Oxa- and thiadiazoles useful on the treatment of drug-susceptible and multidrug-resistant tuberculosis

Advantages and Innovations

Series of oxa- and thiadiazoles:

• are easily accessible in large-scales via simple synthetic procedures
• have high antmycobacterial effect (MIC = 0.03 – 0.2 µM) against drug-susceptible and multidrug-resistant mycobacteria, with no-cross resistance with common antituberculosis drugs
• have mechanism unequal to novel nitro-group containing antitubercular agents benzothiazinones and nitroimidazoles (e.g. delamanid, PA-824)
• have highly selective action - no in vitro effect against bacterial and fungal strains, low toxicity against human cell lines (including isolated human hepatocytes)
• lead compound (T6053) does not display any genotoxicity in human peripheral lymphocytes
• Acute Oral Toxicity – Fixed Dose Procedure. According to the study results the value of LD50 (oral) of T6053, (in female rats) is higher than 1000 mg/kg of body weight
• Repeated Dose (14 days) Toxicity (Oral) of T6053 (GLP principles [OECD Principles of Good Laboratory Practice (as revised in 1997), C (97) 186 (Final)]) - NOAEL (No Observed Adverse Effect Level) was established as 1000 mg/kg/day

Description

Inventor developed a large series of substituted nitro group-containing oxa- and thiadiazoles. Majority of the prepared compounds possess high antmycobacterial effect (minimal inhibitory concentration = 0.03 – 0.5 µM) against drug-susceptible and multidrug-resistant mycobacteria. Structure-activity relationship has been studied and showed, that one part of the molecule can be functionalized with no negative effect on antmycobacterial effect. Hence, this part of the molecule can be used to improve properties like pharmacokinetics or toxicity. Selected compounds with the most promising antitubercular effect were studied on five human cell lines (including isolated human hepatocytes), on eight bacterial and eight fungal strains and showed no toxic effect up to 30 µM. Mechanism of action was proved to be different from those of recently developed nitro-group containing drugs like benzothiazinones and nitroimidazoles. Lead compound (T6053) was studied in vivo - repeated dose (14 days) toxicity (Oral) study (GLP principles [OECD Principles of Good Laboratory Practice (as revised in 1997), C (97) 186 (Final)]) showed that NOAEL (No Observed Adverse Effect Level) is 1000 mg/kg/day. Inventor offers these novel highly active compounds for further development of drugs directed on antituberculosis chemotherapy.

Research team leader

• prof. PharmDr. Alexandr Hrabálek, Csc.

Additional information

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