Supporting Information

"Development of β-Amino Alcohol Derivatives that Inhibit Toll Like Receptor 4 Mediated Inflammatory Response as Potential Antiseptics"

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General Chemistry Methods

All reactions were run under an inert atmosphere of either N_2 or Ar gas. Reaction solvents were purchased anhydrous and of HPLC quality. All other reagents were purchased from Sigma Aldrich and used without further purification. Yields were calculated for material judged homogenous by thin layer chromatography (TLC) and nuclear magnetic resonance (NMR). TLC was performed on Merck Kieselgel 60 F_{254} plates, eluting with the solvent indicated, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of phosphomolybdic acid-hydrate. Glassware for reactions was oven dried at 125 °C prior to use. Column flash chromatography was performed using silica gel (SiO_2) Premium R_f, 60 Å, 200 x 400 mesh from Sorbent Technologies. Nuclear magnetic resonance spectra were acquired on a Bruker spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C) or a Varian Inova-400 (400 MHz for ^1H and 101 MHz for ^{13}C). Chemical shifts for ^1H NMR spectra are reported in parts per million (ppm) and referenced to the signal of residual $CDCl_3$ at 7.26 ppm. Chemical shifts for ^{13}C NMR and DEPT spectra are reported in parts per million (ppm) and referenced to the center line of the residual $CDCl_3$ triplet at 77.23 ppm. Chemical shifts of the unprotonated carbons ('C') for DEPT spectra were obtained by comparison with the ^{13}C NMR spectrum. Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralcel AD-H silica column (length=25 cm) eluting with a mobile phase of an indicated percentage of *i*-PrOH / hexanes with 0.1% Et_2NH and at a flow rate of 0.5 mL/min. Retention times for the major and minor enantiomers were detected with Shimdzu SPD-6A UV spectrometric detector at 254 nm. Optical rotations were obtained on a Jasco P1038 polarimeter (Na D line) using a microcell with a 1 dm path length. Specific rotations ($[\alpha]_D^{20}$, Unit: °cm^2/g) are based on the equation $\alpha = (100 \bullet \alpha) / (l \bullet c)$ and are reported as unitless numbers where the concentration *c* is in g/100 mL and the path

length *l* is in decimeters. Mass spectrometry was obtained at the mass spectrometer facility of the University of Colorado Boulder, Department of Chemistry & Biochemistry on an ESI-qTOF-MS (electrospray-triple quadrupole-time-of-flight mass spectrometer) from Applied Biosystems, PE SCIEX/ABI API QSTAR Pulsar i Hybrid LC/MS/MS. All compounds tested have a purity of ≥95% as determined by TLC, NMR, HRMS, and chiral HPLC for chiral compounds. Compounds were named using ChemBioDraw Ultra 11.0.

General Synthetic Procedure for Racemic Epoxides of Type 2.

Into a 50 mL round bottom flask, a phenol (1 eq) was taken up into acetone (0.4 M). To the solution, K_2CO_3 (3 eq) and epichlorohydrin (4 eq) were added consecutively. The reaction mixture was set to stir at reflux for 24 h. At this time, an additional 4 eq of epichlorohydrin was added and the solution was allowed to stir at reflux for an additional 24 h.

The reaction was cooled to room temperature and the solids were filtered off. The solvent was removed under reduced pressure and the resulting oil was taken up into toluene (20 mL). The organic layer was washed with H_2O (1 x 20 mL), 1 M aqueous NaOH solution (1 x 20 mL), and H_2O (1 x 30 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The resulting material was then purified via flash SiO_2 chromatography.

2-((4-ethyoxyphenoxy)methyl)oxirane) (2b) Similar to the general procedure describe above. The resulting epoxide **2b** was isolated as white fine crystals without the need for purification (0.87 g, 87%); R_f = 0.277 (10% EtOAc/ hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 – 6.69 (m, 4H), 4.16 (dd, *J* = 3.26, 11.04 Hz, 1H), 4.02 – 3.87 (m, 3H), 3.34 (dddd, *J* = 2.68, 3.25, 4.12,

5.87 Hz, 1H), 2.90 (dd, *J* = 4.15, 4.91 Hz, 1H), 2.74 (dd, *J* = 2.66, 4.96 Hz, 1H), 1.39 (t, *J* = 6.99 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.74 (C), 152.80 (C), 115.91 (CH), 115.60 (CH), 69.73 (CH_2), 64.19 (CH_2), 50.49 (CH), 44.97 (CH_2), 15.15 (CH_3); HRMS (ESI^+) = calcd $C_{11}H_{14}O_3Na$ ($M+Na^+$) = 217.0835, found = 217.0826.

2-((3,4-dichlorophenoxy)methyl)oxirane (2e). Similar to the general procedure described above. The resulting yellow oil was purified via flash SiO_2 chromatography (3.0 x 3.5 cm, 20% EtOAc / hexanes) to yield the epoxide (**2e**) as clear oil (0.95 g, 95%); R_f = 0.34 (20% EtOAc / hexanes); 1H NMR (300 MHz, CDCl3) δ 7.35 – 7.31 (m, 1H), 7.03 (d, J = 2.90 Hz, 1H), 6.79 (dd, J = 2.92, 8.90 Hz, 1H), 4.24 (dd, J = 2.88, 11.04 Hz, 1H), 3.89 (dd, J = 5.85, 11.04 Hz, 1H), 3.39 – 3.29 (m, 1H), 2.92 (dd, J = 4.15, 4.84 Hz, 1H), 2.75 (dd, J = 2.64, 4.86 Hz, 1H); 13C NMR (75 MHz, CDCl3) δ 130.97 (CH), 124.79 (C), 116.78 (CH), 114.92 (CH), 112.70 (C), 100.21 (C), 69.54 (CH_2), 50.08 (CH), 44.73 (CH_2); HRMS (ESI^+) = calcd $C_9H_8ClO_3Li$ ($M+Li^+$) = 225.0062, found = 225.0059.

2-((4-(trifluoromethyl)phenoxy)methyl)oxirane (**2f**). Similar to the general procedure described above. The resulting yellow oil was purified via flash SiO_2 chromatography (4 x 6 cm, 10% EtOAc / hexanes) to yield the desired aryl epoxide (**2f**) (1.03 g, 76%); R_f = 0.23 (10% EtOAc / hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 1H), 7.01 – 6.94 (m, 1H), 4.29 (dd, *J* = 2.84, 11.08 Hz, 1H), 3.94 (dd, *J* = 5.91, 11.08 Hz, 1H), 3.35 (tdd, *J* = 2.74, 4.14, 5.58, 5.58 Hz, 1H), 2.90 (dd, *J* = 4.17, 4.84 Hz, 1H), 2.75 (dd, *J* = 2.65, 4.87 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.05 (C), 127.07 (q, $^3J_{CF}$ = 3.74 Hz, CH), 124.75 (q, $^1J_{CF}$ = 271.99 Hz, C),

123.24 (q, $^2J_{CF}$ = 4.3 Hz, C), 114.74 (CH), 69.06 (CH_2), 50.05 (CH), 44.60 (CH_2); HRMS (ESI^+) = calcd $C_{10}H_9F_3O_2Li$ ($M+Li^+$) = 225.0713, found = 225.0709.\

4-(oxiran-2-ylmethoxy)benzonitrile (2g) Similar to the general procedure described above. The resulting yellow oil was purified via flash SiO_2 chromatography (4.0 x 3.5 cm, 10% EtOAc / hexanes) to yield the desired epoxide (**2g**) as a clear oil (0.95 g, 95%); R_f = 0.12 (10% EtOAc / hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, 2H), 7.03 – 6.94 (m, 2H), 4.32 (dd, *J* = 2.84, 11.11 Hz, 1H), 3.97 (dd, *J* = 5.91, 11.12 Hz, 1H), 3.37 (ddt, *J* = 2.73, 2.73, 4.13, 5.88 Hz, 1H), 2.94 (dd, *J* = 4.16, 4.80 Hz, 1H), 2.77 (dd, *J* = 2.64, 4.83 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.87 (C), 134.26 (CH), 119.26 (CH), 115.56 (CH), 104.84 (C), 69.25 (CH_2), 49.99 (CH), 44.72 (CH_2); HRMS (ESI^+) = calcd $C_{10}H_9O_2NNa$ ($M+Na^+$) = 198.0525, found = 198.0521.

2-((4-(allyloxy)phenoxy)methyl)oxirane (2c) To a 25mL round bottom flask with DMF (8.37 mL), hydroquinone (0.82 g, 7.40 mmol, 2 eq) and K_2CO_3 (0.51 g, 3.70 mmol, 1 eq) were added at room temperature. To this stirring mixture, a solution of allyl bromide (0.58 mL, 6.66 mmol, 1.8 eq) and DMF (2.79 mL) was added dropwise over 45 min. The resulting mixture was set to reflux for 22 h.

The brown and cloudy solution was cooled to room temperature and poured into cold H_2O (125 mL). The resulting mixture was neutralized with a 10% aqueous HCl solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were washed with H_2O (3 x 30 mL) and brine (1 x 60 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The resulting oil was purified via flash SiO_2 column chromatography (3.0 x 8.5 cm, 10% EtOAc / hexanes) to yield 4-

(allyloxy)phenol as an clear oil (0.34 g, 34%); R_f = 0.25 (20% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 – 6.71 (m, 4H), 6.05 (ddt, *J* = 5.34, 5.34, 10.57, 17.25 Hz, 1H), 5.40 (dq, *J* = 1.63, 1.63, 1.63, 17.25 Hz, 1H), 5.27 (dq, *J* = 1.41, 1.41, 1.41, 10.47 Hz, 1H), 4.84 (s, 1H), 4.48 (dt, *J* = 1.51, 1.51, 5.35 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.93 (C), 149.79 (C), 133.70 (CH), 117.83 (CH_2), 116.24 (CH), 116.17 (CH), 69.85 (CH_2); HRMS (ESI^+) = calcd $C_9H_{10}O_2Na$ ($M+Na^+$) = 173.0573, found = 173.0567.

A 25 mL round bottom flask with THF (2.85 mL) was cooled to 0 °C. To this cooled flask, NaH (0.13 g, 5.24 mmol, 2 eq) was added and stirred for 10 min. To this solution, 4-(allyloxy)phenol (0.39 g, 2.62 mmol, 1 eq) in THF (2.85 mL) was added dropwise and the mixture was stirred for a further 10 min. Epichlorohydrin (0.82 mL, 10.5 mmol, 4 eq) was added dropwise and reaction mixture was stirred for 10 min at 0 °C then was warmed to room temperature. The reaction then was allowed to stir at reflux for 13 h.

At this time, the reaction was cooled to 0 °C and quenched with ice and cold H_2O. Once the reaction had warmed to room temperature, the solution was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting material was then loaded onto a flash SiO_2 column with toluene and the column flushed with hexanes, then purified (3.0 x 8.0 cm, 5% EtOAc / hexanes) to yield **2c** as an yellow oil (0.27 g, 53%); R_f = 0.26 (10% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 4H), 6.12 – 5.97 (m, 1H), 5.33 (ddq, *J* = 1.43, 1.53, 1.53, 10.48, 33.74 Hz, 2H), 4.49 (dt, *J* = 1.52, 1.52, 5.32 Hz, 2H), 4.17 (dd, *J* = 3.24, 11.04 Hz, 1H), 3.92 (dd, *J* = 5.61, 11.04 Hz, 1H), 3.37 – 3.31 (m, 1H), 2.90 (dd, *J* = 4.14, 4.93 Hz, 1H), 2.74 (dd, *J* = 2.66, 4.95 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.39 (C), 153.00 (C),

133.73 (CH), 117.77 (CH_2), 115.91 (CH), 115.87 (CH), 69.70 (CH_2), 69.67 (CH_2), 50.48 (CH), 44.96 (CH_2); HRMS (ESI^+) = calcd $C_{12}H_{15}O_3$ ($M+H^+$) = 207.1016, found = 207.1019.

Synthesis of Chiral Epoxides

(*R*)-2-((4-ethoxyphenoxy)methyl)oxirane (2i). Into a 25 mL round bottom flask, (*S,S*)-N,N'-Bis(3, 5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (0.078 g, 0.128 mmol, 0.05 eq) was taken up in CH_2Cl_2 (0.8 mL, 0.16 M) and acetic acid (0.02 mL, 0.514 mmol, 4 eq with respect to the catalyst) was added to the room temperature solution. This was allowed to stir open to air for 1.5 h.

The solvent was evaporated off by a stream of argon and the (*S,S*)-salen Co(I)OAc catalyst was taken up in THF (5.14 mL, 0.5 M) and the recemic 2-((4-ethyoxyphenoxy)methyl)oxirane) (**2b**) (0.50 g, 2.57 mmol, 1 eq) was added in one portion. The reaction mixture was cooled to 0 °C for 10 min, at which time, H_2O (0.023 mL, 1.42 mmol, 0.55 eq) was added. After 10 min, the mixture was warmed to room temperature and continued to stir overnight (16 h).

To the resulting dark red solution, PPTS (0.129 g, 4 eq of PPTS / mmol catalyst) in 10 mL of a 1:1 AcCN:CH_2Cl_2 solution was added and the mixture was stirred for an additional 30 min. The solution was filtered through a 5 x 3 cm plug of SiO_2 and the plug was washed with 100 mL of EtOAc. The solvent was removed under reduced pressure and the resulting dark yellow residue was purified via flash SiO_2 chromatography (2.5 x 5 cm, 10% EtOAc / hexanes) to yield the desired chiral epoxide, **2i**, as a yellow oil (0.249 g, quant.); R_f = 0.518 (25% EtOAc / hexanes); $[\alpha]_D^{25}$ = -5.304 (c=0.166, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 – 6.79 (m, 4H), 4.16 (dd, *J* = 3.22, 11.02 Hz, 1H), 3.98 (q, *J* = 6.98, 6.99, 6.99 Hz, 2H), 3.91 (dd, *J* = 5.64, 11.02

Hz, 1H), 3.34 (dddd, *J* = 2.75, 3.20, 4.10, 5.77 Hz, 1H), 2.90 (dd, *J* = 4.22, 4.84 Hz, 1H), 2.74 (dd, *J* = 2.67, 4.95 Hz, 1H), 1.39 (t, *J* = 6.99 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.67 (C), 152.74 (C), 115.84 (CH), 115.53 (CH), 69.66 (CH_2), 64.13 (CH_2), 50.47 (CH), 44.94 (CH_2), 15.13 (CH_3); HRMS (ESI^+) = calcd $C_{11}H_{14}O_3Na$ ($M+Na^+$) = 217.0835, found = 217.0841.

(*S*)-2-((4-ethoxyphenoxy)methyl)oxirane (2h). Similar procedure as described above using (*R*,*R*)-N,N'-Bis(3, 5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II). The dark red residue was purified via flash SiO_2 chromatography (dry loaded, 1.5 x 2 cm, 10% EtOAc / hexanes) to yield the desired chiral epoxide (**2h**) as a yellow oil (0.025 g, 49%); R_f = 0.53 (25% EtOAc / hexanes); $[\alpha]_D^{26}$ = 56.64 (c=1.049, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 – 6.80 (m, 1H), 4.16 (dd, *J* = 3.25, 11.04 Hz, 1H), 3.98 (dd, *J* = 6.96, 13.95 Hz, 1H), 3.92 (dd, *J* = 5.56, 11.00 Hz, 1H), 3.34 (dddd, *J* = 2.68, 3.25, 4.12, 5.84 Hz, 1H), 2.89 (dd, *J* = 4.14, 4.89 Hz, 1H), 2.74 (dd, *J* = 2.67, 4.96 Hz, 1H), 1.39 (t, *J* = 6.99 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.68, 152.74, 115.84, 115.53, 69.67, 64.13, 50.42, 44.96, 15.14; HRMS (ESI^+) = calcd $C_{11}H_{14}O_3Na$ ($M+Na^+$) = 217.0839, found = 217.0835.

(*S*)-2-((4-chlorophenoxy)methyl)oxirane (2j) Into a 20 mL round bottom flask, (*R*,*R*)-N,N'-Bis(3, 5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (0.063 g, 0.108 mmol, 0.05 eq) was taken up in CH_2Cl_2 (0.70 mL, 0.16 M) and acetic acid (0.03 mL, 0.433 mmol, 4 eq with respect to catalyst) was added to the room temperature solution. This was allowed to stir open to air for 1 h.

The solvent was evaporated off by a stream of argon and the (*S*,*S*)-salen Co(I)OAc catalyst was taken up in THF (4.33 mL, 0.5 M) and the recemic 2-((4-

chlorophenoxy)methyl)oxirane (**2d**) (0.400 g, 2.17 mmol, 1 eq) was added in one portion. The reaction mixture was cooled to 0 °C for 20 min, at which time, H_2O (0.02 mL, 1.19 mmol, 0.55 eq) was added. After 10 min, the mixture was warmed to room temperature and continued to stir overnight (16 h).

To the resulting dark brown solution, PPTS (0.109 g, 4 eq PPTS / mmol catalyst) in 5 mL of a 1:1 AcCN:CH_2Cl_2 solution was added and the mixture was stirred for an additional 30 min. The solution was filtered through a 5 x 2 cm plug of SiO_2 and the plug was washed with 100 mL of EtOAc. The solvent was removed under reduced pressure and the resulting dark yellow residue was purified via flash SiO_2 chromatography (2.5 x 6 cm, 10% EtOAc / hexanes) to yield the desired chiral epoxide (**2j**) as a yellow oil (0.144 g, 72%); R_f = 0.22 (10% EtOAc / hexanes); $[\alpha]_D^{25}$ = 6.923 (c=1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 1H), 6.86 – 6.80 (m, 1H), 4.19 (dd, *J* = 2.93, 11.03 Hz, 1H), 3.86 (dd, *J* = 5.85, 11.03 Hz, 1H), 3.32 (dddd, *J* = 2.79, 2.79, 4.14, 5.73 Hz, 1H), 2.88 (dd, *J* = 4.17, 4.87 Hz, 1H), 2.73 (dd, *J* = 2.66, 4.91 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.17 (C), 129.46 (CH), 126.13 (C), 116.03 (CH), 69.15 (CH_2), 50.16 (CH), 44.65 (CH_2); HRMS (ESI^+) = calcd $C_9H_9ClO_2Li$ ($M+Li^+$) = 191.0446, found = 191.0452.

(*R*)-2-((4-chlorophenoxy)methyl)oxirane (2k). Similar procedure described above using (*S,S*)-N,N'-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II). The resulting black residue was purified via flash SiO_2 chromatography (2.5 x 3 cm, 10% EtOAc / hexanes) to yield the desired chiral epoxide (**2k**) as a yellow oil (0.153 g, 61%); R_f = 0.22 (10% EtOAc / hexanes); $[\alpha]_D^{20}$ = -2.63 (c=1.132, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 2H), 6.86 – 6.81 (m, 2H), 4.20 (dd, *J* = 2.94, 11.03 Hz, 1H), 3.87 (dd, *J* = 5.83, 11.03 Hz, 1H), 3.32

(dddd, *J* = 2.81, 2.81, 4.14, 5.71 Hz, 1H), 2.88 (dd, *J* = 4.19, 4.85 Hz, 1H), 2.73 (dd, *J* = 2.65, 4.90 Hz, 1H); ^{13}C NMR (101 MHz, CDCl3) δ 157.18 (C), 129.47 (CH), 126.16 (C), 116.02 (CH), 69.16 (CH_2), 50.15 (CH), 44.67 (CH_2); HRMS (ESI^+) = calcd $C_9H_9ClO_2Li$ ($M+Li^+$) = 191.0445, found = 191.0453.

General Synthetic Procedure for the Pyrazole Fragment Type 6.

In a 25 mL round bottom flask with DMSO (0.72 M), KOH (1.5 eq), and 3, 5-dimethyl-1 H-pyrazole (1 eq) were combined and set to stir. This mixture was then heated at 80 °C for 1 h. The reaction was then cooled to room temperature and the desired benzyl chloride (1 eq) was added and the reaction mixture was stirred for an additional 2 h.

Upon completion, the reaction was poured into H_2O (50 mL) and the solution was extracted with $CHCl_3$ (4 x 50 mL). The resulting organic layers were washed with H_2O (4 x 100 mL) to remove DMSO, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting material was then purified via flash SiO_2 column chromatography.

1-benzyl-3,5-dimethyl-1H-pyrazole (6a). Similar to the general procedure described above. The resulting yellow oil was purified via flash SiO_2 column chromatography (4.0 x 6.0 cm, 5% EtOAc / hexanes) to yield **6a** as an clear oil (1.04 g, 96%); R_f = 0.1 (10% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 3H), 7.13 – 7.02 (m, 2H), 5.85 (s, 1H), 5.22 (s, 2H), 2.25 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.79 (C), 139.39 (C), 137.65 (C), 128.89 (CH), 127.62 (CH), 126.78 (CH), 105.76 (CH), 52.85 (CH_2), 13.78 (CH_3), 11.36 (CH_3); HRMS (ESI^+) = calcd $C_{12}H_{15}N_2$ ($M+H^+$) = 187.1230, found = 187.1234.

1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazole (6b). Similar to the general procedure described above. The resulting yellow was purified via flash SiO_2 column chromatography (3.0 x 6.0 cm, 60% EtOAc / hexanes) to yield **6b** as an yellow oil (1.12 g, 82%); R_f = 0.56 (60% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 1H), 7.24 – 7.11 (m, 2H), 6.58 – 6.49 (m, 1H), 5.89 (s, 1H), 5.30 (s, 2H), 2.26 (s, 3H), 2.15 (d, *J* = 0.69 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.34 (C), 139.93 (C), 135.49 (C), 131.96 (C), 129.41 (CH), 128.75 (CH), 127.73 (CH), 127.47 (CH), 105.83 (CH), 50.13 (CH_2), 13.81 (CH_3), 11.15 (CH_3); HRMS (ESI^+) = calcd $C_{12}H_{14}ClN_2$ ($M+H^+$) = 221.0840, found = 221.0830.

1-(3,4-dichlorobenzyl)-3,5-dimethyl-1H-pyrazole (6d). Similar to the general procedure described above. The resulting yellow oil was purified via flash SiO_2 column chromatography (4 x 5 cm, 10% EtOAc / hexanes) to yield the desired pyrazole (**6d**) as a light yellow oil (2.37 g, 89%); R_f = 0.06 (10% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 1H), 7.17 – 7.10 (m, 1H), 6.91 – 6.86 (m, 1H), 5.87 – 5.83 (m, 1H), 5.14 (s, 2H), 2.23 (s, 3H), 2.14 (d, *J* = 0.69 Hz, 3H); ^{3}C NMR (75 MHz, $CDCl_3$) δ 148.31 (C), 139.32 (C), 137.85 (C), 133.01 (C), 131.75 (C), 130.85 (CH), 128.73 (CH), 126.14 (CH), 106.10 (CH), 51.53 (CH_2), 13.71 (CH_3), 11.26 (CH_3); HRMS (ESI^+) = calcd $C_{12}H_{13}Cl_2N_2$ ($M+H^+$) = 255.0456, found = 255.0451.

3,5-dimethyl-1-(2-(trifluoromethyl)benzyl)-1H-pyrazole (6e). Similar to the general procedure described above. The resulting yellow was purified via flash SiO_2 column chromatography (4.0 x 5.5 cm, 5% EtOAc / hexanes) to yield **6e** as an yellow oil (1.21 g, 92%); R_f = 0.38 (10% EtOAc / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.32 Hz, 1H), 7.48 – 7.28 (m, 2H), 6.54 (d, *J* = 7.67 Hz, 1H), 5.92 (s, 1H), 5.44 (s, 2H), 2.28 (s, 3H), 2.10 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.43 (C), 140.04 (C), 136.76 (C), 132.70 (CH), 127.45 (CH), 127.45 (CH), 126.57 (q, $^1J_{CF}$ = 122.1 Hz, C), 125.98 (q, $^2J_{CF}$ = 23.7 Hz, CH), 106.10 (CH), 49.11 (CH_2), 13.80 (CH_3), 11.02 (CH_3); HRMS (ESI^+) = calcd $C_{13}H_{13}F_3N_2Na$ ($M+Na^+$) = 277.0923, found = 277.0918.

1-(2-bromobenzyl)-3,5-dimethyl-1H-pyrazole (6f). Similar to the general procedure described above. The resulting oil was purified via flash SiO_2 column chromatography (5.5 x 5 cm, 1% EtOAc/hexanes) to give **6f** as a colorless oil (0.100, 75.4%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 1.29, 7.86 Hz, 1H), 7.20 (td, *J* = 1.40, 7.54, 7.64 Hz, 1H), 7.15 – 7.07 (m, 1H), 6.50 – 6.43 (m, 1H), 5.90 (s, 1H), 5.27 (s, 2H), 2.26 (s, 3H), 2.15 (d, *J* = 0.68 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.38, 139.96, 137.07, 132.68, 129.03, 128.10, 127.73, 121.74, 105.85, 52.70, 13.82, 11.18; HRMS (ESI^+) = calcd $C_{12}H_{14}BrN_2$ ($M+H^+$) = 265.0335, found = 265.0325

3,5-dimethyl-1-(2-vinylbenzyl)-1H-pyrazole (6g). Into a round bottom flask, 1-(2-bromobenzyl)-3,5-dimethyl-1H-pyrazole (**6f**) (0.370 g, 1.40 mmol), tetrakis(triphenylphosphine)palladium (0) (0.161 g, 0.140 mmol) and tributylvinyltin (0.452 mL. 1.54 mmol) were combined in 35 mL of freshly distilled toluene. This solution was degassed (3x) then heated to 110 ºC for 10 h. The solvent was removed under reduce pressure and the crude compound was dissolved into diethyl ether (30 mL) and KF/Celite© (1 g) was added. The mixture was allowed to stir at room temperature for 24 h, filtered, and the solvent was removed under reduced pressure to give a yellow oil. This oil was purified via flash SiO_2 column chromatography (5.5 x 5 cm, 1:4 EtOAc / hexanes), to give **6g** as a yellow oil (0.28 g, 94%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 1.56, 7.52 Hz, 1H), 7.24 – 7.12 (m, 2H), 6.98 (dd, *J* =

10.97, 17.33 Hz, 1H), 6.52 (dd, *J* = 3.31, 4.08 Hz, 1H), 5.88 (s, 1H), 5.65 (dd, *J* = 1.37, 17.28 Hz, 1H), 5.38 (dd, *J* = 1.37, 10.96 Hz, 1H), 5.29 (s, 2H), 2.26 (s, 3H), 2.11 (d, *J* = 0.64 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.98, 139.82, 135.94, 134.73, 133.79, 128.42, 127.69, 126.43, 126.29, 117.33, 105.75, 50.51, 13.82, 11.31; HRMS (ESI^+) = calcd $C_{14}H_{17}N_2$ ($M+H^+$) = 213.1388, found = 213.1378.

General Synthetic Procedure for the Amine Fragments of Type 3.

In a 25 mL round bottom flask, methylamine-HCl (3 eq) and paraformaldehyde (6 eq) were combined in absolute EtOH (0.5 M). This solution was stirred for 2 h at 60 °C. At this point, the pyrazole derivative (**6**) (1 eq) was added and the reaction was heated to 75 °C and stirred for 21 h.

Upon completion, the reaction was cooled to room temperature and the solvent was removed under reduced pressure. The resulting compound was taken up into 50 mL of $CHCl_3$ and washed with a saturated aqueous solution of $NaHCO_3$ (1 x 20 mL). The resulting aqueous layer was then extracted with $CHCl_3$ (3 x 30 mL) and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified via flash SiO_2 chromatography.

1-(1-benzyl-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylmethanamine (3a). Similar to the general procedure described above. The resulting yellow oil was loaded onto a flash SiO_2 column with toluene, flushed with hexanes, and then purified with the indicated solvent system (3.0 x 5.5 cm, 50% EtOAc / hexanes with 2% Et_3N) to yield **3a** as an oil (1.00 g, 82%); R_f = 0.1 (50% EtOAc / hexanes with 2% Et_3N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.14 (m, 3H), 7.03

(dd, J = 1.20, 7.66 Hz, 2H), 5.22 (s, 2H), 3.27 (s, 2H), 2.87 (s, 1H), 2.24 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.54 (C), 137.98 (C), 137.77 (C), 128.84 (CH), 127.55 (CH), 126.66 (CH), 114.34 (C), 52.91 (CH_2), 49.06 (CH_2), 40.63 (CH_3), 12.30 (CH_3), 9.94 (CH_3); HRMS (ESI^+) = calcd $C_{14}H_{20}N_3O_3$ ($M+H^+$) = 230.1652, found = 230.1650.

1-(1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylmethanamine (3b). Similar to the general procedure described above. The resulting material was then loaded onto a flash SiO_2 column with toluene, flushed with hexanes than purified with the indicated solvent system (3.0 x 7.0 cm, 40% acetone / hexanes) to yield **3b** as an clear oil (0.35 g, 29%); R_f = 0.47 (40% acetone / hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, J = 1.74, 7.48 Hz, 1H), 7.23 – 7.08 (m, 2H), 6.55 – 6.47 (m, 1H), 5.30 (s, 2H), 3.54 (s, 2H), 2.43 (s, 3H), 2.27 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.47 (C), 138.10 (C), 135.41 (C), 131.94 (C), 129.41 (CH), 128.75 (CH), 127.72 (CH), 127.46 (CH), 115.41 (C), 50.26 (CH_2), 45.09 (CH_2), 36.10 (CH_3), 12.15 (CH_3), 9.70 (CH_3); HRMS (ESI^+) = calcd $C_{14}H_{19}ClN_3$ ($M+H^+$) = 264.1262, found = 264.1264.

1-(1-(3,4-dichlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylmethanamine (3d). Similar to the general procedure described above. The resulting oil was purified via flash SiO_2 chromatography (5 x 5 cm, 200 mL of 60% EtOAc / hexanes with 2% Et_3N then 300 mL of acetone) to give the desired amine (**3d)** as a light yellow oil (0.55 g, 31%); R_f = 0.05 (60% EtOAc / hexanes with 2% Et_3N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.25 Hz, 1H), 7.10 (d, J = 1.94 Hz, 1H), 6.91 – 6.84 (m, 1H), 5.15 (s, 2H), 3.27 (s, 2H), 2.87 (s, 1H), 2.23 (s, 3H), 2.11 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.15 (C), 138.04 (C), 137.92 (C), 133.05 (C), 131.74 (C), 130.86 (CH), 128.67 (CH), 126.09 (CH), 114.73 (C), 51.68 (CH_2), 49.01

(CH_2), 40.63 (CH_3), 12.29 (CH_3), 9.90 (CH_3); HRMS (ESI^+) = calcd $C_{14}H_{18}Cl_2N_3$ ($M+H^+$) = 298.0878, found = 298.0873.

1-(3,5-dimethyl-1-(2-(trifluoromethyl)benzyl)-1H-pyrazol-4-yl)-N-methylmethanamine (3e). Similar to the general procedure described above. The resulting yellow oil was purified via flash SiO_2 column chromatography (3.0 x 7.0 cm, 50% EtOAc / hexanes with 2% Et_3N) to yield **3e** as an yellow oil (0.57 g, 41%); R_f = 0.1 (50% EtOAc / hexanes with 2% Et_3N); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.62 Hz, 1H), 7.45 – 7.27 (m, 2H), 6.49 (d, *J* = 7.39 Hz, 1H), 5.44 (s, 2H), 3.32 (s, 2H), 2.91 (s, 1H), 2.28 (s, 3H), 2.16 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.21 (C), 138.55 (C), 136.88 (C), 132.63 (CH), 127.43 (CH), 127.24 (CH), 126.57 (q, $^1J_{CF}$ = 123 Hz, C), 126.00 (q, $^2J_{CF}$ = 24.3 Hz, CH), 122.75 (C), 114.72 (C), 48.75 (CH_2), 49.09 (CH_2), 40.68 (CH_3), 12.35 (CH_3), 9.62 (CH_3); HRMS (ESI^+) = calcd $C_{15}H_{19}F_3N_3$ ($M+H^+$) = 298.1526, found = 298.1524.

1-(3,5-dimethyl-1-(2-vinylbenzyl)-1H-pyrazol-4-yl)-N-methylmethanamine (3f). Similar to the general procedure described above. The resulting oil was purified via flash SiO_2 chromatography (5 x 4 cm, 2:3:95 MeOH/Et_3N/$CHCl_3$) to give the desired amine (**3f**) as a colorless oil (0.460 g, 90%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 1.43, 7.60 Hz, 1H), 7.26 – 7.10 (m, 2H), 6.98 (dd, *J* = 10.96, 17.31 Hz, 1H), 6.54 – 6.47 (m, 1H), 5.65 (dd, *J* = 1.36, 17.27 Hz, 1H), 5.38 (dd, *J* = 1.35, 10.96 Hz, 1H), 3.57 (s, 2H), 2.43 (s, 3H), 2.28 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.22, 138.31, 135.96, 134.54, 133.77, 128.40, 127.74, 126.47, 126.32, 117.39, 114.36, 77.65, 77.23, 76.81, 50.68, 44.75, 35.56, 12.19, 9.94; HRMS (ESI^+) = calcd $C_{16}H_{22}N_3$ ($M+H^+$) = 256.1808, found = 256.1817.

Synthesis of β-Amino Alcohol Derivatives

Methods A-E are described in detail in the Experimental Section of the manuscript.

(*R*)-1-(((1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)methyl)(methyl)amino)-3-(4-ethoxyphenoxy)propan-2-ol (1k). Synthesized using Method B with (*R*)-2-((4-ethoxyphenoxy)methyl)oxirane (**2i**), (0.05 g, 0.257 mmol, 1 eq) and the amine, 1-(1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylmethanamine (**3b**), (0.075 g, 0.283 mmol, 1.1 eq) over 48 h. The resulting orange oil was purified via flash SiO_2 column chromatography (2.5 x 3 cm, 60% EtOAc / hexanes with 2% Et_3N) to yield the desired chiral alcohol (**1k**) as a clear oil (0.067 g, 57%); R_f = 0.295 (60% EtOAc / hexanes with 2% Et_3N); Assay of enantiomeric excess: HPLC (Chiralcel AD 25 cm column, 20% *i*-PrOH / hexanes with 0.1% Et_2NH; 1.0 mL / min) t_r (major) = 4.39 min, t_r (minor) = 4.90 min; >96% *ee*; $[\alpha]_D^{25}$ = 10.55 (c=0.538, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 1.36, 7.82 Hz, 1H), 7.15 (dtd, *J* = 1.56, 7.43, 7.46, 20.85 Hz, 2H), 6.86 – 6.78 (m, 4H), 6.48 (dd, *J* = 1.59, 7.66 Hz, 1H), 5.30 (s, 2H), 4.08 (dddd, *J* = 4.85, 4.85, 4.85, 9.20 Hz, 1H), 3.97 (q, *J* = 6.98, 6.98, 6.98 Hz, 2H), 3.90 (d, *J* = 4.96 Hz, 2H), 3.40 (ABq, *J* = 12.80 Hz, Δ*v* = 63.70 Hz, 2H), 2.61 (dd, *J* = 9.73, 12.20 Hz, 1H), 2.47 (dd, *J* = 4.11, 12.23 Hz, 1H), 2.26 (s, 3H), 2.25 (s, 2H), 2.12 (s, 3H), 1.38 (t, *J* = 6.98 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.41 (C), 153.00 (C), 148.02 (C), 138.64 (C), 135.29 (C), 131.87 (C), 129.40 (CH), 128.76 (CH), 127.51 (CH), 127.49 (CH), 115.57 (CH), 115.46 (CH),113.70 (C), 71.19 (CH_2), 66.32 (CH), 64.09 (CH_2), 59.46 (CH_2), 51.66 (CH_2), 50.27 (CH_2), 42.06 (CH_3), 15.12 (CH_3), 12.37 (CH_3), 9.81 (CH_3); HRMS (ESI^+) = calcd $C_{25}H_{33}ClN_3O_3$ ($M+H^+$) = 458.2205, found = 458.2186.

(*R*)-1-(((1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)methyl)(methyl)amino)-3-(4-chlorophenoxy)propan-2-ol (1t). Synthesized using Method B with the epoxide, (*R*)-2-((4-chlorophenoxy)methyl)oxirane (**2k**), (0.050 g, 0.271 mmol, 1 eq) and the amine, 1-(1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylmethanamine (**3b**), (0.078 g, 0.298 mmol, 1.1 eq) over 15.5 h. The resulting yellow oil was purified via purified via flash SiO_2 column chromatography (2.5 x 4 cm, 60% EtOAc / hexanes with 2% Et_3N) to yield the desired alcohol (**I-20**) as clear oil (0.118 g, 97%); R_f = 0.375 (60% EtOAc / hexanes with 2% Et_3N); Assay of enantiomeric excess: HPLC (Chiralcel AD 25 cm column, 20% *i*-PrOH / hexanes with 0.1% Et_2NH; 1.0 mL / min) t_r (major) = 11.48 min, t_r (minor) = 12.30 min; >96% *ee*; $[\alpha]_D^{25}$ = 14.23 (c=1.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 1.28, 7.86 Hz, 1H), 7.23 – 7.18 (m, 2H), 7.19 – 7.08 (m, 3H), 6.84 – 6.79 (m, 2H), 6.50 – 6.46 (m, 1H), 5.29 (s, 2H), 4.07 (dddd, *J* = 4.33, 4.33, 4.33, 9.55 Hz, 1H), 3.90 (dd, *J* = 1.84, 4.85 Hz, 2H), 3.90 (dd, *J* = 4.88, 21.07 Hz, 2H), 3.46 (brs, 1H), 3.39 (ABq, *J* = 13.18, Δ*v* = 63.00 Hz, 3H), 2.59 (dd, *J* = 9.69, 12.20 Hz, 1H), 2.45 (dd, *J* = 4.19, 12.23 Hz, 1H), 2.25 (s, 3H), 2.24 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.51 (C), 147.96 (C), 138.61 (C), 135.23 (C), 131.89 (C), 129.44 (CH), 129.40 (CH), 128.76 (CH), 127.52 (CH), 127.44 (CH), 125.91 (C), 115.93 (CH), 113.61 (C), 70.81 (CH_2), 66.14 (CH), 59.21 (CH_2), 51.64 (CH_2), 50.24 (CH_2), 42.05 (CH_3), 12.33 (CH_3), 9.78 (CH_3); HRMS (ESI^+) = calcd $C_{23}H_{28}Cl_2N_3O_3$ ($M+H^+$) = 448.1553, found = 448.1548.

(*S*)-1-(((1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)methyl)(methyl)amino)-3-(4-chlorophenoxy)propan-2-ol (1u). Synthesized using Method E with the epoxide, (*S*)-2-((4-chlorophenoxy)methyl)oxirane (**2j**), (0.050 g, 0.271 mmol, 1 eq) and the amine, 1-(1-(2-

chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylmethanamine, (0.078 g, 0.297 mmol, 1.1 eq) (**3b**). The resulting yellow-orange oil was purified via flash SiO_2 column chromatography (2.5 x 3 cm, 60% EtOAc/hexanes with 2% Et_3N) to yield the desired alcohol (**1u**) as clear oil (0.100 g, 82%); R_f = 0.347 (60% EtOAc / hexanes with 2% Et_3N); Assay of enantiomeric excess: HPLC (Chiralcel AD 25 cm column, 20% *i*-PrOH / hexanes with 0.1% Et_2NH; 1.0 mL / min) t_r (major) = 12.28 min, t_r (minor) = 11.5 min; >96% *ee*; $[\alpha]_D^{25}$ = -10.16 (c=0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 1.26, 7.84 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.20 – 7.08 (m, 3H), 6.84 – 6.79 (m, 2H), 6.48 (dd, *J* = 1.26, 7.60 Hz, 1H), 5.29 (s, 2H), 4.07 (dddd, *J* = 3.20, 3.20, 3.20, 8.00 Hz, 1H), 3.90 (dd, *J* = 4.90, 21.03 Hz, 1H), 3.90 (dd, *J* = 1.73, 4.82 Hz, 1H), 3.39 (ABq, *J* = 13.18 Hz, Δ*v* = 62.4 Hz, 2H), 2.59 (dd, *J* = 9.75, 12.17 Hz, 1H), 2.45 (dd, *J* = 4.14, 12.22 Hz, 1H), 2.25 (s, 3H), 2.24 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.50 (C), 147.97 (C), 138.63 (C), 135.23 (C), 131.89(C), 129.45 (CH), 129.41 (CH), 128.77 (CH), 127.52 (CH), 127.44 (CH), 125.92 (C), 115.92 (CH), 113.60 (C), 70.80 (CH_2), 66.13 (C), 59.21 (CH_2), 51.64 (CH_2), 50.25 (CH_2), 42.05 (CH_3), 12.34 (CH_3), 9.80 (CH_3); HRMS (ESI^+) = calcd $C_{23}H_{28}Cl_2N_3O_2$ ($M+H^+$) = 448.1569, found = 448.1553.

1-(((1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)methyl)(methyl)amino)-3-phenoxypropan-2-ol (1b). Synthesized using Method A with the commercially available epoxide, 2-(phenoxymethyl)oxirane (**2a**), (0.05 g, 0.33 mmol, 1 eq), and the amine 1(1-(2-chlorobenzyl)-3,5-dimehtyl-1*H*-pyrazol-4-yl)-*N*-methylmethanamine (**3b**), (0.096 g, 0.36 mmol, 1.1 eq). The resulting yellow oil was purified via flash SiO_2 column chromatography (2.5 x 4 cm, 100 mL of 50% EtOAc / hexanes with 2% Et_3N followed by 100 mL of EtOAc) to yield the desired alcohol (**1b**) as a light yellow oil (0.136 g, quant.); R_f = 0.394 (50% EtOAc / hexanes

with 2% Et_3N); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 1.73, 7.48 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.21 – 7.08 (m, 2H), 6.98 – 6.87 (m, 3H), 6.49 (dd, *J* = 1.79, 7.50 Hz, 1H), 5.30 (s, 2H), 4.10 (td, *J* = 5.10, 5.10, 5.10, 9.60 Hz, 1H), 3.95 (d, *J* = 4.95 Hz, 2H), 3.40 (ABq, *J* = 13.18 Hz, Δ*v* = 46.46 Hz, 2H), 3.30 (s, 1H), 2.62 (dd, *J* = 9.47, 12.22 Hz, 1H), 2.49 (dd, *J* = 4.26, 12.26 Hz, 1H), 2.26 (s, 3H), 2.26 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.90 (C), 148.01 (C), 138.63 (C), 135.30 (C), 131.90 (C), 129.61 (CH), 129.41 (CH), 128.77 (CH), 127.57 (CH), 127.47 (CH), 121.10 (CH), 114.67 (CH), 113.69 (C), 70.46 (CH_2), 66.30 (CH), 59.47 (CH_2), 51.69 (CH_2), 50.26 (CH_2), 42.10 (CH_3), 12.34 (CH_3), 9.80 (CH_3); HRMS (ESI^+) = calcd $C_{23}H_{29}ClN_3O_2$ ($M+H^+$) = 414.1958, found = 414.1963.

1-(((1-benzyl-3,5-dimethyl-1H-pyrazol-4-yl)methyl)(methyl)amino)-3-(4-ethoxyphenoxy)propan-2-ol (1e). Synthesized using Method A with the amine 1-(1-benzyl-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylmethanamine (**3a**) (0.065 g, 0.283 mmol, 1.1 eq) and the epoxide 2-((4-ethyoxyphenoxy)methyl)oxirane) (**2b**) (0.05 g, 0.257 mmol, 1.0 eq). The resulting yellow oil was then purified via flash SiO_2 column chromatography (2.5 x 3.5 cm, 50% EtOAc / hexanes with 2% Et_3N) to yield **1e** as a clear oil (0.020 g, 19%); R_f = 0.30 (50% EtOAc / hexanes with 2% Et_3N); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 3H), 7.13 – 6.99 (m, 2H), 6.84 (s, 4H), 5.24 (s, 2H), 4.13 – 4.03 (m, 1H), 3.99 (q, *J* = 6.96, 6.98, 6.98 Hz, 2H), 3.91 (d, *J* = 4.98 Hz, 2H), 3.38 (ABq, *J* = 13.20 Hz, *Δv* = 47.08 Hz, 2H), 2.61 (dd, *J* = 9.59, 12.23 Hz, 1H), 2.47 (dd, *J* = 4.18, 12.25 Hz, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 2.13 (s, 3H), 1.40 (t, *J* = 6.99 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.46 (C), 153.07 (C), 147.48 (C), 138.18 (C), 137.50 (C), 128.90 (CH), 127.64 (CH), 126.66 (CH), 115.65 (CH), 115.54 (CH), 113.60 (C), 71.30 (CH_2), 66.36 (CH), 64.16 (CH_2), 59.58 (CH_2), 52.97 (CH_2), 51.69 (CH_2), 42.01 (CH_3), 15.13

(CH_3), 12.32 (CH_3), 10.02 (CH_3); HRMS (ESI^+) = calcd $C_{25}H_{34}N_3O_3$ ($M+H^+$) = 424.2595, found = 424.2586.

1-(4-(allyloxy)phenoxy)-3-(((1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)methyl)(methyl)amino)propan-2-ol (1r). Synthesized using Method A with the amine, 1(1-(2-chlorobenzyl)-3,5-dimehtyl-1*H*-pyrazol-4-yl)-*N*-methylmethanamine (**3b**), (0.058 g, 0.220 mmol, 1.0 eq) and the epoxide 2-((4-(allyloxy)phenoxy)methyl)oxirane (**2c**) (0.05 g, 0.24 mmol, 1.1 eq). The resulting oil was purified via flash SiO_2 column chromatography (3.0 x 5.0 cm, 40% acetone / hexanes with 2% Et_3N) to yield **1r** as a clear oil in a quantitative yield; R_f = 0.36 (40% acetone / hexanes with 2% Et_3N); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 1.41, 7.71 Hz, 1H), 7.23 – 7.06 (m, 2H), 6.83 (s, 3H), 6.56 – 6.44 (m, 1H), 6.15 – 5.96 (m, 1H), 5.39 (dq, *J* = 1.64, 1.64, 1.64, 17.26 Hz, 1H), 5.30 (s, 2H), 5.27 (dq, *J* = 1.42, 2.91, 10.47 Hz, 1H), 4.48 (dt, *J* = 1.53, 1.53, 5.32 Hz, 2H), 4.14 – 3.98 (m, 1H), 3.90 (d, *J* = 4.97 Hz, 2H), 3.40 (ABq, *J* = 13.20 Hz, *Δv* = 47.39 Hz, 2H), 3.31 (br s, 1H), 2.61 (dd, *J* = 9.64, 12.17 Hz, 1H), 2.47 (dd, *J* = 4.17, 12.22 Hz, 1H), 2.26 (s, 2H), 2.25 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.23 (C), 174.90 (C), 157.81 (C), 153.29 (C), 138.68 (C), 135.36 (C), 133.77 (CH), 129.47 (CH), 128.82 (CH), 127.62 (CH), 127.53 (CH), 117.74 (CH_2), 115.88 (CH), 115.64 (CH), 113.75 (C), 71.27 (CH_2), 69.69 (CH_2), 66.39 (CH), 59.55 (CH_2), 51.74 (CH_2), 50.33 (CH_2), 42.12 (CH_3), 12.40 (CH_3), 9.86 (CH_3); HRMS (ESI^+) = calcd $C_{26}H_{33}ClN_3O_3$ ($M+H^+$) = 470.2205, found = 470.2213.

1-(((3,5-dimethyl-1-(2-(trifluoromethyl)benzyl)-1H-pyrazol-4-yl)methyl)(methyl)amino)-3-(4-(trifluoromethyl)phenoxy)propan-2-ol (1x) Synthesized using Method A with the epoxide,

2-((4-(trifluoromethyl)phenoxy)methyl)oxirane (**2f**), (0.05 g, 0.23 mmol, 1 eq) and the amine, 1-(3,5-dimethyl-1-(2-(trifluoromethyl)benzyl)-1H-pyrazol-4-yl)-N-methylmethanamine (**3e**), (0.075 g, 0.251 mmol, 1.1 eq). The resulting oil was purified via flash SiO_2 column chromatography (2.5 x 5 cm, 100 mL of 50% EtOAc / hexanes with 2% Et_3N followed by 100 mL of EtOAc) to yield the desired alcohol (**1x**) as a dark yellow oil (0.058 g, 48%); R_f = 0.28 (50% EtOAc / hexanes with 2% Et_3N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.57 Hz, 1H), 7.53 (d, *J* = 8.41 Hz, 1H), 7.35 (dt, *J* = 7.42, 7.42, 23.52 Hz, 2H), 6.96 (d, *J* = 8.05 Hz, 1H), 6.49 (d, *J* = 7.65 Hz, 1H), 5.44 (s, 2H), 4.11 (td, *J* = 4.42, 8.41, 8.76 Hz, 1H), 4.01 – 3.95 (m, 1H), 3.42 (ABq, *J* = 13.01 Hz, Δ*v* = 66.50 Hz, 2H), 2.63 (t, *J* = 10.98 Hz, 1H), 2.48 (dd, *J* = 3.98, 12.18 Hz, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.34 (C), 155.44 (C), 148.09 (C),138.76 (C), 136.49 (C), 132.69 (CH), 127.51 (CH), 127.41 (CH), 127.16 (q, $^2J_{CF}$ = 3.6 Hz, CH), 127.06 (q, $^2J_{CF}$ = 3.4 Hz, CH), 126.98 (q, $^2J_{CF}$ = 5.3 Hz, CH), 123.14 (C), 114.65 (CH), 113.93 (C), 70.69 (CH_2), 66.07 (CH), 59.16 (CH_2), 51.67 (CH_2), 49.32 (CH_2), 42.09 (CH_3), 12.36 (CH_3), 9.68 (CH_3), Note: signals for the CF_3 quaternary carbons were not observed; HRMS (ESI^+) = calcd $C_{25}H_{28}F_6N_3O_2$ ($M+H^+$) = 516.2056, found = 516.2080.

1-(((3,5-dimethyl-1-(2-(trifluoromethyl)benzyl)-1H-pyrazol-4-yl)methyl)(methyl)amino)-3-(4-ethoxyphenoxy)propan-2-ol (1p) Synthesized using Method A with the amine 1-(3,5-dimethyl-1-(2-(trifluoromethyl)benzyl)-1H-pyrazol-4-yl)-N-methylmethanamine (**3e**) (0.069 g, 0.234 mmol, 1.0 eq), and the epoxide 2-((4-ethyoxyphenoxy)methyl)oxirane) (**2b**) (0.05 g, 0.257 mmol, 1.1 eq). The resulting oil was purified via flash SiO_2 column chromatography (3.0 x 5.5 cm, 35% EtOAc / hexanes with 2% Et_3N) to yield **1p** as a light yellow oil (0.049 g, 43%); R_f = 0.26 (35% EtOAc / hexanes with 2% Et_3N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.12 Hz,

1H), 7.44 – 7.28 (m, 2H), 6.82 (s, 4H), 6.49 (d, *J* = 7.53 Hz, 1H), 5.44 (s, 2H), 4.07 (td, *J* = 4.75, 9.39, 9.39 Hz, 1H), 3.97 (q, *J* = 6.96, 6.98, 6.98 Hz, 2H), 3.90 (d, *J* = 4.96 Hz, 2H), 3.40 (ABq, *J* = 13.20 Hz, *Δv* = 46.77 Hz, 2H), 2.61 (dd, *J* = 9.56, 12.25 Hz, 1H), 2.47 (dd, *J* = 4.21, 12.25 Hz, 1H), 2.27 (s, 3H), 2.25 (s, 3H), 2.07 (s, 3H), 1.38 (t, *J* = 6.98 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.51 (C), 153.06 (C), 148.15 (C), 138.76 (C), 136.58 (q, $^3J_{CF}$ = 6 Hz, C), 132.75 (CH), 127.50 (CH), 127.20 (CH), 126.55 (q,$^1J_{CF}$ = 123 Hz, C), 126.00 (q, $^2J_{CF}$ = 24 Hz, CH), 115.65 (CH), 115.56 (CH), 114.05 (C), 71.27 (CH_2), 66.41 (CH), 64.17 (CH_2), 59.50 (CH_2), 51.71 (CH_2), 49.34 (CH_2), 49.29 (CH_2), 42.14 (CH_3), 15.14 (CH_3), 12.37 (CH_3), 9.70 (CH_3); HRMS (ESI$^+$) = calcd $C_{26}H_{33}N_3O_3F_3$ (M+H$^+$) = 492.2469, found = 492.2447.

1-(((3,5-dimethyl-1-(2-vinylbenzyl)-1H-pyrazol-4-yl)methyl)(methyl)amino)-3-(4-ethoxyphenoxy)propan-2-ol (1o). Synthesized using Method C with 1-(3,5-dimethyl-1-(2-vinylbenzyl)-1H-pyrazol-4-yl)-N-methylmethanamine (**3f**) (0.064 g, 0.250 mmol) and the epoxide, 2-((4-ethoxyphenoxy)methyl)oxirane (**2b**) (0.145 g, 0.750 mmol). The resulting oil was purified via flash SiO_2 column chromatography (5 x 3 cm, 1:25:25 E_3N:EtOAc:hexanes) to yield the alcohol **1o** as a colorless oil (0.047 g, 43%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.40 (m, 1H), 7.25 – 7.10 (m, 2H), 7.05 – 6.89 (m, 1H), 6.82 (d, *J* = 0.79 Hz, 4H), 6.47 (d, *J* = 6.78 Hz, 1H), 5.65 (dd, *J* = 1.37, 17.30 Hz, 1H), 5.38 (dd, *J* = 1.34, 10.96 Hz, 1H), 5.29 (s, 2H), 4.12 – 4.02 (m, 1H), 3.98 (q, *J* = 6.95, 6.99, 6.99 Hz, 2H), 3.90 (d, *J* = 5.08 Hz, 2H), 3.39 (ABq, *J* = 9.00 Hz, *Δv* = 47.60 Hz, 2H), 2.60 (dd, *J* = 9.56, 12.31 Hz, 1H), 2.47 (dd, *J* = 4.17, 12.16 Hz, 1H), 2.25 (s, 3H), 2.24 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.46, 153.06, 147.67, 138.55, 135.90, 134.57, 133.71, 128.42, 127.71, 126.31, 126.27, 117.36, 115.64, 115.53,

113.62, 71.28, 66.36, 64.15, 59.53, 51.70, 50.67, 42.05, 15.14, 12.36, 9.95; HRMS (ESI^+) = calcd $C_{27}H_{36}ClN_3O_3$ ($M+H^+$) = 450.5925, found = 450.5948.

1-(4-chlorophenoxy)-3-(((3,5-dimethyl-1-(2-vinylbenzyl)-1H-pyrazol-4-yl)methyl)(methyl)amino)propan-2-ol (1w). Synthesized using Method A with the amine, 1-(3,5-dimethyl-1-(2-vinylbenzyl)-1H-pyrazol-4-yl)-N-methylmethanamine, (**3f**) (0.064 g, 0.25 mmol) and the epoxide, 2-((4-chlorophenoxy)methyl)oxirane, (**2d**) (0.069 g, 0.37 mmol). The resulting yellow oil was purified via flash SiO_2 column chromatography (5 x 3 cm, 1:25:25 E_3N:EtOAc:hexanes) to give the desired alcohol **1w** as a colorless oil (0.070 g, 63%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.28 Hz, 1H), 7.25 – 7.08 (m, 4H), 6.96 (dd, *J* = 10.95, 17.26 Hz, 1H), 6.83 (d, *J* = 8.95 Hz, 2H), 6.47 (d, *J* = 7.48 Hz, 1H), 5.65 (dd, *J* = 1.06, 17.27 Hz, 1H), 5.38 (dd, *J* = 1.04, 10.98 Hz, 1H), 5.28 (s, 2H), 4.07 (td, *J* = 4.52, 9.26, 9.33 Hz, 1H), 3.91 (d, *J* = 4.85 Hz, 2H), 3.39 (ABq, *J* = 12.00 Hz, *Δv* = 47.6 Hz, 2H), 2.59 (dd, *J* = 9.80, 12.03 Hz, 1H), 2.45 (dd, *J* = 4.15, 12.20 Hz, 1H), 2.25 (s, 3H), 2.25 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.58, 147.65, 138.55, 135.93, 134.54, 133.70, 129.50, 128.41, 127.74, 126.34, 126.27, 125.99, 117.41, 116.00, 113.54, 70.89, 66.17, 59.27, 51.71, 50.69, 42.06, 12.37, 9.96; HRMS (ESI^+) = calcd $C_{25}H_{31}ClN_3O_2$ ($M+H^+$) = 440.2099, found = 440.2113.

1-(((1-(3-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)methyl)(methyl)amino)-3-(4-ethoxyphenoxy)propan-2-ol (1m). Synthesizes using Method A with the epoxide, 2-((4-ethyoxyphenoxy)methyl)oxirane) (**2b**) (0.050 g, 0.257 mmol, 1 eq), the amine, 1-(1-(3-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylmethanamine (**3c**), (0.075 g, 0.283 mmol, 1.1 eq). The resulting yellow oil was purified via purified via flash SiO_2 column

chromatography (2.5 x 3.5 cm, 50% EtOAc / hexanes with 2% Et_3N) to yield the desired alcohol (**1m**) as a clear oil (0.054 g, 46%); R_f = 0.270 (60% EtOAc / hexanes with 2% Et_3N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.19 (m, 2H), 7.02 – 6.99 (m, 1H), 6.91 (dd, *J* = 1.38, 4.07 Hz, 1H), 6.84 – 6.78 (m, 2H), 5.18 (s, 2H), 4.07 (td, *J* = 4.80, 4.80, 4.80, 9.30 Hz, 1H), 3.97 (q, *J* = 6.96, 6.98, 6.98 Hz, 2H), 3.89 (d, *J* = 5.03 Hz, 2H), 3.71 (s, 1H), 3.38 (ABq, *J* = 12.00 Hz, Δ*v* = 47.60 Hz, 2H), 2.59 (dd, *J* = 9.55, 12.22 Hz, 1H), 2.47 (dd, *J* = 4.19, 12.27 Hz, 1H), 2.24 (s, 3H), 2.23 (s, 3H), 2.12 (s, 2H), 1.38 (t, *J* = 6.98 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.28 (C), 152.86 (C), 147.69 (C), 139.37 (C), 138.03 (C), 134.66 (C), 130.04 (CH), 127.72 (CH), 126.59 (CH), 124.61 (CH), 115.45 (CH), 115.35 (CH), 113.53 (C), 71.09 (CH_2), 66.17 (CH), 63.97 (CH_2), 59.40 (CH_2), 52.11 (CH_2), 51.46 (CH_2), 41.83 (CH_3), 14.94 (CH_3), 12.14 (CH_3), 9.81 (CH_3); HRMS (ESI^+) = calcd $C_{25}H_{33}ClN_3O_3$ ($M+H^+$) = 458.2205, found = 458..2226.

1-(((1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)methyl)(methyl)amino)-3-(4-(trifluoromethyl)phenoxy)propan-2-ol (1y). Synthesized using Method A with the epoxide 2-((-4-(trifluoromethyl)phenoxy)methyloxirane (**2f**), (0.05 g, 0.23 mmol, 1 eq) and the amine, 1-(1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylmethanamine (**3b**), (0.066 g, 0.252 mmol, 1.1 eq). The resulting orange oil was purified via flash SiO_2 column chromatography (2.5 x 4 cm, 60% EtOAc /hexanes with 2% Et_3N) to yield the desired alcohol (**1y**) as a clear oil. (0.081 g, 73%); R_f = 0.367 60% EtOAc / hexanes with 2% Et_3N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 2H), 7.35 (dd, *J* = 1.62, 7.53 Hz, 1H), 7.14 (dtd, *J* = 1.65, 7.40, 7.41, 16.51 Hz, 2H), 6.98 – 6.93 (m, 2H), 6.52 – 6.46 (m, 1H), 5.30 (s, 2H), 4.10 (td, *J* = 4.29, 9.52, 9.53 Hz, 1H), 3.99 (s, 1H), 3.98 (d, *J* = 1.05 Hz, 1H), 3.57 (s, 1H), 3.41 (ABq, *J* = 13.50 Hz, *Δv* = 48.70 Hz, 2H), 2.62 (dd, *J* = 9.64, 12.20 Hz, 1H), 2.47 (dd, *J* = 4.18, 12.22 Hz, 1H), 2.26 (s, 3H), 2.26

(s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.38 (C), 148.00 (C), 138.65 (C), 135.27 (C), 131.97 (C), 129.46 (CH), 128.81 (CH), 127.60 (CH), 127.46 (CH), 127.06 (q, $^3J_{C\text{-}F}$ = 3.75 Hz, CH), 124.58 (q, $^1J_{C\text{-}F}$ = 270 Hz, C), 123.36 (q, $^2J_{C\text{-}F}$ = 32.25 Hz, C), 114.68 (CH), 113.60 (C), 70.75 (CH_2), 66.11 (CH), 59.20 (CH_2), 51.70 (CH_2), 50.30 (CH_2), 42.09 (CH_3), 12.36 (CH_3), 9.82 (CH_3); HRMS (ESI^+) = calcd $C_{24}H_{28}ClF_3N_3O_3$ ($M+H^+$) = 482.1817, found = 482.1824.

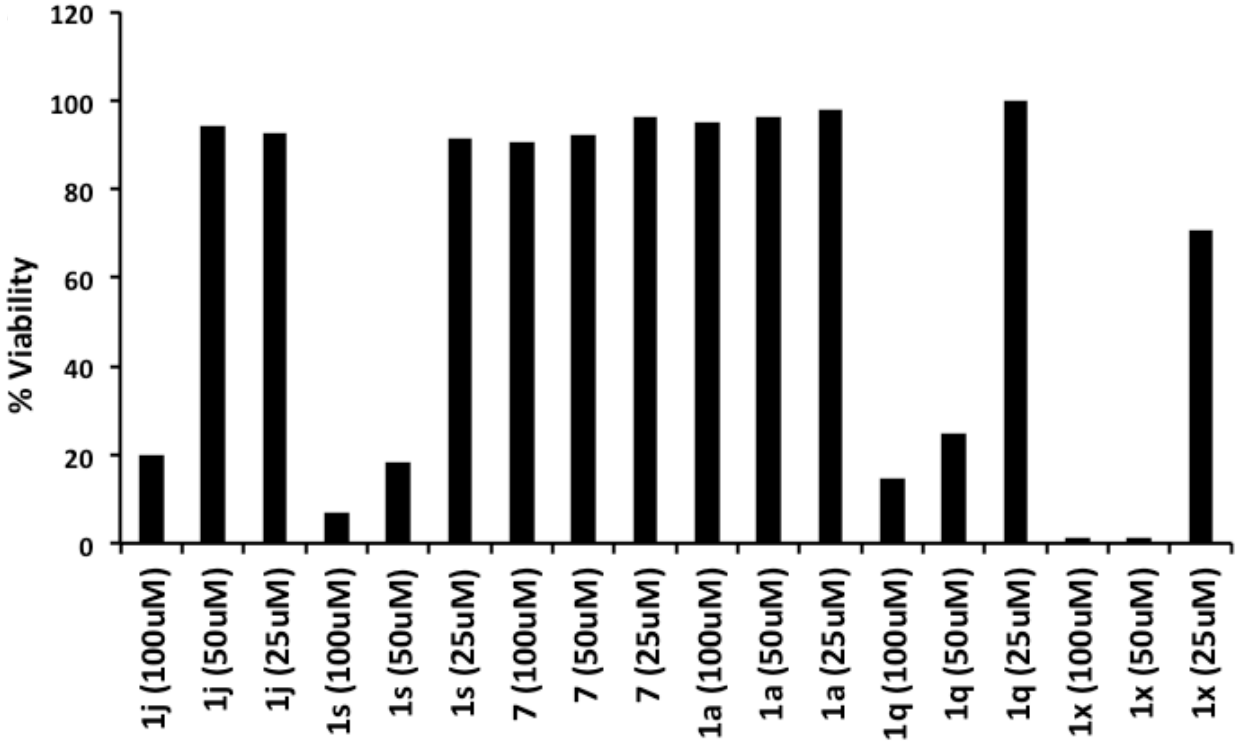
4-(3-(((1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)methyl)(methyl)amino)-2-hydroxypropoxy)benzonitrile (1z) Synthesizes using Method A with the amine, 1-(1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylmethanamine (**3b**) (0.06 g, 0.23 mmol, 1.0 eq), and the epoxide, 4-(oxiran-2-ylmethoxy)benzonitrile (**2g**) (0.044 g, 0.251 mmol, 1.1 eq). The resulting yellow oil was then purified via flash SiO_2 column chromatography (3.0 x 4.0 cm, 50% EtOAc / hexanes with 2% Et_3N) to yield **1z** as an oil (0.025 g, 25%); R_f = 0.09 (60% EtOAc / hexanes with 2% Et_3N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.54 (m, 1H), 7.36 (dd, *J* = 1.34, 7.80 Hz, 1H), 7.23 – 7.08 (m, 1H), 6.99 – 6.91 (m, 1H), 6.50 (dd, *J* = 1.61, 7.58 Hz, 1H), 5.31 (s, 1H), 4.16 – 4.04 (m, 1H), 4.00 (d, *J* = 0.87 Hz, 1H), 3.41 (ABq, *J* = 12.00 Hz, *Δv* = 51.12 Hz, 2H), 2.70 – 2.55 (m, 1H), 2.27 (s, 1H), 2.25 (s, 1H), 2.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.23 (C), 135.27 (C), 134.22 (CH), 129.53 (CH), 128.87 (CH), 127.65 (CH), 127.49 (CH), 115.47 (CH), 113.54 (C), 70.87 (CH_2), 65.98 (CH), 59.07 (CH_2), 51.73 (CH_2), 50.35 (CH_2), 42.09 (CH_3), 12.41 (CH_3), 9.88 (CH_3); HRMS (ESI^+) = calcd $C_{24}H_{31}ClN_4O_2$ ($M+H^+$) = 439.1895, found = 439.1886.

1-(((1-(3,4-dichlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)methyl)(methyl)amino)-3-(4-ethoxyphenoxy)propan-2-ol (1n). Synthesizes using Method C with the addition of K_2CO_3

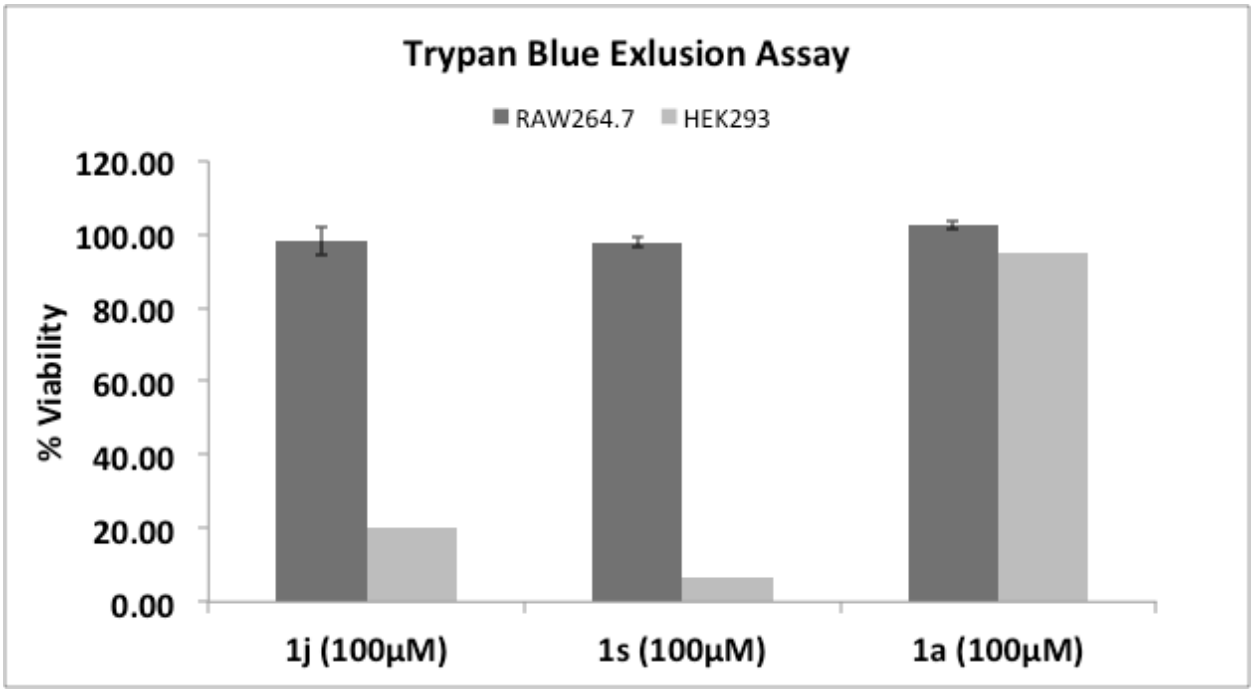
(0.036g, 0.257 mmol, 1 eq) with the amine, 1-(1-(3,4-dichlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylmethanamine (**3d**). (0.084 g, 0.283 mmol, 1.1 eq), and the epoxide, 2-((4-ethyoxyphenoxy)methyl)oxirane) (**2b**) (0.050 g, 0.257 mmol, 1.0 eq). The resulting yellow oil was then purified via flash SiO_2 column chromatography (2.5 x 4.0 cm, 100 mL of 50% EtOAc / hexanes with 2% Et_3N than 100 mL of 100% EtOAc) to yield **1n** as a clear oil (0.043 g, 34%); R_f = 0.15 (80% EtOAc / hexanes with 2% Et_3N); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.26 Hz, 1H), 7.12 (d, *J* = 2.01 Hz, 1H), 6.89 – 6.84 (m, 1H), 6.81 (d, *J* = 3.39 Hz, 4H), 5.15 (s, 2H), 4.06 (td, *J* = 4.81, 9.35, 9.38 Hz, 1H), 3.97 (q, *J* = 6.97, 6.98, 6.98 Hz, 3H), 3.89 (d, *J* = 4.97 Hz, 2H), 3.36 (ABq, *J* = 15.00 Hz, Δ*v* = 45.59 Hz, 2H), 2.58 (dd, *J* = 9.51, 12.21 Hz, 1H), 2.46 (dd, *J* = 4.23, 12.28 Hz, 1H), 2.24 (s, 3H), 2.22 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.49 (C), 153.04 (C), 148.08 (C), 138.11 (C), 137.78 (C), 133.06 (C), 131.83 (C), 130.94 (CH), 128.69 (CH), 126.08 (CH), 115.64 (CH), 115.55 (CH), 114.02 (C), 71.25 (CH_2), 66.40 (CH), 64.16 (CH_2), 59.59 (CH_2), 51.66 (CH_2), 42.08 (CH_3), 29.89 (CH_2), 15.13 (CH_3),12.32 (CH_3), 9.98 (CH_3); HRMS (ESI^+) = calcd $C_{25}H_{32}Cl_2N_3O_3$ ($M+H^+$) = 492.1821, found = 492.1882.

1-(((1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)methyl)(methyl)amino)-3-(3,4-dichlorophenoxy)propan-2-ol (1v) Synthesizes using Method A with the amine, 1-(1-(2-chlorobenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-methylmethanamine (**3b**) (0.055 g, 0.207 mmol, 1.0 eq), and the epoxide, 2-((3,4-dichlorophenoxy)methyl)oxirane (**2e**). (0.050 g, 0.228 mmol, 1.1 eq). The resulting yellow oil was then purified via flash SiO_2 column chromatography (3.0 x 3.5 cm, 60% EtOAc / hexanes with 2% Et_3N) to yield **1v** as an oil (0.076 g, 76%); R_f = 0.23 (60% EtOAc / hexanes with 2% Et_3N); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 1H), 7.31 (d, *J* = 8.89 Hz, 1H), 7.23 – 7.08 (m, 2H), 7.00 (d, *J* = 2.87 Hz, 1H), 6.76 (dd, *J* = 2.91, 8.90 Hz,

1H), 6.54 – 6.46 (m, 1H), 5.31 (s, 2H), 4.12 – 4.02 (m, 1H), 3.93 – 3.89 (m, 2H), 3.40 (ABq, J = 13.20 Hz, $\Delta\nu$ = 50.19 Hz, 2H), 2.60 (dd, J = 9.83, 12.19 Hz, 1H), 2.44 (dd, J = 4.10, 12.21 Hz, 1H), 2.26 (d, J = 0.88 Hz, 6H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.03 (C), 148.02 (C), 138.66 (C), 135.30 (C), 133.05 (C), 132.01 (C), 130.89 (CH), 129.50 (CH), 128.85 (CH), 127.63 (CH), 127.49 (CH), 124.45 (C), 116.63 (CH), 114.76 (CH), 113.60 (C), 71.17 (CH_2), 66.07 (CH), 59.15 (CH_2), 51.72 (CH_2), 50.34 (CH_2), 42.09 (CH_3), 12.40 (CH_3), 9.87 (CH_3); HRMS (ESI^+) = calcd $C_{25}H_{37}Cl_3N_3O_2$ ($M+H^+$) = 482.1169, found = 482.1158.



Supplemental Figure 1. Toxicity test results of **1a, 1j**, **1s, 1x**, **7**, and **1q** using a Trypan Blue Exclusion assay in the HEK293 cells.



Supplemental Figure 2. Cell line dependent toxicity is seen for **1j** and **1s** but not for **1a** in the RAW 264.7 and HEK293 cells.