Electronic supplementary Information

Design, synthesis and biological evaluation of imidazopyridine/pyrimidine-chalcone derivatives as potential anticancer agents

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Contents

General. (**A**) **Chemistry.** All chemicals and reagents were purchased from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) or Spectrochem Pvt. Ltd (Mumbai, India) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 GF-254, and visualization on TLC was achieved by UV light or iodine indicator. Column chromatography was performed with Merck 60–120 mesh silica gel. ^{1}H and ^{13}C spectra were recorded Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI^{+} software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. High-resolution mass spectra (HRMS) were recorded on QSTAR XL Hybrid MS/MS mass spectrometer. Melting points were determined with an Electro thermal melting point apparatus, and are uncorrected.

(**B**) **Biology.** (**a**) **Cell lines.** MCF-7 (Human breast cancer cells) was obtained from ATCC, USA. MCF-7 cells were maintained in Dulbecco's modified Eagle's medium (DMEM) (Invitrogen), supplemented with 10% fetal calf serum and 100 U/mL Pencillin and 100 mg/mL streptomycin sulfate (Sigma). The cells were passaged and maintained at 37 ^{o}C in a humidified atmosphere containing 5% CO_2.

(b) Cell Viability (**MTT based Assay**)**.** Cell viability was assessed by the MTT based assay using WST-1 (premix WST-1 cell proliferation Assay system, Takara), is more sensitive than MTT. Briefly, MCF-7 cells were seeded in a 96-well plate (TPP) at a cell density of 10,000 cells/well. After overnight incubation, the cells were treated with compounds **3a** and **3d–h** and doxorubicin (doxo) and incubated for 24 h. The medium was then discarded and replaced with fresh 100 µL media followed by addition of 1 µL of WST-1 dye. Plates were incubated at 37 ^{o}C for 30 min. Optical density (O.D.) was read at 420 nm using Multimode Varioskan FLASH (Thermo Scientifics).

(c) Cell Cycle Analysis. 5 X 10^{5} MCF-7 cells were seeded in 60 mm dish and were allowed to grow for 24 h. Compounds **3a** and **3d-h** and doxorubicin (Doxo) at 4 µM concentration were added to the culture media and the cells were incubated for an additional 24 h. Harvesting of cells was done with Trypsin-EDTA, fixed with ice-cold

70% ethanol at 4 ^{o}C for 30 min, washed with PBS and incubated with 1 mg/mL RNaseA solution (Sigma) at 37 ^{o}C for 30 min. Cells were collected by centrifugation at 2000 rpm for 5 min and further stained with 250 µL of DNA staining solution [10 mg of Propidium Iodide (PI), 0.1 mg of trisodium citrate, and 0.03 mL of Triton X-100 were dissolved in 100 mL of sterile MilliQ water at room temperature for 30 min in the dark]. The DNA contents of 20,000 events were measured by flow cytometer (DAKO CYTOMATION, Beckman Coulter, and Brea, CA). Histograms were analyzed using Summit Software.

(d) Protein Extraction and Western Blot Analysis. Total cell lysates were isolated from cultured MCF-7 cells after compound treatments as mentioned earlier were obtained by lysing the cells in ice-cold RIPA buffer (1XPBS, 1%NP-40, 0.5% sodium deoxycholate and 0.1% SDS containing protease inhibitors). After centrifugation at 12,000 rpm for 10 min, the protein in supernatant was quantified by Bradford method (BIO-RAD) using Multimode varioscan instrument (Thermo-Fischer Scientifics). Thirty micrograms of protein per lane was applied in 12% SDS polyacrylamide gel. After electrophoresis, the protein was transferred to polyvinylidinedifluoride (PVDF) membrane (Amersham Biosciences). The membrane was blocked at room temperature for 2 h in TBS + 0.1% Tween20 (TBST) containing 5% blocking powder (Santa Cruz). The membrane was washed with TBST for 5 min, and primary antibody was added and incubated at 4 ^{o}C overnight (O/N). Rabbit polyclonal antibodies CDK2 (32 KDa), E2F-1 (50 KDa), cyclin D1 (35 KDa), purchased from Santa Cruz Biotech. Rabbit polyclonal antibodies cyclin E1, (40 KDa), β- Actin (38-53 KDa); Mouse monoclonal antibodies cyclin A (50 KDa). Goat polyclonal antibodies p27 (27 KDa) was purchased from Imgenex Pvt Ltd. After three TBST washes, the membrane was incubated with corresponding horseradish peroxidase-labeled secondary antibody (1:2000) (Santa Cruz) at room temperature for 1 h. Membranes were washed with TBST three times for 15 min and the protein blots were visualized with chemiluminescence reagent (Thermo Fischer Scientifics Ltd.). The X-ray films were developed with developer and fixed with fixer solution.

Table 1. Cell cycle distribution of MCF-7 cell line using **3a** and **3d–h** at 4 μM concentration

Compound	Cell cycle distribution (%)		
	G0/G1	S	G2/M
Control	64.04 ± 1.52	20.17 ± 1.24	15.79 ± 0
3a	85.55 ± 0.79	11.65 ± 0.34	2.80 ± 0.49
3d	92.41 ± 0.41	6.48 ± 0.23	1.11 ± 0.21
3e	95.24 ± 0.11	4.10 ± 0.04	0.66 ± 0.16
3f	97.86 ± 0.15	1.83 ± 0.06	0.31 ± 0.09
3g	90.04 ± 0.42	8.43 ± 0.26	1.53 ± 0.22
3h	74.16 ± 0.43	21.89 ± 0.05	3.95 ± 0.46
Doxo[a]	94.85 ± 0.62	4 ± 0.55	1.15 ± 0.21

The values are mean of three determinations and are reported as mean ± standard error of the mean, [a]Doxo (doxorubicin)

Table 2. Sub G1 phase of MCF-7 cell line using **3a** and **3d–h** at 4 μM concentration

Compound	Sub G1
Control	3.23 ± 0.25
3a	10 ± 0.24
3d	14.4 ± 0.30
3e	18.39 ± 0.51
3f	25.2 ± 1.16
3g	11.31 ± 0.37
3h	10.91 ± 0.67
Doxo[a]	40.74 ±1.97

The values are mean of three determinations and are reported as mean ± standard error of the mean, [a]Doxo (doxorubicin)

Spectral Data and Procedure of Compounds (7a–h, 8a–h and **3a–i).**

Synthesis of 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (7a)

The appropriate 2-aminopyridine **4a** (0.188 g, 20 mmol) was dissolved in 100 mL of acetone and treated with the equivalent of the appropriate 2-bromo-1-(4-methoxyphenyl)ethanone **5a** (4.5 g, 20 mmol). The reaction mixture was refluxed for 2–3 h (according to a TLC test), the resulting salt **6a** was separated by filtration and without further purification, refluxed for 1 h with 200 mL of 2N HCl. Before complete cooling, the solution was cautiously basified by dropwise addition of 15% NH_4OH. The resulting base was collected by filtration and crystallized from ethanol to afford compound **7a** as a white solid, yield 3.9 g, 88%; mp 130–132 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (d, 1H, *J* = 6.79 Hz, pyridine-**H**), 7.84 (d, 2H, *J* = 8.87 Hz, Ar**H**), 7.72 (s, 1H, imidazole-**H**), 7.59 (d, 1H, *J* = 9.06 Hz, pyridine-**H**), 7.11 (t, 1H, *J* = 8.30 Hz, pyridine-**H**), 6.93 (d, 2H, *J* = 8.68 Hz, Ar**H**), 6.72 (t, 1H, *J* = 6.79 Hz, pyridine-**H**), 3.83 (s, 3H, -OC**H**$_3$); MS (ESI): *m/z* 225 $(M+1)^+$.

2-(4-Fuorophenyl)imidazo[1,2-*a*]pyridine (7b)

This compound was prepared according to the method described for compound **7a**, employing compound **4a** (0.188 g, 20 mmol) and compound **5b** (4.34 g, 20 mmol) to obtain the pure product **7b** as a white solid, yield 3.8 g, 90%; mp 160–162 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07 (d, 1H, *J* = 6.79 Hz, pyridine-**H**), 7.87 (dd, 2H, *J* = 8.30, 6.04 Hz, Ar**H**), 7.73 (s, 1H, imidazole-**H**), 7.59 (d, 1H, *J* = 9.06 Hz, Ar**H**), 7.17–7.05 (m, 3H, ArH, pyridine-**H**), 6.73 (t, 1H, *J* = 6.79 Hz, pyridine-**H**); MS (ESI): *m/z* 213 $(M+1)^+$.

2-(3,4-Dimethoxyphenyl)imidazo[1,2-*a*]pyridine (**7c**)

This compound was prepared according to the method described for compound **7a**, employing compound **4a** (0.188 g, 20 mmol) and compound **5c** (4.3 g, 20 mmol) to obtain the pure product **7c** as a pale yellow solid, yield 4.3 g, 85%; mp 80–82 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (d, 1H, *J* = 6.7 Hz, pyridine-**H**), 7.73 (s, 1H , imidazole-**H**), 7.59 (d, 1H, *J* = 9.5 Hz, pyridine-**H**), 7.55 (d, 1H, *J* = 1.5 Hz, pyridine-**H**), 7.38 (dd, 1H, *J* = 8.3, 1.5 Hz, Ar**H**), 7.12 (t, 1H, *J* = 8.3 Hz, Ar**H**), 6.87 (d, 1H *J* = 8.3

Hz, Ar**H**), 6.73 (t, 1H, *J* = 6.7 Hz, pyridine-**H**), 3.99 (s, 3H, -OC**H**$_3$), 3.91 (s, 3H, -OC**H**$_3$); MS (ESI): *m/z* 255 $(M+1)^+$.

2-(Thiophen-2-yl)imidazo[1,2-*a*]pyridine (7d*)*

This compound was prepared according to the method described for compound **7a**, employing compound **4a** (0.188 g, 20 mmol) and compound **5d** (4.1 g, 20 mmol) to obtain the pure product **7d** as a white solid, yield 3.5 g, 89%; mp 83–85 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, 1H, *J* = 6.0 Hz, pyridine-**H**), 7.72 (s, 1H, imidazole-**H**), 7.58 (d, 1H, *J* = 9.0 Hz, pyridine-**H**), 7.43 (d, 1H, *J* = 3.0 Hz, pyridine-**H**), 7.27 (d, 1H, *J* = 4.5 Hz, thiophene-**H),** 7.12 (t, 1H, *J* = 8.3 Hz, thiophene-**H**), 7.06 (t, 1H, *J* = 5.2 Hz, thiophene-**H**), 6.73 (t, 1H, *J* = 6.7 Hz, pyridine-**H**); MS (ESI): *m/z* 201 $(M+1)^+$.

2-(Trifluoromethyl)imidazo[1,2-*a*]pyridine (7e)

This compound was prepared according to the method described for compound **7a**, employing compound **4a** (0.188 g, 20 mmol) and compound **5e** (3.6 g, 20 mmol) to obtain the pure product **7e** as a white solid, yield 3.4 g, 92%; mp 80–82 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.15 (d, 1H, *J* = 6.7 Hz, pyridine-**H**), 7.87 (s, 1H, imidazole-**H**), 7.67 (d, 1H, *J* = 9.2 Hz, pyridine-**H**), 7.32–7.25 (m, 1H, pyridine-**H**), 6.90 (t, 1H, *J* = 6.7 Hz, pyridine-**H**); MS (ESI): *m/z* 187 $(M+1)^+$.

2-(4-Methoxyphenyl)imidazo[1,2-*a*]pyrimidine (7f)

This compound was prepared according to the method described for compound **7a**, employing compound **4b** (0.190 g, 20 mmol) and compound **5a** (4.5 g, 20 mmol) to obtain the pure product **7f** as pale yellow solid, yield 3.9 g, 87%; mp 187–189 °C. ^{1}H NMR($CDCl_3$, 300 MHz): 8.54 (d, 1H, *J* = 7.3 Hz, pyrimidine-**H**), 8.46 (s, 1H, imidazole-**H**), 7.92 (d, 2H, *J* = 6.2 Hz, Ar**H**), 7.82 (d, 1H, *J* = 4.1 Hz, pyrimidine-**H**), 6.94 (d, 2H, *J* = 6.2 Hz, Ar**H**), 6.85 (d, 1H, *J* = 4.1 Hz, pyrimidine-**H**), δ 3.85 (s, 3H, -OC**H**$_3$); MS (ESI): *m/z* 226 $(M+1)^+$.

2-(4-Fluorophenyl)imidazo[1,2-*a*]pyrimidine (7g)

This compound was prepared according to the method described for compound **7a**, employing compound **4b** (0.190 g, 20 mmol) and compound **5b** (4.34 g, 20 mmol) to obtain the pure product **7g** as a pale yellow solid, yield 3.9 g, 92%; mp 228–230 °C. ^{1}H NMR($CDCl_3$, 300 MHz): δ 8.57–8.51 (m, 2H, pyrimidine-**H**), 8.01 (dd, 2H, *J* = 8.8, 5.4 Hz, Ar**H**), 7.88 (s, 1H, imidazole-**H**), 7.14 (t, 2H, *J* = 8.8 Hz, Ar**H**), 6.90 (dd, 1H, *J* = 6.8, 4.1 Hz, pyrimidine-**H**), MS (ESI): *m/z* 214 $(M+1)^+$.

2-(Trifluoromethyl)imidazo[1,2-*a*] pyrimidine (7h*)*

This compound was prepared according to the method described for compound **7a**, employing compound **4b** (0.190 g, 20 mmol) and compound **5e** (3.6 g, 20 mmol) to obtain the pure product **7h** as a white solid, yield 3.3 g, 90%; mp 168–170 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.99 (d, 1H, *J* = 6.9 Hz, pyrimidine-**H**), 8.65 (s, 1H, pyrimidine-**H**), 8.66 (s, 1H, imidazole-**H**), 7.06 (dd, 1H, *J* = 6.9, 4.3 Hz, pyrimidine-**H**); MS (ESI): *m/z* 188 $(M+1)^+$.

Synthesis of 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (8a)

The Vilsmeier reagent was prepared at 0–5 °C by dropping $POCl_3$ (11 mmol) into a stirred solution of DMF (13 mmol) in $CHCl_3$ (5 mL). The 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine **7a** (224 mg, 1mmol) was suspended in chloroform (20 mL). Only for the synthesis of the aldehydes**,** pyridine (12 mmol) was also added. The mixture thus obtained was dropped into the Vilsmeier reagent while maintaining stirring and cooling. The reaction mixture was kept for 3 h at room temperature and under reflux for 4–24 h (according to a TLC test). Chloroform was removed under reduced pressure and the resulting oil was poured onto ice. The crude aldehyde was collected by filtration and crystallized from ethanol to obtain the pure product **8a** as a yellow solid, yield 189 mg, 75%; mp 146–148 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.04 (s, 1H, -C**H**O), 9.66 (d, 2H, *J* = 6.4 Hz, pyridine-**H**), 7.77 (d, 2H, *J* = 8.0 Hz, Ar**H**), 7.55 (t, 1H, *J* = 8.0 Hz, pyridine-**H**), 7.10 (t, 1H *J* = 6.4 Hz, pyridine-**H**), 7.03 (d, 2H, *J* = 8.0 Hz, Ar**H**), 3.88 (s, 3H, -OC**H**$_3$); MS (ESI): *m/z* 253 $(M+1)^+$.

2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (8b)

This compound was prepared according to the method described for compound **8a**, employing compound **7b** (212 mg, 1 mmol) to obtain the pure product **8b** as a white solid, yield 187 mg, 78%; mp 165−167 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.03 (s, 1H, -C**H**O), 9.66 (d, 1H, *J* = 5.9 Hz, pyridine-**H**), 7.82 (d, 2H, *J* = 8.4 Hz, Ar**H**), 7.77 (d, 1H, *J* = 7.6 Hz, pyridine-**H**), 7.57 (t, 1H, *J* = 7.6 Hz, pyridine-**H**), 7.22 (t, 2H, *J* = 8.4 Hz, Ar**H**), 7.12 (t, 1H, *J* = 6.7 Hz, pyridine-**H**); MS (ESI): *m/z* 241 $(M+1)^+$.

2-(3,4-Dimethoxyphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (8c)

This compound was prepared according to the method described for compound **8a**, employing compound **7c** (254 mg, 1 mmol) to obtain the pure product **8c** as a pale yellow solid, yield 215 mg, 76%; mp 158−160 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.07 (s, 1H, -C**H**O), 9.66 (d, 1H, *J* = 6.7 Hz, pyridine-**H**), 7.78 (d, 1H, *J* = 9.0 Hz, pyridine-**H**), 7.57 (t, 1H, *J* = 6.7 Hz, Ar**H**), 7.41(s, 1H, pyridine-**H**), 7.33 (d, 1H, *J* = 8.3 Hz, Ar**H**), 7.11 (t, 1H *J* = 6.7 Hz, pyridine-**H**), 6.98 (d, 1H *J* = 8.3 Hz, Ar**H**), 3.99 (s, 3H, -OC**H**$_3$), 3.96 (s, 3H, -OC**H**$_3$); MS (ESI): *m/z* 283 $(M+1)^+$.

2-(Thiophen-2-yl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (8d)

This compound was prepared according to the method described for compound **8a**, employing compound **7d** (200 mg, 1 mmol) to obtain the pure product **8d** as a yellow solid, yield 178 mg, 78%; mp 132−134 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.31 (s, 1H, -C**H**O), 9.63 (d, 1H, *J* = 6.7 Hz, pyridine-**H**), 7.74 (d, 1H, *J* = 9.0 Hz, pyridine-**H**), 7.61 (d, 1H, *J* = 4.5 Hz, pyridine-**H**), 7.57 (d, 1H, *J* = 1.2 Hz, thiophene-**H**), 7.53 (d, 1H, *J* = 6.0 Hz, thiophene-**H**), 7.18 (t, 1H, *J* = 5.0 Hz, thiophene-**H**), 7.09 (d, 1H, *J* = 6.7 Hz, pyridine-**H**); MS (ESI): *m/z* 229 $(M+1)^+$.

2-(Trifluoromethyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (8e)

This compound was prepared according to the method described for compound **8a**, employing compound **7e** (186 mg, 1 mmol) to obtain the pure product **8e** as a yellow solid, yield 172 mg, 80%; mp 112−114 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.20 (s, 1H, -C**H**O), 9.66 (d, 1H, *J* = 6.98 Hz, pyridine-**H**), 7.88 (d, 1H, *J* = 9.06 Hz, pyridine-**H**),

7.68–7.62 (m, 1H, pyridine-**H**), 7.25 (t, 1H, *J* = 6.42 Hz, pyridine-**H**); MS (ESI): *m/z* 215 $(M+1)^+$.

2-(4-Methoxyphenyl)imidazo[1,2-*a*]pyrimidine-3-carbaldehyde (8f)

This compound was prepared according to the method described for compound **8a**, employing compound **7f** (225 mg, 1 mmol) to obtain the pure product **8f** as a brown solid, yield 192 mg, 76%; mp 178–180 °C. ^{1}H NMR($CDCl_3$, 300 MHz): δ 10.11 (s, 1H, C**H**O), 9.88 (dd, 1H, *J* = 6.7, 2.1 Hz, pyrimidine-**H**), 8.81 (dd, 1H, *J* = 4.1, 2.0 Hz, pyrimidine-**H**), 7.87 (d, 2H, *J* = 8.8 Hz, Ar**H**), 7.16 (dd, 1H, *J* = 6.7, 4.3 Hz, pyrimidine-**H**), 7.05 (d, 2H, *J* = 8.6 Hz, Ar**H**), 3.89 (s, 3H, -OC**H**$_3$); MS (ESI): *m/z* 254 $(M+1)^+$.

2-(4-Fluorophenyl)imidazo[1,2-*a*]pyrimidine-3-carbaldehyde (8g)

This compound was prepared according to the method described for compound **8a**, employing compound **7g** (213 mg, 1 mmol) to obtain the pure product **8g** as a yellow solid, yield 190 mg, 79%; mp 208–210 °C. ^{1}H NMR($CDCl_3$, 300 MHz): δ 10.11 (s, 1H, C**H**O), 9.90 (d, 1H, *J* = 7.2 Hz, pyrimidine-**H**), 8.84 (dd, 1H, *J* = 6.1, 4.2 Hz, pyrimidine-**H**), 7.92 (dd, 2H, *J* = 8.8, 5.6 Hz, Ar**H**), 7.28–7.17 (m, 3H, pyrimidine-**H,** Ar**H**); MS (ESI): *m/z* 242 $(M+1)^+$.

2-(Trifluoromethyl)imidazo[1,2-*a*]pyrimidine-3-carbaldehyde (8h)

This compound was prepared according to the method described for compound **8a**, employing compound **7h** (187 mg, 1 mmol) to obtain the pure product **8g** as a yellow solid, yield 168 mg, 78%; mp 168–170 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.23 (s, 1H, C**H**O), 9.90 (dd, 1H, *J* = 6.7, 1.5 Hz, pyrimidine-**H**), 8.95 (dd, 1H, *J* = 3.7, 2.2 Hz, pyrimidine-**H**), 7.34 (dd, 1H, *J* = 6.7, 3.7 Hz, pyrimidine-**H**); MS (ESI): *m/z* 216 $(M+1)^+$.

Synthesis of (2*E*)-1-(3,4,5-trimethoxyphenyl)-3-(2-(4-methoxyphenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one (3a)

A mixture of 1-(3,4,5-trimethoxyphenyl)ethanone **9a** (210 mg, 1 mmol) and 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde **8a** (253 mg, 1 mmol) was

dissolved in 10 mL ethanol. To this mixture, pottasium hydroxide (40%, 1 mL) was added at 0–5 ^{o}C. The reaction mixture was stirred at room temperature for 45 min. Then this reaction mixture was poured over crushed ice and acidified with dil HCl. The light yellow solid thus obtained was filtered, washed with water and dried. The residue was purified on column chromatography (silica gel with 50% ethyl acetate in hexane) to afford compound **3a** as a yellow solid, yield 360 mg, 81%; mp 132–134 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.49 (d, 1H, *J* = 6.44 Hz, pyridine-**H**), 8.16 (d, 1H, *J* = 16.1 Hz, olefin-**H**), 7.74 (d, 1H, *J* = 8.86 Hz, Ar**H**), 7.72 (d, 1H, *J* = 8.06 Hz, pyridine-**H**), 7.42 (d, 1H, *J* = 16.4 Hz, olefin-**H**), 7.36 (d, 1H, *J* = 8.8 Hz, Ar**H**), 7.27 (d, 1H, *J* = 6.44 Hz, pyridine-**H**), 7.12 (s, 2H, Ar**H**), 7.04 (d, 2H, *J* = 8.86 Hz, Ar**H**), 6.99 (d, 1H, *J* = 8.86 Hz , pyridine-**H**), 3.91 (s, 3H, -OC**H**$_3$), 3.88 (s, 6H, -2×OC**H**$_3$), 3.87 (s, 3H, -OC**H**$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.1, 160.1, 152.9, 150.8, 146.9, 142.1, 133.4, 130.7, 129.1, 127.6, 126.3, 124.6, 120.4, 117.8, 116.8, 114.0, 112.1, 105.6, 60.8, 56.1, 55.1; MS (ESI): *m/z* 445 $(M+1)^+$; HRMS (ESI *m/z*) for $C_{26}H_{25}N_2O_5$, calcd 445.1763, found 445.1771 $(M+1)^+$.

(2*E*)-3-(2-(4-Fluorophenyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)-1-(3,4,5-trimethoxyphenyl) prop-2-en-1-one (3b)

This compound was prepared according to the method described for compound **3a**, employing compound **9a** (210 mg, 1 mmol) and compound **8b** (240 mg 1 mmol) to obtain the pure product **3b** as a yellow solid, yield 337 mg, 78%; mp 168–170 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.49 (d, 1H, *J* = 6.7 Hz, pyridine-**H**), 8.12 (d, 1H, *J* = 16.8 Hz, olefin-**H**), 7.80–7.73 (m, 3H, Ar**H,** pyridine-**H**), 7.44 (d, 1H, *J* = 15.4 Hz, olefin-**H**), 7.38 (s, 1H, pyridine-**H**), 7.25–7.16 (m, 2H, Ar**H**), 7.09 (s, 2H, Ar**H**), 7.06 (d, 1H, *J* = 6.98 Hz, pyridine-**H**), 3.92 (s, 3H, -OC**H**$_3$), 3.89 (s, 6H, -2×OC**H**$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 187.8, 152.9, 146.9, 142.3, 133.2, 131.2, 128.7, 126.4, 127.0, 124.6, 121.4, 118.0, 117.4, 115.8, 115.6, 114.1, 112.3, 105.5, 56.1, 55.2; MS (ESI): *m/z* 433 $(M+1)^+$; HRMS (ESI *m/z*) for $C_{25}H_{22}N_2O_4F$, calcd 433.1539, found 433.1530 $(M+1)^+$.

(2*E*)-1-(3,4,5-Trimethoxyphenyl)-3-(2-(3,4-dimethoxyphenyl)*H*-imidazo[1,2-*a*] pyridin-3-yl)prop-2-en-1-one (3c)

This compound was prepared according to the method described for compound **3a**, employing compound **9a** (210 mg, 1 mmol) and compound **8c** (282 mg, 1 mmol) to obtain the pure product **3c** as a yellow solid, yield 390 mg, 82%; mp 99–101 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (d, 1H, *J* = 7.5 Hz, pyridine-**H**), 8.14 (d, 1H, *J* = 15.1 Hz, olefin-**H**), 7.70 (d, 1H, *J* = 9.0 Hz, pyridine-**H**), 7.43 (d, 1H, *J* = 15.8 Hz, olefin-**H**), 7.40–7.17 (m, 3H, Ar**H**, pyridine-**H**), 7.09 (s, 2H, Ar**H**), 7.01 (d, 1H, *J* = 4.3 Hz, ArH), 6.95 (d, 1H, *J* = 6.6 Hz, pyridine-**H**), 3.92 (s, 6H, -2×OC**H**$_3$), 3.87 (s, 9H, -3×OC**H**$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 188.1, 158.8, 152.9, 149.6, 149.0, 147.0, 129.3, 129.0, 127.6, 126.9, 124.8, 122.2, 120.4, 117.9, 117.0, 113.9, 112.0, 111.0, 110.6, 105.5, 60.8, 56.1, 55.7; MS (ESI): *m/z* 475 $(M+1)^+$; HRMS (ESI *m/z*) for $C_{27}H_{27}N_2O_6$, calcd 475.1869, found 475.1853 $(M+1)^+$.

(2*E*)-1-(3,4,5-Trimethoxyphenyl)-3-(2-(thiophen-2-yl)*H*-imidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one (3d)

This compound was prepared according to the method described for compound **3a**, employing compound **9a** (210 mg, 1 mmol) and compound **8d** (228 mg 1 mmol) to obtain the pure product **3d** as a yellow solid, yield 336 mg, 80%; mp 175–177 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.49 (d, 1H, *J* = 6.6 Hz, pyridine-**H**), 8.28 (d, 1H, *J* = 15.4 Hz, olefin-**H**), 7.71 (d, 1H, *J* = 8.8 Hz, pyridine-**H**), 7.56 (s, 1H, pyridine-**H**), 7.53 (d, 1H, *J* = 15.4 Hz, olefin-**H**), 7.48 (d, 1H, *J* = 5.1 Hz, thiophene-**H**), 7.36 (t, 1H, *J* = 7.3 Hz, thiophene-**H**), 7.21 (s, 2H, Ar**H**), 7.15 (t, 1H, *J* = 4.3 Hz, thiophene-**H**), 7.01 (t, 1H, *J* = 6.6 Hz, pyridine-**H**), 3.93 (s, 9H, -3×OC**H**$_3$); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 188.3, 153.0, 147.1, 142.3, 136.1, 133.4, 129.2, 127.8, 127.7, 127.2, 126.5, 125.2, 117.9, 117.6, 114.1, 112.2, 105.8, 105.6, 56.2, 55.5; MS (ESI): *m/z* 421 $(M+1)^+$; HRMS (ESI *m/z*) for $C_{23}H_{20}N_2O_4NaS$, calcd 443.1041, found 443.1033 (M+Na).

(2*E*)-3-(2-(Trifluoromethyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (3e)

This compound was prepared according to the method described for compound **3a**, employing compound **9a** (210 mg, 1 mmol) and compound **8e** (215 mg, 1 mmol) to obtain the pure product **3e** as a yellow solid, yield 324 mg, 80%; mp 140–142 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.96 (d, 1H, *J* = 6.9 Hz, pyridine-**H**), 8.06 (d, 1H, *J* =18.9 Hz, olefin-**H**), 7.80 (d, 1H, *J* = 18.9 Hz, olefin-**H**), 7.60 (t, 2H, *J* = 7.7 Hz, pyridine-**H**), 7.36 (s, 2H, Ar**H**), 7.28 (t, 1H, *J* = 6.90 Hz, pyridine-**H**), 3.93 (s, 6H, -2×OC**H**$_3$), 3.85 (s, 3H, -OC**H**$_3$); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 187.2, 153.5, 149.1, 145.2, 135.4, 130.3, 127.3, 124.2, 123.5, 122.6, 120.1, 119.3, 115.1, 110.5, 109.7, 55.6, 55.7; ESI-MS: 407 $(M+1)^+$; HRMS (ESI *m/z*) for $C_{20}H_{18}N_2O_4F_3$, calcd 407.1218, found 407.1215 $(M+1)^+$.

(2*E*)-3-(2-(trifluoromethyl)*H*-imidazo[1,2-*a*]pyridin-3-yl)-1-(3,4-dimethoxyphenyl) prop-2-en-1-one (3f)

This compound was prepared according to the method described for compound **3a**, employing compound **9b** (180 mg, 1 mmol) and compound **8e** (214 mg, 1 mmol) to obtain the pure product **3b** as a yellow solid**, y**ield 309 mg, 82%; mp 188–190 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.44 (d, 1H, *J* = 6.9 Hz, pyridine-**H**), 7.99 (d, 1H, *J* = 15.6 Hz, olefin-**H**), 7.78 (d, 1H, *J* = 9.0 Hz, pyridine-**H**), 7.69 (d, 1H, *J* = 15.6 Hz, olefin-**H**), 7.64–7.59 (m, 2H, Ar**H**), 7.43 (t, 1H, *J* = 6.7 Hz, pyridine-**H**), 7.10 (t, 1H, *J* = 6.0 Hz, pyridine-**H**), 6.93 (d, 1H, *J* = 8.3 Hz, Ar**H**), 3.99 (s, 3H, -OC**H**$_3$), 3.97 (s, 3H, -OC**H**$_3$); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 187.1, 153.5, 149.2, 145.3, 136.0, 135.5, 130.5, 127.6, 124.6, 123.5, 120.1, 119.9, 115.2, 110.5, 56.0, 55.8; ESI-MS: 377 $(M+1)^+$; HRMS (ESI *m/z*) for $C_{19}H_{15}N_2O_3F_3Na$, calcd 399.0932, found 399.0926 (M+Na).

(2*E*)-1-(3,4,5-Trimethoxyphenyl)-3-(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyrimidin-3-yl)prop-2-en-1-one (3g)

This compound was prepared according to the method described for compound **3a**, employing compound **9a** (210 mg, 1 mmol) and compound **8f** (253 mg, 1 mmol) to obtain the pure product **3g** as a yellow solid, yield 347 mg, 78%; mp 150–152 °C. ^{1}H NMR($CDCl_3$, 300 MHz): δ 8.78 (d, 1H, *J* = 6.7 Hz, pyrimidine-**H**), 8.57 (s, 1H,

pyrimidine-**H**), 8.00 (d, 1H, *J* = 15.4 Hz, olefin-**H**), 7.72 (d, 2H, *J* = 8.3 Hz, Ar**H**), 7.42 (d, 1H, *J* = 15.4 Hz, olefin-**H**), 7.27 (d, 1H, *J* = 3.5 Hz, pyrimidine-**H**), 7.10 (s, 2H, Ar**H**), 6.97 (d, 2H, *J* = 7.9 Hz, pyrimidine-**H**), 3.95 (s, 3H, -OC**H**$_3$), 3.89 (s, 6H, 2×OC**H**$_3$), 3.86 (s, 3H, -OC**H**$_3$); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 187.7, 160.4, 152.9, 151.8, 151.1, 149.6, 142.3, 135.3, 132.4, 130.2, 128.5, 125.5, 118.4, 116.0, 114.0, 109.7, 105.6, 60.8, 56.1, 55.1; ESI-MS: 446 $(M+1)^+$; HRMS (ESI *m/z*) for $C_{25}H_{24}N_3O_5$, calcd 446.1715, found 446.1735 $(M+1)^+$.

(2*E*)-3-(2-(4-Fluorophenyl)imidazo[1,2-*a*]pyrimidin-3-yl)-1-(3,4,5-trimethoxyphenyl) prop-2-en-1-one (3h)

This compound was prepared according to the method described for compound **3a**, employing compound **9a** (210 mg, 1 mmol) and compound **8g** (241 mg, 1 mmol) to obtain the pure product **3h** as a yellow solid, yield 355 mg, 82%; mp 199–201 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.79 (d, 1H, *J* = 5.6 Hz, pyrimidine-**H**), 8.71 (d, 1H, *J* = 8.0 Hz, Ar**H**), 8.10 (d, 1H, *J* = 15.3 Hz, olefin-**H**), 7.86 (dd, 2H, *J* = 8.8, 5.6 Hz, Ar**H**), 7.44 (d, 1H, *J* = 15.3 Hz, olefin-**H**), 7.27 (d, 1H, *J* = 7.2 Hz, pyrimidine-**H**), 7.22 (d, 1H, *J* = 8.8 Hz, Ar**H**), 7.23 (d, 1H, *J* = 8.0 Hz, pyrimidine-**H**), 7.13 (s, 2H, Ar**H**), 3.93 (s, 3H, -OC**H**$_3$), 3.90 (s, 6H, 2×OC**H**$_3$), ^{13}CNMR ($CDCl_3$, 75 MHz): δ 187.6, 153.1, 151.4, 150.6, 135.2, 133.4, 132.9, 131.4, 131.3, 128.4, 128.1, 121.8, 119.3, 115.7, 110.0, 108.3, 105.8, 56.2, 55.4; ESI-MS: 434 $(M+1)^+$; HRMS (ESI *m/z*) for $C_{24}H_{21}N_3O_4F$, calcd 434.1516, found 434.1528 $(M+1)^+$.

(2*E*)-3-(2-(Trifluoromethyl)imidazo[1,2-*a*]pyrimidin-3-yl)-1-(3,4,5-trimethoxyphen-yl)prop-2-en-1-one (3i)

This compound was prepared according to the method described for compound **3a**, employing compound **9a** (210 mg, 1 mmol) and compound **8h** (215 mg, 1 mmol) to obtain the pure product **3i** as a yellow solid, yield 321 mg, 79%; mp 180–182 °C. ^{1}H NMR($CDCl_3$, 300 MHz): δ 9.16 (d, 1H, *J* = 6.6 Hz, pyrimidine-**H**), 8.78 (d, 1H, *J* = 5.1 Hz, pyrimidine-**H**), 7.88 (d, 1H, *J* = 16.1 Hz, olefin-**H**) 7.67 (d, 1H, *J* = 15.5 Hz, olefin-**H**), 7.25 (d, 1H, *J* = 5.2 Hz, pyrimidine-**H**), 7.08 (s, 2H, Ar**H**), 3.91 (s, 6H, 2×OC**H**$_3$),

3.88 (s, 3H, -OC**H**$_3$); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 187.0, 153.4, 149.1, 145.2, 130.5, 127.6, 124.6, 123.4, 122.9, 120.0, 119.1, 115.2, 110.4, 109.9, 55.9, 55.8; ESI-MS: 408 $(M+1)^+$; HRMS (ESI *m/z*) for $C_{19}H_{16}N_3O_4F_3Na$, calcd 430.0990, found 430.0977 (M+Na).