# Supporting Information

# Discovery of 2-[1-(4-chlorophenyl)cyclopropyl]-3-hydroxy-8-(trifluoromethyl)quinoline-4-carboxylic acid (PSI-421), a P-Selectin Inhibitor with Improved Pharmacokinetic Properties and Oral Efficacy in Models of Vascular Injury

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**Synthesis details and characterization data for intermediates.**

**General Procedure. Synthesis of keto acetates (4a, 4b, 4c, 4d, 4e, 4g)**

**Acid Chloride**: To a 250 mL round bottom flask under a nitrogen atmosphere was added carboxylic acid (30.9 mmol, 1.0 equiv) and 100 mL methylene chloride. To the resulting stirred solution was added oxalyl chloride (3.2 mL. 37.04 mmol. 1.2 equiv) and 3 drops DMF. The mixture was stirred at room temperature until all gas evolution ceased. All volatile materials were then removed *in vacuo* to give an oily solid. This material was redissolved into 50 mL anhydrous THF and added dropwise to 100 mL an ethereal solution of diazomethane cooled to 0 $^{o}$C. The resulting solution was allowed to warm slowly to room temperature and stirred for an additional 12 hours. The solution was then cooled once again to 0 $^{o}$C, and HCl gas was bubbled through the solution for 5 minutes. Crushed ice was then added to the mixture and stirring was continued for 15 minutes. The layers were then separated, and the aqueous layer was extracted with two 50 mL portions of diethyl ether. The combined organic layers were then washed with three 100 mL portions of saturated sodium bicarbonate solution, three 100 mL portions of water and 100 mL of saturated sodium chloride solution. The solution was then dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give intermediate acid chloride.

**Acetate**: To a 20 mL microwave reaction vial was added acid chloride (19.07 mmol, 1.0 equiv) and 15 mL acetone. To the resulting solution was added acetic acid (1.41 mL, 24.8 mmol, 1.3 equiv) and triethylamine (3.5 mL, 24.8 mmol, 1.3 equiv). The vial was sealed and heated to 150 $^{o}$C in a microwave reactor for 30 minutes. The resulting suspension was poured into 200 mL water and extracted with three 100 mL portions of ethyl acetate. The combined organic layers were then washed with three 250 mL

portions water, and 250 mL saturated sodium chloride solution. The organic layer was then dried over magnesium sulfate, filtered and the solvent removed to give a brown oil. This was purified by Biotage Flash 40 to give the desired product **4**.

**2-oxo-3-phenylbutyl acetate** (**4a**)

Acid Chloride (1-chloro-3-phenylbutan-2-one). Colorless oil, used without further analysis (95%).

Acetate (**4a**): waxy tan solid (79%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.44 (d, *J*=7.07 Hz, 3 H) 2.12 (s, 3 H) 3.81 (q, *J*=7.07 Hz, 1 H) 4.52 (d, *J*=16.67 Hz, 1 H) 4.69 (d, *J*=16.67 Hz, 1 H) 7.17 - 7.41 (m, 5 H).

**2-oxo-2-(1-phenylcyclopropyl)ethyl acetate** (**4b**)

Acid chloride: (2-chloro-1-(1-phenylcyclopropyl)ethanone): colorless oil (61%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.28 (q, *J*=3.79 Hz, 2 H) 1.73 (q, *J*=3.37 Hz, 2 H) 4.11 (s, 2 H) 6.58 - 7.80 (m, 5 H).

Acetate (**4b**): white solid (36%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.24 (q, *J*=3.54 Hz, 2 H) 1.69 (q, *J*=3.54 Hz, 2 H) 2.11 (s, 3 H) 4.57 (s, 2 H) 6.35 - 8.47 (m, 5 H).

**3-methyl-2-oxo-3-phenylbutyl acetate** (**4c**)

Acid chloride: 1-chloro-3-methyl-3-phenylbutan-2-one: colorless oil (94%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.55 (s, 6 H) 4.03 (s, 2 H) 6.57 - 7.64 (m, 5 H).

Acetate (**4c**): white solid (74%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.55 (s, 6 H) 2.10 (s, 3 H) 4.56 (s, 2 H) 6.58 - 7.98 (m, 5 H).

**2-(1-(4-Chlorophenyl)cyclopropyl)-2-oxoethyl acetate** (**4d**)

Acid Chloride: 2-Chloro-1-(1-(4-chlorophenyl)cyclopropyl)ethanone: oily yellow solid (98%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.26 (dd, *J*=7.1, 3.4 Hz, 2 H), 1.74 (dd, *J*=7.1, 3.4 Hz, 2 H), 4.08 (s, 2 H), 7.34 - 7.36 (m, 4 H).

Acetate **(4d)**: pale yellow oil (93% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.21 (dd, *J*=6.6, 3.4 Hz, 2 H), 1.70 (dd, *J*=6.6, 3.4 Hz, 2 H), 2.11 (s, 3 H), 4.54 (s, 2 H), 7.33 - 7.40 (m, 4 H).

**2-(1-(4-chlorophenyl)cyclobutyl)-2-oxoethyl acetate** (**4e**)

Acid Chloride: 2-chloro-1-(1-(4-chlorophenyl)cyclobutyl)ethanone: colorless oil (100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.70 - 2.09 (m, 2 H) 2.34 - 2.51 (m, 2 H) 2.66 - 3.00 (m, 2 H) 4.00 (s, 2 H) 7.18 (d, *J*=8.84 Hz, 2 H) 7.36 (d, *J*=8.84 Hz, 2 H).

Acetate **(4e)**: waxy tan solid (67%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.74 - 2.04 (m, 2 H) 2.12 (s, 3 H) 2.33 - 2.49 (m, 2 H) 2.68 - 2.97 (m, 2 H) 4.47 (s, 2 H) 7.18 (d, *J*=8.34 Hz, 2 H) 7.35 (d, *J*=8.34 Hz, 2 H).

**2-(1-(4-methoxyphenyl)cyclopropyl)-2-oxoethyl acetate** (**4g**)

Acid Chloride: 2-chloro-1-(1-(4-methoxyphenyl)cyclopropyl)ethanone: colorless oil (30%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.20 (q, *J*=3.54 Hz, 2 H) 1.66 (q, *J*=3.37 Hz, 2 H) 3.82 (s, 3 H) 4.32 (s, 2 H) 6.89 (d, *J*=8.84 Hz, 2 H) 7.34 (d, *J*=8.84 Hz, 2 H).

Acetate **(4g)**: white solid (40%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.20 (q, *J*=3.54 Hz, 2 H) 1.66 (q, *J*=3.37 Hz, 2 H) 2.11 (s, 3 H) 3.82 (s, 3 H) 4.58 (s, 2 H) 6.89 (d, *J*=8.84 Hz, 2 H) 7.34 (d, *J*=8.84 Hz, 2 H).

**General Procedure. Synthesis of keto acetates (4f, 4h)**

**Acid Chloride**: To a 50 mL round bottom flask equipped with a condenser was added ecarboxylic acid (1.06 mmol, 1.0 equiv) and 25 mL thionyl chloride. The resulting

solution was heated to reflux and allowed to stir for 4 hours. Upon cooling to room temperature, all of the volatiles were removed *in vacuo*. The resulting oil was redissolved into 10 mL THF and added dropwise to 100 mL of ethereal diazomethane solution cooled to 0 $^{o}$C. This mixture was allowed to warm slowly to room temperature and stir for 12 hours. At this time the solution was cooled back down to 0 $^{o}$C, and HCl gas was bubbled through for 3 minutes. Crushed ice was then added to the mixture and stirring was continued for 15 minutes. The layers were then separated, and the aqueous layer was extracted with two 50 mL portions of diethyl ether. The combined organic layers were then washed with three 100 mL portions of saturated sodium bicarbonate solution, three 100 mL portions of water and 100 mL of saturated sodium chloride solution. The solution was then dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give the acid chloride.

**Acetate**: To a 20 mL microwave reaction vial was added acid chloride (19.07 mmol, 1.0 equiv) and 15 mL acetone. To the resulting solution was added acetic acid (1.41 mL, 24.8 mmol, 1.3 equiv) and triethylamine (3.5 mL, 24.8 mmol, 1.3 equiv). The vial was sealed and heated to 150 $^{o}$C in a microwave reactor for 30 minutes. The resulting suspension was poured into 200 mL water and extracted with three 100 mL portions of ethyl acetate. The combined organic layers were then washed with three 250 mL portions water, and 250 mL saturated sodium chloride solution. The organic layer was then dried over magnesium sulfate, filtered and the solvent removed to give a brown oil. This was purified by Biotage Flash 40 to give the desired keto acetate.

**2-(1-(2-chlorophenyl)cyclopropyl)-2-oxoethyl acetate** (**4f**)

Acid chloride: 2-chloro-1-(1-(2-chlorophenyl)cyclopropyl)ethanone: yellow oil (68%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, *J*=3.79 Hz, 2 H) 1.86 (d, *J*=3.79 Hz, 2 H) 4.11 (s, 2 H) 6.78 - 7.81 (m, 4 H)

Acetate (**4f**): yellow oil (68%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, *J*=3.79 Hz, 2 H) 1.86 (d, *J*=3.79 Hz, 2 H) 4.11 (s, 2 H) 6.78 - 7.81 (m, 4 H).

**2-(1-(4-bromophenyl)cyclopropyl)-2-oxoethyl acetate** (**4h**)

Acid Chloride: 1-(1-(4-bromophenyl)cyclopropyl)-2-chloroethanone as a colorless oil (100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.25 (q, *J*=3.96 Hz, 2 H) 1.74 (q, *J*=3.62 Hz, 2 H) 4.08 (s, 2 H) 7.28 (d, *J*=8.59 Hz, 2 H) 7.52 (d, *J*=8.34 Hz, 2 H).

Acetate (**4h**): white solid (30%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.21 (q, *J*=3.87 Hz, 2 H) 1.69 (q, *J*=3.79 Hz, 2 H) 2.11 (s, 3 H) 4.55 (s, 2 H) 7.31 (d, *J*=8.59 Hz, 2 H) 7.51 (d, *J*=8.59 Hz, 2 H).

**General Procedure. Synthesis of hydroxyl ketones (5b-q)**

A mixture of carboxylic acid (12.2 mmol) and 7 mL thionylchloride in 15 mL toluene was heated at 115 °C for 4-16 h (in some cases the reaction was done using thionyl chloride as a solvent and no toluene). Concentration of the reaction mixture gave an oily residue. To this residue was added 10 mL toluene, and the resulting mixture was concentrated to yield a yellow oil. 1,1,2-tris(trimethylsilyloxy)ethane (8.0 mL, 24.4 mmol) was added to the yellow oil. The reaction mixture was heated at 80-100 °C for 12-16 h under $N_2$. At 50 °C, 10 mL dioxane and 2 mL HCl (aq.1N) were added. The resulting mixture was stirred at 80 °C for 2 h. Concentration of the mixture gave a oily residue. Water (10 mL) and diethyl ether (15 mL) were added. The organic layer was

washed with 5 mL saturated $NaHCO_3$, brine, dried over $MgSO_4$. The solid was removed via filtration. Concentration of the filtrate afforded the desired hydroxyl ketone.

**1-Hydroxy-4-methyl-3-phenylpentan-2-one_(5b)**: colorless oil (60%). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.71 (d, *J*=6.8 Hz, 3 H), 0.98 (d, *J*=6.8 Hz, 3 H), 2.43 - 2.55 (m, 1 H), 3.26 (d, *J*=10.7 Hz, 1 H), 4.18 (d, *J*=19.2 Hz, 1 H), 4.27 (d, *J*=19.2 Hz, 1 H), 7.21 - 7.34 (m, 5 H).

**1-Hydroxy-3-methyl-4-phenylbutan-2-one** (**5c**): colorless oil (64%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, *J*=7.0 Hz, 3 H), 2.68 (dd, *J*=13.3, 7.0 Hz, 1 H), 2.76 - 2.89 (m, 1 H), 2.99 (dd, *J*=13.3, 7.6 Hz,, 1 H), 3.94 (dd, *J*=19.3, 4.2 Hz, 1 H), 4.24 (dd, *J*=19.3, 4.2 Hz, 1 H), 7.18 - 7.32 (m, 5 H).

**1-Hydroxy-4-phenylpentan-2-one** (**5d**): colorless oil (74%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, *J*=7.0 Hz, 3 H), 2.64 (dd, *J*=15.7, 7.1 Hz, 1 H), 2.73 (dd, *J*=15.7, 7.1 Hz, 1 H), 3.01 (t, *J*=4.4 Hz, 1 H), 3.30 - 3.42 (m, 1 H), 4.01 (dd, *J*=19.2, 4.4 Hz, 1 H), 4.14 (dd, *J*=19.2, 4.4 Hz, 1 H), 7.17 - 7.34 (m, 5 H).

**3-(4-Chloro-phenyl)-1-hydroxy-4-methyl-pentan-2-one** (**5e**): colorless oil (75%). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.68 - 0.73 (d, *J* = 6.82 Hz, 3 H), 0.97 (d, *J* = 6.32 Hz, 3 H), 2.38 - 2.49 (m, 1 H), 3.24 (d, *J* = 10.36 Hz, 1 H), 4.20 (d, *J* = 19.20 Hz, 1 H), 4.24 (d, *J* = 19.20 Hz, 1 H), 7.19 (d, *J* = 8.59 Hz, 2 H), 7.29 (d, *J* = 8.59 Hz, 2 H).

**1-(1-Phenylcyclopropyl)-2-hydroxyethanone** (**5f**): colorless oil (44%): $^1$H NMR (400 MHz, $CDCl_3$) δ 1.31 (q, *J*=3.7 Hz, 2 H) 1.74 (q, *J*=3.6 Hz, 2 H) 3.18 (t, *J*=4.9 Hz, 1 H) 4.06 (d, *J*=5.1 Hz, 2 H) 7.33 - 7.38 (m, 5 H).

**1-(1-(4-Chlorophenyl)cyclopropyl)-2-hydroxyethanone** (**5g**): yellow oil (83%) $^1$H NMR (400 MHz, $CDCl_3$) d 1.28 (q, *J*=4.0 Hz, 2 H) 1.74 (q, *J*=3.5 Hz, 2 H) 3.16 (t, *J*=4.7 Hz, 1 H) 4.05 (d, *J*=4.8 Hz, 2 H) 7.29 - 7.32 (m, 2 H) 7.33 - 7.37 (m, 2 H).

**1-(1-(3-chlorophenyl)cyclopropyl)-2-hydroxyethanone** (**5h**): colorless oil (46%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.30 (q, *J*=3.79 Hz, 2 H) 1.74 (q, *J*=3.62 Hz, 2 H) 3.16 (t, *J*=4.67 Hz, 1 H) 4.08 (d, *J*=4.80 Hz, 2 H) 5.97 - 8.14 (m, 4 H).

**2-hydroxy-1-(1-(4-(trifluoromethoxy)phenyl)cyclopropyl)ethanone** (**5i**): colorless oil (56%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.30 (q, *J*=3.71 Hz, 2 H) 1.76 (q, *J*=3.62 Hz, 2 H) 3.16 (t, *J*=4.29 Hz, 1 H) 4.05 (d, *J*=4.29 Hz, 2 H) 7.22 (d, *J*=7.83 Hz, 2 H) 7.41 (d, *J*=8.84 Hz, 2 H).

**2-hydroxy-1-(1-(4-(trifluoromethyl)phenyl)cyclopropyl)ethanone** (**5j**): colorless oil (52%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.32 (q, *J*=3.96 Hz, 2 H) 1.79 (q, *J*=3.79 Hz, 2 H) 4.05 (s, 2 H) 7.51 (d, *J*=7.83 Hz, 2 H) 7.64 (d, *J*=8.08 Hz, 2 H).

**2-hydroxy-1-(1-(3-(trifluoromethyl)phenyl)cyclopropyl)ethanone** (**5k**): colorless oil (62%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.34 (q, *J*=3.87 Hz, 2 H) 1.80 (q, *J*=3.62 Hz, 2 H) 3.17 (t, *J*=4.80 Hz, 1 H) 4.04 (d, *J*=4.80 Hz, 2 H) 7.40 - 7.70 (m, 4 H).

**1-(1-(4-fluorophenyl)cyclopropyl)-2-hydroxyethanone** (**5l**): colorless oil (47%). 1H NMR (400 MHz, $CDCl_3$) δ 1.28 (q, *J*=3.79 Hz, 2 H) 1.74 (q, *J*=3.71 Hz, 2 H) 3.18 (t, *J*=4.67 Hz, 1 H) 4.04 (d, *J*=4.55 Hz, 2 H) 6.93 - 7.17 (m, 2 H) 7.27 - 7.46 (m, 2 H).

**2-Hydroxy-1-(1-p-tolyl-cyclopropyl)-ethanone** (**5m**): colorless oil taken forward without purification.

**2-hydroxy-1-(1-(thiophen-2-yl)cyclopropyl)ethanone** (**5n**):_colorless oil (31%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.43 (q, *J*=3.79 Hz, 2 H) 1.80 (q, *J*=3.54 Hz, 2 H) 3.12 (t,

*J*=4.80 Hz, 1 H) 4.28 (d, *J*=4.80 Hz, 2 H) 6.99 (dd, *J*=5.31, 3.54 Hz, 1 H) 7.04 (dd, *J*=3.54, 1.26 Hz, 1 H) 7.28 (dd, *J*=5.31, 1.26 Hz, 1 H).

**2-hydroxy-1-(1-(thiophen-3-yl)cyclopropyl)ethanone** (**5o**): colorless oil (0.062g, 16%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.29 (q, *J*=3.54 Hz, 2 H) 1.69 (q, *J*=3.54 Hz, 2 H) 3.15 (t, *J*=4.80 Hz, 1 H) 4.15 (d, *J*=4.80 Hz, 2 H) 7.05 (dd, *J*=5.05, 1.26 Hz, 1 H) 7.23 (dd, *J*=3.03, 1.52 Hz, 1 H) 7.34 (dd, *J*=4.93, 2.91 Hz, 1 H).

**2-Hydroxy-1-indan-2-yl-ethanone** (**5p**): colorless oil (73%) $^1$H NMR (400 MHz, $CDCl_3$) δ 3.12 - 3.24 (m, 4 H), 3.41 - 3.51 (m, 1 H), 4.84 - 4.86 (d, *J* = 4.55 Hz, 2 H), 7.16 - 7.25 (m, 4 H).

**1-(1,2-Dihydrocyclobutabenzen-1-yl)-2-hydroxyethanone** (**5q**): colorless oil (65%) $^1$H NMR (400 MHz, $CDCl_3$) δ 2.82 - 2.98 (m, 1 H), 3.05 - 3.20 (m, 1 H), 3.46 - 3.51 (m, 1 H), 4.44 - 4.47 (m, 2 H), 7.05 - 7.81 (m, 4 H).

**General Procedure. Synthesis of cyclopropanecarbonitrile (7a, 7c-i)**

To a 25 mL round bottom flask equipped with a condenser was added 2-(4-(trifluoromethyl)phenyl)acetonitrile (4.05 mmol, 1.0 equiv), 1-bromo-2-chloroethane (6.08 mmol, 1.5 equiv), and triethylbenzyl ammonium chloride (0.08 mmol, 0.02 equiv). The resulting mixture was heated to 50 $^o$C in an oil bath, and sodium hydroxide (24.0 mmol, 6.0 equiv dissolved into 1.0 mL water) was added dropwise. The mixture was allowed to stir at 50$^o$C for 16 hours. It was then allowed to cool to room temperature and poured into 50 mL water. This suspension was extracted with three 25 mL portions of methylene chloride, and the combined organic layers then washed with three 50 mL portions of 1.2 N $HCL_{(aq)}$, three 50 mL portions of water, and 50 ml saturated sodium chloride solution. The organic layer was then dried over magnesium sulfate, filtered, and

the solvent removed *in vacuo*. The crude material was purified by Biotage Flash 40, to give the desired product cyclopropanecarbonitrile.

**1-(2-chlorophenyl)cyclopropanecarbonitrile** (**7a**): yellow oil (100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.31 - 1.38 (m, 2 H) 1.71 - 1.79 (m, 2 H) 6.55 - 7.78 (m, 4 H).

**1-(3-chlorophenyl)cyclopropanecarbonitrile** (**7c**): yellow oil (100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.36 - 1.45 (m, 2 H) 1.69 - 1.81 (m, 2 H) 6.38 - 7.94 (m, 4H).

**1-(4-(trifluoromethoxy)phenyl)cyclopropanecarbonitrile** (**7d**): yellow oil (100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.22 - 1.49 (m, 2 H) 1.66 - 1.85 (m, 2 H) 7.20 (d, *J*=7.83 Hz, 2 H) 7.33 (d, *J*=8.84 Hz, 2 H).

**1-(4-(trifluoromethyl)phenyl)cyclopropanecarbonitrile** (**7e**): light yellow oil (86%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.41 - 1.53 (m, 2 H) 1.78 - 1.87 (m, 2 H) 7.40 (d, *J*=8.34 Hz, 2 H) 7.62 (d, *J*=8.34 Hz, 2 H).

**1-(3-(trifluoromethyl)phenyl)cyclopropanecarbonitrile** (**7f**): yellow oil (100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.43 - 1.49 (m, 2 H) 1.77 - 1.86 (m, 2 H) 7.40 - 7.62 (m, 4 H).

**1-(4-fluorophenyl)cyclopropanecarbonitrile** (**7g**): orange oil (93%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.36 (dd, *J*=8.00, 7.00 Hz, 2 H) 1.71 (dd, *J*=8.00, 7.00 Hz, 2 H) 6.95 - 7.12 (m, 2 H) 7.22 - 7.36 (m, 2 H).

**1-(thiophen-2-yl)cyclopropanecarbonitrile** (**7h**): colorless oil (100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.37 - 1.49 (m, 2 H) 1.67 - 1.82 (m, 2 H) 6.94 (dd, *J*=5.18, 3.66 Hz, 1 H) 7.06 (dd, *J*=3.54, 1.26 Hz, 1 H) 7.19 (dd, *J*=5.05, 1.26 Hz, 1 H).

**1-(thiophen-3-yl)cyclopropanecarbonitrile** (**7i**): colorless oil (28%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.27 - 1.41 (m, 2 H) 1.62 - 1.74 (m, 2 H) 6.91 (dd, *J*=5.05, 1.26 Hz, 1 H) 7.18 (dd, *J*=3.03, 1.52 Hz, 1 H) 7.31 (dd, *J*=5.05, 3.03 Hz, 1 H).

**General Procedure. Synthesis of cyclopropanecarboxylic acid (6f, 6p-t, 6v, 6w)**

To a 50 mL round bottom flask equipped with a condenser was added cyclopropanecarbonitrile (2.5 mmol, 1.0 equiv) and 20 mL 4.0 N $LiOH_{(aq)}$. This suspension was heated to reflux in an oil bath and allowed to stir for 15 hours. The resulting mixture was cooled to room temperature and poured into 250 mL 1.2 N HCl. This suspension was extracted with three 75 mL portions of ethyl acetate, and the combined organic layer was washed with three 200 mL portions of water and 200 mL of saturated sodium chloride solution. The organic layer was then dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give the desired cyclopropanecarboxylic acid. Carboxylic acids **6a-e**, **6g**, **6i-o**, **6u**, **6x**, **6y** were commercially available.

**1-(2-chlorophenyl)cyclopropanecarboxylic acid** (**6f**): white solid (90%). This material was taken forward without further analysis.

**1-(3-chlorophenyl)cyclopropanecarboxylic acid** (**6p**): white solid (62%). This material was taken forward without further analysis.

**1-(4-(trifluoromethoxy)phenyl)cyclopropanecarboxylic acid** (**6q**): white solid (73%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.20 - 1.30 (m, 2 H) 1.55 - 1.77 (m, 2 H) 7.14 (d, *J*=8.08 Hz, 2 H) 7.36 (d, *J*=8.59 Hz, 2 H).

**1-(4-(trifluoromethyl)phenyl)cyclopropanecarboxylic acid** (**6r**): white solid (95%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.29 (q, *J*=3.87 Hz, 2 H) 1.72 (q, *J*=3.87 Hz, 2 H) 7.46 (d, *J*=8.08 Hz, 2 H) 7.57 (d, *J*=8.08 Hz, 2 H).

**1-(3-(trifluoromethyl)phenyl)cyclopropanecarboxylic acid** (**6s**): white solid (82%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.26 - 1.32 (m, 2 H) 1.64 - 1.77 (m, 2 H) 7.42 (t, *J*=7.71 Hz, 1 H) 7.49 - 7.57 (m, 2 H) 7.59 (s, 1 H).

**1-(4-fluorophenyl)cyclopropanecarboxylic acid** (**6t**): white solid (98%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.23 (q, *J*=4.04 Hz, 2 H) 1.66 (q, *J*=4.04 Hz, 2 H) 6.91 - 7.04 (m, 2 H) 7.21 - 7.38 (m, 2 H).

**1-(thiophen-2-yl)cyclopropanecarboxylic acid** (**6v**): white solid (85%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.40 (q, *J*=3.96 Hz, 2 H) 1.77 (q, *J*=3.87 Hz, 2 H) 6.90 - 6.93 (m, 1 H) 6.96 (dd, *J*=3.54, 1.26 Hz, 1 H) 7.20 (dd, *J*=5.05, 1.26 Hz, 1 H).

**1-(thiophen-3-yl)cyclopropanecarboxylic acid** (**6w**) white solid (93%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.17 - 1.31 (m, 2 H) 1.62 - 1.70 (m, 2 H) 7.09 (dd, *J*=5.05, 1.01 Hz, 1 H) 7.16 (dd, *J*=3.03, 1.26 Hz, 1 H) 7.21 - 7.29 (m, 1 H).

**5-Chloro-7-(trifluoromethyl)indoline-2,3-dione (3c)**

*N*-(4-Chloro-2-(trifluoromethyl)phenyl)-2-(hydroxyimino)acetamide: In a 1 L round-bottomed flask, anhydrous sodium sulfate (85 g) was dissolved in 230 mL boiling water, with stirring. A hot solution of 4-chloro-2-(trifluoromethyl)aniline (6.5 g, 33 mmol) in 50 mL 1 M hydrochloric acid, 2 mL concentrated hydrochloric acid and 30 mL ethanol was added. A large amount of sodium sulfate and aniline came out of solution at this point, and an additional 60 mL ethanol was added in a vain attempt to redissolve the aniline. Chloral hydrate (6.6 g, 40 mmol) was added, followed by hydroxylamine hydrochloride (7.6 g, 0.11 mol) in 30 mL water. The mixture was then returned to a boil, and ethanol was added until the aniline dissolved again. Boiling was continued for 3 hours, with the flask open to atmosphere. At this point, since about half of the starting

material remained, a condenser was added, the temperature of the oil bath was increased, and the reaction was refluxed overnight. The next day, LC-MS analysis showed that conversion to product had not really increased. The reaction was cooled to 0 °C, and the off-white precipitate collected by filtration. This precipitate, which contained a large amount of sodium sulfate, was taken up in 300 mL water, stirred at room temperature for 1 hour, filtered, taken up in 200 mL water, stirred for 30 minutes, and then filtered one last time and dried under vacuum to give an off-white powder (2.65 g, 30% yield): $^1$H NMR (400 MHz, DMSO-$d_6$) d 7.66 (s, 1 H) 7.76 - 7.86 (m, 3 H) 9.63 (s, 1 H) 12.44 (s, 1 H).

**Isatin (Indoline-2,3-dione)** (**3c**). In a 50 mL Erlenmeyer flask, 4 mL concentrated sulfuric acid was heated to 70 °C, with stirring. *N*-(4-Chloro-2-(trifluoromethyl)phenyl)-2-(hydroxyimino)acetamide was added gradually, trying to keep the temperature below 90 °C. Once it was all added, the reaction was heated at 90 ° for an additional hour. It was then cooled rapidly (ice water bath) to 20 °C, then added quickly to a vigorously stirred mixture of 35 mL ice water and 7 mL ethyl acetate. Once all the ice had melted, the layers were separated, and the aqueous layer extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated to give a brownish-black solid. This was purified by flash chromatography over silica gel (0-6% ethyl acetate in dichloromethane) to give the product (0.633 g, 42% yield): $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.87 (d, *J*=2.0 Hz, 1 H) 7.94 (d, *J*=2.0 Hz, 1 H) 11.58 (s, 1 H).

**7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)indoline-2,3-dione (3g)**

To a 500 mL round bottom flask was added 2-(2-aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (9.0g, 34.75 mmol, 1.0 equiv), chloral hydrate (6.9g, 41.69 mmol, 1.2 equiv), hydroxylamine hydrochloride (8.45g, 122.0 mmol, 3.5 equiv), sodium sulfate (49.34g, 347.0 mmol, 10.0 equiv), 225 mL water and 55 mL 1.2 N HCl. The resulting mixture was heated to 55 $^{o}$C in an oil bath and allowed to stir for 15 hours. At this time the resulting suspension was cooled to room temperature and the precipitated oxime intermediate was isolated by filtration. This white solid was then added to 20 mL concentrated sulfuric acid and heated to 80 $^{o}$C for 10 minutes. 200 mL crushed ice was then added to this red/brown mixture and the resulting suspension was stirred for 30 minutes. The solids were collected by filtration and purified by silica gel chromatography (Biotage Flash 40, 25% ethyl acetate/hexane) to give the desired product as a yellow solid (5.64g, 52%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, *J*=8.34, 7.33 Hz, 1 H) 7.69 (d, *J*=9.35 Hz, 1 H) 7.75 (dd, *J*=7.33, 1.26 Hz, 1 H).

**5-(Trifluoromethyl)indoline-2,3-dione (3m)**

*Tert*-butyl-4-(trifluoromethyl)phenylcarbamate:.In a 250 mL round-bottomed flask, 4-(trifluoromethyl)aniline (7.7 mL, 10 g, 62 mmol) and di-*tert*-butyldicarbonate (13.6 g, 62.1 mmol) were taken up in 60 mL anhydrous tetrahydrofuran and refluxed overnight. After cooling to room temperature, the solvent was evaporated, and the residue taken up in 250 mL ethyl acetate. This solution was washed with 0.5 M citric acid (3 x 125 mL) and brine (125 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated. The crude product, a white solid, was purified by flash chromatography over silica gel (2-20% ethyl acetate in hexanes), evaporated, and azeotroped with hexanes to give a fluffy

white solid (14.4 g, 89% yield): $^1$H NMR (400 MHz, DMSO-$d_6$) δ 1.49 (s, 9 H) 7.59 - 7.63 (m, 2 H) 7.64 - 7.68 (m, 2 H) 9.79 (s, 1 H).

**Ethyl 2-(2-*tert*-butoxycarbonylamino)-5-(trifluoromethyl)phenyl)-2-oxoacetate**: *Tert*-butyl-4-(trifluoromethyl)phenylcarbamate (9.62 g, 36.8 mmol) was placed in a 500 mL round-bottomed flask, azeotroped with hexanes, and dried under vacuum overnight. Then, under nitrogen, 55 mL anhydrous tetrahydrofuran was added by syringe, and the solution cooled to –78 °C (dry ice / acetone). A 1.4 M solution of *sec*-butyllithium in cyclohexane (63 mL, 88 mmol) was added in rapid drops via syringe. The reaction mixture was then warmed to –40 °C (dry ice / acetonitrile) for 2 hours, then cooled back down to –78 °C, at which point diethyl oxalate (6.0 mL, 6.5 g, 49 mmol) was added rapidly in one portion by syringe. Finally, the reaction was allowed to stir for 45 minutes at –78 °C, then quenched with 15 mL 1 M hydrochloric acid. Additional hydrochloric acid was added until the mixture was acidic, and it was then extracted into ether (2 x). The combined ether extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, evaporated and purified by flash chromatography over silica gel (1-10% ethyl acetate in hexanes) to give a viscous light yellow oil (4.46 g, 34% yield): $^1$H NMR (400 MHz, DMSO-$d_6$) δ 1.28 (t, *J*=7.2 Hz, 3 H) 1.44 (s, 9 H) 4.28 (q, *J*=7.2 Hz, 2 H) 7.69 (d, *J*=8.3 Hz, 1 H) 7.91 (d, *J*=2.0 Hz, 1 H) 7.92 - 7.96 (m, 1 H) 10.18 (s, 1 H)

Isatin (**3m**): Ethyl 2-(2-*tert*-butoxycarbonylamino)-5-(trifluoromethyl)phenyl)-2-oxoacetate was taken up in 90 mL each tetrahydrofuran and 3 M hydrochloric acid, and the solution refluxed overnight, until LC-MS and t.l.c. analysis (5% ethyl acetate in dichloromethane) showed complete conversion to product. Upon evaporation of the organic solvent, the product precipitated out of solution. It was collected by filtration,

washing with water, and dried under vacuum to give fluffy, bright yellow crystals (2.22 g, 85% yield): $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.08 (d, *J*=8.3 Hz, 1 H) 7.81 (s, 1 H)

**General Procedure for the synthesis of quinoline salicylic acids (1, 2)**

To a 25 mL round bottom flask equipped with a condenser was added isatin (**3**, 0.7 mmol, 1.0 equiv) and 4 mL ethanol. To this solution was added 10.0 N aqueous sodium hydroxide solution (0.63 mL, 6.3 mmol, 9.0 equiv) and the mixture was heated to reflux in an oil bath. After 5 to 30 minutes a solution of acetate (**4**, 0.91 mmol,, 1.3 equiv) or hydroxyl ketone (**5**, 0.91 mmol,, 1.3 equiv) in 1.0 mL ethanol was added over 20 to 60 minutes. The resulting mixture was allowed to stir at reflux for 3 to 12 hours. Upon cooling to room temperature, and the ethanol removed under reduced pressure. The mixture was acidified to pH 1with 1M HCl and poured into water (in case of **1q** the reaction was acidified with glacial acetic acid). The crude solid obtained was purified by reverse-phase HPLC (water/acetonitrile/0.1% triethyl amine) and lyophilized to give the desired product. The 5,7-dimethylisatin was commercially available.

**Solution stability (physiological buffers and simulated GI fluids):**

The drug solution (1 mg/ml) was prepared in Acetonitrile/Water (50/50 v/v). Physiological buffers (990 µl) and simulated GI fluids were placed in each amber HPLC. Drug solution (10 µl) was added to above solution at time zero (initial time) and mixed thoroughly. Acetonitrile (200 µl) was added to each sample to prevent precipitation of the compound. Each sample therefore contained 20% acetonitrile. The vials were placed in an auto sampler maintained at 37 °C and consecutively injected every 4 hours over a 24 hour period. The percent of compound remaining at each time point was calculated relative to the compound peak area at t=0 as the reference.

*HPLC method:*

| | |
|---|---|
| Column: | Zorbax (Agilent) SB-CN 3□, 4.6 X 150 mm |
| Mobile Phase A: | DI Water (0.1% Formic Acid) |
| Mobile Phase B: | Acetonitrile (0.1% Formic Acid) |
| Flow-rate: | 1 ml/min |
| Injection volume: | 20 □l |
| Temperature: | 45 °C |

Gradient Table:

| Time (min) | % A | % B |
|---|---|---|
| 0 | 45 | 55 |
| 20 | 5 | 95 |
| 25 | 5 | 95 |

Wavelength: $\lambda_1$=214, 238 or 345 nm