

New Anti-Parasitic Agents, Trends and Trials

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ABSTRACT: The continuous threat that parasitic infections pose to human and veterinary health is directing towards the global requirement for safer and more potent antiparasitic drugs. This chapter reviews recent clinical and preclinical trials, new therapeutic approaches, and progress in the development of antiparasitic drugs. The focus is to discuss the development of antiparasitic products based on nature, progress in reprofiling of medication, and new molecular targets in helminth and protozoan parasites. New-generation drugs with better pharmacokinetic characteristics and lower liability for resistance are especially discussed. Another important discussion in this chapter is on the identification of the target by using genetic and proteomic methods, mechanisms of resistance, and how the delivery and bioavailability of medication can be improved by nanotechnology. Clinical trials that are in progress and regulatory issues are also discussed to elucidate translational advancement. Moreover, there are strategies like combination therapies, single-dose regimens, approaches towards microfilaricides, and public-private partnerships coming forth, which are considered as crucial facilitators for attaining disease control and elimination goals. The chapter as a whole provides a detailed summary of how new computational and scientific methods are changing the area of antiparasitic therapy.

Keywords: Antiparasitic agents; Neglected tropical diseases (NTDs); Drug resistance; Molecular classes; Targeted chemogenomic

INTRODUCTION

Infections caused by parasites remain a major and common public health problem. These infections are exceptionally frequent in underdeveloped nations of Africa, Asia, and Latin America. These germs, which are often called parasites, take important nutrients from the body, cause pain and inflammation in the intestines, and can even kill you. Soil-borne worms (helminths) are the most common cause of parasitic diseases. The World Health Organization says that about 24% of people around the world may have parasites that live in the soil (Candela et al., 2023). Globally, maladies including malaria, leishmaniasis, Chagas disease, sleeping sickness, filariasis, and schistosomiasis are responsible for considerable morbidity and death.

As indicated by the World Health Organization (WHO, 2023), malaria was solely responsible for over 240 million occurrences and overall 600,000 mortalities, affecting a varying number of children under the age of five (Theel and Pritt, 2016). In addition to malaria, over a billion people worldwide are afflicted by the group of neglected tropical diseases (NTDs) and other parasitic infections, including schistosomiasis, leishmaniasis, human African trypanosomiasis (HAT), soil-transmitted helminths (STHs), onchocerciasis, cryptosporidiosis, giardiasis, and others. These diseases cause chronic disability, stunted growth and cognitive development in children, and perpetuate cycles of poverty. In addition to highlighting the persistently high

burdens of many of these conditions, global assessments and WHO NTD reporting also show inconsistent progress towards the 2030 control and elimination targets. Medicines continue to play a key role in both case management and elimination strategies due to persistent programmatic gaps, surveillance blind spots, and limited therapeutic options for certain infections (such as pediatric formulations or safe, effective single-dose treatments) (Organization, 2023).

The urgent need for renewed drug development for parasitic diseases can be explained by a number of convergent challenges. First, the main treatments for a number of infections are in danger due to drug resistance. The search for new molecular classes with unique mechanisms of action has been sparked by artemisinin partial resistance, partner-drug failures in some regions of Southeast Asia and Africa, and documented decreased susceptibility to older antimalarials. Second, a large number of NTD treatments on the market are decades old, don't come in kid-friendly forms, or need to be taken for an extended period of time, which makes mass-drug administration (MDA) campaigns and adherence more difficult. One significant programmatic barrier to the control and eradication of onchocerciasis and lymphatic filariasis is the absence of safe, efficient macrofilaricides to eradicate adult filarial worms. Third, the goal of elimination and eradication, which is now incorporated into national plans and WHO strategies for several NTDs, generates a need for medications that prevent transmission (e.g., macrofilaricides or highly active antimalarials that rapidly clear gametocytes), shorter

regimens that can be adjusted to field conditions, and treatments that facilitate easier case management (single-dose oral cures). Funders and developers have directed their attention towards both novel chemical entities and creative development strategies as a result of these technical and programmatic imperatives (Ehrens et al., 2022).

Translational research and clinical testing for antiparasitic agents have significantly accelerated over the last five years (September 2020–September 2025). The variety of approaches are demonstrated by several high-profile developments, including oral bioavailable single-dose candidates for HAT (most notably acoziborole) that promise to streamline case management and lessen the need for hospital-based treatment; next-generation antimalarials with novel targets (like PfATP4 inhibitors and imidazolopiperazines) being assessed in combination regimens to postpone resistance; the repurposing and humanization of veterinary anthelmintics (e.g., emodepside, oxfendazole) towards macrofilaricidal roles; and antibacterials that target the *Wolbachia* endosymbiont of filariae (like ABBV-4083/flubentylol) specifically to deliver sterilizing or macrofilaricidal effects after shorter treatment courses than traditional doxycycline regimens. For historically understudied targets like *Cryptosporidium*, preclinical pipelines have also developed, and bumped-kinase inhibitors (BKIs) are making progress towards first-in-human studies thanks to their strong animal efficacy and safety profiles. The recent explosion in antiparasitic innovation is characterized by a multifaceted approach that includes *de novo* small-molecule discovery, phenotypic screening, repurposing, formulation science, and combination/drug-development partnerships (Kumeso et al., 2023).

However, there are still obstacles to overcome before promising candidates can have an impact on public health. The "valley of death" between academic discovery and late-stage clinical development must be bridged by financing mechanisms; regulatory pathways for NTD drugs require practical, field-relevant endpoints; and preclinical models frequently fail to predict human safety or long-term efficacy (Tarral et al., 2023). Programmatic adoption also depends on cost, compatibility with MDA approaches, safety in special populations (pregnant women, children), and ease of delivery (single-dose vs. multi-day). To move candidates through the clinic and get ready for implementation studies that ask not just "does the drug work?" but also "can it be delivered at scale?", these factors have made public-private partnerships (such as DNDi and MMV), philanthropic funders, and coordinated trial networks in endemic regions crucial during the 2020–2025 period (Tarral et al., 2023, Pépin, 2023).

From September 2020 to September 2025, this chapter examines the key trends in antiparasitic drug development, including candidate agents, translational advancements, and discovery trends. By combining preclinical data and clinical trial results from various parasite groups, highlighting advancements in trial design and regulatory strategy, and identifying ongoing research gaps and priorities for programmatic action, it frames how new pharmacological tools can best support control, elimination, and better patient outcomes over the next ten years.

DISCOVERY AND DEVELOPMENT TRENDS

Significant advancements have been made in the discovery and development of antiparasitic drugs during the last five years. The pressing need to combat growing drug resistance, get past the drawbacks of outdated treatment plans, and meet the elimination targets outlined in the WHO 2030 Roadmap for Neglected Tropical Diseases (NTDs) is what is driving these advancements. Here, we observe the present tendencies that are in progress: the comeback of natural products, target-based and gene-based chemical therapies, phenotypic and intending therapies with new agents, new dosage forms, and modulatory developments.

Target-Based Genomics and Chemogenomics

Owing to the accessibility to exceptional quality parasite genetic makeup and modern computational methods, the idea of development of anti-parasitic medicine has slowly evolved in recent years, focusing on target-based discoveries and moving away from purely phenotypic screening (Arendse et al., 2021). Genomes of important human parasites, including *Plasmodium falciparum*, *Leishmania donovani* or *Leishmania major*, *Trypanosoma brucei*, *Schistosoma mansoni*, and other filarial nematodes, have been sequenced and elucidated (Walochnik and Duchêne, 2016). This has helped researchers to access detailed information about the biochemistry of parasites, including enzymes, transporters, metabolic pathways, and membrane proteins that are unique to a parasite. This data is useful in selecting agents that are less toxic to the host body and aiming those targets in parasites that are absent in the human body (Godinez-Macias et al., 2025, Chaudhary and Roos, 2005).

Researchers are making progress by incorporating computational methods such as identification of essential genes by using algorithms and databases, creating a three-dimensional model of target proteins, docking, predicting binding sites and confirming the validation of CRISPR/Cas9-based function (knocking out genes in parasites) (Thiam et al., 2022). They can now make progress from which protein in a parasite is useful to how we can utilize this protein in the form of a drug. For example, the P-type ATPase pump (PfATP4) of *P. falciparum* regulates sodium efflux and intracellular Na⁺ homeostasis in the parasite and has been confirmed as an antimalarial target, whereas small-molecule inhibitors of PfATP4 induce rapid Na⁺ accumulation leading to death of the parasite. Similarly, imidazopyrazine is a compound that binds the lipid kinase PfPI4K (phosphatidylinositol 4-kinase) and inhibits the growth of all major phases of malaria parasites' life-cycle, including the blood, liver, and transmission stages (Dembele et al., 2017).

Together with these modifications in the identification and validation of the target, the chemogenomics field has grown rapidly. Chemo genomics generally pertains to an organized process that depicts which compound is going to hit which target and in which parasite context by combining genetic information with chemical perturbation. This is done by combining large compound libraries, genetic data of parasites, and functional assays. This helps to avert advanced-stage

collapses of compounds from non-pharmacological and resistant targets. Platforms like the open-access database TDR Targets are gathering parasite target genes, chemical-probe data, and compound-target associations to assist in selecting parasite-specific, chemically tractable targets (Urán Landaburu et al., 2023). In short, the amalgamation of detailed parasite genomics with structural bioinformatics, functional genomics (CRISPR), compound-library screening and chemogenomic mapping is building a robust trend in anti-parasitic drug discovery. It allows more logical and systematic targeting of parasites, better apprehension of complex mechanisms, and clinical candidates.

Phenotypic High-Throughput Screens and Repurposing Screens

Phenotypic high-throughput screens (HTS) remain important because they identify the effect of chemical compounds in the complex biology of parasites. Through whole-cell screening campaigns, imidazolopiperazines and triazolopyrimidines were found to be potent against Plasmodium (LaMonte et al., 2020). Nitroimidazoles such as fexinidazole and the DNDi-0690 series have been generated by HTS in kinetoplastids to treat leishmaniasis (Wijnant et al., 2019). As Repurposing screens test approved drugs in extensive clinical trials, they are especially cost-effective. Ravuconazole and fosravuconazole, antifungals, have shown leishmanicidal action, while bumped-kinase inhibitors (BKIs) for cryptosporidiosis were designed after anticancer kinase inhibitors (Teixeira de Macedo Silva et al., 2018).

Drug Repurposing

The process of repurposing lessens the likelihood of risks, time duration and expense. Examples include the use of antifungals like itraconazole and fosravuconazole for cutaneous leishmaniasis; anticancer agents, including histone deacetylase inhibitors and some kinase inhibitors against apicomplexans like *P. falciparum* and *T. gondii*; antirheumatic, auranofin as an antimicrobial for giardiasis; and veterinary anthelmintics like moxidectin, emodepside, and oxfendazole for human helminthiasis (Bhusal et al., 2024). Between 2020 and 2025, oxfendazole and emodepside have progressed into clinical investigation as macrofilaricides (Risch et al., 2024).

Combination Therapies and Single-Dose Regimens

Resistance is prevented by combination therapies, which also contributes in boosting efficacy. More recent examples include the triple-drug IDA (ivermectin, DEC, and albendazole) in filariasis, miltefosine and paromomycin in leishmaniasis, and ganaplacide and lumefantrine in malaria (Supali et al., 2021). The one-time oral treatment for HAT with

acoziborole demonstrates the potential of single-dose regimens (Kumeso et al., 2023).

Macrofilaricidal Focus for Filariases

The transformation from microfilaricides to macrofilaricides is essential. Flubentylosin, also known as ABBV-4083, is a macrolide antibacterial agent that targets Wolbachia symbionts (Johnston et al., 2021). It is currently undergoing the final stages of trials. Both of the drugs, emodepside, which acts on nematode potassium channels, and oxfendazole, a benzimidazole that is safe for human use, kill the adult macrofilariae (Ehrens et al., 2022). Control of infections has been greatly supported by modern anti-parasitic agents. Treatment of helminthic diseases with albendazole, mebendazole, and ivermectin, and artemisinin-based combination therapies remains the most effective treatment for malaria (Woodrow and White, 2017). Nitroimidazoles, such as metronidazole and tinidazole, are used to treat Protozoal infections like giardiasis and amoebiasis (Colella et al., 2021). However, resistance to these medications is increasingly being reported in Southeast Asia. Resistance against albendazole is developing in soil-transmitted helminths and against artemisinin in Plasmodium falciparum (Leitsch, 2015).

New Anti-Parasitic Agents in Development

Many New anti-parasitic therapeutic agents are currently under development (Table 1). Cipromin (KAE609) is a spiroindolone that affects the PfATP4 transporter and disrupts sodium homeostasis of Plasmodium falciparum (Goldgof et al., 2016). The cytosolic Na⁺ levels of the parasite are kept at low levels by PfATP4, a Na⁺ efflux pump. The parasites rapidly accumulate Na⁺ following treatment with PfATP4 inhibitors and initiate processes that ultimately lead to the death of the parasite (Zagórska and Jaromin, 2023). Artefenomel (OZ439), a synthetic ozonide, is being studied as a long-acting artemisinin-based combination therapy (Goldgof et al., 2016). An amino-acetonitrile derivative, derquantel and monepantel are a modern class of anthelmintics with a clear mechanism of action (Baur et al., 2015).

A ligand-gated ion channel specific to nematodes, MPTL-1, is targeted, which, when bound, causes an unmanageable ion flux that ultimately kills muscle cells by depolarizing and paralyzing them (Table 2). Because of this special mechanism, monepantel has its action against nematodes that are resistant to other drug classes (Baur et al., 2015). When it was first introduced in New Zealand in 2009 for sheep and then for cattle, it displayed greater efficacy against gastrointestinal nematodes, which are resistant to ivermectin and benzimidazoles, except Oesophagostomum spp., which showed reduced activity (Dickie et al., 2020). Earlier resistance cases were developed by sheep, calling attention to

Table 1. Selected emerging anti-parasitic agents

Agent	Target Disease	Development stage	Reference
Cipargamin (KAE609)	Malaria	Phase II/III	Bouwman et al., 2020
Fexinidazole	Sleeping sickness, Leishmaniasis	Approved / Phase III	Imran et al., 2022
Monepantel	Helminth infections	Pre-clinical/Phase I	Tritten et al., 2011
Ganaplacide (KAF156)	Drug-resistant malaria	Phase II	Ogutu et al., 2023
OZ439 (Artefenomel)	Malaria	Phase II	Phyo et al., 2016

the cautionary use (Sales and Love, 2016). Monepantel, either by itself or in conjunction with other anthelmintics, is currently being studied in cattle to ameliorate efficacy, defer resistance, and evaluate pharmacokinetic and pharmacodynamic interactions (Cantón et al., 2023).

Fexinidazole, a 2-substituted-5-nitroimidazole, is the first oral medication developed to cure both stages of human African trypanosomiasis (HAT), which is caused by *Trypanosoma brucei gambiense* and was discovered in 2005 by DNDi and Sanofi (Dickie et al., 2020). The nitroreductase enzyme in the parasite activates it to produce fexinidazole sulfoxide and sulfone, its biologically active metabolites, which is detrimental to proteins and DNA and cause death of the parasite. Fexinidazole expresses excessive oral absorption and effectiveness, when taken with food, particularly in stage 1 HAT (~98%). Its efficacy in stage 2 is insignificantly reduced (approximately 87%) compared to that of nifurtimox-eflornithine therapy (Imran et al., 2022). Its investigation is approved in the USA (2021), DRC (2019), and EU (2018), for diseases like leishmaniasis and Chagas disease. Additionally, substances with anti-malarial properties, such as HIV protease inhibitors, have been discovered through drug repurposing.

Trends in Anti-Parasitic Drug Discovery

The search has moved toward molecular techniques and advanced screening for anti-parasitic drugs. Due to high-

throughput screening, thousands of compounds can be assayed against parasites in vitro (Bogyo, 2023). To find new molecular targets, proteomics and genomics are incorporated. Progressive use of artificial intelligence is helping forecast drug-parasite interactions, while CRISPR-Cas gene editing has illuminated the biology of parasite (Grzybek et al., 2018). Host-directed therapies are a viable approach that increases the immune response of the host or changes pathways of the host cell that are used by parasites (Singh et al., 2019). To improve efficacy and reduce resistance, combination therapies and fixed-dose formulations are also being developed (Wei et al., 2021).

CLINICAL TRIALS LANDSCAPE

To assess new anti-parasitic medications, numerous clinical investigations are being conducted. Phase II studies have exhibited that ciprofloxacin is potent against the resistant strains of malaria (Schmitt et al., 2022). Ganaplacide and lumefantrine, together, are under Phase II studies for a new combination therapy against malaria (Ogutu et al., 2023). Phase III studies on fexinidazole for sleeping sickness have shown optimistic outcomes (Mesu et al., 2018). Moxidectin has been demonstrated to be more effective than ivermectin in tests for onchocerciasis (Opoku et al., 2018). The main challenges in the development of anti-parasitic drugs are that

Table 2. Summary of new anti-parasitic therapeutic agents, their mechanisms, and development status

Drug	Type	Mechanism of Action	Parasite	Development	References
Cipromin (KAE609)	Spiroindolone	Inhibits PfATP4, a Na ⁺ efflux pump in <i>Plasmodium falciparum</i> ; causes intracellular sodium accumulation, leading to osmotic dysregulation and parasite death	<i>Plasmodium falciparum</i> (malaria)	Under clinical development as a novel fast-acting antimalarial	Goldgof et al. 2016; Zagórska and Jaromin 2023
Artefenomel (OZ439)	Synthetic ozonide (artemisinin derivative)	Generates reactive oxygen radicals that damage parasite proteins and membranes; designed for long-acting artemisinin-based combination therapy (ACT)	<i>Plasmodium</i> spp.	Phase II/III trials; potential long-acting ACT component	Goldgof et al., 2016
Derquantel	Amino-acetonitrile derivative (AAD)	Targets MPTL-1, a nematode-specific ligand-gated ion channel; causes uncontrolled ion flux → muscle cell depolarization and paralysis → death	Gastrointestinal nematodes	Approved for veterinary use (sheep, cattle) in combination with abamectin	Baur et al., 2015
Monepantel	Amino-acetonitrile derivative (AAD)	Selectively binds MPTL-1 receptor; effective against nematodes resistant to other drug classes (e.g., benzimidazoles, macrocyclic lactones)	Nematodes (<i>Haemonchus</i> , <i>Teladorsagia</i> , <i>Trichostrongylus</i>)	Introduced in NZ (2009) for sheep; later for cattle; ongoing studies for resistance management and PK/PD evaluation	Baur et al., 2015; Dickie et al., 2020
Fexinidazole	2-Substituted-5-nitroimidazole	Activated by parasite nitroreductase enzyme to form toxic metabolites (sulfoxide and sulfone) that damage parasite DNA and proteins	<i>Trypanosoma brucei gambiense</i> (HAT); also active against <i>Leishmania</i> and <i>T. cruzi</i>	First oral therapy for both stages of HAT; approved in EU (2018), DRC (2019), USA (2021); under investigation for leishmaniasis and Chagas disease	Dickie et al., 2020; Imran et al., 2022
HIV Protease Inhibitors (Repurposed Drugs)	Antiretroviral drugs (e.g., lopinavir, ritonavir)	Inhibit parasite proteases; disrupt metabolic and replication pathways	<i>Plasmodium</i> spp., <i>Leishmania</i> spp.	Drug repurposing under study; promising antimalarial potential	Dickie et al., 2020

while some trials are successful, others are unsuccessful because of toxicity or ineffectiveness (Porta et al., 2023).

FUTURE PERSPECTIVES

The future of anti-parasitic drug development is based upon combining precision medicine (Rao, 2023), drug designing by artificial intelligence, and joint global research initiatives (Rao et al., 2023; Parija and Poddar, 2024). Novel vaccines like RTS, S/AS01 malaria vaccine, represent a cutting-edge research field in parasite control, though challenges exist with efficacy and the time span of protection (Rts, 2015, Organization). For overcoming and preventing resistance, combination therapies will remain a useful choice (Melo et al., 2023). Easy and equal access, affordability, and long lasting funding system must be guaranteed for the effective implementation of new therapies in the endemic domain (Melo et al., 2023; Zheng et al., 2025).

CONCLUSION

Parasitic illnesses continue to pose a grave threat to world health. Although the current medications continue to be of significant benefit, their efficacy is increasingly compromised by resistance and safety problems. Thanks to new anti-parasitic drugs, innovative discovery trends, and the latest clinical trials, more effective treatments are expected. Modifying scientific discoveries into widely available treatments calls for collaborative, multidisciplinary methods and approaches.

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