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Article

Synthesis of Natural and Unnatural Quinolones Inhibiting the Growth and Motility of Bacteria

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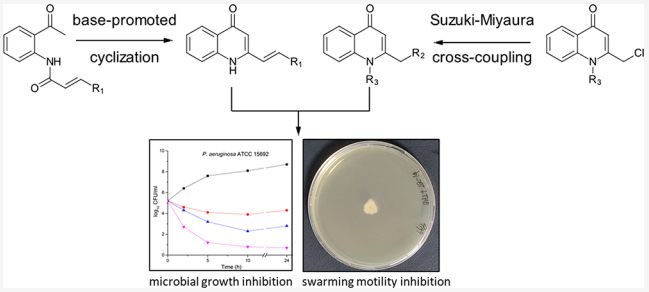
ABSTRACT: Synthesis of a recently discovered *S*-methylated quinolone natural product (**1**) was carried out, in addition to the production of a range of 2-substituted 4-quinolone derivatives (**2**–**11**). Two approaches were used: (i) the base-catalyzed cyclization of *N*-(ketoaryl)amides; (ii) attachment of the substituent to the quinolone core via a Suzuki–Miyaura cross-coupling. Also produced were a small suite of related 2(1*H*)-quinolones (**12**–**19**). The synthesized compounds were assessed for their antimicrobial properties. The alkene-substituted 4-quinolone **8** significantly inhibited the growth of a *Pseudomonas aeruginosa* strain, and both 4-quinolones and 2(1*H*)-quinolones were capable of inhibiting the swarming behavior of *Bacillus subtilis*.



The 2-alkyl-4-quinolones are a group of microbial natural products, the best known of which are the *Pseudomonas* quinolone signal (PQS)[1] and its biosynthetic precursor, 4-hydroxy-2-heptylquinoline (HHQ).[2] These metabolites play a role in quorum sensing of *Pseudomonas aeruginosa*,[3,4] which influences biofilm formation and virulence factor production; inhibition of quinolone production can thus be used as a strategy for the control of pathogenic *Pseudomonas* strains.[5,6] A related suite of compounds are produced in some *Burkholderia* species, where they fulfill a similar role.[7] Other members of the structure class have been reported to possess antialgal,[8] antimalarial, and cytotoxic properties.[9] Structural variation in the majority of the naturally occurring 2-alkyl-4-quinolones centers on the substituent at the 2-position, which usually consists of saturated or unsaturated alkyl chains.

In order to expand the chemical space available for biological investigation, many researchers have taken a synthetic approach.[10] Fluorinated 2-phenyl-4-quinolones have displayed potent cytotoxic properties, acting as tubulin inhibitors,[11] while 2-phenyl-4-quinolone itself has been shown to induce G_2/M phase arrest in a leukemia cell line.[12] In 2007, a two-step synthetic procedure for the synthesis of quinolones was described, using a Cu-catalyzed Camps cyclization to produce a range of 2-substituted 4-quinolones.[13] A 2016 report described the synthesis of a range of HHQ and PQS derivatives in which the heteroatoms in the quinolone ring were replaced,[14] one of which displayed significant inhibitory properties against *P. aeruginosa* elastase, which is a key virulence factor for the microorganism and a potential drug target.[15] Alkylquinolones affect not only the *Pseudomonas* genus, however: reports in 2012 and 2015 revealed that HHQ derivatives could affect the swarming behavior and biofilm formation of *Bacillus* species.[16,17]

Quinolones are also known for their antibiotic properties. Best known of these are the synthetic fluoroquinolones,[18] which possesses significantly different substitution patterns from the naturally occurring 2-alkyl-4-quinolones, but the latter class and its derivatives have also been reported to have antimicrobial properties. 3-Thiocyanate- and selenocyanate-substituted 4-arylquinolones have been shown to possess moderate antimicrobial properties against both Gram-positive and Gram-negative bacteria.[19] In a report by Salvaggio and co-workers, a small suite of quinolone natural products was synthesized using a Suzuki–Miyaura coupling, several members of which were found to retard the growth of *E. coli* and *S. aureus in vitro*.[20] The same method has been used to produce *Burkholderia*-derived quinolones, which possess antimicrobial properties against Gram-positive bacteria.[21]

In a recent report, we described the isolation of several 4-quinolone natural products from a *P. aeruginosa* strain, several of which possessed unusual side chains at the 2-position.[22] These compounds possessed weak cytotoxic activity, but insufficient material was isolated for further biological testing; they thus presented attractive synthetic targets. Of chief interest was an unprecedented compound containing a 2-

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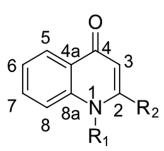
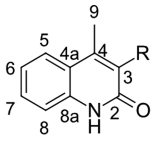
methylthiovinyl group (**1**). We describe here the first synthesis of this unusual natural product, along with a range of 2-substituted 4-quinolone derivatives (**2**−**11**), two of which are also recently discovered natural products (**6**, **8**). In addition, a small suite of related quinolin-2(1*H*)-ones (**12**−**19**) were produced, and the antimicrobial properties of all synthesized compounds were assessed.





	R_1	R_2
1	H	(*E*)-CH=CHSCH$_3$
2	H	(*Z*)-CH=CHSCH$_3$
3	H	(*E*)-CH=CHSCH$_2$CH$_3$
4	H	(*E*)-CH=CHOCH$_3$
5	H	(*E*)-CH=CHOCH$_2$CH$_3$
6	H	CH$_2$C$_6$H$_5$
7	H	p-CH$_2$C$_6$H$_4$SCH$_3$
8	H	(*E*)-CH$_2$CH=CH(CH$_2$)$_3$CH$_3$
9	CH$_3$	CH$_2$C$_6$H$_5$
10	CH$_3$	p-CH$_2$C$_6$H$_4$SCH$_3$
11	CH$_3$	(*E*)-CH$_2$CH=CH(CH$_2$)$_3$CH$_3$

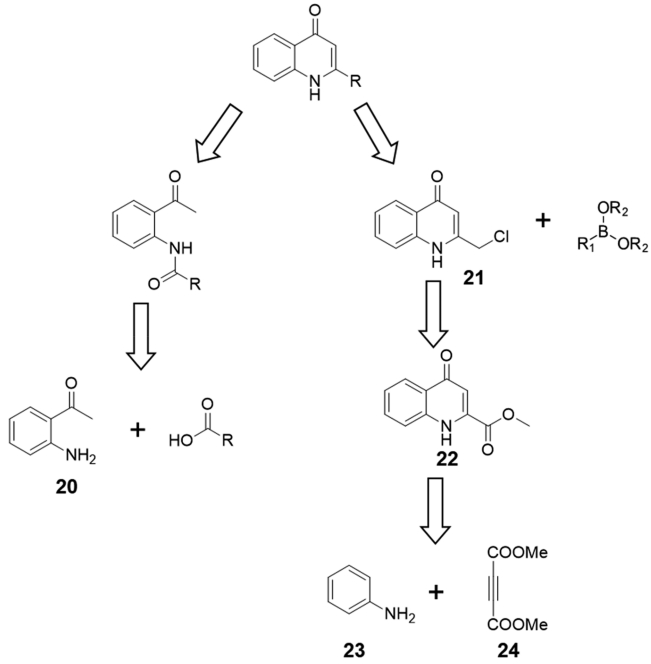
	R
12	CH$_2$SCH$_3$
13	CH$_2$OCH$_3$
14	CH$_2$N(CH$_3$)$_2$
15	CH$_2$SCH$_2$CH$_3$
16	CH(OCH$_3$)$_2$
17	CH(OCH$_2$CH$_3$)$_2$
18	CH(SCH$_3$)$_2$
19	CH(SCH$_2$CH$_3$)$_2$

RESULTS AND DISCUSSION

Retrosynthetic Analysis. 2-Substituted quinolones in which the side chains contain double bonds conjugated to the core nucleus can be synthesized by the base-promoted cyclization of *N*-(ketoaryl)amides.[13] The *N*-(ketoaryl)amides can be obtained by condensation of 2′-aminoacetophenone (**20**) with the corresponding carboxylic acid or acyl chloride starting materials, which are either commercially available or easy to synthesize. Another method is by attaching the substituent at the 2-position of the quinolone core in the final step, via a Suzuki−Miyaura cross-coupling. The halogenated quinolone derivative **21** can be easily obtained from the ester **22**, which in turn is derived from aniline (**23**) and dimethylacetylene dicarboxylate (**24**) by the Conrad−Limpach method, followed by reduction and chlorination.[20]

Synthesis of Quinolones. Initial attempts at the synthesis of the natural product **1** followed the former strategy: 3-methylthioacrylic acid was synthesized by the addition of NaSMe to freshly distilled propiolic acid to yield a mixture of *cis*−*trans* isomers (*trans*:*cis* 40:1).[23] Condensation with 2′-aminoacetophenone (**20**) using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide hydrochloride (EDCI) was attempted, but the reaction did not proceed efficiently, while the reaction using the acid chloride yielded a complex mixture. Thus, an alternative approach was used: first 2′-aminoacetophenone was condensed with propiolic acid to synthesize the propiolamide derivative **25**, using DCC as the coupling agent at 60 °C in tetrahydrofuran (THF), with a yield of 60%. The key intermediate **26** was synthesized by the addition of NaSMe to the alkynyl group in good yield (78%). However, a significant amount of a side product, the bis(methylthio)-propanamide **27**, was also formed, resulting from addition of two NaSMe units to the triple bond. Finally, the target quinolone **1** was achieved by NaOH-promoted cyclization of **26** at 110 °C in dioxane for 1 h (Scheme 2), along with the *Z*-isomer **2**, in a 5:1 ratio. Spectroscopic data for the target quinolone were identical to those for the natural product.[22]

Scheme 1. Retrosynthetic Analysis for Synthesis of 2-Substituted Quinolones



With a synthetic version of the natural product in hand and a viable methodology, our attention turned to the production of derivatives. Using sodium ethanethiolate, the amide **28** was formed from **25** as the major product, with a small amount of the bis-adduct **29** formed as a side product. Cyclization of **28** under basic conditions yielded the ethyl sulfide-substituted quinolone **3**; the *Z*-isomer was not detected. Oxygenated derivatives were also produced, with the conjugated amides **30** and **31** formed by condensation of **20** with the corresponding carbonyl compounds (Scheme 3). The amides were subsequently cyclized under basic conditions to yield the methyl (**4**) and ethyl ether-substituted quinolones (**5**). Yields for the cyclization of the ethers were much lower than those for the sulfides, with significant amounts of unknown side products formed.

The structure of the side product from the cyclization of **31** was determined by !D and 2D NMR experiments. In the proton NMR spectrum, signals corresponding to a 1,2-disubsituted aromatic ring were present, in addition to singlet resonances consistent with the presence of an aromatic methyl group (δ_H 2.78, 3H), two identical ethoxy groups (δ_H 1.27, t, 6H; 3.62, dq, 2H; 3.87, dq, 2H), and a highly deshielded methine (δ_H 6.27, 1H). HRMS analysis revealed a sodium adduct ion consistent with a molecular formula of $C_{15}H_{19}NO_3$. In combination with 2D NMR analysis (Supporting Information), this was sufficient to establish the structure as shown (**17**). The structure of the side product from the methoxylated amide **30** was established in a similar manner (**16**). In order to broaden the structural diversity of these unusual side products for later biological investigations, two additional analogues were produced by base-catalyzed cyclization of the sulfur-containing amides **27** and **29**, synthesized previously, to yield the quinolones **18** and **19**.

Carboxylic acids lacking double bonds were readily condensed with 2′-aminoacetophenone using EDCI as the condensing agent (Scheme 4).[24] In this manner, the amides **32** and **33** were produced by condensation of the appropriate

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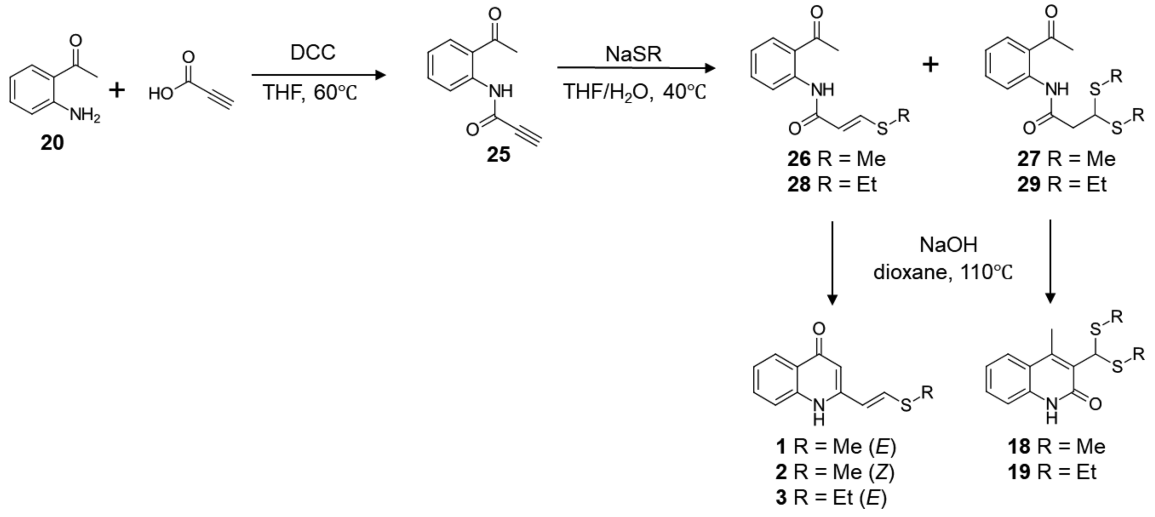
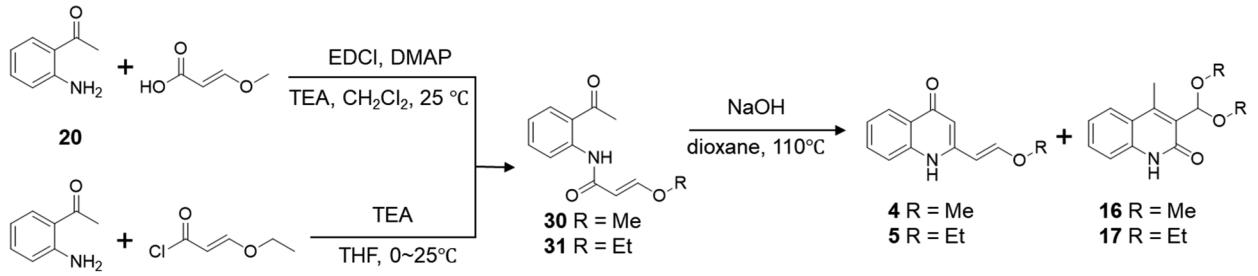
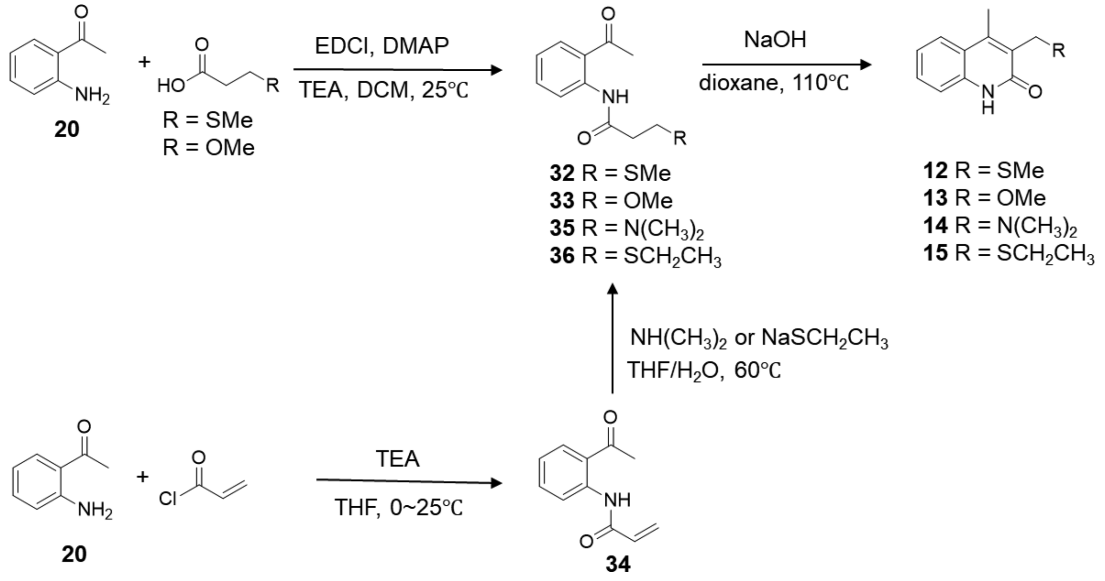
Scheme 2. Synthesis of the Natural Product 1 and Related Sulfur-Containing Quinolones



Scheme 3. Synthesis of Quinolones with Oxygen-Containing Side Chains



Scheme 4. Synthesis of 2(1*H*)-Quinolones 12−15



carboxylic acid with 2′-aminoacetophenone in high yield. Addition of $NH(CH_3)_2$ and $NaSCH_2CH_3$ to the amide **34** yielded further amides **35** and **36**. All four amides were cyclized under basic conditions; unfortunately, the desired cyclization did not take place, leading to the formation of 2(1*H*)-quinolones (**12**−**15**) instead of the desired quinolin-4-ones (Scheme 4). Nevertheless, some 2(1*H*)-quinolones have been shown to possess significant activity against microbial pathogens,[25] and as such the compounds were retained for testing.

Thus, an alternative synthetic approach was required for the synthesis of the remaining quinolones. The 2-(chloromethyl)-quinolone scaffold was formed by the Conrad−Limpach approach[20] in high yield (Scheme 5). Aniline (**23**) was condensed with dimethylacetylene dicarboxylate (**24**) in MeOH at reflux to furnish diester **37**, which underwent polyphosphoric acid (PPA)-promoted intramolecular Friedel−

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Scheme 5. Synthesis of 4-Quinolones 6−11 via Suzuki−Miyaura Cross-Coupling

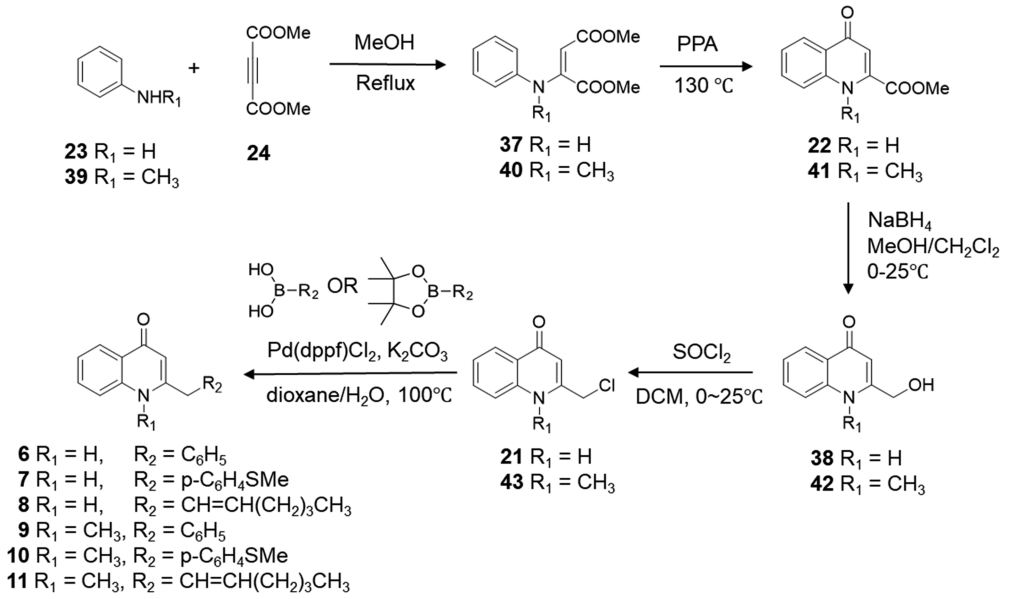

Table 1. Zone of Inhibition (mm) of Active Quinolones against Test Bacteria in Well Diffusion Assays[a]

compound	*Staphylococcus aureus* ATCC 12600	*Staphylococcus epidermidis* ATCC 14990	*Pseudomonas aeruginosa* ATCC 15692	*Bacillus subtilis subsp. spizizenii* ATCC 6633
1	–	–	–	23*
3	13*	–	–	–
7	–	–	29*	–
8	9*	24*	35*	9*
10	–	–	36*	–
ampicillin	39	29	n/t	n/t
ciprofloxacin	n/t	n/t	34	n/t
vancomycin	n/t	n/t	n/t	19

[a]– = no activity; n/t = not tested; * = inhibition halo was hazy/indistinct.

Crafts acylation to obtain 1,4-dihydroquinoline-2-carboxylate **22**. The subsequent reduction of the ester in the presence of sodium borohydride afforded the alcohol **38** in good yield. Substitution of the hydroxy group by chlorination with thionyl chloride led to the formation of the halide-substituted quinolone core **21** in good yield.

In order to produce the quinolone targets, a Suzuki−Miyaura coupling reaction with boronic acid derivatives was used. Commercially available pinacolboronates and boronic acids were reacted with the halide-substituted quinolone **21** under the catalytic action of a dichloro(1,1′-bis-(diphenylphosphanyl)ferrocene)palladium(II) complex, leading to the formation of desired products (**6**−**8**) in good yields. Spectroscopic data for **6** and **8** matched well with literature values for the natural products.[22] The corresponding 1-methyl-substituted quinolones (**9**−**11**) were synthesized using the same methodology from *N*-methylaniline (**39**).

Biological Testing. All quinolones were subjected to preliminary antimicrobial screening using well-diffusion assays against a range of eight Gram-positive and Gram-negative test microbes (Supporting Information Table S1). A small number of quinolones displayed activity in these assays, with **1** displaying activity against *B. subtilis* and **3** against *S. aureus*, while **7** and **10** showed significant inhibition halos against *P. aeruginosa* (Table 1). Most notable though was the unsaturated side chain quinolone **8**, which displayed activity against four of the tested strains. Results for the active compounds showed a distinctive hazy zone of inhibition (Supporting Information Figure S1). Such an effect can be associated with overlong growth times or an excessively concentrated inoculum, but the results were reproducible even with shorter growth times and a more dilute inoculum. Thus, this might represent partial growth inhibition, rather than a bactericidal effect. PQS itself is known to inhibit the growth of *P. aeruginosa*, so it was possible these compounds were exhibiting a similar effect.[26]

In order to further investigate this effect, selected quinolones were assessed for their effects in a growth inhibition assay against *P. aeruginosa*. While the majority of the quinolones tested did not act as straightforward bacteriocides, with residual growth observed even at high concentrations, several of them nevertheless significantly inhibited the growth of *P. aeruginosa*. (Figure 1). The natural product **8** showed strong growth inhibition at all tested concentrations, while the remainder of the 4-quinolones delayed the growth of *P. aeruginosa* by 37−58% at concentrations between 2.1 and 33.4 μg/mL. Compound **8** has been shown to possess antimicrobial properties in a prior report, against the fish pathogen *Tenacibaculum maritimum*.[27] In contrast, the 2(1*H*)-quinolones **18** and **19** had minimal activity.

In order to further assess the effects of the compounds over time, time−kill experiments were conducted on compound **8**, as it was the only compound giving a measurable MIC value

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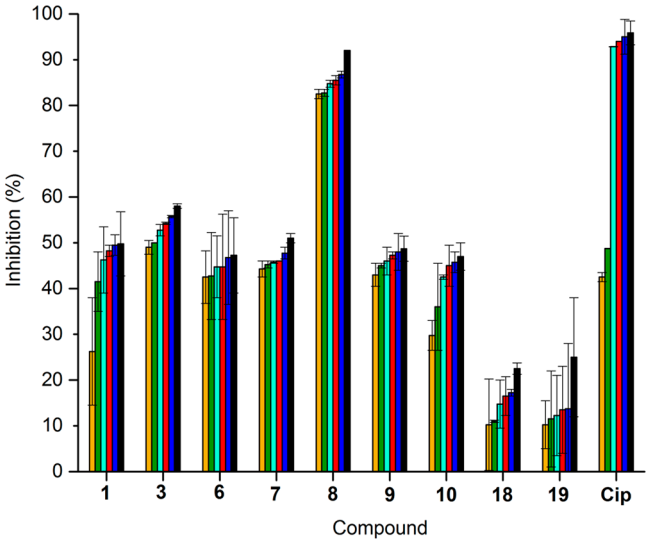

Figure 1. Inhibition of selected compounds against *P. aeruginosa* ATCC 15692, with ciprofloxacin (Cip) as the positive control. For each compound, the six columns from left to right represent the extent of inhibition at final concentrations of 1.1 (yellow), 2.1 (dark green), 4.2 (pale green), 8.4 (pink), 16.7 (blue), and 33.4 (deep purple) μg/mL, respectively.

(33 μg/mL). At 1/4 the MIC value, significant inhibition of growth was observed, with a small drop in CFU values observed after 2 h and very little growth observed out to 24 h (Figure 2). At the MIC value, similar but more dramatic effects were observed, with LogCFU values decreasing steadily until 10 h, before stabilizing. Even at very high concentrations (4 × MIC), while a rapid decrease in CFU values was observed initially, viable bacteria were still detectable after 24 h, in contrast to the positive control (ciprofloxacin). Other quinolones have been shown to possess similar growth inhibitory effects: several *Pseudonocardia*-derived isoprenylated 4-quinolones have shown a similar effect against *E. coli* and *S. aureus* strains, where a significant delay in the onset of growth was observed, though they did not affect the growth of *P. aeruginosa*.[20] In contrast, a sulfur-containing derivative of PQS did not possess any significant growth inhibitory properties,[14] highlighting the very specific substitution patterns required for this activity.

Previous studies have shown that alkylquinolones can affect the swarming motility in a number of microbial species. Swarming motility is the movement of bacteria across a semisolid surface, a process that is involved in both the virulence and antibiotic resistance of many bacterial species.[28] PQS itself is a potent inhibitor of swarming behavior in both *P. aeruginosa* and other Gram-negative and -positive bacteria, while HHQ exhibits more moderate effects.[29,30] Prior synthetic studies have shown that the substitution at the 3-position is also crucial for activity, with a suite of C-3 halogenated derivatives lacking activity against *B. subtilis* swarming motility.[16] In a subsequent study, a range of derivatives substituted at different points around the aromatic ring were produced, with 6-substituted analogues displaying potent activity in inhibiting swarming behavior in *B. atrophaeus*.[17] However, the effect of changing the C-2 substituent has not been investigated in detail to date. Thus, the activity of the quinolones **1**−**19** against the swarming behavior of *B. subtilis* was assessed. Of the 4-quinolones, **6**, **8**, **10**, and **11** possessed comparable swarming inhibition activity to HHQ, while the aromatic sulfide derivative **7** had significantly enhanced activity (Figure 3). 4-Quinolones containing a shorter side chain (**1**−**5**) had weak antiswarming activity; those with a longer chain (**8**) or a bulky aromatic substituent (**6**, **7**) were more active. The effect of *N*-methylation was less clear: *N*-methylated derivatives **9** and **10** lost activity compared to their nonmethylated analogues, though compound **11** did not. For the 2-quinolones, all of the acetal and thioacetal derivatives (**16**−**19**) possessed weak activity, while ether- and sulfide-substituted quinolones **12**, **13**, and **15** were of similar or greater potency to HHQ. Compound **14** possessed significantly lower activity than the former three compounds, which might be attributed to the presence of the ionizable amine group in the side chain of **14**.

Overall, these studies further elucidate the numerous ways in which the alkylquinolones can affect the growth and mobility

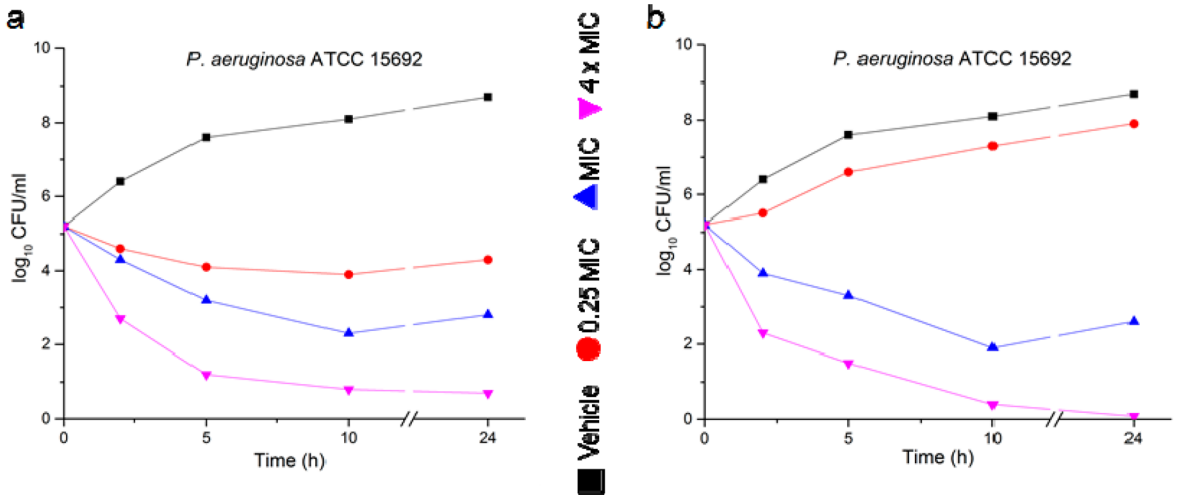

Figure 2. Time−kill curves of compound **8** (a) in comparison with ciprofloxacin (b) showing colony forming units (CFUs) for *P. aeruginosa* ATCC 15692 at different time points. *P. aeruginosa* were supplemented with compound **8** and ciprofloxacin at 0.25 × MIC (red line), at the MIC (MIC, blue line), and at four times the MIC (4 × MIC, purple line) or DMSO (vehicle) (black line). The MIC for **8** was 33 μg/mL, while the MIC value for ciprofloxacin was 4 μg/mL.

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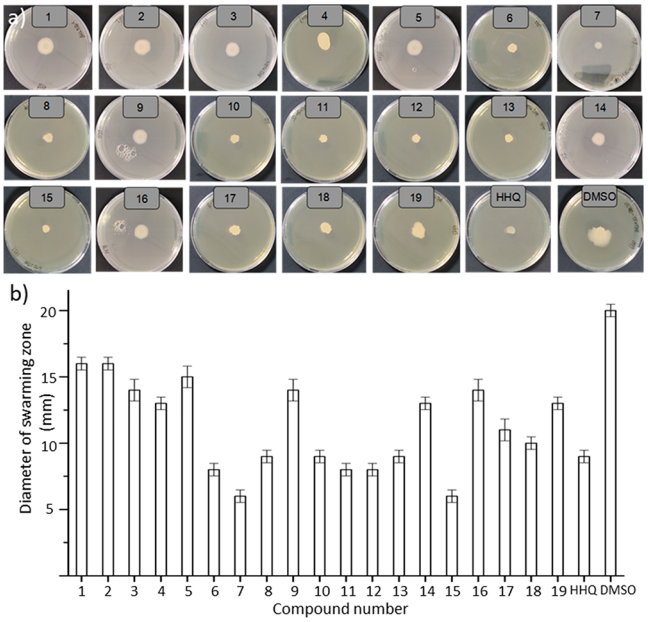

Figure 3. Effect of quinolones **1**–**19** (10 μM) on swarming motility of *B. subtilis* on BHI agar. (a) Visual representation of the data showing representative plates; (b) average diameter of swarming zone from three replicates.

of microbial species. The results suggest that further investigation of aromatic-substituted 4-quinolones may be valuable in the discovery of compounds interfering with bacterial growth and swarming behavior, while the serendipitously obtained 2(1*H*)-quinolones provide an additional avenue of research.

EXPERIMENTAL SECTION

General Experimental Procedures. NMR spectra were recorded on a Bruker Avance III 400 spectrometer and a Bruker Avance III 600 spectrometer with tetramethylsilane as an internal reference. HRESIMS spectra were obtained using a Thermo Fisher Q Exactive HF mass spectrometer or an Agilent 6230 HPLC system with a Bruker microTOF-QII mass spectrometer. Low-resolution MS spectra were acquired using an Agilent 6430 Triple-Quadrupole instrument. HPLC analysis was performed on an Agilent 1260 series HPLC system equipped with a G1311B quaternary pump, a G1315D photodiode array detector, a G1316C thermostated column compartment, and a G1329B autosampler, using a reversed-phase ZORBAX SB-C18 column (3.5 μm, 4.6 × 150 mm; Agilent Technologies). Semipreparative HPLC separation was carried out on a Shimadzu LC-20AR series HPLC instrument equipped with a UV detector and a reversed-phase C18 column (ZORBAX SB-C18, 5 μm, 9.4 × 250 mm). Reagents and solvents used in this study were commercially available (Jiangtian, Heowns, Concord Tianjin). All reactions were monitored by TLC using commercial silica gel plates.

*N-(2-Acetylphenyl)propiolamide (**25**).* A mixture of 1-(2-aminophenyl)ethanone **20** (0.5 g, 3.7 mmol), propiolic acid (0.28 g, 4.1 mmol), and DCC (1.14 g, 5.55 mmol) in THF was heated at 60 °C for 12 h. The reaction mixture was evaporated under reduced pressure, transferred into a separatory funnel, and extracted with H_2O (70 mL) and EtOAc (3 × 50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (hexanes–EtOAc, 25:1 to 5:1) to give the amide **25** as a yellow solid (0.40 g, 55%). A small amount of an *N*-acylurea impurity was present, but the material was used directly for the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 3H), 2.95, (s, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 7.9 Hz, 1H), 7.92 (dd, J = 8.0, 1.5 Hz, 1H), 8.66 (d, J = 8.2 Hz, 1H), 12.12 (s, 1H); ESIMS m/z 188.07 $[M + H]^+$.

*(E)-N-(2-Acetylphenyl)-3-(methylthio)acrylamide (**26**) and N-(2-Acetylphenyl)-3,3-bis(methylthio)propanamide (**27**).* A mixture of compound **25** (100.0 mg, 0.53 mmol) and 20% sodium methanethiol solution (39.3 mg, 0.56 mmol) in THF was heated at 40 °C for 4 h. The mixture was evaporated under reduced pressure, transferred into a separatory funnel, and extracted with H_2O (30 mL) and EtOAc (3 × 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (hexanes–EtOAc, 25:1 to 5:1) to give amide **26** (98.2 mg, 79%) as a pale yellow solid and **27** (25.0 mg, 16%) as a white gum. When the amount of sodium methanethiol was doubled and the temperature increased to 60 °C, the yield of compound **27** was 65%.

Compound **26**: ^{1}H NMR (400 MHz, methanol-d_4) δ 2.43 (s, 3H), 2.65 (s, 3H), 5.91 (d, J = 14.6 Hz, 1H), 7.18 (t, J = 8.7 Hz, 1H), 7.55 (t, J = 8.6 Hz, 1H), 7.76 (d, J = 14.6 Hz, 1H), 8.02 (dd, J = 8.0, 1.3 Hz, 1 H), 8.57 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 14.5, 28.7, 117.4, 121.9, 124.0, 124.3, 133.1, 135.6, 141.5, 146.4, 165.3, 204.6; HRESIMS m/z 258.0549 $[M + Na]^+$ (calcd for $C_{12}H_{13}NO_2S$, 258.0559).

Compound **27**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.17 (s, 6H), 2.67 (s, 3H), 2.88 (d, J = 7.5 Hz, 2H), 4.27 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 8.1 Hz, 1H), 7.90 (dd, J = 8.0, 1.4 Hz, 1H), 8.76 (d, J = 8.1 Hz, 1H), 11.83 (s, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.2, 28.7, 44.8, 50.2, 121.1, 122.0, 122.8, 131.8, 135.4, 140.9, 168.6, 203.1; HRESIMS m/z 306.0592 $[M + Na]^+$ (calcd for $C_{13}H_{17}NO_2S_2$, 306.0593).

*(E)-N-(2-Acetylphenyl)-3-(ethylthio)acrylamide (**28**) and N-(2-Acetylphenyl)-3,3-bis(ethylthio)propanamide (**29**).* The procedure was the same as for the synthesis of compounds **26** and **27**, using sodium ethanethiolate (47.0 mg, 0.56 mmol). Compound **28** (103.0 mg, 78%) as a pale yellow solid and compound **29** (28.2 mg, 17%) were isolated. When the amount of sodium ethanethiolate was doubled and the solution was heated at 60 °C, the yield of compound **29** was 67%.

Compound **28**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.37 (t, J = 7.4 Hz, 3H), 2.66, (s, 3H), 2.86 (q, J = 7.4 Hz, 2H), 5.92 (d, J = 14.8 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.72 (d, J = 14.8 Hz, 1H), 7.88 (dd, J = 8.0, 1.5 Hz, 1H), 8.82 (dd, J = 8.5, 1.0 Hz, 1H), 11.73 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 26.5, 28.7, 117.8, 121.0, 121.8, 122.2, 131.8, 135.3, 141.7, 144.3, 163.6, 203.0; ESIMS m/z 250.08 $[M + H]^+$.

Compound **29**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.28 (t, J = 7.4 Hz, 6H), 2.66, (s, 3H), 2.62–2.78 (m, 4H), 2.91 (d, J = 7.4 Hz, 2H), 4.40 (t, J = 7.4 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.9 Hz, 1H), 7.90 (dd, J = 8.0, 1.5 Hz, 1H), 8.76 (dd, J = 8.5, 0.9 Hz, 1H), 11.82 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.6, 24.9, 28.7, 46.1, 46.7, 121.0, 122.0, 122.7, 131.7, 135.3, 140.9, 168.8, 203.0; ESIMS m/z 312.16 $[M + H]^+$.

General Procedure A for the Synthesis of Amides. A mixture of 1-(2-aminophenyl)ethanone **20** (0.5 g, 3.7 mmol), acid (4.1 mmol), EDCI (0.85 g, 4.44 mmol), 4-dimethylaminopyridine (DMAP) (45.0 mg, 0.37 mmol), and triethylamine (TEA) (0.77 mL, 5.6 mmol) in CH_2Cl_2 was stirred overnight at room temperature (rt). The mixture was transferred into a separatory funnel and extracted with H_2O (30 mL) and CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (hexanes–EtOAc, 25:1 to 5:1).

*(E)-N-(2-Acetylphenyl)-3-methoxyacrylamide (**30**).* General procedure A using (*E*)-3-methoxyacrylic acid (0.42 g, 4.1 mmol) yielded compound **30** (0.44 g, 54%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.73, (s, 3H), 5.38 (d, J = 12.2 Hz, 1H), 7.08 (t, J = 7.8, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.69 (d, J = 12.2 Hz, 1H), 7.88 (dd, J = 8.0, 1.4 Hz, 1H), 8.81 (dd, J = 8.6, 1.2 Hz, 1H), 11.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8, 57.6, 99.8, 121.0, 121.6, 122.0, 131.8, 135.3, 141.8, 161.9, 165.9, 203.0; HRESIMS m/z 242.0794 $[M + Na]^+$ (calcd for $C_{12}H_{13}NO_3$, 242.0788).

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*(E)-N-(2-Acetylphenyl)-3-ethoxyacrylamide (**31**).* A solution of 1-(2-aminophenyl)ethanone **20** (0.2 g, 1.5 mmol) and TEA (0.27 mL, 1.9 mmol) in THF was added dropwise to a solution of (*E*)-3-ethoxyacryloyl chloride (0.22 g, 1.6 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 4 h. Then the mixture was evaporated under reduced pressure, transferred into a separatory funnel, and extracted with H_2O (50 mL) and EtOAc (3 × 30 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give amide **31** (342.1 mg, 98%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7.1 Hz, 3H), 2.66 (s, 3H), 3.95 (q, J = 7.1 Hz, 2H), 5.39 (d, J = 12.2 Hz, 1H), 7.07 (t, J = 7.6, 1H), 7.53 (t, J = 7.9 Hz, 1H), 7.65 (d, J = 12.2 Hz, 1H), 7.88 (dd, J = 8.0, 1.4 Hz, 1H), 8.81 (dd, J = 8.6, 1.2 Hz, 1H), 11.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 28.7, 67.1, 100.3, 121.0, 121.6, 121.9, 131.8, 135.3, 141.9, 161.1, 166.2, 203.0; HRESIMS m/z 256.0960 $[M + Na]^+$ (calcd for $C_{13}H_{15}NO_3$, 256.0944).

*N-(2-Acetylphenyl)-3-(methylthio)propanamide (**32**).* Following general procedure A, using 3-(methylthio)propionic acid (0.49 g, 4.1 mmol) as a starting material, compound **32** (0.81 g, 92%) was obtained as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.56 (s, 3H), 2.65 (t, J = 7.0 Hz, 2H), 2.80 (t, J = 7.0 Hz, 1H), 7.02 (t, J = 7.7, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 8.65 (d, J = 8.0, Hz, 1H), 11.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 28.4, 29.4, 38.2, 120.5, 121.5, 122.3, 131.5, 135.0, 140.6, 170.3, 202.7; HRESIMS m/z 260.0708 $[M + Na]^+$ (calcd for $C_{12}H_{15}NO_2S$, 260.0716).

*N-(2-Acetylphenyl)-3-methoxypropanamide (**33**).* Following general procedure A, using 3-(methoxy)propionic acid (0.42 g, 4.0 mmol) as a starting material, compound **33** (0.77 g, 95%) was obtained as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3H), 2.68 (t, J = 6.0 Hz, 2H), 3.39 (s, 3H), 3.75 (t, J = 6.0 Hz, 2H), 7.08 (m, 1H), 7.51 (m, 1H), 7.85 (t, J = 6.6 Hz, 1H), 8.74 (dd, J = 8.5, 4.8 Hz, 1H), 11.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 39.2, 58.9, 68.3, 121.0, 122.1, 122.5, 131.6, 135.1, 140.8, 170.5, 202.6; ESIMS m/z 222.12 $[M + H]^+$.

*N-(2-Acetylphenyl)acrylamide (**34**).* Using the same procedure as for the synthesis of compound **31**, using 1-(2-aminophenyl)ethanone **20** (0.16 g, 1.2 mmol) and acryloyl chloride (0.12 g, 1.3 mmol) yielded the amide **34** (227.6 mg, 98%) as a white semisolid solid: ^{1}H NMR analysis revealed the presence of minor impurities remaining; the compound was used without additional purification in subsequent reactions. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.68 (s, 3H), 5.79 (dd, J = 10.3, 1.0 Hz, 1H), 6.32 (dd, J = 17.1, 10.3 Hz, 1H), 6.43 (dd, J = 17.1, 1.0 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.92 (dd, J = 8.0, 1.5 Hz, 1H), 8.85 (dd, J = 8.5, 1.0 Hz, 1H), 11.98 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.6, 120.9, 121.9, 122.7, 127.4, 131.8, 132.6, 135.2, 141.1, 164.5, 203.0; HRESIMS m/z 212.0695 $[M + Na]^+$ (calcd for $C_{11}H_{11}NO_2$, 212.0682).

*N-(2-Acetylphenyl)-3-(dimethylamino)propanamide (**35**).* A mixture of compound **34** (100.0 mg, 0.53 mmol) and a 40% dimethylamine aqueous solution (112.5 mg, 1.0 mmol) in THF was heated at 60 °C for 4 h. The mixture was evaporated under reduced pressure and transferred into a separatory funnel and extracted with water (30 mL) and EtOAc (3 × 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (hexanes−EtOAc, 25:1 to 5:1) to give amide **35** (117.8 mg, 95%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 6H), 2.53 (t, J = 6.9 Hz, 2H), 2.57 (s, 3H), 2.66 (t, J = 6.9 Hz, 2H), 7.02 (t, J = 7.6, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.79 (dd, J = 8.0, 1.4 Hz, 1H), 8.64 (dd, J = 8.5, 0.8 Hz, 1H), 11.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6, 36.5, 46.1, 54.9, 121.0, 122.3, 122.3, 131.4, 134.8, 140.5, 171.1, 202.4; HRESIMS m/z 235.1418 $[M + H]^+$ (calcd for $C_{13}H_{19}N_2O_2$, 235.1441).

*N-(2-Acetylphenyl)-3-(ethylthio)propanamide (**36**).* A mixture of compound **34** (100.0 mg, 0.53 mmol) and sodium ethanethiolate (54.0 mg, 0.64 mmol) in THF−H_2O was heated at 60 °C for 4 h. The mixture was evaporated under reduced pressure, transferred into a separatory funnel, and extracted with water (30 mL) and EtOAc (3 × 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (hexanes−EtOAc, 25:1 to 5:1) to give amide **36** (127.7 mg, 96%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.4 Hz, 3H), 2.55 (q, J = 7.4 Hz, 2H), 2.61 (s, 3H), 2.67 (t, J = 7.4 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H), 7.06 (t, J = 7.6, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 8.70 (d, J = 8.5 1H), 11.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 26.0, 26.9, 28.6, 38.8, 120.7, 121.6, 122.4, 131.6, 135.1, 140.8, 170.5, 202.8; ESIMS m/z 274.08 $[M + H]^+$.

General Procedure B for Base-Promoted Cyclization. A resealable oven-dried test tube with a stir bar was charged with *N*-(ketoaryl)amide (1 equiv) and crushed NaOH (3 equiv). Anhydrous 1,4-dioxane was added via syringe and the flask charged with argon gas. Then the reaction was placed in a preheated oil bath at 110 °C, stirred for 1−2 h, and then cooled to rt. The reaction mixture was then dissolved in MeOH, transferred to a round-bottom flask, and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (CH_2Cl_2−MeOH, 100:0 to 10:1).

*(E)- and (Z)-2-(2-(Methylthio)vinyl)quinolin-4(1H)-one (**1** and **2**).* Following general procedure B with compound **26** (36 mg, 0.15 mmol) as starting material produced an organic residue that was purified by silica gel flash chromatography (CH_2Cl_2−MeOH, 100:0 to 10:1) and semipreparative HPLC with 15% MeCN−H_2O to 50% MeCN−H_2O to yield compound **1** as a white solid (15 mg, 45%) and **2** as a white solid (3 mg, 10%).

Compound **1**: ^{1}H NMR (400 MHz, methanol-d_4) δ 2.47 (s, 3H), 6.18 (d, J = 15.5 Hz, 1H), 6.37 (s, 1H), 7.36 (t, J = 7.4 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.68 (d, J = 15.5 Hz, 1 H), 8.17 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 14.4, 105.5, 116.4, 119.1, 125.1, 125.8, 125.9, 133.5, 139.6, 141.4, 149.9, 180.3; HRESIMS m/z 218.0634 $[M + H]^+$ (calcd for $C_{12}H_{11}NOS$, 218.0634).

Compound **2**: ^{1}H NMR (400 MHz, methanol-d_4) δ 2.55 (s, 3H), 6.31 (d, J = 11.2 Hz, 1H), 6.74 (s, 1H), 7.08 (d, J = 11.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.69 (ddd, J = 8.4, 7.0, 1.4 Hz, 1 H), 8.20 (d, J = 8.3 Hz, 1H); HRESIMS m/z 218.0634 $[M + H]^+$ (calcd for $C_{12}H_{11}NOS$, 218.0634).

*(E)-2-(2-(Ethylthio)vinyl)quinolin-4(1H)-one (**3**).* Following general procedure B with compound **28** (44 mg, 0.18 mmol) as starting material, compound **3** was obtained as a pale yellow solid (18 mg, 44%): ^{1}H NMR (600 MHz, methanol-d_4) δ 1.38 (t, J = 7.4, 3H), 2.94 (q, J = 7.5, 2H), 6.26 (d, J = 15.7 Hz, 1H), 6.34 (s, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 15.8 Hz, 1 H), 7.64 (t, J = 7.8 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H); ^{13}C NMR (150 MHz, methanol-d_4) δ 14.6, 27.0, 105.5, 117.5, 119.1, 125.0, 125.8, 125.9, 133.4, 139.2, 141.4, 149.9, 180.2; HRESIMS m/z 232.0790 $[M + H]^+$ (calcd for $C_{13}H_{13}NOS$, 232.0791).

*3-(Bis(methylthio)methyl)-4-methylquinolin-2(1H)-one (**18**).* Following general procedure B, with compound **27** (35 mg, 0.12 mmol) as starting material, compound **18** was obtained as a pale yellow solid (24 mg, 74%): ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.20 (s, 6H), 2.68 (s, 3H), 5.78 (s, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1 H), 11.89 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 16.6, 28.9, 48.2, 115.2, 120.1, 121.9, 124.7, 129.6, 130.3, 137.1, 145.9, 160.4; HRESIMS m/z 288.0489 $[M + Na]^+$ (calcd for $C_{13}H_{15}NOS_2$, 288.0487).

*3-(Bis(ethylthio)methyl)-4-methylquinolin-2(1H)-one (**19**).* Following general procedure B, with compound **29** (18 mg, 0.06 mmol) as starting material, compound **19** was obtained as a pale yellow solid (12 mg, 73%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.4 Hz, 6H), 2.74 (q, J = 7.4 Hz, 4H), 2.81 (s, 3H), 6.16 (s, 1H), 7.24 (t, J = 7.4, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 8.5 1H), 12.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 28.0, 29.8, 43.7, 116.2, 121.6, 122.7, 124.7, 130.4, 130.8, 137.0, 148.2, 162.7; HRESIMS m/z 316.0802 $[M + Na]^+$ (calcd for $C_{15}H_{19}NOS_2$, 316.0800).

*(E)-2-(2-Methoxyvinyl)quinolin-4(1H)-one (**4**) and 3-(Dimethoxymethyl)-4-methylquinolin-2(1H)-one (**16**).* Following general procedure B, with compound **30** (30 mg, 0.12 mmol) as starting material,

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yielded compound **4** as a white solid (5 mg, 23%) and compound **16** as a pale yellow solid (21 mg, 48%).

Compound **4**: ^{1}H NMR (600 MHz, methanol-d_4) δ 3.82 (s, 3H), 5.79 (d, J = 12.9 Hz, 1H), 6.35 (s, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 12.9 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1 H), 8.18 (dd, J = 8.2, 1.1 Hz, 1H); ^{13}C NMR (150 MHz, methanol-d_4) δ 58.2, 99.8, 104.5, 118.9, 124.9, 125.7, 125.9, 133.3, 141.5, 151.4, 157.8, 180.0; HRESIMS m/z 202.0859 [M + H]$^+$ (calcd for $C_{12}H_{11}NO_2$, 202.0863).

Compound **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 3H), 3.54 (s, 6H), 6.08 (s, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.80 (d, J = 8.1, Hz, 1 H), 12.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 56.2, 102.0, 116.3, 121.5, 122.6, 125.0, 126.7, 130.6, 137.8, 149.1, 163.8; HRESIMS m/z 256.0943 [M + Na]$^+$ (calcd for $C_{13}H_{15}NO_3$, 256.0944).

*(E)-2-(2-Ethoxyvinyl)quinolin-4(1H)-one (**5**) and 3-(Diethoxymethyl)- 4-methylquinolin-2(1H)-one (**17**).* Following general procedure B, with compound **31** (40 mg, 0.17 mmol) as the starting material, yielded compound **5** as a white solid (10 mg, 28%) and compound **17** as a pale yellow solid (19 mg, 45%).

Compound **5**: ^{1}H NMR (600 MHz, methanol-d_4) δ 1.36 (t, J = 7.0 Hz, 3H), 4.04 (q, J = 7.0 Hz, 2H), 5.75 (d, J = 12.8 Hz, 1H), 6.33 (s, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.62 (d, J = 12.8 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1 H), 8.16 (d, J = 8.3 Hz, 1H); ^{13}C NMR (150 MHz, methanol-d_4) δ 15.0, 68.2, 100.2, 104.2, 118.9, 124.9, 125.6, 125.8, 133.2, 141.4, 151.6, 157.2, 179.8; HRESIMS m/z 216.1020 [M + H]$^+$ (calcd for $C_{13}H_{13}NO_2$, 216.1019).

Compound **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 6H), 2.78 (s, 3H), 3.62 (dq, J = 9.5, 7.0 Hz, 2H), 3.87 (dq, J = 9.5, 7.1 Hz, 2H), 6.27 (s, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1 H), 12.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 15.5, 63.9, 98.9, 116.3, 121.7, 122.5, 124.9, 127.8, 130.4, 137.8, 148.9, 163.8; HRESIMS m/z 284.1255 [M + Na]$^+$ (calcd for $C_{15}H_{19}NO_3$, 284.1257).

*4-Methyl-3-((methylthio)methyl)quinolin-2(1H)-one (**12**).* Following general procedure B, using compound **32** (375 mg, 1.58 mmol) as starting material, compound **12** was obtained as a pale yellow solid (312 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.58 (s, 3H), 3.96 (s, 2H), 7.23 (ddd, J = 8.3, 7.1, 1.2 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.49 (ddd, J = 8.3, 7.2, 1.3 Hz, 1H), 7.73 (dd, J = 8.2, 1.0 Hz, 1 H), 11.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 16.0, 29.2, 116.3, 121.0, 122.6, 124.7, 128.0, 130.1, 137.2, 145.5, 163.4; HRESIMS m/z 242.0610 [M + Na]$^+$ (calcd for $C_{12}H_{13}NOS$, 242.0610).

*3-(Methoxymethyl)-4-methylquinolin-2(1H)-one (**13**).* Following general procedure B, using **33** (535 mg, 2.42 mmol) as a starting material, compound **13** was obtained as a pale yellow solid (432 mg, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 3.47 (s, 3H), 4.70 (s, 2H), 7.23 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1 H), 11.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 58.5, 65.6, 116.2, 120.9, 122.6, 125.0, 126.7, 130.6, 137.8, 148.8, 163.6; HRESIMS m/z 226.0838 [M + Na]$^+$ (calcd for $C_{12}H_{13}NO_2$, 226.0838).

*3-((Dimethylamino)methyl)-4-methylquinolin-2(1H)-one (**14**).* Following general procedure B, using compound **35** (23 mg, 0.10 mmol) as a starting material, **14** was obtained as a pale yellow solid (19 mg, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 6H), 2.61 (s, 3H), 3.68 (s, 2H), 7.21 (t, J = 7.7 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1 H), 12.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 45.5, 53.8, 116.3, 121.0, 122.4, 124.8, 127.3, 130.1, 137.7, 147.8, 164.3; HRESIMS m/z 217.1336 [M + H]$^+$ (calcd for $C_{13}H_{16}N_2O$, 217.1335).

*3-((Ethylthio)methyl)-4-methylquinolin-2(1H)-one (**15**).* Following general procedure B, using compound **36** (27 mg, 0.11 mmol) as a starting material, compound **15** was obtained as a pale yellow solid (23 mg, 92%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.35 (t, J = 7.4 Hz, 3H), 2.57 (s, 3H), 2.70 (q, J = 7.4 Hz, 2H), 4.00 (s, 2H), 7.22 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.47 (ddd, J = 8.2, 7.1, 1.3 Hz, 1H), 7.71 (dd, J = 8.2, 0.9 Hz, 1 H), 12.63 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.1, 26.8, 27.2, 29.8, 116.4, 121.0, 122.5, 124.6, 128.5, 130.0, 137.3, 145.4, 163.5; HRESIMS m/z 256.0766 [M + Na]$^+$ (calcd for $C_{13}H_{15}NOS$, 256.0767).

*Dimethyl 2-(Phenylamino)maleate (**37**).* To a solution of aniline (**23**) (3.0 g, 32.2 mmol) in MeOH was added dimethylacetylene dicarboxylate (5.3 g, 37.1 mmol), and the mixture was stirred for 12 h at reflux. MeOH was evaporated, CH_2Cl_2 was added (200 mL), and the mixture was washed with saturated aqueous NH_4Cl (2 × 100 mL) and H_2O (2 × 100 mL), dried over $MgSO_4$, and evaporated under reduced pressure to obtain the product **37** as a yellow oil (7.4 g, 98%): ^{1}H NMR analysis revealed the presence of minor impurities remaining; the compound was used without additional purification in subsequent reactions. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 3.69 (s, 3H), 5.38 (s, 1H), 6.87 (d, J = 7.6 Hz, 2H), 7.05 (t, J = 7.4 Hz, 1H), 7.24 (t, J = 7.6 Hz, 2H), 9.68 (s, 1H); ^{13}C NMR data (100 MHz, $CDCl_3$) δ 51.0, 52.5, 93.3, 120.5, 124.0, 129.0, 140.1, 147.8, 164.6, 169.6; HRESIMS m/z 236.0925 [M + H]$^+$ (calcd for $C_{12}H_{13}NO_4$, 236.0917).

*Methyl 4-Oxo-1,4-dihydroquinoline-2-carboxylate (**22**).* A mixture of **37** (5.2 g, 22.1 mmol) and PPA (25.0 g) were heated at 130 °C for 4 h. The resulting slurry was poured into an iced saturated aqueous solution of $NaHCO_3$. The precipitate was filtered and washed with H_2O and Et_2O; the product was obtained as a white solid (4.1 g, 90%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.92 (s, 3H), 6.70 (s, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H); ^{13}C NMR data (100 MHz, DMSO-d_6) δ 53.1, 109.3, 121.9, 123.8, 124.5, 126.3, 131.7, 140.5, 142.5, 163.9, 176.1; ESIMS m/z 204.06 [M + H]$^+$.

*2-(Hydroxymethyl)quinolin-4(1H)-one (**38**).* To a solution of **22** (1.0 g, 4.9 mmol) in a 1:1 mixture of CH_2Cl_2–MeOH (20 mL) was added $NaBH_4$ (0.9 g, 24.5 mmol) at 0 °C. The reaction was left to stir for 2 h at 0 °C and at rt for an additional 2 h. After this time, EtOAc (20 mL) was added at 0 °C followed by the addition of MeOH (10 mL), and the mixture was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (CH_2Cl_2–MeOH, 100:0 to 10:1) to give the product as a white solid (0.4 g, 48%): ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.50 (d, J = 5.9, 2H), 5.76 (t, J = 5.9, 1H), 6.05 (s, 1H), 7.27 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.60 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 8.05 (d, J = 6.9 Hz, 1H), 11.53 (s, 1H); ^{13}C NMR data (150 MHz, DMSO-d_6) δ 60.2, 105.4, 118.3, 122.8, 124.8, 125.1, 131.5, 140.0, 153.2, 177.0; HRESIMS m/z 176.0722 [M + H]$^+$ (calcd for $C_{10}H_{10}NO_2$, 176.0706).

*2-(Chloromethyl)quinolin-4(1H)-one (**21**).* To a solution of **38** (0.2 g, 1.1 mmol) in CH_2Cl_2 was added thionyl chloride (0.83 mL, 11.0 mmol) at 0 °C. The reaction was left to stir at rt for 2 h; then the mixture was evaporated under reduced pressure. A solution of saturated $NaHCO_3$ was added to adjust the pH to 10, and the solid was washed with H_2O and dried to obtain the desired product as a white solid (0.20 g, 98%): ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.71 (s, 2H), 6.20 (s, 1H), 7.32 (t, J = 7.4 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.66 (ddd, J = 7.6, 6.9, 1.4 Hz, 1H), 8.05 (d, J = 8.7 Hz, 1H), 11.91 (s, 1H); ^{13}C NMR data (150 MHz, DMSO-d_6) δ 42.5, 108.9, 118.3, 123.3, 124.8, 132.3, 140.3, 147.7, 155.9, 177.2; ESIMS m/z 194.03 [M + H]$^+$.

*Dimethyl 2-(Methyl(phenyl)amino)maleate (**40**).* To a solution of dimethylacetylene dicarboxylate (6.8 g, 48.3 mmol) in MeOH was added *N*-methylaniline (**39**) (4.5 g, 42.0 mmol) dropwise, and the mixture was stirred for 15 h at reflux. MeOH was evaporated under vacuum, CH_2Cl_2 was added (300 mL), and the mixture was washed with saturated aqueous NH_4Cl (2 × 150 mL) and H_2O (2 × 150 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (hexanes–EtOAc, 10:1 to 5:3) to give compound **40** (9.3 g, 89%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (s, 3H), 3.59 (s, 3H), 3.63 (s, 3H), 4.81 (s, 1H), 7.19 (d, J = 8.1 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H); ^{13}C NMR data (100 MHz, $CDCl_3$) δ 40.3, 50.3, 52.0, 87.7, 126.0, 126.9, 129.0, 144.1, 153.7, 164.7, 167.2; ESIMS m/z 250.11 [M + H]$^+$.

*Methyl 1-Methyl-4-oxo-1,4-dihydroquinoline-2-carboxylate (**41**).* A mixture of **40** (5.0 g, 20.1 mmol) and PPA (25.0 g) was

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heated at 130 °C for 4 h. The resulting slurry was poured into an iced saturated aqueous solution of $NaHCO_3$, and the pH was adjusted to 7 by addition of further saturated $NaHCO_3$. The mixture was extracted with EtOAc (3 × 200 mL), and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (CH_2Cl_2−MeOH, 100:0 to 10:1) to give the product as pink needle crystals (3.2 g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.96 (s, 3H), 6.57 (s, 1H), 7.34 (t, J = 8.6 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.34 (t, J = 5.9 Hz, 1H), 8.33 (d, J = 7.5 Hz, 1H); ^{13}C NMR data (100 MHz, $CDCl_3$) δ 37.3, 53.6, 112.4, 116.1, 124.2, 126.5, 127.1, 133.1, 141.9, 143.8, 164.1, 178.0; HRESIMS m/z 218.0793 $[M + H]^+$ (calcd for $C_{12}H_{11}NO_3$, 218.0812).

*2-(Hydroxymethyl)-1-methylquinolin-4(1H)-one (**42**).* The procedure was the same as for the synthesis of compound **38**, using **41** (0.7 g, 3.2 mmol) as starting material. Compound **42** (0.6 g, 74%) was obtained as an orange solid: ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.72 (s, 3H), 4.59 (d, J = 5.8, 2H), 5.76 (t, J = 5.8, 1H), 6.23 (s, 1H), 7.37 (ddd, J = 7.9, 6.8, 1.0 Hz, 1H), 7.72 (ddd, J = 8.6, 6.8, 1.7 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 8.17 (dd, J = 8.0, 1.4 Hz, 1H); ^{13}C NMR data (150 MHz, DMSO-d_6) δ 33.7, 80.9, 108.5, 116.4, 122.9, 125.3, 126.0, 132.1, 141.8, 154.2, 176.3; ESIMS m/z 190.08 $[M + H]^+$.

*2-(Chloromethyl)-1-methylquinolin-4(1H)-one (**43**).* The procedure was the same as for the synthesis of compound **21**, using **42** (0.2 g, 1 mmol) as starting material. Compound **43** (0.2 g, 90%) was obtained as a white solid: ^{1}H NMR (400 MHz, methanol-d_4) δ 3.86 (s, 3H), 4.88 (s, 2H), 6.38 (s 1H), 7.40 (dt, J = 8.0, 4.0 Hz, 1H), 7.73 (d, J = 3.3 Hz, 2H), ;8.21 (d, J = 8.1 Hz, 1H); ^{13}C NMR data (150 MHz, methanol-d_4) δ 35.7, 44.2, 112.3, 117.8, 125.4, 126.6, 127.1, 134.4, 143.3, 151.9, 179.9; ESIMS m/z 208.1 $[M + H]^+$.

General Procedure C for the Suzuki−Miyaura Cross-Coupling. A mixture of the chloromethylquinolone (1 equiv), boronic acid derivative (1.1 equiv), sodium carbonate (4 equiv), and dichloro(1,1′-bis(diphenylphosphanyl)ferrocene)palladium(II) complex (0.1 equiv) were charged with argon in a sealed flask. 1,4-Dioxane and H_2O (10 mL, 4:1) were added via syringe, and the reaction was heated at 100 °C for 8−10 h. The mixture was filtrated through Celite, washed with MeOH, and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (CH_2Cl_2−MeOH, 100:0 to 10:1).

*2-Benzylquinolin-4(1H)-one (**6**).* Following general procedure C, using the chloromethylquinolone **21** (15 mg, 0.08 mmol) and 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaboroloane (18 mg, 0.09 mmol), compound **6** was obtained as a white solid (18 mg, 95%): ^{1}H NMR (600 MHz, methanol-d_4) δ 4.04 (s, 2H), 6.15 (s, 1H), 7.22−7.33 (m, 5H), 7.36 (ddd, J = 8.1, 7.0, 1.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.66 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H); ^{13}C NMR data (150 MHz, methanol-d_4) δ 40.6, 109.8, 119.1, 125.2, 125.5, 126.0, 128.2, 129.9, 130.0, 133.5, 137.9, 141.6, 155.5, 180.7; HRESIMS m/z $[M + Na]^+$ 258.0888 (calcd for $C_{16}H_{13}NO$ 258.0889).

*2-(4-(Methylthio)benzyl)quinolin-4(1H)-one (**7**).* Following general procedure C, using **21** (17 mg, 0.09 mmol) and 4,4,5,5-tetramethyl-2-((4-methylthio)phenyl)-1,3,2-dioxaborolane (25 mg, 0.10 mmol), compound **7** was obtained as a white solid (24 mg, 98%): ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.45 (s, 3H), 3.91 (s, 2H), 5.87 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 7.0 Hz, 2H), 7.30 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.61 (t, J = 8.4 Hz, 1H), 8.02 (d, J = 6.8 Hz, 1H), 11.64 (s, 1H); ^{13}C NMR data (150 MHz, DMSO-d_6) δ 14.7, 38.2, 108.3, 117.8, 122.7, 124.5, 124.6, 126.2, 129.3, 131.4, 133.9, 136.3, 140.0, 152.1, 176.7; HRESIMS m/z 304.0765 $[M + Na]^+$ (calcd for $C_{17}H_{15}NOS$, 304.0766).

*(E)-2-(Hept-2-en-1-yl)quinolin-4(1H)-one (**8**).* Following general procedure C, using **21** (10 mg, 0.05 mmol) and (*E*)-hex-1-en-1-ylboronic acid (8 mg, 0.06 mmol), compound **8** was obtained as a white solid (12 mg, 93%): ^{1}H NMR (600 MHz, methanol-d_4) δ 0.9 (t, J = 7.2, 3H), 1.31−1.42 (m, 4H), 2.08 (q, J = 7.0 Hz, 2H), 3.41 (d, J = 6.7 Hz, 2H), 5.56−5.65 (m, 1H), 5.71 (dd, J = 14.4, 7.5 Hz, 1H), 6.21 (s, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.68 (t, J = 7.0 Hz, 1H), 8.21 (d, J = 7.1 Hz, 1H); ^{13}C NMR data (150 MHz, methanol-d_4) δ 14.2, 23.2, 32.5, 33.2, 37.8, 108.9, 119.1, 125.1, 125.3, 125.6, 126.0, 133.4, 136.4, 141.6, 155.6, 180.8; HRESIMS m/z 264.1359 $[M + Na]^+$ (calcd for $C_{16}H_{19}NO$, 264.1359).

*2-Benzyl-1-methylquinolin-4(1H)-one (**9**).* Following general procedure C, using **43** (14 mg, 0.06 mmol) and 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (14 mg, 0.07 mmol), **9** was obtained as a white solid (16 mg, 97%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.59 (s, 3H), 4.10 (s, 2H), 6.31 (s, 1H), 7.19 (d, J = 7.1 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.33 (t, J = 7.4 Hz, 2H), 7.38 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 8.6 Hz, 1H), 7.64 (ddd, J = 8.7, 7.0, 1.7 Hz, 1H), 8.47 (dd, J = 8.0, 1.6 Hz, 1H); ^{13}C NMR data (100 MHz, $CDCl_3$) δ 34.8, 41.3, 113.6, 115.4, 123.6, 126.9, 126.9, 127.5, 128.4, 129.3, 132.3, 136.1, 142.3, 152.3, 178.1; HRESIMS m/z $[M + Na]^+$ 272.1045 (calcd for $C_{17}H_{15}NO$, 272.1046).

*1-Methyl-2-(4-(methylthio)benzyl)quinolin-4(1H)-one (**10**).* Following general procedure C, using **43** (14 mg, 0.06 mmol) and 4,4,5,5-tetramethyl-2-((4-methylthio)phenyl)-1,3,2-dioxaborolane (17 mg, 0.07 mmol), compound **10** was obtained as a white solid (16 mg, 96%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.59 (s, 3H), 4.06 (s, 2H), 6.30 (s, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 8.47 (d, J = 7.8 Hz, 1H); ^{13}C NMR data (150 MHz, $CDCl_3$) δ 16.0, 34.7, 40.8, 113.5, 115.4, 123.6, 126.8, 126.9, 127.4, 128.8, 132.4, 132.7, 137.8, 142.2, 152.3, 178.1; HRESIMS m/z 318.0923 $[M + Na]^+$ (calcd for $C_{18}H_{17}NOS$, 318.0923).

*(E)-2-(Hept-2-en-1-yl)-1-methylquinolin-4(1H)-one (**11**).* Following general procedure C, using **43** (14 mg, 0.06 mmol) and (*E*)-hex-1-en-1-ylboronic acid (9 mg, 0.07 mmol), compound **11** was obtained as a white solid (14 mg, 94%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.87 (t, J = 7.1, 3H), 1.25−1.38 (m, 4H), 2.04 (q, J = 6.6 Hz, 2H), 3.41 (d, J = 4.9 Hz, 2H), 3.71 (s, 3H), 5.46−5.60 (m, 2H), 6.25 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.65 (t, J = 8.4 Hz, 1H), 8.44 (d, J = 7.0 Hz, 1H); ^{13}C NMR data (150 MHz, $CDCl_3$) δ 14.0, 22.3, 31.4, 32.3, 34.5, 38.0, 111.9, 115.4, 123.5, 123.9, 126.7, 126.8, 132.2, 135.4, 142.1, 153.3, 178.1; HRESIMS m/z $[M + Na]^+$ 278.1516 (calcd for $C_{17}H_{21}NO$, 278.1515).

Biological Testing. Procedures for agar well diffusion assays,[31] MIC determination and growth inhibition studies,[32] time−kill experiments,[31] and swarming motility assays[16] were adapted from existing protocols. Additional details are given in the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.0c00865.

^{1}H NMR and ^{13}C spectra for all synthesized compounds, COSY, HSQC, and HMBC spectra for compound **17**, and full methods for biological assays (PDF)

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Notes

The authors declare no competing financial interest.

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