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Synthesis, Characterization and Antimicrobial Activity of Thiol Substituted Triazole Amic Acids

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Abstract. Triazole-based compounds exhibit varying pharmacological properties in the treatment of fungal, bacterial and other significant infectious diseases. This study presents the synthesis and characterization of a series of thiol-substituted 1,2,4-triazole amic acids as potential antimicrobial agents. The amic acid compounds were synthesized by condensing 1,2,4- triazole-5-thiol with phthalic anhydride, 3-nitrophthalic anhydride, succinic anhydride and 3,3′4,4′-tetracarboxylic dianhydride. The structures of the thiol-substituted triazole amic acids have been elucidated with CHNS, conductivity, infrared and nuclear magnetic resonance spectral data. The compounds were tested for their antimicrobial susceptibility using four bacterial strains and one fungal strain, namely: *Staphylococcus aureus*, *Streptococcus faecalis*, *Escherichia coli*, *Salmonella paratyphimurium* and *Candida albicans*. The amic acid compounds are non- electrolyte (Λ_M = 9.72 - 17.69 Ω^{-1} cm^2/mol). The relevant IR bands, ^{1}H- and ^{13}C- NMR spectral data suggest that the proposed thiol-substituted amic acids were formed, while the electronic spectra reveal exhibit $\pi \rightarrow \pi^*$ absorption bands at 280 - 315 nm. All the synthesized amic acids exhibited mild anti-bacterial antifungal activity against the tested organisms.

Keywords: 1,2,4-triazole-thiol, amic acids, acid anhydrides, antimicrobial activity, antifungal activity

Introduction

Triazoles are five membered heterocyclic aromatic compounds with vast pharmacological and biological applications (Matin *et al*., 2022; Kumari *et al*., 2021; Kumar *et al*., 2013; Kumar and Kavitha, 2013). Some commercially available drugs contain the triazole nucleus.

Triazole containing drugs are of utmost importance as anti fungal agents with established clinical efficacy. Specifically, fluconazole and itraconazole, Fig. 1 are the first generation clinically endorsed triazole drugs for the incidence of candidiasis and filamentous fungi infections respectively (Falci and Pasqualotto, 2013). Other triazole-based antifungal agents include voriconazole, albaconazole and ravuconazole. In addition, the triazole nucleus is an integral part of several other pharmacological importance drugs, as anti-viral (ribavirin), anti-convulsant (estazolam, loreclezole and alprazolam), anti-cancer (anastrozole), anti-depressant (trazodone) and anti-migraine (rizatriptan) (Aggarwal and Sumran, 2020). The versatility of the triazone ring in drug design is due to the fact that it is a biological isostere of several other heterocyclic compounds such as imidazole, oxazole, pyrazole, thiazole and amide moieties (Aggarwal and Sumran, 2020; Zhou *et al*., 2012). A series of bioactive triazole-derivatives synthesized by (Cui *et al*., 2013; Zoumpoulakis *et al*., 2012) with potential antimicrobial activities from sulphonamide and quinolones moieties respectively. In addition, the antifungal activity of a series of coumarin triazoles (Elias *et al*., 2019) and oxadiazole based triazole (Çavusoglu *et al*., 2018) compounds have been reported in the literature. Similarly, various derivatives of 1,2,4-triazole-3-carboxamide derivatives have been prepared and investigated for their anti-inflammatory (Abdel-Aziz *et al*., 2014) and anti-convulsant activity (Abuelhassan *et al*., 2018). Furthermore, Henen *et al*. (2012) evaluated the antiviral activity of synthesized quinoxaline triazoles as potential antiviral drug agents. In a similar vein, natural piperine derivatives of 1,2,4-triazole-3-thiones were evaluated for their trypanocidal activity (Franklim *et al*., 2013). A lot of other 1,2,4-triazole derivatives with biological significance have been prepared and evaluated for their anti-tumour activity (Shahzad *et al*., 2019; Xu *et al*., 2016; Qin *et al*., 2014) anti-tuberculosis (Li *et al*., 2017; Castelino *et al*., 2016; Dixit *et al*., 2016) and anti-viral activity reported by (Wang *et al*., 2019).

The wide pharmacological applications of the triazole compounds have been largely attributed to the tendency of triazoles to readily bind with various receptors and

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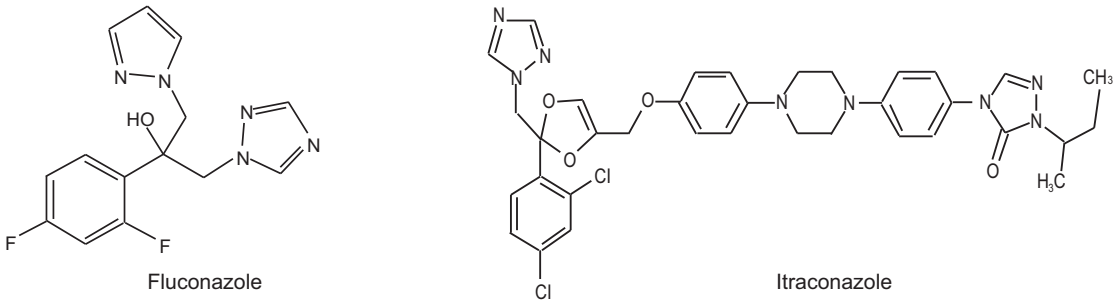

Fig. 1. Structures of fluconazole and itraconazole.

enzymes in the biological systems (Sabah *et al*., 2020; Shneine and Alaraji, 2016; Zang *et al*., 2014; Zhou *et al*., 2012).

Amic acids are obtained from the reaction of amines with acid anhydrides or carboxylic acids and their names are derived from the corresponding carboxylic acid backbone. Some triazole based amic acids using phthalic and succinic anhydride have been reported earlier (Sabah *et al*., 2020; Abdulghani and Sahan, 2012). In addition, some amic acids have been prepared as precursor materials in the synthesis of polyimide (Balasubramanian *et al*., 2019; Takassi *et al*., 2015; Yang *et al*., 2003). The 1,2,3-triazoles have also found use as flame retardants (Sykam *et al*., 2022).

The search for novel and structurally modified triazole-based drugs has been a compelling contemporary research focus aimed at addressing the incidence of multi-drug resistant microbial diseases. Studies have shown that 1,2,4-triazole thiols shows significant biological activities such as antibacterial, antifungal and cytotoxic activities (Ghanaat *et al*., 2021; Aly *et al*., 2020; Gaber *et al*., 2020; Hamzah and Al-Tamini, 2020; Gaber *et al*., 2019; Wu *et al*., 2007; El-Emam, 1991). However, amic acids of thiol substituted triazoles have not been reported.

This study presents the synthesis, characterization and antimicrobial screening of 1,2,4-triazole substituted amic acids by condensing 3-amino-1,2,4-triazole 5-thiol with phthalic anhydride, 3-nitrophthalic anhydride, succinic anhydride and 3,3′,4,4′-benzophenonetetra-carboxylic dianhydride, respectively.

Materials and Methods

All the chemicals and reagents used for this study were sourced from Fluka and Sigma-Aldrich.

The melting points and the conductivity values of the thiol substituted amic acids were determined using Griffin melting point apparatus and Jenway 4510 conductivity meter respectively after calibration. The electronic spectra were obtained using T-80 UV-visible spectrophotometer, while the CHNS analysis was done with the necessary standards using elemental analyzer, Vario EL cube model. The nuclear magnetic resonance spectra were recorded at 27 °C in DMSO-d_6 using a Bruker Avance 500 MHz spectrometer operating at 500 MHz (^{1}H) and 126 MHz (^{13}C) respectively. Infrared spectra of the compounds were recorded neat, using a Bruker TENSOR 27 single channel infrared spectrometer.

Synthesis of the 1,2,4-triazole thiol substituted amic acids. The thiol-substituted amic acids were synthesized by reacting 20 mmol of 3-amino-1,2,4-triazole thiol with 20 mmol of phthalic anhydride, nitrophthalic anhydride, succinic anhydride and 3,3′,4,4′ benzophenone tetra-carboxylic dianhydride respectively. These were done under reflux condition for 4 h in methanol to give the amic acids (Nayak and Mangte, 2021; Al-Majidi *et al*., 2013). The resulting precipitates were filtered under suction, washed with methanol and dried in vacuo over silica gel. The compounds were recrystallized using tetra-choloromethane/dimethyl-formamide (1:1) for ATTP; diethyl ether/ dimethylformamide (1:1) for ATTN; dimethylformamide for ATTS and ATTBC.

The synthesis is illustrated in Fig. 2. The compounds are: 2-(5-mercapto-1H-1,2,4-triazol-3-yl carbamoyl) benzoic acid (ATTP), 2-(5-mercapto-1H-1,2,4-triazol-3-yl) and carbamoyl,3- nitrobenzoic acid (ATTN), 3-(5-mercapto-1H-1,2,4-triazol-3-yl) and carbamoyl, propanoic acid (ATTS) and 4-(1,3-dioxo-1,3-dihydroisobenzofuran-5-carbonyl)-2-(5-mercapto-1H-1,2,4-triazol-3-yl and carbamoyl, benzoic acid (ATTBTC).

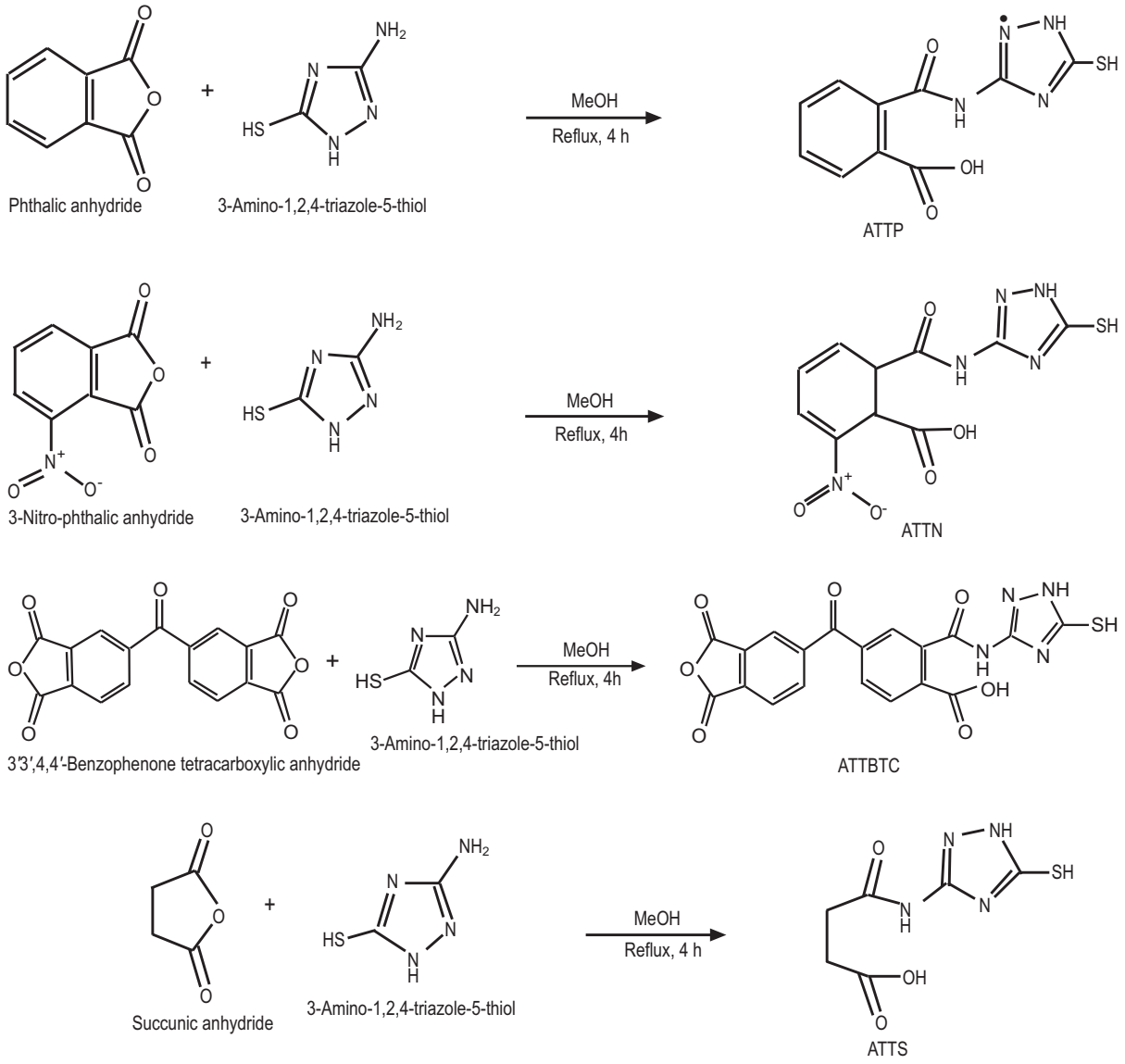

Fig. 2. Reaction schemes for the amic acids.

The thiol-substituted 1,2,4-triazole amic acids were tested for their antimicrobial susceptibility against *Staphylococcus aureus*, *Streptococcus faecalis*, *Escherichia coli*, *Salmonella paratyphimurium* and *Candida albicans* using Agar well diffusion method with gentamycin (antibacterial) and nystatin (antifungal) as the positive control (Sowemimo and Adeniyi, 2022).

Results and Discussion

ATTP. Colour = light cream; yield = 42.40 %; m.p = 298-301 °C; IR (Neat, ν/cm); 3373 w = (triazole ring N-H); 3210 w = (amide N-H); 2902 m = br = (O-H); 2625 w = (S-H); 1638 m = (carboxylic acid C=O); 1584 m (amide C=O);1536 w (triazole C=N); 1482 w (triazole C=N-N), 1420 vw (C-N), 1234 m (carboxylic acid C-O); ^{1}H-NMR (DMSO-d_6, δ (ppm)): 11.90 (1 H, s, COOH), 7.50 – 8.17 (4 H, m, aromatic protons); 5.74 (1H; s, thiol proton (SH); 3.38 (2H, s, br, triazole ring NH and C=O-NH); ^{13}C-NMR (DMSO-d_6, δ (ppm); 195 (COOH); 168 (C=O); 122.99 - 133.38 (aromatic carbons); 130-132 (triazole ring imine (C=N); UV-Vis (nm), 285; Conductance (Ω^{-1} cm^2/mol); 9.72. CHNS analysis; found (calculated, $C_{10}H_8N_4SO_3$) %; C, 44.72 (45.00); H, 3.15 (3.05); N, 21.04 (21.21); S, 11.93 (12.11).

ATTN. Colour: Light cream; yield, 78.35 %; m.p. 140 -142 ºC; IR (Neat, ν/cm); 3510 w (triazole ring N-H);

3375 w (amide N-H); 3103 m; br (O-H); 2500 w (S-H); 1703 m (carboxylic acid C=O); 1585 s (amide C=O); 1569 s (triazole C=N); 1523 s (triazole C=N-N); 1435 s (C-N); 1237 m (carboxylic acid C-O); ^{1}H-MR (DMSO-d_6, δ (ppm); 7.56 – 8.13 (3 H, m, aromatic protons); 5.84 (1H, s, thiol proton (SH); 4.25 (2H, s, br, triazole ring NH and C=O-NH); ^{13}C-NMR (DMSO-d_6, δ (ppm)); 167.57 (COOH); 153.15 (C=O); 126.02-134.69 (aromatic carbons); 134.93 (triazole ring imine (C=N)); UV-Vis (nm), 280; Conductance (Ω^{-1} cm^2/mol): 17.69; CHNS analysis: found (calculated, $C_{10}H_7N_5SO_5$) %; C = 38.45 (38.85); H = 2.10 (2.28); N = 22.80 (22.65); S =10.56 (10.35).

ATTS. Colour: light cream; yield, 53.76%, m.p. 268 - 271 °C, IR (Neat, ν/ cm): 3375 m (triazole ring N-H), 3296 w (C=O- NH), 3166 m, br (O-H), 2615 w (S-H), 1706 m (carboxylic acid C=O), 1635 s (amide C=O), 1584 m (triazole C=N), 1536 m (triazole C=N-N), 1416 m (C-N), 1231 s (carboxylic acid C-O); ^{1}H-NMR (DMSO-d_6, δ (ppm)): 12.04 (1 H, s, COOH); 5.75 (1 H, s, thiol proton (SH); 3.58 (1 H, s, triazole ring (NH); 3.50 (1 H, s, br, amide NH); 2.50 (2 H, s, α -CH2); 2.36 (2 H, s, β-CH_2); ^{13}C-NMR (DMSO-d_6, δ (ppm) 175 (COOH); 163.38 (C=O); 153.06 (triazole ring imine (C=N)); 50 (α-CH_2); 35 (β-CH_2). UV-Vis (nm) 295; Conductance (Ω^{-1} cm^2/mol): 17.46. CHNS analysis: found (calculated, $C_6H_8N_4SO_3$) %: C, 32.97 (33.35); H, 3.48 (3.73); N, 26.12 (25.93); S, 15.10 (14.81).

ATTBTC. Colour: light cream; yield, 92.03%, m.p. 242 - 244 °C, IR (Neat, ν/ cm): 3520 sh (triazole ring N-H), 3300 sh (amide N-H), 3026 m, br (O-H), 2469 w (S-H), 1681 m (biphenyl C=O), 1657 s (anhydride C=O), 1600 sh (carboxylic acid C=O), 1536 s (amide C=O), 1488 m (triazole C=N), 1367 m (triazole C=N-N), 1306 s (C-N), 1238 m (carboxylic acid C-O); ^{1}H-NMR (DMSO-d_6, δ (ppm)): 8.52 (2 H, s, Ar-H); 8.34 (2 H, d, Ar-H); 7.88-8.52 (2 H, d, Ar-H); 5.77 (1 H, s, thiol proton (SH); 3.40 (2H, s, triazole ring and C=O-NH). ^{13}C-NMR (DMSO-d_6, δ (ppm)): 195.16 (biphenyl C=O); 167.70, 167.73 (anhydride C=O); 163.37 (carboxylic acid C=O); 152.99 (amide C=O); 138.94 (triazole ring (C=N-N); 138.34 (triazole ring (C=N); 135.42-131.38 (aromatic carbons).

UV-Vis (nm): 295 and 315. Conductance (Ω^{-1} cm^2/mol): 17.46. CHNS analysis: found (calculated, $C_{19}H_{10}N_4SO_7$), %: C, 51.96 (52.04); H, 2.54 (2.30); N, 13.10 (12.79); S, 6.96 (7.30).

The compounds were obtained in moderate to high yields (42.40 – 92.03%) and were light cream in colour. The compounds have poor solubility in most organic solvents (methanol, ethanol, benzene, ethyl acetate, tetrachloromethane, toluene and diethyl ether), suggestive of their polymeric nature (Adeniyi and Patel, 1999). The compounds are non-electrolytes as indicated by their low conductivity values (9.75 – 17.69 Ω^{-1} cm^2/mol) (Tyagi *et al*., 2017; Ali *et al*., 2013). The experimental CHNS values for the compounds agree with the theoretical values, an indication that the synthesized compounds were obtained in high purity (kaplanek *et al*., 2015; Pouralimardan *et al*., 2007; Adeniyi and Patel, 1999).

NMR spectra. The carboxylic acid proton (COOH) of the thiol substituted amic acids resonated far downfield as a broad singlet at 12.04 – 11.90 ppm due to the existence of an intramolecular hydrogen bonding; the carboxyl proton was however, too weak to be observed in the spectra of ATTN and ATTBTC. The thiol proton, -SH, like the –NH and the –OH protons, is a variable proton and typically resonates at varied chemical shift during NMR analysis (Tyagi *et al*., 2017; Bagihalli *et al*., 2008). These are attributed to various factors, such as different chemical environment, concentration temperature and solvent (Pavia *et al*., 2001). Therefore, the sharp signal at 5.84 – 5.74 ppm is assigned to the thiol, -SH proton of the 5-mercapto-triazole moiety. Also, the spectra of ATTP, ATTN and ATTBTS exhibited a very broad signal at 4.25 – 3.38 ppm due to the triazole ring N- H and the amide N-H (Abdulghani and Sahan, 2012). In the ATTS spectrum, however, the triazole ring N-H resonated as a strong singlet at 3.58 ppm, while the amide N-H appeared broad at 3.50 ppm. Furthermore, the ATTS spectrum exhibited two strong singlets at 2.50 and 2.36 ppm due to the α-CH_2 and β-CH_2 protons. Lastly, the aromatic protons of ATTP, ATTN and ATTBTC were observed at 8.52–7.50 ppm. The 1H-NMR signals were further corroborated with the ^{13}C-NMR spectral data. The carboxylic acid (COOH) signal of the thiol-substituted amic acids resonated at 175–163.37 ppm, while the amide (C=O-NH) signals were observed at 166.87–152.99 ppm. In addition, the far downfield signal in the spectrum of ATTBTC corresponds to the biphenyl carbonyl group of the tetracarboxylic dianhydride moiety (Pavia *et al*., 2001). Furthermore, the C=N, imine signal characteristic of the triazole ring appeared at 162.81 – 153.06 ppm in ATTP, ATTN and ATTS spectra. It was, however, observed at 138.34 ppm in ATTBTC. Lastly, signals

corresponding to the aromatic ring system in ATTP, ATTN and ATTBTC were observed at 140 – 125 ppm while the methylene α-CH_2 and β-CH_2 signals of ATTS appeared at 50 and 35 ppm respectively. Representative NMR spectra as shown in Fig. 3-4.

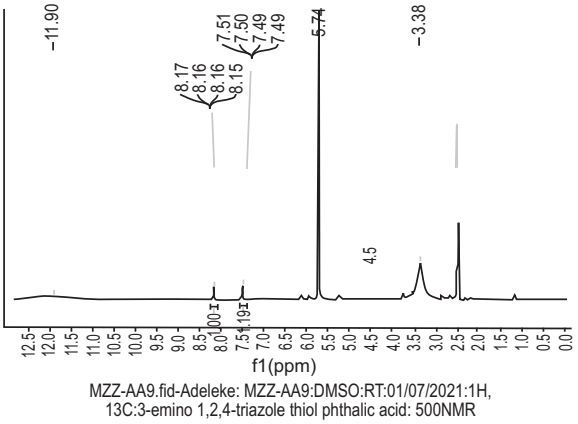

Fig. 3. ^{1}H-NMR spectrum of ATTN.

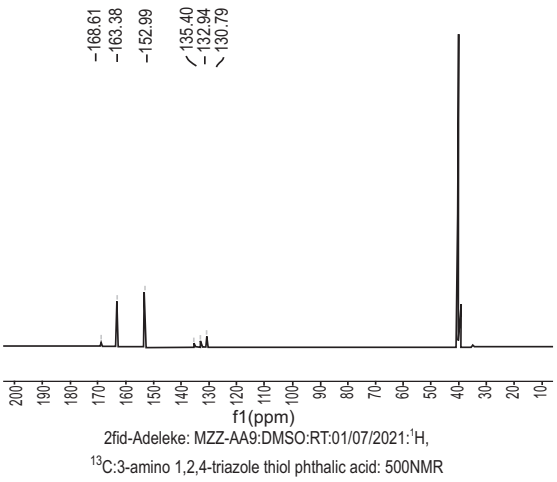

Fig. 4. ^{13}C-NMR spectrum of ATTN.

Infrared and electronic spectra. The infrared spectra for the amic acids. (Fig. 5 show the representative spectrum), exhibit two weak bands at 3373–3296/cm and 3285–3210/cm characteristic of the triazole –NH and the amide –NH (Abdulghani and Sahan, 2012). In addition, the hydroxyl stretching vibration of the thiol-substituted amic acids was observed as a broad band at 3263–2700/cm due to intra-molecular hydrogen bonding and this was corroborated by the presence of the carboxylic acid C-O stretch at 1238–1231/cm. The weak band at 2615–2469/cm corresponds to the ν SH of the thiol-substituted triazole moiety of the amic acids (Tyagi *et al*., 2017; Bagihalli *et al.*, 2008). Furthermore, the infrared spectra of the compounds exhibit medium bands at 1706-1600/cm due to the C=O stretch of carboxylic acid. The amide C=O-NH stretch was, however, observed at 1585–1536/cm in ATTP, ATTN and ATTBTC but appeared at a much higher frequency, 1635/cm in ATTS, which is an aliphatic amic acid. In addition, the infrared spectrum of ATTBTC exhibit bands at 1706/cm and 1635/cm due to the free ν C=O and the anhydride C=O –O –C=O stretching vibrations. The triazole ring C=N and N=C vibrations were observed at 1584–1488/cm and 1538–1367/cm, respectively.

The electronic spectral data for the thiol-substituted amic acids exhibit absorption bands at 280 - 315 nm assigned to $\pi \rightarrow \pi^*$ transitions (Sowemimo and Adeniyi, 2022; Pavia *et al*., 2001; Adeniyi and Patel, 1999). Relatively weak intra-ligand CT bands may be responsible for the light cream colour of the compounds (Sowemimo and Adeniyi, 2022). The representative electronic spectrum for ATTP is presented in Fig. 6.

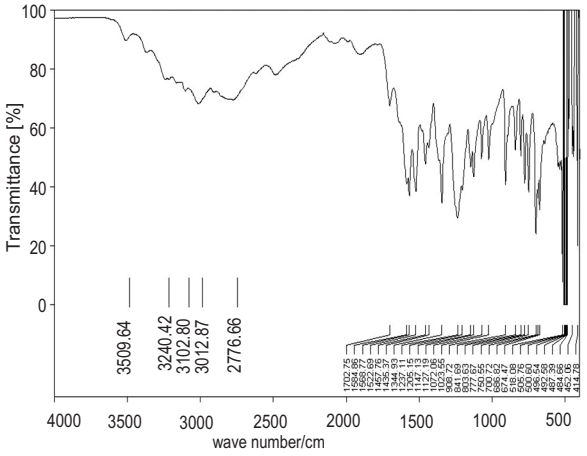

Fig. 5. FTIR spectrum for ATTP.

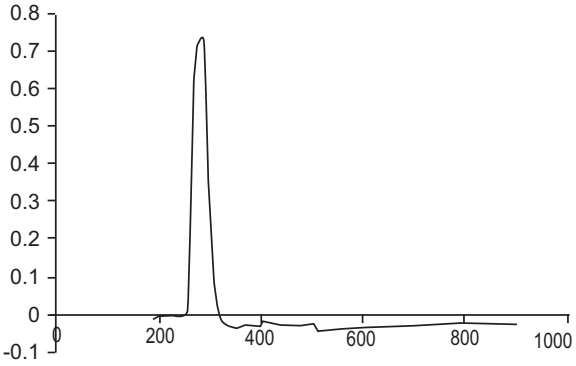

Fig. 6. Electronic spectrum for ATTP.

Antimicrobial study. All the compounds exhibited mild activity against the test organisms. ATTP, ATTS and ATTBTC were most potent against *E. coli*, while ATTN exhibited milder activity against *S. aureus* and *S. faecalis* and *E. coli*. Furthermore, both phthalic and nitrophthalic amic acids (ATTP and ATTN) exhibited similar antifungal activity against *C. albicans* and were relatively more potent than ATTS and ATTBTC. However, all the synthesized thio-substituted amic acids were not as active as gentamycin and nystatin which were the standard antibacterial and antifungal agents respectively (Sowemimo and Adeniyi, 2022). The zones of inhibition for the well diffusion assay are presented in Fig. 7-8.

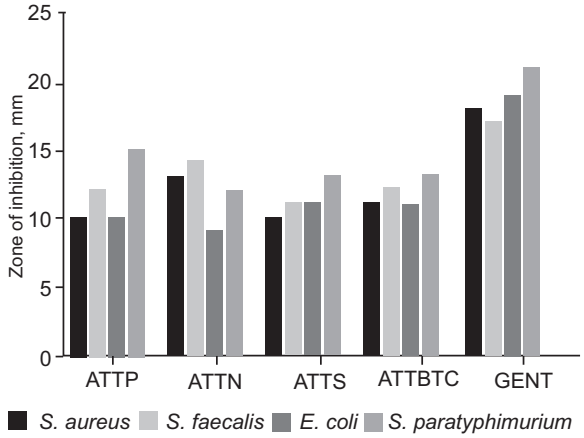

Fig. 7. Antibacterial activity of the compounds.

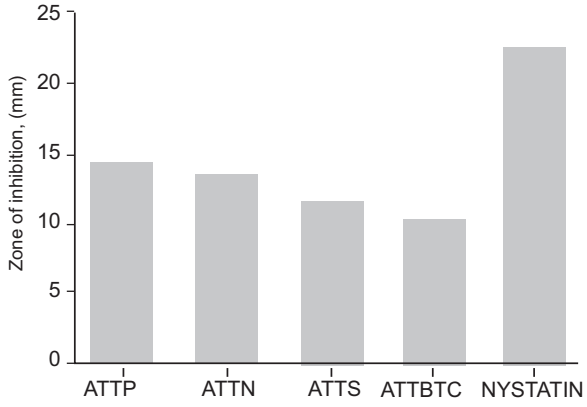

Fig. 8. Anti-fungal activity of the compounds.

Conclusion

The compounds ATTP, ATTN, ATTS and ATTBTC were successfully synthesized and characterized using FT-infrared, proton and carbon-13 NMR, ultraviolet-visible spectroscopy, conductivity and CHNS micro-analyses. The data obtained from the study suggested that novel amic acids were formed. The compounds are mildly active against the four bacteria and fungusas used.

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Conflict of Interest. The authors declare that they have no conflict of interest.

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