Discovery, synthesis and biological evaluation of a series of *N*-(phenylcarbamothioyl)-2-napthamides as inhibitors of Claudin-1

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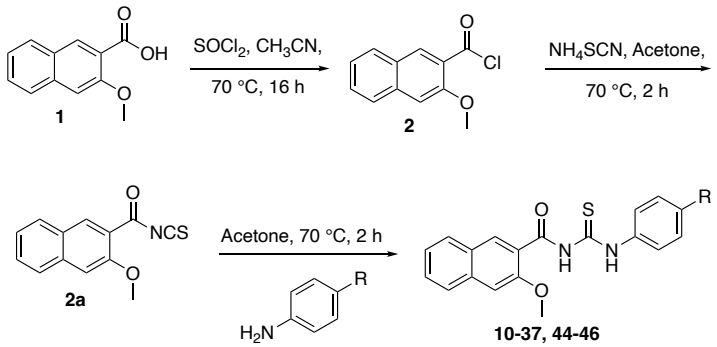
General Experimental Methods.

All ^{1}H & ^{13}C NMR spectra were recorded on Bruker AV-400 (500 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to $\delta^{1}H$ 3.31 or $\delta^{13}C$ 49.0 (CD_3OD) or $\delta^{1}H$ 2.50 or $\delta^{13}C$ 39.5 ($(CD_3)_2SO$) or $\delta^{1}H$ 7.26 or $\delta^{13}C$ 77.2 ($CDCl_3$). Data are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Low resolution mass spectra were obtained on an Agilent 1260 LCMS with electrospray ionization, with a gradient of 5-95% MeCN in 0.1% formic acid water over 4 min. Analytical thin layer chromatography was performed on LuxPlate silica gel 60 F254 plates. Visualization was accomplished with UV light, and/or the use of ninhydrin, anisaldehyde and ceric ammonium molybdate solutions followed by charring on a hotplate. Chromatography on silica gel was performed using Silica Gel 60Å (230-400 mesh) from Sorbent Technologies. Solvents for extraction, washing and chromatography were HPLC grade. All reagents were purchased from Aldrich Chemical Co. (or similar) and were used without purification. All reagents and solvents were commercial grade and purified prior to use when necessary.

Final compounds were purified on a Gilson preparative reversed-phase HPLC system comprised of a 322 aqueous pump with solvent-selection valve, 334 organic pump, GX-271 liquid hander, two column switching valves, and a 159 UV detector. UV wavelength for fraction collection was user-defined, with absorbance at 254 nm always monitored. Column: Phenomenex Axia-packed Luna C18, 50 x 21.2 mm, 5 μm. For Acidic Method: Mobile phase: CH_3CN in H_2O (0.1% formic acid). Gradient conditions: 2.0 min equilibration, followed by user-defined gradient (starting organic percentage, ending organic percentage, duration, typically 15 mins), hold at 95% CH_3CN in H_2O (0.1% TFA) for 2 min, 20 mL/min, 23 °C. Final compounds were confirmed to be >95% purity based on HPLC and measured at 215 and 254 nm.

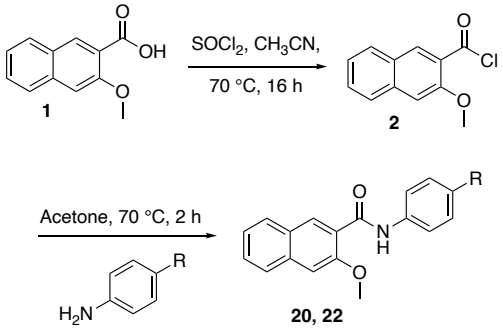
There were no unexpected or unusually high safety hazards encountered for the synthesis of these compounds.

General Procedure A.



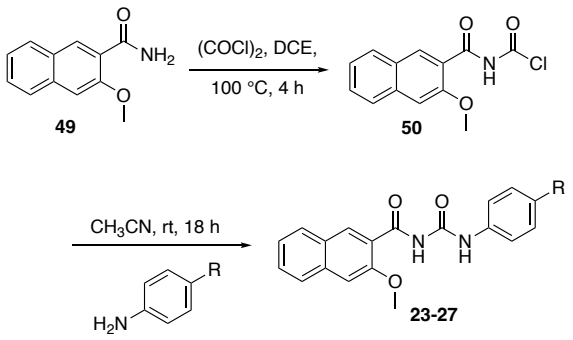
To 3-methoxy-2-naphthoic acid (**1**) in acetonitrile was added thionyl chloride (3 eq) and the reaction mixture was refluxed at 70 °C overnight. The solvent was evaporated in vacuo, then the 3-methoxy-2-naphthoyl chloride (**2**) was dissolved in acetone, followed by the addition of ammonium thiocyanate (1 eq), and the reaction mixture was refluxed at 60 °C for 2 hours. Amine (0.85 eq) was then added in situ to **3** and the reaction mixture was refluxed at 60 °C for 2 hours, then poured on ice and the solid **5** was collected by vacuum filtration. The product was purified by normal phase chromatography Hex/EtAc/MeOH 0-100% and reverse phase chromatography H_2O/ACN 0-95%.

General Procedure B.



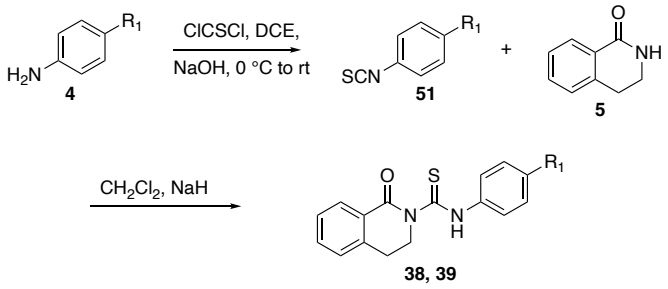
2 was prepared according to the general procedure A. The solvent was evaporated in vacuo then the aromatic amine was added, and the reaction mixture was heated at 70 °C under reflux conditions for 2 hours. The solution was poured on iced and the crude product was then collected by vacuum filtration. The product was purified by normal phase chromatography Hex/EtAc/MeOH 0-100%.

General Procedure C.



To 3-methoxy-2-naphthamide in anhydrous dichloroethane (**10**) was added oxalyl chloride and the reaction mixture was refluxed at 100 °C for 4 h, then the solvent was evaporated in vacuo. To **11** dissolved in acetonitrile was added aromatic amine (**12**) and the reaction mixture was stirred at room temperature for 18 h. The solvent was concentrated in vacuo and the product was purified by normal phase chromatography Hex/EtAc/MeOH 0-100% and reverse phase chromatography H_2O/ACN 0-100%.

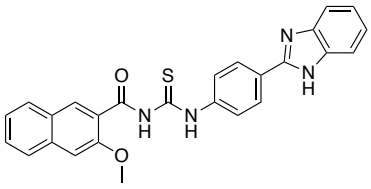
General Procedure D.



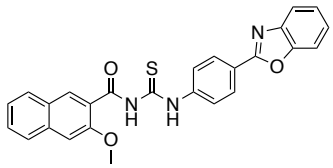
D-1: A 0.5 M solution of thiophosgene in anhydrous DCE was cooled to 0 °C and then the aniline (1 eq) is added followed by NaOH (3 eq). The reaction is warmed to rt and stirred for 3 hours. Next, the reaction is concentrated and taken back up into DCM to load the product onto silica for flash purification. EtOAc: hex (0-30%).

D-2: To the thiocyanate (1 eq) and 3,4-dihydropisoquinolin-1(2*H*)-one (1 eq) was added oxygen-free (bubbled) DCM. After 10 minutes, NaH (2-3 eq) was added and the reaction was stirred at room temp for

20 hours. The reaction was quenched with water and product extracted with DCM. Purified with flash chromatography 0-40% EtOAc: hexanes.

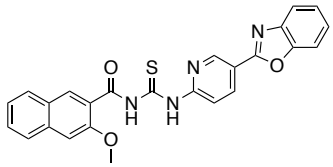


***N*-((4-(1*H*-benzo[d]imidazol-2-yl)phenyl)carbamothioyl)-3-methoxy-2-naphthamide (KVA-E-25B, 10).** Prepared using General Procedure A. Yield = 134.3 mg (14.4 %, yellow powder). LCMS: R_T = 2.825 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 453.14 for $C_{26}H_{20}N_4O_2S$, found 453.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.87 (s, 1H), 11.66 (s, 1H), 11.02 (d, *J* = 21.6 Hz, 1H), 8.48 (s, 1H), 8.30 – 8.27 (m, 2H), 8.19 – 8.16 (m, 2H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.93 (t, *J* = 6.0 Hz, 2H), 7.84 (dt, *J* = 6.6, 3.3 Hz, 3H), 7.65 – 7.60 (m, 2H), 7.56 (dt, *J* = 5.5, 2.6 Hz, 3H), 4.08 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.91, 166.57, 154.38, 149.10, 136.52, 132.74, 129.49, 129.40, 128.96, 127.87, 127.10, 126.25, 125.36, 125.06, 124.75, 122.65, 120.63, 114.58, 107.90, 56.98, 40.48, 40.41, 40.32, 40.24, 40.15, 40.07, 39.98, 39.90, 39.81, 39.65, 39.48.

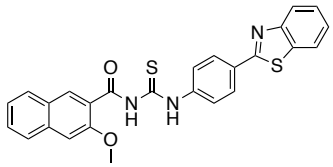


***N*-((4-(benzo[*d*]oxazol-2-yl)phenyl)carbamothioyl)-3-methoxy-2-naphthamide (KVA-E-25C, 11).** Prepared using General Procedure A. Yield = 61.1 mg (10.9%, yellow powder). LCMS: R_T = 3.901 min, ESI-MS: m/z $[M+H]^+$, calc'd 454.11 for $C_{26}H_{19}N_3O_3S$, found 454.1. ^{1}H NMR (500 MHz, DMSO) δ 12.94 (s, 1H), 11.48 (s, 1H), 8.55 (s, 1H), 8.25 (d, J = 8.2 Hz, 2H), 8.06 (d, J = 8.3 Hz, 2H), 8.00 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.74 (dd, J = 26.4, 6.9 Hz, 2H), 7.64 – 7.53 (m, 2H), 7.49 – 7.34 (m, 3H), 4.11 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.25, 165.13, 162.57, 154.27, 150.90, 142.24, 140.89,

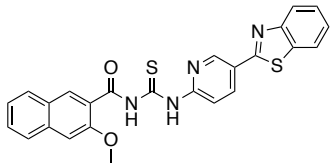
137.00, 135.62, 129.90, 129.65, 128.43, 128.31, 126.64, 125.46, 125.30, 124.91, 124.78, 123.61, 120.13, 119.59, 110.75, 107.45, 56.69.



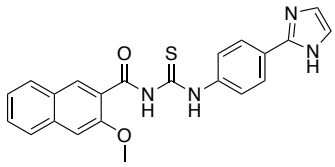
***N*-((5-(benzo[*d*]oxazol-2-yl)pyridin-2-yl)carbamothioyl)-3-methoxy-2-naphthamide (TMW-I-18, 12).** Prepared using General Procedure A. Yield = 5.4 mg (2.4%, white powder). LCMS: R_T = 3.967 min, ESI-MS: m/z $[M+H]^+$, calc'd 455.11 for $C_{25}H_{18}N_4O_3S$, found 455.1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.65 (s, 1H), 11.38 (s, 1H), 9.25 (d, J = 60.1 Hz, 2H), 8.86 (s, 1H), 8.58 (s, 1H), 7.95 (s, 1H), 7.80 (s, 2H), 7.62 (s, 2H), 7.43 (d, J = 44.0 Hz, 3H), 7.31 (s, 1H), 4.21 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.95, 164.11, 160.10, 153.65, 150.23, 147.46, 141.43, 136.40, 136.18, 135.36, 129.88, 129.29, 129.13, 127.76, 126.00, 125.07, 124.85, 124.42, 120.30, 119.68, 114.64, 110.26, 106.81, 56.08.



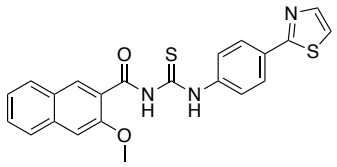
***N*-((4-(benzo[*d*]thiazol-2-yl)phenyl)carbamothioyl)-3-methoxy-2-naphthamide (TMW-I-40, 13).** Prepared using General Procedure A. Yield = 122.8 mg (35.3%, light yellow powder). LCMS: R_T = 3.630 min, ESI-MS: m/z $[M+H]^+$, calc'd 470.09 for $C_{26}H_{19}N_3O_2S_2$, found 470.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.10 (s, 1H), 11.30 (s, 1H), 8.78 (s, 1H), 8.14 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.6 Hz, 2H), 7.91 (dd, J = 14.3, 8.1 Hz, 2H), 7.78 (d, J = 8.3 Hz, 1H), 7.66 – 7.55 (m, 1H), 7.53 – 7.42 (m, 2H), 7.42 – 7.35 (m, 1H), 7.28 (s, 1H), 4.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.27, 167.28, 165.10, 154.26, 154.17, 140.39, 136.98, 135.58, 135.16, 131.47, 129.87, 129.63, 128.30, 128.23, 126.63, 126.54, 125.44, 125.39, 123.84, 123.31, 121.76, 119.61, 107.44, 56.67.



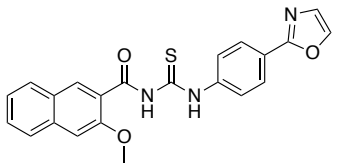
***N*-((5-(benzo[*d*]thiazol-2-yl)pyridin-2-yl)carbamothioyl)-3-methoxy-2-naphthamide (TMW-I-39, 14).** Prepared using General Procedure A. Yield = 5.7 mg (2.43%, white powder). LCMS: R_T = 3.202 min, ESI-MS: m/z $[M+H]^+$, calc'd 471.09 for $C_{25}H_{18}N_4O_2S_2$, found 471.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.59 (s, 1H), 11.36 (s, 1H), 9.16 – 9.12 (m, 1H), 8.86 (s, 1H), 8.49 – 8.39 (m, 1H), 8.11 (d, J = 8.1 Hz, 1H), 8.00 – 7.89 (m, 2H), 7.82 – 7.74 (m, 1H), 7.64 – 7.36 (m, 5H), 7.31 (s, 1H), 4.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.51, 164.71, 164.36, 154.29, 154.19, 147.63, 137.01, 136.61, 135.95, 129.90, 129.75, 128.83, 128.39, 127.31, 127.24, 126.77, 126.63, 125.74, 125.46, 123.54, 121.86, 119.68, 115.52, 107.43, 56.70.



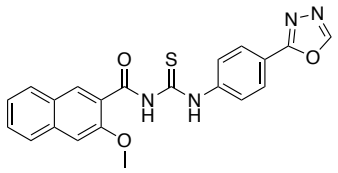
***N*-((4-(1*H*-imidazol-2-yl)phenyl)carbamothioyl)-3-methoxy-2-naphthamide (VM-A-156a, 15).** Prepared according to general procedure A. Yield = 3.0 mg (2%, beige solid). LCMS: R_T = 2.530 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 403.22 for $C_{22}H_{19}N_4O_2S$, found 403.0. ^{1}H NMR (600 MHz, Acetone-d_6) δ 12.99 (s, 1H), 11.28 (s, 1H), 8.79 (s, 1H), 8.07 (d, *J* = 8.7 Hz, 3H), 7.99 – 7.92 (m, 3H), 7.67 (s, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.17 (s, 2H), 4.24 (s, 3H). ^{13}C NMR (150 MHz, Acetone-d_6) δ 179.35, 166.22, 155.68, 146.88, 139.32, 138.38, 135.86, 130.87, 130.64, 130.42, 130.25, 129.53, 128.04, 126.63, 126.55, 124.94, 121.52, 109.26, 57.75.



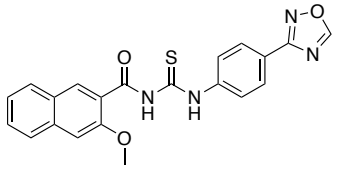
3-methoxy-*N*-((4-(thiazol-2-yl)phenyl)carbamothioyl)-2-naphthamide (VM-A-156b, 16). Prepared according to general procedure A. Yield = 2.4 mg (6%, beige solid). LCMS: R_T = 3.528 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 420.18 for $C_{22}H_{18}N_3O_2S_2$, found 420.0. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.74 (s, 1H), 11.55 (s, 1H), 8.49 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 8.02 (dd, J = 8.8, 2.1 Hz, 2H), 7.95 (d, J = 3.2 Hz, 1H), 7.92 (dd, J = 8.2, 4.6 Hz, 3H), 7.81 (d, J = 3.2 Hz, 1H), 7.63 (ddd, J = 8.2, 7.0, 1.1 Hz, 1H), 7.61 (s, 1H), 7.49 – 7.46 (m, 1H), 4.07 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.98, 166.36, 165.97, 153.92, 143.96, 139.36, 136.04, 132.37, 130.90, 129.00, 128.95, 128.56, 127.43, 126.59, 124.86, 124.54, 122.12, 120.63, 107.41, 56.51.



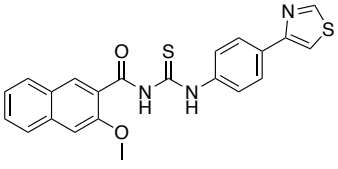
3-methoxy-*N*-((4-(oxazol-2-yl)phenyl)carbamothioyl)-2-naphthamide (KAT-I-131, 17). Prepared using General Procedure A. Yield = 54.7 mg (44.8%, yellow-brown powder). LCMS: R_T = 3.348 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 404.11 for $C_{22}H_{17}N_3O_3S$, found 404.0. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.76 (s, 1H), 11.56 (s, 1H), 8.49 (s, 1H), 8.25 (s, 1H), 8.05 (d, *J* = 8.5 Hz, 3H), 7.99 – 7.90 (m, 3H), 7.66–7.59 (m, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.41 (s, 1H), 4.07 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.47, 166.42, 160.82, 154.38, 140.68, 140.16, 136.52, 132.86, 129.48, 129.42, 129.11, 127.89, 127.08, 126.87, 125.34, 125.13, 124.86, 122.54, 107.89, 56.98, 40.58, 40.49, 40.42, 40.32, 40.25, 40.16, 40.08, 39.99, 39.91, 39.82, 39.66, 39.49.



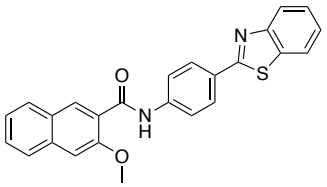
***N*-((4-(1,3,4-oxadiazol-2-yl)phenyl)carbamothioyl)-3-methoxy-2-naphthamide ((VM-A-155b, 18).** Prepared according to general procedure A. Yield = 17.9 mg (9%, pale yellow solid). LCMS: R_T = 3.086 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 405.19 for $C_{21}H_{17}N_4O_3S$, found 405.0. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.79 (s, 1H), 11.60 (s, 1H), 9.37 (s, 1H), 8.48 (s, 1H), 8.10 (d, *J* = 8.7 Hz, 2H), 8.04 (dd, *J* = 8.0, 3.3 Hz, 3H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.61 (s, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 4.07 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 178.19, 166.05, 163.26, 154.54, 153.97, 141.02, 136.04, 132.34, 129.00, 128.95, 127.42, 127.34, 126.61, 124.87, 124.57, 122.15, 120.72, 107.22, 56.35.



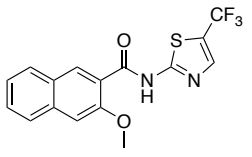
***N*-((4-(1,2,4-oxadiazol-3-yl)phenyl)carbamothioyl)-3-methoxy-2-naphthamide (VM-A-157a, 19).** Prepared according to general procedure A. Yield = 7.3 mg (2%, yellow solid). LCMS: R_T = 3.305 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 405.19 for $C_{21}H_{17}N_4O_3S$, found 405.0. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.77 (s, 1H), 11.58 (s, 1H), 9.73 (s, 1H), 8.48 (s, 1H), 8.11 (d, J = 8.6 Hz, 2H), 8.05 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.6 Hz, 2H), 7.93 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.61 (s, 1H), 7.47 (t, J = 7.5 Hz, 1H), 4.07 (s, 3H). 13C NMR (150 MHz, DMSO-d_6) δ 178.18, 167.54, 166.32, 166.02, 153.95, 140.72, 136.06, 132.38, 129.02, 128.96, 127.73, 127.44, 126.63, 124.89, 124.58, 123.51, 122.15, 107.43, 56.35.



3-methoxy-*N*-((4-(thiazol-4-yl)phenyl)carbamothioyl)-2-naphthamide (VM-A-162a, 20). Prepared according to general procedure A. Yield = 7.9 mg (3%, beige solid). LCMS: R_T = 3.411 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 420.18 for $C_{22}H_{18}N_3O_2S_2$, found 420.0. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.69 (s, 1H), 11.51 (s, 1H), 9.22 (d, *J* = 1.9 Hz, 1H), 8.50 (s, 1H), 8.22 (d, *J* = 1.9 Hz, 1H), 8.06 (dd, *J* = 12.2, 5.4 Hz, 3H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.63 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.61 (s, 1H), 7.49 – 7.46 (m, 1H), 4.08 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.89, 165.94, 154.70, 154.44, 153.92, 137.53, 136.04, 132.40, 132.11, 129.00, 128.96, 127.44, 126.61, 126.42, 124.87, 124.33, 122.09, 114.44, 107.43, 56.52.

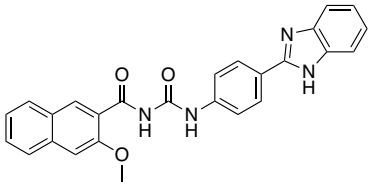


***N*-(4-(benzo[*d*]thiazol-2-yl)phenyl)-3-methoxy-2-naphthamide (VM-A-155a, 21).** Prepared according to general procedure A. Yield = 22.6 mg (16%, orange solid). LCMS: R_T = 3.526 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 411.21 for $C_{25}H_{19}N_2O_2S$, found 411.1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.64 (s, 1H), 8.19 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 8.11 (d, J = 8.7 Hz, 2H), 8.05 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 8.3, 4.1 Hz, 3H), 7.90 (d, J = 8.2 Hz, 1H), 7.58 – 7.56 (m, 1H), 7.55 – 7.53 (m, 1H), 7.52 (s, 1H), 7.46 (dd, J = 9.7, 2.7 Hz, 1H), 7.44 – 7.42 (m, 1H), 3.99 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.00, 165.08, 154.03, 153.67, 141.97, 134.94, 134.33, 129.49, 128.29, 128.06, 127.92, 127.79, 127.51, 127.14, 126.64, 126.57, 125.32, 124.41, 122.63, 122.32, 119.87, 106.53, 55.91.

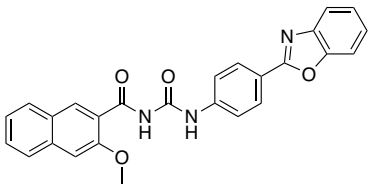


3-methoxy-*N*-(5-(trifluoromethyl)thiazol-2-yl)-2-naphthamide (VM-A-162b, 22). Prepared according to general procedure B. Yield = 33.7 mg (11%, yellow solid). LCMS: R_T = 3.277 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 353.15 for $C_{16}H_{12}F_3N_2O_2S$, found 353.0. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.83 (s, 1H), 8.24

(s, 1H), 8.19 (t, *J* = 1.8 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.61 – 7.58 (m, 1H), 7.54 (s, 1H), 7.46 – 7.43 (m, 1H), 3.98 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.34, 160.72, 154.00, 140.96, 135.56, 130.87, 128.58, 128.43, 127.29, 126.62, 125.54, 124.61, 123.81, 123.61, 122.06, 117.79, 106.79, 56.03.

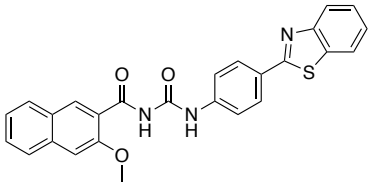


***N*-((4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)carbamoyl)-3-methoxy-2-naphthamide (VM-A-176, 23).** Prepared according to general procedure C. Yield = 2.4 mg (0.5%, white solid). LCMS: R_T = 2.567 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 437.25 for $C_{26}H_{21}N_4O_3$, found 437.1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.89 (s, 1H), 10.88 (s, 1H), 8.27 (s, 1H), 8.18 (d, *J* = 8.7 Hz, 2H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.7 Hz, 2H), 7.60 (t, *J* = 8.1 Hz, 3H), 7.54 (s, 1H), 7.45 (t, *J* = 7.0 Hz, 1H), 7.22 (dd, *J* = 7.9, 5.1 Hz, 2H), 4.00 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 168.17, 153.85, 150.83, 150.52, 139.30, 135.54, 130.63, 128.61, 128.42, 127.47, 127.30, 126.60, 124.61, 124.42, 122.30, 119.90, 106.86, 56.06.

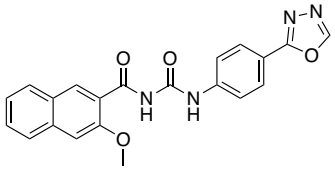


***N*-((4-(benzo[*d*]oxazol-2-yl)phenyl)carbamoyl)-3-methoxy-2-naphthamide (VM-A-178, 24)**. Prepared according to general procedure C. Yield = 5.6 mg (1.3%, white solid). LCMS: R_T = 3.566 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 438.24 for $C_{26}H_{19}N_3O_4$, found 438.1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.97 (s, 1H), 10.90 (s, 1H), 8.27 (s, 1H), 8.23 – 8.18 (m, 2H), 7.99 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.89 – 7.83 (m, 2H), 7.82 – 7.76 (m, 2H), 7.61 – 7.58 (m, 1H), 7.53 (s, 1H), 7.47 – 7.43 (m, 1H), 7.43 – 7.39 (m, 2H), 4.00 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 168.14, 162.11, 153.90, 150.48, 150.15, 141.59,

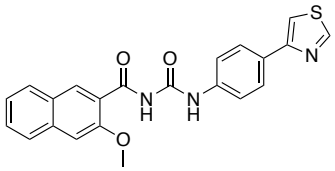
141.00, 135.53, 130.63, 128.61, 128.42, 127.30, 126.60, 125.29, 124.85, 124.60, 124.44, 121.42, 119.96, 119.63, 110.84, 106.84, 56.00.



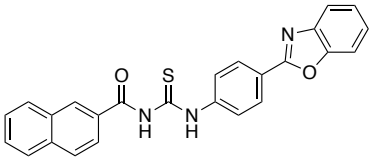
***N*-((4-(benzo[*d*]thiazol-2-yl)phenyl)carbamoyl)-3-methoxy-2-naphthamide (VM-A-180, 25).** Prepared using general procedure C. Yield = 7.1 mg (2%, white solid). LCMS: R_T = 3.807 min., ESI-MS: *m/z* [M + H]$^+$, calc'd 454.21 for $C_{26}H_{20}N_3O_3S$, found 454.1. ^{1}H (600 MHz, DMSO-d_6) δ 10.91 (d, *J* = 4.2 Hz, 2H), 8.27 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 2H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 7.8 Hz, 1H), 7.56 – 7.53 (m, 2H), 7.47 – 7.44 (m, 2H), 4.00 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 168.15, 166.80, 153.83, 153.70, 150.52, 140.50, 135.53, 134.32, 130.67, 128.62, 128.44, 128.22, 128.16, 127.29, 126.65, 126.60, 125.36, 124.62, 124.36, 122.67, 122.33, 120.08, 106.86, 56.00.



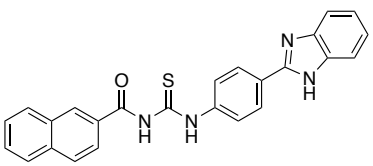
***N*-((4-(1,3,4-oxadiazol-2-yl)phenyl)carbamoyl)-3-methoxy-2-naphthamide (VM-A-179, 26).** Prepared according to general procedure C. Yield = 30.8 mg (4.5%, white solid). LCMS: R_T = 2.899 min., ESI-MS: *m/z* [M + H]$^+$, calc'd 389.22 for $C_{21}H_{17}N_4O_4$, found 389.0. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.92 (d, *J* = 3.9 Hz, 2H), 9.32 (s, 1H), 8.27 (s, 1H), 8.03 (d, *J* = 8.7 Hz, 2H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.61 – 7.58 (m, 1H), 7.53 (s, 1H), 7.46 – 7.43 (m, 1H), 4.00 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 168.17, 163.42, 154.26, 153.86, 150.52, 140.97, 135.55, 130.67, 128.61, 128.44, 127.84, 127.60, 127.29, 126.60, 124.62, 124.35, 120.10, 118.26, 106.86, 56.09.



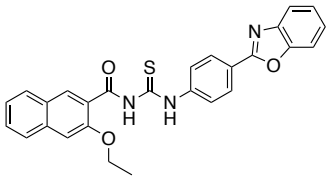
3-methoxy-*N*-((4-(thiazol-4-yl)phenyl)carbamoyl)-2-naphthamide (VM-A-177, 27). Prepared according to general procedure C. Yield = 89.8 mg (23%, white solid). LCMS: R_T = 3.154 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 404.11 for $C_{22}H_{18}N_3O_3S$, found 404.0. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.82 (s, 1H), 10.77 (s, 1H), 9.19 (s, 1H), 8.27 (s, 1H), 8.12 (d, J = 1.9 Hz, 1H), 7.99 (dd, J = 8.2, 6.3 Hz, 3H), 7.90 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.61 – 7.58 (m, 1H), 7.53 (s, 1H), 7.45 (t, J = 7.5 Hz, 1H), 4.00 (s, 3H). 13C NMR (150 MHz, DMSO-d_6) δ 168.09, 154.73, 154.47, 153.87, 150.49, 137.41, 135.53, 130.67, 129.76, 128.61, 128.41, 127.30, 126.83, 126.59, 124.60, 124.37, 119.97, 113.30, 106.86, 56.12.



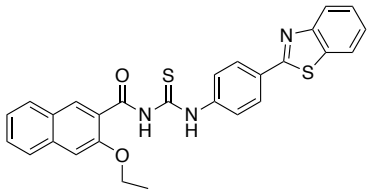
***N*-((4-(benzo[*d*]oxazol-2-yl)phenyl)carbamothioyl)-2-naphthamide (PDS-0330, 28).** Prepared using General Procedure A. Yield = 125.3 mg (30.6 %, light brown powder). LCMS: R_T = 3.549 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 424.11 for $C_{25}H_{17}N_3O_2S$, found 424.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.88 (s, 1H), 11.84 (s, 1H), 8.77 – 8.71 (m, 1H), 8.28 – 8.22 (m, 2H), 8.13 (d, *J* = 8.1 Hz, 1H), 8.09 – 7.99 (m, 5H), 7.81 (ddd, *J* = 9.9, 7.0, 2.1 Hz, 2H), 7.68 (dddd, *J* = 22.6, 8.0, 6.8, 1.3 Hz, 2H), 7.43 (tt, *J* = 7.3, 5.8 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.45, 168.71, 162.31, 150.73, 142.04, 141.66, 135.43, 132.20, 130.61, 129.89, 129.64, 129.24, 128.66, 128.31, 128.18, 127.59, 126.03, 125.42, 124.97, 124.81, 124.22, 120.28, 111.42, 40.55, 40.46, 40.38, 40.29, 40.21, 40.12, 40.05, 39.96, 39.88, 39.79, 39.62, 39.45.



***N*-((4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)carbamothioyl)-2-naphthamide (KVA-E-23B, 29).** Prepared using General Procedure A. Yield = 70.5 mg (32%, off-white solid). LCMS: R_T = 2.594 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 423.13 for $C_{25}H_{19}N_4OS$, found 423.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.90 (s, 1H), 11.88 (s, 1H), 8.75 (d, *J* = 1.8 Hz, 1H), 8.44 – 8.29 (m, 2H), 8.23 – 7.94 (m, 7H), 7.85 – 7.61 (m, 5H), 7.45 (ddd, *J* = 23.1, 6.1, 3.1 Hz, 3H), 6.78 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (125 MHz, DMSO) δ 179.52, 168.67, 154.51, 150.28, 149.74, 141.52, 135.42, 132.19, 131.96, 130.62, 130.29, 129.89, 129.61, 129.23, 128.65, 128.35, 128.17, 127.58, 125.56, 124.96, 124.82, 114.91, 114.06, 113.56, 108.41.

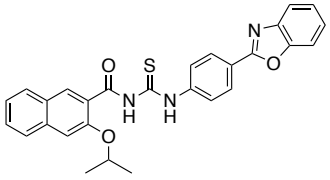


***N*-((4-(benzo[*d*]oxazol-2-yl)phenyl)carbamothioyl)-3-ethoxy-2-naphthamide (TMW-I-26, 30).** Prepared using General Procedure A. Yield = 148.0 mg (67.5%, white powder). LCMS: R_T = 3.590 min, ESI-MS: m/z $[M+H]^+$, calc'd 468.13 for $C_{27}H_{21}N_3O_3S$, found 468.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.95 (s, 1H), 11.58 (s, 1H), 8.66 (s, 1H), 8.25 (d, J = 8.3 Hz, 2H), 8.13 – 7.96 (m, 3H), 7.87 (d, J = 8.3 Hz, 1H), 7.80 – 7.67 (m, 2H), 7.66 – 7.54 (m, 2H), 7.50 – 7.34 (m, 3H), 4.39 (q, J = 6.9 Hz, 2H), 1.62 (t, J = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.28, 165.14, 162.59, 153.76, 150.89, 142.29, 140.92, 137.01, 135.46, 129.79, 129.63, 128.40, 128.16, 126.57, 125.33, 125.25, 124.83, 124.74, 123.49, 120.12, 119.43, 110.73, 108.09, 65.73, 14.92.

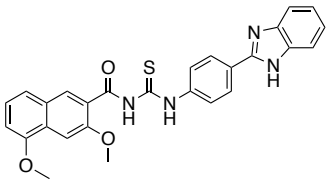


***N*-((4-(benzo[*d*]thiazol-2-yl)phenyl)carbamothioyl)-3-ethoxy-2-naphthamide (TMW-I-41, 31).** Prepared using General Procedure A. Yield = 154.4 mg (43.7%, brown powder). LCMS: R_T = 3.338 min,

ESI-MS: m/z $[M+H]^+$, calc'd 484.11 for $C_{27}H_{21}N_3O_2S_2$, found 484.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.10 (s, 1H), 11.56 (s, 1H), 8.79 (s, 1H), 8.23 – 7.97 (m, 5H), 7.95 – 7.87 (m, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.53 – 7.35 (m, 3H), 7.26 (br. s, 1H), 4.37 (q, J = 7.0 Hz, 2H), 1.76 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.33, 167.26, 165.14, 154.29, 153.78, 140.42, 137.01, 135.46, 135.22, 131.47, 129.79, 129.64, 128.22, 128.18, 126.58, 126.50, 125.34, 123.74, 123.34, 121.76, 119.48, 108.10, 65.74, 14.93.

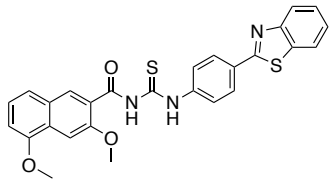


***N*-((4-(benzo[*d*]oxazol-2-yl)phenyl)carbamothioyl)-3-isopropoxy-2-naphthamide (TMW-I-30, 32).** Prepared using General Procedure A. Yield = 73.5 mg (34.5 %, white powder). LCMS: R_T = 3.302 min, ESI-MS: m/z $[M+H]^+$, calc'd 482.15 for $C_{28}H_{23}N_3O_3S$, found 482.1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.16 (s, 1H), 11.70 (s, 1H), 8.81 (s, 1H), 8.31 (d, J = 8.3 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.2 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.62 – 7.56 (m, 2H), 7.44 (t, J = 7.5 Hz, 1H), 7.36 (dd, J = 6.0, 3.2 Hz, 2H), 7.30 (s, 1H), 4.99 (hept, J = 6.1 Hz, 1H), 1.65 (d, J = 6.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.38, 165.28, 162.63, 152.59, 150.92, 142.31, 140.96, 137.01, 135.59, 129.75, 129.62, 128.42, 128.10, 126.52, 125.31, 125.26, 124.86, 124.76, 123.59, 120.18, 120.13, 110.74, 109.54, 73.20, 22.14.

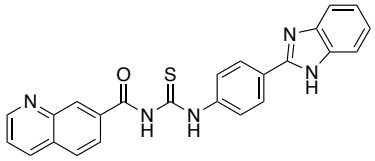


***N*-((4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)carbamothioyl)-3,5-dimethoxy-2-naphthamide (PS-I-5, 33).** Prepared using General Procedure A. Yield = 98.2 mg (47.3%, brown powder). LCMS: R_T = 2.982 min, ESI-MS: m/z $[M+H]^+$, calc'd 482.14. for $C_{27}H_{22}N_4O_3S$, found 482.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ

12.80 (s, 1H), 11.60 (s, 1H), 8.43 (s, 1H), 8.25 (d, J = 8.7 Hz, 2H), 8.06 (d, J = 8.7 Hz, 2H), 7.71 (dd, J = 6.0, 3.2 Hz, 2H), 7.62 (d, J = 9.2 Hz, 2H), 7.48 – 7.29 (m, 4H), 7.11 (d, J = 7.7 Hz, 1H), 4.08 (s, 3H), 4.02 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.99, 165.94, 153.68, 153.60, 149.79, 140.18, 132.13, 128.28, 127.51, 127.48, 125.09, 124.28, 123.60, 122.35, 120.86, 114.69, 107.12, 101.30, 56.38, 55.72.

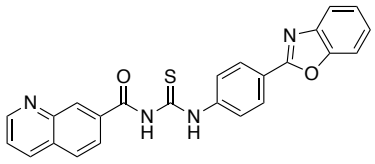


***N*-((4-(benzo[*d*]thiazol-2-yl)phenyl)carbamothioyl)-3,5-dimethoxy-2-naphthamide (PS-I-14, 34).** Prepared using General Procedure A. Yield = 26.5 mg (12.4%, brown powder). LCMS: R_T = 3.358 min, ESI-MS: m/z $[M+H]^+$, calc'd 500.10 for $C_{27}H_{21}N_3O_3S_2$, found 500.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.84 (s, 1H), 11.51 (s, 1H), 8.46 (s, 1H), 8.27 – 7.87 (m, 6H), 7.80 – 7.50 (m, 3H), 7.49 – 7.27 (m, 2H), 7.07 (d, J = 7.7 Hz, 1H), 4.08 (s, 3H), 4.00 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.30, 167.27, 165.21, 154.25, 154.22, 154.05, 140.41, 135.19, 134.99, 131.49, 129.22, 129.08, 128.24, 126.53, 125.38, 123.84, 123.34, 121.77, 121.57, 119.80, 107.17, 102.38, 56.75, 55.79.

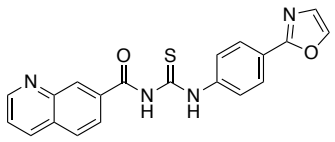


***N*-((4-(1*H*-benzo[d]imidazol-2-yl)phenyl)carbamothioyl)quinoline-7-carboxamide (KAT-I-135, 35).** Prepared using General Procedure A. Yield = 58.9 mg (32.7 %, pale yellow powder). LCMS: R_T = 2.294 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 424.50 for $C_{25}H_{17}N_5OS$, found 424.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.81 (s, 1H), 12.07 (s, 1H), 9.07 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.71 (d, *J* = 1.8 Hz, 1H), 8.52 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.36 – 8.24 (m, 2H), 8.17 (d, *J* = 8.6 Hz, 1H), 8.14 – 8.05 (m, 3H), 7.78 (dt, *J* = 7.1, 3.6 Hz, 2H), 7.72 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.47 (dp, *J* = 7.2, 4.3 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.36,

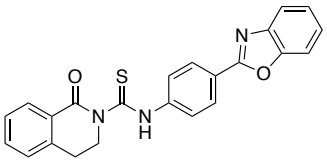
168.33, 152.37, 149.69, 146.91, 136.64, 133.37, 130.91, 130.77, 129.10, 128.46, 125.72, 125.11, 124.91, 124.01, 114.88, 40.49, 40.42, 40.33, 40.25, 40.16, 40.08, 39.99, 39.92, 39.82, 39.66, 39.49.



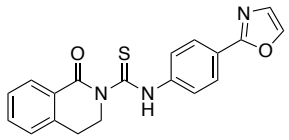
***N*-((4-(benzo[*d*]oxazol-2-yl)phenyl)carbamothioyl)quinoline-7-carboxamide (KAT-I-137A, 36).** Prepared using General Procedure A. Yield = 17.1 mg (15.4 %, light brown powder). LCMS: R_T = 3.083 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 425.11 for $C_{24}H_{16}N_4O_2S$, found 425.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.79 (s, 1H), 12.02 (s, 1H), 9.05 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.69 (d, *J* = 1.7 Hz, 1H), 8.49 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.28 – 8.23 (m, 2H), 8.14 (d, *J* = 8.5 Hz, 1H), 8.11 – 8.03 (m, 3H), 7.84 – 7.78 (m, 2H), 7.69 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.43 (tt, *J* = 7.5, 5.8 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.35, 162.30, 152.40, 150.73, 147.02, 142.05, 141.66, 136.51, 133.34, 130.99, 130.75, 129.05, 128.32, 126.01, 125.70, 125.41, 124.76, 124.23, 123.97, 120.29, 111.42.



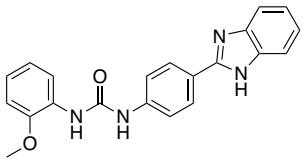
***N*-((4-(oxazol-2-yl)phenyl)carbamothioyl)quinoline-7-carboxamide (KAT-I-137B, 37).** Prepared using General Procedure A. Yield = 19.1 mg (21.3 %, light brown powder). LCMS: R_T = 2.647 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 375.09 for $C_{20}H_{14}N_4O_2S$, found 375.0. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.72 (s, 1H), 12.00 (s, 1H), 9.07 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.69 (d, *J* = 1.9 Hz, 1H), 8.51 (dd, *J* = 8.4, 1.7 Hz, 1H), 8.25 (s, 1H), 8.16 (d, *J* = 8.6 Hz, 1H), 8.09 (dd, *J* = 8.5, 1.9 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 2H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.71 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.41 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.35, 168.34, 160.86, 152.36, 146.95, 140.65, 140.39, 136.59, 133.41, 130.90, 130.74, 129.10, 129.05, 126.84, 125.72, 125.01, 124.89, 123.96, 40.49, 40.42, 40.33, 40.25, 40.16, 40.08, 39.99, 39.91, 39.82, 39.66, 39.49.



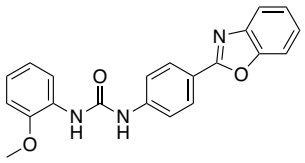
***N*-(4-(benzo[*d*]oxazol-2-yl)phenyl)-1-oxo-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (KAT-I-140C, 38).** Prepared using General Procedure C. Yield: 6.2 mg (13.1 %, pale yellow powder). LCMS: R_T = 3.534 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 400.11 for $C_{23}H_{17}N_3O_2S$, found 400.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.94 (s, 1H), 8.35 – 8.30 (m, 2H), 8.15 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.92 – 7.87 (m, 2H), 7.83 – 7.77 (m, 1H), 7.62 – 7.59 (m, 1H), 7.57 (td, *J* = 7.5, 1.3 Hz, 1H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.30 (d, *J* = 7.5 Hz, 1H), 4.88 – 4.80 (m, 2H), 3.10 (t, *J* = 6.2 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 182.85, 168.66, 162.52, 150.69, 141.92, 141.61, 139.94, 134.01, 129.81, 129.14, 128.38, 127.63, 127.16, 125.31, 124.98, 124.81, 119.89, 110.68, 47.72, 28.18.



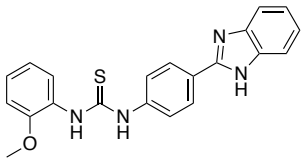
***N*-(4-(oxazol-2-yl)phenyl)-1-oxo-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (KAT-I-140A, 39).** Prepared using General Procedure C. Yield: 17.5 mg (33.7%, yellow powder) LCMS: R_T = 3.061 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 350.1 for $C_{19}H_{15}N_3O_2S$, found 350.0. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.78 (s, 1H), 8.10 – 8.02 (m, 3H), 7.77 – 7.71 (m, 2H), 7.67 (s, 1H), 7.50 (td, *J* = 7.5, 1.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.25 – 7.20 (m, 2H), 4.85 – 4.74 (m, 2H), 3.06 – 3.00 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 183.01, 168.62, 161.51, 140.93, 139.94, 138.73, 133.97, 129.79, 129.17, 128.04, 127.61, 127.13, 125.13, 120.32, 47.74, 28.19.



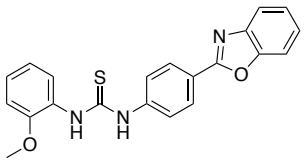
1-(4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)-3-(2-methoxyphenyl)urea (KVA-E-19A, 40). Prepared using General Procedure C. Yield = 25.0 mg (11%, white solid). LCMS: R_T = 2.101 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 359.15 for $C_{21}H_{19}N_4O_2$, found 359.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.75 (s, 1H), 9.59 (s, 1H), 8.34 (s, 1H), 8.25 – 8.04 (m, 3H), 7.71 – 7.59 (m, 2H), 7.57 (s, 2H), 7.18 (dq, *J* = 7.1, 4.0 Hz, 2H), 7.11 – 6.75 (m, 3H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.68, 151.84, 148.19, 141.88, 128.93, 127.75, 123.95, 122.50, 121.04, 118.84, 118.28, 111.25, 56.27.



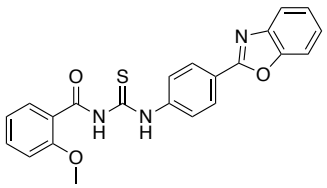
1-(4-(benzo[*d*]oxazol-2-yl)phenyl)-3-(2-methoxyphenyl)urea (KVA-E-19B, 41). Prepared using General Procedure C. Yield = 150.0 mg (62%, white solid). LCMS: R_T = 2.908 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 360.13 for $C_{21}H_{18}N_3O_3$, found 360.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.4, 2.2 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 2H), 7.74 – 7.64 (m, 1H), 7.64 – 7.56 (m, 2H), 7.56 – 7.45 (m, 1H), 7.30 (td, *J* = 6.3, 5.6, 3.1 Hz, 2H), 6.94 (td, *J* = 6.8, 1.9 Hz, 2H), 6.82 (dd, *J* = 7.4, 2.0 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.38, 152.89, 152.82, 150.40, 148.15, 148.09, 143.13, 143.04, 141.38, 128.64, 128.14, 128.07, 124.87, 124.63, 122.65, 121.06, 119.99, 119.97, 119.38, 119.29, 119.10, 118.47, 118.37, 110.52, 110.10, 55.59, 49.83, 49.66, 49.49, 49.31, 49.14, 48.97, 48.80.



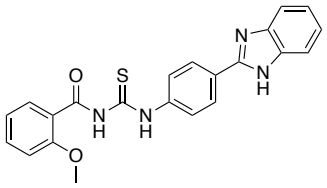
1-(4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)-3-(2-methoxyphenyl)thiourea (KVA-E-20A, 42). Prepared using General Procedure C. Yield = 12.5 mg (10%, off-white solid). LCMS: R_T = 2.082 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 375.13 for $C_{21}H_{19}N_4OS$, found 375.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.5 Hz, 3H), 7.70 – 7.45 (m, 4H), 7.27 – 7.17 (m, 3H), 7.09 – 6.87 (m, 2H), 6.76 (dt, *J* = 25.1, 7.6 Hz, 1H), 3.85 (d, *J* = 5.4 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-I_6) δ 179.52, 168.67, 154.51, 150.28, 149.74, 141.52, 135.42, 132.19, 131.96, 130.62, 130.29, 129.89, 129.61, 129.23, 128.65, 128.35, 128.17, 127.58, 125.56, 124.96, 124.82, 114.91, 114.06, 113.56, 108.41.



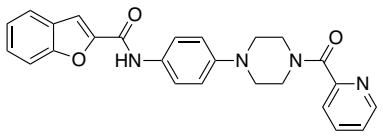
1-(4-(benzo[*d*]oxazol-2-yl)phenyl)-3-(2-methoxyphenyl)thiourea (KVA-E-20B, 43). Prepared using General Procedure C. Yield = 37.5 mg (17%, off-white solid). LCMS: R_T = 2.809 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 376.11 for $C_{21}H_{18}N_3O_2S$, found 376.0. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.28 (s, 1H), 9.44 (s, 1H), 8.22 – 8.12 (m, 2H), 7.93 – 7.83 (m, 3H), 7.83 – 7.72 (m, 2H), 7.47 – 7.38 (m, 2H), 7.25 – 7.16 (m, 1H), 7.10 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.96 (td, *J* = 7.6, 1.4 Hz, 1H), 6.76 – 6.64 (m, 1H), 3.86 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.58, 162.67, 152.61, 150.64, 143.50, 142.13, 129.41, 128.14, 127.80, 126.74, 126.60, 125.70, 125.28, 123.10, 121.87, 120.32, 120.07, 119.19, 113.99, 112.05, 111.28, 56.18.



***N*-((4-(benzo[*d*]oxazol-2-yl)phenyl)carbamothioyl)-2-methoxybenzamide (KVA-E-22A, 44).** Prepared using General Procedure A. Yield = 175.5 mg (37%, off-white solid). LCMS: R_T = 3.457 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 404.11 for $C_{22}H_{18}N_3O_3S$, found 404.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.16 (s, 1H), 11.21 (s, 1H), 8.40 – 8.29 (m, 2H), 8.23 (dd, *J* = 7.9, 1.8 Hz, 1H), 8.13 – 8.01 (m, 2H), 7.88 – 7.76 (m, 1H), 7.68 – 7.56 (m, 2H), 7.40 (dd, *J* = 6.0, 3.2 Hz, 2H), 7.24 – 7.13 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 4.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.21, 165.10, 162.43, 157.97, 150.63, 141.44, 141.02, 135.59, 132.73, 128.44, 125.34, 124.84, 124.28, 123.51, 121.94, 119.83, 118.67, 111.90, 110.69, 56.57.

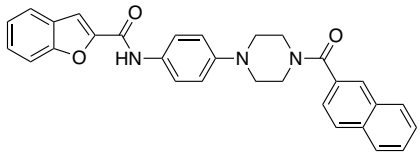


***N*-((4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)carbamothioyl)-2-methoxybenzamide (KVA-E-22B, 45).** Prepared using General Procedure A. Yield = 12.5 mg (10%, off-white solid). LCMS: R_T = 2.409 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 403.12 for $C_{22}H_{19}N_4O_2S$, found 403.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.75 (d, *J* = 4.1 Hz, 1H), 11.32 (s, 1H), 8.30 – 8.15 (m, 2H), 8.08 – 7.87 (m, 3H), 7.75 – 7.58 (m, 3H), 7.32 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.24 (dd, *J* = 6.1, 3.1 Hz, 2H), 7.22 – 7.15 (m, 1H), 4.04 (d, *J* = 1.6 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.90, 158.06, 150.92, 139.55, 135.65, 131.58, 127.94, 127.38, 124.64, 124.50, 122.87, 121.82, 121.80, 120.07, 119.92, 113.35, 57.19.



***N*-(4-(4-picolinoylpiperazin-1-yl)phenyl)benzofuran-2-carboxamide (VM-A-104, 46).** Prepared according to general procedure D. Yield = 52.4 mg (12%, pale yellow solid). LCMS: R_T = 2.538 min., *m/z* $[M + H]^+$, calc'd 427.18 for $C_{25}H_{23}N_4O_3$ found 427.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.7 Hz, 1H), 8.32 (s, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.69 (t, *J* = 7.1 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 10.2 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.30 (d, *J* = 7.4 Hz,

1H), 6.98 (t, *J* = 17.2 Hz, 2H), 4.05 – 3.95 (m, 2H), 3.86 – 3.76 (m, 2H), 3.33 – 3.25 (m, 2H), 3.24 – 3.15 (m, 2H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 167.39, 156.40, 154.71, 153.67, 148.53, 148.24, 137.15, 127.66, 127.08, 124.66, 124.10, 123.82, 122.76, 121.35, 117.54, 111.72, 111.11, 50.48, 50.01, 46.81, 42.12.



***N*-(4-(4-(2-naphthoyl)pierazin-1-yl)phenyl)benzofuran-2-carboxamide (VM-A-109, 47).** Prepared according to general procedure D. Yield = 39.2 mg (8%, white solid). LCMS: R_T = 2.967 min., m/z [M + H]$^+$, calc'd 476.20 for $C_{30}H_{26}N_3O_3$, found 476.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.95 (s, 1H), 7.94 – 7.84 (m, 3H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.61 – 7.48 (m, 5H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 5.7 Hz, 2H), 4.02 (s, 2H), 3.68 (s, 2H), 3.21 (d, *J* = 54.2 Hz, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.51, 156.39, 154.71, 148.57, 133.79, 132.63, 128.42, 127.81, 127.72, 127.19, 127.13, 127.05, 126.79, 124.26, 123.87, 122.81, 121.36, 117.46, 111.74, 111.16, 50.17, 47.69, 42.11, 40.87.

Cell Culture, and Proliferation Assay: Human colon cancer cells SW620, and normal epithelial cells IEC-6 cells were maintained in a humidified atmosphere with 5% CO2 in RPMI plus 1% Pen/Strep and 10% FBS. These cell lines were purchased from ATCC. Cell proliferation was measured using prestoBlue™ cell proliferation assay (#A13261, Thermo Fisher Scientific, 168 Third Avenue Waltham, MA USA 02451), according to the manufacturer's protocol. In a brief, we seeded 3000 cells per well in the appropriate medium into 96-well plate. Following 24 hours, we treated the compounds in various concentrations for 72 hours. Following this, we added 10µl of PrestoBlue reagent to the microplate wells, let them stand for ten minutes at 37 °C, and then read for fluorescence at 560 nm excitation and 590 nm emission.

***In vitro* PK:**

In vitro PK (intrinsic clearance and plasma protein binding) were performed at Q2 Solutions (Indianapolis, IN) (https://www.q2labsolutions.com/en/bioanalytical-adme-laboratories)

***In vivo* PK:**

In vivo PK was performed at Pharmaron, Inc. (Louisville, KY) (https://www.pharmaron.com/services/biosciences/dmpk-for-discovery-preclinical-development/in-vivo-pk)