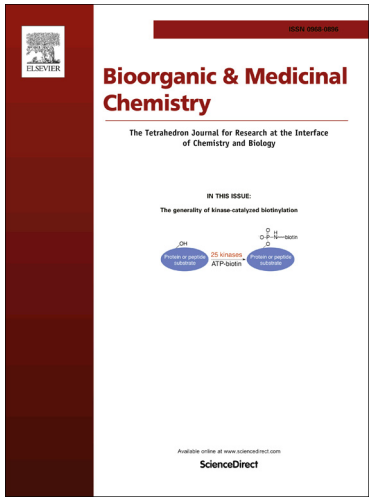

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Synthesis and evaluation of antitubercular activity of fluorinated 5-aryl-4-(hetero)aryl substituted pyrimidines

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ABSTRACT

Various 5-(fluoroaryl)-4-(hetero)aryl substituted pyrimidines have been synthesized based on the Suzuki cross-coupling and nucleophilic aromatic substitution of hydrogen (S_N^H) reactions starting from commercially available 5-bromopyrimidine and their antitubercular activity against *Mycobacterium tuberculosis H37Rv* has been explored. The outcome of the study disclose that, some of the compounds have showed promising activity in micromolar concentration against *Mycobacterium tuberculosis H37Rv*, *Mycobacterium avium*, *Mycobacterium terrae*, and multidrug-resistant strains isolated from tuberculosis patients in Ural region (Russia).The data concerning the "structure - activity" relationship for fluorinated compounds have been discussed.

1. Introduction[1]

Fluorine-containing compounds, especially of heterocyclic nature, have gained attention as biologically actives, and, indeed, many of them are well presented in pharmaceutical market [1-11]. In particular, a great variety of effective antibacterial agents have the structure of fluoroquinolones [1,2,7-14]. In fact, some of the anti-microbial compounds have fluorine atom in their structure [15]. The presence of a fluorine atom in the structure of organic molecules has been shown to modulate their stereoelectronic parameters [14,15]. Further incorporation of fluorine atom not only alters their electronic environment, but also affects pKa value of the neighboring Brønsted acid/base centers, polarity, and lipophilicity, as expressed by the distribution coefficient. Fluorine substituents in bioactive molecules appear to improve often their pharmacological properties, such as better membrane permeability, enhanced hydrophobic binding, and a good stability towards metabolic transformation. This is why development of new fluorine-containing antimycobacterial agents is continued interest for chemists and biologists [18-23].

In continuation of our previous studies in the field of pyrimidine derivatives, as potential antimycobacterial compounds [24-26], we wish to report the synthesis of new 5-(fluoroaryl)-4-(hetero)aryl substituted pyrimidines. In this paper we intend to discuss the effects a fluorine atom or CF_3-group at C(2) and/or C(4) positions on the phenyl substituent in 5-(fluoroaryl)-4-(hetero)arylpyrimidines on their antibacterial activity against *M. tuberculosis*, and other pathogenic strains, such as *M. avium*, *M. terrae*.

2. Results and discussion

2.1. Chemistry

The desired 5-(fluoroaryl)-4-(hetero)aryl substituted pyrimidines have been synthesized based on the palladium-catalyzed Suzuki cross-coupling reaction and nucleophilic aromatic substitution of hydrogen (the S_N^H reaction) [27,28].

Initially 5-(fluoro-aryl)pyrimidines (**3b-k)** were obtained by reacting 5-bromopyrimidine (**1**) with various fluorinated benzeneboronic acids **(2b-k)** by using the aerobic Suzuki cross-coupling reaction conditions in the presence of a new catalyst, namely *trans*-bis(dicyclohexylamine)palladium(II) acetate (DAPCy) (Scheme 1, Table 1) [28]. Whereas 5-phenyl-pyrimidine (**3a**) was obtained from unsubstituted phenylboronic acid (**2a**) by using the method A, as a reference compound for comparison of biological activity (Scheme 1).

Here, we would like to mention that, when the benzeneboronic acid with fluorine substitution at C(2) position (e.g. 2-F-, 2,4-F-, 2-CF_3- or 2,4-CF_3-) reacted with 5-bromopyridine under

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