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Microwave-Assisted Multistep Synthesis of Functionalized 4-Arylquinolin-2(1*H*)-ones Using Palladium-Catalyzed Cross-Coupling Chemistry

Toma N. Glasnov, Wolfgang Stadlbauer, and C. Oliver Kappe*

Institute of Chemistry, Organic and Bioorganic Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

oliver.kappe@uni-graz.at

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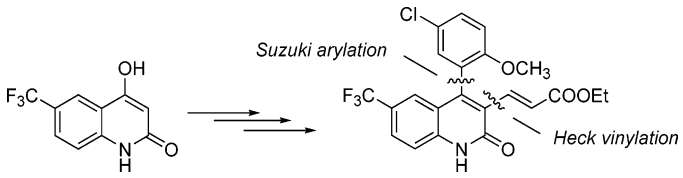

Biologically active 4-aryl-3-alkenyl-substituted quinolin-2(1*H*)-ones have been synthesized in a short and concise manner employing readily available 4-hydroxyquinolin-2(1*H*)-ones as intermediates. Key steps in the synthesis include the derivatization of the quinolin-2(1*H*)-one cores using palladium-catalyzed Suzuki and Heck reactions, installing the 4-aryl and 3-alkenyl substituents. All synthetic transformations (six steps) required for the synthesis of the desired target quinolin-2(1*H*)-one were carried out using controlled microwave-assisted organic synthesis.

Introduction

In recent years, an increasing interest in the synthesis of functionalized 4-arylquinolin-2(1*H*)-ones **1** with promising biological properties has been observed.[1−6] A number of analogues of this class of heterocyclic structure have been reported as lead compounds or are currently undergoing clinical trials (Figure 1). Of particular interest are derivatives of 3-(quinolin-3-yl)acrylates **2** and the corresponding reduced allylic alcohols that have been identified by Bristol-Myers Squibb (BMS) as novel and potent maxi-K channel openers useful for the treatment of male erectile dysfunction.[1] Closely related 4-aryl-3-aminoquinolin-2-ones were found by the same laboratory to possess neuroprotective properties.[2] Another clinically important 4-arylquinolin-2(1*H*)-one is R115777 (ZARNESTRA, **3**).[3] This 6-functionalized quinolinone derivative has emerged as a novel, selective, nonpeptide farnesyl protein inhibitor showing in vitro activity in the nanomolar range, and is currently undergoing human clinical trials as an orally active antitumor agent.[3]

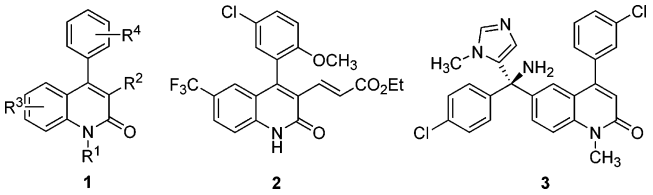

FIGURE 1. Functionalized 4-arylquinolin-2(1*H*)-ones with biological activity.

* To whom correspondence should be addressed. Phone: +43-316-380-5352. Fax: +43-316-380-9840.

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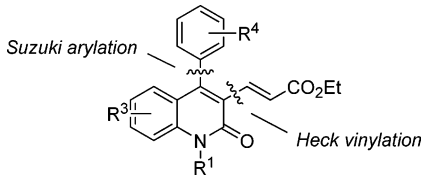

FIGURE 2. Modular strategy for the synthesis of 3-alkenyl-4-arylquinolin-2(1*H*)-ones.

Several other biologically active 4-arylquinolin-2(1*H*)-ones **1** have been described in the literature.[4−6]

A number of different synthetic pathways have been elaborated to access 4-arylquinolin-2(1*H*)-ones of type **1**. In most instances, the generation of the arylquinolinone moiety is achieved by cyclization of a suitable *N*-acyl-*o*-aminobenzophenone precursor,[1−5] or via closely related procedures,[7,8] sometimes involving the reduction of an aryl-1,2-benzisoxazole derivative for the preparation of the aminobenzophenone intermediate.[3] Alternatively, aroylacetanilide derivatives can be cyclized to 4-arylquinolin-2(1*H*)-ones employing suitable reagents such as polyphosphoric acid.[9]

All these procedures, however, suffer from the disadvantage that the aryl ring attached to the C4 position of the quinolinone core has to be introduced very early in the overall synthetic scheme. Therefore, the preparation of analogues, e.g., varying the aryl group at C4, is a cumbersome and lengthy process. In this paper, we describe a novel and flexible synthetic protocol for the synthesis of functionalized 4-arylquinolin-2(1*H*)-ones utilizing transition-metal-catalyzed carbon−carbon bond-forming reactions. Our strategy is based on the "decoration" of readily available quinolin-2(1*H*)-one core structures at the C4 position, using Suzuki cross-coupling chemistry (Figure 2). To highlight the usefulness and flexibility of this process we have applied this method also to the synthesis of target structure **2**, employing a Suzuki/Heck reaction sequence. All synthetic manipulations described herein were carried out utilizing controlled sealed vessel microwave heating in both single-mode and multimode reactors.[10]

Results and Discussion

The key intermediates in our overall synthetic scheme are 4-hydroxyquinolin-2(1*H*)-ones. These heterocycles are useful intermediates for many industrial products, and several methods for their preparation have been reported (see below).[11,12] To verify the practicability of the projected Suzuki and Heck carbon−carbon bond-forming reactions (Figure 2), we have initially performed a model study involving the commercially available (or easily synthesized)[13] 4-hydroxyquinolin-2(1*H*)-one **4** as the starting material (Scheme 1). To obtain a suitable coupling precursor for the Suzuki reaction, quinolinone **4** was treated with phosphorus oxychloride ($POCl_3$) in order to furnish the 4-chloro derivative **5**. Under conventional thermal heating conditions, this substitution reaction is typically carried out using $POCl_3$ as a solvent (106 °C, 3 h).[14] Employing dioxane as solvent and with controlled microwave heating at 120 °C the substitution reaction was completed in 25 min requiring only 2.0 equiv of the $POCl_3$ reagent, providing the desired quinolin-2(1*H*)-one **5** in 82% yield.

For the subsequent palladium-catalyzed Suzuki cross-coupling reaction of activated chloride **5**, phenylboronic acid was used as the coupling partner. This method of synthesizing 4-arylquinolin-2(1*H*)-ones has so far not been reported, although related examples can be found in the recent literature for the preparation of 4-arylcoumarins[15] and 4-aryl-1,8-naphthyridin-2(1*H*)-ones.[16] It is well-known that the performance of Suzuki and other transition-metal-catalyzed transformations can be significantly shortened by direct in-core microwave heating.[10] Taking advantage of the rapid automated processing features of modern microwave reactor instrumentation,[17] the Suzuki reaction **5** → **6** was quickly optimized probing different catalyst/solvent/base combinations, molar ratios of the starting materials in addition to varying reaction time and temperature. The best conversions and isolated product yields were achieved by using a combination of palladium acetate and triphenylphosphine as a catalyst precursor. This allowed us to run the reaction successfully with a comparatively low loading (0.5 mol %) of palladium catalyst.[18] A 3:1 mixture of 1,2-dimethoxyethane (DME) and water proved to be the optimal solvent combination, together with either sodium carbonate or triethylamine as base. For the purpose of reaction homogeneity and postreaction handling, triethylamine ultimately proved to be the base of choice. The optimal temperature/time ratio was found to be 150 °C/30 min. If prolonged irradiation or higher temperatures were used, more of the expected side products resulting from homocoupling or deboronation of the boronic acid were observed by HPLC monitoring. The presence of water in the solvent mixture in the specified amount was also found to be crucial for the reaction to proceed properly. Smaller amounts or its absence led to incomplete conversion; higher amounts led to partial hydrolysis of the reactive chloroquinolinone **5** back to hydroxyquinolinone **4.** Postreaction filtration through a plug of silica gel provided an 83% isolated yield of 1-methyl-4-phenylquinolin-2(1*H*)-one (**6**).

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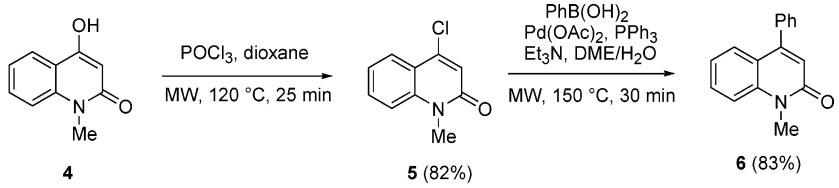
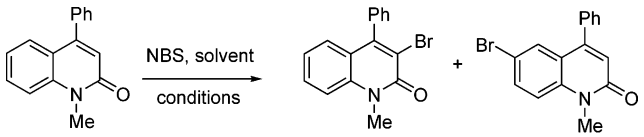
SCHEME 1



4 **5** (82%) **6** (83%)

SCHEME 2



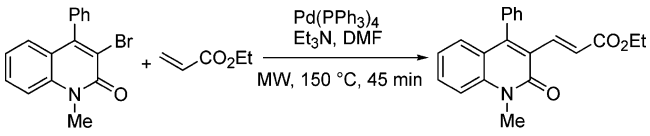
6 **7** **8**

solvent	temp [°C]	time [h]	ratio **7**/**8**
DMF	0 (Δ)	17	92:8
DMF	25 (Δ)	4.5	83:17
DMF	50 (Δ)	3.0	55:45
MeCN	100 (MW)	0.3	5:95

To install the desired acrylic ester moiety at the C3 position of the quinolinone core (Figure 2), we next considered introducing a bromine substituent at the C3 position, resulting in a product that would be ideally set up for a subsequent Heck vinylation. Gratifyingly, bromination of quinolinone **6** with *N*-bromosuccinimide (NBS)[19] in a variety of solvents provided the desired 3-bromo-4-phenylquinolin-2(1*H*)-one (**7**), as well as varying amounts of the undesired 6-bromo isomer **8** (Scheme 2). Both bromoquinolinones were easily identified by NMR spectroscopy and could be separated by automated flash chromatography. The ease of bromination was critically dependent on the polarity of the solvent. While complete bromination in dioxane at room temperature required 12 h, the same transformation—under otherwise identical conditions—was achieved within 8 h in acetonitrile or 4.5 h in DMF. Most important for the outcome of the bromination, however, was the reaction temperature. Bromination with 2.5 equiv of *N*-bromosuccinimide in DMF at room temperature (25 °C), for example, provided a clean 83:17 mixture (HPLC at 215 nm) of 3-bromo- (**7**) and 6-bromoquinolinone (**8**) within 4.5 h. An increase of the reaction temperature to 50 °C led to full consumption of the starting material **6** within 3 h but led to an almost equimolar ratio of bromoquinolinone isomers (**7**/**8** = 55:45). The same temperature dependence on the regiochemistry of bromination was also seen when the brominations were carried out under microwave conditions over a wide temperature range (60−150 °C). In fact, performing the bromination at 100 °C (microwaves, 20 min) in acetonitrile (2.5 equiv of NBS) allowed the selective preparation of the undesired 6-bromoquinolinone isomer **8**, with only trace amounts of the 3-bromo isomer **7** being formed. Apparently, the higher reaction temperatures—while allowing the brominations to be carried out more rapidly—favor the formation of the thermodynamically more stable 6-bromoquinolin-2(1*H*)-one isomer, which was supported by energy calculations on both bromoquinolinones.[20]

Consequently, we have carried out the bromination **6** → **7** at 0 °C (17 h) in DMF in order to obtain a 92:8 selectivity in favor of the desired 3-bromo-1-methyl-4-phenylquinolin-2(1*H*)-one (**7**), resulting in a 79% isolated product yield of **7** after chromatography.

SCHEME 3



7 **9** (81%)

As a last step of our model study, the Heck vinylation of 3-bromo-1-methyl-4-phenylquinolin-2(1*H*)-one (**7**) with ethyl acrylate was investigated (Scheme 3). Previous references in the literature have described Heck vinylations in a series of 3-acetoxy-3-iodoquinolin-2(1*H*)-ones;[21] no examples related to the transformation **7** → **9** have so far been reported. Similar to the experiments described above for the Suzuki arylation, the reaction conditions were optimized using automated microwave synthesis.[10] After some experimentation, successful Heck vinylations were achieved by using 3 mol % tetrakis(triphenylphosphine)palladium(0), 3 equiv of triethylamine as base, and DMF as solvent. Different solvents or lower catalyst loadings resulted in incomplete conversions. Under these optimized conditions, full conversion to the 3-(quinolin-3-yl)acrylate **9** was obtained within 45 min, with only minor amounts (<5%) of debrominated quinolinone **6** being formed as a byproduct. Extractive workup provided an 81% isolated yield of pure Heck product **9**.

Having established the general feasibility of the microwave-assisted Suzuki−Heck sequence for the preparation of 3-(4-phenylquinolin-3-yl)acrylates of type **9**, we turned our attention to the synthesis of the desired multifunctionalized target structure **2**. The synthesis of ethyl 3-[4-(5-chloro-2-methoxyphenyl)-6-(trifluoromethyl)-1,2-dihydro-2-oxoquinolin-3-yl]acrylate (**2**) has been previously described by a group from BMS in 2003 and involves more than 10 linear steps starting from 4-(trifluoromethyl)aniline in its *N*-Boc-protected form.[1] The key step in the synthesis is a base-catalyzed cyclization of an appropriate *N*-acyl-*o*-aminobenzophenone precursor.[1]

Key to our synthetic protocol is the preparation of the required 4-hydroxy-6-(trifluoromethyl)quinolin-2(1*H*)-one

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(20) Both semiempirical (AM1, PM3) and density functional theory calculations (B3LYP/3-21G* or 6-31G*) indicate that the 6-bromoquinolinone isomer is by 1.50−4.50 kcal/mol more stable than the 3-bromo isomer.

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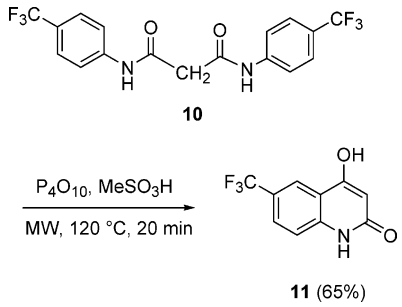
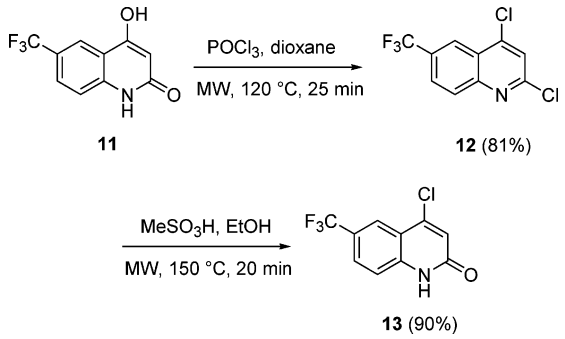
SCHEME 4



SCHEME 5



intermediate **11**. In general, benzo-substituted 4-hydroxyquinolin-2(1*H*)-ones can be obtained by cyclization of malondianilides with suitable cyclization reagents.[11,12] One of the most successful reagents reported in this context is commercially available Eaton's reagent, a 7.7% solution of phosphorus pentoxide in methanesulfonic acid.[11] However, malondianilides derived from anilines bearing strong electron-withdrawing substituents such as the CF_3 group have previously proven difficult to cyclize, providing only moderate yields of the corresponding 4-hydroxyquinolin-2(1*H*)-ones.[11,22]

The required starting material, *N,N*′-bis[4-(trifluoromethyl)phenyl]malonamide (**10**), was prepared in nearly quantitative yield from malonyl dichloride and 4-(trifluoromethyl)aniline following a literature procedure.[23] Careful optimization of the reaction conditions demonstrated that full conversion (HPLC at 215 nm) of the malondianilide **10** to the quinolinone **11** could be obtained by exposing a ca. 0.5 M solution of the starting material in Eaton's reagent to microwave irradiation at 120 °C for 20 min in an argon atmosphere (Scheme 4). The cyclization reaction proved to be rather sensitive to time, temperature, and concentration of the reaction mixture. Elevated reaction temperatures or prolonged microwave irradiation resulted in a significant loss of purity, presumably due to concomitant product decomposition. Precipitation of the crude product with ice−water followed by dissolution in base, filtration, and reprecipitation with acid provided a 65% isolated yield of pure quinolinone product **11**. We have also briefly investigated the cyclization of other, more reactive malondianilides utilizing our optimized microwave protocol. As expected,[11] here the formation of the desired 4-hydroxyquinolin-2(1*H*)-ones was straightforward and proceeded in high yields (80−90%).

As in the model series, the 4-hydroxyquinolin-2(1*H*)-one precursor **11** was then converted to the required 4-chloro derivative **13**. Since selective monochlorination at the C4 position of the N1-unblocked quinolinone **11** was not possible, a straightforward two-step chlorination/hydrolysis sequence was employed (Scheme 5). Treatment of quinolinone **11** with 2 equiv of phosphorus oxychloride in dioxane using the previously described (see above) microwave conditions resulted in the formation of the corresponding 2,4-dichloroquinoline intermediate **12** (81%), which was subsequently selectively hydrolyzed by a methanesulfonic acid/ethanol mixture,[24] again using microwave heating at 150 °C for 20 min, providing the desired 4-chloroquinolinone **13** in 90% yield.

After successfully obtaining the 4-chloroquinolinone **13**, we next performed the key Suzuki cross-coupling step. Employing commercially available 5-chloro-2-methoxyphenylboronic acid (1.2 equiv) together with the optimized protocol elaborated for the model series (see above), we were pleased to observe near-quantitative formation of the desired 4-arylquinolin-2(1*H*)-one **14** (Scheme 6). No adjustments to the reaction conditions were required, providing a 91% isolated product yield.

Bromination of the quinolinone substrate **14** with *N*-bromosuccinimide in DMF at room temperature provided the 3-bromo derivative **15** in near-quantitative yield, although 17 h were required to reach full conversion. The reaction time could be shortened to 9−10 h by performing the reaction at 50 °C. Here, in contrast to our model series (cf. Scheme 2), bromination at other than the desired C3 position of the quinolinone core was not observed, owing to the strongly electron-withdrawing character of the trifluoromethyl substituent. Therefore, bromination under high-temperature microwave conditions (150 °C, MeCN) allowed the preparation of the desired 3-bromo-4-arylquinolin-2(1*H*)-one **14** in a significantly reduced reaction time (50 min).

In the final step of the reaction sequence, Heck vinylation of bromoquinolinone **15** with ethyl acrylate provided the desired target structure **2**. As with the Suzuki protocol, no changes were required to the protocol optimized for the model series (Scheme 3), providing the 3-(quinolin-3-yl)acrylate **2** in 90% yield after purification by flash chromatography. As a byproduct, ca. 5% of debrominated quinolinone **14** was isolated.

The protocol presented herein, therefore, allows the preparation of target structure **2** in seven steps from 4-(trifluoromethyl)aniline in an overall yield of 32%. Importantly, all six steps described in our sequence starting from the known malondianilide **10** were conducted utilizing rapid, controlled microwave heating and did not require any purification by recrystallization or chromatography of the intermediate products. Typically, the isolated intermediates had >95% purity and could

(22) In related work on the direct condensation of anilines with substituted malonates yielding 3-substituted 4-hydroxyquinolin-2(1*H*)-ones, Lange and co-workers established that 4-(trifluoromethyl)aniline proved unreactive and that only the malondianilides could be obtained. See: Lange, J. H. M.; Verveer, P. C.; Osnabrug, J. M.; Visser, G. M. *Tetrahedron Lett.* **2001**, *42*, 1367−1369.

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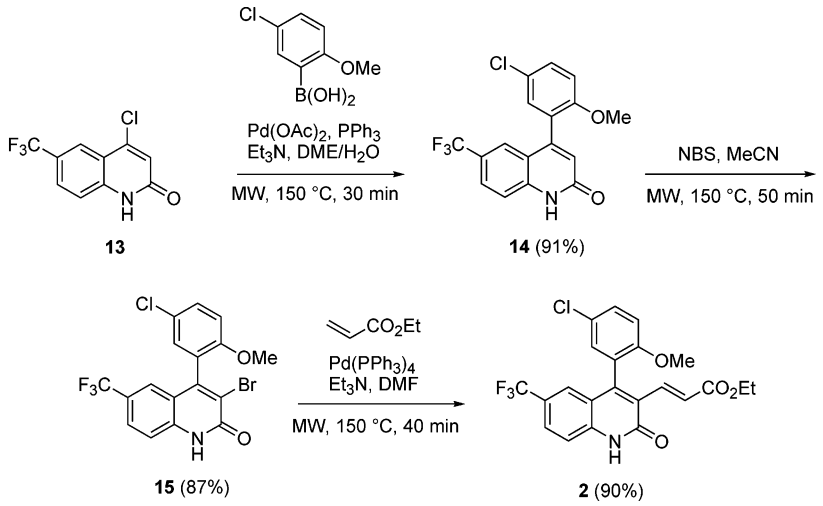
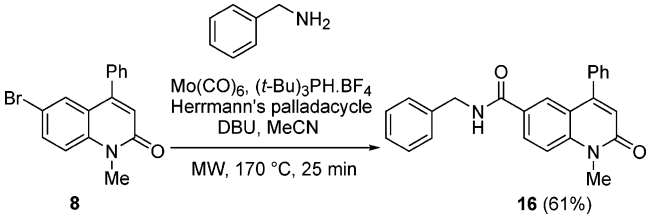
SCHEME 6



SCHEME 7



be carried on without purification in the next step. From the standpoint of generating diversity, the modular and flexible "scaffold decoration" strategy (Figure 2) should allow the rapid preparation of a multitude of 4-arylquinolin-2(1*H*)-one analogues, given the large number of commercially available boronic acids. This represents a clear improvement over existing synthetic approaches to this compound class starting from *N*-acyl-*o*-aminobenzophenones.[1−5] Naturally, other high-speed microwave-assisted transition metal-catalyzed transformations may also be accessible from the 4-chloroquinolin-2(1*H*)-one building blocks.[10,25]

To emphasize this point we have carried out microwave-assisted aminocarbonylation reactions with 6-bromo-4-phenylquinolin-2(1*H*)-one **8**. Introduction of a carbonyl group at the C6 position of the quinolinone core may provide an entry into intermediates for the synthesis of the nonpeptide farnesyl protein inhibitor ZARNESTRA (**3**).[3] Employing the recently reported conditions for performing microwave-assisted aminocarbonylations,[26] using molybdenum hexacarbonyl as a solid source of carbon monoxide and Herrmann's palladacycle (5 mol %) in combination with Fu's salt [(*t*-Bu)$_3$PH·BF$_4$] as a catalyst system, the anticipated quinoline-6-carboxamide **16** was obtained (Scheme 7). Thus, microwave irradiation of arylbromide **8** with benzylamine in acetonitrile as solvent at 170 °C for 25 min provided a 61% yield of amide **16** after chromatographic workup.

Finally, it should be emphasized that during the reaction optimization phase most examples of microwave-assisted syntheses discussed in this paper were typically performed on a comparatively small scale (0.3−2.0 mmol, <5 mL processing volume) in single-mode microwave reactors.[17] Recently, several authors have reported independently the feasibility of directly scaling reaction conditions from small-scale single-mode to larger scale multimode batch microwave reactors (10−500 mL) without reoptimization of the reaction conditions.[27,28] Therefore, many of the microwave reactions described herein were also performed on a larger scale (up to 16 mmol, 56 mL processing volume) in multimode batch reactors[27] in order to access larger product quantities. Importantly, a reoptimization of reaction conditions was not necessary, and products were obtained in similar yields and purities as on a small scale (see the Experimental Section).

Conclusion

In summary, we have developed an efficient synthetic approach for the synthesis of 4-aryl-substituted quinolin-2(1*H*)-ones, a class of compounds with interesting biological activities. The method could be extended to the synthesis of 3-alkenyl-substituted analogues allowing access to important pharmaceutical target structures. The described sequential Suzuki/Heck scaffold decoration method allows the introduction of substituents late in the synthetic scheme, therefore greatly facilitating the preparation of 2(1*H*)-quinolinone analogues with diversity at the C4 and/or the C3 position (combinatorial libraries). Almost all of the synthetic steps described in this paper were carried out by controlled microwave irradiation, including the six-step conversion of malondianilide **10** to the target quinolinone **2** involving a number of different chemical manipulations.

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Experimental Section

General Methods. TLC analysis was performed on precoated plates. ^{1}H NMR spectra were obtained on a 360 or 500 MHz instrument, ^{13}C NMR spectra were recorded on a 360 MHz instrument at 90 MHz. FTIR spectra were recorded using KBr pellets. Low-resolution mass spectra were obtained in the atmospheric pressure chemical ionization (positive or negative APCI) mode. Analytical HPLC analysis was carried out on a C18 reversed-phase analytical column (119 × 3 mm, particle size 5 μm) at 25 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (acetonitrile + 0.1% TFA) at a flow rate of 0.5 mL/min. The following gradient was applied: linear increase from solution 30% B to 100% B in 7 min, hold at 100% solution B for 2 min. All chromatographic product purification was performed with an automated flash chromatography system employing prepacked silica cartridges/samplets.

Microwave Irradiation Experiments. Small-scale microwave-assisted synthesis was carried out in an Emrys synthesizer single-mode microwave cavity producing controlled irradiation at 2450 MHz (Biotage AB, Uppsala).[17] Reaction times refer to hold times at the temperatures indicated, not to total irradiation times. The temperature was measured with an IR sensor on the outside of the reaction vessel. The large-scale microwave syntheses were carried out in a Synthos 3000 multimode batch reactor from Anton Paar GmbH (Graz), utilizing an eight-vessel quartz rotor system following the previously published general protocols.[27] Reaction times were extended by 5−10 min compared to the small-scale runs in order to ensure full conversion. Reaction temperatures were monitored by a gas balloon thermometer inside one reference vessel.

1-Methyl-4-chloroquinolin-2(1*H*)-one (5). To 300 mg (1.7 mmol) of 4-hydroxyquinoline-2(1*H*)-one **4** in a 10 mL microwave process vial were added 520 mg (3.4 mmol, 320 μL) of $POCl_3$ and 2 mL of anhydrous dioxane. After that, the mixture was stirred for 2 min at room temperature to allow complete homogenization. The sealed vial was heated by microwave irradiation for 25 min at 120 °C. After cooling to ambient temperature, the mixture was poured onto 20 mL of ice−water. The resulting solution was neutralized with 0.5 M KOH. After being stirred for 20 min, the precipitate was filtered, washed with water, and dried to give 257 mg (82%) of quinolinone **5**: mp 117−119 °C (lit.[14b] mp 117.5 °C); ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.59 (s, 3H), 6.9 (s, 1H), 7.37 (t, J = 7.56, 1H), 7.59 (d, J = 8.49, 1H), 7.72 (t, J = 7.71, 1H), 7.91 (d, J = 7.91, 1H); MS (pos. APCI) *m/z* 195 (29, M + 2), 193 (100, M$^+$). Microwave scale-up was performed on a 16 mmol scale providing an 80% product yield.

1-Methyl-4-phenylquinolin-2(1*H*)-one (6). A mixture of 121 mg (0.625 mmol) of 4-chloro-1-methylquinolin-2(1*H*)-one (**5**), 82 mg (0.688 mmol, 1.1 equiv) of phenylboronic acid, 190 mg (1.88 mmol, 260 μL, 3 equiv) of Et_3N, 0.7 mg (0.003 mmol, 0.5 mol %) of $Pd(OAc)_2$, and 3.3 mg (0.0125 mmol, 2 mol %) of PPh_3 was dissolved in 1.5 mL of DME/water (3:1). The reaction mixture was stirred for 5 min and then heated by microwave irradiation for 30 min at 150 °C. The resulting solution was subsequently treated with charcoal and filtered through a small plug of silica gel (3 g). The silica plug was washed twice with an additional amount of 2 mL of DME. Evaporation of the solvent produced 119 mg (83%) of quinolinone **6** as a yellow-white solid: mp 146−148 °C (ethanol) (lit.[7] mp 146 °C); IR (KBr) ν_{max} 1665, 1586, 1452, 1377, 1318 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.08 (s, 3H), 6.70 (s, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.43−7.60 (m, 8H); MS (pos. APCI) *m/z* 235 (100, M + 1). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.45; H, 5.64; N, 5.84. Microwave scale-up was performed on a 11.5 mmol scale providing a 80% product yield.

3-Bromo-1-methyl-4-phenylquinolin-2(1*H*)-one (7). A mixture of 100 mg (0.425 mmol) of 1-methyl-4-phenylquinolin-2(1*H*)-one **6** and 267 mg (1.5 mmol, 2.5 equiv) of NBS was dissolved in 3 mL of DMF. The reaction mixture was stirred for 4.5 h at room temperature and the resulting dark yellow solution subsequently poured onto 15 mL of ice−water. After being stirred for 5 min, the precipitate was filtered, washed with water, and dried. Evaporation of the solvent followed by flash chromatography (petroleum ether/ethyl acetate = 2:1) of the crude reaction mixture produced 99 mg (75%) of pure product **7** as white solid: mp 176−177 °C (ethanol); IR (KBr) ν_{max} 1645, 1595, 1547, 1490, 1443, 1412, 1305 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.13−7.17 (m, 2H), 7.28−7.30 (m, 2H), 7.43−7.61 (m, 5H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 31.2, 114.3, 119.1, 121.5, 122.5, 128.4, 128.5, 128.6, 130.8, 137.3, 138.8, 150.5, 158.2; MS (pos. APCI) *m/z* 315 (60, M + 2), 313 (100, M), 234 (10, M − 79). Anal. Calcd for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.45. Found: C, 60.96; H, 3.77 N, 4.44.

6-Bromo-1-methyl-4-phenylquinoline-2(1*H*)-one (8). A mixture of 100 mg (0.425 mmol) of 1-methyl-4-phenylquinolin-2(1*H*)-one (**6**) and 267 mg (1.5 mmol, 2.5 equiv) of NBS was dissolved in 1.5 mL of MeCN. The reaction mixture was stirred for 1 min at room temperature and subsequently heated by microwave irradiation at 100 °C for 20 min. After being cooled to ambient temperature, the mixture was poured onto 15 mL of ice−water and stirred for 5 min. The precipitate was filtered, washed with water, and dried to give 125 mg (95%) of 3-bromoquinolinone **8**: mp 177−179 °C (ethanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 3H), 6.69 (s, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.39−7.67 (m, 7H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 31.4, 115.5, 116.0, 120.5, 122.8, 128,4, 128.9, 130.4, 133.5, 136.6, 137.8, 149.4, 158.0; MS (pos. APCI) *m/z* 315 (100, M + 2), 313 (97, M), 235 (27, M − 78). Anal. Calcd for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.45. Found: C, 60.86; H, 3.64; N, 4.34.

Ethyl 3-(1,2-Dihydro-1-methyl-2-oxo-4-phenylquinolin-3-yl)acrylate (9). To 100 mg (0.32 mmol) of 3-bromo-1-methyl-4-phenylquinolin-2(1*H*)-one (**7**) in a 5 mL microwave process vial were added 50 mg (0.5 mmol, 54 μL, 1.5 equiv) of ethyl acrylate, 101 mg (1.0 mmol, 140 μL, 3.0 equiv) of Et_3N, 11 mg (0.01 mmol, 3 mol %) of $Pd(PPh)_3$, and 1.5 mL of anhydrous DMF. The reaction mixture was stirred for 5 min and subsequently heated by microwave irradiation at 150 °C for 45 min. After being cooled to ambient temperature, the mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 1:1) to give 89 mg (81%) of quinolinone **9**: mp 154−156 °C (methanol); IR (KBr) ν_{max} 1703, 1634, 1608, 1310, 1273 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 3H), 3.84 (s, 3H), 4.13 (q, J = 7.1 Hz, 2H), 7.18−7.58 (m, 11H); MS (pos. APCI) *m/z* 333 (100), 287 (70, M − 46), 259 (15, M − 74). Anal. Calcd for $C_{20}H_{16}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.58; H, 5.58; N, 4.10.

6-(Trifluoromethyl)-4-hydroxyquinolin-2(1*H*)-one (11). To 250 mg (0.64 mmol) of *N,N′*-bis[(4-trifluoromethyl)phenyl]-malonamide (**10**) in a 5 mL microwave process vial was added 1.5 mL of Eaton's reagent (CAS 39394-84-8). The vial was capped and the mixture stirred for 10 min under argon atmosphere. The sealed vial was heated by microwave irradiation at 120 °C for 20 min. After being cooled to room temperature, the resulting dark-colored solution was poured onto ice−water, and the formed precipitate filtered by suction. The product was dissolved in 100 mL of 0.5 M NaOH, and after being sitrred for 1 h, the turbid solution was filtered and the filtrate subsequently acidified with 2 M HCl. The formed precipitate was filtered, washed with water, and dried to give 96 mg (65%) of quinolinone **11**: mp > 330 °C (2-propanol); IR (KBr) ν_{max} 1660, 1640, 1611, 1594, 1562 cm^{-1}; ^{1}H NMR (360 MHz, DMSO-d_6) δ 5.98 (s, 1H), 7.41 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 8.02 (s, 1H), 11.57 (s, 1H), 11.76 (s, 1H); MS (neg. APCI) *m/z* 229 (100, M), 228 (30, M − 1), 187 (16, M − 42). Anal. Calcd for $C_{10}H_6F_3NO_2$: C, 52.41; H, 2.64; N, 6.11. Found: C, 52.67; H, 2.56; N, 6.01. Microwave scale-up was performed on a 3.85 mmol scale providing a 63% product yield.

2,4-Dichloro-6-(trifluoromethyl)quinoline (12). To 300 mg (1.3 mmol) of 6-(trifluoromethyl)-4-hydroxyquinoline-2(1*H*)-one (**11**) in a 10 mL microwave process vial were added 390

mg (2.6 mmol, 240 μL) of $POCl_3$ and 2 mL of anhydrous dioxane. After that, the mixture was stirred for 2 min at room temperature to allow complete homogenization. The sealed vial was heated by microwave irradiation for 15 min at 120 °C. After being cooled to ambient temperature, the mixture was poured onto 20 mL of ice−water. The formed solution was neutralized with 0.5 M KOH. After being stirred for 20 min, the precipitate was filtered, washed with water, and dried to give 280 mg (81%) of quinolinone **11**: mp 98−100 °C (ethanol); IR (KBr) ν_{max} 1574, 1562, 1451 cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6) δ 8.18−8.24 (m, 3H), 8.49 (s, 1H); MS (pos. APCI) *m/z* 269 (18, M + 4), 267 (M + 2), 265 (M), 231 (22, M − 34), 198 (8, M − 68). Anal. Calcd for $C_{10}H_4Cl_2F_3N$: C, 45.15; H, 1.52; N, 5.26. Found: C, 45.05; H, 1.38; N, 5.12. Microwave scale-up was performed on a 7 mmol scale providing a 81% product yield.

4-Chloro-6-(trifluoromethyl)quinoline-2(1*H*)-one (13). To 500 mg (2.0 mmol) of 2,4-dichloro-6-(trifluoromethyl)-quinoline (**12**) in a 10 mL microwave process vial were added 385 mg (4.0 mmol, 260 μL) of $MeSO_3H$ and 4 mL of EtOH. The reaction mixture was stirred for 10 min and subsequently heated by microwave irradiation for 20 min at 150 °C. After being cooled to ambient temperature, the mixture was poured onto 20 mL of ice−water and stirred for 20 min. The precipitate was filtered, washed with water, and dried to give 441 mg (90%) of quinolinone **13**: mp 206−208 °C (toluene); IR (KBr) ν_{max} 3174, 1676, 1632, 1597 cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6) δ 6.98 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.9 Hz, 1H), 8.07 (s, 1H), 12.38 (s, 1H); MS (neg. APCI) *m/z* 249 (30, M + 2), 247 (100, M). Anal. Calcd for $C_{10}H_5ClF_3NO$: C, 48.51; H, 2.04; N, 5.66. Found: C, 48.47; H, 1.87; N, 5.62.

Synthesis of 4-(5-Chloro-2-methoxyphenyl)-6-(trifluoromethyl)quinolin-2(1*H*)-one (14). A mixture of 155 mg (0.625 mmol) of 4-chloro-6-(trifluoromethyl)quinolin-2(1*H*)-one **13**, 127 mg (0.688 mmol, 1.1 equiv) of 5-chloro-2-methoxyphenyl boronic acid, 190 mg (1.88 mmol, 260 μL, 3 equiv) of Et_3N, 0.7 mg (0.003 mmol, 0.5 mol %) of $Pd(OAc)_2$, and 3.3 mg (0.0125 mmol, 2 mol %) of PPh_3 was dissolved in 1.5 mL of DME/water (3:1). The reaction mixture was stirred for 5 min and subsequently heated by microwave irradiation for 30 min at 150 °C. The resulting solution was subsequently treated with charcoal and filtered through a small plug of silica gel (3 g). The silica plug was washed twice with an additional amount of 2 mL of DME. Evaporation of the solvent produced 201 mg (91%) of quinolinone **14** as a yellow-white solid: mp 147−148 °C (methanol); IR (KBr) ν_{max} 1671, 1489, 1315, 1264 cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6) δ 3.68 (s, 3H), 6.53 (s, 1H), 7.25 (d, J = 7.2 Hz, 2H), 7.41 (d, J = 2.6 Hz, 1H), 7.52−7.59 (m, 2H), 7.83 (d, J = 8.7 Hz, 1H), 12.23 (s, 1H); MS (pos. APCI) *m/z* 355 (44, M + 2), 353 (100, M), 338 (12, M − 15). Anal. Calcd for $C_{17}H_{11}ClF_3NO_2$: C, 57.72; H, 3.13; N, 3.96. Found: C, 57.61; H, 3.15; N, 3.99. Microwave scale-up was performed on a 4.0 mmol scale providing a 90% product yield.

3-Bromo-4-(5-chloro-2-methoxyphenyl)-6-(trifluoromethyl)quinolin-2(1*H*)-one (15). To 150 mg (0.425 mmol) of 4-(5-chloromethoxyphenyl)-6-trifluoromethyl)quinolin-2(1*H*)-one **14** in a 10 mL microwave process vial were added 187 mg (1.06 mmol, 2.5 equiv) of NBS and 3 mL of MeCN. The reaction mixture was heated by microwave irradiation for 50 min at 150 °C. The solvent was evaporated and the residue recrystallized from ethanol to give 159 mg (87%) of brominated quinolinone **15** as a white solid: mp 252−254 °C (ethanol); IR (KBr) ν_{max} 1678, 1625, 1610, 1491, 1312 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.75 (s, 3H), 7.06 (d, J = 8.9 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.35 (s, 1H), 7.52 (dd, 6.4, 2.5 Hz, 1H), 7.67 (d, J = 8.6 Hz 1H), 7.78 (d, J = 8.1 Hz, 1H), 12.56 (s, 1H); MS (pos. APCI) *m/z* 435 (22, M + 4), 433 (M + 2), 431 (60, M), 353 (25, M − 78). Anal. Calcd for $C_{17}H_{10}BrClF_3NO_2$: C, 47.20; H, 2.33; N, 3.2. Found: C, 47.20; H, 2.16; N, 3.18.

Ethyl 3-[4-(5-Chloro-2-methoxyphenyl)-6-(trifluoromethyl)-1,2-dihydro-2-oxoquinolin-3-yl]acrylate (2). To 145 mg (0.33 mmol) of 3-bromo-4-(5-chloro-2-methoxyphenyl)-6-(trifluoromethyl)quinolin-2(1*H*)-one **15** in a 5 mL microwave process vial were added 50 mg (0.5 mmol, 54 μL, 1.5 equiv) of ethyl acrylate, 101 mg (1.0 mmol, 140 μL, 3 equiv) of Et_3N, 11 mg (0.01 mmol, 3 mol %) of $Pd(PPh)_3$, and 1.5 mL of anhydrous DMF. The reaction mixture was stirred for 5 min and subsequently heated by microwave irradiation for 45 min at 150 °C. After being cooled to ambient temperature, the mixture was poured onto 10 mL of ice−water and stirred for 5 min. Then the yellow precipitate was filtered, washed with water, and dried. Evaporation of the solvent after flash chromatography (petroleum ether/ethyl acetate = 1:4) produced 133 mg (90%) of quinolinone **2** as a white solid: mp 235−237 °C (methanol); IR (KBr) ν_{max} 1711, 1664, 1625, 1488, 1283 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 3.72 (s, 3H), 4.22 (q, J = 7.1 Hz, 2H), 7.06 (d, J = 8.9 Hz, 1H), 7.14 (d, J = 2.6 Hz, 1H), 7.27−7.60 (m, 5H), 7.77 (d, J = 1.4 Hz, 1H) 12.07 (s, 1H); MS (pos. APCI) *m/z* 454 (37, M + 2), 451 (100, M), 405 (62, M − 46). Anal. Calcd for $C_{22}H_{17}ClF_3NO_4$: C, 58.48; H, 3.79; N, 3.10. Found: C, 58.54; H, 3.51; N, 3.06.

***N*-Benzyl-1,2-dihydro-1-methyl-2-oxo-4-phenylquinoline-6-carboxamide (16).** A mixture of 50 mg (0.16 mmol) of 6-bromo-1-methyl-4-phenylquinolin-2(1*H*)-one (**8**), 73 mg of DBU (0.48 mmol, 72 μL, 3 equiv), 52 mg of benzylamine (0.48 mmol, 53 μL, 3 equiv), 43 mg of $Mo(CO)_6$, 70 mg of $(t\text{-}Bu)_3PH\cdot BF_4$, and 7.5 mg (0.008 mmol, 2 mol %) of Herrmann's palladacycle was dissolved in 2 mL of MeCN. The reaction mixture was stirred for 5 min and then heated by microwave irradiation for 25 min at 170 °C. The resulting solution was purified by flash chromatography using a 1:1 mixture of petroleum ether/EtOAc to afford 36 mg (61%) of quinoline-6-carboxamide (**16**) as a yellowish solid: mp >350 °C (ethanol); IR (KBr) ν_{max} 1642, 1582, 1538 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.7 (s, 3H), 4.43 (d, J = 5.53 Hz, 2H), 6.5 (s, 1H), 7.28 (m, 5H), 7.52 (m, 5H), 7.7 (d, J = 9.11, 1H), 8.03 (s, 1H), 8.18 (d, J = 8.59, 1H), 9.12 (t, J = 5.64, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 29.9, 39.9, 115.7, 119.5, 121.5, 127.2, 127.6, 128.1, 128.7, 129.3, 129.5, 136.7, 140.0, 142.3, 150.9, 161.1, 165.8; MS (pos. APCI) *m/z* 369 (31, M + 1), 368 (100, M), 278, (6, M − 90). Anal. Calcd. for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.44; H, 5.23; N, 7.56.

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