Background

Overview | Existing Products | Get Involved

What is Nucleic Acid Synthesis?

Nucleic acids, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), store genetic information for living organisms. The production and regulation of these biological macromolecules are essential for survival and replication of organisms. Therefore, enzymes involved in these processes are attractive therapeutic targets for a variety of diseases.

Overview

DNA is the primary storage form for genetic information in living organisms. It is composed of two strands of nucleotides connected through a backbone of sugar and phosphates. As cells divide, DNA is replicated to produce new identical DNA copies that are incorporated into the daughter cells. DNA is also transcribed to a related nucleic acid, messenger RNA, that directs the synthesis of proteins. There are numerous enzymes involved in the synthesis of nucleic acids that are potential therapeutic targets including:

- **Synthesis or salvage of purine and pyrimidine bases:** The nucleosides that are the basic building blocks of RNA, and the related nucleotides that are the basic building blocks of DNA, contain the nitrogenous purine bases adenine and guanine, and the pyrimidine bases cytosine, uracil (RNA only), and thymine (DNA only). These bases can be produced through *de novo* synthesis or through recycling. Nucleosides are required to translate DNA to RNA for gene expression and nucleotides are needed to replicate DNA during cell division. A shortage of purine or pyrimidine bases can prevent these essential processes from occurring leading to cell death.
- **DNA winding/unwinding:** In order to access DNA for replication, the two strands of DNA need to be separated. This is achieved primarily through the action of helicases. In conjunction with helicases, another group of enzymes called topoisomerases can nick one (type I) or both strands (type II) of DNA to relieve coiling in DNA that might build up downstream of the site of replication. Inhibition of DNA winding/unwinding can prevent or halt replication, leading to cell death.
- **DNA/RNA polymerases:** Polymerases are a family of enzymes used to replicate DNA, produce messenger RNA from DNA, or reverse transcribe DNA from RNA in viruses. Polymerases are also involved in DNA proofreading, ensuring the fidelity of the genetic code when DNA is replicated.

In each of these processes, numerous enzymes and other proteins are involved. The specific enzymes vary across organisms, especially when compared across mammals, protozoa, bacteria, and viruses. The diversity in enzymes across these organisms contributes to their appeal as therapeutic targets because there is potential to selectively target enzymes from specific organisms.

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Existing Products

There are numerous nucleic acid synthesis inhibitors that are approved for the treatment of a variety of diseases.

Nucleic Acid Synthesis/Regulation	Target Name	Regulatory Status

Pathway		
Nucleotide synthesis	Dihydrofolate reductase (DHFR)	Methotrexate, FDA approved for cancer and several autoimmune diseases
		Sufadoxine-Pyrimethamine (SP), FDA approved for malaria
	Dihydroorotate dehydrogenase (DHODH)	Leflunomide and teriflunomide, FDA approved for rheumatoid arthritis
DNA winding/unwinding	DNA gyrase (Topoisomerase II)	Ciprofloxacin, FDA approved broad spectrum antibiotic
	Eukaryotic topoisomerase II	Suramin and pentamadine, not FDA approved but in widespread use in developing countries for the treatment of stage 1 Human African trypanosomiasis (HAT)
	Topoisomerase IA	Sodium stibogluconate (SSG), not FDA approved but in widespread use in developing countries for the treatment of leishmaniasis
DNA/RNA polymerases	Reverse transcriptase (RNA-dependent DNA polymerase)	Azidothymidine (AZT) and numerous others, FDA approved for HIV

Nucleic Acid Synthesis Inhibitors as Non-Neglected Tropical Disease Therapeutics

There are several diseases that are not related to neglected tropical diseases for which nucleic acid synthesis has been targeted, including:

- Cancer
- Autoimmune diseases (including rheumatoid arthritis)

In order to replicate DNA in dividing cells, nucleotides are needed to build the newly synthesized DNA strand. Therefore, replicating cells are especially sensitive to the inhibition of biosynthetic pathways that produce new nucleotides. Both cancer and autoimmune disease are characterized by increased cellular replication. In the case of cancer, transformed cells rapidly divide forming a tumor. In the case of autoimmune disease, increased proliferation of immune cells contributes to an overactive immune response.

Dihydrofolate reductase (DHFR) and dihydroorotate dehydrogenase (DHODH) are well established therapeutic targets for blocking DNA replication in rapidly dividing cells. DHFR is an enzyme involved in folate biosynthesis and plays a key role in the *de novo* synthesis of the pyrimidines cytosine, thymine, and uracil, important nucleotide building blocks. Inhibition of DHFR by compounds such as methotrexate leads to a shortage in available nucleotides, therefore blocking DNA replication. Similarly, DHODH is an enzyme that is directly involved in pyrimidine synthesis, so its inhibition also leads to a block in DNA synthesis.

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Nucleic Acid Synthesis Inhibitors as Neglected Tropical Disease Therapeutics

Nucleic acid synthesis and repair has been targeted for the treatment of bacterial, protozoan, and viral neglected tropical diseases including:

- Malaria
- Enterotoxigenic *E. coli* (ETEC)
- Leishmaniasis
- Human African Trypanosomiasis (HAT)
- HIV

Sulfadoxine-pyrimethamine (SP or Fansidar) combination treatment was commonly used for the treatment of acute malaria until the late 1990s. The pyrimethamine component of SP is a potent inhibitor of the DHFR enzyme of *Plasmodium falciparum*, the protozoan parasite that causes malaria. As in human cells, inhibition of DHFR in dividing cells leads to cell death by blocking DNA replication. The DHFR enzyme of *P. falciparum* is divergent enough from its human ortholog that selective inhibition is possible; SP is safe enough to use in young children and pregnant women. However, widespread use of SP eventually led to the development of antimalarial drug resistance and the replacement of SP, and other first line antimalarials, with artemisinin combination therapy (ACT) for the treatment of acute malaria in the early 2000s.[1]

Type II topoisomerases, including DNA gyrase and topoisomerase IV, are essential for replication of DNA in bacteria such as ETEC.[2] Unlike mammalian cells, where the genome is stored on multiple linear double stranded DNA chromosomes, bacteria have a single circular piece of double stranded DNA encoding their genome. In order to replicate this circular piece of DNA, the DNA strands must be separated. In circular DNA, when the two strands of DNA are separated for replication it causes supercoiling of the rest of the circle, limiting the progress of replication. To compensate, bacteria use type II topoisomerases to break the DNA circle, relax the supercoiling, and then reconnect the DNA. Taking advantage of this mechanism, numerous broad spectrum antibiotics have been developed targeting type II topoisomerases. Antibiotics based on the fluoroquinolone drug class, including ciprofloxacin and levofloxacin, are the most common topoisomerase II inhibitors and are widely used in the treatment of traveler's diarrhea, including diarrhea caused by ETEC.

Topoisomerases are also the target of three products currently used to treat the eukaryotic protozoan parasitic diseases HAT and leishmaniasis:

- Suramin, treatment of stage 1 HAT caused by *Trypanosoma brucei rhodesiense*
- Pentamadine, treatment for stage 1 HAT caused by *Trypanosoma brucei gambiense*
- Sodium stibogluconate (SSG), treatment for leishmaniasis

Both suramin and pentamadine are believed to target the eukaryotic type II topoisomerases of the parasite.[3] As the parasites that cause HAT are eukaryotic, their type II topoisomerases are more similar to human topoisomerase II than the DNA gyrases of bacteria. Interestingly, evidence suggests that suramin and pentamadine preferentially target the topoisomerase II of the kinetoplast of HAT. It is likely that these products have been effective for the treatment of HAT because: (1) the HAT parasites are dividing rapidly relative to the majority of host cells, thus requiring topoisomerase activity to promote DNA replication and (2) the kinetoplast topoisomerase II appears to be more drug sensitive than the host topoisomerase. Although suramin and pentamadine are effective for the treatment of stage 1 HAT, suramin in particular is associated with severe toxic side effects.

Sodium stibogluconate (SSG) is a pentavalent antimonial used for the treatment of leishmaniasis. Previous analysis of the effects of SSG on the parasite that causes leishmaniasis suggested that SSG works through inhibition of topoisomerase type I.[3] Upon completion of the genome sequence of the parasites that cause leishmaniasis, HAT, and a related disease called Chagas disease, it was discovered that this group of parasites, known collectively as the kinetoplastids, have two divergent type I topoisomerases. The first is a type IB topoisomerase that is found in both the nucleus and in the mitochondria-related organelle that is unique to kinetoplastids known as the kinetoplast. Unlike type IB topoisomerases from other eukaryotes, the kinetoplastid type IB topoisomerase is a heteromultimer. The second type I topoisomerase is a type IA topoisomerase. Again separate copies of the type IA topoisomerase are found in the nucleus and kinetoplast. The type IA topoisomerase in the kinetoplast is significantly divergent from other type IA topoisomerases and is essential for both replication of circular DNA in the kinetoplast and parasite survival.[4] It is not known if SSG inhibits the type IA or B forms of topoisomerase in leishmanisis. However, it is likely that the parasites are sensitive to SSG because they are dividing more rapidly than host cells and because kinetoplast DNA replication is more sensitive to inhibition of topoisomerases.

Viruses often employ unique enzymes in the replication of their genomes. HIV, for instance, has an RNA genome rather than a DNA genome. In mammalian cells, DNA polymerases are enzymes that replicate DNA from a DNA template. In order for the HIV virus to replicate, it must create a DNA copy from the RNA template using an enzyme called reverse transcriptase or RNA-dependent DNA polymerase. The first successful treatment developed for HIV was an HIV reverse transcriptase inhibitor called azidothymidine, better known as AZT.[5] Since the FDA approval of AZT in 1987, more than sixteen different products containing reverse transcriptase inhibitors have been approved for the treatment of HIV.[6]

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References

1. Mita T (2010) “Origins and spread of pfdhfr mutant alleles in Plasmodium falciparum.” *Acta Tropica* **114**: 166-170.
2. Dorman CJ and Corcoran CP (2009) “Bacterial DNA topology and infectious disease.” *Nucleic Acids Research* **37**: 672-678.
3. Das A et al. (2004) “Topoisomerases of kinetoplastid parasites as potential chemotherapeutic targets.” *TRENDS in Parasitology* **20**: 381-387.
4. Scocca JR and Shapiro TA (2008) “A mitochondrial topoisomerase IA essential for late theta structure resolution in African trypanosomes.” *Molecular Microbiology* **67**: 820-829.
5. Tarrago-Litvak L et al. (2002) “Inhibitors of HIV-1 reverse transcriptase and integrase: classical and emerging therapeutical approaches.” *Current Pharmaceutical Design* **8**: 595-614.
6. FDA, Antiretroviral drugs used for the treatment of HIV, available here.

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Pipeline & Analysis

Get Involved

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
Moxifloxacin	Bayer AG Global Alliance for TB Drug Development					
P218	Medicines for Malaria Venture					
CPZEN45	Eli Lilly and Company					
dUTPase inhibitors	Medivir					
Dihydroorotate dehydrogenase (DHODH) inhibitors	Medicines for Malaria Venture Monash University University of Washington UT Southwestern Medical Center					
Quinolones	Centre for Drug Candidate Optimisation Drexel University College of Medicine Medicines for Malaria Venture Oregon Health & Science University University of South Florida					
Genz DHODH	Broad Institute of MIT and Harvard Genzyme Medicines for Malaria Venture					
Mycobacterial gyrase inhibitors	GlaxoSmithKline Global Alliance for TB Drug Development					
Gyrase B inhibitors	AstraZeneca Global Alliance for TB Drug Development					
RNA polymerase inhibitors	AstraZeneca Global Alliance for TB Drug Development Rutgers University					
Topoisomerase I inhibitors	AstraZeneca New York Medical College					

ND201	NeED Pharma	
Gatifloxacin	Bristol-Myers Squibb Company	On Hold
TBK544	Global Alliance for TB Drug Development	On Hold
TBK613	Global Alliance for TB Drug Development	On Hold

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ANALYSIS

Inhibitors of nucleic acid synthesis have been validated as therapeutic targets for a variety of diseases. Beyond the existing inhibitors of these pathways used to treat malaria, HAT, leishmaniasis, ETEC, and HIV, new products targeting these systems are currently in development for the treatment of malaria and tuberculosis. Inhibitors of nucleic acid synthesis have the potential to benefit from the recycling of chemical compound libraries developed through previous drug development programs.

The relative strengths, weaknesses, opportunities, and risk for nucleic acid synthesis system inhibitors that are currently in use or in development for neglected tropical diseases are summarized here.

	Strengths	Weaknesses	Opportunities	Risks
DNA winding/unwinding: DNA gyrase inhibitors				
Relevant neglected tropical diseases: ETEC (multiple, on market) Tuberculosis (moxifloxacin, phase III; additional products in discovery and pre-clinical development) Malaria (quinolones, discovery)	Mechanism of action novel relative to existing products for tuberculosis but well established mechanism of action for treatment of other bacterial infections Mechanism of action novel relative to existing products for malaria specifically targeting the bacterial DNA gyrase-like topoisomerase of the malaria apicomplast organelle DNA gyrases typically divergent from human eukaryotic topoisomerase II enzymes suggesting selective inhibition in neglected tropical diseases possible	Potential for inhibitor cross reactivity with host type II topoisomerases	Improved selectivity for bacterial and parasite derived DNA gyrases Treatment of multi-drug resistant tuberculosis or malaria Addition to combination therapies	Resistance to fluorquinolones is common for ETEC and other non-tuberculosis bacterial infections, suggesting resistance is likely to occur over time in tuberculosis
DNA winding/unwinding: Eukaryotic topoisomerase II inhibitors				
Relevant neglected tropical diseases: HAT (suramin, on market for T.b. rhodesiense stage 1;	Potentially inhibit kinetoplast-localized Top II selectively	Numerous associated toxicities most likely due to off target effects of inhibition of host topoisomerases	Not recommended for further study or development	Will likely be replaced by new products with improved safety

pentamadine, on market for T.b. gambiense stage 1) No new products in development at this time				
DNA winding/unwinding: Topoisomerase I inhibitors				
Relevant neglected tropical diseases: Leishmaniasis (Sodium stibogluconate,SSG, on market) Tuberculosis (topoisomerase I inhibitor, discovery)	SSG has some selectivity for parasite topoisomerase I over other topoisomerases SSG is currently widely used for the treatment of leishmaniasis Unique mechanism of action for tuberculosis relative to on market tuberculosis products	Toxicity associated with SSG may be due to cross reactivity with host topoisomerases Similar toxicity due to cross reactivity may occur for inhibitors developed for tuberculosis	Kinetoplast topoisomerase type IA and IB from the parasites that cause leishmaniasis, Chagas disease and HAT appear to be divergent from human topoisomerases, suggesting selective inhibition may be possible Topoisomerase I from bacteria is generally divergent from mammalian orthologs so selective inhibition may be possible	If selective inhibition cannot be achieved, will likely be replaced by new products with improved safety
Nucleotide synthesis: DHFR				
Relevant neglected tropical diseases: Malaria (sulfadoxine-pyrimethamine, on market; DHFR inhibitor P218, pre-clinical)	DHFR is a well characterized target for malaria that can be safely and selectively inhibited over its human orthologs as demonstrated by SP	DHFR resistance due to SP use is widespread throughout malaria endemic areas	If new products can overcome existing SP resistance, may be useful in future combination therapies Repurposing existing inhibitors and inhibitor libraries to explore DHFR as a therapeutic target for other parasitic protozoa	Risk for resistance may be too high to warrant investment in this line of research
Nucleotide synthesis: DHODH				
Relevant neglected tropical diseases: Malaria (DHODH inhibitors and Genz DHODH inhibitors, discovery	Genetically validated target for malaria Multiple independent product development programs in progress Unique mechanism of action relative to on market antimalarials	No programs have entered human clinical trials, so clinical safety and efficacy not known	Addition to existing products for combination therapies Potential for parallel product development across multiple protozoan neglected tropical diseases Potential to overcome existing drug resistance	Selectivity for parasite enzyme over human ortholog is necessary to prevent host toxicity
DNA/RNA polymerases				
Relevant neglected tropical diseases: HIV (multiple products, on market)	HIV antiretrovirals that inhibit HIV-1 reverse transcriptase have been highly successful	Long term treatment with reverse transcriptase inhibitors can lead to	More basic research to identify potential DNA/RNA polymerase targets in neglected	Potential for drug resistance and host toxicity based on HIV drugs

Tuberculosis (RNA polymerase inhibitor, discovery)	Inhibition of RNA polymerase would be a unique mechanism of action for tuberculosis treatment	drug resistance and host toxicity No programs for tuberculosis RNA polymerase inhibitors have entered human clinical trials so safety and efficacy are not known	tropical diseases	

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Numerous nucleic acid synthesis and regulation system enzymes have been genetically or chemically validated as therapeutic targets for neglected tropical diseases. These validated targets represent the best opportunity for immediate application of existing expertise and small molecule inhibitor libraries across neglected tropical diseases.

Neglected Tropical Disease	Nucleic Acid Synthesis/Regulation Systems		
	Nucleotide synthesis	DNA winding/unwinding	DNA/RNA polymerases
Chagas[1,2,3,4]	DHODH, TcDHFR	Kinetoplast-associated TcTop1A	
HAT[3,4,5,6]	DHODH	Kinetoplast-associated TbTop1A, TbTopII	
HIV[7]			HIV-1 reverse transcriptase
Leishmaniasis[2,3,4]	LmDHFR	Kinetoplast-associated LmTop1A & 1B	
Malaria[8]	DHFR, DHODH	PfTopIB, PfTopII, Apicomplast-associated DNA gyrase	
Tuberculosis[9]		DNA gyrase	RNA polymerase

References

1. Pinheiro MP et al. (2008) “Crystal structure of Trypanosoma cruzi dihydroorotate dehydrogenase from Y strain.” *Biochemical and Biophysical Research Communications* **369**: 812-817.
2. Rodriguez JB (2001) “Specific Molecular Targets to Control Tropical Diseases.” *Current Pharmaceutical Design* **7**: 1105-1116.
3. Scocca JR and Shapiro TA (2008) “A mitochondrial topoisomerase IA essential for late theta structure resolution in African trypanosomes.” *Molecular Microbiology* **67**: 820-829.
4. Das A et al. (2004) “Topoisomerases of kinetoplastid parasites as potential chemotherapeutic targets.” *TRENDS in Parasitology* **20**: 381-387.
5. Arakaki TL et al. (2008) “Characterization of Trypanosoma brucei dihydroorotate dehydrogenase as a possible drug target; structural, kinetic and RNAi studies.” *Molecular Microbiology* **68**: 37-50.
6. Tang SC and Shapiro TA (2010) “Newly identified antibacterial compounds are topoisomerase poisons in African trypanosomes.” *Antimicrobial Agents and Chemotherapies* **54**: 620-626.
7. Tarrago-Litvak L et al. (2002) “Inhibitors of HIV-1 reverse transcriptase and integrase: classical and emerging therapeutical approaches.” *Current Pharmaceutical Design* **8**: 595-614.
8. Garcia-Estrade C et al. (2010) “DNA topoisomerases in apicomplexan parasites: promising targets for drug discovery.” *Proceedings of the Royal Society Biological Sciences* **277**: 1777-1787.
9. Mdluli K and Ma Z (2007) “Mycobacterium tuberculosis DNA gyrase as a target for drug discovery.” *Infectious Disorders – Drug Targets* **7**: 159-168.

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Tools

Get Involved

Databases/Resources

Detailed nucleic acid drug data (i.e., chemical, pharmacological, and pharmaceutical) with comprehensive drug target information (i.e., sequence, structure, and pathway) is available on the DrugBank Database.

Three-dimensional structural information about nucleic acid complexes can be found on the Nucleic Acid Database.

Assays

Historically, DNA synthesis and cell proliferation assays depended on the detection of tritiated thymidine 3H uptake. However, new assay platforms have been developed that eliminate the use of radioactivity and are compatible with automated sample handling, high-throughput screening in microtiter plates, and, more recently, high-content screening (HCS) using live cell assays to image cell function and signaling at the level of the individual cell. These new platforms include fluorescent, luminescent, and colorimetric assays that can determine cell count and detect DNA synthesis.

The CyQUANT® NF Cell Proliferation Assay Kit (Invitrogen) is based on measurement of cellular DNA content by fluorescent dye binding and does not require freeze/thaw cell lysis. The amount of cell proliferation is determined by comparing cell counts for drug treated samples with untreated controls.

TheQuantos™ Cell Proliferation Assay Kit (Agilent) is based on measuring the intensity of fluorescence from the DNA–dye complex with a standard fluorometer. The amount of DNA in a sample is determined by comparing the fluorescence intensity of the sample to a previously generated standard curve. This assay can be run in 96 well formats and be used for high throughput drug screening.

Incorporation of bromodeoxyuridine (BrdU) into DNA during replication has been widely used for many years to measure DNA synthesis. The new generation of Cell Proliferation ELISA BrdU assays (Roche Applied Science) is now compatible with high throughput screening formats. They have good sensitivity and can detect a 20% increase or decrease in DNA synthesis.

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Product Details

CPZEN45

Synonyms:
CPZEN45

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
Ribonucleoside

Molecule Class:

Administration Route:

Notes:

More information on this product is available from the Working Group on New TB Drugs.

Clinical Trials:

Publications:

Dihydroorotate dehydrogenase (DHODH) inhibitors

Synonyms:
Dihydroorotate dehydrogenase (DHODH) inhibitors

Disease:
Malaria

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
Nucleoside biosynthesis inhibitor/Dihydroorotate dehydrogenase (DHODH) inhibitor

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

21517059

dUTPase inhibitors

Synonyms:
dUTPase inhibitors

Disease:
Malaria

Specific Indication:

Product Type:
Drug

PRV Elegible?
No

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
dUTPase inhibitors

Molecule Class:

Administration Route:

Notes:	Clinical Trials:	Publications:
		21246738 16161998

Gatifloxacin

Synonyms:
Gatifloxacin
Tequin
Gatifloxacin

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
No

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
DNA gyrase inhibitor

Molecule Class:
Fluoroquinolones

Administration Route:
Oral

Notes:	Clinical Trials:	Publications:
On market since 1999 as Tequin (Bristol-Myers Squibb) for the treatment of respiratory tract infections. However, clinical trial results (not related to TB development) showed contraindication for patients with diabetes and additional adverse side effects. In 2006 Bristol-Myers Squibb halted production of Tequin, and development of gatifloxicin for TB is now on hold indefinitely. More information on this product is available from the Working Group on New TB Drugs.	NCT00216385	16510739 16510740

Genz DHODH

Synonyms:
Genz DHODH

Disease:
Malaria

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
Nucleoside biosynthesis inhibitor/Dihydroorotate dehydrogenase (DHODH) inhibitor

Molecule Class:

Administration Route:

Notes:	Clinical Trials:	Publications:

Gyrase B inhibitors

Disease:
Tuberculosis (TB)

Specific Indication:

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:

Synonyms:
Gyrase B inhibitors

Product Type:
Drug

PRV Eligible?
Yes

GyrB Inhibitors

Molecule Class:

Administration Route:

Notes:

More information on this product is available from the Working Group on New TB Drugs.

Clinical Trials:

Publications:

Moxifloxacin

Synonyms:
Moxifloxacin
Moxi
8-methoxy fluoroquinolone

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Eligible?
No

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
DNA gyrase inhibitor (topoisomerase II)

Molecule Class:
Fluoroquinolone

Administration Route:
Oral

Notes:

More information on this product is available from the Working Group on New TB Drugs.

Clinical Trials:

NCT00864383
NCT00144417
NCT00164463
NCT01055145
NCT00728507
NCT00396084
NCT00460759
NCT00082173

Publications:

Mycobacterial gyrase inhibitors

Synonyms:
Mycobacterial gyrase inhibitors

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Eligible?
Yes

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
DNA gyrase inhibitor

Molecule Class:

Administration Route:

Notes:

More information on this product is available from the

Clinical Trials:

Publications:

Working Group on New TB Drugs.

ND201

Synonyms:
ND201

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
Topoisomerase II and IV

Molecule Class:
Triazoloquinoline

Administration Route:

Notes:

Clinical Trials:

Publications:

P218

Synonyms:
P218
Dihydrofolate reductase inhibitors

Disease:
Malaria

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
Nucleoside biosynthesis inhibitor/DHFR inhibitor

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

Quinolones

Synonyms:
Quinolones

Disease:
Malaria

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
DNA gyrase inhibitor

Molecule Class:
Quinolones

Administration Route:

Notes:

Clinical Trials:

Publications:

RNA polymerase inhibitors

Synonyms:
RNA polymerase inhibitors

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
RNA polymerase inhibitors

Molecule Class:

Administration Route:

Notes: **Clinical Trials:** **Publications:**

TBK544

Synonyms:
TBK544

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
DNA gyrase inhibitor

Molecule Class:
Quinolone

Administration Route:

Notes: **Clinical Trials:** **Publications:**

TBK613

Synonyms:
TBK613

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:
DNA gyrase inhibitor

Molecule Class:
Quinolone

Administration Route:

Notes: **Clinical Trials:** **Publications:**

Topoisomerase I inhibitors

Disease:
Tuberculosis (TB)

Specific Indication:

Target/Technology:
Nucleic acid synthesis

Mechanism of Action:

Synonyms:
Topoisomerase I inhibitors

Product Type:
Drug

PRV Elegible?
Yes

Topoisomerase I inhibitors

Molecule Class:

Administration Route:

Notes:	Clinical Trials:	Publications: