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Synthesis, Antimicrobial and Antioxidant Properties of Gly-Gly Based Dipeptide

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Abstract: *Background*: The reported rise in drug-resistant bacteria, as well as the prevalence of oxidative stress-related disorders, motivated the need for novel antimicrobial and antioxidants activity. The synthesis of gly-gly based dipeptides bearing sulphonamide functionalities is reported. *Methodology*: The base promoted reaction of appropriate substituted benzenesulphonyl chloride with L-glycine afforded compounds (3a-3b) and the condensation reaction of (3a-3b) with carboxamide derivatives gave the targeted products (7a-7b) using peptide coupling reagent. The characterization of compounds was done using ^{1}HNMR, ^{13}CNMR, FTIR and HRMS. Results: In the *in vitro* antimicrobial activity, compounds 7a (MIC 6.10 mg/mL), 7ai (MIC 7.01 mg/mL), 7b (MIC 7.42 mg/mL), 7bi (MIC 6.32 mg/mL) was most potent against *S. aureus, B. subtilis, P. aeruginosa and E. coli* respectively. Compounds 7a (MIC 6.90 mg/mL) and 7b (MIC 6.48 mg/mL) were most active against *C. Albicans and A. Niger* respectively. Compound 7a and 7bi (85.00% and 88.78% at 25mg/mL) exhibits excellent percentage inhibition antioxidant activities comparable with vitamin C (90.78% at 25mg/mL) and alsocompound 7bi had the best IC_{50} values of 0.7674 mg/mL. *Conclusion*: The synthesized compounds were found to be potent antibacterial, antifungal and antioxidant agents.

Keywords: Synthesis, Benzenesulphonamide, Dipeptide, Antimicrobial Activity, Antifungal Activity, Antioxidant Activity

1. Introduction

Antibiotic-resistant Bacteria species pose significant risks to the global economy and human health [1]. Microbes can develop internal defense mechanisms that make them resistant to antibiotics with certain structural and functional features [1]. Resistance to active therapies develops as a result of horizontal gene transfer and spontaneous mutations. As a result of antibiotic abuse, natural selection allows drug-resistant organisms to thrive and breed, eventually destroying drug-sensitive forms [2]. Antioxidants are naturally occurring chemical molecules that protect living organisms from the detrimental effects of hazardous substances known as free radicals. Body cells manufacture them in response to free

radicals [3-4]. Many diseases, including cancer, diabetes, liver damage, autoimmune disorders, heart ailments, atherosclerosis, and aging, are influenced by free radicals [5]. As a result, antioxidants that neutralize free radicals are critical for both treating and preventing these disorders [6]. Antioxidants are commonly used as catalysts in antiboitics with anti-inflammatory, antifungal, antibacterial, and antiviral activities, as well as in industries to prevent rusting [7]. Because synthetic antioxidants are more efficient and cost-effective than natural antioxidants, they are now used more frequently [8]. Sulfonamides have long been recognized as effective against Gram + and Gram - bacterial strains associated with a number of infectious illnesses [9]. These diverse synthetic medicinal drugs compete with and prevent PABA from binding to the dihydropteroate synthase (DHPS) enzyme, hence blocking the critical bacterial dihydrofolic acid production pathway [10]. Folic acid is a necessary component for bacteria to synthesize DNA and RNA. Sulphonamide is a significant class of medically significant substance present in a wide range of biologically active compounds. Sulphonamide derivatives are also widely used as anti-inflammatory [11], anti-cancer [12], anti-tumor [13, 14], antiviral [15], antimalarial [16-18], anti-diabetic drugs [19], and anti-Alzheimer's disease [20] agents. In this paper, we describe the synthesis of Gly-gly dipeptide carboxamide scaffolds containing sulphonamide moieties that have increased antibacterial and antioxidant activity.

2. Materials and Methods

All reagents and starting materials were purchased from Sigma-Aldrich, which were used without additional purification. The melting points were determined using Fischer John's melting point instrument and are uncorrected. IR spectra were obtained using a KBr disc on a 8400s Fourier Transform Infrared (FTIR) spectrophotometer, and absorption was reported in (cm^{-1}). The IR analysis was conducted at National Research Institute for Chemical Technology (NARICT) in Zaria, Kaduna State. Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) were done using Jeol 400 MHz and the chemical shifts (δ) were measured in parts per million (ppm).

2.1. General Procedure for the Synthesis of (Phenylsulfonyl)Glycine

In a 100 mL round bottom flask fitted with a magnetic stirrer, glycine (1.0 g, 9 mmol), Et_2O (60 mL), and NaOH (11.5 mL, 1.0 M) were added. Appropriate substituted benzenesulphonyl chloride (0.75 g, 4.9 mmol) was added to the solution in one portion. The mixture was agitated at room temperature for 20 h and then extracted with Et_2O. AcOEt was used to extract the aqueous layer after it had been acidified to pH-2 with 1N HCl solution. The organic layers were evaporated at reduced pressure and dried over Na_2SO_4. The crude product was recrystallized from DCM/hexane to get pure sulfonamide.

2.2. General Procedure for the Reaction of Amine with Boc-Amino Acid (5a-5b)

Tert-butoxycarbonyl glycine (0.62 g, 3.0 mmol) and 1,3-dicyclohexylcarbodiimide (0.56 g, 2.95 mmol,) were added to a solution of substituted amine (0.27 g, 2.85 mmol,) in 15 mL of anhydrous THF at 25°C. The mixture was agitated for 5 h at 25°C before being diluted with 25 mL of ethylacetate, filtered to remove the urea byproduct, and concentrated to yield the crude product, which was purified by column chromatography and was sufficiently pure for use in the next step.

2.3. General Procedure for BocDeproctection(6a-6b)

TFA (8 mL) was added to a solution of bocprotected amine (1g, 4.0 mmol) in dry DCM (10 mL) at 0°C. The solution was agitated at room temperature for 6 h. TLC was used to monitor the reactionand after the boc-anhydride had completely vanished, the reaction mixture was concentrated under reduced pressure and 2 N NaOH solutions were added to achieve a pH of 12. The mixture was extracted with 60 mL of ethyl acetate, dried over Na_2SO_4, and filtered. Alkylaminotriflates were obtained by extracting solvents under reduced pressure.

2.4. General Procedure for the Synthesis of Gly-Gly Dipeptides (7a-7b)

Phenylsulfonyl glycine (0.62 g, 3.0 mmol) and 1,3-dicyclohexylcarbodiimide (0.56 g, 2.95 mmol) were added to a solution of deprotected amine (0.27g, 2.85 mmol) in 15 mL of anhydrous THF at 25°C. The mixture was agitated for 5 h at 25°C before being diluted with 25 mL of ethyl acetate, filtered to remove the byproduct urea, and concentrated to furnish crude product of (7a-7b) which was then purified using column chromatography (ethyl acetate/hexane).

2.5. N-(2-oxo-2-(Phenylamino)Ethyl)-2-(Phenylsulfonamido)Acetamide(7a)

Yield (2.8 g, 99.34%), Mp, 90-95°C. FTIR (KBr, cm^{-1}): 3324 (NH), 3034 (C-H aromatics), 2929 (C-H aliphatic), 1625, 1569 (2C=O of amide), 1438 (C=C aromatic), 1345, 1308 (2S=O), 1047, (C-N).^{1}H NMR (DMSOd6) δ: 5.9(m, 10H, Ar-H), 2.5(s, 1H, NH-amine), 3.6(s, 4H, CH_2), 3.5(DMSO). ^{13}C-NMR (DMSOd6)δ: 160(C=0),120-147(Ar-C) 47.68(CH_2), 29.33-40.58 (DMSO). HRMS (m/z) for $C_{16}H_{17}N_3O_4S$: 349.41880 (M^-), calculated, 347.38900.

2.6. ((4-Methylphenyl)Sulfonamido)-N-(2-oxo-2-(Phenylamino)Ethyl)Acetamide (7ai)

Yield (2.0 g, 89%), Mp, 115°C. FTIR (KBr, cm^{-1}): 3321 (NH), 3034(C-H aromatics), 2929 (C-H aliphatic), 1692, 1625 (2C=O of amide), 1435 (C=C aromatic), 1354, 1308 (SO_2), 1241, 1084, (C-N).^{1}H NMR (DMSOd6)δ. 2.4(s,1H,NH-amine), 2.6(s,3H,Ar–CH_3), 4.4(s, 2H,CH_2), 5.6(s, 1H, NH-amide), 7.8-8.1(m,9H Ar-H). ^{13}C-NMR (DMSOd6) δ: 21.61(Ar-CH_3), 47.39-49.37(-CH_2-), 131, 132, 138,149 (Ar-C), 170(C=0). Mass analysis; HRMS (m/z) for

$C_{17}H_{19}N_3O_4S$: 395.20235 (M^-), calculated, 361.4160.

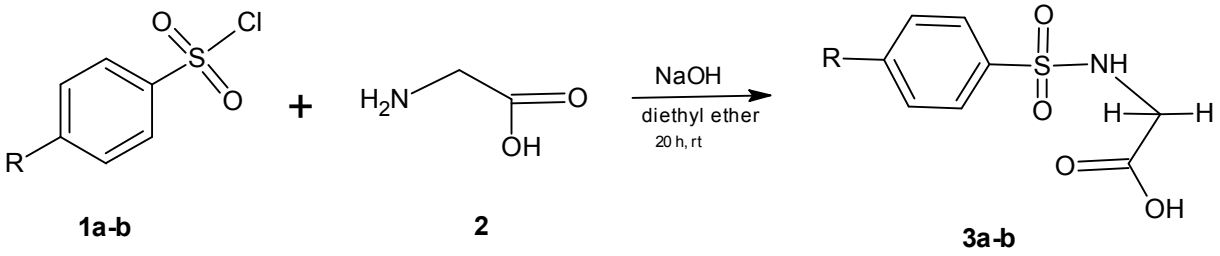
2.7. N-(4-Chlorophenyl)-2-(2-(Phenylsulfonamido)Acetamido)Acetamide(7b)

Yield (1.5 g, 88%), Mp, 118°C. FTIR (KBr, cm^{-1}): 3321 (NH), 3083(C-H aromatics), 2929 (C-H aliphatic), 1625 (C=O of amide), 1438 (C=C aromatic), 1308 (SO_2), 1170, 1088, (C-N), 682 (C-Cl). ^{1}H NMR (DMSOd6) δ: 2.5 (s, 1H, NH-amine), 4.4 (s, 2H,CH_2-), 5.4(s, 1H, amide), 7.6-8.0 (m, 9H, Ar-H). ^{13}C-NMR (DMSOd6) δ: 47.97-49.43(-CH_2-), 135.25, 129.74, 128.86, 126.95 (Ar-C), 157.08(C=0), Mass analysis; HRMS (m/z) for $C_{16}H_{16}ClN_3O_4S$: 383.09785 (M^-), calculated, 381.83100.

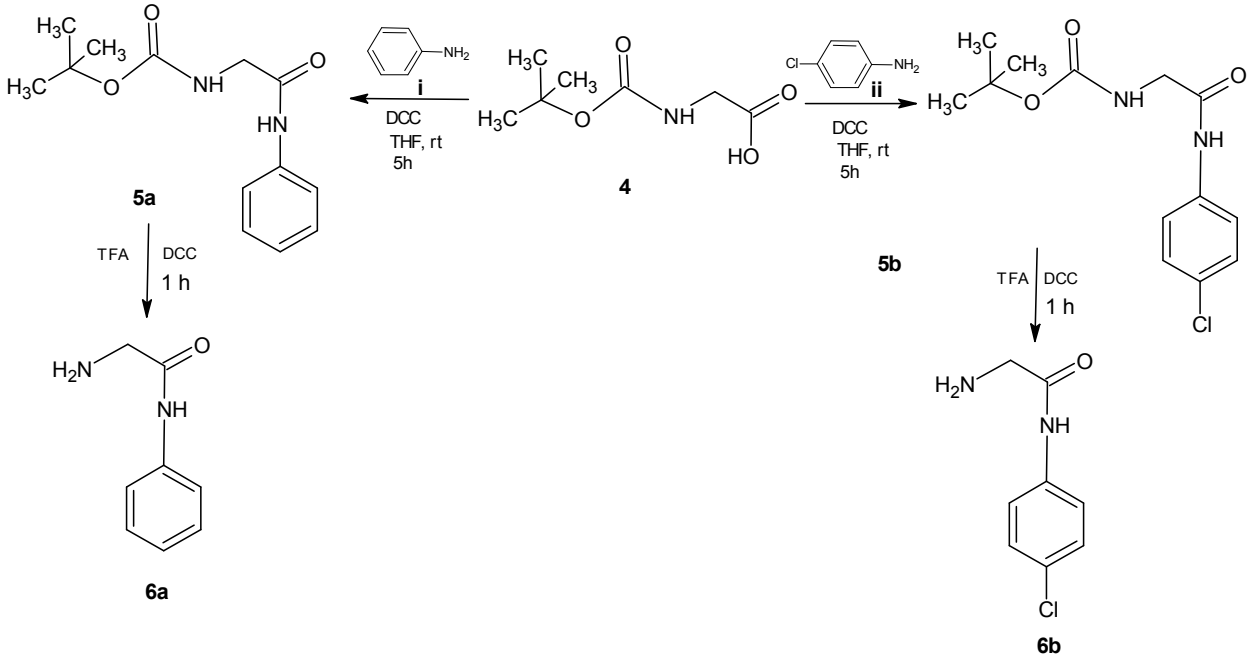
2.8. N-(4-Chlorophenyl)-2-(2-((4-Methylphenyl)Sulfonamido)Acetamido)Acetamide (7bi)

Yield (2.5 g, 93%), Mp, 105°C. FTIR (KBr, cm^{-1}): 3324 (NH), 2926 (C-H aliphatic), 1680, 1625 (2C=O of amide), 1435 (C=C aromatic), 1364 (SO_2), 1207, 1084, (C-N), 663 (C-Cl).^{1}H NMR (DMSOd6)δ:, 2.7(s, 3H, Ar–CH_3), 2.7(s, 1H,NH-SO_2NH), 4.6 (s, 2H, -CH_2-), 5.6(s, 1H, amide), 7.2-8.0(dd, 8H, Ar-H), ^{13}C-NMR (DMSOd6) δ: 21.61(Ar-CH_3), 47.39-49.37 (-CH_2), 129.93, 130.21, 154.74(Ar-C to amide and sulphonamide group), 168(C=0). HRMS (m/z) for $C_{17}H_{18}ClN_3O_4S$: 396.07625 (M^-), calculated, 396.85800.

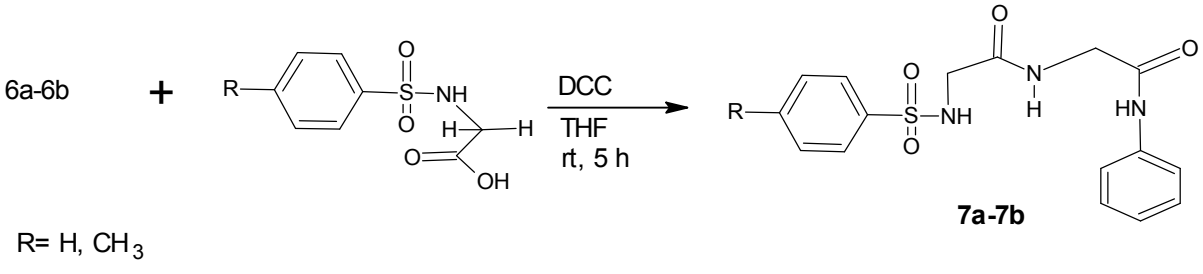
Scheme 1: Synthesis of (phenylsulphonyl)glycine



Scheme 2: Synthesis of carboxamide derivatives



Scheme 3: Synthesis of dipeptide derivatives



2.9. Biological Studies

2.9.1. In Vitro Antimicrobial Properties

The antibacterial activities of the newly synthesized compounds were evaluated using a sensitivity test and a minimum inhibitory concentration (MIC) against freshly cultivated targeted microorganisms. The compounds were evaluated for their in vitro antimicrobial activity by agar dilution method against Gram-positive bacteria, Staphylococcus aureus (ATCC 25923), Bacillus subtilis (ATCC 6633) and Bacillus cereus (ATCC 9946); Gram-negative bacteria, Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853), Klebsiellapneumoniae (ATCC 700603); fungi, Candida albicans (ATCC 2091), Aspergillusniger (MTCC 281). The organisms were obtained from the University of Nigeria Teaching Hospital, Department of Medical Microbiology in Enugu.

2.9.2. Sensitivity Testing

0.15mL of overnight culture of the appropriate bacterium was placed on the sensitivity agar plates. Cups were made in each sector that had been marked with a marker on the underside of the bottom plate after the seeded plates had set. Using a sterile pipette, Six drops of the corresponding synthesized compounds (20 mg/mL) were added to each cup. DMSO was used as the solubility solvent. All the plates were incubated at 40°C for 48 h for fungi and 24 h for bacteria. Zones of clearance around each cup allowed inhibition and the diameter of such zones was measured. The procedure was repeated for gentamycin, ketoconazole. Muller Hinton agar was used for the fungi in place of nutrient agar for bacteria [21].

2.9.3. Minimum Inhibitory Concentration of the Synthesized Compound

The compounds were serially diluted from a 20 mg/mL solution to give 2-0.125 mg/mL derivatives. Six drops of each dilution were added to a cup of seeded microorganisms and agar. The plates were incubated at the prescribed temperature and time. The diameter of the inhibition zone (IZD) was calculated by subtracting the diameter of the zone of inhibition from the borer diameter (8 mm). The graph of IZD^2 against the logarithm of concentration was plotted for each plate containing a specific drugs and a microorganism. The MIC is calculated by taking the antilogarithm of the intercept on the X-axis. Thus, MIC was generally read as the smallest concentration of drug in the series that prevents the development of visible growth of test organism.

2.9.4. In Vitro Antioxidant Properties

DPPH Radical Scavenging Activity

The novel compounds were evaluated for free radical scavenging capabilities using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) approach developed by Shen et al. [22]. 3 mL of a 0.1 mMethanolic solution of DPPH and 1.0 mL of this solution were mixed with 0.9 mL of methanol sample containing 0.8 mg of the sulphonamide compounds at varied concentrations and individual reference drug (vitamin C). The reaction mixture was briskly agitated and placed in the dark at room temperature for 30 min. After 30 min at room temperature, absorbance measurements at 517 nm were taken. Inhibition (%) was calculated using the equation:

$$\text{DPPH radical scavenging activity} = Ac\text{-}As/Ac \times 100$$

where

Ac = Abosbance of control, As =Absorbance of sample

3. Result and Discussion

Chemistry

Sulphonamide and dipeptides are two significant pharmacophores in the fight against microbial drug resistance. To synthesize compounds (7a-7b), we amidated compounds (6a-6b) with substituted benzenesulphonamides produced from L-glycine (2) using a common peptide coupling reagent, dicyclohexylcarbodiimide (DCC). The activation of the carboxylic acid group of glycine was enhanced by DCC and it was preferred as a coupling reagent over 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl). Although DCC activation increases the possibility of racemization of the activated amino acid, but racemization can be avoided by using a racemization suppressing additive such as triazole 1-hydroxybenzotriazole (HOBt). In this study, we synthesized and characterized compounds containing sulphonamide, carboxamide and dipeptides. The reaction of substituted benzenesulfonylchloride (1a-b) with L-glycine (2) gave substituted (phenylsuphonyl)glycine (3a-b). The reaction of commercially available boc-protected glycine with various amines using (DCC) as coupling reagent in tetrahydrofuran yielded the carbamate derivatives of glycine (5a-b). Compounds (6a-b) were synthesized through deprotection of the boc-protected glycine with trifluoroacetic acid (TFA) in dichloromethane (DCM). The amidation of substituted (phenylsuphonyl)glycine (3a-b) with unprotected amides (6a-b) using peptide coupling reagent (DCC) in tetrahydrofuran gave the targeted products (7a-b). In the infrared spectra of the dipeptides, the bands between 3324 and 3321 cm^{-1} for N-H while 1680 and 1625 cm^{-1} for carbonyl of the amide respectively. In the ^{1}H-NMR spectra of the derivatives, the peaks at 8.0-7.2 ppm were assigned to aromatic protons. The carbonyl peaks in the ^{13}C-NMR spectrum, appears between 160 and 168 ppm and peaks ranging from 120-154.7 ppm for aromatic carbons. The high resolution mass spectrometer (HRMS) peak of the derivatives appeared either as molecular ions (M^+) or (M^-). The spectra used for the characterization of the new compounds are available as supporting material.

3.1. In-Vitro Antimicrobial Properties

Table 1. *Results of Minimum Inhibitory Concentration (MIC).*

Compounds	B. cereus	B. subtilis	S. aureus	E. coli	P. aeruginosa	K. pneumonia	C. Albicans	A. niger
7a	7.07	7.64	6.10	6.90	8.01	6.59	6.90	6.96
7ai	7.18	7.01	7.76	7.14	7.42	7.34	7.96	7.81
7b	7.67	8.00	7.52	7.44	7.42	8.18	8.11	6.48
7bi	7.55	7.09	6.68	6.32	6.12	7.67	7.50	8.27
Gentamycin	9.05	9.48	9.50	9.48	9.42	9.55	-	-
Ketoconazole	-	-	-	-	-	-	9.52	9.50

3.2. In Vitro Antioxidant Properties

Table 2. *In vitro antioxidant (%scavenging activity) and IC_{50} values of the synthesized compounds.*

Compds	% inhibition 50 mg / mL	% inhibition 25 mg/mL	% inhibition 12.5 mg/mL	IC50 (mg/mL)
7a	80.17 ±0.11	85.60 ± 0.12	78.96 ± 0.42	0.5674
7ai	78.40 ± 0.12	67.42 ± 0.18	60.34 ± 0.26	0.4891
7b	74.50 ±0.42	76.33 ± 0.31	77.13 ± 0.18	0.3744
7bi	80.50 ± 0.66	88.78 ± 0.31	79.10 ± 0.30	0.7674
Vitamin C	89.88 ± 0.44	90.78 ± 0.40	91.44 ± 0.41	0.7791

Table 1 consists of the minimum inhibitory concentration of the synthesis compounds. Compounds 7a, 7ai, 7b and 7bi had lowest minimum inhibitory concentration MIC: 6.10, 7.01, 7.42 and 6.32) when compared to the standard having inhibited the growth of the bacteria used as test microorganism namely: S. aureus, B. subtilis, P. aeruginosa and E. coli respectively. Compound 7a and 7b had the most potent antifungal activity for C. albican and A. niger respectively. It implies that they can serve as excellent antifungal agents. The finding is consistent with work of Hennicke et al [23].

The in-vitro antioxidant activity (Table 2) revealed that all the compounds had antioxidant activity but compounds 7a and 7bi (85.00% and 88.78% at 25 mg/mL) exhibits excellent percentage inhibition antioxidant activities which entail that better antioxidant potential. The DPPH scavenging assay was carried out under the presumption that protons from antioxidants would neutralize DPPH radicals in which is in agreement with Matuszewska et al [24] that a low IC_{50} indicates high antioxidant activity, and vice versa. As a consequence, compound 7bi demonstrated as much antioxidant activity as Vitamin C (0.7791 mg/mL), which was the greatest degree of antioxidant activity among all synthesized compounds (0.7674 g/ml). Compound 7bi might work effectively as an antioxidant agent in place of Vitamin C because their IC_{50} values are similar.

4. Conclusion

The synthesis of Based Gly-gly dipeptide containing sulphonamide derivatives was successful. The compounds synthesized were screened for their antimicrobial and antioxidant properties and the assigned structures were agreement with the spectral data. The results indicated that compound 7a, 7ai and 7bi had a good antibacterial agent although 7a is the most potent in-vitro antibacterial agents whereas 7bi exhibits most active antioxidant activity which can be regarded as the most promising agent.

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