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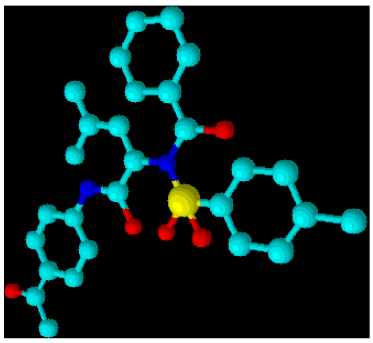
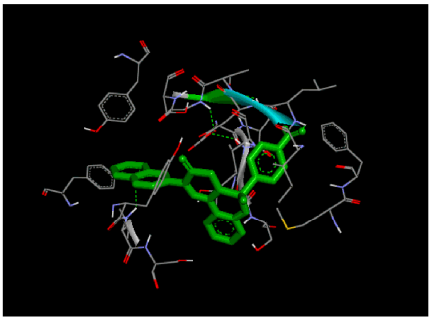
MIC values (antimalarial) **7c: 0.03 uM and 7k: 0.02 uM**

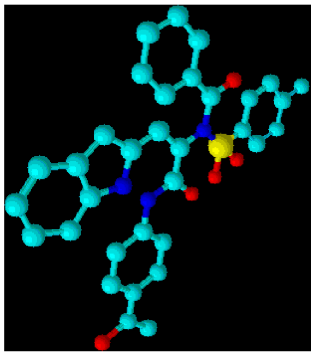
IC_{50} (antioxidant): **7c: 0.045 mM, 7k: 0.73 mM**



7k



active compound docked with plasmepsin II



7c

cyan= carbon, yellow= sulphur, blue= nitrogen, red= oxygen for compound **7c** and **7k**

Synthesis, characterization, molecular docking and in vitro antimalarial properties of new carboxamides bearing sulphonamide

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Abstract

Sulphonamides and carboxamides have shown large number of pharmacological properties against different types of diseases among which is malaria. Twenty four new carboxamide derivatives bearing benzenesulphonamoyl alkanamides were synthesized and investigated for their *in silico* and *in vitro* antimalarial and antioxidant properties. The substituted benzenesulphonyl chlorides (**1a-c**) were treated with various amino acids (**2a-h**) to obtain the benzenesulphonamoyl alkanamides (**3a-x**) which were subsequently treated with benzoyl chloride to obtain the *N*-benzoylated derivatives (**5a-f, i-n** and **q-v**). Further reactions of the *N*-benzoylated derivatives or proline derivatives with 4-aminoacetophenone (**6**) using boric acid as a catalyst gave the sulphonamide carboxamide derivatives (**7a-x**) in excellent yields. The *in vitro* antimalarial studies showed that all synthesized compounds had antimalarial property. Compound **7k**, **7c**, **7l, 7s,** and **7j** had mean MIC value of 0.02, 0.03, 0.05, 0.06 and 0.08 µM respectively comparable with chloroquine 0.06 µM. Compound **7c** was the most potent antioxidant agent with IC_{50} value of 0.045 mM comparable with 0.34 mM for ascorbic acid. In addition to the successful synthesis of the target molecules using boric acid catalysis, the compounds were found to have antimalarial and antioxidant activities comparable with known antimalarial and antioxidant drugs. The class of compounds reported herein have the potential of reducing oxidative stress arising from malaria parasite and chemotherapeutic agent used in the treatment of malaria.

Keywords: antimalarial, antioxidant, carboxamides, plasmepsin II, SAR, sulphonamides

1.0 Introduction

Malaria is among the most serious infectious disease in developing countries. The majority of malaria cases and death is caused by *P. falciparum,* only persistent infections are caused by *P. vivax.* The development of resistance to virtually all the prophylaxis and curative antimalarial agents have compromised the efforts made in the control of this debilitating disease. The spread of multidrug resistant *P. falciparum* has highlighted the urgent need to develop new antimalarial drugs. Drug counterfeiting and non-adherence to treatment regimen have played a key role in the development of resistance specie [1]. For the development of malarial parasite, the degradation of haemoglobin is a necessary step. Haemoglobin catabolism occurs in the food vacuoles

catalysed by the enzyme aspartic proteases also known as plasmepsin [2]. Plasmepsin catalyses the hydrolysis of the bonds linking some important hydrophobic residues in haemoglobins [3]. They are also responsible for the cleavage of small molecule substrates [4]. Their active site contains two aspartic acid residues which acts respectively as proton donor and proton acceptor in the hydrolysis of peptide bonds in proteins. Plasmepsin II cleaves haemoglobin between residues phenylalanine 33 and leucine 34 of α-globin units [5,6]. These roles of plasmepsin II in degradation of haemoglobin makes it good target for antimalarial drugs.

Various sulphonamide derivatives have been reported as potential antimalarial agent. Dominguez *et al* [7], Parai *et al* [8], Nubia *et al* [9], Mistry *et al* [10], Svogie *et al* [11], de Oliveira *et al* [12] and many other researchers have reported derivatives of benzenesulphonamide possessing antimalarial potential utilizing different mechanism of actions (fig. 1).

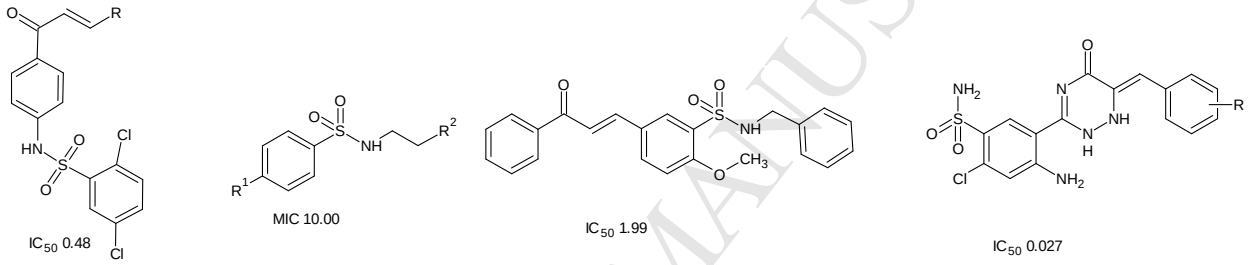


Fig. 1: some examples of antimalarial benzenesulphonamides

Oxidative damage is implicated in various pathological events such as cancer and aging [13]. Mutations resulting from damages to biomolecules such as lipids, proteins, enzymes and DNA in cells and tissues have been linked to high levels of free radicals. Antioxidants have the ability to interrupt an oxidizing chain reaction or stop free radical formation and as such minimizing oxidative damage is primary to prevention or treatment of disease attributable to oxidative damage. Subba *et al* [14] Siddique *et al* [15] Alexiou *et al* [16] Saeedi *et al* [17] and many others have reported the synthesis of some benzenesulphonamide derivatives possessing antioxidant properties (fig. 2).

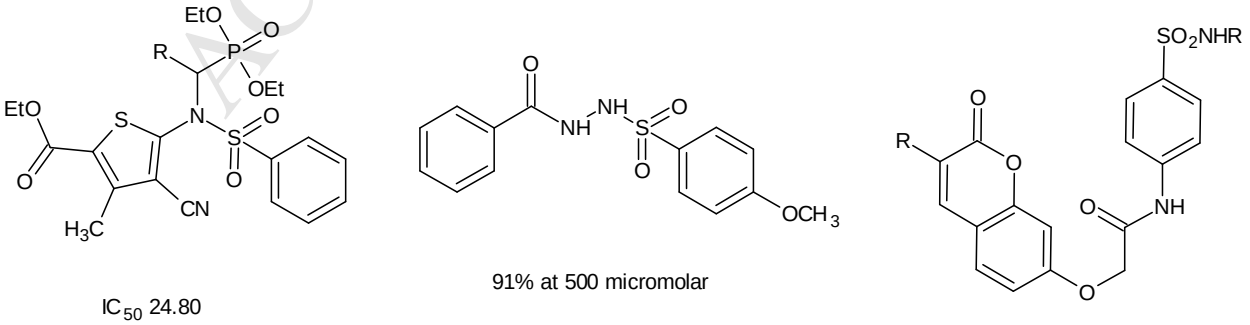


Fig. 2: some examples of antioxidant sulphonamide

A good number of authors have reported the implications of free radicals through oxidative stress in the physiopathogenesis of malaria [18-24]. Potter *et al* [25] suggested that this involvement may be related to the pathogenic mechanisms triggered by malaria parasite. Keller *et al* [26] reported the elevated nitric oxide production in children with malaria. Recent studies have suggested that the generation of reactive oxygen and nitrogen species associated with oxidative stress, plays an important role in the development of systemic complications caused by malaria. Guha *et al* [27] observed that malaria infections induces the generation of hydroxyl radicals in the liver which can lead to the induction of oxidative stress and apoptosis. Ataman and Ginsburg 1993 reported that erythrocytes infected with *P. falciparum* produced $OH^{\cdot}$ radicals and H_2O_2 about twice as compared to normal erythrocyte. Several substances used as antimalarial are pro-oxidants, which is why they have pharmacological power. This is the case for chloroquine, primaquine, artemisinin among others. This effect may be due to the drug's ability to promote direct production of free radicals [28] or by inhibiting molecules with antioxidants activity [29].

The prevalence of carboxamide in biological systems, pharmacologically active molecules and favourable properties of amides makes it one of the most popular and reliable functional group in all branches of organic chemistry [30]. Carboxamide functionality has been shown to appear in over 25% of commercial chemotherapeutic agents [31]. This finding makes the amide bond a sort after bond in the design of new chemotherapeutic agents.

Computational methods have become standard in today's chemistry tool kit. Molecular docking is one of the widely used modelling tools for the study of molecular recognition, which aims to predict the binding mode and binding affinity of a complex formed by two or more constituent molecules with known structure [32].

It is therefore desirable that an antimalarial agent should possess little antioxidant potential to trap the reactive oxygen and nitrogen species produced by malaria parasite and the antimalarial agents.

As a continuation of our search for lead antimalarial agent bearing antioxidant properties, we report in this work the boric acid catalysed synthesis of carboxamides from unactivated carboxylic acids bearing sulphonamide functionality. The synergy arising from the successful incorporation of carboxamide group in compounds containing sulphonamide pharmacophore is exploited in this research.

2.0 Experimental

2.1 Instrumentation

All reactions requiring inert atmosphere were carried out under nitrogen atmosphere. Drying of solvents was achieved using molecular sieve for 48 h. All reagents were purchased from commercial suppliers, Aldrich, Merck, Fluka, Avra, SD fine and Alfa Aesar. Thin layer chromatography was carried out using silica plates purchased from Avra. The plates were visualized under UV light (popular India). FT-IR spectroscopy of the compounds were run in PerkinElmer Spectrum version 10.03.06 and the bands presented in wavenumber. Proton and carbon-13 NMR spectroscopy were run in DMSO-d_6 and CD_3OD, unless otherwise stated on either Jeol 500 MHz or 400 MHz. The chemical shifts were reported in part per million with reference to tetramethylsilane. Mass spectroscopy were carried out using micro TOF electrospray time of flight (ESI-TOF) mass spectrometer, sodium formate was used as the calibrant. All experiments were carried out at Prof. Sandeep Verma's Laboratory, department of Chemistry, Indian Institute of Technology, Kanpur. Melting points were determined using digital melting point apparatus and were uncorrected.

2.2 General procedure for the synthesis of substituted benzenesulphonamoyl alkanamides (3a-p)

Sodium carbonate (Na_2CO_3, 1.590 g, 15 mmol) was added to a solution of amino acids (**2a-h,** 12.5 mmol) in water (15 mL) with continuous stirring until all the solutes had dissolved. The solution was cooled to -5 ^oC and the appropriate benzenesulphonyl chloride (**1a-c,** 15 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 progress of the reaction was monitored using TLC (MeOH/DCM, 1:9). Upon completion, the mixture was acidified using 20% aqueous hydrochloric acid to pH 2. The crystals was filtered via suction and washed with pH 2.2 buffer. The pure products (**3a-x**) were dried over self-indicating fused silica gel in a desiccator.

2.2.1 2-(4-methylphenylsulphonamido) acetic acid (3a)

The amino acid was glycine, yield (2.8410 g, 99.34%), mp, 88.4-88.6 ^oC, FTIR (KBr, cm^{-1}): 3448 (OH of COOH), 3277 (NH), 2957 (C-H aliphatic), 1730 (C=O), 1598, 1440 (C=C), 1354, 1321 (2S=O), 1185 (SO_2-NH), 1111, 1094 (C-N, C-O). ^1H NMR (DMSO-d_6)δ: 7.90-7.88 (t, J=6.3 Hz, 1H, NH), 7.65-7.63 (d, J=8.6 Hz, 2H, ArH), 7.34-7.33 (d, J=8.05 Hz, 2H, ArH), 3.52-3.51 (d, J=5.7 Hz, CH_2), 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6)δ: 170.7 (C=O), 143.1, 138.4, 130.0, 127.1 (aromatic carbons), 44.3 (CH_2), 21.5 (CH_3). HRMS-ESI (m/z): 228.0412 $(M-H)^-$, calculated, 228.0408.

2.2.2 2-(4-methylphenylsulphonamido)-3-phenylpropanoic acid (3b)

The amino acid was L-phenylalanine, yield (3.9848 g, 99.93%), mp, 135.10-135.60 ^{o}C FTIR (KBr, cm^{-1}): 3439 (OH of COOH), 3322 (NH), 3025 (C-H aromatic), 2926 (C-H aliphatic), 1713 (C=O), 1597, 1496, 1456 (C=C), 1344, 1331 (2S=O), 1189, 1157 (SO_2NH), 1136, 1090, 1052 (C-N, C-O). ^{1}H NMR (DMSO-d_6)δ: 8.13-8.11 (d, J= 9.15 Hz, 1H, NH), 7.47-7.45 (d, J=7.45 Hz, 2H, ArH), 7.42-7.41 (d, J= 8.6 Hz, 2H, ArH), 7.21-7.06 (m, 5H, ArH), 3.83-3.81 (dd, J= 3.45, 2.85 Hz, 1H, CH), 2.91-2.87 (dd, J= 5.75, 5.75 Hz, 1H, CH_a of CH_2), 2.69-2.65 (dd, J=8.6, 8.6 Hz, 1H, CH_b of CH_2), 2.31-2.30 (m, 3H, CH_3). ^{13}C NMR (DMSO-d_6)δ: 172.9 (C=O), 142.8, 138.7, 137.2, 129.7, 128.7, 127.0, 126.8, 126.0 (eight aromatic carbons), 57.9, 38.0, 21.5 (three aliphatic carbons). HRMS-ESI (m/z): 320.0958 $(M+H)^+$, calculated, 320.0959.

2.2.3 3-(1*H*-indol-2-yl)-2-{[(4-methylphenyl)sulphonyl]amino}propanoic acid (3c)

The amino acid was L-tryptophan, yield (4.3814 g, 97.880%), FTIR (KBr, cm^{-1}): 3385, 3302 (2NH), 2921, 2858 (C-H aliphatic), 1750 (C=O), 1618, 1598, 1494, 1457, 1429 (C=C), 1321, 1291 (2S=O), 1163, 1131 (SO_2NH), 1082, 1019 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 10.7 (s, 1H, NH of indole), 8.08-8.07 (d, J= 8.60 Hz, 1H, NH of SO_2NH), 7.68-7.67 (d, J= 8.05 Hz, 1H, ArH), 7.44-7.42 (d, J= 8.60 Hz, 2H, ArH), 7.34-7.32 (d, J= 8.00 Hz, 1H, ArH), 7.27-7.23 (t, J= 8.05 Hz, 1H, ArH), 7.14-7.13 (d, J= 8.00 Hz, 2H, ArH), 7.02-6.99 (m, 2H, ArH), 6.90-6.87 (m, 1H, ArH), 3.87-3.82 (dd, J= 7.45, 8.00 Hz, 1H, CH), 3.03-2.98 (dd, J= 6.3, 6.90 Hz, 1H, CH_a, CH_2), 2.83-2.79 (dd, J= 7.45, 7.45 Hz, 1H, CH_b of CH_2), 2.28 (s, 3H, CH_3-Ar). ^{13}C NMR (DMSO-d_6) δ: 173.1494 (C=O), 142.7, 138.5, 136.6, 129.6, 127.4, 126.8, 124.4, 121.3, 118.8, 118.3, 111.9, 109.4 (aromatic carbons), 66.9, 57.1, 21.5 (aliphatic carbons). HRMS-ESI (m/z): 359.1060 $(m+H)^+$, calculated, 569.1062

2.2.4 4-Methyl-2-{[(4-methylphenyl)sulfonyl]amino}pentanoic acid (3d)

The amino acid was L-leucine, yield (3.502 g, 98.26%), mp, 114.10-114.50 ^{o}C. FTIR (KBr, cm^{-1}): 3423 (OH of CO_2H), 3279 (NH), 2949 (C-H aromatic), 2872 (C-H aliphatic), 1706 (C=O), 1598, 1497, 1458, 1420 (C=C), 1384, 1339 (2S=O), 1168, 1152 (SO_2NH), 1122, 1091, 1020 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.98-7.97 (d, J= 8.60 Hz, 1H, NH), 7.62-7.60 (d, J= 8.55 Hz, 2H, Ar-H), 7.32-7.31 (d, J= 8.55 Hz, 2H, ArH), 3.62-3.57 (m, 1H, CH-CO_2H), 2.33 (s, 3H, CH_3-Ar), 1.55-1.50 (m, 1H, CH), 1.36-1.32 (m, 2H, CH_2), 0.77-0.76 (d, J= 6.85 Hz, 3H, CH_3), 0.66-.64 (d, J= 6.30 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ: 173.8 (C=O), 142.9, 138.9, 129.9, 128.6, 127.0, 126.0 (aromatic carbons), 54.5, 41.5, 24.4, 23.1, 21.6 (aliphatic carbons). HRMS-ESI (m/z): 286.1986 $(M+H)^+$, calculated, 286.1989.

2.2.5 3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}pentanoic acid (3e)

The amino acid was L-isoleucine, yield (3.412 g, 95.74%), mp, 130.10-130.40 ^{o}C, FTIR (KBr, cm^{-1}): 3280 (NH), 2970, 2934 (C-H Ar-H), 2883 (C-H aliphatic), 1710 (C=O), 1599, 1496, 1460 (C=C), 1385, 1334 (2S=O), 1185, 1161 (SO_2NH), 1092, 1058, 1020 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.89-7.87 (d, J= 9.2 Hz, 1H, NH), 7.62-7.61 (d, J= 8.05 Hz, 2H, ArH), 7.32-7.30 (d, J= 8.05 Hz, 2H, ArH), 3.51-3.48 (dd, J= 6.30, 6.30 Hz, 1H, CH-CO_2H), 2.33 (s, 3H, CH_3-Ar), 1.62-1.58 (m, 1H, CH), 1.34-1.29 (m, 1H, CH_a of CH_2), 1.09-1.01 (m, 1H, CH_b of CH_2), 0.76-0.70 (dt, J= 6.85, 7.45H, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 172.7 (C=O), 142.9, 138.9, 129.8, 127.1 (aromatic carbons), 60.5, 37.4, 24.9, 21.5, 15.9, 11.4 (aliphatic carbons). HRMS-ESI (m/z): 284.0765 $(M-H)^-$, calculated, 284.0769.

2.2.6 3-Methyl-2-(4-methylphenylsulphonamido)butanoic acid (3f)

The amino acid was L-valine, yield (3.2849 g, 95.56%), mp, 121.90-122.20 ^{o}C, FTIR (KBr, cm^{-1}): 3293 (NH), 2970 (C-H aliphatic), 1708 (C=O), 1598, 1466, 1419 (C=C), 1333, 1289 (2S=O), 1161 (SO_2NH), 1089 (C-N or C-O). ^{1}H NMR (DMSO-d_6) δ: 7.87-7.85 (d, J=9.75 Hz, 1H, NH), 7.68-7.61 (m, 2H, ArH), 7.33-7.22 (m, 2H, ArH), 3.46-3.43 (dd, J= 5.70, 5.75Hz, 1H, CH-CO_2H), 2.33-2.30 (m, 3H, CH_3-Ar), 1.90-1.86 (m, 1H, CH), 0.78-0.64 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 172.7 (C=O), 142.9, 138.9, 129.8, 127.1, 126.2 (aromatic carbons), 61.7, 30.9, 21.5, 19.5, 18.4 (aliphatic carbons). HRMS-ESI (m/z): 271.0881 $(M+H)^+$, calculated, 271.0894.

2.2.7 4-Hydroxy-1-tosylpyrrolidine-2-carboxylic acid (3g)

The amino acid was L-hydroxyproline, yield (3.564 g, 99.86%), mp, 98.40-98.60 ^{o}C. FTIR (KBr, cm^{-1}): 3524 (OH), 2931 (C-H aliphatic), 1708 (C=O), 1600, 1444 (C=C), 1347, 1332 (2S=O), 1200, 1158 (SO_2N), 1090, 1075 (C-N or C-O). ^{1}H NMR (DMSO-d_6) δ: 7.66-7.64 (d, J= 8.00 Hz, 2H, ArH), 7.38-7.36 (d, J= 8.05 Hz, 2H, ArH), 4.18 (s, 1H, O-H), 4.02-3.99 (t, J= 8.05 Hz, 1H, CH-CO_2H), 3.43-3.40 (m, 1H, CH-OH), 3.06-3.04 (d, J=10.3 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.92-1.90 (t, 4.6 Hz, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ: 173.8 (C=O), 143.7, 135.0, 130.1, 127.9 (aromatic carbons), 68.9, 60.2, 56.8, 21.5 (aliphatic carbons). HRMS-ESI (m/z): 286.1097 $(M+H)^+$, calculated, 286.1099.

2.2.8 1-Tosylpyrrolidine-2-carboxylic acid (3h)

The amino acid was L-proline, yield (3.2989 g, 98.09%), mp, 50.40-50.70 ^{o}C, FTIR (KBr, cm^{-1}): 3415 (OH of COOH), 2957 (C-H aliphatic), 1737 (C=O), 1619, 1597, 1494, 1449 (C=C), 1345, 1306 (2S=O), 1199 (SO_2N), 1159, 1095, 1013 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.66-7.65 (d, J=8.6 Hz, 2H, ArH), 7.36-7.34 (d, J= 8.00 Hz, 2H, ArH), 4.05-4.03 (dd, J= 4.55, 5.15

Hz, 1H, CH-COOH), 3.31-3.27 (dd, J= 9.75, 5.15Hz, 1H, CH_a of CH_2-N), 3.11-3.06 (dd, J= 6.85, 7.45 Hz, 1H, CH_b of CH_2-N), 2.31 (s, 3H, CH_3-Ar), 1.81-1.72 (m, 3H), 1.50-1.47 (t, J=5.15 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ: 173.7 (C=O), 143.9, 135.1, 130.3, 127.6 (aromatic carbons), 66.9, 48.9, 30.9, 24.7, 21.4 (aliphatic carbons). HRMS-ESI (m/z): 269.0726 $(m+H)^+$, calculated, 269.0731.

2.2.9 2-Benzenesulphonamido acetic acid (3i)

The amino acid was glycine, yield (2.6856 g, 99.61%), mp, 170.80-171.40 ^oC. FTIR (KBr, cm^{-1}): 3317 (NH), 3060, 2974 (C-H aromatic), 2946 (C-H aliphatic), 1728 (C=O), 1587, 1451, 1428, 1412 (C=C), 1318, 1247 (S=O), 1158, 1130 (SO_2NH), 1095, 1077, 1012 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.02-7.99 (t, J= 12.00 Hz, 1H, NH), 7.77-7.76 (d, J= 7.45 Hz, 2H, ArH), 7.61-7.58 (t, J= 7.45 Hz, 1H, ArH), 7.55-7.52 (t, J= 8.00 Hz, 2H, ArH), 3.55-3.54 (d, J= 6.30 Hz, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ: 170.7 (C=O), 141.2, 132.9, 129.6, 126.9 (aromatic carbons), 44.5 (aliphatic carbon). HRMS-ESI (m/z): 216.1252, calculated, 216.1256.

2.2.10 2-Benzenesulphonamido-3-phenylpropanoic acid (3j)

The amino acid was L-phenylalanine, yield (3.8169 g, 100%), mp, 129.10-129.80 ^oC. FTIR (KBr, cm^{-1}): 3342 (NH), 3195, 3029 (C-H aromatic), 2968 (C-H aliphatic), 1735 (C=O), 1697, 1496, 1447 (C=C), 1375, 1347 (2S=O), 1170, 1108 (SO_2NH), 1093, 1028 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.26-8.24 (d, J= 8.85 Hz, 1H, NH), 7.54-7.50 (m, 3H, ArH), 7.41-7.38 (t, J= 7.45 Hz, 2H, ArH), 7.18-7.12 (m, 3H, ArH), 7.09-7.08 (d, J= 7.15 Hz, 2H, ArH), 3.87-3.82 (ddd, J= 6.00, 5.75, 6.30 Hz, 1H, CH-CO_2H), 2.92-2.88 (dd, J= 5.75, 5.75 Hz, 1H, CH_a of CH_2), 2.70-2.65 (dd, J= 9.00, 9.00 Hz, 1H, CH_b of CH_2). ^{13}C NMR (DMSO-d_6) δ: 172.8 (C=O), 141.6, 137.3, 132.6, 129.7, 129.4, 128.7, 127.1, 126.7 (aromatic carbons), 57.9, 38.3 (aliphatic carbons). HRMS-ESI (m/z): 304.0624 $(M-H)^-$, calculated 304.0627.

2.2.11 2-Benzenesulphonamido-3-(1*H*-indol-3-yl)propanoic acid (3k)

The amino acid was L-tryptophan, yield (4.2805 g, 99.43%), mp, 106.40-106.60 ^oC. FTIR (KBr, cm^{-1}): 3366, 3311 (2NH), 3061 (C-H aromatic), 2936 (C-H aliphatic), 1746 (C=O), 1619, 1550, 1451, 1430 (C=C), 1323, 1235 (2S=O), 1214, 1160 (SO_2NH), 1127, 1091, 1012 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 10.78 (s, 1H, NH of indole), 8.23-8.21 (d, J= 8.60 Hz, 1H, NH), 7.59-7.57 (m, 2H, ArH), 7.49-7.46 (t, J= 6.85 Hz, 1H, ArH), 7.38-7.35 (m, 2H, ArH), 7.28-7.27 (d, J= 8.60 Hz, 2H, ArH), 7.03-7.00 (m, 2H, ArH), 6.92-6.89 (t, J= 7.40 Hz, 1H, ArH), 3.91-3.87 (m, 1H, ArH), 3.05-3.01 (dd, J= 6.85, 6.85 Hz, 1H, CH_a of CH_2), 2.86-2.81 (dd, J= 8.05, 7.45 Hz, 1H,

CH_b of CH_2). ^{13}C NMR (DMSO-d_6) δ: 173.1 (C=O), 141.5, 136.6, 132.6, 129.2, 127.5, 126.7, 124.4, 121.4, 118.9, 118.4, 111.9, 109.4 (aromatic carbons), 57.2, 28.8 (aliphatic carbons). HRMS-ESI (m/z): 344.0835 (M^+), calculated 344.0831.

2.2.12 2-Benzenesulphonamido-4-methylpentanoic acid (3l)

The amino acid was L-leucine, yield (3.0592 g, 90.20%), mp, 105.60-105.90 ^{o}C. FTIR (KBr, cm^{-1}): 3248 (NH), 3068 (C-H aromatic), 2959, 2921, 2874 (C-H aliphatic), 1712 (C=O), 1632, 1469, 1450, 1428 (C=C), 1327, 1314 (2S=O), 1184, 11670 (SO_2NH), 1092, 1077 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.11-8.09 (d, J= 8.72 Hz, 1H, NH), 7.74-7.72 (t, J= 6.88 Hz, 2H, ArH), 7.59-7.49 (m, 3H, ArH), 3.63-3.57 (m, 1H, CH-CO_2H), 1.53-1.46 (m, 1H, CH), 1.35-1.31 (m, 2H, CH_2), 0.78-0.61 (m, 6H, CH_3). ^{13}C NMR (DMSO-d_6) δ: 173.8 (C=O), 141.6, 132.8, 129.5, 126.9, 126.1 (aromatic carbons), 54.5, 41.4, 24.4, 23.1, 21.5 (aliphatic carbons). HRMS-ESI (m/z): 272.1982 (M+H), calculated, 271.1989.

2.2.13 2-Benzenesulphonamido-3-methylpentanoic acid (3m)

The amino acid was L-isoleucine, yield (3.1052 g, 91.55%), mp, 148.00-148.70 ^{o}C. FTIR (KBr, cm^{-1}): 3295 (NH), 2968 (C-H aromatic), 2936, 2883 (C-H aliphatic), 1699 (C=O), 1585, 1450, 1416 (C=C), 1340, 1384 (2S=O), 1168 (SO_2NH), 1092, 1026 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.01-7.99 (d, J= 9.16 Hz, 1H, NH), 7.74-7.72 (d, J= 8.60 Hz, 2H, ArH), 7.58-7.49 (m, 3H, ArH), 3.52-3.49 (dd, J= 7.45, 7.45 Hz, 1H, CH-CO_2H), 1.62-1.57 (m, 1H, CH), 1.33-1.27 (m, 1H, CH_a of CH_2), 1.07-1.00 (m, 1H, CH_b of CH_2), 0.75-0.68 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 172.7 (C=O), 141.6, 132.8, 129.4, 127.0 (aromatic carbons), 60.5, 37.4, 24.9, 15.9, 11.4 (aliphatic carbons). HRMS-ESI (m/z): 271.0879 (M^+), calculated, 271.0878.

2.2.14 2-Benzenesulphonamido-3-methylbutanoic acid (3n)

The amino acid was L-valine, yield (3.2030 g, 99.68%), mp, 143.60-143.80 ^{o}C. FTIR (KBr, cm^{-1}): 3418 (OH CO_2H), 3302 (NH), 2969 (C-H aliphatic), 1703 (C=O), 1585, 1451 (C=C), 1338, 1294 (2S=O), 1169, 1143 (SO_2NH), 1093, 1042 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.99-7.97 (d, J= 9.16 Hz, 1H, NH), 7.74-7.72 (d, J= 6.88 Hz, 2H, ArH), 7.58-7.48 (m, 3H, ArH), 3.48-3.45 (dd, J= 6.44, 5.96 Hz, 1H, CH-CO_2H), 1.92-1.83 (m, 1H, CH), 0.77-0.73 (m, 6H, CH_3). ^{13}C NMR (DMSO-d_6) δ: 172.7 (C=O), 141.7, 132.8, 129.4, 127.0 (aromatic carbons), 61.8, 30.9, 19.5, 18.3 (aliphatic carbons). HRMS-ESI (m/z): 258.1824 (M+H), calculated, 258.1827.

2.2.15 1-(Benzenesulphonyl)-4-hydroxypyrrolidine-2-carboxylic acid (3o)

The amino acid was L-4-hydroxyproline, yield (3.3815 g, 99.99%), mp, 159.00-159.90 ^{o}C. FTIR (KBr, cm^{-1}): 3402 (OH), 2993, 2955 (C-H aliphatic), 1714 (C=O), 1589, 1484, 1450 (C=C), 1385, 1353 (2S=O), 1195, 1158 (SO_2NH), 1158, 1100, 1070 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.78-7.76 (d, J= 7.32 Hz, 2H, ArH), 7.65-7.62 (t, J= 7.36 Hz, 1H, ArH), 7.58-7.54 (t, J= 7.80 Hz, 2H, ArH), 4.18 (s, 1H, OH), 4.06-4.02 (t, J= 7.80 Hz, 1H, CH-CO_2H), 3.45-3.41 (m, 1H, CHOH), 3.10-3.08 (d, J= 11.00 Hz, 2H, CH_2-N), 1.98-1.87 (m, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ: 173.8 (C=O), 137.8, 133.5, 129.6, 127.9 (aromatic carbons), 68.9, 60.2, 56.8, 31.2 (aliphatic carbons). HRMS-ESI (m/z): 271.0518 (M^+), calculated, 271.0514.

2.2.16 1-(Benzenesulphonyl)-pyrrolidine-2-carboxylic acid (3p)

The amino acid was L-proline, yield (3.1911 g, 100%). FTIR (KBr, cm^{-1}): 3066 (C-H aromatic), 2983, 2884 (C-H aliphatic), 1730 (C=O), 1627, 1447 (C=C), 1343, 1292 (2S=O), 1199, 1161 (SO_2NH), 1095, 1073, 1016 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.83-7.78 (m, 2H, ArH), 7.67-7.63 (m, 1H, ArH), 7.59-7.56 (m, 2H, ArH), 4.08-4.05 (dd, J= 4.60, 4.60 Hz, 1H, CH-CO_2H), 3.34-3.28 (m, 1H, CH_a of CH_2N), 3.14-3.08 (m, 1H, CH_b of CH_2N), 1.86-1.71 (m, 3H), 1.53-1.47 (m, 1H). ^{13}C NMR (DMSO-d_6) δ: 173.7 (C=O), 137.7, 133.6, 129.9, 127.6 (aromatic carbons), 60.9, 48.9, 30.9, 24.7 (aliphatic carbons). HRMS-ESI (m/z): 256.1679 (M+H), calculated 256.1682.

2.2.17 2-(4-Nitrophenylsulphonamido)acetic acid (3q)

The amino acid was glycine, yield (2.2152 g, 94.59%), mp, 171.90-172.20 ^{o}C. FTIR (KBr, cm^{-1}): 3417 (OH of CO_2H), 3297 (NH), 3108, 3070 (C-H aromatic), 1732 (C=O), 1605, 1482 (C=C), 1529, 1424 (N-O), 1354, 1333 (2S=O), 1240, 1165 (SO_2NH), 1100, 1087, 1014 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.44-8.41 (t, J= 4.00 Hz, 1H, NH), 8.37-8.35 (d, J= 9.15 Hz, 2H, ArH), 8.02-8.01 (d, J= 8.6 Hz, 2H, ArH), 3.67-3.66 (d, J= 4.00 Hz, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ: 170.7 (C=O), 150.0, 147.0, 128.7, 124.9 (aromatic carbons), 44.3 (aliphatic carbon). HRMS-ESI (m/z): 261.3108 (M+H), Calculated 261.3112.

2.2.18 2-(4-Nitrophenylsulphonamido)-3-phenylpropanoic acid (3r)

The amino acid was L-phenylalanine, yield (3.1530 g, 99.99%), mp, 100.10-100.50 ^{o}C. FTIR (KBr, cm^{-1}): 3417 (OH of CO_2H), 3253 (NH), 3182, 3111 (C-H aromatic), 1753 (C=O), 1607, 1456, 1435 (C=C), 1525, 1403 (N-O), 1347, 1311 (2S=O), 1164, 1124 (SO_2NH), 1103, 1093 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.69-8.67 (d, J= 8.6 Hz, 1H, NH), 8.17-8.15 (d, J= 9.15 Hz, 2H, ArH), 7.72-7.70 (d, J= 8.6 Hz, 2H, ArH), 7.11-7.06 (m, 5H, ArH), 3.95-3.90 (ddd, J= 5.2, 4.6, 5.15 Hz, 1H, CH-CH_2), 2.97-2.93 (dd, J= 5.15, 5.15 Hz, 1H, CH_a of CH_2), 2.70-2.65 (dd, J=

9.75, 9.75 Hz, 1H, CH_b of CH_2). ^{13}C NMR (DMSO-d_6) δ: 172.7 (C=O), 149.6, 147.1, 137.2, 129.7, 128.6, 128.2, 126.9, 124.7 (aromatic carbons), 58.2, 38.1 (aliphatic carbons). HRMS-ESI (m/z): 368.2347 $(M+NH_4)^+$, calculated, 368.2349.

2.2.19 3-(1*H*-Indol-2-yl)-2-(4-nitrophenylsulphonamido)propanoic acid (3s)

The amino acid was L-tryptophan, yield (3.4253 g, 97.94%), mp, 226.90-227.20 ^oC. FTIR (KBr, cm^{-1}): 3448 (OH of CO_2H), 3380, 3295 (2NH), 3108 (C-H of aromatic), 1710 (C=O), 1607, 1459 (C=C), 1525, 1424 (N-O), 1348, 1332 (2S=O), 1167, 1119 (SO_2NH), 1092, 1014 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 10.66 (s, 1H, NH, indole), 8.61-8.59 (d, J= 8.00 Hz, 1H, NH), 7.86-7.84 (m, 2H, ArH), 7.50-7.46 (m, 2H, ArH), 7.24-7.23 (d, J= 7.45 Hz, 1H, ArH), 7.06-7.04 (d, J= 8.00 Hz, 1H, ArH), 6.99 (s, 1H, ArH), 6.89-6.82 (m, 2H, ArH), 3.92-3.87 (ddd, J= 4.00, 2.85, 4.6 Hz, 1H, CH-CO_2H), 3.06-3.02 (dd, J= 4.6, 4.6 Hz, 1H, CH_a of CH_2), 2.81-2.76 (dd, J= 10.3, 9.75 Hz, 1H, CH_b of CH_2). ^{13}C NMR (DMSO-d_6) δ: 173.3 (C=O), 148.9, 146.4, 136.5, 127.4, 126.9, 124.9, 123.8, 121.2, 118.8, 118.2, 111.7, 109.2 (aromatic carbons), 57.0, 28.4 (aliphatic carbons). HRMS-ESI (m/z): 390.3285 $(M+H)^+$, calculated, 390.3289.

2.2.20 4-Methyl-2-nitrophenylsulphonamido)pentanoic acid (3t)

The amino acid was L-leucine, yield (2.8461 g, 99.98%), mp, 142.90-143.20 ^oC. FTIR (KBr, cm^{-1}): 3272 (NH), 3113, 3097, 3074 (C-H aromatic), 2934, 2878 (C-H aliphatic), 1714 (C=O), 1658, 1606, 1469 (C=C), 1531, 1417 (N-O), 1356, 1307 (2S=O), 1168, 1156 (SO_2NH), 1108, 1091, 1010 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.55-8.54 (d, J= 9.15 Hz, 1H, NH), 8.37-8.35 (d, J= 8.6 Hz, 2H, ArH), 7.99-7.97 (d, J= 8.6 Hz, 2H, ArH), 3.74-3.69 (m, 1H, CH-CO_2H), 1.59-1.53 (m, 1H, $CH(CH_3)_2$), 1.41-1.37 (m, 2H, CH_2), 0.81-0.71 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 173.4 (C=O), 149.9, 147.3, 128.7, 124.8 (aromatic carbons), 54.7, 41.2, 24.5, 23.1, 21.4 (aliphatic carbons). HRMS-ESI (m/z): 315.1265 $(M-H)^-$, calculated, 315.1268.

2.2.21 3-Methyl-2-(4-nitrophenylsulphonamido)pentanoic acid (3u)

The amino acid was L-isoleucine, yield (2.7894 g, 97.97%), mp, 131.40-131.70 ^oC. FTIR (KBr, cm^{-1}): 3271 (NH), 3110, 2967 (C-H aromatic), 2879, 2858 (C-H aliphatic), 1705 (C=O), 1647, 1607, 1472 (C=C), 1528, 1428 (N-O), 1361, 1351 (2S=O), 1175, 1142 (SO_2NH), 1092, 1011 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.43-8.42 (d, J= 9.15 Hz, 1H, NH), 8.36-8.34 (d, J= 8.60 Hz, 2H, ArH), 7.99-7.98 (d, J= 8.55 Hz, 2H, ArH), 3.62-3.59 (t, J= 6.00 Hz, 1H, CH-CO_2H), 1.68-1.65 (m, 1H, CH), 1.35-1.30 (m, 1H, CH_a of CH_2), 1.12-1.03 (m, 1H, CH_b of CH_2), 0.78-0.73 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 172.4 (C=O), 149.9, 147.2, 128.7, 124.8 (aromatic

carbons), 60.9, 37.3, 24.8, 15.9, 11.5 (aliphatic carbons). HRMS-ESI (m/z): 317.2387 $(M+H)^+$, calculated, 317.2393.

2.2.22 3-Methyl-2-(4-nitrophenylsulphonamido)butanoic acid (3v)

The amino acid was L-valine, yield (2.7200 g, 99.97 %), mp, 182.60-182.90 ^oC. FTIR (KBr, cm^{-1}): 3415 (OH CO_2H), 3278 (NH), 3113, 2969 (C-H aromatic), 2931, 2873 (C-H aliphatic), 1711 (C=O), 1638, 1607, 1411 (C=C), 1532, 1463 (N-O), 1356, 1312 (2S=O), 1169, 1146 (SO_2NH), 1107, 1091, 1062, 1013 (C-N, C-O). ^1H NMR (DMSO-d_6) δ: 8.44-8.42 (d, J= 9.15 Hz, 1H, NH), 8.36-8.34 (d, J= 8.6 Hz, 2H, ArH), 7.99-7.98 (d, J= 9.15 Hz, 2H, ArH), 3.58-3.55 (dd, J= 5.7, 6.3 Hz, 1H, CH-CO_2H), 1.98-1.91 (m, 1H, CH $(CH_3)_2$), 0.81-0.76 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 172.4 (C=O), 149.9, 147.3, 128.7, 124.8 (aromatic carbons), 61.9, 30.8, 19.6, 18.3 (aliphatic carbons). HRMS-ESI (m/z): 320. 1982 ($M+NH_4$), calculated, 320.1987.

2.2.23 4-Hydroxy-1-(4-nitrophenylsulphonyl)pyrrolidine-2-carboxylic acid (3w)

The amino acid was L-hydroxyproline, yield (2.8459 g, 99.97%), mp, 199.80-200.20 ^oC. FTIR (KBr, cm^{-1}): 3491 (OH), 3416 (OH of CO_2H), 3117, 3024 (C-H aromatic), 2966, 2767 (C-H aliphatic), 1750 (C=O), 1638, 1608, 1457 (C=C), 1527, 1427 (N-O), 1359, 1331 (2S=O), 1184, 1164 (SO_2N), 1136, 1112, 1090, 1015, 1005 (C-N, C-O). ^1H NMR (DMSO-d_6) δ: 8.38-3.36 (d, J= 9.15 Hz, 2H, ArH), 8.04-8.02 (d, J= 8.60 Hz, 2H, ArH), 4.17 (s, 1H, OH), 4.13-4.10 (t, J= 8.6 Hz, 1H, CH-CO_2H), 3.47-3.44 (dd, J= 3.45, 3.40 Hz, 1H, CHOH), 3.21-3.19 (d, J= 10.90 Hz, 2H, CH_2N), 2.04-2.00 (m, 1H, CH_a, CH_2), 1.93-1.88 (m, 1H, CH_b of CH_2). ^{13}C NMR (DMSO-d_6) δ: 173.5, 150.3, 143.6, 129.5, 124.8 (aromatic carbons), 69.0, 60.4, 57.1 (aliphatic carbons). HRMS-ESI (m/z): 303.2987 $(M+H)^+$, calculated, 303.2991.

2.2.24 1-(4-Nitrophenylsulphonyl)pyrrolidine-2-carboxylic acid (3x)

The amino acid was L-proline, yield (2.6051 g, 96.39%), mp, 149.90-150.30 ^oC. FTIR (KBr, cm^{-1}): 3415 (OH of CO_2H), 3111 (C-H aromatic), 2899, 2648 (C-H aliphatic), 1723 (C=O), 1641, 1604, (C=C), 1533, 1447 (N-O), 1353, 1305 (2S=O), 1199, 1165 (SO_2N), 1072, 1024, 1008 (C-N, C-O). ^1H NMR (DMSO-d_6) δ: 8.40-8.36 (m, 2H, ArH), 8.07-8.05 (m, 2H, ArH), 4.19-4.17 (m, 1H, CH-CO_2H), 3.40-3.36 (m, 1H, CH_a of CH_2), 3.23-3.18 (m, 1H, CH_b of CH_2), 1.99-1.92 (m, 1H, CH_a of CH_2), 1.87-1.76 (m, 2H, CH_2), 1.65-1.60 (m, 1H, CH). ^{13}C NMR (DMSO-d_6) δ: 173.4 (C=O), 150.4, 143.8, 129.2, 125.1 (aromatic carbons), 61.1, 48.9, 30.9, 24.7 (aliphatic carbons). HRMS-ESI (m/z): 301.3421 $(M+H)^+$, calculated, 301.3427.

2.3 General Procedure for the Synthesis of *N*-benzoyl Derivatives of Benzenesulphonamides (5a-f, i-n and q-v)

Appropriate benzenesulphonamides (**3a-f, i-n** and **q-v**, 1.0 mmol) was dissolved in NaOH (10%, 10 mL) in a 50 mL round bottom flask. Benzoyl chloride (**4,** 1.1 mmol, 0.2 mL) was transferred into the solution of appropriate benzenesulphonamide and stirred at room temperature. The reaction progress was monitored by TLC (3% MeOH/DCM) to the disappearance of the benzenesulphonamide spot. Upon completion, the solution was transferred into a beaker containing crushed ice and then acidified to pH of 3 with concentrated hydrochloric acid. The solid was collected via suction filtration and transferred into a beaker containing CCl_4 (10 mL) and covered with watch glass boiled for 10 min. the mixture was allowed to cool slightly and then filtered. The products (**5a-f, i-n** and **q-v**) obtained were washed with 10-20 mL of CCl_4 and dried over fused self-indicating silica gel in a dessicator.

2.3.1 {Benzoyl[(4-methylphenyl)sulfonyl]amino}acetic acid (5a)

Yield (0.3281 g, 98.49%), mp, 104.60-104.90 ^{o}C, FTIR (KBr, cm^{-1}): 3072 (C-H aromatic), 1729, 1687 (2C=O), 1601, 1583, 1453, 1423 (C=C), 1327, 1293 (2S=O), 1157, 1186 (SO_2N), 1128, 1094, 1073, 1001 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.65-7.63 (d, J=8.6 Hz, 2H, ArH), 7.57-7.43 (m, 5H, ArH), 7.34-7.33 (d, J=8.05 Hz, 2H, ArH), 3.52-3.51 (d, J=5.7 Hz, CH_2), 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ: 170.7, 167.8 (2C=O), 143.1, 138.4, 133.4, 131.3, 130.0, 129.8, 129.1, 127.1 (aromatic carbons), 44.3, 21.5 (aliphatic carbons). HRMS-ESI (m/z): 333.0679 (M^+), calculated, 333.0671.

2.3.2 2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]-3-phenylpropanoic acid (5b)

Yield (0.4201 g, 99.31%), mp, 100.50-100.80 ^{o}C, FTIR (KBr, cm^{-1}): 3443 (OH of CO_2H), 3072 (C-H aromatic), 1732, 1689 (2C=O), 1603, 1585, 1497, 1454, 1425 (C=C), 1344, 1327, (2S=O), 1187, 1168, 1158 (SO_2N), 1128, 1090, 1027 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.92-7.91 (m, 3H, ArH), 7.60-7.57 (t, J= 7.45 Hz, 2H, ArH), 7.48-7.41 (m, 5H, ArH), 7.20-7.15 (m, 3H, ArH), 7.09-7.07 (d, J= 7.45 Hz, 1H, ArH), 3.83-3.80 (t, J= 6.30 Hz, 1H, CH-CO_2H), 2.91-2.87 (dd, J= 5.75, 5.75 Hz, 1H, CH_a of CH_2), 2.70-2.65 (dd, J= 9.15, 8.55 Hz, 1H, CH_b of CH_2), 2.30 (s, 3H, CH_3-Ar). ^{13}C NMR (DMSO-d_6) δ: 172.8, 167.8 (2C=O), 142.8, 138.7, 137.3, 133.4, 133.2, 131.3, 129.8, 129.7, 129.1, 128.7, 127.0, 126.8 (aromatic carbons), 57.9, 38.4, 21.5 (aliphatic carbons). HRMS-ESI (m/z): 424.2150 (M+H), calculated, 424.2159.

2.3.3 3-(1*H*-indol-2-yl)-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]propanoic acid (5c)

Yield (0.4609 g, 99.74%), mp, 108.60-109.20 ^{o}C, FTIR (KBr, cm^{-1}): 3335 (NH), 3072 (C-H aromatic), 1761, 1688 (2C=O), 1619, 1602, 1584, 1454, 1424 (C=C), 1326, 1292 (2S=O), 1178, 1160 (SO_2N), 1128, 1073, 1027 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 10.73 (s, 1H, NH of indole), 7.92-7.91 (t, J= 7.45 Hz, 3H, ArH), 7.60-7.57 (t, J= 7.45 Hz, 2H, ArH), 7.48-7.42 (m, 5H, ArH), 7.27-7.23 (t, J= 8.60 Hz, 1H, ArH), 7.14-7.12 (d, J= 8.05 Hz, 1H, ArH), 7.02-6.99 (t, J= 7.45 Hz, 1H, ArH), 6.90-6.87 (t, J= 7.45 Hz, 1H, ArH), 3.87-3.82 (dd, J= 7.45, 8.05 Hz, 1H, ArH), 3.03-2.98 (dd, J= 6.30, 6.30 Hz, 1H, CH_a of CH_2), 2.83-2.79 (dd, J= 8.05, 8.00 Hz, 1H, CH_b of CH_2), 2.28 (s, 3H, CH_3-Ar). ^{13}C NMR (DMSO-d_6) δ: 173.1, 167.8 (2C=O), 142.7, 138.5, 136.6, 133.4, 131.3, 129.8, 129.6, 129.1, 127.4, 126.8, 124.4, 121.3, 118.8, 118.3, 111.9, 109.4 (aromatic carbons), 57.1, 28.8, 21.5 (aliphatic carbons). HRMS-ESI (m/z): 480.2135 (M+NH_4), calculated, 480.2132.

2.3.4 4-Methyl-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]pentanoic acid (5d)

Yield (0.3889 g, 99.92%), mp, 98.90-100.10 ^{o}C, FTIR (KBr, cm^{-1}): 3415 (OH of CO_2H), 2968 (C-H aromatic), 2676 (C-H aliphatic), 1705, 1688 (2C=O), 1619, 1602, 1584, 1454, 1424 (C=C), 1327, 1292 (2S=O), 1161, 1128 (SO_2N), 1091, 1073, 1027 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.92-7.90 (t, J= 6.90 Hz, 3H, ArH), 7.62-7.57 (m, 2H, ArH), 7.48-7.45 (t, J= 8.00 Hz, 3H, ArH), 7.32-7.31 (d, J= 8.00 Hz, 1H, ArH), 3.62-3.57 (dd, J= 8.05, 8.55 Hz, 1H, CH-CO_2H), 1.55-1.50 (m, 1H, CH), 1.36-1.30 (m, 2H, CH_2), 0.77-0.76 (d, J= 6.30 Hz, 3H, CH_3), 0.66-0.64 (d, J= 6.30 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ: 173.8, 167.8 (2C=O), 142.9, 138.9, 133.4, 131.3, 129.9, 129.8, 129.1, 127.0 (aromatic carbons), 54.5, 41.5, 24.4, 23.1, 21.6, 21.5 (aliphatic carbons). HRMS-ESI (m/z): 390.2354 (M+H), calculated, 390.2351.

2.3.5 3-Methyl-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]pentanoic acid (5e)

Yield (0.3890 g, 99.95%), mp, 98.10-98.50 ^{o}C, FTIR (KBr, cm^{-1}): 3415 (OH of CO_2H), 3072, 2970 (C-H of aromatic), 1707, 1688 (2C=O), 1602, 1584, 1496, 1454, 1424 (C=C), 1328, 1292 (2S=O), 1186, 1161 (SO_2N), 1128, 1092, 1073, 1027 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.92-7.87 (m, 3H, ArH), 7.62-7.57 (m, 2H, ArH), 7.48-7.45 (t, J= 8.00 Hz, 3H, ArH), 7.31-7.30 (d, J= 8.00 Hz, 1H, ArH), 3.49-3.48 (d, J= 2.3 Hz, 1H, CH-CO_2H), 2.33 (s, 3H, CH_3-Ar), 1.64-1.58 (m, 1H, CH), 1.34-1.27 (m, 1H, CH_a of CH_2), 1.09-1.00 (m, 1H, CH_b of CH_2), 0.76-0.70 (dt, J= 6.30, 6.90 Hz, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 172.7, 167.8 (2C=O), 142.9, 138.9, 133.4, 131.3, 129.8, 129.8, 129.1, 127.1 (aromatic carbons), 60.5, 37.5, 24.9, 21.5, 15.9, 11.4 (aliphatic carbons). HRMS-ESI (m/z): 388.0894 (M-H), calculated, 388.0892.

2.3.6 3-Methyl-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]butanoic acid acid (5f)

Yield (0.372 g, 99.20%), mp, 97.30-97.80 ^{o}C, FTIR (KBr, cm^{-1}): 3415 (OH, CO_2H), 2970 (C-H aliphatic), 1706, 1688 (2C=O), 1618, 1602, 1584, 1454, 1424 (C=C), 1328, 1292 (2S=O), 1185, 1161 (SO_2N), 1127, 1087, 1073 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.92-7.91 (d, J= 7.45 Hz, 2H, ArH), 7.63-7.57 (m, 4H, ArH), 7.48-7.45 (t, J= 8.00 Hz, 2H, ArH), 7.31-7.29 (d, J= 8.00 Hz), 3.45-3.44 (d, J= 4.60 Hz, 1H, CH-CO_2H), 1.90-1.85 (m, 1H, CH), 0.84-0.70 (m, 6H, CH_3). ^{13}C NMR (DMSO-d_6) δ: 172.7, 167.8 (2C=O), 142.9, 138.9, 133.4, 131.3, 129.8, 129.3, 129.1, 127.1 (aromatic carbons), 61.7, 30.9, 21.5, 19.5, 18.4 (aliphatic carbons). HRMS-ESI (m/z): 375.1148 (M^+), calculated, 375.1140.

2.3.7 2-[*N*-(benzenesulfonyl)-1-phenylformamido]acetic acid (5i)

Yield (0.2999 g, 93.92%), mp, 121.60-121.80 ^{o}C, FTIR (KBr, cm^{-1}): 3073, 3011 (C-H aromatic), 2837 (C-H aliphatic), 1732, 1688 (2C=O), 1619, 1603, 1584, 1454, 1425 (C=C), 1327, 1293 (2S=O), 1186, 1128 (SO_2N), 1101, 1073, 1027 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.92-7.90 (t, J= 8.20 Hz, 4H, ArH), 7.60-7.56 (m, 2H, ArH), 7.48-7.44 (t, J= 7.80 Hz, 4H, ArH), 3.54 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ: 174.7, 167.8 (2C=O) 154.1, 151.1, 133.4, 131.3, 129.8, 129.1, 119.4, 112.8 (eight aromatic carbons), 59.0 (aliphatic carbon). HRMS-ESI (m/z): 320.1628 (M+H), calculated, 320.1625.

2.3.8 2-[*N*-(benzenesulphonyl)-1-phenylformamido]-3-phenylpropanoic acid (5j)

Yield (0.4090 g, 99.90%), mp, 94.10-94.90 ^{o}C, FTIR (KBr, cm^{-1}): 3342 (OH of COOH), 3073, 3029 (C-H aromatic), 2968 (C-H aliphatic), 1735, 1688 (C=O), 1603, 1584, 1496, 1453, 1425 (C=C), 1376, 1348 (2S=O), 1170, 1108 (SO_2N), 1094, 1073, 1027, 1000 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.92-7.90 (d, J=8.00 Hz, 4H, ArH), 7.60-7.57 (t, J= 7.45 Hz, 2H, ArH), 7.54-7.50 (t, J= 8.00 Hz, 1H, ArH), 7.47-7.45 (m, 4H, ArH), 7.41-7.38 (t, J= 8.00 Hz, 1H, ArH), 7.17-7.13 (m, 2H, ArH), 7.09-7.08 (d, J= 6.30 Hz, 1H, ArH), 3.85-3.82 (t, J= 5.75 Hz, 1H, CH-COOH), 2.92-2.88 (dd, J= 5.70, 5.70 Hz, 1H, CH_a of CH_2), 2.70-2.65 (dd, J= 9.15, 9.15 Hz, 1H, CH_b of CH_2). ^{13}C NMR (DMSO-d_6) δ: 172.8, 167.8 (2C=O), 141.5, 137.2, 133.4, 132.6, 131.3, 129.8, 129.7, 129.4, 129.1, 128.7, 127.1, 126.7 (twelve aromatic carbons), 57.9, 38.3 (aliphatic carbons). HRMS-ESI (m/z): 410.1874 (M+H), calculated 410.1879.

2.3.9 2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-(1*H*-indol-2-yl)propanoic acid (5k)

Yield (0.4480 g, 99.89%), mp, 110.90-111.40 ^{o}C, FTIR (KBr, cm^{-1}): 3385 (OH of COOH), 3305 (NH of indole), 3072 (C-H of aromatic), 2839 (C-H aliphatic), 1747, 1687 (2C=O), 1602, 1584, 1454, 1425 (C=C), 1339, 1292 (2S=O), 1162, 1129 (SO_2N), 1083, 1027 (C-O, C-N). ^{1}H NMR (DMSOd_6) δ: 10.79 (s, 1H, NH), 7.92-7.90 (m, 3H, ArH), 7.60-7.56 (m, 2H, ArH), 7.49-7.45

(m, 3H, ArH), 7.38-7.35 (t, J= 7.45 Hz, 2H, ArH), 7.28-7.25 (m, 2H, ArH), 7.02-6.99 (t, J= 6.85 Hz, 2H, ArH), 6.91-6.88 (t, J= 7.45 Hz, 1H, ArH), 3.90-3.86 (dd, J= 7.45, 8.05 Hz, 1H, CH-COOH), 3.04-3.00 (dd, J= 6.85, 6.30 Hz, 1H, CH_a of CH_2), 2.84-2.80 (dd, J= 7.45, 7.45 Hz, 1H, CH_b of CH_2). ^{13}C NMR (DMSO-d_6) δ: 173.1, 167.9 (2C=O), 141.4, 136.6, 133.4, 132.6, 131.3, 129.8, 129.2, 129.1, 127.5, 126.7, 124.4, 121.4, 118.9, 118.4, 111.9, 109.4 (sixteen aromatic carbons), 57.2, 28.8 (aromatic carbons). HRMS-ESI (m/z): 449.2109 (M+H), calculated, 449.2111.

2.3.10 2-[*N*-(benzenesulfonyl)-1-phenylformamido]-4-methylpentanoic acid (5l)

Yield (0.3659 g, 97.86%), mp, 90.40-90.70 ^{o}C, FTIR (KBr, cm^{-1}): 3072 (C-H aromatic), 2959, 2874, 2838 (C-H aliphatic), 1721, 1687 (2C=O), 1603, 1584, 1454, 1426 (C=C), 1327, 1292 (2S=O), 1186, 1128 (SO_2N), 1093, 1074, 1027 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.92-7.90 (t, J= 8.60 Hz, 3H, ArH), 7.75-7.73 (d, J= 7.45 Hz, 1H, ArH), 7.59-7.56 (m, 2H, ArH), 7.53-7.50 (t, J= 8.05 Hz, ArH), 7.47-7.44 (t, J= 8.00 Hz, 3H, ArH), 3.64-3.59 (m, 1H, CH-COOH), 1.53-1.48 (m, 1H, CH), 1.38-1.29 (m, 2H, CH_2), 0.83-0.61 (m, 6H, CH_3). ^{13}C NMR (DMSO-d_6) δ: 173.8, 167.9 (2C=O), 141.6, 133.4, 132.8, 131.3, 129.8, 129.5, 129.1, 126.9 (eight aromatic carbons), 54.5, 41.4, 24.3, 23.1, 21.5 (five aliphatic carbons). HRMS-ESI (m/z): 376.2140 (M+H), calculated, 376.2144.

2.3.11 2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-methylpentanoic acid (5m)

Yield (0.3750 g, 99.89%), mp, 87.40-88.10 ^{o}C, FTIR (KBr, cm^{-1}): 3295 (OH of COOH), 3072 (C-H aromatic), 2969, 2883 (C-H aliphatic), 1723, 1698 (C=O), 1619, 1603, 1584, 1454, 1425 (C=C), 1327, 1293 (2S=O), 1169, 1129 (SO_2N), 1092, 1074, 1027 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.90-7.89 (d, J= 7.15 Hz, 2H, ArH), 7.73-7.72 (d, J= 7.15 Hz, 1H, ArH), 7.58-7.54 (m, 2H, ArH), 7.51-7.43 (m, 5H, ArH), 3.51-3.49 (t, J= 6.30 Hz, 1H, CH-COOH), 1.62-1.58 (m, 1H, CH), 1.30-1.25 (m, 1H, CH_a, CH_2), 1.06-0.99 (m, 1H, CH_b, CH_2), 0.73-0.72 (d, J= 6.90 Hz, 3H, $\underline{CH_3}$-CH), 0.68-0.66 (t, J= 7.45 Hz, 3H, $\underline{CH_3}$-CH_2). ^{13}C NMR (DMSO-d_6) δ: 172.7, 167.9 (2C=O), 141.5, 133.4, 132.8, 131.2, 129.8, 129.4, 129.1, 126.9 (eight aromatic carbons), 60.5, 37.4, 24.8, 15.8, 11.3 (five aliphatic carbons). HRMS-ESI (m/z): 376.2141 (M+H), calculated, 376.2146.

2.3.12 2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-methylpentanoic acid (5n)

Yield (0.3050 g, 84.37%), mp, 104.60-104.90 ^{o}C, FTIR (KBr, cm^{-1}): 3302 (OH of COOH), 3073, 2970 (C-H aromatic), 2877 (C-H aliphatic), 1734, 1688 (2C=O), 1603, 1584, 1454, 1425

(C=C), 1327, 1293 (2S=O), 1169, 1129 (SO_2N), 1128, 1093, 1074 (C-O, C-N). ^{1}H NMR (DMSO-d_6) δ: 7.92-7.91 (m, 3H, ArH), 7.75-7.73 (t, J= 7.45 Hz, 1H, ArH), 7.60-7.55 (m, 2H, ArH), 7.52-7.50 (d, J= 7.45 Hz, 1H, ArH), 7.49-7.45 (m, 3H, ArH), 3.50-3.48 (d, J= 6.30 Hz, 1H, CH-COOH), 1.91-1.86 (m, 1H, CH), 0.78-0.73 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 172.7, 167.8 (2C=O), 141.7, 133.4, 132.8, 131.3, 129.8, 129.4, 129.1, 127.0 (eight aromatic carbons), 61.8, 30.9, 19.5, 18.4 (aliphatic carbons). HRMS-ESI (m/z): 360.1984 (M-H), calculated, 360.1983.

2.3.13 2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]acetic acid (5q)

Yield (0.2126 g, 58.36%), mp, 135.00-135.50 ^{o}C, FTIR (KBr, cm^{-1}): 3310 (OH of COOH), 3073, 3009 (C-H aromatic), 2839 (C-H aliphatic), 1703, 1688 (2C=O), 1604, 1584, 1422 (C=C), 1527, 1454 (N-O), 1327, 1290 (2S=O), 1181, 1163 (SO_2N), 1128, 1106, 1074 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.37-8.35 (d, 8.60 Hz, 2H, ArH), 8.02-8.00 (d, J= 8.60 Hz, 2H, ArH), 7.92-7.90 (d, J= 6.85 Hz, 2H, ArH), 7.60-7.57 (t, J= 7.45 Hz, 1H, ArH), 7.48-7.45 (t, J= 8.05 Hz, 2H, ArH), 3.67 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ: 170.7, 167.8 (2C=O), 150.0, 147.0, 133.4, 131.3, 129.8, 129.1, 128.7, 124.9 (aromatic carbons), 44.3 (CH_2). HRMS-ESI (m/z): 363.0254 (M-H), calculated, 363.0265.

2.3.14 2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]-3-phenylpropanoic acid (5r)

Yield (0.4545 g, 100%), mp, 122.50-122.80 ^{o}C, FTIR (KBr, cm^{-1}): 3309 (OH of COOH), 3113, 3073, 3008 (C-H aromatic), 2840 (C-H aliphatic), 1703, 1685 (2C=O), 1604, 1584, 1454, 1421 (C=C), 1527 (N-O), 1327, 1289 (2S=O), 1181, 1163 (SO_2N), 1128, 1106 1074, 1027 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.17-8.15 (m, 2H, ArH), 7.92-7.89 (t, J= 7.36 Hz, 2H, ArH), 7.71-7.69 (m, 2H, ArH), 7.60-7.56 (m, 1H, ArH), 7.48-7.44 (m, 2H, ArH), 7.11-7.04 (m, 5H, ArH), 3.95-3.89 (m, 1H, CH-CO_2H), 2.97-2.92 (dd, J= 4.60, 4.56 Hz, 1H, CH_a of CH_2), 2.70-2.64 (dd, J= 10.08, 10.08 Hz, 1H, CH_b of CH_2). ^{13}C NMR (DMSO-d_6) δ: 172.7, 167.8 (2C=O), 149.6, 147.1, 137.2, 133.4, 131.3, 129.8, 129.7, 129.1, 128.6, 128.2, 126.9, 124.7 (twelve aromatic carbons), 58.2, 38.1 (two aliphatic carbons). HRMS-ESI (m/z): 455.1936 (M+H), calculated, 455.1940.

2.3.15 3-(1*H*-indol-2-yl)-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]propanoic acid (5s)

Yield (0.4932 g, 99.64%), mp, 153.30-153.90 ^{o}C, FTIR (KBr, cm^{-1}): 3448 (OH of COOH), 3294 (NH of indole), 3072 (C-H aromatic), 1705, 1688 (C=O), 1605, 1584, 1454, 1425 (C=C), 1525

(N-O), 1327, 1292 (2S=O),1179, 1167 (SO_2N), 1129, 1092, 1073, 1027 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 10.68 (s, 1H, NH of indole), 7.92-7.89 (m, 3H, ArH), 7.86-7.84 (m, 1H, ArH), 7.60-7.56 (m, 2H, ArH), 7.48-7.44 (m, 3H, ArH), 7.23-7.22 (d, J= 7.80 Hz, 1H, ArH), 7.05-7.03 (d, J= 7.80 Hz, 1H, ArH), 6.99-6.98 (d, J= 2.32 Hz, 1H, ArH), 6.89-6.81 (m, 2H, ArH), 3.90-3.86 (m, 1H, CH-COOH), 3.06-3.01 (dd, J= 4.12, 4.12 Hz, 1H, CH_a of CH_2), 2.81-2.75 (dd, J= 10.08, 10.56 Hz, 1H, CH_b of CH_2). ^{13}C NMR (DMSO-d_6) δ: 173.3, 167.8 (2C=O), 148.9, 144.7, 138.9, 136.5, 133.4, 132.8, 131.3, 129.8, 129.1, 127.3, 124.9, 123.8, 122.4, 118.8, 118.2, 111.7 (sixteen aromatic carbons), 46.4, 36.8 (two aliphatic carbons). HRMS-ESI (m/z): 494.1045 (M+H), calculated 494.1042.

2.3.16 3-Methyl-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]pentanoic acid (5t)

Yield (0.4201 g, 99.93%), mp, 110.40-110.60 ^{o}C, FTIR (KBr, cm^{-1}): 3293 (OH of COOH), 3117, 3072 (C-H aromatic), 2968, 2882 (C-H aliphatic), 1730, 1691 (2C=O), 1619, 1604, 1454, 1410 (C=C), 1531 (N-O), 1349, 1310 (2S=O), 1182, 1129 (SO_2N), 1105, 1073, 1027, 1012 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.36-8.34 (d, J= 8.68 Hz, 2H, ArH), 7.99-7.97 (d, J= 8.72 Hz, 2H, ArH), 7.91-7.89 (t, J= 7.32 Hz, 2H, ArH), 7.58-7.56 (t, J=7.32 Hz, 1H, ArH), 7.48-7.44 (t, J= 7.72 Hz, 2H, ArH), 3.60-3.59 (d, J= 2.28 Hz, CH-COOH), 1.70-1.64 (m, 1H, CH), 1.34-1.28 (m, 1H, CH_a of CH_2), 1.24-1.01 (m, 1H, CH_b of CH_2), 0.78-0.72 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 172.4, 167.8 (2C=O), 149.9, 147.2, 133.4, 131.3, 129.8, 129.1, 128.7, 124.8 (eight aromatic carbons) 60.9, 37.3, 24.8, 15.9, 11.5 (five aliphatic carbons). HRMS-ESI (m/z): 420.0995 (M^+), calculated, 420.0991.

2.3.17 4-Methyl-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]pentanoic acid (5u)

Yield (0.4204 g, 100%), mp, 116.30-116.70 ^{o}C, FTIR (KBr, cm^{-1}):3412 (OH of COOH), 2960 (C-H aliphatic), 1721, 1689 (2C=O), 1603, 1584, 1454, 1410 (C=C), 1531 (N-O), 1348, 1323 (2S=O), 1177, 1149 (SO_2N), 1126, 1091, 1074, 1026 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.36-8.34 (d, J= 8.72 Hz, 2H, ArH), 7.99-7.96 (d, J= 9.16 Hz, 2H, ArH), 7.91-7.89 (t, J= 6.88 Hz, 2H, ArH), 7.60-7.56 (t, J= 7.36 Hz, 1H, ArH), 7.48-7.44 (m, 2H, ArH), 3.76-3.70 (t, J= 5.48 Hz, 1H, CH-COOH), 1.59-1.52 (m, 1H, CH_a of CH_2), 1.43-1.34 (m, 1H, CH_b of CH_2), 0.80-0.79 (d, J= 6.44 Hz, 3H, CH_3), 0.71-0.70 (d, J= 6.40 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ: 173.3, 167.8 (2C=O), 149.9, 147.3, 133.4, 131.3, 129.8, 129.1, 128.7, 124.9 (eight aromatic carbons), 54.7, 41.2, 24.4, 23.1, 21.4 (five aliphatic carbons). HRMS-ESI (m/z): 420.0999 (M^+), calculated, 420.0991.

2.3.18 3-Methyl-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]butanoic acid (5v)

Yield (0.4063 g, 99.98%), mp, 114.10-114.40 ^{o}C, FTIR (KBr, cm^{-1}): 3277 (OH of COOH), 3112, 3073 (C-H aromatic), 2969, 2874 (C-H aliphatic), 1710, 1687 (2C=O), 1606, 1584, 1454, 1424 (C=C), 1532 (N-O), 1356, 1327 (2S=O), 1169, 1146 (SO_2N), 1129, 1091, 1063, 1027, 1013, 1000 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.36-8.33 (d, J=9.16 Hz, 2H, ArH), 8.01-7.99 (d, J=8.72 Hz, 2H, ArH), 7.91-7.89 (t, J= 6.88 Hz, 2H, ArH), 7.60-7.56 (t, J= 7.32 Hz, 2H, ArH), 7.48-7.44 (m, 2H, ArH), 3.57-3.56 (d, J= 2.76Hz, 1H, CH-COOH), 1.98-1.90 (m, 1H, CH), 0.81-0.75 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 172.4, 167.8 (2C=O), 149.9, 147.3, 133.4, 131.3, 129.8, 129.1, 128.7, 124.8 (eight aromatic carbons), 61.9, 30.8, 19.6, 18.3 (four aliphatic carbons). HRMS-ESI (m/z): 405.0732 (M-H), calculated, 405.0736.

2.4 Boric acid catalysed Synthesis of Carboxamide derivatives from carboxylic acid and 4-aminoacetophenone

To a suspension of *N*-benzoyl-substituted-benzenesulphonamides (**5a-f, i-n** and **q-v**, 1.0 mmol) or proline derived benzenesulphonamide (**3g-h, 3o-p** and **3w-x**, 1.0 mmol) in dry toluene (40 mL) equipped with Dean-Stark apparatus for azeotropic removal of water, was added 4-aminoacetophenone (**6,** 1.0 mmol) and boric acid (0.1 mmol) at room temperature and then refluxed for 10 h. On completion (as monitored by TLC), reaction mixture was precipitated into amides by adding about 40 mL *n*-hexane. The carboxamides (**7a-x**) 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.

2.4.1 *N*-(4-acetylphenyl)-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]acetamide (7a)

Yield (0.4500 g, 99.98%), mp, 137.60-137.80 ^{o}C, FTIR (KBr, cm^{-1}): 3226 (NH), 2919 (C-H aliphatic), 1771, 1754, 1682 (3C=O), 1628, 1597, 1517, 1444 (C=C), 1318, 1279 (2S=O), 1196, 1154 (SO_2N), 1094, 1074, 1039, 1016 (C-O, C-N). ^{1}H NMR (DMSO-d_6) δ: 7.68-7.58 (m, 5H, ArH), 7.34-7.29 (m, 3H, ArH), 7.23-7.20 (t, J= 7.45 Hz, 1H, ArH), 7.15-7.10 (m, 2H, ArH), 6.53-6.51 (d, J= 8.6 Hz, 2H, ArH), 3.50 (s, 2H, CH_2), 2.34 (s, 3H, CH_3-C=O), 2.33 (s, 3H, CH_3-Ar). ^{13}C NMR (DMSO-d_6) δ: 187.6, 171.4, 167.5 (3C=O), 143.1, 142.5, 138.2, 131.1, 130.0, 129.7, 129.4, 128.7, 127.5, 127.1, 125.8, 112.9 (twelve aromatic carbons), 48.4, 26.3, 21.3 (three aliphatic carbons). HRMS-ESI (m/z): 450.1498 (M^+), calculated, 450.1499.

2.4.2 *N*-(4-acetylphenyl)-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]-3-phenyl propanamide (7b)

Yield (0.2425 g, 89.78%), mp, 84.20-84.60 ^{o}C, FTIR (KBr, cm^{-1}): 3394 (NH), 3026 (C-H aromatic), 2926 (C-H aliphatic), 1713, 1693, 1639 (3C=O), 1595, 1965, 1516, 1425 (C=C),

1344, 1331 (2S=O), 1178, 1167 (SO_2N), 1090 (C-O, C-N). ^{1}H NMR (DMSO-d_6) δ: 7.91-7.90 (d, J= 6.85 Hz, 1H, ArH), 7.78-7.77 (d, J= 8.05 Hz, 2H, ArH), 7.69-7.68 (d, J= 8.00 Hz, 1H, ArH), 7.63-7.57 (m, 2H, ArH), 7.48-7.40 (m, 2H, ArH), 7.33-7.32 (d, J= 8.00 Hz, 2H), 7.25-7.05 (m, 5H, ArH), 6.92-6.90 (m, 1H, ArH), 6.53-6.52 (d, J= 8.60 Hz, 2H, ArH), 6.47 (s, 1H, NH), 3.55-3.53 (dd, J= 2.85, 2.90 Hz, 1H, CH), 3.16-3.11 (dd, J= 9.75, 10.30 Hz, 1H, CH_a of CH_2), 2.91-2.87 (dd, J= 4.60, 6.85 Hz, 1H, CH_b of CH_2), 2.34 (s, 3H, $\underline{CH_3}$-C=O), 2.30 (s, 3H, $\underline{CH_3}$-Ar). ^{13}C NMR (DMSO-d_6) δ: 195.5 (C=O of acetophenone), 172.8 (C=O of carboxamide), 167.8 (C=O of benzamide), 154.2, 142.8, 138.7, 137.3, 133.4, 131.3, 131.1, 129.8, 129.7, 129.4, 129.1, 128.7, 127.0, 126.8, 125.4, 113.0 (sixteen aromatic carbons), 57.9, 38.4, 26.4, 21.5 (four aliphatic carbons). HRMS-ESI (m/z): 540.1256 (M^+), calculated, 540.1258.

2.4.3 *N*-(4-acetylphenyl)-3-(1*H*-indol-2-yl)-2-[*N*-(4-methylbenzenesulphonyl)-1-phenyl formamido]propanamide (7c)

Yield (0.5001 g, 86.34%), mp, 121.40-121.90 ^{o}C, FTIR (KBr, cm^{-1}): 3366, 3223 (2NH), 1753, 1728, 1623 (3C=O), 1595, 1517, 1493, 1458 (C=C), 1360, 1318 (2S=O), 1179, 1156 (SO_2N), 1091, 1018 (C-O, C-N). ^{1}H NMR (DMSO-d_6) δ: 10.72 (s, 1H, NH of indole), 8.10 (s, 1H, NH of amide), 7.93-7.92 (d, J= 7.45 Hz, 1H, ArH), 7.65-7.63 (d, 8.60 Hz, 3H, ArH), 7.46-7.42 (m, 3H, ArH), 7.29-7.23 (m, 3H, ArH), 7.11-7.10 (d, J= 8.00 Hz, 2H, ArH), 7.03-6.99 (m, 2H, ArH), 6.90-6.87 (t, J= 7.45 Hz, 1H, ArH), 6.57-6.56 (d, J= 8.55 Hz, 3H, ArH), 3.88-3.85 (t, J= 6.85 Hz, 1H, CH-C=O), 3.06-3.02 (dd, J= 6.30, 6.30 Hz, 1H, CH_a of CH_2), 2.86-2.81 (dd, J= 8.00, 7.45 Hz, 1H, CH_b of CH_2), 2.34 (s, 3H, CH_3-C=O), 2.2424 (CH_3-Ar). ^{13}C NMR (DMSO-d_6) δ: 196.1 (C=O of acetophenone), 173.3 (C=O of carboxamide), 168.0 (C=O of benzamide), 154.1, 142.9, 138.2, 136.6, 133.4, 131.2, 129.9, 129.8, 129.4, 129.1, 127.4, 126.8, 125.5, 124.5, 121.5, 118.9, 118.3, 113.2, 111.9, 109.3 (twenty aromatic carbons), 57.1, 28.8, 26.3, 21.4 (four aliphatic carbons). HRMS-ESI (m/z): 579.1476 (M^+), calculated, 579.1475.

2.4.4 *N*-(4-acetylphenyl)-4-methyl-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido] pentanamide (7d)

Yield (0.3562 g, 70.36%), mp, 129.50-130.10 ^{o}C, FTIR (KBr, cm^{-1}): 3368 (NH), 3062 (C-H aromatic), 2957, 2869 (C-H aliphatic), 1725, 1698, 1678 (3C=O), 1598, 1556, 1517, 1496, 1451 (C=C), 1316, 1289 (2S=O), 1179, 1156 (SO_2N), 1092, 1069, 1039, 1017 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.92-7.90 (d, J= 7.80 Hz, 1H, ArH), 7.74-7.70 (t, J= 8.28 Hz, 1H, ArH), 7.62-7.56 (m, 3H, ArH), 7.50-7.44 (m, 3H, ArH), 7.32-7.08 (m, 5H, ArH), 6.69-6.67 (d, J= 8.24 Hz, 1H, ArH), 3.60-3.57 (t, J= 3.2 Hz, 1H, $\underline{CH}$-C=O), 2.31 (s, 3H, $\underline{CH_3}$-C=O), 2.25 (s, 3H, $\underline{CH_3}$-Ar), 1.57-1.53 (m, 1H, CH), 1.36-1.33 (m, 2H, CH_2), 0.80-0.64 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 195.5 (C=O of acetophenone), 173.8 (C=O of carboxamide), 167.8 (C=O of benzamide),

154.1, 142.9, 138.8, 137.9, 133.4, 129.8, 129.4, 129.1, 128.7, 128.0, 127.0, 125.8 (twelve aromatic carbons), 54.4, 41.4, 26.4, 24.4, 23.1, 21.6 (six aliphatic carbons). HRMS-ESI (m/z): 506.1417 (M^+), calculated, 506.1423.

2.4.5 *N*-(4-acetylphenyl)-3-methyl-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido] pentanamide (7e)

Yield (0.4201 g, 82.99%), mp, 64.90-65.30 ^oC, FTIR (KBr, cm^{-1}): 3398 (NH), 3274 (C-H aromatic), 2970 (C-H aliphatic), 1752, 1697, 1641 (3C=O), 1598, 1454, 1418 (C=C), 1335, 1284 (2S=O), 1178, 1162 (SO_2N), 1128, 1092, 1074, 1026 (C-N, C-O). ^1H NMR (DMSO-d_6) δ: 7.92-7.88 (m, 3H, ArH), 7.63-7.56 (m, 5H, ArH), 7.48-7.44 (t, J= 7.80 Hz, 2H, ArH), 7.31-7.29 (d, J= 8.24 Hz, 1H, ArH), 6.53-6.51 (d, J= 8.72 Hz, 2H, ArH), 3.51-3.47 (m, 1H, CH-C=O), 1.64-1.59 (m, 1H, CH), 1.34-1.27 (m, 1H, CH_a of CH_2), 1.08-1.01 (m, 1H, CH_b of CH_2), 0.75-0.68 (dt, J=6.88, 7.36 Hz, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 195.4 (C=O of acetophenone), 172.7 (C=O of carboxamide), 167.8 (C=O of benzamide), 154.1, 142.9, 138.8, 133.4, 131.3, 131.1, 129.8, 129.8, 129.1, 127.1, 125.4, 112.9 (twelve aromatic carbons), 60.5, 37.4, 26.4, 24.9, 21.5, 15.9, 11.4 (seven aliphatic carbons). HRMS-ESI (m/z): 506.1366 (M^+), calculated, 506.1363.

2.4.6 *N*-(4-acetylphenyl)-3-methyl-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido] butanamide (7f)

Yield (0.3899 g, 79.22%), mp, 75.20-75.90 ^oC, FTIR (KBr, cm^{-1}): 3395 (NH), 2970 (C-H aliphatic), 1708, 1653, 1640 (3C=O), 1592, 1564, 1518, 1495, 1466, 1437 (C=C), 1361, 1333 (2S=O), 1179, 1161 (SO_2N), 1090, 1020 (C-N, C-O). ^1H NMR (DMSO-d_6) δ: 7.92-7.85 (m, 2H, ArH), 7.63-7.56 (m, 5H, ArH), 7.48-7.44 (t, J= 7.80 Hz, 1H, ArH), 7.31-7.29 (d, J= 8.24 Hz, 2H, ArH), 6.53-6.51 (d, J= 8.72 Hz, 3H, ArH), 5.98 (s, 1H, NH), 3.45-3.43 (d, J= 5.96 Hz, 1H, CH-C=O), 2.33 (s, 3H, CH_3-C=O), 2.32 (s, 3H, CH_3-Ar), 1.92-1.83 (m, 1H, CH), 0.78-0.73 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 195.4 (C=O of acetophenone), 172.7 (C=O of carboxamide), 167.8 (C=O of benzamide), 154.1, 147.5, 142.9, 138.9, 133.4, 131.3, 131.1, 129.8, 129.1, 127.1, 125.4, 112.9 (twelve aromatic carbons), 61.8, 30.9, 26.4, 21.5, 19.5, 18.4 (six aliphatic carbons). HRMS-ESI (m/z): 492.1716 (M^+), calculated, 492.1718.

2.4.7 *N*-(4-acetylphenyl)-4-hydroxy-1-(4-methylbenzenesulfonyl)pyrrolidine-2-carboxamide (7g)

Yield (0.4000 g, 99.48%), mp, 122.20-122.70 ^oC, FTIR (KBr, cm^{-1}): 3454 (OH), 3390 (NH), 2985, 2960, 2738 (C-H aliphatic), 1757, 1638 (2C=O), 1598, 1496, 1469, 1448, 1402 (C=C), 1345, 1330 (2S=O), 1180, 1156 (SO_2N), 1126, 1091, 1071, 1017 (C-N, C-O). ^1H NMR (DMSO-d_6) δ: 7.65-7.61 (m, 2H, ArH), 7.37-7.35 (d, J=7.80 Hz, 2H, ArH), 7.19-7.12 (m, 2H, ArH),

6.52-6.51 (d, J= 7.32 Hz, 2H, ArH), 4.17 (s, 1H, OH), 4.01-3.98 (t, J= 7.80 Hz, 1H, CH-C=O), 3.43-3.39 (m, 1H, CH-OH), 3.06-3.03 (d, J= 10.56 Hz, 2H, CH_2-N), 2.35 (s, 3H, CH_3-C=O), 2.34 (s, 3H, CH_3-Ar), 1.92-1.86 (m, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ: 195.5 (C=O of acetophenone), 173.8 (C=O of carboxamide), 154.1, 143.7, 134.9, 131.1, 130.1, 127.9, 125.3, 112.9 (eight aromatic carbons), 68.9, 60.2, 56.8, 26.4, 21.5 (five aliphatic carbons). HRMS-ESI (m/z): 403.1303 (M+H), calculated, 403.1304.

2.4.8 *N*-(4-acetylphenyl)-1-(4-methylbenzenesulfonyl)pyrrolidine-2-carboxamide (7h)

Yield (0.3808 g, 98.63%), oil, FTIR (KBr, cm^{-1}): 3376 (NH), 3233 (C-H aromatic), 1737, 1629 (C=O), 1596, 1495, 1443 (C=C), 1339, 1307 (2S=O), 1178, 1158 (SO_2N), 1094, 1011 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.67-7.62 (m, 4H, ArH), 7.37-7.35 (d, J= 8.28 Hz, 2H, ArH), 6.55-6.53 (d, J= 8.68 Hz, 2H, ArH), 4.04-4.02 (m, 1H, CH-C=O), 3.32-3.27 (m, 1H, CH_a of CH_2N), 3.11-3.05 (m, 1H, CH_b of CH_2N), 2.33 (s, 3H, CH_3-C=O), 2.23 (s, 3H, CH_3-Ar), 1.84-1.70 (m, 3H), 1.50-1.46 (m, 1H). ^{13}C NMR (DMSO-d_6) δ: 195.6 (C=O of acetophenone), 173.8 (C=O of carboxamide), 154.1, 144.2, 135.1, 131.1, 130.3, 127.7, 125.4, 113.0 (eight aromatic carbons), 60.9, 48.9, 30.9, 26.3, 24.7, 21.5 (six aliphatic carbons). HRMS-ESI (m/z): 387.1375 (M+H), calculated, 387.1374.

2.4.9 *N*-(4-acetylphenyl)-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]acetamide (7i)

Yield (0.4791 g, 99.58%), mp, 99.10-99.70 ^{o}C FTIR (KBr, cm^{-1}): 3372 (NH), 1736, 1700, 1667 (3C=O), 1594, 1412 (2S=O), 1528 (NO_2), 1350, 1311 (2S=O), 1165, 1108 (SO_2N), 1091, 1108 (C-N). ^{1}H NMR (DMSO-d_6) δ: 8.36-8.34 (m, 4H, ArH), 8.02-7.99 (t, J= 6.88 Hz, 5H), 7.63-7.60 (d, J= 8.20 Hz, 2H), 6.52-6.50 (d, J= 8.72 Hz, 2H, ArH), 5.97 (s, 1H, NH), 3.66 (s, 2H, CH_2), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ: 195.6 (C=O of acetophenone), 170.7 (C=O of carboxamide), 167.4 (C=O of benzamide), 154.1, 149.9, 146.9, 146.1, 131.1, 129.4, 128.9, 128.7, 128.6, 125.8, 124.9, 124.7, 113.0 (twelve aromatic carbons), 44.2, 26.4 (two aliphatic carbons). HRMS-ESI (m/z): 504.2429 (M+Na), calculated, 504.2431.

2.4.10 *N*-(4-acetylphenyl)-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]-3-phenyl propanamide (7j)

Yield (0.5621 g, 98.42%), mp, 105.70-106.20 ^{o}C FTIR (KBr, cm^{-1}): 3371 (NH), 3104 (C-H aromatic), 1746, 1700, 1675 (3C=O), 1594, 1454 (C=C), 1527 (NO_2), 1349, 1307 (2S=O), 1177, 1161 (SO_2N), 1092, 1064, 1043 (C-N). ^{1}H NMR (DMSO-d_6) δ: 8.36-8.34 (d, J= 8.60 Hz, 1H, ArH), 8.18-8.09 (m, 2H, ArH), 7.96-7.91 (m, 1H, ArH), 7.72-7.63 (m, 2H, ArH), 7.24-7.20 (m, 4H, ArH), 7.17-7.09 (m, 4H, ArH), 7.04-7.03 (d, J= 5.15 Hz, 2H, ArH), 6.90-6.88 (m, 1H, ArH), 6.56-6.54 (d, J= 8.55 Hz, 1H, ArH), 3.79-3.76 (dd, J= 8.60 Hz, 3.40 Hz, 1H, CH-C=O), 3.25-3.20 (dd, J= 9.70, 5.10 Hz, 1H, CH_a, CH_2), 3.00-2.95 (dd, J= 8.00, 11.45 Hz, 1H, CH_b of CH_2),

2.26 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ: 196.1 (C=O of acetophenone), 173.1 (C=O of carboxamide), 165.1 (C=O benzamide), 138.9, 137.9, 136.8, 131.1, 129.9, 129.7, 129.4, 129.2, 128.7314, 128.6, 128.2, 125.8, 124.8, 124.7, 124.4, 113.3 (sixteen aromatic carbons), 60.4, 35.5, 26.4 (three aliphatic carbons). HRMS-ESI (m/z): 571.1119 (M^+), calculated, 571.1123.

2.4.11 *N*-(4-acetylphenyl)-3-(1*H*-indol-2-yl)-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenyl formamido]propanamide (7k)

Yield (0.6100 g, 99.97%), mp, 202.20-202.80 ^{o}C FTIR (KBr, cm^{-1}): 3447 (NH of indole), 3381 (NH of carboxamide), 3108 (C-H aromatic), 2926 (C-H aliphatic), 1710, 1689, 1621 (3C=O), 1595, 1557, 1459, 1424 (C=C), 1526 (NO_2), 1348, 1312 (2S=O), 1178, 1167 (SO_2N), 1093, 1013 (C-N). ^{1}H NMR (DMSO-d_6) δ: 10.65 (s, 1H, NH), 8.62-8.60 (d, J= 8.24 Hz, 2H, ArH), 7.91-7.84 (m, 3H, ArH), 7.76-7.70 (m, 1H, ArH), 7.63-7.61 (d, J 8.72 Hz, 1H, ArH), 7.47-7.45 (d, J= 8.72 Hz, 2H, ArH), 7.24-7.22 (d, J= 7.80 Hz, 1H, ArH), 7.14-6.99 (m, 3H, ArH), 6.88-6.74 (m, 3H, ArH), 6.53-6.51 (d, J= 8.72 Hz, 2H, ArH), 3.91-3.87 (dd, J= 9.64, 5.96 Hz, 1H, CH-C=O), 3.06-3.01 (dd, J= 4.16, 3.64 Hz, 1H, CH_a of CH_2), 2.81-2.75 (dd, J= 10.52, 10.52 Hz, 1H, CH_b of CH_2), 2.33 (s, 3H, CH_3-C=O). ^{13}C NMR (DMSO-d_6) δ: 195.4 (C=O of acetophenone), 173.3 (C=O of carboxamide), 164.9 (C=O of benzamide), 148.9, 146.4, 140.8, 138.9, 136.5, 135.2, 133.7, 131.1, 129.4, 127.4, 126.9, 124.9, 123.8, 121.2, 118.8, 118.2, 115.8, 113.1, 111.7, 109.2 (twenty aromatic carbons), 57.1, 28.4, 26.4 (three aliphatic carbons). HRMS-ESI (m/z): 628.1016 ($M+NH_4$), calculated, 628.1018.

2.4.12 *N*-(4-acetylphenyl)-4-methyl-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido] pentanamide (7l)

Yield (0.5092 g, 94.79%), mp, 126.70-126.90 ^{o}C FTIR (KBr, cm^{-1}): 3373 (NH), 3232 (C-H aromatic), 2958, 2870 (C-H aliphatic), 1742, 1698, 1656 (3C=O), 1596, 1556, 1467 (C=C), 1528 (NO_2), 1350, 1307 (2S=O), 1181, 1163 (SO_2N), 1090, 1064, 1012 (C-N). ^{1}H NMR (DMSO-d_6) δ: 8.37-8.32 (m, 4H, ArH), 8.06-7.98 (m, 3H, ArH), 7.65-7.63 (d, J= 8.60 Hz, 2H, ArH), 7.23-7.11 (m, 3H, ArH), 6.57-6.55 (d, J= 8.60 Hz, 2H, ArH), 3.99-3.97 (t, J= 3.50 Hz, 1H, CH-C=O), 3.53-3.50 (m, 1H, $\underline{CH}(CH_3)_2$), 2.35 (s, 3H, CH_3-C=O), 1.76-1.71 (m, 1H, CH_a of CH_2), 1.45-1.35 (m, 1H, CH_b of CH_2), 0.84-0.68 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 195.5 (C=O of acetophenone), 173.6 (C=O of carboxamide), 166.8 (C=O of benzamide), 153.5, 149.9, 149.6, 146.8, 131.1, 129.4, 129.2, 128.7, 125.8, 124.9, 124.7, 113.4 (twelve aromatic carbons), 58.9, 26.4, 24.8, 23.9, 21.9 (five aliphatic carbons). HRMS-ESI (m/z): 560.1337 (M+Na), calculated, 560.1339.

2.4.13 *N*-(4-acetylphenyl)-3-methyl-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido] pentanamide (7m)

Yield (0.5184 g, 96.50%), mp, 142.90-143.20 ^{o}C FTIR (KBr, cm^{-1}): 3373 (NH), 2968, 2887 (C-H aliphatic), 1745, 1688, 1666 (3C=O), 1596, 1556, 1467 (C=C), 1523 (NO_2), 1350, 1307 (2S=O), 1181, 1163 (SO_2N), 1090, 1064 (C-N). ^{1}H NMR (DMSO-d_6) δ: 8.44-8.30 (m, 3H, ArH), 8.08-7.98 (m, 3H, ArH), 7.64-7.62 (d, J= 5.04 Hz, 1H, ArH), 7.21-7.09 (m, 2H, ArH), 6.57-6.55 (d, J= 8.24 Hz, 2H, ArH), 3.61-3.59 (t, J= 3.24 Hz, 1H, CH-C=O), 2.34 (s, 3H, CH_3-C=O), 1.71-1.64 (m, 1H, CH), 1.35-1.29 (m, 1H, CH_a of CH_2), 1.11-1.03 (m, 1H, CH_b of CH_2), 0.81-0.71 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 195.6 (C=O of acetophenone), 172.4 (C=O of carboxamide), 167.9 (C=O of benzamide), 153.5, 149.9, 149.6, 147.2, 137.9, 131.1, 129.4, 128.7, 125.8, 124.8, 124.5, 113.4 (twelve aromatic carbons), 60.9, 37.3, 26.4, 24.8, 15.9, 11.4 (six aliphatic carbons). HRMS-ESI (m/z): 537.1220 (M^+), calculated, 537.1224.

2.4.14 *N*-(4-acetylphenyl)-3-methyl-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido] butanamide (7n)

Yield (0.5209 g, 99.58%), mp, 187.50-187.70 ^{o}C FTIR (KBr, cm^{-1}): 3376 (NH), 2968, 2887 (C-H aliphatic), 1745, 1688, 1666 (3C=O), 1596, 1556, 1467 (C=C), 1523 (NO_2), 1350, 1307 (2S=O), 1181, 1163 (SO_2N), 1090, 1064 (C-N). ^{1}H NMR (DMSO-d_6) δ: 8.43-8.30 (m, 5H, ArH), 8.07-7.98 (m, 4H, ArH), 7.63-7.61 (d, J= 8.72 Hz, 2H, ArH), 6.53-6.51 (d, J= 8.72 Hz, 2H, ArH), 3.53-3.55 (m, 1H, CH-C=O), 2.34 (s, 3H, CH_3-C=O), 1.98-1.92 (m, 1H, $CH(CH_3)_2$), 0.80-0.75 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 196.0 (C=O of acetophenone), 172.4 (C=O of carboxamide), 169.4 (C=O of benzamide), 153.9, 149.9, 149.5, 147.2, 131.1, 128.7, 128.6, 126.7, 124.8, 124.5, 119.4, 113.1 (twelve aromatic carbons), 61.9, 30.8, 26.1, 19.6, 18.3 (five aliphatic carbons). HRMS-ESI (m/z): 523.1476 (M^+), calculated, 523.1473.

2.4.15 *N*-(4-acetylphenyl)-4-hydroxy-1-(4-nitrobenzenesulfonyl)pyrrolidine-2-carboxamide (7o)

Yield (0.4331 g, 100%), mp, 160.80-161.20 ^{o}C FTIR (KBr, cm^{-1}): 3480 (OH), 3415 (NH), 3115 (C-H aromatic), 1748, 1689 (2C=O), 1595, 1403 (C=C), 1527 (NO_2), 1358, 1332 (2S=O), 1184, 1162 (SO_2N), 1090, 1070, 1016, 1006 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 8.37-8.27 (m, 2H, ArH), 8.04-8.01 (d, J= 8.72 Hz, 2H, ArH), 7.63-7.60 (d, J= 8.72 Hz, 1H, ArH), 7.22-7.10 (m, 2H, ArH), 6.56-6.50 (m, 1H, ArH), 5.98 (s, 1H, NH), 4.22 (s, 1H, OH), 4.12-4.08 (t, J= 7.76 Hz, 1H, CH-C=O), 3.46-3.43 (m, 1H, CH-OH), 3.21-3.18 (d, J= 11.00 Hz, 2H, CH_2-N), 2.33 (s, 3H, CH_3-C=O), 2.03-1.99 (t, J= 7.76 Hz, 1H, CH_a of CH_2CHN), 1.93-1.86 (m, 1H, CH_b of CH_2CHN). ^{13}C NMR (DMSO-d_6) δ: 195.5 (C=O of acetophenone), 173.5 (C=O of carboxamide), 150.3, 143.6, 131.1, 129.5, 128.7, 125.8, 124.8, 112.9 (eight aromatic carbons), 69.0, 60.5, 57.1, 26.4, 21.6 (five aliphatic carbons). HRMS-ESI (m/z): 456.2067 (M+Na), calculated, 456.2069.

2.4.16 *N*-(4-acetylphenyl)-1-(4-nitrobenzenesulfonyl)pyrrolidine-2-carboxamide (7p)

Yield (0.4170 g, 99.98%), mp, 99.30-99.90 ^{o}C FTIR (KBr, cm^{-1}): 3378 (NH), 3105 (C-H aromatic), 2957 (C-H aliphatic), 1732, 1684 (2C=O), 1597, 1446, 1402 (C=C), 1529 (NO_2), 1350, 1310 (2S=O), 1162, 1092 (SO_2N), 1010 (C-N). ^{1}H NMR (DMSO-d_6) δ: 8.38-8.29 (m, 2H, ArH), 8.07-8.05 (d, J= 8.68 Hz, 2H, ArH), 7.22-7.08 (m, 4H, ArH), 6.28 (s, 1H, NH), 4.18-4.15 (dd, J= 3.68, 3.68 Hz, 1H, CH-C=O), 3.39-3.34 (t, J= 5.04 Hz, 1H, CH_a of CH_2N), 3.23-3.17 (dd, J= 7.36, 6.88 Hz, 1H, CH_b of CH_2N), 2.25 (s, 3H, CH_3-C=O), 1.99-1.92 (m, 1H, CH_a of CH_2CHC=O), 1.84-1.77 (m, 2H, CH_2), 1.63-1.60 (m, 1H, CH_b of CH_2CHC=O). ^{13}C NMR (DMSO-d_6) δ: 198.4 (C=O of acetophenone), 173.5 (C=O of carboxamide), 150.4, 143.9, 137.9, 131.1, 129.4, 129.2, 128.7, 125.8, 125.1, 112.9 (ten aromatic carbons), 61.2, 48.9, 30.9, 24.7, 21.6 (five aliphatic carbons). HRMS-ESI (m/z): 416.0919 (M-H), calculated, 416.0923.

2.4.17 *N*-(4-acetylphenyl)-2-[*N*-(benzenesulfonyl)-1-phenylformamido]acetamide (7q)

Yield (0.4005 g, 91.75%), mp, 150.40-150.70 ^{o}C, FTIR (KBr, cm^{-1}): 3361 (NH), 3223 (C-H aromatic), 1732, 1683, 1623 (C=O), 1591, 1516, 1445, 1408 (C=C), 1361, 1280 (2S=O), 1214, 1176 (SO_2N), 1071, 1024 (C-N, C-O). ^{1}H NMR (DMSO-d_6) δ: 7.68-7.58 (m, 5H, ArH), 7.34-7.29 (m, 3H, ArH), 7.23-7.20 (t, J= 7.45 Hz, 1H, ArH), 7.15-7.10 (m, 2H, ArH), 6.53-6.51 (d, J= 8.6 Hz, 2H, ArH), 3.50 (s, 2H, CH_2), 2.34 (s, 3H, CH_3-C=O). ^{13}C NMR (DMSO-d_6) δ: 192.8 (C=O of acetophenone), 171.2 (C=O of carboxamide), 162.6 (C=O of benzamide), 155.6, 152.1, 145.5, 140.9, 132.5, 131.1, 130.9, 129.3, 127.4, 119.9, 112.8, 104.3 (twelve aromatic carbons), 48.8, 26.3 (two aliphatic carbons). HRMS-ESI (m/z): 437.1746 (M+H), calculated, 437.1749.

2.4.18 *N*-(4-acetylphenyl)-2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-phenyl propanamide (7r)

Yield (0.4862 g, 92.33%), mp, 61.20-61.70 ^{o}C, FTIR (KBr, cm^{-1}): 3392 (NH), 3225, 3063 (C-H aromatic), 2967 (C-H aliphatic), 1735, 1700, 1650 (3C=O), 1594, 1565, 1514, 1497, 1481, 1447 (C=C), 1375, 1348 (2S=O), 1170, 1108 (SO_2N), 1093, 1027 (C-N). ^{1}H NMR (DMSO-d_6) δ: 7.92-7.90 (d, J= 6.88 Hz, 2H, ArH), 7.63-7.61 (d, J= 8.72 Hz, 2H, ArH), 7.54-7.46 (m, 5H, ArH), 7.41-7.37 (t, J= 7.80 Hz, 2H, ArH), 7.19-7.13 (m, 4H, ArH), 7.09-7.07 (m, 2H, ArH), 6.53-6.51 (d, J= 8.68 Hz, 2H, ArH), 5.99 (s, 1H, NH), 3.86-3.80 (dd, J= 9.16, 6.84 Hz, 1H, <u>CH</u>-C=O), 2.92-2.87 (dd, J= 5.96, 5.96 Hz, 1H, CH_a of CH_2), 2.70-2.64 (dd, J=9.2, 9.16 Hz, CH_a of CH_2), 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ: 195.5 (C=O of acetophenone), 172.8 (C=O of carboxamide), 167.9 (C=O of benzamide), 154.1, 141.5, 137.3, 133.4, 132.7, 131.1, 129.8, 129.7, 129.4, 129.1, 128.7, 128.5, 127.1, 126.7, 125.4, 112.9 (sixteen aromatic carbons), 57.9, 38.3, 26.4 (three aliphatic carbons). HRMS-ESI (m/z): 526.1569 (M^+), calculated, 526.1562.

2.4.19 *N*-(4-acetylphenyl)-2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-(1*H*-indol-2-yl) propanamide (7s)

Yield (0.4986 g, 88.15%), mp, 114.20-114.80 ^{o}C, FTIR (KBr, cm^{-1}): 3382, 3326 (2NH), 3059 (C-H aromatic), 2924 (C-H aliphatic), 1729, 1689, 1622 (3C=O), 1595, 1491, 1458, 1448, 1424 (C=C), 1309, 1286 (2S=O), 1231, 1158 (SO_2N), 1091, 1011 (C-N). ^{1}H NMR (DMSO-d_6) δ: 10.76 (s, 1H, NH of indole), 7.94-7.93 (d, J= 6.85 Hz, 3H, ArH), 7.65-7.64 (d, J= 8.60 Hz, 2H, ArH), 7.60-7.58 (d, J=8.05 Hz, 2H, ArH), 7.49-7.46 (t, J=7.45 Hz, 2H, ArH), 7.38-7.35 (t, J= 7.45 Hz, 2H, ArH), 7.30-7.28 (d, J= 8.00 Hz, 2H, ArH), 7.04-7.01 (m, 2H, ArH), 6.93-6.90 (t, J= 8.05 Hz, 1H, ArH), 6.56-6.54 (d, J= 8.60 Hz, 3H, ArH), 5.98 (s, 1H, NH of amide), 3.94-3.89 (dd, J= 7.45, 7.45 Hz, 1H, CH-C=O), 3.07-3.03 (dd, J= 6.3, 6.3 Hz, 1H, CH_a of CH_2), 2.87-2.83 (dd, J= 7.45, 7.45 Hz, 1H, CH_b of CH_2), 2.35 (s, 3H, CH_3-C=O). ^{13}C NMR (DMSO-d_6) δ: 195.6 (C=O of acetophenone), 173.1 (C=O of carboxamide), 167.9 (C=O of benzamide), 154.1, 141.5, 136.6, 132.6, 131.1, 129.8, 129.4, 129.2, 129.1, 128.7, 127.5, 126.7, 125.4, 124.5, 121.4, 118.9, 118.4, 113.0, 111.9, 109.4 (twenty aromatic carbons), 57.2, 28.8, 26.4 (three aliphatic carbons). HRMS-ESI (m/z): 565.1692 (M^+), calculated, 565.1671.

2.4.20 *N*-(4-acetylphenyl)-2-[*N*-(benzenesulfonyl)-1-phenylformamido]-4-methyl pentanamide (7t)

Yield (0.3998 g, 81.16%), mp, 212.70-212.90 ^{o}C, FTIR (KBr, cm^{-1}): 3392 (NH), 2964, 2876 (C-H aliphatic), 1759, 1736, 1673 (3C=O), 1597, 1448 (C=C), 1385, 1364 (2S=O), 1160, 1142 (SO_2N), 1095, 1072, 1022 (C-N). ^{1}H NMR (DMSO-d_6) δ: 7.92-7.91 (d, J= 7.32 Hz, 2H, ArH), 7.75-7.73 (d, J=7.32 Hz, 2H, ArH), 7.64-7.62 (d, J= 8.24 Hz, 2H, ArH), 7.55-7.42 (m, 5H, ArH), 6.55-6.53 (d, J= 8.24 Hz, 3H, ArH), 3.65-3.60 (t, J= 7.36 Hz, 1H, CH-C=O), 2.33 (s, 3H, CH_3-C=O), 1.54-1.47 (m, 1H, CH), 1.36-1.32 (m, 2H, CH_2), 0.82-0.60 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 195.6 (C=O of acetophenone), 173.8 (C=O of carboxamide), 167.9 (C=O of benzamide), 154.1, 141.6, 133.4, 132.8, 131.1, 129.8, 129.5, 129.2, 129.1, 126.9, 125.4, 113.0 (twelve aromatic carbons), 54.5, 41.4, 26.3, 24.4, 23.3 (five aliphatic carbons). HRMS-ESI (m/z): 515.2961 (M+Na), calculated, 515.2965.

2.4.21 *N*-(4-acetylphenyl)-2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-methyl pentanamide (7u)

Yield (0.4105 g, 83.33%), mp, 270.00-270.60 ^{o}C, FTIR (KBr, cm^{-1}): 3392 (NH), 2964, 2876 (C-H aliphatic), 1759, 1736, 1682 (3C=O), 1597, 1448 (C=C), 1385, 1364 (2S=O), 1160, 1142 (SO_2N), 1095, 1072, 1021 (C-N). ^{1}H NMR (DMSO-d_6) δ: 7.74-7.73 (t, J= 7.45 Hz, 3H, ArH), 7.63-7.61 (d, J= 9.15 Hz, 1H, ArH), 7.58-7.55 (m, 1H, ArH), 7.53-7.50 (m, 3H, ArH), 7.23-7.20 (t, J=7.45 Hz, 2H, ArH), 7.15-7.09 (m, 2H, ArH), 6.53-6.51 (d, J= 8.55 Hz, 2H, ArH), 6.10 (s,

1H, NH), 3.51-3.50 (d, J= 6.30 Hz, 1H, CH-C=O), 2.34 (s, 3H, CH_3-Ar), 1.63-1.59 (m, 1H, CH), 1.31-1.28 (m, 1H, CH_a of CH_2), 1.07-1.01 (m, 1H, CH_b of CH_2), 0.75-0.69 (dt, J= 6.85, 7.45 Hz, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 196.7 (C=O of acetophenone), 172.7 (C=O of carboxamide), 168.6 (C=O of benzamide), 141.7, 139.5, 137.9, 133.8, 132.8, 129.4, 128.7, 127.0, 125.8, 125.7, 112.9, 109.4 (twelve aromatic carbons), 60.5, 37.4, 24.9, 21.6, 15.9, 11.4 (six aromatic carbons). HRMS-ESI (m/z): 492.1238 (M^+), calculated, 492.1239.

2.4.22 *N*-(4-acetylphenyl)-2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-methyl butanamide (7v)

Yield (0.3896 g, 81.40%), mp, black oil, FTIR (KBr, cm^{-1}): 3368 (NH), 3228 (C-H aromatic), 2963 (C-H aliphatic), 1729, 1698, 1626 (3C=O), 1595, 1516, 1447 (C=C), 1360, 1309 (2S=O), 1177, 1158 (SO_2N), 1093, 1056 (C-N). ^{1}H NMR (DMSO-d_6) δ: 7.97-7.91 (m, 2H, ArH), 7.75-7.73 (t, J= 6.88 Hz, 2H, ArH), 7.64-7.62 (m, 3H, ArH), 7.57-7.45 (m, 5H, ArH), 6.55-6.52 (t, J= 6.88 Hz, 2H, ArH), 3.49-3.48 (d, J= 3.24 Hz, 1H CH-C=O), 2.33 (s, 3H, CH_3-C=O), 1.92-1.87 (m, 1H, CH), 0.78-0.73 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ: 195.6 (C=O of acetophenone), 172.7 (C=O of carboxamide), 167.9 (C=O of benzamide), 154.1, 141.6, 133.4, 132.8, 131.1, 129.8, 129.4, 129.1, 128.9, 127.0, 125.4, 113.0 (twelve aromatic carbons), 61.8, 30.9, 26.3, 19.5, 18.3 (five aliphatic carbons). HRMS-ESI (m/z): 501.2299 (M+Na), calculated, 501.2231.

2.4.23 *N*-(4-acetylphenyl)-1-(benzenesulfonyl)-4-hydroxypyrrolidine-2-carboxamide (7w)

Yield (0.3881 g, 100%), mp, 117.20-117.60 ^{o}C, FTIR (KBr, cm^{-1}): 3402 (OH), 3221 (NH), 2993 (C-H aromatic), 2955, 2673 (C-H aliphatic), 1713, 1694 (2C=O), 1596, 1449 (C=C), 1353, 1338 (2S=O), 1212, 1195 (SO_2N), 1099, 1070, 1010 (C-N). ^{1}H NMR (DMSO-d_6) δ: 7.84-7.71 (m, 2H, ArH), 7.65-7.55 (m, 5H, ArH), 6.55-6.53 (d, J= 8.24 Hz, 2H, ArH), 4.18 (s, 1H, OH), 4.06-4.03 (t, J= 6.40 Hz, 1H, CH-C=O), 3.45-3.42 (m, 2H, CH_2), 3.10-3.08 (m, 1H, CH-OH), 2.34 (s, 3H, CH_3-C=O), 1.94-1.88 (m, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ: 195.5 (C=O of acetophenone), 173.8 (C=O of carboxamide), 154.1, 137.9, 133.4, 131.1, 129.8, 127.9, 125.3, 113.0 (eight aromatic carbons), 68.9, 60.3, 56.8, 26.4 (four aliphatic carbons). HRMS-ESI (m/s): 389.1185 (M+H), calculated, 389.1189.

2.4.24 *N*-(4-acetylphenyl)-1-(benzenesulfonyl)pyrrolidine-2-carboxamide (7x)

Yield (0.3724 g, 99.97%), yellowish oil, FTIR (KBr, cm^{-1}): 3230 (NH), 3115 (C-H aromatic), 1748, 1689 (C=O), 1595, 1527, 1403 (C=C), 1358, 1332 (2S=O), 1184, 1162 (SO_2N), 1090, 1070, 1016, 1006 (C-N). ^{1}H NMR (DMSO-d_6) δ: 7.80-7.78 (d, J= 7.45 Hz, 2H, ArH), 7.66-7.56 (m, 5H, ArH), 6.56-6.54 (d, J=8.55 Hz, 2H, ArH), 4.09-4.06 (m, 1H, CH-C=O), 3.32-3.29 (t, J= 6.90 Hz, 1H, CH_a of CH_2-N), 3.13-3.09 (m, 1H, CH_b of CH_2-N), 2.33 (s, 3H, CH_3-C=O), 1.83-1.74 (m, 3H), 1.51-1.48 (t, J= 5.70 Hz, CH). ^{13}C NMR (DMSO-d_6) δ: 195.7 (C=O of

acetophenone), 173.7 (C=O of carboxamide), 154.1, 137.9, 133.6, 131.1, 129.9, 127.6, 125.4, 113.1 (eight aromatic carbons), 60.9, 48.9, 30.6, 26.3, 24.8 (five aliphatic carbons). HRMS-ESI (m/z): 373.1219 (M+H), calculated, 373.1219.

2.5 Docking studies

The docking study was performed using BioVia discovery studio client version 4.5 software. The X-ray crystallographic structures plasmepsin II (4Z22) proteins bound was acquired from the protein data bank (PDB) at a resolution of 2.73 Å. The active site was defined with a 8.500 Å radius around the bound inhibitor which covered all the active sites amino acids of the proteins. A grid-based molecular docking method was used to dock the small molecules into the protein active site. All water molecules, bound inhibitors and other hetero atoms were removed from the macromolecule and polar hydrogen atoms were added. The designed structures were also verified for its valency, missing hydrogen and any structural disorders like connectivity and bond orders. A final minimization of the ligand in the rigid receptor using non-softened potential was performed. For each final pose, the CHARMm energy (interaction energy plus ligand strain) and the interaction energy alone was calculated. The poses were sorted by CHARMm energy and the top scoring (most negative with least root square mean deviation) poses were selected.

2.6 *In vitro* antimalarial studies

The antimalarial activities of the new carboxamides were determined by their inhibition of parasite growth using chloroquine resistant strain of *Plasmodium falciparum.* Effects of inhibitors on parasite development were determined as follows. Sorbitol synchronized, 0.1% parasitemia, ring stage *P. falciparum* strain W2 parasites were cultured under the atmosphere of 3% O_2, 6% CO_2 and 91% N_2 in RPMI-1640 medium supplemented with 10% human serum in the presence of inhibitors for 48 h without media change. Inhibitors were added from 1000× DMSO stocks. After 48 h, the culture medium was removed and replaced with 1% formaldehyde in PBS pH 7.4 for an additional 48 h at room temperature to fix cells. Fixed parasites were transferred into 0.1% Triton-X-100 in PBS containing 1 nM YOYO-1 dye (Molecular Probes). Parasitemia was determined from dot plots (forward scatter vs. fluorescence) acquired on a FACS sort flow cytometer using Cell Quest software (Beckton Dickinson). The MIC of compounds were the minimum concentration at which more than 99% of the parasites, relative to the control, were inhibited from developing to schizonts (parasites with six or more chromatin dots) [33].

2.7 Antioxidant

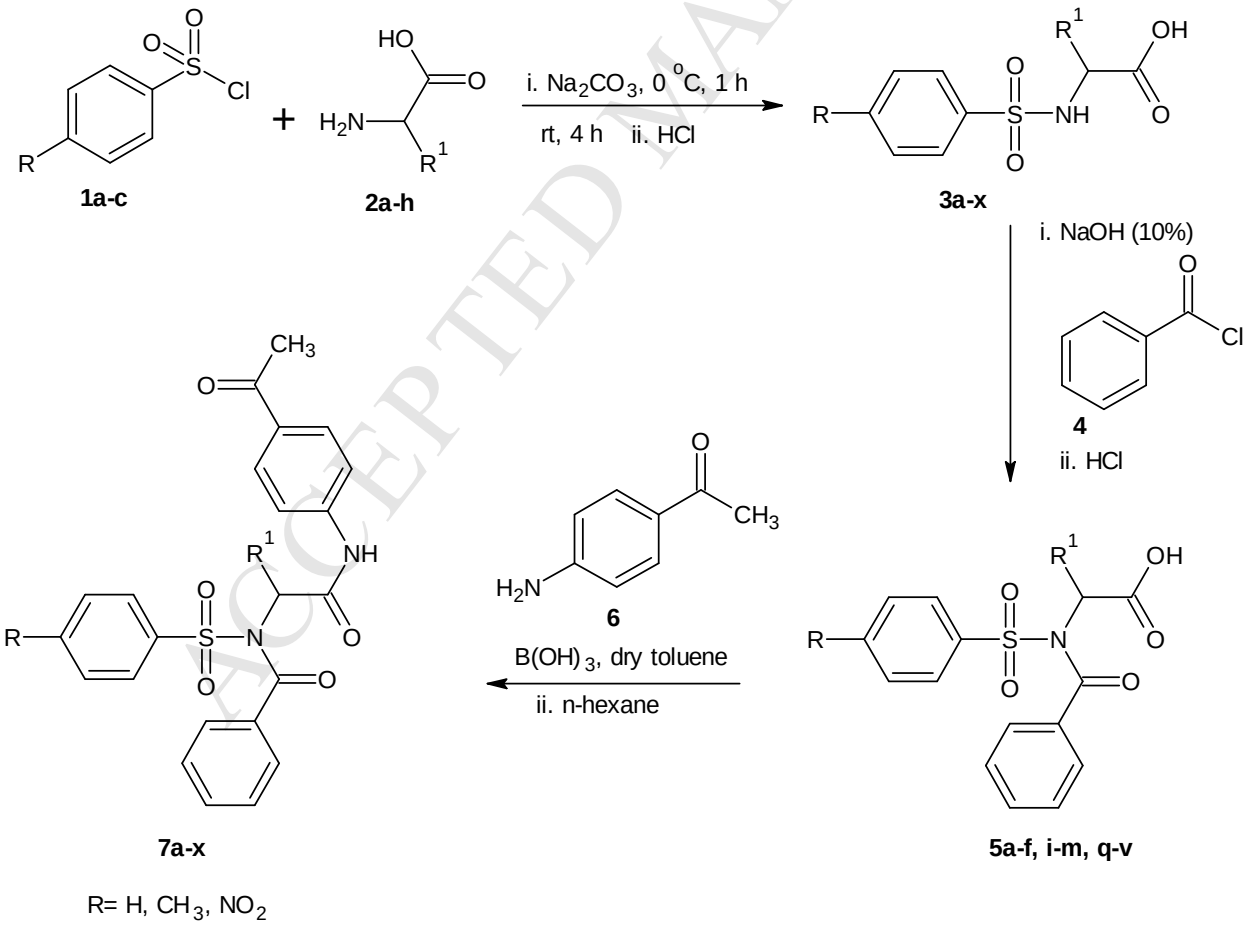
The new carboxamides were screened for free radical scavenging activity by 2,2-diphenyl-1-picrylhydrazyl (DPPH) method [34]. Compounds of different concentrations were prepared in distilled ethanol, 1 mL of each compound solutions having different concentrations (1.0, 2.0, 3.0, 4.0 and 5.0 mg/mL) were taken in different 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 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:

DPPH radical scavenging activity (%) = [(Ac-As)/Ac] *100,

Where Ac = absorbance of control and As = absorbance of samples

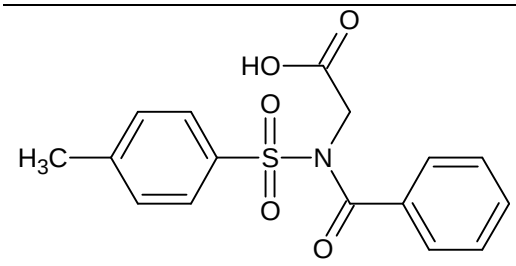
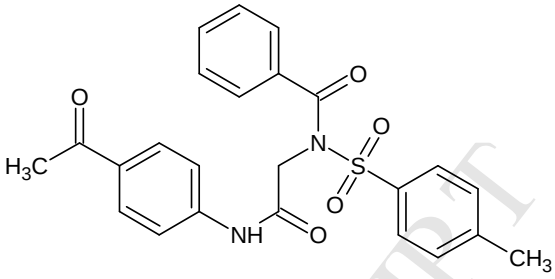
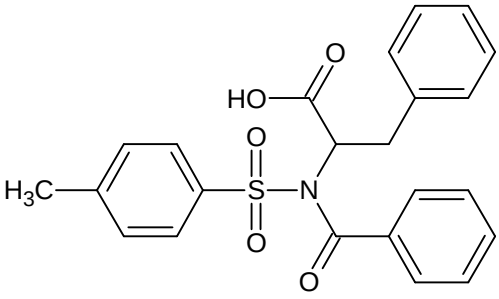
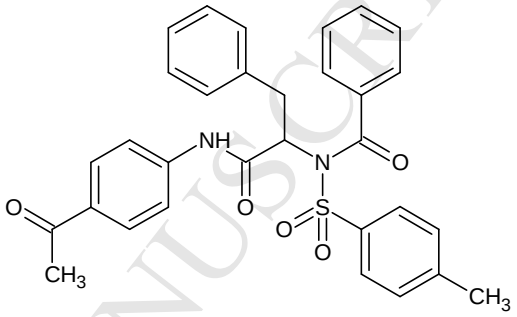
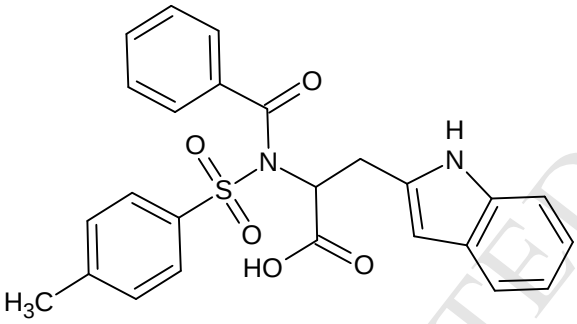
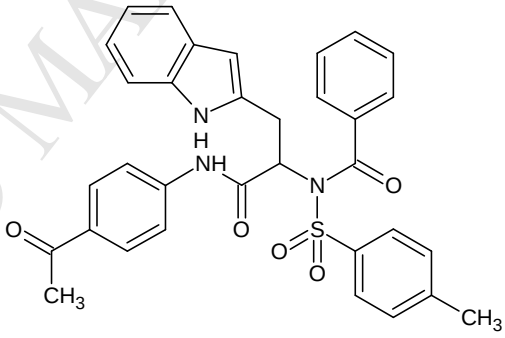
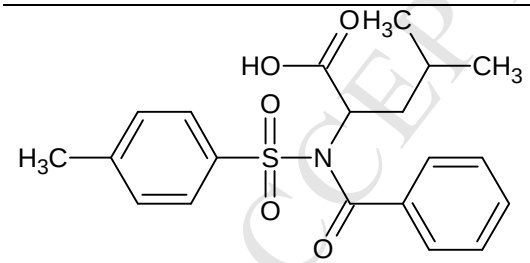
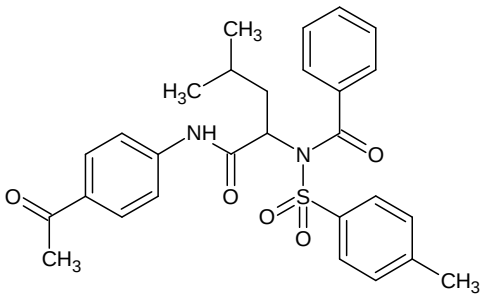
3.0 Results and Discussion

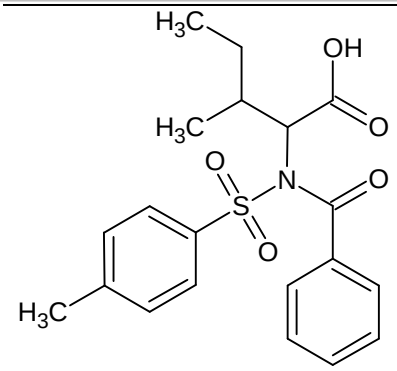
3.1 Chemistry

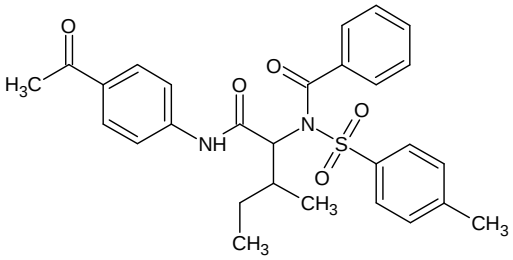


Scheme 1: Protocol for the synthesis of new carboxamide derivatives bearing sulphonamide functionalities.

Table 1: New carboxamides derivatives bearing benzenesulphonamide

Carboxylic acids	New Carboxamide (**7a-x**)	s/n
		**a**
		**b**
		**c**
		**d**





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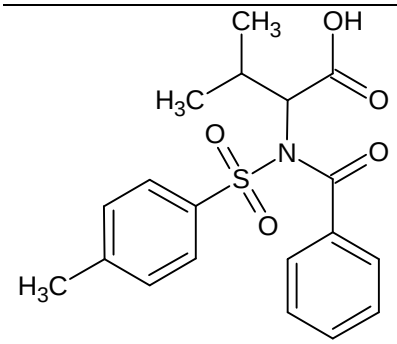

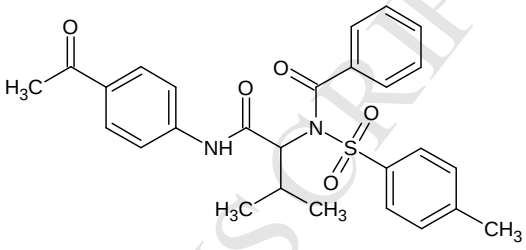

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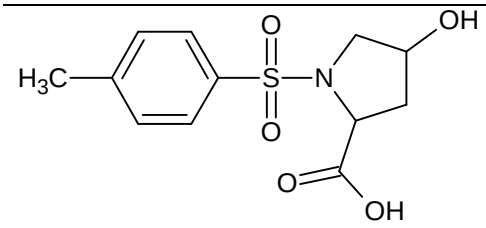

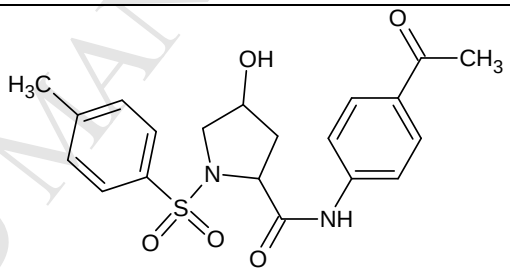

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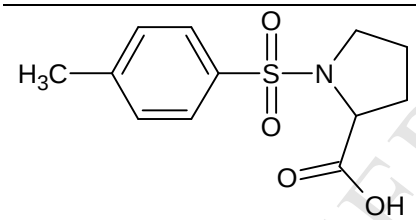

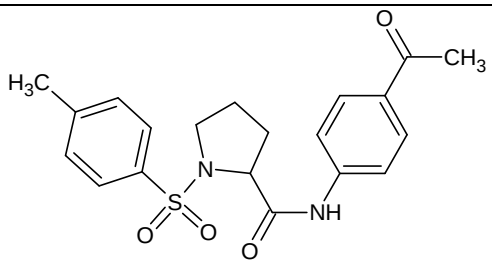

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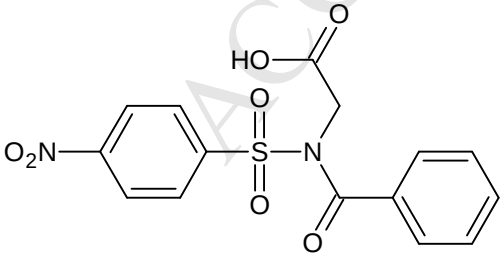

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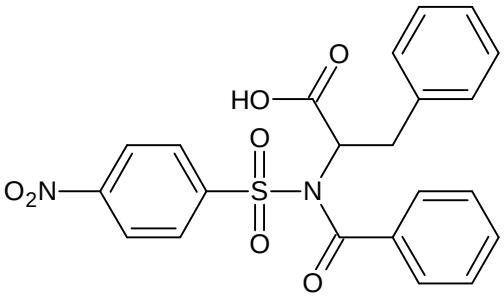

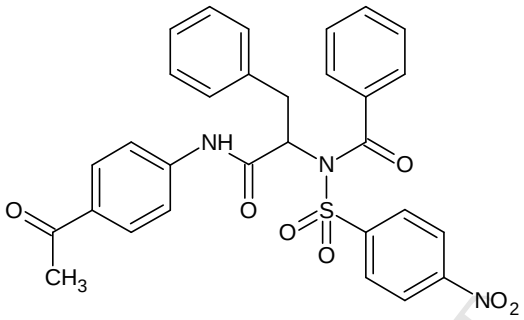

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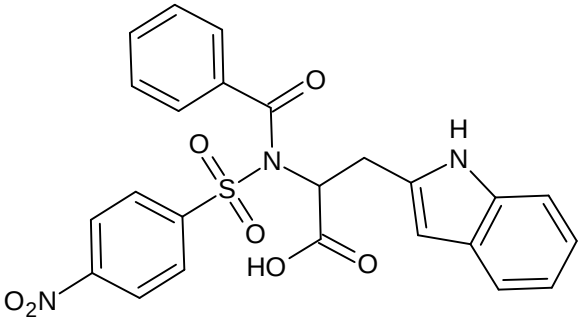

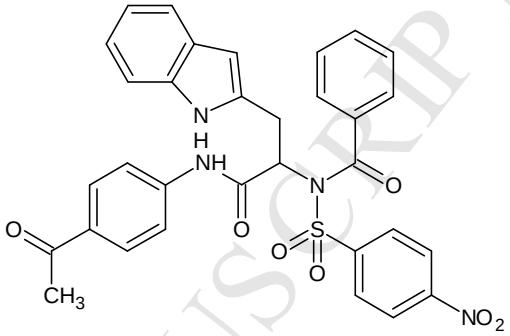

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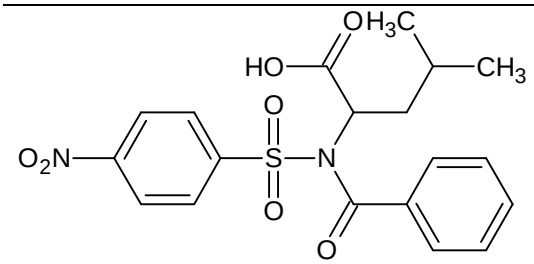

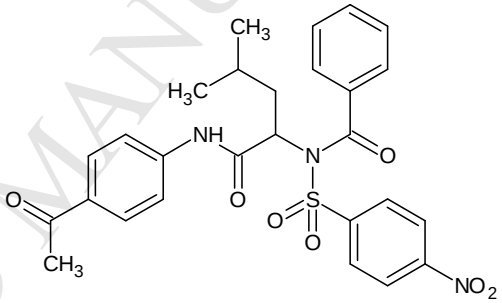

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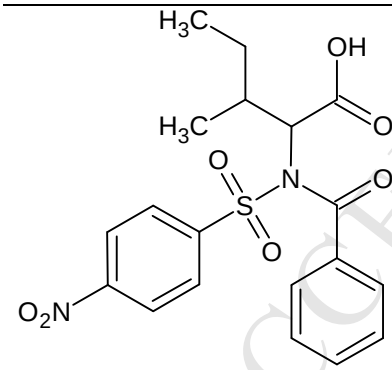

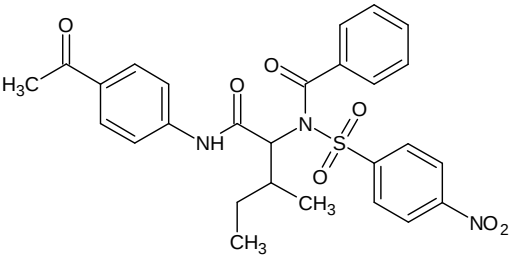

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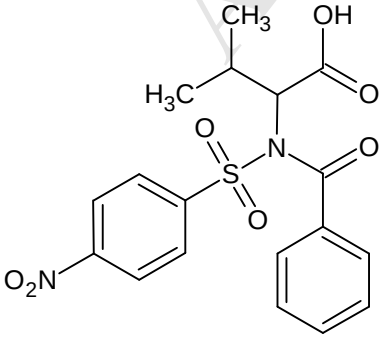

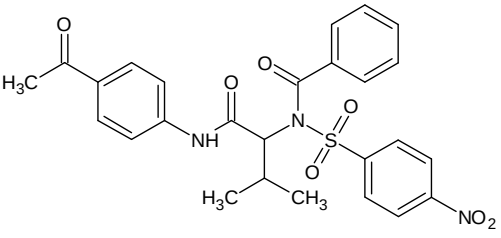

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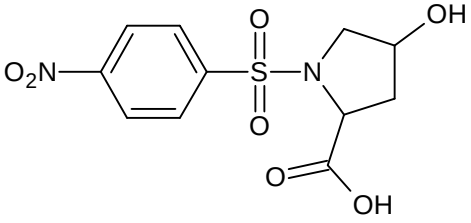

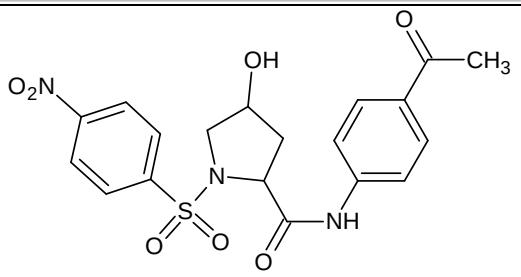

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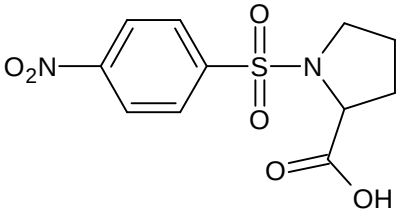

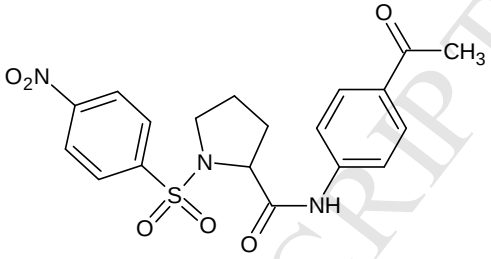

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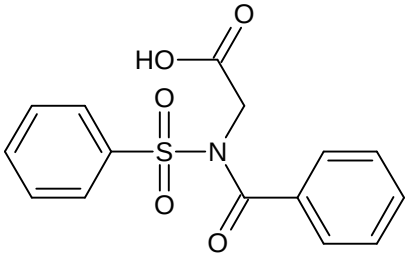

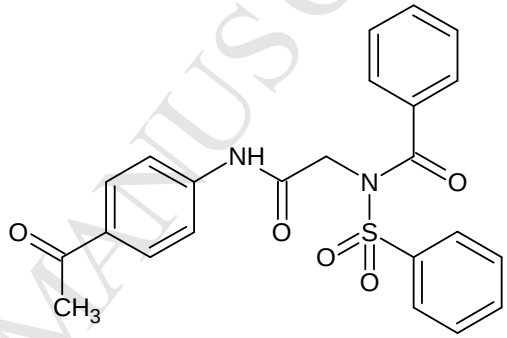

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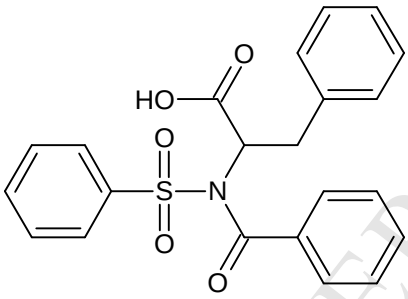

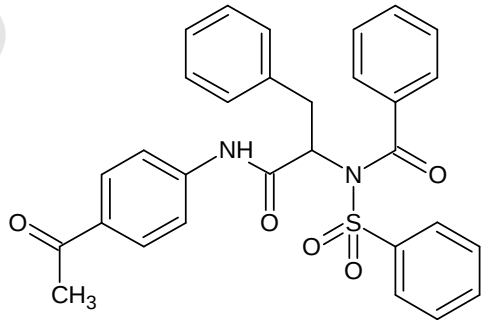

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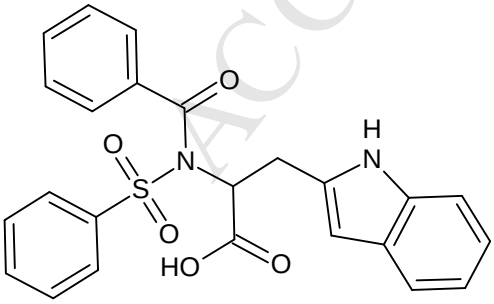

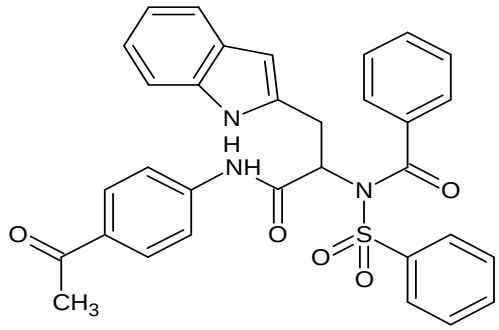

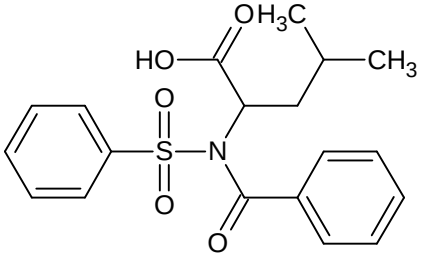

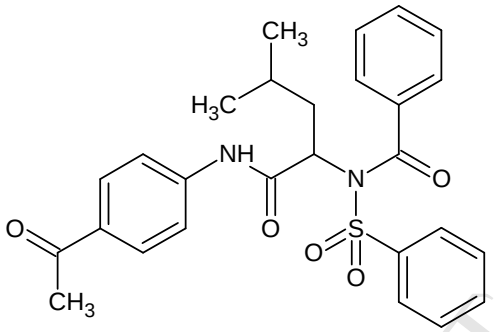

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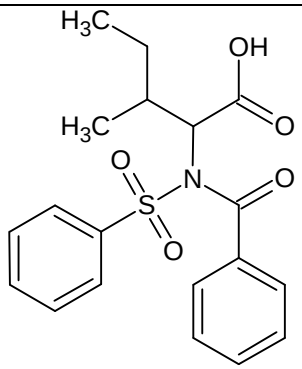

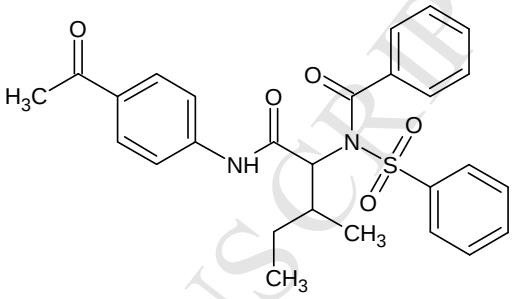

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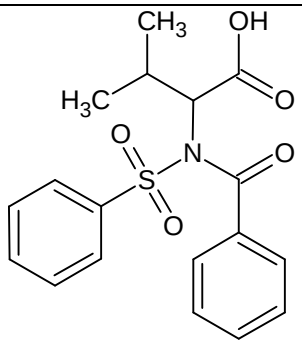

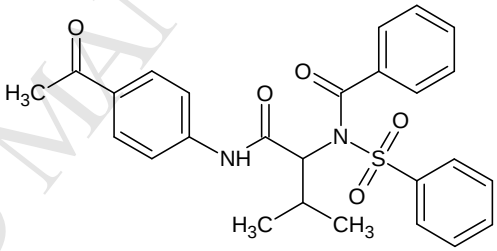

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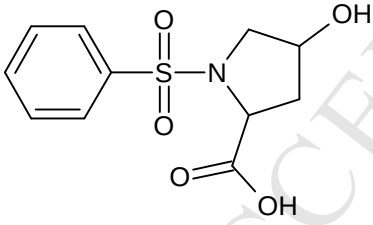

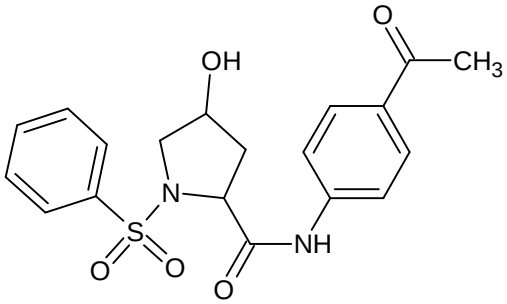

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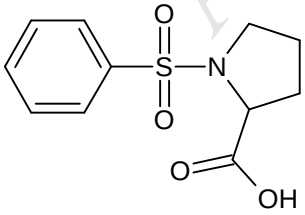

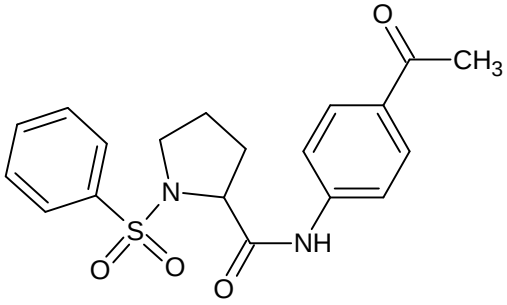

x

To keep the electron withdrawing and electron donating character of the substituents in the molecules, we decided to study several benzenesulphonamoyl alkanamides bearing electron rich and deficient substituents. In the first step, the substituted benzenesulphonamoyl alkanamides (**3a-x**) were synthesized by the reaction of substituted benzenesulphonyl chlorides (**1a-c**) with amino acids (**2a-h**) in the presence of sodium carbonate as base. The *N*-benzoylated derivatives (**5a-f, i-m, q-v**) were obtained by the reaction of the appropriate benzenesulphonamoyl alkanamides (**3a-f, i-m, q-v**) with benzoyl chloride (**4**) in the presence of sodium hydroxide. Further boric acid catalysed amidation of the carboxylic acid end of the *N*-benzoylated derivatives (**5a-f, i-m, q-v**) and 4-aminoacetophenone (**6**) afforded the corresponding carboxamide derivatives (**7a-f, i-m, q-v**). In addition to the *N*-benzoylated derivatives, the proline and 4-hydroxyproline derivatives of substituted benzenesulphonamoyl alkanamides (**3g, h, o, p, w and x**) were also reacted with 4-aminoacetophenone in the presence of catalytic amount of boric acid to afford the carboxamide sulphonamide derivatives **7g, h, o, p, w and x.** The carboxamides were crystallized in their analytical grade using n-hexane. The synthesized compounds were characterised by various spectroscopic techniques like FTIR, ^{1}H NMR, ^{13}C NMR and high resolution mass spectroscopy (HRMS). The presence of a sharp bands between 3448-3415 cm^{-1}, 3385-3248 cm^{-1} and 1753-1699 cm^{-1} assigned to OH of carboxylic acid, NH and C=O respectively were indicative of successful formation of compounds **3a-x**. The disappearance of the N-H band at 3385-3248 cm^{-1} in the *N*-benzoylated deraivatives coupled with the appearance of an additional band at 1685-1689 cm^{-1} is diagnostic of the successful *N*-benzoylation of the sulphonamoyl alkanamides. In the ^{1}H NMR spectra of the *N*-benzoylated derivatives, the disappearance of the NH peak and the appearance of additional aromatic peaks having five protons and the ^{13}C NMR showed the corresponding four additional aromatic carbons.

The IR of all the new carboxamides showed a sharp band between 3398-3221 cm^{-1} and 1759-1708 cm^{-1} corresponding to the NH and C=O band respectively. In the ^{1}H NMR, the singlet appearing between 2.3510-2.2531 ppm corresponds to the CH_3 of acetophenone group. In the ^{13}C NMR spectra, the peaks between 26.3740-24.7426 ppm was due to the CH_3 carbon off acetophenone. These spectral characterization in addition to the HRMS spectra which showed the molecular ion peaks of the compounds were diagnostic of the successful coupling of the 4-aminoacetophenone to the *N*-benzoylated and proline derivatives. The aromatic and aliphatic protons and carbons appeared at the predicted range using BioDraw.

3.2 Drug-likeness of the Dataset

Part of routine check in early drug development processes is the ability of a potentially drug candidate to be orally bioavailable to avoid waste of resources and time [35]. Lipinski proposed certain criteria, known as 'rule of five' (ro5) which have been defined as molecular weight (MW) less than 500, hydrogen bond acceptor (HBA) less than 10, hydrogen bond donor (HBD) less than 5, lipophilicity (log *P*) less than 5. The rule highlights possible bioavailability problem if more than two criteria are violated [36]. It was observed that thirteen of the test compounds have zero violation of all the parameters involved in ro5 while five compounds failed to respect one and two parameters each of the rule. Only compound **s** could pose a drug-like challenge out of all the twenty-four test compounds since it violated more than two parameters of ro5. Number of rotatable bond (NRB) less than five is included in the rule to recognize the effect of molecular flexibility which has been found to contribute to oral bioavailability in rat [37]. As shown in Table 2 all the dataset fall outside the recommended range of values with three candidates having as high as twelve rotatable bonds. Be that as it may, the newly synthesized primary sulphonamides appears to be free of posing any possible drug-like challenge judging from the number of Lipinski violations and therefore, worthy of further consideration.

Table 2: Drug-like Profile of the analogs

Compounds (**7**)	MW	HBA	HBD	Log P	LV	NRB
a	450.515	7	1	3.546	0	9
b	540.64	7	1	5.543	2	11
c	579.677	8	2	5.91	2	11
d	506.623	7	1	5.422	2	11
e	506.623	7	1	5.422	2	11
f	492.596	7	1	4.98	0	10
g	402.471	7	2	1.222	0	6
h	386.472	6	1	2.237	0	6
i	436.488	7	1	3.248	0	9

j	526.613	7	1	5.245	1	11
k	551.623	8	2	5.524	2	10
l	492.596	7	1	5.124	0	11
m	492.596	7	1	5.124	0	11
n	478.569	7	1	4.682	0	10
o	388.444	7	2	0.924	0	6
p	372.445	6	1	1.939	0	6
q	481.485	10	1	3.183	0	10
r	571.61	10	1	5.18	1	12
s	596.62	11	2	5.459	3	11
t	537.593	10	1	5.059	1	12
u	537.593	10	1	5.059	1	12
v	523.566	10	1	4.617	1	11
w	433.441	10	2	0.859	0	7
x	417.442	9	1	1.874	0	7

3.3 Molecular docking

We docked our most potent compounds in the active site of *Plasmodium falciparum* plasmepsin II downloaded from protein data bank with the id 4Z22. The protein was solved at 2.62 Å. Manual docking simulation was performed and thereafter energy minimization of the protein-ligand complex structure revealed that most active compounds possessed good binding mode with very promising interactions with the side chains of the proteins (fig. 3-6). Compounds **7d** and **7k** fitted well in the active site of the protein. Expectedly, compound with nitro group in the para position of the benzenesulphonyl ring possessed the best interaction with the protein possible because of the increased hydrogen bonding between the oxygen of the nitro group and carboxylic acid of the amino acid founds found in the active site of the proteins.

7k

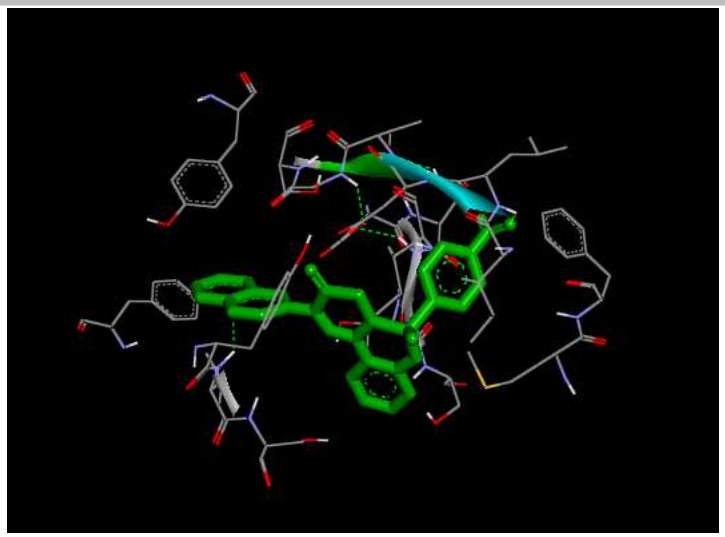

Fig. 3: Plausible binding mode of compound **7k**

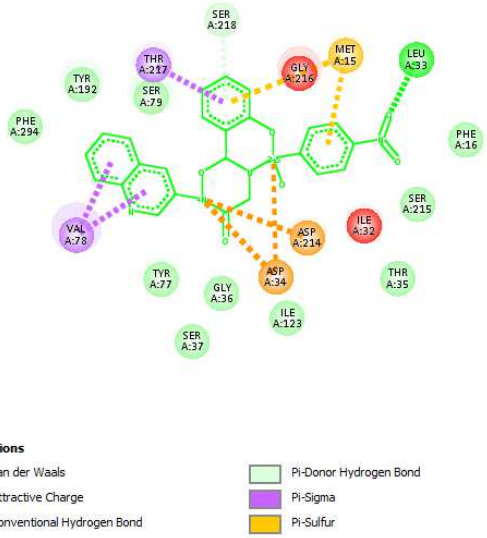

Fig. 4: residues in the active site of plasmepsin II protein interacting with compound 7k

7c

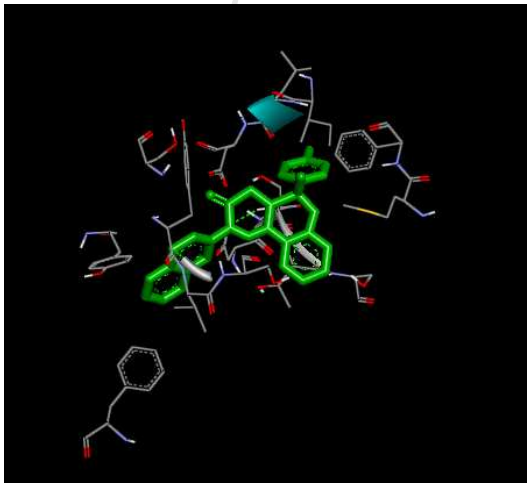

Fig. 5: Plausible binding mode of compound **7c**

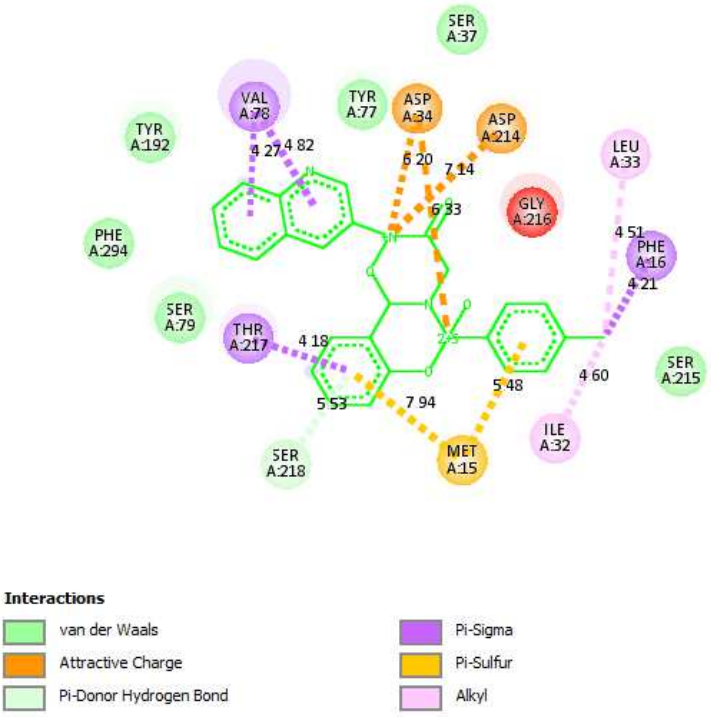

Fig. 6: residues in the active site of plasmepsin II protein interacting with compound 7c

3.4 Biological Screening and Structure Antimalarial-activity Relationship Analysis

Table 3: Biological studies

S/N	MIC of antimalarial (µM)	IC_{50} of DPPH (M)
7a	0.72	0.102
7b	0.78	0.0076
7c	0.03	0.000045
7d	0.17	0.011
7e	5.11	0.010
7f	2.82	0.012
7g	2.27	0.025
7h	1.45	0.036

7i	0.18	0.058
7j	0.08	0.039
7k	0.02	0.00073
7l	0.06	0.0084
7m	0.20	0.050
7n	1.57	0.0068
7o	0.32	0.0071
7p	6.74	0.019
7q	0.97	0.032
7r	0.90	0.011
7s	0.05	0.051
7t	0.26	0.0032
7u	1.25	0.0086
7v	1.70	0.013
7w	0.16	0.0038
7x	0.11	0.069
Chloroquine	0.06	-
Quinine	0.83	-
Ascorbic acid	-	0.00034

The new compounds of the present study includes **a** to **x**, comprising sulphonamides as the scaffold. To determine the in vitro antimalarial activity of the primary sulphonamides, minimum inhibition assay was employed using a chloroquine sensitive *P. falciparum* malaria parasite line (Table 3). Chloroquine and quinine were used as standard antimalarial drugs to compare those of

the test compounds. Compounds **7s, k** and **c** (MIC = 0.05, 0.02 and 0.03 µM) displayed activity better than chloroquine (0.06 µM), whereas about half of the total newly synthesized sulphonamides inhibited the activity of *P. falciparum* parasite at lower MIC range (0.02 – 0.83 µM) than quinine (0.83 µM). On the overall, compound **k** emerged as having the best activity among the newly synthesized compound and relative to both considered standard antimalarial drugs. A consideration of the variable structural features of the test compounds due to the range of incorporated substituents gives hints into the basis for the observed variation in activity.

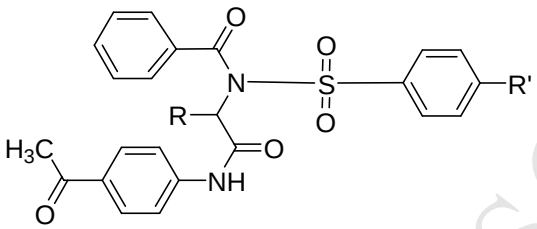

Fig. 7: General structure of compounds a-x

Fig 7, which represent the general structure of compounds **a** to **x**, was used to discuss the observed trend in antimalarial structure activity relationship. Take note that R' was kept constant as methyl group, hydrogen atom or nitro group, while R was varied to give eight derivatives per form of R. The indole substituted compounds for all the forms of R', generally have the greatest potency, followed by R' = toluenyl group derivatives. This suggests the importance of having moiety that can form pi-pi hydrophobic interaction and hydrogen bonding at the given position.

Derivatives where R' = H appears to impart on the overall, the best antimalarial activity. However, exception was observed for compounds w and x where there was improved activity when R' was nitro group, with about a 3 or 10 fold lower MIC respectively than their counterpart compounds having R' = H (Table 3). Across the variations of the R', compounds with R = isoalkyl groups all had relatively low biological activity against *P. falciparum*. Taken together, compound **c, k** and **s** are considered worthy of further attention to develop it into a novel antimalarial drug.

The free radical scavenging activities showed that compounds **7c, 7k, 7t** and **7w** were potential antioxidant agents having fascinating reduction of DPPH free radical. The IC_{50} showed that compound **7c** had ten-fold better antioxidant activity (IC_{50} of 0.045 mM) than ascorbic acid (IC_{50} of 0.34 mM). A look at the table of percentage scavenging activities showed that although compound **7c** was the most potent antioxidant agent, compounds **7t** and **7w** having percentage scavenging of 54.22 and 57.03% respectively at 2 mg/mL was comparable to 58.02%

scavenging activity of compound **7c.** This simply indicate that they can both have comparable therapeutic dose in spite of wide difference in their IC_{50}.

4.0 Conclusion

In this present work, twenty four new derivatives of carboxamides containing sulphonamide functionality have been synthesized from un-activated carboxylic acid using boric acid as a catalyst. All the synthesized analogues were screened for their *in vitro* antimalarial and antioxidant potentials. Compounds **7c, 7k** and **7s** exhibited enhanced antimalarial activities. The molecular docking showed good binding between the two most active antimalarial agent and plasmepsin II suggesting the successful inhibition of the enzyme as a possible mechanism of action of the reported compounds. Interestingly, two of the most active antimalarial agent possessed fascinating antioxidant property. The class of compound reported in this work have the advantage of reducing oxidative stress arising from both malaria parasite and the use of antimalarial agent since the antimalarial agents possess antioxidant activities.

Supporting Document

The FTIR, ^{1}H NMR and ^{13}C NMR and HRMS spectra are available

Acknowledgment

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Declaration

We declare that there are no conflicting interest in this article.

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List of caption

2.2.1 2-(4-methylphenylsulphonamido) acetic acid (3a)

2.2.2 2-(4-methylphenylsulphonamido)-3-phenylpropanoic acid (3b)

2.2.3 3-(1*H*-indol-2-yl)-2-{[(4-methylphenyl)sulphonyl]amino}propanoic acid (3c)

2.2.4 4-Methyl-2-{[(4-methylphenyl)sulfonyl]amino}pentanoic acid (3d)

2.2.5 3-methyl-2-{[(4-methylphenyl)sulfonyl]amino}pentanoic acid (3e)

2.2.6 3-Methyl-2-(4-methylphenylsulphonamido)butanoic acid (3f)

2.2.7 4-Hydroxy-1-tosylpyrrolidine-2-carboxylic acid (3g)

2.2.8 1-Tosylpyrrolidine-2-carboxylic acid (3h)

2.2.9 2-Benzenesulphonamido acetic acid (3i)

2.2.10 2-Benzenesulphonamido-3-phenylpropanoic acid (3j)

2.2.11 2-Benzenesulphonamido-3-(1*H*-indol-3-yl)propanoic acid (3k)

2.2.12 2-Benzenesulphonamido-4-methylpentanoic acid (3l)

2.2.13 2-Benzenesulphonamido-3-methylpentanoic acid (3m)

2.2.14 2-Benzenesulphonamido-3-methylbutanoic acid (3n)

2.2.15 1-(Benzenesulphonyl)-4-hydroxypyrrolidine-2-carboxylic acid (3o)

2.2.16 1-(Benzenesulphonyl)-pyrrolidine-2-carboxylic acid (3p)

2.2.17 2-(4-Nitrophenylsulphonamido)acetic acid (3q)

2.2.18 2-(4-Nitrophenylsulphonamido)-3-phenylpropanoic acid (3r)

2.2.19 3-(1*H*-Indol-2-yl)-2-(4-nitrophenylsulphonamido)propanoic acid (3s)

2.2.20 4-Methyl-2-nitrophenylsulphonamido)pentanoic acid (3t)

2.2.21 3-Methyl-2-(4-nitrophenylsulphonamido)pentanoic acid (3u)

2.2.22 3-Methyl-2-(4-nitrophenylsulphonamido)butanoic acid (3v)

2.2.23 4-Hydroxy-1-(4-nitrophenylsulphonyl)pyrrolidine-2-carboxylic acid (3w)

2.2.24 1-(4-Nitrophenylsulphonyl)pyrrolidine-2-carboxylic acid (3x)

2.3 General Procedure for the Synthesis of *N*-benzoyl Derivatives of Benzene sulphonamides (5a-f, i-n and q-v)

2.3.1 {Benzoyl[(4-methylphenyl)sulfonyl]amino}acetic acid (5a)

2.3.2 2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]-3-phenylpropanoic acid (5b)

2.3.3 3-(1*H*-indol-2-yl)-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido] propanoic acid (5c)

2.3.4 4-Methyl-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]pentanoic acid (5d)

2.3.5 3-Methyl-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]pentanoic acid (5e)

2.3.6 3-Methyl-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]butanoic acid acid (5f)

2.3.7 2-[*N*-(benzenesulfonyl)-1-phenylformamido]acetic acid (5i)

2.3.8 2-[*N*-(benzenesulphonyl)-1-phenylformamido]-3-phenylpropanoic acid (5j)

2.3.9 2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-(1*H*-indol-2-yl)propanoic acid (5k)

2.3.10 2-[*N*-(benzenesulfonyl)-1-phenylformamido]-4-methylpentanoic acid (5l)

2.3.11 2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-methylpentanoic acid (5m)

2.3.12 2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-methylpentanoic acid (5n)

2.3.13 2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]acetic acid (5q)

2.3.14 2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]-3-phenylpropanoic acid (5r)

2.3.15 3-(1*H*-indol-2-yl)-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]propanoic acid (5s)

2.3.16 3-Methyl-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]pentanoic acid (5t)

2.3.17 4-Methyl-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]pentanoic acid (5u)

2.3.18 3-Methyl-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]butanoic acid (5v)

2.4 Boric acid catalysed Synthesis of Carboxamide derivatives from carboxylic acid and 4-aminoacetophenone

2.4.1 *N*-(4-acetylphenyl)-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]acetamide (7a)

2.4.2 *N*-(4-acetylphenyl)-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido]-3-phenyl propanamide (7b)

2.4.3 *N*-(4-acetylphenyl)-3-(1*H*-indol-2-yl)-2-[*N*-(4-methylbenzenesulphonyl)-1-phenyl formamido]propanamide (7c)

2.4.4 *N*-(4-acetylphenyl)-4-methyl-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido] pentanamide (7d)

2.4.5 *N*-(4-acetylphenyl)-3-methyl-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido] pentanamide (7e)

2.4.6 *N*-(4-acetylphenyl)-3-methyl-2-[*N*-(4-methylbenzenesulfonyl)-1-phenylformamido] butanamide (7f)

2.4.7 *N*-(4-acetylphenyl)-4-hydroxy-1-(4-methylbenzenesulfonyl)pyrrolidine-2-carboxamide (7g)

2.4.8 *N*-(4-acetylphenyl)-1-(4-methylbenzenesulfonyl)pyrrolidine-2-carboxamide (7h)

2.4.9 *N*-(4-acetylphenyl)-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]acetamide (7i)

2.4.10 *N*-(4-acetylphenyl)-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido]-3-phenyl propanamide (7j)

2.4.11 *N*-(4-acetylphenyl)-3-(1*H*-indol-2-yl)-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenyl formamido]propanamide (7k)

2.4.12 *N*-(4-acetylphenyl)-4-methyl-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido] pentanamide (7l)

2.4.13 *N*-(4-acetylphenyl)-3-methyl-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido] pentanamide (7m)

2.4.14 *N*-(4-acetylphenyl)-3-methyl-2-[*N*-(4-nitrobenzenesulfonyl)-1-phenylformamido] butanamide (7n)

2.4.15 *N*-(4-acetylphenyl)-4-hydroxy-1-(4-nitrobenzenesulfonyl)pyrrolidine-2-carboxamide (7o)

2.4.16 *N*-(4-acetylphenyl)-1-(4-nitrobenzenesulfonyl)pyrrolidine-2-carboxamide (7p)

2.4.17 *N*-(4-acetylphenyl)-2-[*N*-(benzenesulfonyl)-1-phenylformamido]acetamide (7q)

2.4.18 *N*-(4-acetylphenyl)-2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-phenyl propanamide (7r)

2.4.19 *N*-(4-acetylphenyl)-2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-(1*H*-indol-2-yl) propanamide (7s)

2.4.20 *N*-(4-acetylphenyl)-2-[*N*-(benzenesulfonyl)-1-phenylformamido]-4-methyl pentanamide (7t)

2.4.21 *N*-(4-acetylphenyl)-2-[*N*-(benzenesulfonyl)-1-phenylformamido]-3-methyl pentanamide (7u)

Highlights

- The development of multidrug resistant *Plasmodium* specie threatens the treatment of malaria.
- Carboxamides and sulphonamides have been reported to possess fascinating antimalarial activities.
- Malaria treatment is often associated with generation of free radical species because most antimalarial agents are pro-oxidant.
- Antimalarial agents with accompanied antioxidant activities will eradicate complications in malaria chemotherapy.