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Synthesis of benzotriazole–amino acid–benzenesulfonamide conjugates and phenylsulfonyl-dipeptides

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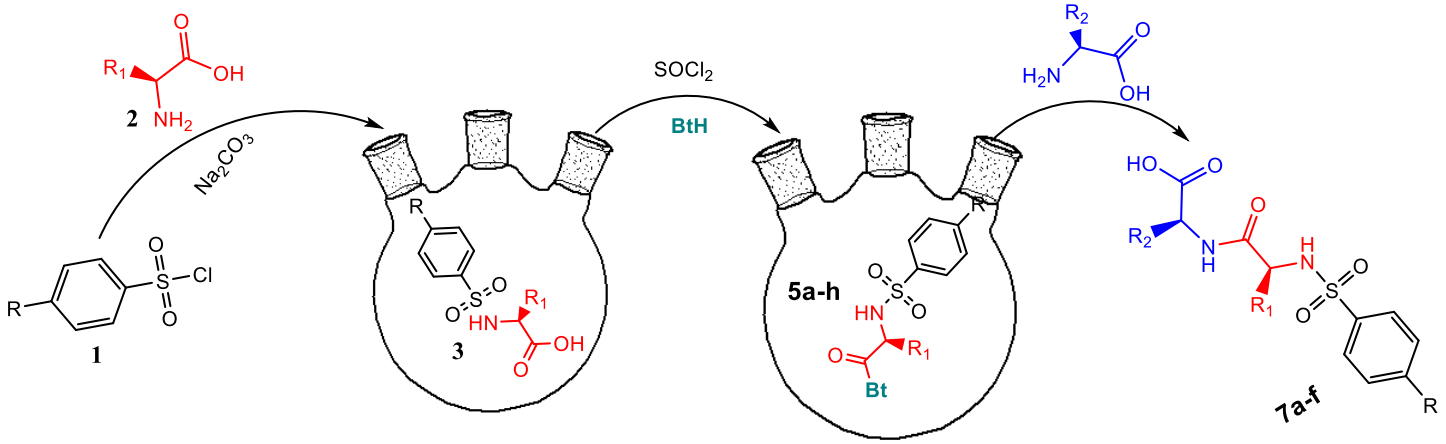
Abstract

L-Amino acids were converted into sulfonamides by reaction with phenylsulfonyl chloride in a basic medium. Subsequent treatment of these sulfonamides with 1*H*-benzotriazole (BtH) and thionyl chloride at room temp erature yielded benzotriazole–amino acid–benzenesulfonamide conjugates with yields ranging from 42% to 68%. Furthermore, the reaction of the benzotriazole derivatives with free glycine and free phenylalanine resulted in the formation of (phenylsulfonyl)dipeptides.



Keywords: Benzensulfonamide, benzotriazole, *L*-amino acids, synthesis

Introduction

Heterocyclic comp ounds of benzo-fused azoles are of great imp ortance in the area of pharmaceutical studies because of their characteristics and uses. Derivatives of benzotriazoles have been researched for many years, and medications with this heterocycle moiety as the primary comp onent have been used extensively in clinical settings, such as human anthelmintics.[2] The wide range of biological activities of benzotriazole hybrids,[3, 4] has been thoroughly investigated, with reported properties such as antibacterial and antiprotozoal,[4] antimycotic,[5] antimycobacterial,[6, 7] antitumor,[8-10] antiviral[11-15] antioxidant[16] activities. Owing to this versatility, 1*H*-benzotriazole (BtH, Fig. 1) is now regarded as a privileged heterocyclic scaffold and continues to play an imp ortant role in heterocyclic synthesis. One of the most typical small-molecule drug modification groups is sulfonamide. The sulfonamide group is useful in drug discovery because of its strong electron-withdrawing capabilities, stability during hydrolysis, polarity, ability to form hydrogen bonds, and strong resistance to oxidation and reduction. It has the potential to alter the site of action in drug design and increase hydrophilicity. A sulfonamide group is present in many commercial therapeutic medications[17, 18]. Sulfonamides are currently considered to be one of the pharmaceutical industry's priority structural motifs. Notably, sulfonamides accounted for nearly 25% of all FDA-approved sulfur-containing drugs in 2019, and their scope of therapeutic application is expanding rapidly, encomp assing antibiotics and treatments for illnesses such as dementia, diabetes, cancer, and central nervous system disorders,[19] as well as carbonic anhydrase inhibition,[20] antibacterial,[21] and antifungal activities[22]. Beyond their established pharmacological relevance, sulfonamides are recognized as privileged structures in drug design because of their ability to act as versatile bioisosteres of carboxylic acids and amides, thereby enhancing binding interactions within enzyme active sites and receptor pockets.[23] Furthermore, sulfonamides often serve as molecular connectors or hinges that link pharmacophoric fragments, yielding hybrid scaffolds with enhanced potency and selectivity.[24] Sulfonamide comp ounds are at the forefront of contemp orary bioactive molecular design due to their favorable physical, chemical, and metabolic stability. Numerous researchers are interested in their synthesis and modification techniques. One of the main areas of study in the field of drug synthesis is the process of creating sulfonamide structures. Since 1985, the benzotriazole approach has been created in response to the vast efforts of A.R. Katritzky.[25] Because of its odorless, non-toxic, stable qualities, extended shelf life, and solubility in a variety of organic solvents, benzotriazole is the favored comp ound in chemical synthesis. Because it has both electron-donating and electron-releasing properties, stabilizing carbonations, and a better leaving group than halogens, it is utilized in a variety of organic processes.[26] In the quest for the synthesis of sulfonamide group containing peptide, different peptide coupling reagents (such combinations as EDC.HCl and HOBT, [27] DCC[28] etc., have been applied. However, the use of *N*-acylbenzotriazoles reagents in the development of sulfonamide-peptide conjugates has rarely been reported.[29-32]

The present work focuses on the design and synthesis of two classes of comp ounds: (i) Benzotriazole–amino acid–benzenesulfonamide conjugates (**5a-h**) and (ii) dipeptide derivatives bearing a phenylsulfonyl group (**7a-e**) in good yields. These hybrid structures were designed to broaden chemical space and furnishing potential frameworks for further biological screening.

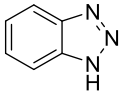
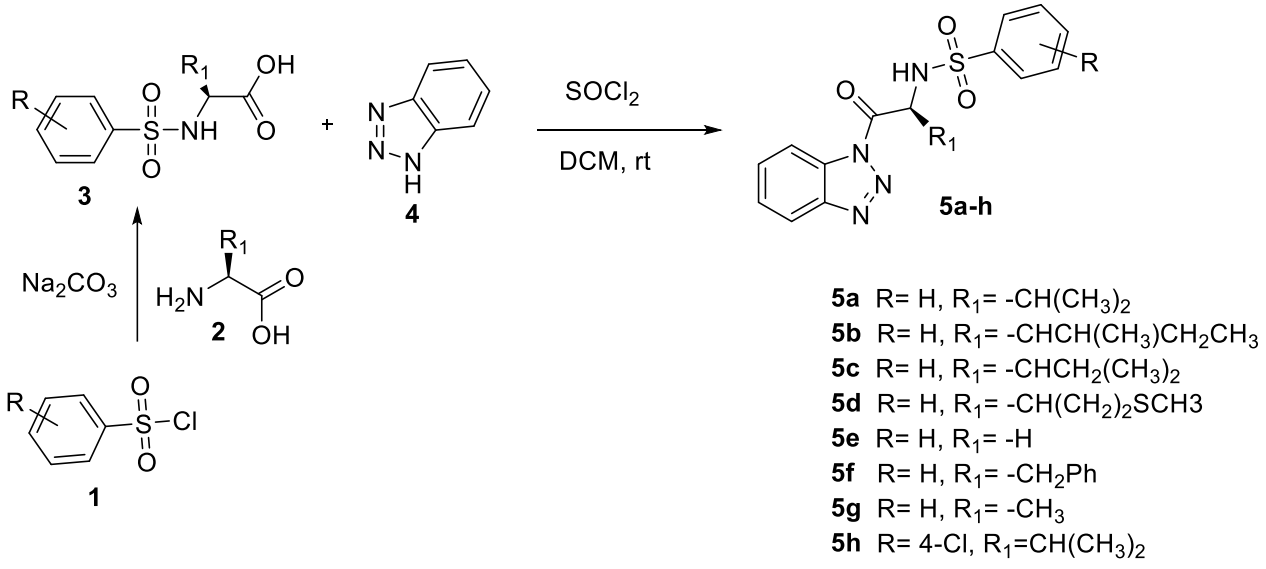


Figure 1. 1*H*-benzotriazole

Results and Discussion

Eight of the twenty natural amino acids **2** (*L*-valine, *L*-Isoleucine, *L*-leucine, *L*-methionine, glycine, *L*-phenylalanine and *L*-alanine) when reacted with benzenesulfonyl chloride **1** in aqueous basic medium at 25 °C for 6h (Scheme 1, Table 1), gave **3** in an excellent yields. The novel benzotriazole–amino acid–benzenesulfonamide conjugates (**5a-h)** were obtained through further reaction of comp ound **3** with 1*H*-benzotriazole and thionyl chloride in DCM at 25 °C for 3 hours (Scheme 1, Table 2) in 42-68% yield. The structures of novel **5a-h** were elucidated using ^{1}H, ^{13}C NMR spectroscopy and HRMS; known comp ounds **3** were verified by assessment of their spectroscopic data and melting points as reported in the literature. The spectra of **5a** displayed the expected ^{13}C NMR chemical shifts at δ 171.2 ppm for C=O of amide, δ 145.9 to 114.3 ppm for aromatic carbons and δ 60.8 to 18.4 ppm for that of aliphatic carbons, respectively. The ^{1}H NMR chemical shifts at δ 8.89 ppm as doublet peak for NH proton, peaks at a range of δ 8.29 to 7.30 ppm as doublet and triplet represent the aromatic protons, while the aliphatic peaks at δ 5.14-5.10 ppm (triplet), δ 2.28-2.19 ppm (multiplet), and δ 0.94 to 0.85 (doublet) were observed for –NHC*H*CH(CH_3)$_2$, -NHCHC*H*(CH_3)$_2$, and -NHCHCH(C*H*$_3$)$_2$, respectively. The phenylsulfonyl-dipeptides (**7a-e**) were obtained in (**59-97%)** through the reaction of the sulfonamide benzotriazole derivatives with free amino acids (glycine and *L*-phenylalanine) (Scheme 2, Table 3). The formation of single peak at δ 12.51 for (-OH proton), triplet peak at δ 8.19 for NH proton and presence of carbonyl carbon peaks of carboxylic acid and amide moieties at δ 171.3 and 170.72 ppm in the spectra confirmed the formation of comp ound **7a.**



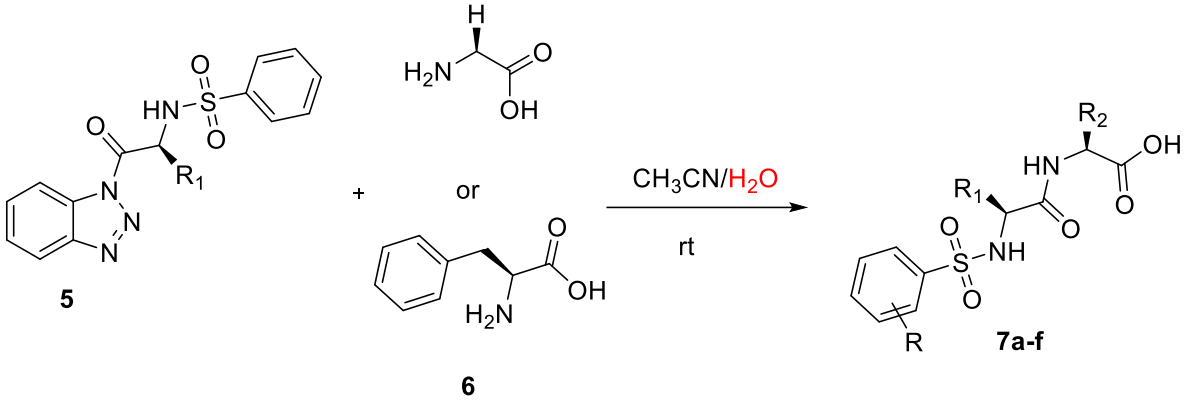
Scheme 1. Synthesis of benzotriazole–amino acid–benzenesulfonamide conjugates **(5a-h)**

Table 1. Conversions of the seven amino acids into benzenesulfonamides (**3**)

Reactants	Products	Yield (%)	mp (°C)/ (Lit. mp)
L-VaL-OH	$PhSO_2Val$	87	143-144/(143.6-143.8)
L-Ile-OH	$PhSO_2Ile$	78	150-151/(148.0-148.70)
L-Leu-OH	$PhSO_2Leu$	89	104-106/(105.6-105.9)
L-Met-OH	$PhSO_2Met$	85	151-153
L-Gly-OH	$PhSO_2Gly$	91	169-171/(170.8-171.4)
L-Phe-OH	$PhSO_2Phe$	69	129.1-129.2
L-Ala-OH	$PhSO_2Ala$	56	120-121
L-Val-OH	$4\text{-}ClPhSO_2Val$	81	115-116

Table 2. Conversions of benzenesulfonamides (**3**) to benzotriazole–amino acid–benzenesulfonamide conjugates (**5a-h**).

Reactant	Product	Yield (%)	mp (°C)
$PhSO_2Val$	$PhSO_2Val\text{-}Bt$	68	146-147 °C
$PhSO_2Ile$	$PhSO_2Ile\text{-}Bt$	64	133-134 °C
$PhSO_2Leu$	$PhSO_2Leu\text{-}Bt$	63	142-143 °C
$PhSO_2Met$	$PhSO_2Met\text{-}Bt$	48	141-142 °C
$PhSO_2Gly$	$PhSO_2Gly\text{-}Bt$	42	185-186 °C
$PhSO_2Phe$	$PhSO_2Phe\text{-}Bt$	53	182-183 °C
$PhSO_2Ala$	$PhSO_2Ala\text{-}Bt$	56	153-154 °C
$4\text{-}ClPhSO_2Val$	$4\text{-}ClPhSO_2Val\text{-}Bt$	63	143-144 °C



7a	R= -H,	R_1= -CH(CH$_3$)CH$_2$CH$_3$,	R_2=-H
7b	R= 4-Cl,	R_1= -CH(CH$_3$)$_2$	R_2=-H
7c	R= -H,	R_1= -CH(CH$_3$)CH$_2$CH$_3$,	R_2= -CH$_2$Ph
7d	R= -H,	R_1= -CH$_3$,	R_2=-H
7e	R= -H,	R_1= -CH(CH$_3$)$_2$	R_2=-H
7f	R= -H,	R_1= -CHCH$_2$(CH$_3$)$_2$,	R_2= -CH$_2$Ph

Scheme 2. Synthesis of phenylsulfonyl-dipeptides **(7a-e)**

Table 3. Conversions of benzotriazole–amino acid–benzenesulfonamide conjugates (**5a**, **5b, 5c, 5g, 5h**) to dipeptides.

Reactant	Product	Yield (%)	mp (°C)
PhSO$_2$Ile-Bt	PhSO$_2$Ile-Gly	76	160-161 °C
4-ClPhSO$_2$Val-Bt	4-ClPhSO$_2$Val-Gly	82	166-167 °C
PhSO$_2$Ile-Bt	PhSO$_2$Ile-Phe	59	230-231 °C
PhSO$_2$Ala-Bt	PhSO$_2$Ala-Gly	60	162-163 °C
PhSO$_2$Val-Bt	PhSO$_2$Val-Gly	97	170-171 °C
PhSO$_2$Leu-Bt	PhSO$_2$Leu-Phe	72	167-168 °C

Conclusions

We present a suitable and cost-effective synthesis of benzotriazole–amino acid–benzenesulfonamide conjugates (**5a-h**), achieving yields ranging from 42% to 68%. Comp ounds **5a**, **5b**, **5c**, **5g**, and **5h** were subsequently converted into dipeptides with yields between 59% and 97% through their reaction with free amino acids, specifically glycine and phenylalanine.

Experimental Section

General. The standard used NMR assignment was tetramethylsilane, ^{1}H NMR and ^{13}C NMR spectra were captured in dimethyl sulfoxide (DMSO-d$_6$) on Avance 400MHz and 101MHz spectrometers, respectively. Perkin-Elmer was used to measure the FTIR spectra. 6200 Series TOF/6500 series Q-TOF (11.0.202.0) were

used to obtain the mass of the comp ounds. Using an uncorrected Gallenkamp MP D350.BM3.5 apparatus, melting points were measured in open glass capillary tubes. The experiment was conducted at the Chemistry Department, İnönü University in Malatya, Turkey. Thin layer chromatography (TLC) on precoated silica gel 60 F254 (mesh) was used to monitor all reactions; spots were visible under a UV lamp .

Synthesis of benzenesulfonamides (3). Various *L*-amino acid (*L*-valine, *L*-Isoleucine, *L*-leucine, *L*-methonine, glycine, *L*-phenylalanine and *L*-alanine) (1.5 mmol) was added to sodium carbonate (Na_2CO_3, 1.82mmol) in water (15 mL) with continuous stirring. Upon the dissolution of the solutes, followed the addition of benzenesulfonyl chloride (1.82 mmol) in drop wise and stirred further to comp letion as monitored using TLC (MeOH/DCM, 1:9). The slurry was acidified using 20% HCl to pH 2. The solid was filtered, washed with water and dried.[30] The data for comp ounds (**3**) affirmed with the literature report.[30]

Synthesis of benzotriazole (Bt)–amino acid–benzenesulfonamide conjugates (5a-h). Thionyl chloride (1.2 eq) was added to a solution of BtH (4.0 eq) in dichloromethane (DCM) to give a yellow solution and allowed to stir for 15 mins followed the addition of benzenesulfonamides (1.0 eq) (**3**) to form a suspension and further stirred for 3h. After the comp letion of the reaction, the suspension was filtered, then the filtrate evaporated and residue dissolved in ethyl acetate, washed with saturated solution of sodium carbonate (3x50 mL), the organic layer was removed under rotary evaporator, and the solid product was triturated with diethyl ether to give **5a-h.**

Bt-Val-Benzenesulfonamide [5a]. Yield: 68%, Mp 146-147 °C. IR (KBr) cm^{-1}: 3229 (NH); 2967 (C-H Aliphatic); 1731 ($C=O_{(amide)}$); 1335 (SO_2-N).^{1}H NMR (400 MHz, DMSO) δ 8.89 (d, *J*= 9.1 Hz, 1H, -N*H*-), 8.28 (d, *J* 8.3 Hz, 1H, Ar-H), 8.02 (d, *J* 8.2 Hz, 1H, Ar-H), 7.78 (t, *J* 7.7 Hz, 1H, Ar-H), 7.65 (t, *J* 8.5 Hz, 3H, Ar-H), 7.36–7.30 (m, 3H, Ar-H), 5.14–5.10 (t, 1H, -NHC*H*CH(CH_3)$_2$), 2.28-2.19 (m, 1H, -NHCHC*H*(CH_3)$_2$), 0.94 (d, *J* 6.7 Hz, 3H, -NHCHCH(C*H*$_3$)$_2$), 0.85 (d, *J* 6.7 Hz, 3H, -NHCHCH(C*H*$_3$)$_2$). ^{13}C NMR (101 MHz, DMSO) δ 171.2 (*C*=$O_{(amide)}$), 145.9, 140.5, 132.7, 131.8, 130.5, 129.3, 127.5, 126.8, 120.8, 114.3 (Ar-*C*), 60.8, 31.3, 19.4, 18.4. HRMS *m*/*z* for $C_{17}H_{18}N_4O_3S$ $[M+Na]^+$ calcd. 358.1100, found 381.0997 $[M+Na]^+$.

Bt-Ile-Benzenesulfonamide [5b]. Yield: 64%, Mp 133-134 °C. IR (KBr) cm^{-1}: 3278 (NH); 2968 (C-H Aliphatic); 1731 ($C=O_{(amide)}$); 1335 (SO_2-N).^{1}H NMR (400 MHz, DMSO) δ 8.97 (d, *J* 8.9 Hz, 1H, -NH), 8.31 (d, *J* 8.3 Hz, 1H, Ar-H), 8.05 (d, *J* 8.2 Hz, 1H, Ar-H), 7.81 (t, *J* 7.7 Hz, 1H, Ar-H), 7.68 (t, *J* 6.8 Hz, 3H, Ar-H), 7.41–7.22 (m, 3H, Ar-H), 5.22 (t, *J* 8.4 Hz, 1H, -NHC*H*CH(CH_3)CH_2CH_3), 2.09–2.03 (m, 1H, -NHCHCH(CH_3)C*H*$_2$$CH_3$), 1.61-1.55 (m, -NHCHCH(CH_3)C*H*$_2$$CH_3$), 1.35–1.24 (m, 1H, -NHCHC*H*(CH_3)CH_2CH_3), 0.82 and 0.79 (2d, *J* 4.0 ve 8.0 Hz, 6H, -NHCHCH(C*H*$_3$)CH_2C*H*$_3$). ^{13}C NMR (101 MHz, DMSO) δ 171.5 (C=$O_{(amide)}$), 145.9, 140.4, 132.8, 131.7, 130.5, 129.5, 129.3, 127.5, 126.8, 120.7, 114.3 (Ar-*C*), 59.2(NH*C*H), 37.3(*C*H_2CH_3), 24.5 (*C*HCH_3), 15.5 (*C*H_3), 10.5 (*C*H_3). HRMS *m*/*z* for $C_{18}H_{20}N_4O_3S$ $[M+Na]^+$ calcd. 372.1256, found 395.1150 $[M+Na]^+$.

Bt-Leu-Benzenesulfonamide [5c]. Yield: 63%, mp 142-143 °C. IR (KBr) cm^{-1}: 3280 (NH); 2964 (C-H Aliphatic); 1734 ($C=O_{(amide)}$); 1334 (SO_2-N). ^{1}H NMR (400 MHz, DMSO) δ 8.91 (d, *J* 7.1 Hz, 1H, NH), 8.27 (d, *J* 8.3 Hz, 1H, Ar-H), 8.04 (d, *J* 8.2 Hz, 1H, Ar-H), 7.81–7.75 (m, 1H, Ar-H), 7.74–7.69 (m, 2H, Ar-H), 7.67–7.60 (m, 1H, Ar-H), 7.48–7.37 (m, 3H, Ar-H), 5.33 (br, 1H, NHC*H*CH_2CH(CH_3)$_2$), 1.74–1.57 (m, 3H, -NHCHC*H*$_2$C*H*(CH_3)$_2$), 0.83 (d, *J* 6.2 Hz, 3H, NHCHCH_2CH(C*H*$_3$)$_2$), 0.72 (d, *J* 6.1 Hz, 3H, NHCHCH_2CH(C*H*$_3$)$_2$). ^{13}C NMR (101 MHz, DMSO) δ 171.8, (C=O) $_{(amide)}$), 145.9, 140.7, 133.0, 131.7, 130.8, 129.5, 127.4, 126.8, 120.7, 114.3 (Ar-C), 53.9 (NH*C*H), 40.6 (CH*C*H_2), 24.6[*C*H(CH_3)$_2$], 23.2 (*C*H_3) and 20.9 (*C*H_3). HRMS *m*/*z* for $C_{18}H_{20}N_4O_3S$ $[M+Na]^+$ calcd. 358.1100, found 395.1149$[M+Na]^+$.

Bt-Met-Benzenesulfonamide [5d]. Yield: 48%, Mp 141-142 °C. IR (KBr) cm^{-1}: 3272 (NH); 2916 (C-H Aliphatic); 1734 ($C=O_{(amide)}$); 1333 (SO_2-N).^{1}H NMR (400 MHz, DMSO) δ 8.99 (bs, 1H, NH), 8.28 (d, *J* 8.3 Hz, 1H, Ar-H), 8.07 (d, *J* 8.2 Hz, 1H, Ar-H), 7.79 (t, *J* 7.6 Hz, 1H, Ar-H), 7.73 (d, *J* 7.4 Hz, 2H, Ar-H), 7.64 (t, *J* 7.7 Hz, 1H, Ar-H), 7.51–

7.45 (m, 1H, Ar-H), 7.42 (t, *J* 7.3 Hz, 2H, Ar-H), 5.50 (dd, *J* 9.5, 3.5 Hz, 1H, -NHC*H*$CH_2CH_2SCH_3$), 2.63–2.54 (m, 1H, -NHCHCH$_2$C*H*$_2$$SCH_3$), 2.46–2.36 (m, 1H, -NHCHCH$_2$C*H*$_2$$SCH_3$), 2.19 (dt, *J* 11.7, 7.7 Hz, 1H, -NHCHC*H*$_2$$CH_2SCH_3$), 2.02 (dd, *J* 14.9, 5.4 Hz, 1H, -NHCHC*H*$_2$$CH_2SCH_3$), 1.94 (s, 3H, -NHCHCH$_2CH_2$SC*H*$_3$). ^{13}C NMR (101 MHz, DMSO) δ 171.3 (C=O$_{(amide)}$), 145.9, 140.9, 133.0, 131.6, 130.9, 129.5, 127.3, 126.8, 120.7, 114.4 (Ar-C), 54.4 (NH*C*H), 31.1 (CH*C*H$_2$), 29.6 (S*C*H$_2$), 14.6 (*C*H$_3$). HRMS *m/z* for $C_{17}H_{18}N_4O_3S_2$ [M+Na]$^+$ calcd. 390.0820, found 413.0712 [M+Na]$^+$.

Bt-Gly-Benzenesulfonamide [5e]. Yield: 42 %, Mp 185-186 °C. IR (KBr) cm^{-1}: 3273 (NH); 2971 (C-H Aliphatic); 1732 (C=O$_{(amide)}$); 1332 (SO$_2$-N).^{1}H NMR (400 MHz, DMSO) δ 8.62 (t, *J* 6.0 Hz, 1H, NH), 8.27 (d, *J* 8.3 Hz, 1H,Ar-H), 8.15 (d, *J* 8.2 Hz, 1H, Ar-H), 7.96–7.86 (m, 2H, Ar-H), 7.85–7.76 (m, 1H, Ar-H), 7.65-7.56 (m, 4H, Ar-H), 4.84 (d, *J* 6.1 Hz, 2H, -NHC*H*$_2$-). ^{13}C NMR (101 MHz, DMSO) δ 168.3 (C=O$_{(amide)}$), 145.7, 141.0, 133.1, 131.5, 131.0, 129.7, 127.1, 127.0, 120.6, 114.1 (Ar-C), 45.98 (NH*C*H). HRMS *m/z* for $C_{14}H_{12}N_4O_3S$ [M+Na]$^+$ calcd. 316.0630, found 339.0527 [M+Na]$^+$.

Bt-Phe-Benzenesulfonamide [5f]. Yield: 53%, Mp 182-183 °C. IR (KBr) cm^{-1}: 3229 (NH); 2967 (C-H Aliphatic); 1731 (C=O$_{(amide)}$); 1335 (SO$_2$-N).^{1}H NMR (400 MHz, DMSO) δ 9.13 (d, *J* 8.9 Hz, 1H, NH), 8.26 (d, *J* 8.3 Hz, 1H, Ar-H), 8.06 (d, *J* 8.2 Hz, 1H, Ar-H), 7.87–7.70 (m, 1H, Ar-H), 7.70–7.58 (m, 1H,Ar-H), 7.50–7.45 (m, 2H, Ar-H), 7.38 (t, *J* 7.4 Hz, 1H, Ar-H), 7.26 (t, *J* 7.7 Hz, 2H, Ar-H), 7.22–7.13 (m, 5H, Ar-H), 5.52 (td, *J* 9.2, 5.3 Hz, 1H, -NHC*H*CH_2Ph), 3.29 (dd, *J* 13.8, 5.3 Hz, 1H, -NHCHC*H*$_2$Ph), 3.01 (dd, *J* 13.8, 9.5 Hz, 1H, -NHCHC*H*$_2$Ph). ^{13}C NMR (101 MHz, DMSO) δ 171.1 (C=O$_{(amide)}$), 145.9, 140.5, 136.4, 132.8, 131.7, 130.7, 129.6, 129.3, 128.8, 127.4, 127.3, 126.5, 120.7, 114.3 (Ar-C), 57.2 (NH*C*H), 37.9 (CH*C*H$_2$). HRMS *m/z* for $C_{21}H_{18}N_4O_3S$ [M+Na]$^+$ calcd. 406.1100, found 429.0998 [M+Na]$^+$.

Bt-Ala-Benzenesulfonamide [5g]. Yield: 56%, Mp 153-154 °C. IR (KBr) cm^{-1}: 3152 (NH); 2984 (C-H Aliphatic); 1737 (C=O$_{(amide)}$); 1332 (SO$_2$-N).^{1}H NMR (400 MHz, DMSO) δ 8.94 (d, *J* 7.3 Hz, 1H, -NH), 8.31 (d, *J* 8.3 Hz, 1H, Ar-H), 8.11 (d, *J* 8.2 Hz, 1H, Ar-H), 7.86–7.76 (m, 3H, Ar-H), 7.72–7.64 (m, 1H, Ar-H), 7.55-7.46 (m, 3H, Ar-H), 5.44-5.37 (m, 1H, -NHC*H*CH$_3$), 1.49 (d, *J* 7.1 Hz, 3H, NHCHC*H*$_3$). ^{13}C NMR (101 MHz, DMSO) δ 171.6 (C=O$_{(amide)}$), 145.9, 141.0, 133.0, 131.7, 130.9, 129.6, 127.3, 126.8, 120.7, 114.4 (Ar-C), 51.4 (NH*C*H), 18.6 (CH*C*H$_3$). HRMS *m/z* for $C_{15}H_{14}N_4O_3S$ [M+Na]$^+$ calcd. 330.0787, found 353.0680 [M+Na]$^+$.

Bt-Val-4-Chlorobenzenesulfonamide [5h]. Yield: 63%, Mp 143-144 °C. IR (KBr) cm^{-1}: 3280 (NH); 2972 (C-H Aliphatic); 1727 (C=O$_{(amide)}$); 1340 (SO$_2$-N).^{1}H NMR (400 MHz, DMSO) δ 9.01 (bs, 1H, NH), 8.28 (d, *J* 8.3 Hz, 1H, Ar-H), 8.01 (d, *J* 8.2 Hz, 1H, Ar-H), 7.79 (t, *J* 7.6 Hz, 1H, Ar-H), 7.64 (dd, *J* 14.6, 8.2 Hz, 3H, Ar-H), 7.33 (d, *J* 8.6 Hz, 2H, Ar-H), 5.11 (d, *J* 6.8 Hz, 1H, -NHC*H*CH(CH$_3$)$_2$), 2.26 (dq, *J* 13.6, 6.8 Hz, 1H, -NHCHC*H*(CH$_3$)$_2$), 0.97 (d, *J* 6.7 Hz, 3H, -NHCHCH(C*H*$_3$)$_2$), 0.87 (d, *J* 6.7 Hz, 3H, -NHCHCH(C*H*$_3$)$_2$). ^{13}C NMR (101 MHz, DMSO) δ 171.0 (C=O$_{(amide)}$), 145.9, 139.4, 137.9, 131.8, 130.5, 129.4, 128.7, 127.5, 120.8, 114.2 (Ar-C), 60.9 (NH*C*H), 31.3 (CH*C*H), 19.4 (*C*H$_3$), 18.5 (*C*H$_3$).. HRMS *m/z* for $C_{17}H_{17}ClN_4O_3S$ [M+Na]$^+$ calcd. 392.0710, found 415.0611 [M+Na]$^+$.

General Procedure for the Synthesis of phenylsulfonyl-dipeptides (7a–f). A solution of *L*-amino acid (*L*-glycine or *L*-phenylalanine) (1.0 equiv.) in acetonitrile–water (CH_3CN/H_2O) was treated with triethylamine, followed by the addition of the corresponding benzotriazole–amino acid–benzenesulfonamide conjugate (1.0 equiv.). The reaction mixture was stirred at room temp erature until comp letion, as monitored by TLC. The acetonitrile was removed under reduced pressure, and the residue was acidified with 6 N HCl. The resulting mixture was extracted with ethyl acetate (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude solid was triturated with diethyl ether to afford the desired products **7a–f**.

(Phenylsulfonyl)-Ile-Gly [7a]. Yield: 76%, Mp 160-161 °C. IR (KBr) cm^{-1}: 3288, 3213 (NH); 2961 (C-H Aliphatic); 1729 (C=O), 1648 (C=O$_{(amide)}$); 1239 (SO$_2$-N). ^{1}H NMR (400 MHz, DMSO) δ 12.51 (s, 1H, OH), 8.19 (t, *J* 5.7 Hz,

1H, NH), 7.83 (d, *J* 9.3 Hz, 1H, NH), 7.79–7.72 (m, 2H, Ar-H), 7.59 (t, *J* 7.4 Hz, 1H, Ar-H), 7.52 (t, *J* 7.5 Hz, 2H, Ar-H), 3.59–3.42 (m, 3H, -NHCH_2CO and –NHC*H*CO), 1.61–1.55 (m, 1H, NHCH(CH(CH_3)CH_2CH_3), 1.51-1.44 (m, 1H, NHCH(CH(CH_3)CH_2CH_3), 1.12–1.01 (m, 1H, NHCH(C*H*(CH_3)CH_2CH_3), 0.76 (dd, *J* 16.1, 7.2 Hz, 6H, NHCH(CH(CH_3)CH_2CH_3). ^{13}C NMR (101 MHz, DMSO) δ 171.3, 170.7 (2C=$O_{(amide)}$) 141.5, 132.6, 129.1, 127.1 (Ar-C), 60.9 (NHCH_2), 40.9 (NH*C*H), 37.3 (*C*H_2*C*H_3), 24.7 (NHCH*C*H), 15.4 (*C*H_3), 11.0 (*C*H_3). HRMS *m/z* for $C_{14}H_{20}N_2O_5S$ $[M+Na]^+$ calcd. 328.1093, found 351.0990 $[M+Na]^+$.

((4-Chlorophenyl)sulfonyl)-Val-Gly [7b]. Yield: 82%, Mp 166-167 °C. IR (KBr) cm^{-1}: 3339, 3232 (NH); 2961 (C-H Aliphatic); 1727, 1640 (C=$O_{(amide)}$); 1328 (SO_2-N).^{1}H NMR (400 MHz, DMSO) δ 12.54 (s, 1H, OH), 8.25 (t, *J* 5.7 Hz, 1H, NH), 7.97 (d, *J* 9.3 Hz, 1H, NH), 7.75 (d, *J* 8.6 Hz, 2H, Ar-H), 7.60 (d, *J* 8.6 Hz, 2H, Ar-H), 3.62–3.43 (m, 3H, NHC*H*CONHCH_2-), 1.83 (dq, *J* 13.6, 6.8 Hz, 1H, -C*H*(CH_3)$_2$), 0.82 (d, *J* 6.7 Hz, 6H, -CH(CH_3)$_2$). ^{13}C NMR (101 MHz, DMSO) δ 171.3 (C=O), 170.7 (C=$O_{(amide)}$), 140.5, 137.4, 129.3, 129.0 (Ar-C), 62.3(NHCH_2), 40.8 (NH*C*H), 31.3 (*C*H), 19.4 (*C*H_3), 18.8 (*C*H_3). HRMS *m/z* for $C_{13}H_{17}ClN_2O_5S$ $[M+Na]^+$ calcd. 348.0547, found 371.0442 $[M+Na]^+$.

(Phenylsulfonyl)-Ile-Phe [7c]. Yield: 59%, Mp 230-231 °C. IR (KBr) cm^{-1}: 3340, 3210 (NH); 2966 (C-H Aliphatic); 1638, 1586 (C=O); 1325 (SO_2-N).^{1}H NMR (400 MHz, DMSO) δ 7.81 (d, *J* 7.4 Hz, 2H, 2NH), 7.57–7.49 (m, 5H, Ar-H), 7.16–7.05 (m, 5H, Ar-H), 3.87 (q, *J* 5.4 Hz, 1H, NHC*H*(COOH)CH_2Ph), 3.42-3.39 (m, 2H, NHC*H*CH(CH_3)CH_2CH_3 and NHCH(COOH)CH_2Ph), 2.88-2.85 (m, 1H, NHCH(COOH)CH_2Ph), 1.56-1.49 (m, 1H, NHCHCH(CH_3)CH_2CH_3), 1.30-1.25 (m, 1H, NHCHCH(CH_3)CH_2CH_3), 0.99-0.95 (m, 1H, NHCHC*H*(CH_3)CH_2CH_3), 0.67–0.60 (m, 6H, NHCHCH(CH_3)CH_2CH_3)). ^{13}C NMR (101 MHz, DMSO) δ 173.3 (C=O), 169.4 (C=$O_{(amide)}$), 141.5, 139.8, 132.6, 130.1, 129.3, 127.9, 127.2, 125.9 (Ar-C), 61.9 (NH*C*H), 55.9 (NH*C*H), 38.2 (CH*C*H_2Ph), 37.7 (CH*C*H), 24.5 (*C*H_2CH_3), 15.6 (*C*H_3), 11.5 (*C*H_3). HRMS *m/z* for $C_{21}H_{26}N_2O_5S$ $[M+Na]^+$ calcd. 418.1562, found 441.1452 $[M+Na]^+$.

(Phenylsulfonyl)-Ala-Gly [7d]. Yield: 60%, Mp 162-163 °C. IR (KBr) cm^{-1}: 3395, 3186 (NH); 2988 (C-H Aliphatic); 1740, 1610 (C=$O_{(amide)}$); 1332 (SO_2-N).^{1}H NMR (400 MHz, DMSO) δ 12.58 (s, 1H, OH), 8.16 (t, *J* 5.7 Hz, 1H, NH), 8.05 (d, *J* 8.4 Hz, 1H, NH), 7.86–7.77 (m, 2H, Ar-H), 7.63 (t, *J* 7.3 Hz, 1H, Ar-H), 7.57 (t, *J* 7.4 Hz, 2H, Ar-H), 3.87-3.80 (m, 1H, -NHC*H*CH_3), 3.65 (d, *J* 5.7 Hz, 2H, NHCH_2COOH), 1.03 (d, *J* 7.1 Hz, 3H, -NHCHCH_3). ^{13}C NMR (101 MHz, DMSO) δ 172.0 (C=O), 171.4 (C=$O_{(amide)}$), 141.5, 132.8, 129.5, 127.0 (Ar-C), 52.2 (NH*C*H), 41.0 (NHCH_2), 19.1(*C*H_3). HRMS *m/z* for $C_{11}H_{14}N_2O_5S$ $[M+Na]^+$ calcd. 286.0623, found 309.0520 $[M+Na]^+$.

(Phenylsulfonyl)-Val-Gly [7e]. Yield: 97%, Mp 170-171 °C. IR (KBr) cm^{-1}: 3388, 3257 (NH); 2966 (C-H Aliphatic); 1732, 1650 (C=$O_{(amide)}$); 1439 (SO_2-N).^{1}H NMR (400 MHz, DMSO) δ 12.57 (s, 1H, OH), 8.24 (t, *J* 5.7 Hz, 1H, NH), 7.87 (d, *J* 9.2 Hz, 1H, NH), 7.83–7.77 (m, 2H, Ar-H), 7.64 (d, *J* 8.5 Hz, 1H, Ar-H), 7.57 (t, *J* 7.4 Hz, 2H, Ar-H), 3.60–3.58 (d, *J* 8.0 Hz, 2H, NHCH_2COOH), 3.52-3.42 (m, 1H, -NHC*H*CH(CH_3))$_2$, 1.90-1.84 (m, 1H, -NHCHC*H*(CH_3))$_2$), 0.85 (dd, *J* 6.7, 2.5 Hz, 6H, -NHCHC*H*(CH_3)$_2$). ^{13}C NMR (101 MHz, DMSO) δ 171.3, 170.8 (C=O), (C=$O_{(amide)}$), 141.5, 132.6, 129.2, 127.1 (Ar-C), 62.3(NH*C*H_2), 40.9 (NH*C*H), 31.2 NHCH*C*H(C*H*$_3$)$_2$), 19.3 (*C*H_3), 18.7 (*C*H_3). HRMS *m/z* for $C_{13}H_{18}N_2O_5S$ $[M+Na]^+$ calcd. 314.0936, found 337.0827 $[M+Na]^+$.

(Phenylsulfonyl)-Leu-Phe [7f]. Yield : 72%, Mp 167-168 °C. IR (KBr) cm^{-1}: 3330, 3170 (NH); 2959 (C-H Aliphatic); 1716, 1641 (C=$O_{(amide)}$); 1334 (SO_2-N).^{1}H NMR (400 MHz, DMSO) δ 8.16 (d, *J* 7.4 Hz, 1H, NH), 7.95 (d, *J* 8.7 Hz, 1H, NH), 7.70 (d, *J* 7.3 Hz, 2H, Ar-H), 7.57 (t, *J* 7.4 Hz, 1H, Ar-H), 7.45 (t, *J* 7.7 Hz, 2H, Ar-H), 7.29 (t, *J* 7.1 Hz, 2H, Ar-H), 7.23 (t, *J* 7.2 Hz, 1H, Ar-H), 7.17 (d, *J* 6.9 Hz, 2H, Ar-H), 4.14 (dd, *J* 13.5, 7.4 Hz, 1H, NHC*H*(COOH)CH_2Ph), 3.75 (dd, *J* 15.6, 7.8 Hz, 1H, NHC*H*CH_2CH(CH_3)$_2$), 2.92 (dd, *J* 13.8, 5.8 Hz, 1H, NHCH(COOH)CH_2Ph), 2.80 (dd, *J* 13.8, 7.8 Hz, 1H, NHCH(COOH)CH_2Ph), 1.55-1.46 (m, 1H, NHCHCH_2C*H*(CH_3)$_2$), 1.26 (t, *J* 7.1 Hz, 2H, NHCHCH_2CH(CH_3)$_2$), 0.78 (d, *J* 6.6 Hz, 3H, NHCHCH_2CH(CH_3)$_2$), 0.67 (d, *J* 6.5 Hz, 3H, NHCHCH_2CH(CH_3)$_2$). ^{13}C NMR (101 MHz, DMSO) δ 173.0 (C=O), 171.4 (2C=$O_{(amide)}$), 141.5, 137.8, 132.6, 129.6, 129.2, 128.6, 127.0, 126.9 (Ar-C), 55.1 (NH*C*H), 53.9 (NH*C*H),, 42.0 (NHCH_2), 37.1 [*C*H(CH_3)$_2$], 24.1 (*C*H_2CH), 23.3 (*C*H_3), 21.7 (*C*H_3).

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Supplementary Material

Supplementary Files contained all the data obtained in this work.

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