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Synthesis, antimycobacterial and antifungal evaluation of some new 1-ethyl-5-(hetero)aryl-6-styryl-1,6-dihydropyrazine-2,3-dicarbonitriles

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ABSTRACT

The Petasis reaction of 6-hydroxy adducts of 1-alkyl-2,3-dicyano-5-arylpyrazinium salts with *trans*-styrylboronic acids proved to proceed smoothly at room temperature to give the corresponding 5-(hetero)aryl-6-styryl substituted 1,6-dihydropyrazine derivatives. Also it has been found that C(6) unsubstituted 1,6-dihydro- or 1,4,5,6-tetrahydropyrazine derivatives can be easy prepared in high yields from the corresponding pyrazinium salts by reduction with triethylsilane. All synthesized compounds were screened in vitro for their antifungal activities against seven pathogenic fungal strains and antimycobacterial activities against *Mycobacterium tuberculosis* $H_{37}Rv$, *avium*, *terrae* and multi-drug-resistant strains isolated from tuberculosis patients in the Ural region (Russia).

Tuberculosis is a severe illness resulting from infection with *Mycobacterium tuberculosis* (MTB). During the last decade a number of incidences of tuberculosis have been increasing rapidly worldwide due to diffusion of multi-drug resistant strains of *Mycobacterium tuberculosis*. In 2012, more than eight million people contracted tuberculosis and more than one million died from the disease, mainly in the underdeveloped countries.[1] Therefore, new effective and safety drugs against tuberculosis, acting through novel mechanisms, are urgently needed for a combination chemotherapy, capable of improving efficacy and delayed onset of resistance. We have recently reported on the synthesis a new series of 5-arylethenyl-4-(het)arylpyrimidines (Fig. 1), which exhibit a good level of activity against multidrug-resistant strain of *Mycobacterium tuberculosis* and a low acute toxicity in white mice.[2] On the other hand, it has been shown that 5-aryl-6-hetaryl substituted 1,6-dihydropyrazine derivatives (Fig. 2) also posses a high antituberculosis activity against *Mycobacterium tuberculosis* $H_{37}Rv$, *avium, terrae* and clinical extensively drug-resistant (XDR) and multi-drug-resistant (MDR) strains.[3]

Based on these data we deemed interesting to investigate the antitubercular activity of novel 1-ethyl-5-(hetero)aryl-6-styryl-1,6-dihydropyrazine-2,3-dicarbonitriles, characterized by replacement of the (hetero)aryl with the styryl group at C(6) position of the pyrazines ring. Also we have planned to compare the obtained biological data with the results for reduced 1-ethyl-5-(hetero)aryl-1,6-dihydropyrazine-2,3-dicarbonitriles. All dihydropyrazines obtained were screened in vitro for their antimycobacterial activities against *Mycobacterium tuberculosis* $H_{37}Rv$, *avium, terrae* and XDR and MDR strains isolated from tuberculosis patients in the Ural region (Russia). It has been found that some of these compounds exhibit a high tuberculostatic activity comparable with that of pyrazinamide.

We have earlier carried out the research study[3] aimed at modification of 6-hydroxy adducts **2a–c** of 1-ethyl-2,3-dicyano-5-(hetero)arylpyrazinium salts **1a–c** by action of various aromatic boronic acids, proceeding according the Petasis reaction[4] (Scheme 1).

The aim of the present study is to examine an opportunity for further modifications of 6-alkoxy adducts **2a–c** with *trans*-2-styrylboronic acids **4** and **5**. It has been established that compounds **2a–c** react readily with *trans*-2-phenylvinylboronic **4** and

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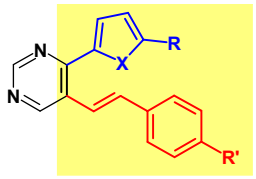


Figure 1. The structures of antitubercular 5-arylethenyl-4-(hetero)arylpyrimidines.

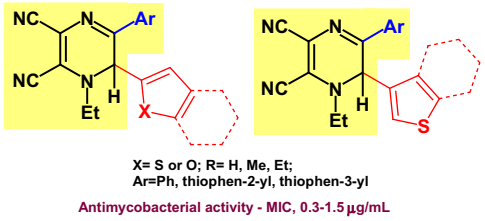


Figure 2. 1-Ethyl-2,3-dicyano-5-(hetero)aryl-6-heteroaryl-1,6-dihydro-pyrazines exhibiting antitiberculosis activity.

trans-2-(biphenyl)vinylboronic **5** acids under mild conditions (CH_2Cl_2, 20 ÷ 25 °C, 24 h) to give 1-ethyl-5-(hetero)aryl-6-styryl-1,6-dihydropyrazine-2,3-dicarbonitriles **6a–c** and 1-ethyl-5-(hetero)aryl-6-thiophen-3-yl-1,6-dihydropyrazine-2,3-dicarbo-nitriles **7a–c** in good yields 77–92% (Scheme 2).

Unequivocal evidence for the structures of all 5-(het)aryl-6-styryl-substituted dihydropyrazines has been obtained by means of ^1H and ^{13}C NMR spectroscopy, and X-ray crystallography analysis performed for racemic 6-(biphenyl-4-yl-vinyl)-1-ethyl-5-thiophen-2-yl-1,6-dihydropyrazine-2,3-dicarbonitrile (**7b**) and 6-(biphenyl-4-yl-vinyl)-1-ethyl-5-thiophen-3-yl-1,6-dihydro-pyrazine-2,3-dicarbonitrile (**7c**) (Figs. 3 and 4).

To prepare 1,2-dihydropyrazines mild reducing agents can be used. For example, it has previously been shown that the regioselective reduction of 3-substituted *N*-acylpyrazinium salts with *n*-Bu_3SnH leads to the corresponding 3-substituted 1,2-dihydropyrazines in good yields.[5] 1-Ethyl-5-(het)aryl-1,6-dihydropyrazine-2,3-dicarbonitriles **8a–c** were obtained by the reaction of 1-ethyl-2,3-dicyano-5-(hetero)arylpyrazinium tetra-fluoroborates **1a–c** with 1 equiv of triethylsilane (Et_3SiH) in dry CH_3CN at room temperature (Scheme 3). It has been found that in these reactions 1-ethyl-5-(hetero)aryl-1,4,5,6-tetrahydro-pyrazine-2,3-dicarbonitriles **9a–c** are formed as by-products. In order to prove the structure

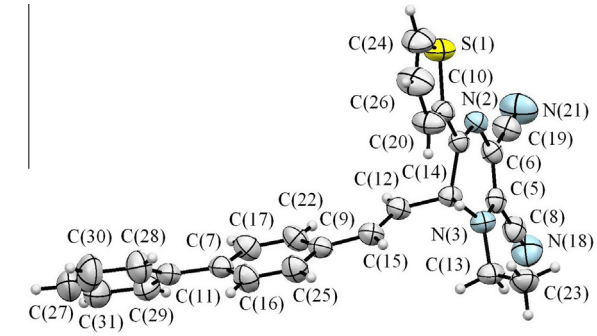


Figure 3. X-ray structure of (±)-**7b**.

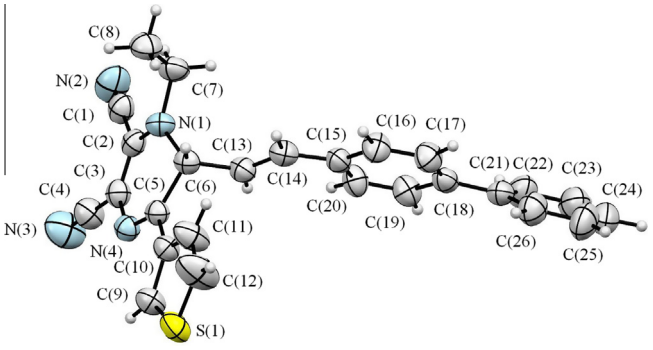
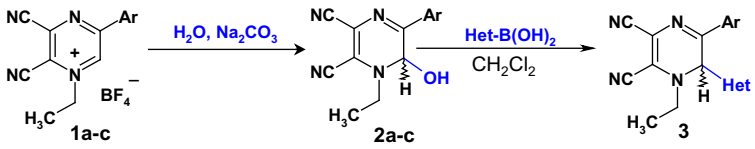
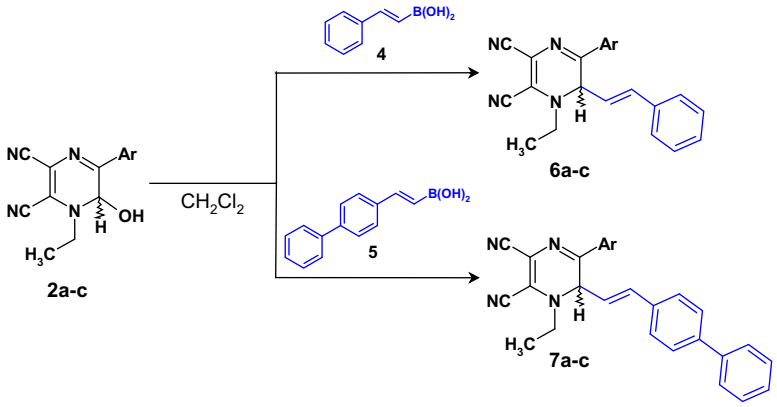


Figure 4. X-ray structure of (±)-**7c**.



Scheme 1. Ar = a: Ph, b: thiophen-2-yl, c: thiophen-3-yl. Het=thiophen-2-yl, thiophen-3-yl, benzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, furan-2-yl.



Scheme 2. Ar = a: Ph, b: thiophen-2-yl, c: thiophen-3-yl.