



# Slovenian NMR Centre

@ National Institute of Chemistry

vabi na SEMINAR:

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z naslovom:

### Design, Synthesis and Activity of New Multiple Drug Resistant Anti-TB Molecules

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#### Kratek povzetek:

Tuberculosis (TB) is caused predominantly by *Mycobacterium tuberculosis* (*Mtb*), which is a life-threatening chronic infection primarily affecting the lungs. It is the greatest cause of mortality and morbidity worldwide. The WHO has reported that 1/3 (nearly 2 billion) of the world population is already infected with TB *bacilli*, which is slowly developing resistance to all frontline drugs giving Multiple Drug Resistant (MDR) and the Excessive Drug Resistant (XDR) strains. Hence, it is generally argued that there is indeed an urgent need to discover new drugs against this deadly disease, which works synergistically with the immune compromised HIV infected patients.

Newly discovered highly potent Diaryl Quinoline-based anti-TB compound TMC207 is currently in phase II clinical trials. It has unique mechanism of action in that it targets the proton pump of ATP synthase of *Mtb* (MIC = 0.030 µg/mL, *Science* **2005**, 307, 223). It has however at least two serious limitations in that the overall yield of the active *R,S* isomer of TMC207 is only 0.17% which requires expensive chiral chromatographic separation, and it also shows drug-drug interactions with Rifampicin, which limits its use with the most important frontline drugs.

In order to develop novel antituberculosis drugs, we have analyzed TMC207 and its complex with ATPase and have synthesized so far >600 new molecules with new scaffolds (putative ATP synthase inhibitors). Our molecules have shown the minimum inhibitory concentrations (MIC) in range of 0.2-6.25µg/mL, which suggests that these molecules have a great potential to be anti-TB "lead" [International Patent Application No. PCT/SE2009/050008].

References: Chattopadhyaya *et al.*, *Eur. J. Med. Chem.* 45, 1854-1867, (2010); *Bioorg. Med. Chem.* 17, 4681-4692, (2009); *ibid* 17, 2830-2841 (2009); *ibid* 18, 2180-2197 (2010).

Predavanje bo v angleščini.

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