

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

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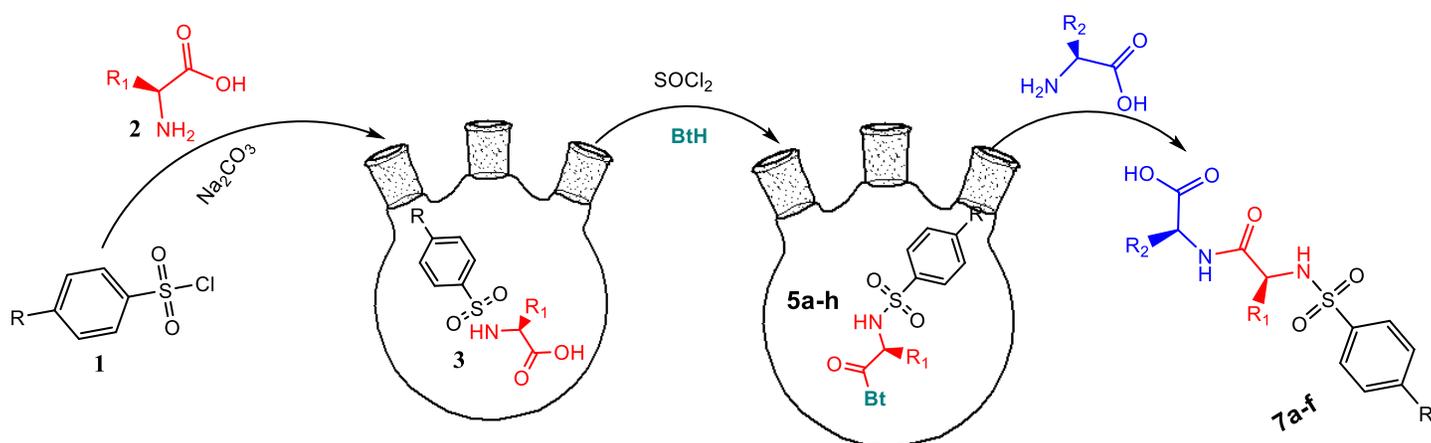
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Abstract

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 temperature 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: Benzenesulfonamide, benzotriazole, *L*-amino acids, synthesis

Introduction

Heterocyclic compounds of benzo-fused azoles are of great importance 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 component 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 antiviral¹¹⁻¹⁵ antioxidant¹⁶ activities. Owing to this versatility, 1*H*-benzotriazole (BtH, Figure 1) is now regarded as a privileged heterocyclic scaffold and continues to play an important 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, encompassing 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 activities²². 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 compounds are at the forefront of contemporary 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 compound 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 DCC²⁸ 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 compounds: (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.

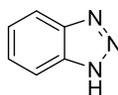
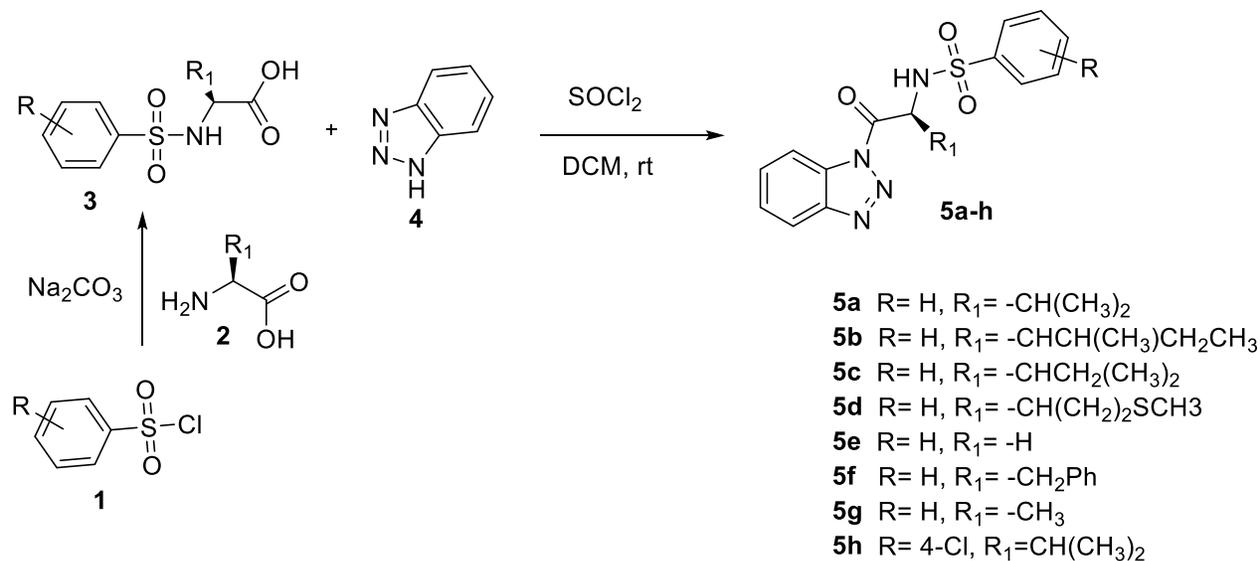


Figure 1. 1*H*-benzotriazole.

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 compound **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 ¹H, ¹³C NMR spectroscopy and HRMS; known compounds **3** were verified by assessment of their spectroscopic data and melting points as reported in the literature. The spectra of **5a** displayed the expected ¹³C 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 ¹H 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 –NHCHCH(CH₃)₂, –NHCHCH(CH₃)₂, and –NHCHCH(CH₃)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 compound **7a**.



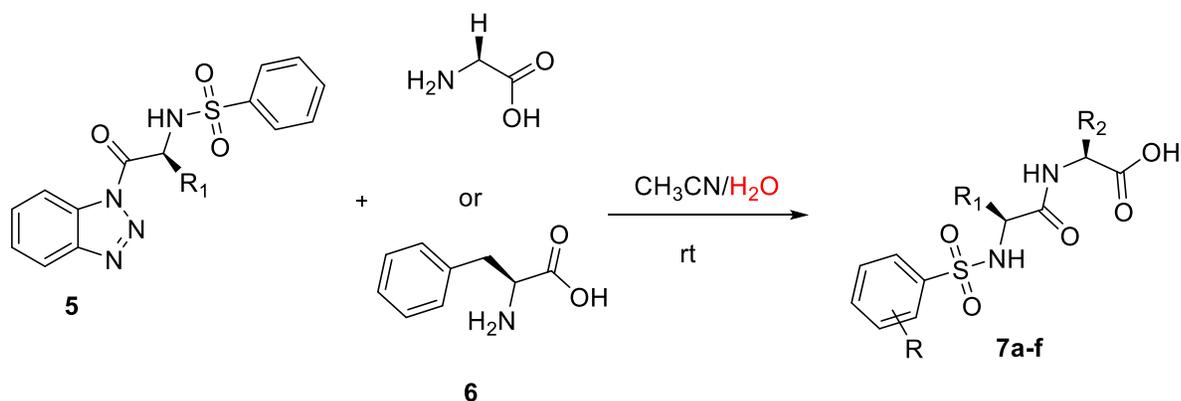
Scheme 1. Synthesis of benzotriazole–amino acid–benzenesulfonamide conjugates (**5a-h**).

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

Reactants	Products	Yield (%)	mp (°C)/ (Lit. mp)
<i>L</i> -Val-OH	PhSO ₂ Val	87	143-144/(143.6-143.8)
<i>L</i> -Ile-OH	PhSO ₂ Ile	78	150-151/(148.0-148.70)
<i>L</i> -Leu-OH	PhSO ₂ Leu	89	104-106/(105.6-105.9)
<i>L</i> -Met-OH	PhSO ₂ Met	85	151-153
Gly-OH	PhSO ₂ Gly	91	169-171/(170.8-171.4)
<i>L</i> -Phe-OH	PhSO ₂ Phe	69	129.1-129.2
<i>L</i> -Ala-OH	PhSO ₂ Ala	56	120-121
<i>L</i> -Val-OH	4-ClPhSO ₂ Val	81	115-116

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

Reactant	Product	Yield (%)	mp (°C)
PhSO ₂ Val	PhSO ₂ Val-Bt	68	146-147 °C
PhSO ₂ Ile	PhSO ₂ Ile-Bt	64	133-134 °C
PhSO ₂ Leu	PhSO ₂ Leu-Bt	63	142-143 °C
PhSO ₂ Met	PhSO ₂ Met-Bt	48	141-142 °C
PhSO ₂ Gly	PhSO ₂ Gly-Bt	42	185-186 °C
PhSO ₂ Phe	PhSO ₂ Phe-Bt	53	182-183 °C
PhSO ₂ Ala	PhSO ₂ Ala-Bt	56	153-154 °C
4-ClPhSO ₂ Val	4-ClPhSO ₂ Val-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%. Compounds **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, ¹H NMR and ¹³C 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 compounds. 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*-methionine, glycine, *L*-phenylalanine and *L*-alanine) (1.5 mmol) was added to sodium carbonate (Na₂CO₃, 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 completion 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 compounds (**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 completion 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 ($\text{C}=\text{O}_{(\text{amide})}$); 1335 ($\text{SO}_2\text{-N}$). ^1H NMR (400 MHz, DMSO) δ 8.89 (d, J = 9.1 Hz, 1H, -NH-), 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, -NHCHCH(CH_3) $_2$), 2.28–2.19 (m, 1H, -NHCHCH(CH_3) $_2$), 0.94 (d, J 6.7 Hz, 3H, -NHCHCH(CH_3) $_2$), 0.85 (d, J 6.7 Hz, 3H, -NHCHCH(CH_3) $_2$). ^{13}C NMR (101 MHz, DMSO) δ 171.2 ($\text{C}=\text{O}_{(\text{amide})}$), 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 $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$ calcd. 358.1100, found 381.0997 $[\text{M}+\text{Na}]^+$.

Bt-Ile-Benzenesulfonamide (5b). Yield: 64%, Mp 133-134 °C. IR (KBr) cm^{-1} : 3278 (NH); 2968 (C-H Aliphatic); 1731 ($\text{C}=\text{O}_{(\text{amide})}$); 1335 ($\text{SO}_2\text{-N}$). ^1H 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, -NHCHCH(CH_3) CH_2CH_3), 2.09–2.03 (m, 1H, -NHCHCH(CH_3) CH_2CH_3), 1.61–1.55 (m, -NHCHCH(CH_3) CH_2CH_3), 1.35–1.24 (m, 1H, -NHCHCH(CH_3) CH_2CH_3), 0.82 and 0.79 (2d, J 4.0 ve 8.0 Hz, 6H, -NHCHCH(CH_3) CH_2CH_3). ^{13}C NMR (101 MHz, DMSO) δ 171.5 ($\text{C}=\text{O}_{(\text{amide})}$), 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(NHCH), 37.3(CH_2CH_3), 24.5 (CHCH_3), 15.5 (CH_3), 10.5 (CH_3). HRMS m/z for $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$ calcd. 372.1256, found 395.1150 $[\text{M}+\text{Na}]^+$.

Bt-Leu-Benzenesulfonamide (5c). Yield: 63%, mp 142-143 °C. IR (KBr) cm^{-1} : 3280 (NH); 2964 (C-H Aliphatic); 1734 ($\text{C}=\text{O}_{(\text{amide})}$); 1334 ($\text{SO}_2\text{-N}$). ^1H 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, NHCHCH $_2$ CH(CH_3) $_2$), 1.74–1.57 (m, 3H, -NHCHCH $_2$ CH(CH_3) $_2$), 0.83 (d, J 6.2 Hz, 3H, NHCHCH $_2$ CH(CH_3) $_2$), 0.72 (d, J 6.1 Hz, 3H, NHCHCH $_2$ CH(CH_3) $_2$). ^{13}C NMR (101 MHz, DMSO) δ 171.8, ($\text{C}=\text{O}$) $_{(\text{amide})}$, 145.9, 140.7, 133.0, 131.7, 130.8, 129.5, 127.4, 126.8, 120.7, 114.3 (Ar-C), 53.9 (NHCH), 40.6 (CHCH_2), 24.6[$\text{CH}(\text{CH}_3)$] $_2$, 23.2 (CH_3) and 20.9 (CH_3). HRMS m/z for $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$ calcd. 358.1100, found 395.1149 $[\text{M}+\text{Na}]^+$.

Bt-Met-Benzenesulfonamide (5d). Yield: 48%, Mp 141-142 °C. IR (KBr) cm^{-1} : 3272 (NH); 2916 (C-H Aliphatic); 1734 ($\text{C}=\text{O}_{(\text{amide})}$); 1333 ($\text{SO}_2\text{-N}$). ^1H 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, -NHCHCH $_2$ CH $_2$ SCH $_3$), 2.63–2.54 (m, 1H, -NHCHCH $_2$ CH $_2$ SCH $_3$), 2.46–2.36 (m, 1H, -NHCHCH $_2$ CH $_2$ SCH $_3$), 2.19 (dt, J 11.7, 7.7 Hz, 1H, -NHCHCH $_2$ CH $_2$ SCH $_3$), 2.02 (dd, J 14.9, 5.4 Hz, 1H, -NHCHCH $_2$ CH $_2$ SCH $_3$), 1.94 (s, 3H, -NHCHCH $_2$ CH $_2$ SCH $_3$). ^{13}C NMR (101 MHz, DMSO) δ 171.3 ($\text{C}=\text{O}_{(\text{amide})}$), 145.9, 140.9, 133.0, 131.6, 130.9, 129.5, 127.3, 126.8, 120.7, 114.4 (Ar-C), 54.4 (NHCH), 31.1 (CHCH_2), 29.6 (SCH $_2$), 14.6 (CH_3). HRMS m/z for $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_3\text{S}_2$ $[\text{M}+\text{Na}]^+$ calcd. 390.0820, found 413.0712 $[\text{M}+\text{Na}]^+$.

Bt-Gly-Benzenesulfonamide (5e). Yield: 42 %, Mp 185-186 °C. IR (KBr) cm^{-1} : 3273 (NH); 2971 (C-H Aliphatic); 1732 ($\text{C}=\text{O}_{(\text{amide})}$); 1332 ($\text{SO}_2\text{-N}$). ^1H 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, -NHCH $_2$ -). ^{13}C NMR (101 MHz, DMSO) δ 168.3 ($\text{C}=\text{O}_{(\text{amide})}$), 145.7, 141.0, 133.1, 131.5, 131.0, 129.7, 127.1, 127.0, 120.6, 114.1 (Ar-C), 45.98 (NHCH). HRMS m/z for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$ calcd. 316.0630, found 339.0527 $[\text{M}+\text{Na}]^+$.

Bt-Phe-Benzenesulfonamide (5f). Yield: 53%, Mp 182-183 °C. IR (KBr) cm^{-1} : 3229 (NH); 2967 (C-H Aliphatic); 1731 ($\text{C}=\text{O}_{(\text{amide})}$); 1335 ($\text{SO}_2\text{-N}$). ^1H 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, -

NHCHCH₂Ph), 3.29 (dd, *J* 13.8, 5.3 Hz, 1H, -NHCHCH₂Ph), 3.01 (dd, *J* 13.8, 9.5 Hz, 1H, -NHCHCH₂Ph). ¹³C 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 (NHCH), 37.9 (CHCH₂). HRMS *m/z* for C₂₁H₁₈N₄O₃S [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 (SO₂-N). ¹H 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, -NHCHCH₃), 1.49 (d, *J* 7.1 Hz, 3H, NHCHCH₃). ¹³C 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 (NHCH), 18.6 (CHCH₃). HRMS *m/z* for C₁₅H₁₄N₄O₃S [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 (SO₂-N). ¹H 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, -NHCHCH(CH₃)₂), 2.26 (dq, *J* 13.6, 6.8 Hz, 1H, -NHCHCH(CH₃)₂), 0.97 (d, *J* 6.7 Hz, 3H, -NHCHCH(CH₃)₂), 0.87 (d, *J* 6.7 Hz, 3H, -NHCHCH(CH₃)₂). ¹³C 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 (NHCH), 31.3 (CHCH), 19.4 (CH₃), 18.5 (CH₃). HRMS *m/z* for C₁₇H₁₇ClN₄O₃S [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 (glycine or *L*-phenylalanine) (1.0 equiv.) in acetonitrile–water (CH₃CN/H₂O) 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 temperature until completion, 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 Na₂SO₄, 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 (SO₂-N). ¹H 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, -NHCH₂CO and -NHCHCO), 1.61–1.55 (m, 1H, NHCH(CH(CH₃)CH₂CH₃), 1.51–1.44 (m, 1H, NHCH(CH(CH₃)CH₂CH₃), 1.12–1.01 (m, 1H, NHCH(CH(CH₃)CH₂CH₃), 0.76 (dd, *J* 16.1, 7.2 Hz, 6H, NHCH(CH(CH₃)CH₂CH₃). ¹³C NMR (101 MHz, DMSO) δ 171.3, 170.7 (2C=O_(amide)) 141.5, 132.6, 129.1, 127.1 (Ar-C), 60.9 (NHCH₂), 40.9 (NHCH), 37.3 (CH₂CH₃), 24.7 (NHCHCH), 15.4 (CH₃), 11.0 (CH₃). HRMS *m/z* for C₁₄H₂₀N₂O₅S [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 (SO₂-N). ¹H 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, NHCHCONHCH₂-), 1.83 (dq, *J* 13.6, 6.8 Hz, 1H, -CH(CH₃)₂), 0.82 (d, *J* 6.7 Hz, 6H, -CH(CH₃)₂). ¹³C 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 (NHCH₂), 40.8 (NHCH), 31.3 (CH), 19.4 (CH₃), 18.8 (CH₃). HRMS *m/z* for C₁₃H₁₇ClN₂O₅S [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 (SO₂-N). ¹H 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, NHCH(COOH)CH₂Ph), 3.42–3.39 (m, 2H, NHCHCH(CH₃)CH₂CH₃ and NHCH(COOH)CH₂Ph), 2.88–2.85 (m, 1H, NHCH(COOH)CH₂Ph), 1.56–1.49 (m, 1H, NHCHCH(CH₃)CH₂CH₃), 1.30–1.25 (m, 1H, NHCHCH(CH₃)CH₂CH₃), 0.99–0.95 (m, 1H, NHCHCH(CH₃)CH₂CH₃), 0.67–0.60 (m, 6H,

NHCHCH(CH₃)CH₂CH₃). ¹³C 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 (NHCH), 55.9 (NHCH), 38.2 (CHCH₂Ph), 37.7 (CHCH), 24.5 (CH₂CH₃), 15.6 (CH₃), 11.5 (CH₃). HRMS *m/z* for C₂₁H₂₆N₂O₅S [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 (SO₂-N). ¹H 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, -NHCHCH₃), 3.65 (d, *J* 5.7 Hz, 2H, NHCH₂COOH), 1.03 (d, *J* 7.1 Hz, 3H, -NHCHCH₃). ¹³C 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 (NHCH), 41.0 (NHCH₂), 19.1(CH₃). HRMS *m/z* for C₁₁H₁₄N₂O₅S [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 (SO₂-N). ¹H 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, NHCH₂COOH), 3.52–3.42 (m, 1H, -NHCHCH(CH₃)₂), 1.90–1.84 (m, 1H, -NHCHCH(CH₃)₂), 0.85 (dd, *J* 6.7, 2.5 Hz, 6H, -NHCHCH(CH₃)₂). ¹³C 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(NHCH₂), 40.9 (NHCH), 31.2 NHCHCH(CH₃)₂, 19.3 (CH₃), 18.7 (CH₃). HRMS *m/z* for C₁₃H₁₈N₂O₅S [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 (SO₂-N). ¹H 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, NHCH(COOH)CH₂Ph), 3.75 (dd, *J* 15.6, 7.8 Hz, 1H, NHCHCH₂CH(CH₃)₂), 2.92 (dd, *J* 13.8, 5.8 Hz, 1H, NHCH(COOH)CH₂Ph), 2.80 (dd, *J* 13.8, 7.8 Hz, 1H, NHCH(COOH)CH₂Ph), 1.55–1.46 (m, 1H, NHCHCH₂CH(CH₃)₂), 1.26 (t, *J* 7.1 Hz, 2H, NHCHCH₂CH(CH₃)₂), 0.78 (d, *J* 6.6 Hz, 3H, NHCHCH₂CH(CH₃)₂), 0.67 (d, *J* 6.5 Hz, 3H, NHCHCH₂CH(CH₃)₂). ¹³C 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 (NHCH), 53.9 (NHCH), 42.0 (NHCH₂), 37.1 [CH(CH₃)₂], 24.1 (CH₂CH), 23.3 (CH₃), 21.7 (CH₃).

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Supplementary Material

Supplementary Files contained all the data obtained in this work.

References

1. McKellar, Q. A.; Scott, E. W, *J. Vet. Pharmacol. Ther.* 1990, 13, 223e247.
<http://doi:10.1111/j.1365-2885.1990.tb00773.x>
2. Piccionello, A. P.; Guarcello, A, *Curr. Bioact. Comp d.* 2010, 6, 266-283.

- <https://doi.org/10.2174/157340710793237308>
3. Suma, B.V.; Natesh, N.N.; Madhavan, V, *J. Chem. Pharm. Res.* 2011, 3, 375-381.
<https://www.researchgate.net/publication/279897455>
 4. Zhang, H. Z.; Gan, L. L.; Wang, H.; Zhou, *Mini-Rev. Med. Chem.* 2017, 17, 122–166.
<https://doi.org/10.2174/1389557516666160630120725>
 5. Kelemen, H.; Orgovan, G.; Szekely-Szentmiklosi, B, *Acta Pharm. Hung.* 2016, 86, 85–98. PMID: 29489080
 6. Carta, A.; Palomba, M.; Briguglio, I.; Corona, P.; Piras, S.; Jabes, D.; Guglierame, P.; Moliccotti, P.; Zanetti, S, *Eur. J. Med. Chem.* 2011, 46, 320-326.
<https://doi.org/10.1016/j.ejmech.2010.11.020>
 7. Carta, A.; Bua, A.; Corona, P.; Piras, S.; Briguglio, I.; Moliccotti, P.; Zanetti, S.; Laurini, E.; Aulic, S.; Fermeglia, M.; Pricl, S., *Eur. J. Med. Chem.* 2019, 161, 399–4
<https://doi.org/10.1016/j.ejmech.2018.10.031>
 8. Ibba, R.; Piras, S.; Corona, P.; Riu, F.; Loddo, R.; Delogu, I.; Collu, G.; Sanna, G.; Caria, P.; Dettori, T.; Carta, A., *Front. Chem.* 2021, 9, 660424.
<https://doi.org/10.3389/fchem.2021.660424>
 9. Riu, F.; Sanna, L.; Ibba, R.; Piras, S.; Bordoni, V.; Scorciapino, M.A.; Lai, M.; Sestito, S.; Bagella, L.; Carta, A, *Eur. J. Med. Chem.* 2021, 222, 113590.
<https://doi.org/10.1016/j.ejmech.2021.113590>
 10. Riu, F.; Ibba, R.; Zoroddu, S.; Sestito, S.; Lai, M.; Piras, S.; Sanna, L.; Bordoni, V.; Bagella, L.; Carta, A, *J. Enzyme. Inhib. Med. Chem.* 2022, 37, 2223–2240.
<https://doi.org/10.1080/14756366.2022.2111680>
 11. Loddo, R.; Novelli, F.; Sparatore, A.; Tasso, B.; Tonelli, M.; Boido, V.; Sparatore, F.; Collu, G.; Delogu, I.; Giliberti, G.; P, La Colla., *Bioorg. Med. Chem.* 2015, 23, 7024–7034.
<http://dx.doi.org/10.1016/j.bmc.2015.09.035>
 12. Plewe, M.B.; Gantla, V.R.; Sokolova, N.v.; Shin, Y.-J.; Naik, S.; Brown, E.R.; Fetsko, A.; Zhang, L.; Kalveram, B.; Freiberg, A.N.; Henkel, G.; McCormacka, K., *Bioorg. Med. Chem. Lett.* 2021, 41, 127983.
<https://doi.org/10.1016/j.bmcl.2021.127983>
 13. Yu, K.-L.; Zhang, Y.; Civiello, R.L.; Kadow, K.F.; Cianci, C.; Krystal, M.; Meanwell, N.A, *Bioorg. Med. Chem. Lett.* 2003, 13, 2141–2144.
[https://doi.org/10.1016/S0960-894X\(03\)00383-4](https://doi.org/10.1016/S0960-894X(03)00383-4)
 14. Ibba, R.; Carta, A.; Madeddu, S.; Caria, P.; Serreli, G.; Piras, S.; Sestito, S.; Loddo, R.; Sanna, G, *Viruses* 2021, 13, 58.
<https://doi.org/10.3390/v13010058>
 15. Bivacqua, R.; Barreca, M.; Spanò, V.; Raimondi, M.V.; Romeo, I.; Alcaro, S.; Andrei, G.; Barraja, P.; Montalbano, A, *Eur. J. Med. Chem.* 2023, 249, 115136.
<https://doi.org/10.1016/j.ejmech.2023.115136>
 16. Jamkandi. C.M.; Disouza. J.I, *Intern. J. Pharm. Pharm. Sci.* 2013, 5, 249-253.
<https://www.researchgate.net/publication/245536656>
 17. Scott, K.A.; Njardarson, J.T, *Top Curr Chem (Cham).* 2028, 5, 01, 376.
<https://doi.org/10.1007/s41061-018-0184-5>
 18. Das, P.; Delost, M.D.; Qureshi, M.H.; Smith, D.T.; Njardarson, J.T, *J Med Chem.* 2019, 62, 09, 4265–4311.
<https://doi.org/10.1021/acs.jmedchem.8b01610>
 19. Devendar, P.; Yang, G.F, *Top Curr Chem (Cham).* 2017, 6, 82, 375.
<https://doi.org/10.1007/s41061-017-0169-9>

20. Buravchenko, G.I.; Scherbakov, A.M.; Krymov, S.K.; Salnikova, D.I.; Zatonsky, G.V.; Schols, D.; Vullo, D.; Supuran, C.T.; Shchekotikhin, A.E., *RSC Adv.*, 2024, 14, 23257.
<https://doi.org/10.1039/D4RA04548C>
21. Hatem, E.Gafer.; Mahmoud, S.A.; El-Sedik, M. S.; TarekAysha, Mohamed H.Abdel-Rhman and Ehab Abdel-latif, *Sci. Rep.* 2024, 14, 10973.
<https://doi.org/10.1038/s41598-024-60908-8>
22. Hamad, A.; Chen, Y.; Khan, M.A.; Jamshidi, S.; Saeed, N.; Clifford, M.; Hind, C.; Sutton, M.J.; Rahman, K.M., *MicrobiologyOpen*. 2021, 10:e1218.
<https://doi.org/10.1002/mbo3.1218>
23. Bredael, K., Geurs, S., Clarisse, D, De Bosscher, K., D'hooghe, M., *J Chem.* 2022, 2022.
<https://doi.org/10.1155/2022/2164558>
24. Zong, Z., Yang, J., Yuan, L., Wang, X., Chen, J. Q., Wu, J., *Org Lett.* 2024, 26, 40, 8626-8631.
<https://doi.org/10.1021/acs.orglett.4c03325>
25. Hall, C.D.; Panda, S. S., *Adv. Heterocyclic Chem.* 2016, 119, 1-23.
<https://doi.org/10.1016/bs.aihch.2016.01.001>
26. Katritzky, A.R.; Rachwal, S.; Hitchings, G.J., *Tetrahedron*, 1991,47, 2683–2732.
[https://doi.org/10.1016/S0040-4020\(01\)87080-0](https://doi.org/10.1016/S0040-4020(01)87080-0)
27. Ezugwu, J.A.; Okoro, U.C.; Ezeokonkwo, M.A.; Bhimapaka, C.; Okafor, S.N.; Ugwu, D.I. and Ugwuja, D.I, *Arch. Pharm.* 2020, 353, 7, 2000074.
<https://doi.org/10.1002/ardp.202000074>
28. Attah, S.I.; Okoro, U.C.; Singh, S.P.; Eze, C.C.; Ibeji, C.U.; Ezugwu, J.A.; Okenyeka, O.U.; Ekoh, O.; Ugwu, D.I.; Eze, F.U., *J. Mol. Struc.*. 2022, 1264, 133280.
<https://doi.org/10.1016/j.molstruc.2022.133280>
29. Küçükbay, H.; Buğday, N.; Küçükbay, F.Z.; Berrino, E.; Bartolucci, G.; Del, P.S.; Capasso, C.; Supuran, C.T., *Bioorg. Chem.* 2019; 83, 414–23.
<https://doi.org/10.1016/j.bioorg.2018.11.003>
30. Buğday, N.; Küçükbay, F.Z.; Küçükbay, H.; Bua, S.; Bartolucci, G.; Leitans. J.; Kazaks, A.; Tars, K.; Supuran, C.T., *Bioorg. Chem.* 2018, 81, 311–8.
<https://doi.org/10.1016/j.bioorg.2018.08.032>
31. Küçükbay, F.Z.; Küçükbay, H.; Tanc, M.; Supuran, C.T., *J. Enzyme. Inhib. Med. Chem.* 2016, 31(6), 1476–83.
<https://doi.org/10.3109/14756366.2016.1147438>
32. Ugwu, D.I.; Okoro, U.C.; Ukoha, P. O.; Okafor, S.; Ibezim, A and Kumar, N. M, *Eur. J. Med. Chem.* 2017, 135, 349-369.
<https://doi.org/10.1016/j.ejmech.2017.04.029>

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