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Synthesis and evaluation of α-glucosidase inhibitory activity of sulfonylurea derivatives

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Abstract: Two series of sulfonylureas derivatives including 24 compounds (**4**, **7**, **5a**–**5o**, **8a**–**8h**), among them 17 new derivatives, have been synthesized and evaluated for their α-glucosidase inhibitory activity. Compounds **5c**, **5h** and **8e** showed significant *in vitro* α-glucosidase inhibition with IC_{50} values of 5.58, 79.85 and 213.36 μM, respectively, comparing with the standard compounds acarbose (IC_{50} = 268.29 μM) and glipizide (IC_{50} = 300.47 μM). The preliminary structure-activity relationships (SARs) of the synthesized compounds were also investigated.

Keywords: α-glucosidase inhibitory activity; sulfonylureas derivatives; synthesis.

1 Introduction

Sulfonylurea derivatives are compounds containing a central *S*-aryl sulfonylurea unit with *p*-substituents on the phenyl ring (R^1) and substituents at the urea's *N*′-terminus (R^2) [1] (Figure 1). They exhibit a wide range of biological activity such as antidiabetic [2], diuretic [3], antitubercular [4], antimalerial [5], anticancer [6], anti-inflammatory [7], thromboxane A2 receptor antagonism activity [8]. Especially sulfonylureas are widely used in medicine as potent blood glucose-reducing agents for the treatment of diabetes. Sulfonylureas alter the plasma membrane of cells to increase their responsiveness to insulin action, by increasing the number of insulin receptors [1]. The side effect of these reagents is, however, associated with hypoglycemia, weight gain and cardiovascular risks. The combination of sulfonylureas with α-glucosidase inhibitors, an add-on therapy, have been reported to improve lipid profiles, decrease body weight, prevent macroangiopathy, reduce the hemoglobin A1c and control the glycemic level in type 2 diabetic patients [9, 10].

The present study is aimed to develop novel sulfonylurea derivatives with increased α-glucosidase inhibitory activity as well as decreasing the diabetic complications during treatment by sulfonylureas. Two series of sulfonylurea derivatives based on the structure of glipizide (Figure 1), an antidiabetic medicament, have been synthesized. Various phenyl and heterocyclic rings were incorporated into the sulfonylurea scaffold. As a result, 24 derivatives (**4**, **7**, **5a**–**5o**, **8a**–**8h**) were obtained, 17 of which (**5a**, **5c**, **5e**, **5g**–**5k**, **5n**, **5o**, **8a**–**8h**) are new. All of the synthesized compounds were evaluated for α-glucosidase inhibition.

2 Results and discussion

2.1 Chemistry

The synthetic routes of compounds **5a**–**5o** and **8a**–**8h** are shown in Schemes 1 and 2, respectively. The structure of glipizide was modified at *N*-phenylethylsulfamoyl moiety (R^1 substitution), while the cyclohexyl ring at the *N*-terminus was maintained (Scheme 1). The desired products were synthesized by a general method for the synthesis of sulfonylurea derivatives by treatment of sulfonamides with appropriate isocyanides in the presence of base (Scheme 1) [1]. Compound **1** (4-(2-aminoethyl)benzenesulfoamide) was used as the starting material. *N*-Boc protection of **1** gave compound **2** which was then reacted with cyclohexyl isocyanate in the presence of K_2CO_3 to afford **3**. Deprotection of **3** with trifluoroacetic acid (TFA) in DCM provided the key intermediate **4**. Finally, coupling of **4** with various of carboxylic acids in the presence of ethyl chloroformate and triethylamine (TEA) gave the target compounds **5a**–**5l**. Instead of $SOCl_2$ or $(COCl)_2$ as reagent to activate carboxylic

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acid, ethyl chloroformate was used to avoid the formation of by-products (Scheme 1). The sulfonylurea derivatives (**5a**–**5l**) were obtained in moderate to good yields (66–82%). Compounds **5m**, **5n** and **5o** were prepared by treatment of 2,3-pyridine dicarboxylic anhydride or phthalic anhydride with amine **4**. According to the literature, the reactivity of 2,3-pyridine dicarboxylic anhydride toward nitrogen nucleophiles under different conditions affords different products [11]. In our study, treatment of **4** with 2,3-pyridine dicarboxylic anhydride in glacial acetic acid at room temperature gave nicotinic acid derivative **5o**. This was compatible with the studies of Ammar YA et al. for the similar reaction [11]. It was reported that refluxing 2,3-pyridine dicarboxylic anhydride with amine in glacial acetic acid for 3 h led to the dicarboxylation of the carboxylic acid group, providing nicotiamide as main product and nicotiimide as as a minor product [11]. However, in our case, nicotiimide **5n** was obtained as the main product, even heating the reaction for 7 h.

The structures of the synthesized compounds were confirmed by means of MS, 1D (^{1}H, ^{13}C) and 2D (HSQC, HMBC) spectra. The ^{1}H NMR spectra of **2** indicated the additional signal of *tert*-butyl group at δ_H = 1.36 ppm (9H, 3 × CH_3), together with the corresponding signals of **1**. The formation of urea cyclohexyl moiety in compound **3** was confirmed by the appearance of the signals at δ_H = 1.65–1.18 ppm (C_6H_{11}), 10.25 ppm (br s, 1H, SO_2NH), and at δ_C = 150.35 ppm (NH*C*ONH), 48.01–24.10 ppm (C_6H_{11}). The lack of the *tert*-butyl signal in the ^{1}H NMR of compound **4** indicated the removing of the protecting group in the structure of **4**. The formation of the amide urea moiety in **4** was further confirmed by the correlation between CON*H*-C_6H_{11} (δ_H = 6.62 ppm)/C-8′ (δ_C = 150.49 ppm), C-1 (δ_C = 48.06 ppm) and C-2, C-6 (δ_C = 32.24 ppm) in HMBC spectrum. The presence of additionally aromatic proton signals as well as the signals of amide groups at δ_H = 8.07–9.83 ppm (CON*H*) and δ_C = 165.0–168.2 ppm (*C*ONH) proved the formation of the sulfoamide derivative (**5a**–**5l**). Compound **5c** showed the signals of an AB substituted aromatic ring at δ_H = 7.38 ppm (d, *J* = 8.5 Hz, 2H, 2‴-H, 6‴-H) and δ_H = 6.79 ppm (d, *J* = 8.5 Hz, 2H, 3‴-H, 5‴-H). The correlation of H-6‴ (δ_H = 8.17 ppm)/*C*ONHCH$_2$ (δ_C = 168.04 ppm) in HMBC spectrum confirmed the formation of amide bond in **5h**. The appearance of four additional aromatic protons signals at δ_H = 7.85–7.81 ppm, and the carbon signals at δ_C = 167.60 (*C*OOH), 134.40 and 131.43 ppm (C–Ar) confirmed the structure of compound **5m**. The aromatic pyridine protons at δ_H = 8.96–7.77 ppm, together with the carbon signals at δ_C = 166.03, 165.93 (*C*ONH imide) indicated the formation of the imide ring in **5n**. The correlation of δ_H = 8.05 ppm (4‴-H)/δ_C = 167.9 ppm (COOH) and δ_H = 8.66 ppm (6‴-H)/δ_C = 165.06 ppm (*C*ONH) was observed in HMBC spectrum of **5o**, suggesting the location of carboxylic acid and amide moiety at C-3‴ and C-2‴ of pyridine ring, respectively. Furthermore, the formation of the amide bond in compound **5o** was confirmed by the correlation of CON*H* (δ_H = 8.76) ppm/C=O (δ_C 165.06 ppm), C-2'' (δ_C = 39.83 ppm).

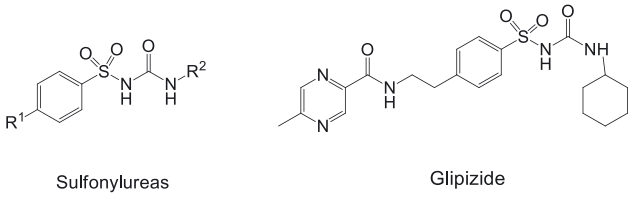
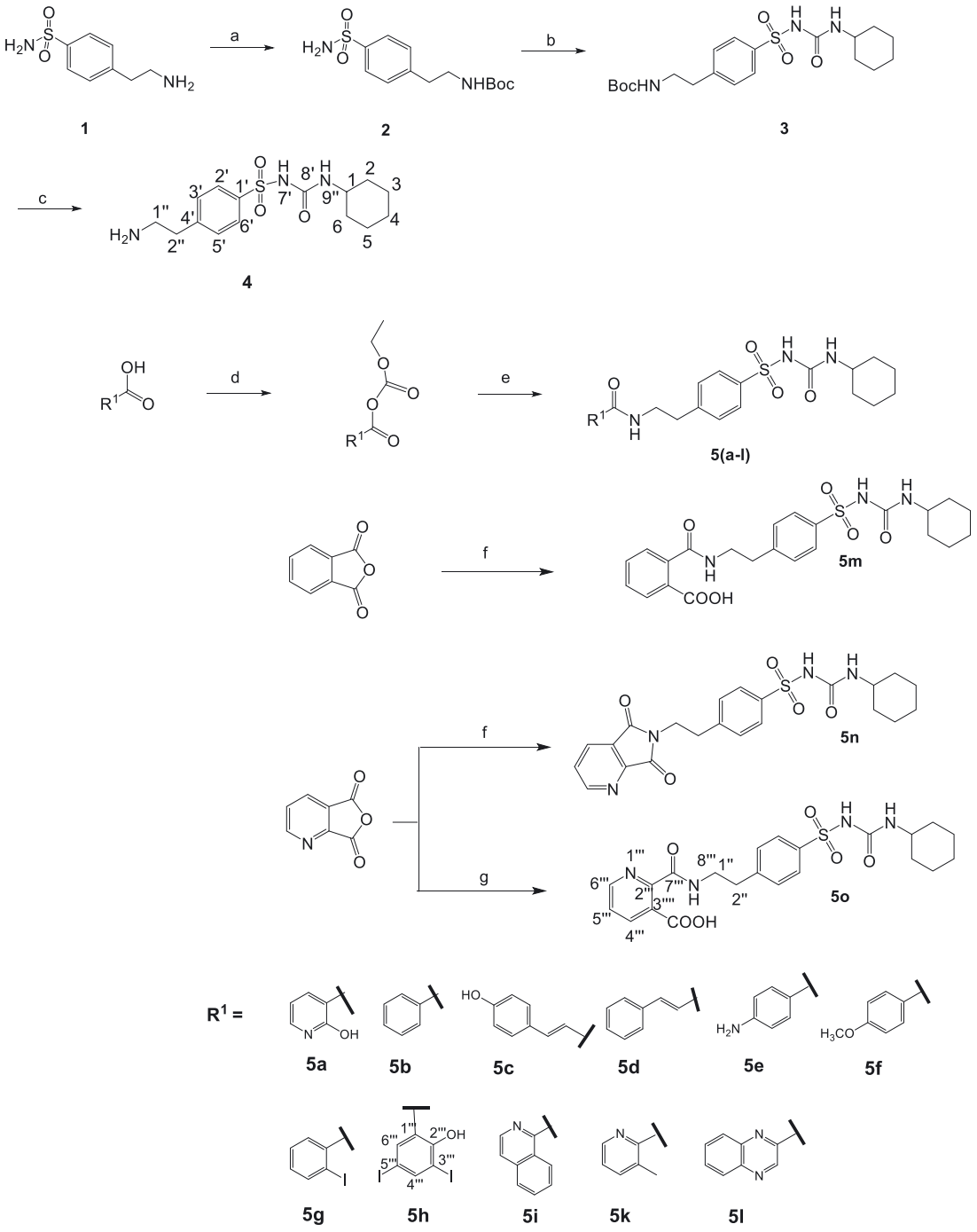


Figure 1: Structures of sulfonylureas and glipizide.

In Scheme 2, various substitutions at *N*-terminus of the urea moiety (R^1) were introduced to provide sulfonylureas mimic glipizide. Compound 5-methylpyrazin-2-carboxylic acid was treated with ethyl chloroformate in the presence of TEA, following by the addition of **1** to yield sulfonamide (**6**). This compound was subsequently refluxed with ethyl chloroformate in the presence of anhydrous potassium carbonate (K_2CO_3) to obtain the key intermediate carbamate **7**. Finally, sulfonylurea derivatives **8a**–**8h** were synthesized by condensation of **7** with various of amines in toluene. The use of toluene as solvents gave the products in the best yields, comparing with other solvents such as dioxane or DMF. The structures of the products were elucidated by means of ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of compound **6** indicated the presence of two singlet signals of pyrazine protons at δ_H = 9.02 ppm (s, 1H, 3‴-H) and δ_H = 8.59 ppm (s, 1H, 6‴-H). The appearance of the NH protons at δ_H = 8.91 ppm (t, *J* = 6.0 Hz, 1H, CON*H*), δ_H = 7.27 ppm (s, 2H, SO_2NH_2) in the ^{1}H NMR spectrum confirmed the structure the amide product **6**. The NMR spectra of **7** exhibited additionally signals at δ_H = 3.99 ppm (q, *J* = 7.0 Hz, 2H) and δ_H = 1.07 ppm (t, *J* = 7.0 Hz, 3H), and at δ_C = 151.01, 61.83 and 13.88 ppm, corresponding to the carbamate moiety (NH*C*OO*C*H$_2$*C*H$_3$). The disappearance of the ethyl ester protons and the presence of aromatic protons at δ_H = 7.01–7.89 ppm in ^{1}H NMR spectra of **8a**–**8h** clearly confirmed the formation of urea derivatives. The carbonyl carbons of the urea groups (NH*C*ONH) were resonated at δ_C = 156–158 ppm in the ^{13}C NMR spectra of **8a**–**8h**.

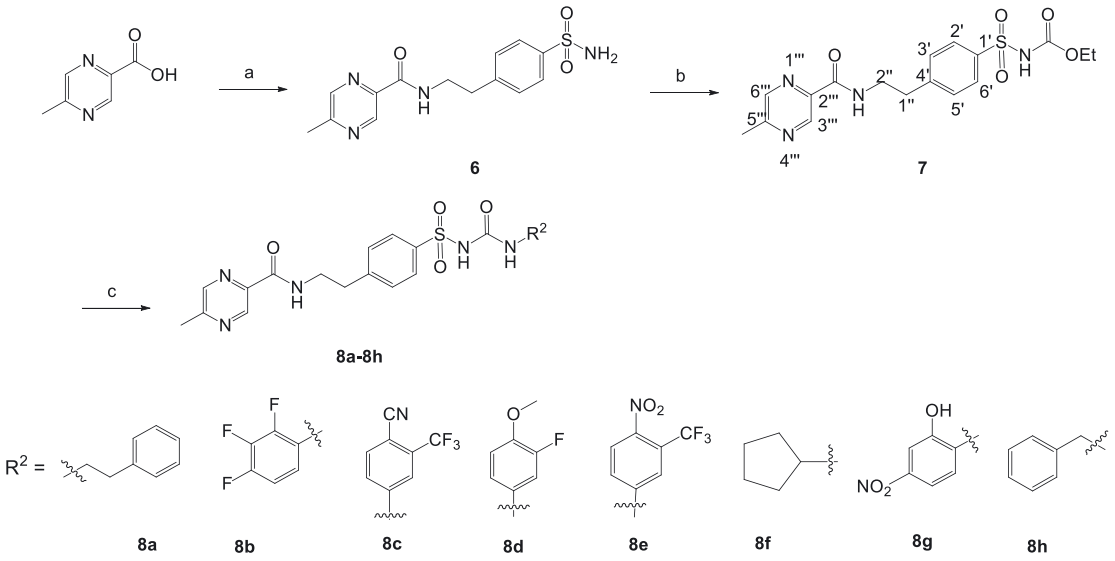
2.2 Biological activity

Twenty-two compounds (**5a**–**5o**, **8a**–**8h**) were evaluated for their ability to inhibit *α*-glucosidase. Acarbose and



Scheme 1: Synthesis of sulfonylurea derivatives (**5a**–**5o**). Reagents and conditions: a) DMF, Boc_2O, r.t., 4 h, 95%; b) Cyclohexyl isocyanate, K_2CO_3, acetone, r.t., 6 h, 96.6%; c) TFA, DCM, r.t., 4 h, 92%; d) $ClCO_2C_2H_5$, TEA, acetone, 0–5 °C, 1 h; e) **4**, TEA, acetone, r.t., 4 h, 69.3–81.1%; f) **4**, acetic acid, reflux, 7 h, (**5m**: 81.5%, **5n:** 66.1%); g) **4**, acetic acid, r.t., 1 h, 72.5%.

glipizide were used as standard compounds to compare with the synthesized derivatives. Compound **5c** (R = 4–OH–C_6H_4) was the most active compound with an IC_{50} value of 5.58 μM, 48 and 60 times much better than the standard drug acarbose and glipizide (IC_{50} of 268.29 and 300.47 μM, respectively). The *p*-substituted hydroxyl group at *trans*-cinnamoyl moiety plays an important role of the activity. This is confirmed due to the observation that compound **5d** without the OH group (R = –C_6H_5) did not show *α*-glucosidase inhibition. Preliminary structure-activity relationships



Scheme 2: Synthesis of sulfonylurea derivatives **8a**–**8h**. Reagents and conditions: a) i. $ClCO_2Et$, TEA, acetone, 0 °C, 1 h; ii. **1**, TEA, acetone, r.t., 3 h, 93.4%; b) K_2CO_3, acetone, $ClCO_2C_2H_5$, reflux, 4 h, 89.2%; c) toluene, R^2NH_2, reflux, 4 h, 68.4–84.2%.

Table 1: *α*-Glucosidase inhibitory activity of sulfonylurea derivatives.

Nr	Compound	IC_{50} (μM)	Nr	Compound	IC_{50} (μM)
1	**5a**	> 350	13	**5n**	> 350
2	**5b**	> 350	14	**5o**	312.12
3	**5c**	5.58	15	**8a**	> 350
4	**5d**	> 350	16	**8b**	> 350
5	**5e**	> 350	17	**8c**	> 350
6	**5f**	> 350	18	**8d**	> 350
7	**5g**	278.88	19	**8e**	213.36
8	**5h**	79.85	20	**8f**	> 350
9	**5i**	322.49	21	**8g**	269.44
10	**5k**	> 350	22	**8h**	> 350
11	**5l**	226.03	23	Acarbose[a]	268.29
12	**5m**	> 350	24	Glipizide[b]	300.47

[a, b]Standard compounds.

(SARs) presumed that *trans*-cinnamoyl derivatives are weak intestinal *α*-glucosidase inhibitors [12]. However, the presence of a hydroxyl group at *para* position enhanced significantly the inhibition, probably because they may form hydrogen bonds with the polar groups (amide, guanidine, peptide, amino, and carboxyl groups) of amino acid residues in the active site of intestinal *α*-glucosidase enzyme [12]. Compound **5h** (R = 2–OH–3,5–di–I–C_6H_2) exhibited good activity with an IC_{50} value of 79.85 μM. Comparing the activity of **5h** with **5g** (R = 2–I–C_6H_4, IC_{50} of 278.88 μM), the installation of OH and disubstituted iodine seems to enhance the activity. Compound **5l**, **5i** and **5o** with heterocyclic substitutions (quinoxaline, isoquinoline and picolinic, respectively) showed moderate activity with IC_{50} values of 226.03, 322.49 and 312.12 μM, respectively (Table 1, Scheme 1). Compound **8e** (R^1 = 3–CF_3–4–NO_2–C_6H_3) and **8g** (R^1 = 2–OH–4–NO_2–C_6H_3) exhibited good activity with an IC_{50} of 213.36 and 269.44 μM, respectively (Table 1, Scheme 2), comparing with acarbose and glipizide (IC_{50} = 268.29 and 300.47 μM), respectively. The introduction of the nitro group into the aromatic rings of the series products in Scheme 2 seems to enhance the *α*-glucosidase inhibitory activity. Other compounds were found to be inactive.

3 Conclusions

In conclusion, 24 sulfonylurea derivatives have been synthesized and evaluated for their *α*-glucosidase inhibitory activity. Among them, compound **5c**, **5h**, **5l** and **8e** exhibited significant *α*-glucosidase inhibition, comparing with the commercially available acarbose and glipizide. The introduction of 4-hydroxyl-*trans*-cinnamoyl moiety at *N*-phenylethylsulfamoyl unit (compound **5c**) considerably increased *α*-glucosidase inhibitory activity. Our newly synthesized sulfonylurea derivatives exhibited promising *α*-glucosidase inhibition, which would be supported for the "add on therapy" to prevent the complications during the treatment of diabetics by sulfonylurea agents. Comprehensive pharmacological investigation of these compounds should be taken under consideration for further research.

4 Experimental section

4.1 Materials and methods

Reagents were purchased from Aldrich and Merck with analytical grade and used without further purification. Solvents for column chromatography were distilled before using. Melting points (in °C) were determined on a Thermo Mel-temp 3.0 (U.S.A). IR spectra were recorded on an IMPACT 410 Nicolet spectrometer. ESI-MS spectra were measured on 1100Agilent LC/MS ion Trap. NMR spectra (^{1}H, ^{13}C, DEPT, HSQC, and HMBC) were recorded on a Bruker Avance 500 MHz. Thin layer chromatography was performed on a pre-coated silica gel 60 F254 (Merck) and were visualized under UV light (λ_{max} = 254 nm) and stained with a solution of 1% (w/w) vanillin in H_2SO_4. Column chromatography was performed on silica gel 300–400 mesh (Merck).

4.2 α-Glucosidase inhibition assay

The assay was performed on 96 well-plates (200 µL per well). The test sample was dissolved in 10% DMSO and diluted further to the concentrations of 1024, 256, 64, 16, 4, 1 µg mL^{-1}. Each concentration of the test sample (10 µL) was incubated at T = 37 °C with phosphate buffer 100 mM (pH = 6.8, 40 µL), α-glucosidase 0.4 U mL^{-1} (25 µL), *p*-nitrophenyl α-D-glucopyranoside 2.5 mM (25 µL). After 30 min, the reaction was stopped by adding 100 µL of 0.1 M Na_2CO_3. The enzyme activities were determined by measuring the absorbance at λ_{max} = 405 nm. The control was prepared using the same procedure replacing the tested sample by distilled water, while activity of the reference was tested by replacing the sample with acarbose. Percentage of inhibition was calculated as followed:

$$\alpha - \text{glucosidase inhibition}\,(\%) = [\text{Abs}_{(\text{negativecontrol})} - \text{Abs}_{(\text{sample})}]/\text{Abs}_{(\text{control})} \times 100\%$$

4.3 Synthesis of *tert*-butyl(4-sulfamoylphenethyl) carbamate (2) [13]

4-(2-Aminoethyl)benzenesulfonamide (**1**) (4.0 g, 0.020 mol) was dissolved in dimethylformamide (DMF) (75 mL). The solution was cooled to 0–5 °C in an ice bath and solution of di-*tert*-butyl dicarbonate (Boc_2O) (4.8 g, 0.022 mol) was added. The ice bath was then removed to allow the reaction to room temperature and kept for 4 h. The reaction solution was then poured into 300 mL water. The white powder was precipitated, filtered and dried to give **2** (5.7 g). Yield: 95.0%, white powder; m.p. 180–182 °C. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.73 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.26 (s, 2H), 6.89 (br s, 1H), 3.17 (q, J = 7.0 Hz, 2H), 2.76 (t, J = 7.0 Hz, 2H), 1.36 (s, 9H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.45, 143.59, 141.94, 128.98, 125.56, 77.51, 40.00, 35.05, 28.16.

4.4 Synthesis of *tert*-butyl-{4-[*N*-(cyclohexylcarbamoyl) sulfamoyl]phenethyl}carbamate (3) [14]

Compound **2** (5.1 g, 0.017 mol) and potassium carbonate (4.7 g, 0.034 mol) in acetone (200 mL) was refluxed for 1 h, followed by addition of cyclohexyl isocyanate (2.70 g, 0.022 mol). The reaction mixture was continuously refluxed for 6 h. The solvent was removed under reduced pressure and the residue was added water (100 mL), neutralized with 1% HCl to pH = 5–6. The product was collected by filtration and washed with water. Pure compound **3** was obtained by recrystallization from ethanol/water (6.99 g). Yield: 96.6 %, white powder; m.p. 213–215 °C. – IR (film, KBr): ν = 3336 (NH), 2932 (–CH, alkane), 1691 (C=C, aromatic), 1536 (C=O, amide), 1351 and 1168 (O=S=O), 1296.52 (C–O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6) δ = 10.25 (s, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 6.88 (t, J = 5.5 Hz, 1H), 6.30 (d, J = 7.5 Hz, 1H), 3.19 (q, J = 7.5 Hz, 2H), 2.78 (t, J = 7.5 Hz, 2H), 1.65–1.63 (m, 2H), 1.59–1.56 (m, 2H), 1.49–1.47 (m, 1H), 1.34 (s, 9H), 1.25–1.18 (m, 2H), 1.15–1.04 (m, 4H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.46, 150.35, 145.20, 138.00, 129.14, 127.13, 77.52, 48.01, 40.00, 35.15, 32.21, 28.16, 24.92, 24.10. – MS ((–)-ESI): m/z (%) = 424.0 (100) [M–H]$^-$. – MS ((+)-ESI): m/z (%) = 448.0 (100) [M+Na]$^+$.

4.5 Synthesis of 4-(2-aminoethyl)-*N*-(cyclohexylcarbamoyl)benzenesulfonamide (4) [14]

In a 100 mL three-necked flask compound **3** (7.3 g, 0.017 mol) was dissolved in 75 mL DCM. The solution was cooled in an ice bath and trifluoroacetic acid (TFA) (20 mL) was added dropwise. The reaction mixture was stirred at room temperature for 4 h, and the solvent was removed under reduced pressure. Cool water (100 mL) was added to the residue and the solid appeared was filtered, washed with distilled water, recrystallized by ethanol/water (20/2) to give the product **4** (5.1 g). Yield: 92.0 %, white solid; m.p. 199–201 °C. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.48 (br s, 1H, 7′-H), 7.93 (br s, 2H, NH_2), 7.85 (d, J = 8.5 Hz, 2H, 2′-H, 6′-H), 7.48 (d, J = 8.5 Hz, 2H, 3′-H, 5′-H), 6.62 (d, J = 8.0 Hz, 1H, N*H*), 3.26–3.28 (1H, m, 1-H), 3.11 (m, 2H, 2″-H), 2.96 (m, 2H, 1''-H), 1.65–1.63 (m, 2H), 1.60–1.57 (m, 2H), 1.49–1.47(m, 1H), 1.24–1.17 (m, 2H,), 1.14–1.01 (m, 2H), 1.09–1.05 (m, 1H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 150.49 (C-8′), 142.78 (C-4′), 138.88 (C-1′), 129.20 (C-3′, C-5′), 127.47 (C-2′, C-6′), 48.06 (C-1), 40.00 (C-2″), 32.74 (C-1''), 32.24 (C-2, C-6), 24.94 (C-4), 24.15 (C-3, C-5). – MS ((+)-ESI): m/z (%) = 325.9 (100) [M+H]$^+$. – MS ((–)-ESI): m/z (%) = 323.9 (100) [M–H]$^-$.

4.6 General procedure for the preparation of sulfonylureas 5a–5l

Appropriate carboxylic acid, (0.01 mol) was dissolved in anhydrous acetone (50 mL) and triethylamine (1.42 mL, 0.01 mol). After 15 min at 0 °C, ethyl chloroformate (0.97 mL, 0.01 mol) was added dropwise and the reaction was kept for 60 min, followed by addition of 4-(2-aminoethyl)-*N*-(cyclohexylcarbamoyl)benzenesulfonamide (**4**) (3.25 g, 0.01 mol) and triethylamine (1.42 mL, 0.01 mol) in anhydrous acetone (20 mL). The resulting mixture was stirred for 4 h at room temperature. Acetone was removed under reduced pressure, and the residue was acidified with 5% HCl to pH ≈ 5. White solid product was collected and washed with water and dried at 65 °C.

4.6.1 *N*-{4-[*N*-(Cyclohexylcarbamoyl)sulfamoyl]phenethyl}-2-hydroxynicotinamide (5a): Yield: 72.0%, white powder; m.p. 170–172 °C. – IR (film, KBr): ν = 3267 (NH), 3114 (OH), 2931.86, (–CH, alkane), 1669 (C=C, aromatic), 1543 (C=O, amide), 1424 (C=N), 1308 and 1147 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.43 (br s, 1H), 10.27 (br s, 1H), 9.83 (t, J = 5.5 Hz, 1H), 8.32 (dd, J = 2.5, 7.5 Hz, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.68 (br s, 1H), 7.47 (d, J = 8.5 Hz, 2H), 6.46 (t, J = 6.5 Hz, 1H), 6.30 (d, J = 8.0 Hz, 1H), 3.58 (q, J = 7.0 Hz, 2H), 2.92 (t, J = 7.0 Hz, 2H),

1.65–1.06 (10H, m). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.25, 162.20, 150.53, 145.08, 143.83, 139.31, 138.25, 129.14, 127.24, 120.23, 106.17, 48.02, 40.00, 35.05, 32.22, 24.94, 24.12. – MS ((+)-ESI): *m/z* (%) = 446.9 (60) $[M+H]^+$. – MS ((–)-ESI): *m/z* (%) = 444.9 (40) $[M-H]^-$.

4.6.2 *N*-{4-[*N*-(Cyclohexylcarbamoyl)sulfamoyl]phenethyl}benzamide (5b) [15]: Yield: 81.1%, white powder; m.p. 189–191 °C. – IR (film, KBr): ν = 3344 (NH), 2934 (–CH, alkane), 1654 (C=C, aromatic, 1536 (C=O, amide), 1343.91 and 1164.09 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 10.27 (br s, 1H), 8.56 (t, *J* = 5.5 Hz, 1H), 7.82–7.78 (m, 4H), 7.53–7.42 (m, 5H), 6.30 (d, *J* = 7.5 Hz, 1H), 3.53 (q, *J* = 6.5 Hz, 2H), 2.95 (t, *J* = 7 Hz, 2H), 1.65–1.06 (m, 10H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.25, 150.43, 145.31, 138.11, 134.5, 131.07, 129.20, 128.23, 127.26, 127.07, 48.03, 40.24, 34.81, 32.24, 24.95, 24.15. – MS ((–)-ESI): *m/z* (%) = 427.7 (100) $[M-H]^-$. – MS ((+)-ESI): *m/z* (%) = 428.7 (70) $[M+H]^+$.

4.6.3 (*E*)-*N*-{4-[*N*-(cyclohexylcarbamoyl)sulfamoyl]phenethyl}-3-(4-hydroxyphenyl)acrylamide (5c): Yield: 76.3%, white powder; m.p. 144–145 °C. – IR (film, KBr): ν = 3313 (OH), 2931.14 (NH), 2854 (–CH, alkane), 1653, (C=C, aromatic, 1535 (C=O, amide), 1341 and 1159 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.28 (br s, 1H, SO_2NH), 9.80 (s, 1H, OH), 8.07 (t, *J* = 6 Hz, 1H, CON*H*), 7.82 (d, *J* = 8.5 Hz, 2H, 2′-H, 6′-H), 7.46 (d, *J* = 8.5 Hz, 2H, 3′-H, 5′-H), 7.38 (d, *J* = 8.5 Hz, 2H, 2‴-H, 6‴-H), 7.32 (d, *J* = 15.5 Hz, 1H, 7‴-H), 6.79 (d, *J* = 8.5 Hz, 2H, 3‴-H, 5‴-H), 6.37 (d, *J* = 15.5 Hz, 1H, 8‴-H), 6.32 (d, *J* = 8.0 Hz, 1H, CON*H*), 3.45 (q, *J* = 7.0 Hz, 2H, 2″-H), 2.88 (t, *J* = 7.0 Hz, 2H, 1″-H), 1.66–1.64 (m, 2H), 1.60–1.57 (m, 2H), 1.50–1.47 (m, 1H), 1.25–1.17 (m, 2H), 1.15–1.06 (m, 4H). – ^{13}C NMR (125 MHz, DMSO-d_6): 165.43 (CONH), 158.78 (C-4‴), 150.45 (C-8′), 145.27 (C-4′), 138.73 (C-7‴), 138.13 (C-1′), 129.16 (2C, C-2‴, C-6‴), 129.14 (2C, C-3", C-5"), 127.22 (2C, C-2′, C-6′), 125.84, 118.49, 115.68 (2C, C-3‴, C-5‴), 48.03 (C-1), 40.00 (C-2″), 34.92 (C-1″), 32.23 (C-2, C-6), 24.93, 24.11 (C-3, C-5). – MS ((+)-ESI): *m/z* (%) = 472.3 $[M+H]^+$.

4.6.4 *N*-{4-[*N*-(cyclohexylcarbamoyl)sulfamoyl]phenethyl}cinnamamide (5d) [16]: Yield: 74.1%, white powder; m.p. 163–164 °C. – IR (film, KBr): ν = 3345 (NH), 2935 (–CH, alkane), 1654 (C=C, aromatic), 1540 (C=O, amide), 1341 and 1162 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.91 (d, *J* = 8.5 Hz, 2H), 7.56–7.55 (m, 3H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 16.5 Hz, 1H), 7.42–7.37(m, 3H), 6.57 (d, *J* = 16.00 Hz, 1H), 3.61 (t, *J* = 7.0 Hz, 2H), 3.46–3.41(m, 1H), 3.00 (t, *J* = 7.0 Hz, 2H), 1.79–1.15 (m, 10H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.94, 150.44, 145.18, 138.59, 138.16, 134.84, 129.36, 129.13, 128.85, 127.44, 127.22, 122.06, 48.01, 40.00, 34.83, 32.21, 24.92, 24.10. – MS ((–)-ESI): *m/z* (%) = 454.0 (100) $[M-H]^-$. – MS ((+)-ESI): *m/z* (%) = 455.9 (40) $[M+H]^+$, 478.1 (100) $[M+Na]^+$.

4.6.5 4 Amino-*N*-{4-[*N*-(cyclohexylcarbamoyl)sulfamoyl]phenethyl}benzamide (5e): Yield: 76.3%, white powder; m.p. 165–166 °C. – IR (film, KBr): ν = 3440 (NH_2), 3336 (NH), 2931 (–CH, alkane), 1688 (C=C, aromatic), 1533 (C=O, amide), 1335 and 1158 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.27 (s, 1H), 8.09 (t, *J* = 5.5 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 6.52 (d, *J* = 8.5 Hz, 2H), 6.31 (d, *J* = 7.5 Hz, 1H), 5.56 (br s, 2H), 3.46 (q, *J* = 7.0 Hz, 2H), 2.90 (t, *J* = 7.0 Hz, 2H), 1.65–1.06 (m, 10H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.25, 151.50, 150.37, 145.55, 137.98, 129.12, 128.57, 127.20, 121.19, 112.48, 48.02, 40.00, 35.12, 32.22, 24.93, 24.11. – MS ((–)-ESI): *m/z* (%) = 443.0 (100) $[M-H]^-$. – MS ((+)-ESI): *m/z* (%) = 445.0 (60) $[M+H]^+$, 467.0 (100) $[M+Na]^+$.

4.6.6 *N*-{4-[*N*-(Cyclohexylcarbamoyl)sulfamoyl]phenethyl}-4-methoxybenzamide (5f) [16]: Yield: 69.9%, white powder; m.p. 209–211 °C. – IR (film, KBr): ν = 3301(NH), 3454 (CH_3), 2940 (–CH, alkane), 1684 (C=C, aromatic), 1529 (C=O, amide), 1256 (C–O), 1340.43 and 1167.70 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.42 (t, *J* = 5.5 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.31 (d, *J* = 8.0 Hz, 1H), 3.81 (s, 3H), 3.51 (q, *J* = 7.0 Hz, 2H), 2.94 (t, *J* = 7.0 Hz, 2H), 1.66–1.07 (m, 10H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.78, 161.48, 150.42, 145.42, 138.07, 129.20, 128.89, 127.24, 126.71, 113.44, 55.30, 48.07, 40.20, 34.92, 32.24, 24.95, 24.14. – MS ((–)-ESI): *m/z* (%) = 458.0 (100) $[M-H]^-$. – MS ((+)-ESI): *m/z* (%) = 459.9 (50) $[M+H]^+$.

4.6.7 *N*-{4-[*N*-(Cyclohexylcarbamoyl)sulfamoyl]phenethyl}-2-iodobenzamide (5g): Yield: 78.1%, white powder; m.p. 160–162 °C. – IR (film, KBr): ν = 3306 (NH), 2934 (–CH, alkane), 1681 (C=C, aromatic), 1534 (C=O, amide), 1335 and 1164 (O=S=O), 1244 (C–I) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.26 (s, 1H), 8.44 (t, *J* = 5.5 Hz, 1H), 7.85–7.79 (m, 3H), 7.50 (m, 1H), 7.42–7.39 (m, 2H), 7.21 (dd, *J* = 1.5 Hz, 8.0 Hz, 1H), 7.15–7.13 (m, 1H), 6.30 (br s, 1H), 3.50 (q, *J* = 7.0 Hz, 2H), 2.95 (t, *J* = 7.0 Hz, 2H), 1.66–1.07 (m, 10H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.79, 150.53, 144.97, 143.03, 138.95, 130.54, 129.23, 129.08, 127.83, 127.79, 127.15, 93.24, 47.99, 41.08, 34.48, 32.23, 24.90, 24.09. – MS ((–)-ESI): *m/z* (%) = 553.9 (30) $[M-H]^-$. – MS ((+)-ESI): *m/z* (%) = 555.9 (70) $[M+H]^+$.

4.6.8 *N*-{4-[*N*-(Cyclohexylcarbamoyl)sulfamoyl]phenethyl}-2-hydroxy-3,5-diiodobenzamide (5h): Yield: 69.3%, white powder; m.p. 178–180 °C. – IR (film, KBr): ν = 3745 (OH phenol), 3297 (NH), 2929 (–CH, alkane), 1682 (C=C, aromatic), 1537 (C=O, amide), 1329 and 1161 (O=S=O), 1274, 1252 (C–I) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.95 (s, 1H), 10.27 (s, 1H, SO_2NH), 9.27 (s, 1H, CON*H*), 8.17 (d, *J* = 2.0 Hz, 1H, 6‴-H), 8.15 (s, 1H, 4‴-H), 7.82 (d, *J* = 8.5 Hz, 2H, 2′-H, 6′-H), 7.47 (d, *J* = 8.5 Hz, 2H, 3′-H, 5′-H), 6.31 (d, *J* = 7.5 Hz, 1H, CON*H*), 3.56 (q, *J* = 7.0 Hz, 2H, 2″-H), 2.96 (q, *J* = 7.0 Hz, 2H, 1"-H), 1.64–1.62 (m, 2H), 1.58–1.56 (m, 2H),1.49–1.46 (m, 1H), 1.24–1.17 (m, 2H), 1.14–1.06 (m, 3H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.04 (CONH), 159.87 (C-2‴), 150.33 (CONH), 149.31 (C-6‴), 144.77 (C-4′), 138.22 (C-1′), 135.11 (C-4‴), 129.16 (C-3′, C-5′), 127.27 (C-2′, C-6′), 88.82 (C-3‴), 81.12 (C-5‴), 48.00 (C-1), 40.28 (C-2″), 34.21 (C-1″), 32.18 (C-2, C-6), 24.92 (C-4), 24.08 (C-3, C-5). – MS ((–)-ESI): *m/z* (%) = 695.8 (15) $[M-H]^-$. – MS ((+)-ESI): *m/z* (%) = 697.7 (15) $[M+H]^+$.

4.6.9 *N*-{4-[*N*-(cyclohexylcarbamoyl)sulfamoyl]phenethyl}isoquinoline-1-carboxamide (5i): Yield: 72.0%, white powder; m.p. 123–124 °C. – IR (film, KBr): ν = 3351 (NH), 2931 (–CH, alkane), 1662 (C=C, aromatic), 1531 (C=O, amide), 1341 and 1161(O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.93 (t, *J* = 5.5 Hz, 1H), 8.72 (d, *J* = 8.5 Hz, 1H), 8.51 (d, *J* = 5.5 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 5.5 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.79 (t, *J* = 8.5 Hz, 1H), 7.68 (t, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 6.30 (d, *J* = 6.5 Hz, 1H), 3.65 (q, *J* = 7.0 Hz, 3H), 3.00 (t, *J* = 7 Hz, 2H), 1.64–1.05 (m, 10H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.15, 151.38, 140.81, 136.49, 130.62, 129.17, 128.28, 127.18, 127.03, 126.54, 125.40, 123.18, 48.06, 40.00, 34.82, 32.33, 25.00, 24.19. – MS ((–)-ESI): *m/z* (%) = 479.0 (100) $[M-H]^-$. – MS ((+)-ESI): *m/z* (%) = 481.0 (40) $[M+H]^+$.

4.6.10 *N*-{4-[*N*-(Cyclohexylcarbamoyl)sulfamoyl]phenethyl}-3-methylpicolinamide (5k): Yield: 74.0%, white powder; m.p. 120–121 °C. – IR (film, KBr): ν = 3345 (NH), 2938 (–CH, alkane), 1673 (C=C, aromatic), 1534 (C=O, amide), 1354 and 1163 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.68 (t, J = 6.0 Hz, 1H), 8.41 (d, J = 4.5 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.42 (dd, J = 4.5, 8.0 Hz, 1H), 6.32 (d, J = 7.5 Hz, 1H), 3.55 (q, J = 7.0 Hz, 2H), 2.94 (t, J = 7.0 Hz, 2H), 2.46 (s, 3H), 1.65–1.16 (m, 10H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.00 (CONH), 150.36, 149.24, 145.69, 145.20, 140.03, 138.07, 133.05, 129.13, 127.16, 125.28, 48.00, 40.00, 34.81, 32.19, 24.90, 24.07, 19.09. – MS ((–)-ESI): m/z (%) = 443.0 (100) $[M–H]^-$. – MS ((+)-ESI): m/z (%) = 444.9 (60) $[M+H]^+$.

4.6.11 *N*-{4-[*N*-(Cyclohexylcarbamoyl)sulfamoyl]phenethyl}quinoxaline-2-carboxamide (5l) [17]: Yield: 76.1%, white powder; m.p. 197–199 °C. – IR (film, KBr): ν = 3324 (NH), 2942 (–CH, alkane), 1687 (C=C, aromatic), 1530 (C=O, amide), 1338 and 1163 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.44 (s, 1H), 9.16 (t, J = 5.5 Hz, 1H), 8.18 (dd, J = 3.5, 6.0 Hz, 2H), 7.98 (m, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 6.26 (d, J = 5.5 Hz, 1H), 3.65 (q, J = 7.5 Hz, 2H), 3.02 (t, J = 7.5 Hz, 2H), 1.63–1.15 (m, 10H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.14, 144.30, 143.63, 142.94, 139.77, 131.85, 131.26, 129.38, 129.07, 127.20, 48.02, 40.00, 34.77, 32.31, 24.98, 24.16. – MS ((–)-ESI): m/z (%) = 480.0 (100) $[M–H]^-$. – MS ((+)-ESI): m/z (%) = 481.9 (70) $[M+H]^+$.

4.7 General procedure for the preparation of sulfonylureas 5m, 5n, 5o

Phthalic anhydride or 2,3-pyridinedicarboxylic anhydride (0.01 mol) in glacial acetic acid (30 mL) was added 4-(2-aminoethyl)-*N*-(cyclohexylcarbamoyl)benzenesulfonamide (**4**) (0.01 mol). The reaction mixture was refluxed for 7 h and the reaction was cooled to room temperature. The white solid was filtered and washed with water, recrystallized in ethanol/water to obtain pure product **5m** or **5n**.

2,3-pyridinedicarboxylic anhydride (0.01 mol) in glacial acetic acid (30 mL) was added 4-(2-aminoethyl)-*N*-(cyclohexylcarbamoyl) benzenesulfonamide (**4**) (0.01 mol). The reaction mixture was stirred at room temperature for 1 h. The white solid was filtered and washed with water, recrystallized in ethanol/water to obtain **5o**.

4.7.1 2-((4-[*N*-(Cyclohexylcarbamoyl)sulfamoyl]phenethyl)carbamoyl)benzoic acid (5m) [18]: Yield: 81.5%, white powder; m.p. 161–163 °C. – IR (film, KBr): ν = 3071 (OH), 3349 (NH), 2935 (-CH, alkane), 1718 (C=O, acid), 1655 (C=C, aromatic), 1536 (C=O, amide), 1342 and 1122 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.24 (s, 1H), 7.85–7.81 (m, 4H), 7.78 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 6.31 (d, J = 8.0 Hz, 1H), 3.85 (t, J = 7.0 Hz, 2H), 3.46 (q, J = 7.0 Hz, 1H), 3.03 (t, J = 7.0 Hz, 2H), 1.64–1.05 (m, 10H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.55, 167.60, 150.35, 144.02, 138.36, 134.40, 131.43, 131.11, 129.22, 127.49, 123.01, 48.03, 40.00, 38.25, 33.25, 34.51, 24.94, 24.13. – MS ((–)-ESI): m/z (%) = 471.9 (100) $[M–H]^-$. – MS ((+)-ESI): m/z (%) = 474.0 (100) $[M+H]^+$.

4.7.2 *N*-(Cyclohexylcarbamoyl)-4-{2-(5,7-dioxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6yl)-ethyl}benzenesulfonamide (5n): Yield: 66.1%, white powder; m.p. 224–226 °C. – IR (film, KBr): ν = 3309 (NH), 2918 (–CH, alkane), 1709 (C=C, aromatic), 1531 (C=O, amide), 1341and 1163 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 10.27 (t, J = 3.5 Hz, 1H, SO_2NH), 8.96 (d, J = 5.0 Hz, 1H,), 8.27 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.77 (t, J = 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 6.28 (d, J = 7.5 Hz, 1H, CONH), 3.88 (t, J = 7.5 Hz, 2H), 3.03 (t, J = 7.5 Hz, 3H), 1.65–1.62(m, 2H), 1.8–1.56 (m, 1H), 1.49–1.46 (m, 1H), 1.23–1.18 (m, 2H), 1.10–1.06 (m, 3H). – ^{13}C NMR (125 MHz, DMSO-*d*6, 25 °C, TMS): δ = 166.03, 165.93, 154.08, 151.31, 150.47, 143.90, 138.50, 131.22, 129.21, 127.83, 127.32, 127.08, 48.03, 40.00, 38.37, 32.21, 24.94, 24.12. – MS ((–)-ESI): m/z (%) = 455.0 (100) $[M–H]^-$. – MS ((+)-ESI): m/z (%) = 456.9 (40) $[M+H]^+$.

4.7.3 3-({4-[*N*-(Cyclohexylcarbamoyl)sulfamoyl]phenethyl}carbamoyl)picolinic acid (5o): Yield: 72.5%, white powder; m.p. 174–176 °C. – IR (film, KBr): ν = 3742 (OH), 3324 (NH), 2936 (–CH, alkane), 1721 (C=O, acid), 1653 (C=C, aromatic), 1540 (C=O, amide), 1338 and 1163 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.76 (t, J = 5.5 Hz, 1H, CON*H*), 8.66 (dd, J = 1.5, 5.0 Hz, 1H, 6‴-H), 8.05 (dd, J = 1.5, 8.0 Hz, 1H, 4‴-H), 7.82 (d, J = 8.5 Hz, 2H, 2′-H, 6′-H), 7.60 (dd, J = 4.5, 7.5 Hz, 1H, 5‴-H), 7.49 (d, J = 8.5 Hz, 2H, 3′-H, 5′-H), 6.36 (d, J = 7.5 Hz, 1H, CON*H*), 3.54–3.50 (m, 3H, 1-H, 2″-H), 2.95 (t, J = 7.5 Hz, 2H, 1″-H), 1.65–1.62 (m, 2H), 1.58–1.56 (m, 2H), 1.13–1.16 (m, 2H), 1.23–1.17 (m, 2H), 1.09–1.07 (m, 2H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.90 (COOH), 165.06 (C-7‴), 150.42 (C-2‴), 150.17 (C-3‴), 149.57 (C-6‴), 145.14 (C-4′), 138.13 (C-1′), 136.77 (C-4‴), 129.11 (C-2′, C-6′), 127.22 (C-3′,C-5′), 125.14 (C-5‴), 48.02 (C-1), 39.83 (C-2″, 34.55 (C-1″), 32.20 (C-2, C-6), 24.92 (C-4), 24.08 (C-3, C-5). – MS ((–)-ESI): m/z (%) = 473.0 (20) $[M–H]^-$. – MS ((+)-ESI): m/z (%) = 474.8 (70) $[M+H]^+$.

4.8 Synthesis of *N*-[2-[4-(aminosulfonyl)phenyl]ethyl]-5-methylpyrazin carboxamide (6) [19]

To a stirred solution of 5-methyl-pyrazin-2-carboxylic acid (0.01 mol) in anhydrous acetone (50 mL) and triethylamine (1.42 mL, 0.01 mol) at 0 °C, ethyl chloroformate (0.97 mL, 0.01 mol) was added dropwise and the reaction was further stirred for 60 min. A solution of 4-(2-aminoethyl)-benzenesulfonamide (2.0 g, 0.01 mol) and triethylamine (1.42 mL, 0.01 mol) in anhydrous acetone was then added. The resulting mixture was stirred for 3 h at room temperature. Acetone was then removed, and the residue was acidified with 5% HCl to pH ≈ 5. The white solid was collected and washed with distilled water. Pure product (**6**) was obtained by recrystallization from ethanol (2.99 g).

Yield: 93.4%, brown powder; m.p. 237–239 °C. – IR (film, KBr): ν = 3309 (NH), 1695 (C=C, aromatic), 1528 (C=O, amide), 1340 and 1158 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.02 (s, 1H), 8.91 (t, J = 6.0 Hz, 1H, CONH), 8.59 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.27 (s, 2H, SO_2NH_2), 3.57 (q, J = 7.0 Hz, 2H), 2.95 (t, J = 7.0 Hz, 2H), 2.58 (s, 3H, CH_3). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.99 (CONH); 156.85 (CONH), 143.54, 142.83, 142.36, 142.04, 129.08, 126.55, 125.68, 40.0, 34.65, 21.31(CH_3). – MS ((–)-ESI): m/z (%) = 319 (100) $[M–H]^-$. – MS ((+)-ESI): m/z (%) = 321 (100) $[M+H]^+$.

4.9 Synthesis of ethyl-({4-[2-(5-methylpyrazine-2-carboxamido)ethyl]phenyl}sulfonyl)-carbamate (7)

N-(4-sulfamoylphenethyl) carboxamide derivatives (**6**) (0.01 mol) were mixed with a solution of ethyl chloroformate (1.23 mL, 0.013 mol), anhydrous potassium carbonate (2.0 g, 014 mmol) in dry acetone (300 mL). The reaction was refluxed for 4 h and the solvent was removed

under reduced pressure. The residue was suspended in water (100 mL), neutralized with 1% HCl. The white solid was filtered and washed with distilled water to obtain 3.5 g of the desired product **7**. Yield: 89.2%, brown powder; m.p. 159–161 °C. – IR (film, KBr): ν = 3349 (NH), 1743 (C=O, carbamate), 1660 (C=C, aromatic), 1518 (C=O, amide), 1340 and 1160 (O=S=O), 1229 (C–O, carbamate) cm^{-1}. – ^1H NMR (500 MHz, DMSO-d_6): δ = 9.01 (d, J = 1.5 Hz, 1H, 3‴-H), 8.92 (t, J = 6.0 Hz, 1H, CON*H*), 8.58 (s, 1H, 6‴-H), 7.80 (d, J = 8.5 Hz, 2H, 2′-H, 6′-H), 7.48 (d, J = 8.5 Hz, 2H, 3′-H, 5′-H), 3.99 (q, J = 7.0 Hz, 2H, COOC*H*$_2$CH$_3$), 3.59 (q, J = 7.0 Hz, 2H, 2″-H), 2.98 (t, J = 7.0 Hz, 2H, 1″-H), 2.57 (s, 3H, CH_3), 1.07 (t, J = 7.0 Hz, 3H, COOCH$_2$C*H*$_3$). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.96 (CONH), 156.77 (C-5‴), 151.01 (NHCOOCH$_2$CH$_3$), 145.65 (C-4′), 142.75 (C-3′″), 142.33 (C-6‴), 142.01 (C-2‴), 137.09 (C-1′), 129.32 (2C, C-3′, C-5′), 127.43 (2C, C-6′, C-2′), 61.83 (COO*C*H$_2$CH$_3$), 40.0 (C-2″), 34.65 (C-1″), 21.25 (CH$_3$.5‴), 13.88 (COO*C*H$_2$CH$_3$).

4.10 General procedure for the preparation of sulfonylurea derivatives (8a–h)

Carbamate derivatives (**7**) (0.01 mol) and amines (0.011 mol) in toluene was refluxed for 4 h. The reaction was then allowed to cool to room temperature. The solid was filtered, washed with water and recrystallized in ethanol.

4.10.1 5-Methyl-*N*-{4-[*N*-(phenethylcarbamoyl)sulfamoyl]phenethyl} pyrazine-2-carboxamide (8a): Yield: 74.9%, white powder; m.p. 191–193 °C. – IR (film, KBr): ν = 3347 (NH), 1674 (C = C, aromatic), 1536 (C=O, amide), 1341 and 1167 (O=S=O) cm^{-1}. – ^1H NMR (500 MHz, DMSO-d_6): δ = 9.01 (d, J = 1.0 Hz, 1H), 8.91 (t, J = 6.0 Hz, 1H), 8.57 (d, J = 1.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.26–7.10 (m, 5H), 3.58 (q, J = 7.0 Hz, 2H), 3.16 (q, J = 7.0 Hz, 2H), 2.95 (t, J = 7.5 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 2.56 (s, 3H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.98, 156.78, 142.78, 142.34, 142.03, 139.21, 137.27, 128.60, 128.58, 128.25, 126.98, 126.0, 40.81, 35.33, 34.70, 33.12, 21.27. – MS ((+)-ESI): m/z (%) = 467.9 (100) $[M+H]^+$. – MS ((–)-ESI): m/z (%) = 465.9 (100) $[M–H]^-$.

4.10.2 5-Methyl-*N*-(4-{*N*-[(2,3,4-trifluorophenyl)carbamoyl] sulfamoyl}phenethyl)pyrazine-2-carboxamide (8b): Yield: 84.2%, white powder; m.p. 179–180 °C. – IR (film, KBr): ν = 3327 (NH), 1651 (C=C, aromatic), 1529 (C=O, amide), 1348 and 1160 (O=S=O) cm^{-1}. – ^1H NMR (500 MHz, DMSO-d_6): δ = 10.98 (s, 1H), 9.02 (dd, J = 1.5, 9.5 Hz, 1H), 8.93 (t, J = 6.0 Hz, 1H), 8.72 (s, 1H), 8.57 (s, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 3.58 (q, J = 6.5 Hz, 2H), 2.95 (t, J = 6.5 Hz, 2H), 2.58 (s, 3H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.99, 156.84, 143.54, 142.82, 142.36, 142.04, 140.5, 140.25, 140.04, 139.89, 138.59, 134.62, 129.07, 125.68, 111.6, 111.47, 40.0, 34.65, 21.31. – MS ((+)-ESI): m/z (%) = 494.0 (100) $[M+H]^+$. – MS ((–)-ESI): m/z (%) = 491.9 (100) $[M–H]^-$.

4.10.3 *N*-[4-(*N*-{[4-Cyano-3-(trifluoromethyl)phenyl]carbamoyl} sulfamoyl)phenethyl]-5-methylpyrazine-2-carboxamide (8c): Yield: 71.9%, white powder; m.p. 165–166 °C. – IR (film, KBr): ν = 3356 (NH), 2227 (C=N), 1658 (C=C, aromatic), 1529 (C=O, amide), 1333 and 1149 (O=S=O), 1183 (CF_3) cm^{-1}. – ^1H NMR (500 MHz, DMSO-d_6): δ = 9.03 (s, 1H), 8.50 (s, 1H), 7.96 (br s, 1H), 7.89 (d, J = 7.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.35 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 7.5 Hz, 1H), 3.66 (t, J = 7.5 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H), 2.61 (s, 3H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.57, 158.6, 144.54, 144.37, 143.44, 136.76, 130.21, 129.98, 128.79, 128.76, 128.67, 128.49, 127.7, 121.94, 117.15, 41.55, 36.28, 21.55. – MS ((+)-ESI): m/z (%) = 533.0 (100) $[M+H]^+$. – MS ((–)-ESI): m/z (%) = 531.0 (100) $[M–H]^-$.

4.10.4 *N*-(4-{*N*-[(3-Fluoro-4-methoxyphenyl)carbamoyl]sulfamoyl} phenethyl)-5-methylpyrazine-2-carboxamide (8d): Yield: 81.9%, white powder; m.p. 181–182 °C. – IR (film, KBr): ν = 3298 (NH), 1650, (C=C, aromatic), 1521 (C=O, amide), 1223 (C–O), 1341 and 1161 (O=S=O) cm^{-1}. – ^1H NMR (500 MHz, DMSO-d_6): δ = 9.01 (d, J = 1.5, Hz, 1H), 8.93 (t, J = 6.0 Hz, 1H), 8.80 (s, 1H), 8.57 (d, J = 1.0 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.28 (dd, J = 2.5, 13.5 Hz, 1H), 7.05 (d, J = 13.0 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H) 3.77 (s, 3H), 3.59 (q, J = 7.0 Hz, 2H), 2.97 (t, J = 7.0 Hz, 2H), 2.57 (s, 3H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.99, 158.08, 156.85, 143.53, 142.83, 142.36, 142.04, 129.21, 129.08, 127.47, 125.68, 116.11, 114.15, 111.85, 109.34, 57.01, 34.76, 34.64, 21.30. – MS ((+)-ESI): m/z (%) = 487.9 (60) $[M+H]^+$. – MS ((–)-ESI): m/z (%) = 485.9 (100) $[M–H]^-$.

4.10.5 5-Methyl-*N*-[4-(*N*-{[4-nitro-3(trifluoromethyl)phenyl] carbamoyl}sulfamoyl)phenethyl]pyrazine-2-carboxamide (8e): Yield: 68.4%, white powder; m.p. 182–183 °C. – IR (film, KBr): ν = 3371 (NH), 1662 (C=C, aromatic), 1547 (C=O, amide), 1494 (NO_2), 1346 and 1149 (O=S=O), 1182 (CF_3) cm^{-1}. – ^1H NMR (500 MHz, DMSO-d_6): δ = 9.73 (s, SO_2NH, 1H), 9.00 (s, H-3‴, 1H), 8.93 (t, J = 6.0 Hz, CONH), 8.57 (s, H-6‴, 1H), 8.12 (d, J = 9.0 Hz, 1H, H-5), 8.02 (d, J = 2.0 Hz, 1H, H-2), 7.88 (d, J = 8.0 Hz, 2H, H-2′, H-6′), 7.80 (dd, J = 2.5, 8.0 Hz, 1H, H-6), 7.50 (d, J = 8.0 Hz, 2H, H-3′, H-5′), 3.59 (q, J = 7.0 Hz, 2H, H-2″), 2.97 (t, J = 7.0 Hz, 2H, H-1″), 2.56 (s, 3H, CH_3). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.01 (C-7′), 156.86 (C-8′), 154.33 (C-5‴), 143.54 (C-2‴), 142.84 (C-4′), 142.80 (C- 6‴), 142.36 (C-3‴), 133.77 (C-1), 129.64 (C-3), 129.09 (2C, C-3′, C-5′), 127.55 (C-2), 125.69 (2C, C-2′, C-6′), 125.17 (C-5), 124.92 (C-4), 123.58 (CF_3), 121.41 (C-1′), 114.48 (C-6), 40.00 (C-2″), 34.78 (C-1″), 21.3 (CH_3). – MS ((+)-ESI): m/z (%) = 552.9 (100) $[M+H]^+$. – MS ((–)-ESI): m/z (%) = 550.9 (100) $[M–H]^-$.

4.10.6 *N*-(4-[*N*-(Cyclopentylcarbamoyl)sulfamoyl]phenethyl)-5-methylpyrazine-2-carboxamide (8f): Yield: 76.4%, white powder; m.p. 202–203 °C. – IR (film, KBr): ν = 3325 (NH), 2957 (CH, alkane), 1683 (C=C, aromatic) 1530 (C=O, amide), 1333 and 1160 (S=O=S) cm^{-1}. – ^1H NMR (500 MHz, DMSO-d_6): δ = 9.02 (d, J = 1.5 Hz, 1H), 8.93 (t, J = 6.0 Hz, 1H), 8.59 (d, J = 1.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 6.38 (d, J = 7.0 Hz, 1H), 3.77–3.70 (m, 1H), 3.58 (q, J = 7.5 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H), 2.57 (s, 3H), 1.75–1.68 (m, 2H), 1.58–1.52 (m, 2H), 1.49–1.42 (m, 2H), 1.29–1.23 (m, 2H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.99, 156.79, 150.82, 145.03, 142.79, 142.35, 142.03, 138.2, 129.13, 127.23, 51.00, 40.00, 34.7, 32.29, 23.05, 21.28. – MS ((+)-ESI): m/z (%) = 431.9 (60) $[M+H]^+$. – MS ((–)-ESI): m/z (%) = 430.0 (100) $[M–H]^-$.

4.10.7 *N*-(4-{*N*-[(2-Hydroxy-4-nitrophenyl)carbamoyl]sulfamoyl} phenethyl)-5-methylpyrazine-2-carboxamide (8g): Yield: 76.9%, white powder; m.p. 196–198 °C. – IR (film, KBr): ν = 3399 (OH), 3234 (NH), 1655 (C=C, aromatic, 1538 (C=O, amide), 1425 (NO_2), 1327 and 1185 (O=S=O), 1153 (C–N) cm^{-1}. – ^1H NMR (500 MHz, DMSO-d_6): δ = 11.24 (s, 2H), 9.0 (d, J = 1.5 Hz, 1H), 8.93 (t, J = 6.0 Hz), 8.77 (s, 1H), 8.57 (d, J = 0.5 Hz, 1H), 8.08 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.70 (dd, J = 2.5, 9.0 Hz, 1H), 7.62 (d, J = 2.5 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 3.57 (q, J = 7.0 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H), 2.56 (s, 3H). – ^{13}C NMR

(125 MHz, DMSO-d_6): δ = 162.99, 156.82, 145.81, 145.51, 143.51, 142.80, 142.77, 142.40, 142.34, 142.03, 135.51, 129.05, 125.66, 118.26, 111.14, 108.62, 40.00, 34.75, 21.26. – MS ((+)-ESI): *m/z* (%) = 501.0 (100) $[M+H]^+$. – MS ((–)-ESI): *m/z* (%) = 498.8 (20) $[M-H]^-$.

4.10.8 *N*-{4-[*N*-(Benzylcarbamoyl)sulfamoyl]phenethyl}-5-methylpyrazine-2-carboxamide (8h): Yield: 84.2%, white powder; m.p. 199–200 °C. – IR (film, KBr): ν = 3339 (NH), 1650 (C=C, aromatic), 1533 (C=O, amide), 1336 and 1163 (O=S=O) cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.02 (d, *J* = 1.0 Hz, 1H), 8.94 (t, *J* = 6.0 Hz, 1H), 8.59 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 7.0 Hz, 2H), 7.19 (t, *J* = 7.0 Hz, 1H), 7.13 (d, *J* = 7.0 Hz, 2H), 6.97 (t, *J* = 6.0 Hz, 1H), 4.15 (d, *J* = 6.0 Hz, 2H), 3.59 (q, *J* = 6.5 Hz, 2H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.57 (s, 3H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.10, 156.88, 151.63, 145.14, 142.86, 142.44, 142.07, 139.15, 138.18, 129.21, 128.25, 127.29, 127.00, 126.85, 42.74, 40.00, 34.77, 21.33. – MS ((–)-ESI)): *m/z* (%) = 451.9 (100) $[M-H]^-$. – MS ((+)-ESI): *m/z* (%) = 453.8 (60) $[M+H]^+$.

Suppoting information

Copies of the spectra are given as supplementary material available online (https://doi.org/10.1515/znb-2020-0134).

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