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Evaluation of Triazole and Isoxazole Derivatives as Potential Anti-infective Agents

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Abstract

A series of isoxazole and triazole derivatives, with interesting bioactive scaffolds, were examined for their *in vitro* antibacterial, antifungal, and antiprotozoal activities. These compounds exhibited antitrypanosomal activity comparable to difluoromethylornithine (DMFO), a drug used in the treatment of human African trypanosomiasis. Isoxazole analogues **1**, **3** and **4**, and triazole derivatives **16**, **17**, **28**, **37**, **40** and **42** showed the highest antitrypanosomal activity with IC₅₀ values of 17.89, 1.82, 10.38, 10.26, 11.77, 9.29, 3.93, 2.11, and 0.93 μM, respectively. Compounds **40** and **42** showed the most potent activity against *Leishmania donovani* amastigotes with IC₅₀ values of 18.28 and 10.54 μM, respectively. Compound **42** showed the most potent activity against *Leishmania donovani* macrophage internalized amastigotes with an IC₅₀ value of 8.32 μM. Conjugate triazoles **40–43** displayed potential antimalarial activity against chloroquine-resistant W2 and chloroquine sensitive D6 *Plasmodium falciparum* strains (IC₅₀ value range from 0.58 to 8.36 μM). Compound **37** showed antibacterial activity against *Staphylococcus aureus*, MRSA and *Mycobacterium intracellulare* with IC₅₀ values of 15.53, 14.22 and 47.45 μM, respectively. None of the compounds exhibited antifungal activity.

Keywords

triazole and isoxazole derivatives; antibacterial and antiprotozoal activity

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1. Introduction

Over the last decades, progress on the pharmacological activity and synthesis of various substituted triazole/isoxazole derivatives has been added to the scientific literature. Through this research, compounds containing a triazole-ring have showed a broad spectrum of activities, including anti-inflammatory (Sana *et al.*, 2018), analgesic (Montes *et al.*, 2017), antitumor (Kaur *et al.*, 2016), anti-diabetic (Park and Pham 2017), and anticonvulsive (Chelamalla *et al.*, 2017) activity. Additionally, there are several reports that highlight the importance of the triazoles motif against microbes: bacteria, fungi, protozoa, and virus (Ashok *et al.*, 2018; Cao *et al.*, 2017; Keivanloo *et al.*, 2016; Kumar *et al.*, 2013). In fact, the triazole ring is found on several marketed antifungal drugs including, terconazole, fluconazole, posaconazole, voriconazole and itraconazole (Nett *et al.*, 2016). Similarly, the isoxazole motif is found in several clinically approved antibiotics including oxacillin, cloxacillin, dicloxacillin and flucloxacillin (Sutherland *et al.*, 1970).

Neglected tropical diseases (NTDs) are disabling and potentially life-threatening infections affecting more than a billion people worldwide (Thao *et al.*, 2014). Human African trypanosomiasis (HAT), commonly known as sleeping sickness, is an NTD caused by the *Trypanosoma brucei* parasite and transmitted to humans through the bite of the tsetse fly (Tiberti *et al.*, 2013). The parasites can travel through the blood-brain barrier and invade the Central Nervous System (CNS), at which time neurological symptoms begin to appear. In the absence of treatment, the disease results in wasting of body tissue, coma, and ultimately death (Gull 2002). The resulting coma is why this infection is called sleeping sickness. Leishmaniasis is a group of tropical diseases caused by a number of species of protozoan parasites belonging to the genus *Leishmania*. Cutaneous leishmaniasis and visceral leishmaniasis have been reported to be the two major forms of leishmaniasis in humans (Peixoto *et al.*, 2011). These NTDs are clearly related to poverty since this population of patients does not have access to appropriate medication and healthcare. NTDs have a huge impact on the economic growth in developing countries (Kotowski *et al.*, 2015).

While malaria is not cataloged as a NTD, it is considered the leading cause of death and morbidity worldwide among infectious diseases. It is caused by parasites that are transmitted to people through the bites of female mosquitoes infected with a *Plasmodium* parasite. There are four main species of the malaria parasite which include *P. falciparum*, *P. malariae*, *P. vivax* and *P. ovale*. According to the World Health Organization (WHO), in 2016 there were approximately 216 million cases of malaria in 91 countries (WHO 2017). The drugs available for the treatment of these endemic diseases are old, expensive, and associated with other problems including safety. The situation is intensified by the quick development of resistance against therapeutic agents, resulting in drug resistant parasites (WHO 2017).

The control of infectious disease requires continued research on bioactive compounds. In this context, biologically active scaffolds such as heterocyclic compounds possessing triazole and isoxazole derivatives could be used as potential leads. There are few examples of the use of these important heterocyclic motifs against NTDs. Different triazole derivatives showed *in vitro* and *in vivo* activity against a variety of strains of *T. cruzi* and *T. brucei*. A group of synthesized metal complexes of triazole-pyrimidine derivatives inhibited

the *in vitro* growth of epimastigotes of *T. cruzi* and procyclic forms of *T. brucei brucei* (Magán *et al.*, 2004). Some isoxazole containing heteroretinoid derivatives showed *in vivo* antileishmanial activity against *Leishmania donovani* in hamsters (Suryawanshi *et al.*, 2012). Giannini and Battistuzzi 2015, reported the antiprotozoal activity against *T. brucei*, *T. cruzi* and *P. falciparum* of a series of 3,4,5 isoxazole and 1,4,5 trisubstituted triazole derivatives. These compounds showed nM range activity and excellent binding to the heat shock protein (Hsp90α), confirming the important role that Hsp chaperone proteins play in the live cycle of the parasite. There have been some efforts to conjugate triazole compounds. For example, 3-nitro-1,2,4-triazole with amides and sulfonamides displayed potent *T. cruzi* activities with IC₅₀ in the nM range (Papadopoulou *et al.*, 2012). Hybrids between 1,2,3-triazole, quinones and sugars showed potential activities against *T. cruzi* (Jardim *et al.*, 2015).

In continuation of our efforts to find novel active agents against NTDs, a library of triazole and isoxazole compounds were evaluated for their *in vitro* antitrypanosomal activity, as well as, antileishmanial, antimalarial and antimicrobial properties.

2. Materials and Methods

2.1 Chemistry

The evaluated compounds: twelve isoxazoles **1–12**, twenty-four triazoles **13–36** and seven triazole conjugates **37–43** were design and synthesized at the Yarmouk University, Jordan. The general experimental procedure and experimental data for isoxazole and dihydroisoxazole derivatives **1–12** have been reported (Abu-Orabi *et al.*, 1988; Abu-Orabi *et al.*, 1999 and Al-Momani 1995). The synthetic protocols for triazole derivatives **13–36** have been previously described (Abu-Orabi 2002). Compounds **37–39** have been synthesized and their experimental data reported (Tashtuosh *et al.*, 1999). Finally, the synthetic process for compounds **40–43** was previously reported (Abu-Orabi *et al.*, 1988).

2.2 Biological evaluation

2.2.1 *In vitro* antimicrobial assay—Compounds **1–43** were tested for antimicrobial activity against a panel of microorganisms obtained from the American Type Culture Collection (Manassas, VA, USA) and included the fungi: *Candida albicans* ATCC 90028, *Candida glabrata* ATCC 90030, *Candida krusei* ATCC 6258, *Cryptococcus neoformans* ATCC 90113, *Aspergillus fumigatus* ATCC 204305, the bacteria *Staphylococcus aureus* ATCC 29213, methicillin-resistant *S. aureus* ATCC 33591 (MRSA), *Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, and *Mycobacterium intracellulare* ATCC 23068. The bioassays were performed as previously described (Ma *et al.*, 2004 and Bharate *et al.*, 2007). Ciprofloxacin and amphotericin B were used as positive drug controls.

2.2.2 *In vitro* antitrypanosomal assays—Blood stage forms of *Trypanosoma brucei brucei* was grown in IMDM medium supplemented with 10% fetal bovine serum. The culture was maintained at 37 °C in 5% CO₂ incubator. Two day old culture of *T. brucei* was diluted to 5,000 parasites/ml. Diluted *T. brucei* parasite culture was dispensed in clear flat bottom culture well plates and treated with test compounds. The antitrypanosomal screening assay was based on Alamar blue based fluorometric growth analysis at concentration range

of 10–0.4 µg/ml. Active compounds were further screened at concentration range 10–0.0032 µg/ml. Pentamidine and difluoromethylornithine were used as positive drug controls. IC₅₀ and IC₉₀ values were computed from dose response growth inhibition curve by XLfit version 5.2.2 (Jain *et al.*, 2016).

2.2.3 *In vitro* antileishmanial assays—Promastigote culture of *Leishmanial donovani* was grown in RPMI medium with 10% FBS with pH 7.4 at 26 °C. Axenic amastigote culture of *Leishmanial donovani* was grown in RPMI medium with 10% FBS with pH 5.5 at 37 °C in 5% CO₂ incubator. The antileishmanial activity of the compounds was tested *in vitro* against promastigotes, axenic amastigotes and macrophage internalized amastigote form of *Leishmania donovani* parasite. Promastigotes and axenic amastigotes assays were based on alamar blue fluorometric growth analysis (Manda *et al.*, 2014). Differentiated THP1 cells were been used in macrophage internalized-amastigote assay. Macrophage internalized amastigote method was based on parasite rescued and transformation assay described earlier, pentamidine and amphotericin B were used as positive standards (Jain *et al.*, 2012).

2.2.4 *In vitro* antimalarial assays—Antimalarial activity was determined *in vitro* against chloroquine sensitive (D6, Sierra Leone) and resistant (W2, Indo China) strains of *Plasmodium falciparum* by a colorimetric assay that determines the parasitic lactate dehydrogenase (pLDH) activity, as described earlier (Hamid *et al.*, 2004).

2.2.5 *In vivo* antimalarial assays—*Plasmodium berghei* (NK-65) parasite was obtained from MR4 (Malaria Research Reference Reagents Resource). Male Swiss albino mice weighing ~20 gram were procured from ENVIGO, USA. Animal studies were done under protocol (Protocol approval number 15-007) approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Mississippi, USA. Blood with high parasitemia was collected by cardiac puncture in Acid-Citrate-Dextrose (ACD) solution from these infected mice washed and diluted with sterile saline to adjust the infected RBC's concentration to 8×10⁷ RBCs/ml. The animals were randomly divided in two different groups with 5 animals in each group and all the mice were inoculated i.p. with 0.5 ml of infected blood for producing the infection. The mice were treated with the test compound oral once daily dose of 11.1 mg/kg from day 0 to 2 post infection. Dose was selected based on maximum tolerated dose of compound **43** in mice.

2.2.6 Cytotoxicity assays—The cultures of Human Acute Monocytic Leukemia Cell Line (THP1 cells) and vero cells were maintained in RPMI medium with 10% FBS in 37 °C 5% CO₂ incubator. For the THP1 cytotoxicity assay, four days' old culture of THP1 cells was diluted with RPMI medium treated with phorbol 12-myristate 13-acetate at 2.5 ng/ml concentration for transformation of the cells to adherent macrophages (Jain *et al.*, 2016). The cytotoxicity assay was done on these differentiated THP1 cells, alamarBlue® cell viability reagent was used to detect fluorometric changes at concentration range of 10–0.4 µg/ml (Jain *et al.*, 2012). Cytotoxicity assay for vero cells was based on the neutral red assay, which was described earlier (Yang *et al.*, 2006).

3. Results and Discussion

A series of twelve isoxazoles **1–12** (Figure 1), twenty-four triazoles **13–36** (Figure 2) and seven triazole conjugates **37–43** (Figure 3) were evaluated for their antibacterial, antifungal, antimalarial antitrypanosomal, antileishmanial and cytotoxicity activities. Out of forty-three tested compounds, twenty-two showed promising antitrypanosomal activity. Four triazole conjugated derivatives (**40–43**) showed *in vitro* antimalarial activity. Most of the antitrypanosomal compounds showed comparable activity to the positive control drug difluoromethylornithine (DFMO).

Antimicrobial activity

The antifungal and antibacterial activities were evaluated against a panel of pathogenic fungi (*Candida albicans*, *C. glabrata*, *C. krusei*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*) and a panel of pathogenic bacteria (*Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *Escherichia coli*, *Pseudomonas aeruginosa* and *Mycobacterium intracellulare*) associated with opportunistic infections. Only compound **37** possessed antibacterial activity against *S. aureus*, and MRSA with IC₅₀ values of 15.53 and 14.22 µM, respectively. Compounds **37**, **40**, **42** and **43** showed significant activity against *M. intracellulare* with IC₅₀ values of 47.45, 44.83, 43.16 and 7.60 µM, respectively. None of the compounds possessed antifungal activity.

Antitrypanosomal activity

Tables 1–3 show the screening results for antitrypanosomal activity of all compounds. Isoxazole **3** showed the most potent activity against *T. brucei* with an IC₅₀ value of 1.82 µM (Table 1). Replacing the tertiary butyl ester on the R₁ with hydrazinocarbonyl **4** led to reduced activity with a value of 10.38 µM. Changing the methyl group on the benzene ring to methoxy **1**, while both R₁ and R₂ were kept as in **3**, did not significantly improve the potency. Modification of the isoxazole in **4** to a 4,5-dihydroisoxazole like in compound **8** lead to lose the biological activity against *T. brucei*. However, modification replacing the hydrazinocarbonyl R₁ with a substituted benzene ring and hydrazinocarbonyl R₂ with a benzyl ester in the dihydroisoxazole core yielded compound **10**, which showed an IC₅₀ value of 11.51 µM against *T. brucei*. Replacing the isoxazole moiety of compound **4** with the triazole moiety and keeping the hydrazinocarbonyl in R₁ and R₂ showed no significant change in the bioactivity against *T. brucei*. In this series **13–24** halogenated monosubstitution in the aromatic ring showed the highest IC₅₀ values for compounds **15** to **18** (Table 2). Further modification with a trimethyl substitution **22** led to an IC₅₀ value of 22.28 µM. Inserting a bulky group at position R₁ and R₂ of the triazole ring, such as the pivaloyloxy in compound **34** led the highest potency for this series, with an IC₅₀ value of 7.44 µM. In general, compounds (**13–36**) containing electronegative groups, such as, halogens showed antitrypanocidal activity. No clear patterns were found to explain the biological effects of the substituents on the benzyl ring.

In the series of conjugate triazole-oxadiazole compounds (**37–39**), compound **37** showed the highest activity with an IC₅₀ value of 3.93 µM. The quinone-triazole conjugate compounds (**40–43**) showed in overall the highest bioactive potency for all the series against *T. brucei*

with IC₅₀ values of 2.12, 4.74, 0.93, and 7.60 μ M, respectively (Table 3). Compound **42** has a strong deactivating substituent and was the most potent against *T. brucei*. Cytotoxicity screening was done for all tested compounds. None of the compounds showed more than 50 % inhibition on differentiated THP1 cells with the exception of compound **42** with an IC₅₀ value of 10.10 μ M.

Antileishmania activity

Antileishmania activity data is shown for active compounds in Tables 1 and 3. For isoxazoles derivatives and triazoles conjugates, analogues **37**, **40**, and **42** exhibited the highest inhibition values for *L. donovani* axenic amastigote with IC₅₀ value of 21.80, 18.28 and 10.54 μ M, respectively. Analogues **37** and **42** have high activity on the macrophage internalized amastigote form of *Leishmania donovani* parasite with IC₅₀ values of 23.54 and 8.32 μ M, respectively.

Antimalarial activity

All compounds **1–43** were tested against *P. falciparum* D6 and W2 strains. Activity was found only for compounds **40–43**. These compounds showed promising action against both chloroquine-resistant (*P. falciparum* W2) and chloroquine-sensitive strains of malaria (*P. falciparum* D6) (Table 3). Compound **43** showed the most potent activity with IC₅₀ values of 0.70 and 0.59 μ M, for D6 and W2, respectively. Replacing the 3-fluoro substitution with chloro **40**, methyl **41**, or nitro **42** groups reduced the activity of this series. All the compounds were evaluated for cytotoxicity against mammalian kidney cell line (Vero) and selectivity index was calculated. Selectivity index values less than 1.2 indicated that antimalarial activity was not due to cytotoxicity. Antimalarial activity of compound **43**, the most potent of all the series was tested *in vivo* in *P. berghei* mouse malaria model for survival (Figure 4). Chloroquine served as the positive control. Compound **43** increased the survival time to 16.2 days when compared to the vehicle control group of mice at a dose of 11.1 mg/kg per day for 3 days.

In conclusion, we report the antimalarial, antileishmanial, antibacterial activities of 43 isoxazole and triazole derivatives. Triazole compounds **13–36** were active against *T. brucei*, while compound **37**, having triazole and oxadiazole rings, showed promising activities against all pathogens. Compounds **40–43** produced the most potent antileishmanial and antimalarial activities. Further explorations of these triazole derivatives can provide lead compounds for antimicrobial agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- 1 R= OCH₃; R₁= OtBu; R₂= NHNH₂
- 2 R= OCH₃; R₁= NHNH₂; R₂= NHNH₂
- 3 R= CH₃; R₁= OtBu; R₂= NHNH₂
- 4 R= CH₃; R₁= NHNH₂; R₂= NHNH₂
- 5 R= OCH₃; R₁= OCH₃; R₂= OCH₃
- 6 R= OCH₃; R₁= OtBu; R₂= OtBu
- 7 R= CH₃; R₁= OEt; R₂= OEt

- 8 R= CH₃; R₁= CONHNH₂; R₂= CONHNH₂
- 9 R= OCH₃; R₁= CO₂Et; R₂= 4-nitrobenzene
- 10 R= OCH₃; R₁= CO₂CH₂Ph; R₂= Benzene
- 11 R= OCH₃; R₁= CO₂Et; R₂= 3-nitrobenzene
- 12 R= OCH₃; R₁= CONHNH₂; R₂= CONHNH₂

Figure 1.
Isoxazole and dihydroisoxazole derivatives (**1–12**)

13 R = 2,6-dichloro

14 R = 2-chloro

15 R = 3-chloro

16 R = 4-chloro

17 R = 2-bromo

18 R = 4-bromo

19 R = 2-fluoro

20 R = 4-fluoro

21 R = 4-CH₃

22 R = 2,4,6-CH₃

23 R = 3-OCH₃

24 R = H

25 R = H; R₁ = H; R₂ = CONHNHCOPh

26 R = 2,3,4,5,6-Pentamethyl; R₁ = CO₂tBu; R₂ = CO₂tBu

27 R = 2,3,4,5,6-Pentamethyl; R₁ = CO₂CH₃; R₂ = CO₂CH₃

28 R = 2,3,4,5,6-Pentamethyl; R₁ = CONHNH₂; R₂ = CONHNH₂

29 R = 2,6-dichloro; R₁ = -CO₂CH₃; R₂ = CO₂CH₃

30 R = 3-fluoro; R₁ = CO₂CH₃; R₂ = CO₂CH₃

31 R = 3-fluoro; R₁ = CO₂tBu; R₂ = CO₂tBu

32 R = 3-fluoro; R₁ = H; R₂ = CO₂CH₃

33 R = 4-fluoro; R₁ = CO₂CH₃; R₂ = CO₂CH₃

34 R = 4-fluoro; R₁ = CO₂tBu; R₂ = CO₂tBu

35 R = 4-fluoro; R₁ = H; R₂ = CO₂CH₃

36 R = 4-fluoro; R₁ = H; R₂ = CO₂CH₂CH₃

Figure 2.
Triazole derivatives (**13–36**)

37 R= 2,3,4,5,6-CH₃

38 R= 4-CH₃

39 R= H

40 R = 3-Cl

41 R= 3-CH₃

42 R= 3-NO₂

43 R= 3-F

Figure 3.
Triazole conjugated derivatives (**37–43**)

Figure 4.
Survival chart for mice in antimalarial study (43)

Table 1*In vitro* antiprotozoal activity of isoxazole (1–7) and dihydroisoxazole (8–12) derivatives

Compound	<i>Leishmania donovani</i> macrophage internalized amastigote		<i>Trypanosoma brucei</i>	
	IC ₅₀ , μ M	IC ₉₀ , μ M	IC ₅₀ , μ M	IC ₉₀ , μ M
1	NA	NA	17.895 $\pm$ 1.079	23.640 $\pm$ 0.843
2	NA	NA	NA	NA
3	28.836 $\pm$ 0.087	>28.952	1.824 $\pm$ 0.086	4.488 $\pm$ 0.819
4	NA	NA	10.385 $\pm$ 3.308	24.792 $\pm$ 5.784
5	NA	NA	NA	NA
6	NA	NA	NA	NA
7	NA	NA	NA	NA
8	NA	NA	NA	NA
9	NA	NA	NA	NA
10	NA	NA	11.509 $\pm$ 2.265	>22.347
11	NA	NA	NA	NA
12	NA	NA	NA	NA
Amp B	0.272 $\pm$ 0.100	0.441 $\pm$ 0.019	NT	NT
DFMO	NT	NT	21.299 $\pm$ 2.013	59.175 $\pm$ 5.748

NA: not active; NT: not tested; Amp B = Amphotericin B; DFMO = difluoromethylornithine

Table 2*In vitro* antiprotozoal activity of triazole derivatives (**13–36**)

Compound	<i>T. brucei</i>	
	IC ₅₀ , μ M	IC ₉₀ , μ M
13	18.277 $\pm$ 4.703	27.023 $\pm$ 0.523
14	22.279 $\pm$ 5.081	32.159 $\pm$ 0.653
15	18.340 $\pm$ 6.856	28.058 $\pm$ 1.866
16	10.268 $\pm$ 0.396	21.665 $\pm$ 1.312
17	11.774 $\pm$ 1.997	24.452 $\pm$ 0.095
18	14.174 $\pm$ 9.934	>28.235
19	25.813 $\pm$ 5.853	>34.099
20	NA	NA
21	NA	NA
22	22.278 $\pm$ 6.227	>31.511
23	NA	NA
24	NA	NA
25	NA	NA
26	NA	NA
27	NA	NA
28	9.293 $\pm$ 3.071	17.689 $\pm$ 7.967
29	NA	NA
30	NA	NA
31	NA	NA
32	41.026 $\pm$ 1.059	>42.514
33	32.838 $\pm$ 0.892	>34.100
34	7.445 $\pm$ 1.209	9.486 $\pm$ 1.436
35	40.218 $\pm$ 1.615	>42.514
36	NA	NA
DFMO	21.299 $\pm$ 2.013	59.175 $\pm$ 5.748

NA: not active; NT: not tested; DFMO = difluoromethylornithine

Table 3

In vitro antiprotozoal activity of triazole conjugates (37–43)

Compound	<i>L. donovani</i> promastigotes			<i>L. donovani</i> Axenic amastigotes			<i>L. donovani</i> macrophage internalized amastigote		<i>T. brucei</i>		<i>P. falciparum</i>	
	IC ₅₀ , μ M	IC ₉₀ , μ M	IC ₉₀ , μ M	IC ₅₀ , μ M	IC ₉₀ , μ M	IC ₉₀ , μ M	IC ₅₀ , μ M	IC ₉₀ , μ M	IC ₅₀ , μ M	IC ₉₀ , μ M	IC ₅₀ (D ₆), μ M	IC ₅₀ (W ₂), μ M
37	NA	NA	NA	21.796 $\pm$ 0.001	>26.777	>26.777	23.537 $\pm$ 2.286	>26.777	3.935 $\pm$ 0.079	4.940 $\pm$ 0.092	NA	NA
38	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
39	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
40	14.625 $\pm$ 5.757	>22.766	>22.766	18.281 $\pm$ 0.592	22.447 $\pm$ 0.016	NA	NA	NA	2.117 $\pm$ 0.147	6.766 $\pm$ 1.918	6.322 $\pm$ 0.363	7.611 $\pm$ 0.838
41	NA	NA	NA	NA	NA	NA	NA	NA	4.741 $\pm$ 1.735	13.514 $\pm$ 0.988	8.367 $\pm$ 3.041	6.606 $\pm$ 0.732
42	16.445 $\pm$ 3.868	>21.722	>21.722	10.536 $\pm$ 0.824	18.149 $\pm$ 1.651	12.879 $\pm$ 5.811	8.321 $\pm$ 0.327	12.879 $\pm$ 5.811	0.926 $\pm$ 0.034	1.200 $\pm$ 0.026	1.909 $\pm$ 0.403	2.886 $\pm$ 0.701
43	NA	NA	NA	NA	NA	NA	NA	NA	7.595 $\pm$ 2.119	10.468 $\pm$ 3.234	0.697 $\pm$ 0.187	0.583 $\pm$ 0.140
Amp B	0.192	0.312	0.312	1.729	2.004	0.441 $\pm$ 0.019	0.272 $\pm$ 0.100	0.441 $\pm$ 0.019	NT	NT	NT	NT
Pent	2.036	3.668	3.668	15.345	16.872	>16.872	6.531	>16.872	NT	NT	NT	NT
DFMO	NT	NT	NT	NT	NT	NT	NT	NT	21.299 $\pm$ 2.013	59.175 $\pm$ 5.748	NT	NT
CQ	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	0.052	0.46

NA: not active; NT: not tested; Amp B = Amphotericin B; Pent = pentamidine; DFMO = difluoromethylornithine; CQ = chloroquine