Perspectives for anti-tuberculosis therapy with additional drug activities to counteract drug resistance

Generally, antibiotic therapies use single antibiotics to combat sensitive bacteria.

The standard of antituberculosis therapy includes four antibacterial agents that all have different modes of activities in the initial phase of a tuberculosis infection with mycobacterium tuberculosis.

So the antituberculosis therapy combines different drugs to ensure a safe antibacterial therapy that reduces a potential drug resistance by combining drugs with additive effects. With the limited number of the used drugs there have been immense efforts to find drugs with a novel mode of antibacterial action.

Similar to the antibacterial therapies with single drugs also the treatment of tuberculosis is possible by the use of only few reserve antibiotics. Clofazimine as save drug belongs to that group with a broader use also in the therapy of leprosy.

Perspective novel drug development?

We synthesized novel 1,4-dihydropyridines that deviate from classical 1,4-dihydropyridines with a nitrogen substitution and without methyl group substitutions at the molecular scaffold to promise undesired pharmacological activities compared to those classical 1,4-dihydropyridines.

The novel presented compounds were accessible in a simple one-pot reaction that means a reaction by mixing the reacting compounds in one reaction flask under heating conditions in alcohol and under acetic acid catalysing conditions. So in one procedure step the target compounds were yielded and also in one step they were purified that means a favourable compound access and spares several consecutive steps of reaction and final compound purification to be attractive for a later production.

In order to get close insight in a potential activity substituent effects have been investigated to influence the mycobacterial growth inhibition activity in a compound screening with a fixed concentration. Favourable substituents have been methoxy functions added at the 4-phenyl residue of the molecular scaffold at the 3-position or at the 4-position of the nitrogen phenyl residue.

Perspective novel drug enhancing activities?

Enhancers of antibacterial drug activities are rare. Such enhancers would be of great favour for therapy because a lower drug concentration in use would reduce the risk for a drug resistance development. Important target structures that mediate an antibacterial drug resistance are

transmembrane efflux pumps that transport the drugs as substrates out of the cells so that effective intracellular drug levels for therapy are no longer reached. In case of an inhibition of such an efflux pump activity the efflux pump mediated resistance would be successfully combated.

Classical 1,4-dihydropyridines have been identified as inhibitors of the human efflux pump P-glycoprotein. We evaluated our novel compounds as inhibitors of P-glycoprotein in a cell line model with sensitivity for the special inhibition of P-glycoprotein and identified such activities.

In case of the inhibition of a mycobacterial efflux pump similar to P-glycoprotein the application of our compounds would be of benefit in use of an antituberculostatic drug as substrate of that efflux pump. Clofazimine is a known substrate of P-glycoprotein and so it was used to investigate a drug enhancing activity by the use of our compounds as inhibitors of such a relevant efflux pump.

From our investigated compounds we used such compounds that showed P-glycoprotein inhibiting effects and practical no mycobacterial growth inhibition. Two compounds with a lower inhibition of P-glycoprotein enhanced the mycobacterial growth inhibition of the used clofazimine drug by 44%. A compound with a higher P-glycoprotein inhibitory activity resulted in an increase of the clofazimine growth inhibition with 55%. Another compound in use with a low mycobacterial growth inhibition and a lower P-glycoprotein inhibition increased the clofazimine growth inhibition to a similar extent.

We identified a novel compound class with mycobacterial growth inhibition activities that is able to increase the activity of clofazimine. So they show a dual inhibition of worth to prevent or combat a drug resistance development by enhancing the respective antituberculostatic drug activity.

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Publication

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