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Photoredox-Mediated Remote C(sp^3)-H Heteroarylation of *N*-Alkyl Sulfonamides

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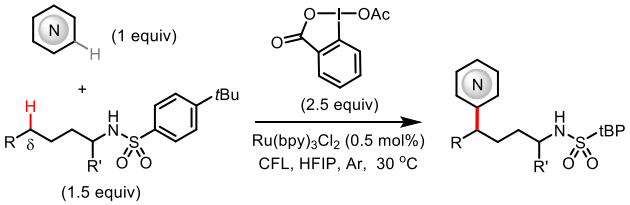


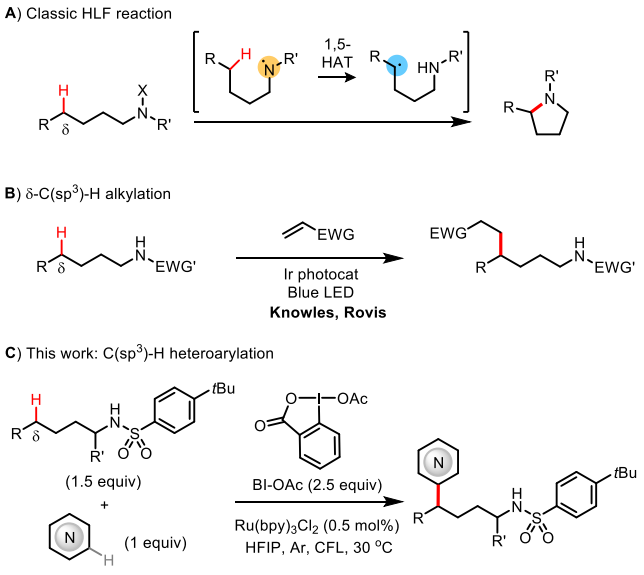
ABSTRACT: A Minisci-type δ-selective C(sp^3)-H heteroarylation of sulfonyl-protected primary aliphatic amines with *N*-heteroarenes under photoredox-catalyzed conditions was developed. The reaction typically uses a slight excess of amine reactant. The use of benziodoxole acetate (BI-OAc) oxidant and hexafluoroisopropanol solvent is critical to achieve high yield. Besides methylene C-H bonds, heteroarylation reactions of δ methyl C-H bonds also worked under more forced conditions. The reactions show a broad scope for both amine and *N*-heteroarene substrates, offering a straightforward method for synthesis of complex δ-heteroarylalkylmines from simple precursors.

INTRODUCTION

Aliphatic amines of various structures are commonly used in organic synthesis.[1] Selective functionalization of the C(sp^3)-H bonds of these amines could potentially streamline the synthesis of complex amines.[2] Among the existing methods[3], radical-mediated reactions featuring a 1,5-hydrogen atom transfer (1,5-HAT) process of nitrogen-radical intermediates offer a convenient strategy to selectively functionalize remote δ C-H bond of alkyl amines.[4] While the classic Hofmann-Loffler-Freytag (HLF) reaction for synthesis of pyrrolidines uses *N*-halo-substituted amine precursors,[5] new protocols of HLF-type reactions can avoid the pre-activation step via *in situ* generation of reactive amine species using various activating reagents (Scheme 1A).[6] More recently, Knowles[7] and Rovis[8] independently reported a redox neutral process for δ C-H alkylation reaction of acyl and sulfonyl protected primary amines with electron-deficient alkenes under photoredox catalysis (Scheme 1B).[9] Herein, we reported a new photoredox-mediated method for δ-C(sp^3)-H heteroarylation of sulfonyl protected primary alkyl amines with *N*-heteroarenes using benziodoxole acetate (BI-OAc) oxidant (Scheme 1C).[10,11]

RESULTS AND DISCUSSION

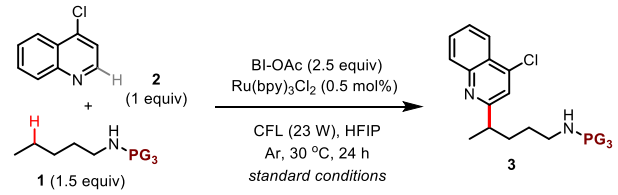
We recently reported a photoredox-mediated δ-selective C–H heteroarylation reaction of free aliphatic alcohols with *N*-heteroarenes using perfluorinated hydroxybenziodoxole (PFBI-OH) as oxidant.[12] Encouraged by these results,



Scheme 1. Radical-mediated remote C-H functionalization of aliphatic amines via 1,5-HAT.

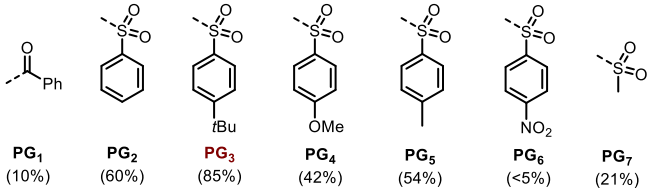
we wondered whether a similar protocol for C-H heteroarylation of alkyl amine substrates can be developed. As shown in Table 1, we were pleased to find that reaction of 1.5 equiv of 4-*tert*-butylphenylsulfonyl pentylamine **1**, 1 equiv of 4-chloroquinoline **2**, 2.5 equiv of benziodoxole

Table 1. Reaction optimization of δ C-H heteroarylation of protected pentylamine.[a]

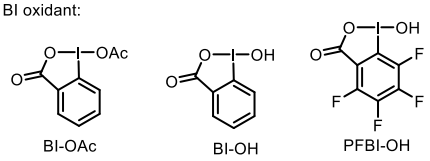


Entry	Change from the standard conditions (equiv of reagents)	Yield of 3 (%)
1	Standard conditions	85 (80[b])
2	BIOAc → PFBI-OH	16
3	BIOAc → BI-OH	37
4	BIOAc → $PhI(OAc)_2$	17
5	BIOAc → $PhI(OTFA)_2$	< 5
6	BIOAc (2.5 → 2 equiv)	61
7	**1** (1.5 → 1.2 equiv)	68
8	**1** (1.5 → 2 equiv)	87
9	$Ru(bpy)_3Cl_2$ (0.5 → 0.1 mol %)	15
10	No $Ru(bpy)_3Cl_2$	< 5
11	CFL → darkness	< 5
12	HFIP → DCM	< 5
13	HFIP → CH_3CN	< 5
14	HFIP → TFE	57
15	+ TEMPO (2.5 equiv)	0

Reactions of **1** with different **PG** under the standard conditions[a]



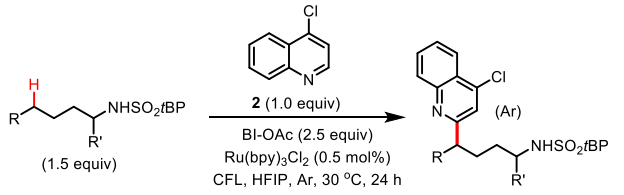
Structure of BI oxidant:

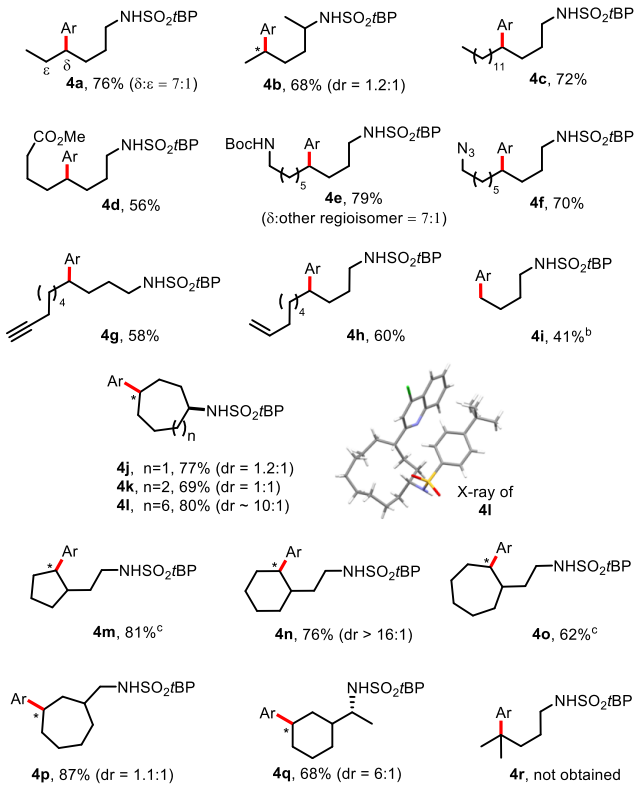


a) Unless otherwise indicated, reactions were conducted with 0.3 mmol of **1** and 0.2 mmol of **2** in 1 mL of solvent at 30 °C, yield of **3** was based on ^{1}H-NMR of crude reaction mixture after workup. b) Isolated yield.

acetate (BI-OAc) and 0.5 mol % of $Ru(bpy)_3Cl_2$ under the irradiation of household compact fluorescent lamp (CFL, 23 W) in hexafluoroisopropanol (HFIP) at 30 °C for 24 hours gave the desired product **3** in 80% isolated yield (entry 1).[13] Replacing BI-OAc with other hypervalent iodine reagents gave lower yield (entry 2-5).[14] Replacing the 4-*tert*-butylphenylsulfonyl group with other acyl or sulfonyl group gave decreased yield under the same reaction conditions. The use of 1.2 and 2.0 equiv of **1** gave **3** in 68% and 87% yield, respectively (entries 7, 8). Photosensitizer $Ru(bpy)_3Cl_2$ and visible light irradiation were critical for the alkylation reaction (entries 10, 11). Use of dichloromethane (DCM) and CH_3CN as solvents gave significantly

Scheme 2. Scope of aliphatic sulfonamides.[a]



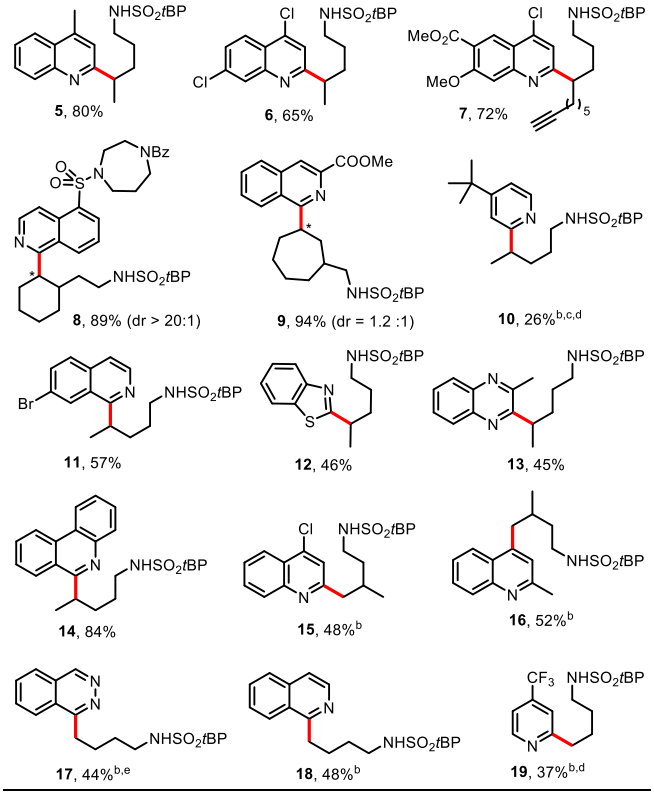


a) Isolated yield on a 0.2 mmol scale. Unless otherwise indicated, excellent δ regioselectivity (δ/other isomers > 20/1) was obtained. b) 3 equiv of sulfonamide and 5 equiv of BI-OAc were used. c) > 20/1 dr was observed. Stereochemistry has not been established.

lower yield (entries 12, 13). Lower loading of photosensitizer $Ru(bpy)_3Cl_2$ (0.1 mol %) resulted in decreased yield (entry 9).

The scope of amines was demonstrated in Scheme 2. Aliphatic sulfonamides of both linear and cyclic aliphatic scaffolds were compatible with this protocol. Most sulfonamides carrying simple linear alkyl chains proceeded with excellent δ regioselectivity (δ/other isomers > 20/1). Notably, reaction of hexylamine gave a moderate regioselectivity (**4a**: ε/ δ ~7/1). Functional groups including ester, carbamate, azido, terminal alkyne and alkene were tolerated (e.g. **4d**–**4h**). Besides the δ methylene C–H bonds, we were pleased to find that the heteroarylation at the more inert δ methyl group also proceeded in moderate yield under more forced conditions (using 3 equiv of amine substrate and 5 equiv of BI-OAc, see **4i**). δ Methylene C–H bonds of cyclic motifs can be heteroarylated in good yield with varied

Scheme 3. Scope of *N*-heteroarenes.[a]

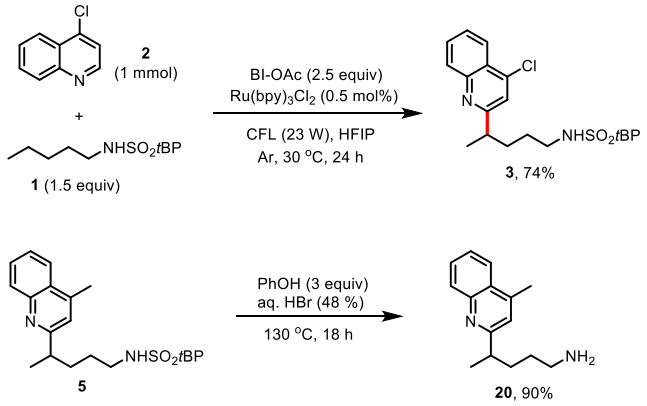


a) Isolated yield on a 0.2 mmol scale. b) 3 equiv of sulfonamide and 5 equiv of BI-OAc were used. c) 48 h. d) No di-alkylated product was detected. e) Trace amount (<5%) of di-alkylated product was detected.

diastereoselectivity (e.g. **4j**–**4q**). For example, reactions of sulfonamides of cyclohexylamine and cyclooctylamine gave **4j** and **4k** in 77% and 69% yield respectively as roughly a 1:1 mixture of diastereomers. Interestingly, reaction of sulfonamide of cyclododecylamine gave the heteroarylated product **4l** in excellent *syn* diastereoselectivity (10/1) under the standard conditions. The structure of **4l** was confirmed by X-ray crystallography. As seen in **4r**, heteroarylation at the methine position gave little desired product probably due to the facile oxidation of the resulting 3° C-radical to a 3° carbocation.[15]

The scope of *N*-heteroarenes was then investigated with selected 4-*tert*-butyl phenylsulfonyl protected aliphatic amines under the optimized conditions (Scheme 3). In general, electron-deficient *N*-heteroarenes showed much higher reactivity than electron-rich ones (e.g. **5** vs **10**). Chemoselectivity typical of Minisci reactions was observed for heteroarenes as seen in quinolines (**5**–**7**), isoquinolines (**9**, **11**) benzothiazole (**12**), quinoxaline (**13**) and phenanthridine (**14**). Reaction of benzoyl protected drug molecule fasudil gave product **8** in 89% yield. As seen in 4-chloroquinoline (**15**), quinaldine (**16**) and isoquinoline (**18**), heteroarylation of δ methyl C-H bond worked in moderate yield under modified conditions with 3 equiv of amine and 5 equiv of BI-OAc. Symmetric phthalazine (**17**) and pyridines (**10**, **19**) mainly gave mono-alkylation products in moderate yields,

Scheme 4. Scale-up reaction and deprotection



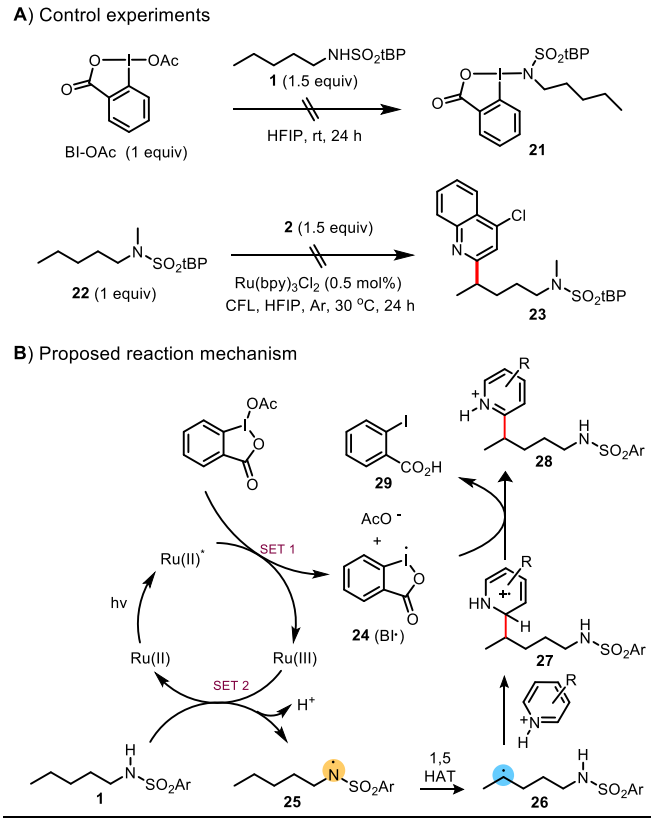
along with significant amount of starting material (~50%) was recovered.

As shown in Scheme 4, the reaction of 4-chloroqunoline **2** with 4-*tert*-butylphenylsulfonyl pentylamine **1** conducted at 1 mmol scale worked well, giving product **3** in 74% yield. The 4-*tert*-phenylsulfonamide group in product **5** can be cleanly removed by the treatment of phenol in the aqueous hydrobromic acid at 130 °C to give free amine product **20** in 90% yield.[16]

Preliminary experiments have been conducted to probe the mechanism of this *N*-heteroarylation reaction (Scheme 5). In our previous C-H heteroarylation reaction of free aliphatic alcohols, perfluorinated hydroxybenziodoxole (PFBI-OH) can readily undergo substitution reaction with alcohols to give a new I-O intermediate, which can be activated by Ru(II)* via single electron transfer (SET) to generate an alkoxyl radical.[12] In contrast, the corresponding substitution product **21** was not observed when mixing BI-OAc with amine substrates. Furthermore, the reaction of **22**, a *N*-methylated derivative of **1**, with 4-chloroquinoline **2** under the standard conditions did not gave any desired alkylation product **23**, supporting the involvement of a *N*-centered radical intermediate in this reaction system (Scheme 5A).[17] Based on the these evidence and the related work by Knowles,[7] Rovis[8] and Itami,[18] the following mechanism is proposed for this reaction system (Scheme 5B). Photoexcited Ru(II)* is first oxidized by BI-OAc via SET, forming Ru(III) and BI• radical **24**. The sulfonamide substrate **1** is oxidized by a Ru(III) species via SET or proton-coupled electron transfer process to form *N*-radical **25**. **25** undergoes 1,5-HAT to generate C-centered radical **26**. Following the typical Minisci reaction pathway,[19,20] **26** reacts with protonated *N*-Heteroarenes to form intermediate **27**. Reaction of **27** with BI• via hydrogen atom abstraction or SET/deprotonation give the final heteroarylation product[21].

In summary, we have developed a new method for δ-selective C(sp^3)-H heteroarylation of sulfonyl-protected primary aliphatic amines with *N*-heteroarenes under photoredox catalysis. The use of the 4-*tert*-butylphenylsulfonyl protecting group for amine, cyclic hypervalent iodine BI-OAc as oxidant, and HFIP solvent is critical to achieve high yield. The method show a broad scope for both amine and

Scheme 5. Mechanistic considerations.



N-heteroarene substrates, offering a straightforward method for synthesis of complex δ-heteroarylalkylmines from simple precursors.

EXPERIMENTAL SECTION

General Information. All commercial materials were used as received unless otherwise noted. The amine starting materials were either purchased from TCI or synthesized according to the reported procedure. $[Ru(bpy)_3]Cl_2$ (98%, Ru > 15.75%, Energy Chemical) and HFIP (99.0%, ACS grade, J&K Chemical) were used as received unless otherwise noted. Hydroxylbenziodoxole (BI-OH) and acetoxybenziodoxole (BI-OAc) were synthesized according to reported procedures and used as freshly prepared.[22] All reactions were carried out in a 4 mL glass vial (Thermo SCIENTIFIC National B7999-2, made from superior quality 33 expansion borosilicate clear glass), sealed with a PTFE cap on bench top. 23 W CFL(made by NVC, 50Hz/S-RR) was used for visible-light promoted reactions. Analytical thin layer chromatography (TLC) were performed on silica gel Huanghai HSGF254 plates and visualization of the developed chromatogram was performed by fluorescence quenching (λmax = 254 nm). Flash chromatography was performed using silica gel (200-300 mesh) purchased from Qingdao Haiyang Chemical Co., China. NMR spectra were recorded on Bruker AVANCE AV 400 instruments and all NMR experiments were reported in units, parts per million (ppm), using residual solvent peaks as internal reference ($CDCl_3$, δ 7.26 for ^1H and δ 77.16 for ^{13}C). Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, br s = broad singlet, m = multiplet. High resolution ESI mass experiments were operated on a Thermo Q Exactive Focus instrument with Quadrupole-Orbitrap mass analyzer.

Procedure for synthesis of 4-*tert*-butylphenylsulfonyl pentylamine 1. Pentan-1-amine (0.22 g, 2.5 mmol, 1.0 equiv), triethylamine (0.28 g, 2.8 mmol, 1.1 equiv) and DMAP (31 mg, 0.25 mmol, 0.1 equiv) were dissolved in DCM (10 mL) at 0 °C. 4-(*tert*-Butyl)benzenesulfonyl chloride (651.6 mg, 2.8 mmol, 1.1 equiv) was added portionwisely. The reaction mixture was stirred at room temperature for 1 hour, then washed with saturated $NaHCO_3$ (aq), and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to give compound **1** in 86% yield (0.67 g) as white solid. Mp 66.5-68.0 °C; R_f = 0.7 (petroleum ether/ethyl acetae = 4:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 6.9 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 4.43 (br s, 1H), 2.97-2.91 (m, 2H), 1.47-1.42 (m, 2H), 1.34 (s, 9H), 1.25-1.21 (m, 4H), 0.83 (t, *J* = 5.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.5, 137.0, 127.1, 126.2, 43.4, 35.3, 31.2, 29.4, 28.8, 22.3, 14.0. HRMS Calcd for $C_{15}H_{26}NO_2S^+$ $[M+H^+]$: 284.1679, Found: 284.1684.

All the *N*-protected amines used in this study were synthesized following the same procedur as compound **1** with the corresponding protecting reagent**.** The starting materials are numbered as **"product number-1",** such as **4a-1** for the pre-heteroarylated amine of compound **4a.** Compounds **1-PG$_1$**,[23] **1-PG$_2$**,[24] **1-PG$_4$**,[25] **1-PG$_5$**,[26] **1-PG$_7$**,[26] **1-PG$_8$**,[23] and **1-PG$_9$**,[27] are known compounds, the spectra data are consistent with those reported in literature.

Procedure for synthesis of 1,1,1-trifluoro-*N*-pentylmethanesulfonamide (1-PG$_{10}$). Pentan-1-amine (0.22 g, 2.5 mmol, 1.0 equiv), triethylamine (0.28 g, 2.8 mmol, 1.1 equiv) and DMAP (31 mg, 0.25 mmol, 0.1 equiv) were dissolved in DCM (10 mL) at -20 °C. Trifluoromethanesulfonic anhydride (0.79 g, 2.8 mmol) was added dropwise, and the mixture was stirred at room temperature for 1 hour. The mixture was then washed with saturated $NaHCO_3$ (aq.) and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography to give compound **1-PG$_{10}$** as a colorless oil in 82% yield (0.45 g). The spectra data of **1-PG$_{10}$** is consistent with the reported in literature.[28]

4-nitro-*N*-pentylbenzenesulfonamide (1-PG$_6$). Yellow solid (0.66 g, 97% yield); mp 61.3-62.4 °C; R_f = 0.7 (petroleum ether/ethyl acetae = 4:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.9 Hz, 2H), 8.06 (d, *J* = 8.9 Hz, 2H), 4.73 (t, *J* = 5.8 Hz, 3H), 3.03-2.98 (m, 2H), 1.52-1.45 (m, 2H), 1.28-1.20 (m, 4H), 0.86-0.83 (t, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.2, 146.1, 128.4, 124.5, 43.5, 29.5, 28.7, 22.2, 14.0. HRMS Calcd for $C_{11}H_{16}N_2NaO_4S^+$ $[M+Na^+]$: 295.0723, Found: 295.0724.

4-(*tert*-butyl)-*N*-hexylbenzenesulfonamide (4a-1). White solid (0.63 g, 85% yield); mp 59.7-61.3 °C; R_f = 0.8 (petroleum ether/ethyl acetae = 4:1). δ ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 4.55 (br s, 1H), 2.97-2.92 (m, 2H), 1.48-1.40 (m, 2H), 1.34 (s, 9H), 1.28-1.20 (m, 6H), 0.83 (t, *J* = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.4, 137.0, 127.0, 126.2, 43.4, 35.3, 31.4, 31.2, 29.7, 26.3, 22.6, 14.1. HRMS Calcd for $C_{16}H_{28}NO_2S^+$ $[M+H^+]$: 298.1835, Found: 298.1840.

4-(*tert*-butyl)-*N*-(hexan-2-yl)benzenesulfonamide (4b-1). White solid (0.67 g, 86% yield); mp 58.6-60.0 °C; R_f = 0.8 (petroleum ether/ethyl acetae = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 4.41 (br s, 1H), 3.33-3.26 (m, 1H), 1.36-1.30 (m, 2H), 1.33 (s, 9H), 1.21-1.08 (m, 4H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.76 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.3, 138.3, 127.0, 126.1, 50.1, 37.3, 35.2, 31.2, 27.7, 22.4, 22.0, 14.1. HRMS Calcd for $C_{16}H_{28}NO_2S^+$ [M+H$^+$]: 298.1835, Found: 298.1831.

4-(*tert*-butyl)-*N*-hexadecylbenzenesulfonamide (4c-1). White solid (0.92 g, 84% yield); mp 64.4-65.4 °C; R_f = 0.8 (petroleum ether/ethyl acetae = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 4.43 (br s, 1H), 2.97-2.92 (m, 2H), 1.48-1.41 (m, 2H), 1.34 (s, 9H), 1.25-1.21 (m, 26H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.5, 137.1, 127.1, 126.2, 43.4, 35.3, 32.1, 31.2, 29.83, 29.80, 29.76, 29.68, 29.58, 29.5, 29.2, 26.7, 22.8, 14.3. HRMS Calcd for $C_{26}H_{48}NO_2S^+$ [M+H$^+$]: 438.3400, Found: 438.3395.

Methyl-8-((4-(*tert*-butyl)phenyl)sulfonamido)octanoate (4d-1). Colorless oil (0.60 g, 65% yield); R_f = 0.2 (petroleum ether/ethyl acetae = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 1H NMR (400 MHz, CDCl3) δ 7.77 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 4.42 (t, *J* = 6.1 Hz, 1H), 3.66 (s, 3H), 2.93 (dd, *J* = 13.5, 6.9 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 1.56 (dd, *J* = 14.3, 7.1 Hz, 2H), 1.50–1.40 (m, 2H), 1.34 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 6H)., 3.66 (s, 3H), 2.96-2.91 (m, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 1.59-1.54 (m, 2H), 1.49-1.42 (m, 2H), 1.34 (s, 9H), 1.27-1.24 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.3, 156.3, 137.0, 127.0, 126.1, 51.5, 43.3, 35.2, 34.0, 31.2, 29.5, 28.9, 28.7, 26.4, 24.8. HRMS Calcd for $C_{19}H_{32}NO_4S^+$ [M+H$^+$]: 370.2047, Found: 370.2042.

***Tert*-butyl-(10-((4-(*tert*-butyl)phenyl)sulfonamido)decyl)carbamate (4e-1)**. Colorless oil (0.96 g, 82% yield); R_f = 0.3 (petroleum ether/ethyl acetae = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 4.61 (s, 1H), 4.51 (br s, 1H), 3.01-3.06 (m, 2H), 2.95-2.90 (m, 2H), 1.45-1.40 (m, 13H), 1.33 (s, 9H), 1.25-1.20 (m, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.4, 156.1, 137.1, 127.0, 126.2, 79.1, 43.4, 40.7, 35.2, 31.2, 30.2, 29.7, 29.5, 29.4, 29.3, 29.2, 28.6, 26.9, 26.6. HRMS Calcd for $C_{25}H_{45}N_2O_4S^+$ [M+H$^+$]: 469.3095, Found: 469.3090.

4-(*tert*-butyl)-*N*-(undec-10-yn-1-yl)benzenesulfonamide (4g-1). White solid (0.84 g, 93% yield); mp 48.6-51.0 °C; R_f = 0.7 (petroleum ether/ethyl acetae = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 4.44 (br s, 1H), 2.96-2.91 (m, 2H), 2.19-2.14 (m, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.53-1.41 (m, 4H), 1.37-1.32 (m, 2H), 1.34 (s, 9H), 1.25-1.18 (m, 8H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.5, 137.0, 127.0, 126.2, 84.9, 68.2, 43.4, 35.3, 31.2, 29.7, 29.4, 29.14, 29.08, 28.8, 28.6, 26.6, 18.5. HRMS Calcd for $C_{21}H_{34}NO_2S^+$ [M+H$^+$]: 364.2305, Found: 364.2301.

4-(*tert*-butyl)-*N*-(undec-10-en-1-yl)benzenesulfonamide (4h-1). White solid (0.80 g, 87% yield); mp 45.5-46.7 °C; R_f = 0.6 (petroleum ether/ethyl acetae = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 5.85-5.75 (m, 1H), 5.00-4.91 (m, 1H), 4.55 (br s, 1H), 2.96-2.91 (m, 2H), 2.05-1.99 (m, 2H), 1.46-1.41 (m, 2H), 1.36-1.31 (m, 2H), 1.34 (s, 9H), 1.27-1.18 (m, 11H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.4, 139.3, 137.1, 127.1, 126.2, 114.3, 43.4, 35.3, 33.9, 31.2, 29.7, 29.49, 29.48, 29.2, 29.0, 26.6. HRMS Calcd for $C_{21}H_{36}NO_2S^+$ [M+H$^+$]: 366.2461, Found: 366.2457.

4-(*tert*-butyl)-*N*-butylbenzenesulfonamide (4i-1). White solid (0.60 g, 89% yield); mp 86.9-88.0 °C; R_f = 0.9 (petroleum ether/ethyl acetae = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 2H), 4.54 (t, *J* = 5.9 Hz, 1H), 2.95-2.92 (m, 2H), 1.48-1.40 (m, 2H), 1.34 (s, 9H), 1.30-1.24 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.4, 137.0, 127.0, 126.2, 43.1, 35.3, 31.8, 31.2, 19.8, 13.7. HRMS Calcd for $C_{14}H_{24}NO_2S^+$ [M+H$^+$]: 270.1522, Found: 270.1525.

4-(*tert*-butyl)-*N*-cycloheptylbenzenesulfonamide (4j-1). White solid (0.67 g, 87% yield); mp 84.5-85.4 °C; R_f = 0.8 (petroleum ether/ethyl acetae = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 4.65-4.55 (m, 1H), 3.39-3.30 (m, 1H), 1.80-1.75 (m, 2H), 1.54-1.40 (m, 8H), 1.39-1.30 (m, 2H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.2, 138.2, 126.9, 126.1, 54.9, 36.01, 35.99, 35.2, 31.2, 28.1, 23.6. HRMS Calcd for $C_{17}H_{28}NO_2S^+$ [M+H$^+$]: 310.1835, Found: 310.1838.

4-(*tert*-butyl)-*N*-cyclooctylbenzenesulfonamide (4k-1). White solid (0.68 g, 84% yield); mp 94.0-95.6 °C; R_f = 0.8 (petroleum ether/ethyl acetae = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 4.51 (d, *J* = 7.6 Hz, 1H), 3.40-3.37 (m, 1H), 1.74-1.68 (m, 2H), 1.59-1.39 (m, 12H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.3, 138.3, 127.0, 126.1, 54.0, 35.2, 32.8, 31.3, 27.4, 25.4, 23.3. HRMS Calcd for $C_{18}H_{30}NO_2S^+$ [M+H$^+$]: 324.1992, Found: 324.1996.

4-(*tert*-butyl)-*N*-cyclododecylbenzenesulfonamide (4l-1). White solid (0.85 g, 90% yield); mp 141.2-142.5 °C; R_f = 0.7 (petroleum ether/ethyl acetae = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 4.24 (d, *J* = 7.8 Hz, 1H), 3.25-3.22 (m, 1H), 1.55-1.47 (m, 2H), 1.34 (s, 9H), 1.31-1.09 (m, 20H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.4, 137.8, 127.2, 126.1, 50.4, 35.3, 31.3, 23.6, 23.5, 23.4, 23.3, 21.3. HRMS Calcd for $C_{22}H_{38}NO_2S^+$ [M+H$^+$]: 380.2618, Found: 380.2621.

4-(*tert*-butyl)-*N*-(2-cyclopentylethyl)benzenesulfonamide (4m-1). White solid (0.66 g, 86% yield); mp 97.9-99.0 °C; R_f = 0.7 (petroleum ether/ethyl acetae = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 4.68 (br s, 1H), 2.97-2.92 (m, 2H), 1.71-1.63 (m, 3H), 1.56-1.48 (m, 2H), 1.46-1.43 (m, 4H), 1.34 (s, 9H), 1.02-0.94 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.4, 137.0, 127.1, 126.2, 42.7, 37.3, 35.9, 35.2, 32.5, 31.2, 25.1. HRMS Calcd for $C_{17}H_{28}NO_2S^+$ [M+H$^+$]: 310.1835, Found: 310.1832.

4-(*tert*-butyl)-*N*-(2-cyclohexylethyl)benzenesulfonamide (4n-1). White solid (0.77 g, 91% yield); mp 122.5-123.8 °C; R_f = 0.7 (petroleum ether/ethyl acetae = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 4.45 (t, *J* = 5.3 Hz, 1H), 2.99-2.94 (m, 2H), 1.64-1.54 (m, 5H), 1.34 (s, 9H), 1.31 (d, *J* = 7.1 Hz, 2H), 1.25 -1.11 (m, 4H), 0.84-0.76

(m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.4, 137.0, 127.1, 126.2, 41.1, 37.1, 35.3, 34.9, 33.1, 31.2, 26.5, 26.2. HRMS Calcd for $C_{18}H_{29}NNaO_2S^+$ $[M+Na^+]$: 346.1811, Found: 346.1813.

4-(*tert*-butyl)-*N*-(2-cycloheptylethyl)benzenesulfonamide (4o-1). White solid (0.76 g, 91% yield); mp 103-104 °C; R_f = 0.8 (petroleum ether/ethyl acetae = 4:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 4.45 (t, *J* = 5.9 Hz, 1H), 2.99-2.94 (m, 2H), 1.59-1.47 (m, 6H), 1.45-1.39 (m, 3H), 1.38-1.29 (m, 4H), 1.34 (s, 9H), 1.11-1.02 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.4, 137.0, 127.1, 126.2, 41.6, 37.7, 36.4, 35.3, 34.3, 31.2, 28.5, 26.3. HRMS Calcd for $C_{19}H_{32}NO_2S^+$ $[M+H^+]$: 338.2148, Found: 338.2151.

4-(*tert*-butyl)-*N*-(cycloheptylmethyl)benzenesulfonamide (4p-1). White solid (0.67 g, 87% yield); mp 109.5-111.0 °C; R_f = 0.8 (petroleum ether/ethyl acetae = 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 4.62 (br s, 1H), 2.77 (t, *J* = 6.6 Hz, 2H), 1.69-1.40 (m, 9H), 1.37-1.29 (m, 2H), 1.33 (s, 9H) 1.18-1.07 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.4, 137.2, 127.0, 126.2, 49.8, 39.4, 35.3, 31.9, 31.2, 28.4, 26.3. HRMS Calcd for $C_{18}H_{30}NO_2S^+$ $[M+H^+]$: 324.1992, Found: 324.1987.

4-(*tert*-butyl)-*N*-(1-cyclohexylethyl)benzenesulfonamide (4q-1). White solid (0.65 g, 85% yield); mp 107.9-109.5 °C; R_f = 0.4 (petroleum ether/ethyl acetae = 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 4.64 (br s, 1H), 3.20-3.11 (m, 1H), 1.66-1.49 (m, 5H), 1.33 (s, 9H), 1.28-1.19 (m, 1H), 1.17-0.99 (m, 4H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.88-0.77 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.2, 138.4, 127.0, 126.0, 54.5, 43.5, 35.2, 31.2, 28.8, 28.5, 26.4, 26.3, 26.2, 18.4. HRMS Calcd for $C_{18}H_{30}NO_2S^+$ $[M+H^+]$: 324.1992, Found: 324.1987.

4-(*tert*-butyl)-*N*-(4-methylpentyl)benzenesulfonamide (4r-1). White solid (0.6 g, 81% yield); mp 86.3-87.8 °C; R_f = 0.6 (petroleum ether/ethyl acetae = 4:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 4.55 (br s, 1H), 2.96-2.91 (m, 2H), 1.48-1.39 (m, 3H), 1.34 (s, 9H), 1.14-1.08 (m, 2H), 0.80 (d, *J* = 6.6 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.4, 137.1, 127.1, 126.2, 43.7, 35.8, 35.3, 31.2, 27.7, 27.6, 22.5. HRMS Calcd for $C_{16}H_{27}NNaO_2S^+$ $[M+Na^+]$: 320.1655, Found: 320.1665.

4-(*tert*-butyl)-*N*-isopentylbenzenesulfonamide (15-1 or **16-1).** White solid (0.61 g, 86% yield); mp 90.6-92.0 °C; R_f = 0.7 (petroleum ether/ethyl acetae = 4:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 4.49 (br s, 1H), 2.99-2.93 (m, 2H), 1.61-1.52 (m, 1H), 1.36-1.30 (m, 2H), 1.34 (s, 9H), 0.82 (d, *J* = 6.6 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.5, 137.0, 127.0, 126.2, 41.6, 38.5, 35.3, 31.2, 25.5, 22.4. HRMS Calcd for $C_{15}H_{25}NNaO_2S^+$ $[M+Na^+]$: 306.1498, Found: 306.1498.

Procedure for Synthesis of *N*-(10-azidodecyl)-4-(*tert*-butyl)benzenesulfonamide (4f-1).[29] HCl/EtOAc (4 N, 1.0 mL) was added to a solution of substrate **4e-1** (0.47 g, 1.0 mmol) in DCM (3 mL), and the reaction mixture was stirred at room temperature for 0.5 h. Then the organic solvent was removed *in vacuo*. The resulting residue was dissolved in MeOH (5 mL). To this solution, $CuSO_4 \cdot 5H_2O$ (6.25 mg, 0.025 mmol), K_2CO_3 (0.97 g, 7.0 mmol) and 1-H-imidazole-1-sulfonyl azide (0.25 g, 1.2 mmol) were added. The reaction mixture was stirred at room temperature for 18 h. Water was added and the organic solvent was removed *in vacuo*. The aqueous phase was adjusted to pH = 1 using HCl (1 N), and extracted with EtOAc. The ombined organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude prouct was purified by flash chromatography on silica gel to give compound **4f-1** as a colorless oil in 85% yield (0.33 g). R_f = 0.2 (petroleum ether/ethyl acetae = 4:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 1H NMR (400 MHz, CDCl3) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 4.99 (t, *J* = 6.1 Hz, 1H), 3.22 (t, *J* = 7.0 Hz, 2H), 2.91 (dd, *J* = 13.4, 6.9 Hz, 2H), 1.60-1.51 (m, 2H), 1.47-1.38 (m, 2H), 1.36-1.28 (m, 11H), 1.23 (m, 10H)., 3.22 (t, *J* = 7.0 Hz, 2H), 2.93-2.88 (m, 2H), 1.59-1.52 (m, 2H), 1.46-1.39 (m, 2H), 1.35-1.28 (m, 2H), 1.32 (s, 9H), 1.26-1.19 (m, 10H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.3, 137.0, 127.0, 126.1, 51.5, 43.3, 35.2, 31.1, 29.6, 29.4, 29.3, 29.11, 29.07, 28.9, 26.7, 26.5. HRMS Calcd for $C_{20}H_{34}N_4O_2SNa^+$ $[M+Na^+]$: 417.2295, Found: 417.2289.

Procedure for synthesis of (4-(isoquinolin-5-ylsulfonyl)-1,4-diazepan-1-yl)(phenyl)methanone (8-1). Fasudil (0.58 g, 2.0 mmol, 1.0 equiv), triethylamine (0.71 g, 7.0 mmol, 3.5 equiv) and DMAP (31 mg, 0.25 mmol, 0.12 equiv) were dissolved in DCM (10 mL) at 0 °C. Benzoyl chloride (0.31 g, 2.2 mmol, 1.1 equiv) was added dropwise, and the reaction mixture was stirred at room temperature for 1 hour. Then the reaction mixture was washed with saturated $NaHCO_3$ (aq), brine. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford compounds **8-1** as yellow solid in 95% yield (0.75 g). mp 137.2-138.5 °C; R_f = 0.5 (dichloromethane/methanol = 40:1). ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.63 (t, *J* = 7.2 Hz, 1H), 8.35-8.24 (m, 2H), 8.14 (t, *J* = 7.1 Hz, 1H), 7.66-7.59 (m, 1H), 7.32-7.20 (m, 5H), 3.83-3.75 (m, 2H), 3.52-3.27 (m, 6H), 2.10-2.03 (m, 1H), 1.78-1.71 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.8, 153.4, 145.3, 136.1, 134.2, 133.8, 133.3, 131.5, 129.7, 129.3, 128.6, 126.6, 126.4, 126.0, 117.4, 51.8, 50.5, 48.7, 48.3, 48.2, 47.9, 46.6, 45.0, 29.8, 27.7. HRMS Calcd for $C_{21}H_{22}N_3O_3S^+$ $[M+H^+]$: 396.1376, Found: 396.1377.

Procedure for Synthesis of 4-(*tert*-butyl)-*N*-methyl-*N*-pentylbenzenesulfonamide (22)[30]. NaH (0.1 g, 2.5 mmol, 2.5 equiv) was added to a solution of compound **1** (0.28 g, 1.0 mmol, 1.0 equiv) in DMF (10 mL) at 0 °C, and the mixture was stirred for 5 min. Then MeI (0.16 g, 1.1 mmol) was added, and the reaction mixture was stirred at room temperature for 0.5 h. Water (10 mL) was added and the resulting mixture was extracted with EtOAc. The combined organic layer was washed with water (10 mL x 3) and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (PE:EA = 15:1) to give compounds **22** as colorless oil in 84% yield (0.62 g). R_f = 0.8 (petroleum ether/ethyl acetae = 4:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 3.01–2.97 (t, *J* = 8.5 Hz, 2H), 2.72 (s, 3H), 1.56-1.48 (m, 2H), 1.34 (s, 9H), 1.32-1.28 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (101

MHz, $CDCl_3$) δ 156.2, 134.7, 127.4, 126.1, 50.2, 35.2, 34.7, 31.2, 28.8, 27.4, 22.4, 14.1. HRMS Calcd for $C_{16}H_{28}NO_2S^+$ [M+H$^+$]: 298.1835, Found: 298.1838.

General Procedure for Minisci Alkylation Reaction. *N*-heteroarene substrate (0.2 mmol, 1.0 equiv), *N*-alkyl sulfonamide (0.3 mmol, 1.5 equiv) and BI-OAc (0.5 mmol, 2.5 equiv) were added to a solution of $Ru(bpy)_3Cl_2$ (0.001 mmol, 0.5 mol%) in HFIP (1.0 mL). The reaction vial was purged with Ar for 1 min and sealed with PTFE cap, then the mixture was stirred at 30 °C under the irradiation of Compact Fluorescent Lamps irradiation (23 W, palced 5 cm away from the vial) for 24 h. The solvent was removed *in vacuo* and the residue was dissolved in DCM (1 mL). K_2CO_3 (approximate 150 mg) was added to the solution, and the resulting mixture was vigorously stirred for 10 min. Then the mixture was filtrated through a pad of Celite and washed with DCM. The filtrate was concentrated *in vacuo* and the residue was purified by preparative thin layer chromatography or flash chromatography on silica gel to give the desired product.

***N*-(4-(4-chloroquinolin-2-yl)pentyl)benzamide (3-PG$_1$)**. Yellow oil (6 mg, 8%, Isolated yield); R_f = 0.2 (petroleum ether/ethyl acetae = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 7.1 Hz, 2H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.49-7.46 (m, 1H), 7.42-7.38 (m, 3H), 6.51 (br s, 1H), 3.52-3.38 (m, 2H), 3.18-3.09 (m, 1H), 2.00-1.90 (m, 2H), 1.83-1.74 (m, 1H), 1.70-1.61 (m 1H), 1.59-1.47 (m, 1H), 1.38 (d, *J* = 6.9 Hz, 3H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.7, 166.5, 148.7, 143.1, 135.0, 131.4, 130.4, 129.4, 128.6, 127.1, 127.0, 125.3, 124.1, 120.0, 42.4, 40.3, 34.4, 27.6, 21.0. HRMS Calcd for $C_{21}H_{22}ClN_2O^+$ [M+H$^+$]: 353.1415, Found: 353.1415.

***N*-(4-(4-chloroquinolin-2-yl)pentyl)benzenesulfonamide (3-PG$_2$)**. Yellow oil (44 mg, 57%, Isolated yield); R_f = 0.3 (petroleum ether/ethyl acetae = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.1 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.3 Hz, 2H), 7.71 (t, *J* = 7.1 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.29 (s, 1H), 5.70 (t, *J* = 5.7 Hz, 1H), 2.99-2.85 (m, 3H), 1.81-1.72 (m, 1H), 1.65-1.56 (m, 1H), 1.48-1.39 (m, 1H), 1.36-1.28 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 148.3, 143.0, 139.9, 132.4, 130.5, 129.2, 129.0, 127.0, 126.9, 125.1, 123.9, 119.8, 43.1, 41.8, 33.5, 27.2, 20.8. HRMS Calcd for $C_{20}H_{22}ClN_2O_2S^+$ [M+H$^+$]: 389.1085, Found: 389.1083.

***N*-(4-(4-chloroquinolin-2-yl)pentyl)-4-methoxybenzenesulfonamide (3-PG$_4$)**. Yellow oil (32 mg, 38%, Isolated yield); R_f = 0.3 (petroleum ether/ethyl acetae = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.73 -7.70 (m, 3H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.31 (s, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.45 (t, *J* = 5.8 Hz, 1H), 3.79 (s, 3H), 3.00-2.83 (m, 3H), 1.84-1.75 (m, 1H), 1.67-1.58 (m, 1H), 1.48-1.41 (m, 1H), 1.39 -1.32 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 162.7, 148.4, 143.0, 131.6, 130.5, 129.3, 129.2, 127.0, 125.2, 124.0, 119.9, 114.2, 55.6, 43.1, 41.9, 33.6, 27.2, 20.9. HRMS Calcd for $C_{21}H_{24}ClN_2O_3S^+$ [M+H$^+$]: 419.1191, Found: 419.1188.

***N*-(4-(4-chloroquinolin-2-yl)pentyl)-4-methylbenzenesulfonamide (3-PG$_5$)**. Yellow oil (39 mg, 49%, Isolated yield); R_f = 0.3 (petroleum ether/ethyl acetae = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.3 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.31 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.44 (t, *J* = 5.8 Hz, 1H), 3.00-2.84 (m, 3H), 2.35 (s, 3H), 1.845-1.75 (m, 1H), 1.67-1.58 (m, 1H), 1.48-1.41 (m, 1H), 1.39-1.32 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 148.5, 143.2, 143.1, 137.0, 130.5, 129.7, 129.3, 127.1, 127.0, 125.2, 124.0, 119.9, 43.1, 41.9, 33.6, 27.2, 21.5, 21.0. HRMS Calcd for $C_{21}H_{24}ClN_2O_2S^+$ [M+H$^+$]: 403.1242, Found: 403.1240.

***N*-(4-(4-chloroquinolin-2-yl)pentyl)methanesulfonamide (3-PG$_7$)**. Colorless oil (10 mg, 15%, Isolated yield); R_f = 0.2 (petroleum ether/ethyl acetae = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 8.2 Hz, 1H), 7.39 (s, 1H), 5.11 (br s, 1H), 3.18-3.04 (m, 3H), 2.88 (s, 3H), 1.98-1.88 (m, 1H), 1.78-1.72 (m, 1H), 1.62-1.44 (m, 2H), 1.36 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 148.5, 143.2, 130.6, 129.3, 127.1, 125.3, 124.1, 120.0, 43.3, 42.1, 40.2, 33.6, 27.8, 21.1. HRMS Calcd for $C_{15}H_{20}ClN_2O_2S^+$ [M+H$^+$]: 327.0929, Found: 327.0929.

4-(*tert*-butyl)-*N*-(4-(4-chloroquinolin-2-yl)pentyl)benzenesulfonamide (3). Yellow oil (71 mg, 80% yield); R_f = 0.5 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.4 Hz, 1H), 8.06 (d, *J* = 7.4 Hz, 1H), 7.75-7.70 (m, 3H), 7.58-7.55 (m, 1H), 7.44-7.42 (m, 2H), 7.33 (s, 1H). 5.49 (br s, 1H), 3.02-2.87 (m, 3H), 1.86-1.77 (m, 1H), 1.68-1.60 (m, 1H), 1.53-1.34 (m, 2H), 1.29 (s, 9H), 1.26 (d, *J* = 6.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 156.2, 148.5, 143.0, 137.0, 130.5, 129.3, 127.0, 126.0, 125.2, 124.0, 119.9, 43.2, 41.9, 35.1, 33.5, 31.1, 27.3, 20.9. HRMS Calcd for $C_{24}H_{30}ClN_2O_2S^+$ [M+H$^+$]: 445.1711, Found: 445.1711.

4-(*tert*-butyl)-*N*-(4-(4-chloroquinolin-2-yl)hexyl)benzenesulfonamide (4a). An inseparable mixture of δ- and ε-arylated products (7:1), yellow oil (70 mg, 76% yield); R_f = 0.5 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.77-7.71 (m, 3H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.35 (s, 1H), 5.28 (br s, 1H), 3.01-2.84 (m, 2H), 2.79-2.72 (m, 1H), 1.79-1.65 (m, 4H), 1.36-1.32 (m, 2H), 1.31 (s, 9H), 0.78 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.2, 156.3, 148.6, 143.1, 137.1, 130.6, 129.5, 127.1, 127.0, 126.14, 126.08, 125.3, 124.1, 120.4, 49.4, 43.3, 35.2, 32.1, 31.2, 28.7, 27.2, 12.1. HRMS Calcd for $C_{25}H_{32}ClN_2O_2S^+$ [M+H$^+$]:459.1868, Found: 459.1866.

4-(*tert*-butyl)-*N*-(5-(4-chloroquinolin-2-yl)hexan-2-yl)benzenesulfonamide (4b). Two separable diastereomers were obtained. For one isomer **4b'**: colorless oil (33 mg, 36% yield); R_f = 0.4 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.31 (s, 1H), 5.47 (br s, 1H), 3.32-3.22 (m, 1H), 2.95-2.86 (m, 1H), 1.69-1.60 (m, 1H), 1.48-1.37 (m, 2H), 1.33-1.28 (m, 1H), 1.30 (s, 9H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.0, 156.3, 148.6, 143.1, 138.0, 130.8, 129.4, 127.1, 126.0,

125.2, 124.0, 120.7, 50.3, 41.9, 34.7, 31.2, 31.1, 22.5, 21.7. HRMS Calcd for $C_{25}H_{32}ClN_2O_2S^+$ [M+H$^+$]: 459.1868, Found: 459.1865. For the another isomer **4b''**: colorless oil (29 mg, 32% yield); R_f = 0.35 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.77-7.73 (m, 3H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.32 (s, 1H), 5.20 (br s, 1H), 3.34-3.24 (m, 1H), 2.93-2.84 (m, 1H), 1.74-1.59 (m, 2H), 1.44-1.30 (m, 2H), 1.28 (s, 9H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.2, 156.2, 148.6, 143.0, 138.2, 130.6, 129.5, 127.01, 126.94, 126.0, 125.2, 124.0, 120.0, 50.5, 41.9, 35.2, 35.0, 32.7, 31.2, 22.3, 20.8. HRMS Calcd for $C_{25}H_{32}ClN_2O_2S^+$ [M+H$^+$]: 459.1868, Found: 459.1867.

4-(*tert*-butyl)-*N*-(4-(4-chloroquinolin-2-yl)hexadecyl)benzenesulfonamide (4c). Colorless oil (86 mg, 72% yield); R_f = 0.6 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.3 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.77-7.70 (m, 3H), 7.62-7.58 (m, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.30 (s, 1H), 5.27 (t, *J* = 5.28 Hz, 1H), 2.99-2.92 (m, 1H), 2.91-2.80 (m, 2H), 1.78-1.60 (m, 4H), 1.43 -1.33 (m, 3H), 1.31 (s, 9H), 1.25-1.18 (m, 18H), 1.10-1.02 (m, 1H), 0.86 (t, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.4, 156.3, 148.6, 143.0, 137.0, 130.6, 129.5, 127.1, 127.0, 126.1, 125.3, 124.1, 120.3, 47.9, 43.3, 13.3, 35.9, 35.2, 32.5, 32.0, 31.2, 29.8, 29.76, 29.74, 29.69, 29.56, 29.46, 27.6, 27.2, 22.8, 14.3. HRMS Calcd for $C_{35}H_{52}ClN_2O_2S^+$ [M+H$^+$]: 599.3433, Found: 599.3431.

Methyl-8-((4-(*tert*-butyl)phenyl)sulfonamido)-5-(4-chloroquinolin-2-yl)octanoate (4d). Colorless oil (59 mg, 56% yield); R_f = 0.5 (petroleum ether/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.77-7.69 (m, 3H), 7.60 (t, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.30 (s, 1H), 5.19 (br s, 1H), 3.61 (s, 3H), 2.97-2.90 (m, 1H), 2.88-2.83 (m, 2H), 2.25 (t, *J* = 7.5 Hz, 2H), 1.83-1.65 (m, 4H), 1.61-1.50 (m, 1H), 1.47-1.36 (m, 2H), 1.34-1.32 (m, 1H), 1.30 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.9, 164.6, 156.3, 148.6, 143.2, 136.9, 130.6, 129.5, 127.1, 127.0, 126.1, 125.3, 124.1, 120.3, 51.6, 47.6, 43.2, 35.2, 35.0, 34.0, 32.4, 31.2, 27.2, 22.9. HRMS Calcd for $C_{28}H_{36}ClN_2O_4S^+$ [M+H$^+$]: 531.2079, Found: 531.2082.

***Tert*-butyl(10-((4-(*tert*-butyl)phenyl)sulfonamido)-7-(4-chloroquinolin-2-yl)decyl)carbamate (4e)**. An inseparable mixture of δ- and other-arylated products (7:1), colorless oil (99 mg, 79% yield); R_f = 0.4 (petroleum ether/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.7 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.75-7.69 (m, 3H), 7.58 (t, *J* = 7.1 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.29 (s, 1H), 5.38 (t, *J* =5.7 Hz, 1H), 4.51 (t, *J* = 6.1 Hz, 1H), 3.05-3.00 (m, 2H), 2.96-2.89 (m, 1H), 2.88-2.78 (m, 2H), 1.77-1.61 (m, 4H), 1.40-1.35 (m, 13H), 1.29 (s, 9H), 1.24-1.20 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.3, 156.2, 148.6, 143.0, 137.0, 130.5, 129.5, 127.00, 126.95, 126.1, 126.0, 125.2, 124.0, 120.3, 79.0， 47.9, 43.2, 40.6, 35.7, 35.1, 32.4, 31.2, 30.0, 29.4, 28.5, 27.4, 27.3, 26.6. HRMS Calcd for $C_{34}H_{49}ClN_3O_4S^+$ [M+H$^+$]: 630.3127, Found: 630.3127.

***N*-(10-azido-4-(4-chloroquinolin-2-yl)decyl)-4-(*tert*-butyl)benzenesulfonamide (4f)**. Yellow oil (78 mg, 70% yield); R_f = 0.3 (petroleum ether/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 7.3 Hz, 1H), 7.76-7.70 (m, 3H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.30 (s, 1H), 5.29 (br s, 1H), 3.19 (t, *J* = 6.9 Hz, 2H), 2.99-2.80 (m, 3H), 1.81-1.60 (m, 4H), 1.52-1.49 (m, 2H), 1.44-1.33 (m, 3H), 1.30 (s, 9H), 1.26-1.21 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.2, 156.2, 148.6, 143.0, 136.9, 130.6, 129.4, 127.1, 127.0, 126.1, 125.2. 124.0, 120.3, 51.5, 47.9, 43.2, 35.7, 35.2, 32.4, 31.2, 29.2, 28.8, 27.4, 27.3, 26.6. HRMS Calcd for $C_{29}H_{39}ClN_5O_2S^+$ [M+H$^+$]: 556.2508, Found: 556.2508.

4-(*tert*-butyl)-*N*-(4-(4-chloroquinolin-2-yl)undec-10-yn-1-yl)benzenesulfonamide (4g). Yellow oil (61 mg, 58% yield); R_f = 0.3 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.76 -7.70 (m, 3H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.30 (s, 1H), 5.33 (br s, 1H), 2.98-2.90 (m, 1H), 2.89-2.79 (m, 2H), 2.12-2.08 (m, 2H), 1.89 (t, *J* = 2.6 Hz, 1H), 1.81-1.59 (m, 4H), 1.45-1.38 (m, 3H), 1.36-1.27 (m, 3H), 1.30 (s, 9H) 1.25-1.21 (m, 1H), 1.14-1.04 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.2, 156.2, 148.6, 143.0, 136.9, 130.5, 129.4, 127.02, 126.95, 126.0, 125.2, 124.0, 120.3, 84.6, 68.3, 47.8, 43.2, 35.6, 35.1, 32.4, 31.2, 28.8, 28.3, 27.2, 27.0.18.4. HRMS Calcd for $C_{30}H_{38}ClN_2O_2S^+$ [M+H$^+$]: 525.2337, Found: 525.2338.

4-(*tert*-butyl)-*N*-(4-(4-chloroquinolin-2-yl)undec-10-en-1-yl)benzenesulfonamide (4h). Colorless oil (63 mg, 60% yield); R_f = 0.4 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.77-7.74 (m, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.30 (s, 1H), 5.79-5.69 (m, 1H), 5.21 (s, 1H), 4.95-4.88 (m, 2H), 3.00-2.92 (m, 1H), 2.91-2.79 (m, 2H), 1.99-1.94 (m, 2H), 1.82-1.59 (m, 4H), 1.42-1.34 (m, 2H), 1.31 (s, 9H), 1.28-1.23 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.3, 156.3, 148.6, 143.1, 139.1, 136.9, 130.6, 129.5, 127.1, 127.0, 126.1, 125.3, 124.1, 120.3, 114.4, 47.9, 43.3, 35.8, 35.2, 33.8, 32.5, 31.2, 29.24, 28.8, 29.2, 28.8, 27.4, 27.2. HRMS Calcd for $C_{30}H_{40}ClN_2O_2S^+$ [M+H$^+$]: 527.2494, Found: 527.2494.

4-(*tert*-butyl)-*N*-(4-(4-chloroquinolin-2-yl)butyl)benzenesulfonamide (4i). Colorless oil (35 mg, 41% yield); R_f = 0.2 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.77-7.73 (m, 3H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.34 (s, 1H), 5.33 (br s, 1H), 3.04-2.99 (m, 2H), 2.89 (t, *J* = 7.4 Hz, 2H), 1.88-1.81 (m, 2H), 1.62-1.55 (m, 2H), 1.31 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.9, 156.4, 148.7, 143.0, 137.1, 130.7, 129.3, 127.05, 127.03, 126.1, 125.1, 124.1, 121.5, 43.0, 37.7, 35.2, 31.2, 28.8, 26.2. HRMS Calcd for $C_{23}H_{28}ClN_2O_2S^+$ [M+H$^+$]: 431.1555, Found: 431.1552.

4-(*tert*-butyl)-*N*-(4-(4-chloroquinolin-2-yl)cycloheptyl)benzenesulfonamide (4j). Two separable diastereomers were obtained. For one isomer **4j':** colorless oil (40 mg, 42% yield); R_f = 0.6 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.58-7.51 (m, 3H), 7.31 (s, 1H), 4.81 (br s, 1H), 3.52-3.47 (m, 1H), 3.03-2.97 (m, 1H), 2.08-1.99 (m, 2H), 1.96-1.89 (m, 2H), 1.80-1.65 (m, 5H), 1.59-1.50 (m, 1H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.0, 156.4, 148.6, 142.8, 138.2, 130.4, 129.4,

126.93, 126.87, 126.2, 125.2, 124.0, 120.0, 55.0, 49.2, 35.6, 35.4, 35.3, 34.2, 31.2, 30.4, 22.2. HRMS Calcd for $C_{26}H_{32}ClN_2O_2S^+$ [M+H$^+$]: 471.1868, Found: 471.1866. For the another isomer **4j''**: yellow oil (33 mg, 35% yield); R_f = 0.2 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.79 (t, *J* = 7.1 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.32 (s, 1H), 7.22 (d, *J* = 9.1 Hz, 1H), 3.79 (br s, 1H), 3.30-3.24 (m, 1H), 2.21-2.11 (m, 1H), 2.00-1.94 (m, 1H), 1.90-1.68 (m, 4H), 1.64-1.60 (m, 2H), 1.53-1.44 (m, 1H), 1.37-1.30 (m, 1H), 1.30 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.8, 155.9, 148.2, 143.2, 139.0, 130.9, 129.4, 127.1, 126.8, 126.0, 125.1, 123.9, 121.0, 53.2, 45.9, 36.5, 35.1, 34.1, 32.4, 31.2, 26.4, 21.6. HRMS Calcd for $C_{26}H_{32}ClN_2O_2S^+$ [M+H$^+$]: 471.1868, Found: 471.1866.

4-(*tert*-butyl)-*N*-(4-(4-chloroquinolin-2-yl)cyclooctyl)benzenesulfonamide (4k). Two separable diastereomers were obtained. For one isomer **4k'**: colorless oil (33 mg, 34% yield); R_f = 0.5 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.32 (s, 1H), 4.99 (d, *J* = 7.3 Hz, 1H), 3.50-3.48 (m, 1H), 3.01-2.97 (m, 1H), 1.92-1.74 (m, 9H), 1.65-1.52 (m, 3H), 1.31 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.5, 156.3, 148.6, 142.8, 138.2, 130.4, 129.4, 127.0, 126.9, 126.1, 125.1, 124.0, 120.3, 53.5, 47.3, 35.2, 32.4, 31.6, 31.5, 31.2, 28.4, 26.1, 23.3. HRMS Calcd for $C_{27}H_{34}ClN_2O_2S^+$ [M+H$^+$]: 485.2024, Found: 485.2021. For the another isomer **4k''**: colorless oil (34 mg, 35% yield); R_f = 0.45 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, CDCl3) δ 8.16 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.74-7.69 (m, 1H), 7.58-7.54 (m, 1H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.31 (s, 1H), 4.85 (d, *J* = 7.3 Hz, 1H), 3.57-3.51 (m, 1H), 3.06-3.00 (m, 1H), 2.04-1.93 (m, 4H), 1.87-1.71 (m, 4H), 1.65-1.42 (m, 4H), 1.32 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.6, 156.3, 148.5, 142.8, 138.2, 130.4, 129.4, 127.0, 126.9, 126.1, 125.1, 124.0, 120.2, 54.0, 48.1, 35.2, 32.3, 31.7, 31.5, 31.2, 29.8, 26.8, 23.3. HRMS Calcd for $C_{27}H_{34}ClN_2O_2S^+$ [M+H$^+$]: 485.2024, Found: 485.2021.

4-(*tert*-butyl)-*N*-(4-(4-chloroquinolin-2-yl)cyclododecyl)benzenesulfonamide (4l). An inseparable mixture of two diastereomers (10:1) was obtained, white solid (86 mg, 80% yield); mp 186.1-187.5 °C; R_f = 0.7 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 8.4 Hz,5 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.73 (t, *J* = 7.0 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.49 (s, 1H), 7.27-7.25 (m, 2H), 4.51 (d, *J* = 8.2Hz, 1H), 3.58-3.52 (m, 1H), 3.08-3.02 (m, 1H), 1.92-1.84 (m, 1H), 1.80-1.70 (m, 3H), 1.68-1.63 (m, 1H), 1.61-1.51 (m, 1H), 1.46-1.28 (m, 12H), 1.20-1.12 (m, 2H), 1.16 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 156.2, 149.0, 142.4, 138.4, 130.2, 129.7, 126.9, 126.7, 125.9, 125.3, 124.0, 121.6, 50.4, 42.6, 35.0, 31.6, 31.2, 31.1, 30.8, 27.6, 24.3, 23.6, 23.1, 23.0, 22.9, 22.1. HRMS Calcd for $C_{31}H_{42}ClN_2O_2S^+$ [M+H$^+$]: 541.2650, Found: 541.2649.

4-(*tert*-butyl)-*N*-(2-(2-(4-chloroquinolin-2-yl)cyclopentyl)ethyl)benzenesulfonamide (4m). Colorless oil (76 mg, 81% yield); R_f = 0.6 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (t, *J* = 7.8 Hz, 2H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.33 (s, 1H), 7.30-7.26 (m, 2H), 6.19 (br s, 1H), 3.03-2.95 (m, 1H), 2.89-2.83 (m, 1H), 2.76-2.68 (m, 1H), 2.54-2.44 (m, 1H), 2.19-2.11 (m, 1H), 1.95-1.88 (m, 1H), 1.78-1.62 (m, 4H), 1.53-1.45 (m, 1H), 1.34-1.30 (m, 1H), 1.26 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.0, 155.9, 148.3, 143.0, 137.0, 130.9, 129.3, 127.1, 126.8,125.8, 125.2, 124.0, 120.8, 53.3, 41.8, 41.5, 35.1, 34.8, 34.5, 33.1, 31.1, 24.7. HRMS Calcd for $C_{26}H_{32}ClN_2O_2S^+$ [M+H$^+$]: 471.1868, Found: 471.1866.

4-(*tert*-butyl)-*N*-(2-(2-(4-chloroquinolin-2-yl)cyclohexyl)ethyl)benzenesulfonamide (4n). An inseparable mixture of two diastereomers (> 16:1) was obtained. Colorless oil (74 mg, 76% yield); R_f = 0.6 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.83-7.77 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.67-7.60 (m, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.33 (s, 1H), 6.10 (br s, 1H), 2.94-2.89 (m, 2H), 2.57-2.52 (m, 1H), 1.94-1.88 (m, 1H), 1.82-1.68 (m, 4H), 1.36-1.33 (m, 2H), 1.30 (s, 9H), 1.19-0.96 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.6, 156.1, 148.6, 143.3, 136.9, 131.0, 129.4, 127.2, 127.1, 126.0, 125.2, 124.1, 121.4, 51.9, 40.8, 37.1, 35.2, 35.1, 33.4, 32.3, 31.2, 26.4, 26.1. HRMS Calcd for $C_{27}H_{34}ClN_2O_2S^+$ [M+H$^+$]: 485.2024, Found: 485.2024.

4-(*tert*-butyl)-*N*-(2-((2-(4-chloroquinolin-2-yl)cycloheptyl)ethyl)benzenesulfonamide (4o). Yellow oil (62 mg, 62% yield); R_f = 0.6 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.34 (s, 1H), 6.15 (t, *J* = 4.4 Hz, 1H), 2.94-2.89 (m, 2H), 2.75-2.70 (m, 1H), 2.18-2.15 (m, 1H), 1.88-1.82 (m, 1H), 1.76-1.67 (m, 3H), 1.60-1.39 (m, 7H), 1.36-1.33 (m, 1H), 1.30 (s, 9H), 1.27-1.20 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.7, 156.0, 148.0, 143.3, 136.9, 131.1, 129.4, 127.3, 127.0, 126.0, 125.1, 124.0, 121.8, 53.7, 41.1, 38.6, 35.2, 34.9, 34.7, 31.8, 31.2, 29.1, 26.2, 26.1. HRMS Calcd for $C_{28}H_{36}ClN_2O_2S^+$ [M+H$^+$]: 499.2181, Found: 499.2179.

4-(*tert*-butyl)-*N*-((3-(4-chloroquinolin-2-yl)cycloheptyl)methyl)benzenesulfonamide (4p). Two separable diastereomers were obtained. For one isomer **4p'**: colorless oil (39 mg, 40% yield); R_f = 0.6 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.76-7.69 (m, 3H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.29 (s, 1H), 6.68 (br s, 1H), 3.14-3.09 (m, 1H), 3.00-2.94 (m, 1H), 2.79-2.72 (m, 1H), 2.23-2.15 (m, 2H), 1.92-1.90 (m, 1H), 1.82-1.76 (m, 2H), 1.65-1.39 (m, 5H), 1.31-1.23 (m, 1H), 1.23 (s, 9H), 1.20-1.08 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.9, 156.0, 148.4, 143.0, 137.1, 130.9, 129.2, 127.1, 127.0, 126.0, 125.1, 123.9, 120.8, 49.7, 43.2, 35.2, 35.0, 34.6, 34.5, 34.3, 31.2, 29.4, 26.9. HRMS Calcd for $C_{27}H_{34}ClN_2O_2S^+$ [M+H$^+$]: 485.2024, Found: 485.2021. For the another isomer **4p''**: colorless oil (45 mg, 47% yield); R_f = 0.4 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.32 (s, 1H), 5.02 (t, *J* = 6.3 Hz, 1H), 3.00-2.95 (m, 1H), 2.83 (t, *J* = 6.3 Hz, 2H), 2.00-1.92 (m,

2H), 1.80-1.71 (m, 4H), 1.68-1.54 (m, 4H), 1.36-1.32 (m, 1H), 1.29 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.5, 156.4, 148.5, 142.9, 137.0, 130.4, 129.3, 127.0, 126.8, 126.1, 125.2, 124.0, 119.9, 49.8, 48.2, 39.1, 38.4, 35.3, 35.2, 31.8, 31.2, 26.4, 25.2. HRMS Calcd for $C_{27}H_{34}ClN_2O_2S^+$ $[M+H^+]$: 485.2024, Found: 485.2024.

4-(tert-butyl)-*N*-(1-(3-(4-chloroquinolin-2-yl)cyclohexyl)ethyl)benzenesulfonamide (4q). Two separable diastereomers were obtained. For one isomer **4q'**: colorless oil (9 mg, 9% yield); R_f = 0.5 (petroleum ether/ethyl acetate = 4:1); ^1H NMR (400 MHz, $CDCl_3$) 8.17 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.40 (s, 1H), 4.45 (d, *J* = 8.6 Hz, 1H), 3.48 -3.39 (m, 1H), 3.08-3.00 (m, 1H), 2.12-2.02 (m, 1H), 1.88-1.79 (m, 3H), 1.71-1.65 (m, 2H), 1.53-1.44 (m, 2H), 1.40-1.37 (m, 1H), 1.32 (s, 9H), 1.05 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.4, 156.4, 148.7, 142.7, 138.1, 130.3, 129.6, 127.1, 126.9, 126.1, 124.0, 120.1, 51.5, 40.8, 39.6, 32.4, 31.4, 31.2, 31.1, 27.3, 21.2, 19.7. HRMS Calcd for $C_{27}H_{33}ClN_2NaO_2S^+$ $[M+Na^+]$: 507.1843, Found: 507.1843. For the another isomer **4q''**: colorless oil (57 mg, 59% yield); R_f = 0.4 (petroleum ether/ethyl acetate = 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.35 (s, 1H), 4.80 (br s, 1H), 3.29-3.19 (m, 1H), 2.82-2.76 (m, 1H), 1.96-1.88 (m, 2H), 1.79 (t, *J* = 11.1 Hz, 2H), 1.56-1.45 (m, 2H), 1.41-1.30 (m, 3H), 1.23 (s, 9H), 0.99 (d, *J* = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.0, 156.3, 148.7, 142.8, 138.0, 130.3, 129.4, 127.0, 126.8, 126.0, 125.3, 124.0, 119.9, 54.3, 47.0, 43.4, 35.1, 34.7, 32.2, 31.1, 27.8, 25.9, 18.7. HRMS Calcd for $C_{27}H_{34}ClN_2O_2S^+$ $[M+H^+]$: 485.2024, Found: 485.2023.

1-((4-(tert-butyl)phenyl)sulfonyl)-2,2-dimethylpyrrolidine (4r-by product). Colorless oil (47 mg, 53% yield). R_f = 0.7 (petroleum ether/ethyl acetate = 4:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 3.39 (t, *J* = 6.2 Hz, 2H), 1.83-1.77 (m, 4H), 1.45 (s, 6H), 1.33 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.6, 138.8, 127.1, 125.8, 65.2, 49.4, 43.1, 35.2, 31.3, 28.4, 22.6. HRMS Calcd for $C_{16}H_{26}NO_2S^+$ $[M+H^+]$: 296.1679, Found: 296.1677.

4-(*tert*-butyl)-*N*-(4-(4-methylquinolin-2-yl)pentyl)benzenesulfonamide (5). Yellow solid (68 mg, 80% yield); mp 128.1-129.4 °C; R_f = 0.1 (petroleum ether/ethyl acetate = 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.73-7.68 (m, 3H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.09 (s, 1H), 5.50 (d, *J* = 5.4 Hz, 1H), 3.03-2.85 (m, 3H), 2.68 (s, 3H), 1.88-1.79 (m, 1H), 1.69-1.60 (m, 1H), 1.48-1.38 (m, 2H), 1.31 (s, 9H), 1.28 (d, *J* = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.9, 156.5, 152.9, 148.3, 137.0, 129.73, 129.68, 129.1, 127.0, 126.2, 125.6, 125.4, 122.8, 118.5, 43.3, 35.2, 34.1, 33.0, 31.2, 27.7, 25.6, 21.3. HRMS Calcd for $C_{25}H_{33}N_2O_2S^+$ $[M+H^+]$: 425.2257, Found: 425.2253.

4-(*tert*-butyl)-*N*-(4-(4,7-dichloroquinolin-2-yl)pentyl)benzenesulfonamide (6). Yellow oil (62 mg, 65% yield); R_f = 0.6 (petroleum ether/ethyl acetate = 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.9 Hz, 1H), 8.06 (d, *J* = 1.8 Hz, 1H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.54-7.50 (m, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.32 (s, 1H), 5.03 (t, *J* = 5.9 Hz, 1H), 3.00-2.90 (m, 3H), 1.87-1.77 (m, 1H), 1.70-1.61 (m, 1H), 1.52-1.37(m, 2H), 1.31 (s, 9H), 1.28 (d, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.6, 156.4, 149.0, 143.0, 137.0, 136.6, 128.4, 128.0, 127.0, 126.1, 125.5, 123.8, 120.3, 43.2, 42.0, 35.2, 33.5, 31.2, 27.5, 20.8. HRMS Calcd for $C_{24}H_{29}Cl_2N_2O_2S^+$ $[M+H^+]$: 479.1321, Found: 479.1322.

Methyl-2-(1-((4-(*tert*-butyl)phenyl)sulfonamido)undec-10-yn-4-yl)-4-chloro-7-methoxyquinoline-6-carboxylate (7). Yellow oil (88 mg, 72% yield); R_f = 0.2 (petroleum ether/ethyl acetate = 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.64 (s, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.33 (s, 1H), 5.50 (br s, 1H), 4.12 (s, 3H), 4.04 (s, 3H), 3.06-2.84 (m, 3H), 2.20-2.17 (m, 2H), 1.98-1.94 (m, 1H), 1.90-1.65 (m, 5H), 1.53-1.47 (m, 4H), 1.45-1.38 (m, 14H). 1.38 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.0, 166.1, 159.8, 156.3, 151.3, 143.8, 136.9, 128.6, 127.0, 126.1, 122.8, 119.2, 119.1, 108.8, 84.6, 68.4, 56.7, 52.7, 47.9, 43.2, 35.7, 35.2, 32.2, 31.2, 28.8, 28.3, 27.2, 27.1, 18.4. HRMS Calcd for $C_{33}H_{42}ClN_2O_5S^+$ $[M+H^+]$: 613.2497, Found: 613.2492.

***N*-(2-(2-(4-((4-benzoyl-1,4-diazepan-1-yl)sulfonyl)isoquinolin-1-yl)cyclohexyl)ethyl)-4-(*tert*-butyl)benzenesulfonamide (8)**. Yellow solid (128 mg, 89% yield). mp 113.9-115.2 °C; R_f = 0.2 (petroleum ether/Acetone = 10:1). ^1H NMR (400 MHz, CD_3OD) δ 8.67 (t, *J* = 8.6 Hz, 1H), 8.59-8.54 (m, 1H), 8.43-8.36 (m, 1H), 8.31 (t, *J* = 6.3 Hz, 1H), 7.81-7.73 (m, 1H), 7.53-7.48 (m, 4H), 7.44-7.38 (m, 4H), 7.27 (d, *J* = 7.7 Hz, 1H), 3.83-3.79 (d, *J* = 4.4 Hz, 2H), 3.66-3.63 (m, 1H), 3.60-3.56 (m, 1H), 3.53-3.43 (m, 4H), 2.69-2.62 (m, 1H), 2.57-2.50 (m, 1H), 2.09-2.03 (m, 2H), 1.88-1.70 (m, 5H), 1.61-1.40 (m, 2H), 1.41-1.35 (m, 1H), 1.31 (s, 9H), 1.21- 1.15 (m, 1H), 1.11-1.06 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.0, 173.8, 167.6, 167.5, 157.2, 144.3, 138.6, 137.3, 136.4, 134.1, 133.6, 133.5, 131.9, 131.8, 130.8, 129.7, 129.3, 127.8, 127.4, 127.3, 127.1, 117.1, 101.3, 52.3, 50.4, 50.0, 48.0, 47.4, 47.3, 46.0, 42.0, 39.7, 39.6, 35.9, 35.7, 35.5, 33.0, 31.5, 31.2, 29.2, 27.4, 27.2. HRMS Calcd for $C_{39}H_{49}N_4O_5S_2^+$ $[M+H^+]$: 717.3139, Found: 717.3134.

Methyl-1-(3-(((4-(*tert-butyl*)phenyl)sulfonamido)methyl)cycloheptyl)isoquinoline-3-carboxylate (9). Two separable diastereomers were obtained. For one isomer **9'**: yellow oil (43 mg, 42% yield); R_f = 0.7 (petroleum ether/ethyl acetate = 3:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 7.94-7.87 (m, 3H), 7.74-7.67 (m, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 6.7 Hz, 1H), 4.10 (s, 3H), 3.98-3.92 (m, 1H), 2.94-2.89 (m, 2H), 2.63-2.55 (m, 2H), 2.34-2.26(m, 1H), 1.93-1.80 (m, 2H), 1.71-1.64 (m, 2H), 1.62-1.52 (m, 1H), 1.46-1.37 (m, 1H), 1.34-1.32 (m, 2H), 1.29 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.9, 167.1, 155.5, 140.0, 137.8, 136.0, 130.5, 129.5, 129.1, 127.6, 127.2, 125.7, 125.2, 122.6, 53.0, 50.1, 39.0, 36.7, 35.6, 35.1, 35.0, 34.9, 31.2, 30.7, 26.4. HRMS Calcd for $C_{29}H_{37}N_2O_4S^+$ $[M+H^+]$: 509.2469, Found: 509.2465. For the another isomer **9''**: yellow oil (53 mg, 52% yield); R_f = 0.5 (petroleum ether/ethyl acetate = 3:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.20-8.17 (m, 1H), 7.94-7.91 (m, 1H), 7.75-7.67 (m, 4H), 7.45 (d, *J* = 8.6 Hz, 2H), 4.94 (br s, 1H), 3.99 (s, 3H), 3.73-3.67 (m, 1H), 2.89-2.78 (m, 2H), 2.05-1.61 (m, 11H), 1.30

(s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.9, 166.8, 156.3, 140.4, 137.0, 136.2, 130.4, 129.4, 129.2, 127.4, 127.0, 126.1, 125.0, 122.7, 52.7, 49.8, 39.7, 37.6, 35.2, 34.9, 31.9, 31.2, 26.5, 25.4. HRMS Calcd for $C_{29}H_{37}N_2O_4S^+$ $[M+H^+]$: 509.2469, Found: 509.2466.

4-(*tert*-butyl)-*N*-(4-(4-(*tert*-butyl)pyridin-2-yl)pentyl)benzenesulfonamide(10). Yellow oil (22 mg, 26% yield); R_f = 0.2 (petroleum ether/ethyl acetate = 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 5.3 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.11-7.09 (m, 1H), 7.06 (d, *J* = 1.2 Hz, 1H), 4.98 (t, *J* = 5.4 Hz, 1H), 2.95-2.86 (m, 2H), 2.83-2.74 (m, 1H), 1.76-1.67 (m, 1H), 1.60–1.41 (m, 3H), 1.33 (s, 9H), 1.29 (s, 9H), 1.21 (d, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.4, 160.9, 156.3, 148.9, 137.0, 127.0, 126.1, 118.7, 43.4, 41.4, 35.2, 34.8, 33.9, 31.2, 30.7, 27.6, 21.2. HRMS Calcd for $C_{24}H_{37}N_2O_2S^+$ $[M+H^+]$: 417.2570, Found: 417.2572.

***N*-(4-(7-bromoisoquinolin-1-yl)pentyl)-4-(*tert*-butyl)benzenesulfonamide (11)**. Colorless oil (56 mg, 57% yield); R_f = 0.3 (petroleum ether/ ethyl acetate = 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.6 Hz, 1H), 8.30 (s, 1H), 7.75-7.69 (m, 4H), 7.48-7.46 (m, 3H), 4.87 (br s, 1H), 3.66-3.58 (m, 2H), 2.98-2.85 (m, 2H), 2.08-1.98 (m, 1H), 1.75-1.66 (m, 1H), 1.58-1.47 (m, 1H), 1.38 (s, 1H),1.32 (s, 9H), 1.30 (d, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.1, 156.4, 142.4, 135.0, 133.4, 129.5, 127.9, 127.11, 127.06, 126.1, 121.2, 119.0, 43.4, 36.1, 35.2, 32.5, 31.2, 27.7, 21.6.HRMS Calcd for $C_{24}H_{30}BrN_2O_2S^+$ $[M+H^+]$: 489.1206, Found: 489.1209.

***N*-(4-(benzo[d]thiazol-2-yl)pentyl)-4-(*tert*-butyl)benzenesulfonamide (12)**. Yellow solid (38 mg, 46% yield); mp 118.3-119.6 °C; R_f = 0.2 (petroleum ether/ ethyl acetate = 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.48-7.44 (m, 3H), 7.38-7.34 (m, 1H), 4.77 (t, *J* = 6.0 Hz, 1H), 3.27-3.18 (m, 1H), 3.04-2.92 (m, 2H), 1.91-1.82 (m, 1H), 1.80-1.71 (m, 1H), 1.58-1.46 (m, 2H), 1.40 (d, *J* = 7.0 Hz, 3H), 1.32 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl3) δ 177.1, 156.5, 153.0, 137.0, 134.7, 127.0, 126.18, 126.16, 125.0, 122.9, 121.7, 43.2, 39.0, 35.3, 34.1, 31.2, 27.3, 21.6. HRMS Calcd for $C_{22}H_{29}N_2O_2S_2^+$ $[M+H^+]$: 417.1665, Found: 417.1660.

4-(*tert*-butyl)-*N*-(4-(3-methylquinoxalin-2-yl)pentyl)benzenesulfonamide (13). Yellow solid (38 mg, 45% yield); mp 107.8-109.0 °C; R_f = 0.1 (petroleum ether/ethyl acetate = 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.05-8.02 (m, 1H), 7.98-7.94 (m, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.68-7.65 (m, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 4.71 (t, *J* = 5.9 Hz, 1H), 3.26-3.17 (m, 1H), 3.00-2.87 (m, 2H), 2.73 (s, 3H), 2.09-2.00 (m, 1H), 1.71-1.62 (m, 1H), 1.58-1.51 (m, 1H), 1.38-1.34 (m, 1H), 1.31 (s, 9H), 1.26 (d, *J* = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.8, 156.4, 153.0, 141.3, 140.9, 137.0, 129.1, 129.0, 128.8, 128.4, 127.0, 126.1, 43.3, 37.2, 35.2, 32.0, 31.2, 27.7, 22.9, 20.5. HRMS Calcd for $C_{24}H_{32}N_3O_2S^+$ $[M+H^+]$: 426.2210, Found: 426.2210.

4-(*tert*-butyl)-*N*-(4-(phenanthridin-6-yl)pentyl)benzenesulfonamide (14). Yellow oil (77 mg, 84% yield); R_f = 0.4 (petroleum ether/ ethyl acetate = 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 8.2 Hz, 1H), 8.55 (d, *J* = 7.9 Hz, 1H), 8.26-8.20 (m, 2H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.75 (t, *J* =8.1 Hz, 1H), 7.70-7.62 (m, 4H), 7.37 (d, *J* = 8.5 Hz, 2H), 5.06 (t, *J* = 5.7 Hz, 1H), 3.81-3.73 (m,1H), 3.01-2.94 (m, 1H), 2.91-2.84 (m, 1H), 2.33-2.24 (m, 1H), 1.77-1.68 (m, 1H), 1.64-1.56(m, 1H), 1.47-1.40 (m, 1H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.28 (s, 9H).$^{13}C\{^1H\}$ NMR δ 164.6, 156.2, 143.7, 137.1, 133.3, 130.4, 130.0, 128.9, 127.4, 127.0, 126.6, 126.0, 125.6, 125.1, 123.5, 122.8, 122.0, 43.3, 36.5, 35.1, 31.6, 31.2, 27.7, 21.6. HRMS Calcd for $C_{28}H_{33}N_2O_2S^+$ $[M+H^+]$: 461.2257, Found: 461.2252.

4-(*tert*-butyl)-*N*-(4-(4-chloroquinolin-2-yl)-3-methylbutyl)benzenesulfonamide (15). Yellow oil (43 mg, 48% yield); R_f = 0.2 (petroleum ether/ethyl acetate = 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.7 Hz, 2H), 7.80-7.76 (m, 3H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.33 (s, 1H), 6.21 (br s, 1H), 3.11-2.98 (m, 2H), 2.85-2.75 (m, 2H), 2.25-2.15 (m, 1H), 1.51-1.45 (m, 2H), 1.31 (s, 9H), 0.90 (d, *J* = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.1, 156.2, 148.5, 143.1, 137.1, 130.9, 129.2, 127.2, 126.1, 125.1, 124.1, 112.3, 44.6, 41.0, 35.2, 31.2, 31.0, 20.2. HRMS Calcd for $C_{24}H_{30}ClN_2O_2S^+$ $[M+H^+]$: 445.1711, Found: 445.1710.

4-(*tert*-butyl)-*N*-(3-methyl-4-(2-methylquinolin-4-yl)butyl)benzenesulfonamide (16). Yellow oil (44 mg, 52% yield); R_f = 0.2 (petroleum ether/ethyl acetate = 3:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.64 (t, *J* = 8.2 Hz, 1H), 7.49-7.45 (m, 3H), 7.04 (s, 1H), 4.66 (br s, 1H), 3.14-3.06 (m, 1H), 3.01-2.93 (m, 2H), 2.76-2.71 (m, 1H), 2.66 (s, 3H), 2.04-1.96 (m, 1H), 1.65-1.56 (m, 1H), 1.47-1.38 (m, 1H), 1.31 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.5, 156.6, 148.3, 146.6, 136.7, 129.5, 129.2, 127.0, 126.2, 126.1, 125.7, 123.6, 123.0, 41.3, 39.7, 36.8, 35.2, 31.4, 31.2, 25.4, 19.6. HRMS Calcd for $C_{25}H_{33}N_2O_2S^+$ $[M+H^+]$: 425.2257, Found: 425.2254.

4-(*tert*-butyl)-*N*-(4-(phthalazin-1-yl)butyl)benzenesulfonamide (17). Yellow oil (35 mg, 44% yield); R_f = 0.1 (petroleum ether/acetone = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.95-7.86 (m, 3H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 5.34 (t, *J* = 6.1 Hz, 1H), 3.33 (t, *J* = 7.6 Hz, 2H), 3.07-3.01 (m, 2H), 2.00-1.92 (m, 2H), 1.73-1.66 (m, 2H), 1.31 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.3, 150.6 137.0, 132.8, 132.3, 127.2, 127.01, 126.98, 126.6, 126.2, 125.7, 124.1, 43.0, 35.2, 32.3, 31.2, 29.4, 25.8. HRMS Calcd for $C_{22}H_{28}N_3O_2S^+$ $[M+H^+]$: 398.1897, Found: 398.1895.

4-(*tert*-butyl)-*N*-(4-(isoquinolin-1-yl)butyl)benzenesulfonamide (18); Yellow oil (38 mg, 48% yield); R_f = 0.3 (petroleum ether/ethyl acetate = 3:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 5.7 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.80-7.76 (m, 3H), 7.65 (t, *J* =7.5 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.49-7.45 (m, 3H), 5.88 (s, 1H), 3.24 (t, *J* = 7.5 Hz, 2H), 3.04-2.99 (m, 2H), 1.91-1.84 (m, 2H), 1.66-1.59 (m, 2H), 1.30 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.2, 156.2, 141.5, 137.0, 136.3, 130.1, 127.5, 127.3, 127.0, 126.1, 125.2, 119.6, 43.1, 35.1, 34.0, 31.2, 29.1, 25.9. HRMS Calcd for $C_{23}H_{29}N_2O_2S^+$ $[M+H^+]$: 397.1944, Found: 397.1940.

4-(*tert*-butyl)-*N*-(4-(4-(trifluoromethyl)pyridin-2-yl)butyl)benzenesulfonamide (19). Yellow oil (31 mg, 37% yield); R_f = 0.2 (petroleum ether/ ethyl acetate = 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 5.1 Hz, 1H), 7.77 (d, *J* = 8.6 Hz, 2H),

7.50 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 4.9 Hz, 2H), 4.77 (t, *J* = 6.1 Hz, 1H), 3.02-2.97 (M, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 1.81-1.74 (m, 2H), 1.60-1.53 (m, 2H), 1.33 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.2, 156.5, 150.3, 139.0(s), 138.8 (q, *J* = 33.7 Hz), 136.9, 127.0, 126.2, 126.2, 123.0 (q, *J* = 273.2 Hz), 118.6 (q, *J* = 3.7 Hz), 117.0 (q, *J* = 6.9, 3.3 Hz), 43.1, 37.5, 35.3, 31.2, 29.2, 26.4. HRMS Calcd for $C_{20}H_{26}F_3N_2O_2S^+$ $[M+H^+]$: 415.1662, Found: 415.1658.

Removal of 4-*tert*-phenylsulfonyl protecting group. A mixture of compound **5** (84.8 mg, 0.2 mmol, 1.0 equiv), phenol (56.4 mg, 0.2 mmol, 1.0 equiv) and HBr (1.0 mL, 48%) was heated to 130 °C for 18 hours in a sealed tube (using heating block). After being cooled to room temperature, the reaction solution was diluted with iced water, then adjusted to pH = 8~9 with K_2CO_3. The resulting mixture was extracted with EtOAc (5 mL x 3). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (DCM:MeOH = 5:1) to give compounds **20** in 90% yield (41 mg) as yellow oil.[16] R_f = 0.3 (Dichloromethane/Methanol = 20:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.12 (s, 1H), 3.05-2.99 (m, 1H), 2.67-2.64 (m, 5H), 1.92 (s, 2H), 1.87-1.79 (m, 1H), 1.73-1.64 (m, 1H), 1.55-1.44 (m, 1H), 1.36-1.30 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.5, 147.7, 144.5, 129.6, 129.1, 127.1, 125.6, 123.7, 120.3, 42.8, 42.2, 34.2, 31.7, 21.0, 19.0. HRMS Calcd for $C_{15}H_{21}N_2^+$ $[M+H^+]$: 229.1699, Found: 229.1697.

ASSOCIATED CONTENT

Supporting Information

Details for mechanistic investigation, copies of the ^1H and ^{13}C NMR spectra, and X-ray structural analysis data of **4l** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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