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Synthesis of 2-triazolyl-imidazo[1,2-*a*]pyridine through one-pot three-component reaction using nano copper oxide assisted click-catalyst

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The synthesis of 2-triazolyl imidazo[1,2-*a*]pyridine (**8a-o**) were accomplished through three component A^3 coupling followed by *5-exo dig* cyclisation by employing 1-alkyl-1,2,3-triazole-4-carbaldehyde, amidine and terminal alkynes using 5 mol% nanocopper oxide together with 10 mol% sodium ascorbate as click-catalyst in ethanol at 70 ˚C. The present protocol was further utilized for the synthesis of 2-(2-triazolyl-imidazo[1,2-*a*]pyridin-3-yl)ethanol (**9a-e**). In addition, the molecular structure of **8c** possesses a C-H…π interaction (H17b…C10) along with peculiar supramolecular layered structure architecture. This protocol features ready recyclability of catalyst, good yields and wide substrates scope. Moreover, the synthesis of triazolyl precursor (1-alkyl-1,2,3-triazol-4-yl)methanol (**4a-f**) have also been achieved through nano copper oxide mediated click-catalyst in water at 70 ˚C.

Introduction

Multicomponent reaction (MCR) is a versatile synthetic strategy to synthesize easily diverse complex molecules in a highly regio- and chemoselective manner having widespread applications in bioscience.[1] These reactions are also explored for complicated natural product synthesis[2a] as well as for the synthesis of highly desirable biomolecular scaffolds through intramolecular C-N bond formation in a cascade reaction.[2b] The library of molecules are usually synthesized by designing a suitable functional group in the substrate followed by another MCR on the same scaffold lead to the widespread application for targeted molecules required for drug discovery process. 'Click Chemistry' admires an unusual attention in synthetic pharmaceuticals due to their outspread application in biological science,[3] glycodendrimers,[4] polymeric materials[5] and in fabrications of hydrogels.[6]

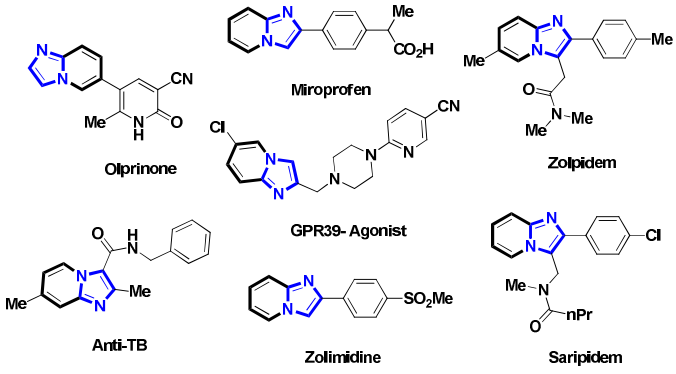
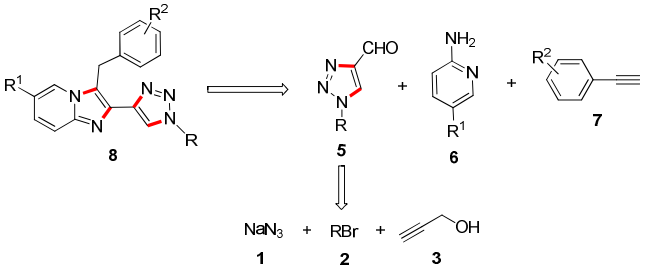


Figure 1. Bioactive molecules containing imidazo[1,2-*a*]pyridine scaffolds

Most of the triazole based heterocyclic entities are found to be potent drugs and they are extensively utilized in biomedical fields.[7] The enlighten combination of Click reaction with MCR may attain the classical synthetic route for bioactive molecules.

Imidazo[1,2-*a*]pyridine are important fused heterocycles exhibiting pharmaceutical properties.[8] This framework shows various biological activities such as antibacterial,[9a,b] antipyretic,[9c] anticancer,[10a] antituberculosis,[10b] GPR39 agonist[11a] and as calcium channel blockers.[11b] The drugs[12] containing imidazo[1,2-*a*]pyridine scaffolds are present in Saripidem,[13a] Zolimidine,[9c] Zolpidem[13b] and Olprinone,[13c] which are depicted in Figure 1.



Scheme 1. Route toward the synthesis of 2-triazolyl-imidazo[1,2-*a*]pyridine

A typical synthetic route for accomplishing imidazo[1,2-*a*]pyridine derivative is three component coupling reaction.[14] However, the synthesis of C(sp^2)-C(sp^2) hybridized triazolyl-imidazo[1,2-*a*]pyridine derivatives are highly desirable and the molecular skeleton containing imidazo[1,2-*a*]pyridine scaffolds along with 1,4-substituted-1,2,3-triazole in a single nuclei such as 2-triazolyl-imidazo[1,2-*a*]pyridine may exhibit an another interesting medicinal property in near future.[1]

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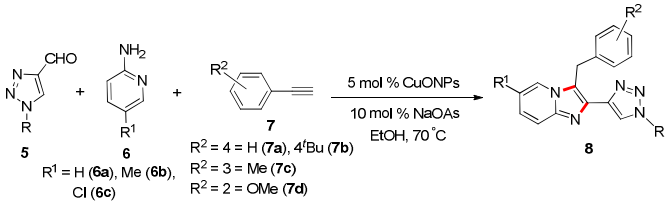


Scheme 2. Synthesis of 2-triazolyl-imidazo[1,2-*a*]pyridine derivatives

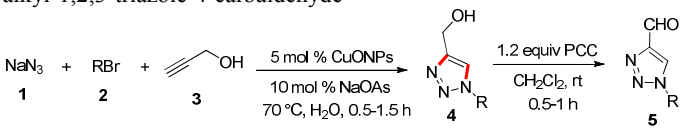
Nanotechnology has emerged as 'Greener Technology' and it might resolve the challenging problem in environmental science. The use of nanocatalyst provides better selectivity, recyclability and eco-friendliness. Recently, heterogeneous catalysts have been explored for various synthetic transformations.[16] Transition metal based nanoparticle is found to be an efficient heterogeneous catalyst[17a] with distinct active sites.[17b] Therefore, a considerable research effort has been devoted to develop transition metal based nanoparticle catalyst in organic synthesis.[18] Copper oxide nanoparticle is extensively used for the synthesis of triazole and oxazole skeleton.[19a-f]

We conceived that copper oxide nanoparticle along with sodium ascorbate might be suitable for the synthesis of 2-triazolyl-imidazo[1,2-*a*]pyridine (**8**). The outline of schematic route for the synthesis of 2-triazolyl-imidazo[1,2-*a*]pyridine is shown in Scheme 1. In this paper we would like to report the synthesis of 2-triazolyl-imidazo[1,2-*a*]pyridine using triazolyl aldehyde, amidine and alkyne in the presence of catalyst copper oxide nanoparticle together with sodium ascorbate in ethanol at 70 ˚C as shown in Scheme 2.

Results and discussion

The required triazole containing aldehydes (**5**) were prepared via two-step sequence. An initial reaction with sodium azide (**1**), alkyl bromide (**2**) and propargyl alcohol (**3**) in the presence of catalytic amount of copper oxide nanoparticle along with sodium ascorbate in water at 70 ˚C afforded (1-alkyl-1,2,3-triazol-4-yl) methanol (**4**), which was finally oxidized by using pyridiniumchlorochromate (PCC) in dichloromethane at room temperature. The synthesized compounds **4a** & **4f** and their investigated biological studies on PM domain construe as effective inhibitor.[19f] The various triazole containing aldehydes (**5**) were synthesized as shown in Table 1.

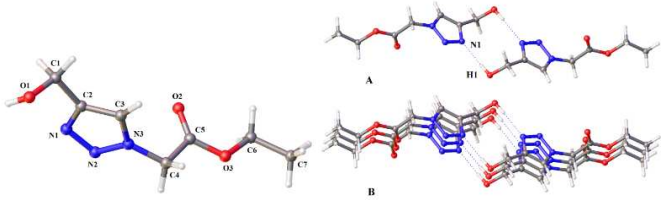
Table 1. Synthesis of (1-alkyl-1,2,3-triazol-4-yl)methanol and 1-alkyl-1,2,3-triazole-4-carbaldehyde[a]



S. No	R(**2**)	Product (**4**)	Yield **4** (%)[b]	Product (**5**)	Yield **5** (%)[b]
1	$C_6H_5CH_2$ (**2a**)	(**4a**)	92	(**5a**)	82
2	4Me-$C_6H_5CH_2$ (**2b**)	(**4b**)	90	(**5b**)	78
3	4Br-$C_6H_5CH_2$ (**2c**)	(**4c**)	86	(**5c**)	76
4	4F-$C_6H_5CH_2$ (**2d**)	(**4d**)	90	(**5d**)	78
5	Allyl (**2e**)	(**4e**)	80	(**5e**)	72
6	Ethoxycarbonylmethyl (**2f**)	(**4f**)	78	(**5f**)	68

[a]The reactions were performed in 10 mmol scale. [b]Isolated yield.

Moreover, the structure of alcoholic triazolyl precursor (**4f**) was confirmed through single X-ray analysis (Figure 2, I). The X-ray data shows an intermolecular hydrogen bonding along with layered structure as shown in Figure 2, II.

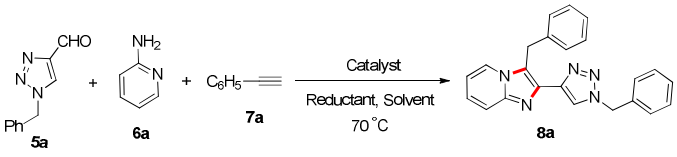


I II

Figure 2. **I**) X-ray structure of **4f**. **II**) A) Intermolecular H-Bonding. B) Layered-structure through intermolecular H-Bonding **4f**

At the outset, trial reactions were carried out with 1-benzyl-1,2,3-triazole-4-carbaldehyde (**5a**), 2-aminopyridine (**6a**) and phenylacetylene (**7a**) to optimize the reaction conditions and the obtained results are represented in Table 2. To pursue our goal, a variety of Cu(II) source were examined with different reducing agent and the best result was obtained with 5 mol% of copper oxide nanoparticle along with 10 mol% sodium ascorbate in ethanol at 70 ˚C (Table 2). In addition Cu(I) source was also examined under the same reaction condition and it yielded to 51% (Table 2, entry 5). On screening the reaction with different polar protic (H_2O, EtOH), polar aprotic (CH_3CN) and nonpolar (toluene) solvents, ethanol was found to be the suitable choice for the synthesis of 2-triazolyl-imidazo[1,2-*a*]pyridine.

Table 2. Optimization of the reaction conditions[a]



S. No	Catalyst	Mol %	Reductant (Mol%)	Solvent	Time (h)	Yield (%)[b]
1	$Cu(NO_3)_2 \cdot 3H_2O$	05	NaOAs (10)	EtOH	12	42
2	$CuCl_2$	05	NaOAs (10)	EtOH	12	45
3	$Cu(OAc)_2 \cdot 2H_2O$	05	NaOAs (10)	EtOH	12	44
4	$CuSO_4 \cdot 5H_2O$	05	NaOAs (10)	EtOH	12	47
5	CuI	05	-	EtOH	16	51
6	CuO Nano Particle	05	-	EtOH	18	25
7	CuO Nano Particle	05	D-Glucose (10)	EtOH	16	35
8	CuO Nano Particle	05	D-Glucose (10)	H_2O	18	52
9	CuO Nano Particle	05	NaOAs (10)	H_2O	16	58
10	$CuCl_2$	05	NaOAs (10)	H_2O	18	31
11	CuO Nano Particle	02	NaOAs (5)	EtOH	11	75
12	CuO Nano Particle	05	NaOAs (10)	EtOH	10	84
13	CuO Nano Particle	10	NaOAs (20)	EtOH	11	78

[a]The reactions were carried out using each 0.5 mmol of 1-benzyl 1,2,3-triazole-4-carbaldehyde (**5a**), 2-aminopyridine (**6a**) and phenylacetylene (**7a**). [b]Isolated yield.

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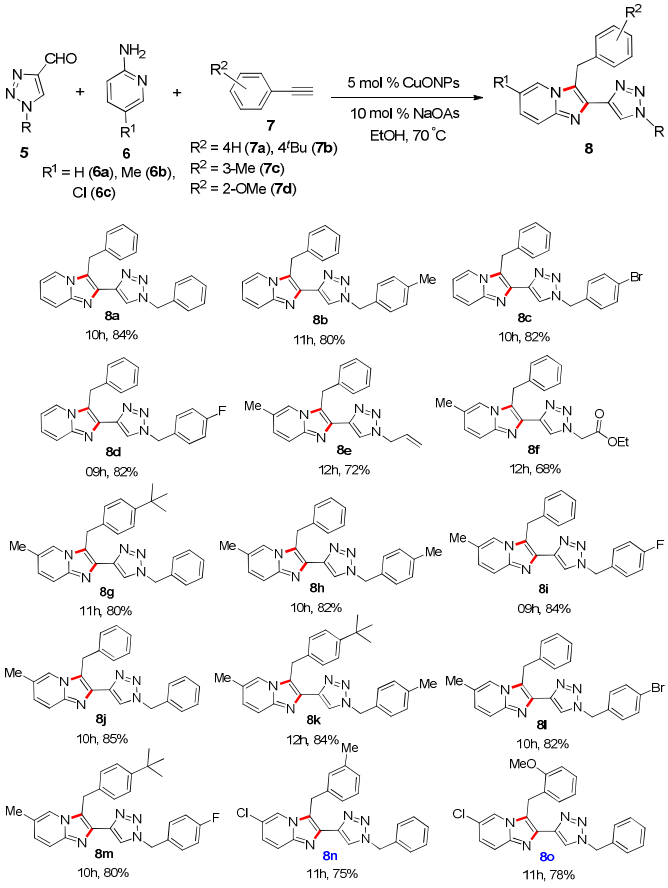
After optimization, we have conducted a reaction with 2-aminopyridine (**6a**), phenylacetylene (**7a**) and with a variety of substituent on triazole-4-carbaldehyde such as 4-methylbenzyl (**5b**), 4-bromobenzyl (**5c**) and 4-fluorobenzyl (**5d**) under similar reaction conditions to obtain the desired product **8b-d** with 80-82% yield. The reaction of 5-methyl-2-aminopyridine (**6b**) and phenylacetylene (**7a**) with allyl (**5e**) and ethoxycarbonylmethyl (**5f**) substituted aliphatic triazole-4-carbaldehyde afford the required product **8e** and **8f** in 72% and 68% yield respectively.

Next, we prompt to investigate the present protocol with 5-methyl-2-aminopyridine (**6b**), 4-*tert* butylphenylacetylene (**7b**) /phenylacetylene (**7a**) and with a variety of substituted triazole-4-carbaldehyde such as benzyl (**5a**), 4-methylbenzyl (**5b**), 4-bromobenzyl (**5c**) and 4-fluorobenzyl (**5d**) derivatives under identical reaction conditions and the desired products **8g-m** were obtained in 80-85% yield. Furthermore, the reaction was performed with benzyl triazole-4-carbaldehyde (**5a**), 5-chloro-2-aminopyridine (**6c**) and with substituted phenylacetylene such as 3-methyl (**7c**) and 2-methoxy (**7d**) under similar reaction conditions afforded the desired product **8n** and **8o** in 75% and 78% yield as shown in Table 3.

Table 3. Synthesis of 2-triazolyl-imidazo[1,2-*a*]pyridine[a,b]



[a]The reactions were performed with 0.5 mmol of 1-alkyl-1,2,3-triazole-4-carbaldehyde (**5**), amidine (**6**) and terminal alkynes (**7**). [b]Isolated yield.

The structure of the compound **8c** was confirmed through single-crystal X-ray analysis which is depicted in Figure 3. The molecule **8c** shows a dimer structure with C-H…π interaction (H17b…C10) and its layered structure embrace a supramolecular assembly which is shown in Figure 4.

In addition, the recyclability of the catalyst was tested with **8c**. The obtained results are displayed in Table 4 and represented graphically in Figure 5. It is found from table 4 that expected 2-triazolyl-imidazo[1,2-*a*]pyridine **8c** was achieved in moderate yield even after five cycles.

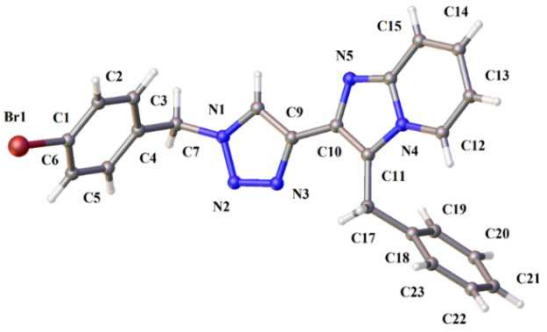
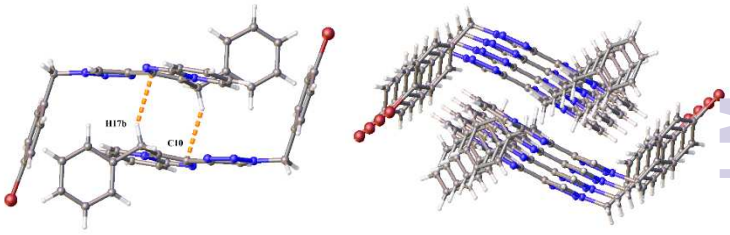


Figure 3. X-ray crystal structure of **8c**



(A) **(B)**

Figure 4. C-H…π interaction (**A**) and Layered structure (**B**) of **8c**

Table 4. Recycle of CuO nanoparticle[a] in **8c**

S. No	No. of. Cycle	mmol	Catalyst Used (mg)	Catalyst Recovered (mg)	Time (h)	Yield (%)
01	01	07	28	25	10	82
02	02	05	20	18	11	78
03	03	04	16	13	12	75
04	04	03	12	09	14	72
05	05	02	08	05	18	68

[a]CuO nanoparticle was filtered from the reaction mixture, washed with ethanol followed by dichloromethane, dried under reduced pressure and reused for next consecutive cycle.

The present protocol was further explored for the synthesis of 2-(2-(1-alkyl-1,2,3-triazol-4-yl)-imidazo[1,2-*a*]pyridin-3-yl) ethanol using propargyl alcohol (**3**), with different substituted triazole-4-carbaldehyde (**5**) and amidine (**6**) in the presence of catalytic amount of copper oxide nanoparticle along with sodium ascorbate under analogues reaction conditions and it offered the corresponding products **9a-e** with 72-78% yield, which is depicted in Table 5.

The plausible mechanism for the formation of 2-triazolyl-imidazo[1,2-*a*]pyridine is outlined in Scheme 3. The copper (II) nanoparticle reduced from sodium ascorbate to copper (I) and thus it react with the incoming alkyne moiety to give the species **I**.[20] The triazolyl aldehyde **5** reacts with amidine **6** to form imine **II**. Then the species **I** reacts with imine **II** which

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leads to **III**. Subsequently, intermediate **III** undergoes favorable *5-exo-dig* cyclisation to form **IV**, which further proceed *via* 1,3-hydrogen shift from **IV** to afford 2-triazolyl-imidazo[1,2-*a*]pyridine **8**.

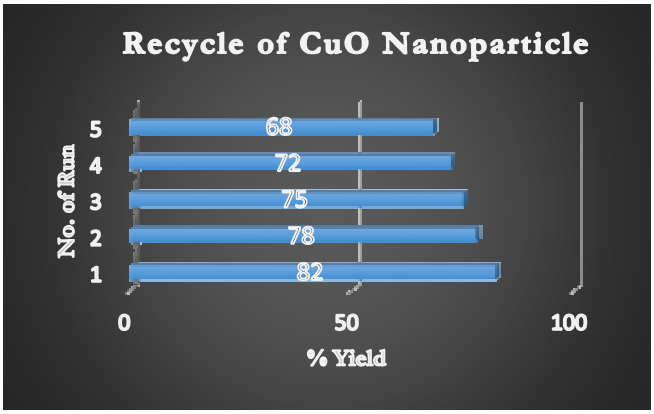
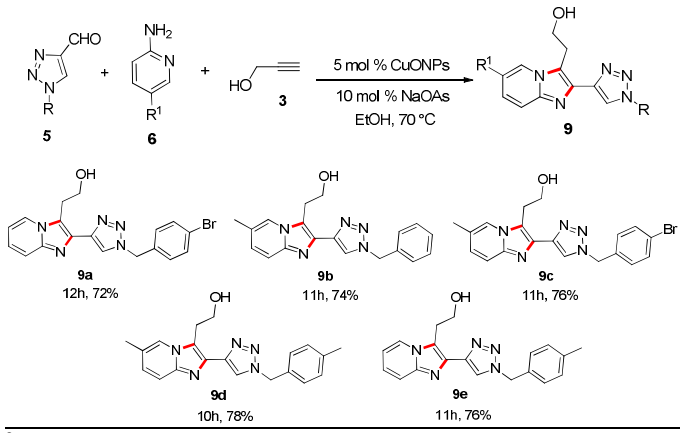
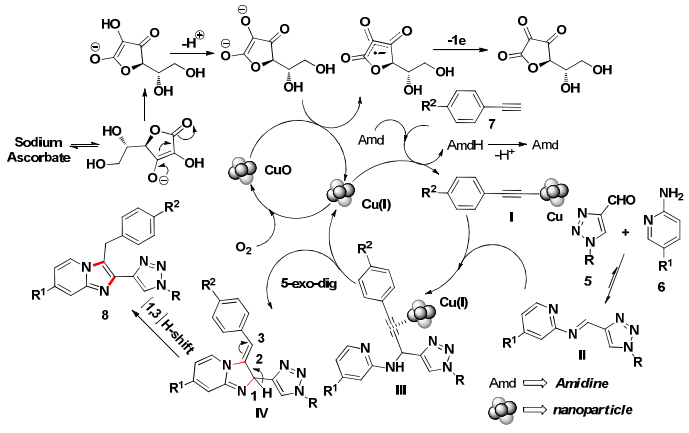


Figure 5. Recycle of catalyst CuO nanoparticle

Table 5. Synthesis of 2-(2-(1-alkyl-1,2,3-triazol-4-yl)-imidazo[1,2-*a*]pyridin-3-yl)ethanol[a,b]



[a]The reactions were carried out in 0.5 mmol scale of 1-alkyl-1,2,3-triazole-4-carbaldehyde (**5**), amidine (**6**) and propargyl alcohol (**3**). [b]Isolated yield.



Scheme 3. Plausible mechanism for the formation of 2-triazolyl-imidazo[1,2-*a*]pyridine

Conclusion

In conclusion, here we described an one-pot three component reaction for the synthesis of 2-triazolyl-imidazo[1,2-*a*]pyridines *via* nano copper oxide catalyzed A^3 coupling of triazolyl aldehyde, amidine and alkyne followed by *5-exo-dig* cyclisation. The decisive aspects of this present protocol are the use of an easy to handle, eco-friendly, recoverable and recyclable catalyst, good yield and wide array of substrate compatibility. Moreover, this is the first reported method for the synthesis of 2-triazolyl-imidazo[1,2-*a*]pyridine by using nano Click-catalyst. We have further explored the protocol for the synthesis of 2-(2-triazolyl-imidazo[1,2-*a*]pyridin-3-yl)ethanol, which may act as a scaffold for the construction of predesigned molecules with promising bioactive applications. In addition, the dimeric and layer structure of **8c** displayed a supramolecular architecture.

General Procedure

I. Synthesis of (1-alkyl-1,2,3-triazol-4-yl)methanol (4) and 1-alkyl-1,2,3-triazole-4-carbaldehyde (5)

Sodium azide (**1**, 10 mmol), alkyl/benzyl bromides (**2**, 10 mmol) and propargylic alcohol (**3**, 10 mmol) was added in 25 mL water followed by catalytic amount of CuO nanoparticle (39.7 mg) and sodium ascorbate (198 mg). Then the reaction mixture was kept for stirring at 70 °C till the completion of reaction as indicated by TLC. The reaction mixture was extracted with DCM (3 x 30 mL), dried over anhydrous sodium sulfate, concentrated *in vacco* and finally purified by silica gel column chromatography to obtain the desired products **4**[21,19c] Subsequently, **4** was dissolved in 25 mL dichloromethane and it was added drop wise to the suspension of PCC in DCM. Then the reaction mixture was stirred at room temperature. After completion of reaction, it was extracted with DCM (3 x 20 mL) and washed with brine solution and the resulting organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then, the crude residue was subjected to silica gel column chromatography and the purified product **5a**[22]**-f** was obtained in good yield.

II. Synthesis of 2-triazolyl-imidazo[1,2-*a*]pyridine (8) and 2-(2-(1-alkyl-1,2,3-triazol-4-yl)-imidazo[1,2-*a*]pyridin-3-yl)ethanol (9)

To a 25mL round bottomed flask were added 1-alkyl-1,2,3-triazole-4-carbaldehyde (**5**, 0.5 mmol), amidine (**6**, 0.5 mmol), CuO nanoparticle (1.99 mg), sodium ascorbate (9.9 mg) and ethanol (2 mL) at room temperature and allow it to stir for 10 min. Later on terminal alkynes (**7**, 0.5 mmol) was added and the resulting mixture was stirred at 70 °C. After completion of reaction as checked by TLC, the reaction mixture was concentrated under reduced pressure. The obtained residue was extracted with DCM (2 x 10 mL) and washed twice with water followed by brine solution and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then the crude residue was purified over a silica gel column chromatography to obtain the pure products of 2-triazolyl-imidazo[1,2-

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a]pyridine **8**. The similar reaction procedure were followed for the synthesis of 2-(2-(1-alkyl-1,2,3-triazol-4-yl)-imidazo[1,2-*a*]pyridin-3-yl)ethanol **9**.

3-benzyl-2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)imidazo[1,2-*a*]pyridine (8a)

Yield 84%, white solid, mp 169-170 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.27 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.76 (br s, 6H), 7.65-7.63 (m, 6H), 5.99 (s, 2H), 5.36 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 145.0, 144.6, 137.3, 134.6, 129.4, 128.9, 128.7, 128.4, 126.8, 125.0, 123.9, 122.1, 120.1, 117.1, 112.7, 54.5, 29.9; IR (KBr)ν_{max} 3139, 3061, 3028, 2923, 2853, 1602, 1536, 1504, 1494, 1454, 1359, 1297, 1225, 1077, 1047 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{20}N_5$ 366.1713 (M + H$^+$); Found 366.1716.

3-benzyl-2-(1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)imidazo[1,2-*a*]pyridine (8b)

Yield 80%, white solid, mp 146-147 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.26-7.22 (m, 6H), 7.19-7.16 (m, 3H), 7.14-7.12 (m, 1H), 6.68 (t, *J* = 6.8 Hz, 1H), 5.54 (s, 2H), 4.93 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 144.8, 138.9, 137.4, 134.7, 131.5, 129.9, 128.8, 128.7, 128.3, 126.7, 124.6, 123.7, 121.7, 119.9, 117.2, 112.3, 54.2, 29.8, 21.3; IR (KBr)ν_{max} 3137, 3053, 3025, 2953, 2923, 2848, 1601, 1516, 1503, 1493, 1453, 1359, 1295, 1219, 1074, 1047 cm^{-1}; HRMS (ESI) Calcd For $C_{24}H_{22}N_5$ 380.1870 (M + H$^+$); Found 380.1870.

3-benzyl-2-(1-(4-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)imidazo[1,2-*a*]pyridine (8c)

Yield 82%, white solid, mp 177-178 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.28-7.21 (m, 7H), 6.89 (t, *J* = 7.2 Hz, 1H), 5.56 (s, 2H), 4.96 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 145.1, 144.9, 137.3, 134.4, 133.7, 132.4, 130.1, 128.9, 128.3, 126.8, 124.8, 123.8, 123.1, 121.9, 120.1, 117.2, 112.5, 53.7, 29.8; IR (KBr)ν_{max} 3142, 3052, 3020, 2948, 2923, 2853, 1601, 1503, 1490, 1453, 1358, 1296, 1225, 1071, 1047 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{19}BrN_5$ 444.0819 (M + H$^+$); Found 444.0815.

3-benzyl-2-(1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)imidazo[1,2-*a*]pyridine (8d)

Yield 82%, white solid, mp 111-112 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.80 (d, *J* = 6.0 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.35 (br s, 2H), 7.27-7.23 (m, 5H), 7.18-7.14 (m, 1H), 7.08 (t, *J* = 8.4 Hz, 2H), 6.71 (br s, 1H), 5.57 (s, 2H), 4.93 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.9, 162.2, 145.0, 144.4, 137.2, 134.0, 130.6, 130.4, 130.3, 129.6, 128.9, 128.4, 128.3, 126.8, 125.1, 123.8, 122.2, 120.1, 117.0, 116.3, 116.2, 112.7, 53.6, 29.8; IR (KBr)ν_{max} 3138, 3064, 3028, 2956, 2924, 2853, 1603, 1511, 1494, 1454, 1359, 1296, 1224, 1073, 1048 cm^{-1}; HRMS (ESI) Calcd For $C_{23}H_{19}FN_5$ 384.1619 (M + H$^+$); Found 384.1618.

2-(1-allyl-1*H*-1,2,3-triazol-4-yl)-3-benzyl-6-methylimidazo[1,2-*a*]pyridine (8e)

Yield 72%, white solid, mp 191-192 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.58 (s, 2H), 7.19-7.12 (m, 6H), 6.03-5.98 (m, 1H), 5.34 (s, 1H), 5.30 (d, *J* = 9.2 Hz, 1H), 4.99 (d, *J* = 4.0 Hz, 2H), 4.86 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.1, 143.7, 137.3, 133.6, 131.2, 128.8, 128.5, 128.3, 126.7, 122.6, 122.1, 121.5, 120.6, 119.8, 116.3, 52.9, 29.7, 18.5; IR (KBr)ν_{max} 3142, 3070, 2962, 2920, 2848, 1598, 1536, 1511, 1491, 1451, 1412, 1366, 1327, 1295, 1222, 1047 cm^{-1}; HRMS (ESI) Calcd For $C_{20}H_{20}N_5$ 330.1713 (M + H$^+$); Found 330.1724.

Ethyl 2-(4-(3-benzyl-6-methylimidazo[1,2-*a*]pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)acetate (8f)

Yield 68%, white solid, mp 109-110 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.58 (s, 1H), 7.58 (d, *J* = 9.2 Hz, 1H), 7.25-7.23 (m, 4H), 7.20-7.18 (m, 1H), 7.03 (d, *J* = 9.2 Hz, 1H), 5.21 (s, 2H), 4.88 (s, 2H), 4.27 (q, *J* = 6.8 Hz, 2H), 2.24 (s, 3H), 1.29 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.3, 144.5, 142.8, 137.4, 133.7, 128.9, 128.4, 128.3, 126.8, 123.5, 122.5, 121.5, 119.9, 116.4, 62.6, 51.2, 29.9, 18.6, 14.3; IR (KBr)ν_{max} 3142, 2978, 2959, 2925, 2854, 1749, 1613, 1539, 1495, 1454, 1376, 1344, 1299, 1262, 1217, 1023 cm^{-1}; HRMS (ESI) Calcd For $C_{21}H_{22}N_5O_2$ 376.1768 (M + H$^+$); Found 376.1796.

2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-3-(4-(tert-butyl)benzyl)-6-methylimidazo[1,2-*a*]pyridine (8g)

Yield 80%, white solid, mp 241-242 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.63 (s, 1H), 7.49 (d, *J* = 9.2 Hz, 1H), 7.38-7.36 (m, 5H), 7.27-7.23 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 9.2 Hz, 1H), 5.58 (s, 2H), 4.85 (s, 2H), 2.26 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 144.9, 144.0, 134.6, 134.4, 129.2, 128.9, 128.6, 127.9, 127.8, 125.7, 122.0, 121.7, 121.4, 119.9, 116.4, 54.4, 34.5, 31.5, 29.1, 18.5; IR (KBr)ν_{max} 3143, 3089, 3064, 2957, 2920, 2866, 1596, 1537, 1511, 1496, 1366, 1341, 1299, 1229, 1047 cm^{-1}; HRMS (ESI) Calcd For $C_{28}H_{30}N_5$ 436.2496 (M + H$^+$); Found 436.2496.

3-benzyl-6-methyl-2-(1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)imidazo[1,2-*a*]pyridine (8h)

Yield 82%, white solid, mp 222-223 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.57 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.26-7.19 (m, 9H), 6.99 (d, *J* = 8.0 Hz, 1H), 5.53 (s, 2H), 4.89 (s, 2H), 2.35 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 138.8, 137.5, 134.5, 131.5, 129.9, 128.7, 128.6, 128.3, 127.7, 126.6, 121.9, 121.6, 121.3, 116.5, 54.2, 29.7, 21.3, 18.5; IR (KBr)ν_{max} 3133, 3065, 3022, 2921, 2853, 1602, 1536, 1514, 1494, 1452, 1344, 1298, 1230, 1047 cm^{-1}; HRMS (ESI) Calcd For $C_{25}H_{24}N_5$ 394.2026 (M + H$^+$); Found 394.2030.

3-benzyl-2-(1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)-6-methylimidazo[1,2-*a*]pyridine (8i)

Yield 84%, white solid, mp 203-204 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 2H), 7.31-7.28 (m, 2H), 7.22-7.14 (m, 7H), 7.00 (t, *J* = 8.8 Hz, 2H), 5.51 (s, 2H), 4.87 (s, 2H), 2.22 (s, 3H);

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^{13}C NMR (150 MHz, $CDCl_3$): δ 163.9, 162.3, 144.1, 143.4, 137.1, 133.2, 130.5, 130.4, 128.9, 128.6, 128.3, 127.9, 126.8, 125.8, 122.9, 122.2, 121.6, 119.9, 116.3, 116.2, 116.1, 53.7, 29.8, 18.5; IR (KBr)ν_{max} 3131, 3062, 3025, 2951, 2919, 2845, 1602, 1537, 1511, 1494, 1453, 1343, 1296, 1227, 1065, 1046 cm^{-1}; HRMS (ESI) Calcd For $C_{24}H_{21}FN_5$ 398.1776 (M + H$^+$); Found 398.1776.

3-benzyl-2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-6-methylimidazo [1,2-*a*]pyridine (8j)

Yield 85%, white solid, mp 242-243 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.57 (s, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.37-7.36 (m, 5H), 7.25-7.23 (m, 4H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.99 (s, *J* = 8.8 Hz, 1H), 5.58 (s, 2H), 4.89 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 145.0, 144.3, 137.6, 134.6, 129.3, 128.9, 128.8, 128.6, 128.4, 127.8, 126.6, 122.1, 121.7, 121.4, 119.7, 116.6, 54.5, 29.8, 18.6; IR (KBr)ν_{max} 3145, 3084, 3062, 3028, 2984, 2915, 2835, 1604, 1538, 1513, 1493, 1454, 1343, 1295, 1209, 1047 cm^{-1}; HRMS (ESI) Calcd For $C_{24}H_{22}N_5$ 380.1870 (M + H$^+$); Found 380.1871.

3-(4-(tert-butyl)benzyl)-6-methyl-2-(1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)imidazo[1,2-*a*] pyridine (8k)

Yield 84%, white solid, mp 189-190 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.62 (s, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 7.27-7.23 (m, 4H), 7.18-7.14 (m, 4H), 7.01 (d, *J* = 9.2 Hz, 1H), 5.52 (s, 2H), 4.84 (s, 2H), 2.39 (s, 3H), 2.25 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 144.7, 143.9, 138.8, 134.4, 131.6, 129.9, 128.7, 127.9, 125.7, 122.1, 121.8, 121.4, 119.9, 116.4, 54.2, 34.5, 31.5, 31.3, 29.1, 21.3, 18.6; IR (KBr)ν_{max} 3139, 3051, 3026, 2962, 2923, 2866, 1616, 1539, 1515, 1454, 1365, 1342, 1301, 1231, 1047 cm^{-1}; HRMS (ESI) Calcd For $C_{29}H_{32}N_5$ 450.2652 (M + H$^+$); Found 450.2652.

3-benzyl-2-(1-(4-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)-6-methylimidazo[1,2-*a*]pyridine (8l)

Yield 82%, white solid, mp 179-180 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.54 (s, 1H), 7.48 (d, *J* = 9.6 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.21-7.13 (m, 7H), 7.03 (d, *J* = 8.8 Hz, 1H), 5.48 (s, 2H), 4.83 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.6, 143.9, 137.4, 133.7, 132.5, 130.2, 128.9, 128.4, 128.3, 126.7, 123.1, 122.5, 122.1, 121.4, 119.9, 116.4, 53.7, 29.9, 18.6; IR (KBr)ν_{max} 3142, 3059, 3025, 2951, 2924, 2853, 1602, 1540, 1512, 1489, 1453, 1342, 1298, 1230, 1046 cm^{-1}; HRMS (ESI) Calcd For $C_{24}H_{21}BrN_5$ 458.0975 (M + H$^+$); Found 458.0979.

3-(4-(tert-butyl)benzyl)-2-(1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)-6-methylimidazo[1,2-*a*] pyridine (8m)

Yield 80%, white solid, mp 201-202 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.64 (s, 1H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.35-7.33 (m, 2H), 7.27-7.25 (m, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.06 (t, *J* = 8.4 Hz, 3H), 5.55 (s, 2H), 4.85 (s, 2H), 2.26 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 161.9, 149.6, 144.3, 143.6, 134.1, 133.3, 130.5, 130.4, 128.7, 127.9, 125.8, 122.7, 122.1, 121.6, 120.1, 116.4, 116.2, 53.7, 34.6, 31.5, 29.9, 18.6; IR (KBr)ν_{max} 3053, 2962, 2920, 2867, 1606, 1545, 1516, 1454, 1420, 1364, 1298, 1225, 1159, 1048 cm^{-1}; HRMS (ESI) Calcd For $C_{28}H_{29}FN_5$ 454.2402 (M + H$^+$); Found 454.2402.

2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-6-chloro-3-(3-methyl benzyl)imidazo[1,2-a]pyridine (8n)

Yield 75%, white solid, mp 199-200 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.83 (s, 1H), 7.48 (d, *J* = 9.6 Hz, 1H), 7.39-7.35 (m, 5H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.11(d, *J* = 9.6 Hz, 1H), 7.02-6.99 (m, 3H), 5.59 (s, 2H), 4.86 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.6, 143.6, 138.7, 136.7, 135.8, 134.5, 129.4, 129.1, 128.9, 128.7, 127.8, 126.0, 125.4, 122.0, 121.7, 120.8, 120.7, 117.6, 54.6, 29.8, 21.6; IR (KBr)ν_{max} 3047, 2984, 2882, 2801, 1612, 1538, 1512, 1471, 1430, 1338, 1312, 1247, 1166, 1064 cm^{-1}; HRMS (ESI) Calcd For $C_{24}H_{21}ClN_5$ 414.1480 (M + H$^+$); Found 414.1486.

2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-6-chloro-3-(2-methoxy benzyl)imidazo[1,2-a]pyridine (8o)

Yield 78%, white solid, mp 203-204 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 (s, 1H), 8.01 (s, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.40-7.35 (m, 5H), 7.18-7.16 (m, 2H), 7.09 (d, *J* = 9.6 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.77 (t, *J* = 7.2 Hz, 1H), 5.58 (s, 2H), 4.84 (s, 2H), 3.95 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 156.9, 144.7, 143.3, 135.5, 134.6, 130.2, 129.4, 129.0, 128.7, 128.1, 125.8, 125.4, 122.6, 121.9, 121.7, 121.2, 120.4, 117.4, 110.6, 55.5, 54.6, 29.9; IR (KBr)ν_{max} 3042, 2978, 2915, 2890, 2812, 1608, 1539, 1515, 1498, 1471, 1335, 1313, 1229, 1078, 1061 cm^{-1}; HRMS (ESI) Calcd For $C_{24}H_{21}ClN_5O$ 430.1429 (M + H$^+$); Found 430.1437.

2-(2-(1-(4-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)imidazo[1,2-*a*]pyridin-3-yl)ethanol (9a)

Yield 72%, yellow solid, mp 199-200 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 6.4 Hz, 1H), 8.01 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 8.8 Hz, 1H), 6.83 (t, *J* = 6.4 Hz, 1H), 5.53 (s, 2H), 4.09 (d, *J* = 5.6 Hz, 2H), 3.60 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 144.8, 134.4, 133.5, 132.5, 130.2, 124.6, 123.6, 123.3, 121.8, 119.7, 117.4, 112.5, 61.5, 53.9, 27.1; IR (KBr)ν_{max}3126, 3051, 2923, 2850, 1591, 1503, 1489, 1432, 1407, 1359, 1298, 1226, 1070, 1045 cm^{-1}; HRMS (ESI) Calcd For $C_{18}H_{17}BrN_5O$ 398.0611 (M + H$^+$); Found 398.0611.

2-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)ethanol (9b)

Yield 74%, yellow solid, mp 119-120 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.82 (s, 1H), 7.41-7.35 (m, 6H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.56 (s, 2H), 4.06 (br s, 2H), 3.57 (br s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 134.4, 129.4, 129.1, 128.6, 127.7, 122.2, 121.7, 121.1, 116.7, 61.4, 54.6, 27.1, 18.6; IR (KBr)ν_{max} 3145, 3062, 3028, 2923, 2855, 1587, 1540, 1512, 1497, 1455, 1366, 1345, 1303, 1230, 1124, 1046 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{20}N_5O$ 334.1663 (M + H$^+$); Found 334.1664.

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2-(2-(1-(4-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)-6-methyl imidazo[1,2-*a*]pyridin-3-yl)ethanol (9c)

Yield 76%, yellow solid, mp 207-208 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.83 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 9.6 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 9.6 Hz, 1H), 5.23 (s, 2H), 4.06 (s, 2H), 3.57 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 144.2, 134.2, 133.5, 132.5, 130.2, 127.8, 123.3, 122.3, 121.7, 121.2, 119.2, 116.7, 110.2, 61.4, 53.9, 27.1, 18.6; IR (KBr)ν_{max} 3144, 3056, 2959, 2923, 2850, 1589, 1488, 1451, 1407, 1341, 1304, 1229, 1069, 1046 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{19}BrN_5O$ 412.0768 (M + H$^+$); Found 412.0766.

2-(6-methyl-2-(1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)imi dazo[1,2-*a*]pyridin-3-yl)ethanol (9d)

Yield 78%, yellow solid, mp 214-215 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.82 (s, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.26-7.22 (m, 2H), 7.19-7.17 (m, 2H), 7.02 (d, *J* = 8.8 Hz, 1H), 5.52 (s, 2H), 4.06 (br s, 2H), 3.57 (br s, 2H), 2.35 (br s 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.3, 138.5, 133.9, 131.3, 129.6, 128.3, 127.4, 121.7, 121.3, 116.2, 60.9, 53.9, 26.5, 21.1, 18.2; IR (KBr)ν_{max} 3141, 3051, 2953, 2922, 2845, 1601, 1553, 1539, 1500, 1456, 1363, 1297, 1215, 1121, 1048 cm^{-1}; HRMS (ESI) Calcd For $C_{20}H_{22}N_5O$ 348.1819 (M + H$^+$); Found 348.1827.

2-(2-(1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)imidazo[1,2-*a*]pyridin-3-yl)ethanol (9e)

Yield 76%, yellow solid, mp 148-149 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.01 (m, 2H), 7.50 (br s, 1H), 7.27-7.17 (m, 5H), 6.81 (br s, 1H), 5.52 (s, 2H), 4.07 (s, 2H), 3.59 (s, 2H), 3.11 (br s, 1H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 141.1, 139.0, 138.9, 134.4, 131.4, 129.9, 128.7, 128.4, 124.7, 123.7, 122.1, 117.4, 112.6, 61.4, 54.4, 27.1, 21.3; IR (KBr)ν_{max} 3148, 3054, 2958, 2929, 2851, 1598, 1551, 1541, 1489, 1448, 1366, 1302, 1216, 1115, 1046 cm^{-1}; HRMS (ESI) Calcd For $C_{19}H_{20}N_5O$ 334.1663 (M + H$^+$); Found 334.1664.

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†Complete crystallographic data of **4f** and **8c** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, **4f** (CCDC no. 979591) and **8c** (CCDC no. 1019691) respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk.Electronic Supplementary Information (ESI) available: [Spectral data (^{1}H and ^{13}C NMR copies) of all the synthesized compounds]. See DOI: 10.1039/b000000x/

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Graphical Abstract

Synthesis of 2-triazolyl-imidazo[1,2-*a*]pyridine through one-pot three-component reaction using nano copper oxide assisted click-catalyst

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