

RETHINKING THE OLD AND TRUSTWORTHY – NEW DRUGS FOR TB

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Novel approaches linking drug candidates to gene association studies are needed to overcome the threat posed by the emergence of drug-resistant *M. Tuberculosis* (MTB). More effective agents against multidrug resistant tuberculosis (MDR-TB) able to shorten the duration of treatment are needed, particularly those targeting the eradication of the latent form of TB.

Drug development with an existing drug as lead compound, with efficacy improvement through structure-based successful manipulation, can be considered an attractive strategy from the economic, pharmaceutical and clinical points of view (1,2).

The rifamycin state-of-the-art suggests that even considering that these drugs display many admirable qualities it is quite possible to devise improved rifamycin analogs against MTB.(3).

The extensive drug-drug interactions seen with rifampin (RFP) have already been somewhat ameliorated with rifabutin (RFB). RFB is a semi-synthetic spiro-piperidyl derivative of ansamycin family of antibiotics (4,5,6).

Aiming to improve its pharmacological properties, novel RFB analogs have been synthesised and tested *in vitro* against *M. tuberculosis* strains.



Figure1: General structure of the new rifamycins synthesized

1. Almeida da Silva, P. E. *et al.*, *Int. J. Antimicrob. Ag.*, 2008, 32:139-144.
2. Barluenga, J. *et al.*, *Bioorg. Med. Chem. Lett.*, 2006, 16:5717-5722.
3. Aristoff, P. A. *et al.*, *Tuberculosis*, 2010, 90:94-118.
4. Moghazeh, S. L. *et al.*, *Antimicrob. Agents Ch.*, 1996, 40:2655-2657.
5. Park, Y. K. *et al.*, *Int. J. Tuberc. Lung D.*, 2002, 6:166-170.
6. Yang, B. *et al.*, *J. Antimicrob. Chemother.* 1998, 42:621-628.

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