ANTI-TUBERCULAR ACTIVITY OF NEW COMPOUNDS

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Purpose of the study. Multi-drug resistant (MDR) and extensively drug resistant (XDR) tuberculosis is a worldwide alarming health problem, as infections in immuno-compromised hosts are; there is an urgent need for new molecules as effective anti-tubercular drugs. Different strategies are being applied to find new drugs. Molecular dynamics simulations were performed to design and synthesise new compounds endowed of anti-tubercular activity. Plant extracts described in folk medicine are a source for natural compounds that can act as new anti-tubercular agents, therefore some plant derivatives were studied for *Mycobacterium* killing activity: newly purified and chemo-enzymatically modified glyceroglycolipids from *Euphorbia*; usnic acid, a main well known lichen metabolite; β-lapachol, a lipophilic *o*-naphthoquinone obtained by sulfuric acid treatment of the naturally occurring compound from *Tabebuia avellanedae*..

Methods. Molecular modelling was performed as described (JAC, 2006) in order to design 16 new compounds that were synthesised by an original synthesis pathway and chemically characterised. Plant extracts were obtained as already described (Bioorg Med Chem, 2006; Biochem Pharmacol, 1996). The killing activity of all compounds was evaluated against *M. tuberculosis* H37Rv, *M. avium* 551 and a panel of *Mycobacterium spp* clinical isolates with different antibiotic susceptibility. Minimal inhibiting concentration of each compound was determined by agar dilution method and by a standardised micro-dilution resazurin assay as described (JAC, 2003).

Results and Conclusions. Some compounds had a killing activity against *M tuberculosis* clinical strains, with a MIC range of 2-32 μg/ml; some had a growth inhibiting activity against *M. avium* with a MIC range of 8-32μg/ml. Studies are being performed on the survival of intracellular mycobacterium bacilli and on infected macrophage viability in the presence of combinations of different referencet drugs and new compounds.

The promising *in vitro* anti-tubercular activity of some molecules will prompt us to evaluate their molecular mechanism of action and additional pharmacological effects in different *in vivo* models.