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Synthesis and bioevaluation of 1,2,3-triazole linked highly substituted pyridine derivatives

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Abstract: We have described one-pot multicomponent synthesis of 2-amino-3,5-dicyano-6-phenylthio-pyridine incorporated1,2,3-triazole derivatives from triazolyl aldehydes, malononitrile and thiophenol in excellent yields. The antitubercular, antifungal and antioxidant activity for all the synthesized derivatives were evaluated. The antifungal activity results show that the compounds **12a**, **12b** and **12g** were observed more potent than Miconazole with MIC value <25 µg/mL. Whereas, the antitubercular screening against MTB H37Rv strain did not produce any promising results. Furthermore, *in silico* ADME properties for all the compounds were also studied and exhibited the potential to be developed as an oral drug candidate.

Keywords: 1,2,3-Triazoles, Multicomponent reactions, Pyridines, Antifungal activity, Knoevenagel condensation

Introduction

The development of new synthetic strategies for diversely functionalized structures with active pharmacophores in a single molecular motif have attracted great attention of organic and medicinal chemist. Heterocyclic skeleton plays an important role among the medicinally active synthetic and natural compounds. Therefore, the development of simple and efficient route for the synthesis of bioactive compounds with heterocyclic skeleton has given new dimension in the drug discovery and development.

Pyridine is one of the privileged heterocycle thatplays an important role in biological, agrochemical and chemical coordination. Pyridine ring present in many naturally occurring compounds such as niacin (Vitamin B_3) and pyridoxine (Vitamin B_6).[1]The biological significance of pyridine moiety is due to its active participation in metabolism *via* oxidation or methylation

pathways forming the corresponding pyridinium ions. Nicotinamide adenine dinucleotide phosphate, $NADP^+$ modulate enzymes of the living system by involving in various oxidation and reduction process in biology.[2]Many pyridine derivatives are known to possess a wide range of pharmacological activities such as antibacterial,[3a] antimicrobial,[3b] antitubercular,[3c] antitumor,[3d] antiviral,[3e] antioxidant,[3f] anticancer,[3g] anticonvulsant,[3h] anti-inflammatory,[3i] anxietic[3j] and antimitotic activities.[3k] Pyridine based compounds act as inhibitors and receptors in biological systems such as Xia inhibitor,[4a] TAK1 inhibitor,[4b] histone deacetylase inhibitor,[4c] progesterone receptor agonist,[4d] Glue R5 receptor,[4e] cannabinoid receptor,[4f] A_3 adenosine receptor[4g] and NK1 receptor antagonist.[4h] Specifically, 3-cyanopyridines possess various biological activities like PIM1 kinase inhibitor,[5] anticancer,[6] Aurora A kinase inhibitor[7] and phosphodiesterase3 (PDE3) inhibitor.[8] In particular, substituted 3,5-dicyanopyridines have attracted much attention due to their diverse biological activity. These compounds represent an important class of privileged heterocyclic scaffold. Different substituents at position C_2, C_4 and C_6 of the pyridine moiety produces a large number of compound libraries with a broad range of biological activities such as antibacterial,[9] antiprion,[10] anticancer,[11] anti-HSV1,[12] anti-HIV[13] and phosphodiesterase inhibitor[14] (**Figure 1**).In addition to this, some of the compounds of this class have been reported as highly selective agonists for adenosine receptors, A2BAR agonist[15] and A1AR agonist[16]. Adenosine receptor plays a vital role in the treatment of cardiovascular disease, metabolic disease, Parkinson's disease and cancer.[17]

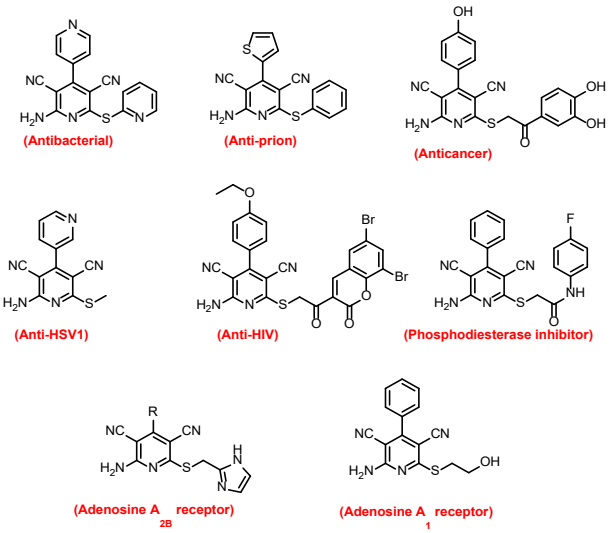


Figure 1. Structures of biologically active 3,5-dicyanopyridines

At the same time, synthesis and bioevaluation of some heteroaryl 2-amino-6-sulfanylpyridine-3,5-dicarbonitriles were also reported (**Figure 2**). Grigorev and coworkers reported[18]the synthesis of **1** as antibacterial and antitumor agent. Kinani *et al.* reported[19]antimicrobial activity of 2-thiophenoxyquinoline-basedpenta-substituted pyridine**2**. Makawana and coworker's reported[20]synthesis and *in vitro* antimicrobial activity of pyridinederivatives bearing the quinoline nucleus, **3**. The drug molecules **4** and **5**[21] in which heteroaryl linked with pyridine scaffold are also presented in **Figure 2**.

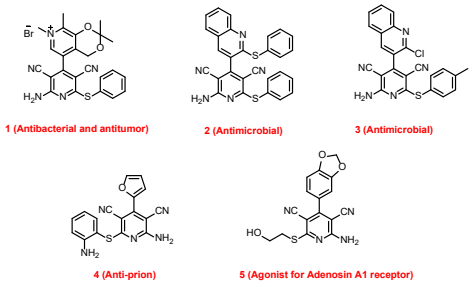


Figure 2. Heteroaryl substituted pyridine derivatives

However, in the last 15 years, a major breakthrough with respect to both affinity and selectivity was achieved with the aminopyridine-3,5-dicarbonitrile series asa new class of adenosine receptor.2-Amino-6-[(2-aminophenyl)thio]-4-(2-furyl) pyridine-3,5-dicarbonitrile acts as a lead compoundthat mimics the dominant negative host-encoded prionprotein (PrPC) mutants, which inhibit an abnormal isoform(PrPSc) formation.[22]

The literature survey reveals that these cyanopyridine derivatives first appeared in the patent literature.[23] However, other than biological applications, 3,5-dicyanopyridine derivatives have been found as synthetic intermediates in the synthesis of pyrido[2,3-*d*]pyrimidines as antihistaminic agents.[24]

From the last few decades, 1,2,3-triazole and its derivatives have got much importance in heterocyclic chemistry due to its interesting physicochemical properties. The literature study discloses that there are several reports on synthesis and biological activity of 1,2,3-triazole containing compounds as antibacterial,[25a] antitubercular,[25b] antifungal,[25b] antioxidant,[25b] nematicidal,[25c] antimicrobial,[25d] COX-inhibitor [25e] and anti-platelet agents.[25f]

On the other hand, multicomponent reaction is one of the useful approaches that provides access to various privileged medicinal scaffolds. Similarly, the synthesis of polysubstituted pyridines were carried out using MCR by condensation and cyclization reaction of corresponding aromatic aldehyde, malononitrile and thiophenol. The synthesis of highly functionlized pyridine derivatives have got much importance due to their synthetic and pharmacological applications. Therefore, several methods were reported[26] for the synthesis of 2-amino-6-sulfanylpyridine-3,5-dicarbonitrile derivatives.

The present scenario utilizes molecular hybridization approach for the design and development of new drug molecules, which includes a combination of two or more heterocyclic moieties in a single molecular framework.[27] On the basis of the biological significance of 3,5-dicyano arylthio pyridines and 1,2,3-triazole scaffolds, we would like to report herein one-pot three-component synthesis of triazole incorporated 3,5-dicyano arylthio pyridine analogues in good to excellent yield. Again biological evaluation and ADME property studies were also performed. The design strategy utilizes molecular hybridization approach for the synthesis of target molecules (**Figure 3**).

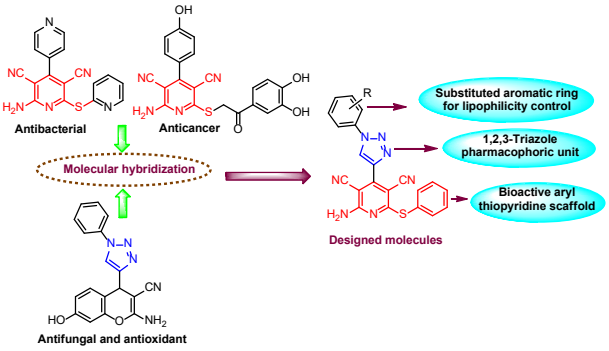
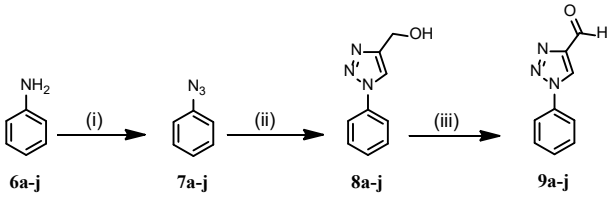


Figure 3. Designing of the 1,2,3-triazole incorporated 3,5-dicyano phenylthio pyridine derivatives

Results and discussion

Chemistry

The1-aryl-1*H*-[1,2,3]triazole-4-carboxaldehydes (**9a-j) (Scheme 1)** were prepared according to the literature method.[28]The commercially available anilines (**6a-j**) were diazotized by using sodium nitrite to form diazonium salt, followed by substitution with sodium azide, afforded the corresponding aryl azides. These aryl azides (**7a-j**) on 1,3-dipolar cycloaddition reaction *via* click chemistry approach with propargyl alcohol in the presence of copper sulfate ($CuSO_4$) and sodium ascorbate tothe corresponding 1-aryl-1,2,3-triazolyl methanols (**8a-j**) in excellent yields. The 1-aryl-1,2,3-triazolyl methanols (**8a-j**) on oxidation by using Collins reagent to form 1-aryl-1*H*-[1,2,3]triazole-4-carboxaldehydes (**9a-j**) in good yields.

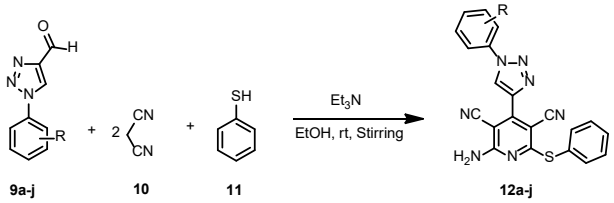


Scheme 1. Synthesis of 1-aryl-1,2,3-triazole carboxaldehydes (**9a-j**)

Reagents and conditions : (i) $NaNO_2$, HCl (10%); NaN_3, 1-2 h, 0 °C; (ii) Propargyl alcohol, $CuSO_4.5H_2O$, Sodium ascorbate, *tert*-BuOH-H_2O (1:1), 24-48 h, rt; (iii) Collins reagent (CrO_3.2Py, CH_2Cl_2), 3-6 h, rt.

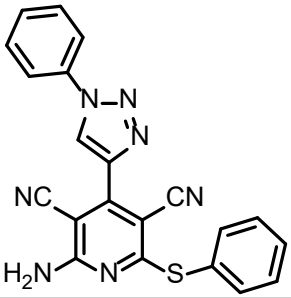
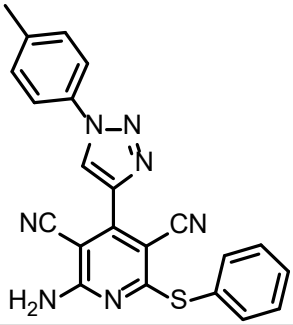
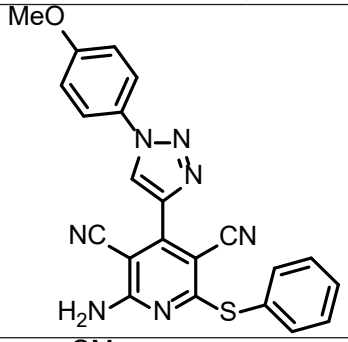
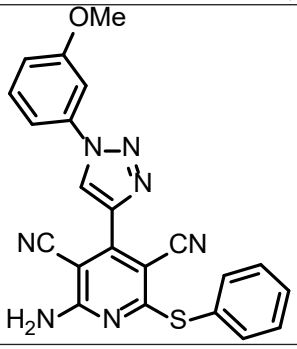
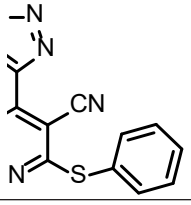
The aryl-1,2,3-triazolyl carbaldehydes (**9a-j)** have many applications in synthetic organic chemistry for the construction of diversely functionalized bioactive molecules like triazolyl nitrone analogues,[29a]triazole based trifluoromethyl derivatives,[29b] bezoxazole-triazole conjugates,[29c] pyridine-triazole conjugates,[29d] triazole-biscoumarines,[29e] triazole appended α-aminophosphonates,[29f] triazole linked bis-pyrazoles,[29g] triazole tethered dihydroquinazolinones,[29h] triazolidene-indolinones,[29i] triazole-tetrazole conjugates,[29j] triazole-chromene conjugates,[29k] triazolyl-pyranopyrazoles[29l] and triazole linked tetrahydrobenzopyran derivatives.[29m]

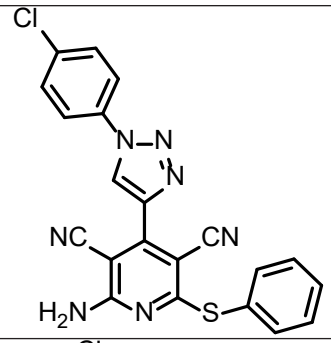
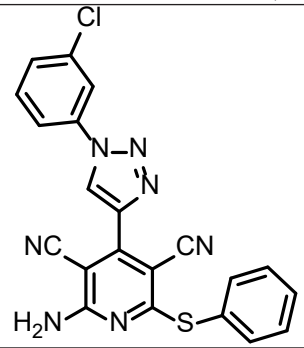
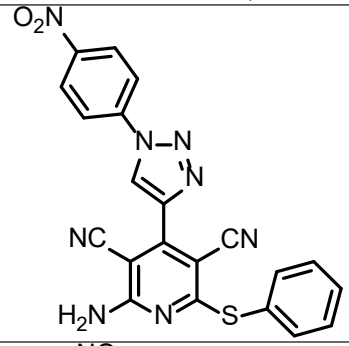
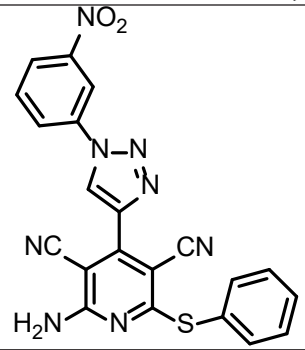
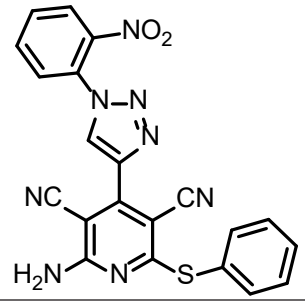
The synthesis of 1,2,3-triazole incorporated 3,5-dicyano phenylthio pyridine derivatives **12a-j**were achieved *via* one-pot three-component reaction of triazolyl aldehyde **9a-j** (1 mmol), malononitrile **10** (2 mmol) and thiophenol **11** (1 mmol) in ethanol (5 mL) using Et_3N as a catalyst with constant stirring at room temperature in good to excellent yields (**Scheme 2**). All the newly synthesized compounds were purified by crystallization method. The time required for the formation of products, yields and physical constants are given in **table 1**.



Scheme 2. Synthesis of 1,2,3-trizole-based 3,5-dicyano phenylthio pyridine derivatives.

Table 1. Structures, yield, melting point and reaction time for the 1,2,3-triazole linked 3,5-dicyano phenylthio pyridine derivatives

Cpd No.	Structure	Time (Minutes)	Yield (%)	Melting point (°C)
12a		115	93	238-240
12b		105	95	244-246
12c		122	95	220-222
12d		125	92	200-202
12e		118	96	243-245

12f		120	98	>270
12g		130	93	232-234
12h		160	91	252-254
12i		163	89	248-250
12j		165	92	253-255

The plausible mechanism for the synthesis of 1,2,3-triazole incorporated 3,5-dicyano phenylthio pyridine derivatives is shown in **Figure 4.** The first step of the mechanism include the formation ofKnoevenegel condensation product **I** from triazolyl aldehyde and malononitrile. The second step includes intramolecular cyclization by the reaction of **I** with second molecule of malononitrile and thiophenol produces intermediate **II** which on air oxidation in the third step forms the final product **III**.

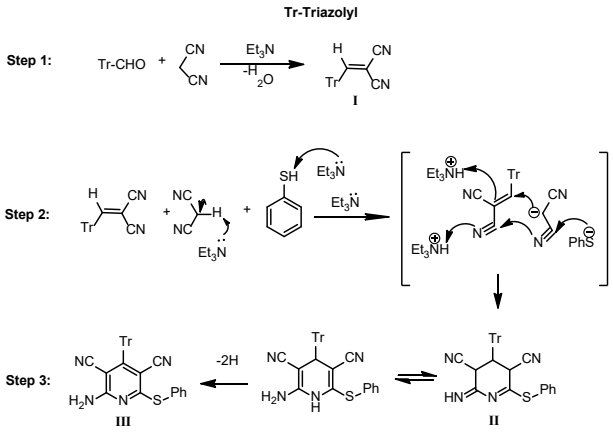


Figure 4. Plausible mechanism for the formation of 1,2,3- trizole-linked3,5-dicyano phenylthio pyridine derivatives.

Biological evaluation

Antitubercular activity

All the newly synthesized 1,2,3-triazole incorporated 3,5-dicyano phenylthio pyridine derivatives **12a-j** were evaluated for their *in vitro* antitubercular activity against H37Rv strain using MABA assay method. The results were mentioned in **Table 2**. All the compounds possess antitubercular activity with MIC ≥ 25 µg/mL. In addition to this, the Clog P value for all the compounds was also calculated. It is the logarithm of its partition coefficient between n-octanol and water. Absorption of drug depends on Clog P value. A higher value of Clog P causes poor absorption. For efficient transport of drug, Clog P value must not be greater than 5.0. From **Table 2**, it is observed that all the compounds possess good hydrophilicity (Clog P ≤ 5).

Table 2. *In vitro* antitubercular and antifungal activity of compounds **12a-j**.

Entry	Antitubercular activity MTB H37Rv MIC (µg/mL)	C L o g P[a]	Antifungal activity MIC (µg/mL)			
			CA	*FO*	*AF*	*AN*
12a	>25	4.28	75.4	25.7	62.5	29.7
12b	>25	4.78	84.4	71.3	73.7	21.7
12c	>25	4.41	94.1	77.2	45.3	39.1
12d	>25	4.41	53.8	81.4	97.1	29.7
12e	>25	4.41	*	189.5	216.4	69.3
12f	>25	5.07	59.1	37.1	79.7	38.4
12g	>25	5.07	44.9	43.1	65.1	19.3
12h	>25	4.29	95.1	72.5	90.3	42.1
12i	>25	4.29	76.1	48.4	75.2	88.2
12j	>25	4.29	91.7	67.4	18.4	37.6
INH	0.1	-1.11	NT	NT	NT	NT
RIF	0.2	-0.67	NT	NT	NT	NT
MIZ	NT	NT	25	25	12.5	25

a calculated by using ChemBioDraw Ultra 12.0, INH: Isoniazid, RIF: Rifampicin, MIZ: Miconazole, *: No activity upto 200 µg/mL, NT: Not tested

Antifungal activity

All the newly synthesized pyridine derivatives were tested for their *in vitro* antifungal activity against the human pathogenic fungal strains like *Candida albicans*, *Fusarium oxysporum*, *Aspergillus flavus* and *Aspergillus niger*and the results were mentioned in **Table 2**. The compounds showed moderate to excellent antifungal activity. Compound **12a** possess excellent antifungal activity against *F. oxysporum* with MIC value 25.7 µg/mL and showed moderate activity against *A. niger* with MIC value of 29.7 µg/mL. Compound **12b** found to be more potent against *A.*

niger than standard Miconazole with MIC value 21.7 µg/mL. Compound **23d** possess moderate activity with MIC value of 29.7 µg/mL against *A. niger*. Compound **12g** exhibited excellent activity against *A. niger* with MIC value of 19.3 µg/mL. The remaining compounds from the series did not show any promising antifungal activity.

Antioxidant activity

All the compounds **12a-j** were screened for their *in vitro* DPPH radical scavenging activity in comparison with the standard drug BHT. The antioxidant activity results showed that none of the compound possesses antioxidant activity at the concentration upto 200 µg/mL.

Computational study

In silico ADME prediction

In silico ADME prediction (**Table 3**) shows that all the compounds exhibited good % absorption (%ABS) ranging from 52.75 to 68.55%. It is promising to note that none of the compounds from the series violated Lipinski's rule of five (mi LogP ≤ 5).

Experimental section

Materials and methods

All the solvents and reagents were purchased from commercial suppliers Spectrochem Pvt. Ltd., Sigma Aldrich, and Rankem India Ltd. and are used without further purification. The progress of each reaction was monitored by ascending thin layer chromatography (TLC) using TLC aluminum sheets, silica gel 60 F_{254} precoated, Merck, Germany and locating the spots using UV light as the visualizing agent or iodine vapors. Melting points were determined in open capillary method and are uncorrected. Infrared (IR) spectra were recorded on a Bruker FT-IR spectrometer.^{1}H NMR spectra were recorded DMSO-d_6) on Bruker Avance 400 MHz NMR spectrometer. ^{13}C NMR spectra were recorded (DMSO-d_6) on Bruker Avance 100 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard.

General procedure for the synthesis of 1,2,3-triazole linked 3,5-dicyano phenylthio pyridine derivatives (12a-j)

Table 3. Pharmacokinetic parameters for good oral bioavailability.

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHNH	Lipinski's violations	Drug-likeness model score
Rule	-	-	-	-	< 500	≤ 5	< 10	< 5	≤ 1	-
12a	68.55	117.22	4	334.30	395.45	3.17	7	2	0	-0.39
12b	68.55	117.22	4	350.86	409.48	3.62	7	2	0	-0.42
12c	65.37	126.45	5	359.85	425.48	3.23	8	2	0	-0.40
12d	65.37	126.45	5	359.85	425.48	3.43	8	2	0	-0.31
12e	65.37	126.45	5	359.85	425.48	3.39	8	2	0	-0.48
12f	68.55	117.22	4	347.84	429.90	3.85	7	2	0	-0.14
12g	68.55	117.22	4	347.84	429.90	4.04	7	2	0	-0.40
12h	52.75	163.04	5	357.64	440.45	3.13	10	2	0	-0.54
12i	52.75	163.04	5	357.64	440.45	3.32	10	2	0	-0.53
12j	52.75	163.04	5	357.64	440.45	3.30	10	2	0	-0.65

% ABS: Percentage absorption, TPSA: Topological polar surface area, MV: Molecular volume, MW: Molecular weight, milog p: Logarithm of partition coefficient of compound between n-octanol and water, n-ON: Number of hydrogen bond acceptors, n-OHNH: Number of hydrogen bonds donors, n-ROTB: Number of rotatable bonds

A mixture of appropriate triazolyl aldehyde **9(a-j)** (1 mmol), malononitrile **10** (2 mmol), thiophenol **11** (1 mmol) and triethyl amine (0.5 ml) in ethanol (10 ml) was stirred at room temperature for 3-4 hours. The progress of the reaction was monitored by TLC (ethyl acetate:n-hexane). After the completion of the reaction, the reaction mixture was poured on crushed ice, filtered, washed with water, dried and crystallized from hot ethanol. The products **12a-j** were obtained in good to excellent yields.

Selected Spectral data

2-Amino-4-(1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-6-(phenylthio) pyridine-3,5-dicarbonitrile (12e): IR ν_{max} (cm^{-1}): 3331 and 2213.^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 9.1 (s, 1H), 7.87 (s, 2H), 7.78 (d, 1H, J = 8 Hz), 7.63-7.59 (m, 3H), 7.50-7.57 (m, 3H), 7.38 (d, 1H, J= 8 Hz), 7.20 (t, 1H, J = 8 Hz) and 3.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 166.9, 160, 151.3, 146.1, 139, 134.8, 131.2, 129.7, 129.4, 128.5, 127.1, 125.3, 125, 121, 115.3, 115.1, 113.2, 92, 85.6 and 56.2. MS: *m/z* calcd for $C_{22}H_{16}N_7OS$ $[M+H]^+$: 426.1137 and found: 426.

Experimental protocol for biological activity

Antitubercular activity

The antitubercular activity of the newly synthesized compounds **(12a-j)** have been screened for their in vitro effects against Mtb H37Rv (ATCC 27294) by using microplate Alamar Blue assay[30] for the determination of MIC in triplicates. The MIC (in µg/mL) was recorded as the lowest concentration/highest dilution of the compounds/control drugs that completely inhibited the growth of MTB cultures. The MIC values of the compounds **(12a-j)** have been compared with standard drugs (rifampicin and isoniazid). The experimental method for antitubercular activity is briefly described as follows.

Initially, the inoculum was prepared from fresh LJ medium re-suspended in 7H9-S medium (7H9 broth, 0.1% casitone, 0.5% glycerol, supplemented oleic acid, albumin, dextrose, and catalase [OADC]), adjusted to a McFarland tube No. 1 and diluted 1:20; 100 µL was used as inoculum. Each drug stock solution was thawed and diluted in 7H9-S at fourfold the final highest concentration tested. Serial twofold dilutions of each drug were prepared directly in a sterile 96-well microtiter plate using 100-µL 7H9-S. A growth control containing no antibiotic and a sterile control were also prepared on each plate. Sterile water was added to all perimeter wells to avoid evaporation during the incubation. The plate was covered, sealed in plastic bags, and incubated at 37°C in normal atmosphere. After 7-day incubation, 30 µL of Alamar Blue solution was added to each well, and the plate was re-incubated overnight. A change in color from blue (oxidized state) to pink (reduced) indicated the growth of bacteria, and the MIC was defined as the lowest concentration of drug that prevented this change in color.

Antifungal activity

Antifungal activity was determined by standard agar dilution method as per CLSI (formerly, NCCLS) guidelines.[31] The synthesized compounds and

standard miconazole were dissolved in DMSO solvent. The medium yeast nitrogen base was dissolved in phosphate bufer of pH 7, and it was autoclaved at 110 °C for 10 min. With each set, a growth control without the antifungal agent and solvent control DMSO were included. The fungal strains were freshly subcultured onto Sabouraud dextrose agar (SDA) and incubated at 25 °C for 72 h. The fungal cells were suspended in sterile distilled water and diluted to get 105 cells/mL. Ten microliters of standardized suspension was inoculated onto the control plates and the media incorporated with the antifungal agents. The inoculated plates were incubated at 25 °C for 48 h. The readings were taken at the end of 48 and 72 h. The minimum inhibitory concentration (MIC) was the lowest concentration of drug preventing growth of macroscopically visible colonies on drug-containing plates when there was visible growth on the drug-free control plates.

Conclusions

In summary, a novel triazole functionalized highly substituted pyridine derivatives were designed and synthesized. All the newly synthesized compounds were screened for their *in vitro* antitubercular activity against H37Rv strain and found to be inactive. Furthermore, all the compounds were evaluated for *in vitro* antifungal activity against four fungal strains. The antifungal activity results show that the compounds **12a**, **12b** and **12g** are more potent than Miconazole with MIC value < 25 µg/mL. Further, antioxidant activity results showed that none of the compound is found to be a good antioxidant agent. In addition to this, ADME properties for all the compounds were also studied.

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