Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting Information

Synthesis and *in vitro* biological evaluation of pyrazole group-containing analogues for PDE10A

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Contents of Supporting Information

Experimental Section

General

All analytical grade chemicals and reagents were purchased from Sigma-Aldrich and were used without further purification unless otherwise specified. Flash column chromatography was conducted using Scientific Adsorbents, Inc. silica gel, 60 Å. Melting points were determined using MEL-TEMP 3.0 apparatus and uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on a Varian Mercury-VX spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. All chemical shift values are reported in ppm (δ). Peak multiplicities were recorded as singlet, s; doublet, d; triplet, t; multiplet, m. Elemental analyses (C, H, N) were determined by Atlantic Microlab, Inc. (Norcross, GA).

4-(Benzyloxy)-N-methoxy-N-methylbenzamide

1,1-Carbonyldiimidazole (CDI) (4.22 g, 26 mmol) was added into a solution of 4-(benzyloxy) benzoic acid (4.57 g, 20 mmol) in dichloromethane (DCM) (150 mL) at 0 ^{o}C under nitrogen atmosphere. The reaction mixture was stirred for 2 h at room temperature. Then O, N-dimethylhydroxyl amine (2.53 g, 26 mmol) and triethylamine (TEA) (5 mL) were added into previous reaction mixture slowly at 0 ^{o}C. The mixture was warmed to room temperature and stirred overnight. The reaction mixture was washed with saturated aqueous sodium bicarbonate solution (30 mL), dried and concentrated under vacuum. The residue was purified by silica gel column chromatography with ethyl acetate (EtOAc) -hexane (1:1, v/v) to give the title compound as a white solid (5.31 g, 98%). mp: 65 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ 7.70-7.75 (m, 2H), 7.34-7.46 (m, 5H), 6.98-6.99 (m, 2H), 5.11 (s, 2H), 3.57 (s, 3H), 3.36 (s, 3H).

1-(4-(Benzyloxy)phenyl)-2-(pyridin-4-yl)ethanone

4-Picoline (0.34 g, 3.68 mmol) was added dropwise into an ice-cold solution of lithium diisopropyl amide (LDA) (0.76 mL, 2.0 M in THF/heptane/ethylbenzene) in tetrahydrofuran (THF) (20 mL). After the reaction mixture was stirred for 30 min, the anion was cooled to -78 ^{o}C with acetone-dry ice bath. This cooled picoline anion solution was added slowly into a solution of 4-(benzyloxy)-N-methoxy-N-methylbenzamide (100 mg, 0.36 mmol) in THF (10 mL) at -78 ^{o}C. After 30 min, acetic acid (4 mL) was added into the above cold solution dropwise; the reaction mixture was slowly warmed to room temperature. DCM (100 mL) was added and the solution was washed with saturated sodium bicarbonate aqueous solution (30 mL). The organic phase was dried over anhydrous sodium sulfate. After filtrating and concentrating, the residue was purified by silica gel column chromatography using EtOAc-hexane (4:1, v/v) to afford aimed product as a yellow solid (82 mg, 73%). mp: 166 °C. ^{1}H NMR ($CDCl_3$): δ 8.53 (d, J = 3.0 Hz, 2H), 7.97 (d, J = 4.3 Hz, 2H), 7.01-7.42 (m, 9H), 5.14 (s, 2H), 4.23 (s, 2H).

4-(3-(4-(Benzyloxy)phenyl)-1-methyl-1H-pyrazol-4-yl)pyridine (4)

1-(4-(Benzyloxy)phenyl)-2-(pyridin-4-yl)ethanone (2.00 g, 6.6 mmol) was added into N-Dimethoxymethyl-N,N-dimethylamine (8 mL) and the reaction mixture was refluxed for 1 h. Excess N-Dimethoxymethyl-N,N-dimethylamine was removed under vacuum. The residue was dissolved in ethanol (EtOH) (20 mL). After methylhydrazine (0.31 g, 6.6 mmol) and concentrated sulfuric acid (0.1 mL) were added into the above solution, the reaction mixture was stirred for 1 h at room temperature. After removing the solvent by evaporation, DCM (100 mL) was added into the residue and then washed with saturated aqueous sodium bicarbonate solution (30 mL), dried and concentrated under vacuum. The residue was purified by silica gel column chromatography using EtOAc-hexane-TEA gradient (EtOAc/hexane/TEA, 1:5:0.06, v/v/v; EtOAc/hexane/TEA, 1:1:0.02, v/v/v and EtOAc/TEA, 1:0.01, v/v) and compound **4** was eluted as the first component. After removing the solvent, compound **4** was obtained as a white solid (1.01 g, 45%). mp: 144 °C

(decomposed). ^{1}H NMR ($CDCl_3$): δ 8.39-8.41 (m, 2H), 7.50 (s, 1H), 7.27-7.50 (m, 7H), 7.09-7.11 (m, 2H), 6.87-6.91 (m, 2H), 5.01 (s, 2H), 3.90 (s, 3H).

4-(5-(4-(Benzyloxy)phenyl)-1-methyl-1H-pyrazol-4-yl)pyridine (5)

In the above procedure, compound **5** was the second component eluted from silica gel column chromatography using EtOAc-hexane-TEA gradient (EtOAc/hexane/TEA, 1:5:0.06, v/v/v; EtOAc/hexane/TEA, 1:1:0.02, v/v/v and EtOAc/TEA, 1:0.01, v/v). Compound 5 was obtained (0.38 g, 17 %) as a white solid. mp: 158 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ 8.31-8.33 (m, 2H), 7.75 (s, 1H), 7.31-7.41 (m, 4H), 7.14-7.18 (m, 3H), 6.97-7.02 (m, 4H), 5.06 (s, 2H), 3.68 (s, 3H).

4-(1-Methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenol (6)

Palladium on activated charcoal (10% Pd, 0.02 g) was added into a solution of **4** (0.20 g, 0.58 mmol) in EtOH-EtOAc (EtOH/EtOAc, 1:1, v/v, 20 mL). Hydrogen gas was pumped into the reaction vial until the pressure reached 40 psi and the reaction vial was sealed and stirred overnight. After filtering and concentrating. the residue was purified by silica gel column chromatography with methanol (MeOH) - DCM (1:30, v/v) to afford aimed product **6** as a white solid (136 mg, 93%). mp: 235 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ 9.58 (s, 1H), 8.43-8.44 (d, J = 2.2 Hz, 2H), 8.13 (s, 1H), 7.16-7.20 (m, 4H), 6.75 (d, J = 4.2 Hz, 2H), 3.88 (s, 3H).

4-(1-Methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenol (7)

Following the similar procedure for synthesizing 4-(1-Methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenol **6** but starting with 4-(5-(4-(benzyloxy)phenyl)-1-methyl-1H-pyrazol-4-yl)pyridine **5**, compound **7** was obtained as a white solid (138 mg, 94%). mp: 208 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ 9.9 (s, 1H), 8.35 (d, J = 2.1 Hz, 2H), 7.99 (s, 1H), 7.11-7.20 (m, 4H), 6.90 (d, J = 4.1 Hz, 2H), 3.65 (s, 3H).

4-Methoxy-2-methylquinoline (8b)

Sodium methoxide (583 mg, 10.8 mmol) was added into a solution of 4-chloro-2-methylquinoline (1.91 g, 10.8 mmol) in MeOH (50 mL), and the mixture was refluxed for 3 h. After removing the solvent, water (60 mL) was added into the residue and then extracted with ether (3 x 100 mL). After using anhydrous sodium sulfate to dry organic layer, the solvent was removed by evaporation. The crude product was purified by silica gel column chromatography using EtOAc-hexane (1:1, v/v) to afford **8b** as a white solid (1.40 g, 75%). mp: 80 °C. ^{1}H NMR ($CDCl_3$): δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.65-7.62 (m, 1H), 7.45-7.42 (m, 1H), 6.61 (s, 1H), 4.01 (s, 3H), 2.69 (s, 3H).

8-Methoxy-2-methylquinoline (8f)

Potassium carbonate (K_2CO_3) (5.52 g, 40 mmol) was added into the solution of 2-ethylquinolin-8-ol (3.18 g, 20 mmol) in dimethylformamide (DMF) (18 mL), and methyl iodide (CH_3I) (2.84 g, 20 mmol) was added into the above mixture under nitrogen atmosphere. After the reaction mixture was stirred overnight at room temperature, the excess CH_3I was removed by evaporation. The reaction mixture was diluted by adding water (150 mL) and extracted with EtOAc (3 x 150 mL). The organic layer was dried, concentrated and the crude product was purified by silica gel column chromatography using EtOAc-hexane (1:1, v/v) to afford **8f** as a white solid (3.21 g, 93%). mp: 125 °C. ^{1}H NMR ($CDCl_3$): δ 8.01 (d, *J* = 8.4 Hz, 1H), 7.43-7.30 (m, 3H), 7.05-7.02 (m, 1H), 4.08 (s, 3H), 2.80 (s, 3H).

Procedure A: general method for the synthesis of substituted 2-bromomethylquinoline compounds 9a-f

2-(Bromomethyl)-3-methoxyquinoline (9a)

A mixture of **8a** (0.82 g, 4.7 mmol) and N-bromosuccinimide (NBS) (0.84 g, 4.7 mmol) in carbon tetrachloride (CCl_4) (100 mL) was refluxed and azobisisobutyronitrile (AIBN) (0.04 g, 0.24 mmol) was added into the above solution. After the reaction mixture was refluxed for an additional 3 h, and then it was cooled to 10 ^{o}C. The reaction mixture was filtered

and the organic solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography using EtOAc-DCM (1:4, v/v) to afford compound **9a** as a pink solid (0.61 g, 52%). mp: 101.6 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ 8.03 (d, *J* = 4.2 Hz, 1H), 7.72 (d, *J* = 4.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.41 (s, 1H), 4.78 (s, 2H), 4.02 (s, 3H).

2-(Bromomethyl)-4-methoxyquinoline (9b)

Following procedure A, starting with **8b**, compound **9b** was obtained as a pink solid (0.59 g, 50%). ^{1}H NMR ($CDCl_3$): δ 8.16 (d, *J* = 4.2 Hz, 1H), 7.98 (d, *J* = 4.0 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 6.91 (s, 1H), 4.66 (s, 2H), 4.09 (s, 3H).

2-(Bromomethyl)-4-methoxyquinoline (9c)

Following procedure A, starting with 5-methoxy-2-methylquinoline, compound **9c** was obtained as a pink solid (0.62 g, 53%). ^{1}H NMR ($CDCl_3$): δ 7.86 (d, *J* = 4.0 Hz, 1H), 7.51 (d, *J* = 4.1 Hz, 1H), 7.23 (d, *J* = 1 Hz, 1H), 7.12 (d, *J* = 4.0 Hz, 1H), 7.04 (dd, *J* = 3.4, 1.2 Hz, 1H), 4.68 (s, 2H), 4.01 (s, 3H).

2-(Bromomethyl)-6-methoxyquinoline (9d)

Following procedure A, starting with 6-methoxy-2-methylquinoline, compound **9d** was obtained as a pink solid (0.65 g, 55%). mp: 99 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 9.3 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.37 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.07 (d, *J* = 2.7 Hz, 1H), 4.69 (s, 2H), 3.93 (s, 3H).

2-(Bromomethyl)-7-methoxyquinoline (9e)

Following procedure A, starting with 7-methoxy-2-methylquinoline, compound **9e** was obtained as a pink solid (0.71 g, 60%). mp: 86 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 9.3 Hz, 1H), 7.44-7.39 (m, 2H), 7.19-7.18 (m, 1H), 4.68 (s, 2H), 3.95 (s, 3H).

2-(Bromomethyl)-8-methoxyquinoline (9f)

Following procedure A, starting with **8f**, compound **9f** was obtained as a pink solid (0.73 g, 62%). mp: 116 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ 8.13 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.47-7.36 (m, 2H), 7.07 (d, *J* = 7.2 Hz, 1H), 4.79 (s, 2H), 4.09 (s, 3H).

Procedure B: General Method for the Synthesis of Compounds 10a-f and 11a-f

3-Methoxy-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy) methyl)quinolone (10a)

A solution of **6** (0.25 g, 1.00 mmol) in anhydrous DMF (10 mL) was treated at 0 ^{o}C with sodium hydride (0.036 g, 1.5 mmol); after additional 30 min, **9a** (0.26 g, 1.0 mmol) was added into the reaction mixture. The stirred mixture was allowed to warm to room temperature overnight. Water (30 mL) was added into the reaction mixture and then extracted with DCM (3 x 60 mL). The combined organic layers were washed with 1M sodium hydroxide (30 mL) and the organic layer was dried and concentrated. The residue was purified by silica gel chromatography using MeOH-DCM (1:30, v/v) to afford the desired product **10a** as a white solid (0.22 g, 53%). ^{1}H NMR ($CDCl_3$): δ 8.42 (d, *J* = 5.3 Hz, 2H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.44 (m, 3H), 7.44 – 7.29 (m, 3H), 7.12 (d, *J* = 5.1 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 5.38 (s, 2H), 3.92 (d, *J* = 10.2 Hz, 3H). Free base was converted to the corresponding oxalate salt by adding oxalic acid in EtOAc to **10a** in EtOAc. mp: 191.4 °C (decomposed). Anal. ($C_{26}H_{22}N_4O_2 \bullet 1.5H_2C_2O_4$) C, H, N.

4-Methoxy-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy) methyl)quinolone (10b)

Following procedure B, starting with compounds **6** and **9b**, compound **10b** was obtained as a white solid (0.24 g, 58%). ^{1}H NMR ($CDCl_3$): δ 8.49-8.46 (m, 2H), 8.19 (d, *J* = 9.9 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.73-7.68 (m, 1H), 7.58-7.57 (m, 1H), 7.52-7.47 (m, 1H), 7.42-7.38 (m, 2H), 7.18-7.15 (m, 2H), 7.05-7.02 (m, 3H), 5.36 (s, 2H), 4.06 (s, 3H), 3.97 (s, 3H). The free base was converted to the oxalate salt. mp: 162.2 °C (decomposed). Anal. ($C_{26}H_{22}N_4O_2 \cdot 2H_2C_2O_4 \cdot H_2O$) C, H, N.

5-Methoxy-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy) methyl)quinolone (10c)

Following procedure B, starting with compounds **6** and **9c**, compound **10c** was obtained as a white solid (0.23 g, 59%). ^{1}H NMR (CDCl3): δ 8.48 – 8.39 (m, 2H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.41 – 7.31 (m, 3H), 7.16 – 7.10 (m, 3H), 7.00 – 6.94 (m, 2H), 5.34 (s, 2H), 3.92 (s, 6H). The free base was converted to the oxalate salt. mp: 189.6 °C (decomposed). Anal. ($C_{26}H_{22}N_4O_2 \cdot 2H_2C_2O_4$) C, H, N.

6-Methoxy-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy) methyl)quinolone (10d)

Following procedure B, starting with compounds **6** and **9d**, compound **10d** was obtained as a white solid (0.20 g, 50%). ^{1}H NMR ($CDCl_3$): δ 8.46 (dd, *J* = 1.8, 4.5 Hz, 2H), 8.09-7.95 (m, 2H), 7.63-7.56 (m, 2H), 7.40-7.36 (m, 3H), 7.17-7.14 (m, 2H), 7.08-7.07 (m, 1H), 7.02-6.99 (m, 2H), 5.36 (s, 2H), 3.95 (s, 3H), 3.92 (s, 3H). The free base was converted to the oxalate salt. mp: 197.8 °C (decomposed). Anal. ($C_{26}H_{22}N_4O_2 \cdot 2H_2C_2O_4$) C, H, N.

7-Methoxy-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy) methyl)quinolone (10e)

Following procedure B, starting with compounds **6** and **9e**, compound **10e** was obtained as a white solid (0.22 g, 53%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36-8.33 (m, 2H), 8.01-7.98 (m, 1H), 7.61-7.58 (m, 1H), 7.49 (s, 1H), 7.43-7.40 (m, 1H), 7.29-7.22 (m, 3H), 7.10-7.04 (m, 3H), 6.92-6.88 (m, 2H), 5.25 (s, 2H), 3.85 (s, 6H). The free base was converted to the oxalate salt. mp: 189.4 °C (decomposed). Anal. ($C_{26}H_{22}N_4O_2 \cdot 1.5H_2C_2O_4 \cdot H_2O$) C, H, N.

8-Methoxy-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)quinolone (10f)

Following procedure B, starting with compounds **6** and **9f**, compound **10f** was obtained as a white solid (0.25 g, 59%). ^{1}H NMR ($CDCl_3$): δ 8.47-8.44 (m, 2H), 8.17-8.13 (m, 1H), 7.74-7.70 (m, 1H), 7.55 (d, *J* = 2.4 Hz, 1H), 7.45-7.37 (m, 4H), 7.17-7.14 (m, 2H), 7.08-6.99 (m, 3H), 5.48 (s, 2H), 4.07 (s, 3H), 3.93 (s, 3H). The free base was converted to the oxalate salt. mp: 183.2 °C (decomposed). Anal. ($C_{26}H_{22}N_4O_2 \bullet 2H_2C_2O_4$) C, H, N.

3-Methoxy-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinolone (11a)

Following procedure B, starting with compounds **7** and **9a**, compound **11a** was obtained as a white solid (0.19 g, 46%). ^{1}H NMR ($CDCl_3$): δ 8.39 – 8.25 (m, 2H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.76 – 7.69 (m, 1H), 7.60 – 7.47 (m, 2H), 7.44 (s, 1H), 7.17 (s, 4H), 7.08 – 6.96 (m, 2H), 5.44 (s, 2H), 3.98 (s, 3H), 3.72 (s, 3H). The free base was converted to the oxalate salt. mp: 224.1 °C (decomposed). Anal. ($C_{26}H_{22}N_4O_2 \bullet H_2C_2O_4 \bullet H_2O$) C, H, N.

4-Methoxy-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinolone (11b)

Following procedure B, starting with compounds **7** and **9b**, compound **11b** was obtained as a white solid (0.20 g, 48%). ^{1}H NMR ($CDCl_3$): δ 8.38-8.36 (m, 2H), 8.22-8.19 (m, 1H), 8.02 (m, 1H), 7.82 (s, 1H), 7.72 (m, 1H), 7.54-7.51 (m, 1H), 7.25-7.15 (m, 4H), 7.07-7.04 (m, 3H), 5.38 (s, 2H), 4.03 (s, 3H), 3.75 (s, 3H). The free base was converted to the oxalate salt. mp: 204.4 °C (decomposed). Anal. ($C_{26}H_{22}N_4O_2 \bullet 2H_2C_2O_4$) C, H, N.

5-Methoxy-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinolone (11c)

Following procedure B, starting with compounds **7** and **9c**, compound **11c** was obtained as a white solid (0.18 g, 45%). ^{1}H NMR ($CDCl_3$): δ 8.36 (d, *J* = 4.7 Hz, 2H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.79 (s, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 2.5 Hz, 1H), 7.24 – 7.17 (m, 3H), 7.15 – 7.07 (m, 2H), 7.05 – 6.98 (m, 2H), 5.39 (s, 2H), 3.94 (s, 3H), 3.72 (s, 3H). The free base was converted to the oxalate salt. mp:177.8 °C (decomposed). Anal. ($C_{26}H_{22}N_4O_2 \bullet 2.5H_2C_2O_4$)

C, H, N.

6-Methoxy-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinolone (11d)

Following procedure B, starting with compounds **7** and **9d**, compound **11d** was obtained as a white solid (0.20 g, 48%). ^{1}H NMR ($CDCl_3$): δ 8.37-8.35 (m, 2H), 8.16-8.14 (m, 1H), 7.97 (m, 1H), 7.82 (s, 1H), 7.67-7.65 (m, 1H), 7.43-7.37 (m, 1H), 7.25-7.04 (m, 7H), 5.40 (s, 2H), 3.94 (s, 3H), 3.74 (s, 3H). The free base was converted to the oxalate salt. mp: 216.8 °C (decomposed). Anal. ($C_{26}H_{22}N_4O_2 \bullet 2H_2C_2O_4$) C, H, N.

7-Methoxy-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinolone (11e)

Following procedure B, starting with compounds **7** and **9e**, compound **11e** was obtained as a white solid (0.19 g, 46%). ^{1}H NMR ($CDCl_3$): δ 8.42-8.40 (m, 2H), 8.21-8.18 (m, 1H), 7.85 (s, 1H), 7.78-7.75 (m, 1H), 7.62-7.59 (m, 1H), 7.46-7.45 (m, 1H), 7.28-7.07 (m, 7H), 5.45 (s, 2H), 4.00 (s, 3H), 3.78 (s, 3H). The free base was converted to the oxalate salt. mp: 173.4 °C (decomposed). Anal. ($C_{26}H_{22}N_4O_2 \bullet 2H_2C_2O_4$) C, H, N.

8-Methoxy-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinolone (11f)

Following procedure B, starting with compounds **7** and **9f**, compound **11f** was obtained as a white solid (0.18 g, 42%). ^{1}H NMR ($CDCl_3$): δ 8.47-8.44 (m, 2H), 8.17-8.13 (m, 1H), 7.74-7.70 (m, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.45-7.37 (m, 4H), 7.17-7.14 (m, 2H), 7.08-6.99 (m, 3H), 5.48 (s, 2H), 4.07 (s, 3H), 3.79 (s, 3H). The free base was converted to the oxalate salt. mp: 185.3 °C (decomposed). Anal. ($C_{26}H_{22}N_4O_2 \bullet 2H_2C_2O_4$) C, H, N.

4-Bromo-N-methoxy-N-methylbenzamide (13)

CDI (1.77 g, 11 mmol) was added slowly to a solution of **12** (2.18 g, 10.9 mmol) in THF (30 mL) at room temperature and the mixture was stirred for 2 h, and then N,O-dimethylhydroxylamine hydrochloride (1.30 g, 13.3 mmol) and TEA (5

mL) were added. The reaction mixture was continually stirred overnight. The mixture was washed with saturated aqueous sodium bicarbonate solution, then dried over anhydrous sodium sulfate, and concentrated in vacuum. The residue was purified on silica gel column chromatography using EtOAc-hexane (1:2, v/v) to afford compound **13** as a colorless liquid (2.65 g, quantitative). ^{1}H NMR ($CDCl_3$): δ 7.44-7.39 (m, 4H), 3.40 (s, 3H), 3.21 (s, 3H).

1-(4-Bromophenyl)-2-(pyridin-4-yl)ethanone (14)

4-Picoline (0.34 g, 3.68 mmol) was added dropwise into the solution of lithium diisopropyl amide (LDA) (0.76 mL, 2.0 M in THF/heptane/ethylbenzene) in THF (20 mL) pre-cooled with ice-bath. After 30 min, the reaction mixture was cooled to -78 ^{o}C with acetone-dry ice bath. Picoline anion solution was slowly added into a solution of **13** (0.088 g, 0.36 mmol) in THF (30 mL) pre-cooled to -78 ^{o}C. After stirring for additional 30 min, acetic acid (4.0 mL) was added dropwise into above cooled reaction mixture and slowly warm to room temperature. After DCM (100 mL) was added into the reaction mixture, the solution was washed with saturated sodium bicarbonate aqueous solution. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography using EtOAc-hexane (2:1, v/v) to afford the aimed product **14** as a yellow solid (82 mg, 83%). mp: 131 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ 8.56 (dd, J = 2.7, 1.8 Hz, 2H), 7.87-7.84 (m, 2H), 7.64-7.61 (m, 2H), 7.18 (dd, J = 2.7, 1.8 Hz, 2H), 4.25 (s, 2H).

4-(3-(4-Bromophenyl)-1-methyl-1H-pyrazol-4-yl)pyridine (15)

Compound **14** (1.82 g, 6.6 mmol) was added into N-dimethoxymethyl-N,N-dimethylamine (16 mL) and the reaction mixture was refluxed for 1 h. Excess N-dimethoxymethyl-N,N-dimethylamine was removed under vacuum. The residue was dissolved in EtOH (20 mL). After methylhydrazine (0.31 g, 6.6 mmol) and concentrated sulfuric acid (0.1 mL) were added into the above solution, the reaction mixture was stirred for 1 h at room temperature. After removing the solvent by

evaporation, DCM (100 mL) was added into the residue and then washed with saturated aqueous sodium bicarbonate solution (30 mL), dried and concentrated under vacuum. The residue was purified by silica gel column chromatography EtOAc-hexane-TEA gradient (EtOAc/hexane/TEA, 1:5:0.06, v/v/v; EtOAc/hexane/TEA, 1:1:0.02, v/v/v and EtOAc/TEA, 1:0.01, v/v) and gave the title compound **15** as a yellow solid (1.01 g, 45 %). mp: 138 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ 8.51-8.49 (m, 2H), 7.59 (s, 1H), 7.49-7.46 (m, 2H), 7.36-7.33 (m, 2H), 7.16-7.14 (m, 2H), 3.99 (s, 3H).

4-(5-(4-Bromophenyl)-1-methyl-1H-pyrazol-4-yl)pyridine (16)

In the above procedure, compound **16** was obtained (0.52 g, 25%) as the second component eluted from silica gel column chromatography using EtOAc-hexane-TEA gradient (EtOAc/hexane/TEA, 1:5:0.06, v/v/v; EtOAc/hexane/TEA, 1:1:0.02, v/v/v and EtOAc/TEA, 1:0.01, v/v) and as a yellow solid. mp: 110 °C (decomposed). ^{1}H NMR ($CDCl_3$): δ 8.43-8.41 (m, 2H), 7.82 (s, 1H), 7.65-7.63 (m, 2H), 7.21-7.18 (m, 2H), 7.04-7.01 (m, 2H), 3.77 (s, 3H).

4-(1-Methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)benzenethiol (17)

Sodium thiomethoxide (0.75 g, 8.02 mmol) was added into a solution of **15** (0.50 g, 1.59 mmol) in dimethylacetamide (10 mL). The reaction mixture was heated at 150 ^{o}C for 2 h and cooled down to room temperature. The mixture was diluted with EtOAc (25 mL) and water (25 mL), and neutralized with aqueous 1M hydrochloric acid. The organic layer was separated first; the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic solution were washed with water, then brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography using MeOH-DCM (1:15, v/v) to afford **17** (0.35 g, 81%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.26-8.28 (m, 2H), 7.53 (s, 1H), 7.46-7.44 (m, 2H), 7.33-7.30 (m, 2H), 7.13-7.12 (m, 2H), 3.99 (s, 3H).

4-(1-Methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)benzenethiol (18)

Following the procedure for synthesizing compound **17**, but staring with 4-(5-(4-bromophenyl)-1-methyl-1H-pyrazol-4-yl)pyridine **16** afforded compound **18** (0.33 g, 78%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.26 (m, 2H), 7.69 (s, 1H), 7.54-7.50 (m, 2H), 7.18-7.13 (m, 2H), 6.92-6.89 (m, 2H), 3.65 (s, 3H).

Procedure C: General Method for the Synthesis of Compounds 10g-j and 11g-j

4-Methoxy-2-(((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenyl)thio)methyl)quinolone (10g)

Sodium hydride (15 mg, 0.66 mmol) was added into a solution of **17** (0.12 g, 0.44 mmol) in anhydrous DMF (10 mL) pre-cooled with ice-bath; after 30 min, compound **9b** (0.11 g, 0.44 mmol) was added into the reaction mixture that was stirred and allowed to warm up to room temperature overnight. Water (30 mL) was added into the reaction mixture and extracted with DCM (3 x 60 mL). The combine organic layers were washed with 1M sodium hydroxide (30 mL). After the organic layer was dried, filtrated and concentrated, the residue was purified via silica gel chromatography eluted with MeOH-DCM (1:20, v/v) to afford compound **10g** (82 mg, 43%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.35 (m, 2H), 8.07-8.04 (m, 1H), 7.94-7.87 (m, 2H), 7.62-7.57 (m, 2H), 7.50 (s, 1H), 7.48-7.36 (m, 2H), 7.19 (m, 1H), 7.09-7.03 (m, 2H), 6.83 (m, 1H), 4.34 (s, 2H), 4.01 (s, 3H), 3.91 (s, 3H). Free base was converted to the corresponding oxalate salt by adding oxalic acid into **10e** in EtOAc and then recrystallized. mp: 176 °C (decomposed). Anal. ($C_{26}H_{22}N_4OS \bullet H_2C_2O_4$) C, H, N.

6-Methoxy-2-(((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenyl)thio)methyl)quinolone (10h)

Following procedure C, starting with compounds **17** and **9d**, compound **10h** was obtained (89 mg, 47%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.45-8.43 (m, 2H), 7.98-7.91 (m, 2H), 7.52 (s, 1H), 7.48-7.45 (m, 1H), 7.36-7.32 (m, 5H), 7.12-7.10 (m, 2H), 7.04-7.03 (m, 1H), 4.43 (s, 2H), 4.03 (s, 3H), 3.91 (s, 3H). The free base was converted to the oxalate salt. mp: 213.8 °C (decomposed). Anal. ($C_{26}H_{22}N_4OS \bullet 2H_2C_2O_4$) C, H, N.

7-Methoxy-2-(((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenyl)thio)methyl)quinolone (10i)

Following procedure C, starting with compounds **17** and **9e**, compound **10i** was obtained (99 mg, 52%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.44 (m, 2H), 8.00-7.90 (m, 1H), 7.78-7.76 (m, 1H), 7.66-7.37 (m, 5H), 7.21-7.03 (m, 5H), 4.34 (s, 2H), 4.00 (s, 3H), 3.94 (s, 3H). The free base was converted to the oxalate salt. mp: 164.9 °C (decomposed). Anal. ($C_{26}H_{22}N_4OS \bullet H_2C_2O_4$) C, H, N.

8-Methoxy-2-(((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenyl)thio)methyl)quinolone (10j)

Following procedure C, starting with compounds **17** and **9f,** compound **10j** was obtained (76 mg, 40%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.44-8.42 (m, 2H), 8.07-8.04 (m, 1H), 7.61-7.55 (m, 2H), 7.43-7.34 (m, 6H), 7.12-7.04 (m, 3H), 4.56 (s, 2H), 4.07 (s, 3H), 3.95 (s, 3H). The free base was converted to the oxalate salt. mp: 168.4 °C (decomposed). Anal. ($C_{26}H_{22}N_4OS \bullet 2H_2C_2O_4$) C, H, N.

4-Methoxy-2-(((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenyl)thio)methyl)quinolone (11g)

Following procedure C, starting with compounds **18** and **9b**, compound **11g** was obtained (78 mg, 41%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.34-8.32 (m, 2H), 8.17-8.10 (m, 1H), 7.97-7.90 (m, 1H), 7.79 (m, 1H), 7.71-7.61 (m, 1H), 7.52-7.42 (m, 4H), 7.16-7.14 (m, 2H), 6.99-6.97 (m, 2H), 4.48 (s, 2H), 4.05 (s, 3H), 3.70 (s, 3H). The free base was converted to the oxalate salt. mp: 169.2 °C (decomposed). Anal. ($C_{26}H_{22}N_4OS \bullet 2H_2C_2O_4$) C, H, N.

6-Methoxy-2-(((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenyl)thio)methyl)quinolone (11h)

Following procedure C, starting with compounds **18** and **9d**, compound **11h** was obtained (82 mg, 43%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.34-8.32 (m, 2H), 7.86-7.80 (m, 2H), 7.42-7.33 (m, 2H), 7.23-7.21 (m, 5H), 7.01-6.99 (m, 2H), 6.92-6.91 (m, 1H), 4.32 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H). The free base was converted to the oxalate salt. mp: 178.2 °C (decomposed). Anal. ($C_{26}H_{22}N_4OS \bullet H_2C_2O_4$) C, H, N.

7-Methoxy-2-(((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenyl)thio)methyl)quinolone (11i)

Following procedure C, starting with compounds **18** and **9e**, compound **11i** was obtained (76 mg, 40%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.34 (m, 2H), 7.99-7.96 (m, 1H), 7.71 (m, 1H), 7.72-7.61 (m, 1H), 7.48-7.37 (m, 4H), 7.21-7.15 (m, 4H), 6.92-6.91 (m, 1H), 4.49 (s, 2H), 4.05 (s, 3H), 3.70 (s, 3H). The free base was converted to the oxalate salt. mp: 160.2 °C (decomposed). Anal. ($C_{26}H_{22}N_4OS \bullet 2H_2C_2O_4$) C, H, N.

8-Methoxy-2-(((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenyl)thio)methyl)quinolone (11j)

Following procedure C, starting with compounds **18** and **9f,** compound **11j** was obtained (82 mg, 43%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.33-8.32 (m, 2H), 8.13-8.10 (m, 1H), 7.79-7.78 (s, 1H), 7.68-7.66 (m, 1H), 7.48-7.37 (m, 5H), 7.16-7.08 (m, 2H), 6.99-6.97 (m, 2H), 4.61 (s, 2H), 4.07 (s, 3H), 3.70 (s, 3H). The free base was converted to the oxalate salt. mp: 163.5 °C (decomposed). Anal. ($C_{26}H_{22}N_4OS \bullet 2H_2C_2O_4$) C, H, N.

2-(4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenyl)isoindoline-1,3-dione (19)

A mixture of **15** (1.35 g, 4.30 mmol), potassium phthalimide (0.90 g, 5.16 mmol), and copper (I) iodide (1.60 g, 5.16 mmol) in freshly distilled dimethylacetamide (50 mL) was refluxed for 72 h under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was treated with 0.6 M hydrochloric acid (50 mL). The resulting precipitate was removed by filtration. The filtrate was extracted with DCM (3 × 60 mL). The combined organic solution was dried with anhydrous sodium sulfate and concentrated. The residue was purified on silica gel column using EtOAc-hexane-TEA (1:1:0.01, v/v/v) to give **19** (1.47 g, 90%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.52-8.49 (m, 2H), 7.97-7.95 (m, 2H), 7.81-7.78 (m, 2H), 7.63-7.61 (m, 3H), 7.47-7.44 (m, 2H), 7.27-7.22 (m, 2H), 4.01 (s, 3H).

4-(1-Methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)aniline (20)

A solution of **19** (0.50 g, 1.3 mmol) and hydrazine hydrate (0.20 g, 4 mmol) in EtOH (30 mL) was refluxed for 4 h under nitrogen atmosphere. After removing the solvent, DCM (100 mL) was used to dissolve the residue. After washing with 1 M sodium hydroxide (30 mL) aqueous solution, the organic solution was dried over anhydrous sodium sulfate, filtrated and concentrated. The residue was purified on silica gel column using MeOH-DCM (1:15, v/v) to afford compound **20** (0.26 g, 80%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.47-8.45 (m, 2H), 7.56 (s, 1H), 7.24-7.18 (m, 4H), 6.68-6.64 (m, 2H), 3.96 (s, 3H).

2-(4-(1-Methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenyl)isoindoline-1,3-dione (21)

Following procedure for synthesizing compound **19**, but starting with compounds **16**, compound **21** was obtained (1.50 g, 92%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.97-7.95 (m, 2H), 7.83-7.78 (m, 3H), 7.59 (s, 1H), 7.24-7.18 (m, 2H), 7.05-7.07 (m, 2H), 6.65-6.78 (m, 3H).

4-(1-Methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)aniline (22)

Following the procedure of synthesizing compound **20**, but starting with compound **21**, compound **22** was obtained (0.26 g, 81%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.83 (s, 1H), 7.59 (s, 1H), 7.24-7.18 (m, 2H), 7.05-7.07 (m, 2H), 6.65-6.78 (m, 3H), 3.75 (s, 3H).

Procedure D: General Method of Synthesizing Compounds 10k-n and 11k-n

N-((4-methoxyquinolin-2-yl)methyl)-4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)aniline (10k)

A mixture of **20** (50 mg, 0.19 mmol), **9b** (51 mg, 0.19 mmol) and sodium carbonate (105 mg, 0.95 mmol) in anhydrous acetonitrile (10 mL) was stirred at 80 ^{o}C overnight. After water (30 mL) was added into the reaction mixture, the reaction mixture was extracted with DCM (3 x 50 mL). After the organic layer was dried, filtrated and concentrated, the residue

was purified via silica gel chromatography using MeOH-DCM (1:10, v/v) to afford compound **10k** (37 mg, 47%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.18-8.08 (m, 2H), 7.87-7.75 (m, 4H), 7.69-7.64 (m, 1H), 7.52-7.47 (m, 2H), 7.19-7.16 (m, 1H), 6.72-6.70 (m, 2H), 6.23 (s, 2H), 4.47 (s, 2H), 4.17-4.00 (m, 7H). Free base was converted to the corresponding oxalate salt by adding oxalic acid in EtOAc to **10k** in EtOAc. mp: 256 °C (decomposed). Anal. ($C_{26}H_{23}N_5O \cdot 2.5H_2C_2O_4$) C, H, N.

N-((6-methoxyquinolin-2-yl)methyl)-4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)aniline (10l)

Following procedure D, starting with compounds **20** and **9d**, compound **10l** was obtained (39 mg, 49%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.37 (s, 1H), 8.18 (d, *J* = 9 Hz, 1H), 7.88-7.79 (m, 4H), 7.37 (m, 1H), 7.21-7.11 (m, 3H), 6.76-6.73 (m, 2H), 6.13 (s, 2H), 4.49 (s, 2H), 4.00-3.94 (m, 7H). The free base was converted to the oxalate salt. mp: 209 °C (decomposed). Anal. ($C_{26}H_{23}N_5O \cdot 3H_2C_2O_4$) C, H, N.

N-((7-methoxyquinolin-2-yl)methyl)-4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)aniline (10m)

Following procedure D, starting with compounds **20** and **9e**, compound **10m** was obtained (33 mg, 43%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.36 (s, 1H), 8.12 (d, *J* = 9 Hz, 1H), 7.88 (m, 3H), 7.68 (d, *J* = 9 Hz, 1H), 7.20-7.15 (m, 4H), 6.70 (s, 2H), 6.14 (s, 2H), 4.47 (s, 2H), 3.98-3.91 (m, 7H). The free base was converted to the oxalate salt. mp: 201.2 °C (decomposed). Anal. ($C_{26}H_{23}N_5O \cdot 2.5H_2C_2O_4$) C, H, N.

N-((8-methoxyquinolin-2-yl)methyl)-4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)aniline (10n)

Following procedure D, starting with compounds **20** and **9f**, compound **10n** was obtained (31 mg, 40%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.27 (s, 1H), 8.20 (d, *J* = 9 Hz, 1H), 7.93 (d, *J* = 9 Hz, 1H), 7.79 (m, 2H), 7.49-7.35 (m, 2H), 7.11-7.03 (m, 3H), 6.67-6.64 (m, 2H), 6.11 (s, 2H), 4.56 (s, 2H), 3.98-3.92 (m, 7H). The free base was converted to the oxalate salt. mp: 236.2 °C (decomposed). Anal. ($C_{26}H_{23}N_5O \cdot 3H_2C_2O_4$) C, H, N.

N-((4-methoxyquinolin-2-yl)methyl)-4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)aniline (11k)

Following procedure D, starting with compounds **22** and **9b**, compound **11k** was obtained (38 mg, 48%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.12-8.07 (m, 2H), 7.97-7.87 (m, 4H), 7.67-7.40 (m, 3H), 7.00-6.98 (m, 1H), 6.81-6.74 (m, 2H), 6.18 (s, 2H), 4.44 (s, 2H), 3.91 (s, 3H), 3.72 (m, 3H). The free base was converted to the oxalate salt. mp: 186.3 °C (decomposed). Anal. ($C_{26}H_{23}N_5O \cdot 3H_2C_2O_4$) C, H, N.

N-((6-methoxyquinolin-2-yl)methyl)-4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)aniline (11l)

Following procedure D, starting with compounds **22** and **9d**, compound **11l** was obtained (48 mg, 48%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.08 (s, 2H), 7.99 (s, 1H), 7.79 (d, *J* = 4.8 Hz, 1H), 7.59 (d, *J* = 3.0 Hz, 1H), 7.33-7.30 (m, 1H), 7.04-6.99 (m, 3H), 6.83-6.81 (m, 2H), 6.35 (s, 2H), 4.46(s, 2H), 3.91 (m, 3H), 3.72 (m, 3H). The free base was converted to the oxalate salt. mp: 177.4 °C (decomposed). Anal. ($C_{26}H_{23}N_5O \cdot 3H_2C_2O_4$) C, H, N.

N-((7-methoxyquinolin-2-yl)methyl)-4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)aniline (11m)

Following procedure D, starting with compounds **22** and **9e**, compound **11m** was obtained (30 mg, 41%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.09-8.02 (m, 3H), 7.91-7.88 (m, 1H), 7.67-7.61 (m, 3H), 7.19-7.15 (m, 2H), 7.00-6.97 (m, 2H), 6.84-6.81 (m, 1H), 6.32 (s, 2H), 4.45 (s, 2H), 3.90 (s, 3H), 3.71 (m, 3H). The free base was converted to the oxalate salt. mp: 168.7 °C (decomposed). Anal. ($C_{26}H_{23}N_5O \cdot 2.5H_2C_2O_4$) C, H, N.

N-((8-methoxyquinolin-2-yl)methyl)-4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)aniline (11n)

Following procedure D, starting with compounds **22** and **9f**, compound **11n** was obtained (33 mg, 42%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.26-8.18 (m, 3H), 7.99 (s, 1H), 7.61-7.37 (m, 4H), 7.11-7.01 (m, 2H), 6.98-6.81 (m, 2H), 6.38 (s,

2H), 4.46 (s, 2H), 3.91 (s, 3H), 3.72 (m, 3H). The free base was converted to the oxalate salt. mp: 198.6 °C (decomposed). Anal. ($C_{26}H_{23}N_5O \cdot 2.5H_2C_2O_4$) C, H, N.

***In Vitro* Assay**

The PDE10A *in vitro* binding assay followed published procedures.[1-5] PDE activity was measured using the Phosphodiesterase [^{3}H]cAMP Scintillation Proximity Assay (SPA) (Cat. #TRKQ7090, Perkin Elmer, Waltham, MA) with minor modifications. Recombinant human PDE10A containing catalytic domain of human PDE10A (Swiss-Prot accession number Q9Y233) was purchased from Enzo Life Sciences Inc., Farmingdale, NY. Recombinant human PDE3A and 3B, PDE4A and PDE4Bwere purchased from EMD Chemicals, Inc., San Diego, CA. Optimal concentrations of enzymes were tested in the linear range of the enzyme activation curves with substrate. Inhibitor compounds were tested along with compound whose IC_{50} values are known (e.g.: MP-10) as an internal control for each PDE assay. All inhibitors were dissolved in DMSO, and a series of dilution was performed prior to screening in order to obtain desired concentrations. The serial diluted compounds were added to 96-well plate 10 µL/well, and then diluted PDE enzyme were added to each well: 50 µL PDE enzyme in PDE buffer (50 mM Tris-HCl pH = 7.4, 8 mM MgCl2, 1 mg/mL BSA, 2 mM EGTA) and allowed to incubate on ice for 5 min. A 50 µL radiolabeled substrate ([^{3}H]cAMP) with fixed concentration of 40 nCi/mL in ultra-pure water was then added to each well (the substrate concentration used in the assay is 1/3 of the Km concentration) and plates were incubated on ice for 20 min to give ~30% substrate turnover. Then the reaction was terminated with 50 µL yttrium silicate SPA beads (8 mg/mL stock in ultra-pure water). Plates were allowed to settle for 1.5 h at room temperature and counted on a Trilux Micro-Beta Counter (PerkinElmer, Waltham, MA). Radioactivity of each inhibitor compound with unit of CPM (Counts Per Minute), was plotted against inhibitor concentration in GraphPad Prism program (GraphPad Software, Inc., La Jolla, CA) and inhibitor IC_{50} values were calculated based on the non-linear regression with the "one site receptor competitive binding" model built in the program. All compounds were

independently assayed for at least two times and the fitting R squares were at least 90%. All results were described as fitted IC_{50} ± standard derivations with unit of nM.

Table 1 Elemental Analysis of New Analogues

Compounds	Molecular Formulas	Calculated			Found		
		C	H	N	C	H	N
10a	$C_{26}H_{22}N_4O_2 \cdot 1.5H_2C_2O_4$	62.47	4.52	10.05	62.22	4.55	10.10
10b	$C_{26}H_{22}N_4O_2 \cdot 2H_2C_2O_4 \cdot H_2O$	58.06	4.55	9.03	58.17	4.52	8.98
10c	$C_{26}H_{22}N_4O_2 \cdot 2H_2C_2O_4$	59.80	4.35	9.30	59.65	4.60	9.29
10d	$C_{26}H_{22}N_4O_2 \cdot 2H_2C_2O_4$	59.80	4.35	9.30	59.71	4.42	9.17
10e	$C_{26}H_{22}N_4O_2 \cdot 1.5H_2C_2O_4 \cdot H_2O$	60.52	4.73	9.73	60.81	4.69	9.94
10f	$C_{26}H_{22}N_4O_2 \cdot 2H_2C_2O_4$	59.80	4.35	9.30	59.62	4.47	9.15
10g	$C_{26}H_{22}N_4OS \cdot H_2C_2O_4$	63.62	4.58	10.60	63.52	4.72	10.43
10h	$C_{26}H_{22}N_4OS \cdot 2H_2C_2O_4$	58.25	4.24	9.06	58.17	4.48	9.01
10i	$C_{26}H_{22}N_4OS \cdot H_2C_2O_4$	63.62	4.58	10.60	63.44	4.76	10.47
10j	$C_{26}H_{22}N_4OS \cdot 2H_2C_2O_4$	58.25	4.24	9.06	58.10	4.35	8.96
10k	$C_{26}H_{23}N_5O \cdot 2.5H_2C_2O_4$	57.58	4.36	10.83	57.41	4.59	10.63
10l	$C_{26}H_{23}N_5O \cdot 3H_2C_2O_4$	55.57	4.23	10.13	55.33	4.42	10.31
10m	$C_{26}H_{23}N_5O \cdot 2.5H_2C_2O_4$	57.58	4.36	10.83	57.51	4.46	10.72
10n	$C_{26}H_{23}N_5O \cdot 3H_2C_2O_4$	55.57	4.23	10.13	55.46	4.30	10.03
11a	$C_{26}H_{22}N_4O_2 \cdot H_2C_2O_4 \cdot H_2O$	63.39	4.94	10.56	63.59	4.74	10.56
11b	$C_{26}H_{22}N_4O_2 \cdot 2H_2C_2O_4$	59.80	4.35	9.30	59.63	4.45	9.17
11c	$C_{26}H_{22}N_4O_2 \cdot 2.5H_2C_2O_4$	57.50	4.20	8.65	57.39	4.46	8.64
11d	$C_{26}H_{22}N_4O_2 \cdot 2H_2C_2O_4$	59.80	4.35	9.30	59.71	4.47	9.21
11e	$C_{26}H_{22}N_4O_2 \cdot 2H_2C_2O_4$	59.80	4.35	9.30	59.68	4.50	9.13
11f	$C_{26}H_{22}N_4O_2 \cdot 2H_2C_2O_4$	59.80	4.35	9.30	59.72	4.38	9.17
11g	$C_{26}H_{22}N_4OS \cdot 2H_2C_2O_4$	58.25	4.24	9.06	58.11	4.36	9.00
11h	$C_{26}H_{22}N_4OS \cdot H_2C_2O_4$	63.62	4.58	10.60	63.50	4.70	10.33
11i	$C_{26}H_{22}N_4OS \cdot 2H_2C_2O_4$	58.25	4.24	9.06	58.12	4.44	8.82
11j	$C_{26}H_{22}N_4OS \cdot 2H_2C_2O_4$	58.25	4.24	9.06	58.08	4.32	8.87
11k	$C_{26}H_{23}N_5O \cdot 3H_2C_2O_4$	55.57	4.23	10.13	55.42	4.29	10.29
11l	$C_{26}H_{23}N_5O \cdot 3H_2C_2O_4$	55.57	4.23	10.13	55.38	4.35	10.02
11m	$C_{26}H_{23}N_5O \cdot 2.5H_2C_2O_4$	57.58	4.36	10.83	57.29	4.56	10.58
11n	$C_{26}H_{23}N_5O \cdot 2.5H_2C_2O_4$	57.58	4.36	10.83	57.51	4.40	10.78

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