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BRIEF ARTICLE

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A New Class of Phenazines with Activity against a Chloroquine Resistant *Plasmodium falciparum* Strain and Antimicrobial Activity

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Supporting Information

ABSTRACT: New phenazines were synthesized by oxygenation of 1- and 2-naphthol with transition metal peroxo complexes and in situ reaction with 1,2-diamines. The title compounds were evaluated for in vitro antimalarial activity against *Plasmodium falciparum* and chloroquine-resistant strains. Phenazines **12**, **27**, and **28** were most prominent in growth inhibition. In vivo protection against cerebral malaria was observed with the phenazines **11**, **12**, **20**, and **27**, whereas partial protection was provided by **19**.

INTRODUCTION

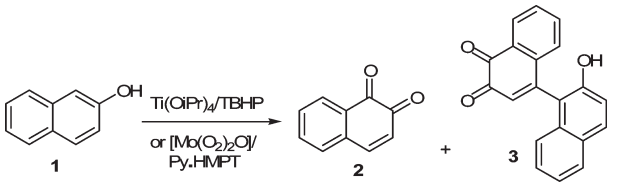
Malaria is still a worldwide problem of public health, affecting 300−00 million people and causing about 2.5 million deaths annually, mainly among children less than 5 years old.[1] Today, chloroquine-resistant strains of *P. falciparum* (and to some extent of *P. vivax*) are common in all endemic areas throughout the world. The high incidence of resistance against chloroquine is the most important reason for the increasing spread of malaria. New families of active compounds are needed as well as polychemotherapy, associating molecules with independent mechanisms of action, to decrease the risk of resistance.[2] Natural and synthetic phenazines have attracted considerable attention because of their interesting biological activities, including broad-spectrum antibiotic, antimicrobial, trypanocidal, antihepatitis C viral replication, and antitumor activities.[7] They have also been described as antipasmodial[3] and dual inhibitors of topoisomerases I and II.[4] The interesting biological activities and the recent reports as antiplasmodial agents prompted us to explore the development of efficient and economical syntheses of new classes of phenazines and to investigate their antiplasmodial effects.

CHEMISTRY

Synthesis of Phenazines from 2-Naphthols. The chemical basis of our synthesis of new phenazine derivatives was a discovery made almost 20 years ago by our group.[5] Treatment of phenols such as 2-naphthol (**1**) with transition metal alkoxides and *tert*-butyl hydroperoxide (TBHP) or other oxodiperoxo complexes such as the Mimoun complex ($[Mo(O_2)_2O]\cdot Py\cdot$HMPT) afforded *o*-quinones such as **2**. However, in the presence of the transition metal catalysts, the unreacted phenols present in the mixture immediately reacted with the *o*-quinones formed to yield Michael adducts such as **3** (Scheme 1).[5a]

This kind of "dimerization" was previously also observed by Wanzlick.[6] In the present investigation, the simultaneous formation of *o*-quinones **2** and **3** was a welcome increase in diversity in the phenazine synthesis. In the following section we describe the systematic variation of the substitution pattern on the naphthalene and the 1,2-diamine parts to create a large diversity of different phenazines to be tested in our antimalaria program.

Scheme 1



In the first series, differently substituted 2-naphthols (**1** and **4**−**6**) were treated with Mimoun's oxodiperoxo molybdenum complex (Mimoun complex, $[Mo(O_2)_2O]\cdot Py\cdot$HMPT) at room temperature (Scheme 2), analogous to methods developed previously in our laboratory.[5a,b] In addition, we investigated the possibility of an in situ phenazine formation by addition of *o*-phenylenediamine after completion of the oxidation process. TLC analysis showed the rapid transformation of 2-naphthol (**1**) to the *o*-quinone **2** and the Michael adduct **3**, followed by in situ conversion to phenazines **7** and **11**, respectively, after addition of *o*-phenylenediamine.

Thus, our existing method for the flexible and concise one-step synthesis of *o*-quinones was extended to an operationally simple one-pot phenazine synthesis. The simplest oxidant and the mildest reaction conditions were possible using the Mimoun complex, easily prepared in two steps from MoO_3.[7] The phenazines were formed from possible monomeric and "dimeric" *o*-quinone intermediates **2** and **3** and could easily be separated by silica gel chromatography because of the considerable difference in molecular weight and structural differences. Using this simple

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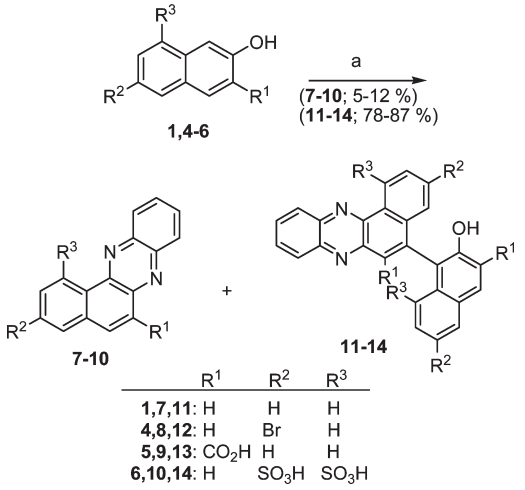
Scheme 2[a]



[a] Reagents and conditions: (a) $[Mo(O_2)_2O]\cdot Py\cdot HMPT$, room temp, 20 h, then $C_6H_4(NH_2)_2$, AcOH, room temp, 12 h.

Scheme 3

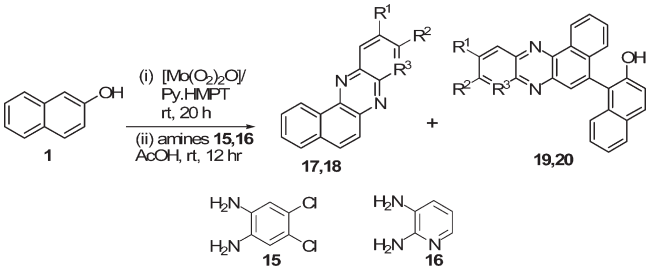


Table 1. One Pot Synthesis of Phenazines 17−20

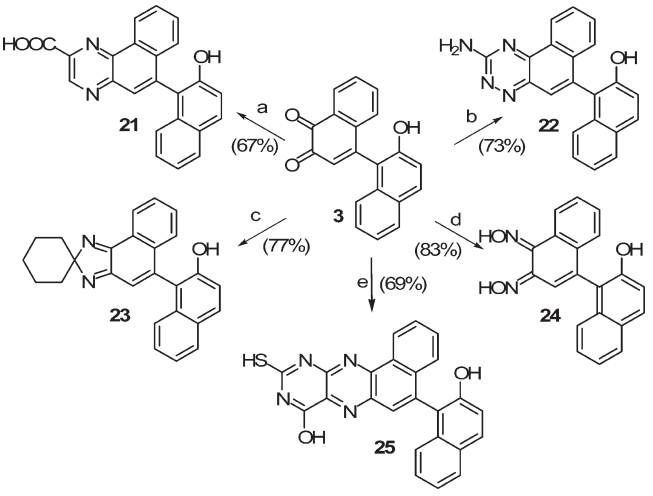
entry	R^1	R^2	R^3	amine	minor phenazine (%)	major phenazine (%)
1	Cl	Cl	CH	**15**	**17** (9)	**19** (82)
2	H	H	N	**16**	**18** (7)	**20** (78)

procedure, we prepared a number of new types of the two classes of phenazines, **7**−**10** derived from monomeric, and **11**−**14** from the "dimeric" *o*-quinones by varying the substituents R^1−R^3 on the 2-naphthols (**1**, **4**−**6**, Scheme 2).

To introduce further diversity in the synthesis of substituted phenazines, the 1,2-diamine part was varied and 4,5-dichlorobenzene-1,2-diamine (**15**) and pyridine-2,3-diamine (**16**) were used for condensation with the initially formed *o*-quinones **2** and **3** (Scheme 3). The yields and conditions are listed in Table 1.

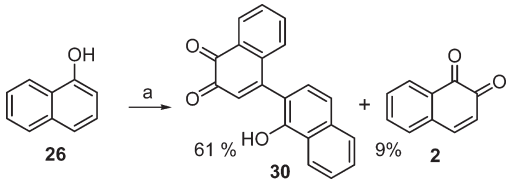
Next, nonaromatic 1,2-diamines are used to condense with *o*-quinone **3**. For this purpose, the *o*-quinone **3** was prepared (59%) by our methodology,[5a,b] using the transition metal complex $Ti(O\text{-}i\text{-}Pr)_4$ with *tert*-butyl hydroperoxide (TBHP). Condensation of the Michael adduct **3** with 2,3-diaminopropionic acid was accompanied by spontaneous aromatization[8] to yield the desired **21** in 67% yield (Scheme 4). Similarly, the 1,2,4-triazine **22** was prepared in 73% yield by reaction of **3** with aminoguanidine in ethanol.[9] The conversion of *o*-quinone **3** to the corresponding 2,2-spirocyclohexane derivative **23** occurred in 77% yield by refluxing in

Scheme 4[a]



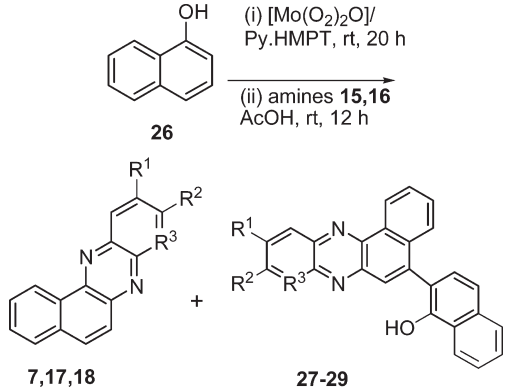
[a] Reagents and conditions: (a) 2,3-diaminopropionic acid, MeOH, reflux, 5 h; (b) aminoguanidine, MeOH, reflux, 4 h; (c) cyclohexanone, $CH_3CO_2NH_4$, reflux, 1 h; (d) $NH_2OH.HCl$, EtOH, room temp, 24 h; (e) 5,6-diamino-2-mercaptopyrimidin-4-ol, AcOH, 35 °C, 8 h.

Scheme 5[a]



[a] Reagents and conditions: (a) $Ti(O\text{-}i\text{-}Pr)_4$/TBHP, −6 °C, 7 h.

Scheme 6



acetic acid with cyclohexanone in the presence of excess NH_4OAc.[10] The open chain 1,2-dioxime **24** was readily prepared by reaction of **3** with hydroxylamine hydrochloride in 83% yield. Finally, the condensation of a heterocyclic ring to a phenazine was achieved by condensation of *o*-quinone **3** with 5,6-diamino-2-mercaptopyrimidin-4-ol in the presence of acetic acid to afford **25** in 69% yield.

Synthesis of Phenazines from 1-Naphthol. Further diversity was created by replacing the starting 2-naphthol (**1**) with 1-naphthol (**26**) in the oxygenation with $[Mo(O_2)_2O]\cdot Py\cdot HMPT$. In this reaction, apparently the same *o*-naphthoquinone

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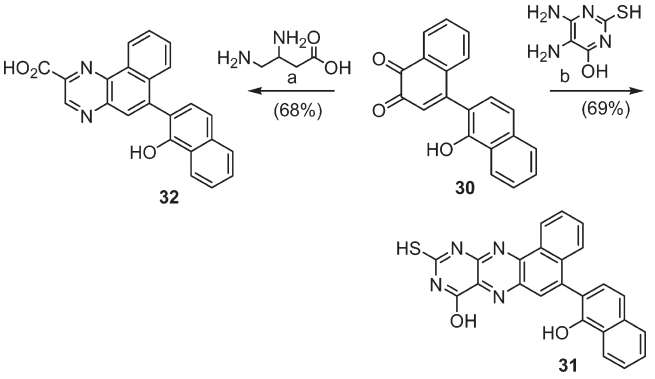
Table 2. One Pot Synthesis of Phenazines 7, 17, 18, and 27−29

entry	R^1	R^2	R^3	amine	minor phenazine (%)	major phenazine (%)
1	H	H	CH	*o*-phenylenediamine	**7** (9)	**27** (82)
2	Cl	Cl	CH	4,5-dichlorobenzene-1,2-diamine (**15**)	**17** (7)	**28** (81)
3	H	H	N	pyridine-2,3-diamine (**16**)	**18** (7)	**29** (81)

Scheme 7[a]



[a] Reagents and conditions: (a) 2,3-diaminopropionic acid, MeOH, reflux, 5 h; (b) 5,6-diamino-2-mercaptopyrimidin-4-ol, AcOH, 35 °C, 8 h.

(**2**) was initially formed in the oxygenation of **26**. However, a new regioisomer **30** (Scheme 5) by addition to the *o*-naphthoquinone **3** was formed, generated from 2-naphthol (**1**).

In the in situ condensation reaction of the reaction mixture from the oxygenation with $[Mo(O_2)_2O]\cdot Py\cdot HMPT$ and the aromatic diamines *o*-phenylenediamine, **15**, and **16**, the same monomeric phenazines **7**, **17**, and **18** and the "dimeric" phenazines **27**−**29** were formed as shown in Schemes 2 and 3 (Scheme 6, Table 2).

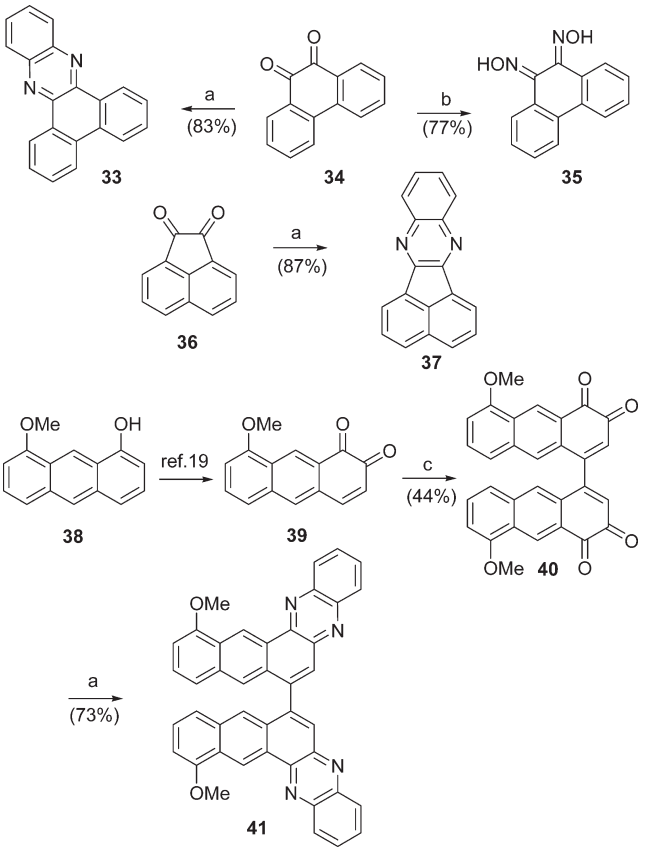
In the next series, the *o*-quinone **30** (61%) prepared in the oxygenation of 1-naphthol (**26**) using the transition metal complex $Ti(O\text{-}i\text{-}Pr)_4$ with TBHP as described above, was reacted with 5,6-diamino-2-mercaptopyrimidin-4-ol in the presence of acetic acid to afford the corresponding phenazine **31** in 69% yield (Scheme 7). Finally, condensation of the Michael adduct **30** with 2,3-diaminopropionic acid was accompanied by spontaneous aromatization to yield the desired compound **32** in 68% yield.

In a final series, two known *o*-quinones **34** and **36** were used as starting material to prepare the phenazines **33** and **37** (Scheme 8). The bisoxime **35**, available from **34**, was also included in the test series. In a previous investigation we studied the oxygenation of the anthracenol **38** to the corresponding *o*-anthraquinone **39** with $[Mo(O_2)_2O]\cdot Py\cdot HMPT$. The dimerization of **39** occurred by treatment with BBr_3 to afford **40** in 44% yield. This dimeric *o*-anthraquinone **40** was converted to the bis-phenazine **41** by treatment with *o*-phenylenediamine in the presence of AcOH.

■ STRUCTURE−ACTIVITY RELATIONSHIPS (SARS)

The antiplasmodial activities of a selection representing the chemical diversity of the synthesized compounds were tested in an in vitro malaria assay against a chloroquine-sensitive strain of *P. falciparum*, strain NF54, according to previously described protocols of Moloney[11] and Trager.[12] Phenazines **11** and **27** showed significant antiplasmodial activities (Tables 3 and 4,

Scheme 8[a]



[a] Reagents and conditions: (a) $C_6H_4(NH_2)_2$, AcOH, 35 °C, 8 h; (b) HO-NH_2.HCl, EtOH, room temp, 24 h; (c) BBr_3, CH_2Cl_2, −78 °C, 5 min.

Figures 1 and 2). These results encouraged us to prepare a chemical library. Tables 3 and 4 give the IC_{50} values for derivatives in which the "dimeric" 1,2-naphthoquinone core structure of **11** and **27** was unchanged, and only the quinoxaline region of the molecule was modified. The nature of the substituents in this part of the molecule (**19** and **28**) or change of the quinoxaline part to pyridino[2,3-*b*]pyrazine (**20** and **29**), pyrazine (**21** and **32**), pyrimidine (**25** and **31**), and 1,2,4-triazine (**22**) proved to be very important for antimalarial activity. In general, the data show that any structural deviation in this region, i.e., from quinoxaline to pyrazine, pyrimidine, and 1,2,4-triazine, results in a loss of antimalarial activity. A comparison of the IC_{50} of compounds **27** and **29** clearly confirms the importance of change of the quinoxaline part to the pyridino[2,3-*b*]pyrazine part in contributing to antimalarial activity. It suggests that the nitrogen atom in pyridine is required for activity. Interestingly, comparison of the two phenazine regioisomers (**11** and **27**) with IC_{50} of 4.11 and 0.88 μM (Tables 3 and 4), respectively, showed a difference of a factor of 4.

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Table 3. In Vitro Activity (% Parasitemia ± Standard Error of the Mean) of 11, 12, 19, 20, 24, 27, and 28 against *Plasmodium falciparum* NF54 at a Given Concentration[a]

day	untreated	chloro-quine 0, 032 μM	**11**, 20 μM[b]	**12**, 10 μM[b]	**19**, 20 μM[b]	**20**, 20 μM[b]	**24**, 10 μM[b]	**27**, 3 μM[b]	**28**, 3 μM[b]
1	0.97 ± 0.10	0.06 ± 0.003	0.23 ± 0.05	0.14 ± 0.02	0.14 ± 0.02	0.04 ± 0.01	0.94 ± 0.10	0.27 ± 0.04	0.17 ± 0.03
2	1.20 ± 0.12	0.00 ± 0	0.07 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.20 ± 0.04	0.11 ± 0.02	0.15 ± 0.02
3	2.55 ± 0.21	0.00 ± 0	0.02 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.04 ± 0.02	0.02 ± 0.01	0.00 ± 0.00
4	2.73 ± 0.16	0.00 ± 0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
IC_{50} (72 h)		0.012 μM (24 h)	4.11 μM	0.64 μM	5.05 μM	5.23 μM	3.73 μM	0.88 μM	0.51 μM

[a] Parasitemia on day 0 was 0.45 ± 0.05 for all groups. [b] Concentration of compound.

Table 4. In Vitro Activity of Phenazines Based on 3 and 30 against the *Plasmodium falciparum* Strain NF54

	In vitro activity of phenazines based on **3**		In vitro activity of phenazines based on **30**	
Structural elements		IC_{50} (μM) 72h		IC_{50} (μM) 72h
	**3**	not effective	**30**	not effective
	**11**	4.11	**27**	0.88
	**19**	5.05	**28**	0.51
	**20**	5.23	**29**	not effective
	**21**	not effective	**32**	not effective
	**22**	not effective	---	---
	**23**	not effective	---	---
	**24**	3.73	---	---
	**25**	not effective	**31**	not effective

In the next series, **12**−**14**, the quinoxaline part of **11** was kept constant, and only the right-hand side of the core structure was modified by different substituents. The bromine substituted phenazine **12** showed a more than 6-fold activity improvement compared to **11**. On the other hand, a substituent like CO_2H (**13**) and SO_3H (**14**) decreased the activity (data not shown). The dimeric 1,2-naphthoquinones **3** and **30** showed weak antiplasmodial activity compared to **24**, the oxime of **3**, confirming the importance of nitrogen incorporation into the 1,2-naphthoquinones. Acenaphthylene-1,2-dione, phenanthrene-9,10-dione, and the dimeric quinone **40** were also converted to the phenazines **33**, **37**, and **41**, respectively, and did not show significant antiplasmodial activity (data not shown).

In summary, the data indicate that substances from three out of seven schemes of the phenazine class of compounds had in vitro inhibitory effects against *Plasmodium falciparum*. The phenazines **12**, **27**, and **28** were most prominent in growth inhibition with IC_{50} ranging from 0.51 to 0.88 μM. The phenazine **11** and substitution in the phenylenediamine (**19**, **20**), as well as the related bisoxime **24**, showed antiplasmodial activity but with less efficiency.

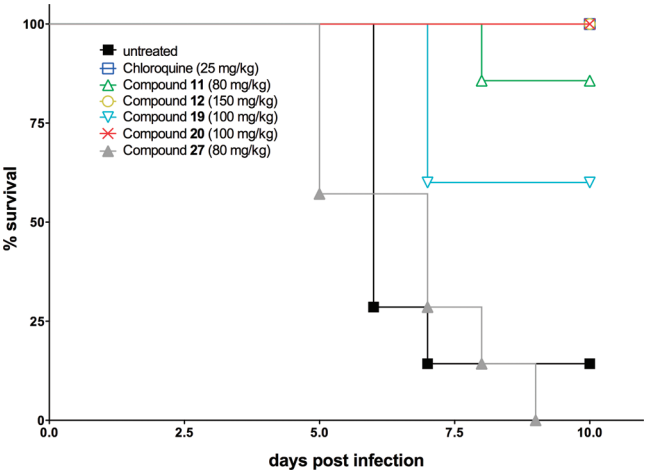

Figure 1. Survival of *P. berghei* infected mice treated with **11**, **12**, **19**, **20**, and **27**.

IN VIVO PROTECTION AGAINST CEREBRAL MALARIA OF MICE INFECTED WITH *P. BERGHEI* ANKA

We further investigated whether the substances with higher in vitro activity could protect C57BL/6 mice against cerebral malaria. Infection of C57BL/6 mice causes cerebral malaria in 80−100% of infected mice. Substances were given ip from day 3 to day 9 after infection with *P. berghei* ANKA. We found that in vivo protection against cerebral malaria was observed with phenazine **20**, whereas partial protection was provided by **11** and **19** (Figure 1). However, these substances did not clear the parasites from the blood as did treatment with chloroquine, and therefore, animals died of anemia after day 10 (Figure 2). Only **12** was able to reduce parasitemia significantly during days 5−7. This indicates that other inhibitory effects might play a role, as phenazines have been described as dual inhibitors of topoisomerases I and II and also are known to inhibit T cell proliferation and interfere with oxidative burst.

In summary, structurally new antimalarial lead structures chemically derived from simple naphthols are presented. It is noteworthy that from the selected compounds, only the pseudodimers were active, and only the phenazines, the azaphenazines, and the dichlorophenazines.

EXPERIMENTAL SECTION

Materials and Methods. For general methods and instrumentation see ref 13. In the ^{13}C NMR spectra, some of the signals are overlapping. The purity of tested samples was determined by elemental analysis, and purity of all tested samples was more than 95%.

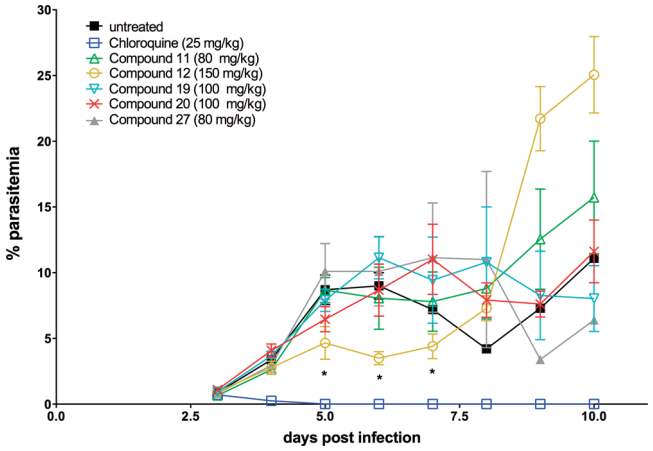

Figure 2. Parasitemia of mice infected with *P. berghei* and treated with **11**, **12**, **19**, **20**, and **27**.

General Procedure for the Synthesis of Phenazines (7−14). A solution of the respective 2-naphthol (1 mmol) in CH_2Cl_2 (10 mL) was treated with 6.01 g (2 mmol) of $[Mo(O_2)_2O]\cdot Py\cdot HMPT$ and stirred for 20 h at 20 °C. Then 10 mL of acetic acid and 6 g (4 mmol) of the respective 1,2-diamine were added, and stirring was continued for 12 h at 20 °C. The organic layer was washed with $NaHCO_3$, dried over Na_2SO_4, and concentrated. The purification was carried out by flash column chromatography, eluting with *n*-hexane/ethyl acetate. The resulting residue was purified by column chromatography on silica gel, eluting with *n*-hexane/EtOAc (90/10) to yield pure phenazines.

Benzo[*a*]phenazine (7). Yellow crystals, mp 230−233 °C. IR ν_{max} ($CHCl_3$): 1707, 1434, 1363, 750, 700. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (1H, dd, J = 8.0, 1.5 Hz), 8.45 (1H, dd, J = 8.0, 1.5 Hz), 8.40 (dd, J = 8.0, 1.5 Hz, 1H), 8.09 (d, J = 8.0, 1H), 7.95 (m, 1H, m, 3H), 7.85 (m, 3H). HREIMS m/z $C_{16}H_{10}N_2$ $[M]^+$ calcd 230.0844, found 230.0834. Anal. ($C_{16}H_{10}N_2$) C, H, N.

3-Bromobenzo[*a*]phenazine (8). Yellow crystals, mp 290−293 °C. IR ν_{max} ($CHCl_3$): 1707, 1434, 1363, 750, 700. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (1H, d, J = 8.0 Hz), 8.34 (1H, dd, J = 8.0, 1.5 Hz), 8.28 (1H, dd, J = 8.0, 1.5 Hz), 8.05 (1H, d, J = 2.0 Hz), 8.01 (1H, s), 7.88 (4H, m). HREIMS m/z $C_{16}H_9BrN_2$ $[M]^+$ calcd 307.9949, found 307.9929. Anal. ($C_{16}H_9BrN_2$) C, H, N.

Benzo[*a*]phenazine-6-carboxylic Acid (9). Yellow crystals, mp 245−247 °C. IR ν_{max} ($CHCl_3$): 1700, 1430, 1363, 750, 700. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (1H, dd, J = 8.0, 1.5 Hz), 8.41 (1H, dd, J = 8.0, 1.5 Hz), 8.31 (dd, J = 8.0, 1.5 Hz, 1H), 8.15 (dd, J = 8.0, 1.5 Hz, 1H), 8.09 (s, J = 8.0, 1H), 7.92 (m, 2H), 7.85 (m, 2H). HREIMS m/z $C_{17}H_{10}N_2O_2$ $[M]^+$ calcd 274.0742, found 274.0735. Anal. ($C_{17}H_{10}N_2O_2$) C, H, N.

Benzo[*a*]phenazine-3,6-disulfonic Acid (10). Yellow crystals, mp 277−278 °C. IR ν_{max} ($CHCl_3$): 2930, 1700, 1430, 1363, 750, 700. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (1H, dd, J = 8.0, 1.5 Hz), 8.40 (1H, d, J = 1.5 Hz), 8.15 (dd, J = 8.0, 1.5 Hz, 1H), 8.01 (s, J = 8.0, 1H), 7.92 (m, 2H), 7.85 (m, 2H). HREIMS m/z $C_{16}H_{10}N_2O_6S_2$ $[M]^+$ calcd 389.998, found 389.990. Anal. ($C_{16}H_{10}N_2O_6S_2$) C, H, N.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Synthesis details; elemental analysis data and spectroscopic details of **8**, **11**−**14**, and **17**−**41**; and antimicrobial activity of **3**, **7**-**14**, **21**, **23**, and **32**-**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

CQ, chloroquine; TBHP, *tert*-butyl hydroperoxide; HMPT, hexamethylphosphotriamide; TLC, thin layer chromatography; AcOH, acetic acid; Py, pyridine; MeoH, methanol

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