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Synthesis and Evaluation of Antiparasitic Activities of New 4-[5-(4-Phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine Derivatives

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A series of new 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine derivatives, prepared by two synthetic routes, were in vitro assayed against three *Trypanosoma* strains, *Leishmania donovani,* and *Plasmodium falciparum* K1. Seven out of 17 compounds showed moderate to very good activity against blood stage *T. b. rhodesiense*, with **10** and **17** exhibiting highest potency (IC_{50} of 1.0 and 1.1 μM, respectively). Interestingly, the β-diketone precursors **1**−**3** had good antitrypanosomal activity toward the insect stage, with IC_{50} values of 1.0−3.4 μM. Among different compounds with moderate activity against *T. cruzi*, compound **17** showed the lowest IC_{50} value of 9.5 μM; thus, the series seemed to act selectively toward the different *Trypanosoma* parasites. Eight compounds were moderately active against *L. donovani*, with **2**, **3**, and **12** being the most promising ones (IC_{50} values of 2.3−5.2 μM), whereas compound **14** was the only derivative with good activity against *P. falciparum* (IC_{50} of 3.7 μM).

Introduction

Trypanosomiasis, leishmaniasis, and malaria belong to the major parasitic diseases distributed throughout the world. Human African Trypanosomiasis (HAT,[a] sleeping sickness) is a vector-borne parasitic disease transmitted by a protozoan parasite of the genus *Trypanosoma* via the bites of infected tsetse flies. Two different forms of HAT are known. The chronic form (90% of reported cases) is caused by *Trypanosoma brucei gambiense* (*T. b. gambiense*) infection, whereas *Trypanosoma brucei rhodesiense* (*T. b. rhodesiense*) is responsible for the acute form of the disease. Both forms are fatal if untreated. About 0.5 million people on the African continent are affected, causing 50 000 deaths per year. Another parasite occurring in South and Central America, *Trypanosoma cruzi* (*T. cruzi*), enters the human body through broken skin via the feces of the blood-feeding triatominae bugs, leading to South American Trypanosomiasis or Chagas' disease, which affects 8 to 11 million people and is responsible for 13 000 deaths annually.[1]

Leishmaniases is also a vector-borne disease caused by blood- and tissue-dwelling protozoan parasites of the genus *Leishmania* that are transmitted by phlebotomine sandflies. The infection in man results in a broad range of clinical manifestations involving the skin, mucous membranes and visceral organs. *Leishmania donovani* (*L. donovani*) is the causative agent of visceral leishmaniasis, the most severe form of the disease, which is almost always fatal if left untreated.[2] Leishmaniasis is endemic in areas of the tropics, subtropics, and southern Europe, and it affects annually about 2 million people, with approximately 350 million individuals at risk worldwide.[3]

Malaria is one of the world's most important infectious diseases in terms of both mortality and morbidity. There are about 0.5 billion clinical attacks every year, including 2−3 million severe attacks, with more than 1 million deaths annually. The disease is caused by four different species of the malaria parasite of which *Plasmodium falciparum* (*P. falciparum*) is the most virulent and potentially deadly. The parasites are transmitted via the bites of infected mosquitoes of the genus *Anopheles*.[4]

Generally, the presently used drugs on the market possess severe side effects and do not provide complete eradication of the disease. In addition, drug resistance develops rapidly and has become a major problem in the treatment of neglected diseases. Therefore, new efficacious chemotherapeutic agents and novel targets are urgently needed.[5] There has been a revival of drug research and development regarding neglected parasitic diseases compared to the last 15 years, and a number of drug development projects are currently ongoing. Approved drugs are being improved (e.g., arthemisinin, trimethoprim, aminoquinolines),[5] but also, new potential drug targets have emerged and have been validated (e.g., fatty acid biosynthesis, hemoglobin degradation, protein prenylation, purine metabolism, erogsterol biosynthesis),[5−7] and novel chemical classes are being pursued for treatment of protozoan parasitic diseases (e.g., diamindines, synthetic peroxides, protease inhibitors, triclosan).[5,8−10] However, only few enter preclinical/clinical phases; thus, discovering lead compounds with antiparasitic activity remains a crucial step to sustain the progress achieved to date.

In the course of our search for new antiprotozoal lead compounds, we investigated the antitrypanosomal and antiplasmodial activity of new 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine derivatives and their synthetic precursors. This report presents the synthesis of the compounds and their activity against the parasites.

Results and Discussion

Chemistry. Two different synthetic routes were used to synthesize 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine

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[a] Abbreviations. HAT, Human African Trypanosomiasis; WHO, World Health Organization; TDR, Program for Research and Training in Tropical Diseases; TLC, thin layer chromatography; EtOH, ethanol; MeOH, methanol; Et_2O, diethylether; THF, tetrahydrofuran; Boc, tert-butoxycarbonyl.

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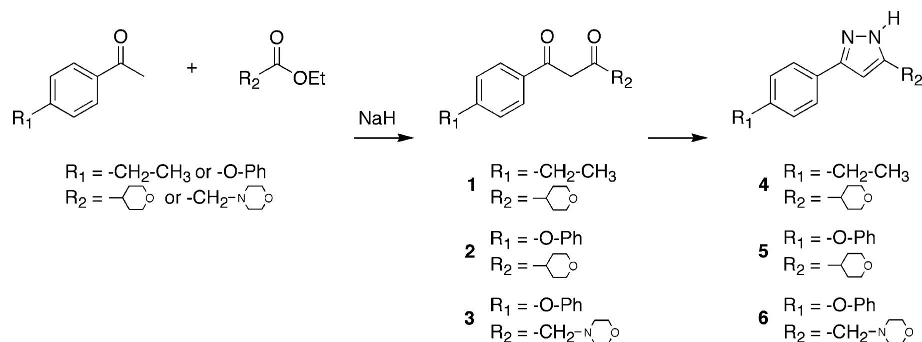
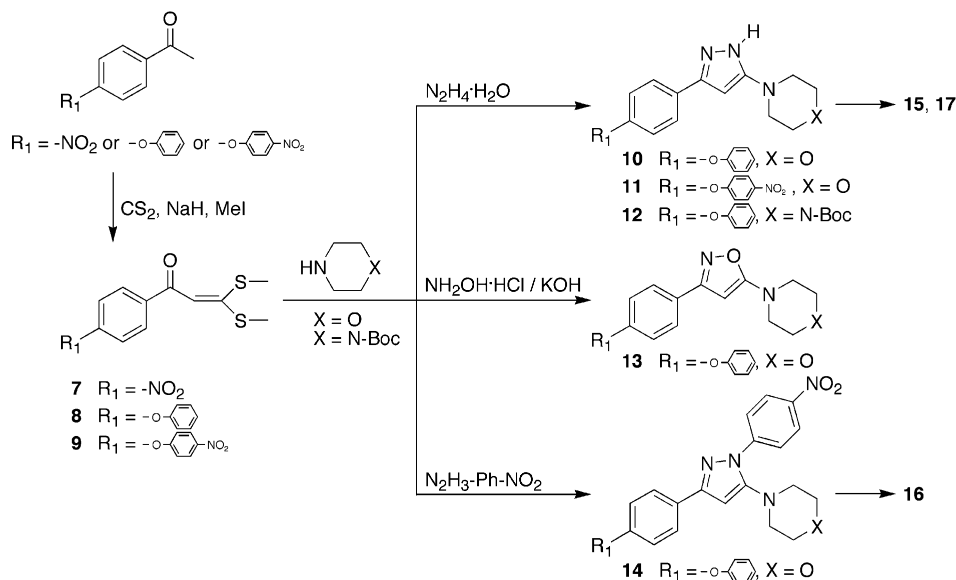
Scheme 1. Synthesis Strategy using β-diketones



Scheme 2. Synthesis Strategy using 2,2-Bis(methylthio)vinyl Ketones



derivatives. The first approach, depicted in Scheme 1, proceeds via a condensation reaction between the corresponding substituted acetophenones and the substituted ethyl carboxylate to form the β-diketones **1**−**3**[11]. Compounds **4**−**6** were prepared through cyclization using hydrazine hydrate in EtOH.[12] Scheme 2 illustrates the second approach, in which substituted acetophenones were reacted with carbon disulfide and methyl iodide in the presence of sodium hydride to give 4-phenoxyphenyl-2,2-bis(methylthio)vinyl ketones **7**−**9**.[13] The formation of the five-member ring systems was accomplished through a one-pot, two-step protocol featuring a prior displacement of one of the methylthio groups of the 4-phenoxyphenyl-2,2-bis(methylthio)-vinyl ketones **7**−**9** by the respective amines (i.e., morpholine and Boc-protected piperazine) in refluxing EtOH followed by in situ cyclization of the resulting *N,S*-acetals with hydrazine hydrate, hydroxylamine, or 4-nitrophenylhydrazine.[14,15]

The 4-phenoxyphenyl-2,2-bis(methylthio)vinyl ketones **7**−**9** were refluxed with morpholine or Boc-protected piperazine and cyclized by the addition of hydrazine hydrate in portions to give the desired products **10**−**12**. Similarly, compound **13** was obtained using morpholine and hydroxylamine as the reactants, whereas the reaction with morpholine and 4-nitrophenylhydrazine gave compound **14**. The final conversion of the nitro groups of **11** and **14** to amino groups and the deprotection of the protected piperazine of **12** were carried out under standard conditions using catalytic hydrogenation or reaction with sodium dithionite for the reduction steps and trifluoroacetic acid as the deprotection agent, respectively.[15,16] The structures of 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine (**10**), 4-[4-(5-morpholine-4-yl-1*H*-pyrazol-3-yl)-phenoxy]phenylamine (**15**), 4-[5-morpholine-4-yl-3-(4-phenoxyphenyl)-pyrazol-1-yl]phenylamine (**16**), and 1-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]piperazine (**17**) are shown in Figure 1.

Antiprotozoal Activity. The activity of compounds **1**−**17** toward *T. b. rhodesiense*, *T. b. cruzi, L. donovani*, and *P. falciparum* as well as their cytotoxicity is presented in Table 1. As a general observation, all compounds exhibit very low cellular toxicity (at least more than 1800-fold lower) compared to podophyllotoxin used as the standard. The antiparasitic potential of all compounds was analyzed by applying the WHO/TDR screening activity criteria specified for each parasite.[17] Among the newly prepared derivatives, compounds **5**, **6**, **10**, **11**, **12**, **13**, and **17** exhibit moderate to very good activity against *T. b. rhodesiense* (blood trypomastigotes). Compounds **10** and **17** are the most potent ones, with IC_{50} values around 1 μM. However, compound **17** shows a threefold increased toxicity on L6 cells compared to that of **10**. Interestingly, compounds **5**, **6**, **10**, **11**, **12, 13**, and **17** act in a stage-specific manner, thus inhibiting preferably blood trypomastigotes of *T. b. rhodesiense* and not the procyclic (insect stage) form. In contrast, the β-diketone precursors **1**−**3** exhibit good antitrypanosomal activity (IC_{50} values of 1.0−3.4 μM) toward the procyclic form of *T. b. rhodesiense*, giving evidence for stage-specific targets within the parasite cell. In line with the WHO/TDR activity criteria for *T. cruzi*, several compounds (**1**−**8**, **10**, **12**, **13**, and **16**) are moderately active against *T. cruzi*. Compound **17** is the most promising hit, with an IC_{50} value of 9.5 μM, which means only a fourfold reduced potency when compared to that of the

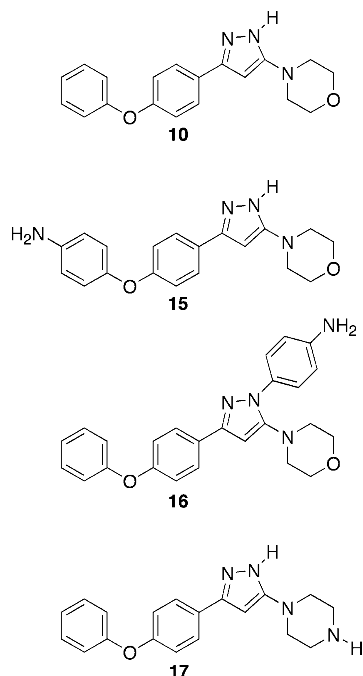


Figure 1. Structures of the most potent antitrypanosomal 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine (**10**) and its amino-substituted derivatives 4-[4-(5-morpholine-4-yl-1*H*-pyrazol-3-yl)-phenoxy]phenylamine (**15**), 4-[5-morpholine-4-yl-3-(4-phenoxyphenyl)-pyrazol-1-yl]phenylamine (**16**), and 1-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]piperazine (**17**).

benznidazole standard (IC_{50} of 2.13 μM); thus, **17** could therefore be an interesting structure for further development. Eight compounds (**1**−**3**, **5**, **9**, **10**, **12**, and **14**) show moderate growth inhibition toward *L. donovani*, with **2**, **3**, and **12** exhibiting the most promising activity (IC_{50} values of 2.3−5.2 μM). Compound **14** is the only derivative with good activity against *P. falciparum* K1. Several other compounds (**12**, **13**, **16**, and **17**) are only moderately active against the malaria parasite. Due to the good antiplasmodial activity and the very low cytotoxicity (IC_{50} > 203 μM), compound **14** represents a promising starting point for further structural optimization.

Structure Activity Relationship. Overall, the lowest IC_{50} values and highest potencies of the series were achieved toward *T. b. rhodesiense* among all different parasites; thus, the new 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine derivatives seem to act with considerable selectivity toward *T. b. rhodesiense*. Therefore, the discussion will focus on antitrypanosmal activity. An important element for activity is conferred by the pyrazol moiety. It is not only crucial for antiparasitic activity but also for blood stage selectivity. Indeed, the β-diketone derivatives **1**−**3** only act toward the insect stage of the parasite, whereas ring closure to the pyrazol (compounds **5** and **6**) leads to compounds active against blood stage parasites. A pyrazol ring is found to be very important for activity toward the clinically more relevant blood stage. Whereas the lack of the pyrazol group leads to inactive compounds, the substitution by an isoxazole derivative (**13**) leads to a sixfold reduced activity compared to the most potent compound **10**. In addition, substitution with nitrophenyl (**14**) or aminophenyl (**16**) also results in strongly reduced activity. The importance of the morpholine moiety of the best compound (**10**) becomes evident when looking at derivatives exploring this position. While the piperazine derivative (**17**) maintains full activity, the introduction of a tetrahydropyran (**5**) or a bridging methylene group between the pyrazol and the morpholine ring (**6**) leads to a fourfold reduction of the activity. Interestingly, compound **12**, carrying an additional voluminous Boc substitution on the piperazine ring, exhibits similar activity as that of compounds **5**, **6**, and **17** with respect to *T. b. rhodesiense*. The comparison of compounds **4** and **5** allows the dissection of the role of the phenoxy ring in the compounds. Indeed, replacing it by an ethylene group (as found in compound **4**) reduces efficacy ninefold, indicating the phenoxy ring in the compounds to be important for biological activity. Further substitution with a nitro group (**11**) reduces potency 4-fold or 18-fold with an amino group at the same position (**15**) when compared to that of compound **10**.

Conclusion

We report the synthesis of new 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine derivatives as well as their synthesis precursors and present their antiprotozoal activity and their general cytotoxicity. Compound **10**, 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine, and compound **17**, 1-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]piperazine, are the most potent antitrypanosomals of the series and exhibit the same selectivity toward *T. b. rhodesiense* while exhibiting low cytotoxicity. The inhibition results on blood stage and insect stage forms of the parasite indicate stage-specific action, which may be due to stage-specific expression of the so-far unknown intracellular target(s) of these compounds. Further investigation on stage-specific target expression profiles will be needed to enlighten the observed specificity. To this end, work is in progress to identify the corresponding target(s) within the unicellular parasite using a chemical proteomics approach and to elucidate the mechanism of action on a molecular level.

Experimental Section

Chemistry. The chemicals were purchased from Sigma-Aldrich or Fluka (Switzerland) unless otherwise noted. All final products were characterized by ^{1}H NMR, ^{13}C NMR, MS, IR analysis, and melting points. Melting points were found with a digital melting point apparatus Büchi B-540; IR spectra were obtained with an infrared spectrometer system Paragon 500 FT (Perkin-Elmer) in KBr discs, and frequencies are reported in cm^{-1}; thin-layer chromatography (TLC) was carried out with TLC plates (Fluka, silica gel 60 F_{254} 0.2 mm, 20 × 20 cm, aluminum cards); the substances were detected in UV light at 254 nm; and MS was performed with an API 150EX MS System, TurboIonspray, MDS SCIEX (AB Applied Biosystems). The material for column chromatography was silica gel 60 (Fluka) (230−400 mesh), pore diameter 60 Å; NMR spectra were recorded on Varian Gemini 300. The chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) as the internal standard.

1-(4-Ethyl-phenyl)-3-(tetrahydropyran-4-yl)propane-1,3-dione (1). To a mixture of methyl tetrahydro-2*H*-pyran-4-carboxylate (2.88 g, 20 mmol) and ethylacetophenone (1.48 g, 10 mmol) in toluene (40 mL), a dispersion of 60% NaH in mineral oil (0.8 g, 20 mmol) was added in small portions. When the effervescence ceased, the mixture was refluxed for 6.5 h with vigorous stirring. The mixture was allowed to cool to room temperature and then poured into H_2O (70 mL). Hydrochloric acid was added until the pH was acidic, giving rise to an orange oil that was extracted with Et_2O (2 × 50 mL). The combined extracts were dried on Na_2SO_4 and afforded a reddish oil after solvent evaporation. The residue was purified by column chromatography (silica gel, dichloromethane) to yield **1** as a light-yellow crystalline solid (0.49 g, 18.8%). MS: calcd mass for M^+, 261.33; found, 261.5. Mp 57.7 °C. IR (KBr, cm^{-1}): 2968, 1609, 1117. NMR δ_H (300 MHz, $CDCl_3$): 1.26 (3H, t, J = 7.8 Hz), 1.83 (4H, m), 2.57 (1H, m), 2.71 (2H, q, J = 7.5 Hz), 3.47 (2H, m), 4.06 (2H, dt, J = 3.3, 3.6 Hz), 6.17 (1H, s), 7.28 (2H, d, J = 9.0 Hz), 7.81 (2H, d, J = 9.0 Hz), 16.29 (1H, s, br); δ_C (300 MHz, $CDCl_3$): 15.20 (CH_3), 28.87

Table 1. Antiparasitic Activity of Compounds **1**−**17** Expressed as IC_{50} (μM)[a]

	T. b. rhodesiense		*T. b. cruzi*	*L. donovani*	*P. falciparum* K1[b]L6-cells	L-6 cells
stage	blood	procyclic	amastigotes	amastigotes	erythrocyte	
1	20.9	3.4	54.9	9.8	>19	201.5
2	25.8	1.8	54.6	4.6	>15	231.0
3	18.9	1.0	20.6	5.2	>15	112.3
4	28.6	7.8	113.9	15.1	>19	164.6
5	3.2	43.0	59.0	6.4	>15	89.6
6	4.1	54.9	45.3	15.6	>14	149.7
7	223.8	>334	54.6	20.2	>18	40.5
8	51.4	16.6	24.4	9.7	>15	34.5
9	45.9	>249	>83	5.7	>13	155.8
10	1.0	40.7	52.0	8.0	>15	61.6
11	4.4	93.4	>81	22.3	>13	>245
12	2.9	17.6	12.8	2.3	8.1	30.0
13	5.9	75.2	46.5	12.7	10.5	171.9
14	28.8	>203	>67	4.8	3.7	>203
15	17.7	>267	>89	20.3	>14	>267
16	10.3	61.7	22.0	10.5	6.5	61.6
17	1.1	4.7	9.5	25.8	6.6	18.0
melarsoprol	0.01	0.13				
benznidazole			2.13			
miltefosine				0.26		
chloroquine					0.23	
podophyllotoxin						0.01

[a] Values represent the average of four determinations (two determinations of two independent experiments); errors for individual measurements differed by less than 50%. [b] Resistant to chloroquine and pyrimethamine.

(CH_2), 29.18 (2CH_2), 44.00 (CH), 67.38 (2CH_2), 93.88 (CH), 127.15 (2CH), 128.14 (2CH), 132.49, 149.37, 184.71, 196.96.

1-(4-Phenoxyphenyl)-3-(tetrahydropyran-4-yl)propane-1,3-dione (2). To a mixture of methyl tetrahydro-2*H*-pyran-4-carboxylate (1.44 g, 10 mmol) and 4-phenoxyacetophenone (2.12 g, 10 mmol) in THF (40 mL) was added a dispersion of 60% NaH in mineral oil (0.8 g, 20 mmol) in small portions. When the effervescence ceased, the mixture was refluxed for 3.5 h with vigorous stirring. The mixture was allowed to cool to room temperature and then poured into H_2O (70 mL). Hydrochloric acid was added until the pH was acidic, yielding a deep-orange oil that was extracted with Et_2O (5 × 30 mL). The dried combined extracts were evaporated, and the resulting yellowish solid was recrystallized from hexane to yield **2** as a white/yellow crystalline solid (0.63 g, 19.3%). MS: calcd mass for M^+, 325.37; found, 325.3. Mp 87.7 °C. IR (KBr, cm^{-1}): 2949, 1722, 1586, 1489, 1241, 1121. NMR δ_H (300 MHz, $CDCl_3$): 1.83 (4H, m), 2.58 (1H, m), 3.46 (2H, m), 4.01 (2H, m), 6.13 (1H, s), 7.01 (2H, d, J = 9.0 Hz), 7.08 (2H, d, J = 9.0 Hz), 7.19 (1H, t, J = 7.2 Hz), 7.38 (2H, d, J = 9.0 Hz), 7.87 (2H, d, J = 9.0 Hz); acidic H could not be detected because of solvent exchange effects; δ_C (300 MHz, $CDCl_3$): 28.37 (CH_2), 29.22 (CH_2), 39.69 (CHa), 43.83 (CHb), 66.96 (CH_2), 67.38 (CH_2), 93.61 (CH_2), 117.63 (2CH), 120.02 (2CH), 124.49 (CH), 129.14 (2CH), 130.02 (2CH), 155.61, 161.50, 179.64, 184.52, 196.21.

4-Morpholine-4-yl-1-(4-phenoxyphenyl)butane-1,3-dione (3). To a mixture of ethyl morpholine acetate (3.46 g, 20 mmol) and 4-phenoxyacetophenone (2.12 g, 10 mmol) in toluene (40 mL), a dispersion of 60% NaH in mineral oil (0.8 g, 20 mmol) was added in small portions. When the effervescence ceased, the mixture was refluxed for 2 h with vigorous stirring. The mixture was allowed to cool to room temperature and then poured into H_2O (70 mL). Hydrochloric acid was added until the pH was acidic. The organic phase contained byproducts and was discarded. The pH of the water phase was set to 6, and the product was extracted with ethyl acetate. Solvent evaporation afforded a clear oil that was further purified with basic wash steps, and white crystals of **3** were formed (1.92 g, 56.6%). MS: calcd mass for M^+, 340.39; found, 340.5. Mp 164.2 °C. IR (KBr, cm^{-1}): 2957, 2855, 2811, 1602, 1488, 1239, 1116. NMR δ_H (300 MHz, DMSO): 2.41(4H, s, br), 2.79 (2H, s, br), 3.58 (4H, s, br), 5.88 (1H, s, br), 6.93 (2H, d, J = 8.4 Hz), 7.03 (2H, d, J = 7.5 Hz), 7.15 (1H, t, J = 7.5 Hz), 7.40 (2H, t, J = 7.8 Hz), 7.76 (2H, d, J = 8.4 Hz); acidic H could not be detected because of solvent exchange effects; δ_C (300 MHz, DMSO): 53.84 (2CH_2), 66.28 (2CH_2), 68.35 (CH_2, br), 91.38 (CH_2, br), 117.33 (2CH), 118.98 (2CH), 123.66 (CH), 128.33 (2CH), 130.10 (2CH), 138.87, 156.39, 157.41, 179.97, 187.24.

3-(4-Ethyl-phenyl)-5-(tetrahydropyran-4-yl)-1*H*-pyrazol (4). Hydrazine hydrate (0.08 g, 1.54 mmol) was added to an EtOH (10 mL) solution of **1** (0.2 g, 0.77 mmol), and the reaction mixture was refluxed for 4−5 h. The organic phase was evaporated, and the resulting oil was purified by column chromatography (silica gel, ethyl acetate) to give a white solid of **4** (93.0 mg, 47.1%). MS: calcd mass for M^+, 257.35; found 257.5. Mp 106.5 °C. IR (KBr, cm^{-1}): 3209, 2964, 1580, 1456, 1079. NMR δ_H (300 MHz, $CDCl_3$): 1.26 (3H, t, J = 7.8 Hz), 1.88 (4H, m), 2,67 (2H, q, J = 7.5 Hz), 2.95 (1H, m), 3.50 (2H, m), 4.06 (2H, m), 4.50 (1H, NH, br, variable), 6.37 (1H, s), 7.24 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.2 Hz); δ_C (300 MHz, $CDCl_3$): 15.43 (CH_3), 28.64 (CH_2), 32.40 (2CH_2), 33.47 (CH), 67.64 (2CH_2), 99.76 (CH), 125.84 (2CH), 128.19, 128.41 (2CH), 144.88, 148.24, 153.06.

3-(4-Phenoxyphenyl)-5-(tetrahydropyran-4-yl)-1*H*-pyrazol (5). Hydrazine hydrate (0.12 g, 2.47 mmol) was added to an EtOH (20 mL) solution of **2** (0.4 g, 1.23 mmol), and the reaction mixture was refluxed for 19 h. The organic phase was evaporated, and the resulting oil was purified by column chromatography (silica gel, ethyl acetate) to give a white solid of **5** (31.2 mg, 7.9%). MS: calcd mass for M^+, 321.39; found, 321.5. Mp 134.5 °C. IR (KBr, cm^{-1}): 3236, 2939, 1590, 1490, 1242, 1110. NMR δ_H (300 MHz, $CDCl_3$): 1.86 (4H, m), 2.96 (1H, m), 3.52 (2H, m), 4.07 (2H, m), 4.3 (1H, NH, br, variable), 6.35 (1H, s), 7.02 (2H, d, J = 9.0 Hz), 7.05 (2H, d, J = 7.5 Hz), 7.14 (1H, t, J = 7.5 Hz), 7.35 (2H, d, J = 7.5 Hz), 7.65 (2H, d, J = 9.0 Hz); δ_C (300 MHz, $CDCl_3$): 32.33 (2CH_2), 33.26 (CH), 67.57 (2CH_2), 99.75 (CH), 118.82 (2CH), 119.28 (2CH), 123.72 (CH), 127.45 (2CH), 129.86 (2CH), 148.49, 152.31, 156.89, 157.32.

4-[5-(4-Phenoxyphenyl)-2*H*-pyrazol-3-ylmethyl]morpholine (6). Hydrazine hydrate (0.15 g, 2.95 mmol) was added to an EtOH (20 mL) solution of **3** (0.5 g, 1.47 mmol), and the reaction mixture was refluxed for 16 h. Acetic acid was added until a pH 5 was reached; then, the reaction solution was extracted with ethyl acetate (20 mL), and the organic phase was washed with a saturated $NaHCO_3$ solution (3×) and brine. The resulting crude product (320 mg) from the evaporated organic phase was purified by column chromatography (silica gel, ethyl acetate/MeOH 9:1) to give a beige solid of **6** (37.8 mg, 7.7%). MS: calcd mass for M^+, 336.41; found, 336.5. Mp 133.6 °C. IR (KBr, cm^{-1}): 3094, 2921, 2862, 2829,

1588, 1490, 1236, 1114. NMR δ_H (300 MHz, $CDCl_3$): 2.55 (4H, s, br), 3.64 (2H, s), 3.75 (4H, m), 6.47 (1H, s), 7.04 (2H, d, J = 8.7 Hz), 7.04 (2H, d, J = 8.7 Hz), 7.12 (1H, t, J = 5.1 Hz), 7.34 (2H, t, J = 8.1 Hz), 7.69 (2H, d, J = 8.4 Hz); the NH signal could not be detected because of solvent exchange effects; δ_C (300 MHz, $CDCl_3$): 53.36 ($2CH_2$), 54.27 (CH_2), 66.52 ($2CH_2$), 102.62 (CH), 119.02 (4CH), 123.46 (CH), 127.01 (2CH), 129.79 (2CH), 157.30.

3,3-Bis(methylsulfanyl)-1-(4-nitrophenyl)propenone (7). *N,N*-Dimethylacetamide (1 mL; 10.8 mmol) was added to a stirred (30 min) solution of 4-nitroacetophenone (826 mg; 5 mmol), 60% NaH in mineral oil (0.45 g; 11 mmol), CS_2 (0.5 mL; 8.3 mmol), and MeI (1 mL; 16.6 mmol) in toluene (30 mL) at 25−30 °C. Stirring was continued overnight before the mixture was poured into ice water. The whole mixture was extracted with ethyl acetate, and the organic phase was washed with H_2O, dried over $MgSO_4$, and concentrated. The solid residue was washed with ethyl acetate to give an insoluble, yellow precipitate of **7** (0.12 g, 8.8%). MS: calcd mass for M^+, 270.3; found, 270.1. Mp 171.9 °C. IR (KBr, cm^{-1}): 1621, 1595, 1517, 1347. NMR δ_H (300 MHz, $CDCl_3$): 2.57 (3H, s), 2.60 (3H, s), 6.72 (1H, s), 8.04 (2H, d, J = 9.0 Hz), 8.29 (2H, d, J = 9.0 Hz); δ_C (300 MHz, $CDCl_3$): 15.18 (CH_3), 17.48 (CH_3), 108.46 (CH), 123.74 (2CH), 128.60 (2CH), 144.51, 149.43, 170.42, 183.24.

3,3-Bis(methylsulfanyl)-1-(4-phenoxy)phenyl]propenone (8). *N,N*-Dimethylacetamide (4.87 mL; 52.7 mmol) was added to a stirred (30 min) solution of 4-phenoxyacetophenone (5.16 g; 24.3 mmol), 60% NaH in mineral oil (2.14 g; 53.5 mmol), CS_2 (2.43 mL; 40.3 mmol), and MeI (5.1 mL; 81.7 mmol) in toluene (50 mL) at 25−30 °C. Stirring was continued overnight; then, the mixture was poured into ice water. The whole mixture was extracted with ethyl acetate, and the organic phase was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue was recrystallized from EtOH to give orange needles of **8** (3.72 g, 48.4%). MS: calcd mass for M^+, 317.4; found, 317.3. Mp 114.2 °C (lit. 105−107 °C).[13] IR (KBr, cm^{-1}): 1617, 1584, 1230 (lit. 1612, 1580).[13] NMR δ_H (300 MHz, $CDCl_3$): 2.53 (3H, s), 2.56 (3H, s), 6.74 (1H, s), 7.00 (2H, d, J = 8.7 Hz), 7.07 (2H, d, J = 7.5 Hz), 7.18 (1H, t, J = 7.5 Hz), 7.38 (2H, t, J = 7.5 Hz), 7.91 (2H, d, J = 8.7 Hz); δ_C (300 MHz, $CDCl_3$): 15.05 (CH_3), 17.32 (CH_3), 109.27 (CH), 117.47 (2CH), 119.92 (2CH), 124.27 (CH), 129.83 (2CH), 129.94 (2CH), 133.92, 155.8, 160.79, 165.77, 184.45.

3,3-Bis(methylsulfanyl)-1-[4-(4-nitrophenoxy)phenyl]propenone (9). *N,N*-Dimethylacetamide (2 mL; 21.7 mmol) was added to a stirred (30 min) solution of 4-acetyl-4′-nitrodiphenyl ether (2.57 g; 10 mmol), 60% NaH in mineral oil (0.9 g; 22 mmol), CS_2 (1 mL; 16.6 mmol), and MeI (2.1 mL; 33.2 mmol) in toluene (20 mL) at 25−30 °C. Stirring was continued overnight; then, the mixture was poured into ice water. The whole mixture was extracted with ethyl acetate, and the organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The residue was recrystallized from EtOH to give orange needles of **9** (1.9 g, 52%). MS: calcd mass for M^+, 362.4; found, 362.3. Mp 138.7 °C. IR (KBr, cm^{-1}): 1620, 1585, 1507, 1337, 1248. NMR δ_H (300 MHz, $CDCl_3$): 2.54 (3H, s), 2.58 (3H, s), 6.73 (1H, s), 7.08 (2H, d, J = 9.0 Hz), 7.12 (2H, d, J = 8.7 Hz), 7.98 (2H, d, J = 8.7 Hz), 8.23 (2H, d, J = 9.0 Hz); δ_C (300 MHz, $CDCl_3$): 15.04 (CH_3), 17.33 (CH_3), 108.81 (CH), 117.97 (2CH), 119.64 (2CH), 125.96 (2CH), 130.09 (2CH), 136.13, 143.14, 157.74, 162.13, 167.22, 184.02.

4-[5-(4-Phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine (10). To a solution of **8** (0.25 g; 0.79 mmol) in EtOH (10 mL) was added morpholine (0.07 mL; 0.81 mmol), and the reaction mixture was refluxed for 3 h. It was then brought to room temperature, and hydrazine hydrate (0.06 g; 1.2 mmol) in EtOH (4 mL) was added dropwise over a period of 10 min. Then, the reaction mixture was refluxed for another 16 h. The solvent was removed under reduced pressure, and the oily residue was purified by column chromatography (silica gel, ethyl acetate) to give a white solid of **10** (30.4 mg, 12%). MS: calcd mass for M^+, 322.38; found, 322.3. Mp 171.6 °C. IR (KBr, cm^{-1}): 3268, 2967, 2826, 1590, 1246, 1107. NMR δ_H (300 MHz, $CDCl_3$): 3.21 (4h, t, J = 4.6 Hz), 3.82 (4h, t, J = 4.9 Hz), 5.90 (1H, s), 7.02 (4H, dd, J = 8.4, 7.5 Hz), 7.14 (1H, t, J = 7.2 Hz), 7.35 (2H, t, J = 7.5 Hz), 7.49 (2H, d, J = 8.4 Hz); the NH signal could not be detected because of solvent exchange effects; δ_C (300 MHz, $CDCl_3$): 47.50 ($2CH_2$), 66.25 ($2CH_2$), 89.31 (CH), 118.38 (2CH), 119.68 (2CH), 122.52, 124.15 (CH), 127.33 (2CH), 129.96 (2CH), 156.05, 159.21, 167.63, 169.24.

4-{5-[4-(4-Nitrophenoxy)phenyl]-2*H*-pyrazol-3-yl}morpholine (11). To a solution of **9** (1 g; 2.8 mmol) in EtOH (30 mL) was added morpholine (0.6 mL; 7 mmol), and the reaction mixture was refluxed for 12 h. It was then brought to room temperature, and hydrazine hydrate (0.27 g; 5.5 mmol) in EtOH (5 mL) was added dropwise over a period of 10 min. Then, the reaction mixture was refluxed for another 12 h (monitored by NMR). The solvent was removed under reduced pressure, and the residue (1.43 g) was purified by column chromatography (silica gel, ethyl acetate/petroleum ether 9:1) to give yellow crystals of **11** (0.64 g, 63%). MS: calcd mass for M^+, 367.38; found, 367.3. Mp 72.5 °C. IR (KBr, cm^{-1}): 3110, 2960, 2854, 1590, 1515, 1343, 1247, 1111. NMR δ_H (300 MHz, $CDCl_3$): 3.25 (4H, t, J = 4.8 Hz), 3.86 (4H, t, J = 4.9 Hz), 5.97 (1H, s), 7.06 (2H, d, J = 7.0 Hz), 7.14 (2H, d, J = 6.7 Hz), 7.61 (2H, d, J = 6.7 Hz), 8.23 (2H, d, J = 7.0 Hz); the NH signal could not be detected because of solvent exchange effects; δ_C (300 MHz, $CDCl_3$): 48.50 ($2CH_2$), 66.39 ($2CH_2$), 88.67 (CH), 117.34 (2CH), 120.76 (2CH), 125.98 (2CH), 127.32 (2CH), 127.56, 142.86, 144.71, 154.77, 159.33, 162.77.

4-[5-(4-Phenoxyphenyl)-2*H*-pyrazol-3-yl]piperazine-1-carboxylic Acid Tert-Butyl Ester (12). To a solution of **8** (1 g; 3.2 mmol) in EtOH (16 mL) was added tert-butylpiperazine-1-carboxylate (1-Boc-piperazine) (0.62 g; 3.32 mmol), and the reaction mixture was refluxed for 19 h. It was then brought to room temperature, and hydrazine hydrate (0.32 g; 6.3 mmol) in EtOH (5 mL) was added dropwise. Then, the reaction mixture was refluxed for another 23 h (monitored by TLC). The solvent was removed under reduced pressure, and the oily residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether 6:4, and 1% triethylamine) to give a yellow solid of **12** (0.26 g, 19.3%). MS: calcd mass for M^+, 421.52; found, 421.3. Mp 178 °C. IR (KBr, cm^{-1}): 3332, 2976, 2969, 2835, 1668, 1589, 1243, 1172. NMR δ_H (300 MHz, $CDCl_3$): 1.48 (9H, s), 3.23 (4H, t, J = 6.0 Hz), 3.55 (4H, t, J = 5.1 Hz), 5.92 (1H, s), 7.01 (2H, d, J = 8.7 Hz), 7.05 (2H, d, J = 7.9 Hz), 7.15 (1H, t, J = 7.3 Hz), 7.37 (2H, t, J = 7.9 Hz), 7.50 (2H, d, J = 8.7 Hz); the NH signal could not be detected because of solvent exchange effects; δ_C (300 MHz, $CDCl_3$): 28.42 ($3CH_3$), 48.13 ($2CH_2$), 80.03 ($2CH_2$), 88.67 (CH), 118.74 (2CH), 119.42 (2CH), 123.90 (CH), 124.23, 127.28 (2CH), 129.88 (2CH), 145.76, 154.67, 156.34, 158.19.

4-[3-(4-Phenoxyphenyl)isoxazol-5-yl]morpholine (13). To a solution of **8** (1 g; 3.2 mmol) in EtOH (16 mL) was added morpholine (0.7 mL; 8 mmol), and the reaction mixture was refluxed for 48 h. It was then brought to room temperature, and hydroxylamine hydrochloride (0.44 g; 6.3 mmol) and potassium hydroxide (0.37 g; 6.6 mmol) were added. This suspension was refluxed for another 24 h (monitored by NMR). The solvent was then removed under reduced pressure, and the residue was taken up in 0.5 M Na_2CO_3 and extracted with dichloromethane (3×). The combined extracts were washed with basic brine, dried (Na_2SO_4), and evaporated. After a final recrystallization in EtOH, **13** was received as white crystals (0.4 g, 39.3%). MS: calcd mass for M^+, 323.37; found, 323.5. Mp 135.1 °C. IR (KBr, cm^{-1}): 2867, 1590, 1253, 1111. NMR δ_H (300 MHz, $CDCl_3$): 3.32 (4H, t, J = 4.8 Hz), 3.83 (4H, t, J = 4.8 Hz), 6.09 (1H, s), 7.03 (2H, d, J = 7.8 Hz), 7.06 (2H, d, J = 9.0 Hz), 7.17 (1H, t, J = 7.5 Hz), 7.38 (2H, t, J = 7.8 Hz), 7.68 (2H, d, J = 9.0 Hz); δ_C (300 MHz, $CDCl_3$): 47.50 ($2CH_2$), 66.25 ($2CH_2$), 89.31 (CH), 118.38 (2CH), 119.68 (2CH), 122.52, 124.15 (CH), 127.33 (2CH), 129.96 (2CH), 156.05, 159.21, 167.63, 169.24.

4-[2-(4-Nitrophenyl)-5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]-morpholine (14). To a solution of **8** (1 g; 3.2 mmol) in EtOH (16 mL) was added morpholine (0.7 mL; 8 mmol), and the reaction mixture was refluxed for 60 h. It was then brought to room temperature, and 4-nitrophenylhydrazine (0.97 g; 6.3 mmol) was added. Then, the reaction mixture was refluxed for another 48 h

(monitored by MS and NMR). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether 4:6, followed by ethyl acetate/petroleum ether 5:5). The residue was recrystallized from ethyl acetate to give **14** (103.8 mg, 7.4%) as orange crystals. MS: calcd mass for M^+, 443.48; found, 443.3. Mp 183.4 °C. IR (KBr, cm^{-1}): 2970, 1592, 1520, 1329, 1240, 1114. NMR δ_H (300 MHz, $CDCl_3$): 3.32 (4H, t, $J = 4.7$ Hz), 3.86 (4H, t, $J = 4.8$ Hz), 6.01 (1H, s), 6.97 (2H, dt, $J = 9.0$, 2.1 Hz), 7.07 (2H, dd, $J = 8.5$, 1.0 Hz), 7.20 (3H, m), 7.40 (4H, m), 8.13 (2H, dt, $J = 9.6$, 2.1 Hz); δ_C (300 MHz, $CDCl_3$): 47.80 ($2CH_2$), 66.50 ($2CH_2$), 97.49 (CH), 118.26 (2CH), 119.78 (2CH), 123.18 (2CH), 124.25 (CH), 124.41 (2CH), 124.74, 129.99 (2CH), 130.21 (2CH), 144.29, 144.70, 145.05, 155.89, 158.50, 159.99.

4-[4-(5-Morpholine-4-yl-1*H*-pyrazol-3-yl)phenoxy]phenylamine (15). To the solution of **11** (0.3 g; 0.8 mmol) in MeOH or ethyl acetate was added palladium-on-carbon (<10% of the product). After the degassing the liquid under vacuum, the solution was kept under H_2 overnight at room temperature. Adding dichloromethane to the solution stopped the reaction; then, the solution was washed with activated carbon and filtered over celite. Solvent evaporation yielded pure **15** as a white powder (0.28 g, 98.7%). MS: calcd mass for M^+, 337.4; found, 337.5. Mp 197.1 °C. IR (KBr, cm^{-1}): 3417, 3343, 3198, 2964, 1618, 1506, 1274, 1249, 1112. NMR δ_H (300 MHz, $CDCl_3$): 3.20 (4H, t, $J = 4.8$ Hz), 3.65 (2H, NH_2, s), 3.81 (4H, t, $J = 4.8$ Hz), 5.88 (1H, s), 6.68 (2H, dt, $J = 8.8$, 2.1 Hz), 6.88 (2H, dt, $J = 8.8$, 2.1 Hz), 6.92 (2H, d, $J = 9.0$ Hz), 7.42 (2H, d, $J = 9.0$ Hz), 10.35 (1H, NH, s); δ_C (300 MHz, $CDCl_3$): 48.51 ($2CH_2$), 66.52 ($2CH_2$), 88.62 (CH), 116.26 (2CH), 117.37 (2CH), 121.29 (2CH), 123.92, 126.71 (2CH), 143.02, 144.63, 147.96, 159.29, 160.13.

4-[5-Morpholine-4-yl-3-(4-phenoxyphenyl)pyrazol-1-yl]-phenylamine (16). To a solution of **14** (70 mg; 0.158 mmol) in hot ethanol (11.25 mL) was added gradually a solution of sodium dithionite (0.28 g; 1.58 mmol) in 1 mL of water. The mixture was refluxed for 1 h, cooled to room temperature, and filtered to remove inorganic matter. The filtrate was diluted with 3 volumes of water; then, the pH was brought to 9 with Na_2CO_3, and the solution was extracted with ethyl acetate (5×). The combined extracts were dried over Na_2SO_4, and the solvent removed. The crude product was purified by column chromatography (silica gel, ethyl acetate/MeOH, first 9:1, then 7:3) to give **16** as a brown solid (30.3 mg, 46.5%). MS: calcd mass for M^+, 413.5; found, 413.5. Mp 160.7 °C. IR (KBr, cm^{-1}): 3439, 3331, 2964, 1629, 1588, 1292, 1232, 1114. NMR δ_H (300 MHz, $CDCl_3$): 3.28 (4H, t, $J = 4.8$ Hz), 3.85 (4H, t, $J = 4.8$ Hz), 5.91 (1H, s), 6.60 (2H, dt, $J = 9.0$, 2.1 Hz), 6.88 (2H, dt, $J = 9.0$, 2.1 Hz), 7.02 (2H, d, $J = 7.5$ Hz), 7.05 (2H, d, $J = 8.7$ Hz), 7.15 (1H, t, $J = 7.5$ Hz), 7.17 (2H, d, $J = 8.7$ Hz), 7.35 (2H, t, $J = 7.2$ Hz); the NH_2 signal could not be detected because of solvent exchange effects; δ_C (300 MHz, $CDCl_3$): 48.37 ($2CH_2$), 66.67 ($2CH_2$), 93.09 (CH), 115.08 (CH), 118.02 (2CH), 119.41 (2CH), 123.75 (2CH), 125.54, 126.66 (2CH), 129.81 (2CH), 129.94 (2CH), 156.34, 157.30.

1-[5-(4-Phenoxyphenyl)-2*H*-pyrazol-3-yl]piperazine (17). Trifluoroacetic acid (2 mL) was added slowly under argon to an ice-cooled solution of **12** (169.7 mg; 0.4 mmol) in dichloromethane (2 mL). The mixture was stirred on ice for 1 h and then poured onto cold water (10 mL). The pH of the solution was brought to 9 by adding concentrated ammonia, and then, the product was extracted into dichloromethane (3 × 20 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo to yield a white precipitation of **17** (116.7 mg, 90.3%). MS: calcd mass for M^+, 321.4; found, 321.5. Mp 213.3 °C. IR (KBr, cm^{-1}): 3266, 3147, 2952, 1591, 1244. NMR δ_H (300 MHz, DMSO): 2.79 (4H, t, br, $J = 5.1$ Hz), 3.03 (4H, t, br, $J = 5.1$ Hz), 6.07 (1H, s, br), 7.04 (2H, d, $J = 7.8$ Hz), 7.04 (2H, d, $J = 7.8$ Hz), 7.16 (1H, t, $J = 7.2$ Hz), 7.41 (2H, t, $J = 7.8$ Hz), 7.69 (2H, d, $J = 8.7$ Hz), 12.19 (1H, NH, s, br); the second NH signal could not be detected because of solvent exchange effects; δ_C (300 MHz, DMSO): 45.11 ($2CH_2$), 49.06 ($2CH_2$), 88.23 (CH, br), 118.72 (2CH), 118.81 (2CH), 123.61 (CH), 126.54 (2CH), 130.12 (2CH), 119.23, 124.03, 128.45, 156.11, 156.50.

Antiprotozoal Activity. The tests were performed at pH 7.4 as microplate assays using *T. b. rhodesiense* (STIB900), *T. cruzi* (Tulahuen C4), *L. donovani* (MHOM-ET-67/L82), and *P. falciparum* K1 (resistant to chloroquine and pyrimethamine), and the cytotoxicity was assessed with rat skeletal myoblasts (L-6 cells), as described earlier.[18] Compounds were measured in duplicate in the range of 0.2 to 19.5 μM, and IC_{50} values were calculated from the sigmoidal inhibition curves. The assay was repeated in duplicate for active compounds while using concentrations as low as 3.5 nM. The following substances were used as reference standards: melarsoprol (*T. b. rhodesiense*), benznidazole (*T. cruzi*), miltefosine (*L. donovani*), chloroquine (*P. falciparum*), and podophyllotoxin (cytotoxicity assay).

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Supporting Information Available: Analytical and spectral characterization data (^1H, ^{13}C NMR, MS, HRMS, and HPLC). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Barrett, M. P.; Burchmore, R. J.; Stich, A.; Lazzari, J. O.; Frasch, A. C.; Cazzulo, J. J.; Krishna, S. The trypanosomiases. *Lancet* **2003**, *362*, 1469−1480.
(2) Campos-Ponce, M.; Ponce, C.; Ponce, E.; Maingon, R. D. *Leishmania chagasi/infantum*: further investigations on *Leishmania* tropisms in atypical cutaneous and visceral leishmaniasis foci in Central America. *Exp. Parasitol.* **2005**, *109*, 209−219.
(3) Piscopo, T. V.; Mallia Azzopardi, C. Leishmaniasis. *Postgrad. Med. J.* **2007**, *83*, 649−657.
(4) Greenwood, B. M.; Bojang, K.; Whitty, C. J.; Targett, G. A. Malaria. *Lancet* **2005**, *365*, 1487−1498.
(5) Renslo, A. R.; McKerrow, J. H. Drug discovery and development for neglected parasitic diseases. *Nat. Chem. Biol.* **2006**, *2*, 701−710.
(6) Perozzo, R.; Kuo, M.; Sidhu, A. S.; Valiyaveettil, J. T.; Bittman, R.; Jacobs, W. R., Jr.; Fidock, D. A.; Sacchettini, J. C. Structural elucidation of the specificity of the antibacterial agent triclosan for malarial enoyl acyl carrier protein reductase. *J. Biol. Chem.* **2002**, *277*, 13106−13114.
(7) Surolia, N.; Surolia, A. Triclosan offers protection against blood stages of malaria by inhibiting enoyl-ACP reductase of *Plasmodium falciparum*. *Nat. Med.* **2001**, *7*, 167−173.
(8) Tasdemir, D.; Lack, G.; Brun, R.; Ruedi, P.; Scapozza, L.; Perozzo, R. Inhibition of *Plasmodium falciparum* fatty acid biosynthesis: evaluation of FabG, FabZ, and FabI as drug targets for flavonoids. *J. Med. Chem.* **2006**, *49*, 3345−3353.
(9) Freundlich, J. S.; Anderson, J. W.; Sarantakis, D.; Shieh, H. M.; Yu, M.; Valderramos, J. C.; Lucumi, E.; Kuo, M.; Jacobs, W. R., Jr.; Fidock, D. A.; Schiehser, G. A.; Jacobus, D. P.; Sacchettini, J. C. Synthesis, biological activity, and X-ray crystal structural analysis of diaryl ether inhibitors of malarial enoyl acyl carrier protein reductase. Part 1: 4′-substituted triclosan derivatives. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5247−5252.
(10) Go, M. L. Novel antiplasmodial agents. *Med. Res. Rev.* **2003**, *23*, 456−487.
(11) Campo, J. A.; Cano, M.; Heras, J. V.; Lagunas, M. C.; Perles, J.; Pinilla, E.; Torres, M. R. Investigation of structural characteristics of bis(β-diketonato)copper(II) complexes containing alkoxy or aryloxy side chains: X-ray structures of 1,3-bis(4-butoxyphenyl)propane-1,3-dione, bis[1,3-bis(4-butoxyphenyl)propane-1,3-dionato-κO,κO′]-copper(II) and bis[1,3-bis(4-phenoxyphenyl)propane-1,3-dionato-κO,κO′]copper(II). *Helv. Chim. Acta* **2001**, *84*, 2316−2329.
(12) Tanitame, A.; Oyamada, Y.; Ofuji, K.; Fujimoto, M.; Suzuki, K.; Ueda, T.; Terauchi, H.; Kawasaki, M.; Nagai, K.; Wachi, M.; Yamagishi, J. Synthesis and antibacterial activity of novel and potent DNA gyrase inhibitors with azole ring. *Bioorg. Med. Chem.* **2004**, *12*, 5515−5524.
(13) Tomisawa, K.; Kameo, K.; Matsunaga, T.; Saito, S.; Hosoda, K.; Asami, Y.; Sota, K. Studies on hypolipidemic agents. III. Omega-(4-phenoxybenzoyl)-alkanoic acid derivatives. *Chem. Pharm. Bull. (Tokyo)* **1986**, *34*, 701−712.
(14) Mahata, P. K.; Syam Kumar, U. K.; Sriram, V.; Ila, H.; Junjappa, H. 1-Bis(methoxy)-4-bis(methylthio)-3-buten-2-one: Useful three carbon synthon for synthesis of five and six membered heterocycles

with masked (or unmasked) aldehyde functionality. *Tetrahedron* **2003**, *59*, 2631−2639.

(15) Kerrigan, F.; Martin, C.; Thomas, G. H. Synthesis of arylpiperazines via palladium-catalysed aromatic amination reactions of bromoarenes with *N*-tert-butoxycarbonylpiperazine. *Tetrahedron Lett.* **1998**, *39*, 2219−2222.

(16) Hudlicky, M. *Reduction in organic chemistry*, 2nd. ed.; American Chemical Society: Washington, DC, 1996; pp 91−101.

(17) Nwaka, S.; Hudson, A. Innovative lead discovery strategies for tropical diseases. *Nat. Rev. Drug. Discov.* **2006**, *5*, 941−955.

(18) Orhan, I.; Sener, B.; Atici, T.; Brun, R.; Perozzo, R.; Tasdemir, D. Turkish freshwater and marine macrophyte extracts show in vitro antiprotozoal activity and inhibit FabI, a key enzyme of *Plasmodium falciparum* fatty acid biosynthesis. *Phytomedicine* **2006**, *13*, 388−393.

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