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Synthesis and antimycobacterial activity of *N*-(2-aminopurin-6-yl) and *N*-(purin-6-yl) amino acids and dipeptides

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ABSTRACT

Synthetic routes to novel *N*-(purin-6-yl)- and *N*-(2-aminopurin-6-yl) conjugates with amino acids and glycine-containing dipeptides were developed. *In vitro* testing of 42 new and known compounds made it possible to reveal a series of *N*-(purin-6-yl)- and *N*-(2-aminopurin-6-yl) conjugates exhibiting significant antimycobacterial activity against *Mycobacterium tuberculosis H37Rv*, *M. avium*, *M. terrae*, and multidrug-resistant *M. tuberculosis* strain isolated from tuberculosis patients in the Ural region (Russia). *N*-(2-Aminopurin-6-yl)- and *N*-(purin-6-yl)-glycyl-(*S*)-glutamic acids were the most active compounds.

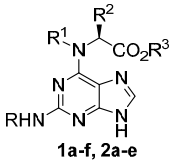
Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. TB is a major global health problem. It is one of the leading causes of death worldwide.[1] Every year TB kills 1.5 million people. In 2014, there were an estimated 9.6 million new TB cases.[1b] Despite a substantial progress in TB diagnostics and treatment, the resistance to the standard anti-TB drugs is still growing. Thus, in 2014, there were an estimated 480,000 new cases of multidrug-resistant TB (MDR-TB) worldwide and approximately 190,000 deaths from MDR-TB.[1b] So, the search for new efficient anti-TB agents with a new mechanism of action remains an urgent task.[2]

Due to the important role of purine nucleobases in the metabolism of living organisms, purine derivatives seem to be a promising class of compounds for design of new drugs based thereon. It has been found that some derivatives of purine[3] and 6-aminopurine[4] exhibit high activity against *M. tuberculosis*. At the same time, the mechanism of antimycobacterial activity of purine derivatives remains currently unclear.[3c, 5]

Modification of various biologically active compounds by introduction of amino acid moieties into their structure is one of the most important approaches to achieve the optimal pharmacokinetic and pharmacodynamic characteristics of potential drugs.[6] Recently, the study of amino acid-containing nucleobases as mycobacteria growth inhibitors has attracted considerable interest; it has been reported that some purine conjugates with amino acid derivatives possess antibacterial properties.[3c, 7]

The purpose of this work was to obtain the 2-aminopurine and purine conjugates with amino acids and short peptides and to study their ability to inhibit the growth of *M. tuberculosis* in experiments in vitro.

Derivatives of N^{α}-(2-aminopurin-6-yl)amino acids **1a-f** and **2a-e** (Fig. 1) were obtained by us earlier.[8] Compounds **1b-f** and **2b-e** were synthesized starting from *tert*-butyl esters of (*S*)-amino acids (alanine, valine, phenylalanine, proline and aspartic acid) and had *S*-configuration.



1a-f, 2a-e

1a-f: R = Ac, R^3 = *t*-Bu
2a-e: R = R^3 = H

1a, 2a: $R^1 = R^2 = H$
1b, 2b: R^1 = H, R^2 = Me
1c, 2c: R^1 = H, R^2 = *i*-Pr
1d, 2d: R^1 = H, $R^2 = CH_2Ph$
1e, 2e: R^1-$R^2 = (CH_2)_3$
1f: R^1 = H, $R^2 = CH_2CO_2t$-Bu

Figure 1. Structures of N^{α}-(2-aminopurin-6-yl)amino acid derivatives.

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