On the Knorr Synthesis of 6-Bromo-4-methylquinolin-2(1*H*)-one

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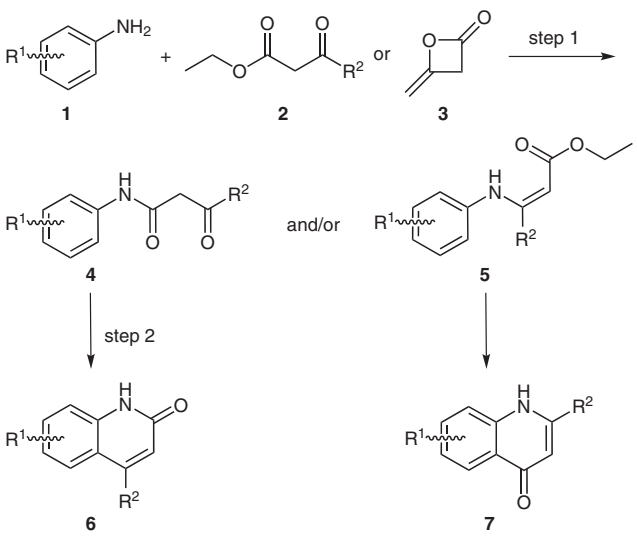
Abstract: In the course of our work on infectious diseases, we were led to prepare 6-bromo-2-chloro-4-methylquinoline as a starting material. Since surprisingly little has been reported in the literature, the two synthetic steps to this compound were investigated. The synthesis involves a condensation between β-keto esters and 4-bromoaniline and the cyclization of the resulting anilides into 6-bromoquinolin-2(1*H*)-one, otherwise known as the Knorr reaction. The ^{1}H NMR monitoring of the first step allowed us to optimize the conditions leading specifically to the anilide without the occurrence of the alternative crotonate. To illustrate the scope of our finding, few additional anilides featuring electron-attracting groups were prepared. The study of their cyclization revealed some unsuspected steric effect governing this second step. Aside from rectifying a few claims in this chemistry, this study led to a three-step preparation of 6-bromo-2-chloro-4-methylquinoline in 48% overall yield from 4-bromoaniline.

Key words: acylation, cyclization, heterocycles, quinolines, carbocation

As depicted in Scheme 1, the Knorr[1–3] as well as Conrad–Limpach reactions[4–6] are very useful for the synthesis of quinolin-2(1*H*)-ones **6** or quinolin-4(1*H*)-ones **7**, respectively, from anilines **1**.[7] The preparation of compounds **6** first involves a condensation reaction between anilines **1** and β-keto esters **2** leading to anilides **4**. However, depending on the reaction conditions and the substrates considered, this is often fraught with the occurrence of the corresponding crotonates **5**[8] and previous work demonstrated a degree of interconversion possible between them.[1,9–12] The occurrence of this mixture was actually the source of some initial confusion regarding the structures of the reaction products **6** and **7**.[13] The use of the fairly toxic diketene **3**, instead of ethyl acetoacetate, secured the regioselectivity of this step[14–16] and a more recent report using *tert*-butyl acetoacetate[17] can also allay this problem. Moreover, condensation between anilines and ethoxyacryloyl chlorides also lead to anilides featuring the same functional degree.[18] However, even in the occurrence of a mixture of **4** and **5**, its treatment in hot concentrated sulfuric acid leads to a cyclization of **4** into the quinolin-2(1*H*)-ones **6**,[1] – other strong acids have been used for electron-rich substrates[19,20] – whereas at high temperature (260 °C), crotonates **5** undergo a pericyclic cyclization into quinolin-4(1*H*)ones **7**.[4,5] Interestingly, the use of polyphosphoric acid at 170 °C for the preparation of quinolin-4(1*H*)ones **7** is sometime possible although, depending on the reaction concentration as well as the substrate considered, the isomeric quinolin-2(1*H*)-ones **6** are sometime obtained.[10,11,21–23]



Scheme 1 The Knorr and Conrad–Limpach syntheses

An extensive literature search for the preparation of 6-bromo-4-methylquinolin-2(1*H*)-one (**14**), pointed out that two reports only mentioned its isolation.[24,25] An additional paper describes a 29% yield via the cyclization of **12** using an excess of polyphosphoric acid.[22] In two instances, anilide **12** was obtained from the reaction of 4-bromoaniline (**8**) and diketene (**3**) and was cyclized in concentrated sulfuric acid at 120 °C in either 25.8%[16] or 52%[26] yield. A far more optimistic claim[27] will be commented upon in the following. As depicted in Scheme 2 and Table 1, many at-

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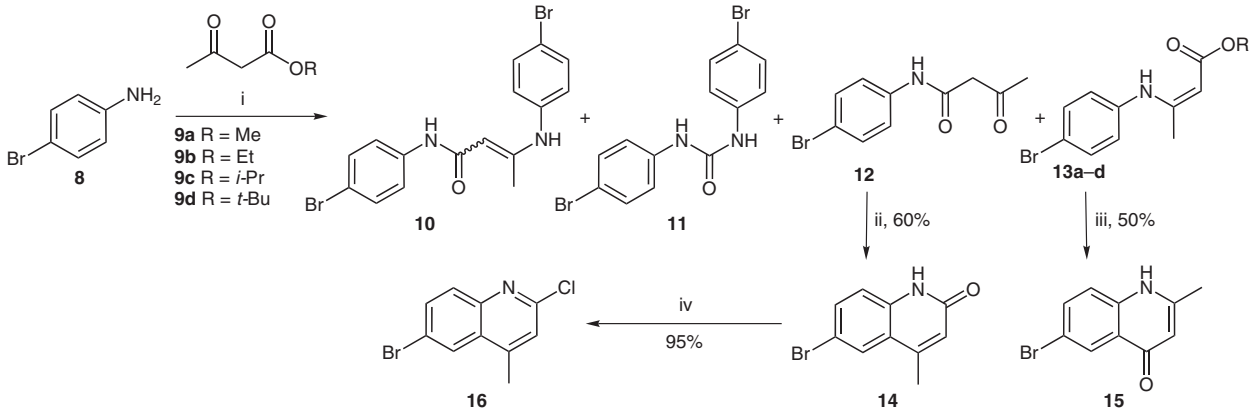


Scheme 2 *Reagents and conditions*: (i) MW, 1.7 mmol scale in 1 mL of solvent (see Table 1); (ii) H_2SO_4, 95 °C, 2 h; (iii) Ph_2O, 260 °C, 5 min, $POCl_3$, 80 °C, 12 h.

tempts were made to optimize the first step of this synthesis and, in order to shorten the reaction durations, we took recourse to microwave irradiation. Following the identification of the reaction products **10**–**13**, the ^{1}H NMR monitoring of the crude mixture of these attempts was essential in this optimization. Entries 1–3 point out that, in acetonitrile, reaction of aniline **8** and ethyl acetoacetate (**9b**) selectivity leads to anilide **12**. However, this is not the case if the temperature is raised beyond a threshold as urea **11** could be isolated (entry 4). This side reaction is actually described in Knorr's report.[1] Interestingly, the conversion into anilide **12** appears to reach a plateau, despite any reasonable increase of heating time, temperature, or change of solvents (entries 5–7). Even with a fivefold excess of aniline **8**, close to 15% of ethyl acetoacetate (**9b**) was still remaining in the reaction medium after extensive heating (entry 8). One previously reported[17] solution to this problem is the use of *tert*-butyl acetoacetate (**9d**). Indeed, contrary to ethanol or isopropanol (entry 9), the evolving *tert*-butyl alcohol does not hinder the reaction (entry 10) and we could isolate compound **12** in 84% yield. Adding ethanol to a solution of **12** in acetonitrile and heating the mixture revealed the slow occurrence of aniline **8**, as well as crotonate **13b**. Most importantly, we found out that water is detrimental to the preparation of **12**, either if the reactants are not dry or if water is deliberately added to the reaction. In the latter case, crotonate **12** and anilide **13c** were occurring at about the same rate (entry 11). The bis-condensation product **10** was sometime observed in the course of these attempts. Its preparation could not be fully achieved using the reported methods (i.e., stirring **8** and **12** in water in the presence of a phase transfer agent).[28,29] It turned out that the best conversion of **8** and **12** into **10** was achieved by heating these compounds in ethyl acetate in the presence of magnesium sulfate followed by extensive drying under high vacuum to remove most of the unreacted material. Acetic acid or *p*-toluenesulfonic acid (PTSA) as well as, under conventional heating, 4 Å molecular sieve were detrimental to the preparation of **12** (entries 12–14). This probably explains the use of small amounts of pyridine described in the literature,[24,30] which seems to have little effect per se (entry 15); aside from quenching any acid possibly present in the reaction. Concerning the use of solvent, a report[31] has claimed that heating a mixture of aniline **8** and ethyl acetoacetate (**9b**) with a domestic microwave oven (in an open vessel), leads to a 93% yield of anilide **12**. The fact that we only observed a mixture of compounds **10**–**12** and **13b**, when heating the same mixture in a chemistry-devoted microwave oven (entry 16), is at the very least puzzling. Another article[27] actually reports the direct preparation of **14** (in 91% yield) by heating a mixture of aniline **8** ethyl acetoacetate (**9b**) along with a small amount of PTSA in a similar domestic microwave oven. Our attempts under these conditions at various temperature were met with very little success as a mixture of compounds, including **12** and **13b**, was observed by ^{1}H NMR spectroscopy (entry 17). Moreover, under similar reaction conditions, a report from 1982 describes the dimerization of such anilides into pyridones.[32] In the same category, we also checked claims[33,34] describing the synthesis of various quinolin-2(1*H*)-ones in high yields using indium chloride. In our hands, we only saw the quick occurrence of the crotonate **13b**, as expected in light of all the reports describing acid-catalyzed preparation of such compounds.[8,30,35] To specifically[1] prepare compound **13b** from **8** and **9b**, 10 days at room temperature without solvent were necessary to obtain a mixture of the depicted crotonate and its isomer with or without the addition of PTSA. Interestingly, upon heating the crude mixture in cyclohexane, not only the reaction was completed but an isomerization also took place and pure isomer **13b** was isolated in 97% yield (entry 18). For comparison purposes, we then prepared the isomeric quinolin-4(1*H*)-one **15** by thermal cyclization of crotonate **13b** in 50% yield.[35]

Finally, cyclization of pure anilide **12** in 95–98% sulfuric acid (up to 0.1 mol of **12** in 200 mL) at 95 °C turned out to proceed in 60% yield. Interestingly, an attempt with the tenfold more concentrated conditions (1 mol of anilide in 185 mL) usually employed[3] led to an incomplete reaction. Finally, treatment of the resulting quinolone **14** with phosphorus oxychloride gave the target building block **16** in 95% yield.

Table 1 Optimization Attempts for the Preparation of Anilide **12**

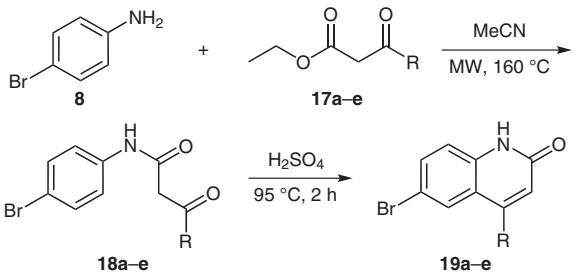
	Ratio **8**/**9a–d**	Solvent[a]	Additive	Temp (°C)/ Time (h)	**8** (%)[b]	**12** (%)[b]	**13a–d** (%)[b]	Comments
1	1:1.1 (**9b**)	MeCN	–	130/1	55	45	–	
2	1:1.1 (**9b**)	MeCN	–	160/0.5	38	62	–	
3	1:1.5 (**9b**)	MeCN	–	160/0.5	28	72	–	
4	1:1.1 (**9b**)	MeCN	–	200/1	0	64	8	8% of **10**; 5% **11** isolated
5	1:1 (**9b**)	acetone	–	130/1	45	50	–	5% of unidentified material
6	1:1 (**9b**)	EtOH	–	130/0.5	>95	<5	–	
7	1:1 (**9b**)	THF	–	130/0.5	55	45	–	
8	5:1 (**9b**)	MeCN	–	150/2	-	85	–	still 15% of unreacted **9b**
9	1:1 (**9c**)	MeCN	–	130/1	50	50	–	
10	1:1.1 (**9d**)	MeCN	–	160/0.5	8	92	–	84% of **12** isolated
11	1:1 (**9c**)	MeCN	–	130/0.5	33	33	25	H_2O present, 8% of **10**
12	1:1 (**9b**)	MeCN	AcOH (3 equiv)	130/0.5	33	26	33	8% of **10**
13	1:1 (**9b**)	MeCN	4 Å MS	130/0.5	58	18	20	4% of **10** (conventional heating)
14	1:1 (**9b**)	MeCN	PTSA (0.01 equiv)	130/0.5	40	43	8	8% of **10**
15	1:1 (**9b**)	MeCN	pyridine (1 equiv)	130/0.5	66	33	–	
16	1:1 (**9b**)	neat		18/72	70	–	30	
17	1:1 (**9b**)	neat	PTSA (0.01 equiv)	130/0.2	23	39	9	16% of **10**; 12% of **11**
18	1:1 (**9b**)	neat	PTSA (0.01 equiv)	18/240	10	0	90	97% yield of **13b** upon workup

[a] Unless otherwise stated, all solvents were dried over 4 Å molecular sieves.
[b] Yields estimated from ^{1}H NMR spectra.

With these optimized conditions, we also tried to prepare an array of quinolin-2(1*H*)-ones featuring various substituents. As depicted in Table 2, reaction of **8** with β-keto esters **17a–e** gave anilides **18a–e** in yields only reflecting, as above, the incompleteness of this condensation step when using ethyl β-keto esters. Moreover, drying the trifluoromethylated β-keto ester **17e** over 4 Å molecular sieves was essential to obtain the anilide **18e** in an unexpectedly acceptable yield; without the addition of water[12,36] or triethylamine[37] as reported for related examples. Decreasing the temperature to 130 °C in this specific case also lessened the incidence of decomposition. The full NMR characterization of this anilide was somehow problematic since, as noted before for such compounds,[37] it exists both as an enol and a hydrate in solution. By refluxing a sample in 2 M hydrochloric acid, we could shift this equilibrium to the fully hydrated form and thus assign all the NMR signals to each structure (see experimental part). Cyclization attempts of anilides **17a–d** in hot concentrated sulfuric acid pointed out an unexpected steric effect. While the corresponding 4-ethylquinolin-2(1*H*)-one (**19a**) was obtained in 57% yield, the 4-propyl and 4-isopropyl-bearing derivatives **19b** and **19c** were isolated in 34 and 11% yield, respectively, and the *tert*-butylanilide **18d** failed to cyclize as extensive hydrolysis was the sole result. Unexpectedly, the cyclization of the trifluoromethyl anilide **18e** took much longer to be completed. After two hours at 95 °C, about 50% of unreacted material could be recovered. Upon heating for 12 hours, the quinolin-2(1*H*)-one **19e** was then isolated in a remarkable 83% yield. Moreover, in light of some contradictions between the reported structural data[36,38] for this compound, a full NMR study of **19e** was performed. It is the fluorine–carbon long distance correlation between the fluorines and C-5 as well as C-6, which allowed this structure assignment. As very different ^{1}H NMR data were reported[38] for a substance obtained via the cyclization of anilide **18e** in polyphosphoric acid, our results strongly suggest a more thorough characterizations of any of the 4-trifluoromethylquinolin-2(1*H*)-one-bearings compound previously prepared by this method.[38,39] A substituent effect was actually reported to direct the outcome of the cyclization of various 4,4,4-trifluoroacetoacetanilides when using a mixture of phosphorus pentoxide and methanesulfonic acid.[12] A more recent report also describes the occurrence of 2-trifluoromethylquinolin-4(1*H*)-ones when using polyphosphoric acid.[37]

tert-Butyl acetoacetate (**9d**) was also condensed with anilines **20a–j** featuring various electron-attracting

Table 2 Preparation of Anilides **18a–e** and Quinolones **19a–e**

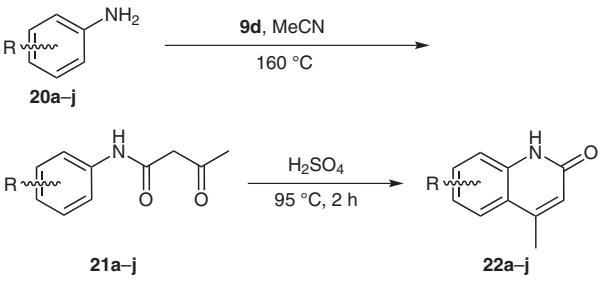


	R	**18** (%)[a]	**19** (from **18**) (%)[a]
a	Et	38	57
b	Pr	36	34
c	*i*-Pr	41	11
d	*t*-Bu	39	0 (hydrolysis)
e	CF_3	62 (at 130 °C)	83 (12 h)

[a] Isolated yields.

groups to give anilides **21a–j**, which were isolated in the yields provided in Table 3. Cyclization of the 2-bromoanilide **21a** in hot sulfuric acid only proceeded in 15% yield. This could reflect a steric hindrance, if a double protonation involving the nitrogen is required for this reaction.[11,20] However, cyclization of the homologous 2-fluoroanilide **21b** occurred in a similar 14% yield (20% have been reported in the past[23]), thus rather reflecting electronic effects on such double protonation. Cyclization of the 3-bromoanilide **21c** led to a much better 88% yield of 7-bromoquinol-2(1*H*)-one isomer **22c** containing traces of the alternative 5-bromoquinol-2(1*H*)-one. A cyclization attempt in the case of the 2,5-dihalogenated anilide **21d** only led to its complete hydrolysis. Cyclization of the 3-iodoanilide **21e** led to a 5:95 mixture of 5- and 7-iodoquinol-2(1*H*)-ones in 88% yield, which could not be separated at this stage. Cyclization of the 4-iodo derivative **21f** in hot sulfuric acid led to observable iodine evolution. However, following precipitation in water, compound **22f** was isolated in 56% yield. Only traces of the 6-trifluoromethylquinoline **22g** were observed from the 4-trifluoromethylanilide **21g**, along with extensive hydrolysis (including hydrolysis of the trifluoromethyl group). From the 3-trifluoromethylanilide **21h**, a complete hydrolysis of the amide bond was the sole reaction observed. The 4 carboxy-bearing anilides **21i** also failed to cyclize under the same reaction conditions. Following a report focusing on electron-rich anilides,[20] attempts with triflic acid (neat, up to 90 °C) failed to cyclize the electron-poor 4-trifluoromethylanilide **21g**, although a modest 6% of quinolone **22f** was obtained from 4-iodoanilide **21f**. Unexpectedly, the 4-nitroanilide **21j** underwent extensive hydrolysis in hot sulfuric acid although it had been reported to cyclize in unspecified yields.[24,40] This problem was also noted in 1930 and the author resorted to the 6-nitration of 4-methylquinolin-2(1*H*)-one to prepare **22j**.[40]

Table 3 Preparation of Anilides **21a–j** and Quinolones **22a–f**



	R	**21** (%)[a]	**22** (from **21**) (%)[a]
a	2-Br	56	15 (8-Br)
b	2-F	70	14 (8-F)
c	3-Br	71	88 (7-Br; 1% of 5-Br)
d	2,5-Br_2	37	0 (hydrolysis)
e	3-I	61	88 (7-I; 5% of 5-I)
f	4-I	66	56 (6-I)
g	4-CF_3	71	traces and hydrolysis
h	3-CF_3	74	0 (hydrolysis)
i	4-CO_2Me	61	0 (hydrolysis)
j	4-NO_2	68	0 (hydrolysis)

[a] Isolated yields.

However, since it seemed conceivable that the concentrated sulfuric acid of used in much older reports could be either closer to a 100% purity or much more diluted than the currently 95–98% available, few attempts were made. Accordingly, we either dried the available 95–98% sulfuric acid, by the addition of increasing amount of oleum, or diluted it up to 70% with water. From compound **21j**, the sole results of these attempts were its complete hydrolysis back into aniline **20j**.

This work clarifies and corrects some facts about the Knorr reaction and also offers a robust preparation of some halogenated quinol-2(1*H*)-ones, notably compound **14**. From these compounds, as in our work on pyrazoles,[41–43] we prepared building blocks such as the bis-halogenated quinoline **16**. These derivatives, featuring two nucleophilic centers with a difference of reactivity, allow the generation of vast array of new chemical entities in very few steps. Hopefully, we will report in the future their preparations as well as their effects on biological processes.

A Biotage initiator 2 microwave oven was used for reactions mentioning such heating method (infrared temperature monitoring; the irradiation time stated are the actual reaction time at the temperature mentioned). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts (δ) are given in ppm with respect to the TMS signal and coupling constants (*J*) are given in Hertz. High-

resolution mass spectra (HRMS-ES) were obtained using a Waters Micromass Q-Tof with an electrospray ion source.

1,3-Bis(4-bromophenyl)urea (11)
In a biotage tube (10 mL), aniline **8** (0.34 g, 2.61 mmol), and ethyl acetoacetate (**9b**; 0.26 g, 2.61 mmol) were dissolved in MeCN (1 mL, dried over 4 Å molecular sieves). This was heated in a microwave oven at 200 °C for 1 h before concentrating the solution to dryness. The residue was dispersed in EtOH (20 mL), filtered, washed with EtOH (50 mL), and dried to yield compound **11** (0.025 g, 5%); mp >260 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.40–7.80 (m, 8 H), 8.82 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 113.9, 120.7, 132.0, 139.4, 152.7.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}{}^{79}Br_2N_2O$: 368.9238; found: 368.9218.

N-(4-Bromophenyl)-3-(4-bromophenylamino)but-2-enamide (10)
Aniline **8** (0.2 g, 1.16 mmol), anilide **12** (0.3 g, 1.16 mol), and $MgSO_4$ (0.7 g, 5. mmol) were heated at 80 °C in EtOAc (10 mL) under a moisture-protected atmosphere for 12 h. The resulting suspension was filtered and concentrated to dryness under high vacuum to yield **10** (0.38 g, 79%) as a white powder still containing 10% of unreacted anilide **12**.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.05 (s, 3 H), 4.89 (s, 1 H), 7.08–7.14 (m, 2 H), 7.40–7.45 (m, 2 H), 7.46–7.50 (m, 2 H), 7.56–7.61 (m, 2 H), 9.66 (s, 1 H), 11.20 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.6, 21.2, 114.0, 116.2, 121.1, 125.1, 131.8, 132.4, 139.4, 139.7, 155.8, 168.7.

HRMS-ES; this compound readily fragments in positive mode: *m*/*z* [M – H]$^-$ calcd for $C_{16}H_{14}{}^{79}Br_2N_2O$; 406.9395: found: 406.9445.

Ethyl 3-(4-Bromophenylamino)but-2-enoate (13b)
Aniline **8** (3.53 g, 0.020 mol), ethyl acetoacetate (**9b**; 2.80 g, 0.021 mol), and PTSA (0.03g, 0.002 mol) were left to stir for 10 days. The resulting solid was heated to reflux in cyclohexane (50 mL), the cold solution was filtered, and concentrated to dryness to yield the pure isomer **13b** (5.70 g, 97%) as colorless crystals; mp 50 °C (Lit.[35] mp 54 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.20 (t, *J* = 7.0 Hz, 3 H), 2.02 (d, *J* = 0.5 Hz, 3 H), 4.03 (q, *J* = 7.0 Hz, 2 H), 4.73 (q, *J* = 0.5 Hz, 1 H), 7.15 (m, 2 H), 7.52 (m, 2 H), 10.33 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.9, 20.3, 58.7, 87.1, 117.2, 126.0, 132.4, 138.8, 158.8, 169.7.

^{15}N NMR (40 MHz, DMSO-d_6): δ = –263 (NH enamine), –248 (NH amide).

HRMS-ES: this compound readily fragments into 4-bromoacetylaniline in positive mode; *m*/*z* [M – H]$^-$ calcd for $C_{12}H_{14}{}^{79}Br\,NO_2$: 282.0130; found: 282.0187.

6-Bromo-2-methylquinolin-4(1*H*)-one (15)
Compound **13b** (2.77 g, 9.75 mmol) was heated to reflux in diphenyl ether (20 mL) for 5 min. The resulting cooled suspension was diluted in cyclohexane (30 mL) filtered, washed thoroughly with cyclohexane (3 × 50 mL), and left to dry in open air to yield compound **15** as a beige powder (1.16 g, 50%); mp >260 °C (Lit.[35] mp 338 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3 H), 5.95 (s, 1 H), 7.47 (d, *J* = 8.8 Hz, 1 H), 7.75 (dd, *J* = 2.2, 8.8 Hz, 1 H), 8.11 (d, *J* = 2.2 Hz, 1 H), 11.69 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.9, 109.2, 115.7, 120.8, 126.4, 127.4, 134.6, 139.4, 150.7, 175.8.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8{}^{79}BrNO_2$: 237.9868; found: 237.9800.

6-Bromo-2-chloro-4-methylquinoline (16)
Compound **14** (10 g, 0.042 mol) and $POCl_3$ (40 mL, 0.42 mol) were heated at 80 °C for 18 h in a flask protected by a $CaCl_2$ guard tube. The resulting mixture was poured onto excess of H_2O and ice (100 mL), and the resulting precipitate was filtered and dried to give compound **16** (10.1 g, 95%) as a white powder. Note: If necessary (i.e., if crude anilide was used) compound **16** can be recrystallized over charcoal in cyclohexane; mp 140 °C (Lit.[22] mp 139–139.8 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.66 (d, *J* = 1.0 Hz, 3 H), 7.51 (d, *J* = 1.0 Hz, 1 H), 7.86 (d, *J* = 9.1 Hz, 1 H), 7.92 (dd, *J* = 2.2 and 9.1 Hz, 1 H), 8.28 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.4, 120.7, 123.6, 127.4, 128.5, 131.0, 134.1, 146.1, 148.8, 150.7.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_8H_7{}^{79}Br^{35}ClN$: 255.9478; found: 255.9478.

Acetoacetanilides; General Procedure
In a biotage tube (10 mL), the respective aniline (0.01 mol) and β-keto ester (0.011 mol, dried over 4 Å molecular sieves) were dissolved in MeCN (4.5 mL, dried over 4 Å molecular sieves). This was heated in a microwave oven at 160 °C for 30 min (pressure reached 10 bar) before concentrating the solution to dryness. The resulting residues were further purified as described below.

***N*-(4-Bromophenyl)-3-oxobutanamide (12)**
Obtained as colorless crystals in 84% yield after a dispersion in boiling cyclohexane (50 mL); mp 143 °C (Lit.[44] mp 137.5 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.21 (s, 3 H), 3.55 (s, 2 H), 7.48 (m, 2 H), 7.54 (m, 1 H), 10.17 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.92 (s, 3 H), 5.18 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 10.05 (s, 1 H), 13.64 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.1, 52.3, 114.9, 121.0, 131.5, 138.2, 170.4, 202.6.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}{}^{79}BrNO_2$: 255.9973; found: 255.9946.

***N*-(4-Bromophenyl)-3-oxopentanamide (18a)**
Obtained in 38% yield as colorless crystals after a recrystallization from toluene (three crops); mp 141 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.95 (t, *J* = 7.1 Hz, 3 H), 2.57 (q, *J* = 7.1 Hz, 2 H), 3.54 (s, 2 H), 7.46 (m, 2 H), 7.56 (m, 2 H), 10.17 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.07 (t, *J* = 7.1 Hz, 3 H), 2.21 (q, *J* = 7.1 Hz, 2 H), 5.19 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 10.03 (s, 1 H), 13.65 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 7.9, 36.1, 51.7, 115.5, 121.5, 132.0, 138.7, 165.8, 205.5.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}{}^{79}BrNO_2$: 270.0130; found: 270.0112.

***N*-(4-Bromophenyl)-3-oxohexanamide (18b)**
Obtained in 36% yield as colorless crystals after a recrystallization from toluene (two crops); mp 119 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.86 (t, *J* = 7.1 Hz, 3 H), 1.54 (m, 2 H), 2.57 (t, *J* = 7.1, 2 H), 3.54 (s, 2 H), 7.50 (m, 4 H), 10.17 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 0.92 (t, *J* = 7.1 Hz, 3 H), 1.54 (m, 2 H), 2.12 (t, *J* = 7.1 Hz, 2

H), 5.19 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 10.02 (s, 1 H), 13.64 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.9, 16.9, 44.7, 52.0, 115.4, 121.5, 132.0, 138.7, 165.7, 205.0.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}{}^{79}BrNO_2$: 284.0286; found: 270.0220.

***N*-(4-Bromophenyl)-4-methyl-3-oxopentanamide (18c)**
Obtained in 41% yield as colorless crystals after a recrystallization from cyclohexane; mp 109 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.05 (d, *J* = 6.9 Hz, 6 H), 2.75 (sept, *J* = 6.9 Hz, 1 H), 3.62 (s, 2 H), 7.49 (m, 2 H), 7.57 (m, 2 H), 10.18 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.10 (d, *J* = 6.9 Hz, 6 H), 2.40 (sept, *J* = 6.9 Hz, 1 H), 5.20 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 10.08 (s, 1 H), 13.73 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.2, 40.8, 49.9, 115.4, 121.4, 132.0, 138.7, 165.8, 208.6.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}{}^{79}BrNO_2$: 284.0286; found: 284.0339.

***N*-(4-Bromophenyl)-4,4-dimethyl-3-oxopentanamide (18d)**
Obtained in 39% yield as colorless crystals after a recrystallization in cyclohexane; mp 124 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.41 (s, 9 H), 3.67 (s, 2 H), 7.48 (m, 2 H), 7.55 (m, 1 H), 10.20 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.41 (s, 3 H), 5.27 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 10.08 (s, 1 H), 13.95 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 26.8, 44.8, 46.6, 115.3, 121.4, 132.0, 138.8, 166.2, 209.9.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{16}{}^{79}BrNO_2$: 298.0443; found: 298.0447.

***N*-(4-Bromophenyl)-4,4,4-trifluoro-3-oxobutanamide (18e)**
A heating temperature of 130 °C instead of 160 °C somewhat lowered the formation of a side product. The crude mixture was then dissolved in EtOAc (50 mL), washed with aq 2 M HCl (3 × 25 mL) and then with brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated to dryness. The resulting residue was recrystallized from cyclohexane (three crops) to yield compound **18e** in 62% yield as a mixture of an enol and a hydrate form in variable proportions. By refluxing a sample in aq 2 M HCl (15 mL) followed by a filtration, mostly pure hydrate could be obtained (with little loss of material); mp 127 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ (hydrated form) = 2.77 (s, 2 H), 7.30 (br s, 2 H), 7.52 (m, 2 H), 7.58 (m, 2 H), 10.35 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ (hydrated form) = 40.5, 92.6 (q, *J* = 31 Hz), 116.0, 121.9, 123.7 (q, *J* = 287 Hz), 132.1, 138.1, 168.6.

From the NMR spectra of the mixture of an enol and a hydrate form described above, the following signals could be assigned to the enol form:

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.93 (s, 1 H), 7.52 (m, 2 H), 7.58 (m, 2 H), 10.35 (s, 1 H), 13.5 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 95.3, 116.9, 119.2 (q, *J* = 273 Hz), 122.3, 132.3, 137.3, 156.4 (q, *J* = 35 Hz), 168.3.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9{}^{79}BrF_3NO_3$ (hydrated form): 327.9796; found: 327.9796.

***N*-(2-Bromophenyl)-3-oxobutanamide (21a)**
Obtained in 56% yield as colorless crystals after a recrystallization from cyclohexane (two crops); mp 85 °C (Lit.[25] mp 95–97 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.23 (s, 3 H), 3.65 (s, 2 H), 7.11 (m, 1 H), 7.38 (m, 1 H), 7.65 (m, 1 H), 7.71 (m, 1 H), 9.71 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.92 (s, 3 H), 5.32 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 9.49 (s, 1 H), 13.64 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.6, 51.8, 117.4, 126.8, 127.3, 128.5, 133.1, 136.5, 165.8, 203.4.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}{}^{79}BrNO_2$: 255.9973; found: 255.9936.

***N*-(2-Fluorophenyl)-3-oxobutanamide (21b)**
Obtained in 70% yield as colorless crystals after dilution of the oily residue in EtOAc (50 mL), successive washing of the organic layer with aq 2 M HCl (25 mL) and brine (25 mL), drying of this organic layer ($MgSO_4$) and concentration to dryness under a high vacuum to remove some unreacted **9d**; mp 75 °C (Lit.[23] mp 75 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.20 (s, 3 H), 3.65 (s, 2 H), 7.15 (m, 2 H), 7.25 (m, 1 H), 7.97 (m, 1 H), 9.88 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.92 (s, 3 H), 5.37 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 9.70 (s, 1 H), 13.64 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.5, 52.2, 115.9 (d, *J* = 19 Hz), 124.1, 124.8, 125.6 (d, *J* = 7 Hz), 126.4 (d, *J* = 11 Hz), 153.8 (d, *J* = 244 Hz), 166.0, 203.3.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}FNO_2$: 196.0774; found: 196.0740.

***N*-(3-Bromophenyl)-3-oxobutanamide (21c)**
Obtained in 71% yield as colorless crystals after a dispersion of the crude compound in boiling cyclohexane; mp 110 °C (Lit.[16] mp 94–95 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.21 (s, 3 H), 3.56 (s, 2 H), 7.27 (m, 2 H), 7.44 (m, 1 H), 7.95 (m, 1 H), 10.22 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.93 (s, 3 H), 5.18 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 10.05 (s, 1 H), 13.57 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.6, 52.8, 118.3, 121.9, 122.0, 126.5, 131.2, 140.9, 165.9, 203.0.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}{}^{79}BrNO_2$: 255.9973; found: 255.9942.

***N*-(2,5-Dibromophenyl)-3-oxobutanamide (21d)**
Obtained in an unoptimized 37% yield as colorless crystals after a recrystallization from cyclohexane (2 crops); mp 124 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.22 (s, 3 H), 3.68 (s, 2 H), 7.32 (dd, *J* = 2.2, 8.5 Hz, 1 H), 7.62 (d, *J* = 8.5 Hz, 1 H), 8.01 (d, *J* = 2.2 Hz, 1 H), 9.80 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.94 (s, 3 H), 5.34 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 9.58 (s, 1 H), 13.41 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.7, 51.7, 115.6, 120.8, 128.3, 129.7, 134.8, 138.0, 166.1, 203.5.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9{}^{79}Br_2NO_2$: 333.9078; found: 333.9082.

***N*-(3-Iodophenyl)-3-oxobutanamide (21e)**
Obtained in 61% yield as colorless crystals after a recrystallization from toluene; mp 111 °C (Lit.[45] mp 110–112 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.21 (s, 3 H), 3.55 (s, 2 H), 7.11 (t, *J* = 8.0 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.49 (dd, *J* = 8.0, 1.7 Hz, 1 H), 8.10 (d, *J* = 1.7 Hz, 1 H), 10.15 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.93 (s, 3 H),

5.17 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 9.97 (s, 1 H), 13.58 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.6, 52.8, 95.0, 118.8, 127.7, 131.3, 132.4, 140.7, 165.8, 203.0.

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{10}H_{10}INO_2$: 303.9835; found: 303.9853.

_N_-(4-Iodophenyl)-3-oxobutanamide (21f)
Obtained in 66% yield as colorless crystals after a recrystallization from toluene; mp 150 °C (Lit.[46] mp 144 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.20 (s, 3 H), 3.55 (s, 2 H), 7.40 (m, 2 H), 7.65 (m, 1 H), 10.15 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.92 (s, 3 H), 5.18 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 9.97 (s, 1 H), 13.65 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.6, 52.8, 87.3, 121.7, 137.8, 139.2, 165.7, 203.1.

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{10}H_{10}INO_2$: 303.9835; found: 303.9828.

3-Oxo-_N_-[4-(trifluoromethyl)phenyl]butanamide (21g)
Obtained in 71% yield as colorless crystals after a dispersion of the crude compound in boiling cyclohexane (50 mL); mp 157 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.22 (s, 3 H), 3.61 (s, 2 H), 7.67 (m, 2 H), 7.86 (m, 2 H), 10.41 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.94 (s, 3 H), 5.24 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 10.23 (s, 1 H), 13.59 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.6, 52.8, 119.8, 123.9 (q, *J* = 32 Hz), 125.0 (q, *J* = 270 Hz), 126.5, 142.9, 166.2, 202.9.

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{11}H_{10}F_3NO_2$: 246.0742; found: 246.0684.

3-Oxo-_N_-(3-(trifluoromethyl)phenyl)butanamide (21h)
Obtained in 74% yield as colorless crystals after a dispersion of the crude compound in boiling cyclohexane (50 mL); mp 114 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.22 (s, 3 H), 3.59 (s, 2 H), 7.40 (m, 1 H), 7.53 (m, 1 H), 7.75 (m, 1 H), 8.08 (m, 1 H), 10.42 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.94 (s, 3 H), 5.20 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 10.23 (s, 1 H), 13.54 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.7, 52.8, 115.5, 120.2, 123.0, 124.5 (q, *J* = 273 Hz), 129.4 (q, *J* = 32 Hz), 130.5, 140.1, 166.1, 203.0.

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{11}H_{10}F_3NO_2$: 246.0854; found: 246.0815.

Methyl 4-(3-Oxobutanamido)benzoate (21i)
Obtained in 61% yield as colorless crystals after a recrystallization in toluene; mp 112 °C (Lit.[47] mp 119 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.22 (s, 3 H), 3.60 (s, 2 H), 3.82 (s, 3 H), 7.72 (m, 2 H), 7.93 (m, 2 H), 10.38 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.94 (s, 3 H), 3.82 (s, 3 H), 5.24 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 10.21 (s, 1 H), 13.60 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.7, 52.3, 52.9, 118.9, 124.6, 130.8, 143.7, 166.1, 166.2, 203.0.

Some NMR data have been previously described for this compound.[48]

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{12}H_{13}NO_4$: 236.0923; found: 236.0892.

_N_-(4-nitrophenyl)-3-oxobutanamide (21j)
Obtained in 47% yield as a yellow powder after a recrystallization in toluene, mp 129 °C (Lit.[24] mp 122–124 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.23 (s, 3 H), 3.65 (s, 2 H), 7.80 (m, 2 H), 8.23 (m, 2 H), 10.66 (s, 1 H). Additional signals (1/10th in intensity) belong to the enol form: 1.96 (s, 3 H), 5.25 (s, 1 H), CH_{arom} undifferentiated from the main tautomeric form, 10.50 (s, 1 H), 13.48 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.7, 52.9, 119.2, 125.4, 142.7, 145.2, 166.5, 202.9.

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{10}H_{10}{}^{79}BrN_2O_4$: 223.0719; found: 223.0688.

Cyclization of Anilides; General Procedure
In a flask protected from moisture by a $CaCl_2$ guard tube, the respective anilide (2.5 mmol) was heated at 95 °C in concd H_2SO_4 (3 mL) for 2 h. Upon cooling, the solution was poured into H_2O (300 mL) and (except for **22a**,**b**) the resulting precipitate was filtered, thoroughly washed with H_2O, and dried in an oven under reduced pressure.

6-Bromo-4-methylquinolin-2(1*H*)-one (14)
Yield: 60%; white powder; mp >240 °C (Lit.[24] mp 292–294 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.41 (s, 3 H), 6.44 (s, 1 H), 7.26 (d, *J* = 8.8 Hz, 1 H), 7.65 (dd, *J* = 2.2, 8.8 Hz, 1 H), 7.84 (d, *J* = 2.2 Hz, 1 H), 11.69 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.8, 114.0, 118.0, 121.8, 122.4, 127.4, 133.3, 138.2, 147.5, 161.8.

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{10}H_8{}^{79}BrNO_2$: 237.9868; found: 237.9831.

6-Bromo-4-ethylquinolin-2(1*H*)-one (19a)
Yield: 57%; white powder; mp 239 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.22 (t, *J* = 7.1 Hz, 3 H), 2.82 (q, *J* = 7.1 Hz, 2 H), 6.39 (s, 1 H), 7.27 (d, *J* = 8.7 Hz, 1 H), 7.65 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.89 (d, *J* = 2.1 Hz, 1 H), 11.70 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.2, 24.5, 114.1, 118.2, 120.4, 121.0, 126.9, 133.2, 138.4, 152.6, 161.9.

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{11}H_{10}{}^{79}BrNO$: 252.0024; found: 251.9978.

6-Bromo-4-propylquinolin-2(1*H*)-one (19b)
Yield: 34%; white powder; mp 211 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.97 (t, *J* = 7.3 Hz, 3 H), 1.63 (m, 2 H), 2.75 (t, *J* = 7.2 Hz, 2 H), 6.38 (s, 1 H), 7.26 (d, *J* = 8.7 Hz, 1 H), 7.63 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.87 (d, *J* = 2.1 Hz, 1 H), 11.71 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.1, 22.0, 33.3, 114.1, 118.2, 121.1, 121.5, 127.0, 133.2, 138.5, 151.0, 161.8.

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{12}H_{12}{}^{79}BrNO$: 266.0181; found: 266.0137.

6-Bromo-4-isopropylquinolin-2(1*H*)-one (19c)
Yield: 11%; white powder; mp 180 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.2 (d, *J* = 6.9 Hz, 6 H), 3.39 (sept, *J* = 6.9 Hz, 1 H), 6.40 (s, 1 H), 7.28 (d, *J* = 8.7 Hz, 1 H), 7.64 (dd, *J* = 8.7, 2.0 Hz, 1 H), 7.95 (d, *J* = 2.0 Hz, 1 H), 11.76 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.5, 28.0, 114.2, 118.4, 118.44, 120.5, 126.7, 133.2, 138.5, 157.0, 162.1.

HRMS-ES: *m/z* [M + H]$^+$ calcd for $C_{12}H_{12}{}^{79}BrNO$: 266.0181; found: 266.0173.

6-Bromo-4-(trifluoromethyl)quinolin-2(1*H*)-one (19e)
Obtained as described above in a 83% yield, although after a 12 h long heating time instead of 2 h. As some contradictory ^{1}H NMR data were reported in the past,[36,38] extensive NMR experiments on a Varian NMR system operating at a ^{1}H frequency of 500 MHz, were made to ascertain the structure of compound **19e**. A F/C HMBC experiment (with a 120 ms multiple bond delay) pointed out a correlation between the fluorines and C-5 of the quinoline ring only compatible with the depicted structure; mp 227 °C (sub.).

Our ^{1}H NMR data in acetone-d_6 provided below, agree with the one partially reported on page 120 of a patent.[36]

^{1}H NMR (500 MHz, DMSO-d_6 used as internal reference: δ = 2.50): δ = 6.97 (s, 1 H, H-3), 7.32 (d, *J* = 8.9 Hz, 1 H, H-8), 7.63 (d, *J* = 2.0 Hz, 1 H, H-5), 7.72 (dd, *J* = 8.9, 2.0 Hz, 1 H, H-7), 12.39 (s, 1 H, H-1).

For comparison with the ^{1}H spectra previously reported:[38]

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.02 (s, 1 H), 7.53 (d, *J* = 8.80 Hz, 1 H), 7.81 (dd, *J* = 8.8, 1.9 Hz, 1 H), 7.63 (d, *J* = 1.9 Hz, 1 H), 11.22 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6 used as internal reference: δ = 40.0): δ = 114.9 (s, C-4a), 114.9 (s, C-8a), 119.0 (d, $J_{C,H}$ = 166 Hz, C-8), 122.7 (dq, $J_{C,F}$ = 275 Hz, $J_{C,H}$ = 4 Hz,CF_3), 123.7 (d, $J_{C,H}$ = 173 Hz, C-3), 126.3 (d, $J_{C,H}$ = 168 Hz, C-5), 134.7 (d, $J_{C,H}$ = 169 Hz, C-7), 135.8 (dq, $J_{C,F}$ = 30 Hz, $J_{C,H}$ = 4 Hz, C-4), 139.3 (t, $J_{C,H}$ = 8 Hz, C-6), 160.1 (s, C-2).

^{19}F NMR (470 MHz, DMSO- d_6): δ = –61.1 (referenced with internal capillary containing TFA 99%: δ = –76.55).

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_5{}^{79}BrF_3NO$: 289.9428; found: 289.9362.

8-Bromo-4-methylquinolin-2(1*H*)-one (22a)
Obtained as a white powder in 10% yield by precipitation. An additional 5% of compound **22a** was obtained by extraction of the neutralized filtrate with EtOAc followed by a dispersion of the resulting residue in cyclohexane to remove the aniline also extracted; mp 192 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.45 (s, 3 H), 6.51 (s, 1 H), 7.17 (t, *J* = 7.9 Hz, 1 H), 7.76 (m, 1 H), 7.84 (m, 1 H), 10.19 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6, D1 set to 10 s): δ = 19.1, 109.0, 122.0, 123.4, 125.3, 134.3, 136.4, 148.8, 161.7; one signal missing.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8{}^{79}BrNO_2$: 237.9868; found: 237.9804.

8-Fluoro-4-methylquinolin-2(1*H*)-one (22b)
The diluted solution was extracted with EtOAc (3 × 50 mL), the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated to dryness. The resulting residue was recrystallized from toluene to yield compound **22b** as a white powder in 14% yield; mp 250 °C (Lit.[23] mp 235 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.42 (s, 3 H), 6.47 (s, 1 H), 7.18 (m, 1 H), 7.40 (m, 1 H), 7.54 (m, 1 H), 11.55 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.1, 115.9 (d, *J* = 17 Hz), 121.0 (d, *J* = 3 Hz), 121.8 (*J* = 8 Hz), 122.2, 122.5, 127.8 (d, *J* = 13 Hz), 148.2, 149.5 (d, *J* = 242 Hz), 161.7.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8FNO_2$: 178.0668; found: 178.0651.

7-Bromo-4-methylquinolin-2(1*H*)-one (22c)
Yield: 88%; white powder. Traces of the 5-bromo isomer can be detected on the ^{1}H NMR spectra; mp >250 °C (Lit.[24] mp 286–288 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.45 (s, 3 H), 6.47 (s, 1 H), 7.40 (m, 1 H), 7.53 (m, 1 H), 7.69 (m, 1 H), 11.67 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.8, 118.0, 119.2, 121.7, 123.7, 124.9, 127.2, 140.2, 148.1, 161.9.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8{}^{79}BrNO_2$: 237.9869; found: 237.9833.

7-Iodo-4-methylquinolin-2(1*H*)-one (22e)
Yield: 88%; white powder containing about 5% of the 5-iodo isomer; mp >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.44 (s, 3 H), 6.42 (s, 1 H), 7.50 (m, 2 H), 7.68 (d, *J* = 1.5 Hz, 1 H), 11.56 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.7, 97.3, 119.5, 121.9, 124.0, 127.0, 130.6, 140.2, 148.2, 161.7.

HRMS-ES: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8INO_2$: 285.9729; found: 285.9664.

6-Iodo-4-methylquinolin-2(1*H*)-one (22f)
Yield: 56%; white powder; mp >250 °C (Lit.[49] mp 290 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.40 (s, 3 H), 6.41 (s, 1 H), 7.12 (d, *J* = 8.6 Hz, 1 H), 7.78 (dd, *J* = 8.6, 1.9 Hz, 1 H), 7.98 (d, *J* = 1.9 Hz, 1 H), 11.65 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.8, 85.4, 118.1, 122.2, 122.3, 133.3, 138.6, 147.4, 161.8.

HRMS: *m*/*z* calcd for $C_{10}H_8NO_2I$ – H: 283.9572; found: 283.9587.

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