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Novel approach to synthesis of substituted 3-aminoquinolines from nitroarenes and protected ethyl aminocrotonate

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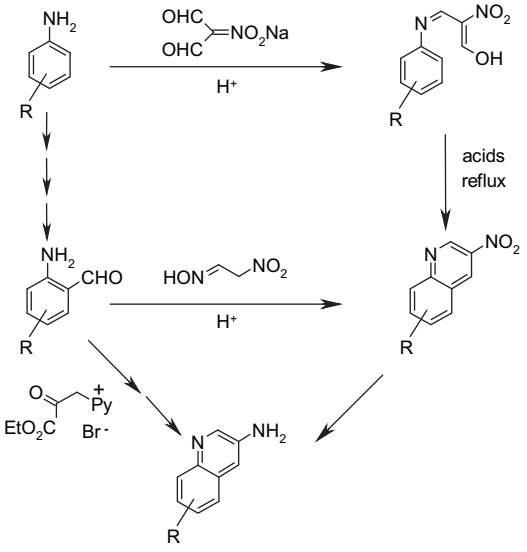
ABSTRACT

The addition of mono- and dianions of ethyl *N*-pivaloyl-3-aminocrotonate to substituted nitroarenes, followed by action of silylating or acylating agent, leads to 3-aminoquinoline carboxylic acid derivatives. Hydrolysis and decarboxylation of the latter, carried out efficiently under relatively mild conditions, afford 3-aminoquinolines diversely substituted in the benzo-fused ring.

1. Introduction

3-Aminoquinolines are frequently employed in synthesis and modifications of a variety of potentially biologically active compounds.[1] In particular, 3-aminoquinoline terminated dipeptides have been found to exhibit interesting pharmacological properties.[1a–c] Taking part in a project directed towards compounds of similar structure and of potential biological activity, we were required to synthesize 3-aminoquinolines bearing numerous different substituents, such as Cl, Br, F, CF_3 and others, in the benzo-fused ring. Literature reports on synthesis of such derivatives, which have no additional substituents in the heterocyclic part of the molecule, or have such substituents, which could be easily removed, are rare. A majority of them are based upon the reduction of the corresponding 3-nitroquinolines. Preparation of the latter can be accomplished by nitration of the quinoline ring, or much more conveniently and regioselectively, by construction of the heterocyclic ring on substituted aniline derivative.[2] The latter approach involves two pathways (Scheme 1). The first one is based on a two-step condensation of the appropriate aniline with the sodium salt of nitromalonaldehyde[3]—an explosive compound prepared from mucobromic acid.[4] Although the first step, formation of Schiff bases (anils), is usually efficient, the cyclization step leading to the bicyclic skeleton requires selected conditions of acidic catalysis and produces variable results. The electrophilic character of the reaction limits the whole synthesis to anilines bearing electron-donating substituents.[3b] This method has been applied to preparation of 6-methyl- and 6-methoxy- derivatives of 3-aminoquinolines.[3a,b]



Scheme 1. Common synthetic pathways leading to 3-aminoquinolines.

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Another, more general method, which could be suitable also for electron deficient systems, is the Friedlander-type condensation,[5] which comprises reaction of 2-formylanilines with nitroacetaldehyde oxime (metazonic acid)[6]—a product of self-condensation of nitromethane under basic conditions.[7] The drawback of this method is that the desired 2-formylanilines are usually unstable and their preparation from easily available substrates is difficult.[8–10] Directed metallation of *N*-protected anilines[8] or bromoanilines[9] followed by action of dimethylformamide, and reduction of *ortho*-nitro aryl aldehydes[10] are employed in this respect.

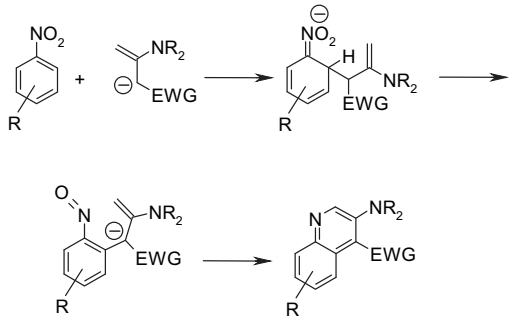
An interesting synthesis of a few substituted 3-aminoquinolines, omitting preparation of corresponding nitroquinolines, comprises condensation of substituted 2-formylanilines with 1-(2-ethoxy carbonyl-2-oxoethyl)pyridinium bromide, which, followed by aminolysis with pyrrolidine, leads to 3-aminoquinoline-2-carboxy lates.[11] In view of possible further decarboxylation of the latter, it can be considered as a potential precursor of the target 3-aminoquinolines. The method, however, also depends on availability of appropriate 2-formylanilines.

The considerations presented above and also attempted preparations of selected target 3-aminoquinolines, carried out according to known schemes, led us to the conclusion, that synthesis of 3-aminoquinolines in general, and particularly those bearing electronwithdrawing groups, is a really demanding task and made us think about an alternative, shorter and/or more effective way of their preparation.

Working for the last decade on synthesis of polycyclic nitrogen compounds we have found that the combination of a base and a Lewis acid promoted multistep reactions of nitroarenes with properly functionalized precursors of allylic anions, leading to various substituted quinolines and other bicyclic heterocycles with a fused pyridine ring.[12] Similar approach was successful also in transformations of nitroarenes—depending on the structure of the nucleophilic agent—into 1-hydroxyindole,[13] 2,1-benzisoxazole[14,15b] or acridine[15,16] systems. The role of the Lewis acid could be played efficiently also by silylating[12a–c,15,16] or acylating agents.[16] Thus we decided to adopt this methodology for synthesis of the title compounds.

2. Results and discussion

As we have found earlier, the reaction of nitroarenes with allylic carbanions leads to a new fused pyridine ring via addition of the more nucleophilic centre of the ambident anion at the *ortho* position with formation of σ^H-adducts, followed by transformation of the nitro group into a nitroso group—promoted by base and Lewis acid, silyl or acyl halide—then completed by condensation of the nitroso function with a side-chain allylic anion. Accordingly, the assumed course of the reaction leading to 3-aminoquinoline derivatives, is depicted on Scheme 2.



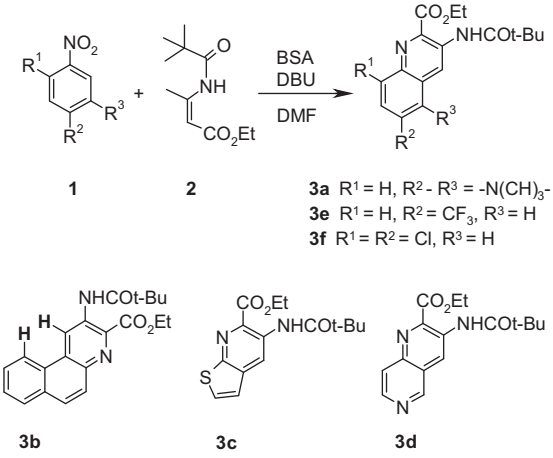
Scheme 2. Projected synthesis of substituted 3-aminoquinoline precursors.

The ester group was chosen for stabilization of the allylic anion, bearing in mind its further removal from the expected cyclization product. In preliminary experiments, commercial and cheap ethyl-3-aminocrotonate was employed.

On the basis of our earlier results, two procedures were examined for the reaction—the so called 'one-pot' procedure[12] and the 'step-by-step' method.[16] The first one consists of mixing the substrates with *N*,*O*-bis-trimethylsilylacetamide (BSA) and DBU in DMF at ambient temperature, for an adequate—usually prolonged—time. In the second procedure, deprotonation of the aminocrotonate with strong base, formation of σ^H-adducts with the nitroarene, its transformation into nitroso compound promoted by pivaloyl chloride and final cyclization—although carried out in the same pot—were time-separated. The process was carried out at −78 °C in order to attain possibly high stability of the intermediate σ^H-adduct.

Unfortunately, for ethyl 3-aminocrotonate treated with nitroarenes such as 4-chloro- and 2,4-dichloronitrobenzene, neither of the above methods led to the desired products. Hence, one can suppose, that protection of the amino function to avoid its deprotonation is necessary to generate the allylic anion. However, attempted reactions of an *N*,*N*-disubstituted derivative, namely ethyl-3-phthalimidocrotonate, were also unsuccessful. On the other hand, *N*-benzoyl and *N*-pivaloyl aminocrotonates gave positive preliminary results, and the latter—more promising—was subjected to the further inspection.

Thus, when ethyl 3-(*N*-pivaloylamino)crotonate[17] **2** was reacted with substituted nitrobenzenes and selected heterocyclic nitroarenes (**1**) under 'one-pot' conditions, the slow reactions led to the 3-aminoquinoline derivatives, but the yields were generally low. Only the more electrophilic 6-nitroquinoline (**1a**) gave the cyclization product in moderate 30% yield, while substituted nitrobenzenes (**1e**,**f**) reacted very poorly (Scheme 3, Table 1).



Scheme 3. One-pot synthesis of precursors of 3-aminoquinolines.

Table 1
One-pot condensation of nitroarenes **1** with **2**

Entry	Nitroarene			**3**	Yield [a]/%
	R1	R2	R3		
1	H	–N(CH)$_3$–		**a**	30
2	H	–(CH)$_4$–		**b**	20
3		[b]		**c**	18
4		[c]		**d**	11
5	H	CF_3	H	**e**	6
6	Cl	Cl	H	**f**	2

[a] Isolated.
[b] 2-Nitrothiophen.
[c] 4-Nitropyridine.

Surprisingly, the isolated cyclization product **3** did not have the expected structure, with the ethoxycarbonyl group at position 2 of the quinoline system. The substitution pattern was unambiguously determined by means of 1D NOESY experiments applied to **3b**, in which protons at positions 1 (singlet, 10.5 ppm) and 10 (multiplet, around 8.7 ppm) demonstrated a strong NOE effect. In this case numbering of the ring positions obeys the rules for benzoquinoline systems (corresponding protons are indicated on Scheme 3).

Formation of **3** implies that addition of **2** to the nitroaromatic ring occurred with its terminal carbon atom 4. It is obvious that action of the base (DBU) on **2** should preferentially lead to the abstraction of the amide proton with formation of the most stable, strongly delocalised allylic anion $\mathbf{2}^{-}\boldsymbol{N}$ (Fig. 1). Apparently, its nucleophilicity is too low to produce σ^{H}-adducts with nitroarenes. Instead, less stable allylic anion $\mathbf{2}^{-}\boldsymbol{C}$ or, maybe, dianion $\mathbf{2}^{2-}$, although formed in very low concentrations, are reactive enough to react with the nitroarene, leading to the cyclization products **3**.

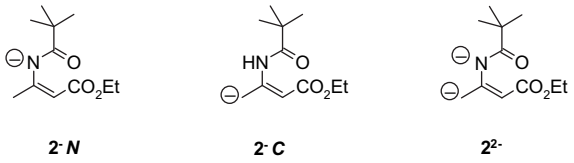
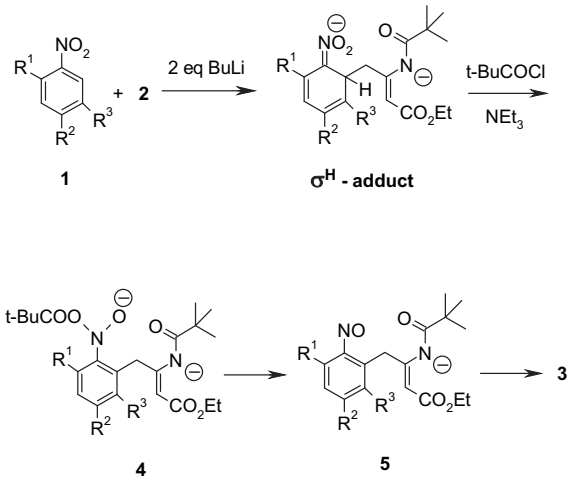


Figure 1. Possible anions generated from **2**.

In the light of these results, we decided to produce a more reactive nucleophile from **2**, by generating its dianion $\mathbf{2}^{2-}$ in higher concentration. This process required stronger base for the second deprotonation, therefore we applied the 'step-by-step' procedure (Scheme 4).



Scheme 4. Reaction pathway of the step-by-step synthesis of **3**.

Preliminary attempts at generation of dianion $\mathbf{2}^{2-}$ were done by means of NaH and *n*-BuLi added consecutively as in the usual methodology used for generation of dianions from β-dicarbonyl compounds.[18] Optimization of selected reaction conditions of the model reaction of **2** with **1f** (Table 2) revealed that this procedure could be simplified by use of *n*-BuLi alone as a base in the presence of 2.2 equiv of HMPA. It was found that the yield of products **3** was somewhat improved by use of a twofold excess of nitroarene **1**, the unreacted part of which could be easily recovered. This observation may indicate the importance of the σ^{H}-adduct formation step, as the excess of **1** shifts its equilibrium. On the other hand, conversion of **1**, which, in many cases, is much higher than the yield of the product, and sometimes exceeds stoichiometric amount (the cases when the yield based on consumed **1** is lower than that, based on **2** in Table 3) show that also some side reactions can be responsible for observed requirement of the excess of the nitroarene. In the reactions finished at room temperature a difficult to separate product of pivaloylation of $\mathbf{2}^{2-}$ was formed in substantial amounts.[19] Its formation was, however, suppressed by quenching the reaction mixture at −78 °C.

Table 2
Step-by-step synthesis of **3f** from **1f** and **2** carried out under various reaction conditions

Entry	Base/equiv		HMPA/equiv.	**1f**:**2** ratio	Procedure[a]	Yield[b]/%
	NaH	*n*-BuLi				
1	1.3	1.2	—	1	A	23
2	1.3	1.2	2	1	A	34
3	1.4	2	2	0.9	A	45
4	1.1	2[c]	2	0.9	A	30
5	1.3	2	4	1.4	A	31
6	1.3	2	2	3	B	54
7	—	3	2	3	B	49
8	—	2.2	2	2	B	57
9	—	2.2	2	1	B	41

[a] Procedure A: dianion of **2** was treated with **1f** for 10 min at −78°C then 4 equiv of Et_3N and 4 equiv of pivaloyl chloride were added. The mixture was heated to room temperature, stirred for 2 h and quenched. B: as procedure A, but after addition of pivaloyl chloride the mixture was stirred at −78°C for 2 h, then quenched at that temperature.
[b] Isolated by column chromatography. Based on **2**.
[c] LDA instead of *n*-BuLi was used.

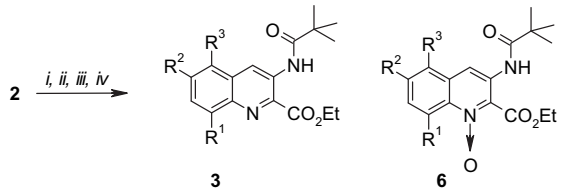
Table 3
Step-by-step condensation of substituted nitroarenes **1** with dianion of **2**

Entry	R1	R2	R3	**3**	Yield[a]/%	
					Based on **2**	On consumed **1**
1	H	CF_3	H	**e**	24	18
2	Cl	Cl	H	**f**	57	41
3	F	H	H	**g**	44	40
4	Cl	H	H	**h**	47	52
5	Br	H	H	**i**	34 (9)[b]	35 (9)[b]
6	Cl	H	CH_2OCOt-Bu	**j**	47	78
7	Cl	H	CF_3	**k**	47	34
8	Br	Cl	H	**l**	48	32
9	Cl	CO_2t-Bu	H	**m**	40	31
10	Cl	H	Cl	**n**	31	52
11	CN	Cl	H	**o**	23	26
12	CO_2t-Bu	Cl	H	**p**	20 (7)[b]	26 (9)[b]
13	Cl	OMe	H	**q**	13 (13)[b]	25 (25)[b]
14	CO_2t-Bu	H	H	**r**	20	20
15	CN	H	H	**s**	16	—[c]
16	H	CN	H	**t**	16	23
17	H	F	H	**u**	17[d]	28
18	H	Cl	H	**v**	5	25

[a] Isolated yields.
[b] Yield of **6** in parentheses.
[c] Not estimated.
[d] Prior to the quench the reaction mixture was warmed to room temperature and stirred overnight.

It is worth mentioning, that the product obtained in the model reaction of **1f** with the dianion $\mathbf{2}^{2-}$ was identical with that isolated from the 'one-pot' reaction of **1f**, and this result was actually a reason to disprove the initially assumed structure of the latter product, shown in Scheme 2.

On the basis of the results of introductory experiments, conditions presented in Table 2, entry 8, and procedure B were chosen, and applied in the step-by-step reactions of **2** with numerous differently substituted nitroarenes (Scheme 5, Table 3). Intentionally, most of the substituents are of electronwithdrawing character, since such electron deficient aromatic substrates were difficult to transform into corresponding aminoquinolines following known methods (see above).



Scheme 5. Reagents and conditions: (i) 2.2 equiv of HMPA, 2.2 equiv of BuLi/THF −78 °C (ii) 2 equiv of **1** (iii) 4 equiv of NEt_3, 4 equiv of *t*-BuCOCl (iv) H_2O −78 °C.

All products of the 'step-by-step' reactions were assumed to have a structure of **3**, i.e., ethoxycarbonyl substituent in vicinity of the ring nitrogen, on the basis of the expected reactivity of the dianion $\mathbf{2}^{2-}$. This assumption was confirmed by ^{1}H NMR selective NOESY 1D spectra of **3h** in which protons at positions 4 (s, 9.07 ppm) and 5 (dd, 8.01 ppm) showed evident NOE effect.

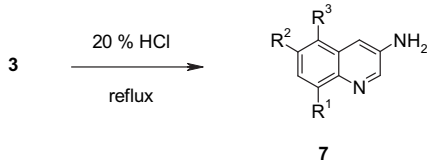
The results indicate that although electronegative groups facilitate formation of σ^H-adducts—an inevitable intermediate in the synthesis—activation of the aromatic ring is not the most important factor governing the entire, multistep process. The best results were obtained from nitroarenes with the *ortho*-position occupied by a halogen atom (Table 3, entries 2–10), and the effect of additional activation of the ring by strong EWG (CF_3, CO_2t-Bu) at the *meta* or *para* positions was not observed (entries 7 and 9). Moreover, replacing the *ortho*-halogen atom in **1** with CO_2t-Bu and CN groups led to significantly worse results (entries 14 and 15). Apparently, the helpful role of the *ortho*-halogens is an effect of a combination of their electronegativity, activating the ring for nucleophilic addition at the other *ortho* position, and adequate steric hindrance, which may facilitate formation of the nitroso intermediates (**4** → **5**, Scheme 4) and also increases resistance of the latter against possible side reactions. 2-Iodonitrobenzene did not enter the reaction; it seems that steric effect of the exceptionally bulk *ortho*-halogen significantly reduces electrophilic reactivity of the nitroaromatic ring.

In a few cases (entries 5, 12 and 13), along with formation of **3**, noticeable amounts of their *N*-oxides (**6**) are produced (Scheme 5). Their origin is unknown yet. Possibly, they come from the oxidation of σ^H-adducts (e.g., by the excess of the nitroarene) and subsequent intramolecular condensation of the nitro, instead of the nitroso, group.

temperature prior to the quench. From the reaction performed in the usual way i.e., when quenched at −78 °C, the only defined product isolated was nitroso compound **5uH** (Scheme 4, **H** refers to the protonated form). It was unstable, but could be isolated, purified and fully characterized including the ^{15}N NMR spectrum, confirming the nitroso form against the tautomeric oxime structure. Nitroso derivatives were often postulated as intermediates in reactions of nitroarenes with nucleophiles leading to various nitrogen heterocycles, but to our knowledge, they have never been isolated from such reactions.[20]

Compound **5uH** could be transformed to quinoline **3u** either under the previous reaction conditions or under improved conditions, consisting of trimethylsilyl chloride and Et_3N in DMF at room temperature. In both cases the reactions were not very efficient (11 and 24% yield, respectively), which may explain the low yield of **3u** obtained in the reaction of **2** with **1u** (Table 3, entry 17). The exceptional behaviour of 4-fluoronitrobenzene can be rationalized by strong conjugation of the lone pair of *para*-fluorine with the nitroso group, which could stabilize and decrease the reactivity of the latter.

Transformation of the protected ethoxycarbonyl aminoquinolines **3** into desired aminoquinolines **7** was accomplished by prolonged heating with concentrated hydrochloric acid (Scheme 6, Table 4). Since the hydrolyses of both the ester and the amide groups were relatively fast, which was observed by monitoring the reaction, the rate of the whole process depended on decarboxylation of the intermediate carboxylic acids. Under the conditions applied, hydrolysis of all ester functions as well as the ArOMe group took place, which resulted in formation of the corresponding carboxylic acids (**7m**, **p**), hydroxymethyl (**7j**) and hydroxy (**7q**) quinolines.



Scheme 6. Hydrolysis and decarboxylation of **3**.

Table 4
Hydrolysis of **3** to substituted 3-aminoquinolines **7**

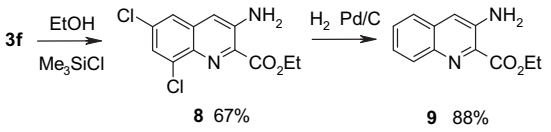
Entry	3	Time/days	7	R1	R2	R3	Yield[a]/%	Total yield **1**->**7** based on **2**/%
1	**a**	6	**a**	H	–N(CH)$_3$–		72	22
2	**b**	10	**b**	H	–(CH)$_4$–		56	11
3	**e**	2	**e**	H	CF_3	H	91[b]	22
4	**f**	2	**f**	Cl	Cl	H	67	38
5	**g**	2	**g**	F	H	H	~100[b]	44
6	**h**	2	**h**	Cl	H	H	~100[b]	47
7	**j**	2	**j**	Cl	H	CH_2OH	57	27
8	**k**	3	**k**	Cl	H	CF_3	84[b]	40
9	**l**	2	**l**	Br	Cl	H	81[b]	39
10	**m**	2	**m**	Cl	COOH	H	~100[b]	40
11	**n**	3	**n**	Cl	H	Cl	81[b]	25
12	**p**	2	**p**	COOH	Cl	H	93[b]	19
13	**q**	2	**q**	Cl	OH	H	86	11

[a] Isolated yield.
[b] Isolated and characterized as hydrochloride.

In the reactions of *para*-substituted nitroarenes, in which the *ortho*-substituent is absent (entries 1, 16–18) the yields of the products were rather low and the consumption of **2** comparatively high. Among them, 4-fluoronitrobenzene turned out to be an exceptional case. The expected aminoquinoline derivative **3u** was obtained, in low yield, when the reaction was warmed to room

Besides the total hydrolysis/decarboxylation described above, the amide function of **3** can be cleaved selectively. Heating **3f** with trimethylsilyl chloride in ethanol gave **8** in 67% yield (Scheme 7).

The reaction was used to provide additional confirmation of the structure of **3**. Hydrogenolysis of **8** led to dechlorinated ethyl-3-aminoquinoline-2-carboxylate **9**, a compound described in the



Scheme 7.

literature.[11a] While the melting point of not crystallized material was unreliable, ^{1}H NMR spectra taken in the same solvent matched very well reported chemical shifts. However, coupling constants reported in the literature, J=5 Hz for all vicinal protons, including those of the ethyl group, seem to be erroneous.

3. Conclusions

Searching for a general and possibly short method for the synthesis of substituted 3-aminoquinoline building blocks, a novel approach was demonstrated. Starting from substituted nitrobenzenes, step-by-step reaction with the dianion of protected 3-aminocrotonate ester, promoted by Et_3N/pivaloyl chloride, leads to *N*-acylated 3-aminoquinoline-2-carboxylates. For more electrophilic nitroarenes the simplified 'one-pot' procedure for the reaction can be used. Efficient hydrolysis/decarboxylation of the products yields the desired 3-aminoquinolines. The method, although not general, enables the preparation of certain 3-aminoquinolines substituted with halogens and some other electronwithdrawing groups in the benzo-fused ring in synthetically acceptable yields, offering a useful alternative to the known methods. Intermediate 2-ethoxycarbonyl derivatives of 3-aminoquinoline can also be considered as a starting point to build additional condensed rings.[10b,21]

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (500 MHz) (500 MHz for ^{1}H and 125 MHz for ^{13}C spectra), Varian-NMR-vnmrs600 (600 MHz for ^{1}H spectra) and a Varian Mercury 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C spectra) instruments. Chemical shifts δ are expressed in ppm referred to TMS, coupling constants in Hertz. Mass spectra (EI, 70 eV) were obtained on an AMD-604 spectrometer. Silica gel Merck 60 (230–400 mesh) was used for flash column chromatography. THF was distilled from sodium/benzophenone ketyl prior to use. HMPA was dried over CaH_2, distilled and stored over molecular sieves. 2-Nitronaphtalene was obtained according to the literature method.[22] All other reagents and starting nitroarenes, except **1j**, **m**, **p**, **r** were commercially available.

4.2. Synthesis of *tert*-butyl esters 1m, p, r

4.2.1. General procedure. To a suspension of the corresponding nitrobenzoic acid (50 mmol) in CH_2Cl_2 (100 mL), DMF (0.2 mL, 2.6 mmol, 5% mol) was added. The mixture was cooled to ~10 °C and oxalyl chloride (6.5 mL, 9.6 g, 75 mmol) was added in portions over 30 min. The mixture was stirred for 30 min, then the cooling bath was removed and the mixture was stirred overnight at room temperature (clear orange-brown solution was formed). The solvent was evaporated under vacuum. The obtained benzoyl chloride was used in the next step without purification. A solution of corresponding acid chloride (~50 mmol) in dry THF (80 mL) was cooled to 0 °C and a solution of *t*-BuOK (6.8 g, 60 mmol) in THF (90 mL) was added dropwise (~20 min). The cooling bath was removed and the mixture was stirred overnight at room temperature. Water (80 mL) was added. The mixture was concentrated, extracted with AcOEt (3×50 mL), the combined extracts were washed with water, dried and evaporated. The products were purified by short column chromatography (SiO_2/hexane, then hexane/AcOEt, 13:1).

*4.2.2. tert-Butyl 3-chloro-4-nitrobenzoate (**1m**).* Yield 10.5 g, 82%. Yellowish solid; mp 51–53 °C. R_f (hexane/AcOEt 8:1) 0.50; IR (KBr, cm^{-1}) ν_{max}: 3103, 2987, 1713, 1584, 1530, 1293, 1136; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.51 (9H, s, *t*-Bu), 7.88 (1H, dd, J=8.7 Hz, J=2.3 Hz, H-6), 7.92 (1H, d, J=2.3 Hz, H-2), 8.09 (1H, d, J=8.7 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 83.1, 125.2, 116.9, 128.5, 132.8, 136.3, 150.1, 162.6; MS (EI, 70 eV, m/z (%)): 257 (1, M$^+$), 186 (13), 185 (13), 184 (47), 57 (100), 56 (40), 41 (15). Anal. Calcd for $C_{11}H_{12}ClNO_4$: C, 51.27; H, 4.69; N, 5.44. Found: C, 51.29; H, 4.89; N, 5.40.

*4.2.3. tert-Butyl 5-chloro-2-nitrobenzoate (**1p**).* Yield 8.8 g, 69%. Yellow-orange oil. R_f (hexane/AcOEt 5:1) 0.46; IR (KBr, cm^{-1}) ν_{max}: 3111, 2988, 1725, 1543, 1338, 1292, 1137; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.57 (9H, s, *t*-Bu), 8.05 (1H, dd, J=8.3 Hz, J=1.7 Hz, H-4), 8.13 (1H, d, J=1.7 Hz, H-6), 8.19 (1H, d, J=8.3 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.2, 83.8, 126.0, 129.3, 129.7, 132.0, 138.3, 146.0, 162.4; MS (EI, 70 eV, m/z (%)): 257 (1, M$^+$), 184 (22), 57 (100), 56 (41), 41 (18); HRMS (ESI, MeOH): (M+Na)$^+$ found 280.0353. $C_{11}H_{12}{}^{35}ClNO_4Na$ requires 280.0347.

*4.2.4. tert-Butyl 2-nitrobenzoate (**1r**).* Yield 8.7 g, 78%. Yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.51 (9H, s, *t*-Bu), 7.77–7.80 (1H, m, Ar-H), 7.81–7.83 (2H, m, Ar-H), 8.00–8.03 (1H, m, Ar-H); MS (EI, 70 eV, m/z (%)): 223 (1, M$^+$), 168 (15), 151 (21), 150 (72), 76 (13), 57 (100), 56 (36), 51 (10), 41 (22); HRMS (ESI, MeOH): (M+Na)$^+$, found 246.0745. $C_{11}H_{13}NO_4Na$ requires 246.0737.

4.3. 4-Chloro-3-nitrobenzyl pivalate (1j)

To a solution of 4-chloro-3-nitrobenzyl alcohol (1.5 g, 8.0 mmol) in pyridine (20 mL), pivaloyl chloride (1.2 mL, 1.18 g, 9.8 mmol) was added and the solution was stirred at room temperature for 3 days. Pyridine was evaporated under high vacuum at room temperature and water (20 mL) was added to the residue. The mixture was extracted with AcOEt (2×25 mL), the combined extracts were washed with 2 M HCl (10 mL), water (2×10 mL), dried and evaporated to obtain 2.15 g (99%) of the pure product.

1j: Yellow-orange oil. R_f (hexane/AcOEt 5:1) 0.32; IR (KBr, cm^{-1}) ν_{max}: 3082, 2935, 1732, 1542, 1358, 1151; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.19 (9H, s, *t*-Bu), 5.17 (2H, s, C$\underline{H}_2$), 7.69 (1H, dd, J=8.3, 2.0 Hz, H-6), 7.80 (1H, d, J=8.3 Hz, H-5), 8.06 (1H, d, J=2.0 Hz, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.1, 38.8, 63.9, 124.5, 126.5, 132.0, 132.1, 137.0, 147.9, 177.9; MS (EI, 70 eV, m/z (%)): 271 (1, M$^+$), 170 (25), 169 (17), 124 (11), 89 (16), 57 (100), 41 (12); (ESI, MeOH): 294 (M+Na)$^+$. HRMS (ESI): (M+Na)$^+$, found 294.0516. $C_{12}H_{14}{}^{35}ClNO_4Na$ requires 294.0504.

4.4. One-pot synthesis of 2-ethoxycarbonyl-3-(*N*-pivaloylamino)quinolines 3

4.4.1. General procedure. To a solution of nitroarene **1** (5 mmol) and ethyl [*N*-(2,2-dimethylpropanoyl)amino]but-2-enoate (**2**, 1066 mg, 5 mmol) in dry DMF (10 mL) was added *N*,*O*-bis(trimethylsilyl)-acetamide (5.1 g, 6.1 mL, 25 mmol) and DBU (3.8 g, 3.7 mL, 25 mmol) and the reaction mixture was stirred at room temperature for 3–10 days while monitored by TLC. The mixture was then poured into saturated NH_4Cl and 3–4 times extracted with AcOEt. The extract was dried with Na_2SO_4 and the solvent was evaporated.

The residue was chromatographed to obtain pure products. The yields are given in Table 1.

*4.4.2. Ethyl 3-[(2,2-dimethylpropanoyl)amino]pyrido[2,3-g]quinoline-2-carboxylate (**3a**).* Yield 0.56 g, 30%. White powder; mp 234–237 °C (AcOEt). R_f (hexane/AcOEt 1:1) 0.13; IR (KBr, cm^{-1}) ν_{max}: 3286, 2959, 1693, 1668, 1580, 1550, 1498, 1317, 1218; ^1H NMR (400 MHz, DMSO-d_6) δ 1.33 (9H, s, *t*-Bu), 1.41 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.46 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.82 (1H, dd, J=8.4 Hz, J=4.4 Hz, Ar-H), 8.13–8.21 (2H, m, Ar-H), 9.08 (1H, dd, J=4.4 Hz, J=1.5 Hz, Ar-H), 9.10–9.13 (1H, m, Ar-H), 9.92 (1H, s, Ar-H), 10.78 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 27.5, 40.6, 63.0, 121.3, 121.8, 124.3, 128.0, 131.3, 132.1, 132.3, 134.0, 136.3, 142.2, 148.7, 151.2, 167.5, 178.9; MS (EI, 70 eV, *m*/*z* (%)): 352 (14), 351 (59, M^+), 307 (17), 295 (12), 294 (67), 278 (17), 248 (35), 222 (51), 221 (11), 220 (27), 196 (19), 195 (95), 194 (16), 193 (31), 192 (22), 168 (26), 167 (17), 166 (12), 165 (15), 140 (14), 139 (14), 57 (100), 41 (29). Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.04; H, 6.01; N, 11.85.

*4.4.3. Ethyl 2-[(2,2-dimethylpropanoyl)amino]benzo[f]quinoline-3-carboxylate (**3b**).* Yield 0.35 g, 20%. Pale-yellow solid; mp 180–181 °C. R_f (hexane/AcOEt 2:1) 0.38; IR (KBr, cm^{-1}) ν_{max}: 3295, 2959, 1694, 1667, 1550, 1510, 1305, 1217; ^1H NMR (600 MHz, $CDCl_3$) δ 1.44 (9H, s, *t*-Bu), 1.56 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.61 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.68–7.70 (2H, m, Ar-H), 8.0 (1H, d, J=9.5 Hz, Ar-H), 7.89–7.91 (2H, m, Ar-H), 8.72–8.74 (1H, m, Ar-H), 10.52 (1H, s, Ar-H), 11.46 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.1, 27.1, 61.8, 122.5, 123.6, 127.0, 127.3, 127.8, 128.3, 128.8, 128.9, 130.5, 132.2, 133.8, 137.5, 142.4, 166.3, 177.3; MS (EI, 70 eV, *m*/*z* (%)): 351 (23), 350 (100, M^+), 306 (12), 294 (14), 293 (72), 277 (15), 247 (29), 221 (43), 219 (19), 194 (42), 192 (21), 166 (11), 57 (31), 41 (11). Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.93; H, 6.51; N, 8.06.

*4.4.4. Ethyl 5-[(2,2-dimethylpropanoyl)amino]thieno[2,3-b]pyridine-2-carboxylate (**3c**).* Yield 0.28 g, 18%. Pale-brown solid; mp 140–144 °C. R_f (hexane/AcOEt 2:1) 0.41; IR (KBr, cm^{-1}) ν_{max}: 3295, 2959, 1694, 1667, 1550, 1510, 1305, 1217; ^1H NMR (400 MHz, DMSO-d_6) δ 1.26 (9H, s, *t*-Bu), 1.35 (3H, t, J=7.1 Hz, OCH_2CH_3), 4.38 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.63 (1H, d, J=6.1 Hz, Ar-H), 8.05 (1H, d, J=6.1 Hz, Ar-H), 8.89 (1H, s, Ar-H), 10.03 (1H, s, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.0, 27.0, 61.7, 121.8, 125.0, 129.3, 130.0, 130.6, 143.6, 157.3, 165.1, 176.8; MS (EI, 70 eV, *m*/*z* (%)): 306 (39, M^+), 249 (11), 222 (19), 203 (12), 176 (27), 57 (100), 41 (17). Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.83; H, 5.96; N, 9.12.

*4.4.5. Ethyl 3-[(2,2-dimethylpropanoyl)amino]-1,6-naphthyridine-2-carboxylate (**3d**).* Yield 0.17 g, 11%. Orange-brown solid; mp 120–131 °C. R_f (AcOEt) 0.32; IR (KBr, cm^{-1}) ν_{max}: 3293, 2966, 1697, 1684, 1535, 1523, 1293, 1206; ^1H NMR (400 MHz, DMSO-d_6) δ 1.29 (9H, s, *t*-Bu), 1.38 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.42 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.95–8.01 (1H, m, Ar-H), 8.74 (1H, d, J=5.9 Hz, Ar-H), 9.11 (1H, d, J=0.7 Hz, Ar-H), 9.48 (1H, d, J=0.7 Hz, Ar-H), 10.52 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.0, 27.0, 39.3, 62.1, 121.3, 123.9, 127.4, 132.8, 144.7, 145.4, 146.0, 153.1, 165.4, 177.1; MS (EI, 70 eV, *m*/*z* (%)): 301 (35, M^+), 244 (12), 145 (24), 57 (100), 41 (10); HRMS (EI): M^+, found 301.1415. $C_{16}H_{19}N_3O_3$ requires 301.1426.

*4.4.6. Ethyl 3-[(2,2-dimethylpropanoyl)amino]-6-(trifluoromethyl)-quinoline-2-carboxylate (**3e**).* Yield 0.11 g, 6%. White crystals; mp 139–143 °C (hexane). R_f (hexane/AcOEt 5:1) 0.24; IR (KBr, cm^{-1}) ν_{max}: 3316, 2959, 1698, 1684, 1542, 1290, 1121, 1059; ^1H NMR (400 MHz, DMSO-d_6) δ 1.29 (9H, s, *t*-Bu), 1.39 (3H, t, J=7.1 Hz, OCH_2CH_3), 4.43 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.97 (1H, dd, J=8.9 Hz, J=2.0 Hz, Ar-H), 8.27 (1H, dd, J=8.9 Hz, J=0.7 Hz, Ar-H), 8.59 (1H, br s, Ar-H), 9.17 (1H, s, H-4), 10.56 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6)[23] δ 14.5, 27.4, 62.5, 124.4 (q, J_{C-F}=273 Hz, CF_3), 124.7 (q, J_{C-F}=3 Hz), 126.4 (q, J_{C-F}=4 Hz), 128.6, 128.7, 129.1 (q, J_{C-F}=32 Hz, C–CF_3), 131.4, 133.4, 143.3, 144.1, 166.1, 177.5; MS (EI, 70 eV, *m*/*z* (%)): 368 (23, M^+), 311 (33), 295 (11), 237 (11), 212 (39), 210 (10), 209 (10), 57 (100), 41 (15). Anal. Calcd for $C_{18}H_{19}F_3N_2O_3$: C, 58.69; H, 5.20; N, 7.60. Found: C, 58.44; H, 5.29; N, 7.54.

*4.4.7. Ethyl 6,8-dichloro-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate (**3f**).* Yield 38 mg, 2%. Pale-yellow solid; mp 155–159 °C. R_f (hexane/AcOEt 2:1) 0.52; IR (KBr, cm^{-1}) ν_{max}: 3292, 2962, 1698, 1556, 1434, 1303, 1194, 1080; ^1H NMR (400 MHz, DMSO-d_6) δ 1.29 (9H, s, *t*-Bu), 1.38 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.43 (2H, q, J=7.2 Hz, OCH_2CH_3), 8.05 (1H, d, J=2.2 Hz, Ar-H), 8.21 (1H, d, J=2.2 Hz, Ar-H), 9.05 (1H, s, H-4), 10.64 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.0, 27.0, 62.0, 125.7, 126.6, 129.2, 130.8, 132.9, 133.6, 134.2, 137.4, 140.9, 165.6, 177.1; MS (EI, 70 eV, *m*/*z* (%)): 370 (9), 368 (13, M^+), 313 (13), 311 (21), 239 (13), 214 (20), 212 (33), 57 (100), 41 (27). HRMS (EI): calcd for $C_{17}H_{18}{}^{35}Cl_2N_2O_3$: 368.0694; found: 368.0686. Anal. Calcd for $C_{17}H_{18}Cl_2N_2O_3$: C, 55.30; H, 4.91; N, 7.59. Found: C, 54.94; H, 5.09; N, 7.14.

4.5. Step-by-step synthesis of 2-ethoxycarbonyl-3-(*N*-pivaloylamino)-quinolines 3

4.5.1. General procedure. To a solution of ethyl *N*-pivaloyl-3-aminocrotonate **2** (0.60 g, 2.83 mmol) and HMPA (1.1 mL, 1.12 g, 6.3 mmol) in dry THF (16 mL) at −78 °C under argon, 1.6 M BuLi in hexane (3.8 mL, 6.1 mmol) was added in portions in 3 min. After the addition was complete, the solution was stirred at that temperature for 30 min (a yellow colour was formed). A solution of the nitroarene **1** (5.66 mmol) in THF (2.0 mL) was added (colour changed to orange-brown immediately) and the resultant mixture was stirred for 10 min. Et_3N (1.8 mL, 1.31 g, 13 mmol) was added and then pivaloyl chloride (1.6 mL, 1.57 g, 13 mmol) was added in portions (14 min). After the addition was complete, the solution was stirred at −78 °C for 2 h. The cooling bath was removed, water (15 mL) was added immediately, the mixture was warmed to room temperature and stirred for 5 min. The layers were separated, the aqueous layer was extracted with AcOEt (2×15 mL) and the combined extracts were dried end evaporated. The products were purified by column chromatography (SiO_2, hexane, then hexane/AcOEt). The yields are given in Table 3.

In some cases (**3m**, **p**, **r**, **u**) products after column chromatography contained *t*-$BuCO_2H$. To remove the acid, the products were dissolved in AcOEt (30 mL), washed with 10% K_2CO_3 (15 mL), water (2×10 mL), dried and evaporated to dryness.

*4.5.2. Ethyl 8-fluoro-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate (**3g**).* Yield 397 mg, 44%. Yellow-brown solid; mp 128–131 °C. R_f (hexane/AcOEt 2:1) 0.44; IR (KBr, cm^{-1}) ν_{max}: 3303, 2968, 1689, 1543, 1464, 1291, 1216, 1108; ^1H NMR (400 MHz, DMSO-d_6) δ 1.29 (9H, s, *t*-Bu), 1.39 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.43 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.55–7.60 (1H, m, Ar-H), 7.66–7.71 (1H, m, Ar-H), 7.84–7.87 (1H, m, Ar-H), 9.09 (1H, d, J=1.6 Hz, H-4), 10.60 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.7, 27.7, 62.6, 113.7 (d, J_{C-F}=18 Hz), 124.1 (d, J_{C-F}=4 Hz), 127.4 (d, J_{C-F}=2 Hz), 130.0 (d, J_{C-F}=9 Hz), 131.5, 133.5 (d, J_{C-F}=13 Hz), 133.7, 140.9, 158.0 (d, J_{C-F}=257 Hz), 166.5, 177.8; MS (EI, 70 eV, *m*/*z* (%)): 319 (21), 318 (100, M^+), 274 (23), 262 (12), 261 (77), 245 (20), 215 (16), 189 (17), 162 (54), 160 (12), 57 (35), 41 (11); HRMS (EI): M^+, found 318.1369. $C_{17}H_{19}FN_2O_3$ requires 318.1380.

*4.5.3. Ethyl 8-chloro-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate (**3h**).* Yield 446 mg, 47%. Pale-yellow solid; mp 131–134 °C. R_f (hexane/AcOEt 5:1) 0.27; IR (KBr, cm^{-1}) ν_{max}: 3303, 2975, 1686, 1673, 1555, 1525, 1290, 1216, 1086; ^1H NMR (400 MHz, DMSO-

d_6) δ 1.29 (9H, s, *t*-Bu), 1.39 (3H, t, J=7.1 Hz, OCH_2CH_3), 4.43 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.66 (1H, dd, J=8.2 Hz, J=7.5 Hz, H-6), 7.93 (1H, dd, J=7.5 Hz, J=1.2 Hz, Ar-H), 8.01 (1H, dd, J=8.2 Hz, J=1.2 Hz, Ar-H), 9.07 (1H, s, H-4), 10.57 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.0, 27.0, 61.9, 127.0, 127.7, 129.1, 129.2, 130.5, 132.7, 132.8, 138.8, 140.9, 165.8, 177.1; MS (EI, 70 eV, m/z (%)): 336 (21), 334 (61, M^+), 290 (22), 279 (21), 278 (10), 277 (60), 261 (18), 231 (14), 207 (10), 205 (38), 203 (13), 180 (29), 179 (14), 178 (99), 176 (15), 175 (11), 114 (11), 57 (100), 41 (20). Anal. Calcd for $C_{17}H_{19}ClN_2O_3$: C, 60.99; H, 5.72; N, 8.37. Found: C, 60.80; H, 5.64; N, 8.26.

*4.5.4. Ethyl 8-bromo-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate (**3i**).* Yield 365 mg, 34%. Pale-yellow solid; mp 126–129 °C. R_f (hexane/AcOEt 2:1) 0.48; IR (KBr, cm^{-1}) ν_{max}: 3304, 2965, 1690, 1678, 1554, 1526, 1438, 1288; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (9H, s, *t*-Bu), 1.39 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.43 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.59 (1H, dd, J=8.1 Hz, J=7.5 Hz, H-6), 8.05 (1H, dd, J=8.1 Hz, J=1.2 Hz, Ar-H), 8.12 (1H, dd, J=7.5 Hz, J=1.2 Hz, Ar-H), 9.05 (1H, s, H-4), 10.56 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.0, 27.0, 61.9, 124.3, 127.7, 127.8, 129.7, 130.4, 132.7, 132.8, 139.7, 141.2, 165.7, 177.1; MS (EI, 70 eV, m/z (%)): 381 (18), 380 (89), 379 (19), 378 (89, M^+), 336 (42), 335 (13), 334 (41), 324 (13), 323 (84), 322 (11), 321 (79), 307 (21), 305 (23), 277 (20), 275 (19), 251 (38), 250 (11), 249 (50), 247 (16), 225 (11), 224 (88), 223 (15), 222 (100), 221 (16), 197 (10), 195 (11), 141 (11), 114 (10), 57 (39), 41 (16); HRMS (EI): M^+, found 378.0570. $C_{17}H_{19}{}^{79}BrN_2O_3$ requires 378.0579.

*4.5.5. Ethyl 8-bromo-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate 1-oxide (**6i**)[24].* Yield 101 mg, 9%. Yellow oil. R_f (hexane/AcOEt 5:1) 0.22; IR (film in CH_2Cl_2, cm^{-1}) ν_{max}: 3276, 2970, 1740, 1702, 1672, 1629, 1481, 1239, 1137; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.23 (9H, s, *t*-Bu), 1.27 (3H, t, J=7.1 Hz, OCH_2CH_3), 4.23 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.09 (1H, dd, J=8.7 Hz, J=7.0 Hz, H-6), 7.68 (1H, dd, J=8.7 Hz, J=0.6 Hz, Ar-H), 7.79 (1H, dd, J=7.0 Hz, J=0.6 Hz, Ar-H), 8.50 (1H, s, H-4), 10.28 (1H, s, NH); MS (EI, 70 eV, m/z (%)): 396 (28), 394 (26, M^+), 324 (16), 323 (95), 322 (16), 321 (96), 283 (13), 269 (10), 266 (11), 264 (11), 238 (16), 210 (12), 165 (19), 57 (100), 41 (21); HRMS (EI): M^+, found 394.0544. $C_{17}H_{19}{}^{79}BrN_2O_4$ requires 394.0528.

*4.5.6. Ethyl 8-chloro-3-[(2,2-dimethylpropanoyl)amino]-5-{[(2,2-dimethylpropanoyl)oxy]methyl}quinoline-2-carboxylate (**3j**).* Yield 598 mg, 47%. Yellow solid; mp 102–105 °C. R_f (hexane/AcOEt 2:1) 0.46; IR (KBr, cm^{-1}) ν_{max}: 3313, 2964, 1733, 1694, 1540, 1296, 1144, 1039; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.13 (9H, s, OC(O)*t*-*Bu*), 1.27 (9H, s, NH*t*-*Bu*), 1.38 (3H, t, J=7.1 Hz, OCH_2CH_3), 4.43 (2H, q, J=7.1 Hz, OCH_2CH_3), 5.46 (2H, s, Ar-CH_2), 7.70 (1H, d, J=7.7 Hz, Ar-H), 7.90 (1H, d, J=7.7 Hz, Ar-H), 9.24 (1H, s, H-4), 10.62 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6)[23] δ 13.9, 26.9, 61.9, 63.1, 123.5, 128.3, 128.8, 129.7, 131.4, 133.2, 133.3, 138.7, 140.0, 165.6, 177.0; MS (EI, 70 eV, m/z (%)): 448 (20, M^+), 391 (18), 365 (19), 364 (16), 363 (76), 347 (23), 319 (15), 317 (21), 292 (13), 279 (15), 263 (16), 57 (100), 41 (18); HRMS (EI): M^+, found 448.1752. $C_{23}H_{29}{}^{35}ClN_2O_5$ requires 448.1765.

*4.5.7. Ethyl 8-chloro-3-[(2,2-dimethylpropanoyl)amino]-5-(trifluoromethyl)quinoline-2-carboxylate (**3k**).* Yield 535 mg, 47%. Yellow solid; mp 110–113 °C. R_f (hexane/AcOEt 2:1) 0.56; IR (KBr, cm^{-1}) ν_{max}: 3281, 2955, 1699, 1563, 1317, 1169, 1145, 1085; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (9H, s, *t*-Bu), 1.40 (3H, t, J=7.1 Hz, OCH_2CH_3), 4.43 (2H, q, J=7.1 Hz, OCH_2CH_3), 8.04 (1H, d, J=8.1 Hz, Ar-H), 8.11 (1H, d, J=8.1 Hz, Ar-H), 9.40 (1H, s, H-4), 10.83 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.0, 26.9, 62.2, 122.0, 123.1 (q, J_{C-F}=31 Hz, C–CF_3), 123.6 (q, J_{C-F}=273 Hz, CF_3), 126.3, 127.6, 128.3, 134.4, 138.4, 138.5, 140.4, 165.4, 177.6; MS (EI, 70 eV, m/z (%)): 404 (13), 402 (37, M^+), 358 (11), 347 (13), 345 (37), 329 (13), 246 (20), 57 (100), 41 (15); HRMS (EI): M^+, found 402.0951. $C_{18}H_{18}{}^{35}ClF_3N_2O_3$ requires 402.0958.

*4.5.8. Ethyl 8-bromo-6-chloro-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate (**3l**).* Yield 563 mg, 48%. Orange solid; mp 162–168 °C (decomp.). R_f (hexane/AcOEt 5:1) 0.41; IR (KBr, cm^{-1}) ν_{max}: 3291, 2960, 1698, 1689, 1557, 1434, 1300, 1172, 1081; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (9H, s, *t*-Bu), 1.38 (3H, t, J=7.1 Hz, OCH_2CH_3), 4.43 (2H, q, J=7.1 Hz, OCH_2CH_3), 8.20 (1H, d, J=2.2 Hz, Ar-H), 8.25 (1H, d, J=2.2 Hz, Ar-H), 9.04 (1H, s, H-4), 10.63 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.0, 27.0, 62.0, 125.7, 126.2, 126.7, 130.6, 132.4, 133.2, 133.6, 138.3, 141.2, 165.5, 177.1; MS (ESI, MeOH): 413 $(M+H)^+$, 435 $(M+Na)^+$. Anal. Calcd for $C_{17}H_{18}BrClN_2O_3$: C, 49.36; H, 4.39; N, 6.77. Found: C, 49.18; H, 4.53; N, 6.68.

*4.5.9. 6-tert-Butyl 2-ethyl 8-chloro-3-[(2,2-dimethylpropanoyl)amino]quinoline-2,6-dicarboxylate (**3m**).* Yield 491 mg, 40%. Pale-yellow solid; mp 218–219 °C (AcOEt). R_f (hexane/AcOEt 8:1) 0.33; IR (KBr, cm^{-1}) ν_{max}: 3297, 2981, 1719, 1689, 1560, 1272, 1154, 1086; ^{1}H NMR (500 MHz, CD_3COCD_3) δ 1.37 (9H, s, *t*-*Bu*CONH–), 1.48 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.66 (9H, s, *t*-*Bu*O–), 4.56 (2H, q, J=7.1 Hz, OCH_2CH_3), 8.23 (1H, d, J=1.5 Hz, Ar-H), 8.58 (1H, d, J=1.5 Hz, Ar-H), 9.66 (1H, s, H-4), 11.10 (1H, br s, NH); ^{13}C NMR (125 MHz, THF-d_8) δ 13.4, 26.7, 27.3, 40.05, 62.2, 81.6, 125.8, 127.2, 128.7, 130.5, 132.3, 134.4, 135.6, 137.5, 140.2, 163.3, 167.2, 177.1; MS (EI, 70 eV, m/z (%)): 436 (22), 435 (17), 434 (56, M^+), 390 (11), 378 (10), 361 (25), 321 (67), 249 (20), 224 (14), 222 (61), 57 (100), 41 (20). Anal. Calcd for $C_{22}H_{27}ClN_2O_5$: C, 60.76; H, 6.26; N, 6.44. Found: C, 60.85; H, 6.22; N, 6.45.

*4.5.10. Ethyl 5,8-dichloro-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate (**3n**).* Yield 325 mg, 31%. Yellow-orange solid; mp 172–175 °C (decomp.). R_f (hexane/AcOEt 2:1) 0.55; IR (KBr, cm^{-1}) ν_{max}: 3273, 2965, 1692, 1562, 1328, 1092; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (9H, s, *t*-Bu), 1.39 (3H, t, J=7.1 Hz, OCH_2CH_3), 4.44 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.88 (1H, d, J=8.1 Hz, Ar-H), 7.94 (1H, d, J=8.1 Hz, Ar-H), 9.38 (1H, s, H-4), 10.78 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.0, 27.0, 62.1, 123.3, 128.2, 128.3, 128.8, 129.2, 132.3, 134.1, 138.9, 140.8, 165.5, 177.4; MS (EI, 70 eV, m/z (%)): 370 (14), 368 (44, M^+), 326 (10), 324 (15), 313 (33), 311 (51), 297 (12), 295 (16), 239 (12), 214 (18), 57 (100), 41 (22); HRMS (EI): M^+, found 368.0684. $C_{17}H_{18}{}^{35}Cl_2N_2O_3$ requires 368.0694.

*4.5.11. Ethyl 6-chloro-8-cyano-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate (**3o**).* Yield 236 mg, 23%. Orange solid; mp 135–138 °C. R_f (hexane/AcOEt 5:1) 0.27; IR (KBr, cm^{-1}) ν_{max}: 3281, 2966, 2238, 1742, 1705, 1542, 1292, 1208, 1086, 1020; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (9H, s, *t*-Bu), 1.37 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.42 (2H, q, J=7.2 Hz, OCH_2CH_3), 8.50 (1H, d, J=2.2 Hz, Ar-H), 8.56 (1H, d, J=2.2 Hz, Ar-H), 9.09 (1H, s, H-4), 10.64 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 13.9, 26.9, 62.2, 113.7, 115.6, 126.9, 129.9, 131.6, 132.6, 134.0, 135.9, 140.0, 142.3, 165.3, 177.2; MS (EI, 70 eV, m/z (%)): 359 (12, M^+), 203 (22), 85 (14), 57 (100), 41 (17); HRMS (EI): M^+, found 359.1041. $C_{18}H_{18}{}^{35}ClN_3O_3$ requires 359.1037.

*4.5.12. 8-tert-Butyl 2-ethyl 6-chloro-3-[(2,2-dimethylpropanoyl)amino]quinoline-2,8-dicarboxylate (**3p**).* Yield 250 mg, 20%. Pale-yellow solid; mp 166–168 °C (decomp.). R_f (hexane/AcOEt 5:1) 0.12; IR (KBr, cm^{-1}) ν_{max}: 3286, 2974, 1726, 1694, 1546, 1298, 1176, 1159; ^{1}H NMR (500 MHz, CD_3COCD_3) δ 1.35 (9H, s, NH*t*-*Bu*), 1.46 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.67 (9H, s, O*t*-*Bu*), 4.53 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.72 (1H, d, J=2.3 Hz, Ar-H), 8.12 (1H, d, J=2.3 Hz, Ar-H), 9.48 (1H, s, H-4), 11.19 (1H, br s, NH); ^{13}C NMR (125 MHz, DMSO-d_6)[23] δ 14.5, 27.5, 28.3, 62.4, 82.9, 125.9, 127.9, 128.3, 130.5, 133.4, 134.0, 136.7, 138.2, 140.2, 166.1, 166.3, 177.6; MS (EI, 70 eV, m/z (%)):

436 (12), 434 (36, M^+), 361 (19), 336 (67), 335 (32), 334 (100), 321 (49), 306 (14), 305 (17), 303 (16), 288 (14), 277 (18), 261 (16), 260 (13), 252 (17), 251 (14), 250 (28), 249 (25), 231 (12), 222 (20), 204 (18), 178 (10), 176 (14), 57 (93), 41 (31), 40 (14). Anal. Calcd for $C_{22}H_{27}ClN_2O_5$: C, 60.76; H, 6.26; N, 6.44. Found: C, 60.75; H, 6.24; N, 6.28.

*4.5.13. 8-tert-Butyl 2-ethyl 6-chloro-3-[(2,2-dimethylpropanoyl)-amino]quinoline-2,8-dicarboxylate 1-oxide (**6p**).* Yield 92 mg, 7%. Orange solid; mp 149–152 °C. R_f (hexane/AcOEt 5:1) 0.33; IR (KBr, cm^{-1}) ν_{max}: 3335, 2977, 1703, 1680, 1623, 1482, 1286, 1217, 1140; ^1H NMR (400 MHz, DMSO-d_6) δ 1.24 (9H, s, NH*t-Bu*), 1.28 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.59 (9H, s, O*t-Bu*), 4.24 (2H, q, J=7.1 Hz, OCH_2CH_3), 6.09 (1H, s, Ar-H), 7.94 (1H, s, Ar-H), 8.11 (1H, s, Ar-H), 10.34 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6)[23] δ 14.0, 26.7, 27.7, 60.7, 82.4, 109.3, 117.7, 121.0, 124.1, 128.9, 136.1 152.4, 161.6, 162.0, 165.8, 176.4; MS (EI, 70 eV, m/z (%)): 450 (8, M^+), 323 (11), 321 (30), 264 (16), 85 (18), 57 (100); HRMS (EI): M^+, found 450.1563. $C_{22}H_{27}{}^{35}ClN_2O_6$ requires 450.1558.

*4.5.14. Ethyl 8-chloro-6-methoxy-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate (**3q**).* Yield 137 mg, 13%. Orange solid; mp 126–129 °C. R_f (hexane/AcOEt 5:1) 0.22; IR (KBr, cm^{-1}) ν_{max}: 3292, 2965, 1693, 1675, 1610, 1310, 1205, 1156, 1090; ^1H NMR (400 MHz, DMSO-d_6) δ 1.29 (9H, s, *t*-Bu), 1.38 (3H, t, J=7.2 Hz, OCH_2CH_3), 3.93 (3H, s, OMe), 4.43 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.43 (1H, d, J=2.6 Hz, Ar-H), 7.62 (1H, d, J=2.6 Hz, Ar-H), 9.11 (1H, s, H-4), 10.75 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.0, 27.0, 39.5, 56.1, 61.9, 104.7, 121.7, 125.3, 131.8, 133.8, 133.9, 134.8, 136.5, 158.8, 166.2, 177.1; MS (EI, 70 eV, m/z (%)): 366 (6), 364 (14, M^+), 320 (13), 307 (17), 261 (16), 235 (28), 210 (12), 208 (34), 57 (100), 41 (35); HRMS (EI): M^+, found 364.1186. $C_{18}H_{21}{}^{35}ClN_2O_4$ requires 364.1190.

*4.5.15. Ethyl 8-chloro-6-methoxy-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate 1-oxide (**6q**).* Yield 140 mg, 13%. Yellow-brown solid; mp 133–137 °C. R_f (hexane/AcOEt 2:1) 0.42; IR (KBr, cm^{-1}) ν_{max}: 3286, 2963, 1711, 1677, 1422, 1619, 1554, 1177; ^1H NMR (400 MHz, DMSO-d_6) δ 1.25 (9H, s, *t*-Bu), 1.27 (3H, t, J=7.1 Hz, OCH_2CH_3), 3.82 (3H, s, OMe), 4.23 (2H, q, J=7.1 Hz, OCH_2CH_3), 6.04 (1H, s, Ar-H), 6.80 (1H, d, J=2.0 Hz, Ar-H), 7.44 (1H, d, J=2.0 Hz, Ar-H), 10.25 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.1, 26.8, 56.1, 60.6, 93.9, 108.1, 117.1, 120.9, 127.1, 137.0, 153.0, 156.7, 160.0, 165.9, 176.5; MS (EI, 70 eV, m/z (%)): 382 (5), 380 (18, M^+), 251 (11), 225 (10), 224 (14), 223 (25), 57 (100), 41 (35); HRMS (EI): M^+, found 380.1123. $C_{18}H_{21}{}^{35}ClN_2O_5$ requires 380.1139.

*4.5.16. 8-tert-Butyl 2-ethyl 3-[(2,2-dimethylpropanoyl)amino]quinoline-2,8-dicarboxylate (**3r**).* Yield 231 mg, 20%. Yellow-orange oil. R_f (hexane/AcOEt 2:1) 0.48; IR (KBr, cm^{-1}) ν_{max}: 3323, 2976, 1698, 1540, 1301, 1166, 1094; ^1H NMR (500 MHz, CD_3COCD_3) δ 1.38 (9H, s, NH*t-Bu*), 1.49 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.70 (9H, s, O*t-Bu*), 4.56 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.73 (1H, dd, J=8.2 Hz, J=7.0 Hz, H-6), 7.81 (1H, dd, J=7.0 Hz, J=1.2 Hz, Ar-H), 8.08 (1H, dd, J=8.2 Hz, J=1.2 Hz, Ar-H), 9.56 (1H, s, H-4), 11.17 (1H, br s, NH); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 14.6, 27.7, 28.5, 40.9, 63.1, 82.3, 125.3, 128.0, 129.4, 130.1, 130.8, 135.5, 136.5, 137.1, 140.5, 168.2, 168.3, 178.2; MS (EI, 70 eV, m/z (%)): 400 (36, M^+), 327 (23), 301 (19), 300 (82), 287 (26), 271 (10), 269 (14), 254 (10), 245 (15), 243 (13), 216 (30), 215 (19), 170 (20), 142 (18), 57 (100), 41 (23); HRMS (EI): M^+, found 400.2005. $C_{22}H_{28}N_2O_5$ requires 400.1998.

*4.5.17. Ethyl 8-cyano-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate (**3s**).* Yield 150 mg, 16%. Yellow solid; mp 124–127 °C. R_f (hexane/AcOEt 5:1) 0.38; IR (KBr, cm^{-1}) ν_{max}: 3297, 2975, 2233, 1708, 1686, 1547, 1297, 1103; ^1H NMR (400 MHz, DMSO-d_6) δ 1.29 (9H, s, *t*-Bu), 1.39 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.44 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.83 (1H, dd, J=8.3 Hz, J=7.2 Hz, H-6), 8.36–8.40 (2H, m, Ar-H), 9.13 (1H, s, H-4), 10.58 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.0, 27.0, 62.1, 111.8, 116.9, 128.1, 128.5, 129.1, 133.0, 133.3, 136.1, 141.5, 142.4, 165.4, 177.1; MS (EI, 70 eV, m/z (%)): 325 (32, M^+), 281 (23), 268 (31), 252 (11), 222 (11), 197 (11), 196 (12), 194 (10), 170 (13), 169 (100), 167 (10), 57 (37), 41 (11); HRMS (EI): M^+, found 325.1422. $C_{18}H_{19}N_3O_3$ requires 325.1426.

*4.5.18. Ethyl 6-cyano-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate (**3t**).* Yield 148 mg, 16%. Yellow-orange solid; mp 155–158 °C. IR (KBr, cm^{-1}) ν_{max}: 3316, 2966, 2231, 1694, 1630, 1534, 1296, 1186, 1085; ^1H NMR (400 MHz, DMSO-d_6) δ 1.29 (9H, s, *t*-Bu), 1.38 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.42 (2H, q, J=7.2 Hz, OCH_2CH_3), 8.01 (1H, dd, J=8.8 Hz, J=1.8 Hz, Ar-H), 8.19–8.23 (1H, m, Ar-H), 8.73 (1H, d, J=2.0 Hz, Ar-H), 9.09 (1H, s, H-4), 10.57 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.0, 27.0, 62.1, 111.3, 118.5, 127.6, 128.4, 129.5, 130.7, 133.0, 134.4, 143.2, 143.5, 165.5, 177.1; MS (EI, 70 eV, m/z (%)): 325 (28, M^+), 268 (35), 252 (14), 169 (29), 85 (12), 57 (100), 41 (21); HRMS (EI): M^+, found 325.1433. $C_{18}H_{19}N_3O_3$ requires 325.1426.

*4.5.19. Ethyl 6-fluoro-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate (**3u**).* The reaction was carried out according to the general procedure except, that after addition of all reactants, the reaction was warmed to room temperature, stirred overnight and then quenched.

Yield 155 mg, 17%. Pale-orange solid; mp 138–140 °C. R_f (hexane/AcOEt 2:1) 0.36; IR (KBr, cm^{-1}) ν_{max}: 3308, 2965, 1683, 1543, 1446, 1307, 1202, 1147; ^1H NMR (400 MHz, CD_3COCD_3) δ 1.36 (9H, s, *t*-Bu), 1.47 (3H, t, J=7.1 Hz, OCH_2CH_3), 4.53 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.53–7.59 (1H, m, Ar-H), 7.68–7.72 (1H, m, Ar-H), 8.09–8.14 (1H, m, Ar-H), 9.48 (1H, s, H-4), 11.14 (1H, br s, NH); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 14.4, 27.6, 40.9, 63.0, 111.0 (d, J_{C-F}=22 Hz), 119.8 (d, J_{C-F}=26 Hz), 124.5 (d, J_{C-F}=6 Hz), 131.9 (d, J_{C-F}=11 Hz), 133.7 (d, J_{C-F}=10 Hz), 135.7, 136.5 (d, J_{C-F}=3 Hz), 140.9, 163.0 (d, J_{C-F}=248 Hz), 168.2, 178.1; MS (EI, 70 eV, m/z (%)): 318 (26, M^+), 261 (26), 215 (13), 162 (18), 160 (12), 57 (100), 41 (17); HRMS (EI): M^+, found 318.1371. $C_{17}H_{19}FN_2O_3$ requires 318.1380.

*4.5.20. Ethyl 6-chloro-3-[(2,2-dimethylpropanoyl)amino]quinoline-2-carboxylate (**3v**).* Yield 51 mg, 5%. Orange solid; mp 142–145 °C. R_f (hexane/AcOEt 2:1) 0.42; IR (KBr, cm^{-1}) ν_{max}: 3307, 2968, 1701, 1684, 1630, 1536, 1304, 1200, 1089; ^1H NMR (400 MHz, DMSO-d_6) δ 1.29 (9H, s, *t*-Bu), 1.38 (3H, t, J=7.1 Hz, OCH_2CH_3), 4.42 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.74 (1H, dd, J=9.0 Hz, J=2.4 Hz, H-7), 8.08 (1H, d, J=9.0 Hz, H-8), 8.18 (1H, d, J=2.4 Hz, H-5), 9.02 (1H, s, H-4), 10.61 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ 14.0, 27.0, 61.9, 126.0, 126.1, 129.7, 129.9, 131.4, 132.9, 133.6, 140.3, 141.2, 165.9, 177.0; MS (ESI, MeOH): 357 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 357.0962. $C_{17}H_{19}ClN_2O_3Na$ requires 357.0976.

4.6. Ethyl 3-[(2,2-dimethylpropanoyl)amino]-4-(5-fluoro-2-nitrosophenyl)but-2-enoate (5uH)

The reaction was carried out according to the general procedure for step-by-step synthesis of **3**. After workup and column chromatography the product was dissolved in AcOEt (30 mL), washed with 10% K_2CO_3 (15 mL), water (2×10 mL), dried and evaporated to dryness.

5uH: Yield 720 mg, 27%. Green solid; mp 81–83 °C (decomp.) R_f (hexane/AcOEt 32:1) 0.30; IR (film, cm^{-1}) ν_{max}: 3230, 2969, 1705, 1672, 1632, 1501, 1246; ^1H NMR (500 MHz, CD_3COCD_3) δ 1.20–1.24 (12H, m, *t*-Bu +OCH_2CH_3), 4.15 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.95 (1H, s,=C*H*–COOEt), 5.51 (2H, s, Ar-CH_2), 6.45 (1H, dd, J=9.0 Hz, J=5.6 Hz, Ar-H), 7.10–7.15 (1H, m, Ar-H), 7.48 (1H, dd, J=9.0 Hz,

J=2.7 Hz, Ar-H), 11.62 (1H, br s, NH); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 13.6, 26.6, 34.6, 40.1, 59.8, 98.5, 110.2 (d, J_{C-F}=11 Hz), 114.2 (d, J_{C-F}=24 Hz), 117.6 (d, J_{C-F}=23 Hz), 145.3 (d, J_{C-F}=10 Hz), 156.4, 161.6 (d, J_{C-F}=3 Hz), 167.3 (d, J_{C-F}=257 Hz), 168.8, 176.7; ^{15}N NMR (50.7 MHz, CD_3COCD_3): −249.1 (NH), 525.4 (NO); MS (ESI, MeOH): 359 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 359.1367. $C_{17}H_{21}FN_2O_4Na$ requires 359.1378.

4.7. Cyclisation of 5uH to 3u

4.7.1. Reaction with Me_3SiCl. To a solution of **5uH** (168 mg, 0.50 mmol) in DMF (2.5 mL), Et_3N (0.280 mL, 204 mg, 2.0 mmol) and Me_3SiCl (0.160 mL, 137 mg, 1.26 mmol) were added subsequently. The solution was stirred at room temperature for 80 min. Water (5 mL) was added and the mixture was extracted with AcOEt (3×7 mL). The combined extracts were washed with water (2×10 mL), dried and evaporated. The product was purified by column chromatography (SiO_2, hexane/AcOEt, 4:1) and 38 mg (24%) of the pure **3u** was obtained.

4.7.2. Reaction with pivaloyl chloride. To a solution of **5uH** (133 mg, 0.40 mmol) in THF (3 mL), Et_3N (0.070 mL, 51 mg, 0.50 mmol) and *t*-BuCOCl (0.07 mL, 69 mg, 0.57 mmol) were subsequently added. The solution was stirred overnight at room temperature. The reaction was worked-up as above and 14 mg (11%) of **3u** was obtained.

4.8. Hydrolysis of 3 into 7

4.8.1. General procedure. A suspension of **3** (0.40–0.45 mmol) in 20% HCl (16 mL) was heated to reflux for the time specified in Table 4. Fresh portions of 20% HCl (16 mL) was added after one day. To isolate the products as hydrochlorides, the mixture was evaporated to dryness under high vacuum and the residue was washed with hot AcOEt (2×10 mL). The product was dissolved in MeOH, filtered and the filtrate was evaporated to dryness. To obtain products as free bases, the reaction mixture was neutralised with solid K_2CO_3 to attain pH=8. The mixture was then extracted with AcOEt, the extract was dried and the solvent evaporated. The products were purified by column chromatography (SiO_2/AcOEt).

*4.8.2. Pyrido[3,4-g]quinolin-3-amine (**7a**).* Yield 64 mg, 72%. Pale-brown solid; mp 199–201 °C. R_f (AcOEt) 0.08; IR (KBr, cm^{-1}) ν_{max}: 3334, 3184, 1604, 1501, 1276; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.93 (2H, br s, NH_2), 7.66 (1H, dd, J=8.2 Hz, J=4.5 Hz, Ar-H), 7.77 (1H, dd, J=9.2 Hz, J=0.6 Hz, Ar-H), 7.97 (1H, dd, J=9.2 Hz, J=0.6 Hz, Ar-H), 8.07 (1H, d, J=2.6 Hz, Ar-H), 8.51 (1H, d, J=2.6 Hz, Ar-H), 8.91–8.95 (2H, m, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 109.4, 121.2, 123.7, 125.5, 125.9, 131.1, 131.7, 138.4, 141.4, 143.9, 147.7, 150.0; MS (ESI, MeOH): 196 $(M+H)^+$; HRMS (ESI): $(M+H)^+$, found 196.0867. $C_{12}H_{10}N_3$ requires 196.0869.

*4.8.3. Benzo[g]quinolin-3-amine (**7b**).* Yield 50 mg, 56%. Pale-brown solid; mp 151–153 °C. R_f (AcOEt) 0.21; IR (KBr, cm^{-1}) ν_{max}: 3346, 3050, 1628, 1600, 1401, 825; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.82 (2H, br s, NH_2), 7.60–7.76 (4H, m, Ar-H), 7.92–7.96 (1H, m, Ar-H), 8.09 (1H, d, J=2.4 Hz, Ar-H), 8.48 (1H, d, J=2.4 Hz, Ar-H), 8.52–8.56 (1H, m, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 109.5, 122.8, 124.7, 126.1, 126.2, 126.9, 127.9, 128.3, 128.6, 131.8, 139.2, 140.7, 143.5; MS (ESI, MeOH): 195 $(M+H)^+$; HRMS (ESI): $(M+H)^+$, found 195.0915. $C_{13}H_{11}N_2$ requires 195.0917.

*4.8.4. 6-(Trifluoromethyl)quinolin-3-amine hydrochloride (**7e**·HCl).* Yield 98 mg, 91%. Brown solid; mp 178–184 °C. IR (KBr, cm^{-1}) ν_{max}: 3293, 2539, 1632, 1578, 1305, 1122; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (3H, t, J_{N-H}=50.8 Hz, NH_3^+), 7.62–7.71 (2H, m, Ar-H), 8.13 (1H, d, J=8.8 Hz, Ar-H), 8.28–8.32 (1H, m, Ar-H), 8.74 (1H, d, J=2.3 Hz, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 119.3, 122.0, 123.9 (q, J_{C-F}=273 Hz, CF_3), 124.6, 124.7, 128.3 (q, J_{C-F}=32 Hz, C–CF_3), 129.0, 134.9, 143.6; MS (EI, 70 eV, m/z (%)): 213 (15), 212 (100, M^+), 185 (18), 38 (17), 36 (55); HRMS (EI): M^+, found 212.0557. $C_{10}H_7F_3N_2$ requires 212.0561.

*4.8.5. 6,8-Dichloroquinolin-3-amine (**7f**).* Yield 58 mg, 67%. Light beige powder; mp 210–214 °C (toluene). R_f (hexane/AcOEt 1:1) 0.20; IR (KBr, cm^{-1}) ν_{max}: 3443, 3320, 3210, 1618, 1481, 1423; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.12 (2H, br s, NH_2), 7.14 (1H, d, J=2.6 Hz, Ar-H), 7.52 (1H, d, J=2.3 Hz, Ar-H), 7.75 (1H, d, J=2.3 Hz, Ar-H), 8.54 (1H, d, J=2.6 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 110.4, 123.6, 123.7, 130.2, 131.5, 133.5, 134.9, 144.1, 144.2; MS (EI, 70 eV, m/z (%)): 216 (10), 214 (63), 213 (14), 212 (100, M^+), 187 (14), 185 (21), 150 (16), 123 (11), 114 (11); HRMS (EI): M^+, found 211.9915. $C_9H_6{}^{35}Cl_2N_2$ requires 211.9908.

*4.8.6. 8-Fluoroquinolin-3-amine hydrochloride (**7g**·HCl).* Yield 89 mg, ~100%. Brown solid; mp 225–235 °C. IR (KBr, cm^{-1}) ν_{max}: 3311, 3183, 2428, 1641, 1616, 1563, 1283; ^{1}H NMR (400 MHz, CD_3OD) δ 5.0 (3H, br s, NH_3^++OH from solvent), 7.49 (1H, ddd, J=11.0 Hz, J=7.8 Hz, J=1.0 Hz, Ar-H), 7.65–7.71 (1H, m, Ar-H), 7.77 (1H, d, J=8.4 Hz, Ar-H), 8.10–8.11 (1H, m, Ar-H), 8.70 (1H, d, J=2.5 Hz, Ar-H); ^{13}C NMR (100 MHz, CD_3OD) δ 113.8 (d, J=16.4 Hz), 123.0 (d, J=15.1 Hz), 123.8 (d, J=4.3 Hz), 124.0 (d, J=2.6 Hz), 131.0 (d, J=8.2 Hz), 133.4, 136.5, 145.8, 154.0 (d, J=253.7 Hz) MS (ESI, MeOH): 163 $(M+H)^+$, 185 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 185.0477. $C_9H_7FN_2Na$ requires 185.0485.

*4.8.7. 8-Chloroquinolin-3-amine hydrochloride (**7h**·HCl).* Yield 96 mg, ~100%. Brown solid; mp 240–245 °C. IR (KBr, cm^{-1}) ν_{max}: 3302, 3135, 2553, 1654, 1622, 1549, 1270; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (3H, t, J_{N-H}=50.8 Hz, NH_3^+), 7.54–7.58 (1H, m, Ar-H), 7.76 (1H, dd, J=7.4 Hz, J=1.2 Hz, Ar-H), 7.84–7.90 (2H, m, Ar-H), 8.83 (1H, d, J=2.6 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 120.5, 126.2, 127.3, 128.0, 129.8, 130.5, 135.6, 138.7, 142.8; MS (EI, 70 eV, m/z (%)): 180 (33), 179 (15), 178 (100, M^+), 151 (17), 116 (11), 89 (12), 36 (27); HRMS (EI): M^+, found 178.0300. $C_9H_7{}^{35}ClN_2$ requires 178.0298.

*4.8.8. (3-Amino-8-chloroquinolin-5-yl)methanol (**7j**).* Hydrolysis was carried out in 20% H_2SO_4 at 120 °C for 2 days, then worked-up as described in the general procedure.

Yield 90 mg, 57%. Pale-brown solid; mp >265 °C. R_f (hexane/AcOEt 1:1) 0.22; IR (KBr, cm^{-1}) ν_{max}: 3404, 3328, 3225, 2868, 1611, 1112; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.77 (2H, d, J=5.4 Hz, CH_2OH), 5.26 (1H, t, J=5.4 Hz, CH_2OH), 5.89 (2H, br s, NH_2), 7.34–7.37 (2H, m, Ar-H), 7.43 (1H, d, J=7.6 Hz, Ar-H), 8.51 (1H, d, J=2.6 Hz, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 60.6, 108.5, 123.0, 124.6, 128.8, 131.3, 135.2, 136.2, 142.9, 143.0; MS (EI, 70 eV, m/z (%)): 210 (26), 209 (16), 208 (100, M^+), 207 (13), 193 (12), 192 (11), 191 (35), 181 (14), 180 (13), 179 (41), 173 (54), 156 (10), 145 (37), 144 (24), 118 (10), 117 (15), 116 (12), 89 (12); HRMS (EI): M^+, found 208.0398. $C_{10}H_9{}^{35}ClN_2O$ requires 208.0403.

*4.8.9. 8-Chloro-5-(trifluoromethyl)quinolin-3-amine hydrochloride (**7k**·HCl).* Yield 105 mg, 84%. Brown solid; mp>270 °C. IR (KBr, cm^{-1}) ν_{max}: 3296, 3177, 1644, 1552, 1277, 1131, 1097; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (1H, m, Ar-H), 7.41 (3H, t, J_{N-H}=50.7 Hz, NH_3^+), 7.60 (1H, d, J=8.0 Hz, Ar-H), 7.81 (1H, d, J=8.0 Hz, Ar-H), 8.67 (1H, d, J=2.4 Hz, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 107.3, 121.1 (q, J_{C-F}=30 Hz, C–CF_3), 122.4, 124.2 (q, J_{C-F}=273 Hz, CF_3), 125.8 (q, J_{C-F}=6 Hz), 127.1, 136.1, 137.6, 144.2, 144.5; MS (EI, 70 eV, m/z (%)): 248 (32), 247 (12), 246 (100, M^+), 225 (10), 207 (12), 38 (11), 36

(46); HRMS (EI): (M^+) found 246.0174. $C_{10}H_6{}^{35}ClF_3N_2$ requires 246.0172.

*4.8.10. 8-Bromo-6-chloroquinolin-3-amine hydrochloride (**7l**·HCl).* Yield 90 mg, 81%. Brown solid; mp 230–235 °C. IR (KBr, cm^{-1}) ν_{max}: 3359, 3159, 2797, 1633, 1544, 1274, 1085; ^1H NMR (400 MHz, DMSO-d_6) δ 7.42 (1H, d, J=2.2 Hz, Ar-H), 7.45 (3H, t, J_{N-H}=50.7 Hz, NH_3^+), 7.80 (1H, d, J=2.2 Hz, Ar-H), 7.92 (1H, d, J=2.2 Hz, Ar-H), 8.66 (1H, d, J=2.2 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 114.2, 124.6, 124.8, 128.1, 130.9, 131.0, 136.4, 141.4, 144.7; MS (ESI, MeOH): 257 $(M+H)^+$; HRMS (ESI): $(M+H)^+$, found 256.9473. $C_9H_7{}^{79}Br{}^{35}ClN_2$ requires 256.9476.

*4.8.11. 3-Amino-8-chloroquinoline-6-carboxylic acid hydrochloride (**7m**·HCl).* Yield 120 mg, ~100%. Brown solid; mp >265 °C. IR (KBr, cm^{-1}) ν_{max}: 3419, 3092, 1716, 1639, 1559, 1291, 1206; ^1H NMR (400 MHz, DMSO-d_6) δ 7.36–7.60 (4H, H+NH_3^+), 7.92 (1H, d, J=1.7 Hz, Ar-H), 8.34 (1H, d, J=1.7 Hz, Ar-H), 8.74 (1H, d, J=2.7 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 115.5, 123.8, 128.0, 129.1, 130.1, 132.2, 138.1, 142.1, 145.7, 166.2; MS (ESI, MeOH): 223 $(M+H)^+$; HRMS (ESI): $(M+H)^+$, found 232.0274. $C_{10}H_8{}^{35}ClN_2O_2$ requires 232.0269.

*4.8.12. 5,8-Dichloroquinolin-3-amine hydrochloride (**7n**·HCl).* Yield 92 mg, 81%. Brown solid; mp >265 °C. IR (KBr, cm^{-1}) ν_{max}: 3285, 3154, 2556, 1640, 1546, 1405, 1265; ^1H NMR (400 MHz, DMSO-d_6) δ 7.36 (3H, t, J_{N-H}=51.0 Hz, NH_3^+), 7.43–7.49 (2H, m, Ar-H), 7.56 (1H, d, J=8.0 Hz, Ar-H), 8.62 (1H, d, J=2.2 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 108.0, 123.4, 126.5, 126.7, 128.5, 131.5, 136.4, 144.1, 144.3; MS (ESI, MeOH): 213 $(M+H)^+$; HRMS (ESI): $(M+H)^+$, found 212.9990. $C_9H_7{}^{35}Cl_2N_2$ requires 212.9981.

*4.8.13. 3-Amino-6-chloroquinoline-8-carboxylic acid hydrochloride (**7p**·HCl).* Yield 114 mg, 93%. Brown solid; mp >265 °C. IR (KBr, cm^{-1}) ν_{max}: 3166, 1683, 1548, 1404, 1184; ^1H NMR (400 MHz, DMSO-d_6) δ 7.45 (3H, t, J_{N-H}=50.7 Hz, NH_3^+), 7.61 (1H, d, J=2.6 Hz, Ar-H), 8.01 (1H, d, J=2.4 Hz, Ar-H), 8.23 (1H, d, J=2.3 Hz, Ar-H), 8.76 (1H, d, J=2.7 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 115.3, 124.9, 128.7, 129.5, 131.2, 131.9, 133.4, 141.1, 144.0, 165.8; MS (ESI, MeOH): 223 $(M+H)^+$; 245 $(M+Na)^+$; HRMS (ESI): $(M+H)^+$, found 223.0262. $C_{10}H_8{}^{35}ClN_2O_2$ requires 223.0269.

*4.8.14. 3-Amino-8-chloroquinolin-6-ol (**7q**).* Yield 79 mg, 86%. Brown solid; mp 121–126 °C (decomp.). R_f (AcOEt) 0.34; IR (KBr, cm^{-1}) ν_{max}: 3389, 3017, 1618, 1502, 1365, 1156; ^1H NMR (400 MHz, DMSO-d_6) δ 5.75 (2H, br s, NH_2), 6.77 (1H, d, J=2.6 Hz, Ar-H), 6.95 (1H, d, J=2.6 Hz, Ar-H), 7.04 (1H, d, J=2.5 Hz, Ar-H), 8.28 (1H, d, J=2.5 Hz, Ar-H), 9.94 (1H, s, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 105.9, 110.2, 116.2, 132.0, 132.03, 132.9, 140.8, 143.3, 155.1; MS (EI, 70 eV, m/z (%)): 196 (33), 194 (100, M^+), 167 (14), 158 (5), 131 (13), 104 (9); HRMS (EI): M^+, found 194.0239. $C_9H_7{}^{35}ClON_2$ requires 194.0247.

4.9. Ethyl 3-amino-6,8-dichloroquinoline-2-carboxylate (8)

A solution of **3f** (1.33 g, 3.6 mmol) in anhydrous EtOH (15 mL) and Me_3SiCl (10 mL) was heated at 90 °C in an ampoule for 4 days. After cooling down, the solvent was evaporated and to the residue was added AcOEt (50 ml) and saturated $NaHCO_3$. The aqueous layer was separated and extracted with AcOEt (2×50 mL). Combined organic extracts were dried with Na_2SO_4 and the solvent was evaporated. The crude product was chromatographed to yield 690 mg (67%) of the product.

8: Yellow solid; mp 137–140 °C. R_f (hexane/AcOEt 2:1) 0.32; IR (KBr, cm^{-1}) ν_{max}: 3477, 3370, 2973, 2926, 1691, 1608, 1258, 1199; ^1H NMR (400 MHz, DMSO-d_6) δ 1.37 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 4.42 (2H, q, J=7.1 Hz, $OC\underline{H}_2$), 6.74 (2H, br s, $N\underline{H}_2$), 7.51 (1H, d, J=0.4 Hz, H-4), 7.63 (1H, d, J=2.3 Hz, H-7), 7.84 (1H, dd, J=2.3, 0.4 Hz, H-5); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.1, 61.3, 116.5, 123.5, 125.2, 132.2, 132.3, 133.9, 134.4, 134.7, 144.5, 165.9; MS (EI, 70 eV, m/z (%)): 286 (20), 284 (30, M^+), 212 (100), 185 (35), 148 (13); HRMS (EI): M^+, found 284.0110. $C_{12}H_{10}{}^{35}Cl_2N_2O_2$ requires 284.0119.

4.10. Ethyl 3-aminoquinoline-2-carboxylate (9)

To a solution of **8** (215 mg, 0.75 mmol) in AcOEt (30 mL) was added Et_3N (1 mL), and 10% Pd/C (50 mg). The mixture was stirred under H_2 atmosphere at room temperature for 12 h. The catalyst was then filtered off, the filtrate was washed with water and dried with Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography, to obtain 142 mg (88%).

9: Yellow crystals; mp 163–166 °C (AcOEt) (lit.[11a] 148–150 °C). ^1H NMR (600 MHz, DMSO-d_6) δ 1.37 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 4.40 (2H, q, J=7.1 Hz, $OC\underline{H}_2$), 6.41 (2H, br s, $N\underline{H}_2$), 7.40 (1H, ddd, J=8.4, 6.8, 1.3 Hz, Ar-H), 7.47 (1H, ddd, J=8.2, 6.8, 1.1 Hz, Ar-H), 7.51 (1H, s, Ar-H), 7.66 (1H, app. d, J=8.2 Hz, Ar-H), 7.85 (1H, app. d, J=8.4 Hz, Ar-H). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.37; H, 5.40; N, 12.81.

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19. This side-product has been identified as ethyl 2-(2,2-dimethylpropanoyl)-3-[(2,2-dimethylpropanoyl)amino]but-2-enoate. Orange oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (9H, s), 1.20 (9H, s), 1.20 (3H, t, J=7.1 Hz), 2.19 (3H, s), 4.18 (2H, q, J=7.1 Hz), 11.44 (1H, br s); MS (ESI, MeOH): 320 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 320.1816. $C_{16}H_{27}NO_4Na$ requires 320.1832.
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23. A signal of the quaternary carbon atom of the pivaloyl group (ca. 40 ppm) overlapped with those of DMSO, and was not identified.
24. A compound was not isolated in pure form.