CONCEPT LIFE SCIENCES

DELIVERING SCIENCE

INFOGRAPHIC

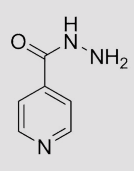
HIGHLIGHTS IN THE DEVELOPMENT OF NEW TREATMENTS TARGETING MDR-TUBERCULOSIS

Tuberculosis (TB) primarily results from an infection with Mycobacterium tuberculosis in the lungs and other parts of the body such as the gut. It can generally be cured with first line treatment within several months; however, TB is one of the top 10 causes of death worldwide (W.H.O.) and is a leading killer of immuno-compromised (HIV+) patients. In 2017, 10 million people were diagnosed and 1.6 million died from TB. A major challenge of TB treatment is the facile development of drug resistance, in particular to Isoniazid and Rifampicin. Below is an overview of current treatment regimens and highlighted therapies in clinical development.

FIRST LINE TREATMENT

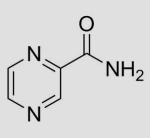
Treatment of latent TB with isoniazid alone or with rifampicin.

New onsets of active TB are treated with a cocktail of 4 antibiotics (Voractiv/Rimstar – below) for 2 months and then a combination of Isoniazid and Rifampicin for 4 months.



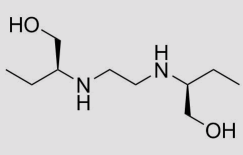
ISONIAZID

(1952)



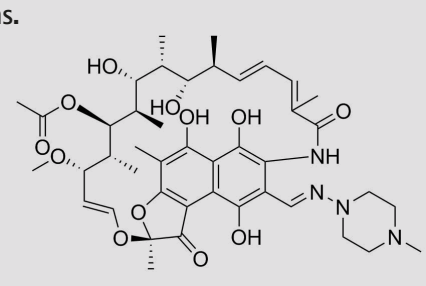
PYRAZINAMIDE (PZA)

(Made in 1936 and commercial in 1972)



ETHAMBUTOL

(1961)



RIFAMPICIN

(discovered in 1965, marketed in Italy in 1968, FDA approval 1971)

RESISTANCE

SECOND LINE TREATMENT (FOR MDR-TB) WHEN RESISTANT TO RIFAMPICIN

Since December 2018, W.H.O. recommends the replacement of injectable therapies with oral drugs as treatment.

If resistance to the first line treatment is observed, a cocktail of Group A drugs is taken. If this is ineffective, then this is followed by group B and finally group C. Research continues to develop alternative therapies.

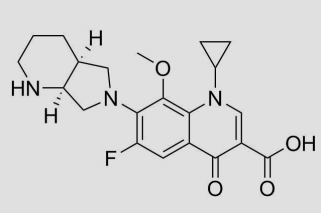
Group A
Fluoroquinolones (eg Moxifloxacin)
Bedaquiline
Linezolid

RESISTANCE

Group B
Clofazimine
Cycloserine or Terizidone

RESISTANCE

Group C
Delamanid
Meropenem
Ethionamide or Prothionamide
P-Aminosalicylic acid (PAS)
Ethambutol and other combinations



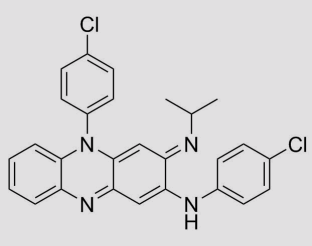
MOXIFLOXACIN

(Avelox, Bayer)

Target: DNA Gyrase

Good for HIV+ TB treatment as there are no drug-drug interactions with anti-retrovirals

Notable hERG inhibition

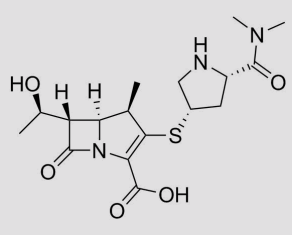


CLOFAZIMINE

(Lamprene, Novartis)

Target: Guanine bases of bacterial DNA

Very long half-life with accumulation of drug leading to unwanted side effects



MEROPENEM

(Merem)

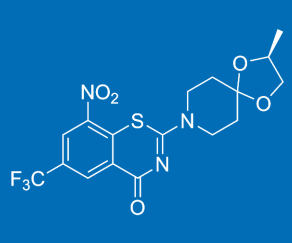
Target: Penicillin-binding protein

Administered intravenously

Dosing must be adjusted for altered kidney function and for haemofiltration

NEW DRUGS IN DEVELOPMENT 2016-2018 (FOR MDR AND XDR-TB)

PHASE 1 CLINICAL TRIALS

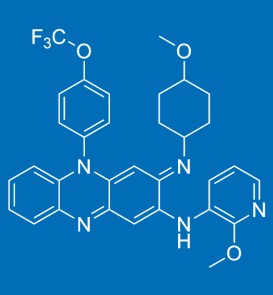


BTZ-043

(University of Munich)

Target: DprE1
(inhibition of cell wall formation)

BTZ043 has presented favourable in vitro (ADMET) and in vivo pharmacokinetic profiles



TBI-166

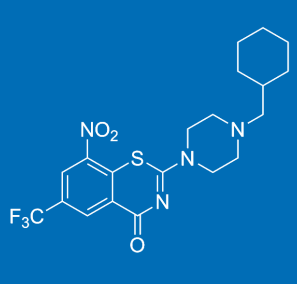
(Institute of Materia Medica, CAMS & PUMC)

Target: unknown

Phase 1 Jan 2018

Lead optimisation of Clofazimine (group B) Bactericidal activity against TB

Improved PK (shorter half-life) leading to decreased side effects



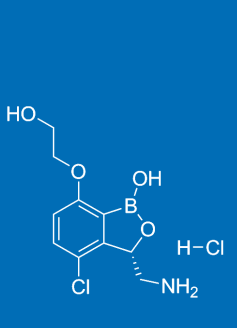
MACOZINONE / PBTZ-169

[Innovative Medicines for Tuberculosis, Bill & Melinda Gates Foundation, Nearmedic Plus (Russia)]

Target: DprE1

Phase 1 (April 2018) Phase 2a initiated

Lead optimisation of BTZ-043 with a streamlined synthesis and improved PK/PD profile



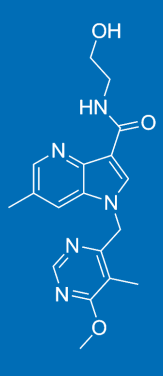
GSK3036656

(GSK)

Target: Leucyl-tRNA synthetase (LeuRS)

Phase 2a planned

Non-genotoxic in an Ames assay, a negative in vitro micronucleus assay and an in vivo rat micronucleus assay when dosed orally up to 2000 mg/kg



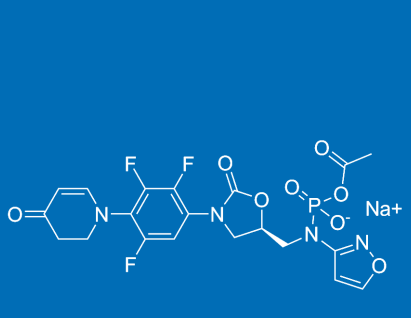
TBA-7371 / AZ7371

(TB Alliance)

Target: DprE1

Phase 1a.

Current investigations centred around drug-drug interactions



CONTEZOLID ACEFOSAMIL MRX-4

(MicuRx Pharmaceuticals, Inc)

(prodrug of MRX-1)

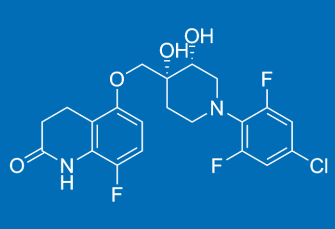
Target: Ribosomes (protein synthesis inhibition)

Effective against MRSA, PRSP, PISP

MRX-1 in Phase 3

Orally administered MRX-1 showed non-inferior efficacy from linezolid in systemic and local infection mouse models

PHASE 2 CLINICAL TRIALS



OPC-167832

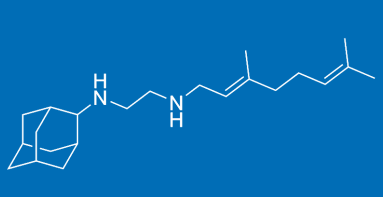
(Otsuka pharmaceutical)

Target: DprE1

FDA Fast track in 2016.

Human trials in progress.

Very potent against whole-cell Mycobacterium tuberculosis (MTB): 0.00024 to 0.002 µg/mL



SQ109

(Sequella)

Target: MmpL3.

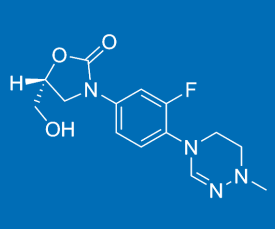
Expected replacement of Ethambutol as first line treatment.

Increases activity of isoniazid and rifampicin.

Discovered by screening a combinatorial library of more than 63,000 compounds with a whole-bacterium HTS.

Phys-Chem profile breaks Lipinsky's rules (clogP>5).

3 phase I in USA, 2 phase II in Africa, Phase IIb in Russia (completed)



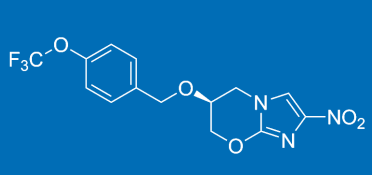
DELPAZOLID / LCB01-0371

(LegoChem Biosciences, Inc.)

Target: Ribosomes (protein synthesis inhibition)

The alcohol moiety is present to circumvent potential target-based resistance mechanisms - Interactions predictive by computational chemistry

PHASE 3 & MARKET



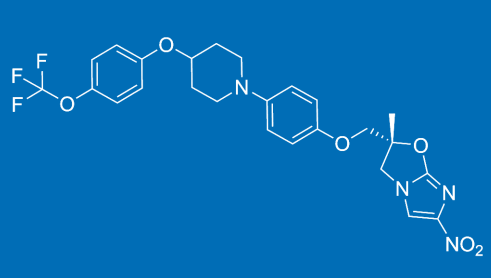
PRETOMANID / PA-824

(Pathogenesis Corporation / TB Alliance).

Target: mechanism of action complex

Active against all known drug resistant TB strain isolates.

Microarray analysis of the mode of action showed a mixed effect both on genes responsive to cell wall inhibition and respiratory poisoning



DELAMANID / OPC-67683

(Otsuka Pharma) (prodrug)

Target: Deazaflavin dependent nitro reductase, converting to a reactive intermediate metabolite that blocks the manufacture of mycolic acids which destabilises bacterial cell wall.

Metabolised by CYP3A4. Not to be used with CYP inducers.

Marketed in Europe, South Korea and Japan in 2014

Sources: who.int | nhs.uk | tbfacts.org | newtbdrugs.org

marketing@conceptlifesciences.com
conceptlifesciences.com