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ORIGINAL ARTICLE

Synthesis and biological evaluation of pyrimidinyl sulphonamide derivatives as promising class of antitubercular agents

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Nucleophilic chloro cyclocondensation;
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Abstract A small library of compounds are synthesized and evaluated for their *in vitro* antitubercular activity against Mycobacterium tuberculosis H37RV. Two compounds, -[(2′,4′-dinitrophenyl) sulphonyl]-4-(p-aminophenylsulphonylamino)-6-(2′-chlorophenyl)-pyrimidine-5-carboxamide $\mathbf{F_b}$ and 2-hydrazino-4-(p-aminophenylsulphonylamino)-6-(2′-chlorophenyl)-pyrimidine-5-carboxamide $\mathbf{D_b}$ were found to be the most active compounds *in vitro* with MIC of 0.02 μg/mL against MTB and were more potent compared to isoniazid (MIC: 0.03 μg/mL).

1. Introduction

Tuberculosis (TB) is a contagious and airborne disease caused by *Mycobacterium tuberculosis* bacteria. It is a disease of poverty and mostly TB deaths are in the developing world including the majority of adults in their productive years [1]. Tuberculosis is often seen in those people who have weak immune system and it is the major reason of fatality among those infected with HIV [2]. The occurrence of both multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), the indigence for more effective chemotherapy for the treatment of TB [3]. The recent chemotherapy DOTS (directly observed therapy short-course) for TB and DOTS-Plus (DOTS plus Second-line TB drugs) for MDR-TB given compliance treatment has up to 95% cure rate [4,5]. The fatality of the disease owing to the origin of multidrug-resistant TB poses a challenge to build a novel agent to cure the drug resistant type of TB disease [6]. After many attempts in the design and synthesis of new therapeutic agent by pharmaceutical companies and academic institutions, the recent therapeutic agents are inadequate to cure TB [7]. The currently recommended treatment for latent TB infection is isoniazid given for six to nine months. The long duration of this therapy and the potential toxicities of isoniazid means there is a major compliance problem associated with the treatment regimen. Although new drugs are needed to shorten the duration of treatment of latent TB infection, the safety profile for these drugs must be excellent, because

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most patients with latent infection are destined never to experience activation of their TB [8]. Therefore, the need for newer, more effective drugs that can achieve multiple goals in improving TB control is pressing. Recognizing these serious facts, we initiated a programme to synthesize and screen diverse heterocyclic entities like pyridines, phenothiazines and pyrimidines as potential anti-tubercular agents. Based on our previous results [9,10,11,14], we set upon a programme of making antitubercular agents, using the central dihydropyrimidine as the template and adding versatile substituents on the various positions of dihydropyrimidine ring and subjected them to antimycobacterial screening.

Over the years, molecular hybridization based drug design approach [12] has been exploited by many researchers in order to develop some promising new hybrid chemical entities (NHCEs), displaying significant therapeutic values. The combination of two pharmacophores into a single molecular skeleton is a well established approach for designing more potent drugs with a significant increase in activity. A hybrid molecule acting on manifold targets is considered to be a better drug candidate than drug combinations, since administration of single drug will have more predictable pharmacokinetic and pharmacodynamic properties with improved patient compliance [13].

Owing to their well appreciated antitubercular and antimicrobial properties, we envisaged to design hybrid structures having substituted pyrimidine and sulphonamide motifs connected with a linker (Scheme 1). Therefore, in view of the above facts and in continuation of our search on biologically active hybrid molecules [9,14], herein we report the synthesis of novel hybrid analogues ($\mathbf{A_{a-h}}$ to $\mathbf{F_{a-h}}$) with their subsequent antimycobacterial screening against Mycobacterium tuberculosis H37Rv (ATCC 27294) in BACTEC 12B medium using the microplate alamar Blue® assay (MABA). The above facts reveal that it is a crucial situation to fight against TB hence to develop a new therapeutic agent which is more potent than the existing drug and have a new mode of action (see Schemes 2–4).

2. Experimental

2.1. Materials and methods

All research chemicals were purchased from Sigma–Aldrich and used as such for the reactions. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel GF254 plates from E-Merck Co and compounds visualized either by exposure to UV. Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on SHIMADZU-FTIR-8400 spectrophotometer using the KBr pellet method. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300-MHz NMR spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectrum was recorded on a JOEL SX 102/DA-600-Mass spectrometer and elemental analysis was carried out using a Heraus C,H,N rapid analyser.

2.1.1. Preparation of 2-mercapto-4-amino-5-cyano-6-(aryl)-1,6-dihydropyrimidine (*1*)

A mixture of substituted aromatic aldehyde (0.01 M), malononitrile (0.01 M), thiourea (0.01 M) and con. HCl (3 ml) in ethanol (30 ml) was heated under refluxed condition for 4 h. Then the reaction mixture was kept at room temperature for 2 h. The yellow crystalline product was obtained. The product was isolated and recrystallized from ethanol. Similarly, other compounds ($\mathbf{1_{a-h}}$) were synthesized.

2.1.2. Preparation of 2-mercapto-4-amino-6-(aryl)-pyrimidine-5-carboxamide (*2*)

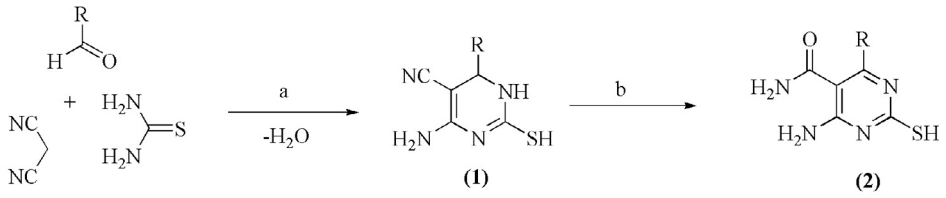
A mixture of **(1)** (0.01 M) was dissolved in conc. sulphuric acid (20 ml) below 5 °C and kept for 48 h. at room temperature. The content was poured into ice cold water and filtered. The product was isolated and crystallized from ethanol. Similarly, other compounds ($\mathbf{2_{a-h}}$) were synthesized.

2.1.3. Preparation of 2-mercapto-4-(p-acetamidophenylsulphonylamino)-6-(aryl)-pyrimidine-5-carboxamide (*3*)

A mixture of **(2)** (0.01 M) and p-acetamidophenylsulpho nylchloride (0.01 M) in pyridine (15 ml) was heated under refluxed condition for 12 h. Then the reaction mixture was poured into crushed ice. The product so obtained was recrystallized from ethanol. Similarly, other compounds ($\mathbf{3_{a-h}}$) were synthesized.

*2.1.3.1. Preparation of 2-mercapto-4-(p-aminophenylsulphonylamino)-6-(aryl)-pyrimidine-5-carboxamide (**A_{a-h}**).* A mixture of **(3)** (0.01 M) and con. HCl (4 ml) in ethanol (25 ml) was heated under refluxed condition for 6 h. Then the reaction mixture was poured into crushed ice. The product so obtained was recrystallized from ethanol.

*2.1.3.1.1. 2-Mercapto-4-(p-aminophenylsulphonylamino)-6-phenyl-pyrimidine-5-carboxamide (**A_a**).* Yield (47%), mp 170–172 °C; ^{1}H NMR ($CDCl_3$) δ = 2.79 (s, 1H, SH), 4.76 (s, 2H, NH_2), 6.43–6.45 (m, 2H, Ar-H), 7.06 (s, 2H, NH_2), 7.39–7.42 (m, 3H, Ar-H), 7.42–7.43 (d, 2H, Ar-H, J = 4 Hz), 7.49–7.51 (m, 2H, Ar-H), 7.62 (s, 1H, NH); ^{13}C NMR (δ) 178.1, 170.9, 168.8, 167.8, 151.2, 132.8, 129.8, 129.2, 128.7 128.3, 127.1, 116.1, 109.3; Anal. Calcd: C, 50.86; H, 3.77; N, 17.44; O,



Condition: **(a)** Methanol, HCl and refulx **(b)** Conc. H_2SO_4 at 0°C

Scheme 1