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FULL-LENGTH PAPER

Exploring a sulfone linker utilizing trimethyl aluminum as a cleavage reagent: solid-phase synthesis of sulfonamides and ureas

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Abstract A novel and efficient cleavage reagent, trimethyl aluminum, for traceless sulfinate-functionalized resin has been developed. The synthesis of sulfonamide and urea derivatives via a traceless solid-phase sulfone linker strategy through six synthetic steps comprising utilization of trimethyl aluminum as a novel cleavage reagent was also established. An insight of the plausible mechanism of the cleavage reaction was discussed.

Keywords Trimethyl aluminum · Traceless · Solid-phase synthesis · Sulfone linker · Sulfinate-functionalized resin · Sulfonamides · Ureas

Introduction

Since the introduction of the concept of solid-phase peptide synthesis in the late 1950s [1], solid-phase synthesis of small organic molecules has emerged as an important tool in modern chemical biology and medicinal chemistry research [2,3]. The use of solid support can avoid extensive workup, recrystallization, and chromatographic purification of the product. It also allows for easy automation of the synthesis process and convenient handling of polar molecules throughout the synthesis. One of the key challenges in solid-phase synthesis involves immobilizing the substrates (or reagents) onto the solid support, thus driving the demand for the development of new and innovative linkers [4–6]. The ideal linker should allow easy attachment of the starting material to the support, be stable against a planned set of reaction conditions and enable selective cleavage at the end of the synthesis without causing damage to the product [7,8]. The presence of these appendages is acceptable if the final products comprise these functional groups of linker; however, complications may arise if these vestigial functionalities are redundant and affect the activities of the compounds.

Sodium benzenesulfinate has been widely used in the preparation of sulfone, which plays an important role in organic synthesis [9]. Nevertheless, the application of sulfinate-functionalized resin in solid-phase synthesis has received relatively less attention. Previous reports from other laboratories [10–12] have demonstrated the use of sulfinate-functionalized resin as a solid support for solid-phase organic synthesis (SPOS). It has been shown that the resulting sulfone linker derived from sulfinate-functionalized resin to be a versatile and robust tether that offers various on-resin functionalization or cleavage without additional changes. Several cleavage strategies including Swern oxidation [10] (Scheme 1a), oxidation-elimination [13] (Scheme 1b), elimination-cyclization [12] (Scheme 1c) have been established to liberate the target molecules from the sulfinate-functionalized resin. However, relatively little endeavors have been spent on the development of novel cleavage strategies for sulfinate-functionalized resin. In these regards, our goal is to develop

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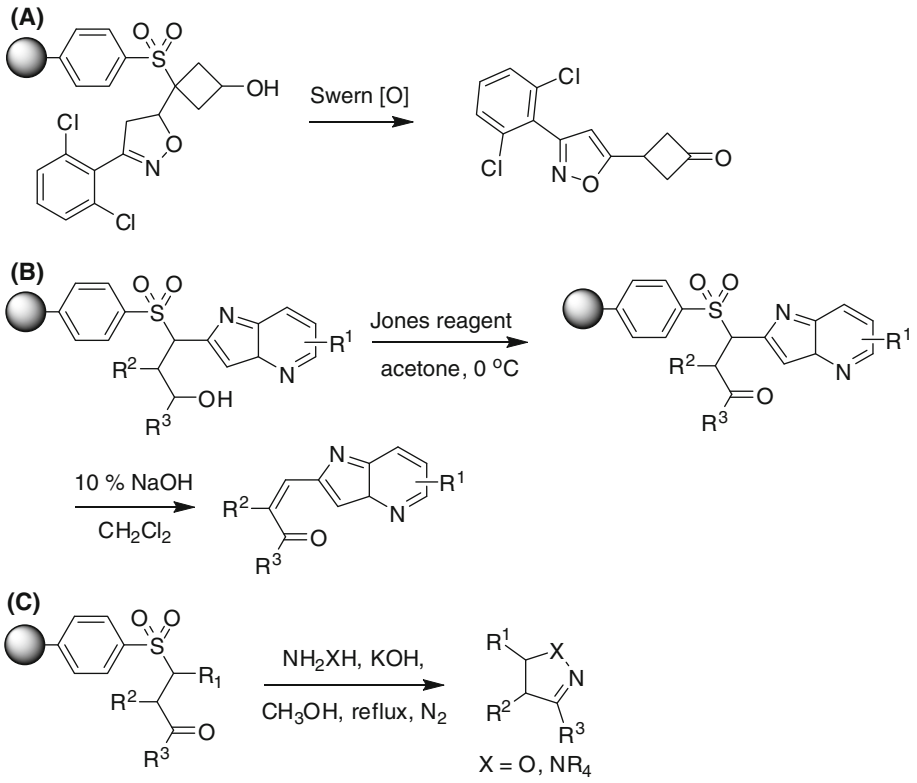
Scheme 1 Cleavage strategies for sulfinate-functionalized resin



sulfone linker for SPOS and to explore sulfone-based chemical transformations and novel cleavage strategy.

Compounds containing the urea or sulfonamide functionalities have diverse activities [14–18] such as soluble epoxide hydrolase inhibitors [19,20], carbonic anhydrase IX inhibitor [21], selective aggrecanase inhibitors [22], *c*-Met kinase inhibitors [23], and tyrosine kinase-3 (FLT3) inhibitors [24] (Fig. 1). Many solution-phase synthetic methods are available for the preparation of ureas [25–27] and sulfonamides [28–30]; however, to the best of our knowledge, there are few reports on the solid-phase synthesis of these compounds [31–33]. Herein, we describe the utilization of trimethyl aluminum as a novel cleavage reagent for sulfone linker toward the synthesis of sulfonamides and urea derivatives.

Results and discussion

Previous reports [10–13] have detailed the use of a sulfinate-functionalized resin (styrene/divinyl benzene copolymer beads) as the starting point for their synthetic strategies. The sulfone linker derived from this sulfinate resin provides tether that is robust to various chemical transformations and is "traceless" when cleaved under appropriate conditions. Herein, we report the sulfinate-functionalized resin-based chemistry to the synthesis of sulfonamides and ureas as well as novel cleavage strategy for sulfone linker.

Solution-phase synthesis of ureas and sulfonamides

Prior to the solid-phase synthesis approach, preliminary solution-phase studies were carried out to survey the requisite reaction conditions and establish the modifications for SPOS. To begin our investigation, 1-(2-phenyl-1-(phenylsulfonyl)ethyl)-4-vinylbenzene **4** was prepared by treating sodium benzenesulfinate **1** with 1-(chloromethyl)-4-vinyl benzene in the presence of NaI under refluxing methanol for 18 h to give 1-(phenylsulfonylmethyl)-4-vinylbenzene **2** in 92 % yield (Scheme 2). Subsequent alkylation of **2** with benzyl bromide and dimsyl anion provided 1-(2-phenyl-1-(phenylsulfonyl)-ethyl)-4-vinylbenzene **3** in moderate yield (50 %) [34]. The moderate yield is due to the presence of accompanying dialkylation byproduct. Attempts to α-alkylate 1-(phenylsulfonylmethyl)-4-vinylbenzene **2** with $n-$BuLi in THF resulted only in decomposition. Oxidative cleavage of the vinyl group of **3** with ozone gave **4** in good yield (80 %). Reductive amination of benzaldehyde **4** with *n*-hexylamine was achieved by magnesium sulfate in THF and sodium borohydride. The sulfonamide **6** was accessed by treatment of secondary amine **5** with *p*-toluenesulfonyl chloride in the presence of triethylamine in 72 % isolated yield. The viability of the cleavage reaction was first attempted by a reaction of

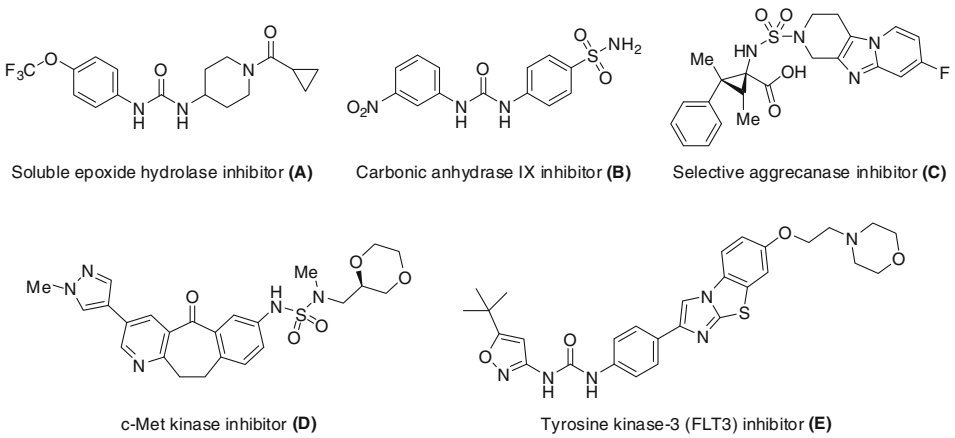


Fig. 1 Sulfonamide or urea-containing biological relevant heterocyclic system

benzenesulfonamide **6** with phenyl magnesiumbromide/zinc chloride [35]. However, no reaction took place in tetrahydrofuran at room temperature. Using samarium (II) iodide [36] as the cleavage reagent in tetrahydrofuran also did not provide the target product. However, employment of the lithium naphthalenide [37] as cleavage reagent led to considerable enhancement of the reaction yields (Scheme 3).

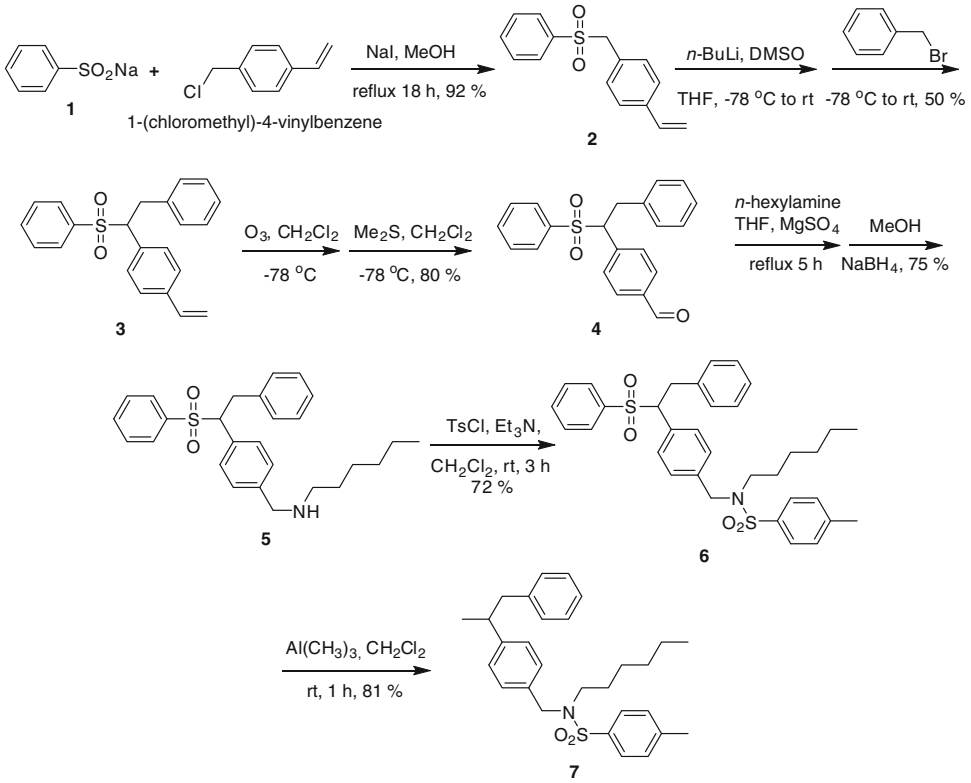
Trimethyl aluminum is a versatile reagent encountered in numerous organic transformations [38–40]. It usually acts as a nonreactive methyl donor or Lewis acid and has good functional group tolerance in various organic reactions. Trimethyl aluminum has been employed in the conversion of heteroaromatic esters to methyl ketones [41], stereoselective methyl transfer to aldehydes [42], synthesis of polysubstituted aluminoisoxazoles and pyrazoles [43], new Mannich-type reaction of hydrazones [44], and aluminum-mediated C-glycoside synthesis [45]. Padwa et al. [46] have demonstrated the introduction of a methyl substituent on the carbon atom adjacent to the sulfone by trimethylaluminum in the total synthesis of (±)-desoxyeseroline. Following the precedent success of Padwa, trimethyl aluminum was ultimately selected as an optimum cleavage reagent for this sulfone linker. The use of trimethyl aluminum in toluene was found to provide the best results in terms of reaction rate and yield (81 %). It is noteworthy that the cleavage reaction with trimethyl aluminum did not cleave the sulfonamide bond of the targeted molecules. Plausible steps involved in the trimethyl aluminum-mediated cleavage of sulfone linker are depicted in Scheme 4. Initially, the sulfone is expected to be activated by the trimethyl aluminum. The lone pair on the oxygen donated to trimethyl aluminum to form an activated zwitter ionic complex **A**, which spontaneously converted to **B** through electron transfer. Subsequent methyl addition and expulsion of the sulfone–aluminum complex furnished the targeted product **7** (Scheme 4).

Solid-phase 1-(1-phenylpropan-2-yl)-4-vinylbenzene synthesis

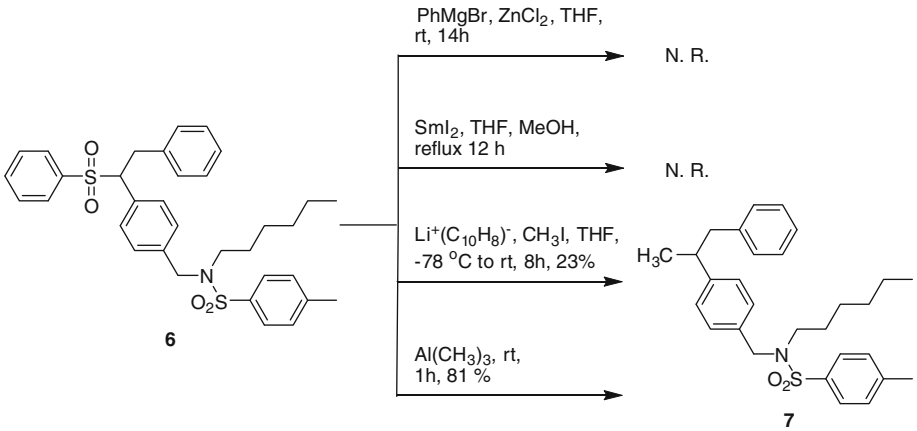
With a successful solution-phase route to sulfonamide **7** in hand, we turned to the development of a viable solid-phase protocol and began with the preparation of polymer bound benzenesulfinate **8** (Scheme 5) [11]. Polystyrene/1 % divinylbenzene sodium sulfinate (**8**, 100–200 mesh) in NaI/DMF was allowed to react with 1-(chloromethyl)-4-vinylbenzene at 80 °C (Scheme 5). The aim of employment of DMF/methanol as cosolvent is to swell the polymer support whereas methanol was used in solution phase synthesis. The formation of **9** was amenable to KBr FTIR monitoring (i.e., appearance of the sulfone stretch at 1316, 1151 cm^{-1}). Treatment of **9** with dimsyl anion [35] at −78 °C followed by addition of 4-(bromomethyl)benzonitrile gave resin **10**, which could be reliably analyzed with FTIR for the appearance of a new cyano stretch (υ_{max} 2,133 cm^{-1}). At this stage, sulfinate-functionalized resin **10** was cleaved for our solid-phase studies because the feasibility of this proposed synthetic route up to now can be confirmed and the optimized cleavage reagent can be verified on the solid support. Hence, we proceeded to cleave resin **10** with trimethyl aluminum which gave 1-(1-phenylpropan-2-yl)-4-vinylbenzene **11** in good yield (34 %, Scheme 5).

With the providential cleavage strategy to access the vinylbenzene **11** established, we proceeded to develop the solid-phase route to the targeted compounds. Treatment of **10** with ozone in dichloromethane afforded the benzaldehyde resin **12**. This transformation was monitored by FTIR for the appearance of a new aldehyde stretch (υ_{max} 1,700 and 2,840 cm^{-1}). Reductive amination of resinous sulfinate **12** with primary amines and sodium borohydride generated secondary benzylamines **13**. This transformation was monitored by FTIR for the disappearance of the bezaldehyde stretch

Scheme 2 Solution-phase study



Scheme 3 Optimization of the cleavage reagents

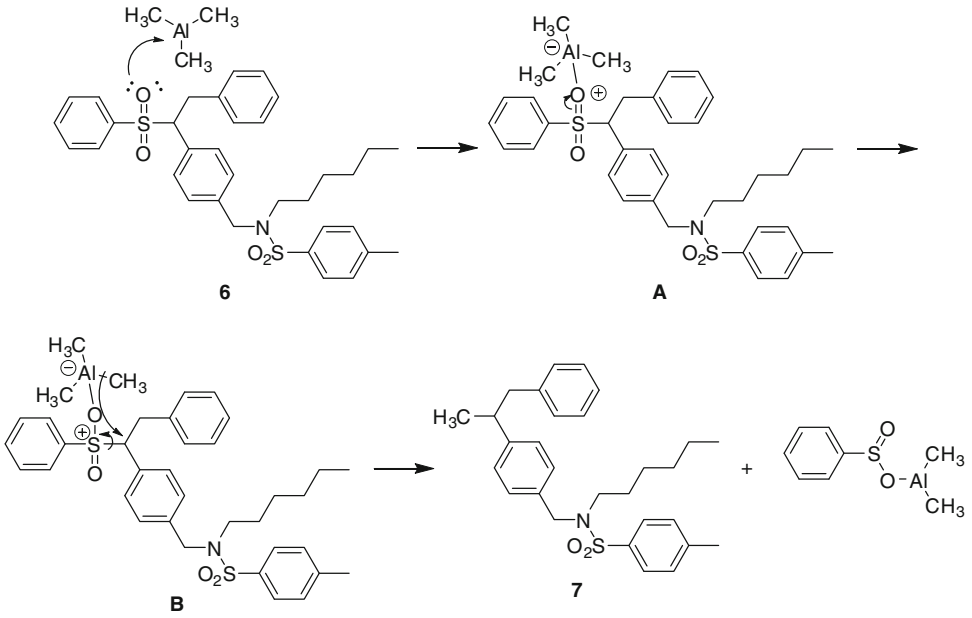


(υ_{max} 1,700 cm^{-1} and 2,840 cm^{-1}). Subsequent treatment of resin **13** with sulfonyl chlorides and isocyanates in Et_3N/CH_2Cl_2 gave sulfonamide **14** and urea **15**, respectively. Since this transformation delivered no reliably diagnostic absorption signals in the IR spectrum, the subsequent release step was undertaken with some trepidation. Fortunately, cleavage of resin **14** and **15** by trimethyl aluminum successfully provided the sulfonamide**16** and urea **17** in 11–15 % overall yields from starting resin **8**, indicating an average yield of greater than 70 % for each step of the six solid-phase reactions. To illustrate the versatility of this methodology, a representative set of compounds (**16** and **17**) was prepared (see Scheme 6; Table 1).

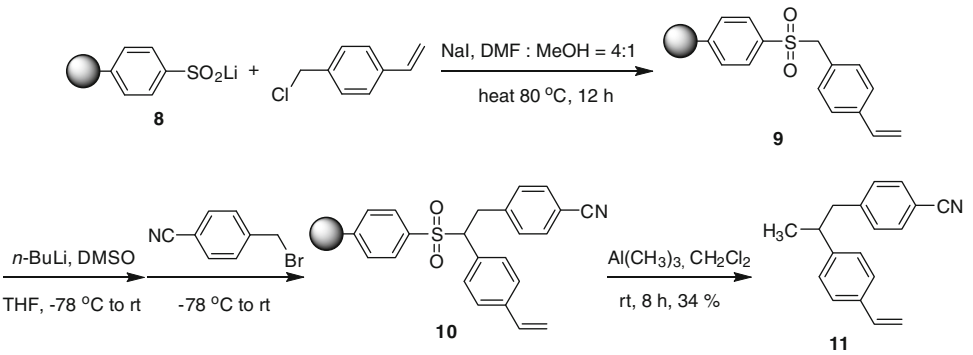
Conclusions

In conclusion, trimethyl aluminum was found to be a novel and efficient cleavage reagent for sulfinate-functionalized resin. Our experimental results suggest that the sulfone linker is stable and robust under various reaction conditions and can efficiently deliver the targeted products by this novel cleavage strategy. The cleavage reagent was further extended to

Scheme 4 Plausible mechanism for cleavage of sulfone linker by trimethyl aluminum



Scheme 5 Preliminary study of cleavage strategy and solid-phase organic synthesis of **11**



the synthesis of sulfonamides and ureas with diverse functionalities. This novel cleavage strategy provides an efficient entry to the sulfonamides and urea derivatives under mild conditions and is compatible with a wide range of substrate. The remarkable features of the present novel cleavage reagent are its practical simplicity and broad scope of applicability, which makes it useful in organic synthesis.

Experimental section

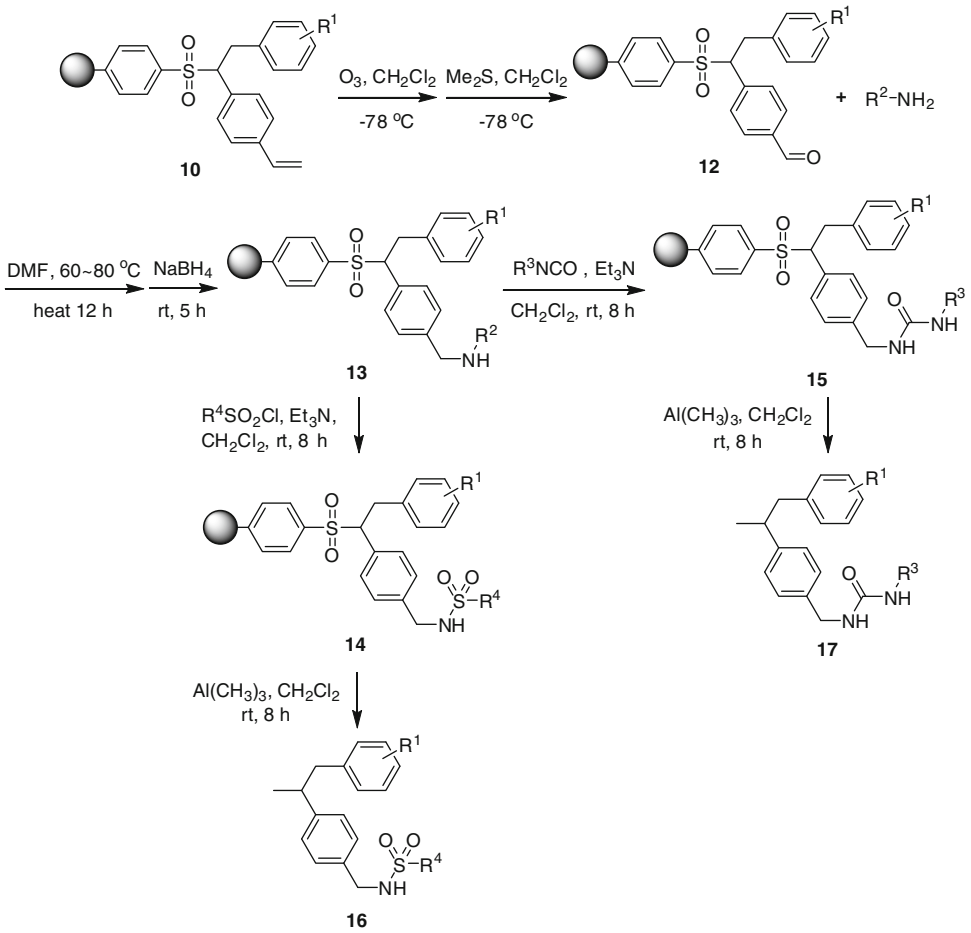
Solution-phase synthesis of 1-benzenesulfonylmethyl-4-vinylbenzene (**2**)

To a solution of benzenesulfinic acid sodium salt (1.81 g, 11.0 mmol) in methanol (15 mL), 4-vinyl benzylchloride (1.53 g, 10.0 mmol) and NaI (catalyst) were added. The reaction mixture was refluxed at 60 − 80 °C for 18 h. Then a saturated aq. $Na_2S_2O_3$ solution was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was washed with H_2O, brine, and then dried over $MgSO_4$. The crude product was crystallized from CH_2Cl_2 and hexane (v/v= 1/1) to yield compound **2** (2.61 g, 92 %) as a white solid: mp 133−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.27 (m, 7H), 7.04 (d, 8.2 Hz, 2H), 6.68 (dd, J = 10.9 Hz, 17.6 Hz, 1H), 5.75 (dd, J = 17.6 Hz, 0.7 Hz, 1H), 5.28 (dd, J = 10.9 Hz, 0.7 Hz, 1H), 4.30 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0 (C), 137.8 (C), 136.0 (CH), 133.7 (CH), 130.9 (CH), 128.9 (CH), 128.6 (CH), 127.4 (C), 126.3 (CH), 114.8 (CH_2), 62.6 (CH_2); IR (KBr): 1230, 1144 cm^{-1}; HRMS-EI (M^+) calcd for $C_{15}H_{14}O_2S$ 258.0715, found 258.0712.

Solution-phase synthesis of 1-(1-benzenesulfonyl-2-phenyl-ethyl)-4-vinyl-benzene (**3**)

n-BuLi (2.5 M in hexane, 8.50 mL) was added to a dry mixture of DMSO (2.75 g, 35.3 mmol) in THF (150 mL) at

Scheme 6 Solid-phase organic synthesis of sulfonamide **16** and urea **17**

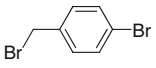
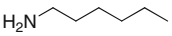
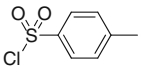
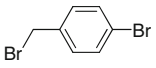
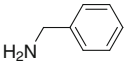
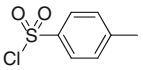
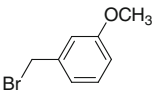
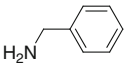
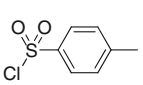
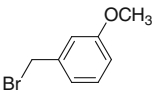
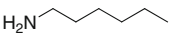
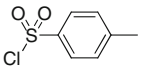
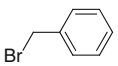
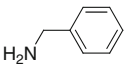
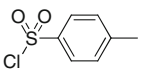
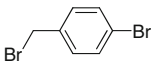
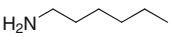
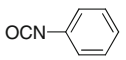
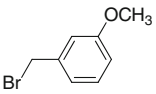
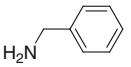
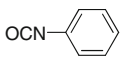
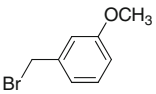
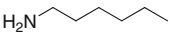
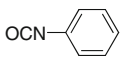
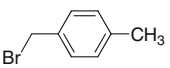
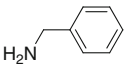
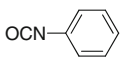
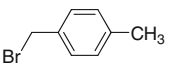
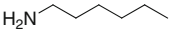
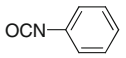
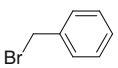
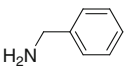
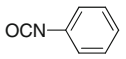


−78 °C under nitrogen. The reaction mixture was warmed to room temperature and stirred for 1 h. To this mixture a solution of **2** (1.82 g, 7.05 mmol) in THF was added at −78 °C, the reaction mixture was allowed to warm to room temperature and allowed to react for 1 h. The mixture was cooled to −78 °C, a solution of benzyl bromide (1.33 g, 7.76 mmol) in THF (20 mL) was added, the reaction mixture was allowed to warm to room temperature, and it was further stirred for 1 h. After completion of the reaction, water was added to quench the reaction, the aqueous layer was extracted with CH_2Cl_2, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$. The crude product was purified by column chromatography using hexane/AcOEt (v/v= 4/1) as eluent to give **3** (0.82 g, 50 %) as a white solid: mp 105–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63–6.97 (m, 14H), 6.63 (dd, J = 10.9 Hz, 17.6 Hz, 1H), 5.71 (dd, J = 17.6 Hz, 0.7 Hz, 1H), 5.25 (dd, J = 10.9 Hz, 0.7 Hz, 1H), 4.30 (dd, J = 3.2 Hz, 11.7 Hz, 1H), 3.83 (dd, J = 3.2 Hz, 13.8 Hz, 1H), 3.41 (dd, J = 13.8 Hz, 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8 (C), 137.2 (C), 136.7 (C), 136.0 (CH), 133.5 (CH), 131.0 (C), 130.2 (CH), 128.9 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 126.6 (CH), 126.1 (CH), 114.6 (CH_2), 72.7 (CH), 33.6 (CH_2); IR (KBr): 1447, 1306, 1145, 1084, 610 cm^{-1}; HRMS-EI (M^+) calcd for $C_{22}H_{20}O_2S$ 348.1184, found 348.1193.

Solution-phase synthesis of 4-(1-benzenesulfonyl-2-phenyl-ethyl)-benzaldehyde (**4**)

A solution of **3** (0.82 g, 23.6 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C, and ozone was bubble through it at −78 °C until the solution turned light blue. After ozonolysis completion, the solution was added excess Me_2S at −78 °C. Then, the reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated, and the crude product was purified by column chromatography to give compound **4** (0.62 g, 75 %) as a white solid: mp 111 − 113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.70–6.93 (m, 14H), 4.40 (dd, J = 3.2 Hz, 11.8 Hz, 1H), 3.85 (dd, J = 3.2 Hz, 13.9 Hz, 1H), 3.42 (dd, J = 13.9 Hz, 11.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5 (CH), 138.5 (C), 136.9 (C), 136.2 (C), 136.0 (C), 133.9 (CH), 130.6 (CH), 129.4 (CH), 128.9 (CH), 128.8 (CH), 128.8 (CH), 128.5 (CH), 126.8 (CH), 72.7 (CH), 33.8 (CH_2); IR (KBr): 1680, 1302, 1139, 523 cm^{-1}; HRMS-EI (M^+) calcd for $C_{21}H_{18}O_3S$ 348.1184, found 348.1193.

Table 1 Reaction substrate scope of solid-phase synthesis of sulfonamides and ureas

Entry	Benzyl Bromide	R^2NH2	R^3NCO or R^4SO_2Cl	LRMS	isolate yield (%)[a]
16a				541	14
16c				547	13
16d				499	12
16f				493	15
16j				469	14
17b				506	11
17e				464	11
17g				458	15
17h				448	12
17i				442	11
17k				434	13

[a] Yields were determined on weight of purified samples through six synthetic steps on the support.

Solution-phase synthesis of [4-(1-benzenesulfonyl-2-phenyl-ethyl)-benzyl]-hexylamine (**5**)

To a solution of compound **4** (0.62 g, 17.7 mmol) in THF (25 mL), *n*-hexylamine (0.20 g, 19.5 mmol) and $MgSO_4$ (4 g) were added and the reaction mixture was refluxed for 5 h. The original solvent, THF, was removed by rotary evaporation and new solvent, methanol (20 mL), was added. After changing the solvent, $NaBH_4$ (0.09 g, 27.3 mmol) was added at 0 °C. Thereafter, the reaction mixture was warmed to room temperature and allowed to react for 1 h. Then, the crude product was filtered to remove $MgSO_4$. The crude product was extracted with CH_2Cl_2, and the organic layer was washed with H_2O and brine, and then dried over $MgSO_4$. The crude product was purified by column chromatography using hexane/acetone (v/v= 2/1) as eluent to give **5** (0.58 g, 75 %) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–6.93 (m, 14H), 4.31 (dd, J = 3.1 Hz, 11.7 Hz,1H), 3.80 (dd, J = 3.1 Hz, 13.8 Hz, 1H), 3.66 (s, 2H), 3.39 (dd, J = 11.7 Hz, 13.8 Hz, 1H), 2.52 (t, J = 7.1 Hz, 2H), 1.48–1.27 (m, 8H), 0.87 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8 (C), 136.9 (C), 136.5 (C), 133.1 (CH), 129.7 (C), 129.7 (CH), 128.6 (CH), 128.6 (CH), 128.2 (CH), 128.0 (CH), 127.60 (CH), 126.2 (CH), 72.2 (CH), 53.0 (CH_2), 49.0 (CH_2), 33.4 (CH_2), 31.4 (CH_2), 29.6 (CH_2), 26.6 (CH_2), 22.2 (CH_2), 13.7 (CH_3); IR (KBr): 2927, 1306, 1145, 612 cm^{-1}; HRMS-EI (M^+) calcd for $C_{27}H_{33}NO_2S$ 435.2232, found 435.2242.

Solution-phase synthesis of *N*-[4-(1-benzenesulfonyl-2-phenyl-ethyl)-benzyl]-*N*-hexyl-4-methyl-benzene-sulfonamide (**6**)

To a solution of compound **5** (0.34 g, 0.78 mmol) in CH_2Cl_2 (10 mL), Et_3N (0.08 g, 0.78 mmol) and TsCl (0.18 g, 0.94 mmol) were added and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated, and the crude product was purified by column chromatography to give compound **6** (0.33 g, 72 %) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–6.93 (m, 18H), 4.32 (dd, J = 2.9 Hz, 11.6 Hz, 1H), 4.21 (s, 2H), 3.80 (dd, J = 2.9 Hz, 13.8 Hz, 1H), 3.37 (dd, J = 11.6 Hz, 13.8 Hz, 1H), 2.99 (t, J = 7.3 Hz, 2H), 2.38 (s, 3H), 1.06–1.26 (m, 8H), 0.81 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0 (C), 137.2 (C), 136.9 (C), 136.5 (C), 136.4 (C), 133.4 (CH), 130.9 (C), 129.9 (CH), 129.4 (CH), 128.6 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 126.8 (CH), 126.4 (CH), 72.2 (CH), 51.3 (CH_2), 48.0 (CH_2), 33.4 (CH_2), 30.8 (CH_2), 27.6 (CH_2), 26.0 (CH_2), 22.2 (CH_2), 21.2 (CH_3), 13.7 (CH_3); IR (KBr): 2929, 1337, 1306, 1146, 1086 cm^{-1}; HRMS-EI (M^+) calcd for $C_{34}H_{39}NO_4S_2$ 589.2320, found 589.2331.

Solution-Phase Synthesis of *N*-Hexyl-4-methyl-*N*-[4-(1-methyl-2-phenyl-ethyl)-benzyl]-benzenesulfonamide (**7**)

To a solution of compound **6** (0.33 g, 0.56 mmol) in CH_2Cl_2 (10 mL), trimethylaluminum (2.0 M, 2.24 mL, 4.48 mmol) was added at 0 °C and the reaction mixture was warmed to room temperature to react for 1 h. After reaction completion, saturated aq. NH_4Cl solution was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$. The solvent was evaporated and gave the yellow oil compound **7** (0.21 g, 81 %) without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2H), 7.02–7.70 (m, 11H), 4.26 (s, 2H), 2.75–3.08 (m, 5H), 2.40 (s, 3H), 1.06–1.27 (m, 11H), 0.80 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3 (C), 142.9 (C), 140.5 (C), 137.1 (C), 134.0 (C), 129.5 (CH), 129.0 (CH), 128.2 (CH), 127.9 (CH), 127.0 (CH), 127.0 (CH), 125.7 (CH), 51.5 (CH_2), 47.9 (CH_2), 44.9 (CH_2), 41.4 (CH), 31.1 (CH_2), 27.7 (CH_2), 26.1 (CH_2), 22.3 (CH_2), 21.4 (CH_3), 21.0 (CH_3), 13.8 (CH_3); IR (KBr): 2926, 1339, 1159, 1091, 656, 549 cm^{-1}; HRMS-EI (M^+) calcd for $C_{29}H_{37}NO_2S$ 463.2545, found 463.2554.

Preparation of sulfinated-functionalized resin (**8**)

Cyclohexane (200 mL) was distilled directly into a flask-containing polystyrene (40 g). Under a nitrogen atmosphere, TMEDA (30 mL) was introduced, the mixture was cooled to 0 °C with gentle stirring, and *n*-BuLi (2.5 M, 153 mL) was added. The resin changed from off-white to orange and the reaction mixture was refluxed for 18 h. The resulting brown lithiated polymer was washed with dry THF (3×500 mL), cooled to −78 °C, and SO_2 (g) was bubbled through the THF-swollen polymer for 1 h. The reaction was quenched by addition of H_2O (1-h slow addition), the polymer was washed with THF, THF/H_2O (4/1), THF, and ether, and the collected resin was dried under high vacuum for 24 h. IR (KBr): 2923, 1634, 1600, 1493, 1452, 1131, 1027, 966 cm^{-1}.

Solid-phase synthesis of polymer-bound 1-benzenesulfonylmethyl-4-vinyl-benzene (**9**)

Sulfinated-functionalized resin **8** (10.0 g) was swollen in DMF and methanol (4:1) (100 mL), 4-vinyl benzylchloride (8.47 g, 50.0 mmol), and NaI (10.0 g) were added. The reaction mixture was heated at 60 − 80 °C for 12 h. The resin was filtered and washed sequentially with MeOH (50 mL × 3), DCM (50 mL × 3), MeOH (50 mL × 3), ether (50 mL × 3) and dried overnight in a vacuum oven at 40 °C to afford resin **9**. IR (KBr): 2920, 2849, 1599, 1492, 1452, 1320, 1302, 1148, 1126, 697 cm^{-1}.

General procedures for the synthesis of polymer-bound 1-(1-benzene-sulfonyl-2-phenyl-ethyl)-4-vinyl-benzene

To a solution of resin **9** (1.1 g) in THF (20 mL), dry DMSO (25.0 equiv) and *n*-BuLi (2.5 M in hexane, 15.0 equiv) were added at −78 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. Thereafter the mixture was cooled to −78 °C, a solution of benzyl bromide (5.0 equiv) in THF (20 mL) was added, and the reaction mixture was warmed to room temperature and stirred for 1 h. The resin was filtered and washed sequentially with MeOH (50 mL × 3), DCM (50 mL × 3), MeOH (50 mL × 3), ether (50 mL × 3), and dried overnight in a vacuum oven at 40 °C to afford products.

Synthesis of polymer-bound 4-[2-benzenesulfonyl-2-(4-vinyl-phenyl)-ethyl]-benzonitrile (**10**)

IR (KBr): 2921, 2227, 1600, 1493, 1452, 1302, 1141, 698 cm^{-1}.

Synthesis of polymer-bound 1-(1-benzenesulfonyl-2-(4-bromo)phenyl -ethyl)-4-vinyl-benzene (**10a**).

IR (KBr): 2923, 1598, 1490, 1451, 1300, 1140, 1085, 1072, 1011, 698 cm^{-1}.

Synthesis of polymer-bound 1-(1-benzenesulfonyl-2-(3-methoxy)-phenyl-ethyl)-4-vinylbenzene (**10d**)

IR (KBr): 3024, 2917, 1600, 1492, 1452, 1259, 1139, 1041, 758, 697 cm^{-1}.

Synthesis of polymer-bound 1-(1-benzenesulfonyl-2-(4-methyl) phenyl-ethyl)-4-vinylbenzene (**10h**)

IR (KBr): 3023, 2921, 1599, 1513, 1492, 1452, 1300, 1138, 758, 697, 619 cm^{-1}.

Synthesis of polymer-bound 1-(1-benzenesulfonyl-2-phenyl-ethyl) -4-vinylbenzene (**10j**)

IR (KBr): 3025, 2921, 1600, 1493, 1452, 1300, 1138, 1084, 749, 697 cm^{-1}.

General procedures for the synthesis of polymer-bound 4-(1-benzenesulfonyl-2-phenyl-ethyl)-benzaldehyde

The solution of olefin resin (4.3 g) in CH_2Cl_2 (50 mL) was cooled to −78 °C, and ozone was bubble through it at −78 °C until the solution turned light blue. The resin was filtered and washed sequentially with MeOH (50 mL × 3), DCM (50 mL × 3), MeOH (50 mL × 3), ether (50 mL × 3) and dried overnight in a vacuum oven at 40 °C to afford products.

Synthesis of polymer-bound 4-[1-benzenesulfonyl-2-(4-bromo-phenyl) -ethyl]-benzaldehyde (**12a**)

IR (KBr): 2924, 1704, 1606, 1490, 1451, 1301, 1139, 1011, 758, 698 cm^{-1}.

Synthesis of polymer-bound 4-[1-benzenesulfonyl-2-(3-methoxy -phenyl)-ethyl]-benzaldehyde (**12d**)

IR (KBr): 3025, 2922, 1701, 1601, 1492, 1452, 1302, 1260, 1140, 1083, 1041, 757, 697 cm^{-1}.

Synthesis of polymer-bound 4-(1-benzenesulfonyl-2-p-tolyl-ethyl) -benzaldehyde (**12h**)

IR (KBr): 3024, 2921, 1702, 1605, 1493, 1452, 1302, 1139, 1084, 1042, 759, 698 cm^{-1}.

Synthesis of polymer-bound 4-(1-benzenesulfonyl-2-phenyl-ethyl) -benzaldehyde (**12j**)

IR (KBr): 3025, 2923, 1704, 1602, 1493, 1452, 1386, 1302, 1139, 1084, 759 cm^{-1}.

General procedures for the synthesis of polymer-bound hexylamine and bezylamine

To a solution of benzaldehyde resin (2.0 g) in DMF (30 mL) was added *n*-hexyl amine or benzyl amine (5.0 equiv) and refluxed for 12 h. Then, $NaBH_4$ (5.0 equiv) was added at 0 °C and stirred for 5 h at room temperature. The resin was filtered and washed sequentially with MeOH (50 mL × 3), DCM (50 mL × 3), MeOH (50 mL × 3), ether (50 mL × 3) and dried overnight in a vacuum oven at 40 °C to afford products.

Synthesis of polymer-bound 4-[1-benzenesulfonyl-2-(4-bromo -phenyl)-ethyl]-benzyl-hexylamine (**13a**)

IR (KBr): 3025, 2930, 1599, 1490, 1451, 1300, 1139, 1011, 698 cm^{-1}.

Synthesis of polymer-bound 4-[1-benzenesulfonyl-2-(4-bromo -phenyl)-ethyl]-benzyl-benzylamine (**13c**)

IR (KBr): 3024, 2923, 1600, 1491, 1452, 1301, 1141, 1011, 758, 698, 620 cm^{-1}.

Synthesis of polymer-bound 4-[1-benzenesulfonyl-2-(3-methoxy -phenyl)-ethyl]-benzyl-benzylamine (**13d**)

IR (KBr): 3024, 2921, 1601, 1493, 1452, 1302, 1142, 759, 698, 620 cm^{-1}.

Synthesis of polymer-bound 4-[1-benzenesulfonyl-2-(3-methoxy -phenyl)-ethyl]-benzyl-hexylamine (**13f**)

IR (KBr): 3024, 2923, 1601, 1493, 1452, 1139, 1084, 1040, 758, 697 cm^{-1}.

Synthesis of polymer-bound [4-(1-benzenesulfonyl-2-*p*-tolyl-ethyl) -benzyl]-benzylamine (**13h**)

IR (KBr): 3024, 2923, 1600, 1493, 1452, 1301, 1183, 1139, 1040, 759, 697 cm^{-1}.

Synthesis of polymer-bound [4-(1-benzenesulfonyl-2-*p*-tolyl-ethyl) -benzyl]-hexylamine (**13i**)

IR (KBr): 3024, 2923, 1600, 1493, 1452, 1301, 1138, 1040, 759, 697 cm^{-1}.

Synthesis of polymer-bound [4-(1-benzenesulfonyl-2-phenyl-ethyl) -benzyl]-benzylamine (**13j**)

IR (KBr): 3025, 2923, 1600, 1492, 1452, 1297, 1136, 757, 696 cm^{-1}.

General procedures for the synthesis of polymer-bound sulfonamide and urea

To a solution of swollen amine resin (2.0 g) in CH_2Cl_2 (20 mL), Et_3N (10 mmol, 5.0 equiv) and TsCl (10 mmol, 5.0 equiv) or phenyl isocyanate (10.0 mmol, 5.0 equiv) were added and the reaction mixture was stirred at ambient temperature for 8 h. The resin was filtered and washed sequentially with MeOH (50 mL × 3), DCM (50 mL × 3), MeOH (50 mL × 3), ether (50 mL × 3) and dried overnight in a vacuum oven at 40 °C to afford products.

Synthesis of polymer-bound*N*-4-[1-Benzenesulfonyl-2-(4-bromo-phenyl)-ethyl]-benzyl-*N*-hexyl-4-methyl-benzenesulfonamide (**14a**)

IR (KBr): 2925, 2853, 1599, 1491, 1452, 1303, 1155, 1143, 1089, 1011, 760, 698 cm^{-1}.

Synthesis of polymer-bound 1-4-[1-benzenesulfonyl-2-(4-bromo -phenyl)-ethyl]-benzyl-1-hexyl-3-phenylurea (**15b**)

IR (KBr): 2922, 1665, 1596, 1525, 1490, 1442, 1301, 1139, 1010, 753, 698 cm^{-1}.

Synthesis of polymer-bound*n*-4-[1-benzenesulfonyl-2-(4-bromo-phenyl)-ethyl]-benzyl-*N*-benzyl-4-methyl-benzenesulfonamide (**14c**)

IR (KBr): 3024, 2921, 1600, 1492, 1452, 1304, 1144, 1011, 758, 698, 618 cm^{-1}.

Synthesis of polymer-bound*N*-4-[1-benzenesulfonyl-2-(3-methoxy-phenyl)-ethyl]-benzyl-*N*-benzyl-4-methyl-benzenesulfonamide (**14d**)

IR (KBr): 3026, 2925, 1600, 1493, 1452, 1304, 1143, 1087, 759, 698 cm^{-1}.

Synthesis of polymer-bound 1-4-[1-benzenesulfonyl-2-(3-methoxy -phenyl)-ethyl]-benzyl-1-benzyl-3-phenylurea (**15e**)

IR (KBr): 3025, 2924, 1671, 1600, 1493, 1453, 1302, 1141, 1040, 756, 698 cm^{-1}.

Synthesis of polymer-bound*N*-4-[1-benzenesulfonyl-2-(3-methoxy-phenyl)-ethyl]-benzyl-*N*-hexyl-4-methyl-benzenesulfonamide (**14f**)

IR (KBr): 3024, 2924, 1600, 1492, 1452, 1138, 1085, 1028, 756 cm^{-1}.

Synthesis of polymer-bound 1-4-[1-benzenesulfonyl-2-(3-methoxy -phenyl)-ethyl]-benzyl-1-hexyl-3-phenylurea (**15g**)

IR (KBr): 3024, 2922, 1670, 1600, 1492, 1452, 1302, 1140, 1040, 755, 697 cm^{-1}.

Synthesis of polymer-bound 1-[4-(1-benzenesulfonyl-2-p-tolyl-ethyl) -benzyl]-1-benzyl-3-phenylurea (**15h**)

IR (KBr): 3025, 2921, 1671, 1599, 1493, 1452, 1302, 1220, 1140, 756, 699 cm^{-1}.

Synthesis of polymer-bound 1-[4-(1-benzenesulfonyl-2-p-tolyl-ethyl) -benzyl]-1-hexyl-3-phenylurea (**15i**)

IR (KBr): 3023, 2921, 1668, 1597, 1493, 1444, 1302, 1139, 1041, 756, 699 cm^{-1}.

Synthesis of polymer-bound*N*-[4-(1-benzenesulfonyl-2-phenyl-ethyl)-benzyl]-*N* -benzyl-4-methyl-benzenesulfonamide (**14j**)

IR (KBr): 3023, 2920, 1701, 1636, 1600, 1492, 1451, 1300, 1136, 756, 696 cm^{-1}.

Synthesis of polymer-bound 1-[4-(1-benzenesulfonyl-2-phenyl-ethyl) -benzyl]-1-benzyl-3-phenylurea (**15k**)

IR (KBr): 3026, 2925, 1671, 1599, 1493, 1452, 1301, 1139, 757, 697 cm^{-1}.

General procedures for cleavage of the products from the solid support

To a solution of swollen resin (2.0 g) in CH_2Cl_2 (30 mL), trimethylaluminum (2.0 M in toluene, 32.0 mmol) was added at 0 °C and the reaction mixture was warmed to room temperature and reacted for 8 h. The reaction mixture was poured into a flask containing ice and the aqueous layer was extracted with CH_2Cl_2, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/ethyl acetate = 4/1) and preparative TLC to give products as yellow oil with overall yields in the range of 11–15 %.

Synthesis of 4-[2-(4-vinyl-phenyl)-propyl]-benzonitrile (**11**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.13–7.05 (m, 4H), 6.68 (dd, J = 10.9 Hz, 17.6 Hz, 1H), 5.70 (dd, J = 17.6 Hz, 0.6 Hz, 1H), 5.20 (dd, J = 0.6 Hz, 10.9 Hz, 1H), 3.03–2.84 (m, 3H), 1.26 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2 (C), 145.3 (C), 136.4 (CH), 135.7 (C), 131.8 (CH), 129.8 (CH), 127.1 (CH), 126.2 (CH), 119.0 (C), 113.2 (CH_2), 109.7 (C), 44.9 (CH_2), 41.3 (CH), 21.3 (CH_3); IR (KBr): 2926, 2927, 2226, 1700, 1606,832 cm^{-1}; HRMS-EI (M^+) calcd for $C_{18}H_{17}N$ 247.1361, found 247.1357.

Synthesis of *N*-4-[2-(4-bromo-phenyl)-1-methyl-ethyl]-benzyl-N-hexyl-4-methyl-benzenesulfonamide (**16a**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.3 Hz, 2H), 7.29 (dd, J = 8.3 Hz, J = 2.0 Hz, 4H), 7.16 and 7.05 (ABq, J = 8.1 Hz, 4H), 6.87 (d, J = 8.3 Hz, 2H), 4.25 (s, 2H), 3.03 (t, J = 7.5 Hz, 2H), 2.71–2.80 (m, 3H), 2.41 (s, 3H), 1.05–1.29 (m, 11H), 0.78 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8 (C), 143.0 (C), 139.5 (C), 137.2 (C), 134.3 (C), 131.1 (CH), 130.8 (CH), 129.6 (CH), 128.3 (CH), 127.1 (CH), 127.1 (CH), 119.6 (C), 51.5 (CH_2), 48.0 (CH_2), 44.3 (CH_2), 41.4 (CH), 31.2 (CH_2), 27.8 (CH_2), 26.2 (CH_2), 22.4 (CH_2), 21.5 (CH_3), 21.2 (CH_3), 13.9 (CH_3); IR (KBr): 2957, 2927, 1488, 1339, 1158, 1091, 1011, 656, 549 cm^{-1}; HRMS-EI (M^+) calcd for $C_{29}H_{36}BrNO_2S$ 541.1650, found 541.1666.

Synthesis of 1-4-[2-(4-bromo-phenyl)-1-methyl-ethyl]-benzyl-1-hexyl-3-phenylurea (**17b**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.12 (m, 11H), 6.90 (d, J = 8.3 Hz, 2H), 6.25 (s, 1H), 4.52 (s, 2H), 3.38 (t, J = 7.6 Hz, 2H), 2.99–2.74 (m, 3H), 1.38–1.23 (m, 11H), 0.86–0.91(b, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5 (C), 146.0 (C), 139.5 (C), 139.2 (C), 135.3 (C), 131.2 (CH), 130.9 (CH), 128.9 (CH), 127.8 (CH), 127.0 (CH), 123.0 (CH), 119.8 (CH), 119.8 (C), 50.7 (CH_2), 48.3 (CH_2), 44.3 (CH_2), 41.5 (CH), 31.6(CH_2), 28.5 (CH_2), 26.7 (CH_2), 22.6 (CH_2), 21.4 (CH_3), 14.1 (CH_3); IR (KBr): 2923, 1339, 1158, 1093, 1011, 657, 550 cm^{-1}; HRMS-EI (M^+) calcd for $C_{29}H_{35}BrNO_2$ 506.1933, found 506.1946.

Synthesis of *N*-benzyl-*N*-4-[2-(4-bromo-phenyl)-1-methyl-ethyl]-benzyl-4-methyl-benzenesulfonamide (**16c**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.35–6.87 (m, 15H), 4.23–4.33 (m, 4H), 2.93–2.63 (m, 3H), 2.46 (s, 3H), 1.21 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8 (C), 143.2 (C), 139.6 (C), 137.8 (C), 135.8 (C), 133.4 (C), 131.1 (CH), 130.8 (CH), 129.7 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 127.6 (CH), 127.3 (CH), 127.0 (CH), 50.4 (CH_2), 50.3 (CH_2), 44.3 (CH_2), 41.4 (CH), 21.5 (CH_3), 21.2 (CH_3); HRMS-EI (M^+) calcd for $C_{30}H_{30}BrNO_2S$ 547.1181, found 547.1158.

Synthesis of *N*-benzyl-*N*-4-[2-(3-methoxy-phenyl)-1-methyl-ethyl]-benzyl-4-methyl-benzenesulfonamide (**16d**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.2 Hz, 2H), 7.31–6.91 (m, 12H), 6.72–6.59 (m, 3H), 4.34 (s, 2H), 4.29 (s, 2H), 3.74 (s, 3H), 2.99–2.66 (m, 3H), 2.44 (s, 3H), 1.20 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3 (C), 146.4 (C), 143.2 (C), 142.3 (C), 137.9 (C), 135.9 (C), 133.2 (C), 129.7 (CH), 129.1 (CH), 128.7 (CH), 128.7 (CH), 128.4 (CH), 127.6 (CH), 127.3 (CH), 127.1 (CH), 121.5 (CH), 114.9 (CH), 111.00 (CH), 55.1 (CH_3), 50.3 (CH_2), 50.2 (CH_2), 44.9 (CH_2), 41.4 (CH), 21.5 (CH_3), 21.2 (CH_3); HRMS-EI (M^+) calcd for $C_{31}H_{33}NO_3S$ 499.2181, found 499.2179.

Synthesis of 1-benzyl-1-4-[2-(3-methoxy-phenyl)-1-methyl -ethyl]-benzyl-3-phenylurea (**17e**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–6.2 (m, 18H), 6.33 (s, 1H), 4.61 (s, 2H), 4.56 (s, 2H), 3.74 (s, 3H), 3.04–2.71 (m, 3H), 1.25 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 (C), 155.9 (C), 146.7 (C), 142.2 (C), 138.9 (C), 137.3 (C), 134.6 (C), 129.0 (CH), 128.9 (CH), 128.8 (CH), 127.7 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH),

123.0 (CH), 121.6 (CH), 119.8 (CH), 114.9(CH), 111.1 (CH), 55.1 (CH_3), 50.8 (CH_2), 50.5 (CH_2), 44.9 (CH_2), 41.4 (CH), 21.3 (CH_3); IR (KBr): 2925, 1646, 1598, 1531, 1444 cm^{-1}; HRMS-EI (M^+) calcd for $C_{31}H_{32}N_2O_2$ 464.2464, found 464.2473.

Synthesis of *N*-hexyl-*N*-4-[2-(3-methoxy-phenyl)-1-methyl-ethyl]-benzyl-4-methyl-benzenesulfonamide (**16f**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.2 Hz, 2H), 7.33–7.10 (m, 7H), 6.74–6.62 (m, 3H), 4.28 (s, 2H), 3.76 (s, 3H), 3.10–2.73 (m, 5H), 2.45 (s, 3H), 1.31–1.08 (m, 11H), 0.81 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 (C), 146.5 (C), 143.0 (C), 142.3 (C), 137.3 (C), 134.1 (C), 129.6 (CH), 129.0 (CH), 128.3 (CH), 127.2 (CH), 127.1 (CH), 121.6 (CH), 114.8 (CH), 111.1 (CH), 55.1 (CH_3), 51.5 (CH_2), 47.9 (CH_2), 45.0 (CH_2), 41.4 (CH), 31.2 (CH_2), 27.8 (CH_2), 26.2 (CH_2), 22.4 (CH_2), 21.5 (CH_3), 21.2 (CH_3), 13.9 (CH_3); IR (KBr): 2926, 1338, 1260, 1157, 1090, 655, 549 cm^{-1}; HRMS-EI (M^+) calcd for $C_{30}H_{39}NO_3S$ 493.2651, found 493.2662.

Synthesis of 1-hexyl-1-4-[2-(3-methoxy-phenyl)-1 -methyl-ethyl]-benzyl-3-phenylurea (**17g**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.09 (m, 10H), 6.72–6.63(m, 3H), 6.26 (s, 1H), 4.52 (s, 2H), 3.74 (s, 3H), 3.38 (t, J = 7.6 Hz, 2H), 3.04–2.73 (m, 3H), 1.32–1.23 (m, 11H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 (C), 155.5 (C), 146.6 (C), 142.2 (C), 139.1 (C), 135.0 (C), 129.0 (CH), 128.8 (CH), 127.7 (CH), 126.9 (CH), 122.8 (CH), 121.6 (CH), 119.7 (CH), 114.9 (CH), 111.1 (CH), 55.1 (CH_3), 50.7 (CH_2), 48.2 (CH_2), 44.9 (CH_2), 41.4 (CH), 31.6 (CH_2), 28.4 (CH_2), 26.7 (CH_2), 22.6 (CH_2), 21.3 (CH_3), 14.0 (CH_3); IR (KBr): 2957, 2927, 1641, 1596, 1531, 1444, 1260 cm^{-1}; HRMS-EI (M^+) calcd for $C_{30}H_{38}N_2O_2$ 458.2933, found 458.2940.

Synthesis of 1-benzyl-1-[4-(1-methyl-2-p-tolyl-ethyl)-benzyl]-3-phenylurea (**17h**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–6.95 (m, 18H), 6.33 (s, 1H), 4.64 (s, 2H), 4.57 (s, 2H), 3.02–2.70 (m, 3H), 2.31 (s, 3H), 1.25 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0 (C), 146.9 (C), 39.0 (C), 137.5 (C), 137.4 (C), 135.4 (C), 134.7 (C), 129.0 (CH), 129.0 (CH), 128.9 (CH), 128.9 (CH), 127.8 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 123.1 (CH), 119.8 (CH), 50.9 (CH_2), 50.6 (CH_2), 44.6 (CH_2), 41.6 (CH), 21.3 (CH_3), 21.1 (CH_3); HRMS-EI (M^+) calcd for $C_{31}H_{32}N_2O$ 448.2515, found 448.2523.

Synthesis of 1-hexyl-1-[4-(1-methyl-2-p-tolyl-ethyl)-benzyl]-3-phenylurea (**17i**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–6.97 (m, 13H), 6.27 (s, 1H), 4.54 (s, 2H), 3.40 (t, J = 7.6 Hz, 2H), 3.02–2.71 (m, 3H), 2.30 (s, 3H), 1.33–1.23 (m, 11H), 0.90 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5 (C), 146.7 (C), 139.1 (C), 137.5 (C), 135.3 (C), 134.9 (C), 129.0 (CH), 128.8 (CH), 128.8 (CH), 127.7 (CH), 126.9 (CH), 122.9 (CH), 119.7 (CH), 50.8 (CH_2), 48.3 (CH_2), 44.5 (CH_2), 41.6 (CH), 31.6 (CH_2), 28.4 (CH_2), 26.7 (CH_2), 22.6 (CH_2), 21.2 (CH_3), 21.0 (CH_3), 14.0 (CH_3); HRMS-EI (M^+) calcd for $C_{30}H_{38}N_2O$ 442.2984, found 442.2983.

Synthesis of*N*-benzyl-4-methyl-N-[4-(1-methyl-2-phenyl-ethyl)-benzyl]-benzenesulfonamide (**16j**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 6.6 Hz, 2H), 7.33–6.94 (m, 16H), 4.31 (s, 2H), 4.29 (s, 2H), 3.01–2.71 (m, 3H), 2.46 (s, 3H), 1.22 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4 (C), 143.2 (C), 140.6 (C), 137.7 (C), 135.8 (C), 133.1 (C), 129.6 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 125.8 (CH), 50.3 (CH_2), 50.2 (CH_2), 44.9 (CH_2), 41.5 (CH), 21.5 (CH_3), 21.1 (CH_3); IR (KBr): 2926, 1741, 1455, 1159, 1094 cm^{-1}; HRMS-EI (M^+) calcd for $C_{30}H_{31}N_2OS$ 469.2075, found 469.2079.

Synthesis of 1-benzyl-1-[4-(1-methyl-2-phenyl-ethyl)-benzyl]-3-phenylurea (**17k**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–6.98 (m, 19H), 6.34 (s, 1H), 4.61 (s, 2H), 4.54 (s, 2H), 3.06–2.74 (m, 3H), 1.24 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9 (C), 146.6 (C), 140.5 (C), 138.9 (C), 137.3 (C), 134.6 (C), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.8 (CH), 128.1 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 125.9 (CH), 123.0 (CH), 119.8 (CH), 50.8 (CH_2), 50.5 (CH_2), 44.9 (CH_2), 41.5 (CH), 21.2 (CH_3); IR (KBr): 2927, 1742, 1456, 1163 cm^{-1}; HRMS-EI (M^+) calcd for $C_{30}H_{30}N_2O$ 4345.2358, found 434.2354.

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