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New carboxamides bearing benzenesulphonamides: Synthesis, molecular docking and pharmacological properties

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ABSTRACT

Ten new derivatives of benzenesulphonamide bearing carboxamide functionality were synthesized and investigated for their *in vitro* antimicrobial, antioxidant and *in vivo* anti-inflammatory activities. Compound **9d** inhibited carrageenan induced rat-paw oedema at 93.81, 88.79 and 86.09% at 1 h, 2 h and 3 h administration respectively. In the antimicrobial activity, compound **9a** (6.54, 6.69 and 6.64 mg/mL) was most potent against *S. aureus*, *B. subtilis* and *C. albicans* respectively, compound **9e** (6.45 and 6.46 mg/mL) was most active against *P. aeruginosa* and *A. niger* respectively while compound **9i** (6.24 mg/mL) was most active against *E. coli*. Only compound **9a** (IC_{50} 0.3052 mg/mL) had comparable activity with Vitamin C (IC_{50} 0.2090 mg/mL) in the antioxidant assay.

1. Introduction

Inflammation is part of the body's immune response to stimuli. It is favourable at first because it initiates healing processes. Inflammation can be self-perpetuating causing more inflammation in response to existing inflammation [1], thus it is of great concern (see Fig. 1).

Inflammatory diseases are prevalent worldwide and inflammation remains a common and poorly controlled disease which in extreme form of allergy, autoimmune diseases and rejection of transplanted organs can be life threatening [2]. Chronic inflammation has been linked to a variety of diseases including cardiovascular diseases, cancer, diabetes, arthritis, Alzheimer's disease, pulmonary disease, etc. [2–5].

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drug that include drugs that provide anti-inflammatory, analgesic and antipyretic effects. The most widely used among this group are ibuprofen (**1**), naproxen (**2**), aspirin (**3**), indomethacin (**4**), and diclofenac (**5**) [6].

Inhibiting cyclooxygenase-2 leads to the desirable anti-inflammatory, analgesic and antipyretic activities of NSAIDs whereas the inhibition of cyclooxygenase-1 leads to undesirable side effects like gastrointestinal bleeding [7], central nervous system (CNS) effects [8], kidney problem [9] and increased risk of stroke [10,11]. The problem associated with most NSAIDs is that they inhibit the activities of COX-1 and COX-2 and thereby the synthesis of prostaglandins and thromboxane [6]. The need for the development of new anti-inflammatory agents given the associated risks with current anti-inflammatory drugs (Scheme 1) is therefore eminent.

One of the early responses of host innate immunity is the Reactive-Oxygen-Species (ROS) production in reaction to microbial invaders. Free oxygen radicals are highly toxic to pathogens and are utilized as a tool to prevent colonization of tissues by microorganism [12]. Oxidative stress occurs when oxygen radical formation and levels exceed those of antioxidants, tumorgenesis and immune-response [12–14].

Extracellular microorganisms have been demonstrated to inhibit ROS production contributing to persistence of infection. Some of these microorganisms are opportunistic pathogens implicated in chronic inflammatory conditions including cystic fibrosis [15]. These opportunistic pathogens produce secondary metabolite which interfere with phagocytic engulfment of apoptic cells [16]. This secondary metabolite mediate this process by reducing ROS levels in host cells, likely leading to enhanced inflammation at sites of infections due to failure of phagocytose dying cells [16].

Sulphonamides and carboxamides functionalities have been reported to have wide biological activities ranging from anticancer [17], antitubercular [18], anti-inflammatory [19], antioxidant [20], antimicrobial [21], antimalarial [22], etc. but there are few reports of their successful combination in drug molecules.

This work was designed based on the reported biological activities of sulphonamides and carboxamides and the need to develop newer

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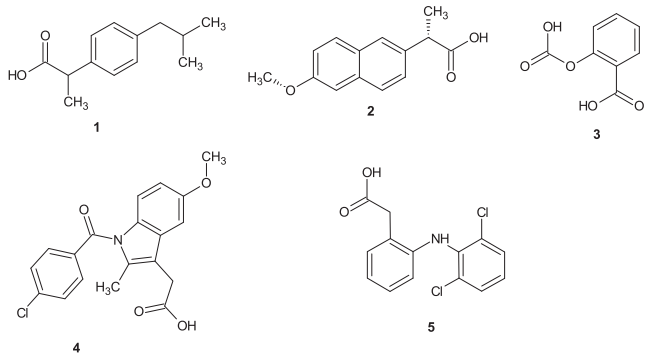


Fig. 1. Examples of NSAIDs.

anti-inflammatory agents that will have an added advantage of reducing the reactive oxygen species generated during microbial invasion while also acting as antimicrobial agent.

2. Experimental

2.1. Synthesis of substituted benzenesulphonamoyl alkanamides (8a–j)

Sodium carbonate (Na_2CO_3, 1.59 g, 15 mmol) was added to a solution of amino acids (**7**, 12.5 mmol) in water (15 mL) with continuous stirring until all the solutes dissolved. The solution was cooled to −5 °C and the appropriate benzenesulphonyl chloride (**6**, 15 mmol) was added in four portions over a period of 1 h. The slurry was further stirred at room temperature for 4 h. The progress of the reaction was monitored using TLC (MeOH/DCM) 1:9). Upon completion, the mixture was acidified using 20% aqueous hydrochloric acid to pH2. The pure products (**8a–j**) were dried over self-indicating fused silica gel in a desiccator [23].

2.2. Palladium catalysed amidation of unactivated carboxylic acid and propyl amines

To a suspension of substituted benzenesulphonamides (**8a–j**, 1.0 mmol) in dry toluene (40 mL) equipped with Dean-Stark apparatus for azeotropic removal of water was added propyl amine (1.0 mmol) and $Pd_2(dba)_3$ (0.1 mmol) at room temperature and then refluxed for 12 h. On completion (as monitored by TLC) the amide products were precipitated out from the reaction mixture by adding 40 mL *n*-hexane. The carboxamides (**9a–j**) were obtained via suction filtration, washed with *n*-hexane and dried over fused silica gel or concentrated using rotary evaporator and dried over vacuum in the case of oily products.

2.2.1. 1-[(4-Methylphenyl)sulphonyl]-N-propylpyrrolidine-2-carboxamide (9a)

Yield (0.24 g, 77.4%), Mp = 124–126 °C. Uv (λmax): 203.00 nm. FTIR (KBr, cm^{-1}): 3432 (NH), 2971 (C−H aromatic), 2904, 2803 (C−H aliphatic), 1634 (C═O), 1573, 1461, 1446 (C═C), 1394, 1338 (2S═O), 1156, 1122 (SO_2NH), 1092, 1055 (C−N). ^{1}HNMR ($DMSO_{d6}$, 400 MHz)δ: 7.67–7.65 (d, *J* = 7.80 Hz, 2H, ArH), 7.35–7.33 (d, *J* = 7.80 Hz, 2H, ArH), 4.37 (t, *J* = 7.2 Hz, 1H, NH), 3.85–3.83 (d, *J* = 8.24 Hz, 1H, CH−C═O), 3.23 (t, *J* = 7.01 Hz, 2H, CH_2−N), 3.12–3.08 (t, *J* = 7.36 Hz, 2H, CH_2−NH), 2.66–2.62 (m, 2H, CH_2−CH−C═O), 2.38–2.34(m, 3H, CH_3−Ar), 1.69 (m, 2H,CH_2−CH_2−CH_2−CH−C═O), 1.53–1.47 (m, 2H, CH_2−CH_3), 0.86–0.82 (t, *J* = 5.54 Hz, 3H, CH_3-CH_2).^{13}CNMR ($DMSO_{d6}$, 400 MHz)δ: 167.85 (C═O), 133.42, 131.25, 129.97, 129.79, 129.11, 127.07 (six aromatic carbons), 67.83, 38.16, 33.26, 23.30, 21.53, 18.90, 9.91, 9.34 (eight aliphatic carbons). HRMS (*m/z*) for $C_{15}H_{22}N_2O_3S$: 311.1431 (M + H), calculated 311.1429.

2.2.2. 1-(Phenylsulphonyl)-N-propylpyrrolidine-2-carboxamide (9b)

Yield (0.27 g, 93.1%). Mp, 116–118 °C. Uv (λmax): no peak was found above the threshold FTIR (KBr, cm^{-1}): 3496 (NH), 2967 (C−H aromatic), 2929, 2878 (C−H aliphatic), 1626. (C═O), 1577, 1448, (C═C), 1398, 1334 (2S═O), 1256, 1189, 1156 (SO_2NH), 1092, 1059 (C−N).^{1}HNMR ($DMSOd_6$, 400 MHz)δ: 7.78 (m, 2H, ArH), 7.59–7.53 (m, 3H, ArH), 4.42 (s, 1H, NH), 3.86 (t, *J* = 6.32 Hz, 1H, CH−C═O), 3.24 (t, *J* = 5.87 Hz, 2H, CH_2−N), 3.13–3.11 (m, 2H, CH_2−NH), 2.65–2.63 (m, 2H, CH_2−CH−C═O), 1.70 (m, 2H, CH_2−CH_2−CH−C═O), 1.52–1.40 (m, 2H, CH_2, CH_2−CH_3), 0.84–0.83 (t, *J* = 5.32 Hz, 3H, CH_3).^{13}CNMR ($DMSOd_6$, 400 MHz)δ: 175.31 (C═O), 139.12, 132.99, 129.63, 127.55, (four aromatic carbons), 63.81, 48.75, 40.90, 31.20, 24.67, 19.44, 11.54, (seven aliphatic carbons). HRMS (*m/z*) for $C_{14}H_{20}N_2O_3S$: 297.1275 (M + H), calculated, 296.1273.

2.2.3. 4-Methyl-2-{[(4-methylphenyl)sulphonyl]amino}-N-propylpentanamide (9c)

Yield (0.25 g, 78.8%), Mp, 120–122 °C. Uv (λmax): 202.00 nm. FTIR (KBr, cm^{-1}): 3224 (NH), 3064 (C−H aromatic), 2956, 2866 (C−H aliphatic), 1722 (C═O), 1640, 1558,1461 (C═C), 1390, 1312 (2S═O), 1211, 1156 (SO_2NH), 1014, 973 (C−N). ^{1}HNMR ($DMSOd_6$, 400 MHz)δ: 7.96–7.94 (d, *J* = 6.88 Hz, 1H, NH), 7.59–7.57 (d, *J* = 6.40 Hz, 2H, ArH), 7.30–7.29 (d, *J* = 7.32 Hz, 2H, ArH), 4.51 (d, *J* = 6.8 Hz, 1H, NH), 3.10 (t, *J* = 6.92 Hz, 1H, CH−C═O), 2.60–2.57 (t, *J* = 6.40 Hz, 2H, CH_2-NH), 2.32 (s, 3H, CH_3−Ar), 1.74–1.71 (t, *J* = 6.88 Hz, 2H, CH_2−CH−C═O), 1.47–1.41 (m, 2H, CH_2−CH_2−NH), 1.32–1.28 (t, *J* = 5.52 Hz, 3H, CH_3−CH_2), 0.91–0.82 (m, 1H,$CH(CH_3)_2$), 0.80–0.74 (dd, J_1 = 5.92, J_2 = 5.04 Hz, 6H, $2(CH_3)$). ^{13}CNMR ($DMSOd_6$, 400 MHz)δ: 173.85 (C═O), 142.74, 138.29, 129.85, 127.23, (four aromatic carbons), 56.29, 43.32, 24.50, 23.51, 22.67, 21.46, 21.20, 11.43, (eight aliphatic carbons). HRMS (*m/z*) for $C_{16}H_{27}N_2O_3S$: 327.1744 (M + H), calculated, 326.1742.

2.2.4. 4-Methyl-2-[(phenylsulphonyl)amino]-N-propylpentanamide (9d)

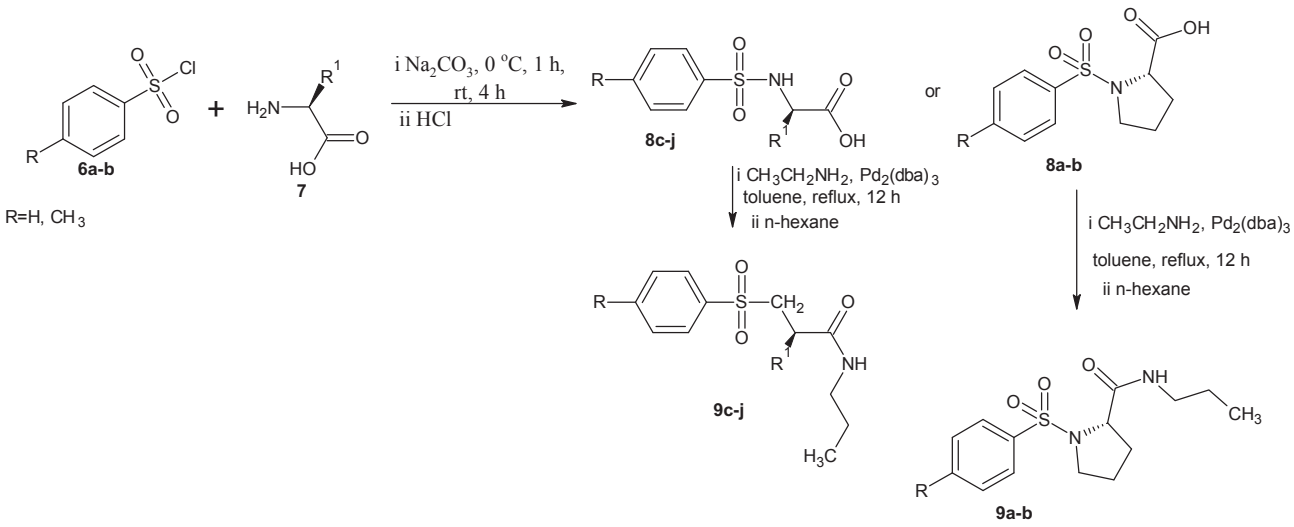
Yield (0.27 g, 87.1%), Mp, 98–100 °C. Uv (λmax): 213.00 nm. FTIR (KBr, cm^{-1}): 3265 (NH), 3071 (C−H aromatic), 2959, 2866 (C−H aliphatic), 1722 (C═O), 1573, 1446 (C═C), 1394 1312 (2S═O), 1223, 1249, 1167 (SO_2NH), 1096, 1021 (C−N).^{1}HNMR ($DMSOd_6$, 400 MHz)δ: 7.76–7.70 (m, 2H, ArH), 7.58–7.46 (m, 3H, ArH), 7.27 (m, 2H, NH), 3.24–3.18 (m, 1H, 1H, CH-C═O), 2.61–2.51 (m, 2H, CH_2−NH), 1.69–1.65 (m, 1H, $CH(CH_3)_2$), 1.45–1.26 (m, 4H, $2CH_2$), 0.86–0.80 (t, *J* = 6.20 Hz, 3H,CH_3−CH_2), 0.78–0.71 (m, 6H, $2(CH_3)$).^{13}CNMR ($DMSOd_6$, 400 MHz)δ: 174.09 (C═O), 141.34, 132.59, 129.38, 127.13, (four aromatic carbons), 56.38, 43.22, 24.50, 23.48, 22.59, 19.12, 11.46, (seven aliphatic carbons). HRMS (*m/z*) for $C_{15}H_{24}N_2O_3S$: 312.1509 (M^+), calculated, 312.1508.

2.2.5. 2-(4-Methylbenzenesulfonamido)-4-(methylsulfanyl)-N-propylbutanamide (9e)

Yield (0.34 g, 97.1%), Mp = 118–120 °C. Uv (λmax): 213.00 nm. FTIR (KBr, cm^{-1}): 3250 (NH), 3049 (C−H aromatic), 2964, 2918, 2878 (C−H aliphatic), 2624 (S−CH_3), 1640 (C═O), 1584, 1521, 1435, 1402 (C═C), 1361, 1314 (2S═O), 1204, 1156 (SO_2NH), 1088, 1044 (C−N). ^{1}HNMR ($DMSOd_6$, 400 MHz)δ: 8.01 (d, *J* = 7.2 Hz, 1H, NH), 7.62–7.58 (m, 2H, ArH), 7.32–7.28 (m, 2H, ArH), 7.07 (s, 1H, NH), 3.18–3.15 (m, 1H, CH−C═O), 2.63–2.59 (t, *J* = 6.40 Hz, CH_2−NH), 2.32–2.31 (t, *J* = 6.8 Hz, 2H, CH_2−S), 2.25 (s, 3H, CH_3−S), 1.92–1.90 (t, *J* = 7.6 Hz, 3H, CH_3−ArH), 1.75–1.74 (m, 2H, CH_2−CH_2−S), 1.49–1.42 (m, 2H, CH_2−CH_2−NH), 0.84–0.79 (t, *J* = 6.0 Hz, 3H, CH_3−CH_2).^{13}CNMR ($DMSOd_6$, 400 MHz)δ: 172.17 (C═O), 143.00, 137.85, 129.99, 128.62, 127.27, 126.00, (six aromatic carbons), 56.64, 33.50, 29.87, 21.48, 21.09, 15.02, 11.41, (seven aliphatic carbons). HRMS (*m/z*) for $C_{15}H_{23}N_2O_3S_2$: 343.1152 (M-H), calculated, 344.1150.

2.2.6. 2-Benzenesulfonamido-4-(methylsulfanyl)-N-propylbutanamide (9f)

Yield (0.34 g, 97.1%), Mp = 98–100 °C. Uv (λmax): 213.00 nm.



Scheme 1. Synthetic route to the new carboxamides.

FTIR (KBr, cm^{-1}): 3198 (NH), 3080 (C—H aromatic), 2919 (C—H aliphatic), 2530 (S—CH_3)1718 (C═O), 1595, 1495 (C═C), 1398, 1319 (2S═O), 1215, 1152 (SO_2NH), 1088.4, 967.6 (C—N, C—O).^{1}HNMR (DMSOd_6, 400 MHz)δ: 8.01–7.99 (d, *J* = 8.60 Hz, 1H, NH), 7.77–7.75 (m, 2H, ArH), 7.62–7.60 (m, 3H, ArH), 5.18 (t, *J* = 6.2 Hz, 1H, NH), 3.84–3.81 (m, 1H, CH—C═O), 2.60–2.61 (t, *J* = 6.40 Hz, CH_2—NH), 2.30–2.29 (t, *J* = 6.8 Hz, 2H, CH_2-S), 2.55 (s, 3H, CH_3—S), 1.65–1.62 (m, 2H, CH_2—CH_2—S), 1.50–1.48 (m, 2H, CH_2—CH_2—NH), 0.92–0.89 (t, *J* = 6.0 Hz, 3H, CH_3—CH_2). ^{13}C NMR (DMSOd_6, 400 MHz)δ: 171.67 (C═O), 142.73,132.85,129.99, 128.62, (six aromatic carbons), 54.56, 32.50, 29.87, 26.67, 24.48, 18.64, 15.46, (seven aliphatic carbons). HRMS (*m/z*) for $C_{14}H_{23}N_2O_3S_2$: 331.1149 (M + H), calculated, 331.1152.

2.2.7. 3-Hydroxy-2-{[(4-methylphenyl)sulphonyl]amino}-N-propylbutanamide (9g)

Yield (0.28 g, 90.3%). Brownish oil. Uv (λmax): 214.00 nm. FTIR (KBr, cm^{-1}): 3391 (OH), 3020 (C—H aromatic), 2971, 2881 (C—H aliphatic), 1617 (C═O), 1514, 1461 (C═C), 1394, 1323. (2S═O), 1163, 1126 (SO_2NH), 1037, 954 (C—N, C—O).^{1}HNMR (DMSOd_6,400 MHz)δ: 7.89–7.88 (d, *J* = 7.86 Hz, 2H, ArH), 7.62.-7.56 (m, 2H, ArH), 7.45 (m, *J* = 5.4 Hz, 2H, NH), 4.86 (s, br, 1H, OH), 3.89–3.87 (t, *J* = 5.26 Hz, 1H, CH—C═O),3.20–3.18 (m, 1H, CH—OH), 2.86–2.79 (m, 2H, CH_2—NH), 2.32–2.30 (m,3H, CH_3-Ar), 1.46–1.44 (m, 2H, CH_2-CH_2-NH), 0.97–0.95 (d, *J* = 6.40 Hz, 3H, CH_3—CHOH), 0.86–0.84 (t, *J* = 6.42 Hz, 3H, CH_3—CH_2).^{13}C NMR (DMSOd_6, 400 MHz)δ: 173.63 (C═O), 148.53, 132.80, 128.56, 127.72, (four aromatic carbons), 67.91, 60.49, 40.85, 21.78, 20.97, 19.34, 11.37, (seven aliphatic carbons). HRMS (*m/z*) for $C_{14}H_{21}N_2O_4S$: 313.1224 (M-H), calculated, 313.1222.

2.2.8. 3-hydroxy-2-[(phenylsulphonyl)amino]-N-propylbutanamide (9h)

Yield (0.29 g, 96.7%). Brownish oil. Uv (λmax): 349.00 nm. FTIR (KBr, cm^{-1}): 3343 (OH), 3235 (NH), 3010 (C—H aromatic), 2974, (C—H aliphatic), 1602(C═O), 1580, 1528, 1446, (C═C), 1379, 1312 (2S═O), 1159 (SO_2NH), 1014, 947 (C—N). ^{1}HNMR (DMSOd_6, 400 MHz)δ: 8.01 (d, *J* = 4.8 Hz, 1H, NH), 7.76–7.74 (d, *J* = 7.76 Hz, 2H, ArH), 7.59–7.49 (m, 2H, ArH), 5.2 (t, *J* = 6.92 Hz, 1H, NH), 3.98 (s, br, 1H, OH), 3.75–3.73 (t, *J* = 5.26 Hz, 1H, CH—C═O), 3.19–3.18 (m, 1H, CH—OH), 2.66–2.63 (m, 2H, CH_2—NH), 1.49–1.44 (m, 2H, CH_2—CH_2—NH), 0.92–0.91 (d, *J* = 6.40 Hz, 3H, CH_3—CHOH), 0.84–0.81 (t, *J* = 7.32 Hz, 3H, CH_3—CH_2).^{13}CNMR (DMSOd_6, 400 MHz)δ: 171.60 (C═O), 140.63, 132.90, 129.56, 127.20, (four aromatic carbons), 67.91, 60.49, 40.85, 20.97, 19.34, 11.37, (six aliphatic carbons). HRMS (*m/z*) for $C_{13}H_{20}N_2O_4S$: 300.1146 (M^+), calculated 300.1144.

2.2.9. 3-Hydroxy-2-{[(4-methylphenyl)sulphonyl]amino}-N-propylpropanamide (9i)

Yield (0.33 g, 98.2%), Mp, 115–116 °C. Uv (λmax): 213.00 nm. FTIR (KBr, cm^{-1}): 3425 (OH), 3288 (NH), 3040 (C—H aromatic), 2945 (C—H aliphatic), 1729. (C═O), 1607, 1509, 1446 (C═C), 1379, 1312 (2S═O), 1200, 1118,1156 (SO_2NH), 1092.1, 969.1.5C-N, C—O).^{1}HNMR (DMSOd_6, 400 MHz)δ: 8.23–8.21 (d, *J* = 7.42 Hz, 1H, NH), 7.88–7.87 (d, *J* = 6.90 Hz, 2H, ArH), 7.66–7.64 (t, *J* = 6.40 Hz, 2H, ArH), 4.12 (t, *J* = 7.21 Hz, 1H, NH), 3.60–3.58 (m, 1H, CH),3.21 (s-br, 1H, OH), 1.69–1.67 (t, *J* = 6.40 Hz, 2H, CH_2═NH), 1.40–1.38 (t, *J* = 5.22 Hz, 2H, CH_2═OH), 1.10–1.08 (m, 2H, CH_3), 0.88–0.86 (m, 3H, CH_3).^{13}CNMR (DMSOd_6, 400 MHz)δ: 170.66 (C═O), 149.44, 147.64, 129.72, 123.64, (four aromatic carbons), 60.89, 37.32, 24.85, 21.44, 16.46, 11.42, (six aliphatic carbons). HRMS (*m/z*) for $C_{13}H_{20}N_2O_4S$: 301.1223 (M + H), calculated, 301.1222.

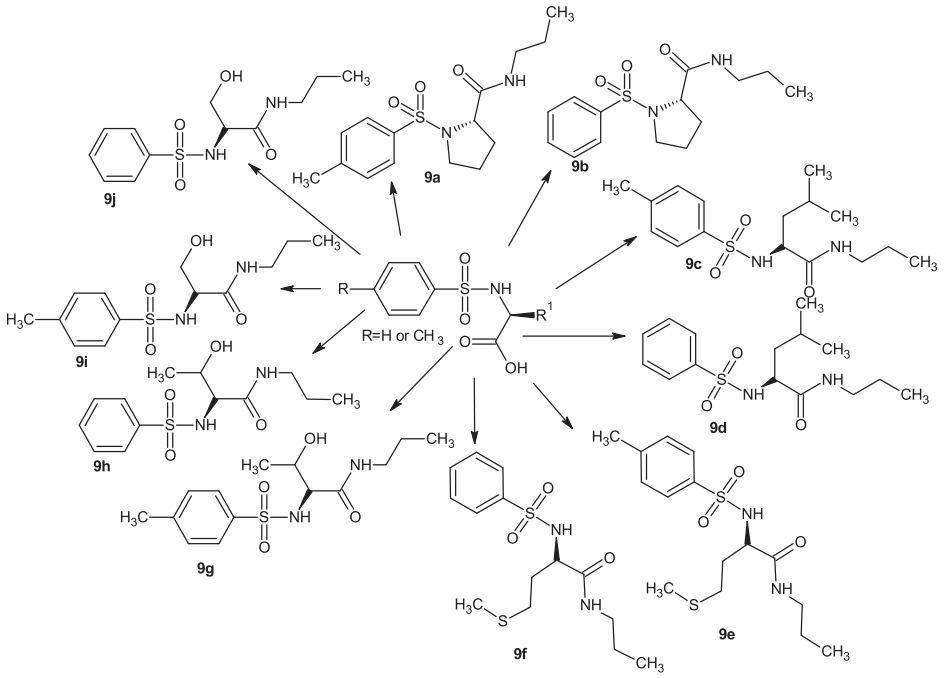
2.2.10. 3-Hydroxy-2-[(phenylsulphonyl)amino]-N-propylpropanamide (9j)

Yield (0.27 g, 96.4%), brownish oil. Uv (λmax): 213.00 nm. FTIR (KBr, cm^{-1}): 3403 (OH), 3160 (NH), 3060 (C—H aromatic), 2968, 2881 (C—H aliphatic), 1602 (C═O), 1509, 1446 (C═C), 1386, 1319 (2S═O), 1257, 1156 (SO_2NH), 1093, 1021 (C—N, C—O).^{1}H NMR (DMSOd_6, 400 MHz)δ: 8.43–8.42 (d, *J* = 7.32 Hz, 1H, NH), 8.36–8.34 (d, *J* = 6.88 Hz, 2H, ArH), 7.99–7.98 (t, *J* = 6.84 Hz, 3H, ArH), 4.76 (t, *J* = 4.63 Hz, 1H, NH), 3.62–3.59 (m, 1H, CH), 3.30 (s-br, 1H, OH), 1.68–1.65 (t, *J* = 5.04 Hz, 2H, CH_2—NH), 1.35–1.30 (t, *J* = 5.03 Hz, 2H, CH_2—OH), 1.12–1.03 (m, 2H,CH_3—CH_2), 0.78–0.76 (m, 3H, CH_3).^{13}C NMR (DMSOd_6, 400 MHz)δ: 172.36 (C═O), 149.93, 147.24, 128.72, 124.78, (four aromatic carbons), 60.89, 37.32, 24.85, 22.45, 15.96, 11.46, (five aliphatic carbons). HRMS (*m/z*) for $C_{12}H_{18}N_2O_4S$: 285.0833 (M-H), calculated, 285.0831.

2.3. In silico studies

2.3.1. Molecular docking studies

Three drugs targets were selected to study the *in silico* antioxidant, anti-inflammatory and antibacterial activities of the synthesized compounds. The targets used forthe antioxidant and aniinflammatory studies are the human peroxiredoxin 5 (PDB code: 1HD2) and phosphodiesterase 4 (PDE4) (PDB: 4WCU) respectively. Glucosamine-6-phosphate synthase (PDB Code: 2VF5) was used for antibacteria study.



Scheme 2. Propylamine derivatives of carboxamide.

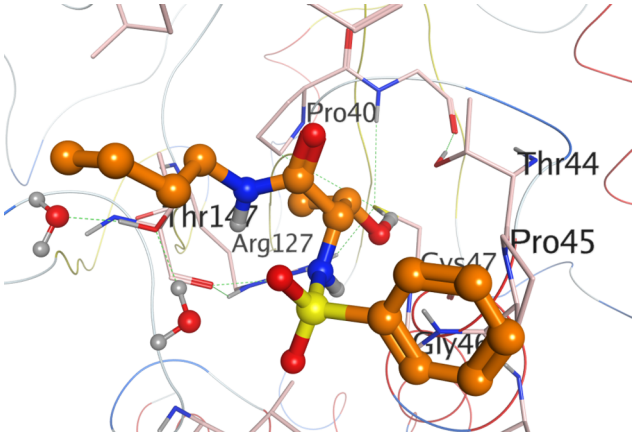


Fig. 2. Binding pose of compound **9b** in the binding cavity of 1HD2.

Table 1
Binding free energy, ΔG (kcal/mol).

COMP	Antioxidant target 1HD2	Anti-inflammatory target 4WCU	Antibacteria target 2VF5
9a	−10.56	−10.80	−11.16
9b	−13.86	−10.76	−11.48
9c	−10.40	−9.71	−11.67
9d	−10.93	−11.22	−10.90
9e	−12.66	−11.22	−12.81
9f	−11.17	−11.28	−11.04
9g	−11.91	−10.05	−10.80
9h	−11.66	−11.05	−11.58
9i	−11.84	−10.43	−11.29
9j	−10.66	−9.66	−11.08
Standard drug	−13.04	−11.38	−16.74

Standard drugs used: antioxidant = Vitamin C; Anti-inflammatory = indomethacin; Antibacteria = ciprofloxacin.

The 3-Dimensional crystal structures of 1HD2, 4WCU and 2VF5withtheirco-crystallized ligands were retrieved from protein data bank repository (https://www.rcsb.org/). These proteins were treated in Discovery Studio where multiple chains and water of crystallization were removed. The synthesized compounds were drawn using Accelrys Draw 4.1. Both the prepared proteins and compounds were energy minimized using MMFF94x force field. The energy minimized compounds were docked into the binding cavities of the proteins. The binding free energy for each compound against the target was calculated. Biovia Discovery Studio v16.1.0.15350 software was used for analysis of molecular docking studies. Molinspiration software (*www.molinspiration.com*) was used to generate the physicochemical properties in Table 7.

2.3.1.1. Drug targets. Peroxisomes are essential organelles which participate in multiple important metabolic processes, including the β-oxidation of fatty acids, plasmalogen synthesis and the metabolism of reactive oxygen species (ROS) [24]. Human peroxiredoxin 5 (PRDX5) (PDB code: 1HD2), a peroxisome, is a thioredoxin reductase which reduces H_2O_2, alkyl hydroperoxides and peroxynitrite [25]. PRDX5 is a novel type of mammalian thioredoxin peroxidase widely expressed in tissues and located cellularly to mitochondria, peroxisomes and cytosol. Functionally, PRDX5 has been implicated in antioxidant protective mechanisms as well as in signal transduction in cells [26].

Phosphodiesterase-4 (PDE4) (PDB code: 4WCU) is an enzyme found in some specific cell types that is involved in the degradation of the second messenger, cAMP. As a result, 4WCU has a pivotal role in cell signalling. This has made it a target for clinical drug development of various indications, including anti-inflammation and several others [27].

Glucosamine-6-phosphate synthase (GlcN-6-P) (PDB code: 2VF5) is a very useful target in antimicrobial chemotherapy as outlined by Ezeokonkwo et al. [28] and Festus et al. [29]. 2VF5 is responsible for the metabolism of hexosamine which is an important process in the biosynthesis of amino sugars. In the biosynthesis of amino sugars, uridine 5′-diphospho-*N*-acetyl-d-glucosamine (UDP-GlcNAc) is formed. UDP-GlcNAc an important component of peptido glycan layer mostly found in the bacterial and fungal cell walls. Inactivation of GlcN-6-P synthase for a short period is very dangerous for fungal cells.

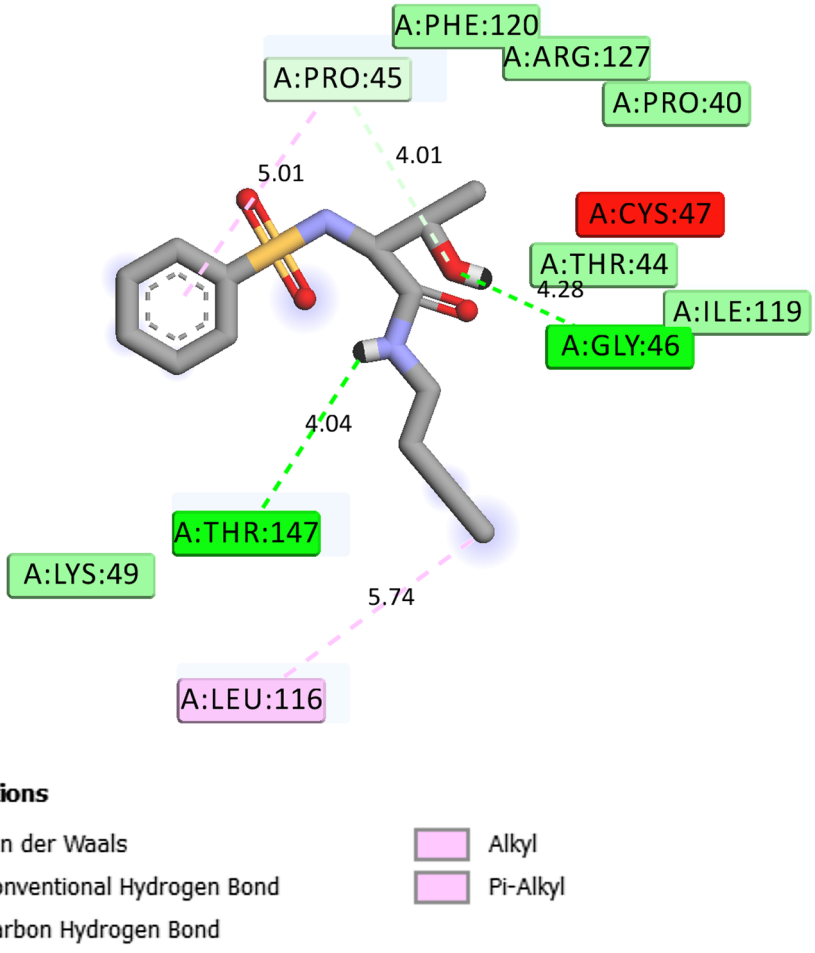


Fig. 3. Stick representation of compound **9b** interacting with the amino acid residues of 1HD2.

2.4. Biological studies

2.4.1. In vivo anti-inflammatory activities determination

Male albino rats weighing 300 g where purchased from the Department of Biochemistry, University of Nigeria, Nsukka and kept at room temperature in a light controlled animal house. They were fasted with free access to water at least 12 h prior to the experiments. The tested compounds were prepared as suspension in vehicle (0.5% methylcellulose) and celecoxib was used as a standard drug. The positive control received celecoxib while the negative control received only the vehicle. Oedema was produced by injecting 0.2 mL of a solution of 1% carrageenan in the hind paw. The rats were injected intraperitoneally with 1 mL suspension in 0.5% methylcellulose of the tested compounds and reference drug. Paw volume was measured by water displacement with aplethysmometer (UGO BASILE) before, 0.5 h, 1 h, 2 h, and 3 h after treatment. The percentage was calculated by the following equation [30]:

$$\text{Anti - inflammatory activity } (\%) = (1 - -\text{D/C})\text{x}100$$

where D represents the difference in paw volume before and after drug administration to the rats and C represents the difference of volume in the control groups. The approval for the use of animal was obtained from the University of Nigeria committee on experimental animal use.

2.4.2. In vitro antimicrobial activity

The antimicrobial properties of the novel compounds were investigated in form of the general sensitivity testing and minimum inhibitory concentration (MIC) with respect to freshly cultured targeted organisms. The seven organisms used in this study were clinical isolates of two Gram positive bacteria (*Staphylococcus aureus, Bacillus cereus*), three gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa and Salmonella typhi*) and two fungi (*Candida albican, Aspergillus niger*) obtained from the Department of Pharmaceutics, University of Nigeria, Nsukka.

2.4.2.1. Antimicrobial sensitivity testing. Sensitivity test agar plates were seeded with 0.1 mL of overnight culture of microorganism. The seeded plates were allowed to set after which cups were made in each sector previously drawn on the backside of the bottom plate using marker. Using sterile pipette, each cup was filled with six drops of their corresponding carboxamides (100 mg/mL). The solubility solvent was DMF. All the plates were incubated at 37 °C for 24 h for bacteria and 48 h for fungi. Zones of clearance round each cup were measured and the diameter of the cork borer subtracted to get the inhibition zone diameter (IZD). The procedure was repeated for ciprofloxacin (standard antibacterial), fluconazole (standard antifungal) and DMF (solvent). Muller Hinton agar was used for the fungi in place of nutrient agar for bacteria [31].

2.4.2.2. Minimum inhibitory concentration (MIC) testing. Serial dilutions of the carboxamides were prepared from 100 mg/mL solution of the compounds to give 100, 50, 25 and 12.5 mg/mL. Six drops of each dilution was added to the corresponding cup of seeded microorganisms and the agar plate previously marked. The cork borer used to make the cup is 8 mm in diameter. The plates were incubated at 37 °C for 24 h and 48 h in the case of fungi. The diameter of zone of inhibition was measured and the value subtracted from the diameter of the borer to give the inhibition zone diameter (IZD). The graph of IZD^2 against the

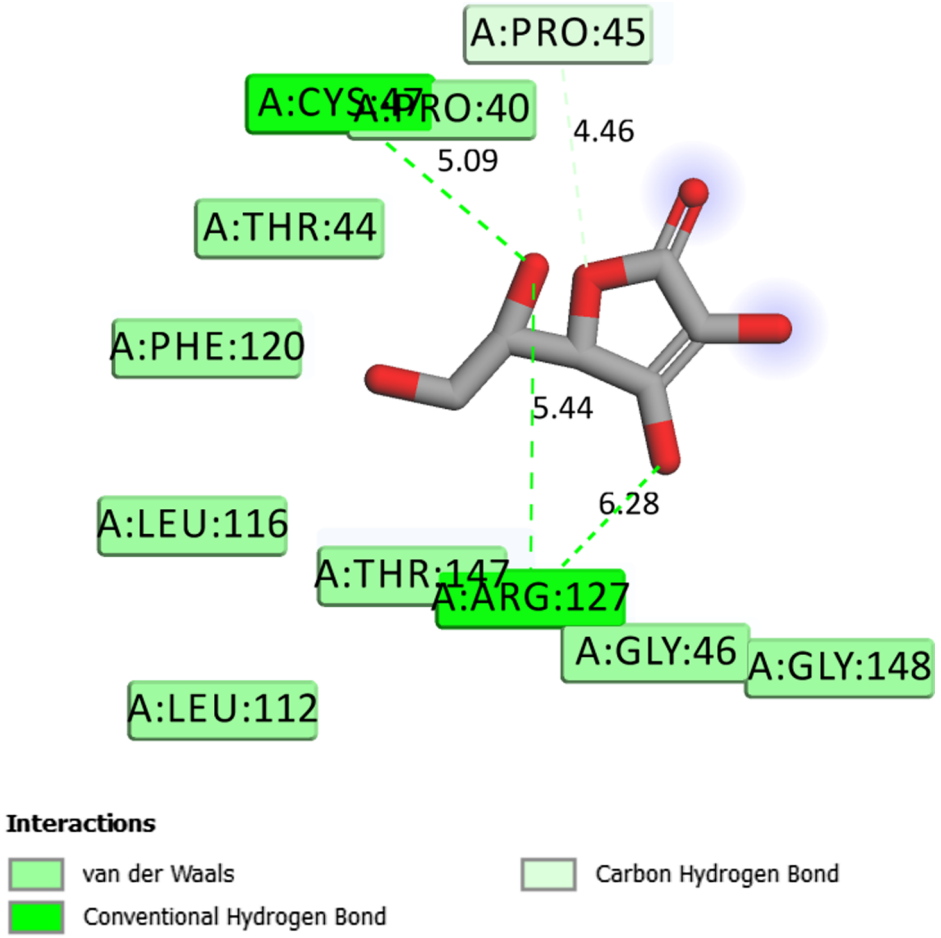


Fig. 4. Stick representation of vitamin C interacting with the amino acid residues of 1HD2.

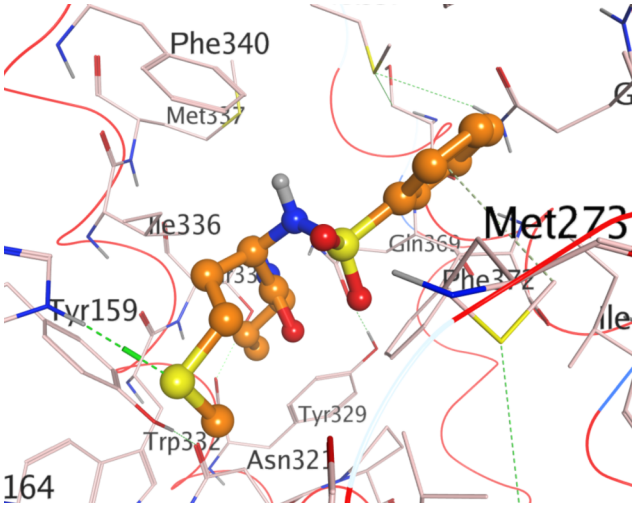


Fig. 5. Binding pose of compound **9f** in the binding cavity of 4WCU.

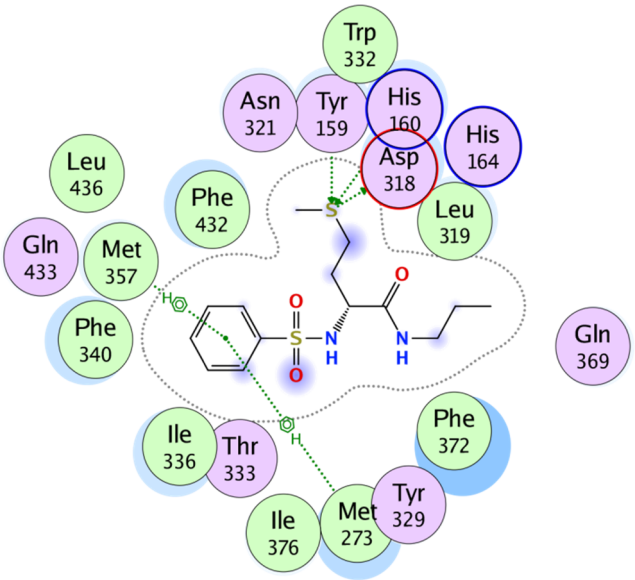


Fig. 6. 2D representation of compound **9f** interacting with the amino acid residues of 4WCU.

log of concentration was plotted for each plate containing a specific compound and a microorganism. The anti-log of the intercept on x-axis gave the MIC [31]. The procedure was repeated for ciprofloxacin and fluconazole.

2.4.3. In vitro antioxidant studies

2.4.3.1. DPPH radical scavenging activity. The new carboxamides were screened for free radical scavenging activity by 2,2-diphenyl-1-picrylhydrazyl (DPPH) method [32]. Compounds of different concentrations were prepared in distilled ethanol, 1 mL of each compound solutions having different concentrations (1.0, 2.0, 3.0, 4.0 and 5.0 mg/mL) were taken indifferent test tubes, 4 mL of 0.1 mM ethanol solution of DPPH was added and shaken vigorously. The test tubes were then incubated in the dark room temperature for 20 min. A

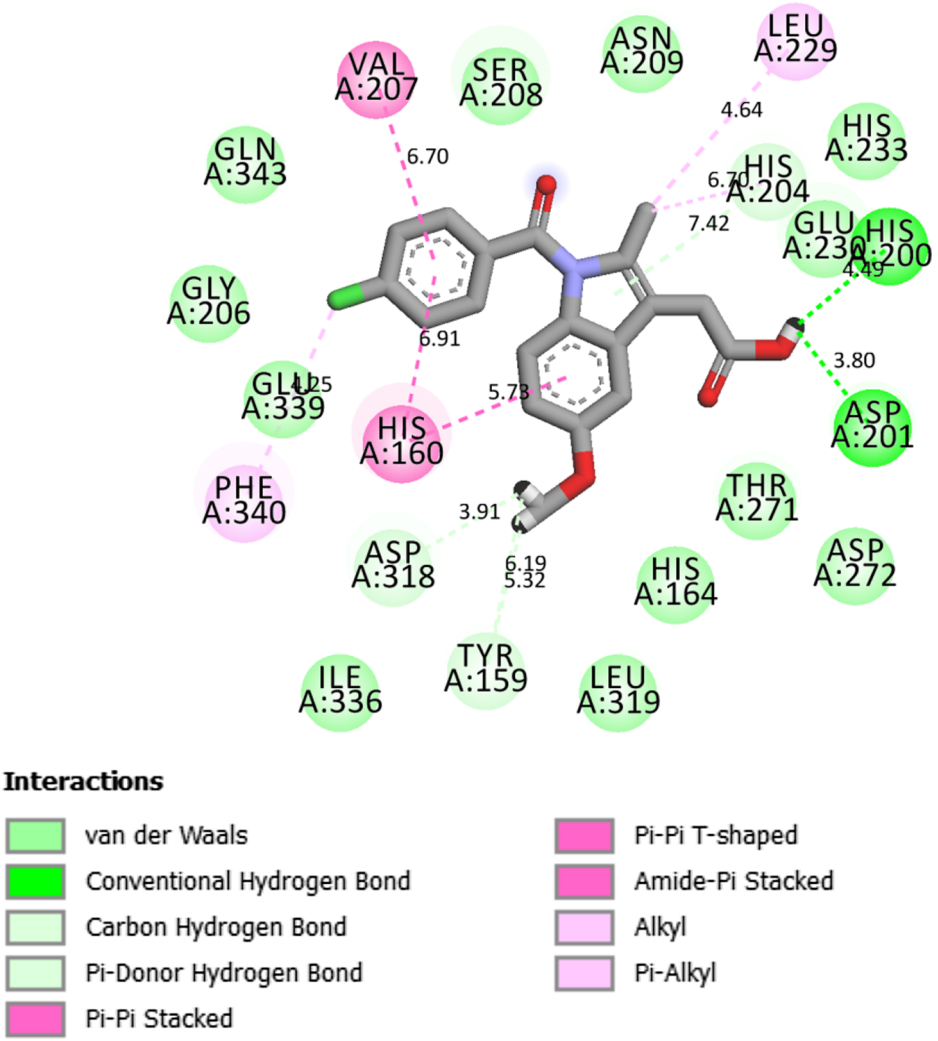


Fig. 7. 2D representation of binding interaction of indomethacin and the amino acid residues of 4WCU.

Table 2
In vivo anti-inflammatory.

Sample no	1 h (%)	2 h (%)	3 h (%)
9a	87.61	78.45	74.78
9b	86.73	82.76	79.13
9c	91.15	86.21	85.22
9d	93.81	88.79	86.09
9e	91.15	89.66	84.35
9f	86.44	80.56	79.67
9g	91.15	86.21	84.35
9h	92.92	87.93	86.96
9i	87.55	77.56	72.90
9j	86.73	81.90	80.00
Indomethacin	78.76	71.55	66.09

DPPH blank was prepared without the compound and ethanol was used for the baseline correction. Changes (decrease) in the absorbance at 517 nm were measured using a UV–Visible spectrometer. The radical scavenging activities were expressed as the inhibition percentage and were calculated using:

$$\text{DPPH radical scavenging activity} = \frac{\text{Ac} - \text{As}}{\text{Ac}} * 100$$

where Ac = Absorbance of control, As = Absorbance of sample.

3. Results and discussion

3.1. Chemistry

Substituted benzenesulphonamides (**8a–j**) were synthesized from the reaction of various L-amino acids (**7**) and substituted benzenesulphonyl chloride (**6**) in aqueous medium. Reaction of compounds (**8a–j**) with the appropriate alkyl amine in the presence of catalytic amount of $Pd_2(dba)_3$ afforded the target compounds (**9a–j**, Scheme 2) which were characterized using UV, FTIR, NMR and HRMS.

3.1.1. Spectral characterisation

The FTIR spectra of the carboxamides showed N—H band between 3496 and 3160 cm^{-1}. The C=O band appeared between 1729 and 1602 cm^{-1}. These bands indicates successful coupling of the aliphatic amines with the benzenesulphonamides.

In the proton NMR spectra of the derivatives, the diagnostic peaks at 3.13–3.08 ppm in the pyrrolidine derivatives (**9a–b**) assigned to CH_2-NH, 2.86–2.51 ppm assigned to CH_2-NH of **9c–j** derivatives, 1.53–1.26 ppm assigned to CH_2—CH_3 and 0.92–0.79 assigned to CH_3—CH_2 are supportive of the formation of the target product.

The carbon-13 NMR showed all the peaks expected of successful coupled products. The C=O peak appeared between 167.85 and 175.31 ppm. All the aromatic and aliphatic peaks were accounted for in the carbon-13 NMR.

The high resolution mass spectrometer (HRMS) peak of the

Table 3
General sensitivity of compounds against microorganism.

Sample no	*E. coli*	*S. aureus*	*P. aeroginosa*	*S. typhi*	*B. subtilis*	*C. albicans*	*A. niger*
9a	7	8	7	7	6	8	–
9b	4	3	9	5	5	4	–
9c	6	10	9	6	5	5	–
9d	–	–	11	10	–	–	8
9e	4	12	8	4	12	4	8
9f	–	6	8	–	6	–	–
9g	10	13	–	10	–	–	–
9h	11	8	6	–	–	4	3
9i	8	12	10	6	6	6	4
9j	15	26	18	12	18	13	11
ciprofloxacin	26	25	25	25	26	–	–
Fluconazole	–	–	–	–	–	24	27

– = No inhibition.

Table 4
Minimum inhibitory concentration (MIC).

Sample no	*E. coli*	*S. aureus*	*P. aeroginosa*	*S. typhi*	*B. subtilis*	*C. albicans*	*A. niger*
9a	8.55	6.54	8.67	8.60	6.69	6.64	–
9b	–	–	7.36	–	–	–	–
9c	7.18	7.91	7.54	7.28	–	–	–
9d	–	–	7.64	7.86	–	–	6.63
9e	–	8.96	6.45	–	8.74	–	6.46
9f	–	7.07	6.85	–	6.98	–	–
9g	7.72	8.53	–	7.91	–	–	–
9h	7.42	6.86	6.64	–	–	–	–
9i	6.24	8.75	7.89	7.30	7.42	7.60	6.98
9j	8.80	9.84	9.04	8.97	9.26	8.96	7.64
ciprofloxacin	9.65	8.39	9.05	8.68	9.56	–	–
Fluconazole	–	–	–	–	–	9.05	8.39

Table 5
In vitro anti-oxidant (% scavenging activity).

Sample no	0.05 mg/mL (%)	0.10 mg/mL (%)	0.15 mg/mL (%)	0.20 mg/mL (%)	0.25 mg/mL (%)
9a	4.63	12.08	21.34	30.08	38.56
9b	2.31	4.76	7.58	11.31	14.91
9c	2.96	7.46	12.08	18.89	22.11
9d	3.86	8.48	15.17	21.08	26.35
9e	2.44	6.43	9.90	12.60	15.30
9f	2.31	4.76	7.58	11.31	14.91
9g	3.21	7.71	12.08	18.64	22.37
9h	3.21	6.17	8.61	11.57	16.20
9i	2.33	4.70	7.58	11.66	14.89
9j	3.60	7.33	9.90	12.60	18.51

Table 6
In vitro antioxidant activities (IC_{50}).

Sample no	IC_{50} (mg/mL)
9a	0.3052
9b	0.6617
9c	0.6446
9d	0.4333
9e	0.8088
9f	0.6680
9g	0.5613
9h	0.5762
9i	0.6510
9j	0.4888
Vitamin C	0.2090

derivatives appeared either as molecular ions (M^+), $M+H^+$ or $M-H^-$. The results corresponded tothree decimals with the calculated values. The spectra used for the characterisation of the new compounds are available as supporting materials.

3.2. *In silico* studies

3.2.1. *Molecular docking studies*

Compound **9b** was well fitted into the binding cavity of human peroxiredoxin 5, 1HD2 as showed in Fig. 2. The binding free energy of compound was comparable to vitamin C (Table 1). Fig. 3 shows the stick representation of **9b** interacting with different amino acid residues of 1HD2. There were two H-bonding interactions observed. Firstly, the H atom of the compound interacted with THR 147 and secondly, O-atom interacted with GLY 46. Other forms of interactions include van der waals, C—H bonding, alkyl and π-alkyl interactions. These significant interactions are essential to the observed strong binding affinity between **9b** and 1HD2. Fig. 4 shows the stick representation of vitamin C interacting with different amino acid residues of 1HD2. ARG 127 formed two H-bonding with the OH group in vitamin C. Also CYS 47 formed another H-bond. Compound **9b** and vitamin C did not interact with the same amino acids in 1HD2. This could possibly imply that both exhibit different mechanisms of action towards the same target (see Fig. 5).

The synthesized compounds showed good binding interaction with the phosphodiesterase 4 (PDE4). Fig. 6 which shows the 2D representations of the binding pose of **9f** in the binding site of 4WCU, revealed a well situated compound in the same binding cavity as the co-crystallized ligand. It further shades light on the different interactions of **9f** with the amino acids of the drug target. The sulphide, S in compound **9f** seems to contribute significantly in the binding of the compound to the receptor. The S-8, through H-donor interaction, is bound to the OD1 of ASP 318 (intermolecular distance of interaction is 3.40 Å). Again, through two H-acceptor interactions, S-8 interacted with CE2 of TYR 159 and NE2 of HIS 160 respectively. The π-electrons of the six-membered aromatic ring interacted with CE of MET 273 and MET 357 respectively through π-H bondings (see Fig. 7).

Table 7
Physicochemical properties of the compounds.

Sample no	MilogP	TPSA (Å^2)	NA	MW	HBA	HBD	NV	NRB	Volume	%ABS
9a	2.07	66.48	21	310.42	5	1	0	5	282.76	86.06
9b	1.62	66.48	20	296.39	5	1	0	5	266.20	86.06
9c	3.08	75.27	22	326.46	5	2	0	8	309.57	83.03
9d	2.63	75.27	21	312.44	5	2	0	8	293.01	83.03
9e	2.22	75.27	22	344.50	5	2	0	9	311.11	83.03
9f	1.77	75.27	21	330.48	5	2	0	9	294.55	83.03
9g	2.55	75.27	21	312.44	5	2	0	7	292.77	83.03
9h	2.10	75.27	20	298.41	5	2	0	7	276.20	83.03
9i	0.79	95.50	20	300.38	6	3	0	7	267.64	76.05
9j	0.35	95.50	19	286.35	6	3	0	7	251.07	76.05

TPSA: total polar surface area; NA: number of atoms; MW: molecular weight; HBA: hydrogen bond acceptor; HBD: hydrogen bonddonor; NV: numberof violations; NRB: number of rotatable bond.

3.3. Biological studies

3.3.1. In vivo anti-inflammatory activities

The *in vivo* anti-inflammatory activity showed that all the novel compounds (Table 2) tested had fascinating inhibition of inflammation (93.81–86.73%) when compared with NSAID indomethacin (78.76%) at 1 h. The most active was compound **9d** with percentage inhibition of 93.81% at 1 h. The compounds showed better anti-inflammatory activities at 1 h of the experiment. It was observed that the anti-inflammatory activities decreased with increase in time.

The structure activity relationship study revealed that the *p*-toluenesulphonamide derivatives of L-proline, L-methionine and L-serine were more active than the benzenesulphonamide derivatives while the benzenesulphonamide derivaties of L-leucine and L-threonine were more active than the *p*-toluenesulphonamide derivatives. This finding reveals that the presence of methyl group increases the anti-inflammatory activity of the derivatives. Compounds **9c–9h** with more methyl groups showed more anti-inflammatory activity.

3.3.2. In vitro antimicrobial activities

3.3.2.1. General sensitivity (inhibiton zone diameter, mm). See Table 3.

3.3.2.2. Minimum inhibitory concentration (mg/mL). The antimicrobial studies revealed that most of the novel compounds (MIC 9.84–6.24 mg/mL) were more potent than the reference drugs (MIC 9.65–8.39 mg/mL) against the tested microorganisms (Table 4). Compound **9i** (MIC 6.24 mg/mL) was the most active against *E. coli*. Compounds **9a** and **9h** (MIC 6.54 and 6.86 mg/mL) respectively were the most potent against *S. aureus*. Compound **9e** (MIC 6.45 mg/mL) was most active against *P. aeroginosa*. The most active compounds against *S. typhi* were **9c** and **9i** (MIC 7.28 and 7.30 mg/mL) respectively. Compound **9a** (6.69 mg/mL) was the most potent against *B. subtilis*. Compound **9a** (6.64 mg/mL) was the most active against *C. albicans*, while compound **9e** (6.46 mg/mL) was the most potent against *A. niger*.

Structure activity relationship study revealed that the *p*-toluenesulphonamide derivatives possessed better antimicrobial property than the benzenesulphonamide analogues. This finding underscores the importance of the methyl group at position 4 in the phenyl ring mimicking the structure of *p*-aminobenzoic acid needed for the synthesis of folic acid by the organisms. Considering the various amino acids used, the L-serine derivatives **9i** and **9j** showed broad spectrum antimicrobial activity against all the microorganisms tested. This finding shows that the OH of the L-serine played an important role in the antimicrobial activity of the derivatives

3.3.3. In vitro antioxidant activities

3.3.3.1. In vitro antioxidant activities (% scavenging activity). See Table 5.

3.3.3.2. In vitro antioxidant activities (IC_{50}). The *in vitro* antioxidant activities (Table 6) revealed that all the novel compounds had antioxidant activities though lower than Vitamin C. Only compounds **9a**, (IC_{50} 0.3052 mg/mL) had comparable activity with Vitamin C (IC_{50} 0.2090 mg/mL) at 0.25 mg/mL.

DPPH assay is used to predict antioxidant activities by mechanism in which the compounds tested inhibit lipid oxidation, so scavenging of DPPH radical and therefore determine free radical scavenging capacity. The method is used widely due to relatively short time required for the analysis. DPPH free radical is very stable and reacts with compounds that can donate hydrogen atoms. The assay measures the reducing ability of antioxidants toward the DPPH radical.

The SAR study showed that the benzenesulphonamide derivatives were more active among the various amino acids used. This is so, given the electron donating effect of the methyl group in the *p*-toluenesulphonamide derivatives. The presence of OH groups in compounds **9g–9j** accounted for their noticeable increased antioxidant activity in the DPPH assay.

3.4. Physicochemical properties

Table 7 shows the physicochemical properties of the synthesized compounds which are useful in the assessment of the drug-likeness.

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. The compounds reported in this research possessed TPSA less than 140 and NRB less than 10 and as such would not pose oral bioavailability problems if formulated.

4. Conclusion

In this paper, we have described an efficient, ecofriendly, and versatile approach to obtain substituted benzenesulphonamides bearing carboxamide. All the compounds were evaluated for their anti-inflammatory, antimicrobial and oxidant activities. Compound **9d** was most active anti-inflammatory agent, compound **9a** was the most active against *S. aurues, B. subtilis C. albicans*, compound **9e** was mostactive against *P. aeroginosa*while compounds **9c** and **9i** were the most active against *S. thyphi*. Only compound **9a** had comparable activity with Vitamin C

5. Disclosure statement

The authors declare that there is no conflicting interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103265.

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