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Handbook of Anti-Tuberculosis Agents

Global Alliance for TB Drug Development
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Areas covered include:

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- immunogenetics
- pathogenetics
- microbiology
- microbial physiology
- pathogenesis
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- molecular epidemiology
- diagnostics
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- drug resistance

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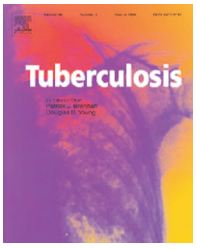

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Disclaimer

The information compiled by the Global Alliance for TB Drug Development (TB Alliance) in the TB Drug Database is for research purposes only. This database is intended to provide a source of information about chemical compounds currently being used to treat TB, as well as additional compounds being examined for use in the future to treat TB.

It does not include information that has necessarily been considered or approved by any drug regulatory authority and should not be used by physicians to inform the prescribing of medication. Furthermore, no representation is made concerning the efficacy, safety, appropriateness or suitability of any of the chemical compounds contained in the TB Drug Database.

This information in the TB Drug Database has been compiled from numerous peer-reviewed studies. The TB Alliance does not warrant that the information contained therein is accurate or complete and is not responsible for any errors or omissions that may be found in such information or for results obtained from the use of such information.

You are encouraged to consult other sources and confirm the information contained in the TB Drug Database.

The TB Drug Database is a work in progress, with a goal to provide information for all the drugs listed below. If erroneous or otherwise inaccurate information is brought to the attention of the TB Alliance, a reasonable effort will be made to correct or delete. Please send your comments to *database@tballiance.org*

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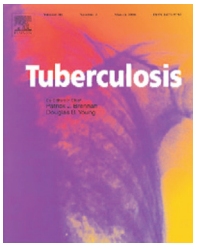

Introduction

Tuberculosis (TB), disproportionally affecting the world's poorest populations, remains one of the biggest public health problems in the 21st century. The spread of multidrug-resistant TB (MDR-TB) and the appearance of extensively drug-resistant TB (XDR-TB) pose new challenges for the prevention, treatment and control of this deadly disease. The control of TB is complicated by the fact that about a third of the world's population have latent TB, that is, they are infected with *Mycobacterium tuberculosis*, the causative pathogen of TB, but are asymptomatic. About 10% of those latently infected eventually develop active disease during their lifetime. Although most of the *M. tuberculosis*-infected individuals remain asymptomatic, they serve as the reservoir for the pathogen, making control of this disease a significant challenge. Infection by the human immunodeficiency virus (HIV) markedly enhances the rate of both new *M. tuberculosis* infection and activation of latent infection. The treatment of HIV and *M. tuberculosis* coinfection is another significant problem due to the difficulty of the coadministration of anti-TB and anti-HIV drugs as a result of drug–drug interactions. Unfortunately, most drugs that are used today for the treatment of TB were developed 40 or more years ago. Treatment of TB is both lengthy and complicated. New regimens that can shorten and simplify the treatment duration of active disease, that are effective against MDR- and XDR-TB, and that allow for coadministration with antiretroviral drugs are urgently needed.

The Global Alliance for TB Drug Development (TB Alliance) was founded in 2000 with the goal of developing new TB therapies that address the significant unmet medical needs in treating this disease. During the course of executing our drug discovery and development programs, we often need to locate information about the existing drugs and drugs in development. We have found that information relevant to TB drug research is very scattered and frequently resides in decades-old original literature. There are few places where comprehensive data can be found on more than one aspect of the various drugs. Many reviews cover single topics in depth, concentrating, for example, on comparisons of clinical options, animal models or physical characteristics. Researchers often need to spend a significant amount of time locating important information as a comprehensive source of such data is lacking. Recognizing this need, the TB Alliance is developing a TB drug database as a resource for the TB drug research community. The materials published in this issue of *Tuberculosis* represent our initial effort towards this goal.

In this TB drug database, we attempt to bring together information on all approved drugs used to treat tuberculosis, on drugs in clinical development for TB, and on some approved drugs being investigated for potential use in TB such as thioridazine. A total of 27 drugs are included in the current version of the database. Referenced data include physical characteristics, basic biology, efficacy and safety in humans, and absorption, distribution, metabolism and excretion (ADME). However, this database is designed to be an overview of TB drug information rather than an in-depth comprehensive review of all aspects of TB treatment. For further information on any specific compound or any specific aspect of these compounds, we suggest the reader use this database as a starting point for further literature exploration.

This database is divided into sections on individual drugs. References are provided with each drug. In addition, the following sources have been used:

- DrugBank: http://redpoll.pharmacy.ualberta.ca/drugbank/
- FDA labels: these can be sometimes accessed via DrugBank, alternatively through the FDA web site at http://www.fda.gov/default.htm
- Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 10th Edition. Hardman J, Limbird L (editors), McGraw Hill publications. On-line at http://www.accessmedicine.com/resourceTOC.aspx?resourceID=28
- Merck Index: http://www.merckbooks.com/mindex/
- Physician's Desk Reference: http://www.pdr.net/home/pdrHome.aspx

The TB Alliance would like to acknowledge the many individuals who have contributed to the development of the TB drug database and this manuscript. Primary information on the TB drugs was compiled and the manuscript drafted by Dr. Anne M. Gurnett and summer intern Nelson Chiu. Dr. Zhenkun Ma, Dr. Ann M. Ginsberg and Dr. Melvin Spigelman were involved in the conceptualization and design of the database. Dr. Zhenkun Ma, Dr. Khisi Mdluli, Dr. Priya Eddy and Dr. Takushi Kaneko were involved in the editing and proofreading of the database and this publication. During the development of this manuscript, we have also received valuable comments from various individuals working for drug sponsors on their respective compounds. These individuals are Dr. Karel De Beule (Tibotec, on TMC-207), Dr. Didier Leboulleux (sanofi-aventis, on rifapentine), Dr. Lawrence Geiter (Otsuka, on OPC-67683), and Dr. Marina Protopopova (Sequella, on SQ-109). Their valuable suggestions are greatly appreciated. Finally, the TB Alliance would like to acknowledge Dr. Patrick Brennan, editor of *Tuberculosis*, and Eelkje Sparrow together with other individuals from Elsevier for their help in making this special issue possible.

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List of abbreviations

AMI	Amikacin
CAP	Capreomycin
CIP	Ciprofloxacin
CLA	Clarithromycin
CLOF	Clofazimine
CYS	Cycloserine
ETA	Ethionamide
ETH	Ethambutol
GATI	Gatifloxacin
INH	Isoniazid
KAN	Kanamycin
LEV	Levofloxacin
LIN	Linezolid
MAC	*Mycobacterium avium* complex
MDR	Multidrug resistant
MIC	Minimum inhibitory concentration
MOXI	Moxifloxacin
MTB	*Mycobacterium tuberculosis*
OFL	Ofloxacin
PAS	Para-aminosalicylic acid
PRO	Prothionamide
PZA	Pyrazinamide
RIF	Rifampin
RIFAB	Rifabutin
RIFAP	Rifapentine
RIFAZ	Rifalazil
STR	Streptomycin
THZ	Thioridazine
TMC	TMC-207
XDR	Extensively drug resistant

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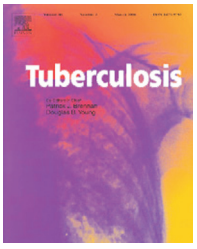
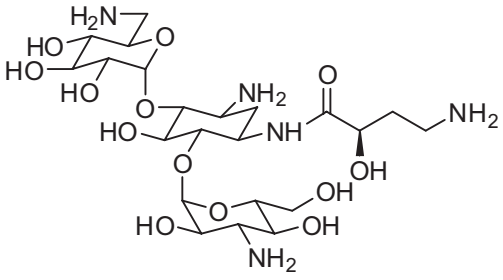


Amikacin

Generic and additional names: Amikacin
CAS name: O-3-Amino-3-deoxy-α-D-glucopyranosyl-(16)-O-[6-amino-6-deoxy-α-D-glucopyranosyl-(14)]-N1-[(2S)-4-amino-2-hydroxy-1-oxobutyl]-2-deoxy-D-streptamine
CAS registry #: 37517-28-5
Molecular formula: $C_{22}H_{43}N_5O_{13}$
Molecular weight: 585.60
Intellectual property rights: Generic
Brand names: Sulfate-Amiglyde-V (Fort Dodge); Amikin, Amiklin, BB-K8, Biklin (Bristol-Myers Squibb); Lukadin (San Carlo); Mikavir (Salus); Novamin (Bristol-Myers Squibb); Pierami (Fournier)



Polarity: Log P −9.048 [DrugBank]
Formulation and optimal human dosage: Dose 1 g daily i.v. or intramuscularly (i.m.)[1]

Basic biology information

Drug target/mechanism: Amikacin (AMI), streptomycin (STR) and kanamycin (KAN) are all aminoglycosides. AMI inhibits protein synthesis by binding tightly to the conserved A site of 16S rRNA in the 30S ribosomal subunit.[1]

Drug resistance mechanism: Ribosomal changes in the 16S rRNA[2] lead to possible cross-resistance with other class members, STR and KAN, but this is not always complete. For example, KAN, AMI and capreomycin (CAP) were still efficacious *in vitro* when resistance to STR had developed.[3] See also the *Drug resistance mechanism* section for STR.

In-vitro potency against MTB: MIC *M. tuberculosis* (H37Rv): 0.5–1 μg/ml.[4]

Spectrum of activity: Aminoglycosides are used mainly in infections involving aerobic, Gram-negative bacteria, such as *Pseudomonas*, *Acinetobacter* and *Enterobacter*. *Mycobacterium tuberculosis* is also sensitive to this drug. Gram-positive bacteria can also be treated with the drug but less toxic alternatives tend to be utilized. Synergistic effects with the aminoglycosides and beta lactams have resulted in use of this combination treatment for streptococcal infections, especially endocarditis [DrugBank].

Other in-vitro activity: AMI showed bactericidal activity against all the drug-sensitive clinical isolates of *M. tuberculosis* tested and was superior to both KAN and CAP, with bactericidal activity at 2 μg/ml against 5 of 5 drug-resistant strains tested.[4]

AMI had no bactericidal activity, but did cause significant reduction in bacterial load when *M. tuberculosis*-infected macrophages were treated using aminoglycosides; there was a 1–2 log reduction in CFU, 99% killing using STR 30 μg/ml or KAN 30 μg/ml or AMI 20 μg/ml.[4]

In-vivo efficacy in animal model: AMI was the most active of the aminoglycosides tested (STR, AMI and KAN dosed at 200 mg/kg 6 times weekly) in a mouse model of tuberculosis (2.3×10^7 CFU *M. tuberculosis* administered i.v. followed by dosing 1 day later). STR reduced the CFU in the spleen by almost 1 log. All three drugs were less efficacious than Isoniazid (INH) at 25 mg/kg. All the mice in the drug-treated groups survived whereas the control mice died within 30 days.[5]

Efficacy in humans

Even though AMI showed the best *in vivo* activity among the aminoglycosides it has not been widely used clinically to treat tuberculosis probably due to a combination of drug costs and toxicity.[5] Although aminoglycosides remain important drugs for treating diseases caused by *M. tuberculosis* (reviewed in Peloquin et al. 2004[6]), they are no longer first line. The aminoglycosides and CAP cannot be administered orally.

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Human	2.3	–	26±4	~0.27	~1.3 ml·min/kg	6.3±1.4 mg/kg dose given 3 times daily to steady state [Goodman & Gilman's]

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Human: Chan et al. give a value for C_{max} of 35–45 μg/ml, with no dose given[1]

Human metabolic pathway: Primarily eliminated through the kidney

Safety and Tolerability

Animal toxicity: LD_{50} in mice of solutions pH 6.6, pH 7.4: 340 mg/kg, 560 mg/kg i.v. [Merck Index]

Human drug–drug interactions: Concurrent use of other aminoglycosides and gentamycin, tobramycin, viomycin and cyclosporin is not recommended. AMI should not be used with potent diuretics (ethacrynic acid or furosemide) as they can cause ototoxicity and may increase the concentrations of AMI in tissues and serum [DrugBank].

Human potential toxicity: The aminoglycosides and CAP are known for their ototoxicities, and incidences may be as high as 3–10%.[1,5]

Human adverse reactions: As with all aminoglycosides, toxic effects can occur due to effects to the eighth cranial nerve resulting in hearing loss, loss of balance, or both. AMI primarily affects auditory function. In addition neurotoxicity (muscle paralysis and apnoea) and nephrotoxicity have been observed. In addition rashes, fever, headache, tremor, nausea, anaemia and hypotension have been observed [DrugBank].

References

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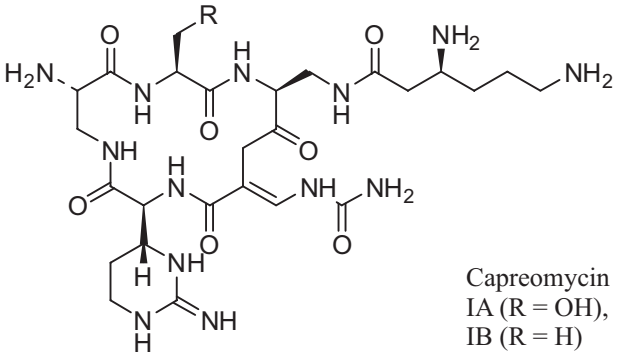
Capreomycin

Generic and additional names: Capreomycin sulfate
CAS name: 3,6-diamino-N-[[(8E)-15-amino-11-(2-amino-3,4,5,6-tetrahydropyrimidin-4-yl)-8-[(carbamoylamino)methylidene]-2-(hydroxymethyl)-3,6,9,12,16-pentaoxo-1,4,7,10,13-pentazacyclohexadec-5-yl]methyl]hexanamide sulfuric acid
CAS registry #: 11003-38-6
Molecular formula: $C_{25}H_{46}N_{14}O_{12}S$
Molecular weight: 766.786
Intellectual property rights: Generic. Polypeptide antibiotic isolated from *Streptomyces capreolus*.
Brand names: Capastat, Capastat sulfate, Capreomycin, Capreomycin sulphate, Ogostal, Capreomycin IA, Capreomycin IB



Capreomycin IA (R = OH), IB (R = H)

Solubility: Soluble in water. Practically insoluble in most organic solvents [Merck Index].
Polarity: pKa in 66% aqueous DMF: 6.2, 8.2, 10.1, 13.3 [Merck Index]. Log P −9.609 [DrugBank].
Stability: Stable in aqueous solution at pH 4–8; unstable in strongly acidic or strongly basic solutions [Merck Index].
Formulation and optimal human dosage: 1 g vial, 1 g daily, i.v. or intramuscularly (i.m.)

Basic biology information

Drug target/mechanism: Capreomycin (CAP) is a polypeptide antibiotic [FDA label]. The mode of action is not fully understood although CAP clearly interacts with the ribosome and inhibits protein synthesis. A gene-chip experiment in *Mycobacterium tuberculosis* demonstrated the up-regulation of several ribosomal proteins (e.g. RpsR, RplI, RplY and RplJ), Rv2907c (16S rRNA processing protein) and Rv1988 (methyltransferase). The expression data support the interaction of CAP with ribosomal components although a number of genes unrelated to protein synthesis are also affected.[1] As CAP has such potent activity against the persistent forms of TB the drug may have a target or secondary target outside the ribosome; the gene-chip data may lead to discovery of new targets for CAP.[1]

Drug resistance mechanism: Resistance is associated with ribosomal changes in the 16S rRNA;[2] there is possible cross-resistance with streptomycin (STR), but this is not always complete. For example, kanamycin (KAN), amikacin (AMI) and CAP were still efficacious *in vitro* when resistance to STR had developed.[3] In addition, CAP was still efficacious *in vitro* in several strains resistant to STR, AMI and KAN.[3] It has been shown that one mechanism of resistance to CAP is via inactivation of a ribosomal methylase TlyA. Interestingly, many bacteria lack *tlyA* and may be naturally resistant to CAP through this mechanism.[4] No cross-resistance has been observed between CAP and isoniazid (INH), aminosalicylic acid, cycloserine (CYS), ethionamide (ETA), or ethambutol (ETH) [DrugBank]. See also the *Drug resistance mechanism* section for STR.

In-vitro potency against MTB: MIC *M. tuberculosis* (H37Rv): 2 μg/ml.[5]

Spectrum of activity: CAP is active against *M. tuberculosis* and *M. avium*.

Other in-vitro activity: It has been demonstrated that CAP has bactericidal activity against non-replicating forms of *M. tuberculosis* equal only to metronidazole.[6] The treatment of *M. tuberculosis* within macrophages using aminoglycosides and CAP resulted in ~1 log reduction in CFU at day 7 using

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	0.18±0.05	34±6.4	94±19 (15 minutes post dose)	–	–	I.V. injection of 120 mg/kg CAP[8]
Human	–	–	32 (range 20–47)	–	–	Dose: 1 g CAP i.m.

STR (30 μg/ml), CAP (30 μg/ml), KAN (30 μg/ml) and just greater than a 2 log reduction at day 7 with AMI (20 μg/ml).[5] The MBC/MIC ratio of 2 for CAP is similar to that for STR, KAN and AMI.[7]

In-vivo efficacy in animal model: CAP and CAP liposome formula showed efficacy against *M. avium* in the beige mouse model.[8] Klemens et al. showed modest activity of CAP (150 mg/kg) in a mouse model against a clinically resistant isolate of *M. tuberculosis*.[9]

Efficacy in humans

The aminoglycosides and CAP cannot be administered orally. CAP is recommended for pulmonary infections caused by CAP-susceptible *M. tuberculosis* when primary agents [INH, rifampin (RIF), ETH, aminosalicylic acid, and STR] have been ineffective [DrugBank]. CAP has been administered as a secondary TB treatment for more than 25 years, but its use is limited due to renal and auditory toxicities.

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Mouse: Spleen, kidney and lung AUC values after i.v. injection of 120 mg/kg CAP to mice were 184, 982 and 60 μg·h/ml, respectively.[8]
- Human: Not bioavailable via oral administration. Higher C_{max} when given i.m. compared with i.v. Low serum concentrations at 24 hours. No accumulation after 30 days at a dose of 1 g/day [FDA label].

Human metabolic pathway: CAP is excreted in urine with 52% as the unchanged drug excreted in 12 hours. Urine concentration averaged 1.68 μg/ml during the 6 hours following a 1-g dose. It is not known if CAP is excreted in human milk [DrugBank].

Safety and Tolerability

Animal toxicity: LD_{50} in mice, rats (mg/kg): 250, 325 i.v.; 514, 1191 s.c., [Merck Index]

In teratology studies, a low incidence of "wavy ribs" was noted in litters of female rats treated with 50 mg/kg daily of CAP [FDA label].

Animal safety pharmacology: Renal and eighth-cranial-nerve toxicity; cataracts developed in 2 dogs on doses of 62 mg/kg and 100 mg/kg for prolonged periods.

Human drug–drug interactions: Other parenteral antituberculosis agents (e.g. STR) have similar toxic effects, particularly on cranial nerve and renal function, and simultaneous administration of these agents with CAP is not recommended. Skin rashes were reported when CAP and other antituberculosis drugs were given together [FDA label].

There is an increased risk of damage to the kidneys and ears if capreomycin is taken with vancomycin, cisplatin, or aminoglycoside antibiotics.

There is an increased risk of kidney damage if capreomycin is taken with colistin.

Human potential toxicity: CAP demonstrates many of the auditory side effects in common with the aminoglycosides. In addition it is associated with renal effects due to kidney tubulopathy leading to alkalosis.[2] In 36% of 722 CAP-treated patients elevation of blood urea nitrogen (BUN) above 20 mg/100 ml was observed [FDA label]. BUN elevation or any renal damage indicates that CAP dosage should be reduced or discontinued [FDA label]. Periodic determinations of liver function are recommended during CAP treatment. Leukocytosis and leukopenia have been observed. Most patients have eosinophilia exceeding 5% while receiving daily injections of CAP; this decreased with reduction of the CAP dosage to 2 or 3 g weekly. Signs of potential side effects, especially nephrotoxicity; hypersensitivity; hypokalemia; neuromuscular blockade; auditory and vestibular ototoxicity; and pain, hardness, unusual bleeding, or a sore at the place of injection [FDA label].

Human adverse reactions: Pain and excessive bleeding at the injection site have been reported, sterile abscesses have been noted, and rare cases of thrombocytopenia [DrugBank].

Possible side effects are blood disorders, rash (allergic reaction), hearing disturbances, damage to the kidneys, alteration in results of liver function tests and disturbances in the levels of chemical components (electrolytes) in the blood.

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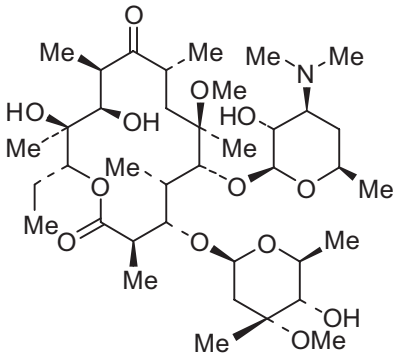
Clarithromycin



Generic and additional names: Clarithromycin
CAS name: 6-O-Methylerythromycin
CAS registry #: 81103-11-9
Molecular formula: $C_{38}H_{69}NO_{13}$
Molecular weight: 747.95
Intellectual property rights: Generic
Brand names: Biaxin (Abbott); Clathromycin (Taisho); Cyllind (Abbott); Klacid (Abbott); Klaricid (Abbott); Macladin (Guidotti); Naxy (Sanofi Winthrop); Veclam (Zambon); Zeclar (Abbott)
Solubility: Clarithromycin is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water [FDA label]. Water solubility 0.33 mg/l [DrugBank].
Polarity: Log P 2.69 [DrugBank]. Other authors have obtained values of Log P = 1.7 at pH 7.4.[1]
Acidity/basicity: pKa 8.99 [DrugBank]
Melting point: 217–220°C [DrugBank]
Formulation and optimal human dosage: Biaxin is available as immediate-release tablets, extended-release tablets, and granules for oral suspension.
Each Biaxin tablet contains 250 mg or 500 mg of clarithromycin.
After constitution, each 5 ml of Biaxin suspension contains 125 mg or 250 mg of clarithromycin.
Dose 250–1000 mg daily, higher amounts given in multiple doses [FDA label].

Basic biology information

Drug target/mechanism: Clarithromycin (CLA), a macrolide antibiotic similar to erythromycin and azithromycin, binds to the 50S ribosomal subunit resulting in inhibition of protein synthesis [DrugBank].
Drug resistance mechanism: Macrolide resistance is commonly caused by ErmB-driven methylation of the 23S rRNA resulting in a substantial loss in drug binding. *Mycobacterium tuberculosis* and *M. smegmatis* are both intrinsically resistant to the macrolides, and resistance can be induced in both species.[2,3] In *M. tuberculosis* the *ermB* gene was upregulated up to 30× baseline when bacteria were incubated with the drug; induction followed a bell-shaped curve with maximum upregulation at 2–4 μg/ml.[2] Newer macrolides with lower MICs for *M. tuberculosis* have been reported[4] and details about the induction of *ermB* with these analogs will be informative.
Other bacterial resistance: most strains of meticillin-resistant and oxacillin-resistant staphylococci are resistant to CLA [FDA label]. About 3.5% of *Helicobacter pylori* strains tested were resistant to CLA; treatment of *H. pylori* infections with CLA alone was not recommended due to risk of unacceptable rates of resistance development [FDA label].
In-vitro potency against MTB: MIC *M. tuberculosis* (H37Rv): 8 μg/ml at pH 7.4.[5]
MIC against a panel of *M. tuberculosis* clinical isolates was 1.3–10 μg/ml compared with >10 μg/ml for erythromycin.[6]
Spectrum of activity: CLA has relatively poor *in vitro* activity against *M. tuberculosis* but has better activity against *M. avium* (MIC_{90} 8 μg/ml), and *M. kansasii* (MIC_{90} ⩽0.5 μg/ml). In fact the authors conclude that CLA could be useful for treatment of the slowly growing nontuberculous mycobacteria with the exception of *M. simiae*.[7] CLA is 8–32-fold more active than erythromycin against *M. avium*.[1]
CLA is active *in vitro* against a variety of aerobic and anaerobic Gram-positive and Gram-negative microorganisms as well as most microorganisms of the *M. avium* complex (MAC). The 14-OH CLA metabolite has antimicrobial activity with a

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	13.3	16.83	3.74	–	–	200 mg/kg single oral dose in neutropenic mice[18]
Human	2.33	2.99±1.97	0.6±0.43	386±332	198±98 ml/min	200 mg single oral dose average in 39 healthy human volunteers[19]

somewhat different spectrum from the parent; for example, with *M. avium* isolates the 14-OH metabolite is 4–7 times less active than CLA.

CLA has *in vitro* and clinical activity against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Str. pyogenes*, *Haemophilus influenzae*, *H. parainfluenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *M. avium* and *M. intracellulare*. CLA has *in vitro* activity, but untested clinical activity, against streptococci, *Bordetella pertussis*, *Legionella pneumophila*, *Pasteurella multocida*, *Clostridium perfringens* and *Propionibacterium acnes* [FDA label].

Other in-vitro activity: CLA has been reported to be inactive against *M. tuberculosis* with MICs 64–128 μg/ml against clinical isolates.[8] However others have indicated that MICs, though high, can be measured.[9,10] Nine *M. tuberculosis* strains resistant to isoniazid (INH)/rifampin (RIF)/streptomycin (STR)/ethambutol (ETH) were examined for CLA MICs: 4 strains >16 μg/ml, 2 strains with 16 μg/ml and 2 strains with 2 μg/ml.[11] A substantial number of reports describe *in vitro* synergy of CLA with various first-line TB drugs and with antibiotics that inhibit cell-wall biosynthesis. CLA had little or no synergy with INH or RIF alone but significant synergy when INH/RIF/CLA were tested together[12] and with the combination INH/RIF/ETH/CLA.[13] ETH enhanced CLA activity in all the clinical isolates tested, as did DMSO and Tween 80, indicating that this enhancement may result from cell-wall damage resulting in better penetration of CLA into the mycobacterium; synergy with vancomycin was also demonstrated.[10] Conflicting results have been reported for CLA effects on *M. tuberculosis*-infected macrophages, especially with regard to synergy. One group reported synergy when *M. tuberculosis* was cultured in macrophages with CLA and pyrazinamide (PZA) with a FIC (fractional inhibitor concentration) of 0.5; when CLA was mixed with RIF the FIC was 1 indicating an additive effect.[14] However others reported synergy when *M. tuberculosis*-infected macrophages were treated with CLA and RIF.[15] High intracellular drug concentration of CLA in macrophages was observed.[14] CLA was active against *M. avium* complex in mouse and human macrophage cell culture [FDA label].

In-vivo efficacy in animal model: In vivo studies using a mouse model of *M. tuberculosis* (H37Rv) showed weak efficacy with CLA but the drug did protect mice from tuberculosis-induced mortality; CLA (200 mg/kg daily) had significantly poorer efficacy than INH (25 mg/kg daily) when mice were treated for up to 8 weeks.[15] In the same mouse model CLA (200 mg/kg) was slightly more efficacious than thiacetazone (60 mg/kg); in combination studies CLA and INH (25 mg/kg) were more active than INH and thiazoacetone or INH and STR (200 mg/kg).[15] Further studies on the activity of CLA with various drug combinations are needed. CLA was more effective against *M. avium in vivo* compared with erythromycin and amikacin and equal to amikacin (AMI)/ETH/RIF and CLA/AMI.[1]

Efficacy in humans

Published data on CLA treatment for TB in humans are scarce, although several reviews advocate its use.[16,17] CLA is approved for use for the following: upper respiratory tract infections, sinisititis, bronchitis exacerbation due to *Haemophilus* spp. and *Moraxella*, community-acquired pneumonia, uncomplicated skin and skin structure, duodenal ulcers, and disseminated mycobacterial infections with *M. avium* or *M. intracellulare*. Patients taking CLA 500 mg twice daily for ~11 months for the treatment of MAC were 69% less likely to exhibit MAC bacteremia and a significant survival rate was manifested [FDA label]. CLA is approved for use in children above 6 months and in geriatric populations, with no special treatment recommended for these groups.

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Rat: PK of CLA in rats is superior to that of erythromycin, with 15–73 times higher concentrations in plasma and tissues; the peak level of CLA in lung was especially high.[20]
- Human: PK of 14-OH metabolite is not linear with parent drug.[19] Bioavailability is ~50% [FDA label].

CLA is 70% plasma bound.[18] Steady-state peak plasma CLA concentrations of 1–2 μg/ml were reached in 2–3 hours with a 250-mg dose administered every 12 hours, and 3–4 μg/ml with a 500-mg dose administered every 8–12 hours. No significant differences in steady-state drug levels were seen with hepatic impaired or AIDS patients compared to healthy subjects. Extended-release tablets resulted in lower and later steady-state peak but equivalent AUCs [FDA label].

Good tissue penetration with 5 times more drug in lung compared with plasma and penetration into the middle ear [FDA label].

Human metabolic pathway: CLA is first metabolized to 14-OH CLA. The elimination half-life for CLA is 3–4 hours with 250 mg twice daily, and 5–7 hours with 500 mg 2–3 times daily. CLA is mainly excreted by liver and kidney, 30–40% excreted in urine depending on dose, an additional 10% excreted in urine as active metabolite, 14-OH CLA. It is not known if CLA is excreted into human milk [FDA label].

Safety and Tolerability

Animal toxicity: LD_{50} of CLA i.v. in mice was 184 mg/kg and 227 mg/kg in two separate studies. This was several times higher than the LD_{50} in rats (64 mg base/kg). These values were lower than those obtained following administration to mice by other routes. Signs of toxicity in both species were decreased activity, ataxia, jerks, tremors, dyspnea and convulsions.[21]

Adverse effects were found on fetal development in monkeys, rats and mice; serum drug concentrations in the foetus are significantly higher than those in the mother [FDA label].

Hepatotoxicity occurred in all species tested (dog, rat, monkey): in rats and monkeys at doses 2 times greater than, and in dogs at doses comparable to, the maximum human daily dose [FDA label].

Renal tubular degeneration, testicular atrophy, corneal opacity and lymphoid depletion were all observed in animal testing [FDA label].

Human drug–drug interactions: CLA inhibits cytochrome CYP3A4 and P-glycoprotein. Concomitant administration of CLA with cisapride, pimozide, or terfenadine is contraindicated due to cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) probably because of inhibition of hepatic metabolism of these drugs. Fatalities have been reported. Concomitant dosing of astemizole is not recommended for similar reasons and because of clinical experience with erythromycin [FDA label].

Human potential toxicity: CLA should not be used during pregnancy due to adverse effects seen in fetal development in monkeys, rats and mice.

Hepatotoxicity: increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice. Hepatic dysfunction may be severe but is usually reversible [FDA label].

Cardiac: QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes, have been associated with CLA [FDA label].

Hypoglycaemia occurs in rare cases [FDA label].

Human adverse reactions: Reactions are generally mild and the drug is well tolerated especially with slow-release tablets of Biaxin. In phase-1 clinical trials CLA appears to be safe and well tolerated up to 1200 mg/day as single oral dose.[19]

Adverse effects most commonly seen were gastrointestinal (diarrhoea, vomiting, abdominal pain and nausea), headache, and rash [FDA label].

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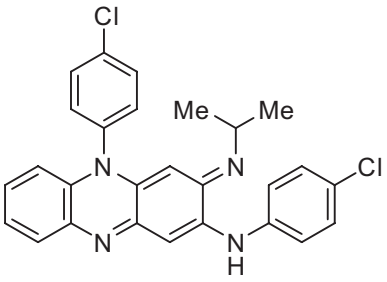
Clofazimine



Generic and additional names: 3-(p-chloroanilino)-10-(p-chlorophenyl)-2,10-dihydro-2-(isopropylimino)phenazine; 2-(4-chloroanilino)-3-isopropylimino-5-(4-chlorophenyl)-3,5-dihydrophenazine; 2-p-chloroanilino-5-p-chlorophenyl-3,5-dihydro-3-isopropyliminophenazine
CAS name: N,5-bis(4-chlorophenyl)-3-(1-methylethylimino)-5H-phenazin-2-amine
CAS registry #: 2030-63-9
Molecular formula: $C_{27}H_{22}Cl_2N_4$
Molecular weight: 473.40
Intellectual property rights: Generic. Clofazimine was first synthesized in 1954 as an anti-tuberculosis lichen-derived compound. The drug was thought to be ineffective against tuberculosis but in 1959 Chang demonstrated its effectiveness against leprosy. After clinical trials the product was launched in 1969 as Lamprene. Marketed by Novartis as Lamprene.
Brand names: Lampren(e) (Novartis)
Derivatives: Riminophenazine analogs B4154 and B 4157.[1]
Solubility: Soluble in dilute acetic acid, DMF. Soluble in 15 parts of chloroform, 700 parts of ethanol, 1000 parts of ether. Practically insoluble in water [Merck Index].
Polarity: Log P 7.132 [DrugBank]
Acidity/basicity: pKa 8.51 [DrugBank]
Melting point: 210–212°C [DrugBank]
Formulation and optimal human dosage: Lamprene, 50 mg clofazimine. Daily dose 1–2 tablets (50–100 mg).[2] Clofazimine is a substituted iminophenazine bright-red dye.

Basic biology information

Drug target/mechanism: The mode of action of clofazimine (CLOF) is not defined. Studies have implicated membrane perturbations[3] in *Staphylococcus aureus*, inhibition of phospholipase A2[4] and effects on potassium transporters.[5] Metabolic labeling is not specifically inhibited[3] and it is antagonized by tocopherol and lysophospholipase A.[6] CLOF has a high redox potential (–0.17 V at pH 7) and may result in generation of hydrogen peroxide.[7,8] Transcriptional analysis demonstrated that CLOF clustered with known respiratory modulators such as phenothiazines, cyanide and azide. This indicates that it may inhibit bacterial cell growth by interfering with electron transport.[9]
Drug resistance mechanism: Laboratory and clinical mutants have been difficult to generate. There is some controversy about activity against specific rifampin (RIF)- and isoniazid (INH)-resistant strains (see *Other in-vivo activity* section). In *Mycobacterium leprae* Lamprene does not show cross-resistance with dapsone or RIF.
In-vitro potency against MTB: MIC *M. tuberculosis* (H37Rv): 0.1 μg/ml.[10]
Spectrum of activity: Lamprene is described as mycobacteria specific [FDA label] while CLOF MICs of ⩽1 μg/ml have been reported for staphylococci, *Streptomyces* species, bacilli and *Listeria*.[6]
Other in-vitro activity: CLOF MICs were found by De Logu et al. to be higher against RIF- and pyrazinamide (PZA)-resistant *M. tuberculosis* strains compared to wild type (WT) (*M. tuberculosis* MICs: H37Rv 0.78 μ/ml; PZA-resistant 6.25 μg/ml; RIF-resistant 6.25 μg/ml; INH-resistant 0.39 μg/ml),[11] however Reddy et al.[1] showed sensitivity against INH-, RIF- and ethambutol (ETH)-resistant strains (*M. tuberculosis* MICs: H37Rv 0.12 μ/ml; multidrug-resistant (MDR) 0.12–2 μg/ml; RIF-resistant 0.25–

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Human	70 days after prolonged treatment	1.5*	0.145*	–	–	*200 mg fasting oral dose[20] (administered with PAS, cycloserine, ETH and pyridoxime), T_{max} 6.23 h.

0.5 μg/ml; INH-resistant 0.12 μg/ml).[1] Both agree that INH-resistant strains generally remain sensitive to CLOF but there may be some increases in the MICs for RIF-resistant, PZA-resistant and MDR strains. CLOF and one analog showed efficacy against *M. tuberculosis*-infected macrophages with activity at 0.5 μg/ml equivalent to that of INH at 0.1 μg/ml; another analog was less effective.[1] Possible synergy with INH has been reported.[12] CLOF was found bactericidal.[3]

In-vivo efficacy in animal model: Early experiments with CLOF in tuberculosis models showed efficacy in hamsters and mice with less activity in monkeys and guinea pigs (reviewed in Reddy et al. 1996[1]). The compound was virtually abandoned for tuberculosis but eventually developed for use in leprosy. MDR-TB renewed interest in the compound and in 1996 efficacy was demonstrated in *M. tuberculosis*-infected mice with weekly dosing 3 days post infection continuing for 12 weeks. No organisms were recovered from lungs although spleens still showed signs of infection. In the same model some efficacy was observed with once and twice weekly dosing.[1]

Liposome-encapsulated drugs tend to accumulate in macrophages and are released at slower rates than the free counterpart (reviewed in Adams et al. 1999[13]) and have been described as less toxic to cells *in vitro* and *in vivo*.[14] Using a mouse model representing acute, established and chronic *M. tuberculosis* infection significant efficacy with liposome-encapsulated CLOF was demonstrated. Free CLOF was maximally tolerated at 5 mg/kg in mice at which dose it was ineffective; encapsulated CLOF was used at 50 mg/kg and showed efficacy and no signs of toxicity.[13] Nanosuspension for use with i.v. formulation of CLOF was as efficacious as liposome encapsulation.[15] While these experiments do suggest that encapsulating drug can reduce toxicity, the maximum drug dose tolerated in mice was reported as 5 mg/kg whereas others have found 20 mg/kg and higher tolerable doses in the same animal (compare Reddy et al. 1996[1] and Adams et al. 1999[13]).

Controversy about drug carry-over in animal models clouds simple interpretation of some of the reported *in-vivo* activity.[16]

In addition to its antimicrobial activity, the drug has other pharmacological activity such as its anti-inflammatory effects, pro-oxidative activity and immunopharmacological properties.[8]

Efficacy in humans

CLOF is recommended as a second-line compound for use in combination with other drugs for the treatment of drug-resistant tuberculosis (reviewed in Mukherjee et al. 2004[17] and du Toit et al. 2006[18]). Treatment of human tuberculosis patients with CLOF in combination with LIN and other drugs has been described.[2] CLOF was first launched by Novartis as Lamprene in 1969 as an anti-leprosy agent (reviewed in Sansarricq 2004[19]).

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Rat: High levels (1–3.6 mg/g wet weight tissue) were observed in rat tissue having reticulo-endothelial components following oral treatment of 20 mg/kg for several months;[21] other tissues had relatively low drug levels (range 3–114 μg/g of wet tissue).
- Human: 45–62% oral absorption rate. The average serum concentrations in leprosy patients treated with 100 mg and 300 mg daily were 0.7 μg/ml and 1.0 μg/ml, respectively (Lamprene FDA label). CLOF is highly lipophilic and tends to be deposited predominantly in fatty tissue and in cells of the reticuloendothelial system [FDA label]. CLOF concentrates in macrophages, and serum levels are often low or undetectable.[1] Cannot be given i.v. unless formulated (Adams et al. 1999,[13] reviewed in Peters et al. 2000[22]). A high-fat meal increases bioavailability but intra-subject variation needs to be examined more carefully.[20]

Human metabolic pathway: CLOF half-life following repeated oral doses is minimally 70 days; in a 24-hour (post 300 mg dose) urine collection parent drug or metabolites were negligible. Lamprene passes into breast milk. Metabolism of Lamprene is hepatic. Three metabolites have been identified but it is unclear if metabolites are pharmacologically active. Metabolite I: hydrolytic dehalogenation of CLOF; metabolite II: hydrolytic deamination reaction followed by glucuronidation; metabolite III: probably a hydroxylated CLOF glucuronide. Absorption varies

from 45% to 62% following oral administration in leprosy patients. Food increases bioavailability and rate of absorption (Lamprene FDA label).
Crystalline deposits of the drug have been seen at autopsy in mesenteric lymph nodes, adrenals, subcutaneous fat, liver, bile, gall bladder, spleen, small intestine, muscles, bones, and skin [FDA label].

Safety and Tolerability
Animal toxicity: Acute toxicity: LD_{50} orally in mice, rats, and guinea pigs: >4 g/kg; in rabbit: 3.3 g/kg. CLOF toxicity has been decreased by the use of liposome-encapsulated drug with no reported change in the MIC.[14]
Reproductive toxicity: At 25 times normal human dose CLOF impaired fertility in rats; fetal toxicity in mice was found at 12–25 times normal human dose, i.e., retardation of fetal skull ossification, increased incidence of abortions and stillbirths, and impaired neonatal survival. The skin and fatty tissue of offspring became discolored approximately 3 days after birth, which was attributed to the presence of Lamprene in the maternal milk (Reddy et al. 1999[8] and FDA label).
Genotoxicity: CLOF was Ames negative but inhibited growth of human fibroblasts at 2.5 μg/ml, showed dose-related changes in mitotic indexes, and showed elevated incidence of chromosomal aberrations in mice treated with 40 mg/kg daily for seven days.[23,24]
No long-term carcinogenicity studies in animals have been conducted with Lamprene. Lamprene was not teratogenic in laboratory animals at dose levels equivalent to 8 times (rabbit) and 25 times (rat) the usual human daily dose.
Animal safety pharmacology: Elevated levels of albumin, serum bilirubin, and AST (SGOT); eosinophilia; hypokalemia.
Human drug–drug interactions: Dapsone may inhibit the anti-inflammatory activity of Lamprene [FDA label].
Human potential toxicity: Gastrointestinal toxicity: Abdominal pain, diarrhoea, nausea, vomiting or gastrointestinal intolerance occur in 40–50% of patients on Lamprene. There are reports of death following severe abdominal symptoms. Autopsies have revealed crystalline deposits of CLOF in various tissues including the intestinal mucosa, liver, spleen, and mesenteric lymph nodes. Ames test reveals no evidence of carcinogenicity risk but long-term studies are incomplete (Reddy et al.[8] and FDA label).
It has been found that Lamprene crosses the human placenta. The skin of infants born to women who had received the drug during pregnancy was found to be deeply pigmented at birth. No evidence of teratogenicity was found in these infants. There are no adequate and well-controlled studies in pregnant women. Lamprene should be used during pregnancy only if the potential benefit justifies the risk to the foetus [FDA label].
Human adverse reactions: Gastrointestinal toxicity: abdominal and epigastric pain, diarrhoea, nausea, vomiting, gastrointestinal intolerance (40–50%).
Reddish black reversible skin discoloration may take several months or years to disappear after the conclusion of therapy. Eye pigmentation may arise due to CLOF crystal deposits, also general eye irritation. Discoloration of urine, faeces, sputum, sweat; elevated blood sugar; elevated erythrocyte sedimentation rate [FDA label].
CNS: Headache, dizziness, drowsiness, fatigue and taste disorder. Some patients developed depression because of the skin discoloration.
Skin: Pigmentation from pink to brownish-black in 75–100% of the patients within a few weeks of treatment; ichthyosis and dryness (8–28%); rash and pruritus (1–5%).
Depression secondary to skin discoloration; two suicides have been reported.

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Cycloserine

Generic and additional names: D-4-Amino-3-isoxazolidone; orientomycin
CAS name: D-4-Amino-3-isoxazolidinone
CAS registry #: 68-41-7
Molecular formula: $C_3H_6N_2O_2$
Molecular weight: 102.09
Intellectual property rights: Generic, marketed 1952
Brand names: Closina; Farmiserina (Farmitalia); Micoserina; Oxamycin (Merck & Co.); Seromycin (Lilly)
Solubility: Soluble in water, slightly soluble in methanol, propylene glycol. Forms salts with acids and bases [Merck Index].
Polarity: Log P −1.631 [DrugBank]
Acidity/basicity: Aqueous solutions have a pH around 6 [Merck Index]
Stability: Neutral or acid solutions are unstable. Aqueous solutions buffered to pH 10 with sodium carbonate can be stored without loss for one week at +4°C [Merck Index].
Melting point: 147°C [DrugBank]
Formulation and optimal human dosage: 250 mg tablet, dose is 500–750 mg daily[1]

Basic biology information

Drug target/mechanism: Cycloserine (CYS) is an analog of the amino acid D-alanine. CYS inhibits alanine racemase (Alr, converts L-alanine to D-alanine) and D-alanine:D-alanine ligase (Ddl) which synthesizes the pentapeptide core using D-alanine; both enzymes are essential in the synthesis of peptidoglycan and subsequently in cell-wall biosynthesis and maintenance.[1] In *Mycobacterium smegmatis* inactivation of Alr or Ddl resulted in increased sensitivity to CYS while overexpression of Alr resulted in resistance (reviewed in Zhang 2005[2]). Alr appears to be the major target in *M. smegmatis*. The precise target of CYS has not yet been demonstrated using genetic manipulation in *M. tuberculosis* (reviewed in Zhang 2005[2]).
Drug resistance mechanism: In a 1999 Italian study 10% of the *M. tuberculosis* clinical isolates examined were resistant to CYS.[3] In a very large study from Taiwan 693 *M. tuberculosis* strains were examined and the overall resistance rates for individual drugs were assessed; rates for CYS were 81.8% resistant in 1996 and 51.6% resistant in 2000, however the actual rates for this study have not been validated.[4] In a third study, *M. tuberculosis* CYS resistance rates were 7.4%.[5] Although the precise mutation has not been identified in *M. tuberculosis*, in *M. smegmatis* overexpression of the alanine racemase gene is necessary and sufficient to confer resistance.[6]
In-vitro potency against MTB: MIC *M. tuberculosis* (H37Rv): 25 μg/ml.[7]
Spectrum of activity: CYS is a broad-spectrum antibiotic. It is most often used in combination with up to 5 drugs to treat *M. avium* complex (MAC) and tuberculosis [DrugBank]. CYS may be bactericidal or bacteristatic, depending on local concentration effects as well as efficacy against the particular strain involved [DrugBank].
Other in-vitro activity: CYS (50 μg/ml) resulted in killing <1 log (80%) of the initial innoculum when tested against *M. tuberculosis* in macrophages.[7] CYS showed synergistic activity with an experimental drug β-chloro-D-alanine which reduced the MIC from 50 to 2.5 μg/ml.[8] An experimental surfactant CRL8131 had a synergistic effect when tested against *M. tuberculosis*-infected macrophages with CYS.[9]
In-vivo efficacy in animal model: CYS (300 mg/kg) was administered 5× weekly to mice for 30 days with drug beginning 1 day after infection. Lung CFUs were not significantly reduced and spleen CFUs reduced from log 5.57 to log 5.26. CYS is known to have a high excretion rate in mice (reviewed in Fattorini et al. 2003[10]).

Efficacy in humans

CYS is a bacteristatic agent; when used to treat tuberculosis, it is administered orally as 250 mg doses

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Human	10	–	25–30*	-	-	*C_{max} after a dose of 250 mg every 12 hours [DrugBank]

2–3 times daily.[1] It is an effective agent but severe toxicity has limited its use.[1] CYS rapidly and almost completely absorbed (70–90%) from the gut following oral administration [DrugBank].

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Human: Half-life is longer in renally impaired patients [DrugBank].

Human metabolic pathway: Excretion is primarily renal, with 50% excreted unchanged within 12 hours, 70% excreted within 24 hours. Widely distributed to most body fluids and tissues, including CSF, breast milk, bile, sputum, lymph tissue, lungs, and ascitic, pleural, and synovial fluids, CYS crosses the placenta [DrugBank].

Safety and Tolerability

Animal toxicity: Oral LD_{50} in mouse is 5290 mg/kg, and in rat is over 5000 mg/kg [DrugBank].

Animal safety pharmacology: CNS: Convulsions were induced in chicks with CYS but coadministration of pyridoxine reversed the effects.

Human drug–drug interactions: CYS may interfere with the PK and absorption of isoniazid (INH) and thionamide [DrugBank]. It should be used with care in alcoholics (increased risk of seizures), patients with a history of mental illness (CYS may increase anxiety and depression) and patients with a history of seizures [DrugBank].

Human potential toxicity: CNS toxicity is common: dose-related neuropsychiatric effects, drowsiness, slurred speech;[1] up to 50% of patients on 1 g drug/day exhibit some of these symptoms which are reduced as the dose drops to 250 mg 2–3 times/day.[1] CYS should not be given to patients with renal impairment where a creatinine clearance of <50 ml per minute is observed. Administration of 200–300 mg of pyridoxine daily may help to prevent CYS-related neurotoxicity [DrugBank].

Human adverse reactions: Symptoms of CYS overdose are generally neuropsychiatric and include convulsions, seizures, slurred speech, paralysis and unconsciousness [DrugBank].

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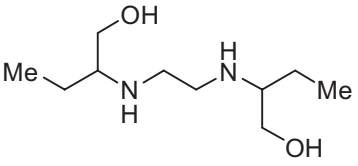
Ethambutol



Generic and additional names: Ethambutol; (+)-2,2′-(ethylenediimino)di-1-butanol; d-N,N′-bis(1-hydroxymethylpropyl)ethylenediamine; EMB
CAS name: 2,2′-(1,2-Ethanediyldiimino)bis-1-butanol
CAS registry #: 74-55-5
Molecular formula: $C_{10}H_{24}N_2O_2$
Molecular weight: 204.31
Intellectual property rights: Generic, first used in TB treatment in 1966
Brand names: Aethambutolum, D-Ethambutol, Dadibutol, Diambutol, EMB, Ethambutol HCL, Etibi, Myambutol, Tibutol
Solubility: Dihydrochloride: Soluble in water, DMSO; sparingly soluble in ethanol; difficult to dissolve in acetone and chloroform [Merck Index]
Polarity: Log P −0.14 [DrugBank]
Acidity/basicity: ETH HCl has two apparent dissociation constants, $pKa_1 = 6.35$, $pKa_2 = 9.35$. In solution at neutrality the monohydrochloride predominates[1]
Melting point: ETH, 88°C; ETH HCl, 200°C [Merck Index]
Formulation and optimal human dosage: Available as 100 and 400 mg tablets. 15 mg/kg daily or up to 25 mg/kg but risk of ocular toxicity. Weekly dose, 30 mg/kg 3 times/week [FDA label].

Basic biology information

Drug target/mechanism: Ethambutol (ETH) inhibits arabinosyl transferases involved in cell-wall biosynthesis; in *Mycobacterium smegmatis* two polymers seem to be directly affected, arabinogalactan (AG) and lipoarabinomannan (LAM). AG forms part of the mucolyl-AG-peptidoglycan layer which anchors the peptidoglycan layer to the lipid-mycolic acid outer layer. LAM appears to be attached to the cell membrane via phosphatidyl-inositol.[2] In *M. smegmatis*, ETH inhibited synthesis of arabinan completely and inhibited AG synthesis most likely as a consequence of this; more than 50% of the cell arabinan was released from the bacteria following ETH treatment, whereas no galactan was released.[2] Multiple arabinosyl transferase enzymes exist but the *embB* gene product seems to be the main target in *M. avium*,[3] and in a study of *M. tuberculosis* resistant mutants 60% had changes in the *embB* gene.[4] However knock-outs in *M. smegmatis* of *embA*, *embB* and *embC* were all viable; *embB* was the slowest growing.[5] *embA* and *embB* appear to be involved in the synthesis of AG whereas *embC* is associated with LAM synthesis.[6]
Drug resistance mechanism: Mutations in *M. tuberculosis embA* or *embB* resulted in MICs of 10–50 μg/ml although *embB* mutations may be more common.[3] One of the most common mutations in *M. tuberculosis* is Met306 in *embB*, which is often replaced by isoleucine, leucine or valine.[4] Resistance can be transferred through expression of *M. tuberculosis* ETH-resistant *embB* gene in a wild-type recipient (reviewed in Ramaswamy et al. 2000[4]). Mutants in multiple *emb* genes may have even higher MICs. ETH mutants (~25% in some studies) with no changes in the *emb* genes have also been identified.[4] Stepwise mutations appear to occur, no cross-resistance with other TB agents has been observed [FDA label].
In-vitro potency against MTB: MIC *M. tuberculosis* (H37Rv): 0.5 μg/ml.[7]
Spectrum of activity: ETH is effective against actively growing microorganisms of the genus *Mycobacterium*, including *M. tuberculosis*. Nearly all strains of *M. tuberculosis* and *M. kansasii* as well as a number of strains of the *M. avium* complex (MAC) are sensitive to ETH.[8]
Other in-vitro activity: When *M. tuberculosis*-infected macrophages were treated with ETH, the log CFUs following treatment for 3 days were as follows: 3 μg/ml = 4.32; 6 μg/ml = 4.17; control value = 4.8. The MICs for *M. avium* (MTCC

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	-	-	3.5*	-	-	*C_{max} in mice orally dosed with 16 mg/kg[14]
Human	2.6	24.9	5.0	–	467 ml/min	Prospective study PK evaluated after 2 months daily treatment with 100+ patients, dose median value 24.5 mg/kg.[15] FDA label on myambutol: C_{max} 2–5 μg/ml (2–4 h after dosing), drug undetectable 24 hours after last dose except in cases of renal insufficiency.

1723) and *M. smegmatis* (MTCC 6) were 15 μg/ml and 0.18 μg/ml, respectively.[9]

In-vivo efficacy in animal model: In vivo in mouse (drug given orally 15 days post i.v. infection 1×/week for 5 weeks) log CFU reductions: untreated, 5.07; 100 mg/kg, 4.59.[9] In a mouse efficacy study ETH was dosed for 12 weeks with isoniazid (INH) or alternate days with rifampin (RIF) and pyrazinamide (PZA); CFUs in this study group were significantly lower than ETH, PZA, INH and RIF dosed together 3 times weekly.[10] The complexity of the experimental conditions and observations in this work using only 4 drugs serves to illustrate the difficulty in optimizing the dose for TB treatment.

Efficacy in humans

ETH is described as "fourth drug" for empiric treatment of *M. tuberculosis* and *M. avium*.[11] ETH is used as an adjunct in the treatment of pulmonary tuberculosis especially in cases of suspected drug resistance. ETH should not be used alone due to the real risk of resistant mutants. ETH plus INH or streptomycin (STR) have both been recommended [FDA label]. Treatment regime most often used: initially INH, RIF, PZA, ETH daily for 2 months followed by INH and RIF 3 times weekly for 4 months [DrugBank]. Specific doses and specific treatment times vary and details can be found in many sources including Centers for Disease Control [http://www.cdc.gov/mmwR/preview/mmwrhtml/rr5211a1.htm] and the World Health Organization [http://www.who.int/en/].

In a human clinical study in 100 patients ETH appeared to lack sterilizing activity and may inhibit sterilizing activities of other TB drugs at least in the first 14 days of treatment;[12] when used as the primary drug in an intermittent regimen ETH-treated patients exhibited a high relapse rate (reviewed in Mitchison 2004[13]). The standard 15 mg/kg daily is marginally effective. According to Mitchison[13] ETH has not been adequately tested for its efficacy in a combinatorial treatment regimen.

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Human: Bioavailability from oral dose is ~75–80%. ETH levels appear to increase with age, and patients with a history of TB exhibited lower drug levels.[15] Details of ETH human PK can be found in Peloquin et al. (1999).[11]
- Elephant: PK of ETH gave a 1–2 hour half-life.[16]

Human metabolic pathway: Hepatic: Compound is metabolized to an aldehydic intermediate, followed by conversion to a dicarboxylic acid. Mainly renal excretion, 50% excreted unchanged, 8–15% as metabolites. 20–22 percent excreted in the faeces. No drug accumulation with single daily doses of 25 mg/kg in patients with normal kidney function, marked accumulation in patients with renal insufficiency. ETH is excreted into breast milk [FDA label].

Safety and Tolerability

Animal drug–drug interactions: No significant drug–drug interactions noted.

Animal toxicity: LD_{50} in mice (g/kg): 2.8 orally; 2.21 i.p. [Merck Index]. Oral rat LD_{50}: 4 g/kg.

In rhesus monkeys given high doses over several months neurological signs were observed and the severity of these was proportional to drug concentrations in serum [FDA label].

Reproductive toxicology: ETH is teratogenic in mice and rabbits when administered in high doses. Birth abnormalities seen in mice and rabbits given high doses included cleft palate and skeletal malformations [FDA label].

When pregnant mice or rabbits were treated with high doses of ETH, fetal mortality was slightly but not significantly ($P > 0.05$) increased. Female rats treated

with ETH displayed slight but insignificant ($P > 0.05$) decreases in fertility and litter size.

In foetuses born of mice treated with high doses of ETH during pregnancy, a low incidence of cleft palate, exencephaly and abnormality of the vertebral column were observed. Minor abnormalities of the cervical vertebra were seen in the newborn of rats treated with high doses of ETH during pregnancy. Rabbits receiving high doses of ETH during pregnancy gave birth to two foetuses with monophthalmia, one with a shortened right forearm accompanied by bilateral wrist-joint contracture and one with hare lip and cleft palate.

Animal safety pharmacology: Toxicological studies in dogs on high prolonged doses produced evidence of myocardial damage and failure, and depigmentation of the tapetum lucidum of the eyes, the significance of which is not known [FDA label]. Degenerative changes in the central nervous system, apparently not dose-related, have also been noted in dogs receiving ETH over a prolonged period.

In the rhesus monkey, neurological signs appeared after treatment with high doses given daily over a period of several months. These were correlated with specific serum levels of ETH and with definite neuroanatomical changes in the central nervous system. Focal interstitial carditis was also noted in monkeys which received ETH in high doses for a prolonged period.

Human drug–drug interactions: ETH interacts with antacids; it is recommended to avoid concurrent administration of ETH with aluminium-hydroxide containing antacids for at least 4 hours following ETH administration as oral absorption may be inhibited; patients coadministered antacids and drug showed a reduction of 20% in serum concentration and 13% in urinary excretion.[11]

A decrease in renal excretion of ETH occurs when given together with RIF.[17]

Human potential toxicity: Optic neuropathy and occasional hepatotoxicity are seen. Concentration above 10 μg/ml can adversely affect vision. This effect may be related to dose and duration of treatment; it is generally reversible when administration of the drug is discontinued promptly. In rare cases recovery may be delayed for up to one year or more. Irreversible blindness has been reported [FDA label].

Optic neuropathy including optic neuritis or retrobulbar neuritis occurring in association with ETH therapy may be characterized by one or more of the following events: decreased visual acuity, scotoma, color blindness, and/or visual defect. These events have also been reported in the absence of a diagnosis of optic or retrobulbar neuritis [FDA label].

Patients should be advised to report promptly to their physician any change of visual acuity [DrugBank].

Human adverse reactions: The most common toxic effect of ETH is optic neuropathy, generally reversible although irreversible blindness has been reported. Hepatotoxicity has been reported; baseline and periodic assessment of hepatic function should be performed during treatment. Other side effects that have been observed are pruritus, joint pain, gastrointestinal upset, abdominal pain, malaise, headache, dizziness, mental confusion, disorientation, and possible hallucinations [FDA label]. Specifically in 12 human cases receiving prophylactic ETH (~23 mg/kg) and PZA (~17 mg/kg) daily for a median of 119 days, 7 of 19 had elevated liver enzymes (alanine and aspartate aminotransferases) and treatment was discontinued; the authors suggest close monitoring of liver toxicity when these two drugs are used together for prophylaxis.[18]

No differences in safety or tolerability were observed in elderly patients [FDA label].

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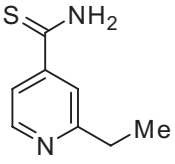
Ethionamide



Generic and additional names: Ethionamide
CAS name: 2-Ethyl-4-pyridinecarbothioamide
CAS registry #: 536-33-4
Molecular formula: $C_8H_{10}N_2S$
Molecular weight: 166.24
Intellectual property rights: Generic
Brand names: Trecator (Wyeth); Nisotin; Trescatyl (M&B); Aetina; Ethimide; Iridocin (Bayer); Tio-Mid
Derivatives: Prothionamide is the propyl analog of ethionamide
Solubility: Very sparingly soluble in water, ether. Sparingly soluble in methanol, ethanol, propylene glycol. Soluble in hot acetone, dichloroethane. Freely soluble in pyridine [Merck Index].
Polarity: Log P 0.705 [DrugBank]
Melting point: 163°C [DrugBank]
Formulation and optimal human dosage: Supplied in 250 mg tablets, recommended dose 750 mg orally [FDA label]
Therapy is usually initiated at 250 mg daily, with gradual titration to optimal doses as tolerated by the patient. A regimen of 250 mg daily for 1 or 2 days, followed by 250 mg twice daily for 1 or 2 days with a subsequent increase to 1 g in 3 or 4 divided doses has been reported [FDA label].

Basic biology information

Drug target/mechanism: Mode of action of the activated form of ethionamide (ETA) is via inhibition of the *inhA* gene product enoyl-ACP reductase.[1,2] The wild-type (WT) *inhA* gene from *Mycobacterium tuberculosis* conferred resistance to isoniazid (INH) and ETA when it was overexpressed in *M. smegmatis* and *M. bovis*.[1] In this regard its mechanism of action is thought to be identical to INH although the pathway of activation is distinct from that of INH. ETA is activated by a *katG*-independent mechanism leading to the formation of an S-oxide metabolite that has considerably more activity than the parent drug (reviewed in Baulard et al. 2000[3]). In a series of papers describing experiments in *M. tuberculosis*, *M. bovis* and *M. smegmatis*, *ethA* (also called *etaA*), which codes for a flavin mono-oxygenase, is reported to be responsible for activation of ETA; expression of this gene is in part controlled by *ethR* (also called *etaR*), a transcriptional repressor gene.[3–5] *M. tuberculosis* mutants overexpressing EtaA were hypersensitive to drug while EtaR over-expressors were drug resistant.[5] The active forms of ETA and prothionamide (PRO) have been crystallized with *M. tuberculosis* and *M. leprae* InhA.[6]

Drug resistance mechanism: Due to the distinct activation mechanisms between INH and ETA, clinically derived *M. tuberculosis* ETA mutants, often cross-resistant with thiacetazone or thiocarlide, are not cross-resistant with INH. This apparent discrepancy arises because many naturally occurring ETA mutants harbor changes in the enzymes responsible for drug activation.[3] Laboratory-derived mutants in the target gene *inhA* do show cross-resistance between INH and ETA. There is complete cross-resistance between PRO and ETA.[7] Thiocarlide and thiacetazone are likely activated by EthA but have a distinct mode of action.[6]

In-vitro potency against MTB: MIC *M. tuberculosis* (H37Rv): 0.25 μg/ml.[8]

Spectrum of activity: ETA has activity against *M. tuberculosis*, *M. bovis* and *M. smegmatis*.[3] ETA also has activity against *M. leprae* (reviewed in Fajardo et al. 2006[9] and Wang et al. 2007[6]).

Other in-vitro activity: ETA and PRO are bactericidal. MIC against *M. tuberculosis* H37Rv in macrophages is 6.25–12.5 μg/ml.[10]

In-vivo efficacy in animal model: ETA was less active than the equivalent dose of INH in a mouse model of tuberculosis: ETA had activity against WT *M. tuberculosis* in a mouse model when drug was

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Human	1.92	7.67	2.16	93.5 L (sugar-coated tablet)	–	Mean PK for 250 mg oral dose using film-coated tablet in healthy adults [FDA label].

administered one week after infection and continued at 5 doses/week for 4 weeks; the log CFUs/lung for control, ETA 25 mg/kg, ETA 50 mg/kg, ETA 75 mg/kg and INH 25 mg/kg were 8.01, 6.67, 6.79, 6.58, and 5.59 respectively.[11] Using a clinical isolate of *M. tuberculosis* resistant to rifampin (RIF) (MIC 64 μg/ml), pyrazinamide (PZA) (MIC > 256 μg/ml) and INH (MIC 1 μg/ml), but sensitive to ETA (MIC 2 μg/ml against resistant strain compared with 4 μg/ml against H37Rv), ETA demonstrated activity in a mouse model (compound given by oral gavage 5 times a week for 4 weeks) of *M. tuberculosis* with a log reduction of 2.96 and 0.43 in lung CFUs using 125 mg/kg and 50 mg/kg, respectively. INH worked better than expected against this strain in the mouse with a log reduction in lung CFUs of 1.65 and 2.19 at 25 mg/kg and 75 mg/kg, respectively. RIF and PZA were inactive or very weakly active.[12]

Efficacy in humans

In second-line therapy for drug-resistant TB, ETA should be administered with other agents due to rapid resistance development when the drug is used as monotherapy. Use of the drugs ETA and PRO is increasing in light of MDR-TB.[6] ETA is used interchangeably with PRO.[6]

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Human: PK parameters differed between healthy subjects and TB patients, resulting in a lower AUC for TB patients, possibly due to decrease in bioavailability.[13] A 500 mg dose appears to be the minimum required to achieve serum concentrations above the MIC.[13] There is little effect of food or antacids on the PK of ETA; the drug can be administered with food if drug tolerance is an issue.[14]

Human metabolic pathway: ETA is widely distributed throughout body tissues and fluids. Extensive metabolism occurs mostly in the liver; ETA is metabolized to the *M. tuberculosis* active metabolite sulfoxide, and several inactive metabolites. Less than 1% of a dose appears in the urine as unchanged drug, the remainder is excreted in the urine as inactive metabolites [FDA label].

Safety and Tolerability

Animal toxicity: Teratogenic potential in rabbits and rats.

Human drug–drug interactions: ETA can potentiate the effects of other TB drugs and may increase levels of INH and cycloserine (CYS). Excess ethanol use in combination with ETA can lead to psychotic reactions. Contraindicated in hepatitis patients [FDA label].

Human potential toxicity: Blood glucose levels require monitoring during treatment [FDA label].

Gastrointestinal: most common side effects are nausea, vomiting, diarrhoea, abdominal pain, excessive salivation, metallic taste, stomatitis, anorexia and weight loss. The effect is dose related with approximately 50% of patients unable to tolerate 1 g as a single dose [FDA label].

Hepatotoxic effects are common and occur at a fairly high rate although they tend to be less serious than with the related drug PRO.[7] Hepatic effects are described as transient [FDA label], but as described by Chan[15] may continue even after the drug is discontinued.

Other side effects: hypothyroidism, peripheral neuropathy and other CNS conditions including blurred vision and headaches.[15,16]

Human adverse reactions: Most common side effects were gastric, with nausea and vomiting [FDA label].

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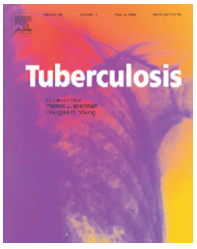
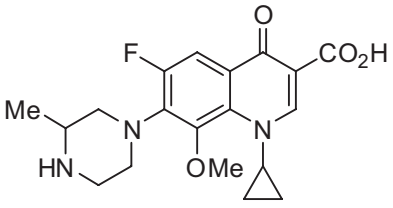


Gatifloxacin



Generic and additional names: Gatifloxacin
CAS name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid
CAS registry #: 112811-59-3
Molecular formula: $C_{19}H_{22}FN_3O_4$
Molecular weight: 375.39
Intellectual property rights: Kyorin Pharmaceutical Co.
Brand names: Tequin (Bristol-Myers Squibb); Zymar (Allergan)
Derivatives: Gatifloxacin is a quinolone/fluoroquinolone antibiotic related to ciprofloxacin, enoxacin, fleroxacin, gemifloxacin, grepafloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin, rufloxacin, sparfloxacin, temafloxacin, trovafloxacin and sitafloxacin
Solubility: 60 mg/ml at pH 4 [DrugBank]
Polarity: Log P 1.81 [DrugBank]
Melting point: 182–185°C [DrugBank]
Formulation and optimal human dosage: 400 mg tablets, dose is 400 mg daily

Basic biology information

Drug target/mechanism: Gatifloxacin (GATI) is a C8-methoxy fluoroquinolone (see moxifloxacin [MOXI] for details on mechanism of action).

Drug resistance mechanism: MOXI and GATI were both found to have mutant prevention concentrations below the C_{max}, GATI $MPC/C_{max} = 0.41$.[1] The C8 methoxy appears to make GATI effective against some other quinolone-resistant MTB isolates (reviewed in Dong et al. 2000[1]).

Also see MOXI.

In-vitro potency against MTB: MIC *M. tuberculosis* (H37Rv): 0.25 μg/ml;[2] others have determined GATI MIC to be lower at 0.03 μg/ml, and MOXI MIC 0.037 μg/ml[1].

M. tuberculosis clinical isolates (23 strains): MIC range 0.007–0.12 μg/ml.[3]

Spectrum of activity: See MOXI.

Other in-vitro activity: MIC_{99} against *M. tuberculosis* is 0.03 μg/ml;[4] *M. tuberculosis* MPC is 1.5 μg/ml.[1] GATI performed better than ofloxacin, levofloxacin (LEV) and ciprofloxacin but equal to MOXI against 100-day-old cultures of *M. tuberculosis* and against these same cultures following treatment with 100 mg/ml rifampin (RIF).[5]

In-vivo efficacy in animal model: In animal models of tuberculosis GATI, MOXI and sparfloxacin are the most active of the fluoroquinolone compounds although in general the class is not known for its superior TB activity in mice, however combinations of MOXI and GATI with isoniazid (INH) and RIF were very promising.[4]

Efficacy in humans

GATI was compared with other fluoquinolones in an EBA study, where monotherapy of GATI (400 mg), MOXI (400 mg), LEV (1000 mg) or INH (300 mg) was administered daily for seven days. The fluoroquinolones exhibit early bactericidal activity (EBA) from days 0–2 slightly less than that found with INH but greater extended EBA (days 2–7) compared with INH.[6] GATI performed almost as well as MOXI at both early and extended time points.[6]

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Human: Protein binding 20%, 96% bioavaliable. Level in tissues is often higher than in serum, ratio saliva:serum is 0.9:1. Often found in high levels in lung parenchyma [FDA label].

Human metabolic pathway: GATI is primarily excreted unchanged through the kidney, with >70% recovered from urine unchanged within 48 hours of dosing. GATI undergoes limited biotransformation in humans with less than 1% of the dose excreted in

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Human	7.8±1.3	33.0±6.2	3.8±1.0	2.0±0.3	151±46 ml/min	Dose 400 mg orally (see table in Drlica et al. 2003;[4] see also Johnson et al. 2006[6]).

the urine as ethylenediamine and methylethylenediamine metabolites. GATI is widely distributed throughout the body [FDA label].

Safety and Tolerability

Animal toxicity: No increase in neoplasms was found in mice given GATI in the diet for 18 months at doses up to 81 mg/kg/day in males and 90 mg/kg/day in females; similar results were seen in rats. GATI tested negative in the majority of strains in the Ames test but was positive in the TA102 strain; it was also positive in *in vitro* gene-mutation assays in Chinese hamster V-79 cells and *in vitro* cytogenetics assays in Chinese hamster lung cells [FDA label].

Teratogenic effect: Skeletal malformations were observed in the offspring of rats given 200 mg/kg/day orally or 60 mg/kg/day intravenously during organogenesis. GATI is slightly foetotoxic at these doses and is not recommended for use during pregnancy [FDA label].

Phototoxicity: no evidence in the hairless mouse or guinea pig models [FDA label].

Animal safety pharmacology: Cardiac: GATI had no effect on QT prolongation in the anaesthetized dog using 10 mg/kg bolus doses [FDA label].

CNS: there was no increase pro convulsant risk in mice dosed up to 100 mg/kg GATI in combination with the NSAID Fenbufen [FDA label].

Human drug–drug interactions: No P450 interactions have been observed with GATI (Fish and North 2001[7] and FDA label).

Co-administration with multivalent cations significantly decreases GATI absorbance from the gut.[7]

Some quinolones have been shown to increase theophylline serum concentrations and interfere with caffeine metabolism [DrugBank].

Human potential toxicity: QTc prolongation: Fluoroquinolones are associated with a low incidence of cardiac toxicity; GATI is thought to have a similar risk for cardiac toxicities as the other quinolones (reviewed in Owens and Ambrose 2005[8]). In a rising single dose of 400, 800 and 1200 mg in healthy volunteers GATI was associated with an increase in QTc interval which corresponded to GATI serum levels [FDA label].

Hepatic: GATI has been associated with severe liver toxicity and hepatic failure.[9]

Glucose homeostasis: the GATI product label mentions the possibility of hypoglycaemia and this risk may increase in the elderly (reviewed in Owens and Ambrose 2005[8]).

Arthropathies and tendonitis: Both toxicities have been reported for the quinolone class although LEV appears to be the quinolone associated with the highest tendonitis rates (reviewed in Owens and Ambrose 2005[8]).

Phototoxicity: not reported for GATI (reviewed in Owens and Ambrose 2005[8]).

Human adverse reactions: GATI is generally well tolerated, with most common side effects being CNS (dizziness, headaches) and gastrointestinal (nausea and diarrhoea). Adverse CNS-related effects were higher with quinolones in general than with other systemic antibiotics. GATI was generally somewhat less well tolerated than a MOXI or a LEV comparator in terms of gastrointestinal and CNS effects (reviewed in Owens and Ambrose 2005[8]). One case of a possible GATI-related seizure has been reported although in general GATI, MOXI and LEV are thought to lack the specific structural motif associated with seizures (reviewed in Owens and Ambrose 2005[8]).

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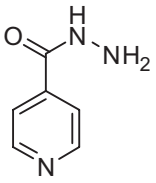
Isoniazid



Generic and additional names: isonicotinic acid hydrazide; isonicotinoylhydrazine; isonicotinylhydrazine; INH; rimitsid; tubazid
CAS name: pyridine-4-carbohydrazide
CAS registry #: 54-85-3
Molecular formula: $C_6H_7N_3O$
Molecular weight: 137.14
Intellectual property rights: Generic. First synthesized in 1912, first used clinically in 1952.
Brand names: Cotinazin (Pfizer); Dinacrin (Winthrop); Ditubin (Schering); Hycozid (Takeda); Iscotin (Daiichi); Isobicina (Maggioni); Isocid (CID); Isolyn (Abbott); Isonex (Dumex); Isonizida (Bial); Isozid (Fatol); Laniazid (Lannett); Mybasan (Antigen); Neoteben (Bayer); Nicizina (Pfizer); Niconyl (Parke-Davis); Nicotibina (Lapetit); Nydrazid (Bristol-Myers Squibb); Pycazide (Smith & Nephew); Pyricidin (Nepera); Rimifon (Roche); Tibinide (Ferrosan); Tubilysin (Orion)
Derivatives: Isoniazid 4-aminosalicylate
Isoniazid 4-pyridinecarboxylic acid 2-(sulfomethyl)
Isoniazid methanesulfonate sodium (derivative)
Solubility: Solubility in water: ~14% at 25°C, ~26% at 40°C; in ethanol: ~2% at 25°C, ~10% in boiling ethanol; in chloroform: ~0.1%. Practically insoluble in ether, benzene [Merck Index].
Polarity: Log P −0.64
Acidity/basicity: pH of a 1% aqueous solution 5.5 to 6.5 [Merck Index]
Melting point: 171.4°C [DrugBank]
Formulation and optimal human dosage: 5 mg/kg for adults, 10–20 mg/kg for children. Adult dosing generally 300 mg capsule administered orally, once daily; or 15 mg/kg up to 900 mg/day, two or three times/week, ideally dose administered one hour before or two hours after a meal. Concomitant administration of pyridoxine (B6) recommended for malnourished patients, adolescents, and those predisposed to neuropathy (e.g. diabetic).
Can also be given intramuscularly or intravenously [DrugBank].

Basic biology information

Drug target/mechanism: Isoniazid (INH) is a prodrug activated by catalase-peroxidase hemoprotein, KatG. INH inhibits InhA, a nicotinamide adenine dinucleotide (NADH)-specific enoyl-acyl carrier protein (ACP) reductase involved in fatty acid synthesis. Vilchèze et al.[1] reported that transfer of *inhA* mutant gene, S94A, into wild-type (WT) *Mycobacterium tuberculosis* was sufficient to confer resistance to INH and ethionamide (ETA), demonstrating that this is the target for INH. Prior to this publication some controversy had existed over the precise mode of action of this target, in part due to the difference in the INH susceptibility of *M. tuberculosis* and *M. smegmatis*, and the presence of INH conferring mutations in a number of other genes, for example *kasA*.[2] The role of the *kasA* gene product, β-ketoacyl ACP synthase,[2] and the precise nature of the INH metabolites responsible for activity remain to be determined. The crystal structures of *M. tuberculosis* InhA and the related enzyme MabA are both solved.[3–5]
Drug resistance mechanism: Resistance mutations occur in the target gene (*inhA*) and in the activating enzyme KatG.
inhA: Specific mutations in, or overexpression of, the target *inhA* gene generate organisms with increased MICs for INH and ethionamide (ETA), with MICs at least 5 times higher than WT.[1]
KatG: INH is a prodrug activated by catalase-peroxidase hemoprotein, KatG. Mutations in the *katG* gene lead to high-level resistance (200× MIC) and ~50% of INH-resistant clinical isolates carry such a mutation, often S315T.[5] INH-resistant mutants with

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	1.7±0.17	52.2±2.2	28.2±3.8	–	–	Single oral dose of 25 mg/kg[13]
Guinea pig	3.5±0.7	10.9±1.8	1.7±0.3	–	–	Single oral dose 10 mg/kg[15,16]
Human	FA:1.54±0.3 SA: 3.68±0.59	FA: 19±6.1 SA: 48.2±1.5	FA: 5.4±20 SA: 7.1±1.9	–	–	Single oral dose of 6.2 mg/kg.[13] FA = fast acetylators, SA = slow acetylators.

changes in the genes *ahpC* (alkyl hydroperoxide reductase), *kasA*[2] and *ndh* (NADH dehydrogenase) have also been observed.[6,7]

In-vitro potency against MTB: MIC *M. tuberculosis* (H37Rv): 0.025 μg/ml.[8]

Spectrum of activity: INH is a bactericidal agent active against organisms of the genus *Mycobacterium*, specifically *M. tuberculosis*, *M. bovis* and *M. kansasii*. INH is bactericidal to rapidly-dividing mycobacteria, but is bacteristatic if the mycobacterium is slow-growing. INH is highly specific, being active against only a subset of the mycobacteria and largely ineffective against other microorganisms; this is in part due to several unusual aspects of metabolism, exemplified in *M. tuberculosis*, including unusually high KatG activity and a defective drug efflux mechanism.[9]

Other in-vitro activity: INH is bactericidal only over the first 48 hours in culture; after this the effect is mostly bacteristatic presumably because all the actively growing organisms are killed rapidly, leaving the "persistors". This reflects the effect seen *in vivo* with efficacy only against the fast-growing organisms.[10] MICs of INH were decreased in the presence of plumbagin and clofazimine (CLOF), both of which can generate superoxides.[11] Many drug combinations seem to synergize with INH *in vitro*; little additional activity was observed when INH alone was tested with a variety of known anti-TB drugs including rifampin (RIF), however significant synergy was seen when RIF and INH were tested in combination with gatifloxacin (GATI) (FIC 0.39–0.65), sparfloxacin (FIC 0.39–0.48), ciprofloxacin (FIC 0.43–0.68), clarithromycin (CLA) (FIC 0.48–0.55) and ETH (FIC 0.7–1).[12] Synergy at the MIC level was also seen with INH in combination with levofloxacin (LEV), with ETH and LEV, and with ETH, RIF and LEV.[13] INH effects on the bacteria within a macrophage seem somewhat controversial. Jayaram et al.[10] report that INH inhibits growth of *M. tuberculosis* in macrophages at 0.05 μg/ml, but no bactericidal activity was observed even at 32 μg/ml. In these experiments, despite the rapidly growing bacteria, bactericidal activity was not observed. To explain this it was postulated that the pH within the vacuole containing the bacteria was not conducive to drug action.[10] Rastogi et al.,[8] on the other hand, report that INH is active and bactericidal when *M. tuberculosis* is tested within macrophages.

In-vivo efficacy in animal model: Activity in mice (dosed 14 days after infection using 6 times weekly gavage at 25 mg/kg for 8 weeks) reduced log CFU from 6.13 (control) to 3.47.[13] Good efficacy against *M. tuberculosis* in guinea pigs, mice, and monkeys was found at 10 mg/kg, but no increase in efficacy when the drug was administered at 100 mg/kg. Bactericidal activity of INH slows down after the first 2–3 weeks in mice, and CFUs stabilize at a low level after 2–3 months of treatment.[9] INH-resistant organisms may emerge after longer treatment with INH monotherapy.[9] Labana et al.[14] showed that efficacy of INH in mice could be maintained, while reducing the therapeutic dose by one third, with the use of liposome encapsulation.

Efficacy in humans

INH has high early bactericidal activity that kills actively growing bacteria and causes rapid decrease in sputum bacilli for the first 2 weeks of treatment, then slows down for non-growing bacterial populations (reviewed in Zhang 2003[9]).

For patients with low-level primary INH resistance (<1% bacilli resistant to 1 μg/ml INH), treatment is still suggested. Drug can be administered by oral, IV or IM routes. Treatment regime most often used: initially INH, RIF, PZA, ETH daily for 2 months followed by INH and RIF 3 times weekly for 4 months [DrugBank]. Specific doses and specific treatment times vary and details can be found in many sources including Centers for Disease Control [http://www.cdc.gov/mmwR/preview/mmwrhtml/rr5211a1.htm] and the World Health Organization [http://www.who.int/en/]. INH can be used prophylactically in the case of latent disease.

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Mouse: Linear PK (oral dose) over 0.1–120 mg/kg. In aerosol infection model AUC_{24}/MIC is predictive

of antimicrobial activity.[10] Antagonism between INH, RIF and PZA is found in mice.[17]
- Guinea pig: Bioavailability 58%. Pandey et al.[15,16] report some guinea pig PK comparing INH and RIF using single oral dose at 12 mg/kg.
- Human: Drug concentration in lung is similar to those in serum.[9] INH levels appear to increase with age.[18] Close to 100% bioavailable under most circumstances.

Animal metabolic pathway: Primarily hepatic.
Human metabolic pathway: Primarily hepatic. INH is acetylated to give N-acetylisoniazid, then biotransformed to isonicotinic acid and monoacetylhydrazine. The rate of acetylation is genetically determined (50% of blacks and whites are slow acetylators [SA], 85% of Eskimos and Asians are fast acetylators [FA]). Slow acetylators are characterized by a relative lack of hepatic N-acetyltransferase. INH is found widely distributed in all body fluids (cerebrospinal, pleural, ascitic), tissues, organs, and excreta (saliva, sputum, faeces); it passes through the placental barrier and into milk. Excretion is primarily renal [FDA label, Jayaram et al. 2004[10]].

Safety and Tolerability
Animal drug–drug interactions: INH (100 mg/kg daily for 4 days by oral gavage) in rats leads to an upregulation in CYP2E but not CYP3A. A 566% increase was also seen in liver 4-nitrophenyl hydroxylase activity.[19]
Antagonism between INH, RIF and PZA can be observed in mice under specific circumstances even though these drugs are used in combination in humans.[13,17] In the initial phase of infection (first 2 months) INH/RIF was as efficacious as INH/RIF/PZA but less active than RIF/PZA. At the end of the continuation phase (6 months treatment) with INH/RIF or INH/RIF/PZA or RIF/PZA all animals were apparently sterilized. After 6 months (drug free) more animals relapsed in the INH/RIF or INH/RIF/PZA group compared with the RIF/PZA group, suggesting antagonism between INH and RIF/PZA.[17] The cause of the apparent antagonism is most likely to be the effect of INH on the RIF AUC and C_{max}, both of which were decreased in the presence of INH.[17] Such antagonism may not be apparent in humans because the generally accepted experimental use level of INH is higher in mice compared with the standard human dose.[13]
Animal toxicity: Acute toxicity: LD_{50} in mice (mg/kg), 151 i.p., 149 i.v. [Merck Index].
Reproductive toxicity: INH has embryocidal effects in rats and rabbits when administered orally during pregnancy, but no congenital anomalies were found in reproduction studies in mammalian species (mice, rats and rabbits) [DrugBank].
Hepatotoxicity: INH administered in encapsulated form once or twice a week was as effective as free drug and showed less liver toxicity as measured by ALT, alkaline phosphatase and bilirubin levels.[14,20] Favorable results were achieved with an INH-Schiff base analog to block *in vivo* acetylation by arylamine N-acetyltransferase (NAT). The acetylated drug is inactive. The Schiff-base analog demonstrated an increase in mouse LD_{50} to ~1000 mg/kg from ~150 mg/kg for INH[21] and may be less toxic *in vivo*. INH and RIF dosed simultaneously in rabbits caused an elevation in phosholipids and a reduction in phosphatidylcholine, cardiolipin and inorganic phosphates, possibly via a choline deficiency, which may lead to the observed liver toxicity.[22]
INH has been shown to induce pulmonary tumors in a number of mouse strains. INH has not been shown to be carcinogenic in humans [Package Insert, Drugs.com].
INH has been found to be weakly mutagenic in strains TA 100 and TA 1535 of *Salmonella typhimurium* (Ames assay) without metabolic activation [Package Insert, Drugs.com].
In vitro studies of a variety of animal cell lines demonstrated that INH toxicity results from the induction of apoptosis with associated disruption of mitochondrial membrane potential and DNA strand breaks.[20]
Animal safety pharmacology: CNS: Convulsions were induced in chicks with INH and a corresponding rise in GABA was observed, however coadministration of pyridoxine reversed the effects.[23] INH binds to pyridoxal-5-phosphate, the active form of pyridoxine (vitamin B6), to form INH-pyridoxal hydrazones. Pyridoxal-5-phosphate is a cofactor for glutamic acid decarboxylase and GABA transaminase in the GABA synthetic pathway. INH overdose results in decreased pyridoxal-5-phosphate, decreased GABA synthesis, increased cerebral excitability, and seizures. Co-ingestion of ethanol potentiates toxicity by enhancing degradation of phosphorylated pyridoxine. INH also inhibits lactate dehydrogenase, an enzyme that converts lactate to pyruvate.
Human drug–drug interactions: INH interacts with the cytochrome P450 system, especially CYP2E1, where it shows a biphasic inhibition–induction; it causes increases in serum concentrations of various drugs, especially phenytoin and carbamazepine, increases the effects of warfarin and theophylline, inhibits metabolism of benzodiazepines, and inhibits monoamine oxidase and histaminase (reviewed in Self et al. 1999[24]).
INH should not be administered with food, as studies have shown that this significantly reduces its bioavailability.

Human potential toxicity: Hepatitis: Risk of developing severe and sometimes fatal hepatitis is associated with INH usage, and risk increases with age and with daily alcohol consumption. In a study in the 1970s 10–25% of those monitored developed at least sub-clinical hepatic effects (reviewed in Sanders and Sanders 1979[23]). The drug is acetylated *in vivo* and slow acetylators generally experience higher blood levels and a potential for increase in toxicity.[25] Acetyl hydrazine is released from acetylated INH and may be at least one of the toxic components.[23]

CNS: Peripheral neuropathy: chronic use of INH can produce peripheral neuropathy but this can be prevented by the concurrent administration of pyridoxine.

Since INH is known to cross the placental barrier, neonates of INH-treated mothers should be carefully observed for any evidence of adverse effects. A diagnosis of mesothelioma in a child with prenatal exposure to INH and no other apparent risk factors has been reported [Package Insert, Drugs.com].

Human adverse reactions: CNS effects: Peripheral neuropathy is the most common CNS-related toxic effect. It is dose-related, occurs most often in the malnourished and in those predisposed to neuritis (e.g., alcoholics and diabetics), and is usually preceded by paraesthesias of the feet and hands. The incidence is higher in "slow acetylators". Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment and toxic psychosis [DrugBank].

Hepatitis: INH does carry a specific warning of the potential for liver toxicity. Liver toxicity and hepatitis risks are increased with concomitant use of carbamazepine, phenobarbital, RIF, and alcohol abuse. Elevated serum transaminase (SGOT SGPT), bilirubinaemia, bilirubinuria, jaundice, and occasionally severe and sometimes fatal hepatitis can occur with normal dosing regimens. The common prodromal symptoms of hepatitis are anorexia nausea, vomiting, fatigue, malaise, and weakness. Mild hepatic dysfunction, evidenced by mild and transient elevation of serum transaminase levels, occurs in 10–20% of patients taking INH. This abnormality usually appears in the first 1–3 months of treatment but can occur at any time during therapy. In most instances enzyme levels return to normal, and generally there is no necessity to discontinue medication during the period of mild serum transaminase elevation. The frequency of progressive liver damage increases with age. It is rare in persons under 20, but occurs in up to 2.3% of those over 50 years of age [Zhang 2003,[9] DrugBank].

Gastrointestinal: effects such as nausea, vomiting, epigastric distress and dark urine can occur but are rare.[9]

Haematological effects: agranulocytosis; hemolytic, sideroblastic, or aplastic anaemia, thrombocytopenia; and eosinophilia can occur.[9]

Endocrine and metabolic: pyridoxine deficiency, pellagra, hyperglycaemia, acidosis and gynecomastia can occur.[9]

Hypersensitivity: fever, skin rashes, lymphadenopathy and vasculitis can occur.[10]

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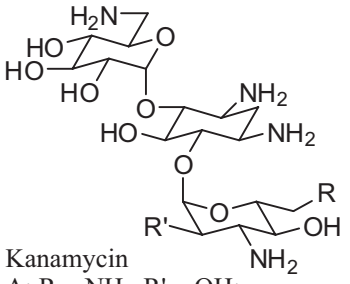
Kanamycin

Generic and additional names: -
CAS name: 2-(Aminomethyl)-6-[4,6-diamino-3-[4-amino-3,5-dihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-2-hydroxy-cyclohexoxy]-tetrahydropyran-3,4,5-triol
CAS registry #: 8063-07-8
Molecular formula: $C_{18}H_{36}N_4O_{11}$
Molecular weight: 582.58
Intellectual property rights: Generic
Brand names: Aminodeoxykanamycin, Bekanamycin, Kanamycin A, Kanamycin B, Kanamycin Base, Kanamycin Sulfate, Kantrex, Kenamycin A, Klebcil, Nebramycin Factor 5
Derivatives: Kanamycin A, Kanamycin B, Kanamycin C



Kanamycin
A: R = NH_2, R' = OH;
B: R = NH_2, R'=NH_2;
C: R = OH, R' = NH_2.

Solubility: Kanamycin A sulfate is freely soluble in water. Practically insoluble in the common alcohols and nonpolar solvents.
Kanamycin B – Bekanamycin, aminodeoxykanamycin – is soluble in water, formamide; slightly soluble in chloroform, isopropyl alcohol; practically insoluble in the common alcohols and nonpolar solvents.
Kanamycin C is soluble in water; slightly soluble in formamide; practically insoluble in the common alcohols and nonpolar solvents [Merck Index].
Polarity: Log P –7.936 [DrugBank]
Formulation and optimal human dosage: 1 g vial, dose 1 g daily i.v. or intramuscularly (i.m.)[1]

Basic biology information

Drug target/mechanism: Kanamycin (KAN) is an aminoglycoside antibiotic having the same mode of action as streptomycin (STR); it inhibits protein synthesis by tightly binding to the conserved A site of 16S rRNA in the 30S ribosomal subunit.[1] It is in the same class as amikacin (AMI) and STR.
Drug resistance mechanism: Ribosomal changes in *Mycobacterium tuberculosis* 16S rRNA[2] lead to possible cross-resistance with other class members, STR and AMI, but this is not always complete. For example, KAN, AMI and capreomycin (CAP) were still efficacious *in vitro* when resistance to STR had developed.[3] See also the *Drug resistance mechanism* section for STR.
In-vitro potency against MTB: MIC *M. tuberculosis* (H37Rv): 2 μg/ml.[4]
Spectrum of activity: Aminoglycosides are used mainly in infections involving aerobic, Gram-negative bacteria, such as *Pseudomonas*, *Acinetobacter* and *Enterobacter*. *M. tuberculosis* is also sensitive to this drug. Gram-positive bacteria can also be treated with the drug but less toxic alternatives tend to be utilized. Synergistic effects with the aminoglycosides and beta lactams have resulted in use of this combination treatment for streptococcal infections, especially endocarditis [DrugBank].
Other in-vitro activity: KAN demonstrated good bactericidal activity against drug-sensitive *M. tuberculosis* clinical isolates, but when tested against drug-resistant isolates it had bactericidal activity against only 2 out of 5 strains when tested at 8 μg/ml.[4]
KAN had no bactericidal activity, but did cause significant reduction in bacterial load when *M. tuberculosis*-infected macrophages were treated using aminoglycosides; there was a 1–2 log reduction in CFU, 99% killing using STR 30 μg/ml or KAN 30 μg/ml or AMI 20 μg/ml.[4]
In-vivo efficacy in animal model: AMI was the most active of the aminoglycosides tested (STR, AMI and KAN dosed at 200 mg/kg 6 times weekly) in a mouse model of tuberculosis (2.3×10^7 CFU *M. tuberculosis* administered i.v. followed by dosing 1 day later). STR reduced the CFU in the spleen by almost 1 log.

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Human	2.5	–	22	–	–	7.5 mg/kg dose given i.v. Intravenous administration of KAN over a period of one hour resulted in serum concentrations similar to those obtained by intramuscular administration [DrugBank].

All three drugs were less efficacious than isoniazid (INH) at 25 mg/kg. All the mice in the drug-treated groups survived whereas the control mice died within 30 days.[5]

Efficacy in humans

Aminoglycosides remain important drugs for treating diseases caused by *M. tuberculosis*[6] but they are no longer considered first-line agents. The aminoglycosides and CAP cannot be administered orally. KAN is more toxic than STR and has the weakest antibacterial activity of the aminoglycosides in clinical use.[5]

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Chan et al. give a value for C_{max} of 35–45 μg/ml, with no dose given.[1]

Human metabolic pathway: Primarily eliminated through the kidney.

Safety and Tolerability

Animal toxicity: Oral mouse LD_{50}: 17,500 mg/kg. Oral rat LD_{50}: >4000 mg/kg. Oral rabbit LD_{50}: >3000 mg/kg [DrugBank].

Animal safety pharmacology: Ototoxicities were observed in guinea pigs [FDA label].

Human drug–drug interactions: In vitro mixing of an aminoglycoside with beta-lactam type antibiotics (penicillins or cephalosporins) may result in a reduction in aminoglycoside serum half-life or serum levels especially when renal function is impaired. A history of hypersensitivity or toxic reaction to one aminoglycoside contraindicates the use of any other aminoglycoside [DrugBank]. Also see STR and AMI.

Human potential toxicity: The aminoglycosides and CAP are known for their ototoxicities, and incidences may be as high as 3–10%.[1] Bowel lesions can increase drug absorption [DrugBank].

Human adverse reactions: KAN may lead to eighth-cranial-nerve impairment, intestinal obstruction, renal function impairment, or ulcerative lesions of the bowel.

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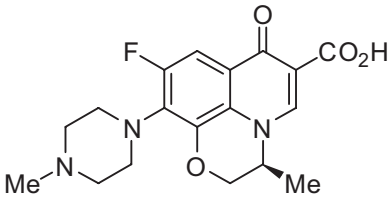
Levofloxacin

Generic and additional names: S-(−)-form of Ofloxacin
CAS name: 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid
CAS registry #: 100986-85-4; 138199-71-0 (hemihydrate)
Molecular formula: $C_{18}H_{20}FN_3O_4$
Molecular weight: 361.37
Intellectual property rights: Generic



Brand names: Cravit (Daiichi); Levaquin (Ortho-McNeil); Tavanic (Aventis); Quixin (Santen)
Derivatives: Levofloxacin is a quinolone/fluoroquinolone antibiotic related to ciprofloxacin, enoxacin, fleroxacin, gatifloxacin, gemifloxacin, grepafloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin, rufloxacin, sparfloxacin, temafloxacin, trovafloxacin, sitafloxacin
Solubility: Freely soluble in glacial acetic acid, chloroform; sparingly soluble in water [Merck Index].
Polarity: Log P 1.268 [DrugBank]
Formulation and optimal human dosage: 500 mg tablet, dose 500–1000 mg daily

Basic biology information

Drug target/mechanism: Levofloxacin (LEV) is described as a second-generation quinolone along with ciprofloxacin (CIPRO) and ofloxacin (OFL). See moxifloxacin (MOXI) for mode of action details.
Drug resistance mechanism: See MOXI.
In-vitro potency against MTB: MIC Mycobacterium tuberculosis H37Rv: 0.5 μg/ml.[1]
Spectrum of activity: See MOXI.
Other in-vitro activity: MIC_{99} for LEV is 0.2 μg/ml against *M. tuberculosis*[2] which is lower than the MIC of 0.5 μg/ml obtained by Rastogi et al.[1] In general most authors agree that MOXI has the lowest MIC against *M. tuberculosis* when comparing this compound to CIPRO, OFL and LEV.[3] Specifically, Rodriguez et al.[3] reported MICs of ⩾2 μg/ml with CIPRO for 12 strains (21.8%), with OFL for 11 strains (20%), with LEV for five strains (9%) and with MOXI for two strains (3.6%). A minimum inhibitory concentration of ⩽0.5 μg/ml was obtained for CIPRO in 23 strains (41.8%), for OFL in 34 strains (61.8%), for LEV in 45 strains (81.8%) and for MOXI in 46 strains (83.6%).[3] One strain had an MIC of 128 μg/ml for CIPRO, 4 μg/ml for OFL and 2 μg/ml for LEV and MOXI.[3] LEV performed significantly less well than MOXI and gatifloxin (GATI) against 100-day-old cultures of *M. tuberculosis* (representing the persistent form of *M. tuberculosis*) and against these same cultures following treatment with 100 μg/ml rifampin (RIF).[4] LEV was active against *M. tuberculosis*-infected macrophages at 0.5 μg/ml (reviewed in Berning 2001[5]).
In-vivo efficacy in animal model: When LEV was tested against a mouse model of tuberculosis (10^7 organisms given i.v., dosing began 1 day after infection and continued for 28 days) INH and RIF were superior; no differences were found between between LEV and ethambutol (ETH) or pyrazinamide (PZA) against organism load in the spleen. At equal doses LEV was better than OFL but inferior to sparfloxacin.[6] Similar results were found in a short-course (2 days) treatment regimen.[7]

Efficacy in humans

LEV was compared with other fluoroquinolones in an EBA study, where monotherapy of GATI (400 mg), MOXI (400 mg), LEV (1000 mg) or INH (300 mg) was administered daily for seven days. The fluoroquinolones exhibit early bactericidal activity (EBA) from days 0–2 slightly less than that found with INH but greater extended EBA (days 2–7) compared with INH.[8] EBA activity between the three fluoroquinolones was similar on days 2–7 but LEV was better at days 0–2 compared with MOXI and GATI.[8] LEV is used in combination with other drugs to treat human tuberculosis, for example at 750 mg/daily;[5] it is generally used in a second-line treatment regimen.[2]

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	1.02	3.17 μg·h/ml	–	–	–	Single i.v. dose of 10 mg/kg to mice[9]
Monkey	1.86	31.79 μg·h/ml	8.5	–	0.79 l/h/kg	Single 25 mg/kg oral dose to male rhesus monkeys[10]
Human	7.7–8.9	71.4–110.0 μg·h/ml	7–12	1.5	–	Dose 750 mg oral.[5]

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Oral bioavailability 85–95%.[5]

Human metabolic pathway: LEV and OFL are cleared primarily by the kidney.[5]

Safety and Tolerability

Animal drug–drug interactions: In-vitro and *in-vivo* studies in animals indicate that LEV is neither a P450 enzyme inducer nor an inhibitor in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme-related interactions with other drugs or agents are anticipated.[11]

Animal toxicity: Acute toxicity: The median lethal dose (LD_{50}) values obtained in mice and rats after oral administration of LEV were in the range 1500–2000 mg/kg. Administration of 500 mg/kg p.o. to monkeys induced little effect apart from vomiting.

Repeated dose toxicity: Studies of one and six months duration by gavage have been carried out in the rat and monkey. Doses were 50, 200, 800 mg/kg/day and 20, 80, 320 mg/kg/day for 1 and 6 months in the rat and 10, 30, 100 mg/kg/day and 10, 25, 62.5 mg/kg/day for 1 and 6 months in the monkey. Signs of reaction to treatment were minor in the rat with slight effects principally at 200 mg/kg/day and above in reducing food consumption and slightly altering haematological and biochemical parameters. The No Observed Adverse Effect Level (NOAEL) in these studies was concluded to be 200 and 20 mg/kg/day after 1 and 6 months respectively. Toxicity after oral dosing in the monkey was minimal with reduced body weight at 100 mg/kg/day together with salivation, diarrhoea and decreased urinary pH in some animals at this dose. No toxicity was seen in the 6-month study. The NOAELs were concluded to be 30 and 62.5 mg/kg/day after 1 and 6 months respectively.

Reproductive toxicity: LEV caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day or intravenous doses up to 100 mg/kg/day. LEV was not teratogenic in rats at oral doses as high as 810 mg/kg/day, or at intravenous doses as high as 160 mg/kg/day. No teratogenicity was observed when rabbits were dosed orally with up to 50 mg/kg/day or intravenously with up to 25 mg/kg/day. LEV had no effect on fertility and its only effect on foetuses was delayed maturation as a result of maternal toxicity.

Genotoxicity: LEV did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung cells *in vitro* at or above 100 μg/ml, in the absence of metabolic activation. *In-vivo* tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential.

Phototoxic potential: Studies in the mouse after both oral and intravenous dosing showed LEV to have phototoxic activity only at very high doses. LEV did not show any genotoxic potential in a photomutagenicity assay, and it reduced tumor development in a photocarcinogenicity assay.

Carcinogenic potential: No indication of carcinogenic potential was seen in a two-year study in the rat with dietary administration (0, 10, 30 and 100 mg/kg/day).

Toxicity to joints: In common with other fluoroquinolones, LEV showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals [see Levaquin product monograph for complete toxicity listings].

Animal safety pharmacology: In mice, the CNS stimulatory effect of quinolones is enhanced by concomitant administration of non-steroidal anti-inflammatory drugs. In dogs, LEV administered at 6 mg/kg or higher by rapid intravenous injection produced hypotensive effects. These effects were considered to be related to histamine release.[11] Some quinolones including LEV have been associated with prolongation of the QT interval and some cases of arrhythmias. LEV has a hERG IC_{50} of 915 μM, which is not as potent an inhibitor of the hERG channel as some other quinolones such as Sparfloxacin (18μM), Grepafloxacin (50 μM) and MOXI (129μM).[12]

Human drug–drug interactions: No significant drug interactions have been observed in patients taking concurrent treatment of LEV and theophylline, cyclosporin, digoxin, probenecid, cimetidine or zidovudine. However, disturbances in blood glucose levels have been reported in patients taking LEV with an antidiabetic drug. Similarly, drug interactions have been observed in patients treated with LEV and warfarin resulting in an enhancement of the anticoagulant effects of oral warfarin and its derivatives (Product Monograph, Levaquin, Janssen-Ortho Inc).

Human potential toxicity: Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class.

As with other quinolones and with LEV, disturbances of blood glucose, including symptomatic hyper- and hypoglycaemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide) or with insulin.

The reports of arrhythmias generally involve patients with either concurrent medical conditions such as myocardial infarction or congenital QT prolongation or those taking concurrent medications, such as amiodarone and sotalol, which prolong the QT interval.[11] Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using LEV with concomitant drugs that can result in prolongation of the QT interval (e.g. class IA or class III antiarrhythmics) or in patients with risk factors for Torsades de pointes (e.g. known QT prolongation, uncorrected hypokalemia).[11]

Human adverse reactions: The incidence of drug-related adverse reactions in patients during Phase 3 clinical trials conducted in North America was 6.2%. Among patients receiving LEV therapy, 4.3% discontinued LEV therapy due to adverse experiences.

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including LEV.

LEV should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold.

Peripheral neuropathies have been associated with LEV use.

The following adverse reactions can occur during LEV treatment:

- hypersensitivity reactions: skin rash, hives or other skin reactions, angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction;
- tendon disorders: tendonitis or tendon rupture, with the risk of serious tendon disorders being higher in those over 65 years of age, especially those on corticosteroids.
- phototoxicity, prolongation of the QT interval.[11]

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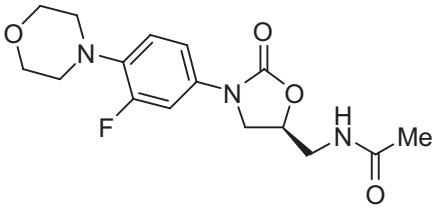
Linezolid



Generic and additional names: Linezolid
CAS name: N-[[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide
CAS registry #: 165800-03-3
Molecular formula: $C_{16}H_{20}FN_3O_4$
Molecular weight: 337.35
Intellectual property rights: Pfizer
Brand names: Zyvox, Zyvoxid (Pfizer)
Derivatives: Dong-A Pharmaceutical has reported several new oxazolidinones (DA-7157, DA-7218 and DA-7867) having somewhat improved *in-vitro* potency, compared to linezolid, against *Mycobacterium tuberculosis*, *M. kansasii* and *M. marinum*[1,2]
Solubility: In water up to 3 mg/ml [DrugBank]
Polarity: Log P 0.232 [DrugBank]
Melting point: 181.5–182.5°C [Merck Index]
Formulation and optimal human dosage: Zyvox tablets for oral administration contain 400 mg or 600 mg linezolid.
Zyvox i.v. injection is supplied as a 2 mg/ml isotonic solution for intravenous infusion.
Doses: oral or i.v. 600 mg every 12 hours for serious infections and 400 mg every 12 hours for uncomplicated infection [FDA label].

Basic biology information

Drug target/mechanism: Linezolid (LIN) is first in a new class of oxazolidinone antibiotics, and inhibits protein synthesis by a mechanism not shared by other antibiotics. LIN binds to 23S rRNA inhibiting translation in the early phase preventing the proper binding of formyl-methionine tRNA. LIN also inhibits mammalian mitochondrial protein synthesis, using isolated mitochondria, with an IC_{50} of 12.7 μg/ml.[3]
Drug resistance mechanism: No LIN cross-resistance has been observed with sensitive *Mycobacterium tuberculosis* or pan-resistant *M. tuberculosis* strains.[4] Resistance mutations occur in *Staphylococcus aureus* at the low frequency of 1 in 10^{-10} to 10^{-11} and are found in the 23S rRNA [FDA label]. LIN-resistant clinical mutants have been found in *S. aureus*[5] and in the enterococci.[6] LIN inhibits bacterial protein synthesis through a mechanism of action different from that of other antibacterial agents; therefore, cross-resistance between LIN and other classes of antibiotics is unlikely. However, a recent publication[7] has identified LIN-resistant *M. tuberculosis* clinical isolates; specifically, 1.9% of 210 strains had MICs of 4 μg/ml (1 strain) and 8 μg/ml (3 strains). No mutations were detected in the following proteins associated with the LIN target: 23S rRNA, ribosomal proteins L4 and L22, Erm-37 methyltransferase and WhiB7 putative regulator protein. A mutation in an efflux pump or drug transport is postulated.[7]
In-vitro potency against MTB: M. tuberculosis H37Rv: MIC 0.25 μg/ml.[8]
Spectrum of activity: LIN is active against a broad range of Gram-positive organisms and certain Gram-negative species in addition to the mycobacteria. LIN is bacteristatic against enterococci and staphylococci and bactericidal for the majority of strains of streptococci.
Other in-vitro activity: LIN is active against *M. tuberculosis* MDR strains; MIC_{90}s of 1–8 μg/ml have been reported for 39 MDR *M. tuberculosis* clinical strains, the highest MICs being associated with strains resistant to isoniazid (INH), rifampin (RIF), ethambutol (ETH) and streptomycin (STR) or resistant to INH, RIF and ETH.[4] The MIC range for LIN against *M. bovis* including drug-resistant strains is 0.125–0.5 μg/ml.[9] The IC_{50} and IC_{90} for *M. tuberculosis* cultured in macrophages are 32 μg/ml and 64 μg/ml, respectively.[10] MPC90 (mutant prevention

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	0.55*, 0.65**	10.1*, 7.34**	6.5*	0.63	16.3 ml/min/kg*	Single dose *10 mg/kg i.v. **10 mg/kg oral[15]
Rat	1.0±0.1*, 1.1±0.3**	15.5±1.6*, 42.6±6.6**	15±0.8**	0.72±0.02*	10.5±1.1 ml/min/kg*	Single dose *10 mg/kg i.v. **25 mg/kg oral[15]
Rabbit	–	–	25.8*, 54.8**	–	–	Daily dose *50 mg/kg, **75 mg/kg; results at 5 days[16]
Dog	3.91±0.38*, 3.61±0.36**	214±37*, 206±51**	67.2±21.2*, 28.2±4.1**	0.63±0.05*	1.99±0.33 ml/min/kg*	Single dose *25 mg/kg i.v. **25 mg/kg oral[15]
Human	4.26*, 4.4**	91.4*, 80.2**	12.7*, 12.9**	–	127 ml/min*, 138 ml/min**	Single dose *600 mg i.v. **600 mg oral [FDA label]

concentration) for *M. tuberculosis* is estimated at 1.2 μg/ml.[11]

In-vivo efficacy in animal model: In a mouse model with drug administered 1 day after infection LIN (100 mg/kg) was less efficacious than INH (25 mg/kg); when drug was given 7 days post infection LIN was efficacious in a dose-dependent manner but the experimental oxazolidinone PNU100480 performed better.[12] LIN reached high concentrations in tissue; PK and susceptibility data indicate that LIN should prove useful in TB treatment.[11]

Efficacy in humans

Few clinical studies describing LIN treatment for human TB have been published. In two studies, one with 5 patients (2 patients with *M. bovis* infections and 3 with MDR tuberculosis)[13] and another with 8 patients,[14] individuals infected with MDR-TB who had been refractory to previous treatment were given LIN with other drug combinations. In the Fortun study LIN was administered at 600 mg or 1200 mg daily; in all cases cultures from respiratory samples were sterile after 6 weeks of treatment, and 3 patients demonstrated clinical and microbiological cure after treatment for 5–24 months.[13] In the other study 8 HIV-negative patients who had failed at least 3 cycles of TB drugs were treated with LIN at 600 mg daily together with other drug combinations. The treatments did show some efficacy in terms of culture conversion in all patients by 82 days; although several individuals died of respiratory failure, some completed or were still on therapy at the time of publication.[13] Myelosupression and peripheral neuropathy were observed in both studies, despite an attempt to reduce the dose from 1200 mg to 600 mg daily[14] to combat these adverse effects.

LIN is approved for treatment of uncomplicated and complicated skin and skin-structure infections, pneumonia, nosocomial infections and enterococci including sepsis. It is approved for use in children (zyvox FDA label).

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Mouse: Bioavailability 73%.[15]
- Rat: Bioavailability 100%, widely and evenly distributed in tissues and plasma.[15]
- Dog: Bioavailability 97%.[15]
- Human: Bioavailability ~100%.
  Plasma protein binding is 31% [FDA label]. There is a 1:1 ratio between plasma and inflammatory fluid.[17] Excellent penetration into bronchial mucosa and bronchioalveolar fluid was found, with ratios of 1:0.79:0.71:8.35 for plasma : bronchial mucosa : macrophages : epithelial lining fluid.[18]

Animal metabolic pathway: Bioavailability is close to 100% in rat, dog and human. Protein binding is low, at about 35%, and the drug is well distributed throughout the body in dog and rat. LIN circulates in mouse, rat, dog and human mainly as the parent drug; any circulating metabolites have insignificant antibacterial activity. Between 21% and 34% of the drug is excreted as the parent compound in mouse, rat and dog; renal excretion is the main elimination route in mouse, rat and dog.[15]

Human metabolic pathway: LIN is metabolized to two inactive ring-opened forms, aminoethoxyacetic and hydroxyethyl glycine derivatives. 30% of the dose is excreted in urine as LIN and 70% of the dose as the two major metabolites, with a small amount present in faeces (~10% of the dose) also as the metabolites. Little is known about LIN in human milk although the

drug is secreted into milk of experimental animals [FDA label].

Safety and Tolerability

Animal drug–drug interactions: LIN does not induce, nor is significantly metabolized by, cytochrome P450 enzymes; neither does it inhibit the clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4) [FDA label].

Animal toxicity: In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and spleen were observed [FDA label].

The drug is very evenly distributed throughout the body in mouse, rat and dog, with tissue and plasma levels equivalent in many cases.[15] Mild reversible anaemia was caused by treatment of mice with 50 mg/kg for 4 days.[19]

Carcinogenicity: Although lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of LIN, no mutagenic or clastogenic potential was found in a battery of tests, including the Ames and AS52 assays, an *in-vitro* unscheduled DNA synthesis (UDS) assay, an *in-vitro* chromosome aberration assay in human lymphocytes, and an *in-vivo* mouse micronucleus assay.

Reproductive toxicology: LIN did not affect the fertility or reproductive performance of adult female rats. It reversibly decreased fertility and reproductive performance in adult male rats when given at doses 50 mg/kg/day, with exposures approximately equal to or greater than the expected human exposure level (exposure comparisons are based on AUCs). Epithelial cell hypertrophy in the epididymis may have contributed to the decreased fertility by affecting sperm maturation. Similar epididymal changes were not seen in dogs. Although the concentrations of sperm in the testes were in the normal range, the concentrations in the cauda epididymis were decreased, and sperm from the vas deferens had decreased motility.

Mildly decreased fertility occurred in juvenile male rats treated with LIN through most of their period of sexual development (50 mg/kg/day from days 7 to 36 of age, and 100 mg/kg/day from days 37 to 55 of age, with exposures ranging from 0.4-fold to 1.2-fold that expected in humans based on AUCs). No histopathological evidence of adverse effects was observed in the male reproductive tract [FDA label].

Animal safety pharmacology: In rats and dogs the effect of drug treatment was similar to toxicity observed in humans. Bone-marrow effects were observed including hypocellularity and decreased hematopoiesis, decreased extramedullary hematopoiesis in spleen and liver, and decreased levels of circulating erythrocytes, leukocytes, and platelets. Lymphoid depletion occurred in thymus, lymph nodes, and spleen. Generally, the lymphoid findings were associated with anorexia, weight loss, and suppression of body weight gain [FDA label].

Human drug–drug interactions: LIN is a reversible, nonselective inhibitor of monoamine oxidase and has the potential for interaction with adrenergic and serotonergic agents including serotonin reuptake inhibitors [FDA label], serotonin-boosting antidepressants such as paxil, prozac, and zoloft, as well as other antidepressants such as elavil and tofranil, and decongestants such as sudafed and entex.

Over-the-counter cold medicines and cough syrups that contain pseudoephedrine can cause drug interactions with LIN.

While taking zyvox, it is important to avoid eating large amounts of foods that contain the chemical "tyramine". While taken with a class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs), there is a chance of developing serotonin syndrome. Symptoms include euphoria, drowsiness, rapid muscle contraction and relaxation, restlessness, dizziness, sweating, coordination problems, and fever [FDA label].

Human potential toxicity: Myelosuppresion: LIN causes reversible myelosuppression (including anaemia, leucopenia, pancytopenia, and thrombocytopenia) in patients especially when the drug is administered for prolonged periods of time.

Neurotoxicity: Peripheral and optic neuropathy have been reported in patients treated with zyvox. Visual blurring has occurred in patients treated with zyvox for less than 28 days and visual function tests are recommended for patients taking this drug for longer than 3 months [FDA label].

Gastrointestinal: acidosis has been reported in patients treated with zyvox [FDA label].

Human adverse reactions: The most common adverse events in patients treated with zyvox were diarrhoea, headache and nausea [FDA label].

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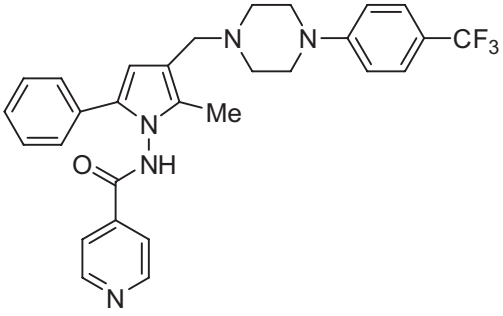
journal homepage: http://intl.elsevierhealth.com/journals/tube

LL-3858

Generic and additional names: LL-3858, Sudoterb
Intellectual property rights: Lupin Ltd

Lupin has identified three compounds that have demonstrated significant *in vitro* and *in vivo* activity against sensitive and resistant strains of *Mycobacterium tuberculosis*. Pre-clinical studies are in progress [Lupin website, 2006]



Basic biology information

Drug target/mechanism: Not known; LL-3858 is a pyrrole derivative
In-vitro potency against MTB: M. tuberculosis MIC: 0.12–0.025 μg/ml.[1,2]
Other in-vitro activity: The compound demonstrates *in vitro* synergy with rifampin. It is bactericidal in 12 days with concentration-dependent killing.[1,2] Other pyrroles have shown activity against TB.[3]
In-vivo efficacy in animal model: In mouse models of 12 weeks duration 12.5 mg/kg LL-3858 showed good efficacy and complete clearance from lung and spleen not seen with the other compounds tested. No relapse was observed up to 2 months following the final dose.[1]

Efficacy in humans

Web releases (for example Media coverage summary 7 – 2004) indicate that clinical trials may begin but the Lupin website does not post any further information on this compound.

ADME data

PK in mice is better than with INH in terms of half-life, C_{max} and AUC.[1]

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Moxifloxacin

Generic and additional names: Moxifloxacin Hydrochloride
CAS name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid hydrochloride
CAS registry #: 186826-86-8
Molecular formula: $C_{21}H_{24}FN_3O_4 \cdot HCl$
Molecular weight: 437.89
Intellectual property rights: Bayer
Brand names: Actimax (Sankyo); Actira (Bayer); Avelox (Bayer); Octegra (Bayer); Proflox (Esteve); Vigamox (Alcon)
Derivatives: Moxifloxacin is a quinolone/fluoroquinolone antibiotic related to ciprofloxacin, enoxacin, fleroxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, lomefloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin, rufloxacin, sparfloxacin, temafloxacin, trovafloxacin, sitafloxacin
Solubility: Soluble in water
Polarity: Log P 2.033 [DrugBank]
Melting point: 238–242°C [DrugBank]
Formulation and optimal human dosage: Avelox tablets: containing moxifloxacin hydrochloride (equivalent to 400 mg moxifloxacin).
Avelox i.v.: 250 ml latex-free flexibags as a sterile, preservative-free, 0.8% sodium chloride aqueous solution of moxifloxacin hydrochloride (containing 400 mg moxifloxacin).
400 mg daily dose

MOXI

Basic biology information

Drug target/mechanism: Moxifloxacin (MOXI: 8-methoxy-quinolone), and quinolones in general, exert their effects by trapping a DNA–drug–enzyme complex and specifically inhibiting ATP-dependent enzymes topoisomerase II (DNA gyrase) and topoisomerase IV. In most bacteria gyrase facilitates DNA unwinding and topoisomerase IV activates decatenation. DNA gyrase (reviewed in Champoux 2001[1]), an essential enzyme involved in the replication, transcription and repair of bacterial DNA, consists of two components arranged in a GyrA2/GyrB2 complex encoded by the *gyrA* and *gyrB* genes. Topoisomerase IV, encoded by *parC* and *parE*, appears to be absent from *Mycobacterium tuberculosis* and from several other bacteria including *Helicobacter pylori* and *Treponema palladium*.[2] Recently the single *M. tuberculosis* type II topoisomerase has been cloned into *Escherichia coli* and exhibits classical supercoiling activity as well as enhanced decatenation, cleavage and relaxation activities.[3] This is presumably the single target for MOXI in the mycobacteria.

Drug resistance mechanism: Resistance to MOXI occurs at a rate of 1.8×10^{-9} to $<1 \times 10^{-11}$ *in vitro* for Gram-positive bacteria [FDA label]. There is no known cross-resistance between MOXI and other classes of antimicrobials, however cross-resistance has been observed between MOXI and other fluoroquinolones. Resistance (3–5-fold higher than wild-type [WT]) can arise in *M. tuberculosis* from changes in either *gyrA* or *gyrB*; furthermore specific mutations in *gyrA* resulted in hypersensitivity to quinolones.[4] Most mutations conferring changes in drug sensitivity occur in a quinolone-resistant region in *gyrA* and more rarely in *gyrB*. Both resistance and hypersensitivity were reflected in the IC_{50}s of DNA gyrase overexpressed and purified from the concomitant *M. tuberculosis* strains.[4] Many MDR clinical strains are sensitive to MOXI (resistance is defined as MIC > 2 μg/ml) even where they are also resistant to ofloxacin (OFL); however several strains in the same study were resistant to MOXI and OFL and in these cases the mutation was often in *gyrA* (A94G). The authors conclude that careful

monitoring of resistance to MOXI is warranted in clinical settings.[5]

In-vitro potency against MTB: M. tuberculosis H37Rv: MIC 0.5 μg/ml.[4]

M. tuberculosis H37Rv comparative MICs for quinolones: ciprofloxacin 0.5 μg/ml, OFL 0.71 μg/ml, levofloxacin (LEV) 0.35 μg/ml, MOXI 0.177 μg/ml, gatifloxacin (GATI) 0.125 μg/ml.[6]

Spectrum of activity: MOXI has broad Gram-positive and Gram-negative activity. It shows *in-vitro* and clinical efficacy against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Str. pyogenes*, *Haemophilus influenzae*, *H. parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. MOXI has activity against mycobacteria in addition to *M. tuberculosis*; MOXI is more active against *M. kansasii* than *M. avium* complex: specifically MIC_{90} for *M. avium* > *M. intracellulare* > *M. kansasii* at 4, 2 and 2 μg/ml respectively. MIC_{90} for *M. chelonae* > *M. fortuitum* at 16 and 0.5 μg/ml, respectively.[7]

Other in-vitro activity: MPC90 against *M. tuberculosis* strains: MOXI 1 μg/ml, LEV 1 μg/ml, ciprofloxacin 4 μg/ml, OFL 2 μg/ml.[8]

MOXI, like other quinolones, is bactericidal. The bactericidal activity of MOXI against *M. tuberculosis* was decreased somewhat when ethambutol (ETH) or high rifampin (RIF) and MOXI were tested together, indicating some antagonism between these drugs[9] although this activity is not necessarily reflected *in vivo*;[10] antagonism between RIF or chloramphenicol and another quinolone (ciprofloxacin) has been reported previously.[11] A comparison of quinolones, using an *in-vitro* model designed to predict sterilizing activities, showed MOXI with the greatest bactericidal effect against slow-growing bacteria, and the best activity against persistors.[6] MOXI also outperformed other quinolones when the MPCs and MPC/AUC ratios were compared.[12]

In-vivo efficacy in animal model: In a mouse model designed to mimic human disease, regimens containing MOXI/RIF/pyrazinamide (PZA) reduced treatment time by up to 2 months compared to regimens with isoniazid (INH)/RIF/PZA.[13] Similar results with a stable cure were reached after 4 months in mice treated twice weekly with RIF/MOXI/PZA compared to cure in 6 months when daily treated with RIF/INH/PZA.[14] 100 mg/kg MOXI in mice gave activity comparable to INH; increased dose in mice to 400 mg/kg MOXI daily resulted in spleen CFU counts lower than for INH 25 mg/kg (log CFU 1.4 for INH compared with log CFU 0.4 for MOXI) although the differences were not statistically significant.[15] AUC/MIC ratio correlated best with *in-vivo* efficacy for the fluoroquinolones in a mouse model of tuberculosis.[16] MOXI in a prodrug formulation conjugated to danyl-carboxymethyl glucan may have advantages *in vivo* if it can be administered orally.[17]

Efficacy in humans

Human trials with MOXI show promise for shortening treatment time and reducing toxicity.[14] Using early bactericidal activity (EBA) at 5 days as a comparator MOXI (400 mg/daily) is as efficacious as INH (300 mg/daily) and better than RIF (600 mg/daily). Using time to reduce viable counts by 50% (vt50) INH outperformed MOXI and RIF (Rodríguez et al. 2004,[18] see also Lu and Drlica 2003[19]). In a similar study, comparing MOXI or ETH combined with INH/RIF/PZA, patients achieved negative culture status earlier with the inclusion of MOXI.[20]

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Human: Bioavailability 90%. Alveolar macrophage/plasma ratio ~21. MOXI is well absorbed from the gastrointestinal tract. Food has little effect on absorption. No significant differences in PK due to gender, race or age are found; no specific studies in pediatric patients have been reported [FDA label].

Human metabolic pathway: Approximately 52% of the oral or intravenous dose is metabolized via glucuronide and sulphate conjugation. The sulphate conjugate accounts for 38% of the dose, and the glucuronide conjugate accounts for 14% of the dose. Excretion as unchanged drug: 20% in urine and 25% in faeces; 96±4% excretion as known metabolites or parent drug. No changes in renal excretion in patients with decreased renal function [FDA label].

Safety and Tolerability

Animal drug–drug interactions: The cytochrome P450 system is not involved in metabolism of MOXI. *In-vitro* studies indicate that MOXI does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2, indicating that MOXI is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes [FDA label].

Animal toxicity: The minimal lethal oral dose in mice is 435–758 mg/kg but 1300 mg/kg for rat and 1500 mg/kg for cynomolgus monkey. Intravenous LD_{50} is 105–130 mg/kg for mice and 112–146 mg/kg for rat. MOXI is considered moderately toxic after single oral or i.v. doses.[23]

Arthropathy: quinolones have been implicated in arthropathy in humans and animals; in juvenile dogs arthropathy was observed at 30 mg/kg for 28 days

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	1.3*	184 norm*	137 norm*	–	–	*9.2 mg/kg oral single dose; C_{max} and AUC normalized to a dose of 9.2 mg/kg[21,22]
Rat	1.3*	310 norm*	312 norm*	–	–	*9.2 mg/kg oral single dose; C_{max} and AUC normalized to a dose of 9.2 mg/kg[21,22]
Dog	9*	4090 norm*	251 norm*	–	–	*9.2 mg/kg oral single dose; C_{max} and AUC normalized to a dose of 9.2 mg/kg[21,22]
Monkey	7.2*	760 norm*	86 norm*	–	–	*9.2 mg/kg oral single dose; C_{max} and AUC normalized to a dose of 9.2 mg/kg[21,22]
Human	12*, 11.5–15.6**	618 norm*, 36.1±9.1**	430 norm*, 3.1±1**	–	–	*1.4 mg/kg oral single dose; C_{max} and AUC normalized to a dose of 9.2 mg/kg,[21,22] **Single 400 mg oral dose in healthy young adults [FDA label]

(1.5× normal human dose) but similar symptoms were not seen in adult rats and monkeys at up to 500 mg/kg and 135 mg/kg respectively.[23]

Ocular toxicity: Electroretinographic and histopathologic changes were seen at 90 mg/kg/day in an oral 4-week specialized lens study in beagle dogs using slit lamp and biochemical investigations. No adverse effects on the lens were observed in 6-month chronic studies in rats or monkeys at doses as high as 500 mg/kg or 250 mg/kg respectively.[23]

Generally MOXI shares liabilities with the other quinolones but without the phototoxicity seen with sparfloxacin.[23]

Animal safety pharmacology: Cardiovascular: there were marginal effects on QT interval in dogs during week 1 at a dose of 90 mg/kg/day.[23]

In monkeys using telemeterized evaluation, MOXI had no significant effect on mean arterial pressure, heart rate, PR or QRS intervals. MOXI produced significant dose-related increases in QTc at doses of 30 mg/kg (C_{max} 5.5±0.6μM), 100 mg/kg (C_{max} 16.5±1.6 μM), and 175 mg/kg (C_{max} 17.3±0.7 μM) with peak increases of 22 (8%), 27 (10%), and 47 (18%) ms, respectively.[24]

MOXI has an *in-vitro* human cardiac K channel hERG IC_{50} of 129 μM, which is not as potent an inhibitor of the hERG channel as some other quinolones such as sparfloxacin (18μM) or grepafloxacin (50 μM), but more potent than the hERG IC_{50} for LEV (915 μM) and OFL (1420 μM).[25]

Human drug–drug interactions: The only fluoroquinolone known to inhibit the P450 system is ciprofloxacin inhibiting CYP1A2 (reviewed in Berning 2001[26]). Specifically, no changes were observed in the metabolism of itraconazole, theophylline, warfarin, digoxin, atenolol, oral contraceptives, or glyburide. Itraconazole, theophylline, warfarin, digoxin, probenecid, morphine, ranitidine, and calcium did not significantly affect the pharmacokinetics of MOXI [FDA label]. Antacids and iron-containing products should be avoided 4 hours before or after MOXI dosing due to the potential for reduction in the AUC.

Human potential toxicity: Cardiovascular events: QT prolongation was observed in 0.1–3% of patients; drugs which exacerbate these symptoms – such as Solatol, a general antiarrhythmic – should be avoided [FDA label]. Prolongation of the QT interval is a general feature of the fluoroquinolones and MOXI does cause QT prolongation which limits the maximum dose (reviewed in Falagas et al. 2007[27]). Torsades de pointes can be a result of the prolongation in QTc (reviewed in Falagas et al. 2007[27]). Specifically, MOXI caused a QTc increase when given once daily at 400 mg, whereas twice daily doses of LEV and CIPRO had no effect on this parameter. However at higher doses all the fluoroquinolones cause an increase in the QTc interval (reviewed in Falagas et al. 2007[27]). In a clinical trial of more than 7900 patients no cardiovascular morbidity or mortality attributable to QTc prolongation occurred with MOXI treatment [FDA label].

Arthropathy: quinolones are associated with specific tendinitis-type events, and LEV seems to be associated with the highest rates among these drugs. MOXI is not recommended for treatment of athletes in training. Cessation of treatment usually reverses

these effects which may be more serious in the elderly (reviewed in Owens and Ambrose 2005[28]).
Hypoglycaemia is mentioned as a possible side effect [FDA label] although few events have been recorded (reviewed in Owens and Ambrose 2005[28]).
Phototoxicity is not a clinically relevant event during MOXI treatment (reviewed in Owens and Ambrose 2005[28]).
Human adverse reactions: In clinical trials with 6700 patients receiving the 400 mg dose, adverse events reported in MOXI trials were described as mild to moderate in severity. MOXI was discontinued due to adverse reactions thought to be drug-related in 3.6% of orally treated patients. Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 3% of MOXI-treated patients were nausea (7%), diarrhoea (6%) and dizziness (3%). Additional clinically relevant events that occurred in 0.1% to <3% of patients were:

- body as a whole: abdominal pain, headache, asthenia, injection site reaction (including phlebitis), malaise, moniliasis, pain, allergic reaction;
- cardiovascular: tachycardia, palpitation, vasodilation, QT interval prolonged;
- digestive: vomiting, abnormal liver function test, dyspepsia, dry mouth, flatulence, oral moniliasis, constipation, GGTP increased, anorexia, stomatitis, glossitis;
- haemic/lymphatic: leukopenia, eosinophilia, prothrombin decrease (prothrombin time prolonged/ International Normalized Ratio (INR) increased), thrombocythemia;
- metabolic/nutritional: lactic dehydrogenase increased, amylase increased;
- muscular: arthralgia, myalgia;
- CNS: insomnia, nervousness, vertigo, somnolence, anxiety, tremor;
- skin: rash (maculopapular, purpuric, pustular), pruritus, sweating, urticaria;
- special senses: taste perversion;
- urogenital: vaginal moniliasis, vaginitis [FDA label].

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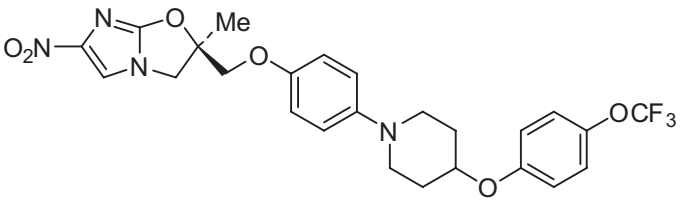
OPC-67683



Generic and additional names: OPC-67683
CAS name: (R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]-phenoxymethyl}-2,3-dihydroimidazo[2,1-b]-oxazole
CAS registry #: 681492-22-8
Molecular formula: $C_{25}H_{25}N_4F_3O_6$
Molecular weight: 534.48
Intellectual property rights: Otsuka Pharmaceutical Co., Ltd.
Brand names: N/A
Derivatives: See structurally similar compound PA-824
Solubility: Water
Formulation and optimal human dosage: A patent for OPC-67683 was filed by Otsuka in 2003. A phase I OPC-67683 clinical trial was performed in Japan in early 2006, but results are currently unavailable. Otsuka filed a patent through the Patent Cooperative Treaty (PCT) process to cover 2,3-dihydro-6-nitroimidazo-(2,1-b)oxazole compounds for TB treatment.

Basic biology information

Drug target/mechanism: OPC-67683 is closely related to PA-824 and may share a similar mode of action. The compound has been shown to inhibit mycolic acid biosynthesis and kill *Mycobacterium tuberculosis in vitro*. Similar to PA-824, OPC-67683 is a prodrug and requires activation by *M. tuberculosis* for activity; experimentally isolated OPC-67683-resistant mycobacteria did not metabolize the compound and a mutation in the *M. tuberculosis* Rv3547 gene (responsible for activating PA-824) among the resistant organisms suggests that this enzyme is involved in activating OPC-67683.[1] Matsumoto et al.[1] suggest the possibility that generation of a radical intermediate during drug activation could be responsible for the killing activity of OPC-67683.[1]
OPC-67683 inhibits mycolic acid synthesis, specifically inhibiting incorporation of ^{14}C-acetate and fatty acid. IC_{50} of 21 and 36 ng/ml for incorporation into methoxy- and ketomycolate respectively were reported. Changes in the morphology of the cell wall were observed.[2]
Drug resistance mechanism: OPC-67683 is active against strains resistant to rifampin (RIF), ethambutol (ETH), pyrazinamide (PZA), isoniazid (INH) and streptomycin (STR).[1] A spontaneous mutation rate is not available. Mutations in *M. tuberculosis* Rv3547, the gene responsible for activating PA-824, have been found among experimentally generated resistant organisms.[1] See also the *Drug target/mechanism* section.
In-vitro potency against MTB: M. tuberculosis H37Rv: MIC 0.012 μg/ml.[1]
Spectrum of activity: OPC-67683 is described as mycobacteria specific.[1] It is active against *M. kansasii* and *M. tuberculosis* while PA-824 showed activity only against *M. tuberculosis*.[3]
Other in-vitro activity: Activity (MIC) of OPC-67683 against INH-, RIF-, ETH- and STR-resistant strains of *M. tuberculosis* was unchanged from the activity of OPC-67683 against the wild-type control. No evidence of antagonism was observed when OPC-67683 was examined *in vitro* in combination with other known TB drugs (RIF, INH, ETH, STR). Intracellular post-antibiotic activity was estimated using the H37Rv strain in THP1 cells; OPC-67683 activity at 0.1 μg/ml was equal to RIF at 3 μg/ml and superior to INH and PA-824. Results suggest that even brief exposure to the drug may kill *M. tuberculosis* in cells.[1]
In-vivo efficacy in animal model: OPC-67683 is orally active in a mouse lung model. Daily dosing regimen (beginning 28 days post i.v. infection) for 28 days:

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	5.9	5.7	0.43	–	–	Data for mouse PK given at 3 mg/kg single dose oral.[4]
Rat	6.4	7.5	0.50	–	–	Data for rat PK given at 3 mg/kg single dose oral.[4]
Dog	17	8.3	0.33	–	–	Data for dog PK given at 3 mg/kg single dose oral.[4]

CFU reduction of >95% was achieved using OPC-67683, RIF, INH, ETH, STR and PZA at 0.625, 3.5, 5, >160, 40 and 160 mg/kg, respectively;[1] similar results were seen in BALB/c nude or immunocompetent mice.[1] In long-term treatments over 6 months, regimens including OPC-67683 were superior to regimens without OPC-67683, and indicated that this drug could reduce the length of treatment by up to 2 months. Specifically, mice were treated with OPC-67683, RIF and PZA for 2 months followed by OPC-67683 for another 2 months; alternately mice were treated with RIF, INH, ETH and PZA for 2 months followed by RIF and INH for 4 months. Drugs were used at: OPC 2.5 mg/kg, RIF 5 mg/kg, PZA 100 mg/kg, ETH 100 mg/kg, and INH 10 mg/kg. At 3 months after start of therapy colonies were seen in 1/6 of the OPC-treated mice and in 0/6 at 4 months, whereas all the animals using the alternate regime were still showing signs of infection at 4 months.[1]

Efficacy in humans

Phase I and Phase II studies have been conducted but results are not available.

ADME data

See table 1 for main PK characteristics. Additional ADME data are also provided by Matsumoto et al.[1]

Other ADME data:

- Mouse: 42% orally bioavailable. Following 3 mg/kg single oral dose in mice: C_{max} plasma 0.4 μg/ml < lung 1.3 μg/ml (Miyamoto et al. 2005,[4] also see Matsumoto et al. 2006[1]).
- Rat: 35% orally bioavailable. Drug concentrations following 3 mg/kg single oral dose in rat: Liver > kidney > heart, lung > plasma, spleen (Miyamoto et al. 2005,[4] also see Matsumoto et al. 2006[1]).
- Dog: 60% orally bioavailable (Miyamoto et al. 2005,[4] also see Matsumoto et al. 2006[1]).
- Human: *In vitro* OPC-67683 was not metabolized to any significant extent by human liver microsomes, and there was no effect on CYP enzyme activities at levels up to 100 μM.[1]

Animal metabolic pathway: OPC-67683 was not significantly metabolized by liver microsomes and no major metabolites were identified in any of the species tested using labeled or unlabeled drug.[4]

OPC-67683 was significantly metabolized after exposure to *M. bovis* BCG strain, giving one major metabolite, the desnitro-imidazooxazole.[1]

Safety and Tolerability

Animal drug–drug interactions: OPC-67683 was not an inhibitor of CYP enzymes using liver microsomal preparations.[1]

Animal toxicity: Other similar compounds such as metronidazole are mutagenic, but OPC-67683 was found not to be genotoxic; there was no correlation between mutagenicity and the antibacterial properties.[1,5]

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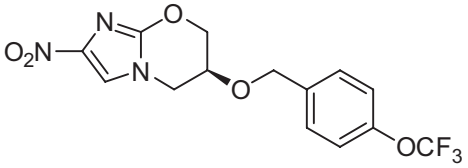
PA-824

Generic and additional names: PA-824
CAS name: (3S)-8-nitro-3-[[4-(trifluoromethoxy)phenyl]methoxy]-5-oxa-1,7-diazabicyclo[4.3.0]nona-6,8-diene
Molecular formula: $C_{14}H_{12}F_3N_3O_5$
Molecular weight: 359



Intellectual property rights: TB Alliance and Novartis
Derivatives: See structurally similar compound OPC-67683. The TB Alliance has also initiated an investigation of PA-824 nitroimidazole analogs, currently in the discovery phase of development [TB Alliance]
Polarity: Log P 3.393
Formulation and optimal human dosage: Not approved for use in humans.

Basic biology information

Drug target/mechanism: PA-824 possibly acts via generation of radicals having non-specific toxic effects; however the drug has been shown to inhibit mycolic acid and protein biosynthesis.[1]

Specific inhibition of mycolic acid and protein synthesis: using *Mycobacterium bovis* BCG strain, in the presence of PA-824, protein synthesis (incorporation of ^{35}S) and lipid synthesis (uptake of ^{14}C-acetate into mycolic acid precursors) were both inhibited in a drug-dependent manner.[1] Concentrations of hydroxymycolate, a precursor for ketomycolate, rose significantly under low drug (<1 μg/ml) but fell as drug concentrations increased; ketomycolate concentrations decreased with increasing drug, suggesting that PA-824 might act at or around this metabolic step. Protein synthesis was also inhibited in a drug-dependent manner but an intriguing accumulation in labeled proteins at <1 μg/ml drug remains to be explained.[1]

Non-specific effects: the related compound metronidazole, an antibacterial and antiprotozoal drug, is thought to act by damaging DNA; a RecR mutant in *M. bovis* BCG strain was more sensitive to metronidazole compared to WT (Sander et al. 2001,[2] reviewed in Samuelson 1999[3]). PA-824 may also exhibit some of its effects through the generation of radicals.[4,5]

PA-824 activation: PA-824 is active as the reduced form of the parent drug, requiring cofactor-420-dependent glucose-6-phosphate dehydrogenase (FGD1) reduction of an aromatic nitro group. Cofactor 420 (F420) is a flavin-containing molecule with limited distribution in the archaea and Gram-positive bacteria.[1] *In vitro* oxidized F420 was reduced by partially purified FDG1 in the presence of glucose-6-phosphate; addition of PA-824 neither inhibited the reaction nor was PA-824 itself metabolized, indicating that another as yet unknown factor is required for activation.[6]

Drug resistance mechanism: In vitro resistance frequency with PA-824 in *M. tuberculosis* is ~6.5×10^{-7}, equivalent to isoniazid (INH);[6] no cross-resistance with other known mechanisms has been identified.

Target directed mutants: no mutants outside the drug activating pathway have been reported to date.

Drug activating pathway: Mutations in some of the genes encoding the PA-824 activating machinery, F420-dependent glucose-6-phosphate dehydrogenase and F420 biosynthesis pathway gene Rv1173, have been shown to be resistant to PA-824. Intriguingly mutants in another gene of unknown function, Rv3547, were resistant to PA-824 but sensitive to a closely related analog CGI-17341; this suggests that Rv3547 may be able to bind drug and distinguish between the related analogs based on differential affinity.[6]

In-vitro potency against MTB: M. tuberculosis H37Rv MICs: 0.15–0.3 μg/ml[6] and 0.13 μg/ml[1] compared to INH 0.03 μg/ml.

Spectrum of activity: PA-824 has very specific activity, possibly due to its unique reducing activity; it appears to be limited to the MTB complex as there is very limited efficacy against *M. smegmatis* and *M. avium*.[7] Weak activity against *M. ulcerans* has

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	12.8±1 (S); 18.3±1 (M)	327.6±77.1 (S); 396.8±97.9 (M)	21.4±5.7 (S); 25±3.6 (M)	–	–	Single (S) or 5 oral doses/week for 2 months (M) in mice using 100 mg/kg.[13]

been reported,[8] and *M. leprae* is resistant to PA-824 presumably because it lacks the gene encoding Rv3547.[9] OPC-67683 is active against *M. kansasii* and *M. tuberculosis* while PA-824 showed activity only against *M. tuberculosis*.[10]

Other in-vitro activity: PA-824 is bactericidal against replicating and non-growing *M. tuberculosis*.[1] MICs for PA-824 were superior to INH when tested against a panel of drug-resistant clinical isolates.[11] Bactericidal activity at 4-fold MIC was evident following post-treatment drug dilution.[1] Activity of PA-824 against *M. tuberculosis* under reduced oxygen tension was equivalent to that of metronidazole; the latter is a related compound known to inhibit growth of non-replicating *M. tuberculosis* under anaerobic conditions. CGI-17341, a mutagenic compound related to PA-824, was much less efficacious, having even less activity than INH, which is known to be relatively inactive under these anaerobic conditions.[1]

PA-824 MIC_{90} against 29 *M. ulcerans* isolates was >16 μg/ml.[8]

In-vivo efficacy in animal model: PA-824 has potent activity during the continuation treatment phase, indicating that it is active against persistent bacilli and has the potential to shorten therapy.[12]

PA-824 has oral activity against both replicating and non-replicating forms of *M. tuberculosis*.[12] Compared with 328 related nitroimidazopyrans PA-824 demonstrated the best *in vivo* activity at 25 mg/kg in mice, suggesting superior PK.[1] At 10 days treatment in a mouse model (both lung and spleen burdens monitored) using 25 mg/kg, PA-824 was equivalent to INH (25 mg/kg); it also equaled INH over a 28-day dosing period in a guinea pig model where drug dosing was delayed for 30 days post infection. In each case the window between toxicity and efficacy was significant.[1] PA-824 demonstrated activity in the continuation phase equivalent to rifampin (RIF)/INH: both treatments showed sterilizing activity in an *in vivo* model with 2 months dosing RIF/INH/pyrazinamide (PZA) followed by 4 months dosing with RIF/INH or PA-824.[12] Selection of resistant mutants was reduced when PA-824 and INH were coadministered.[12]

PA-824 failed to protect against *M. ulcerans* in a footpad model.[8]

Efficacy in humans

Studies are ongoing.

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Mouse: Concomitant dosing of RIF/PZA/INH with PA-824 did not significantly affect the PK for the latter and had minimal effects on RIF/INH PK.
- Monkey: 40% bioavailability [TB Alliance].

Safety and Tolerability

Animal toxicity: Toxic thresholds in mice: 1000 mg/kg single dose and 500 mg/kg daily dose for 28 days.[1] Compounds in the nitroimidazole series have been described as radiosensitizers which selectively sensitize hypoxic cells to the lethal effect of radiation. The analog CGI-17341 has been shown to be mutagenic,[1,7] however PA-824 lacks the mutagenic properties previously associated with bicyclic nitroimidazoles. Using 100 mg/kg, 5 oral doses/week for 2 months in mice no change in organ weight was found compared to untreated controls.[11] 14-days repeat dose studies in monkey and rat have been completed but data not released [TB Alliance].

Human drug–drug interactions: Minimal potential to induce P450 enzymes [TB Alliance].

Human adverse reactions: PA-824 is not yet approved for human use but is in clinical trials.

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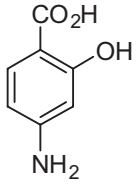
Para-aminosalicylic acid



Generic and additional names: para-aminosalicylic acid; PAS
CAS name: 4-Amino-2-hydroxybenzoic acid
CAS registry #: 65-49-6
Molecular formula: $C_7H_7NO_3$
Molecular weight: 153.14
Intellectual property rights: Generic, marketed 1946
Brand names: PASER (Jacobus); Rezipas (Bristol-Myers Squibb)
Derivatives: Schiff-base analogs of PAS with improved activity have been reported[1]
Solubility: One gram dissolves in about 500 ml water, in 21 ml alcohol. Slightly soluble in ether. Practically insoluble in benzene. Soluble in dilute nitric acid or dilute sodium hydroxide [Merck Index].
Polarity: Log P 1.012 [DrugBank]
Acidity/basicity: pKa 3.25; pH of 0.1% aq solution: 3.5 [Merck Index].
Melting point: 150.5°C [DrugBank]
Formulation and optimal human dosage: Tablet 500 mg, dose is 8–12 g daily in 2–3 doses. Peloquin et al.[2] describe the advantages of twice daily dosing with granules as opposed to once daily dosing.

Basic biology information

Drug target/mechanism: Para-aminosalicylic acid (PAS) was previously thought to target dihydropteroate synthase (DHPS), the target of sulfonamide drugs, but Nopponpunth et al.[3] demonstrated that PAS was a poor *in vitro* inhibitor of the enzyme. Rengarajan et al.[4] demonstrated that transposon-directed disruption of the *Mycobacterium bovis* thymidylate synthase gene, *thyA*, results in resistance to PAS and an MIC of >27 μg/ml; enzyme activity of thymidylate synthase in the PAS-resistant transposon mutants was reduced. Evidence from a 1975 paper indicates that PAS could interfere with iron acquisition by the bacteria. Recent data[5] on ABC transporters and virulence in *M. tuberculosis* and carboxymycobactin inhibitors could renew interest in the area of iron uptake in mycobacteria as a drug target.
Drug resistance mechanism: Mutations in *thyA* have been found in *M. tuberculosis* PAS-resistant clinical isolates.[4]
In-vitro potency against MTB: M. tuberculosis H37Rv: MIC_{90} 0.3–1 μg/ml.[3]
Spectrum of activity: PAS is used with other anti-tuberculosis drugs (most often isoniazid [INH]) for the treatment of all forms of active tuberculosis [DrugBank]. Some renewed interest in PAS as a second-line TB treatment results from relatively infrequent use of this drug in the clinic and concomitant lack of resistance.[4]
Other in-vitro activity: PAS is bacteristatic. The aminosalicylic acid MIC for *M. tuberculosis* in 7H11 agar was <1.0 μg/ml for nine strains including three multidrug-resistant (MDR) strains, but 4 and 8 μg/ml for two other MDR strains. PAS is inactive *in vitro* against *M. avium* [DrugBank].
In-vivo efficacy in animal model: The free drug has a short serum half-life of one hour. It is desirable to keep drug serum concentrations above 1 μg/ml due to lack of post-antibacterial effect and bacteristatic nature. The drug may require a twice-daily dosing regimen.

Efficacy in humans

PAS is now mostly used as a second-line drug for the treatment of MDR *M. tuberculosis*; it was considered first line but was replaced by ethambutol (ETH) in the early 1960s.[6] It is bacteristatic but may help to slow development of resistance to other drugs, especially INH and streptomycin (STR) [DrugBank].

ADME data

See table 1 for main PK characteristics.
Other ADME data:

- Rat: Rats given 5 mg PAS by inhalation had a peak lung concentration of 10× MIC. Normalizing this

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Human	0.75–1	–	9–35 (median 20)	–	–	Single 4 g dose in healthy adults. A level above 1 μg/ml was maintained for 8 hours [DrugBank].

and comparing to human dose gives efficacy at 11 mg/kg compared to 57 mg/kg needed for oral dosing.[7]

- Human: Following a comparison of once- or twice-daily (4 g) dosing Peloquin et al.[2] recommend a twice-daily dose to maintain drug about 1 μg/ml for the treatment of MDR-TB.
  50–60% is protein bound [DrugBank]. Administering PAS with food increases the C_{max} by 50% and the AUC by 70%; divalent cations reduced C_{max} and AUC.[8]

Human metabolic pathway: Within 2 hours of dosing up to 10% of the drug is acetylated in the stomach to N-acetylated PAS, a known hepatotoxin. 80% of drug is excreted in the urine with half of this as the acetylated form [DrugBank].

Safety and Tolerability

Animal toxicity: LD_{50} orally in mice: 4 g/kg. LD_{50} orally in rabbits: 3.650 g/kg [DrugBank].

Human drug–drug interactions: PAS may decrease the amount of digoxin and vitamin B12; vitamin B12 supplement may be required [DrugBank].

Human potential toxicity: Metabolism of PAS produces a toxic inactive metabolite under acid conditions [DrugBank].

Gastrointestinal: toxicity included gastrointestinal events leading to poor compliance (described in Rengarajan et al. 2004[4]). The currently available granule formulation reduces nausea; it is recommended to take the granules with acid beverage.[2]

Human adverse reactions: PAS is contraindicated for patients with serious renal disease due to build up of toxic metabolites, especially the acetylated forms. PAS interferes with uptake of vitamin B12 and with thyroid metabolism. Vitamin supplements can reverse the former issue and thyroxine reverses the latter [DrugBank].

Dermatological side effects: skin rash, erythematous, maculopapular and pruritic lesions often starting on face and neck (reviewed in Wilson et al. 2003[9]).

Other toxicities: lymphadenopathy, jaundice, leukocytosis, conjunctivitis, headaches and joint pains (reviewed in Wilson et al. 2003[9]).

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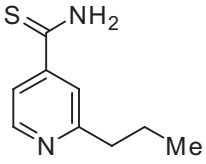
Prothionamide



Generic and additional names: Prothionamide; 2-propylthioisonicotinamide; prothionamide; 2-propyl-4-thiocarbamoylpyridine
CAS name: 2-Propyl-4-pyridinecarbothioamide
CAS registry #: 14222-60-7
Molecular formula: $C_9H_{12}N_2S$
Molecular weight: 180.27
Intellectual property rights: Generic
Derivatives: Prothionamide is the propyl analog of ethionamide
Solubility: Soluble in ethanol, methanol; slightly soluble in ether, chloroform; practically insoluble in water [Merck Index].
Formulation and optimal human dosage: 250 g tablet, 500–750 mg daily

Basic biology information

Drug target/mechanism: Prothionamide (PRO), see ethionamide (ETA).
Drug resistance mechanism: There is complete cross-resistance between PRO and ETA, and resistance emerges rapidly.[1]
In-vitro potency against MTB: MIC Mycobacterium tuberculosis H37Rv: ~0.5 μg/ml.[2]
Spectrum of activity: PRO has activity against mycobacterial species including *M. leprae* and *M. avium*.[2] PRO killed *M. leprae* more quickly than did ETA.[3]
Other in-vitro activity: See ETA. ETA and PRO are bactericidal.[2]
In-vivo efficacy in animal model: PRO is as active as ETA against *M. tuberculosis* in mice.[4] See also ETA.

Efficacy in humans

PRO is used interchangeably with ETA according to Wang et al.[2] In a clinical trial with leprosy patients PRO (250 or 500 mg/day) outperformed ETA at the same dose.[3] PRO has been reported as better tolerated than ETA in humans.[4]

ADME data

See table 1 for main PK characteristics.
Other ADME data:

- Human: PRO, like ETA, is rapidly eliminated, with the half-life for PRO being slightly less than for ETA. Plasma concentrations for PRO are less than for ETA.[4]

Human metabolic pathway: Conversion to the active sulfoxide metabolite takes place with PRO and ETA; the sulfoxides are then metabolized to the nicotinamide and nicotinic acid forms, both of which have no anti-bacterial activity. Other metabolites such as N-methylation and oxidation of the pyridine ring are also formed. Of the total dose given, 0.16% is excreted as PRO and 1.2% excreted as PRO sulfoxide; less than 0.1% is excreted unchanged in the faeces.[4]

Safety and Tolerability

Animal toxicity: LD_{50} in mice, rats (g/kg): 1.0, 1.32 orally [Merck Index].
Human drug–drug interactions: Hepatotoxicity is considerably increased when PRO is used in combination therapy with rifampicin and thiacetazone.[5]
Human potential toxicity: PRO has been described as more toxic[1] or less toxic[4] than ETA. PRO should be avoided during pregnancy or in women of child-bearing potential unless the benefits outweigh its possible hazards.[5]
Human adverse reactions: Most common adverse reactions are dose-related gastrointestinal disturbances, anorexia, excessive salivation, a metallic taste, nausea, vomiting, abdominal pain and diarrhoea.
CNS disturbances include depression, anxiety, psychosis, headache, postural hypotension and asthenia.
Peripheral and optic neuropathy and pellagra-like syndrome have occurred.
Hepatitis may occur especially when given in association with rifampicin.

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Human	1.38	–	–	–	–	250 mg dose in humans. C_{max} for ETA is about 1.8 times higher than for PRO, with the same ratios being observed for the sulfoxide metabolites.[4]

Other side effects include hypersensitivity reactions, alopecia, dermatitis, endocrine disturbances, hypoglycaemia, and hypothyroidism with or without goiter.[5]

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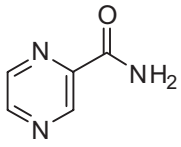
Pyrazinamide



Generic and additional names: Pyrazinamide; pyrazinoic acid amide; pyrazine carboxylamide
CAS name: Pyrazinecarboxamide
CAS registry #: 98-96-4
Molecular formula: $C_5H_5N_3O$
Molecular weight: 123.11
Intellectual property rights: Generic, first synthesized in 1936
Brand names: Pezetamid (Hefa-Frenon); Pyrafat (Fatol); Pirilène (Cassenne); Piraldina (Bracco); Tebrazid (Searle); Unipyranamide (Unichem); Zinamide (Merck & Co.)
Derivatives: Morphazinamide; pyrazinamide Mannich bases also active[1]
Solubility: Soluble in chloroform, methylene chloride; less soluble in benzene; sparingly soluble in water [Merck Index]
Polarity: Log P −1.884 [DrugBank]
Melting point: 192°C [DrugBank]
Formulation and optimal human dosage: 500 mg tablets available.
Dose 20–25 mg/kg daily, or 50–70 mg/kg three times a week. Pyrazinamide is also available as part of fixed-dose combinations with other TB drugs such as isoniazid and rifampicin (Rifater® is an example).

Basic biology information

Drug target/mechanism: The mechanism of action of pyrazinamide (PZA) is poorly understood: pyrazinoic acid (POA), the active moiety of PZA, has been shown to inhibit various functions at acid pH in *Mycobacterium tuberculosis*.[2,3] Experimental evidence suggests that PZA diffuses into *M. tuberculosis* and is converted into POA by pyrazinamidase (PZAase); the *in vitro* susceptibility of a given strain of the organism corresponds to its PZAase activity. PZAase is also called nicotinamidase and metabolizes both PZA and nicotinamide. Once converted, a portion of the POA exits the cell and, providing the media pH is acidic, on protonation re-enters as protonated POA, which may help to disrupt membrane potential (reviewed in Zhang and Mitchison 2003[4]). An inefficient efflux system causes protonated POA to diffuse in at a faster rate than the efflux of POA. In fact, resperine – an inhibitor of a multidrug-resistant efflux pump – can sensitize the cells to PZA.[3] The accumulation of POA and protonated POA lowers the intracellular pH to a suboptimal level that may inactivate many pathways including fatty acid synthase and membrane transport function. However it is widely accepted that POA may not have a specific target, but rather that cellular acidification causes inhibition of major processes.[4] Weak acids such as benzoic acid, UV and respiratory chain inhibitors (e.g. sodium azide) enhance the action of PZA.[5,6] Continuing studies on individual targets such as the nicotinic acid pathway may lead to alternate proposals.

Drug resistance mechanism: No target-specific mutants have been isolated to date. PZA-resistant mutations are usually found in the converting enzyme PZAase.[7] The mutations are unusually located, spread throughout the gene, but there are three areas of clustered mutations around amino acids 3–71, 61–85 and 132–142.[8] A crystal structure of PZAase is now available from *Pyrococcus horikoshii* and, although it only shares 37% identity with the *M. tuberculosis* enzyme, it may help in understanding the PZAase mutations in *M. tuberculosis*.[9] Labeled PZA accumulates, probably as POA, inside sensitive but not resistant *M. tuberculosis*, presumably because of the lack of the converting enzyme (reviewed in Zhang and Mitchison 2003[4]). A small number of PZA mutations occur outside the *pncA* gene (coding for PZAase) but these have not been characterized.[8]

In-vitro potency against MTB: MICs for *M. tuberculosis* are reported as 6–50 μg/ml at pH 5.5 (reviewed in Zhang and Mitchison 2003[4]) but >2000 μg/ml

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	1.05±0.14	303.8±17.9	146.1±13.0	–	–	Single oral dose of 150 mg/kg[17]
Guinea pig	5.3±0.6	185±6.5	23.8±2.1	–	–	Single oral dose 25 mg/kg[19,20]
Human	9.6±1.8	502±101	38.7±5.9	–	–	Single oral dose of 27±4 mg/kg[17]

for *Escherichia coli* and *M. smegmatis* at the same pH. Careful monitoring is required during MIC measurements as bacterial density and serum albumin can affect results.[4,10]

Specifically, MIC_{90} at pH 5.5 is 50 μg/ml, at pH 5.8 is 100 μg/ml, at pH 5.95 is 200 μg/ml.[10]

Spectrum of activity: PZA is presumed to be specific for *Mycobacterium* species, exerting its antibacterial properties under specific conditions (acidic pH). *M. bovis* and *M. leprae* are innately resistant to PZA. PZAase is widely distributed in bacteria yet efficacy of PZA is limited to *M. tuberculosis* and few other organisms. All bovine mycobacterial strains lack PZase activity due to a point mutation in the *pncA* gene. *M. smegmatis* is also PZA resistant probably due to a very efficient efflux system which does not allow POA to accumulate within the cell.[4]

Other in-vitro activity: Anaerobic conditions enhanced the activity of PZA.[5] Older cultures of *M. tuberculosis* appear to be somewhat more sensitive to PZA[11] and have a weaker membrane potential compared to fresh cultures.[3] Under some conditions bactericidal activity is inversely proportional to [^{3}H]uridine uptake, reflecting the activity of PZA against persistent bacilli *in vivo*.[11] An elegant experiment showed PZA activity against *E. coli* persistors following treatment with ampicillin.[6] PZA activity against *M. tuberculosis* in macrophages is controversial[12] although many authors do report some activity.[4] PZA has been shown to be effective in whole blood assays[13] where blood harvested from a drug-treated donor was used as a medium in which to grow the bacilli.

In-vivo efficacy in animal model: PZA has little *in-vivo* activity over the first few days but has activity against persistors late in the course of infection; this drug has greater activity against slow-growing organisms as compared with its activity against actively replicating forms (reviewed in Zhang and Mitchison 2003[4]). Regimens with PZA have better long-term outcomes in terms of organ sterility compared with those without PZA (reviewed in Grosset et al. 1992[14]). In a series of critical observations when mice were dosed with rifampin (RIF) and PZA together (but not separately) no bacilli could be detected after 12 weeks of therapy,[15] however 12 weeks after treatment cessation bacilli could be detected in some animals.[16] This model, now called the Cornell model of TB infection, provides a method to determine the effect of compounds on dormant bacilli.

As a single agent in mice, PZA (i.v. infection, drug administered at 150 mg/kg 6 times/week, beginning 14 days post infection) was slightly less effective compared to isoniazid (INH) at 2, 4 and 8 weeks, about equivalent with RIF at 2 and 4 weeks but less effective by 8 weeks.[17]

Efficacy in humans

PZA is generally used in combination with other drugs such as INH and RIF in the treatment of *Mycobacterium tuberculosis*. Treatment regime most often used: initially INH, RIF, PZA, ETH daily for 2 months followed by INH and RIF 3 times weekly for 4 months [DrugBank]. Specific doses and specific treatment times vary and details can be found in many sources including Centers for Disease Control [http://www.cdc.gov/mmwR/preview/mmwrhtml/rr5211a1.htm] and the World Health Organization [http://www.who.int/en/]. PZA shortens therapy from ~11 months to ~6 months by killing organisms not affected by other TB drugs, especially those in acidic environments. PZA used in the first two months of treatment reduces the duration of treatment required, PZA also reduced the relapse rate from 22% to 8% when added to a combination with INH and streptomycin (STR) (reviewed in Zhang and Mitchison 2003[4] and Mitchison 2000[18]). It crosses inflamed meninges and is an essential part of the treatment of tuberculosis meningitis.

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Guinea pig: Bioavailability 92%.
- Human: Protein binding is 10–20%. PZA is rapidly and well absorbed from the gastrointestinal tract. It crosses the meninges.

Human metabolic pathway: Metabolized in the liver by a microsomal deamidase to POA, the metabolic products are excreted by the kidneys. PZA is widely

distributed to most fluids and tissues, including liver, lungs, kidneys, and bile. PZA has excellent penetration into CSF, ranging from 87% to 105% of the corresponding serum concentration.

Safety and Tolerability

Animal drug–drug interactions: Antagonism occurs between INH, RIF and PZA in mice (see INH article for details).[14]

Animal toxicity: Guinea pigs receiving daily oral doses of 25 mg/kg PZA for 8 weeks were evaluated for hepatotoxicity 7 days after final dose; ALT levels in serum: control animals 45.2±1.2 U/ml, PZA-treated animals 152±39.5 U/ml, animals treated with PZA in an alginate formula 46.5±5.7 U/ml. Hepatotoxicity, evident after 8 weeks of drug treatment, was reversed with alginate formulation which did not affect efficacy.[21] It is worth noting that a review indicates PZA does not work well against TB in guinea pig models.[4] Similar changes were seen in rats given 35 mg/kg oral PZA with INH and RIF for 45 days, toxicity being somewhat reversed by the addition of specific plant extracts.[22]

Carcinogenicity: In lifetime bioassays in rats and mice, PZA was administered in the diet at concentrations of up to 10,000 ppm. This resulted in estimated daily doses for the mouse of 2 g/kg, or 40 times the maximum human dose, and for the rat of 0.5 g/kg, or 10 times the maximum human dose. PZA was not carcinogenic in rats or male mice and no conclusion was possible for female mice due to insufficient numbers of surviving control mice.

PZA was not mutagenic in the Ames bacterial test, but induced chromosomal aberrations in human lymphocyte cell cultures.

Animal safety pharmacology: No systemic adverse effects were found, except equivocal findings relating to fetal weight, when PZA was administered to mice at 8× therapeutic dose (1200 mg/kg, orally) giving a C_{max} 9–12× that of the therapeutic dose.[23]

Human drug–drug interactions: Due to potential for liver toxicity alcohol intake should be limited during PZA treatment. PZA may decrease the effects of allopurinol (Zyloprim). PZA has been reported to interfere with ACETEST® and KETOSTIX® urine tests to produce a pink-brown color [DrugBank].

Human potential toxicity: Hepatitis: The principal adverse effect is a hepatic reaction. Hepatotoxicity appears to be dose related, and may appear at any time during therapy. Gastrointestinal disturbances including nausea, vomiting and anorexia have also been reported [DrugBank].

At 40–50 mg/kg daily ~15% of individuals show liver toxicity effects, however at the currently recommended dose of 15–30 mg/kg daily the hepato-toxicity risk decreases significantly. Other common side effects can include gastrointestinal distress which often abates on further dosing, and increases in serum uric acid. The latter is observed as POA competes with uric acid for renal filtration; uric acid levels and accompanying polyarthralgia decrease when drug is administered 2 or 3 times a week.[24]

PZA should not be used to treat latent tuberculosis because the rate of liver toxicity is unacceptably high.

Human adverse reactions:

Side effects include liver injury, arthralgias, anorexia, nausea and vomiting, dysuria, malaise and fever, sideroblastic anaemia.

Adverse effects on the blood clotting mechanism or vascular integrity, and hypersensitivity reactions such as urticaria, pruritis and skin rashes may occur.

PZA is contraindicated in persons with severe liver damage or with acute gout.

PZA should be discontinued and not be resumed if signs of hepatocellular damage or hyperuricemia accompanied by an acute gouty arthritis appear [DrugBank].

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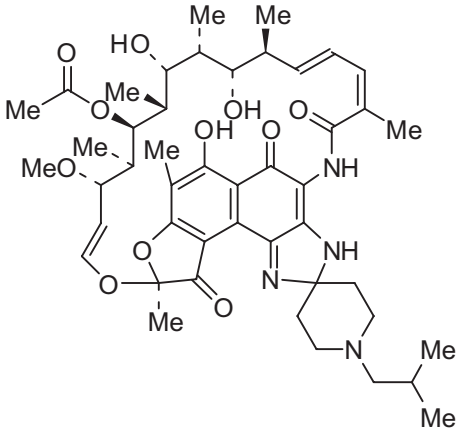
Rifabutin

Generic and additional names: Rifabutin
CAS name: 1′,4-didehydro-1-deoxy-1,4-dihydro-5′-(2-methylpropyl)-1-oxorifamycin XIV
CAS registry #: 72559-06-9
Molecular formula: $C_{46}H_{62}N_4O_{11}$
Molecular weight: 847.005
Intellectual property rights: Generic
Brand names: Ansamycin, Alfacid, Ansatipin, Ansatipine, Antibiotic LM 427, Mycobutin, RBT
Derivatives: KRM-1648 (also called Rifalazil or ABI-1648), rifapentine
Solubility: Rifabutin is a red-violet powder soluble in chloroform and methanol, sparingly soluble in ethanol, and very slightly soluble in water [Merck Index]. Water solubility is 0.19 mg/ml [DrugBank]



Polarity: Log P 4.218 [DrugBank]
Formulation and optimal human dosage: Rifabutin is a spiro-piperidyl-rifamycin derived from rifamycin-S. Dose 300 mg 1× daily, Capsules 150 mg, Pharmacia

Basic biology information

Drug target/mechanism: See rifampin (RIF).

Drug resistance mechanism: As with RIF, most of the clinical *Mycobacterium tuberculosis* mutations resulting in resistance to rifabutin (RIFAB) are in the *rpoB* gene, generally confined to the RIF-resistance determining region (RDR). Some mutations confer resistance to all the rifamycin analogs whereas others were found to be specific to RIF and rifapentine (RIFAP) but not to KRM-1648 (RIFAL) or RIFAB.[1] A significant number of publications on these mutations can be found[1–3] and most of the authors agree that both position and type of substitution play a role in sensitivity to the rifamycins; as a general rule, mutations at codons 511 and 516 result in resistance to RIF and RIFAP but sensitivity to RIFAL and RIFAB, while mutations at codon 531 result in high-level resistance to all the rifamycin analogs. A few rifamycin-resistant mutations are found outside the RDR; in *Escherichia coli* there are some mutational hot spots outside the core region of *rpoB* which result in rifamycin resistance, and the same may apply in *M. tuberculosis*. No rifamycin-resistant *M. tuberculosis* mutations outside *rpoB* have been mapped, but mutations outside the RDR or alteration in drug transporters or membrane permeability are suspected in these cases.[2]

In-vitro potency against MTB: M. tuberculosis H37Rv MICs: RIFAP 0.031 μg/ml, RIFAB <0.015 μg/ml, RIF 0.25 μg/ml.[1]

Spectrum of activity: RIFAB and RIFAP are active against the same spectrum of mycobacteria as RIF although differences in absolute MICs have been identified. RIFAB and RIFAP are more active than RIF *in vitro* against the *M. avium* complex (MAC), *M. tuberculosis*, and *M. leprae*.[4,5]

Other in-vitro activity: RIFAB MICs: *M. africanum* ATCC 25420 0.063 μg/ml, *M. bovis* ATCC 19210 0.125 μg/ml.[6] MICs for other strains are provided in the same paper.[6]

Activity against *M. avium*: RIFAB 0.06 μg/ml; RIFAP 0.125 μg/ml.[7]

Greater efficacy was seen against *Toxoplasma gondii in vitro*, with RIFAP being better than RIFAB *in vitro*, but atovaquone, a known *T. gondii* treatment, outperformed them both. No host-cell toxicity was observed at efficacious levels of 10 μg/ml. RIFAP and RIFAB were active *in vivo* in a mouse model, where they showed superior activity to atovaquone at 50 mg/kg but inferior activity at 100 mg/kg. Again RIFAP outperformed RIFAB at both levels.[8]

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Human	45±17 (range 16–69)	–	375±267 ng/ml	–	0.69±0.32 l/h/kg	300 mg single oral dose to healthy volunteers [FDA label]

In-vivo efficacy in animal model: The antimicrobial activities of RIF, RIFAB and RIFAP were compared in BCG-vaccinated and *M. tuberculosis*-infected immunocompetent mice. Using an equal weight basis both RIFAP and RIFAB were more bactericidal than RIF. The activity of RIF was significantly reduced when drug was administered to mice three times a week instead of six times a week, however significant bactericidal activity was still observed in mice treated with RIFAP, 10 mg/kg up to once every two weeks, or RIFAB, 10 mg/kg twice weekly. The bactericidal activity of RIFAB, 10 mg/kg six times/week for 6 weeks, or RIFAP, 10 mg/kg twice/week for 12 week, was comparable to that of RIF, 10 mg/kg six times/week for 12 weeks in mice.[9] Pharmacokinetic experiments comparing RIF, RIFAB and RIFAP demonstrated that RIFAP had the highest serum peak level (C_{max}) and the longest half-life, whereas RIFAB displayed the lowest C_{max} and the shortest half-life.[9]

In vivo (mouse) against *M. avium* RIFAB showed better activity than RIF and slightly better activity than RIFAP.[7] See also the *In vivo efficacy* section for RIFAP.

Efficacy in humans

RIFAB is significantly more lipid soluble than is RIF, resulting in higher tissue uptake, a larger volume of distribution, lower maximum plasma concentrations, lower trough concentrations, a longer terminal half-life, and higher tissue-to-plasma drug concentration ratios. RIFAB is recommended for HIV patients because it induces microsomal enzymes significantly less than RIF and has the potential to have a reduced effect on the serum concentrations of protease inhibitors.[10] One risk/benefit study reported an increase in AUC for RIFAB (RIFAB 300 mg 2× weekly, Nelfinavir 1250 mg 2× daily) and its metabolite deacetyl-RIFAB with patients receiving Nelfinavir; however the drug levels were still within acceptable limits. The data confirm the provisional CDC guideline that dosage adjustment is unnecessary when 600 mg doses of RIFAB are administered twice weekly with Nelfinavir. The effect on Nelfinavir levels was negligible.[11] However other studies have shown the development of RIF-resistant organisms with RIFAB in HIV patients due to a decrease in RIFAB AUC levels for patients with low CD4 counts.[12,13] Burman et al.[14] note that both RIFAB and RIFAP exhibit idiosyncratic clinical efficacy; RIFAB is active despite unfavorable C_{max}/MIC ratios while RIFAP exhibits sub-optimal clinical performance despite a very favorable C_{max}/MIC ratio. These phenomena may be partly explained by differences in protein binding and in intracellular penetration.[14]

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Human: Lung : plasma ratio is 6.5 [FDA label]. Average bioavailability is 20% but this may decrease with multiple doses [FDA label, Goodman & Gilman's}]. RIFAB is 71% protein bound; ratio of extracellular to intracellular concentration is 3.5 for RIFAB and 5 for RIF.[14] Repeated doses do not appear to affect clearance of RIFAP but do affect clearance of RIF and RIFAB; with repeated doses the AUC of RIFAB is lowered but the half-life is unaffected. Steady-state levels of RIF and RIFAB are achieved after 6 days of daily dosing (reviewed in Burman et al. 2001[14]).

Animal metabolic pathway: In a comprehensive publication[15] on RIFAB metabolism in rats, rabbits, monkeys and man 31-hydroxy-RIFAB was detected as the major metabolite in the plasma of all species between 8 and 24 hours post dosing; 25-deacetyl-RIFAB was only found in rats and man. The excretion route for RIFAB is renal and fecal; trace amounts are excreted as the parent compound in the urine of rabbits and monkeys, whereas these amounts are 8.5% and 4.6% in rat and man, respectively.[15]

Human metabolic pathway: 5–10% of RIFAB is excreted unchanged in the urine compared with 13–24% of RIF.[14] 53% of total dose was excreted in urine as parent or metabolites and 30% in faeces [DrugBank]. Plasma elimination half-life is 32–67 hours.[14] RIFAB is metabolized to at least 20 components, 7 of which have been identified in human urine; these include 25-O-deacetyl-RIFAB, 30-hydroxy-RIFAB, 31-hydroxy-RIFAB, 32-hydroxy-RIFAB, 32-hydroxy-25-O-deacetyl-RIFAB and 25-O-deacetyl-RIFAB-N-oxide.[14]

Safety and Tolerability

Animal toxicity: Liver abnormalities (increased bilirubin and liver weight), occurred in all species

tested, in rats at doses 5 times, in monkeys at doses 8 times, and in mice at doses 6 times the recommended human daily dose. Testicular atrophy occurred in baboons at doses 4 times the recommended human dose, and in rats at doses 40 times the recommended human daily dose [FDA label].

Human drug–drug interactions: In general the rifamycins do induce CYP3A in gut and liver but not in neutrophils and lymphocytes. The relative induction of CYP3A by the rifamycins is RIF > RIFAP > RIFAB, although this is generally reversed 1–2 weeks following drug cessation (reviewed in Burman et al. 2001[14]). Other microsomal enzymes are also affected, namely CYP1A2, CYP2C and CYP2D6. Rifamycins in general should not be given with azole antifungals as subtherapeutic serum concentrations of the latter can result (reviewed in Burman et al. 2001[14]), although the FDA label indicates a decrease in the drug levels of itraconazole, but not fluconazole, when given with RIFAB.

Human potential toxicity: RIFAB may rarely be associated with myositis and uveitis; the uveitis incidence did increase with increasing RIFAB dose [FDA label]. Diarrhoea, fever, heartburn, indigestion, loss of appetite, nausea, skin itching and/or rash have all been associated with RIFAB treatment. The "flu-like" symptoms associated with RIF treatment also occur in patients taking RIFAB.[16] Thrombocytopenia has also been linked to RIFAB [FDA label].

Human adverse reactions: Hepatitis frequency is similar to that seen with RIF, and probably not associated with the rifamycins alone but with these drugs in combinations with other TB treatments.[14]

Cardiovascular: similar to RIF.

Respiratory: similar to RIF.

CNS: similar to RIF.

Gastrointestinal: similar events and frequency with RIF, RIFAB and RIFAP (nausea, vomiting, diarrhoea).

Uveitis, corneal deposits, neutropenia, arthralgias and skin discoloration have all been associated with RIFAB treatment; these symptoms were exacerbated with high RIFAB (>600 mg/day) and with RIFAB and other CYP3A inhibitors such as clarithromycin. Dose reductions ablated these findings (reviewed in Burman et al. 2001[14]).

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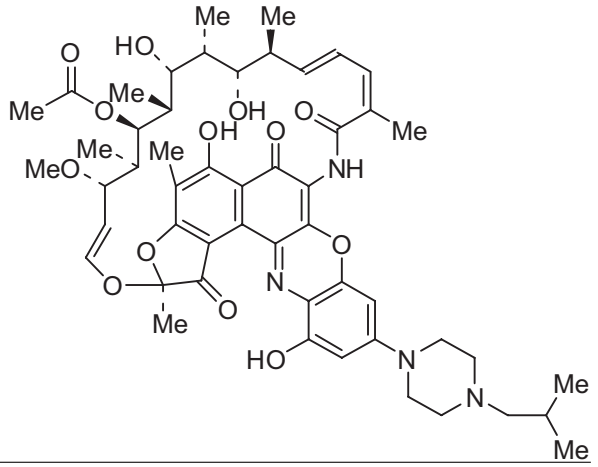
Rifalazil

Generic and additional names: Rifalazil (also known as KRM-1648 or ABI-1648)
CAS name: 3′-Hydroxy-5′-(4-isobutylpiperazinyl)benzoxazinorifamycin
CAS registry #: 129791-92-0
Molecular formula: $C_{51}H_{64}N_4O_{13}$
Molecular weight: 941.08
Intellectual property rights: Kaneka Corp
Derivatives: Rifampin; Rifapentine; Rifabutin.
Solubility: Rifalazil (or KRM-1648) has a relatively high water solubility of more than 2000 mg/ml at pH 2 and a low solubility of less than 0.1 mg/ml at greater than pH 5.[1]



Basic biology information

Drug target/mechanism: See Rifampin (RIF)

Drug resistance mechanism: As with all rifamycins, most of the clinical *Mycobacterium tuberculosis* mutations resulting in resistance to rifapentine (RIFAP) and rifalazil (RIFAL) are in the *rpoB* gene, generally confined to the RIF-resistance determining region (RDR). Some mutations confer resistance to all the rifamycin analogs whereas others were found to be specific to rifampin (RIF) and RIFAP but not to RIFAL or rifabutin (RIFAB).[2] A significant number of publications on these mutations can be found,[2,3] and most of the authors agree that both position and type of substitution play a role in sensitivity to the rifamycins; as a general rule, mutations at codons 511 and 516 result in resistance to RIF and RIFAP but sensitivity to RIFAL and RIFAB; mutations at codon 531 result in high-level resistance to all the rifamycin analogs. A 1996 publication which examined 24 RIF-resistant isolates showed that RIFAL was better at overcoming this resistance than RIFAP.[4] A few rifamycin-resistant mutations are found outside the RDR; in *Escherichia coli* there are some mutational hot spots outside the core region of *rpoB* which result in rifamycin resistance, and the same may apply in *M. tuberculosis*. No RIF-resistant *M. tuberculosis* mutations outside *rpoB* have been mapped, but alteration outside the RDR or in drug transporter or membrane permeability is suspected in these cases.[3]

In-vitro potency against MTB: M. tuberculosis H37Rv MICs: RIFAP 0.031 μg/ml, RIFAB <0.015 μg/ml, RIF 0.25 μg/ml, RIFAL (listed as KRM-1648) <0.015 μg/ml.[2] Other authors note that RIFAL has 64-fold lower MIC against *M. tuberculosis* compared with RIF, and is 4–8-fold more active compared with RIFAB (reviewed in Dietze et al. 2001[5]).

Spectrum of activity: RIFAL is active against many of the mycobacteria with a similar spectrum to the other rifamycins; it has superior activity against several species compared with RIF.[6] Outside the mycobacteria RIFAL has a similar spectum as RIF, RIFAP and RIFAB.

Other in-vitro activity: RIFAL has excellent cell penetration possibly because it is more lipophilic than RIF,[3] it has similar activity against the isolated target (reviewed in Tomioka 2000[7]). Yang[3] ranks the rifamycins in the following order of decreasing MIC: RIF > RIFAP > RIFAL. Activity has been demonstrated *in vitro* for *M. kansasii*, *M. marinum*, *M. scrofulaceum*, *M. avium*, *M. fortuitum*, *M. intracellulare* and *M. chelonae*.[6] RIFAL is active against *M. tuberculosis* and *M. intracellulare* in macrophages with activity equal to RIFAP but superior to RIF.[6] RIFAL demonstrated activity against the *M. avium* complex (MAC) that was superior to clarithromycin; potentiation was observed in combination with ethambutol.

RIFAL has exceptional activity against *Chlamydia trachomatis*; MIC for RIF is 0.004 μg/ml, for RIFAL 0.00025 μg/ml.[8]

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Rat	15.6	6.1	0.16	–	0.64 l/h/kg	30 mg/kg oral dose[1]
Human	8.7±2.7	852.1±407.1 ng·h/ml	24.5±14.7 ng/ml	–	–	The half-life data reported here[5] were obtained following the first RIFAL dose with 25 mg oral drug. The AUC and C_{max} data are for a single 25 mg oral dose in male fasted volunteers.[15]

In-vivo efficacy in animal model: RIFAL, similar to RIFAB but unlike RIF, has high tissue levels but low plasma levels in mice. RIFAL had a better therapeutic window against *M. tuberculosis* in mice compared with RIFAB and RIFAP and was active against some moderately RIF-resistant strains. RIFAL also had better activity against MAC in mice compared to the other rifamycins (reviewed in Tomioka et al. 1992[9] and Tomioka 2000[7]).

Long-term treatment of *M. tuberculosis*-infected mice to determine the conditions (comparing RIFAL 20 mg/kg, INH 25 mg/kg +/− PZA 150 mg/kg) under which RIFAL treatment would result in sterilization showed that although all animals were negative at 10 weeks, 2–3 of 8 mice relapsed three months after treatment.[10]

Success with RIFAL in the treatment of other bacterial diseases, for example *Clostridium difficile* and *Chlamydia*, has been reported (Anton et al. 2004;[11] reviewed in Suchland et al. 2006[12]).

Efficacy in humans

In a randomized open-label phase-2 clinical trial RIFAL was used in the first 2 weeks of treatment with smear-positive patients. RIFAL was administered once weekly at 10 or 25 mg with isoniazid 5 mg/kg daily. Adverse events with RIFAL were the same as with other treatments used in the study although statistically insignificant increases in flu-like symptoms were observed at the high RIFAL dose; transient decreases in absolute neutrophil counts were noted in 10–20% of the RIFAL patients. Due to issues with the control no conclusions could be drawn as to drug efficacy in this study (Dietze et al. 2001;[5] http://www.case.edu/affil/tbru/trials.htm]. No drug-resistant organisms were seen. No further *M. tuberculosis* clinical trials have been reported. De Souza[13] reports severe side effects in a clinical trial of RIFAL but provides no reference.

ActivBiotics has reported a phase-2/3 RIFAL trial in patients with peripheral arterial disease and high antibody titers to *Chlamydia pneumoniae*. The trial did not show the expected improvement in heart-disease symtoms although no specific reference was made to the microbiological outcome of the trial.[14]

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Mouse: PK data have been published but are not readily accessible.[16]
- Rat: PK data for a variety of doses have been reported by Hosoe et al.[1] Bioavailability for 3, 30 and 100 mg/kg doses was 26.9%, 13% and 4.7%, respectively. Protein binding ~99.5%.[1]
- Dog: Protein binding 99.8%.[1] PK data for a variety of doses have been reported by Hosoe et al.[1] Bioavailability for 3, 30 and 100 mg/kg doses was 42.9%, 21.0% and 8.0%, respectively.[1]
- Human: Half-life 61 hours, C_{max} 44 ng/ml (attributed to Rose et al. 1999 in review by Dietze et al.[5]). RIFAL may not be absorbed as well by TB patients as by uninfected controls.[5]
  RIFAL was safe and well tolerated under fed and fasting conditions when given at a single dose of 25 mg/mg.[15] RIFAL reaches high intracellular concentrations and has excellent tissue penetration.[17]

Animal metabolic pathway: Two major metabolites of RIFAL were identified from mouse urine; one was 25-deacetyl rifalazil, the other was probably 32-hydroxy rifalazil. Both metabolites were also obtained following incubation of the parent drug with pooled human liver microsomes. The antimicrobial activities of the metabolites were similar to that of the parent drug.[18]

Safety and Tolerability

Animal drug–drug interactions: RIFAL does not induce P450 enzymes and is not metabolized by these enzymes[1] thus the drug–drug interactions may be less compared with the other rifamycins (reviewed in Dietze et al. 2001[5]).

Human adverse reactions: In clinical trials 10 mg and 25 mg once weekly doses of RIFAL were generally well tolerated; dose-related flu-like symptoms were

observed similar as seen with RIF; other observations included a transient decrease in blood counts including platelets, white cells and absolute neutrophil numbers; similar numbers were seen in the RIF arm.[5]

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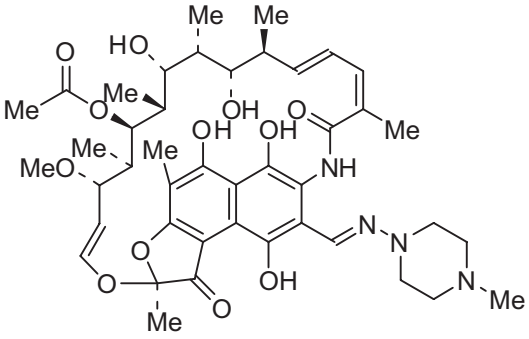
Rifampin



Generic and additional names: 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-methyl-1-piperazinyl)formimidoyl]-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-1,11(2H)-dione 21-acetate; rifampicin; rifaldazine; rifamycin AMP; R/AMP

CAS name: 3-{[(4-Methyl-1-piperazinyl)imino]methyl}rifamycin

CAS registry #: 13292-46-1

Molecular formula: $C_{43}H_{58}N_4O_{12}$

Molecular weight: 822.94

Intellectual property rights: Generic. Parent compound originally identified as a natural product from Amycolatopsis at Lapetit, Milan, Italy.[1] Lapetit collaborated with Ciba-Geigy in the early development of this compound.[1]

Brand names: Rifampin, rifampicin, rifamycin. Abrifam (Abbott); Eremfat (Fatol); Rifa (Grünenthal); Rifadin(e), Rifaldin (Aventis); Rifapiam (Piam); Rifaprodin (Almirall); Rifoldin (Aventis); Rimactan(e) (Novartis)

Derivatives: Rifapentine, rifalazil, rifabutin

Solubility: Freely soluble in chloroform and DMSO; soluble in ethyl acetate, methanol, tetrahydrofuran; slightly soluble in acetone, water, carbon tetrachloride [Merck Index]

Polarity: Log P 3.719 [DrugBank]

Acidity/basicity: pKa 1.7 for the 4-hydroxy and pKa 7.9 for the 3-piperazine nitrogen [Merck Index]

Stability: Very stable in DMSO; rather stable in water [Merck Index].

Melting point: 183ºC [DrugBank]

Formulation and optimal human dosage: 300 mg tablets (Mycobution, Upjohn). Dose 10 mg/kg, in a single daily administration, not to exceed 600 mg/day, oral or i.v.

Rifampin is also available as part of fixed-dose combinations with other TB drugs such as isoniazid and pyrazinamide (Rifater® is an example).

Basic biology information

Drug target/mechanism: Rifampin (RIF) inhibits the essential *rpoB* gene product β-subunit of DNA-dependent RNA polymerase activity, acting early in transcription.[2] It is thought to bind to the β subunit, close to the RNA/DNA channel, and physically blocks the transit of the growing RNA chain after 2–3 nucleotides have been added. In *Escherichia coli* bactericidal action may come from the triggering of apoptosis via activation of the "suicide gene module" *mazEF*, and the same system has been identified in *Mycobacterium tuberculosis*.[3] RIF does not inhibit the mammalian enzyme.

Drug resistance mechanism: >97% of mutants occur in RIF-resistant determining region (RDR), a 81 bp stretch of the *rpoB* gene. Both clinical and laboratory derived mutants are seen around amino acids 513–531, most resulting in profound resistance (32 to 256 μg/ml). S522L may be the exception, with MICs 8–16 μg/ml, but these mutants may be unfit and are rarely found in the clinic.[4] In *E. coli* most mutants in *rpoB* appear to be uniformly resistant to all rifamycins tested.[5] Many *M. tuberculosis* RIF-resistant mutants are cross-resistant with rifapentine (RIFAP) and rifabutin (RIFAB) but others do show some differential sensitivity. The *M. tuberculosis* Beijing strain, well known for its high frequency of mutations, was equally likely to harbor changes in the *rpoB* gene as non-Beijing strains.[6] The prevalence of RIF-resistant mutants in a sensitive

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	7.61±1.32	139.7±10.7	10.58±0.28	–	–	Single oral dose of 10 mg/kg[15]
Guinea pig	4.3±0.7	8.4±1.1	1.2±0.3	–	–	Single oral dose of 12 mg/kg[16,17]
Human	2.46	117.93 μg·h/ml	14.91 μg/ml	–	–	Single oral dose of 10–15 mg/kg.[15]

population is 1×10^{-6}, which is less than the number of isoniazid (INH)-resistant mutants at 1×10^{-5}.[7]

In-vitro potency against MTB: M. tuberculosis H37Rv: MIC 0.4 μg/ml;[8] other authors report MIC values in the range of 0.1–0.39 μg/ml against H37Rv.[9,10]

Spectrum of activity: RIF is bactericidal with a very broad spectrum of activity against most Gram-positive and some Gram-negative organisms (including *Pseudomonas aeruginosa*) and *M. tuberculosis* [DrugBank].

RIF has clinical efficacy against a wide variety of organisms, including *Staphylococcus aureus*, *Legionella pneumophila*, Group-A *Streptococcus*, *Brucella* spp., *Haemophilus influenzae*, and *Neisseria meningitidis*, as well as *in vitro* activity against penicillin-resistant *Str. pneumoniae*, *N. gonorrhoeae*, *Chlamydia trachomatis*, *H. ducreyi*, and many Gram-negative rods. Due to rapid emergence of resistant bacteria it is restricted to treatment of mycobacterial infections, where the customary use of combination drugs delays resistance development, and the treatment of asymptomatic meningococcal carriers [DrugBank].

Other in-vitro activity: RIF MIC_{90} for *M. tuberculosis* is 0.25 μg/ml compared with RIFAP 0.06 μg/ml.[11] RIF exhibited exposure-dependent killing kinetics on *M. tuberculosis* in macrophages, the MIC being the same as MIC in broth.[12] RIF protein binding is 83%; this results in an increase in MIC from 0.1 μg/ml to 1 μg/ml in the presence of 50% serum.[12] RIF was bactericidal with a 6 log reduction but EC_{50} (concentration at which half maximum CFU decrease was observed) decreased over time in culture, demonstrating an exposure (concentration × time)-dependent killing.[12] No synergy was observed when RIF was tested with INH, however significant synergy was seen when RIF and INH were tested in combination with gatifloxacin (GATI) (FIC 0.42), sparfloxacin (FIC 0.39), clarithromycin (CLA), ethambutol (ETH) and streptomycin (STR) (FICs 0.6–0.7).[13] Synergy at the MIC level was also seen with RIF in combination with ETH and levofloxacin (LEV), and RIF in combination with ETH, INH and LEV.[14]

In-vivo efficacy in animal model: The advantages of RIF as an important sterilizing drug have been demonstrated many times in animal models (reviewed in Mitchison 2000[7]). Various treatment regimens have been described, perhaps the most illustrative being complete sterilization of mice given 25 mg/kg INH and 25 mg/kg RIF for 9 months, but when RIF was withdrawn in the last 3 months and INH was continued alone a 20% relapse rate was observed (reviewed in Mitchison 2000[7]). Evaluation of the early effects of RIF in mice, with an aerosol infection model and delayed drug treatment until infection reached stationary phase, demonstrated a 3.6 and 4.07 $\log_{10}$ CFU reduction in bacterial burden in the lung using 270 mg/kg with 6 or 12 daily doses, respectively. The decrease in CFUs was linear with dose from 1 to 150 mg/kg/day when mice were treated for 6 or 12 days. The authors concluded that AUC/MIC was the best predictor of activity *in vivo*.[12] Increases in dose to 810 mg/kg for 6 days did provide sterilization of the mice but these dose equivalents remain untested in humans due to toxicity concerns.

Efficacy in humans

Treatment regime most often used: initially INH, RIF, pyrazinamide (PZA), ETH daily for 2 months followed by INH and RIF 3 times weekly for 4 months [DrugBank]. Specific doses and specific treatment times vary and details can be found in many sources including Centers for Disease Control [http://www.cdc.gov/mmwR/preview/mmwrhtml/rr5211a1.htm] and the World Health Organization [http://www.who.int/en/]. RIF exhibits very effective activity against persistors in the continuation phase of treatment. Mitchison[7] suggests that a dose increase from 600 mg to 900 mg daily would accelerate the sterilization process.

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Mouse: 83% plasma binding.[12]
- Guinea pig: Bioavailability 51%.
- Human: Bioavailability ~70%. At the 600 mg 2× weekly dose: C_{max}: 8–20 μg/ml, time to C_{max} 1.5–2 hour, half-life 2–5 hours, protein binding 85% (reviewed in Burman et al. 2001[18]).

Human metabolic pathway: Metabolism is mainly hepatic with 13–24% of the drug excreted unchanged in the urine. The drug is present in plasma as parent and deacetyl-RIF. RIF PK/PD is characterized by auto-upregulation of hepatic and gut metabolism with time such that the pharmacokinetics of RIF change with repeated administration; steady state is usually reached by the sixth daily dose of 600 mg/kg. RIF diffuses well to most body tissues and fluids, including the cerebrospinal fluid (CSF); concentrations in the liver, gallbladder, bile, and urine are higher than those found in the blood; therapeutic concentrations are achieved in the saliva, reaching 20% of serum concentrations; RIF crosses the placenta, with fetal serum concentrations at birth found to be approximately 33% of the maternal serum concentration; it penetrates into aqueous humour; it is distributed into breast milk [DrugBank].

Safety and Tolerability

Animal drug–drug interactions: Antagonism occurs between INH, RIF and PZA in mice (see INH article for details).[15]

Animal toxicity: Acute toxicity: LD_{50} in mice, rats (mg/kg): 885, 1720 orally; 260, 330 i.v.; 640, 550 i.p. [Merck Index].

Chronic toxicity: Chronic exposure may cause nausea and vomiting and unconsciousness [FDA label].

Hepatotoxicity: Liver abnormalities were seen in all species tested (rats 5 times, monkeys 8 times and mice 6 times recommended daily human dose). RIF administered in encapsulated form once or twice a week was as effective as free drug and showed less liver toxicity as measured by ALT, alkaline phosphatase and bilirubin levels.[19,20] INH and RIF dosed simultaneously in rabbits caused an elevation in phospholipids and a reduction in phosphatidylcholine, cardiolipin and inorganic phosphates, possibly via a choline deficiency, which may lead to the observed liver toxicity.[21]

Reproductive toxicology: Testicular atrophy was seen in baboons at 4 times recommended daily human dose. Teratogenicity was seen in rats at 15–25 recommended daily human dose [Physicians' Desk Reference].

The available studies on mutagenicity indicate absence of a mutagenic effect.[22] An increase of hepatomas seen in female mice has been reported in one strain of mice, following one year's administration of RIF at a dosage of 2–10% of the maximum human dosage.[22]

Animal safety pharmacology: RIF has been reported to have an immunosuppressive effect in some animal experiments [FDA label].

Human drug–drug interactions: RIF induces certain cytochrome P450s, mainly 3A4 isozyme. The RIF dose of 600 mg/day was established partly to limit the CYP3A induction potential (reviewed in Burman et al. 2001[18]).

The drug affects the metabolism of the following drugs: acetaminophen, astemizole, carbamazepine, corticosteroids, cyclosporin, dapsone, ketoconazole, methadone, phenobarbital, phenytoin, quinidine, terfenadine, theophylline, verapamil and warfarin (reviewed in Douglas and McLeod 1999[23]). Generally, although RIF induces CYP3A and lowers the plasma concentrations of some other drugs, its own PK is largely unaffected by this induction. The drug can also induce CYP1A2, CYP2C and CYP2D6. RIF causes up to a 70% reduction in the AUC of indinavir, however the CDC has laid out specific guidelines for the coadministration of the two drugs (reviewed in Burman et al. 2001[18] and Back et al. 2002;[24] see also Morbidity and Mortality Weekly Reports for CDC guidelines).

Human potential toxicity: Hepatotoxicity is generally rare with RIF alone but preexisting conditions can be exacerbated. A Montreal study showed a rate of frank liver toxicity at 0.05/100 following RIF administration, this was compared with rates of 3 and 10 times greater for INH and PZA, respectively.[25]

For RIF (10 mg/kg), clinically apparent hepatotoxicity has been reported to occur in 2–5% of cases and altered liver function tests in 10–15%.[26]

Human adverse reactions: Hepatitis and serious hypersensitivity reactions including thrombocytopenia, hemolytic anaemia, renal failure have been reported.[1] Asymptomatic elevations of serum transaminase enzymes, increase in serum bile acids and bilirubin concentrations can occur. Marked elevation of serum alkaline, phosphatase and bilirubin suggests RIF toxicity.

Cardiovascular: Hypotension and shock.

Respiratory: Shortness of breath.

CNS: Rare cases of organic brain syndrome have been reported (i.e. confusion, lethargy, ataxia, dizziness and blurring of vision). Peripheral neuropathy, affecting the limbs, muscles and joints in the form of numbness and pain, has been reported.

Gastrointestinal: Nausea, vomiting, diarrhoea.

RIF causes orange-red staining of all body fluids.

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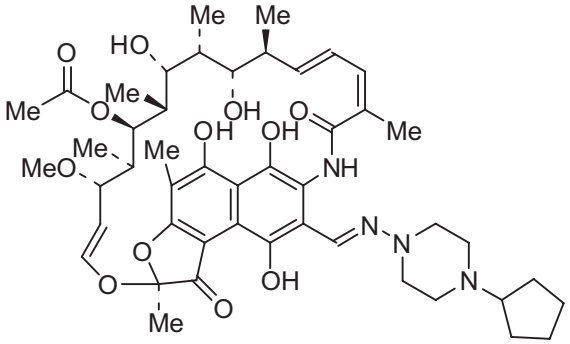
Rifapentine

Generic and additional names: Rifapentine
CAS name: 3{[(4-cyclopentyl-1-piperazinyl)imino]methyl}-rifamycin
CAS registry #: 61379-65-5
Molecular formula: $C_{47}H_{64}N_4O_{12}$
Molecular weight: 877.031
Intellectual property rights: Generic
Brand names: Priftin
Derivatives: KRM-1648 (also called Rifalazil or ABI-1648), rifabutin
Polarity: Log P 5.29 [DrugBank]
Formulation and optimal human dosage: 600 mg 2× weekly
Capsules 150 mg Aventis



Basic biology information

Drug target/mechanism: See rifampin (RIF).
Drug resistance mechanism: As with RIF, most of the clinical *Mycobacterium tuberculosis* mutations resulting in resistance to rifapentine (RIFAP) and KRM-1648 (RIFAL) are in the *rpoB* gene, generally confined to the rif-resistance determining region (RDR). Some mutations confer resistance to all the rifamycin analogs whereas others were found to be specific to RIF and RIFAP but not to RIFAL or rifabutin (RIFAB).[1] A significant number of publications on these mutations can be found[1–3] and most of the authors agree that both position and type of substitution play a role in sensitivity to the rifamycins: as a general rule, mutations at codons 511 and 516 result in resistance to RIF and RIFAP but sensitivity to RIFAL and RIFAB, while mutations at codon 531 result in high-level resistance to all the rifamycin analogs. A few rifamycin-resistant mutations are found outside the RDR; in *Escherichia coli* there are some mutational hot spots outside the core region of *rpoB* which result in rifamycin resistance, and the same may apply in *M. tuberculosis*. No RIF-resistant *M. tuberculosis* mutations outside *rpoB* have been mapped, but mutations outside the RDR or alteration in drug transporters or membrane permeability are suspected in these cases.[2]
In-vitro potency against MTB: M. tuberculosis H37Rv MICs: RIFAP 0.031 μg/ml, RIFAB <0.015 μg/ml, RIF 0.25 μg/ml.[1]
Spectrum of activity: RIFAB and RIFAP are active against the same spectrum of mycobacteria as RIF although differences in absolute MICs have been identified. RIFAB and RIFAP are more active than RIF *in vitro* against the *M. avium* complex (MAC), *M. tuberculosis*, and *M. leprae*.[4,5]
Other in-vitro activity: RIFAP MIC: *M. africanum* ATCC 25420 0.031 μg/ml, *M. bovis* ATCC 19210 0.063 μg/ml.
RIFAP metabolite 25-O-deacetyl-RIFAP MIC: *M. africanum* ATCC 25420 0.125 μg/ml, *M. bovis* ATCC 19210 0.125 μg/ml. MICs for other strains are provided in the same paper.[6]
Yang[2] ranks the rifamycins in the following order of decreasing MIC: RIF > RIFAP > RIFAL.
Activity against *M. avium*: MIC RIFAB 0.06 μg/ml; RIFAP 0.0125 μg/ml.[7]
Post-antibiotic effects were measured with RIFAP giving 20 hours at 20 μg/ml, the longest compared with isoniazid (INH) and moxifloxacin (MOXI); the addition of MOXI (2 μg/ml) to RIFAP (10 μg/ml) increased this to 137 hours.[8]
RIFAP was more efficacious than RIFAB against *Toxoplasma gondii in vitro*, but atovaquone, a known *T. gondii* treatment, outperformed them both. No host-cell toxicity was observed at efficacious levels of 10 μg/ml. RIFAP and RIFAB were active *in vivo* in a mouse model, where they showed superior activity to atovaquone at 50 mg/kg but inferior activity at

100 mg/kg. Again RIFAP outperformed RIFAB at both levels.[9]

In-vivo efficacy in animal model: Mouse studies in a *M. tuberculosis* model demonstrated that high RIFAP (equivalent to 10–15 mg/kg in humans) was more effective than a lower dose (equivalent to 5 mg/kg in humans).[10] Treatment failure was observed with all weekly dose regimens using RIFAP alone, but successful outcomes resulted when RIF was substituted for RIFAP in the continuation phase; specifically, INH, RIF and pyrazinamide (PZA) were given for two months daily followed by RIFAP, INH weekly for four months.[10] The antimicrobial activities of RIF, RIFAB and RIFAP were compared in BCG-vaccinated and *M. tuberculosis*-infected immunocompetent mice. Using an equal weight basis both RIFAP and RIFAB were more bactericidal than RIF. The activity of RIF was significantly reduced when drug was administered to mice three times a week instead of six times a week, however significant bactericidal activity was still observed in mice treated with RIFAP, 10 mg/kg up to once every two weeks, or RIFAB, 10 mg/kg twice weekly. The bactericidal activity of RIFAB, 10 mg/kg 6×/week for 6 weeks, or RIFAP, 10 mg/kg 2×/week for 12 weeks, was comparable to that of RIF, 10 mg/kg 6×/week for 12 weeks in mice.[11] Pharmacokinetic experiments comparing RIF, RIFAB and RIFAP demonstrated that RIFAP had the highest serum peak level (C_{max}) and the longest half-life, whereas RIFAB displayed the lowest C_{max} and the shortest half-life.[11] Chapuis et al.[12] showed various degrees of bactericidal activity in mice after daily treatment with RIF plus PZA for 13 weeks, INH daily for 26 weeks, or RIFAP once weekly for 13 or 26 weeks or once every two weeks for 26 weeks. The activity of RIFAP was significantly enhanced when INH was added at the same dosing frequency. After chemotherapy was stopped no relapses or very few relapses were observed in normal mice that had been treated with RIF + PZA daily for 13 weeks, or RIFAP alone or RIFAP + INH once weekly for 26 weeks. The latter three regimens and RIFAP + INH once weekly for 13 weeks may be applied for fixed-duration preventive therapy in human immunodeficiency virus (HIV)-negative subjects.[12] Previously it had been shown in mice that the most active weekly regimen (RIF, MOXI, INH) was less effective than the standard 6-month daily regimen recommended by the WHO (RIF, INH, PZA).[13] Using a similar mouse model with weekly treatments, RIFAP increased to 15 mg/kg and MOXI increased to 400 mg/kg, there was relapse in 11% of cases 3 months after treatment cessation. Regardless of RIFAP dose relapse was completely ablated if mice were treated with a regimen which included MOXI at 400 mg/kg for 5/7 days for the first 2 weeks.[14]

In vivo (mouse) against *M. avium* RIFAB showed better activity than RIF and slightly better activity than RIFAP.[7]

Efficacy in humans

RIFAP was approved for human use in 1998. It is a long-acting rifamycin with use restricted to HIV-negative patients who are sputum negative at two months post treatment (reported in Veziris et al. 2005[14]). The clinical data generated with this drug strive to quantitate the effect of RIFAP's 12-hour half-life, high plasma binding (~98%) with the obvious benefits of weekly dosing. A 2004 study[15] reported that there were no drug-related adverse effects from once weekly RIFAP at up to 1200 mg. The study was conducted to evaluate the high dose and concluded that further trials were justified.[15] Similarly, Weiner et al.[16] demonstrated that low INH serum concentrations were associated with the failure of the weekly RIFAP/INH regimen. Weekly RIFAP success was documented for the treatment of latent TB in high-risk situations[17] when it was shown that weekly RIFAP/INH (900 mg of each for 12 weeks) was better tolerated than daily RIF/PZA (RIF 450–600 mg/PZA 750–1500 mg for 8 weeks); efficacy was almost the same in the two groups, with 0.52% relapse in the daily treatment groups and 1.46% failure in the weekly treatment. The sterilizing effects of RIFAP versus RIF were compared in an EBA study;[18] five daily doses of RIF (150–600 mg) or one dose of RIFAP (300–1200 mg) were compared and data showed that the 1200 mg dose of RIFAP was necessary to prevent bacterial regrowth and development of RIF resistance. Burman et al.[19] note that both RIFAB and RIFAP exhibit idiosyncratic clinical efficacy; RIFAB is active despite unfavorable C_{max}/MIC ratios while RIFAP exhibits sub-optimal clinical performance despite a very favorable C_{max}/MIC ratio; these phenomena may be partly explained by differences in protein binding and in intracellular penetration (reviewed in Burman et al. 2001[19]).

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Mouse: Half-life of the compound alone is 14–18 hours.[21]
- Human: RIFAP was 70% bioavailable [FDA label]. RIFAP is 97% protein bound; ratio of extracellular to intracellular concentration is 24–60 for RIFAP, and 5 for RIF.[19] Repeated doses do not appear to affect clearance of RIFAP but do affect clearance of RIF and RIFAB; with repeated doses the AUC of

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	–	309±35.5*, 474±5.8**	11.1±0.39*, 16.7±1.1*	–	–	Single dose in mice of *10 mg/kg and **15 mg/kg with single dose of MOXI 100 mg/kg[20]
Human	13.19±7.38	319.54±91.52	15.05±4.62	–	2.03±0.6 l/h	Dose 300 mg/day, PK determined at day 10 [FDA label]. PK for the 25-deactyl RIFAP metabolite is as follows: $T_{1/2}$ = 13.35±2.67 h; C_{max} = 6.26±2.06 μg/ml; AUC = 215.88±86 μg·h/ml [FDA label].

RIFAB is lowered but the half-life is unaffected. Steady-state levels of RIF and RIFAB are achieved after 6 days of daily dosing (reviewed in Burman et al. 2001[19]).

Animal metabolic pathway: In rat, RIFAP was rapidly taken up by the liver but diffused slowly into tissues. Oral absorption was 84% after a 3 mg/kg dose. Higher concentration was found in lungs compared with plasma. 92% of the dose is eliminated in faeces.[21]

Human metabolic pathway: About 10% of RIFAP is excreted unchanged in the urine compared with 13–24% of RIF. Plasma elimination half-life is 14–18 hours.[19] 17% and 70% of the total dose was recovered in urine and faeces, respectively, and >80% of the total dose was excreted within 7 days. RIFAP and 25-O-deacetyl-RIFAP accounted for 99% of the total radioactivity in plasma. Slight gender-related differences in PK were observed [FDA label].

Safety and Tolerability

Animal toxicity: Teratogenic effects: RIFAP was teratogenic in rats and rabbits. In rats at 0.6× the human dose equivalents given during organogenesis some pups had cleft palate, delayed ossification and an increase in the number of ribs. In rabbits at 0.3–1.3× human dose equivalents 4 of 431 pups had irregular ossification of facial tissues, arhinia and microphthalmia and abnormalities in ovarianagenesis.

Non-teratogenic effects: Increases in stillborn pups were found in rats and rabbits at 0.3× and 1.3× human dose equivalents, respectively [DrugBank].

Carcinogenicity: RIFAP was negative in the Ames test, the *in vitro* point mutation test in *A. nidulans*, gene conversion assay in *Saccharomyces cerevisiae*, CHO/HGRPT forward mutation assay, and others. 25-deacetyl-RIFAP was positive in an *in vitro* chromosomal aberration assay [FDA label].

Human drug–drug interactions: In general the rifamycins do induce CYP3A in gut and liver but not in neutrophils and lymphocytes. The relative induction of CYP3A by the rifamycins is RIF > RIFAP > RIFAB, although this is generally reversed 1–2 weeks following drug cessation (reviewed in Burman et al. 2001[19]). Other microsomal enzymes are also affected, namely CYP1A2, CYP2C and CYP2D6. Rifamycins in general should not be given with azole antifungals as subtherapeutic serum concentrations of the latter can result (reviewed in Burman et al. 2001[19]) although the FDA label indicates a decrease in the drug levels of itraconazole, but not fluconazole, when given with RIFAB.

Human potential toxicity: The "flu-like" symptoms observed with RIF treatment are not seen as frequently with RIFAP[19] when 2× weekly RIF and 1× weekly RIFAP are compared. This may be due to a decreased immune reaction to RIFAP compared with RIF, or because RIFAP has a longer half-life thus exposing the immune system to a distinct regimen of drug.[19]

Human adverse reactions: Hepatitis frequency is similar to that seen with RIF, and probably not associated with the rifamycins but with drug combinations.[19]

Cardiovascular: similar to RIF.

Respiratory: similar to RIF.

CNS: similar to RIF.

Gastrointestinal: similar events and frequency as with RIF, RIFAB and RIFAP (nausea, vomiting, diarrhoea).

Similar as with RIF, skin and body-fluid discoloration may result from RIFAP dosing [FDA label].

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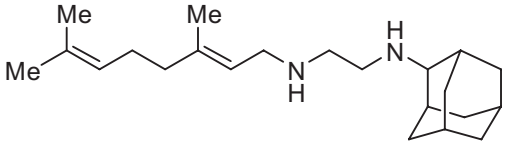
SQ109



Generic and additional names: SQ-109
NSC722041
SQ109 Ditrifluoroacetate salt, HCl salt
CAS name: N-[(2E)-3,7-dimethyl-2,6-octadienyl]-N′-tricyclo[3.3.1.13,7]dec-2-yl-1,2-ethanediamine dihydrochloride
CAS registry #: 627526-76-5
Molecular formula: $C_{22}H_{38}N_2$
Molecular weight: 330.6
Intellectual property rights: Sequella
Derivatives: A combinatorial library of 67,238 analogs was made based on the ethylene-diamine core of ethambutol[1,2]
Polarity: Calculated log P (KowWin): 6.45 [NAID home AIDS # 207396]

Basic biology information

Drug target/mechanism: SQ109 is a novel 1,2-ethylenediamine-based ethambutol (ETH) analog; no specific studies on mode of action are available. No effects on EmbA or -B, the target of ETH, were seen with a proteomic approach comparing the effects of 24-hour drug on *Mycobacterium tuberculosis* H37Rv. A few proteins, such as ATP-dependent DNA/RNA helicase and β-keto-acyl-acyl carrier protein synthase, were differentially regulated by isoniazid (INH) and SQ109 or ETH; INH treatment resulted in down-regulation of the helicase and up-regulation of the synthase whereas treatment with ETH or SQ109 resulted in up-regulation of the helicase and down-regulation of the synthase.[3]

Based on activity against ETH-resistant strains and differences in behavior of ETH and SQ109 in gene-array studies Protopopova et al.[1,4] postulate that SQ109 has a distinct mechanism of action or activating mechanism compared with ETH.

Drug resistance mechanism: Specific resistance mechanisms were not studied but SQ109 was active against RIF-resistant organisms.[4]

In-vitro potency against MTB: *M. tuberculosis* H37Rv MICs reported by Sequella: MIC 0.11 μg/ml (BACTEC), MIC 0.35 μg/ml broth dilution.[2] MICs on drug-sensitive and -resistant clinical isolates 0.16–0.64 μg/ml, indistinguishable from H37Rv.[4]

Sequella also reported SQ109 MICs in a separate publication: *M. tuberculosis* Erdman 0.7 μM; *M. tuberculosis* ETH-resistant 1.4 μM in Alamar Blue, 0.99 μM in BACTEC; *M. tuberculosis* INH-resistant 1.4 μM; *M. tuberculosis* RIF-resistant ⩽0.7.[1]

Spectrum of activity: SQ-109 is somewhat specific for mycobacteria: *M. tuberculosis* 0.25–5 μg/ml, *M. bovis* 0.25 μg/ml, and *M. marinum* 8 μg/ml,[5] but little activity against *M. avium* and *M. smegmatis*.[4] Some activity against *Candida albicans* (4–8 μg/ml) including fluconazole-resistant strains,[5] other analogs of this class being tested.

Other in-vitro activity: Synergistic activity was observed between SQ109 and INH or rifampin (RIF) against H37Rv. Synergy between SQ109, but not ETH, and RIF was found using RIF-resistant strains. Additive effects occurred with streptomycin (STR) and SQ109; no synergistic effects, positive or negative, were seen between pyrazinamide (PZA) or ETH and SQ109.[4] Intracellular activity against *M. tuberculosis*-infected RAW cells: MIC_{99} 0.5 μg/ml.[1]

In-vivo efficacy in animal model: SQ109 was effective as an oral dose in mice (drug administered 20 days after infection, drug 5× weekly for 45 days at 1 mg/kg) and is 100 times more effective than ETH; highest activity observed in lung.[1] Oral administration of SQ109 (0.1–25 mg/kg) was dose dependent and 10–25 mg/kg was as effective as ETH at 100 mg/kg but less effective than INH at 25 mg/kg.[6] Low protein binding was observed with SQ109.[7]

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	5.2±1.1*	0.254±0.184*	0.135±0.01*	11.83±1.49**	3788±1768 ml/kg/h**	*Oral dose of 25 mg/kg, **i.v. dose of 3 mg/kg.[6]
Rat	8.2*	0.99*	0.64*	9.96**	1575 ml/kg/h**	*13 mg/kg single oral, **1.5 mg/kg i.v.dose[7]
Dog	19.6±4.8*	0.087±0.016*	0.011±0.002*	29.2±6.9**	2471±319 ml/kg/h**	*3.75 mg/kg single oral, **4.5 mg/kg i.v. dose[7]

Substitution of EMB (100 mg/kg) with SQ109 (10 mg/kg) in a regimen containing RIF and INH resulted in better clearance of tissue bacteria and 25–30% decrease in time to standard of care effects, whether or not PZA was included in the regimen, or whether analysis was done at 1 or 2 months.[8]

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Mouse: Oral bioavailability 8%.[7,9] Levels in lung and spleen were up to 120-fold higher than in plasma, and 10× higher than MIC.[6]
- Rat: Oral bioavailability 12%, highest drug concentration in liver > lung > spleen > kidney.[7]
- Dog: SQ109 partially degrades (30–40%) in dog and human plasma but is stable in rat and mouse plasma.[9] Very high clearance and volume of distribution was found in dog compared with mouse and rat, oral bioavailability 2.4–5%.[7]
- Human: SQ109 degraded in dog and human plasma but was stable in rat and mouse plasma.[9] Plasma binding is higher (10–20%) in humans compared with 5–10% in rat and mouse.[7]

Animal metabolic pathway: Elimination of drug in the urine (22%) and in faeces (5.6%) was observed in rats dosed with labeled compound.[7]

Human metabolic pathway: In vitro analysis of microsomal treatment showed the compound is metabolized by oxidation, epoxidation and N-dealkylation.[7]

Safety and Tolerability

Animal drug–drug interactions: The compound is metabolized in the presence of liver microsomes to the following extent in a 10-minute incubation: mouse 48%, rat 23%, dog 51%.[7]

Animal toxicity: Metabolism seems to be extensive both in the animal and *in vitro*, and the toxicity profile for these molecules needs to be examined.[7]

Human drug–drug interactions: The compound is metabolized by CYP2D6 and CYP2C19, up to 58% of parent being metabolized in 10-minute incubation with microsomes; insignificant metabolism is found in the presence of CYP3A4.[7]

Human potential toxicity: A phase-1 double-blind, placebo-controlled study completed in May 2007 found that oral doses of SQ109 up to 300 mg, the highest dose tested, were safe and well tolerated, with no serious adverse effects reported at any dose. No measurable clinically meaningful changes in blood chemistry, haematology or ECG were observed, the drug had a wide tissue distribution, and plasma levels were as expected from animal studies. The drug does have a long half-life of 61 hours [Sequella press release, May 2007].

"Sequella plans to conduct an additional Phase 1b clinical study to demonstrate safety of daily administration of SQ109 alone, and then in combination with other TB drugs to evaluate safety and efficacy in patients with pulmonary TB. Additional clinical studies will begin Q2 2007." [Sequella press release, May 2007].

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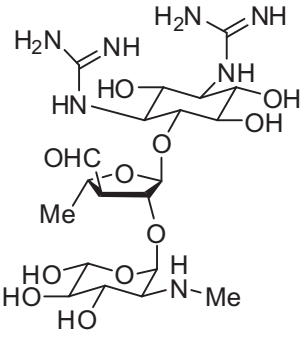
Streptomycin



Generic and additional names: Streptomycin A
CAS name: O-2-Deoxy-2-(methylamino)-α-L-glucopyranosyl-(12)-O-5-deoxy-3-C-formyl-α-L-lyxofuranosyl-(14)-N,N′-bis(aminoiminomethyl)-D-streptamine
CAS registry #: 57-92-1
Molecular formula: $C_{21}H_{39}N_7O_{12}$
Molecular weight: 581.57
Intellectual property rights: Generic
Brand names: Sesquisulfate-AgriStrep (Merck & Co.); Streptobrettin (Norbrook); Vetstrep (Merck & Co.).
Solubility: The salts are very soluble in water; but almost insoluble in alcohol, chloroform, ether [Merck Index].
Polarity: Log P −8.005 [DrugBank]
Formulation and optimal human dosage: Dose 1 g daily i.v. or intramuscularly (i.m.)[1]

Basic biology information

Drug target/mechanism: Streptomycin (STR) was the first aminoglycoside antibiotic identified; it inhibits protein synthesis by binding tightly to the conserved A site of 16S rRNA in the 30S ribosomal subunit (reviewed in Chan et al. 2003[1]). It is in the same class as amikacin (AMI) and kanamycin (KAN).

Drug resistance mechanism: Ribosomal changes in the 16S rRNA and ribosomal protein S12 are associated with STR resistance in *Mycobacterium tuberculosis*.[1,2] Cross-resistance with other class members (KAN and AMI) and the macrocycle polypeptide capreomycin (CAP) exists, but this is not always complete or reciprocal; for example,[3] KAN, AMI and CAP were still efficacious *in vitro* when resistance to STR had developed.[3] In general AMI appears to be active against STR-resistant strains of *M. tuberculosis* while strains resistant to AMI are equally resistant to STR. CAP is generally active against STR-resistant *M. tuberculosis* strains but CAP-resistant strains are often sensitive to AMI.[2]

In-vitro potency against MTB: M. tuberculosis H37Rv: MIC 1 μg/ml.[4]

Spectrum of activity: Aminoglycosides are used mainly in infections involving aerobic, Gram-negative bacteria, such as *Pseudomonas*, *Acinetobacter* and *Enterobacter*. *M. tuberculosis* is also sensitive to this drug. Gram-positive bacteria can also be treated with the drug but less toxic alternatives tend to be utilized. Synergistic effects with the aminoglycosides and beta lactams have resulted in use of this combination treatment for streptococcal infections, especially endocarditis [DrugBank].

Other in-vitro activity: STR is active (MIC 1 μg/ml) against H37Rv and a number of *M. tuberculosis* clinical strains including an MDR strain with resistance to isoniazid (INH) and rifampin (RIF).[4] In a study comparing the bactericidal activity of several agents, RIF and INH were superior against drug-sensitive strains followed by ethionamide (ETA) and STR, with ethambutol (ETH) and cycloserine (CYS) having marginal bactericidal activity.[4]

STR had no bactericidal activity, but did cause significant reduction in bacterial load when *M. tuberculosis*-infected macrophages were treated using aminoglycosides; there was a 1–2 log reduction in CFU, 99% killing using STR 30 μg/ml or KAN 30 μg/ml or AMI 20 μg/ml.[4]

In-vivo efficacy in animal model: AMI was the most active of the aminoglycosides tested (STR, AMI and KAN dosed at 200 mg/kg 6 times weekly) in a mouse model of tuberculosis (2.3×10^7 CFU *M. tuberculosis* administered i.v. followed by dosing 1 day later). STR reduced the CFU in the spleen by almost 1 log. All three drugs were less efficacious than INH at 25 mg/kg. All the mice in the drug-treated groups survived whereas the control mice died within 30 days.[5]

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Human	–	–	25–50	–	–	1 g i.m. Following intramuscular injection of 1 g of STR, as the sulfate, a peak serum level of 25–50 μg/ml is reached within 1 hour, diminishing slowly to about 50% after 5–6 hours [DrugBank].

Efficacy in humans

STR was the first drug approved for the treatment of tuberculosis following human trials in 1947. STR is the least toxic of the three aminoglycosides, STR, AMI and KAN.[6] It is clinically effective as a single agent but resistance development is unacceptably rapid. The aminoglycosides cannot be administered orally. Historically prescribed with INH, STR probably had little overall effect in this combination (reviewed in Grosset and Ji 1998[7]).

Aminoglycosides remain important drugs for treating diseases caused by *M. tuberculosis* (reviewed in Peloquin et al. 2004[6]) but they are no longer first line.

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Human: All the aminoglycosides are administered parenterally. Chan et al.[1] give a value for C_{max} of 35–45 μg/ml, with no dose given.

Human metabolic pathway: Primarily eliminated through the kidney, between 29% and 89% of a 600 mg dose is excreted in the urine within 24 hours [DrugBank]. STR passes through the placenta with serum levels in the cord blood similar to maternal levels. Small amounts are excreted in milk, saliva, and sweat.

Safety and Tolerability

Animal toxicity: Oral rat with STR sulfate LD_{50} 430 mg/kg; side effects include nausea, vomiting, and vertigo, paraesthesia of face, rash, fever, urticaria, angioneurotic edema, and eosinophilia [DrugBank].

Human drug–drug interactions: Concurrent use of other aminoglycosides and gentamycin, tobramycin, viomycin and cyclosporin is not recommended. Care should be taken post anaesthesia or post dosing with muscle relaxants as respiratory paralysis can occur [DrugBank].

Human potential toxicity: STR for use in humans carries a warning about serious neurotoxic effects; risk of severe neurotoxic reactions (including cochlear and vestibular dysfunction, optic nerve dysfunction, peripheral neuritis, arachnoiditis, and encephalopathy) increases in patients with impaired renal function or pre-renal azotemia [FDA label]. 8th Cranial Nerve, ototoxicity and nephrotoxicity.[2] The aminoglycosides and CAP are known for their ototoxicities, and incidences may be as high as 3–10%.[1] The following reactions are common: vestibular ototoxicity (nausea, vomiting, and vertigo); paraesthesia of face; rash; fever; urticaria; angioneurotic edema; and eosinophilia [DrugBank].

Human adverse reactions: STR is contraindicated in patients with renal impairment. The toxicity seen in renal impaired patients is directly linked to the inability to excrete the drug at the same rate as normal individuals [DrugBank].

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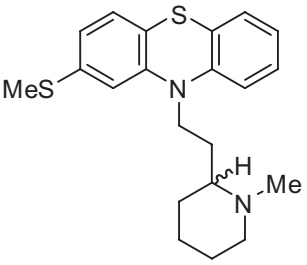
Thioridazine



Generic and additional names: Thioridazine;
2-methylmercapto-10-[2-(N-methyl-2-piperidyl)ethyl]phenothiazine;
3-methylmercapto-N-[2′-(N′-methyl-2-piperidyl)ethyl]phenothiazine;
Thioridazine-2-sulfoxide
CAS name: 10-[2-(1-Methyl-2-piperidinyl)ethyl]-2-(methylthio)-10H-phenothiazine
CAS registry #: 50-52-2
Molecular formula: $C_{21}H_{26}N_2S_2$
Molecular weight: 370.57
Intellectual property rights: Generic
Brand names: Aldazine (Alphapharm); Mellaril, Melleretten, Mallorol (Novartis); Novoridazine (Novopharm); Orsanil (Orion); Ridazin (Taro); Stalleril (Pharmacal)
Solubility: Soluble in alcohol (1 in 6), chloroform (1 in 0.81), ether (1 in 3); freely soluble in dehydrated alcohol; practically insoluble in water at 0.0336 mg/l [Merck Index].
Polarity: Log P 6.552 [DrugBank]
Acidity/basicity: pKa 9.5 [DrugBank].
Melting point: 73ºC [DrugBank]
Formulation and optimal human dosage: The usual starting dose for adult schizophrenic patients is 50–100 mg three times a day, with a gradual increment to a maximum of 800 mg daily if necessary. Supplied as oral suspension or as tablets from 10 to 200 mg. Some phenothiazines can be administered i.v.

Basic biology information

Drug target/mechanism: Thioridazine (THZ) is a phenothiazine; other members of this class include chlorpromazine and trifluoperazine. These closely related compounds and their analogs are active against TB and have been used to probe the mechanism of action of the phenothiazines as TB agents. Phenothiazines in general, and THZ in particular, have been described as exerting their anti-tuberculosis effects via calmodulin[1,2] or by inhibiting NADH2-menaquinone-oxidoreductase (Ndh2).[3] The phenothiazines, especially THZ, are also inhibitors of the voltage-gated Kv 1.3 channels and are thought to exert their anti-psychotic activity through a blockade of dopamine receptors, particularly the D2 populations.[4]

Calmodulin: the evidence for calmodulin involvement is circumstantial; calmodulin-type genes have been found in *Mycobacterium tuberculosis*,[1] the phenothiazines have been described as calmodulin antagonists,[4] and trifluoperazine, a related phenothiazine, has been crystallized with calmodulin in various stoichiometries.[5]

Ndh2: Several authors[6,7] have demonstrated that the phenothiazines inhibit succinate dehydrogenase and type II NDH (NADH-quinone oxidoreductase),[7] cause depletion of ATP levels, and alter NADH/NAD and menaquinol/menaquinone ratios;[6] these activities implicate oxidative phosphorylation as the target for phenothiazines.[6,7] Trifluoperazine and two closely related analogs inhibit Ndh2 with an IC_{50} around 12 μM.[3] Trifluoperazine inhibits the consumption of oxygen in isolated *M. tuberculosis* membranes at a site upstream of cytochrome C.[7] Ndh2, part of the electron transport chain and therefore implicated in oxygen consumption, is a non-proton-pumping oxidoreductase present in two forms, Ndh and NdhA, and chlorpromazine inhibits both subtypes with an IC_{50} of 10 μM.[7]

In-vitro potency against MTB: M. tuberculosis ATCC 27294: MIC 10 μg/ml compared with chlorpromazine 15 μg/ml.[8]

Spectrum of activity: The phenothiazines as a class have shown antibacterial activity against the mycobacteria.[8] Chlorpromazine has shown activity against *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *M. tuberculosis*, atypical

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Human	30±7	–	25–150 ng/ml	21±9	8.6±2.9 ml·min/kg	Chlorpromazine probably 100 mg oral dose [Goodman & Gilman's, pp. 497–8].

mycobacteria, influenza virus, measles virus, and herpes simplex virus. Phenothiazines as a class have shown activity against intestinal anaerobes, *Bacteroides* spp., *Prevotella* spp. and *Fusobacterium* (reviewed in Kristiansen and Amaral 1997[9]). THZ has demonstrable activity against *Trypanosoma cruzi in vitro* and *in vivo*.[10,11] THZ had activity against two strains of malaria, the 3D7 drug-resistant strain and the W2 drug-sensitive strain, with IC_{50}s of 2.6 and 1.9 μM, respectively; this activity is thought to be target-based as a number of THZ analogs including chlorprothixene were also active.[12]

Other in-vitro activity: Phenothiazines appear to be equally active on starved (representative of persistent state) or log phase cells unlike rifampin (RIF), which has some activity on the starved cells, or isoniazid (INH), which has no activity on starved cells.[13] Synergistic activity at the MIC level between RIF and streptomycin (STR), but not INH, and the phenothiazines has been reported.[14] MICs for phenothiazines are much higher than the corresponding values in macrophages as the drug concentrates inside cells.[8] The MICs in macrophages for inhibiting *M. tuberculosis* growth have been reported as 0.23–3.6 μg/ml[15] and 0.1 μg/ml.[8] In the latter studies there were no cytotoxic effects on the macrophages at the concentrations required for efficacy.[8] Finally, Bate et al.[16] demonstrated that novel phenothiazine derivatives inhibited *M. tuberculosis* in the non-replicating state at MICs that were lower than those under actively growing conditions.

In-vivo efficacy in animal model: Weak *in vivo* efficacy (1 log reduction from control compared with 3 logs for RIF at 12.5 mg/kg) was achieved with a phenothiazine analog at 100 mg/kg for 11 days in an acute model where drug was administered on infection and one day post infection.[7]

Efficacy in humans

No published data are available, but there are suggestions that THZ is being used in the clinic presumably for MDR and XDR cases. One group have recommended treatment with THZ for compassionate use in TB patients.[17]

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Human: Chlorpromazine has 32% oral bioavailability but may decrease to ~20% with repeated dose, 95% protein bound [Goodman & Gilman's, pp. 497–8].

Animal metabolic pathway: In rats sulfoxidation in position 2 of the thiomethyl substituent and in the thiazine ring are main metabolic pathways of THZ. In contrast to humans, in the rat N-desmethylthioridazine is formed in appreciable amount. The maximum concentrations of THZ and its metabolites in the brain appeared later than in plasma. The peak concentrations and AUC values of THZ and its metabolites were higher in the brain than in plasma corresponding to their longer half-lives in the brain as compared to plasma. The drug was not taken up by the brain as efficiently as other phenothiazines. Chronic treatment with THZ produced significant increases (with the exception of THZ ring sulfoxide) in the plasma concentrations of the parent compound and its metabolites, which was accompanied with the prolongation of their plasma half-lives.[17]

Human metabolic pathway: Less than 1% is excreted in urine. Active metabolites for chlorpromazine are 7-hydroxy-chlorpromazine and possibly N-oxide chlorpromazine. Metabolites for THZ are numerous but S-oxidation at the 5 position to more active compounds (mesoridazine and sulphoridazine) is considered the main route.[18]

Safety and Tolerability

Animal drug–drug interactions: Imipramine (5 mg/kg) and amitriptyline (10 mg/kg) elevated serum levels of THZ 20- and 30-fold respectively when administered to rats i.p. for 2 weeks. Increases of a similar magnitude were found in the brain. Imipramine and amitriptyline also inhibited THZ metabolism resulting in an increase in the ratio of THZ to its metabolites. Cytochrome P450 was implicated in these changes.[18]

Animal toxicity: Orally in rats, LD_{50} 956–1034 mg/kg [DrugBank].

Animal safety pharmacology: QT prolongation was seen in anaesthetized guinea pigs with THZ.[19]

Human drug–drug interactions: CYP2C19 and especially CYP2D6 are involved in the metabolism of THZ. THZ is also an inhibitor of CYP1A2 and CYP3A2.
THZ use should be avoided in combination with other drugs that are known to prolong the QTc interval and in patients with congenital long-QT syndrome or a history of cardiac arrhythmias [DrugBank].
Drugs that inhibit cytochrome P450 2D6 isozyme should be avoided (e.g., fluoxetine and paroxetine); other drugs (e.g., fluvoxamine, propranolol, and pindolol) inhibit the metabolism of THZ and result in elevated levels adding to the potential for toxicity [DrugBank]. S-oxidation at the 5 position to more active compounds (mesoridazine and sulphoridazine) is considered the main route but oxidation at the 5 position to THZ 5-sulfoxide, an inactive metabolite, also occurs.[18]
Human potential toxicity: THZ has been shown to prolong the QTc interval in a dose-dependent fashion. This effect may increase the risk of serious, potentially fatal, ventricular arrhythmias, such as torsade de pointes-type arrhythmias [DrugBank]. There are many publications on the phenothiazines and cardiac toxicity (reviewed in Kim and Kim 2005[20]) although many describe the most serious complications, such as arrhythmias and sudden death, as rare.[20] The underlying cause for these toxicities is inhibition of the hERG channels; IC_{50}s for inhibition of human hERG expressed in CHO cells are THZ 224nM, perphenazine 1003nM, trifluoperazine 1406nM and chlorpromazine 1561nM.[20] THZ is not generally considered to be the most toxic of the phenothiazines although its effect on cardiac function may be the most serious of the group (reviewed in Kim and Kim 2005[20] and Amaral et al. 2001[21]). Indeed THZ, considered a low-potency phenothiazine, has been associated with numerous cases of "torsades de pointes" compared with other drugs in the class; perphenazine and trifluoperazine, considered high-potency, are considered safer as far as cardiotoxicity is concerned (reviewed in Kim and Kim 2005[20]). The class has demonstrable hypotensive effects although these symptoms usually regress with continued dosing [Goodman & Gilman's, pp. 497–8]; ironically, chlorpromazine has been used to treat over 500 emergency cases of hypertension.[22]
Oxidation at the 5 position to THZ 5-sulfoxide, an inactive metabolite, is considered an issue as this metabolite may contribute to cardiotoxicity. The relatively similar MICs for these drugs[21] perhaps indicate that the mechanisms for cardiac toxicity and bacterial killing are not identical and that an analog with lower toxicity could be synthesized.
Central nervous system side effects occur. These are mainly drowsiness, dizziness, fatigue, and vertigo.
THZ also causes an unusually high incidence of impotence and anorgasmia due to a strong alpha-blocking activity. Painful ejaculation or no ejaculation at all is also sometimes seen.
Autonomous side effects (dry mouth, urination difficulties, obstipation, induction of glaucoma, postural hypotension, and sinus tachycardia) occur obviously less often than with most other mildly potent antipsychotics.
The serious and sometimes fatal blood damage agranulocytosis is seen more frequently (approximately 1/500 to 1/1000 patients) with THZ than with other typical phenothiazines (1/2000 to 1/10,000 patients).
Human adverse reactions: Possible adverse events include agitation, blurred vision, coma, confusion, constipation, difficulty in breathing, dilated or constricted pupils, diminished flow of urine, dry mouth, dry skin, excessively high or low body temperature, extremely low blood pressure, fluid in the lungs, heart abnormalities, inability to urinate, intestinal blockage, nasal congestion, restlessness, sedation, seizures, and shock [DrugBank].

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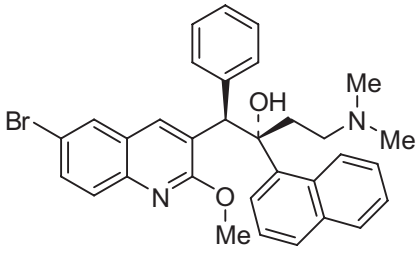
TMC-207

Generic and additional names: TMC-207; also known as R207910
CAS name: 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol
CAS registry #: 654653-93-7
Molecular formula: $C_{32}H_{31}BrN_2O_2$
Molecular weight: 555.51
Intellectual property rights: Johnson & Johnson has obtained patents for this compound. Its subsidiary, Tibotec, is currently managing human clinical trials of this compound.



Derivatives: 20 molecules in series have an MIC below 0.5 μg/ml
Formulation and optimal human dosage: Reasonable bioavailability was found with oral solutions. Solid formulations are under development. Oral administration achieved high *in vivo* activity.

Basic biology information

Drug target/mechanism: TMC-207 (R207910, TMC) is a first-in-class diarylquinone, distinct from any marketed compounds. The compound, identified by screening against *Mycobacterium smegmatis*, has a unique mechanism of action (MOA) targeting the c subunit of ATP synthase. ATP synthase is divided into F0 and F1 multi-subunit complexes; F1 is cytoplasmic, F0 is membrane associated and consists of a multimeric complex of proteins in the configuration a, b2, c9–12. The mode of action was identified through drug-resistant mutants harboring alterations in the *atpE* gene; this gene codes for ATP synthase c subunit, and changes at D32V and A63P were associated with resistance.[1] The compound did not inhibit gyrase activity when tested against the purified enzyme, indicating that this molecule does not share MOA with quinolones. Solid proof of the MOA comes from complementation of *M. smegmatis* with a mutant *atpE* gene D32V rendering the normally sensitive wild-type strain drug resistant; following these complementation experiments the mutation D32V remained stable and no other changes were found.[1]

Additional experiments to validate ATP synthase c subunit as the drug target include (a) overexpression of the mutant target protein gene (*atpE*) in *M. smegmatis* leading to increased MIC for TMC; (b) demonstration of a dose-dependent decrease in ATP in TMC-treated *M. tuberculosis*; (c) immobilized TMC bound specifically and exclusively to *M. smegmatis* ATP synthase subunits.[2]

Drug resistance mechanism: Spontaneous resistance rate for *M. tuberculosis* was 5×10^{-7} and 5×10^{-8} at 4× and 8× MIC respectively, similar to rates observed with rifampin (RIF).[1] Mutants were unchanged in their sensitivity to RIF, isoniazid (INH), ethambutol (ETH), moxifloxacin (MOXI), streptomycin (STR) and amikacin (AMI). Mutations were found in the *atpE* gene at D32V and A63P.[1] Both mutations, in a highly conserved area, are within the membrane spanning region.[3] No other mutation-related changes were found when the genomes of the resistant *M. tuberculosis* and two resistant *M. smegmatis* strains were sequenced to near completion.[1] No mutations were identified within *gyrA* and *gyrB*, demonstrating that TMC does not have the same MOA as quinolones.[1] Complementation of wild-type *M. smegmatis* with the mutant *atpE* gene D32V rendered the strain drug resistant.[1]

In-vitro potency against MTB: M. tuberculosis H37Rv: MIC 0.06 μg/ml (0.03–0.12 μg/ml).[1]

Spectrum of activity: TMC appears to be specific for *Mycobacterium*, having activity against *M. tuberculosis*, *M. bovis*, *M. avium*, *M. kansasii*, *M. smegmatis* and *M. ulcerans*, significantly poorer activity against *Corynebacterium* and *Helicobacter pylori*, and essentially no activity against staphylococci, enterococci or *Eschericia coli*.[1] The compound also showed efficacy in a mouse leprosy model.[4]

Table 1

Species	Half-life (h)	AUC (mg·h/l)	C_{max} (μg/ml)	Volume distribution (l/kg)	Clearance (ml/h)	PK methodology
Mouse	47*, 59**	5.0*, 19.4**	0.4*, 1.1**	–	–	Single dose of *6.25 or **25 mg/kg[1]
Human	–	7.91, 24*, 52**	–	–	–	AUCs for a once-daily dose at 50, *150 and **400 mg/day for 14 days.[1]

Other in-vitro activity: TMC is defined as bactericidal *in vitro* as demonstrated by a 3 log reduction in CFU after 12 days treatment of a log phase culture; no increase in activity was observed with a 10-fold increase in drug concentration, indicating that killing was time- and not concentration-dependent. TMC is active against MDR-TB.[1]

In-vivo efficacy in animal model: TMC exhibits potent early and late bactericidal activity. Oral administration achieved high *in vivo* activity.

"Non-established" mouse infection model: in mice treated 5× weekly for 4 weeks starting day 1 after infection, 50 mg/kg TMC was more efficacious than 25 mg/kg INH, a drug known for excellent early bactericidal activity. In the same model a minimal effective dose (MED) of 6.25 mg/kg prevented gross lung lesions and 12.5 mg/kg gave 3 log reduction (bactericidal) in CFU in lung and spleen; the MED and bactericidal doses are very similar, suggesting killing is time-, not concentration-dependent.[1]

Persistent model: in mice dosed 5× weekly starting 4 weeks after infection TMC (25 mg/kg) performed better than RIF alone and equal to standard compounds RIF/INH/pyrazinamide (PZA). When TMC was added to, or substituted for, any of the standard compounds a greater decrease in CFUs was observed especially after 1 month of treatment. TMC has potential to shorten treatment time.[1] When combined with second-line drugs used for treatment of MDR-TB, namely AMI, ETA, MOXI and PZA, addition of TMC showed an improvement in activity including sterilization of tissues from treated animals.[5]

Efficacy in humans

In clinical trials.

ADME data

See table 1 for main PK characteristics.

Other ADME data:

- Mouse: 1:22 plasma:lung ratio, all other tissues lower ratio but higher than in plasma. Half-life in tissues ranged from 28 to 92 hours compared to 44–64 in plasma.[1]
- Human: Peak levels were reached at 5.5 h (median). Average serum concentrations with a once-daily dose at 50 mg, 150 mg and 400 mg/day for 14 days were 0.33 μg/ml, 1.0 μg/ml and 2.2 μg/ml respectively. "Effective" half-life is 24 hours (suggested by data from multiple ascending-dose studies). PK was linear up to 700 mg (highest dose tested) with both AUC and C_{max} increasing linearly with dose; drug concentration in serum declined triexponentially.[1]

Safety and Tolerability

Animal safety pharmacology: Preclinical safety in dogs and rats together with genetic toxicology and general safety pharmacology indicated that there were no adverse events or toxicities precluding trials in humans.[1]

Human adverse reactions: Repeated oral doses in healthy human subjects showed no serious adverse reactions when drug was administered at 50, 150 and 400 mg daily for 14 days or up to 700 mg as a single dose.[1]

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