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NOVEL 4-AMINOSALICYLIC ACID ANALOGUES ACTIVE AGAINST MULTIDRUG-RESISTANT TUBERCULOSIS

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Spread of drug-resistant *Mycobacterium tuberculosis* (*Mtb.*), together with latent tuberculosis (TB), COVID-19 co-infection and increasing prevalence of non-tuberculous mycobacteria (NTM), is a serious threat for public health justifying a strong need for new antimycobacterial agents. Modification of established drugs to obtain derivatives with improved properties represents a viable approach[1].

p-Aminosalicylic acid (PAS) is a prodrug targeting folate biosynthesis used for treatment of TB. Recently, we have published three promising PAS derivatives and their peptide conjugates as antitubercular agents[1].

Therefore, we have designed a series of novel imines and ureas based on PAS scaffold (free acid, esters, amides). Ureas were prepared from aliphatic, alicyclic, and phenylalkyl isocyanates, imines from halogenated salicylaldehydes in good yields. Some compounds were prepared to be conjugable with oligotuftsin-based peptides to improve especially their cellular uptake. Peptides were prepared by solid phase synthesis and coupled with small molecules on resin or in solution[1].

The compounds were evaluated against a panel of mycobacteria (H_{37}Rv and drug-resistant *Mtb.*, NTM) and other microbes, for their cytotoxic/cytostatic action, cellular uptake and intracellular antimycobacterial activity.

Our PAS derivatives inhibited all mycobacterial strains with MIC ranging from 1 μM including multidrug- and extensively resistant TB strains (MIC ≥2 μM). In general, they showed higher potency than the parent PAS. Ureas were more active than imines, favouring *n*-alkyls from C_8 to C_{13}, cycloheptyl and 1-adamantyl. Most derivatives lacked cytotoxic or cytostatic effect on eukaryotic cell lines (e.g., HepG2, MonoMac6). Their coupling with oligotuftsin peptides improved physicochemical properties, cellular uptake, and intracellular activity against mycobacteria. Their mechanism of action is under investigation.

The project National Institute of virology and bacteriology (Programme EXCELES, ID Project No. LX22NPO5103) – Funded by the European Union – Next Generation EU.

REFERENCES

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