Supporting Information

Discovery of Potent Orally Bioavailable WD Repeat Domain 5 (WDR5) Inhibitors Using a Pharmacophore-Based Optimization

Kevin B. Teuscher,[1] Kenneth M. Meyers,[1] Qiangqiang Wei,[1] Jonathan J. Mills,[1] Jianhua Tian,[4] Joseph Alvarado,[1] Jiqing Sai,[1] Mayme Van Meveren,[1] Taylor M. South,[1] Tyson A. Rietz,[1] Bin Zhao,[1] William J. Moore,[6] Gordon M. Stott,[6] William P. Tansey,[1,2] Taekyu Lee,[1] and Stephen W. Fesik[1,3,5*]

[1]Department of Biochemistry, [2]Department of Cell and Developmental Biology, and [3]Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-0146, United States

[4] Molecular Design and Synthesis Center, Vanderbilt Institute of Chemical Biology, and [5]Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37232-0142, United States

[6]Leidos Biomedical Research, Frederick National Laboratory for Cancer Research, Frederick, Maryland 21701-4907, United States

*To whom correspondence should be addressed: stephen.fesik@vanderbilt.edu

Vanderbilt University, Nashville, TN 37232, Phone: (615)-322-6303

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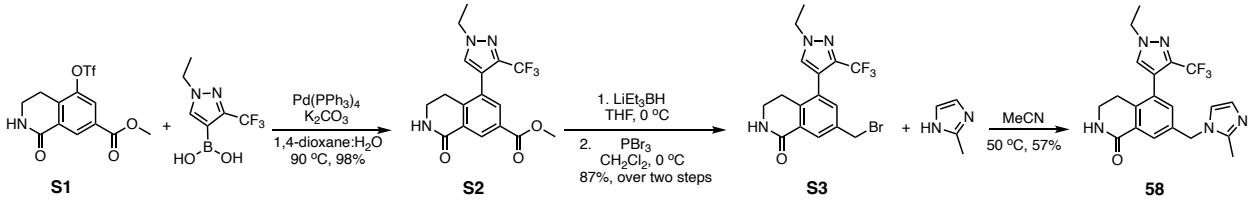
Scheme S1.[a] **Synthesis of 58**



[a]Compound **S1** was synthesized according to the previously reported procedure.[1]

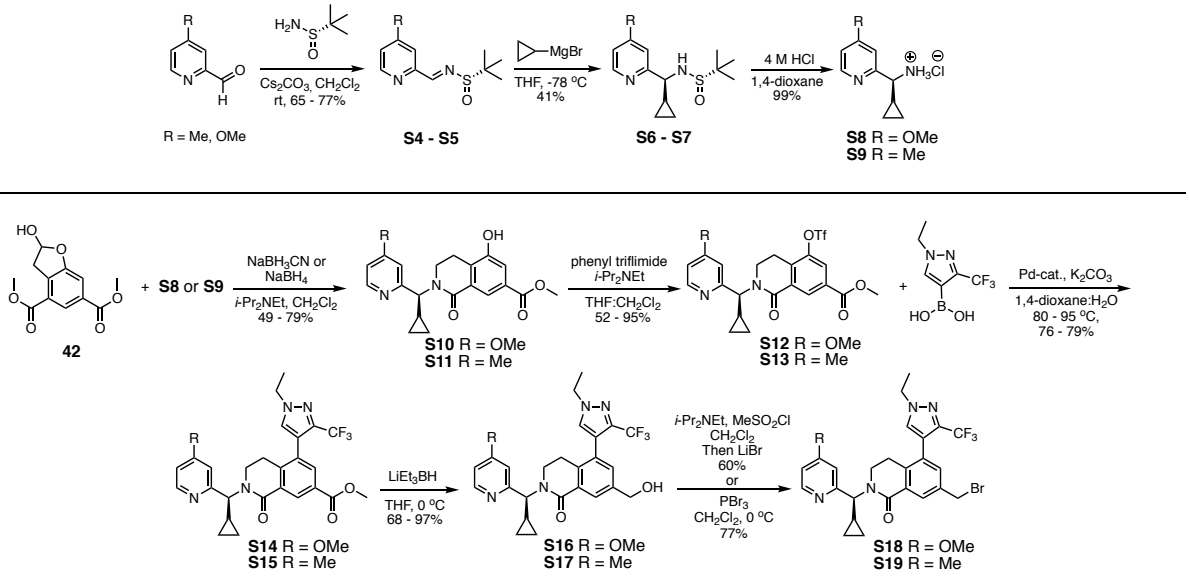
Methyl 5-(1-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-7-carboxylate (S2). Compound **S1** (2.0 g, 5.7 mmol, 1 equiv), (1-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)boronic acid (1.3 g, 6.2 mmol, 1.1 equiv), K_2CO_3 (1.96 g, 14.2 mmol, 2.5 equiv), and tetrakis(triphenylphosphine)palladium(0) (196 mg, 0.17 mmol, 0.03 equiv), were dissolved in 1,4-dioxane/H_2O (25 mL, 4:1). The reaction mixture was placed under an argon atmosphere, heated to 80 °C for 14 h, and then cooled to room temperature. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Combi-flash Rf, EtOAc/hexanes = 0−100% gradient) to obtain the title compound (2.6 g, 5.7 mmol, 98% yield). LCMS (method 2, ESI): *m/z* = 368.0 $[M + H]^+$.

7-(Bromomethyl)-5-(1-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (S3). A solution of lithium triethylborohydride (1 M THF, 17 mL, 17.2 mmol, 3 equiv) was added dropwise to a solution of **S2** (2.1 g, 5.7 mmol, 1 equiv) in THF at 0 °C. The reaction was stirred for 40 min, then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting benzyl alcohol was used without further purification. LCMS (method 2, ESI): *m/z* = 340.0 $[M + H]^+$. PBr_3 (1.0 mL, 11.4 mmol, 2 equiv) was added to a solution of the

benzyl alcohol (1 equiv) in CH_2Cl_2 at 0 °C. The reaction was stirred and slowly warmed to room temperature. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The title compound was used without further purification (2.0 g, 5.7 mmol, 87% yield, 2 steps). LCMS (method 2, ESI): *m/z* = 402.9 $[M + H]^+$.

5-(1-Ethyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-7-((2-methyl-1*H*-imidazol-1-yl)methyl)-3,4-dihydroisoquinolin-1(2*H*)-one (58). 2-Methyl-1*H*-imidazole (557 mg, 6.8 mmol, 3 equiv) was added to a solution of **S3** (909 mg, 2.3 mmol, 1 equiv) in acetonitrile (15 mL) at 23 °C. The reaction mixture was stirred for 12 h at 50 °C, then cooled to ambient temperature, filtered and concentrated. The residue was purified by preparative reversed-phase HPLC (Phenomenex Gemini C18, MeCN/H_2O = 15–95% gradient, 0.1% TFA) followed by neutralization with saturated aqueous $NaHCO_3$ to obtain the title compound (522 mg, 1.3 mmol, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 2.1 Hz, 1H), 7.34 (d, *J* = 1.1 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.94 (d, *J* = 1.4 Hz, 1H), 6.85 (d, *J* = 1.4 Hz, 1H), 5.97 (s, 1H), 5.09 (s, 2H), 4.26 (q, *J* = 7.3 Hz, 2H), 3.48 (td, *J* = 6.5, 2.8 Hz, 2H), 2.78 (t, *J* = 6.5 Hz, 2H), 2.34 (s, 3H), 1.58 (t, *J* = 7.3 Hz, 3H); LCMS (method 2, ESI): *m/z* = 404.0 $[M + H]^+$.

Scheme S2. Synthesis of S18 – S19



(*S*,*E*)-*N*-((4-Methoxypyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (S4). Cesium carbonate (1.0 g, 3.1 mmol 1.5 equiv) was added to a solution of (*S*)-2-methylpropane-2-sulfinamide (0.28 g, 2.1 mmol, 1 equiv) and 4-methoxypicolinaldehyde (0.25 g, 2.1 mmol, 1 equiv) in CH_2Cl_2 (10 mL). The reaction was stirred at rt for 16 h, and then filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography (Combi-flash Rf, EtOAc/hexanes = 5−75% gradient) to obtain the title compound (0.38 g, 1.60 mmol, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.58 (d, J = 5.8 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H), 6.94 (dd, J = 5.8. 2.6 Hz, 1H), 3.94 (s, 3H), 1.31 (s, 9H); LCMS (method 2, ESI): R_t = 0.85 min, m/z = 241.2 $[M + H]^+$.

(*S*,*E*)-2-Methyl-*N*-((4-methylpyridin-2-yl)methylene)propane-2-sulfinamide (S5). Cesium carbonate (7.13 g, 21.9 mmol, 1.5 equiv) was added to a solution of (*R*)-2-methylpropane-2-sulfinamide (2.2 g, 18.2 mmol, 1.1 equiv) and 4-methoxypicolinaldehyde (2.0 g, 16.5 mmol, 1 equiv) in CH_2Cl_2 (200 mL). The reaction was stirred at rt for 16 h, and then filtered through celite

and concentrated under reduced pressure. The residue was purified by flash chromatography (Combi-flash Rf, EtOAc/hexanes = 5−75% gradient) to obtain the title compound (3.7 g, 16.0 mmol, quant.). LCMS (method 2, ESI): R_t = 1.301 min, *m/z* = 225.1 $[M + H]^+$.

(*S*)-*N*-((*S*)-Cyclopropyl(4-methoxypyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide (S6). A 1.0 M solution of cyclopropyl magnesium bromide in 2-methyltetrahydrofuran (3.2 mL, 3.2 mmol, 2.0 equiv) was added dropwise to a solution of **S4** (0.38 g, 1.6 mmol, 1 equiv) in THF (10 mL) at -78°C. After 30 min, the reaction was quenched with saturated aqueous NH_4Cl (30 mL), stirred for 30 min, and then filtered. The filtrate was extracted with EtOAc, the combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The major diastereomer was isolated by preparative reversed-phase HPLC (Phenomenex Gemini C18, MeCN:H_2O = 5−30%, 0.1% TFA) to afford the title compound (0.15 g, 0.53 mmol, 33% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 5.8 Hz, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 6.72 (dd, *J* = 5.8. 2.6 Hz, 1H), 4.11 (d, *J* = 4.4 Hz, 1H), 3.84 (s, 3H), 3.64 (dd, *J* = 9.1, 4.4 Hz, 1H), 1.35–1.22 (m, 1H), 1.20 (s, 9H), 0.74–0.68 (m, 1H), 0.58–0.44 (m, 3H); LCMS (method 2, ESI): R_t = 0.95 min, *m/z* = 283.2 $[M + H]^+$.

(*S*)-*N*-((*S*)-Cyclopropyl(4-methylpyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide (S7). A 3.4 M solution of cyclopropyl magnesium bromide in 2-methyltetrahydrofuran (7.4 mL, 25.1 mmol, 1.5 equiv) was added dropwise to a solution of **S5** (3.75 g, 16.7 mmol, 1 equiv) in THF (10 mL) at -78°C. After 30 min, the reaction was quenched with saturated aqueous NH_4Cl (30 mL), stirred for 30 min, and then filtered. The filtrate was extracted with EtOAc, the combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The major diastereomer was isolated by flash chromatography (Combi-flash Rf, EtOAc/hexanes = 0–100% gradient) to afford the title compound (1.82 g, 6.83 mmol, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.39 (d, J = 5.0 Hz, 1H), 7.15 (s, 1H), 7.00 (d, J = 4.9 Hz, 1H), 5.00 (d, J = 4.9 Hz, 1H), 3.80 (dd, J = 8.2, 5.1 Hz, 1H), 2.35 (s, 3H), 1.27 (s, 9H), 1.18–1.12 (m, 1H), 0.64–0.59 (m, 1H), 0.58–0.50 (m, 2H), 0.45–0.38 (m, 1H); LCMS (method 2, ESI): R_t = 1.023 min, m/z = 267.1 $[M + H]^+$.

(*S*)-Cyclopropyl(4-methoxypyridin-2-yl)methanamine hydrochloride (S8). A 4.0 M solution of HCl in 1,4-dioxane (1.33 mL, 5.3 mmol, 10 equiv) was added to a solution of **S6** (0.15 g, 0.53 mmol, 1 equiv) in MeOH (4 mL). The reaction was stirred at room temperature for 2 h and followed by TLC. The reaction mixture was concentrated under reduced pressure to provide the title compound (0.11 g, 0.526 mmol, 99% yield), which was used without further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 8.73 (d, J = 5.8 Hz, 1H), 7.86 (d, J = 2.6 Hz, 1H), 7.60 (dd, J = 5.8, 2.6 Hz, 1H), 4.23 (s, 3H), 4.06 (d, J = 10.6 Hz, 1H), 1.62–1.53 (m, 1H), 1.03–0.95 (m, 1H), 0.84–0.77 (m, 2H), 0.75–0.68 (m, 1H); LCMS (method 2, ESI): R_t = 0.45 min, m/z = 179.2 $[M + H]^+$.

(*S*)-Cyclopropyl(4-methylpyridin-2-yl)methanamine hydrochloride (S9). A 4.0 M solution of HCl in 1,4-dioxane (17 mL, 68.3 mmol, 10 equiv) was added to a solution of **S7** (1.82 g, 6.83 mmol, 1 equiv) in THF (50 mL). The reaction was stirred at rt for 2 h and followed by TLC. The reaction mixture was concentrated under reduced pressure to provide the title compound (1.33 g, 6.7 mmol, 99% yield), which was used without further purification. LCMS (method 2, ESI): R_t = 0.579 min, m/z = 163.2 $[M + H]^+$.

Methyl (*S*)-2-(cyclopropyl(4-methoxypyridin-2-yl)methyl)-5-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-7-carboxylate (S10). Dimethyl 2-hydroxy-2,3-dihydrobenzofuran-4,6-dicarboxylate **42** (1.9 g, 7.6 mmol, 1 equiv), **S8** (2.5 g, 9.9 mmol, 1.3 equiv), and *N,N*-diisopropylethylamine (4.0 mL, 22.8 mmol, 3 equiv) were dissolved in CH_2Cl_2 and stirred at 30 °C for 30 min. Then sodium cyanoborohydride (1.4 g, 22.9 mmol, 3 equiv) was added and the reaction was stirred at 30 °C for 3 h. The reaction mixture was concentrated and dissolved in 1,4-

dioxane and heated at 110 °C overnight. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The title compound (2.30 g, 6.0 mmol, 79% yield) was used without further purification. LCMS (method 2, ESI): R_t = 1.14 min, *m/z* = 383.1 $[M + H]^+$.

Methyl (*S*)-2-(cyclopropyl(4-methylpyridin-2-yl)methyl)-5-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-7-carboxylate (S11). Dimethyl 2-hydroxy-2,3-dihydrobenzofuran-4,6-dicarboxylate **42** (3.4 g, 13.5 mmol, 1 equiv), **S9** (2.84 g, 17.5 mmol, 1.3 equiv), and *N,N*-diisopropylethylamine (7 mL, 40.6 mmol, 3 equiv) were dissolved in CH_2Cl_2 and stirred at 30 °C for 30 min. Then sodium borohydride (0.81 g, 30.5 mmol, 2.5 equiv) was added and the reaction was stirred at 30 °C for 3 h. The reaction mixture was concentrated and dissolved in 1,4-dioxane and heated at 110 °C overnight. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The title compound (2.44 g, 6.7 mmol, 49% yield) was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.1 Hz, 1H), 8.28 (s, 1H), 7.58 (s, 1H), 7.29 (s, 1H), 7.02 (d, *J* = 4.3 Hz, 1H), 5.08 (d, *J* = 10.1 Hz, 1H), 3.85 (s, 3H), 3.73–3.64 (m, 2H), 3.03–2.95 (m, 1H), 2.92–2.84 (m, 1H), 2.33 (s, 3H), 1.22–1.18 (m, 1H), 0.81–0.75 (m, 1H), 0.66–0.60 (m, 1H), 0.56–0.49 (m, 2H); LCMS (method 2, ESI): R_t = 1.137 min, *m/z* = 367.0 $[M + H]^+$.

Methyl (*S*)-2-(cyclopropyl(4-methoxypyridin-2-yl)methyl)-1-oxo-5-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate (S12). Phenyl triflimide (3.2 g, 9.0 mmol, 1.5 equiv) was added to a solution of **S10** (2.3 g, 6.0 mmol, 1 equiv) and triethylamine (2.5 mL, 18 mmol, 3 equiv) in THF/CH_2Cl_2 (5:1) at 23 °C and stirred for 14 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined

organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Combi-flash Rf, EtOAc/hexanes = 0–50% gradient) to obtain the title compound (2.9 g, 5.7 mmol, 95% yield). LCMS (method 2, ESI): R_t = 1.48 min, *m/z* = 514.9 $[M + H]^+$.

Methyl (*S*)-2-(cyclopropyl(4-methylpyridin-2-yl)methyl)-1-oxo-5-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate (S13). Phenyl triflimide (2.8 g, 7.9 mmol, 1.2 equiv) was added to a solution of **S11** (2.4 g, 6.6 mmol, 1 equiv) and triethylamine (2.3 mL, 16.4 mmol, 2.5 equiv) in THF/CH_2Cl_2 (5:1) at 23 °C and stirred for 14 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Combi-flash Rf, EtOAc/hexanes = 0–100% gradient) to obtain the title compound (1.7 g, 3.4 mmol, 52% yield). LCMS (method 2, ESI): R_t = 1.636 min, *m/z* = 498.9 $[M + H]^+$.

Methyl (*S*)-2-(cyclopropyl(4-methoxypyridin-2-yl)methyl)-5-(1-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-7-carboxylate (S14). Compound **S12** (2.0 g, 3.9 mmol, 1 equiv), (1-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)boronic acid (0.97 g, 4.68 mmol, 1.2 equiv), potassium carbonate (1.3 g, 9.7 mmol, 2.5 equiv), and tetrakis(triphenylphosphine)palladium(0) (224 mg, 0.19 mmol, 0.05 equiv), were dissolved in 1,4-dioxane/H_2O (4:1). The reaction mixture was placed under an argon atmosphere, heated to 80 °C for 14 h, and then cooled to room temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Combi-flash Rf, EtOAc/hexanes = 0−100% gradient) to obtain the title

compound (1.6 g, 3.1 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 1.8 Hz, 1H), 8.37 (d, *J* = 5.7 Hz, 1H), 8.0 (d, *J* = 1.8 Hz, 1H), 7.38 (s, 1H), 6.98 (d, *J* = 2.5Hz, 1H), 6.72 (dd, *J* = 5.7, 2.5 Hz, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.26 (q, *J* = 7.3 Hz, 2H), 3.91 (s, 3H), 3.84 (s, 3H), 3.76–3.68 (m, 2H), 2.82–2.72 (m, 2H), 1.68–1.61 (m, 1H), 1.56 (t, *J* = 7.3 Hz, 3H), 0.80–0.75 (m, 1H), 0.64–0.59 (m, 1H), 0.55–0.48 (m, 2H); LCMS (method 2, ESI): R_t = 1.47 min, *m/z* = 529.0 $[M + H]^+$.

Methyl (*S*)-2-(cyclopropyl(4-methylpyridin-2-yl)methyl)-5-(1-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-7-carboxylate (S15). Compound **S13** (1.7 g, 3.4 mmol, 1 equiv), (1-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)boronic acid (0.92 g, 4.4 mmol, 1.3 equiv), potassium carbonate (1.4 g, 10.2 mmol, 3 equiv), and $PdCl_2$(dppf) (125 mg, 0.17 mmol, 0.05 equiv), were dissolved in 1,4-dioxane/H_2O (3:1). The reaction mixture was placed under an argon atmosphere, heated to 95 °C for 2 h, and then cooled to room temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Combi-flash Rf, EtOAc/hexanes = 3:1 isocratic) to obtain the title compound (1.3 g, 2.6 mmol, 76% yield). LCMS (method 2, ESI): R_t = 1.595 min, *m/z* = 513.0 $[M + H]^+$.

(*S*)-2-(Cyclopropyl(4-methoxypyridin-2-yl)methyl)-5-(1-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-7-(hydroxymethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (S16). A solution of lithium triethylborohydride (1 M THF, 13.2 mL, 13.2 mmol, 3 equiv) was added dropwise to a solution of **S14** (2.3 g, 4.4 mmol, 1 equiv) in THF at 0 °C. The reaction was stirred for 40 min, then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and concentrated under reduced

pressure. The residue was purified by flash chromatography (Combi-flash Rf, EtOAc/hexanes = 0–100% gradient) to obtain the title compound (1.5 g, 3.0 mmol, 68% yield). LCMS (method 2, ESI): R_t = 1.29 min, *m/z* = 501.0 $[M + H]^+$.

(*S*)-2-(Cyclopropyl(4-methylpyridin-2-yl)methyl)-5-(1-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-7-(hydroxymethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (S17). Sodium borohydride (1.10 g, 29.1 mmol, 20 equiv) was added to a solution of **S15** (1.3 g, 2.54 mmol, 1 equiv) in EtOH. The reaction was refluxed for 5 h, then cooled and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Combi-flash Rf, EtOAc/hexanes = 0–100% gradient) to obtain the title compound (1.2 g, 2.46 mmol, 97% yield). LCMS (method 2, ESI): R_t = 1.329 min, *m/z* = 485.1 $[M + H]^+$.

(*S*)-7-(Bromomethyl)-2-(cyclopropyl(4-methoxypyridin-2-yl)methyl)-5-(1-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (S18). A solution of **S16** (0.59 g, 1.2 mmol, 1 equiv) in CH_2Cl_2 (12 mL) was cooled in an ice bath. *N*,*N*-Diisopropylethylamine (0.4 mL, 2.4 mmol, 2 equiv) and methanesulfonyl chloride (0.14 mL, 1.8 mmol, 1.5 equiv) were added and the reaction was stirred for 1 h. The reaction was diluted with saturated aqueous $NaHCO_3$ and the layers were separated. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. This material was dissolved in THF (8 mL). Lithium bromide (0.26 g, 3.0 mmol, 2.5 equiv) was added and reaction mixture was refluxed for 1 h. The reaction was concentrated under reduced pressure and the crude product was diluted with EtOAc and washed with water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Combi-flash Rf,

EtOAc/hexanes = 0–100% gradient) to obtain the title compound (0.4 g, 0.71 mmol, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 5.7 Hz, 1H), 8.15 (d, *J* = 1.9 Hz, 1H), 7.38 (d, *J* = 5.9 Hz, 1H), 7.37 (s, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.72 (dd, *J* = 5.7, 2.4 Hz, 1H), 5.04 (d, *J* = 10.0 Hz, 1H), 4.50 (s, 2H), 4.26 (q, *J* = 7.3 Hz, 2H), 3.84 (s, 3H), 3.76–3.63 (m, 2H), 2.77–2.64 (m, 2H), 1.68–1.61 (m, 1H), 1.56 (t, *J* = 7.3 Hz, 3H), 0.78–0.75 (m, 1H), 0.64–0.59 (m, 1H), 0.55–0.48 (m, 2H); LCMS (method 2, ESI): R_t = 1.55 min, *m/z* = 562.9 $[M + H]^+$.

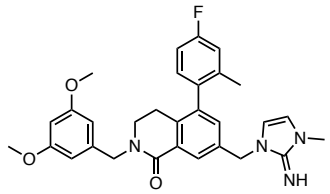
(*S*)-7-(Bromomethyl)-2-(cyclopropyl(4-methylpyridin-2-yl)methyl)-5-(1-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (S19). PBr_3 (0.7 mL, 0.74 mmol, 3 equiv) was added to a solution of **S17** (1.2 g, 2.48 mmol, 1 equiv) in CH_2Cl_2 at 0 °C. The reaction was stirred and slowly warmed to room temperature. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The title compound (1.05 g, 1.9 mmol, 77% yield) was used without further purification. LCMS (method 2, ESI): R_t = 1.656 min, *m/z* = 546.9 $[M + H]^+$.

Table S1. X-ray Data Collection and Refinement Statistics for 20 and 37

Compound	**20**	**37**
PDB Accession Code	7U9Y	7UAS
Data Collection		
Space group	P 21 21 2	P1
Cell dimensions		
a, b, c (Å)	81.259, 86.122, 41.094	46.743, 53.857, 64.519
α, β, γ (º)	90, 90, 90	107.96, 91.31, 109.39
Resolution (Å)	29.55 – 1.90 (1.93 – 1.90)	28.43 – 1.81 (1.85 – 1.81)
Rmerge (%)	9.9 (61.8)	6.5 (25.2)
Mean I / σI	23.4 (3.4)	22.6 (1.0)
Completeness (%)	100 (99.9)	97.2 (90.0)
Redundancy	8.0 (7.9)	3.3 (2.8)
Structure Refinement		
No. Reflections	23276	49755
R_{work} / R_{free}	0.1476 / 0.1887	0.1372 / 0.1749
R.m.s. deviations		
Bond lengths (%)	0.008	0.008
Bond angles (º)	0.905	1.063
Ramachandran		
Preferred regions (%)	95.38	95.67
Allowed regions (%)	4.62	4.33
Disallowed regions (%)	0	0

Related to Figures 5 and 6. Last resolution shell numbers are in parentheses.

Figure S1. Compound 1 LCMS Trace



1

Chemical Formula: $C_{30}H_{31}FN_4O_3$
Exact Mass: 514.24
Molecular Weight: 514.60

LCMS Method 2: Phenomenex Kinetex 2.6 μm XB-C18 100 Å, LC column (50 mm × 2.1 mm); 2 min gradient, 5 − 95% MeCN:H_2O, and 0.1% TFA acid.

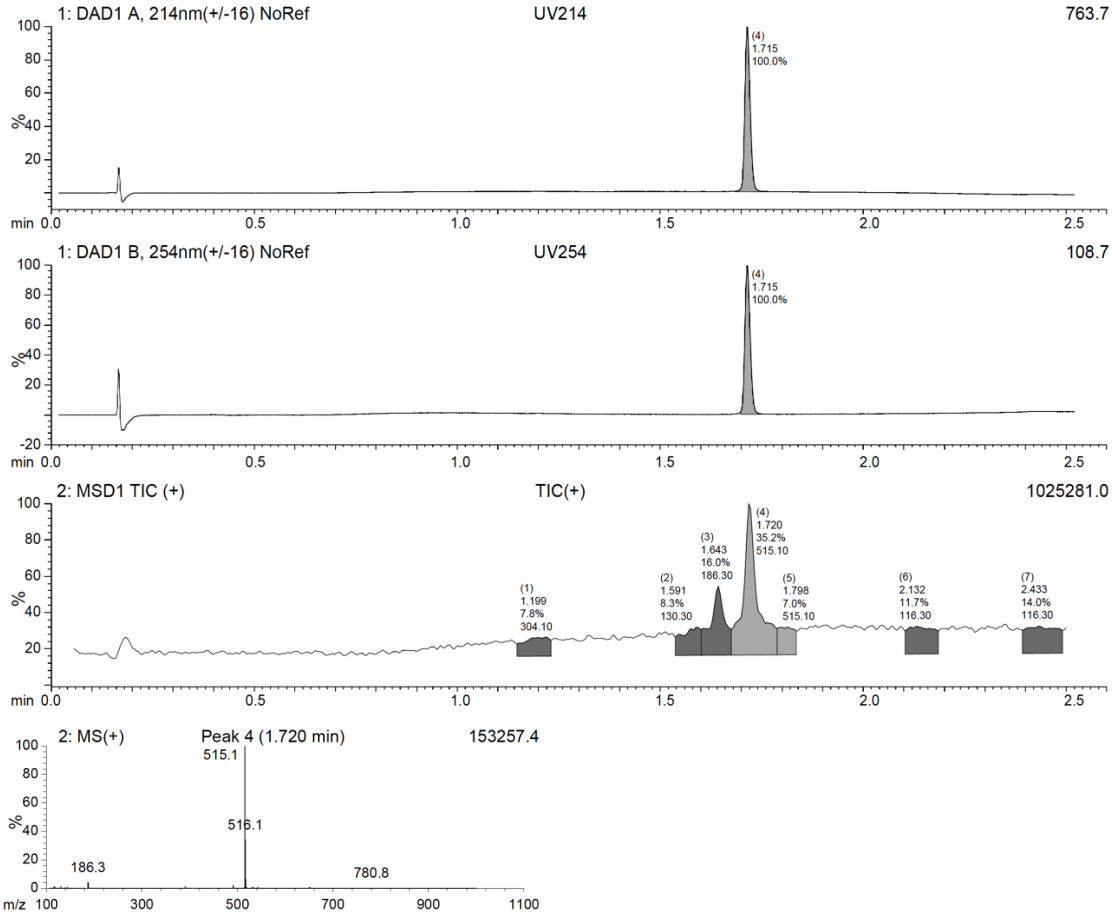
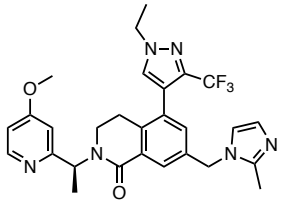


Figure S2. Compound 34 LCMS Trace



34

Chemical Formula: $C_{28}H_{29}F_3N_6O_2$
Exact Mass: 538.23
Molecular Weight: 538.58

LCMS Method 2: Phenomenex Kinetex 2.6 μm XB-C18 100 Å, LC column (50 mm × 2.1 mm); 2 min gradient, 5 − 95% MeCN:H_2O, and 0.1% TFA acid.

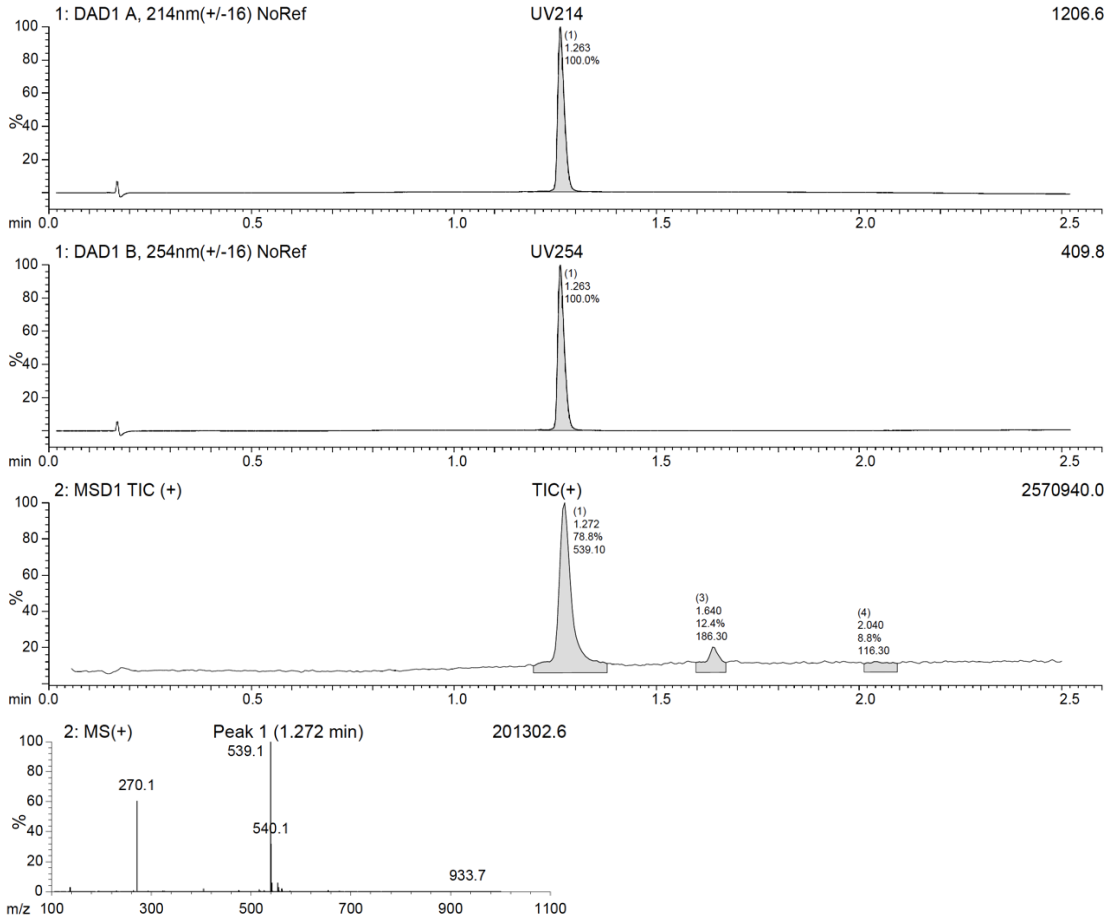
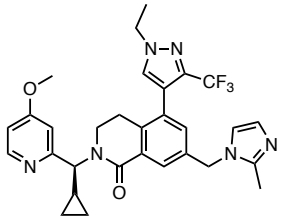


Figure S3. Compound 36 LCMS Trace



36

Chemical Formula: $C_{30}H_{31}F_3N_6O_2$
Exact Mass: 564.25
Molecular Weight: 564.61

LCMS Method 2: Phenomenex Kinetex 2.6 μm XB-C18 100 Å, LC column (50 mm × 2.1 mm); 2 min gradient, 5 − 95% MeCN:H_2O, and 0.1% TFA acid.

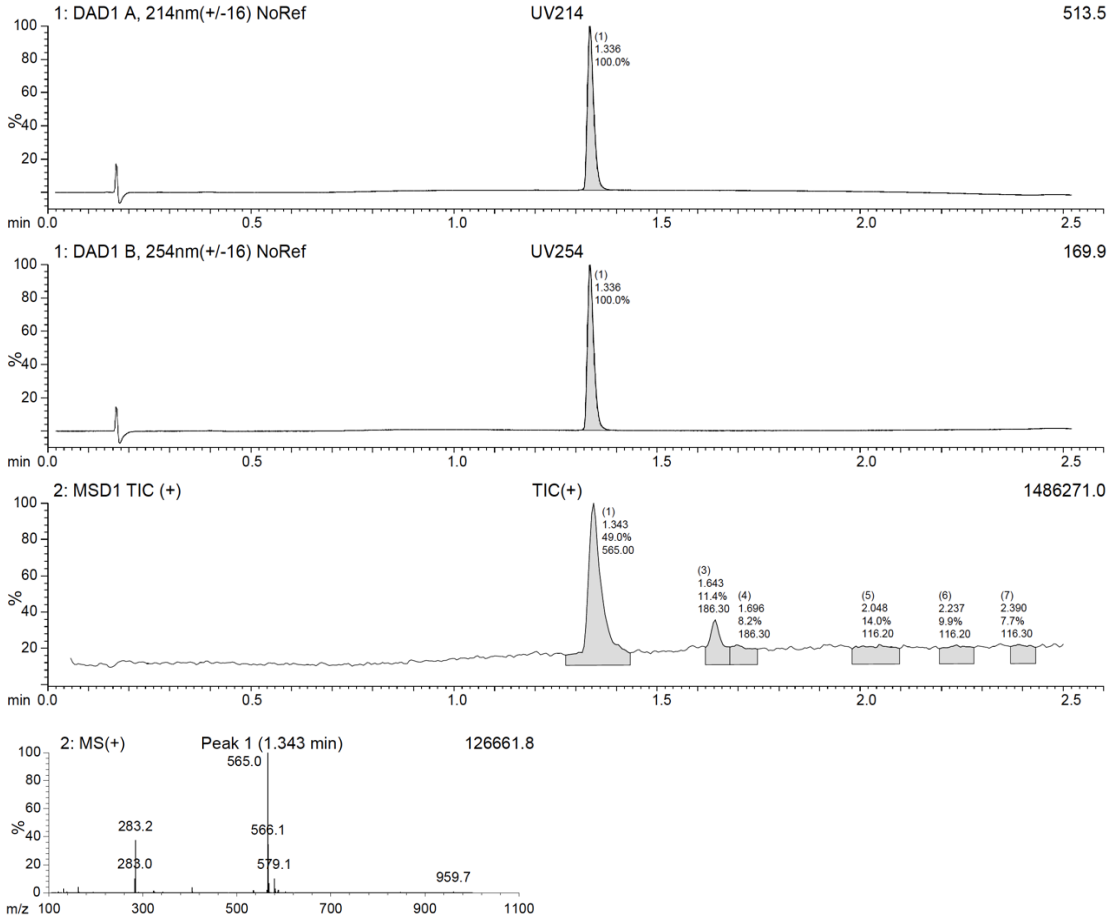
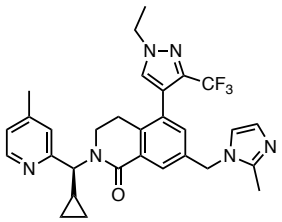


Figure S4. Compound 37 LCMS Trace



37

Chemical Formula: $C_{30}H_{31}F_3N_6O$
Exact Mass: 548.25
Molecular Weight: 548.61

LCMS Method 2: Phenomenex Kinetex 2.6 μm XB-C18 100 Å, LC column (50 mm × 2.1 mm); 2 min gradient, 5 − 95% MeCN:H_2O, and 0.1% TFA acid.

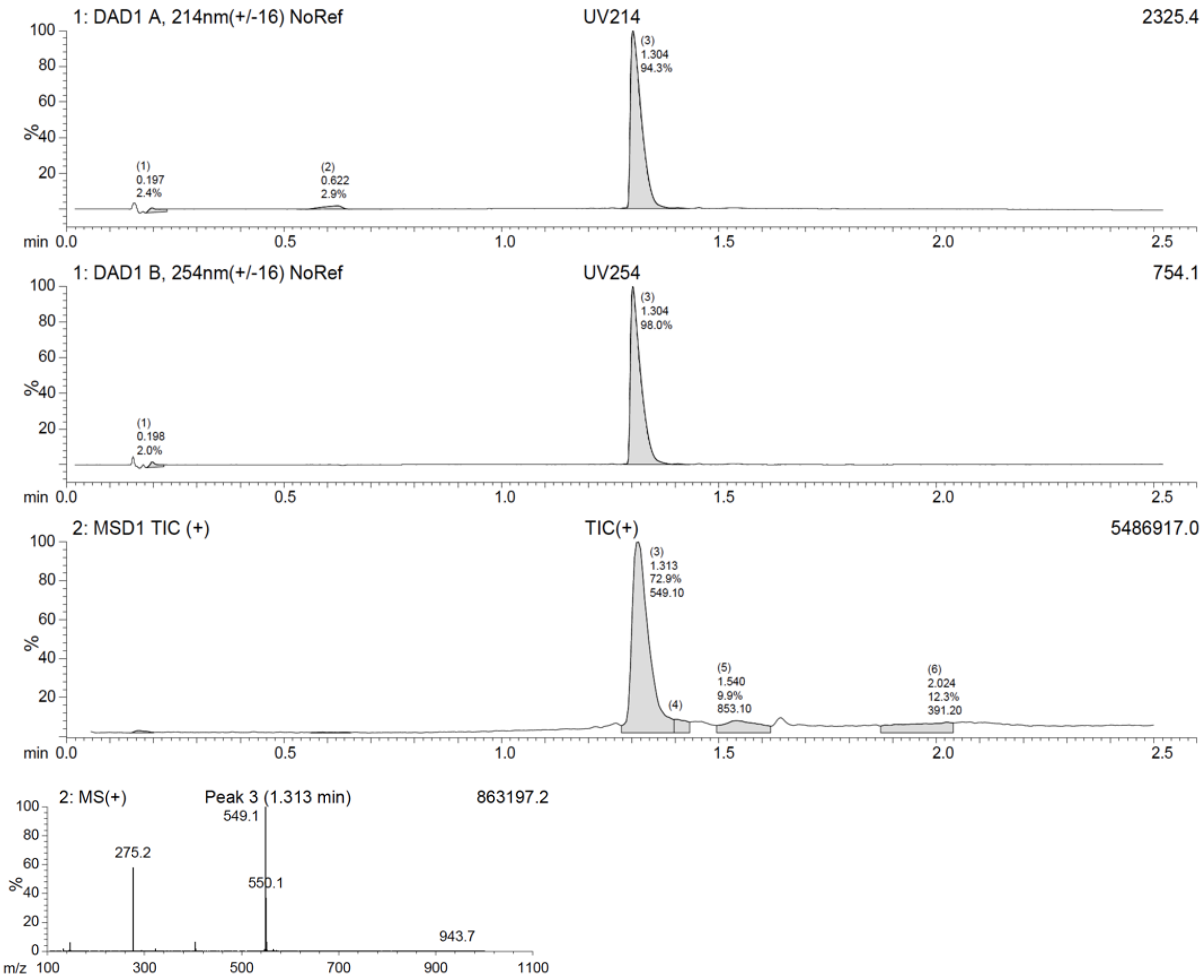
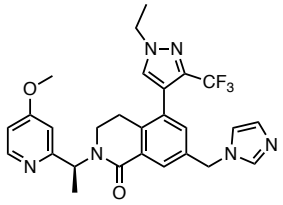


Figure S5. Compound 38 LCMS Trace



38

Chemical Formula: $C_{27}H_{27}F_3N_6O_2$
Exact Mass: 524.21
Molecular Weight: 524.55

LCMS Method 2: Phenomenex Kinetex 2.6 μm XB-C18 100 Å, LC column (50 mm × 2.1 mm); 2 min gradient, 5 − 95% MeCN:H_2O, and 0.1% TFA acid.

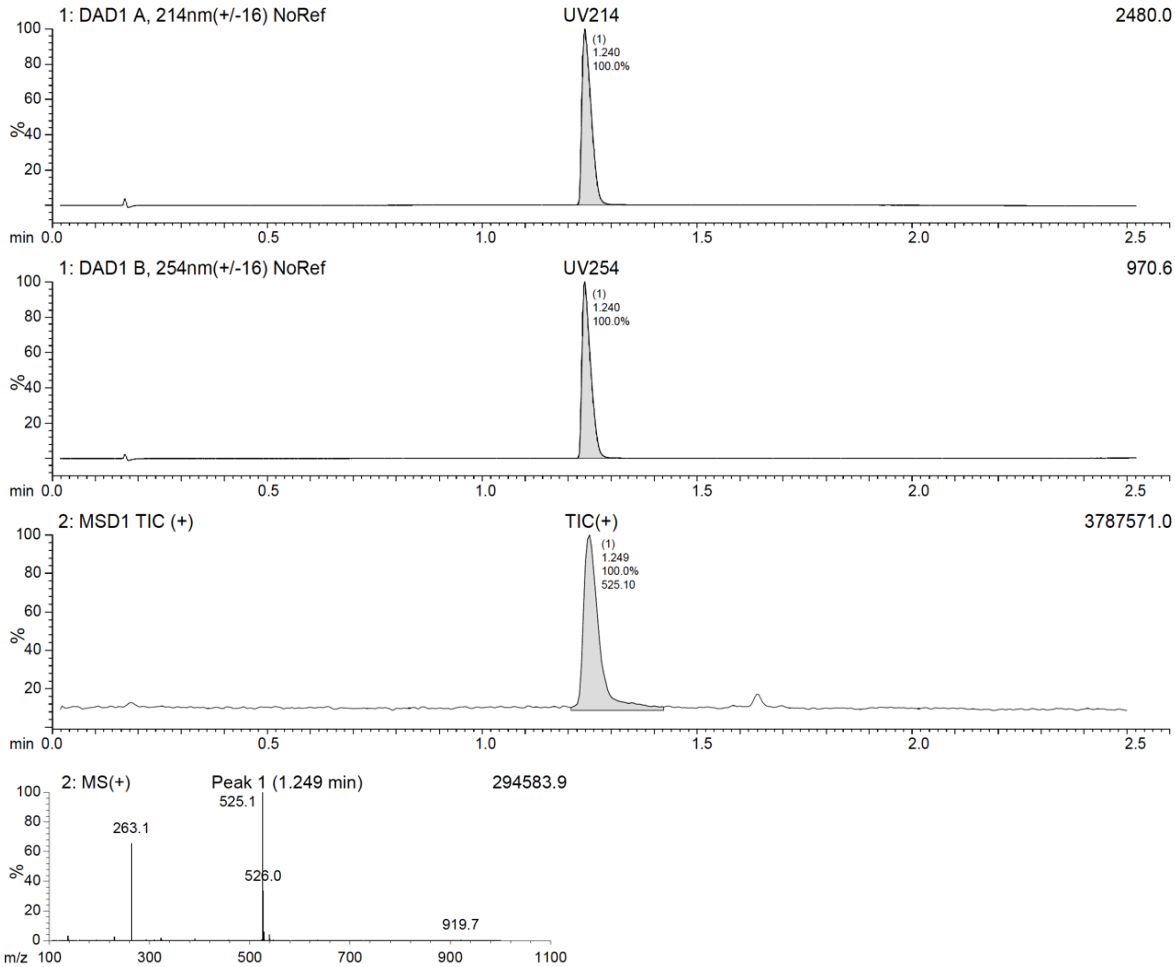
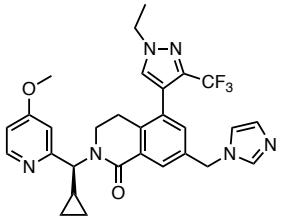


Figure S6. Compound 40 LCMS Trace



40

Chemical Formula: $C_{29}H_{29}F_3N_6O_2$
Exact Mass: 550.23
Molecular Weight: 550.59

LCMS Method 2: Phenomenex Kinetex 2.6 μm XB-C18 100 Å, LC column (50 mm × 2.1 mm); 2 min gradient, 5 − 95% MeCN:H_2O, and 0.1% TFA acid.

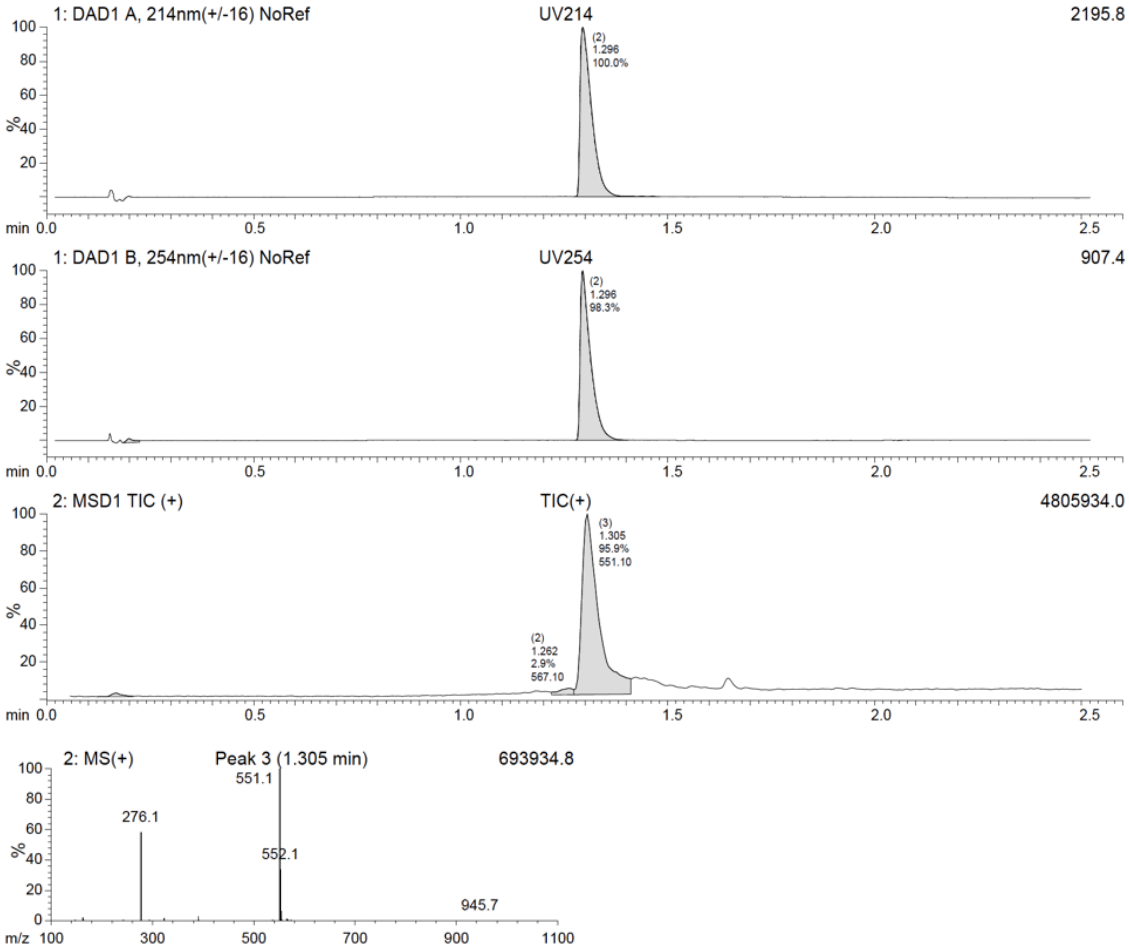
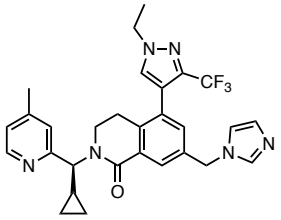


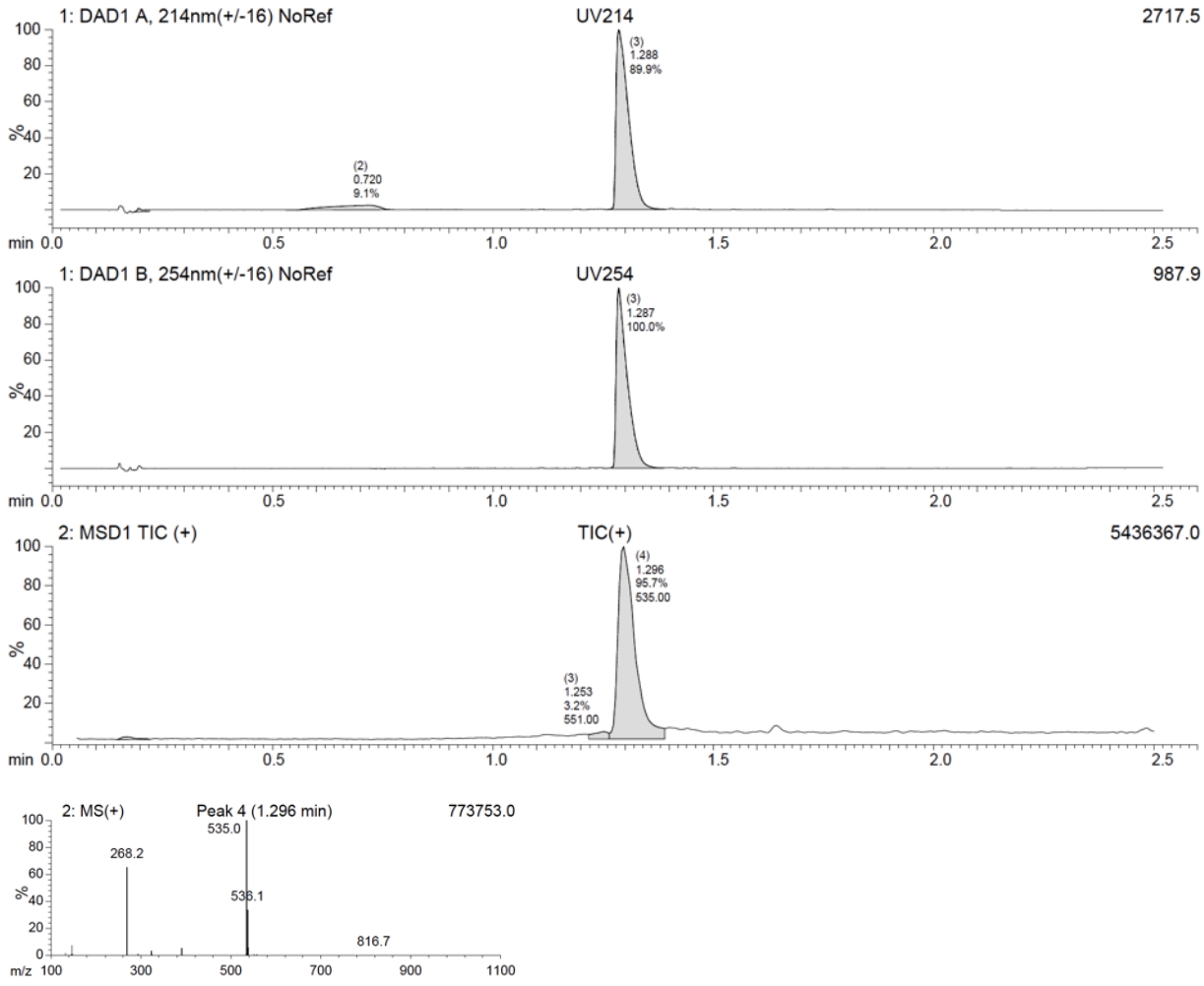
Figure S7. Compound 41 LCMS Trace



41

Chemical Formula: $C_{29}H_{29}F_3N_6O$
Exact Mass: 534.24
Molecular Weight: 534.59

LCMS Method 2: Phenomenex Kinetex 2.6 μm XB-C18 100 Å, LC column (50 mm × 2.1 mm); 2 min gradient, 5 − 95% MeCN:H_2O, and 0.1% TFA acid.



References

(1) Tian, J.; Teuscher, K. B.; Aho, E. R.; Alvarado, J. R.; Mills, J. J.; Meyers, K. M.; Gogliotti, R. D.; Han,C.; Macdonald, J. D.; Sai, J.; Shaw, J. G.; Sensintaffar, J. L.; Zhao, B.; Rietz, T. A.; Thomas, L. R.; Payne, W. G.; Moore, W. J.; Stott, G. M.; Kondo, J.; Inoue, M.; Coffey, R. J.; Tansey, W. P.; Stauffer, S. R.; Lee, T.; Fesik, S. W. Discovery and structure-based optimization of potent and selective WD repeat domain 5 (WDR5) inhibitors containing a dihydroisoquinolinone bicyclic core. *J. Med. Chem*. **2020**, *63* (2), 656 – 675.