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Stability, activation and antymycobacterial activity of pyrazinoic acid esters

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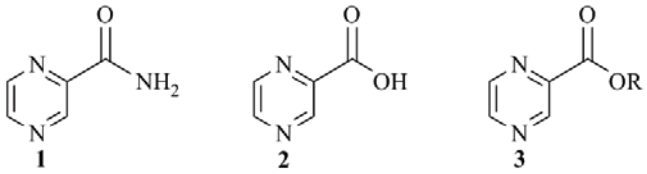
Tuberculosis is a leading infectious cause of morbility and mortality world-wide, especially in developing countries Pyrazinamide (PZA), a first line agent for the treatment of tuberculosis, is itself a prodrug that requires activation by the bacterial pyrazinamidase to form its active metabolite pyrazinoic acid (POA) 2, which has poor absorption and significant serum binding. Resistance to PZA is attributed to mutations in the mycobacterial gene encoding pyrazinamidase. Since PZA is in fact a prodrug of POA, other prodrugs, like esters 3, could have activity against M. tuberculosis. These esters could circumvent resistance to PZA because they are activated by different mycobacterial enzymes.



Pyrazinamide (PZA), Pyrazionoic acid (POA) and Pyrazinoate esters

In order to be effective in vivo, these compounds must be resistant to hydrolysis by the human enzymes – (eg. plasma and liver esterases) - but should be readily hydrolyzed by the mycobacterial enzymes at the site of action. Using model esters we were able to select appropriate groups that slow plasma and liver hydrolysis of the prodrugs but do not affect the mycobacterial activation of the compounds and we pursued the work with the synthesis of a series of lipophilic esters. Results on the stability, plasma hydrolysis and antimycobacterial activity of the prodrugs will be presented.

Biography

Luis Constantino is a Ph.D in Medicinal Chemistry and is a Lecturer (Prof. Auxiliar) at the University of Lisbon. He has worked for the University since he earned his degree in Pharmacy. He is an expert at patents related issues in his field and is also an expert for the EMEA. His current research interests are drug metabolism and drug development.

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