BOOK OF PROCEEDINGS
(Available at: http://acsnigeria.org/publications/proceedings)

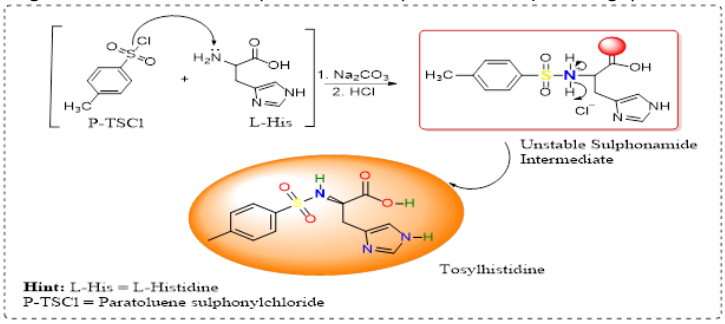
# Histidine-Derived Sulphonamides Bearing Carboxamide Functionality: Synthesis, *In Silico* Molecular Docking, and *In Vitro* Pharmacological Activities

Amarachi C. Achigamonye*, Uchechukwu C. Okoro, Efeturi A. Onoabedje, Obinna U. Okenyeka, and Joy C. Ezugwu
[1]Pure and Industrial Chemistry, University of Nigeria, Nsukka

**Corresponding Author's email:** amarachiachigamonye@gmail.com; **Tel:** +234(0)8068947753

## ABSTRACT

The synthesis of histidine-derived sulphonamides bearing carboxamides' functionality as potential antimalarial and antioxidant agents has been reported. The reaction between para–toluene sulphonyl chloride (a) and L-histidine (b) in a basic solution afforded tosyl histidine intermediate (c), which was then coupled with various secondary amines to obtain the corresponding carboxamides (d – h). The structure of the produced compounds was elucidated using Fourier Transform Infrared (FTIR), Proton, and Carbon -13 ($^{1}$H-NMR and $^{13}$C-NMR) Nuclear Magnetic Resonance Spectroscopic techniques, and subsequently underwent *in vitro* and *in silico* molecular docking evaluations for antimalarial and antioxidant activities, demonstrating favorable results. The result from the docking studies indicates that compound d (-7.8 kcal/mol) would be a better antimalarial agent than artesunate (-7.4 kcal/mol), while compound g (-8.0 kcal/mol) outperformed ascorbic acid (-6.5 kcal/mol) as an antioxidant agent. Similarly, the *in vitro* antimalarial and antioxidant activity evaluation confirmed compounds (d and g) to be the most potent antimalarial agent, while compound g displayed the most promising antioxidant activity. The synthesized compounds have been confirmed to possess the potential to function as antimalarial and antioxidant agents.




**KEYWORDS:** Histidine, Sulphonamides, Carboxamides, Antimalarial, Antioxidant, Molecular Docking,

## 1. INTRODUCTION

Metabolic processes and environmental pollutants are the primary sources of free radicals in the human body[1]. This can lead to various diseases, including malaria, cancer, heart disease, premature aging, inflammation, and reduced immunological function, rendering the body more vulnerable to infections[2-4]. Various plasmodium parasites, including *falciparum, vivax, malariae, ovale, and knowlesi* are the major causative agent of Malaria[5]. Sulphonamides and their carboxamides analog are valuable medicinal molecules due to their low toxicity and outstanding inhibition potential[6]. They have been established to exhibit a range of pharmacological activities, such as antimalarial[7], anticonvulsant[8], antihypertensive[9], anthelmintic[10], and HIV Protease inhibitors[11], among others. The World Health Organization's 2018[12], malaria report indicated approximately two hundred and nineteen (219) million cases of the disease in eighty-seven (87) countries in 2017, resulting in four hundred and thirty-five thousand (435,000) fatalities, predominantly among women and children in Africa. Despite a period of remarkable success in the war against malaria, progress appears to have slowed down. This is attributed to the parasite's rising resistance to already available antimalarial drugs. Incorporating bioactive amino acids like serine and methionine into the sulphonamide structure is a viable strategy for addressing malaria-resistant parasites and improving biological efficacy[13]. This study combined biologically active amino acids like L-histidine with bioactive sulphonamide compounds containing carboxamide functionality into a single pharmacophore. It assessed

their effectiveness against malaria-resistant parasites and their ability to reduce oxidative stress. The synthesized compounds demonstrated effective inhibition against the parasite development due to their synergistic activity.

## 2. MATERIALS AND METHODS

### 2.1. Instrumentation

All analytical grade reagents were purchased from Bristol Scientific Company Limited Liverpool Road, Apapa, Lagos, Nigeria, and used without further purification. Infrared spectra were obtained using a PerkinElmer FTIR spectrophotometer with potassium bromide. Nuclear Magnetic Resonance ($^{1}$H-NMR and $^{13}$C-NMR) Spectroscopy was determined using Jeol 400MHz at Rhodes University, Faculty of Pharmacy, Artillery Road, Makhanda 6139 Grahamstown, South Africa. Chemical shifts were given in parts per million (ppm), reported in delta (δ) scale, and referenced to tetramethylsilane. The Biochemistry Department of the University of Nigeria, conducted the *in vitro* activity evaluation while the Department of Chemistry conducted the molecular docking investigation.

### 2.2. Method of synthesis

#### *2.2.1. Synthesis of tosyl histidine (c)*

Sodium trioxocarbonate (IV) ($Na_2CO_3$) 2.5 g (12 mmol) was added to a suspension of L-histidine 2.0 g (b) (10 mmol) in water ($H_2O$) (12 ml). The clear solution was cooled to -5$^{o}$C using an ice pack and para-toluene sulphonyl chloride (a) 2.2 g (12 mmol) was added in four batches over an hour. The mixture was then adjusted to room temperature and left to stand for about four (4) hours while continuously stirred with a magnetic stirrer. Upon completion of the reaction, it was acidified with 20% concentrated hydrochloric acid solution to a potential of Hydrogen (pH) of 2.0 and left undisturbed for about 12 hours for the crystallization process to proceed to completion. The crystallized crude product was then filtered via suction, washed with a buffer solution with a potential of Hydrogen (pH) of about 2.2, and dried in a desiccator to afford tosyl histidine (c).

#### *2.2.2. Synthesis of L-histidine-based carboxamides derivatives (d – h)*

To a solution of tosyl histidine intermediate (0.74 mmol) in dichlormethane (10 ml) was added triethylamine (1.11 mmol), *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide.hydrochloride (0.93 mmol) and 1-hydroxybenzotriazole (0.74 mmol) at 0$^{o}$C. After stirring for 15 minutes, the corresponding amine (0.80 mmol) was added and stirred at the same temperature for about one hour. The resulting mixture was adjusted to room temperature and stirred for 19-20 hours as monitored with a Thin Layer Chromatographic plate (TLC). Upon completion of the reaction, it was diluted with Dichloromethane (DCM), and washed with 50 milliliters of water twice to obtain the aqueous and organic layer. The organic layer was then purified with 1Molar HCl (50 ml), 5% $NaHCO_3$ (50 ml), and brine solution (50 ml), and dried over $Na_2SO_4$ to obtain the crystallized compounds (d – h) which were further analyzed.

### *2.3.* In silico Studies

#### *2.3.1. Molecular docking*

Molecular docking studied two human diseases, antimalarial and antioxidant. The drug target selected for antimalarial was *Lactate dehydrogenase* (PDB entry: 1LDG) while the drug target for antioxidants was *Catalase* (PDB entry: 1TGC). The 3-dimensional structures of the drug target were downloaded from the protein data bank (PDB), (http://www.pdb.org) database, and loaded into the molecular operating environment. Similarly, the standard drugs ascorbic acid (antioxidant) and artesunate (antimalarial) were obtained from PubChem. The co-crystallized ligand was removed from the corresponding protein structures. Hydrogen atoms were introduced to the proteins after the water molecules were extracted. The

ligands were created, optimized, and then docked after choosing the X, Y, and Z center coordinates and grid dimensions. Image preparation and docking were conducted using AutoDock Vina (Scripps Research Institute, San Diego, California, USA), BIOVIA Discovery Studio, and molecular visualization software such as PyMOL to generate 3D structures.

#### *2.3.2. Antimalarial inhibitory activity by Lactate Dehydrogenase (LDH) method*

The synthetic compounds' *in vitro* antimalarial efficacy was evaluated by inhibiting the produced parasite protein lactate dehydrogenase (pLDH) according to the method described by Borgati[14]. The assay mixture contained 1.7 ml of tris (phosphate) buffer, 1.0 ml of 1.8 nm sodium pyruvate, 0.1 ml of 5 mmol Nicotinamide adenine dinucleotide (NAD) + hydrogen (H), and 0.1 ml of 0.5 mM of five (5) synthesized compounds (d - h). The chemical reaction was initiated by adding 0.1 ml of LDH extract and a spectrophotometric microplate reader was used to read the absorbance of 1.316 at 340 nm. The standard drug, artesunate was also prepared with the same method. The last stage of glycolysis involves the interconversion of pyruvate to lactate, which is catalyzed by the enzyme, Lactate Dehydrogenase.

Percentage inhibition was calculated using the formula thus:

$$\%\ inhibition = [\frac{\mathrm{Af} - \mathrm{Ai}}{\mathrm{Af}}\ \mathrm{X100}]$$

Where $A_f$ = initial absorbance of 1.316 nm at 340 nm $A_i$ = final absorbance of the synthesized compounds

#### *2.3.3. Antioxidant activity by 2,2-diphenyl-1-picryhydrazyl (DPPH) method*

The *in vitro* DPPH antioxidant activity of the synthesized compounds (d – h) was investigated by their ability to inhibit the generated stable free radicals according to the standard protocol reported by Sribalan[15]. 2 mg of DPPH was dissolved in 10 ml of methanol to prepare the stock solution. The solution was filtered, yielding a useable combination with an absorbance of 0.973 at 517 nm. After adding 1 mL (0.5 mM) of the synthesized compounds to 3 mL of DPPH useable mixture in a test tube, it was left to settle at room temperature for half an hour in the absence of light. Ascorbic acid was similarly prepared by mixing 1 mL DPPH solution with double distilled water. The absorbance was determined using a spectrophotometer as the purple color of DPPH turned yellow by accepting hydrogen from the antioxidants at 517 nm. The percentage of DPPH radical scavenging activity was calculated with the formula thus;

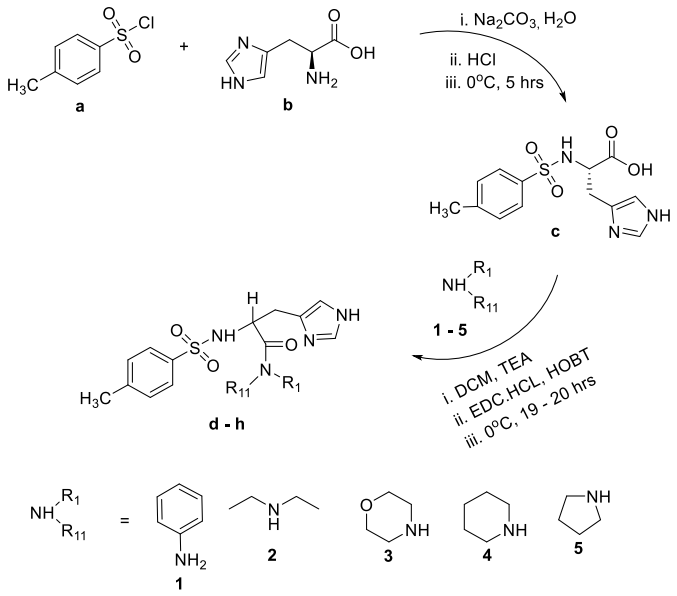
$$\%\ \text{of DPPH activity} = [\frac{Ac - As}{Ac}]\ \mathrm{x}\ 100$$

Where Ac = control reaction absorbance and As = sample absorbance

## 3. RESULTS AND DISCUSSION

### 3.1. Results

The reaction of para-toluene sulphonyl chloride (a) with L-histidine (b) yielded tosyl histidine (c) which had the acid functionality subsequently amidated with five (5) secondary amines by nucleophilic substitution reaction to obtain the corresponding carboxamides (d – h).




**Scheme 1:** The synthetic route

### *3.1.1. Tosylhistidine (Intermediate) (c)*

Appearance: white solid, M.P: 195 – 196°C, FTIR (KBR) $cm^{-1}$ 3476, 3444 (N-H band), 3137 (OH of COOH), 3096, 3029 (C-H aromatic), 2981, 2954 (C-H aliphatic), 1729 (assigned to C=O of COOH), 1535, 1496 (C=C aromatic), 1187, 1122 (2S=O).

### *3.1.2. 3-(1H-imidazol-4-yl)-2-((4-methylphenyl) sulfonamido)-N-phenylpropanamide (d):*

Appearance: thick oily black liquid, yield 1.62 g (78.6%).
FTIR (KBR) $cm^{-1}$ 3674, 3463, 3299 (N-H), 3187 (C-H aromatics), 2981, 2789 (C-H aliphatic), 1284 (S=O), 1620 (C=O), 1071 ($SO_2NH$).
$^1$H NMR (DMSO-$d_6$) δ: 9.60 (s, 1H, NH-C=O), 8.7 (s, 1H, CH=N), 8.3 (s, 1H, NH-$SO_2$), 7.7 (s, 1H, CH-NH), 7.7-7.1 (d, 9H, Ar-H), 4.8 (t, 1H, CH-$CH_2$), 3.0 (d, 2H, $CH_2$-CH), 2.4 (s, 3H, $CH_3$). $^{13}$C-NMR (DMSO-$d_6$) δ: 173.0 (C=O), 142.33, 140.89, 136.40, 129.63, 128.99, 127.26, 125.29, 121.70, 120.35, 109.33 (aromatic carbons), 77.35, 28.50, 21.53 (aliphatic carbons).

### *3.1.3. N,N-diethyl-3-(1H-imidazol-4-yl)-2-((4-methylphenyl)sulfonamido)propanamide (e)*

Appearance: dark brown solid, yield 0.83 g, (75.4%), M.P: 149 – 150°C.
FTIR (KBR) $cm^{-1}$ 3567, 3395 (N-H), 3100 (C-H aromatics), 2853, 2705 (C-H aliphatic), 1618 (C=O), 1247 (S=O).
$^1$H NMR (DMSO-$d_6$) δ: 13.2 (HN-CH=N), 8.2 (s, 1H, CH=N), 7.7 (s, 1H, HN-$SO_2$), 7.7-7.4 (d, 4H, Ar-H), 7.60 (s, 1H, CH-NH), 3.9 (t, 1H, CH-$CH_2$), 3.3 (q, 2H, $CH_2$-$CH_3$), 2.4 (d, 2H, $CH_2$-CH), 2.3 (s, 3H, $CH_3$), 1.2 (t, 3H, $CH_3$-$CH_2$).
$^{13}$C-NMR (DMSO-$d_6$) δ: 165.0 (C=O), 142.91, 137.44, 129.60, 127.05, 125.07, 120.21, 109.42 (aromatic carbons), 76.71, 42.00, 32.00, 21.48, 14.14 (aliphatic carbons).

### *3.1.4. N-(3-(1H-imidazol-4-yl)-1-morpholino-1-oxopropan-2-yl)-4 methylbenzenesulphonamide (f)*

Appearance: light yellow oily liquid, yield 1.16 g (63.7%).
FTIR (KBR) $cm^{-1}$ 3596, 3546, 3347 (N-H), 3243 (C-H aromatics), 2864, 2697 (C-H aliphatic), 1267 (S=O), 1631 (C=O), 1126 ($SO_2NH$).

$^1$H NMR (DMSO-$d_6$) δ: 8.2 (s, 1H, CH=N), 7.8 (s, 1H, HN-$SO_2$), 7.7 (s, 1H, CH-NH), 7.7-7.3 (d, 4H, Ar-H), 3.9 (t, 1H, CH-$CH_2$), 3.6 (t, 4H, $CH_2$-O-$CH_2$), 3.1 (t, 4H, $CH_2$-N-$CH_2$), 2.5 (d, 2H, $CH_2$-CH), 2.1 (s, 3H, $CH_3$).
$^{13}$C-NMR (DMSO-$d_6$) δ: 165.0 (C=O), 143.97, 132.06, 129.76, 128.70, 125.07, 120.21, 109.42 (aromatic carbons), 77.35, 76.71, 66.11, 46.00, 21.56 (aliphatic carbons).

***3.1.5. N*-(3-(1*H*-imidazol-4-yl)-1-oxo-1-(piperidin-1-yl)propan-2-yl)-4 methylbenzenesulphonamide (g)**
Appearance: light brown oily liquid, yield 1.53 g (84.1%).
FTIR (KBR) cm$^{-1}$ 3597, 3426 (N-H), 3072 (C-H aromatic) 2933, 2762 (C-H aliphatic), 1612 (C=O), 1458 (C=C aromatics), 1310 (S=O), 1117 ($SO_2$NH).
$^1$H NMR (DMSO-$d_6$) δ: 13.5 (s, 1H, HN-CH=N), 8.6 (s, 1H, HC=N), 8.2 (s, 1H, HN-$SO_2$), 7.8 (s, 1H, CH-NH), 7.6-7.3 (d, 4H, Ar-H), 4.3 (t, 1H, CH-$CH_2$), 3.5 (t, 4H, $CH_2$-N-$CH_2$), 2.9 (d, 2H, $CH_2$-CH), 2.4 (s, 3H, $CH_3$), 1.5 (t, 6H, $CH_2$-$CH_2$-$CH_2$).
$^{13}$C-NMR (DMSO-$d_6$) δ: 169.0 (C=O), 143.30, 140.56, 133.27, 129.03, 128.50, 127.77, 117.96 (aromatic carbons), 76.72, 46.94, 30.94, 25.17, 23.53, 21.52 (aliphatic carbons).

***3.1.6. N*-(3-(1*H*-imidazol-4-yl)-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)-4-methylbenzenesulphonamide (h)**
Appearance: sticky ox-blood solid product, yield 1.40 g (81.0%), M.P: 119 – 120$^O$C.
FTIR (KBR) cm$^{-1}$ 3486, 3395 (N-H), 3096 (C-H aromatic) 2873, 2761 (C-H aliphatic), 1628 (C=O), 1489 (C=C aromatics), 1287 (S=O), 1123 ($SO_2$NH).
$^1$H NMR (DMSO-$d_6$) δ: 8.4 (s, 1H, HC=N), 8.2 (s, 1H, NH-$SO_2$), 7.8 (s, 1H, CH-HN), 7.7-7.3 (d, 4H, ArH), 4.1 (t, 1H, CH-$CH_2$), 3.5 (t, 4H, $CH_2$-N-$CH_2$), 2.9 (d, 2H, $CH_2$-CH), 2.4 (s, 3H, $CH_3$), 1.7 (t, 4H, $CH_2$-$CH_2$).
$^{13}$C-NMR (DMSO-$d_6$) δ: 172.0 (C=O), 143.31, 136.64, 133.99, 129.61, 128.96, 127.60, 125.80 (aromatic carbons), 54.19, 47.91, 37.96, 25.20, 21.52 (aliphatic carbons).

### 3.2. Molecular Docking Evaluation

**Table 1:** Results of *in silico* antimalarial and antioxidant activities evaluation*

**Table 1,** below shows the binding affinity of the five (5) synthesized compounds and standard drugs against the enzyme, *Lactate dehydrogenase for antimalarial activity evaluation and the enzyme, catalases for antioxidant activity evaluation respectively*. The surface interaction of the synthesized compounds against the enzymes and the amino acid residues were further illustrated in **Figure 1**.

| **Compounds** | **Antimalarial** | **Antioxidant** |
|---|---|---|
| | 3LDH | 2CAS |
| d | -7.8 | -7.3 |
| e | -6.3 | -6.8 |
| f | -7.0 | -7.0 |
| g | -7.5 | -8.0 |
| h | -6.8 | -7.2 |
| Standard | -7.4 | -6.5 |

*3LDH and 2CAS are drug targets for antimalarial and antioxidant
Standard drugs for 3LDH = artesunate; 2CAS = ascorbic acid*

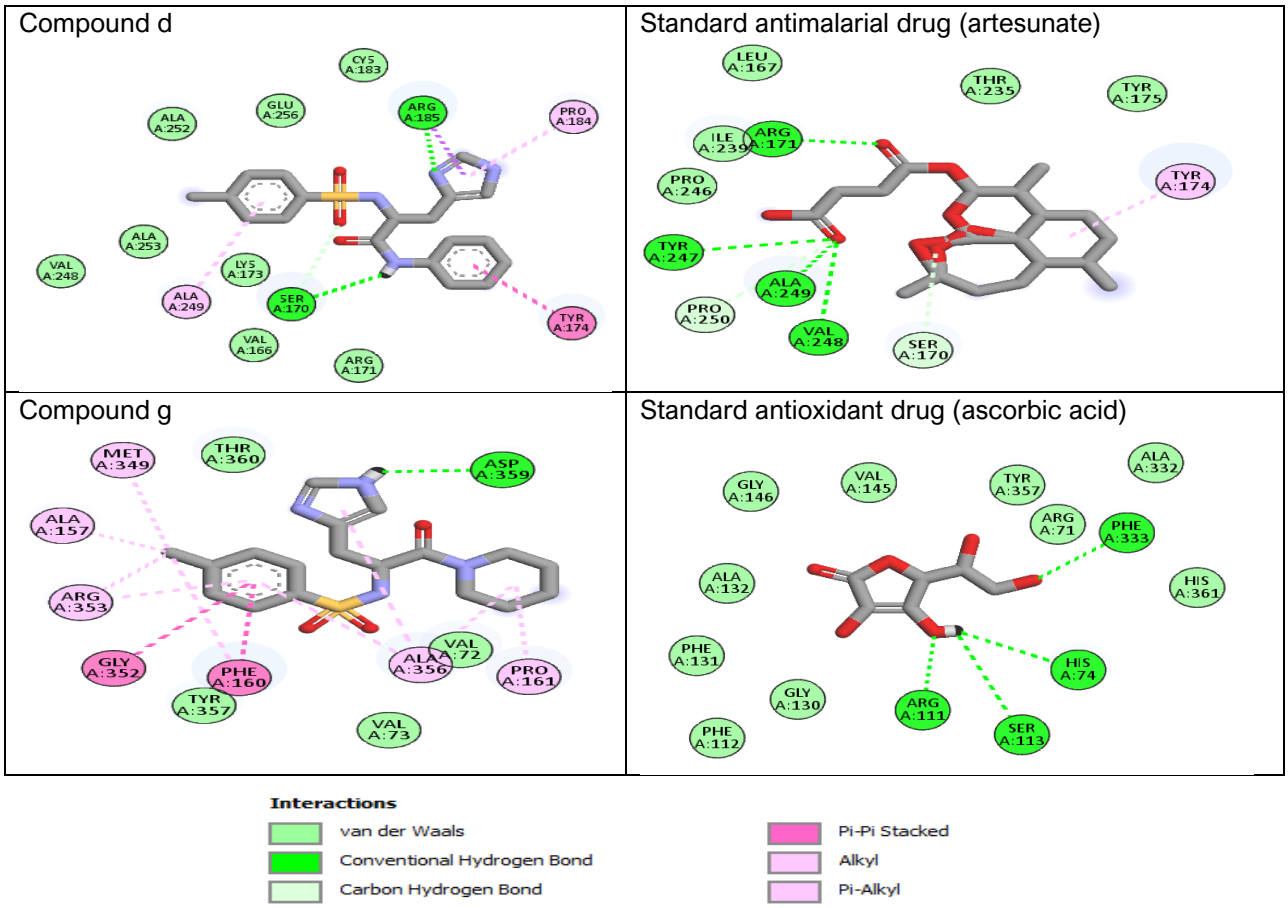



**Figure 1:** Surface interaction of compounds against *Lactate Dehydrogenase* for antimalarial and *Catalases* for antioxidant

### 3.3. *in vitro* antimalarial and antioxidant activity evaluation

**Table 2:** *Lactate Dehydrogenase* inhibitory activity*

Table 2, reveals the Lactate Dehydrogenase inhibitory studies result of the synthesized compounds and standard antimalarial drug with their various absorbance and percentage inhibition potential respectively.

| Compound | Absorbance | Percentage (%) inhibition |
|---|---|---|
| d | 0.301 | 77.12 |
| e | 0.565 | 57.07 |
| f | 0.437 | 66.79 |
| g | 0.279 | 78.80 |
| h | 0.544 | 58.66 |
| ART | 0.318 | 75.83 |

The standard antimalarial drug used is artesunate*

**Table 3:** DPPH radical scavenging inhibitory activity*

Table 3, depicts the DPPH radical scavenging inhibitory studies result of the synthesized compounds and standard antioxidant drug with their various absorbance and percentage inhibition potential respectively.

| Compounds | Absorbance | Percentage (%) inhibition |
|---|---|---|
| d | 0.259 | 73.38 |
| e | 0.380 | 60.95 |
| f | 0.322 | 66.91 |
| g | 0.202 | 79.23 |
| h | 0.316 | 67.52 |
| AA | 0.273 | 71.94 |

The standard antioxidant drug used is ascorbic acid*

### 3.2. Discussion

#### *3.2.1. In silico* antimalarial and antioxidant activities

Table 1 displays the calculated binding energies of the compounds. Interestingly, all the synthesized compounds showed a strong binding affinity with all the drug receptors employed in this study. For the antimalarial activity evaluation, most of the compounds tested on the parasitic *Lactate Dehydrogenase* receptor exhibited good *in silico* antimalarial activity. However, compared to artesunate (-7.4 kcal/mol), compounds d and g with binding energy (-7.8 and -7.5 kcal/mol), demonstrated good binding affinity. On the other hand, for the antioxidant activity evaluation, all the compounds tested on oxidant *Catalases* receptor revealed all the synthesized compounds (d – h) with binding energy ranging from (-8.0 to -6.5 kcal/mol) as having better binding affinity in comparable with ascorbic acid (-6.5 kcal/mol). The synthesized compounds tend to possess the potential to function as antimalarial and antioxidant agents.

Figure 1 displayed the surface interactions of compounds against *Lactate Dehydrogenase* and *Catalases* respectively. For the interactions against Lactate Dehydrogenase, Compound d shows two (2) main conventional H-bonds (Ser-170 and Arg-185). Furthermore, residues Val-166, Arg-171, Lys-173, Cys-183, Val-248, Ala-252, Ala-253, and Glu-256 are situated close to the complex, suggesting the possibility of Van der Waals interactions as well as Pi-Alkyl interactions with Tyr-174, Pro-184, and Ala-249. Moreover, the standard, artesunate shows four (4) main conventional H-bond (Arg-171, Tyr-247, Val-248, and Ala-249) and possible Van der Waals interactions with Leu-167, Ser-170, Tyr-175, Thr-235, Ile-239, Pro-246, and Pro-250 respectively. Similarly, for the interactions against *Catalases,* compound g reveals an H-bond (Asp-359), and possible Van der Waals interactions (Val-72, Val-73, Tyr-357, and Thr-360) residues are located close to the complex. The standard (ascorbic acid) shows four (4) main conventional H-bonds (His-74, Phe-333, Arg-111, and Ser-113). Additionally, it reveals possible Van der Waals interactions with Arg-71, Phe-112, Gly-130, Phe-131, Ala-132, Val-145, Gly-147, Ala-332, Tyr-357, and His-361 respectively.

#### *3.2.2. In vitro* antimalarial activity evaluation: *Lactate Dehydrogenase* inhibitory activity

Table 2 showed that all the synthesized compounds (d – h) demonstrated significant antimalarial activity. However, compounds d and g displayed the most promising antimalarial activities, inhibiting the protozoan parasite's growth, plasmodium falciparum which was used as a test microorganism and hence being the most potent antimalarial agent.

### *3.2.3. In vitro* antioxidant activity evaluation: DPPH Scavenging inhibitory activity

Table 3 shows that all of the produced compounds (d – h) possessed potent antioxidant activity, which will reduce the progression of oxidative stress. However, compounds d and g showed excellent antioxidant activities out of all the tested compounds. Surprisingly, compound g outperformed ascorbic acid in the antioxidant activity evaluation and hence possesses the potential to decrease DPPH inhibition due to its increased absorbance.

## 4. CONCLUSION

The synthesis of histidine-derived sulphonamides bearing carboxamide functionality, molecular docking and *in vitro* pharmacological properties were successful. Five sulphonamides bearing carboxamide functionality (d – h) were synthesized. Spectral analytical techniques have been used to determine the structures of the compounds. *In vitro,* antimalarial and antioxidant studies of the synthesized compounds indicated that compounds (d and g) exhibited remarkable antimalarial and antioxidant properties, and this was supported by molecular docking assessment where they showed good free binding affinity to the amino acid residues.

## REFERENCES

(1) Nimse, S. B., & Pal, D. Free radicals, natural antioxidants, and their reaction mechanisms. *RSC advances* **2015**, *5* (35), 27986-28006. DOI: 10.1039/C4RA13315C

(2) Jiang, D. J., Dai, Z., & Li, Y. J. Pharmacological effect of xanthones as cardiovascular protective agents. *Cardiovascular Drug Reviews* **2004**, *22 (2),* 91-102. https://doi.org/10.1111/j.1527-3466.2004.tb00133.x.

(3) Cheng, J. H., Huang, A. M., Hour, T. C., Yang, S. C., Pu, Y. S., & Lin, C. N. Antioxidant xanthone derivatives induce cell cycle arrest and apoptosis and enhance cell death induced by cisplatin in NTUB1 cells associated with ROS. *European Journal of Medicinal Chemistry* **2011**, *46* (4), 1222 - 1231. https://doi.org/10.1016/j.ejmech.2011.01.043.

(4) Stefoska-Needham, A., Beck, E., Johnson, S., & Tapsell, L. Sorghum: An underutilized cereal whole grain with the potential to assist in preventing chronic disease. *Food Reviews International* **2015**, *31* (4), 401- 437. https://doi.org/10.1080/87559129.2015.1022832.

(5) Sinha, S., Sarma, P., Sehgal, R., & Medhi, B. Development in assay methods for in vitro antimalarial drug efficacy testing: A systematic review. *Frontiers in Pharmacology* **2017**, 8, 754. DOI: 10.3389/fphar.2017.00754.

(6) Perlovich, G. L., Strakhova, N. N., Kazachenko, V. P., Volkova, T. V., Tkacher, V. V., Schaper, K. J., & Raevsky, O. A. Sulphonamides are subject to the study of molecular interactions in crystals and solution; sublimation, solubility, salvation, distribution, and crystal structure. *International Journal of Pharmaceutics* **2008**, 349 (1 - 2), 300 - 313.

(7) Onoabedje, E. A., Ibezim, A., Okoro, U. C., & Batra, S. New Sulphonamide Pyrrolidine carboxamide derivatives: Synthesis, molecular docking, antiplasmodial and antioxidant activities. *PloS One* **2021,** *16 (2),* e0243305. doi.org/10.1371/journal.pone.0243305

(8) Ahmad, G., Rasoola, N., Rizwana, K., Imran, I., Zahoor, A. F., Zubair, M., Sadiq, A., & Rashid, U. Synthesis, *in-vitro* cholinesterase inhibition, *in-vivo* anticonvulsant activity, and *in-silico* exploration of *N*-(4-methylpyridin-2-yl)thiophene-2-carboxamide analogs. *Bioorganic Chemistry* **2019**, *92*,103216. https://doi.org/10.1016/j.bioorg.2019.103216

(9) Alam, O., Khan, S. A., Siddiqui, N., Ahsan, W., V erma, S. P., & Gilani, S. J. Antihypertensive activity of newer 1,4-dihydro-5-pyrimidine carboxamides: Synthesis and pharmacological evaluation. *European Journal of Medicinal Chemistry* **2010,** *45* (11), 5113-5119. DOI: 10.1016/j.ejmech.2010.08.022.

(10) Ugwu, D. I., Okoro, U. C., & Mishra, N. K. Synthesis, characterization, and anthelmintic activity evaluation of pyrimidine derivatives bearing carboxamide and sulphonamide moieties. *Journal of the Serbian Chemical Society* **2018a,** *83* (4), 401 - 409. DOI: 10.2298/JSC170127109U.

(11) Stranix, B. R., Lavallee, J. F., Sevingny, G., Yelle, J., Perron, V., Leberre, N., Herbart, D., & Wu, J. J. Lysine sulphonamides as novel HIV-protease inhibitors: Nε-acyl aromatic α-amino acids. *Bioorganic & Medicinal Chemistry Letters* **2006,** *16 (13),* 3459 - 3462.

(12) WHO Media Center, Fact Sheet on Malaria. https://www.who.int/en/news-room/fact-sheets/detail/malaria. (Revised 24 June, **2018**).

(13) Egbujor, M. C., Okoro, U. C., Okafor, S., & Nwankwo, N. E. Design, synthesis, and molecular docking of novel serine-based sulphonamide bioactive compounds as potential antioxidant and antimicrobial agents*. Indo-American Journal of Pharmaceutical Science* **2019,** *6 (6),* 12232 - 12240.

(14) Borgati, T., Pereira, G., & Brandão, G. Synthesis by click reactions and antiplasmodial activity of lupeol 1, 2, 3-triazole derivatives. *Journal of the Brazilian Chemical Society* **2017,** 28 (10), 1850 - 1856. https://doi.org/10.21577/0103-5053.20170013

(15) Sribalan, R., Banuppriya, G., Kirubavathi, M., Jayachitra, A., & Padmini, V. Multiple biological activities and molecular docking studies of newly synthesized 3-(pyridin-4-yl)-1H-pyrazole-5-carboxamide chalcone hybrids. *Bioorganic & Medicinal Chemistry Letters* **2016,** *26* (23), 5624 - 5630. https://doi.org/10.1016/j.bmcl.2016.10.075