CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.3250306

Available online at: http://www.iajps.com *Research Article*

DESIGN, SYNTHESIS AND MOLECULAR DOCKING OF NOVEL SERINE-BASED SULPHONAMIDE BIOACTIVE COMPOUNDS AS POTENTIAL ANTIOXIDANT AND ANTIMICROBIAL AGENTS.

***Egbujor, Melford. C[1], Okoro, Uchechukwu. C[2], Okafor, Sunday[3], Nwankwo, N.E[4]**

[1]Department of Industrial Chemistry, Renaissance University, Ugbawka, Enugu, Nigeria

[2]Synthetic Organic Chemistry Division, Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, Nigeria

[3]Department of Pharmaceutical and Medicinal Chemistry, University of Nigeria, Nsukka, Nigeria.

[4]Natural Science Unit, School of General Studies, University of Nigeria, Nsukka, Nigeria.

Article Received: April 2019 **Accepted:** May 2019 **Published:** June 2019

Abstract:

*Synthesis of new L-serine-based sulphonamide bioactive compounds as potential antioxidant and antimicrobial agents is reported. The reaction of p-toluenesulphonyl chloride (**a**) with L-serine(**b**) afforded 3-hydroxy-2-{[(4-methylphenyl) sulphonyl]amino}propanoic acid (**c**) which was acylated to afford the N-acylated compound **d**. Then chlorination and aminolysis of compound **d** gave 2-{acetyl[(4-methylphenyl) sulphonyl] amino}-3-hydroxypropanamide (**e**) which on nickel catalyzed amidation with aryl and heteroaryl halides afforded the various final products. The characterization of the title compounds was done with FTIR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis. The in vitro antimicrobial and antioxidant activities were determined. The compounds were subjected to in silico evaluation and the molecular docking studied bacterial infection, fungal infections and oxidative stress. Compound **d** was confirmed to be the most potent antimicrobial agents while, compounds **c** and **h** displayed the best antioxidant activities. The drug-likeness investigation demonstrated that all the tested compounds were likely drugs with excellent oral bioavailability. Similarly, the molecular docking revealed that compound **g** (-11.19 kcal/mol) could be a more preferable antibacterial agent than penicillin (-10.89 kcal/mol) while compound **c** (-10.97kcal/mol) outperformed ketoconazole as an antifungal agent.The potentiality of the synthesized compounds to function as antimicrobial and antioxidant agents was confirmed.*

Keywords: *Serine; carboxamide; sulphonamide; antimicrobial activity; antioxidant activity; molecular docking.*

Corresponding author:

Egbujor, Melford Chuka,

Department of Industrial Chemistry, Renaissance University, Ugbawka, Enugu, Nigeria

Tel: *+234(0)8037530299*

E-mail:egbujormc@gmail.com

QR code

Please cite this article in press Egbujor, Melford Chuka et al., ***Design, Synthesis and Molecular Docking Of Novel Serine-Based Sulphonamide Bioactive Compounds As Potential Antioxidant And Antimicrobial Agents.,****Indo Am. J. P. Sci, 2019; 06(06).*

INTRODUCTION:

The general public health is presently being threatened by the prevalence of antimicrobial resistant microorganism (Xiangke 2016) and multiple oxidative stress related diseases. Certain amino acids have been found to exhibit considerable inhibitory activities against bacterial growth (Rowley 1953) (Amos 1954). Saito and Yamada in 2001 established that L-serine was the most effective amino acid in bacterial growth inhibition (Saito and Yamada in 2001). Moreover, L-serine in addition to its numerous biological activities was discovered to possess excellent antioxidant activities on plasma lipids levels in hypercholesterolemic mammals (Morahedian 2006). Similarly bioactive compounds of sulphonamide and Carboxamide functionalities have been used as antimicrobial agents (Raul *et al.*, 2011), anticancer agents (Yelland *et al.*,2007), antimalaria agents (Verhaeghe *et al.*, 2008), antiretroviral agents (Jiao *et al.*,2010) and hypertensive agents (Ananthanarayanan*et al.*,1993)respectively.

Unfortunately, while the antimicrobial resistance menace is increasing, the rate at which novel antibiotics are developed is rather sluggish (Arias 2009). The observed decline in the drug efficacy of the existing antibiotics and the preponderance of oxidative stress related diseases is also worrisome and therefore needs an imminent solution. The combination of biologically active amino acids especially L-serine with bioactive compounds of sulphonamide and carboxamide is obviously an urgent approach to improve drug potency for the effective management of antimicrobial resistance (Egbujor and Okoro 2019) (Cottarel 2007) and oxidative stress related diseases(Morahedian 2006). This research is necessitated by the fact that L-serine potentiates sulphonamide and carboxamide activities against microbial infections and oxidative stress hence the need to couple all the pharmacophores into a drug molecule for the best synergistic action.

MATERIAL AND METHODS:

Instrumentation

Reagents were sourced from Sigma Aldrich. The melting points of compounds were determined with electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FTIR8400s spectrophotometer using KBr. ^{1}H-NMR spectra were recorded on 400MHz, bruker spectrometer in $CDCl_3$ or DMSO and chemical shifts were recorded in part per million (ppm) using tetramethylsilane as a standard. The elemental analysis was done with elemental analyzer (Exeter Analytical Inc.model:CE440). For reactions requiring inert atmosphere, nitrogen gas was used. Precipitation of compounds was in analytical grade and reactions were monitored by TLC on precoated silica gel.

Chemistry

Method of synthesis of 3-hydroxy-2-{[(4-methylphenyl)sulphonyl]amino}propanoic acid (c)

L-serine (**b)** (12.5mmol) was dissolved in water (15ml) and 2.80g Na_2CO_3 (26.25mmol) was added and stirred. It was cooled to 0^{o}C and 2.6g of *p*-toluenesulphonylchloride(**a**) (15mmol) was added in five portions within 1 hour interval. The slurry was stirred using a magnetic stirrer for 4 hours at room temperature and acidified to pH of 2 with 2M hydrochloric acid for recrystallization. The reaction was monitored with TLC (MeOH/DCM, 1:7). The reaction content was allowed to settle overnight and the products were afforded by suction filtration after which it was washed with tartaric acid (pH2.2) and dried in desiccators.

3-hydroxy-2-{[(4-methylphenyl) sulphonyl]amino}propanoic acid(c): Appearance: white solids, yield 2.84(72.1%), mp, 92-94^{0}C, IR(KBr)cm^{-1} : 3404(N-H), 3281(O-H of COOH), 2956(CH aromatic), 1734(C=O of COOH), 1588(C=C aromatic), 1372, 1171(S=O two bands), 809(Ar-H). ^{1}HNMR (DMSO, 400MHz) δ: 7.794-7.772(m, 2H, ArH), 7.687-7.518 (m, 2H, ArH), 4.743(s, IH, OH), 3.554-3.519(m,IH, COOH), 2.483-2.476 (m, 3H, CH_3-C=O), 1.879 (s, IH, CH-OH). ^{13}CNMR (CD_3OD/DMSO, 400MHz) δ: 170.235(C=O), 133.419, 129.815, 124.875, 124.253, 124.017, 123.767 (aromatic carbons), 60.322, 47.232, 34.674 (aliphatic carbons). Anal.calcd.(%) for $C_9H_{11}NO_5S$ (259.10): C, 46.32, H, 5.07, N, 5.41, S, 12.35. Found: C, 46.33, H, 5.09, N, 5.40, S, 12.36

Acylation of 3-hydroxy-2-{[(4-methylphenyl) sulphonyl]amino}propanoic acid

2grams of 3-hydroxy-2-{[(4-methylphenyl) sulphonyl]amino}propanoic acid was introduced to a 100ml beaker; concentrated hydrochloric acid (9ml) and distilled water (25ml) were added to the beaker and stirred. In a different beaker, sodium acetate (16.6g) was dissolved in distilled water (50ml). Then, acetic anhydride (13.4ml) was added in four portions to the HCl solution over an hour interval after which it was poured into the sodium acetate solution. The mixture was vigorously stirred with a glass rod and immersed in an ice bath for 1 hourperiod and filtered to afford compound **d**

2-{Acetyl[(4-methylphenyl)sulfonyl]amino}--3-hydroxypropanoic acid(d)

Yield 2.30g (96.4%), mp.202-203^{0}C, IR (KBr)cm^{-1}: 3653 (OH free), 3288 (OH of COOH), 3064(C-H aliphatic), 1998 (C-H aromatic), 1823, 1726 (2C=O), 1449,1406 (C=C), 1318, 1231 (2S=O), 1163(SO_2-NH), 1069 (C-N), 724(Ar-H). ^{1}HNMR (DMSO/$CDCL_3$) 400MHz) δ: 10.236(m,2H,OH),7.486-7.466 (d, J= 8.0Hz, 2H, ArH), 7.024-7.003 (d, J= 91.2 Hz, 2H, ArH), 2.201 (S, 3H CH_3 C=O), 2.167 (S, 3H, CH_3Ar). ^{13}CNMR (DMSO/$CDCl_3$, 400 MHz)δ: 170.124, 169.122, 2(C=O), 141.848, 140.309, 129.488, 128.881, 126.855, 125.747, (aromatic carbons) 78.684, 78.358, 78.031, 39.293 (aliphatic carbons). Anal.calcd.(%) for $C_{12}H_{15}NO_6S$ (301.32): C, 47.80, H, 4.97, N, 4.64, S, 10.63. Found: C, 47.80, H, 4.95, N, 4.66, S, 10.62.

Chlorination and aminolysis of 2-{Acetyl[(4-methylphenyl)sulfonyl]amino}-3-sulfanylpropanoic acid (d)

Chlorination

A three necked flask(250ml) containing 2-{Acetyl[(4-methylphenyl)sulfonyl]amino}-3-sulfanylpropanoic acid (**d**) (1mmol) and acetone (10ml) was equipped with magnetic stirring bar and closed, the content was cooled to 0^{o}C. The mixture was stirred at 80^{o}C under reflux for 3 hours, and was taken to water bath at 80^{o}C to evaporate excess thionyl chloride. Acetone (20ml) was added and evaporated twice and the acid chloride was obtained.

Aminolysis

The acid chloride was immediately dissolved in acetone (20ml) and cooled to 0-5^{o}C, crystallized with ammonia (2ml) and then allowed to stay overnight after which it was filtered and washed with acetone to afford compound **e.**

2-{acetyl[(4-methylphenyl)sulphonyl]amino}-3-hydroxypropanamide (e)

Yield 3.14g (93.6%), mp.213-214^{0}C, IR (KBr)cm^{-1}: 3168(O-H), 2989, 2870(2N-H), 2064(C-H aliphatic), 2012(C-H aromatic), 1804, 1736(2C=O), 1595, 1449 (C=C). 1155, 1118 (2S=O), 1006 (C-N), 8678 (Ar-H). ^{1}HNMR (DMSO, 400MHz) δ: 7.160-7.129 (d, J= 12.4Hz,2H, ArH) 7.110-7.031 (d, J= 31.6Hz, 2H, ArH), 3.451 (s, H_2, NH_2), 3.239 (S, 3H, CH_3 –C=O). 2.476 (s, 3H, CH_3-Ar) 2.473 (s,IH, OH) 2.267 (s,IH,CH). ^{13}CNMR (CD_3OD/DMSO, 400 MHz) δ: 171.876, 170.234, 2(C=O), 133.417, 129.813, 124.873 124.251, 124.015, 123.765, (aromatic carbons), 78.654, 71.453, 68.541, 42.673(aliphatic carbons). Anal.calcd.(%) for $C_{12}H_{16}N_2O_5S$ (300.33): C, 47.95, H, 5.33, N, 9.32, S, 10.65. Found: C, 47.93, H, 5.35, N, 9.30, S, 10.66.

Nickelcatalysed synthesis of serine-based carboxamides derivatives.

Preparation of bis(triphenylphosphine)nickel(II)chloride complex

L.M Venanzi (Venanzi 1958) reaction procedure was used, nickel(II)chloride hexahydrate catalyst(2.37g, 10mmol) was dissolved in distilled water(2ml) and dilution with glacial acetic acid (50ml). In another beaker, triphenylphosphine ligand(5.25g, 20mmol) was dissolved in 25ml glacial acetic acid and poured into the nickel(II)chloride hexahydrate catalyst solution. There was formation of green precipitate which was allowed to settle for 24hours. The co-ordination compound a dark blue crystal was obtained on filtration, washed with glacial acetic acid and dried in the desiccator.

Cysteine-based sulphonamoyl carboxamide derivatives

The complex compound bis(triphenylphosphine) nickel(II)chloride(6.54g, 10mmol) and ligand triphenylphosphine(5.25g, 30mmol) were added to a three necked flask (250ml). With the help of a syringe, *t*-butanol(4ml) and distilled water(2ml) were added as solvents in the ratio of 2:1 and the mixture was stirred for 10mins at room temperature under nitrogen inert atmosphere. Then the mixture was heated at 80^{o}C for 1.5min followed by the addition of2-{acetyl[(4-methylphenyl)sulphonyl]amino}-3-hydroxypropanamide(10mmol), K_2CO_3(1.38g,10mmol), substituted aryl halide (4-chloroaniline) and heteroaryl halides(4-amino-3-chloropyridine and 5-chloro-4,6-diaminopyrimidine). The solvents *t*-butanol and H_2O were further added in the ratio of 2:1 under inert atmosphere and the mixture was refluxed and stirred for 1hour at 100^{o}C-110^{O}C, cooled to room temperature. On addition of ethyl acetate the crystals were formed and washed with water to afford compounds **f-h**.

2-{acetyl[(4-methylphenyl)sulphonyl]amino}-N-(4-aminophenyl)-3-hydroxypropanamide (f)

Yield 3.15g (93.6%), mp.95-96^{0}C, IR (KBr)cm^{-1}:3608 (OH free), 3309, 3278 (2N-H), 3000 (C-H aliphatic) 1992 (C-H aromatic), 1815, 1715 (2C=O) 1580 (C=C), 1308, 1278 (2S=O), 1135(SO_2-NH), 1121 (C-N) 741 (ArH). ^{1}HNMR (DMSO, 400MHz) δ: 7.501 -7.481 (d, J= 0.02Hz, 2H, ArH), 7.286 (m, 2H, ArH), 7.159-7.128 (d, J= 12.4Hz,2H, ArH) 7.109-7.030 (d, J= 31.6Hz, 2H, ArH), 3.840 (s, H_2, NH_2) 2.481 (s, 3H, CH_3 C=O), 2.476 (s, 3H, CH_3-Ar) 2.473 (s,IH, OH) 2.267 (s,IH,CH). ^{13}C-

NMR($CDCl_3$/ACN, 400MHz) δ: 170.444, 169.333,2(C=O), 137.189, 133.737, 133.554, 129.062, 128.827, 128.410, 125,908, 123.564, 121.675, 119.809, 116.865, 113.654(aromatic carbon), 79.472, 79.146, 78.820, 40.385 (aliphatic carbons). Anal.calcd.(%) for $C_{18}H_{21}N_3O_5S$ (391.44): C, 55.18, H, 5.36, N, 10.73, S, 8.17. Found: C, 55.20, H, 5.38, N, 10.71, S, 8.19.

2-{acetyl[(4-methylphenyl)sulphonyl]amino}-N-(4-aminopyridine-3-yl)-3-hydroxypropanamide (g)

Yield 3.05g (91.5%), mp.96-97^{0}C, IR (KBr) cm^{-1}:3753(O-H), 3519,3377(2N-H), 2922 (C-H aliphatic), 1982 (C-H aromatic) 1810,1710 (2C=O), 1617 (C=N), 1252, 1177 (2S=O), 1126, 1039 (SO_2N), 1018 (C-N), 983, 918 (C=C), 812(Ar-H). ^{1}HNMR (DMSO, 400MHz)δ: 8.081 (m, 2H, ArH), 7.264 (m, 2H, ArH,) 6.485(s, 2H, ArH), 3.317 (s, 2H, NH_2), 2.464 (s, 3H, CH_3 –C=O), 2.246 (s, 3H, CH_3-Ar), 1.758 (s, IH, CH), 1.384 (s, IH, OH). ^{13}CNMR (DMSO/$CDCl_3$, 400MHz)δ: 170.332, 169.441, 2(C=O), 156.543(C=N), 137.189, 133.737, 133.554, 129.062, 128.827, 128.410, 125.113, 123.675, 120.653, 117.908, 114.321(aromatic carbon), 79.472, 79.146, 78.820, 40.385 (aliphatic carbons). Anal.calcd.(%) for $C_{17}H_{20}N_4O_5S$ (392.43): C, 51.98, H, 5.10, N, 14.27, S, 8.15. Found: C, 51.96, H, 5.12, N, 14.29, S, 8.20.

2-{acetyl[(4-methylphenyl)sulphonyl]amino}-N-(4,6-diaminopyrimidine-5-yl)-3-hydroxypropanamide (h)

Yield 3.19g (94.3%), mp106-105^{0}C, IR (KBr) cm^{-1}:3339 (N-H), 3198 (C-H aliphatic) (C-H aromatic), 1625, 1620 (C=N), 1580 (N-H), 1177, 1121 (2S=O) 1036 (C-N), 890 (C=C), 723(Ar-H). ^{1}HNMR (DMSO, 400MHz) δ: 7.481 (m, 2H, ArH), 7.460 (d, J = 7.4Hz, 2H, ArH) 7.109 (m, 2H, ArH), 7.081 (m, 1H, ArH), 3.238 (S, 3H, CH_3 –C=O). 2.574 (m, 4H, $2NH_2$), 2.316 (m, 3H, CH_3 –Ar). ^{13}CNMR (DMSO, 400MHz) δ:170.890, 169.334, 2(C=O), 157.841, 155.432 (C=N) 144: 269, 139.238, 128.880, 125.898, 123.554, 120.305, 118.654, 115.564 (aromatic carbons), 40.035, 39.831, 39.618, 39.413, (aliphatic carbon). Anal.calcd.(%) for $C_{16}H_{20}N_6O_5S$ (408.43): C, 47.01, H, 4.90, N, 20.57, S, 7.83. Found: C, 47.02, H, 4.92, N, 20.59, S, 7.84.

Antimicrobial studies

Using Agar dilution method (Wiegand *et al.*,2008), all the synthesized compounds were evaluated for their in vitroantimicrobial activity against pathogenic microorganisms such S*taphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa, Salmonella typhi* bacteria and *Candida albicans, and Aspergillus niger* fungi which were clinical isolates procured from pharmaceutical microbiology and biotechnology laboratories, University of Nigeria, Nsukka. The standardization of organisms was carried out with 0.5 McFarland turbid equivalents. All the synthesized compounds were dissolved in DMSO to obtain a concentration of 1mg/ml. The compounds were prepared in different concentrations from 0.1mg/ml to1.0mg/ml in DMSO. Then molten agar plates of various concentrations of the title compound were allowed to gel and the plates were fragmented into seven equal using a permanent marker and the test microorganisms were streaked on the divisions and labeled. The incubation of the culture plates was done on molten agar slants at 37^{o}c for 24hours and the plates were observed for microbial susceptibility to the agents. Ofloxacin was used as a standard for antibacterial activity and Fluconazole for antifungal activity. The minimum inhibitory concentrations for all the synthesized and standard compounds are given in **table 1**.

Antioxidant activity by DPPH method

The antioxidant activities of the synthesized compounds were investigated *in vitro* by the inhibition of generated stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical according to Blois procedure (Blois 1958). The DPPH solution preparation involved dissolving 1.89 mg of DPPH in 100 ml of methanol. Also various concentrations (50, 100 and 200 µg/ml) of the DPPH soluion were prepared. 2 mg of the sythesized compounds were weighed and dissolved in 10 ml of the solvent. Then the stock solution of 200µg/ml was diluted to obtain 100 and 50 µg/ml for each of the synthesized compounds. Ascorbic acid was also prepared with the same method as a standard and 1ml of DPPH solution was added to 2 ml solution of the compound and ascorbic acid. The mixture was shaken and allowed to stay undisturbed for 30minutes in the dark at room temperature. Then absorbance was recorded in triplicate with spectrophotometer at the wavelength of 517 nm against the corresponding blank solution. The percentage scavenging DPPH radical inhibitions were calculated by using:

DPPH radical scavenging activity (%)

$$= \frac{\mathbf{Abs_{control}} - \mathbf{Abs_{sample}}}{\mathbf{Abs_{control}}} \times \mathbf{100}$$

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

The 50% inhibitory concentrations (IC_{50}) of the compounds were calculated by plotting the graph of percentage inhibition against the concentration of the synthesized compounds used.

***In silico* procedure**

Physicochemical properties

The*in silico* method was used to generate the physicochemical properties of the sythesized compounds and important parameters were recorded. The parameters such as the number of hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), number of rotatable bond (NRB), octanol/water partition coefficient logP(o/w), molecular weight of the compounds (MW), total polar surface area (TPSA) and aqueous solubility (SlogP) were computed using the descriptors calculator in Molecular Operating Environment (MOE, 2018) and the drug-likeness of compounds was evaluated in compliance with Lipinski's rule of five.

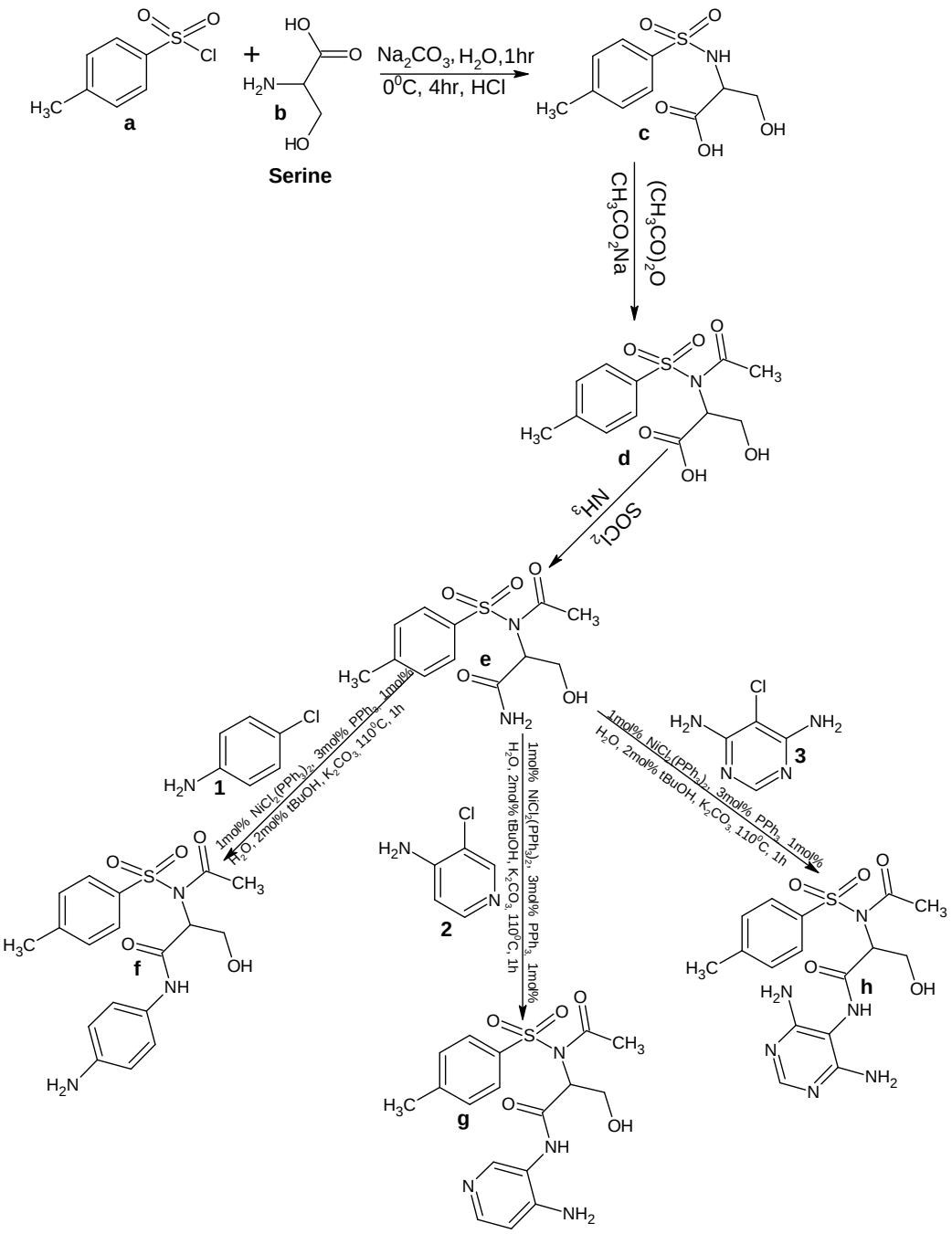
Molecular docking

The molecular docking studied three human diseases such as bacterial infection and fungal infections and oxidative stress. The drug targets selected for antibacterial was *E. coli* DNA gyrase in complex with 1-ethyl-3-[8-methyl-5-(2-methyl-pyridin-4-yl)-isoquinolin-3yl]urea (PDB code: **5MMN**) while the drug target for antifungal was urate oxidase from *Aspergillus flavus* complexed with uracil (PDB code: **1WS3),** the selected drug target for antioxidant was human peroxiredoxin 5 (PDB code: **1HD2)**. From the Protein Data Bank (PDB), (http://www.pdb.org) database, the 3-Dimensional structures of the drug targets were downloaded and loaded into Molecular Operating Environment (MOE, 2018),the preparation and energy minimization of the ligand molecules was done with the help of the QickPrep in MOE and MMFF94 force field respectively. The prepared compounds interacted with each of the receptors through molecular docking and this process helps a flexible compound docking for various compound conformers within the rigid receptor. Then the perfect conformation for each test compound was chosen and the interaction was observed with the Discovery studio.

RESULTS:

Chemistry

The reaction of *p*-toluenesulphonyl chloride (**a**) with L-serine(**b**) afforded 3-hydroxy-2-{[(4-methylphenyl) sulphonyl]amino}propanoic acid (**c**) which was subjected to acylation to afford the *N*-acylated derivative 2-{Acetyl[(4-methylphenyl)sulfonyl] amino}--3-hydroxypropanoic acid (**d).** The acylation reaction is to ensure that the amino acid end of the sulphonamide is protected against unwanted side reactions. Then chlorination and immediate aminolysis of compound **d** gave2-{acetyl[(4-methylphenyl)sulphonyl]amino}-3-hydroxy propanamide (**e)** which was subjected to nickel catalyzed amidation with aryl and heteroaryl halides to obtain the final products (**f-h**).The purpose of the chlorination and aminolysis is to ensure that there is a formation of carboxamide functional group at the un-activated carboxylic acid end of the L-serine(http://www.britannica.com)as shown in **scheme 1.**



Scheme 1: The synthetic route

Antimicrobial Evaluation

Table 1: Antimicrobial activities of compounds

Minimum inhibitory concentration (mg/ml) of compounds

Compound No	*E.coli*	*S.typhi*	*S.aureus*	*B. sub*	*Ps.aerug*	*C.albicans*	*A. niger*
c	0.9	+	0.9	0.8	0.9	+	+
d	0.6	0.9	0.7	0.4	0.9	0.6	0.9
e	0.9	0.8	+	0.8	0.6	0.7	+
f	0.4	0.5	0.5	0.4	+	+	+
g	0.6	0.4	0.7	0.8	+	+	+
h	0.8	0.9	0.5	0.5	0.7	0.8	+
Ofloxacin	0.005	0.005	0.010	0.020	0.025	+	+
Fluconazole	+	+	+	+	+	0.020	0.005

Key: + = no activity.

Table 2: Percentage inhibition and IC_{50} values of compounds

Compounds	200 µg/ml % inhibition	100 µg/ml % inhibition	50 µg/ml % inhibition	IC_{50} (µg/ml) Values
Ascorbic acid	96.83± 0.001	97.68 ± 0.001	97.31 ± 0.001	0.989
c	95.60 ± 0.002	92.37 ± 0.001	81.17 ± 0.001	0.999
d	79.12 ± 0.001	82.17 ± 0.001	79.55 ± 0.001	1.230
e	77.96 ± 0.001	77.17 ± 0.001	74.97 ± 0.001	1.293
f	48.29 ± 0.001	92.13 ± 0.001	73.44 ± 0.003	1.389
g	64.90 ± 0.001	90.66 ± 0.001	29.49 ± 0.001	1.615
h	85.59 ± 0.001	87.07 ± 0.001	80.03 ± 0.003	1.173

Key: The standard antioxidant drug used is Ascorbic acid.

Results of Molecular Docking Evaluation

Table 3: Physicochemical properties of synthesized compounds

Mol	HBA	HBD	NRB	logP(o/w)	SlogP	TPSA	MW	lip_violation
c	5	4	5	0.23	0.28	103.70	259.28	0
d	5	2	8	1.87	1.74	91.75	301.32	0
e	5	2	6	0.55	0.62	117.77	300.33	0
f	5	3	7	0.79	1.11	129.80	391.44	0
g	6	3	7	0.45	0.51	142.69	392.43	0
h	6	3	9	0.99	1.54	161.37	408.43	0

Table 4: Results of *In silico* Antibacterial, Antifungal and Antioxidant Activities evaluations.

Compound	Antibacterial	Antifungal	Antioxidant
	5MMN	**1WS3**	**1HD2**
c	-10.83	-10.97	-12.39
d	-10.54	-10.48	-12.28
e	-8.98	-9.40	-12.31
f	-10.03	-9.01	-11.02
g	-11.19	-9.41	-11.24
h	-11.19	-9.13	-12.56
Standard drug	-10.89	-10.85	-14.82

Key: 5MMN, **1WS3**and **1HD2aredrug targets for antibacterial, antifungal and antioxidant activities**.

Standard drugs for **5MMN**= Penicillin; **1WS3**= Ketoconazole; **1HD2 = α**-Tocopherol.

DISCUSSION:

Antimicrobial activity evaluation

Table **1** reveals that all the synthesized compounds displayed considerable antimicrobial activities. Compounds **d, f, g** and **h** displayed the best antibacterial activities having inhibited the growth of all the bacteria used as test microorganism namely S*taphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa, Salmonella typhi* while compound **d** had the best antifungal activities having inhibited the growth of all the fungi such as *Candida albicans and Aspergillus niger*. Summarily, compound **d** was the only compound that inhibited the growth of all the bacteria and fungiand therefore the most potent antimicrobial agent synthesized.

Antioxidant activity evaluation

Table 2 revealed that all the title compounds exhibited antioxidant activities which would prevent or slows down the progress of oxidative stresses. Compounds **c** and **h** had excellent antioxidant activities. Compound **c** (95.60% inhibition at 200µg/ml) displayed almost the same antioxidant activity as ascorbic acid (96.83% inhibition at 200µg/ml). It is also important to note that lower IC_{50} value implies better antioxidant potential and the IC_{50} value of compound **c** 0.999µg/mg is comparatively almost the same with that of ascorbic acid 0.989µg/ml. The implication is that compound **c** can serve as antioxidant agent just like ascorbic acid.

Evaluation of drug-likeness and oral bioavailability of compounds.

Table**3** showed the physicochemical properties of the synthesized compounds. With reference to Lipinski's ro5 which stipulates that the drug-likeness of a drug candidate is established if the lipophilicity (logP) ≤ 5, number of hydrogen bond acceptor (HBA) ≤ 10, molecular weight (MW) ≤ 500 and number of hydrogen bond donor (HBD) ≤ 5.Similarly,Verber's principle corroborates that topological polar surface area (TPSA) as a surrogate property for mammalian cell permeability is guided by the rule that compounds having(TPSA) ≤140 Å2 can permeate the cell and have a good oral bioavailability while TPSA ≤ 90 Å2 implies the ability to permeate the blood-brain-barrier (BBB)and the central nervous system(CNS). NRB ≤10 is also essential for good oral bioavailability (Verber*et al.*,2002) (Vanderwaterbeemd *et al.*,1997). Based on the governing principles mentioned above, all the tested compounds exhibited excellent drug-likeness and good oral bioavailability. Compounds **c, d, e** and **f** have the ability to permeate the cell, have good oral bioavailability but cannot permeate the blood-brain-barriers and the central nervous system.

***In silico* Antibacterial and Antifungal Activities results.**

Table **4** showed the calculated free binding energies (binding affinities) of the compounds. Obviously, all the compounds displayed strong binding affinities with all the drug receptors employed in this study. For the antibacterial evaluation, all compounds tested on the DNA gyrase receptor **5MMN** exhibited good *in silico* antibacterial activity especially compounds **c, d, f** and **g**. Compound **g** displayed a better binding affinity (-11.19 kcal/mol) than penicillin (-10.89 kcal/mol). The implication is that compound **g** could be a more preferable antibacterial agent than penicillin. On the other hand, the antifungal evaluation demonstrated that compounds **c** and **d** displayed the best binding affinity (-10.97 and -10.48kcal/mol) comparable with ketoconazole (-10.85 kcal/mol) and obviously compound **c** outperformed ketoconazole. Similarly, all the title compounds exhibited good *in silico* antioxidant activities but none of the compounds displayed a higher binding affinities with **1HD2** than α-tocopherol (-14.82 kcal/mol).

CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest associated with this work.

REFERENCES:

1. Amos H, Cohen G. Amino acid ultilization in bacterial growth.2.A study of threonine-isoleucine relationships in mutants of Escherichia coli. *Biochem J*, 1954;57: 338.
2. Ananthanarayanan VS, Tetreault S, Saint-Jean A. *J. Med. Chem.*1993; 36:1332.
3. Arias, CA, Murray BE. Antibiotic-resistant bugs in the 21st century a clinical super-challenge. *N Engl J Med* 2009; 360: 439 – 43.
4. Cottarel G, WierZbowski J. Combination drugs, an emerging option for antibacterial therapy. *Trends biotechnol* 2007;25;547;-55.
5. Egbujor, M.C., and Okoro, U.C. "New methionine-based *p*-toluenesulphonamoyl carboxamide derivatives as antimicrobial and antioxidant agents: Design, synthesis and molecular docking", *JPRI*, 2019; 28(1): 1-12, Article no. JPRI .49472.
6. Halliwell, Barry. "Oxidative stress and cancer: have we moved forward? *Biochem.J*.2007; 401(1):1-11.
7. http://www.britannica.com.
8. Hwang, O. Role of oxidative stress in Parkinson's disease". *Exp Neurobiol*.2013;22(1):1-7.
9. Jiao, ZG, He, HQ, Zeng, CC, Tan, JJ , Hu, LM, Wang, CX. *Molecules* 2010;**15:** 1917.
10. Morahedian Ahmad, Gholam Ali Naderi, Gholam Reza Dashti, SedighehAsgary, FoziehZadhoosh. Antioxidant effects of L- serine against falty streak formation in hypercholesterolemic animals. *ARYA therosclerosis* 2006; vol2. No3.
11. Raul, SJ, More, AH , Mahajan, SS, *Intl. J. of Research in Pharmacy and Chemistry*. 2011;**1(4):** 991.
12. Rowley D. Cohen G. Amino acid utilization in bacterial growth. 2. A study of threomine – isoleuine relationships in minutes of Escherichia coli. *Biochem J* 1954: 57: 338.
13. Saito KTK, Yamada K. Growth inhibition by L – Serine in Bacillus subtillis MF920. Nippon shokuhinkagakuGakkaishi (Jpn. J. Food. Chem) 2001; 8: 117-20.
14. Van de waterbeemd H, Carter, RE, Grassy G, Kubinyi H, Martins YC, Tute MS and Willet, P. Grossory of terms used in computational drug design. 1997; 69(5): 1137-1152.
15. VenanziLM .Tetrahedral Nickel (11) complexes and the factors determining their formation. *Journal of Chemical Society*. 1958. p. 719-724.
16. Verber, DF, Johnson, SR, Cheng, HY, Smith, BR, Ward, KW, Kopple, K.D: Molecular properties that influence the oral bioavailability of drug candidates. *J.Med Chem*. 2002;45(12):2615-23.
17. Verhaeghe P, Azas N, Gasquet M, Hutter S,. Ducros C. *Bioorg. Med. Chem. Lett*. 2008; **18**: 401.
18. XiangkeDuan, Xue Huang, Xiaogu Wang, Shuangquan Yan, Siyao Guo, AbualgasimElgailiAbdaulla, Changwu Huang, JianpingXie. L-Serine potentiates fluoroquinolone activity against Escherichia coli by enhancing endogenous reactive oxygen species production. Journal of Anti-microbial chemotherapy, 2016; 71(8): 2192-2199.
19. Yelland MJ, Nikles CJ, McNairn N, Del Mar CB, Schluter PJ *Rheumatology*. 2007;**46:** 140.