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PAPER

Cu-Mn spinel oxide catalyzed synthesis of imidazo[1,2-a]pyridines through domino three-component coupling and 5-exo-dig cyclization in water[#¤]

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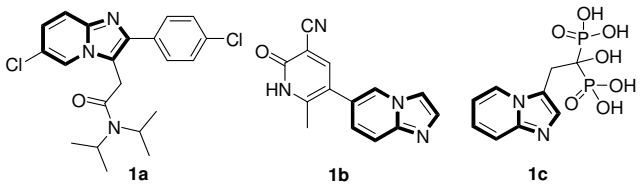
An efficient and eco-friendly synthesis of therapeutically important and structurally diverse imidazo[1,2-a]pyridines using recyclable bimetallic Cu-Mn spinel oxide catalyst in aqueous medium have been developed. The Cu-Mn catalyzed domino three-component coupling of 2-aminopyridine, aldehyde and alkyne followed by 5-*exo-dig* cycloisomerization produced desired imidazo[1,2-a]pyridines in good yields. The efficiency of this protocol could be attributed to the presence of these metals in multiple oxidation states (Cu^{+2}, Mn^{+2}, Mn^{+3} and Mn^{+4}) in bimetallic Cu-Mn catalyst. The advantages of this protocol over previous reports include the use of aqueous medium, recyclable catalyst, shorter reaction times and no requirement of any additive. This is the first method for synthesis of imidazo[1,2-a]pyridines which utilizes water as a reaction medium.

Introduction

Imidazo[1,2-a]pyridine[1] scaffold represents an important class of biologically active compounds[1] and is a core structure of several drug molecules such as zolpidem (anxiolytic, **1a**), olprinone (cardiotonic, **1b**) and minodronic acid (for osteoporosis, **1c**) etc. (Figure 1).



1a **1b** **1c**

Figure 1. Examples of imidazo[1,2-a]pyridine containing drugs

Due to biological importance of this scaffold, several methods have been developed for their synthesis,[2] many of which are elegant multi-component approaches.[2b, 2h-q] A three-component coupling (3CC) of 2-aminopyridine, aldehyde and alkyne in presence of metal catalyst and/or additive is one of the most attractive method for synthesis of imidazo[1,2-a]pyridine scaffold.[2h-m] Various catalysts employed for this 3CC protocol include CuI/$NaHSO_4$-Silica,[2h] CuCl/$Cu(OTf)_2$,[2i] $CuSO_4$/TsOH,[2j] $InBr_3$/Et_3N,[2k] Cu-MOFs,[2l] and $CuSO_4$/glucose.[2m] In addition, Liu and coworkers[3] reported synthesis of imidazo[1,2-a]pyridines *via* tandem amination/cycloisomerization of aryl propargylic alcohols with 2-aminopyridines using $ZnCl_2$/CuCl catalytic system. These methods suffers from one or other drawbacks such as use of homogeneous catalysts, requirement of anhydrous conditions, and need of additive (such as TsOH,[2j] Et_3N,[2k] and glucose[2m]) in addition to the metal catalyst. The only report on heterogeneous catalyst for this 3CC is the use of Cu-MOFs, however this protocol[2l] requires the use of anhydrous toluene as a reaction medium and furthermore the substrate scope has not been explored. Thus, the development of a hazard-free, waste-free, energy-efficient green protocol is highly desirable for an economical synthesis of this class of compounds.

In recent years, bimetallic catalysts have been extensively used as efficient recyclable catalysts for various organic transformations such as bimetallic Mg-Fe for synthesis of α-hydroxyphosphonates,[2a] Ir-Pd for alkylation of 1,3-dimethylbarbituric acids,[4] Cu-Ni and Cu-Co catalysts for selective hydrogenation of furfuraldehyde,[5] Cu-Mn for regioselective halogenation of phenols,[5] selective *ortho*-methylation of phenols,[6] and ligand-free Huisgen [3+2] cycloaddition reaction.[4] In continuation to our efforts towards development of efficient synthetic methodologies for preparation of biologically important scaffolds,[6-7] herein we report recyclable

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Cu-Mn spinel oxide catalyzed synthesis of imidazo[1,2-a]pyridines under aqueous conditions (Figure 2). Although there exists numerous Cu-catalyzed methods for this 3CC, all these methods requires dry solvents and an additive. The advantages of this protocol include the use of water as a reaction medium, no need of additive, recyclable catalyst, shorter reaction times and good yields.

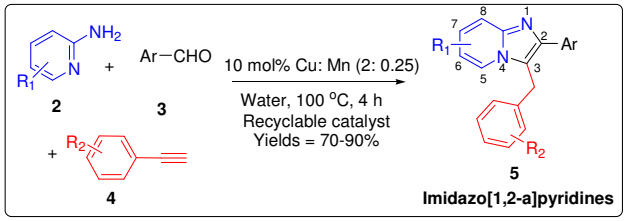


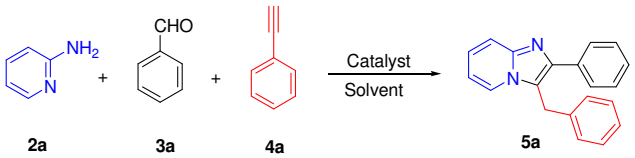
Figure 2. Synthesis of imidazo[1,2-a]pyridines using recyclable Cu-Mn bimetallic catalyst in water

Results and discussion

To develop an efficient green protocol for synthesis of imidazo[1,2-a]pyridines, various Cu-based heterogeneous catalysts were investigated. The reaction between 2-aminopyridine (**2a**), benzaldehyde (**3a**) and phenyl acetylene (**4a**) was used as a model reaction (Table 1). The catalyst screening was started with the Clay supported Cu(II),[6] which did not produced desired product (entries 1 and 2). Next, we screened various bimetallic Cu-Mn catalysts varying in the composition (Cu-Mn **A**: Cu: Mn = 2: 0.25; Cu-Mn **B**: Cu: Mn = 1: 0.25; and Cu-Mn **C**: Cu: Mn = 3: 0.25) using ethanol as a reaction medium. Among these three Cu-Mn catalysts, Cu: Mn **A** catalyst produced imidazo[1,2-a]pyridine **5a** only in <10% yield (entry 3), however Cu-Mn **B** and Cu: Mn **C** catalysts produced **5a** in 82 and 50% yields, respectively (entries 4 and 5). Addition of additive to the reaction medium (e.g. reducing agent) led to decrease in the reaction yield (entry 6). The solvent optimization studies (entries 7-10) identified water as the best solvent producing higher yields (entry 8). Increase in the catalyst leading from 10 to 100 mol% (entries 8, 11-13) led to increase in the yield, however 10 mol% loading was found to be efficient (entry 8) producing 85% yield of the product.

As a control experiment, the catalytic activity of $CuCl_2$ and $MnCl_2$ salts (entries 14-19) was also investigated using optimized protocol. Reaction moved only with $CuCl_2$ (30% yield; entry 14) and not with $MnCl_2$ (entry 15). Further, when $CuCl_2$ (10 mol%) and $MnCl_2$ (10 mol%) were used together for this 3CC, there was no significant improvement in the yield of **5a** (entries 17-18). These results clearly indicated the significance of combining Cu and Mn metals in the form of bimetallic heterogeneous Cu-Mn spinel oxide. Next, we tested $CuCl/Cu(OTf)_2$[2i] for this 3CC. As reported earlier,[2i] it produced **5a** in good yield when toluene was used as a solvent (entry 20). When $CuCl/Cu(OTf)_2$ catalyzed 3CC was carried out in water, product **5a** was still formed, but only in 55% yield. Thus, after numerous optimization experiments, we chose 10 mol% of Cu-Mn – B in water (entry 8, Table 1) as a optimized reaction condition for further studies.

Table 1. Optimization of reaction conditions for synthesis of imidazo[1,2-a]pyridines.



Entry	Catalyst[a] (mol%)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	Clay-Cu(II) (10)	EtOH	80	4	0
2	Clay-Cu(II)(10) + NaN_3 (20)	EtOH	80	4	0
3	Cu-Mn – A (10)	EtOH	80	4	<10
4	Cu-Mn – B (10)	EtOH	80	4	82
5	Cu-Mn – C (10)	EtOH	80	4	50
6	Cu-Mn – B (10) + glucose (20)	EtOH	80	4	55
7	Cu-Mn – B (10)	ACN	90	6	70
8	Cu-Mn – B (10)	Water	100	4	85
9	Cu-Mn – B (10)	EtOH: Water (1:1)	90	4	82
10	Cu-Mn – B (10)	ACN: Water (1:1)	90	4	74
11	Cu-Mn – B (20)	Water	100	4	82
12	Cu-Mn – B (50)	Water	100	4	85
13	Cu-Mn – B (100)	Water	100	4	90
14	$CuCl_2$ (10)	Water	100	4	30
15	$MnCl_2$ (10)	Water	100	4	0
16	$CuCl_2$ (10)	Water	100	10	30
17	$CuCl_2$ (10)+$MnCl_2$(10)	EtOH	90	12	35
18	$CuCl_2$(10)+$MnCl_2$ (10)	Water	100	12	38
19	$CuCl/ Cu(OTf)_2$	water	100	4	55
20	$CuCl/ Cu(OTf)_2$	toluene	100	4	78

[a] Cu-Mn catalysts A-C vary in their composition. **A**: Cu: Mn = 2: 0.25; **B**: Cu: Mn = 1: 0.25; **C**: Cu: Mn = 3: 0.25.
[b] Isolated yield after silica gel column chromatography.

Next, we studied the scope of this MCR protocol for various substituted aminopyridines, benzaldehydes and phenyl acetylenes. The 2-aminopyridine (**2a**) and EWG or EDG substituted 2-aminopyridines participated well in this reaction as depicted in Figure 3, 4 and 5, respectively. The 2-aminopyridine (**2a**) on treatment with various aldehydes and phenyl acetylenes produced corresponding imidazo[1,2-a]pyridines **5a-j** in 72-85% yields (Figure 3). The 2-aminopyridine substituted with EWG (such as halogens) or EDG (such as methyl) produced corresponding products **5k-t** and **5u-w** in 76-90% and 70-83% yields, respectively (Figure 4 and 5). Similarly, benzaldehydes with both EWGs (e.g. Cl, F) as well as EDGs (e.g. OMe) participated in this MCR protocol. The heterocyclic aldehydes produced desired products in good yields (e.g. **5c, 5p, 5v** and **5w**). Notably, the sterically hindered substrates such as 2-chlorobenzaldehyde (examples **5b** and **5w**) also participated effectively in this 3CC to afford respective products. The phenyl acetylene as well as substituted phenyl acetylenes produced corresponding imidazo[1,2-a]pyridines in good yields. Notably the sterically hindered phenyl acetylene viz. 2-chloro-phenyl acetylene also participated well in this 3CC producing corresponding product **5j** in 75% yield.

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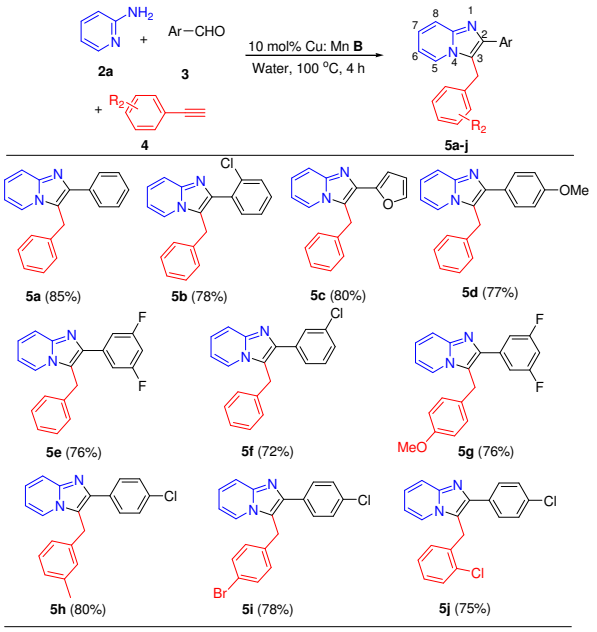

Figure 3. Substrate scope for 3CC of 2-aminopyridine (**2a**) with various aldehydes and phenyl acetylenes

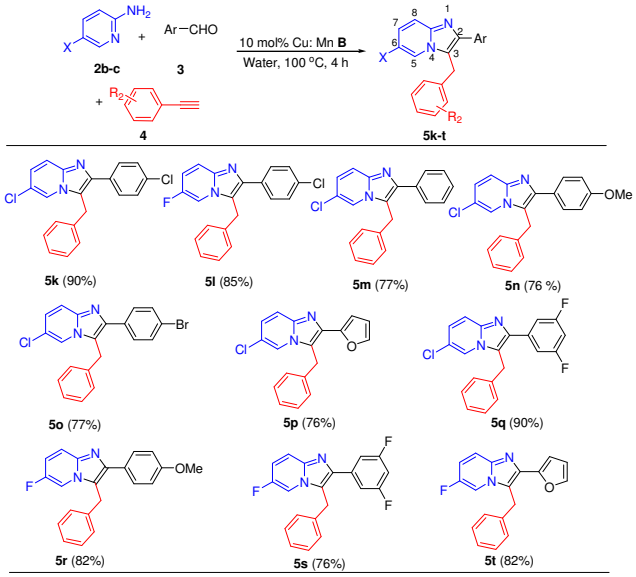

Figure 4. Substrate scope for 3CC of 5-halo substituted 2-aminopyridines **2b-c** with various aldehydes and phenyl acetylenes

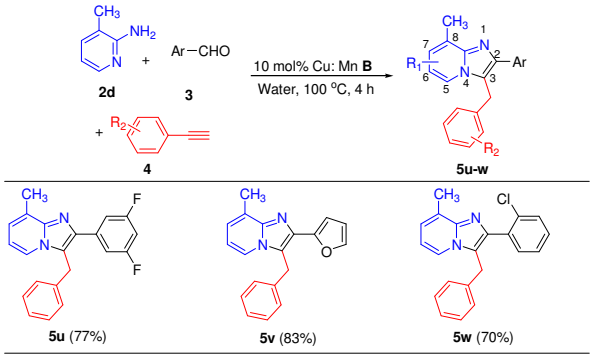

Figure 5. Substrate scope for 3CC of 3-methyl 2-aminopyridine (**2d**) with various aldehydes and phenyl acetylenes

The recyclability of Cu-Mn **B** catalyst was checked to prove the heterogeneous nature and its repeated use. The reaction of 2-aminopyridine (**2a**), benzaldehyde (**3a**) and phenylacetylene (**4a**) in water in presence of 10 mol% Cu-Mn **B** led to the formation of 3-benzyl-2-phenyl-imidazo[1,2-a]pyridine (**5a**) in 85, 80, 78, 76% yield over four cycles respectively. In this recyclability study, catalyst was recovered by filtration after each experiment. The SEM image of the used bimetallic catalyst showed similar morphology and the structural integrity after 4th run, which clearly indicated that the Cu-Mn catalyst is robust, recyclable and was not affected under the reaction conditions of this MCR protocol. The % of catalyst receovered after each run and % yield of the product is depicted in the Figure 6.

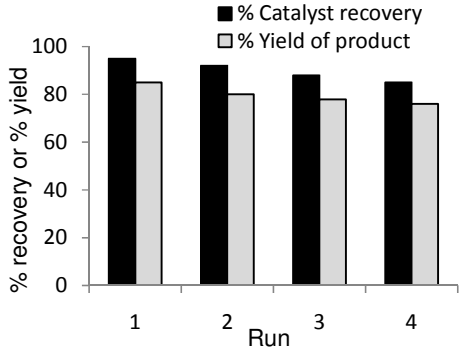

Figure 6. Recyclability results of Cu-Mn **B** catalyst for synthesis of 3-benzyl-2-phenyl-imidazo[1,2-a]pyridine (**5a**). The 100 mg of catalyst was used for first experiment. In each cycle, 10 mol% of catalyst was used.

In order to understand the efficiency and catalytic activity as a function of catalyst composition, physical nature and surface acidity, the Cu-Mn catalysts were characterized for specific surface area, X-ray diffraction pattern, oxidation state (using XPS analysis) and scanning electron microscopy (SEM) analysis. Among the three Cu–Mn spinel oxide catalysts (**A–C**) with varying amount of copper, the best conversion was observed in Cu-Mn spinel oxide (**B**). XRD studies of all three Cu-Mn catalysts indicated that Cu–Mn spinel oxide **B** shows the presence of distinct Mn–Cu phases with comparatively less intensity of tenorite. The presence of distinct Mn–Cu phases in the form of near spherical nanoparticles and comparatively larger surface area (49.79 m^2/g) of Cu–Mn spinel oxide (**B**) might be responsible for enhanced yield. The oxidation states of both metals in Cu-Mn catalyst B was determined by XPS analysis. Figure 7a shows the high resolution narrow scans of Mn 2p for Cu-Mn catalyst B. The observed spin-orbit splitting between the two main peak positions of Mn – Mn $2p_{3/2}$ and $Mn2p_{1/2}$ could be deconvoluted into three peaks each and the distance between them was ~ 12 eV.[8] The observed binding energy peaks are broad and asymmetric, which suggests the coexistence of Mn in multivalent states as Mn^{2+}, Mn^{3+} and Mn^{4+} ions. The asymmetric index β value was found to be 1.36, which is the evidence for the multiplet splitting of the Mn 2p level.[9] Figure 7b shows the high resolution narrow scans of Cu 2p for Cu-Mn catalyst B. The observed binding energy peaks at ~ 934 eV and ~ 955 eV are due to Cu $2p_{3/2}$ and Cu $2p_{1/2}$, respectively and can be attributed to Cu in +2 oxidation state. Thus, the XPS analysis indicated that the Cu exists in Cu^{2+} oxidation state and Mn in the multi-states (Mn^{2+}, Mn^{3+} and Mn^{4+}). Thus, the improved efficiency of Cu and Mn metals when combined in the form of bimetallic catalyst, over individual metals (Table 1, entries 14-18) could be attributed to the existence of these metals in multiple oxidation states (Cu^{+2}, Mn^{+2}, Mn^{+3} and Mn^{+4}) in bimetallic Cu-Mn catalyst. The possible

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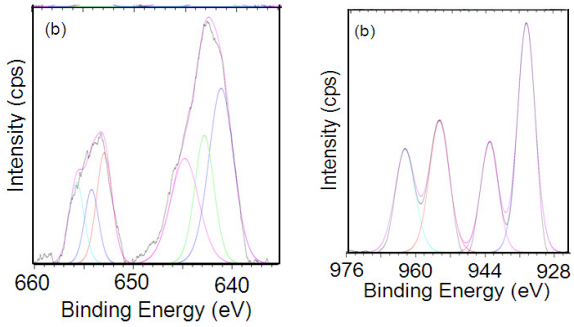
mechanism for Cu-Mn catalyzed domino three-component coupling and 5-*exo-dig* cyclization is depicted in section S4 of ESI.



(a) (b)

Figure 7. High resolution narrow X-ray photoelectron spectra (XPS) for Cu-Mn catalyst B

All imidazo[1,2-a]pyridines were screened for anti-proliferative activity against a panel of cancer cell lines. Among tested analogs, compounds **5e**, **5n** and **5r** showed moderate cytotoxicity towards MIAPaCa-2, PC-3, HL-60 and A549 cell lines (20-38% growth inhibition at 10 μM; see section S3 of ESI).

Conclusion

In summary, we have developed simple and efficient Cu-Mn catalyzed green protocol for synthesis of structurally diverse medicinally important imidazo[1,2-a]pyridines. This protocol is superior to all known protocols as it involves the use of recyclable catalyst and water as a reaction medium and does not require any additive. Thus, the developed method finds wide utility in economical and environment-friendly synthesis of this class of compounds.

Experimental section

General information. All chemicals were obtained from Sigma-Aldrich Company and used as received. ^{1}H, ^{13}C and DEPT NMR spectra were recorded on Brucker-Avance DPX FT-NMR 500 and 400 MHz instruments. Chemical data for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$, 7.26 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz or 100 MHz: chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from referenced to the carbon resonance of the solvent ($CDCl_3$, 77 ppm). ESI-MS and HRMS spectra were recorded on Agilent 1100 LC-Q-TOF and HRMS-6540-UHD machines. IR spectra were recorded on Perkin-Elmer IR spectrophotometer. Melting points were recorded on digital melting point apparatus. XRD spectra and Scanning electron micrograph were obtained on XRD Mini-Flex Rigaku Model and Jeol.JEM100C-XII electron microscope respectively. XPS analysis was performed on a KRATOS-AXIS 165 instrument.

General procedure for synthesis of imidazo[1,2-a]pyridines 5a-w: The mixture of 2-aminopyridine (**2**, 1 mmol) and benzaldehyde (**3**, 1 mmol) was stirred for 15 min. Water (3 mL) was added, followed by addition of phenyl acetylene (**4**, 1.5 mmol). Then, Cu-Mn catalyst (10 mol %) were added, and resulting mixture was refluxed at 100 °C for 4 h. Completion of the reaction was monitored by TLC. Reaction mixture was filtered through Whatman filter paper, residue washed with water (25 mL x 3). The product was extracted from the aqueous filtrate with methylene chloride. Combined organic layers were concentrated on vacuo rotavapor to get crude product, which was purified by column chromatography on neutral alumina (100–300 mesh) using EtOAc/hexane as mobile phase, to get products **5a-w** in 70-90% yield. Compounds **5a**,[2j, 2m] **5b**,[3] **5c**,[2k] **5d**,[3] **5f**,[2k] **5k**[2m] and **5m**[2m] were characterized by comparison of their spectral data with literature values. Spectral data for all compounds is provided below.

3-Benzyl-2-phenyl-imidazo[1,2-a]pyridine (5a):[2j, 2m] Brown crystalline solid; m.p. 153-154 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.78 (m, 2H), 7.70-7.67 (m, 2H), 7.43 (t, J = 6.6 Hz, 2H), 7.37-7.27 (m, 4H), 7.20-7.16 (m, 3H), 6.71 (t, J = 6.8 Hz, 1H), 4.50 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.8, 144.0, 136.7, 135.8, 129.1, 128.7, 128.2, 127.8, 127.7, 127.0, 124.3, 123.5, 117.7, 117.5, 112.3, 29.8; IR ($CHCl_3$): ν_{max} 3400, 3058, 3027, 2850, 1632, 1602, 1503, 1493, 1359, 1271 cm^{-1}; ESI-MS: *m/z* 285.20 [M+H$^+$]; HRMS (ESI): HRMS: *m/z* 285.1388 calcd for $C_{20}H_{16}N_2 + H^+$ (285.1386).

3-Benzyl-2-(2-chlorophenyl)-imidazo[1,2-a]pyridine (5b):[3] Brown crystalline solid; m.p. 112-113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69-7.66 (m, 2H), 7.56-7.53 (m, 1H) 7.50-7.48 (m, 1H) 7.34-7.31 (m, 2H) 7.24 (d, J = 7.8 Hz, 2H), 7.20-7.15 (m, 2H), 7.07 (d, J = 4.0 Hz, 2H), 6.69 (t, J = 8.0 Hz, 1H), 4.28 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.6, 142.1, 136.5, 133.5, 132.6, 129.8, 129.6, 128.8, 127.9, 126.8, 126.7, 124.2, 123.8, 117.6, 112.3, 30.1; IR ($CHCl_3$): ν_{max} 3391, 3060, 2923, 2852, 1633, 1494, 1501, 1387, 1361, 1041 cm^{-1}; ESI-MS: *m/z* 319.10 [M+H]$^+$; HRMS: *m/z* 319.1001 calcd for $C_{20}H_{15}ClN_2 + H^+$ (319.0997).

3-Benzyl-2-(furan-2-yl)-imidazo[1,2-a]pyridine (5c):[2k] Brown crystalline solid; m.p. 101-102 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.28-7.14 (m, 6H), 6.92 (d, J = 4.1 Hz, 1H), 6.68 (t, J = 8.0 Hz, 1H), 6.52-6.51 (m, 1H), 4,56 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.3, 145.0, 142.1, 136.7, 135.3, 128.5, 128.1, 126.6, 124.3, 122.8, 118.1, 117.5, 112.2, 111.2, 107.4, 29.7; IR ($CHCl_3$): ν_{max} 3391, 2918, 1602, 1635, 1452, 1494, 1352, 1195, 1009 cm^{-1}; ESI-MS: *m/z* 275.10 [M+1]; HRMS: *m/z* 275.1181 calcd for $C_{18}H_{14}N_2O + H^+$ (275.1179).

3-Benzyl-2-(4-methoxyphenyl)-imidazo[1,2-a]pyridine (5d):[3] White crystalline solid; m.p. 135-136°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (m, 4H), 7.33-7.28 (m, 4H), 7.18 (m, 2H), 7.00 (d, J = 4.1 Hz, 2H), 6.77 (m, 1H), 4.51 (s, 2H), 3.87 (s, 3H); IR ($CHCl_3$): ν_{max} 3400, 2923, 2853, 1742, 1613, 1502, 1453, 1248, 1023 cm^{-1}; ESI-MS: *m/z* 315.10 [M+1]+; HRMS: *m/z* 315.1495 calcd for $C_{21}H_{18}N_2O + H^+$ (315.1492).

3-Benzyl-2-(3,5-difluorophenyl)-imidazo[1,2-a]pyridine (5e): White solid; m.p. 141-142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77-7.71 (m, 2H), 7.36-7.31 (m, 6H), 7.15 (d, J = 8.0 Hz, 2H), 6.84-6.77 (m, 2H), 4.52 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.0 (d, $^{1}J_{CF}$ = 265.4 Hz), 145.3, 144.2, 136.9, 135.5, 129.3, 127.5, 127.1, 123.4, 118.8, 118.4, 117.4, 113.3, 111.2 (d, $^{2}J_{CF}$ = 26.4 Hz), 103.1 (t, $^{2}J_{CF}$ = 52.6 Hz), 28.8; ^{19}F NMR (376.50 MHz, $CDCl_3$): δ -109.14 (t, J = 3.8 Hz, 2F); IR ($CHCl_3$): ν_{max} 3400, 3034, 2922, 1625, 1595, 1494, 1431, 1390, 1238, 1116 cm^{-1}; ESI-MS: *m/z* 321.20 [M+1]$^+$); HRMS: *m/z* 321.1200 calcd for $C_{20}H_{14}F_2N_2 + H^+$ (321.1198).

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3-Benzyl-2-(3-chlorophenyl)-imidazo[1,2-a]pyridine (5f):[2k] White crystalline solid; m.p. 137-138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.75 (m, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 4.0 Hz, 1H), 7.31-7.19 (m, 6H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.75 (t, *J* = 8.0 Hz, 1H), 4.43 (s, 2H); IR ($CHCl_3$): ν_{max} 3435, 2923, 2852, 1734, 1601, 1494, 1453, 1361, 1249, 1079 cm^{-1}; ESI-MS: *m/z* 319.10 $[M+1]^+$; HRMS: *m/z* 319.1001 calcd for $C_{20}H_{15}ClN_2 + H^+$ (319.0997).

2-(3,5-Difluorophenyl)-3-(4-Methoxybenzyl)-imidazo[1,2-a]pyridine (5g): Yellow crystalline solid; m.p. 135-136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.75 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0, 1H), 7.34 (d, *J* = 4.0 Hz, 2H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 4.0 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.79-6.74 (m, 2H), 4.43 (s, 2H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.6 (d, $^1J_{CF}$ = 242.7 Hz), 158.1, 144.0, 140.3, 136.8, 128.4, 127.2, 124.7, 123.0, 118.5, 117.1, 113.9, 112.1, 110.2 (d, $^2J_{CF}$ = 20.1 Hz), 102.7 (t, $^2J_{CF}$ = 52.8 Hz), 54.5, 28.6; ^{19}F NMR (376.50 MHz, $CDCl_3$): *δ* -109.60 (t, *J* = 7.5 Hz, 2F); IR ($CHCl_3$): ν_{max} 3400, 2922, 2849, 1730, 1625, 1596, 1511, 1433, 1390, 1363, 1247, 1034 cm^{-1}; ESI-MS: *m/z* 351.10 $[M+1]^+$; HRMS: *m/z* 351.1309 calcd for $C_{21}H_{16}F_2N_2O + H^+$ (351.1304).

2-(4-Chlorophenyl)-3-(3-Methylbenzyl)-imidazo[1,2-a]pyridine (5h): Brown sticky solid; m.p. 129-130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65-7.58 (m, 2H), 7.32 (d, *J* = 12.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.86-6.81 (m, 2H), 6.63 (t, *J* = 4.0 Hz, 1H), 4.34 (s, 2H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.1 142.8, 138.9, 136.4, 133.7, 133.5, 131.3, 129.3, 129.0, 128.9, 128.3, 127.8, 124.6, 124.5, 123.4, 117.1, 112.4, 29.5, 21.3; IR ($CHCl_3$): ν_{max} 3434, 2922, 1740, 1619, 1464, 1219, 1020 cm^{-1}; ESI-MS: *m/z* 333.00 $[M+1]^+$; HRMS: *m/z* 333.1141 calcd for $C_{21}H_{17}ClN_2 + H^+$ (333.1153)

3-(4-Bromobenzyl)-2-(4-chlorophenyl)-imidazo[1,2-a]pyridine (5i): Yellow sticky solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69-7.65 (m, 4H), 7.44-7.41 (dd, *J* = 8.0, 12.0 Hz, 4H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.75 (t, *J* = 8.0 Hz, 1H), 4.41 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.9, 144.1, 136.5, 134.8 133.8, 133.1, 130.3, 130.2, 129.8, 125.5, 124.1, 121.8, 118.6, 118.0, 113.5, 30.6; IR ($CHCl_3$): ν_{max} 3398, 2922, 1740, 1634, 1486, 1464, 1018, 771 cm^{-1}; ESI-MS: *m/z* 398.90 $[M+1]^+$; HRMS: *m/z* 398.7021 calcd for $C_{20}H_{14}BrClN_2 + H^+$ (398.7030)

3-(2-Chlorobenzyl)-2-(4-chlorophenyl)-imidazo[1,2-a]pyridine (5j): Yellow solid; m.p. 105-106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.65 (m, 4H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.27-7.23 (dd, *J* = 8.0, 16.0 Hz, 2H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.77 (t, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 4.51 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.1, 143.5, 134.1, 134.0, 133.8, 132.8, 129.9, 129.3, 128.9, 128.5, 128.4, 127.5, 124.7, 123.3, 117.7, 116.7, 112.6, 27.7; IR ($CHCl_3$): ν_{max} 3399, 2923, 1634, 1486, 1467, 1384, 1254, 1038, 749 cm^{-1}; ESI-MS: *m/z* 353.00 $[M+1]^+$; HRMS: *m/z* 353.0615 calcd for $C_{20}H_{14}Cl_2N_2 + H^+$ (353.0607)

3-Benzyl-6-chloro-2-(4-chlorophenyl)-imidazo[1,2-a]pyridine (5k):[2m] Brown crystalline solid; m.p. 153-154 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (s, 1H), 7.70-7.67 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.35-7.28 (m, 4H), 7.17-7.10 (m, 2H), 4.44 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.8, 143.1, 135.8, 134.1, 132.4, 129.34, 129.29, 128.9, 127.5, 127.3, 125.9, 121.2, 120.8, 118.6, 117.8, 29.6; IR ($CHCl_3$): ν_{max} 3400, 2920, 1730, 1601, 1521, 1486, 1402, 1325, 1096 cm^{-1}; ESI-MS: *m/z* 353.00 $[M+1]^+$; HRMS: *m/z* 353.0612 calcd for $C_{20}H_{14}Cl_2N_2 + H^+$ (353.0607).

3-Benzyl-2-(4-chlorophenyl)-6-fluoro-imidazo[1,2-a]pyridine (5l): Cream colored solid; m.p. 193-194 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.69-7.66 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.35-7.28 (m, 3H), 7.15 (m, 3H), 4.45 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.4 (d, $^1J_{CF}$ = 237.7 Hz), 144.1, 142.4, 135.7, 134.1, 132.4, 129.3, 129.0, 127.6, 127.3, 119.4, 118.0, 117.9, 116.8 (d, $^2J_{CF}$ = 25.2 Hz), 110.2 (d, $^2J_{CF}$ = 41.5 Hz), 29.9; ^{19}F NMR (376.50 MHz,$CDCl_3$) δ -139.22 (s, 1F); IR ($CHCl_3$): ν_{max} 3400, 3043, 2924, 1651, 1572, 1510, 1534, 1488, 1370, 1195, 1147, 1014 cm^{-1} ESI-MS: *m/z* 337.00 $[M+1]^+$; HRMS: *m/z* 337.0909 calcd for $C_{20}H_{14}ClFN_2 + H^+$ (337.0902).

3-Benzyl-6-chloro-2-phenyl-imidazo[1,2-a]pyridine (5m):[2m] Cream colored solid; m.p. 172-173 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (m, 3H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.32-7.19 (m, 4H), 7.12-7.06 (m, 3H), 4.36 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.8, 134.2, 129.2, 128.9, 128.7, 128.2, 128.1, 128.1, 127.8, 127.6, 127.5, 127.2, 126.2, 122.5, 121.2, 119.3, 118.1, 115.7, 29.8; IR ($CHCl_3$): ν_{max} 3400, 3082, 2921, 2851, 1738, 1603, 1521, 1493, 1449, 1325, 1251, 1094 cm^{-1}; ESI-MS: *m/z* 319.10 $[M+1]^+$; HRMS: *m/z* 319.1001 calcd for $C_{20}H_{15}ClN_2$+H^+ (319.0997).

3-Benzyl-6-chloro-2-(4-methoxyphenyl)-imidazo[1,2-a]pyridine (5n): Yellow crystalline solid; m.p. 166-167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (m, 3H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.35-7.28 (m, 3H), 7.15 (m, 3H), 6.99 (d, *J* = 8.0 Hz, 2H), 4,45 (s, 2H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.2, 144.9, 143.0, 136.1, 129.5, 129.2, 127.7, 127.1, 126.5, 121.1, 120.7, 117.7, 117.5, 114.2, 55.1, 29.6; IR ($CHCl_3$): ν_{max} 3400, 2921, 2850, 1611, 1577, 1500, 1453, 1325, 1249, 1041, 1029 cm^{-1}; ESI-MS: *m/z* 349.00 $[M+1]^+$; HRMS: *m/z* 349.1105 calcd for $C_{21}H_{17}ClN_2O + H^+$ (349.1102).

3-Benzyl-2-(4-bromophenyl)-6-chloro-imidazo[1,2-a]pyridine (5o): White crystalline solid; m.p. 118-119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (s, 1H), 7.71-7.65 (m, 3H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.38-7.27 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.47 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.6, 142.9, 135.7, 132.5, 131.9, 129.6, 129.3, 127.51, 127.2, 126.3, 122.6, 121.3, 121.0, 118.3, 117.7, 29.5; IR ($CHCl_3$): ν_{max} 3400, 2921, 2851, 1742, 1601, 1521, 1423, 1343, 1399, 1020 cm^{-1}; ESI-MS: *m/z* 396.9 $[M+1]^+$; HRMS: *m/z* 397.0102 calcd for $C_{20}H_{14}BrClN_2 + H^+$ (397.0102).

3-Benzyl-6-chloro-2-(furan-2-yl)-imidazo[1,2-a]pyridine (5p): Brown yellow solid; m.p. 149-150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.53 (s, 1H), 7.33-7.12 (m, 6H), 6.94 (s, 1H), 6.55 (d, *J* = 4.0 Hz, 1H), 4.61 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.5, 143.1, 142.3, 136.2, 128.5, 127.9, 126.5, 126.1, 121.0, 120.2, 118.6, 117.2, 111.5, 108.1, 29.5; IR ($CHCl_3$): ν_{max} 3400, 2919, 1602, 1520, 1494, 1454, 1403, 1324, 1253, 1070 cm^{-1}; ESI-MS: *m/z* 308.9 $[M+1]^+$; HRMS: *m/z* 309.0795 calcd for $C_{18}H_{13}ClN_2O + H^+$ (309.0789).

3-Benzyl-6-chloro-2-(3,5-difluorophenyl)-imidazo[1,2-a]pyridine (5q): White crystalline solid; m.p. 181-182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.35-7.02 (m, 8H), 6.82 (brs, 1H), 4.49 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.3 (d, $^1J_{CF}$ = 240.2 Hz),143.1, 142.5, 137.1, 135.5, 129.38, 127.6, 126.3, 121.4, 121.1, 119.2, 118.1, 110.9 (d, $^2J_{CF}$ = 26.4 Hz), 103.3 (t, $^2J_{CF}$ = 40.0 Hz), 29.5; ^{19}F NMR (376.5 MHz, $CDCl_3$): *δ* -109.29 (t, *J* = 7.5 Hz, 2F); IR ($CHCl_3$): ν_{max} 3400, 3050, 2850, 1624, 1591, 1522, 1451, 1430, 1387, 1116, 1047 cm^{-1}; ESI-MS: *m/z* 354.9 $[M+1]^+$; HRMS: *m/z* 355.0813 calcd for $C_{20}H_{13}ClF_2N_2 + H^+$ (355.0808).

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3-Benzyl-6-fluoro-2-(4-methoxyphenyl)-imidazo[1,2-a]pyridine (5r): Cream colored solid; m.p. 156-157 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d *J* = 8.0 Hz, 2H),7.68-7.62 (m, 2H), 7.36-7.29 (m, 3H), 7.16-7.06 (m, 3H), 7.00 (d, *J* = 8.0 Hz, 2H), 4,46 (s, 2H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.5, 153.2 (d, $^1J_{CF}$ = 235.0 Hz) 145.2, 142.2, 136.2, 129.3, 129.0, 127.6, 127.1, 126.7, 118.4, 117.7, 115.9 (d, $^2J_{CF}$ = 25.0 Hz), 114.2, 109.9 (d, $^2J_{CF}$ = 30.0 Hz), 55.0, 30.0; ^{19}F NMR (376.50 MHz, $CDCl_3$): *δ* -139.84 (s, 1F); IR ($CHCl_3$): ν_{max} 3400, 2921, 2853, 1738, 1650, 1611, 1536, 1502, 1370, 1248, 1220, 1046 cm^{-1}; ESI-MS: *m/z* 333.0 $[M+1]^+$; HRMS: *m/z* 333.1402 calcd for $C_{21}H_{17}FN_2O + H^+$ (333.1398).

3-Benzyl-6-fluoro-2-(3,5-difluorophenyl)-imidazo[1,2-a]pyridine (5s): Cream colored solid; m.p. 145-146 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.70-7.66 (m, 2H), 7.37-7.28 (m, 5H), 7.19-7.12 (m, 3H), 6.82 (t, *J* = 8.0 Hz, 1H), 4,48 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.1 (d, $^1J_{CF}$ = 247.0 Hz), 153.5 (d, $^1J_{CF}$ = 239.0 Hz), 143.1, 142.4, 137.4, 135.4, 129.1, 127.7, 127.3, 120.0, 118.3, 117.0 (d, $^2J_{CF}$ = 26.0 Hz), 110.6 (d, $^2J_{CF}$ = 31.0 Hz), 110.2 (d, $^2J_{CF}$ = 41.0 Hz), 103.2 (t, $^2J_{CF}$ = 26.0 Hz), 29.9; ^{19}F NMR (376.5 MHz, $CDCl_3$): *δ* -109.35 (t, *J* = 7.5 Hz, 2F), -138.64 (s, 1F); IR ($CHCl_3$): ν_{max} 3400, 2920, 2851, 1625, 1537, 1429, 1384, 1211, 1117 cm^{-1}; ESI-MS: *m/z* 333.0 $[M+1]^+$; HRMS: *m/z* 339.1106 calcd for $C_{20}H_{13}F_3N_2 + H^+$ (339.1104).

3-Benzyl-6-fluoro-2-(furan-2-yl)-imidazo[1,2-a]pyridine (5t): Yellow crystalline solid; m.p. 166-167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70-7.68 (m, 1H), 7.65-7.63 (m, 1H), 7.54 (s, 1H), 7.34-7.28 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.96 (s, 1H), 6.56 (s, 1H), 4.62 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.3 (d, $^1J_{CF}$ = 223.9 Hz), 142.7, 142.2, 136.0, 129.1, 128.0, 127.1, 119.6, 117.5, 117.4, 117.3, 117.0, 111.7, 110.3 (d, $^2J_{CF}$ = 49.0 Hz), 108.6, 30.1; ^{19}F NMR (376.50 MHz, $CDCl_3$): *δ* -138.95 (s, 1F); IR ($CHCl_3$): ν_{max} 3400, 2922, 2852, 1650, 1537, 1453, 1384, 1219, 1020 cm^{-1}; ESI-MS: *m/z* 293.0 $[M+1]^+$; HRMS: *m/z* 293.1084 calcd for $C_{18}H_{13}FN_2O$ + H^+ (293.1085).

3-Benzyl-2-(3,5-difluorophenyl)-8-methyl-imidazo[1,2-a]pyridine (5u): Yellow crystalline solid; m.p. 164-165 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.28-7.18 (m, 5H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.74-6.68 (m, 1H), 6.60 (t, *J* = 8.0 Hz, 1H), 4.31 (s, 2H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1 (d, $^1J_{CF}$ = 222.3 Hz), 144.9, 136.2, 128.5, 127.7, 127.5, 126.8, 121.3, 119.1, 113.2, 111.1 (d, $^2J_{CF}$ = 31.4 Hz), 103.2 (d, $^2J_{CF}$ = 26.0 Hz), 29.50, 16.7; ^{19}F NMR (376.50 MHz, $CDCl_3$): *δ* -109.65 (t, *J* = 3.8 Hz, 2F); IR ($CHCl_3$): ν_{max} 3396, 2921, 2851, 1738, 1624, 1348, 1155, 1021 cm^{-1}; ESI-MS: *m/z* 335.0 $[M+1]^+$; HRMS: *m/z* 335.1354 calcd for $C_{21}H_{16}F_2N_2 + H^+$ (335.1354).

3-Benzyl-2-(furan-2-yl)-8-methyl-imidazo[1,2-a]pyridine (5v): Brown crystalline solid; m.p. 131-132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, *J* = 4.0 Hz, 1H), 7.44 (s, 1H), 7.21-7.09 (m, 5H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.80 (brs, 1H), 6.55 (t, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 4.0 Hz, 1H), 4.51 (s, 2H), 2.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.5, 136.8, 128.9, 127.7, 127.2, 126.8, 121.2, 121.0, 118.5, 112.6, 111.0, 29.7, 17.4 (one C signal not observed); IR ($CHCl_3$): ν_{max} 3400, 2921, 2851, 1738, 1630, 1578, 1453, 1384, 1020 cm^{-1}; ESI-MS: *m/z* 289.0 $[M+1]^+$; HRMS: *m/z* 289.1336 calcd for $C_{19}H_{16}N_2O$ + H^+ (289.1335).

3-Benzyl-2-(2-chlorophenyl)-8-methyl-imidazo[1,2-a]pyridine (5w): Cream colored solid; m.p. 162-163 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 4.0 Hz, 1H), 7.18-7.11 (m, 5H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 4.0 Hz, 1H), 6.58 (t, *J* = 8.0 Hz, 1H), 4.23 (s, 2H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.2, 142.4, 136.7, 136.5, 134.1, 132.8, 129.7, 128.8, 128.0, 126.7, 121.7, 30.1, 17.3; IR ($CHCl_3$): ν_{max} 3401, 2923, 2856, 1700, 1632, 1578, 1458, 1384, 1026 cm^{-1}; ESI-MS: *m/z* 333.0 $[M+1]^+$; HRMS: *m/z* 333.1156 calcd for $C_{21}H_{17}ClN_2 + H^+$ (333.1153).

Preparation and characterization of Cu-Mn catalysts A-C. A series of copper-manganese mixed oxides (A–C) were prepared by the coaddition of the aqueous solutions of $CuCl_2 \cdot 2H_2O$ and $MnCl_2 \cdot 4H_2O$ in a molecular weight ratio (2: 0.25; 1: 0.25; 3: 0.25, respectively) at a rate of 1 mL min−1 under vigorous mechanical stirring at room temperature to form a uniform solution. Then ammonia solution was added drop by drop until it reached pH 8.5–8.7 and was allowed to stand overnight to form a gel, filtered, and washed with double distilled water until free from chloride ions. After being kept overnight at room temperature, the cake was allowed to dry in an air oven at 110 °C for 24 h and finally calcined (10 °C min^{-1}) in a muffle furnace at 425 °C for 3 h. Catalysts were adequately characterized to understand the efficiency of catalytic activity. X-ray diffraction (XRD), specific surface area, scanning electron micrograph (SEM) and XPS analysis were studied and are provided in the ESI.

Recyclability of Cu-Mn catalyst B: The recyclability of Cu-Mn **B** catalyst was checked using a model reaction between 2-aminopyridine (**2a**), benzaldehyde (**3a**) and phenylacetylene (**4a**). The mixture of **2a** (100 mg, 1 mmol) and **3a** (113 mg, 1 mmol) was stirred for 15 min. Water (3 mL) was added followed by addition of **4a** (163 mg, 1.5 mmol). Then, Cu-Mn catalyst (10 mg, 10 mol%) was added, and resulting mixture was refluxed at 100 °C for 4 h. The reaction mixture was filtered through Whatman filter paper followed by washing with 3 x 25 mL water. Recovered catalyst was dried in oven and reused in next cycle. The catalyst was recycled 4 times and the amount of catalyst recovered and percentage yield of the **5a** was determined.

Cell culture and cell proliferation assay. Human promyelocytic leukemia cell lines HL-60, human pancreatic cancer cell line MIAPaCa-2 and human prostate cancer cell line PC-3 were purchased from Sigma Aldrich, India (ECACC, type). HL-60 and PC-3 cells were grown in RPMI growth medium whereas MIAPaCa-2 and A549 cells were grown in MEM medium containing 10% FCS, 100U penicillin and 100 mg streptomycin per mL medium. Cells were grown in CO_2 incubator (Thermocon Electron Corporation, Houston, TX) at 37 ºC with 95% humidity and 5% CO_2 gas environment. Cells treated with tested materials were dissolved in DMSO while the untreated control cultures received only the vehicle (DMSO < 0.2%). Cells were seeded in 96 well plates and exposed to tested compounds at 10, 30 and 100 µM concentrations for 48 h time interval. MTT dye (2.5 mg/ml in PBS) was added 4 hrs priors to experiment termination. The plates were then centrifuged at 1500 rpm for 15 min and the supernatant was discarded, while the MTT formazan crystals were dissolved in 150 µl of DMSO. The OD was measured at 570 nm with reference wavelength of 620 nm and the % growth inhibition was determined.[10]

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Notes and references

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