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Stereochemistry matters: Inhibition of carbonic anhydrase II by amino acid derived sulfamates depends on their absolute configuration

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ABSTRACT

Aminoalcohols were converted into the corresponding enantiomeric phenylsulfonamide sulfamates. These compounds proved to be inhibitors of carbonic anhydrase II. Interestingly, a sulfamate derived from (*S*)-tryptophan was no inhibitor at all while its (*R*) configurated enantiomer was an excellent inhibitor of carbonic anhydrase II (CA II). A rationale can be deduced from molecular modeling studies. The sulfamates derived from (*R*) or (*S*) proline held very low inhibition constants for this enzyme as $K_i = 0.77$ μM and 0.70 μM, respectively.

1. Introduction

The enzyme carbonic anhydrase II (CA II) has recently become the focus of increasing scientific interest [1–11] because inhibitors of this enzyme have been shown to be synergistic in the treatment of glioblastoma, which is otherwise very difficult to treat [12]. Spacered aryl-substituted type **A** sulfonamides (Fig. 1) have been shown [13] to be effective inhibitors of CA II. CA II has been detected not only in glioblastoma but also in astrocytoma, oligodendroglioma and medulloblastoma [14,15]. The presence of CA II has also been documented in oligoastrocytoma [16]. Glioblastoma is considered to be the most common and lethal type of brain tumor, with an average survival time of about 15 months after diagnosis [17,18].

In glioblastoma, there is a correlation between malignancy and CA II expression [15,16]. A high level of expression usually results in a shorter remaining lifespan. Therefore, it was of primary interest to synthesize first-in-class type **B** compounds and determine their CA II inhibitory properties.

2. Results and discussion

The synthesis of model compound **1b** can be carried out in a number of ways and, on the basis of preliminary tests, we decided to use the very simple synthesis shown in Scheme 1, which not only promised high yields but also provided sufficient degrees of freedom to make in future as many modifications as possible [19]. Analogue syntheses were described very early in the scientific literature and proved to be very robust and reliable.

The reaction of benzenesulfonyl chloride with ethanolamine afforded the sulfonamide **1a**, known from the literature [20–22], in 95 % yield, whose reaction with sulfamoyl chloride afforded the model compound **1b** in 82 % isolated yield.

Compound **1b** proved to be an inhibitor of CA II in preliminary tests (vide infra; concentration of the inhibitor: 10 μM); accompanying molecular modeling calculations suggested that substituents in the α-position should have an influence on the extent of inhibition. The use of readily available amino alcohols derived from α-aminocarboxylic acids would also allow conclusions to be drawn about the possible influence of the absolute configuration of the final products obtained.

The reaction of benzenesulfonyl chloride with the enantiomerically pure amino alcohols (both enantiomers of alaninol, leucinol, prolinol, valinol, phenylalaninol, methioninol, tryptophanol and (*S*, *S*)-isoleucinol) gave the products **2a** – **16a**, whose reaction with sulfamoyl chloride afforded the final products **2b**–**16b**.

In their ^{1}H NMR spectra, the aminoalkylbenzenesulfonamides **2a**-**16a** are characterized by the signal for NH at $\delta = 7.3$–7.6 ppm and that for OH at $\delta = 4.4$–4.8 ppm. In the ^{13}C NMR spectra the CH_2–OH group is found in the range $\delta = 60$–65 ppm, as expected. In the ATR-IR spectra the *C*–N valence vibration is found at $\nu = 1306$–1331 cm^{-1}, the SO_2 valence vibration between $\nu = 1151$–1165 cm^{-1} and the *C*–O valence vibration at about $\nu = 1050$ cm^{-1}. As expected, the UV-VIS-Spectra show the max absorption for the benzenesulfonyl residue at $\lambda = 221$ nm.

Biological testing of the compounds was performed in 96-well microtiter plates and yielded the inhibition data summarized in Table 1; Fig. 2 depicts the inhibition percentages. Acetazolamide (**AAZ**) was included as a positive control [23–26].

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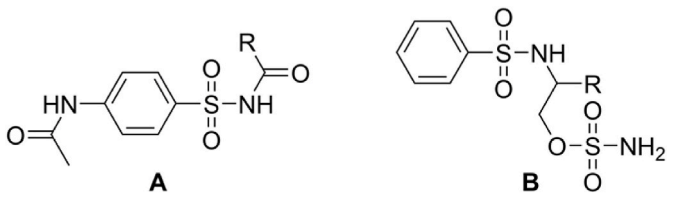


Fig. 1. Structures known CA II inhibitors of type **A**, and of presumptive inhibitors type **B**.

For the enantiomeric sulfamates derived from Ala, Leu, Phe, Pro and Val, approximately equal inhibition-% were determined; at a concentration of 10 μM, inhibition-% between 50 and 98 % was achieved; the product **12b** derived from (*S*, *S*)-isoleucine did not prove to be a very good inhibitor at all.

Interestingly, the product **16b** derived from (*S*)-Trp did not show any inhibitory activity, whereas the product **15b** derived from (*R*)-Trp proved to be one of the most potent inhibitors and 97.9 % inhibition was achieved. In comparison, 99.3 % inhibition was measured for the standard **AAZ** at the same concentration.

Extra measurements were performed to determine their respective inhibition constants K_i. Representative Dixon plots for compounds **6b** and **7b** are depicted in Fig. 3. For **15b** (derived from (*R*)-Trp) a Dixon and a Cornish-Bowden plot are depicted in Fig. 4.

For these compounds K_i values as low as 0.77 and 0.70 μM were observed, respectively.

Molecular modeling calculations were carried out to gain a better understanding. As exemplified for **6**–**9** (Fig. 5; high resolution picture can be found in the supplementary materials file) no significant differences in their respective mode of binding were observed for these compounds.

This result is in excellent agreement with the results from the bioassays. As far as compounds **15b** and **16b** are concerned, it was found that the amino group of the sulfamate of compounds **15 b**/**16b** binds to the Zn^{2+}, with **16b** (Fig. 6) forming an additional bond with the oxygen. Another bond occurs with Thr199 of the enzyme.

In **15b** (see c), a sidechain donor interaction is expected from the amino group of the BSC residue to Thr200, with Thr200 thereby acting as both an acceptor and a sidechain donor, forming a bond with an oxygen of the sulfamate residue. In addition, an aromatic H interaction with Phe131 and the aromatic indole ring system is possible, which is not expected for **16b**. From the measured inhibition percentage, it could be concluded that the interactions of **16b** with CA II is possibly too weak and its binding in the active site is not sufficiently stabilized so that no enzyme inhibitory activity is detected, whereas in the (*R*) configuration the additional aromatic H interactions and the side chain donor/acceptor interactions ensure good binding in the enzyme's pocket so that high inhibition percentages was measured.

Table 1
Results from the inhibition assays for CA II (concentration of inhibitor 10 μM); experiments were performed in triplicate with each 3 replicas. Acetazolamide (**AAZ**) was used as a positive control. Compounds **1a** – **16a** showed no inhibition at all.

Compound	[%] inhibition	compound	[%] inhibition
AAZ	99.3 ± 0.1	**1b**	64.8 ± 0.4
2b	85.3 ± 0.2	**3b**	69.4 ± 1.7
4b	89.1 ± 0.6	**5b**	74.5 ± 0.3
6b	98.3 ± 0.1	**7b**	97.5 ± 0.2
8b	50.9 ± 1.5	**9b**	72.3 ± 0.5
10b	81.2 ± 2.2	**11b**	69.6 ± 0.8
12b	69.1 ± 1.0	**13b**	<5
14b	<5	**15b**	97.9 ± 0.2
16b	<5		

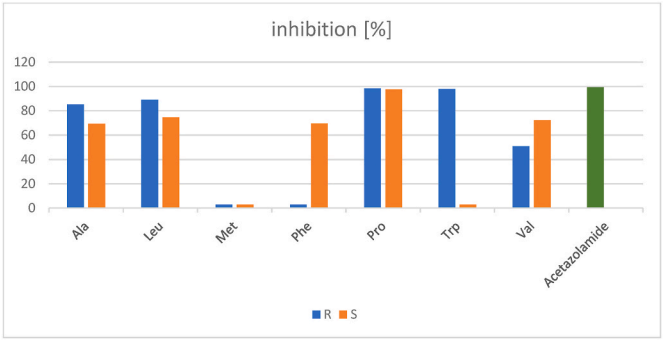
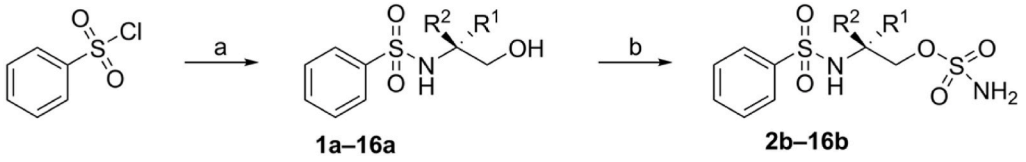


Fig. 2. Inhibition of CA II by amino acid derived sulfamates; acetazolamide was used as a positive control.

3. Conclusion

As a result of this first series of compounds, it has been shown that apparently amino acid derived (*R*)-configured compounds are better inhibitors of CA II than their (*S*)-configured enantiomers. It was also shown that the presence of relatively large, bulky residue in α-position can induce higher inhibitory activity, which can be explained by additional stabilizing interactions in the active site of the enzyme. These compounds therefore proved suitable for further derivatization to produce even better inhibitors. The absolute configuration of tryptophan derivatives, as exemplified by compounds **15b** and **16b**, significantly



1 $R^1 = R^2 = H$
2 $R^1 = CH_3$, $R^2 = H$ (from (*R*)-Ala)
3 $R^1 = H$, $R^2 = CH_3$ (from (*S*)-Ala)
4 $R^1 = CH_2\text{-}CH(CH_3)_2$, $R^2 = H$ (from (*R*)-Leu)
5 $R^1 = H$, $R^2 = \text{-}CH_2\text{-}CH(CH_3)_2$ (from (*S*)-Leu)
6 $R^1 = CH_2$-pyrrolidin-2-yl, $R^2 = H$ (from (*R*)-Pro)
7 $R^1 = H$, $R^2 = CH_2$-pyrrolidin-2-yl (from (*S*)-Pro)
8 $R^1 = CH(CH_3)_2$, $R^2 = H$ (from (*R*)-Val)
9 $R^1 = H$, $R^2 = CH(CH_3)_2$ (from (*S*)-Val)
10 $R^1 = CH_2$-Phe, $R^2 = H$ (from (*R*)-Phe)
11 $R^1 = H$, $R^2 = CH_2$-Phe (from (*S*)-Phe)
12 $R^1 = CH(CH_3)\text{-}CH_2\text{-}CH_3$ (from (*S*)-Isoleu), R = H
13 $R^1 = CH_2\text{-}CH_2\text{-}S\text{-}CH_3$, $R^2 = H$ (from (*R*)-Met)
14 $R^1 = H$, $R^2 = CH_2\text{-}CH_2\text{-}S\text{-}CH_3$ (from (*S*)-Met)
15 $R^1 = CH_2$-(1H-indol-3-yl), $R^2 = H$ (from (*R*)-Trp)
16 $R^1 = H$, $R^2 = CH_2$-(1H-indol-3-yl) from (*S*)-Trp)

Scheme 1. Reactions and conditions: a) DCM, NEt_3, 20 °C 3–24 h; b) DCM, NEt_3, sulfamoyl chloride, 0 °C → 20 °C, 3–24 h.

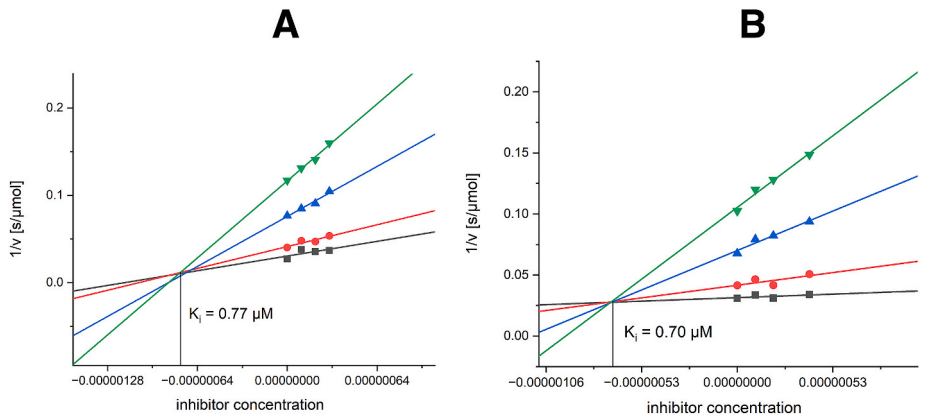


Fig. 3. Dixon plots for compounds **6b** (A, (*R*)-Pro derived, concentration of inhibitor: 0.1, 0.2, 0.3 µM) and **7b** (B, (*S*)-Pro-derived, concentration of the inhibitor: 0.1, 0.2, 0.4 µM).

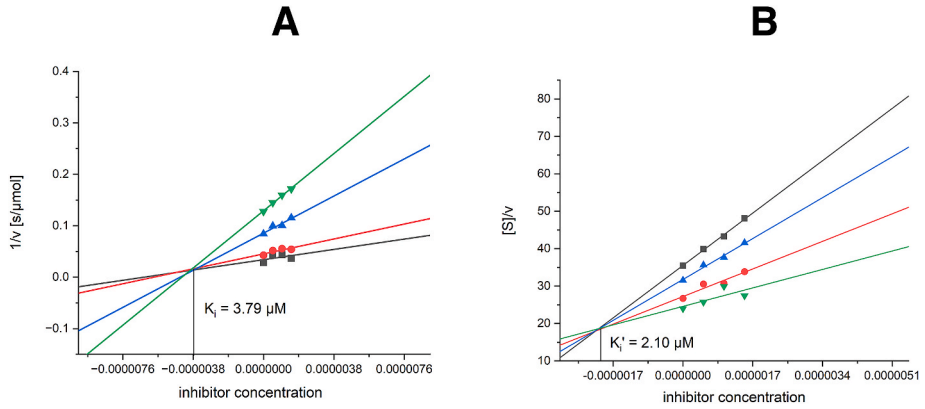


Fig. 4. Dixon (**A**) and Cornish-Bowden plot (**B**) for (*R*)-Trp derived compound **15b** (concentration of the inhibitor: 0.5, 1, 1.5 µM).

influences their interactions with CA II. Molecular modeling studies shed light on the binding modes of these enantiomers with CA II. Compound **15b** likely forms strong interactions within the active site, such as aromatic hydrogen interactions and side chain donor/acceptor interactions, contributing to its potent inhibitory activity. In contrast, compound **16b** exhibits significantly weaker interactions, which are obviously insufficient to stabilize the binding ofvthe molecule to the enzyme. The active site of the CA II enzyme likely has stereochemical preferences for certain ligands. Compound **15b**, with its specific spatial arrangement and functional groups, fits snugly into the active site, allowing for optimal binding interactions. This facilitates effective inhibition of the enzyme. Conversely, compound **16b**, holding a different absolute configuration, fails to achieve effective binding orientations within the active site, thus resulting in the absence of inhibitory activity. In summary, the stereochemistry of tryptophan derivatives dictates their interactions with CA II, impacting their inhibitory activity. Compound **15b**, with its (*R*)-configuration, demonstrated potent inhibition due to favorable interactions and high binding affinity, while compound **16b**, holding a (*S*)-configuration, exhibits weaker interactions and lack of inhibitory activity, underscoring the importance of absolute configuration in enzyme inhibition.

4. Experimental

4.1. General

Equipment and conditions of the assay were previously described [23–26]. Sulfamoyl chloride (SC), benzenesulfonyl chloride (BSC) and both (*R*)- and (*S*)- amino-alcohols (enantiomerically pure) were obtained from Sigma-Aldrich GmbH (Taufkirchen, Germany) and used as received.

4.2. Syntheses

4.2.1. Synthesis of the sulfonamides (General Procedure A, GPA) *1a–16a*

To a solution containing the corresponding amino-alcohol (1.5 equiv.) in dry dichloromethane (DCM, 12 mL), dry triethylamine (2 equiv., TEA) and BSC (1 equiv.) were added at 22 °C. The reaction mixture was stirred at 22 °C for 3 h. The volatiles were removed under diminished pressure, and the residue was subjected to column chromatography (SiO_2) to yield **1a–16a**.

4.2.2. Synthesis of the sulfamates (General procedure B, GPB) *1b–16b*

To a solution of **1a–16a** (1 equiv.) in dry DCM (10 mL), TEA (4 equiv.) was added, followed by the slow addition of SC (4 equivalents). The reaction mixture was stirred at 22 °C for 3–24 h. The volatiles were removed under reduced pressure, and the residue was subjected to column chromatography (SiO_2) to afford **1b–16b**.

4.3. CA II assay

Carbonic anhydrase II (bCAII, ≥3000 W-A units/mg from bovine erythrocytes) as well as 4-nitrophenyl acetate (4-NA) were purchased from Sigma-Aldrich GmbH (Taufkirchen, Germany).

BMG Labtech Spectrostar Omega (BMG Labtech, Ortenberg, Germany) working in the slow kinetics mode (measuring the absorbance at a wavelength of λ = 415 nm with center scanning) was used for the enzymatic studies. In short: A mixture of 4-NA solution (125 µL, 6 mM in

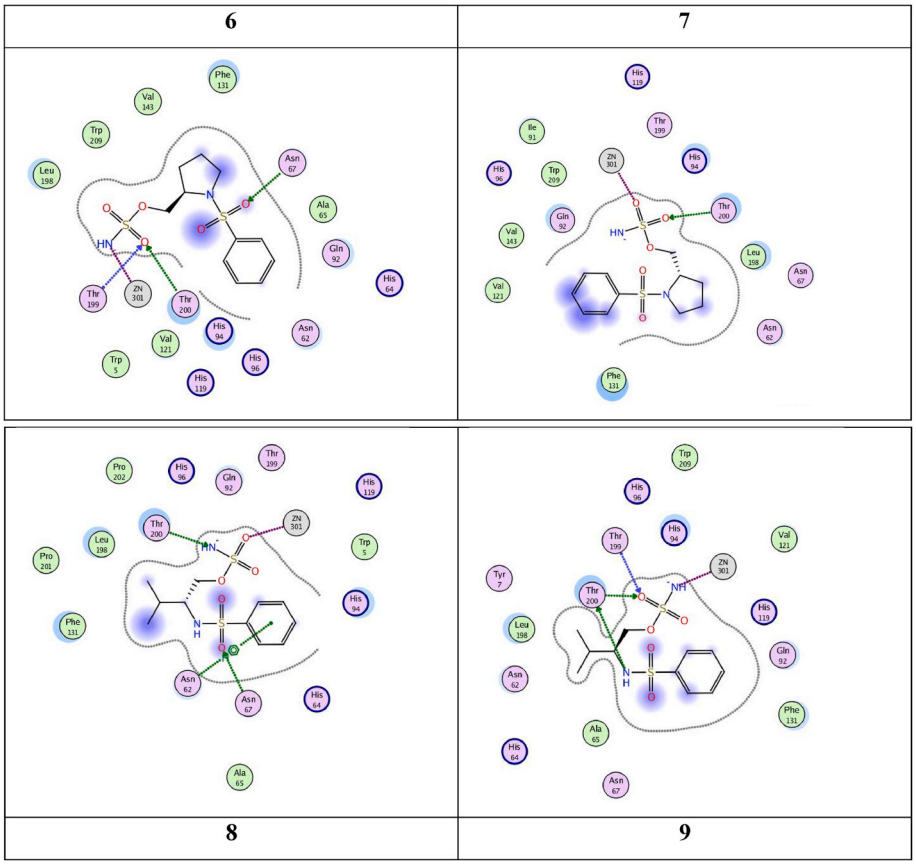


Fig. 5. 2D representation of binding and location of compounds **6**–**9** in the active site of CA II.

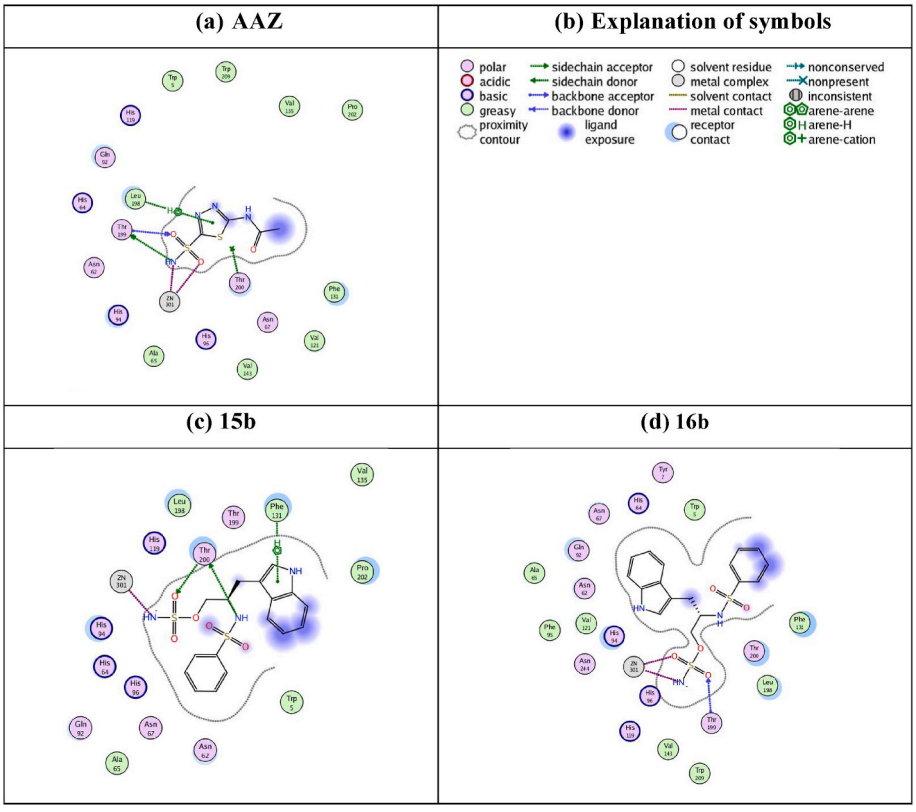


Fig. 6. 2D representation of selected interactions of compounds reference compound acetazolamide (a), and compounds **15b** (c) and **16b** (d).

50 mM Tris-HCl buffer, pH 8), enzyme solution (25 μL, 0.3 mg/mL) and compounds solutions (25 μL, 3 different concentrations and water as a blank) was incubated at 37 °C for 20 min. The substrate (25 μL, [4-NA] = 0.75 mM, 0.50 mM, 0.25 mM, 0.15 mM) was added to start the enzymatic reaction. The absorbance data was recorded under a controlled temperature of 37 °C for 30 min at 1 min intervals at λ = 415 nm. The relative inhibition was determined as the quotient of the slopes (compound divided by blank) of the linear ranges.

4.4. Individual syntheses

4.4.1. N-(2-Hydroxyethyl)benzene sulfonamide (**1a**)

Following GPA from BSC (500 mg, 2.83 mmol), TEA (0.78 mL, 5.66 mmol) and 2-amino-ethanol (259 mg, 4.25 mmol) **1a** (542 mg, 95 %) was obtained as a white, waxy solid; R_f = 0.07 (SiO_2, hexanes/ethyl acetate, 6:4); m. p. = 78–79 °C (lit. [19]: 79–80 °C); UV–Vis (MeOH): λ_{max} (log ε) = 220 nm (3.95); IR (ATR): ν = 3500*br*, 3274*br*, 2939*w*, 2883*w*, 1479*w*, 1447 *m*, 1309*s*, 1093 *m*, 1055 *m*, 999*w*, 949 *m*, 881*w*, 804*w*, 753 *m*, 718 *m*, 688 *m*, 582 *m*, 567 *m*, 450*w* cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.82–7.78 (m, 2H, 2-H, 2′-H), 7.66–7.56 (m, 4H, 3-H, 3′-H, 4-H, NH), 4.67 (t, J = 5.4 Hz, 1H, OH), 3.40–3.35 (m, 2H, 6-H), 2.79 (t, J = 6.4 Hz, 2H, 5-H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 140.6 (C-1), 132.3 (C-4), 129.2 (C-3), 126.4 (C-2), 59.9 (C-6), 45.1 (C-5) ppm; MS (ESI, MeOH): m/z = 200.0 (60 %, $[M - H]^-$); analyss calcd. for $C_8H_{11}NSO_3$ (201.24): C 47.75, H 5.51, N 6.96; found: C 47.50, H 5.76, N 6.69.

4.4.2. (R)-N-(1-Hydroxypropane-2-yl)-benzenesulfonamide (**2a**)

Following GPA from (*R*)-alaninol (350 mg, 4.66 mmol), TEA (1 mL, 7.78 mmol) and BSC (650 mg, 3.89 mmol) **2a** (772 mg, 77 %) was obtained as a colorless, viscous oil; R_f = 0.55 (SiO_2, hexanes/ethyl acetate, 3:7); $[\alpha]_D^{20}$ = +18.94° (*c* 0.200, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.03); IR (ATR) ν = 3498*w*, 3272*w*, 3067*vw*, 2976*w*, 2938*w*, 2880*w*, 1447 *m*, 1429 *m*, 1307*s*, 1292 *m*, 1232*w*, 1156*vs*, 1088*s*, 1047*s*, 971*s*, 890 *m*, 755*s*, 719*s*, 689*vs*, 639 *m*, 581*vs*, 569*vs*, 479*s*, 427 *m*, 422 *m*, 415 m cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.85–7.79 (m, 2H, 5-H, 9-H), 7.65–7.56 (m, 3H, 6-H, 7-H, 8-H), 7.50 (d, J = 5.0 Hz, 1H, NH), 4.63 (s, 1H, OH), 3.33–3.25 (m, 1H, 2-H), 3.14–3.05 (m, 2H, 1-H), 0.87 (d, J = 6.3 Hz, 3H, 3-H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.9 (C-4), 132.1 (C-7), 129.1 (C-6, C-8), 126.3 (C-5, C-9), 65.0 (C-1), 51.0 (C-2), 17.6 (C-3) ppm; MS (ESI, MeOH): m/z = 238.2 (78 %, $[M+Na]^+$), 254.2 (9 %, $[M+K]^+$), 260.2 (16 %, $[M+2Na–H]^+$); analysis calcd. for $C_9H_{13}NO_3S$ (215.27): C 50.22, H 6.09, N 6.51; found: C 50.01, H 6.31, N 6.37.

4.4.3. (S)–N-(1-Hydroxypropane-2-yl)-benzenesulfonamide (**3a**)

Following GPA from (*S*)-alaninol (260 mg, 3.45 mmol), TEA (0.9 mL, 5.76 mmol) and BSC (500 mg, 2.88 mmol) **3a** (520 mg, 70 %) was obtained as a colorless, viscous oil [27,28]; R_f = 0.56 (SiO_2, hexanes/ethyl acetate, 3:7); $[\alpha]_D^{20}$ = −19.65° (*c* 0.276, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.02); IR (ATR) ν = 3495*w*, 3272 *m*, 3068*vw*, 2976*w*, 2938*w*, 2880*w*, 1636*vw*, 1586*vw*, 1447 *m*, 1307*s*, 1292 *m*, 1233*w*, 1156*vs*, 1088*s*, 1047*s*, 971*s*, 927*w*, 890 *m*, 755*s*, 719*s*, 688*vs*, 639 *m*, 581*vs*, 569*vs*, 480*s*, 426 *m*, 421 *m*, 413 m cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.85–7.79 (m, 2H, 5-H, 9-H), 7.65–7.55 (m, 3H, 6-H, 7-H, 8-H), 7.50 (d, J = 4.9 Hz, 1H, NH), 4.66 (t, J = 5.4 Hz, 1H, OH), 3.32–3.25 (m, 1H, 2-H), 3.14–3.06 (m, 2H, 1-H), 0.87 (d, J = 6.4 Hz, 3H, 3-H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.9 (C-4), 132.1 (C-7), 129.1 (C-6, C-8), 126.3 (C-5, C-9), 65.0 (C-1), 50.9 (C-2), 17.5 (C-3) ppm; MS (ESI, MeOH): m/z = 238.2 (78 %, $[M+Na]^+$), 254.2 (9 %, $[M+K]^+$), 260.2 (17 %, $[M+2Na–H]^+$); analysis calcd. for $C_9H_{13}NO_3S$ (215.27): C 50.22, H 6.09, N 6.51; found: C 49.97, H 6.23, N 6.42.

4.4.4. (R)-N-(1-Hydroxy-4-methylpentane-2-yl)-benzenesulfonamide (**4a**)

Following GPA from (*R*)-leucinol (408 mg, 3.48 mmol), TEA (0.78 mL, 5.66 mmol) and BSC (500 mg, 2.83 mmol) **4a** (572 mg, 64 %) was obtained as a white solid; R_f = 0.72 (SiO_2, hexanes/ethyl acetate, 3:7); m. p. = 104.5–106.5 °C; $[\alpha]_D^{20}$ = +33.92° (*c* 0.176, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.04); IR (ATR) ν = 3508*w*, 3172*w*, 2957 *m*, 2932*w*, 2870*w*, 1467*w*, 1448 *m*, 1433 *m*, 1387*w*, 1367*w*, 1341*w*, 1309*s*, 1289*w*, 1203*vw*, 1165*vs*, 1125*w*, 1091*s*, 1073*w*, 1062*w*, 1032*vs*, 1020 *m*, 999*w*, 975*w*, 962 *m*, 941 *m*, 922*w*, 888*w*, 827*w*, 806*w*, 758*s*, 721*s*, 690*s*, 672*w*, 599*s*, 580*s*, 558*vs*, 497 *m*, 473 *m*, 461 *m*, 415 m cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.84–7.76 (m, 2H, 8-H, 12-H), 7.67–7.53 (m, 3H, 9-H, 10-H, 11-H), 7.46 (d, J = 7.3 Hz, 1H, NH), 4.59 (t, J = 5.3 Hz, 1H, OH), 3.29–3.17 (m, 1H, 1-H_a), 3.13–2.96 (m, 2H, 1-H_b, 2-H), 1.49–1.37 (m, 1H, 4-H), 1.34–1.24 (m, 1H, 3-H_a), 1.34–1.24 (m, 1H, 3-H_b), 0.73 (d, J = 6.6 Hz, 3H, 5-H), 0.54 (d, J = 6.5 Hz, 3H, 6-H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 142.0 (C-7), 132.1 (C-10), 129.0 (C-9, C-11), 126.3 (C-8, C-12), 64.1 (C-1), 53.2 (C-2), 40.5 (C-3), 23.6 (C-4), 23.2 (C-5), 21.4 (C-6) ppm; MS (ESI, MeOH): m/z = 280.3 (100 %, $[M+Na]^+$); analysis calcd. for $C_{12}H_{19}NO_3S$ (257.35): C 56.01, H 7.44, N 5.44; found: C 55.81, H 7.63, N 5.20.

4.4.5. (S)–N-(1-Hydroxy-4-methylpentane-2-yl)-benzenesulfonamide (**5a**)

Following GPA from (*S*)-leucinol (406 mg, 3.46 mmol), TEA (0.78 mL, 5.66 mmol) and BSC (500 mg, 2.83 mmol) **5a** (420 mg, 47 %) was obtained as a white solid [28]; R_f = 0.71 (SiO_2, hexanes/ethyl acetate, 3:7); m. p. = 104.5–106.5 °C; $[\alpha]_D^{20}$ = −35.19° (*c* 0.118, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.04); IR (ATR) ν = 3506*w*, 3171*w*, 3065*vw*, 2956*w*, 2932*w*, 2869*w*, 1467*w*, 1448*w*, 1433*w*, 1387*w*, 1367*w*, 1341*vw*, 1309 *m*, 1289*w*, 1202*vw*, 1165*vs*, 1125*w*, 1091*s*, 1073*w*, 1062*w*, 1032*vs*, 1019 *m*, 998*w*, 974*w*, 962 *m*, 941 *m*, 922*w*, 888*w*, 827*w*, 806*w*, 758*s*, 721*s*, 690*s*, 672*w*, 599*s*, 580*s*, 558*vs*, 497 *m*, 473 *m*, 460 *m*, 429*w*, 416 m cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.86–7.75 (m, 2H, 8-H, 12-H), 7.66–7.53 (m, 3H, 9-H, 10-H, 11-H), 7.46 (*d*, J = 7,3 Hz, 1H, NH), 4.59 (t, J = 5.4 Hz, 1H, OH), 3.28–3.20 (m, 1H, 1-H_a), 3.12–2.98 (m, 2H, 1-H_b, 2-H), 1.51–1.36 (m, 1H, 4-H), 1.35–1.22 (m, 1H, 3-H_a), 1.15–1.02 (m, 1H, 3-H_b), 0.73 (d, J = 6.6 Hz, 3H, 5-H), 0.54 (d, J = 6.5 Hz, 3H, 6-H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 142.0 (C-7), 132.1 (C-10), 129.0 (C-9, C-11), 126.3 (C-8, C-12), 64.0 (C-1), 53.0 (C-2), 40.4 (C-3), 23.6 (C-4), 23.2 (C-5), 21.4 (C-6) ppm; MS (ESI, MeOH): m/z = 279.9 (100 %, $[M+Na]^+$); analysis calcd. for $C_{12}H_{19}NO_3S$ (257.35): C 56.01, H 7.44, N 5.44; found: C 55.73, H 7.68, N 5.21.

4.4.6. (R)-[(1-Phenylsulfonyl)pyrrolidin-2-yl]-methanol (**6a**)

Following GPA from (*R*)-prolinol (349 mg, 3.45 mmol), TEA (0.78 mL, 5.66 mmol) and BSC (500 mg, 2.83 mmol) **6a** (511 mg, 61 %) was obtained as a colorless, viscous oil; R_f = 0.62 (SiO_2, hexanes/ethyl acetate, 3:7); $[\alpha]_D^{20}$ = +83.85° (*c* 0.309, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 222 nm (4.02); IR (ATR) ν = 3511*w*, 3065*vw*, 2953*w*, 2877*w*, 1585*vw*, 1477*w*, 1446 *m*, 1331*s*, 1310 *m*, 1291*w*, 1251*w*, 1198 *m*, 1155*vs*, 1091*s*, 1073 *m*, 1043*s*, 1014 *m*, 989 *m*, 928*w*, 900*w*, 875*w*, 820*w*, 757 *m*, 736 *m*, 718*s*, 692*s*, 613*s*, 591*vs*, 571*vs*, 535 *m*, 439*w*, 406*w* cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.86–7.79 (m, 2H, 7-H, 11-H), 7.75–7.59 (m, 3H, 8-H, 9-H, 10-H), 4.82 (t, J = 5.6 Hz, 1H, OH), 3.62–3.48 (m, 2H, 1-H), 3.40–3.23 (m, 2H, 5-H), 3.12–2.98 (m, 1H, 2-H), 1.87–1.65 (m, 2H, 3-H), 1.49–1.23 (m, 2H, 4-H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 136.8 (C-6), 133.0 (C-9), 129.4 (C-8, C-10), 127.2 (C-7, C-11), 63.8 (C-1), 61.0 (C-2), 49.0 (C-5), 27.6 (C-3), 23.3 (C-4) ppm; MS (ESI, MeOH): m/z = 264.2 (100 %, $[M+Na]^+$), 504.5 (35 %, $[2\ M\ +\ Na]^+$); analysis calcd. for $C_{11}H_{15}NO_3S$ (241.31): C 54.75, H 6.27, N 5.80; found: C 54.55, H 6.63, N 5.61.

4.4.7. (S)-((1-Phenylsulfonyl)pyrrolidin-2-yl)-methanol (**7a**)

Following GPA from (*S*)-prolinol (351 mg, 3.47 mmol), TEA (0.78 mL, 5.66 mmol) and BSC (500 mg, 2.83 mmol) **7a** (393 mg, 47 %) was obtained as a colorless, viscous oil [29–31]; R_f = 0.62 (SiO_2, hexanes/ethyl acetate, 3:7); $[\alpha]_D^{20}$ = −84.06° (*c* 0.248, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 222 nm (4.03); IR (ATR) ν = 3510*w*, 3064*vw*,

2953*w*, 2877*w*, 1638*vw*, 1585*vw*, 1477*w*, 1446 *m*, 1331*s*, 1310 *m*, 1291*w*, 1251*w*, 1198 *m*, 1155*vs*, 1091*s*, 1073 *m*, 1043*s*, 1014 *m*, 989 *m*, 928*w*, 900*w*, 875*w*, 820*w*, 757 *m*, 736 *m*, 718*s*, 691*s*, 613*s*, 591*vs*, 571*vs*, 535 *m*, 480 *m*, 440 *m*, 419*w*, 404*w* cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.88–7.78 (m, 2H, 7-H, 11-H), 7.77–7.56 (m, 3H, 8-H, 9-H, 10-H), 4.82 (t, J = 5.6 Hz, 1H, OH), 3.62–3.48 (m, 2H, 1-H), 3.39–3.23 (m, 2H, 5-H), 3.11–2.98 (m, 1H, 2-H), 1.83–1.68 (m, 2H, 3-H), 1.49–1.30 (m, 2H, 4-H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 136.8 (C-6), 133.0 (C-9), 129.4 (C-8, C-10), 127.2 (C-7, C-11), 63.7 (C-1), 61.0 (C-2), 49.0 (C-5), 27.6 (C-3), 23.3 (C-4) ppm; MS (ESI, MeOH): m/z = 264.2 (100 %, $[M+Na]^+$), 504.5 (8 %, $[2\ M\ +\ Na]^+$); analysis calcd. for $C_{11}H_{15}NO_3S$ (241.31): C 54.75, H 6.27, N 5.80; found: C 54.46, H 6.57, N 5.63.

4.4.8. (*R*)-*N*-(1-Hydroxy-3-methylbutane-2-yl)benzenesulfonamide (**8a**)

Following GPA from (*R*)-valinol (353 mg, 3.42 mmol), TEA (0.78 mL, 5.66 mmol) and BSC (500 mg, 2.83 mmol) **8a** (560 mg, 67 %) was obtained as a white solid; R_f = 0.71 (SiO_2, hexanes/ethyl acetate, 3:7); m. p. = 76.0–78.0 °C; $[\alpha]_D^{20}$ = +2.79° (*c* 0.258, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.09); IR (ATR) ν = 3499*w*, 3284*w*, 3067*vw*, 2963*w*, 2877*w*, 2741*vw*, 1724*vw*, 1639*vw*, 1578*vw*, 1465*w*, 1447 *m*, 1391*w*, 1370*w*, 1319*s*, 1310*s*, 1292 *m*, 1156*vs*, 1093*s*, 1072*s*, 1039*s*, 1000 *m*, 988 *m*, 965 *m*, 951 *m*, 925*w*, 908 *m*, 861*w*, 815*w*, 755*s*, 720*s*, 689*s*, 654 *m*, 595*vs*, 563*vs*, 523*s*, 469 *m*, 460 *m*, 440 *m*, 419 m cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.91–7.74 (m, 2H, 7-H, 11-H), 7.65–7.50 (m, 3H, 8-H, 9-H, 10-H), 7.32 (d, J = 8.4 Hz, 1H, NH), 4.47 (t, J = 5.4 Hz, 1H, OH), 3.26–3.07 (m, 2H, 1-H), 3.02–2.87 (m, 1H, 2-H), 1.93–1.76 (m, 1H, 3-H), 0.72 (*dd*, J = 9.8, 6.9 Hz, 6H, 4-H, 5-H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 142.1 (C-6), 132.0 (C-9), 128.9 (C-8, C-10), 126.4 (C-7, C-11), 61.0 (C-1), 60.0 (C-2), 27.5 (C-3), 19.3 (C-4), 16.9 (C-5) ppm; MS (ESI, MeOH): m/z = 266.3 (100 %, $[M+Na]^+$), 288.3 (9 %, $[M+2Na–H]^+$); analysis calcd. for $C_{11}H_{17}NO_3S$ (243.3): C 54.30, H 7.04, N 5.76; found: C 54.03, H 7.32, N 5.50.

4.4.9. (*S*)–*N*-(1-Hydroxy-3-methylbutane-2-yl)benzenesulfonamide (**9a**)

Following GPA from (*S*)-valinol (361 mg, 3.49 mmol), TEA (0.78 mL, 5.66 mmol) and BSC (500 mg, 2.83 mmol) **9a** (420 mg, 47 %) was obtained as a white solid [28]; R_f = 0.68 (SiO_2, hexanes/ethyl acetate, 3:7); m. p. = 76.0–78.0 °C; $[\alpha]_D^{20}$ = −2.95° (*c* 0.151, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.08); IR (ATR) ν = 3465 *m*, 3199*w*, 3067*vw*, 2960*w*, 2926*w*, 2903*w*, 2880*w*, 1474 *m*, 1466 *m*, 1448*w*, 1389*w*, 1370*w*, 1357*w*, 1315 *m*, 1304*s*, 1288 *m*, 1220*w*, 1180*w*, 1165*s*, 1141*w*, 1118*w*, 1097*s*, 1074 *m*, 1035*vs*, 1007*w*, 998*w*, 955*vw*, 910 *m*, 847*w*, 773*w*, 754*s*, 720*s*, 687*s*, 673*w*, 600*vs*, 570*vs*, 538 *m*, 518*s*, 483 *m*, 463 *m*, 428*w*, 412*w* cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 7.83–7.79 (m, 2H, 7-H, 11-H), 7.63–7.53 (m, 3H, 8-H, 9-H, 10-H), 7.32 (d, J = 8.5 Hz, 1H, NH), 4.48 (s, 1H, OH), 3.22–3.10 (m, 2H, 1-H), 2.98–2.90 (m, 1H, 2-H), 1.89–1.77 (m, 1H, 3-H), 0.72 (*dd*, J = 12.3, 6.9 Hz, 6H, 4-H, 5-H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 142.1 (C-6), 132.0 (C-9), 128.9 (C-8, C-10), 126.4 (C-7, C-11), 61.0 (C-1), 60.0 (C-2), 27.5 (C-3), 19.3 (C-4), 16.9 (C-5) ppm; MS (ESI, MeOH): m/z = 266.3 (100 %, $[M+Na]^+$), 288.3 (7 %, $[M+2Na–H]^+$); analysis calcd. for $C_{11}H_{17}NO_3S$ (243.3): C 54.30, H 7.04, N 5.76; found: C 54.11, H 7.27, N 5.48.

4.4.10. (*R*)-*N*-(1-Hydroxy-3-phenylpropane-2-yl)benzenesulfonamide (**10a**)

Following GPA from (*R*)-phenylalaninol (522 mg, 3.46 mmol), TEA (0.78 mL, 5.66 mmol) and BSC (500 mg, 2.83 mmol) **10a** (882 mg, 87 %) was obtained as a white solid; R_f = 0.46 (SiO_2, hexanes/ethyl acetate, 1:1); m. p. = 87.0–89.0 °C; $[\alpha]_D^{20}$ = +51.93° (*c* 0.09, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (3.83); IR (ATR) ν = 3517 *m*, 3296 *m*, 3091*vw*, 3067*vw*, 3055*vw*, 3040*vw*, 3022*vw*, 2940*w*, 2927*w*, 2884*vw*, 1606*vw*, 1585*vw*, 1498*w*, 1491*w*, 1484*w*, 1459*w*, 1449 *m*, 1424 *m*, 1381*w*, 1346*w*, 1323*s*, 1310*s*, 1304*s*, 1270*w*, 1224 *m*, 1200*w*, 1155*vs*, 1096 *m*, 1080*s*, 1067*s*, 1032*s*, 1003 *m*, 980*s*, 925 *m*, 902*w*, 887 *m*, 847 *m*, 818*w*, 755 *m*, 747*vs*, 722*s*, 705*s*, 686*s*, 660*s*, 595*vs*, 567*vs*, 545*vs*, 510*vs*, 448*s*, 431 *m*, 412 m cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 7.67–7.60 (m, 3H, 11-H, 15-H, NH), 7.56–7.51 (m, 1H, 13-H), 7.48–7.41 (m, 2H, 12-H, 14-H), 7.20–7.10 (m, 3H, 6-H, 7-H, 8-H), 7.08–7.02 (m, 2H, 5-H, 9-H), 4.75 (t, J = 5.4 Hz, 1H, OH), 3.32–3.24 (m, 2H, 1-H), 3.23–3.15 (m, 1H, 2-H), 2.82 (*dd*, J = 13.6, 5.8 Hz, 1H, 3-H_a), 2.49–2.42 (m, 1H, 3-H_b) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.7 (C-10), 138.3 (C-4), 131.9 (C-13), 129.1 (C-5, C-9), 128.9 (C-12, C-14), 128.0 (C-6, C-8), 126.1 (C-11, C-15), 126.0 (C-7), 62.7 (C-1), 57.0 (C-2), 37.0 (C-3) ppm; MS (ESI, MeOH): m/z = 314.3 (100 %, $[M+Na]^+$); analysis calcd. for $C_{15}H_{17}NO_3S$ (291.37): C 61.83, H 5.88, N 4.81; found: C 61.64, H 6.02, N 4.61.

4.4.11. (*S*)–*N*-(1-Hydroxy-3-phenylpropane-2-yl)benzenesulfonamide (**11a**)

Following GPA from (*S*)-phenylalaninol (523 mg, 3.46 mmol), TEA (0.78 mL, 5.66 mmol) and BSC (500 mg, 2.83 mmol) **11a** (608 mg, 60 %) was obtained as a white solid; R_f = 0.72 (SiO_2, hexanes/ethyl acetate, 3:7); m. p. = 87.2–89.2 °C (lit. [28]: 64–66 °C; $[\alpha]_D^{20}$ = +49.96° (*c* 0.162, MeOH) (lit. [28]: $[\alpha]_D^{20}$ = +18.7° (*c* 0.005 $CHCl_3$)); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.02); IR (ATR) ν = 3516 *m*, 3296 *m*, 3092*vw*, 3067*vw*, 3055*vw*, 3040*vw*, 3022*vw*, 2939*w*, 2927*w*, 2884*w*, 1606*vw*, 1498*w*, 1491*w*, 1484*w*, 1458*w*, 1449 *m*, 1424 *m*, 1381*w*, 1346*w*, 1323*s*, 1310 *m*, 1304 *m*, 1270*w*, 1224*w*, 1200*w*, 1181*vw*, 1155*vs*, 1096 *m*, 1080*s*, 1067*s*, 1032*s*, 1003*w*, 981*s*, 926 *m*, 902*w*, 887 *m*, 847 *m*, 818*w*, 755 *m*, 747*vs*, 722*s*, 705*s*, 686*s*, 661*s*, 596*vs*, 568*vs*, 545*vs*, 525 *m*, 510*vs*, 495*s*, 448*s*, 425 *m*, 415 m cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 7.66–7.61 (m, 3H, 11-H, 15-H, NH), 7.56–7.51 (m, 1H, 13-H), 7.47–7.42 (m, 2H, 12-H, 14-H), 7.19–7.10 (m, 3H, 6-H, 7-H, 8-H), 7.07–7.03 (m, 2H, 5-H, 9-H), 4.75 (t, J = 5.4 Hz, 1H, OH), 3.30–3.23 (m, 2H, 1-H), 3.21–3.15 (m, 1H, 2-H), 2.82 (*dd*, J = 13.6, 5.8 Hz, 1H, 3-H_a), 2.46 (*dd*, J = 13.6, 7.0 Hz, 1H, 3-H_b) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.7 (C-10), 138.3 (C-4), 131.9 (C-13), 129.1 (C-5, C-9), 128.9 (C-12, C-14), 128.0 (C-6, C-8), 126.1 (C-11, C-15), 126.0 (C-7), 62.7 (C-1), 57.0 (C-2), 37.0 (C-3) ppm; MS (ESI, MeOH): m/z = 314.4 (100 %, $[M+Na]^+$), 336.4 (7 %, $[M+2Na–H]^+$); analysis calcd. for $C_{15}H_{17}NO_3S$ (291.37): C 61.83, H 5.88, N 4.81; found: C 61.50, H 6.03, N 4.62.

4.4.12. *N*-((2*S*,3*S*)-1-Hydroxy-3-methylpentane-2-yl)benzenesulfonamide (**12a**)

Following GPA from (*S*)-isoleucinol (399 mg, 3.40 mmol), TEA (0.78 mL, 5.66 mmol) and BSC (500 mg, 2.83 mmol) **12a** (585 mg, 67 %) was obtained as a colorless, waxy solid [28]; R_f = 0.73 (SiO_2, hexanes/ethyl acetate, 3:7); m. p. = 61–63 °C (lit. [28]: 58–60 °C; $[\alpha]_D^{20}$ = −0.14° (*c* 0.166, MeOH) (lit. [28]: $[\alpha]_D^{20}$ = +25.0° (c 0.006 $CHCl_3$)); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.04); IR (ATR) ν = 3497*w*, 3287 *m*, 3063*vw*, 2963*w*, 2932*w*, 2875*w*, 1723*vw*, 1481*w*, 1463*w*, 1448 *m*, 1430 *m*, 1379*w*, 1321*s*, 1286 *m*, 1246*w*, 1157*vs*, 1093 *m*, 1072*s*, 1027 *m*, 1002 *m*, 993 *m*, 978 *m*, 967 *m*, 941 *m*, 893 *m*, 872*w*, 825*w*, 805*w*, 752*s*, 721*s*, 689*s*, 647 *m*, 585*vs*, 560*vs*, 533*s*, 487 *m*, 463 *m*, 439 *m*, 428 *m*, 420 m cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.85–7.78 (m, 2H, 8-H, 12-H), 7.64–7.52 (m, 3H, 9- H, 10-H, 11-H), 7.34 (d, J = 8.3 Hz, 1H, NH), 4.44 (t, J = 5.0 Hz, 1H, OH), 3.28–3.12 (m, 2H, 1-H), 3.04–2.95 (m, 1H, 2-H), 1.59–1.45 (m, 1H, 3-H), 1.41–1.28 (m, 1H, 4-H), 1.04–0.82 (m, 1H, 4-H), 0.77–0.68 (m, 6H, 5-H, 6-H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 142.1 (C-7), 132.0 (C-10), 128.9 (C-9, C-11), 126.4 (C-8, C-12), 60.6 (C-1), 59.3 (C-2), 35.1 (C-3), 23.8 (C-4), 15.2 (C-6), 11.5 (C-5) ppm; MS (ESI, MeOH): m/z = 280.4 (100 %, $[M+Na]^+$); analysis calcd. for $C_{12}H_{19}NO_3S$ (257.35): C 56.01, H 7.44, N 5.44; found: C 55.76, H 7.73, N 5.08.

4.4.13. (*R*)-*N*-(1-Hydroxy-4-(methylthio)butane-2-yl)benzenesulfonamide (**13a**)

Following GPA from (*R*)-methioninol (414 mg, 3.06 mmol), TEA (0.71 mL, 5.10 mmol) and BSC (450 mg, 2.55 mmol) **13a** (662 mg, 94 %)

was obtained as a colorless, viscous oil; $R_f = 0.61$ (SiO_2, hexanes/ethyl acetate, 3:7); $[\alpha]_D^{20} = +20.73°$ (*c* 0.107, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 222 nm (4.05); IR (ATR) ν = 3490*w*, 3276*w*, 3067*vw*, 2918*w*, 1478*w*, 1447 *m*, 1428 *m*, 1318 *m*, 1308*s,* 1292 *m*, 1152*vs,* 1091*s,* 1072 *m*, 1051 *m*, 1000*w*, 979 *m*, 857*w*, 755 *m*, 719*s,* 689*s,* 671*w*, 647*w*, 582*s,* 559*s,* 427*vw* cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 7.83–7.79 (m, 2H, 7-H, 11-H), 7.64–7.59 (m, 1H, 9- H), 7.59–7.55 (m, 3H, NH, 8-H, 10-H), 4.70 (t, *J* = 5.4 Hz, 1H, OH), 3.32–3.26 (m, 1H, 1- H_a), 3.19–3.12 (m, 2H, 1-H_b, 2-H), 2.28 (*ddd*, *J* = 12.9, 9.2, 5.3 Hz, 1H, 4-H_a), 2.10 (*ddd*, *J* = 12.9, 9.1, 6.6 Hz, 1H, 4-H_b), 1.86 (s*,* 3H, 5-H), 1.74 (*dddd*, *J* = 13.6, 8.9, 6.5, 4.1 Hz, 1H, 3-H_a), 1.43 (*dtd*, *J* = 13.9, 8.6, 5.2 Hz, 1H, 3-H_b) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 141.9 (C-6), 132.2 (C-9), 129.0 (C-8, C-10), 126.3 (C-7, C-11), 63.4 (C-1), 54.2 (C-2), 30.5 (C-3), 29.4 (C-4), 14.3 (C-5) ppm; MS (ESI, MeOH): *m*/z = 297.9 (100 %, $[M+Na]^+$); analysis calcd. for $C_{11}H_{17}NO_3S_2$ (275.38): C, 47.98; H, 6.22; N, 5.09; found: C 47.73, H 6.48, N 5.98.

4.4.14. (S)–N-(1-Hydroxy-4-(methylthio)butane-2-yl)benzenesulfonamide (14a)

Following GPA from (*S*)-methioninol (414 mg, 3.06 mmol), TEA (0.71 mL, 5.10 mmol) and BSC (450 mg, 2.55 mmol) **14a** (635 mg, 91 %) was obtained as a colorless, viscous oil; $R_f = 0.63$ (SiO_2, hexanes/ethyl acetate, 3:7); $[\alpha]_D^{20} = -21.82°$ (*c* 0.113, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 222 nm (3.93); IR (ATR) ν = 3495*w*, 3274*w*, 2918*w*, 1478*w*, 1447 *m*, 1428 *m*, 1318 *m*, 1308*s,* 1292 *m*, 1152*vs,* 1091*s,* 1073 *m*, 1051 *m*, 1000*w*, 978 *m*, 857*w*, 755 *m*, 719*s,* 689*s,* 647*w*, 582*s,* 560*s,* 444*w* cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.83–7.78 (m, 2H, 7-H, 11-H), 7.65–7.54 (m, 4H, NH, 8-H, 9-H, 10-H), 4.70 (t, *J* = 5.2 Hz, 1H, OH), 3.31–3.24 (m, 1H, 1-H_a), 3.21–3.09 (m, 2H, 1-H_b, 2-H), 2.28 (*ddd*, *J* = 12.9, 9.2, 5.3 Hz, 1H, 4-H_a), 2.10 (*ddd*, *J* = 13.0, 9.1, 6.6 Hz, 1H, 4-H_b), 1.87 (s*,* 3H, 5-H), 1.74 (*dddd*, *J* = 13.7, 9.2, 6.6, 4.1 Hz, 1H, 3-H_a), 1.42 (*ddt*, *J* = 13.9, 8.6, 5.3 Hz, 1H, 3-H_b) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.9 (C-6), 132.2 (C-9), 129.1 (C-8, C-10), 126.3 (C-7, C-11), 63.4 (C-1), 54.2 (C-2), 30.5 (C-3), 29.4 (C-4), 14.3 (C-5) ppm; MS (ESI, MeOH): *m*/z = 297.9 (100 %, $[M+Na]^+$); analysis calcd. for $C_{11}H_{17}NO_3S_2$ (275.38): C 47.98, H 6.22, N 5.09; found: C 47.75, H 5.94, N 4.82.

4.4.15. (R)-N-(1-Hydroxy-3-(1h-indol-3-yl)propane-2-yl) benzenesulfonamide (15a)

Following GPA from (*R*)-tryptophanol (453 mg, 2.38 mmol), TEA (0.55 mL, 3.96 mmol) and BSC (350 mg, 1.98 mmol) **15a** (501 mg, 77 %) was obtained as an off-white solid; $R_f = 0.85$ (SiO_2, hexanes/ethyl acetate, 3:7); m. p. = 100.0–102.0 °C; $[\alpha]_D^{20} = +69.68°$ (*c* 0.028, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.52); IR (ATR) ν = 3404 *m*, 3297*w*, 2925*w*, 1457 *m*, 1447 *m*, 1421 *m*, 1307*s,* 1253*w*, 1232*w*, 1179*w*, 1153*vs,* 1090*s,* 1031*s,* 1011 *m*, 1001*w*, 971 *m*, 879*w*, 840*w*, 741*vs,* 719*s,* 686*s,* 591*s,* 569*s,* 555*s,* 546*vs,* 503 *m*, 498 *m*, 490 *m*, 476*w*, 459 *m*, 441*w*, 424 m cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.72–10.67 (m, 1H, NH_{indole}), 7.71–7.66 (m, 2H, 13-H, 17-H), 7.57 (d, *J* = 7.1 Hz, 1H, NH), 7.53–7.46 (m, 1H, 15-H), 7.44–7.38 (m, 2H, 14-H, 16-H), 7.32–7.24 (m, 2H, 7-H, 10-H), 7.05–6.98 (m, 2H, 5-H, 8-H), 6.94–6.87 (m, 1H, 9- H), 4.67 (*t*, *J* = 5.4 Hz, 1-H, OH), 3.32–3.18 (m, 3H, 1-H, 2-H), 2.91 (*dd*, *J* = 14.4, 6.9 Hz, 1H, 3-H_a), 2.62 (*dd*, *J* = 14.3, 5.8 Hz, 1H, 3-H_b) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.7 (C-12), 136.1 (C-6), 131.8 (C-15), 128.7 (C-14, C-16), 127.2 (C-11), 126.2 (C-13, C-17), 123.6 (C-5), 120.7 (C-8), 118.1 (C-9, C-10), 111.3 (C-7), 110.4 (C-4), 62.5 (C-1), 56.0 (C-2), 27.0 (C-3) ppm; MS (ESI, MeOH): *m*/z = 352.9 (16 %, $[M+Na]^+$); analysis calcd. for $C_{17}H_{18}N_2O_3S$ (330.40): C 61.80, H 5.49, N 8.48; found: C 61.55, H 5.71, N 8.29.

4.4.16. (S)–N-(1-Hydroxy-3-(1h-indol-3-yl)propane-2-yl) benzenesulfonamide (16a)

Following GPA from (*S*)-tryptophanol (516 mg, 2.71 mmol), TEA (0.63 mL, 4.52 mmol) and BSC (400 mg, 2.26 mmol) **16a** (589 mg, 79 %) was obtained as a white solid; $R_f = 0.85$ (SiO_2, hexanes/ethyl acetate, 3:7); m. p. = 100.0–101.0 °C; $[\alpha]_D^{20} = -67.23°$ (*c* 0.175, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.57); IR (ATR) ν = 3476*w*, 3418*w*, 3346*w*, 3145*w*, 3056*w*, 2919*w*, 2885*w*, 1479*w*, 1458 *m*, 1446 *m*, 1417 *m*, 1381*w*, 1354*w*, 1346*w*, 1325 *m*, 1311 *m*, 1304 *m*, 1231*w*, 1289 *m*, 1254*w*, 1170 *m*, 1158*s,* 1149*s,* 1093*s,* 1054 *m*, 1039*s,* 1026*s,* 999*w*, 962 *m*, 926*w*, 888 *m*, 840*w*, 812*w*, 770*w*, 757*w*, 745 *m*, 736*vs,* 719*s,* 687*vs,* 641*w*, 596*s,* 586*s,* 568*s,* 548*vs,* 462*w*, 428 s cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.72–10.67 (m, 1H, NH_{indole}), 7.70–7.65 (m, 2H, 13-H, 17-H), 7.56 (d, *J* = 7.0 Hz, 1H, NH), 7.53–7.47 (m, 1H, 15-H), 7.44–7.38 (m, 2H, 14-H, 16-H), 7.30–7.26 (m, 2H, 7-H, 10-H), 7.05–6.99 (m, 2H, 5-H, 8-H), 6.93–6.87 (m, 1H, 9- H), 4.66 (*t*, *J* = 5.4 Hz, 1-H, OH), 3.32–3.18 (m, 3H, 1-H, 2-H), 2.91 (*dd*, *J* = 14.4, 6.9 Hz, 1H, 3-H_a), 2.61 (*dd*, *J* = 14.3, 5.8 Hz, 1H, 3-H_b) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.7 (C-12), 136.1 (C-6), 131.8 (C-15), 128.7 (C-14, C-16), 127.2 (C-11), 126.2 (C-13, C-17), 123.6 (C-5), 120.7 (C-8), 118.1 (C-9, C-10), 111.3 (C-7), 110.4 (C-4), 62.5 (C-1), 56.0 (C-2), 27.0 (C-3) ppm; MS (ESI, MeOH): *m*/z = 352.9 (7 %, $[M+Na]^+$); analysis calcd. for $C_{17}H_{18}N_2O_3S$ (330.40): C 61.80, H 5.49, N 8.48; found: C 61.62, H 5.72, N 8.21.

4.4.17. 2-(Phenylsulfonamido]ethyl sulfamate (1b)

Following GPB from **1a** (175 mg, 0.87 mmol), **1b** (202 mg, 82 %) was obtained as a white, waxy solid; $R_f = 0.38$ (SiO_2, chloroform/ethyl acetate, 4:6); m. p. = 71–73 °C; UV–Vis (MeOH): λ_{max} (log ε) = 221 nm (3.92); IR (ATR): ν = 3342 *m*, 3263 *m*, 3258 *m*, 1447*w*, 1379*s*, 1356 *m*, 1313*s*, 1178*s*, 1153*s*, 1112*w*, 1093 *m*, 1074*w*, 1053 *m*, 1003 *m*, 952*s*, 914 *m*, 899 *m*, 884 *m*, 835*s*, 754 *m*, 722*s*, 689*s*, 675 *m*, 623 *m*, 597 *m*, 585*s*, 562*s*, 544*vs*, 508 *m*, 499 *m*, 474*w*, 442*w* cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.95–7.90 (m*,* 1H, NH), 7.83–7.78 (m*,* 2H, 2-H), 7.69–7.57 (m*,* 3H, 3-H, 4-H), 7.50 (s, 2H, NH_2), 4.00 (t*,* *J* = 5.7 Hz, 2H, 5-H), 3.05 (q*,* *J* = 5.6 Hz, 2H, 6-H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 140.2 (C-1), 132.5 (C-4), 129.3 (C-3), 126.4 (C-2), 67.5 (C-6), 41.5 (C-5) ppm; MS (ESI, MeOH): *m/z* = 303.1 (100 %, $[M+Na]^+$); anal. calcd. for $C_8H_{12}N_2S_2O_5$ (280.31): C 34.28, H 4.32, N 9.99; found: C 33.01, H 4.52, N 9.86.

4.4.18. (R)-2-(Phenylsulfonamido)propyl sulfamate (2b)

Following GPB from **2a** (300 mg, 1.39 mmol), TEA (0.77 mL, 5.56 mmol) and SC (645 mg, 5.56 mmol) **2b** (187 mg, 46 %) was obtained as a white solid; $R_f = 0.72$ (SiO_2, $CHCl_3$/ethyl acetate, 4:6); m. p. = 107.9–109.9 °C; $[\alpha]_D^{20} = +46.65°$ (*c* 0.104, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (3.79); IR (ATR) ν = 3399*w*, 3288 *m*, 3122*vw*, 3069*vw*, 3001*vw*, 2953*vw*, 1572*w*, 1481*vw*, 1447*w*, 1429*w*, 1382 *m*, 1366 *m*, 1327*s,* 1295 *m*, 1260*w*, 1168*s,* 1151*s,* 1125 *m*, 1090 *m*, 1057*w*, 1024*w*, 1005 *m*, 961*s,* 937*s,* 900 *m*, 840 *m*, 834*s,* 752 *m*, 720*s,* 684*s,* 650 *m*, 619*s,* 612*s,* 565*s,* 549*vs,* 496 *m*, 475*s,* cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.89 (d, *J* = 7.6 Hz, 1H, NH), 7.85–7.80 (m, 2H, 5-H, 9-H), 7.68–7.56 (m, 3H, 6-H, 7-H, 8-H), 7.49 (s*,* 2H, NH_2), 3.90 (*dd*, *J* = 9.7, 4.9 Hz, 1H, 1-H), 3.78 (*dd*, *J* = 9.7, 6.3 Hz, 1H, 1-H), 3.48–3.39 (m, 1H, 2-H), 0.90 (d, *J* = 6.8 Hz, 3H, 3-H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 141.4 (C-4), 132.4 (C-7), 129.2 (C-6, C-8), 126.3 (C-5, C-9), 71.5 (C-1), 47.8 (C-2), 17.1 (C-3) ppm; MS (ESI, MeOH): *m*/z = 316.9 (100 %, $[M+Na]^+$); analysis calcd. for $C_9H_{14}N_2O_5S_2$ (294.34): C 36.73, H 4.79, N 9.52; found: C 36.39, H 4.95, N 9.33.

4.4.19. (S)-2-(Phenylsulfonamido)propyl sulfamate (3b)

Following GPB from **3a** (200 mg, 0.93 mmol), TEA (0.52 mL, 3.72 mmol) and SC (430 mg, 3.72 mmol) **3b** was obtained as a white solid (184 mg, 67 %); $R_f = 0.71$ (SiO_2, $CHCl_3$/ethyl acetate, 4:6); m. p. = 107.7–109.7 °C; $[\alpha]_D^{20} = -47.83°$ (*c* 0.133, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (3.78); IR (ATR) ν = 3399*w*, 3287 *m*, 3122*vw*, 3069*vw*, 3001*vw*, 2953*vw*, 2849*vw*, 1573 *m*, 1481*vw*, 1447*w*, 1429*w*, 1382 *m*, 1366 *m*, 1327*s,* 1295 *m*, 1260*w*, 1168*s,* 1151*s,* 1125 *m*, 1090 *m*, 1057*w*, 1024*w*, 1005 *m*, 960*s,* 937*s,* 900 *m*, 834*s,* 752 *m*, 720*s,* 684*s,* 649 *m*,

618*s,* 612*s,* 565*s,* 548*vs,* 496 *m*, 475*s,* 403 m cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.89 (d, J = 7.6 Hz, 1H, NH), 7.86–7.80 (m, 2H, 5-H, 9-H), 7.67–7.56 (m, 3H, 6-H, 7-H, 8-H), 7.49 (s, 2H, NH_2), 3.90 (*dd*, J = 9.7, 4.9 Hz, 1H, 1- H), 3.78 (*dd*, J = 9.7, 6.3 Hz, 1H, 1-H), 3.48–3.38 (m, 1H, 2-H), 0.90 (d, J = 6.8 Hz, 3H, 3-H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 141.4 (C-4), 132.4 (C-7), 129.2 (C-6, C-8), 126.3 (C-5, C-9), 71.5 (C-1), 47.8 (C-2), 17.1 (C-3) ppm; MS (ESI, MeOH): *m/*z = 316.9 (100 %, $[M+Na]^+$), 338.9 (5 %, $[M+2Na–H]^+$); analysis calcd. for $C_9H_{14}N_2O_5S_2$ (294.34): C 36.73, H 4.79, N 9.52; found: C 36.44, H 4.87, N 9.39.

4.4.20. (R)-4-Methyl-2-(phenylsulfonamido)pentyl sulfamate (**4b**)

Following GPB from **4a** (202 mg, 0.79 mmol), TEA (0.43 mL, 3.11 mmol) and SC (361 mg, 3.12 mmol) **4b** (185 mg, 70 %) was obtained as a colorless, viscous oil; R_f = 0.71 (SiO_2, $CHCl_3$/ethyl acetate, 4:6); $[\alpha]_D^{20}$ = +83.25° (*c* 0.055, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (3.81); IR (ATR) ν = 3277 *m*, 3104*vw*, 3070*vw*, 2959*w*, 2871*w*, 1558*w*, 1468*w*, 1448 *m*, 1427*w*, 1365*s,* 1324*s,* 1309*s,* 1230*w*, 1178*s,* 1153*vs,* 1091*s,* 1073 *m*, 1026*w*, 986*s,* 921*s,* 804*s,* 755*s,* 719*s,* 689*s,* 635 *m*, 593*vs,* 567*vs,* 550*vs,* 490*s,* 419 *m*, 407 m cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.87 (d, J = 7.4 Hz, 1H, NH), 7.84–7.80 (m, 2H, 8-H, 12-H), 7.66–7.56 (m, 3H, 9-H, 10-H, 11-H), 7.48 (s, 2H, NH_2), 3.91 (*dd*, J = 9.6, 4.0 Hz, 1H, 1-H_a), 3.81 (*dd*, J = 9.6, 6.2 Hz, 1H, 1-H_b), 1.40–1.28 (m, 1H, 4-H), 1.25–1.12 (m, 3H, 2-H, 3-H), 0.70 (d, J = 6.6 Hz, 3H, 5-H), 0.46 (d, J = 6.5 Hz, 3H, 6-H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 141.2 (C-7), 132.4 (C-10), 129.1 (C-9, C-11), 126.4 (C-8, C-12), 70.9 (C-1), 50.1 (C-2), 39.9 (C-3), 23.4 (C-4), 22.9 (C-5), 21.1 (C-6) ppm; MS (ESI, MeOH): *m/*z = 358.9 (100 %, $[M+Na]^+$), 374.9 (7 %, $[M+K]^+$), 380.9 (13 %, $[M+2Na–H]^+$). analysis calcd. for $C_{12}H_{20}N_2O_5S_2$ (336.42): C 42.84, H 5.99, N 8.33; found: C 42.64, H 6.27, N 8.05.

4.4.21. (S)-4-Methyl-2-(phenylsulfonamido)pentyl sulfamate (**5b**)

Following GPB from **5a** (200 mg, 0.78 mmol), TEA (0.43 mL, 3.11 mmol) and SC (365 mg, 3.15 mmol) **5b** (170 mg, 65 %) was obtained as a colorless, viscous oil; R_f = 0.72 (SiO_2, $CHCl_3$/ethyl acetate, 4:6); $[\alpha]_D^{20}$ = −81.61° (*c* 0.036, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (3.81); IR (ATR) ν = 3277 *m*, 3103*vw*, 3070*vw*, 2959*w*, 2871*w*, 1622*vw*, 1559*w*, 1468*w*, 1448 *m*, 1427*w*, 1365*s,* 1324*s,* 1309*s,* 1230*w*, 1178*s,* 1153*vs,* 1091*s,* 1073 *m*, 1026*w*, 985*s,* 921*s,* 804*s,* 755*s,* 719*s,* 689*s,* 635 *m*, 592*vs,* 567*vs,* 550*vs,* 489*s,* 416 *m*, 409 *m*, 403 m cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.87 (d, J = 7.4 Hz, 1H, NH), 7.84–7.80 (m, 2H, 8-H, 12-H), 7.66–7.56 (m, 3H, 9-H, 10-H, 11-H), 7.48 (s, 2H, NH_2), 3.90 (*dd*, J = 9.6, 4.0 Hz, 1H, 1-H_a), 3.81 (*dd*, J = 9.6, 6.2 Hz, 1H, 1-H_b), 1.38–1.31 (m, 1H, 4-H) 1.24–1.15 (m, 3H, 2-H, 3-H), 0.70 (d, J = 6.6 Hz, 3H, 5-H), 0.47 (d, J = 6.5 Hz, 3H, 6-H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 141.2 (C-7), 132.4 (C-10), 129.1 (C-9, C-11), 126.4 (C-8, C-12), 70.9 (C-1), 50.1 (C-2), 39.9 (C-3), 23.4 (C-4), 22.9 (C-5), 21.1 (C-6) ppm; MS (ESI, MeOH): *m/*z = 358.9 (100 %, $[M+Na]^+$), 374.9 (7 %, $[M+K]^+$), 380.9 (13 %, $[M+2Na–H]^+$); analysis calcd. for $C_{12}H_{20}N_2O_5S_2$ (336.42): C 42.84, H 5.99, N 8.33; found: C 42.56, H 6.21, N 8.04.

4.4.22. (R)-(1-(Phenylsulfonyl)pyrrolidin-2-yl)methyl sulfamate (**6b**)

Following GPB from **6a** (200 mg, 0.83 mmol), TEA (0.47 mL, 3.32 mmol) and SC (390 mg, 3.37 mmol) **6b** (207 mg, 78 %) was obtained as a colorless, viscous oil); R_f = 0.67(SiO_2, $CHCl_3$/ethyl acetate, 4:6); $[\alpha]_D^{20}$ = +97.66° (c 0.116, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 222 nm (3.81); IR (ATR) ν = 3336 *m*, 3253 *m*, 3121*vw*, 2983*w*, 2918*vw*, 2849*vw*, 2687*vw*, 1756*vw*, 1698*vw*, 1583*vw*, 1572*w*, 1478*vw*, 1461*w*, 1447 *m*, 1380 *m*, 1363*s,* 1320*s,* 1313*s,* 1293 *m*, 1252*w*, 1242*w*, 1204 *m*, 1178*s,* 1153*vs,* 1115 *m*, 1089*s,* 1049 *m*, 1023*w*, 1002 *m*, 987*s,* 970*s,* 933 *m*, 913*s,* 872 *m*, 837*s,* 764*s,* 717*s,* 691*s,* 664 *m*, 596*s,* 571*vs,* 542*vs,* 501 *m*, 489 *m*, 471 *m*, 420 *m*, 407 m cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.87–7.84 (m, 2H, 7-H, 11-H), 7.75–7.71 (m, 1H, 9- H), 7.65–7.62 (m, 2H, 8-H, 10-H), 7.58 (s, 2H, NH_2), 4.16 (*dd*, J = 9.7, 3.6 Hz, 1H, 1-H_a), 4.00 (*dd*, J = 9.7, 7.4 Hz, 1H, 1-H_b), 3.85–3.78 (m, 1H, 2-H), 3.34–3.29 (m, 1H, 5-H_a), 3.10–3.04 (m, 1H, 5-H_b), 1.81–1.72 (m, 2H, 3-H), 1.59–1.49 (m, 1H, 4-H_a), 1.47–1.40 (m, 1H, 4-H_b) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 136.2 (C-6), 133.3 (C-9), 129.6 (C-8, C-10), 127.4 (C-7, C-11), 70.3 (C-1), 57.7 (C-2), 49.2 (C-5), 28.0 (C-3), 23.4 (C-4) ppm; MS (ESI, MeOH): *m/*z = 169.9 (13 %, $[M + H + NH_4]^{2+}$), 343.0 (100 %, $[M+Na]^+$); analysis calcd. for $C_{11}H_{16}N_2O_5S_2$ (320.38): C 41.24, H 5.03, N 8.74; found: C 40.97, H 5.36, N 8.51.

4.4.23. (S)-(1-(Phenylsulfonyl)pyrrolidin-2-yl)methyl sulfamate (**7b**)

Following GPB from **7a** (190 mg, 0.79 mmol), TEA (0.46 mL, 3.31 mmol) and SC (390 mg, 3.37 mmol) **7b** (130 mg, 52 %) was obtained as a colorless, viscous oil; R_f = 0.65 (SiO_2, $CHCl_3$/ethyl acetate, 4:6); $[\alpha]_D^{20}$ = −98.42° (*c* 0.043, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 222 nm (3.82); IR (ATR) ν = 3367*w*, 3273*w*, 3104*vw*, 2960*vw*, 2881*vw*, 1756*vw*, 1561*w*, 1447 *m*, 1367*s,* 1331*s,* 1312 *m*, 1292*w*, 1247*w*, 1177*s,* 1155*vs,* 1092*s,* 1075 *m*, 1046 *m*, 987*s,* 925*s,* 823 *m*, 779 *m*, 755*s,* 738 *m*, 718*s,* 691*s,* 657 *m*, 615*s,* 597*s,* 571*vs,* 550*vs,* 497*s,* 408 m cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.87–7.84 (m, 2H, 7-H, 11-H), 7.76–7.71 (m, 1H, 9-H), 7.67–7.62 (m, 2H, 8-H, 10-H), 7.58 (s, 2H, NH_2), 4.16 (*dd*, J = 9.7, 3.6 Hz, 1H, 1-H_a), 4.00 (*dd*, J = 9.7, 7.4 Hz, 1H, 1-H_b), 3.85–3.79 (m, 1H, 2-H), 3.34–3.30 (m, 1H, 5-H_a), 3.11–3.03 (m, 1H, 5-H_b), 1.81–1.71 (m, 2H, 3-H), 1.57–1.50 (m, 1H, 4-H_a), 1.47–1.40 (m, 1H, 4-H_b) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 136.2 (C-6), 133.3 (C-9), 129.6 (C-8, C-10), 127.4 (C-7, C-11), 70.3 (C-1), 57.7 (C-2), 49.2 (C-5), 28.0 (C-3), 23.4 (C-4) ppm; MS (ESI, MeOH): *m/*z = 170.0 (13 %, $[M + H + NH_4]^{2+}$), 342.9 (100 %, $[M+Na]^+$); analysis calcd. for $C_{11}H_{16}N_2O_5S_2$ (320.38): C 41.24, H 5.03, N 8.74; found: C 40.93, H 5.41, N 8.52.

4.4.24. (R)-3-Methyl-2-(phenylsulfonamido)butyl sulfamate (**8b**)

Following GPB from **8a** (201 mg, 0.83 mmol), TEA (0.45 mL, 3.29 mmol) and SC (384 mg, 3.32 mmol) **8b** (212 mg, 80 %) was obtained as a colorless, viscous oil; R_f = 0.63 (SiO_2, $CHCl_3$/ethyl acetate, 4:6); $[\alpha]_D^{20}$ = −36.07° (*c* 0.028, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (3.85); IR (ATR) ν = 3610*vw*, 3280 *m*, 3106*vw*, 2967*w*, 2878*vw*, 1816*vw*, 1708*vw*, 1558*w*, 1464*w*, 1448 *m*, 1365*s,* 1322*s,* 1178*s,* 1158*vs,* 1091*s,* 1044 *m*, 979*s,* 954*s,* 925*s,* 795 *m*, 755*s,* 720*s,* 688*s,* 654 *m*, 591*s,* 549*vs,* 527*s,* 467 *m*, 447 *m*, 434 *m*, 424 *m*, 410 *m*, 402 m cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.85–7.77 (m, 3H, NH, 7-H, 11-H), 7.65–7.54 (m, 3H, 8-H, 9-H, 10-H), 7.47 (s, 2H, NH_2), 3.94–3.79 (m, 2H, 1-H), 3.25–3.13 (m, 1H, 2-H), 1.83–1.65 (m, 1H, 3-H), 0.73 (d, J = 6.8 Hz, 3H, 4-H), 0.67 (d, J = 6.9 Hz, 3H, 5-H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 141.4 (C-6), 132.3 (C-9), 129.1 (C-8, C-10), 126.4 (C-7, C-11), 68.5 (C-1), 57.2 (C-2), 28.1 (C-3), 18.7 (C-4), 17.4 (C-5) ppm; MS (ESI, MeOH): *m/*z = 344.9 (100 %, $[M+Na]^+$), 360.8 (6 %, $[M+K]^+$); analysis calcd. for $C_{11}H_{18}N_2O_5S_2$ (322.39): C 40.98, H 5.63, N 8.69; found: C 40.63, H 5.87, N 8.35.

4.4.25. (S)-3-Methyl-2-(phenylsulfonamido)butyl sulfamate (**9b**)

Following GPB from **9a** (200 mg, 0.82 mmol), TEA (0.45 mL, 3.29 mmol) and SC (380 mg, 3.30 mmol) **9b** (200 mg, 75 %) was obtained as a colorless, viscous oil; R_f = 0.61 (SiO_2, $CHCl_3$/ethyl acetate, 4:6); $[\alpha]_D^{20}$ = +34.93° (*c* 0.041, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (3.84); IR (ATR) ν = 3281 *m*, 3105*vw*, 2967*w*, 2878*vw*, 1558*w*, 1464*w*, 1448 *m*, 1365*s,* 1322*s,* 1178*s,* 1158*vs,* 1091*s,* 1044 *m*, 979*s,* 954*s,* 925*s,* 842 *m*, 795 *m*, 754*s,* 720*s,* 688*s,* 669 *m*, 653 *m*, 591*s,* 550*vs,* 527*s,* 408 m cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.85–7.77 (m, 3H, NH, 7-H, 11-H), 7.66–7.53 (m, 3H, 8-H, 9-H, 10-H), 7.47 (s, 2H, NH_2), 3.93–3.81 (m, 2H, 1-H), 3.24–3.13 (m, 1H, 2-H), 1.79–1.69 (m, 1H, 3-H), 0.73 (d, J = 6.8 Hz, 3H, 4-H), 0.67 (d, J = 6.9 Hz, 3H, 5-H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 141.4 (C-6), 132.3 (C-9), 129.1 (C-8, C-10), 126.4 (C-7, C-11), 68.5 (C-1), 57.2 (C-2), 28.1 (C-3), 18.7 (C-4), 17.4 (C-5) ppm; MS (ESI, MeOH): *m/*z = 344.9 (100 %, $[M+Na]^+$), 366.9 (3 %, $[M+2Na–H]^+$); analysis calcd. for $C_{11}H_{18}N_2O_5S_2$ (322.39): C 40.98, H 5.63, N 8.69; found: C 40.73, H 5.88, N 8.27.

*4.4.26. (R)-3-Phenyl-2-(phenylsulfonamido)propyl sulfamate (**10b**)*

Following GPB from **10a** (197 mg, 0.77 mmol), TEA (0.38 mL, 2.77 mmol) and SC (320 mg, 2.77 mmol) **10b** (225 mg, 78 %) was obtained as a colorless, viscous oil; $R_f = 0.71$ (SiO_2, $CHCl_3$/ethyl acetate, 4:6); $[\alpha]_D^{20} = +65.75°$ (*c* 0.056, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 216 nm (3.42); IR (ATR) ν = 3612*vw*, 3538*vw*, 3277*w*, 3065*w*, 3030*vw*, 2956*vw*, 1603*vw*, 1585*w*, 1557*w*, 1497*w*, 1479*w*, 1448 *m*, 1365*s,* 1322 *m*, 1309 *m*, 1178*s,* 1154*vs,* 1091*s,* 1001 *m*, 988*s,* 932*s,* 812 *m*, 747*s,* 719*s,* 700*s,* 687*s,* 629 *m*, 595*s,* 566*vs,* 551*vs,* 508*s,* 503*s,* 479*s,* 428*s,* 418 s cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.07 (d, *J* = 8.0 Hz, 1H, NH), 7.61–7.57 (m, 2H, 11-H, 15-H), 7.56–7.51 (m, 3H, 12-H, 13-H, 14-H), 7.46–7.40 (m, 2H, 5-H, 9-H), 7.17–7.12 (m, 3H, 6-H, 7-H, 8-H), 7.05–7.00 (m, 2H, NH_2), 3.96–3.85 (m, 2H, 1-H), 3.59–3.53 (m, 1H, 2-H), 2.76 (*dd*, *J* = 13.8, 6.1 Hz, 1H, 3-H_a), 2.49–2.44 (m, 1H, 3-H_b) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.1 (C-10), 137.1 (C-4), 132.1 (C-13), 129.0 (C-5, C-9), 129.0 (C-12, C-14), 128.2 (C-6, C-8), 126.3 (C-11, C-15), 126.1 (C-7), 70.0 (C-1), 53.9 (C-2), 36.7 (C-3) ppm; MS (ESI, MeOH): *m*/z = 392.8 (100 %, $[M+Na]^+$); analysis calcd. for $C_{15}H_{18}N_2O_5S_2$ (370.44): C 48.64, H 4.90, N 7.56; found: C 48.41, H 5.12, N 7.39.

*4.4.27. (S)-3-Phenyl-2-(phenylsulfonamido)propyl sulfamate (**11b**)*

Following GPB from **11a** (200 mg, 0.78 mmol), TEA (0.38 mL, 2.77 mmol) and SC (323 mg, 2.79 mmol) **11b** (166 mg, 58 %) was obtained as a colorless, viscous oil; $R_f = 0.71$ (SiO_2, $CHCl_3$/ethyl acetate, 4:6); $[\alpha]_D^{20} = -66.17°$ (*c* 0.012, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 216 nm (3.43); IR (ATR) ν = 3277 *m*, 3065*vw*, 3030*vw*, 2926*vw*, 2857*vw*, 1603*vw*, 1585*vw*, 1556*w*, 1497*w*, 1480*w*, 1448 *m*, 1365*s,* 1322 *m*, 1310 *m*, 1178*s,* 1154*vs,* 1090*s,* 1049*w*, 1001 *m*, 988*s,* 929*s,* 850 *m*, 811*s,* 747*s,* 719*s,* 700*s,* 687*s,* 629 *m*, 594*s,* 566*vs,* 551*vs,* 508*s,* 478*s,* 441*s,* 421*s,* 413*s,* 406 s cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.07 (d, *J* = 8.0 Hz, 1H, NH), 7.60–7.50 (m, 5H, 12-H, 13-H, 14-H, NH_2), 7.46–7.39 (m, 2H, 11-H, 15-H), 7.18–7.10 (m, 3H, 6-H, 7-H, 8-H), 7.06–6.99 (m, 2H, 5-H, 9-H), 3.93 (*dd*, *J* = 9.7, 4.3 Hz, 1H, 1-H_a), 3.88 (*dd*, *J* = 9.7, 5.4 Hz, 1H, 1-H_b), 3.61–3.52 (m, 1H, 2-H), 2.75 (*dd*, *J* = 13.8, 6.1 Hz, 1H, 3-H_a), 2.48–2.45 (m, 1H, 3-H_b) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 141.1 (C-10), 137.1 (C-4), 132.1 (C-13), 129.0 (C-5, C-9), 129.0 (C-12, C-14), 128.2 (C-6, C-8), 126.3 (C-11, C-15), 126.1 (C-7), 70.0 (C-1), 53.9 (C-2), 36.7 (C-3) ppm; MS (ESI, MeOH): *m*/z = 392.8 (100 %, $[M+Na]^+$), 408.8 (14 %, $[M+K]^+$), 762.7 (3 %, $[2\ M\ +\ Na]^+$); analysis calcd. for $C_{15}H_{18}N_2O_5S_2$ (370.44): C 48.64, H 4.90, N 7.56; found: C 48.37, H 5.13, N 7.46.

*4.4.28. (2S,3S)-3-methyl-2-(phenylsulfonamido)pentyl sulfamate (**12b**)*

Following GPB from **12a** (204 mg, 0.79 mmol), TEA (0.44 mL, 3.18 mmol) and SC (367 mg, 3.17 mmol) **12b** (130 mg, 52 %) was obtained as a colorless, viscous oil; $R_f = 0.70$ (SiO_2, $CHCl_3$/ethyl acetate, 4:6); $[\alpha]_D^{20} = -41.48°$ (*c* 0.021, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (3.81); IR (ATR) ν = 3604*vw*, 3537*vw*, 3280*w*, 3106*vw*, 2967*w*, 2879*w*, 1624*vw*, 1559*w*, 1448 *m*, 1365*s,* 1323 *m*, 1310 *m*, 1178*s,* 1157*vs,* 1090*s,* 1024 *m*, 978*s,* 923*s,* 831 *m*, 808 *m*, 755*s,*720*s,* 689*s,* 588*s,* 549*vs,* 475*s,* 462*s,* 442*s,* 427 *m*, 418 *m*, 408 m cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.85 (d, *J* = 8.1 Hz, 1H, NH), 7.83–7.79 (m, 2H, 8-H, 12-H), 7.65–7.59 (m, 1H, 10-H), 7.59–7.54 (m, 2H, 9-H, 11-H), 7.46 (s, 2H, NH_2), 3.93 (*dd*, *J* = 10.0, 5.4 Hz, 1H, 1-H_a), 3.87 (*dd*, *J* = 10.0, 4.9 Hz, 1H, 1-H_b), 3.25 (*dq*, *J* = 7.8, 5.3 Hz, 1H, 2-H), 1.48–1.42 (m, 1H, 4-H_a), 1.31–1.23 (m, 1H, 4-H_b), 0.91–0.83 (m, 1H, 3- H), 0.73 (d, *J* = 6.9 Hz, 3H, 5-H), 0.65 (t, *J* = 7.4 Hz, 3H, 6-H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 141.6 (C-7), 132.3 (C-10), 129.1 (C-9, C-11), 126.4 (C-8, C-12), 68.4 (C-1), 56.1 (C-2), 35.3 (C-3), 24.0 (C-4), 14.6 (C-6), 11.1 (C-5) ppm; MS (ESI, MeOH): *m*/z = 359.0 (100 %, $[M+Na]^+$); analysis calcd. for $C_{12}H_{20}N_2O_5S_2$ (336.42): C 42.84, H 5.99, N 8.33; found: C 42.66, H 5.25, N 42.31.

*4.4.29. (R)-4-(Methylthio)-2-(phenylsulfonamido)butyl sulfamate (**13b**)*

Following GPB from **13a** (300 mg, 1.10 mmol), TEA (0.61 mL, 4.38 mmol) and SC (506 mg, 4.38 mmol) **13b** (176 mg, 46 %) was obtained as a colorless, viscous oil; $R_f = 0.53$ (SiO_2, $CHCl_3$/ethyl acetate, 4:6); m. p. = 62.5–65.3 °C; $[\alpha]_D^{20} = +43.50°$ (c 0.01, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.07); IR (ATR) ν = 3247*w*, 3097*w*, 3024*w*, 2891*w*, 1447 *m*, 1325 *m*, 1235 *m*, 1153*vs,* 1092*s,* 1072 *m*, 1039*s,* 997 *m*, 916*w*, 885*w*, 755*s,* 723*s,* 689*s,* 623*w*, 580*s,* 548*vs,* 484*w* cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.88–7.84 (m, 2H, 7-H, 11-H), 7.85–7.80 (m, 1H, NH), 7.73–7.68 (m, 1H, 9-H), 7.67–7.55 (m, 4H, 8-H, 10-H, NH_2), 4.25–4.17 (m, 1H, 2-H), 3.55–3.48 (m, 1H, 4-H_a), 3.43–3.36 (m, 1H, 1-H_a), 3.36–3.27 (m, 2H, 1-H_b, 4-H_b), 2.82 (s, 3H, 5-H), 2.37–2.24 (m, 1H, 3-H_a), 2.13–2.05 (m, 1H, 3-H_b) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 140.2 (C-6), 132.9 (C-9), 129.5 (C-8, C-10), 126.5 (C-7, C-11), 55.1 (C-2), 47.8 (C-1), 41.1 (C-4), 33.0 (C-3), 25.7 (C-5) ppm; MS (ESI, MeOH): *m*/z = 297.8 (100 %, $[M+Na]^+$); analysis calcd. for $C_{11}H_{18}N_2O_5S_3$ (354.45): C 37.27, H 5.12, N 7.90; found: C 36.97, H 5.38, N 7.72.

*4.4.30. (S)-4-(Methylthio)-2-(phenylsulfonamido)butyl sulfamate (**14b**)*

Following GPB from **14a** (300 mg, 1.10 mmol), TEA (0.61 mL, 4.38 mmol) and SC (506 mg, 4.38 mmol) **14b** (206 mg, 53 %) was obtained as a white solid; $R_f = 0.58$ (SiO_2, $CHCl_3$/ethyl acetate, 4:6); m. p. = 63.0–65.0 °C; $[\alpha]_D^{20} = -43.84°$ (*c* 0.025, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.04); IR (ATR) ν = 3248*w*, 3100*w*, 3024*w*, 2886*w*, 1446 *m*, 1324 *m*, 1312 *m*, 1234 *m*, 1153*vs,* 1092*s,* 1072 *m*, 1039*s,* 997 *m*, 886*w*, 755*s,* 721*s,* 689*s,* 623*w*, 580*s,* 549*vs* cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.88–7.84 (m, 2H, 7-H, 11-H), 7.82–7.79 (m, 1H, NH), 7.73–7.68 (m, 1H, 9-H), 7.67–7.56 (m, 4H, 8-H, 10-H, NH_2), 4.23–4.17 (m, 1H, 2-H), 3.55–3.47 (m, 1H, 4-H_a), 3.42–3.35 (m, 1H, 1-H_a), 3.33–3.26 (m, 2H, 1-H_b, 4-H_b), 2.81 (s, 3H, 5-H), 2.34–2.25 (m, 1H, 3-H_a), 2.14–2.04 (m, 1H, 3-H_b) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 140.3 (C-6), 132.9 (C-9), 129.5 (C-8, C-10), 126.5 (C-7, C-11), 55.1 (C-2), 47.8 (C-1), 41.1 (C-4), 33.0 (C-3), 25.7 (C-5) ppm; MS (ESI, MeOH): *m*/z = 297.9 (100 %, $[M+Na]^+$); analysis calcd. for $C_{11}H_{18}N_2O_5S_3$ (354.45): C 37.27, H 5.12, N 7.90; found: C 36.97, H 5.36, N 7.67.

*4.4.31. (R)-3-(1H-Indol-3-yl)-2-(phenylsulfonamido)propyl sulfamate (**15b**)*

Following GPB from **15a** (190 mg, 0.56 mmol), TEA (0.31 mL, 2.24 mmol) and SC (259 mg, 2.24 mmol) **15b** (116 mg, 49 %) was obtained as a white solid; $R_f = 0.78$ (SiO_2, $CHCl_3$/ethyl acetate, 4:6); m. p. = 69.0–72.0 °C; $[\alpha]_D^{20} = +65.31°$ (*c* 0.038, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.56); IR (ATR) ν = 3401*w*, 3280*w*, 1457*w*, 1447 *m*, 1423*w*, 1359 *m*, 1320 *m*, 1309 *m*, 1179*s,* 1154*vs,* 1089*s,* 1033*w*, 1025*w*, 1001 *m*, 986 *m*, 928 *m*, 817 *m*, 742*s,* 719 *m*, 686*s,* 592*s,* 579 *m*, 567*s,* 550*s,* 515 *m*, 506 *m*, 499 *m*, 490 *m*, 481*w*, 470 *m*, 458 *m*, 424 *m*, 413*w* cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.76 (s, 1H, NH_{indole}), 8.04 (d, *J* = 7.5 Hz, 1H, NH), 7.70–7.64 (m, 2H, 13-H, 17-H), 7.54–7.46 (m, 3H, NH_2, 15-H), 7.45–7.38 (m, 2H, 14-H, 16-H), 7.31–7.26 (m, 1H, 10-H), 7.11–6.99 (m, 3H, 5-H, 7-H, 8-H), 6.89 (*ddt*, *J* = 8.0, 7.0, 1.0 Hz, 1H, 9-H), 3.92 (*dq*, *J* = 9.7, 4.6 Hz, 2H, 1-H), 3.59–3.50 (m, 1H, 2-H), 2.88 (*dd*, *J* = 14.3, 7.8 Hz, 1H, 3-H_a), 2.63 (*dd*, *J* = 14.2, 6.8 Hz, 1H, 3-H_b) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.0 (C-12), 136.1 (C-6), 132.1 (C-15), 128.8 (C-14, C-16), 126.8 (C-11), 126.2 (C-13, C-17), 124.0 (C-5), 120.8 (C-8), 118.3 (C-9), 117.7 (C-10), 111.4 (C-7), 109.1 (C-4), 69.7 (C-1), 52.8 (C-2), 26.8 (C-3) ppm; MS (ESI, MeOH): *m*/z = 431.8 (100 %, $[M+Na]^+$); analysis calcd. for $C_{17}H_{19}N_3O_5S_2$ (409.48): C 49.87, H 4.68, N 10.26; found: C 49.65, H 4.97, N 10.01.

*4.4.32. (S)-3-(1H-Indol-3-yl)-2-(phenylsulfonamido)propyl sulfamate (**16b**)*

Following GPB from **16a** (300 mg, 0.91 mmol), TEA (0.50 mL, 3.64 mmol) and SC (421 mg, 3.64 mmol) **16b** (146 mg, 39 %) was obtained as a white solid; $R_f = 0.77$ (SiO_2, $CHCl_3$/ethyl acetate, 4:6); m. p. = 69.0–72.0 °C; $[\alpha]_D^{20} = -66.24°$ (*c* 0.021, MeOH); UV/Vis (MeOH): λ_{max} (log ε) = 221 nm (4.58); IR (ATR) ν = 3400*w*, 3276*w*, 1457*w*, 1447 *m*, 1423*w*, 1360 *m*, 1320 *m*, 1309 *m*, 1178*s,* 1155*vs,* 1089*s,* 1001 *m*, 987 *m*,

929 *m*, 817 *m*, 768*w*, 742*s*, 719 *m*, 687 *m*, 627*w*, 593*s*, 567*s*, 550*s*, 512 *m*, 504 *m*, 468*w*, 459*w*, 424 m cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.79–10.73 (m, 1H, NH_{indole}), 8.04 (d, J = 7.5 Hz, 1H, NH), 7.70–7.64 (m, 2H, 13-H, 17-H), 7.58–7.46 (m, 3H, NH_2, 15-H), 7.44–7.38 (m, 2H, 14-H, 16-H), 7.30–7.25 (m, 1H, 10-H), 7.10–6.99 (m, 3H, 5-H, 7-H, 8-H), 6.88 (*ddd*, J = 8.0, 7.0, 1.0 Hz, 1H, 9-H), 3.92 (*qd*, J = 9.7, 4.6 Hz, 2H, 1-H), 3.59–3.49 (m, 1H, 2-H), 2.87 (*dd*, J = 14.4, 7.8 Hz, 1H, 3-H_a), 2.63 (*dd*, J = 14.4, 6.6 Hz, 1H, 3-H_b) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 141.0 (C-12), 136.1 (C-6), 132.1 (C-15), 128.8 (C-14, C-16), 126.8 (C-11), 126.2 (C-13, C-17), 124.0 (C-5), 120.8 (C-8), 118.3 (C-9), 117.7 (C-10), 111.4 (C-7), 109.0 (C-4), 69.7 (C-1), 52.8 (C-2), 26.8 (C-3) ppm; MS (ESI, MeOH): *m/z* = 431.7 (100 %, $[M+Na]^+$); analysis calcd. for $C_{17}H_{19}N_3O_5S_2$ (409.48): C 49.87, H 4.68, N 10.26; found: C 49.61, H 4.87, N 9.97.

CRediT authorship contribution statement

Toni C. Denner: Writing – review & editing, Writing – original draft, Investigation. **Elsa L. Klett:** Writing – review & editing, Writing – original draft, Investigation. **Niels V. Heise:** Writing – review & editing, Writing – original draft, Investigation. **René Csuk:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmcr.2024.100162.

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