Pak. J. Chem. 12(1-2): 01-07, 2022
ISSN (Print): 2220-2625 Research article
ISSN (Online): 2222-307X DOI: 10.15228/2022.v12.i01-2.p01

Synthesis and Spectral Characterization of Triazole-based Amic Acids

A. A. Adeniyi*, A. O. Sobola, M. O. Sowemimo, A. O. Eshilokun
Department of Chemistry, Lagos State University, Ojo, Lagos, Nigeria
*Corresponding author: E-mail: lekeadeniyi@yahoo.com

ABSTRACT
The need to develop synthetic chemical pathways to discover new antimicrobial agents with enhanced activity cannot be over-emphasized. The focus of this study is to synthesize and characterize a set of amic acids containing the 1,2,4-triazole nucleus. The amic acids were prepared from one pot addition reaction involving 3-amino-1,2,4-triazole, 3,5-diamino-1,2,4-triazole, succinic anhydride, phthalic anhydride, 3-nitrophthalic anhydride, and 3,3'4,4'-benzophenone tetracarboxylic dianhydride. The compounds were characterized by solubility, conductance measurement, CHN microanalyses, ^{1}H and ^{13}C NMR, IR, and UV-VIS spectroscopic techniques. The compounds were obtained in high yield, and the spectral data indicate the formation of the N-triazole-based amic acids. The amic acids were non-electrolytes in DMSO.

Keywords: 1, 2, 4-triazole, succinic anhydride, 3,3'4,4'-benzophenone tetracarboxylic dianhydride, amic acids, spectroscopy

1. INTRODUCTION
The chemistry of the triazole-based compounds has received overwhelming attention due to their diverse pharmacological activity and roles as coordinating ligands. 1, 2, 4 –triazole-based drugs have proven pharmacological activities with varying medicinal applications. For instance, fluconazole, traconazole and terconazole are common azole antifungal agents [1, 2]; ribavirin is a potent antiviral N-nucleoside [3] while triazolam, alprazolam and estadam are used as tranquilizers [4]. These compounds are commercially available and contain the 1, 2, 4 triazole nucleus (Figure 1). It follows, therefore, that the biological activity of triazole-based drugs depends mainly on the nature of the substituents and the subsequent derivatives of the compounds. The synthesis and antimicrobial activity of a series of carbothioamide derivatives, triazolothiadizoles, and vinyl derivatives possessing the triazole nucleus have been reported by Bayrak et al. [5], Prasad et al. [6], and Stingaci et al. [7], respectively. In addition, several biologically important molecules with the 1, 2, 4- triazole pharmacophore have been investigated for their anti-viral activity. Chung et al. [8] reported the effectiveness of D-ribofuranosyl-3-ethynyl-[1,2,4] triazole against hemorrhagic fever with renal syndrome [HFRS) which is a severe illness caused by hantavirus. Furthermore, a series of potent anticonvulsant agents have been prepared as open-chain analogs of 7-alkoxy-4,5-dihydro[1, 2, 4] triazole [4, 3-a] quinolones by Chen et al. [9]. Also, diaryl-1,2,4-triazoles bearing N-hydroxyurea moiety exhibited potent anti-inflammatory activity by acting as dual inhibitors of cyclooxygenase-2 and 5-lipoxygenase [10]. In addition, 1,2,4-triazole-5-thione N-manich derivatives with naproxen moiety possess antinociceptive and anti-inflammatory activity [11]. Also, a triazole-derivative with 2, 5-dichlorothiophene substituted pyrazole has been reported to possess significant antimicrobial and analgesic activity [12]. More importantly, compounds with the triazole-based moiety have been extensively investigated as potential anti-tumor agents [13-19].Studies have shown that the biological efficacy of bioactive compounds could be synergistically enhanced if it is presented as composite molecules such as amic acids.

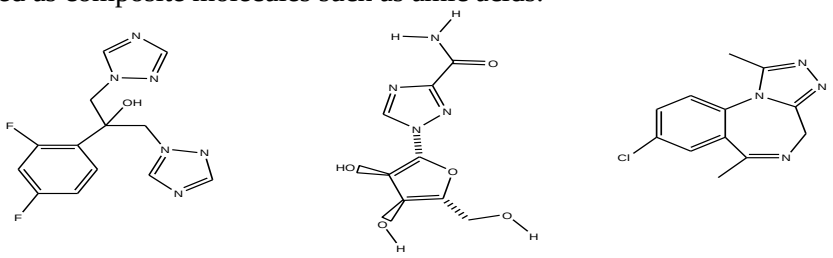


Figure 1: Examples of 1, 2, 4-triazole based drugs

Amic acids are the partial amide of a dicarboxylic acid; they have both the carboxylic and amide functional groups (cf. amino acids contain carboxylic acid and an amino group). They are obtained through a one-pot addition reaction involving acid anhydride and an amino group such as amino acids 1, 2, 4 triazole compounds. A search through the literature showed that most of the research on the 4-amino- 1, 2, 4-triazole compound involves condensation with aldehyde or ketone group to form Schiff bases [17, 20-22]; only a handful of reports is available on amic acids with the triazole nucleus [23]. It also suffices to mention that amic acids have mostly been prepared in the polymeric form [24-26] for their analytical properties. Amic acids possessing the versatile pharmacologically enriched triazole nucleus are expected to possess promising biological activities. The aim of this study, is to synthesize and characterize seven amic acids as follows: 3-amino-1,2,4-triazole phthalic amic acid (ATP), 3,5-diamino-1,2,4-triazole phthalic amic acid (DTP), 3-amino-1,2,4- triazole nitrophthalic amic acid (ATN), 3-amino-1,2,4-triazole succinic amic acid (ATS), 3-amino-

1,2,4-triazole3,3',4,4'-benzophenone tetracarboxylic dianhydride amic acid (ATBTC), 3, 5-diamino-1,2,4-triazole nitrophthalic amic acid (DTN) and 3,5-diamino-1,2,4-triazole 3,3',4,4'-benzophenone tetracarboxylic dianhydride amic acid (DTBTC).

2. EXPERIMENTAL

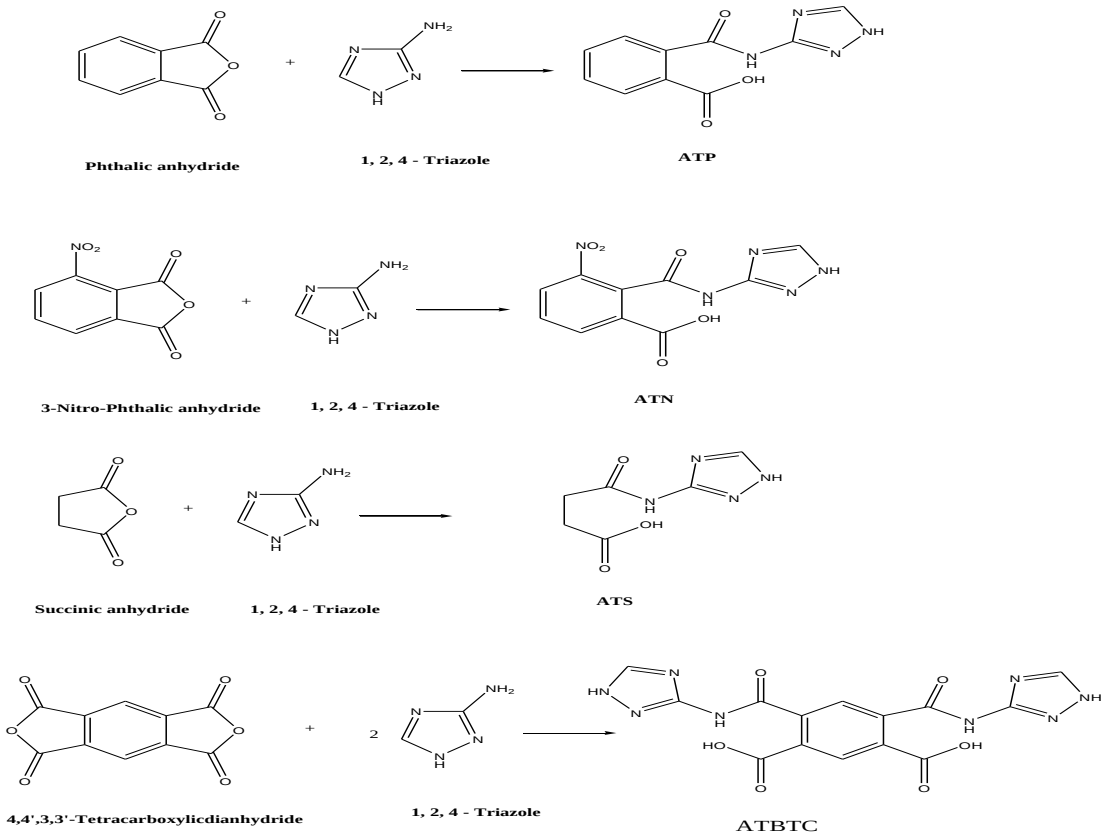
All the chemicals and reagents were purchased from Sigma-Aldrich and were used without further purification. The ^{1}H and ^{13}C NMR spectra were obtained using Bruker AVANCE 500 MHz spectrometer. The samples were dissolved in deuterated dimethyl sulfoxide (DMSO-d_6), with TMS as the internal standard. The FT-IR spectra were recorded neat using a Bruker TENSOR 27 single-channel infrared spectrometer, while the electronic absorption spectra were obtained from the T80 UV-VIS spectrometer. The elemental analysis, CHN, was done using an elemental analyzer, while the melting points of the compounds were determined using the Griffin melting point apparatus. The CHN, IR, and NMR analyses were carried out at the School of Chemistry, University of Witwatersrand, Johannesburg, South Africa.

2.1 Synthesis of the triazole-based amic acids

The various triazole-based amic acids were synthesized by reacting 3-amino-1,2,4-triazole and 3,5-diamino-1,2,4-triazole with succinic anhydride, phthalic anhydride, 3-nitro-phthalic anhydride, and 3,3'4,4'-benzophenone tetracarboxylic dianhydride, respectively, under reflux condition [23]. The syntheses of the amic acids are shown in Schemes 1 and 2.

2.1.1 ATP, ATN, ATS & ATBTC

0.036 mol (3 g) of 3-amino-1,2,4-triazole was dissolved in 25 ml of methanol and reacted with 25 ml methanolic solution of 0.036 mol (6.95 g) of phthalic anhydride in 250 ml round bottom flask under reflux condition for 4 hr. The resulting light cream precipitate was filtered under suction, washed with methanol, and dried in a vacuum desiccator over silica gel [27]. It was later recrystallized using ethyl acetate and DMF solvent mixture. Compounds, ATN, ATS, and ATBTC were similarly synthesized from their respective anhydrides, 3-nitrophthalic anhydride, succinic anhydride, and 3,3'4,4'-benzophenone tetracarboxylic dianhydride. Table 1 shows the physical and analytical data of the compounds.

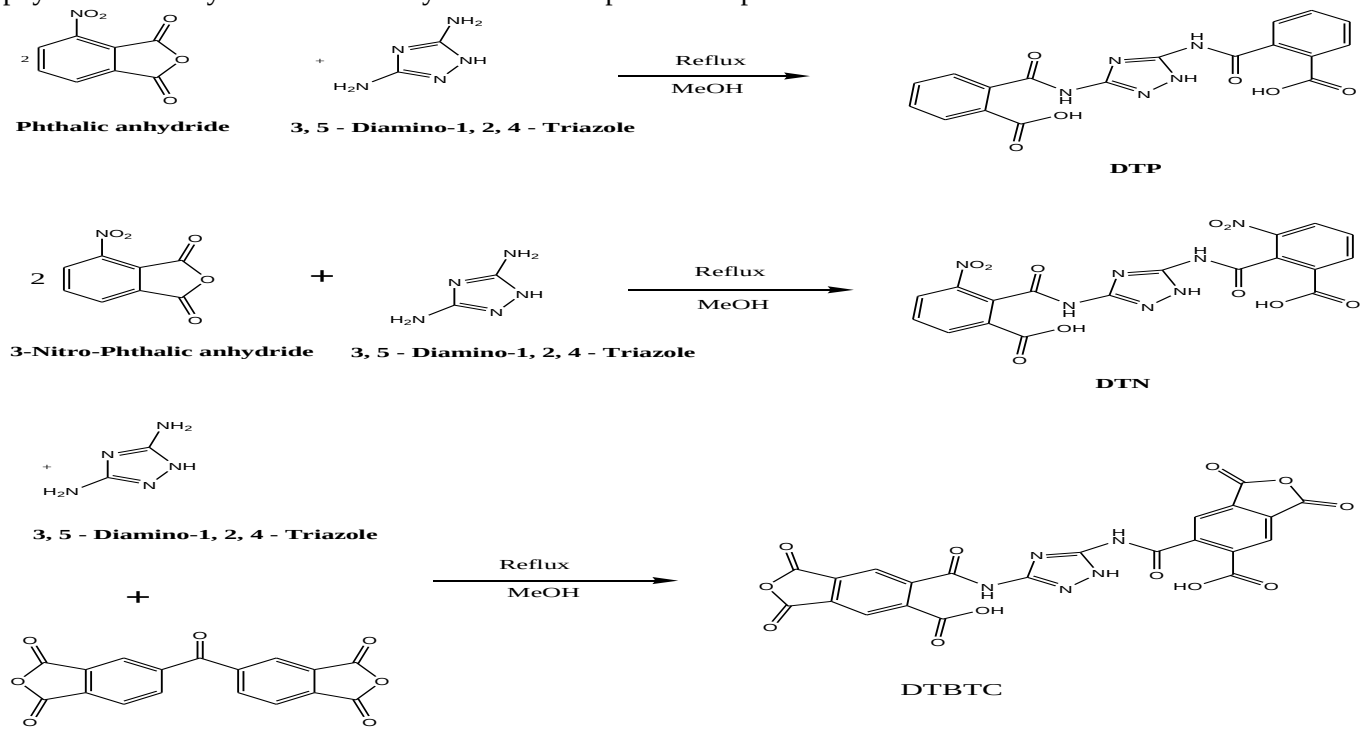


Scheme 1: Syntheses of ATP, ATN, ATS ad ATBTC

2.1.2 *DTP, DTN & DTBTC*

0.036 mol (3 g) of 3, 5-diamino-1,2,4-triazole was dissolved in 25 ml of methanol and reacted with 25 ml methanolic solution of 0.072 mol (13.90 g) of phthalic anhydride in 250 ml round bottom flask under reflux condition for 4 hr. The resulting off-white precipitate was filtered under suction, washed with methanol, and dried in a vacuum desiccator over silica gel. It was recrystallized using CCl_4/DMF solvent mixture. A similar procedure was employed to synthesize DTN

and DTBTC using nitrophthalic anhydride and 3,3',4,4'-benzophenone tetracarboxylic dianhydride, respectively. The physical and analytical data of the synthesized compounds are presented in Table 1.



Scheme 2: Syntheses of DTP, DTN, and DTBTC

3. RESULTS AND DISCUSSION

The electronic spectral data and the ^{1}H- and ^{13}C-NMR spectral data for the N-triazole-based amic acids are presented in the text, while the analytical and the infrared spectral data are presented in Tables 1 and 2, respectively.

3.1.1 ATP

Yield: 87.40% (9.53 g). ^{1}H-NMR (500 MHz, DMSO-d_6, δ, ppm:11.85 (1H, s, br, COOH), 8.06-7.52 (4H, m, Ar-H), 7.45(1H, s, triazole-HC=N), 5.75(2H, s, br, amide-NH and triazole-NH); ^{13}C-NMR: 168.71 (C=O, acid), 168.10 (C=O, amide), 167.75 (HN-C=N, triazole), 158.24(N-CH=N, triazole), 147.98, 137.31, 134.91, 132.15, 131.89, 130.88, 130.72, 130.42, 130.02 and 128.40 (Ar-C). UV-VIS (nm): 310.

3.1.2 ATN

Yield: 98.90% (9.98 g). ^{1}H-NMR (500 MHz, DMSO-d_6, δ, ppm: 8.19 (1H, d), 8.18 (1H, d), 7.54 (1H, t), 7.45 (1H, s, triazole-HC=N), 5.75 (2H, s, br, amide-NH and triazole-NH). ^{13}C-NMR: 166.72 (C=O, acid), 166.67(C=O, amide), 157.69(HN-C=N, triazole), 147.83(N-CH=N, triazole), 147.21, 135.23, 132.72, 131.79, 130.55, 127.46 (Ar-C). UV-VIS (nm): 280, 310.

3.1.3 ATS

Yield: 98.40% (5.20 g). ^{1}H-NMR (500 MHz, DMSO-d_6, δ, ppm: 11.35 (1H, s, -O.H.), 7.45 (1H, s, 5-H of triazole ring), 5.75 (2H, s, br, amide-NH and triazole-NH), 2.40(4H,s, $\alpha-$ and $\beta-CH_2$). ^{13}C-NMR: 174.43(COOH), 173.95 (CO-NH), 157.70 (C_3-triazole ring), 148.12(C_5-triazole ring) and 29.88(2C, $\alpha-$ and $\beta-CH_2$). UV-VIS (nm): 270.

3.1.4 ATBTC

Yield: 94.70% (15.31 g). ^{1}H-NMR (500 MHz,), DMSO-d_6), δ (ppm): 8.25(1H, s), 8.05(2 H, d), 7.92(2H, d), 7.61(1H, s, 5'-H of triazole ring), 5.98 (2H, s, br, amide-NH and triazole-NH). ^{13}C-NMR: 194.42 (C=O, ketone), 168.36(COOH), 167.81(CO-NH), 157.10(C_3-triazole ring), 146.61(C_5-triazole ring), 138.30, 132.09, 131.93, 130.96(Ar-C). UV-VIS (nm): 280, 310.

3.1.5 DTP

Yield: 90.56% (10.60 g). ^{1}H-NMR (500 MHz, DMSO-d_6, δ, ppm: 7.96-7.53 (8 H, m, Ar-H), 6.45(4H, s, br, amide-NH and triazole-NH). ^{13}C-NMR: 169.00 (COOH, CO-NH), 155.28 (C_3 and C_5-triazole-ring), 134.54, 131.07 and 130.96 (Ar-C). UV-VIS (nm): 280.

3.1.6 DTN

Yield: 86.90% (4.53 g). ^{1}H-NMR (500 MHz, DMSO-d_6, δ, ppm: 8.14 (2 H, d), 8.00 (2H,d), 7.63 (2H, t), 5.50 (4H, s, br, amide-NH and triazole-NH). ^{13}C-NMR: 167.65(COOH), 167.20(CO-NH), 156.88(C_3-triazole ring), 149.16 (C_5-triazole ring), 134.81, 134.43, 133.08, 129.64 and 126.43 (Ar-C). UV-VIS (nm): 285.

3.1.7 DTBTC

Yield: 94.66% (23.87 g). ^{1}H-NMR (500 MHz, DMSO-d_6, δ, ppm: 8.30(2H, s), 8.11(4H,d), 7.91(4H, d). 5.52(4H, s, br, amide-NH and triazole-NH). ^{13}C-NMR: 194.59 (C=O, ketone), 168.26(COOH), 167.80 (CO-NH), 162.82 (C_3-triazole ring), 153.40 (C_5-triazole ring), 138.47, 138.30, 134.21, 132.44, 131.93 and 131.48 (Ar-C). UV-VIS (nm): 280, 310.

Table-1: Physical and analytical data of the amic acids

Compd.	Colour	% Yield	Melting Point (℃)	Molecular Formula	% Found (Calculated)			Λ (μS)
					C	H	N	
ATP	Light cream	87.40	114-117	$C_{10}H_8N_4O_3$	52.00 (51.73)	3.22 (3.47)	23.90 (24.13)	12.10
ATN	Off-white	98.90	155-157	$C_{10}H_7N_5O_5$	43.41 (43.33)	2.32 (2.55)	25.62 (25.27)	12.71
ATS	Off-white	98.40	121-123	$C_6H_8N_4O_3$	39.63 (39.11)	4.57 (4.32)	29.80 (30.43)	18.51
ATBTC	Cream	94.70	148-150	$C_{19}H_{10}N_4O_7$	55.89 (56.14)	2.32 (2.48)	13.64 (13.80)	17.53
DTP	Off-white	90.56	182-185	$C_{18}H_{13}N_5O_6$	54.20 (54.71)	3.30 (3.32)	17.85 (17.72)	14.10
DTN	Off white	86.90	105-108	$C_{18}H_{11}N_7O_{10}$	44.25 (44.45)	2.31 (2.28)	19.86 (20.20)	38.90
DTBTC	Cream	94.66	163-165	$C_{36}H_{17}N_5O_4$	57.85 (58.13)	2.53 (2.31)	9.36 (9.42)	16.34

Table-2: Relevant IR data (cm^{-1}) of the compounds

Compd.	ν_{N-H}	ν_{OH}	$\nu_{C=O}$	$\nu_{C=C}$	$\nu_{C=N}$	$\nu_{N=C-N}$	$\nu_{N-N=C}$	ν_{C-O}
ATP	3248 w	2998 s	1671s	1553 s	1485 s	1376 s	1305 s	1281 s
ATN	3385 m	2815 s	1679 s	1526 s	1460 m	1379 m	1344 s	1261 s
ATS	3376 m	2805 s	1681 s	1564 w	1412 m	1392 m	1320 m	1269 m
ATBTC	3350 w	3100 s	1693 m	1573 m	1462 s	1361 m	1288 m	1178 m
DTP	3458 m	2750 s	1671 s	1582 m	1540 m	1369 m	1293 s	1160 w
DTN	3305 m	3150 s	1688 s	1611 m	1576 m	1459 s	1345 s	1297 s
DTBTC	3382 w	3100 s	1702 w	1601 w	1542 w	1432 m	1363 m	1273 m

Where: s, m, w = strong, medium, and weak, respectively

3.2.1 Physical properties of the compounds

The triazole-based amic acids were obtained in high yield as either off-white or cream precipitates. The CHN analysis values were in good agreement with the calculated values, indicating the purity of the compounds. The CHN values revealed that the dianhydrides viz: succinic anhydride, phthalic anhydride, and 3-nitrophthalic anhydride reacted with the 3-amino-1,2,4-triazole and 3,5-diamino-1,2,4-triazole in a ratio 1:1 and 2:1 respectively. On the other hand, the 3, 3' 4, 4'-tetracarboxylic benzophenone reacted as 1:2 and 2:1, respectively. Furthermore, the synthesized compounds were non-electrolytes in DMSO, as indicated by their low conductivity values [28].

3.2.2. NMR spectral data for the compounds

For the amic acids, the carboxylic hydroxyl proton, COOH, resonated far-downfield as a broad signal around 12 ppm. In the same vein, both the amide-NH and the triazole ring-NH of the N-triazole-based amic acids appeared in the same region as a broad signal at 6.45 - 5.50 ppm, Figure 2. The 5'-H of the triazole ring signals for ATP, ATN, and ATS were observed at 7.61 – 7.45 ppm. The methylene signals for ATS were observed up-field as a strong singlet at 2.40 ppm and 29.88 ppm in the ^{13}C spectrum [23]. Figure 2 shows the ^{1}H NMR spectrum of ATN.

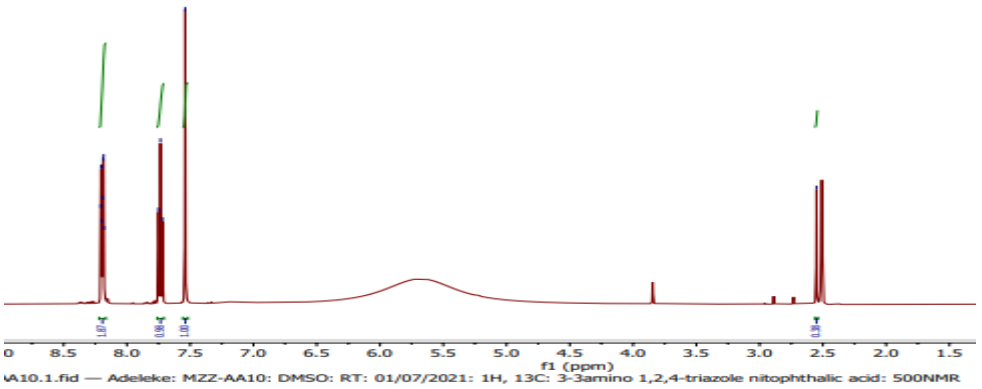


Figure 2: ^{1}H-NMR spectrum of ATN

The amide carbon signal (CO-NH) was observed close to the carboxylic acid signal in all the triazole-based amic acids, as shown in Figure 3. In addition, the triazole- C_3 and C_5 resonated at a higher frequency than the aromatic carbon and were observed at 162.82 – 155.28 ppm and 158.24–157.11 ppm [29].

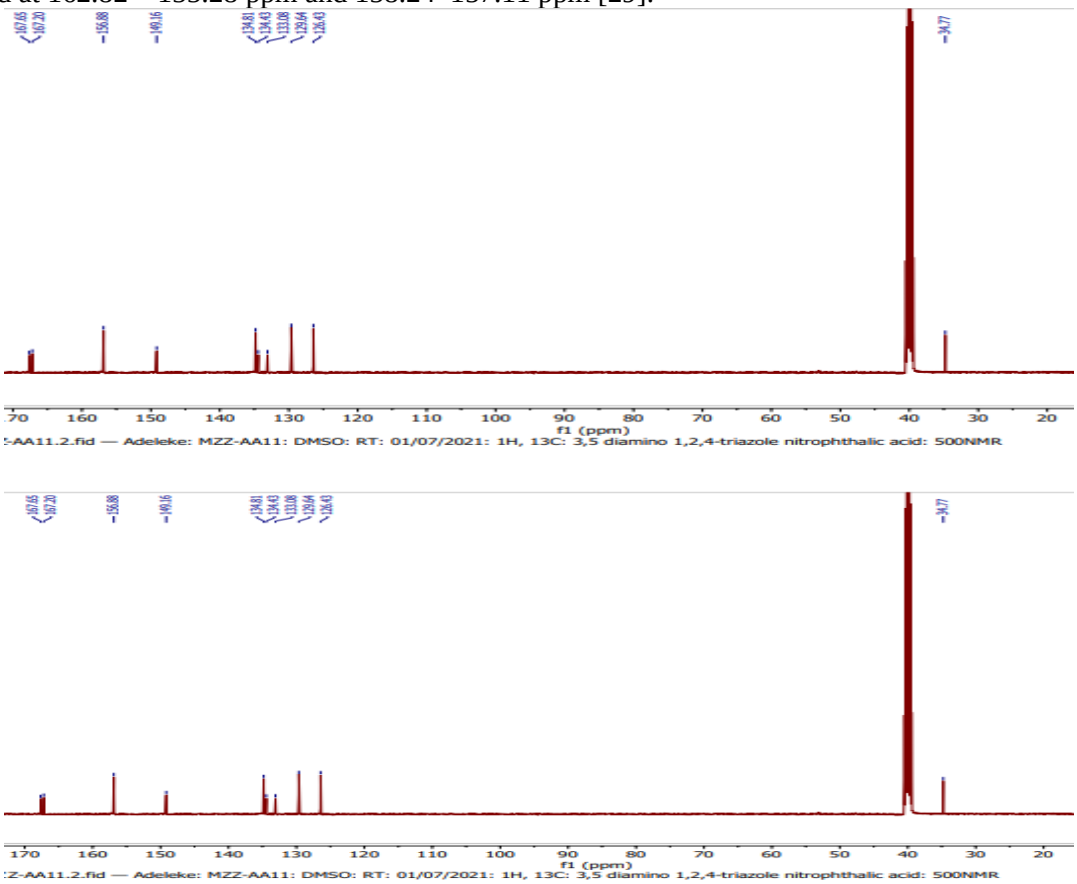


Figure 3: ^{13}C-NMR spectrum for ligand DTN

3.2.3 Infrared and electronic spectral data for the compounds

The relevant infrared spectral data for the compounds are presented in Table 2. The bands at 3498-3248 cm^{-1} and 3320 - 3178 cm^{-1} respectively are assigned to the triazole-NH and the amide-NH [30]. The OH stretch of the carboxylic acid, COOH, appeared as broadband at a lower frequency due to the existence of hydrogen bonding [29] in the amic acids. In the same vein, the hydrogen bonding effect may be responsible for the reduction in the ν C=O of the triazole-based amic acids [29]. The $\nu_{C=O}$ of the carboxylic acid and the amide group were observed as strong signals at 1702 – 1671 cm^{-1} and 1618 – 1569 $cm^{-1,}$ respectively. The bands due to the triazole ring were observed at 1582 – 1462 cm^{-1}, 1553 – 1412 $cm^{-1,}$ and 1294 – 1218 cm^{-1} corresponding to $\nu_{C=N}$, $\nu_{N=C-N}$ and ν_{N-N} respectively [23, 29]. Figure 4 is the FT-IR spectrum of DTP. The electronic spectra of the triazole-based amic acids exhibit bands between 270- 310 nm. These bands are assigned to n → π* and π → π* transitions of the aromatic and triazole rings, respectively [23, 27]. Figure 5 is the UV-VIS spectrum of ATBTC.

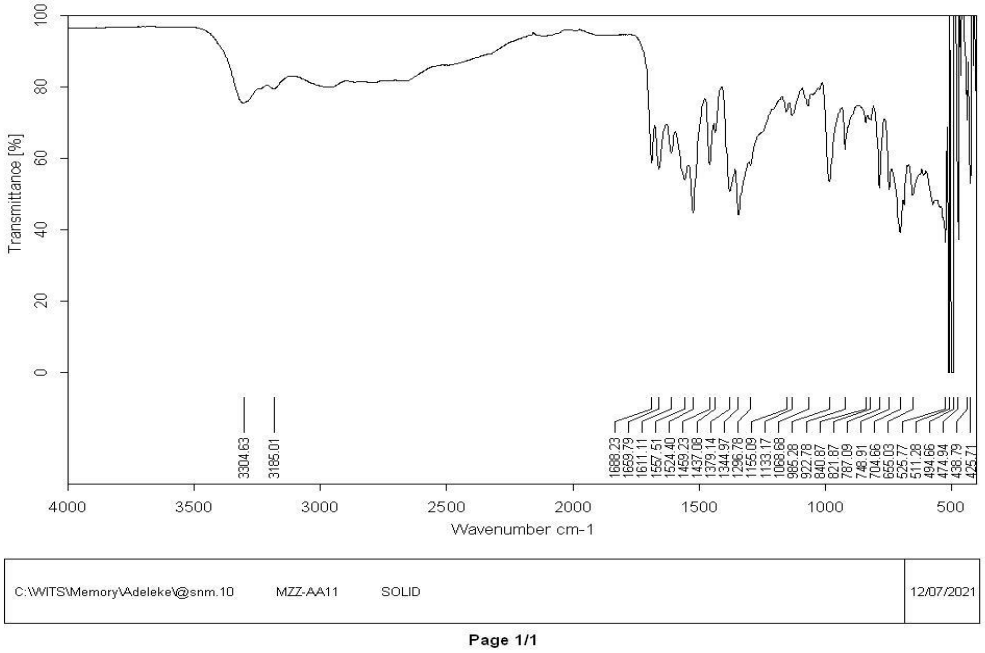


Figure 4: FT-IR spectrum of DTP

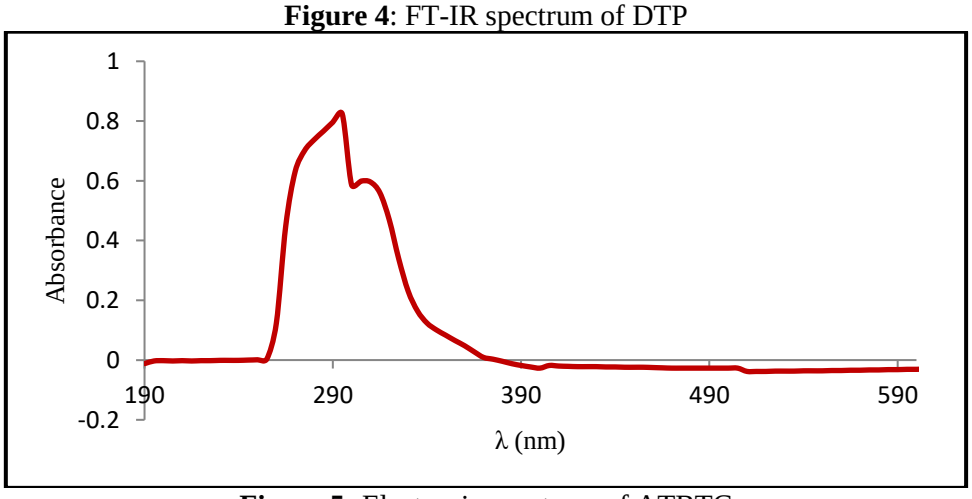


Figure 5: Electronic spectrum of ATBTC

4. CONCLUSION

The reaction of 3-amino- and 3,5-diamino-1,2,4-triazole with acid anhydrides yielded the N-triazole-based amic acids and the N-triazole-based diamic acids, respectively. CHN microanalyses and spectral data have substantiated the structures of the amic acids. The spectral data indicated the formation of the amic acid functional groups, CO-OH and CO-NH. A final structural elucidation by X-ray diffraction studies and possible biological evaluation of the compounds is desirable.

ACKNOWLEDGEMENT

The authors are grateful to the Lagos State University, Ojo, for providing the 2019 TETFund institutional-based grant (IBR) for conducting this research.

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Received: 25th October, 2021 **Accepted: 5th January, 2022**