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Pyrano[4,3-*b*]quinolines Library Generation via Iodocyclization and Palladium-Catalyzed Coupling Reactions

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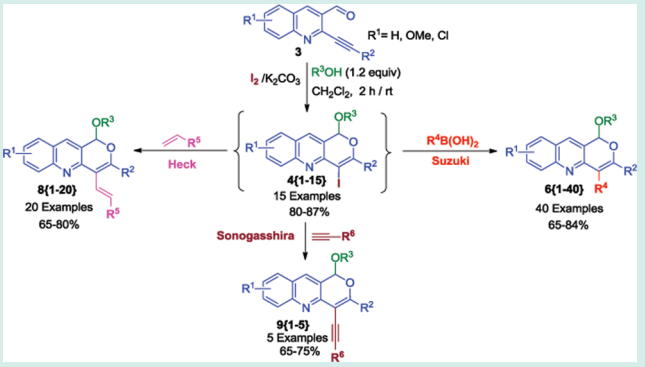
Supporting Information

ABSTRACT: Synthesis of a 80-member library of novel pyrano[4,3-*b*]quinolines in solution-phase is reported. The key intermediate, 4-iodopyrano[4,3-*b*]quinolines were synthesized by the electrophilic iodocyclization of corresponding *ortho*-alkynyl aldehydes in good to excellent yields under mild reaction conditions. Subsequently a diverse set of libraries was generated by employing palladium-catalyzed Suzuki−Miyaura, Heck, and Sonogashira coupling reactions on 4-iodopyrano[4,3-*b*]-quinolines. In this way, a series of structurally different and biologically interesting molecules were obtained. Some of the selected compounds were screened against 3D7 strains of *Plasmodium falciparum* for antimalarial activity. Suzuki coupling products **6**{*3*} and **6**{*21*} and Heck coupling product **8**{*12*} exhibit promising antimalarial activity.



KEYWORDS: iodocyclization, cross-coupling, pyranoquinoline, rutaceae, *Plasmodium falciparum*

INTRODUCTION

In recent years combinatorial chemistry and high-throughput screening (HTS) has emerged as a powerful tool in the drug discovery process. Heterocyclic systems containing nitrogen atoms often play important roles as the scaffolds of bioactive substances. Quinoline is one of the most popular N-heteroaromatics incorporated into the structure of many pharmaceuticals. It is known that many quinoline-containing compounds exhibit a wide spectrum of pharmacological activities such as antiasthmatic, anti-inflammatory, and antimalarial activities.[1] The plant family *Rutaceae* is known[2] to be a prolific source of pyranoquinoline and furoquinoline alkaloids. These alkaloids have been reported[3] to be associated with interesting pharmacological as well as biological properties and have been synthesized by several methods.

Different families of nitrogen-containing heterocycles are currently used in cancer chemotherapy. For instance, the quinazolines[4] gefitinib, erlotinib, and canertinib are EGFR tyrosine kinase inhibitors indicated for the treatment of colorectal, renal, gynecologic, and prostate cancer. Quinolines[5] are structural analogues of quinazolines that are being explored for cancer chemotherapy with a number of compounds (EKB-569, HKI-272, and SNS-595) in different phases of clinical trials. Cikotiene et al. screened the pyranoquinoline compounds against the Gram-positive and the Gram-negative strains.[6] Magedov et al. reported the antiproliferative and antitubulin activities of pyrano[3,2-*c*]-pyridones and pyrano[3,2-*c*]quinolones.[7]

The development of efficient synthesis of pyranoquinolines has been the focus of much research for several decades and continues to be an active and rewarding research area. However, most of the existing methods suffer from limited scope or availability of starting materials, or require multistep procedures.[8,9] Iodine mediated and Pd(II)-catalyzed coupling reactions with aryl iodides have been extensively used for the preparation of numerous biologically active molecules.[10] These coupling reactions have been used as a facile method for the synthesis of substituted aryl compounds from aryl halides.[11]

In continuation of our efforts to adapt heterocyclization chemistry to a high-throughput format,[12] we herein report the library synthesis of pyrano[4,3-*b*]quinoline using alkyne cyclization chemistry as the key step. Pyrano[4,3-*b*]quinoline moiety has not been much explored and due to its presence in synthetic and natural biologically active compounds,[13] a library on pyrano[4,3-*b*]-quinoline has been synthesized.

RESULT AND DISCUSSION

The key intermediate 4-iodopyranoquinolines (**4**) required for this library synthesis were prepared by using our alkyne iodocyclization chemistry[14] (Scheme 1). Subsequent diversification

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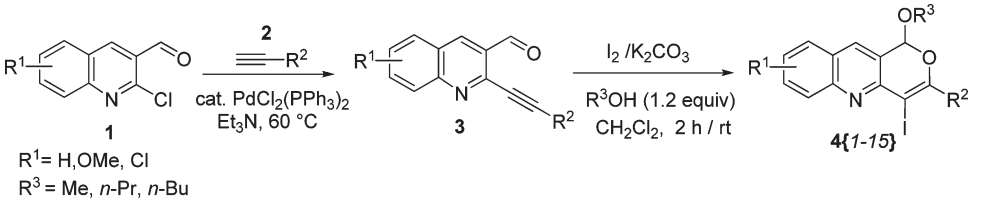
Scheme 1. Synthesis of 4-Iodopyrano[4,3-*b*]quinolines



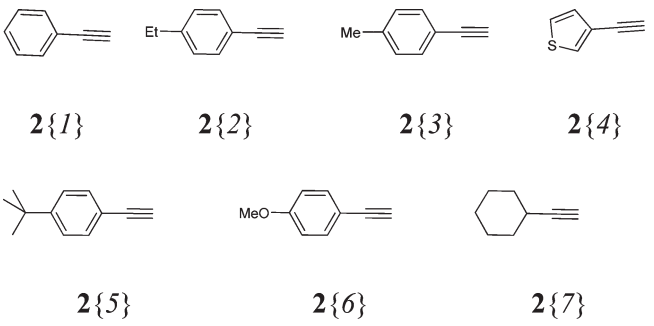


Figure 1. Terminals alkynes **2**{*1*−*7*} used for the Sonogashira reaction.

by various palladium-catalyzed cross-coupling reactions should afford a diverse set of pyrano[4,3-*b*]quinolines.

The starting material 2-alkynylquinoline-3-carbaldehydes (**3**) were prepared by Sonogashira coupling of 2-chloroquinoline-3-carbaldehydes (**1**) with various terminal alkynes (**2**)[14b] (Scheme 1). Accordingly a set of 4-iodopyranoquinoline **4**{*1*−*15*} were synthesized from (**3**) by electrophilic iodocyclization reaction. We have chosen 2-chloro-6-methoxy-3-quinolinecarbaldehyde and 2,6-dichloro-3-quinolinecarbaldehyde as the starting material. The methoxy and chloro group present in the starting substrate should enhance the biological activity of final compounds.

The terminal alkynes **2**{*1*−*7*} used for Sonogashira reaction, were chosen on the basis of commercially available acetylenes. Heteroatoms were included in the acetylenes to impart drug-like, hydrogen bond donor or acceptor properties to pyranoquinolines (Figure 1). Sulfur atom present in acetylene **2**{*4*} increases the probability of molecules to act like drugs.

According to our designed strategy, the 4-iodopyranoquinolines **4**{*1*−*15*} were synthesized by iodocyclization reaction of *ortho*-alkynylaldehyde (**3**) at room temperature in good yields (Figure 2).

These iodocyclized products (**4**) are the key components for library generation and subsequently elaborated by palladium-catalyzed cross-coupling reactions and afford a diverse set of pyranoquinolines (Scheme 2).

We obtained aryl substituted pyranoquinolines **6**{*1*−*40*} by the palladium-catalyzed Suzuki-Miyaura reaction[15] of the iodopyranoquinoline intermediates **4**{*1*−*15*} with various boronic acids (Table 1). The boronic acids were chosen on the basis of their commercial availability and their ability to provide the indispensable diversity and drug-like properties to the cross-coupled pyranoquinoline products. For instance, the methoxy−containing boronic acids **5**{*2*} and **5**{*7*} increases the polarity and yield of the pyranoquinolines (Figure 3). The fluorine-containing boronic acid **5**{*8*} was chosen with a view toward its importance of fluorine in medicinal chemistry and this boronic acid afforded good yields of coupled product.

Boronic acids **5**{*5*} and **5**{*6*} containing sulfur and nitrogen heteroatoms were used to enhance the biological properties of coupling products. It was found that boronic acid **5**{*3*} having benzodioxane group and **5**{*9*} having isopropoxy group reacted well but afforded the desired product in comparatively lower yield as compared to other boronic acids.

A brief examination of the reaction conditions suggested that heating at 80 °C for 2 h in presence of $Pd(PPh_3)_2Cl_2$ catalyst and base in DMF/H_2O was sufficient for obtaining desired products in good yields, no high temperature heating was required. However in some cases coupling products were obtained in low yields due to deiodonation of iodopyranoquinoline (**4**) in presence of Pd(II)-catalyst and base.

The formation of products **6**{*1*−*40*} were confirmed by the ^{1}H NMR, ^{13}C NMR, and X-ray crystallographic data of compound[16] **6**{*7*} (Figure 4).

The pyranoquinoline **8**{*1*−*20*} have been prepared by the Heck reaction[17] using acrylates (Table 2). A small acrylate sub library (Figure 5) for the Heck reaction was chosen. By allowing the compound to react under Heck reaction condition in the presence of the acrylates **7**{*1*−*5*}, we obtained the acryl substituted pyranoquinoline products **8**{*1*−*20*}.

For instance, the acryl substrate **7**{*1*−*5*} were chosen with a view toward increasing the biological activity of pyranoquinolines. Acrylonitrile **7**{*5*} reacted well but the yield obtained was comparatively lower than other acrylates. *N*, *N*-dimethylacrylate **7**{*3*} was highly reactive and afforded the desired product in appreciable yields. The reaction conditions for Heck reaction suggested that heating at 120 °C for 2 h in presence of 10 mol % Pd(II)-catalyst and 2.5 equiv of base in DMF was sufficient for obtaining desired products in good yields.

By using acrylates for Heck reaction we have prepared a small library of ester substituted pyranoquinolines. The presence of ester group will impart biological significance to these compounds.

Next, we employed the Sonogashira coupling reaction of 4-iodopyranoquinoline **4**{*1*} with terminal alkynes to produce another set of pyranoquinolines **9**{*1*−*5*}[14b] (Table 3).

In vitro antimalarial activity of some selected substituted pyranoquinoline scaffolds was determined against 3D7 strains of *Plasmodium falciparum* using SYBR green based florescence assay (Table 4). It is evident from Table 4 that presence of substituents at 1, 4, and 8 position of the pyranoquinoline scaffolds plays an important role for the activity. Suzuki coupling products **6**{*3*} and **6**{*21*} with methoxy group at 1 position of the scaffold showed good antimalarial activity with IC_{50} values ranging from 1.9 to 2.1 μM (entries 1 and 3). However, increase in chain length at 1 position of the scaffolds drastically decreased the antimalarial activity with IC_{50} value >100 μg/mL (entry 2). Heck coupling product **8**{*12*}, with ethyl acrylate

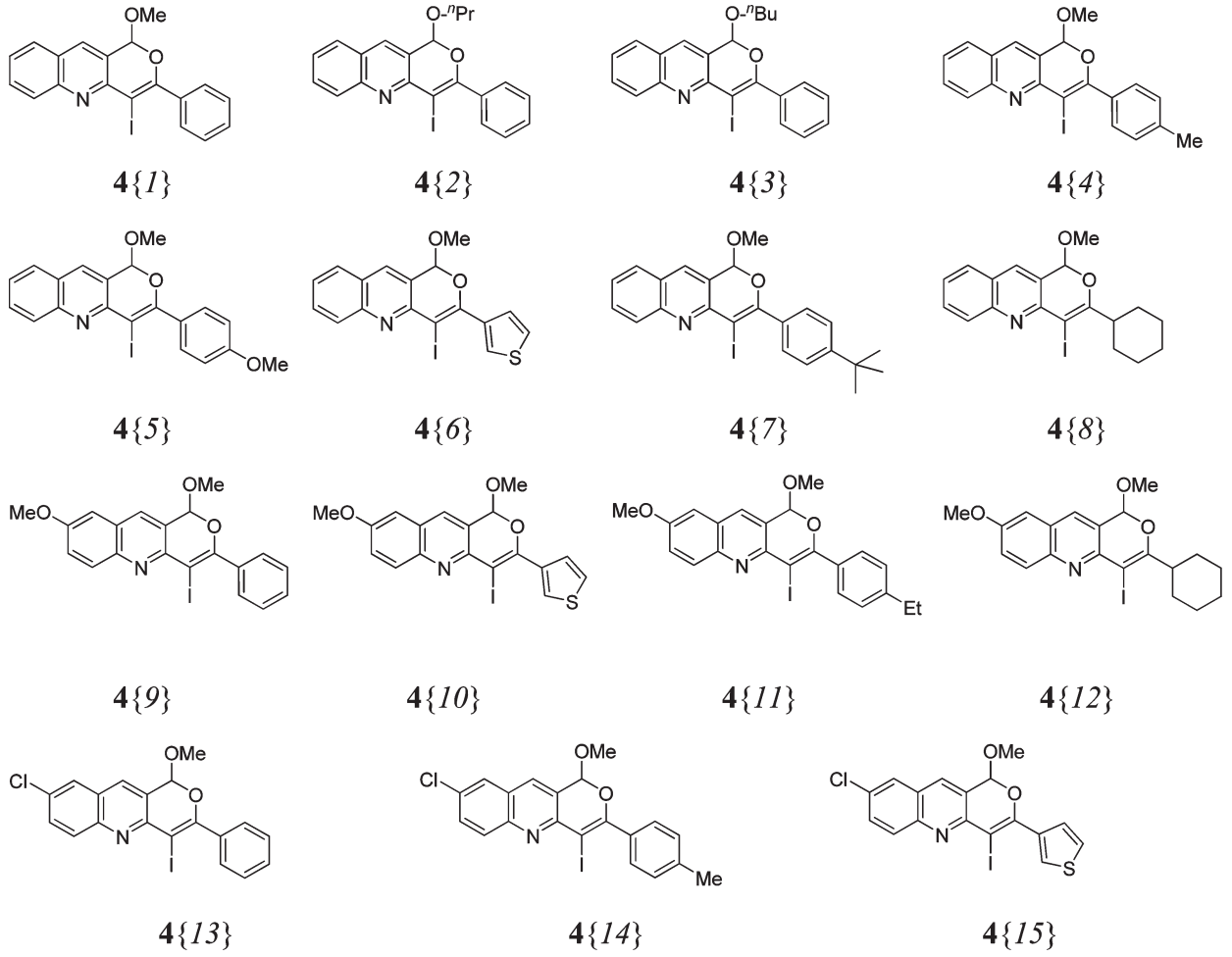
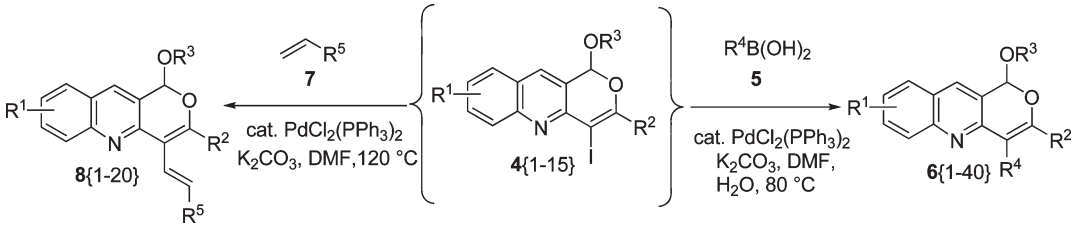


Figure 2. Key intermediate 4-pyrano[4,3-*b*]quinoline **4**{*1*−*15*}.

Scheme 2. Library generation of Pyrano[4,3-b]quinolines from the 4-Iodopyranoquinolines



substitution at 4 position of the scaffold having electron-donating thiophene ring and methoxy group at 3 and 8 position, respectively, showed good antimalarial activity (entry 5); however, compound **8**{*15*} with acrylonitrile substitution at 4 position and electron-donating thiophene ring and methoxy group at 3 and 8 position showed moderate activity (entry 7). Compounds **8**{*1*} and **8**{*20*} with acrylonitrile substitution at 4 position and compound **8**{*13*} with amide functionality at 4 position were found ineffective (entries 4, 6, and 8). Compounds which showed IC_{50} less than 10 μg/mL were further analyzed for toxicity to mammalian HeLa cell line and they were found nontoxic up to a concentration of 50 μg/mL (Table 4).

CONCLUSION

In summary, we have designed a novel pyrano[4,3-*b*]quinoline library in solution phase which has been rapidly constructed utilizing iodocyclization and palladium catalyzed cross-coupling reactions. Diversely substituted pyranoquinolines have been achieved because of the high efficiency, good substrate generality, mild conditions and commercially available building blocks. Some of the selected Suzuki and Heck coupling products were screened against 3D7 strains of *Plasmodium falciparum* for antimalarial activity. Suzuki coupling products **6**{*3*}, **6**{*21*} and Heck coupling product **8**{*12*} exhibit promising antimalarial activity. Further studies on the biological mechanism of action of pyrano-[4,3-*b*]quinoline are in progress and will be reported in due course.

Table 1. Library Data of Compounds 6{*1*−*40*} Synthesized via Suzuki Reaction[a]

entry	iodo pyranoquinoline	boronic acid	product	yield[b]%
1	4{*1*}	5{*1*}	6{*1*}	81
2	4{*1*}	5{*2*}	6{*2*}	82
3	4{*1*}	5{*3*}	6{*3*}	70
4	4{*1*}	5{*4*}	6{*4*}	80
5	4{*1*}	5{*5*}	6{*5*}	82
6	4{*1*}	5{*6*}	6{*6*}	78
7	4{*1*}	5{*8*}	6{*7*}	80
8	4{*2*}	5{*4*}	6{*8*}	74
9	4{*3*}	5{*4*}	6{*9*}	80
10	4{*3*}	5{*2*}	6{*10*}	78
11	4{*4*}	5{*1*}	6{*11*}	79
12	4{*4*}	5{*5*}	6{*12*}	80
13	4{*4*}	5{*8*}	6{*13*}	78
14	4{*5*}	5{*4*}	6{*14*}	79
15	4{*5*}	5{*5*}	6{*15*}	82
16	4{*6*}	5{*1*}	6{*16*}	84
17	4{*6*}	5{*2*}	6{*17*}	78
18	4{*6*}	5{*4*}	6{*18*}	80
19	4{*7*}	5{*2*}	6{*19*}	79
20	4{*8*}	5{*1*}	6{*20*}	80
21	4{*8*}	5{*2*}	6{*21*}	79
22	4{*8*}	5{*3*}	6{*22*}	77
23	4{*8*}	5{*7*}	6{*23*}	68
24	4{*9*}	5{*4*}	6{*24*}	72
25	4{*9*}	5{*6*}	6{*25*}	80
26	4{*9*}	5{*7*}	6{*26*}	68
27	4{*10*}	5{*3*}	6{*27*}	70
28	4{*10*}	5{*4*}	6{*28*}	79
29	4{*11*}	5{*5*}	6{*29*}	81
30	4{*11*}	5{*8*}	6{*30*}	77
31	4{*11*}	5{*9*}	6{*31*}	65
32	4{*12*}	5{*8*}	6{*32*}	76
33	4{*12*}	5{*9*}	6{*33*}	68
34	4{*13*}	5{*4*}	6{*34*}	80
35	4{*13*}	5{*5*}	6{*35*}	82
36	4{*13*}	5{*6*}	6{*36*}	78
37	4{*13*}	5{*8*}	6{*37*}	76
38	4{*13*}	5{*9*}	6{*38*}	68
39	4{*14*}	5{*4*}	6{*39*}	80
40	4{*15*}	5{*9*}	6{*40*}	70

[a] The reactions were performed using iodo pyranoquinolines **4** (0.25 mmol), 1.2 equiv of the boronic acids **5**, 2.5 equiv of K_2CO_3, 10 mol % $Pd(PPh_3)_2Cl_2$ in 2.0 mL of DMF/H_2O (4:1) under nitrogen condition at 80 °C for 2 h. [b] Yield of isolated product

EXPERIMENTAL PROCEDURES

General Procedure for the Synthesis of 4-Iodo-1*H*-pyrano[4,3-*b*]quinolines 4{*1*−*15*}. Into a solution of the 2--(alkynyl)quinoline-3-carbaldehyde **3** (1.0 mmol), K_2CO_3 (2.5 equiv), and I_2 (2.5 equiv) in CH_2Cl_2 (2.0 mL), the nucleophile (1.2 equiv) was added, and the solution was stirred at room temperature until the total disappearance of the starting material as determined by TLC analysis. The reaction mixture was then quenched with saturated aq $Na_2S_2O_3$ and water. The resulting solution was extracted using ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography (Silica gel 100−200 mesh, hexane/EtOAc) to afford pure compounds.

4-Iodo-1-methoxy-3-(thiophen-3-yl)-1H-pyrano[4,3-b]quinoline ***4***{*6*}. The product was obtained as yellow solid. mp: 146−148 °C. Yield: 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21−8.14 (m, 2H), 7.95 (s, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.76−7.72 (m, 2H), 7.50 (t, J = 7.2 Hz, 1H), 7.38−7.37 (m, 1H), 6.21 (s, 1H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 152.4, 148.9, 148.1, 137.1, 132.8, 130.2, 129.5, 129.4, 128.8, 127.5, 126.4, 124.7, 122.1, 100.2, 77.5, 56.3. HRMS (ESI): calcd for $[C_{17}H_{12}INO_2S]^+$ requires m/z 420.9633, found 420.9640.

General Procedure for the Synthesis of Compounds 6{*1*−*40*}. To a vial was added the 4-iodopyranoquinoline **4** (0.25 mmol), the boronic acid **6** (1.2 equiv), 10 mol % $Pd(PPh_3)_2Cl_2$, K_2CO_3 (2.5 equiv), and DMF/H_2O (4:1). The solution was flushed with nitrogen and then heated to 80 °C until TLC revealed complete conversion of the starting material. The solution was allowed to cool and diluted with H_2O and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by column chromatography to afford the corresponding product.

4-(1-Methoxy-3-phenyl-1H-pyrano[4,3-b]quinolin-4-yl)-N,N-dimethylaniline ***6***{*5*}. The product was obtained as yellow solid. mp: 156−158 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.44−7.39 (m, 3H), 7.29−7.20 (m, 5H), 6.71 (d, J = 8.7 Hz, 2H), 6.28 (s, 1H), 3.73 (s, 3H), 2.96 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 152.6, 150.4, 149.5, 148.9, 135.8, 132.9, 132.6, 130.0, 129.5, 128.6, 128.2, 127.6, 127.4, 126.7, 125.5, 123.1, 122.8, 117.5, 112.2, 100.0, 56.0, 40.6. HRMS (ESI): calcd for $[C_{27}H_{24}N_2O_2]^+$ requires m/z 408.1838, found 408.1836.

General Procedure for the Synthesis of Compounds 8{*1*−*20*}. To a vial was added the 4-iodopyranoquinoline **4** (0.25 mmol), the acrylates **7** (1.2 equiv), 10 mol % $Pd(PPh_3)_2Cl_2$, K_2CO_3 (2.5 equiv), and DMF (2.0 mL). The solution was flushed with nitrogen, and then heated to 120 °C until TLC revealed complete conversion of the starting material. The solution was allowed to cool and diluted with H_2O and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by column chromatography to afford the corresponding product.

(E)-Methyl 3-(1-methoxy-3-p-tolyl-1H-pyrano[4,3-b]quinolin-4-yl)acrylate ***8***{*1*}. The product was obtained as yellow solid. mp: 174−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (d, J = 8.8 Hz, 1H), 8.09 (s, 1H), 7.82−7.79 (m, 3H), 7.73 (t, J = 7.3 Hz, 1H), 7.54−7.51 (m, 3H), 7.28 (d, J = 8.0 Hz, 2H), 6.21 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 169.0, 162.6, 148.9, 148.2, 141.1, 139.5, 132.9, 130.8, 130.5, 130.2, 129.4, 129.2, 127.6, 126.5, 126.3, 122.7, 119.2, 111.0, 100.7, 56.7, 51.3, 21.5. HRMS (ESI): calcd for $[C_{24}H_{21}NO_4]^+$ requires m/z 387.1471, found 387.1475.

General Procedure for the Synthesis of Compounds 9{*1*−*5*}. To a vial was added the 4-iodopyranoquinoline

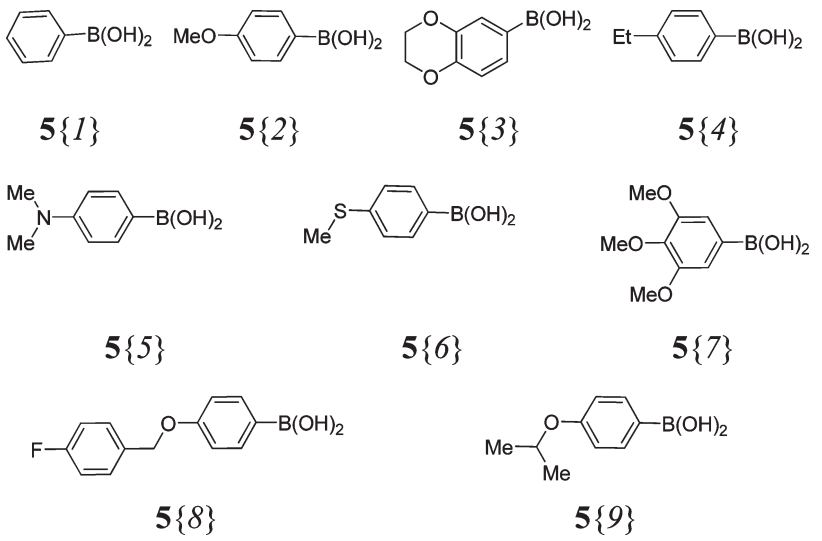


Figure 3. Boronic acids 5{*1*−*9*} used for Suzuki reaction.

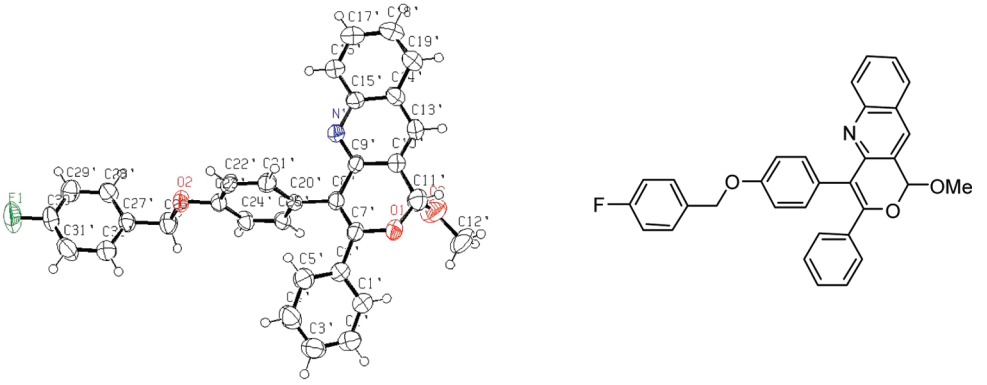


Figure 4. ORTEP plot of single crystal structure of compound **6**{*7*}.

4 (0.25 mmol), the alkynes **2** (1.2 equiv), 10 mol % $Pd(PPh_3)_2Cl_2$, and Et_3N (2.5 equiv) in CH_3CN (2.0 mL). The solution was flushed with nitrogen, and then heated to 65 °C until TLC revealed complete conversion of the starting material. The solution was allowed to cool and diluted with H_2O and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by column chromatography to afford the corresponding product.

1-Methoxy-3-phenyl-4-(p-tolylethynyl)-1H-pyrano[4,3-b]quinoline ***9***{*2*}. The product was obtained as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27−8.21 (m, 3H), 8.07 (s, 1H), 7.82−7.80 (d, J = 8.4 Hz, 1H), 7.72 (td, J = 7.3 and 1.4 Hz, 1H), 7.47−7.43 (m, 6H), 7.13 (d, J = 8.8 Hz, 2H), 6.32 (s, 1H), 3.75 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 159.5, 149.1, 149.0, 137.8, 134.2, 132.9, 131.3, 130.2, 130.0, 129.8, 129.0, 128.9, 127.9, 127.6, 127.1, 126.1, 122.0, 121.1, 101.0, 100.4, 95.9, 84.1, 56.4, 20.7. HRMS (ESI): calcd for $[C_{28}H_{21}NO_2]^+$ requires m/z 403.4718, found 403.4711.

Procedure for Antimalarial Screening. Compounds were screened for antimalarial activity using SYBR Green fluorescence based assay of *P. falciparum* growth in microtiter plate wells in vitro. To check parasite growth inhibition by the above extracts, malaria parasites were grown in vitro.[18] Chloroquine sensitive 3D7 strain of *P. falciparum* was used in culture. The parasite was cultured in RPMI 1640 supplemented with HEPES, sodium bicarbonate, gentamycin, 10% human serum or albumax, and human erythrocytes. The parasite was grown in plates incubated at 370C in carbon dioxide incubator. The parasitemia was monitored by microscopic examination of blood smears after staining with Giemsa stain. For various studies the parasite cultures would be prepared after synchronization.

In vitro drug susceptibility testing in *P. falciparum* will be determined by a SYBR Green I-based fluorescence method described previously by Smilkstein and Riscoe.[19] Stock solutions of each test drug were prepared in DMSO/sterile distilled water. The 50% inhibitory concentration (IC_{50}) was determined by analysis of dose−response curves.

Determination of Therapeutic Potential of Purified Antiplasmodial Molecules. Therapeutic index is a ratio of toxic concentration (TC_{50}) for host to inhibitory concentration (IC_{50}) for the pathogen. Therapeutic indices will be determined by measuring the cytotoxicity of test molecules on mammalian cells. Animal cell line Hela was used to determine drug toxicity by using MTT assay for mammalian cell viability as described by Mosmann in 1983.[20]

Table 2. Library Data of Compounds 8{*1*−*20*} Synthesized via Heck Reaction[a]

entry	iodo pyranoquinoline	reactant	product	yield[b]%
1	4{*4*}	7{*1*}	8{*1*}	80
2	4{*4*}	7{*3*}	8{*2*}	75
3	4{*4*}	7{*4*}	8{*3*}	70
4	4{*5*}	7{*1*}	8{*4*}	78
5	4{*5*}	7{*2*}	8{*5*}	75
6	4{*5*}	7{*4*}	8{*6*}	68
7	4{*6*}	7{*1*}	8{*7*}	79
8	4{*6*}	7{*3*}	8{*8*}	78
9	4{*9*}	7{*1*}	8{*9*}	80
10	4{*9*}	7{*4*}	8{*10*}	72
11	4{*10*}	7{*1*}	8{*11*}	79
12	4{*10*}	7{*2*}	8{*12*}	75
13	4{*10*}	7{*3*}	8{*13*}	78
14	4{*10*}	7{*4*}	8{*14*}	71
15	4{*10*}	7{*5*}	8{*15*}	65
16	4{*11*}	7{*1*}	8{*16*}	77
17	4{*11*}	7{*2*}	8{*17*}	75
18	4{*12*}	7{*1*}	8{*18*}	78
19	4{*12*}	7{*3*}	8{*19*}	76
20	4{*12*}	7{*5*}	8{*20*}	66

[a] Reactions were performed using 4-iodopyranoquinolines **4** (0.25 mmol), 1.2 equiv of the acrylates 7, 2.5 equiv of K_2CO_3, 10 mol % $Pd(PPh_3)_2Cl_2$ in 2.0 mL of DMF under nitrogen condition at 120 °C for 2 h. [b] Yield of the isolated product

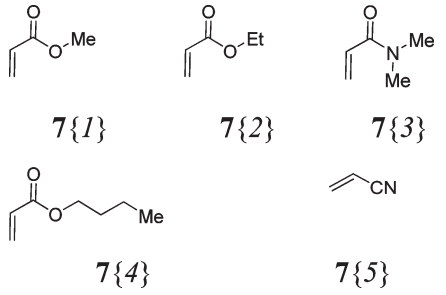
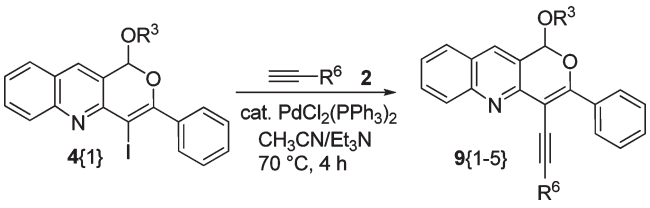


Figure 5. Acrylates used for Heck reaction 7{*1*−*5*}.

Table 3. Library data of Compounds 9{*1*−*5*} Synthesized via Sonogashira Reaction[a]



entry	iodo pyranoquinoline	reactant	product	yield[b]%
1	4{*1*}	2{*2*}	9{*1*}	70
2	4{*1*}	2{*3*}	9{*2*}	75
3	4{*1*}	2{*4*}	9{*3*}	72
4	4{*1*}	2{*5*}	9{*4*}	68
5	4{*1*}	2{*6*}	9{*5*}	65

[a] Reactions were performed using 4-iodopyranoquinolines **4** (0.25 mmol), 1.2 equiv of the alkynes, 2.5 equiv of Et_3N, 10 mol % $Pd(PPh_3)_2Cl_2$ in 2.0 mL of CH_3CN under nitrogen condition at 70 °C for 4 h. [b] Yield of the isolated product

Table 4. Antimalarial Activity of Pyranoquinolines against 3D7 Strains of *Plasmodium falciparum*[a]

entry	compounds	IC_{50} Pf3D7 (μg/mL)	TC_{50} HeLa (μg/mL)
1	6{*3*}	1.9	>50
2	6{*10*}	>100	
3	6{*21*}	2.1	>50
4	8{*1*}	28	
5	8{*12*}	2	>50
6	8{*13*}	>100	
7	8{*15*}	9	>50
8	8{*20*}	>100	
9	chloroquine	0.021	
10	artemisnin	0.0045	

[a] Experiment was performed in triplicate.

■ ASSOCIATED CONTENT

Supporting Information. X-ray crystallographic data of compound 6{*7*} and copies of ^1H and ^{13}C NMR spectra are reported for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Arcadi, A.; Chiarini, M.; Giuseppe, S. D.; Marinelli, F. A New Green Approach to the Friedlander Synthesis of Quinolines. *Synlett* **2003**, 203–206. (b) Wangab, X. S.; Zhanga, M. M.; Zenga, Z. S.; Shiab, D. Q.; Tuab, S. J. Clean Procedure for Synthesis of Chromeno[4,3-*b*]-benzo[*f*]quinolin-6-one Derivatives: Reaction of *N*-Arylidenenaphthalen-2-amine with 4-Hydroxycoumarin in Aqueous Media. *Synth. Commun.* **2006**, *36*, 2047–2057.

(2) (a) Grundon, M. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: London, 1988; Vol. 32, pp 341−439. (b) Sainsbury, M. In *Rodd's Chemistry of Carbon Compounds*; Coffey, S., Ed.; Elsevier Publishing Co.: New York, 1978; Vol. IVG, pp 171−225.

(3) (a) Rideau, M.; Yerchere, C.; Hibon, P. Alcalofdes Dihydrofuroquinoleiques de Quelques Rutaceae: Isolement, Structure, Proprietes Biologiques. *Phytochemistry* **1979**, *18*, 155–159. (b) Das, B. P.; Chowdhury, D. N.; Chowdhury, B.; Mester, I. *Indian J. Chem.* **1982**, *21B*, 76–79.

(4) (a) Sirisoma, N.; Pervin, A.; Zhang, H.; Jiang, S.; Willardsen, J. A.; Anderson, M. B.; Mather, G.; Pleiman, C. M.; Kasibhatla, S.; Tseng, B.; Drewe, J.; Cai, S. X. Discovery of *N*-(4-Methoxyphenyl)-N,2-dimethylquinazolin-4-amine, a Potent Apoptosis Inducer and Efficacious Anticancer Agent with High Blood Brain Barrier Penetration. *J. Med. Chem.* **2009**, *52*, 2341–2351. (b) Krug, M.; Hilgeroth, A. Recent Advances in the Development of Multi-kinase Inhibitors. *Mini-Rev. Med.*

Chem. **2008**, *8*, 1312–1327. (c) Zhang, Y.; Xu, W. Progress on Kinesin Spindle Protein Inhibitors as Anti-cancer Agents. *Anticancer Agents Med. Chem.* **2008**, *8*, 698–704. (d) Welch, S. A. Moore, Erlotinib, M. Success of a Molecularly Targeted Agent for the Treatment of Advanced Pancreatic Cancer. *J. Future Oncol* **2007**, *3*, 247–254. (e) Herbst, R. S.; Kies, M. S. Gefitinib: Current and Future Status in Cancer Therapy. *Clin. Adv. Hematol. Oncol.* **2003**, *1*, 466–472.

(5) (a) Srivastava, S. K.; Jha, A.; Agarwal, S. K.; Mukherjee, R.; Burman, A. C. Synthesis and Structure−Activity Relationships of Potent Antitumor Active Quinoline and Naphthyridine Derivatives. *Anticancer Agents Med. Chem.* **2007**, *7*, 685–709. (b) Hradil, P.; Hlavác, J.; Soural, M.; Hajdúch, M.; Kolár, M.; Vecerová, R. 3-Hydroxy-2-phenyl-4(1*H*)-quinolinones as Promising Biologically Active Compounds. *Mini-Rev. Med. Chem.* **2009**, *9*, 696–702. (c) Rudys, S.; Ríos-Luci, C.; Pérez-Roth, E.; Cikotiene, I.; Padrón, J. M. Antiproliferative Activity of novel Benzo[*b*][1,6]naphthyridines in Human Solid Tumor Cell Lines. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1504–1506.

(6) Magedov, I., V.; Manpadi, M.; Ogasawara, M., A; Dhawan, A., S.; Rogelj, S.; Slambrouck, S., V.; Steelant, W., F., A.; Evdokimov, N., M.; Uglinskii, P., Y.; Elias, E., M.; Knee, E., J.; Tongwa, P.; Antipin, M., Y.; Kornienko, A. Structural Simplification of Bioactive Natural Products with Multicomponent Synthesis. 2. Antiproliferative and Antitubulin Activities of Pyrano[3,2-*c*]pyridones and Pyrano[3,2-*c*]quinolones. *J. Med. Chem.* **2008**, *51*, 2561–2570.

(7) (a) Mabire, D.; Coupa, S.; Adelinet, C.; Poncelet, A.; Simonnet, Y.; Venet, M.; Wouters, R.; Lesage, A. S. J.; Beijsterveldt, L. V.; Bischoff, F. Synthesis, Structure−Activity Relationship, and Receptor Pharmacology of a New Series of Quinoline Derivatives Acting as Selective, Noncompetitive *m*Glu1 Antagonists. *J. Med. Chem.* **2005**, *48*, 2134–2153. (b) Michael, J. P. Quinoline, Quinazoline and Acridone Alkaloids. *Nat. Prod. Rep.* **2002**, *19*, 742–760. (c) Michael, J. P. Quinoline, Quinazoline and Acridone Alkaloids. *Nat. Prod. Rep.* **2003**, *20*, 476–493.

(8) (a) Godet, T.; Vaxelaire, C.; Michel, C.; Milet, A.; Belmont, P. Silver versus Gold-Catalysis in Tandem Reactions of Carbonyl Functions onto Alkynes: A Versatile Access to Furoquinoline and Pyranoquinoline cores. *Chem.—Eur. J.* **2007**, *13*, 5632–5641. (b) Marco-Contelles, J.; León, R.; López, M. G.; García, A. G.; Villarroya, M. Synthesis and Biological Evaluation of New 4*H*-Pyrano[2,3-*b*]quinoline Derivatives that Block Acetylcholinesterase and Cell Calcium Signals, and cause Neuroprotection against Calcium overload and Free Radicals. *Eur. J. Med. Chem.* **2006**, *41*, 1464–1469. (c) Butenschon, I.; Moller, K.; Hansel, W. Angular Methoxy-Substituted Furo- and Pyranoquinolinones as Blockers of the Voltage-Gated Potassium Channel Kv1.3. *J. Med. Chem.* **2001**, *44*, 1249–1256. (d) Kalita, K. P.; Baruah, B.; Bhuyan, P. J. Synthesis of Novel Pyrano[2,3-*b*]quinolines from Simple Acetanilides via Intramolecular 1,3-dipolar Cycloaddition. *Tetrahedron Lett.* **2006**, *47*, 7779–7782.

(9) (a) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. Cyclization of Carbonyl Groups onto Alkynes upon Reaction with IPy_2BF_4 and their Trapping with Nucleophiles: A Versatile Trigger for Assembling Oxygen Heterocycles. *J. Am. Chem. Soc.* **2003**, *125*, 9028–9029. (b) Barluenga, J.; Vazquez-Villa, H.; Merino, I.; Ballesteros, A.; Gonzalez, J. M. The Reaction of *o*-Alkynylarene and Heteroarene Carboxaldehyde Derivatives with Iodonium Ions and Nucleophiles: A Versatile and Regioselective Synthesis of 1*H*-Isochromene, Naphthalene, Indole, Benzofuran, and Benzothiophene Compounds. *Chem.—Eur. J.* **2006**, *12*, 5790–5805.

(10) (a) Yue, D.; Ca, N. D.; Larock, R. C. Syntheses of Isochromenes and Naphthalenes by Electrophilic Cyclization of Acetylenic Arenecarboxaldehydes. *J. Org. Chem.* **2006**, *71*, 3381–3388. (b) Yue, D.; Ca, N. D.; Larock, R. C. Efficient Syntheses of Heterocycles and Carbocycles by Electrophilic Cyclization of Acetylenic Aldehydes and Ketones. *Org. Lett.* **2004**, *6*, 1581–1584. (c) Mehta, S.; Larock, R. C. Iodine/Palladium Approaches to the Synthesis of Polyheterocyclic Compounds. *J. Org. Chem.* **2010**, *75*, 1652–1658.

(11) (a) Cho, C. H.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. Parallel Synthesis of a Multi-Substituted Benzo[*b*]furan Library. *J. Comb. Chem.* **2008**, *10*, 941–947. (b) Roy, S.; Roy, S.; Neuenswander, B.; Hill, D.; Larock, R. C. Solution-Phase Synthesis of a Diverse Isocoumarin Library. *J. Comb. Chem.* **2009**, *11*, 1128–1135. (c) Roy, S.; Roy, S.; Neuenswander, B.; Hill, D.; Larock, R. C. Palladium and Copper-Catalyzed Solution Phase Synthesis of a Diverse Library of Isoquinolines. *J. Comb. Chem.* **2009**, *11*, 1061–1065.

(12) (a) Verma, A. K.; Keshwarwani, T.; Singh, J.; Tandon, V.; Larock, R. C. A Copper-Catalyzed Tandem Synthesis of Indolo- and Pyrrolo[2,1-*a*]isoquinolines. *Angew. Chem., Int. Ed.* **2009**, *48*, 1138–1143. (b) Verma, A. K.; Singh, J.; Choudhary, R.; Larock, R. C. Benzotriazole: An Excellent Ligand for the Copper-Catalyzed *N*-Arylation of Indoles. *Tetrahedron* **2009**, *65*, 8434–8439. (c) Tiwari, R. K.; Singh, J.; Verma, A. K.; Singh, D.; Chandra, R. Highly Efficient One Pot Synthesis of 1-Substituted 1,2,3,4-Tetrahydropyrazino[1,2-*a*]indoles. *Tetrahedron* **2005**, *61*, 9513–9518. (d) Verma, A. K.; Singh, J.; Sankar, V. K.; Choudhary, R.; Chandra, R. Benzotriazole: An Excellent Ligand for Cu-Catalyzed *N*-Arylation of Imidazoles with Aryl and Heteroaryl Halides. *Tetrahedron Lett.* **2007**, *48*, 4207–4210. (e) Chaudhary, P.; Nimesh, S.; Yadav, V.; Verma, A. K.; Kumar, R. Synthesis, Characterization and in-vitro Biological Studies of Novel Cyano Derivatives of *N*-Alkyl and *N*-Aryl Piperazine. *Eur. J. Med. Chem.* **2007**, *42*, 471–476. (f) Verma, A. K.; Bansal, S.; Singh, J.; Tiwari, R. K.; Sankar, V. K.; Tandon, V.; Chandra, R. Synthesis and In-vitro Cytotoxicity of Halo-derivatives of Noscapine. *Bioorg. Med. Chem.* **2006**, *14*, 6733–6736. (g) Katritzky, A. R.; Verma, A. K.; He, H. Y.; Chandra, R. Novel Synthesis of 1,2,3,4-Tetrahydropyrazino[1,2-*a*]indoles. *J. Org. Chem.* **2003**, *68*, 4938–4940.

(13) (a) Camps, P.; Formosa, X.; Galdeano, C.; Torrero, D., M.; Ramírez, L.; Gomez, E.; Isambert, N.; Lavilla, R.; Badia, A.; Clos, M., V.; Bartolini, M.; Mancini, F.; Andrisano, V.; Arce, M., P.; Franco, M., I., R.; Huertas, O.; Dafni, T.; Luque, F., J. Pyrano[3,2-*c*]quinoline-6-Chlorotacrine Hybrids as a Novel Family of Acetylcholinesterase- and β-Amyloid-Directed Anti-alzheimer Compounds. *J. Med. Chem.* **2009**, *52*, 5365–5379. (b) Goudar, M., A.; Jayadevappa, H.; Sudhakara, A.; Mahadevan, K., M. Imino Diels-Alder Reactions: Efficient Synthesis of Pyrano and Furanoquinolines Catalyzed by Antimony (III) Sulfate. *Lett. Org.Chem.* **2008**, *5*, 628–632.

(14) (a) Verma, A. K.; Aggarwal, T.; Rustagi, V.; Larock, R. C. Solvent-Controlled Selective Electrophilic Cyclization and Oxidative Esterification of *o*-Alkynyl Aldehydes. *Chem Comm.* **2010**, *46*, 4064–4066. (b) Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. Iodine-Mediated Solvent-Controlled Selective Electrophilic Cyclization and Oxidative Esterification of *o*-Alkynyl Aldehydes: An Easy Access to Pyranoquinolines, Pyranoquinolinones, and Isocumarins. *J. Org. Chem.* **2010**, *75*, 7691–7703.

(15) (a) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.

(16) CCDC 808029 **4**{7} contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/request/cif.

(17) Heck, R. F. Palladium-Catalyzed Vinylation of Organic Halides. *Org. React.* **1982**, *27*, 345–390.

(18) Trager, W.; Jensen, J. B. Human Malaria Parasites in Continuous Culture. *Science* **1976**, *193*, 673–675.

(19) Smilkstein, M.; Sriwilaijaroen, N.; Kelly, J. X.; Wilairat, P.; Riscoe, M. Simple and Inexpensive Fluorescence-Based Technique for High-Throughput Antimalarial Drug Screening. *Antimicrob. Agents Chemother.* **2004**, *48*, 1803–1806.

(20) Mosmann, T. Rapid Colorimetric Assay for Cellular Growth and Survival: Application to Proliferation and Cytotoxicity Assays. *J. Immunol. Methods* **1983**, *65*, 55–63.