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Synthesis of Multi-Target Benzene-Sulphonamide Derivatives for the Treatment of Trypanosomiasis

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Abstract

Some derivatives of benzene-sulphonamides were synthesized via condensation reaction. Pharmacokinetic parameters were evaluated to assess the oral bioavailability, permeability and transport properties of the compounds. Molecular docking studies were performed on farnesyl diphosphate synthase, pteridine reductase, ornithine decarboxylase and rhodesain to assess the potential of the reported compounds in treating human African trypanosomiasis. All the compounds showed good binding to the target proteins assayed.

Keywords: Farnesyl diphosphate synthase; Pteridine reductase; Ornithine decarboxylase; Rhodesain; Human African Trypanosomiasis

Introduction

The need for increasing life span and wellbeing among humans and live-stocks has been a challenging task combating research exponents and the pharmaceutical industries global, following the emergence of plaguing diseases and conditions in the last few decades. However, sulphonamide is a biologically active moiety present in several drugs and is considered to be useful isosteres of carboxylic acids and carboxamides in drug discovery [1]. The sulphonamide family were the first antibiotic to be used systemically [2] because of their low cost and relative efficiency [3]. They are extensively used as high-ceiling diuretics, [4,5] anti-thyroid and anti-inflammatory agents [6]. They perform their function via the mechanistic pathway of inhibition of the conversion of *p*-aminobenzoic acid, thus creating embargo on utilization of *p*-aminobenzoic acid by bacteria in folic acid synthesis which accounts for the formation of purine and DNA [7]. Sulphonamide compounds have been reported to show wide application as antitumor and anticancer agent [8] owing to their inhibition of cancerous cell growth and cessation of tumor invasion [9]. Other applications of sulphonamides range from antiretroviral [10], carbonic anhydrase inhibitors [11-15], anti-dandruff, COX-II and receptor tryosin inhibitors [14], glucosidase inhibitors, anti-influenza [16], anti-helmintics [17], antimalarial [18], and anti-trypanosomal properties [19]. Moreover, chiral sulfonamides containing stereogenic centers have also emerged recently in pharmaceuticals. For example, ramatroban is a drug for the treatment of coronary artery disease and asthma [20,21], whereas MK-7246 targets respiratory diseases [22,23]. Other chiral sulfonamide drugs focus on type II diabetes [24] and Alzheimer's disease [25] (Figure 1). They have also found utility as veterinary drugs [26] and, due to the ease of administration and non-interaction with defense mechanism of host, some derivatives are used in treatment of gastrointestinal and urinary tract infections [27]. These wide applicability of sulphonamides in chemotherapy makes them a sort after functionality in developing new biological agents.

However, human African trypanosomiasis (HAT), also known as sleeping sickness, is a protozoan parasitic infection caused by *Trypanosoma brucei rhodesiene* or *Trypanosoma brucei gambiense* [28]. Reports have shown that HAT occurs in 36 countries in sub-Saharan Africa and about 60 million people worldwide are at risk from developing the disease [29]. The annual incidence of the disease is approximately 300,000 cases, and the area of Africa that is infested by the tsetse fly encompasses approximately ten million square kilometers [30,31], which is a third of the land mass of Africa. During the haemolymphatic phase, trypanomastigotes circulate within the blood and lymphatic system causing some early symptoms which tend to be non-specific such as malaise, headache, arthralgia, generalized weakness, and weight loss [32]. Multiple organs may be infected [33] and if not treated sufficiently, the late (encephalitic) phase ensues as parasites penetrate the blood brain barrier displaying wide insidious and potential clinical phenotype as they infect [33] the central nervous system and recovery of patients at this level is unlikely [34]. Presently, no vaccine is available for the prevention of HAT and the curative treatment depends on a small number of drugs (pentamidine, suramin, melarsoprol and eflornithine). The first three drugs were developed for over 60 years and even eflornithine came in 1990 (almost 30 years ago). The current drugs have been associated with severe side effects with melarsoprol being the most toxic and cause reactive encephalopathy in 5-10% of treated patients. Again, the efficacy of these drugs is limited by parasite resistance, lack of broad spectrum activity and parasite stage-specific activity. For instance, eflornithine is active against only *T. b. gambiense* at the last stage of the disease. There is therefore urgent need to develop broad spectrum drugs with reduced side effect that can also handle the different stages of the parasite. In this regard, interest in proteases resulted from the observation that they are involved in a wide range of physiological and pathophysiological events such as host invasion, host protein degradation, differentiation and host immune response escape when trypanosome peptidases including surface peptidases, cysteine peptidases and serine peptidases are release into the host's bloodstream. Consequently, a promising strategy for fighting trypanosome may be to target the major cysteine proteases such as rhodesain in *T. brucei*-induced acute HAT.

The presence of sulphonamide in most current chemotherapeutic agents informs the desire to explore sulphonamides in the design for potential HAT drugs. In continuation of the ongoing search for lead anti-trypanosomal drugs, we report herein, the successful synthesis of

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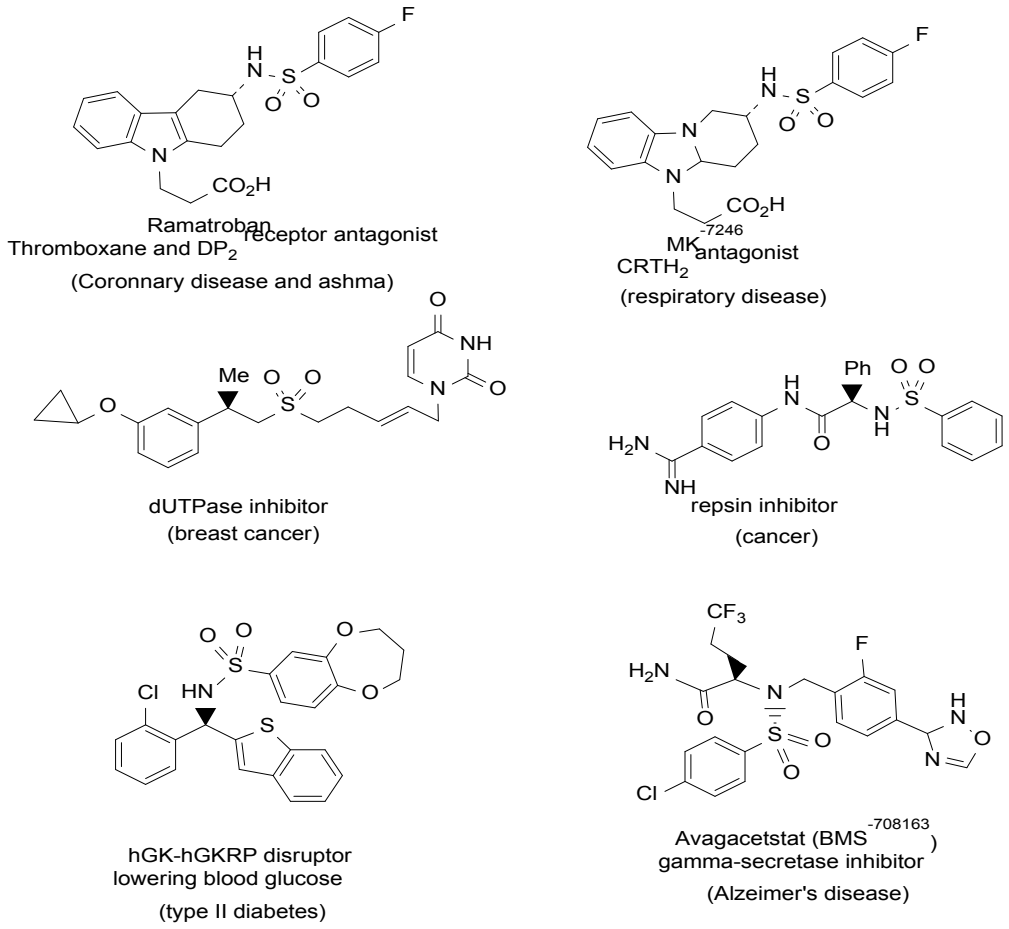


Figure 1: Chiral sulfonamide drugs focus on type II diabetes and Alzheimer's disease.

thirteen new sulphonamide derivatives with the potential to inhibit pteridine reductase, ornithine decarboxylase, farnesyl diphosphate synthase and rhodesain.

Experimental Procedure

All reagents were purchased from Aldrich, Germany. Thin layer chromatography was carried out using silica plates purchased from Avra. FTIR spectroscopy of the compounds was run in Bruker FT-IR spectrometer with Alph's Platinum ATR single reflection diamond and the bands presented in wavenumber. The 1D and 2D NMR spectroscopy were run in Jeol 400 MH_Z using DMSO-d6 as solvent. The chemical shifts were reported in part per million with reference to tetramethylsilane. The molecular mass of the compounds were obtained using high resolution positive ion electrospray ionization on Brucker 10152 mass spectrometer pos_tune_low_msq.m. Melting points were determined using Fischer John's melting point apparatus of the Department of Pure and Industrial Chemistry, University of Nigeria. The molecular docking and quantitative structure activities relationship experiments were performed at the Department of Pharmaceutical and Medicinal Chemistry, University of Nigeria.

Synthesis of substituted benzene-sulphonamides using grinding technique

Amino acid (**2a-2d,** 5 mmol) was grounded into fine powder for 5 mins and Na_2CO_3 (5 mmol) was added and the mixture pulverized for 15 mins. 4-Nitrobenzenesulphonyl chloride (**1,** 5 mmol) was added to the mixture and grinding continued for 2 h with intermittent addition of small quantity of water. The product was washed, filtered and dried in hot air oven at 50°C.

3-Methyl-2-{[4-nitrophenylsulphonyl]amino}butanoic acid (3a)

The amino acid was L-valine, yield (1.50 g, 99.3%), colour: pale yellow, m.p.: 184-186°C. FTIR (KBr, cm^{-1}): 3350 (NH) 3100 (C-H aromatic), 2925 (CH aliphatic) 2560, (OH of COOH), 1650 (C=O), 1600 (C=C), 1550, 1320 (NO_2), 1209, 1145 (SO_2), 1088 (C-O), 1061 (C-N), 692 (S-N). ^{1}H NMR (DMSO-d6, 400 MH_Z) δ: 8.30 (m, 2H, ArH), 8.04 (d, *J*=8.00H_Z, 1H, NH), 7.98 (m, 2H, ArH), 4.25 (s, 1H, OH exchangeable with HDO), 3.26 (d, *J* =4.00 H_Z, 1H, CH-C=O) I.97 (m, 1H, $CH(CH_3)_2$), 0.86 (d, *J* =8.00 Hz, 3H, CH_3-CH), 0.73 (d, *J* =4.00 H_Z, 3H, CH_3-CH). ^{13}C NMR (DMSO-d6, 100 MH_Z) δ: 174.1, 152.8, 151.1, 146.8, 128.6, 127.2, 124.1 (six aromatic carbons), 63.7, 31.2, 19.5, 17.3 (four aliphatic carbons). DEPT: two CH_3 appeared at 19.5 and 17.3 ppm; no CH_2; six CH appeared at 146.8, 128.6, 127.2, 124.1, 63.7 and 31.2 ppm and three tertiary carbons at 174.1, 152.8 and 151.1 ppm. The HSQC analysis was in agreement with the assignment. MS (M/Z) for $C_{11}H_{15}N_2O_6S$: 303.0267 [M+H]+.

2-{[(4-Nitrohenyl)sulphonyl]amino}propanoic acid (3b)

The amino acid was L-alanine. Yield 1.20 g, (88.2%), colour: white, m.p.: 162-164°C. FTIR (KBr, cm^{-1}); 3335 (NH), 3128 (C-H of aromatic),

2951 (CH aliphatic), 2550 (OH of COOH), 1787 (C=O), 1611 (C=C), 1518, 1289 (NO_2), 1234, 1112 (SO_2), 1093, 1013 (C-O, C-N), 718 (S-N). ^{1}H NMR (DMSO-d6, 400 MH_Z) δ: 8.33 (m, 2H, ArH), 8.03 (m, 2H, ArH), 7.93 (d, *J* =8.00H_Z, 1H, NH), 4.16 (s, 1H, OH exchangeable with HDO), 3.13 (m, 1H, CH), 1.10 (d, *J* =4.00 H_Z, 3H, CH_3). ^{13}C NMR (DMSO-d6, 100 MHz,) δ: 174.02, 153.4, 149.2, 134.9, 125.6 (four aromatic carbons) 60.4, 14.2 (two aliphatic carbons). DEPT: One CH_3 that appeared at 14.2 ppm; no CH_2; three CH appeared at 134.9, 125.6 and 60.4 ppm and three tertiary carbons at 174.2, 153.4 and 149.2 ppm. HSQC experiment was in agreement with the assignment. MS (M/Z) for $C_9H_{11}N_2O_6S$: 275.1206 [M+H]+.

2-{[(4-Nitrophenyl)sulphonyl]amino}pentanenoic acid (3c)

The amino acid was L-glutamic acid. Yield (1.77g, 70.5%), colour: pale green, m.p. 79-80°C. FTIR (KBr, cm^{-1}). 3468 (NH), 3102, 3069 (C-H aromatic), 2917, 2863 (CH aliphatic), 2625, 2599(OH of COOH), 1725, 1698 (CO), 1604, 1579 (C=C), 1520, 1352 (NO_2), 1306, 1177 (SO_2), 1121, 1078, 1034, 1007 (C-N, C-O). ^{1}H NMR (DMSO-d6, 400 MH_Z), δ:1093 (S, OH of COOH), 8.38 (d, *J* =8.00 H_Z, 1H, NH), 8.18 (m, 2H, ArH), 7.82 (m, 2H, ArH), 3.88 (m, 1H, CH), 2.44 (m, 1H, CH_a of CH_2COOH), 2.33 (m, 1H, CH_b of CH_2-COOH) 1.99(m, 2H, CH_2 of CH_2-CH_2-COOH). ^{13}C NMR (DMSO-d6, 100 MH_Z) δ: 173.7, 171.1, 154.3, 147.8, 127.4, 123.9, 51.7, 29.7, 25.7. DEPT: no CH_3, two CH_2 that appeared at 29.7 and 25.7 ppm; three CH that appeared at 127.4, 123.9 and 51.7 ppm and four tertiary carbons that appeared at 173.7, 171.1, 154.3 and 147.8 ppm. HSQC experiment were in agreement with the assignment. MS (M/Z) for $C_{11}H_{13}N_2O_8S$: 333.0264 [M+H]+.

3-(4-hydroxyphenyl)-2-{[nitrophenyl)sulphonyl]amino} propanoic acid (3d)

The amino acid was L-tyrosine. Yield 95%, m.p. >300°C. colour: brown. FTIR (KBr, cm^{-1}): 3498 (OH), (br, OH), 3415 (NH), 3009 (C-H aromatic), 2987 (CH aliphatic), 2672 (OH of COOH), 1754 (C=O), 1587 (C=C), 1523, 1345 (NO_2), 1309, 1148 (SO_2), 1242, 1109, 1031, 1011 (C-N, C-O), 713(S-N). ^{1}H NMR (DMSO-d6, 400 MH_Z)δ: 7.71 (m, 1H, ArH), 7.52 (m, 1H, ArH), 7.38 (m, 1H, ArH), 7.11(m, 1H, ArH), 6.43 (m, 1H, ArH), 6.11(m, 1H, ArH), 3.28 (m, 1H, CH), 2.33 (dd, *J* =4.02, 1.69 H_Z, 1H, CH_a of CH_2), 2.02(dd, *J* =4.38, 2.08 H_Z, 1H, CH_b of CH_2). ^{13}C NMR (DMSO-d6, 100 MH_Z) δ: 171.5 (C=O), 150.6, 148.9, 147.3, 146.2, 136.2, 130.4, 129.4, 127.3, 126.5, 124.0, 123.4, 122.8 (twelve aromatic carbons), 56.9, 36.7 (two aliphatic carbons). DEPT: No CH_3; one CH_2 that appeared at 36.7 ppm; nine CH appeared at 136.2, 130.4, 129.4, 127.3, 126.5, 124.0, 123.4, 122.8 and 56.9 ppm and five tertiary carbons at 171.5, 150.6, 148.9, 147.3 and 146.2 ppm. The HSQC spectrum corroborated the previous assignments. MS (M/Z) for $C_{15}H_{15}N_2O_7S$: 367.0686 [M+H]+.

Synthesis of compounds 5a-5e

Sodium carbonate (Na_2CO_3, 5 mmole was added to a solution of amino acids (**4a-4e,** 5 mmol) in water (15 mL) with continues stirring until all the solutes had dissolved. The solution was cooled to -5°C and 4-nitrobenzenesulphonyl chloride (**1,** 5 mmol) was added in four portions over a period of 1 h. The slurry was further stirred at room temperature for about 4 h. The mixture was acidified using 20% aqueous hydrochloric acid to pH 2. The products were filtered via suction and washed with pH 2.2 buffer. The purified products were dried using hot air oven.

4-(methylsulphonyl)-2-{(4-nitrophenyl)sulphonyl)amino} butanoic acid (5a)

The amino acid was L-methionine. Yield 0.83 g, (88.4%) colour: white. m.p. 58-60°C. FTIR (KBr, cm^{-1}): 3435 (NH), 3112 (CH aromatic), 2895 (CH aliphatic), 2777 (OH of COOH), 1725 (C=O), 1635 (C=C), 1520, 1288 (NO_2), 1211, 1160 (SO_2), 1103, 1087, (C-O, C-N), 681 (S-N). ^{1}H NMR (DMSO-d6, 400 MH_Z) δ: 8.61 (d, *J* =8.00 H_Z, 1H, NH), 8.38 (m, 2H, ArH), 8.01 (m, 2H, ArH), 3.93 (m, IH, CH), 3.46 (s, 1H, OH exchangeable with HDO), 2.41 (m, 1H, CH_a of CH_2-CHN), 2.32 (m, 1H, CH_b of CH_2-CHN), 2.32 (m, 1H, CH_b of CH_2-CHN), 1.93 (s, 3H, CH_3), 1.86 (m, 1H, CH_a of CH_2S), 1.75 (m, 1H, CH_b of CH_2-S). ^{13}C NMR (DMSO-d6, 100 MH_Z) δ: 172.7 (C=O), 149.9, 147.2, 128.6, 124.8 (four aromatic carbons); 54.9, 31.8, 29.7, 14.8 (four aliphatic carbons). DEPT: one CH_3 at 14.8 ppm, two CH_2 at 31.8 and 29.7 ppm, three CH at 54.9, 124.8 and 128.6 ppm and three tertiary carbons at 147.2, 149.9 and 172.7. The HSQC were in agreement with the assignment. MS (M/Z) $C_{11}H_{15}N_2O_6S_2$: 335.0104 [M+H]+.

2-{[(4-nitrophenyl]sulphonyl)amino}-3-phenylpropanoic acid (5b)

The amino acid was L-phenylalanine. Yield 98%, colour: milky. FTIR (KBr, cm^{-1}), 3409 (NH), 3109 (CH aromatic), 2896 (CH aliphatic), 1749 (C=O), 1606, 1586 (C=C), 1523, 1329 (NO_2), 1267, 1157 (SO_2), 1109, 1092, 1031, 1012 (C-O, C-N), 701 (S-N). ^{1}H NMR (DMSO-d6, 400 MH_Z) δ: 8.71 (d, *J* =8.00 H_Z, 1H, NH), 8.18 (m, 2H, ArH), 7.73 (m, 2H, ArH), 7.09 (m, 4H, ArH), 3.95 (m, 1H, CH), 2.97 (m, 1H, CH_a of CH_2), 2.69 (m, 1H, CH_b of CH_2), 3.37 (s, 1H OH of COOH exchangeable with HDO). ^{13}C NMR (DMSO-d6, 100 MH_Z) δ: 172.6. (C=O), 149.6, 147.1, 137.1, 129.6, 128.6, 128.1, 126.8 and 124.6 (eight aromatic carbons), 58.1 and 38.00 (two aliphatic carbons. DEPT: No CH_3 shown, one CH_2 at 38.0 ppm, six CH at 58.1, 124.8, 128.1, 128.6, 129.6 ppm and four tertiary carbons at 137.1, 147.1, 149,6 and 172.6 ppm. The HSQC were in agreement with the assignment. MS (M/Z) $C_{15}H_{15}N_2O_6S$: 351.0643 [M+H]+.

3-Methyl-2-{[(4-nitrophyl)sulphonyl)amino}pentanoic acid (5c)

The amino acids were L-isoleucine. Yield 1.34 g, (84.5%), colour: white. m.p. 169-170°C. FTIR (KBr, cm^{-1}): 3266 (NH), 3108 (C-H aromatic), 2965 (CH aliphatic), 2569 (OH of COOH), 1702 (C=O), 1606 (C=C), 1526, 1307 (NO_2), 1234, 1142 (NO_2), 1090, 1011 (C-O, C-N), 720 (S-N). ^{1}H NMR (DMSO-d6, 400 MH_Z) δ 8.20 (d, *J* =8.00 H_Z, 1H, NH), 8..12(m, 2H, ArH), 7.76 (m, 2H, ArH), 3.38 (t, *J* =4.00H_Z, 1H, CH of CH-COOH), 1.45(m, 1H, CH-CH_3), 1.09(m, 2H, CH_3), 0.84 (d, *J* =4.00 H_Z, 3H, CH_3-CH). 0.53 (t, *J* =4.00 H_Z, CH_3-CH_2). ^{13}C NMR (DMSOd6, 100 MH_Z), δ: 177.0 (C=O), 154.6, 151,9, 133.4, 129.5 (four aromatic carbons), 66.6, 41.9, 29.5, 20.6, 16.1 (five aliphatic carbons). DEPT: two CH_3 at 20.6 and 16.1; one CH_2 at 29,5; four CH at 133.4, 129.5, 65.6 and 41.9 ppm and three tertiary carbons at 177.0, 154.6 and 151.9 ppm. MS (M/Z) $C_{12}H_{17}N_2O_6S$: 317.0418 [M+H]+.

4-Methyl-2-{[(4-nitrophyl)sulphonyl]amino}pentanoic acid (5d)

The amino acid was L-leucine. Yield 1.25 g (78.8%) colour: white. m.p.: 174-175°C. FTIR (KBr, cm^{-1}): 3267 (NH), 3096 (CH aromatic), 2933 (CH aliphatic), 2650 (OH of COOH), 1710 (C=O), 1605 (C=C), 1530, 1305 (NO_2), 1262, 1154 (SO_2), 1089, 1010 (C-N, C-O), 687 (S-N). ^{1}H NMR (DMSO-d6, 400 MH_Z) δ: 8.36 (m, 2H, ArH) 8.06 (m, 2H, ArH), 4.9 (s, 1H, OH exchangeable with HDO), 3.92 (m, 1H, CH of CH-COOH), 1.76 (m, 1H, CH of $CH(CH_3)_2$) 1.52 (m, 2H, CH_2), 0.89 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d6, 100 MH_Z) δ: 172.8 (C=O), 149.2, 145.9, 127.5, 123.0 (four aromatic carbons), 53.7, 40.7 23.4, 21.1, 19.4 (five aliphatic carbons). DEPT: Two CH_3 at 21.1 and 19.4 ppm, one CH_2 at 40.7 ppm, four CH at 23.4, 53.7, 123.0, and 127.5 ppm; three tertiary

carbons at 145.9, 149.2 and 172.8 ppm. The HSQC were in agreement with the assignment. MS (M/Z) $C_{12}H_{17}N_2O_6S$: 317.0792 [M+H]+.

2-{[4-nitrophenyl)sulphonyl]-3-sulphonylproanoic acid (5e)

The amino acid was L-cysteine. Yield: 1.04 g (94.6%), colour: white, m.p. 202-203°C. FTIR (KBr, cm^{-1}): 3460 (NH), 3011 (C-H aromatic), 2969 (C-H aliphatic), 256 (OH of CO_2H), 1720 (C=O), 1620, 1581 (C=C), 1519, 1337 (NO_2), 1297, 1193 (SO_2), 1090, 1011, 1043 (C-N, C-O), 675 (S-N). ^{1}H NMR (DMSO- d6, 400 MH_Z) δ: 7.52 (m, 2H, ArH), 7.22 (m, 2H, ArH), 3.67 (s, 1H, OH exchangeable with HDO), 3.41 (s, 1H, CH), 1.83 (d, *J* = 400H_Z, 2H, CH_2), 0.52 (s, 1H, S-H). ^{13}C NMR (DMSO-d6, 100 MH_Z) δ: 174.3 (C=O), 152.4, 143.8, 127.6, 121.1 (four aromatic carbons), 54.9, 41.2 (two aliphatic carbons). DEPT: No CH_3, one CH_2 at 41.2 ppm; three CH at 127.6, 121.1 and 54.9 ppm and three tertiary carbons at 174.3, 152.4, and 143.8 ppm. The HSQC were in agreement with the assignment. MS (M/Z) for $C_9H_{11}N_2O_6S_2$: 307.1487 [M+H]+.

Synthesis of compounds 10-13

A solution of aromatic amines (**6-9,** 5 mmol) in methanol (3 mL) was mixed with a solution of 4-nitrobenzenesulphonyl chloride (**1,** 6.5 mmol) in methanol (6 mL) and allowed to stand at room temperature for 24 h. The crystals formed were filtered, washed with methanol and dried using hot air oven.

4-nitro-*N*-(pyrimidin-2-yl)benzenesulphonamide (10)

The aromatic amine is 2-aminopyrimidine. Yield 1.41 g (94.7%), colour: pale yellow, m.p. 210-212°C. FTIR (KBr, cm^{-1}): 3344 (NH), 3120, 3077 (CH aromatic) 1638, 1621 (C=N), 1519, 1352 (NO_2), 1316, 1163 (SO_2), 1191, 1119, 1075, 1025, 1004 (C-N), 691 (S-N). ^{1}H NMR (DMSO- d6, 400 MH_Z) δ: 9.72 (s, 1H, NH), 9.23 (d, *J*=8.04 H_Z, 2H, ArH), 9.13 (m, 1H, ArH), 8.82 (m, 2H, ArH), 8.47 (m, 2H, ArH), 7.60 (t, *J*=8.00 H_Z, 1H, ArH). ^{13}C NMR (DMSO-d6, 100 MH_Z) δ: 156.4, 154.5, 147.9, 127.5, 123.9 110.4 (seven aromatic carbons). DEPT: no CH_3, no CH_2, four CH at 158.5, 127.5, 123.4 and 110.4 and three tertiary carbons at 156.4, 154.5 and 147.9 ppm. The HSQC were in agreement with the assignment. MS (M/Z): $C_{10}H_9N_4O_4S$: 281.0325 [M+H]+.

N-(1,3-benzothiazol-2-yl)-4-nitrobenzenesulphonamide (11)

The aromatic amine was 2-aminobenzothiazole. Yield: 2.5 g (90.6%); colour: white, m.p. 230-230°C. FTIR (KBr, cm^{-1}): 3229 (NH), 3010 (CH aromatic), 1614 (C=N), 1602, 1583 (C=C), 1521, 1375 (NO_2), 1303, 1205 (SO_2), 1184, 1122, 1101 (C-N), 707 (S-N). ^{1}H NMR (DMSO-d6, 400 MH_Z)δ: 9.78 (s, 1H, NH), 8.18 (m, 2H, ArH), 7.89 (m, 1H, ArH), 7.84 (m, 2H, ArH), 7.49 (m, 1H, ArH), 7.44 (m, 1H, ArH), 7.30 (m, 1H, ArH). ^{13}C NMR (DMSO-d6, 100 MH_Z) δ: 169.7 (C=N), 154.5, 147.8, 139.0, 128.1, 127.4, 124.8, 124.3, 123.8, 123.6, 114.6 (ten aromatic carbons). DEPT: No CH_3 and CH_2, six C-H carbons at 127.4, 124.8, 124.3, 123.8, 123.6 and 114.6 ppm; five tertiary carbons at 169.7, 154.5, 147.8, 139.0 and 128.1 ppm. The HSQC were in agreement with the assignment. MS (M/Z) for $C_{13}H_9N_3O_4S_2$: 336.0384 [M+H]+.

N-(4-methylyridin-2-yl)-4-nitrobenzenesulphonamide (12)

The aromatic amine was 2-amino-4-picoline. Yield: 1.62 g (89. 2%), colour: pale yellow, m.p. 194-196°C. FTIR (KBr, cm^{-1}): 3374 (NH) 3170, 3101, 3034 (C-H aromatic), 2906, 2856, 2812 (C-H aliphatic), 1634 (C=N), 1601 (C=C), 1586, 1121, 1106 (C-N), 87 (S-N). ^{1}H NMR (DMSO-d6, 400 MH_Z) δ: 12.96 (s, IH, NH), 8.19 (d, *J*=8.00 H_Z, 2H, ArH), 7.83 (m, 4H, ArH), 6. 74 (m, 1H, ArH), 6.69 (m, 1H, ArH), 2.28 (S, 3H, CH_3). ^{13}C NMR (DMSO-d6, 100 MH_Z)δ: 156.8, 154.2, 153.9, 147.8, 135.6, 127.4, 123.9, 114.6, 112.4 (nine aromatic carbons), 21.6 (one aliphatic carbon). DEPT: one CH_3 at 21.6 ppm, No CH_2, five CH at 135.6, 127.4, 123.9, 114.6 and 112.4 ppm; four tertiary carbons at 156.8, 154.2, 153.9 and 147.8 ppm. The HSQC were in agreement with the assignment. MS (M/Z) for $C_{12}H_{12}N_3O_4S$: 294.0535 [M+H]+.

N-(quinolin-4-yl)-4-nitrobenzenesulphonamide (13)

The aromatic amine was 3-aminoquinoline. Yield: 96%, colour: pale brown, m.p. 266-268°C. FTIR (KBr, cm^{-1}): 3368 (NH), 3010, (C-H aromatic), 1632 (C=N), 1604, 1586 (C=C), 1531, 1309 (NO_2), 1352, 1112 (SO_2), 1101, 1009 (C-N), 782 (S-N). ^{1}H NMR (DMSO-d6, 400 MH_Z)δ: 8.72 (s, 1H, NH), 8.33 (m, ArH), 8.15(m, 2H, ArH), 8.05 (m, 1H, ArH), 7.88 (m, 1H, ArH), 7.78 (m, 1H, ArH), 7.66 (m, 1H, ArH), 7.37 (s, 1H, ArH), 7.24 (s, 1H, ArH). ^{13}C NMR (DMSO-d6, 100 MH_Z)δ: 154.3, 150.5, 147.8, 144.6, 143.8, 135.3, 131.7, 130.3, 129.2, 128.4, 127.1, 125.2, 123.8, 122.3, 120.7. DEPT: NO CH_3 and CH_2; ten CH appeared at 135.3, 131.6, 130.3, 129.2, 128.4, 127.1, 125.2, 123.8, 122.3, 120.7 ppm; five tertiary carbons appeared at 154.3, 150.5, 147.8, 144.6 and 143.8 ppm. The HSQC were in agreement with the assignment. MS (M/Z) for $C_{15}H_{12}N_3O_4S$: 330.0341 [M+H]+.

Results and Discussion

The reactions of 4-nitrobenzenesulphonyl chloride (1) with various amino acids (2a-d and 4a-e) in the presence of sodium carbonate gave various benzensulphonamides (3a-3d, 5a-5e) in excellent yield (Schemes 1 and 2). Further reactions of compound 1 with various heterocyclic amines (6-9) gave the corresponding heteroaryl derivatives of benzene-sulphonamides (10-13) in good yield (Scheme 3).

The analytical and spectral data of the synthesized compounds are given in the supplementary material to this paper. The spectral characterizations are in agreement with the structures.

In the FTIR spectra, the diagnostic bands at 3468-3229 cm^{-1} were assigned to N-H stretching vibrations. The bands between 1787-1650 and 2600-2510 cm^{-1} in the amino acid derivatives were assigned to the C=O and O-H of the carboxylic acid group respectively. The bands between 1550 and 1289 cm^{-1} were assigned to the NO_2 stretching whereas the bands at 1638 and 1614 cm^{-1} were assigned to the C=N of the heterocyclic rings. These bands are indicative of successful formation of target molecules.

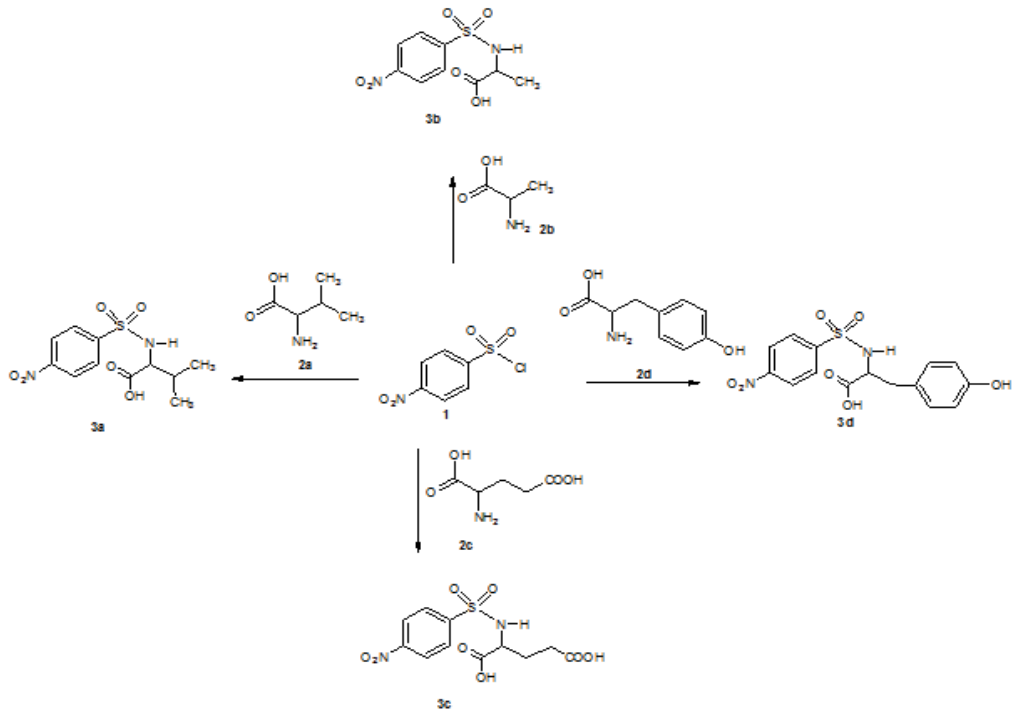
In the proton NMR, all the expected protons appeared within the range. The carbon-13 NMR peaks were indicative of successful formation of desired products. The DEPT analysis was in agreement with the ^{1}H and ^{13}C NMR assignment. HSQC analysis further confirmed the coupling of protons to specific carbon as already assigned in the ^{1}H and ^{13}C NMR. The successful formation of the target molecules were further confirmed by the appearance of [M+H]+ peak for all the compounds in the mass spectrometer. The summaries of the benzene-sulphonamides prepared are shown in Schemes 1-3 and the full characterization provided in the experimental section.

Molecular docking studies

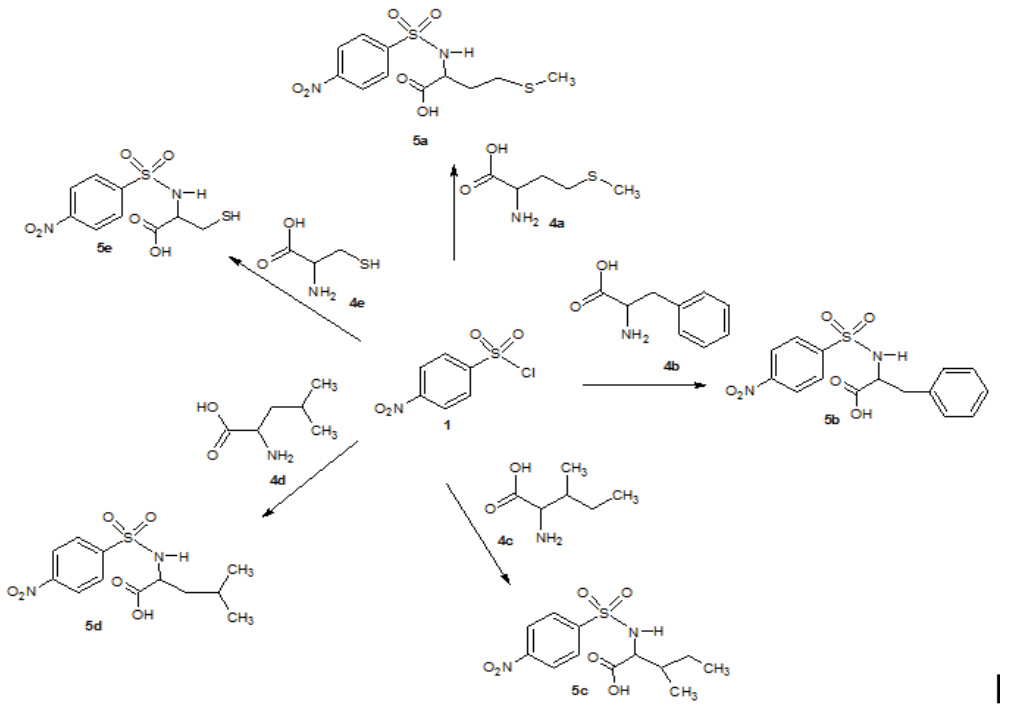
Drug targets: In this study, we used two important drug targets namely: farnesyl diphosphate synthase and rhodesain. These were gotten from *T. brucei.*

***T. brucei* pteridine reductase (PDB Code: 2X9G):** Pteridine reductase (PTR1; EC1.5.1.33), is an important target for drug development against parasitic Trypanosoma. It is an enzyme peculiar to trypanosomatid parasites which play critical role in the provision of reduced biopterins necessary for metacyclogenesis [35].

***T. brucei* ornithine decarboxylase (PDB Code: 1UQ4):** Ornithine decarboxylase is a known drug target against African sleeping

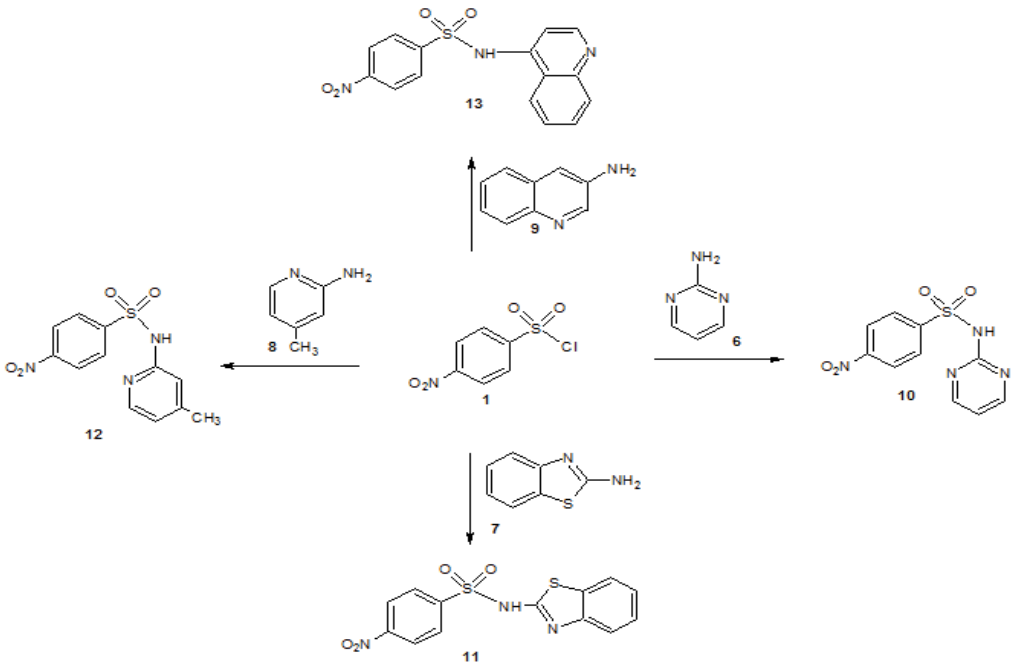


Scheme 1: Synthesis of compounds 3a-3d.



Scheme 2: Synthesis of compounds 5a-5e.

sickness, caused by *T. brucei*. 1UQ4 catalyzes the first committed step in the biosynthesis of the polyamines responsible for cell growth and differentiation [36]. Inhibition of 1UQ4 causes cell growth retardation and death, and have been used clinically for the treatment



Scheme 3: Synthesis of heteroaryl derivatives of benzenesulphonamide.

of *Trypanosoma brucei*, the causative agent of African sleeping sickness [37,38].

Farnesyl diphosphate synthase (FDS, PDB Code: 2EWG): FDS has been shown to catalyze the formation of farnesyl diphosphate through consecutive condensation of two molecules of isopentenyl diphosphate with dimethylallyl diphosphate in the isoprenoid biosynthetic pathway. This provides a precursor for the synthesis of ubiquinones, dolichols, sterols, heme *a*, and of course the prenylation of certain proteins [39]. There are so many scientific reports that validated the use of FDS as a therapeutic target in *T. brucei* [40,41].

Rhodesain (PDB Code: 6EXQ): Rhodesain (RD) is a parasitic, human cathepsin like cysteine protease produced by *Trypanosoma brucei* species and a potential drug target for the treatment of human African trypanosomiasis (HAT). It is complexed with a macrolactam inhibitor.

Retrieval and preparation of drug targets: The 3-dimensional crystal structures of 2X9G (1.1 Å), 1UQ4 (2.9 Å), 6EXQ (2.5 Å) and 2EWG (2.48 Å) were retrieved from the protein data bank (https://www.rcsb.org). The structures of the compounds were drawn using Accelrys Draw 4.1. Both the prepared compounds and proteins were energy minimized using the MMFF94x forcefield and subsequently used for molecular docking studies. The molecular docking and visualization of results were carried out using the method outlined in Ezeokonkwo et al., [42].

Validation of docking protocols using 6EXQ complex: For the purpose of validation of the docking protocol, the protein target, 6EXQ was retrieved with its co-crystallized ligand (a macrolactam inhibitor). The macrolactam inhibitor was retrieved from the 6EXQ complex. It was then docked into the binding cavity of the protein data, with a view of seeing the position in the binding cavity with respect to the co-crystallized ligand already in the target (Table 1).

Lipinski's rule of five helps to evaluate the bioavailability for oral formulations. An oral drug with a good bioavailability should have MW ≤ 500, HBD ≤ 5, HBA ≤ 10, and Log P(o/w) ≤ 5. A violation of more than one parameter may be an indication of poor bioavailability. Table 2 shows that the synthesized compounds are in agreement with the Lipinski's rule of five. In addition, the TPSA, which is a reflection of the compound's hydrophilicity, is very important in protein-ligand interaction. NRB ≤ 10 and TPSA ≤ 140 Å [2] would have a high probability of good oral bioavailability in rats [18,42].

Compounds	Binding free energy (kcal/mol)			
	2EWG	6EXQ	2X9G	1UQ4
3a	-14.64	-11.18	-10.68	-11.22
3b	-14.15	-9.91	-11.23	-11.71
3c	-16.69	-10.46	-12.05	-13.74
3d	-16.68	-10.59	-12.23	-13.16
5a	-15.63	-9.59	-11.51	-11.74
5b	-15.05	-10.39	-11.88	-12.21
5c	-15.12	-10.39	-11.25	-12.27
5d	-14.60	-10.34	-10.96	-12.12
5e	-15.54	-10.11	-10.66	-13.38
10	-16.54	-11.02	-12.11	-13.43
11	-15.86	-10.91	-12.01	-12.78
12	-16.11	-11.08	-11.23	-12.93
13	-16.66	-9.95	-10.88	-13.15
Co-crystallized inhibitor	-20.68	-11.24	-14.09	-15.04

Table 1: Binding free energy (kcal/mol) of compounds.

In Figure 2, we observed that the docked ligand (green) is superimposed on the co-crystallized ligand (purple) with RMSD<2 Å. This implies that the docked ligand occupies the same binding sites as the original co-crystallized ligand, thereby validating the docking protocols applied in the molecular docking of our synthesized compounds.

Table 1 shows the binding free energy (kcal/mol) of compounds

Comp	MW	HBA	NBA	NRB	logP(o/w)	TPSA	LVN
3a	302.31	4	3	6	1.88	129.29	0
3b	274.25	4	3	5	0.90	129.29	0
3c	332.29	6	5	8	0.60	166.59	0
3d	366.35	5	4	7	2.13	149.52	0
5a	334.37	4	3	8	1.56	129.29	0
5b	350.35	4	3	7	2.44	129.29	0
5c	316.33	4	3	7	2.32	129.29	0
5d	316.33	4	3	7	2.32	129.29	0
5e	306.32	4	3	6	1.01	168.09	0
10	280.26	4	1	4	0.58	117.77	0
11	335.36	3	1	4	3.22	104.88	0
12	293.30	3	1	4	2.10	104.88	0
13	329.34	3	1	4	2.79	104.88	0

MW: Molecular Weight; Log P(O/W): Octanol/Water Partition Coefficient; HBD: Number of Hydrogen Bond Donor; HBA: Number of Hydrogen Bond Acceptor; TPSA: - Total Polar Surface Area; NRB: Number of Rotatable Bonds; LVN: - Lipinski's Violation Number.

Table 2: Physicochemical properties of the compounds. Table 2 shows the physicochemical properties of the synthesized compounds which are useful in the assessment of the drug-likeness.

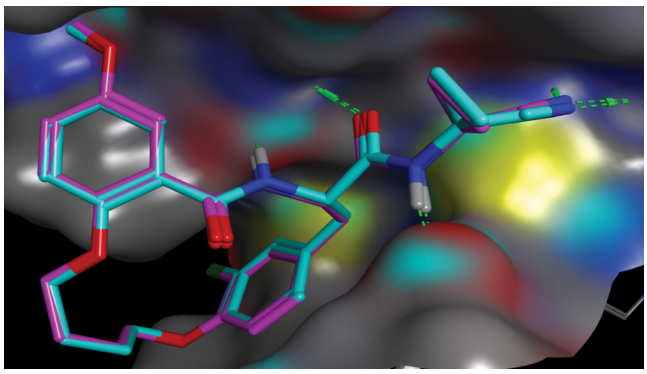


Figure 2: Validation of docking protocols using 6exq complex - The docked ligand (green) is superimposed on the co-crystallized ligand (purple).

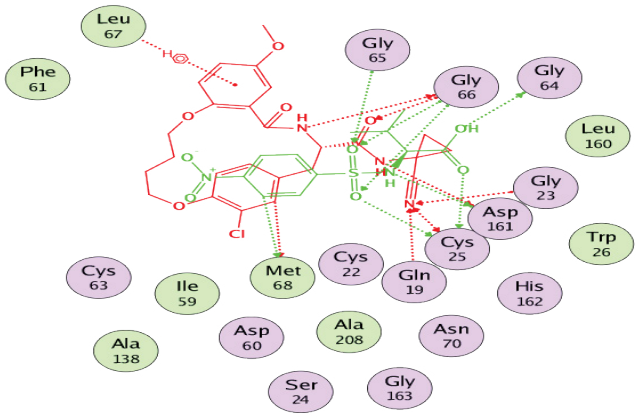


Figure 3: Co-crystallized ligand (red) and compound 3a (green) being overlaid in the binding cavity of 6EXQ.

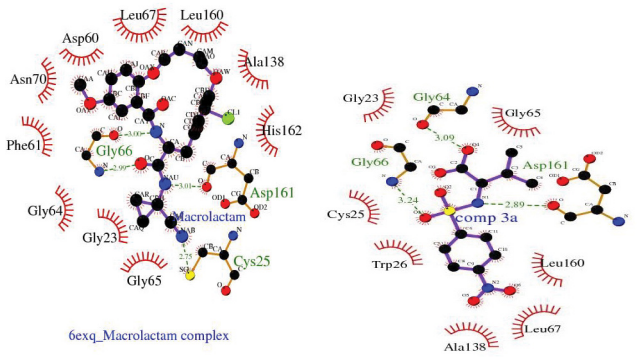


Figure 4: Ligplot+ showing H-bonding interactions of (a) co-crystallized ligand (Macrolactam inhibitor) and (b) compound 3a with *T. brucei* rhodesain.

against 2EWG and 6EXQ. The result revealed that all the synthesized compounds have strong binding affinity with the targets. All compounds showed higher binding affinity to 2EWG when compared with the co-crystallized inhibitors. Compound **3c** had the highest binding affinity as shown in its lowest binding energy (-16.69 kcal/mol). Compound **3a** also had the highest binding affinity with 6EXQ. Subsequently, compounds **3a** and **3c** were chosen for further investigation to represent others.

After the molecular docking, we compared the binding of the co-crystallized ligand with the amino acid residues of 6EXQ to that of compound **3a** by overlaying both in the binding cavity of the protein. This is clearly illustrated in Figure 3. We observed the following similarities between compound **3a** and the macrolactam inhibitor: the phenyl groups in both compounds interacted with methionine 68. Other amino acid residues that both compounds interacted with include Cys 24, Asp 161 and Gly 66. In addition to this, the OH group and O atom of compound **3a** made a H-bonding contact with Gly 64 and Gly 65 respectively. These different chemical interactions between compound 3a and the receptor could probably explain why the compound has a similar binding affinity as the co-crystallized inhibitor as shown in Table 1. Further insight on the nature of the H-bonds are shown in the ligplot+ diagram in Figure 4. There are three distinct H-bonds shown in the ligplot+ for each compound-protein complex. The H-bond length of compound **3a** with Gly 66 (3.09Å) is comparable to the H-bond length of macrolactam inhibitor-Gly 66 (3.00Å). Likewise, the H-bond length of compound **3a** with Asp 161 (2.89Å) is comparable to the H-bond length of macrolactam inhibitor-Asp 161 (3.01Å). Figure 5 shows the binding mode of compound **3a** in the binding cavity of 6EXQ.

Compound **3c** had a significant binding affinity with 2EWG. Its binding pose in the binding cavity of the receptor is shown in Figure 6. H-bonds are shown in the ligplot+ diagram in Figure 7. From Figures 6 and 7, Arg 50, Arg 112, Gln 252, Lys 212 and Lys 278 formed H-bonds

with compound **3c**. Arg 50 formed two H-bonds through the two O-atoms of the nitro group through a bond length of 2.88 and 2.99 Å respectively. The H-bond lengths for other interactions can be seen in Figure 7. These strong H-bonding interactions could possible explain the high binding affinity that **3c** has with 2EWG.

In Figure 8, there are series of hydrogen bonds that helped to position key functional groups to interact with ligands. ND2 ASN 93, CA ALA 94, NE ARG 14, N HIS 35, N SER 37, N SER 37 donate hydrogen bonds to the O-1, O-3, O-15, O-24, O-24 and O-25 respectively of compound **3d**.

The co-crystallized ligand in 1UQ4 and compound **3c** essentially interacted in similar ways (Figure 9). HIS 197 formed a pi-pi interaction with the aromatic ring of compound **3c** and the phosphate of the native ligand. This residue plays an essential catalytic role in ornithine decarboxylase. This can be seen clearly in the decreased k_{cat} by 25-fold when HIS 197 residue is mutated to ALA [43-46]. Both the

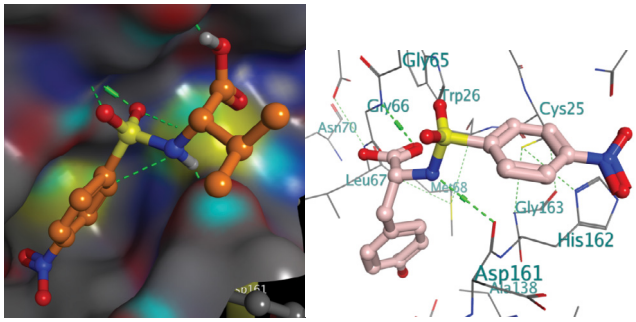


Figure 5: The binding mode of compound 3a in the binding cavity of 6EXQ.

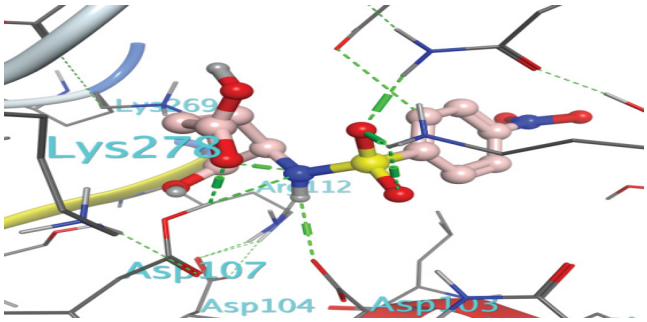


Figure 6: The binding mode of compound 3c in the binding cavity of 2EWG.

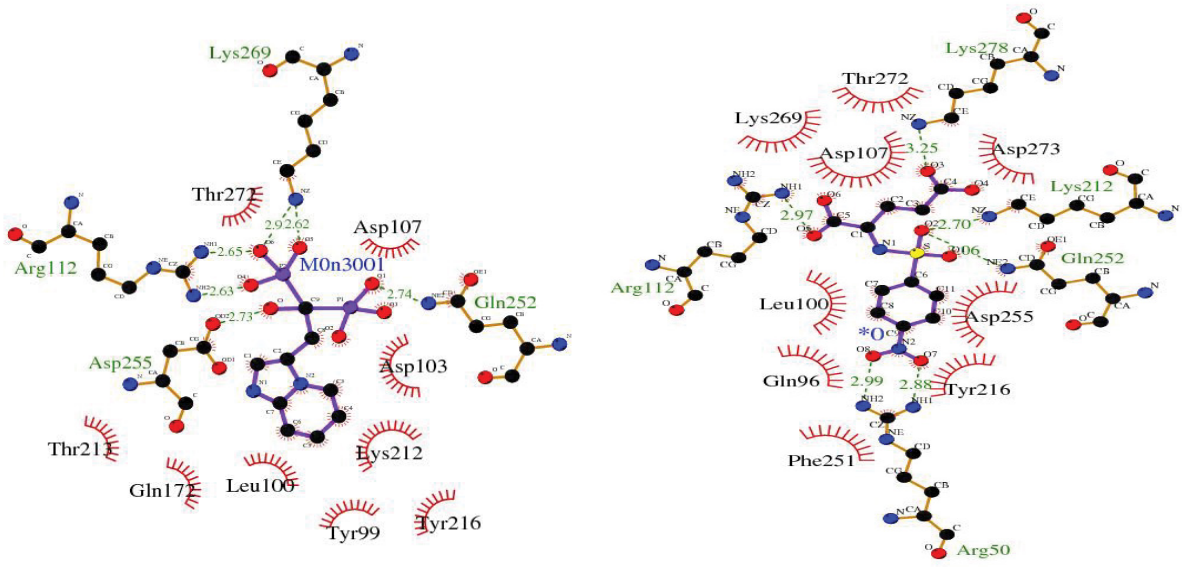


Figure 7: Ligplot+ showing H-bonding interactions of (a) co-crystallized ligand (minodronate) and (b) compound 3c with *T. brucei* farnesyl diphosphate synthase.

native ligand and **3c** interacted with GLU 274 through H-bonding. This is an important residue which plays key roles in the stability of the complex as its mutation to Ala decreases k_{cat} by 50-fold. Other forms of interactions are shown in Figure 9.

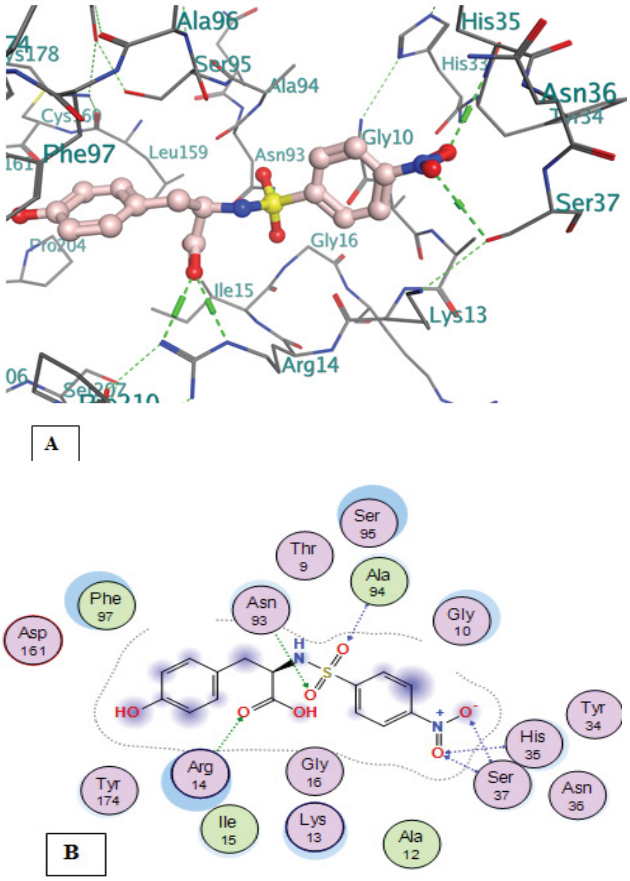


Figure 8: (A) The binding mode of compound 3d in the binding cavity of 2X9G. (B) 2D representation of the molecular interactions of 3d with 2X9G.

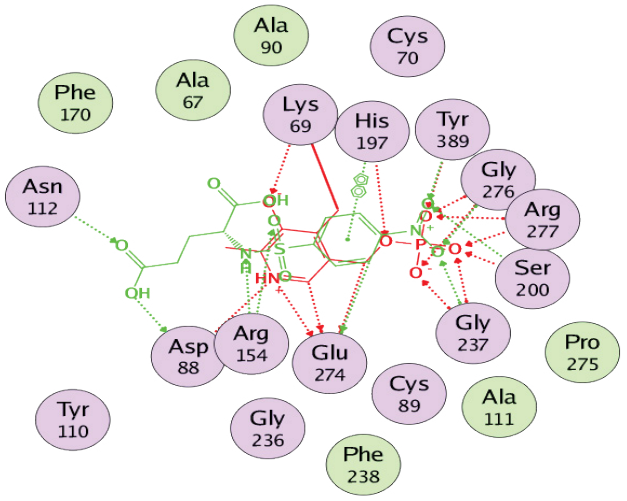


Figure 9: Co-crystallized ligand (red) and compound 3c (green) being overlaid in the binding cavity of 1UQ4.

Conclusion

Thirteen new derivatives of benzenesulphonamide were synthesized following simple condensation reaction protocol and characterized using FTIR, ^{1}H-NMR, ^{13}C-NMR, DEPT, HSQC and high resolution mass spectrometer. The compounds showed good pharmacokinetic properties and would not pose oral bioavailability, permeability and transport problems if developed as drugs. The reported compounds showed good binding when docked against farnesyl diphosphate synthase, rhodesain, pteridine reductase and ornithine decarboxylase to assess their potential as possible drugs for the treatment of human African trypanosomiasis.

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