Tanzania Journal of Science 47(3): 1296-1302, 2021
ISSN 0856-1761, e-ISSN 2507-7961

Synthesis and Antimicrobial Activities of 1-((5-Chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide

Oluwaseyi B Ovonramwen[1]*, Bodunde J Owolabi[1] and Abiodun Falodun[2]
[1*]*Department of Chemistry, Faculty of Physical Sciences, University of Benin, P.M.B. 1154, Benin City, Edo State, Nigeria.*
[2]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Benin, Nigeria.*
**Corresponding author, e-mail: adebuloyeoluwaseyi@yahoo.com*
Co-authors' e-mails: owolabibodunde@yahoo.com; faloabi@uniben.edu
Received 25 May 2021, Revised 17 Aug 2021, Accepted 23 Aug 2021, Published Aug 2021
DOI: https://dx.doi.org/10.4314/tjs.v47i3.36

Abstract

A new 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide was synthesized from methyl-1-[(5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl]pyrrolidine-2-carboxylate and ethylamine. The compound methyl-1-[(5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl]pyrrolidine-2-carboxylate was synthesized from methyl pyrrolidine-2-carboxylate and 5-chloro-4-chlorosulfonyl-1-ethyl-2-methyl-imidazole. The compounds were characterized based on FTIR, ^{1}H, ^{13}C NMR, and DEPT 135 analysis. Antimicrobial activities of the 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide against Gram-positive (methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, and *Bacillus subtilis*), Gram-negative (*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*), and *Candida albicans* were carried out using the standard microbiological method. The newly synthesized 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide had no activities against the tested organisms.

Keywords: 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide; methyl-1-[(5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl]pyrrolidine-2-carboxylate; *L*-proline; ethylamine.

Introduction

Carboxamides are one of the most investigated compounds in organic synthesis and active pharmaceutical compounds (Eze et al. 2019, Saber et al. 2020). They are generally obtained from carboxylic acids and amines (D'Amaral et al. 2021, Zarecki et al. 2020). The inherent acid and base reactivity of the precursors often hamper the reaction. In most cases, carboxamides are prepared from the corresponding activated carboxylic acid derivatives such as acid chlorides (Bibi et al. 2019, González-Lópeza et al. 2020) acid anhydrides (Mevan Dissanayake et al. 2019, Gondi et al. 2019), and esters (Bildirici et al. 2018, Gondi et al. 2019) with suitable amines in the presence of a base such as sodium carbonate (Bildirici et al. 2018), sodium hydroxide (Sehmi et al. 2020), or triethylamine (González-Lópeza et al. 2020). The preparation is either from direct *in situ* or separate synthetic step of amidation reaction without further purification. The work reported in this paper aimed at the synthesis of 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide from methyl-

1-[(5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl]pyrrolidine-2-carboxylate and ethylamine and screened against Gram-positive (methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, and *Bacillus subtilis*), Gram-negative (*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*), and *Candida albicans*.

Materials and Methods

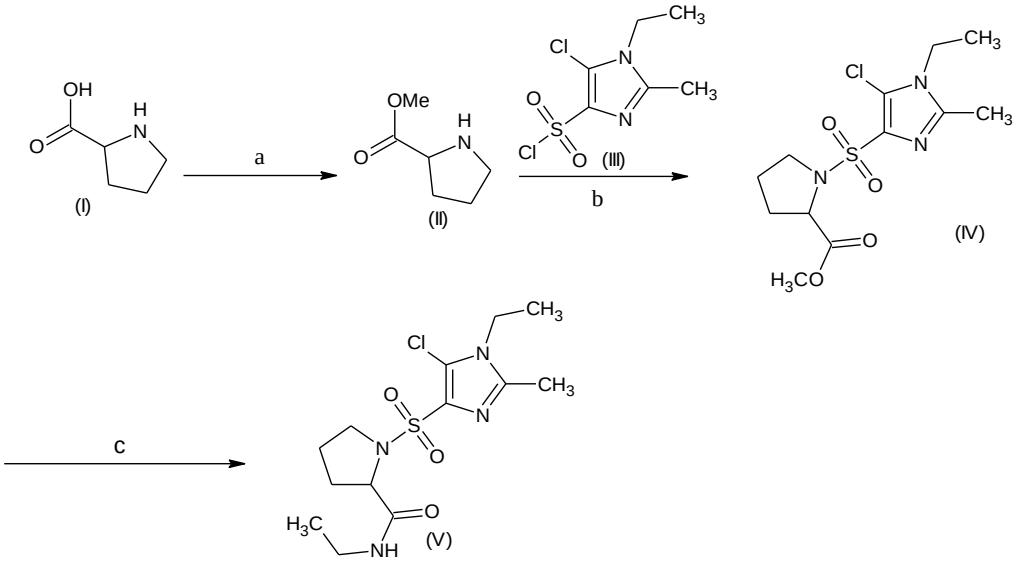
All the reagents were obtained from commercial stores and were used without further purification. The reactions were monitored with TLC silica gel plates view under UV light. Melting points were measured uncorrected on Stuart SMP-10. FT-IR spectra were recorded using a CARY 630 instrument (Agilent Technologies, USA). ^{1}H, ^{13}C NMR, and DEPT 135 spectra were recorded on a Bruker AVANCE 500 spectrometer in $CDCl_3$ with TMS as internal standard. Chemical shifts are expressed as parts per million. Chemical shift data of multiplicity were presented as: (-s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet-), and coupling constants in Hertz (Hz).

Methods

Synthesis of methyl pyrrolidine-2-carboxylate (II)

Thionyl chloride (5 mL, 0.042 mol) was added dropwise to *L*-proline (2.50 g, 0.022 mol) (I) in methanol (30 mL) for 30 min at 0 °C in a flat bottom flask. The mixture was left at room temperature for 1 h and then heated to reflux for 2 h. The solvent was evaporated and triturated twice with methanol to afford a yellow oil (2.78 g, 98%) (Scheme 1).

$C_6H_{11}NO_2$: yellow oil, ^{1}H-NMR (500 MHz, $CDCl_3$, δ in ppm): 1.95-1.98 (m, 2 H), 2.18-2.22 (m, H), 2.40-2.44 (m, H), 3.26 (s, H), 3.45-3.48 (m, 2 H), 3.86 (s, 3 H, OCH_3), 4.49-4.51 (d, H, *J* = 10 Hz, CH); ^{13}C-NMR ($CDCl_3$) 24.50 (CH_2), 30.08 (CH_2), 54.05 (OCH_3), 50.77 (CH_2), 64.55 (CH), 171.8 (C=O, ester).



Reaction conditions: a) $SOCl_2$, MeOH, 0 °C; 30 min, reflux; 2 h; b) 10% Na_2CO_3, RT 2 h; c) $CH_3CH_2NH_2$, RT 30 min, reflux 3 min.

Scheme 1: Synthesis of 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide.

Synthesis of 5-chloro-1-ethyl-2-methylimidazole-4sulfonyl chloride (III)

In a 250 mL flat bottom flask equipped with reflux condenser, chilled distilled chlorosulphonic acid (22.5 mL, 1.02 mol) was carefully added to 5-chloro-1-ethyl-2-methylimidazole (5 g, 0.10 mol), portion-wise. The mixture was fitted to a calcium chloride guard tube and then heated to reflux for 3 h. The solution was cooled, poured in crushed ice and filtered immediately to get the product (3 g) (Ovonramwen et al. 2021).

$C_6H_8C_{l2}N_2O_2S$: brown powder; yield 53.52%; m. p. 116–117 °C; R_f, 0.89 ($CHCl_3$); FTIR (ATR), *V*/cm^{-1}: 2981, 2853, 1638, 1508, 1498, 1437, 1377, 1351, 1263, 1226, 1187, 1142, 787, 722, 666 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 1.29–1.30 (t, 3 H, *J* = 10 Hz, CH_3), 2.39 (s, 3 H, CH_3), 3.95-4.01 (q, 2 H, *J* = 5 and 10 and 5 Hz, CH_2).

Synthesis of methyl-1-[(5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl]pyrrolidine-2-carboxylate (IV)

To methyl pyrrolidine-2-carboxylate (II) (2.58 g, 0.02 mol) and 4.9 g (0.02 mol) of 5-chloro-4-chlorosulfonyl-1-ethyl-2-methyl-imidazole (III) in a 250 mL flat bottom flask, were dissolved in 20 mL of 10% Na_2CO_3. The mixture was stirred at 25-28 ^{o}C for 2 h to yield brown oil (4 g, 58.8%).

$C_{12}H_{18}ClN_3O_4S$: brown oil; yield 58.8%; R_f, 0.91 (EtOAc); FT-IR (ATR, neat, *V*/cm^{-1}): 3061 (aromatic), 2978 (CH_3), 2943, 2866 (CH_2), 1648 (C=O), 1568 (C=N, str), 1450 (ring C-H), 1354 (S=O, SO_2 as, str), 1260 (C-N bend, str), 1176 (S=O, SO_2 sy, str), 1065 (ring CH_2, str), 664 (C–Cl, str) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 1.28-1.31 (t, 3 H, *J* = 10 and 5 Hz, CH_3, imidazole), 1.90-1.94 (m, 2 H, CH_2, pyrrolidine), 2.28-2.32 (m, 2 H, CH_2, pyrrolidine), 2.40 (s, 3 H, CH_3, imidazole), 3.28-3.32 (m, 2 H, CH_2, pyrrolidine), 3.82 (s, 3 H, OCH_3), 3.96-4.00 (q, 2 H, *J* = 5 and 10 and 5 Hz, CH_2, imidazole), 4.45-4.47 (d, H, *J* = 10 Hz, CH, pyrrolidine); ^{13}C NMR ($CDCl_3$, δ in ppm): 13.85 (CH_3, imidazole), 14.72 (CH_3, imidazole), 24.55 (CH_2, pyrrolidine), 30.13, (CH_2, pyrrolidine), 38.50 (CH_2, imidazole), 51.05 (CH_2, pyrrolidine), 54.43 (OCH_3), 62.87 (CH, pyrrolidine), 120.87 (C-5), 129.85 (C-4), 145.45 (C-imidazole), 172.15 (C=O).

Synthesis of 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide (V)

Ethylamine (0.68 g, 0.015 mol) was added to methyl-1-[(5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl]pyrrolidine-2-carboxylate (IV) (1.73 g, 0.005 mol) in a flat bottom flask, stirred at room temperature for 30 min, then heated to reflux for 3 min, cooled and triturated with water. The product was recrystallized from ethanol to produce brown crystals 1.65 g, 88.5%.

$C_{13}H_{21}ClN_4O_3S$: brown crystals; yield 88.5%; R_f, 0.79 (MeOH: hex, 9:1); m. p. 172-174 ^{o}C; FT-IR (ATR, neat, *V*/cm^{-1}): 3381 (NH), 2982 (CH_3), 2933, 2876 (CH_2), 1659 (C=O), 1528 (C=N, str), 1450 (ring C-H), 1357 (S=O, SO_2 as, str), 1252 (C-N bend, str), 1189, 1156 (S=O, SO_2 sy, str), 1118 (C-N bend, str), 1059 (ring CH_2, str), 846, 813 (S–O, str), 760, 664 (C–Cl, str) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 1.15-1.18 (t, 3 H, *J* = 10 and 5 Hz, CH_3, amine), 1.34-1.37 (t, 3 H, *J* = 10 and 5 Hz, CH_3, imidazole), 1.86-1.90 (m, 2 H, CH_2, pyrrolidine), 2.27-2.31 (m, 2 H, CH_2, pyrrolidine), 2.43 (s, 3 H, CH_3, imidazole), 3.30-3.34 (m, 2 H, CH_2, pyrrolidine), 3.47-3.50 (q, 2 H, *J* = 5 and 5 and 5 Hz, CH_2, amine), 3.98-4.02 (q, 2 H, *J* = 5 and 10 and 5 Hz, CH_2, imidazole), 4.45-4.47 (d, H, *J* = 10 Hz, CH, pyrrolidine), 7.24 (br, NH); ^{13}C NMR ($CDCl_3$, δ in ppm): 13.87 (CH_3, imidazole), 14.74 (CH_3, amine), 14.82 (CH_3, imidazole), 24.65 (CH_2, pyrrolidine), 30.13, (CH_2, pyrrolidine), 34.50 (CH_2, imidazole), 40.04 (CH_2, amine), 49.77(CH_2, pyrrolidine), 62.62 (CH, pyrrolidine), 121.17 (C-5), 130.65 (C-4), 144.81 (C-imidazole), 171.13 (C=O).

Antimicrobial activities

Determination of zone of inhibition

The microbial activities of the synthesized 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-

yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide against clinical isolated Gram-positive bacteria (methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), and *B. subtilis*), Gram-negative bacteria (*P. aeruginosa*, *E. coli*, *K. pneumoniae*), and *C. albicans* were determined by the agar well plate method. Sterile nutrient and Sabouraud dextrose agar plates were prepared for bacteria and fungi, respectively. The organisms were cultured and subcultured using the standard microbiological method. The standardized inoculum of test organisms was spread uniformly. Five wells were bored using a sterile borer (8 mm), the bases were sealed with 50 µL molten agar and 100 µL of the test concentrations of 5, 10, 20 mg/mL, standard antibiotic, and the solvent control (methanol and water, 1:1) were added to the wells. The plates were left on the table for 1 h for the test solution to diffuse into the medium and then incubated at 37 °C for 18–24 h. The resultant zones of inhibition of microbial growth around the well were measured in mm. The test was performed in triplicate. Standard antibiotics ciprofloxacin (30 mg/mL), and itraconazole (50 mg/mL) were tested against bacteria and fungi, respectively as the positive control (Ovonramwen et al. 2021).

Results and Discussion

L-proline was reacted with thionyl chloride and methanol to afford the methyl pyrrolidine-2-carboxylate which correlated with literature data. This was later reacted with 5-chloro-4-chlorosulfonyl-1-ethyl-2-methyl-imidazole to give methyl-1-[(5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl]pyrrolidine-2-carboxylate. The ester was reacted with ethylamine to produce 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide. The synthesized 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide was assigned the structure by detailed analysis of FTIR, ^{1}H, ^{13}C NMR, and DEPT (Figures 1–4). The FT-IR spectrum of 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide exhibited absorption bands of N–H, C=O, and C–H at 3381, 1659, and 2982-2876 cm^{-1}, respectively (Pretsch et al. 2009, Ambrożkiewicz et al. 2020). The N–H vibrational stretching gave the absorption band of a secondary amine of the amide which buttressed the formation of a new functional group. The ^{1}H-NMR data of the imidazole ring correlated with our previous work (Ovonramwen et al. 2021). The ^{1}H-NMR spectrum supported the claim of the proposed structure by the appearance of the alkyl and NH signals with their respective integration and multiplicity as well as the disappearance of OCH_3 signal. This showed there were bond breaking and bond formation. The ^{13}C-NMR spectrum also corroborated this with an upfield shift in resonance of C=O of the methyl ester at 172.15 to 171.13 ppm of the 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide (Zarecki et al. 2020) because of less electronegativity of the nitrogen in the amide.

The compound 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide was tested for the antimicrobial activities but showed no *in vitro* antimicrobial activities against Gram-positive bacteria (MSSA, MRSA, and *B. subtilis*), Gram-negative bacteria (*P. aeruginosa*, *E. coli*, *K. pneumoniae*) and *C. candidas* which is in line with literature (Tunc 2019, Alhameed et al. 2020, Ovonramwen et al. 2021). Therefore, the 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide had no effect on the tested organisms perhaps other organisms.

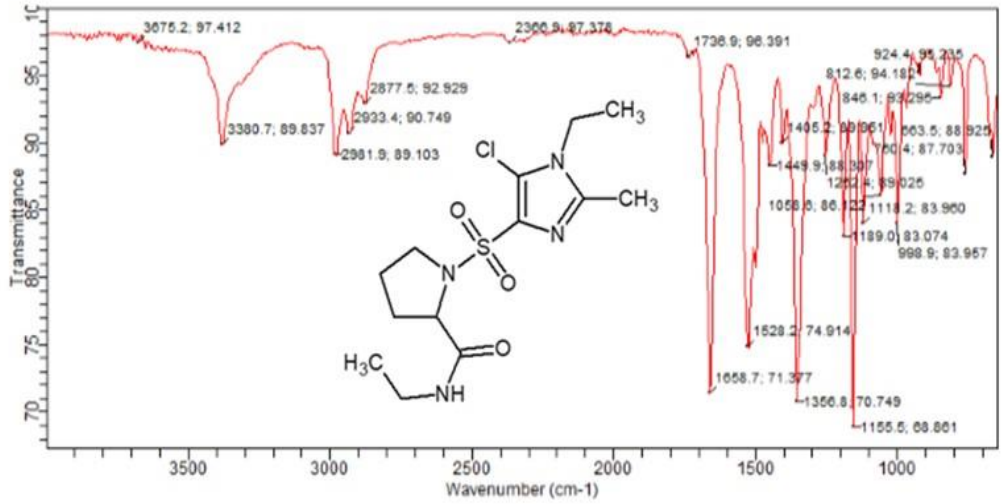


Figure 1: FTIR of 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide.

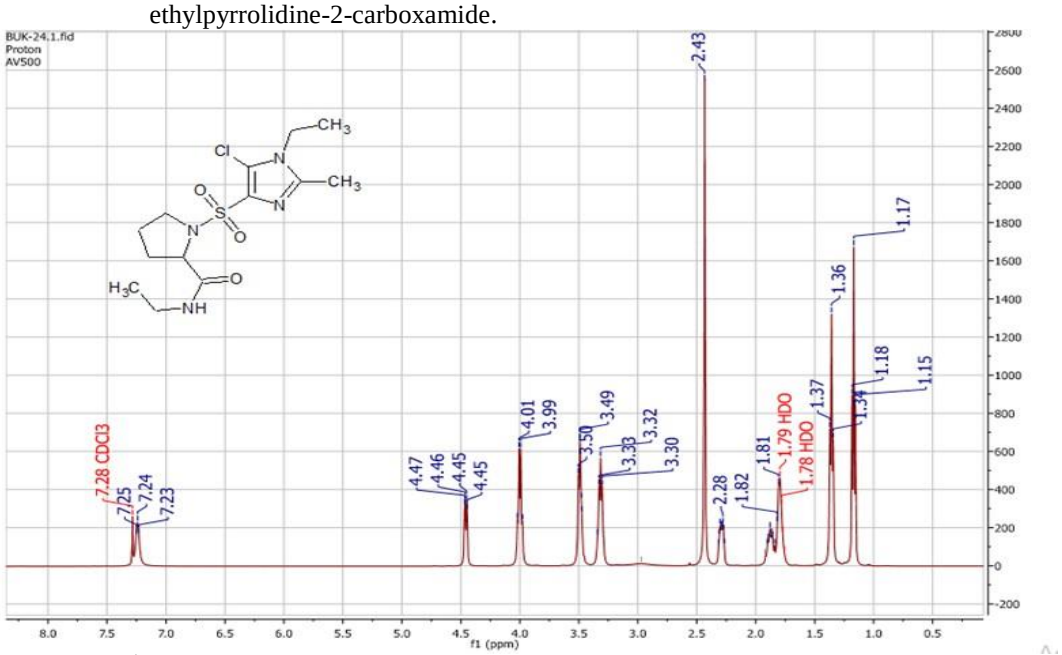


Figure 2: ^{1}H-NMR spectrum of 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide in $CDCl_3$.

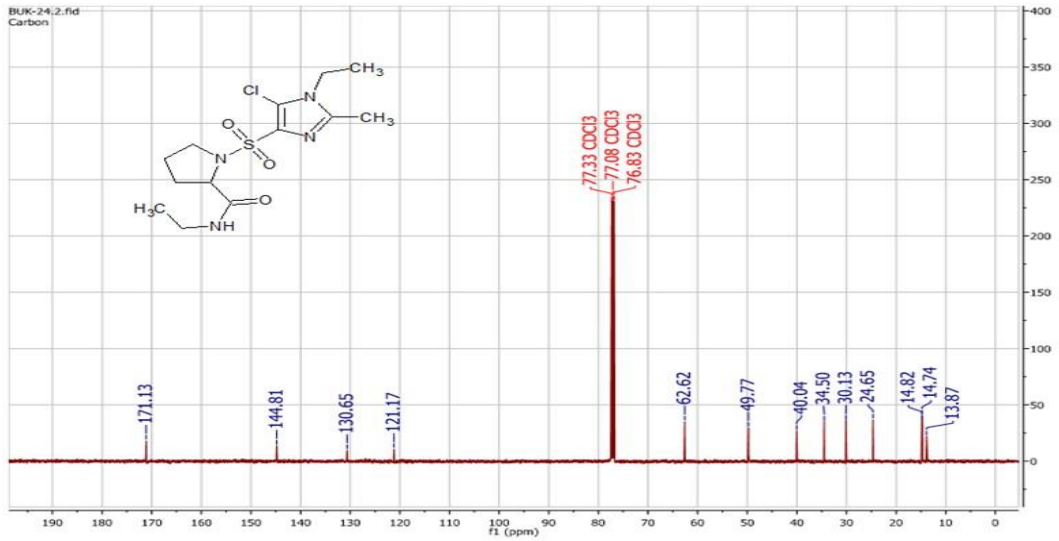


Figure 3: ^{13}C spectrum of 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide in $CDCl_3$.

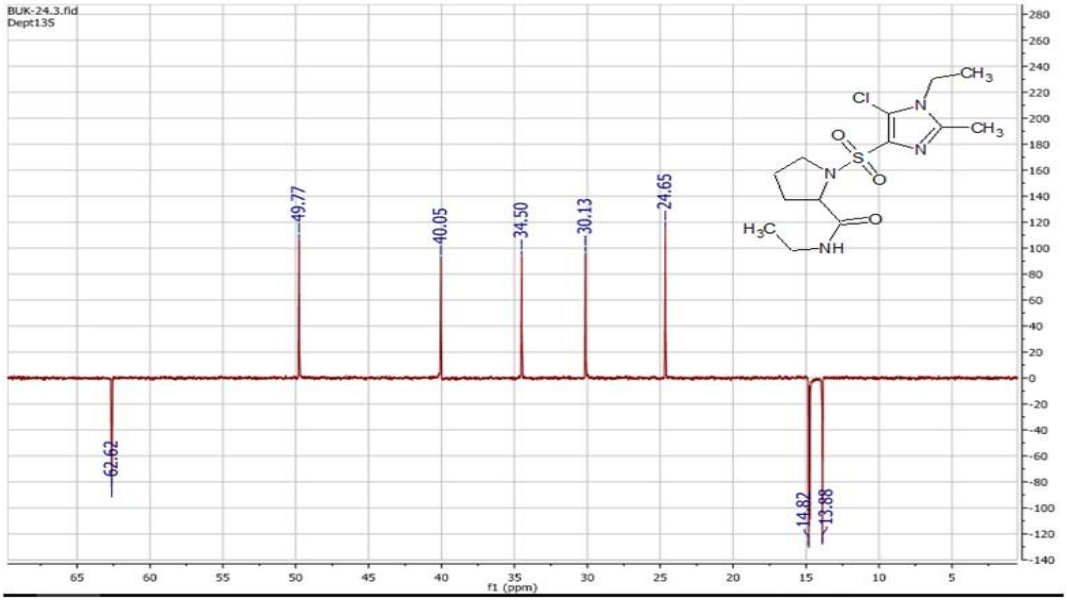


Figure 4: DEPT 135 spectrum of 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide in $CDCl_3$.

Conclusion

The new 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide was synthesized from methyl-1-[(5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl]pyrrolidine-2-carboxylate and ethylamine. The intermediate methyl-1-[(5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl]pyrrolidine-2-carboxylate was synthesized from methyl pyrrolidine-2-carboxylate and 5-chloro-4-chlorosulfonyl-1-ethyl-2-methyl-imidazole. The compounds

were characterized based on FTIR, ^{1}H, ^{13}C NMR, and DEPT 135 analysis. The compound 1-((5-chloro-1-ethyl-2-methyl-1*H*-imidazol-4-yl)sulfonyl)-*N*-ethylpyrrolidine-2-carboxamide had no activities against the tested organisms.

Acknowledgments

Authors appreciate Dr. Zulfiqar Ali of University of Mississippi, USA for NMR characterization.

References

Alhameed RA, Almarhoon Z, Bukhari SI, ElFaham A and de la Torre BG and Albericio F 2020 Synthesis and antimicrobial activity of a new series of thiazolidine-2,4-diones carboxamide and amino acid derivatives. *Molecules* 25(1): 105.

Ambrożkiewicz W, Kučerová-Chlupáčová M, Janďourek O, Konečná K, Paterová P, Bárta P, Vinšová J, Doležal M and Zitko J 2020 5-Alkylamino-N-phenylpyrazine-2-carboxamides: Design, preparation, and antimycobacterial evaluation. *Molecules* 25(7): 1561.

Bildirici I, Cetin A, Menges N and Alan Y 2018 Synthesis and SAR studies of pyrazole-3-carboxamides and -3-carbonyl thioureides including chiral moiety: Novel candidates as antibacterial agents. *J. Serb. Chem. Soc.* 83(7-8): 795-807.

Bibi H, Nadeem H, Abbas M and Arif M 2019 Synthesis and anti-nociceptive potential of isoxazole carboxamide derivatives. *BMC Chem.* 13: 6.

D'Amaral MC, Jamkhou N and Adler MJ 2021 Efficient and accessible silane-mediated direct amide coupling of carboxylic acids and amines. *Green Chem*. 23(1): 288-295.

Eze FU, Okoro UC, Ugwu DI and Okafor SN 2019 Biological activity evaluation of some new benzenesulphonamide derivatives. *Front. Chem*. 7: 634.

Gondi SR, Bera AK and Westover KD 2019 Green synthesis of substituted anilines and quinazolines from isatoic anhydride-8-amide. *Sci. Rep.* 9: 14258.

González-López̀eza E, León-Jaramillo J, Trilleras J, Grande-Tovar CD, Peralta-Ruiz Y and Quiroga J 2020 Synthesis and evaluation of the fungal activity of new pyrazole-carboxamides against *Colletotrichum gloeosporioides*. *J. Braz. Chem. Soc.* 31(9): 1917-1925.

Mevan Dissanayake DMM, Melville AD and Vannucci AK 2019 Electrochemical anion pool synthesis of amides with concurrent benzyl ester synthesis. *Green Chem.* 21(11): 3165-3171.

Ovonramwen OB, Owolabi BJ and Falodun A 2021 Synthesis and antimicrobial activities of some new sulfonyl phenoxides. *Tanz. J. Sci.* 47(2): 745-753.

Pretsch E, Bühlmann P, Badertscher M 2009 Structure Determination of Organic Compounds. SpringerVerlag Berlin Heidelberg 4 ed. pp. 269-324.

Saber AF, Zaki RM, El-Dean AMK and Radwan SM 2020 Synthesis, reactions, and spectral characterization of some new biologically active compounds derived from thieno[2,3-c]pyrazole-5-carboxamide. *J. Heterocycl. Chem.* 57(1): 238-247.

Sehmi A, Ouici HB, Guendouzi A, Ferhat M, Benali O and Boudjella F 2020 Corrosion inhibition of mild steel by newly synthesized pyrazole carboxamide derivatives in HCl acid medium: experimental and theoretical studies. *J. Electrochem. Soc*. 167(15): 155508.

Tunc T 2019 Synthesis and antimicrobial study of new benzimidazole Schiff bases bearing *p*-toluene sulfonamide moiety. *J. Chil. Chem. Soc*. 64(4): 4590-4592.

Zarecki AP, Kolanowski JL and Markiewicz WT 2020 Microwave-assisted catalytic method for a green synthesis of amides directly from amines and carboxylic acids. *Molecules* 25(8): 1761.