Triazoles in Therapies for Parasitic Diseases

Subjects: Tropical Medicine

Contributor: Exequiel O. J. Porta

This entry provides a concise overview of the advancements and potential of triazole-based compounds in developing new treatments for major parasitic diseases, such as malaria, leishmaniasis, Chagas disease, and schistosomiasis. It also highlights their mechanisms of action, the application of advanced therapeutic strategies like nanomedicine and drug repurposing, and future perspectives in combating these globally prevalent infections.

triazoles parasitic diseases click chemistry antiparasitic malaria anthelmintic neglected tropical diseases Chagas disease leishmaniasis combination therapy

1. Introducción

Parasitic diseases, caused by protozoa and helminths, continue to impose a severe global health and economic burden, particularly prevalent in tropical and subtropical regions. Neglected Tropical Diseases (NTDs) alone required interventions for approximately 1.62 billion people in 2022 (**Figure 1**), with an estimated annual cost of USD 0.5 billion in lower-middle-income countries. Malaria, caused by *Plasmodium protozoa*, accounts for approximately 600,000 annual deaths and has a significant economic impact, slowing GDP-per-capita growth in sub-Saharan Africa. Similarly, schistosomiasis reduces agricultural output, and leishmaniasis outbreaks disrupt economic development. The efficacy of many existing antiparasitic drugs has declined due to drug resistance, suboptimal safety, and incomplete cures in chronic infections, necessitating the search for new or repurposed therapies with novel mechanisms of action.[1]

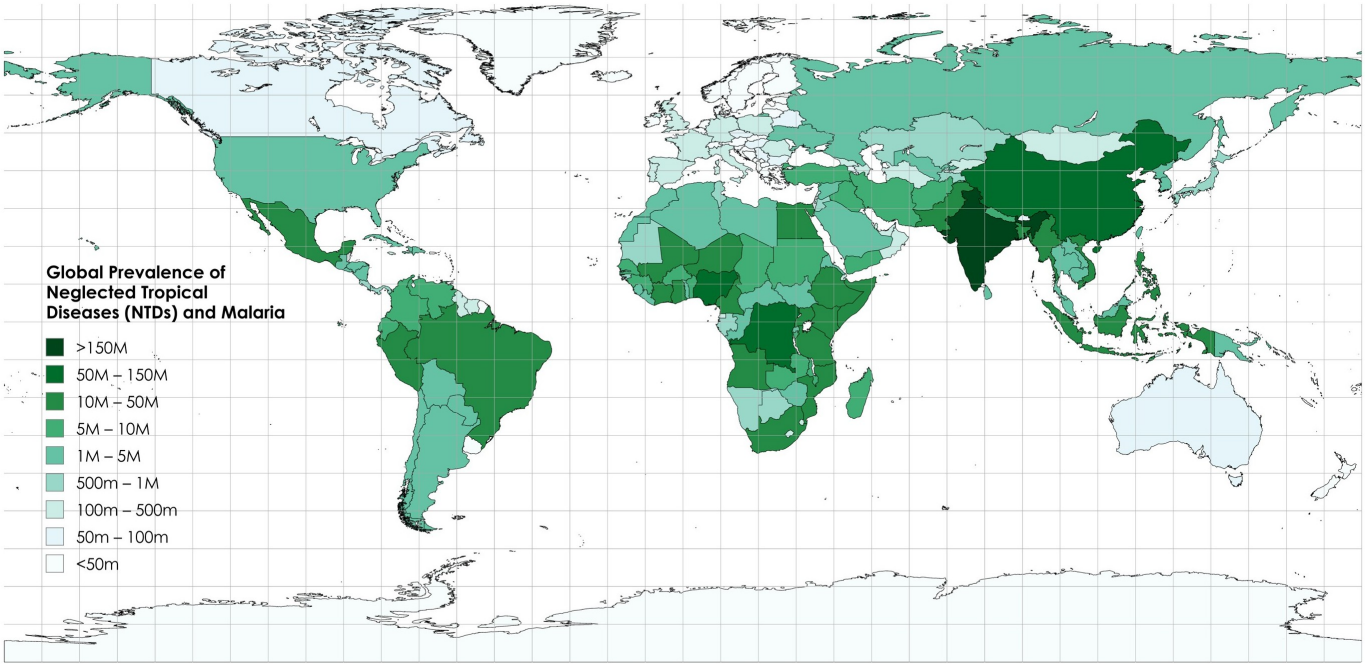

Figure 1. Global prevalence of NTDs and malaria, collectively affecting over 1.62 billion people worldwide in 2022.[1]

Triazoles, a versatile class of five-membered aromatic heterocycles containing three nitrogen atoms, have emerged as promising scaffolds in antiparasitic drug discovery. They exist as two constitutional isomers, 1,2,3-triazoles and 1,2,4-triazoles, each capable of adopting three tautomeric forms (**Figure 2**). This structural versatility contributes to their broad-spectrum bioactivity and favorable drug-like properties, including good oral bioavailability, high metabolic stability, and low toxicity. The unique structure of triazoles enables them to form multiple non-covalent interactions, such as hydrogen bonds, π-π stacking, and dipole interactions, with biological targets. In human medicine, 1,2,4-triazole rings are prominently featured in triazole antifungals like fluconazole, itraconazole, and posaconazole, which have revolutionized the treatment of systemic mycoses. The 1,2,3-triazole, while less common in approved drugs, serves as a rigid, metabolically stable linker or core structure, capable of stabilizing protein-ligand complexes through diverse binding modes.

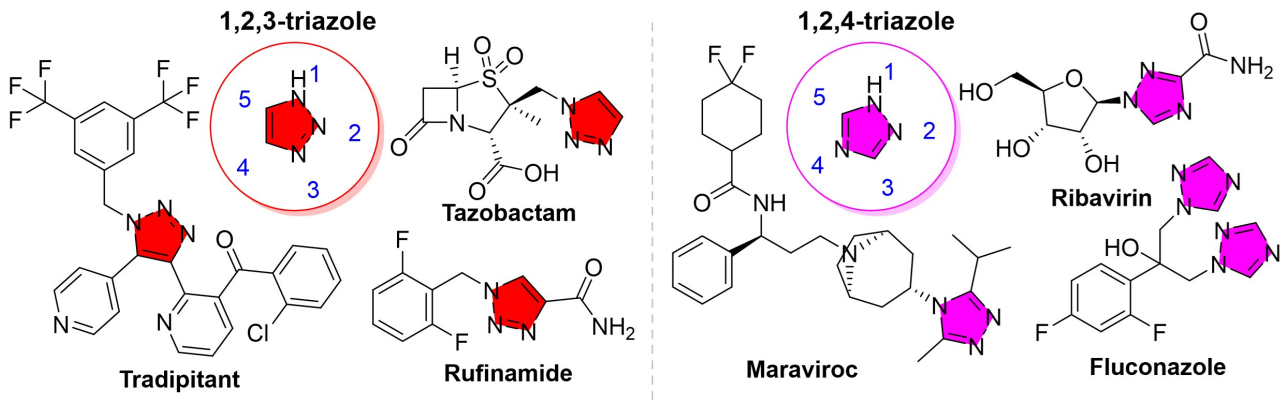

Figure 2. Representative drug molecules incorporating 1,2,3-triazole (in red) and 1,2,4-triazole (in magenta) heterocycles.[1]

A defining mechanistic feature of triazoles, particularly 1,2,4-triazoles, is their ability to coordinate to metalloproteins, notably cytochrome P450 enzymes (CYPs) (**Figure 3**). Triazole antifungals inhibit fungal CYP51 (lanosterol 14α-demethylase) by binding tightly to the heme iron, blocking sterol demethylation and disrupting cell membrane integrity. Many protozoan parasites, such as *T. cruzi* and *Leishmania* spp., also depend on sterol biosynthesis via a similar CYP51 enzyme. Consequently, clinical antifungal triazoles like ketoconazole, fluconazole, itraconazole, posaconazole, and ravuconazole have shown antiproliferative effects on these parasites. High-resolution structures reveal that posaconazole binds to *T. cruzi* CYP51 in a manner almost identical to how ketoconazole binds human CYP51, indicating a conserved active site geometry. Beyond CYP51, triazole-containing compounds can target other parasite metalloproteins or enzymes, leveraging their coordination chemistry to inhibit essential metalloenzymes.

The advent of "click chemistry", specifically the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC), has profoundly impacted the synthesis and modification of triazoles, expanding the chemical space for antiparasitic drug discovery. CuAAC allows for the high-yield, modular assembly of 1,4-disubstituted 1,2,3-triazoles, enabling the creation of triazole-based hybrid molecules that link two bioactive pharmacophores. In antiparasitic research, these hybrids include quinoline-triazole conjugates, triazole-artemisinin hybrids, and triazole-benzimidazole hybrids, designed to achieve dual action or improve pharmacokinetic properties. Some 1,2,3-triazole hybrids have even demonstrated the ability to target multiple stages of a parasite's lifecycle, which is highly attractive for diseases like malaria. Moreover, click chemistry can be performed in a biocompatible, metal-free manner, facilitating the attachment of triazoles to biomolecules or surfaces for targeted drug delivery systems, thus enhancing treatment efficacy and safety.

Triazoles generally confer favorable pharmacokinetic properties to drug molecules, often exhibiting long half-lives in humans (e.g., fluconazole: ~30 h, posaconazole: ~35 h), which permits less frequent dosing. The metabolic inertness of the triazole ring, particularly 1,2,3-triazoles, ensures that the drug's core remains intact. However, a notable caveat is that some triazoles can inhibit human drug-metabolizing CYP enzymes, such as CYP3A4, leading to potential drug-drug interactions. This is particularly relevant in co-endemic regions where polypharmacy is common, as CYP3A4 inhibition can alter the pharmacokinetics of co-administered therapies for diseases like HIV and tuberculosis. Newer triazoles, like isavuconazole, have been designed to exhibit a less complex interaction profile and more predictable pharmacokinetics, reflecting the evolution of triazole drug design towards optimizing safety while retaining potency.

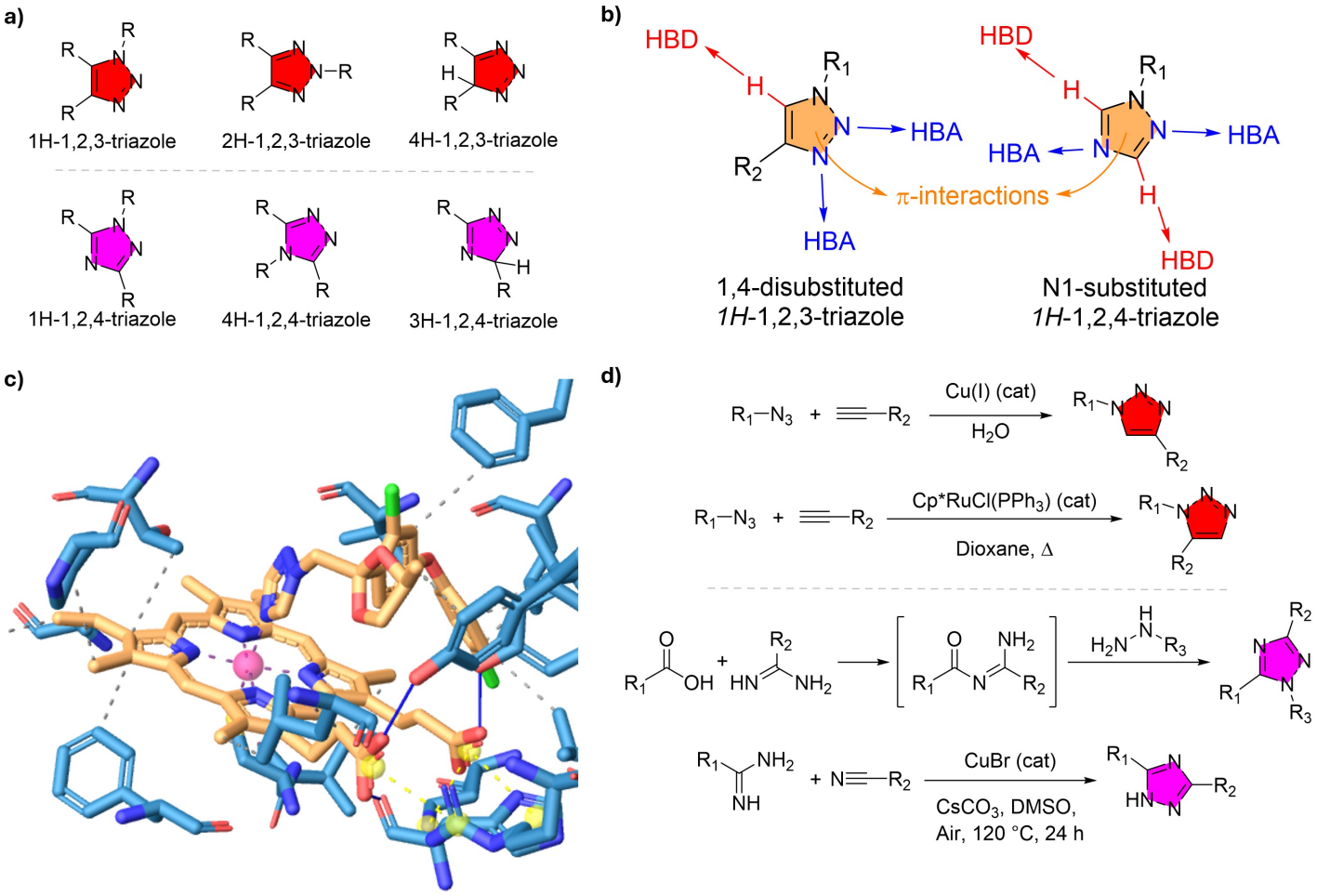

Figure 3. Triazole isomers, properties, and synthesis. (**a**) Chemical structures of six triazole isomers. (**b**) Illustration of hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) properties of triazoles, along with potential π interactions. (**c**) Representative metal-binding mode of a triazole ligand within a CYP51, depicted with PLIP (PDB ID: 5EAH). (**d**) Common synthetic routes for triazole formation.[1]

2. Current Progress of Triazole-Based Therapies for Protozoan Parasitic Diseases

Triazole-based compounds have demonstrated robust *in vitro* and *in vivo* activities against protozoan parasitic diseases, with recent studies focusing on refining their structural features to improve potency and selectivity, thereby addressing drug resistance.

2.1. Triazole-Based Therapies for Protozoan Parasitic Infections

2.1.1. American Trypanosomiasis (Chagas Disease)

Chagas disease, caused by *Trypanosoma cruzi*, exemplifies both the promise and challenges of repurposing triazoles. Standard treatments like benznidazole and nifurtimox are highly toxic and show suboptimal efficacy in chronic infections. Given *T. cruzi*'s reliance on ergosterol-like sterols for membrane integrity, antifungal azoles have been hypothesized to inhibit parasite sterol synthesis. Preclinical studies confirmed this: posaconazole and

ravuconazole showed potent anti-*T. cruzi* activity in cell culture and mouse models, even against nitrofuran-resistant strains, suggesting a radical cure. However, clinical trials, such as the Phase II STOP-CHAGAS trial, revealed limitations. While posaconazole monotherapy led to high rates of initial parasite clearance, significant parasitological relapse was observed after six months post-therapy, with only 13.3% of patients remaining PCR-negative at 180 days. In contrast, benznidazole monotherapy maintained efficacy (86.7% PCR-negative at 180 days), and combination therapy with benznidazole did not significantly outperform benznidazole alone in long-term cure rates. These outcomes suggest that while posaconazole is highly active during dosing, it fails to eradicate chronic infections, likely due to persisting parasite forms in tissue niches where drug levels are insufficient, or potential adaptive upregulation of the sterol pathway. Despite these setbacks, triazoles remain important for acute infections or reactivations in immunosuppressed patients. Ongoing strategies include optimizing combination therapy, such as sequential therapy, to target niches poorly penetrated by benznidazole while eliminating persisters. Medicinal chemists are also designing triazoles tailored to selectively bind *T. cruzi*'s CYP51 or other essential parasite enzymes with higher affinity than human counterparts. Research has yielded promising candidates like VNI, a vinyl-imidazole inhibitor potent against *T. cruzi* CYP51, which cures acute Chagas disease in mice.

2.1.2. Leishmaniasis

Leishmaniasis, caused by *Leishmania* parasites, presents a diverse clinical spectrum, from self-healing cutaneous lesions to fatal visceral infections. Current treatments are limited by toxicity, high cost, and drug resistance. Triazoles have shown promise due to their ability to inhibit *Leishmania* sterol 14α-demethylase (CYP51), which is crucial for parasite viability. Posaconazole and ravuconazole have demonstrated potent *in vitro* and *in vivo* activity against various *Leishmania* species. Clinical studies, particularly for cutaneous leishmaniasis (CL), suggest that triazoles can induce parasite clearance, but often with high relapse rates when used as monotherapy, similar to Chagas disease. Combination therapies, such as itraconazole with allopurinol, have shown increased effectiveness. While triazoles are not standard therapy for visceral leishmaniasis (VL), they remain part of the drug pipeline, especially for cutaneous forms, and hold potential for patients with concurrent fungal infections.

2.1.3. Human African Trypanosomiasis (HAT)

HAT, also known as sleeping sickness, is caused by *Trypanosoma brucei* subspecies. While historical treatments were toxic, newer drugs like fexinidazole have significantly improved outcomes. Research into triazoles for HAT has been limited, and they are not currently part of HAT treatment guidelines. Prospects for their use remain uncertain unless a unique niche, such as combination with fexinidazole to prevent resistance, is identified.

2.1.4. Malaria

Malaria, caused by *Plasmodium* parasites, has not traditionally been treated with triazole-containing drugs, but significant research is underway. The 1,2,4-triazole derivative DSM265, a potent inhibitor of *Plasmodium falciparum* dihydroorotate dehydrogenase (PfDHODH), an enzyme essential for pyrimidine biosynthesis, represents a major advance. DSM265 exhibits potent in vitro activity against various *P. falciparum* strains, including

drug-resistant ones, and has a long half-life, making it suitable for single-dose treatment. Clinical trials combining DSM265 with other antimalarial drugs have shown high cure rates, offering a promising alternative to increasingly ineffective artemisinin-based combination therapies (ACTs). These efforts address critical challenges in malaria, including drug resistance and suboptimal pharmacokinetics.

2.1.5. Toxoplasmosis and Other Protozoan Parasitic Diseases

Toxoplasma gondii, an apicomplexan parasite, causes toxoplasmosis. Standard therapy often leads to severe side effects, prompting interest in safer alternatives. Certain 1,2,4-triazole-based compounds have shown promise in suppressing *T. gondii* growth *in vitro*. Triazoles are also being explored for other protozoan infections, such as cryptosporidiosis, which is caused by *Cryptosporidium parvum* and is a significant cause of diarrheal disease. Compounds targeting *C. parvum* inosine 5'-monophosphate dehydrogenase, a crucial enzyme for parasite purine metabolism, have included triazole derivatives.

2.2. Triazole-Based Therapies for Helminthic Infections

2.2.1. Schistosomiasis

Schistosomiasis remains one of the most devastating parasitic diseases globally, second only to malaria. Current treatments rely heavily on praziquantel (PZQ), which has limitations including rapid metabolism and reduced efficacy against immature parasites. A promising strategy to enhance PZQ's activity is co-administration with triazole CYP450 inhibitors, which block PZQ's rapid metabolism and prolong its systemic exposure. Fluconazole has been shown to significantly inhibit *S. mansoni* CYP450, reducing worm development and liver egg burden. Similarly, itraconazole demonstrated synergistic effects when combined with PZQ, leading to a greater reduction in worm load. Beyond modulating drug metabolism, triazoles are also emerging as direct antiparasitic agents by targeting novel enzymatic pathways in schistosomes. An innovative approach involves the structure-based design of triazole-based inhibitors of *S. mansoni* histone deacetylase 8 (smHDAC8), which is crucial for parasite development and survival. Recent synthetic advances have expanded the chemical space of triazole compounds, with phthalimide analogs and mercaptotriazoles demonstrating potent antischistosomal activity with favorable ADME profiles and low cytotoxicity.

2.2.2. Other Helminthic Infections

A breakthrough approach has been the application of bioorganometallic chemistry to triazole antifungals. Attaching an organometallic fragment like metallocene to a fluconazole scaffold has created compounds with entirely new activity profiles against helminths, including *Brugia* (lymphatic filariasis) and *Trichuris* (intestinal helminthiasis). These modified triazoles target pathways absent in humans but essential for worm survival. Medicinal chemists have also synthesized various 1,2,4-triazole-based compounds and assessed their activity against model nematodes, with some N^1-substituted derivatives showing significant anthelmintic effects, even surpassing albendazole in potency. Novel 1,2,3-benzotriazole derivatives have also shown potent, dose-dependent activity against *Pheretima posthuma*, rivaling or surpassing albendazole.

3. Resistance, Safety, and Future Considerations

As triazole-based antiparasitic therapies advance, resistance, safety, and practical considerations become pivotal. While drug resistance mechanisms (e.g., target mutations, enzyme overexpression, efflux pump activation) are well-documented in fungi, similar phenomena could emerge in parasitic organisms if these agents are deployed as monotherapies. For *T. cruzi*, pharmacodynamic resistance, where parasites evade drug pressure by entering dormant states or residing in tissue niches with insufficient drug levels, is a key factor in chronic Chagas treatment failure.

Combination therapy is crucial for overcoming persistence by pairing drugs with different mechanisms of action, targeting both replicating and quiescent parasites simultaneously. This strategy has proven successful in HIV and tuberculosis treatment and can involve combining triazoles with fast-acting cidal drugs to eliminate persisters and prevent resistant mutants. Currently, resistance to triazoles in parasites has not become a widespread clinical issue, primarily because these drugs are not yet widely used as monotherapies.

Regarding safety, while generally safer than older antiparasitic drugs, triazoles can cause side effects such as hepatic toxicity, skin reactions, gastrointestinal upset, and, in some cases, endocrine disturbances. Drug-drug interactions, particularly due to CYP3A4 inhibition by some triazoles, are a concern in regions where polypharmacy is common. However, newer triazoles like isavuconazole are designed with improved specificity and fewer problematic interactions.

The multifaceted role of triazoles in advanced antiparasitic therapies is evident. They enhance the pharmacokinetic profile of existing drugs like PZQ by inhibiting CYP450 enzymes and serve as direct antiparasitic agents by targeting novel parasite enzymes (e.g., smHDAC8). The emergence of diverse analogs, including phthalimide and mercaptotriazole derivatives, further expands the discovery landscape with promising *in vitro* and *in vivo* activities. Future research should focus on optimizing these compounds for improved bioavailability, selectivity, and safety, as well as exploring synergistic combinations with current therapies. Advances in structure-based drug design and chemical synthesis will continue to refine these candidates, ultimately contributing to more effective management of parasitic diseases. Each new triazole optimized for a parasitic target brings us a step closer to safer, more effective, and more accessible treatments, ultimately moving the needle toward disease elimination and better health for affected populations.

References

1. Jaime A. Isern; Renzo Carlucci; Guillermo R. Labadie; Exequiel O. J. Porta; Progress and Prospects of Triazoles in Advanced Therapies for Parasitic Diseases. *Trop. Med. Infect. Dis.*. **2025**, *10*, 142.