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Research Article

Synthesis and Investigations of Antimicrobial and Antioxidant properties of New Val-Tyro based Arylsulphonamoyl Dipeptide Carboxamide Derivatives

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Abstract

Sulphonamides and carboxamides serve important roles in pharmacology. Four new dipeptide carboxamide derivatives with benzensulphonamide functionality were synthesized and their antibacterial, antioxidant activities were investigated. The base promoted reaction of substituted benzenesulphonyl chloride with L-valine gave compound (13a-13b) in excellent yields. Compounds (18a-18d) were achieved by amidation of substituted benzenesulphonamoyl derivatives with carboxamide derivatives (17) using peptide coupling reagents. The chemical structures were confirmed by FTIR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectroscopic techniques. The antimicrobial properties were determined by agar dilution method and the antioxidant properties were also investigated. Compounds 18a, 18b and 18d was confirmed to be the most potent antibacterial agent that inhibited the growth of bacteria while Compounds 18a and 18c displayed the most active antifungal agent. Compound 18b and 18d showed the best antioxidant activities with IC_{50} value of 0.63 mg/mL and 0.64 mg/mL respectively.

1. Introduction

Due to their antimalarial properties, sulphonamide derivatives may prevent the parasite from producing folate, which is essential for its survival [1, 2]. For instance, dapsone and sulfadiazine were the first sulfa drugs used in clinical settings to treat malaria infections [1].They form the basis for various categories of drugs that exhibit carbonic anhydrase inhibitory properties [3], antibacterial effects [4], anticancer capabilities [5], anti-HIV actions [6], antidiabetic benefits [7], anti-influenza properties [8, 9], and anti-inflammatory [10], antimicrobial [11], antitrypanosomal [12], anticonvulsant [13], anti-insomnia [14], diuretic [15], antileukemic activities [16] and for Alzheimer's disease among others. Drug molecules contain pharmacophores called carboxamides [17]. They have been demonstrated to possess antibacterial and antioxidant properties [18], antioxidant and carbonic anhydrase enzyme inhibitor properties [19], According to Gajanan and Vagdevi, [20], sulphasalazine (1) is used to treat rheumatoid arthritis; sulphabenzamide (2) is used to treat mucous membranes; sulphamethizole (3) is used to treat bacterial infections; sulphacetamide sodium (4) is used for superficial ocular punctures; and sulphadiazine (5) is used to treat urinary tract infections.

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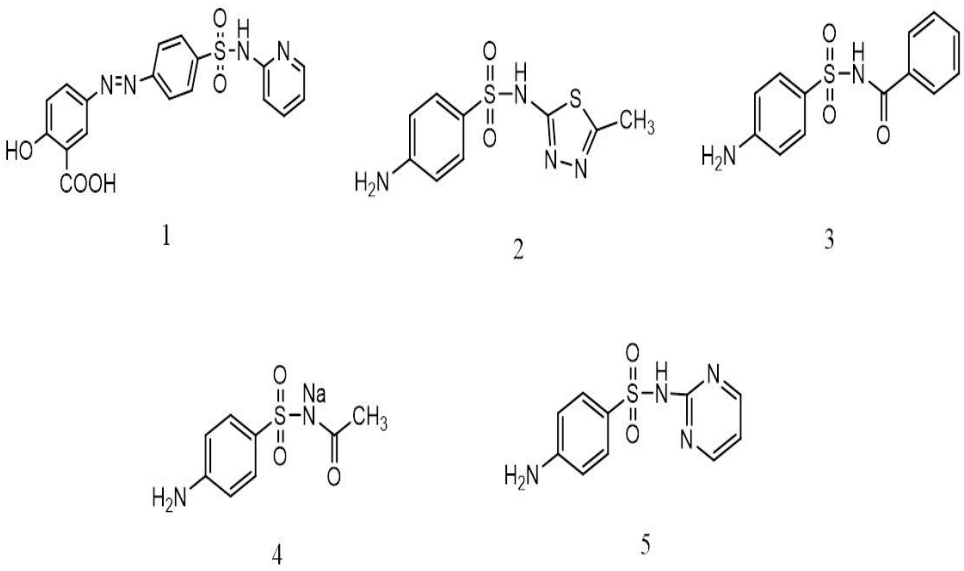

Figure 1: Examples of antimalarial sulphonamide

Furosemide (6) marketed as Lasix is a sulphonamide derivative used to treat fluid build-up due to heart failure, liver scarring or kidney disease [21]. Sulphadoxime (7) is an ultra long lasting sulphonamide used in combination with pyrimethamine to treat or prevent malaria [22]. Sildenafil (8) marketed as Viagra is a sulphonamide derivative used in the treatment of male erectile dysfunction [23]. Brinzolamide (9) and dorzolamide (10) are sulphonamide derivatives used as carbonic anhydrase II inhibitors. They are used to lower intraocular pressure in patients with open-angle glaucoma or ocular hypertension [24].

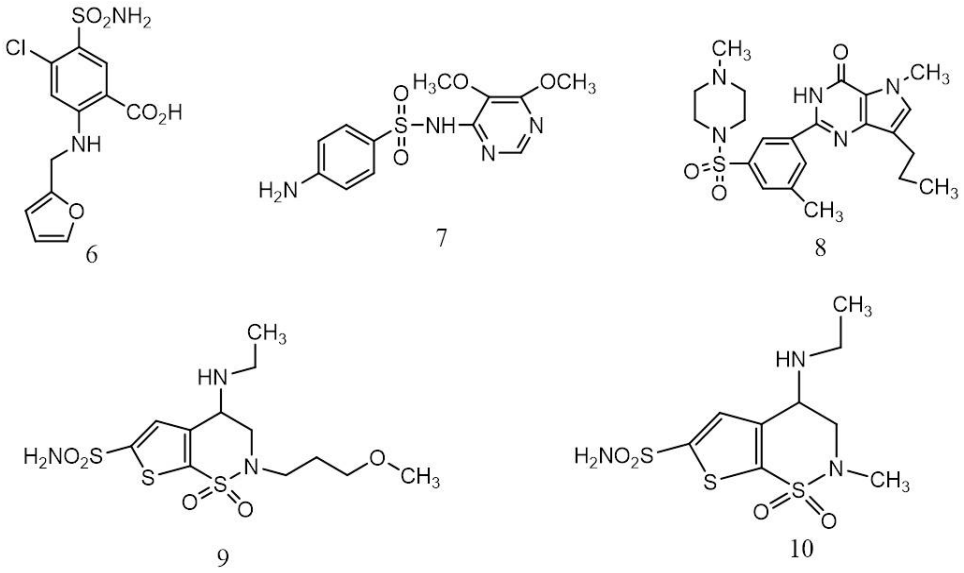

Figure 2: Examples of non-antibiotic sulphonamides

Many therapeutically utilized medications, including antimalarial, anti-inflammatory, anticancer, anti-HIV, and antiviral medications, contain dipeptides and peptide scaffolds, which are important structural motifs [25–27]. Promising pharmacological effects have been described for both synthetic and naturally produced dipeptides and peptides [28–31]. Therefore, it is anticipated that the development of synthetic antibacterial and antioxidant medicines will significantly lower the incidence of dangerous diseases.

2. Materials and methods

2.1. Materials

All chemical reagents and solvents used were purchased from, Sigma Aldrich and used with-out purification. 1H NMR and 13C NMR spectra were recorded on Jeol 400 MHz spectrometers in CDCl 3 and DMSO_*d*6 using TMS as internal standard. FT-IR spectroscopy of the compounds were run in PerkinElmer Spectrum version 8400s and the bands presented in wavenumber. Melting points were determined in open capillary tubes, using John's melting-point apparatus and are uncorrected. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F 254 (mesh); sports were visualized un-der UV light. The antimicrobial activity studies took place at

the Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka while the antioxidant studies were carried out at the Biochemistry Department, University of Nigeria, Nsukka.

General procedure for the synthesis of substituted benzenesulphonamides derivatives(13a-13b)

Sodium carbonate (Na_2CO_3, 26.25 mmol) was weighed and added to a solution of L-valine (12.5 mmol) in distilled water (50 mL) with continuous stirring using a magnetic stirrer until all the solute dissolved. The solution was cooled to $-5^{\circ}C$ and appropriate substituted benzenesulphonylchloride (12 mmol) were added in four portions over a period of 1 h. The slurry was further stirred for 4 h at room temperature. The progress of the reaction was monitored using thin layer chromatography (TLC) (MeOH/DCM) 1:9). Upon completion, the mixture was acidified using 20% aqueous hydrochloric acid to pH of 2. The organic portion was extracted with dichloromethane (3×50 mL), brine (2×50 mL) and the crude products were obtained by suction filtration. The crude products were dried over fuse silica gel in desiccators and recrystallized from methanol to give pure solid products (13a-13b).

General procedure of preparing boc-protected substituted alkanamide derivatives (16)

A mixture of *tert*-butoxycarbonyl tyrosine (16.90 mmol), 1-ethyl-3-(3-dimethyl aminopropyl carbodiimide hydrochloride (15.80 mmol) EDC, 1-hydroxybenzotriazole, HOBt, (12.90 mmol), triethylamine, TEA (20.0 mmol) and three different amines respectively in dichloromethane (40 ml) were added into a 100 mL round bottom reaction flask and stirred at room temperature for 17 h. The progress of the reaction was monitored using thin layer chromatography (TLC). At the end of reaction, the content of the flask was transferred into a separating funnel diluted with DCM (40 mL), washed with 1N HCl (50 mL), 5% sodium bicarbonate solution (50 mL) and brine (50 mL). The organic portion obtained was dried using anhydrous sodium sulphate and the solvent was removed under reduced pressure to give the crude products (17) which was then purified by column chromatography using silica gel [26]. The compounds were characterized.

General Procedure for the Synthesis of arylsulphonamoyl 'Val-Tyr' Dipepetide Derivatives (18a -18d)

The carbamate derivatives (17) were stirred in 10% trifuoroacetic acid/ dichloromethane (TFA/DCM) to remove the *boc*-proctecting group. After which the solvent was evaporated to obtain the substituted alkanamides in excellent yield. To a solution of appropriate substituted benzenesulphonamide (16.90 mmol), 1-ethyl-3-(3-dimethyl aminopropyl carbodiimide hydrochloride (15.80 mmol) EDCl, 1-hydroxybenzotriazole, HOBt, (12.90 mmol), triethylamine, TEA (20.0 mmol) andsubstituted protected alkanamide derivative (1.84 mmol) in dichloromethane (40 ml) was added into a 100 mL round bottom reaction flask and stirred at room temperature for 17 h. The reaction was monitored using TLC and at the end of reaction, the content of the flask was transferred into a separating funnel, diluted with DCM (40 mL), washed with 1N HCl (50 mL), 5% sodium bicarbonate solution (50 mL) and brine (50 mL). The organic portion obtained was dried using anhydrous sodium sulphate and the solvent was removed under reduced pressure to obtain the crude product which were then purified by column chromatography using silica gel and 3% methanol/dichloromethane to furnish (18a-18d) [26].

Phenylsulphonyl)valine (13a)

Yield 90.34%, mp, 157.9°C (lit m.p 160.5°C). FTIR (KBr, cm^{-1}): 3380 (OH), 3257 (NH), 3108 (C-Haromatics) 1744 (C=0), 1502, 1449 (C=C), 1349 (SO_2). ^{1}H NMR ($DMSO_{d6}$) δ: 13.20 (s. 1H, OH of carboxylic acid), 7.92 (d, 1H, SO_2-NH), 7.60 (d, 2H, Ar-H), 3.85 (s, 2H, CH_2). ^{13}C-NMR ($DMSO_{d6}$) δ: 171.2 (C=O), 144.5 - 130.3 (aromatic carbons), 44.5 - 22.5 (aliphatic carbon).]

Tosylvaline (13b)

Yield 89.40%, mp, 138.8°C (lit m.p 140.5°C). FTIR (KBr, cm^{-1}): 3287 (NH), 3108 (C-Haromatics), 2922 (C-H aliphatics), 1707 (C=O), 1535, 1431 (C=C), 1341 (-SO_2-). ^{1}H NMR ($DMSO_{d6}$) δ: 13.10 (s. 1H, OH of carboxylic acid), 7.80 (d, 1H, SO_2-NH), 7.70 (d, 2H, Ar-H), 3.86 (s, 2H, CH_2), 2.4432 (s, 3H, Ar-CH_3). ^{13}C-NMR ($DMSO_{d6}$) δ: 172.64 (C=O), 137.46 - 106.31 (aromatic carbons), 44.54 - 22.56 (aliphatic carbon).

***N*-(3-(4-hydroxyphenyl)-1-(1H-imidazol-1-yl)-1-oxopropan-2-yl)-(phenylsulphonamido) butanamide (18a)**

Yield (2.5g, 80%), Mp 125°C. FTIR (KBr, cm^{-1}): 3324 (NH), 2929 (C-H aliphatic), 1684, 1625 (C=O of amide), 1438 (C=C aromatic), 1345, 1308 (SO_2), 1185, 1088 (C-N). ^{1}H NMR ($DMSO_{d6}$) δ: 9.20 (s, 1H, Ar-OH), 8.81 (d, 1H, -SO_2-NH), 7.66 (dd, 4H, Ar-H), 5.58 (s, 1H, NH amide), 4.55 (d, 4H, CH_2), 3.4 (s, 2H CH_2), 3.2 (s, 2H, CH_2). ^{13}C-NMR ($DMSO_{d6}$) δ: 170 and 169.9 (2C=0), 145.27, 138.18, 128.41, 125.97, 117.19 (aromatic carbons), 79.57, 79.44, 78.91 (aliphatic carbons).

***N*-(3-(4-hydroxyphenyl)-1-(1H-imidazol-1-yl)-1-oxopropan-2-yl)- 3-methyl-2-((4-methylphenyl)sulphonamido) butanamide (18b)**

Yield (2.0g, 94%), Mp 40°C. FTIR (KBr, cm^{-1}): 3321 (NH), 2927 (C-H aliphatic), 1674, 1650 (C=O of amide), 1430 (C=C aromatic), 1355, 1320 (SO_2), 1190, 1075 (C-N). ^{1}H NMR ($DMSO_{d6}$) δ: 9.20 (s, 1H, Ar-OH), 8.81 (d, 1H, -SO_2-NH), 7.66 (dd, 4H, Ar-H), 5.58 (s, 1H, NH amide), 4.55 (d, 4H, CH_2), 3.4 (s, 2H CH_2), 3.2 (s, 2H, CH_2). ^{13}C-NMR ($DMSO_{d6}$) δ: 169 (C=0), 147.37, 133.18, 129.24, 125.97, 118.29 (aromatic carbons), 80.57, 79.44, 78.91 (aliphatic carbons).

***N*-(1-((4-bromophenyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-3-methyl-2-(phenylsulphonamido) butanamide (18c)**

Yield (1.0g, 89%), Mp 140°C. FTIR (KBr, cm^{-1}): 3324 (NH), 3063 (C-H aromatics), 2929 (C-H aliphatic), 1684, 1625 (C=O of amide), 1438 (C=C aromatic), 1349, 1312, (SO_2), 1215, 1181, 1129 (C-N). ^{1}H NMR ($DMSO_{d6}$) δ : 9.30 (s, 1H, Ar-OH), 8.80 (d, 1H, -SO_2-NH), 7.85 (dd, 4H, Ar-H), 3.58 (s, 2H, CH_2), 2.44 (Ar-CH_3). ^{13}C-NMR ($DMSO_{d6}$) δ: 172 and 175 (2C=0), 145.27, 138.18, 128.41, 125.97,

117.19 (aromatic carbons), 79.57, 79.44, 78.91 (aliphatic carbons).

***N*-(1-((4-bromophenyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-3-methyl-2-((4-methylphenylsulphonamido) butanamide (18d)**

Yield (2.0g, 79%), Mp 160°C. FTIR (KBr, cm^{-1}): 3320 (NH), 3073 (C-H aromatics), 2927 (C-H aliphatic), 1670, 1645 (C=O of amide), 1440 (C=C aromatic), 1345, 1320, (SO_2), 1240, 1170, 1129 (C-N). ^{1}H NMR ($DMSO_{d6}$) δ: 9.30 (s, 1H, Ar-OH), 8.80 (d, 1H, -SO_2-NH), 7.95 (dd, 4H, Ar-H), 3.68 (s, 2H, CH_2), 2.44 (Ar-CH_3). ^{13}C-NMR ($DMSO_{d6}$) δ : 170 and 171 (2C=0), 148.30, 136.28, 127341, 124.87, 116.90 (aromatic carbons), 79.57, 79.44, 78.91 (aliphatic carbons).

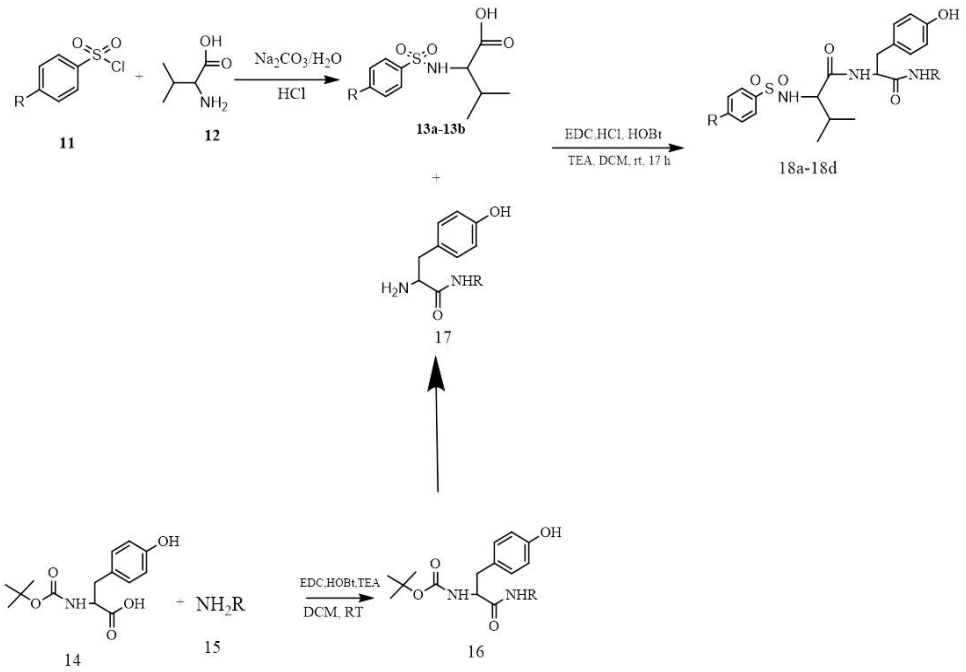

Figure 3: Synthesis of Dipeptide bearing sulphonamide, reagents and conditions. (i) Na_2CO_3, H_2O, $-5°C$ - 0^oC, r.t, 4 h. (ii) EDCI, HOBt, TEA, DCM, amine 17 h (iii) TFA/DCM (iv) EDCI, HOBt, TEA, 17 h

3. Biological studies

3.1. Antimicrobial studies

All the synthesized compounds were evaluated according to the method described by Vincent [32] using Agar dilution method for their *in vitro* antimicrobial activity against pathogenic microorganisms such *Staphylococcus aureus, Bacillus subtilis, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Candida albicans, Aspergillus niger*, which were clinical isolates procured from Department of Medical Microbiology, University of Nigeria Teaching Hospital, Enugu. The standardization of organisms was carried out with 0.5 McFarland turbid equivalents. The newly synthesized compounds were dissolved in DMSO and prepared at various concentrations ranging from 2-0.125 mg/mL. 0.15mL of the appropriate bacterium's overnight culture was placed on the molten agar plates. Cups were made in each sector designated with a marker on the underside of the bottom plate after the seeded plates had set. Six drops of the appropriate synthesized compounds (20 mg/mL) were placed in each cup. Fungi plates were incubated at 40°C for 48 h, while bacteria plates were incubated for 24 h. Clearance zones around each cup allowed inhibition, and their diameters were measured. The process was repeated using gentamycin and ketoconazole. Muller Hinton agar was utilized for fungi instead of nutrient agar for the bacteria.

3.2. Antioxidant activity by DPPH radical scavenging activity

The new compounds were tested for their free radicals utilizing the 1, 1-diphenyl-2-picrylhydrazyl (DPPH) method as described by Shen et al (2010). Compounds of different concentrations were prepared in ethanol, with 1 mL of each containing solutions having different concentrations (12.5, 25 and 50 mg/mL) were taken in different test tubes, 5 mL of 0.1 mM ethanol solution of DPHH was added and shaken vigorously. The test tubes were then incubated in a dark room temperature for 30 min. A blank DPHH was prepared without the compounds and ethanol was used for the baseline correction. Changes in absorbance at 517 nm were measured using UV-Visible spectrometer. The radical scavenging activities were calculated as a percentage of inhibition using the equation:

$$\text{DPPH radical scavenging activity} = \frac{A_c - A_s}{A_c} \times 100$$

where,
A_c = Absorbance of control,
A_s =Absorbance of sample.

4. Results and Dicussion

4.1. Chemistry

Sulphonamide and dipeptides are two significant pharmacophores that are ordered in accordance with their roles in the fight against microbial drug resistance. To synthesize compounds (18a-18d), we employed the use of conventional peptide coupling reagent, 1-hydroxybenzotriazole (HOBt) and 1- ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl) in the amidation of compounds (13a-13b) with substituted benzene- sulphonamides (1) derived from L-Valine (2). The activation of the carboxylic acid group of L-amino acid was increased with (HOBt) because (EDC.HCl) alone could not activate the carboxylic acid functionality. The use of HOBt and (EDC.HCl) was aimed to boost the coupling rates and reduce the risk of racemization. In this study, we synthesized and characterized compounds containing sulphonamide, carboxamide and dipeptides. The reaction of substituted benzenesulfonyl chloride (11) with L-valine (12) gave substituted benzenesulfonamide derivatives (13a-13b). The reaction of commercially available boc-protected tyrosine (14) with various amines (15) using HOBt, EDC.HCl and triethylamine as coupling reagent in DCM gave (16) which were deprotected with DCM/TFA for 1 h to yield carbamate derivatives of tyrosine (17). The amidation of Substituted benzenesulfonamide derivatives (13a-13b) with unprotected amides (17) using HOBt, EDC.HCl, TEA as peptide coupling reagents gave the targeted products (18a-18d). In the infrared spectra of the dipeptides, the bands between 3324 and 3321 cm^{-1} for N-H while 1674 and 1650 cm^{-1} for carbonyl of the amide respectively. In the ^{1}H-NMR spectra of the derivatives, the peaks at 8.81-8.80 ppm were assigned to aromatic protons. The carbonyl peaks in the ^{13}C-NMR spectrum, appears between 169 and 175ppm and peaks ranging from 116.90-148.30 ppm for aromatic carbons. The high resolution mass spectrometer (HRMS) peak of the derivatives appeared either as molecular ions (M^{+}) or (M^{-}). The results corresponded to the three decimals with the calculated values. The spectra used for the characterization of the new compounds are available as supporting material.

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
18a	9.08	9.68	9.77	9.57	9.25	7.18	7.99	8.80
18b	7.24	7.14	7.20	8.16	8.43	8.69	7.58	8.84
18c	7.88	7.99	10.40	7.90	7.55	7.78	8.27	8.15
18d	7.21	7.13	7.17	8.07	8.28	8.47	8.10	-
Gentamycin	10.45	10.48	10.50	10.48	10.42	10.55	-	-
Ketoconazole	-	-	-	-	-	-	10.52	10.50

4.2. Antimicrobial activity evaluation

Table 1 showed that all the synthesized compounds displayed antibacterial activities. The data in Table 1 revealed that compounds 18a, 18b and 18d with MIC value (7.18, 7.24, 7.14, 7.20, 7.21, 7.13 and 7.17 mg/mL) had an excellent antibacterial activities for *B.cereus, B.subtilis, S.aureus, K.pneumonia* respectively except compound 18c with MIC value (10.40 mg/mL) that have comparable activity with the standard drug (MIC 10.50). Compounds 18a and 18c showed best antifungal activities which inhibits the growth of fungi, against *C albicans and A niger* respectively.

Table 2: Result of *In vitro* antioxidant % inhibition and IC_{50} values of the synthesized compounds

Compds	% inhibition 50 mg / Ml	% inhibition 25 mg/mL	% inhibition 12.5 mg/mL	IC_{50} (mg/mL
18a	95.84 ± 0.16	89.97 ± 0,21	90. 86 ± 0.28	0.70
18b	94.39 ± 0.38	95.75 ± 0.31	94.58 ± 0.20	0.63
18c	94.74 ± 0.30	90.77 ± 0.35	91. 86 ± 0.40	0.71
18d	92.48 ± 0.88	95.75 ± 0.38	94.38 ± 0.50	0.64
Ascorbic acid	93.88 ± 0.44	95.78 ± 0.40	89.44 ± 0.41	0.75

The antioxidant activity shown in Table 1 revealed that all the synthesized compounds exhibited antioxidant activities. Compound 18b and I8d displayed almost the same percentage inhibition antioxidant activity as ascorbic acid at 25 mg/mL which indicates that the lower IC_{50} value the better antioxidant potential as described by Matuszewska (2018). This implies that compound 18b and 18d can serve as antioxidant agent's alternative to ascorbic acid.

5. Conclusion

In conclusion, four new Val-Tyro dipeptide sulphonamoyl carboxamides bearing moieties of pharmacological importance were synthesized and successfully characterized using spectroscopic techniques. The structures assigned complied with the spectral data. Compound 18a, 18b, and 18d were found to be the more active potent antibacterial agent while 18a and 18c were the most potent against antifungal agents while Compounds 18b and 18d have the most active antioxidant activity and might be considered the most promising agent.

Article Information

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