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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, molecular docking, antimicrobial, and antioxidant activities of new phenylsulfamoyl carboxylic acids of pharmacological interest

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Abstracts

The research explores the facile synthesis of some new phenylsulfamoyl carboxylic acids, their molecular docking, antimicrobial, and antioxidant activities. The procedure involved the mild reaction of amino acids with benzenesulfonyl chloride in a medium of aqueous base. The compounds were characterized using FTIR, ^{1}H-NMR, ^{13}C-NMR, and an elemental analysis. They were tested for their antimicrobial activities against S*taphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa, Salmonella typhi, Candida albicans, and Aspergillus niger* microorganisms. The antioxidant activity of the compounds were measured in vitro by the inhibition of generated stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical. The molecular docking was carried out properly and five different disease conditions were studied, namely: trypanosomiasis, malaria, bacterial, fungal infections, and oxidative stress. From the results, compounds **4c**, **4d**, **4e**, and **4g** possess more excellent in vitro antibacterial and antifungal activities than the standard drug Ofloxacin used. Compound **4e** displayed the most excellent antioxidant activity. Compound **4g** showed significant 2D interaction with amino acid residue of urate oxidase from *Aspergillus flavus* complexed with uracil. Interestingly, compounds **4a**, **4c**, **4d**, **4e**, and **4g** exhibited excellent antibacterial, antifungal, antioxidant, antitrypanosome, and antimalaria activities comparable to the corresponding standard drugs such as Penicillin, Ketoconazole; α-Tocopherol, Melarsoprol, and Chloroquine respectively. All the compounds were confirmed drug-like according to "Lipinski's rule of five". The compounds were found to be promising antibacterial, antifungal, antioxidant, and antitrypanosome agents.

Keywords Phenylsulfamoyl carboxylic acids · Antibacterial activity · Antifungal activity · Antioxidant activity · Molecular docking

Introduction

Compounds containing sulfonyl and amide groups are widely recognized as pharmaceutical compounds because of their excellent exhibition of a wide range of biological activities such as antimicrobial, antioxidant, anti-inflammatory, and anticancer (Madigan et al. 2012, Supuran et al. 2003). They are said to be the most widely used antibacterial agents employed in veterinary medicine, simply because they are cheap and relatively efficacious in the treatment and management of common bacterial diseases (Scozzafawa et al. 2003). The sulfa drugs generally comply with the principle of selective toxicity which takes advantage of some biological differences between the cells of mammals and bacterial (Henry 1943). Every bacterium cell needs folic acid for growth and replication. In humans, folic acid being a vitamin can be supplied by food and are diffused or transported into mammalian cells. On the contrary, folic acid does not permeate bacterial cell walls and therefore bacterial depend on synthesize of folic acid from *p*-aminobenzoic acid (Lehne 1994). Indeed, sulfonyl and amide groups when combined

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together play essential role in medicine, chemical, and pharmaceutical industries. However, there is a reduction in wide use of these drugs, probably because bacterial strains are developing resistance to the old existing sulfonamides, also toxicity, bioavailability, and drug potency of these drugs have been of great concern (Levy 2002; Karch 2011). This can be attributed to the fact that many researchers have limited their research to the conventional method of preparing sulfonamides using ordinary amines, and only a few detailed antimicrobial, antioxidant, and molecular docking studies have been reported (Greenfield and Grisanu 2008; Bonk et al. 2007). Amino acids are human friendly as opposed to amines (Lubec et al. 1991). α-Amino acids have been found better coupling partners in drug synthesis than ordinary amines because of the issues of odor, solubility, toxicity, and bioavailability (Bandelin and Walter 2006; Remko and Vonder-Lieth 2004; Crystal and Ron 2010). Moreover, α-amino acids are naturally occurring and the most important group of amino acids in the biological world (Young 1994). The use of α-amino acids in the research work is targeted at achieving improved drug potency with minimal or no toxicity. Therefore, an urgent need to intensify research on the synthesis of new phenylsulponamoyl carboxylic acids using biologically active amino acids and subjecting them to detailed antimicrobial, antioxidant, and molecular docking studies in order to maximize their usefulness has necessitated the research work.

Materials and methods

Chemistry

Reagents were purchased from Sigma-Aldrich. Melting points of the compounds synthesized were determined using electrothermal melting point apparatus and are uncorrected. Infrared spectra data were recorded on 8400s Fourier Transform Infrared (FTIR) (ABU, Zaria, Kaduna State, Nigeria). Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR) were run on 400 MHz using NMR spectrophotometer at Sandeep Verma Laboratory, Department of Chemistry, Indian Institute of Technology, Kanpur. Chemical shifts were reported in δ scale (neat). The antimicrobial studies were carried out at the Department of Microbiology, University of Nigeria, Nsukka. The antioxidant studies were carried out at the Biochemistry Department, University of Nigeria, Nsukka

General procedure for the synthesis of phenylsulfamoyl carboxylic acids

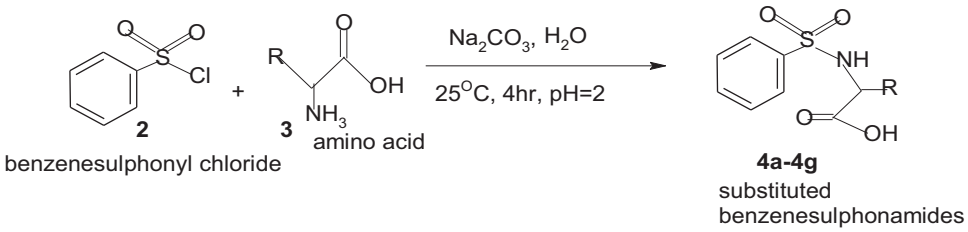
Using a 100 ml beaker, amino acid (25 mmol) was dissolved in water (30 ml) and sodium carbonate (5.58 g, 52.50 mmol) was added with continuous stirring to ensure complete dissolution of the solutes. The clear solution was cooled to 0 °C followed by the addition of benzenesulfonyl chloride (5.72 g, 30 mmol) in three portions for 1 h interval. Then the slurry was stirred for 5 h at room temperature and the reaction mixture was acidified to pH 2 with 2 M hydrochloric acid (HCl) to facilitate crystallization. It was allowed to settle down for at least 12 h and the product was separated through suction filtration. The filtered crude product was washed with tartaric acid (pH2.2) and dried to obtain substituted benzenesulfonamides alkanamides (**4a**–**4g**) in good to excellent yields (61–98.5%) shown in Scheme 1.

2-[(phenylsulfonyl)amino]propanoic acid (4a)

The amino acid used was analine, yield 3.83 g (82.6%), mp 117–118 °C, IR(KBr) cm^{-1}: 3328, 3268 (N–H), 3066 (C–H aromatic), 2991 (CH aliphatic), 1722 (C=O of COOH), 1154, 1087 (SO_2 two bands), 725 (Ar–H). ^{1}H-NMR (DMSO-d_6) δ: 10.63 (s, IH, OH of COOH), 8.16–8.15 (d, $J = 8.4$ Hz, 1H, NH–CH), 7.84–7.81 (d, $J = 8.53$ Hz, 2H, Ar–H), 7.67–7.57 (m, 3H, Ar–H), 3.78–3.73 (dd, $J_1 = 7.30$ Hz, $J_2 = 8.37$ Hz, 1H, NH–CH–CH_3), 1.14–1.12 (d, $J = 7.20$ Hz, 3H, CH_3–CH). ^{13}CNMR (CD_3N, 400 MH_Z) δ: 170.282, (C=O), 149.9 (2CH, 2C-5), 141.1 (2CH, 2C-3), 131.6 (CH, C-4), 129.6 (C, C-2), 64.3 (CH_3, C-7), 45.3 (C, CH, C-6). Anal. calcd. for $C_9H_{10}NO_4S$ (228.0): C, 47.35, H, 4.38, N, 6.14. Found: C, 47.34, H, 4.40, N, 6.20.

1-(phenylsulfonyl)pyrrolidine-2-carboxylic acid (4b)

The amino acid used was proline, yield 3.13 g (95.8%), mp 74–76 °C. IR(KBr) cm^{-1}: 3065 (CH aromatic), 2981 (O–H of COOH), 1722 (C=O of COOH), 1334, 1155 (S=O two



Scheme 1 Synthesis of substituted benzenesulfamoyl carboxylic acids

bands), 689 (Ar–H). ^{1}H-NMR ($CDCl_3$) δ: 10.09–9.98 (s, 1H, OH of COOH), 7.82–7.79 (d, $J = 8.77$ Hz, 2H,Ar–H), 7.58–7.49 (m, 3H, Ar–H), 4.79–4.78 (d, $J = 5$ Hz, 1H, CH–COOH), 3.78–3.75 (d, $J = 10$ Hz, 1H, CH of CH_2–N), 3.25–3.19 (d, $J_1 = 2.8$ Hz, $J_2 = 10$ Hz, 1H, CH of CH_2–N), 2.19–2.15 (m, IH, CH), 1.73–1.68 (m, 3H, CH_2, and CH), 1.49–1.44 (m, 1H, CH), 1.35–1.26 (m, 1H,CH). ^{13}C–NMR (DMSO-d_6) δ: 170.5 (C=O), 143.8 (2CH, 2C-5), 134.9 (2CH, 2C-3), 129.7 (CH, C-4), 127.4 (C, C-2), 67.3 (CH_2, C-7), 60.7 (CH_2, C-8), 48.8 (CH_2, C-9), 30.6 (CH, C-6). Anal. calcd. for $C_{11}H_{12}NO_4S$ (254.12): C, 51.94, H, 4.72, N, 5.51. Found: C, 51.89, H, 4.40, N, 5.46.

2-[(phenylsulfonyl)amino]-3-sulfanylpropanoic acid (4c)

The amino acid used was cysteine, yields 2.85 g (84.3%), mp 175–178 °C. IR(KBr) cm^{-1} : 3291 (N–H), 3168 (OH of COOH), 3063 (C–H aromatic), 2571 (S–H), 1736 (C=O of COOH), 1587 (C=C aromatic), 1326, 1151 (S=O two bands), 685 (Ar–H). ^{1}H-NMR (DMSO-d_6) δ: 10.96 (s, 1H, OH of COOH), 8.37–8.34 (d, $J = 8.41$ Hz, 1H, NH–CH), 7.79–7.77 (d, $J = 8.65$ Hz, 2H, Ar–H), 7.65–7.54 (m, 3H, Ar–H), 3.94–3.89 (dd, $J_1 = 8.41$ Hz, $J_2 = 20.01$ Hz, 1H, NH–CH–CH), 2.93–2.88 (dd, $J_1 = 5.61$ Hz, $J_2 = 20.10$ Hz, 1H, CH of CH_2–S), 2.62–2.56 (dd, $J_1 = 8.23$ Hz, $J_2 =$ 20.10 Hz, 1H, CH of CH_2–SH). 171.3 (C=O), 143.6 (2CH, 2C-5), 134.3 (2CH, 2C-3), 122.4 (CH, C-4), 120.5(C, C-2), 77.402, 77.1 (CH, C-6), 76.8 (CH_2, C-7). Anal. calcd. for $C_9H_{10}NO_4S_2$ (260.10): C, 41.52, H, 3.84, N, 5.38. Found: C, 41.47, H, 3.80, N, 5.42.

4-[(methylsulfanyl)-2-(phenylsulfonyl)amino]butanoic acid (4d)

The amino acid used was methionine, yield 2.90 g (82.1%), mp 127–129 °C, IR(KBr) cm^{-1}: 3324 (N–H), 3205 (OH of COOH), 3063 (CH aromatic), 1595 (C=C aromatic), 1312, 1162 (S=O two bands), 756 (Ar–H). ^{1}H-NMR (DMSO-d_6) δ: 10.74 (s, 1H, OH of COOH), 8.23–8.21 (d, $J = 8.7$ Hz, 1H, NH–CH), 7.78–7.76 (d, $J = 8.54$ Hz, 2H, Ar–H), 7.65–7.56 (m, 3H, Ar–H), 3.88–3.85 (dd, $J_1 = 4.10$ Hz, J_2 $= 8.81$ Hz, 1H, NH–CH–CH_3), 2.38–2.27 (m, 2H, CH_2S), 1.92 (s, 3H, CH_3), 1.84–1.75 (m, 2H, CH_2–CH_2–S). ^{13}CNMR (DMSO, 400 MHz) δ:171.3 (C=O), 146.5 (2CH, 2C-5), 137.4 (2CH, 2C-3), 133.8 (CH, C-4), 132.7 (C, C-2), 49.7 (CH, C-6), 48.4 (CH_2, C-7), 47.2 (CH_2, C-8), 47.0 (CH_3, C-9). Anal. calcd. for $C_{11}H_{14}NO_4S_2$ (288.14): C, 45.81, H, 4.86, N, 4.86. Found: C, 45.77, H, 4.40, N, 5.79.

3-hydroxy-2-[(phenylsulfonyl)amino]propanoic acid (4e)

The amino acid used was serine, yield 2.00 g (70.1%), mp 140–142 °C, IR(KBr) cm^{-1}: 3421 (N–H), 3287 (O–H of COOH), 2967 (CH aromatic), 1725 (C=O of COOH), 1449 (C=C aromatic), 1319, 1162 (S=O two bands), 760 (Ar–H). ^{I}HNMR (DMSO, 400 MHz) δ: 7.793–7.771 (m, 2H, ArH), 7.688–7.519 (m, 2H, ArH), 4.742 (s, IH, OH), 3.553–3.518 (m, IH, COOH), 2.482–2.475 (m, 3H, CH_3–C=O), 1.878 (s, IH, CH–OH). ^{13}CNMR (CD_3OD/ DMSO, 400 MHz) δ: 170.2 (C=O), 143. 4 (2CH, 2C-5), 130.8 (2CH, 2C-3) 125.9 (CH, C-4), 124.2 (C, C-2). Anal. calcd. for $C_9H_{10}NO_5S$ (244.10): C, 44.24, H, 4.10, N, 5.74. Found: C, 44.19, H, 4.10, N, 5.79.

3-hydroxy-2-[(phenylsulfonyl)amino]butanoic acid (4f)

The amino acid used was threonine, yield 2.99 g (88.9%), mp 143–145 °C. IR(KBr) cm^{-1}: 3533 (OH free), 3287 (N–H), 3063 (C–H aromatic), 2945 (O–H of COOH), 1714 (C=O of COOH), 1326, 1162 (S=O two bands), 685 (Ar–H). ^{1}H-NMR (DMSO-d_6) δ: 10.55 (s, 1H, OH of COOH), 7.82–7.81 (d, $J = 8.7$ Hz, 2H, Ar–H), 7.69–7.66 (d, $J = 9.3$ Hz, 1H, NH–CH), 7.61–7.53 (m, 3H, Ar–H), 3.99–3.98 (dd, $J_1 = 3.61$ Hz, $J_2 = 6.41$ Hz, 1H, CH–CH–CH_3), 3.69–3.67 (dd, $J_1 = 3.60$ Hz, $J_2 = 9.20$ Hz, 1H, NH–CH–CH), 2.08 (s, 1H, OH), 1.02–1.01 (d, $J =$ 6.40 Hz, 3H, CH_3–CH). ^{13}CNMR (DMSO, 400 MHz) δ: 171.4 (C=O), 141.9 (2CH, 2C-5), 133.8 (2CH, 2C-3), 129.4 (CH, C-4), 126.9 (C, C-2), 67.6 (CH, C-6). 61.6 (CH_2, C-7). for $C_{10}H_{12}NO_5S$ (258.12): C, 46.49, H, 4.65, N, 5.42. Found: C, 46.52, H, 4.69, N, 5.38.

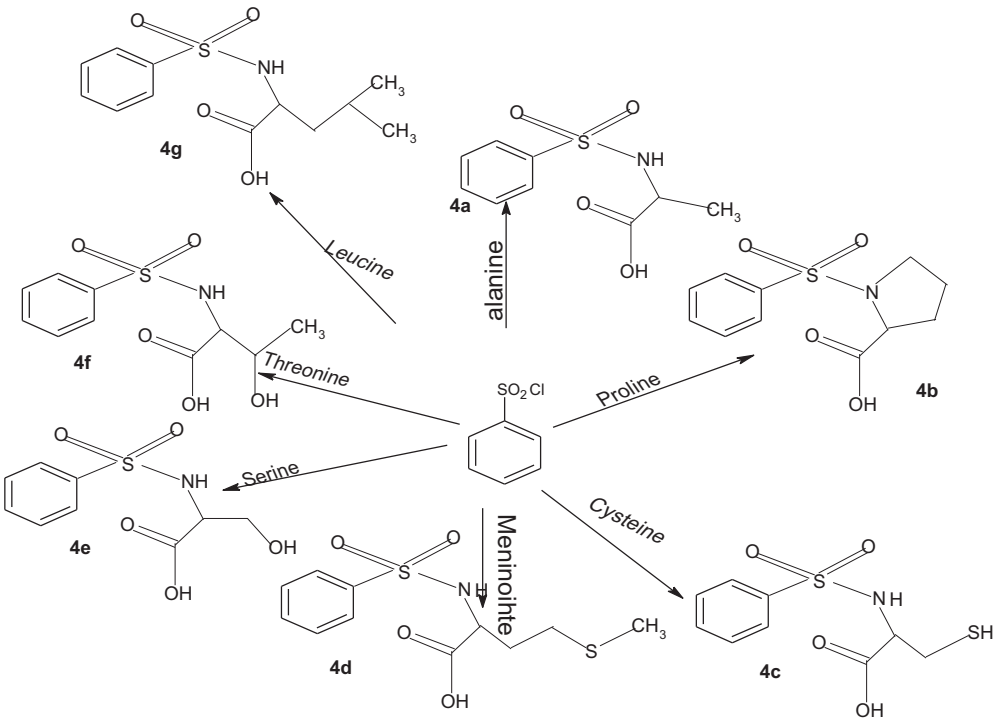
4-methyl-2-[(phenylsulfonyl)amino]pentanoic acid (4g)

The amino acid used is leucine, yield 2.82 g (88.1%), mp. 113–115 °C. IR(KBr) cm^{-1}: 3242 (N–H), 2959 (OH of COOH), 2922 (C–H aromatic), 1707 (C=O of COOH), 1312, 1166 (S=O two bands), 689 (Ar–H). ^{1}H-NMR, (DMSO-d_6) δ: 8.07 (d, $J = 8.62$ Hz, 1H), 7.66 (d, $J =$ 8.16 Hz, 1H), 7.51 (dd, $J_1 = 5.67$ Hz, $J_2 = 7.45$ Hz, 1H), 7.36 (d, $J = 8.08$ Hz, 1H), 7.16 (d, $J = 7.97$ Hz, 1H), 3.64 (d, $J = 8.30$ Hz, 1H), 2.31 (s, 3H), 1.57 (dd, $J_1 = 6.56$ Hz, $J_2 = 12.94$ Hz, 2H), 1.35 (m, 1H), 0.81 (d, $J = 6.61$ Hz, 3H), 0.68 (d, $J = 6.50$ Hz, 3H). ^{13}CNMR (DMSO, 400 MHz) δ: 171.2 (C=O), 137.1 (2CH, 2C-5), 133.8 (2CH, 2C-3), 133.6 (CH, C-4) 132.5 (C, C-2), 40.1 (CH, C-6), 39.8 (CH_2, C-7). Anal. calcd. for $C_{12}H_{18}NO_4S$ (263.10): C, 54.73, H, 6.84, N, 5.32. Found: C, 54. 69, H, 6.80, N, 5.28. (Scheme 2).

Antimicrobial studies procedure

The test microorganisms used

The test microorganisms used (*Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas*



Scheme 2 Synthetic pathway for new phenylsulfamoyl carboxylic acids

aeruginosa, Salmonella typhi, Candida albicans, and Aspergillus niger) were clinical isolates obtained from the department of pharmaceutical microbiology and biotechnology laboratory, University of Nigeria, Nsukka.

Standardization of the test organism suspension

The organisms were standardized using 0.5 McFarland turbid equivalents.

Control test (standard)

The standard antibiotic used was ofloxacin, ciprofloxacin, and fluconazole.

Experimental

A total of 4.0 ml of sample suspension of stock concentration 50 mg/ml was transferred to the sterile Petri dish, a 16.0 ml volume of double strength sterile molten agar was transferred to the same plate to mix uniformly thus, 1 mg/ml concentration was obtained. The other concentrations 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, and 0.1 mg/ml, were obtained using the same $C_1V_1=C_2V_2$ formula. The molten agar plates with different concentrations of the sample were allowed to gel. The plates were divided into seven equal parts with permanent marker. The test microorganisms were streaked on the segments, and labeled. The culture plates were incubated in inverted position at 37 °C for 24 h, and at 25 °C for 48 h. After the due period of incubation, the plates were observed for sensitivity and resistivity of the organisms to the agents, and the observation was recorded. The plates were further incubated for another 24 h at 37 °C, and 48 h at 25 °C to determine whether the activity was bacteriostatic or bactericidal. The observation was also recorded.

Antioxidant studies procedure

Antioxidant activity by DPPH method

The antioxidant behavior of the synthesized compounds were measured in vitro by the inhibition of generated stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical. The DPPH solution was prepared by dissolving 1.9 mg of DPPH in 100 ml of methanol. Three different concentrations (50, 100, and 200 µg/ml) of the DPPH soluion were prepared. Two milligrams of each of the synthesized compounds was weighed out and dissolved in 10 ml of appropriate solvent. The stock solution (200 µg/ml) was diluted further to get 100 and 50 µg/ml for each of the samples. The standard solution of ascorbic acid was prepared in similar manner. One milliliter of DPPH solution was added to 2 ml solution of the samples and ascorbic acid. The reaction mixture was vortexed thoroughly and left in the dark at room temperature for 30 min. The absorbance of the mixture was

measured (in triplicate) spectrophotometrically at 517 nm against the corresponding blank solution. The percentage scavenging DPPH radical inhibitions were calculated by using the following formula:

$$\text{DPPH radical scavenging activity}\,(\%) = \frac{\mathbf{Abs_{control}} - \mathbf{Abs_{sample}}}{\mathbf{Abs_{control}}} \times 100 \quad (1)$$

where, $Abs_{control}$ was the absorbance of DPPH radical and n-hexane/methanol, Abs_{sample} was the absorbance of DPPH radical and sample/standard.

In silico methodology

Physicochemical properties

The physicochemical properties of the synthesized compounds were generated in silico. They include Molecular weight (MW), number of hydrogen bond acceptor (HBA), number of hydrogen bond donor (HBD), number of rotatable bond (NRB), octanol/water partition coefficient logP (o/w), aqueous solubility (SlogP) and topological polar surface area (TPSA). These parameters were computed by descriptors calculator in Swiss dock and PreADME online servers. The drug-likeness was evaluated using Lipinski's rule of five.

Toxicity prediction

ProTox-II webserver was used to predict the toxicity of the synthesized compounds (Banerjee et al. 2018). The following toxicity endpoints were computed:

Predicted median lethal dose (LD_{50});

Organ toxicity (hepatotoxicity);

Toxicity endpoints including carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity;

Nuclear receptor signaling pathways including androgen receptor (AR) and estrogen receptor alpha (ER).

Molecular docking

Five different disease conditions were studied, namely: trypanosomiasis, malaria, bacterial and fungal infections, and oxidative stress. A drug target was chosen for each of the disease conditions for molecular docking studies. The drug targets for antitrypanosomiasis: *T. brucei* farnesyl diphosphate synthase complexed with minodronate (PDB code: **2EWG**); antimalarial: plasmepsin II, a hemoglobin-degrading enzyme from *Plasmodium falciparum*, in complex with pepstatin A (PDB code: 1SME); antibacterial: *E. coli* DNA gyrase in complex with 1-ethyl-3-[8-methyl-5-(2-methyl-pyridin-4-yl)-isoquinolin-3yl]urea (PDB code: **5MMN**); antifungal: urate oxidase from *Aspergillus flavus* complexed with uracil (PDB code: **1WS3**), and antioxidant: human peroxiredoxin 5 (PDB code: **1HD2**). The 3-dimensional structures of these drug targets were downloaded from the Protein Data Bank (PDB), (http://www.pdb.org) database. The prepared compounds were then subjected to interact with each of the receptors through molecular docking using PyRx. The protocol facilitates flexible compound docking for various compound conformers within the rigid receptor. Best conformation for each compound was chosen and the interaction was visualized in Discovery studio. The docking protocol was validated as shown in Fig. 1 with rmsd = 2.4 Å (Ekennia Anthony et al. 2018).

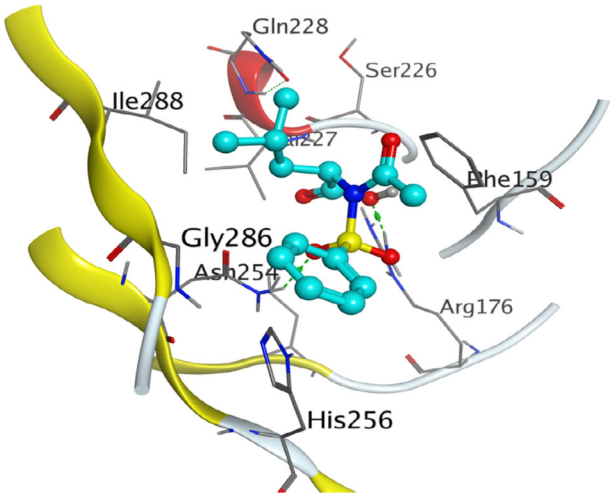


Fig. 1 The 2D representation of the interactions of compound 4g with the amino acid residues of 1WS3

Results and discussion

The synthesis of *para*-toluene sulfonamides was achieved by the reaction of p-toluene sulfonyl chloride with amino acids in a basic medium at temperature below 0 °C. Then the reaction mixture was stirred for 4 h at room temperature to generate *para*-toluene sulfonamides (**4a–4g**).

Reaction mechanism

When in an aqeous medium, an amino acid forms a zwitterions by the transfer of an ^{+}H ion from one end of the molecule to the other (Price et al. 1997). The reaction mechanism is represented in (Scheme 3) below.

Antimicrobial studies results

The antimicrobial Studies (Table 1) revealed that compounds **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, and **4g** have outstanding

Scheme 3 Reaction mechanism for new phenylsulphonamoyl carboxylic acids

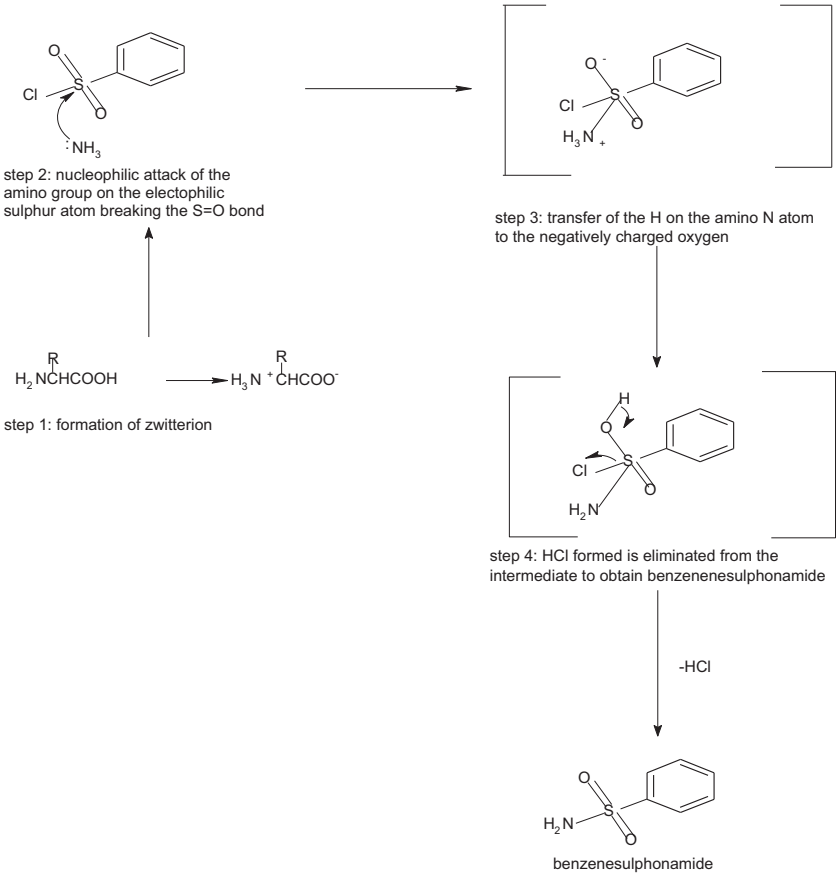


Table 1 Antimicrobial activities of compounds (**4a**–**4g**)

Minimum inhibitory concentration (MIC)(mg/ml)							
Compounds	*E. coli*	*S. typhi*	*S. aureus*	*B. sub*	*Ps. aerug*	*C. albicans*	*A. niger*
4a	ND	0.9	1.0	0.5	ND	0.7	0.9
4b	0.5	0.7	0.9	0.7	0.7	ND	0.9
4c	0.6	0.7	ND	0.9	ND	1.0	ND
4d	0.9	0.8	ND	0.8	ND	1.0	ND
4e	1.0	0.7	0.8	0.9	ND	0.7	ND
4f	0.9	0.9	0.8	0.6	0.9	0.9	0.8
4g	0.9	0.9	0.8	0.8	ND	ND	ND
Ofloxacin	0.5	1.0	1.0	2.0	2.0	ND	ND
Ciprofloxacin	2.0	1.5	2.0	2.0	2.0	ND	ND

ND not determined

antimicrobial (antibacterial and antifungal) activities when compared with commercial standard drug. It was also observed that compounds **4c**, **4d**, **4e**, and **4g** possess more excellent antibacterial and antifungal activities than the commercial standard drugs Ofloxacin used. This suggest that these new phenylsulfamoyl carboxylic acids can serve as better antibacterial and antifungal agents than standard commercial drugs and therefore should be considered accordingly.

Antioxidant studies results

The in vitro antioxidant studies (Table 2) showed that some of the tested compounds had antioxidant activities. Compounds **4c**, **4d**, and **4e**, showed impressive antioxidant activities. Only compound **4e** (96.70% inhibition at 200 µg/ml) had almost the same antioxidant activity with the standard ascorbic acid (96.83% inhibition at 200 µg/ml). This suggests that compounds **4e** was the most potent

Table 2 Antioxidant activities results

	200 µg/ml		100 µg/ml		50 µg/ml	
Sample	% inhibition	Std	% inhibition	Std	% inhibition	Std
Ascorbic acid	96.83	0.001	97.68	0.001	97.31	0.001
4c	94.26	0.012	82.30	0.002	37.91	0.011
4d	93.53	0.001	82.78	0.000	72.83	0.001
4e	96.70	0.000	73.50	0.001	71.79	0.000
4f	87.30	0.001	86.32	0.002	79.55	0.001

Table 3 Physicochemical properties

Mol	HBA	HBD	NRB	logP(o/w)	SlogP	TPSA	MW	LV
4a	4	3	4	0.97	0.44	83.47	229.26	0
4b	4	2	3	0.81	0.92	74.68	255.29	0
4c	4	3	5	1.08	0.35	122.27	261.32	0
4d	4	3	7	1.62	1.17	83.47	289.38	0
4e	5	4	5	−0.07	−0.59	103.70	245.25	0
4f	5	4	5	0.40	−0.20	103.70	259.28	0
4g	5	2	7	2.33	1.72	91.75	313.37	0

MW molecular weight, *HBD* hydrogen bond donor, *HBA* hydrogen bond acceptor, *logP(o/w)* octanol/water partition coefficient, *SlogP* aqueous solubility, *TPSA* topological polar surface area, *LV* Lipinski violation

antioxidant agent and therefore further derivatization of the potent compound **4e** is necessary to improve the drug-likeness.

Physicochemical properties results

The physicochemical properties to evaluate the drug-likeness of the synthesized compounds are shown in Table 3. Lipinski's rule of five (Ro5) is very important in assessing the drug-likeness of a molecule. According to this rule, a molecule must have molecular weight value of ≤500, hydrogen bond donor ≤5, hydrogen bond acceptor ≤10, and partition coefficient (Log *P*) value ≤5. Violation of more than one parameter may pose a challenge to the bioavailability of the molecule in case of oral formulation. From the results in Table 1, the synthesized compounds are in agreement with (Ro5).

Pharmacokinetics studies

The Pharmacokinetics profiles of the synthesized compounds are shown in Table 4. All the compounds showed a high gastrointestinal absorption. None of the compounds is a blood–brain barrier permeantm and therefore will not have any effect on the central nervous system (CNS). It was also observed that none of the compounds bound to the permeability glycoprotein (Pgp), an important protein of the cell membrane that pumps many foreign substances out of cells. The compounds did not inhibit any of the Cytochrome P450 enzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4). The log of skin permeability coefficient (log Kp) obtained for the compounds ranged from −7.92 to −5.96 cm/s.

Toxicity studies

The predicted toxicity of all the compounds is listed in Table 5. These compounds are inactive for hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. They are also inactive for nuclear receptor signaling AR and ER. The predicted LD50 for compounds ranged from 1200 to 2070 mg/kg.

Molecular docking results

The calculated free binding energy after molecular docking is given in Table 6. Our compounds showed strong binding affinities with all the receptors used for this study. Among all the compounds tested on 2EWG, 4 and 24 gave the lowest binding energy (highest binding affinity) of 15.01 and 15.19 kcal/mol, respectively. However, the standard drug for the treatment of trypanosomiasis (melarsoprol) showed highest binding affinity with 2EWG (−19.36 kcal/mol). Likewise, compound 43 showed the highest binding affinity (−13.49 kcal/mol) with the *Plasmodium falciparum* pepstatin A receptor (1SME) when compared with the standard drug (chloroquine) for malaria treatment, whose binding affinity is −10.08 kcal/mol. For the DNA gyrase receptor, compound 56 had more binding affinity with it (−11.93 kcal/mol) than with penicillin (−10.89 kcal/mol). The recptor for antifungal study, 1WS3 has highest binding affinity with compound 14 (−11.88 kcal/mol), which was better than that of ketoconazole (−10.38 kcal/mol). Finally, compounds 4 and 56 outperformed α-tocopherol in their binding affinities with **1HD2**. The binding affinities of 4 and 56 were −14.90 and −14.68 kcal/mol when compared with the standard drug (−9.34 kcal/mol).

To gain further insight into the molecular interactions of these compounds with the receptors, we examined their binding poses in the binding cavities of the drug receptors. These have been shown in Figs. 2 and 3.

Table 4 Pharmacokinetics profiles of the compounds

Comp	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
4a	High	No	No	No	No	No	No	No	−6.64
4b	High	No	No	No	No	No	No	No	−7.01
4c	High	No	No	No	No	No	No	No	−7.32
4d	High	No	No	No	No	No	No	No	−6.55
4e	High	No	No	No	No	No	No	No	−7.92
4f	High	No	No	No	No	No	No	No	−7.69
4g	High	No	No	No	No	No	No	No	−5.96

Table 5 Toxicity report

Comp	LD50 (mg/kg)	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	Androgen receptor (AR)	Estrogen receptor alpha (ER)
4a	1200	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
4b	1200	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
4c	1200	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
4d	2070	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
4e	1200	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
4f	2070	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
4g	2000	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive

Table 6 In silico antitrypanosomal, antimalerial, antibacterial, antifungal, and antioxidant activities

Compound	Antitrypanosomiasis 2EWG	Antimalaria 1SME	Antibacterial 5MMN	Antifungal 1WS3	Antioxidant 1HD2
4a	−13.40	−13.25	−10.36	−10.81	−12.73
4b	−12.87	−11.66	−10.17	−11.05	−11.83
4c	−14.34	−11.40	−10.84	−10.66	−13.42
4d	−14.21	−11.46	−10.43	−11.65	−12.79
4e	−14.48	−11.80	−10.68	−10.79	−13.49
4f	−13.85	−12.48	−10.58	−10.46	−12.18
4g	−13.25	−11.15	−11.03	−11.88	−12.41
Standard drug	−14.36	−10.08	−10.89	−10.85	−14.82

Standard drugs for 2EWG—Melarsoprol; 1SME—Chloroquine; 5MMN—Penicillin; 1WS3—Ketoconazole; 1HD2—α-Tocopherol

ADMET parameters

In silico antibacterial activities

The in silico antifugal studies (Table 6) revealed that compounds **4b, 4d**, and **4g** with binding energies −11.05, −11.65, and −11.88 kcal/mol, respectively possess more excellent antifungal activities that the commercial standard drug with binding energy −10.85 kcal/mole. This suggest that these new phenylsulfamoyl carboxylic acids can serve as better antifungal agents that standard commercial drugs and therefore should be considered accordingly.

In silico antioxidant activities

The in silico antioxidant studies (Table 6) revealed that only compounds **4c** and **4e** (−13.42 and 13.49 kcal/mol) had comparable binding energy with α-tocopherol (−14.82 kcal/mol). Compounds **4c** and **4e** are the most promising but not as effective as the standard ascorbic acid.

In silico antitrypanosomal activities

The in silico antitrypanosomal studies (Table 6) revealed that compounds **4c**, **4d**, and **4e**, having binding energy

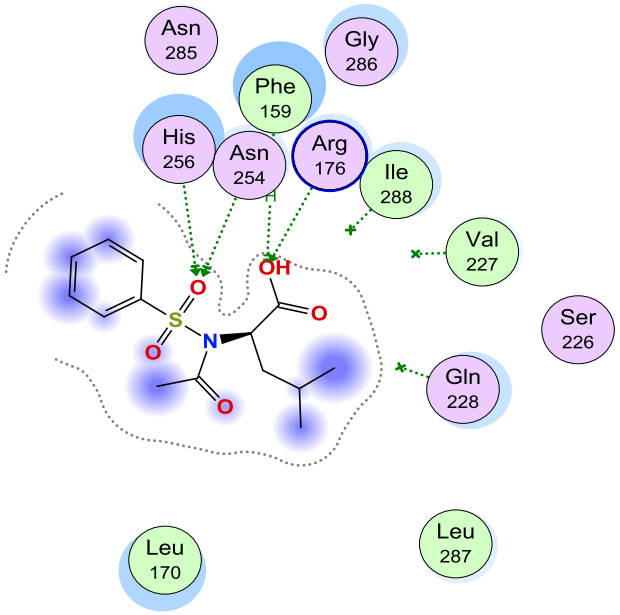


Fig. 2 Validation of the docking protocol

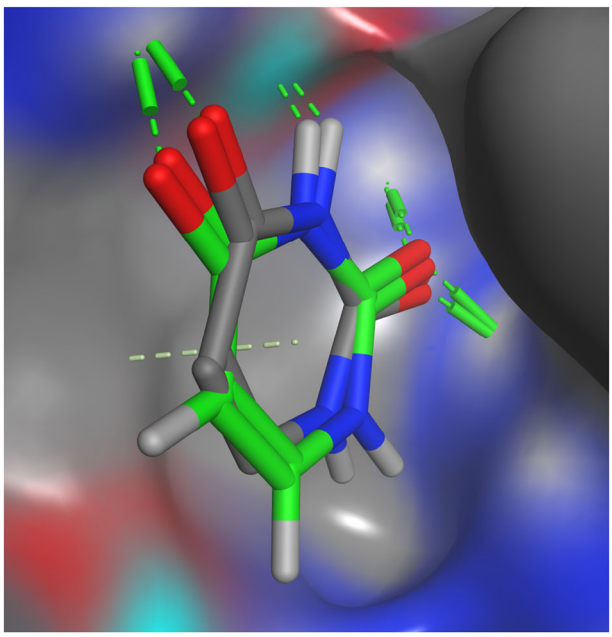


Fig. 3 The binding pose of compound 4g in the binding cavity of 1WS3

−14.34, −14.21, and −14.48 kcal/mol, respectively are comparable to the standard drug Melarsoprol (−14.36 kcal/mol). It implies that the new phenylsulfamoyl carboxylic acids can serve as inhibitors of *Trypanosome Brucei* and therefore should be considered in the treatment of trypanosomiasis (sleeping sickness).

In silico antimalarial activities

The in silico Antimalarial Studies (Table 6) revealed that all the compounds **4a**–**4g** with binding energy (−13.25, −11.66, −11.40, −11.46, −11.80, −12.48, −11.15 kcal/mol) against *Plasmodium Falciparuim* as excellent inhibitor of dihydrofolate reductase. These new phenylsulfamoyl carboxylic acids when compared with the most potent standard antimalaria agent Chloroquine (−10.08 kcal/mol) showed better binding energies with compound **4f**, being the most excellent and therefore can be used as antimalarial agents.

Figures 2 and 3 revealed how compound **4g** occupied the binding sites of 1WS3 and the necessary interactions between the 14 and the receptor. The H of the O-19 of 14 interacted with the π electrons from the 6-ring PHE 159 through H–π interactions. The intermolecular distance and energy of interaction were given to be 3.05 Å and −0.2 kcal/mol, respectively. Also, O-19 of 4 interacted with NH1 ARG 176 through H–acceptor interaction. Two other H-bond were observed. These were between O-21 and ND2 of ASN 254, and O-21 and CE1 of HIS 256.

Conclusion

In conclusion, a facile synthesis of phenylsulfamoyl carboxylic acids (**4a**–**4g**) was successful. The assigned structures were in agreement with the spectral data. They were also subjected to antimicrobial, antioxidant and in silico studies and were found to possess interesting biological and pharmacological activities. The findings demonstrated that compounds **4d**, **4e**, and **4g** possess more excellent in vitro antibacterial and antifungal activities and therefore potent antibacterial and antifungal agents. Compound **4e** displayed the most excellent antioxidant activity is therefore promising antioxidant agent. The molecular docking revealed that compound **4g** showed significant 2D interaction with amino acid residue of urate oxidase from *Aspergillus flavus* complexed with uracil and compounds **4a**, **4c**, **4d**, **4e**, and **4g** exhibited excellent antibacterial, antifungal, antioxidant, antitrypanosome, and antimalaria activities similar to the corresponding standard drugs. The synthesized compounds are potent antibacterial, antifungal, antioxidant, antitrypanosome, and antimalaria agents.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Bandelin FJ, Walter M (2006) The solubility of various sulphonamides employed in urinary tract infections. J Am Pharm Assoc 48:177–181

Banerjee P, Eckert AO, Schrey AK, Preissner R (2018) ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Res 46:W257–W263

Bonk JD, Amos DT, Olson ST (2007) Synthesis of benzenesulfonamide derivatives and biological evaluation. Synth Commun 37 (12):2039–2050

Crystal LL, Ron OB (2010) Review of advances in metabolic bioavailability of amino acids. Livest Sci J 133(1–3):4–9

Ekennia AC, Osowole AA, Onwudiwe D, Babahan I, Ibeji CU, Okafor S, Ujam OT (2018) Synthesis, characterization, molecular docking, biological activity and density functional theory studies of novel 1,4-naphthoquinone derivatives and Pd(II), Ni(II) and Co (II) complexes. Appl Organometal Chem 32(5);e403. https://doi.org/10.1002/aoc.4310

Greenfield A, Grisanu C (2008) Convinent synthesis of primary sulfonamides. Tetrahedron Lett 49:6300–6303

Henry RJ (1943) The mode of action of sulphonamides. Bacteriol Rev 7(40):175–262

Karch AM (2011) Focus on nursing pharmacology, 5th ed. Wolters Kluwer Health, Lippincott Williams, Philadelphia, p 115.

Lehne RA (1994) Pharmacology for nursing care, 2nd ed. W.B. Saunders company, Philadelphia

Lubec B, Herknere K, Bruckner H (1991) Amino Acids, 1:289.

Levy SB (2002) The antibiotics paradox: how the misuse of antibiotics destroy their curative powers, 2nd ed. Perseus Publ, Cambridge, Massachusetts, p 51

Madigan M, Martinko J, Stahl D and Clarck D (2012) Brock biology of microorganisms, 13 ed. Pearson Education, San Francisco, California, p 797

Price WD, Jockusch RA, Williams ER (1997) Is arginine a Zwitterion in the gas phase? J Am Chem Soc 119(49):11988–11989

Remko M, Vonder Lieth CW (2004) Theoretical study of gas-phase acidity, Pka, lipophilicity, and solubility of some biologically active sulfonamides. Bioorg Med Chem 12(20):5395–5403

Scozzafawa A, Owa T, Mastrolorenzo A, Supuran CT (2003) Anticancer and antiviral sulfonamides. Curr Med Chem 10(11):925–953

Supuran GJ, Casini A, Scozzafava A (2003) Sulfonamide type; anticancer, anti-inflammator, and antiviral agents. Med Res Rev 23:535–558

Young VR (1994) Adult amino acid requirement: the case for a major revision in current recommendations. J Nutr 124(8):1517–1523