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

Bhagwati Gauni,[a] Krunal Mehariya,[b] Anamik Shah,[c]* Srinivas Murty Duggirala[d]*

Keywords: Antibacterial; 1,4-Dihydropyridines, 1,2,3-Triazoles.

The purpose of this study was the synthesis of a novel series of 1,2,3-triazole-1,4-dihydropyridine-3,5-dicarbonitrile derivatives **(3a-3o)** via Cu(I) catalyzed reaction between a terminal alkyne and substituted alkyl or aryl azides. The synthesized triazoles were characterized by ^{1}H NMR, ^{13}C NMR, and single crystal X-Ray. They were screened *in vitro* for antibacterial activity against a set of 10 bacterial cultures by the broth microdilution method. The significant antibacterial activity with MIC: 50 μg mL^{-1} was displayed by compounds **3j** and **3h** against *Pseudomonas aeruginosa* and compounds **3c** and **3g** against *Salmonella paratyphi* as well as compound **3f** against *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Proteus vulgaris*, and *Shigella flexneri*. Compound **3e** was the only compound that was found to inhibit *Escherichia coli* with MIC: 200 μg mL^{-1}.

* Corresponding Authors
E-Mail: b.gauni@gmail.com
[a] Department of Microbiology, Gujarat Vidyapith, Sadra-382320, D; Gandhinagar, Gujarat, India
[b] National Facility for Drug Discovery Complex, Department of Chemistry, Saurashtra University, Rajkot-360005, India
[c] Gujarat Vidyapith, Nr. Income Tax Office, Ashram Rd, Ahmedabad, Gujarat 380014
[d] Department of Microbiology, Gujarat Vidyapith, Sadra-382320, D;Gandhinagar, Gujarat, India

INTRODUCTION

Antibiotic resistance is presently contemplated as a chief public health issue.[1] As per the WHO report of April 2019, currently, every year, almost 700,000 people die as a result of drug-resistant diseases and this situation will push about 24 million people into extreme poverty by 2030. Due to the re-emergence of devastating bacterial infections, antimicrobial resistance has left behind the relevance of modern medicines.[2] Therefore, the development of new compounds with antimicrobial activity is the crucial mission of this century.

The involvement of medicinal chemistry in the biological and pharmaceutical field is broad that accounts for drug development, detection, design, and recognition of bioactive compounds. Heterocyclic compounds are of crucial importance in medicinal chemistry. They are getting strong interest in the context to synthesize and process different types of compounds having pharmacological and biological properties.[3] Currently, a general trend of research is synthesizing new drugs by modification of existing biologically active matrices and molecular design of the structural entities.[4] In search of new antimicrobials, medicinal chemists generally confide in N-heterocyclic compounds. In this line, 1,2,3-triazoles have been scrutinized as a substantial class of synthetically versatile heterocyclic compounds.

Azoles are a class of heterocyclic compounds having a five-membered ring that consists of at least one nitrogen atom and one more heteroatom like nitrogen, oxygen, or sulfur in the ring. They are present in many biologically active compounds as well as they are excellent ligands for the synthesis of coordinated polymers and metal-organic frameworks.[5] 1,2,3-Triazole is a component of this family and can be efficiently synthesized by the copper-catalyzed click reaction of azides with alkynes.[6]

Triazole is a significant heterocyclic skeleton with extensive biological activities and 1,2,3-Triazoles are the influential class in the triazole series.[5] These compounds are engaging for synthesis since they acquire diversified pharmacological properties functioning as antimicrobial,[7,8,9,10,11,12] antimalarial,[13] antiviral,[14] antitumoral,[15] anti-inflammatory,[11] antitubercular,[16] anti-HIV,[17] activities.

These diverse pharmacological activities are accredited to a 1,2,3-triazole moiety and it can apply various noncovalent interactions that can enhance the solubility and binding ability to biomolecular targets.[18] 1,2,3-Triazole can function as the isostere of amide, ester, carboxylic acid, and other heterocycles that makes it a common pharmacophore in several drugs.[14] Thus, 1,2,3-triazole derivatives play a compelling role in the development of new drugs.

There are several 1,2,3-triazole containing molecules on the market or are in the final stage of clinical trials. Promising pharmaceuticals based on 1,2,3-triazoles include the anticancer compound carboxyamidotriazole (CAI), the nucleoside derivative non-nucleoside reverse transcriptase inhibitor tert-butyldimethylspiroaminooxathioledioxide (also known as TSAO), β-lactam antibiotic Tazobactum, the cephalosporin Cefatrizine (Figure-1).[19]

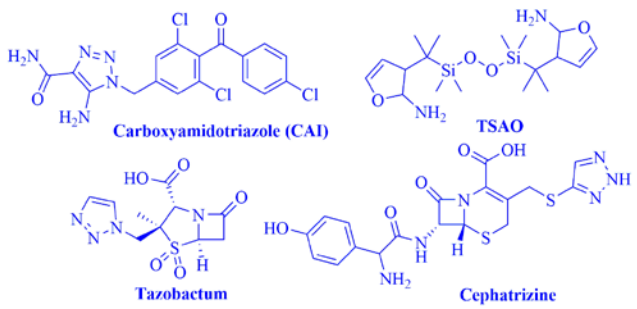


Figure 1. Promising pharmaceuticals based on 1,2,3-triazoles

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 factor A *Staphylococcus aureus* via hydrogen bonds and hydrophobic interactions, respectively.[24]

Methyl derivative of acridone-1,2,3-triazole displayed significant antibacterial activity against *Staphylococcus aureus* (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 -NO_2 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 obtained from 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-NO_2 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 inhibit DNA 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 Gyrase B 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 piperazine C4 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 at the para and chlorine at the meta position of the aromatic ring 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-nitrophenyl substituent 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 and relevant 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 synthesized compounds 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 parts per million (δ) using Tetramethylsilane (TMS) as the internal standard with coupling constants (*J*) reported in hertz (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 -OCH_3(-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 synthesis of 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 conditions produced 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 was confirmed 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-dicarbonitrile 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 5×10^5 CFU mL^{-1} in each well. A stock solution (10 μg mL^{-1}) of each compound was prepared in 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) and 2,6-dimethyl-4-(3-(prop-2-yn-1-yloxy)phenyl)-1,4-dihydropyridine-3,5-dicarbonitrile (**1a**, 1.0 mmol) were added to a mixture of copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol) dissolved in *t*-BuOH:H_2O (1:1 mixture, 3 mL) at room temperature. The reaction mixture was stirred at room temperature for 3-6 h, and monitored by TLC. The resulting mixture was poured into $CHCl_3$ (5 mL) and H_2O (3 mL), and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (5 mL) three times. The combined organic layer was concentrated in vacuo. The residue was purified by short column chromatography on silica gel (60−120 mesh) eluted with ethyl acetate: hexane (6:4) to give **3a**; ^{1}H NMR (DMSO–d_6) 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–d_6) 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 derivatives (**3a-3o**) is given in Table 1.

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

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); ^{1}H NMR (DMSO–d_6) δ 2.04 s (6H, 2×CH_3), 3.76 s (3H, –OCH_3), 4.39 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}C NMR (DMSO–d_6) 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)phenyl)-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) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–d_6) 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–d_6) 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 (0.01 mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–d_6) δ 2.04 s (6H, 2×CH_3), 2.38 s (3H, CH_3), 3.76 s (3H, –OCH_3), 4.36 s (1H, –CH), 5.21 s (2H, –CH_2), 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–d_6) 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–d_6) δ 2.04 s (6H, 2×CH_3), 3.76 s (3H, CH_3), 3.84 s (3H, –OCH_3), 4.36 s (1H, –CH), 5.20 s (2H, –CH_2), 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–d_6) 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–d_6) δ 2.04 s (6H, 2×CH_3), 3.76 s (3H, –OCH_3), 4.36 s (1H, –CH), 5.22 s (2H, –CH_2), 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–d_6) 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–d_6) δ 2.04 s (6H, 2×CH_3), 3.76 s (3H, OCH_3), 4.36 s (1H, –CH), 5.25 s (2H, –CH_2), 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–d_6) 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–d_6) 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}C NMR (DMSO–d_6) 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–d_6) 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–d_6) 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)meth-oxy)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–d_6) 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–d_6) 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**, 1.0 mmol), copper(II) sulfate pentahydrate solution (0.01 mmol) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–d_6) 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–d_6) 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-methoxyphe-nyl)-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**, 1.0 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), 3.77 s (3H, –CH_3), 4.35 s (1H, –CH), 5.12 s (2H, –CH_2), 5.62 s (2H, –CH_2), 6.77–6.85 t (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 (1.2 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), 4.38 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-dicarbonitrile (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) and sodium ascorbate (0.25 mmol); ^{1}H NMR (DMSO–d_6) δ 2.05 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-detector distance 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 represents the 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, 6245 were unique (R_{int} = 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 was applied, 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 $\Sigma w(F_o^2-F_c^2)^2/(N_o^2-N_v)]^{1/2}$, 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 N_2-C_{20} is near to that of a typical Aromatic C–N bond

(1.47). The bond length for 1.153(6) Å for C_9-N_5 and 1.145(7) Å for C_8-N_6 are near to that of a typical C≡N Cyano bond length (1.16). The bond angles for C_4-C_5-C_6, C_2-C_3-C_4 which illustrate that 123.7(4)°, 124.2(3)° of C_2, C_3, C_4, C5, C_6 all adopt sp^2 hybrid orbit to form C=C double bonds. The bond angles for C_{12}-O_1-C_{16} and C_{13}-O_2-C_{17} is 117.1(4)° and 118.9(4)°, which illustrate that C_{12}, O_1, C_{16}, C_{13}, O_2, C_{17} all adopt sp^2 hybrid orbit to form C-O-C Single bond. In this molecule, N_2-N_3-N_4 bond angle is 107.6(4)° of the 1,2,3-triazole core is planar. A study of torsion angles of N_2, N_3, N_4, C18 is 0.6(5) and C_{19}, N_2, N_3, N_4 is -0.3 (5)°.

Crystal Structure Determination and Refinements (3e)

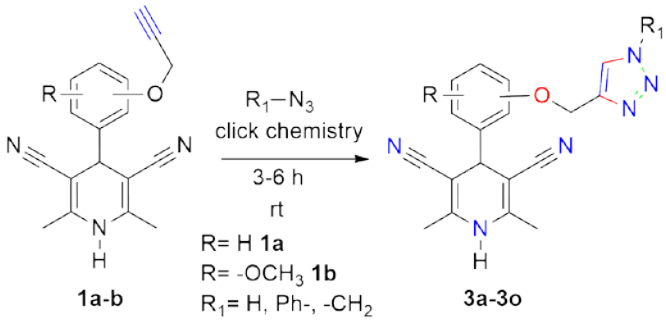
A colorless prism crystal of **3e** having M.F. $C_{26}H_{24}N_6O_3 \cdot C_2H_6OS$ and approximate dimensions of 0.670 × 0.560 × 0.560 mm was mounted on a glass fiber. Data Reduction of the 14263 reflections that were collected, 6382 were unique (R_{int} = 0.0248), equivalent reflections were merged. 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 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 6382 observed reflections and 352 variable parameters and converged. The standard deviation of observation of unit weight was 1.51 and calculated by $\Sigma w(F_o^2-F_c^2)^2/(N_o^2-N_v)]^{1/2}$, 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 1.87 and -0.71 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 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}, F_{000} = 616.00, μ(Mo-Kα) = 2.054 cm^{-1}, Radiation is Mo-Kα (λ = 0.71075 Å). Final refinement parameters: R_1 [$I > 2\sigma(I)$] = 0.1057, wR_2 = 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 N_4-C_{20} is near to that of a typical Aromatic C–N bond (1.47). The bond length for 1.154(6) Å for C_9-N_2 and 1.150(7) Å for C_8-N_3 are near to that of a typical C≡N Cyano bond length (1.16). The bond angles for C_2-C_3-C_4 and C_4-C_5-C_6, which illustrate that 124.6(4)°, 124.1(4)° of C_2, C_3, C_4, C_5, C_6 all adopt sp^2 hybrid orbit to form C=C double bonds. The bond angles for C_{12}-O_2-C_{17} and C_{23}-O_3-C_{26} is 116.9(3)° and 118.4(4)°, which illustrate that C_{12}, O_2, C_{17}, C_{23}, O_3, C_{26} all adopt sp^2 hybrid orbit to form C-O-C Single bond. In this molecule, the N_4-N_5-N_6 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 C_{19}-N_4-N_5-N_6 is –0.4(4)° and N_4-N_5-N_6-C_{18} is –0.398(5)° are showing that the 1,2,3 triazole ring in the same plane. A study of torsion angles of N_2, N_3, N_4, C18 is 0.6(5) and C_{19}, N_2, N_3, N_4 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	R_1	MF	MW	M.P. (°C)	Yield (%)
3a	**3**	H	–3–O_2NPh	$C_{24}H_{19}N_7O_3$	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–O_2NPh	$C_{24}H_{19}N_7O_3$	453.45	250–251	68
3i	**3**	H	–CH_2Ph	$C_{25}H_{22}N_6O$	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–O_2NPh	$C_{25}H_{21}N_7O_4$	483.47	266–267	61
3l	**4**	3–OMe	–CH_2Ph	$C_{26}H_{24}N_6O_2$	452.50	268–269	69
3m	**3**	H	–4–BrPh	$C_{24}H_{19}BrN_6O$	487.35	202–203	69
3n	**3**	H	–CH_2CN	$C_{20}H_{17}N_7O$	371.39	240–241	65
3o	**4**	3–OMe	–CH_2(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**) was developed 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.

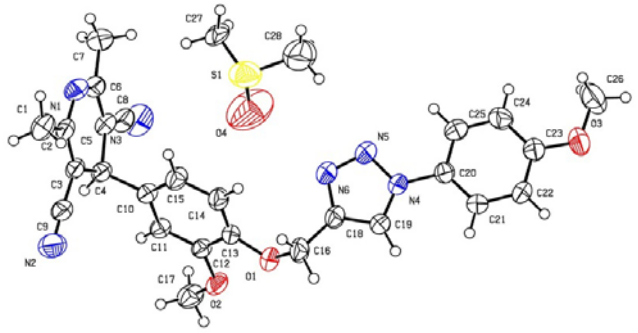


Figure 2. PLATON version of **3d** with data block ellipsoid plot drawn at 50% probability (CCDC 1969216).

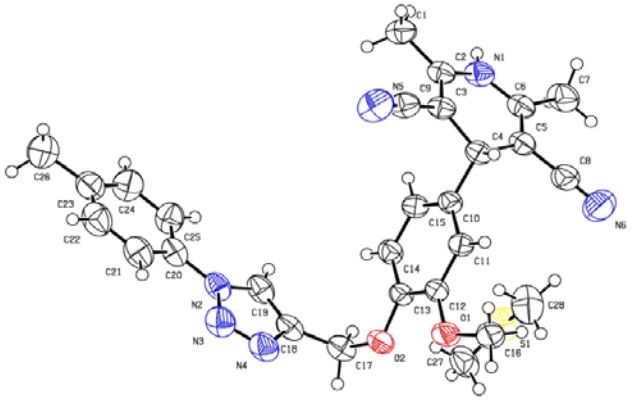


Figure 3. PLATON version of **3e** with data block ellipsoid plot drawn at 50% probability (CCDC 1996628).

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 due to the presence of 3-O_2N and 4-OMe group attached to triazole 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} similar to 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}, which is 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_2Ph at R_1 but a different functional group at R, i.e., -H and -OMe. Inhibitory activity 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_2N and -2-O_2NPh, respectively. Compound **3a** with -3-O_2NPh inhibited *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*.

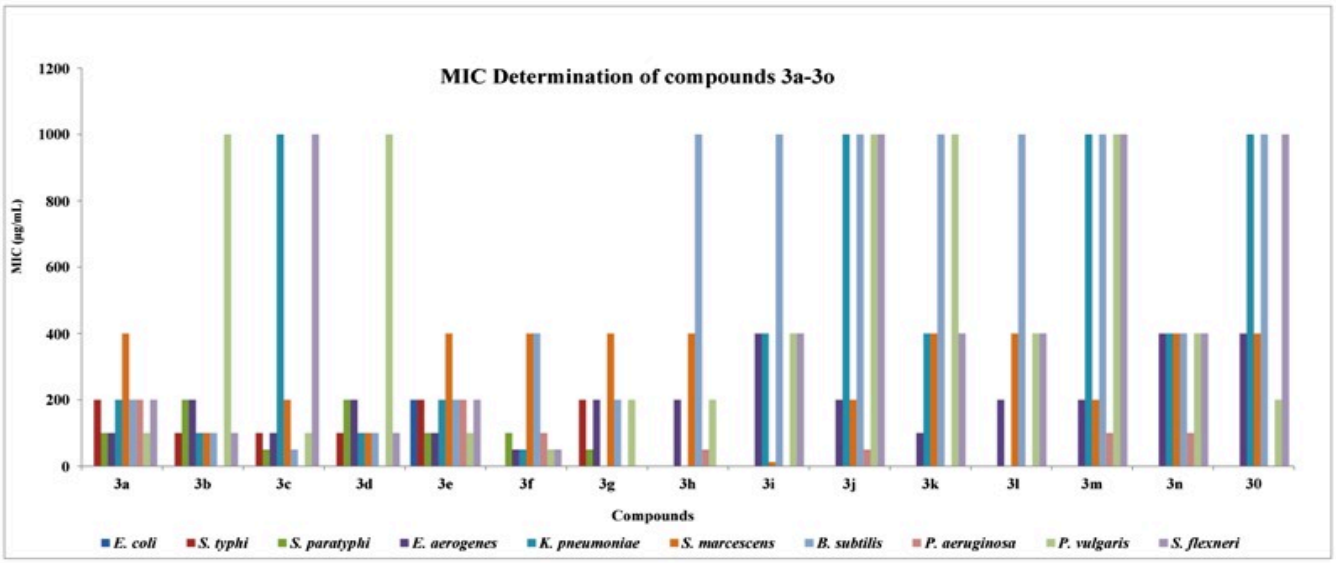


Figure 4. MIC Determination of compounds **3a-3o**

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 than the 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 inhibited *P. aeruginosa* with MIC: 50 μg mL^{-1} that is much lower than MIC >1000 μg mL^{-1} given by compound **3d**. Compound **3j** showed equal potency with the standard for *P. aeruginosa* by inhibiting it with MIC: 50 μg mL^{-1} that is similar to the MIC: 50 μg mL^{-1} given by standard Tetracycline. Compound **3d** (MIC 100 μg mL^{-1}) was found to be more potent than standard (MIC: 400 μg mL^{-1}) against *S. flexneri* while equipotent to the standard against *K. pneumoniae* with MIC 100 μg mL^{-1}. Among compounds **3c** and **3g**, both are having common functional group -4-NCPh at R_1 but different functional groups (-H and 3-MeO respectively) at R position. Compound **3c** inhibited *B. subtilis* with MIC: 50 μg mL^{-1} compared to MIC 200 μg mL^{-1} given by compound **3g**.

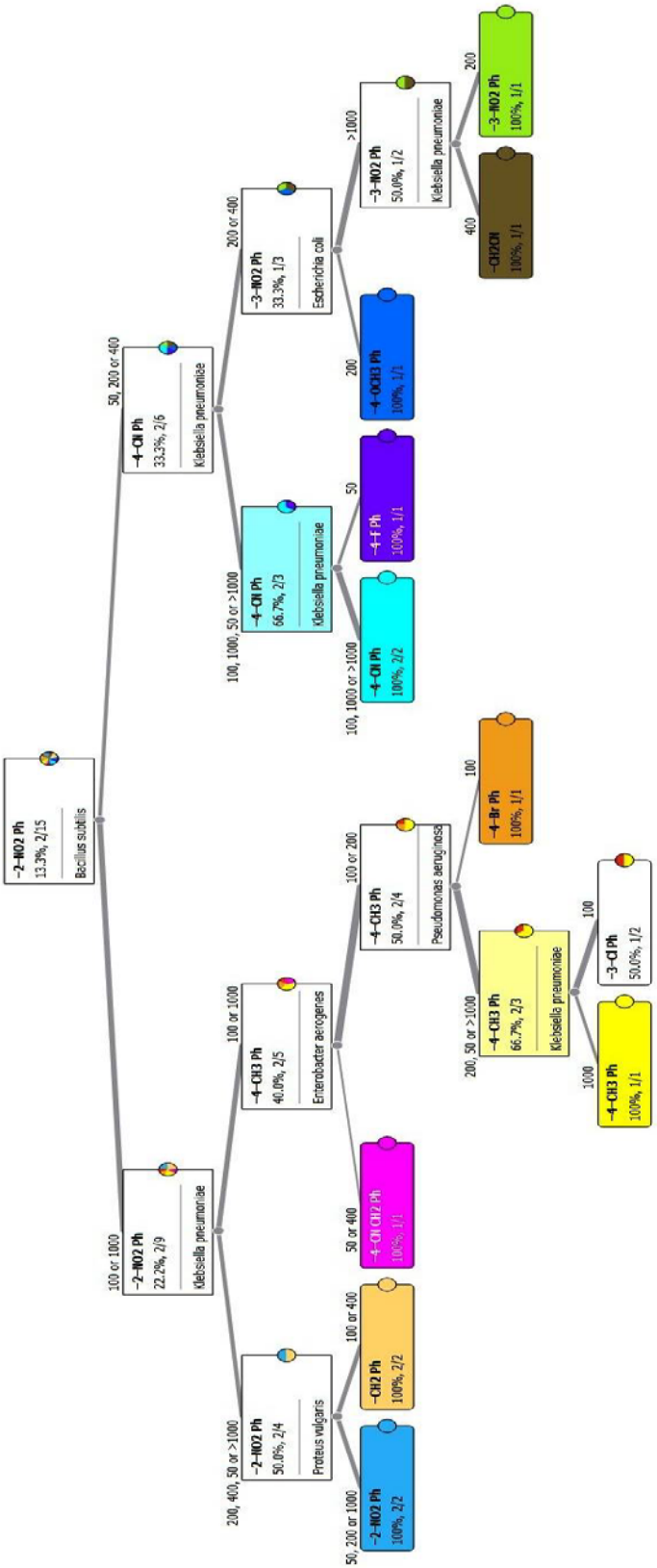


Figure 5. A meta-analysis of antibacterial activity based on functional groups of triazoles.

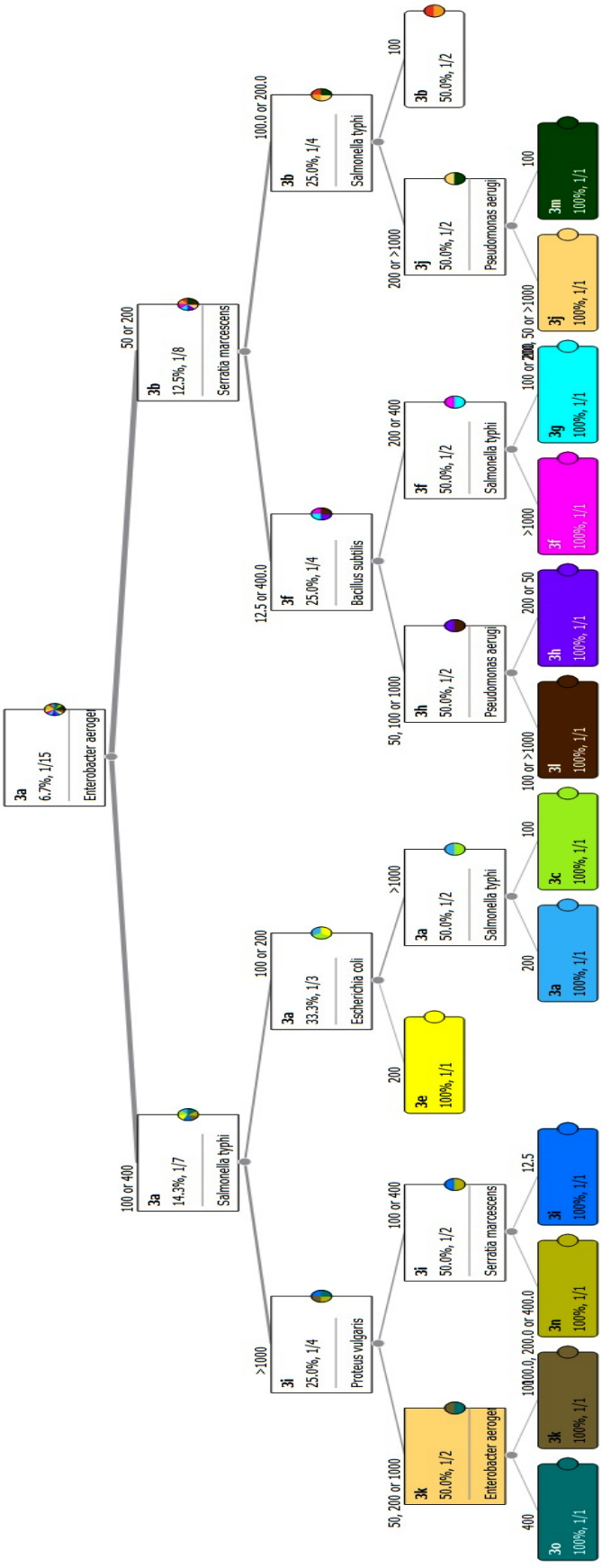


Figure 6. A meta-analysis of antibacterial activity of various synthesized triazole compounds (**3a-3o**).

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 R_1. 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 R_1), 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 R_1) 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 R_1).

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-$CNCH_2$Ph groups at R_1 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

This study reports the successful synthesis of 1,2,3-triazole-1,4-dihydropyridine-3,5-dicarbonitrile derivatives **(3a-3o)** in good yields and antibacterial activity of these derivatives containing triazole moiety against a wide range of bacterial strains. Besides, both crystal structures of **3d** and **3e** were herein reported for the first time. The *in vitro* antibacterial activity study revealed that all the compounds tested showed potent antibacterial activity which support the importance of these compounds as candidates for therapeutically efficient agents against bacteria. Among all compounds, **3e** inhibited all test bacterial strains.

This probably occurs due to the presence of –4–MeOPh group in the structure of compound **3e**. The lowest MIC was displayed by compounds **3j** and **3h** due to the presence of –4–MePh and –2–O_2NPh groups at the fourth and second positions, respectively. These results confirmed that the integration of various functional groups to the 1,2,3-triazole moiety was greatly beneficial for the antibacterial activities, which could not only intensify the inhibition remarkably but also broaden their antimicrobial spectrum. These compounds are found to be promising for future antibacterial drugs.

ACKNOWLEDGMENTS

The authors would like to express their thanks to the National Facility for Drug Discovery Complex, Department of Chemistry, Saurashtra University, Rajkot as well as Department of Microbiology, Gujarat Vidyapith, Sadra for the Laboratory Facility.

REFERENCES

[1]López-Pueyo, M. J., Barcenilla-Gaite, F., Amaya-Villar, R., Garnacho-Monteroc, J., Antibiotic multiresistance in critical care units, *Intensive Medicine*, **2011**, *35(1)*, 41-53. https://doi.org/10.1016/j.medin.2010.07.011

[2]New report calls for urgent action to avert antimicrobial resistance crisis, https://www.who.int/news-room/detail/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis (Accessed on 29/07/**2019**).

[3]Gomtsyan, A., Heterocycles in drugs and drug discovery, *Chem. Heterocycl. Comp.*, **2012**, *48*, 7-10. https://doi.org/10.1007/s10593-012-0960-z

[4]Mishra, B. B., Kumar, D., Mishra, A., Mohapatra, P. P., Tiwari, V. K., Cyclo-Release Strategy in Solid-Phase Combinatorial Synthesis of Heterocyclic Skeletons, *In Advances in Heterocyclic Chemistry*, Katritzky, A. R., Academic Press publications, San Diego, USA, **2012,** *107*, 42-95. https://doi.org/10.1016/B978-0-12-396532-5.00002-0

[5]Belay, Y., Coetzee, L.C., Williams, D.B.G., Muller, A., Synthesis of novel 1,2,3-triazole based polycarboxylic acid functionalised ligands for MOF systems, *Tetrahedron Lett.*, **2019**, *60*, 501-503. https://doi.org/10.1016/j.tetlet.2019.01.014

[6]Yoo, E. J., Ahlquist, M., Kim, S. H., Bae, I., Fokin, V. V., Sharpless, K. B., Chang, S., Copper-Catalyzed synthesis of N-Sulfonyl-1,2,3-triazoles: Controlling Selectivity, *Angew. Chem.-Int. Ed. Engl.*, **2007**, *46*, 1730-1733. https://doi.org/10.1002/anie.200604241

[7]Bourne, Y., Kolb H. C., Radic, Z., Sharpless, K. B., Taylor, P., Marchot, P., Freeze-frame inhibitor captures acetylcholinesterase in a unique conformation, *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 1449-1454. https://doi.org/10.1073/pnas.0308206100

[8]Chen, M., Lu, S. L., Yuan, G. P., Yang, S., Du, X., Synthesis and Antibacterial Activity of some Heterocyclic β-Enamino Ester Derivatives with 1,2,3-triazole, *Heterocycl. Commun.*, **2000**, *5*, 421-426. https://doi.org/10.1515/HC.2000.6.5.421

[9]Reddy, B. J., Reddy, V. P., Goud, G. L., Rao, Y. J., Synthesis of novel 1-benzyl/aryl-4-{[(1-aryl-1H-1,2,3-triazol-4-yl)methoxy]methyl}-1H-1,2,3-triazole derivatives and evaluation of their antimicrobial activity, *Russ. J. Gen. Chem.*, **2016**, *6*, 1424-1429. https://doi.org/10.1134/S107036321606030X

[10]Fu, X., Albermann, C., Zhang, C., Thorson, J. S., Diversity of Vancomycin Structure via Chemoselective Ligation, *Org. Lett.*, **2005**, *7*, 1513-155. https://doi.org/10.1021/ol0501626

[11]Zhang, B., Comprehensive review on the antibacterial activity of 1,2,3-triazole Hybrids, *Eur. J. Med. Chem.*, **2019**, *168*, 357-372. https://doi.org/10.1016/j.ejmech.2019.02.055

[12]Yan, W., Wang, X., Li, K., Li, T. X., Wang, J. J., Yao, K. C., Cao, L. L., Zhao, S. S., Ye, Y. H., Design, synthesis, and antifungal activity of carboxamide derivatives possessing 1,2,3-triazole as potential succinate dehydrogenase inhibitors, *Pestic. Biochem. Physiol.*, **2019**, *156*, 160-169. https://doi.org/10.1016/j.pestbp.2019.02.017

[13]Devender, N., Gunjan, S., Chhabra, S., Singh, K., Pasam, V. R., Shukla, S. K., Sharma, A., Jaiswal, J., Singh, S. K., Kumar, Y., Lal, J., Trivedi, A. K., Tripathi, R., Tripathi, R. P., Identification of β-Amino Alcohol Grafted 1,4,5 Trisubstituted 1,2,3-Triazoles as Potent Antimalarial agents, *Eur. J. Med. Chem.*, **2016**, *109*, 187-198. https://doi.org/10.1016/j.ejmech.2015.12.038

[14]Bonandi, E., Christodoulou, M. S., Fumagalli, G., Perdicchia, D., Rastelli, G., Passarella, D., The 1,2,3-triazole ring as a bioisostere in medicinal Chemistry, *Drug Discovery Today*, **2017**, *22(10)*, 1572-1581. http://dx.doi.org/doi:10.1016/j.drudis.2017.05.014

[15]Pokhodylo, N., Shyyka, O., Matiychuk, V., Synthesis and anticancer activity evaluation of new 1,2,3-triazole- 4-carboxamide derivatives, *Med. Chem. Res.*, **2014**, *23*, 2426-2438. http://dx.doi.org/doi:10.1007/s00044-013-0841-8

[16]Boechat, N., Ferreira, V. F., Ferreira, S. B., Ferreira, M. L. G., Da Silva, F. C., Bastos, M. M., Costa, M. S., Lourenco, M. C. S., Pinto, A. C., Krettli, A. U., Aguiar, A. C., Teixeira, B. M., Da Silva, N. V., Martins, P. R. C., Bezerra, F. A. F. M., Camilo, A. L. S., Da Silva, G. P., Costa, C. P. C., Novel 1,2,3-Triazole Derivatives for Use against Mycobacterium tuberculosis H37Rv (ATCC 27294) Strain, *J. Med. Chem.*, **2011**, *54*, 5988-5999. https://doi.org/10.1021/jm2003624

[17]Da Silva, F. C., De Souza, M. C., Frugulhetti, Castro, H. C., Souza S. L., De Souza, T. M., Rodrigues, D. Q., Souza, A. M., Abreu, P. A., Passamani, F., Rodrigues, C. R., and Ferreira, V. F., Synthesis, HIV-RT inhibitory activity and SAR of 1-benzyl-1H-1,2,3-triazole derivatives of carbohydrates, *Eur. J. Med. Chem.*, **2009**, *44*, 373-383. https://doi.org/10.1016/j.ejmech.2008.02.047

[18]Gao, C., Chang, L., Xu, Z., Yan, X. F., Ding, C., Zhao, F., Wu, X., Feng, L. S., Recent advances of tetrazole derivatives as potential antitubercular and antimalarial agents, *Eur. J. Med. Chem.*, **2019**, *163*, 404-412. https://doi.org/10.1016/j.ejmech.2018.12.001

[19]Agalave, S. G., Maujan, S. R., Pore, V. S., Click Chemistry: 1,2,3 - Triazoles as Pharmacophores, *Chem. -Asian J.*, **2011**, *10*, 2696-2718. https://doi.org/10.1002/asia.201100432

[20]Kolb, H. C., Finn, M. G., Sharpless, K. B., Click Chemistry: Diverse Chemical Function from a Few Good Reactions, *Angew. Chem.-Int. Ed. Engl.*, **2001**, *11*, 2004-2021. https://doi.org/10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5

[21]Steve, N., Michel, B., Sravendra, R., Wolfgang, H. B., The CuAAC: Principles, Homogeneous and Heterogeneous Catalysts, and Novel Developments and Applications, *Macromol. Rapid Comm.*, **2020**, *41*, 1900359-1900391, https://doi.org/10.1002/marc.201900359

[22]Rolf, H., Kinetics and reaction mechanisms: selected examples from the experience of forty years, *Pure Appl. Chem.*, **2009**, *61*, 613-628, https://doi.org/10.1351/pac198961040613

[23]Palacios, F., Herran, E., Rubiales, G., Alonso, C., Regioselective synthesis of pyridines and dihydropyridines derived from β-amino acids and aminophosphonates by reaction of N-vinylic phosphazenes with α, β-unsaturated ketones, *Tetrahedron*, **2007**, *63*, 5669-5676. https://doi.org/10.1016/j.tet.2007.03.146

[24]Keivanloo, A., Sepehri, S., Bakherad, M., Eskandari, M., Click Synthesis of 1,2,3-Triazoles-Linked 1,2,4-Triazino[5,6-b]indole, Antibacterial Activities and Molecular Docking Studies, *Chemistry Select*, **2020**, *5(13)*, 4091-4098. https://doi.org/10.1002/slct.202000266

[25]Aarjane, M., Slassi, S., Tazi, B., Maouloua, M., Amine, A., Synthesis, antibacterial evaluation and molecular docking studies of novel series of acridone- 1,2,3-triazole derivatives, *Struct. Chem.*, **2020**, *1-9*, https://doi.org/10.1007/s11224-020-01512-0

[26]Hussain, M., Qadri, T., Hussain, Z., Saeed, A., Channar, P. A., Shehzadi, S. A., Hassan, M., Larik, F. A., Mahmood, T., Malik, A., Synthesis, antibacterial activity and molecular docking study of vanillin derived 1,4-disubstituted 1,2,3-triazoles as inhibitors of bacterial DNA synthesis, *Heliyon*, **2019**, *5(11)*, e02812. https://doi.org/10.1016/j.heliyon.2019.e02812

[27]Yadav, P., Lal, K., Kumar, L., Kumar, A., Kumar, A., Paul, A. K., Kumar, R., Designed chalcone-1,2,3-triazole conjugates as potential antimicrobial agents synthesis, crystal structure and antimicrobial potential of some fluorinated chalcone-1,2,3-triazole conjugates, *Eur. J. Med. Chem.*, **2018**, *155*, 263-274. http://doi.org/10.1016/j.ejmech.2018.05.055

[28]Govindaiah, S., Sreenivasa, S., Ramakrishna, R. A., Rao, T. M. C., Nagabhushana, H., Regioselective Synthesis, Antibacterial, Molecular Docking and Fingerprint Applications of 1-Benzhydrylpiperazine Derivatized 1,4-Disubstituted 1,2,3-Triazoles, *Chemistry Select*, **2018**, *3*, 8111-8117, https://doi.org/10.1002/slct.201801364

[29]Morsy, H. A., Mohammed, S. M., Hamid, A. M. A., Moustafa, A. H., El-Sayed, H. A., Click Synthesis of 1,2,3-Triazole Nucleosides Based on Functionalized Nicotinonitriles, *Russ. J. Org. Chem.*, **2020**, *56(1)*, 143-147. https://doi.org/10.1134/S1070428020010224

[30]Archana, S., Dinesh, M., Ranganathan, R., Ponnuswamy, A., Kalaiselvi, P., Chellammal, S., Subramanian, G., Murugavel, S., Water mediated one-pot synthesis and biological evaluation of 1,2,3-triazolyl-1,4-dihydropyridine hybrids, *Res. Chem. Intermed.*, **2017**, *43(1)*, 187-202. https://doi.org/10.1007/s11164-016-2614-8

[31]Vatmurge, N. S., Hazra, B. G., Pore, V. S., Shirazi, F., Deshpande, M. V., Kadreppa, S., Chattopadhyay, S., Gonnade, R. G., Synthesis and biological evaluation of bile acid dimers linked with 1,2,3-triazole and bis-β-lactam, *Org. Bioorg. Chem.*, **2008**, *6*, 3823-3830. https://doi.org/10.1039/b809221d

[32]Phillips, O. A., Udo, E. E., Abdel-Hamid, M. E., Varghese, R., Synthesis and antibacterial activity of novel 5-(4-methyl-1H-1,2,3-triazole) methyl oxazolidinones, *Eur. J. Med. Chem.*, **2009**, *44(8)*, 3217-3227. https://doi.org/10.1016/j.ejmech.2009.03.024

[33]Reddy, L. V. R., Reddy, P. V., Mishra, N. N., Shukla, P. K., Yadav, G., Srivastava, R., Shaw, A. K., Synthesis and biological evaluation of glycal-derived novel tetrahydrofuran1,2,3-triazoles by 'click' chemistry, *Carbohydr. Res.*, **2010**, *345(11)*, 1515-1521. https://doi.org/10.1016/j.carres.2010.03.031

[34]Singh, H., Sindhu, J., Khurana, J. M., Sharma, C., Aneja, K. R., A Facile Eco-Friendly One-Pot Five-Component Synthesis of Novel 1,2,3-Triazole-Linked Pentasubstituted 1,4-Dihydropyridines and their Biological and Photophysical Studies, *Aust. J. Chem.*, **2013**, *66*, 1088–1096. http://dx.doi.org/10.1071/CH13217

[35]Reddy, B. J., Reddy, V. P., Goud, G. L., Rao, Y. J., Premkumar, Supriya, K., Synthesis of novel 1-benzyl/aryl-4-{[(1-aryl-1H-1,2,3-triazol-4-yl)methoxy]methyl}-1H-1,2,3-triazole derivatives and evaluation of their antimicrobial activity, *Russ. J. Gen. Chem.*, **2016**, *6*, 1424-1429. https://doi.org/10.1134/S107036321606030X

[36]Pflugrath, J. W., The finer things in X-ray diffraction data Collection, *Acta Cryst. Sect. D.*, **1999**, *55*, 1718-1725. https://doi.org/10.1107/S090744499900935X

[37]Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M., Polidori, G., Camalli, M., SIR92 - a program for automatic solution of crystal structures by direct methods, *J. Appl. Cryst.*, **1994**, *27*, 435.

https://doi.org/10.1107/S002188989400021X

[38]Cromer, D. T., Waber, J. T., *Atomic Scattering Factors for X-Rays*, *International Tables for X-ray Crystallography*, volume-4, The Kynoch Press, Birmingham, England, Table 2.2 A, 71-147, **1974**.

[39]Ibers, J. A., Hamilton, W. C., Dispersion corrections and crystal structure refinements, *Acta Cryst.*, **1964**, *17*, 781-782. https://doi.org/10.1107/S0365110X64002067.

[40]Creagh, D. C., McAuley, W. J., *The International Tables for X-Ray Crystallography*, (A.J.C. Wilson, ed.), Volume-C Table 4.2.6.8, Kluwer Academic Publishers, Boston, 219-222, **1992**. https://doi.org/10.1107/97809553602060000592

[41]Creagh, D. C., Hubbell, J. H., *The International Tables for X-Ray Crystallography*, (A.J.C. Wilson, ed.), Volume-C Table 4.2.4.3,Kluwer Academic Publishers, Boston, 200-206, **1992**. https://doi.org/10.1107/97809553602060000592

[42]Crystal Structure Analysis Package, (CrystalStructure 4.0) Rigaku Corporation (2000-2010) Tokyo 196-8666, Japan.

[43]Sheldrick, G. M., A short history of SHELX, *Acta Cryst., Sect. A.* **2008**, 64, 112-122. https://doi.org/10.1107/S0108767307043930

[44]Wayne, P. A., CLSI. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*, 11th Edition. CLSI Standard M07, **2018**. https://clsi.org/standards/products/microbiology/documents/m07/

[45]Valgas, C., De-Souza, S. M., Smania, E. F., Smania, Jr. A., Screening methods to determine antibacterial activity of natural products, *Braz. J. Microbiol.*, **2007**, *38*, 369-380. https://doi.org/10.1590/S1517-83822007000200034

[46]Wiegand, I., Hilpert, K., Hancock, R. E., Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances, *Nat. Protoc.*, **2008**, *3*, 163-175. https://doi.org/10.1038/nprot.2007.521

[47]Breed, R. S., Murray, E. G. D., Hitchens, A. P., *Bergey's Manual of Determinative Bacteriology*, 6th Edition, The Williams & Wilkins Company: Baltimore, USA, pp. 443-544, **1948**.

This paper was presented at the International Conference "

CONFERENCE ON MOLECULAR STRUCTURE & INSTRUMENTAL APPROACHES"

at RK University, Rajkot (Gujarat-India) on 26-27th November 2020

Received: 04.12.2020.
Accepted: 11.12.2020