Electronic Supplementary Material (ESI) for MedChemComm.

Supporting information

Synthesis and biological evaluation of Chalcone-linked pyrazolo[1,5-*a*]pyrimidines as potential anticancer agents

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Supporting Data

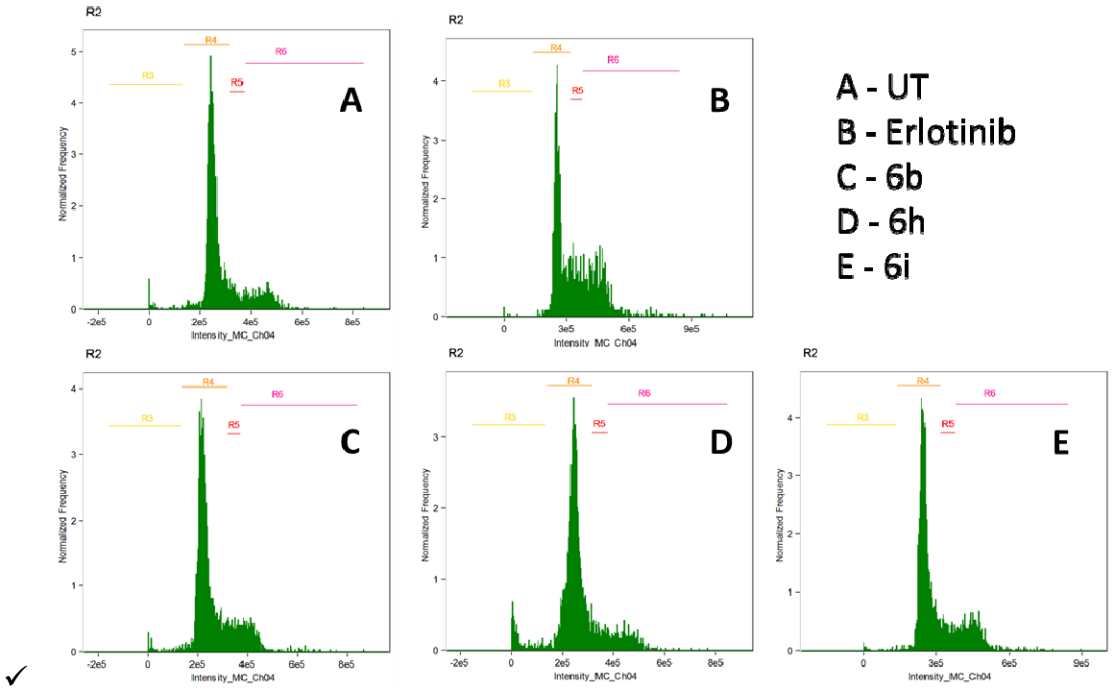

Fig. 1 . Flow cytometric analysis for HEK cell line displaying no difference in treated and untreated cell.

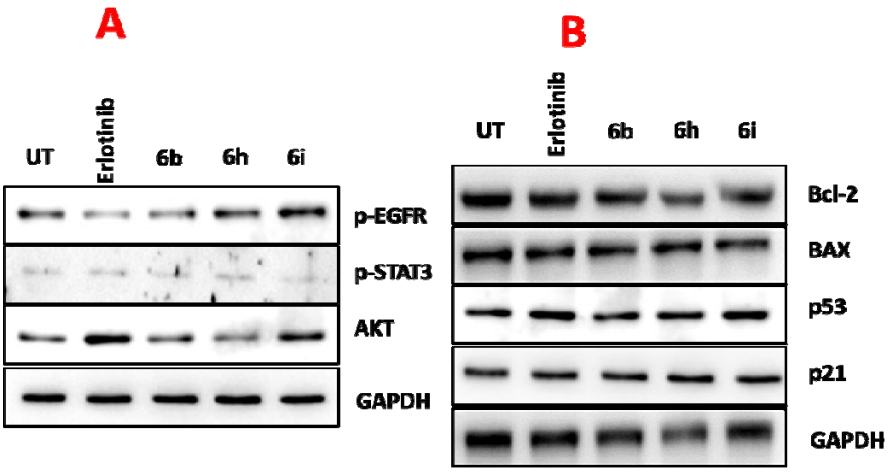

Fig. 2. Western blot analysis on HEK cell line A) Effect of **6b**, **6h** and **6i** on p-EGFR, p-STAT3 and AKT. B) Effect of **6b**, **6h** and **6i** on Bcl-2, BAX, p53, p21.

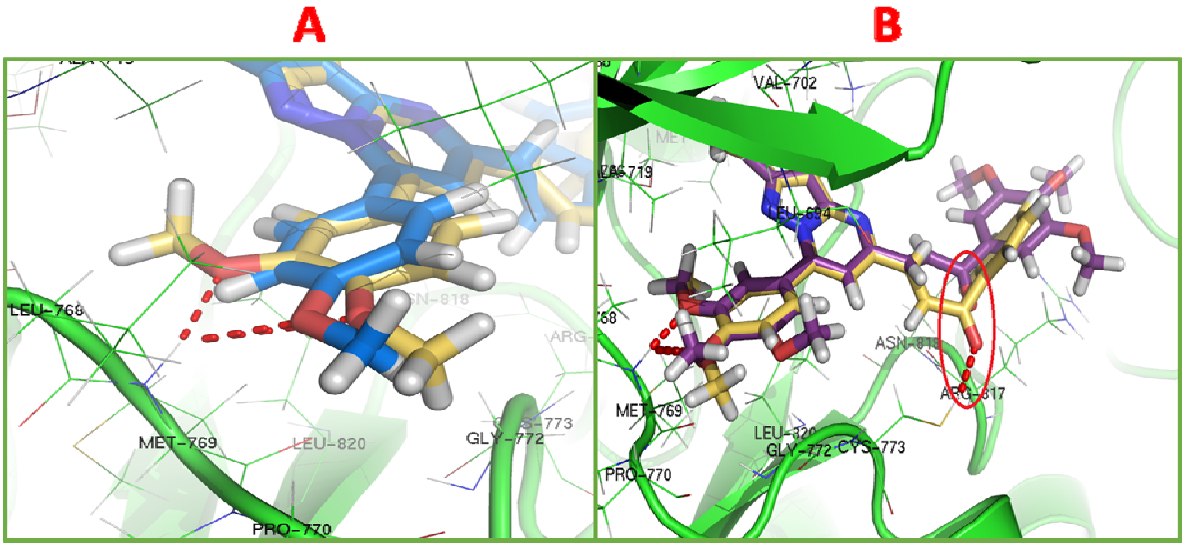

Fig. 3 A) Docking pose showing the differences hydrogen bonding between 4-methoxy substituted hybrids **6b** (blue color) and 3,4-dimethoxy substituted hybries **6j** (Yellow color). B) Docking pose highlighted the difference in hydrogen bondign in the **6j** (yellow color) and **6p** (voilet color) with Cys773.

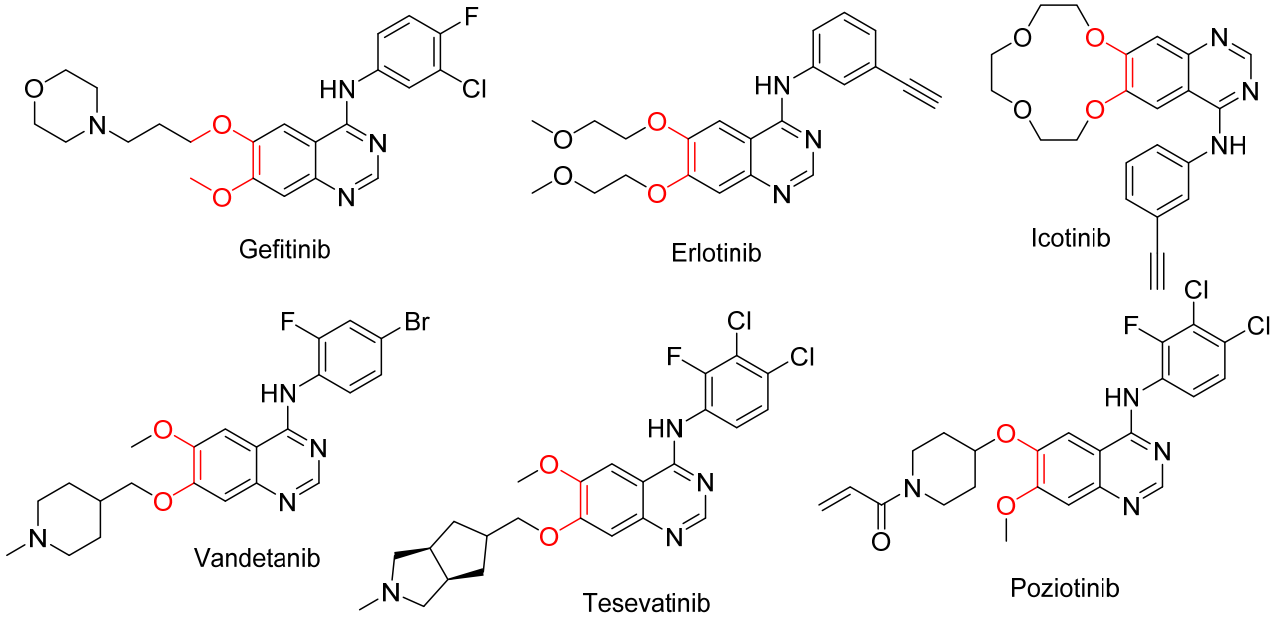

Fig. 4 Chemical structures of drugs acting on EGFR with dialkoxy groups.

Experimental Section

Biology

Maintenance of cell culture and evaluation of anti-proliferative activity:

Mammalian cell lines (A549, MDAMB-231 and DU-145) employed during the course of experiments were purchased from American Type Culture Collection (ATCC, USA). The cells were grown in Dulbecco's modified Eagle's medium (DMEM), which is supplemented with respective antibiotics and 10% fetal bovine serum. Cells were maintained in incubator at 37℃ with 5% CO2 and 95% air. For the estimation of anti-proliferative activity of the compounds, MTT cell proliferation assay was utilized [1]. For the assay, cells were seeded into a 96 well plate at a seeding density of $1*10^4$ cells/well and five different concentrations (0.01µM, 0.1µM, 1µM, 10µM and 100µM) of compounds were treated in triplicates. Post-treatment (24hrs), 5µl of 10% MTT was aliquoted in each well and incubated for 60 minutes at 37℃. After the incubator, plates were air-dried and 100 µl DMSO was added to each well and absorbance reading were calculated with Varioscan Flash multimode plate reader at 560nm. Depending on the absorbance values, IC50 was calculated with mean ± SD.

Flow cytometry analysis:

To evaluate the effect of compound on distribution of cell cycle, flow cytometry analysis was performed with the help of Becton Dickinson MoFlo Legacy flow cytometer. A549 cells were grown in 60mm dishes and treated with compounds for 24 hours before fixation with 70% ethanol. Cells were stained with staining solution containing 100 µg of RNase A and 0.05 mg of Propidium iodide (PI) for 30 minutes in dark at 37℃. Post incubation, cells were analysed and histograms of cell cycle distribution were plotted by Summit V4.3 software.[1]

Immunocytochemistry:

A549 cells were grown on 18mm cover slips at seeding density of 1*10,000 cells/well in a 6-well plate. The cells were then treated with the compounds and incubated for 24hours. Untreated sample was used as negative control, whereas Erlotinib was positive control. Post incubation, cells were fixed with 4% p-formaldehyde, followed by permebilization with 0.2% Triton-X for 5 minutes. Cells were then washed with PBS (twice) and primary antibody, followed by secondary antibody were incubated for 2 hours and 1 hour respectively. Finally, DAPI (Vector Shield) was employed as counterstain and mounted onto slides to be further analysed with the help of

fluorescent confocal microscope (FLOW VIEW FV 1000 series) and FV10ASW 1.7 series software.[2]

Western blotting:

Cells were grown in 100mm plates for immunoblotting. Post-treatment, cells were trypsinized and lysed with the help of RIPA buffer supplemented with protease inhibitor and phosphatase inhibitor. The protein fraction was collected after centrifuging for 15minutes at 12,000 rpm. Protein levels were calculated with Bradford assay and separated through SDS-PAGE. Gels were further transferred to a nitrocellulose membrane and probed with respective antibody. The secondary antibody conjugate upon developing with Luminal reagent produced Chemiluminescence, which was captured using the Biorad imaging system (Chemdoc MP).[3]

Isolation of RNA and gene expression analysis:

For gene expression analysis, cells were grown in 60mm dishes and treated with compounds for 24hours. Post-treatment, cells were collected and RNA was isolated with Trizol reagent [2]. RNA was confirmed with agarose gel electrophoresis and cDNA was produced with RNA to cDNA EcoDry™ Premix (Oligo dT). Primers for specific gene were employed for each samples and the levels of expression were evaluated by polymerase chain reaction, followed by agarose gel electrophoresis.

Chemistry

General

All chemicals and reagents were obtained 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 plate containing 60 GF-254, and visualization was achieved by UV light or iodine indicator. Column chromatography was performed with Merck 60–120 mesh silica gel. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ and DMSO-d_6 by using Varian and Avance instruments. Chemical shifts are expressed in parts per million (δ in ppm) downfield from internal TMS and coupling constants are expressed in Hz. ^{1}H NMR spectroscopic data are reported in the following order: multiplicity (s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet), coupling constants in Hz, number of protons. HRMS analyses were acquired on Agilent Q-TOF-Mass Spectrometer

6540-UHD and carried out in the ESI techniques at 70 eV. Melting points were determined with an Electrothermal melting point apparatus, and are uncorrected.

General Procedure for preparation of compounds (9a-c).

Small pieces of metal sodium were added to the ethanol and allowed to react completely. To the solutions diethyl oxalate were added at 0 ºC and stirred for ¼ h. To this mixture acetophenones were added and stirred for 4 h. After reaction completion, solvent was removed and mixture was suspended in water extracted with EtOAc. Combined organic phases washed with brine, dried over Na_2SO_4, concentrated in vacuo. The resulting solid was purified using column chromatography on silica to afford pure compound (**9a-c**).

General procedure for preparations of compounds (10a-c).

To the solution of compound (**9a-c**) in ethanol, 3-amino-5-phenylpyrazole added followed by 4-5 drops of Conc. HCl. The mixture was refluxed for 4 h, the precipitate was formed. Mixture was cooled to room temperature and precipitated was collected using vacuum filtration, and washed with ethanol to afford pure yellow crystalline compound (**10a-c**).

Ethyl 7-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (10a).

Yellow solid; 90% yield; Mp: 152–154 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.9 H, 2H), 8.01 (d, *J* = 7.0 2H), 7.68 (s, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 14.6 1H), 7.26 (s, 1H), 7.12 (d, *J* = 8.5 2H), 4.55 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 3H), 1.49 (t, *J* = 7.1 Hz, 3H); MS (ESI): m/z 374 $[M + H]^+$.

Ethyl 7-(3,4-dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (10b).

Yellow solid; 92% yield; Mp: 183–185 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (m, 3H), 7.87 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.71 (s, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.41 (t, J = 14.5 Hz, 1H), 7.27 (s, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 4.02 (s, 3H), 4.01 (s, 3H), 1.50 (t, *J* = 14.3 Hz, 3H); MS (ESI): m/z 404 $[M + H]^+$.

Ethyl 2-phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidine-5-carboxylate (10c).

Yellow solid; 95% yield; Mp: 194–196 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 7.2 Hz, 2H), 7.72 (s, 1H), 7.57 (s, 2H), 7.53 (t, J = 14.8 Hz, 2H), 7.44 (t, J = 15.7 Hz, 1H), 7.30 (s, 1H), 4.57 (q, J = 7.1 Hz, 1H), 3.99 (s, 9H), 1.51 (t, J = 7.1 Hz, 3H); MS (ESI): m/z 434 $[M + H]^+$.

General Procedure for preparation of compounds (11a-c) pyrazolo[1,5-*a*]pyrimidine-5-carbaldehydes.

To the solution of ester (**10a-c**) in DCM, DIBAL-H were added at -78 ºC and reaction was stirred for ½ h. The reaction was quenched using diluted HCl and allow to come to room temperature. Aqueous layer was extracted with DCM and dried with Na_2SO_4 and concentrated in vacuo. The solid was purified with column chromatography.

7-(4-Methoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine-5-carbaldehyde (11a).

Yellow solid; 80% yield; Mp: 214–216 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.05 (s, 1H), 8.31 (d, *J* = 8.9 Hz, 2H), 8.06 (d, *J* = 7.2 Hz, 2H), 7.53 (s, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.30 (s, 1H), 7.13 (d, *J* = 8.9 Hz, 2H), 3.94 (s, 3H); MS (ESI): m/z 330 $[M + H]^+$.

7-(3,4-Dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine-5-carbaldehyde (11b).

Yellow solid; 80% yield; Mp: 184–187 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.06 (s, 1H), 8.06 (d, *J* = 7.0 Hz, 2H), 8.01 (d, *J* = 2.1 Hz, 1H), 7.89 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.55 (s, 1H), 7.50 (t, *J* = 14.8 Hz, 2H), 7.44 (t, *J* = 14.6 Hz, 1H), 7.31 (s, 1H), 7.09 (d, J = 8.5 Hz, 1H), 4.03 (s, 3H), 4.02 (s, 3H); MS (ESI): m/z 360 $[M + H]^+$.

2-Phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidine-5-carbaldehyde (11c).

Yellow solid; 80% yield; Mp: 186–189 ºC; 1H NMR (500 MHz, CDCl3) δ 10.06 (s, 1H), 8.05 (d, J = 7.2 Hz, 2H), 7.56 (s, 2H), 7.55 (s, 1H), 7.50 (t, J = 7.2 Hz, 2H), 7.46–7.42 (m, 1H), 7.33 (s, 1H), 3.99 (s, 3H), 3.99 (s, 6H); MS (ESI): m/z 390 $[M + H]^+$.

General procedure for preparations of compounds (6a-q)

To the solution of aldehyde and barium hydroxide in methanol, acetophenones were added and stirred for 4-6 h. The precipitate were filtered and wash with small amount of methanol and purified using column chromatography.

(*E*)-3-(7-(4-Methoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)-1-phenylprop-2-en-1-one (**6a**) This compound was prepared according to general procedure, by employing **10a** (100

mg, 0.30 mmol) and acetophenones (36 mg, 0.30 mmol) to obtain pure product **6a** as yellow color solid. 119 mg; 91 % yield; Mp: 217-219 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.8 Hz 2H), 8.13 (d, *J* = 8.3 Hz, 2H), 8.11 (s, 1H), 8.04 (m, d, *J* = 7.17 Hz, 2H), 7.80 (d, *J* = 15.4 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.14 - 12 (m, 4H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 161.9, 156.7, 151.8, 151.1, 145.9, 141.6, 137.5, 133.3, 132.8, 131.2, 129.1, 128.8, 128.7, 127.7, 126.6, 122.9, 114.0, 106.7, 94.1, 55.5; HRMS calculated for $C_{28}H_{21}O_2N_5$ $[M + H]^+$ 432.1707, found 432.1708.

(*E*)-1-(4-Methoxyphenyl)-3-(7-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (**6b**) This compound was prepared according to general procedure, by employing **10a** (100 mg, 0.30 mmol) and 4-methoxy-acetophenones (45 mg, 0.30 mmol) to obtain pure product **6b** as yellow color solid; 125 mg; 89 % yield; Mp: 223-225 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.8 Hz 2H), 8.13 (d, *J* = 8.3 Hz, 2H), 8.11 (s, 1H), 8.04 (m, d, *J* = 7.17 Hz, 2H), 7.80 (d, *J* = 15.4 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.14 - 12 (m, 4H), 7.02 (d, *J* = 8.9 Hz, 2H), 3.94 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.2, 161.8, 156.7, 151.8, 151.1, 145.9, 141.6, 133.3, 132.8, 131.2, 130.4, 129.1, 128.8, 128.7, 127.7, 126.6, 122.9, 114.0, 106.7, 94.1, 56.1, 55.5; HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 462.1812, found 462.1812.

(*E*)-1-(3,4-Dimethoxyphenyl)-3-(7-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (**6c**) This compound was prepared according to general procedure, by employing **10a** (100 mg, 0.30 mmol) and 3,4-dimethoxy-acetophenones (54 mg, 0.30 mmol) to obtain pure product **6c** as yellow color solid; 134 mg; 90 % yield; Mp: 235-237 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.9 Hz, 2H), 8.17 (d, *J* = 15.3 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 2H), 7.85 – 7.77 (m, 2H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.15 – 7.09 (m, 4H), 6.96 (d, *J* = 8.4 Hz, 1H), 3.99 (d, *J* = 1.8 Hz, 6H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.1, 162.0, 156.7, 153.8, 152.1, 151.2, 149.4, 146.0, 140.8, 132.9, 131.3, 130.8, 129.1, 128.8, 127.5, 126.7, 123.8, 123.0, 114.1, 110.8, 110.0, 107.0, 94.0, 56.2, 56.1, 55.5. HRMS calculated for $C_{30}H_{25}O_4N_3$ $[M + H]^+$ 492.1918, found 492.1918.

(*E*)-3-(7-(3,4-Dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)-1-phenylprop-2-en-1-one (**6d**) This compound was prepared according to general procedure, by employing **10b**

(100 mg, 0.28 mmol) and acetophenones (34 mg, 0.28 mmol) to obtain pure product **6d** as yellow color solid; 111 mg; 87 % yield; Mp: 240-241 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 – 8.10 (m, 3H), 8.06 – 7.99 (m, 3H), 7.84 – 7.77 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 11.9 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 1H), 4.03 (s, 3H), 4.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.2, 156.7, 151.8, 151.6, 151.2, 148.6, 145.9, 141.5, 137.5, 133.3, 132.8, 129.1, 128.8, 128.8, 128.8, 127.8, 126.5, 123.1, 123.0, 112.6, 110.9, 107.0, 94.1, 56.2, 56.1; HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 462.1812, found 462.1813.

(*E*)-3-(7-(3,4-Dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)-1-(p-tolyl)prop-2-en-1-one (**6e**) This compound was prepared according to general procedure, by employing **10b** (100 mg, 0.28 mmol) and 4-methyl-acetophenones (38 mg, 0.28 mmol) to obtain pure product **6e** as yellow color solid; 119 mg; 90 % yield; Mp: 236-237 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 15.4 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 4H), 8.01 (d, *J* = 2.1 Hz, 1H), 7.83 – 7.76 (m, 2H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 10.3 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 1H), 4.03 (s, 3H), 4.02 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 156.7, 152.0, 151.6, 151.2, 148.7, 145.9, 144.3, 141.1, 135.0, 132.8, 129.5, 129.2, 129.0, 128.8, 128.0, 126.6, 123.2, 123.08, 112.7, 111.0, 107.0, 94.1, 56.2, 56.1, 21.8; HRMS calculated for $C_{30}H_{25}O_3N_3$ $[M + H]^+$ 476.1969, found 476.1969.

(*E*)-3-(7-(3,4-Dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)-1-(3,4-dimethylphenyl)prop-2-en-1-one (**6f**) This compound was prepared according to general procedure, by employing **10b** (100 mg, 0.28 mmol) and 3,4-dimethyl-acetophenones (41 mg, 0.28 mmol) to obtain pure product **6f** as yellow color solid; 116 mg; 85 % yield; Mp: 252-254 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 15.4 Hz, 1H), 8.04 (d, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 1.9 Hz, 1H), 7.90 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.84 – 7.75 (m, 2H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 51H), 4.03 (s, 3H), 4.01 (s, 3H), 2.38 (s, 2H), 2.36 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 156.7, 152.1, 151.6, 151.3, 148.7, 145.9, 143.1, 141.0, 137.3, 135.5, 132.5, 130.01, 129.9, 129.2, 128.8, 128.0, 126.7, 126.6, 123.2, 123.1, 112.7, 111.0, 107.1, 94.0, 56.2, 56.1, 20.8, 19.9; HRMS calculated for $C_{31}H_{27}O_3N_3$ $[M + H]^+$ 490.2125, found 490.2125.

(*E*)-3-(7-(3,4-Dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (**6g**) This compound was prepared according to general procedure, by employing **10b** (100 mg, 0.28 mmol) and 4-methoxy-acetophenones (42 mg, 0.28 mmol) to obtain pure product **6g** as yellow color solid; 110 mg; 80 % yield; Mp: 243-245 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 – 8.14 (m, 3H), 8.04 (d, *J* = 8.5 Hz, 2H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.84 – 7.75 (m, 2H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 10.0 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 2H), 4.03 (s, 3H), 4.02 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.3, 163.9, 156.7, 152.1, 151.6, 151.3, 148.7, 145.9, 140.7, 132.9, 131.3, 130.6, 129.1, 128.8, 127.8, 126.6, 123.2, 123.1, 114.0, 112.7, 111.0, 107.1, 94.0, 56.2, 56.1, 55.6; HRMS calculated for $C_{30}H_{25}O_4N_3$ $[M + H]^+$ 492.1918, found 492.1918.

(*E*)-1-(3,4-Dimethoxyphenyl)-3-(7-(3,4-dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (**6h**) This compound was prepared according to general procedure, by employing **10b** (100 mg, 0.28 mmol) and 3,4-dimethoxy-acetophenones (50 mg, 0.28 mmol) to obtain pure product **6h** as yellow color solid; 126 mg; 87 % yield; Mp: 256-258 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, *J* = 15.3 Hz, 1H), 8.08 – 8.00 (m, 3H), 7.87 – 7.77 (m, 3H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4, 1H), 7.13 (d, *J* = 10.6 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 4.03 (s, 3H), 4.02 (s, 3H), 4.00 (s, 3H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.1, 156.6, 153.8, 152.0, 151.6, 151.2, 149.4, 148.6, 145.9, 140.6, 132.8, 130.8, 129.1, 128.8, 127.5, 126.5, 123.8, 123.2, 123.0, 112.6, 110.9, 110.7, 110.0 107.1, 93.9, 56.1, 56.0; HRMS calculated for $C_{31}H_{27}O_5N_3$ $[M + H]^+$ 522.2023, found 522.2024.

(*E*)-3-(7-(3,4-Dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**6i**) This compound was prepared according to general procedure, by employing **10b** (100 mg, 0.28 mmol) and 3,4,5-dimethoxy-acetophenones (59 mg, 0.28 mmol) to obtain pure product **6i** as yellow color solid; 125 mg; 82 % yield; Mp: 261-263 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 15.3 Hz, 1H), 8.08 – 8.01 (m, 3H), 7.85 – 7.79 (m, 2H), 7.48 (t, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.38 (s, 2H), 7.14 (d, *J* = 4.0 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 1H), 4.03 (s, 3H), 4.02 (s, 3H), 3.99 (s, 6H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 156.8, 153.3, 151.8, 151.7, 151.2, 148.7, 146.0, 143.1, 141.4, 132.9,

132.8, 129.9, 129.2, 128.8, 128.2, 127.4, 126.6, 123.2, 123.1, 112.7, 111.6, 111.0, 107.3, 106.5, 94.0, 61.1, 56.6, 56.2, 56.1; HRMS calculated for $C_{32}H_{29}O_6N_3$ $[M + H]^+$ 552.2130, found 552.2131.

(*E*)-1-(4-Chlorophenyl)-3-(7-(3,4-dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (**6j**) This compound was prepared according to general procedure, by employing **10b** (100 mg, 0.28 mmol) and 4-chloroacetophenones (43 mg, 0.28 mmol) to obtain pure product **6j** as yellow color solid; 103 mg; 75 % yield; Mp: 249-251 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 15.3 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 2H), 8.05 -7.99 (m, 3H), 7.84 – 7.78 (m, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.50 – 7.44 (m, 3H), 7.43 – 7.39 (m, 1H), 7.12 (d, *J* = 4.8 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 1H), 4.03 (s, 3H), 4.01 (s, 3H); HRMS calculated for $C_{29}H_{22}O_3N_3Cl$ $[M + H]^+$ 496.1422, found 496.1423.

(*E*)-1-Phenyl-3-(2-phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (**6k**) This compound was prepared according to general procedure, by employing **10c** (100 mg, 0.26 mmol) and acetophenones (31 mg, 0.26 mmol) to obtain pure product **6K** as yellow color solid; 102 mg; 89 % yield; Mp: 245-247 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 – 8.10 (m, 3H), 8.04 (d, *J* = 7.1 Hz, 2H), 7.81 (d, *J* = 15.4 Hz, 1H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.58 – 7.52 (m, 4H), 7.48 (t, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 1.4 Hz, 2H), 4.00 (s, 6), 3.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.1, 156.8, 153.2, 151.9, 151.1, 145.9, 141.3, 140.7, 137.5, 133.3, 132.7, 129.2, 128.8, 128.7, 128.2, 128.1, 127.9, 126.5, 125.7, 107.3, 107.1, 94.2, 61.0, 56.4; HRMS calculated for $C_{30}H_{25}O_4N_3$ $[M + H]^+$ 492.1918, found 492.1916.

(*E*)-3-(2-Phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)-1-(p-tolyl)prop-2-en-1-one (**6l**) This compound was prepared according to general procedure, by employing **10c** (100 mg, 0.26 mmol) and 4-methylacetophenones (35 mg, 0.26 mmol) to obtain pure product **6l** as yellow color solid; 109 mg; 84 % yield; Mp: 248-250 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 15.3 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 4H), 7.82 (d, *J* = 15.3 Hz, 1H), 7.53 (s, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.13 (s, 2H), 3.99 (d, *J* = 1.6 Hz, 9H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.5, 156.7, 153.2, 152.0, 151.1, 145.9, 144.4, 140.9, 140.7, 134.9, 132.7, 129.5, 129.2, 128.9, 128.8, 128.0, 126.5, 125.8, 107.4, 107.1, 94.2, 61.0, 56.4, 21.7; HRMS calculated for $C_{31}H_{27}O_4N_3$ $[M + H]^+$ 506.2075, found 506.2076.

(*E*)-1-(3,4-Dimethylphenyl)-3-(2-phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (**6m**) This compound was prepared according to general procedure, by employing **10c** (100 mg, 0.26 mmol) and 3,4-dimethylacetophenones (38 mg, 0.26 mmol) to obtain pure product **6m** as yellow color solid; 113 mg; 85 % yield; Mp: 257-259 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 15.4 Hz, 1H), 8.05 – 8.01 (d, *J* = 7.2 Hz,2H), 7.90 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 15.4 Hz, 1H), 7.53 (s, 2H),7.48 (t, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 1.9 Hz, 2H), 4.00 (s, 6H), 3.99 (s, 3H), 2.38 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 156.7, 153.1, 152.1, 151.1, 145.9, 143.2, 140.7, 140.6, 137.2, 135.3, 132.7, 129.9, 129.9, 129.2, 128.8, 128.1, 126.6, 126.5, 125.8, 107.5, 107.1, 94.7, 94.1, 61.0, 56.4, 20.1, 19.8; HRMS calculated for $C_{32}H_{29}O_4N_3$ $[M + H]^+$ 520.2231, found 520.2231.

(*E*)-1-(4-Methoxyphenyl)-3-(2-phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (**6n**) This compound was prepared according to general procedure, by employing **10c** (100 mg, 0.26 mmol) and 4-methoxyacetophenones (39 mg, 0.26 mmol) to obtain pure product **6n** as yellow color solid; 107 mg; 80 % yield; Mp: 251-253 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 – 8.13 (m, 3H), 8.03 (d, *J* = 7.1 Hz, 2H), 7.80 (d, *J* = 15.3 Hz, 1H), 7.53 (s, 2H), 7.48 (t, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.13 (s, 2H), 7.02 (d, *J* = 8.9 Hz, 1H), 4.00 (s, 6H), 3.99 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.2, 163.9, 156.7, 153.2, 152.1, 151.1, 145.9, 140.6, 140.4, 132.7, 132.2, 130.5, 129.2, 128.8, 127.9, 126.5, 125.8, 114.0, 107.5, 107.1, 94.1, 61.0, 56.4, 55.5; HRMS calculated for $C_{31}H_{27}O_5N_3$ $[M + H]^+$ 522.2023, found 522.2024.

(*E*)-1-(3,4-Dimethoxyphenyl)-3-(2-phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (**6o**) This compound was prepared according to general procedure, by employing **10c** (100 mg, 0.26 mmol) and 3,4-dimethoxyacetophenones (47 mg, 0.26 mmol) to obtain pure product **6o** as yellow color solid; 126 mg; 89 % yield; Mp: 264-266 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 15.3 Hz, 1H), 8.05 (d, *J* = 15.3 Hz,7.1 2H), 7.86 – 7.77 (m, 2H), 7.68 (d, *J* = 1.9 Hz, 1H), 7.53 (s, 2H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.14 (s, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 4.00 (s, 9H), 4.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.0, 156.7, 153.8, 153.1, 152.1, 151.1, 149.4, 145.9, 140.6, 140.4, 132.7, 130.7,

129.2, 128.8, 127.6, 126.5, 125.7, 123.8, 110.6, 109.9, 107.6, 107.1, 94.1, 61.0, 56.4, 56.1, 56.1; HRMS calculated for $C_{32}H_{29}O_6N_3$ $[M + H]^+$ 552.2129, found 552.2129.

(*E*)-3-(2-Phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**6p**) This compound was prepared according to general procedure, by employing **10c** (100 mg, 0.26 mmol) and 3,4,5-trimethoxyacetophenones (55 mg, 0.26 mmol) to obtain pure product **6p** as yellow color solid; 122 mg; 82 % yield; Mp: 271-173 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 15.3 Hz, 1H), 8.05 – 8.02 (m, 2H), 7.82 (d, *J* = 15.3 Hz, 1H), 7.54 (s, 2H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.38 (s, 2H), 7.14 (d, *J* = 6.2 Hz, 2H), 4.00 (d, *J* = 1.5 Hz, 9H), 3.99 (s, 6H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 156.8, 153.2, 153.2, 151.8, 151.1, 146.0, 143.0, 141.1, 140.7, 132.7, 132.6, 129.2, 128.8, 127.5, 126.5, 125.7, 107.7, 107.1, 106.4, 94.1, 61.0, 56.5, 56.4, 56.3; HRMS calculated for $C_{33}H_{31}O_7N_3$ $[M + H]^+$ 582.2235, found 582.2235.

(*E*)-1-(4-Chlorophenyl)-3-(2-phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (**6q**) This compound was prepared according to general procedure, by employing **10c** (100 mg, 0.26 mmol) and 4-chloroacetophenones (40 mg, 0.26 mmol) to obtain pure product **6o** as yellow color solid; 96 mg; 71 % yield; Mp: 253-255 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 6.5 Hz, 2H), 8.26 (d, *J* = 7.0 Hz, 2H), 8.20 – 8.11 (m, 1H), 8.04 (d, *J* = 6.4 Hz, 2H), 7.86 (d, *J* = 14.2 Hz, 1H), 7.59 – 7.33 (m, 6H), 7.15 (d, *J* = 5.5 Hz, 1H), 4.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6, 157.2, 153.3, 151.1, 146.2, 143.00, 142.2, 132.6, 129.8, 129.4, 129.2, 129.1, 128.9, 126.9, 126.6, 124.1, 124.0, 118.7, 107.7, 107.2, 94.5, 61.1, 56.5; HRMS calculated for $C_{30}H_{24}O_4N_3Cl$ $[M + H]^+$ 521.1528, found 521.1529.

General procedure for preparations of compounds (13a, b)

A solution of trimethylaluminum was added dropwise to a suspension of N,O-dimethylhydroxylamine hydrochloride in CH_2Cl_2 (15 mL) at 0° C. The clear solution was stirred at 0° C. for 45 minutes and at room temperature for 40 minutes. To this solution of compound (**11a, b**) in CH_2Cl_2 was added dropwise. The stirring was continued for 2 hours at room temperature. The reaction mixture was cooled to 0° C and 10 percent HCl was carefully added dropwise. The aqueous phase was extracted with EtOAc, washed with brine water, dried (Na_2SO_4) and filtered. The residue after evaporation of the solvent was chromatographed on silica gel eluding with EtOAc/Hex to give **13a, b**.

General procedure for preparations of compounds (14a, b)

A solution of Mehtyl magnesium bromide in diethylether was added to the stirred solution of amide (**14a, b**) in dry tetrahydrofuran at 0 ºC and stirred for 2 h. After completion of reaction saturated aqueous ammonium chloride solution was added, and the THF was removed in vaccum followed by ethyl acetate was added. Extracted with ethyl acetate and washed with brine water, dried over anhydrous Na2SO4 and purified with column chromatography.

1-(7-(3,4-Dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)ethan-1-one (14a)

Yellow solid; 82% yield; Mp: 172-174 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.0 Hz, 2H), 8.01 (d, *J* = 2.1 Hz, 1H), 7.88 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.67 (s, 2H), 7.48 (t, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.24 (s, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 2.81 (s, 3H); MS (ESI): m/z 373 $[M + H]^+$.

1-(2-Phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)ethan-1-one (14b)

Yellow solid; 82% yield; Mp: 186-188 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 6.9, Hz, 2H), 7.66 (s, 1H), 7.56 (s, 2H), 7.48 (t, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 3.98 (s, 9H), 2.82 (s, 2H); MS (ESI): m/z 403 $[M + H]^+$.

General procedure for preparations of compounds (7a-k)

To the solution of compounds (**7a-k**) and barium hydroxide in methanol, different aldehydes were added and stirred for 4-6 h. The precipitate were filtered and wash with small amount of methanol and purified using column chromatography.

(*E*)-1-(7-(3,4-Dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)-3-phenylprop-2-en-1-one (7a) This compound was prepared according to general procedure, by employing **14a** (100 mg, 0.27 mmol) and benzaldehyde (29 mg, 0.27 mmol) to obtain pure product **7a** as yellow color solid. 105 mg; 85 % yield; Mp: 241-243 ºC; 1H NMR (400 MHz, CDCl3): δ 8.39 (d, J = 16.0 Hz, 1H), 8.08 – 8.03 (m, 3H), 8.01 (d, J = 16.0 Hz, 1H), 7.92 (dd, J = 8.5, 2.1 Hz, 1H), 7.82 (s, 1H), 7.79 (dd, J = 6.5, 3.1 Hz, 2H), 7.53 – 7.40 (m, 5H), 7.29 (s, 1H), 7.09 (d, J = 8.5 Hz, 1H), 4.03 (s, 3H), 4.02 (s, 3H); HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 462.1812, found 462.1813.

(*E*)-1-(7-(3,4-Dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)-3-(p-tolyl)prop-2-en-1-one (7b) This compound was prepared according to general procedure, by employing **14a** (100 mg, 0.27 mmol) and 4-methylbenzaldehyde (32 mg, 0.27 mmol) to obtain pure product **7b** as yellow color solid. 113 mg; 89 % yield; Mp: 249-251 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 16.0 Hz, 1H), 8.06- 8.03 (m, 3H), 8.00 (d, *J* = 2.8 Hz, 1H), 7.91 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.81 (s, 1H), 7.67 (t, *J* = 8.2 Hz, 2H), 7.50 – 7.46 (t, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 2H), 7.24 (d, *J* = 9.3 Hz, 1H), 7.07 (d, *J* = 9.3, 2H), 4.03 (s, 3H), 4.01 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.1, 156.7, 151.9, 151.6, 150.2, 148.6, 146.2, 145.6, 141.5, 132.7, 132.3, 129.7, 129.2, 129.1, 128.9, 126.5, 123.4, 118.9, 112.6, 110.9, 104.1, 103.1, 95.7, 56.2, 56.1, 21.7; HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 476.1969, found 476.1969.

(*E*)-1-(7-(3,4-Dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (7c) This compound was prepared according to general procedure, by employing **14a** (100 mg, 0.27 mmol) and 4-methoxybenzaldehyde (37 mg, 0.27 mmol) to obtain pure product **7c** as yellow color solid. 120 mg; 91 % yield; Mp: 256-258 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 15.9 Hz, 1H), 8.07 – 8.04 (m, 3H), 7.97 (d, *J* = 15.9 Hz, 1H), 7.92 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.82 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.27 (s, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.03 (s, 3H), 4.01 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.0, 162.0, 156.7, 152.1, 151.6, 150.3, 148.6, 146.2, 145.3, 132.8, 130.9, 129.2, 128.9, 127.9, 126.6, 123.4, 117.6, 114.4, 112.7, 110.9, 110.7, 104.1, 95.6, 56.2, 56.1, 55.5; HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 491.1845, found 491.1846.

(*E*)-1-(7-(3,4-Dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (7d) This compound was prepared according to general procedure, by employing **14a** (100 mg, 0.27 mmol) and 3,4,5-trimethoxybenzaldehyde (53 mg, 0.27 mmol) to obtain pure product **7e** as yellow color solid. 133 mg; 90 % yield; Mp: 271-273 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 15.8 Hz, 1H), 8.07 – 8.05 (m, 3H), 7.97 – 7.90 (m, 2H), 7.83 (s, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.31 (s, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.01 (s, 2H), 4.03 (s, 3H), 4.02 (s, 3H), 3.98 (s, 6H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.9, 156.8, 153.5, 151.9, 151.7, 150.2, 148.6, 146.4, 145.7, 140.8, 132.7,

130.5, 129.3, 128.9, 126.5, 123.4, 123.2, 119.0, 112.6, 110.9, 106.3, 104.1, 95.7, 61.1, 56.4, 56.2, 56.1; HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 552.2129, found 552.2129.

(*E*)-3-(4-Chlorophenyl)-1-(7-(3,4-dimethoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (7e) This compound was prepared according to general procedure, by employing **14a** (100 mg, 0.27 mmol) and 4-chlorobenzaldehyde (38 mg, 0.27 mmol) to obtain pure product **7f** as yellow color solid. 105 mg; 79 % yield; Mp: 249-251 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 16.0 Hz, 1H), 8.08 – 8.02 (m, 4H), 7.81 (s, 1H), 7.77 – 7.69 (m, 4H), 7.53 – 7.46 (m, 2H), 7.46 – 7.39 (m, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.28 (s, 1H), 7.08 (d, *J* = 1.6 Hz, 1H), 4.03 (s, 3H), 4.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.0, 156.9, 151.7, 150.2, 148.7, 146.4, 143.9, 136.8, 133.6, 132.7, 130.1, 129.3, 128.9, 128.6, 126.6, 123.4, 123.2, 120.5, 112.6, 110.9, 110.8, 104.0, 95.8, 56.2, 56.1; HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 496.1422, found 496.1423.

(*E*)-3-Phenyl-1-(2-phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (7f) This compound was prepared according to general procedure, by employing **14b** (100 mg, 0.25 mmol) and benzaldehyde (27 mg, 0.25 mmol) to obtain pure product **7g** as yellow color solid. 112 mg; 92 % yield; Mp: 251-253 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 16.0 Hz, 1H), 8.08 – 7.98 (m, 5H), 7.83 – 7.78 (m, 4H), 7.60 (s, 2H), 7.54 – 7.41 (m, 10H), 7.31 (s, 1H), 4.00 (s, 1H), 3.99 (s, 1H); HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 492.1918, found 492.1918.

(*E*)-1-(2-Phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)-3-(p-tolyl)prop-2-en-1-one (7g) This compound was prepared according to general procedure, by employing **14b** (100 mg, 0.25 mmol) and 4-methylbenzaldehyde (30 mg, 0.25 mmol) to obtain pure product **7h** as yellow color solid. 105 mg; 84 % yield; Mp: 249-251 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 16.0 Hz, 1H), 8.06 (d, *J* = 7.0 Hz, 2H), 8.00 (d, *J* = 16.0 Hz, 1H), 7.82 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.60 (s, 2H), 7.49 (t, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.31 (s, 1H), 7.28 (s, 1H), 4.00 (s, 6H), 3.99 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.9, 156.9, 153.2, 152.0, 150.2, 146.3, 145.7, 141.6, 140.8, 132.6, 132.3, 129.7, 129.3, 129.1, 128.9, 126.5, 125.9, 118.8, 107.3, 104.5, 95.9, 61.1, 56.5, 21.7; HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 506.2074, found 506.2075.

(*E*)-3-(4-Methoxyphenyl)-1-(2-phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (7h) This compound was prepared according to general procedure, by employing **14b** (100 mg, 0.25 mmol) and 4-methyxybenzaldehyde (34 mg, 0.25 mmol) to obtain pure product **7i** as yellow color solid. 115 mg; 89 % yield; Mp: 258-260 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 15.9 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 15.9 Hz, 1H), 7.82 (s, 1H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.60 (s, 2H), 7.49 (t, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.30 (s, 1H), 6.98 (d, *J* = 8.7 Hz, 2H), 4.00 (s, 6H), 3.99 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.9, 162.1, 156.9, 153.1, 152.2, 150.2, 146.3, 145.5, 140.8, 132.7, 130.9, 129.3, 128.9, 127.8, 126.5, 125.9, 117.5, 114.5, 107.3, 104.6, 95.8, 61.1, 56.5, 55.5; HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 522.2023, found 522.2023.

(*E*)-3-(3,4-Dimethoxyphenyl)-1-(2-phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (7i) This compound was prepared according to general procedure, by employing **14b** (100 mg, 0.25 mmol) and 3,4-dimethyxybenzaldehyde (42 mg, 0.25 mmol) to obtain pure product **7j** as yellow color solid. 116 mg; 85 % yield; Mp: 263-265 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 15.9 Hz, 1H), 8.05 (d, *J* = 7.1 Hz, 2H), 7.97 (d, *J* = 15.9 Hz, 1H), 7.82 (s, 1H), 7.60 (s, 2H), 7.49 (t, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.36 (dd, *J* = 5.4, 2.7 Hz, 1H), 7.33 – 7.30 (m, 2H), 6.93 (d, *J* = 8.3 Hz, 1H), 4.02 (s, 3H), 4.00 (s, 6H), 3.99 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.9, 156.9, 153.2, 152.2, 151.9, 150.2, 149.3, 146.4, 145.9, 140.8, 132.6, 129.3, 128.9, 128.1, 126.5, 125.9, 124.2, 117.6, 111.1, 110.4, 107.3, 104.6, 95.8, 61.1, 56.5, 56.1, 56.1; HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 552.2129, found 552.2129.

(*E*)-1-(2-Phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (7j) This compound was prepared according to general procedure, by employing **14b** (100 mg, 0.25 mmol) and 3,4,5-trimethyxybenzaldehyde (49 mg, 0.25 mmol) to obtain pure product **7k** as yellow color solid. 128 mg; 91 % yield; Mp: 272-274 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 15.9 Hz, 1H), 8.06 (d, *J* = 7.2 Hz, 2H), 7.94 (d, *J* = 15.9 Hz, 1H), 7.83 (s, 1H), 7.60 (s, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.33 (s, 1H), 7.01 (s, 2H), 4.00 (s, 6H), 4.00 (s, 3H), 3.98 (s, 6H), 3.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.8, 157.0, 153.5, 153.2, 152.0, 150.2, 146.4, 145.9, 140.9, 140.8, 132.6, 130.5,

129.4, 128.9, 126.5, 125.8, 118.9, 107.3, 106.3, 104.5, 95.9, 61.1, 56.5, 56.4; HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 582.2235, found 582.2235.

(*E*)-3-(4-Chlorophenyl)-1-(2-phenyl-7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)prop-2-en-1-one (7k) This compound was prepared according to general procedure, by employing **14b** (100 mg, 0.25 mmol) and 4-chlorobenzaldehyde (35 mg, 0.25 mmol) to obtain pure product **7l** as yellow color solid. 104 mg; 80 % yield; Mp: 254-256 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 16.0 Hz, 1H), 8.05 (d, *J* = 7.0 Hz, 2H), 7.94 (d, *J* = 16.0 Hz, 1H), 7.81 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.59 (s, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.46 – 7.40 (m, 3H), 7.31 (s, 1H), 4.00 (s, 6H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.9, 157.0, 153.2, 151.7, 150.2, 146.4, 144.0, 140.8, 136.8, 133.5, 132.5, 130.2, 129.4, 129.3, 128.9, 126.5, 125.8, 120.3, 107.3, 104.4, 96.0, 61.1, 56.5; HRMS calculated for $C_{29}H_{23}O_3N_3$ $[M + H]^+$ 526.1528, found 526.1529.

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