ADVANCES IN THE MEDICINAL CHEMISTRY OF NEGLECTED TROPICAL DISEASE AND RELATED INFECTIOUS DISEASES

Editors: Igor Jose dos Santos Nascimento Ricardo Olimpio de Moura

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Advances in the Medicinal Chemistry of Neglected Tropical Disease and Related Infectious Diseases

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FOREWORD

Infectious diseases caused by neglected tropical pathogens continue to present significant global health challenges, especially in regions with limited economic and healthcare resources. The chemical structures of therapeutic agents targeting these diseases often rely heavily on heteroatom-rich scaffolds, notably structures that contain nitrogen, which provide a foundation for improved pharmacokinetic and pharmacodynamic properties.

This volume presents a comprehensive account of the critical advancements in medicinal chemistry aimed at addressing Neglected Tropical Diseases (NTDs) and related infections, emphasizing the significance of innovative strategies in drug design, scaffold-hopping methodologies, and target-based approaches utilizing both natural and synthetic compounds. Particular emphasis is placed on the incorporation of heteroatoms to improve solubility, lipophilicity, and hydrogen bonding capacity, as well as to optimize the ADME/Tox profiles of prospective drug candidates. Moreover, the distinctive biological functions of several chemical scaffolds offer molecular mimicry of natural metabolites, thereby facilitating the identification of agents with broad-spectrum bioactivity and enhanced therapeutic indices.

In addition to reviewing the core structures and biological targets, this work explores diverse synthetic methodologies employed to expand the drug-like chemical space. It highlights the significance of Structure-Activity Relationship (SAR) studies in optimizing lead compounds for efficacy and selectivity. Through the integration of classical medicinal chemistry with emerging approaches, including computational modeling and high-throughput screening, new avenues are being unveiled for addressing diseases that have historically been neglected due to limited commercial interest.

KEY FEATURES

- 1. Comprehensive insights into innovative compounds for NTDs and related infectious diseases.
- 2. Integration of natural products, synthetic compounds, and drug repurposing approaches.
- 3. Insights into target-based drug design and mechanistic pathways.
- 4. Application of advanced computational, experimental, and screening techniques.
- 5. Multidisciplinary strategies to address drug resistance and improve therapeutic outcomes.

It is our firm belief that this volume will stand as a valuable reference and an enduring source of inspiration for medicinal chemists, pharmacologists, and global health researchers committed to overcoming the burden of neglected diseases through advances in molecular innovation.

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PREFACE

Neglected tropical diseases are a conjunct of infectious diseases that affect several countries around the world, mainly those with tropical and subtropical conditions, affecting the population living in poverty and without basic sanitation, causing severe damage to the health of the population and economy of the countries. They are considered "neglected" due to the low investment of pharmaceutical companies in P&D for new drugs against these diseases. Thus, despite alarming statistics, there are few drugs to treat these conditions, with scientific research institutions being the main ones for developing new agents against these conditions [1 - 4].

In view of this, the book "Advances in the Medicinal Chemistry of Neglected Tropical Disease and Related Infectious Diseases" appears, highlighting the main developments in recent years against this disease, mainly in innovative compounds and molecular targets that can be explored in subsequent drug design studies.

This first edition is organized into ten chapters, namely:

Chapter 1 "Medicinal Chemistry of Neglected Tropical Diseases (NTDs): From Targets to Drugs," briefly introduces these diseases and some actual drug targets explored in the drug design process. The authors provide great material focusing on epidemiological, clinical manifestations, and current treatments. In addition, the structure, functions, and the most promising inhibitors of the N-myristoyltransferase, nitroreductases, topoisomerases, pyrimidine synthesis pathway, and mitochondrial alterations are shown and provide its importance in the drug design and development process. Finally, this chapter can guide research worldwide to discover a promising drug against several NTDs.

Chapter 2 "Advancements in Antileishmanial Drug Discovery: Targeting Druggable Pathways and Overcoming Treatment Challenges" explores the latest developments in synthetic, semi-synthetic, and natural compounds identified in in silico, in vitro, and in vivo assays against leishmaniasis and a brief introduction about some new targets used in the design process. In addition, the authors provide information about the primary chemical scaffolds explored against leishmaniasis, such as flavonoids and chalcones, naphthoquinones and iridoids, saponins, quinolines, lignans, terpenes and terpenoids, and others synthetic nucleus. Finally, the drug target of each scaffold is proposed, and this information can be used in the drug design of further compounds.

Chapter 3 "Chagas Diseases: State Of the Art and New Perspectives," provides new information about Chagas diseases, including the physiopathology and the drugs used in the clinical treatment. In addition, the authors provide new insights into the drug design and discovery process, highlighting the main explored drug targets, the chemical scaffolds used, and novel promising drugs in clinical practice.

Chapter 4 "Novel Agents against Human African Trypanosomiasis: Updates on Medicinal Chemistry and Target Identification," highlights the clinical manifestations and current treatments against Trypanosoma brucei, an etiological agent of the sleeping sickness, or human African trypanosomiasis. Furthermore, the most prominent drug targets are shown, such as protein tyrosine kinases (PTKs), mitogen-activated protein kinases (MAPKs), heat shock proteins (HSPs), kinetoplastid proteasome, Tb Cathepsin L (TbCatL), Tb UDP-Glucose 4'-Epimerase (TbGalE), and others that provide new insights in drug design to researchers worldwide.

Chapter 5 "Schistosomiasis: State Of the Art and New Perspectives" similar to the previous chapters, provides information about the life cycle of the schistosome and other parameters such as clinical manifestations and the current drug treatment. In addition, some repurposed drugs are explored as having promising potential against this disease, and the main research focuses on new drug targets, highlighting HDAC and Sirtuin inhibitors, histone methylation, protein kinases, protease, CYP450, transporters inhibitors, and others that can be a promising intervention in the drug design of antischistosomal drugs.

Chapter 6 "Progress In Medicinal Chemistry For Neglected Tropical Diseases: A Focus On DENV Drug Discovery (2014 - 2023)," explores the potential of classical drug targets of dengue virus and highlights the main features to design anti-dengue drugs. Similar to the chapters above, the functions of some non-structural targets, such as protease, RdRp, methyltransferase, and structural targets, such as E protein and others, were characterized. Thus, this chapter provides critical information for designing innovative anti-dengue compounds.

Chapter 7, "Malaria: State Of the Art and New Perspectives," discusses the actual drug treatment and its difficulties due to the parasite's resistance and the urgency to discover new drugs to overcome this. For this, it is necessary to explore new targets, as shown in the manuscript, such as channels/transporters, aquaporin channel, Plasmodial surface anion channel, hexose transporter, choline transporter, apicoplast, cyclin-dependent protein kinases (CDKs), nucleic acid metabolism, mitochondrial system, redox system, shikimate pathway, isoprenoid biosynthesis, parasite proteases, membrane biosynthesis, and pfTBP–pfTFIIB interface. Finally, the authors highlight the main chemical scaffolds explored that can provide an innovative drug against this disease.

Chapter 8 "On The Trail of Zika Virus: Understanding its Druggable Targets," explores the structural and non-structural proteins used in the drug design against the Zika virus. Thus, the authors provide critical information about the structure, functions, and main inhibitors of the NS1, NS2A, NS2B, NS3, NS2B/NS3, NS4B, NS5, envelop (E) protein, prM, capsid (C) protein, and some alternatives pathways that can be promising to discover an innovative anti-Zika drug.

Chapter 9 "Mycobacterium tuberculosis: Recent Advances in Drug Discovery and Targets – A SAR-Based Approach," explores the epidemiology and insights into drug design and development against tuberculosis. Thus, the authors highlight the importance of identifying new targets to provide an innovative drug and overcome the parasite's resistance to the actual clinical drugs of this disease. For this, targets such as DNA gyrase, shikimate pathway, adenosine kinases, and others are shown, highlighting their structure and functions. In addition, the authors provide exceptional work on the structure-activity relationship (SAR) to provide critical information on the structural features of the most actual discovered inhibitors.

Chapter 10 "Drug discovery in Fasciola hepatica: Few Steps in the Last Ten Years," highlights the urgency to discover new flukicide drugs and explores the drug design and discovery against Fasciola hepatica. For this, the authors provide excellent material about the explored drug targets, such as cathepsin Ls, triosephosphate isomerase, thioredoxin glutathione reductase, and other biological structures of the fasciola that do not have an experimental inhibitor, as well as the inhibitors identified in phenotypic drug screenings, and the function of the drug repurposing to discover drugs against fasciola. This chapter can provide new horizons for the readers and critical information to use in drug design against these diseases.

We hope our book will serve as a guide for researchers worldwide and help discover drugs against these diseases, ending these threatening agents.

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REFERENCES

- [1] Nascimento IJ, dos S, Cavalcanti M, de AT, de Moura RO. Exploring nmyristoyltransferase as a promising drug target against parasitic neglected tropical diseases. Eur J Med Chem 2023; 258: 115550.
- [2] De Souza M, Medeiros DC, de Moura RO, dos Santos Nascimento IJ. Pharmacokinetic limitations to overcome and enable K777 as a potential drug against chagas disease. Curr Pharm Des 2023; 29: 2359-60.
- [3] Dos Santos Nascimento IJ, de Moura RO. Targeting cysteine and serine proteases to discover new drugs against neglected tropical diseases. Curr Med Chem 2024; 31: 2133-4.
- [4] Dos Santos Nascimento IJ, de Aquino TM, da Silva-Júnior EF. Cruzain and rhodesain inhibitors: Last decade of advances in seeking for new compounds against american and african trypanosomiases. Curr Top Med Chem 2021; 21: 1871-99.

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CHAPTER 1

Medicinal Chemistry of Neglected Tropical Diseases (NTDs): From Targets to Drugs

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Abstract: Neglected Tropical Diseases (NTDs) are a group of infectious diseases that affect thousands of people all over the world. These diseases mainly affect the population that lives in poverty and lack sanitation, prevalent mainly in tropical and subtropical countries. In this sense, they are called "neglected" due to the low investment in P&D in pharmaceutical companies' discovery and development of new agents. Thus, developing new drugs against these diseases is one of the two biggest challenges for academic researchers around the world, and increasingly, there is a need for advances in medicinal chemistry methods and the identification of molecular targets for the design of innovative drugs that can put an end to these threats. Finally, here we will present methods used in medicinal chemistry in recent years in the design of drugs against these agents, with a focus on the development of new compounds against *N*-myristoyltransferase, nitroreductases, topoisomerases, pyrimidine synthesis pathway, and mitochondrial alterations constantly explored against various NTDs. We hope this chapter serves as a guide for researchers worldwide searching for innovative drugs that can finally help these people and improve the health of the world's population.

Keywords: CADD, Chagas diseases, Chikungunya, Dengue, Drug design, Drug discovery, Fasciola, leprosy, Leishmaniasis, Malaria, NTDs, Schistosomiasis, Sleeping sickness, Tuberculosis, Zika.

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INTRODUCTION

Neglected Tropical Diseases (NTDs) are a group of 20 infectious diseases prevalent worldwide, recognized by the World Health Organization (WHO) [1]. These diseases are intrinsically linked to the socioeconomic situation and environment of the patient's residence, affecting the poor population and those without basic sanitation [2]. NTDs pose a significant threat to public health in tropical, subtropical, and rural regions due to the conducive environment for the etiological agent of these diseases [3]. Poverty, particularly the lack of proper sanitation and limited access to medical care and follow-up, is another contributing factor to the high incidence of these diseases [4]. In general, NTDs can contribute to the perpetuation of poverty in a region. This is because the symptoms of NTDs can impede an individual's productivity and professional development, significantly impacting the regional economy [2, 5].

NTDs affect approximately 1.7 billion people worldwide, with Africa being the continent most vulnerable to these diseases, accounting for 40% of the population affected by NTDs globally [6]. This is primarily due to environmental conditions conducive to developing these diseases and inadequate sanitation. However, urbanization has led to a significant increase in NTDs in urban and peri-urban regions over the years, which has generated greater attention and caution towards these diseases [7]. Another risk factor in the spread of NTDs is the environmental impact caused by deforestation, fires, and climate change due to global warming. Many of these diseases go through complex transmission cycles between humans and animals, which can be induced to leave or expand their habitats due to these global stigmas [3, 8].

Due to these factors, public health organizations are developing new intervention strategies to control, eliminate, or eradicate these diseases [9]. These approaches offer a holistic and multisectoral approach to treating and preventing NTDs [10 - 12]. Strategies to control NTDs include preventive chemotherapy and transmission control (PCT), innovative and intensified disease management (IDM), vector ecology and management (VEM), veterinary public health measures, and the provision of safe water, sanitation, and hygiene (WASH) [13]. Other strategies, such as conditional cash transfer programs and social marketing interventions, can also reduce the incidence of NTDs. These programs aim to improve access to medical care and raise awareness among the population [13, 14].

However, the development of new drugs to mitigate NTDs remains the most promising strategy for controlling and eliminating these diseases despite the diverse intervention strategies employed [15]. Addressing the challenges of

developing these drugs is crucial to achieving this objective. Among the challenges associated with NTD treatment are the lengthy duration of therapy. which can exceed two months, the high incidence of adverse effects that require treatment during and after drug use, and various contraindications that can directly affect patient adherence to NTD treatment [16]. In addition to clinical factors, the discovery of new drugs faces a long, complex, and costly journey through several rigorous stages. Together, these factors indicate the key challenges that must be addressed in developing new drugs for NTDs [17].

In the face of numerous challenges, medicinal chemistry seeks new techniques and methods for developing drugs for NTDs [18]. These include implementing machine learning, applying pharmacogenomics in the development process, and the Target-Based Drug Design (TBDD) approach [19]. The increased availability of data from high-throughput screening (HTS) has made machine learning an essential tool in discovering new drugs, enabling models to be trained to predict biological activities of compounds before laboratory work [20]. Pharmacogenomics has been applied at various stages in developing new drugs and analyzing the interactions between compounds and DNA through in vitro and in silico assays [21]. The Target-Based Drug Design (TBDD) approach involves testing selected drugs against biological targets of parasites. This approach is a critical stage in the discovery and development of new drugs, as using inappropriate targets is a leading cause of failure in the final stages of the new drug discovery process [1]. Therefore, validating a promising biological target is crucial in discovering new drugs [22].

Designing and discovering new drugs against NTDs is a challenge and is necessary to improve new approaches to obtain success in a short time and with less financial investment. From this perspective, this chapter will approach the main advances in medicinal chemistry to discover new drugs against NTDs, focusing on new drug targets such as N-myristoyltransferase, nitroreductases, topoisomerases, pyrimidine synthesis pathway, and mitochondrial alterations. We hope our findings help researchers worldwide search for an innovative drug to stop these threatening agents and improve the world population's health.

NEGLECTED TROPICAL DISEASES: A CONSTANT THREAT

In 2005, the WHO distributed a list of neglected tropical diseases. The list included a diverse group of tropical infections, predominantly chronic and parasitic, that disproportionately affect people living in poverty. The list consists of leishmaniasis - cutaneous (CL), mucocutaneous (MCL), and visceral (VL), trypanosomiasis (Chagas disease and sleeping sickness), which are caused by the infectious agents Leishmania spp. and Trypanosomacruzi or Trypanosoma brucei,

Advancements in Antileishmanial Drug Discovery: Targeting Druggable Pathways and Overcoming Treatment Challenges

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Abstract: Over the last decades, neglected tropical diseases (NTDs), especially leishmaniasis, have been the focus of several drug discovery programs. The identification of the pathogen druggable targets and the ability to map the differences between parasites and human enzymes have contributed to the increased interest in the development of new lead compounds. Despite this progress, there remain substantial gaps with respect to developing efficient medications that can be the foundation for surmounting the acquired resistance and overcoming treatment failure. With this background in mind, this chapter will discuss the validated drug targets with a special focus on the reported structural determinants of activity of novel antileishmanial agents. The aim is to introduce an updated overview of the medicinal chemistry aspects of leishmaniasis to the scientific community.

Keywords: Current treatment, Leishmaniasis, Natural antiparasitic agents, Neglected tropical diseases, Semisynthetic antileishmanial agents, Synthetic drugs.

INTRODUCTION

Leishmaniasis is a neglected tropical disease (NTD) endemic in Asia, Africa, the Americas, and the Mediterranean region [1]. The causative agent of the disease is an intracellular parasite related to the order *Kinetoplastidae*, the family

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Trypanosomatidae, and the genus Leishmania [2, 3]. On the other hand, the vector responsible for the transmission of the parasite to humans through its bite is the infected female sandfly, mainly of the *Phlebotomus* and *Lutzomyia* genera, belonging to the subfamily *Phlebotominae* [1]. Based on the development site of the parasite in the gut of the sandfly, the mammalian Leishmania species are divided into two subgenera: Leishmania, which includes the species that develop only in the midgut and foregut, and Viannia, which develop in the Phlebotomus hindgut before migrating to the midgut and foregut [1, 4]. According to the WHO (12 January 2023), an estimated 700,000 to 1 million new cases occur annually, although only a small fraction of those infected by parasites eventually develop the disease [5]. The disease can be categorized into four clinical forms: Visceral leishmaniasis (VL), Cutaneous leishmaniasis (CL), Mucocutaneous leishmaniasis (MCL), and post kala-azar dermal leishmaniasis (PKDL), caused by over 20 Leishmania species. However, the clinical manifestations and their severity depend on the *Leishmania* species involved and the triggered immune response of the host. Generally, while cutaneous leishmaniasis is the most common, visceral leishmaniasis is the most severe form that can be fatal if left untreated [6].

LIFE CYCLE

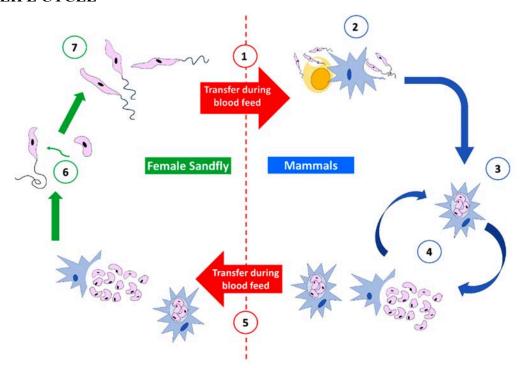


Fig. (1). Life cycle of Leishmania.

According to the Fig. (1), the life cycle of *Leishmania* follows the following steps: 1) Infected female sandfly, the insect vector, bites a healthy host and takes a blood meal, thereby injecting the infective stage (i.e., motile promastigotes) through their proboscis. 2) At the puncture wound, the promastigotes are phagocytosed by macrophages and other types of mononuclear phagocytic cells. 3) Promastigotes transform into non-motile amastigotes, which multiply by simple division inside the phagolysosome. 4) The amastigotes are released because of the host immune response-mediated cytolytic environment and proceed to infect other mononuclear phagocytic cells, where they survive as intracellular parasites. 5) Sandfly takes a blood meal from an infected person, thereby ingesting infected cells. 6) In the gut (in the foregut, midgut, and hindgut for leishmanial organisms in the Viannia subgenus; in the midgut and foregut for organisms in the *Leishmania* subgenus), the amastigotes transform into flagellated promastigotes. These survive extracellularly and multiply by binary fission. 7) After multiplication, the virulent promastigotes migrate to the proboscis, ready to infect a healthy host during the next blood meal. The presence of an anticoagulant in the saliva of the vector prevents the blood from coagulating at the bite site, thereby allowing a successful transmission of the parasite [1, 2, 6, 7].

FORMS OF THE DISEASE

Leishmaniasis is a vector-borne disease with various clinical manifestations that depend on the virulence characteristics of the parasite and the effectiveness of the host's immune response. Four main clinical forms can be identified: A) cutaneous leishmaniasis (CL), B) mucocutaneous leishmaniasis (MCL), C) visceral or kala-azar (VL), and D) Post-kala-azar dermal leishmaniasis (PKDL) [6].

Cutaneous Leishmaniasis (Localized Cutaneous Leishmaniasis)

This form of the disease occurs in the body areas exposed to insects' bites; in decreasing order of frequency, the ears, nose, upper lip, cheeks, legs, hands and forearms, and ankles are affected. After exposure, the incubation period can range from 1 to 4 weeks. However, it can last up to several years [1]. Generally, skin lesions that develop in cutaneous leishmaniasis can persist for months, but in some cases, they can last for years before they spontaneously heal, leaving flat, hypopigmented scars [6, 8].

Mucocutaneous Leishmaniasis (MCL)

MCL is a rare and severe variant of CL that can take place years after the initial cutaneous manifestations have resolved. It can result in facial deformities due to mucosal lesions, which lead to partial or complete destruction of mucosal linings of the nose, throat, and mouth. This form of disease is caused by the spread of the

Chagas Diseases: State of the Art and New Perspectives

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Abstract: American trypanosomiasis, also known as Chagas Disease (CD), is a Neglected Tropical Disease (NTD) of the infectious type, having the protozoan parasite *Trypanosoma cruzi* (*T. cruzi*) as the etiologic agent. The CD is usually transmitted to human hosts by means of the Triatomine bug bites, and it is endemic in regions characterized by substandard environmental conditions, such as Central and South America. The globalization of goods and people significantly contributed to spreading CD to regions not previously affected and/or not adequate for the proliferation of transmitting bugs. This chapter reviews the main features of the disease, its main symptoms, the actual therapies, and the most advanced, although not for clinical use and currently considered for further development.

Keywords: Chagas Disease (CD), Chronic Chagas Cardiomyopathy (CCC), Benznidazole, Fosravuconazole Llysine ethanolate (E1224), *Trypanosoma cruzi* (*T. cruzi*), Nifurtimox, Neglected Tropical Disease (NTD), Posaconazole, Ravuconazole.

INTRODUCTION

Neglected tropical diseases (NTDs) account for almost 20 diverse conditions, which are mostly present as endemic within the tropical areas of the planet. They usually spread amongst the lowest social classes and disproportionately affect women and children over males. Such diseases primarily impact individuals' health and have significant effects at social and economic levels. Overall, the epidemiology of NTDs is quite complex as it is usually associated with multistep life cycles, and it is often strictly related to environmental circumstances. For instance, the majority of NTDs are vector-borne and nourished from animal reservoirs [1]. Among the NTDs is the American trypanosomiasis, also named

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Chagas Disease (CD) after the Brazilian physician and researcher Carlos Ribeiro Justiniano Chagas, who discovered the disease in 1909 and demonstrated its etiological agent being the protozoan parasite Trypanosoma cruzi (T. cruzi) [2, 3].

To date, about 7 million people worldwide are estimated to be infected with T. cruzi. Usually, the transmission of such a parasite occurs by means of the Triatomine insect bites, or alternatively through the ingestion of foods and beverages or organ transplantation contaminated with the bug excrements. Some clinical cases of infections were reported to occur through the maternal-fetal route [4, 5].

The CD was traditionally endemic in Central and South America, specifically in regions characterized by substandard environmental conditions that are ideal for the proliferation of Triatomines. In the modern era, the globalization of goods and people highly contributed to the spread of CD to regions not previously affected [6 - 10].

Many actions are considered to control CD, and among others are insecticide spraying to eliminate vector bugs and educational programs for the exposed population to raise awareness of the pathology and the vectors. Besides such activities, research activities focused on the development of efficient diagnostic tools and treatment options are continuously pursued. As a result, a significative reduction of new infections is reported, which, however, does not impede CD from being considered a public health priority [6, 11 - 17].

T. cruzi Transmission

The life cycle of T. cruzi involves an invertebrate vector, such as the Triatomine insects, which include members of the *Reduviidae* family and a vertebrate host (i.e., humans). It evolves through developmental stages associated with the three distinct morphological forms of trypomastigote, amastigote, and epimastigotes, as reported in Fig. (1A-C) [3].

The amastigote and epimastigote forms of *T. cruzi* both replicate through binary fission, respectively, within the hindgut and mammalian cells of the triatomine vector, while trypomastigote stages are not endowed with replicative ability. Areas of exposed mucous membranes (i.e., eyes or lips) or skin are usually bitten by triatomine bugs, which subsequently defecate or urinate close to the bite sites. As a result, the infecting parasite enters the body through any skin break and invades the closest tissues before spreading deeper up to the heart and gastrointestinal system [3]. Thus host blood results rich in circulating trypomastigotes, hence turning the vectors into infected ones by sucking blood. Moreover, such

infectious stages may develop within the insect gut, where they multiply into epimastigotes [14 - 16].

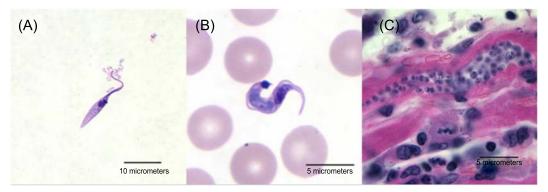


Fig. (1). *Trypanosoma cruzi* and its morphological forms. **(A)** Epimastigotes form and are capable of replication in culture (Giemsa-stain). **(B)** A smear of peripheral blood with trypomastigote within an acute Chagas disease-affected patient (Giemsa-stain). **(C)** Patients with chronic Chagas disease, view of a cardiac myocyte with amastigotes inside (hematoxylin and eosin stain) [3].

Besides the classical diffusion by triatomine bites, *T. cruzi* can also be transmitted to human hosts by means of:

- Oral transmission is due to the consumption of food contaminated with *T. cruzi* and/or water. Such transmission is associated with a higher incidence of more severe case outbreaks and mortality than vector-borne disease [17].
- Vertical or congenital transmission from an infected mother (especially with high parasitic load) to newborns during pregnancy or childbirth [18].
- Transfusion of whole blood or platelets [19, 20], solid organs, and bone marrow transplants from infected donors [21]. Specific accidents that occurred in biologic laboratories have been identified as an unintentional source of *T. cruzi* transmission [4, 22].

Pathogenesis of Chagas Disease

Since *T. cruzi* inoculation occurs, the pathogenesis and the symptomatology of CD have evolved over time, with the protozoan load increasing within the host. As a result, the disease slowly becomes relevant symptomatology and is associated with higher degrees of health risks (Fig. 2).

Organ dysfunction or damage is mainly associated with the acute phase of the disease due to the host's strong inflammatory response and the action of the parasite itself. Hence, tissues such as skeletal, cardiac, and smooth muscles may present *T. cruzi* as a nest of amastigote form. Moreover, the central nervous system (CNS), gonads, and mononuclear phagocytes may also be infected [24,

CHAPTER 4

Novel Agents against Human African Trypanosomiasis: Updates on Medicinal Chemistry and Target Identification

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Abstract: Also known as sleeping sickness, human African trypanosomiasis (HAT) is caused by protozoan parasites of the genus Trypanosoma transmitted between humans by the bites of tsetse flies (glossina). HAT is caused by two parasite subspecies -Trypanosoma brucei gambiense (accounting for 92% of reported cases and causes chronic illness) and Trypanosoma brucei rhodesiense (accounting for 8% of reported cases and is responsible for the acute form of the disease). The former can advance, affecting the central nervous system, while the latter can develop rapidly with multiple organs, including the brain, being invaded. If left untreated, HAT is generally fatal. According to the World Health Organization, in the period 2016 – 2020, about 55 million people were at risk of infection, with nearly 1000 cases reported in 2018. Current treatment options have limitations such as complex administration procedures, limited effectiveness, emergence of drug resistance, and undesirable side effects. Therefore, new drugs are required. In this book chapter, we summarize current efforts aimed at identifying new drug candidates and their corresponding mechanisms of action. We highlight medicinal chemistry optimization efforts for different candidates while giving detailed insights into the mechanism of function for the corresponding drug targets. Such information is of value as it equips drug discovery scientists with information about chemical modifications, which can lead to improvement in certain physicochemical and biological properties of new chemical entities.

Keywords: HSPs, HAT, MAPKs, Protein tyrosine kinases, Rhodesain, Sleeping sickness, T. b. gambiense, T. b. rhodesiense.

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INTRODUCTION

HAT, also known as sleeping sickness, is a devastating parasitic disease caused by the blood- and tissue-borne parasites of the genus *Trypanosoma* [1]. As of 2022, the estimated number of HAT cases globally was 799. This low number of HAT cases is a result of global control efforts by the World Health Organisation, national control programs, bilateral cooperation, and non-governmental organizations during the 1990s and 2000s [2, 3]. However, any relaxation in these efforts can cause a resurgence, as was observed in 1970. After 1970, the number of cases continued to increase, and by 1998, almost 40,000 cases were reported, with an estimated 300,000 undetected and untreated cases. Recent risk estimates for the period 2016 to 2020 were 55 million people, with only 3 million at moderate risk [3]. Unfortunately, the population with the highest risk of acquiring HAT mainly lives in rural and remote communities, which tend to have limited access to healthcare, thereby complicating its quick diagnosis and treatment [4].

Transmission of *Trypanosoma* parasites occurs when an infected tsetse fly bites a mammalian host, such as a human, introducing the parasites into the bloodstream [1]. In the mammalian host, the parasite proliferates as slender bloodstream forms (BFs), which rely solely on glycolysis for energy production. These slender BFs develop into non-replicating stumpy BFs, which then develop into procyclic forms (PFs) after transmission to the fly [5, 6]. As the parasites transition, they undergo morphological and metabolic changes, such as switching from glycolysis to oxidative phosphorylation and changing their surface coat from variant surface glycoproteins to procyclins [7]. The PFs then develop into epimastigotes and then to mammalian-infective metacyclic trypomastigotes [5].

There are two main forms of HAT, each with different epidemiological characteristics. Approximately 92% of HAT cases are caused by *Trypanosoma brucei gambiense*, which causes the slowly progressing form known as West African sleeping sickness [3]. This is normally found in countries such as Angola, the Central African Republic, the Democratic Republic of the Congo, and Sudan. It mainly affects rural and forested areas [2]. The primary vector responsible for transmitting *T. b. gambiense* is the tsetse fly belonging to the *Glossina palpalis* group. Humans are the primary reservoir host for *T. b. gambiense*, although it can also infect other mammals, including non-human primates [1, 8]. *T. b. rhodesiense* is responsible for 8% of HAT cases and causes the faster-progressing form known as East African sleeping sickness [3]. It is more prevalent in savannah and woodland areas occurring normally in countries such as Uganda, Kenya, Tanzania, and Zambia [2]. The primary vector responsible for transmitting *T. b. rhodesiense* is the tsetse fly belonging to the the *Glossina morsitans* group.

In addition to humans, a range of domestic and wild animals can serve as reservoir hosts for T. b. rhodesiense [1, 8].

In this book chapter, we discuss current diagnosis and treatment strategies against the Trypanosoma parasites. We also discuss the use of target-based drug discovery methods to identify HAT targets and provide a few examples of novel HAT targets where the structure-activity relationship has been used to identify small molecule inhibitors for these targets.

CURRENT DIAGNOSIS AND TREATMENT STRATEGIES FOR HAT

HAT is diagnosed using clinical examination, serological tests, and microscopic evaluation of body fluids [9]. There are two main stages of HAT. During the early stage, which is referred to as the hemolymphatic stage, symptoms include fever, headaches, joint pain, and lymphadenopathy. This stage is followed by a meningoencephalitic stage, when the parasite invades the central nervous system, causing personality changes, sleep disturbances, and neurological disorders [3]. It is important to identify the form and stage of the disease, as the treatment of HAT is dependent on this. The second stage of infection requires drugs that can cross the blood-brain barrier for them to be effective. Treatment for gambiense-HAT has relied on pentamidine, effornithine, nifurtimox, and fexinidazole (Fig. 1), whereas for *rhodesiense-HAT*, the main treatment options are suramin, melarsoprol, and effornithine (Fig. 1) [10]. Early treatment is recommended as it improves treatment outcomes. Treatment outcome is monitored by follow-up for up to 24 months and involves clinical as well as laboratory assessments. Some assessments require cerebrospinal fluid as the parasites may remain viable and reproductive [10].

Management of HAT in resource-limited health facilities poses a challenge for the patient and carers [11]. Most of the HAT medications need complex methods of administration and strict adherence to the treatment course, with some necessitating prolonged hospitalization. For drugs such as fexinidazole, patients need to have consumed a meal to ensure the drug absorption is sufficient and that the active metabolites reach therapeutic levels [12]. HAT medications are also known to cause adverse reactions in some patients, such as nausea, vomiting, and decreased appetite. Nifurtimox-effornithine combination therapy, or NECT, may cause side effects such as abdominal pain, nausea, and vomiting but may also trigger seizures and occasional psychotic reactions and hallucinations [12]. The drive for new drugs against neglected diseases such as HAT is driven by the medical need for improved drugs that are easier to administer, with improved efficacy, and are more tolerable.

CHAPTER 5

Schistosomiasis: State of the Art and New Perspectives

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Abstract: Schistosomiasis, a neglected tropical disease, affects millions worldwide. Treatment and control strategies rely entirely on the single drug praziquantel (PZQ), making the prospect of resistance emergence worrisome. The pressing need to introduce new antischistosomal agents necessitates exploring and repurposing chemotherapeutic history besides designing novel leads. In this context, this chapter summarizes the parasite life cycle, its clinical manifestations, and the progress in schistosomiasis chemotherapy with an overview of the validated drug targets, the emergence of drug resistance, and vaccination trials.

Keywords: Current schistosomiasis treatment, Neglected tropical diseases, Repurposed antischistosomal agents, Resistance, Schistosomiasis, Specific schistosomal targets, Vaccination.

INTRODUCTION

Schistosomiasis is one of the most important neglected tropical diseases (NTD) that is caused by blood flukes of the genus Schistosoma. Nearly 250 million humans are affected by this disease, which is associated with poverty as its transmission is connected with a lack of hygiene, poor access to safe water, and lack of adequate sanitation. Among the five species that can infect humans, the three most common are *Schistosoma haematobium*, *Schistosoma japonicum*, and *Schistosoma mansoni* [1, 2]. As controlling the disease is currently based on the

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use of praziquantel, scientists are working on the identification and characterisation of potential new targets and drug repurposing to develop new treatment methods. In addition, researchers are working to develop a vaccine to help control the disease in combination with the drug of choice employed.

THE LIFE CYCLE OF SCHISTOSOMA

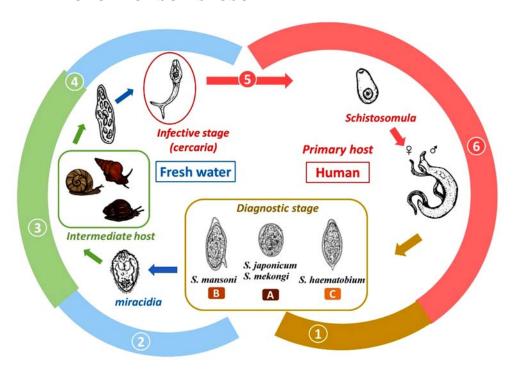


Fig. (1). Schematic representation of the life cycle of Schistosoma.

The life cycle of Schistosoma follow the following steps (Fig 1): 1. Depending on the species of the parasite, the eggs are released through faeces or urine of infected patients contaminating fresh water. 2. In appropriate conditions, the released eggs hatch setting free larvae called miracidia which infect snails. 3. Each species of Schistosoma parasite infects a certain genus of the snail. While S. haematobium infects snails of the genus Bulinus, the intermediate hosts of S. japonicum are snails of the genus Oncomelania. However, S. mekongi larvae infect snails of the genus Neutricula and the miracidia of S. mansoni infect snails of the genus Biomphalaria. 4. After entering the intermediate host, the miracidium loses its ciliated plates, thereby turning into a mother sporocyst, which produces daughter sporocysts. The latter either produces the next larval stage known as cercaria or produces more daughter sporocysts. 5. When the cercariae penetrate the human skin, they shed their forked tails turning into

another larval form called the schistosomula. These migrate throughout the body's tissues through the blood circulation. 6. The liver is the location where the schistosomula mature into male and female adult worms. After copulation, the pair migrates and resides in the mesenteric venules, the locations of which are determined according to the species of the parasite. While the copulated worms of S. haematobium often exist in the bladder and ureters, they can be found in the rectal venules. However, the adult worm pairs of S. japonicum occur more frequently in the small intestine. The worms of **S. mansoni** reside in either large or small intestines. After reaching their different destinations they deposit numerous eggs which are eliminated in urine or faeces so that the cycle can continue [3 - 5].

CLINICAL MANIFESTATIONS OF HUMAN SCHISTOSOMIASIS

Clinically, schistosomiasis consists of two phases namely (i) acute schistosomiasis and (ii) chronic schistosomiasis.

Acute Schistosomiasis

It is a systemic hypersensitivity induced by the penetrating, migrating, and maturing larvae as well as eggs. It can be divided into two clinical pictures: (i) cercarial dermatitis or swimmer's itch and (ii) Katayama fever or syndrome. Generally, the severity of the symptoms is related to the larval burden and the immune response to the presented antigens [6, 7].

Cercarial Dermatitis or Swimmer's Itch

Within 24 hours after contact with the infective cercariae, the affected person develops an itch and a rash that can last for up to 3 weeks. The rash that is provoked by the penetration of the cercariae, develops with papules and vesicles and is usually self-limiting unless a secondary infection takes place [6, 8].

Katayama Fever or Syndrome

The Katayama fever currently known as Katayama syndrome is a symptom complex resulting from the hypersensitivity reaction to the migrating eggs and schistosomula. The symptoms start 2 to 12 weeks post-infection during the maturation of the schistosomula into the adult form which then mates and lays eggs. The severity of the symptoms is related to the infecting species. The symptoms start suddenly and include fatigue, fever, malaise, myalgia, urticaria, eosinophilia, and non-productive cough. Other pulmonary, abdominal, and neurological symptoms can also take place [6, 9].

CHAPTER 6

Progress in Medicinal Chemistry for Neglected Tropical Diseases: A Focus on Denv Drug Discovery (2014-2023)

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Abstract: Dengue is still a major concern as we are yet to identify a potent inhibitor, and unfortunately, there is loss of life associated with this disease; however, the fatalities are low, but every year, dengue is an added burden to the medical infrastructure. In a world hit by COVID-19 pandemic, dengue is yet another serious burden. To date, we do not have any approved medicine to combat this disease. Symptomatic treatment to reduce the fever and intensive care facilities for critical patients is the only treatment protocol adopted as of now. Earlier, it was a disease of tropical nations of the world, but now it has been observed that it has extended its reach beyond the tropical and subtropical nations. The WHO data suggest that the year 2023 saw a record over 5000 reported cases of death due to dengue in about 80 countries across the world. These data further call for the urgency in identifying inhibitors for dengue. In the book chapter, we have compiled the efforts made so far in the last decade to give a DENV inhibitor. Our extensive survey of the literature indicated that protease of DENV was the most explored target and besides these targets like NS5 methyltransferase, RdRp, and E proteins did report few molecules. The success of proteases for drug discovery in diseases like HIV and HCV has encouraged researchers to exploit the DENV proteases. In this book chapter, we identified varying scaffolds contributing to the inhibition of Dengue virus and by different mechanisms.

Keywords: DENV, Dengue virus, E protein, HTS, HTVS, Molecular docking, NS5 methyltransferase, RdRp.

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INTRODUCTION

Dengue fever, a mosquito-borne disease caused by the dengue virus, is now considered a global public health problem that threatens half of the world's population. According to the World Health Organization (WHO), more than 3.9 billion people are at risk of infection and more than 20,000 die each year [1 - 3]. There are four closely related serotypes of the dengue virus (DENV 1–4), which is a single-stranded RNA virus belonging to the Flaviviridae family. Even though over 80% of cases of dengue are often mild, certain patients may experience severe infections that can result in coagulopathy and plasma leakage, which can be fatal and affect organ function as well as circulatory shock [4] Given that there is no clinically approved antiviral medication to treat dengue infection, treatment options for dengue infection are now restricted to supportive measures including careful fluid delivery and close observation during the critical phase, with the projected annual cost of dengue illness reaching US\$8.9 billion worldwide, this has major economic repercussions [5].

The positive-sense, single-stranded genomic RNA of the dengue virus is 11 kb long and codes for a precursor polyprotein(5'-C-prME-NS1-NS2A-NS2B- NS3-NS4A-NS4BNS5-3'), which is cleaved into three structural proteins (capsid protein C, membrane protein prM and envelope protein E) and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5). Among these, the human mediator of IRF3 activation (MITA), a crucial adaptor protein, is cleaved by the NS2B/NS3 protease complex, which hence suppresses the host type I interferon (IFN) pathway. The E protein is important in the host cell-mediated viral attachment and its fusion with the membrane of the host cell [6, 7]. Once the viral replicase complex is assembled, the polyprotein precursor is processed by NS2B/NS3 proteins [6–9]. The N- and C-terminal sections of the NS5 contain RNA methyltransferase (MTase) and RNA-dependent RNA-polymerase (RdRp) respectively which are fused through a 9-amino acid linker [6 - 9]. E, NS5, and NS2B/NS3 proteins are thought to be viable candidates for the discovery of antiviral therapies based on their essential roles [10, 11].

A promising alternative is the design of small molecules directed to the allosteric site. The allosteric sites of DENV NS2B/NS3pro and other DENV proteins have been examined in several publications in the literature to find more powerful inhibitors [12 - 17]. In DENV NS2B/NS3pro, this binding site is located behind the active site and is formed mainly by the residues NS3-Asp71, NS3-Lys73, NS3-Lys74, NS3-Trp83, NS3-Leu85, NS3-Gly87, NS3-Glu88, NS3-Trp89, NS3-Glu91, NS3-Thr118, NS3-Thr120, NS3-Val147, NS3-Leu149, NS3-Asn152, NS3-Val155, NS3-Ala164, NS3-Ile165 and NS3-Asn167 [12] Furthermore, during replication, the DENV RdRp plays a pivotal role in synthesizing both

positive- and negative-stranded RNA [18 - 20]. It presents an appealing possibility for the development of novel antiviral medications because it has no mammalian counterpart and its sequence is conserved across all four serotypes with approximately 65% homology [21, 22].

While coming across research in the field of dengue, the most putative target was found to be dengue protease. To some extent, very few research groups have targeted RdRp, while we also came across a few E protein inhibitors. This book chapter aims to accommodate the progress made in the last 10 years while encompassing chemical entities/scaffolds reported by various researchers across the globe. This chapter outlines our efforts in this area, offering insight into potential directions for the advancement of antiviral treatments in the future and assisting in the battle against the dengue virus.

TARGETS FOR DENGUE

Several potential drug targets for the Dengue virus include:

NS2B/NS3 Protease

Inhibiting the NS2B/NS3 protease can disrupt viral polyprotein processing, preventing viral replication.

NS5 Protein

Targeting the NS5 containing MTase and RdRp domain can hinder the viral replication process.

E protein

Blocking host cell receptors, such as dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), can prevent viral entry into host cells

Other Non-structural Proteins

Various viral proteins involved in RNA synthesis, such as NS1,NS2B, NS4A, and NS4B are potential targets for antiviral intervention.

Protease

The dengue virus protease (Fig. 1) is a crucial enzyme involved in the replication process of DENV. This enzyme is responsible for cleaving the viral polyproteins, a necessary step in the formation of mature and infectious virions. The DENV protease is a serine protease that relies on a serine residue in its active site for its

CHAPTER 7

Malaria: State of the Art and New Perspectives

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Abstract: Malaria continues to endanger over half of the world's population, claiming 1-2 million lives each year. The main causative agents are *Plasmodium falciparum* (Pf) and Plasmodium vivax (Pv). Both cause widespread mortality and morbidity, and they impose a significant socioeconomic burden, particularly in poor nations. The emergence and dissemination of resistance to currently available antimalarial medications have generated a crisis scenario among experts. Unfortunately, artemisinin-resistant parasitic strains have been observed in Southeast Asia. Several approaches that include, combination therapy, exploitation of natural products, drug resistance reversers, covalent bitherapy, identification of novel targets, and development of vaccines, have been explored to surmount the issue of drug resistance. In the absence of effective vaccinations, the disease has been mostly managed with chemotherapy and chemoprophylaxis. Over the past year, breakthroughs in technology such as molecular evolutionary and population genetic techniques have exposed the malaria parasite genome, considerably contributing to the understanding of the targets and dissemination of parasite treatment resistance. The rapid discovery and molecular characterization of novel targets have paved the path for the development of new antimalarial medicines. To find chemically varied, efficacious medications, new pharmacophores, and validated targets are necessary. Functional genomics and structure-based drug design can help in the search for novel potential targets and therapeutic candidates. Once the putative targets are validated, which are capable of providing effective and safe drugs, they can be used for screening compounds to discover new leads, which, successively, can be utilized in the lead optimization process. Combinatorial chemistry, along with as well as high throughput screening technologies, is used to generate huge numbers of structurally diverse compounds. This chapter discusses possible chemotherapeutic targets for antimalarial therapy and their locations inside the malaria parasite, as well as new lead compounds for rationally designing new antimalarial medicines.

Keywords: Apicoplast, Aquaporins, CDKs, Medicinal chemistry, NPPs, Plasmodium vivax, Plasmodium falciparum.

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INTRODUCTION

Malaria still poses a threat to about half of the world's population, which claims 1-2 million lives annually. Among the four species of malaria parasite, two strains, *Plasmodium falciparum* (Pf) and Plasmodium vivax, are the predominant causal agents. They have developed resistance to nearly all existing antimalarial drugs [1, 2]. Both are major socioeconomic burdens, particularly for emerging nations, and are to blame for the high rates of death and morbidity. Researchers are now facing a serious predicament as a result of the formation and spread of resistance to currently available antimalarial medications. Unfortunately, in recent reports, artemisinins-resistant parasitic strains have been observed in Southeast Asia [3 - 5]. Moreover, no viable therapeutic candidate for malaria has been made available for clinical usage in the pipeline.

To overcome the problem of drug resistance, several strategies have been investigated, including combination therapy, natural products, drug resistance reversers, covalent biotherapy, identification of novel targets, and vaccine development [6]. All these strategies need to be specifically focused on lowering the price of the drug discovery process so that developing nations can benefit to the fullest.

Chemotherapy and chemoprophylaxis have been the mainstays of illness management in the absence of viable vaccinations. Over the past year, advancements in technology such as molecular evolutionary and population genetic techniques have exposed the malaria parasite genome, which has considerably contributed to understanding the targets and dissemination of parasite treatment resistance [7].

The rapid identification and molecular characterisation of novel targets have offered a new path for developing new antimalarial medicines. Additionally, the advent of high throughput screening and combinatorial chemistry coupled with bioinformatics has revolutionized the drug discovery process [8]. To design new antimalarial medications, this book chapter focuses on prospective chemotherapeutic targets for antimalarial therapy and their locations inside the malaria parasite. It also emphasizes the ongoing development of the targets and particular inhibitors.

Chemotherapeutic Targets for Antimalarial Therapy

The primary metabolic distinctions between the malaria parasite and its host form the basis of the current arsenal of antimalarial medications. Antimalarial drug design has identified key processes of *P. falciparum* as targets, including heme detoxification, fatty acid biosynthesis, nucleic acid metabolism, and oxidative

stress. Although most of them have been used for decades, their usage is currently limited due to the advent of resistance [9]. The literature claims that no antimalarial medication is now in use that was created to inhibit a recognized therapeutic target in a completely logical manner. Rather, anti-malarial potency has always been found by investigations using *in vitro* or animal models. As a result, the target of action for most current medicines within the malaria parasite is unknown [10]. Furthermore, for most medications, the processes behind the establishment of resistance are poorly known. Genetic, molecular, and pharmacological approaches have shown that several targets of older treatments are resistant due to changes in their key transporters or enzymes [11]. Also, the list of drug resistance does not exclude artemisinin and its derivatives, which are the most effective anti-malarial drugs. Artemisinins are potent inhibitors of phosphatidylinositol-3-kinase (PfPI3K). P. falciparum Kelch13 (PfKelch13) contains a significant marker of artemisinin resistance, the C580Y mutation, which has been linked to elevated PfPI3K in clinically resistant strains [12]. Thus, medication resistance resulting from mutations is a significant concern and the identification of new targets is mandatory to design new drugs against resistant malarial parasites.

The Need for New Target for Anti-malarial Drugs

The emergence and dissemination of resistance to conventional antimalarial medications due to genetic changes have resulted in the development of novel antimalarial compounds with distinct mechanisms of action. However, malaria elimination necessitates a comprehensive strategy that includes new and old medications, vaccines, vector control, and public health control issues [13]. The most innovative technique is most likely to identify novel targets and then produce compounds that act on these targets. This can be accomplished in two ways: by focusing on validated targets to find novel chemical entities, or by investigating the malaria parasite's vital metabolic pathways to find new possible targets. The search for new potential targets becomes crucial because, the dearth of structural diversity in the armory of antimalarial drugs, except artemisinin-type compounds, led to considerable cross-resistance between drugs with existing targets.

Consequently, the hunt for new potential targets has become imperative. Furthermore, to find safe and effective compounds, new targets need to be carefully verified [14, 15]. To combat the problem of resistance, new target discovery and the search for inhibitors tailored to these targets are currently widely employed strategies. Therefore, screening of inhibitors specific for new target proteins of the malaria parasite has been utilized to identify therapeutic targets and is now being studied [16].

On the Trail of Zika Virus: Understanding its Druggable Targets

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Abstract: The Zika virus (ZIKV) is responsible for the infection of millions of people, causing mild flu-like symptoms and even severe symptoms, which are related to the nervous system, including Guillain-Barré syndrome and microcephaly. Nonetheless, it still remains with no antiviral treatments or effective vaccine to prevent it. Thus, several efforts have been addressed to discover a medicinal alternative to disrupt the ZIKV infection worldwide. Notwithstanding these facts, this chapter will focus on the main antiviral targets associated with ZIKV and their inhibitors identified so far. In principle, viral and host factors related to the ZIKV life cycle could be targeted for the development of novel drugs. In fact, there are some macromolecular targets that could be further investigated aiming to develop anti-ZIKV drugs, some of which remain still a few explored. In summary, this chapter encourages the exploration of new opportunities for medicinal chemists to design novel anti-ZIKV agents, providing a solid hope for future treatments against this disease.

Keywords: Flavivirus, Non-structural proteins, Structural proteins, ZIKV.

INTRODUCTION

ZIKV belongs to the *Flaviviridae* family, which also includes other pathogens with a significant impact on human health, such as Yellow Fever virus (YFV), Dengue virus (DENV), and West Nile virus (WNV), which are transmitted by infected mosquitoes (arthropod-borne viruses). ZIKV genome is composed of a single -strand positive-sense RNA (ssRNA(+)) that encodes a single open-reading frame (ORF). It is flanked by 5'-untranslate region (UTR) and 3'-structural proteins (named capsid (C), pre-membrane (prM), end envelope (E)), which are involved in the assembly of new viral particles; whereas seven non-structural proteins (named NS1, NS2A, NSB, NS3, NS4A, NS4B, and NS5) responsible for

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viral genome replication by processing the polyprotein; particle assembly; and evasion of innate antiviral response [1]. Seven G-rich sequences have been found in the coding regions for prM, E, NS1 (two G-rich sequences, NS1A and NS1B), NS3, and NS5 (two G-rich sequences, NS5A and NS5B) proteins, and one G-rich sequence has been also found at the 3'-end of the ZIKV genome.

These G-rich sequences may fold to form the RNA G-quadruplex structures of two G-tetrads under physiological conditions. ZIKV RNA G-quadruplex sequences have been found to play important biological roles in virus entry, transcription, translation, and genome stability [2 - 6]. Regarding the ZIKVrelated epidemiologic aspects, it was first reported in 1947 as a mild and obscure human pathogen, which was isolated from febrile sentinel rhesus monkeys in Uganda. ZIKV has emerged as a major threat to public health, being an arthropod-borne virus with rapid dissemination in regions with tropical and subtropical climates [7, 8]. Still, it is genotypically classified into three strains, being East African, West African, and Asian lineages. Still, the Asian lineage is further classified by geographical origin, named Micronesian, Cambodian, and Malaysian [2, 9]. Generally, the ZIKV infection is asymptomatic, otherwise, it causes symptoms similar to the common flu, or mild symptoms (known as Zika fever). On the other hand, some cases can evolve into neurological complications due to ZIKV tropism, manifesting Guillain-Barré syndrome in adults, whereas microcephaly in fetuses and/or newborns [7, 10, 11]. Currently, there are no drugs or vaccines to treat or even prevent ZIKV infection, respectively. However, research works have described several drug-like compounds targeting ZIKV, such as chelerythrine chloride [12], chalcones [13], lycorine [14], gemcitabine, saliphenylhamide, and obatoclax [15]. Throughout this chapter, the reader will be guided into discussions involving the main ZIKV targets associated with the development of antiviral drugs within the last five years. Furthermore, advances in the discovery of new classes of active molecules against ZIKV will be covered, as well.

NON-STRUCTURAL PROTEINS OF ZIKA VIRUS AND THEIR **INHIBITORS**

Non-Structural Protein 1

Non-Structural Protein 1 (NS1). The NS1 is a highly conserved glycoprotein that presents several functions in Flaviviruses and is found in elevated concentrations during acute infection by ZIKV. It is also related to ZIKV tropism, proinflammatory and immunogenic processes, as well as, it exerts pathogenic effects on vascular permeability tissues [16]. The NS1 similarity index among flaviviruses is very high and among ZIKV strains the similarity is greater than 90% [17]. Its general role includes immune invasion, interactions with ribosomal subunits during the viral replication complex, RNA replication, and when produced extracellularly, it interacts with host immunological factors to improve immune evasion and pathogenesis [18]. In the extracellular environment, NS1 forms multimeric structures that can dimerize, in which trimers of dimers (hexamers) can be formed *via* hydrophobic interactions; being potential biomarkers in diagnosis [19, 20].

The mature form of NS1 presents a dimer of identical monomeric subunits. The structurally conserved monomer has three domains, being a small N-terminal β hairpin (residues 1–29), a "wing" domain (residues 30–180), and, the largest, Cterminal "β-ladder" domain (residues 181–352) [21, 22] (Fig. 1). A threestranded β-sheet is formed by segments comprising the wing and β-ladder domains, involving residues 30–37 and 152–180 [16, 21]. As aforementioned, the intracellular dimer form of NS1 plays a role in genome replication, while the secreted hexamer one plays a role in immune evasion [17]. The dimerized form of NS1 is constituted by a β-hairpin (swapped domain), which is composed of the Nterminus of each monomer, consisting of two β-strands, from which extends a wing-ladder domain and the β-ladder [19]. Extracellularly, NS1 dimers are secreted as a proteolipid particle forming a putative barrel-shaped hexameric coat [16]. Within the hexamer, the main dimerization characteristic is attributed to the β-ladder domain, which presents a significant number of contact regions at the dimeric interface. Then, the virulence can be reduced by eliminating dimer formation, which can be done through point mutations in the β -ladder domain. Comparing the crystal structures of Flavivirus β-ladder dimers with the internal domain of the NS1 dimer, both maintain highly-conversed structural aspects. DNA synthesis depends on the dimeric form of NS1, which binds to the endoplasmic reticulum membrane after being formed. Structurally, this domain consists of 10 β-strands arranged like a ladder rung and connected through short loops or turns, except a 53-long residue (composed of 219–272 residues), called as "spaghetti loop", located between \(\beta 13 \) and \(\beta 14 \) strands. The presence of the spaghetti loop gives rise to two different surfaces: the membrane side of the continuous \(\beta\)-sheet and the luminal side of the irregular loop surface [19].

A recent study demonstrated that there is an association between secreted NS1 and High-Density Lipoprotein (HDL). HDL binds to SR-B1 (scavenger receptor class B type 1), which functions as a receptor and can trigger proinflammatory responses in cultured cells. Evidence have shown that sNS1 probably does not exist as hexamers, either in the blood of infected patients or supernatants, but rather is found mainly in the dimeric form complexed with HDL. This fact is justified due to the initial evidence of sNS1 as hexameric structures, which were found in less than 3.5% of the particles, with the tetrameric form being the main

Mycobacterium tuberculosis: Recent Advances in Drug Discovery and Targets – A SAR-Based Approach

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Abstract: Tuberculosis (TB) is a highly contagious and potentially life-threatening infectious disease caused by the bacterium Mycobacterium tuberculosis (MTB). Despite significant progress in medical science, TB remains a global health concern, affecting millions of people worldwide. Efforts to combat this disease have led to the development of various treatment regimens, and research in TB drug discovery continues to be a crucial area of study. Identifying the new drug targets is essential in the fight against MDR TB, TDR TB, and XDR TB. Owing to the current situation, the key aspect of modern drug discovery is based on the concept of structural information along with functional activity relationships to combat tuberculosis disease. The structure-activity relationship (SAR) involves understanding the relationship between a compound's chemical structure and its biological activity. The line of treatment of MTB addresses multiple targets, such as various ribosomal targets, including the exit tunnel of the 50S subunit of ribosome, DNA gyrase (GyrB), Inosine-5'-monophosphate dehydrogenase (IMPD), Adenosine kinases (AK), Chorismate mutase (CM), and many other targets as well. This chapter provides a complete insight into the existing medications versus newly developed drug molecules based on SAR, their protein targets, modes of action, and mechanisms of resistance. By comprehending the intricate relationship between the chemical structure of drugs and their biological activity, it is possible to develop more effective therapies to combat this deadly disease.

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Keywords: Drugs, *Mycobacterium tuberculosis*, Protein targets, Resistance mechanism, Structural activity relationship.

INTRODUCTION

Mycobacterium tuberculosis (MTB) is a pathogen that causes tuberculosis (TB), a major health problem of the world. According to the reports of WHO, 10.6 million humans had been diagnosed with TB in 2021 globally, up by 4.5% from 2020, while 1.6 million patients died because of the illness. Out of these cases, approximately 450000 cases were those of multidrug-resistant TB, which was 3.1% more in comparison to 2020 (437,000 cases). India, along with seven other countries, constituted over two-thirds of the total tuberculosis (TB) patient count (Fig. 1).

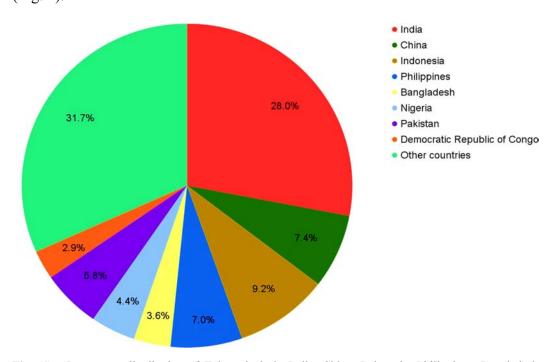


Fig. (1). Percentage distribution of Tuberculosis in India, China, Indonesia, Philippines, Bangladesh, Nigeria, Pakistan and Democratic Republic of Congo.

WHO aims to reduce cases by 80% and deaths by 90% by 2030. World TB Day 2023 theme is "Yes! We can end TB!" [1]. Discussing major characteristics of MTB, they are a human-specific, non-motile, rod-shaped, acid-fast bacterium with a slow growth rate [2]. The cell wall of MTB is a pivotal element in its pathogenesis and is involved in interactions with the host immune system and antimicrobial agents. Understanding the composition, architecture, and function of

the MTB cell wall has been the subject of intense research due to its direct relevance to tuberculosis pathogenesis and drug resistance. A distinctive hallmark of the MTB cell wall is its high lipid content, notably mycolic acids, which comprise long-chain α-alkyl and β-hydroxy fatty acids, that form a unique, lipidrich layer. This layer contributes significantly to the impermeability of the cell wall and its resilience against environmental stresses. Recent research has highlighted the involvement of mycolic acids in modulating the host cell responses and evading immune detection, thus playing a critical role in the establishment and persistence of MTB infection. Additionally, the MTB cell wall contains other essential components such as, teichoic acid arabinogalactan, LAMlipoarabinomannan, lipopolysaccharide membrane-associated protein, lipoteichoic acid, outer membrane; peptidoglycan, plasma membrane, lipoprotein, and GLglycolipid (Fig. 2) [3 - 5].

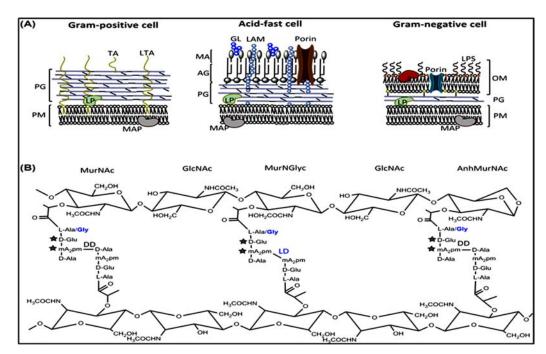


Fig. (2). (A) Comparison between various types of cell walls, here, TA-teichoic acid, AG - arabinogalactan, LAM-lipoarabinomannan, LPS-lipopolysaccharide, MAP-membrane-associated protein, LTA-lipoteichoic acid, MA-mycolic acid, OM, outer membrane; PG- peptidoglycan, PM, plasma membrane, LP-lipoprotein, GL-glycolipid (B) The distinctive characteristics of mycobacterial cells, indicated in blue, are revealed by the PG structure. The stars show remnants that go through amidation [5].

Indeed, emerging research has uncovered the significance of proteins embedded within the cell wall of MTB. These proteins, often referred to as "molecular machines," are essential for various critical processes, including nutrient uptake,

Drug Discovery in *Fasciola hepatica*: Few Steps in the Last Ten Years

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Abstract: Fascioliasis, caused by trematode parasites of the *Fasciola spp.* remains a significant global health concern, affecting both humans and livestock. This neglected tropical disease, along with other food-borne trematodes, impacts over 10% of the world's population, resulting in substantial economic losses exceeding \$3 billion annually in the livestock industry. Since no vaccine has been developed so far, current disease control relies mainly on drugs, particularly triclabendazole, which although effective, faces challenges due to reported resistance in many regions. With Fasciola hepatica being the common fluke, its wide distribution and intricate life cycle, emphasize the importance of understanding parasite epidemiology and biology and addressing drug resistance. However, few efforts have been pursued in the last decade to develop new drugs against fascioliasis. There are different approaches to drug discovery. Screening methodologies may target essential parasite proteins through in silico or in vitro studies, employing protein docking and molecular dynamic simulations. This enables the rapid identification of potential drug candidates for subsequent in vitro or in vivo testing. Alternatively, phenotypic screenings with cultured parasites offer a broader understanding of drug efficacy but present challenges in terms of automation and the unknown mode of action of the drug candidates. Also, drug repurposing has emerged as a promising strategy in recent years. This approach accelerates the drug development process, addressing the lengthy timelines typically associated with bringing novel drugs to the market. This chapter provides a comprehensive overview of drug discovery efforts in the last ten years for fascioliasis treatment. In-depth discussions on drugs targeting specific F. hepatica molecular components are presented followed by phenotypic screenings with synthetic and natural compounds. The chapter concludes with a review of some scarce initiatives in drug repurposing, providing an overview of the various strategies employed to address drug discovery in fascioliasis.

Keywords: Anthelmintic, Cathepsin L, Drug development, Drug repurposing, *Fasciola gigantica*, *Fasciola hepatica*, Fascioliasis, Fasciolicide activity, Flukicidal activity, Foodborne trematode disease.

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INTRODUCTION

The discovery of new anthelmintics faces challenges that are unique to antiparasitic drug discovery. Less than five new classes of anthelmintics have been approved for animal use in the 21st century [1]. Fascioliasis, caused by trematodes parasites of the Fasciola genus, poses significant challenges for both human health and the livestock industry. The liver flukes, together with lung flukes and intestinal flukes, form a group known as the Food-Borne Trematodes, neglected tropical diseases affecting more than 10% of the world population [2]. Among these, Fasciola hepatica is known as the common fluke, it has a worldwide distribution, affecting a variety of hosts including ruminants, horses, wild animals like deer, rabbits, hares, and humans, resulting in substantial losses in production and clinical disease, with roughly estimated costs exceeding \$3 billion annually for the global livestock industry [3]. It not only impacts animals but also represents a significant public health problem, especially in regions of South America, Asia, and Africa, where millions of people are estimated to be at risk of infection [2, 4]. Thus, the disease is not anymore considered merely as a secondary zoonosis but is also recognized as an important human parasitic disease.

The indirect life cycle of F. hepatica, involving lymnaeid snails as intermediate hosts, underscores the importance of understanding and addressing epidemiology and drug resistance. The parasite's ability to modulate the host's immune system and affect susceptibility and diagnosis of other diseases, such as bovine tuberculosis, adds complexity to the landscape [3]. Disease control relies primarily on the use of drugs, especially triclabendazole (TCBZ), which is effective against multiple stages of the parasite. However, resistance to this and other drugs reported in many countries has intensified the search for alternative control strategies [5]. Efforts to overcome TCBZ resistance led to the synthesis of TCBZ bioisosteres, among these, one of the most relevant is compound alpha (5chloro-2-(methylthio)-6-(1-naphthyloxy)-1H-benzimidazole), whose fasciolicide activity has been demonstrated in vivo and is currently undergoing efficacy and safety studies, apparently being an alternative with reduced environmental contamination to control fascioliasis [6]. However, the urgency of developing new drugs and control measures is accentuated by growing concerns about flukicide resistance, as well as drug residues in meat and milk, leading to restrictions in use and longer withdrawal periods [3, 7].

DIFFERENT APPROACHES TO DRUG DISCOVERY IN F. HEPATICA

Drug screening approaches against the liver fluke may be directed to an isolated target, usually an enzyme or another essential parasite protein, or be performed on in vitro cultured flukes. The former studies have the advantage of being rapidly executed, they can be first done in silico through protein docking and molecular dynamic simulations, to narrow down the number of molecules to be then tested in an in vitro assay and allow the performance of high-throughput studies. This also, favors the optimization of the structure-activity relationship over the target. However, translation into in vitro flukicide activity is not always straightforward. In contrast, phenotypic screenings with cultured parasites have the advantage of overcoming this difficulty but are not easily automatized, and usually, the mode of action of the active compounds is unknown, which hinders drug structure optimization to eliminate unwanted effects without compromising its biological potency. Another strategy to overcome resistance is drug repurposing (testing of old drugs for new applications), which has become an attractive alternative in recent years since it shortens the long time required to bring novel drugs to the market.

This chapter will summarize the drug discovery efforts done over the last 10 years for fascioliasis treatment. First, the later findings about drugs that act over a specific *F. hepatica* molecular target and their structure-activity relationships are discussed in detail. Then, phenotypic screenings performed with different synthetic and natural compounds are presented. In the end, some efforts towards drug repurposing are depicted.

PROTEIN TARGETS FOR DRUG DEVELOPMENT

Cathepsin Ls

Cathepsin Ls are key protease enzymes secreted by the liver fluke Fasciola hepatica, which play a crucial role in the parasitic life cycle and pathogenesis. Cathepsins are integral to various physiological processes, including tissue invasion, immune evasion, and nutrient acquisition within the host organism [8, 9], which make them interesting molecular targets. FhCL1 and FhCL3 are the main enzymes secreted by the adult and newly excysted juvenile stages, respectively [10]. Cathepsin Ls are compact globular proteins consisting of an Nterminal prodomain and a catalytic domain connected by a flexible linker. The catalytic domain contains the active site, characterized by the triad Cys-His-Asn, which facilitates the enzyme's proteolytic activity. X-ray crystallography studies have provided high-resolution insights into the three-dimensional architecture of cathepsin L, highlighting its substrate-binding pockets and the structural basis for substrate specificity [11, 12]. Understanding the tridimensional structure of cathepsin L is pivotal for designing targeted inhibitors and developing therapeutic strategies. Both in silico and in vitro studies have been performed since enzyme activity can be easily measured by monitoring the cleavage of a fluorescent short

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