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Direct Oxytosylation of 8-Amidoquinolines by Koser's Reagent: An Efficient Strategy for 5-Substituted 8-Amidoquinolines

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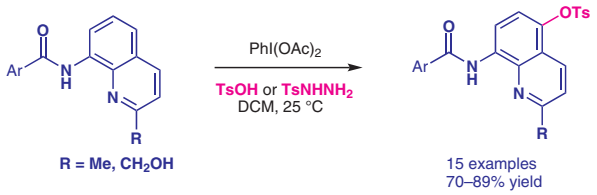

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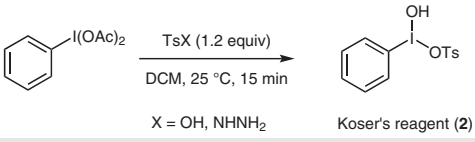
Abstract A metal-free remote oxytosylation of 8-amidoquinolines has been achieved using Koser's reagent to produce 5-tosyloxy-8-amidoquinolines in good yields. This method is compatible with various functional groups present on the aromatic ring.

Key words Koser's reagent, C–H activation, 8-amidoquinolines, oxytosylation, hypervalent iodine reagents

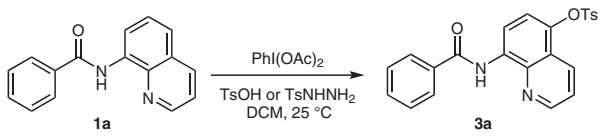
Introduction of oxygen functionality on aromatic and heteroaromatic ring is a challenging task in organic synthesis.[1] Recently, a few strategies have been developed for the oxytosylation of aromatic systems through a C–H bond oxidation.[2] In recent years, 8-amidoquinolines have successfully been employed for the aromatic C–H bond functionalization.[3] On the other hand, a remote functionalization of 8-amidoquinolines have been reported with diversified reagents to generate 5-substituted 8-amidoquinolines through a C–H activation.[4] In recent years, Koser's reagent **2** has gained importance as a versatile and effective source for oxytosylation of organic compounds.[5] Recently, Shen et al.[6] reported the iodobenzene-catalyzed synthesis of aryl sulfonate esters by the remote functionalization of aminoquinolines at room temperature using peracetic acid as oxidant. However, there have been no reports on oxytosylation of 8-amidoquinolines at C-5 position using Koser's reagent.

Following our interest on C–H functionalization,[7] we herein report an efficient strategy for the synthesis of 5-tosyloxy-8-amidoquinolines using Koser's reagent, which is generated in situ from $PhI(OAc)_2$ and *p*-toluenesulfonic acid (*p*-TSA). The required precursors were prepared from 8-aminoquinoline and the corresponding carboxylic acid using EDCI and DMAP in CH_2Cl_2 at 0 °C under nitrogen atmosphere.[8] The Koser's reagent was prepared from *p*-toluenesulfonic acid or *p*-toluenesulfonyl hydrazide using readily available (diacetoxyiodo)benzene (Scheme 1).[9]



Scheme 1 Preparation of Koser's reagent

To optimize the reaction conditions, the oxytosylation of *N*-(quinolin-8-yl)benzamide (**1a**) with *p*-toluenesulfonic acid or *p*-toluenesulfonyl hydrazide was attempted in the presence of 20 mol% $PhI(OAc)_2$ in dichloromethane (Scheme 2).



Scheme 2 Oxytosylation of *N*-(quinolin-8-yl)benzamide (**1a**)

The product **3a** was isolated in low yield (20%) under these conditions (Table 1, entry 1). Therefore, the above reaction was carried out using a stoichiometric amount of $PhI(OAc)_2$. Interestingly, the product **3a** was obtained in excellent yield under the above conditions (entry 2). However, no reaction was observed in the absence of $PhI(OAc)_2$ (entry 3). The product **3a** was obtained only in 40% yield when the reaction was performed in acetonitrile (entry 4).

These initial findings encouraged us to study the scope of this methodology. This method is compatible with different 8-amidoquinolines bearing chloro-, bromo-, fluoro-, methyl-, and trifluoromethyl substituents on the aromatic

Table 1 Optimization of Reaction Conditions in the Formation of **3a**[a]

Entry	$PhI(OAc)_2$(equiv)	*p*-TSA (equiv)	Solvent	Time (h)	Yield (%)
1	0.2	1.2	CH_2Cl_2	1.0	20
2	1.05	1.2	CH_2Cl_2	12	86
3	0	1.2	CH_2Cl_2	6	0
4	1.0	1.2	MeCN	12	40

[a] Reaction was performed in 1.5 mmol scale at 25 °C.

ring of the carboxylic acid moiety (Scheme 3). The substituent present on the aryl group of 8-amidoquinolines had shown significant effect on the conversion. The presence of halide or methyl group on the aryl ring gave the product in good yield. The reaction was quite successful not only with aromatic but also with heteroaromatic substrates (**3k**). However, the reaction was unsuccessful with amides derived from 8-aminoquinoline and carboxylic acids like 4-nitrobenzoic acid and acetic acid (**3p** and **3q**). Similarly, the amide derived from aniline and benzoic acid also failed to give the desired product (**3r**). Furthermore, no desired product was obtained either with 8-aminoquinoline or with NBoc, and NCbz derivative of 8-aminoquinoline. All the products were thoroughly characterized by NMR, IR, and mass spectrometry. The reaction is highly selective and no oxytosylation was observed on the aryl ring of the carboxylic acid moiety (Scheme 3). This method was successfully applied for a gram scale (1.2 g) synthesis of product **3d**.

Finally, the structure of **3a** was confirmed unambiguously by a single crystal X-ray structural analysis (Figure 1).[10]

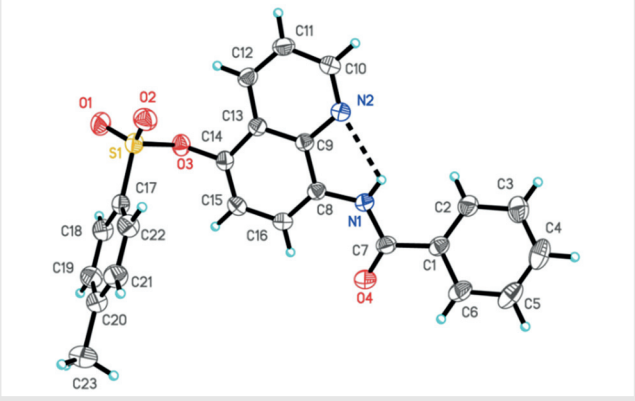
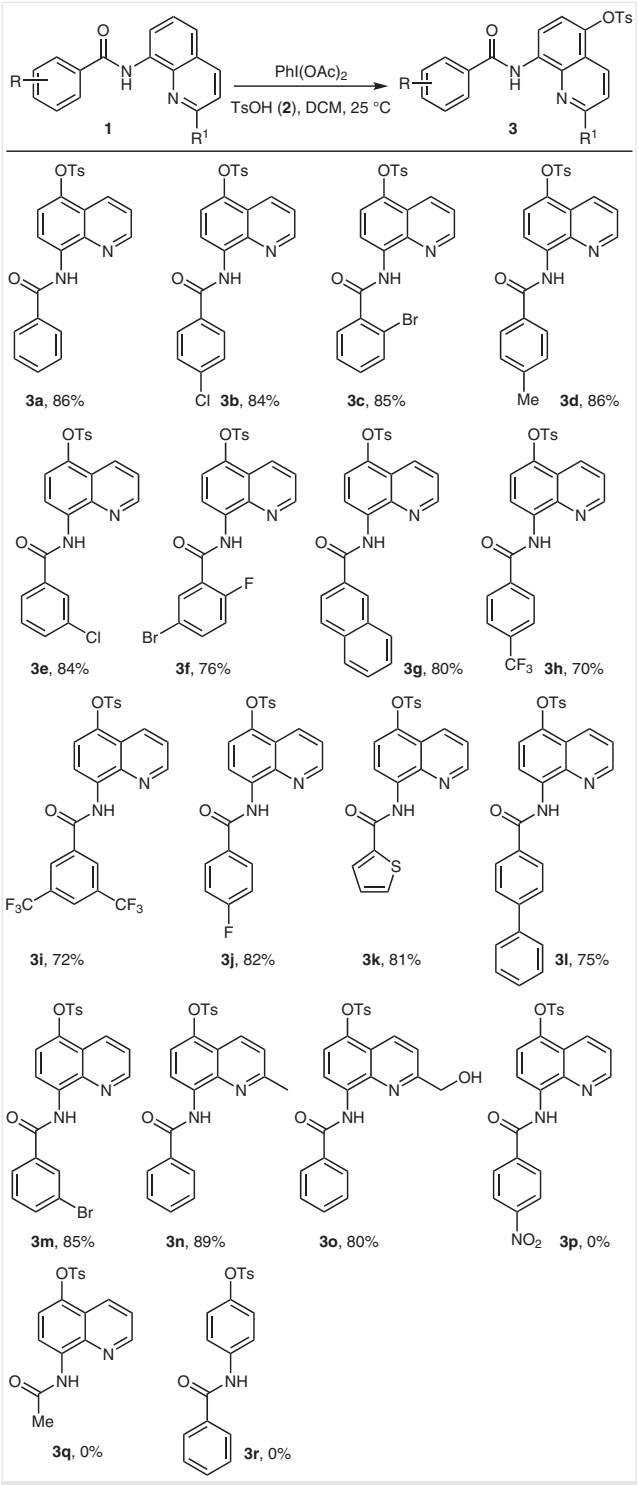
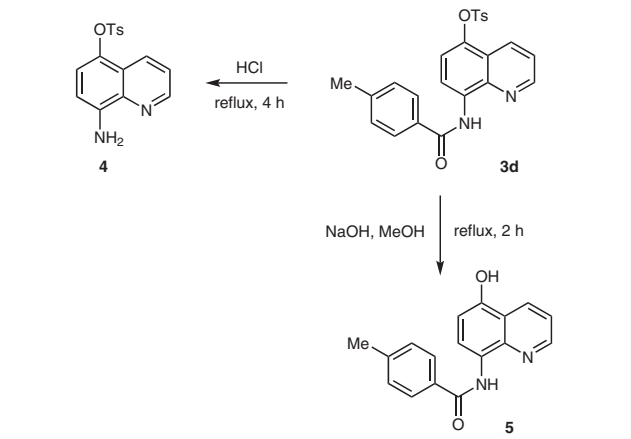


Figure 1 ORTEP diagram of **3a**

In addition, a differential deprotection of both tosyl and amide groups has been achieved by merely changing the reaction conditions (Scheme 4). Deprotection of the amide functionality was achieved to give the product **4** using HCl without affecting the tosyl group. The selective deprotection of tosyl group was accomplished to produce product **5** using NaOH in methanol (Scheme 4).

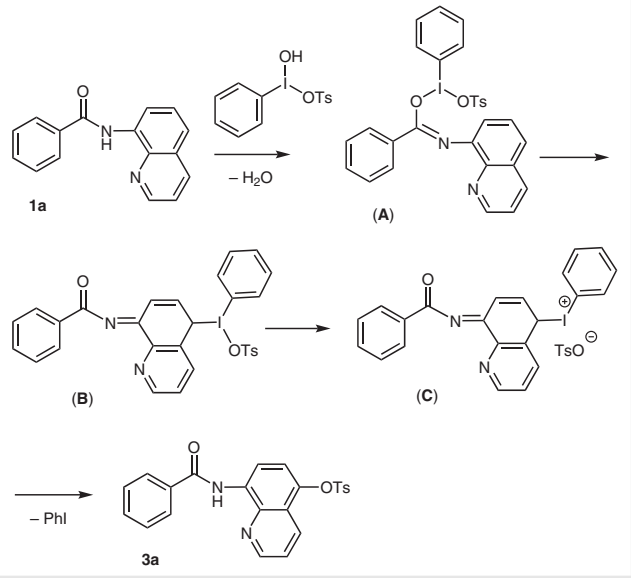


Scheme 3 Scope of the reaction. Yield refers to pure products after chromatography.



Scheme 4 Deferential deprotection of amide and tosyl groups

Mechanistically, the reaction proceeds likely through a sequential formation of intermediates **A** to **C** from 8-amidoquinoline **1a** and Koser's reagent.[11] Finally, the displacement of aryliodonium ion by tosylate anion would give the desired product **3a** (Scheme 5).



Scheme 5 A plausible reaction path way

In conclusion, we have developed a novel strategy for the direct oxytosylation of 8-amidoquinolines using Koser's reagent. The present strategy provides a rapid access to C-5 substituted 8-amidoquinolines in a single step process under mild conditions. It is totally a metal-free approach.

^{1}H NMR spectra were recorded at 500 MHz, 300 MHz, and 400 MHz, and ^{13}C NMR at 125 MHz, 100 MHz, and 75MHz. For ^{1}H NMR, TMS was used as an internal standard (δ = 0) and the values are reported as follows: chemical shift, multiplicity, integration (standard abbreviations), and the coupling constants in Hz. For ^{13}C NMR, $CDCl_3$ (δ = 77.00) was used as internal standard and spectra were obtained with complete proton decoupling. DMSO (δ = 2.50) for ^{1}H NMR and DMSO (δ = 39.43) for ^{13}C NMR. Low-resolution MS and HRMS data were obtained using ESI ionization. IR spectra were recorded on an FT-IR spectrophotometer (neat) and reported in cm^{-1}. Melting points were measured on micro melting point apparatus. Glass syringes were used to transfer solvents. Crude products were purified by column chromatography on silica gel of 60–120 or 100–200 mesh. TLC plates were visualized by exposure to UV light and/or by exposure to I_2 vapors and/or by exposure to methanolic acidic solution of 2-naphthol followed by heating (<1 min) on a hot plate (≦250 °C).

N-(Quinolin-8-yl)benzamides 1; General Procedure

To a solution of the respective carboxylic acid (6 mmol), the corresponding 8-aminoquinoline (6 mmol), and DMAP (73 mg, 0.6 mmol) in anhyd CH_2Cl_2 (30 mL) was added a solution of EDCI (1.38 g, 7.2 mmol) in CH_2Cl_2 (30 mL) through a dropping funnel at 0 °C under N_2 atmosphere. The mixture was allowed to stir at r.t. for overnight. After completion, the mixture was diluted with CH_2Cl_2 (50 mL). The organic layer was washed with aq 1 N HCl (15 mL), followed by aq $NaHCO_3$ (15 mL), brine (25 mL), and dried ($NaSO_4$). The organic solvent was removed by evaporation and the residue was purified by column chromatography using EtOAc/hexane to afford the desired pure *N*-(quinolin-8-yl)arylamide **1**.

N-(Quinolin-8-yl)benzamide (1a)

White solid; yield: 188 mg (94%); mp 68–70 °C.

IR (neat): 3350, 3053, 1982, 1673, 1530, 1480, 1385, 1264, 1177, 1070, 825, 757, 689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.40 (br s, 1 H), 8.93 (dd, *J* = 4.1, 1.4 Hz, 1 H), 8.25 (dd, *J* = 8.3, 1.4 Hz, 1 H), 8.10 (d, *J* = 7.2 Hz, 2 H), 8.02 (d, *J* = 9.0 Hz, 1 H), 7.51–7.67 (m, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.3, 148.2, 138.6, 136.3, 135.0, 134.5, 131.8, 128.8, 127.9, 127.2, 121.7, 121.6, 116.5.

HRMS (EI): *m*/*z* (M + Na)$^+$ calcd for $C_{16}H_{12}N_2ONa$: 271.0842; found: 271.0868.

4-Chloro-*N*-(quinolin-8-yl)benzamide (1b)

Yellow solid; yield: 186 mg (93%); mp 100–102 °C.

IR (neat): 3332, 1674, 1530, 1477, 1327, 1261, 1089, 897, 751, 662 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.6 (br s, 1 H), 8.86 (dd, *J* = 7.6, 1.3 Hz, 1 H), 8.78 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.10 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.96 (d, *J* = 8.5 Hz, 2 H), 7.38–7.56 (m, 5 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.1, 148.3, 138.6, 138.0, 136.3, 134.3, 133.4, 129.0, 128.6, 127.9, 127.3, 121.8, 121.7, 116.5.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{16}H_{12}ClN_2O$: 283.0632; found: 283.0639.

2-Bromo-*N*-(quinolin-8-yl)benzamide (1c)

Light brown solid; yield: 178 mg (89%); mp 86–88 °C.

IR (neat): 3334, 2924, 2853, 1673, 1529, 1480. 1420, 1324, 1259, 1065, 896, 792, 653 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.66 (br s, 1 H), 8.87 (dd, *J* = 7.4, 1.3 Hz, 1 H), 8.82 (dd, *J* = 4.1, 1.5 Hz, 1 H), 8.19 (t, *J* = 1.8 Hz, 1 H), 8.14 (dd, *J* = 8.2, 1.5 Hz, 1 H), 7.95 (d, *J* = 7.7 Hz, 1 H), 7.67 (d, *J* = 7.9 Hz, 1 H), 7.50–7.57 (m, 2 H), 7.42–7.46 (m, 1 H), 7.38 (t, *J* = 7.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.8, 148.4, 138.6, 137.0, 136.4, 134.8, 134.2, 130.6, 130.3, 127.9, 127.4, 125.6, 123.0, 122.0, 121.7, 116.7.

HRMS (EI): *m*/*z* $(M)^+$ calcd for $C_{16}H_{11}BrN_2O$: 327.0128; found: 327.0150.

4-Methyl-*N*-(quinolin-8-yl)benzamide (1d)

White solid; yield: 184 mg (92%); mp 136–138 °C.

IR (neat): 3348, 2972, 1674, 1610, 1532, 1418, 1284, 1181, 1117, 944, 826, 753, 662 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.66 (br s, 1 H), 8.98 (dd, *J* = 7.6, 1.2 Hz, 1 H), 8.84 (dd, *J* = 4.4, 1.6 Hz, 1 H), 8.56 (s, 1 H), 8.09–8.14 (m, 2 H), 7.98–8.01 (m, 1 H), 7.95 (d, *J* = 8.5 Hz, 1 H), 7.86–7.89 (m, 1 H), 7.49–7.60 (m, 4 H), 7.41–7.44 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.4, 148.2, 142.3, 138.8, 136.3, 134.7, 132.3, 129.4, 128.8, 128.0, 127.4, 127.3, 121.6, 121.5, 116.4, 21.5.

HRMS (EI): *m*/*z* $(M + H)^+$ calcd for $C_{17}H_{15}N_2O$: 263.1178; found: 263.1184.

3-Chloro-*N*-(quinolin-8-yl)benzamide (1e)

Yellow solid; yield: 186 mg (93%); mp 80–82 °C.

IR (neat): 3736, 3355, 3055, 2358, 1670, 1536, 1476, 1383, 1330, 1255, 1176, 904, 787, 762, 727, 678, 648 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.56 (br s, 1 H), 8.82 (dd, *J* = 7.4, 1.4 Hz, 1 H), 8.73 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.03 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.98 (t, *J* = 1.8 Hz, 1 H) , 7.84 (dt, *J* = 7.8, 1.1 Hz, 1 H), 7.32–7.50 (m, 5 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.7, 148.3, 138.6, 136.8, 136.3, 134.9, 134.1, 131.8, 130.0, 127.9, 127.7, 127.3, 125.1, 122.0, 121.7, 116.6.

HRMS (EI): *m*/*z* $(M + H)^+$ calcd for $C_{16}H_{12}ClN_2O$: 283.0633; found: 283.0636.

5-Bromo-2-fluoro-*N*-(quinolin-8-yl)benzamide (1f)

Brown solid; yield: 178 mg (89%); mp 280–282 °C.

IR (neat): 3327, 3129, 2924, 1638, 1548, 1502, 1276, 1054, 1007, 820, 781, 656 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.06 (br s, 1 H), 8.89 (dd, *J* = 7.0, 1.4 Hz, 1 H), 8.81 (dd, *J* = 4.0, 1.3 Hz, 1 H), 8.30 (dd, *J* = 6.6, 2.5 Hz, 1 H), 8.11 (d, *J* = 8.1 Hz, 1 H), 7.47–7.49 (m, 3 H), 7.39–7.44 (m, 1 H), 7.07 (t, *J* = 8.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 160.7, 159.9, 158.2, 148.5, 136.2, 136.1, 134.7, 134.4, 127.9, 127.3, 123.7, 123.6, 122.3, 121.7, 118.3, 118.0, 117.6, 117.3.

HRMS (EI): *m*/*z* $(M + H)^+$ calcd for $C_{16}H_{11}BrFNO$: 345.0033; found: 345.0043.

***N*-(Quinolin-8-yl)-2-naphthamide (1g)**

Colorless solid; yield: 176 mg (88%); mp 118–120 °C.

IR (neat): 3354, 3046, 1668, 1525, 1482, 1322, 1129, 830, 771, 674 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.66 (br s, 1 H), 8.98 (dd, *J* = 7.6, 1.2 Hz, 1 H), 8.84 (dd, *J* = 4.4, 1.6 Hz, 1 H), 8.56 (s, 1 H), 8.09–8.14 (m, 2 H), 7.98–8.01 (m, 1 H), 7.95 (d, *J* = 8.5 Hz, 1 H), 7.86–7.89 (m, 1 H), 7.49–7.60 (m, 4 H), 7.41–7.44 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.4, 148.3, 138.8, 136.4, 134.9, 134.6, 132.7, 132.3, 129.2, 128.7, 128.0, 127.9, 127.89, 127.83, 127.5, 126.8, 123.7, 121.7.

HRMS (EI): *m*/*z* $(M + H)^+$ calcd for $C_{20}H_{15}N_2O$: 299.1178; found: 299.1181.

***N*-(Quinolin-8-yl)-4-(trifluoromethyl)benzamide (1h)**

White solid; yield: 180 mg (90%); mp 92–94 °C.

IR (neat): 3343, 2929, 1669, 1539, 1480, 1326, 1141, 1065, 1013, 828, 600 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.66 (br s, 1 H), 8.84 (d, *J* = 7.4 Hz, 1 H), 8.75 (d, *J* = 4.1 Hz, 1 H), 8.07 (t, *J* = 8.8 Hz, 3 H), 7.70 (d, *J* = 8.0 Hz, 2 H), 7.42–7.52 (m, 2 H), 7.34–7.39 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.7, 148.3, 138.5, 138.2, 136.3, 134.0, 133.2 (q, $J_{C,F}$ = 32.6 Hz), 127.8, 127.6, 127.2, 125.7, 125.7, 124.8, 122.6, 122.1, 121.7, 116.6.

HRMS (EI): *m*/*z* $(M + H)^+$ calcd for $C_{17}H_{12}F_3N_2O$: 317.0896; found: 317.0884.

***N*-(Quinolin-8-yl)-3,5-bis(trifluoromethyl)benzamide (1i)**

Pale yellow solid; yield: 176 mg (88%); mp 156–158 °C.

IR (neat): 3334, 3062, 1677, 1545, 1487, 1376, 1276, 1189, 1119, 896, 761, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.78 (br s, 1 H), 8.84–8.88 (m, 2 H), 8.48 (s, 2 H), 8.19 (dd, *J* = 8.3, 1.5 Hz, 1 H), 8.08 (s, 1 H), 7.56–7.60 (m, 2 H), 7.47–7.52 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.2, 148.6, 138.6, 137.2, 136.5, 133.7, 132.4 (q, $J_{C,F}$ = 33.6 Hz), 127.9, 127.5, 127.3, 125.32, 125.30, 125.2, 122.6, 121.9, 116.9.

HRMS (EI): *m*/*z* $(M + H)^+$ calcd for $C_{18}H_{11}F_6N_2O$: 385.0770; found: 385.0775

4-Fluoro-*N*-(quinolin-8-yl)benzamide (1j)

White solid; yield: 182 mg (91%); mp 89–90 °C.

IR (neat): 3447, 3351, 3061,1666, 1541, 1506, 1485, 1330, 1224, 1165, 1012, 822, 757, 649 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.66 (br s, 1 H), 8.89 (dd, *J* = 7.4, 1.3 Hz, 1 H), 8.82 (dd, *J* = 4.1, 1.6 Hz, 1 H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1 H), 8.05–8.10 (m, 2 H), 7.50–7.59 (m, 2 H), 7.43–7.46 (m, 1 H), 7.20 (t, *J* = 8.6 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.2, 164.2, 163.7, 148.3, 138.7, 136.4, 134.4, 131.3, 129.7, 129.6, 128.0, 127.4, 121.8, 121.7, 116.5, 115.9, 115.7.

HRMS (EI): *m*/*z* $(M + H)^+$ calcd for $C_{16}H_{12}FN_2O$: 267.0928; found: 267.0935.

***N*-(Quinolin-8-yl)thiophene-2-carboxamide (1k)**

Pale yellow solid; yield: 150 mg (75%); mp 88–90 °C.

IR (neat): 3346, 3073, 2924, 1651, 1533, 1483, 1355, 1267, 1115, 1055, 819, 731, 643 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.58 (br s, 1 H), 8.82–8.85 (m, 2 H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.83 (dd, *J* = 3.7, 1.1 Hz, 1 H), 7.50–7.59 (m, 3 H), 7.44–7.48 (m, 1 H), 7.16–7.19 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.0, 148.3, 140.1, 138.5, 136.3, 134.3, 130.9, 128.4, 127.99, 127.90, 127.4, 121.75, 121.71, 116.5.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{14}H_{11}N_2OS$: 255.0586; found: 255.0593.

N-(Quinolin-8-yl)-[1,1′-biphenyl]-4-carboxamide (1l)

White solid; yield: 170 mg (85%); mp 139–141 °C.

IR (neat): 3359, 3026, 2360, 1664, 1536, 1483, 1386, 1327, 1258, 1177, 1002, 895, 824, 743, 643 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.77 (br s, 1 H), 8.95 (d, *J* = 7.6 Hz, 1 H), 8.84 (d, *J* = 3.9 Hz, 1 H), 8.14 (d, *J* = 8.2 Hz, 3 H), 7.74 (d, *J* = 8.0 Hz, 2 H), 7.64 (d, *J* = 7.4 Hz, 2 H), 7.36–7.60 (m, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.1, 148.3, 144.6, 140.0, 138.8, 136.4, 134.6, 133.8, 129.0, 128.1, 128.0, 127.8, 127.5, 127.4, 127.2, 121.7, 116.6.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{22}H_{17}N_2O$: 325.1335; found: 325.1366.

3-Bromo-*N*-(quinolin-8-yl)benzamide (1m)

Light brown solid; yield: 178 mg (89%); mp 88–90 °C.

IR (neat): 3421, 3333, 2924, 1673, 1526, 1476, 1419, 1325, 1256, 1062, 901, 828, 733 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.65 (br s, 1 H), 8.88 (dd, *J* = 7.4, 1.5 Hz, 1 H), 8.83 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.19 (t, *J* = 1.8 Hz, 1 H), 8.15 (dd, *J* = 8.2, 1.5 Hz, 1 H), 7.96 (dt, *J* = 7.9, 1.0 Hz, 1 H), 7.68 (d, *J* = 7.9 Hz, 1 H), 7.51–7.59 (m, 2 H), 7.43–7.48 (m, 1 H), 7.39 (t, *J* = 7.7 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.6, 148.3, 138.5, 136.9, 136.3, 134.7, 134.1, 130.6, 130.2, 127.9, 127.3, 125.6, 123.0, 122.0, 121.7, 116.6.

HRMS (EI): *m*/*z* (M)$^+$ calcd for $C_{16}H_{11}BrN_2O$: 327.0128; found: 327.0129.

N-(2-Methylquinolin-8-yl)benzamide (1n)

White solid; yield: 299 mg (92%); mp 88–90 °C.

IR (neat): 3331, 3025, 1668, 1541, 1467, 833, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77 (s, 3 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 7.47–7.59 (m, 5 H), 8.04–8.10 (m, 3 H), 8.90 (dd, *J* = 7.0, 1.9 Hz, 1 H), 10.81 (s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 165.3, 157.2, 138.1, 136.5, 135.3, 133.9, 131.7, 128.8, 127.2, 126.4, 126.1, 122.4, 121.4, 116.5, 25.4.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{17}H_{15}N_2O$: 263.1184; found: 263.1169.

N-[2-(Hydroxymethyl)quinolin-8-yl]benzamide (1o)

Colorless solid; yield: 290 mg (85%); mp 116–118 °C.

IR (neat): 3444, 3332, 3049, 2929, 1646, 1542, 1408, 1065, 693 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 4.96 (s, 2 H), 7.56–7.71 (m, 6 H), 8.09 (d, *J* = 7.4 Hz, 2 H), 8.34 (d, *J* = 8.5 Hz, 1 H), 8.80 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (100.6 MHz, CD_3OD): δ = 166.0, 160.0, 137.8, 136.9, 134.7, 133.8, 131.8, 128.6, 127.2, 126.9, 126.2, 122.0, 119.4, 116.7, 65.0.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{17}H_{15}N_2O_2$: 279.1134; found: 279.1115.

4-Nitro-*N*-(quinolin-8-yl)benzamide (1p)
Yellow solid; yield: 120 mg (60%); mp 154–156 °C.

IR (neat): 3444, 3352, 3102, 2924, 2853, 1677, 1517, 1479, 1340, 1256, 1107, 824, 708 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.79 (br s, 1 H), 8.89 (dd, *J* = 5.9, 2.9 Hz, 1 H), 8.86 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.36 (d, *J* = 8.8 Hz, 2 H), 8.20 (d, *J* = 8.6 Hz, 3 H), 7.58–7.61 (m, 2 H), 7.48–7.53 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.1, 149.7, 148.5, 140.5, 138.6, 136.5, 133.9, 128.4, 128.0, 127.4, 124.0, 122.5, 121.9, 116.9.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{12}N_3O_3$ (M + H)$^+$: 294.0873; found: 294.0880.

N-(Quinolin-8-yl)acetamide (1q)

Colorless solid; yield: 158 mg (79%); mp 76–78 °C.

IR (neat): 3286, 2924, 1665, 1533, 1481, 1422, 1377, 1320, 1257, 1092, 1004, 824, 789, 691 cm^{-1}.

^{1}HNMR (500 MHz, $CDCl_3$): δ = 9.78 (br s, 1 H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.76 (dd, *J* = 7.3, 1.2 Hz, 1 H), 8.14 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.41–7.55 (m, 3 H), 2.35 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 168.8, 148.1, 138.2, 136.4, 134.5, 127.9, 127.4, 121.6, 121.4, 116.4.

HRMS (EI): *m*/*z* (M + Na)$^+$ calcd for $C_{11}H_{10}N_2ONa$: 209.0685; found: 209.0681.

Oxytosylation; General Procedure

To a solution of $PhI(OAc)_2$ (509 mg, 1.58 mmol) in CH_2Cl_2 (10 mL) was added $TsOH·H_2O$ (342 mg, 1.8 mmol). The resulting suspension was stirred for 15 min at r.t. and then a solution of 8-amidoquinoline **1b** (423 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) was added rapidly. The progress of the reaction was monitored by TLC. Upon completion, the mixture was diluted with H_2O and extracted with CH_2Cl_2 and the combined organic extracts were concentrateds under reduced pressure. The resulting residue was purified by column chromatography using EtOAc/hexane to afford the pure tosyloxyamide **3b**.

8-Benzamidoquinolin-5-yl 4-Methylbenzenesulfonate (3a)

White solid; yield: 156 mg (86%); mp 174–176 °C.

IR (neat): 3353, 2922, 1673, 1529, 1485, 1369, 1182, 1002, 859, 808, 708, 662, 639 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.59 (br s, 1 H), 8.86 (dd, *J* = 4.1, 1.5 Hz, 1 H), 8.79 (d, *J* = 8.6 Hz, 1 H), 8.41 (dd, *J* = 8.4, 1.5 Hz, 1 H), 8.05 (dd, *J* = 8.3, 1.2 Hz, 2 H), 7.77 (d, *J* = 8.3 Hz, 2 H), 7.52–7.61 (m, 3 H), 7.50 (dd, *J* = 8.4, 5.1 Hz, 1 H), 7.33 (d, *J* = 7.9 Hz, 2 H), 7.03 (d, *J* = 8.5 Hz, 1 H), 2.46 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.5, 149.0, 145.8, 139.6, 138.9, 134.8, 133.9, 132.0, 131.4, 130.0, 128.9, 128.7, 127.3, 123.0, 122.2, 119.9, 115.3, 21.7.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{23}H_{19}N_2O_4S$: 419.1060; found: 419.1095.

8-(4-Chlorobenzamido)quinolin-5-yl 4-Methylbenzenesulfonate (3b)

White solid; yield: 152 mg (84%); mp 106–108 °C.

IR (neat): 3346, 2922, 1674, 1531, 1482, 1372, 1181, 1090, 1002, 856, 754, 664 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.60 (br s, 1 H), 8.85 (dd, *J* = 4.2, 1.2 Hz, 1 H), 8.75 (d, *J* = 8.6 Hz, 1 H), 8.39 (dd, *J* = 8.5, 1.2 Hz, 1 H), 7.98 (d, *J* = 8.3 Hz, 2 H), 7.77 (d, *J* = 8.2 Hz, 2 H), 7.48–7.52 (m, 3 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 7.03 (d, *J* = 8.5 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 164.3, 149.0, 145.9, 139.8, 138.8, 138.4, 133.6, 133.1, 132.0, 131.5, 130.0, 129.1, 128.7, 123.0, 122.3, 119.9, 115.3, 21.7.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{23}H_{18}ClN_2O_4S$: 453.0670; found: 453.0678.

8-(2-Bromobenzamido)quinolin-5-yl 4-Methylbenzenesulfonate (3c)

White solid; yield: 153 mg (85%); mp 138–140 °C.

IR (neat): 3334, 3070, 2921, 1664, 1531, 1371, 1170, 1047, 1002, 851, 799, 668 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.56 (br s, 1 H), 8.84 (dd, *J* = 4.1, 1.6 Hz, 1 H), 8.74 (d, *J* = 8.5 Hz, 1 H), 8.36 (dd, *J* = 8.3, 1.0 Hz, 1 H), 8.16 (s, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (d, *J* = 8.2 Hz, 2 H), 7.68 (d, *J* = 7.9 Hz, 1 H), 7.50 (dd, *J* = 8.4, 5.1 Hz, 1 H), 7.40 (t, *J* = 7.7 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.04 (d, *J* = 8.5 Hz, 1 H), 2.44 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.8, 149.1, 145.9, 139.8, 138.8, 136.7, 135.0, 133.4, 132.0, 131.3, 130.6, 130.3, 130.0, 128.6, 125.6, 123.1, 122.9, 122.3, 119.8, 115.4, 21.7.

HRMS (EI): *m*/*z* (M)$^+$ calcd for $C_{23}H_{17}BrN_2O_4S$: 497.0165; found: 497.0188.

8-(4-Methylbenzamido)quinolin-5-yl 4-Methylbenzenesulfonate (3d)

White solid; yield: 156 mg (86%); mp 122–124 °C.

IR (neat): 3362, 3926, 1671, 1530, 1468, 1370, 1184, 1002, 857, 735, 659, 537 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.73 (br s, 1 H), 8.85 (dd, *J* = 4.1, 1.5 Hz, 1 H), 8.78 (d, *J* = 8.6 Hz, 1 H), 8.39 (dd, *J* = 8.4, 1.5 Hz, 1 H), 7.94 (d, *J* = 8.1 Hz, 2 H), 7.76 (d, *J* = 8.3 Hz, 2 H), 7.49 (dd, *J* = 8.5, 4.2 Hz, 1 H), 7.33 (t, *J* = 8.3 Hz, 4 H), 7.02 (d, *J* = 8.5 Hz, 1 H), 2.46 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.4, 148.9, 145.8, 142.6, 139.5, 138.8, 134.0, 132.0, 131.9, 131.3, 130.0, 129.5, 128.7, 127.3, 123.0, 122.2, 119.9, 115.1, 21.7, 21.5.

HRMS (EI): *m*/*z* (M + Na)$^+$ calcd for $C_{24}H_{20}N_2O_4SNa$: 455.1605; found: 455.1620.

8-(3-Chlorobenzamido)quinolin-5-yl 4-Methylbenzenesulfonate (3e)

White solid; yield: 152 mg (84%); mp 146–148 °C.

IR (neat): 3333, 3077, 2920, 2363, 1666, 1531, 1370, 1170, 1002, 851, 799, 718, 660 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.59 (br s, 1 H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.75 (d, *J* = 8.5 Hz, 1 H), 8.39 (dd, *J* = 8.5, 1.6 Hz, 1 H), 8.02 (t, *J* = 1.8 Hz, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.76 (d, *J* = 8.3 Hz, 2 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.45–7.52 (m, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.04 (d, *J* = 8.5 Hz, 1 H), 2.46 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.0, 149.1, 145.9, 139.8, 138.8, 136.5, 135.1, 133.5, 132.1, 132.0, 131.4, 130.1, 130.0, 128.6, 127.7, 125.2, 123.0, 122.3, 119.9, 115.4, 21.7.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{23}H_{18}ClN_2O_4S$: 453.0670; found: 453.0676.

8-(2-Bromo-5-fluorobenzamido)quinolin-5-yl 4-Methylbenzenesulfonate (3f)

Light brown solid; yield: 138 mg (76%); mp 120–122 °C.

IR (neat): 3449, 3334, 2923, 2853, 1669, 1540, 1468, 1398, 1366, 1260, 1171, 1042, 995, 853, 788, 661 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.73 (br s, 1 H), 8.86 (dd, *J* = 4.1, 1.3 Hz, 1 H) , 8.79 (d, *J* = 8.5 Hz, 1 H), 8.38 (dd, *J* = 8.4, 1.3 Hz, 1 H), 8.31 (dd, *J* = 6.7, 2.5 Hz, 1 H), 7.77 (d, *J* = 8.3 Hz, 2 H), 7.61–7.66 (m, 1 H), 7.49 (dd, *J* = 8.5, 4.1 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.14 (dd, *J* = 11.0, 8.8 Hz, 1 H),7.06 (d, *J* = 8.5 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.7, 160.1, 158.2, 149.2, 145.8, 140.1, 138.9, 136.59, 136.5, 134.7, 133.8, 132.0, 131.3, 130.0, 128.6, 123.5, 123.3, 122.9, 122.3, 119.8, 118.4, 118.1, 117.7, 116.1, 21.7.

HRMS (EI): *m*/*z* (M)$^+$ calcd for $C_{23}H_{16}BrFN_2O_4S$: 515.0071; found: 515.0088.

8-(2-Naphthamido)quinolin-5-yl 4-Methylbenzenesulfonate (3g)

White solid; yield: 145 mg (80%); mp 126–128 °C.

IR (neat): 3358, 2922, 1667, 1529, 1488, 1367, 1182, 1048, 1005, 857, 730, 657 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.73 (br s, 1 H), 8.88 (dd, *J* = 4.1, 1.4 Hz, 1 H), 8.84 (d, *J* = 8.5 Hz, 1 H), 8.55 (s, 1 H), 8.40 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.96–8.10 (m, 3 H), 7.91 (d, *J* = 8.8 Hz, 1 H), 7.77 (d, *J* = 8.3 Hz, 2 H), 7.56–7.61 (m, 2 H), 7.50 (dd, *J* = 8.5, 4.1 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.06 (d, *J* = 8.6 Hz, 1 H), 2.46 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.5, 149.0, 145.8, 139.6, 138.9, 135.0, 133.9, 132.7, 132.09, 132.01, 131.4, 130.0, 129.2, 128.8, 128.7, 128.0, 127.8, 126.9, 123.6, 123.0, 122.2, 119.9, 115.3, 21.7.

HRMS (EI): *m*/*z* (M)$^+$ calcd for $C_{27}H_{20}N_2O_4S$: 469.1217; found: 469.1235.

8-[4-(Trifluoromethyl)benzamido]quinolin-5-yl 4-Methylbenzenesulfonate (3h)

White solid; yield: 126 mg (70%); mp 132–134 °C.

IR (neat): 3355, 1678, 1532, 1487, 1327, 1186, 1065, 1002, 858, 737, 660 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.66 (br s, 1 H), 8.85 (d, *J* = 3.9 Hz, 1 H), 8.76 (d, *J* = 8.5 Hz, 1 H), 8.40 (d, *J* = 8.4 Hz, 1 H), 8.15 (d, *J* = 8.0 Hz, 2 H), 7.75–7.83 (m, 4 H), 7.50 (dd, *J* = 8.4, 4.1 Hz, 1 H), 7.30–7.36 (m, 2 H), 7.05 (d, *J* = 8.5 Hz, 1 H), 2.46 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.0, 149.1, 145.9, 140.0, 138.8, 138.0, 133.6 (q, $J_{C,F}$ = 33.6 Hz), 133.4, 132.0, 131.5, 130.0, 128.6, 127.7, 125.98, 125.94, 123.0, 122.4, 119.9, 115.5, 21.7.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{24}H_{18}F_3N_2O_4S$: 487.0934; found: 487.0939.

8-[3,5-Bis(trifluoromethyl)benzamido]quinolin-5-yl 4-Methylbenzenesulfonate (3i)

White solid; yield: 130 mg (72%); mp 132–134 °C.

IR (neat): 3285, 3063, 2927, 1678, 1541, 1366, 1280, 1132, 1047, 852, 796, 684 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.73 (br s, 1 H), 8.86 (dd, *J* = 4.1, 1.3 Hz, 1 H), 8.79 (d, *J* = 8.5 Hz, 1 H), 8.38 (dd, *J* = 8.4, 1.3 Hz, 1 H), 8.31 (dd, *J* = 6.7, 2.5 Hz, 1 H), 7.77 (d, *J* = 8.3 Hz, 2 H), 7.61–7.66 (m, 1 H), 7.49 (dd, *J* = 8.5, 4.1 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 8.5 Hz, 2 H), 7.09 (d, *J* = 8.5 Hz, 1 H), 2.46 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.4, 149.3, 145.9, 140.3, 138.8, 136.9, 132.9, 132.7, 132.4, 132.1, 132.0, 131.6, 130.0, 128.6, 127.5, 125.5, 124.0, 123.1, 122.5, 121.8, 119.8, 115.9, 21.7.

HRMS (EI): *m*/*z* (M + Na)$^+$ calcd for $C_{25}H_{17}F_6N_2O_4SNa$: 555.0808; found: 555.0846.

8-(4-Fluorobenzamido)quinolin-5-yl 4-Methylbenzenesulfonate (3j)

White solid; yield: 148 mg (82%); mp 182–184 °C.

IR (neat): 3349, 3072, 2923, 1674, 1598, 1532, 1485, 1372, 1328, 1233, 1182, 1000, 854, 736, 662 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.6 (br s, 1 H), 8.86 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.76 (d, *J* = 8.5 Hz, 1 H), 8.41 (dd, *J* = 8.5, 1.5 Hz, 1 H), 8.04–8.09 (m, 2 H), 7.77 (d, *J* = 8.3 Hz, 2 H), 7.50 (dd, *J* = 8.4, 5.1 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.23 (t, *J* = 8.5 Hz, 2 H), 7.03 (d, *J* = 8.6 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.1, 164.1, 149.0, 145.8, 139.7, 138.8, 133.7, 132.0, 131.5, 131.02, 131.00, 130.0, 129.7, 129.6, 128.7, 123.0, 122.3, 119.9, 116.0, 115.9, 115.3, 21.7.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{23}H_{18}FN_2O_4S$: 437.0966; found: 437.0974.

8-(Thiophene-2-carboxamido)quinolin-5-yl 4-Methylbenzenesulfonate (3k)

White solid; yield: 146 mg (81%); mp 130–132 °C.

IR (neat): 3339, 3072, 2921, 1657, 1534, 1487, 1369, 1191, 1094, 994, 848, 720, 668 cm^{-1}.

^{1}H NMR (500 MHz,$CDCl_3$): δ = 10.48 (br s, 1 H), 8.85 (dd, *J* = 2.8, 1.3 Hz, 1 H), 8.68 (d, *J* = 8.5 Hz, 1 H), 8.38 (d, *J* = 8.3 Hz, 1 H), 7.81 (dd, *J* = 2.4, 1.0 Hz, 1 H), 7.75 (d, *J* = 8.2 Hz, 2 H), 7.59 (d, *J* = 4.8 Hz, 1 H), 7.47–7.51 (m, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.18 (t, *J* = 4.2 Hz, 1 H), 7.02 (d, *J* = 8.5 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.0, 149.0, 145.8, 139.6, 138.6, 133.6, 132.0, 131.4, 131.2, 130.0, 128.6, 128.3, 127.9, 123.0, 122.2, 119.9, 115.2, 21.7.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{21}H_{17}N_2O_4S_2$: 425.0624; found: 425.0644.

8-([1,1′-Biphenyl]-4-ylcarboxamido)quinolin-5-yl 4-Methylbenzenesulfonate (3l)

White solid; yield: 136 mg (75%); mp 134–136 °C.

IR (neat): 3427, 3355, 2922, 2853, 1669, 1530, 1485, 1345, 1183, 1100, 997, 843, 789, 676 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.7 (br s, 1 H), 8.88 (dd, *J* = 4.0, 1.2 Hz, 1 H), 8.81 (d, *J* = 8.5 Hz, 1 H), 8.41 (dd, *J* = 8.4, 1.3 Hz, 1 H), 8.13 (d, *J* = 8.3 Hz, 2 H), 7.78 (d, *J* = 7.7 Hz, 4 H), 7.66 (d, *J* = 7.2 Hz, 2 H), 7.46–7.54 (m, 3 H), 7.39–7.44 (m, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.04 (d, *J* = 8.5 Hz, 1 H), 2.46 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.2, 149.0, 145.8, 144.9, 139.9, 139.6, 138.9, 133.9, 133.4, 132.1, 131.4, 130.0, 129.0, 128.7, 128.1, 127.8, 127.5, 127.2, 123.0, 122.2, 119.9, 115.3, 21.7.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{29}H_{23}N_2O_4S$: 495.1373; found: 495.1375.

8-(3-Bromobenzamido)quinolin-5-yl 4-Methylbenzenesulfonate (3m)

Colorless solid; yield: 153 mg (85%); mp 106–108 °C.

IR (neat): 3426, 3334, 3068, 2924, 2661, 2550, 1688, 1531, 1481, 1371, 1306, 1168, 1046, 940, 804, 744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.58 (br s, 1 H), 8.87 (d, *J* = 4.0 Hz, 1 H), 8.74 (d, *J* = 8.5 Hz, 1 H), 8.40 (d, *J* = 8.4 Hz, 1 H), 8.18 (s, 1 H), 7.95 (d, *J* = 7.7 Hz, 1 H), 7.76 (d, *J* = 8.1 Hz, 2 H), 7.71 (d, *J* = 7.7 Hz, 1 H), 7.51 (dd, *J* = 8.4, 4.1 Hz, 1 H), 7.42 (t, *J* = 7.8 Hz, 1 H) , 7.33 (d, *J* = 8.0 Hz, 2 H), 7.04 (d, *J* = 8.5 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 163.9, 149.1, 145.9, 139.9, 138.8, 136.7, 136.6, 135.0, 133.4, 133.1, 132.0, 131.4, 130.6, 130.4, 130.0, 128.6, 125.6, 123.1, 123.0, 122.3, 119.8, 115.5, 21.7.

HRMS (EI): *m*/*z* (M)$^+$ calcd for $C_{23}H_{17}BrN_2O_4S$: 497.0165; found: 497.0180.

8-Benzamido-2-methylquinolin-5-yl 4-Methylbenzenesulfonate (3n)

Colorless solid; yield: 220 mg (89%); mp 184–186 °C.

IR (neat): 3340, 3055, 2921, 1668, 1531, 1367, 1183, 1024, 819, 631 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3 H), 2.76 (s, 3 H), 6.92 (d, *J* = 8.5 Hz, 1 H), 7.32 (d, *J* = 8.6 Hz, 2 H), 7.37 (d, *J* = 8.6 Hz, 1 H), 7.52–7.63 (m, 3 H), 7.76 (d, *J* = 8.3 Hz, 2 H), 8.04 (d, *J* = 6.6 Hz, 2 H), 8.29 (d, *J* = 8.5 Hz, 1 H), 8.74 (d, *J* = 8.5 Hz, 1 H), 10.74 (s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 165.4, 158.2, 145.8, 139.8, 138.4, 134.9, 133.2, 132.08, 132.02, 131.48, 129.98, 128.92, 128.7, 127.2, 123.1, 121.1, 118.8, 115.2, 25.3, 21.8.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{24}H_{21}N_2O_4S$: 433.1222; found: 433.1187.

8-Benzamido-2-(hydroxymethyl)quinolin-5-yl 4-Methylbenzenesulfonate (3o)

Viscous liquid; yield: 192 mg (80%).

IR (neat): 2923, 2853, 1742, 1460, 1376, 720 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 3 H), 5.00 (s, 2 H), 7.00 (d, *J* = 8.6 Hz, 1 H), 7.34 (d, *J* = 7.9 Hz, 2 H), 7.51–7.58 (m, 4 H), 7.77 (d, *J* = 8.4 Hz, 2 H), 8.00 (d, *J* = 8.3 Hz, 2 H), 8.43 (d, *J* = 8.6 Hz, 1 H), 8.80 (d, *J* = 8.6 Hz, 1 H), 10.39 (s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 165.4, 159.2, 145.9, 134.8, 133.2, 132.5, 132.2, 130.0, 129.0, 128.7, 127.3, 127.1, 122.3, 119.8, 119.6, 116.1, 65.1, 21.8.

HRMS (EI): *m*/*z* (M + H)$^+$ calcd for $C_{24}H_{21}N_2O_5S$: 449.1171; found: 449.1145.

Gram-Scale Synthesis of 8-(4-Methylbenzamido)quinolin-5-yl 4-Methylbenzenesulfonate (3d)

To a solution of $PhI(OAc)_2$ (1.54 g, 4.78 mmol, 1.05 equiv) in CH_2Cl_2 (10 mL) was added $TsOH·H_2O$ (1.04 mg, 5.4 mmol, 1.2 equiv) and the resulting suspension was stirred for 5 min at r.t. Then, a solution of 4-methyl-*N*-(quinolin-8-yl)benzamide (**1d**; 1.2 g, 4.58 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was added rapidly to the above suspension. The progress of the reaction was monitored by TLC. Upon completion, the mixture was diluted with CH_2Cl_2 (30 mL) and H_2O (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4). The solvent was removed by evaporation and the residue was purified by flash chromatography to give the product **3d** as a white solid; yield: 1.6 g (3.7 mmol, 81%).

Deprotection of the Amide Functionality; 8-Aminoquinolin-5-yl 4-Methylbenzenesulfonate (4)

A solution of 8-(4-methylbenzamido)quinolin-5-yl 4-methylbenzenesulfonate (**3d**; 500 mg, 1.16 mmol) in aq 2 M HCl (20 mL) was heated under reflux for 3 h. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was quenched with aq $NaHCO_3$ and diluted with CH_2Cl_2 (30 mL). The organic layer was washed with H_2O (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4). Removal of the solvent followed by purification on silica gel afforded the product **4** as a brown solid; yield: 90 mg (80%); mp 118–120 °C.

IR (neat): 3488, 3385, 2923, 1592, 1478, 1357, 1171, 1044, 849, 789, 660 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.72 (dd, *J* = 4.1, 1.4 Hz, 1 H), 8.15 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.73 (d, *J* = 8.3 Hz, 1 H), 7.33 (dd, *J* = 8.5, 4.1 Hz, 1 H), 7.27 (d, *J* = 7.9 Hz, 2 H), 6.95 (d, *J* = 8.3 Hz, 1 H), 6.70 (d, *J* = 8.3 Hz, 1 H), 2.42 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 147.9, 145.4, 143.3, 137.8, 135.3, 132.4, 130.5, 129.7, 128.6, 123.3, 121.8, 120.4, 107.8, 21.7.

MS (ESI): *m*/*z* = 314 $(M + Na)^+$.

Deprotection of the Tosyl Group; *N*-(5-Hydroxyquinolin-8-yl)-4-methylbenzamide (5)

To a stirred solution of 8-(4-methylbenzamido)quinolin-5-yl 4-methylbenzenesulfonate (**3d**; 500 mg, 1.16 mmol) in anhyd MeOH (15 mL) was added NaOH (51 mg, 1.3 mmol) and heated to reflux for 1 h. The progress of the reaction was monitored by TLC. Upon completion, MeOH was removed under reduced pressure. The mixture was diluted with CH_2Cl_2 (30 mL). The organic layer was washed with H_2O (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) The solvent was removed by evaporation and the residue was purified by flash chromatography to give the product **5** as a white solid; yield: 100 mg (84%); mp 214–216 °C.

IR (neat): 3328, 1644, 1548, 1503, 1283, 1189, 1010, 740, 664 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.19 (br s, 1 H), 9.14 (s, 1 H), 7.67 (d, *J* = 3.0 Hz, 1 H), 7.36 (d, *J* = 8.2 Hz, 2 H), 6.67 (d, *J* = 7.9 Hz, 2 H), 6.33 (dd, *J* = 8.2, 4.1 Hz, 1 H), 6.14 (d, *J* = 7.7 Hz, 2 H), 5.74 (d, *J* = 8.2 Hz, 1 H), 1.20 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.4, 147.2, 147.0, 140.1, 137.5, 130.3, 129.8, 127.6, 125.1, 124.5, 118.9, 118.0, 115.8, 106.3, 19.4.

HRMS (EI): *m*/*z* $(M + H)^+$ calcd for $C_{17}H_{15}N_2O_2$: 279.1128; found: 279.1161.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610212. Copies of ^1H and ^{13}C NMR spectra of products are provided.

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