

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

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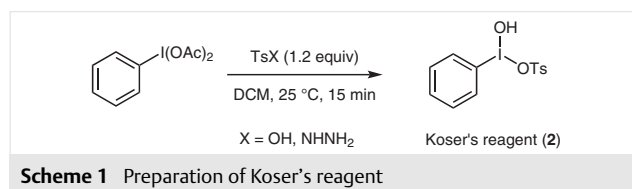
Abstract A metal-free remote oxytosylation of 8-amidoquinolines has been achieved using Koser's reagent to produce 5-tosyloxy-8-amidoquinolines in good yields. This method is compatible with various functional groups present on the aromatic ring.

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

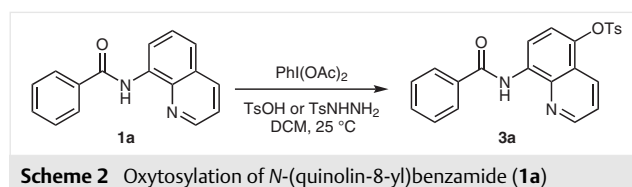
Introduction of oxygen functionality on aromatic and heteroaromatic ring is a challenging task in organic synthesis.¹ Recently, a few strategies have been developed for the oxytosylation of aromatic systems through a C–H bond oxidation.² In recent years, 8-amidoquinolines have successfully been employed 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 $\text{PhI}(\text{OAc})_2$ 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 atmo-

sphere.⁸ The Koser's reagent was prepared from *p*-toluenesulfonic acid or *p*-toluenesulfonyl hydrazide using readily available (diacetoxyiodo)benzene (Scheme 1).⁹



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% $\text{PhI}(\text{OAc})_2$ in dichloromethane (Scheme 2).



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 $\text{PhI}(\text{OAc})_2$. Interestingly, the product **3a** was obtained in excellent yield under the above conditions (entry 2). However, no reaction was observed in the absence of $\text{PhI}(\text{OAc})_2$ (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

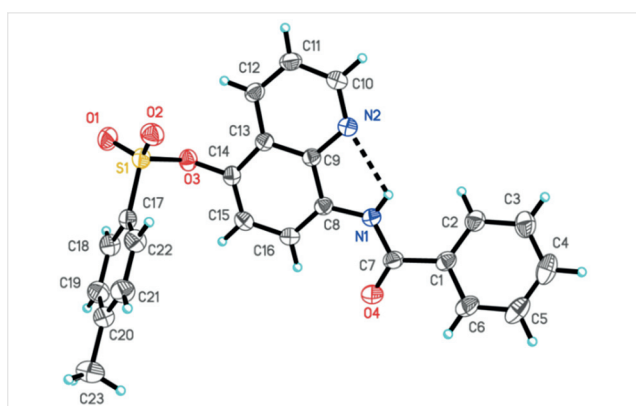
Table 1 Optimization of Reaction Conditions in the Formation of **3a**^a

Entry	PhI(OAc) ₂ (equiv)	<i>p</i> -TSA (equiv)	Solvent	Time (h)	Yield (%)
1	0.2	1.2	CH ₂ Cl ₂	1.0	20
2	1.05	1.2	CH ₂ Cl ₂	12	86
3	0	1.2	CH ₂ Cl ₂	6	0
4	1.0	1.2	MeCN	12	40

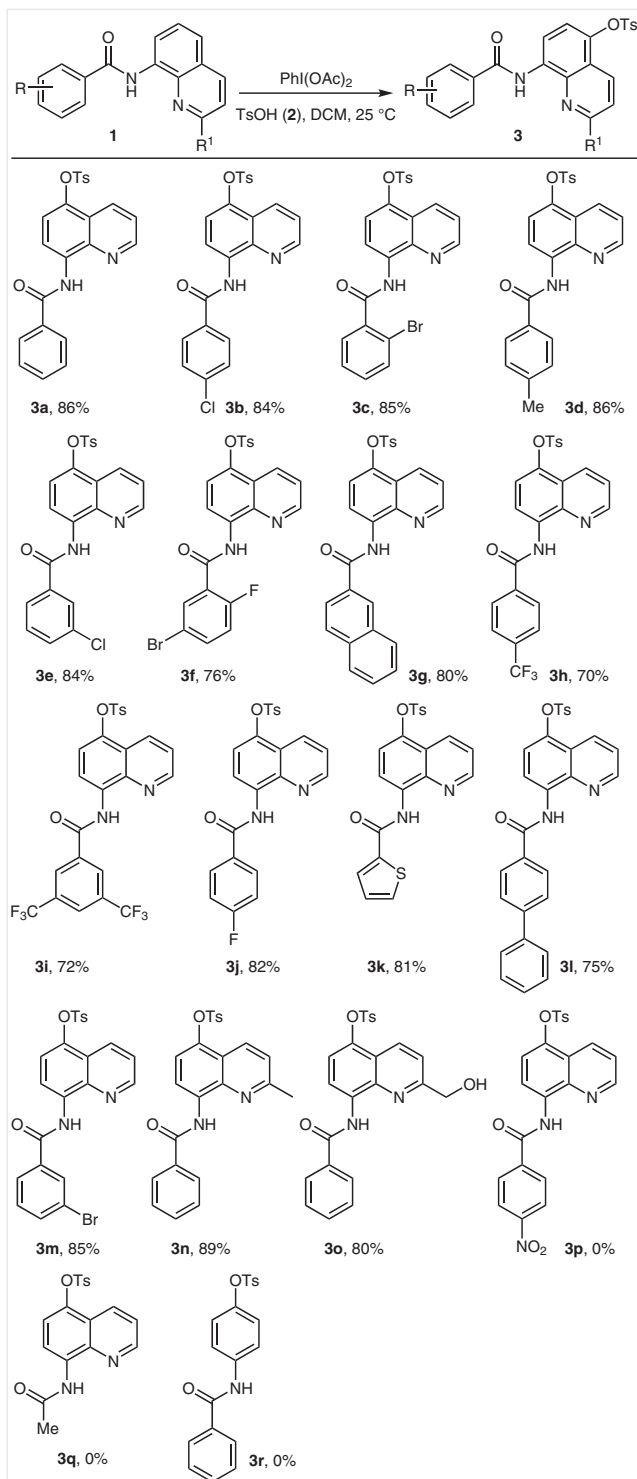
^a Reaction was performed in 1.5 mmol scale at 25 °C.

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**.

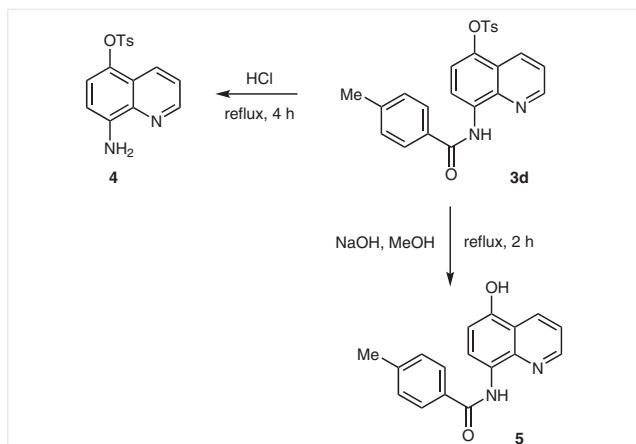
Finally, the structure of **3a** was confirmed unambiguously by a single crystal X-ray structural analysis (Figure 1).¹⁰

**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 deprotec-

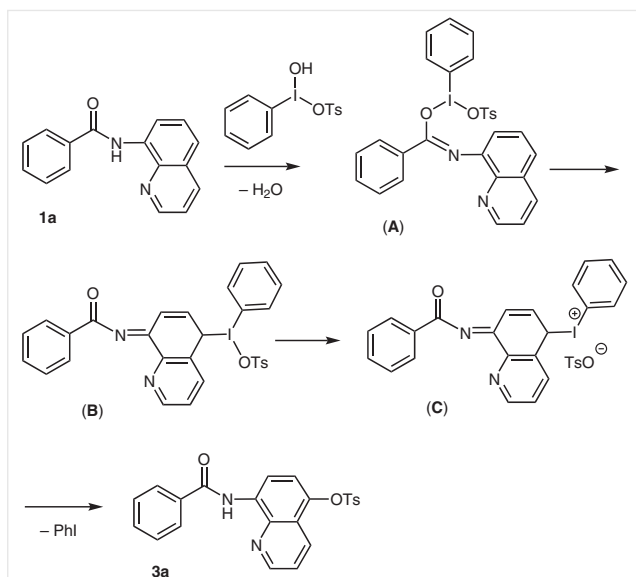
**Scheme 3** Scope of the reaction. Yield refers to pure products after chromatography.

tion of tosyl group was accomplished to produce product **5** using NaOH in methanol (Scheme 4).



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 arylidonium ion by tosylate anion would give the desired product **3a** (Scheme 5).



Scheme 5 A plausible reaction pathway

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.

¹H NMR spectra were recorded at 500 MHz, 300 MHz, and 400 MHz, and ¹³C NMR at 125 MHz, 100 MHz, and 75 MHz. For ¹H NMR, TMS was used as an internal standard ($\delta = 0$) and the values are reported as follows: chemical shift, multiplicity, integration (standard abbrevia-

tions), and the coupling constants in Hz. For ¹³C NMR, CDCl₃ ($\delta = 77.00$) was used as internal standard and spectra were obtained with complete proton decoupling. DMSO ($\delta = 2.50$) for ¹H NMR and DMSO ($\delta = 39.43$) for ¹³C 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 I₂ vapors and/or by exposure to methanolic acidic solution of 2-naphthol followed by heating (<1 min) on a hot plate (1250 °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 CH₂Cl₂ (30 mL) was added a solution of EDCI (1.38 g, 7.2 mmol) in CH₂Cl₂ (30 mL) through a dropping funnel at 0 °C under N₂ atmosphere. The mixture was allowed to stir at r.t. for overnight. After completion, the mixture was diluted with CH₂Cl₂ (50 mL). The organic layer was washed with aq 1 N HCl (15 mL), followed by aq NaHCO₃ (15 mL), brine (25 mL), and dried (NaSO₄). 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.

¹H NMR (400 MHz, CDCl₃): $\delta = 10.40$ (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).

¹³C NMR (CDCl₃, 100 MHz): $\delta = 165.3, 148.2, 138.6, 136.3, 135.0, 134.5, 131.8, 128.8, 127.9, 127.2, 121.7, 121.6, 116.5$.

HRMS (EI): m/z ($M + Na$)⁺ calcd for C₁₆H₁₂N₂O₂: 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.

¹H NMR (500 MHz, CDCl₃): $\delta = 10.6$ (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).

¹³C NMR (CDCl₃, 100 MHz): $\delta = 164.1, 148.3, 138.6, 138.0, 136.3, 134.3, 133.4, 129.0, 128.6, 127.9, 127.3, 121.8, 121.7, 116.5$.

HRMS (EI): m/z ($M + H$)⁺ calcd for C₁₆H₁₂ClN₂O: 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.

¹H NMR (500 MHz, CDCl₃): $\delta = 10.66$ (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 $\text{C}_{16}\text{H}_{11}\text{BrN}_2\text{O}$: 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} .

^1H 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 ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}$: 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} .

^1H 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 ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{16}\text{H}_{12}\text{ClN}_2\text{O}$: 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} .

^1H 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 ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{16}\text{H}_{11}\text{BrFN}_2\text{O}$: 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} .

^1H 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 ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{20}\text{H}_{15}\text{N}_2\text{O}$: 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} .

^1H 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_{CF} = 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 ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{N}_2\text{O}$: 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} .

^1H 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_{CF} = 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 ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{18}\text{H}_{11}\text{F}_6\text{N}_2\text{O}$: 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} .

^1H 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 ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{16}\text{H}_{12}\text{FN}_2\text{O}$: 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} .

^1H 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 C₁₄H₁₁N₂O₅: 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.

¹H NMR (500 MHz, CDCl₃): 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).

¹³C NMR (CDCl₃, 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 C₂₂H₁₇N₂O: 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.

¹H NMR (500 MHz, CDCl₃): 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).

¹³C NMR (CDCl₃, 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 C₁₆H₁₁BrN₂O: 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.

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (100.6 MHz, CDCl₃): 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 C₁₇H₁₅N₂O: 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.

¹H NMR (400 MHz, CD₃OD): 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).

¹³C NMR (100.6 MHz, CD₃OD): 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 C₁₇H₁₅N₂O₂: 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.

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (CDCl₃, 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 C₁₆H₁₂N₂O₃ ($M + H$)⁺: 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.

¹H NMR (500 MHz, CDCl₃): 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).

¹³C NMR (CDCl₃, 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 C₁₁H₁₀N₂ONa: 209.0685; found: 209.0681.

Oxytosylation; General Procedure

To a solution of PhI(OAc)₂ (509 mg, 1.58 mmol) in CH₂Cl₂ (10 mL) was added TsOH·H₂O (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 CH₂Cl₂ (5 mL) was added rapidly. The progress of the reaction was monitored by TLC. Upon completion, the mixture was diluted with H₂O and extracted with CH₂Cl₂ and the combined organic extracts were concentrated 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.

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (CDCl₃, 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 C₂₃H₁₉N₂O₄S: 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.

¹H NMR (500 MHz, CDCl₃): 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 ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{23}\text{H}_{18}\text{ClN}_2\text{O}_4\text{S}$: 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} .

^1H 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 $\text{C}_{23}\text{H}_{17}\text{BrN}_2\text{O}_4\text{S}$: 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} .

^1H 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 ($\text{M} + \text{Na}$)⁺ calcd for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_4\text{SNa}$: 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} .

^1H 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 ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{23}\text{H}_{18}\text{ClN}_2\text{O}_4\text{S}$: 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} .

^1H 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 $\text{C}_{23}\text{H}_{16}\text{BrFN}_2\text{O}_4\text{S}$: 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} .

^1H 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 $\text{C}_{27}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$: 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} .

^1H 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_{CF} = 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 ($\text{M} + \text{H}$)⁺ calcd for $\text{C}_{24}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_4\text{S}$: 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} .

^1H 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 C₂₅H₁₇F₆N₂O₄SNa: 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.

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (CDCl₃, 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 C₂₃H₁₈FN₂O₄S: 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.

¹H NMR (500 MHz, CDCl₃): 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).

¹³C NMR (CDCl₃, 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 C₂₁H₁₇N₂O₄S₂: 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.

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (CDCl₃, 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 C₂₉H₂₃N₂O₄S: 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.

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (CDCl₃, 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 C₂₃H₁₇BrN₂O₄S: 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.

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (100.6 MHz, CDCl₃): 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 C₂₄H₂₁N₂O₄S: 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.

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (100.6 MHz, CDCl₃): 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 C₂₄H₂₁N₂O₅S: 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 CH₂Cl₂ (10 mL) was added TsOH·H₂O (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 CH₂Cl₂ (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 CH₂Cl₂ (30 mL) and H₂O (20 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried (Na₂SO₄). 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 NaHCO₃ and diluted with CH₂Cl₂ (30 mL). The organic layer was washed with H₂O (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried (Na₂SO₄). 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, CDCl₃): 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).

¹³C NMR (CDCl₃, 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 CH₂Cl₂ (30 mL). The organic layer was washed with H₂O (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried (Na₂SO₄). 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, CDCl₃): 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).

¹³C NMR (CDCl₃, 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 C₁₇H₁₅N₂O₂: 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 ¹³C NMR spectra of products are provided.

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