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Antituberculous activity of some aryl semicarbazone derivatives

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Abstract—During the course of our work on the synthesis and screening of new drugs for tuberculosis, we have identified N1-(4-acetamido phenyl)-N4-(2-nitro benzylidene) semicarbazone (**1b**), which inhibited in vitro *Mycobacterium tuberculosis* $H_{37}Rv$; 100% inhibition at 1.56 μg/mL. This paper is first of its kind in which aryl semicarbazones are reported to possess antimycobacterials potency greater than *p*-aminosalicylic acid, ethionamide, ethambutol, ciprofloxacin and kanamycin.

1. Introduction

Tuberculosis (TB) is one of the most common infectious diseases known to man. About 32% of the world's population (1.86 billion people) is infected with TB. Every year, approximately 8 millions of these infected people develop active TB, and almost 2 millions of these would die from the diseases.[1] The incidence of TB infection has steadily risen in the last decade and this increase can be attributed to a similar increase in human immunodeficiency virus (HIV) infection.[2] The association of TB and HIV infections is so dramatic that, in some cases, nearly two-thirds of the patients diagnosed with TB are also HIV-1 seropositive.[3] Furthermore, numerous studies have shown that TB is a cofactor in the progression of HIV infection.[4] The reemergence of TB infection is further complicated by an increase in cases, which are resistant to conventional antitubercular drug therapy. The increasing rate of multi drug resistant TB does not only create problems for the treatment, but also the costs are exploding. Thus, new drugs are necessary to overcome the current problems of therapy. In the course of screening to discover new compounds employed in the chemotherapy of tuberculosis, we identified semicarbazones derivatives, which inhibited in vitro *Mycobacterium tuberculosis* $H_{37}Rv$. We present preliminary results concerning the synthesis and the initial in vitro antituberculous activity of first representative compound of this family.

2. Chemistry

The synthesis of various phenyl semicarbazones was achieved by the method described previously.[5] Appropriately substituted aniline was treated with sodium cyanate in the presence of glacial acetic acid to yield appropriate phenyl urea. The urea derivative on condensation with hydrazine hydrate in ethanol in the presence of sodium hydroxide gave the appropriate phenyl semicarbazide. The semicarbazones (**1a**–**1e**, **2a**–**2e**) were prepared by reaction of the appropriate aldehyde with appropriate phenyl semicarbazide (Scheme 1). The compounds of this study were identified by spectral data. In general, IR spectra showed the C=N peak at 1610–1590 cm^{-1} and the NH stretching vibrations at 3450 cm^{-1}. The semicarbazone derivatives exhibited characteristic amide bonds at 3300–3240 cm^{-1} and 1700–1670 cm^{-1} and absorption band at 820 cm^{-1} was characteristic of a substituted phenyl ring. The ^1H NMR spectrum revealed that the hydrazine (=NNH) proton attached to the phenyl ring at 8.75–9.6 and the aryl NH proton that showed a singlet at 5.7–6.9 were D_2O exchangeable.

3. Antimycobacterial activity

Primary screening was conducted at 6.25 μg/mL against *M. tuberculosis* strain $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using a broth microdilution assay, the microplate alamar blue assay (MABA).[6] The preliminary results are summarized along with the data for standard drugs such as isoniazid, ethionamide,

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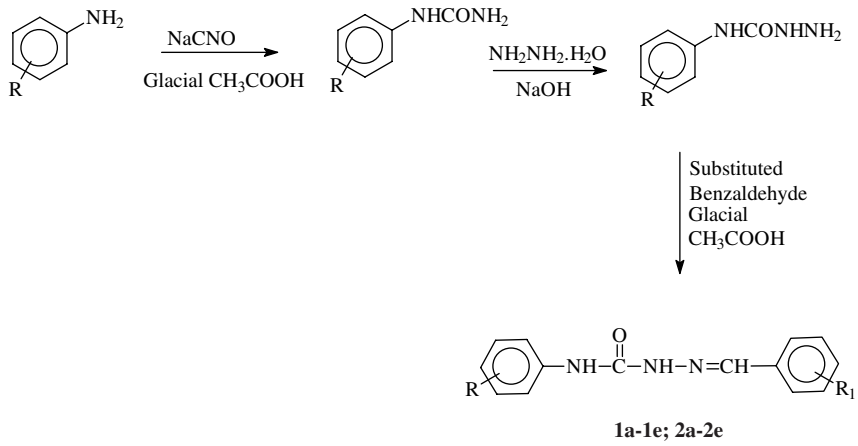
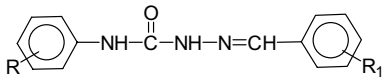


Scheme 1. Synthetic protocol of aryl semicarbazones.

Table 1. Antimycobacterial activity of semicarbazones



Compound	R	R_1	Concentration in μg/mL	Percent inhibition
1a	4-$NHCOCH_3$	2-NO_2	6.25	90
1b	4-$NHCOCH_3$	3-NO_2	1.56	100
1c	4-$NHCOCH_3$	4-NO_2	6.25	95
1d	4-$NHCOCH_3$	2-OH	6.25	5
1e	4-$NHCOCH_3$	4-$N(CH_3)_2$	6.25	2
2a	3-Cl, 2-CH_3	2-NO_2	6.25	10
2b	3-Cl, 2-CH_3	3-NO_2	6.25	58
2c	3-Cl, 2-CH_3	4-NO_2	6.25	24
2d	3-Cl, 2-CH_3	2-OH	6.25	0
2e	3-Cl, 2-CH_3	4-$N(CH_3)_2$	6.25	0
Isoniazid			0.05	95
Ethionamide			2.50	90
p-Aminosalicylic acid			8.00	92
Ethambutol			1.88	90
Ciprofloxacin			2.00	95
Kanamycin			5.00	90
Rifampicin			0.125	95

p-aminosalicylic acid, ethambutol, ciprofloxacin, kanamycin and rifampicin in Table 1. Among the compounds tested **1a**–**c** were found to be the most active compounds against *M. tuberculosis* with percentage inhibition of 90–100%. The MIC for **1b** was 1.56 μg/mL and was more potent than the commonly used antitubercular agents like *p*-aminosalicylic acid, ethionamide, ethambutol, ciprofloxacin and kanamycin. Regarding substituents in the aryl semicarbazone moiety 4-acetamido group was found to be active, whereas 3-chloro 2-methyl substituents were less active or inactive. In the benzaldehyde moiety nitro substituents were found to be useful, among them the order of activity was 3-nitro > 4-nitro > 2-nitro.

4. Conclusion

In the present study we have discovered aryl substituted semicarbazones as a new lead in the antitubercular field. These results need to be refined in terms of active concentration and toxicity. Further studies to acquire more information about structure–activity relationships are in progress in our laboratory.

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References and notes

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