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Short communication

Synthesis and antitubercular activities of substituted benzoic acid *N*′-(substituted benzylidene/furan-2-ylmethylene)-*N*-(pyridine-3-carbonyl)-hydrazides

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ABSTRACT

A series of benzoic acid hydrazones and its nicotinyl derivatives (**1**–**10**) were prepared and evaluated for their antitubercular activity towards a strain of *Mycobacterium tuberculosis* (MTB). The structures of newly synthesized compounds were confirmed by infrared (IR) and ^{1}H-nuclear magnetic resonance (NMR) spectral data and elemental analysis. The *in vitro* antitubercular activity of synthesized compounds against MTB was carried out in Middlebrook 7H11agar medium supplemented with OADC by agar dilution method. The antitubercular activity results indicated that nicotinic acid *N*-(3,5-dinitro-benzoyl)-*N*′-(4-methoxy-benzylidene)-hydrazide (**1**) is the most potent among the synthesized compounds with MIC of 3.5×10^{-3} μM.

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1. Introduction

Tuberculosis (TB) is most serious infectious lung disease in the world, claims over two million lives worldwide each year and dwells hidden in as many as two billion people [1]. It is estimated that between 2005 and 2020, one billion people will be new infected, over 125 million people will get sick and 30 million will die of tuberculosis if control is not further strengthened. The worsening situation has prompted the world health organization (WHO) to declare tuberculosis a global public health crisis [2]. The first line drugs currently used for treatment of tuberculosis are streptomycin, isoniazid, ethambutol, pyrazinamide and rifampicin. Moreover the emergence of multi drug resistant (MDR) strains of *mycobacterium tuberculosis*, which are insensitive to one or more of the first line drugs, isoniazid and rifampicin, has further worsened the situation. Furthermore, the association of TB and HIV infections has caused an urgent need in search of alternative chemotherapeutics for *Mycobacterium tuberculosis* infections [3].

Although many compounds are in clinical trials, it is astonishing that with this background, there have been no new drugs registered to treat TB in the past four decades. This reflects the inherent difficulties in discovery and clinical testing of new agents and the lack of pharmaceutical industry research in this area [4].

There are two basic approaches to develop a new drug for tuberculosis: (a) synthesis of analogue, modifications or derivatives of existing compounds for shortening and improving TB treatment and (b) searching for novel structures that TB organism has never been presented with before, for the treatment of MDR-TB [5].

Hydrazide derivatives represent an overwhelming and rapid developing field in modern medicinal chemistry. A degree of respectability has been bestowed for hydrazide derivatives due to their antimicrobial, antitubercular, antitumour, analgesic and anti-inflammatory, trypanocidal, leishmanicidal, anti-HIV, anthrax lethal factor inhibitory, antidiabetic and antimalarial properties [6–15].

Prompted by these observations and in continuation of our research into bioactive molecules [16–21], we designed the synthesis with a series of substituted benzoic acid N′-(substituted benzylidene/furan-2-ylmethylene)-N-(pyridine-3-carbonyl)-hydrazides (**1**–**10**) with the aim of obtaining more potent antitubercular compounds to improve current chemotherapeutic antitubercular treatments.

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2. Results and discussion

2.1. Chemistry

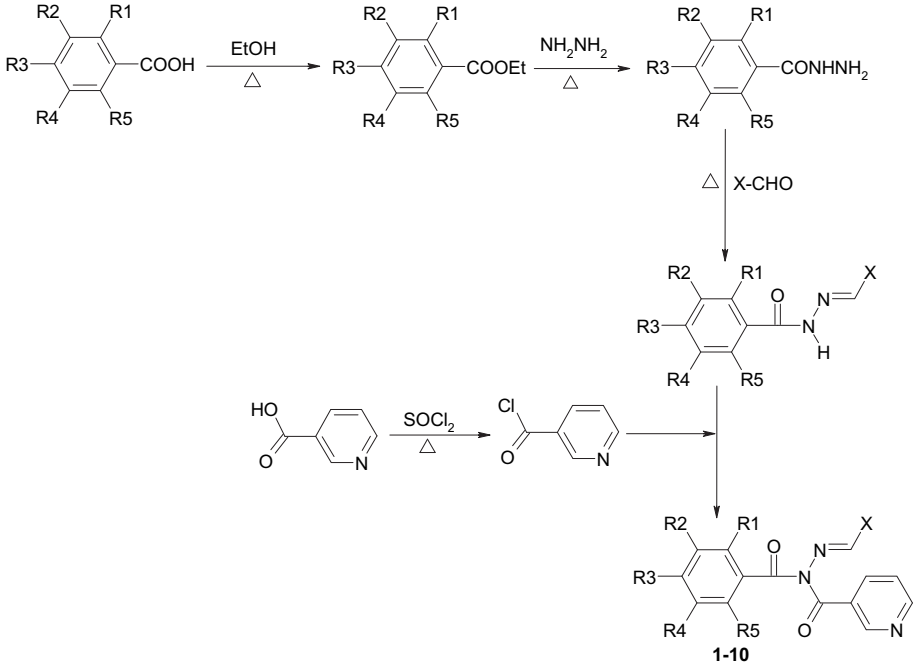
The different carboxylic acids were refluxed with ethanol in the presence of sulphuric acid to yield their ethyl esters. The ethyl ester was refluxed with hydrazine-hydrate in ethanol to yield the corresponding hydrazides. The substituted hydrazides were then condensed with substituted aromatic aldehydes to yield the substituted benzoic acid benzylidene/furan-2-yl-methylene hydrazides. Further the reaction of substituted benzoic acid benzylidene/furan-2-yl-methylene hydrazides with nicotinyl chloride resulted in the formation of title compounds (**1**–**10**) (Scheme 1). It is important to note here that the yield of the synthesized compounds were very poor. The low yield of synthetic compounds may be attributed to any one or more of the following reasons [22]: (a) the reaction may be reversible and position of equilibrium is unfavorable to the product; (b) the incursion of side reactions leading to the formation of by-products; (c) the premature work-up of the reaction before its completion; (d) the volatilization of products during reaction or work-up; (e) the loss of product due to incomplete extraction, inefficient crystallization or other work-up procedures; (f) the presence of contaminants in the reactants or reagents leading to a less efficient reaction. The physicochemical data of synthesized compounds are presented in Table 1. The synthesized compounds were characterized by their IR and ^{1}H-NMR as well by elemental analysis studies. The elemental analysis results were within ±0.4% of the theoretical values.

The appearance of medium out of plane deformation bands (C—C bending) at 738.7 cm^{-1} and 810.9 cm^{-1} indicated the presence of 1,3-disubstituted benzene ring ($ArNO_2$) and 1,4-disubstituted benzene ring ($ArOCH_3$) in compound **4**. In contrast, the 1,3,5-trisubstituted benzene ring (compound **1**) showed C—C out of plane band deformation at 725.2 cm^{-1}. The presence of 3-substituted pyridine in structures of compounds (**1**–**10**) was confirmed by strong out of plane deformation bands (C—H bending) at 820–770 cm^{-1} which were visible from their IR spectra. The presence of aromatic primary amino group is indicated by the existence of NH stretch in compound **6** [3396.4 cm^{-1} (symm.); 3550.0 cm^{-1} (asymm)] and **10** [3404.1 cm^{-1} (symm.); 3535.2 cm^{-1} (asymm)]. Moreover presence of NO_2 group in compounds **1, 4** and **7** were indicated by appearance of asymmetric and symmetric NO_2 stretching bands at 1560–1510 cm^{-1} and 1365–1335 cm^{-1} respectively. The presence of furan-2-ylmethylene group in compound **10** was confirmed by the appearance of IR bands at 920.9 cm^{-1} and 1020.2 cm^{-1} corresponds to CH-out of plane bending and ring breathing respectively. The C=O stretch of tertiary amide of nicotinic acid moiety in synthesized compounds (**1**–**10**) is demonstrated by the appearance of IR absorption band at 1670–1630 cm^{-1}. Further the presence of pyridine ring in the synthesized compounds were confirmed by the presence of IR bands at 1615–1565 cm^{-1} corresponds to C=C and C=N stretching of pyridine ring.

^{1}H-NMR spectra study gave the multiplet signal between 6.50 and 7.70 δ ppm which is indicative of aromatic proton. The compound **1, 4** and **6** showed singlet at δ 3-85–3-95 due to presence of OCH_3 of $ArOCH_3$. Similarly the presence of NH_2 group in compounds **6** and **10** were confirmed by the presence of δ 3.92. The presence of multiplets at δ 7.10–7.40 and 7.83–8.02 indicated the presence of aromatic protons of furan (3H) and benzene (4H) ring of compound **10**. Further the presence of pyridine ring in synthesized compounds (**1**–**10**) was indicated by the appearance of δ at 7.70–9.90.

2.2. Antitubercular activity

The *in vitro* antitubercular activity of synthesized compounds against MTB, was carried out in Middlebrook 7H11agar medium supplemented with OADC by agar dilution method and the results are presented in Table 1. In general the antitubercular activity of synthesized hydrazides (Table 1) were not appreciable except nicotinic acid *N*-(3,5-dinitro-benzoyl)-*N*′-(4-methoxy-benzylidene)-hydrazide (**1**) and nicotinic acid *N*-(2-chloro-5-nitro-benzoyl)-*N*′-(3,4-dimethoxy-benzylidene)-hydrazide (**5**). Compound **1**



Scheme 1. Scheme for the synthesis of substituted benzoic acid *N*′-(substituted benzylidene/furan-2-ylmethylene)-*N*-(pyridine-3-carbonyl)-hydrazides.

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