Bioorganic & Medicinal Chemistry Letters xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and antiplasmodial evaluation of novel (4-aminobutyloxy)quinolines

Stéphanie Vandekerckhove [a], Christian Müller [b,†], Dieter Vogt [b], Carmen Lategan [c], Peter J. Smith [c], Kelly Chibale [d], Norbert De Kimpe [a,*], Matthias D'hooghe [a,*]

[a] Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium
[b] Department of Chemical Engineering and Chemistry, Laboratory for Homogeneous Catalysis and Coordination Chemistry, Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands
[c] Medical School, University of Cape Town, K45, OMB Groote Schuur Hospital, Observatory 7925, South Africa
[d] Department of Chemistry and Institute of Infectious Disease & Molecular Medicine, University of Cape Town, Rondebosch 7701, South Africa

ARTICLE INFO

Article history:
Received 12 September 2012
Revised 19 October 2012
Accepted 22 October 2012
Available online xxxx

Keywords:
Quinolines
Antimalarial agents
Rh-catalyzed hydroformylation
Reductive amination

ABSTRACT

A variety of 5-, 6- and 8-(4-aminobutyloxy)quinolines as novel oxygen analogues of known 4- and 8-(4-aminobutylamino)quinoline antimalarial drugs was generated from hydroxyquinolines through a three-step approach with a rhodium-catalyzed hydroformylation as the key step. Antiplasmodial assays of these new quinolines revealed micromolar potency for all representatives against a chloroquine-sensitive strain of *Plasmodium falciparum*, and three compounds showed submicromolar activity against a chloroquine-resistant strain of *P. falciparum* with IC_{50}-values ranging between 150 and 680 nM.

Malaria remains a major issue in health control, mostly among African children and pregnant women, with 216 million clinical cases and roughly 655,000 deaths worldwide in 2010.[1] Quinoline compounds, and especially the potent, inexpensive chloroquine **1** (Fig. 1), have a long history in the treatment of malaria.[2,3] However, the spread of chloroquine resistance within *Plasmodium falciparum* strains has complicated medicinal treatment of malaria in the affected areas. Despite the promising progress regarding the development of live sporozoite-based vaccines[4,5] and new compounds with antimalarial activity,[6] there is still an urgent need for new antimalarial agents active against drug-resistant malaria strains. Many important antimalarial drugs comprise a quinoline system as the core unit, and systematic synthetic modifications of these structures have led to a variety of antimalarial drugs and lead candidates with diverse substitutions around the quinoline ring.[7–10] Literature reports on chloroquine analogues reveal that replacement of the nitrogen atom at the 4-position of the quinoline ring by oxygen or sulfur results in compounds with lower antimalarial potency.[9] This introduction of oxygen or sulfur was suggested to cause a significant reduction of the quinolyl nitrogen's basicity, inflicting the 4-*O* and 4-*S* analogues to be monoprotic weak bases compared to the diprotic weak basic 4-aminoquinoline derivatives. In spite of the lower antimalarial potency of these compounds, an improved resistance index (RI) was observed.[8,9] Since the rise of chloroquine resistance, novel drug design has been focused on diverse substitutions around the quinoline ring, but especially the potency of 4-substituted (amino)quinolines has been unraveled extensively.[8–13] Other, but far less thorough studies have been performed concerning the synthesis and antimalarial evaluation of 8-substituted quinolines,[6,14,15] although the elaboration of this class has mainly been focused on the derivatization of known 8-aminoquinoline antimalarial drugs such as pamaquine **2** and primaquine **3** (Fig. 1).[14–17]

In both cases the modification of the quinoline side chain has been well examined,[10,12,13,18–22] however, substitution of the amino group by oxygen or sulfur equivalents has only been described for 4-substituted quinolines so far.[8,9] Given the fact that 4-*O* (and 4-*S*) analogues showed improved RI's and toxicological advantages compared to 4-amino derivatives,[9] and knowing that the decrease in antimalarial activity of 4-*O* and 4-*S* chloroquine derivatives correlates to the decrease in basicity of the quinolyl nitrogen atom as a result of this particular substitution pattern (i.e., *para*-positioning),[9] the introduction of a functionalized alkoxy side chain at a more remote position with respect to the quinoline nitrogen atom might result in an overall beneficial effect with regard to the antiplasmodial activity of these novel structures. Thus, in the present paper, the preparation of new 8-(4-aminobutyloxy)quinolines is described as well as the assessment of their antiplasmodial

* Corresponding authors. Tel.: +32 9 2649394; fax: +32 9 2646221.
E-mail addresses: norbert.dekimpe@UGent.be (N. De Kimpe), matthias.dhooghe@UGent.be (M. D'hooghe).
† Current address: Freie Universität Berlin, Fabeckstrasse 34-36, D-14195 Berlin, Germany

0960-894X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2012.10.094

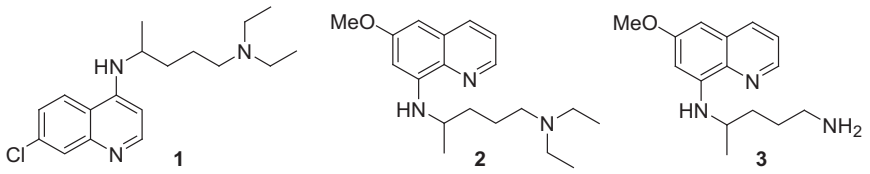
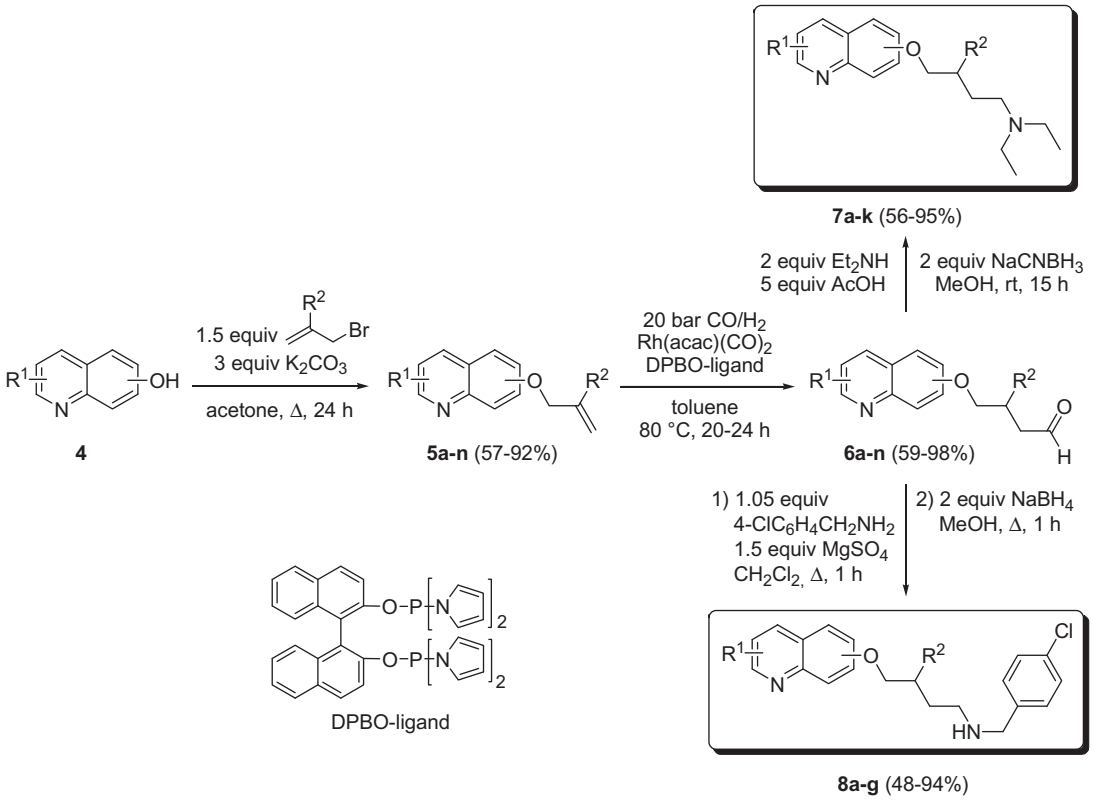


Figure 1. Structures of chloroquine, pamaquine and primaquine.

activity. In addition, the scope of this study was further extended toward the synthesis and biological evaluation of novel 5- and 6-(4-aminobutyloxy)quinolines as well. It should be mentioned that the synthesis of 4-substituted quinolines can be easily accomplished through nucleophilic aromatic substitution starting from 4-chloroquinolines.[9] Unfortunately this method is not extendable toward the preparation of the desired quinolines bearing a functionalized side chain at, for example, the 5-, 6- or 8-position, which made a novel approach of side chain introduction necessary. The implementation of a rhodium-catalyzed hydroformylation as the key step in the synthesis of functionalized quinoline systems was used and shown to be a powerful tool to accomplish this objective.

At first, a variety of allyloxyquinolines **5a–n** was prepared through O-alkylation of 5-, 6- and 8-hydroxyquinolines **4** upon treatment with 1.5 equiv of allyl bromide or 2-methylallyl bromide (in order to introduce structural diversity) in acetone under reflux for 24 h in the presence of three equiv of potassium carbonate (Scheme 1). Subsequently, the obtained quinolines **5** were evaluated as substrates for a rhodium-catalyzed hydroformylation toward the corresponding linear aldehydes. It should be noted that [(2-methyl-)2-propenyloxy]quinolines have not been studied so far as potential substrates for a catalytic hydroformylation reaction. Initially, quinolines **5** were subjected to standard hydroformylation conditions, that is, applying syngas (20 bar CO/H_2, 1:1) using (acetylacetonato)dicarbonylrhodium(I) [$Rh(acac)(CO)_2$] as a catalyst precursor (substrate/Rh = 500/1) and xantphos (ligand/Rh = 4) as a ligand in toluene at 80 °C (2 h preformation, 20 h reaction).[23] This method gave satisfying results for non-substituted (2-propenyloxy)quinolines (R^1 = H), but when substituted (2-propenyloxy)quinolines **5** (R^1 = Cl, I, Br) were used, only partial conversion was obtained (5–75%). Elevating the reaction temperature (120 °C), changing the solvent (2-Me-THF) or prolonging the reaction time (40–115 h) had no or a negative influence on the conversion. The same problem arose when (2-methyl-2-propenyloxy)quinolines **5** (R^2 = CH_3) were used as substrates, even those bearing no additional substituents on the quinoline ring (R^1 = H). It seemed that steric hindrance prevented the catalyst to reach the double bond in these cases. Subsequently, triphenylphosphine, a typical monodentate ligand which is less rigid than the bidentate xantphos, was used, but unfortunately conversion dropped even further (5–15%), also when large quantities of the ligand were utilized (20–40 equiv). The use of tris(2,4-di-*tert*-butylphenyl)phosphite,[24,25] a ligand that is typically used for hydroformylation of internal and sterically more demanding olefins,[26] gave no conversion at all. Other ligands known to be very selective toward the formation of linear aldehydes are bidentate phosphordiamidite ligands.[27] Thus, in a final attempt, the pyrrole-containing phosphordiamidite ligand DPBO (Scheme 1) was used, a ligand with a



Scheme 1. Synthesis of 4-(quinolinyloxy)butyraldehydes 6 via [(2-methyl-)2-propenyloxy]quinolines 5 and their conversion into (4-aminobutyloxy)quinolines **7** and **8**.

2,2′-binaphthol backbone that has recently been evaluated for the hydroformylation of styrene.[28] Fortunately, the use of this DPBO-ligand resulted in good to excellent conversion of non-substituted (R^1 = H) as well as substituted quinolines **5** (R^1 = Cl, I, Br) into the corresponding 4-(quinolinyloxy)butyraldehydes **6** under standard hydroformylation reaction conditions (20 bar CO/H_2 (1:1), substrate/Rh = 500:1, ligand/Rh = 4, toluene, 80 °C, preformation: 1 h, reaction: 20–24 h). As expected, this ligand was selective toward the formation of linear aldehydes, and no branched aldehydes were formed.

This hydroformylation step proved to be a very efficient method for the generation of a 4-oxobutyloxy side chain as an anchor point for further derivatization, and comprises the first example of the successful integration of homogenous catalysis within the synthesis of aminoalkyloxyquinolines as potential antimalarial candidates. The introduction of an aldehyde functionality within the side chain indeed created a lot of possibilities for further synthetic elaborations. In light of the target compounds (chloroquine and pamaquine analogues), imination of aldehydes **6** followed by a reduction toward the corresponding amines comprised the next synthetic steps. In this study, diethylamine and 4-chlorobenzylamine were selected as the amines to undergo condensation with aldehydes **6**. The choice for diethylamine is evident from the established importance of the diethylamino moiety in antimalarial agents, whereas 4-chlorobenzylamine was selected based on previous studies in which the incorporation of this group has shown to be advantageous with respect to antiplasmodial activity.[29,30]

When performing the reductive amination of 4-(quinolinyloxy) butyraldehydes **6** in a one-pot reaction using 2 equiv of diethylamine and 2 molar equiv of sodium cyanoborohydride in the presence of 5 equiv of acetic acid in methanol at room temperature, full conversion to the desired [4-(diethylamino) butyloxy]quinolines **7** was obtained in moderate to excellent yields (56–95%) (Scheme 1, Table 1). However, when the primary amine 4-chlorobenzylamine was used, the same reaction conditions did not result in full conversion to the desired amines **8**, but dimerization occurred as well and tertiary amines were formed. Fortunately, this was easily overcome by performing the reductive amination in a stepwise fashion. Firstly, aldehydes **6** were treated with 1.05 equiv of 4-chlorobenzylamine in the presence of 1.5 equiv of magnesium sulfate in dichloromethane under reflux for 1 h to afford the corresponding imines, which were immediately reduced utilizing 2 molar equiv of sodium borohydride in methanol under reflux for 1 h, furnishing the desired [4-(4-chlorobenzylamino)butyloxy]quinolines **8** in moderate to excellent yields (48–94%) (Scheme 1, Table 1).

Table 1
Substitution pattern and yields of quinolines **7** and **8**

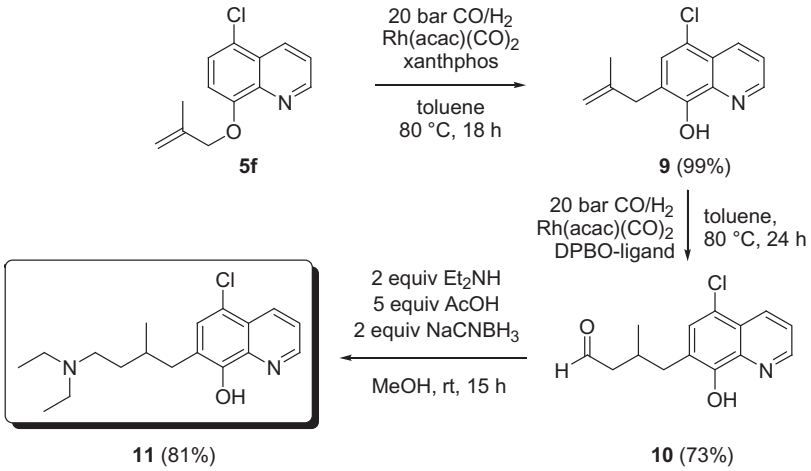
Entry	Compound	Quinolin-5-, 6- or 8-yl	R^1	R^2	Yield (%)
1	**7a**	8-yl	H	H	56
2	**7b**	8-yl	5-Cl	H	57
3	**7c**	8-yl	5-Cl, 7-I	H	75
4	**7d**	8-yl	H	CH_3	89
5	**7e**	8-yl	5, 7-di-Cl	CH_3	89
6	**7f**	8-yl	2-CH_3, 5-Cl, 7-Cl	CH_3	60
7	**7g**	8-yl	5-Cl, 7-I	CH_3	89
8	**7h**	8-yl	5,7-di-I	CH_3	61
9	**7i**	8-yl	5,7-di-Br	CH_3	95
10	**7j**	6-yl	H	H	91
11	**7k**	5-yl	H	H	60
12	**8a**	8-yl	5-Cl	H	53
13	**8b**	8-yl	H	CH_3	94
14	**8c**	8-yl	2-CH_3, 5-Cl, 7-Cl	CH_3	48
15	**8d**	8-yl	5,7-di-I	CH_3	76
16	**8e**	6-yl	H	H	58
17	**8f**	5-yl	H	H	56
18	**8g**	5-yl	H	CH_3	84

After an initial attempt to hydroformylate compound **5f** using (acetoacetonato)dicarbonylrhodium(I) as a catalyst and xantphos as a ligand, no aldehyde formation was observed. On the other hand, the elevated reaction temperature (80 °C) had caused (2-methyl-2-propenyloxy)quinoline **5f** to undergo a Claisen rearrangement, yielding 5-chloro-7-(2-methyl-2-propenyl)quinolin-8-ol **9** in quantitative yield (Scheme 2). It should be noted that no Claisen rearrangement was observed when allyl ether **5f** was heated at 80 °C in toluene for 18 h. Subsequently, compound **9** was evaluated as an alternative substrate for hydroformylation using DPBO as the ligand. In this way, 4-(5-chloro-8-hydroxyquinolin-7-yl)-3-methylbutyraldehyde **10** was obtained as the sole reaction product in 73% yield. Finally, aldehyde **10** was subjected to reductive amination using diethylamine and sodium cyanoborohydrate in methanol in the presence of acetic acid, rendering 5-chloro-7-(4-diethylamino-2-methylbutyl)quinolin-8-ol **11** in high yield and purity (Scheme 2).

In the next phase, the newly synthesized quinolines **7**, **8** and **11** were screened for their in vitro antiplasmodial activity. All samples were tested against a chloroquine-sensitive (CQS) strain of *P. falciparum* (D10). Subsequently, only those samples showing promising antimalarial activity were tested against a chloroquine-resistant (CQR) strain of *P. falciparum* (Dd2) and screened for in vitro cytotoxicity against a mammalian cell-line, Chinese Hamster Ovarian (CHO) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT)-assay. Continuous in vitro cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen,[31] and quantitative assessment of antiplasmodial activity in vitro was determined via the parasite lactate dehydrogenase assay using a modified method described by Makler.[32] The test samples were tested in triplicate on one occasion.[33] The MTT-assay was used as a colorimetric assay for cellular growth and survival, and compares well with other available assays.[34,35] The tetrazolium salt MTT was used to measure all growth and chemosensitivity. The test samples were tested in triplicate on one occasion.[36]

The results of the biological evaluation are summarized in Table 2. This study shows that all representatives display micromolar potencies against the chloroquine-sensitive D10 strain of *P. falciparum*, with 12 of the 19 samples having IC_{50}-values between 10 and 1 μM (Table 2). Interestingly, the most active compounds were more potent against the chloroquine-resistant Dd2 strain of the parasite (IC_{50} = 150–680 nM). While **8c** exhibits moderate cytotoxicity (SI = 2), quinolines **7f**, **8e** and **8f** have good to very good selectivity indexes at the concentrations tested (SI = 29–57). Overall, compound **11** appeared to be the most active against both parasite strains (IC_{50} (D10) = 1.01 μM, IC_{50} (Dd2) = 0.15 μM) with a SI of 5.

With regard to structure–activity relationships, this assay shows that the presence of a methyl group in the side chain or the presence of at least one chloro atom on the quinoline core is salutary for the antiplasmodial activity of these compounds, and that both the diethylamino group and the 4-chlorobenzylamino group at the terminus of the side chain can be of interest with regard to their antimalarial properties. Based on the observations made in this work, it can be concluded that the introduction of substituents bearing a β-methyl group (instead of the usual α-methyl group in known antimalarial drugs) at the less explored 5-, 6- or 8-positions of the quinoline nucleus might provide promising prospects and opportunities within antimalarial drug design. Finally, it appears that compound **11**, recovered after a Claisen rearrangement, gives the best overall results, which could be attributed to the intramolecular hydrogen bonding between



Scheme 2. Synthesis of 5-chloro-7-(4-diethylamino-2-methylbutyl)quinolin-8-ol **11**.

Table 2
IC_{50}-values of quinolines **7**, **8** and **11** tested for in vitro antimalarial activity and cytotoxicity

Entry	Compound	D10: IC_{50} (μM)	Dd2: IC_{50} (μM)	CHO: IC_{50} (μM)	SI[a]	RI[b]
1	**7a**	49.19	ND	ND	ND	ND
2	**7b**	17.18	ND	ND	ND	ND
3	**7c**	9.02	ND	ND	ND	ND
4	**7d**	100.20	ND	ND	ND	ND
5	**7e**	8.08	ND	ND	ND	ND
6	**7f**	3.95	0.68	224.46	57	0.17
7	**7g**	12.97	ND	ND	ND	ND
8	**7h**	13.89	ND	ND	ND	ND
9	**7i**	8.65	ND	ND	ND	ND
10	**7j**	6.02	ND	ND	ND	ND
11	**7k**	10.24	ND	ND	ND	ND
12	**8a**	9.99	ND	ND	ND	ND
13	**8b**	5.64 (n = 6)	ND	ND	ND	ND
14	**8c**	2.44	0.26	4.11	2	0.11
15	**8d**	9.15	ND	ND	ND	ND
16	**8e**	7.29 (n = 6)	>1	211.45	29	ND
17	**8f**	7.01 (n = 6)	ND	237.35	34	ND
18	**8g**	23.08	ND	ND	ND	ND
19	**11**	1.01 (n = 6)	0.15	4.80	5	0.15
20	CQ	0.04 (n = 28)	0.34	ND	ND	8
21	Emetine	ND	ND	0.17	ND	ND

ND = not determined.
[a] SI (selectivity index) = IC_{50} CHO/IC_{50} D10.
[b] RI (resistance index) = IC_{50} Dd2/IC_{50} D10.

the 8-hydroxyl group and the quinoline nitrogen atom.[37] It should also be noted that calculated properties of the novel compounds prepared in this work (molecular weight, *c*Log*P*, total polar surface area, rotatable bonds, hydrogen bond donors, hydrogen bond acceptors and fractional sp^3 character) correspond well with those of their commercially available analogues chloroquine **1** and pamaquine **2**, which underlines the importance of these new structures as templates for further elaboration and optimization.

In conclusion, the preparation of 5-, 6- and 8-(4-aminobutyloxy) quinolines as new classes of quinoline derivatives was established through a three-step pathway consisting of (i) O-allylation, (ii) rhodium-catalyzed hydroformylation of the thus obtained [(2-methyl-)2-propenyloxy]quinolines and (iii) reductive amination. Furthermore, the biological relevance of this novel class of compounds was demonstrated by evaluation of its in vitro antiplasmodial activity and cytotoxicity. Three new compounds showed submicromolar activity against a chloroquine-resistant strain of *P. falciparum*, pointing to the promising potential of these new structures as novel antimalarial pharmacophores.

Acknowledgments

The authors are indebted to Ghent University (BOF) for financial support. The authors would also like to thank ir. J. Weemers (TU/e) and ir. L. Broeckx (TU/e) for their assistance with the catalytic hydroformylation experiments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.10.094.

References and notes

1. WHO. World Malaria Report 2011.
2. Chauhan, P. M. S.; Srivastava, S. K. *Curr. Med. Chem.* **2001**, *8*, 1535.
3. Jefford, C. W. *Curr. Med. Chem.* **1803**, *2001*, 8.
4. Kumar, K. A.; Sano, G.; Boscardin, S.; Nussenzweig, R. S.; Nussenzweig, M. C.; Zavala, F.; Nussenzweig, V. *Nature* **2006**, *444*, 937.

5. Aide, P.; Dobano, C.; Sacarlal, J.; Aponte, J. J.; Mandomando, I.; Guinovart, C.; Bassat, Q.; Renom, M.; Puyol, L.; Macete, E.; Herreros, E.; Leach, A.; Dubois, M. C.; Demoitie, M. A.; Lievens, M.; Vekemans, J.; Loucq, C.; Ballou, W. R.; Cohen, J.; Alonso, P. L. *Vaccine* **2011**, *29*, 6059.
6. Burrows, J. N.; Chibale, K.; Wells, T. N. C. *Curr. Top. Med. Chem.* **2011**, *11*, 1226.
7. Kumar, A.; Katiyar, S. B.; Agarwal, A.; Chauhan, P. M. S. *Curr. Med. Chem.* **2003**, *10*, 1137.
8. Iwaniuk, D. P.; Whetmore, E. D.; Rosa, N.; Ekoue-Kovi, K.; Alumasa, J.; de Dios, A. C.; Roepe, P. D.; Wolf, C. *Bioorg. Med. Chem.* **2009**, *17*, 6560.
9. Natarajan, J. K.; Alumasa, J. N.; Yearick, K.; Ekoue-Kovi, K. A.; Casabianca, L. B.; de Dios, A. C.; Wolf, C.; Roepe, P. D. *J. Med. Chem.* **2008**, *51*, 3466.
10. Yearick, K.; Ekoue-Kovi, K.; Iwaniuk, D. P.; Natarajan, J. K.; Alumasa, J.; de Dios, A. C.; Roepe, P. D.; Wolf, C. *J. Med. Chem.* **1995**, *2008*, 51.
11. Hwang, J. Y.; Kawasuji, T.; Lowes, D. J.; Clark, J. A.; Connelly, M. C.; Zhu, F. Y.; Guiguemde, W. A.; Sigal, M. S.; Wilson, E. B.; DeRisi, J. L.; Guy, R. K. *J. Med. Chem.* **2011**, *54*, 7084.
12. Sparatore, A.; Basilico, N.; Casagrande, M.; Parapini, S.; Taramelli, D.; Brun, R.; Wittlin, S.; Sparatore, F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3737.
13. Ekoue-Kovi, K.; Yearick, K.; Iwaniuk, D. P.; Natarajan, J. K.; Alumasa, J.; de Dios, A. C.; Roepe, P. D.; Wolf, C. *Bioorg. Med. Chem.* **2009**, *17*, 270.
14. Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245.
15. Kaur, K.; Jain, M.; Khan, S. I.; Jacob, M. R.; Tekwani, B. L.; Singh, S.; Singh, P. P.; Jain, R. *Med. Chem. Commun.* **2011**, *2*, 300.
16. Vale, N.; Moreira, R.; Gomes, P. *Eur. J. Med. Chem.* **2009**, *44*, 937.
17. Kaur, K.; Jain, M.; Khan, S. I.; Jacob, M. R.; Tekwani, B. L.; Singh, S.; Singh, P. P.; Jain, R. *Eur. J. Med. Chem.* **2012**, *52*, 230.
18. Kumar, A.; Srivastava, K.; Kumar, S. R.; Puri, S. K.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7059.
19. Gordey, E. E.; Yadav, P. N.; Merrin, M. P.; Davies, J.; Ward, S. A.; Woodman, G. M. J.; Sadowy, A. L.; Smith, T. G.; Gossage, R. A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4512.
20. Sunduru, N.; Sharma, M.; Srivastava, K.; Rajakumar, S.; Puri, S. K.; Saxena, J. K.; Chauhan, P. M. S. *Bioorg. Med. Chem.* **2009**, *17*, 6451.
21. Kouznetsov, V. V.; Gomez-Barrio, A. *Eur. J. Med. Chem.* **2009**, *44*, 3091.
22. O'Neill, P. M.; Ward, S. A.; Berry, N. G.; Jeyadevan, J. P.; Biagini, G. A.; Asadollaly, E.; Park, B. K.; Bray, P. G. *Curr. Top. Med. Chem.* **2006**, *6*, 479.
23. van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741.
24. Kamer, P. C. J.; Reek, J. N. H.; H., J. N.; van Leeuwen, P. W. N. M. In *Catalysis by Metal Complexes*; Kluwer Academic Publishers: Dordrecht (The Netherlands), 2000. Vol. 22 (Rhodium catalyzed hydroformylation), p. 35.
25. van Leeuwen, P. W. N. M. In *Catalysis by Metal Complexes*; Kluwer Academic Publishers: Dordrecht (The Netherlands), 2000. Vol. 22 (Rhodium catalyzed hydroformylation), p 1.
26. van Leeuwen, P. W. N. M.; Roobeek, C. F. *J. Organomet. Chem.* **1983**, *258*, 343.
27. van der Slot, S. C.; Duran, J.; Luten, J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **2002**, *21*, 3873.
28. Boymans, E. H.; Janssen, M.; Müller, C.; Lutz, M.; Vogt, D. unpublished results.
29. D'hooghe, M.; Kenis, S.; Vervisch, K.; Lategan, C.; Smith, P. J.; Chibale, K.; De Kimpe, N. *Eur. J. Med. Chem.* **2011**, *46*, 579.
30. D'hooghe, M.; Vandekerckhove, S.; Mollet, K.; Vervisch, K.; Dekeukeleire, S.; Lehoucq, L.; Lategan, C.; Smith, P. J.; Chibale, K.; De Kimpe, N. *Beilstein J. Org. Chem.* **2011**, *7*, 1745.
31. Trager, W.; Jensen, J. B. *Science* **1976**, *193*, 673.
32. Makler, M. T.; Ries, J. M.; Williams, J. A.; Bancroft, J. E.; Piper, R. C.; Gibbins, B. L.; Hinrichs, D. J. *Am. J. Trop. Med. Hyg.* **1993**, *48*, 739.
33. The test samples were prepared to a 20 mg/mL stock solution in 100% DMSO. Stock solutions were stored at −20 °C. Further dilutions were prepared in complete medium on the day of the experiment. Samples were tested as a suspension if not completely dissolved. Chloroquine (CQ) was used as the reference. A full dose–response was performed for all compounds to determine the concentration inhibiting 50% of parasite growth (IC_{50}-value). Test samples were tested at a starting concentration of 100 μg/mL, which was then serially diluted twofold in complete medium to give 10 concentrations; with the lowest concentration being 0.2 μg/mL. The same dilution technique was used for all samples. CQ was tested at a starting concentration of 100 ng/mL against a CQS strain. The highest concentration of solvent to which the parasites were exposed to had no measurable effect on the parasite viability.
34. Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55.
35. Rubinstein, L. V.; Shoemaker, R. H.; Paull, K. D.; Simon, R. M.; Tosini, S.; Skehan, P.; Scudiero, D. A.; Monks, A.; Boyd, M. R. *J. Natl. Cancer I* **1990**, *82*, 1113.
36. The test samples were prepared to a 2 mg/mL stock solution in 10% DMSO and were tested as a suspension. Test compounds were stored at −20 °C until use. Dilutions were prepared on the day of the experiment. Emetine was used as the reference drug in all experiments. The initial concentration of emetine was 100 μg/mL, which was serially diluted in complete medium with 10-fold dilutions to give 6 concentrations, the lowest being 0.001 μg/mL. The same dilution technique was applied to all test samples. The highest concentration of solvent to which the cells were exposed to had no measurable effect on the cell viability. The 50% inhibitory concentration (IC_{50}) values were obtained from full dose-response curves, using a non-linear dose–response curve fitting analysis via GraphPad Prism v.4 software.
37. Madrid, P. B.; Liou, A. P.; DeRisi, J. L.; Guy, R. K. *J. Med. Chem.* **2006**, *49*, 4535.