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Triarylimidazo[1,2-*a*]pyridine-8-carbonitriles: solvent-free synthesis and their anti-cancer evaluation

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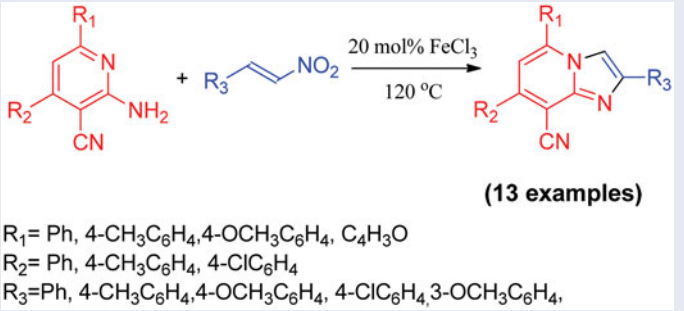
ABSTRACT

In this study, we have presented the synthesis of novel 2,5,7-triarylimidazo[1,2-*a*]pyridine-8-carbonitriles from 2-amino-4,6-diarlypyridine-3-carbonitrile and nitrostyrene using $FeCl_3$ (20 mol%) as Lewis acid under solvent-free conditions. A library of compounds with diverse substitutions have also been synthesized and screened for *in-vitro* anti-cancer activity against various cell lines such as A549 (Lung), HCT-116 (Colon), SW-620 (Colon), and MIAPACA (Pancreas).

GRAPHICAL ABSTRACT



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KEYWORDS
Imidazo[1,2-a]pyridines; ferric chloride; nitrostyrene; diarlypyridine-3-carbonitrile

Introduction

Imidazopyridine represents an important class among polynitrogen containing heterocycles and exhibits a plethora of biological activity. Imidazo[1,2-*a*]pyridine, in particular, is one of the most significant structural unit in the area of natural products and pharmaceuticals.[1] Despite this, it also finds its application in material science.[2,3] Imidazo[1,2-*a*]pyridines display interesting biological activities over a broad range of therapeutic classes such as antineoplastic,[4] antiviral,[5] anti-tubercular,[6] anti-inflammatory,[7] anti-diabetic,[8] antipyretic,[9] antihypertensive,[10] anticonvulsant,[11] antibacterial,[12] CDK2 inhibitor,[13] molluscicidal,[14] and kinase inhibitor.[15] Their effects

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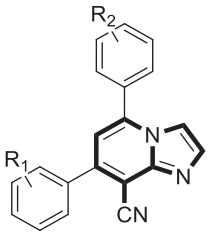
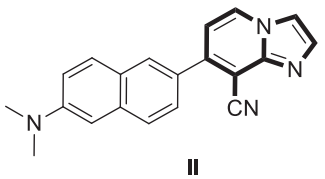
on neuroactive steroids[16] and inhibitory role on NO synthase[17] have also been documented. They have also been reported as GABA and benzodiazepine receptor agonists,[18] β-amyloid formation inhibitors,[19] histamine H2 receptor antagonists,[20] and cardiotonic agents.[21] Their role as inhibitors of cyclooxygenase-2 (COX-2),[22] cholesterol acyltransferase,[23] and geranylgeranyl transferase[24] have also been reported.

Some marketed drugs such as zolpidem (used in the treatment of insomnia), alpidem (as anxiolytic agent), olprinone (for the treatment of acute heart failure), zolimidine (used for the treatment of peptic ulcer), necopidem and saripidem (as anxiolytic agent), miroprofen (analgesic), and minodronic acid (for the treatment of osteoporosis) contain imidazo[1,2-*a*] pyridine moiety as their core structure (Figure 1).[25] GSK812397 is another drug which contains imidazo[1,2-*a*]pyridine nucleus and is used for the treatment of HIV infection.[26] Rifaximin is an antibiotic, used to prevent and treat traveler's diarrhea,[27] and soraprazan is found to be potent inhibitor of gastric H, K-ATPase and is used to treat gastric acid related diseases.[28]

Imidazo[1,2-*a*]pyridine-8-carbonitriles such as **I** and **II** have been reported as selective inhibitor of mammalian osteoclast cell activity[29] and binding agents to β-amyloid plaques.[30]

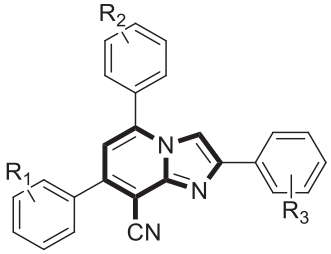


I



II

In the light of significance of imidazopyridines in medicinal chemistry and material science, several methods for their synthesis are reported.[31–38] In continuation of our interest in the synthesis of pyridines[39–41] and imidazopyridines,[42,43] we contemplated the synthesis of highly functionalized imidazo[1,2-*a*]pyridine-8-carbonitriles of general structure **A** for their anti-cancer evaluation.



A

Results and discussion

At the beginning of our study, 2-amino-4,6-diphenylpyridine-3-carbonitrile and (*E*)-(2-nitrovinyl)benzene were chosen as model substrates and reaction was performed as per

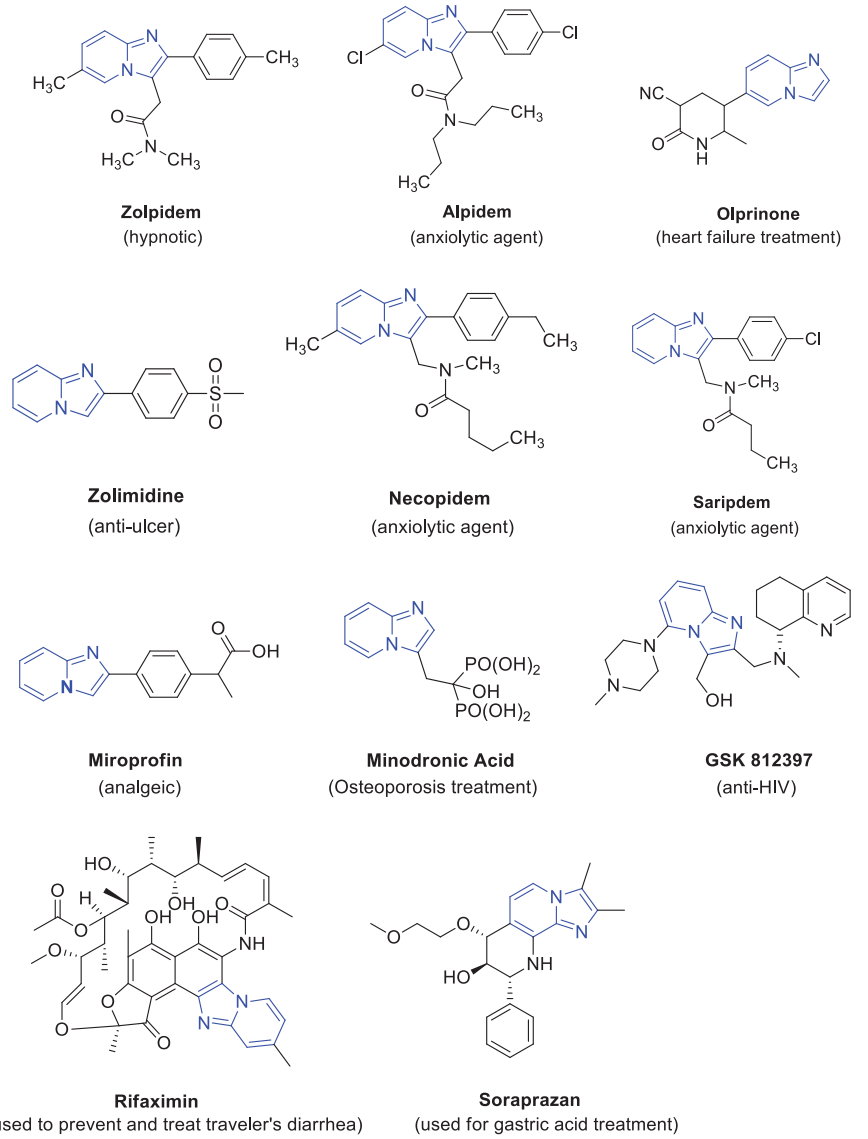


Figure 1. Few marketed drugs containing imidazo[1,2-*a*]pyridine scaffold.

the procedure (20 mol% $FeCl_3$ as catalyst in DMF at 80 °C) reported by Hajra et al.[31] The desired product, 2,5,7-triphenylimidazo[1,2-*a*]pyridine-8-carbonitrile was obtained after 15 h of reaction in 34% yield only. In order to improve the yield of the reaction various solvents such as $CHCl_3$, EtOH, MeOH, DCE, isopropanol, and CH_3CN were used in place of DMF, but none was found to be beneficial (Table 1, Entry 2–7). In another experiment, the reaction was conducted without any solvent at 80 °C; a marginal improvement in the yield was witnessed. Raising the temperature of solvent-free reaction led us to realize that at 120 °C, the best yield was obtained (Table 1, Entry 8–13). Replacing $FeCl_3$ with various other catalysts such as $FeSO_4$, $Fe(NO_3)_3$, $ZnCl_2$, $CuSO_4$, $SbCl_3$, $Bi(NO_3)_3$, as well as I_2/DMSO did not result in improving the yield of

Table 1. Optimization of reaction conditions.

S. No.	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	$FeCl_3$	DMF	80	15	34
2	$FeCl_3$	$CHCl_3$	60	15	32
3	$FeCl_3$	EtOH	80	15	42
4	$FeCl_3$	MeOH	60	15	35
5	$FeCl_3$	DCE	90	15	30
6	$FeCl_3$	iso-propanol	90	15	28
7	$FeCl_3$	CH_3CN	80	15	34
8	$FeCl_3$	-	80	0.5	52
9	$FeCl_3$	-	90	0.5	65
10	$FeCl_3$	-	100	0.5	68
11	$FeCl_3$	-	110	0.5	72
12	**$FeCl_3$**	–	**120**	**0.5**	**75**
13	$FeCl_3$	-	130	0.5	75
14	$FeSO_4$	-	120	0.5	n.r
15	$Fe(NO_3)_3$	-	120	0.5	n.r
16	I_2	DMSO	120	0.5	n.r
17	$ZnCl_2$	-	120	0.5	n.r
18	$CuSO_4$	-	120	0.5	32
19	$SbCl_3$	-	120	0.5	n.r
20	$Bi(NO_3)_3$	-	120	0.5	n.r

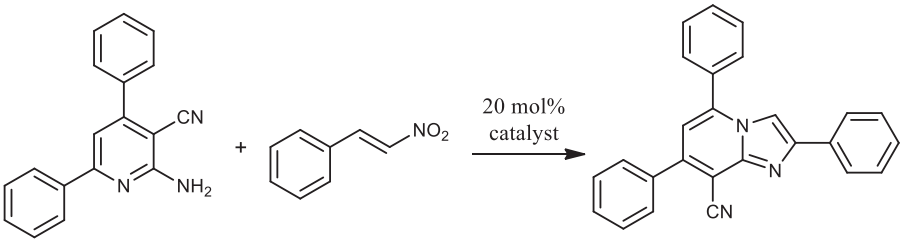
alsolated yields.

Table 2. Scanning of catalyst concentration.

S. No.	$FeCl_3$ (mol %)	Yield[a] (%)
1	10	23
2	**20**	**75**
3	30	75
4	50	65
5	100	57
6	0	n.r

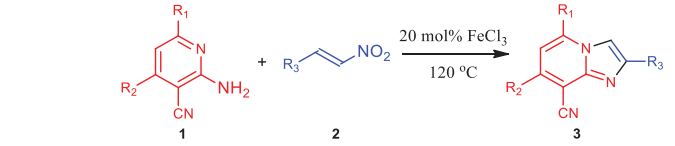
Reaction conditions: 2-amino-4,6-diphenylpyridine-3-carbonitrile (1 mmol), (*E*)-(2-nitrovinyl)benzene (1 mmol) at 120 °C.
alsolated yields

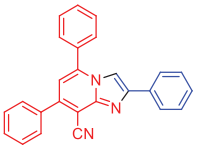
the reaction (Table 1, Entry 14–20). In order to scan the amount of catalyst required, the reaction was performed with different amounts of catalyst (10, 20, 30, 50, and 100 mol%), and it was witnessed that 20 mol% of the catalyst gave the best yield of the product (Table 2).



Having established the optimal reaction conditions, we turned our attention toward the scope of reaction for the synthesis of various 2,5,7-triarylimidazo[1,2-*a*]pyridine-8-carbonitrile (**3a–m**). Various electron donating and electron withdrawing groups on 2-amino-4,6-diarlypyridine-3-carbonitrile and 2-nitrostyrene were well tolerated in this transformation. 2-Amino-4,6-diarlypyridine-3-carbonitrile bearing heterocyclic moiety

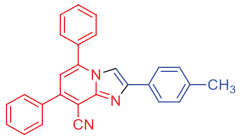
also gave the desired product (**3m**) in good yield. With 1-nitrobutene, the reaction did not occur and the starting material was recovered intact.





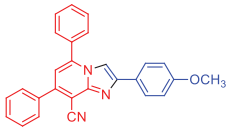
3a,30 min

75%



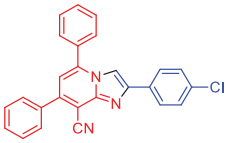
3b,30 min

73%



3c,40 min

71%



3d,45 min

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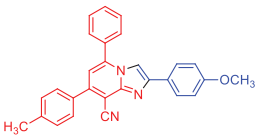

3e ,45 min

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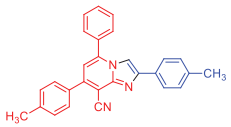

3f,45 min

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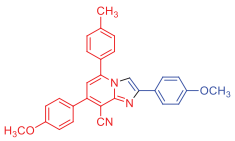
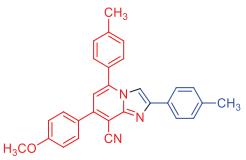


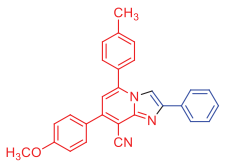
3g,50 min

76%



3h,60 min

74%



3i,30 min

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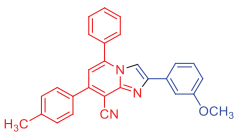
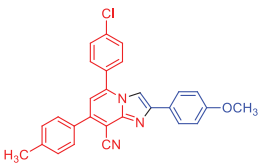


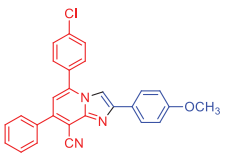
3j,30 min

74%



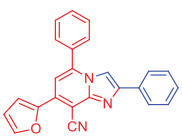
3k,40 min

74%



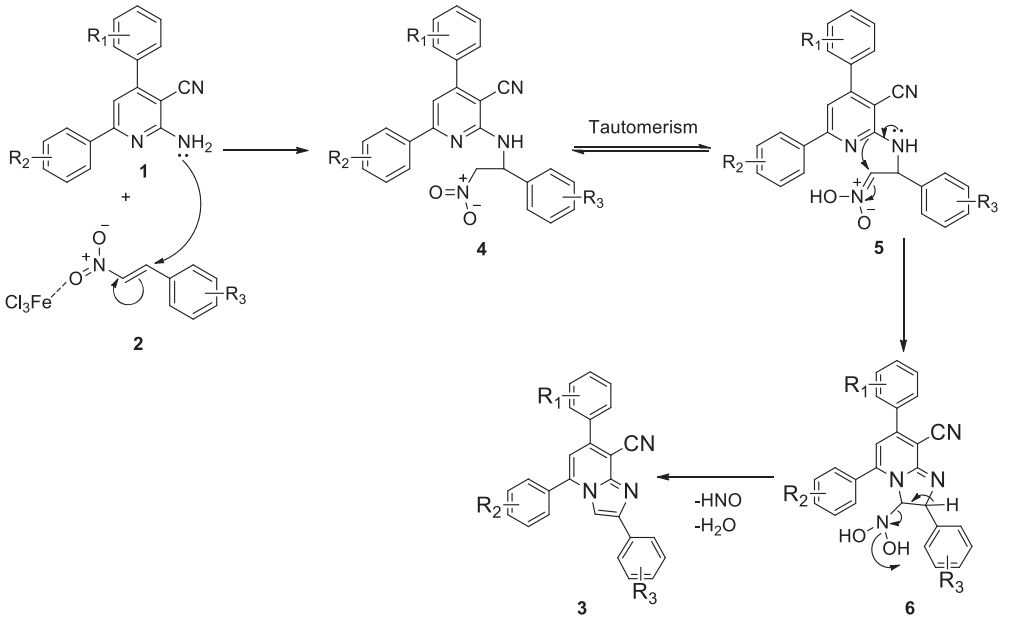
3l,30 min

72%



3m,45 min

73%



Scheme 1. Plausible mechanism for the synthesis of 2,5,7-triarylimidazo[1,2-*a*] pyridine-8-carbonitrile

A mechanistic rationale portraying the probable sequence of events is shown in Scheme 1. The first step of the reaction is Michael addition of 2-amino-4,6-diarlypyridine-3-carbonitrile on nitroolefins to form intermediate **4**. $FeCl_3$ increases the electrophilicity of the nitroolefins and thus facilitate the addition of 2-amino-4,6-diarlypyridine-3-carbonitrile. Nitro intermediate **4** tautomerises to **5**, which undergoes intramolecular cyclization followed by nitroxyl and water elimination to generate the final product **3**.

Pharmacological report on in-vitro *anti-cancer activity evaluation of the synthesized compounds*

Method

The study of the anticancer activity of the synthesized molecules has been carried out at Pharmacology Department, IIIM, Jammu. All the synthesized molecules were tested for *in vitro* cytotoxicity against various human cancer cell lines. In brief, a three-day MTT cytotoxicity assay was performed, which was based on the principle of uptake of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide), a tetrazolium salt, by the metabolically active cells where it is metabolized by active mitochondria into a blue colored formazan product that is read spectrophotometrically. MTT was dissolved in phosphate buffered saline with a pH of 7.4 to obtain an MTT concentration of 2.5mg/ml; the resulting mixture was filtered through a 0.22-micron filter to sterilize and remove a small amount of insoluble residue. The stock solution (1×10^{-2} M) of the compounds was prepared in dimethyl sulphoxide (DMSO) and were further diluted with growth medium (RPMI-1640 with 2 mM glutamine, pH 7.4, 10% fetal bovine serum, 100 µg/mL streptomycin, and 100 units/ml penicillin) to obtain desired concentration. The cells were grown

Table 3. IC_{50} values of the synthesized compounds against some cell lines (μM).

SAMPLE	A549 (Lung)	MIA PACA (Pancreas)	SW-620 (Breast)	HCT-116 (Colon)
3a	21.23	30.41	27.43	20.89
3b	30.43	**9.27**	32.55	30.56
3c	29.78	11.21	27.41	32.66
3d	27.56	30.55	32.57	26.71
3e	27.99	32.46	31.68	35.55
3f	32.90	20.76	22.31	29.70
3g	29.53	32.79	31.50	28.53
3h	29.62	33.57	28.01	26.52
3i	32.71	27.51	28.90	26.84
3j	19.52	27.39	24.09	21.83
3k	20.03	18.43	28.77	26.93
3l	28.99	18.64	25.94	20.11
3m	17.49	32.95	28.05	22.55

- IC_{50} >10 μM indicate that the compound is not active.
- IC_{50} values were calculated using Prism software.
- Paclitaxel was used as positive control for A549.
- Camptothecin was used as positive control for MIA PACA.
- 5-Fluorouracil was used as positive control for SW-620 and HCT-116.

From the data, it is observed that compound **3b** showed significant activity against MIAPACA cell line.

in tissue culture flasks in growth medium at 37 °C in an atmosphere of 5% CO_2 and 95% relative humidity in a CO_2 incubator. For each type of tumor cell, 70,000–10,000 cells per well per 100 μL were seeded in a 96-well culture plate and incubated with the individual compounds in a CO_2 incubator for a total of 24 h.

The final concentration range of compounds was 10–50 μM. Control cells, not treated with the compounds, were similarly incubated. The assay was terminated by adding 100 μg (20 μl) of MTT to each well, then incubating for additional 4 h, and finally adding 150 μl of DMSO to each well to lyse the cells and dissolve formazan. The plate was read spectrophotometrically at 570 nm and the percentage of cytotoxicity calculated using the formula:

$$\text{Cytotoxicity percentage} = 100 \times [1\text{–}X/R_1)],$$

where X = (absorbance of treated sample at 570 nm) – (absorbance of blank at 570 nm) and R_1 = absorbance of blank at 570 nm.

The IC_{50} values of the cytotoxicity, [the concentration at which 50% of the cells are killed *in vitro*] was calculated for each cell line treated with the test compounds The four human cancer cell-lines screened are A549 (Lung), HCT-116 (Colon), SW-620 (Colon) and MiaPaca (Pancreas).

Anti-cancer activity (in-vitro)

The results in terms of IC_{50} values of *in-vitro* cytotoxicity of the synthesized compounds are shown in Table 3.

Experimental

General

All the experiments were performed in an oven dried glass apparatus. All the commercially available reagents were purchased from *Aldrich* and were used without further

purification. Melting points (°C) were measured in open glass capillaries using Perfit melting point apparatus and are uncorrected. The progress of reaction was monitored using thin layer chromatography (TLC) using silica gel pre-coated aluminum sheets (60 F254, Merck). The crude products were purified using silica gel column chromatography (petroleum ether/EtOAc).Visualization of spots was effected by exposure to ultraviolet light (UV) at 365 nm and 254 nm, iodine vapors and 2% 2,4-dinitrophenylhydrazine in methanol containing few drops of H_2SO_4, draggendroff reagent, and anisaldehyde reagent. Solvents used in purification were distilled prior to use. Recrystallization was achieved with ethanol. IR spectra (ν, cm^{-1}) were recorded on Perkin–Elmer FTIR spectrophotometer using KBr discs. ^1H and 13 C NMR were recorded on Bruker AC-400 spectrometer operating at 400 MHz for ^1H and 100 MHz for 13 C with tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in δ (ppm) downfield from TMS. All the ^{13}C NMR spectra are proton decoupled. *J* values are given in Hertz (Hz). The abbreviations s, d, dd, t, q, and m in ^1H NMR spectra refer to singlet, doublet, doublet of doublet, triplet, quartet, and multiplet, respectively. Solvents were removed using Heidolph rotary evaporator. For the HRMS measurement, Quadrupole time of flight (QTOF) was used.

Procedure for the synthesis of 2,5,7-triphenylimidazo[1,2-a]pyridine-8-carbonitrile (3a)

A mixture of 2-amino-4,6-diphenylpyridine-3-carbonitrile (1 mmol), 2-nitro-1-phenylethylene (1 mmol) and $FeCl_3$ (20 mol%) was taken in 25 ml round bottomed flask and dipped in preheated oil bath maintained at 120 °C. The reaction was continued till its completion (30 min). The resultant was column chromatographed to give the pure product.

2,5,7-Triphenylimidazo[1,2-a]pyridine-8-carbonitrile (3a)

Yellow solid, M.P: 270–272 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00–7.99 (m, 3H), 7.78–7.72 (m, 4H), 7.69–7.63 (m, 3H), 7.58–7.51 (m, 3H), 7.43 (t, $J = 7.4$ Hz, 2H), 7.36 (t, $J = 7.3$ Hz, 1H), 6.96 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 145.0, 141.3, 136.3, 133.1, 132.7, 130.8, 129.6, 129.0, 128.6, 128.2, 126.4, 115.5, 114.0, 107.4, 97.6. IR (KBr, υ_{max} cm^{-1}): 3055, 2223, 1614, 1477, 1261. HRMS (ESI): calcd. for $C_{26}H_{17}N_3$ $[M + H]^+$, 372.1502; found: 372.1478.

Conclusion

In conclusion, a protocol has been developed for the synthesis of novel 2,5,7-triarylimidazo[1,2-*a*]pyridine-8-carbonitrile from readily available starting materials. The reaction occurred in the presence of 20 mol% $FeCl_3$ under solvent-free conditions. A library of compounds with diverse substitutions has also been synthesized. 2,5,7-Triarylimidazo[1,2-*a*]pyridine-8-carbonitrile (3 a-m) were screened for *in-vitro* anti-cancer activity against various cell lines such as A549 (Lung), HCT-116 (Colon), SW-620

(Colon) and MIAPACA (Pancreas) and only the compound **3b** showed significant activity against MIA PACA cell line.

Full experimental details, ^{1}H and ^{13}C NMR spectra can be found *via* the "Supplementary content" section of this article's webpage.

Acknowledgments

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