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FACILE SYNTHESIS AND SPECTROSCOPIC CHARACTERIZATION OF SULFONAMIDE BEARING DIVERSIFIED CARBOXAMIDE AND HYDRAZINE CARBOXAMIDE MOIETIES

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ABSTRACT

This current research describes the eco-friendly synthesis of *N*-(s-phenyl)-3-phenyl-2-(phenyl sulfonamido) propanamides which are sulfonamide bearing diversified carboxamide moieties. The incorporation of amido functionality into the sulfonamide moieties was herein achieved in three steps in a cost-effective manner by starting from cheap amino acid, phenyl alanine which was reacted with benzenesulfonyl chloride to produce sulfonamide which upon subsequent esterification followed by amidation furnished carboxamido-incorporated sulfonamide analogs **9a-j** in good to excellent yield. The completion of reaction processes was authenticated with Thin Layer Chromatography (TLC) and the chemical structures were validated through the elemental analysis result as well as spectroscopic means which include FT-IR, UV, ^{1}H and ^{13}C NMR. The technique used herein was found to be efficient and cost-effective for the production of the series of carboxamide diversified sulfonamide derivatives.

Keywords: sulfonamide, spectroscopy, column chromatography, condensation, esterification.

INTRODUCTION

Sulfonamides are the oldest and remain one of the commonly utilized antimicrobial therapeutics in veterinary medicine,[1] broadly owing to cost-effectiveness and their relative efficacy in some common bacterial diseases.[2] Sulfonamide are still widely used for conditions such as acne and urinary tract infections caused by bacteria resistant to other antibiotics.[3] Sulfonamides constitute a privileged class among pharmacological agents by possessing properties including carbonic anhydrase enzyme (CA) inhibition, as well as diuretic, hypoglycemic, antibacterial, antiviral, and metalloprotease inhibitory effects.[4] The discovery of valuable antimicrobial properties of azo dye called prontosil by Domagk's paved way for the identification of sulfanilamide as the first efficient agent in therapeutic research.[5] The systematic review into the past work and usefulness of sulfonamides, unequivocally expresses that apart from the provision of earlier efficient treatment of pathogenic diseases,[5,6] these class of compounds also unveiled unprecedented revolution in medicine[7] for the new drug development.[8] They are preferred due to the ease of administration,[9] wide spectrum of antimicrobial activity,[10] noninterference with the host defense mechanism and relative freedom from problems of super-infection.[11]

The biological importance of sulfonamide derivatives is due to their structural resemblance to the naturally occurring *p*-aminobenzoic acid (PABA). The mechanism of action of sulfonamides is well understood to be via competitive inhibitory nature they conferred on *p*-aminobenzoic acid (PABA) thereby resulting in the disruption of the folic acid metabolic pathway and causing inhibition of multiplication of bacteria.[12] The structural similarity between sulfonamide and *para*-aminobenzoic acid (PABA) has led to the speculation that it might inhibit dihydropteroate synthase (DHPS) in the folate biosynthetic pathway and cause disruption in the synthesis of tetrahydrofolic acid which is a basic growth factor essential for the

metabolic process of bacteria.[13] This allows them to interact with the biopolymers of the living system.[14] Some commercially available sulfonamide-based drugs that have done healing magic in the therapeutic world are the sulpha drugs **1-6** shown in Fig.-1. Apart from the already marketed drugs, there are many other sulfonamides that are being investigated currently for their promising activity against several malignancies.

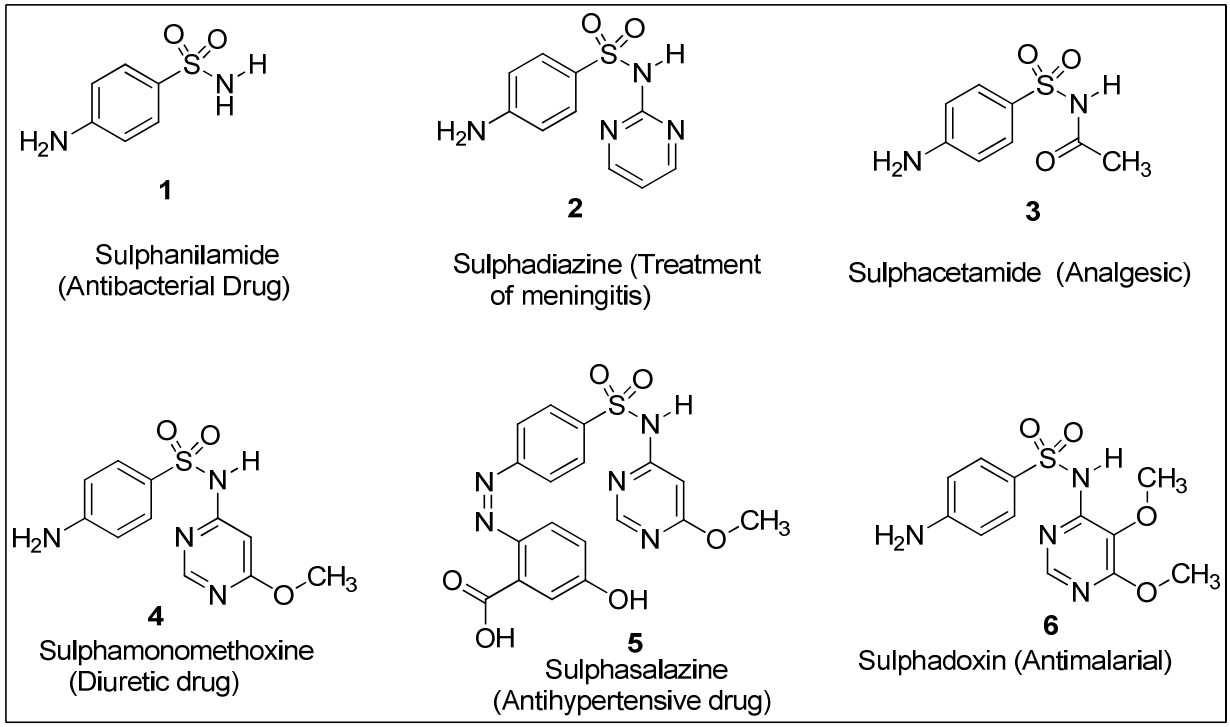


Fig.-1: Selected Commercially available sulfonamide-based drugs

In addition, sulfonamide motif contains a vital functionality owing to its numerous array of documented pharmacological properties which include antimalarial,[15] antibacterial,[16] anticancer,[17] antioxidant,[18] antitubercular,[19] anti-HIV,[20] antitumor,[21] anticonvulsant,[22] antidepressant[23] activities among others. Tolbutamide, the first sulfonylurea anti-diabetic drug, was approved in the United States in 1957 for the treatment of type 2 diabetics.[24] Similarly, amido containing compounds were known to have highly enhanced pharmacological properties which include, but not limited to including antitubercular,[25] analgesic, anti-inflammatory, insecticidal, antifungal and antitumor properties. The development of amide is a basic process of high importance in the study of organic compounds.[26,27] Design of effective methodology for amide preparation stands as an excellent idea because of their significance in basic sciences, leading to many varieties of commercial and medicinal utilization and as crucial synthons in organic synthetic chemistry.[26,28]

Therefore, it was envisaged that inserting of amide group into the sulfonamide moieties might lead to boosting or enhancement of antibacterial activity of such templates. Hence, it is conceivable to design the synthetic route in this present work in such a way to have amide functionality being incorporated within the framework of the synthesized sulfonamides. This might probably lead to the discovery of compounds with increased biological activity for future drug design and help in the comparative study of pharmacological properties of the ordinary sulfonamide to that of amide-bearing sulfonamide derivatives.

EXPERIMENTAL

All chemical compounds used were purchased from Sigma-Aldrich, USA and British Drug House Chemicals, UK. Solvents used were purified and dried by standard methods where necessary. Melting

points of solid compounds were established using Stuart melting point machine. The Infrared spectral data were determined with the aid of KBr pellet using the Perkin Elmer infrared Spectrophotometer and the frequencies of absorption were duly measured in wave number (cm^{-1}) from 4000 cm^{-1} to 500 cm^{-1}. The Ultraviolet-Visible (UV-vis.) spectral data were generated in either dichloromethane (CH_2Cl_2), or Dimethyl sulphoxide (DMSO) solvents using UV-Genesys Spectrophotometer. The absorbance was plotted against the wavelength λ_{max} (nm) and the obtained molar absorptivity was used to calculate Log ε_{max}. The reaction completion and degree of purity of the synthesized sulfonamide products were monitored by Thin Layer Chromatography. Furthermore, the ^{1}H NMR and ^{13}C NMR spectral analysis were carried out on NMR Bruker DPX 400 Spectrometer operating at the machine frequencies of 400 MHz and 100 MHz respectively using either $CDCl_3$ or DMSO-d_6, as a solvent for sample preparation prior to analyses. The standard abbreviation was used for the multiplicity. The acid value was confirmed with the aid of pH meter model PHB4. DHG-9023A Vacuum Oven was used to dry the solid where necessary while evaporation of the solvent was done using IKA® RV 10 Rotary evaporator. The determination of % composition of carbon, hydrogen, and nitrogen of the synthesized sulfonamides was carried out with Flash EA 1112 elemental analyzer. The result of % found of these elements was in concordance with that of % calculated values (Table-1).

Synthesis

Synthesis of 3-phenyl-2-(phenyl sulfonamide)propanoic acid, 7

1.113 g of Na_2CO_3 was tipped into a mixture of phenylalanine (6.00 mmol, 0.83 g) and distilled water (6 ml) with continuous stirring at room temperature till complete disappearance of the solute. The mixture placed in an ice bath until the temperature of 10 ^oC was attained; then followed by the addition of benzene sulfonyl chloride (6.00 mmol, 0.83 ml) batch-wisely three times for 1 h and warmed up to a room temperature also with stirring for 10 h. The reacting solution was worked upon. The first stage, the solution was poured into a separating funnel while the quantity of DCM was added to it, then it was shaking together for 15 mins and then allow to separate. The excess benzene sulfonyl chloride was collected into a 250 ml beaker while the expected product was collected into another big beaker for the better surface area. Secondly, the product collected into a big beaker was also worked upon by adding 2M HCl until pH of 2.1 was reached and the sulfonamide crystallized out immediately. The product was filtered with a filter paper and spread on the beach to dry to afford 91% yieldo of **7**. ^{1}H-NMR (400 MHz, DMSOd_6) δ_H: 7.61-7.59 (d, J = 8.28 Hz, 2H, Ar-H), 7.24-7.21 (m, 5H, Ar-H), 7.10-7.08 (m, 3H, Ar-H), 5.16-5.13 (d, J = 8.68 Hz, 1H, NH-CH), 4.21-4.17 (m, 1H, CH), 3.12-3.08 (dd, J_1 = 5.48 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 3.03-2.98 (dd, J_1 = 6.40 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2). ^{13}C-NMR (100 MHz, DMSOd_6) δ_C: 178.1 (C=O), 143.9, 136.6, 134.9, 129.8 (2 × CH), 129.6 (2 × CH), 128.8 (2 × CH), 127.4, 127.2 (2 × CH), 56.5 (CH), 39.0 (CH_2) ppm. IR (KBr) ν_{max}/cm^{-1}: 3435 (N-H), 3350 (OH), 3050 (C-H aromatic), 2925 (CH aliphatic), 2852 (CH aliphatic), 1730 (C=O of COOH), 1605 (C=C), 1575 (C=N), 1375 (SO_2, 1st band), 1225 (C=N), 1146 (SO_2, 2nd band), 1082 (C=N), 945 (=C-H), 724 (Ar-H).

Synthesis of ethyl 3-phenyl-2-(phenylsulfonamido)propanoate, 8

3-Phenyl-2-(phenylsulfonamido)propanoic acid **7** (6.55 mmol, 2.00 g) was tipped into 15 ml of absolute EtOH under continuous stirring at room temperature for about 15 mins, followed by the addition of concentrated H_2SO_4 (0.30 ml) drop-wisely and stirred at room temperature for additional 15 mins. The resulting solution was refluxed for 2 h and the solvent was evaporated to dryness with rotary evaporator. The resulting solid was triturated with cold water. It was filtered and air-dried to obtain 3-phenyl-2-(phenylsulfonamido)propanoate, **8** in 66% yield**.** ^{1}H-NMR (400 MHz, DMSOd_6) δ_H: 7.63-7.61 (d, J = 8.32 Hz, 2H, Ar-H), 7.25-7.18 (m, 5H, Ar-H), 7.13-7.10 (m, 3H, Ar-H), 5.88-5.86 (d, J = 9.44 Hz, 1H, NH-CH), 4.31-4.25 (m, 1H, CH), 3.13-3.09 (dd, J_1 = 5.48 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 3.04-2.99 (dd, J_1 = 6.40 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 2.79-2.74 (q, J = 7.12 Hz, 2H, CH_2-CH_3), 0.88-0.84 (t, J = 7.12 Hz, 3H, CH_3-CH_2). ^{13}C-NMR (100 MHz, DMSOd_6) δ_C: 175.7 (C=O), 143.1, 136.6, 134.8, 129.9 (2 × CH), 129.5 (2 × CH), 128.8 (2 × CH), 127.5, 127.1 (2 × CH), 56.7 (CH), 42.5 (CH_2), 39.3 (CH_2), 19.2 (CH_3) ppm. IR (KBr) ν_{max}/cm^{-1}: 3435 (N-H), 3042 (C-H aromatic), 2925 (CH aliphatic), 2852 (CH aliphatic),

1745 (C=O of ester), 1605 (C=C), 1574 (C=N), 1452 (CH_2 deformation), 1377 (SO_2, 1st band), 1225 (C=N), 1146 (SO_2, 2nd band), 1082 (C-N), 946 (=C-H), 725 (Ar-H).

General procedure for synthesis of targeted sulfonamide derivatives, 9a-j

Ethyl 3-phenyl-2-(phenyl sulfonamide)propanoate, **8** (3.30 mmol, 1.00 g), was transferred into 250 ml quick fit flask containing absolute EtOH (15 ml); then the resulting solution was allowed to stir at ambient temperature for 15 mins. The corresponding amino-containing nucleophile (3.30 mmol) was weighed and transferred into the solution and stirred for extra 15 mins at the same ambient condition. The reacting solution was then refluxed for 2 h and the solvent was evaporated to afford crude solids which were recrystallized from methanol to furnish the corresponding amido-bearing sulfonamide motifs **9a-j** in varying yields.

Synthesis of *N*,3-diphenyl-2-(phenyl sulfonamide)propanamide, 9a

Reactive intermediate **8** (3.30 mmol, 1.00 g) reacted with aniline (3.30 mmol, 0.30 ml) to afford *N*,3-diphenyl-2-(phenylsulfonamido)propanamide, **9a** in 86% yield. ^{1}H-NMR (400 MHz, $DMSOd_6$) δ_H: 11.08 (s, 1H, NH-CO), 7.62-7.60 (d, J = 8.34 Hz, 2H, Ar-H), 7.45-7.43 (d, J = 8.00 Hz, 2H, Ar-H), 7.27-7.24 (m, 5H, Ar-H), 7.20-7.18 (m, 3H, Ar-H), 7.15-7.12 (m, 3H, Ar-H), 5.88-5.86 (d, J = 9.42 Hz, 1H, NH-CH), 4.31-4.25 (m, 1H, CH), 3.13-3.09 (dd, J_1 = 5.48 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 3.04-2.99 (dd, J_1 = 6.40 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2). ^{13}C-NMR (100 MHz, $DMSOd_6$) δ_C: 171.3 (C=O), 145.1, 143.8, 136.7, 134.9, 130.2 (2 × CH), 129.8 (2 × CH), 129.6 (2 × CH), 128.8 (2 × CH), 127.4, 127.2 (2 × CH), 119.1, 115.2 (2 × CH), 56.5 (CH), 39.0 (CH_2) ppm. IR (KBr) ν_{max}/cm^{-1}: 3415 (N-H), 2930 (C-H aliphatic), 2850 (C-H aliphatic), 1685 (C=O), 1610 (C=C aromatic), 1491 (N-H amide), 1459 (CH_2 deformation), 1377 (SO_2, 1st band), 1140 (SO_2, 2nd band), 1073 (C-N), 952 (=C-H), 848 (C=C out of plane bending), 743 (Ar-H, bending and ring puckering). λ_{max}/nm (log ε_{max}): 207 (5.01), 244 (5.47), 286 (5.11), 583 (2.00).

Synthesis of *N*-(3-nitrophenyl)-3-phenyl-2-(phenylsulfonamido)propanamide, 9b

Reactive intermediate **8** (3.30 mmol, 1.00 g) reacted with 3-nitroaniline (3.30 mmol, 0.45 g) to afford *N*-(3-nitrophenyl)-3-phenyl-2-(phenylsulfonamido) propanamide, **9b** in 87% yield. ^{1}H-NMR (400 MHz, $DMSOd_6$) δ_H: 11.10 (s, 1H, NH-CO), 8.01 (s, 1H, Ar-H), 7.62-7.60 (d, J = 8.34 Hz, 2H, Ar-H), 7.47-7.46 (d, J = 6.20 Hz, 1H, Ar-H), 7.27-7.24 (m, 5H, Ar-H), 7.20-7.18 (m, 3H, Ar-H), 7.14-7.12 (m, 2H, Ar-H), 5.87-5.84 (d, J = 9.04 Hz, 1H, NH-CH), 4.31-4.25 (m, 1H, CH), 3.14-3.10 (dd, J_1 = 5.86 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 3.04-2.99 (dd, J_1 = 6.44 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2). ^{13}C-NMR (100 MHz, $DMSOd_6$) δ_C: 171.3 (C=O), 145.1, 144.2, 143.8, 136.7, 134.9, 130.2 (2 × CH), 129.8 (2 × CH), 129.6 (2 × CH), 128.8 (2 × CH), 127.4, 127.2 (2 × CH), 119.1, 115.3, 56.4 (CH), 39.1 (CH_2) ppm. IR (KBr) ν_{max}/cm^{-1}: 3422 (N-H), 3029 (C-H aromatic), 2923 (C-H aliphatic), 2853 (C-H aliphatic), 1685 (C=O amide), 1600 (C=C aromatic), 1579 (C=N), 1459 (CH_2 deformation), 1420 (CH_2 deformation), 1377 (SO_2, 1st band), 1352 (N=O stretching), 1228 (C-N), 1127 (SO_2, 1st band), 921 (=C-H), 735 (Ar-H). λ_{max}/nm (log ε_{max}): 206 (4.72), 227 (4.20), 251 (3.99), 374 (4.23).

Synthesis of *N*-(4-chlorophenyl)-3-phenyl-2-(phenylsulfonamido)propanamide, 9c

Reactive intermediate **8** (3.30 mmol, 1.00 g) reacted with 4-chloroaniline (3.30 mmol, 0.42 g) to afford *N*-(4-chlorophenyl)-3-phenyl-2-(phenylsulfonamido)propanamide, **9c** in 74% yield. ^{1}H-NMR (400 MHz, $DMSOd_6$) δ_H: 11.04 (s, 1H, NH-CO), 7.62-7.60 (d, J = 8.26 Hz, 2H, Ar-H), 7.42-7.40 (d, J = 8.00 Hz, 2H, Ar-H), 7.25-7.21 (m, 5H, Ar-H), 7.16-7.14 (d, J = 8.12 Hz, 2H, Ar-H), 7.10-7.07 (m, 3H, Ar-H), 5.16-5.14 (d, J = 7.68 Hz, 1H, NH-CH), 4.20-4.17 (m, 1H, CH), 3.12-3.07 (dd, J_1 = 6.02 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 3.03-2.98 (dd, J_1 = 6.40 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2). ^{13}C-NMR (100 MHz, $DMSOd_6$) δ_C: 171.3 (C=O), 145.1, 143.9, 142.7, 136.6, 134.9, 129.8 (2 × CH), 129.6 (2 × CH), 128.8 (2 × CH), 127.4, 127.2 (2 × CH), 123.7 (2 × CH), 115.2 (2 × CH), 56.7 (CH), 39.2 (CH_2) ppm. IR (KBr) ν_{max}/cm^{-1}: 3350 (N-H, 2° amine), 3100 (C-H aromatic), 2925 (C-H aliphatic), 2852 (C-H aliphatic), 1685 (C=O amide), 1620 (C=C aromatic), 1599 (C=N), 1496 (CH_2, deformation), 1377 (SO_2, 1st band), 1220 (C=N), 1130 (SO_2 2nd

band), 1074 (C-N), 745 (Ar-H), 698 (C-Cl bending). λ_{max}/nm (log ε_{max}): 207 (4.71), 251 (3.70), 269 (3.64), 323 (4.14).

Synthesis of *N*-(naphthalen-1-yl)-3-phenyl-2-(phenylsulfonamido)propanamide, 9d

Reactive intermediate **8** (3.30 mmol, 1.00 g) reacted with α-naphthylamine (3.30 mmol, 0.47 g) to afford *N*-(naphthalen-1-yl)-3-phenyl-2-(phenylsulfonamido)propanamide, **9d** in 65% yield. ^{1}H-NMR (400 MHz, $DMSOd_6$) δ_H: 11.05 (s, 1H, NH-CO), 8.16-8.14 (d, *J* = 7.24 Hz, 1H, Ar-H), 8.04-8.02 (d, *J* = 7.66 Hz, 1H, Ar-H), 7.61-7.59 (d, *J* = 8.28 Hz, 2H, Ar-H), 7.57-7.53 (m, 3H, Ar-H), 733-7.32 (d, *J* = 7.04 Hz, 1H, Ar-H), 7.24-7.21 (m, 5H, Ar-H), 7.17-7.15 (d, *J* = 7.14 Hz, 1H, Ar-H), 7.10-7.08 (m, 3H, Ar-H), 5.16-5.13 (d, *J* = 8.68 Hz, 1H, NH-CH), 4.21-4.18 (m, 1H, CH), 3.11-3.08 (dd, J_1 = 5.50 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 3.02-2.98 (dd, J_1 = 6.38 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2). ^{13}C-NMR (100 MHz, $DMSOd_6$) δ_C: 171.0 (C=O), 145.3, 143.1, 139.8, 136.6, 134.8, 133.2, 132.4, 130.1, 129.9 (2 × CH), 129.5 (2 × CH), 128.8 (2 × CH), 127.5, 127.1 (2 × CH), 125.7, 123.4, 119.9, 119.2, 115.2, 56.7 (CH), 39.3 (CH_2) ppm. IR (KBr) ν_{max}/cm^{-1}: 3400(N-H), 3045 (CH aromatic), 2924 (CH aliphatic), 2854 (C-H aliphatic), 1605 (C=C aromatic), 1555 (C=N), 1511 (N-H 2^o amine), 1461 (CH_2 deformation), 1377 (SO_2 1st band), 1216 (C=N), 1130 (SO_2 2nd band), 1073 (C-N), 912 (=C-H), 766 (Ar-H). λ_{max}/nm (log ε_{max}): 209 (4.69), 269 (4.16), 332 (5.43), 578 (3.23).

Synthesis of *N*-(1-hydrazinyl-1-oxo-3-phenylpropane-2-yl) benzenesulfonamide, 9e

Reactive intermediate **8** (3.30 mmol, 1.00 g) reacted with hydrazine hydrate (3.30 mmol, 0.16 ml) to afford *N*-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)benzenesulfonamide, **9e** in 54% yield. ^{1}H-NMR (400 MHz, $DMSOd_6$) δ_H: 11.00 (s, 1H, NH-CO), 7.62-7.60 (d, *J* = 8.32 Hz, 2H, Ar-H), 7.24-7.21 (m, 5H, Ar-H), 7.10-7.08 (m, 3H, Ar-H), 5.40 (s, 2H, NH_2), 5.14-5.11 (d, *J* = 8.60 Hz, 1H, NH-CH), 4.20-4.17 (m, 1H, CH), 3.13-3.08 (dd, J_1 = 5.82 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 3.02-2.97 (dd, J_1 = 6.44 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2). ^{13}C-NMR (100 MHz, $DMSOd_6$) δ_C: 172.1 (C=O), 143.9, 136.3, 134.7, 129.9 (2 × CH), 129.4 (2 × CH), 128.8 (2 × CH), 127.4, 127.1 (2 × CH), 56.4 (CH), 39.1 (CH_2) ppm. IR (KBr) ν_{max}/cm^{-1}: 3450 (N-H), 3100 (CH aromatic), 2924, 2854 (C-H aliphatic), 1627 (C=C aromatic), 1560 (C=N), 1459 (CH_2 deformation), 1377 (SO_2 1st band), 1226 (C=N), 1129 (SO_2 2nd band), 1074 (C-N), 913 (=C-H), 746 (Ar-H). λ_{max}/nm (log ε_{max}): 206 (4.57), 242 (4.33), 545 (4.32), 584 (4.34).

Synthesis of *N*-(1-(2-(2,4-dinitrophenyl)hydrazinyl)-1-oxo-3-phenylpropan-2-yl)benzene sulfonamide, 9f

Reactive intermediate **8** (3.30 mmol, 1.00 g) reacted with 2,4-dinitrophenylhydrazine (3.30 mmol, 0.65 g) to afford *N*-(1-(2-(2,4-dinitrophenyl)hydrazinyl)-1-oxo-3-phenylpropan-2-yl) benzene sulfonamide, **9f** in 82% yield. ^{1}H-NMR (400 MHz, $DMSOd_6$) δ_H: 11.05 (s, 1H, NH-CO), 10.00 (s, 1H, NH), 8.82 (s, 1H, Ar-H), 828-8.25 (d, *J* = 12.36 Hz, 1H, Ar-H), 7.69-7.66 (d, *J* = 9.72 Hz, 1H, Ar-H), 7.31-7.25 (m, 6H, Ar-H), 7.00 (s, 5H, Ar-H), 5.20 (s, 1H, NH), 3.92 (m, 1H, CH), 3.12-3.07 (dd, J_1 = 6.02 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 3.03-2.98 (dd, J_1 = 6.40 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2). ^{13}C-NMR (100 MHz, $DMSOd_6$) δ_C: 171.3 (C=O), 143.1, 141.7, 139.7, 139.1, 136.6, 134.8, 129.9 (2 × CH), 129.3 (2 × CH), 128.7 (2 × CH), 127.5, 127.1 (2 × CH), 125.7, 123.2, 119.6, 56.8 (CH), 39.1 (CH_2) ppm. IR (KBr) ν_{max}/cm^{-1}: 3367 (N-H), 2924 (C-H of CH_2), 1676 (C=O of amide), 1601 (C=C), 1489 (CH_2 deformation), 1376 (SO_2), 1182 (SO_2, 2nd band), 1092 (C-N), 980 (=C-H) 747 (Ar-H). λ_{max}/nm (log ε_{max}): 209 (4.83), 254 (4.73), 278 (4.75), 362 (5.46).

Synthesis of 2-(3-phenyl-2-(phenyl sulfonamide)propanoyl)hydrazinecarboxamide, 9g

Reactive intermediate **8** (3.30 mmol, 1.00 g) reacted with semicarbazide (3.30 mmol, 0.25 g) to afford 2-(3-phenyl-2-(phenylsulfonamido)propanoyl)hydrazinecarboxamide, **9g** in 55% yield. ^{1}H-NMR (400 MHz, $DMSOd_6$) δ_H: 11.05 (s, 1H, NH-CO), 10.54 (s, 1H, NH), 8.41 (s, 1H, NH of NH_2), 7.95 (s, 1H, NH of NH_2), 7.61-7.59 (d, *J* = 8.30 Hz, 2H, Ar-H), 7.24-7.20 (m, 5H, Ar-H), 7.11-7.08 (m, 3H, Ar-H), 5.13-5.11 (d, *J* = 7.86 Hz, 1H, NH-CH), 4.20-4.16 (m, 1H, CH), 3.13-3.08 (dd, J_1 = 5.82 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 3.02-2.98 (dd, J_1 = 6.40 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2). ^{13}C-NMR (100 MHz, $DMSOd_6$) δ_C: 172.9

(C=O), 172.1 (C=O), 143.9, 136.3, 134.7, 129.9 (2 × CH), 129.4 (2 × CH), 128.8 (2 × CH), 127.4, 127.1 (2 × CH), 56.2 (CH), 39.4 (CH_2) ppm. IR (KBr) ν_{max}/cm^{-1}: 3422, 3419 (NH_2, 2 bands), 3367 (N-H), 3035 (CH aromatic), 2928 (C-H of CH_2), 1687 (C=O of amide), 1676 (C=O of amide), 1615 (C=C), 1575 (C=N), 1485 (CH_2 deformation), 1375 (SO_2), 1175 (SO_2, 2nd band), 1095 (C-N), 965 (=C-H), 745 (Ar-H). λ_{max}/nm (log ε_{max}): 212 (4.73), 230 (3.68), 251 (3.92), 329 (3.59).

Synthesis of *N*-pentyl-3-phenyl-2-(phenylsulfonamido)propanamide, 9h

Reactive intermediate **8** (3.30 mmol, 1.00 g) reacted with *n*-pentylamine (3.30 mmol, 0.43 ml) to afford *N*-pentyl-3-phenyl-2-(phenylsulfonamido)propanamide, **9h** in 89% yield. ^{1}H-NMR (400 MHz, $DMSOd_6$) δ_H: 7.61-7.59 (d, *J* = 8.28 Hz, 2H, Ar-H), 7.24-7.21 (m, 5H, Ar-H), 7.10-7.08 (m, 3H, Ar-H), 5.89-5.87 (d, *J* = 8.88 Hz, 1H, NH-CH), 4.30-4.26 (m, 1H, CH), 3.44-3.43 (t, *J* = 3.28 Hz, 2H, NCH_2CH_2), 1.96-1.93 (m, 4H, 2 × CH_2), 1.49-1.46 (m, 2H, CH_2), 3.12-3.08 (dd, J_1 = 5.48 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 3.03-2.98 (dd, J_1 = 6.40 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 0.90-0.88 (t, *J* = 3.96 Hz, 2H, CH_3CH_2). ^{13}C-NMR (100 MHz, $DMSOd_6$) δ_C: 171.7 (C=O), 143.8, 136.6, 134.9, 129.9 (2 × CH), 129.6 (2 × CH), 128.7 (2 × CH), 127.4, 127.2 (2 × CH), 56.4 (CH), 39.1 (CH_2), 30.3 (CH_2), 23.8 (CH_2), 23.5 (CH_2), 22.9 (CH_2), 18.6 (CH_3) ppm. IR (KBr) ν_{max}/cm^{-1}: 3367 (N-H), 3044 (CH aromatic), 2922 (C-H of CH_2), 1685 (C=O of amide), 1620 (C=C), 1575 (C=N), 1460 (CH_2 deformation), 1377 (SO_2, 1st band), 1178 (SO_2, 2nd band), 1089 (C-N), 943 (=C-H), 725 (Ar-H). λ_{max}/nm (log ε_{max}): 212 (4.87), 548 (4.57), 575 (4.53), 593 (4.54).

Synthesis of *N*-cyclohexyl-3-phenyl-2-(phenylsulfonamido)propanamide, 9i

Reactive intermediate **8** (3.30 mmol, 1.00 g) reacted with cyclohexylamine (3.30 mmol, 0.33 g) to afford *N*-cyclohexyl-3-phenyl-2-(phenylsulfonamido)propanamide, **9i** in 63% yield. ^{1}H-NMR (400 MHz, $DMSOd_6$) δ_H: 7.62-7.59 (d, *J* = 8.68 Hz, 2H, Ar-H), 7.25-7.21 (m, 5H, Ar-H), 7.11-7.08 (m, 3H, Ar-H), 5.88-5.86 (d, *J* = 8.16 Hz, 1H, NH-CH), 4.30-4.26 (m, 1H, CH), 4.21-4.18 (quintet, *J* = 5.68 Hz, 1H, $CH(CH_2)_2$) 3.44-3.42 (t, *J* = 3.68 Hz, 2H, NCH_2CH_2), 3.12-3.08 (dd, J_1 = 5.48 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 3.03-2.98 (dd, J_1 = 6.40 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 1.61-1.58 (m, 4H, 2 × CH_2), 1.49-1.46 (m, 4H, 2 × CH_2), 1.20-1.17 (m, 2H, CH_2). ^{13}C-NMR (100 MHz, $DMSOd_6$) δ_C: 171.7 (C=O), 143.8, 136.6, 134.9, 129.9 (2 × CH), 129.6 (2 × CH), 128.7 (2 × CH), 127.4, 127.2 (2 × CH), 56.4 (CH), 39.1 (CH_2), 30.3 (CH_2), 23.8 (CH_2), 23.5 (CH_2), 22.9 (CH_2), 18.6 (CH_3) ppm. IR (KBr) ν_{max}/cm^{-1}: 3365 (N-H), 3040 (CH aromatic), 2928 (C-H of CH_2), 1685 (C=O of amide), 1620 (C=C), 1575 (C=N), 1460 (CH_2 deformation), 1377 (SO_2, 1st band), 1175 (SO_2, 2nd band), 1090 (C-N), 943 (=C-H), 721 (Ar-H). λ_{max}/nm (log ε_{max}): 221 (5.43), 260 (5.44), 578 (3.80), 584 (3.80).

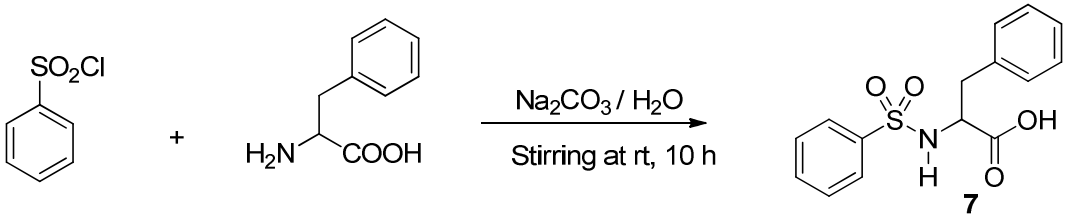
Synthesis of *N*-hexadecyl-3-phenyl-2-(phenylsulfonamido)propanamide, 9j

Reactive intermediate **8** (3.30 mmol, 1.00 g) reacted with hexadecylamine (3.30 mmol, 0.79 g) to afford *N*-hexadecyl-3-phenyl-2-(phenylsulfonamido)propanamide, **9j** in 91% yield. ^{1}H-NMR (400 MHz, $DMSOd_6$) δ_H: 7.61-7.59 (d, *J* = 8.28 Hz, 2H, Ar-H), 7.24-7.21 (m, 5H, Ar-H), 7.10-7.08 (m, 3H, Ar-H), 5.89-5.87 (d, *J* = 8.88 Hz, 1H, NH-CH), 4.30-4.26 (m, 1H, CH), 3.46-3.45 (t, *J* = 3.06 Hz, 2H, NCH_2CH_2), 3.12-3.08 (dd, J_1 = 5.48 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 3.03-2.98 (dd, J_1 = 6.40 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2), 1.54-1.51 (m, 2H, CH_2), 1.46-1.1.42 (m, 2H, CH_2), 1.29-1.20 (m, 24H, 12 × CH_2), 0.90-0.87 (t, *J* = 4.22 Hz, 2H, CH_3CH_2). ^{13}C-NMR (100 MHz, $DMSOd_6$) δ_C: 171.7 (C=O), 143.8, 136.6, 134.9, 129.9 (2 × CH), 129.6 (2 × CH), 128.7 (2 × CH), 127.4, 127.2 (2 × CH), 56.4 (CH), 39.9 (CH_2), 39.1 (CH_2), 30.3 (CH_2), 29.7 (8 × CH_2), 29.1 (2 × CH_2), 26.7 (CH_2), 23.5 (CH_2), 22.9 (CH_2), 15.9 (CH_3) ppm. IR (KBr) ν_{max}/cm^{-1}: 3367 (N-H), 3044 (CH aromatic), 2922 (CH aliphatic), 2848 (CH aliphatic), 1687 (C=O of amide), 1615 (C=C), 1575 (C=N), 1460 (CH_2 deformation), 1376 (SO_2, 1st band), 1175 (SO_2, 2nd band), 1093 (C-N), 943 (=C-H), 725 (Ar-H). λ_{max}/nm (log ε_{max}): 212 (5.12), 265 (5.23), 378 (4.89), 545 (3.80).

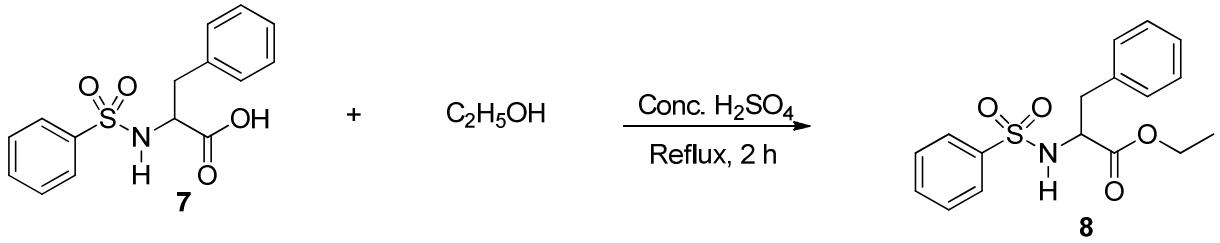
RESULTS AND DISCUSSION

In the continuation of the research endeavor to design and derived more bioactive sulfonamide frameworks,[12,29] we have herein reported the synthesis of functionalized carboxamide-based sulfonamide derivatives via a facile synthetic route. Synthesis of the precursor **7**, reactive intermediate **8** and the targeted

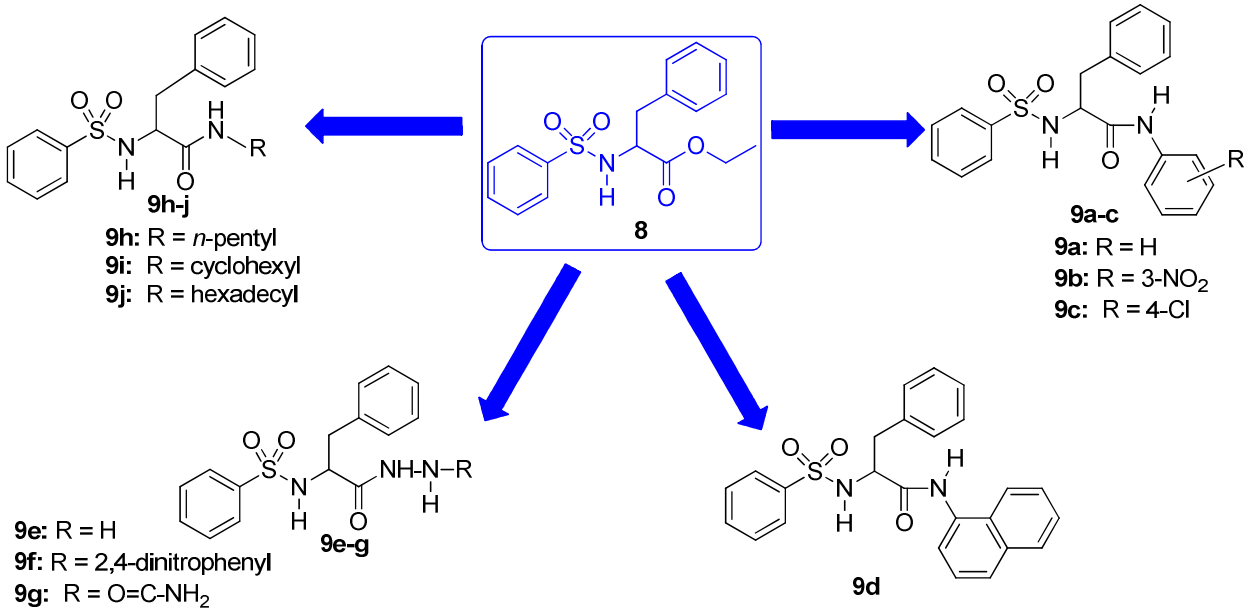
carboxamide-based sulfonamide final products **9a-j** were accomplished according to the steps illustrated in Schemes 1, 2 and 3 respectively. The synthesis began with the reaction of benzenesulfonyl chloride with L-phenyl alanine in the presence of sodium carbonate solution at ambient temperature for 10 h to afford 3-phenyl-2-(phenyl sulfonamido) propanoic acid, **7** (Scheme 1). This was achieved in excellent yield via our earlier reported method.[29] Secondly, the precursor **1** was esterified with absolute ethanol for 2 h in the presence of a mineral acid catalyst to afford ethyl 3-phenyl-2-(phenyl sulfonamide)propanoate, **8** (Scheme 2). The reaction of reactive intermediate sulfonamide **8** with aniline derivatives **a-c** via refluxing in the presence of ethanol afforded compounds **9a-c,** while the treatment of the compound **8** with α-naphthylamine **d** furnished compound **9d**. When the reactive sulfonamide **8** was heated under reflux in the presence of hydrazine hydrate **e**, 2,4-dinitrophenylhydrazine **f** and semicarbazide **g**, the corresponding sulfonamide-based hydrazine carboxamide **9e-g** were obtained in varying yields as shown in Table 1. Finally, the thermal reaction of **8** with three aliphatic amines *n*-pentylamine **h**, cyclohexylamine **i** and hexadecylamine **j**, over 2 h of refluxing provided a convenient route to access the corresponding sulfonamides **9h-j**. The synthetic route for accessing all the final titled products **9a-j** is as shown in Scheme 3.



Scheme-1: Pathway for the synthesis of 3-phenyl-2-(phenyl sulfonamide)propanoic acid, 7



Scheme-2: Pathway for the synthesis of ethyl 3-phenyl-2-(phenyl sulfonamide)propanoate, 8



Scheme-3: Synthetic route to *N*-substituted-3-phenyl-2-(phenylsulfonamido)propanamide, 9a-j

The result of the physicochemical parameter which includes molecular formula, melting point, yield, R_f, and color and elemental analysis was herein reported (Table-1). The final products' molecular formula varied from 305.35 for compound **9a** to 528.79 for **9j**. All the synthesized compounds had definite melting points except compound **9h** alone which was not determined because of its semi-solid nature at room temperature. The melting point of all the compounds was high, with **9b** having lowest at the value of 173-175 ^oC and **7** having the highest value of 296-298 ^oC**.** These high melting point values might be attributable to the amide bond formation and the tendency for hydrogen bond existence therein. The percentage yields of targeted compounds ranged from good to excellent in nature. Coincidentally, the first (precursor **7**) and the last compound (sulfonamide **9j**) had the same yield of 91% which was the highest yield recorded herein while targeted compound **9e** had the lowest yield (55%) among the series. The Thin Layer Chromatography (TLC) was used to monitor the progress and completion of the reaction as well as to ascertain the purity level of the compounds synthesized. The R_f calculated from the TLC varied from 0.44 for precursor **7** to 0.87 for sulfonamide **9d**. Although, three different solvent ratio combination were used as eluents, the precursor **7** exhibiting lowest R_f was an indication of high polarity due to the presence of COOH in **7**. This further corroborated the highest melting point observed in precursor **7** among all the compound synthesized herein. This behavior in precursor **7** might be as a result of the existence of stronger intramolecular hydrogen bonding in COOH than in the amide formed later after conversion to **9a-j**.

Table-1: Physicochemical parameter for the synthesized compounds 9a-j and precursors

Code	Mol. Formular (Mol. Weight)	M. Pt (^oC)	Yield (%)	Rf	Colour	Elemental Analysis % Calcd. (%Found)		
7	$C_{15}H_{15}NO_4S$ (305.35)	296-298	91	0.44^y	offwhite powder	59.00 (58.82)	4.95 (5.01)	4.59 (4.68)
8	$C_{17}H_{19}NO_4S$ (333.40)	241-243	66	0.53^x	White pellet	61.24 (61.41)	5.74 (5.92)	4.20 (4.39)
9a	$C_{21}H_{20}N_2O_3S$ (380.46)	219-221	86	0.80^x	White powder	66.29 (66.45)	5.30 (5.35)	7.36 (7.55)
9b	$C_{21}H_{19}N_3O_5S$ (425.46)	173-175	87	0.80^y	Yellow pellet	59.28 (59.47)	4.50 (4.69)	9.88 (10.04)
9c	$C_{21}H_{19}N_2O_3SCl$ (414.91)	209-212	74	0.82^z	White powder	60.79 (60.95)	4.62 (4.45)	6.75 (6.83)
9d	$C_{25}H_{22}N_2O_3S$ (430.52)	191-192	65	0.87^z	Lilac powder	69.75 (69.91)	5.15 (4.98)	6.51 (6.70)
9e	$C_{15}H_{17}N_3O_3S$ (319.38)	269-272	54	0.64^y	White powder	56.41 (56.25)	5.37 (5.52)	13.16 (12.97)
9f	$C_{21}H_{19}N_5O_7S$ (485.47)	188-190	82	0.69^y	Red powder	51.95 (52.09)	3.94 (4.04)	14.43 (14.60)
9g	$C_{16}H_{18}N_4O_4S$ (362.40)	208-210	55	0.84^x	Brown crystal	53.03 (52.91)	5.01 (4.93)	15.46 (15.63)
9h	$C_{20}H_{26}N_2O_3S$ (374.50)	Semi solid	89	0.48^x	Slurry cream	64.14 (63.99)	7.00 (6.85)	7.48 (7.64)
9i	$C_{21}H_{26}N_2O_3S$ (386.51)	244-246	63	0.51^x	Cream powder	65.26 (65.19)	6.78 (6.87)	7.25 (7.43)
9j	$C_{31}H_{48}N_2O_3S$ (528.79)	224-227	91	0.58^y	Powder ash	70.41 (70.55)	9.15 (8.97)	5.30 (5.50)

Solvent ratio x = (DCM/Methanol; 9:1), y = (DCM/Hexane; 9:1), z = (DCM/Hexane; 8:2)

The spectroscopic characterization of the synthesized compounds was investigated using infrared, ultraviolet, ^1H and ^{13}C NMR. The ^1H NMR spectra of all synthesized compounds have been analyzed in DMSO-d_6 over the scan range of 0 to 13 δ ppm. The spectroscopic result of compound **9a** was given in detail as a representative of the final products **9a-j**. The most downfield signal in **9a** was 1H singlet of an amide at δ_H 11.08 ppm. A doublet at δ_H 7.62-7.60 ppm was attributed to 2H aromatic linked to sulfonyl group and with a *J* value of 8.34 Hz, while the doublet assigned at δ_H 7.45-7.43 ppm was 2H aromatic linked to amide moieties and with a coupling constant of 8.00 Hz. All other eleven protons of aromatic

resonated as a 5H multiplet at δ_H 7.27-7.24 ppm, 3H multiplet at δ_H 7.20-7.18 ppm and 3H multiplet at δ_H 7.15-7.12 ppm. These aromatic proton values were consistent with those earlier reported by Kushwaha *et al.*,[25] who synthesized and investigated some amide derivatives for their biological activity. The proton of NH signal linked CH resonated as a doublet at δ_H 5.88-5.86 ppm, while that of its CH neighbor was noticed as a multiplet at δ_H 4.31-4.25 ppm. This chemical shift in CH was due to deshielding effect as an inserted CH between sulfonamide and amide functionalities. The most upfield signal was that of CH_2 linked to benzene and they resonated separately as a 1H doublet of doublet each at δ_H 3.13-3.09 ppm and 3.04-2.99 ppm respectively. The ^{13}C NMR spectra of all the synthesized compounds have been analyzed in DMSO-*d*$_6$ over the scan range of 0 to 200 ppm. The ^{13}C-NMR spectrum was run at 100 MHz using DMSO-*d*$_6$ and compound **9a** was observed to have its most downfield signal at 171.3 ppm which was for carbonyl of the amide. Eighteen aromatic carbon were found from 145.1 ppm to 115.2 ppm while methane carbon (CH) was found at 56.5 ppm in compound **9a**. The least signal was that of methylene (CH_2) which resonated at 39.0 ppm. In the overall for targeted products **9a-j**, the most deshielded carbon was found in **9g** with signal at 172.9 ppm which was due to the presence of carbonyl of amide and it fell within the range of the values earlier reported by Ajani *et al.*,[26] who synthesized and examined spectroscopic features of some bioactive sulfonamide containing motifs. The most shielded carbon atom among the final product was found in **9j** with chemical shift of 18.5 ppm which depicted the presence of CH_3 attached to long aliphatic carbon chains. However, it is worthy to note that the chemical shift of C=O of precursor **7** (δ_c 178.5 ppm) was higher than that of all the final products **9a-j** (δ_c 171.1-172.9 ppm), which implied that there was an obvious synthetic modification on the COOH of precursor **7** to have led to the final product which was bearing C=O of amide. The careful evaluation of infrared spectral feature of compound **9a** revealed that the absorption frequency at 3415 cm^{-1} was for N-H functionality and it was doubly confirmed by the presence of bending vibration bands at 1491 cm^{-1} and C-N functionality at 1073 cm^{-1}. The absorption frequencies at 2930 cm^{-1} and 2850 cm^{-1} were for C-H of aliphatic which was confirmed by the occurrence of CH_2 deformation at 1459 cm^{-1} which were consistent with an earlier report.[30] The absorption frequencies at 1685 cm^{-1} as well as 1610 cm^{-1} in compounds **9a** showed the presence carbonyl of amide and C=C aromatic respectively. The two sulfonyl bands were present at 1377 cm^{-1} and 1140 cm^{-1}. This fell within the range earlier reported by Ajani *et al*.[12] for some bioactive sulfonamides. The UV spectrum of **9a** was run in methanol and the wavelength λ_{max} was recorded in nanometer (nm) alongside with the log ε_{max}. Generally, the electronic transition of UV-visible spectra of all synthesized compounds in methanol led to the λ_{max} values from 206 nm to 593 nm. Specifically speaking for **9a,** the first wavelength was observed at 207 nm (Log ε_{max} 5.01) which was as a result of $\pi \rightarrow \pi^*$ transition peculiar to C=C of the benzene ring. Other transitions were observed in the UV spectrum of **9a** giving rise to λ_{max} values at 244 nm (Log ε_{max} 5.47), 286 nm (Log ε_{max} 5.11) and 583 nm (Log ε_{max} 2.00). The bathochromic shift observed at the higher wavelengths between 244 nm to 583 nm was due to the occurrence of $\pi \rightarrow n$ transition that was resulting from the presence of the chromophoric moieties and auxochromic group attached to the ring system. The delocalization of their lone pairs played a key role in the bathochromic shift occurrence experienced herein.

CONCLUSION

Based on the results, it can be concluded that the synthesis of the sulfonamide bearing diversified carboxamide was successfully achieved. The characterization carried out authenticated the structures of the targeted products as envisaged. The technique used herein was found to be efficient and cost-effective for the production of the series of new sulfonamide derivatives. The targeted compounds are good candidates for further study for antimicrobial investigation and could probably be the potential source of chemotherapeutic drugs.

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