***OXA- AND THIADIAZOLES USEFUL ON THE TREATMENT OF DRUG-SUSCEPTIBLE AND MULTIDRUG-RESISTANT TUBERCULOSIS***

# Keywords (completed by CPPT)

# Technology keywords

Drug-susceptible, multidrug-resistant, antimycobacterial effect, nitro group-containing oxa- and thiadiazoles, pharmacokinetics, toxicity, drug

# Market keywords

Drug, antimycobacterial effect, drug-resistant

# NACE keywords

C21 - Manufacture of basic pharmaceutical products and pharmaceutical preparations

# Summary

Inventors of the Faculty of Pharmacy in Hradec Králové developed a large series of substituted nitro group-containing oxa- and thiadiazoles, with high antimycobacterial effect against drug-susceptible and multidrug-resistant mycobacteria, and easily accessible via simple synthetic procedures. One part of the molecule can be used to improve properties like pharmacokinetics or toxicity. Mechanism of action was proven to be different from those of nitro-group containing drugs like benzothiazinones and nitroimidazoles.

# Description

Inventor of the Faculty of Pharmacy in Hradec Králové developed a large series of substituted nitro group-containing oxa- and thiadiazoles. Majority of the prepared compounds possess high antimycobacterial 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 antimycobacterial 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.

*New features:*

* Mechanism of action different from nitro-group containing drugs like benzothiazinones and nitroimidazoles.
* Simple synthetic procedure allows to use one part of the molecule to improve properties like pharmacokinetics or toxicity

# Advantages

Series of oxa- and thiadiazoles:

* are easily accessible in large-scales via simple synthetic procedures
* have high antimycobacterial 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.

# Developmental stage

Already on the market Project already started

Available for demonstration Project in negotiations- urgent

Concept stage Proposal under development

Field tested/ evaluated Proposal under development

Under development/ lab tested

Inventor offers these novel highly active compounds for further development of drugs directed on antituberculosis chemotheraphy.

# IPR status

Granted patent or patent application essential Trade Marks

Patent(s) applied for but not yet granted Copyright

Patents granted Design Rights

Secret Know-How Exclusive Rights

Other (registered design, plant variety, etc.)

# Partner sought

* We are interested in partners for further development of drugs directed on antituberculosis chemotheraphy.

# Type of partnership considered

Manufacturing agreement Financial agreement

Research cooperation agreement Join venture agreement

Services agreement Licence agreement

Technical cooperation agreement

Commercial agreement with technical assistance

# Research team

[prof. PharmDr. Alexandr Hrabálek, Csc.](http://is.cuni.cz/webapps/whois2/osoba/1451700271706331/?lang=cs)

<http://is.cuni.cz/webapps/whois2/osoba/1451700271706331/?lang=cs>

# Team capacity in relation to the project

Team specialists are available for consultation

1. **External links (e.g. publications, leaflets, etc.)**

* <https://portal.faf.cuni.cz/Groups/Potential-antituberculotics/Research/>

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