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New vistas in quinoline synthesis

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Abstract—The gold-catalyzed Friedlander reaction was applied to the condensation of 2-aminoarylketones with β-keto-esters, β-diketones, β-keto-amides, and β-keto-sulfones to afford a diverse range of 2,3,4-trisubstituted quinolines in 3–82% yield. The seven-membered rings 1,3-cycloheptadione and azepane-2,4-dione reacted smoothly in 75% yield. An alternative procedure for the synthesis of 3-(methanesulfonyl)quinolines was developed and provided an entry into late stage manipulation of the 4-position of these quinolines. The requisite 2-aminoarylketones for the Friedlander reaction were prepared in one pot by modified Sugasawa reaction using gallium(III) chloride and boron(III) chloride in 12–54% yield.

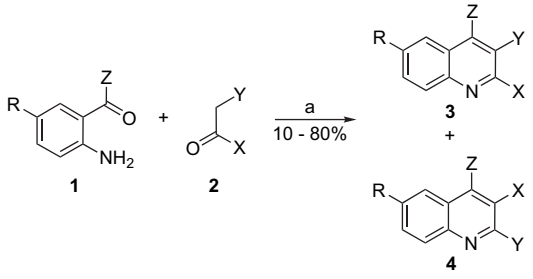
1. Introduction

In the course of a medicinal chemistry program directed at the synthesis of novel $GABA_B$ enhancers,[1] we were challenged with a number of synthetic strategies to address various substitution patterns on the quinoline nucleus. During this endeavor, we capitalized on recent developments regarding the gold-catalyzed green Friedlander condensation discovered by Arcadi.[2] During the review of this paper, Adapa[3] published a much improved neodymium(III) nitrate hexahydrate catalyzed Friedlander condensation.

The Friedlander condensation[4] has been previously performed under neutral (150 °C, neat),[5] basic (NaOH, EtOH), and acidic (H_2SO_4, AcOH)[6] conditions. The Friedlander condensation is a two-step process including enamine formation and cyclodehydration. In its gold-catalyzed version, $NaAuCl_4$ catalyzes the first step. The ratio of regioisomers formed in the Friedlander condensation is strongly dependent on the method and the substrates used in the process.

2. Gold-catalyzed Friedlander reaction

Starting from 2-aminoarylketones **1**, we have applied the protocol of Arcadi[2] to a wide range of 1,3-diones **2** including β-keto-esters, β-diketones, β-keto-amides, and β-keto-sulfones (Scheme 1, Table 1). The method proved to be general and robust and afforded the desired products in unoptimized yields of 3–82% in unoptimized reaction time of 0.5 h to 4 days under reflux in ethanol or 2-propanol in the presence of 2–3 mol % of sodium tetrachloroaurate.



Scheme 1. Generalized gold-catalyzed green Friedlander reaction: (a) 3 mol % $NaAuCl_4 \cdot 2H_2O$, EtOH or ^{i}PrOH, 80 °C, 0.5 h to 4 d; X, Y, Z, and R as defined in Table 1.

The condensation of 2-aminobenzophenones **1** (Z=Ph) and unsymmetrical 1,3-diones **2** led to regioisomeric mixtures of quinolines **3** and **4** if the two carbonyl groups present in **2** had similar reactivity with regard to enamine formation, e.g., **3e**, **4e** and **3f**, **4f** (Table 1).

1,1,1-Trifluoro-2,4-pentanedione[2] (**2h**) and 1-cyclopropyl-1,3-butanedione (**2i**) gave exclusively the regioisomers **3h** and **3i** (Scheme 2).

This can be rationalized by the preferred hydrate formation rather than imine/enamine formation of the carbonyl group next to the CF_3 group in **2h**. The marked regioselectivity observed with **2i** came as a surprise but reflects the lower reactivity of the carbonyl group adjacent to the cyclopropyl residue.

Keywords: Sodium tetrachloroaurate; Gold-catalyzed Friedlander reaction; Regioselectivity; 3-(Methanesulfonyl)quinolines; Sugasawa reaction; Gallium chloride.
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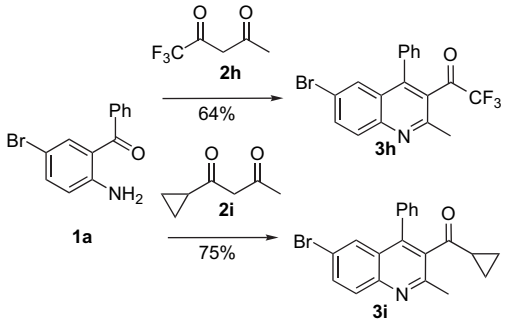
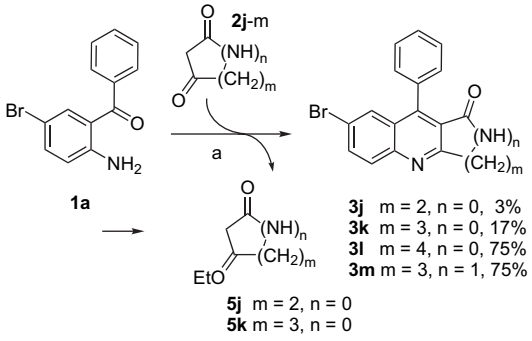
Table 1. Quinolines **3** and **4** synthesized by the gold-catalyzed green Friedlander reaction depicted in Scheme 1

No	X	Y	Z	R	Time	Yield (%)
3a	Me	CO_2Et	Ph	Br	2 d	52[a]
3b	Me	COMe	Ph	Br	1 d	44[b]
3c	Et	COEt	Ph	Br	1 d	37[a]
3d	^{i}Pr	CO^{i}Pr	Ph	Br	4 d	46[a]
3e	^{i}Bu	COMe	Ph	Br	1 d	9[a]
4e	Me	CO^{i}Bu	Ph	Br	1 d	55[a]
3f	CH_2OMe	COMe	Ph	Br	1 d	15[a]
4f	Me	$COCH_2OMe$	Ph	Br	1 d	21[a]
3g	Me	COPh	Ph	Br	1 d	61[a]
3h	Me	$COCF_3$	Ph	Br	14 h	64[c]
3i	Me	CO^{c}Pr	Ph	Br	1 d	75[c]
3j	$CO(CH_2)_2$		Ph	Br	2 d	3[a]
3k	$CO(CH_2)_3$		Ph	Br	2 d	17[a]
3l	$CO(CH_2)_4$		Ph	Br	1 d	75[a]
3m	$CONH(CH_2)_3$		Ph	Br	0.5 h	75[a]
3n	Me	COMe	CH_2Cl	OCF_3	1 d	82[a]
3o	Me	CONHPh-4-Cl	Ph	Br	3 d	66[c]
3p	Me	CONHPh	Ph	Br	4 d	50[c]
3q	Me	CONHMe	Ph	Br	3 d	40[c]
3r	Me	$CONMe_2$	Ph	Br	4 d	21[c]
3s	Me	$NH(CH_2)_2OH$	Ph	Br	1 d	50[c]
3t	Me	CO morpholine	Ph	Br	1 d	29[c]
3u	Me	SO_2Me	Ph	Br	4 d	33[c]

[a] $NaAuCl_4\cdot 2H_2O$ (3 mol%), 1,3-dione (1.5 equiv), EtOH, 80 °C.
[b] $NaAuCl_4\cdot 2H_2O$ (3 mol%), 1,3-dione (1.5 equiv), acetylacetone, 140 °C.
[c] $NaAuCl_4\cdot 2H_2O$ (3 mol%), 1,3-dione (1.5 equiv), ^{i}PrOH, 80 °C.



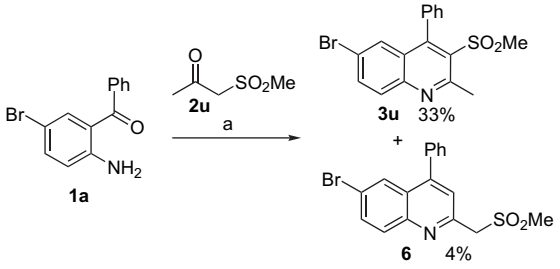
Scheme 2. Exclusive regioisomer formation in the gold-catalyzed Friedlander reaction with special 1,3-diketones.



Scheme 3. Gold-catalyzed Friedlander reaction with cyclic 1,3-diones.

The cyclic five-, six-, and seven-membered 1,3-diones **2j**–**m** led to 2,3-annulated quinolines **3j**–**m** in 3, 17, 75, and 75% yield, respectively (Scheme 3). The five- and six-membered 1,3-diones **2j** and **2k** were predominantly transformed to enol ethyl ethers **5j** and **5k**, respectively, by reaction with the solvent. These by-products were very difficult to separate from the products. The Friedlander reactions of the seven-membered 1,3-diones 1,3-cycloheptadione (**2l**) and β-keto-caprolactam (**2m**)[7–9] proceeded both in excellent 75% yield. This demonstrates that the seven-membered rings have the optimal ring size for the Friedlander condensation.

Secondary and tertiary β-keto-amides led to exclusive formation of the 3-(carboxamido)quinolines **3o**–**t** (Table 1). Even β-keto-sulfones, like methanesulfonylacetone (**2u**), underwent gold-catalyzed Friedlander reaction, although very sluggishly: after 4 days under reflux we obtained 3-(methanesulfonyl)quinoline **3u** in 33% isolated yield. A regioisomer **6** could be isolated from the reaction mixture in 4% yield (Scheme 4). A previous synthesis of 3-(methanesulfonyl)quinolines using $MeSO_2Cl$ and KCN reported yields of 3–36%.[10]

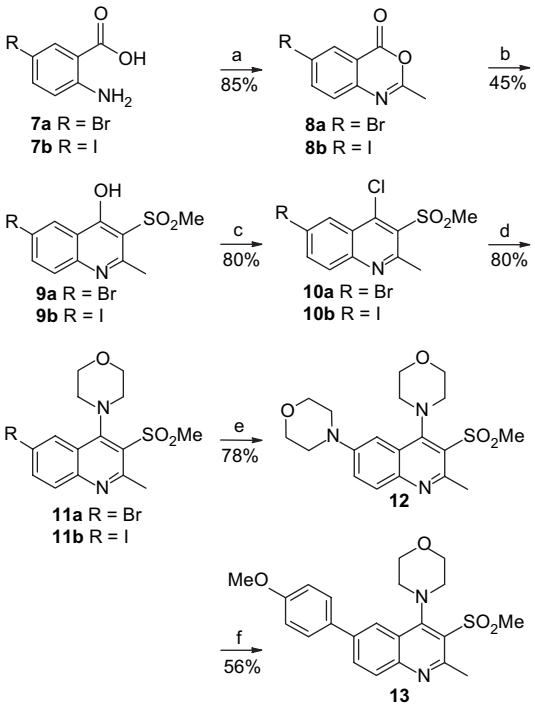


Scheme 4. Gold-catalyzed Friedlander reaction with β-keto-sulfones: (a) 3 mol % $NaAuCl_4\cdot 2H_2O$, 1,3-dione (1.5 equiv), ^{i}PrOH, 80 °C, 4 days.

3. Synthesis of 3-(methanesulfonyl)quinolines

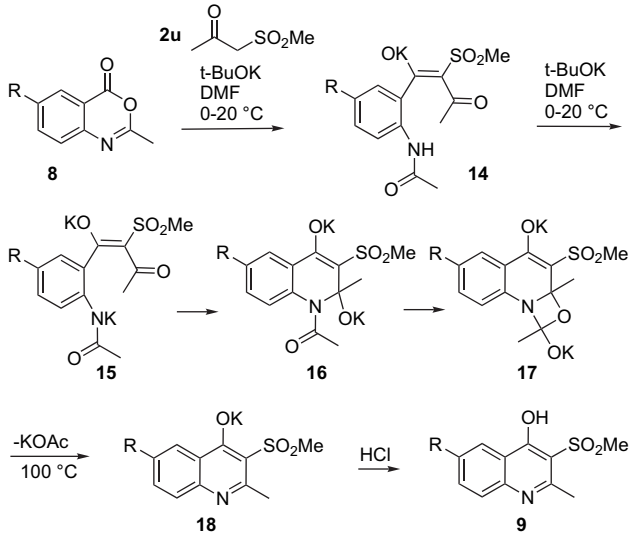
We have also developed an alternative synthesis of 3-(methanesulfonyl)quinolines (Scheme 5), starting from

2-methyl-4*H*-3,1-benzoxazin-4-ones (**8a**,**b**), which are readily available on large scale from anthranilic acids **7a**,**b**.



Scheme 5. (a) Ac_2O, neat, 100 °C, 1 h; (b) $MeCOCH_2SO_2Me$, ^{t}BuOK (2 equiv), DMF, 100 °C, 0.5 h; (c) $POCl_3$ (1.1 equiv), Me_2NTol (2 equiv), toluene, 110 °C, 7 h; (d) morpholine (1.2 equiv), DIPEA (1.2 equiv), DMF, 100 °C, 30 min; (e) morpholine (1.2 equiv), $Pd_2(dba)_3$+X-PHOS (1+2 mol %), ^{t}BuOH, Cs_2CO_3 (1.5 equiv), 110 °C, 2 h; (f) 4-MeO-PhB$(OH)_2$ (1.5 equiv), K_3PO_4 (3 equiv), $Pd(PPh_3)_4$ (3 mol %), dioxane, reflux, 7 h.

Following literature precedent[11–13] for analogous transformations, we speculated that treating benzoxazinone with only 1 equiv of the potassium salt of methanesulfonylacetone in DMF would lead to ring opening. Adding a second equivalent of ^{t}BuOK would induce ring closure and finally potassium acetate would be eliminated under forcing conditions. This proposed mechanism is depicted in Scheme 6.



Scheme 6. Proposed mechanism for the transformation of benzoxazine **8** to 3-(methanesulfonyl)quinoline **9**.

Practically, these proposals worked out as planned. The potassium salt of methanesulfonylacetone (**2u**) was readily formed by treating cold DMF solution with ^{t}BuOK. The benzoxazinone **10** was added and the ring opening was allowed to proceed for 4 h at 20 °C to afford **14**. After cooling, a second equivalent of the base was added, which led to the formation of a red transient dianion **15**, which rapidly cyclized sequentially to **16** and **17** while warming up to 20 °C within 15 min. Finally, the mixture was heated at 100 °C for 30 min to induce aromatization accompanied by loss of potassium acetate to afford **18**. After cooling, **18** was neutralized with 4 N HCl and all solvents were removed under high vacuum. The solid **9** was mixed vigorously with water, which led to the formation of a filterable precipitate that could be further purified by digestion with hot MeOH, which mainly dissolved further impurities. This one-pot protocol afforded the 4-hydroxy-3-(methanesulfonyl)quinolines **9a**,**b** in 45% yield without chromatographic purification.

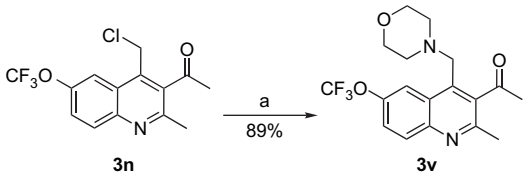
4. Late stage modifications of quinolines

This opened up the avenue for introducing new substituents in the 4-position of quinolines **9a**,**b**. The 4-hydroxyl groups of **9a**,**b** were readily transformed to chloro-leaving groups by treatment with $POCl_3$ and *N*,*N*-dimethyl-*p*-toluidine in toluene under reflux for 7 h. These 4-chloro intermediates **10a**,**b** were crystalline, shelf-stable materials. They could be readily derivatized by treatment with secondary amines, like morpholine in DMF at 100 °C in the presence of Hünig's base to afford **11a**,**b** in 80% yield (Scheme 5).

Moreover, we found that the 6-bromo and 6-iodo quinolines **11a**,**b** readily underwent Buchwald amination[14–16] with a variety of secondary amines. Optimal conditions employed 1 mol % of $Pd_2(dba)_3$, 2 mol % of X-PHOS ligand, and 1.5 equiv of Cs_2CO_3 in *tert*-butanol at 110 °C for 2 h in a sealed tube (Scheme 5).

Suzuki–Miyaura[17,18] couplings of **11a** were performed in the presence of catalytic amounts of $Pd(PPh_3)_4$ with arylboronic acids and K_3PO_4 in dioxane under reflux for 8 h. 4-Methoxyphenylboronic acid afforded 6-aryl-quinoline **13** in 56% yield (Scheme 5).

The 4-chloromethylquinoline **3n** was subjected to further derivatization with morpholine to afford the 4-(morpholinomethyl)quinoline **3v** in 89% yield (Scheme 7).

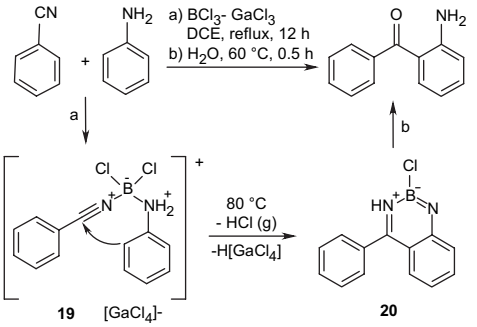


Scheme 7. (a) Morpholine (2 equiv), K_2CO_3, EtOH, 20 °C, 24 h.

5. 2-Aminoarylketones via Sugasawa reaction

2-Aminobenzophenones **1** (Z=Ar) were first prepared by Sternbach,[19,20] as the first step of his famous benzodiazepine

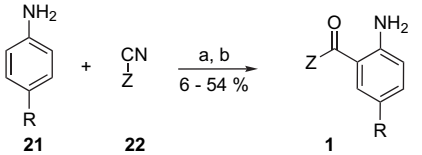
synthesis, from neat aniline and benzoyl chloride with $ZnCl_2$ at 200 °C. While many 2-aminobenzophenones are nowadays commercially available and many alternative protocols have been reported,[21–23] our method of choice to prepare non-commercial items was via the Sugasawa reaction,[24,25] which starts from an aniline and a (benzo)nitrile in the presence of stoichiometric amounts of $AlCl_3$ and BCl_3. The process research groups of Merck and Novartis have improved the yield of the Sugaswa reaction by replacing $AlCl_3$ with $GaCl_3$,[26] and by driving off efficiently the liberated HCl gas.[27] These observations led to a revised mechanism of the Sugasawa reaction (Scheme 8).[27]



Scheme 8. Mechanism of the Sugasawa reaction.

The two Lewis acids $GaCl_3$ and BCl_3 act synergistically probably to form a highly reactive BCl_2-species, which is able to attack the delocalized lone pair of the aniline and directs the Friedel–Crafts-type acylation selectively to the *ortho*-position. The Merck process research group has found NMR evidence for the positively charged complex **19**, which forms upon addition of the benzonitrile and which has $[GaCl_4]^-$ as counter ion. The intramolecular collapse of complex **19** is accompanied by the expulsion of HCl gas and affords the BCl-bis-imino-complex **20**, which is then hydrolyzed by heating the acidic reaction mixture in the presence of water.

The Sugasawa reaction is a capricious protocol whose yields are strongly substrate dependent. We obtained best results when using fresh commercial granular anhydrous $GaCl_3$, which is soluble in 1,2-dichloroethane (DCE), in contrast to $AlCl_3$, which is insoluble, in combination with a fresh commercial 1 M solution of BCl_3 in DCM. We have screened a range of substrates (Scheme 9, Table 2) and have obtained yields in the range of 12–54%. The presence of methoxy groups, dioxomethylene groups or nitrogen heteroatoms either in the aniline **21** or in the benzonitrile **22** was deleterious and led to yields below 20%. Practically



Scheme 9. Substrate screening for the Sugasawa reaction: (a) $GaCl_3$ (1.2 equiv), aniline **21** (1 equiv), 1 M BCl_3 in DCM (1.1 equiv), nitrile **22** (1 equiv), DCE, −10 °C to 80 °C, 16 h; (b) DCM/H_2O 2:1, 80 °C, 0.5 h. R and Z as defined in Table 2.

Table 2. 2-Aminoarylketones **1** prepared via the Sugasawa reaction depicted in Scheme 9

No.	R	Z	Yield (%)
1b	OCF_3	CH_2Cl	54
1c	OCF_3	2,3-F_2-Ph	37
1d	OCF_3	3-CF_3O-Ph	30
1e	OCF_3	4-F-Ph	26
1f	OCF_3	3-Cl-Ph	20
1g	OCF_3	3-F,4-MeO-Ph	19
1h	OCF_3	4-MeO-Ph	12
1i	Br	4-$MeSO_2$-Ph	54
1j	Br	4-F-Ph	43
1k	Br	4-Cl-Ph	33
1l	^{t}Bu	Ph	39

useful yields in the range of 20–50% were achieved with halogen, methanesulfonyl, trifluoromethoxy, and *tert*-butyl substituents. The Sugasawa reaction of chloroacetonitrile[28] gave 54% yield with 4-(trifluoromethoxy)aniline but failed to react with 4-(piperidino)aniline (Table 2).

In summary, we have successfully used the gold-catalyzed version of the Friedlander condensation to introduce a variety of substituents in the 2-, 3-, and 4-position of the quinoline nucleus. A new approach to 3-(methanesulfonyl)quinolines was discovered, which allowed us to introduce secondary amines in the 4-position of these quinolines. Further, late stage transformations in the 6-position of these quinolines via Buchwald aminations and Suzuki couplings worked well. The scope of the Sugasawa reaction was explored in the search for rapid access to 2-aminoarylketones, the starting materials for the Friedlander condensation.

6. Experimental

6.1. General experimental methods

All reactions were performed under a gentle stream of nitrogen in solvents of puriss quality. All extractions were performed classically in separatory funnels with technical grade solvents. All flash chromatographic separations were run on a Biotage Horizon™ or Jones Flashmaster II™ apparatus with pre-packed cartridges: Isolute SPE Flash Si™ (IST), Isolute SPE Flash NH_2™ (IST), or Si-Amine™ (Silicycle). The former is referred to as silica gel and the latter two are referred to as aminated silica gel in the procedures below. Chromatography samples were absorbed on Bulk Isolute Sorbent™ (IST) with AcOEt and thoroughly dried at HV before starting chromatography. All solvents for chromatography and crystallization were of technical grade. All final products were dried at HV (0.1 mbar) at ambient temperature and for at least 5 h unless otherwise noted.

6.1.1. (2-Amino-5-bromo-phenyl)phenyl-methanone[29] (1a). 2-Aminobenzophenone (30 g, 152 mmol) was suspended in acetic acid (300 mL). Potassium bromide (19.9 g, 167 mmol), sodium perborate tetrahydrate (28 g, 183 mmol), and ammonium molybdate tetrahydrate (1.5 g) were added and stirring continued for 3 h at 0 °C. The resulting thick yellow precipitate was diluted with ice water (300 mL), filtered off, washed with ice water, and dried at HV/50 °C. One obtained a yellow solid (40.3 g, 96%). ^{1}H NMR (400 MHz,

$CDCl_3$): δ=6.06 (br s, 2H, NH_2), 6.64 (d, J=9 Hz, 1H, ArH), 7.35 (dd, J_1=9 Hz, J_2=2 Hz, 1H, ArH), 7.48 (m, 2H, ArH+Ph), 7.55 (m, 2H, Ph), 7.63 (m, 2H, Ph); LRMS (EI) m/z=275/277 (M), 274 (M−H).

6.2. General method A (Sugasawa reaction)

2-Aminoarylketones ***1***: a 5-necked glass flask fitted with stirrer, Hickmann condenser, thermometer, septum, nitrogen inlet and outlet connected to a washing bottle containing 30% NaOH, was flushed with nitrogen and then charged with the content of a fresh ampoule of gallium(III) chloride (5 g, 29 mmol). 1,2-Dichloroethane (80 mL) was added and the resulting solution was cooled at −10 °C in a ice/MeOH mixture. Aniline **21** (24 mmol) was added slowly while keeping the temperature below 0 °C. A fresh commercial 1 M solution of boron trichloride in DCM (27 mL) was added at −10 °C via a syringe fitted with a Teflon stop-cock while keeping the temperature below 0 °C. Finally, the nitrile **22** was added (24 mmol) and the mixture was allowed to warm to 20 °C and then heated in an oil bath at 90 °C over 1–2 h. During this operation, DCM was distilled off (50 mL) and a reflux temperature of 80 °C was achieved. At this point, the Hickmann condenser was replaced by a normal reflux condenser and the reaction mixture was heated under reflux for 14 h. The reaction mixture was cooled in ice and hydrolyzed slowly with water (40 mL) and then heated at 80 °C for 30 min in order to hydrolyze the imine. The reaction mixture was cooled again and then extracted with DCM and water. The crude product was purified by chromatography on silica gel in the indicated solvent mixture.

6.2.1. 1-(2-Amino-5-trifluoromethoxy-phenyl)-2-chloroethanone (1b). From 4-(trifluoromethoxy)aniline and chloroacetonitrile according to method A. No chromatography needed. Brown-yellow solid, 54% yield, HPLC purity 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.62 (s, 2H, CH_2Cl), 6.37 (br s, 2H, NH_2), 6.69 (d, J=9 Hz, 1H, 3-H), 7.20 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 4-H), 7.48 (d, J=2 Hz, 1H, 6-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=192.07, 150.68, 136.32, 128.65, 123.65, 120.355 (d, J_{CF}=1012 Hz), 118.50, 113.14, 47.43; IR: ν_{max}=3453, 3343, 1663, 1636, 1599, 1551, 1487, 1247, 1203, 1178, 1148, 1001, 864, 825, 811 cm^{-1}; LRMS (EI) m/z=253 (M, 55), 204 (M−CH_2Cl, 25); HRMS (FT-ICR) m/z calcd for $C_9H_7ClF_3NO_2$ (MH^+): 254.01902; found: 254.01897.

6.2.2. (2-Amino-5-trifluoromethoxy-phenyl)-(3,4-difluoro-phenyl)methanone (1c). From 4-(trifluoromethoxy)-aniline and 3,4-difluorobenzonitrile according to method A. Chromatography on silica gel with a gradient of AcOEt (0–20%) in heptane. Yellow oil, 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.05 (br s, 2H, NH_2), 6.74 (d, J=9 Hz, 1H, 3-H), 7.22 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 4-H), 7.19 (d, J=2 Hz, 1H, 6-H), 7.28 (m, 2H, 6-H+PhF_2), 7.40 (m, 1H, PhF_2), 7.50 (m, 1H, PhF_2); ^{13}C NMR (400 MHz, DMSO-d_6): δ=194.03, 151.41 (dd, J_{1CF}=1000 Hz, J_{2CF}=48 Hz), 150.93, 149.27 (dd, J_{1CF}=988 Hz, J_{2CF}=48 Hz), 136.39, 136.03, 128.33, 126.15, 125.47, 120.3 (d, J_{CF}=1016 Hz), 118.40, 118.01, 117.62, 115.02; IR: ν_{max}=3470, 3355, 1585, 1545, 1513, 1248, 1214, 1180, 1148, 816, 786, 781 cm^{-1}; LRMS (EI) m/z=317 (M, 100), 316 (M−H, 95); HRMS (FT-ICR) m/z calcd for $C_{14}H_8F_5NO_2$ (MH^+): 318.05480; found: 318.05467.

6.2.3. (2-Amino-5-trifluoromethoxy-phenyl)-(3-trifluoromethoxy-phenyl)methanone (1d). From 4-(trifluoromethoxy)aniline and 3-(trifluoromethoxy)benzonitrile according to method A. Chromatography on silica gel with a gradient of AcOEt (0–20%) in heptane. Yellow oil, 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.17 (br s, 2H, NH_2), 6.74 (d, J=9 Hz, 1H, 3-H), 7.21 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 4-H), 7.27 (d, J=2 Hz, 1H, 6-H), 7.24 (m, 1H, $PhOCF_3$), 7.55 (m, 3H, $PhOCF_3$); ^{13}C NMR (400 MHz, DMSO-d_6): δ=194.77, 151.08, 148.00, 147.98, 141.09, 135.96, 135.94, 130.68, 128.48, 127.56, 125.35, 123.82, 120.255 (d, J_{CF}=1012 Hz), 120.015 (d, J_{CF}=1020 Hz), 118.50, 114.78; IR: ν_{max}=3471, 3360, 1635, 1585, 1553, 1482, 1437, 1244, 1203, 1146, 863, 810, 773 cm^{-1}; LRMS (EI) m/z=365 (M, 100), 364 (M−H, 80), 280 (30); HRMS (FT-ICR) m/z calcd for $C_{15}H_9F_6NO_3$ (MH^+): 366.05594; found: 366.05588.

6.2.4. (2-Amino-5-trifluoromethoxy-phenyl)-(4-fluoro-phenyl)methanone (1e). From 4-(trifluoromethoxy)aniline and 4-fluorobenzonitrile according to method A. Chromatography on silica gel with a gradient of AcOEt (0–20%) in heptane. Yellow oil, 26% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.03 (br s, 2H, NH_2), 6.73 (d, J=9 Hz, 1H, 3-H), 7.15 (m, 2H, 6-H+PhF_2), 7.28 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 4-H), 7.15 (m, 2H, PhF_2), 7.68 (m, 2H, PhF_2); ^{13}C NMR (400 MHz, DMSO-d_6): δ=195.28, 163.905 (d, J_{CF}=996 Hz), 150.71, 136.02, 135.45, 131.46, 127.96, 125.35, 120.305 (d, J_{CF}=1012 Hz), 118.30, 115.56; IR: ν_{max}=3446, 3330, 1631, 1599, 1557, 1490, 1241, 1210, 1156, 1100, 985, 919, 902, 852, 783 cm^{-1}; LRMS (ESI) m/z=298 (M−H); HRMS (FT-ICR) m/z calcd for $C_{14}H_9F_4NO_2$ (MH^+): 300.06422; found: 300.06417.

6.2.5. (2-Amino-5-trifluoromethoxy-phenyl)-(3-chloro-phenyl)methanone (1f). From 4-(trifluoromethoxy)aniline and 3-chlorobenzonitrile according to method A. Chromatography on silica gel with a gradient of AcOEt (0–20%) in heptane. Yellow oil, 20% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.14 (br s, 2H, NH_2), 6.73 (d, J=9 Hz, 1H, 3-H), 7.21 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 4-H), 7.27 (m, 1H, PhCl), 7.42 (m, 2H, PhCl), 7.50 (m, 1H, PhCl), 7.63 (d, J=2 Hz, 1H, 6-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=195.03, 151.03, 141.01, 135.95, 133.27, 131.13, 130.32, 128.43, 128.17, 127.13, 125.49, 120.30 (q, J_{CF}=1012 Hz), 118.46, 114.94; IR: ν_{max}=3455, 3349, 2924, 2854, 1645, 1602, 1562, 1488, 1467, 1299, 1262, 1211, 1152, 985, 922, 884, 817, 765, 714, 684, 669, 652 cm^{-1}; LRMS (EI) m/z=315 (M, 100), 314 (M−H, 95), 280 (M−Cl, 45); HRMS (FT-ICR) m/z calcd for $C_{14}H_9ClF_3NO_2$ (MH^+): 316.03467; found: 316.03458.

6.2.6. (2-Amino-5-trifluoromethoxy-phenyl)-(3-fluoro-4-methoxy-phenyl)methanone (1g). From 4-(trifluoromethoxy)aniline and 3-fluoro-4-methoxybenzonitrile according to method A. Chromatography on silica gel with a gradient of AcOEt (0–20%) in heptane. Yellow oil, 19% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.98 (s, 3H, OMe), 5.90 (br s, 2H, NH_2), 6.73 (d, J=9 Hz, 1H, 3-H), 7.02 (t, J=8 Hz, 1H, 5-H′), 7.18 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 4-H), 7.32 (d, J=2 Hz, 1H, 6-H), 7.45 (d, J=8 Hz, 1H, 5-H′),

7.48 (dd, J_1=12 Hz, J_2=2 Hz, 1H, 1-H′); ^{13}C NMR (400 MHz, DMSO-d_6): δ=194.10, 150.94 (d, J_{CF}=967 Hz), 150.38, 136.09, 131.29, 127.62, 126.70, 125.15, 120.335 (d, J_{CF}=1012 Hz), 118.15, 116.42 (d, J_{CF}=72 Hz), 116.00, 113.15, 56.27; IR: ν_{max}=3455, 3346, 1633, 1605, 1572, 1552, 1516, 1483, 1286, 1252, 1203, 1151, 1136, 1105, 1021, 887, 819, 778, 763 cm^{-1}; LRMS (EI) *m/z*=329 (M, 100), 328 (M−H, 95), 314 (M−Me, 25); HRMS (FT-ICR) *m/z* calcd for $C_{15}H_{11}F_4NO_3$ (MH^+): 330.07478; found: 330.07479.

6.2.7. (2-Amino-5-trifluoromethoxy-phenyl)-(4-methoxy-phenyl)methanone (1h). From 4-(trifluoromethoxy)-aniline and 4-methoxybenzonitrile according to method A. Chromatography on silica gel with a gradient of AcOEt (0–20%) in heptane. Yellow oil, 12% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.89 (s, 3H, OMe), 5.86 (br s, 2H, NH_2), 6.71 (d, *J*=8 Hz, 1H, 3-H), 6.97 (d, *J*=7 Hz, 2H, PhOMe), 7.17 (dd, J_1=8 Hz, J_2=2 Hz, 1H, 4-H), 6.33 (d, *J*=2 Hz, 1H, 6-H), 7.68 (d, *J*=7 Hz, 2H, PhOMe); ^{13}C NMR (400 MHz, DMSO-d_6): δ=195.16, 162.17, 150.14, 136.01, 135.99, 131.25, 130.95, 127.22, 125.04, 120.20 (q, J_{CF}=1000 Hz), 117.95, 116.56, 113.96, 55.42; IR: ν_{max}=3462, 3355, 1638, 1587, 1557, 1485, 1266, 1241, 1169, 1142, 1027, 980, 847, 826, 778, 666 cm^{-1}; LRMS (ESI) *m/z*=312 (MH^+); HRMS (FT-ICR) *m/z* calcd for $C_{15}H_{12}F_3NO_3$ (MH^+): 312.08420; found: 312.08405.

6.2.8. (2-Amino-5-bromo-phenyl)-(4-methanesulfonyl-phenyl)methanone (1i). From 4-bromoaniline and 4-(methylsulfonyl)benzonitrile according to method A. Chromatography on silica gel with a gradient of AcOEt (0–50%) in heptane. Yellow solid, 54% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.13 (s, 3H, Me), 6.27 (br s, 2H, NH_2), 6.67 (d, *J*=9 Hz, 1H, 3-H), 7.40 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 4-H), 7.41 (d, *J*=2 Hz, 1H, 6-H), 7.77 (dd, J_1=7 Hz, J_2= 2 Hz, 2H, Ph), 8.07 (dd, J_1=7 Hz, J_2=2 Hz, 2H, Ph); ^{13}C NMR (400 MHz, DMSO-d_6): δ=195.51, 151.23, 143.76, 142.59, 137.22, 135.02, 129.12, 127.14, 119.52, 116.88, 104.17, 43.28; IR: ν_{max}=3472, 3365, 2924, 2824, 1640, 1611, 1588, 1548, 1466, 1398, 1377, 1314, 1302, 1240, 1154, 1138, 1086, 940, 769, 674 cm^{-1}; LRMS (ESI) *m/z*= 354 (MH^+); HRMS (FT-ICR) *m/z* calcd for $C_{11}H_{10}BrNO_3S$ (MH^+): 315.96375; found: 315.96370.

6.2.9. (2-Amino-5-bromo-phenyl)-(4-fluoro-phenyl)-methanone (1j). From 4-bromoaniline and 4-fluorobenzonitrile according to method A. Chromatography on silica gel with a gradient of AcOEt (0–50%) in heptane. Yellow solid, 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.99 (br s, 2H, NH_2), 6.67 (d, *J*=9 Hz, 1H, 3-H), 7.17 (m, 2H, PhF), 7.36 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 4-H), 7.50 (d, *J*=2 Hz, 1H, 6-H), 7.67 (m, 2H, PhF); ^{13}C NMR (400 MHz, DMSO-d_6): δ=195.30, 163.83 (d, J_{CF}=992 Hz), 150.68, 136.54, 135.63, 135.60, 134.83, 131.425 (d, J_{CF}=36 Hz), 119.28, 117.81, 115.455 (d, J_{CF}=84 Hz), 104.13; IR: ν_{max}=3436, 3330, 1629, 1595, 1575, 1538, 1502, 1467, 1403, 1292, 1235, 1222, 1155, 938, 852, 816, 803, 779 cm^{-1}; LRMS (EI) *m/z*=294 (M, 100), 293 (M−H, 80), 213 (M−HBr, 25); HRMS (FT-ICR) *m/z* calcd for $C_{13}H_9BrFNO$ (MH^+): 293.99243; found: 293.99240.

6.2.10. (2-Amino-5-bromo-phenyl)-(4-chloro-phenyl)methanone (1k). From 4-bromoaniline and 4-chlorobenzonitrile according to method A. Chromatography on silica gel with a gradient of AcOEt (0–50%) in heptane. Yellow solid, 33% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.05 (br s, 2H, NH_2), 6.64 (d, *J*=9 Hz, 1H, 3-H), 7.36 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 4-H), 7.47 (m, 2H, PhCl), 7.49 (d, *J*=2 Hz, 1H, 6-H), 7.58 (m, 2H, PhCl); ^{13}C NMR (400 MHz, DMSO-d_6): δ=195.42, 150.80, 137.84, 136.71, 136.15, 134.84, 130.47, 128.51, 119.32, 117.47, 104.11; IR: ν_{max}=3489, 3371, 1630, 1603, 1579, 1543, 1468, 1292, 1233, 1161, 1084, 939, 815, 777, 677 cm^{-1}; LRMS (EI) *m/z*=308/310 (M, 100), 309/311 (M−H, 80), 229 (M−HBr, 25); HRMS (FT-ICR) *m/z* calcd for $C_{13}H_9BrClNO$ (MH^+): 309.96288; found: 309.96283.

6.2.11. (2-Amino-5-*tert*-butyl-phenyl)phenyl-methanone (1l). From 4-bromoaniline and 4-*tert*-butylaniline according to method A. Chromatography on silica gel with a gradient of AcOEt (0–20%) in heptane. Yellow solid, 39% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.20 (s, 9H, ^{t}Bu), 5.90 (br s, 2H, NH_2), 6.70 (d, *J*=9 Hz, 1H, 3-H), 7.35 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 4-H), 7.45 (m, 3H, Ph+3-H), 7.50 (m, 1H, Ph), 7.65 (m, 2H, Ph); ^{13}C NMR (400 MHz, DMSO-d_6): δ=197.80, 149.77, 140.01, 135.92, 132.01, 130.91, 129.30, 128.62, 128.11, 116.86, 115.58, 33.31, 30.90; IR: ν_{max}=3433, 3318, 2950, 1619, 1577, 1550, 1485, 1304, 1240, 1174, 956, 827, 710, 654 cm^{-1}; LRMS (ESI) *m/z*=254 (MH^+); HRMS (FT-ICR) *m/z* calcd for $C_{17}H_{19}NO$ (MH^+): 254.15394; found: 254.15382.

6.3. General method B (Friedlander reaction)

Quinolines: 2-aminoarylketone **1** (0.1–1 g scale) and 1,3-dione **2** (1.5 equiv) and sodium tetrachloroaurate(III) dihydrate (0.025 equiv) were heated under nitrogen in the EtOH or ^{i}PrOH (10% w/w solution) and reacted for the indicated time at 80 °C (see Table 2). The reaction mixture was evaporated to dryness and the residue purified as described below.

6.3.1. 6-Bromo-2-methyl-4-phenyl-quinoline-3-carboxylic acid ethyl ester (3a). Compound **1a** (3 g, 11 mmol), ethylacetoacetate (**21**) (2.1 mL, 16 mmol), and sodium tetrachloroaurate(III) dihydrate (0.13 g) in ethanol (30 mL) were refluxed at 95 °C for 2 days. The solvent was evaporated. The product was purified by flash chromatography on aminated silica gel with heptane/AcOEt 85:15. One obtained 2.09 g (52%) of yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.96 (t, *J*=7 Hz, 3H, CO_2Et), 4.06 (q, *J*=7 Hz, 2H, CO_2Et), 2.76 (s, 3H, CH_3), 7.34 (m, 2H, Ph), 7.50 (m, 3H, Ph), 7.70 (d, *J*=2 Hz, 1H, 5-H), 7.78 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.94 (d, *J*=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=167.09, 154.69, 145.70, 144.63, 134.18, 133.59, 130.97, 129.07, 128.96, 128.53, 127.72, 127.69, 125.78, 119.99, 61.21, 23.30, 13.36; IR: ν_{max}=2978, 1716, 1566, 1556, 1477, 1377, 1308, 1220, 1064, 1013, 837, 711 cm^{-1}; LRMS (EI) *m/z*=369/371 (M, 100), 324/326 (M−Et, 50); HRMS (FT-ICR) *m/z* calcd for $C_{19}H_{16}BrNO_2$ (MH^+): 370.04372; found: 370.04373.

6.3.2. 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)ethanone (3b). Compound **1a** (0.3 g, 1 mmol) and sodium tetrachloroaurate(III) dihydrate (13 mg) in acetylacetone (3 mL) were refluxed for 24 h. The solvent was evaporated. The

product was purified by flash chromatography on aminated silica gel with heptane/AcOEt 67:33. One obtained 161 mg (44%) of orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.99 (s, 3H, COMe), 2.67 (s, 3H, Me), 7.34 (m, 2H, Ph), 7.53 (m, 3H, Ph), 7.74 (d, J=2 Hz, 1H, 5-H), 7.79 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.94 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=204.70, 154.01, 145.44, 142.36, 135.29, 133.90, 133.25, 130.92, 129.69, 129.28, 128.90, 127.47, 125.96, 119.90, 31.73, 23.46; IR: ν_{max}=1701, 1567, 1554, 1476, 1353, 1193, 1158, 1064, 961, 830, 790, 764, 705 cm^{-1}; LRMS (EI) m/z=339/341 (M, 60), 324/326 (M−Me, 100); HRMS (FT-ICR) m/z calcd for $C_{18}H_{14}BrNO$ (MH^+): 340.03315; found: 340.03294.

6.3.3. 1-(6-Bromo-2-ethyl-4-phenyl-quinolin-3-yl)propan-1-one (3c). Compound **1a** (1 g, 3.6 mmol) and 3,5-heptanedione (0.736 mL, 5.4 mmol) were refluxed in EtOH (15 mL) in the presence of sodium tetrachloroaurate dihydrate (43 mg, 0.1 mmol) for 24 h. The brown reaction mixture was evaporated to dryness and purified by chromatography on silica gel in heptane/AcOEt 20:1. One obtained 500 mg (37%) of white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.82 (t, J=7 Hz, 3H, Me), 1.40 (t, J=7 Hz, 3H, Me), 2.22 (q, J=7 Hz, 2H, CH_2CO), 2.87 (q, J=7 Hz, 2H, CH_2Me), 7.32 (m, 2H, Ph), 7.51 (m, 3H, Ph), 7.73 (d, J=2 Hz, 1H, 5-H), 7.77 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.97 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=207.57, 158.54, 145.57, 142.48, 135.19, 133.94, 133.17, 131.13, 129.82, 129.20, 128.82, 127.42, 125.94, 119.90, 37.47, 29.19, 12.92, 7.39; IR: ν_{max}=2977, 2937, 1699, 1570, 1475, 1433, 1374, 958, 831, 706 cm^{-1}; LRMS (EI) m/z=369/371 (M, 20), 338/340 (M−Et, 100), 312 (M−Et−CO, 20), 230 (M−Et−CO−HBr, 20), 230 (25); HRMS (FT-ICR) m/z calcd for $C_{20}H_{18}BrNO$ (MH^+): 368.06445; found: 368.06437.

6.3.4. 1-(6-Bromo-2-isopropyl-4-phenyl-quinolin-3-yl)-2-methyl-propan-1-one (3d). Compound **1a** (0.5 g, 2 mmol), 2,6-dimethyl-3,5-heptanedione (0.424 g, 3 mmol), and sodium tetrachloroaurate(III) dihydrate (0.022 g) in EtOH (5 mL) were refluxed at for 4 days. The solvent was evaporated. The product was purified by flash chromatography on aminated silica gel with heptane/AcOEt 85:15 gradient. One obtained 328 mg (46%) of a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.82 (d, J=7 Hz, 6H, CO^{i}Pr), 1.41 (d, J=7 Hz, 6H, Ar^{i}Pr), 2.22 (sept, J=7 Hz, 1H, CO^{i}Pr), 2.95 (sept, J=7 Hz, 1H, Ar^{i}Pr), 7.33 (m, 2H, Ph), 7.51 (m, 3H, Ph), 7.74 (d, J=2 Hz, 1H, 5-H), 7.76 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.97 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=210.71, 162.92, 145.79, 142.90, 134.17, 134.15, 133.21, 131.18, 130.07, 129.23, 128.83, 127.38, 125.97, 119.91, 41.72, 33.89, 22.63, 17.40; IR: ν_{max}=2969, 2954, 1691, 1555, 1442, 1082, 975, 832, 705 cm^{-1}; LRMS (EI) m/z=395/397 (M, 10), 352/355 (M−^{i}Pr, 100); HRMS (FT-ICR) m/z calcd for $C_{22}H_{22}BrNO$ (MH^+): 396.09575; found: 396.09566.

6.3.5. 1-(6-Bromo-2-isobutyl-4-phenyl-quinolin-3-yl)-ethanone (3e) and 1-(6-bromo-2-methyl-4-phenyl-quinolin-3-yl)-3-methyl-butan-1-one (4e). Compound **1a** (1 g, 3.6 mmol) and 6-methyl-2,4-heptanedione (696 mg, 5.4 mmol) were refluxed in EtOH (15 mL) in the presence of sodium tetrachloroaurate dihydrate (43 mg, 0.1 mmol) for 24 h. The brown reaction mixture was evaporated to dryness and purified by chromatography on silica gel in heptane/AcOEt 20:1. One obtained two products, first eluted was the minor component **3e** (120 mg, 9%), then the major component **4e** (730 mg, 55%) both as white soft crystals.

Compound **3e**. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.98 (d, J=7 Hz, 6H, CH_2CHMe_2), 1.98 (s, 3H, COMe), 2.35 (sept, J=7 Hz, 1H, CH_2CHMe_2), 2.78 (d, J=7 Hz, 2H, CH_2CHMe_2), 7.33 (m, 2H, Ph), 7.53 (m, 3H, Ph), 7.73 (d, J=2 Hz, 1H, 5-H), 7.78 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.96 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=204.67, 156.73, 145.44, 142.53, 135.68, 133.98, 133.25, 131.16, 129.79, 129.25, 128.85, 127.46, 125.98, 119.97, 44.59, 32.25, 27.81, 22.42; IR: ν_{max}=2951, 2924, 2854, 1701, 1601, 1562, 1551, 1464, 1353, 1197, 1156, 1065, 828, 703 cm^{-1}; LRMS (EI) m/z=381/383 (M, 15), 366/368 (M−Me, 30), 338/340 (M−COMe, 100); HRMS (FT-ICR) m/z calcd for $C_{21}H_{20}BrNO$ (MH^+): 382.08010; found: 382.08003.

Compound **4e**. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.65 (d, J=7 Hz, 6H, $COCH_2CHMe_2$), 2.00 (sept, J=7 Hz, 1H, $COCH_2CHMe_2$), 2.10 (d, J=7 Hz, 2H, CH_2CHMe_2), 2.65 (s, 1H, ArMe), 2.78 (d, J=7 Hz, 2H, CH_2CHMe_2), 7.32 (m, 2H, Ph), 7.52 (m, 3H, Ph), 7.72 (d, J=2 Hz, 1H, 5-H), 7.77 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.93 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=206.09, 154.11, 145.39, 142.43, 135.11, 133.66, 133.18, 130.91, 129.97, 129.18, 128.78, 127.37, 126.01, 119.86, 52.54, 23.25, 22.60, 21.76; IR: ν_{max}=2956, 1693, 1571, 1366, 1156, 1001, 827, 697 cm^{-1}; LRMS (EI) m/z=381/383 (M, 15), 324/326 (M−^{i}Pr, 100), 217 (50); HRMS (FT-ICR) m/z calcd for $C_{21}H_{20}BrNO$ (MH^+): 382.08010; found: 382.07997.

6.3.6. 1-(6-Bromo-2-methoxymethyl-4-phenyl-quinolin-3-yl)ethanone (3f) and 1-(6-bromo-2-methyl-4-phenyl-quinolin-3-yl)-2-methoxy-ethanone (4f). Compound **1a** (1 g, 3.6 mmol) and 1-methoxy-pentane-2,4-dione (706 mg, 5.4 mmol) were stirred under nitrogen in EtOH (15 mL) in the presence of sodium tetrachloroaurate dihydrate (43 mg, 0.1 mmol) for 30 h. One of the products precipitated spontaneously from the reaction mixture. The suspension was stirred in ice for 10 min, and the crystals were filtered off and washed with cold EtOH. One obtained 195 mg (14%) of **3f** as beige crystals. The mother liquor was evaporated and subjected to silica gel chromatography with a heptane/AcOEt gradient from 100:0 to 67:33. The first eluted compound (80 mg, 6%) corresponded to the crystalline material **3f** and the second was its regioisomer **4f** obtained as brown crystals (278 mg, 20%).

Compound **3f**. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.95 (s, 3H, COMe), 3.38 (s, 3H, OMe), 4.75 (s, 2H, CH_2OMe), 7.34 (m, 2H, Ph), 7.54 (m, 3H, Ph), 7.76 (d, J=2 Hz, 1H, 5-H), 7.80 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.98 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=202.80, 155.03, 144.72, 143.13, 134.48, 133.69, 133.48, 131.31, 129.64, 129.29, 128.87, 127.57, 126.98, 120.85, 74.46, 58.14, 31.21; IR: ν_{max}=1696, 1559, 1479, 1202, 1109, 1066, 958, 840, 767, 709 cm^{-1}; LRMS (EI) m/z=369/371 (M, 10), 341 (M−OCH_2, 80), 338/340 (M−OMe, 100); HRMS (FT-ICR) m/z calcd for $C_{19}H_{16}BrNO_2$ (MH^+): 370.04372; found: 370.04359.

Compound **4f**. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.67 (s, 3H, ArMe), 3.07 (s, 3H, OMe), 3.74 (s, 2H, COC*H*$_2$OMe), 7.35 (m, 2H, Ph), 7.53 (m, 3H, Ph), 7.75 (d, J=2 Hz, 1H, 5-H), 7.80 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.95 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=204.54, 154.43, 145.70, 143.67, 133.53, 133.46, 132.30, 130.96, 129.92, 129.34, 128.80, 127.45, 125.74, 120.00, 77.33, 58.06, 23.29; IR: ν_{max}=1699, 1579, 1572, 1554, 1476, 1367, 1195, 1110, 1040, 978, 827, 706 cm^{-1}; LRMS (EI) m/z=369/371 (M, 5), 324/326 (M−CH_2OMe, 100); HRMS (FT-ICR) m/z calcd for $C_{19}H_{16}BrNO_2$ (MH^+): 370.04372; found: 370.04354.

6.3.7. (6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-phenyl-methanone (3g). Compound **1a** (1 g, 3.6 mmol) and 1-phenyl-1,3-butanedione (881 mg, 5.4 mmol) were refluxed in EtOH (15 mL) in the presence of sodium tetrachloroaurate dihydrate (43 mg, 0.1 mmol) for 24 h. Upon evaporation, the product precipitated. The crystals were filtered off and washed with EtOH. One obtained 900 mg (61%) of beige crystals. ^{1}H NMR (400 MHz, DMSO-d_6): δ=2.48 (s, 3H, Me), 7.22 (m, 2H, Ph), 7.34 (m, 3H, Ph), 7.40 (m, 2H, COPh), 7.55 (m, 2H, COPh+5-H), 7.61 (m, 2H, COPh), 7.79 (dd, J_1=8 Hz, J_2=2 Hz, 1H, 7-H), 8.06 (d, J=8 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=196.60, 154.65, 145.84, 143.99, 136.11, 134.17, 133.67, 133.33, 132.82, 131.08, 129.72, 129.14, 128.92, 128.73, 128.25, 127.56, 126.25, 119.96, 23.56; IR: ν_{max}=1672, 1596, 1576, 1569, 1557, 1478, 1447, 1230, 961, 830, 695 cm^{-1}; LRMS (ESI) m/z=402 (MH^+); HRMS (FT-ICR) m/z calcd for $C_{23}H_{16}BrNO$ (MH^+): 402.04880; found: 402.04867.

6.3.8. 1-(6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)-2,2,2-trifluoro-ethanone (3h). Compound **1a** (4 g, 14 mmol) was dissolved in ^{i}PrOH (50 mL), 1,1,1-trifluoro-2,4-pentanedione (2.68 g, 17 mmol) and sodium tetrachloroaurate(III) dihydrate (140 mg, 0.4 mmol) were added and stirring under reflux continued over night. The reaction mixture was evaporated to dryness and the residue purified by flash chromatography on silica gel with heptane/AcOEt 20:1 to give a light yellow solid (3.7 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.67 (s, 3H, ArMe), 7.31 (m, 2H, Ph), 7.52 (m, 3H, Ph), 7.80 (d, J=2 Hz, 1H, 5-H), 7.86 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.98 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=188.425 (q, J_{CF}=148 Hz), 153.49, 146.50, 146.46, 134.94, 132.39, 131.10, 130.17, 130.07, 128.99, 127.72, 127.32, 125.08, 120.87, 114.465 (q, J=1164 Hz), 23.42; IR: ν_{max}=1742, 1564, 1475, 1288, 1206, 1145, 1113, 1063, 961, 903, 834, 763, 708, 701, 670 cm^{-1}; LRMS (EI) m/z=393/395 (M, 50), 324/326 (M−CF_3, 100), 296/298 (M−CF_3−CO, 20), 217 (M−CF_3−CO−Br, 70); HRMS (FT-ICR) m/z calcd for $C_{18}H_{11}BrF_3NO$ (MH^+): 394.00489; found: 394.00475.

6.3.9. (6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)cyclopropyl-methanone (3i). Compound **1a** (1g, 3.62 mmol) was dissolved in ^{i}PrOH (20 mL), 1-cyclopropyl-2,4-pentanedione (0.548 g, 4.32 mmol) and sodium tetrachloroaurate(III) dihydrate (43 g, 0.1 mmol) were added and stirring under reflux continued over night. Evaporated to dryness and purified by flash chromatography on silica gel with heptane/AcOEt 1:2 to give a light yellow solid (1 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.69 (m, 2H, ^{c}Pr), 0.94 (m, 2H, ^{c}Pr), 1.79 (m, 1H, ^{c}Pr), 2.69 (s, 3H, ArMe), 7.34 (m, 2H, Ph), 7.50 (m, 3H, Ph), 7.76 (d, J=2 Hz, 1H, 5-H), 7.77 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.94 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=206.68, 154.08, 145.53, 143.02, 135.92, 134.14, 133.19, 130.95, 129.85, 128.99, 128.58, 127.52, 126.14, 119.83, 23.58, 23.40, 12.67; IR: ν_{max}=1681, 1566, 1479, 1443, 1394, 1366, 1030, 986, 828, 759, 700 cm^{-1}; LRMS (EI) m/z=365/367 (M, 100), 324/326 (M−^{c}Pr, 95); HRMS (FT-ICR) m/z calcd for $C_{20}H_{16}BrNO$ (MH^+): 366.04880; found: 366.04862.

6.3.10. 7-Bromo-9-phenyl-2,3-dihydro-cyclopenta[*b*]quinolin-1-one (3j). Compound **1a** (1 g, 3.6 mmol) and 1,3-cyclopentadione (533 mg, 5.4 mmol) were heated under reflux in EtOH (15 mL) in the presence of sodium tetrachloroaurate dihydrate (43 mg, 0.1 mmol) for 24 h. The brown reaction mixture was evaporated to dryness and purified by chromatography on silica gel in heptane/AcOEt 3:1–1:1 (repeated once!). One obtained a 352 mg (29%) of brown sticky crystals, which contained only 3% of **3j** and consisted mainly of 3-ethoxy-cyclopent-2-enone (**5j**).

Compound **3j**. ^{1}H NMR (400 MHz, DMSO-d_6): δ=2.78 (m, 2H, COC*H*$_2$CH$_2$), 3.33 (m, 2H, COCH$_2$C*H*$_2$), 7.38 (m, 2H, Ph), 7.58 (m, 3H, Ph), 7.70 (m, 1H, 5-H), 8.04 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 8.07 (d, J=9 Hz, 1H, 8-H); LRMS (EI) m/z=336/338 (M, 100), 335/337 (M−H, 50), 322/324 (M−Br, 95).

Compound **5j**. ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.31 (t, J=7 Hz, 3H, OCH$_2$C*H*$_3$), 2.29 (m, 2H, CH$_2$CH$_2$), 2.56 (m, 2H, CH$_2$CH$_2$), 4.07 (q, J=7 Hz, 2H, OC*H*$_2$CH$_3$), 5.35 (s, 1H, =CH).

6.3.11. 7-Bromo-9-phenyl-3,4-dihydro-2*H*-acridin-1-one (3k). Compound **1a** (1 g, 3.6 mmol) and 1,3-cyclohexanedione (609 mg, 5.4 mmol) were heated under reflux under nitrogen in EtOH (15 mL) in the presence of sodium tetrachloroaurate dihydrate (43 mg, 0.1 mmol) for 48 h. The brown reaction mixture was evaporated to dryness and purified by chromatography on silica gel in heptane/AcOEt 2:1–1:1. Despite poor separation, the product crystallized upon evaporation, the crystals were triturated in heptane/AcOEt 10:1, filtered, and washed with little heptane/AcOEt 10:1. One obtained 215 mg (17%) of yellow crystals. ^{1}H NMR (400 MHz, DMSO-d_6): δ=2.17 (d, J=7 Hz, 2H, COCH$_2$C*H*$_2$CH$_2$), 2.66 (d, J=7 Hz, 2H, COC*H*$_2$CH$_2$CH$_2$), 3.28 (d, J=7 Hz, 2H, COCH$_2$CH$_2$C*H*$_2$), 7.21 (m, 2H, Ph), 7.39 (m, 1H, 5-H), 7.49 (m, 3H, Ph), 7.97 (m, 2H, 7-H+8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=197.21, 163.12, 148.82, 146.51, 136.68, 134.55, 130.68, 128.96, 128.18, 128.07, 127.60, 124.42, 119.64, 33.79, 20.62; IR: ν_{max}=2955, 1687, 1546, 1474, 1426, 1211, 1134, 1015, 837, 695 cm^{-1}; LRMS (EI) m/z=351/353 (M, 100), 350/352 (M−H, 85), 322/324 (M−CHO, 45); HRMS (FT-ICR) m/z calcd for $C_{19}H_{14}BrNO$ (MH^+): 352.03315; found: 352.03303.

6.3.12. 2-Bromo-11-phenyl-6,7,8,9-tetrahydro-cyclohepta[*b*]quinolin-10-one (3l). Compound **1a** (1 g, 3.6 mmol) and 1,3-cycloheptanedione (0.623 mL, 5.4 mmol) were heated under reflux under nitrogen in EtOH (15 mL) in the presence of sodium tetrachloroaurate dihydrate (43 mg,

0.1 mmol) for 20 h. The product precipitated spontaneously from the reaction mixture. The suspension was stirred in ice for 10 min, and the crystals were filtered off and washed with cold EtOH. One obtained 996 mg (75%) of beige crystals. ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.87 (m, 2H, $COCH_2CH_2CH_2CH_2$), 1.96 (m, 2H, $COCH_2CH_2CH_2CH_2$), 2.65 (t, J=6 Hz, 2H, $COCH_2CH_2CH_2CH_2$), 3.07 (t, J=7 Hz, 2H, $COCH_2CH_2CH_2CH_2$), 7.33 (m, 2H, Ph), 7.50 (m, 3H, Ph), 7.55 (m, 1H, 5-H), 7.93 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 8.02 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=207.35, 157.39, 145.95, 144.21, 134.50, 134.47, 133.31, 131.11, 129.16, 128.47, 128.04, 126.94, 119.85, 42.66, 36.16, 24.26, 23.41; IR: ν_{max}=2945, 1691, 1583, 1570, 1556, 1477, 1376, 1122, 952, 827, 760, 707, 666 cm^{-1}; LRMS (EI) m/z=365/367 (M, 80), 336/338 (M−Et, 100), 258 (M−CO–Br, 45); HRMS (FT-ICR) m/z calcd for $C_{20}H_{16}BrNO$ (MH^+): 366.04880; found: 366.04867.

6.3.13. 9-Bromo-11-phenyl-2,3,4,5-tetrahydro-azepino[4,3-*b*]quinolin-1-one (3m). Compound **1a** (2 g, 7.2 mmol), azepane-2,4-dione (1.01 g, 8 mmol), and sodium tetrachloroaurate(III) (72 mg, 0.18 mmol) were heated under nitrogen in EtOH (20 mL) for 30 min. The product precipitated spontaneously upon cooling in ice. One obtained 2 g (75%) of white crystals. ^{1}H NMR (400 MHz, DMSO-d_6): δ=2.01 (br m, 2H, $CONHCH_2CH_2CH_2$), 3.10 (m, 4H, $CONHCH_2CH_2CH_2$), 7.35 (m, 2H, Ph), 7.50 (m, 3H, Ph), 7.59 (m, 1H, 5-H), 7.92 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 8.02 (d, J=9 Hz, 1H, 8-H), 8.20 (m, 1H, CONH); ^{13}C NMR (400 MHz, DMSO-d_6): δ=168.45, 157.51, 146.15, 145.77, 135.24, 133.09, 131.17, 129.37, 129.15, 128.26, 127.97, 127.31, 119.67, 38.11, 33.46, 28.84; IR: ν_{max}=3179, 3064, 1655, 1640, 1582, 1570, 1476, 1344, 1327, 1146, 1065, 923, 830, 765, 709, 673 cm^{-1}; LRMS (ESI) m/z=367 (MH^+); HRMS (FT-ICR) m/z calcd for $C_{19}H_{15}BrN_2O$ (MH^+): 367.04405; found: 367.04396.

6.3.14. 1-(4-Chloromethyl-2-methyl-6-trifluoromethoxy-quinolin-3-yl)ethanone (3n). Compound **1b** (300 mg, 1.18 mmol), acetylacetone (0.121 mL, 1.18 mmol) and sodium tetrachloroaurate(III) dihydrate (8 mg, 0.02 mmol) were refluxed in EtOH (4 mL) for 4 h. Evaporated to dryness and purified by chromatography on silica gel in heptane/AcOEt 80:20. One obtained 309 mg (82%) of white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.67 (s, 3H, ArMe), 2.70 (s, 3H, COMe), 4.79 (s, 2H, CH_2Cl), 7.63 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.89 (d, J=2 Hz, 1H, 5-H), 8.10 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=204.86, 154.28, 146.29, 145.51, 137.11, 136.06, 131.68, 124.17, 123.92, 120.125 (q, J_{CF}=1020 Hz), 116.00, 38.43, 32.43, 23.16; IR: ν_{max}=1698, 1588, 1500, 1256, 1206, 1162, 1064, 832 cm^{-1}; LRMS (EI) m/z=317/319 (M, 50), 302/304 (M−Me, 100), 282 (M−Me−HF, 10), 272 (M−COMe, 20); HRMS (FT-ICR) m/z calcd for $C_{14}H_{11}ClF_3NO_2$ (MH^+): 318.05032; found: 318.05014.

6.3.15. 6-Bromo-2-methyl-4-phenyl-quinoline-3-carboxylic acid (4-chloro-phenyl)amide (3o). Compound **1a** (0.5 g, 2 mmol) was dissolved in ^{i}PrOH (5 mL). Then 4′-chloroacetoacetanilide (0.575 g, 3 mmol) and sodium tetrachloroaurate(III) dihydrate (22 mg) were added and the mixture was refluxed for 3 days. After cooling, the precipitated product was filtered off. One obtained 538 mg (66%) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.84 (s, 3H, Me), 6.87 (s, 1H, NH), 7.07 (m, 2H, PhCl), 7.21 (m, 2H, PhCl), 7.42 (m, 2H, Ph), 7.50 (m, 3H, Ph), 7.75 (d, J=2 Hz, 1H, 5-H), 7.80 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.95 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=165.36, 155.31, 145.56, 143.61, 137.20, 134.04, 133.21, 131.31, 130.97, 129.26, 128.78, 128.67, 128.34, 127.66, 127.64, 126.32, 121.10, 119.80, 23.11; IR: ν_{max}=3288, 1648, 1598, 1531, 1478, 1490, 1400, 1319, 1242, 828, 763, 703 cm^{-1}; LRMS (ESI) m/z=451 (MH^+); HRMS (FT-ICR) m/z calcd for $C_{23}H_{16}BrClN_2O$ (MH^+): 451.02073; found: 451.02064.

6.3.16. 6-Bromo-2-methyl-4-phenyl-quinoline-3-carboxylic acid phenylamide (3p). Compound **1a** (0.5 g, 2 mmol) was dissolved in ^{i}PrOH (5 mL). Then acetoacetanilide (0.48 g, 3 mmol) and sodium tetrachloroaurate(III) dihydrate (22 mg) were added and the mixture was refluxed for 4 days. After cooling, the precipitated product was filtered off. One obtained 374 mg (50%) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.86 (s, 3H, COMe), 6.90 (br s, 1H, NH), 7.12 (m, 2H, Ph), 7.25 (m, 3H, Ph), 7.45 (m, 2H, Ph), 7.50 (m, 3H, Ph), 7.75 (d, J=2 Hz, 1H, 5-H), 7.80 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.95 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=165.23, 155.43, 145.49, 143.45, 138.29, 134.14, 133.10, 131.57, 130.95, 129.31, 128.73, 128.70, 128.31, 127.66, 126.40, 123.98, 119.70, 23.10; IR: ν_{max}=3384, 3221, 3035, 1657, 1599, 1558, 1498, 1481, 1444, 1381, 1333, 1259, 1074, 953, 828, 753, 688 cm^{-1}; LRMS (ESI) m/z=417 (MH^+); HRMS (FT-ICR) m/z calcd for $C_{23}H_{17}BrN_2O$ (MH^+): 417.05970; found: 417.05952.

6.3.17. 6-Bromo-2-methyl-4-phenyl-quinoline-3-carboxylic acid methylamide (3q). Compound **1a** (0.5 g, 2 mmol) was dissolved in ^{i}PrOH (5 mL). Then *N*-methylacetoacetamide (0.42 mL, 3 mmol) and sodium tetrachloroaurate(III) dihydrate (22 mg) were added and the mixture was refluxed for 3 days. After cooling, the precipitated product was filtered off and recrystallized from AcOEt. One obtained 257 mg (40%) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.63 (s, 3H, Me), 2.77 (s, 3H, CONH*Me*), 5.28 (br s, 1H, NH), 7.37 (m, 2H, Ph), 7.51 (m, 3H, Ph), 7.71 (d, J=2 Hz, 1H, 5-H), 7.77 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.92 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=167.10, 155.70, 145.32, 143.14, 134.35, 132.79, 131.89, 130.90, 129.33, 128.58, 128.20, 127.59, 126.39, 119.50, 25.56, 23.04; IR: ν_{max}=3468, 3217, 3006, 1634, 1578, 1565, 1483, 1393, 1328, 1262, 1159, 1145, 1067, 848, 762, 708, 698 cm^{-1}; LRMS (ESI) m/z=355 (MH^+); HRMS (FT-ICR) m/z calcd for $C_{18}H_{15}BrN_2O$ (MH^+): 355.04405; found: 355.04390.

6.3.18. 6-Bromo-2-methyl-4-phenyl-quinoline-3-carboxylic acid dimethylamide (3r). Compound **1a** (0.5 g, 2 mmol) was dissolved in ^{i}PrOH (5 mL). Then *N*,*N*-dimethylacetoacetamide (0.46 mL, 3 mmol) and sodium tetrachloroaurate(III) dihydrate (22 mg) were added and the mixture was refluxed for 4 days. The solvent was evaporated and the residue was purified by flash chromatography on aminated silica gel in heptane/AcOEt 2:1. One obtained 138 mg (21%) of an orange solid. ^{1}H NMR (400 MHz,

$CDCl_3$): δ=2.59 (s, 3H, $CONMe_2$), 2.70 (s, 3H, Me), 2.82 (s, 3H, $CONMe_2$), 7.29 (m, 1H, Ph), 7.48 (m, 2H, Ph), 7.52 (m, 2H, Ph), 7.73 (d, J=2 Hz, 1H, 5-H), 7.75 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.93 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=167.02, 155.14, 145.51, 142.36, 133.97, 132.80, 130.96, 130.27, 129.43, 128.89, 128.86, 128.54, 128.18, 127.48, 126.23, 119.62, 37.21, 33.58, 22.94; IR: ν_{max}=1628, 1568, 1477, 1400, 1378, 1258, 1154, 1053, 830, 703 cm^{-1}; LRMS (EI) m/z=368/370 (M, 30), 353/355 (M−Me, 35), 324/326 (M−NMe_2, 25), 217 (35); HRMS (FT-ICR) m/z calcd for $C_{19}H_{17}BrN_2O$ (MH^+): 369.05970; found: 369.05960.

6.3.19. 6-Bromo-2-methyl-4-phenyl-quinoline-3-carboxylic acid (2-hydroxy-ethyl)amide (3s). Compound **1a** (0.5 g, 2 mmol) was dissolved in ^{i}PrOH (5 mL). Then *N*-(2-hydroxyethyl)acetoacetamide (0.4 g, 3 mmol) and sodium tetrachloroaurate(III) dihydrate (22 mg) were added and the mixture was refluxed for 1 day. After cooling, the precipitated product was filtered off. One obtained 346 mg (50%) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.33 (br s, 1H, OH), 2.78 (s, 3H, Me), 3.28 (m, 4H, $NHCH_2CH_2OH$), 5.75 (br s, 1H, NH), 7.42 (m, 2H, Ph), 7.55 (m, 3H, Ph), 7.69 (d, J=2 Hz, 1H, 5-H), 7.77 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.93 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=166.62, 155.66, 145.29, 143.08, 134.31, 132.71, 131.86, 130.88, 129.42, 128.54, 128.12, 127.56, 126.39, 119.42, 59.17, 41.19, 23.02; IR: ν_{max}=3318, 3249, 1657, 1633, 1560, 1537, 1480, 1073, 831, 762, 710 cm^{-1}; LRMS (ESI) m/z=384 (MH^+); HRMS (FT-ICR) m/z calcd for $C_{19}H_{17}BrN_2O_2$ (MH^+): 385.5462; found: 385.5450.

6.3.20. (6-Bromo-2-methyl-4-phenyl-quinolin-3-yl)morpholin-4-yl-methanone (3t). Compound **1a** (0.5 g, 2 mmol) was dissolved in ^{i}PrOH (5 mL). Then *N*-acetoacetylmorpholine (0.47 g, 3 mmol) and sodium tetrachloroaurate(III) dihydrate (22 mg) were added and the mixture was refluxed for 1 day. The solvent was evaporated and the residue was purified by flash chromatography on aminated silica gel in heptane/AcOEt 2:1. One obtained 215 mg (29%) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.71 (s, 3H, Me), 2.98 (m, 2H, NCH_2CH_2O), 3.07 (m, 1H, NCH_2CH_2O), 3.20 (m, 1H, NCH_2CH_2O), 3.40 (m, 1H, NCH_2CH_2O), 3.52 (m, 2H, NCH_2CH_2O), 3.60 (m, 1H, NCH_2CH_2O), 7.30 (m, 1H, Ph), 7.53 (m, 4H, Ph), 7.77 (m, 2H, 5-H+7-H), 7.93 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=165.72, 155.23, 145.65, 142.45, 133.79, 132.93, 130.97, 129.57, 129.47, 129.35, 129.04, 128.73, 128.19, 127.52, 126.05, 119.68, 65.83, 65.65, 45.88, 23.06; IR: ν_{max}=2977, 2855, 1616, 1580, 1463, 1435, 1269, 1231, 1110, 1018, 1006, 833, 704 cm^{-1}; LRMS (ESI) m/z=411 (MH^+); HRMS (FT-ICR) m/z calcd for $C_{21}H_{19}BrN_2O_2$ (MH^+): 411.07027; found: 411.07011.

6.3.21. 6-Bromo-3-methanesulfonyl-2-methyl-4-phenyl-quinoline (3u). Compound **1a** (10 g, 36 mmol), methanesulfonylacetone (7.4 g, 54 mmol), and sodium tetrachloroaurate(III) dihydrate (720 mg, 1.8 mmol) were heated under reflux in 2-propanol (100 mL) for 4 days. The resulting suspension was evaporated to dryness. The residue was dissolved in DCM (100 mL) and excess methanesulfonylacetone was removed by extraction with 1 N NaOH (2×100 mL). The aqueous layers were back-extracted with DCM (100 mL) and all organic layers were washed with 50% NaCl solution. The crude product was purified twice by chromatography on silica gel in DCM and then crystallized from DCM/heptane by evaporation of DCM. One obtained 4.6 g (33%) of beige crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.88 (s, 3H, SO_2Me), 3.15 (s, 3H, COMe), 7.31 (m, 2H, Ph), 7.41 (d, J=2 Hz, 1H, 5-H), 7.56 (m, 3H, Ph), 7.85 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.94 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=156.40, 149.80, 145.86, 135.29, 134.81, 132.73, 130.61, 128.99, 128.88, 128.40, 127.84, 127.81, 120.39, 45.39, 26.77; IR: ν_{max}=1596, 1556, 1539, 1469, 1441, 1302, 1142, 1065, 968, 835, 754, 702 cm^{-1}; LRMS (EI) m/z=375/377 (M, 100), 296/298 (M−SO_2Me, 70), 217 (85); HRMS (FT-ICR) m/z calcd for $C_{17}H_{14}BrNO_2S$ (MH^+): 376.00014; found: 376.00002.

6.3.22. 6-Bromo-2-methanesulfonylmethyl-4-phenyl-quinoline (6). Compound **1a** (5 g, 18 mmol), methanesulfonylacetone (4.9 g, 36 mmol) and sodium tetrachloroaurate(III) dihydrate (360 mg, 0.9 mmol) were heated under reflux in 2-propanol (50 mL) for 4 days. The resulting precipitate was filtered off and washed with 2-propanol and then purified by chromatography on silica gel in DCM. Two products were isolated and crystallized from heptane/DCM. One obtained 4.1 g (57%) of **3v** and 300 mg (4%) of **6**. Compound **3v** was contaminated with methylsulfonylacetone, thus further purified by extraction with DCM and 1 N NaOH. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.01 (s, 3H, SO_2Me), 4.60 (s, 2H, CH_2SO_2Me), 7.31 (m, 2H, Ph), 7.54 (m, 6H, Ph+3-H), 7.83 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.99 (d, J=9 Hz, 1H, 8-H), 8.10 (d, J=2 Hz, 1H, 5-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=151.23, 147.43, 146.45, 136.27, 133.09, 131.65, 129.31, 129.09, 129.02, 127.14, 126.40, 124.29, 120.63, 61.79, 40.79; IR: ν_{max}=1589, 1481, 1287, 1131, 956, 827, 774, 700 cm^{-1}; LRMS (EI) m/z=375/377 (M, 20), 296/298 (M−SO_2Me, 100), 217 (70); HRMS (FT-ICR) m/z calcd for $C_{17}H_{14}BrNO_2S$ (MH^+): 376.00014; found: 376.00015.

6.4. New 3-(methanesulfonyl)quinoline synthesis

6.4.1. 6-Bromo-2-methyl-4*H*-3,1-benzoxazin-4-one (8a). 2-Amino-5-bromobenzoic acid (25 g, 116 mmol) was added in portions to acetic anhydride (150 mL) giving a slightly exothermic reaction to 30 °C. The suspension was heated under reflux for 2 h. The product crystallized spontaneously upon cooling. After stirring in ice for 30 min, the crystals were filtered off and washed twice with heptane. The crystals were thoroughly dried at 0.1 mbar/50 °C. One obtained 22.4 g (85%) of beige crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.46 (s, 3H, Me), 7.42 (d, J=8 Hz, 1H, 1-H), 7.87 (dd, J_1=8 Hz, J_2=2 Hz, 1H, 3-H), 8.31 (d, J=2 Hz, 1H, 4-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=160.68, 158.07, 145.14, 139.35, 129.71, 128.37, 120.11, 118.34, 20.99; IR: ν_{max}=1755, 1640, 1596, 1466, 1250, 1181, 1053, 968, 902, 836, 781, 697, 676 cm^{-1}; LRMS (EI) m/z=239/241 (M, 100), 224/226 (M−Me, 40), 195/197 (M−CH_2CO, 75); HRMS (FT-ICR) m/z calcd for $C_9H_6BrNO_2$ (MH^+): 239.96547; found: 239.96545.

6.4.2. 6-Iodo-2-methyl-4*H*-3,1-benzoxazin-4-one (8b). 2-Amino-5-iodobenzoic acid (25.4 g, 96.6 mmol) was added

in portions to cold acetic anhydride (100 mL). The suspension was first stirred without cooling then the resulting thick precipitate was heated under reflux for 1 h (red solution). The product crystallized spontaneously upon cooling. After stirring in ice for 30 min, the crystals were filtered off and washed twice with heptane. The crystals were thoroughly dried at 0.1 mbar/50 °C. One obtained 25.1 g (90%) of beige crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.45 (s, 3H, Me), 7.26 (d, J=8 Hz, 1H, 1-H), 8.06 (dd, J_1=8 Hz, J_2=2 Hz, 1H, 3-H), 8.51 (d, J=2 Hz, 1H, 4-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=160.74, 157.90, 145.45, 144.99, 135.68, 128.15, 118.41, 92.87, 21.06; IR: ν_{max}=1752, 1627, 1593, 1465, 1375, 1259, 1040, 962, 834, 697 cm^{-1}; LRMS (EI) m/z=287 (M, 100), 272 (M−Me, 15), 243 (15); HRMS (FT-ICR) m/z calcd for $C_9H_6INO_2$ (MH^+): 287.95160; found: 287.95159.

6.4.3. 6-Bromo-3-methanesulfonyl-2-methyl-quinolin-4-ol (9a). Methanesulfonylacetone (12.6 g, 92.9 mmol) was dissolved in DMF (200 mL) and cooled in ice under nitrogen. Then ^{t}BuOK (11.7 g, 102 mmol) was added (exothermic, 20 °C) and stirring without cooling continued for 15 min. Cooled in ice again, then **8a** (22.3 g, 92.9 mmol) was added and then stirred without cooling for 4 h. Cooled in ice again, then ^{t}BuOK (11.7 g, 102 mmol) was added and the resulting red solution was stirred at 20 °C for 15 min and then heated at 100 °C for 30 min. After cooling, 4 M HCl (30 mL) was added and the mixture was evaporated thoroughly at 0.1 mbar/50 °C. The residue was suspended in water (200 mL) and stirred vigorously for 30 min, which led to the formation of a filterable precipitate. This solid was filtered off and washed with water (50 mL). One obtained 14.25 g (48.5%) of white crystals. ^{1}H NMR (400 MHz, DMSO-d_6): δ=2.74 (s, 3H, ArMe), 3.29 (s, 3H, SO_2Me), 7.56 (d, J=9 Hz, 1H, 8-H), 7.90 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 8.19 (d, J=2 Hz, 1H, 5-H), 12.3 (s, 1H, OH); ^{13}C NMR (400 MHz, DMSO-d_6): δ=172.00, 153.92, 137.54, 135.79, 127.20, 126.65, 120.86, 118.90, 117.52, 43.60, 19.58; IR: ν_{max}=3267, 3223, 3168, 1615, 1587, 1567, 1501, 1474, 1384, 1282, 1271, 1126, 1109, 961, 814 cm^{-1}; LRMS (ESI) m/z=315/317 (MH^+); HRMS (FT-ICR) m/z calcd for $C_{11}H_{10}BrNO_3S$ (MH^+): 315.96375; found: 315.96375.

6.4.4. 6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-ol (9b). Methanesulfonylacetone (13 g, 95 mmol) was dissolved in DMF (200 mL) and cooled in ice under nitrogen. Then ^{t}BuOK (11.2 g, 100 mmol) was added (exothermic, 20 °C) and stirring without cooling continued for 15 min. Cooled in ice again, then **8b** (27.4 g, 95.4 mmol) was added and then stirred without cooling for 4 h. Cooled in ice again, then ^{t}BuOK (11.2 g, 100 mmol) was added and the resulting red solution was stirred at 20 °C for 15 min and then heated at 100 °C for 30 min. After cooling, 4 M HCl (30 mL) was added and the mixture was evaporated thoroughly at 0.1 mbar/50 °C. The residue was suspended in water (200 mL) and stirred vigorously for 30 min, which led to the formation of a filterable precipitate. This solid was filtered off and washed with water (50 mL). The crude product was heated to reflux in MeOH (60 mL) in order to dissolve mainly impurities. The suspension was allowed to cool to 20 °C again and the solid was filtered off. One obtained 15.1 g (43%) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ=2.73 (s, 3H, ArMe), 3.29 (s, 3H, SO_2Me), 7.41 (d, J=9 Hz, 1H, 8-H), 8.03 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 8.38 (d, J=2 Hz, 1H, 5-H), 12.3 (s, 1H, OH); ^{13}C NMR (400 MHz, DMSO-d_6): δ=171.84, 153.84, 141.15, 137.84, 133.43, 126.83, 120.59, 118.92, 89.71, 43.56, 19.59; IR: ν_{max}=3269, 1616, 1585, 1565, 1382, 1286, 1272, 1126, 1111, 961, 824 cm^{-1}; LRMS (EI) m/z=363 (M, 100), 284 (15); HRMS (FT-ICR) m/z calcd for $C_{11}H_{10}INO_3S$ (MH^+): 393.94988; found: 393.949883.

6.4.5. 6-Bromo-4-chloro-3-methanesulfonyl-2-methyl-quinoline (10a). Compound **9a** (6 g, 19 mmol) and *N*,*N*-dimethyl-*p*-toluidine (5.5 mL, 38 mmol) were dissolved in toluene (60 mL) and heated under argon to reflux. Then phosphorous oxychloride (1.9 mL, 20.9 mL) was added and heating under reflux continued for 6.5 h. The product precipitated spontaneously upon cooling to 20 °C, the crystals were filtered off and washed with little toluene. One obtained 4.19 g (66%) of light brown crystals. Since the product is somewhat soluble in toluene, the mother liquor was extracted with 3 N HCl (2×) and satd NaCl (2×). The residue was purified by chromatography on silica gel in DCM. One obtained 1.17 g (18%) of additional material. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.10 (s, 3H, ArMe), 3.38 (s, 3H, SO_2Me), 7.93 (m, 2H, 7-H+8-H), 8.54 (d, J=2 Hz, 1H, 5-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=171.98, 153.85, 137.49, 135.69, 127.14, 126.68, 120.86, 118.78, 117.52, 43.57, 19.33; IR: ν_{max}=3002, 1545, 1468, 1312, 1145, 1130, 966, 930, 822, 757 cm^{-1}; LRMS (EI) m/z=333/335 (M, 100), 254/256 (M−SO_2Me, 35), 242/244 (30); HRMS (FT-ICR) m/z calcd for $C_{11}H_9BrClNO_2S$ (MH^+): 333.92987; found: 333.92981.

6.4.6. 4-Chloro-6-iodo-3-methanesulfonyl-2-methyl-quinoline (10b). Compound **9b** (14.7 g, 40.5 mmol) and *N*,*N*-dimethyl-*p*-toluidine (11.7 mL, 81 mmol) were dissolved in toluene (150 mL) and heated under argon to reflux. Then phosphorous oxychloride (4.1 mL, 44.5 mmol) was added and heating under reflux continued for 9.5 h. The thick suspension became gradually a dark solution. The reaction mixture was allowed to cool and then extracted with DCM (not soluble in toluene), cold 1 N HCl (2×), and satd NaCl (2×). The product was crystallized from heptane/DCM. One obtained 12 g (78%) of white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ=309 (s, 3H, ArMe), 3.37 (s, 3H, SO_2Me), 7.75 (d, J=9 Hz, 1H, 8-H), 8.10 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 8.74 (d, J=2 Hz, 1H, 5-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=171.83, 153.74, 141.10, 137.74, 133.40, 126.82, 120.54, 118.85, 89.72, 43.54, 19.42; IR: ν_{max}=1541, 1466, 1461, 1335, 1311, 1143, 1132, 1042, 968, 924, 825, 816, 759, 657 cm^{-1}; LRMS (EI) m/z=380 (M, 100), 302 (M−SO_2Me, 25), 290 (25); HRMS (FT-ICR) m/z calcd for $C_{11}H_9ClINO_2S$ (MH^+): 381.91600; found: 381.91594.

6.4.7. 6-Bromo-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline (11a). Compound **10a** (11.5 g, 34.4 mmol), morpholine (3.3 mL, 37.8 mmol), and *N*,*N*-diisopropyl ethyl amine (6.5 mL, 37.8 mmol) were heated at 100 °C in dry DMF (10 mL) for 30 min. The reaction mixture was evaporated to dryness and the residue was extracted with DCM, 10% Na_2CO_3, and satd NaCl. The crude product was stirred and heated at 80 °C in AcOEt (80 mL)

for 10 min, the resulting suspension was cooled in ice, the crystals were filtered off and washed with little cold AcOEt. One obtained 10.8 g (81%) of white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.02 (s, 3H, ArMe), 3.41 (s, 3H, SO_2Me), 3.53 (m, 4H, NCH_2), 3.98 (m, 4H, OCH_2), 7.84 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.91 (d, J=9 Hz, 1H, 8-H), 8.40 (d, J=2 Hz, 1H, 5-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=158.33, 156.68, 147.45, 134.93, 131.56, 131.45, 126.92, 126.82, 119.71, 66.47, 51.78, 44.41, 26.52; IR: ν_{max}=3006, 2962, 2854, 1544, 1478, 1365, 1298, 1286, 1141, 1127, 1111, 994, 978, 851, 830, 761, 663 cm^{-1}; LRMS (ESI) m/z=385/387 (MH^+); HRMS (FT-ICR) m/z calcd for $C_{15}H_{17}BrN_2O_3S$ (MH^+): 385.02160; found: 385.02142.

6.4.8. 6-Iodo-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline (11b). Compound **10b** (1 g, 2.62 mmol), morpholine (274 mg, 3.1 mmol) and *N*-ethyldiisopropylamine (406 mg, 3.1 mmol) were heated at 100 °C in dry DMF (10 mL) for 30 min. The reaction mixture was evaporated to dryness and the residue extracted with DCM, 10% Na_2CO_3, and satd NaCl. Chromatography on silica gel DCM/AcOEt 5:1. One obtained 913 mg (80%) of yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.86 (s, 3H, ArMe), 3.42 (m, 4H, NCH_2), 3.52 (s, 3H, SO_2Me), 3.85 (m, 4H, OCH_2), 7.74 (d, J=9 Hz, 1H, 8-H), 8.10 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 8.56 (d, J=2 Hz, 1H, 5-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=158.16, 156.30, 147.61, 140.11, 133.14, 131.28, 130.99, 127.17, 92.79, 66.37, 51.71, 44.35, 26.46; IR: ν_{max}=2961, 2850, 1546, 1475, 1363, 1298, 1286, 1260, 1135, 1126, 1111, 993, 977, 831, 760 cm^{-1}; LRMS (ESI) m/z=433 (MH^+); HRMS (FT-ICR) m/z calcd for $C_{15}H_{17}IN_2O_3S$ (MH^+): 433.00773; found: 433.00733.

6.4.9. 3-Methanesulfonyl-2-methyl-4,6-di-morpholin-4-yl-quinoline (12). A tube placed under argon was charged with tris(dibenzylideneacetone)dipalladium chloroform complex (11 mg, 0.010 mmol), 2-dicyclohexylphosphino -2′,4′,6′-triisopropylbiphenyl (10 mg, 0.021 mmol), and cesium carbonate (254 mg, 0.78 mmol). Compound **11a** (200 mg, 0.52 mmol) in *tert*-butanol (10 mL) was added, followed by morpholine (0.054 g, 0.62 mmol). The tube was sealed and heated at 110 °C for 2 h. The reaction mixture was cooled to 20 °C, diluted with heptane, filtered through dicalite and purified directly by flash chromatography on silica gel in heptane/AcOEt 30:70 to give a yellow solid (159 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.01 (s, 3H, ArMe), 3.31 (m, 4H, NCH_2), 3.40 (s, 3H, SO_2Me), 3.52 (m, 4H, NCH_2), 3.95 (m, 8H, OCH_2), 7.37 (d, J=2 Hz, 1H, 5-H), 7.55 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 7.94 (d, J=9 Hz, 1H, 8-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=155.77, 153.53, 148.89, 144.42, 131.57, 129.95, 126.54, 124.10, 104.81, 66.59, 66.02, 50.99, 48.25, 44.75, 26.29; IR: ν_{max}=2957, 1610, 1539, 1496, 1434, 1369, 1293, 1255, 1138, 1105, 967, 896, 843, 764 cm^{-1}; LRMS (ESI) m/z=392 (MH^+); HRMS (FT-ICR) m/z calcd for $C_{19}H_{25}N_3O_4S$ (MH^+): 392.16385; found: 392.16367.

6.4.10. 3-Methanesulfonyl-6-(4-methoxy-phenyl)-2-methyl-4-morpholin-4-yl-quinoline (13). Compound **11a** (200 mg, 0.52 mmol), 4-methoxyphenylboronic acid (118 mg, 0.78 mmol), potassium phosphate (330 mg, 1.55 mmol), and tetrakis(triphenylphosphine)palladium (18 mg, 0.016 mmol) in dioxane (5 mL) were heated under reflux under argon for 7 h. Chromatography on silica gel DCM/AcOEt gradient 100:0–80:20. One obtained 120 mg (56%) of white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.90 (s, 3H, ArMe), 3.50 (m, 4H, NCH_2), 3.54 (s, 3H, SO_2Me), 3.84 (s, 3H, OMe), 3.88 (m, 4H, OCH_2), 7.13 (m, 2H, *Ph*OMe), 7.77 (m, 2H, *Ph*OMe), 8.02 (d, J=9 Hz, 1H, 8-H), 8.14 (dd, J_1=9 Hz, J_2=2 Hz, 1H, 7-H), 8.35 (d, J=2 Hz, 1H, 5-H); ^{13}C NMR (400 MHz, DMSO-d_6): δ=159.50, 157.56, 157.08, 147.97, 137.80, 131.47, 131.27, 130.88, 129.89, 128.29, 125.90, 121.16, 114.79, 66.56, 55.28, 51.85, 44.58, 26.54; IR: ν_{max}=2858, 1610, 1548, 1519, 1486, 1295, 1181, 1139, 1109, 994, 826, 759 cm^{-1}; LRMS (ESI) m/z=413 (MH^+); HRMS (FT-ICR) m/z calcd for $C_{22}H_{24}N_2O_4S$ (MH^+): 413.15295; found: 413.15274.

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