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Short communication

Synthesis and antitubercular activity of imidazo[2,1-*b*]thiazoles

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Abstract – A number of selected imidazo[2,1-*b*]thiazoles entered the screening at the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) and one of these compounds, 2-chloro-6-phenylimidazo[2,1-*b*]thiazole, showed antitubercular activity. On this basis we planned the synthesis of new analogues bearing a substituted ring at the 6 position. For one compound only (2-chloro-6-*p*-chlorophenylimidazo[2,1-*b*]thiazole) the 5-nitroso derivative was also prepared. The antitubercular activity of these compounds was compared with the known analogues lacking the chlorine at the 2 position. 5-Nitroso-6-*p*-chlorophenylimidazo[2,1-*b*]thiazole showed potent antitubercular activity. © 2001 Éditions scientifiques et médicales Elsevier SAS

antitubercular activity / imidazo[2,1-b]thiazoles / nitroso derivatives

1. Introduction

Despite the ready availability of effective treatments, tuberculosis remains a major public health threat worldwide. The emergence of drug resistant strains of *Mycobacterium tuberculosis*, particularly multiple drug resistant strains [1–4] has complicated treatment protocols and raises the concern that tuberculosis may once again become an incurable disease. For this reason it is critical to discover new drugs acting with a mechanism different from those of presently used antitubercular drugs. The numerous reviews recently reported in the literature are a proof of the renewed interest towards this pathology [5–11].

A number of selected imidazo[2,1-*b*]thiazoles entered the screening at the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) and one of these compounds, 2-chloro-6-phenylimidazo[2,1-*b*]thiazole (**3a**) (*figure 1*) showed antitubercular activity. On this basis we planned the synthesis of new analogues bearing a substituted ring at the 6 position. For one compound only (**3c**), the 5-nitroso derivative was also prepared (**4c**). The antitubercular activity of these compounds was compared with the known analogues lacking the chlorine at the 2 position.

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2. Chemistry

The 2-chloroimidazothiazoles **3** were prepared by the reaction of 2-amino-5-chlorothiazole (**1a**) with the appropriate bromoacetophenones **2**. Only the 6-*p*-aminophenyl derivative **3n** was obtained from 2-chloro-6-*p*-nitrophenylimidazo[2,1-*b*]thiazole (**3m**) by reduction with iron in acetic acid. The 5-nitroso derivative **4c** was prepared by treating 2-chloro-6-*p*-chlorophenylimidazo[2,1-*b*]thiazole (**3c**) with sodium nitrite in acetic acid. All the new 2-chloro derivatives **3** and **4** are reported in *tables I and II*.

3. Biological results

Seven of the 14 compounds showed inhibitory activity >0% at the screening concentration of 6.25 $\mu g\,mL^{-1}$. The antitubercular profile of these com-

pounds is reported in *table III*, in comparison with the analogues lacking the chlorine at the 2 position. It is interesting to note that the 2-chloro derivatives showed moderate to good increases in activity in almost every case with only two exceptions (**3k** vs. **5k** and **4c** vs. **6c**). Compound **6c**, one of the exceptions, showed significant antitubercular activity at the primary screening concentration, and this high preliminary activity warranted higher level screening. A minimum inhibitory concentration (MIC) was determined for **6c** of 0.390 μg mL^{-1} (see footnote to *table III*).

4. Discussion

For this series of imidazo[2,1-*b*]thiazoles and the corresponding 2-chloro derivatives, several compounds demonstrated significant antitubercular activity. For five out of the seven pairs (2-H vs. 2-Cl substituted), the 2-chloro analogue showed modest to good increases in activity versus its 2-H counterpart. There may be several explanations for this increased activity including greater hydrophobicity, an electron withdrawing effect on the imidazo[2,1-*b*]thiazole ring system, or a specific interaction of the larger 2-substituent with a specific mycobacterial target protein. It is notable that two of the pairs contradict this trend and that compound **6c** showed potent activity against *M. tuberculosis* $H_{37}Rv$, as indicated by its low MIC value of 0.390 μg mL^{-1}. This excellent MIC compares quite favourably with the gold standard in antitubercular treatment, rifampin (MIC range in the MABA assay of 0.015–0.250 μg mL^{-1}). As such, these imidazothiazoles may represent a potential class of leads for development of a new antitubercular agent. In order to confirm the most evident result (for a potent antitubercular activity, position 2 should not bear a chlorine when a nitroso group is present at the 5 position) a series of 30 additional nitroso derivatives is now under evaluation at TAACF.

5. Experimental protocols

5.1. Chemistry

The melting points are uncorrected. Analyses (C, H, N) were within ±0.4% of the theoretical values. Bakerflex plates (silica gel IB2-F) were used for TLC and Kieselgel 60 (Merck) for column chromatography: the eluent was petroleum ether–acetone in various proportions. The IR spectra were recorded in Nujol on a Nicolet Avatar 320 ESP; ν_{max} is expressed in cm^{-1} (*table I*). The ^{1}H-NMR spectra were recorded in $(CD_3)_2SO$ on a Varian Gemini (300 MHz) spectrometer; the chemical shift (referenced to solvent signal) is expressed in δ (ppm) and J in Hz, with the following abbreviations: ar = aromatic, it = imidazo[2,1-*b*]thiazole, py = pyridine (*table II*).

5.1.1. General procedure for the synthesis of the imidazo[2,1-b]thiazoles (3)

2-Amino-5-chlorothiazole (50 mM) was dissolved in acetone (100 mL) and treated with the appropriate

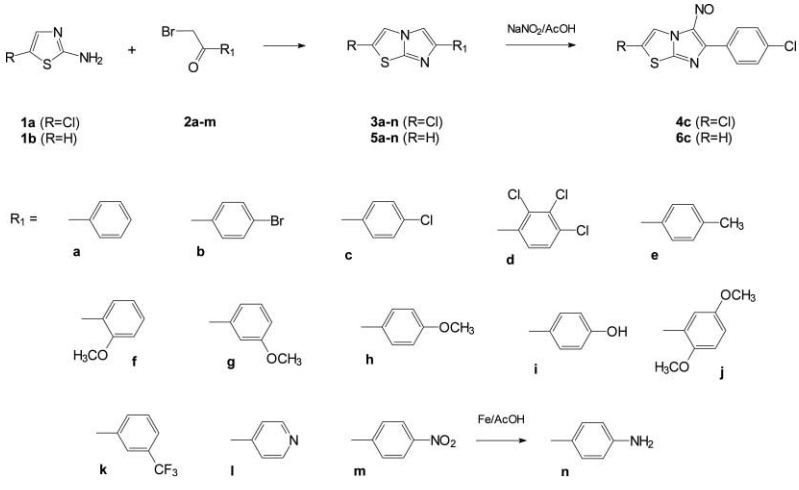

Figure 1.

Table I. 2-Chloroimidazo[2,1-*b*]thiazoles (**3a**–**n**, **4c**).

Compound	Formula (MW)	Yield (%)	M.p., (°C) or Ref.	ν_{max} (cm^{-1})
3a	$C_{11}H_7ClN_2S$ (234.7)	–	[12]	–
3b	$C_{11}H_6BrClN_2S$ (313.6)	58	233–235	1535, 1185, 995, 730
3c	$C_{11}H_6Cl_2N_2S$ (269.1)	–	[13]	–
3d	$C_{11}H_4Cl_4N_2S$ (338.0)	52	248–250	1525, 1200, 1000, 735
3e	$C_{12}H_9ClN_2S$ (248.7)	–	[14]	–
3f	$C_{12}H_9ClN_2OS$ (264.7)	62	118–120	1235, 1060, 1025, 710
3g	$C_{12}H_9ClN_2OS$ (264.7)	59	108–110	1605, 1035, 995, 730
3h	$C_{12}H_9ClN_2OS$ (264.7)	–	[15]	–
3i	$C_{11}H_7ClN_2OS$ (250.7)	–	[15]	–
3j	$C_{13}H_{11}ClN_2O_2S$ (294.8)	–	[16]	–
3k	$C_{12}H_6ClF_3N_2S$ (302.7)	57	121–123	1620, 1170, 1000, 730
3l	$C_{10}H_6ClN_3S$ (235.7)	48	173–175	1605, 1000, 830, 725
3m	$C_{11}H_6ClN_3O_2S$ (279.7)	53	258–260	1600, 1000, 850, 725
3n	$C_{11}H_8ClN_3S$ (249.7)	61	198–200	3400-3140, 1610, 995, 705
4c	$C_{11}H_5Cl_2N_3OS$ (298.1)	82	150–152 (dec.)	1590, 1250, 1160, 1090

2-bromo-1-arylethanone (50 mM). The reaction mixture was refluxed for 3 h and the resulting salt was treated, without further purification, with 20 mL of ethanol and 400 ml 2N HCl. After 1 h reflux, the solution was cautiously basified by dropping 15% NH_4OH. The resulting base was collected by filtration. All the compounds were crystallized from ethanol, except **3l**, which was crystallized from acetone–petroleum ether.

*5.1.2. 2-Chloro-6-p-aminophenylimidazo[2,1-b]thiazole (**3n**)*

2-Chloro-6-*p*-nitrophenylimidazo[2,1-*b*]thiazole (**3m**) (3.5 mM) was treated with 50% AcOH (60 mL) and iron powder (50 mM). The mixture was stirred overnight at room temperature (r.t.) and treated with 2 N NaOH until pH ~ 6 was reached. The crude compound **3n** was separated by filtration and purified by column chromatography.

*5.1.3. 2-Chloro-6-p-chlorophenyl-5-nitrosoimidazo-[2,1-b]thiazole (**4c**)*

2-Chloro-6-*p*-chlorophenylimidazo[2,1-*b*]thiazole (**3c**) (5 mM) was dissolved in AcOH (40 mL) and treated, under cooling and stirring, with $NaNO_2$ (10 mM) dissolved in H_2O (10 mL). After 2 h at r.t., the green precipitate was separated by filtration and crystallized from AcOH.

5.2. Antitubercular activity

Primary screening was conducted at 6.25 μg mL^{-1} against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using a broth microdilution assay, the Microplate Alamar Blue Assay (MABA) [17]. Compounds exhibiting fluorescence were tested in the BACTEC 460 radiometric system [17]. Compounds demonstrating at least 90% inhibition in the primary screen were retested at lower concentrations against *M. tuberculosis* $H_{37}Rv$ to determine the MIC using MABA. The MIC is defined as the lowest concentration effecting

Table II. ^{1}H-NMR of compounds **3** and **4**.

Compound	δ (ppm), J (Hz)
3b	7.59 (2H, d, ar, $J = 8.4$); 7.79 (2H, d, ar, $J = 8.4$); 8.29 (1H, s, it); 8.30 (1H, s, it)
3d	7.74 (1H, d, ar, $J = 8.7$); 8.12 (1H, d, ar, $J = 8.7$); 8.30 (1H, s, it); 8.50 (1H, s, it)
3f	3.93 (3H, s, OCH_3); 7.02 (1H, t, ar, $J = 7.8$); 7.11 (1H, d, ar, $J = 7.8$); 7.27 (1H, t, ar, $J = 7.8$); 8.11 (1H, d, ar, $J = 7.8$); 8.17 (1H, s, it); 8.25 (1H, s, it)
3g	3.81 (3H, s, OCH_3); 6.85 (1H, td, $J = 8.2$, ar); 7.32 (1H, t, ar, $J = 8.2$); 7.42 (2H, m, ar); 8.28 (1H, s, it); 8.31 (1H, s, it)
3k	7.62 (2H, m, ar); 8.15 (2H, m, ar); 8.34 (1H, s, it); 8.43 (1H, s, it)
3l	7.80 (2H, m, H_{py}-3 and H_{py}-5); 8.36 (1H, s, it); 8.51 (1H, s, it); 8.58 (2H, m, H_{py}-2 and H_{py}-6)
3m	8.11 (2H, d, ar, $J = 9.0$); 8.28 (2H, d, ar, $J = 9.0$); 8.39 (1H, s, it); 8.54 (1H, s, it)
3n	5.30 (2H, broad s, NH_2); 6.58 (2H, d, ar, $J = 7.7$); 7.48 (2H, d, ar, $J = 7.7$); 7.92 (1H, s, ar); 8.22 (1H, s, ar)
4c	7.69 (2H, d, ar, $J = 9$); 8.54 (2H, d, ar, $J = 9$); 8.75 (1H, s, it)

Table III. Antitubercular activity of the 2-Cl derivatives **3**, **4** and the corresponding 2-H analogues **5**, **6**. [a]

Compound 2-Cl	TAACF code	Inhibition (%)	Compound 2-H [Ref.]	TAACF code	Inhibition (%)
3a	141184	29	**5a** [18]	106754	0
3e	141183	13	**5e** [19]	112360	0
3f	141188	47	**5f** [20]	145478	23
3h	141190	78	**5h** [20]	145479	74
3k	141193	74	**5k** [21]	145480	83
3m	141195	37	**5m** [22]	124248	0
4c	141197	6	**6c** [b] [22]	124252	100

[a] In this assay, typical percent inhibition values at a concentration of 6.25 μg mL^{-1} for the standard TB drugs isoniazid, ethambutol and rifampin are 97, 98 and 98%, respectively. A rifampin standard was also run with each set of compounds and the MIC ranged in this assay from 0.015 to 0.250 μg mL^{-1}.
[b] The MIC for this compound was determined to be 0.390 μg mL^{-1}.

a reduction in fluorescence of 99% relative to controls [17].

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