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A facile synthesis of sulfonylureas via water assisted preparation of carbamates

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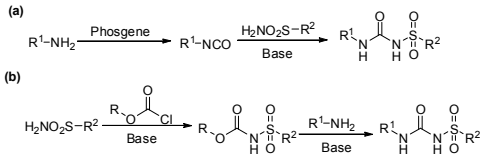
A novel and simple approach to the synthesis of Sulfonylureas has been reported. It involved the reaction of various amines with diphenyl carbonate to yield the corresponding carbamates, which subsequetly reacted with different sulphonamides to produce different sulfonylureas in excellent yields. The first reaction of diphenyl carbonate with amines was carried out in aqueous:organic (H_2O:THF, 90:10) medium at room temperature to produce carbamates that paved a straightforward route to sulfonylureas after reaction with sulfonamides. Above process avoided traditional multistep protocols and use of hazardous, irritant, toxic and moisture sensitive reagents such as phosgene, isocyanates and/or chloroformates.

Introduction

Sulfonylurea derivatives were the first oral hypoglycemic agents that have been in use for the treatment of type II diabetics for almost eight decades.[1] All sulfonylurea hypoglycemic drugs act by releasing insulin from the β cells of pancreas.[2] Along with their secretogogues action, sulfonylureas are also reported to have insulin sensitizers activities.[3-5] In addition, these molecules exhibited other therapeutic uses such as their use as diuretic agents (e.g. torasemide)[6], agents active against mycobacterium tuberculosis,[7,8] antimalarial[9], antifungal[10,11] anticancer agents[12,13] and Zinc Metalloenzyme Modulators.[14] More interestingly sulfonylureas are also reported to act as herbicides (e.g., chlosulfuron).[15-17] Most commonly, sulfonylureas are prepared either by treatment of a sulphonamide with an isocyanate in the presence of a base[18,19] or by converting the sulfonamides into their carbamate derivatives, which upon treatment with amines provide the corresponding sulfonylureas,[20,21] Scheme 1. Isocyanate synthesis involves the use of phosgene,[22] a highly toxic chemical, which requires special handling on scale.[23] Similarly carbamate of sulfonamides are prepared from chloroformates which are, subsequently, synthesized from phosgene.[24]



Scheme 1. Sulfonylurea synthesis **(a)** via isocyanate; **(b)** via carbamate.

Although above processes to sulfonylureas have been optimized/modified to minimize the hazards associated with the manufacturing of these molecules but a facile, environmentally benign process deemed desirable for such an important class of molecules. Increasing regulatory pressure, market competition and environmental awareness also dictate the development of an improved manufacturing process of sulfonylureas. One such ideal process would be devoid of any hazardous reagents/solvents. In the present paper a novel and simple approach to the synthesis of sulfonylureas without any use of phosgene, isocyanates and/or chloroformates has been reported.

Results and discussion

Carbamates of amines have already been used in sulfonylureas synthesis[25] but the process to synthesize above carbamates did involve the use of either phosgene gas or chloroformates.[24] Alkyl[26,27] and aryl[28] carbonates, both, have also been used to synthesize carbamates. As compared to aryl carbonates, the synthesis of alkyl carbonates gave various side products.[29] The reactivity of carbamates with nucleophiles is related to *pKa* values of the released alcohols hence *O*-alkyl carbamates do not react efficiently[30,31] as compare to *O*-aryl carbamates. Aryl carbonates have successfully been used for the synthesis *O*-Aryl carbamates using aromatic amines only.[28] Literature search also revealed that *N*-alkyl *O*-aryl carbamates have been synthesized from reaction of aliphatic amines with chlorofomates.[31] As most of the antidiabetic sulfonylureas have aliphatic *N*-side chains therefore *N*-alkyl *O*-aryl carbamates are required for the synthesis of these molecules. Keeping in view the low cost of aryl carbonate such as diphenyl carbonate (DPC), it appeared a synthetic challenge to prepare *N*-alkyl *O*-aryl carbamates from the reaction of aryl carbonated with primary amines. Therefore, our investigation started with the reaction of diphenyl carbonate with primary aliphatic amines to produce carbamates as the key intermediates which were then

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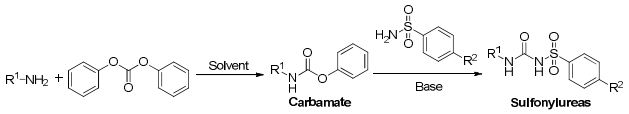
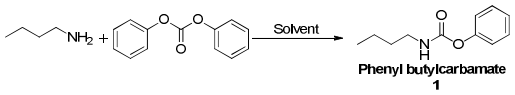
converted in to sulfonylureas. The overall process executed to synthesize various sulfonylureas is depicted in Scheme 2.



Scheme 2. New route to sulfonylureas via carbamates.

Our first target was to synthesize Tolbutamide-currently used as an antidiabetic drug. The synthesis of required intermediate, phenyl butylcarbamate, was explored as shown in Table 1. The use of organic solvents gave the desired product (carbamate) in a very low isolated yield (22-30%). The major side product of the reaction was identified as a symmetrical urea i.e. *N*,*N*`-dibutylurea. The formation of symmetrical urea seemed obvious as the carbmate intermediate was expected to react further with *n*-butyl amine. In order to improve the yield of the carbamate formation and/or to minimize the side reaction *i.e.* the formation of symmetrical urea, several solvents and solvent mixtures were tried, and the results are listed in Table 1. Although, in organic solvents, carbamate yield was low but the reaction was over within 2 hours. To our surprise, the yield of carbamate increased to 83% in aqueous medium (Table 1, entry 7), but 8 hours were required for the reaction to go to completion. The aqueous: organic (Water:THF, 90:10) mixture gave an optimal yield of carbamate (83%) in 7 hours of reaction time, (Table 1, entry 8). Further increase in the amount of organic solvent led to poor yields. The variation in molar ratio of diphenyl carbonate in a range of 1.0 to 1.5 as compare to amine made no significant impact on the outcome of the reaction.

Table 1

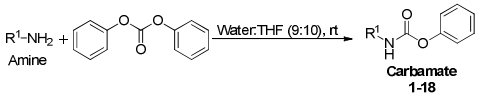


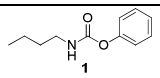
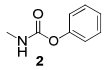
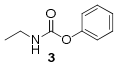
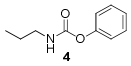
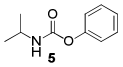
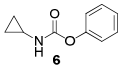
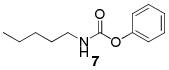
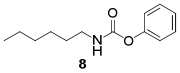
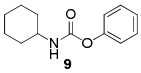
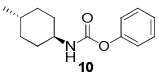
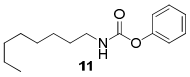
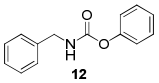
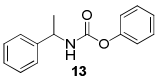
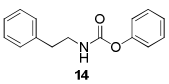
entry	Solvent	Time (hrs)[a]	Carbamate[b]
1	Acetonitrile, rt	2	**30**
2	THF, rt	2	**26**
3	Acetone, rt	2	**22**
4	DCM, rt	2	**23**
5	DCE, rt	2	**24**
6	DMF, rt	2	**28**
7	Water, rt	8	**83**
8	Water:THF (90:10), rt	7	**83**
9	Water:THF (80:20), rt	6	**78**
10	Water:THF (70:30), rt	5	**71**
11	Water:THF (60:40), rt	4	**62**
12	Water:THF (50:50), rt	3	**51**
13	Water:THF (40:60), rt	3	**40**

[a]The reaction times were obtained from the consumption of amine as followed by TLC.
[b]Isolated % yield.

After establishing the optimal conditions for the preparation of carbamates, the scope and generality of the procedure was explored. As given in Table 2, aliphatic cyclic and acyclic (straight and branched chain) primary amines afforded the desired carbamates in good to excellent yields, (Table 2, entries 1-11). Furthermore, the method worked well for benzyl amine and other aralkyl amines, (Table 2, entries 12-14). The reaction of secondary alkyl amines also proceeded smoothly and the expected carbamates were obtained in good yields, (Table 2, entries 15-18). In order to synthesize carbamate of aromatic amine, aniline was used, but with aniline no detectable amount of carbamate was produced. Low basicity (pka≈4.6) of aniline as compared to departing phenol (pka≈9.95) accounts for the observed outcome. Likewise, other arylamines such as 3-chloroaniline, 4-cyanoaniline and *N*-methylaniline and heteroarylamines (2-aminothiazole, 2-aminopyridine, 2-aminopyrimidine) showed no visible sign of formation of corresponding carbamates under the reaction conditions used to generate carbamates of alkyl and aryalkyl amines.

Table 2



Entry	Amine	Carbamates	Time (hrs)	Yield[a]
1	Butyl amine		8	83
2	Methyl amine		7	88
3	Ethyl amine		7	85
4	Propyl amine		7	87
5	Isopropyl amine		9	78
6	Cyclopropyl amine		9	75
7	Pentyl amine		8	84
8	Hexyl amine		8	83
9	Cyclohexyl amine		8	85
10	*trans*-4-Methyl cyclohexyl amine		8	84
11	Octyl amine		8	84
12	Benzyl amine		8	85
13	1-phenylethyl amine		8	86
14	2-phenylethyl amine		8	85

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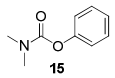
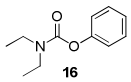
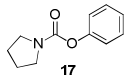
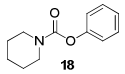
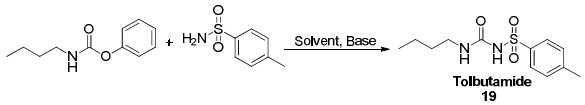
15	Dimethyl amine	 15	8	86
16	Diethyl amine	 16	8	84
17	Pyrrolidine	 17	7	85
18	Piperidine	 18	6	78

[a]Isolated % yield.

In order to synthesize the Tolbutamide 4-methyl benzenesulfonamide was reacted with phenylbutyl carbamate in acetonitrile without any base but no product was detected, (Table 3, entry 1). The reaction was also performed in DMF in order to attain a higher reaction temperature (Table 3, entry 2) but again no reaction was observed. Then, the reaction was investigated in various bases (Table 3, entries 3-14). The use of inorganic bases such as K_2CO_3, NaOH, Cs_2CO_3 and LiOH gave poor results, most likely due to the hydrolysis of carbamate intermediate. Organic bases such as Pyridine, DMAP, Triethylamine and DBU gave good yields. Optimal yield was achieved when the reaction was carried out either in a 1:6 v/v mixture of acetonitrile and triethylamine (Table 3, entry 12) in 12 hours or in the presence of a catalytic amount of DBU (Table 3, entry 14) in four hours. The use of triethylamine alone, as a solvent, for the reaction led to poor yields of sulfonylurea possibly due to low solubility of reactants and/or products, (Table 3, entry 13).

Table 3

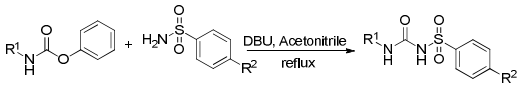


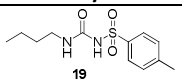
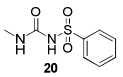
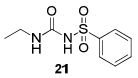
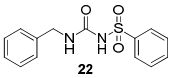
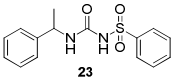
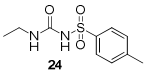
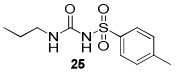
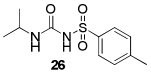
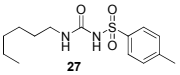
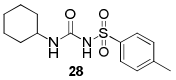
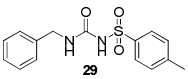
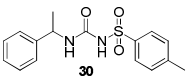
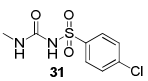
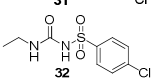
Entry	Solvent/Base	Time (hrs)[a]	Sulfonylurea[b]
1	Acetonitrile, reflux	12	nd
2	DMF, reflux		nd
3	Acetonitrile, K_2CO_3, reflux		42
4	Acetonitrile, NaOH, reflux	12	45
5	Acetonitrile, Cs_2CO_3, reflux	12	50
6	Acetonitrile, LiOH, reflux	12	50
7	Acetonitrile, TEA, reflux	12	60
8	Acetonitrile, Pyridine, reflux	12	62
9	Acetonitrile, DMAP, reflux	12	65
10	Acetonitrile:TEA (1:2), reflux	12	63
11	Acetonitrile:TEA (1:4), reflux	12	70
12	Acetonitrile:TEA(1:6), reflux	12	80
13	TEA, reflux	12	70
14	Acetonitrile, DBU, reflux	4	80

[a]The reaction times were obtained from the consumption of carbamate as followed by TLC.
[b]Isolated % yield.
nd=not detected

As shown in Table 4, the above optimized reaction conditions have successfully been extended to synthesize other sulfonylureas by reacting different carbamates with a variety of sulphonamides. By applying present methodology another antidiabetic drug, Chlorpropamide (**33**) was also synthesized in an isolated yield of 85%.

Table 4



Entry	R_1	R_2	Sulfonylurea	Yield[a]
1	Butyl	CH_3	 19	80
2	Methyl	H	 20	82
3	Ethyl	H	 21	81
4	Benzyl	H	 22	85
5	1-phenylethyl	H	 23	83
6	Ethyl	CH_3	 24	81
7	Propyl	CH_3	 25	82
8	Isopropyl	CH_3	 26	81
9	Hexyl	CH_3	 27	74
10	Cyclohexyl	CH_3	 28	83
11	Benzyl	CH_3	 29	80
12	1-phenylethyl	CH_3	 30	82
13	Methyl	Cl	 31	81
14	Ethyl	Cl	 32	82

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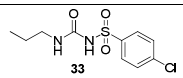
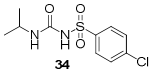
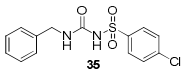
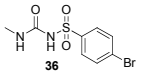
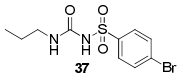
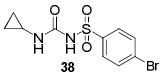
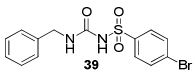
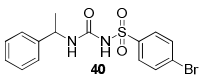
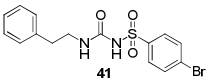
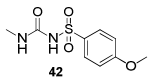
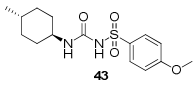
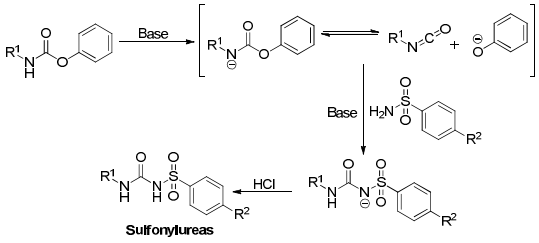
15	Propyl	Cl	 **33**	85
16	Isopropyl	Cl	 **34**	83
17	Benzyl	Cl	 **35**	84
18	Methyl	Br	 **36**	83
19	Propyl	Br	 **37**	81
20	Cyclopropyl	Br	 **38**	80
21	Benzyl	Br	 **39**	84
22	1-phenylethyl	Br	 **40**	81
23	2-phenylethyl	Br	 **41**	79
24	Methyl	Methoxy	 **42**	85
25	*trans*-4-Methyl cyclohexyl	Methoxy	 **43**	86

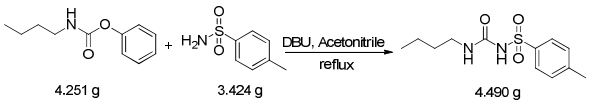
[a]Isolated % yield.

After successfully synthesizing the sulfonylureas, we decided to synthesize trisubstituted sulfonylureas by the reaction of carbamates of secondary amines (**15**-**18**) with different sulphonamides but no reaction was observed in either case. Based on above observations on reactions of carbmates of secondary amines and literature review,[32] it seems reasonable to conclude that above reactions proceed via the formation of an isocynate intermediate and a base is required to extract hydrogen from the carbamate to generate it. The resulting isocyanate reacts quickly with sulphonamide to produce the desired sulfonylurea (Scheme 3). In carbamates of secondary amines as no proton is available hence reaction did not proceed even in the presence of a suitable base.



Scheme 3. Possible routes to sulfonylureas via base catalysed formation of isocyanates.

Moreover, to further demonstrate the practicality of the above methodology, Tolbutamide, a marketed antidiabetic sulfonylurea was synthesized on gram scale and the desired product was obtained in 83% isolated yield (Scheme 4).



Scheme 4. Gram scale synthesis of Tolbutamide.

Conclusions

In conclusion, an efficient, cost-effective, easy and green method has been developed for the preparation of sulfonylureas without any use of hazardous, irritant, toxic and moisture sensitive reagents such as phosgene, isocyanates and/or chloroformates. This efficient procedure has a broad substrate scope, and consistently afforded sulfonylureas in good to excellent yields. In addition, the procedure is operationally simple, potentially scalable and significantly benign as compared to current methodologies available for the synthesis of these important antidiabetic compounds.

Experimental

All reagents and solvents were used as received from Sigma Aldrich and Alfa Aesar. Melting points were determined on a Büchi melting point apparatus. ^{1}H and ^{13}C NMR spectra were obtained in DMSO-d_6 as solvent using a 400 MHz and 100 MHz spectrometer, respectively, with Me_4Si as an internal standard. Coupling constants (*J* values) are reported in Hz. High resolution mass spectra (HRMS) were obtained using electron spray ionisation (ESI) technique and as TOF mass analyser. Thin layer chromatography was performed on pre coated silica gel plates (F254, Merck). Column chromatography was performed on silica gel (60-120 mesh).

Typical procedure for the synthesis of carbamates (1-18)

Finely powdered diphenyl carbonate (15 mmol) was suspended in a mixture of THF (4 mL) and water (36 mL). The resulting suspension was stirred at room temperature followed by dropwise addition of amine (15 mmol). The reaction continued at room temperature and was monitored by TLC. After completion of reaction, as indicated by TLC, the reaction mixture was extracted with ethyl acetate, and the organic layer was washed with cold aquous NaOH solution (10%) and then with brine. Organic layer was dried over anhydrours Na_2SO_4, concentrated under reduced pressure and purified by column chromatography using hexane:ethyl acetate mixture as eluent to afford the desired carbamate.

Phenyl butyl carbamate (1)

White solid, mp 38-40 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.72 (t, *J*=5.6 Hz, 1H), 7.37 (t, *J*=7.9 Hz, 2H), 7.19 (t, *J*=7.4 Hz, 1H), 7.08 (d, *J*=7.5 Hz, 2H), 3.06 (quartet, *J*=6.9 Hz, 2H), 1.45(quintet, *J*=7.5 Hz, 2H), 1.32(sextet, *J*=7.6 Hz, 2H), 0.89 (t, *J*=7.3 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 154.8, 151.5, 129.6, 125.2, 122.1, 40.5, 31.8, 19.8, 14.0. HRMS (ESI): calcd. for $C_{11}H_{15}NNaO_2$ $[M+Na]^+$, 216.1000, found: 216.1000.

Phenyl methyl carbamate (2)

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White solid, mp 83-85 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.59 (d, *J*=4.1 Hz, 1H), 7.37 (t, *J*=8.3 Hz, 2H), 7.19 (t, *J*=7.4 Hz, 1H), 7.09 (d, *J*=7.5 Hz, 2H), 2.67 (d, *J*=4.6 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 155.3, 151.5, 129.6, 125.3, 122.2, 27.5. HRMS (ESI): calcd. for $C_8H_9NNaO_2$ $[M+Na]^+$, 174.0531, found: 174.0536.

Phenyl ethyl carbamate (3)

White solid, mp 48-50 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.71 (t, *J*=4.8 Hz, 1H), 7.36 (t, *J*=8.2 Hz, 2H), 7.18 (t, *J*=7.4 Hz, 1H), 7.08 (d, *J*=7.6 Hz, 2H), 3.09 (quintet, *J*=7.1 Hz, 2H), 1.08 (t, *J*=7.2 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 154.6, 151.5, 129.6, 125.2, 122.2, 35.7, 15.3. HRMS (ESI): calcd. for $C_9H_{11}NNaO_2$ $[M+Na]^+$, 188.0687, found: 188.0687.

Phenyl propyl carbamate (4)

White solid, mp 56-58 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.73 (t, *J*=5.4 Hz, 1H), 7.36 (t, *J*=8.3 Hz, 2H), 7.18 (t, *J*=7.4 Hz, 1H), 7.08 (d, *J*=7.5 Hz, 2H), 3.03 (quartet, *J*=6.9 Hz, 2H), 1.48 (sextet, *J*=7.2 Hz, 2H), 0.88 (t, *J*=7.4 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 154.8, 151.5, 129.6, 125.2, 122.1, 42.6, 22.9, 11.6. HRMS (ESI): calcd. for $C_{10}H_{13}NNaO_2$ $[M+Na]^+$, 202.0844, found: 202.0840.

Phenyl isopropyl carbamate (5)

White solid, mp 80-82 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.66 (d, *J*=7.6 Hz, 1H), 7.37 (t, *J*=8.2 Hz, 2H), 7.19 (t, *J*=7.4 Hz, 1H), 7.08 (d, *J*=7.6 Hz, 2H), 3.71-3.60 (m, 1H), 1.12 (d, *J*=6.5 Hz, 6H). ^{13}C-NMR (100 MHz, DMSO-d_6): 153.9, 151.5, 129.6, 125.2, 122.2, 43.1, 22.8. HRMS (ESI): calcd. for $C_{10}H_{13}NNaO_2$ $[M+Na]^+$, 202.0846, found: 202.0846.

Phenyl cyclopropyl carbamate (6)

White solid, mp 73-75 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.92 (br. s, 1H), 7.36 (t, *J*=7.9 Hz, 2H), 7.19 (t, *J*=7.3 Hz, 1H), 7.09 (d, *J*=7.8 Hz, 2H), 2.55 (sextet, *J*=3.4 Hz, 1H), 0.65-0.51 (m, 4H). ^{13}C-NMR (100 MHz, DMSO-d_6): 155.4, 151.4, 129.6, 125.3, 122.2, 23.5, 6.2. HRMS (ESI): calcd. for $C_{10}H_{11}NNaO_2$ $[M+Na]^+$, 200.0687, found: 200.0687.

Phenyl pentyl carbamate (7)

White solid, mp 48-50 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.72 (t, *J*=5.5 Hz, 1H), 7.37 (t, *J*=8.2 Hz, 2H), 7.19 (t, *J*=7.4 Hz, 1H), 7.09 (d, *J*=7.5 Hz, 2H), 3.05 (quartet, *J*=6.9 Hz, 2H), 1.47 (quintet, *J*=7.1 Hz, 2H), 1.33-1.26 (m, 4H), 0.88 (t, *J*=7.0 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 154.7, 151.6, 129.6, 125.2, 122.1, 40.8, 29.3, 28.9, 22.2, 14.3. HRMS (ESI): calcd. for $C_{12}H_{17}NNaO_2$ $[M+Na]^+$, 230.1157, found: 230.1160.

Phenyl hexyl carbamate (8)

White solid, mp 44-46 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.72 (t, *J*=5.4 Hz, 1H), 7.37 (t, *J*=8.1 Hz, 2H), 7.19 (t, *J*=7.3 Hz, 1H), 7.08 (d, *J*=7.6 Hz, 2H), 3.05 (quartet, *J*=6.8 Hz, 2H), 1.46 (quintet, *J*=7.1 Hz, 2H), 1.35-1.22 (m, 6H), 0.87 (t, *J*=6.9 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 154.7, 151.6, 129.6, 125.2, 122.1, 40.9, 31.4, 29.6, 26.3, 22.5, 14.3. HRMS (ESI): calcd. for $C_{13}H_{19}NNaO_2$ $[M+Na]^+$, 244.1313, found: 244.1309.

Phenyl cyclohexyl carbamate(9)

White solid, mp 138-140 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.69 (d, *J*=7.8 Hz, 1H), 7.36 (t, *J*=8.1 Hz, 2H), 7.18 (t, *J*=7.4 Hz, 1H), 7.08 (d, *J*=7.5 Hz, 2H), 3.36-3.26 (m, 1H), 1.83-1.54 (m, 5H), 1.28-1.09 (m, 5H). ^{13}C-NMR (100 MHz, DMSO-d_6): 153.9, 151.5, 129.6, 125.2, 122.2, 50.2, 32.9, 25.5, 25.0. HRMS (ESI): calcd. for $C_{13}H_{17}NNaO_2$ $[M+Na]^+$, 242.1157, found: 242.1154.

Phenyl ((1r,4r)-4-methylcyclohexyl)carbamate (10)

White solid, mp 175-177 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.68 (d, *J*=7.9 Hz, 1H), 7.36 (t, *J*=8.1 Hz, 2H), 7.18 (t, *J*=7.3 Hz, 1H), 7.08 (d, *J*=7.6 Hz, 2H), 3.34-3.18 (m, 1H), 1.85 (d, *J*=10.1 Hz, 2H), 1.67 (d, *J*=12.2 Hz, 2H), 1.29-1.22 (m, 3H), 1.03-0.91 (m, 2H), 0.86 (d, *J*=6.4 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 153.9, 151.5, 129.6, 125.2, 122.2, 50.3, 33.9, 32.8, 31.8, 22.6. HRMS (ESI): calcd. for $C_{14}H_{19}NNaO_2$ $[M+Na]^+$, 256.1313, found: 256.1309.

Phenyl octyl carbamate (11)

White solid, mp 40-42 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.72 (t, *J*=5.6 Hz, 1H), 7.36 (t, *J*=8.2 Hz, 2H), 7.18 (t, *J*=7.4 Hz, 1H), 7.08 (d, *J*=7.5 Hz, 2H), 3.04 (quartet, *J*=6.7 Hz, 2H), 1.46 (quintet, *J*=6.8 Hz, 2H), 1.37-1.18 (m, 10H), 0.86 (t, *J*=7.0 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 154.7, 151.5, 129.6, 125.2, 122.1, 40.8, 31.7, 29.6, 29.2, 29.1, 26.7, 22.5, 14.4. HRMS (ESI): calcd. for $C_{15}H_{23}NNaO_2$ $[M+Na]^+$, 272.1626, found: 272.1628.

Phenyl benzyl carbamate (12)

White solid, mp 82-84 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 8.31 (t, *J*=6.1 Hz, 1H), 7.39-7.24 (m, 7H), 7.19 (t, *J*=7.8 Hz, 1H), 7.11 (d, *J*=7.7 Hz, 2H), 4.28 (d, *J*=6.1 Hz, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6): 155.1, 151.5, 139.7, 129.7, 128.8, 127.6, 127.4, 125.4, 122.2, 44.4. HRMS (ESI): calcd. for $C_{14}H_{13}NNaO_2$ $[M+Na]^+$, 250.0844, found: 250.0838.

Phenyl (1-phenylethyl) carbamate (13)

White solid, mp 105-107 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 8.35 (d, *J*=8.1 Hz, 1H), 7.39-7.33 (m, 6H), 7.24 (t, *J*=6.9 Hz, 1H), 7.18 (t, *J*=7.3 Hz, 1H), 7.08 (d, *J*=7.8 Hz, 2H), 4.73 (quintet, *J*=7.4 Hz, 1H), 1.42 (d, *J*=7.0 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 154.1, 151.4, 145.0, 129.7, 128.8, 127.2, 126.3, 125.3, 122.2, 50.8, 23.2. HRMS (ESI): calcd. for $C_{15}H_{15}NNaO_2$ $[M+Na]^+$, 264.1000, found: 264.0992.

Phenyl phenethyl carbamate (14)

White solid, mp 93-95 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.84 (t, *J*=5.5 Hz, 1H), 7.38-7.29 (m, 4H), 7.25-7.17 (m, 4H), 7.06 (d, *J*=7.6 Hz, 2H), 3.29 (quartet, *J*=6.1 Hz, 2H), 2.79 (t, *J*=7.1 Hz, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6): 154.7, 151.5, 139.6, 129.6, 129.1, 128.8, 126.6, 125.3, 122.1, 42.4, 35.7. HRMS (ESI): calcd. for $C_{15}H_{15}NNaO_2$ $[M+Na]^+$, 264.1000, found: 264.0991.

Phenyl dimethylcarbamate (15)

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White solid, mp 43-45 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.38 (t, *J*=7.5 Hz, 2H), 7.21 (t, *J*=7.5 Hz, 1H), 7.11 (d, *J*=8.4 Hz, 2H), 3.03 (s, 3H), 2.90 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 154.4, 151.8, 129.6, 125.5, 122.3, 36.7, 36.5. HRMS (ESI): calcd. for $C_9H_{12}NO_2$ $[M+H]^+$, 166.0868, found: 166.0865.

Phenyl diethylcarbamate (16)

Viscous liquid; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.38 (t, *J*=7.6 Hz, 2H), 7.21 (t, *J*=7.3 Hz, 1H), 7.11 (d, *J*=7.5 Hz, 2H), 3.39 (quartet, *J*=6.6 Hz, 2H), 3.30 (quartet, *J*=6.7 Hz, 2H), 1.19 (t, *J*=5.8 Hz, 3H), 1.11 (t, *J*=6.4 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 153.7, 151.7, 129.6, 125.4, 122.2, 42.1, 41.9, 14.5, 13.7. HRMS (ESI): calcd. for $C_{11}H_{16}NO_2$ $[M+H]^+$, 194.1181, found: 194.1177.

Phenyl pyrrolidine-1-carboxylate (17)

White solid; mp 74-76 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.38 (t, *J*=8.2 Hz, 2H), 7.21 (t, *J*=7.3 Hz, 1H), 7.13 (d, *J*=7.5 Hz, 2H), 3.49 (t, *J*=6.6 Hz, 2H), 3.33 (t, *J*=6.3 Hz, 2H), 1.93-1.82 (m, 4H). ^{13}C-NMR (100 MHz, DMSO-d_6): 152.6, 151.6, 129.6, 125.4, 122.3, 46.6, 46.4, 25.7, 24.9. HRMS (ESI): calcd. for $C_{11}H_{13}NNaO_2$ $[M+Na]^+$, 214.0844, found: 214.0838.

Phenyl piperidine-1-carboxylate (18)

White solid; mp 78-80 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.38 (t, *J*=8.2 Hz, 2H), 7.21 (t, *J*=7.3 Hz, 1H), 7.11 (d, *J*=7.5 Hz, 2H), 3.55 (br. s, 2H), 3.40 (br. s, 2H), 1.62-1.55 (m, 6H). ^{13}C-NMR (100 MHz, DMSO-d_6): 53.3, 151.8, 129.6, 125.5, 122.3, 45.5, 45.0, 25.9, 25.5, 24.1. HRMS (ESI): calcd. for $C_{12}H_{15}NNaO_2$ $[M+Na]^+$, 228.1000, found: 228.0968.

General procedure for the synthesis of sulfonylureas (19-43)

Sulfonamide (2 mmol) and carbamate (2.2 mmol) were dissolved in acetonitrile (15 mL), then DBU (3 mmole) was added, and the reaction mixture was refluxed. The reaction was monitored by TLC. After completion of the reaction, as indicated by TLC, solvent was evaporated under reduced pressure. The residue was then dissolved in ethyl acetate and extracted with 0.1N HCl. Organic layer was washed with brine, dried over Na_2SO_4, and concentrated again under reduced pressure. The crude product was purified by crystallization using hexane-ethyl acetate mixture to afford the desired sulfonylurea.

N-(butylcarbamoyl)-4-methylbenzenesulfonamide (19)

White solid, mp 128-130 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.77 (d, *J*=8.3 Hz, 2H), 7.39 (d, *J*=8.0 Hz, 2H), 6.44 (t, *J*=5.3 Hz, 1H), 2.93 (quartet, *J*=6.8 Hz, 2H), 2.37 (s, 3H), 1.28 (quintet, *J*=7.3 Hz, 2H), 1.15 (sextet, *J*=7.1 Hz, 2H), 0.80 (t, *J*=7.3 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.7, 144.0, 137.8, 129.8, 127.6, 39.2, 31.7, 21.4, 19.7, 13.9. HRMS (ESI): calcd. for $C_{12}H_{18}N_2NaO_3S$ $[M+Na]^+$, 293.0936, found: 293.0932.

N-(methylcarbamoyl)benzenesulfonamide (20)

White solid, mp 148-150 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.89 (d, *J*=5.7 Hz, 2H), 7.67-7.60 (m, 3H), 6.41 (br. s, 1H), 2.50 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 152.3, 140.8, 133.5, 129.4, 127.5, 26.6. HRMS (ESI): calcd. for $C_8H_{10}N_2NaO_3S$ $[M+Na]^+$, 237.0310, found: 237.0313.

N-(ethylcarbamoyl)benzenesulfonamide (21)

White solid, mp 125-127 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.92 (d, *J*=7.3 Hz, 2H), 7.70 (t, *J*=7.3 Hz, 1H), 7.63 (t, *J*=7.2 Hz, 2H), 6.56 (t, *J*=5.1 Hz, 1H), 2.98 (quintet, *J*=7.1 Hz, 2H), 0.95 (t, *J*=7.2 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.8, 140.3, 133.7, 129.5, 127.5, 34.6, 15.1. HRMS (ESI): calcd. for $C_9H_{12}N_2NaO_3S$ $[M+Na]^+$, 251.0466, found: 251.0469.

N-(benzylcarbamoyl)benzenesulfonamide (22)

White solid, mp 179-181 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.92 (d, *J*=7.4 Hz, 2H), 7.69 (t, *J*=7.4 Hz, 1H), 7.60 (t, *J*=7.2 Hz, 2H), 7.29-7.21 (m, 3H), 7.13 (d, *J*=7.0 Hz, 2H), 7.04 (t, *J*=5.7 Hz, 1H), 4.16 (d, *J*=5.9 Hz, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.4, 140.1, 139.0, 133.1, 129.0, 128.2, 127.1, 126.9, 126.8, 42.6. HRMS (ESI): calcd. for $C_{14}H_{14}N_2NaO_3S$ $[M+Na]^+$, 313.0623, found: 313.0620.

N-((1-phenylethyl)carbamoyl)benzenesulfonamide (23)

White solid, mp 166-168 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.86 (d, *J*=7.5 Hz, 2H), 7.65 (t, *J*=7.3 Hz, 1H), 7.56 (t, *J*=7.3 Hz, 2H), 7.26 (t, *J*=7.3 Hz, 2H), 7.18 (t, *J*=7.8 Hz, 3H), 6.95 (d, *J*=7.7 Hz, 1H), 4.60 (quintet, *J*=7.1 Hz, 1H), 1.27 (d, *J*=6.9 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.1, 144.3, 140.3, 133.7, 129.5, 128.8, 127.5, 127.3, 126.0, 49.4, 22.9. HRMS (ESI): calcd. for $C_{15}H_{16}N_2NaO_3S$ $[M+Na]^+$, 327.0779, found: 327.0769.

N-(ethylcarbamoyl)-4-methylbenzenesulfonamide (24)

White solid, mp 139-141 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.77 (d, *J*=8.3 Hz, 2H), 7.39 (d, *J*=8.0 Hz, 2H), 6.45 (t, *J*=5.3 Hz, 1H), 2.96 (quintet, *J*=7.1 Hz, 2H), 2.37 (s, 3H), 0.93 (t, *J*=7.1 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.6, 144.0, 137.9, 129.8, 127.6, 34.5, 21.4, 15.3. HRMS (ESI): calcd. for $C_{10}H_{14}N_2NaO_3S$ $[M+Na]^+$, 265.0623, found: 265.0628.

4-methyl-N-(propylcarbamoyl)benzenesulfonamide (25)

White solid, mp 152-154 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.78 (d, *J*=8.2 Hz, 2H), 7.39 (d, *J*=8.1 Hz, 2H), 6.45 (t, *J*=5.3 Hz, 1H), 2.90 (quartet, *J*=6.7 Hz, 2H), 2.38 (s, 3H), 1.32 (sextet, *J*=7.2 Hz, 2H), 0.75 (t, *J*=7.4 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.3, 143.5, 137.4, 129.3, 127.1, 125.5, 40.8, 22.3, 20.9, 10.9. HRMS (ESI): calcd. for $C_{11}H_{16}N_2NaO_3S$ $[M+Na]^+$, 279.0779, found: 279.0782.

N-(isopropylcarbamoyl)-4-methylbenzenesulfonamide (26)

White solid, mp 171-173 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.77 (d, *J*=8.3 Hz, 2H), 7.39 (d, *J*=8.1 Hz, 2H), 6.27 (d, *J*=7.5 Hz, 1H), 3.65-3.54 (m, 1H), 2.37 (s, 3H), 0.99 (d, *J*=6.5 Hz, 6H). ^{13}C-NMR (100 MHz, DMSO-d_6): 150.4, 143.5, 137.3, 129.3, 127.1, 41.3, 22.2, 20.9. HRMS (ESI): calcd. for $C_{11}H_{16}N_2NaO_3S$ $[M+Na]^+$, 279.0779, found: 279.0779.

N-(hexylcarbamoyl)-4-methylbenzenesulfonamide (27)

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White solid, mp 95-97 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.77 (d, *J*=8.2 Hz, 2H), 7.39 (d, *J*=8.1 Hz, 2H), 6.43 (t, *J*=5.2 Hz, 1H), 2.93 (quartet, *J*=6.7 Hz, 2H), 2.38 (s, 3H), 1.33-1.13 (m, 8H), 0.82 (t, *J*=7.0 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.7, 143.9, 137.9, 129.8, 127.6, 39.5, 31.3, 29.5, 26.2, 22.4, 21.4, 14.3. HRMS (ESI): calcd. for $C_{14}H_{22}N_2NaO_3S$ [M+Na]$^+$, 321.1249, found: 321.1249.

N-(cyclohexylcarbamoyl)-4-methylbenzenesulfonamide (28)

White solid, mp 171-173 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.77 (d, *J*=8.4 Hz, 2H), 7.40 (d, *J*=8.1 Hz, 2H), 6.32 (d, *J*=7.6 Hz, 1H), 3.29-3.22 (m, 1H), 2.38 (s, 3H), 1.65-1.42 (m, 5H), 1.22-1.05 (m, 5H). ^{13}C-NMR (100 MHz, DMSO-d_6): 150.9, 144.0, 137.9, 129.8, 127.6, 48.5, 32.7, 25.4, 24.6, 21.4. HRMS (ESI): calcd. for $C_{14}H_{20}N_2NaO_3S$ [M+Na]$^+$, 319.1092, found: 319.1097.

N-(benzylcarbamoyl)-4-methylbenzenesulfonamide (29)

White solid, mp 176-178 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.78 (d, *J*=8.1 Hz, 2H), 7.39 (d, *J*=8.0 Hz, 2H), 7.30-7.18 (m, 3H), 7.11 (d, *J*=6.9 Hz, 2H), 7.01 (t, *J*=5.7 Hz, 1H), 4.14 (d, *J*=5.8 Hz, 2H), 2.37 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 152.1, 144.2, 139.5, 137.7, 129.9, 128.7, 127.6, 127.4, 127.3, 43.1, 21.4. HRMS (ESI): calcd. for $C_{15}H_{16}N_2NaO_3S$ [M+Na]$^+$, 327.0779, found: 327.0779.

4-methyl-N-((1-phenylethyl)carbamoyl)benzenesulfonamide (30)

White solid, mp 130-132 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.77 (d, *J*=7.4 Hz, 2H), 7.38 (d, *J*=7.4 Hz, 2H), 7.29-7.22 (m, 5H), 6.89 (d, *J*=6.5 Hz, 1H), 4.63 (quintet, *J*=6.3 Hz, 1H), 2.38 (s, 3H), 1.30 (d, *J*=6.4 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.0, 144.4, 144.0, 137.8, 129.8, 128.7, 127.7, 127.3, 126.2, 49.3, 23.0, 21.4. HRMS (ESI): calcd. for $C_{16}H_{18}N_2NaO_3S$ [M+Na]$^+$, 341.0936, found: 341.0933.

4-chloro-N-(methylcarbamoyl)benzenesulfonamide (31)

White solid, mp 192-194 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.90 (d, *J*=8.7 Hz, 2H), 7.68 (d, *J*=8.6 Hz, 2H), 6.45 (quartet, *J*=3.6 Hz, 1H), 2.51 (d, *J*=4.5 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 152.2, 139.6, 138.4, 129.7, 129.6, 26.6. HRMS (ESI): calcd. for $C_8H_9ClN_2NaO_3S$ [M+Na]$^+$, 270.9920, found: 270.9917.

4-chloro-N-(ethylcarbamoyl)benzenesulfonamide (32)

White solid, mp 147-149 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.91 (d, *J*=8.7 Hz, 2H), 7.68 (d, *J*=8.7 Hz, 2H), 6.53 (t, *J*=5.2 Hz, 1H), 2.97 (quintet, *J*=7.1 Hz, 2H), 0.94 (t, *J*=7.2 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.5, 139.6, 138.4, 129.6, 129.5, 34.6, 15.2. HRMS (ESI): calcd. for $C_9H_{11}ClN_2NaO_3S$ [M+Na]$^+$, 285.0077, found: 285.0068.

4-chloro-N-(propylcarbamoyl)benzenesulfonamide (33)

White solid, mp 128-130 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.90 (d, *J*=8.6 Hz, 2H), 7.68 (d, *J*=8.6 Hz, 2H), 6.54 (t, *J*=5.1 Hz, 1H), 2.89 (quartet, *J*=6.6 Hz, 2H), 1.32 (sextet, *J*=7.2 Hz, 2H), 0.74 (t, *J*=7.4 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.7, 139.5, 138.5, 129.6, 129.5, 41.3, 22.8, 11.5. HRMS (ESI): calcd. for $C_{10}H_{13}ClN_2NaO_3S$ [M+Na]$^+$, 299.0233, found: 299.0226.

4-chloro-N-(isopropylcarbamoyl)benzenesulfonamide (34)

White solid, mp 153-155 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.90 (d, *J*=8.6 Hz, 2H), 7.68 (d, *J*=8.6 Hz, 2H), 6.37 (d, *J*=7.4 Hz, 1H), 3.62-3.53 (m, 1H), 1.00 (d, *J*=6.5 Hz, 6H). ^{13}C-NMR (100 MHz, DMSO-d_6): 150.9, 139.6, 138.4, 129.6, 129.5, 41.9, 22.7. HRMS (ESI): calcd. for $C_{10}H_{13}ClN_2NaO_3S$ [M+Na]$^+$, 299.0233, found: 299.0229.

N-(benzylcarbamoyl)-4-chlorobenzenesulfonamide (35)

White solid, mp 199-201 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.91 (d, *J*=8.7 Hz, 2H), 7.68 (d, *J*=8.7 Hz, 2H), 7.29-7.21 (m, 3H), 7.13-7.07 (m, 3H), 4.15 (d, *J*=5.9 Hz, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.9, 139.5, 139.4, 138.6, 129.7, 129.6, 128.7, 127.4, 127.3, 43.1. HRMS (ESI): calcd. for $C_{14}H_{13}ClN_2NaO_3S$ [M+Na]$^+$, 347.0233, found: 347.0233.

4-bromo-N-(methylcarbamoyl)benzenesulfonamide (36)

White solid, mp 185-187 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.80 (s, 4H), 6.45 (d, *J*=2.9 Hz, 1H), 2.48 (d, *J*=3.6 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 157.2, 144.6, 137.2, 134.4, 132.3, 31.3. HRMS (ESI): calcd. for $C_8H_9BrN_2NaO_3S$ [M+Na]$^+$, 314.9415, found: 314.9406.

4-bromo-N-(propylcarbamoyl)benzenesulfonamide (37)

White solid, mp 133-135 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.82 (s, 4H), 6.53 (br. s, 1H), 2.89 (quartet, *J*=6.2 Hz, 2H), 1.32 (sextet, *J*=7.1 Hz, 2H), 0.75 (t, *J*=7.2 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.2, 139.5, 132.0, 129.2, 126.9, 40.8, 22.3, 11.0. HRMS (ESI): calcd. for $C_{10}H_{13}BrN_2NaO_3S$ [M+Na]$^+$, 344.9707, found: 344.9698.

4-bromo-N-(cyclopropylcarbamoyl)benzenesulfonamide (38)

White solid, mp 138-140 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.82 (s, 4H), 6.73 (br. s, 1H), 2.40 (sextet, *J*=2.9 Hz, 1H), 0.55 (quartet, *J*=5.6 Hz, 2H), 0.34 (br. s, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6): 152.6, 139.9, 132.5, 129.8, 127.5, 22.8, 6.4. HRMS (ESI): calcd. for $C_{10}H_{11}BrN_2NaO_3S$ [M+Na]$^+$, 340.9571, found: 340.9559.

N-(benzylcarbamoyl)-4-bromobenzenesulfonamide (39)

White solid, mp 201-203 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.83 (s, 4H), 7.32-7.20 (m, 3H), 7.18-7.02 (m, 3H), 4.15 (d, *J*=5.8 Hz, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.4, 139.3, 138.9, 132.1, 129.2, 128.2, 127.1, 126.9, 126.8, 42.7. HRMS (ESI): calcd. for $C_{14}H_{13}BrN_2NaO_3S$ [M+Na]$^+$, 392.9707, found: 392.9702.

4-bromo-N-((1-phenylethyl)carbamoyl)benzenesulfonamide (40)

White solid, mp 130-132 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.82 (s, 4H), 7.31-7.20 (m, 5H), 7.04 (d, *J*=7.7 Hz, 1H), 4.63 (quintet, *J*=7.2 Hz, 1H), 1.31 (d, *J*=6.9 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 155.7, 149.1, 144.5, 137.3, 134.5, 133.5, 132.3, 132.1, 130.9, 54.2, 27.6. HRMS (ESI): calcd. for $C_{15}H_{15}BrN_2NaO_3S$ [M+Na]$^+$, 404.9884, found: 404.9875.

4-bromo-N-(phenethylcarbamoyl)benzenesulfonamide (41)

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White solid, mp 122-124 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.84-7.78 (m, 4H), 7.25 (t, *J*=7.5 Hz, 2H), 7.18 (t, *J*=7.3 Hz, 1H), 7.12 (d, *J*=7.1 Hz, 2H), 6.51 (t, *J*=5.2 Hz, 1H), 3.19 (quartet, *J*=6.8 Hz, 2H), 2.64 (t, *J*=7.1 Hz, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6): 151.6, 139.9, 139.3, 132.5, 129.7, 129.0, 128.8, 127.5, 126.6, 41.1, 35.5. HRMS (ESI): calcd. for $C_{15}H_{15}BrN_2NaO_3S$ $[M+Na]^+$, 406.9864, found: 406.9854.

4-methoxy-N-(methylcarbamoyl)benzenesulfonamide (42)

White solid, mp 149-151 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.83 (d, *J*=8.9 Hz, 2H), 7.11 (d, *J*=8.9 Hz, 2H), 6.37 (quartet, *J*=4.2 Hz, 1H), 3.84 (s, 3H), 2.50 (d, *J*=4.4 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): 163.0, 152.6, 132.4, 129.9, 114.5, 56.1, 26.6. HRMS (ESI): calcd. for $C_9H_{12}N_2NaO_4S$ $[M+Na]^+$, 267.0415, found: 267.0407.

4-methoxy-N-(((1r,4r)-4-methylcyclohexyl)carbamoyl) benzenesulfonamide (43)

White solid, mp 185-187 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 10.25 (br. s, 1H), 7.82 (d, *J*=8.8 Hz, 2H), 7.11 (d, *J*=8.9 Hz, 2H), 6.25 (d, *J*=7.5 Hz, 1H), 3.83 (s, 3H), 3.19-3.16 (m, 1H), 1.68 (d, *J*=10.1 Hz, 2H), 1.59 (d, *J*=12.1 Hz, 2H), 1.33-1.01 (m, 3H), 0.95-0.75 (m, 5H). ^{13}C-NMR (100 MHz, DMSO-d_6): 163.1, 151.0, 132.2, 130.0, 114.5, 56.1, 48.9, 33.8, 32.7, 31.6, 22.5. HRMS (ESI): calcd. for $C_{15}H_{22}N_2NaO_4S$ $[M+Na]^+$, 349.1198, found: 349.1185.

Gram scale synthesis of Tolbutamide

4-methylbenzenesulfonamide (20 mmol, 3.424 g) and phenyl butylcarbamate (22 mmol, 4.251 g) were dissolved in acetonitrile (150 mL), then DBU (30 mmole, 4.49 mL) was added, and the reaction mixture was refluxed. The reaction was monitored by TLC. After completion of the reaction, as indicated by TLC, solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and extracted with 0.1N HCl. Organic layer was washed with brine, dried over Na_2SO_4, and concentrated again under reduced pressure. The crude product was purified by crystallization using hexane-ethyl acetate mixture to afford the 4.490 g of Tolbutamide in an isolated yield of 83%.

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A facile synthesis of Sulfonylureas via water assisted preparation of Carbamates

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Graphical abstract: