Abstract

COMPOUNDS COMBINING PYRAZINAMIDE AND *P*-AMINOSALICYLIC ACID FRAGMENTS AS POTENTIAL ANTITUBERCULARS II

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A series of new compounds combining pyrazinamide and *p*-aminobenzoic acid was prepared and *in vitro* tested for antimycobacterial activity against *M. tuberculosis*, *M. avium, M. kansasii, M. aurum* and *M. smegmatis.* Previously prepared 4-(5-chloropyrazine-2-carboxamido)-2-hydroxybenzoic acid (R^1 = OH) exerted micromolar activity against *M.tuberculosis* and low *in vitro* cytotoxicity in HepG2 cells.

Para-Aminosalicylic acid (PAS) has significant antitubercular properties based on its resemblance to *p*-aminobenzoic acid and interference with the folate pathway in mycobacteria. To assess the role of the PAS fragment, we designed and prepared derivatives with modified substitution on the phenyl ring (R^1). Further modification was the exchange of 5-Cl on the pyrazine core for (alkyl)amino substituent (**JZ-OZ)**, which was a successful modification in previous series. Final compounds were described by melting point, elementary analysis, IR spectroscopy and ^{1}H, ^{13}C NMR.

Changing the PAS fragment, when we removed or replaced the OH-group at position 2, the antimycobacterial activity decreased. By masking the functional groups - COOH and - OH (we prepared internal cyclic ester), the antimycobacterial activity did not reduce. The longer the alkylamino chain on the pyrazine core, the higher lipophilicity of the compound. This could affect the penetration through the cell membrane.

New compound 2-hydroxy-4-(5-(propylamino)pyrazine-2-carboxamido)benzoic acid **(JZ-OZ-2)** proved the best (micromolar) activity against *M. tuberculosis* (MIC= 0,78 μg.ml^{-1}).

The importance of the PAS fragment and the advantage of the longer alkylamino chain were confirmed. Structure-activity relationships were discussed.