HDAC Inhibitors as Antiparasitic Agents

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Ongoing therapy for human parasite infections has a few known drugs but with serious side effects and the problem of drug resistance, impelling us to discover novel drug candidates with newer mechanisms of action. Universally, this has boosted the research in the design and development of novel medicinal agents as antiparasitic drugs with a novel mode of action. Histone deacetylase inhibitors (HDACis) are used in a vast variety of diseases due to their anti-inflammatory properties. Drug repurposing strategies have already approved HDACis as cancer therapeutics and are now under investigation for many parasitic infections. Along with the expression of the gene, histone deacetylase (HDAC) enzymes also act as a slice of great multi-subunit complexes, targeting many non-histones, changing systemic and cellular levels signaling, and producing different cell-based specified effects. Zinc (Zn^{2+})- and nicotinamide adenine dinucleotide (NAD^{+})-dependent HDACs of parasites play pivotal roles in the alteration of gene expression of parasites. Some of them are already known to be responsible for the survival of several parasites under odd circumstances; thus, targeting them for therapeutic interventions will be novel for potential antiparasitic targets.

histone deacetylase | parasite | hydroxamate | sirtuin | cyclictetrapeptide

1. Introduction

Parasitic disease globally affects a large number of humans and makes up one of the most concerning health problems, with notable morbidity and mortality. It is more prevalent in underdeveloped regions and developing countries. In 2020, 241 million cases and 627,000 deaths were reported worldwide due to malaria [1]. Similarly, in 2015, there were about 214 million clinical patients of malaria, with a mortality of 438,000 [2]. Apart from this disease, other parasitic diseases such as Leishmaniasis, Schistosomiasis, Lymphatic filariasis, and Trypanosomiasis cause notable health burdens. About 250 million patients have been infected with *Leishmania* and *Schistosoma* parasite infection [1][3][4]. Every year, the death toll resulting from parasitic diseases is increasing. Some research studies have suggested that these parasites may impair efficient immune responses, increasing the morbidity and mortality of COVID-19 patients. Alternatively, it has also been found that no discernible variations in disease severity were observed between co-infected individuals and naïve COVID-19 cases [5].

RTS,S/AS01 (Mosquirix) and R21/Matrix-M are some of the recently approved vaccines for malaria by the WHO. However, the unavailability of vaccines for various human parasitic diseases makes the problem more urgent. Further, prevention and treatment are also sometimes difficult because of the side effects and developed drug resistance against the currently available therapeutics [6][7][8][9][10]. Thus, identifying novel druggable targets and chemotherapies with newer modes of action is of dire need. Small molecules that react with histones are effective

for post-translational modifications of these epigenetic regulatory proteins and are gaining interest as a chemical arsenal as well as probable new leads that could suppress the parasite growth mechanisms [11][12][13].

Clinically, repurposing of the approved drugs is intriguing due to its efficiency in identifying novel applications. This approach expedites market availability and reduces economic costs compared to de novo drug discovery for parasitic diseases in tropical regions [14]. Based upon this approach, drugs approved as histone deacetylase inhibitors (HDACis) for the treatment of cancer are now being repurposed to target various parasitic diseases. However, the repurposing, especially with HDACis, faces hurdles. Variations in HDACis pharmacological profiles between diseases complicate the translation of efficacy from one condition to another. Regulatory complexities hinder their smooth transition, demanding robust evidence for safety and efficacy in the new therapeutic context. Ensuring safety necessitates understanding long-term effects, potential side effects, and interactions with existing treatments, which is also challenging. The absence of standardized drug testing methods adds complexity to evaluating HDAC inhibitors' effectiveness in novel indications.

Histone and many non-histone proteins are being processed by HDACs that are occasionally called lysine deacetylases (KDACs). Histone/lysine deacetylases remove the acetyl group from histones and other associated proteins, while acetyltransferases append acetyl groups to such proteins. Similarly, the corresponding demethylases and methyltransferases eliminate and attach methyl groups to lysine side chains of proteins, respectively [15]. These post-translational alterations in the eukaryotes synchronize the regulation of transcription, cell cycle, and apoptosis [16][17][18][19]. Some human disorders, like cancers, express an altered expression of epigenetic regulatory proteins/enzymes and could be druggable targets [15][20][21]. HDACis are being investigated for their potential as antiparasitic drugs based on their mechanism of action in cancer, which include cell differentiation, cell cycle arrest, apoptosis induction, and immune system regulation. Studies have demonstrated that HDACis can cause parasites to undergo apoptosis, halt their growth, and alter the host immune system's reaction to parasitic diseases. Furthermore, it has been discovered that HDACis promote apoptosis and other cell-damaging processes, which may be pertinent in the context of parasite infections, in order to increase tumor cell death [22]. Similarly, several epigenetic regulatory proteins exhibited a vital role during the evolution and life cycle of parasitic pathogens, with little resemblance or remarkable dissimilarity in principle catalytic domains to human proteins, making them compelling antiparasitic drug targets [11][23][24][25][26][27]. Homologs of HDAC have been identified in most parasitic pathogens of humans. The non-identical category of HDACishave exhibited their action in some of these resistance parasites, such as *Plasmodium*, *Leishmania*, and *Schistosoma* species [11][25][26]. Several HDACis have already received approval for therapeutic applications in various cancer types, making them potential candidates for addressing parasitic diseases. Noteworthy among the approved HDACis used in the management of peripheral or cutaneous T-cell lymphoma and applied in combination therapy for multiple myeloma are Belinostat (**1**) (PXD101), Panobinostat (**2**) (LBH-589), Vorinostat (**3**) (SAHA), and Romidepsin (**4**) (FK228) [28][29][30][31] (**Figure 1**).

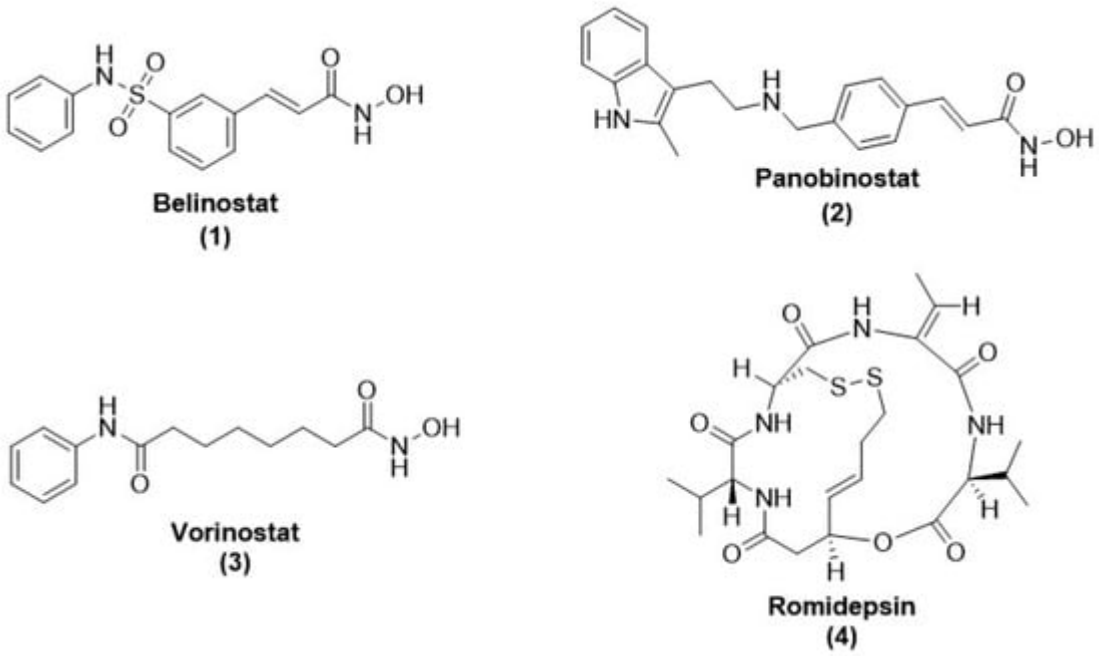

Figure 1. Chemical structure of FDA-approved drugs acting as HDAC inhibitors. These HDACis have anti-cancer properties.

2. Opportunities of HDAC Inhibitors as Antiparasitic Agent

2.1. HDAC Inhibitors as Antimalarial Agent

For decades, HDAC inhibitors have been employed as antimalarials. Apicidin (a fungal-derived HDACi) was initially identified as an effective HDACi against Apicomplexan protozoa and *Plasmodium* parasites [32]. Ever since, many modified HDACi classes have been documented as potent antimalarial agents.

2.1.1. Cyclictetrapeptide HDAC Inhibitors

Darkin-Ratray et al. observed in vitro potent activity of apicidin (**5**) against *P. falciparum*, *T. gondii* and other protozoan parasites. Hyperacetylation of histones was observed in *P. falciparum* upon treatment with apicidin. It inhibited the recombinant PfHDAC1 enzymatic activity (IC_{50} = 1 nM) [32][33]. Notable alterations were observed during the transcriptional phase of the intra-erythrocytic cycle of *P. falciparum*, with altered expression by other genes [34][35]. These findings revealed a similar effect produced by the compound as in HDACis on higher eukaryotic cells [36][37]. Apicidin caused parasitic histone protein hyperacetylation and genome-wide transcriptional alteration in the protozoan [33][34]. The derivatives of a quinolone, but not derivatives of N-substituted indole, showed their selectivity (up to ~200-fold) for *P. falciparum* versus mammalian cells at the whole-cell level [38][39][40]. In another study, a comparison was made between apicidin and a series of synthetic analogues for *T. cruzi, T. brucei*, *P. falciparum*, and *L. donovani* [41]. The cyclic tetrapeptide compound FR235222 (**6**), isolated from *Acremonium* species in the fermentation broth, showed its potential against tachyzoites of *T. gondii* and drug-sensitive and drug-resistant *P. falciparum*-infected erythrocytes with IC_{50} value of 10 nM [42] (**Figure 2**).

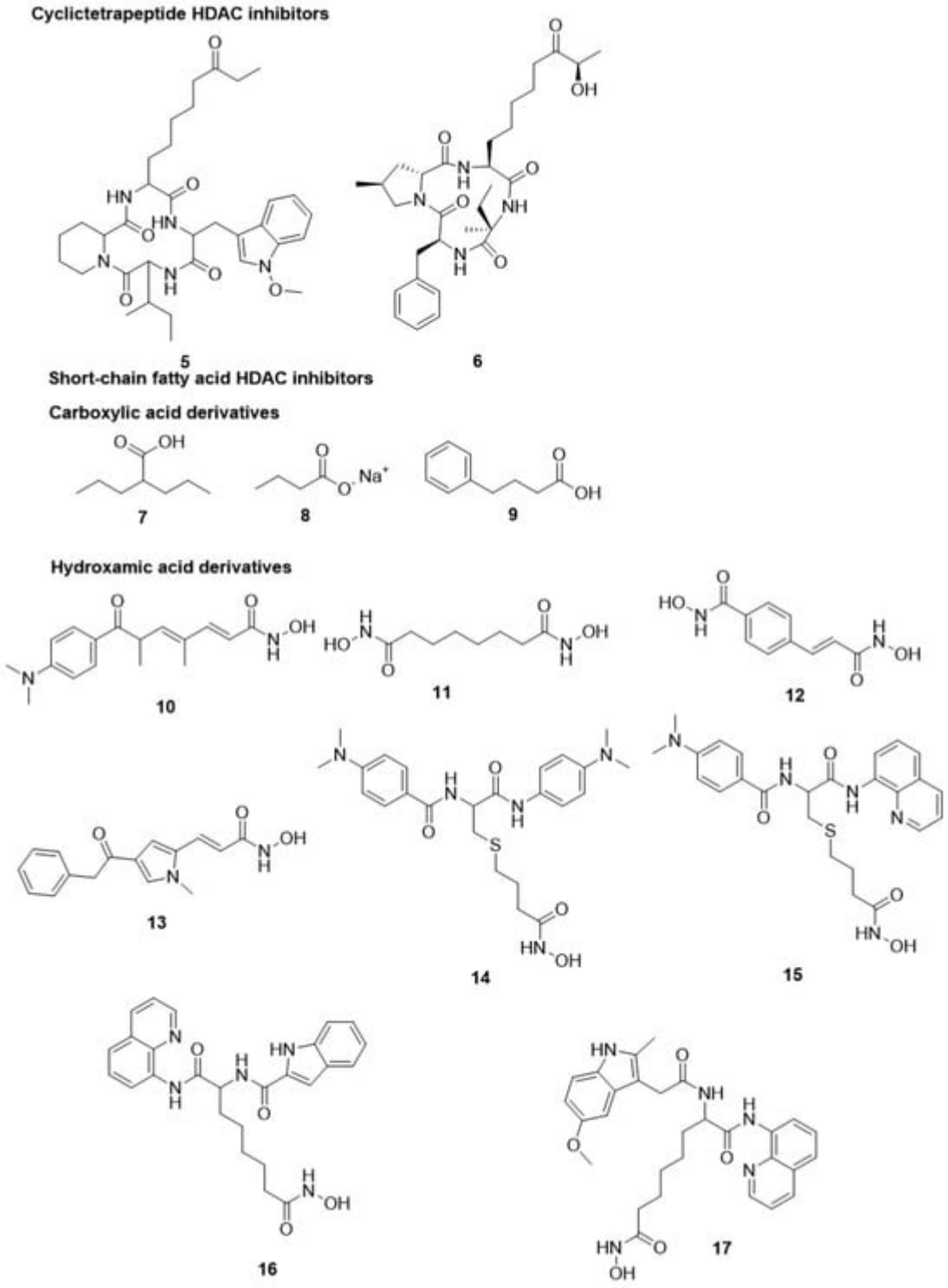

Figure 2. Chemical structure of cyclictetrapeptide and short-chain fatty acid HDAC inhibitors. Cyclictetrapiptide, carboxylic acid hydroxamic acid derivatives have shown HDAC inhibitory activity.

2.1.2. Short-Chain Fatty Acid HDAC Inhibitors

Several drugs, like valproic acid, sodium butyrate, and its derivatives, are short-chain fatty acid HDACis. These HDAC inhibitors possess weak inhibitory activity in opposition to mammalian HDACs but are also active on additional targets, making their effects tough to ascribe beyond HDAC inhibition. However, some of these

compounds have manifested clinical efficacy. Valproic acid (**7**), an antiepileptic drug, has been extensively used as a mood stabilizer and is now investigated in several clinical trials for HDAC-pertinent diseases [43]. All compounds, valproic acid, sodium butyrate (**8**), and 4-phenyl butyrate (**9**), displayed weak selectivity towards the parasite in comparison to HS69 mammalian cells and produced relatively weak activity against tachyzoites of *T. gondii*, with IC_{50} values of 1.0, 1.6, and 5.4 mM, respectively [44][45]. Similarly, valproic acid only displayed moderate activity against *P. falciparum* and *S. mansoni*. Particularly, with *S. mansoni*, an ~80% reduction in miracidia development was observed upon treatment with 50 mM valproic acid after 4 h. Nonetheless, there is a loss of viability of schistosomula up to 30% at 5 mM concentration after 7-day continued exposure [46]. Still, valproic acid has so far not been evaluated in animal models for any parasitic disease [45][46] (**Figure 2**).

2.1.3. Hydroxamate-Based HDAC Inhibitors

Several natural and modified HDACis for class I/II, such as trichostatin A (TSA, **10**), vorinostat or suberoylanilide hydroxamic acid (SAHA, **3**), suberoyl bis-hydroxamate (SBHA, **11**), MW2796 (**12**), and aroyl-pyrrolyl hydroxyamide (APHAs, **13**), have been considered for their antimalarial potential [47]. These compounds displayed inhibitory potential against *P. falciparum* but exhibited a lack of selectivity affecting the mammalian host cells. However, compound **11** showed effective sensitivity for the parasite compared to cytotoxicity against mammals [11][25][33][48][49][50][51].

TSA hampered PfHDAC1 activity, with an IC_{50} value of 0.6 nM in parasites. It is more potent than SAHA against *P. falciparum*, with IC_{50} values of 0.008–0.120 µM compared to SAHA 0.025–2.2 µM. However, SAHA showed improvement in the selectivity up to 200-fold toward the parasite [11][25][49]. In contrast, compound **11** is less potent with IC_{50} 0.8–2.3 µM but showed higher selectivity towards the parasite than compound **3**. Further, this comparative study was conducted in *P. berghei*-infected BALB/c mice; the administration of compound **11** at an i.p. dose of 200 mg/kg twice a day for 3 days showed significant inhibition of peripheral parasitemia, indicating a cytostatic effect, but the efficacy was not observed in the mice [49]. The early report about compound **11** suggested that hydroxamate-based HDACis would probably be powerful antimalarial agents [11][25][51]. Hence, encouraged by such outcomes, various HDACis displayed in vitro activity with better selectivity against *P. falciparum* than compounds **3** and **11**.

Over the years, the screening of zinc-binding hydroxamic acid compounds revealed varying levels of inhibition of HDACs. These structural patterns resulted in the identification of extensive pharmacophoric groups binding to other important sites for HDACs. The CAP group acts as an enzyme surface identification moiety of protein and binds at the catalytic tunnel entrance. The linker region connects the CAP with the zinc-binding group site. This site is an expandable polar connection unit (CU) that lies between the CAP protein and the linker [11][25][48][52] (**Figure 2**).

Some L-cysteine-based compounds with thioether linker regions, such as compound **14** and 2-aminobutyric-acid-based compound **15** (2-ASA-9), displayed indistinguishable in vitro antiparasitic activity. Compound **14** displayed an IC_{50} value of 48 nM against chloroquine-resistant (Dd2), and compound **15** showed IC_{50} values of 71 and 19 nM against both Dd2 and chloroquine-sensitive (3D7) strains, respectively, of *P. falciparum*. Compound **15**

displayed improved selectivity over the mammalian cells. Among them, compounds **15** and **11** produced a noticeable hyperacetylation of histones in *P. falciparum*, which led to the inhibition of the growth of *P. falciparum* in erythrocytes at early and later stages in the parasite life cycle [53]. One reported study revealed that compounds **10**, **5**, and **15** were explored for their gene expression effects, indicating genome-based alteration of transcription in a range of 2–21% following HDAC inhibition in *P. falciparum*. However, these three inhibitors overall displayed dissimilar effects on gene expression profile. However, tubulin II was found to be one of the sets of genes that were upregulated after treatment with three HDACis. Hence, they could be recognized as markers of transcription in *P. falciparum* induced by structurally variable HDACis. Thus, this marker might be used for the development of HDACis identified as antimalarial candidates [54].

Compounds **15**, **16**, and **3** were also the earliest HDACis tested against the second most crucial human-infecting malaria parasite *P. vivax.* It causes significant morbidity linked to malaria due to relapses as the parasite remains dormant in the liver [25]. In an ex vivo study, all three hydroxamates inhibited the growth of multidrug-resistant *P. falciparum* and *P. vivax* directly isolated from infected patients [55]. Furthermore, a similar activity profile was observed for compounds **3**, **15**, and **16** against *P. falciparum* with IC_{50} values of 310, 533, and 266 nM, respectively, as well as *P. vivax* with IC_{50} values of 170, 503, and 278 nM, respectively. HDACis target multiple species of malaria parasites that infect humans; hence, they are highly favorable for further clinical studies. Several series of 2-aminosuberic acid compounds were tested, including compound **17** carrying non-steroidal anti-inflammatory drug (NSAID) components near CAP against *P. falciparum*, for their inhibitory potential. Compound **17** showed the utmost potential against *P. falciparum*, with an IC_{50} value of 0.013 µM, but the selectivity towards the parasite compared to compound **15** did not prevail [56].

Patel et al. performed a high-throughput assay to study the antimalarial efficacy of approximately 2000 HDACis obtained from the compound library. The library was characterized by a moiety of acyl hydrazone as CU and with diverse moieties for CAP protein and zinc-binding group along with the hydrophobic linker length such as 4–6 methylene units [57]. The study revealed that numerous compounds strongly inhibited the growth of *P. falciparum* and also hampered recombinant PfHDAC1 enzymatic activity. Among them, seventeen derivatives displayed a low range of nanomolar antiparasitic activity for acetylation of histone along with minimal perturbation of human myeloma MM1S cells as an indicator of selectivity [33]. Within this series, the selective inhibition of *P. falciparum* growth was highly enhanced by the existence of ortho-substituents, such as bromine and hydroxyl, in the aromatic group of CAP protein along with the presence of metal chelator or hydroxamic acid and five methylene units as a linker (compound **18**) [33]. Another study by Kozikowski et al. on two series of suberoyl amide hydroxamates substituted moieties of triazolyl phenyl and phenyl thiazolyl as CAP protein groups [49][58]. The triazolyl phenyl-based compound **19** showed high efficacy against the multidrug-resistant strains of *P. falciparum* (C2A and C235), with IC_{50} values in a range of 0.017–0.035 µM. It was 10-fold more potent compared to its counter congeners such as chloroquine and mefloquine. Compound **19** was 23-fold highly selective for C235 over mammalian cells [58]. In a group of 50 phenyl, thiazolyl hydroxamate-based HDACi, three compounds were highly potent with IC_{50} values < 3 nM and showed 600-fold selectivity against *P. falciparum* compared to mammalian cells. Compound **20** (WR301801) was the most favorable HDACi derivative, with IC_{50} values 0.6–16 nM for several drug-resistant strains, D6, W2, C235, and C2A, of *P. falciparum*. It displayed notable inhibition of HDAC activity in nuclear

extracts of *P. falciparum* with IC_{50} ~10 nM along with a strong in situ parasitic histones hyperacetylation [49]. In another report, compound **20**, upon oral administration as monotherapy, at doses of up to 640 mg/kg demonstrated a notable suppression of parasitemia but did not rehabilitate *P. berghei*-infected mice. However, some mice, but not all mice, were rehabilitated upon treatment with compound **20** (52 mg/kg) when co-administered with a subcurative dose of chloroquine (64 mg/kg) [49]. Similarly, compound **20** on oral administration at a dose of 32 mg/kg/day for 3 days to Aotus monkeys infected with *P. falciparum* resulted in suppression of the parasite but not complete elimination [49]. Another reported study showed that compound **20** (50 mg/kg/day for 4 days) on i.p. injection with an experimental follow-up period of 6 weeks enhanced survival of infected mice infected with *P. berghei* and irreversibly downregulated the parasitemia [59]. However, the optimization of the pharmacokinetic properties of compound **20** would show advantageous results as it is quickly hydrolyzed to the corresponding inactive carboxylic acid [49]. These findings suggest the potential of HDACi in mono/combination therapy for malaria treatment [11][25][49][59]. Oyelere et al., reported a series of aryl triazolyl hydroxamate-based HDACis that were screened for their inhibitory activity against *L. donovani* promastigote stages and asexual blood stage of *P. falciparum* [60]. Several compounds displayed improved inhibitory activity and selectivity than compound **3** against D6 and W2 strains of *P. falciparum*. Although several compounds are less active against *P. falciparum*, they showed a modest potency of inhibition against *L. donovani*, with 2- to 4-fold better IC_{50} values than compound **3** and equivalent to the standard drug miltefosine, used to treat visceral Leishmaniasis. Antiparasitic activity depends on polymethylene linker length and the nature of the CAP group. The CAP moiety showed maximum activity against both parasites when 5 and 6 methylene units were present in the spacer region between the CAP and the ZBG. Compounds **21** and **22**, with a CAP protein (3′-biphenyltriazolyl moiety) and linker (6 and 5 methylene units), showed the highest selectivity and activity against *P. falciparum*. Compound **22** also showed its activity against *L. donovani* with an IC_{50} of 32 µM [60]. Based upon this concept, Oyelere et al., tested five tricyclic ketolide-based phenyltriazolyl HDACi for antimalarial and antileishmanial activities [61]. During the study, it was noticed that compound **23**, with six methylene units as the optimal linker present between the CAP and hydroxamic acid, displayed optimal antimalarial activity. Similarly, compound **24**, hydroxamic acid with nine methylene units, displayed the best antileishmanial activity, but the study does not correlate with the PfHDAC1 inhibition [61]. Particularly, compound **23** displayed IC_{50} in the range of 0.144–0.148 µM against both chloroquine-sensitive (D6) and chloroquine-resistant (W2) *P. falciparum* strains. However, the compound displayed 7 to 10-fold lesser activity than compound **3** and 10-fold high selectivity against mammalian Vero cells without antileishmanial activity. Further, compound **24** showed anti-*L. donovani* activity with an IC_{50} of 5 µM, which was 16-fold stronger than compound **3** with an IC_{50} of 81 µM [61] (**Figure 3**).

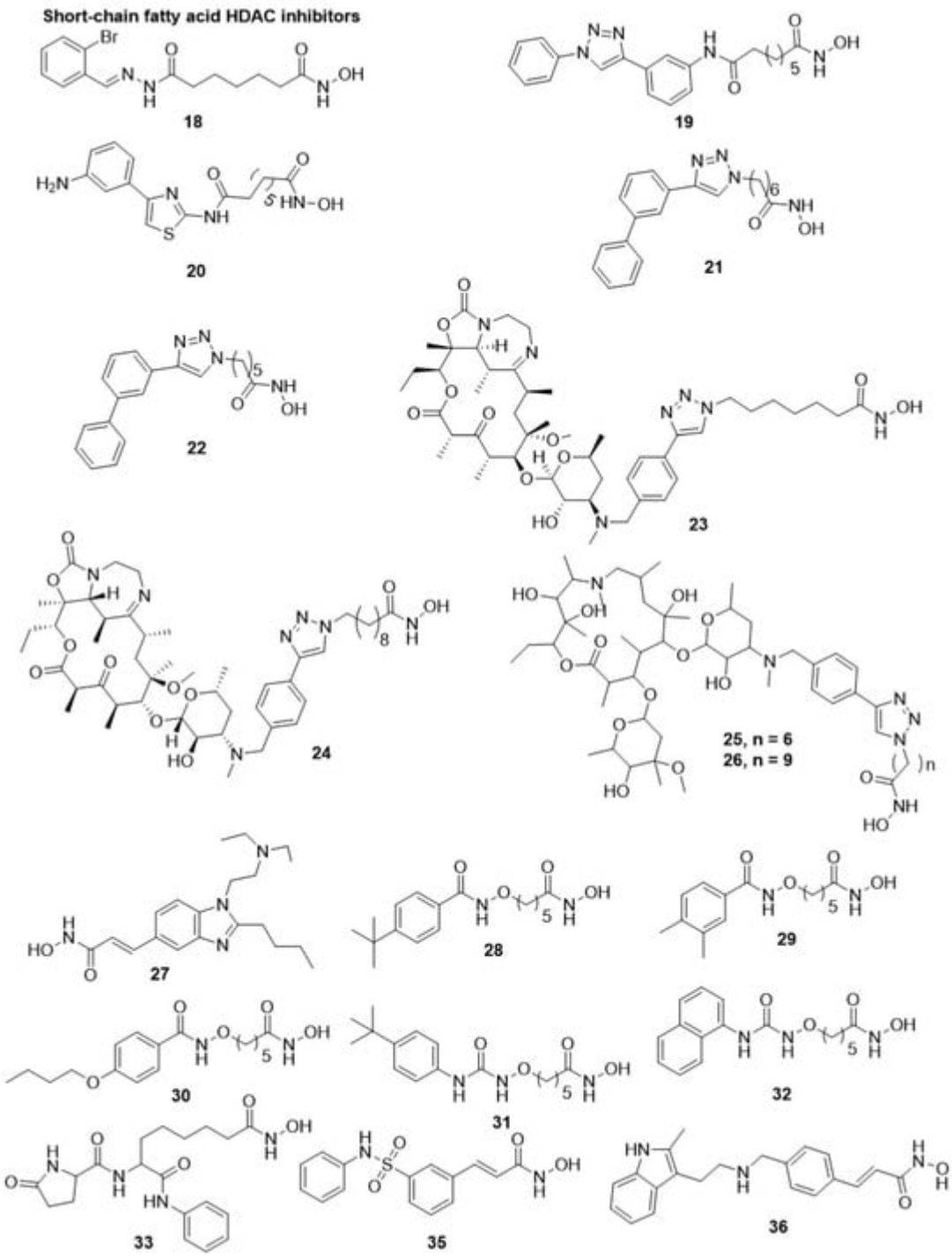

Figure 3. Chemical structure of hydroxamic acid HDAC inhibitors. The short chain fatty acid displays diverse HDAC inhibition.

Oyelere et al., further investigated and described the antimalarial and antileishmanial potential of 14 and 15-membered nonpeptide macrocyclics connected to a moiety of phenyltriazolyl, a CAP protein group, as HDACis. All compounds inhibited the proliferation of chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *P. falciparum* [62]. However, the best activity and selectivity against *P. falciparum* were attained for the six methylene units linker between CAP (triazole ring) and ZBG group (hydroxamate). Among them, compound **25**, a skeleton of 15-membered macrolide with an IC_{50} value of 29 nM against PfHDAC1 enzyme, manifested 11-fold higher

antiplasmodial activity with 14-fold enhanced selectivity over mammalian Vero cells compared to compound **3**. Surprisingly, the linker group having five to seven methylene units was lacking anti-*L. donovani* activity on the promastigote stage for both skeletons of a macrolide, whereas the compound having eight or nine methylene units as linker displayed the highest activity similar to ketolide-based HDACis, but distinct from the structure–activity relationship was noticed in aryl triazolyl hydroxamates [60].

Specifically, compound **26** with a skeleton of 14-membered macrolide and methylene units linker was 25-fold more active than compound **3** with an IC_{50} value of 81 µM, showing the best antileishmanial activity, with IC_{50} values of 3.2 and 4.7 µM against promastigote and amastigote stages of the parasite, respectively [62]. Andrews et al., identified compound **27** (pracinostat or SB939), an orally active anticancer HDACi, having antiplasmodial activities [63]. Furthermore, compound **27** strongly hampered the proliferation of the asexual-stage of *P. falciparum* in mammalian erythrocytes, with IC_{50} values in the range of 0.08–0.15 µM. Compound **27** also caused hyperacetylation on histone and non-histone proteins in the parasite and displayed selectivity over mammalian cells ranging 4 to >1250-fold over tested cell lines [63]. Additionally, an additive effect was first observed for its combination with lopinavir, a protease inhibitor, as antimalarial targeting a liver stage. Compounds **27** strongly inhibit the exo-erythrocytic stage of *P. berghei* in human HepG2hepatocytes, with an IC_{50} value of 150 nM [63]. The oral administration of compound **27** up to a dose of 100 mg/kg/day decreased peripheral parasitemia and total parasite load in the ANKA mouse model infected with *P. berghei*. However, the administration of compound **27** to mice fended off the occurrence of cerebral malaria-like symptoms up to 2–3 weeks after the intervention but did not affect hyperparasitemia in the treated animals [63]. Oyelere et al. also explored a group of 21 HDACi with Pentyloxyamide as a linker and substituted benzene ring as CAP for their effect against different stages of *Plasmodium*, such as *P. falciparum* (a sexual blood stage (3D7) cell line), *P. berghi* (tissue schizontocidal stage), and late stage of *P. falciparum* gametocyte (IV and V). All compounds exhibited antimalarial activity against *P. falciparum* asexual form with potency and selectivity enhanced as the bulkiness of alkyl/alkoxy substituents in the phenyl ring at the *para* position were increased regarding compound **28**. Three derivatives, compounds **28**, **29**, and **30**, showed their activity against all three stages of *P. falciparum* with IC_{50} values of 0.09, 0.12, and 0.17 µM, respectively. Several compounds of this series displayed better selectivity against the parasite compared to compound **3** for the asexual and exo-erythrocytic life cycle stages of the parasite [64]. Further, Oyelere et al., described the structure–activity relationship and antimalarial activity of a group of HDACi based on alkoxyurea. Some compounds actively inhibited *P. falciparum* (3D7cell line) and showed gametocytocidal activities at early and late-developmental stages with IC_{50} values ranging 1.68–6.65 µM [65][66]. Structure–activity relationship study revealed that the hydroxamic acid as a zinc-binding group and 5 methylene units as a linker were important for antiplasmodial activity N-methyl hydroxamic acid, o-hydroxyanilide and o-amino anilide were inactive as a zinc-binding group, while the short-chain analogues with linker less than 5 methylene units displayed lower potency [65]. Furthermore, the 4th position is substituted with bulky alkyl/alkoxy substituent of the phenyl ring of the CAP group. When this group is replaced with bulky aromatic rings leads to the development of more potent and effective compounds against asexual and gametocyte forms of *P. falciparum*, as denoted by the 4-tert-butyl derivative (**31**) and 1-naphthyl derivative (**32**). However, compounds **31** and **32** did not display better potency than compound **3**,

but, under the test condition, **32** displayed higher selectivity than compound **3** along with gametocidal activity in the asexual and later stages [66].

In 2015, Giannini et al., evaluated twelve analogues for their antiparasitic activity against *P. falciparum*, *T. cruzi*, *L. donovani*, *G. lamblia*, and *T. brucei*. These twelve analogues were differentiated at the α position of the anilide (CU) and meta position of the phenyl ring (CAP) and substituted with β-lactam-carboxamides and trifluoro methyl groups, respectively. Additionally, a thiol or hydroxamic acid is present as a zinc-binding group. Compound **33** of this series displayed a significant IC_{50} of 0.019 µM against *P. falciparum* [67]. In 2015, Andrews et al., described the potential of four clinically approved HDACi, compounds **34** (romidepsin or FK228), **35** (belinostat), **36** (panobinostat), and **3**, for cancer treatment against *P. falciparum* and *T. brucei* parasites. All compounds inhibited the growth of *P. falciparum* parasite, with IC_{50} values ranging from 0.09–0.13, 0.025–2.2, 0.06–0.13, and 0.01–0.03 µM, respectively. Interestingly only compound **34** was active against the bloodstream form of *T. brucei*, with an IC_{50} value of 35 nM, despite lacking mammalian cell selectivity. These four HDACi inhibited the *P. falciparum* nuclear extract deacetylase activity and recombinant PfHDAC1 due to hyperacetylation of non-histone protein and contrastingly affecting histones (H3 and H4) acetylation. Compounds **3** and **35** did not show selectivity towards malaria parasites over mammalian HEK29 and NFF 3 cells [66] (**Figure 4**).

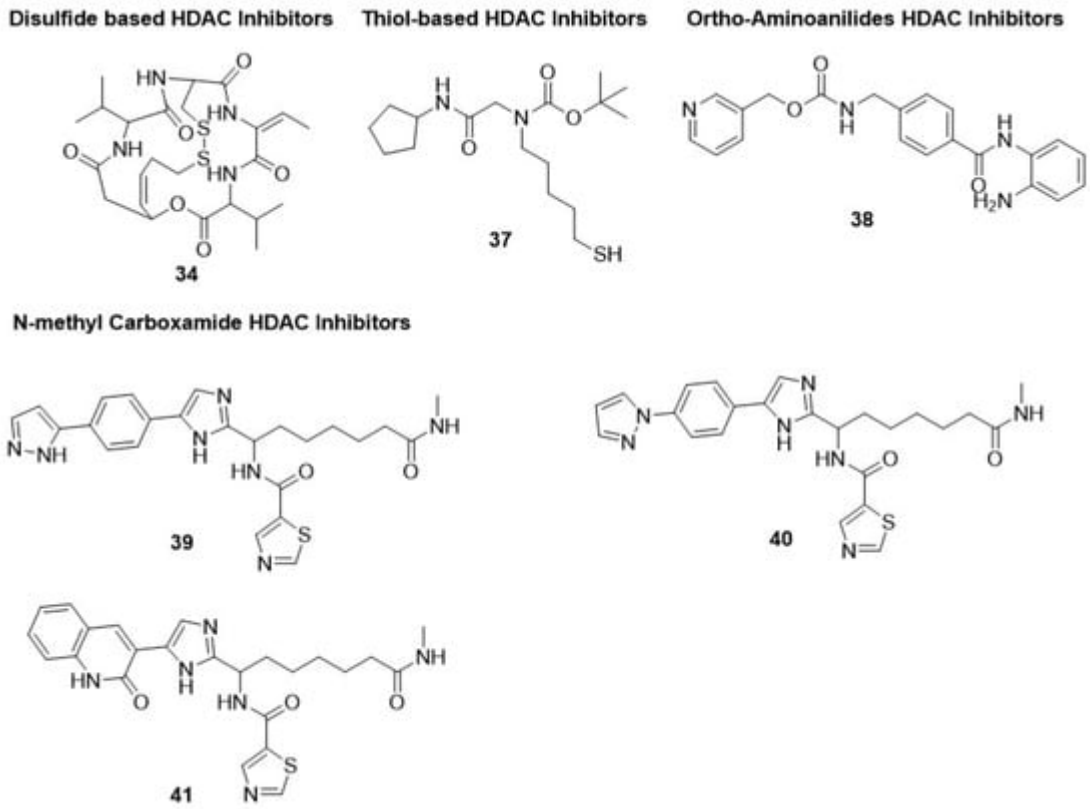

Figure 4. Chemical structure of disulfide-based, thiol-based, orthoamino-anilide-based, and N-methylcarboxamide-based HDAC inhibitors. These inhibitors displayed anti-malarial activity.

2.1.4. Thiol-Based HDAC Inhibitors

Thiol-based HDAC6-selective inhibitor **37** displayed poor inhibitory potential against chloroquine-sensitive (3D7) and chloroquine-resistant (Dd2) strains of *P. falciparum*, with IC_{50} values in the range of 15.2–19.9 μM [68]. Thus, further verification is needed to validate the antimalarial potential of hydroxamate-based pan-HDACi [53] (**Figure 4**).

2.1.5. Ortho-Aminoanilides HDAC Inhibitors

A similar inference can be made by choosing an *ortho*-amino anilide group as a zinc-binding group. The precursor of these HDACi in the class-I-HDAC-selective inhibitor is denoted as compound **38** (MS275 or entinostat) [62][63][69]. Multiple trials have been completed on compound **38**, revealing its potential as a PfHDAC1 inhibitor and parasitic proliferation inhibitor, with IC_{50} values of 0.94 and 8 μM, respectively [11][25][33][48][53]. Compounds **39**, **40**, and **41** are N-methyl carboxamide derivatives that displayed antimalarial potential against *P. falciparum* [70] (**Figure 4**).

2.2. Antimalarial Class-III HDAC (Sirtuin) Inhibitors

Fewer Sir2 inhibitors have been tested against *P. falciparum*-infected erythrocytes for their antiproliferative activity and inhibition of the recombinant PfSir2A protein [11][25]. Generally, the Sir2 inhibitors showed moderate activity against the growth of *P. falciparum*. A poor homology has been observed between the parasite and other eukaryotic Sir2 proteins [71][72]. Several known natural and synthetic sirtuin inhibitors that have been investigated over the years for growth inhibition of *P. falciparum.* Compound **42** (sirtinol), **43** (splitomycin), **44** (surfactin), and **45** (hyperforin) displayed IC_{50} values in the range of 9–13, >10, 9, and 1.5–2 μM, respectively, against *P. falciparum* [69][73][74][75]. Compound **46** (nicotinamide) is a Sir2-catalysed reaction product and causes non-competitive inhibition of both acetylated peptide and NAD^+ but less active at the whole-cell level, with an IC_{50} value of 9.9 mM for retarding parasite growth [76]. Nicotinic acid, also a product of Sir2-dependent enzymatic pathways, did not show this effect [76].

Compounds **44** and **46** displayed different activity against PfSir2A, with IC_{50} values of 35 and 51 μM, respectively. Meanwhile, compounds **43** and **44** showed less active activity, with IC_{50} values of >400 and >50 μM, respectively. Chakrabarty et al., synthesized analogues of lysine-based tripeptide based on a mechanism of competition with the binding pocket of PfSir2 [77]. From the four analogues, three analogues showed equivalent or improved activity, with IC_{50} values in the range of 23–34 μM against PfSir2A in contrast to compounds **44** and **46** [77]. Compound **47** was highly potent against PfSir2A and also tested against *P. falciparum*-infected erythrocytes where it displayed parasitic inhibitory potential similar to compounds **34** and **36** with an IC_{50} value of 9.8 μM [77]. Resveratrol (**48**) and isonicotinic acid (**49**) are activators of hSIRT1 that moderately inhibit *P. falciparum* growth, but during in vitro testing against recombinant PfSir2A, no enzymatic activation or inhibition was reported [75][78]. However, this is fully anticipated as PfSir2A and PfSir2B are not required for the growth and development of the parasite and share a few homological sequences with Sir2 proteins of other eukaryotes [71][72]. In addition, several compounds, **42**, **43**, **46,** and, to a lesser extent, compound **44,** displayed lower inhibitory potential against PfSir2A and the in vitro antiproliferative effects due to their multiple unrelated characters at a single gene locus. Thus, the identification and development of inhibitors with a notable enhancement of potency against PfSir2 and the selectivity towards sirtuins of humans could be a functional gadget considering *P. falciparum* sirtuins' biology and their pharmacological

validation as a target of drugs that either directly or indirectly produce antiparasitic activity through obstructing the parasite avoidance from the host innate immune system [71][72] (**Figure 4**).

2.3. Antitrypanosomal HDAC Inhibitors

A few compounds were tested against the *Trypanosoma* species. Compound **10** appeared to prevent the spread of the bloodstream form of *T. brucei* at a concentration of 7 µM but without affecting a silent variant surface glycoprotein expression site [79]. Another study was conducted where the similar compound **10** hampered recombinant TbDAC3 and TbDAC1 activity by >50% at 5 µM concentration. However, this compound cannot alter the acetylation of the histone protein of the parasite at a concentration of 0.3 µM [61]. Further, four HDACis, compounds **34**, **3**, **35**, and **36**, were also tested by Engel et al., for the inhibition of trypanosomal and malaria parasites [80]. The result of the study revealed that all inhibitors effectively inhibit *T. brucei* but all of them displayed cytotoxicity towards the human NFF and HEK 293 cells at lower concentrations, with a selectivity index less than 1 [47]. However, compound **34** is highly potent against *T. brucei* with an IC_{50} value of 35 µM.

In 2012, several clinically approved hydroxymates-based HDACis like long-chain amides, sulphonamides, heterocycle-containing acrylamides, and sulphonylpiperazines were tested against a cultured bloodstream form of *T. brucei* for their inhibitory effect [81]. The result of the study indicated that long-chain amides with IC_{50} values > 10 µM displayed a notable inhibitory property on the growth in the range of IC_{50} values 0.034–1.54 µM. Among them, sulphonylpiperazines with heteroaryl ring attached to the piperazine moiety displayed potent inhibition. Compound **50** displayed an IC_{50} value of 34 µM and was able to induce parasite death at 2 µg/mL within 4 h after treatment. All four compounds displayed powerful inhibition of the hHDAC activity, with IC_{50} values in the range of 0.010–0.212 µM [81] (**Figure 5**).

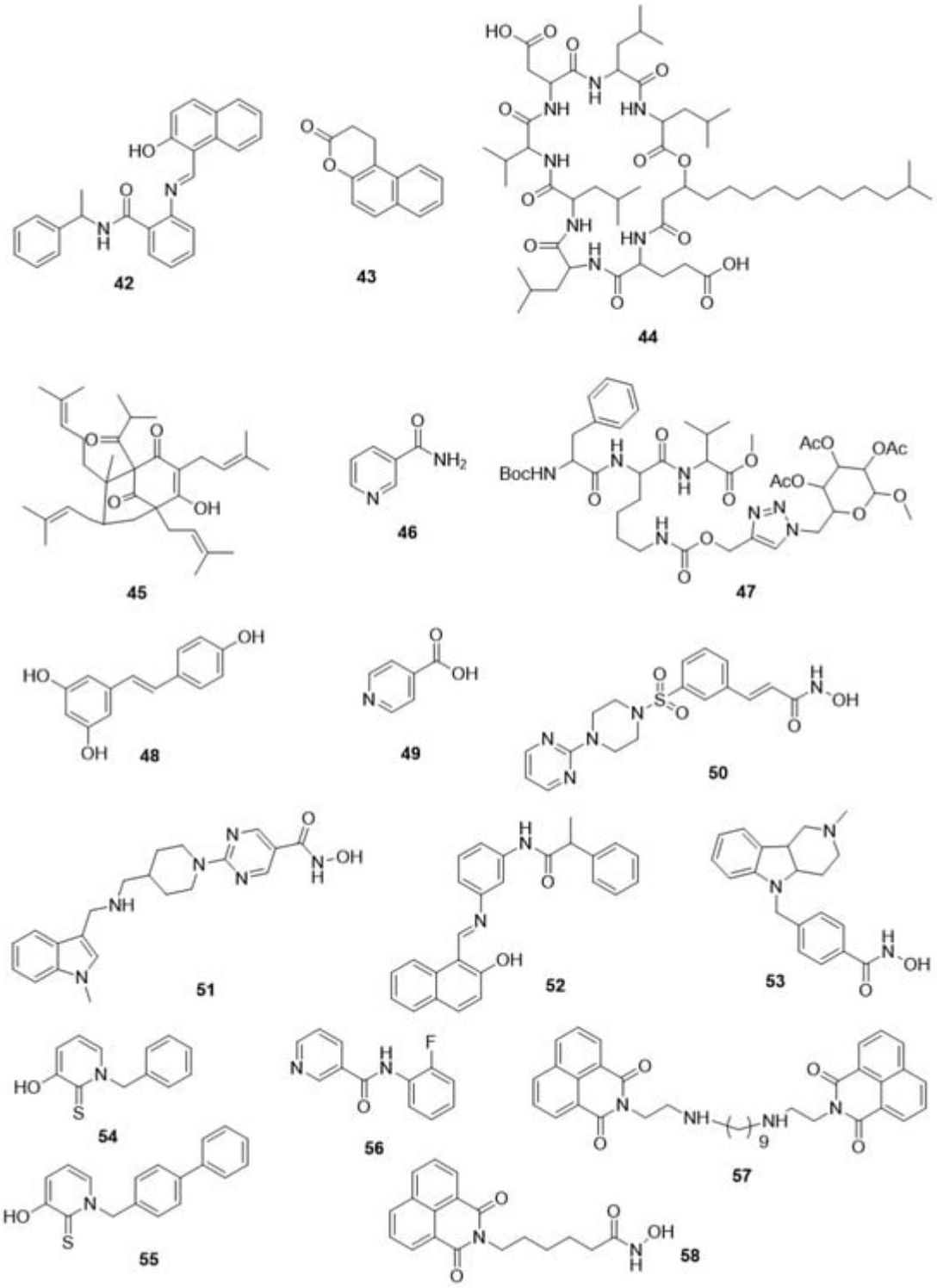

Figure 5. Chemical structure of other HDAC inhibitors. Diverse chemical structure shows varying range of parasitic HDAC inhibition.

Lately, two recently approved hydroxymate-based HDACis (**36**, **51**) and four hydroxymate-based HDACis that are already available as anticancer agents under clinical trial were investigated to determine their inhibitory capacity on the proliferation of *T. brucei* in the cultured bloodstream. The result of the study revealed that all compounds moderately inhibited the parasite, with EC_{50} ranging 0.029 to 11 μM. The most effective compound was **51**

(quisinostat) [82]. Compounds **35** and **36**, anticancer drugs, were unable to destroy the cultured parasites at the human-tolerated doses after a single dose administration. Furthermore, compound **36**, a sustained-acting HDACi when administered with Human African Trypanosomiasis (HAT) drugs, like pentamidine, suramin, melarsoprol, and nifurtimox, did not display a synergistic effect [82]. Accordingly, the application of these two HDACis as single agents or in combination for repurposing in HAT treatment is ruled out. Overall, there is lack of associations between the potency against any isoform of hHDAC and the prevention of *T. brucei* proliferation. From this idea, the author proposed that HDAC of trypanosome might have a distinctive specificity that could be used for the development of powerful HDACis having selectivity towards the parasite over hHDACs [82].

2.4. Antitrypanosomal Class-III HDAC (Sirtuin) Inhibitors

Compound **46** has been described as a putative inhibitor of *T. cruzi* sirtuin TcSir2rp1 and a growth inhibitor of the parasite at its developmental stages, including trypomastigote and epimastigote. It is evident by a notable inhibition in the number of amastigotes in the *T. cruzi*-infected macrophages [83]. However, besides SIRT inhibition, it also possesses a pleiotropic response; i.e., one gene influences many phenotypic expressions [83]. Similarly, Moretti et al., characterized two sirtuins, TcSir2rp1 and TcSir2rp3, of *T. cruzi* and described that compound **52**, an antitumor agent in a different model of cancer, could be a potential SIRTi and inhibit growth and differentiation of *T. cruzi* [78][84][85][86]. Compound **52** diminished the proliferation of epimastigote, with an EC_{50} value of 10.6 µM, and prevented its transformation into infective forms. Furthermore, the activity of the recombinant TcSir2rp3 was hampered by compound **52**, resulting in an IC_{50} value of <1 µM. Hence, it could be proposed that the antiparasitic activity of the compound occurred via TcSir2rp3 inhibition.

Experimental evidence holds up this finding that, with the addition of compound **52**, the overexpression of TcSir2rp3 and all phenotypic effects were reduced. Appreciably, compound **52** reduced parasitemia in a *T. cruzi*-infected BALB/c mouse model at a lower dose in comparison to a higher in vivo dose that is used for cancer treatment. Nonetheless, compound **52** was not able to prevent the mortality of mice at this dose. Thus, rationally, it can be used to develop a more potent and selective isoform-based SIRTi of the parasite as a potential agent against *T. cruzi* infection [84].

Furthermore, a molecular docking study of pan-SIRTi regarding compounds **42**, **46**, and SIRTi (thiobarbiturate derivatives) of class-III inhibitors revealed that there was strong correlation between human mitochondrial SIRT5 and TcSir2rp3 with respect to strength and binding mode [87]. Although the comparison of TcSir2rp3 catalytic pocket with human protein SIRT5 homologous through in silico surface and structural analysis has permitted the recognition of insignificant but notable structural differences at specific inhibitory catalytic domains, that would probably be used for the development of preferable TcSir2rp3 inhibitors with higher specificity towards *T. cruzi* [87].

2.5. Antileishmanial HDAC Inhibitors

The response of *Leishmania* parasite towards HDACi indicates the HDACs' specificity and importance for survivability [11][60][61][62][88]. Both antimalarial and antileishmanial properties of hydroxamate-based class-I/II

HDACis were discussed by Oyelere et al. [62]. Furthermore, they studied the effect of 3-hydroxypyridine-2-thiones (3HPTs) on the *L. donovani* survivability in amastigote and promastigote forms, which were earlier described as inhibitors of hHDAC6/hHDAC8 [88]. Compound **3**, the pan-HDACi, along with compound **53** (tubastatin A), another hydroxamate-based HDACi, and the reference compound PCI-34051, a selective inhibitor of hHDAC6 and hHDAC8, was taken [88]. Compound **53**, an hHDAC6-selective inhibitor, produced equal antileishmanial activity at both the developmental stages of *L. donovani*. This effect was not observed with compound **3** and PCI-34051, a selective hHDAC8 inhibitor. The result also revealed that compounds **54** and **55**, 3-HPT-derived HDACi, produced cytotoxicity both at intracellular and extracellular species of *L. donovani*, with IC_{50} values ranging from 0.1 to 6.5 µg/mL. Thus, the investigator suggested that the antileishmanial efficacy resulted in *L. donovani* due to inhibition of HDAC6. This paves a new way for protozoan HDAC6-like activity besides selective isoform inhibitors that might develop a more attentive therapeutic primary plan for Leishmaniasis treatment [88].

2.6. Antileishmanial Class-III HDAC (Sirtuin) Inhibitors

Still, a smaller number of SIRTis furnished with antileishmanial activity have been described [11]. Compound **44** demonstrated developmental-stage-specific antiproliferative properties against *L. infantum* parasites [89]. The compound led to apoptotic cell death due to DNA double helix breakage and inhibited the multiplication of axenic amastigotes but did not alter the growth of parasite promastigotes with an IC_{50} value of >60 µM [89]. Overexpression of LmSir2rp1 of parasite results in less susceptibility towards the fragmentation of DNA on the treatment of compound **12** [89].

Similarly, compound **46** can inhibit the growth of *L. major*; even LmSir2rp1 overexpression did not protect the parasite against this compound [90]. Several in silico and biochemical studies disclosed significant differences between the LmSir2rp1 and catalytic domains of human SIRTs [91]. In another in vitro investigation, four compounds effectively inhibited the axenic amastigote growth of *L. infantum*, but compound **56**, a nicotinamide derivative, inhibited LmSir2rp1 [92]. Later, an investigation revealed that compounds **42** and **46** can also inhibit the recombinant LiSir2rp1, with IC_{50} values of 194, and 40 µM, respectively, but similar results were also observed against the human SIRT1 enzyme. Thus, selectivity towards the parasite was lacking [93]. Furthermore, Tavares et al., described antileishmanial activity and structure–activity relationship study of twelve compounds belonging to bis-naphthalimidopropyl (BNIP) derivatives that varied in the central alkyl chains length, with 2, 3, or 4 nitrogen atoms, connecting two moieties of BNIP [93]. All derivatives of BNIP could suppress LiSir2rp1, with IC_{50} values ranging from 7 to 54.7 µM, and displayed selectivity for hSIRT1 in certain cases. The inhibition and selectivity of LiSir2rp1 seem to rely on linker group length and total charge. Diamine BNIP derivatives having linker 4–7 methylene units were less effective than 8–12 methylene linker units. Further, the additions of the positive amino group to the linker do not affect the selectivity or efficacy.

Compound **57** (BNIP9), having nine methylene units in the linker group, displayed IC_{50} value of 5.7 µM against parasitic LiSir2rp1 with 17-fold enhancement in specificity over hSIRT1 [93]. Furthermore, the derivatives of BNIP could inhibit the intracellular development of *L. infantum* amastigotes, with IC_{50} values ranging from 1–10 µM. Still, a linear interaction between LiSir2rp1 inhibitory property and antiproliferative effects in the amastigote stage could

not be established. Certain derivatives are committed to have favorable antileishmanial efficacy, as shown in *L. infantum*-infected BALB/c mouse model [94].

2.7. Antitoxoplasma HDAC Inhibitors

Several HDACis belonging to class I/II with the cyclic tetrapeptides displayed inhibitory activity on the growth of *Toxoplasma gondii*. Compound **5** with IC_{50} values ranging from 3 to 15 nM showed its potential but did not possess selectivity over the mammalian cells [32]. The cyclic tetrapeptide compound **6** obtained from the fermentation broth of *Acremonium* species showed rapid growth inhibitory effects against tachyzoites of *T. gondii*, with IC_{50} value of 10 nM and 13-fold specificity over human foreskin fibroblasts [42]. These compounds are effective against drug-sensitive and resistant *P. falciparum-infected* erythrocytes. Compound **6** caused hyperacetylation of H4 histone of *T. gondii* through specific inhibition of TgHDAC3 enzyme. The sensitivity for compounds **5** and **6** was reduced due to single-point mutations within TgHDAC3 (T99A and T99I). Hence, these compounds targeted TgHDAC3, providing genetic proof. Intriguingly, compound **6** displayed turning off the enzyme inhibition due to the insertion of two residues (T99 and A98) within the TgHDAC3 catalytic site. This indicated the presence of a simple safeguard in the HDAC3 family of Apicomplexan, which is not available in any other HDACs of eukaryotes [42].

In addition, altered gene expression and stage-specific transformation in *T. gondii* were completed by TgHDAC3. The treatment with compound **6** converts the replicative tachyzoite to the non-replicative bradyzoite [95]. A successive study narrates that compound **6** was effective in *T. gondii* cysts treated ex vivo and also affected converted cysts and bradyzoites. Particularly, compound **6** diminished the capacity of bradyzoites for conversion to tachyzoites beyond cyst wall injury; thus, isolated free bradyzoites after cell wall lysis were not able to multiply. Ultimately, the cysts formerly treated with compound **6** injected in mice did not produce infection.

Similar studies were conducted for compound **6** cognate (W363 and W399), which is highly active against tachyzoites and afforded better selectivity of 48–62 fold over human foreskin fibroblast cells. Hence, it could be preferable for in vivo studies in the near future [96]. However, compounds **7**, **8,** and **9** displayed poor activity against tachyzoites of *T. gondii* and showed lower selectivity over HS69 mammalian cells [45]. Hydroxamate-based HDACis have also been assessed against *T. gondii* parasites in the tachyzoite stage [44]. Among them, compounds **10**, **58** (scriptaid), and **3** hampered tachyzoites of *T. gondii*, showing IC_{50} values of 41, 39, and 83 nM, respectively. However, compound **11** displayed 2–5 times lower potential than others, with IC_{50} of 213 nM [44]. Likewise, compounds **3** and **58** displayed improved selectivity towards the *P. falciparum* parasite than compound **10** over mammalian cells [44]. Surprisingly, compounds **10**, **3**, and **48** at low concentrations of 1–50 nM reduced the infectivity of *T. gondii* tachyzoite through suppression of proliferation and survival [44]. Very few facts are available on the effectiveness of HDACis belonging to class III against several species of *Toxoplasma*. A single report suggested that compound **46** is inactive against tachyzoites of *T. gondii*, with an IC_{50} value of 50 mM [44].

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