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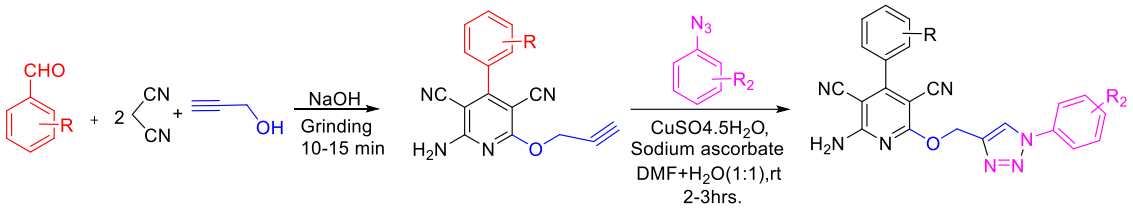
Design, Synthesis and Molecular Docking Studies of Novel Pyridine and 1,2,3-Triazole Hybrid Molecules

Mahesh Mallugari[a]; Koteshwar Rao Ravulapelly[a]*; Jagadeshwar Vannada[a]*
[a]Department of Chemistry, University College of Science, Osmania University, Saifabad, Hyderabad-500004, Telangana, India. Corresponding author's email ID: oujagan@gmail.com

Abstract
The novel molecular hybrids using substituted pyridines and triazole were synthesized efficiently. Molecular docking studies were performed using these newly synthesized substituted pyridines tethered with triazoles to predict their activity using Glide docking module towards CDK2 protein. Furthermore, the percentage of human oral absorption was also predicted using QikProp tool. Most of the designed hybrid molecules indicated that they were responsible for CDK2 protein inhibition and it was found that these compounds may be utilized to develop prospective CDK2 protein inhibitors for the treatment of cancer.



Keywords: CDK2 protien, anti-cancer drugs, substituted pyridines, 1,2,3-triazoles, hybrid molecules

INTRODUCTION

Cancer is a major disease that causes serious health problems in the world. Nearly 20 million new cases added and approximately 9.7 million deaths occurred worldwide as per the reports by World Health Organization (WHO). Cancer results from the uncontrolled growth of abnormal cells in several parts of the body. There is an urgent need for effective and selective inhibitors for the treatment of cancer which is a life changing disease. The molecular hybrids have emerged as a wonderful strategy in the field of drug design and development.[1] The molecular hybrids are made by the fusion of two or more active pharmacophores into a single entity, either directly or with the help of a linker.[2] This approach allows us to develop a multi-targeted drugs with enhanced efficacy, selectivity and improved pharmacokinetics.[3] Moreover, the hybrid drug molecules may diminish the risk of multidrug resistance.[4,5] This offers us a treasured tool in the fight against intricate diseases, together with cancer and microbial infections.[6,7]
Substituted pyridine[8,9,10] and 1,2,3-triazole[13,14,15] moieties play a crucial role in medicinal chemistry and pharmaceutical industry due to their profound biological activity and their ability to control various biological targets. These heterocycles exhibit distinguished medicinal properties, including anticancer, antimicrobial, enzyme inhibitory activity and anti-inflammatory activity, making them essential scaffolds in the design of novel therapeutic agents.[11,12] Also, 1,2,3-triazole tethered pyridine derivatives have gained recognition as privileged frameworks in drug discovery, owing to their synthetic accessibility, structural versatility, and broad-spectrum biological potential.[16,17] These heterocyclic frameworks can be efficiently synthesized using existing literature procedures through a simple condensation reaction using Bronsted base under solvent-free conditions using mortar–pestle method, followed by a [3+2] azide–alkyne cycloaddition using copper catalyst. Furthermore, the newly synthesized hybrid molecules have been evaluated using molecular docking studies to predict their medicinal properties to explore them as therapeutic candidates.

Results and Discussions

A series of novel 1,2,3-triazole tethered substituted pyridine derivatives were synthesized via a concise two-step approach. Initially, a series of multi-substituted pyridine derivatives were prepared as mentioned in the **Scheme 1** and utilized as key intermediates. [18,19]

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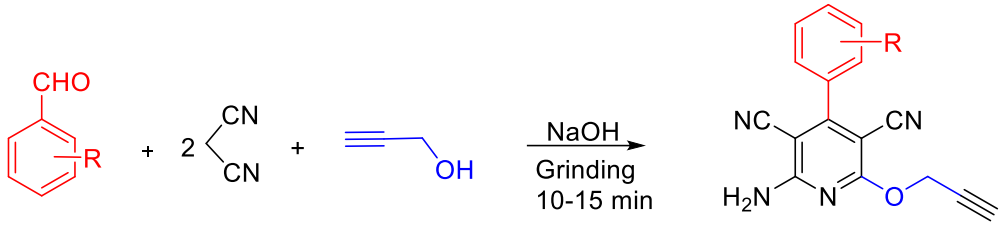
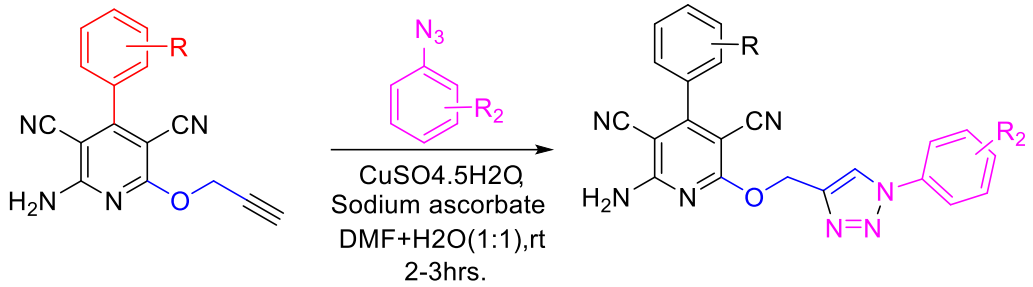
Scheme 1: Synthesis of substituted pyridines.



Subsequently, a copper-catalyzed [3+2] azide–alkyne cycloaddition reaction was employed to construct the 1,2,3-triazole moiety **Scheme 2**.[20] The structurally distinct series of multi-substituted pyridine derivatives tethered with 1,2,3-triazoles were synthesized as illustrated below.

Scheme 2: Synthesis of pyridine and triazole hybrid molecules.



Optimization of Reaction Condition

To establish the optimal conditions for the synthesis of substituted pyridines, a model three-component reaction was initially performed using propargyl alcohol (1 mmol), malononitrile (2 mmol), and benzaldehyde (1 mmol) in a round-bottomed flask at 70 °C for 5 hours. Product formation was not observed when the reaction was carried out in water even after 24h (**Table 1, entry 1**) or ethanol (**Table 1, entry 2**) under catalyst-free conditions. To improve efficiency, the reaction was repeated in ethanol in the presence of NaOH and no required product formation after 4 hours (**Table 1, entry 3**). However, performing the reaction in water even with NaOH failed to produce the target compound (**Table 1, entry 4**). Then a solvent-free, mechanochemically assisted method was next explored by considering the increasing focus on sustainable and green synthetic protocols, especially to avoid toxic solvents. The reaction was performed under solvent-free conditions by grinding a mixture of aromatic aldehyde (1 mmol), malononitrile (2 mmol), and propargyl alcohol (3 mmol) in the presence of NaOH as a Bronsted base using a mortar and pestle at room temperature. This mechanochemical approach significantly enhanced both the reaction rate and the product yield, affording the desired product within 15-20 minutes and yielded 82% for the desired product (**Table 1, entry 9**).

Table 1: Optimization of reaction condition for the synthesis of propargyl-oxy substituted pyridines.

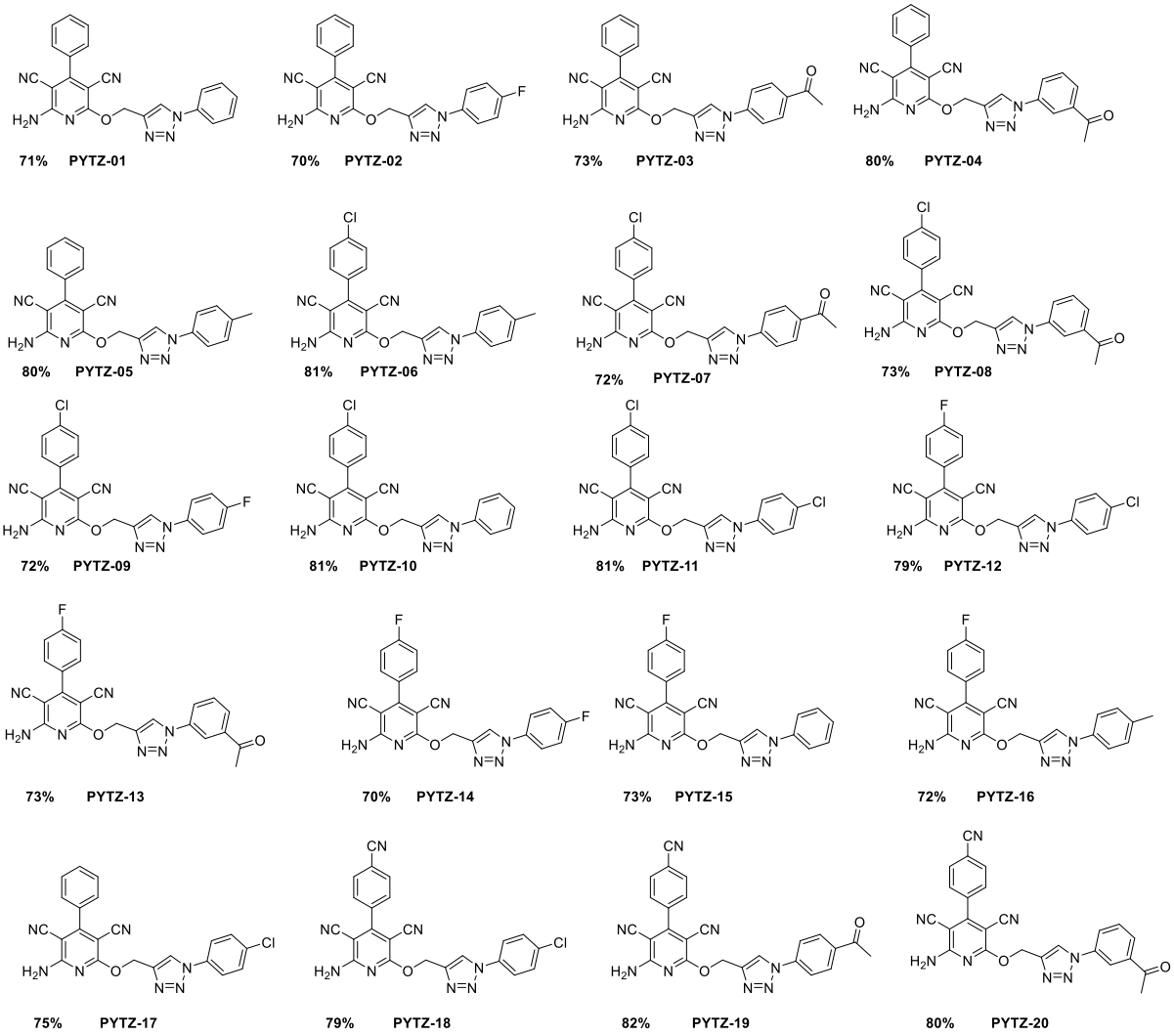
Entry	base	solvent	Temp (°C)	Equivalency of propargyl alcohol	Time (min)	Yield (%)[a]
1	NaoH	MeOH	0	1	30min	No rxn
2	NaoH	MeOH	0	2	30 min	No rxn
3	NaoH	MeOH	25	2	40min	No rxn
4	KOH	MeOH	25	2	40min	No rxn
5	NaOH	EtOH	0	2	45min	No rxn
6	Et_3N	EtOH	0	2	50min	No rxn
7	NaOH	None	0	1	30min	35[b]
8	NaOH	None	0	2	30 min	50[b]
9	**NaOH**	**None**	**0**	**3**	**20min**	**82**[b]
10	KOH	None	0	3	30min	40[b]
11	Et_3N	None	0	3	40min	No rxn[b]
12	K_2CO_3	None	0	3	40min	No rxn[b]
13	K_2CO_3	EtOH	0	3	40min	No rxn

[a] isolated yield, [a] mechanical grinding reaction,

Using above optimized reaction condition, we have synthesized several substituted pyridines particularly with propargyl-oxy group as substituent at 6-position of the pyridine ring. Later, the propargyl-oxy substituted pyridines were used to synthesize corresponding 1,2,3-triazoles using well known click chemistry through [3+2] cycloaddition with aryl azides as mentioned in **Scheme 2**.

Almost all types of azides having both withdrawing and donating groups reacted well and provided corresponding 1,2,3-triazole tethered pyridine molecules in good to excellent yields and the results are summarized in **Table 2**.

Table 2: Novel 1,2,3 triazole tethered substituted pyridine molecules



Molecular Docking Studies

The single crystal XRD structure of the protein CDK2 (PDB ID: 1GIJ) was retrieved from the RCSB Protein Data Bank.[21] Protein preparation and energy minimization were performed by applying the OPLS2005 force field using the Protein Preparation Wizard in the Schrödinger suite. The co-crystallized ligand was removed prior to grid generation, which was carried out with a grid box of dimensions 10 × 10 × 10 Å. The van der Waals radius scaling for nonpolar receptor atoms was set to 0.9 to optimize the docking environment.[22]

The synthesized compounds PYTZ-1 – PYTZ-2 were initially drawn using the 2D Sketcher module in Maestro's Build Panel and subsequently converted to 3D structures. The LigPrep module was employed to generate energetically favorable conformers of each molecule. Molecular docking was then conducted at the active site of CDK2 using the Glide docking module.[23] The QikProp tool was utilized to predict the percent human oral absorption.[24] The synthesized molecules were docked with CDK2 protein at active site. These docked results proved that molecules PYTZ-02, PYTZ-17, PYTZ01, PYTZ-05 and PYTZ-

04 protein-ligand complexes showed the best glide score, maximum human oral absorption and glide energy at the CDK2 protein active site. These molecules were repeatedly interacted with Val83 (hydrogen bond) and Leu134, Ala144, Gln85, Asp86, Ile10, Val18, Ala31, Val64 (Hydrophobic interactions) indicating that these residues were responsible for CDK 2 inhibition. **Figure 1** illustrations Three-dimensional structures of PYTZ-02, PYTZ-17, PYTZ01, PYTZ-05 and PYTZ-04 protein-ligand complexes visualized by Discovery Studio 4.0. Consequently, PYTZ-02, PYTZ-17, PYTZ-01, PYTZ-05, and PYTZ-04 compounds may be utilized to develop prospective CDK2 protein inhibitors for the treatment of cancer.[25]

Table1: Molecular docking results for synthesized compounds against CDK2 protein

Compound ID	Glide energy	Glide Score	Human Oral Absorption	Intermolecular interactions of docked complex
PYTZ-01	-41.99	-7.23	100	**H-Bond** Val83 **Hydrophobic** Leu134, Ala144, Phe80, Gln85, Asp86, Ile10, Val18, Ala31, Val64
PYTZ-02	-44.59	-7.56	100	**H-Bond** Val83 **Hydrophobic** Leu134, Ala144, Gln85, Asp86, Ile10, Val18, Ala31, Val64
PYTZ-03	-40.46	-6.88	99	**H-Bond** Gln85 **Hydrophobic** Leu134, Ala144, Phe80, Gln85, Asp86, Ile10, Val18, Ala31, Val64
PYTZ-04	-45.67	-7.08	100	**Hydrophobic** Leu134, Ala144, Phe80, Ile10, Val18, Ala31, Val64
PYTZ-05	-41.09	-7.17	100	**Hydrophobic** Leu134, Ala144, Phe80, Gln85, Asp86, Ile10, Val18, Ala31, Val64
PYTZ-06	-41.23	-5.56	91	**H-Bond** Glu08, Asp86 **Hydrophobic** Leu134, Ala144, Ile10, Val64, His82, Ala31, Phe80
PYTZ-07	-48.73	-5.08	89	**H-Bond** Lys33, Asp86, Thr89 **Hydrophobic** Leu134, Ala144, Ile10, His82, Ala31
PYTZ-08	-54.95	-6.19	97	**H-Bond** His84, Lys33 **Hydrophobic** Leu134, Ala144, Ile10, Val18
PYTZ-09	-41.13	-5.01	85	**H-Bond** Asp86, Thr89 **Hydrophobic** Leu134, Ile10, His82, Ala31
PYTZ-10	-39.59	-5.02	86	**H-Bond** Asp86, Thr89 **Hydrophobic**

				Leu134, Ala144, Ile10, Val18, Val64, Ala31
PYTZ-11	-45.66	-5.83	95	**H-Bond** Ile10, Asp86 **Hydrophobic** Leu134, Ala144, Ile10, Val18, Ala31, Phe80, His82
PYTZ-12	-43.55	-5.03	87	**H-Bond** Glu8, Lys9, Asp86, Thr89 **Hydrophobic** Leu134, Ala144, Ile10, Ala31, Val64, Phe80, Val18
PYTZ-13	-50.54	-6.77	98	**H-Bond** Val83, Lys33 **Hydrophobic** Leu134, Ala144, Ile10, Val18, Ala31, Val64
PYTZ-14	-47.49	-6.24	98	**H-Bond** Val83, Gly13, Glu81 **Hydrophobic** Leu134, Ala144, Ile10, Val18, Ala31, Val64
PYTZ-15	-46.02	-5.11	89	**H-Bond** Glu8, Asp86 **Hydrophobic** Leu134, His82, Ile10, Ala31
PYTZ-16	-47.97	-6.05	96	**H-Bond** Glu81, Gly13, Val83 **Hydrophobic** Leu134, Ala144, Ile10, Val18, Ala31
PYTZ-17	-44.30	-7.46	100	**H-Bond** Val83 **Hydrophobic** Leu134, Ala144, Gln85, Asp86, Ile10, Val18, Ala31, Val64
PYTZ-18	-45.79	-5.76	94	**H-Bond** Ile10, Lys33 **Hydrophobic** Leu134, Ala144, Ile10, Val18, Ala31, Lys33
PYTZ-19	-48.71	-5.04	89	**Hydrophobic** Leu134, Ala144, Ala31, Ile10, Val18
PYTZ-20	-52.23	-5.75	93	**H-Bond** Ile10 **Hydrophobic** Leu134, Ala144, Ile10, Val18, His82

Figure 1: Three dimensional representations of PYTZ-01, PYTZ-02, PYTZ-04, PYTZ-05 and PYTZ-17 molecules docked into the CDK2 protein active site.

PYTZ-02 **PYTZ-17**

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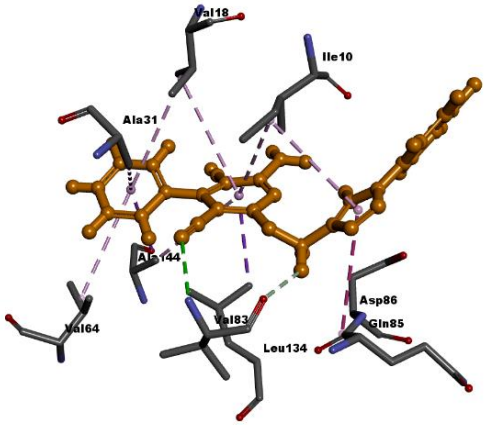
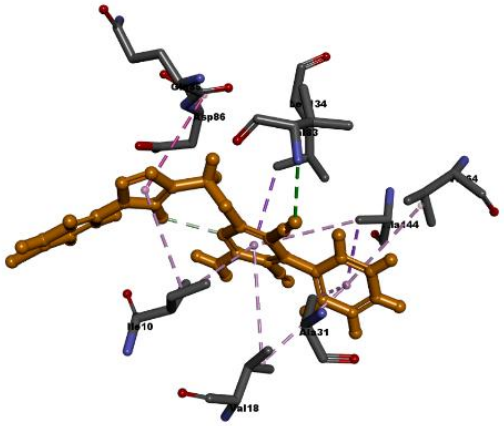
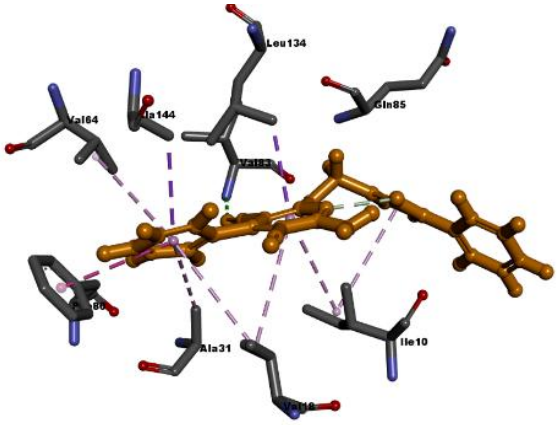


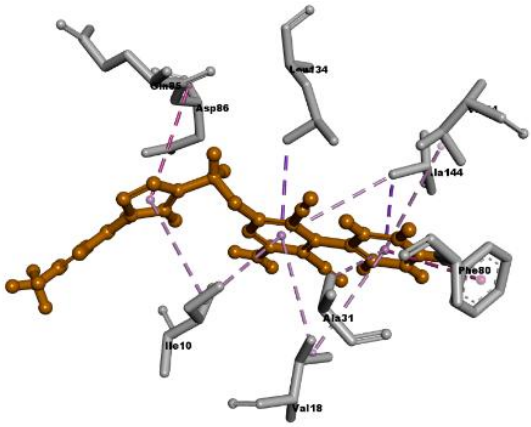
PYTZ-01

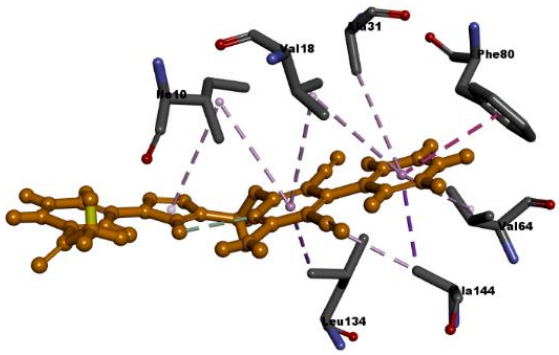


PYTZ-05



PYTZ-04





Conclusion

An efficient synthesis of novel substituted pyridine tethered with 1,2,3-triazoles is achieved in good to excellent yields. These newly synthesized molecules were subjected to molecular docking studies toward CDK2 protein and for our delight we found that several molecules shown good binding affinity and based on the protein-ligand complexes these can inhibit the CDK2 protein. More particularly PYTZ-02, PYTZ-17, PYTZ-01, PYTZ-05, and PYTZ-04 compounds may be utilized to develop prospective CDK2 protein inhibitors for the treatment of cancer.

Experimental Section

All chemicals and reagents were obtained from commercial suppliers and used without further purification. The purity of synthesized compounds was monitored by thin-layer chromatography (TLC) on silica gel plates (E. Merck, Mumbai, India). Melting points were determined using a VEEGO programmable melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer 100S FTIR spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrometer in DMSO-d_6 or $CDCl_3$, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million (δ, ppm). Mass spectra were obtained on a Perkin-Elmer mass spectrometer operating at 12.5 eV. Elemental analyses (CHNS) were performed on a Carlo Erba EA 1108 CHNS-O elemental analyser.

General Procedure for the Synthesis of Pyridine Derivatives

A mixture of substituted benzaldehydes (1 mmol), malononitrile (2 mmol), propargyl alcohol (3 mmol) and sodium hydroxide (NaOH) was placed in a mortar and grinded using a pestle for 15–20 minutes. The progress of the reaction was monitored by TLC using a 3:7 mixture of ethyl acetate and n-hexane. Upon completion, the reaction mixture was transferred into water. The resulting solid was collected by filtration and purified by recrystallization from ethanol to yield the pure pyridine derivatives.

General Procedure for the Synthesis of Aromatic Azides

The synthesis of aromatic azides was carried out under inert conditions. A 2N HCl solution was added to the respective aromatic amines dissolved in dichloromethane (CH_2Cl_2), followed by the slow addition of an aqueous sodium nitrite ($NaNO_2$) solution at 0 °C with continuous stirring for 15 minutes to generate the diazonium salt. To this diazonium solution, sodium azide (NaN_3) was added dropwise at 0 °C, and the mixture was then stirred at room temperature for 15 minutes. After the reaction, the mixture was allowed to stand until phase separation occurred. The organic layer was separated, washed successively with saturated sodium bicarbonate ($NaHCO_3$) and brine, then dried over anhydrous sodium sulfate (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude aryl azides.

General Procedure for the Synthesis of 1,2,3-Triazoles

To a solution of propargylated pyridine (1.0 mmol) and the corresponding aryl azide (1.5 mmol.) in dry *N*-methylformamide (25 mL), copper (II) sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$, 0.01 equiv.) and sodium ascorbate (0.04 equiv.) were added as the catalytic system. The reaction mixture was stirred at room temperature for 3-4 hours. Upon completion, as monitored by TLC, the mixture was extracted with ethyl acetate and ice-cold water (3 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using 15% ethyl acetate in hexane to yield the pure 1,2,3-triazole derivatives.

Experimental Data

1. 2-amino-4-phenyl-6-((1-phenyl-1H-1,2,3-triazol-4-yl)-methoxy)-pyridine-3,5-dicarbonitrile (PYTZ-01): White solid mp. 162–163 °C; **^{1}H NMR (300 MHz, DMSO)** δ 9.07 (s, 1H), 9.07(s, 1H), 7.94-8.69 (br, 2H (NH_2)), 7.91 (d, *J* = 6 Hz, 2H), 7.65-7.46 (*m*, 8H), 5.61 (s, 2H); **^{13}C NMR (126 MHz, DMSO)** δ 165.21, 161.50, 161.38, 143.06, 136.98, 134.55, 130.79, 130.42, 129.38, 129.15, 128.81, 125.07, 120.75, 115.88, 115.34, 84.20, 83.92, 60.43; **IR (KBr, cm^{-1}):** 3335, 3132, 2218, 1552, 1269, 980, 853; **HRMS (ESI)** m/z calcd for $C_{22}H_{15}N_7NaO$ [M + Na^+], 416.1235; Found 416.1239.

2. 2-amino-6-((1-(4-fluorophenyl-1H-1,2,3-triazol-4-yl)-methoxy)-4-phenylpyridine-3,5-dicarbonitrile (PYTZ-02): White solid; mp. 215–216 °C; **^{1}H NMR (300 MHz, DMSO)** δ 9.04 (s, 1H), 8.0-8.6 (br, 2H (NH_2)), 7.96-8.10 (m, 2H), 7.40 – 7.61 (m, 7H), 5.60 (s, 2H); **^{13}C NMR (75 MHz, DMSO)** δ 165.20, 163.88, 161.51, 161.38, 160.62, 143.08, 134.54, 133.56, 133.53, 130.79, 129.16, 128.80, 125.31, 123.22, 123.11, 117.45, 117.14, 115.87, 115.33, 84.20, 83.90, 60.39; **IR (KBr, cm^{-1}):** 3337, 3130, 2216, 1548, 1259, 982, 858; **HRMS (ESI)** m/z calcd for $C_{22}H_{14}FN_7NaO$ [M + Na^+], 434.1141; Found 434.1158.

3. 2-((1-(4-acetylphenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-6-amino-4-phenylpyridine-3,5-dicarbonitrile (PYTZ-03): White solid; mp. 210–211 °C; **^{1}H NMR (300 MHz, DMSO)** δ 9.19 (s, 1H), 8.19 (d, *J* = 9 Hz, 2H), 8.09 (d, *J* = 6 Hz, 2H), 7.49 – 7.59 (m, 5H), 5.62 (s, 2H), 2.65 (s, 3H); **^{13}C NMR (75 MHz, DMSO)** δ 197.45, 165.19, 161.52, 161.38, 143.42, 139.94, 137.02, 134.53, 130.80, 130.59, 129.16, 128.81, 125.17, 120.42, 115.86, 115.33, 84.23, 83.91, 60.33, 27.34; **IR (KBr, cm^{-1}):** 3305, 3130, 2218, 1687, 1552, 968, 853; **HRMS (ESI)** m/z calcd for $C_{24}H_{18}N_7O_2$ [M + H^+], 436.1522; Found 436.1513.

4. 2-((1-(3-acetylphenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-6-amino-4-phenylpyridine-3,5-dicarbonitrile (PYTZ-04): White solid; mp. 208–209 °C; **^{1}H NMR (400 MHz, DMSO)** δ 9.19 (s, 1H), 8.40 (s, 1H), 8.16-8.20 (m, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 8.0 Hz, 1H), 7.58 – 7.50 (m, 5H), 5.62 (s, 2H), 2.69 (s, 3H); **^{13}C NMR (101 MHz, DMSO)** δ 197.63, 165.20, 161.52, 161.38, 143.24, 138.73, 137.29, 134.55, 131.03, 130.79, 129.16, 129.02, 128.81, 125.31, 125.16, 119.97, 115.85, 115.32, 84.21, 83.89, 60.37, 27.47; **IR (KBr, cm^{-1}):** 3321, 3128, 2223, 1629, 1551,1294, 962, 848; **HRMS (ESI)** m/z calcd for $C_{24}H_{18}N_7O_2$ [M + H^+], 436.1522; Found 436.1513.

5. 2-amino-4-phenyl-6-((1-p-tolyl)-1H-1,2,3-triazol-4-yl)-methoxy)-pyridine-3,5-dicarbonitrile (PYTZ-05): White solid; mp 205–206 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.09 (s, 1H), 7.62 (d, *J* = 8 Hz, 2H), 7.51-7.56 (m, 5H), 7.33 (d, *J* = 8 Hz, 2H), 5.89-5.93 (br, s, 2H), 5.71 (s, 2H), 2.43 (s, 3H); **^{13}C NMR (101 MHz,**

$CDCl_3$) δ 165.66, 161.19, 160.86, 139.41, 134.63, 133.39, 131.07, 130.45, 129.11, 128.53, 120.73, 115.53, 114.45, 86.55, 84.94, 61.40, 21.27; **IR (KBr, cm^{-1}):** 3299, 3218, 2216, 1526,1279, 948, 897; **HRMS (ESI)** m/z calcd for $C_{23}H_{17}N_7NaO$ [M + Na^+], 430.1392; Found 430.1405.

6. 2-amino-4-(4-chlorophenyl)-6-((1-p-tolyl-1H-1,2,3-triazol-4-yl)-methoxy)-pyridine-3,5-dicarbonitrile (PYTZ-06): White solid; mp. 184–185 °C; **^{1}H NMR (400 MHz, DMSO)** δ 9.01 (s, 1H), 7.85-8.65 (br, 2H (NH_2)), 7.78 (d, *J* = 8 Hz, 2H), 7.65 (d, *J* = 8 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 8 Hz, 2H), 5.59 (s, 2H), 2.39 (s, 3H); **^{13}C NMR (126 MHz, DMSO)** δ 165.14, 161.30, 160.32, 142.89, 139.04, 135.73, 134.73, 133.39, 130.82, 130.76, 129.32, 124.93, 120.59, 115.74, 115.23, 84.17, 83.91, 60.48, 21.08; **IR (KBr, cm^{-1}):** 3295, 3131, 2219, 1556, 1288, 988, 816; **HRMS (ESI)** m/z calcd for $C_{23}H_{17}ClN_7O$ [M + H^+], 442.1183; Found 442.1173.

7. 2-((1-(4-acetylphenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-6-amino-4-(4-chlorophenyl) pyridine-3,5-dicarbonitrile (PYTZ-07): White solid; mp. 190–191°C; **^{1}H NMR (400 MHz, DMSO)** δ 9.19 (s, 1H), 8.20 (d, *J* = 8 Hz, 2H), 8.09 (d, *J* = 8 Hz, 2H), 7.65 (d, *J* = 8 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 5.61 (s, 2H), 2.65 (s, 3H); **^{13}C NMR (75 MHz, DMSO)** δ 197.45, 165.11, 161.30, 160.34, 143.37, 139.93, 137.03, 135.75, 133.37, 130.82, 130.59, 129.34, 125.19, 120.42, 115.73, 115.21, 84.22, 83.90, 60.36, 27.35; **IR (KBr, cm^{-1}):** 3308, 3126, 2216, 1685, 1542,1225, 948, 863; **HRMS (ESI)** m/z calcd for $C_{24}H_{17}ClN_7O_2$ [M + H^+], 470.1132; Found 470.1119.

8. 2-((1-(3-acetylphenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-6-amino-4-(4-chlorophenyl) pyridine-3,5-dicarbonitrile (PYTZ-08): White solid; mp. 184–185 °C; **^{1}H NMR (400 MHz, DMSO)** δ 9.18 (s, 1H), 8.39 (s, 1H), 8.18 (d, *J* = 8 Hz, 1H), 8.10 (d, *J* = 8 Hz, 1H), 7.80 (t, *J* = 8 Hz, 1H), 7.65 (d, *J* = 8 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 5.61 (s, 2H), 2.69 (s, 3H); **^{13}C NMR (75 MHz, DMSO)** δ 197.64, 165.12, 161.31, 160.34, 143.20, 138.72, 137.27, 135.75, 133.37, 131.04, 130.82, 129.33, 129.04, 125.31, 125.13, 119.93, 115.73, 115.22, 84.20, 83.88, 60.41, 27.46; **IR (KBr, cm^{-1}):** 3318, 3110, 2218, 1686, 1551,1269, 978, 843; **HRMS (ESI)** m/z calcd for $C_{24}H_{17}ClN_7O_2$ [M + H^+], 470.1132; Found 470.1119.

9. 2-amino-4-(4-chlorophenyl)-6-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-pyridine-3,5-dicarbonitrile (PYTZ-09): White solid; mp. 189–190 °C; **^{1}H NMR (400 MHz, DMSO)** δ 9.03 (s, 1H),7.99-8.56 (br, 2H (NH_2)), 7.92 – 7.98 (m, 2H), 7.65 (d, *J* = 8 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 7.49 (t, *J* = 8 Hz, 2H), 5.59 (s, 2H); **^{13}C NMR (101 MHz, DMSO)** δ 165.12, 163.47, 161.30, 161.03, 160.34, 143.03, 135.74, 133.53, 133.51, 133.38, 130.81, 129.33, 125.31, 123.20, 123.12, 117.42, 117.18, 115.73, 115.22, 84.19, 83.89, 60.42; **IR (KBr, cm^{-1}):** 3316 3112, 2212, 1561,1276, 987, 839; **HRMS (ESI)** m/z calcd for $C_{22}H_{13}ClFN_7NaO$ [M + Na^+], 468.0751; Found 468.0763.

10. 2-amino-4-(4-chlorophenyl)-6-((1-phenyl-1H-1,2,3-triazol-4-yl)-methoxy)-pyridine-3,5-dicarbonitrile (PYTZ-10): white solid; mp. 182–183 °C; **^{1}H NMR (400 MHz, DMSO)** δ 9.06 (s, 1H), 8.0-8.5 (bs, 2H (NH_2)), 7.90 (d, *J* = 8.0, 2H), 7.61-7.67 (m, 4H), 7.49 – 7.58 (m, 3H), 5.60 (s, 2H); **^{13}C NMR (126 MHz, DMSO)** δ 165.14, 161.31, 160.33, 143.01, 136.97, 135.74, 133.39, 130.82, 130.43, 129.39, 129.33, 125.08, 120.74, 115.74, 115.23, 84.19, 83.91, 60.46; **IR (KBr, cm^{-1}):** 3325, 3116, 2222, 1556,1275, 968, 823; **HRMS (ESI)** m/z calcd for $C_{22}H_{14}ClN_7NaO$ [M + Na^+], 450.0846; Found 450.0851.

11. 2-amino-4-(4-chlorophenyl)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-pyridine-3,5-dicarbonitrile (PYTZ-11): White solid; mp. 186–187 °C; **^{1}H NMR (400 MHz, DMSO)** δ 9.07 (s, 1H), 7.98-8.70 (br, 2H (NH_2)), 7.95 (d, *J* = 8 Hz, 2H), 7.71 (d, *J* = 8 Hz, 2H), 7.65 (d, *J* = 8 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 5.60 (s, 2H); **^{13}C NMR (101 MHz, DMSO)** δ 165.11, 161.29, 160.33, 143.18, 135.74, 133.68, 133.37, 130.81, 130.41, 129.33, 125.13, 122.42, 115.73, 115.21, 84.19, 83.89, 60.39; **IR (KBr, cm^{-1}):** 3331, 3121, 2212, 1559,1275, 948, 851; **HRMS (ESI)** m/z calcd for $C_{22}H_{13}Cl_2N_7NaO$ [M + Na^+], 468.0751; Found 468.0763.

12. 2-amino-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-4-(4-fluorophenyl)-pyridine-3,5-dicarbonitrile (PYTZ-12): White solid; mp. 192-193 °C; **^{1}H NMR (300 MHz, DMSO)** δ 9.08 (s, 1 H), 8.00-8.48 (br, 2H (NH_2)), 7.92 (d, *J* = 9 Hz, 2H), 7.71 (d, *J* = 9 Hz, 2H), 7.57-7.63 (m, 2H), 7.42 (t, *J* = 9 Hz, 2H), 5.60 (s, 2H); **^{13}C NMR (101 MHz, DMSO)** δ 165.14, 164.83, 162.37, 161.31, 160.54, 143.19, 135.77, 133.68, 131.49, 131.40, 130.92, 130.89, 130.41, 125.13, 122.42, 116.41, 116.19, 115.81, 115.29, 84.34, 84.03, 60.36; **IR (KBr, cm^{-1}):** 3300, 3128, 2218, 1546,1234, 938, 863; **HRMS (ESI)** m/z calcd for $C_{22}H_{13}ClFN_7NaO$ [M + Na^+], 468.0751; Found 468.0763.

13. 2-((1-(3-acetylphenyl)-1H-1,2,3-triazol-4-yl)-methoxy)6-amino-4-(4-fluorophenyl)-pyridine-3,5-dicarbonitrile (PYTZ-13): White solid; mp. 186-187 °C; **^{1}H NMR (400 MHz, DMSO)** δ 9.18 (s, 1H), 8.39 (s, 1H), 8.18 (d, *J* = 8 Hz, 1H), 8.10 (d, *J* = 8 Hz, 1H), 7.80 (t, *J* = 8 Hz, 1H), 7.58 – 7.63 (m, 2H), 7.42 (t, *J* = 8 Hz, 2H), 5.62 (s, 2H), 2.69 (s, 3H); **^{13}C NMR (101 MHz, DMSO)** δ 197.65, 165.15, 164.83, 162.37, 161.33, 160.54, 143.22, 138.72, 137.27, 131.49, 131.40, 131.04, 130.92; **IR (KBr, cm^{-1}):** 3316, 3120, 2221, 1688, 1554,1261, 968, 849; **HRMS (ESI)** m/z calcd for $C_{24}H_{17}FN_7O_2$ [M + H$^+$], 454.1427; Found 454.1421.

14. 2-amino-4-(4-fluorophenyl)-6-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-pyridine-3,5-dicarbonitrile (PYTZ-14): White solid; mp. 194-195 °C; **^{1}H NMR (400 MHz, DMSO)** δ 9.04 (s, 1H), 8.8-8.0(br, 2H (NH_2)), 7.97 – 7.93 (m, 2H), 7.58 – 7.61 (m, 2H), 7.50 (t, *J* = 8 Hz, 2H), 7.42 (t, *J* = 8 Hz, 2H), 5.59 (s, 2H); **^{13}C NMR (101 MHz, DMSO)** δ 165.15, 164.83, 163.47, 162.37, 161.32, 161.03, 160.53, 143.04, 133.55, 133.53, 131.49, 131.40, 130.93, 130.91, 125.32, 123.20, 123.11, 117.41, 117.18, 116.40, 116.18, 115.82, 115.29, 84.34, 84.04, 60.40; **IR (KBr, cm^{-1}):** 3332, 3131, 2224, 1562,1269, 969, 859; **HRMS (ESI)** m/z calcd for $C_{22}H_{13}F_2N_7NaO$ [M + Na$^+$], 452.1047; Found 452.1057.

15. 2-amino-4-(4-fluorophenyl)-6-((1-phenyl-1H-1,2,3-triazol-4-yl)-methoxy)-pyridine-3,5-dicarbonitrile (PYTZ-15): White solid; mp. 189-190 °C; **^{1}H NMR (400 MHz, DMSO)** δ 9.06 (s, 1H), 7.9-8.7 (br, 2H (NH_2)), 7.90 (d, *J* = 8 Hz, 2H), 7.58-7.66(m, 4H), 7.53 (t, *J* = 8 Hz, 1H), 7.42 (t, *J* = 8 Hz, 2H), 5.60 (s, 2H); **^{13}C NMR (101 MHz, DMSO)** δ 165.16, 164.83, 162.37, 161.32, 160.53, 143.02, 136.98, 131.49, 131.41, 130.94, 130.92, 130.43, 129.39, 125.09, 120.75, 116.40, 116.18, 115.83, 115.30, 84.33, 84.06, 60.43; **HRMS (ESI)** m/z calcd for $C_{22}H_{14}FN_7NaO$ [M + Na$^+$], 434.1141; Found 434.1158.

16. 2-amino-4-(4-fluorophenyl)-6-((1-p-tolyl-1H-1,2,3-triazol-4-yl)methoxy)pyridine-3,5-dicarbonitrile (PYTZ-16): White solid; mp 192-193 °C. **^{1}H NMR (400 MHz, DMSO)** δ 9.01 (s, 1H), 7.96-8.40(br 2H (NH_2)) ,7.78 (d, *J* = 8 Hz, 2H), 7.63 – 7.58 (m, 2H), 7.39 – 7.45 (m, 4H), 5.59 (s, 2H), 2.39 (s, 3H). **^{13}C NMR (126 MHz, DMSO)** δ 165.16, 164.58, 162.61, 161.32, 160.52, 142.90, 139.03, 134.74, 131.48, 131.41, 130.94, 130.92, 124.93, 120.59, 116.37, 116.20, 115.83, 115.30, 84.32, 84.05, 60.45, 21.08; **IR (KBr, cm^{-1}):** 3298, 3110, 2218, 1546,1228, 935, 842; **HRMS (ESI)** m/z calcd for $C_{23}H_{17}FN_7O$ [M + H$^+$], 426.1478; Found 426.1484.

17. 2-amino-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-4-phenylpyridine-3,5-dicarbonitrile (PYTZ-17): White solid; mp. 220–221 °C; **^{1}H NMR (300 MHz, DMSO)** δ 9.08 (s, 1H), 7.97-8.45 (br, 2H (NH_2)), 7.95 (d, *J* = 9 Hz, 2H), 7.71 (d, *J* = 9 Hz, 2H), 7.58 – 7.49 (m, 5H), 5.60 (s, 2H); **^{13}C NMR (101 MHz, DMSO)** δ 165.19, 161.51, 161.37, 143.22, 135.78, 134.54, 133.67, 130.79, 130.41, 129.15, 128.80, 125.11, 122.43, 115.86, 115.31, 84.21, 83.91, 60.36; **IR (KBr, cm^{-1}):** 3301, 3101, 2218, 1561,1269, 967, 849; **HRMS (ESI)** m/z calcd for $C_{22}H_{14}ClN_7NaO$ [M + Na$^+$], 450.0846; Found 450.0851.

18. 2-amino-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-4-(4-cyanophenyl)-pyridine-3,5-dicarbonitrile (PYTZ-18): White solid; mp. 194–195 °C; **^{1}H NMR (400 MHz, DMSO)** δ 9.08 (s, 1H), 8.10-8.60(br,2H (NH_2)), 8.07 (d, *J* = 8 Hz, 2H), 7.95 (d, *J* = 8 Hz, 2H), 7.70 – 7.76 (m, 4H), 5.60 (s, 2H); **^{13}C NMR (75 MHz, DMSO)** δ 165.03, 161.23, 159.85, 143.12, 139.15, 135.76, 133.69, 133.19, 130.42, 129.99, 125.17, 122.42, 118.64, 115.49, 114.99, 113.55, 84.07, 83.78, 60.46; **IR (KBr, cm^{-1}):** 3308, 3116, 2214, 1549,1265, 952, 863; **HRMS (ESI)** m/z calcd for $C_{23}H_{13}ClN_8NaO$ [M + Na$^+$], 475.0798; Found 475.0798.

19. 2-((1-(4-acetylphenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-6-amino-4-(4-cyanophenyl)-pyridine-3,5-dicarbonitrile (PYTZ-19): White solid; mp. 198–200 °C; **^{1}H NMR (300 MHz, DMSO)** δ 9.19 (s, 1H), 8.19 (d, *J* = 9.0 Hz, 2H), 8.06 – 8.10 (m, 4H), 7.75 (d, *J* = 9.0 Hz, 2H) 5.63 (s, 2H), 2.65 (s, 3H); **^{13}C NMR (75 MHz, DMSO)** δ 197.42, 165.03, 161.23, 159.86, 143.30, 139.93, 139.15, 137.04, 133.19, 130.60, 129.99, 125.24, 120.41, 118.65, 115.49, 114.99, 113.56, 84.10, 83.78, 60.43, 27.35; **IR (KBr, cm^{-1}):** 3329, 3114, 2218,1678, 1549,1259, 968, 865; **HRMS (ESI)** m/z calcd for $C_{25}H_{17}N_8O_2$ [M + H$^+$], 461.1474; Found 461.1467.

20. 2-((1-(3-acetylphenyl)-1H-1,2,3-triazol-4-yl)-methoxy)-6-amino-4-(4-cyanophenyl)-pyridine-3,5-dicarbonitrile (PYTZ-20): White solid; mp. 195–196 °C; **^{1}H NMR (300 MHz, DMSO)** δ 9.19 (s, 1H), 8.39 (s, 1H), 8.18 (d, *J* = 12 Hz, 1H), 8.04-8.13 (m, 3H), 7.72-7.84(m, 3H), 5.63 (s, 2H), 2.69 (s, 3H); **^{13}C NMR (101 MHz, DMSO)** δ 197.63, 165.04, 161.24, 159.85, 143.13, 139.15, 138.71, 137.26, 133.18, 131.04, 129.05, 125.35, 125.12, 119.90, 118.65, 115.50, 115.01, 113.55, 84.06, 83.75, 60.47, 27.46; **IR**

(KBr, cm^{-1}): 3292, 3118, 2220,1628, 1548,1253, 951, 862; **HRMS (ESI)** m/z calcd for $C_{25}H_{17}N_8O_2$ [M + H^+], 461.1474; Found 461.1467.

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