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New isoleucine derived dipeptides as antiprotozoal agent: Synthesis, in silico and in vivo studies.

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ABSTRACT

The increasing emergence of malaria drug-resistant parasites and the deficiency in effective chemotherapy for trypanosomiasis represents a huge challenge in infectious disease treatment in tropical regions. As regards to developing effective antiprotozoal agents, ten new ile-gly dipeptide sulphonamide derivatives were synthesized by condensing compound **(10)** with **(8a-j)**using peptide coupling reagents. Compounds**11b, 11i** and **11j** were most potent in clearing *Trypanosome brucei* in mice with **11b** showing comparable activity with diminazene aceturate. In the antimalarial study, **11b** was the most active compound, even better than the standard. Molecular docking result suggests good interaction between the reported compounds and the target protein. The results of haematological analysis, liver and kidney function tests showed that the compounds had no adverse effect on the blood and organs. Compound **11b** stands out amongst the derivatives haven shown better activity in both the antimalarial and antitrypanosomal assay.

1. Introduction

In the tropical regions of the world, protozoan parasites cause severe diseases with human African trypanosomiasis (HAT) and malaria being at the top of the list. The noted toxicities of current antitrypanosomaldrugsandthe worldwide resurgence of malaria, accompanied by the springing up of widespread drug-resistant protozoan parasites motivated this research.HAT otherwise refers to as sleeping sickness is caused by infections of *Trypanosome brucei rhodesiense* and *T.b. gambiense* in humans in Sub-Saharan Africa, and has remained a disease with no effective treatment. About 500,000 people are infected with sleeping sickness leading to the death of almost 100,000 people every year [1]. Recent research progress suggests that a vaccine against the disease is far from being successful leaving chemotherapy as the only available means of controlling trypanosomiasis. There are only 4 registered drugs at present for the treatment of HAT. Pentamidine **(1)** and suramin **(2)** are used for the treatment of the disease in an early stage. However, in the second stage of the disease, the trypanosomes must have invaded the central nervous system (CNS) and this become deadly if untreated. Melarsoprol **(3)** and eflornithine **(4)** are used for treatment at this stage. However, the few registered drugs are associated with severe side effects such as poor oral availability, high cost, toxicity, lack of efficacy and long treatment regimen [2]. Because of this, there is an urgent need to develop new, cheap and safe alternative chemotherapy against trypanosomiasis.

Malaria is usually caused due to infection with *Plasmodium spp* and is one of the most devastating diseases in developing countries. The World Health Organization (WHO) malaria report in 2017 [3] estimated about 216 million cases of malaria and 445,000 deaths worldwide with 90% of cases and 91% of deaths affecting the African region [4]. Numerous highly active drugs such as quinine, chloroquine, mefloquine, artesunate and their analogues are available for the treatment of malaria, but unfortunately, significant resistance to almost all these drugs has been developed even to the "last resort"artemisinin-derivatives, first cases of delayed clinical efficacy havebeen reported [5]. The main contributors to widespread resistance in malaria parasite are an inappropriate use of antimalaria drugs and the use of monotherapies or substandard and counterfeit medicine [6]. However, the surfacing of extensive resistance to the available antimalaria drugs accompanied by a worldwide resurgence of malaria underscores the need to develop new antimalarial agents that are efficient, safe and synthetically economical [7,8].

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Sulphonamides have been the centre of drug structures as they are quite stable and well-tolerated in human beings [9]. Sulfadoxine, sulfadiazine and sulfalene are effective malaria drugs that possesssulphonamide groups attached to a heterocyclic ring. In addition, several sulphonamide derivatives have been reported as antimalarial [10], antibacterial [9], anticancer [11], antidiabetic [12], antitrypanosomal [13,14] agents. Sulphonamide is an important pharmacophore and its coupling with other moieties such as peptides always affords new biologically active compounds [15]. Peptides are amongst the most versatile bioactivemolecules and play crucial roles in the human body and other organisms [16], because of their good solubility, permeability and bioavailability. Short peptides incorporatesulphonamide or heterocyclic moieties also exhibit numerous biological properties such as carbonic anhydrase inhibitory [17], chemotactic activity [18], antimicrobial [19,20] and antioxidant [21] activities. However, Ugwuja et al.,(2019) [22] recently reported Glycine derived dipeptide sulphonamides having interesting antimalaria and antibacterial properties. Again Val-Val-derived dipeptides as an antimalaria and antioxidant agent was also reported [23]. These reports encouraged us to seek a solution to the problems of multidrug resistance, insecticide-resistant malaria parasite and lack of adequate chemotherapeutic agent in managing trypanosomiasis.

In the interest of discovering new antiprotozoal agents, and to exploit the synergistic activity coming up from the successful combination of sulphonamide and peptides in drug molecule, we report here the synthesis of ten new benzenesulphonamide derivatives incorporating dipeptide moiety with interesting antitrypanosomal and antimalarial activity.

2. Material and methods

2.1. Instrumentation

All reagents were of analytical grade and were procured fromAvra, Spectrochem, Aldrich, Merck, SRL, SD fine and Fluka. They were used without further purification. Silica plates that were used for thin-layer chromatography were purchased from Avra, spots were visualized under UV light and in the oven with ninhydrin. Purification by column chromatography was achieved using Merck silica gel (60 – 120 mesh). Proton and carbon-13 NMR were carried outusing Jeol 400 MHZ or 500 MHZin dimethyl sulfoxide(DMSO)-d_6 and chemical shifts presented in part per million (ppm) with reference to tetramethylsilane. Micro TOF electronspray time of flight (ESI-TOF) mass spectrometer (AerodynReseachInc.USA) was used for mass determination, with formate as calibrant. FT-IR spectra of the derivatives were achieved using PerkinElmer spectrum version 10.03.06 and the bands are given in wavenumber. Melting points were determined using a glass capillary tube on Stuart melting point apparatus and were uncorrected. All experiments were carried out at Prof. Sandeep Verma Laboratory, Department of Chemistry, Indian Institute of Technology Kanpur, India.

2.2. Synthesis of 3-methyl-2-(phenylsulphonamido)pentanoic acid (**10**)

The procedure by Ugwu et al. [14] with little modifications was adopted for the synthesis of compound **10**. The detail of the procedure is available as supporting information.

Yield 94%, mp, 148.00–148.60 °C. FTIR (KBr,cm^{-1}): 3295 (NH), 3066(C–H aromatic), 2968, 2936, 2883 (C–H aliphatic), 1699 ($C = O$ of carboxylic acid). ^{1}H NMR (400 MHz, DMSO–d_6) δ: 12.54 (s, 1H, OH), 8.01 (d, J = 9.2 Hz, 1H, NH), 7.72–7.74 (m, 2H, ArH), 7.54 (dt, J = 23.8, 7.0 Hz, 3H, ArH), 3.48–3.56 (m, 1H, CH), 1.57–1.64 (m, 1H, CH), 1.25–1.33 (m, 1H, CHa of CH_2), 1.00–1.07 (m, 1H, CHb of CH_2), 0.68–0.75 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO–d_6, 100 MHz) δ: 172.6 ($C = O$), 141.5, 132.8, 129.4, 127.0 (aromatic carbons), 60.5, 37.3, 24.8, 15.8, 11.4 (aliphatic carbons). HRMS-ESI (m/z) for $C_{12}H_{17}NO_4S$: 272.0950 $(M + H)^+$, calculated, 272.0951.

2.3. Synthesis of compounds (***7a-j***)

The procedure according to (Sharma and Soman, 2016) [24] with little modification was used for the synthesis of these compounds. 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride EDC.HCl (0.53 g, 2.7 mmol), 1-hydroxybenzotriazole HOBt (0.25 g, 1.84 mmol), triethylamine TEA(2.19 mmol) and amines (1.84 mmol) were added to a solution of Boc-glycine (**8**, 0.32 g, 1.84 mmol) in dichloromethane DCM (20 mL) at 0 °C. The resulting mixture was allowed to stir at room temperature for 16–19 h and was being monitored using TLC. Upon completion, the mixture was diluted with DCM, washed with 1 N HCl (50 mL), 5% sodium bicarbonate solution(50 mL) and brine (50 mL). It was dried using anhydrous sodium sulphate and the solvent was removed under diminished pressure to give the crude product which was further purified by column chromatography using silica gel and 5% methanol/dichloromethane. The spectra data are available as supporting information.

2.4. Synthesis of compounds (***11a-j***)

Compounds **(7a-j)** were deprotected by stirring in 50% trifluoroacetic acid in dichloromethane (TFA/DCM (1:1)) for 40 min as monitored by TLC, the solvent was then evaporated to give the substituted acetamides**(8a-j).** To a solution of compound **6** (1.84 mmol) in DCM (20 mL), EDCl (2.7 mmol), HOBt (1.84 mmol) and TEA (1.84 mmol) were added at 0 °C and after stirring for 10 min, compounds **(8a-j)**was also added**.** The reacting mixture was further stirred at room temperature for 16 - 19 h as being monitored using TLC. On completion of the reaction, it was diluted with DCM, washed with 1 N HCl (50 mL), 5% sodiumbicarbonate solution(50 mL) and brine (50 mL). It was dried using anhydrous sodium sulphate and the solvent was removed under diminished pressure to give the crude product which was further purified by column chromatography using silica gel and 5% methanol/dichloromethane to give the pure product **(11a-j).**

2.4.1. N-*(2-(4-Chlorophenylamino)–2-oxoethyl)–3-methyl-2-(phenylsulfonamido)pentanamide (**11a**)*

Yield 90%, mp 142–144 °C. FTIR (KBr,cm^{-1}): 3337, 3248 (NH), 3060 (C–H aromatic), 2970, 2928, 2876 (C–H aliphatic), 1677, 1640 (2C=O), 1595, 1526, 1493 ($C = C$), 1388, 1343 (SO_2), 1166, (SO_2–N), 1204, 1093, 1063 (C–N), 729 (C–Cl). ^{1}HNMR (400 MHz, DMSO–d_6) δ 9.92 (s, 1H, NH), 8.28 (d, J = 9.8 Hz, 1H, NH), 7.83 (t, J = 9.5 Hz, 1H, NH), 7.74 (d, J = 6.7 Hz, 2H, ArH), 7.52 (dd, J = 29.9, 7.9 Hz, 5H, ArH), 7.33 (d, J = 8.5 Hz, 2H, ArH), 3.64–3.71 (m, 1H, CH), 3.55 (d, J = 9.8 Hz, 2H, CH_2), 1.49–1.61 (m, 1H, CH), 1.32–1.49 (m, 1H, CHa of CH_2), 0.94–1.09 (m, 1H, CHb of CH_2), 0.72 (dd, J = 17.1, 6.7 Hz, 6H, $2CH_3$). ^{13}C NMR (DMSO–d_6, 100 MHz) ∂: 171.0,167.9, (2C=O), 141.4, 138.3, 132.7, 129.2, 127.3, 127.2, 121.0 (aromatic carbons), 61.0, 42.9, 37.2, 24.7, 15.5, 11.0 (aliphatic carbons). HRMS-ESI (m/z) for $C_{20}H_{24}ClN_3O_4S$: 438.1253 $(M + H)^+$, calculated, 438.1249 $(M + H)^+$.

2.4.2. N-*(2-(4-Bromophenylamino)–2-oxoethyl)–3-methyl-2-(phenylsulfonamido)pentanamide (**11b**)*

Yield 85%, mp 146–147 °C.FTIR (KBr,cm^{-1}): 3333, 3249 (NH), 3060 (C–H aromatic), 2969, 2929, 2875 (C–H aliphatic), 1680, 1640 (2C=O), 1592, 1526, 1490 ($C = C$), 1343, 1286 (SO_2), 1166, (SO_2–N), 1213, 1093, 1072 (C–N), 594 (C-Br). ^{1}H NMR (400 MHz, DMSO–d_6) δ 9.92 (s, 1H, NH), 8.22 (t, J = 5.5 Hz, 1H, NH), 7.84 (d, J = 8.5 Hz, 1H, NH), 7.72–7.75 (m, 2H, ArH), 7.44–7.55 (m, 7H,

ArH), 3.66 (dd, J = 16.8, 5.8 Hz, 1H, CH), 3.54 (dd, J = 16.5, 6.1 Hz, 2H, CH_2), 1.52 (q, J = 11.0 Hz, 1H, CH), 1.34–1.45 (m, 1H, CHa of CH_2), 1.01 (td, J = 13.9, 7.1 Hz, 1H, CHb of CH_2), 0.67–0.82 (m, 6H, $2CH_3$). 13C NMR (DMSO–d_6, 100 MHz) δ 171.0,167.9, (2C=*O*), 141.4, 138.3, 132.7, 132.2, 129.2, 127.3, 121.4 (aromatic carbons), 61.0, 42.9, 37.2, 24.8, 15.5, 11.0 (aliphatic carbons). HRMS-ESI (*m/z*) for $C_{20}H_{24}BrN_3O_4S$: 482.0747 $(M + H)^+$, calculated, 482.0744 $(M + H)^+$.

2.4.3. 3-Methyl-N-(2-oxo-2-(p-tolyamino)ethyl)-2-(phenylsulfonamido)pentanamide (**11c**)

Yield 79%, mp 140–142 °C. FTIR (KBr,cm^{-1}): 3334, 3244 (NH), 3060 (C–H aromatic), 2967, 2929, 2875 (C–H aliphatic), 1671, 1640 (2C=*O*), 1597, 1531 (*C* = *C*), 1389, 1344 (SO_2), 1167, (SO_2–N), 1215, 1146, 1065, 1021 (C–N). ^{1}H NMR (400 MHz, DMSO–d_6)δ 9.66 (s, 1H, NH), 8.20 (t, J = 5.5 Hz, 1H, NH), 7.85 (d, J = 8.5 Hz, 1H, NH), 7.73–7.75 (m, 2H, ArH), 7.55 (d, J = 7.3 Hz, 1H, ArH), 7.47 (dd, J = 8.2, 6.4 Hz, 2H, ArH), 7.41 (d, J = 8.5 Hz, 2H, ArH), 7.07 (d, J = 8.5 Hz, 2H, ArH), 3.50–3.68 (m, 3H, CH and CH_2), 2.20 (s, 3H, CH_3-Ar), 1.51–1.60 (m, 1H, CH), 1.42 (q, J = 10.6 Hz, 1H, CHa of CH_2), 0.98–1.05 (m, 1H, CHb of CH_2), 0.66–0.74 (m, 6H, $2CH_3$) ^{13}C NMR (DMSO–d_6, 100 MHz) ∂: 171.0,167.9, (2C=*O*), 141.4, 136.8, 132.7, 129.6, 129.2, 127.2, 119.4 (aromatic carbons), 61.0, 42.9, 37.2, 24.7, 20.9, 15.5, 11.0 (aliphatic carbons). HRMS-ESI (*m/z*) for $C_{21}H_{27}N_3O_4S$: 418.1809 $(M + H)^+$, calculated, 418.1795 $(m + H)^+$.

2.4.4. 3-Methyl-N-(2-(naphthalene-1-ylamino)–2-oxoethyl)–2-(phenylsulfonamido)pentanamide (**11d**)

Yield 91%, mp 150–152 °C. FTIR (KBr,cm^{-1}): 3329, 3240 (NH), 3061 (C–H aromatic), 2964, 2930, 2877 (C–H aliphatic), 1675, 1638 (2C=*O*), 1531, 1505 (*C* = *C*), 1389, 1340 (SO_2), 1167, (SO_2–N), 1207, 1094, 1063 (C–N). ^{1}H NMR (400 MHz, DMSO–d_6) δ 9.80 (s, 1H, NH), 8.32 (d, J = 5.5 Hz, 1H, NH), 8.01 (t, J = 3.4 Hz, 1H, NH), 7.90 (d, J = 9.2 Hz, 2H, ArH), 7.75 (d, J = 7.3 Hz, 3H, ArH), 7.63 (d, J = 7.3 Hz, 1H, ArH), 7.44–7.54 (m, 6H, ArH), 3.54–3.89 (m, 3H, CH and CH_2), 1.38–1.60 (m, 2H, CH and CHa of CH_2), 0.96–1.06 (m, 1H, CHb of CH_2), 0.65–0.74 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO–d_6, 100 MHz) ∂: 171.0,168.5, (2C=*O*), 141.4, 134.2, 133.7, 132.7, 129.2, 128.6, 127.2, 126.6, 126.3, 126.1, 125.8, 123.2,121.9 (aromatic carbons), 61.1, 42.9, 37.2, 24.7, 15.5, 11.0 (aliphatic carbons). HRMS-ESI (*m/z*) for $C_{24}H_{27}N_3O_4S$: 454.1808 $(M + H)^+$, calculated, 454.1795 $(M + H)^+$.

2.4.5. 3-Methyl-N-(2-oxo-2-(phenylamino)ethyl)–2-(phenylsulfonamido)pentanamide (**11e**)

Yield 90%, mp 146–148 °C. FTIR (KBr,cm^{-1}): 3330, 3245 (NH), 3060 (C–H aromatic), 2967, 2931, 2875 (C–H aliphatic), 1674, 1640 (2C=*O*), 1600, 1537, 1499 (*C* = *C*), 1391, 1346 (SO_2), 1166, (SO_2–N), 1215, 1145, 1093, 1065 (C–N).^{1}H NMR (400 MHz, DMSO–d_6)δ 9.76 (s, 1H, NH), 8.21 (t, J = 5.8 Hz, 1H, NH), 7.84 (d, J = 8.5 Hz, 1H, NH), 7.73–7.75 (m, 2H, ArH), 7.46–7.56 (m, 5H, ArH), 7.27 (t, J = 7.9 Hz, 2H, ArH), 7.00 (t, J = 7.3 Hz, 1H, ArH), 3.67 (dd, J = 16.8, 5.8 Hz, 1H, CH), 3.55 (dt, J = 16.5, 4.6 Hz, 2H, CH_2), 1.51–1.59 (m, 1H, CH), 1.36–1.46 (m, 1H, CHa of CH_2), 0.98–1.05 (m, 1H,CHb of CH_2), 0.66–0.75 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO–d_6, 100 MHz) ∂: 171.0, 167.7, (2C=*O*), 141.3, 139.2, 132.7, 129.3, 127.1, 123.8, 119.5 (aromatic carbons), 61.1, 42.9, 37.1 26.1,24.7, 15.2, 11.1 (aliphatic carbons). HRMS-ESI (*m/z*) for $C_{20}H_{25}N_3O_4S$: 404.1645 $(M + H)^+$, calculated, 404.1639 $(M + H)^+$.

2.4.6. N-(2-(4-Methoxyphenylamino)–2-oxoethyl)–3-methyl-2-(phenylsulfonamido)pentanamide (**11f**)

Yield 89%, mp 140–141 °C. FTIR (KBr,cm^{-1}): 3324, 3244 (NH), 3061 (C–H aromatic), 2961, 2933, 2877 (C–H aliphatic), 1669, 1639 (2C=*O*), 1599, 1536, 1515 (*C* = *C*), 1343, 1252 (SO_2), 1166, (SO_2–N), 1214, 1107, 1093, 1075, 1032 (C–N, C–O).^{1}H NMR (400 MHz, DMSO–d_6) δ 9.60 (s, 1H, NH), 8.19 (t, J = 5.8 Hz, 1H, NH), 7.69–7.74 (m, 2H, NH and ArH), 7.42–7.61 (m, 6H, ArH), 6.83 (d, J = 9.2 Hz, 2H,ArH), 3.61–3.66 (m, 4H, OCH_3 and CH), 3.50–3.55 (m, 2H, CH_2), 1.46–1.61 (m, 1H, CH), 1.33–1.46 (m, 1H, CHa of CH_2), 0.99 (td, J = 14.0, 6.5 Hz, 1H, CHb of CH_2), 0.65–0.72 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO–d_6, 100 MHz) ∂: 170.9, 167.2, (2C=*O*), 155.7, 141.3, 132.7, 132.4, 129.2, 127.2, 121.0, 114.4 (aromatic carbons), 61.1, 55.7, 42.9, 37.5 24.7, 15.2, 11.1 (aliphatic carbons). HRMS-ESI (*m/z*) for $C_{21}H_{27}N_3O_5S$: 434.1743 $(M + H)^+$, calculated, 434.1744 $(M + H)^+$.

2.4.7. N-(2-(4-Fluorophenylamino)–2-oxoethyl)–3-methyl-2-(phenylsulfonamido)pentanamide (**11 g**)

Yield80%, mp 151–153 °C.FTIR (KBr,cm^{-1}): 3335, 3246 (NH), 3061 (C–H aromatic), 2971, 2931, 2877 (C–H aliphatic), 1674, 1642 (2C=*O*), 1534, 1512 (*C* = *C*), 1389, 1344 (SO_2), 1167, (SO_2–N), 1221, 1145, 1095 (C–N), 1062 (C-F). ^{1}H NMR (400 MHz, DMSO–d_6) δ 9.99 (s, 1H, NH), 8.28 (t, J = 5.8 Hz, 1H, NH), 7.88 (d, J = 9.2 Hz, 1H, NH), 7.73 (d, J = 7.3 Hz, 2H, ArH), 7.44–7.57 (m, 5H, ArH), 7.09 (t, J = 8.9 Hz, 2H, ArH), 3.50–3.67 (m, 3H, CH and CH_2), 1.56 (m, 1H, CH), 1.40 (m, 1H, CHa of CH_2), 0.98–1.04 (m, 1H, CHb of CH_2), 0.65–0.73 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO–d_6, 100 MHz) ∂: 170.9, 167.7, (2C=*O*), 141.4, 135.8, 132.7, 129.2, 127.2, 121.2, 121.1, 115.9, 115.7 (aromatic carbons), 61.2, 42.8, 37.2 24.8, 15.5, 11.1 (aliphatic carbons). HRMS-ESI (*m/z*) for $C_{20}H_{24}FN_3O_5S$: 444.1378 $(M+Na)^+$, calculated, 444.1364 $(M+Na)^+$

2.4.8. N-(2-(3-Chlorophenylamino)–2-oxoethyl)–3-methyl-2-(phenylsulfonamido)pentanamide (**11 h**)

Yield 90%, mp 142–144 °C. FTIR (KBr,cm^{-1}): 3313, 3239 (NH), 3064 (C–H aromatic), 2961, 2929, 2875 (C–H aliphatic), 1676, 1640 (2C=*O*), 1596, 1530, 1481 (*C* = *C*), 1388, 1344 (SO_2), 1166, (SO_2–N), 1214, 1145, 1093, 1075 (C–N), 732 (C–Cl). ^{1}H NMR (400 MHz, DMSO–d_6)δ 9.98 (s, 1H, NH), 8.22 (t, J = 5.5 Hz, 1H, NH), 7.84 (d, J = 8.5 Hz, 1H, NH), 7.73 (d, J = 7.3 Hz, 3H, ArH), 7.44–7.55 (m, 3H, ArH), 7.27–7.38 (m, 2H, ArH), 7.05–7.07 (m, 1H, ArH), 3.66 (dd, J = 16.5, 5.5 Hz, 1H, CH), 3.53 (dd, J = 16.8, 7.0 Hz, 2H, CH_2), 1.49–1.55 (m, 1H, CH), 1.41 (q, J = 6.7 Hz, 1H, CHa of CH_2), 0.97–1.04 (m, 1H, CHb of CH_2), 0.66–0.74 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO–d_6, 100 MHz) ∂: 171.1, 168.2, (2C=*O*), 141.4, 140.8, 133.6, 131.1, 129.2, 127.2, 123.5, 118.9, 117.9 (aromatic carbons), 61.0, 42.9, 37.2 24.7, 15.5, 11.1 (aliphatic carbons). HRMS-ESI (*m/z*) for $C_{20}H_{24}ClN_3O_4S$: 460.1071 $(M+Na)^+$, calculated, 460.1068 $(M+Na)^+$.

2.4.9. 3-Methyl-N-(2-oxo-2-(m-tolylamino)ethyl)–2-(phenylsulfonamido)pentanamide (**11i**)

Yield 76%, mp 144–146 °C.FTIR(KBr,cm^{-1}): 3316, 3236 (NH), 3061 (C–H aromatic), 2969, 2929, 2875 (C–H aliphatic), 1673, 1638 (2C=*O*), 1614, 1537, 1489 (*C* = *C*), 1389, 1344 (SO_2), 1166, (SO_2–N), 1212, 1145, 1093, 1073 (C–N). ^{1}H NMR (400 MHz, DMSO–d_6) δ 9.68 (s, 1H, NH), 8.20 (d, J = 5.5 Hz, 1H, NH), 7.85 (d, J = 8.5 Hz, 1H, ArH), 7.74 (d, J = 7.3 Hz, 2H, ArH), 7.46–7.54 (m, 3H, ArH), 7.30–7.36 (m, 2H, ArH), 7.14 (t, J = 7.6 Hz, 1H, NH), 6.82 (d, J = 7.3 Hz, 1H, ArH), 3.63–3.67 (m, 1H, CH), 3.51–3.54 (m, 2H, CH_2), 2.23 (s, 3H, CH_3-Ar), 1.50–1.58 (m, 1H, CH), 1.36–1.47 (m, 1H, CHa of CH_2), 1.01 (dd, J = 22.0, 14.6 Hz, 1H, CHb of CH_2), 0.66–0.74 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO–d_6, 100 MHz) ∂: 170.9, 167.8, (2C=*O*), 141.4, 139.2, 138.5, 132.7, 129.2, 129.1, 127.2, 124.5, 120.0, 116.7 (aromatic carbons), 61.1, 42.9, 37.2, 24.8, 21.7, 15.6, 11.1 (aliphatic carbons). HRMS-ESI (*m/z*) for $C_{21}H_{27}N_3O_4S$: 418.1801 $(M + H)^+$, calculated, 418.1795 $(M + H)^+$.

2.4.10. N-(2-(2,6-Dimethylphenylamino)–2-oxoethyl)–3-methyl-2-(phenylsulfonamido)pentanamide (**11j**)

Yield 81%, mp 148–149 °C. FTIR (KBr,cm^{-1}): 3258 (NH), 3064 (C–H aromatic), 2965, 2930, 2876 (C–H aliphatic), 1641, 1594

Table 1
Physiochemical properties calculation of the new analogs.

Cpd. No.	HBA	HBD	NoRB	Log p	TPSA	MW	Lipinski violation
11a	4	3	9	3.37	104.37	437.948	0
11b	4	3	9	3.58	104.37	482.399	0
11c	4	3	9	3.08	104.37	417.530	0
11d	4	3	9	4.00	104.37	453.563	0
11e	4	3	9	2.78	104.37	403.503	0
11f	5	3	10	2.74	113.60	433.529	0
11 g	4	3	9	2.93	104.37	421.493	0
11h	4	3	9	3.41	104.37	437.948	0
11i	4	3	9	3.12	104.37	417.530	0
11j	4	3	9	3.37	104.37	431.557	0

HBA = hydrogen bond acceptor, HBD = hydrogen bond donor, NoRB = number of rotatable bond, TPSA = topological polar surface area, MW = molecular weight, logp = octanol-water partition coefficient.

(2C=*O*), 1524, 1466 (*C* = *C*), 1381, 1344 (SO_2), 1166, (SO_2–N), 1225, 1094, 1072, 1044 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H, NH), 8.27 (t, J = 5.8 Hz, 1H, NH), 7.88 (d, J = 8.5 Hz, 1H, NH), 7.73–7.75 (m, 2H, ArH), 7.51 (dt, J = 28.1, 7.3 Hz, 3H, ArH), 7.01 (s, 3H, ArH), 3.71 (dd, J = 16.5, 6.1 Hz, 1H, CH), 3.51–3.61 (m, 2H, CH_2), 2.08 (s, 6H, $2CH_3$-Ar), 1.50–1.61 (m, 1H, CH), 1.31–1.42 (m, 1H, CHa of CH_2), 0.97–1.05 (m, 1H, CHb of CH_2), 0.64–0.71 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6, 100 MHz) δ:171.1, 167.6 (2C=*O*), 141.3, 135.7, 135.2, 132.7, 129.3, 128.1, 127.2, 126.9 (aromatic carbons), 61.0, 42.4, 37.2, 24.7, 18.6, 15.5, 11.1 (aliphatic carbons). HRMS-ESI (*m/z*) for $C_{22}H_{29}N_3O_4S$: 432.1956 $(M + H)^+$, calculated 432.1952 $(M + H)^+$.

2.5. In silico studies

2.5.1. Physiochemical evaluation

The physiochemical properties, including molecular weight (MW), octanol/water partition coefficient (Log P(o/w)), hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), topological polar surface area (TPSA) and number of rotatable bond (NoRB) of the new derivatives were calculated using molinspiration and the drug-likeness was evaluated using Lipinski's rule of five (Table 1).

2.5.2. Molecular docking study

Molecular docking studies were carried out to have a better understanding of the interaction of the synthesized compounds at molecular level with pathogenic organisms. Two receptors were used for this study: *T. brucei* farnesyl diphosphate synthase (PDB Code: 2EWG) for antitrypanosomal study and lactate dehydrogenase (PDB ID: 1CET) from *Plasmodium falciparum* for antimalarial study. The co-crystallized inhibitor for each receptors 1CET and 2EWG are chloroquine and minodronate respectively. The 3D crystal structures with their co-crystallized ligands for the drug targets were obtained from protein data bank repository (https://www.rcsb.org/). The downloaded 3D structures were prepared in Discovery Studio Visualizer 4.1 in which the needed chains were selected while the multiple ligands and non-protein parts were deleted. ACD/ChemSketch 2015 version was used to draw the 2D structures of the synthesized compounds. The compounds were docked against the druggable targets. The binding energy of the compounds was calculated using London dG scoring function and results are presented in Table 2.

2.6. Biological studies

Animal use The use of animal for this study was approved by the University of Nigeria ethical committee for animal use for the PhD research work of Ekoh Ogechi Chinelo PG/PhD/15/78,254.

Table 2
Binding free energy (ΔG kcal/mol) of **11a-j**.

	Antitrypanosomiasis	Antimalaria
Compounds	2EWG: Scoring function-*London dG*	1CET: Scoring function-*London dG*
11a	−7.94	−6.14
11b	−5.54	−6.14
11c	−7.32	−6.26
11d	−7.31	−6.08
11e	−7.52	−5.57
11f	−8.16	−5.89
11 g	−7.09	−5.78
11h	−5.99	−6.10
11i	−6.43	−5.95
11j	−7.73	−6.29
Native ligand	−6.32	−5.67
Standard drug	−5.27	−5.52

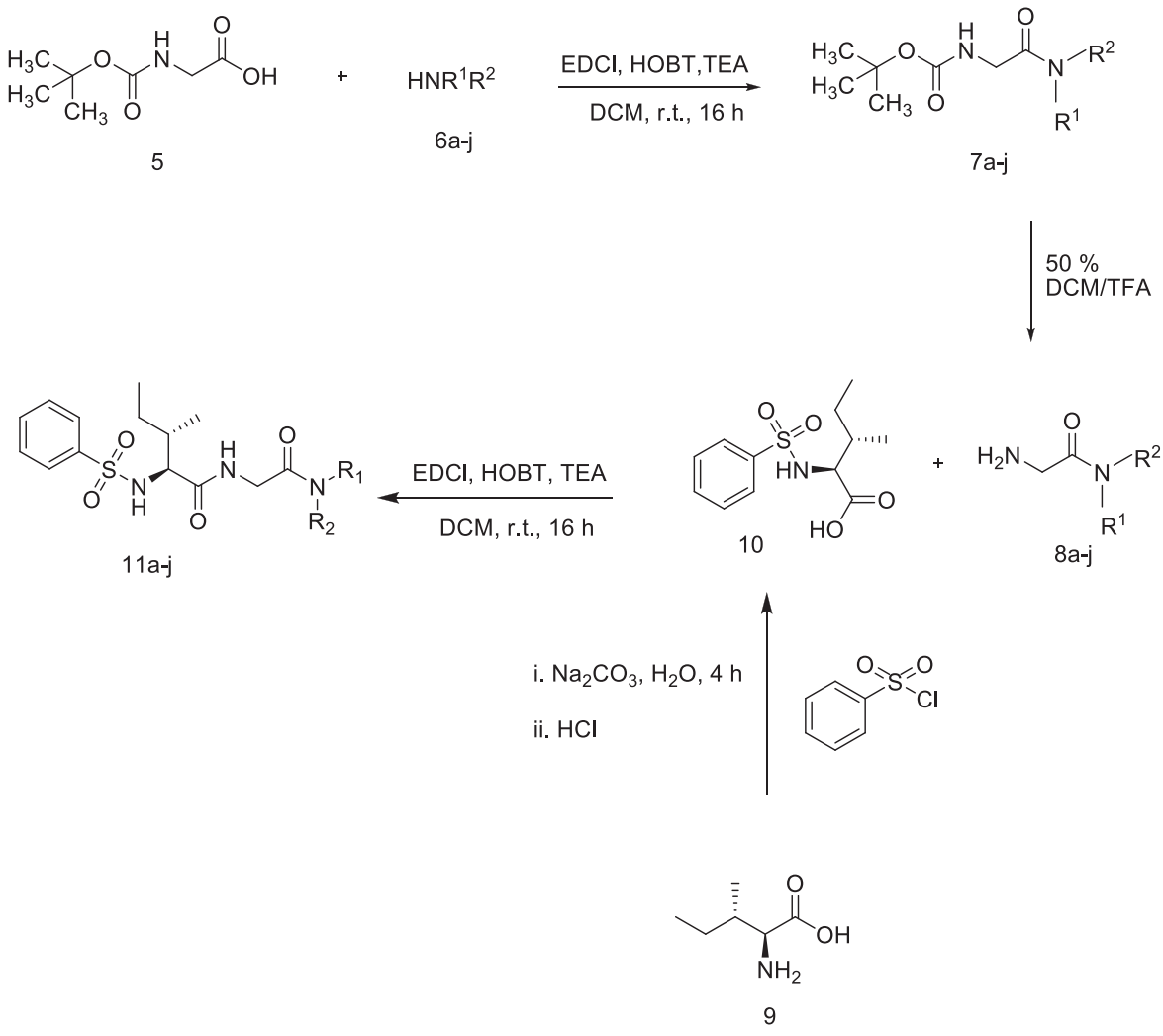
Standard drug: chloroquine for antimalaria and melarsoprol for antitrypanosomal.

2.6.1. In vivo *antitrypanosomal test*

The method described and used by Tekaet *al* [25]for the *in vivo*antitrypanosomal study against T*rypanosomabrucei* with some modification was employed for the experimental design and treatment of mice. In brief, heavily infected donor mice obtained from the Department of Veterinary Anatomy, Faculty of Veterinary Medicine, University of Nigeria, Nsukka were subjected to retro-orbital puncture through the medial canthus of the eye and blood was collected and instantly diluted with PBS to serve as inoculum. Healthy albino mice were distributed at random into thirteen groups of four mice per group, 2000 trypanosomes/mice in 0.2 mL of blood was given intraperitoneally to all the mice except the ones in group 13. [26].The animals were allowed to grow parasitaemia (approximately 10^7) and the percentage parasitaemia was determined before the animals began to receive treatment. The synthesized compounds (100 mg/kg body weight) were orally administered to animals in groups 1–10, DiminazeneAceturate (7 mg/kg) was given to the mice in group 11, group12 was infected but not treated and group 13 was neither infected nor treated. The formulations were given to the groups orally every morning for 7 days and the degree of parasitaemia was determined by wet blood film prepared from tail blood at X40 magnification. The number of parasites seen was counted using the method described by Herbert and Lumsden [27] and the results expressed as the log of an absolute number of parasites per mL of blood.

2.6.2. In vivo *antimalarial assay*

Samples of chloroquine-sensitive *Plasmodium berghei*(NK-65) was obtained from the National Institute of Medical Research (NIMR), Yaba, Lagos, Nigeria. The method by Peter et al. [28]for the antiplasmodial assay against *Plasmodium berghei* infection with some modifications was adopted for the experimental design and treatment of mice.In brief, about fifty-two infected mice of both sexes weighing 18–24 g obtained from the Department of Veterinary Anatomy, Faculty of Veterinary Medicine, University of Nigeria, Nsukka were randomly divided intogroups (test groups and three control groups) of four mice each.The inoculum was prepared from a donor mouse with rising parasitaemia of about 45%. Five days after infection, percentage parasitaemia was determined and animals begin to receive treatment. For each of the synthesized compound **(11a-j),** animals received a daily oral dose of 100 mg/kg body weight for four consecutive days, Artemetherlumefantrine (4/24 mg/kg body weight) was given to the mice in the positive control group, the negative control group was not treated while the other group was not infected. On the fifth day,Giemsa-stained thin blood smears were prepared from the tail of each animal to determine parasitaemia and percentage inhibition [29]. The percentage



Scheme 1. Synthetic route to the new dipeptide sulphonamide derivatives.

of parasite inhibition was estimated using the following equation:% inhibition = [(A-B)/A] × 100

A corresponds to the average parasitaemia of the untreated group, B corresponds to the average parasitaemia of the treated group.

2.6.3.Haematological. analysis

Twenty-four hours following the final treatment, the mice were slain by cervical dislocation and the blood samples were gathered by heart puncture. The haematological parameters carried out were packed cell volume (PVC),haemoglobin(HB) and red blood cell (RBC) count, the blood samples were gathered into EDTA bottles and analysed by automated machine (Automated CBC analyzer: Sysmex KX-21).

2.6.4. Liver function tests (LFTs)

The standard laboratory procedure [30] was used for liver function test evaluation. The liver function tests performed with the blood of the mice fed with the new compounds were Aspartate Aminotransferase (AST), Alanine Transaminase (ALT) and Alkaline Phosphatase (ALP)

2.6.5. Renal or kidney function test

Kidney function tests performed in this study were serum urea, creatinine and uric acid, adopting a standard method [31].

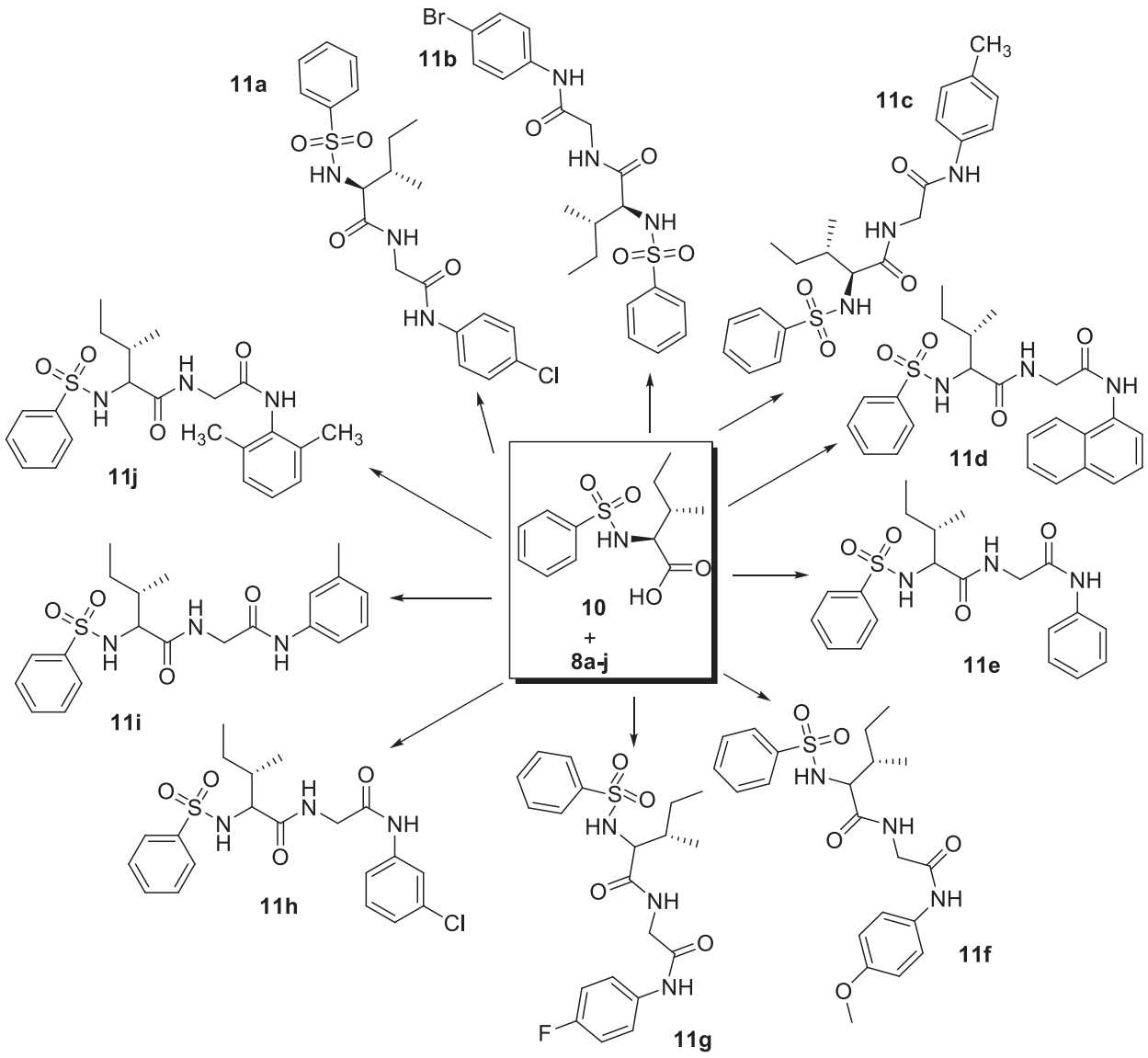
3. Results and discussion

3.1. Chemistry

3-Methyl-2-(phenylsulphonamido)pentanoic acid **(10)** was synthesized in excellent yield (96.97%) by reactingL-isoleucine **(9)** with benzenesulphonyl chloride in the presence of sodium carbonate at 0 °C for 4 h.Boc-protected acetamides**(7a-j)** were synthesized by reacting commercially available Boc-glycine **(5)** with substituted anilines **(6a-j)** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride EDCI, 1-hydroxybenzotriazole HOBT and triethylamine TEA. Compounds **7a-j**were deprotected by the addition of 50% TFA in DCM to give **8a-j** which on further reaction with compound **(10)** in the presence of peptide coupling reagents EDCI, HOBT and TEA furnished the desired dipeptide sulphonamides (**11a-j**, scheme 1) which were characterized using FTIR,^{1}H NMR, ^{13}C NMR and high-resolution mass spectroscopy (HRMS) Scheme 2.

3.1.1. Spectral characterization

The FTIR spectra of the dipeptide derivatives showed two strong N–H bands between 3337 and 3236 cm^{-1}. The two *C = O* amide carbonyl bands appeared between 1680 and 1594 cm^{-1}. The SO_2–N bands appeared between 1167 and 1166. These bands are an



Scheme 2. Isoleucine derived dipeptide sulfonamide derivatives.

indication of successful coupling of the acetamides**(8a-j)** with benzenesulphonamide**(10)**.

In the ^{1}H NMR spectra of the derivatives, the diagnostic peaks at 3.51–3.61 ppm due to the interaction of CH_2 and NH of glycine, 1.49–1.61 ppm due to the interaction of CH and CH_2 of isoleucine and 6.82–9.99 ppm due to NH protons and aromatic protons are supportive of the target products formation.

The carbon-13 NMR showed all the peaks expected of successful coupled products. The two $C = O$ peaks appeared from 167.6–171.1 ppm, the peaks assigned to aromatic carbons appeared between 155.7 and 114.4 ppm while the peaks assigned to aliphatic carbons appeared between 61.1–11.0 ppm.

The high-resolution mass spectrometer (HRMS) peak of the derivatives appeared either as $M + H^+$ or M+Na^+ adduct. The results corresponded with the calculated values. The spectra used for the characterization of the new compounds are available as **supporting materials**

3.1.1.1. In silico studies. **Physicochemical properties** Physicochemical properties of compounds have been used by Medicinal Chemists long ago to predict or estimate pharmacokinetic properties [32]. Drug-likeness has also been used as aparameter to predict the balance amongst the molecular propertiesof a compound that influences its pharmacodynamics andpharmacokinetic properties [14] The absorption, distribution, metabolism, and excretion of the drug can be optimized using the physicochemical parameters.

The physicochemical properties of the synthesized compounds **(11a-j)** which are useful in the assessment of drug-likeness are presented in Table 1. Lipinski's rule of five helps to evaluate the bioavailability for oral formulations. Lipinski's rule states that, in general, an orally active drug has no more than one violation of the following criteria [33]: No more than 5 hydrogen bond donors (the total number of nitrogen–hydrogen and oxygen–hydrogen bonds) No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms). A violation of more than one parameter may be an indication of poor bioavailability. Table 1 reveals that compounds **11a-j** are in agreement with Lipinski's rule of five, therefore all thecompounds reported have a good balance between compound solubility and its penetration of the lipid bilayers and hence arelikely going to have good oral bioavailability.

Molecular Docking Binding free energy is an indication of the binding affinity of a ligand on the protein. It measures the

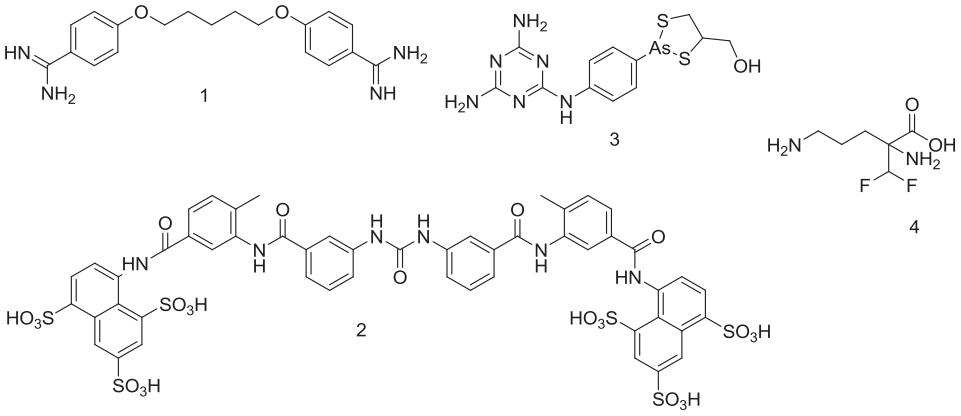


Fig. 1. Examples of commercial antitrypanosomal agents.

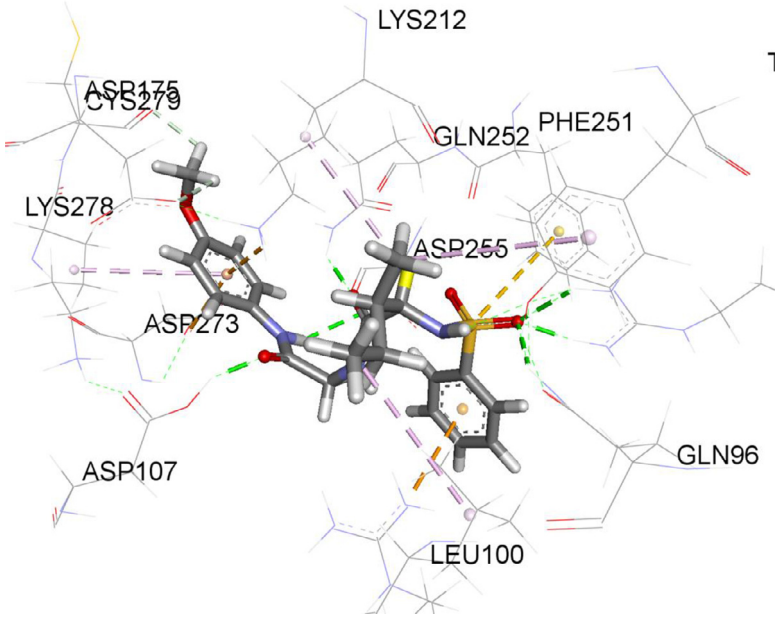


Fig. 2. Stereoview of compound11f in the binding cavity of 2EWG.

inhibition of the protein or enzyme in the presence of both the inhibitor. The free energy of binding is given as the dissociation constant K_d which is the ratio of the concentration of the products (complexes) to reactants (protein and ligand). It shows the extent to which biological macromolecules interact with each other or with various small molecules through noncovalent interactions to form a specific complex. The higher the binding affinity, we will expect a interactions between the biological macromolecules (drug targets) and the ligands. These effective interactions will result in the molecules eliciting biological activities. These predictions are made through docking calculations.

Table 2 shows the binding free energy (kcal/mol) of the synthesized compounds with the drug targets used, namely; *T. brucei* farnesyl diphosphate synthase complexed with minodronate (2EWG) and *Plasmodium falciparum* lactate dehydrogenase complexed with chloroquine (1CET). The compounds showed a reasonable binding affinity with the targets. The molecular docking studies against 2EWG target showed that the compounds had more binding affinitythan the native ligand (minodronate) and the standard drug (melarsoprol) for the treatment of trypanosomiasis. Compound **11f** showed the highest binding affinity with and hence was singled out for further studies to enable us to understand its mechanism of action. Likewise, there was no significant difference in the binding affinity of the compounds and those of the standards against1CET. Compound **11j** has been chosen to represent the group for further studies. Fig. 1

Figs. 2 and 5 show the stereo views of compounds **11f** and **11j** in the binding cavities of 2EWG and 1CET respectively. The compounds fitted well into the binding cavities of the respective targets thereby making extensive chemical interactions with their amino acid residues. Fig. 3 shows the 2D representation of binding interactions of compound **11f** with the amino acid residues of 2EWG while Fig. 6 shows the 2D representation of the binding interactions of compound **11j** with the amino acid residues of 1CET. There were numerous effective and significant chemical interactions observed leading to high binding affinities of these compounds with these targets. The detailed chemical interactions leading to high binding affinities are shown in Table 3 for **11f**-2EWG and Table 4 for **11j**-1CET interactions. To understand the nature of the atoms of the compounds interacting with various amino acid residues, Figs. 4 and 7 show the numbering of compounds **11f** and **11j** respectively using Chem Draw.

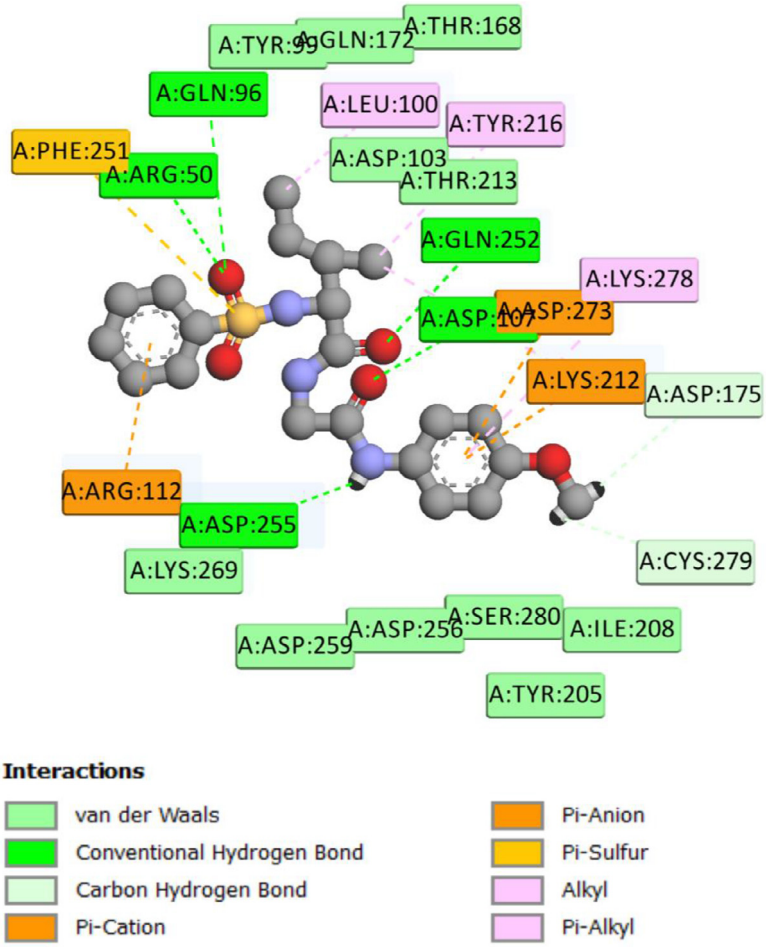


Fig. 3. 2-Dimensional representation of binding interactions of compound 11f with the amino acid residues of 2EWG.

Table 3
Summary of interactions between compound 11f and 2EWG.

Receptor	Ligand	Distance (Å)	Category	Typeof interaction
ARG50	O-10	2.42	Hydrogen Bond	Conventional Hydrogen Bond
GLN96	O-10	2.41	Hydrogen Bond	Conventional Hydrogen Bond
ASP107	O-21	1.72	Hydrogen Bond	Conventional Hydrogen Bond
GLN252	O-17	1.93	Hydrogen Bond	Conventional Hydrogen Bond
ASP255	HN-22	2.65	Hydrogen Bond	Conventional Hydrogen Bond
ASP175	H1–30	2.85	Hydrogen Bond	Carbon Hydrogen Bond
CYS279	H3–30	2.44	Hydrogen Bond	Carbon Hydrogen Bond
ARG112	Phenyl	3.68	Electrostatic	Pi-Cation
LYS212	methoxy phenyl	2.78	Hydrogen Bond;Electrostatic	Pi-Cation;Pi-Donor Hydrogen Bond
ASP273	methoxy phenyl	3.33	Electrostatic	Pi-Anion
PHE251	S-7	5.45	Other	Pi-Sulfur
LEU100	C-15	5.48	Hydrophobic	Alkyl
LYS212	methoxy phenyl	4.15	Hydrophobic	Alkyl
TYR216	C-14	5.11	Hydrophobic	Pi-Alkyl
LYS278	methoxy phenyl	4.74	Hydrophobic	Pi-Alkyl

3.2. Biological studies

3.2.1. In vivo antitrypanosomal activities

Table 5 shows the *in vivo*antitrypanosomal activity of compounds **11a-j** on mice infected with *T. bruccei.* The result of the study reveals that there were variations in the parasitaemia levels of all the groups treated with the synthesized compounds and diminazeneaceturate. The parasitaemia levels in the treated groups are relatively low as compared to the infected untreated control. However, compounds **11a-j** displayed mild to moderate in vivo antitrypanosomal activity. The best results were obtained with animals treated with **11b, 11i** and **11j** in which there was a continuous reduction in the activity of trypanosomes and parasitaemia level from day 1 to the final day of treatment. Compound **11b** which showed the best activity amongst the groups treated with the synthesized derivatives has a comparable activity with the standard drug (diminazeneaceturate).

3.2.2. In vivo antimalarial activities

The method by De Souza et al. [34] was employed for the interpretation of the in vivo antimalarial activity of the synthesized compounds against *P. berghei* (NK-65). Compounds that

Table 4
Summary of interactions between compound 11j and 2EWG.

Receptor	Ligand	Distance (Å)	Category	Typeof interaction
GLY99	O-21	2.09	Hydrogen Bond	Conventional Hydrogen Bond
THR101	O-9	2.75	Hydrogen Bond	Conventional Hydrogen Bond
ASP53	NH-18	2.38	Hydrogen Bond	Conventional Hydrogen Bond
THR101	O-10	2.97	Hydrogen Bond	Carbon Hydrogen Bond
PHE100	Phenyl	5.96	Hydrophobic	Pi-Pi Stacked
ALA98	C-30	3.64	Hydrophobic	Alkyl
ILE54	C-29	4.56	Hydrophobic	Alkyl
ILE119	C −29	4.86	Hydrophobic	Alkyl
VAL26	C-30	5.38	Hydrophobic	Alkyl
ILE54	C-30	5.00	Hydrophobic	Alkyl
PHE52	C-30	5.02	Hydrophobic	Pi-Alkyl
ILE54	2,6-dimethylphenyl	4.04	Hydrophobic	Pi-Alkyl
ALA98	2,6-dimethylphenyl	4.29	Hydrophobic	Pi-Alkyl
ILE119	2,6-dimethylphenyl	4.43	Hydrophobic	Pi-Alkyl

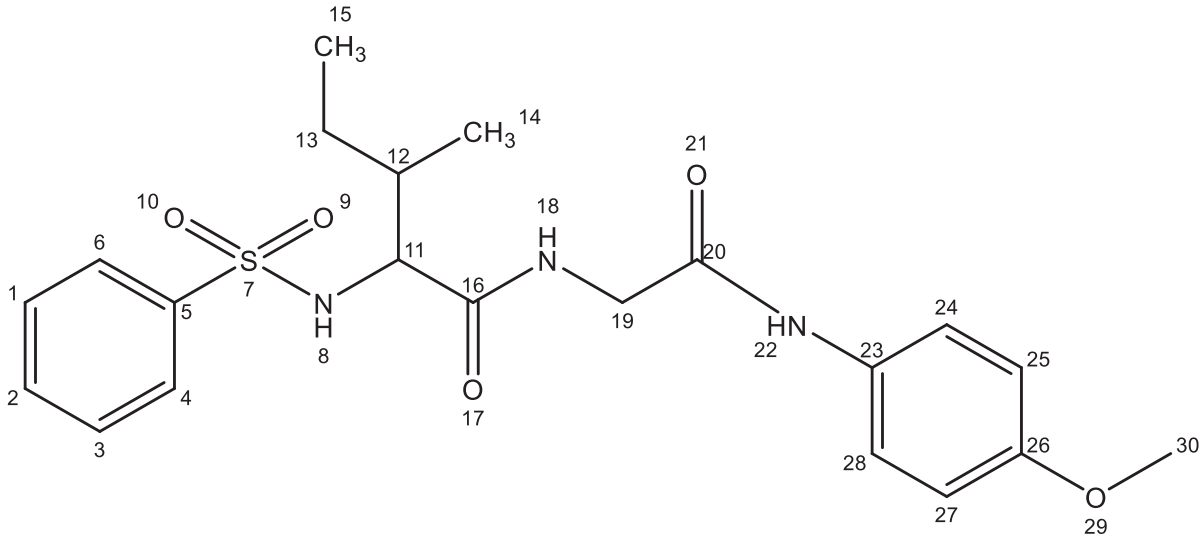


Fig. 4. Compound 11f showing the atom numbering.

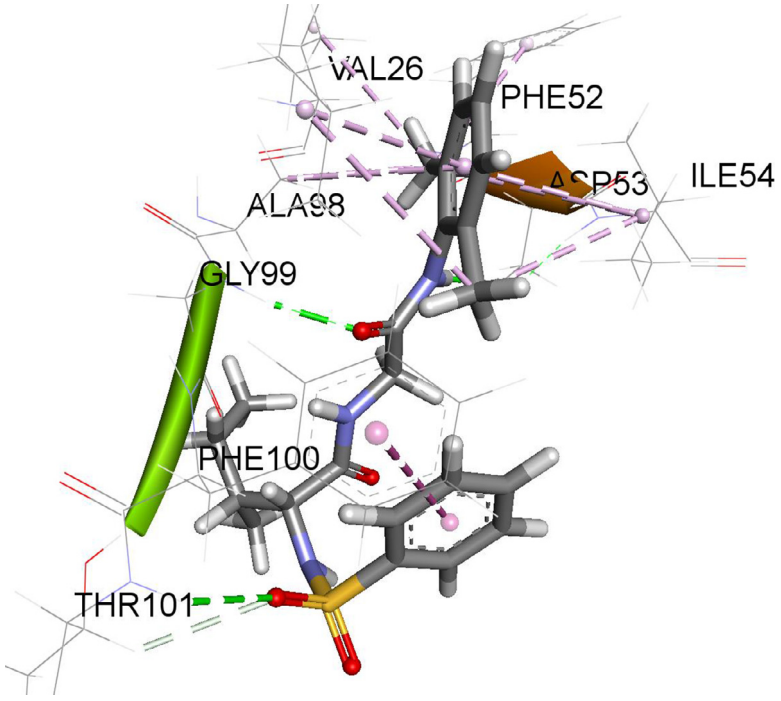


Fig. 5. Stereoview of compound 11j in the binding cavity of 1CET.

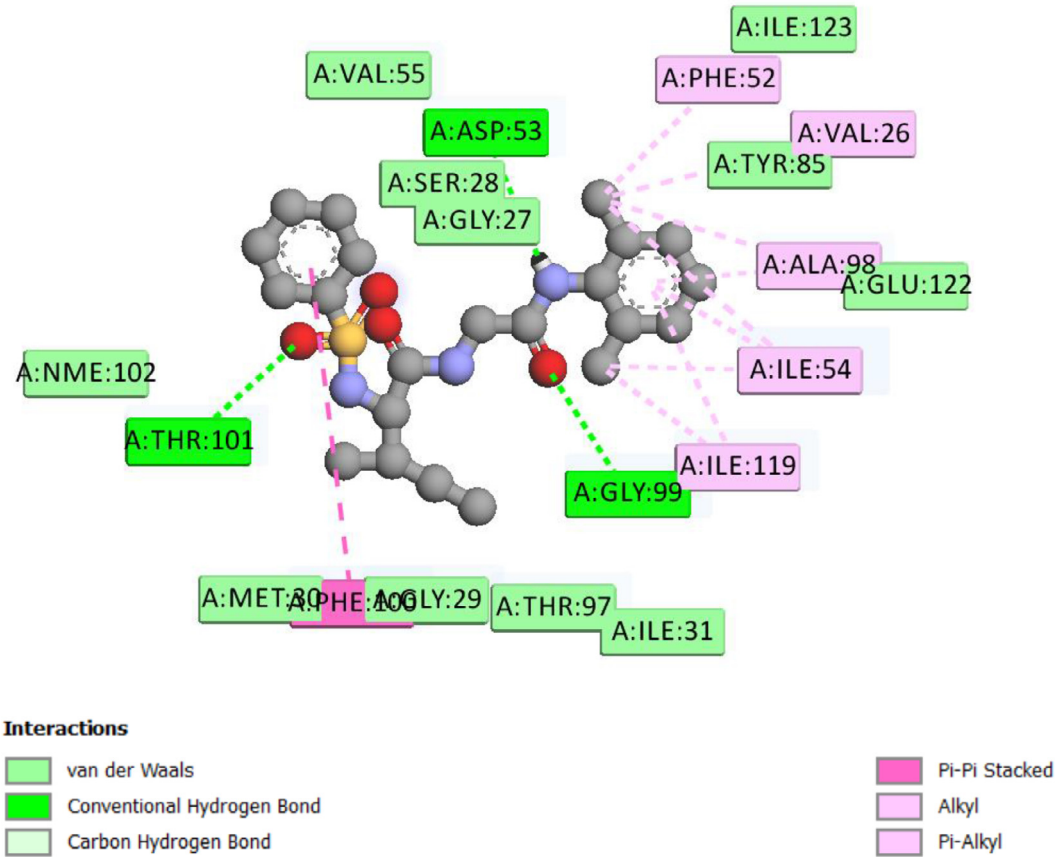


Fig. 6. 2-Dimensional representation of binding interactions of compound 11j with the amino acid residues of 1CET.

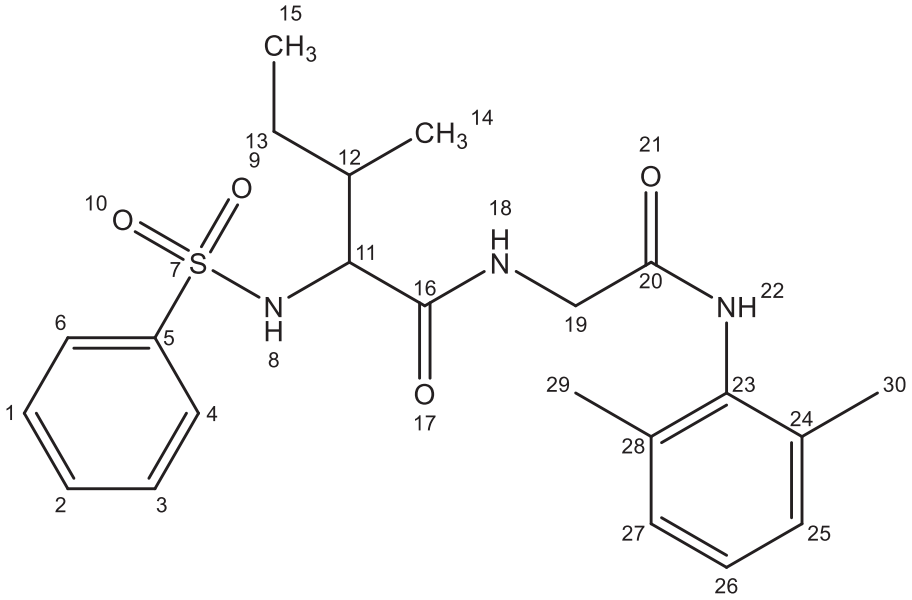


Fig. 7. Compound 11j showing the atom numbering.

reduced parasitaemia by 40% were considered active, whereas those that reduced parasitaemia by 30–40% and by less than 30% were considered partially active and inactive respectively. Apart from **11c**, all the compounds including the control drug reduced the parasitaemia level by at least 40% (Table 6). However, comparing the compounds ability to inhibit parasitaemia to that of the control drug, compounds **11b, 11a**and **11i** (%inhibition = 81.25, 77.80 and 76.23% respectively) showed better or comparable activity with artemether-lumenfantrine(79.89%). These compounds should be considered for further studies because of their promising activities.

3.2.3. Haematological analysis

Evaluation of the complete blood count provides huge information on the haematological status in disease condition [35]. Anaemia is usually assessed by evaluating the packed cell

Table 5
Effects of compounds 11a-j on parasite count in mice infected with *T. brucei*.

Compounds	Parasitaemia level (log number/mL) Day 1	Day 3	Day 5	Day 7
11a	6.70	6.77	5.31	5.91
11b	7.12	4.50	3.05	0.60
11c	7.11	8.32	6.38	7.82
11d	7.20	7.06	4.39	5.05
11e	6.93	5.30	4.33	3.10
11f	7.01	7.01	5.20	5.00
11 g	6.99	6.29	3.00	5.04
11h	7.22	7.36	5.00	4.49
11i	7.01	5.23	3.42	2.01
11j	7.00	6.09	3.25	2.23
DA	7.23	5.84	2.37	0.52
NTC	6.98	7.29	8.45	8.88

DA: Diminazeneaceturate, NTC: Non treated control.

Table 6
Percentage inhibition of *P. berghei* parasite in mice.

Compounds	% Inhibition
11a	77.80
11b	81.25
11c	31.33
11d	50.68
11e	57.00
11f	73.63
11 g	40.67
11h	52.82
11i	76.23
11j	54.39
Arte lum	79.77
NTC	–
NIC	–

Arte lum: Artemetherlumefantrine, NTC: Non treated control, NIC: Non infected control.

Table 7
Haematological analysis after treatment.

Compound	PCV (%)	HB (g/dL)	RBC ($\times 10^6$/µL)
11a	36.9	11.4	7.2
11b	37.6	12.4	7.4
11i	37.9	12.0	6.8
Control	38.2	12.8	7.6

Table 8
Liver function tests.

compounds	AST (µL)	ALT (µL)	ALP (µL)
11a	57.6	20.0	0.79
11b	56.2	19.4	0.80
11i	56.9	20.3	0.84
Control	57.4	20.3	0.82

volume (PCV), haemoglobin (HB), and red blood cell (RBC) count in malaria patients [36]. Table 7 shows the haematological parameters of *P. berghei* infected mice after treatment. The result revealed that there is no significant decrease in the parameters of the treated groups when compared with the control.

3.2.4. Liver function test

Liver function test is a group of blood tests that are used to check how well the liver is working. They detect inflammation and damage to the liver. The liver function test carried out in this research is presented in Table 8. The result of this study shows that the administration of 100 mg/kg of the synthesized compounds in mice did not cause a significant increase or decrease in the serum AST,ALT and ALP when compared with the control.

Table 9
Kidney function test.

Compounds	Urea (mg/dl)	Creatinine(mg/dl)	Uric acid (mg/dl)
7d	12.4	0.6	3.5
7i	11.7	0.6	3.3
7j	12.0	0.5	3.4
Control	12.4	0.5	3.2

3.2.5. Kidney function test

These are common laboratory tests used to evaluate how well the kidneys are functioning. It is observed from Table 9 that there is no significant change in the serum level of urea, creatinine and uric acid of mice fed with 100 mg/kg of the reported derivatives when compared with the control.

4. Conclusion

Ten new Ile-gly dipeptide sulphonamide derivatives have been successfully synthesized using an efficient, versatile and ecofriendly approach. The structures of the synthesized compounds are consistent with spectral data. All the compounds were investigated for their in vivo antitrypanosomal and antimalarial activities in mice. The synthesized compounds showed mild to moderate antitrypanosomal activity except for compound **11b** that had a comparable activity with diminazene aceturate at day 7 of the treatment period. In the antimalarial activity study, compounds**11b, 11f** and**11i** showed good antimalarial activity with percentage inhibition of parasite growth in the range of 73.63–77.80% comparable with artemether/lumenfantrine (79.77%). The results of the haematological analysis, liver and kidney function tests showed that there were no significant changes in the parameters tested when compared with the control. The physicochemical parameter predictions indicate that the compounds would not pose oral bioavailability, transport and permeability problems if developed further to drug molecules The molecular docking studies showed good interaction between the synthesized compounds and the protein targets for antitrypanosomal and antimalarial activities. The synthesized derivatives are promising drug candidates for trypanosomiasis and malaria. Furthermore, Compound **11b** stands out amongst the derivatives having shown good activity in both the antimalarial and antitrypanosomal assay.

Declaration of Competing Interest

The authors declare that there is no conflict of interest

CRediT authorship contribution statement

Ogechi C. Ekoh: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing - original draft, Visualization, Project administration, Funding acquisition. **Uchechukwu C. Okoro:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Rafat Ali:** Investigation, Writing - review & editing, Supervision. **David I. Ugwu:** Investigation, Writing - review & editing, Project administration. **Sunday N. Okafor:** Software. **James A. Ezugwu:** Formal analysis.

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