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Design of new antituberculotics

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Parts of the presentation

1. **Tuberculosis** (basic facts, statistics & current situation, mortality, resistance)
2. **Treatment**
    - 2.1. First-line drugs
    - 2.2. Second-line drugs
3. **New drug candidates**
    - 3.1. Pre-clinical development
    - 3.2. Clinical development
    - 3.3. Optimizing the use of approved and repurposed drugs

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Tuberculosis (TB)

- **Multisystemic infectious** and communicable disease
- One of the leading causes of death worldwide
- Until the COVID-19 pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS

- WHO has published a **global TB report** every year since 1997 (to provide a comprehensive and up-to-date assessment of the status of the TB epidemic)[1]

[1] https://www.who.int/publications/i/item/9789240037021

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Tuberculosis (TB) – basic facts

- Old disease (affected humans for thousands of years)
- Active / latent form
- Caused by the bacillus ***Mycobacterium tuberculosis*** (*M. avium, M. fortuitum, M. kansasii*)
- Germs are spread from person to person through the air by expel infectious droplets (caught, squeeze or split)
- Infects mainly the lungs (pulmonary TB), also affects other organs and tissues (extrapulmonary TB)
- Most of the infected people live in low- and middle-income countries, BUT TB is present all over the world
- About half of all people with TB can be found in 8 countries: Bangladesh, China, India, Indonesia, Nigeria, Pakistan, Philippines and South Africa[1]

[1] https://www.who.int/publications/i/item/9789240037021

Mycobacterium tuberculosis

- **Slowly growing**, **aerobic** bacteria
- They can grow within body cells (an intracellular parasitic bacterium).
- **Divides every 16 to 20 hours** (extremely slow rate compared with other bacteria, which usually divide in less than an hour).
- Unique outer membrane lipid bilayer cell wall with **mycolic acid**, which helps them to protect against host immune system
- It may take 9 weeks for these slow-growing bacteria to grow on specialised media.

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Tuberculosis (TB) – statistics

- About a **quarter of the world´s population is infected** with *M. tuberculosis* (2 billion people) BUT only 5-15% of these people will fall ill with active form of the disease (the rest have TB infection but are not ill and cannot transmit the disease)[1]
- Mostly affects **adults** (90%), but all age groups are vulnerable, more cases among **men** than women[2]
- People with **weak immune system** - higher risk of infection (**HIV infection** – 18 times more likely to develop active tuberculosis)[2]
- **Other risk factors**: undernutrition, diabetes, smoking and alcohol consumption

[1] https://www.who.int/publications/i/item/9789240037021
[2] https://www.who.int/news-room/fact-sheets/detail/tuberculosis

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Global TB report

- Concept of a „**high burden country**“ (HBC)
- 3 global HBC lists for 2021-2025:[1]
  - TB
  - HIV-associated TB
  - MDR-TB and RR-TB
- TB data profiles are available online for all 215 countries
- Free **WHO TB Report mobile app**

[1] https://www.who.int/publications/i/item/9789240037021

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Countries in the 3 global lists of high-burden countries in the period of 2021-2025 by WHO[1]

COUNTRY	TB	TB/HIV	MDR/ RR-TB
Angola	■		■
Azerbaijan			■
Bangladesh	■		■
Belarus			■
Botswana		■	
Brazil	■	■	
Cameroon		■	
Central African Republic	■	■	
China	■	■	■
Congo	■	■	
Democratic People's Republic of Korea	■		■
Democratic Republic of the Congo	■	■	■
Eswatini		■	
Ethiopia	■	■	
Gabon	■	■	
Guinea		■	
Guinea-Bissau		■	
India	■	■	■
Indonesia	■	■	■
Kazakhstan			■
Kenya	■	■	
Kyrgyzstan			■
Lesotho	■	■	
Liberia	■	■	
Malawi		■	
Mongolia	■		■
Mozambique	■	■	■
Myanmar	■	■	■
Namibia	■	■	
Nepal			■
Nigeria	■	■	■
Pakistan	■		■
Papua New Guinea	■		■
Peru			■
Philippines	■	■	■
Republic of Moldova			■
Russian Federation		■	■
Sierra Leone	■		
Somalia			■
South Africa	■	■	■
Tajikistan			■
Thailand	■	■	
Uganda	■	■	
Ukraine			■
United Republic of Tanzania	■	■	
Uzbekistan			■
Viet Nam	■		■
Zambia	■	■	■
Zimbabwe		■	■

[1] https://www.who.int/publications/i/item/9789240037021

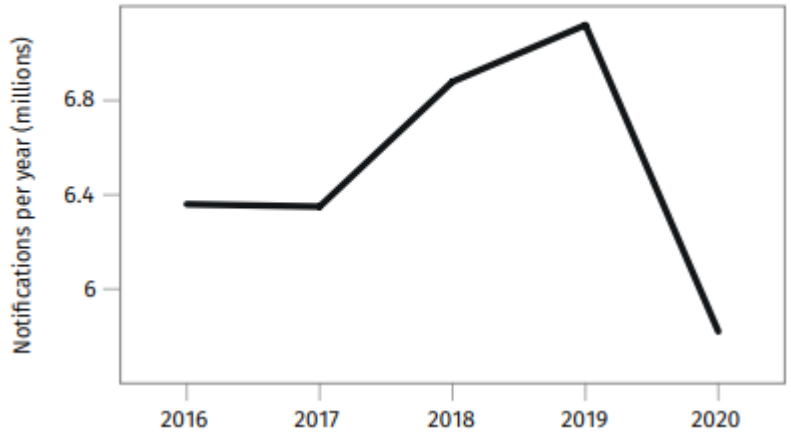
Tuberculosis- current situation

- **Large global drop** in the number of people **newly diagnosed** with TB and reported in 2020, compared with 2019
- 2019 – 2020 **18% decrease**
- Reduction in the regions of:
  - South-East Asia
  - Western Pacific

These 2 regions accounted for most (84%) of the global reduction (namely India 41%, Indonesia 14%, Philippines 12%, China 8%)

  - African Region (2,5%)
  - European Region

Global trend in case notifications of people newly diagnosed with TB, 2016–2020



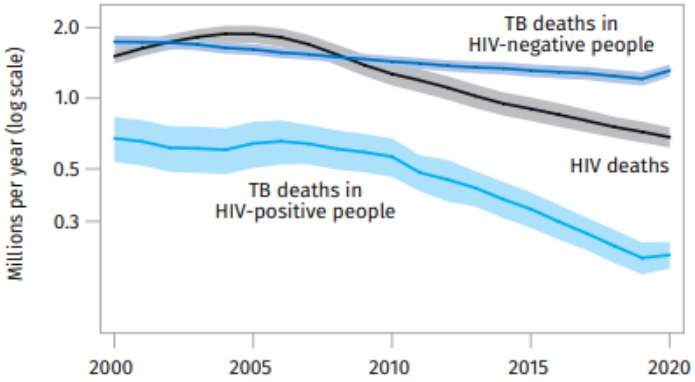
https://www.who.int/publications/i/item/9789240037021

Tuberculosis - mortality

- TB – **13th leading cause of death worldwide**
- Increasing number of deaths in 2020
- Number of deaths officially classified as caused by TB -1.5 million
  - including 214 000 people with HIV[1]
- TB remains one of the world´s top infectious killers

Global trends in the estimated number of deaths caused by TB and HIV, 2000–2020[a,b]

Shaded areas represent uncertainty intervals.

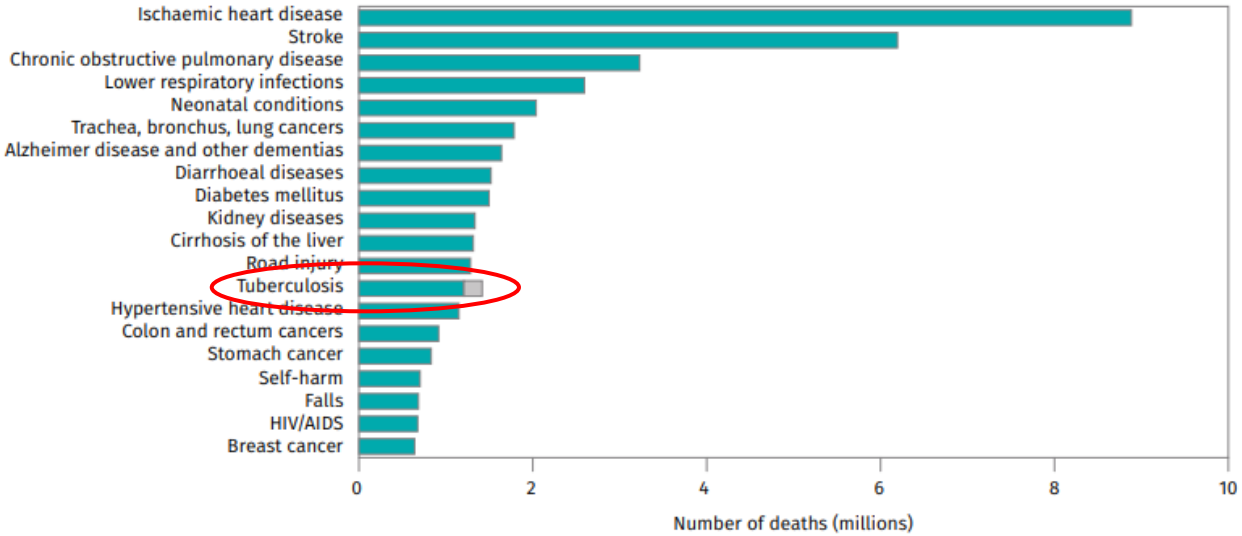


[a] For HIV/AIDS, the latest estimates of the number of deaths in 2020 that have been published by UNAIDS are available at http://www.unaids.org/en/. For TB, the estimates for 2020 are those published in this report.

[b] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

Top causes of death worldwide in 2019[a,b]

Deaths from TB among HIV-positive people are shown in grey.



[a] This is the latest year for which estimates for all causes are currently available. See WHO estimates, available at https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death

[b] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

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Tuberculosis (TB) - treatment

- **Curable and preventable**
- Without treatment – mortality rate from TB is high
- Effective drug treatments were first developed in the 1940s
- Currently recommended treatment: 6-month regiment of four first-line drugs: **isoniazid**, **rifampicin**, **ethambutol** and **pyrazinamide**
- 85% of patients with TB disease can be successfully treated with a 6-month drug regiment – universal health coverage[1]
- Vaccine for prevention of TB – **BCG vaccine** (bacille Calmette-Guérin) – prevents severe forms of TB in children

[1] https://www.who.int/news-room/fact-sheets/detail/tuberculosis

Tuberculosis (TB) – resistance

- **Rifampicin-resistant TB (RR-TB)**
- **Multidrug-resistant TB (MDR-TB)** defined as resistance to isoniazid and rifampicine

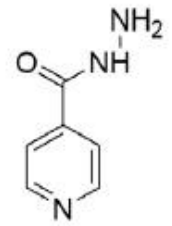
  (the most powerful anti-TB drugs)
  - treatment is longer (up to 2 years), more toxic and more expensive – **second-line drugs**
  - HIV/AIDS antiretroviral therapies are not compatible with the current TB regiment because of shared drug toxicities and drug interactions (rifampicin-induced cytochrome P_{450} activation)

- Urgent need for research and development of new drug structures with activity against

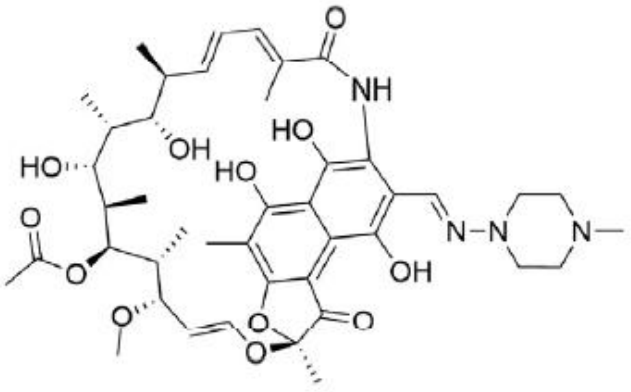
  resistant bacteria

Treatment: first-line drugs

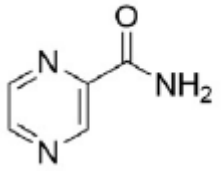
- More than **40 years old**
- **Non-compliance** of the patients



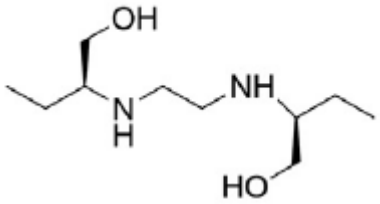
Isoniazid



Rifampicin



Pyrazinamide



Ethambutol

Drug	Effect on bacterial cell	Target	Mechanism of action
First-line drugs			
Isoniazid (INH)	Bactericidal	Multiple targets. The main target is NADH-dependent enoyl acyl carrier protein reductase	Inhibits cell wall mycolic acid biosynthesis. (It has effects on DNA, lipids, carbohydrates and NAD metabolism)
Rifampicin	Bactericidal	β subunit of RNA polymerase	Inhibits RNA synthesis
Pyrazinamide	Bactericidal (pH 5.5–6) / bacteriostatic	S1 component of the 30S ribosomal subunit	Inhibits protein translation and membrane energetics
		Membrane energy potential and membrane transport	Inhibits pantothenate and co-enzyme A synthesis
		Aspartate decarboxylase PanD	Inhibits PDIM synthesis
		Mycocerosic acid synthase and phenolthiocerol synthesis type-I polyketide synthases	
Ethambutol	Bacteriostatic	Arabinosyl transferases	Inhibits cell-wall arabinogalactan synthesis

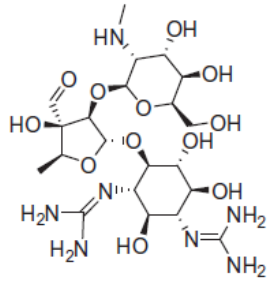
CHETTY, Sarentha, Muthusamy RAMESH, Ashona SINGH-PILLAY a Mahmoud E. S. SOLIMAN. Recent advancements in the development of anti-tuberculosis drugs. *Bioorganic & Medicinal Chemistry Letters* [online]. 2017, **27**(3), 370–386. ISSN 0960-894X. Dostupné z: doi:10.1016/j.bmcl.2016.11.084

Treatment: second-line drugs

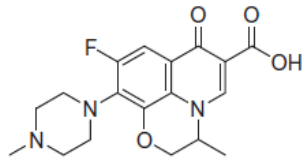
- Treatment is:
  - **longer** (up to 2 years)
  - **more toxic**
  - **more expensive**

Second and third-line drugs

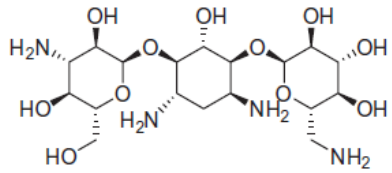
Streptomycin	Bactericidal	S12 protein and 16S rRNA components of 30S ribosomal subunit	Inhibits protein synthesis
Ofloxacin	Bactericidal	DNA gyrase and DNA topoisomerase	Inhibits DNA supercoiling
Kanamycin, Amikacin	Bactericidal	30S ribosomal subunit	Inhibits protein synthesis
Capreomycin	Bactericidal	Interbridge B2a between 30S and 50S ribosomal subunits	Inhibits protein synthesis
Ethionamide	Bacteriostatic	NADH-dependent enoyl acyl carrier protein reductase (InhA)	Inhibits mycolic acid synthesis
PAS	Bacteriostatic	Dihydropteroate synthase	Inhibits folate biosynthesis
Cycloserine	Bacteriostatic	D-Alanine racemase and ligase	Inhibits peptidoglycan synthesis
Linezolid	Bactericidal	50s ribosomal subunit	Inhibits protein synthesis



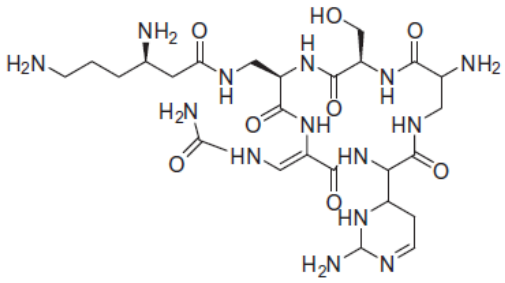
Streptomycin



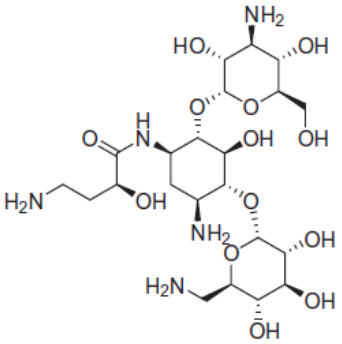
Ofloxacin



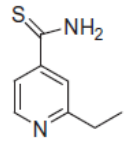
Kanamycin



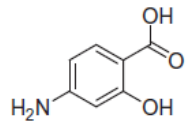
Capreomycin



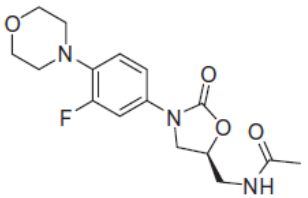
Amikacin



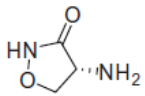
Ethionamide



para-amino salicylic acid



Linezolid



Cycloserine

CHETTY, Sarentha, Muthusamy RAMESH, Ashona SINGH-PILLAY a Mahmoud E. S. SOLIMAN. Recent advancements in the development of anti-tuberculosis drugs. *Bioorganic & Medicinal Chemistry Letters* [online]. 2017, **27**(3), 370–386. ISSN 0960-894X. Dostupné z: doi:10.1016/j.bmcl.2016.11.084

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New drug candidates

- Since the 1990´s, there has been a resurgence of interest in new anti-TB drugs development, as TB once became an internationally significant public health risk.
- **Rapid appearance of resistance** to the available drugs, **bacterial persistence**, **latency**, **long-treatment durations** – results in poor adherence and urgency of new drug development

- **Ideal properties** of the new regiment:[1]
  - A shorter treatment duration
  - A good bactericidal and sterilising activity against all TB bacterial sub-population
  - A better safety and tolerability profile than existing anti-TB drugs
  - Compatibility with other drugs used in TB chemotherapy and for those patients co-infected with HIV

[1] CHETTY, Sarentha, Muthusamy RAMESH, Ashona SINGH-PILLAY a Mahmoud E. S. SOLIMAN. Recent advancements in the development of anti-tuberculosis drugs. *Bioorganic & Medicinal Chemistry Letters* [online]. 2017, **27**(3), 370–386. ISSN 0960-894X. Dostupné z: doi:10.1016/j.bmcl.2016.11.084

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New drug candidates

- Currently, there are a number of drug candidates in different phases of the discovery, pre-clinical and clinical development
- There are also a number of ongoing trials using repurposed drugs in different combinations and doses of drugs that are currently on the market

Compounds with anti-TB activity currently in the hit to lead stage of the pipeline (http://www.newtbdrugs.org).

Hit-to-lead		
Chemical class/mechanism of action	Developer/sponsor	Target
Actinomycete metabolites – cyclic peptide (Ecumicin)	University of Illinois, Myongi University	clpC1
Adamantanids	University of Illinois,	Unknown
Malate Synthase Inhibitors	Texas A&M University	Malate synthase
Menaquinone Synthase Inhibitor	Colorado State University	Men A
Energy Metabolism Inhibitors	UPenn, TB Alliance	ATP synthase
Isoprenoid biosynthesis inhibitors	Lilly Alliance, Sanofi	Unknown
Phosphoenolpyruvate carboxykinase inhibitors	Roche Pharmaceuticals	PEPCK-C
RNA Polymerase Inhibitors	TB Alliance, Rutgers University	RNA Polymerase
ATP Synthesis Inhibitors	TB Alliance, Calibr	Nde-2

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Compounds with anti-TB activity currently in the lead optimization stage of the Pipeline (http://www.newtbdrugs.org).

Lead optimization		
Drug (chemical class)	Developer/sponsor	Mechanism of action and target
Arylsulfonamides	TB Alliance, GSK,	Inhibits tryptophan biosynthesis
Bortezomid	SPRINT-TB (National University of Singapore)	Mtb proteasome inhibitor
Cyclopeptides	TB Alliance, Sanofi	Unknown
Diarylquinolones	TB Alliance, Janssen	ATP Synthase
DprE Inhibitors (Azaindoles)	TB Alliance, Calibr	Affects cell-wall biosynthesis by DprE1 inhibition
Indazoles	TB Alliance, GSK	Affects cell-wall biosynthesis by Enoyl acyl reductase (InhA) inhibition
Indoles	SPRINT-TB (National University of Singapore)	Inhibit the ZipA-FtsZ interaction
Oxazolidinones	Sanofi, TB Alliance	Protein synthesis inhibitors by binding to the 50s ribosomal subunit of the 23S rRNA
MmpL3 Inhibitors (Indolcarboxamide)	TB Alliance	Inhibits transportation of metabolites from the cytosol of Mtb and ATP synthesis
PKS-13	Dundee, Texas A & M University	Polyketide synthase inhibitor
Thiadiazole	GSK, ORCHID	Affects cell-wall biosynthesis by Enoyl acyl reductase (InhA) inhibition
Oxaboroles	Anacor Pharmaceuticals, GSK	Inhibits protein synthesis by LeuRS inhibition
Macrolides	TB Alliance, Sanofi	Inhibits protein synthesis by 30S Ribosomal subunit inhibition
Pyrazinamide/Nicotinamide Analogues	TB Alliance, Yonsei University	Inhibits membrane energetics
Pyridomycin (Natural product of Dactylosporangium fulvum or Streptomyces pyridomyceticus)	Ecole Polytechnique Federale de Lausanne	Directly targets NADH-dependent enoyl ACP-reductase (InhA)F by competing for the NADH-binding site
Pyrimidines	AstraZeneca	Inhibitors of NDH-2
Ruthenium (II) phosphine/diamine/picolinate complexes	UNESP/School of Pharmaceutical Sciences	Unknown
SPR-113	Kanury Rao, Sundeep Duggar	Inhibits the anti-lipolytic G protein-coupled receptor, GPR109A
Spectinamides (SPR10199)	St Jude Children's Research Hospital, University of Tennesse Health Centre, Colorado State University, University of Zurich, Microbiotix	Inhibits protein synthesis by 16s Ribosomal subunit inhibition
Squaramides	TB Alliance	Blocks endocytic receptor-mediated mechanisms
TL1 Inhibitors (Capuramycins)	Sequella	Inhibits cell wall peptidoglycan biosynthesis by translocase 1 inhibition
Ureas	Sanofi, TB Alliance	Inhibits DNA Gyrase B (GyrB) ATPase
Xanthones	SPRINT-TB (National University of Singapore)	Interferes with the bacterial cell membrane

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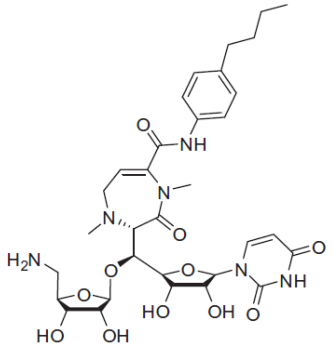
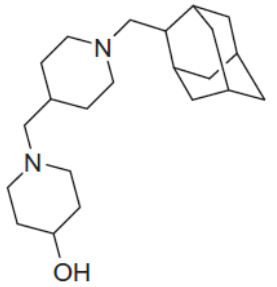
Pre-clinical development



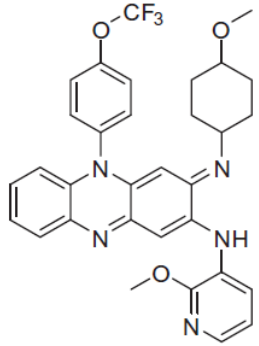
CPZEN-45

- **CPZEN-45**
  - **Nucleoside antibiotic**, which works through the inhibition of decaprenyl-phosphate-GlcNAc-1-phosphate transferase
  - In vitro activity against both replicating and non-replicating bacteria
  - Efficacy against both drug-sensitive and MDR-TB in murine models



SQ-609

- **SQ-609**
  - **Dipiperidine pharmacophore**
- **TBI-166**
  - **Riminophenazine class** of drugs
  - Clofazimine (antileprotic drug) – several undesirable properties (urine discoloration, poor solubility,...)
  - Obtained through lead optimization to keep the efficacy without undesirable properties



TBI-166

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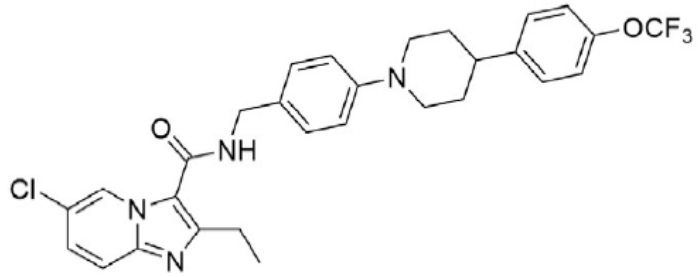
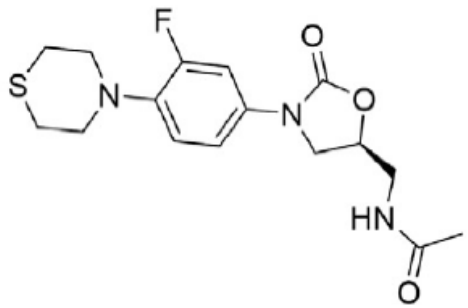
Clinical development



Q-203

- **Q203**
  - Optimised from an **imidazole[1,2-α]pyridine amide**
  - Works in anaerobic and aerobic conditions
  - Inhibition against both intra-cellular and extra-cellular TB as well as replicating and non-replicating bacteria
  - Target: respiratory cytochrome bc1 complex – inhibition of the synthesis of ATP

- **Sutezolid (PNU-100480)**
  - Analogue of **linezolid**
  - Superior antimycobacterial activity and safety profile compared with linezolid



Sutezolid (PNU-100480)

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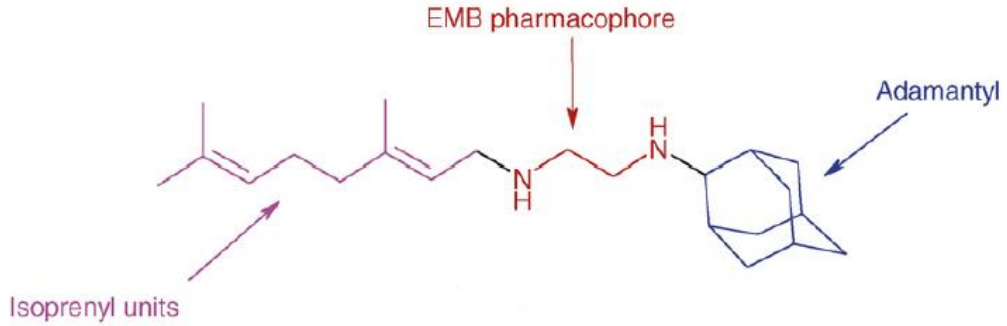

- **SQ109**
  - **Diamine analogue of ethambutol**
  - Unsaturated isoprenyl units and a bulky adamantyl ring
  - Limited bioavailability
  - Large volume of distribution into various tissues, particularly the lungs
  - Rapidly metabolised in the liver
  - Mechanism of action: inhibition of the cell wall synthesis
  - Oral administration with a long half-life (once-a-week dosing)

  - Combined administration with rifampicin exhibit synergistic in vitro activity without antagonistic interactions
  - Combination with isoniazid exhibit synergistic in vivo

RIVERS, Emma C. a Ricardo L. MANCERA. New anti-tuberculosis drugs in clinical trials with novel mechanisms of action. *Drug Discovery Today* [online]. 2008, **13**(23), 1090–1098. ISSN 1359-6446. Dostupné z: doi:10.1016/j.drudis.2008.09.004

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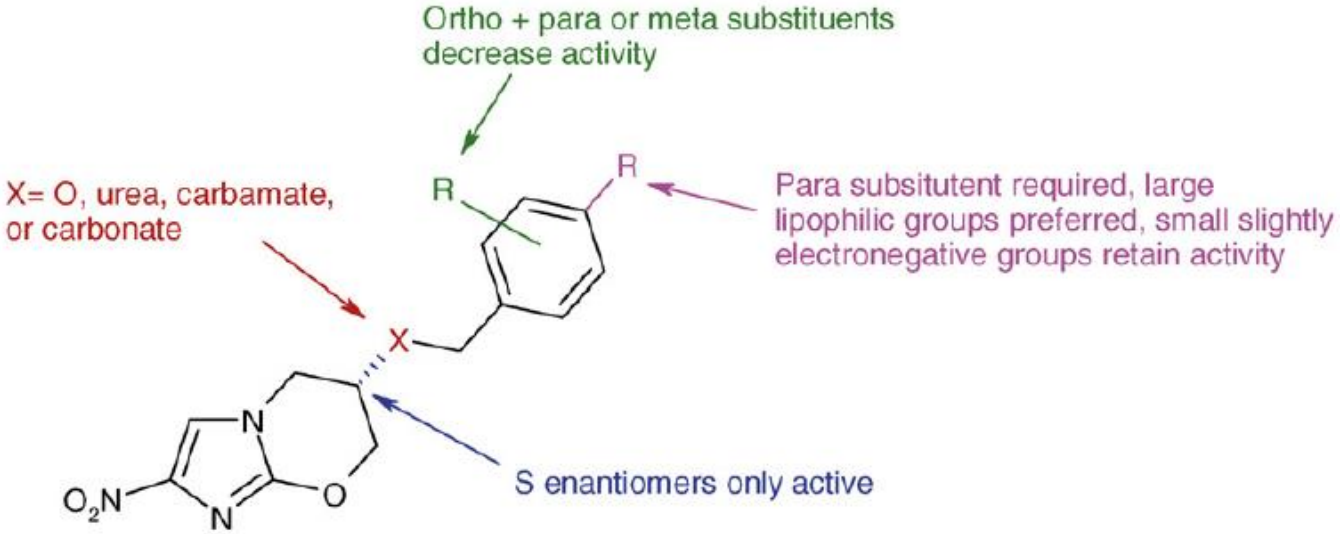
Clinical development

- **Pretomanid (PA-824)**
  - Bicyclic nitroimidazofurans – active against *M. tuberculosis* – MUTAGENIC
  - **Bicyclic nitroimidazo[2,1-b]oxazine** – equal activity without mutagenic features
  - **Prodrug** (metabolised by *M. tuberculosis)*- probably bioreduction of its aromatic nitro group to a reactive nitro radical anion intermediate



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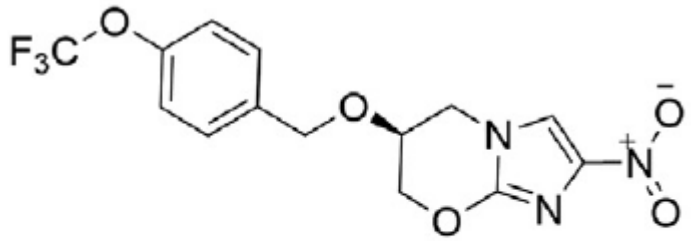
Clinical development

- **Pretomanid (PA-824)**



Pretomanid

  - NO cross-resistance to other current anti-TB drugs
  - Treatment of latent TB (activity against persistent bacilli)
  - Long half-life, accumulate in the body
  - Mechanism of action: two-fold
    1. Inhibition of *M. tuberculosis* cell wall lipid and protein synthesis
    2. Activity against non-replicating bacteria – probably due to the production of nitric oxide which is most likely generated on conversion of the prodrug to its active form
  - Combination with moxifloxacine – particularly effective with no relaps

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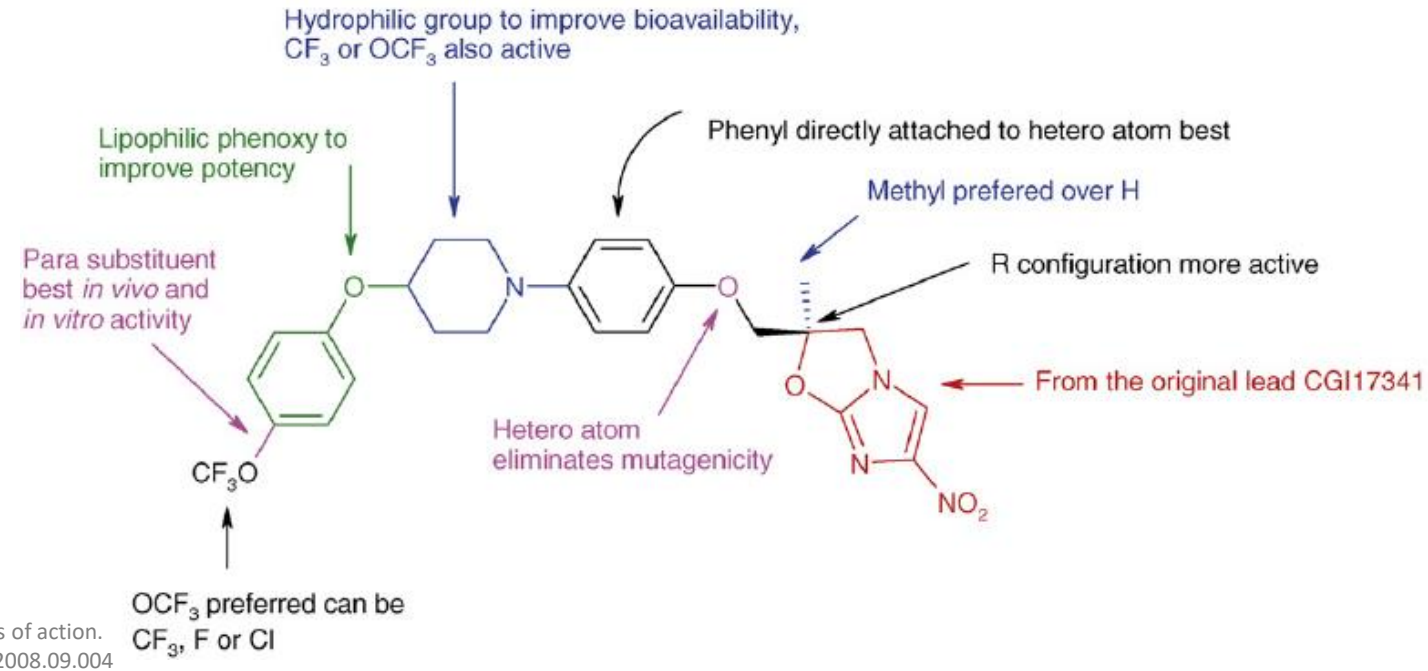
Clinical development

- **Delamanid (OPC-67683)**
  - **6-nitro-2,3-dihydroimidazo[2,1-b]oxazole**
  - **Prodrug** – *M. tuberculosis* metabolises the drug and produces <u>one main metabolite</u>:

    desnitro-imidazooxazole



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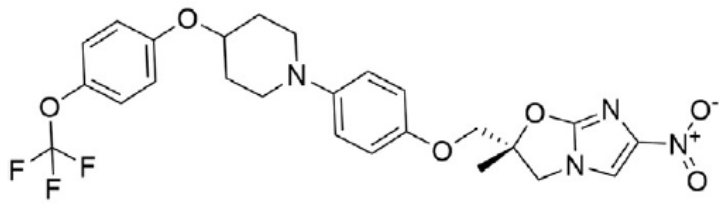
Clinical development



Delamanid

- **Delamanid (OPC-67683)**
  - Excellent in vitro activity against drug-susceptible and resistant *M. tuberculosis* strains
  - NO cross-resistance to any current first-line drugs
  - **Infrequent and low dosing**
  - Long half-life, lack of metabolization by CYP enzymes
  - **Efficacy in immunocompromised mice** – potential treatment of co-infected TB/HIV patients
  - Mechanism of action: inhibition of methoxy-mycolic and keto-mycolic acid synthesis
  - Combination with the first-line drugs – NO antagonistic interactions
  - Combination of delamanid, linezolid, levofloxacin and pyrazinamide

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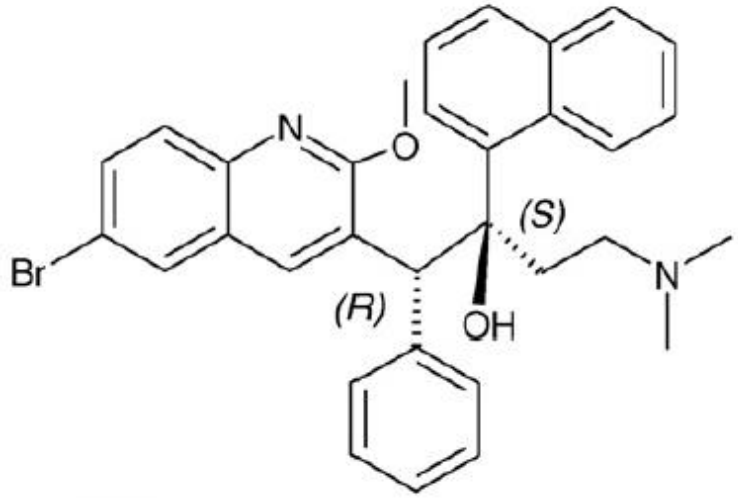
Clinical development



- **Bedaquiline (TMC-207)**
  - **Diarylquinoline**
  - Mechanism of action: inhibition of Mycobacterium membrane-subunit c of ATP synthase
  - Excellent activity against drug-susceptible, MDR-TB and RR-TB
  - NO cross-resistance to current first-line drugs
  - Use of TMC207 alone appears to be at least as effective as a combination of rifampicin, isoniazid and pyrazinamide
  - Orally well-absorbed with a long half-life (single weekly dosing)
  - Metabolised by CYP3A4 – **incompatible with anti-retrovirals**
  - Synergistic effect for the combination TMC207 and pyrazinamide – 2 months to completely eradicate lung *M. tuberculosis* (pyrazinamide indirectly inhibites aTP synthesis)
  - **Bedaquiline – Pretonamid – Pyrazinamide** combination is currently in phase III clinical trials for the treatment of MDR-TB

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Drugs in pre-clinical and clinical development in the TB pipeline (http://www.newtbdrugs.org).

Drug	Developer/Sponsor	Stage of clinical development	Chemical class	Mechanism of action and target
Pre-clinical development				
CPZEN-45	Lilly TB Drug Discovery initiative	Early stage development	Caprazamycin derivative (Nucleoside antibiotic)	Inhibition of cell-wall biosynthesis through decaprenyl-phosphate-GlcNAc-1-phosphate transferase, WecA (Rv1302) inhibition
SQ-609	Sequella Inc.	Early stage	Dipiperidine	Inhibition of cell-wall biosynthesis
TBI-166	TB Alliance Institute of Materia Medica (IMM)	Early stage	Riminophenazine	Accumulation of lysophospholipids, through phospholipase A 2 (PLA 2) activity stimulation
Spectinamide 1599	St Jude Children's Research Hospital, University of Tennessee, Colorado State University, University of Zurich and Microbiotix	Early stage	Spectinomycin analogues	Inhibits protein synthesis by 16s Ribosomal subunit inhibition
BTZ-043	University of Munich, Hans-Knöll-Institut (HKI), German Center for Infection Research (DZIF)	GLP Toxicity	Benzothiazinone	Inhibits Mtb cell wall synthesis by blocking the decaprenyl-phosphoribose-2′-epimerase (DprE1)
PBTZ-169	Innovative Medicine for Tuberculosis (iM4TB)	GLP Toxicity	Benzothiazine	Inhibits cell-wall biosynthesis through DprE1 inhibition
TBA-7371	AstraZeneca	GLP Toxicity	Benzothiazinone	Inhibitor of DprE1, disrupting cell-wall biosynthesis
GSK-070	Anacor Pharmaceuticals, GSK, TB Alliance	GLP Toxicity	Oxaborole	Leucyl-tRNA synthetase inhibitor
Clinical development				
Q203	Qurient Co. Ltd	Phase I	Imidazopyridine	Inhibits mycobacterial growth through Cytochrome bc1 complex inhibition
Sutezolid (PNU-100480)	Sequella	Phase II	Oxazolidinones	Bacterial ribosome
SQ-109	Sequella, NIH	Phase II	Ethylenediamine	MmpL3
High Dose Rifampicin	CDC, Sanofi-aventis	Phase II (DS-TB), Phase III (LBTI)	Rifamycin	Inhibits transcription through RNA polymerase inhibition
AZD5847	AstraZeneca	Phase II	Oxazolidinone	Inhibits protein synthesis through 50s ribosomal subunit inhibition
Levofloxacin	CDC, NIAID	Phase II	Fluoroquinolone	Inhibits enzymes necessary to separate DNA, thus inhibiting cell replication
Pretomanid (PA-824)	TB Alliance	Phase III (Bedaquiline-Pretomanid-Pyrazinamide regimen)	Nitroimidazole	Inhibits cell-wall mycolic acid biosynthesis through of ketomycolates inhibition
Bedaquiline (TMC-207) for MDR-TB	TB Alliance Janssen	Phase II (Bedaquiline-Pretomanid-Pyrazinamide regimen), Phase III (MDR-TB)	Diarylquinoline	Inhibit ATP synthesis through ATP synthase inhibition
Bedaquiline-Pretomanid-Linezolid (NiX-TB regimen)	TB Alliance, Janssen	Phase III	New Investigational Drugs	Treatment of patients with XDR-TB
Bedaquiline-Linezolid (MDR-TB)	TB Alliance, WHO	Phase III	Diarylquinoline	Treatment regimen for patients with MDR-TB
Delamanid (OPC-67683)	Otsuku Pharmaceuticals Co. Ltd	Phase III (MDR-TB)	Nitro-dihydro-imidazooxozole	Inhibits cell-wall methoxy-mycolic and keto-mycolic acid synthesis biosynthesis
Rifapentine-Moxifloxacin (Drug Sensitive TB)	CDC, Sanofi-aventis	Phase III	Rifamycin	Inhibits transcription through RNA polymerase inhibition
Pretomanid-Moxifloxacin-Pyrazinamide	TB Alliance, STAND Trial	Phase III	New chemical entity	Inhibits DNA and ATP synthesis

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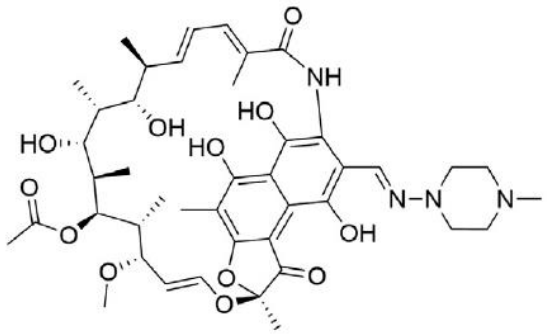
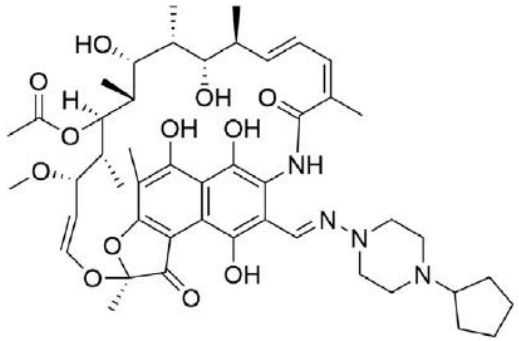
Optimizing the use of approved and repurposed drugs

- **Rifampicin**
  - Higher doses of 15 or 20 mg/kg
  - **Increase in dose had no corresponding increase in adverse effects**

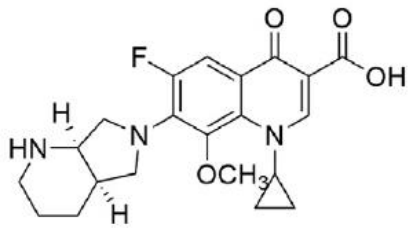


Rifampicin (High dose)

- **Rifapentine**
  - Reducing the treatment durations of drug-susceptible TB and the treatment of latent TB
  - Once-weekly dosing



Rifapentine



Moxifloxacin

- **Moxifloxacin**

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Summary

- A number of new anti-TB drugs have been developed in recent years with novel mechanism of action, exhibit excellent activity against *M. tuberculosis* and reduce the duration of treatment and dosing.
- The structure **OPC-67683 (Delamanid)** may be effective in **HIV/AIDS patients** and **TMC207(Bedaquiline)** may be effective against **MDR-TB**.
- There are a number of other drug molecules in clinical or pre-clinical trials, although there is limited information available.
- These developments give hope that within the next decade more effective anti-TB drugs may be achieved.

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Thank you for your attention.