamide **4b**: ($C_{16}H_{13}FN_4O_2S_2 \cdot HCl$) (412.87); mp 225-226 °C; yield: 86%; IR, ν : 3151, 3115 (NH), 1684 (CO, thiazolidine), 1627 (CO) cm^{-1} ; 1H NMR, δ : 10.48 (1H, s, NH), 8.03 (1H, d, 3-H), 7.60 (2H, t, H-3,5), 7.25 (2H, t, H-2,6), 6.15 (1H, s, N⁺H), 5.95 (1H, s, N-CH-S), 4.00, 3.85 (1H, 1H, 2d, J=16 Hz, CH₂-S), 2.25 (3H, s, 6-CH₃) ppm.
- N-[2-(4-Chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-methylimidazo[2,1-b][1,3]thiazole-5-carboxamide.HCl **4c**: ($C_{16}H_{13}ClN_4O_2S_2 \cdot HCl$) (429.33); mp 231-233 °C; yield: 91%; IR, ν : 3154, 3084 (NH), 1711 (CO, thiazolidine), 1669 (CO) cm^{-1} ; 1H NMR, δ : 10.36 (1H, s, NH), 7.98 (1H, d, 3-H), 7.58 (2H, d, H-3,5), 7.50 (1H, d, 2-H), 7.48 (2H, d, H-2,6), 5.93 (1H, s, N-CH-S), 5.37 (1H, s, N⁺H), 4.00, 3.50 (1H, 1H, 2d, J=16 Hz, CH₂-S), 2.50 (3H, s, 6-CH₃) ppm; EIMS (70 eV) (m/z) = 394 (M⁺+2-HCl, 0.6), 392 (M⁺-HCl, 1).
- N-[2-(4-Bromophenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-methylimidazo[2,1-b][1,3]thiazole-5-carboxamide **4d**: ($C_{16}H_{13}BrN_4O_2S_2$) (437.31); mp 151-153 °C; yield: 95%; IR, ν : 3305, 3044 (NH), 1702 (CO, thiazolidine), 1648 (CO) cm^{-1} ; 1H NMR, δ : 10.09 (1H, s, NH), 7.90 (1H, d, 3-H), 7.61 (2H, d, H-3,5), 7.50 (2H, d, H-2,6), 7.36 (1H, d, 2-H), 5.90 (1H, s, N-CH-S), 3.96, 3.86 (1H, 1H, 2d, J=16 Hz, CH₂-S), 2.20 (3H, s, 6-CH₃) ppm.
- N-[2-(4-Methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-methylimidazo[2,1-b][1,3]thiazole-5-carboxamide **4e**: ($C_{17}H_{16}N_4O_2S_2 \cdot 2H_2O$) (408.49); mp 232-234 °C; yield: 67%; IR, ν : 3277, 3117 (NH), 1701 (CO, thiazolidine), 1652 (CO) cm^{-1} ; 1H NMR, δ : 10.29 (1H, s, NH), 7.92 (1H, d, 3-H), 7.49 (1H, d, 2-H), 7.40 (2H, d, H-3,5), 7.19 (2H, d, H-2,6), 5.89 (1H, s, N-CH-S), 3.92, 3.80 (1H, 1H, 2d, J=16 Hz, CH₂-S), 2.30 (3H, s, CH₃), 2.24 (3H, s, 6-CH₃) ppm.
- N-[2-(2-Nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]-6-methylimidazo[2,1-b][1,3]thiazole-5-carboxamide **4g**: ($C_{16}H_{13}N_5O_4S_2$) (403.42); mp 184-187 °C; yield: 97%; IR, ν : 3235 (NH), 1702

(CO, thiazolidine), 1664 (CO) cm^{-1} ; ^1H NMR, δ : 10.15 (1H, s, NH), 8.10 (1H, d, 3-H), 7.94 (2H, d, H-3,5), 7.89 (1H, d, H-4), 7.65 (1H, t, H-3), 7.37 (1H, d, 2-H), 6.28 (1H, s, N-CH-S), 4.00, 3.78 (1H, 1H, 2d, $J=16$ Hz, $\text{CH}_2\text{-S}$), 2.25 (3H, s, 6- CH_3) ppm.

N-(5-methyl-2-phenyl-4-oxo-1,3-thiazolidin-3-yl)-6-methylimidazo[2,1-*b*][1,3]thiazole-5-carboxamide **5a**: ($\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_2\text{S}_2 \cdot 0.5\text{H}_2\text{O}$) (381.46); mp 120-125 °C; yield: 70%; IR, ν : 3125, 3085 (NH), 1705 (CO, thiazolidine), 1652 (CO) cm^{-1} ; ^1H NMR, δ : 10.30 (1H, s, NH), 7.88 (1H, d, 3-H), 7.53-7.32 (6H, m, C_6H_5 and 2-H), 5.89 (1H, s, N-CH-S), 4.15 (1H, q, $J=6.91$ Hz, CO-CH-S), 2.13 (3H, s, 6- CH_3), 1.58 (3H, d, CH_3) ppm; EIMS(70eV) (m/z) = 372 (M^+ , 30).

N-(2-(4-Fluorophenyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl)-6-methylimidazo[2,1-*b*][1,3]thiazole-5-carboxamide **5b**: ($\text{C}_{17}\text{H}_{15}\text{FN}_4\text{O}_2\text{S}_2$) (390.44); mp 199 °C; yield: 87%; IR, ν : 3233 (NH), 1705 (CO, thiazolidine), 1658 (CO) cm^{-1} ; ^1H NMR, δ : 10.00 (1H, s, NH), 7.86 (1H, d, 3-H), 7.76 (2H, t, H-3,5), 7.56 (1H, d, 2-H), 7.22 (2H, t, H-2,6), 5.89 (1H, s, N-CH-S), 4.15 (1H, q, $J=6.88$ Hz, CO-CH-S), 2.16 (3H, s, 6- CH_3), 1.58 (3H, d, CH_3) ppm.

N-(5-Methyl-2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl)-6-methylimidazo[2,1-*b*][1,3]thiazole-5-carboxamide **5c**: ($\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_2\text{S}_2 \cdot 2\text{H}_2\text{O}$) (422.52); mp 115-117 °C; yield: 60%; IR, ν : 3260, 3154, 3114 (NH), 1709 (CO, thiazolidine), 1651 (CO) cm^{-1} ; ^1H NMR, δ : 10.02 (1H, s, NH), 7.85 (1H, d, 3-H), 7.40-7.33 (3H, m, 2-H and H-2,6), 7.19 (2H, d, $J=8$ Hz, H-3,5), 5.84 (1H, s, N-CH-S), 4.11 (1H, q, $J=7.01$ Hz, CO-CH-S), 2.30 (3H, s, CH_3 -4), 2.18 (3H, s, 6- CH_3), 1.58 (3H, d, CH_3 thiazolidine) ppm.

N-(5-Methyl-2-(2-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl)-6-methylimidazo[2,1-*b*][1,3]thiazole-5-carboxamide **5g**: ($\text{C}_{17}\text{H}_{15}\text{N}_5\text{O}_4\text{S}_2 \cdot 1.5\text{H}_2\text{O}$) (444.50); mp 238 °C; yield: 51%; IR, ν : 3233, 3121 (NH), 1705 (CO, thiazolidine), 1663 (CO) cm^{-1} ; ^1H NMR, δ : 10.07 (1H, s, NH), 8.09-7.80 (4H, m, 3-H and H-3,5,6), 7.63 (1H, t, H-4), 7.34 (1H, d, 2-H), 6.25 (1H, s, N-CH-S), 4.20 (1H, q, $J=6.94$ Hz, CO-CH-S), 2.27 (3H, s, 6- CH_3), 1.55 (3H, d, CH_3 thiazolidine) ppm.

N-(4-oxo-2-phenyl-1,3-thiazinan-3-yl)-6-methylimidazo[2,1-*b*][1,3]thiazole-5-carboxamide **6a**: ($\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_2\text{S}_2$) (372.45); mp 148-149 °C; yield: 52%; IR, ν : 3126, 3084 (NH), 1670, 1635 (CO) cm^{-1} ; ^1H NMR, δ : 9.84 (1H, s, NH), 7.73 (1H, d, 3-H), 7.74-7.27 (6H, m, C_6H_5 and 2-H), 6.01 (1H, s, N-CH-S), 3.17-2.84 (4H, m, $\text{CH}_2\text{-CH}_2\text{-S}$), 2.00 (3H, s, 6- CH_3) ppm.

N-(2-(4-Methylphenyl)-4-oxo-1,3-thiazinan-3-yl)-6-methylimidazo[2,1-*b*][1,3]thiazole-5-carboxamide **6c**: ($\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_2\text{S}_2 \cdot \text{H}_2\text{O}$) (404.47); mp 188 °C; yield: 70%; IR, ν : 3119 (NH), 1657, 1624 (CO) cm^{-1} ; ^1H NMR, δ : 9.89 (1H, s, NH), 7.71 (1H, d, 3-H), 7.31-7.28 (3H, m, 2-H and H-3,5), 7.15 (2H, d, H-2,6), 5.95 (1H, s, N-CH-S), 3.16-2.85 (4H, m, $\text{CH}_2\text{-CH}_2\text{-S}$), 2.27 (3H, s, 6- CH_3), 1.97 (3H, s, CH_3) ppm; EIMS(70 eV) (m/z) = 386 (M^+ , 100).

6-Methylimidazo[2,1-*b*][1,3]thiazole-5-carbonyl azide **7** (**3**): To a suspension of **2** (0.005 mol) in 25 ml of water, 5 ml of HCl(20%) was added. The solution was cooled on ice while stirring was treated dropwise with aqueous NaNO_2 (0.006 mol in 4 ml of water). After the reaction was completed, the precipitate was collected by filtration, washed with cold water and dried. mp 116 °C; yield: 95%; IR, ν : 2245 (CON_3) cm^{-1} ; ^1H NMR, δ : 8.17 (1H, d, 3-H), 7.50 (1H, d, 2-H), 2.53 (3H, s, 6- CH_3) ppm. The product was used for further reactions without purifications.

Ethyl 6-methylimidazo[2,1-*b*][1,3]thiazol-5-ylcarbamate **8**: 0.005 Mol of **7** in 40 ml of absolute $\text{C}_2\text{H}_5\text{OH}$ was refluxed for 5 hours then $\text{C}_2\text{H}_5\text{OH}$ was removed in vacuo. The product thus obtained was recrystallized from $\text{C}_2\text{H}_5\text{OH}$ (96%). ($\text{C}_9\text{H}_{11}\text{N}_3\text{O}_2\text{S}$) (225.27); mp 161-162 °C; yield: 62%; IR, ν : 3146, 3122 (NH), 1721 (CO) cm^{-1} ; ^1H NMR, δ : 9.03 (1H, s, NH), 7.53 (1H, d, 3-H), 7.13 (1H, d, 2-H), 4.14 (2H, q, CH_2), 2.00 (3H, s, 6- CH_3), 1.21 (3H, t, CH_3) ppm; EIMS(70 eV) (m/z) = 225 (M^+ , 45).

N-(6-Methylimidazo[2,1-*b*][1,3]thiazol-5-yl)hydrazinecarboxamide **9**: 0.005 Mol of **8** in 0.025 mol of hydrazine was refluxed for 6 hours. The precipitate formed after cooling was filtered, washed with water, dried and recrystallized from $\text{C}_2\text{H}_5\text{OH}$ (96%). ($\text{C}_7\text{H}_9\text{N}_5\text{OS}$) (211.24); mp 209-210 °C; yield: 62%; IR, ν : 3311-3092 (NH, broad), 1627 (CO) cm^{-1} ; ^1H NMR, δ : 9.34 (1H, s, CONH), 8.05 (1H, d, 3-H), 7.94 (1H, s, NH), 7.35 (1H, d, 2-H), 6.06 (2H, s, NH_2), 2.52 (3H, s, 6- CH_3) ppm; EIMS(70 eV) (m/z) = 211 (M^+ , 1).

Aldehyde *N*-(6-methylimidazo[2,1-*b*][1,3]thiazol-5-yl)semicarbazones **10**: **10a,b** were obtained according to the general method given under **3** using 0.0025 mol of **9** and 0.003 mol of the appropriate aldehyde.

Benzaldehyde *N*-(6-methylimidazo[2,1-*b*][1,3]thiazol-5-yl)semicarbazone **10a**: ($\text{C}_{14}\text{H}_{13}\text{N}_5\text{OS}$) (299.34); mp 206-207 °C; yield: 78%; IR, ν : 3375, 3197 (NH), 1686 (CO) cm^{-1} ; ^1H NMR, δ : 10.90 (1H, s, NH), 9.00 (1H, s, NH), 7.98 (1H, s, N=CH), 7.90-7.80 (2H, m, H-2,6), 7.60 (1H, d, 3-H), 7.50-7.35 (3H, m, H-3,4,5), 7.15 (1H, d, 2-H), 2.15 (3H, s, 6- CH_3) ppm.

4-Fluorobenzaldehyde N-(6-methylimidazo[2,1-b][1,3]thiazol-5-yl)semicarbazone 10b:

(C₁₄H₁₂FN₃OS) (317.34); mp 216-219 °C; yield: 68%; IR, v: 3300-3200 (NH, broad), 1678 (CO) cm⁻¹; ¹H NMR, δ: 10.87 (1H, s, NH), 8.97 (1H, s, NH), 7.93 (1H, s, N=CH), 7.90-7.88 (2H, m, H-2,6), 7.55 (1H, d, 3-H), 7.23 (2H, t, H-3,5), 7.11 (1H, d, 2-H), 2.52 (3H, s, 6-CH₃) ppm; EIMS(70eV) (m/z) = 317 (M⁺, 2).

N-(6-Methylimidazo[2,1-b][1,3]thiazol-5-yl)-N'-(2-aryl-4-oxo-1,3-thiazolidin-3-yl)ureas 11: The compounds 11a, 11b were obtained according to the general method given under 4-6 using 0.0025 mol of appropriate semicarbazone and 3-5 ml of mercaptoacetic acid.

N-(6-Methylimidazo[2,1-b][1,3]thiazol-5-yl)-N'-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)urea 11a: (C₁₆H₁₅N₅O₂S₂) (373.44); mp 254-259 °C; yield: 78%; IR, v: 3375, 3267, 3199 (NH), 1690 (CO thiazolidine), 1670 (CO) cm⁻¹; ¹H NMR, δ: 8.70 (1H, s, NH), 8.30 (1H, s, NH), 7.50-7.19 (6H, m, 3-H and C₆H₅), 7.05 (1H, d, 2-H), 5.80 (1H, s, N-CH-S), 3.83, 3.72 (1H, 1H 2d, J=16Hz, CH₂S), 1.98 (3H, s, 6-CH₃) ppm; EIMS(70eV) (m/z) = 373 (M⁺, 20).

N-(6-Methylimidazo[2,1-b][1,3]thiazol-5-yl)-N'-(2-(4-fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl)urea 11b: (C₁₆H₁₄FN₅O₂S₂·H₂O) (409.45); mp 280-282 °C; yield: 72%; IR, v: 3267, 3109(NH), 1690 (CO thiazolidine), 1670 (CO) cm⁻¹; ¹H NMR, δ: 8.80 (1H, s, NH), 8.40 (1H, s, NH), 7.60-7.50 (2H, m, H-2,6), 7.24-7.19 (3H, m, 3-H and H-3,5), 7.12 (1H, d, 2-H), 5.81 (1H, s, N-CH-S), 3.83, 3.72 (1H, 1H, 2d, J=16Hz, CH₂S), 1.97 (3H, s, 6-CH₃) ppm; EIMS(70eV) (m/z) = 391(M⁺, 1).

Antimycobacterial activity

Antimycobacterial screen was conducted at 12.5 µg/ml against *Mycobacterium tuberculosis* H₃R_v in BACTEC 12B medium using the BACTEC 460 radiometric system at National Institute of Allergy and Infectious Diseases, USA. Rifampine (minimal inhibitory concentration 0.025 µg/ml) was used as the standard. All the compounds were inactive against *M. tuberculosis* H₃R_v at 12.5 µg/ml and not selected for further evaluation at higher concentration to determine their actual MIC (5).

RESULTS AND DISCUSSION

Ethyl 6-methylimidazo[2,1-b][1,3]thiazole-5-carboxylate 1 was reacted with hydrazine hydrate to give 2. Condensation of 2 with appropriate aromatic aldehydes yielded the corresponding hydrazones 3a-g which on condensation with mercaptoacetic acid, 2-mercaptopropanoic acid or 3-mercaptopropanoic acid afforded the 4-oxo-1,3-thiazolidines 4a-e, g, 5a, b, e, g and 4-oxo-1,3-thiazinanes 6a, e respectively. The IR spectra of compounds 4 and 5 showed CO bands at 1711-1680 cm⁻¹ providing confirmatory evidence for ring closure. ¹H NMR spectra of compounds 4, 5 displayed two doublets at about 4.00-3.50 ppm and a quartet at about 4.20-4.11 ppm, respectively, due to the inequivalence of the protons (SCH₂ and SCH) (6). The singlet of N=CH at about 8.75-8.26 ppm in the spectra of 3 was shifted upfield to 6.28-5.84 ppm by the loss of the sp² character of the involved C atom. From the reaction of arylidene 6-methylimidazo[2,1-b][1,3]thiazol-5-carbohydrazides with 3-mercaptopropanoic acid only two compounds, 6a and 6e could be obtained. Our attempts to prepare the others failed. The IR spectra of 6a and 6e showed two carbonyl bands at about 1670-1657 cm⁻¹ and 1635-1624 cm⁻¹. In the ¹H NMR spectra of 4-oxo-1,3-thiazinanes, multiplets at about 3.17-2.84 ppm due to endocyclic CH₂CH₂ protons provided firm support for the structures. Further support was the resonance of the C-H proton at position 2 of the 1,3-thiazinane ring in the spectra of 6a (6.01 ppm) and 6e (5.95 ppm). The upfield shifts observed here again are consistent with the change in the hybridization state of the involved carbon atom. CI mass spectra of 3a, c, f, g and EI mass spectra of 4a, c, 5a, 6e displayed quasi-molecular and molecular ions, respectively. On the other hand reaction of 2 with NaNO₂/H⁺ yielded 6-methylimidazo[2,1-b][1,3]thiazole-5-

carbonyl azide 7. The IR spectrum of 7 displayed a strong band at 2245 cm^{-1} due to azide stretching (3). Heating 7 with absolute ethanol led to ethyl N-(6-methylimidazo[2,1-b][1,3]thiazole-5-yl)carbamate 8 via Curtius reaction. 8 showed characteristic peaks at 3146 , 3122 and 1721 cm^{-1} due to NH and C=O groups. The absence of azide peak at 2245 cm^{-1} also supported the formation of 8. Hydrazinolysis of 8 gave N-(6-methylimidazo[2,1-b][1,3]thiazol-5-yl)hydrazinecarboxamide 9. The NH and C=O absorption peaks were observed at 3311 - 3092 and 1627 cm^{-1} respectively, in the IR spectrum of 9. In the $^1\text{H-NMR}$ spectrum, NH_2 , NH and CONH protons appeared at 6.06, 7.94 and 9.34 ppm, respectively. EI mass spectra of 8 and 9 showed molecular ions. 9 was condensed with aromatic aldehydes to afford aldehyde N-(6-methylimidazo[2,1-b][1,3]thiazol-5-yl)semicarbazones 10a,b which were cyclized to give N-(6-methylimidazo[2,1-b][1,3]thiazol-5-yl)-N'-(2-aryl-4-oxo-1,3-thiazolidin-3-yl)urea 11a,b. The IR spectra of 10 and 11 showed two separate bands resulting from the NH and C=O bands of amide function at about 3375 - 3109 and 1686 - 1670 cm^{-1} , respectively. A new C=O band at 1690 cm^{-1} in the spectra of 11a,b provided evidence for the 4-oxo-1,3-thiazolidine structure. On the other hand the singlet of N=CH at about 7.98-7.93 ppm in the spectra of 10a,b were shifted upfield to 5.81-5.80 ppm in the spectra of 11a,b. EI mass spectra of 10b and 11a,b displayed molecular ions which confirmed molecular weights. All compounds were evaluated for *in vitro* antimycobacterial activity against *M. tuberculosis* H₃₇R_v at the concentration of $12.5\text{ }\mu\text{g ml}^{-1}$ and were found to be ineffective against the microorganism at this concentration.

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