Synthesis S. Liu et al. Paper

Hexafluoroisopropyl *N*-Fluorosulfonyl Carbamate: Synthesis and Its Facile Transformation to Sulfamoyl Ureas

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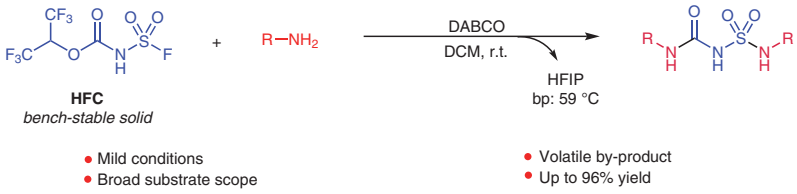

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Abstract The synthesis of hexafluoroisopropyl *N*-fluorosulfonyl carbamate (HFC) and its facile transformation to sulfamoyl ureas are reported . Unlike liquid chlorosulfonyl isocyanate (CSI) and fluorosulfonyl isocyanate (FSI), which are corrosive and moisture-sensitive, HFC is a white solid and displays satisfactory bench-stability and unique reactivity, which facilitates its double ligation with amines to directly afford a series of sulfamoyl ureas under ambient conditions. It is worth noting that HFC will serve as an efficient surrogate to CSI and FSI for laboratory use, especially for accessing the bioactive sulfamoyl ureas under mild conditions.

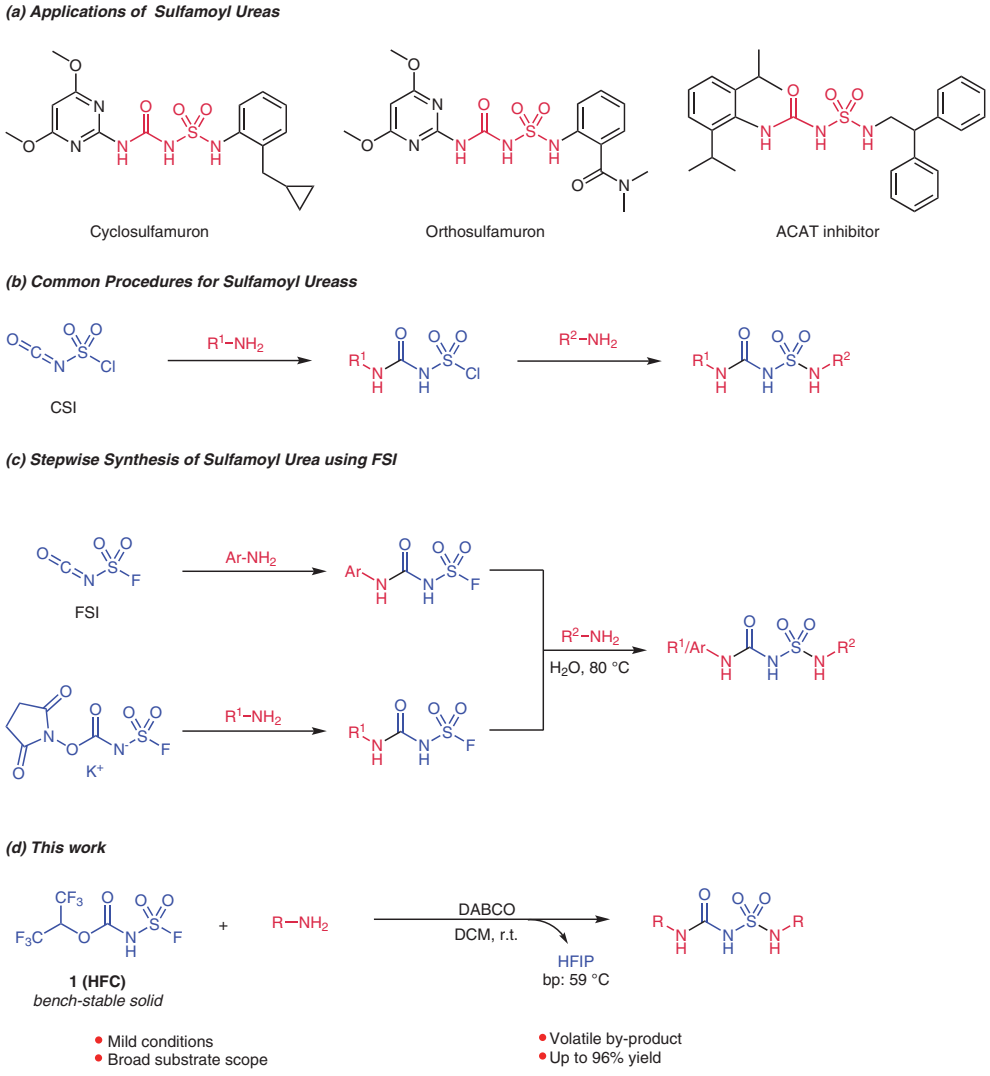
Keywords sulfamoyl ureas, reagent, hexafluoroisopropanol, bench-stability, DABCO

The family of sulfamoyl ureas has been reported as highly efficient and low-toxic herbicides.[1] Cyclosulfamuron[2] and orthosulfamuron[3] are two commercialized herbicides inhibiting the acetolactate synthetase (ALS) of weeds (Scheme 1a). Meanwhile, sulfamoyl ureas have shown bioactivity as the inhibitor of human acyl-CoA: cholesterol *O*-acyl-transferase (ACAT)[4] (Scheme 1a). To access these valuable scaffolds,[5] chlorosulfonyl isocyanate (CSI) has been widely used in previous studies.[6] CSI is a corrosive liquid that reacts violently with water[7] Therefore, handling CSI in laboratories normally requires a moisture-free environment and safety precautions. The reactions between CSI and amines are exothermic and low-temperature apparatus is needed during the scale-up processes. CSI initially reacts with an amine once to deliver the chlorosulfonyl urea intermediate, which further reacts with another amine to generate the sulfamoyl urea (Scheme 1b).

Fluorosulfonyl isocyanate (FSI)[6e] is a liquid that is synthesized from the halogen exchange reaction[8] of CSI. Similar to CSI, FSI is corrosive and moisture-sensitive. It also reacts rapidly with alcohols/amines[9] which is exothermic and normally performed under low temperature. The reactions between anilines and FSI proceed smoothly to afford fluorosulfuryl ureas in good to excellent yields. However, the use of primary and secondary aliphatic amines generally leads to mixed products.

The remaining S(VI)–F bonds on fluorosulfuryl ureas are less reactive than the corresponding S(VI)–Cl bonds, which require the elevated temperature and the use of water as the solvent for activation[10] (Scheme 1c).

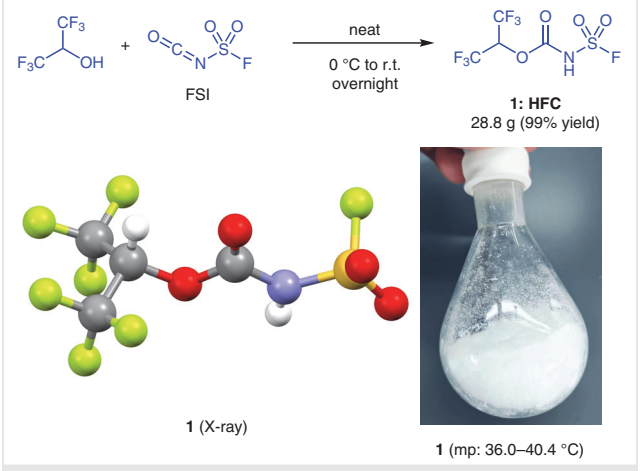
The adducts from FSI and N,O-nucleophiles have shown different reactivity and stability compared with FSI[11] For instance, the adduct from FSI and *N*-hydroxysuccinimide is isolated as a bench-stable potassium salt[9] However, it exhibits lower reactivity than FSI, which reacts with a series of aromatic and aliphatic amines in CH_3CN at elevated temperature to give the corresponding fluorosulfuryl ureas. While developing novel reagents for the synthesis of sulfamoyl ureas, we discovered that the adduct (hexafluoroisopropyl *N*-fluorosulfonyl carbamate, HFC, **1**) from FSI and hexafluoroisopropanol (HFIP) displays satisfactory bench-stability and it reacts with amines twice to directly generate sulfamoyl ureas under ambient conditions (Scheme 1d).



Scheme 1 (a) Applications of sulfamoyl ureas; (b–d) Different methods for synthesis of sulfamoyl ureas

Herein we report its facile synthesis and transformation to sulfamoyl ureas, which will provide a new avenue for accessing these bioactive molecules.

We first synthesized HFC by mixing HFIP and FSI neatly under 0 °C and gradually warming it up to room temperature overnight (Scheme 2). After pumping off all the volatiles, the product HFC was isolated as a white solid (mp: 36.0 to 40.4 °C). Owing to its synthetic simplicity, we were able to perform a 0.1 mole-scale synthesis of HFC with an isolated yield of 99% (Scheme 2). The structure of HFC was confirmed by the single crystal X-ray diffraction (Scheme 2). We then tested the bench-stability of HFC and found that it kept stable on the bench for at least 24 hours and in the refrigerator (4 °C) for at lease 6 months (see details in the Supporting Information). Compared with CSI and FSI, such stability allowed us to handle it more conveniently in the laboratory.

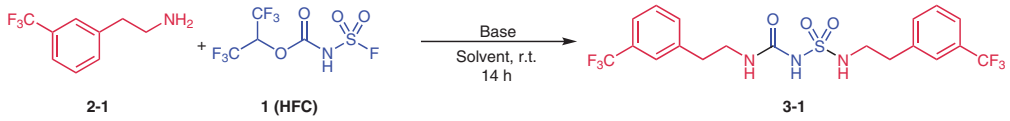


Scheme 2 Synthesis of reagent HFC (**1**)

With the new reagent on hand, we evaluated its reactivity towards amines under various conditions. The model reaction between HFC and 3-(trifluoromethyl)phenylethylamine (**2-1**) was found to be sensitive to the variation of base and solvent (Table 1). After a throughout screen, dichloromethane (DCM) was identified as the solvent of choice with 1,4-diazabicyclo[2.2.2]octane (DABCO) as the base of choice. The model reaction gave higher yields in DCM and chloroform (Table 1, entries 1 and 2), whereas trace amounts of products were produced in DMSO, DMF, and MeCN (entries 3–5). DABCO also played a key role in promoting the successive ligation between HFC and the amine (entries 6–12). Interestingly, switching the base to 1-azabicyclo[2.2.2]octane (ABCO), which was structurally similar to DABCO, led to a much lower yield (entry 7). Additionally, other nitrogenous bases such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), triethylamine, and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) failed to facilitate the model reaction (entries 8–10). The use of inorganic bases such as K_2CO_3 and KF gave a trace amount of product (entries 11 and 12). Moreover, we found that the amount of DABCO had a remarkable impact on the ligation process (entries 6 and 13–16). For instance, no product was detected when DABCO was absent (entry 6) and the addition of 1 equivalent DABCO led to a low yield of 30% (entry 13). Increasing the amount of DABCO was beneficial as the desired sulfamoyl urea was produced quantitatively (monitored by ^{19}F NMR spectroscopy) in the presence of 3.0 equivalents of DABCO (entry 16). Finally, the optimized condition was achieved by stirring the DCM solution of the amine (0.5 mmol), HFC (2.4 equiv), and DABCO (3.0 equiv) at room temperature for 14 hours, which afforded the sulfamoyl urea in a 94% isolated yield (entry 16).

Next, we explored the substrate scope under the optimized condition. Due to the stability of HFC, we were able to perform the reactions without using the anhydrous condition, which was user-friendly. To our delight, a set of primary and secondary aliphatic amines were converted to the

Table 1 Optimization of the Reaction Conditions[a]

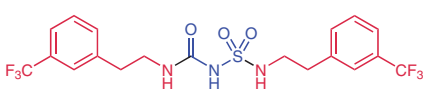


2-1 **1 (HFC)** **3-1**

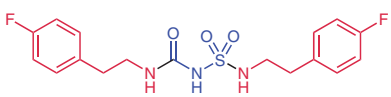
Entry	**1** (equiv)	Base (equiv)	Solvent	Yield (%)[b]
1	2.4	DABCO (2.0)	DCM	86
2	2.4	DABCO (2.0)	$CHCl_3$	83
3	2.4	DABCO (2.0)	DMSO	trace
4	2.4	DABCO (2.0)	DMF	trace
5	2.4	DABCO (2.0)	MeCN	24
6	2.4	–	DCM	trace
7	2.4	ABCO (3.0)	DCM	40
8	2.4	TMEDA (3.0)	DCM	18
9	2.4	Et_3N (3.0)	DCM	16
10	2.4	DBU (3.0)	DCM	trace
11	2.4	K_2CO_3 (3.0)	DCM	trace
12	2.4	KF (3.0)	DCM	trace
13	2.4	DABCO (1.0)	DCM	30
14	2.4	DABCO (1.6)	DCM	58
15	2.4	DABCO (2.4)	DCM	94
16	**2.4**	**DABCO (3.0)**	**DCM**	**>99 (94)[c]**
17	1.0	DABCO (3.0)	DCM	58
18	1.4	DABCO (3.0)	DCM	80
19	2.0	DABCO (3.0)	DCM	91
20	3.0	DABCO (3.0)	DCM	85

[a] Reaction conditions: The amine **2-1** (0.5 mmol), HFC, and base in solvent (5 mL), r.t., 14 h.
[b] Yields were determined by peak integration on ^{19}F NMR spectra with $PhCF_3$ as internal standard.
[c] Isolated yield.

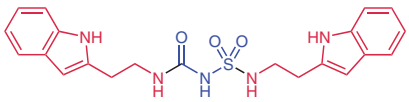
Table 2 Sulfamoyl Ureas Synthesized with HFC[a]



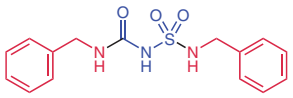
3-1 (94%)



3-2 (90%)



3-3 (81%)



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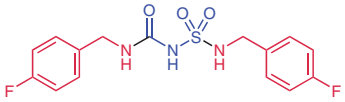
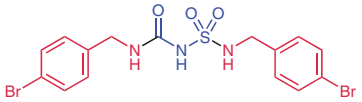
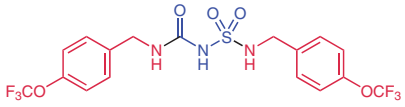


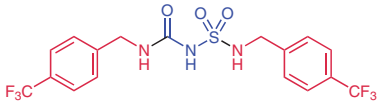
3-5 (80%)



3-6 (81%)



3-7 (83%)



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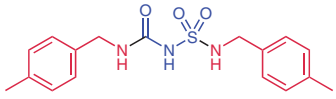

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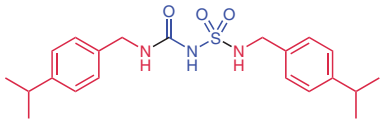
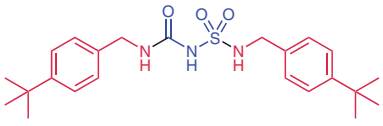
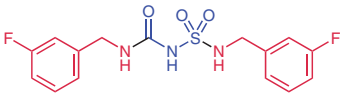


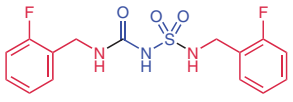
3-10 (82%)



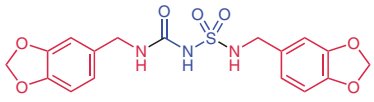
3-11 (85%)



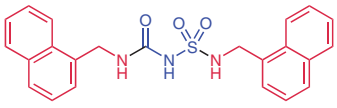
3-12 (84%)



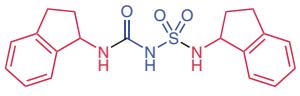
3-13 (81%)



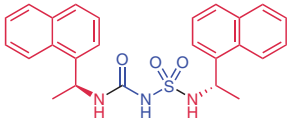
3-14 (92%)



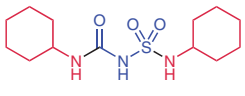
3-15 (87%)



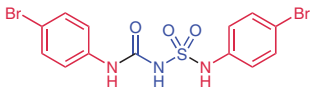
3-16 (87%)



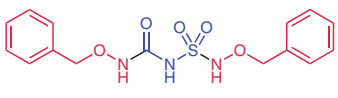
3-17 (91%)



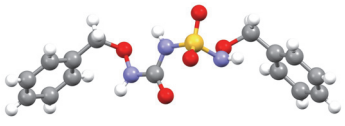
3-18 (88%)

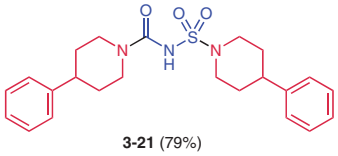


3-19 (45%)

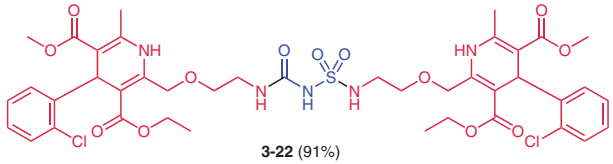


3-20 (89%)





3-21 (79%)



3-22 (91%)

[a] Isolated yield under the optimal conditions using **2** (1 mmol) and HFC (**1**, 1.2 mmol).

corresponding sulfamoyl ureas in good to excellent yields (Table 2, 3-1 to **3-18** and **3-20** to **3-22**). The benzylamine derivatives bearing halogen, methyl, *tert*-butyl, isopropyl, trifluoromethyl, and trifluoromethoxyl functionalities were well-tolerated in our protocol (Table 2, 3-4 to **3-17**). Besides, cyclohexylamine, benzyloxyamine, and phenylpiperidine reacted smoothly with HFC (Table 2, 3-18, 3-20 and **3-21**). Notably, the drug molecule amlodipine was transformed into the disubstituted product with high efficiency (Table 2, 3-22). However, it was noteworthy that the aromatic amine 4-bromoaniline gave a lower yield (Table 2, 3-19) than those aliphatic amines.

To achieve a detailed comparison, we performed the reactions between **2-1** and HFC/FSI/CSI under the optimized conditions, respectively, and monitored them using LC-MS (Figure 1, see details in the Supporting Information). LC-MS analysis revealed that **2-1** was fully converted to the sulfamoyl urea **3-1** by HFC in a quantitative yield, whereas the reaction between **2-1** and FSI produced a mixture of **2-1**, **3-1**, and the fluorosulfonyl urea **4-1**. CSI displayed a better performance than FSI in transforming the starting material **2-1** to the desired product **3-1**, though a small amount of **2-1** remained after the same reaction time (14 h). Considering that CSI and FSI are corrosive and moisture-sensitive liquid, HFC can serve as an efficient surrogate to CSI and FSI, particularly for synthesizing sulfamoyl ureas in laboratories.

We next conducted a preliminary mechanistic study on the successive ligations of HFC. Compound **4-1** was synthesized and isolated, which was then reacted with amine **2-1** in DCM with DABCO as the base. We monitored the reaction using LC-MS and found that similar to the reaction between FSI and **2-1**, a mixture of **2-1**, **4-1**, and the product **3-1** was obtained after 24 hours (see details in the Supporting Information). This result indicated that the formation of FSI or **4-1** as key intermediate during the reaction between HFC and **2-1** was not favored. We then proposed a plausible mechanism for this process in Scheme 3. HFC first undergoes deprotonation in the presence of DABCO due to the acidic nature of the N–H bond, generating the aza-sulfene intermediate **6** as the key initial step.[11c] This highly reactive intermediate further couples with an amine to form sulfamoyl carbamate intermediate **5**. Subsequently, **5** reacts with DABCO to produce the zwitterionic intermediate **7**, a carbamate group transfer reagent,[6c,9] which undergoes a substitution reaction with another amine to produce the sulfamoyl urea product **3**.

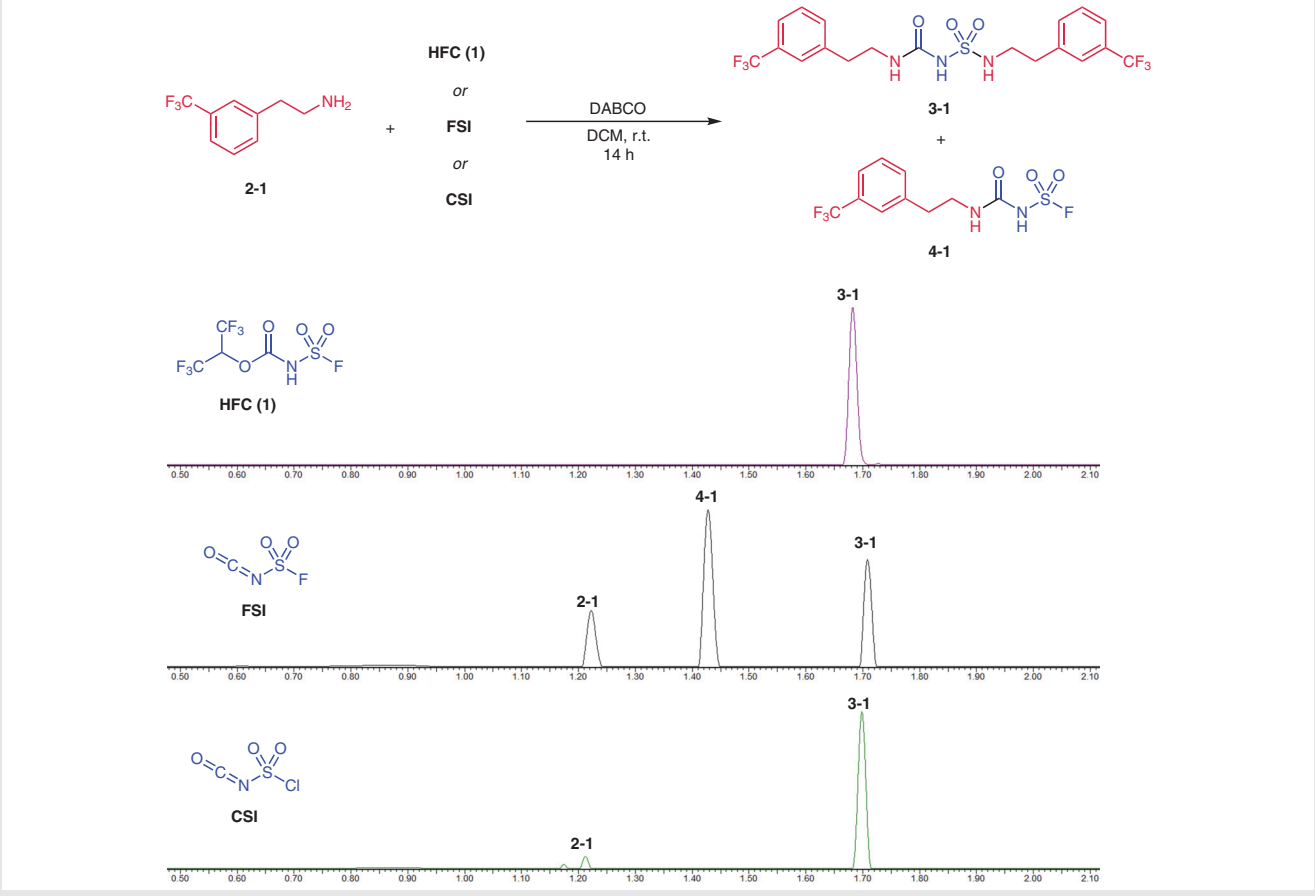
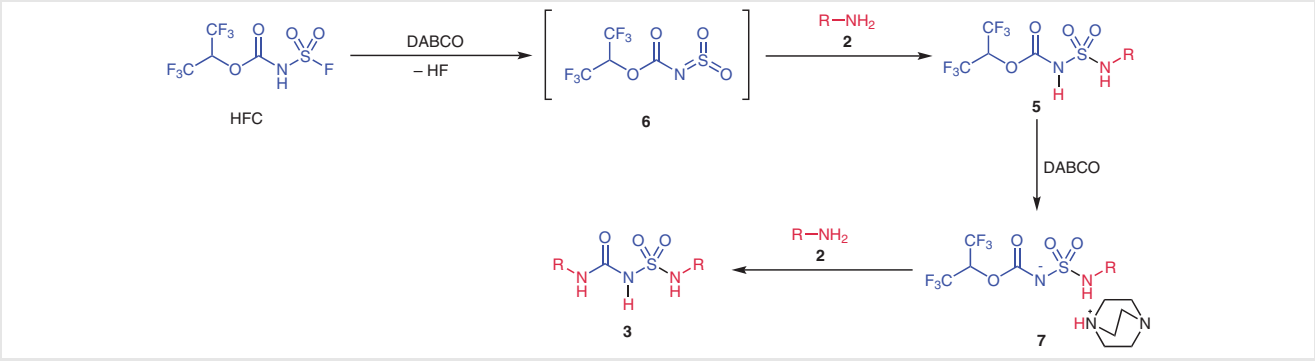


Figure 1 Comparison of reactivity between HFC, FSI, and CSI. Shown are UPLC-MS traces of the crude reaction mixture.



Scheme 3 Proposed mechanism for the reaction

In conclusion, we have successfully developed a new reagent HFC for the facile synthesis of sulfamoyl ureas. The production of HFC is synthetically convenient and amenable to scale-up. Compared with CSI and FSI, HFC is a bench-stable solid, which is ideal for laboratory use. Under ambient conditions, HFC reacts smoothly with a variety of amines to afford the sulfamoyl ureas, in contrast to the cases of CSI and FSI, which require the use of anhydrous conditions and low temperature. We believe that HFC will serve as an efficient surrogate to CSI and FSI, especially for accessing the bioactive sulfamoyl ureas under mild conditions.

For general experimental details, see the Supporting Information.

Synthesis of 1,1,1,3,3,3-Hexafluoropropan-2-yl (Fluorosulfonyl)-carbamate (HFC, 1)

According to the previous literature,[9] a 100 mL round-bottom glass bottle was charged with 1,1,1,3,3,3-hexafluoropropan-2-ol (16.8 g, 100 mmol) and cooled to 0 °C, and fluorosulfuryl isocyanate (12.5 g, 100 mmol) was added dropwise. The resulting mixture was stirred at r.t. for 12 h and monitored by ^{19}F NMR spectroscopy. After completion, the mixture was evacuated to remove unreacted compounds to give 1,1,1,3,3,3-hexafluoropropan-2-yl (fluorosulfonyl)carbamate (HFC, **1**) as a white solid; yield: 28.8 g (99%); mp 36.0–40.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1 H), 5.68 (hept, *J* = 5.7 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.23, 119.85 (q, *J* = 282.5 Hz), 69.49 (hept, *J* = 35.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = 55.2 (s, 1 F), –73.3 (d, *J* = 5.7 Hz, 6 F).

ESI-HRMS: *m*/*z* calcd for $C_4HF_7NO_4S$ [M – H]$^-$: 291.9520; found: 291.9520.

Synthesis of Sulfamoyl Ureas; General Procedure

A 20 mL glass bottle was charged with amine **2** (1 mmol), DABCO (1.5 mmol), and DCM. Subsequently, HFC (1.2 mmol) was added, and the reaction mixture was stirred at r.t. (monitored by TLC and LC-MS). After completion, the mixture was concentrated under vacuum and further purified by column chromatography on silica gel to afford the title compound **3**.

3-{2-[3-(Trifluoromethyl)phenyl]ethyl}-1-({2-[3-(trifluoromethyl)phenyl]ethyl}sulfamoyl)urea (3-1)

Following the general procedure, the compound **3-1** was prepared as a white solid; yield: 227 mg (94%); mp 72.0 °C (dec.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.00 (s, 1 H), 7.51–7.30 (m, 8 H), 6.17 (t, *J* = 5.8 Hz, 1 H), 5.67 (t, *J* = 6.1 Hz, 1 H), 3.37 (q, *J* = 6.8 Hz, 2 H), 3.26 (q, *J* = 6.9 Hz, 2 H), 2.87 (t, *J* = 7.3 Hz, 2 H), 2.79 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.3, 139.4, 138.8, 132.3, 131.0 (q, *J* = 10.3 Hz), 130.9 (q, *J* = 10.3 Hz), 129.2, 129.2, 125.5 (q, *J* = 3.5 Hz), 124.2 (q, *J* = 273.4 Hz), 123.8 (q, *J* = 3.9 Hz), 123.6 (q, *J* = 3.9 Hz), 120.2, 44.5, 41.1, 35.5, 35.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.5 (s, 3 F), –62.5 (s, 3 F).

ESI-HRMS: *m*/*z* calcd for $C_{19}H_{20}F_6N_3O_3S$ [M + H]$^+$: 484.1124; found: 484.1124.

3-[2-(4-Fluorophenyl)ethyl]-1-{[2-(4-fluorophenyl)ethyl]sulfamoyl}urea (3-2)

Following the general procedure, the compound **3-2** was prepared as a white solid; yield: 173 mg (90%); mp 113.7 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.87 (s, 1 H), 7.45 (t, *J* = 5.9 Hz, 1 H), 7.27–7.19 (m, 4 H), 7.13–7.04 (m, 4 H), 6.25 (t, *J* = 5.7 Hz, 1 H), 3.28 (q, *J* = 6.7 Hz, 2 H), 3.10–3.02 (m, 2 H), 2.79–2.66 (m, 4 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.1 (d, *J* = 3.3 Hz), 159.7 (d, *J* = 2.9 Hz), 152.2, 135.3 (d, *J* = 3.1 Hz), 135.1 (d, *J* = 3.0 Hz), 130.5 (d, *J* = 5.2 Hz), 115.0 (d, *J* = 21.1 Hz), 44.4, 40.6, 34.5, 34.0.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –112.15 to –112.27 (m, 1 F), –112.27 to –112.36 (m, 1 F).

ESI-HRMS: *m*/*z* calcd for $C_{17}H_{20}F_2N_3O_3S$ [M + H]$^+$: 384.1188; found: 384.1188.

3-[2-(1*H*-Indol-3-yl)ethyl]-1-{[2-(1*H*-indol-3-yl)ethyl]sulfamoyl}urea (3-3)

Following the general procedure, the compound **3-3** was prepared as a yellow solid; yield: 172 mg (81%); mp 156.4 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.83 (s, 2 H), 9.89 (s, 1 H), 7.52 (dd, *J* = 12.9, 7.8 Hz, 2 H), 7.47 (t, *J* = 5.7 Hz, 1 H), 7.33 (d, *J* = 7.1 Hz, 2 H), 7.15 (dd, *J* = 14.9, 2.4 Hz, 2 H), 7.09–7.03 (m, 2 H), 6.96 (q, *J* = 6.8 Hz, 2 H), 6.32 (t, *J* = 5.6 Hz, 1 H), 3.38–3.31 (m, 2 H), 3.20–3.10 (m, 2 H), 2.90 (t, *J* = 7.8 Hz, 2 H), 2.83 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.2, 136.3, 136.2, 127.1, 127.0, 122.8, 122.8, 120.9, 118.3, 118.1, 111.4, 111.4, 111.2, 43.7, 25.5, 25.0.

ESI-HRMS: *m*/*z* calcd for $C_{18}H_{24}N_5O_3S$ [M + H]$^+$: 390.1594; found: 390.1594.

3-Benzyl-1-(benzylsulfamoyl)urea (3-4)

Following the general procedure, the compound **3-4** was prepared as a colorless oil; yield: 142 mg (89%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.01 (s, 1 H), 8.00 (t, *J* = 6.2 Hz, 1 H), 7.38–7.29 (m, 6 H), 7.28–7.23 (m, 4 H), 6.71 (t, *J* = 6.0 Hz, 1 H), 4.25 (d, *J* = 5.9 Hz, 2 H), 4.13 (d, *J* = 6.1 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.3, 139.4, 137.9, 128.4, 128.2, 127.6, 127.2, 127.1, 126.9, 46.3, 42.7.

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{18}N_3O_3S$ [M + H]$^+$: 320.1063; found: 320.1063.

3-[(4-Fluorophenyl)methyl]-1-{[(4-fluorophenyl)methyl]sulfamoyl}urea (3-5)

Following the general procedure, the compound **3-5** was prepared as a white solid; yield: 143 mg (80%); mp 170.9 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.01 (s, 1 H), 8.02 (t, *J* = 6.2 Hz, 1 H), 7.34 (dd, *J* = 8.5, 5.7 Hz, 2 H), 7.28 (dd, *J* = 8.5, 5.7 Hz, 2 H), 7.20–7.13 (m, 2 H), 7.11 (t, *J* = 7.9 Hz, 2 H), 6.71 (t, *J* = 6.0 Hz, 1 H), 4.21 (d, *J* = 5.9 Hz, 2 H), 4.10 (d, *J* = 6.1 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.5 (d, *J* = 11.9 Hz), 160.1 (d, *J* = 11.6 Hz), 152.2, 135.7 (d, *J* = 2.9 Hz), 134.1 (d, *J* = 3.0 Hz), 129.6 (d, *J* = 8.2 Hz), 129.2 (d, *J* = 8.1 Hz), 115.1 (d, *J* = 15.7 Hz), 114.8 (d, *J* = 15.7 Hz), 45.5, 42.0.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –115.70 to –115.90 (m, 1 F), –115.93 to –116.12 (m, 1 F).

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{16}F_2N_3O_3S$ [M + H]$^+$: 356.0875; found: 356.0875.

3-[(4-Bromophenyl)methyl]-1-{[(4-bromophenyl)methyl]sulfamoyl}urea (3-6)

Following the general procedure, the compound **3-6** was prepared as a white solid; yield: 193 mg (81%); mp 182.2 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.07 (s, 1 H), 8.07 (t, *J* = 6.2 Hz, 1 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 7.48 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 6.74 (t, *J* = 5.9 Hz, 1 H), 4.20 (d, *J* = 5.9 Hz, 2 H), 4.10 (d, *J* = 6.1 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.2, 139.0, 137.5, 131.2, 131.0, 129.8, 129.4, 120.1, 119.9, 45.6, 42.1.

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{16}Br_2N_3O_3S$ [M + H]$^+$: 475.9274; found: 475.9274.

3-{[4-(Trifluoromethoxy)phenyl]methyl}-1-({[4-(trifluoromethoxy)phenyl]methyl}sulfamoyl)urea (3-7)

Following the general procedure, the compound **3-7** was prepared as a white solid; yield: 203 mg (83%); mp 160.7 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.12 (s, 1 H), 8.11 (t, *J* = 6.2 Hz, 1 H), 7.44 (d, *J* = 8.7 Hz, 2 H), 7.38 (d, *J* = 8.7 Hz, 2 H), 7.31 (d, *J* = 8.3 Hz, 2 H), 7.26 (d, *J* = 8.2 Hz, 2 H), 6.81 (t, *J* = 5.9 Hz, 1 H), 4.26 (d, *J* = 5.9 Hz, 2 H), 4.17 (d, *J* = 5.8 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.3, 147.4, 147.3, 139.1, 137.6, 129.4, 129.0, 120.9, 120.8, 120.1 (q, *J* = 256.9 Hz), 45.5, 42.0.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.95 to –57.03 (m, 6 F).

ESI-HRMS: *m*/*z* calcd for $C_{17}H_{16}F_6N_3O_5S$ [M + H]$^+$: 488.0709; found: 488.0709.

3-{[4-(Trifluoromethyl)phenyl]methyl}-1-({[4-(trifluoromethyl)-phenyl]methyl}sulfamoyl)urea (3-8)

Following the general procedure, the compound **3-8** was prepared as a white solid; yield: 200 mg (87%); mp 141.2 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.19 (s, 1 H), 8.20 (t, *J* = 6.2 Hz, 1 H), 7.69 (s, 1 H), 7.63–7.58 (m, 4 H), 7.58–7.49 (m, 3 H), 6.88 (t, *J* = 6.1 Hz, 1 H), 4.32 (d, *J* = 6.0 Hz, 2 H), 4.22 (d, *J* = 6.2 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.4, 141.1, 139.6, 131.4 (d, *J* = 30.6 Hz), 129.3 (d, *J* = 20.2 Hz), 129.1 (q, *J* = 31.3 Hz), 129.0 (q, *J* = 31.3 Hz), 124.3 (q, *J* = 273.2 Hz), 124.3 (q, *J* = 273.2 Hz), 124.0 (q, *J* = 3.9 Hz), 123.8 (q, *J* = 3.9 Hz), 123.6 (q, *J* = 3.6 Hz), 45.7, 42.3.

^{19}F NMR (377 MHz, DMSO-d_6): δ = –61.01 to –61.18 (m, 6 F).

ESI-HRMS: *m*/*z* calcd for $C_{17}H_{16}F_6N_3O_3S$ [M + H]$^+$: 456.0811; found: 456.0811.

3-[(4-Methylphenyl)methyl]-1-{[(4-methylphenyl)methyl]sulfamoyl}urea (3-9)

Following the general procedure, the compound **3-9** was prepared as a white solid; yield: 166 mg (96%); mp 173.3 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.95 (s, 1 H), 7.92 (t, *J* = 6.2 Hz, 1 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 7.15 (d, *J* = 1.7 Hz, 4 H), 7.10 (d, *J* = 7.8 Hz, 2 H), 6.65 (t, *J* = 5.9 Hz, 1 H), 4.20 (d, *J* = 5.8 Hz, 2 H), 4.08 (d, *J* = 6.1 Hz, 2 H), 2.29 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.2, 136.4, 136.1, 136.0, 134.8, 128.9, 128.8, 127.6, 127.2, 46.1, 42.5, 20.7.

ESI-HRMS: *m*/*z* calcd for $C_{17}H_{22}N_3O_3S$ [M + H]$^+$: 348.1376; found: 348.1376.

3-{[4-(Propan-2-yl)phenyl]methyl}-1-({[4-(propan-2-yl)phenyl]-methyl}sulfamoyl)urea (3-10)

Following the general procedure, the compound **3-10** was prepared as a white solid; yield: 167 mg (82%); mp 143.4 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.96 (s, 1 H), 7.91 (t, *J* = 6.2 Hz, 1 H), 7.25–7.15 (m, 8 H), 6.68 (t, *J* = 5.9 Hz, 1 H), 4.22 (d, *J* = 5.8 Hz, 2 H), 4.09 (d, *J* = 5.9 Hz, 2 H), 2.86 (pd, *J* = 6.9, 2.7 Hz, 2 H), 1.20 (d, *J* = 2.3 Hz, 6 H), 1.18 (d, *J* = 2.3 Hz, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.2, 147.2, 147.1, 136.8, 135.2, 127.6, 127.2, 126.2, 126.1, 46.1, 42.5, 33.1, 23.9.

ESI-HRMS: *m*/*z* calcd for $C_{21}H_{30}N_3O_3S$ [M + H]$^+$: 404.2002; found: 404.2002.

3-[(4-*tert*-Butylphenyl)methyl]-1-{[(4-*tert*-butylphenyl)methyl]-sulfamoyl}urea (3-11)

Following the general procedure, the compound **3-11** was prepared as a white solid; yield: 184 mg (85%); mp 134.0 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.97 (s, 1 H), 7.91 (t, *J* = 6.1 Hz, 1 H), 7.34 (t, *J* = 8.2 Hz, 4 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 6.69 (t, *J* = 6.0 Hz, 1 H), 4.23 (d, *J* = 5.8 Hz, 2 H), 4.10 (d, *J* = 6.1 Hz, 2 H), 1.27 (s, 18 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.2, 149.5, 149.3, 136.4, 134.9, 127.4, 126.9, 125.1, 124.9, 46.1, 42.4, 34.2, 31.2.

ESI-HRMS: *m*/*z* calcd for $C_{23}H_{34}N_3O_3S$ [M + H]$^+$: 432.2315; found: 432.2315.

3-[(3-Fluorophenyl)methyl]-1-{[(3-fluorophenyl)methyl]sulfamoyl}urea (3-12)

Following the general procedure, the compound **3-12** was prepared as a white solid; yield: 149 mg (84%); mp 160.2 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.12 (s, 1 H), 8.13 (t, *J* = 6.3 Hz, 1 H), 7.42–7.29 (m, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 7.12–7.02 (m, 4 H), 6.79 (t, *J* = 6.0 Hz, 1 H), 4.26 (d, *J* = 6.0 Hz, 2 H), 4.17 (d, *J* = 6.2 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.4 (d, *J* = 11.6 Hz), 161.0 (d, *J* = 11.6 Hz), 152.4, 142.6 (d, *J* = 7.0 Hz), 141.1 (d, *J* = 7.4 Hz), 130.3 (d, *J* = 8.3 Hz), 130.1 (d, *J* = 8.3 Hz), 123.5 (d, *J* = 2.8 Hz), 123.1 (d, *J* = 2.6 Hz), 114.3, 114.1, 113.9 (d, *J* = 5.9 Hz), 113.7 (d, *J* = 7.7 Hz), 113.5, 45.7, 42.3.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –113.49 (q, *J* = 9.4 Hz, 1 F), –113.41 (q, *J* = 9.4 Hz, 1 F).

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{16}F_2N_3O_3S$ [M + H]$^+$: 356.0875; found: 356.0875.

3-[(2-Fluorophenyl)methyl]-1-{[(2-fluorophenyl)methyl]sulfamoyl}urea (3-13)

Following the general procedure, the compound **3-13** was prepared as a white solid; yield: 144 mg (81%); mp 145.6 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.08 (s, 1 H), 8.06 (t, *J* = 6.2 Hz, 1 H), 7.44 (t, *J* = 6.9 Hz, 1 H), 7.38–7.26 (m, 3 H), 7.22–7.10 (m, 4 H), 6.74 (t, *J* = 6.0 Hz, 1 H), 4.30 (d, *J* = 5.9 Hz, 2 H), 4.20 (d, *J* = 6.0 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 161.2 (d, *J* = 21.4 Hz), 158.8 (d, *J* = 21.9 Hz), 152.2, 130.0 (d, *J* = 4.1 Hz), 129.4 (d, *J* = 4.4 Hz), 129.2 (d, *J* = 8.2 Hz), 129.1 (d, *J* = 8.1 Hz), 126.2, 124.8 (d, *J* = 14.4 Hz), 124.4 (d, *J* = 3.5 Hz), 124.2 (d, *J* = 3.3 Hz), 115.2 (d, *J* = 15.2 Hz), 115.0 (d, *J* = 15.2 Hz), 36.8, 36.7.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –118.86 to –119.04 (m, 1 F), –119.04 to –119.26 (m, 1 F).

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{16}F_2N_3O_3S$ [M + H]$^+$: 356.0875; found: 356.0875.

3-[(2*H*-1,3-Benzodioxol-5-yl)methyl]-1-{[(2*H*-1,3-benzodioxol-5-yl)methyl]sulfamoyl}urea (3-14)

Following the general procedure, the compound **3-14** was prepared as a white solid; yield: 186 mg (92%); mp 160.2 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.94 (s, 1 H), 7.92 (t, *J* = 6.2 Hz, 1 H), 6.90–6.80 (m, 4 H), 6.79–6.70 (m, 2 H), 6.63 (t, *J* = 5.9 Hz, 1 H), 5.98 (d, *J* = 2.4 Hz, 4 H), 4.14 (d, *J* = 5.9 Hz, 2 H), 4.03 (d, *J* = 6.1 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.2, 147.3, 147.2, 146.3, 146.2, 133.3, 131.7, 120.9, 120.5, 108.2, 108.1, 107.9, 107.9, 100.9, 46.2, 42.6.

ESI-HRMS: *m*/*z* calcd for $C_{17}H_{18}N_3O_7S$ [M + H]$^+$: 408.0860; found: 408.0860.

3-[(Naphthalen-1-yl)methyl]-1-{[(naphthalen-1-yl)methyl]sulfamoyl}urea (3-15)

Following the general procedure, the compound **3-15** was prepared as a white solid; yield: 182 mg (87%); mp 180.5 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.08 (s, 1 H), 8.12 (t, *J* = 6.2 Hz, 3 H), 7.97 (t, *J* = 7.9 Hz, 2 H), 7.92–7.84 (m, 2 H), 7.63–7.52 (m, 5 H), 7.50 (d, *J* = 5.5 Hz, 2 H), 7.48–7.43 (m, 1 H), 6.86 (t, *J* = 5.7 Hz, 1 H), 4.78 (d, *J* = 5.7 Hz, 2 H), 4.61 (d, *J* = 5.9 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.2, 134.6, 133.4, 133.3, 132.9, 130.9, 130.8, 128.6, 128.5, 128.0, 127.8, 126.4, 126.3, 126.3, 125.9, 125.8, 125.5, 125.4, 125.3, 123.5, 123.4, 44.6, 40.8.

ESI-HRMS: *m*/*z* calcd for $C_{23}H_{22}N_3O_3S$ [M + H]$^+$: 420.1376; found: 420.1376.

3-(2,3-Dihydro-1*H*-inden-1-yl)-1-[(2,3-dihydro-1*H*-inden-1-yl)sulfamoyl]urea (3-16)

Following the general procedure, the compound **3-16** was prepared as a white solid; yield: 162 mg (87%); mp 175.2 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.91 (s, 1 H), 8.10 (d, *J* = 8.5 Hz, 1 H), 7.41–7.33 (m, 1 H), 7.32–7.17 (m, 7 H), 6.63 (d, *J* = 8.0 Hz, 1 H), 5.19 (qd, *J* = 7.8, 3.6 Hz, 1 H), 4.82 (q, *J* = 7.9 Hz, 1 H), 2.99–2.88 (m, 2 H), 2.87–2.71 (m, 2 H), 2.50–2.38 (m, 2 H), 2.01–1.73 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.1, 152.1, 143.6, 143.0, 142.9, 142.8, 142.6, 142.6, 127.7, 126.5, 126.5, 126.4, 126.3, 124.7, 124.5, 124.3, 123.7, 58.3, 58.3, 54.6, 33.5, 33.5, 33.4, 33.4, 29.7, 29.5.

ESI-HRMS: *m*/*z* calcd for $C_{19}H_{22}N_3O_3S$ [M + H]$^+$: 372.1376; found: 372.1376.

3-[(1*S*)-1-(Naphthalen-1-yl)ethyl]-1-{[(1*S*)-1-(naphthalen-1-yl)ethyl]sulfamoyl}urea (3-17)

Following the general procedure, the compound **3-17** was prepared as a white solid; yield: 206 mg (91%); mp 174.1 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.74 (s, 1 H), 8.41 (d, *J* = 7.5 Hz, 1 H), 8.13 (t, *J* = 10.6 Hz, 2 H), 7.97 (d, *J* = 7.7 Hz, 1 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.87 (t, *J* = 4.9 Hz, 1 H), 7.75 (d, *J* = 8.2 Hz, 1 H), 7.66 (d, *J* = 7.2 Hz, 1 H), 7.61–7.48 (m, 6 H), 7.34 (t, *J* = 7.7 Hz, 1 H), 6.76 (d, *J* = 7.6 Hz, 1 H), 5.60 (pent, *J* = 7.0 Hz, 1 H), 5.37 (t, *J* = 7.3 Hz, 1 H), 1.55–1.46 (m, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 151.3, 139.8, 139.7, 133.5, 133.3, 130.2, 129.6, 128.7, 128.7, 127.5, 127.2, 126.3, 126.2, 125.7, 125.5, 125.5, 123.2, 123.1, 122.7, 122.4, 49.3, 45.0, 23.1, 22.0.

ESI-HRMS: *m*/*z* calcd for $C_{25}H_{26}N_3O_3S$ [M + H]$^+$: 448.1689; found: 448.1689.

3-Cyclohexyl-1-(cyclohexylsulfamoyl)urea (3-18)

Following the general procedure, the compound **3-18** was prepared as a white solid; yield: 134 mg (88%); mp 155.7 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.54 (s, 1 H), 7.39 (d, *J* = 7.6 Hz, 1 H), 6.12 (d, *J* = 7.8 Hz, 1 H), 3.49–3.35 (m, 1 H), 3.10–2.96 (m, 1 H), 1.82–1.69 (m, 4 H), 1.69–1.57 (m, 4 H), 1.55–1.45 (m, 2 H), 1.34–1.01 (m, 10 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 151.3, 52.4, 47.8, 32.9, 32.4, 25.1, 25.0, 24.6, 24.2.

ESI-HRMS: *m*/*z* calcd for $C_{13}H_{26}N_3O_3S$ [M + H]$^+$: 304.1689; found: 304.1689.

3-(4-Bromophenyl)-1-[(4-bromophenyl)sulfamoyl]urea (3-19)

Following the general procedure, the compound **3-19** was prepared as a colorless oil; yield: 100 mg (45%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.48 (s, 1 H), 8.68 (s, 1 H), 7.49 (d, *J* = 8.8 Hz, 2 H), 7.44 (d, *J* = 8.8 Hz, 2 H), 7.33 (d, *J* = 8.8 Hz, 2 H), 7.15 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 149.8, 137.7, 137.3, 131.9, 131.6, 121.4, 120.8, 115.7, 114.6.

ESI-HRMS: *m*/*z* calcd for $C_{13}H_{10}Br_2N_3O_3S$ [M – H]$^-$: 445.8815; found: 445.8815.

3-(Benzyloxy)-1-[(benzyloxy)sulfamoyl]urea (3-20)

Following the general procedure, the compound **3-20** was prepared as a white solid; yield: 156 mg (89%); mp 155.7 °C (dec.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1 H), 7.86 (s, 1 H), 7.44–7.30 (m, 11 H), 4.96 (s, 2 H), 4.82 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.8, 135.1, 133.9, 129.7, 129.6, 129.5, 129.2, 129.0, 128.7, 79.8, 79.5.

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{18}N_3O_5S$ $[M + H]^+$: 352.0962; found: 352.0962.

4-Phenyl-*N*-((4-phenylpiperidin-1-yl)sulfonyl)piperidine-1-carboxamide (3-21)

Following the general procedure, the compound **3-21** was prepared as a colorless oil; yield: 168 mg (79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 4 H), 7.28–7.18 (m, 6 H), 4.23 (d, *J* = 13.4 Hz, 1 H), 4.00 (d, *J* = 12.7 Hz, 2 H), 3.17 (t, *J* = 11.2 Hz, 2 H), 2.98 (t, *J* = 12.9 Hz, 2 H), 2.82–2.61 (m, 2 H), 1.95 (d, *J* = 13.5 Hz, 4 H), 1.78 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.8, 145.1, 145.0, 128.7, 128.6, 126.8, 126.6, 126.6, 47.5, 45.1, 42.4, 41.8, 33.0, 32.9.

ESI-HRMS: *m*/*z* calcd for $C_{23}H_{30}N_3O_3S$ $[M + H]^+$: 428.2002; found: 428.2002.

3-Ethyl 5-Methyl 4-(2-Chlorophenyl)-2-((2-((*N*-((2-((4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl)methoxy)ethyl)carbamoyl)sulfamoyl)amino)ethoxy)methyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (3-22)

Following the general procedure, the compound **3-22** was prepared as a yellow solid; yield: 419 mg (91%); mp 97.0 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.01 (s, 1 H), 8.47 (s, 1 H), 8.39 (s, 1 H), 7.58 (t, *J* = 5.9 Hz, 1 H), 7.33 (t, *J* = 6.4 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7.24–7.18 (m, 2 H), 7.11 (t, *J* = 7.6 Hz, 2 H), 6.50–6.42 (m, 1 H), 5.30 (s, 2 H), 4.67–4.48 (m, 4 H), 4.03–3.89 (m, 4 H), 3.56–3.45 (m, 10 H), 3.28 (q, *J* = 5.6 Hz, 2 H), 3.14 (q, *J* = 5.6 Hz, 2 H), 2.31 (s, 3 H), 2.30 (s, 3 H), 1.09 (td, *J* = 7.1, 1.8 Hz, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 167.1, 166.3, 152.4, 145.8, 145.8, 145.5, 145.3, 145.1, 144.7, 131.1, 131.0, 131.0, 128.9, 127.8, 127.4, 102.6, 101.9, 101.9, 101.7, 69.3, 68.8, 66.6, 66.4, 59.4, 59.3, 50.5, 42.5, 36.7, 36.6, 18.3, 18.2, 14.1.

ESI-HRMS: *m*/*z* calcd for $C_{41}H_{50}Cl_2N_5O_{13}S$ $[M + H]^+$: 922.2497; found: 922.2497.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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