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Synthesis and antimycobacterial activity of new imidazo[2,1-*b*]thiazole derivatives

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Introduction

The imidazo[2,1-*b*]thiazole system constitutes the main part of the well-known antihelmintic-immunomodulatory agent levamisole. Thiosemicarbazides and 4-thiazolidinones are associated with a broad spectrum of biological properties including antimycobacterial activity [1, 2]. These observations prompted the synthesis of some new thiosemicarbazides and 4-thiazolidinones incorporating an imidazo[2,1-*b*]thiazole moiety, with the objective of screening their antimycobacterial activity.

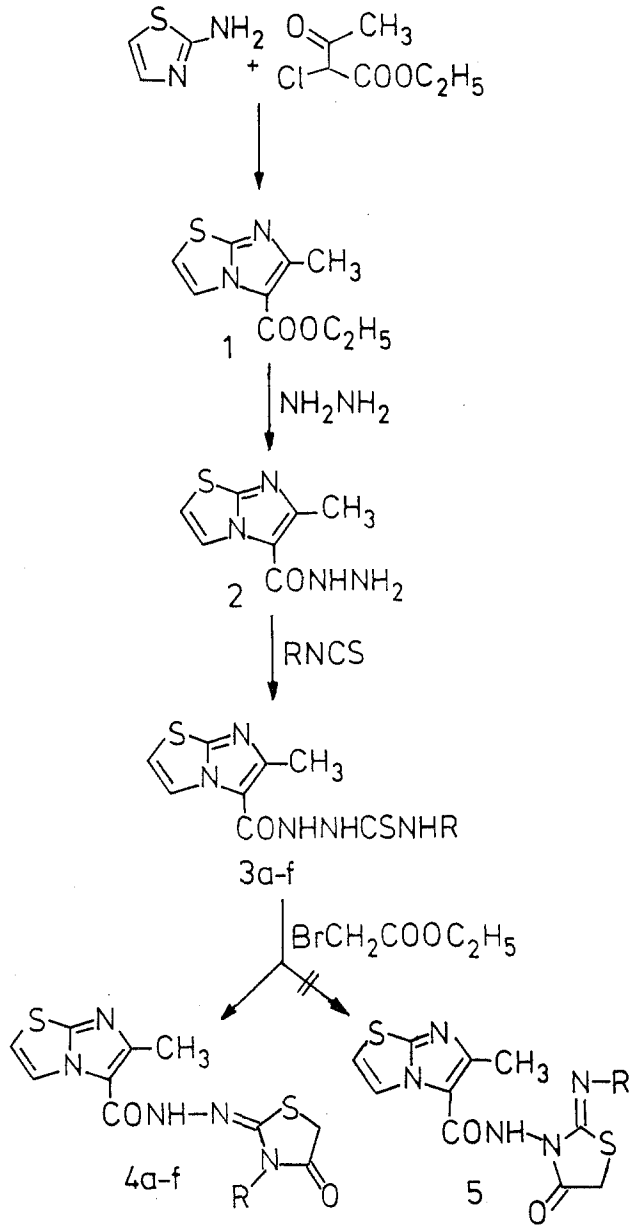
Chemistry

Ethyl 6-methylimidazo[2,1-*b*]thiazole-5-carboxylate **1** [3] reacted with hydrazine hydrate to give the hydrazide **2** [4]. 1-[(6-Methylimidazo[2,1-*b*]thiazole-5-yl)-carbonyl]thiosemicarbazide, **3a**, was obtained by refluxing **2** with potassium thiocyanate in aqueous hydrochloric acid. The reaction of appropriate alkyl isothiocyanates with **2** yielded 1-acyl-4-alkylthiosemicarbazide derivatives **3b–f**. On treatment with ethyl bromoacetate and sodium acetate, **3a–f** furnished the 4-thiazolidinones, **4a–f** (scheme 1).

The IR spectra of **3a–f** and **4a–f** showed CO bands at 1670–1625 cm^{-1} (CONH-N). A new strong band at 1728–1700 cm^{-1} in the spectra of **4a–f** provided firm support for the thiazolidinone system. After the reaction with ethyl bromoacetate, the product displayed only an additional singlet (2H) at about 4.07–3.94 ppm, which proved ring closure in **4a–f**. Since the thiol forms of **3a–f** are responsible for the formation of the thiazolidinones, 2 products **4** and **5** may be considered. It is well established that the enethiol formation involves the NH group adjacent to the more electron-withdrawing moiety [5]. Thus, the anticipated structure is **4**. Hydrolytic cleavage was carried out to further confirm this structural assignment. The hydrolysis of **4a** yielded 2,4-dioxothiazolidine as the hydrolytic product, whereas the compounds with structure **5** would have given 2,4-dioxothiazolidine having an imidazo[2,1-*b*]thiazole moiety at the 3 position. The structures of all derivatives were supported by elemental analysis and spectral data. All the compounds exhibited molecular ions (except **3c**) with different intensities (table I). Spectral data of some representative derivatives are given in the *Experimental protocols*.

Results and discussion

The antimycobacterial activities of **2**, **3a–f** and **4a–f** were evaluated by *in vitro* screening against the $H_{37}Rv$ strain of *Mycobacterium tuberculosis* [6]. Only **3a** and **4a** showed inhibition, with MIC values of 100 and 200 μg/ml, respectively. From the results it is clear that none of the compounds have any remarkable antimycobacterial activity when compared with INH (MIC < 6.25 μg/ml). It is, however, evident that introduction of alkyl groups results in loss of activity [7].



Scheme 1.

Experimental protocols

Chemistry

Melting points were estimated with a Büchi melting point apparatus and are uncorrected. IR (KBr) and ^{1}H-NMR ([d_6]DMSO) spectra were recorded on Perkin-Elmer 577 (Grating) and Bruker AC 200 or Varian LX 300 instruments, respectively. EIMS and CIMS (CH_4) were recorded at Pennsylvania State University, USA, or at Sittingbourne Research Center, UK. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer. The values found (C, H, N) were within ± 0.4% of the theoretical values.

*Ethyl 6-methylimidazo[2,1-b]thiazole-5-carboxylate **1***
2-Aminothiazole (0.1 mol) was refluxed with ethyl 2-chloroacetoacetate in 30 ml absolute EtOH for 24 h. The solvent was evaporated under reduced pressure and the residue was triturated with water, filtered, dried and used without further purification, mp 96–98°C, yield 35%.

*6-Methylimidazo[2,1-b]thiazole-5-carbohydrazide **2***
Compound **1** (0.025 mol) was refluxed with 0.25 mol of H_2N-NH_2·H_2O in 15 ml EtOH (96%) for 16 h and allowed to stand overnight. The crystalline solid that separated out was filtered, washed with cold water, dried and recrystallized from EtOH (96%), mp 183–185°C, yield 65%.

*1-[(6-Methylimidazo[2,1-b]thiazole-5-yl)carbonyl]thiosemicarbazide **3a***
A solution of **2** (0.01 mol), potassium thiocyanate (0.02 mol), HCl (37%, 10 ml) and water (200 ml) was refluxed 3 h. After cooling, the compound was precipitated by the addition of NaOH (10%), filtered, washed with water, dried and recrystallized from EtOH (96%). **3a**: IR (cm^{-1}): 1625 (CO). ^{1}H-NMR: δ (ppm) = 9.42 (s, 1H, N^1H), 9.21 (s, 1H, N^2H), 8.08 (d, 1H, 3-H, J = 4.5 Hz), 7.49 (s, 2H, NH_2), 7.32 (d, 1H, 2-H, J = 4.5 Hz), 2.55 (s, 3H, 6-CH_3).

*1-[(6-Methylimidazo[2,1-b]thiazole-5-yl)carbonyl]-4-alkylthiosemicarbazides **3b–f***
Compound **2** (0.01 mol), the appropriate isothiocyanate (0.01 mol) and 25 ml absolute EtOH were refluxed for 3 h. The solid that separated out was filtered and recrystallized from EtOH (96%). **3b**: IR (cm^{-1}): 1655 (CO). ^{1}H-NMR: δ (ppm) = 9.46 (s, 1H, N^1H), 9.28 (s, 1H, N^2H), 8.07 (d, 1H, 3-H, J = 4.5 Hz), 8.00 (s, 1H, N^4H), 7.35 (d, 1H, 2-H, J = 4.5 Hz), 2.90 d, 3H, CH_3), 2.54 (s, 3H, 6-CH_3).

*2-[(6-Methylimidazo[2,1-b]thiazole-5-yl)carbonyl]hydrazono-3-nonsubstituted/alkyl-4-thiazolidinones **4a–f***
The appropriate thiosemicarbazide **3a–f** (0.01 mol) and ethyl bromoacetate (0.011 mol) were refluxed in 30 ml absolute EtOH in the presence of 0.04 mol anhydrous CH_3COONa for 3–14 h and cooled. The crystals were washed with water, dried and recrystallized from EtOH (96%). **4a**: IR (cm^{-1}): 1720 (CO, ring), 1690 (CO). ^{1}H-NMR: δ (ppm) = 11.56 (s, 1H, NH ring), 9.98 (s, 1H, CONH), 7.99 (d, 1H, 3-H, J = 4.4 Hz), 7.32 (d, 1H, 2-H, J = 4.4 Hz), 3.94 (s, 2H, S-CH_2), 2.52 (s, 1H, 6-CH_3). **4b**: IR (cm^{-1}): 1700 (CO, ring), 1685 (CO). ^{1}H-NMR: δ (ppm) = 10.24 (s, 1H, CONH), 8.01 (d, 1H, 3-H, J = 4.4 Hz), 7.36 (d, 1H, 2-H, J = 4.4 Hz), 4.06 (s, 2H, S-CH_2), 3.16 (s, 3H, CH_3), 2.52 (s, 3H, 6-CH_3).

*Hydrolysis of **4a***
Compound **4a** (0.5 g) was refluxed with 10 ml H_2SO_4 (40%) for several hours. The acidic solution was checked by TLC (MeOH, silica gel 60 HF_{254}) using 2,4-dioxothiazolidine [8] as the reference.

Antimycobacterial activity

M tuberculosis H_{37}Rv strain was prepared as a 7-d-old culture on Lowenstein–Jensen medium and was used to study antimycobacterial activity. This culture was suspended in 4 ml

Table I. Physicochemical and MS data of imidazo[2,1-*b*]thiazole derivatives.

Compound	*R*	*Mp (°C)*	*Yield (%)*	*Formula (molecular mass)*	*MS*[a] *(rel int %)*
3a	H	222	41	$C_8H_9N_5OS_2 \cdot H_2O$ (273.33)	255 (M^+, 2.8)
3b	CH_3	198	86	$C_9H_{11}N_5OS_2$ (269.34)	269 (M^+, 1.9)
3c	C_2H_5	212	80	$C_{10}H_{13}N_5OS_2$ (283.36)	
3d	C_3H_7	200	61	$C_{11}H_{15}N_5OS_2$ (297.39)	297 (M^+, 3.9)
3e	C_4H_9	197	58	$C_{12}H_{17}N_5OS_2 \cdot H_2O$ (329.44)	312 (MH^+, 24.4)
3f	C_3H_5	186	68	$C_{11}H_{13}N_5OS_2$ (295.37)	295 (M^+, 0.1)
4a	H	238	73	$C_{10}H_9N_5O_2S_2$ (295.33)	296 (MH^+, 5.7)
4b	CH_3	215	74	$C_{11}H_{11}N_5O_2S_2 \cdot H_2O$ (327.38)	309 (M^+, 12.4)
4c	C_2H_5	181	70	$C_{12}H_{13}N_5O_2S_2$ (323.38)	324 (MH^+, 66.9)
4d	C_3H_7	212	73	$C_{13}H_{15}N_5O_2S_2$ (337.41)	337 (M^+, 11.1)
4e	C_4H_9	187	87	$C_{14}H_{17}N_5O_2S_2$ (351.44)	352 (MH^+, 55.1)
4f	C_3H_5	208	70	$C_{13}H_{13}N_5O_2S_2$ (335.39)	336 (MH^+, 12.4)

[a]**3a**, **3b**, **3d**, **3f**, **4b** and **4d** EI; **3e**, **4a**, **4c**, **4e** and **4f** CI (CH_4).

saline with the aid of glass beads. The mixture was shaken with a Vortex mixer for about 1 min. The suspension so obtained was diluted with saline to give a final concentration of 10^4 CFU/ml.

A solution of **2**, **3a–f** and **4a–f** was prepared at concentrations of 200, 100, 50, 25, 12.5 and 6.25 µg/ml in a mixture of distilled water and ethanol (1:1), and then 0.25 ml of this solution were added to 3 tubes containing Lowenstein–Jensen medium. The tubes were inclined and incubated overnight at 37°C for the absorption of the compound into the medium. Isoniazid (INH) was used as the standard. The final inoculum (0.1 ml) was added to each tube containing the compound and to 3 other tubes containing compound-free medium as controls. The tubes were capped, incubated at 37°C and read weekly for 4 weeks. The minimum concentration at which no growth was observed was taken as the MIC value.

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