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Endochin Optimization: Structure−Activity and Structure−Property Relationship Studies of 3-Substituted 2-Methyl-4(1*H*)-quinolones with Antimalarial Activity

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Since the 1940s endochin and analogues thereof were known to be causal prophylactic and potent erythrocytic stage agents in avian models. Preliminary screening in a current in vitro assay identified several 4(1*H*)-quinolones with nanomolar EC_{50} against erythrocytic stages of multidrug resistant W2 and TM90-C2B isolates of *Plasmodium falciparum*. Follow-up structure−activity relationship (SAR) studies on 4(1*H*)-quinolone analogues identified several key features for biological activity. Nevertheless, structure−property relationship (SPR) studies conducted in parallel revealed that 4(1*H*)-quinolone analogues are limited by poor solubilities and rapid microsomal degradations. To improve the overall efficacy, multiple 4(1*H*)-quinolone series with varying substituents on the benzenoid quinolone ring and/or the 3-position were synthesized and tested for in vitro antimalarial activity. Several structurally diverse 6-chloro-2-methyl-7-methoxy-4(1*H*)-quinolones with EC_{50} in the low nanomolar range against the clinically relevant isolates W2 and TM90-C2B were identified with improved physicochemical properties while maintaining little to no cross-resistance with atovaquone.

Introduction

Malaria continues its devastating impact on the health of human populations in tropical regions, with over 243 million cases and the death of almost 1 million individuals each year.[1−3] The hardest hit region is sub-Saharan Africa, which accounts for an estimated 85% of all deaths, occurring primarily in children less than 5 years of age. The two most prevalent species causing human disease are *Plasmodium falciparum* and *P. vivax*, both of which are increasingly difficult to treat and control because of the emergence of drug resistance and lack of preventive drugs for the populations at highest risk, predominantly children and pregnant women. During the past 3 decades, *P. falciparum*, one of the five malaria species infecting humans, has developed resistance to every commonly available antimalarial drug, including recent evidence of reduced parasite clearance with artemisinin combinations, the most relevant modern treatment.[4,5] The rapid spread of these resistant parasites has dramatically hindered the successful treatment of patients to the point that some drugs have been rendered virtually useless in many parts of the world.

The World Health Organization has reacted to this monumental malaria problem by promoting the widespread use of artemisinin combination therapy (ACT[a]) in malaria endemic countries.[6] Nevertheless, emergence of ACT resistant malaria in Asian countries signals the importance of developing new antimalarials.[7,8] History has shown that once resistance to a new drug emerges, it quickly spreads and usually confers cross-resistance to the class. Therefore, the identification and development of novel chemotypes are extremely important. Perhaps no larger challenge to this goal is the capability of designing new agents that eliminate the liver stages of the malaria parasite, particularly the dormant forms (hypnozoites) of the relapsing malaria species (*P. vivax* and *P. ovale*). Currently, primaquine is the only drug approved for clinical use that kills dormant liver stages of parasite development, thus preventing relapse, while simultaneously reducing infectivity of mature gametocytes, thus contributing to reduced transmission (Figure 1). Unfortunately, primaquine is toxic for patients with glucose 6-phosphate dehydrogenase deficiency and has poor pharmacokinetics, requiring 14 daily doses to achieve radical cures; thus, new antirelapse radical cure agents are urgently needed.[9,10] Ideally, exoerythrocytic stage agents would possess potent activity against erythrocytic stages while simultaneously preventing the transmission of the parasite from either the host to the vector or vice versa.

Recent understanding of the mechanism of action and resistance to current drugs suggests that previously discovered leads remain viable candidates provided renewed efforts overcome chemotype specific hurdles.[11] One example of this challenge is endochin (**1**) which in the 1940s was identified to be a causal prophylactic (kill growing liver stage parasites) and potent erythrocytic stage agent in avian malaria models,

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[a] Abbreviations: EC_{50}, half maximal effective concentration; ED_{50}, half maximal effective dose; ACT, artemisinin combination therapy; WRAIR, Walter Reed Army Institute of Research; SAR, structure−activity relationship; SPR, structure−property relationship; XPHOS, (2-(dicyclohexylphosphino)-2′,4′,6′-triisopropyl-1,1′-biphenyl; TEA, triethylamine; Bn, benzyl; DCM, dichloromethane; $Pd_2(dba)_3$, tris-(dibenzylideneacetone)dipalladium(0); Ph, phenyl; DMF, *N*,*N*-dimethylformamide; HPLC, high performance liquid chromatography; nOe, nuclear overhauser effect; RPMI, Roswell Park Memorial Institute; RI, resistance index; Ac, acetyl; rt, room temperature; CI, cytotoxicity index.

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yet the lead languished because of inadequate preclinical models and a poor understanding of parasite biochemistry.[12] Approximately 25 years later, Casey tested a focused series of 3-alkenyl- and 3-alkyl-2-methyl-4(1*H*)quinolones, but no antimalarial activity was observed in the utilized preclinical screen (Rane single dose rodent malaria model).[13,14] A simultaneous evaluation of coccidiostat quinolone ester analogues identified compound ICI56,780,[15] which displayed causal prophylactic (single dose of 30 mg/kg subcutaneous) and blood schizonticidal activity (ED_{50} = 0.05 mg/kg) in rodent malaria models. This compound and another structurally related 4(1*H*)-quinolone ester were later shown to have antirelapse activity in *P. cynomolgi* infected rhesus monkeys (10−30 mg/kg subcutaneous).[16] Unfortunately a high degree of resistance to these agents was obtained after one passage in *P. berghei* infected mice, and a lack of oral bioavailability led to their abandonment.[15]

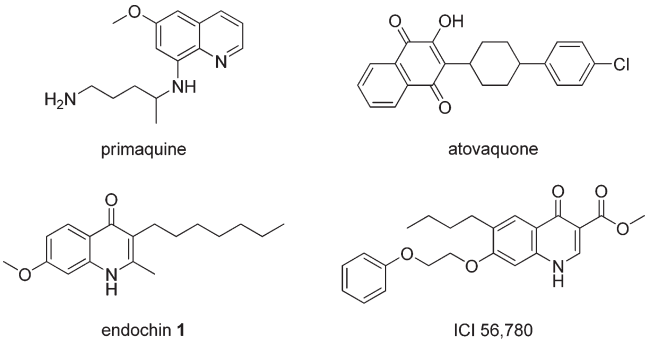
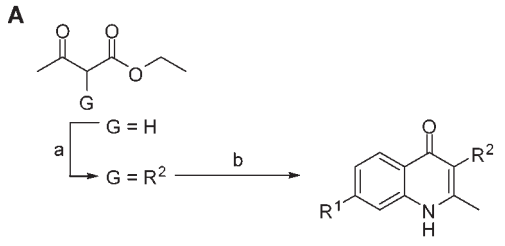


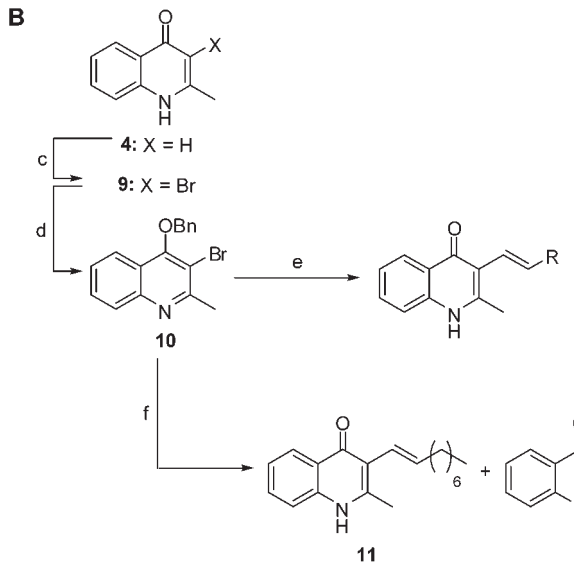
Figure 1. Structures of several antimalarials including **1**.

Since the aforementioned studies were conducted over 20 years ago without adequate evaluation in current preclinical efficacy models and without assessment for proper druglike properties, the 4(1*H*)-quinolone series has recently gained attention by several research teams. More than 40 4(1*H*)-quinolone and quinolone ester analogues obtained from the Walter Reed Army Institute of Research (WRAIR) chemical inventory were re-evaluated in a current erythrocytic in vitro study.[17] Surprisingly, several 4(1*H*)-quinolones were found to have remarkable in vitro potency in the low nanomolar range against erythrocytic stages of multidrug resistant isolates and clones of *P. falciparum* (D6 and TM90-C2B), while the cross-resistance with atovaquone was not found to be complete across the chemical series. Additionally, Riscoe and Winter reported similar results with **1** and analogues thereof.[18] Most compounds displayed in vitro antiplasmodial activities with EC_{50} values in the low nanomolar range against a panel of *P. falciparum* isolates (D6, Dd2, and TM90-C2B) as well as negligible cross-resistance and cytotoxicity. Also, preliminary mechanism of action studies based on oxygen consumption by *P. yoelii* infected erythrocytes indicate that the 4(1*H*)-quinolones target the cytochrome bc_1 complex, which is responsible for the parasite's respiration. These data suggest that analogues of **1** have great potential as novel antimalarials. To better understand the structure−activity and the structure−property relationships (SAR and SPR), we systematically

Scheme 1. Synthesis of 3-Substituted 4(1*H*)-Quinolones **1**−**17** via Conrad−Limpach Cyclization or Heck Cross-Coupling[a]



Compound	R^1	R^2	Yield
1	$-OCH_3$	$-(CH_2)_6CH_3$	28 %
2	$-OCH_3$	-H	43 %
3	-H	$-(CH_2)_6CH_3$	69 %
4	-H	-H	-[i]
5	-H	$-(CH_2)_8CH_3$	30 %
6	-H	-cyclohexyl	36 %
7	-H	-Ph	63 %
8	-H	-Bn	81 %



Compound	R	Yield
14	$-CO_2{}^tBu$	83 %
15	-Ph	73 %
16	-*m*-nitrophenyl	96 %
17	-*p*-phenol	14 %[ii]

11 12 13

[a]Reaction conditions: (a) Na, R^2X, EtOH (anh), reflux, overnight; (b) R^1-aniline, AcOH, benzene, Dean−Stark trap, reflux, overnight, then Ph_2O, reflux, 15 min; (c) KBr (20% aq), Br_2, 2 M NaOH, room temp, 2−12 h; (d) BnCl, Bu_3BnNCl, NaOH, DCM/H_2O (1:1), room temp; (e) $Pd_2(dba)_3$, XPHOS, TEA, toluene, alkene; (f) $Pd_2(dba)_3$, XPHOS, TEA, toluene, 1-nonene, 130 °C. (i) Compound **4** is commercially available. (ii) See Supporting Information.

designed and synthesized a series of 3-substituted 2-methyl-4(*1H*)-quinolones to evaluate their antimalarial activity and physicochemical properties.

Results and Discussion

Synthetic Chemistry. Previously, a series of diverse 4(1*H*)-quinolones from WRAIR was tested for antimalarial activity suggesting that the 3-position and the benzenoid ring of the 4(1*H*)-quinolone are important for biological activity.[17] Several series of compounds with varying substitutions at these positions have been synthesized following the Topliss operational schemes which are based upon physicochemical parameters related to hydrophobicity, electronics, and sterics.[19,20] Additionally, a series of *N*-alkyl-4-quinolones and *O*-alkyl-4-quinolinols were synthesized locking the quinolone scaffold into either one of the two possible tautomeric forms to test the significance of the hydrogen bond donor capabilities of the 4(1*H*)-quinolones. By use of various synthetic strategies, a total of 79 compounds were synthesized and tested. Initially, compound **1** and its analogues **2**−**4** were prepared to determine the necessity of the heptyl and methoxy substituents (Scheme 1). According to a known procedure,[21] 2-heptyl-substituted ethyl acetoacetate was prepared from ethyl acetoacetate and heptyl bromide (Scheme 1A). Subsequent Conrad−Limpach cyclization of ethyl acetoacetate and its 2-heptyl analogue with aniline and 3-methoxyaninline furnished 4(1*H*)-quinolones **1**−**4** in good yields. Furthermore, via the same synthetic protocol, a series of 4(1*H*)-quinolones, which differ in the substitution at the 3-position, was prepared. 3-Alkyl and 3-aryl-4(*1H*)-quinolones **5**−**8** were synthesized in good yields from aniline. 3-Alkenyl-4(1*H*)-quinolones **11**−**17** were prepared by an alternative route utilizing a Heck cross-coupling protocol as the key step (Scheme 1B). Bromination of quinolone **4** followed by *O*-benzylation gave intermediate **10**. Heck cross-coupling of bromide **10** with 1-nonene yielded a mixture of 3-alkenyl-4(1*H*)-quinolone isomers (**11**−**13**), which were separated by reversed-phase preparative HPLC. Similarly, 4(1*H*)-quinolones **11**−**17** were prepared starting from bromide **10** using the same Heck cross-coupling protocol as above. Coupling of the free N−H quinolone (**9**) provided minimal to no product. The amine was protected as the *O*-benzyl precursor and subjected to Heck cross-coupling conditions. Interestingly, the cross-coupling adduct with tandem deprotection of the benzyl moiety was obtained. To the best of our knowledge, this tandem reaction sequence has not been reported in Heck cross-couplings and is currently being studied by our group.

Next, a series of 3-bromo-4(1*H*)-quinolones was synthesized to investigate whether varying the substituents of the benzenoid ring affects the antimalarial activity. Conrad−Limpach cyclization of various para-substituted anilines with ethyl acetoacetate followed by bromination at the 3-position yielded the corresponding 3-bromo-4(1*H*)-quinolones **18**−**22** each possessing a unique substituent at the 6-position (Scheme 2A). Additionally, a small series of 3-alkynyl-4(*1H*)-quinolones was prepared to test whether a carbon−carbon triple bond at the 3-position would improve biological activity. Following a known procedure,[22] bromides **9**, **18**, and **21**−**22** were first *O*-benzylated using phase transfer catalysis conditions to furnish *O*-benzyl intermediates **23a**−**26a** and then subjected to Sonogashira cross-coupling[23] conditions with 1-hexyne. Analogous to the previous Heck cross-coupling reactions, the Sonogashira cross-coupling step was accompanied by tandem debenzylation furnishing 6-substituted-3-hexynyl-4(1*H*)-quinolones **23b**−**26b**.

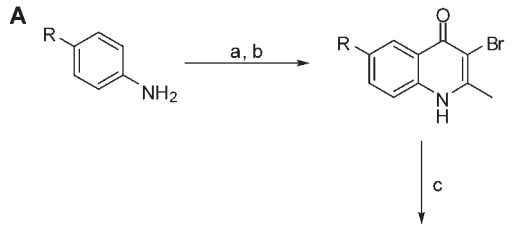
A series of compounds was prepared in which the benzenoid ring was substituted with a methoxy or a chloro substituent at the 5-, 6-, 7-, or 8-position, elaborating upon the previous set of 4(1*H*)-quinolones (Scheme 2B). Conrad−Limpach cyclization of *p*-methoxy- or *p*-chloroanilines with commercially available ethyl-2-benzyl- or 2-phenyl-acetoacetate afforded 6-methoxy- or 6-chloro-4(1*H*)-quinolones **27**−**30** while cyclization of ortho-substituted anilines gave 8-methoxy- or 8-chloro-4(1*H*)-quinolones **31**−**34**. Dichloro-3-phenyl-4(1*H*)-quinolones **35**−**37** were directly obtained from corresponding dichoroanilines. The cyclization with *m*-methoxy- or *m*-chloroanilines furnished mixtures of 5- and 7-substituted 4(1*H*)-quinolones, which has traditionally been a problematic outcome (Scheme 2C). Much to our delight, recrystallization of these mixtures from DMF produced the major isomers **38a**−**42a** while the resulting mother liquor could be purified via preparative HPLC to isolate the minor isomers **38b**−**42b**.

A selected number of *N*-methyl-4-quinolones or *O*-methyl-4-quinolinols were prepared by alkylation of the corresponding 3-benzyl-4(1*H*)-quinolones **27**, **28**, **30**, and **39a** (Scheme 3). The alkylation conditions generated mixtures of *N*- and *O*-methylated compounds in an approximately 2:1 ratio which, by column chromatography, were separated into the *N*-methylated 4(1*H*)-quinolones **43a**−**46a** and the *O*-methylated quinolinols **43b**−**46b**. By use of routine 1D nOe experiments, compounds **43a**−**46a** were shown to display a correlation between the *N*-methyl and the 2-methyl group, while correlations between the *O*-methyl group and the proton at the 5-position were observed for compounds **43b**−**46b**. This nOe data reinforces the difference in the chemical shift of the carbonyl carbon versus the phenolic carbon.

Finally, a series of 6-halo-7-methoxy-4(1*H*)-quinolones was prepared based on results from compounds **1**−**46**, combining the 6,7-disubstitution pattern while simultaneously incorporating the most active substituents at the 3-position (Scheme 4), and screened for activity. 4-Chloro-3-methoxyaniline (**47**) was prepared starting from 2,5-dichloroanisole using sodium amide conditions,[24] while 4-bromo and 4-fluoromethoxyanilines were commercially available. Starting with 4-halo-3-methoxyanilines, 3-phenyl- and 3-ethylquinolones **48**−**53** were prepared. With 3-substituted 6-chloro-7-methoxy-4(1*H*)-quinolones, **54**−**60** were prepared from 2-substituted β-ketoesters via Conrad−Limpach cyclization, while with intermediates **61**−**63**, 4(1*H*)-quinolones **64**−**67** were synthesized via cross-coupling reactions. Analogous to the 3-alkenyl-4(1*H*)-quinolones **11**−**13**, compounds **65** and **66** were synthesized as a mixture and subsequently separated into their constituent isomers by reversed-phase preparative HPLC.

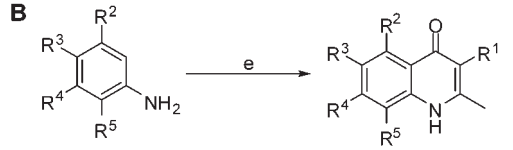
Antimalarial Activity. All synthesized compounds were routinely tested against the clinically relevant multidrug resistant malarial strains W2 (chloroquine and pyrimethamine resistant) and TM90-C2B (chloroquine, mefloquine, pyrimethamine, and atovaquone resistant). The human malaria parasite *P. falciparum* has been grown in vitro in dilute human erythrocytes in RPMI 1640 media containing 10% heat inactivated plasma.[25] Concentration response data have been analyzed by a nonlinear regression logistic dose response model, and the 50% inhibition for each compound

Scheme 2. Synthesis of 5-, 6-, 7-, or 8-Substituted 4(1*H*)-Quinolones **18**−**42**[a]

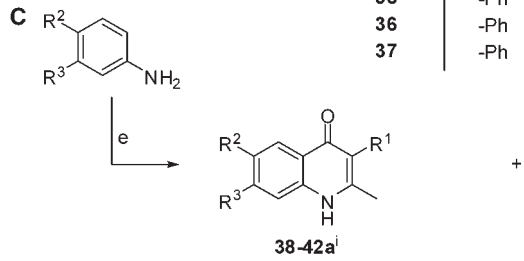


Compound	R	Yield[i]
18	-OCH_3	77 %
19	-CH_3	60 %
20	-Br	70 %
21	-Cl	66 %
22	-F	67 %

Compound	R	Yield
23b	-OCH_3	32 %
24b	-H	25 %
25b	-Cl	28 %
26b	-F	31 %



Compound	R^1	R^2	R^3	R^4	R^5	Yield
27	-Bn	-H	-OCH_3	-H	-H	65 %
28	-Bn	-H	-Cl	-H	-H	77 %
29	-Ph	-H	-OCH_3	-H	-H	95 %
30	-Ph	-H	-Cl	-H	-H	12 %
31	-Bn	-H	-H	-H	-OCH_3	59 %
32	-Bn	-H	-H	-H	-Cl	54 %
33	-Ph	-H	-H	-H	-OCH_3	46 %
34	-Ph	-H	-H	-H	-Cl	27 %
35	-Ph	-H	-H	-Cl	-Cl	17 %
36	-Ph	-H	-Cl	-H	-Cl	14 %
37	-Ph	-Cl	-H	-Cl	-H	13 %



Compound	R^1	R^2	R^3
38a	-Ph	-Cl	-Cl
39a	-Bn	-H	-OCH_3
40a	-Bn	-H	-Cl
41a	-Ph	-H	-OCH_3
42a	-Ph	-H	-Cl

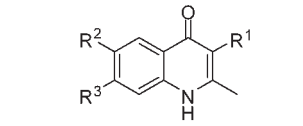
Compound	R^1	R^2	R^3	Yield (a+b)
38b	-Ph	-Cl	-Cl	54 % (1:1)
39b	-Bn	-H	-OCH_3	71 % (4:1)
40b	-Bn	-H	-Cl	45 % (3:2)
41b	-Ph	-H	-OCH_3	63 % (4:1)
42b	-Ph	-H	-Cl	92 % (1:1)

[a]Reaction conditions: (a) ethyl acetoacetate, AcOH, benzene, Dean−Stark trap, reflux, overnight then Ph_2O, reflux, 15 min; (b) KBr (20% aq), Br_2, 2 M NaOH, room temp, 2−12 h; (c) BnCl, Bu_3BnNCl, NaOH, DCM/H_2O (1:1); (d) $Pd(Cl)_2(PPh_3)_2$, CuI, TEA, DMF, 1-hexyne, 130 °C; (e) ethyl 2-benzyl- or 2-phenyl-acetoacetate, AcOH, benzene, Dean−Stark trap, reflux, overnight, then Ph_2O, reflux, 15 min. (i) Recrystallized from DMF. (ii) Preparative HPLC separation of isomer **b**.

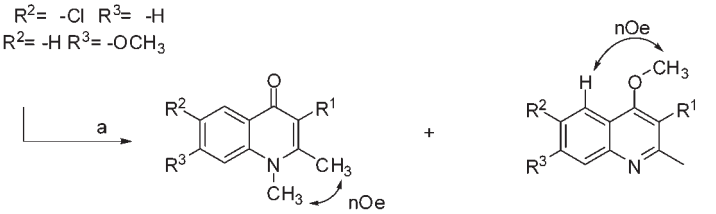
against the individual strains has been calculated as the effective concentrations (EC_{50}). The emergence of resistance and cross-resistance with atovaquone is a major concern for any new antimalarial chemotype series, especially for compounds that target the cytochrome bc_1 complex. The resistance index (RI) of each 4(1*H*)-quinolone has been calculated as the ratio of the effective concentrations of W2 and TM90-C2B (RI = EC_{50}(TM90-C2B)/EC_{50}(W2)). Compounds with RI = 0.3−3.0 are desirable, whereas compounds with an RI > 10 or RI < 0.1 are likely to have clinically relevant levels of cross-resistance with atovaquone and are not candidates for additional preclinical studies. For both chloroquine and atovaquone a > 3-fold increase in the in vitro EC_{50} is associated with clinically relevant resistance.[26,27]

Heat inactivated plasma has been shown to play an integral role for the correct determination of the EC_{50} constants and ultimately the calculation of the resistance index. Although Albumax-supplemented media have been reported to deliver the most consistent results for in vitro screening,[28] the testing of the 4(1*H*)-quinolones from the WRAIR inventory in assay conditions containing heat inactivated plasma rendered reproducible data with significantly increased cross-resistance to atovaquone in comparison to the testing in media containing Albumax; therefore,

Scheme 3. Synthesis of *N*-Methyl-4(1*H*)-quinolones **43a**−**46a** and O-Methylated 4-Quinolinols **43b**−**46b**[a]



27: R^1= -Bn, R^2= -OCH_3, R^3= -H
28: R^1= -Bn, R^2= -Cl, R^3= -H
30: R^1= -Ph, R^2= -Cl R^3= -H
39a: R^1= -Bn, R^2= -H R^3= -OCH_3

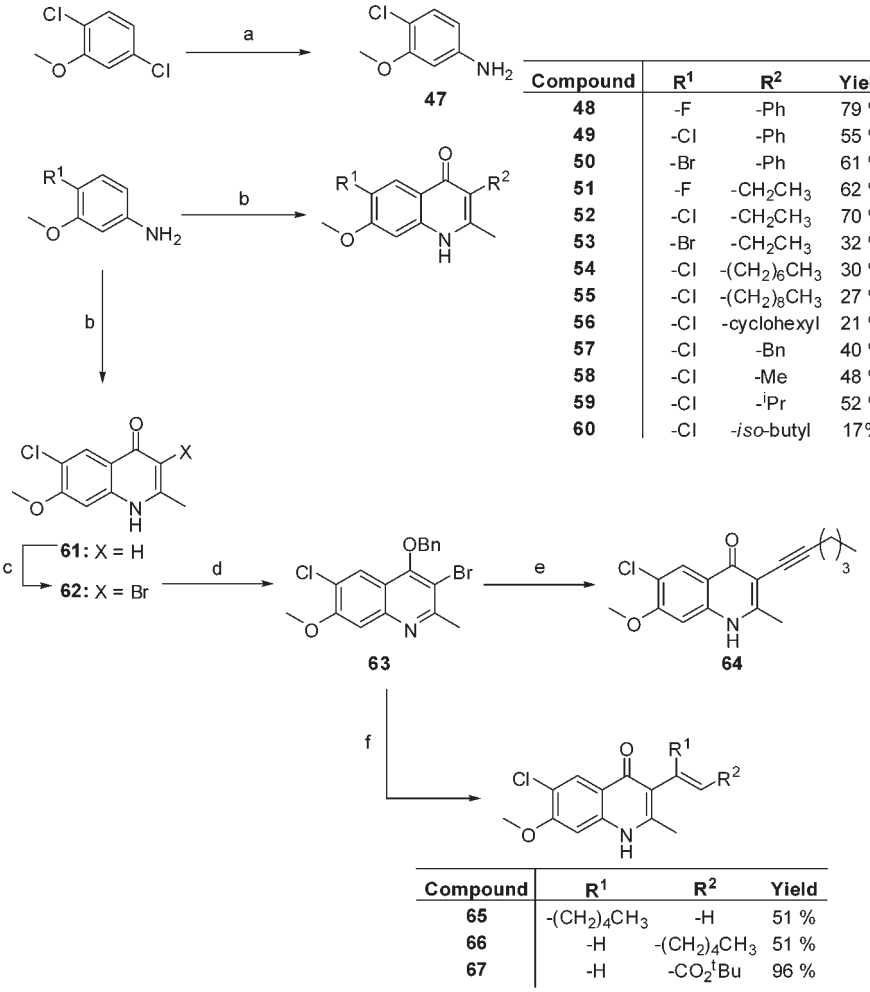


Compound	R^1	R^2	R^3
43a	-Bn	-OCH_3	-H
44a	-Bn	-Cl	-H
45a	-Ph	-Cl	-H
46a	-Bn	-H	-OCH_3

Compound	R^1	R^2	R^3	Yield (a+b)
43b	-Bn	-OCH_3	-H	75 %
44b	-Bn	-Cl	-H	77 %
45b	-Ph	-Cl	-H	83 %
46b	-Bn	-H	-OCH_3	61 %

[a]Reaction conditions: (a) Cs_2CO_3, DMF, MeI, 0 °C to room temp, 5−10 h.

Scheme 4. Synthesis of 3-Substituted 6-Halo-7-methoxy-4(1*H*)-quinolones **47**−**67**[a]



Compound	R^1	R^2	Yield
48	-F	-Ph	79 %
49	-Cl	-Ph	55 %
50	-Br	-Ph	61 %
51	-F	-CH_2CH_3	62 %
52	-Cl	-CH_2CH_3	70 %
53	-Br	-CH_2CH_3	32 %
54	-Cl	-$(CH_2)_6CH_3$	30 %
55	-Cl	-$(CH_2)_8CH_3$	27 %
56	-Cl	-cyclohexyl	21 %
57	-Cl	-Bn	40 %
58	-Cl	-Me	48 %
59	-Cl	-^{i}Pr	52 %
60	-Cl	-*iso*-butyl	17%[i]

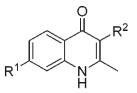
Compound	R^1	R^2	Yield
65	-$(CH_2)_4CH_3$	-H	51 %
66	-H	-$(CH_2)_4CH_3$	51 %
67	-H	-$CO_2{}^t$Bu	96 %

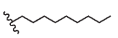
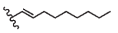
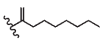
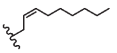
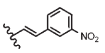
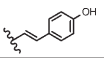
[a] Reaction conditions: a) Na, $NH_3(l)$; b) ethyl 2-substituted-acetoacetate, AcOH, benzene, Dean−Stark trap, reflux, overnight then Ph_2O, reflux, 15 min; c) KBr (20% aq.), Br_2, 2 M NaOH, r.t. 12 h; d) BnCl, Bu_3BnNCl, NaOH, DCM/H_2O (1:1); e) $Pd(Cl)_2(PPh_3)_2$, CuI, TEA, DMF, 1-hexyne, 130 °C; f) $Pd_2(dba)_3$, XPHOS, TEA, toluene, acrylate or alkene, 130 °C. [i]See Supporting Information for preparation.

heat inactivated plasma was used for all in vitro assessment for analogues of **1**.

Structure−Activity Relationship Studies. Quinolone **1** displayed EC_{50} in the low nanomolar range against TM90-C2B

Table 1. SAR Study Focusing on Substituent at the 3-Position



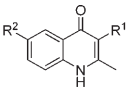
Compound	R^1	R^2	EC50 W2 (nM)	EC50 TM90-C2B (nM)	RI	EC50 J774 (μM)	CI
1	$-OCH_3$		8.59	46.6	5.42	>34.8	>747
2	$-OCH_3$	-H	>13212	12512	>0.95	>52.8	>4.2
3	-H		93.2	105	1.13	5.1	48.3
4	-H	-H	>44696	>62820	>1.41	>62.8	>1.0
5	-H		24.1	39.8	1.65	2.8	69.9
6	-H		590.7	2231	3.77	>41.4	>18.6
7	-H		711	537.6	0.76	>42.5	>79.1
8	-H		>5014	6203	>1.23	>40.1	>6.5
9	-H	-Br	453	77.6	0.92	>42.0	>542
11	-H		12.9	15.0	1.17	28.0	187
12	-H		39.6	33.7	0.85	89.1	265
13	-H		101.9	187	1.83	48.5	26.0
14	-H		>8351	>8351	>1.00	>40.0	>4.8
15	-H		>9079	>9080	>1.00	>36.3	>4.0
16	-H		4599	1489	0.32	>32.6	>21.9
17	-H		>9014	>9015	>1.00	>36.1	>4.0

and single digit nanomolar activity for W2 in the current in vitro assay; nevertheless, in previous studies, 4(1*H*)-quinolone **1** failed to display in vivo efficacy in rodent malaria models. This inconsistency in antimalarial activity was believed to be directly related to the structure of **1**. The highly lipophilic *n*-heptyl substituent rich in different conformations has been considered to be prone to metabolism, while the methoxy group in the 7-position is likely to undergo demethylation. Thus, a series of 4(1*H*)-quinolones **2**−**4** and **9** were designed initially to identify the key structural features of **1** that render its unique antimalarial activity. For analogue **2**, in which the lipophilic chain at the 3-position has been replaced by a hydrogen, at least a 300- to 1000-fold reduction in potency was observed. In contrast, the removal of the methoxy group in **1** furnished 3-heptyl-2-methyl-4(1*H*)-quinolone **3** with only a 10-fold decrease of potency. Finally, the 2-methyl-4(1*H*)-quinolone **4** became completely devoid of antimalarial activity, while introduction of a bromo substituent at the 3-position restored modest antimalarial activity for quinolone **9**. These results suggest that the substituent at the 3-position is of primary importance, while the substituents on the benzenoid ring affect the antimalarial activity to a lesser extent. The dramatic potency increase for 4(1*H*)-quinolones substituted at the 3-position with a heptyl or a bromo substituent also strongly suggests the presence of a hydrophobic pocket with a reasonable volume in proximity to the 4(1*H*)-quinolone binding pocket.

Consequently, a series of 3-substituted-4(1*H*)-quinolones was designed to further correlate the antimalarial activity with the nature of the residue at the 3-position (Table 1). In comparison to quinolone **3**, elongation of the lipophilic chain by two methylene units increased the potency of quinolone **5** by about 3-fold. This result is in agreement with the previous observation that shortening the lipophilic chain results in a decrease of antimalarial activity. Furthermore, the potency of the 3-alkyl-substituted 4(1*H*)-quinolones changed when the hydrophobic chain contained a carbon−carbon double bond. In comparison to 4(1*H*)-quinolone **5**, introduction of a *Z*-configured olefin as the side chain of quinolone **13** decreased the antimalarial activity while quinolones **11**, possessing an *E*-configured olefin and **12** possessing a 1,1-disubstituted olefin, are more potent by a factor of approximately 7 and 3, respectively. Strikingly, the potencies of the alkenyl-substituted 4(1*H*)-quinolones **11**−**13** depend on the geometry of the carbon−carbon double bond. In contrast to the *Z*-alkene side chain of **13**, the conformational rigidity of the *E*-configured 3-substituent seems to match the conformation of the saturated heptyl group of **5**.

Next, *E*-configured α,β-unsaturated ester **14** and *E*-configured stilbene-like quinolones **15**−**17** have been shown to have poor EC_{50} in the micromolar range. These observations could possibly be explained by the assumption that a significant extension of the conjugated π-system to the side chain may not favor binding to the biological target. Next, quinolones **6**−**8** were designed with the intent of replacing

Table 2. SAR Study Focusing on Substituents in the Benzenoid Ring



Compound	R^1	R^2	EC_{50} W2 (nM)	EC_{50} T90-C2B (nM)	RI	EC_{50} J774 (μM)	CI
18	-Br	$-OCH_3$	3000	1165	0.39	>37.3	>32.0
19	-Br	$-CH_3$	288	261	0.90	19.6	74.9
20	-Br	-Br	1404	339	0.24	>31.5	>92.9
21	-Br	-Cl	845	126	0.14	21.7	172
22	-Br	-F	929	125	0.13	>39.1	>313
23b		$-OCH_3$	>9213	>9213	>1.00	>36.8	>4.0
24b		-H	8288	>10359	>1.25	8.90	>0.9
25b		-Cl	>9065	43066	>4.75	>36.3	>0.84
26b		-F	>9642	>9641	>1.00	>38.6	>4.0

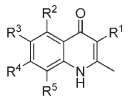
the flexible side chain to rigidify the 4(1*H*)-quinolone through installation of cyclic residues at the 3-position. Substitution of the *n*-heptyl side chain of **3** by a cyclohexyl, benzyl, or phenyl substituent yielded moderately active 4(1*H*)-quinolones **6**−**8** with EC_{50} in the higher nanomolar range.

Subsequently, compounds varying in the 6-position on the benzenoid ring have been prepared and tested (Table 2). Synthetic considerations combined with modest antimalarial activities obtained for quinolones **7**, **8**, and **9** led to the design of a variety of 2-methyl-4(1*H*)-quinolones substituted with bromo, phenyl, and benzyl substituents at the 3-position. First, 3-bromo-2-methyl-4(1*H*)-quinolones substituted with a methoxy, bromo, chloro, and fluoro substituents at the 6-position were screened. Of these compounds, the methoxy analogue **18** appeared the least active while the chloro and fluoro analogues **21** and **22** exhibited the best activity. Moreover, to complement the previous study with the 3-alkenyl-4(1*H*)-quinolones **11**−**13**, a 6-substituted quinolone series possessing linear geometry at the 3-position was designed and synthesized. The 3-alkynyl-substituted 4(1*H*)-quinolones **23b**−**26b**, nevertheless, displayed poor activities with EC_{50} of 8 μM or higher.

Furthermore, an approach following the Topliss operational scheme for aromatic substitutions has been conducted to 5-, 6-, 7-, and 8- positions (Table 3). This was achieved utilizing methoxy, chloro, and dichloro substitutions with 3-phenyl- and 3-benzyl-2-methyl-4(1*H*)-quinolone as the main scaffold. All dichloro-4(1*H*)-quinolones **35**−**38**, displayed EC_{50} in the micromolar range and thus seemed inferior to the monosubstituted compounds. For 3-phenyl-substituted compounds, testing against the W2 strain revealed activity trends in which the potency decreased according to $7 \gg 8 > 6 \sim 5$ position for the methoxy-substituted compounds and $7 \sim 6 \gg 5 > 8$ position for the chloro-substituted compounds. For the TM90-C2B strain, the same substitution dependence was identified for the methoxy-4(1*H*)-quinolones; however, the chloro-substituted compounds followed the inhibitory trend of $6 > 7 \gg 5 >$ 8-position. These results demonstrate that substituents at the 5- and 8-positions are not tolerated, while substituents at the 6- and 7-positions influence the antimalarial activity as well as the resistance index. In comparison to 4(1*H*)-quinolone **7**, for example, the 6-chloro substituent in **30** increases the antimalarial potency by a factor of 3 for W2; however, it does not change the activity against TM90-C2B. This strain-specific potency enhancement consequently reverses the resistance index from 0.76 to 3.18. On the contrary, the methoxy group at the 7-position of compounds such as **1**, **39a**, or **41a** improves the activity for both strains whereby the enhancement is more prominent for W2 in comparison to TM90-C2B. A possible explanation for the observed substituent effects is that the chloro and methoxy substituents are influencing the electronic nature of the 4(1*H*)-quinolone core. The 6-chloro substituent increases the acidity of the quinolone N−H and possibly strengthens the binding between the 4(1*H*)-quinolone and the target. In contrast, the electron donating nature of the methoxy group at the 7-position improves the carbonyl's capacity to accept hydrogen bonds in the binding pocket.

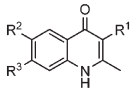
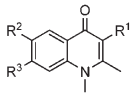
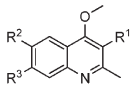
In general, a 4(1*H*)-quinolone is in equilibrium with the tautomeric 4-quinolinol form and it has been reported that the equilibrium lies in favor of the 4(1*H*)-quinolone in both the solid and solution state.[29] Thus, a study was designed to lock a particular 4-quinolone in one of its two tautomeric forms (keto and enol-ether) via methylation. These compounds were then screened to determine the difference in activities (Table 4). A small set of *N*-methylated 3-benzyl-substituted 4-quinolones **43a**−**46a** and their *O*-methylated versions **43b**−**46b** have been shown to be reduced of antimalarial activity in comparison to their 4(1*H*)-quinolone congeners **27**, **28**, **30**, and **39a**. Differences in activities among analogues are negligible for compounds such as **27**, **43a**, and **43b**, which are all approximately 9 μM. However, the 6-chloro-3-phenyl-4-quinolones **30**, **45a**, and **45b** display up to 40-fold differences in activity between the methylated and nonmethylated compounds. It is noted that compounds at ≥ 8 μM are approaching or at the limit of experimentally observed inhibition; compounds such as this are considered to be inactive within our assay, and thus, the analogue set of **30**, **45a**, and **45b** provides the most insight, suggesting the necessity of the free 4(1*H*)-quinolone core for enhanced activity.

Table 3. SAR Study Focusing on Positions 5−8 on the Quinolone Ring



Compound	R^1	R^2	R^3	R^4	R^5	EC_{50} W2 (nM)	EC_{50} TM90-C2B (μM)	RI	EC_{50} J774 (μM)	CI
39b	-Bn	$-OCH_3$	-H	-H	-H	6442	2113	0.33	11.2	5.33
27	-Bn	-H	$-OCH_3$	-H	-H	>8950	23744	>2.65	>23.7	>1.0
39a	-Bn	-H	-H	$-OCH_3$	-H	733	1384	1.89	>35.8	>25.9
31	-Bn	-H	-H	-H	$-OCH_3$	>2238	>5454	>2.44	>35.8	>6.5
41b	-Ph	$-OCH_3$	-H	-H	-H	8154	5075	0.62	>37.7	>7.4
29	-Ph	-H	$-OCH_3$	-H	-H	>9423	>9423	>1.00	>37.7	>4.0
41a	-Ph	-H	-H	$-OCH_3$	-H	287	269	0.93	>37.7	>140.3
33	-Ph	-H	-H	-H	$-OCH_3$	2063	1665	0.81	>37.7	>22.6
40b	-Bn	-Cl	-H	-H	-H	630	5261	8.35	>35.2	>6.7
28	-Bn	-H	-Cl	-H	-H	2471	3276	1.33	>35.2	>10.7
40a	-Bn	-H	-H	-Cl	-H	2168	15679	7.23	>35.2	>2.2
32	-Bn	-H	-H	-H	-Cl	>8811	>8811	>1.00	>35.2	>4.0
42b	-Ph	-Cl	-H	-H	-H	5064	4740	0.93	>37.1	>7.8
30	-Ph	-H	-Cl	-H	-H	244	777	3.18	>37.1	>47.7
42a	-Ph	-H	-H	-Cl	-H	216	1858	8.59	>37.1	>19.9
34	-Ph	-H	-H	-H	-Cl	>9269	>9269	>1.00	>37.1	>4.0
38b	-Ph	-Cl	-Cl	-H	-H	659	3211	4.87	>32.9	>10.2
38a	-Ph	-H	-Cl	-Cl	-H	569	350	0.61	>32.9	>93.3
35	-Ph	-H	-H	-Cl	-Cl	>8219	>8219	>1.00	>32.9	>4.0
36	-Ph	-H	-Cl	-H	-Cl	>8219	>8219	>1.00	>32.9	>4.0
37	-Ph	-Cl	-H	-Cl	-H	2147	3437	1.60	>32.9	>9.5

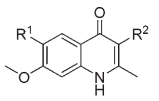
Table 4. Activity of *N*-Methyl-4-quinolones and *O*-Methyl-4-quinolinols against W2 and TM90-C2B

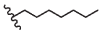
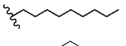
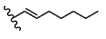
Tautomeric Structure	Compound	R^1	R^2	R^3	EC_{50} W2 (μM)	EC_{50} TM90-C2B (μM)
	**27**	-Bn	$-OCH_3$	-H	>8.95	>8.95
	28	-Bn	-Cl	-H	2.47	3.27
	30	-Ph	-Cl	-H	0.24	0.78
	39a	-Bn	-H	$-OCH_3$	0.73	1.38
	**43a**	-Bn	$-OCH_3$	-H	>8.52	8.06
	44a	-Bn	-Cl	-H	>8.40	>8.40
	45a	-Ph	-Cl	-H	>8.80	>8.80
	46a	-Bn	-H	$-OCH_3$	>8.52	7.84
	**43b**	-Bn	$-OCH_3$	-H	>8.52	>8.52
	44b	-Bn	-Cl	-H	>8.40	>8.40
	45b	-Ph	-Cl	-H	>8.80	>8.80
	46b	-Bn	-H	$-OCH_3$	>8.52	>8.52

Finally, a series of compounds with the most promising substituents at the 3-, 6-, and 7-positions incorporated into the same molecule were tested (Table 5) with the rationale that the substituents may enhance the antimalarial activity in an additive or synergistic fashion. Chloro and fluoro substituents at the 6-position have previously been identified to modestly improve the antimalarial activity. For example, the methoxy group in **1** contributes approximately a 10-fold increase in potency against W2 than **3**. Thus, compounds containing the 6-halo-7-methoxy substituency **48**−**53** have been screened to identify the substituent combination yielding the greatest synergy. Of these compounds, the best antimalarial activity was obtained with the chloromethoxy-disubstituted compounds **49** and **52** with EC_{50} values in the lower nanomolar range while the bromomethoxy and fluoromethoxy-disubstituted 4(1*H*)-quinolones **48**, **50**, **51**, and **53** lost potency by a factor of 5 or more. Ultimately, 6-chloro-7-methoxy-4(1*H*)-quinolones **54**−**67** possessing various substituents at the 3-position were screened and, in general, a slight increase in potency was observed for the TM90-C2B strain. Although the 6-chloro-7-methoxy-4(1*H*)-quinolone **61**, lacking a group at the 3-position, is a poor inhibitor of W2 and TM90-C2B with EC_{50} values in the single digit micromolar range, it demonstrates a 30-fold potency increase in comparison to 2-methyl-4(1*H*)-quinolone **4**. For compound **58**, an EC_{50} of 27 nM was determined, which corresponds to a 2-fold gain in activity in comparison to compound **1**. The most active compounds are analogues **54** and **55** with activities lower than 3 nM for TM90-C2B and lower than 13 nM for W2. 3-Alkenyl-substituted analogues **65** and **66** exhibit slightly decreased activities than **54**−**55**. Heck adduct **67** had slightly decreased activity than **1** of 61.7 nM for W2 and 53.6 nM for TM90-C2B; however, it exhibited a RI of approximately 1. Importantly, the proficiency of the 6-chloro-7-methoxy backbone is clearly manifested in the identification of multiple 4(1*H*)-quinolones that surpass the biological activity of the original compound **1**.

Strain Selectivity and Resistance Index. In vitro testing demonstrates that most of the 4(1*H*)-quinolone compounds exhibit moderate strain dependence (RI) with up to 3-fold differences in their EC_{50} values against W2 and TM90-C2B. The most potent 4(1*H*)-quinolones tend to be marginally more potent against TM90-C2B than against W2 (Table 5

Table 5. SAR Study of 6-Halo-7-methoxy-4(1*H*)-quinolones



Compound	R^1	R^2	EC_{50} W2 (nM)	EC_{50} TM90-C2B	RI	EC_{50} J774 (μM)	CI
48	-F		167	83.0	0.50	>35.3	>425
49	-Cl		26.2	15.3	0.58	>33.4	>2,173
50	-Br		79.4	25.0	0.31	>29.1	>1,164
51	-F		368	161	0.44	9.4	58.3
52	-Cl		48.2	27.6	0.57	19.0	689
53	-Br		179	36.3	0.20	>33.9	>933
54	-Cl		12.3	2.95	0.22	>37.1	>10,520
55	-Cl		6.03	1.59	0.26	>28.7	>18,038
56	-Cl		237	397	1.68	>32.7	>82.3
57	-Cl		93.7	68.6	0.73	>31.9	>465
58	-Cl	$-CH_3$	56.6	27.3	0.48	12.2	449
59	-Cl	$-^{i}Pr$	112	194	1.72	21.7	112
60	-Cl	$-^{i}Bu$	86.4	63.3	0.73	>35.7	>564
61	-Cl	-H	3,175	1,856	0.58	>44.7	>24.1
64	-Cl		2,156	4,212	1.95	15.0	3.6
65	-Cl		39.4	14.8	0.38	18.9	1,278
66	-Cl		31.5	10.6	0.34	>31.2	>2,947
67	-Cl		61.7	53.6	0.87	>28.6	>533
atovaquone			0.54	6,232	11,540	n.d	n.d.
chloroquine			163.9	48.2	0.29	n.d	n.d.

and Figure 2). Noticeable exceptions to this trend are the 7-chloro-substituted-4(1*H*)-quinolones **40a** and **42a** which inhibit W2 10-fold greater than TM90-C2B. In contrast, the very potent compounds **49**, **54**, **55**, and **65** tend to be modestly more potent against TM90-C2B than against W2. To further analyze strain selectivity and tendency to induce resistance, the entire 4-(1*H*)-quinolone compound series was divided into various classes based on substitution of the benzenoid ring (Figure 2A) and substitution at the 3-position (Figure 2B). The pEC_{50} values for W2 were plotted against the pEC_{50} values for TM90-C2B. All 4(1*H*)-quinolones exhibiting single digit EC_{50} constants for TM90-C2B are exclusively substituted with a chloro substituent at the 6-position and with methoxy substituent at the 7-position. Furthermore, it also generally appears that 6-halo-7-methoxy-4(1*H*)-quinolones have the tendency to inhibit TM90-C2B more potently than W2. In contrast, for the substituents at the 3-position, no obvious correlation or strain preference is observed.

Cytotoxicity. An important quality of the 4(1*H*)-quinolones is their selectivity to inhibit parasite growth selectively over mammalian cells. In a 96-well plate format, the cytotoxicity of the test compounds to J774 mammalian cells has been assessed in vitro (Table 5).[30] The cytotoxicity index (CI) of each compound has been calculated as the ratio of the EC_{50} value for J774 and the value of TM90-C2B ($CI = EC_{50}(J774)/EC_{50}(TM90\text{-}C2B)$). Of all the compounds tested, none displayed signs of cytotoxicity at concentrations lower than 2 μM. Thus, it is not surprising that most 4(1*H*)-quinolones displaying potent antimalarial activity also possess CI values of several thousand, indicating that they are selective, nontoxic chemotypes.

Structure−Property Relationship Studies. To assess potential compound liabilities, physicochemical properties including aqueous solubility, $\log D_{7.4}$, permeability, and hepatic microsomal stability were determined (Table 6).[31] Since the in vitro efficacy assay was performed in presence of 10% of heat inactivated plasma, protein binding was regarded to be of secondary importance, and therefore, the compounds were not tested for protein binding. Solubility and $\log D_{7.4}$ for each compound were determined utilizing HPLC-based methods. Passive transcellular permeability was determined using the standard parallel artificial membrane permeability assay (PAMPA). Microsomal stability was assessed for a subset of 4(1*H*)-quinolones along with **1** in the presence of human and murine liver microsomes.[31]

The distribution coefficients and the permeabilities of almost all 4(1*H*)-quinolones are within the acceptable ranges ($1 < \log D_{7.4} < 4$; $P_e > 50 \times 10^{-6}$ cm^{-1}). A plot of in vitro activity against $\log D_{7.4}$ values revealed a trend in which the $\log D_{7.4}$ slightly increases with an increase in potency against W2 and TM90-C2B (Figure 3). Evidently, the lipophilicity of

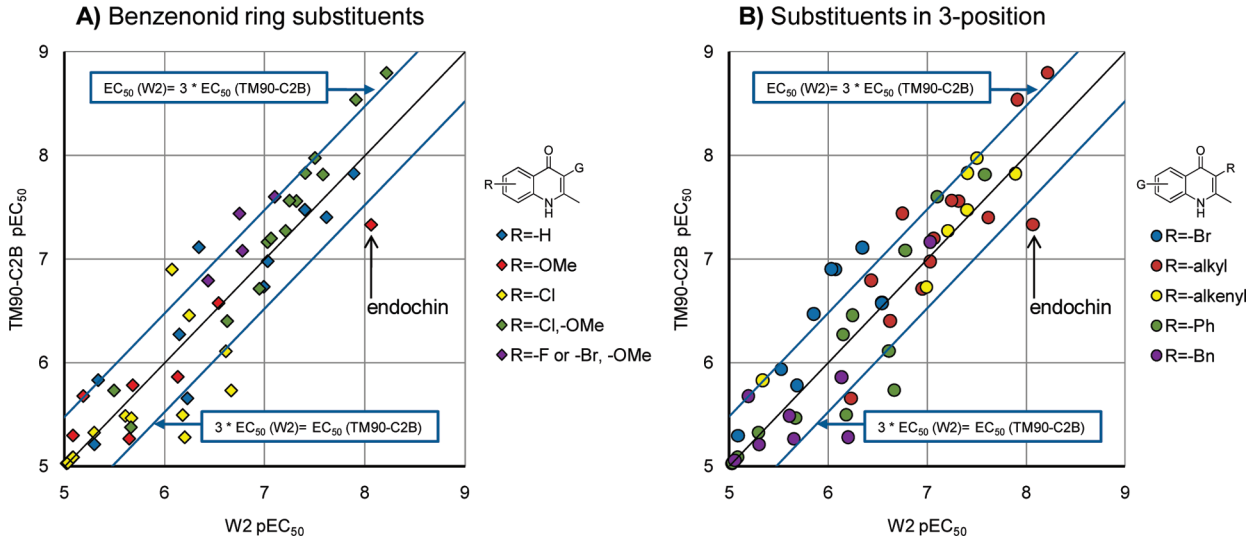


Figure 2. Plot of pEC_{50} for TM90-C2B vs pEC_{50} for W2. Note that only compounds with precisely determined EC_{50} constants for the two strains W2 and TM90-C2B have been included in these two plots ($EC_{50} < 10\ \mu M$). The compounds localized in the plot area between the blue diagonal lines possess an RI value between 0.3 and 3: (A) The 4(1*H*)-quinolones have been divided into categories based on their substituents on the benzenoid ring (R = H, OCH_3, Cl (including di-Cl), 6-Cl-7-OCH_3, 6-Br-7-OCH_3, and 6-F-7-OCH_3). (B) The 4(1*H*)-quinolones have been divided into categories based on their substituents at the 3-position (R = Br, alkyl, alkenyl, Ph, Bn). The pEC_{50} values are calculated as the $-\log_{10} EC_{50}$.

Table 6. Physicochemical Properties of Selected 4(1*H*)-Quinolones[a]

					permeability[b] P_e (10^{-6} cm/s)		microsomal stability[c] $T_{1/2}$ (min)	
compound	MW (g/mol)	log *D* pH 7.4	mp °C	solubility (μM)	pH 7.4	pH 4.0	mouse	human
1	287.40	3.69	216−218	**	679	1020	7.9	10.2
48	283.30	1.72	361−363	***	124	192	nd	nd
49	299.75	1.65	329−330	***	48.3	105	21.3	128.3
50	344.20	2.20	328−329	*	330	306	nd	nd
51	235.25	1.20	306−307	*	91.1	172	nd	nd
52	251.71	2.43	326−328	****	57.3	96.4	28.4	33.8
53	296.16	1.70	325−327	**	75.1	81.9	nd	nd
54	321.84	3.83	238−239	*	<0.01	<0.01	nd	nd
56	305.80	3.04	313−314	***	630	1236	nd	nd
57	313.78	1.99	254−255	**	566	575	nd	nd
61	223.66	1.95	nd	**	25.2	11.9	62.4	161.2
65	319.83	3.58	nd	**	755	768	nd	nd
67	349.81	1.81	nd	***	261	249	43.9	60.3

[a] (*) Solubility < 2 μM. (**) 2 μM < solubility < 5 μM. (***) 5 μM < solubility < 10 μM. (****) 10 μM < solubility < 20 μM. (*****) Solubility > 20 μM. nd: not determined. [b] Passive transcellular permeability (effective permeability P_e). [c] In vitro metabolic stability using liver microsomes. $T_{1/2}$ corresponds to degradation half-time.

the entire 4(1*H*)-quinolone compound series is considered to be well balanced, since the majority of the compounds possess an optimal log $D_{7.4}$ between 1 and 3. Nevertheless, with the exception of 3-phenyl-substituted 6-chloro-7-methoxy-4(1*H*)-quinolone **49**, a distribution coefficient of 3.8 or higher has been determined for 4(1*H*)-quinolones **1**, **54**, and **55** with EC_{50} in the single digit nanomolar range.

For 4(1*H*)-quinolone **1**, an aqueous solubility with less than 2 μM has been identified as a major liability. In comparison, 6-chloro-7-methoxy-4(1*H*)-quinolones **54** and **66** with alkyl and alkenyl substituents, respectively, at the 3-position and compound **56**, the cyclohexyl analogue, displayed similar or diminished aqueous solubilities. Improvements have been observed for **67** possessing an α,β-unsaturated ester substituent. Furthermore, compound **49** with a shortened 3-alkyl substituent and **52** with a phenyl substituent possess slightly better solubility than **1**. Finally, as exemplified with **51**−**53**, the 6-fluoro- and 6-bromo-7-methoxy-4(1*H*)-quinolones are less soluble than their 6-chloro congener **52**.

Given that the log $D_{7.4}$ values of the entire compound series are moderate and in the acceptable range, the solubility appears worse than predicted by the distribution coefficients. Strong lattice energy and intermolecular hydrogen bonding are possible reasons for the unusual solubility, and this hypothesis is strongly supported by the fact that structural features perturbing the crystal packing and/or the intermolecular hydrogen bonds of the 4(1*H*)-quinolones increase the solubility. For instance, blocking of the 5- or 8-positions with a methoxy or a chloro substituent, as seen in compounds **31**, **39b**, **41b**, and **42b**, dramatically increases the aqueous solubility in comparison to the 4(1*H*)-quinolones, which are methoxy- or chloro-substituted in 6- or 7-position.[31] Furthermore, *N*-methyl-4(1*H*)-quinolones **43a**−**46a** or *O*-methyl-4(1*H*)-quinolinols **43b**−**46b** also seem to possess better aqueous solubilities in comparison to the corresponding N(1*H*)-quinolones

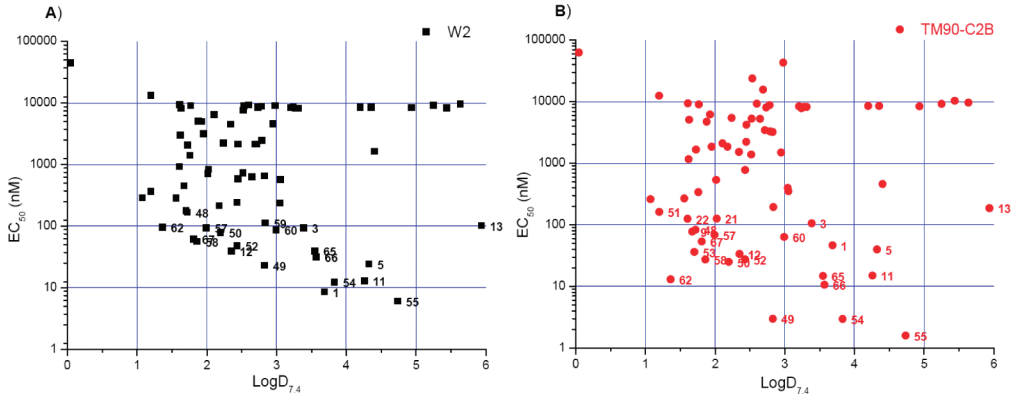


Figure 3. Plot of in vitro efficacy versus distribution coefficient log $D_{7.4}$: (A) plot for W2; (B) plot for TM90-C2B. Compounds with EC_{50} exceeding 100 nM are not labeled.

27, **28**, **30**, or **39a**. Nevertheless, the structural modifications leading to compounds with better solubility are combined with significant losses in antimalarial activity.

Finally, microsomal stability of a selected set of compounds has been determined. Compound **1** has poor microsomal stabilities with half-lives of 10 min or shorter in murine and human systems. Comparison of the half-lives of compounds **1**, **52**, and **61** suggests that the long and flexible alkyl chain at the 3-position is prone to metabolic degradation in hepatic microsomes. Replacing the 3-heptyl-substituent with a phenyl residue as in compound **49**, an electron-deficient carbon−carbon double bond in **67**, or a short ethyl group as in **52** yields 4(1*H*)-quinolones with prolonged half-lives of 25 min or longer.

Conclusions

An initial study with 4(1*H*)-quinolone **1** and its analogues **2**−**5** suggested that the 4(1*H*)-quinolone scaffold, the 7-methoxy-group, and the alkyl chain at the 3-position are important for inhibitory activity. Parallel testing of the same 4(1*H*)-quinolones for key physicochemical properties identified poor aqueous solubility and rapid degradation in microsomes as the compound's major liabilities. Subsequently, a total of 79 2-methyl-4(1*H*)-quinolones with varying substituents at the 1-, 3-, 4-, 5-, 6-, 7-, and/or 8-positions have been synthesized and tested against the clinically relevant isolates TM90-C2B and W2 with the objective to obtain detailed SAR data. The best antimalarial activities were observed if (a) the 4(1*H*)-quinolone nitrogen and oxygen were unsubstituted, (b) the benzenoid ring was disubstituted with 6-chloro- and 7-methoxy groups, (c) the 5- and 8-position of the benzenoid ring were unsubstituted, and (d) the 4(1*H*)-quinolone's 3-position was substituted with an alkyl-, alkenyl-, or aryl-group. Among the most active 4(1*H*)-quinolones against the multidrug resistant isolate of *P. falciparum* TM90-C2B were compounds **49**, **52**, **54**, **55**, **56**, and **65**, with EC_{50} in the low nanomolar range surpassing the potency of **1**. Importantly, no cytotoxicity was observed at 4(1*H*)-quinolone concentrations lower than 2 μM providing cytotoxicity indices of 1000 or more for the best compounds. Furthermore, this SAR study also demonstrated that, in comparison to atovaquone or chloroquine, the majority of the 4(1*H*)-quinolones lack any cross resistance. Though the exact mechanism of action is not known at this point, due to structural similarities between the 3-substituted 4(1*H*)-quinolones and atovaquone or GSK's pyrridones[32] in conjunction with the oxygen consumption testing,[18] cytochrome bc_1 is probably the parasite target inhibited by the 3-substituted 4(1*H*)-quinolones.

In parallel to the SAR testing, a SPR study focusing on solubility, distribution coefficient, permeability, and microsomal stability identified significant differences between the best inhibitors **49**, **56**, and **65** particularly in the microsomal stability and aqueous solubility. 3-Aryl-substituted 4(1*H*)-quinolone **49** displayed better solubility and stability in comparison to **1**, 3-alkenyl-, and 3-alkyl-4(1*H*)-quinolones **55** and **65**. These results suggest that 3-phenyl-2-methyl-4(1*H*)-quinolone **49** is better suited as a platform for further development, despite it being slightly less potent in comparison to 3-alkyl- or 3-alkenyl-substituted compounds **55** and **65**. Testing of frontrunner compounds for exoerythrocytic stage activity as well as in vivo efficacy in rodent malaria models is currently under investigation.

Experimental Section

All reagents and anhydrous solvents were obtained from Aldrich Chemical Co. and used without further purification unless otherwise noted. Ethyl 2-phenylacetoacetate and 2,5-dichloroanisole were bought from Alfa Aesar. 4-Fluoro-3-methoxyaniline was bought from Oakwood Products, Inc., while 4-bromo-3-methoxyaniline was bought from TCI America. The identity of all title compounds was verified via ^{1}H NMR, ^{13}C NMR, and HPLC/HRMS. The chemical purity of the titled compounds was determined using the following conditions: an Agilent 1100 series LC/MSD with a Eclipse XDB-C18 (4.6 mm × 100 mm, 5 μm) reversed phase column; method, 10% (v/v) of acetonitrile (+0.05% TFA) in 90% (v/v) of H_2O (+0.05% TFA), ramped to 100% acetonitrile (+0.05% TFA) over 9 min, and held at 100% acetonitrile for 4 min with a flow rate of 0.7 mL/min, UV detector, 254 nm. The purity of each compound was ≥95% in this analysis. NMR spectra were recorded at ambient temperature on a 400 or 500 MHz Varian NMR spectrometer in the solvent indicated. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm), downfield of TMS and were measured relative to the signals for chloroform (7.26 ppm) and dimethyl sulfoxide (2.50 ppm). All ^{13}C NMR spectra were reported in ppm relative to the signals for chloroform (77 ppm) and dimethyl sulfoxide (39.5 ppm) with ^{1}H decoupled observation. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (Hz), whereas ^{13}C NMR analyses were obtained at 101 MHz and reported in terms of chemical shift. NMR data were analyzed by using MestReNova Software, version 5.3.2-4936. High resolution mass spectra (HRMS) were performed on an Agilent LC/MSD TOF system

G3250AA. Isomers were separated by reverse phase HPLC system (Waters Prep LC 4000 system with Waters 996 photodiode array detector, Agilent column Eclipse XDB-C18, 5 μm, 9.4 mm × 250 mm). Compounds were eluted using a gradient elution of 70/30 to 50/50 A/B over 30 min at a flow rate of 5.0 mL/min, where solvent A was water and solvent B was acetonitrile. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 precoated plates (0.25 mm) from EMD Chemical Inc., and components were visualized by ultraviolet light (254 nm). Silicycle silica gel 230−400 (particle size 40−63 μm) mesh was used for all flash column chromatography.

General Procedure A: Preparation of 3-Substituted 2-Methylquinolin-4(1*H*)-ones (3, 5−8, 28, 29, 31−37, 38a,b−42a,b, 47, 49−55). Quinolin-4-ones were prepared by using one of the standard procedures for Conrad−Limpach reaction.[21] An oven-dry 100 mL round-bottom flask attached to a Dean−Stark trap equipped with a reflux condenser was charged with an aniline (0.025 mol), corresponding ethyl acetoacetate (0.25−0.05 mol),[33−35] benzene (25 mL), and glacial acidic acid (1 mL). The mixture was heated at 100 °C until no more water was separated (3−24 h). The benzene was distilled under reduced pressure, and the resulting enamine was then used in the next step without further purification. Biphenyl ether (30 mL) was stirred and heated at reflux, while enamine was added rapidly through the dropping funnel. Stirring and refluxing continued for 10−15 min until no more ethanol separated within the Dean−Stark trap. The mixture was then allowed to cool to room temperature while precipitation arose. The solid was filtered off and washed with hexane and acetone. Ice cold methanol washing may be necessary in some cases. No further purification was needed. Compounds **1**, **2**, **27**, **30**, **35**, **48**, **56**, **57**, **58**, **60** were prepared by slightly different procedures using $CaSO_4$ instead of Dean−Stark trap and ethanol as a solvent in order to obtain enamine.[36] The cyclization reaction was performed as described above. The yield is reported over the two steps. Compound **4** was bought from Sigma-Aldrich.

General Procedure B: Halogenation of Substituted 2-Methylquinolin-4(1*H*)-one (9, 18, 19, 20, 21, 22, 62). The halogenation was done following a procedure reported by Renault et al.[37] Thus, 1.2 equiv of a 16% solution of bromine in 30% aqueous potassium bromide was added dropwise to a stirred solution or slurry of 2-methylquinolin-4(1*H*)-one in 2 M solution of sodium hydroxide at rt. Stirring was continued until LCMS indicated absence of starting material (3−24 h). In some cases more than 1.2 equiv of halogen was needed. The mixture was then acidified with acetic acid. The precipitate was collected by filtration, washed with water, and recrystallized from DMF.

General Procedure C: Benzylation of 3-Bromo-2-methylquinolin-4(1*H*)-one (10, 23a, 25a, 26a, 63). The benzylation was done following a procedure reported by McKillop et al.[22] Thus, a mixture of dichloromethane (50 mL), water (50 mL), 3-bromo-2-methylquinolin-4(1*H*)-one (10 mmol), sodium hydroxide (15 mmol), benzyl chloride (30 mmol), and benzyltributylammonium chloride (1 mmol) was stirred at rt between 8 and 24 h. The organic layer was separated and then washed with H_2O (×2, 100 mL), brine (×1, 100 mL), and finally 1 M NH_4OH and then dried over Na_2SO_4. The crude material was purified further via flash chromatography on silica gel.

General Procedure D: Heck Coupling of 4-(Benzyloxy)-3-bromo-2-methylquinoline (11−17, 65−67). An oven-dried Schlenk tube was flame-dried and backfilled with argon (×3). The tube was then charged with quinoline (100 mg, 1.5 mmol), $Pd_2(dba)_3$ (36 mg, 0.039 mmol), XPHOS (37 mg, 0.078 mmol), alkene (0.277 mL, 1.8 mmol), and anhydrous triethylamine (1.31 mL, 0.01 mmol). The Schlenk tube was fitted with a rubber septum and then evacuated and backfilled with argon (this process was repeated three times). Dry toluene (8 mL) was added through the septum via syringe, and the resulting solution was stirred for 1 min while purging with argon before replacing the rubber septum with the Teflon screwcap. The reaction was set to the oil bath at 135 °C until completion was observed via HPLC analysis. The crude product was brought to a boil in chloroform/methanol and filtered over Celite and then concentrated in vacuo. The residual material was diluted in hexane and filtered off. More soluble products were purified via flash chromatography.

General Procedure E: Sonogashira Coupling of 4-(Benzyloxy)-3-bromo-2-methylquinoline (23b−26b, 64). An oven-dried Schlenk tube was flame-dried and backfilled with argon (×3). The tube was then charged with quinoline (0.2 g, 0.5 mmol), $Pd(PPh_3)_2(Cl)_2$ (18 mg, 0.025 mmol), CuI (6 mg, 0.025 mmol), alkyne (0.277 mL, 1.8 mmol), and anhydrous triethylamine (0.5 mL, 3.5 mmol). The Schlenk tube was fitted with a rubber septum and then evacuated and backfilled with argon (this process was repeated three times). Dry DMF (3 mL) was added through the septum via syringe, and the resulting solution was stirred for 1 min while purging with argon before replacing the rubber septum with the Teflon screwcap. The reaction was set to the oil bath at 135 °C until completion was observed via HPLC analysis. The crude product was filtered over Celite and then concentrated in vacuo. The residual material was purified via flash chromatography.

General Procedure F: Methylation of 3-Benzyl-2-methylquinolin-4(1*H*)-one (43a,b−46a,b). To a flame-dried-backfilled round-bottom flask was added quinolone (0.72 g, 2.8 mmol) and Cs_2CO_3 (1.37 g, 4.2 mmol). DMF (14.5 mL) was added, and this slurry was allowed to stir at rt for 1 h. Next, iodomethane (0.88 mL, 14 mmol) was added dropwise, and the reaction was left until completion was observed via HPLC analysis. The mixture was the poured onto water (20 mL) and then diluted with chloroform (20 mL). The organic layer was then washed with water (20 mL) twice followed by brine (20 mL). The organic layer was then dried over sodium sulfate and concentrated in vacuo. The crude compound was columned via flash chromatography (Hex/EtOAc gradient).

3-Heptyl-7-methoxy-2-methylquinolin-4(1*H*)-one (1). Compound **1** was prepared following modified general procedure A using $CaSO_4$. The precipitate was collected, washed with hexane, and recrystallized from ethanol to give 27% yield as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 11.16 (s, 1H), 7.92 (d, J = 6.4 Hz, 1H), 6.85−6.79 (m, 2H), 3.83 (s, 3H), 2.45−2.41 (m, 2H), 2.33 (s, 3H), 1.37−1.24 (m, 10H), 0.86 (t, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.16, 161.23, 145.01, 140.79, 126.89, 118.66, 117.82, 112.26, 98.19, 55.25, 31.30, 29.24, 28.67, 24.68, 22.08, 17.40, 13.93. HRMS (ESI) calcd for $C_{18}H_{25}NO_2$ $[M + H]^+$: 288.195 81. Found: 288.194 95.

7-Methoxy-2-methylquinolin-4(1*H*)-one (2). Compound **2** was prepared following modified general procedure A using $CaSO_4$. The precipitate was collected and washed with hexane to give 43% yield over the two isomers (3:1, 7- and 5-substituted isomers, respectively). Recrystallization from methanol gave the desired isomer exclusively as a white solid, mp = 249−250 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.38 (s, 1H), 7.92 (d, J = 9.6 Hz, 1H), 6.86 (d, J = 6.7 Hz, 2H), 5.81 (s, 1H), 3.83 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 176.34, 161.64, 149.11, 141.81, 126.58, 118.80, 112.46, 108.10, 98.82, 55.33, 19.36. HRMS (ESI) calcd for $C_{11}H_{11}NO_2$ $[M + H]^+$: 190.086 26. Found: 190.085 59.

3-Heptyl-2-methylquinolin-4(1*H*)-one (3). Compound **3** was prepared following general procedure A. Yield: 69%, mp = 229−230 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.33 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 2.46 (d, J = 7.9 Hz, 2H), 2.37 (s, 3H), 1.40−1.23 (m, 10H), 0.85 (t, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.45, 145.60, 139.11, 130.80, 125.04, 123.33, 122.13, 119.15, 117.36, 31.31, 29.27, 28.69, 28.60, 24.79, 22.10, 17.46, 13.94. HRMS (ESI) calcd for $C_{17}H_{23}NO$ $[M + H]^+$: 258.185 24. Found: 258.185 76.

2-Methyl-3-nonylquinolin-4(1*H*)-one (5). Compound **5** was prepared following general procedure A. Yield: 30%, mp = 215−216 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.35 (s, 1H), 8.05

(d, J = 7.8 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 2.47 (d, J = 6.5 Hz, 2H), 2.38 (s, 3H), 1.26 (d, J = 16.9 Hz, 14H), 0.85 (t, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 176.19, 146.28, 139.81, 131.47, 125.73, 124.03, 122.80, 119.84, 118.05, 31.95, 29.97, 29.71, 29.39, 29.26, 25.47, 22.74, 18.12, 14.58. HRMS (ESI) calcd for $C_{19}H_{27}NO$ $[M + H]^+$: 286.216 54. Found: 286.215 38.

3-Cyclohexyl-2-methylquinolin-4(1*H*)-one (6). Compound **6** was prepared following general procedure A. Yield: 36%, mp = 286−287 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.21 (s, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.20 (t, J = 7.3 Hz, 1H), 2.40 (s, 3H), 2.34−2.20 (m, 2H), 1.79−1.62 (m, 3H), 1.46−1.12 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.77, 145.39, 138.92, 130.73, 125.05, 124.40, 122.41, 122.08, 117.16, 28.91, 26.90, 25.76, 18.25. HRMS (ESI) calcd for $C_{16}H_{19}NO$ $[M + H]^+$: 242.153 94. Found: 242.153 42.

2-Methyl-3-phenylquinolin-4(1*H*)-one (7). Compound **7** was prepared following general procedure A. Yield: 52%. ^{1}H NMR (400 MHz, DMSO) δ 11.63 (s, 1H), 8.09 (d, J = 8.0, 1H), 7.63 (t, J = 7.6, 1H), 7.53 (d, J = 8.2, 1H), 7.39 (t, J = 7.4, 2H), 7.31−7.23 (m, 4H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.52, 147.16, 140.02, 136.89, 132.10, 131.67, 128.42, 127.12, 126.01, 125.06, 123.36, 121.56, 118.24, 19.54. HRMS (ESI) calcd for $C_{16}H_{13}N$ $[M + H]^+$ 236.106 99, found 236.107 95.

3-Benzyl-2-methylquinolin-4(1*H*)-one (8). Compound **8** was prepared following general procedure A. Yield: 81%, mp = 283−284 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.51 (s, 1H), 8.11 (d, J = 7.7 Hz, 1H), 7.59 (t, J = 7.1 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.32−7.06 (m, 7H), 3.90 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.62, 147.03, 141.32, 139.21, 131.08, 128.07, 127.99, 125.42, 125.22, 123.57, 122.49, 118.14, 117.56, 29.93, 17.83. HRMS (ESI) calcd for $C_{17}H_{15}NO$ $[M + H]^+$: 250.122 64. Found: 250.121 82.

3-Bromo-2-methylquinolin-4(1*H*)-one (9). Compound **9** was prepared using general procedure B. Yield: 96%. ^{1}H NMR (250 MHz, DMSO) δ 8.09 (d, J = 8.1, 1H), 7.65 (t, J = 7.6, 1H), 7.53 (d, J = 8.2, 1H), 7.34 (t, J = 7.5, 1H), 2.54 (s, 3H). ^{13}C NMR (63 MHz, DMSO) δ 171.05, 148.63, 138.61, 131.82, 125.24, 123.61, 122.73, 117.84, 105.90, 21.38. HRMS (ESI) calcd for $C_{10}H_8BrNO$ $[M + H]^+$: 237.986 20. Found: 237.987 11.

4-(Benzyloxy)-3-bromo-2-methylquinoline (10). Compound **10** was prepared following general procedure C. Yield: 70%. ^{1}H NMR (400 MHz, CD_2CL_2) δ 8.00 (d, J = 8.4, 1H), 7.96 (d, J = 8.4, 1H), 7.68 (ddd, J = 8.4, 7.0, 1.3, 1H), 7.58 (d, J = 6.6, 2H), 7.44 (m, 4H), 5.19 (s, 2H), 2.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.60, 159.46, 148.09, 136.32, 130.22, 128.92, 128.89, 128.84, 128.54, 126.53, 123.84, 122.11, 112.42, 76.20, 26.72. HRMS (ESI) calcd for $C_{17}H_{14}BrNO$ $[M + H]^+$: 328.033 15. Found: 328.033 37.

(*E*)-2-Methyl-3-(non-1-enyl)quinolin-4(1*H*)-one (11). Compound **11** was prepared similarly to general procedure D. An oven-dried Schlenk tube was flame-dried and backfilled with argon (×3). The tube is then charged with 4-(benzyloxy)-3-bromo-2-methylquinoline (1.15 g, 3.5 mmol), $Pd_2(dba)_3$ (180 mg, 0.175 mmol), XPHOS (190 mg, 0.35 mmol), alkene (1.08 mL, 6.3 mmol), and anhydrous triethylamine (2.9 mL, 21.0 mmol). The Schlenk tube was fitted with a rubber septum and then evacuated and backfilled with argon (this process was repeated three times). Dry toluene (20 mL) was added through the septum via syringe, and the resulting solution was stirred for 1 min while purging with argon before replacing the rubber septum with the Teflon screwcap. The mixture was added to an oil bath at 130 °C for 3 days. The crude mixture was prepurified using flash chromatography to obtain a mixture of **11**, **12**, and **13**. Yield: 64%. Then the oil was dissolved in minimal MeOH and purified further using preparative HPLC to obtain the three compounds **11**, **12**, and **13**. Other isomers were generated; however, they were unable to be adequately purified by preparative HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 8.2, 1H), 7.70 (d, J = 8.3, 1H), 7.48 (t, J = 7.5, 1H), 7.28−7.23 (m, 1H), 6.47−6.38 (m, 2H), 2.56 (d, J = 14.8, 3H), 2.06 (dd, J = 12.0, 6.9, 2H), 1.30−1.14 (m, 10H), 0.82 (t, J = 6.9, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.14, 148.11, 139.29, 135.69, 131.33, 125.74, 124.85, 123.50, 122.90, 118.52, 117.69, 34.34, 32.01, 31.78, 29.72, 29.44, 29.37, 22.84, 19.66. HRMS (ESI) calcd for $C_{19}H_{25}NO$ $[M + H]^+$: 284.200 89. Found: 284.201 12.

2-Methyl-3-(non-1-en-2-yl)quinolin-4(1*H*)-one (12). Compound **12** was prepared using modified procedure D, as mentioned above for **11**. The crude mixture was prepurified using flash chromatography to obtain the mixture of **11**, **12**, and **13**. Then the oil was dissolved in minimal MeOH and purified further using preparative HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.1, 1H), 7.69 (d, J = 8.3, 1H), 7.49 (t, J = 7.6, 1H), 7.29−7.24 (m, 1H), 5.22 (s, 1H), 4.89 (s, 1H), 2.47 (s, 3H), 2.44−2.36 (m, 2H), 1.36 (br t, 2H), 1.23−1.14 (m, 8H), 0.81 (t, J = 6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.64, 147.97, 146.25, 140.03, 131.38, 125.58, 124.76, 123.45, 123.39, 118.76, 115.64, 36.90, 32.05, 29.87, 29.47, 28.16, 22.81, 19.33,14.26. HRMS (ESI) calcd for $C_{19}H_{25}NO$ $[M + H]^+$: 284.200 89. Found: 284.201 12.

(*Z*)-2-Methyl-3-(non-2-enyl)quinolin-4(1*H*)-one (13). Compound **13** was prepared using modified procedure D, as mentioned above for **11**. The crude mixture was prepurified using flash chromatography to obtain the mixture of **11**, **12**, and **13**. Then the oil was dissolved in minimal MeOH and purified further using preparative HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (s, 1H), 8.37 (d, J = 8.0, 1H), 7.57 (d, J = 8.3, 1H), 7.50 (dd, J = 11.1, 4.1, 1H), 7.28 (d, J = 7.5, 1H), 5.55−5.33 (m, 2H), 3.42 (d, J = 5.2, 2H), 2.49 (s, 3H), 1.87 (d, J = 6.3, 2H), 1.22 (br m, J = 24.5, 10H), 0.83 (t, J = 6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.20, 147.86, 139.65, 131.30, 130.81, 127.25, 125.94, 124.37, 123.30, 118.62, 118.09, 32.62, 31.89, 29.62, 29.07, 28.56, 22.78, 18.63, 14.25. HRMS (ESI) calcd for $C_{19}H_{25}NO$ $[M + H]^+$: 284.200 89. Found: 284.201 12.

(*E*)-*tert*-Butyl 3-(2-Methyl-4-oxo-1,4-dihydroquinolin-3-yl)-acrylate 14. Compound **14** was prepared following general procedure D. Yield: 83%. ^{1}H NMR (400 MHz, DMSO) δ 12.05 (s, 1H), 8.13 (d, J = 8.0, 1H), 7.66 (t, J = 7.6, 1H), 7.57 (d, J = 16, 1H), 7.54 (d, J = 8, 1H) 7.39−7.33 (m, 2H), 2.59 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 176.19, 168.12, 153.11, 138.75, 137.74, 132.55, 126.08, 125.50, 124.61, 119.16, 118.63, 112.63, 79.58, 28.63, 18.98. HRMS (ESI) calcd for $C_{17}H_{19}NO_3$ $[M + H]^+$: 286.144 39. Found: 286.143 77.

(*E*)-2-Methyl-3-styrylquinolin-4(1*H*)-one (15). Compound **15** was prepared following general procedure D. Yield: 71%. ^{1}H NMR (400 MHz, DMSO) δ 8.15 (d, J = 8.0, 1H), 8.08 (d, J = 16.0, 1H), 7.62 (t, J = 7.5, 1H), 7.53 (d, J = 7.9, 3H), 7.37−7.30 (m, 3H), 7.20 (d, J = 7.6, 1H), 7.14 (d, J = 16.0, 1H), 2.62 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.87, 149.33, 139.70, 138.80, 131.88, 129.82, 129.28, 127.34, 126.51, 125.99, 125.23, 123.77, 123.30, 118.34, 115.09, 19.19. HRMS (ESI) calcd for $C_{18}H_{15}NO$ $[M + H]^+$: 262.122 64. Found: 262.122 80.

(*E*)-2-Methyl-3-(3-nitrostyryl)quinolin-4(1*H*)-one (16). Compound **16** was prepared following general procedure D. Yield: 96%. ^{1}H NMR (400 MHz, DMSO) δ 12.62 (s, 1H), 8.30 (s, 1H), 8.24 (d, J = 15.9, 1H), 8.15 (d, J = 7.9, 1H), 8.02 (dd, J = 13.2, 4.9, 2H), 7.74 (d, J = 8.2, 1H), 7.65−7.59 (m, 2H), 7.35−7.29 (m, 2H), 2.71 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.88, 150.75, 149.10, 141.86, 138.95, 132.77, 131.85, 130.69, 126.96, 126.48, 125.89, 125.32, 123.94, 121.56, 120.46, 118.63, 114.31, 18.99. HRMS (ESI) calcd for $C_{18}H_{14}N_2O_3$ $[M + H]^+$: 307.107 72. Found: 307.108 30.

(*E*)-3-(4-Hydroxystyryl)-2-methylquinolin-4(1*H*)-one (17). Compound **17** was prepared starting from 3-bromo-1,2-dimethylquinolin-4(1*H*)-one (0.4 g, 1.6 mmol) and 1-methoxy-4-vinylbenzene (0.19 mL, 1.4 mmol) following general procedure D. The resulting Heck adduct (1.2 mmol) was demethylated by refluxing sodium ethanethiolate (2.0 g, 24 mmol) in DMF for 12 h. Both methyl groups were removed, thus yielding the title

compound in 14% yield. ^{1}H NMR (500 MHz, CD_3OD) δ 8.28 (d, J = 8.2, 1H), 7.63 (s, 1H), 7.57 (d, J = 16.3, 1H), 7.52 (d, J = 8.3, 1H), 7.39 (dd, J = 7.8, 6.3, 3H), 7.01 (dd, J = 16.3, 2.0, 1H), 6.81−6.77 (m, 2H), 2.65 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 177.22, 156.97, 148.73, 138.68, 132.28, 131.54, 130.47, 127.33, 125.29, 124.45, 123.62, 118.60, 117.54, 117.11, 115.27, 18.16. HRMS (ESI) calcd for $C_{18}H_{15}NO_2$ $[M + H]^+$: 278.117 56. Found: 278.117 56.

3-Bromo-6-methoxy-2-methylquinolin-4(1*H*)-one (18). Compound **18** was prepared following general procedure B. Yield: 77%, mp = 262− 264 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.11 (s, 1H), 7.49 (dd, J = 13.3, 5.9 Hz, 2H), 7.31 (dd, J = 9.0, 2.9 Hz, 1H), 3.83 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 170.32, 155.74, 147.37, 133.23, 123.78, 122.26, 119.62, 105.11, 104.46, 55.36, 21.27. HRMS (ESI) calcd for $C_{11}H_{10}BrNO_2$ $[M + H]^+$: 267.996 77. Found: 267.997 89.

3-Bromo-2,6-dimethylquinolin-4(1*H*)-one (19). Compound **19** was prepared following general procedure B. Yield: 60%, mp = 266− 268 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.07 (s, 1H), 7.88 (s, 1H), 7.51−7.41 (m, 2H), 2.54 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 170.74, 148.07, 136.68, 133.19, 132.93, 124.36, 122.69, 117.73, 105.66, 21.32, 20.70. HRMS (ESI) calcd for $C_{11}H_{10}BrNO$ $[M + H]^+$: 252.001 85. Found: 252.001 14. HRMS (ESI) calcd for $C_{19}H_{25}NO$ $[M + H]^+$: 284.200 89. Found: 284.201 12.

3,6-Dibromo-2-methylquinolin-4(1*H*)-one (20). Compound **20** was prepared following general procedure B. Yield: 70%, mp = 295− 296 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.30 (s, 1H), 8.16 (d, J = 2.2 Hz, 1H), 7.81 (dd, J = 8.8, 2.2 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.73, 149.16, 137.42, 134.52, 127.23, 123.98, 120.46, 116.07, 106.16, 21.43. HRMS (ESI) calcd for $C_{10}H_7Br_2NO$ $[M + H]^+$: 315.896 72. Found: 315.897 22.

3-Bromo-6-chloro-2-methylquinolin-4(1*H*)-one (21). Compound **21** was prepared following general procedure B. Yield: 66%, mp = 288− 290 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.31 (s, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.70 (dd, J = 8.8, 2.2 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.84, 149.10, 137.15, 131.91, 128.11, 124.05, 123.57, 120.30, 106.12, 21.40. HRMS (ESI) calcd for $C_{10}H_7BrClNO$ $[M + H]^+$: 271.947 23. Found: 271.947 88.

3-Bromo-6-fluoro-2-methylquinolin-4(1*H*)-one (22). Compound **22** was prepared following general procedure B. Yield: 67%, mp = 282− 285 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.29 (s, 1H), 7.73 (dd, J = 9.3, 2.4 Hz, 1H), 7.60 (qd, J = 9.1, 3.8 Hz, 2H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 170.18, 159.57, 157.16, 148.72, 135.29, 123.69, 120.50, 109.28, 105.40, 21.35. HRMS (ESI) calcd for $C_{10}H_7BrFNO$ $[M + H]^+$: 255.976 78. Found: 255.977 63.

4-(Benzyloxy)-3-bromo-6-methoxy-2-methylquinoline (23a). Compound **23a** was prepared using general procedure C. Yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 9.2, 1H), 7.55 (d, J = 6.3, 2H), 7.41 (t, J = 7.5, 3H), 7.30 (dd, J = 9.2, 2.8, 1H), 7.13 (d, J = 2.8, 1H), 5.19 (s, 2H), 3.76 (s, 3H), 2.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.72, 157.92, 156.47, 144.20, 136.60, 130.37, 128.93, 128.85, 128.68, 124.80, 122.82, 112.96, 99.96, 55.62, 26.37. HRMS (ESI) calcd for $C_{18}H_{16}BrNO2$ $[M + H]^+$: 358.043 72. Found: 358.045 07.

4-(Benzyloxy)-3-bromo-6-chloro-2-methylquinoline (25a). Compound **25a** was prepared using general method C. Yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 9.3, 2H), 7.60 (dd, J = 8.9, 2.3, 1H), 7.56 (d, J = 6.8, 2H), 7.46−7.39 (m, 3H), 5.20 (s, 2H), 2.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.87, 158.74, 146.40, 135.96, 132.54, 131.11, 130.58, 129.02, 128.93, 128.62, 124.63, 121.16, 113.43, 26.72. HRMS (ESI) calcd for $C_{17}H_{13}BrClNO$ $[M + H]^+$: 361.994 18. Found: 361.994 14.

4-(Benzyloxy)-3-bromo-6-fluoro-2-methylquinoline (26a). Compound **26a** was prepared using general procedure C. Yield: 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 9.2, 5.2, 1H), 7.57 (d, J = 6.5, 3H), 7.47−7.40 (m, 4H), 5.20 (s, 2H), 2.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.71 (d, J = 247 Hz), 159.04, 158.77, 145.18, 136.03, 131.52 (d, J = 9 Hz), 128.99, 128.94, 128.61, 124.76, 120.34 (d, J = 25.25), 113.44, 105.86 (d, J = 23.23 Hz), 26.58. HRMS (ESI) calcd for $C_{17}H_{13}NBrFO$ $[M + H]^+$: 346.023 73. Found: 346.024 79.

3-(Hex-1-ynyl)-6-methoxy-2-methylquinolin-4(1*H*)-one (23b). Compound **23b** was prepared using general method E. Yield: 32%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 9.2, 1H), 7.45 (d, J = 2.8, 1H), 7.25 (dd, J = 9.2, 2.8, 1H), 6.53 (s, 1H), 3.98 (s, 3H), 2.89 (t, J = 7.5, 2H), 2.80 (s, 4H), 1.82−1.77 (m, 2H), 1.48 (m, 2H), 0.99 (t, J = 7.4, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.79, 157.65, 154.44, 150.98, 141.11, 130.64, 121.57, 119.84, 116.93, 101.40, 101.39, 98.41, 55.89, 30.22, 28.42, 22.77, 22.56, 14.07. HRMS (ESI) calcd for $C_{17}H_{19}NO_2$ $[M + H]^+$: 270.148 86. Found: 270.149 72.

3-(Hex-1-ynyl)-2-methylquinolin-4(1*H*)-one (24b). Compound **24b** was prepared using general method E. Yield: 15%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.0, 1H), 8.07 (d, J = 8.1, 1H), 7.57 (t, J = 7.3, 1H), 7.49 (t, J = 7.4, 1H), 6.48 (s, 1H), 2.85−2.78 (m, 5H), 1.79−1.72 (m, 2H), 1.43 (dd, J = 14.7, 7.3, 2H), 0.95 (t, J = 7.3, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.87, 154.72, 153.74, 145.16, 128.84, 127.82, 125.90, 121.36, 119.84, 116.41, 101.23, 30.11, 28.28, 22.88, 22.47, 13.98. HRMS (ESI) calcd for $C_{16}H_{17}NO$ $[M + H]^+$: 240.138 29. Found: 240.139 28.

6-Chloro-3-(hex-1-ynyl)-2-methylquinolin-4(1*H*)-one (25b). Compound **25b** was prepared using general method E. Yield: 25%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 2.3, 1H), 7.98 (d, J = 9.0, 1H), 7.51 (dd, J = 9.0, 2.3, 1H), 6.52 (s, 1H), 2.87 (d, J = 7.5, 2H), 2.79 (s, 3H), 1.80−1.75 (m, 2H), 1.48−1.43 (m, 2H), 0.98 (d, J = 7.3, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.51, 154.10, 153.70, 143.52, 131.65, 130.66, 128.50, 122.02, 119.00, 116.99, 101.36, 30.10, 28.32, 22.98, 22.47, 13.98. HRMS (ESI) calcd for $C_{16}H_{16}ClNO$ $[M + H]^+$: 274.099 32. Found: 274.100 55.

6-Fluoro-3-(hex-1-ynyl)-2-methylquinolin-4(1*H*)-one (26b). Compound **26b** was prepared using general method E. Yield: 31%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 9.2, 5.2, 1H), 7.78 (dd, J = 8.8, 2.8, 1H), 7.40−7.33 (m, 1H), 6.56 (s, 1H), 2.89 (t, J = 7.6, 2H), 2.82 (s, 3H), 1.84−1.77 (m, 2H), 1.50−1.45 (m, 2H), 0.99 (t, J = 7.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.44, 160.38 (d, J = 247.5), 152.98, 142.12, 131.38 (d, J = 9.09), 121.83, 117.41 (d, J = 41), 116.86, 116.67, 104.88 (d, J = 24.24), 101.34, 30.09, 28.30, 22.77, 22.47, 13.97. HRMS (ESI) calcd for $C_{16}H_{16}FNO$ $[M + H]^+$: 258.128 87. Found: 258.129 03.

3-Benzyl-6-methoxy-2-methylquinolin-4(1*H*)-one (27). Compound **27** was prepared following modified general procedure A using $CaSO_4$. Yield: 65%, mp = 294− 295 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.50 (s, 1H), 7.52 (d, J = 2.4 Hz, 1H), 7.46 (d, 1H), 7.27−7.06 (m, 6H), 3.91 (s, 2H), 3.82 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.94, 155.10, 146.08, 141.46, 133.89, 128.06, 128.03, 125.40, 124.50, 121.63, 119.34, 117.23, 104.45, 55.23, 30.04, 17.75. HRMS (ESI) calcd for $C_{18}H_{17}NO_2$ $[M + H]^+$: 280.133 21. Found: 280.132 37.

3-Benzyl-6-chloro-2-methylquinolin-4(1*H*)-one (28). Compound **28** was prepared following general procedure A. Yield: 77%, mp = 328− 329 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.69 (s, 1H), 8.03 (d, J = 2.3 Hz, 1H), 7.62 (dd, J = 8.8, 2.4 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.24−7.08 (m, 5H), 3.89 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.45, 147.61, 140.99, 137.75, 131.22, 128.11, 127.98, 127.12, 125.51, 124.50, 124.12, 120.07, 118.58, 29.91, 17.89. HRMS (ESI) calcd for $C_{17}H_{14}ClNO$ $[M + H]^+$: 284.083 67. Found: 284.083 30.

6-Methoxy-2-methyl-3-phenylquinolin-4(1*H*)-one (29). Compound **29** was prepared following general procedure A. Yield: 95%, mp = 362− 362 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.62 (s, 1H), 7.50 (d, J = 8.9 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.32−7.21 (m, 4H), 3.82 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.11, 155.20, 145.54, 136.50, 134.01, 131.02, 127.71, 126.33, 125.35, 121.77, 119.91, 119.35, 104.69, 55.28, 18.82. HRMS (ESI) calcd for $C_{17}H_{15}NO_2$ $[M + H]^+$: 266.117 56. Found: 266.117 18.

6-Chloro-2-methyl-3-phenylquinolin-4(1*H*)-one (30). Compound **30** was prepared following modified general procedure A using

$CaSO_4$. Yield: 12%, mp = 347−348 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.86 (s, 1H), 8.01 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.42−7.22 (m, J = 29.9, 18.5, 7.1 Hz, 5H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.64, 147.13, 137.97, 135.77, 131.51, 130.87, 127.79, 127.27, 126.59, 125.36, 124.19, 121.14, 120.13, 18.90. HRMS (ESI) calcd for $C_{16}H_{12}ClNO$ $[M + H]^+$: 269.060 74. Found: 269.059 82.

3-Benzyl-8-methoxy-2-methylquinolin-4(1*H*)-one (31). Compound **31** was prepared following general procedure A. Yield: 59%, mp = 188− 189 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 7.68 (dd, J = 6.9, 2.2 Hz, 1H), 7.23−7.10 (m, 7H), 3.98 (s, 3H), 3.90 (s, 2H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.33, 148.08, 147.07, 141.21, 130.04, 128.07, 127.97, 125.42, 124.49, 122.27, 118.74, 116.55, 110.52, 56.10, 29.98, 17.50. HRMS (ESI) calcd for $C_{18}H_{17}NO_2$ $[M + H]^+$: 280.133 21. Found: 280.132 05.

3-Benzyl-8-chloro-2-methylquinolin-4(1*H*)-one (32). Compound **32** was prepared following general procedure A. Yield: 54%, mp = 230− 231 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.57 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 6.7 Hz, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.23−7.09 (m, 5H), 3.91 (s, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.16, 148.43, 140.78, 135.79, 131.45, 128.15, 127.96, 125.55, 125.12, 124.67, 122.97, 120.79, 119.24, 29.96, 17.79. HRMS (ESI) calcd for $C_{17}H_{14}ClNO$ $[M + H]^+$: 284.083 67. Found: 284.082 95.

8-Methoxy-2-methyl-3-phenylquinolin-4(1*H*)-one (33). Compound **33** was prepared following general procedure A. Yield: 46%, mp = 233− 234 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 7.65 (d, J = 6.4 Hz, 1H), 7.38 (t, J = 7.0 Hz, 2H), 7.25 (dd, J = 24.1, 6.7 Hz, 5H), 4.01 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.59, 148.14, 146.52, 136.36, 130.96, 130.15, 127.75, 126.44, 125.35, 122.45, 121.51, 116.63, 110.90, 56.18, 18.70. HRMS (ESI) calcd for $C_{17}H_{15}NO_2$ $[M + H]^+$: 266.117 56. Found: 266.117 05.

8-Chloro-2-methyl-3-phenylquinolin-4(1*H*)-one (34). Compound **34** was prepared following general procedure A. Yield: 27%, mp = 298−299 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.71 (s, 1H), 8.08 (dd, J = 8.0, 1.1 Hz, 1H), 7.81 (dd, J = 7.6, 1.2 Hz, 1H), 7.40 (t, J = 7.4 Hz, 2H), 7.35−7.27 (m, 2H), 7.24 (d, J = 7.0 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.42, 147.89, 135.95, 135.74, 131.73, 130.82, 127.85, 126.72, 125.99, 124.75, 123.12, 121.89, 120.83, 18.97. HRMS (ESI) calcd for $C_{16}H_{12}ClNO$ $[M + H]^+$: 270.068 02. Found: 270.068 71.

7,8-Dichloro-2-methyl-3-phenylquinolin-4(1*H*)-one (35). Compound **35** was prepared following modified general procedure A using $CaSO_4$. Yield: 17%, mp = 336−337 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.41 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.24 (d, J = 7.1 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.96, 148.68, 137.43, 135.48, 134.80, 130.75, 127.89, 126.82, 125.62, 124.28, 123.78, 122.24, 19.18. HRMS (ESI) calcd for $C_{16}H_{11}Cl_2NO$ $[M + H]^+$: 304.029 05. Found: 304.029 52.

6,8-Dichloro-2-methyl-3-phenylquinolin-4(1*H*)-one (36). Compound **36** was prepared following general procedure A. Yield: 14%, mp = 318− 319 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.91 (s, 1H), 8.00 (d, J = 4.6 Hz, 1H), 7.41 (t, J = 7.3 Hz, 2H), 7.33 (t, J = 7.3 Hz, 2H), 7.23 (d, J = 7.0 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.26, 148.51, 135.36, 134.97, 131.33, 130.75, 127.94, 127.08, 126.91, 126.42, 123.81, 122.51, 122.16, 19.02. HRMS (ESI) calcd for $C_{16}H_{11}Cl_2NO$ $[M + H]^+$: 304.029 05. Found: 304.027 86.

5,7-Dichloro-2-methyl-3-phenylquinolin-4(1*H*)-one (37). Compound **37** was prepared following general procedure A. Yield: 13%, mp = 305− 306 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.68 (s, 1H), 7.51 (d, J = 1.9 Hz, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.31 (dd, J = 11.8, 4.6 Hz, 2H), 7.21 (d, J = 7.0 Hz, 2H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.75, 145.78, 142.25, 135.49, 134.88, 134.07, 130.83, 127.79, 126.71, 124.74, 123.11, 119.03, 116.26, 18.58. HRMS (ESI) calcd for $C_{16}H_{11}Cl_2NO$ $[M + H]^+$: 304.029 05. Found: 304.027 55.

6,7-Dichloro-2-methyl-3-phenylquinolin-4(1*H*)-one (38a). Compound **38a** was prepared following general procedure A. Yield: 54% over the two isomers (1:1, 5,6- and 6,7-disubstituted isomers, respectively). Desired isomer was separated by recrystallization from DMF. ^{1}H NMR (400 MHz, DMSO) δ 11.83 (s, 1H), 8.15 (s, 1H), 7.75 (s, 1H), 7.39 (d, J = 6.6 Hz, 2H), 7.32 (d, J = 6.3 Hz, 1H), 7.24 (d, J = 6.6 Hz, 2H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.27, 147.65, 138.40, 135.36, 133.99, 131.37, 130.79, 127.85, 126.77, 125.49, 124.06, 121.57, 119.41, 19.00. HRMS (ESI) calcd for $C_{16}H_{11}Cl_2NO$ $[M + H]^+$: 304.029 05. Found: 304.027 78.

5,6-Dichloro-2-methyl-3-phenylquinolin-4(1*H*)-one (38b). Compound **38b** was prepared following general procedure A. Yield: 54% over the two isomers (1:1, 5,6- and 6,7-disubstituted isomers, respectively). Desired isomer was separated by preparative HPLC. ^{1}H NMR (400 MHz, DMSO) δ 11.77 (s, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 6.3 Hz, 2H), 7.32 (d, J = 6.2 Hz, 1H), 7.22 (d, J = 6.3 Hz, 2H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.71, 145.79, 140.54, 135.80, 132.26, 130.98, 129.98, 127.95, 127.39, 126.83, 123.10, 121.61, 118.45, 18.59. HRMS (ESI) calcd for $C_{16}H_{11}Cl_2NO$ $[M + H]^+$: 304.029 05. Found: 304.027 73.

3-Benzyl-7-methoxy-2-methylquinolin-4(1*H*)-one (39a). Compound **39a** was prepared following general procedure A. Yield: 71% over the two isomers (4:1, 7- and 5-substituted isomers, respectively). Desired isomer was separated by recrystallization from methanol as a white solid, mp = 272−273 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.33 (s, 1H), 8.00 (d, J = 9.6 Hz, 1H), 7.20 (d, J = 4.3 Hz, 4H), 7.10 (dt, J = 8.7, 4.2 Hz, 1H), 6.91−6.85 (m, 2H), 3.86 (s, 2H), 3.83 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.27, 161.45, 146.43, 141.42, 140.89, 128.05, 127.99, 127.06, 125.38, 118.00, 117.69, 112.60, 98.39, 55.30, 29.82, 17.77. HRMS (ESI) calcd for $C_{18}H_{17}NO_2$ $[M + H]^+$: 280.133 21. Found: 280.132 80.

3-Benzyl-5-methoxy-2-methylquinolin-4(1*H*)-one (39b). Compound **39b** was prepared following general procedure A. Yield: 71% over the two isomers (4:1, 7- and 5-substituted isomers, respectively). Desired isomer was separated by preparative HPLC as a white solid, mp = 258−259 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.14 (s, 1H), 7.43 (t, J = 8.1 Hz, 1H), 7.25−7.06 (m, 5H), 6.99 (d, J = 8.3 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 3.80 (s, 2H), 3.77 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.48, 159.46, 144.53, 141.97, 141.53, 131.39, 128.00, 125.32, 119.77, 114.19, 109.50, 103.47, 55.49, 29.90, 17.39. HRMS (ESI) calcd for $C_{18}H_{17}NO_2$ $[M + H]^+$: 280.133 21. Found: 280.131 90.

3-Benzyl-7-chloro-2-methylquinolin-4(1*H*)-one (40a). Compound **40a** was prepared following general procedure A. Yield: 45% over the two isomers (1.5:1, 7- and 5-substituted isomers, respectively). Desired isomer was separated by double recrystallization from methanol as a white solid, mp = 318− 319 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.57 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.51 (s, 1H), 7.30−7.07 (m, 6H), 3.88 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.09, 147.57, 141.01, 139.91, 135.67, 128.11, 127.98, 127.60, 125.50, 122.89, 122.14, 118.83, 116.65, 29.83, 17.93. HRMS (ESI) calcd for $C_{17}H_{14}ClNO$ $[M + H]^+$: 284.083 67. Found: 284.083 28.

3-Benzyl-5-chloro-2-methylquinolin-4(1*H*)-one (40b). Compound **40b** was prepared following general procedure A. Yield: 45% over the two isomers (1.5:1, 7- and 5-substituted isomers, respectively). Desired isomer was separated by preparative HPLC. ^{1}H NMR (400 MHz, DMSO) δ 11.54 (s, 1H), 7.47 (q, J = 7.9 Hz, 2H), 7.17 (dd, J = 32.9, 6.4 Hz, 6H), 3.84 (s, 2H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.82, 146.02, 141.82, 141.11, 132.03, 130.84, 128.09, 127.98, 125.46, 125.10, 119.83, 119.53, 117.25, 30.00, 17.62. HRMS (ESI) calcd for $C_{17}H_{14}ClNO$ $[M + H]^+$: 284.083 67. Found: 284.082 82.

7-Methoxy-2-methyl-3-phenylquinolin-4(1*H*)-one (41a). Compound **41a** was prepared following general procedure A. Yield: 63% over the two isomers (4:1, 7- and 5-substituted isomers, respectively). Desired isomer was separated by recrystallization

from DMF as a white solid, mp = 346− 349 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.45 (s, 1H), 7.97 (d, J = 8.9 Hz, 1H), 7.38 (t, J = 6.9 Hz, 2H), 7.28 (t, J = 7.3 Hz, 1H), 7.23 (d, J = 7.3 Hz, 2H), 6.93−6.85 (m, 2H), 3.86 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.46, 161.65, 146.01, 141.13, 136.31, 131.02, 127.67, 127.20, 126.32, 120.51, 118.74, 112.60, 98.59, 55.36, 18.85. HRMS (ESI) calcd for $C_{17}H_{15}NO_2$ $[M + H]^+$: 266.117 56. Found: 266.117 88.

5-Methoxy-2-methyl-3-phenylquinolin-4(1*H*)-one (41b). Compound **41b** was prepared following general procedure A. Yield: 63% over the two isomers (4:1, 7- and 5-substituted isomers, respectively). Desired isomer was separated by preparative HPLC. ^{1}H NMR (400 MHz, DMSO) δ 11.40 (s, 1H), 7.49 (t, J = 8.2 Hz, 1H), 7.37 (t, J = 7.4 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 7.19 (d, J = 7.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 3.77 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.44, 159.54, 144.70, 142.08, 136.33, 131.88, 131.01, 127.65, 126.35, 122.48, 114.68, 109.70, 103.98, 55.65, 18.43. HRMS (ESI) calcd for $C_{17}H_{15}NO_2$ $[M + H]^+$: 266.117 56. Found: 266.117 17.

7-Chloro-2-methyl-3-phenylquinolin-4(1*H*)-one (42a). Compound **42a** was prepared following general procedure A. Yield: 92% over the two isomers (1:1, 7- and 5-substituted isomers, respectively). Desired isomer was separated by recrystallization from DMF as a white solid, mp = 357− 359 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.70 (s, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.55 (d, J = 1.7 Hz, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.34−7.27 (m, 2H), 7.24 (d, J = 7.1 Hz, 2H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.33, 147.06, 140.05, 135.97, 135.71, 130.87, 127.79, 127.74, 126.62, 123.06, 122.98, 121.47, 116.67, 18.92. HRMS (ESI) calcd for $C_{16}H_{12}ClNO$ $[M + H]^+$: 270.068 02. Found: 270.068 67.

5-Chloro-2-methyl-3-phenylquinolin-4(1*H*)-one (42b). Compound **42b** was prepared following general procedure A. Yield: 92% over the two isomers (1:1, 7- and 5-substituted isomers, respectively). Desired isomer was separated by preparative HPLC. ^{1}H NMR (400 MHz, DMSO) δ 11.62 (s, 1H), 7.54− 7.18 (m, 8H), 2.16 (s, 3H). HRMS (ESI) calcd for $C_{16}H_{12}ClNO$ $[M + H]^+$: 270.068 02. Found: 270.067 23.

3-Benzyl-6-methoxy-1,2-dimethylquinolin-4(1*H*)-one (43a). Compound **43a** was prepared following general procedure F. Yield: 90% as a mixture of OMe and NMe tautomers (1:1, respectively), mp = 215−216 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.75 (d, J = 9.4, 1H), 7.67 (d, J = 2.8, 1H), 7.31 (dd, J = 9.3, 3.0, 1H), 7.23−7.18 (m, 4H), 7.13−7.09 (m, 1H), 4.02 (s, 2H), 3.85 (s, 3H), 3.74 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.21, 155.03, 149.10, 141.47, 135.71, 128.08, 127.92, 125.69, 125.40, 121.39, 118.76, 118.38, 105.39, 55.28, 35.22, 31.00, 17.87. HRMS (ESI) calcd for $C_{19}H_{19}NO_2$ $[M + H]^+$: 294.148 86. Found: 294.149 03.

3-Benzyl-4,6-dimethoxy-2-methylquinoline (43b). Compound **43b** was prepared following general procedure F. Yield: 90% as a mixture of OMe and NMe tautomers (1:1, respectively), mp = 115− 116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 9.0, 1H), 7.31 (dt, J = 5.9, 2.7, 2H), 7.24 (t, J = 5.7, 2H), 7.17 (t, J = 7.3, 1H), 7.11 (d, J = 7.3, 2H), 4.24 (s, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.69, 158.27, 157.51, 144.67, 139.63, 130.55, 128.65, 128.21, 126.27, 124.07, 123.20, 121.59, 100.09, 62.03, 55.70, 32.08, 23.73. HRMS (ESI) calcd for $C_{19}H_{19}NO_2$ $[M + H]^+$: 294.148 86. Found: 294.149 03.

3-Benzyl-6-chloro-1,2-dimethylquinolin-4(1*H*)-one (44a). Compound **44a** was prepared following general procedure F. Yield: 75% as a mixture of OMe and NMe tautomers (1:2, respectively), mp = 192− 193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 2.0, 1H), 7.52 (dd, J = 9.1, 2.1, 1H), 7.39 (d, J = 9.1, 1H), 7.23−7.13 (m, 5H), 4.11 (s, 2H), 3.71 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.56, 149.44, 141.04, 139.70, 131.99, 129.28, 128.49, 128.32, 126.56, 126.47, 125.90, 121.87, 117.07, 35.32, 31.84, 18.59. HRMS (ESI) calcd for $C_{18}H_{16}ClNO$ $[M + H]^+$: 298.099 32. Found: 298.099 20.

3-Benzyl-6-chloro-4-methoxy-2-methylquinolin-4(1*H*)-one (44b). Compound **44b** was prepared following general procedure F. Yield: 61% as a mixture of OMe and NMe tautomers (1:2.7, respectively), mp = 82−84 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.94 (d, J = 8.9, 1H), 7.58 (d, J = 8.9, 1H), 7.25− 7.08 (m, 5H), 4.23 (s, 2H), 3.88 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.53, 160.77, 146.90, 139.16, 131.65, 130.67, 130.10, 128.72, 128.15, 126.41, 124.81, 123.29, 121.13, 62.72, 32.01, 24.03. HRMS (ESI) calcd for $C_{18}H_{16}ClNO$ $[M + H]^+$: 298.099 32. Found: 298.099 20.

6-Chloro-1,2-dimethyl-3-phenylquinolin-4(1*H*)-one (45a). Compound **45a** was prepared following general procedure F. Yield: 83% as a mixture of OMe and NMe tautomers (1:2.4, respectively) as a pink solid, mp = 208−209 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 2.6, 1H), 7.54 (dd, J = 9.1, 2.6, 1H), 7.41 (dd, J = 17.0, 8.4, 3H), 7.33−7.28 (m, 1H), 7.23−7.18 (m, 2H), 3.77 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.92, 148.73, 139.90, 136.82, 132.19, 130.91, 129.41, 128.57, 127.29, 126.60, 124.85, 117.09, 35.41, 20.10. HRMS (ESI) calcd for $C_{17}H_{14}ClNO$ $[M + H]^+$ 284.083 67, found 284.084 82.

6-Chloro-4-methoxy-2-methyl-3-phenylquinoline-4(1*H*)-one (45b). Compound **45a** was prepared following general procedure F. Yield: 83% as a mixture of OMe and NMe tautomers (1:2.4, respectively) as a white crystalline solid, mp = 92−94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.29−7.12 (m, 5H), 3.91 (s, 3H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.02, 159.87, 145.84, 138.86, 131.17, 130.34, 129.82, 128.13, 127.15, 125.91, 123.98, 122.29, 121.67, 31.34, 23.83. HRMS (ESI) calcd for $C_{17}H_{14}ClNO$ $[M + H]^+$ 284.083 67, found 284.084 82.

3-Benzyl-7-methoxy-1,2-dimethylquinolin-4(1*H*)-one (46a). Compound **46a** was prepared following general procedure F. Yield: 75% as a mixture of OMe and NMe tautomers (1:2, respectively), mp = 220− 222 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.9, 1H), 7.22 (m, J = 7.9, 4H), 7.12 (t, J = 6.8, 1H), 6.99−6.94 (m, 1H), 6.80 (d, J = 1.3, 1H), 4.13 (s, 2H), 3.92 (s, 3H), 3.66 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.35, 162.68, 148.75, 142.99, 141.52, 129.39, 128.41, 128.37, 125.71, 121.07, 120.01, 111.43, 98.41, 55.69, 35.13, 31.71, 18.66. HRMS (ESI) calcd for $C_{19}H_{19}NO_2$ $[M + H]^+$: 294.148 86. Found: 294.149 03.

3-Benzyl-4,7-dimethoxy-2-methylquinoline (46b). Compound **46b** was prepared following general procedure F. Yield: 75% as a mixture of OMe and NMe tautomers (1:2, respectively), mp = 126− 128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 9.1, 1H), 7.38 (d, J = 2.2, 1H), 7.24 (d, J = 7.5, 2H), 7.19−7.14 (m, 2H), 7.11 (d, J = 7.4, 2H), 4.22 (s, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 2.56 (s, 3H). HRMS (ESI) calcd for $C_{19}H_{19}NO_2$ $[M + H]^+$: 294.148 86. Found: 294.149 03.

4-Chloro-3-methoxyaniline (47). An amount of 900 mL of ammonia was condensed at −78 °C. Then 1 g of thinly shaven strips of sodium was added followed by 1.0 g of iron(III) nitrate nonahydrate. Upon disappearance of the deep blue color 25 g of thinly shaven strips of sodium was added. After 30 min of stirring at −78 °C, 50 g of 2,5-dichloroanisole was added as a solution in hexane (70 mL) dropwise and the mixture was warmed to −45 °C for 2 h. Upon completion the ammonia was allowed to evaporate. The crude pot was then diluted in chloroform, and 100 g of NH_4Cl was added slowly. The mixture was taken up in a separatory funnel and washed with H_2O (×3) followed by brine (×1). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting solid can be used without further purification. Yield: 99%. ^{1}H NMR (400 MHz, DMSO) δ 6.98 (d, J = 8.4, 1H), 6.34 (d, J = 1.8, 1H), 6.16 (dd, J = 8.4, 1.9, 1H), 5.23 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 154.90, 149.16, 129.68, 107.02, 106.74, 98.66, 55.38. HRMS (ESI) calcd for C_7H_8ClNO $[M + H]^+$: 157.036 72. Found: 157.036 12.

6-Fluoro-7-methoxy-2-methyl-3-phenylquinolin-4(1*H*)-one (48). Compound **48** was prepared following general procedure A. Yield: 79%, mp = 361− 362 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.62 (s, 1H), 7.69 (d, J = 11.8 Hz, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 7.23 (d, J = 7.8 Hz, 2H), 7.10

(d, J = 7.3 Hz, 1H), 3.95 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.39, 151.04 (d, J = 64.64), 149.52 (d, J = 245.43), 146.84, 137.83, 136.77, 131.65, 128.40, 127.11, 120.80, 118.58, 110.79 (d, J = 9.1), 101.20, 56.81, 19.57. HRMS (ESI) calcd for $C_{17}H_{14}FNO_2$ $[M + H]^+$: 284.108 13. Found: 284.108 20.

6-Chloro-7-methoxy-2-methyl-3-phenylquinolin-4(1*H*)-one (49). Compound **49** was prepared following modified general procedure A using $CaSO_4$. Yield: 55%, mp = 329−330 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.63 (s, 1H), 7.99 (s, 1H), 7.38 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.23 (d, J = 6.9 Hz, 2H), 7.06 (s, 1H), 3.96 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.48, 156.66, 146.42, 139.59, 135.85, 130.94, 127.75, 126.53, 126.17, 120.78, 118.78, 117.94, 99.40, 56.37, 18.85. HRMS calcd for $C_{17}H_{14}ClNO_2$ $[M + H]^+$: 300.078 58. Found: 300.079 01.

6-Bromo-7-methoxy-2-methyl-3-phenylquinolin-4(1*H*)-one (50). Compound **50** was prepared following general procedure A. Yield: 61%, mp = 328− 329 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.67 (s, 1H), 8.16 (s, 1H), 7.38 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 7.23 (d, J = 7.0 Hz, 2H), 7.04 (s, 1H), 3.95 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.34, 157.28, 146.52, 140.18, 135.88, 130.91, 129.54, 127.73, 126.49, 120.82, 119.46, 107.01, 99.26, 56.47, 18.88. . HRMS calcd for $C_{17}H_{14}BrNO_2$ $[M + H]^+$: 344.028 07. Found: 344.027 52.

3-Ethyl-6-fluoro-7-methoxy-2-methylquinolin-4(1*H*)-one (51). Compound **51** was prepared following general procedure A. Yield: 62%, mp = 306− 307 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.34 (s, 1H), 7.66 (d, J = 11.9 Hz, 1H), 7.02 (d, J = 7.3 Hz, 1H), 3.92 (s, 3H), 2.45 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.96, 151.07 (d, J = 14.14), 149.27 (d, J = 244.42), 145.73, 137.47, 120.33, 117.68, 110.45 (d, J = 19.19), 100.89, 56.71, 18.58, 17.92, 14.11. HRMS calcd for $C_{13}H_{14}FNO_2$ $[M + H]^+$: 236.108 13. Found: 236.107 13.

3-Ethyl-6-chloro-7-methoxy-2-methylquinolin-4(1*H*)-one (52). Compound **52** was prepared following general procedure A. Yield: 70%, mp = 326− 328 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.36 (s, 1H), 7.96 (s, 1H), 6.99 (s, 1H), 3.92 (s, 3H), 2.49−2.42 (q, 2H), 2.35 (s, 3H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.97, 156.25, 145.39, 139.33, 125.91, 120.35, 117.93, 117.49, 99.19, 56.27, 17.90, 17.26, 13.47. HRMS calcd for $C_{13}H_{14}ClNO_2$ $[M + H]^+$: 252.078 58. Found: 252.078 28.

3-Ethyl-6-bromo-7-methoxy-2-methylquinolin-4(1*H*)-one (53). Compound **53** was prepared following general procedure A. Yield: 32%, mp = 325− 327 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.36 (s, 1H), 8.13 (s, 1H), 6.95 (s, 1H), 3.91 (s, 3H), 2.48−2.43 (q, 2H), 2.35 (s, 3H), 0.98 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.88, 156.89, 145.40, 139.85, 129.32, 120.42, 118.61, 106.58, 98.97, 56.36, 17.90, 17.26, 13.41. HRMS calcd for $C_{13}H_{14}BrNO_2$ $[M + H]^+$: 296.028 07. Found: 296.028 21.

6-Chloro-3-heptyl-7-methoxy-2-methylquinolin-4(1*H*)-one (54). Compound **54** was prepared following general procedure A. Yield: 30%, mp = 238− 239 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.34 (s, 1H), 7.95 (s, 1H), 6.98 (s, 1H), 3.92 (s, 3H), 2.46−2.40 (m, 2H), 2.34 (s, 3H), 1.25 (d, J = 10.4 Hz, 10H), 0.84 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.16, 156.23, 145.52, 139.31, 125.92, 119.08, 117.86, 117.47, 99.16, 56.25, 31.31, 29.23, 28.68, 28.56, 24.70, 22.10, 17.45, 13.94. HRMS calcd for $C_{18}H_{24}ClNO_2$ $[M + H]^+$: 322.156 83. Found: 322.157 20.

6-Chloro-7-methoxy-2-methyl-3-nonylquinolin-4(1*H*)-one (55). Compound **55** was prepared following general procedure A. Yield: 27%, 219−220 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.33 (s, 1H), 7.95 (s, 1H), 6.97 (s, 1H), 3.91 (s, 3H), 2.45−2.39 (m, 2H), 2.33 (s, 3H), 1.35−1.20 (m, 14H), 0.84 (t, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.16, 156.22, 145.48, 139.31, 125.92, 119.07, 117.86, 117.46, 99.14, 56.23, 31.28, 29.25, 29.01, 28.71, 28.53, 24.69, 22.07, 17.43, 13.91. HRMS calcd for $C_{20}H_{28}ClNO_2$ $[M + H]^+$: 350.188 13. Found: 350.187 66.

6-Chloro-3-cyclohexyl-7-methoxy-2-methylquinolin-4(1*H*)-one (56). Compound **56** was prepared following general procedure A. Yield: 21%, mp = 313−314 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.23 (s, 1H), 7.94 (s, 1H), 6.96 (s, 1H), 3.91 (s, 3H), 2.37 (s, 3H), 2.23 (d, J = 11.1 Hz, 2H), 1.70 (m, 3H), 1.44−1.17 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 174.38, 156.18, 145.33, 139.11, 125.98, 122.36, 118.92, 117.38, 98.97, 56.25, 28.92, 26.85, 25.72, 18.25. HRMS calcd for $C_{17}H_{20}ClNO_2$ $[M + H]^+$: 306.125 53. Found: 306.124 93.

3-Benzyl-6-chloro-7-methoxy-2-methylquinolin-4(1*H*)-one (57). Compound **57** was prepared following modified general procedure A using $CaSO_4$. Yield: 40%, mp = 254−255 °C. ^{1}H NMR (500 MHz, DMSO) δ 11.49 (s, 1H), 8.02 (s, 1H), 7.20 (dd, J = 8.9, 5.3 Hz, 4H), 7.10 (ddd, J = 8.6, 6.3, 2.5 Hz, 1H), 6.99 (s, 1H), 3.92 (s, 3H), 3.86 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.26, 156.40, 146.89, 141.15, 139.41, 128.09, 127.99, 126.05, 125.46, 118.04, 117.82, 99.31, 56.27, 29.84, 17.83. HRMS calcd for $C_{18}H_{16}ClNO_2$ $[M + H]^+$: 314.094 23. Found: 314.093 30.

6-Chloro-7-methoxy-2,3-dimethylquinolin-4(1*H*)-one (58). Compound **58** was prepared following modified general procedure A using $CaSO_4$. Yield: 40%, mp = 337−338 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.40 (s, 1H), 7.96 (s, 1H), 6.97 (s, 1H), 3.92 (s, 3H), 2.32 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.37, 156.18, 145.72, 139.21, 125.86, 117.50, 113.99, 99.17, 56.24, 17.96, 10.3. HRMS calcd for $C_{12}H_{12}ClNO_2$ $[M + H]^+$: 238.062 93. Found: 238.063 11.

6-Chloro-3-isopropyl-7-methoxy-2-methylquinolin-4(1*H*)-one (59). Compound **59** was prepared following modified general procedure A using $CaSO_4$. Yield: 52%, mp = 289−291 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.23 (s, 1H), 7.94 (s, 1H), 6.95 (s, 1H), 3.91 (s, 3H), 3.11−2.96 (m, 1H), 2.35 (s, 3H), 1.27 (d, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 174.32, 156.19, 144.99, 139.15, 125.92, 122.80, 118.85, 117.41, 98.95, 56.24, 26.76, 20.13, 18.06. HRMS calcd for $C_{14}H_{16}ClNO_2$ $[M + H]^+$: 266.094 23. Found: 266.094 93.

6-Chloro-3-isobutyl-7-methoxy-2-methylquinolin-4(1*H*)-one (60). Compound **60** was prepared from **62** (0.1 g, 0.3 mmol), Pd-$(PPh_3)_4$ (16 mgs, 0.014 mmol), K_3PO_4 (0.242 g, 0.6 mmol), isobutylboronic acid (87 mg, 0.45 mmol), toluene (0.9 mL), and H_2O (0.1 mL) in an oven-dried flame-dried Schlenk tube backfilled with argon (3×) for 14 h at 100 °C. Yield: 17%. Product was isolated using preparative HPLC. ^{1}H NMR (400 MHz, DMSO) δ 11.82 (s, 1H), 8.03 (s, 1H), 7.08 (s, 1H), 3.94 (s, 3H), 2.39 (s, 5H), 1.85 (dt, J = 13.5, 6.8, 1H), 0.85 (d, J = 6.6, 6H). ^{13}C NMR (101 MHz, DMSO) δ 174.12, 159.07, 158.70, 157.12, 147.93, 139.97, 126.46, 118.78, 99.98, 56.90, 34.23, 28.36, 23.14, 18.81.

6-Chloro-7-methoxy-2-methylquinolin-4(1*H*)-one (61). Compound **61** was prepared following modified general procedure A using $CaSO_4$. Yield: 63%. ^{1}H NMR (400 MHz, DMSO) δ 11.53 (s, 1H), 7.94 (s, 1H), 6.99 (s, 1H), 5.85 (s, 1H), 3.92 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.91, 157.26, 150.24, 141.01, 126.28, 119.54, 118.51, 108.93, 100.29, 56.97, 20.07. HRMS calcd for $C_{11}H_{10}ClNO_2$ $[M + H]^+$: 224.047 28. Found: 224.046 34.

3-Bromo-6-chloro-7-methoxy-2-methylquinolin-4(1*H*)-one (62). Compound **62** was prepared using general procedure B. Yield: 90%. ^{1}H NMR (400 MHz, DMSO) δ 12.06 (s, 1H), 7.95 (s, 1H), 6.98 (s, 1H), 3.93 (s, 3H), 2.57 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 171.38, 156.81, 151.15, 139.12, 126.16, 118.77, 114.82, 99.29, 85.78, 56.40, 26.08. HRMS (ESI) calcd for $C_{11}H_9BrClNO_2$ $[M + H]^+$: 301.957 80. Found: 301.957 64.

4-(Benzyloxy)-3-bromo-6-chloro-7-methoxy-2-methylquinoline (63). Compound **63** was prepared using general method C. Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.54 (d, J = 6.5, 2H), 7.45−7.40 (m, 3H), 7.37 (s, 1H), 5.19 (s, 2H), 4.01 (s, 3H), 2.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.20, 158.71, 156.61, 148.23, 136.03, 128.99, 128.91, 128.64, 124.69, 122.92, 118.92, 110.79, 108.32, 56.63, 26.72. HRMS calcd for $C_{11}H_9ClBrNO_2$ $[M + H]^+$: 301.958 34. Found: 301.958 51.

6-Chloro-3-(hex-1-ynyl)-7-methoxy-2-methylquinolin-4(1*H*)-one (64). Compound **64** was prepared using general method E. Yield: 26%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.53

(s, 1H), 6.50 (s, 1H), 4.02 (s, 3H), 2.85 (t, J = 7.5, 2H), 2.79 (s, 3H), 1.76 (d, J = 7.5, 2H), 1.45 (d, J = 7.5, 2H), 0.96 (d, J = 7.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.69, 154.95, 154.50, 147.25, 145.31, 123.53, 120.75, 120.53, 111.11, 109.26, 101.19, 56.51, 30.13, 28.27, 23.09, 22.47, 14.31. HRMS calcd for $C_{17}H_{18}ClNO_2$ $[M + H]^+$: 304.109 88. Found: 304.110 05.

6-Chloro-3-(hept-1-en-2-yl)-7-methoxy-2-methylquinolin-4(1*H*)-one (65). Compound **65** was prepared using general procedure D. The crude mixture was prepurified using flash chromatography to obtain the mixture of isomers. Then the resulting crude oil was dissolved in minimal MeOH and purified further using preparative HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.38 (s, 1H), 5.35 (s, 1H), 4.94 (s, 1H), 3.92 (s, 3H), 2.55 (s, 3H), 2.35−2.28 (m, 2H), 1.36−1.23 (br m, 6H), 0.81 (t, J = 6.9, 3H). HRMS calcd for $C_{18}H_{22}ClNO_2$ $[M + H]^+$: 320.141 18. Found: 320.141 74.

(*E*)-6-Chloro-3-(hept-1-enyl)-7-methoxy-2-methylquinolin-4(1*H*)-one (66). Compound **66** was prepared using general procedure D. The crude mixture was prepurified using flash chromatography to obtain the mixture of isomers. Then the resulting crude oil was dissolved in minimal MeOH and purified further using preparative HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.29 (s, 1H), 5.40 (dd, J = 12.2, 5.3, 2H), 3.96 (s, 3H), 3.39 (br d, 2H), 2.56 (s, 3H), 1.90 (br d, 2H), 1.20 (s, 4H), 0.81 (s, 3H). HRMS calcd for $C_{18}H_{22}ClNO_2$ $[M + H]^+$: 320.141 18. Found: 320.141 74.

(*E*)-*tert*-Butyl 3-(6-Chloro-7-methoxy-2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)acrylate (67). Compound **67** was prepared following general procedure D. Yield: 96%. ^{1}H NMR (400 MHz, DMSO) δ 12.06 (s, 1H), 8.04 (s, 1H), 7.53 (d, J = 15.4, 1H), 7.32 (d, J = 15.4, 1H), 7.06 (s, 1H), 3.96 (s, 3H), 2.55 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 174.69, 168.00, 157.57, 153.00, 139.03, 137.48, 126.88, 119.80, 119.67, 119.47, 112.60, 100.56, 79.65, 57.14, 28.62, 19.01. HRMS calcd for $C_{18}H_{20}ClNO_4$ $[M + H]^+$: 350.115 36. Found: 350.115 75.

In Vitro Parasite Culturing. *P. falciparum* clone W2/Indochina and TM90C2B/Thailand were grown in continuous culture using RPMI 1640 media containing 10% heat-inactivated type A+ human plasma, sodium bicarbonate (2.4 g/L), HEPES (5.94 g/L), and 4% washed human type A+ erythrocytes. Cultures were gassed with a 90% N_2, 5% O_2, and 5% CO_2 mixture followed by incubation at 37 °C.

Assay Preparation. Test compounds at 5 mg/mL in DMSO were diluted at least 1:400 and then serially diluted in duplicate over 11 concentrations. *P. falciparum* cultures with >70% ring stage parasites were diluted to 0.5−0.7% parasitemia and 1.5% hematocrit in RPMI 1640 media. In 96-well plates a volume of 135 μL/well of parasitized erythrocytes was added on top of 15 μL/well of the test compound. A separate plate containing chloroquine, dihydroartemisinin, and atovaquone was added to each set of assay plates as control drugs. A Beckman Coulter Biomek 3000 was used to dispense test compounds, control drugs, and parasitized erythrocytes into the microtiter plates. Positive and negative controls were included in each plate. Positive controls consisted of drug-free parasitized erythrocytes, and negative controls consisted of parasitized erythrocytes dosed with a high concentration of chloroquine or dihydroartemisinin that ensured 100% parasite death. Assay plates were placed into a plastic gassing chamber and equilibrated with 90% N_2, 5% O_2, and 5% CO_2 mixture and then incubated at 37 °C for 72 h. After 72 h of incubation the assay plates were frozen at −80 °C until later processed for parasite growth determinations.

SYBR Green I Processing. Assay plates were removed from −80 °C and allowed to thaw at room temperature. By use of the Beckman Biomek 3000, 100 μL was transferred from the assay plates into 96-well black assay plates. Next, 100 μL of SYBR green I (Invitrogen) in 2× lysis buffer (0.2 μL of SYBR green I/mL of 2× lysis buffer [0.008% saponin, 0.08% Triton X-100, 20 mM Tris, and 5 mM EDTA]) was dispensed into each well of the 96-well black assay plate using the Beckman Coulter Biomek 3000. Upon addition of SYBR green I the microtiter plates were incubated for 1 h in the dark. Relative fluorescence units (RFU) were read using a Molecular Devices Spectramax microplate reader.

Data Analysis. Data analysis was performed using a custom database manager (Dataspects, Inc.). Nonlinear regression analysis was used to calculate EC_{50}.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and nOe results of select compounds for characterization. A complete table summarizing SPR of the synthesized compounds is given. This material is available free of charge via the Internet at http://pubs.acs.org.

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