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A Facile and Eco-Friendly Method for the Synthesis of Sulfonamide and Sulfonate Carboxylic Acid Derivatives—X-ray Structure, Hirshfeld Analysis and Spectroscopic Characterizations

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Abstract: The search for a simple and efficient method for the synthesis of sulfonamide and sulfonate derivatives under mild and eco-friendly conditions is of continuing interest. Sulfonyl chlorides are still the best choice as starting materials for the preparation of target products. Here, we report a simple, efficient and eco-friendly method for the synthesis of sulfonamide and sulfonate carboxylic acid derivatives under green conditions using water and sodium carbonate as HCl scavengers to produce the products with high yields and purities. Two derivatives, 4-(tosyloxy)benzoic acid (**5a**) and 4-((4-methylphenyl)sulfonamido)benzoic acid (**5b**), were reacted with 2-morpholinoethan-1-amine under green conditions, where OxymaPure/diisopropylcarbodiimide (DIC) was used as a coupling reagent and 2-MeTHF as a solvent to give the target product with high yield and purity. nuclear magnetic resonance (NMR) and elemental analysis confirmed the structures of all obtained products. X-ray crystallography confirmed the structures of products **4b**, **4c** and **7a**. The molecular packing of the three compounds (**4b**, **4c** and **7a**) was analyzed using Hirshfeld topology analysis. Mainly, H ... O hydrogen bonding interactions dominated the packing. These methods of preparation and coupling merit further attention for the development of new derivatives that might have significant biological applications.

Keywords: sulfonamides; sulfonates; green synthesis; X-ray; Hirshfeld

1. Introduction

Since the commercialization of Prontosil [1] as a drug in 1935, intense surveys have been made and a huge number of sulfonamide derivatives and their biological applications have been reported [2–11]. Several methods for the synthesis of sulfonamide from different substrates have been reported, for example, using sulfonyl chloride and amines [12,13] using a chlorinating agent with the corresponding sulfurated starting materials [14–17] or using non-conventional methods such as transition metals [18] or Grignard reagents [19]. In addition, all the reported methods use organic

solvents such as dichloromethane and/or toxic activating agents such as thionyl chloride for the synthesis of sulfonamides. Furthermore, multi-step synthesis methods that are time-consuming for purifications are usually needed [20].

Searching for a simple and efficient method for the synthesis of novel sulfonamides under mild conditions is of ongoing concern [21,22]. The use of sulfonyl chlorides and amines as starting materials still is the method of choice [23], where organic solvents and organic amine bases are used to scavenge the HCl generated from the reaction [24,25]. An elevated temperature is required in some cases, especially for the less reactive amines. Other protocol is the modified Schotten–Baumann conditions [26], where a two-phase system of organic solvents and basic aqueous solution (Na_2CO_3 or NaOH) is used [27]. Due to the hydrolysis of sulfonyl chloride under these conditions, excess reagent must be used to ensure a complete reaction. Furthermore, the isolation and purification of the sulfonamide is not always straightforward. Recently, water has been used as a green solvent for several chemical reactions because of safety and environmental concerns [28,29].

Herein, we report a facile, environmentally benign method for sulfonamide amino acid and sulfonate acid synthesis at room temperature using water in the presence of Na_2CO_3 as HCl scavengers following the reported literature [30]. The desired sulfonamide and sulfonate carboxylic acid derivatives are easily isolated in excellent yields and purities.

In addition, here, we report the coupling reaction of sulfonamide and sulfonate carboxylic acid derivatives with amine under eco-friendly conditions using our previously reported method [31–34]. This method for the synthesis of sulfonamide and sulfonate carboxylic acid derivatives eliminates the use of expensive toxic organic solvents and organic bases. In addition, isolation and purification of the products only involves filtration and no waste, which makes it ideal for green chemistry. The structures of two sulfonamides, carboxylic acid and one of the coupled products were confirmed by X-ray single crystal structure measurements.

2. Experimental

2.1. Materials and Methods

p-Toluenesulfonyl chloride, *p*-hydroxybenzoic acid, *p*-aminobenzoic acid, 2-morpholinoethan-1-amine and amino acids were purchased from commercial sources and were used without further purification. Melting points were determined with a Mel-Temp apparatus (Sigma-Aldrich Chemie GmbH, 82024 Taufkirchen, Germany) and are uncorrected. Magnetic resonance spectra (^{1}H NMR and ^{13}C NMR spectra) were recorded on a JEOL 400 MHz spectrometer (JEOL, Ltd., Tokyo, Japan). Elemental analyses were performed on Perkin-Elmer 2400 elemental analyzer (Perkin-Elmer, Inc., 940 Winter Street, Waltham, MA, USA).

2.2. X-ray Measurements

Single crystals for compounds **4b**, **4c** and **7a** were obtained by slow evaporation from their solvent of crystallization (ethylacetate-n-hexane; 4:6) at room temperature. The crystallographic measurements of **4b**, **4c** and **7a** were collected on a Bruker D8 Quest diffractometer with graphite monochromated Mo-Kα radiation at λ = 0.71073 Å and 293 (2) K using a photon detector. Cell refinement and data reduction were carried out using SAINT [35], and a multi-scan absorption correction was made using SADABS [36]. All calculations were performed using the SHELXTL program package [37,38]. The crystal data and structure refinement details are listed in Table 1. The CIF files with the Cambridge Crystallographic Data Center CCDC numbers 1524756 (**4b**), 1524754 (**4c**) and 1524879 (**7a**) contain the supplementary crystallographic data for the measured compounds. This can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. In addition, Crystal Explorer 3.1 program [39] was used to quantitatively analyze the different intermolecular interactions in the studied compounds [40].

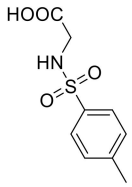
Table 1. Crystal data and structure refinement for the studied complexes.

	4b	**4c**	**7a**
Empirical formula	$C_{10}H_{13}NO_4S$	$C_{11}H_{15}NO_4S$	$C_{20}H_{24}N_2O_5S$
Formula weight	243.27	257.3	404.47
Temperature/K		293(2)	
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	P-1	$P2_1/c$	$P2_1/c$
a/Å	5.2492(4)	10.9634(7)	17.4251(18)
b/Å	10.7610(7)	5.4574(3)	5.2003(5)
c/Å	11.6185(8)	21.2783(14)	22.117(2)
α/°	115.002(2)	90	90
β/°	101.701(2)	100.633(3)	99.179(5)
γ/°	90.120(2)	90	90
Volume/Å^3	579.57(7)	1251.26(13)	1978.5(3)
Z	2	4	4
ρ_{calc} g/cm^3	1.394	1.366	1.358
μ/mm^{-1}	0.278	0.261	0.198
F(000)	256	544	856
Crystal size/mm^3	0.51 × 0.28 × 0.25	0.56 × 0.42 × 0.05	0.03 × 0.09 × 0.65
Radiation		Mo-Kα (λ = 0.71073 Å)	
2Θ range for data collection/°	4.2 to 66.42	4.9 to 52	4.08 to 50.00
Index ranges	$-8 \leq h \leq 8$ $-16 \leq k \leq 16$ $-17 \leq l \leq 17$	$-12 \leq h \leq 13$ $-6 \leq k \leq 6$ $-26 \leq l \leq 26$	$-20 \geq h \leq 20$ $-6 \leq k \leq 6$ $-26 \leq l \leq 26$
Reflections collected	33,710	13,336	39,573
Independent reflections	4428 [R_{int} = 0.0582]	2455 [R_{int} = 0.0906]	3479 [R_{int} = 0.2468]
Data/restraints/parameters	4428/0/154	2455/0/163	3479/0/254
Goodness-of-fit on F^2	1.019	1.028	1.013
Final R indexes [I ≥ 2σ (I)]	R_1 = 0.0558, wR_2 = 0.1281	R_1 = 0.0708, wR_2 = 0.1726	R_1 = 0.0761, wR_2 = 0.1492
Final R indexes [all data]	R_1 = 0.1017, wR_2 = 0.1478	R_1 = 0.1027, wR_2 = 0.1919	R_1 = 0.1787, wR_2 = 0.1967
Largest diff. peak/hole/e Å^{-3}	0.40/−0.29	0.42/−0.36	−0.31/0.40
CCDC	1524756	1524754	1524879

2.3. General Method for Synthesis of Sulfonamide Carboxylic Acid **4a-c** *and* **5a-c**

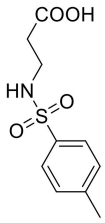
p-Toluenesulfonyl chloride (12 mmol) was added over a period of time of 15 min to an aqueous mixture of amino acid or hydroxyl acid (10 mmol) and Na_2CO_3 (12 mmol) in water (50 mL) at 0 °C. After complete addition, the reaction mixture was stirred for a further 4–6 h at room temperature and then acidified at 0 °C with 10% HCl. The precipitate was collected by filtration, washed with water, dried, and then recrystallized from ethylacetate-n-hexane to produce the target product.

2.3.1. 2-(4-Methylphenylsulphonamido) Acetic Acid, **4a** (Figure S1, Supplementary Materials)



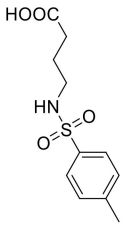
White solid in yield 91%; mp 123–125 °C (Lit. [41] mp 89 °C, yield 81%); ^{1}H NMR (DMSO-d_6): δ = 2.36 (3H, s, –CH_3), 3.52 (2H, s, –CH_2NH), 7.36 (2H, d, *J* = 8 Hz, Ar–$H_{3'}$, $H_{5'}$), 7.65 (2H, d, *J* = 8 Hz, Ar–$H_{2'}$, $H_{6'}$), 7.91 (1H, s, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 16.8 (CH_3), 39.5 (CH_2), 122.6, 125.3, 133.5, 138.4, 166.0 (COOH) ppm. Anal. Calc. for $C_9H_{11}NO_4S$ (229.04): C, 47.15; H, 4.84; N, 6.11. Found: C, 47.32; H, 4.95; N, 6.33.

2.3.2. 3-((4-Methylphenyl)sulfonamido)propanoic Acid, **4b** (Figure S2, Supplementary Materials)



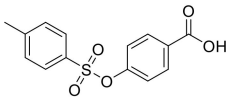
White crystals in yield 89%; mp 112–113 °C (Lit. [42] mp 118–119 °C, yield 83%); ^{1}H NMR (DMSO-d_6): δ = 2.34 (2H, t, J = 7.2Hz, –CH_2CO), 2.38 (3H, s, –CH_3), 2.88 (2H, td, J = 6 Hz, J = 6.8 Hz, –CH_2NH), 7.39 (2H, d, J = 8 Hz, Ar–$H_{3'}$, $H_{5'}$), 7.58 (1H, t, J = 6 Hz, NH), 7.67 (2H, d, J = 8 Hz, Ar–$H_{2'}$, $H_{6'}$), 12.26 (1H, s, COOH) ppm; ^{13}C NMR (DMSO-d_6): δ = 20.9 (CH_3), 34.1, 38.6 (CH_2), 126.5, 129.8, 137.3, 142.7, 172.3 (COOH) ppm. Anal. Calc. for $C_{10}H_{13}NO_4S$ (243.06): C, 49.37; H, 5.39; N, 5.76. Found: C, 49.54; H, 5.43; N, 5.92.

2.3.3. 4-((4-Methylphenyl)sulfonamido)butanoic Acid, **4c** (Figure S3, Supplementary Materials)



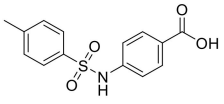
White crystals in yield 90%; mp 123–124 °C; ^{1}H NMR (DMSO-d_6): δ = 1.57 (2H, tt, J = 7.2 Hz, J = 7.6 Hz, –$CH_2$$CH_2$$CH_2$), 2.19 (2H, t, –$CH_2$CO), 2.37 (3H, s, –$CH_3$), 2.71 (2H, td, –$CH_2$NH), 7.38 (2H, d, J = 8 Hz, Ar–$H_{3'}$, $H_{5'}$), 7.52 (1H, t, J = 6 Hz, NH), 7.65 (2H, d, J = 8 Hz, Ar–$H_{2'}$, $H_{6'}$), 12.03 (1H, s, COOH) ppm; ^{13}C NMR (DMSO-d_6): δ = 20.9 (CH_3), 24.5, 30.6, 41.9 (CH_2), 126.5, 129.6, 137.6, 142.5, 173.9 (COOH) ppm. Anal. Calc. for $C_{11}H_{15}NO_4S$ (257.07): C, 51.35; H, 5.88; N, 5.44; S, 12.46. Found: C, 51.58; H, 6.01; N, 5.68; S, 12.23.

2.3.4. 4-((4-methylphenylsulfonyl)oxy)benzoic Acid, **5a** (Figure S4, Supplementary Materials)



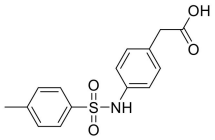
White solid in yield 94%; mp 162–163 °C (Lit. [43], yield 98%); ^{1}H NMR ($CDCl_3$): δ = 2.43 (3H, s, –CH_3), 7.08 (2H, d, J = 8.8 Hz, Ar–H), 7.31 (2H, d, J = 8.8 Hz, Ar–H), 7.70 (2H, d, J = 8 Hz, Ar–H), 8.03 (2H, d, J = 8.8 Hz, Ar–H), 10.00 (1H, s.br, COOH) ppm; ^{13}C NMR ($CDCl_3$): δ = 21.7 (CH_3), 122.5, 127.9, 128.5, 129.9, 132.0, 145.8, 153.7, 170.8 (COOH) ppm. Anal. Calc. for $C_{14}H_{12}O_5S$ (292.31): C, 57.53; H, 4.14. Found: C, 57.63; H, 4.33.

2.3.5. 4-((4-Methylphenyl)sulfonamido)benzoic Acid, **5b** (Figure S5, Supplementary Materials)



Off-white solid in yield 93%; mp 229–231 °C (Lit. [30,44], mp 231 °C, yield 98%); ^{1}H NMR (DMSO-d_6): δ = 2.29 (3H, s, –CH_3), 7.18 (2H, d, J = 8.8 Hz, Ar–H), 7.33 (2H, d, J = 8.4 Hz, Ar–H), 7.69 (2H, d, J = 8.8 Hz, Ar–H), 7.78 (2H, d, J = 8 Hz, Ar–H), 10.80 (1H, s, COOH) ppm; ^{13}C NMR (DMSO-d_6): δ = 21.0 (CH_3), 118.1, 125.5, 126.8, 129.8, 130.5, 136.4, 142.1, 143.6, 166.8 (COOH) ppm. Anal. Calc. for $C_{14}H_{13}NO_4S$ (291.06): C, 57.72; H, 4.50; N, 4.81. Found: C, 57.86; H, 4.63; N, 4.97.

2.3.6. 2-(4-((4-Methylphenyl)sulfonamido)phenyl)acetic Acid, **5c** (Figure S6, Supplementary Materials)

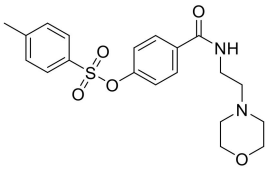


Paige colored solid in yield 88%; mp 141–143 °C (Lit. [30], yield 81%); ^{1}H NMR (DMSO-d_6): δ = 2.31 (3H, s, –CH_3), 3.43 (2H, s, –CH_2CO), 7.00 (2H, d, *J* = 8.8 Hz, Ar–H), 7.08 (2H, d, *J* = 8 Hz, Ar–H), 7.32 (2H, d, *J* = 8.4 Hz, Ar–H), 7.63 (2H, d, *J* = 8.8 Hz, Ar–H), 10.20 (1H, s, NH), 12.20 (1H, s, COOH) ppm; ^{13}C NMR (DMSO-d_6): δ = 21.6 (CH_3), 40.5 (CH_2), 120.5, 127.3, 130.3, 130.7, 131.3, 136.9, 137.4, 143.8, 173.2 (COOH) ppm. Anal. Calc. for $C_{15}H_{15}NO_4S$ (305.07): C, 59.00; H, 4.95; N, 4.59. Found: C, 59.27; H, 4.83; N, 4.23.

2.4. General Method for Preparation of **7a-b**

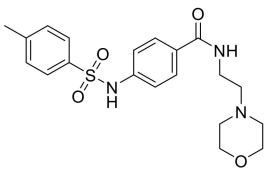
Carboxylic acid **5a** or **5b** (2 mmol) was mixed with OxymaPure (2 mmol) in 2-MeTHF (10 mL) at 0 °C followed by the addition of diisopropylcarbodiimide (DIC, 2 mmol) dropwise under stirring. The reaction mixture was preactivated for 10 min at 0 °C, and then 2-morpholinoethan-1-amine **6** (2 mmol) was added dropwise, and stirring was maintained for 1 h at the same temperature and then at room temperature for 24 h. The solvent was removed, and the crude product was dissolved in ethylacetate and washed with 1 N hydrochloric acid (2 × 10 mL), saturated solution of sodium carbonate (2 × 10 mL) and sodium chloride solution (10 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to produce the target product, which then recrystallized from ethylacetate-n-hexane to produce the target products **7a** and **b** with excellent yield and purity.

2.4.1. 4-((2-Morpholinoethyl)carbamoyl)phenyl 4-methylbenzenesulfonate, **7a** (Figure S7, Supplementary Materials)



White solid in yield 88%; mp 127–128 °C;^{1}H NMR ($CDCl_3$): *δ* = 2.42 (3H, s, –CH_3), 2.46–2.49 (4H, m, –CH_2NCH_2), 2.57 (2H, t, *J* = 5.6 Hz, *J* = 6.8 Hz, –$CH_2$$CH_2$NH), 3.50 (2H, q, *J* = 5.2 Hz, *J* = 6.4 Hz, $CH_2$$CH_2$NH), 3.70 (4H, t, *J* = 4.4 Hz, *J* = 5.2 Hz, –CH_2OCH_2), 6.75 (1H, s, NH), 7.04 (2H, dd, *J* = 8.8 Hz, *J* = 2.4 Hz, Ar–H), 7.29 (2H, d, *J* = 8.8 Hz, Ar–H), 7.68 (4H, dd, *J* = 8.8 Hz, *J* = 3.2 Hz, Ar–H); ^{13}C NMR ($CDCl_3$): δ = 21.7 (CH_3), 36.0, 53.3, 56.9, 66.9 (CH_2), 122.5, 122.6, 128.6, 129.8, 129.9, 132.1, 133.4, 145.7, 151.8, 166.2 (CONH) ppm. Anal. Calc. for $C_{20}H_{24}N_2O_5S$ (404.14): C, 59.39; H, 5.98; N, 6.93; S, 7.93. Found: C, 59.54; H, 6.04; N, 7.12; S, 7.69.

2.4.2. 4-((4-Methylphenyl)sulfonamido)-N-(2-morpholinoethyl)benzamide, **7b** (Figure S8, Supplementary Materials)



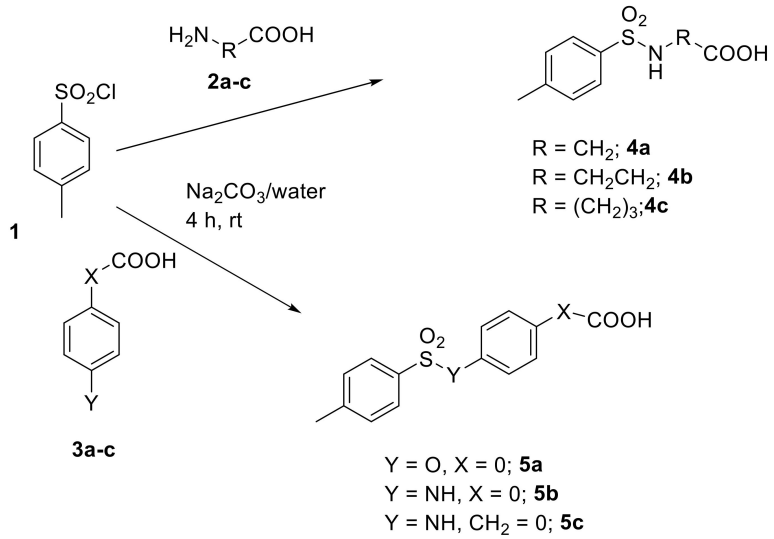
White solid in yield 84%; mp 148–150 °C; ^{1}H NMR ($CDCl_3$): *δ* = 2.37 (3H, s, –CH_3), 2.55 (4H, m, –CH_2N CH_2), 2.64 (2H, t, *J* = 5.2 Hz, *J* = 6 Hz, –$CH_2$$CH_2$NH), 3.56 (2H, q, *J* = 4.8 Hz, *J* = 5.2 Hz, *J* = 6 Hz,

- CH_2NHCO), 3.75 (4H, t, *J*= 4.4 Hz, $–CH_2OCH_2$), 6.80 (1H, s, NH), 7.15 (2H, d, *J*= 8.8 Hz, Ar–H), 7.23 (2H, d, *J* = 8 Hz, Ar–H), 7.67 (2H, d, *J* = 8.8 Hz, Ar–H), 7.70 ppm (2H, d, *J* = 8 Hz, Ar–H); ^{13}C NMR ($CDCl_3$): δ = 21.5 (CH_3), 35.9, 53.3, 57.0, 66.7 (CH_2), 119.8, 127.2, 128.3, 130.0, 136.0, 139.8, 144.2, 166.6 (CONH) ppm. Anal. Calc. for $C_{20}H_{25}N_3O_4S$ (403.16): C, 59.53; H, 6.25; N, 10.41; S, 7.95. Found: C, 59.65; H, 6.34; N, 10.21; S, 8.21.

3. Results and Discussion

3.1. Chemistry

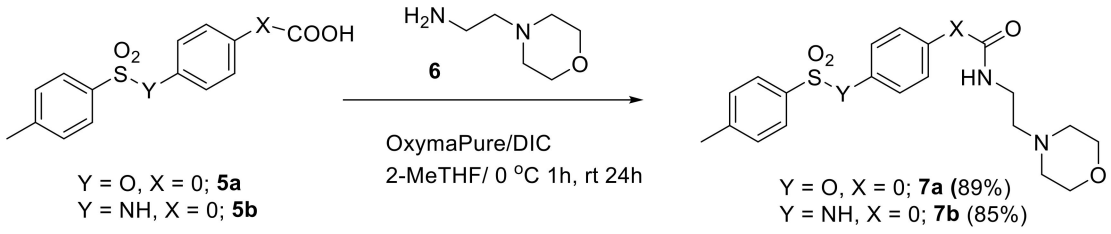
Sulfonyl chlorides are still the best choice as starting materials for the preparation of sulfonamide derivatives. A typical method involves dropwise addition of tosyl chloride **1** (1.2 equiv.) into an aqueous solution of amino acid **2a–c**, **3b-c** or *p*-hydroxybenzoic acid **3a** in the presence of Na_2CO_3 (1.2 equiv.) as HCl scavengers [30]. The desired products **4a–c** and **5a–c** were easily isolated by normal acidification with 10% HCl with excellent yields and purities as observed by spectral data (Figures S1–S6, Supplementary Materials) and single crystal X-ray diffraction (Scheme 1).



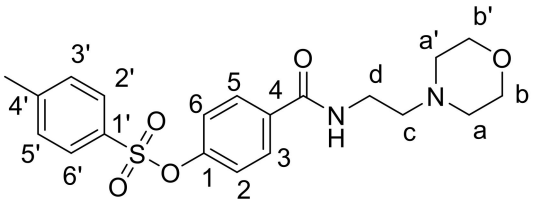
Scheme 1. Synthesis of sulfonamide amino acid and sulfonate derivatives.

Recently, 2-methyltetrahydrofuran (2-MeTHF) was reported as one of the greenest solvents for peptide synthesis [31–34]. In addition; OxymaPure was reported to be a safe and reactive additive compared to other additives used in coupling reactions [45]. Accordingly, we used the reported method DIC-OxymaPure [45] to couple the sulfonamide and sulfonate carboxylic acid derivatives **5a–b** with 2-morpholinoethan-1-amine **6**.

The reaction mixture of carboxylic acid **5a** or **5b**, OxymaPure and DIC in 2-MeTHF was preactivated for 10 min at 0 °C, followed by the addition of amine **6** at the same temperature, and then the reaction mixture was left at room temperature for 24 h to produce target product **7a** or **7b** (Scheme 2) with excellent yields and purities.



Scheme 2. Reaction of sulfonamide and sulfonate with amine using OxymaPure/DIC.



The ^{1}H NMR spectra of **7a** (Figure S7, Supplementary Materials) showed a singlet peak at δ 2.42 related to the methyl group of the tosyl moiety, a multiplet at δ 2.46–2.49 corresponding to the two methylene protons (*Ha*,*Ha′*) of the morpholine ring, a triplet at δ 2.57 corresponding to the methylene proton (*Hc*), a quartet at δ 3.50 related to the methylene protons (*Hd*), a triplet at δ 3.70 related to the two methylene groups of the morpholine moiety (*Hb*,*Hb′*), a singlet at δ 6.75 (NH), a doublet of doublet related to the two protons (*H2*,*H6*), a doublet of doublet at δ 7.04 related to the two protons (*H3′*,*H5′*), a doublet at δ 7.29 related to the two protons (*H3*,*H5*) and a doublet at δ 7.68 corresponding to the two protons (*H2′*,*H6′*). The ^{13}C NMR for **7a** showed signal peaks at δ 21.7 (CH_3), 36.0, 53.3, 56.9, 66.9 (*Cd*, *Cc*, *Ca*,*a′* and *Cb*,*b′*, respectively), 122.5 (*C2*,*6*), 128.6 (*C4*), 129.9 (*C2′*,*6′*), 132.1 (*C3*,*5*), 133.4 (*C1′*), 145.7 (*C4′*), 150.2 (*C1*) and 166.2 (CONH); the structure of **7a** was further confirmed by single crystal X-ray diffraction.

3.2. X-ray Structure Determination

The structures of two sulfonamide amino acids (**4b** and **4c**) and one of the synthesized sulfonate carboxylic acid derivative (**7a**) were confirmed using single crystal X-ray diffraction. The structure features of these compounds are presented and the crystal details as well as the refinements results are listed in Table 1. More information can be obtained from the crystallographic information files (CCDC number: 1524756, 1524754 and 1524879 for compounds **4b**, **4c** and **7a**, respectively).

The molecular structure showing the thermal ellipsoids and atom numbering of **4b** is shown in Figure 1. The structure crystallized in the triclinic crystal system and P-1 point group with Z = 2 and the asymmetric unit of this compound comprises one molecule. A list of the geometric parameters (bond distances and angles) is shown in Table 2. The packing of **4b** molecules occurs via alternative N–H . . . O and O–H . . . O hydrogen bridges (data shown in Table 3). Dimers of **4b** form by two similar N–H . . . O hydrogen bonds that occur between the NH groups as a hydrogen donor with one of the sulfonate oxygen atoms in another molecule as a hydrogen acceptor. These dimeric units are interconnected via the COOH ends by strong O–H . . . O hydrogen bridges leading to the formation of the one-dimensional hydrogen bridges shown in Figure 2.

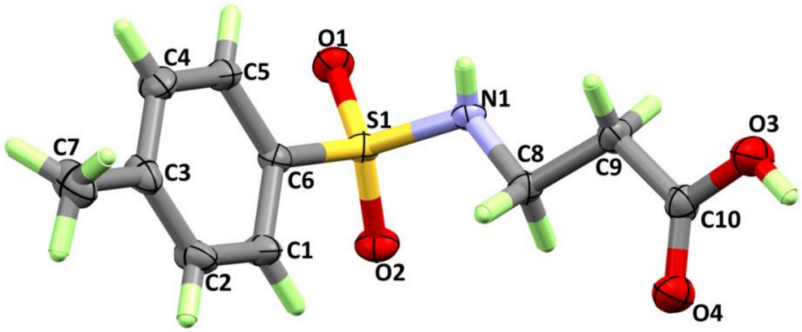


Figure 1. Atom numbering and thermal ellipsoids at a 30% probability level for **4b**.

Table 2. Bond lengths (Å) and angles (°) for **4b**.

S1–O1	1.4352(15)	S1–N1	1.6187(17)
O3–C10	1.309(3)	N1–C8	1.467(2)
C1–C6	1.387(3)	C3–C4	1.388(3)
C4–C5	1.376(3)	C8–C9	1.502(3)
S1–O2	1.4314(16)	S1–C6	1.7564(17)
O4–C10	1.207(3)	C1–C2	1.383(3)
C2–C3	1.382(3)	C3–C7	1.511(4)
C5–C6	1.388(3)	C9–C10	1.491(3)
O1–S1–O2	119.67(9)	C2–C3–C7	120.2(2)
O2–S1–N1	106.58(9)	C4–C5–C6	119.3(2)
S1–N1–C8	119.30(14)	C1–C6–C5	120.37(17)
C2–C3–C4	118.6(2)	O3–C10–O4	123.3(2)
C3–C4–C5	121.3(2)	O1–S1–C6	108.38(8)
S1–C6–C5	119.91(15)	N1–S1–C6	107.99(8)
C8–C9–C10	113.16(19)	C1–C2–C3	121.2(2)
O4–C10–C9	123.5(2)	C4–C3–C7	121.2(2)
O1–S1–N1	105.43(9)	S1–C6–C1	119.66(14)
O2–S1–C6	108.28(9)	N1–C8–C9	107.99(17)
C2–C1–C6	119.23(19)	O3–C10–C9	113.2(2)

Table 3. Hydrogen bonds [Å and °] of the studied compounds.

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
		4b		
N1–H1N1 . . . O1 [ii]	0.74(2)	2.26(2)	2.970(2)	161(2)
O3–H1O3 . . . O4 [iii]	0.79(4)	1.88(4)	2.656(3)	170(4)
		4c		
N1–H1N1 . . . O1 [iv]	0.82(5)	2.17(4)	2.963(4)	166(5)
O3–H1O3 . . . O4 [v]	0.85(5)	1.84(5)	2.668(4)	167(5)
		7a		
N1–H1B...O4 [i]	0.86	2.20	3.025(6)	159.7
C9–H9A . . . O2 [i]	0.93	2.75	3.511(7)	139.4

(i) x,-1+y,z; (ii)-x,-y,1-z; (iii)2-x,1-y,2-z; (iv) 1-x,-y,-1-z and (v) 2-x,2-y,-1-z.

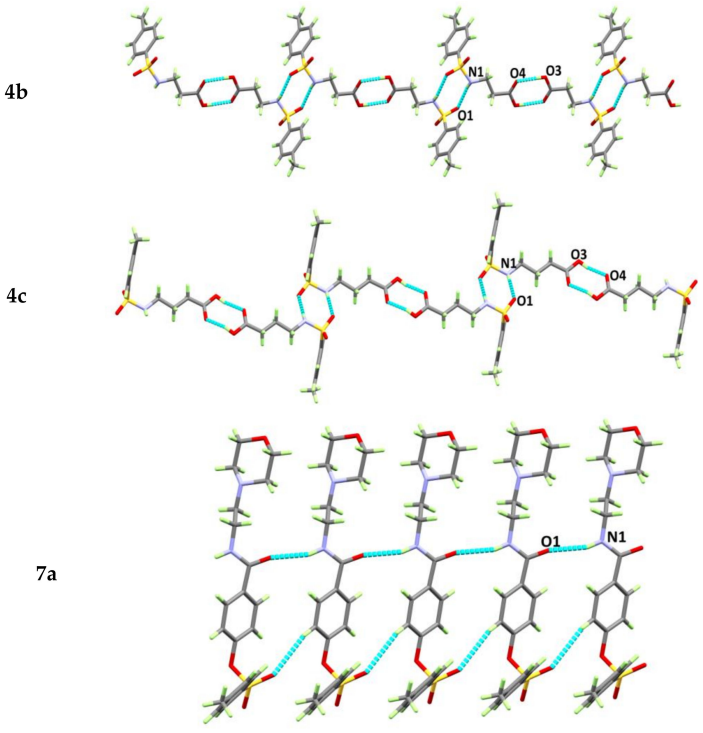


Figure 2. Hydrogen bond polymers of **4b**, **4c** and **7a**.

The molecular structure of **4c** is shown in Figure 3. The structure crystallized in the monoclinic crystal system and $P2_1/c$ point group with Z = 4 and the asymmetric unit of this compound comprises one of its molecular formula. A list of the geometric parameters (bond distances and angles) is shown in Table 4. Similar to that in **4b**, the molecular packing of **4c** molecules occurs via alternative N–H . . . O and O–H . . . O hydrogen bridges (Table 3). The only notable difference is that the hydrogen bonds are slightly shorter than those in **4b** (Table 3 and Figure 2).

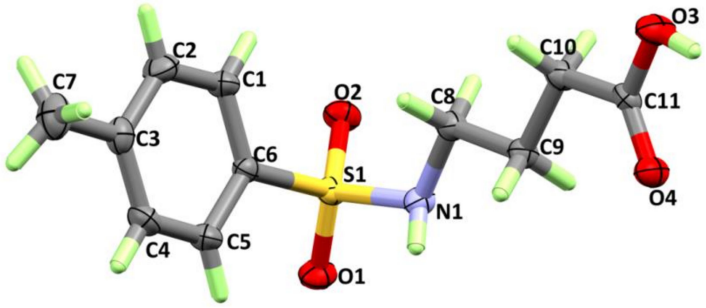


Figure 3. Atom numbering and thermal ellipsoids at a 30% probability level for **4c**.

Table 4. Bond lengths (Å) and angles (°) for **4c**.

S1–O1	1.431(3)	S1–N1	1.618(3)
O3–C11	1.323(5)	N1–C8	1.472(5)
C1–C6	1.376(5)	C3–C4	1.377(6)
C4–C5	1.370(6)	C8–C9	1.497(5)
C10–C11	1.490(5)	S1–C6	1.758(4)
S1–O2	1.426(3)	C1–C2	1.381(6)
O4–C11	1.212(4)	C3–C7	1.506(6)
C2–C3	1.395(6)	C9–C10	1.511(6)
C5–C6	1.391(5)		
O1–S1–O2	119.50(17)	C4–C5–C6	119.7(3)
O2–S1–N1	106.80(18)	C1–C6–C5	120.2(4)
S1–N1–C8	119.0(2)	C9–C10–C11	113.9(3)
C2–C3–C4	117.3(4)	O4–C11–C10	124.3(3)
C3–C4–C5	121.9(4)	O1–S1–C6	109.48(18)
S1–C6–C5	119.9(3)	N1–S1–C6	107.46(17)
C8–C9–C10	110.7(3)	C1–C2–C3	122.2(4)
O3–C11–C10	113.2(3)	C4–C3–C7	121.7(4)
O1–S1–N1	105.28(17)	S1–C6–C1	119.8(3)
O2–S1–C6	107.73(16)	N1–C8–C9	110.4(3)
C2–C1–C6	118.8(4)	O3–C11–O4	122.5(3)
C2–C3–C7	121.0(4)		

The molecular structure showing thermal ellipsoids and atom numbering of **7a** is shown in Figure 4. The structure crystallized in the monoclinic crystal system and $P2_1/c$ point group with Z = 4 and the asymmetric unit of this compound comprises one of its molecular formulae. A list of the geometric parameters (bond distances and angles) is shown in Table 5. This compound contains two aromatic rings where the angle between the planes passing through them is 46.0°, while the aliphatic morpholine ring shows the typically known chair form in the structure of **7a**. If a plane is drawn passing through the base of this chair, one could note that this plane and the central phenyl ring mean plane make an angle of 83.7°, indicating that both rings are nearly perpendicular. The packing of this compound is dominated mainly by strong N–H . . . O hydrogen bridges between the amide N–H and the carbonyl oxygen atom. In addition, the packed molecules are held together by weak C–H . . . O interactions between H9A from one of the phenyl moieties and the sulfonate O(2) atom. The hydrogen bond parameters are listed in Table 3, and presentation of the one-dimensional hydrogen bond network of **7a** is shown above in Figure 2.

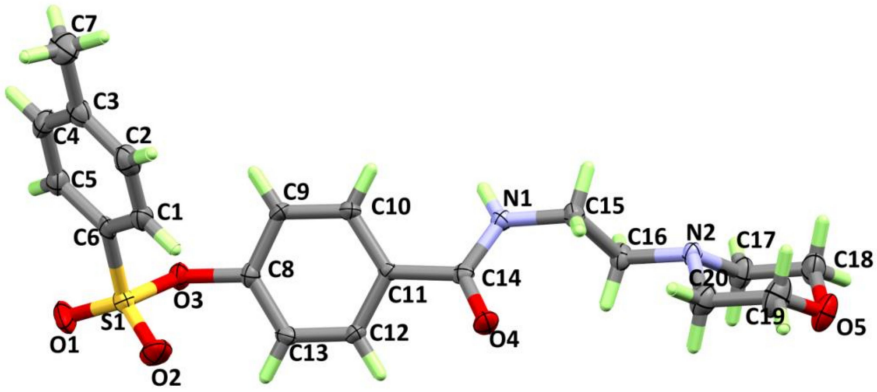


Figure 4. Atom numbering and thermal ellipsoids at a 30% probability level for **7a**.

Table 5. Bond lengths (Å) and angles (°) for **7a**.

S1–O1	1.428(4)	S1–O2	1.430(4)
O3–C8	1.422(6)	O4–C14	1.232(6)
N1–C14	1.333(6)	N1–C15	1.459(6)
N2–C20	1.443(8)	C1–C2	1.359(9)
C3–C4	1.399(9)	C3–C7	1.500(9)
C8–C9	1.372(8)	C8–C13	1.369(7)
C11–C12	1.386(6)	C11–C14	1.500(7)
C17–C18	1.495(9)	C19–C20	1.513(9)
C1–C6	1.392(9)	C2–C3	1.384(9)
C4–C5	1.379(9)	C5–C6	1.381(8)
C9–C10	1.381(8)	C10–C11	1.392(7)
C12–C13	1.365(7)	C15–C16	1.516(7)
S1–O3	1.595(4)	S1–C6	1.747(6)
O5-C18	1.416(8)	O5–C19	1.430(9)
N2–C16	1.454(6)	N2–C17	1.471(7)
O1-S1-O2	120.4(3)	O3–C8–C9	118.3(5)
O2–S1–O3	107.6(2)	C8–C9–C10	118.1(5)
S1–O3–C8	118.9(3)	C10–C11–C14	123.1(4)
C16–N2–C17	111.3(4)	C8–C13–C12	118.7(4)
C2–C1–C6	119.0(5)	N1–C14–C11	116.8(4)
C2–C3–C7	122.2(6)	N2–C17–C18	110.2(5)
C4–C5–C6	119.4(6)	N2–C20–C19	111.5(5)
C1–C6–C5	120.6(6)	O1–S1–C6	110.0(3)
C9–C8–C13	122.6(5)	O3–S1–C6	105.5(2)
C10–C11–C12	118.7(5)	C14–N1–C15	121.6(4)
C11–C12–C13	121.2(5)	C17–N2–C20	107.0(4)
O4–C14–C11	120.7(4)	C2–C3-C4	117.9(6)
N2–C16–C15	110.5(4)	C3-C4–C5	120.8(6)
O5–C19–C20	110.8(5)	S1–C6–C5	118.8(5)
O1–S1–O3	103.4(2)	O3–C8–C13	119.1(4)
O2–S1–C6	108.9(3)	C9–C10–C11	120.7(5)
C18–O5–C19	110.0(5)	C12–C11–C14	118.2(4)
C16–N2–C20	111.3(4)	O4–C14–N1	122.5(5)
C1–C2–C3	122.3(6)	N1–C15–C16	113.1(4)
C4–C3–C7	119.9(5)	O5–C18–C17	111.6(5)
S1–C6–C1	120.6(4)		

3.3. Hirshfeld Analysis

In order to quantify the most important intermolecular interactions in the studied compounds, we performed a Hirshfeld topology analysis (Figure 5). The intense red spots in the d_{norm} maps of the studied crystals indicate the presence of significantly short intermolecular contacts compared to the van der Waal sum of the two elements sharing this interaction. These red spots appeared as

sharp spikes in the corresponding fingerprint plots and were found to be related to the polar O . . . H hydrogen bonding interactions (region a). The other less important intermolecular interactions appeared as faded red spots in the d_{norm} map, and the broad peaks in the fingerprint plots are due to the hydrophobic C . . . H and H . . . H interactions (regions b and c). Full quantitative determination of all possible intermolecular contacts is graphically presented in Figure 6. It is clear that the H . . . H, O . . . H and C . . . H contacts showed the highest contributions among the intermolecular interactions which reveals the importance of these contacts in the molecular packing of the studied compounds.

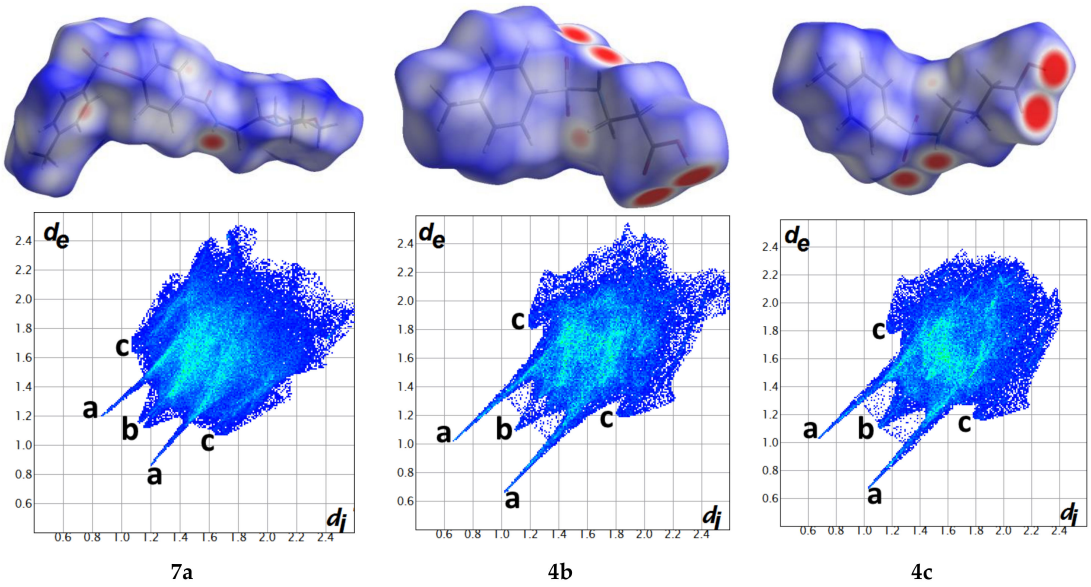


Figure 5. The d_{norm} surfaces (**upper**) and fingerprint plots (**lower**) of the studied compounds. The Sharpe spikes refer to the strong O . . . H hydrogen bonding interactions (a), while the broad peaks refer to the weak hydrophobic C . . . H (b) and H . . . H (c) contacts.

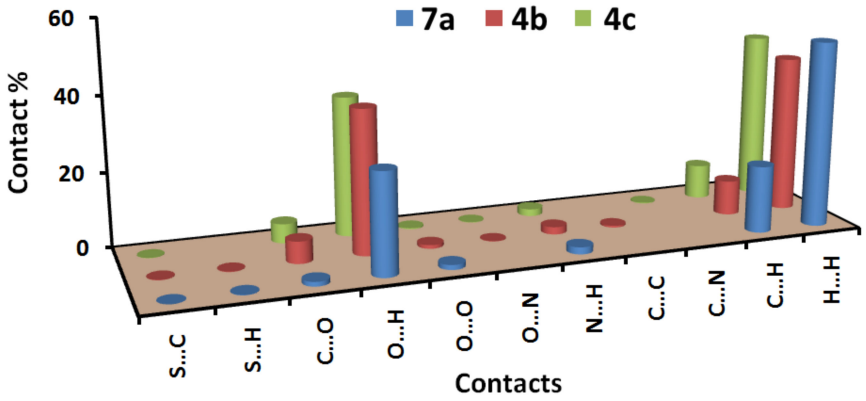


Figure 6. Quantification of the intermolecular interactions in the studied compounds.

4. Conclusions

The reaction of sulfonyl chlorides with amino acids or *p*-hydroxybenzoic acid in water with sodium carbonate as an HCl scavenger (green conditions) produced products with high yields and purities. NMR and elemental analysis confirmed the structures of the prepared compounds. The structures of **4b** and **4c** were also confirmed by X-ray crystallography. The use of OxymaPure/DIC with 2-MeTHF as a solvent (eco-friendly condition) produced the target products with high yield and purity as confirmed by NMR and elemental analysis. Crystallographic measurements confirmed the structure of one product from the synthesized compounds. Using Hirshfeld topology analysis, the packing of the studied compounds was controlled by strong O . . . H hydrogen bonds (27.1–38.5%)

as well as weak C ... H (9.3–18.1%) and H ... H (42.4–50.3%) interactions. The reported methods of preparation and coupling merit further attention for the development of new derivatives that might have significant biological applications.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4352/9/1/35/s1. Figure S1: ^{1}H NMR and ^{13}C for compound **4a**, Figure S2: ^{1}H NMR and ^{13}C for compound **4b**; Figure S3: ^{1}H NMR and ^{13}C for compound **4c**; Figure S4: ^{1}H NMR and ^{13}C for compound **5a**; Figure S5: ^{1}H NMR and ^{13}C for compound **5b**; Figure S6: ^{1}H NMR and ^{13}C for compound **5c**; Figure S7: ^{1}H NMR and ^{13}C for compound **7a**; Figure S8: ^{1}H NMR and ^{13}C for compound **7b**.

Author Contributions: The syntheses were carried out by Z.A. and A.E.-F.; X-ray structure analyses were carried out by S.M.S. and H.A.G. All authors carried out the results and discussion and were contributed in the first and the final version.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Török, E.; Moran, E.; Cooke, F. *Oxford Handbook of Infectious Diseases and Microbiology*; Oxford University Press: Oxford, UK, 2016.
2. Selvam, P.; Chandramohan, M.; Clercq, E.D.; Witvrouw, M.; Pannecouque, C. Synthesis and anti-HIV activity of 4-[(1,2-dihydro-2-oxo-3H-indol-3-ylidene)amino]-*N*(4,6-dimethyl-2-pyrimidinyl)-benzene sulfonamide and its derivatives. *Eur. J. Pharm. Sci.* **2001**, *14*, 313–316. [CrossRef]
3. Stokes, S.S.; Albert, R.; Buurman, E.T.; Andrews, B.; Shapiro, A.B.; Green, O.M.; McKenzie, A.R.; Otterbein, L.R. Inhibitors of the acetyltransferase domain of *N*-acetylglucosamine-1-phosphate-uridylyltransferase/glucosamine-1-phosphate-acetyltransferase (GlmU). Part 2: Optimization of physical properties leading to antibacterial aryl sulfonamides. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7019–7023. [CrossRef] [PubMed]
4. Abbate, F.; Casini, A.; Owa, T.; Scozzafava, A.; Supuran, C.T. Carbonic anhydrase inhibitors: E7070, a sulfonamide anticancer agent, potently inhibits cytosolic isozymes I and II, and transmembrane, tumor-associated isozyme IX. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 217–223. [CrossRef] [PubMed]
5. Ezabadi, I.R.; Camoutsis, C.; Zoumpoulakis, P.; Geronikaki, A.; Soković, M.; Glamočilija, J.; Ćirić, A. Sulfonamide-1,2,4-triazole derivatives as antifungal and antibacterial agents: Synthesis, biological evaluation, lipophilicity, and conformational studies. *Bioorg. Med. Chem.* **2008**, *16*, 1150–1161. [CrossRef] [PubMed]
6. Zareef, M.; Iqbal, R.; Gamboa, N.; de Dominguez, A.; Rodrigues, J.; Zaizi, J.H.; Arfan, M.; Supuran, C. Synthesis and antimalarial activity of novel chiral and achiral benzenesulfonamides bearing 1, 3, 4-oxadiazole moieties. *J. Enzym. Inhib. Med. Chem.* **2007**, *22*, 301–308. [CrossRef] [PubMed]
7. Stranix, B.R.; Lavalle, J.F.; Sevigny, G.; Telle, J.; Perron, V.; Leberre, N.; Harbart, D.; Wu, J.J. Lysine sulfonamides as novel HIV-protease inhibitors: Nε-Acyl aromatic alpha-amino acids. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3459–3462. [CrossRef] [PubMed]
8. Supuran, C.T.; Scozzafava, A.; Casini, A. Carbonic anhydrase inhibitors. *Med. Res. Rev.* **2003**, *23*, 146–189. [CrossRef]
9. Supuran, C.T.; Casini, A.; Scozzafava, A. Protease inhibitors of the sulfonamide type: Anticancer, antiinflammatory, and antiviral agents. *Med. Res. Rev.* **2003**, *5*, 535–558. [CrossRef]
10. Chiaramonte, N.; Romanelli, M.N.; Teodori, E.; Supuran, C.T. Amino acids as building blocks for carbonic anhydrase inhibitors. *Metabolites* **2018**, *8*, 36. [CrossRef]
11. Chinthakindi, P.K.; Arvidsson, P.I. Sulfonyl fluorides (SFs): More than click reagents. *Eur. J. Org. Chem.* **2018**, *2018*, 3648–3666. [CrossRef]
12. Kim, J.-G.; Jang, D.O. Mild and efficient indium metal catalyzed synthesis of sulfonamides and sulfonic esters. *Synlett* **2007**, *16*, 2501–2504.
13. Jafarpour, M.; Rezaeifard, A.; Golshani, T. Efficient organic transformations mediated by $ZrOCl_2 \cdot 8H_2O$ in Water. *Phosphorus Sulfur Silicon Relat. Elem.* **2010**, *186*, 140–148. [CrossRef]
14. Luca, L.D.; Giacomelli, G. An Easy Microwave-assisted synthesis of sulfonamides directly from sulfonic acids. *J. Org. Chem.* **2008**, *73*, 3967–3969. [CrossRef] [PubMed]

15. Rad, M.N.S.; Khalafi-Nezhad, A.; Asrari, Z.; Behrouz, S.; Amini, Z.; Behrouz, M. One-pot synthesis of sulfonamides from primary and secondary amine derived sulfonate salts using cyanuric chloride. *Synthesis* **2009**, *23*, 3983–3988. [CrossRef]
16. Veisi, H.; Ghorbani-Vagheic, R.; Hemmati, S.; Mahmoodi, J. Convenient One-Pot Synthesis of sulfonamides and sulfonyl azides from thiols using *N*-chlorosuccinimide. *Synlett* **2011**, *16*, 2315–2320. [CrossRef]
17. Caddick, S.; Wilden, J.D.; Judd, D.B. Direct synthesis of sulfonamides and activated sulfonate esters from sulfonic acids. *J. Am. Chem. Soc.* **2004**, *126*, 1024–1025. [CrossRef]
18. Flegeau, E.F.; Harrison, J.M.; Willis, M.C. One-Pot Sulfonamide synthesis exploiting the palladium-catalyzed sulfination of aryl iodides. *Synlett* **2016**, *27*, 101–105. [CrossRef]
19. Woolven, H.; González-Rodríguez, C.; Marco, I.; Thompson, A.L.; Willis, M.C. DABCO-*bis*(sulfur dioxide), DABSO, as a convenient source of sulfur dioxide for organic synthesis: Utility in sulfonamide and sulfamide preparation. *Org. Lett.* **2011**, *13*, 4876–4878. [CrossRef]
20. Katritzky, A.R.; Abdel-Fattah, A.A.A.; Vakulenko, A.V.; Tao, H. N-Sulfonylbenzotriazoles as advantageous reagents for C-sulfonylation. *J. Org. Chem.* **2005**, *70*, 9191–9197. [CrossRef]
21. Wright, S.W.; Hallstrom, K.N. A Convenient preparation of heteroaryl sulfonamides and sulfonyl fluorides from heteroaryl thiols. *J. Org. Chem.* **2006**, *71*, 1080–1084. [CrossRef]
22. Pandya, R.; Murashima, T.; Tedeschi, L.; Barrett, A.G.M. Facile one-pot synthesis of aromatic and heteroaromatic sulfonamides. *J. Org. Chem.* **2003**, *68*, 8274–8276. [CrossRef]
23. Andersen, K.K. *Comprehensive Organic Chemistry*; Jones, D.N., Ed.; Pergamon Press: Oxford, UK, 1979; Volume 3.
24. Holmes, T.J.J.; Lawton, R.G. Preparation of non-symmetrical *p*-benzoquinone diimines for evaluation as protein cleavage reagents. *J. Org. Chem.* **1983**, *48*, 3146–3150. [CrossRef]
25. Yasuhara, A.; Kameda, M.; Sakamoto, T. Selective Monodesulfonylation of *N*, *N*-disulfonylarylamines with tetrabutylammonium fluoride. *Chem. Pharm. Bull.* **1999**, *47*, 809–812. [CrossRef]
26. Low, C.M.R.; Broughton, H.B.; Kalindjian, S.B.; McDonald, I.M. Novel oxathiazinones as gastrin ligands: Unexpected products from the Scho-Mén-Baumann reaction of arylsuphonyl chlorides with derivatives of aspartic acids. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 325–330. [CrossRef]
27. Hu, W.; Guo, Z.; Chu, F.; Bai, A.; Yi, X.; Cheng, G.; Li, J. Synthesis and biological evaluation of substituted 2-sulfonyl-phenyl-3-phenyl-indoles: A new series of selective COX-2 inhibitors. *Bioorg. Med. Chem.* **2003**, *11*, 1153–1160. [CrossRef]
28. Narayan, S.; Muldoon, J.; Fin, M.G.; Folkin, V.V.; Kolb, H.C.; Sharpless, K.B. "On water": Unique reactivity of organic compounds in aqueous suspension. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275–3279. [CrossRef] [PubMed]
29. Lindstrom, U.M. Stereoselective organic reactions in water. *Chem. Rev.* **2002**, *102*, 2751–2772. [CrossRef]
30. Deng, X.; Mani, N.S. A facile, environmentally benign sulfonamide synthesis in water. *Green Chem.* **2006**, *8*, 835–838. [CrossRef]
31. Kumar, A.; Jad, Y.E.; El-Faham, A.; de la Torre, B.G.; Albericio, F. Green solid-phase peptide synthesis 4. δ-valerolactone and *N*-formylmorpholine as green solvents for solid-phase peptide synthesis. *Tetrahedron Lett.* **2017**, *58*, 2986–2988. [CrossRef]
32. Jad, Y.E.; Govender, T.; Kruger, H.G.; El-Faham, A.; de la Torre, B.G.; Albericio, F. Green solid-phase peptide synthesis (GSPPS) 3. Green solvents for Fmoc removal in peptide chemistry. *Org. Process Res. Dev.* **2017**, *21*, 365–369. [CrossRef]
33. Jad, Y.E.; Acosta, G.; Govender, T.; Kruger, H.; El-Faham, A.; de la Torre, B.G.; Albericio, F. Green solid-phase peptide synthesis-2.1, 2-Methytetrahydrofuran and ethyl acetate for solid-phase peptide synthesis under green conditions. *ACS Sustain. Chem. Eng.* **2016**, *4*, 6809–6814. [CrossRef]
34. Al Musaimi, O.; Jad, Y.E.; Kumar, A.; El-Faham, A.; Collins, J.M.; Basso, A.; de la Torre, B.G.; Albericio, F. Greening the solid-phase peptide synthesis process. *2-MeTHF for the incorporation of the first amino acid and precipitation of peptides after global deprotection. Org. Process Res. Dev.* **2018**, *22*, 1809–1816.
35. *SAINT*, version 4; Siemens Analytical X-ray Instruments Inc.: Madison, WI, USA, 1995.
36. Sheldrick, G.M. *SADABS; Program for Empirical Absorption Correction of Area Detector Data*; University of Goettingen: Goettingen, Germany, 1996.
37. Sheldrick, G.M. SHELXT-Integrated space-group and crystal-structure determination. *Acta Cryst.* **2015**, *A71*, 3–8. [CrossRef] [PubMed]

38. Spek, A.L. Structure validation in chemical crystallography. *Acta Cryst.* **2009**, *D65*, 148–155. [CrossRef] [PubMed]
39. Wolff, S.K.; Grimwood, D.J.; McKinnon, J.J.; Turner, M.J.; Jayatilaka, D.; Spackman, M.A. *Crystal Explorer*; University of Western Australia: Perth, Australia, 2012; version 3.1.
40. Spackman, M.A.; Jayatilaka, D. Hirshfeld surface analysis. *CrystEngComm* **2009**, *11*, 19–32. [CrossRef]
41. Fidan, I.; Salmas, R.E.; Arslan, M.; Sentürk, M.; Durdagi, S.; Ekinci, D.; Sentürk, E.; Cosgun, S.; Supuran, C.T. Carbonic anhydrase inhibitors: Design, synthesis, kinetic, docking and molecular dynamics analysis of novel glycine and phenylalanine sulfonamide derivatives. *Bioorg. Med. Chem.* **2015**, *23*, 7353–7358. [CrossRef]
42. Hill, R.R.; Moore, S.A.; Roberts, D.R. The Photochemistry of *N*-*p*-Toluenesulfonyl peptides: The peptide bond as an electron donor. *Photochem. Photobiol.* **2005**, *81*, 1439–1446. [CrossRef]
43. Korsager, S.; Taaning, R.H.; Skrydstrup, T. Effective palladium-catalyzed hydroxycarbonylation of aryl halides with substoichiometric carbon monoxide. *J. Am. Chem. Soc.* **2013**, *135*, 2891–2894. [CrossRef]
44. Mustafa, G.; Khan, I.U.; Ashraf, M.; Afzal, I.; Shahzad, S.A.; Shafiq, M. Synthesis of new sulfonamides as lipoxygenase inhibitors. *Bioorg. Med. Chem.* **2012**, *20*, 2535–2539. [CrossRef]
45. Subiros-Funosas, R.; Prohens, R.; Barbas, R.; El-Faham, A.; Albericio, F. Oxyma: An efficient additive for peptide synthesis to replace the benzotriazole-based HOBt and HOAt with a lower risk of explosion. *Chem. Eur. J.* **2009**, *15*, 9394–9403. [CrossRef]

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