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NOVEL 1,2,3-TRIAZOLE-1,4-DIHYDROPYRIDINE-3,5-DICARBONITRILE DERIVATIVES: SYNTHESIS AND ANTIBACTERIAL EVALUATION

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INTRODUCTION

One of the most pressing concerns in modern public health is the rise of antibiotic-resistant bacteria.1 Worldwide, drug-resistant illnesses are already killing over 700,000 people year and are projected to force 24 million more into severe poverty by 2030, according to a World Health Organisation study from April 2019. Antimicrobial resistance has rendered contemporary therapies obsolete as a result of the resurgence of catastrophic bacterial illnesses.2 Consequently, the most pressing task facing humanity this century is the discovery of novel antibacterial chemicals.
Medicinal chemistry plays a vital role in the pharmaceutical and biological fields, handling tasks such as drug discovery, design, detection, and identification of bioactive chemicals. In medicinal chemistry, heterocyclic molecules play a key role. A lot of people are starting to take an interest in their ability to process and synthesise various chemicals with biological and pharmacological characteristics.3 One prevalent area of study right now is the synthesis of novel pharmaceuticals by molecular engineering of structural entities and the alteration of already physiologically active matrices.4 Medicinal chemists often rely on N-heterocyclic molecules when they are searching for novel antimicrobials. Along these lines, 1,2,3-triazoles have been studied extensively as a large family of heterocyclic compounds with great synthetic versatility.
One notable class within the triazole series is 1,2,3-triazoles, which are a heterocyclic skeleton with several biological functions.5 The compounds' diverse pharmacological characteristics make them attractive for synthesis; they include antibacterial, antiviral, antitumoral, anti-inflammatory, antitubercular, anti-HIV, and antitumoral actions, among others.

Thanks to its 1,2,3-triazole moiety, which may boost solubility and binding capacity to biomolecular targets via a variety of noncovalent interactions, it has broad pharmacological effects.18 The versatility of 1,2,3-triazole as an isostere of many heterocycles, including amides, ester, carboxylic acids, and others, makes it a frequently used pharmacophore in various medications.14 Consequently, 1,2,3-triazole derivatives are very significant in the creation of novel pharmaceuticals.

One may find a number of compounds containing 1,2,3-triazole either already available for purchase or nearing completion of clinical studies. A few examples of promising pharmaceuticals derived from 1,2,3-triazoles are the anticancer drug carboxyamidotriazole (CAI), the β-lactam antibiotic Tazobactum, the cephalosporin Cefatrizine, and the nucleoside derivative non-nucleoside reverse transcriptase inhibitor tert-butyldimethylspiroaminooxathioledioxide (TSAO) (Figure-1).19

Keywords: 1,4-Dihydropyridines and 1,2,3-triazoles are antibacterial.

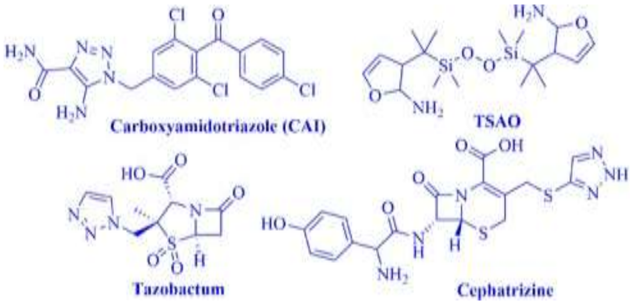


Figure 1. Promising pharmaceuticals based on 1,2,3-triazoles

The approach for developing an expanding set of powerful, selective, and modular blocks that work reliably in both small- and large-scale applications is called click chemistry.[20] Copper-catalyzed azide-alkyne cycloaddition (CuAAC) for the reactions that are capable of building blocks of complex compounds has been widely applied in pharmacological and medicinal applications. On that account, CuAAC has thoroughly emerged in research within the past few years in the fields of organic synthesis, polymer chemistry as well as biochemistry.[21,22] The concept of "click" chemistry was established by Sharpless and co- workers in 2001.[23] Click chemistry comprising good yield, temperature, mild reaction condition, and few by-products, has found applications in many research fields. The 1,2,3- triazole having aromatic five-membered heterocyclic ring containing π-excessive three nitrogen atoms and two carbon atoms with two double bonds have attracted significant attention over recent decades due to their extensive biological activities used in the pharmacological and medicinal applications.[20] Described more than one century ago behavior of 1,4-dihydropyridine derivatives (1,4-DHPs) is exhibiting a wide range of biological activity.

New derivatives of 1,2,3-triazole-linked 1,2,4- triazino[5,6-*b*] indole by the Cu(I)-catalyzed click reaction were determined for their binding modes to three enzyme active sites by molecular docking study. Some of these derivatives were found to bind to active sites of dihydrodipicolinate reductase of *Escherichia coli*, undecaprenyl diphosphate synthase (UPPS) of *Micrococcus luteus* and fibrinogen-binding MSCRAMM, clumping factorA *Staphylococcus aureus* via hydrogen bonds and hydrophobic interactions, respectively.[24]

Methyl derivative of acridone-1,2,3-triazole displayed significant antibacterial activity against *Staphylococcusaureus* (MRSA) with MIC:19.6 µg mL^{-1} and it also played a key role in bond interaction with Ala 7 and hydrophobic interaction into DHFR active site of dihydropteroate synthase (DHPS) in methicillin-resistant *Staphylococcus aureus* (MRSA). Most of the tested compounds displayed moderate activity against *Escherichia coli* and *Klebsiella pneumoniae* with the MIC values between 56.6 - 74.0 µg mL^{-1}.[25]

Some vanillin-derived 1,2,3-triazoles and bis 1,2,3- triazoles substituted with various aromatic rings synthesized using click chemistry concept were found to have potent antibacterial activity. Among them, mono 1,2,3-triazoles, compounds having electron-withdrawing -Br and -NO2 groups at 3- and 4- position of aryl group were more active against Gram-positive bacteria (MIC: 5 µg mL^{-1}). Methyl derivative of bis 1,2,3-triazoles was the most active in the series for most of the Gram-positive and Gram-negative strains (MIC: 5 µg mL^{-1}). It was found as a lead inhibitor of bacterial DNA synthesis due to conformational fitting in the active site of targeted protein Thymidylate kinase (TMPK), which is an essential enzyme in bacterial DNA biosynthesis.[26]

Among few fluorinated chalcone-triazole hybrids obtainedfrom propargylated chalcones and organic azides, derivative with a 4-nitro group (MIC: 0.0032 µmol mL^{-1}) was found to more potent than the standard Ciprofloxacin (MIC: 0.0047 µmol mL^{-1}) against *E. coli* and *S. epidermidis*. While compound with -OMe functional group was also active against *E. coli* with MIC value of 0.0032 µmol mL^{-1}. The activity results displayed the synergistic effect of biological activity when two pharmacophoric units, i.e., chalcone and 1,2,3-triazole are conjugated. Furthermore, the docking study revealed that the most potent derivative with a 4-NO2 group was found to form the most stable binding confirmation into the active site of topoisomerase II DNA gyrase B. Thus, these chalcone triazole conjugates could be thought to possible topoisomerase.[27]

2-Chloro-6-fluorobenzyl substituted 1,2,3-triazole and 2,4-dichlorobenzylTriazole among ten 1,4-disubstituted

1,2,3-triazoles having benzhydryl piperazine chemical scaffold were found to have excellent antibacterial activity against Gram-positive *S. aureus* (zone of inhibition 16.33 mm and 16.45 mm respectively) and Gram-negative *E. coli* (zone of inhibition 15.63 mm and 16.15 mm respectively). By docking study, it was also found that these two compounds make several hydrogen bonds with DNA GyraseB of bacteria.[28]

Functionalized 1,2,3-triazole nucleosides, 4-chlorophenyl derivative **3a**, and 3-methylthiophen derivative **3b** displayed significant antibacterial activity against many Gram-positive and Gram-negative organisms. The 4-chlorophenyl derivative of functionalized 1,2,3-triazole nucleosides inhibited *E. coli* ATCC 10536 with a zone of inhibition of
30 mm that was nearer to zone obtained by standard Cefotaxime (34 mm). While 3-methylthiophen derivative inhibited *M. luteus* ATCC 10240 (35 mm) that was higher than standard (28 mm) at the concentration of 40 μg mL^{-1}.[29]

In the library of 1,2,3-triazolyl-1,4-dihydropyridine hybrids, derivatives with methyl ester, ethyl ester, cyano, phenacyl, and benzyl functional group showed equipotent activity (10 μg mL^{-1}) to the standard Tetracycline against *Proteus mirabilis* with MIC: 10 μg mL^{-1}. In more, cyano, phenacyl, and benzyl derivatives of 1,2,3-triazolyl-1,4-dihydropyridine hybrids were equal potent against *Escherichia coli* with MIC: 30 μg mL^{-1}a nd more potent against *Klebsiella pneumoniae* (MIC: 8 μg mL^{-1} compared to reference drug (MIC: 10 μg mL^{-1}).[30]

Some 1,2,3-triazole-linked β-lactam-bile acid conjugates showed moderate to good antifungal and antibacterial activity against *Candida albicans*, *Candida neoformans*, *Fusarium oxysporum*, *Escherichia coli*, and *Staphylococcus aureus*.[31] Between the series of 5-(4-methyl-1,2,3- triazole)methyl oxazolidinones, the compound with substitution of the isopropylcarbonyl group at the piperazineC4 position was found to be potent against all tested susceptible and resistant Gram-positive pathogenic bacteria.[32] In one study, octyl triazole derivatives of the glycal derived novel tetrahydrofuran 1,2,3-triazoles displayed both antibacterial and antifungal activity at MIC: 12.5 μg mL^{-1}.[33] 1,2,3-triazole-linked pentasubstituted 1,4-dihydropyridine derivative having the presence of fluorine atthe para and chlorine at the meta position of the aromaticring inhibited *B. subtilis* and *S. aureus* at 64 μg mL^{-1}.[34] 1- benzyl/aryl-4-{[(1-aryl-1H-1,2,3-triazol-4-yl)methoxy]- methyl}-1H-1,2,3-triazole derivative having 3-nitrophenylsubstituent was found to be best inhibitory against *E. coli*(32 mm), *P. aeruginosa* (12 mm), *S. aureus* (31 mm) and *B.subtilis* (13 mm) compared to standard drug Amoxycillin(30 mm, 10 mm, 30 mm and 12 mm respectively).[35]

In view of the noteworthy bio-potential of the 1,2,3- triazole nucleus to develop novel bioactive therapeutic agents, we targeted our work on the synthesis and evaluation of the novel 1,2,3-triazole-1,4-dihydropyridine-3,5-dicarbonitrile derivatives as antibacterial agents against ten bacteria. The synthesized compounds had contributed to some key structures with interesting antibacterial activity.

In the present study, to improve the inhibitory function of 1,4-dihydropyridine-3,5-dicarbonitrile, the functionalized derivatives 3a-3o were synthesized via CuAAC click chemistry from 1,4-dihydropyridine-3,5-dicarbonitrile andrelevant aryl/alkyl azides. The biological importance scaffolds DHPs with 1,2,3-triazole combine install together in a single scaffold for increasing importance in pharmaceutical and biological fields. We search for the design and synthesis of pharmacologically important new heterocycles linked in antibacterial activity. The synthesizedcompounds had contributed to some key structures with interesting antibacterial activity.

EXPERIMENTAL

Compound solvents and reagents were reagent grade and used without purification unless otherwise noted. The melting points were recorded on a Fargo melting point apparatus and are uncorrected. Reaction progress was monitored using analytical thin-layer chromatography (TLC) on 0.25mmMerck F-254 silica gel glass plates. Visualization was achieved by UV light (254 nm). Mass spectra were recorded on the Shimadzu GC-MS-QP-2010 model using the Direct Injection Probe technique. ^{1}H and^{13}C NMR spectra were recorded with a Bruker AVANCE 400 MHz spectrometer; Chemical shifts are reported in partsper million (δ) using Tetramethylsilane (TMS) as the internal standard with coupling constants (*J*) reported inhertz (Hz). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, a double doublet. Here, Ar and Ph are representing aromatic ring while -OCH3(-OMe) is representing methoxy group.

In this study, 1,2,3-triazole-1,4-dihydropyridine-3,5-dicarbonitrile derivatives (3a-3o) were synthesized. All of them are reported for the first time here. The initial synthesisof the 1,2,3-triazole-1,4-dihydropyridine-3,5-dicarbonitrile derivatives is illustrated in Scheme-1. Different 1,4- dihydropyridine-3,5-dicarbonitrile derivatives 1a-b were synthesized by substituted propargylated benzaldehyde derivatives with 3-aminocrotononitrile in glacial acetic acid in a stoppered flask and stirred for 1 hour at room temperature under nitrogen atmosphere. The 1,3-dipolar cycloaddition between propargylated 1,4-dihydropyridine- 3,5-dicarbonitrile derivatives and alkyl and aryl-substituted azides derivatives under click chemistry conditionsproduced novel 1,2,3-triazole-1,4-dihydropyridine-3,5- dicarbonitrile derivatives 3a-3o were synthesized in quantitative yields. Different aromatic azides with various substitutions, including electron-withdrawing and electron- donating groups, have been used. The propargylation of – CH_2 group of the different 1,2,3-triazole 1,4- dihydropyridine-3,5-dicarbonitrile derivatives wasconfirmed by the presence of a signal at δ 5.20–5.26 s (2H, –CH_2). The formation of 1,2,3-triazoles was confirmed by the resonance of the proton in the 1,2,3 triazole ring at a δ 8.70–8.80 s (1H, –CH) as a single. The structure was further supported by the ^{13}C NMR spectra, which showed the C-atom signals corresponding to triazole derivatives.

Preparation of propargylated-1,4-dihydropyridine-3,5-dicarbo-nitrile derivatives (1a-1b)

A mixture of propargylated benzaldehyde derivatives (0.01 mol) and 3-aminocrotononitrile (0.02 mol) was taken in glacial acetic acid in a flask and stirred for 1 hour at room temperature. During the reaction, progress and the completion of the reaction were checked by silica gel-G F254 thin layer chromatography using ethyl acetate: hexane (3:2) as a mobile phase. After the completion of the reaction, the crystalline product was separated which was filtered and washed with diethyl ether.

General procedure for preparation of compounds 3a-3o

To a solution of propargylated-1,4-dihydropyridine-3,5- dicarbonitrile derivatives (1a-1b) (0.01 mol) in dry DMF (5 mL), anhydrous sodium hydride (15 mmol) was added and stirred for 5 min. After adding propargyl bromide (12 mmol),the resulting mixture was stirred at room temperature overnight. Upon completion of the reaction, water (20 mL) was added and the whole was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuum and the residue was purified by silica gel (60–120 mesh) column chromatography using hexane–ethyl acetate.

Antimicrobial activity of synthesized 1,2,3-triazole derivatives

Minimum Inhibition Concentration (MIC) of all 1,2,3-triazole-1,4-dihydropyridine-3,5-dicarbonitrile derivatives was determined by using the two-fold microdilution method,the standard methodology that is given by NCCLS.[44] Both Gram-positive and Gram-negative bacterial strains used for the *in-vitro* antibacterial study were procured from culture collection centers. Bacterial cultures of *Salmonella typhi* (MTCC 733), *Salmonella paratyphi* (MTCC 735), *Escherichia coli* (MTCC 1610 T) and *Proteus vulgaris* (MTCC 1771 T) were procured from MTCC, IMTECH,Chandigarh, whereas cultures of *Klebsiella pneumoniae* (MCC 3094), *Pseudomonas aeruginosa* (MCC 3097), *Enterobacter aerogenes* (MCC 3092) and *Shigella flexneri* (MCC 3095) were procured from NCMR, NCCS, Pune.

Clinical isolates of *Serratia marcescens* and *Bacillus subtilis*were collected from a local pathology laboratory in Ahmedabad and identified using biochemical tests prescribed in Bergey's Manual of Determinative Bacteriology, Sixth Edition.[47] The bacterial cultures were maintained on nutrient agar slants at 2±4 °C. For the microdilution method, a standardized inoculum for each bacterial strain was prepared to get the inoculum size of approximately

Compound **3b** was prepared from 1-azido-3- chlorobenzene (1.2 mmol), 2,6-dimethyl-4-(3-(prop-2-yn-1-yloxy)phenyl)-1,4-dihydropyridine-3,5-dicarbonitrile (1a, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol); ^1H NMR (DMSO–d_6) δ 2.04 s (6H, 2×CH_3), 3.76 s (3H, –OCH_3), 4.39

DMSO. Further dilutions of stock solution were prepared in

DMSO to get working concentration ranging from 25 μg mL^{-1} to 2000 μg mL^{-1}. 100 µL of each dilution was distributed in 96 well microtiter plates with double strength (2X) Mueller Hinton broth (MH broth) to obtain an actual concentration ranging from 12.5 μg mL^{-1} to 1000 μg mL^{-1} in each test well of a microtiter plate.

For standard, Penicillin and Tetracycline antibiotic solutions were prepared in working concentration ranging from 25 μg mL^{-1} to 2000 μg mL^{-1} was used which was added in the same way as test solutions to get actual concentrations ranging from 12.5 μg mL^{-1} to 1000 μg mL^{-1} in standard wells.These microtiter plates were then kept at 37 °C for 24-36 h incubation. Each test and growth control well were inoculated with 50 µL of a bacterial suspension having standard inoculum size. Following the incubation period, bacterial growth was detected by optical density using Biolog Microplate Reader. MIC values were defined as the lowest concentration of each compound that completely inhibited microbial growth. [45,46]

4-(3-Methoxy-4-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)- methoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5- dicarbonitrile (3a)

To a solution of 1-azido-3-nitrobenzene (1.2 mmol) and2,6-dimethyl-4-(3-(prop-2-yn-1-yloxy)phenyl)-1,4-dihydro- pyridine-3,5-dicarbonitrile (**1a**, 1.0 mmol) were added to amixture of copper(II) sulfate pentahydrate solution (0.01mmol) and sodium ascorbate (0.25 mmol) dissolved in *t*-BuOH:H_2O (1:1 mixture, 3 mL) at room temperature. Thereaction mixture was stirred at room temperature for 3-6 h,and monitored by TLC. The resulting mixture was pouredinto $CHCl_3$ (5 mL) and H_2O (3 mL), and the organic layerwas separated. The aqueous layer was extracted with $CHCl_3$ (5 mL) three times. The combined organic layer wasconcentrated in vacuo. The residue was purified by shortcolumn chromatography on silica gel (60−120 mesh) elutedwith ethyl acetate: hexane (6:4) to give **3a**; ^{1}H NMR(DMSO–*d6*) δ 2.04 s (6H, 2×CH_3), 3.76 s (3H, –OCH_3), 4.36 s (3H, –CH), 5.22 s (2H, –CH_2), 6.80–6.82 d (1H, *J* = 8.2 Hz, Ar-H), 6.88–6.89 d (1H, J = 1.48 Hz, Ar-H), 7.89–7.93 d (1H, *J* = 8.20 Hz, Ar-H), 8.33–8.35 t (1H, *J* = 6.88 Hz, Ar-H), 8.43–8.45 t (1H, *J* = 7.84 Hz, Ar-H), 8.77 s (1H, Ar-H), 9.21 s (1H, Ar-H), 9.49 s (1H, –NH); ^{13}C NMR (DMSO–*d6*) δ 17.73, 55.50, 61.55, 82.77, 111.55, 113.90, 114.88, 119.35, 119.81, 123.17, 123.50, 126.18, 131.51, 137.11, 137.49, 144.30, 146.40, 146.83, 148.49, 149.02.

By following the same procedure, the following compounds were synthesized. Analytical data and yields of 1,2,3-triazole 1,4-dihydropyridine-3,5-dicarbonitrile deriva- tives (**3a-3o**) is given in Table 1.s (3H, –CH), 5.22 s (2H, –CH_2), 6.81–6.87 d (2H, *J* = 24.2 Hz, 2×Ar-H), 7.20–7.22 d (1H, *J* = 6.04 Hz, Ar-H), 7.58–7.63 t (2H, *J* = 6.92 Hz, Ar-H), 7.95 s (2H, 2×ArH), 8.08 s (2H, 2×ArH), 9.03 s (1H, Ar-H), 9.49 (s, 1H, NH); ^{13}CNMR (DMSO–*d6*) δ 17.74, 55.50, 61.58, 82.78, 111.55, 113.88, 118.74, 119.35, 119.81, 119.96, 123.20, 128.54, 131.59, 134.18, 137.46, 137.57, 144.02, 146.40, 146.85, 149.01.

4-(3-((1-(4-Cyanophenyl)-1H-1,2,3-triazol-5-yl)methoxy)phe- nyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (3c)

Compound **3c** was prepared from 4-azidobenzonitrile (1.2 mmol), 2,6-dimethyl-4-(3-(prop-2-yn-1-yloxy)phenyl)-1,4- dihydropyridine-3,5-dicarbonitrile (1a, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) andsodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–*d6*) δ 2.04 s (6H, 2×CH_3), 4.39 s (1H, –CH), 5.28 s (2H, –CH_2), 6.89–6.92 t (2H, *J* = 6.12 Hz, 2×Ar-H), 7.08–7.09 d (1H, *J* = 6.04 Hz, Ar-H), 7.34–7.38 t (2H, *J* = 7.80 Hz, Ar-H), 8.10–8.12 d (2H, *J* = 8.48 Hz, 2×Ar-H), 8.16–8.18 d (2H, *J* = 8.56 Hz, 2×Ar-H), 9.12 s (1H, Ar-H), 9.53 s (1H, –NH); ^{13}C NMR (DMSO–*d6*) δ 17.13, 60.92, 82.47, 111.11, 113.25, 114.52, 118.07, 119.24, 120.37, 120.53, 123.13, 130.01, 134.25, 139.44, 144.32, 145.67, 146.76, 158.25.

4-(3-Methoxy-4-((1-(p-tolyl)-1H-1,2,3-triazol-4-yl)methoxy)- phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (3d)

Compound **3d** was prepared from 1-azido-4- methylbenzene (1.2 mmol), 2,6-dimethyl-4-(3-(prop-2-yn-1-yloxy)phenyl)-1,4-dihydropyridine-3,5-dicarbonitrile (**1b**, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–*d6*) δ 2.04 s (6H, 2×CH3), 2.38 s (3H, CH3), 3.76 s (3H, –OCH3), 4.36 s (1H, –CH), 5.21 s (2H, –CH2), 6.80– 6.98 dd (2H, *J* = 8.16 and 1.24 Hz, 2×Ar-H), 7.21–7.23 d (1H, *J* = 8.24 Hz, Ar-H), 7.39–7.41 d (2H, *J* = 8.12 Hz, 2×Ar-H), 7.79–7.81 d (2H, *J* = 8.24 Hz, 2×Ar-H), 8.90 s (1H, Ar-H), 9.49 s (1H, –NH); ^{13}C NMR (DMSO–*d6*) δ 17.74, 20.54, 55.48, 61.61, 82.79, 111.53, 113.82, 119.35, 119.81, 120.01, 122.88, 130.21, 134.30, 137.39, 138.36, 143.70, 146.39, 146.90, 149.01, 162.26.

4-(3-Methoxy-4-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4- yl)methoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5- dicarbonitrile (3e)

Compound **3e** was prepared from 1-azido-4- methoxybenzene (1.2 mmol), 4-(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5- dicarbonitrile (**1b**, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–*d6*) δ 2.04 s (6H, 2×CH3), 3.76 s (3H, CH3), 3.84 s (3H, –OCH3), 4.36 s (1H, –CH), 5.20 s (2H, –CH2), 6.79-6.82 dd (2H, *J* = 1.60 and 1.60 Hz, Ar-H), 6.87–6.87 d (1H, *J* = 1.56 Hz, A-rH), 7.13–7.16 d (2H, *J* = 8.96 Hz, 2×Ar-H), 7.21–7.23 d (1H, *J* = 8.24 Hz, Ar-H), 7.82–7.84 d (1H, *J* = 8.92 Hz, Ar-H), 8.85 s (1H, Ar-H), 9.49 s (1H, –NH); ^{13}C NMR (DMSO–*d6*) δ 17.74, 30.73, 55.48, 55.53, 61.62, 82.79, 111.52, 113.80, 114.85, 119.36, 119.80, 121.82, 122.98, 129.96, 137.36, 143.57, 146.39, 146.91, 148.99, 159.28, 162.27.

4-(4-((1-(4-Fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3- methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5- dicarbonitrile (3f)

Compound **3f** was prepared from 1-azido-4-fluorobenzene (1.2 mmol), 4-(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicar-bonitrile (**1b**, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–*d6*) δ 2.04 s (6H, 2×CH3), 3.76 s (3H, –OCH3), 4.36s (1H, –CH), 5.22 s (2H, –CH2), 6.80–6.82 d (1H, *J* = 7.80 Hz, Ar-H), 6.88 s (1H, Ar-H), 7.21–7.23 d (1H, *J* = 8.08 Hz,Ar-H), 7.47–7.49 d (2H, *J* = 8.24 Hz, 2×Ar-H), 7.97 s, (2H, 2×ArH), 8.94 s (1H, Ar-H), 9.50 s (1H, –NH); ^{13}C NMR (DMSO–*d6*) δ 17.74, 55.48, 61.58, 82.79, 111.53, 113.84, 116.59, 116.82, 119.36, 119.81, 122.49, 122.58, 123.26, 133.11, 137.42, 143.86, 146.40, 146.87, 149.01, 160.44, 162.88.

4-(4-((1-(4-Cyanophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-3- methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5- dicarbonitrile (3g)

Compound **3g** was prepared from 4-azidobenzonitrile (1.2 mmol), 4-(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (**1b**, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–*d6*) δ 2.04 s (6H, 2×CH3), 3.76 s (3H, OCH3), 4.36 s (1H, –CH), 5.25 s (2H, –CH2), 6.80–6.82 d (2H, *J* = 7.80 Hz, 2×Ar-H), 6.88 s (1H, Ar-H), 7.20–7.22 d (1H, *J* = 7.96 Hz, Ar-H), 8.10–8.19 dd (4H, *J* = 7.76 and 7.76 Hz, 4×Ar- H), 9.12 s (1H, Ar-H), 9.50 s (1H, –NH); ^{13}C NMR (DMSO–*d6*) δ 17.74, 55.50, 61.53, 82.77, 111.10, 111.55, 113.91, 118.08, 119.36, 119.81, 120.54, 123.25, 134.26, 137.50, 139.44, 144.36, 146.41, 146.81 149.02.

2,6-Dimethyl-4-(3-((1-(3-nitrophenyl)-1H-1,2,3-triazol-5-yl)- methoxy)phenyl)-1,4-dihydropyridine-3,5- dicarbonitrile (3h)

Compound **3h** was prepared from 1-azido-3-nitrobenzene (1.2 mmol), 2,6-dimethyl-4-(3-(prop-2-yn-1-yloxy)phenyl)- 1,4-dihydropyridine-3,5-dicarbonitrile (**1a**, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–*d6*) δ 2.04 s (6H, 2×CH_3), 4.39 s (1H, –CH), 5.29 s (2H, –CH_2), 6.89–6.93 d (2H, *J* = 7.56 Hz, 2×Ar-H), 7.08–7.10 d (1H, *J* = 6.80 Hz, Ar-H), 7.35–7.38 t (1H, *J* = 6.72 Hz, Ar-H), 7.90–7.94 t (1H, *J* = 7.68 Ar-H), 8.34–8.44 dd (2H, *J* = 7.68, 2×Ar-H), 8.76 s (1H, Ar-H), 9.22 s (1H, Ar-H), 9.54 s (1H, –NH); ^{13}CNMR (DMSO–*d6*) δ 17.73, 60.94, 82.47, 113.25, 114.54,114.88, 119.23, 120.36, 123.19, 123.38, 126.18, 130.01, 131.54, 137.12, 144.25, 145.67, 146.76, 148.49, 158.26.

4-(3-((1-Benzyl-1H-1,2,3-triazol-5-yl)methoxy)phenyl)-2,6- dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (3i)

Compound **3i** was prepared from (azidomethyl)benzene (1.2 mmol), 2,6-dimethyl-4-(3-(prop-2-yn-1-yloxy)phenyl)- 1,4-dihydropyridine-3,5-dicarbonitrile (**1a**, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–*d6*) δ 2.04 s (6H, 2×CH_3), 4.38 s (1H, –CH), 5.15 s (2H, –CH_2), 5.62 s (2H, –CH_2), 6.87–6.89 d (2H, *J* = 7.44 Hz, 2×Ar-H), 7.01–7.03 d (1H, *J* = 8.60 Hz, Ar-H), 7.34–7.40 m (6H, 6×Ar-H), 8.32 s (1H, Ar-H), 9.54 s (1H, Ar-H), 9.54 s (1H, –NH); ^{13}C NMR (DMSO–*d6*) δ 17.74, 52.84, 60.98, 82.49, 113.15, 114.49, 119.27, 120.17, 124.77, 127.94, 128.14, 128.75, 129.91, 135.95, 145.65, 146.76, 158.38.

2,6-Dimethyl-4-(3-((1-(p-tolyl)-1H-1,2,3-triazol-5-yl)methoxy)phenyl)-1,4-dihydropyridine-3,5-dicarbonitrile (3j)

Compound **3j** was prepared from 1-azido-4- methylbenzene (1.2 mmol), 2,6-dimethyl-4-(3-(prop-2-yn-1-yloxy)phenyl)-1,4-dihydropyridine-3,5-dicarbonitrile (**1a**, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–*d6*) δ 2.04 s (6H, 2×CH_3), 2.38 s (3H, –CH_3), 4.39 s (1H, –CH), 5.25 s (2H, –CH_2), 6.89–6.93 d (2H, J = 7.48 Hz,2×Ar-H), 7.07–7.09 d (1H, *J* = 6.92 Hz, Ar-H), 7.36–7.41 t (3H, *J* = 12.44 Hz, 3×Ar-H), 7.79–7.80 d (2H, *J* = 7.20 Hz, 2×Ar-H), 8.91 s (1H, Ar-H), 9.55 s (1H, –NH); ^{13}C NMR (DMSO–*d6*) δ 17.73, 20.55, 24.22, 61.00, 82.49, 113.21, 114.51, 119.25, 120.02, 120.28, 122.76, 129.98, 130.20, 134.31, 138.36, 143.63, 145.68, 146.75, 158.35.

4-(3-Methoxy-4-((1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)- methoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5- dicarbonitrile (3k)

Compound **3k** was prepared from 1-azido-2-nitrobenzene (1.2 mmol), 4-(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (**1b**, 1.0mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–*d6*) δ 2.04 (s, 6H, 2×CH_3), 3.76 (s, 3H, –OCH_3), 4.36 (s, 3H, –CH), 5.22 (s, 2H, –CH_2), 6.80–6.82 (d, 1H, J = 8.2 Hz, ArH), 6.88–6.89 (d, 1H, J = 1.48 Hz, ArH), 7.89–7.93 (d, 1H, J = 8.20 Hz, ArH), 8.33–8.35 (t, 1H, J = 6.88 Hz, ArH), 8.43–8.45 (t, 1H, J = 7.84 Hz, ArH), 8.77 (s, 1H, ArH), 9.21 (s, 1H, ArH), 9.49 (s, 1H, –NH); ^{13}C NMR (DMSO–*d6*) δ 17.73, 55.50, 61.55, 82.77, 111.55, 113.90, 114.88, 119.35, 119.81, 123.17, 123.50, 126.18, 131.51, 137.11, 137.49, 144.30, 146.40, 146.83, 148.49, 149.02.

4-(4-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)-3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (3l)

Compound **3l** was prepared from (azidomethyl)benzene (1.2 mmol), 4-(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (**1b**, 1.0mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR(DMSO–d_6) δ 2.05 s (6H, 2×CH_3), 3.77 s (3H, –CH_3), 4.35 s (1H, –CH), 5.12 s (2H, –CH_2), 5.62 s (2H, –CH_2), 6.77–6.85t (2H, *J* = 6.88 Hz, 2×Ar-H), 7.14–7.16 d (1H, *J* = 8.24 Hz, Ar-H), 7.33–7.40 m (5H, 5×Ar-H), 8.29 s (1H, Ar-H), 9.49 (s, 1H, –NH); ^{13}C NMR (DMSO–d_6) δ 17.74, 52.81, 55.43, 61.66, 82.80,, 111.46, 113.68, 119.35, 119.75, 124.81, 127.96, 128.13, 128.75, 135.97, 137.25, 146.37, 146.90, 148.95.

4-(3-((1-(4-Bromophenyl)-1H-1,2,3-triazol-5-yl)methoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (3m)

Compound **3m** was prepared from 1-azido-4- bromobenzene (1.2 mmol), 2,6-dimethyl-4-(3-(prop-2-yn-1-yloxy)phenyl)-1,4-dihydropyridine-3,5-dicarbonitrile (**1a**, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–d_6) δ 2.05 s (6H, 2×CH_3), 4.39 s (1H, –CH), 5.25 s (2H, –CH_2), 6.89–6.92 t (2H, *J* = 6.20 Hz, 2×Ar-H), 7.08– 7.09 t (1H, *J* = 6.96 Hz, Ar-H), 7.34–7.38 t (1H, *J* = 7.56 Hz,Ar-H), 7.80–7.82 d (2H, *J* = 8.16 Hz, 2×Ar-H), 7.89–7.91 d (2H, *J* = 8.24 Hz, 2×Ar-H), 9.00 s (1H, Ar-H), 9.54 s (1H, – NH); ^{13}C NMR (DMSO–d_6) δ 17.74, 60.95, 82.48, 113.23, 114.51, 119.24, 120.32, 121.40, 122.06, 122.93, 129.99, 132.76, 135.74, 143.97, 145.67, 146.75, 158.30.

4-(3-((1-(Cyanomethyl)-1H-1,2,3-triazol-5-yl)methoxy)phenyl)- 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (3n)

Compound **3n** was prepared from 2-azidoacetonitrile (1.2mmol), 2,6-dimethyl-4-(3-(prop-2-yn-1-yloxy)phenyl)-1,4-dihydropyridine-3,5-dicarbonitrile (**1a**, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–d_6) δ 2.05s (6H, 2×CH_3), 4.38 s (1H, –CH), 5.20 s (2H, –CH_2), 5.25 s (2H, –CH_2), 6.89 s (2H, 2×Ar-H), 7.03–7.05 d (1H, *J* = 7.32 Hz, Ar-H), 7.33–7.36 t (1H, *J* = 7.36 Hz, Ar-H), 8.41 s (1H, Ar-H), 9.54 s (1H, –NH); ^{13}C NMR (DMSO–d_6) δ 17.74, 60.69, 82.47, 113.13, 114.48, 115.04, 119.26, 120.25, 125.62, 129.95, 143.32, 145.67, 146.77, 158.27.

4-(4-((1-(4-Cyanobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)-3- methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-di- carbonitrile (3o)

Compound **3o** was prepared from 4-(azidomethyl)benzonitrile (1.2 mmol), 4-(3-methoxy-4- (prop-2-yn-1-yloxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (**1b**, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) andsodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–d_6) δ2.05 s (6H, 2×CH_3), 3.73 s (3H, –OCH_3), 4.35 s (1H, –CH), 5.14 s (2H, –CH_2), 5.75 s (2H, –CH_2), 6.77–6.79 m (1H, Ar-H), 6.85–6.86 d (1H, *J* = 1.68 Hz, Ar-H), 7.17–7.16 d (1H, *J* = 8.32 Hz, Ar-H), 7.46–7.48 d (2H, *J* = 8.12 Hz, 2×Ar-H), 7.85–7.87 d (2H, *J* = 8.16 Hz, 2×Ar-H), 8.34 s (1H, Ar-H), 9.49 s (1H, Ar-H); ^{13}C NMR (DMSO–d_6) δ 17.73, 52.16, 55.45, 61.64, 82.79, 110.92, 111.48, 113.76, 118.51, 119.35, 119.76, 125.14, 128.70, 132.72, 137.30, 141.43, 143.16, 146.38, 146.84, 148.98.

Crystal Structure Determination

Crystal data of **3d** and **3e** were made on a Rigaku SCX mini diffractometer using graphite monochromated Mo-Kα radiation. The crystal to detector distance is fixed at 52 mm with a detector. The data were collected at a temperature of 20±1°C to a maximum 2θ value of 55.0° A total of 540 oscillation images were collected. The first and second sweep of data was done using ω oscillations from -120.0 to 60.0° in 1.0° steps. The exposure rate was 8.0 [sec/°]. The detector swing angle was -30.80°. The crystal-to-detectordistance was 52.00 mm. The readout was performed in the 0.146 mm pixel mode. Both crystals of **3d** and **3e** crystallize in triclinic space group P-1(#2). Figure 2 and 3 representsthe ORTEP of the molecules **3d** and **3e**, respectively, with thermal ellipsoids drawn at 50% probability.

Crystal Structure Determination and Refinements (3d)

A colorless prism crystal of **3d** having M.F. $C_{26}H_{24}N_6O_2 \cdot C_2H_6OS$ and approximate dimensions of 0.455 × 0.321 × 0.300 mm was mounted on a glass fiber. Data Reduction of the 13915 reflections that were collected, 6245were unique (Rint = 0.0551), equivalent reflections were merged. Data were collected and processed using Crystal Clear.[36] The linear absorption coefficient μ, for Mo-Kα radiation, is 1.582 cm^{-1}. Empirical absorption correction wasapplied, which resulted in transmission factors ranging from 0.445 to 0.954. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods[37] and expanded using Fourier techniques. The non- hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. Hydrogen atoms associated with heteroatoms were refined independently in the isotropic approximation. The final cycle of full-matrix least-squares refinement [SHELXL97, $\Sigma w(F_o^{2}-F_c^{2})^2$ where w = Least Squares weights] on F^2 was based on 6245 observed reflections and 343 variable parameters and converged. The standard deviation of observation of unit weight was 1.03 and calculated by $\Sigma w(F_o^{2}-F_c^{2})^2/(N_o-N_v)]^{1/2}$, where: N_o = number of observations N_v = number of variables. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.67 and -0.55 e $Å^{-3}$ respectively. Neutral atom scattering factors were taken from Cromer and Waber.[38] Anomalous dispersion effects were included in F Calculation[39] the values for Δf' and Δf" were those of Creagh and McAuley.[40] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[41] All calculations were performed using the crystal structure.[42] Crystallographic software package except for refinement, which was performed using [Direct Methods (SHELXD)] SHELXL-97.[43] Crystal Lattice Parameters a = 7.9223(9) Å, b = 11.361(2) Å, c = 16.227(2) Å, α = 73.440(4)°, β = 89.413(4)°, γ= 79.452(4)°, V = 1374.9(3) $Å^3$,Z value is 2, D_{cal} = 1.258 g cm^{-3}, F_{000} = 616.00, μ(Mo-Kα) = 2.054 cm^{-1}, Radiation is Mo-Kα (λ = 0.71075 Å). Final refinement parameters: R_1 [I > 2σ(I)] = 0.0960, wR_2 = 0.3082), R (All reflections) = 0.1310, Goodness of Fit Indicator = 1.095, Max Shift/Error in Final Cycle = 0.001, Maximum peak in Final Diff. Map = 0.67 e $Å^{-3}$, Minimum peak in Final Diff. Map = -0.55 e $Å^{-3}$ X-ray diffraction results were deposited at the Cambridge Crystallographic Data Center **(CCDC 1969216).** The X-ray crystal structure determination shows that the interatomic distances 1.355(5) Å for N2-C20 is near to that of a typical Aromatic C–N bond

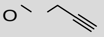
(1.47). The bond length for 1.153(6) Å for C9-N5 and 1.145(7) Å for C8-N6 are near to that of a typical C≡NCyano bond length (1.16). The bond angles for C4-C5-C6, C2-C3-C4 which illustrate that 123.7(4)°, 124.2(3)° of C2, C3, C4, C5, C6 all adopt sp^2 hybrid orbit to form C=C double bonds. The bond angles for C12-O1-C16 and C13-O2-C17 is 117.1(4)° and 118.9(4)°, which illustrate that C12, O1, C16, C13, O2, C17 all adopt sp^2 hybrid orbit to form C-O-C Single bond. In this molecule, N2-N3-N4 bond angle is 107.6(4)° of the 1,2,3-triazole core is planar. A study of torsion angles of N2, N3, N4, C18 is 0.6(5) and C19, N2, N3, N4 is -0.3 (5)°.

Crystal Structure Determination and Refinements (3e)

A colorless prism crystal of **3e** having M.F. $C_{26}H_{24}N_6O_3 \cdot C_2H_6OS$ and approximate dimensions of 0.670 × 0.560 × 0.560 mm was mounted on a glass fiber. Data Reduction of the 14263 reflections that were collected, 6382 were unique (R_{int} = 0.0248), equivalent reflections were merged. Data were collected and processed using Crystal Clear.[36] The linear absorption coefficient μ, for Mo-Kα radiation, is 1.603 cm^{-1}. Empirical absorption correction was applied, which resulted in transmission factors ranging from 0.684 to 0.914. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods[37] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. Hydrogen atoms associated with heteroatom were refined independently inthe isotropic approximation. The final cycle of full-matrix least-squares refinement [SHELXL97, $\Sigma w(F_o^{2}-F_c^{2})^2$ where w = Least Squares weights] on F^2 was based on 6382 observed reflections and 352 variable parameters and converged.

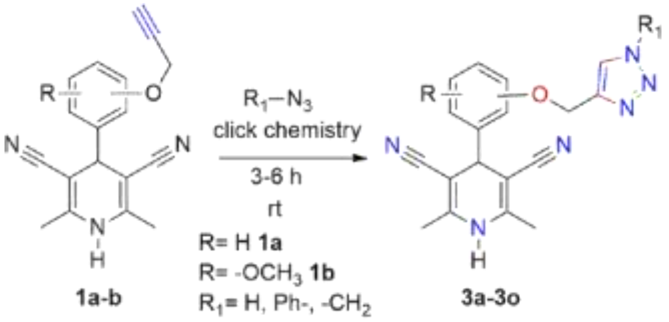
The standard deviation of observation of unit weight was 1.51 and calculated by $\Sigma w(F^{2}-F^{2})^{2}/(N^{2}-N)]^{1/2}$, where: N = number of observations, N_V = number of variables. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 1.87 and-0.71 e Å^{-3}, respectively. Neutral atom scattering factorswere taken from Cromer and Waber.[38] Anomalous dispersion effects were included in F Calculation[39]; the values for Δf' and Δf'' were those of Creagh and McAuley.[40] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[41] All calculations were performed using the crystal structure.[42] Crystallographic softwarepackage except for refinement, which was performed using Direct Methods (SHELXD and SHELXL-97).[43] Crystal Lattice Parameters a = 9.570(1) Å, b = 10.577(2) Å, c = 14.595(2) Å, α = 73.440(4)°, β = 89.413(4)°, γ = 79.452(4)°,V = 1374.9(3) Å3, Z value is 2, D_{cal} = 1.258 g cm^{-3}, F000 = 616.00, μ(Mo-Kα) = 2.054 cm^{-1}, Radiation is Mo-Kα (λ = 0.71075 Å). Final refinement parameters: $R1$ [$I > 2\sigma(I)$] = 0.1057, $wR2$ = 0.3850, R (All reflections) = 0.1315, Goodness of Fit Indicator = 1.512, Max Shift/Error in Final Cycle = 0.004, Maximum peak in Final Diff. Map = 1.87 e Å^{-3}, Minimum peak in Final Diff. Map = -0.71 e Å^{-3}. X-ray diffraction results were deposited at the Cambridge Crystallographic Data Center (CCDC 1996628). The X-ray crystal structure determination shows that the interatomic distances 1.434(5) Å for N4-C20 is near to that of a typical Aromatic C–N bond (1.47). The bond length for 1.154(6) Å for C9-N2 and 1.150(7) Å for C8-N3 are near to that of a typical C≡N Cyano bond length (1.16). The bond angles for C2-C3-C4 and C4-C5-C6, which illustrate that 124.6(4)°, 124.1(4)° of C2, C3, C4, C5, C6 all adopt sp^{2} hybrid orbit to form C=C double bonds. The bond angles for C12-O2-C17 and C23-O3-C26 is 116.9(3)° and 118.4(4)°, which illustrate that C12, O2, C17, C23, O3, C26 all adopt sp^{2} hybrid orbit to form C-O-C Single bond. In this molecule, the N4-N5-N6 bond angle is 106.4(3)° of the 1,2,3-triazole core is the planar aromatic ring. A study of the torsion angles, asymmetric parameters and least-squares plane calculations reveals that the three-membered ring of 1,2,3 triazole C19-N4-N5-N6 is –0.4(4)° and N4-N5-N6-C18 is –0.398(5)° are showing that the 1,2,3 triazole ring in the same plane. A study of torsion angles of N2, N3, N4, C18 is 0.6(5) and C19, N2, N3, N4 is -0.3(5)°.

Table 1. Analytical data and yields of 1,2,3-triazole 1,4-dihydropyridine-3,5-dicarbonitrile derivatives (3a-3o).

Compound		**R**	**R₁**	**MF**	**MW**	**M.P. (°C)**	**Yield (%)**
3a	**3**	H	–3–O₂NPh	$C_{24}H_{19}N_7O_3$	453.45	256–257	70
3b	**3**	H	–3–ClPh	$C_{24}H_{19}ClN_6O$	442.90	228–229	72
3c	**3**	H	–4–NCPh	$C_{25}H_{19}N_7O$	433.46	220–221	75
3d	**4**	3–OMe	–4–MePh	$C_{26}H_{24}N_6O_2$	452.50	264–265	68
3e	**4**	3–OMe	–4–MeOPh	$C26H_{24}N_6O_3$	468.50	268–269	71
3f	**4**	3–OMe	–4–FPh	$C_{25}H_{21}FN_6O_2$	456.47	258–259	70
3g	**4**	3–OMe	–4–NCPh	$C_{26}H_{21}N_7O_2$	463.49	270–271	73
3h	**3**	H	–2–O₂NPh	$C_{24}H_{19}N_7O_3$	453.45	250–251	68
3i	**3**	H	–CH₂Ph	$C_{25}H_{22}N_6O$	422.48	260–261	67
3j	**3**	H	–4–MePh	$C_{25}H_{22}N_6O$	422.48	240–241	70
3k	**4**	3–OMe	–2–O₂NPh	$C_{25}H_{21}N_7O_4$	483.47	266–267	61
3l	**4**	3–OMe	–CH₂Ph	$C_{26}H_{24}N_6O_2$	452.50	268–269	69
3m	**3**	H	–4–BrPh	$C_{24}H_{19}BrN_6O$	487.35	202–203	69
3n	**3**	H	–CH₂CN	$C_{20}H_{17}N_7O$	371.39	240–241	65
3o	**4**	3–OMe	–CH₂(4-NC)Ph	$C_{27}H_{23}N_7O_2$	477.51	272–273	75

RESULTS AND DISCUSSIONS

The general route for the synthesis of 1,2,3-triazole-1,4- dihydropyridine-3,5-dicarbonitrile derivatives (**3a-3o**) wasdeveloped with the reaction of **1a-1o** alkynes with alkyl and aryl azides at room temperature for 3-6 h.



Scheme-1

Scheme 1. The general route for the synthesis of 1,2,3-triazole-1,4-dihydropyridine-3,5-dicarbonitrile derivatives.

The yield and melting points of prepared derivatives are given in Table 1. The structure of compounds **3d** and **3e** are given in Figures 2 and 3, respectively. The other structural data are given in Supplementary material.

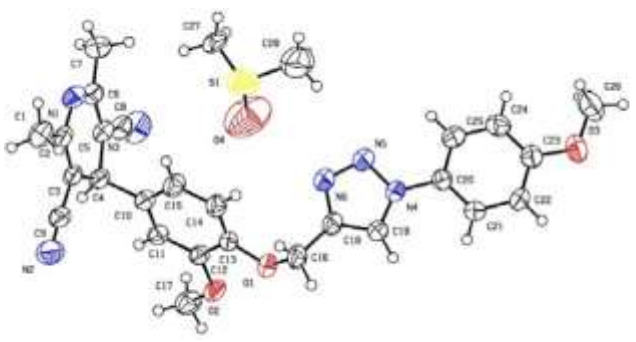


Figure 2. PLATON version of **3d** with data block ellipsoid plotdrawn at 50% probability (CCDC 1969216).

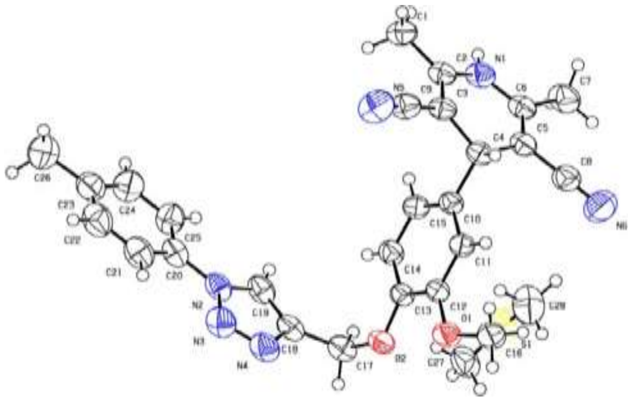


Figure 3. PLATON version of **3e** with data block ellipsoid plotdrawn at 50% probability (CCDC 1996628).

Antimicrobial activity of synthesized 1,2,3-triazole derivatives

Results of antibacterial activity of 1,2,3-triazole derivatives are represented in Table 1 and Figure 4. For *S. flexneri*, nine of the compounds show good potency. Compounds **3b** and **3d** displayed more potency with MIC value of 100 μg mL^{-1} due to the presence of 3-Cl and 4-Me groups respectively, while compounds **3a** and **3e** displayed twofold lower MIC (200 μg mL^{-1}) compared to standard dueto the presence of 3-O$_2$N and 4-OMe group attached totriazole ring. In more, compounds **3i**, **3k**, **3l**, and **3n** (400 μg mL^{-1}) were found to be equipotent compared to the standard antibiotic Tetracycline. Compounds **3h**, **3j**, and **3f** displayed prominent activity having MIC values of 50 μg mL^{-1} similarto Tetracycline against *P. aeruginosa* and *P. vulgaris* respectively and this potency was observed due to the presence of 2-NO$_2$, 4-Me and 4-F groups attached to the triazole rings of **3h**, **3j**, and **3f** respectively. Comparatively, the derivative of 1,2,3-triazolyl-1,4-dihydropyridine having the propargyloxy group at the ortho position of the phenyl ring inhibited *P. mirablis* and *K. pneumoniae* with the MIC: 70 μg mL^{-1}.[30]

The MIC value of compound **3i** was 12.5 μg mL$^{-1,}$ whichis twofold lower than Tetracycline (25 μg mL^{-1}) against *S. marcescens* that is due to the methylene group attached to the triazole ring. The MIC value of compound **3f** was found to be similar to Tetracycline against *E. aerogenes*. The compound **3e** was the only one that is active against *E. coli* (MIC: 50 μg mL^{-1}) due to the presence of 4-OMe group attached to the triazole ring.

The meta-analysis of antibacterial activity

A meta-analysis of our experimental findings of antibacterial activity was done by Orange3-3.27.1- Miniconda software. As shown in Figures 5 and 6, if we compare the observations among compounds with different groups, it can be seen that various functional groups at the various position of core structure inhibited different test organisms with varying MICs. Compound **3k** (3-MeO at R) inhibited *K. Pneumoniae* and *S. flexneri* with MIC: 400 μg mL^{-1} that is lower than MIC shown by compound **3h**. On the other hand, compound **3h** (-H at R) inhibited *P. aeruginosa* with MIC: 50 μg mL^{-1} that is much lower than the MIC given by compound **3k**. Compound 3h also inhibited *P. vulgaris* with MIC: 50 μg mL^{-1} that is much lower than the MIC given by **3k** (MIC: 1000 μg mL^{-1}).In comparison to standard antibiotic Tetracycline, compound **3h** inhibited *P. aeruginosa* with similar MIC: 50 μg mL^{-1}. Compounds **3i** and **3l** have common functional group -CH$_2$Ph at R$_1$ but a different functional group at R, i.e., -H and -OMe. Inhibitoryactivity of both compounds was nearly similar for all organisms, but compound **3i** (-H) inhibited *S. marcescens* with MIC 12.5 μg mL^{-1} that compared to **3l** (-OMe group) with MIC: 400 μg mL^{-1}. Besides, for *K. pneumoniae* MIC value of 400 μg mL^{-1} was observed with compound **3i** while >1000 μg mL^{-1} was observed with compound **3l**. Furthermore, compounds **3a** and **3h** are different from the functional group at the R$_1$ position, i.e., -3-O$_2$N and -2-O$_2$NPh, respectively. Compound **3a** with -3-O$_2$NPhinhibited *S. typhi* and *S. paratyphi* with MIC of 200 μg mL^{-1} and 100 μg mL^{-1} compared to **3h** that inhibited both organisms with >1000 μg mL^{-1}.

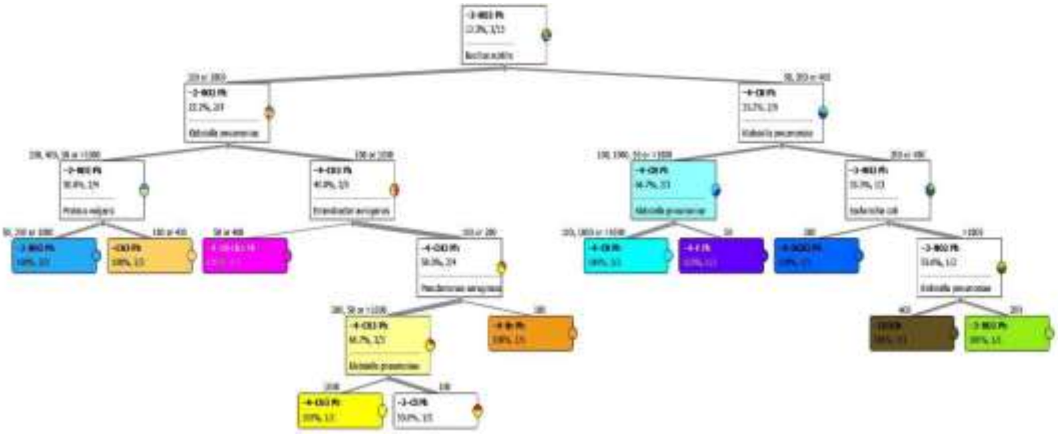
Table 2. Antibacterial activity of 1,2,3-triazole-1,4-dihydropyridine-3,5-dicarbonitrile derivatives (**3a**-**3o**).

Compound	**EC**	**ST**	**SP**	**EA**	**KP**	**SM**	**BS**	**PA**	**PV**	**SF**
						MIC (μg mL^{-1})				
3a	-	200	100	100	200	400	200	200	100	200
3b	-	100	200	200	100	100	100	-	1000	100
3c	-	100	50	100	1000	200	50	-	100	1000
3d	-	100	200	200	100	100	100	-	1000	100
3e	200	200	100	100	200	400	200	200	100	200
3f	-	-	100	50	50	400	400	100	50	50
3g	-	200	50	200	-	400	200	-	200	-
3h	-	-	-	200	-	400	1000	50	200	-
3i	-	-	-	400	400	12.5	1000	-	400	400
3j	-	-	-	200	1000	200	1000	50	1000	1000
3k	-	-	-	100	400	400	1000	-	1000	400
3l	-	-	-	200	-	400	1000	-	400	400
3m	-	-	-	200	1000	200	1000	100	1000	1000
3n	-	-	-	400	400	400	400	100	400	400
30	-	-	-	400	1000	400	1000	-	200	1000
Tetracycline	12.5	12.5	12.5	50	100	25	-	50	50	400
Penicillin	-	-	-	-	-	-	100	-	-	-

Legend: EC – *E. coli*, SP – *S. typhi*, SP – *S. paratyphi*, EA – *E. aerogenes*, KP – *K. pneumoniae*, SM – *S. marcescens*, BS – *B. subtilis*,
PA – *P. aeruginosa*, PV – *P. vulgaris*, SF – *S. flexneri*.

compound **3a** also inhibited *K. pneumoniae* and *S. flexneri* with MIC: 200 µg mL^{-1} compared to MIC: 1000 µg mL^{-1} given by compound **3h**. Compound **3a** (MIC: 200 µg mL^{-1}) was shown to be more potent against *S. flexneri* compared to standard antibiotic Tetracycline (MIC: 400 µg mL^{-1}).

If we compare the compounds **3d** and **3j**, it can be observed that **3d** inhibited *S. typhi* and *S. paratyphi* with MIC: 100 and 200 µg mL^{-1} respectively that is lower thanthe MIC >1000 µg mL^{-1} given by compound **3j**. Compound **3d** also inhibited *K. pneumoniae, B. subtilis,* and *S. flexneri* with lower MIC (100 µg mL^{-1}) compared to MIC (1000 µg mL^{-1}) given by **3j**. Compound **3j** having -H at R position



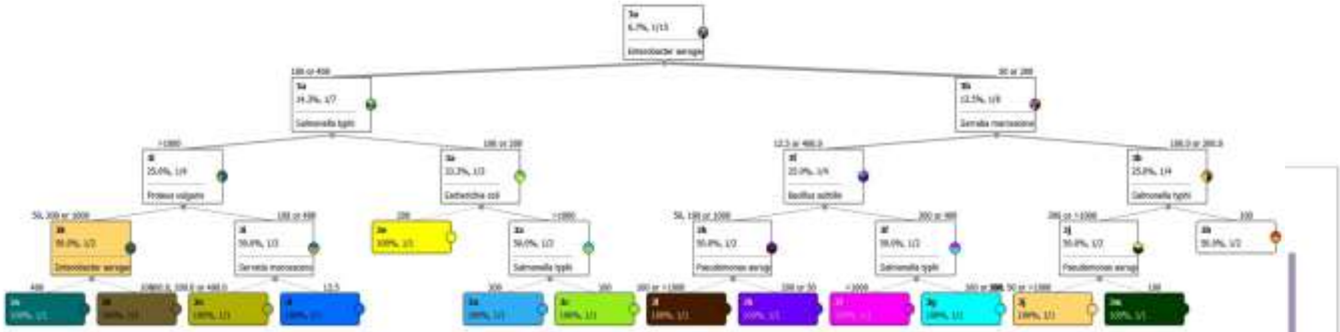
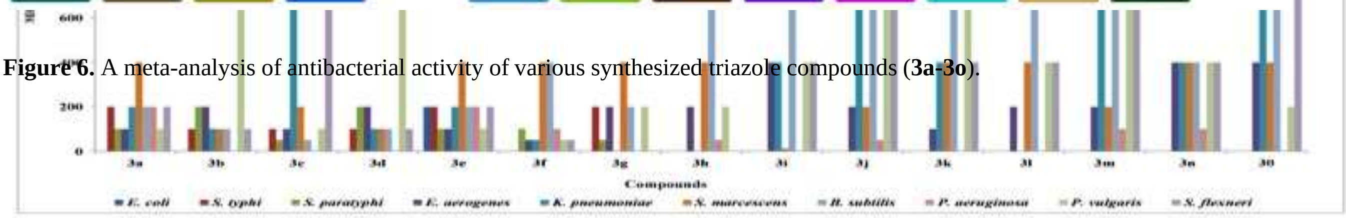


Figure 6. A meta-analysis of antibacterial activity of various synthesized triazole compounds (**3a-3o**).



Compound **3e** was the only compound (-4-MeOPh) that inhibited *E. coli* with MIC: 200 µg mL^{-1} between compounds **3d**, **3e**, **3f**, **3g**, **3k**, **3l** and **3o** having common 3-MeO at R but different functional groups at R1. From the literature, it was found that cyano, phenacyl, and benzyl derivatives of 1,2,3-triazolyl-1,4-dihydropyridine hybrids were potent against *Escherichia coli* with MIC: 30 µg mL^{-1}.[30] Some fluorinated chalcone-triazole hybrids having - OMe functional group was also reported to be active against *E. coli* with MIC value of 0.0032 µmol mL^{-1}.[27]

Compound **3e** (MIC 200 µg mL^{-1}) was also found to be more potent against *S. flexneri* compared to standard (MIC 400 µg mL^{-1}). Among the compounds **3g** and **3o** (common 3-OMe at R but -4-NCPh at R1), compound 3g inhibited *S. typhi* and *S. paratyphi* with MIC 200 and 50, respectively. Between the compounds, **3f** and **3m**, compound **3f** (3-OMe at R and -4 FPh at R1) inhibited *S. typhi*, *E. aerogenes, K. pneumoniae, P. vulgaris, S. flexneri* with MIC 100, 50, 50, 50 and 50 µg mL^{-1}respectively that is lower than the MIC obtained by compound **3m** (-H at R and -4BrPh at R1).

Compound **3f** was found to equipotent to standard against *P. vulgaris* and *E. aerogenes* with MIC: 50 µg mL^{-1} while more potent compared to standard (MIC 400 µg mL^{-1} and 100 µg mL^{-1}) against *S. flexneri* and *K. pneumoniae* (MIC: 50 µg mL^{-1}). Between the compounds, **3g** and **3o** that possesses common -3-OMe but -4-CNPh and -4-CNCH2Ph groups at R1 position exhibited almost similar activity against test organisms except for **3g** that inhibited *S. typhi* and *S. paratyphi* with MIC: 200 and 50 µg mL^{-1} respectively, which is lower than the MIC (>1000 µg mL^{-1}) given by compound **3o**.

CONCLUSION

The antibacterial efficacy of these triazole-containing derivatives against a variety of bacterial strains, as well as the effective synthesis of 1,2,3-triazole-1,4-dihydropyridine-3,5-dicarbonitrile derivatives (3a-3o), are detailed in this paper. Also, this is the first place where either a 3d or 3e crystal structure has been described. Each of the chemicals studied had strong antibacterial activity in the in vitro investigation, lending credence to the idea that they may be useful therapeutic agents in the fight against germs. No bacterial strain was suppressed by any of the chemicals tested, but 3e stood out.

Compound 3e's structure likely contains a -4-MeOPh group, which causes this to happen. Because of the - 4-MePh and -2-O2NPh groups at the fourth and second positions, respectively, compounds 3j and 3h exhibited the lowest MIC. The antibacterial activities were significantly improved and the inhibition was significantly amplified and extended when different functional groups were integrated to the 1,2,3-triazole moiety, as shown by these data. Future antibacterial treatments may benefit from these chemicals.

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