

## *Supplementary Material*

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## 1 General procedure for the synthesis of compounds

**Procedure for the synthesis of the common intermediate (4-fluoro-2,3-dihydro-1H-indol-5-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine dihydrochloride (17)** (Axten et al., 2013).

**4-fluoro-2,3-dihydro-1H-indole (12).** A solution of 4-fluoroindole (1.423 g, 10.53 mmol) in acetic acid was cooled in an ice bath. Sodium cyanoborohydride (1.456 g, 23.17 mmol) was added portion-wise and the reaction was allowed to warm to room temperature and stir for 1h. The reaction mixture was cooled in an ice bath and neutralized with 50% wt/wt NaOH keeping the internal temperature <15 °C. Water was added (10 ml), and the mixture was extracted with ether (3x15 ml). The combined ether extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica flash column chromatography (EtOAc/heptane) to obtain the intermediate 4-fluoro-2,3-dihydro-1H-indole (1.094 g, 7.98 mmol, 76 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>), δ 2.93 (t, *J* = 8.61 Hz, 2H), 3.47 (dt, *J* = 1.91, 8.63 Hz, 2H), 6.28 (t, *J* = 8.64 Hz, 1H), 6.30 (d, *J* = 7.74 Hz, 1H), 6.90 (t, *J* = 7.97 Hz, 1H), 6.92 (d, *J* = 15.95 Hz, 1H); *t*<sub>R</sub> 0.50 min. MS (ESI) *m/z* 138.1 [M+H]<sup>+</sup>.

***tert*-butyl 4-fluoroindoline-1-carboxylate (13).** A round-bottomed flask was charged with 4-fluoro-2,3-dihydro-1H-indole **12** (1.000 g, 7.310 mmol), di-*t*-butyldicarbonate (1.680 ml, 7.310 mmol), *N,N*-Di-iso-propylethylamine (2.550 ml, 14.630 mmol), 4-Dimethylaminopyridine (10.11 μl, 0.073 mmol) and DCM to give a yellow solution that was stirred for 2 days. The reaction mixture was diluted with 0.1 M HCl and extracted with DCM. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered through a pad of silica gel, and concentrated to dryness to afford *tert*-butyl 4-fluoroindoline-1-carboxylate (1.490 g, 6.280 mmol, 86 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>), δ 1.50 (s, 9H), 3.07 (t, *J* = 8.40 Hz, 2H), 3.96 (t, *J* = 8.48 Hz, 2H), 6.76 (t, *J* = 8.52 Hz, 1H), 7.19 (q, *J* = 7.24 Hz, 1H), 7.48 (br. s, 1H); *t*<sub>R</sub> 2.12 min. MS (ESI) *m/z* 182.2 [M+H]<sup>+</sup>.

***tert*-butyl 5-bromo-4-fluoroindoline-1-carboxylate (14).** *N*-bromosuccinimide (1.372 g, 7.71 mmol) was added to a stirring solution of 1,1-dimethylethyl 4-fluoro-2,3-dihydro-1H-indole-1-carboxylate **13** (1.463 g, 6.17 mmol) in DCM. The reaction was stirred at room temperature for 1h. Then, the reaction mixture was diluted with water (10 ml) and saturated aqueous Na<sub>2</sub>CO<sub>3</sub> (10 ml). The mixture was extracted with DCM (3 x 10 ml), and the organic layer dried over Na<sub>2</sub>SO<sub>4</sub>, filtered through pad of silica gel, and concentrated to dryness to obtain *tert*-butyl 5-bromo-4-fluoroindoline-1-carboxylate (1.85 g, 6.18 mmol, 94 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.49 (s, 9H), 3.11 (t, *J* = 8.62 Hz, 2H), 3.97 (t, *J* = 8.73 Hz, 2H), 7.37 - 7.48 (m, 2H); *t*<sub>R</sub> 2.27 min. MS (ESI) *m/z* 218.1 [M-Boc+2H]<sup>+</sup>.

*1,1-dimethylethyl 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indole-1-carboxylate (15)*. A round bottom flask was charged with 1,1-dimethylethyl 5-bromo-4-fluoro-2,3-dihydro-1H-indole-1-carboxylate **14** (1.850 g, 6.180 mmol), bis(pinacolato)diboron (2.350 g, 9.270 mmol), potassium acetate (1.820 g, 18.54 mmol) and 1,4-dioxane to give a yellow suspension. The mixture was stirred and purged with argon for 2 minutes. Then 1,1'-Bis(diphenylphosphino)ferrocenepalladium(II)dichloride-DCM adduct (0.058 g, 0.071 mmol) was added to the reaction mixture, which was stirred at 80°C for 16 h. The cooled reaction mixture was diluted with water (5 ml) and saturated aqueous NaHCO<sub>3</sub> (5 ml), then extracted with EtOAc (3 x 15ml). The combined organic extracts were washed with water (15 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered through pad of silica gel and concentrated in vacuo. The residue was purified by silica flash column chromatography (EtOAc/Heptane) to give 1,1-dimethylethyl 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indole-1-carboxylate (1.482 g, 4.08 mmol, 66% yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.17 (s, 12H), 1.27 (s, 12H), 1.50 (s, 9H), 3.04 (t, *J* = 8.71 Hz, 2H), 3.97 (t, *J* = 8.74 Hz, 2H), 7.29 - 7.54 (m, 2H); *t*<sub>R</sub> 2.35 min. MS (ESI) *m/z* 182.1 [M/2], 308.1 [M-Boc+2H]<sup>+</sup>.

*1,1-dimethylethyl 5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoro-2,3-dihydro-1H-indole-1-carboxylate (16)*. A flask was charged with 5-bromo-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-4-amine **38** (0.838 g, 3.690 mmol), *tert*-butyl 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1-carboxylate **15** (1.470 g, 4.060 mmol), K<sub>3</sub>PO<sub>4</sub> tribasic (1.560 g, 7.380 mmol), 1,4-dioxane and water to give a yellow suspension at room temperature under argon. The reaction was stirred and purged with argon for 5 minutes. Then, tri(*tert*-butylphosphonium)tetrafluoroborate (0.054 g, 0.185 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.085 g, 0.092 mmol) were added to the reaction mixture, which was heated to 90°C for 2 h. After cooling to room temperature, the precipitated solids were collected by filtration and washed with water (10 ml) and then with ether (15 ml). The solids were dissolved in DCM/MeOH 9:1. The solution was filtered through pad of Celite and concentrated to give 1,1-dimethylethyl 5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoro-2,3-dihydro-1H-indole-1-carboxylate (0.970 g, 2.530 mmol, 69 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.51 (s, 9H), 3.10 – 3.18 (m, 2H), 3.73 (s, 3H), 4.01 (t, *J* = 8.6 Hz, 2H), 6.02 (br. s, 2H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.23 (s, 1H), 7.57 (br. s, 1H), 8.13 (s, 1H); *t*<sub>R</sub> 1.74 min. MS (ESI) *m/z* 384.3 [M+H]<sup>+</sup>.

*(4-fluoro-2,3-dihydro-1H-indol-5-yl)-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride (17)*. *Tert*-butyl 5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindoline-1-

carboxylate **16** (0.940 g, 2.452 mmol) was suspended in 1,4-dioxane and HCl 4N in 1,4-dioxane (13.54 ml, 54.20 mmol) was added at room temperature. A compact brown solid quickly formed in the solution. The mixture was then stirred at room temperature overnight. Then the reaction was filtered and the collected solid was washed with ether (10 ml) and dried to afford (4-fluoro-2,3-dihydro-1*H*-indol-5-yl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride (0.924 g, 2.59 mmol, 94% yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>), δ 3.16 (t, *J* = 8.07 Hz, 2H), 3.70 (t, *J* = 8.10 Hz, 2H), 3.84 (s, 3H), 6.93 (d, *J* = 7.34 Hz, 1H), 7.21 (t, *J* = 7.64 Hz, 1H), 7.61 (s, 1H), 8.51 (s, 1H); *t*<sub>R</sub> 1.09 min. MS (ESI) *m/z* 284.2 [M+H]<sup>+</sup>.

**Procedure for the synthesis of the coupling reagent 5-bromo-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (38)** (Axten et al., 2012).

**4-chloro-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (36)** (Lumb J., Trevor et al., 2004). In a round-bottom flask 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (2.200 g, 14.33 mmol) was dissolved in DMF (30 ml). After cooling down to 0°C, iodomethane (1.784 ml, 28.70 mmol) was added dropwise, and the reaction mixture was allowed to stir at room temperature for 2 h. Then, the reaction was quenched with water (20 mL) and extracted with EtOAc (3 x 30 ml). The combined organic extracts were dried using anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by silica flash column chromatography (EtOAc/heptane) to obtain 4-chloro-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.980 g, 11.81 mmol, 82 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.85 (s, 4H), 6.64 (d, *J* = 3.5 Hz, 1H), 7.74 (d, *J* = 3.5 Hz, 1H), 8.64 (s, 1H); *t*<sub>R</sub> 1.22 min. MS (ESI) *m/z* 168.1 [M+H]<sup>+</sup>.

**4-chloro-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (37)**. To a stirring solution of 4-chloro-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.817 g, 10.84 mmol) in DCM (16 mL) *N*-bromosuccinimide (2.412 g, 13.55 mmol) was added portion wisely at 0°C for 1 h and the reaction was stirred for 4 h at room temperature. The solvent was evaporated, and the solid was washed with water (3 x 15 ml) and dried to afford 5-bromo-4-chloro-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (2.409 g, 9.77 mmol, 90 % yield). <sup>1</sup>H NMR (400 MHz, DMSO *d*<sub>6</sub>) δ 3.82 (s, 4H), 7.99 (s, 1H), 8.67 (s, 1H). ); *t*<sub>R</sub> 1.60 min. MS (ESI) *m/z* 248.0, 249.9 [M+H]<sup>+</sup>.

**5-bromo-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (38)**. A suspension of 5-bromo-4-chloro-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.000 g, 4.060 mmol) in 30% aqueous ammonia (5 mL) was stirred for 2 days at 100 °C in a sealed vessel. The mixture was allowed to cool to room temperature

and filtered. The collected solid was washed with Et<sub>2</sub>O (2 x 10 ml) and dried to afford 5-bromo-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.820 g, 3.610 mmol, 89 % yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.84 (s, 3H), 6.72 (br. s, 2H), 7.38 (s, 1H), 8.11 (s, 1H); *t*<sub>R</sub> 0.27 min. MS (ESI) *m/z* 229.0, 230.1 [M+H]<sup>+</sup>.

**General procedure A for the synthesis of the corresponding pyridyl acetic acid (41 and 42)** (Biscoe and Buchwald, 2009).

A stirring solution of the corresponding 5-substituted-2-chloropyridine (1 eq) and 1,1-dimethylethyl acetate (2 eq) in toluene (3 ml) was purged with argon gas for 10 min, and then *t*-BuXPhos palladium(II) phenethylamine chloride (0.1 eq) was added. The reaction was cooled down to 0°C in an ice bath and LHMDS 1M in toluene (3 eq), was added dropwise over 1h. After the addition, the reaction was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (2 ml), extracted with EtOAc (3 x 10 ml), and the combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> filtered and concentrated *in vacuo*. The residual oil was purified by silica flash column chromatography (EtOAc/Heptane) to yield the intermediate **39** and **40**.

Trifluoroacetic acid (10 eq) was added dropwise to a stirring solution of the corresponding acetate and triethylsilane (2.5 eq) in DCM at room temperature. After addition, the mixture was stirred at room temperature overnight. The reaction was concentrated *in vacuo* and diethyl ether was added (20 ml) to the residual oil, which caused an exothermic precipitation of the product. The mixture was allowed to cool down and the solid was isolated by filtration, washed with diethyl ether (3 x 5 ml) and dried to give the corresponding TFA salts **41** and **42**.

*5-(tert-butyl)-2-(carboxymethyl)pyridin-1-ium 2,2,2-trifluoroacetate (41)*. General procedure A with *tert*-butyl 2-(5-(*tert*-butyl)pyridin-2-yl)acetate **39** (0.074 g, 0.297 mmol) to obtain 5-(*tert*-butyl)-2-(carboxymethyl)pyridin-1-ium 2,2,2-trifluoroacetate (0.042 g, 0.137 mmol, 46 %). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.33 (s, 9H), 2.62 (s, 2H), 7.69 (d, *J* = 8.37 Hz, 1H), 8.33 (q, *J* = 3.54 Hz, 1H), 8.65 (d, *J* = 2.09 Hz, 1H); *t*<sub>R</sub> 0.43 min. MS (ESI) *m/z* 194.2 [M+H]<sup>+</sup>.

*5-benzyl-2-(carboxymethyl)pyridin-1-ium 2,2,2-trifluoroacetate (42)*. General procedure A with *tert*-butyl 2-(5-benzylpyridin-2-yl)acetate **40** (0.203 g, 0.716 mmol) to obtain 5-benzyl-2-(carboxymethyl)pyridin-1-ium 2,2,2-trifluoroacetate (0.172 g, 0.504 mmol, 70 % yield). <sup>1</sup>H NMR (400

MHz, DMSO-*d*<sub>6</sub>)  $\delta$  3.95 (s, 2H), 4.07 (s, 2H), 7.20 - 7.35 (m, 5H), 7.65 (d,  $J$  = 8.12 Hz, 1H), 8.06 (dd,  $J$  = 2.08, 8.12 Hz, 1H), 8.69 (d,  $J$  = 1.78 Hz, 1H);  $t_R$  1.15 min. MS (ESI)  $m/z$  228.2 [M+H]<sup>+</sup>.

**General procedure B for the corresponding pyridyl acetic acid (44–46)** (Spiekermann, 2019).

To a mixture of the corresponding methyl-2-substituted pyridinyl acetate (1 eq) in THF (1.5 mL), water (1.5 mL) and MeOH (3 mL), lithium hydrate (3 eq) was added. The reaction mixture was stirred at 20 °C for 2 h. On completion, the reaction was concentrated *in vacuo* and the residue was acidified by 1.0 N HCl to pH = 3.0, washed with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to give the intermediates **44–46**.

**2-(5-cyclopropylpyridin-2-yl)acetic acid (44)** (Molander and Gormisky, 2008). A stirring solution of cyclopropyltrifluoro-4-borane, potassium salt (0.354 g, 2.391 mmol), CataXium (0.023 g, 0.065 mmol), palladium(II)acetate (9.76 mg, 0.043 mmol) and cesium carbonate (2.124 g, 6.52 mmol) was flushed with argon. Then, methyl 2-(5-bromopyridin-2-yl)acetate (0.500 g, 2.173 mmol) was added and then suspended in 10 ml of a 9:1 mixture of toluene/water and heated to 100 °C for 24 h. Cooled to room temperature, and diluted with water (5 mL), the reaction mixture was extracted with DCM (3 x 5 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Hep/EtOAc) to obtain methyl 2-(5-cyclopropylpyridin-2-yl)acetate **43** (0.185 g, 0.967 mmol, 45 % yield).

General procedure B with methyl 2-(5-cyclopropylpyridin-2-yl)acetate **43** (0.175 g, 0.915 mmol) to obtain 2-(5-cyclopropylpyridin-2-yl)acetic acid (0.162 g, 0.824 mmol, 90 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  0.89 (dt,  $J$  = 4.6, 7.0 Hz, 2H), 1.11 (dd,  $J$  = 3.7, 6.8 Hz, 2H), 2.14 (tt,  $J$  = 5.0, 8.3 Hz, 1H), 4.10 (s, 2H), 7.76 (d,  $J$  = 8.3 Hz, 1H), 8.05 (dd,  $J$  = 2.2, 8.2 Hz, 1H), 8.65 (d,  $J$  = 2.3 Hz, 1H);  $t_R$  0.26 min. MS (ESI)  $m/z$  178.1 [M+H]<sup>+</sup>.

**2-(5-bromopyridin-2-yl)acetic acid (45)**. General procedure B with methyl 2-(5-bromopyridin-2-yl)acetate (0.300 g, 1.304 mmol) to obtain 2-(5-bromopyridin-2-yl)acetic acid (0.232 g, 1.074 mmol, 82 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  3.74 (s, 2H), 7.35 (d,  $J$  = 8.3 Hz, 1H), 8.01 (dd,  $J$  = 2.5, 8.3 Hz, 1H), 8.61 (d,  $J$  = 2.6 Hz, 1H), 12.52 (s, 1H);  $t_R$  1.12 min. MS (ESI)  $m/z$  218.1, 219.1 [M+H]<sup>+</sup>.

*2-(pyridin-4-yl)acetic acid (46)*. General procedure B with methyl 2-(pyridin-4-yl)acetate (0.500 g, 3.310 mmol) to obtain 2-(pyridin-4-yl)acetic acid (0.140 g, 1.021 mmol, 31 % yield). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 3.79 (d, *J* = 2.4 Hz, 2H), 7.81 (d, *J* = 6.2 Hz, 2H), 8.59 (d, *J* = 7.3 Hz, 2H); *t*<sub>R</sub> 0.29 min. MS (ESI) *m/z* 138.0 [M+H]<sup>+</sup>.

*2-(5-phenylpyridin-2-yl)acetic acid (47)* (Deng et al., 2011).

A mixture of phenylboronic acid (0.423 g, 3.470 mmol), 2-(5-bromopyridin-2-yl)acetic acid (0.500 g, 2.314 mmol), tetrakis(triphenylphosphine)palladium(0) (0.535 g, 0.463 mmol) and potassium carbonate (0.960 g, 6.940 mmol) was suspended in 10 ml of a 9:1 mixture of 1,4-dioxane/water and heated to 100 °C for 1 h. Then the palladium residues were filtered and the filtrate was diluted with 30 ml of methanol and purified by reversed phase flash chromatography (water/MeOH) to obtain 2-(5-phenylpyridin-2-yl)acetic acid **47** (0.430 g, 2.017 mmol, 87 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.39 (s, 2H), 7.34 – 7.41 (m, 2H), 7.47 (dd, *J* = 6.9, 8.4 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.87 (dd, *J* = 2.5, 8.1 Hz, 1H), 8.65 (d, *J* = 2.4 Hz, 1H); *t*<sub>R</sub> 1.48 min. MS (ESI) *m/z* 214.1 [M+H]<sup>+</sup>.

**General procedure C for the synthesis of final compounds (18–34)** (Axten et al., 2013).

A solution of 5-(2,3-dihydro-1*H*-indol-5-yl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride (1 eq), the corresponding 3-pyridinylacetic acid or 3-arylacetic acid substituent (1.1 eq), HATU (1 eq), and DIPEA (5 eq) in DMF (3ml) was stirred at room temperature overnight. Water (2 ml) was poured into the mixture and stirred for 30 minutes. The resulting suspension was filtered and then the collected solid was washed with water (3 x 3ml) and then dried to afford the desired product **18–22, 25, 28, 31** and **32** or purified by reversed phase flash chromatography (water/ACN) to obtain compounds **23, 24, 26, 27, 29, 30, 33** and **34**.

*1-(5-(4-amino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-fluoropyridin-2-yl)ethan-1-one (18)* General procedure C with 5-(2,3-dihydro-1*H*-indol-5-yl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride **17** (0.100 g, 0.280 mmol) and 2-(5-bromopyridin-2-yl)acetic acid (0.600 g, 0.281 mmol) to obtain 1-(5-(4-amino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-fluoropyridin-2-yl)ethan-1-one (0.038 g, 0.090 mmol, 64 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.17 – 3.28 (m, 2H), 3.73 (s, 3H), 4.07 (s, 2H), 4.32 (t, *J* = 8.7 Hz, 2H), 6.05 (br.s, 2H), 7.12 – 7.34 (m, 2H), 7.38 – 7.57 (m, 1H), 7.72 (dt, *J* = 9.4, 18.3, Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 8.14 (s, 1H), 8.50 (s, 1H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 24.45, 31.24, 44.48, 49.06,

101.22, 107.50, 112.63 (d,  $J = 2.3$  Hz), 117.50 (d,  $J = 14.7$  Hz), 119.34 (d,  $J = 22.8$  Hz), 124.04 (d,  $J = 20.6$  Hz), 125.74 (d,  $J = 2.2$  Hz), 126.19 (d,  $J = 4.4$  Hz), 131.34 (d,  $J = 1.8$  Hz), 137.26 (d,  $J = 23.3$  Hz), 144.94 (d,  $J = 8.0$  Hz), 150.60, 151.99, 152.34 (d,  $J = 3.6$  Hz), 156.03 (d,  $J = 243.1$  Hz), 157.42, 157.55, 168.88; HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{22}H_{18}F_2N_6O$  421.1583, found 421.1595.

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-chloropyridin-2-yl)ethan-1-one* (**19**) General procedure C with 5-(2,3-dihydro-1*H*-indol-5-yl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride **17** (0.100 g, 0.280 mmol) and 2-(5-chloropyridin-2-yl)acetic acid (0.050 g, 0.309 mmol) to obtain 1-(5-(4-amino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-chloropyridin-2-yl)ethan-1-one (0.078 g, 0.179 mmol, 64 % yield).  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.24 (t,  $J = 8.5$  Hz, 2H), 3.73 (s, 3H), 4.08 (s, 2H), 4.32 (t,  $J = 8.4$  Hz, 2H), 6.03 (br. s, 2H), 7.19 (t,  $J = 8.0$  Hz, 1H), 7.26 (s, 1H), 7.44 (d,  $J = 8.4$  Hz, 1H), 7.86 – 7.96 (m, 2H), 8.13 (s, 1H), 8.57 (d,  $J = 2.5$  Hz, 1H);  $^{13}C$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  24.44, 31.24, 44.60, 49.05, 101.21, 107.45, 112.62 (d,  $J = 3.2$  Hz), 117.48 (d,  $J = 9.7$  Hz), 119.38 (d,  $J = 21.6$  Hz), 122.26, 125.73, 126.33, 129.91, 131.36 (d,  $J = 2.4$  Hz), 136.82, 144.87 (d,  $J = 9.3$  Hz), 147.94, 150.58, 152.10, 154.81, 156.17 (d,  $J = 294.9$  Hz), 168.69; HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{22}H_{18}ClFN_6O$  437.1287, found 437.1270

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-bromopyridin-2-yl)ethan-1-one* (**20**) General procedure C with 5-(2,3-dihydro-1*H*-indol-5-yl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride **17** (0.050 g, 0.140 mmol) and 2-(5-fluoropyridin-2-yl)acetic acid **45** (0.020 g, 0.140 mmol) to obtain 1-(5-(4-amino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-bromopyridin-2-yl)ethan-1-one (0.086 g, 0.179 mmol, 64 % yield).  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.24 (t,  $J = 8.4$  Hz, 2H), 3.74 (s, 3H), 4.06 (s, 2H), 4.32 (t,  $J = 8.4$  Hz, 2H), 6.13 (br.s, 2H), 7.19 (t,  $J = 8.1$  Hz, 1H), 7.28 (s, 1H), 7.38 (d,  $J = 8.3$  Hz, 1H), 7.90 (d,  $J = 8.2$  Hz, 1H), 8.04 (dd,  $J = 2.5, 8.3$  Hz, 1H), 8.15 (s, 1H), 8.65 (d,  $J = 2.5$  Hz, 1H).  $^{13}C$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  24.44, 31.47, 44.67, 49.06, 96.03, 100.85, 108.18, 112.72 (d,  $J = 2.9$  Hz), 116.95 (d,  $J = 14.8$  Hz), 118.98, 119.59 (d,  $J = 23.7$  Hz), 126.56, 126.84, 131.32 (d,  $J = 2.5$  Hz), 139.61, 145.10 (d,  $J = 9.5$  Hz), 149.88, 150.13, 155.26 (d,  $J = 242.3$  Hz), 156.05, 168.64; HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{22}H_{18}BrFN_6O$  481.0782, found 481.0778.

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-methylpyridin-2-yl)ethan-1-one* (**21**) General procedure C with 5-(2,3-dihydro-1*H*-indol-5-yl)-7-methyl-7*H*-



pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride **17** (0.1 g, 0.28 mmol) and 2-(5-Methylpyridin-2-yl)acetic acid (0.040 g, 0.281 mmol) to obtain 1-(5-(4-amino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-methylpyridin-2-yl)ethan-1-one (0.085g, 0.204 mmol, 72.7%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 2.31 (3H, s), 3.25 (2H, t, *J* = 8.28 Hz), 3.82 (3H, s), 3.98 (2H, s), 4.32 (2H, t, *J* = 8.35 Hz), 5.21 (2H, s), 6.97 (1H, s), 7.22 (1H, t, *J* = 7.91 Hz), 7.29 (1H, d, *J* = 7.87 Hz), 7.48 (1H, d, *J* = 6.69 Hz), 8.08 (1H, d, *J* = 8.14 Hz), 8.31 (1H, s), 8.37 (1H, s); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 18.24, 24.64, 31.40, 45.80, 49.27, 101.77, 107.89, 113.32 (d, *J* = 3.74 Hz), 117.59 (d, *J* = 14.57 Hz), 118.74 (d, *J* = 22.94 Hz), 123.54, 125.39, 131.27, 131.83, 137.56, 144.79 (d, *J* = 7.55 Hz), 149.98, 150.80, 151.83, 151.87, 156.07 (d, *J* = 244.76 Hz), 156.95, 168.87; HRMS (ESI) *m/z* [M+H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>21</sub>FN<sub>6</sub>O 417.1834, found 417.1819.

1-(5-(4-amino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-(trifluoromethyl)pyridin-2-yl)ethan-1-one (**22**) General procedure C with 5-(2,3-dihydro-1*H*-indol-5-yl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride **17** (0.074 g, 0.210 mmol) and 2-(5-(trifluoromethyl)pyridin-2-yl)acetic acid (0.470 g, 0.229 mmol) to obtain 1-(5-(4-amino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-(trifluoromethyl)pyridin-2-yl)ethan-1-one (0.041 g, 0.086 mmol, 41 %). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.26 (t, *J* = 8.44 Hz, 2H), 3.73 (s, 3H), 4.22 (s, 2H), 4.34 (t, *J* = 8.44 Hz, 2H), 6.04 (s, 2H), 7.19 (t, *J* = 8.08 Hz, 1H), 7.26 (s, 1H), 7.64 (d, *J* = 8.24 Hz, 1H), 7.90 (d, *J* = 8.20 Hz, 1H), 8.14 (s, 1H), 8.21 (dd, *J* = 1.98, 8.22 Hz, 1H), 8.92 (q, *J* = 0.76 Hz, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 24.03, 30.82, 44.79, 48.63, 100.76, 107.02, 112.25 (d, *J* = 10.2 Hz), 117.19 (d, *J* = 14.2 Hz), 118.86, 118.98 (d, *J* = 24.4 Hz), 124.91, 125.11 (d, *J* = 40.2 Hz), 130.94, 133.92 (d, *J* = 5.0 Hz), 144.40 (d, *J* = 8.5 Hz), 145.78, 150.17, 151.61, 155.60 (d, *J* = 242.4 Hz), 157.15, 160.27, 161.18, 167.98; HRMS (ESI) *m/z* [M+H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>18</sub>F<sub>4</sub>N<sub>6</sub>O 471.1551 found 471.1534.

1-(5-(4-amino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-methoxypyridin-2-yl)ethan-1-one (**23**) General procedure C with 5-(2,3-dihydro-1*H*-indol-5-yl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride **17** (0.19 g, 0.53 mmol) and 2-(pyridin-4-yl)acetic acid (0.09 g, 0.58 mmol) to obtain 1-(5-(4-amino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-methoxypyridin-2-yl)ethan-1-one (0.180 g, 0.416 mmol, 78 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.23 (t, *J* = 8.4 Hz, 2H), 3.74 (s, 3H), 3.82 (s, 3H), 3.98 (s, 2H), 4.31 (t, *J* = 8.5 Hz, 2H), 6.02 (s, 2H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.39 (dd, *J* = 3.0, 8.6 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 8.14 (s, 1H), 8.22 (d, *J* = 2.9 Hz, 1H); <sup>13</sup>C NMR

(101 MHz, DMSO-  $d_6$ )  $\delta$  24.45, 31.22, 44.55, 49.09, 56.01, 101.23, 107.48, 112.61 – 112.63 (m), 117.44 (d,  $J$  = 14.9 Hz), 119.29 (d,  $J$  = 23.0 Hz), 121.70, 124.99, 125.67, 131.32 (d,  $J$  = 2.6 Hz), 145.03 (d,  $J$  = 8.1 Hz), 147.72, 150.63, 152.11, 154.65, 156.02 (d,  $J$  = 243.0 Hz). 157.63, 169.30; HRMS (ESI)  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>21</sub>FN<sub>6</sub>O<sub>2</sub> 433.1783, found 433.1773.

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-cyclopropylpyridin-2-yl)ethan-1-one* (**24**). General procedure C with 5-(4-fluoroindolin-5-yl)-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride **17** (0.100 g, 0.281 mmol) and 2-(5-cyclopropylpyridin-2-yl)acetic acid **44** (0.060 g, 0.337 mmol), to obtain 1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-cyclopropylpyridin-2-yl)ethan-1-one (0.028 g, 0.063 mmol, 23 % yield). <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  0.64 – 0.77 (m, 2H), 0.93 – 1.04 (m, 2H), 1.93 (ddd,  $J$  = 5.2, 8.7, 13.5 Hz, 1H), 3.22 (t,  $J$  = 8.4 Hz, 2H), 3.73 (s, 3H), 3.98 (s, 2H), 4.31 (t,  $J$  = 8.4 Hz, 2H), 6.04 (s, 2H), 7.12 – 7.30 (m, 3H), 7.39 (dd,  $J$  = 2.5, 8.1 Hz, 1H), 7.90 (d,  $J$  = 8.2 Hz, 1H), 8.13 (s, 1H), 8.33 (d,  $J$  = 2.4 Hz, 1H); <sup>13</sup>C NMR (101 MHz, DMSO- $d_6$ )  $\delta$  9.64, 12.83, 24.44, 31.23, 45.07, 49.13, 101.22, 107.51, 112.49 – 112.78 (m), 116.24, 117.43 (d,  $J$  = 15.0 Hz), 124.20, 125.71 (t,  $J$  = 2.1 Hz), 127.40 (d,  $J$  = 7.4 Hz), 131.31 (t,  $J$  = 2.7 Hz), 133.17, 137.70, 147.56, 150.60, 152.03, 152.77, 157.57, 169.15; HRMS (ESI)  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>25</sub>H<sub>23</sub>FN<sub>6</sub>O 443.1990, found 443.1982.

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-(tert-butyl)pyridin-2-yl)ethan-1-one* (**25**) General procedure C with 5-(2,3-dihydro-1H-indol-5-yl)-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride **17** (0.040 g, 0.112 mmol) and 2-(5-(tert-butyl)pyridin-2-yl)acetic acid **41** (0.038 g, 0.124 mmol) to obtain 1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-(tert-butyl)pyridin-2-yl)ethan-1-one (0.012 g, 0.025 mmol, 23 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.33 (s, 9H), 3.27 (t,  $J$  = 8.42 Hz, 2H), 3.83 (s, 3H), 3.99 (s, 2H), 4.36 (t,  $J$  = 8.48 Hz, 2H), 5.15 (br.s, 2H), 6.97 (s, 1H), 7.23 (t,  $J$  = 7.99 Hz, 1H), 7.33 (d,  $J$  = 8.20 Hz, 1H), 7.68 (dd,  $J$  = 2.44, 8.16 Hz, 1H), 8.09 (d,  $J$  = 8.28 Hz, 1H), 8.32 (s, 1H), 8.59 (d,  $J$  = 2.08 Hz, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  24.64, 31.10, 31.56, 33.58, 45.64, 49.33, 101.48, 108.62, 113.47 (d,  $J$  = 2.99 Hz), 117.00 (d,  $J$  = 13.74 Hz), 118.92 (d,  $J$  = 23.08 Hz), 123.42, 125.90 (d,  $J$  = 1.94 Hz), 131.17, 134.21, 144.67, 145.06, 147.07, 149.65, 150.24, 151.68, 154.80, 155.89, 168.91; HRMS (ESI)  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>26</sub>H<sub>27</sub>FN<sub>6</sub>O 459.2303, found 459.2306.

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-hydroxypyridin-2-yl)ethan-1-one (26)* To a solution of **23** (0.100 g, 0.231 mmol) in anhydrous DCM (5 ml) was added borontribromide 17 % DCM solution (0.694 ml, 0.694 mmol) dropwise at 0 °C under nitrogen atmosphere. The reaction was stirred for 3 days at 0°C. The cooled mixture was diluted with water and saturated aqueous NaHCO<sub>3</sub>, (10 ml) extracted with EtOAc (3 x 15 ml) and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was purified by silica flash column chromatography (10% MeOH in DCM) to obtain 1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-hydroxypyridin-2-yl)ethan-1-one (0.035 g, 0.084 mmol, 36 % yield) <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.22 (t, *J* = 8.5 Hz, 2H), 3.74 (s, 3H), 3.91 (s, 2H), 4.30 (t, *J* = 8.5 Hz, 2H), 6.02 (s, 2H), 7.09 – 7.22 (m, 3H), 7.26 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 8.05 (d, *J* = 2.7 Hz, 1H), 8.14 (s, 1H), 9.79 (s, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 24.44, 31.22, 44.64, 49.07, 101.23, 107.50, 112.62 (d, *J* = 8.1 Hz), 117.41 (d, *J* = 14.7 Hz), 119.29 (d, *J* = 23.1 Hz), 123.26, 124.94, 125.68, 131.32 (d, *J* = 2.8 Hz), 137.49, 145.06 (d, *J* = 8.0 Hz), 146.08, 150.63, 152.10, 152.79, 157.23, 157.63, 169.45.; HRMS (ESI) *m/z* [M+H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>19</sub>FN<sub>6</sub>O<sub>2</sub> 419.1626, found 419.1627.

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(pyridin-4-yl)ethan-1-one (27)* General procedure C with 5-(2,3-dihydro-1H-indol-5-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine dihydrochloride **17** (0.100 g, 0.280 mmol) and 2-(pyridin-4-yl)acetic acid **46** (0.040 g, 0.280 mmol) to obtain 1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(pyridin-4-yl)ethan-1-one (0.078 g, 0.194 mmol, 69 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.18 – 3.30 (m, 2H), 3.73 (s, 3H), 3.95 (s, 2H), 4.19 – 4.38 (m, 2H), 6.03 (s, 2H), 7.12 – 7.38 (m, 4H), 7.91 (d, *J* = 8.1 Hz, 1H), 8.14 (s, 1H), 8.47 – 8.58 (m, 2H); <sup>13</sup>C NMR (101 MHz, DMSO *d*<sub>6</sub>) δ 24.47, 31.23, 41.61, 48.95, 101.21, 107.41, 112.62 (d, *J* = 3.5 Hz) 117.58 (d, *J* = 15.1 Hz), 119.33 (d, *J* = 22.9 Hz), 125.73, 131.37 (d, *J* = 3.5 Hz), 144.43, 144.89 (d, *J* = 8.2 Hz), 149.87, 150.62, 152.11, 154.81, 156.02 (d, *J* = 243.1 Hz), 168.62; HRMS (ESI) *m/z* [M+H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>19</sub>FN<sub>6</sub>O 403.1677, found 403.1658.

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-benzylpyridin-2-yl)ethan-1-one (28)* General procedure C with 5-(2,3-dihydro-1H-indol-5-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine dihydrochloride **17** (0.107 g, 0.300 mmol) and 2-(5-benzylpyridin-2-yl)acetic acid **42** (0.075 g, 0.221 mmol) to obtain 1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-benzylpyridin-2-yl)ethan-1-one (0.098 g, 0.200 mmol, 67 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.26 (t, *J* = 8.36 Hz, 2H), 3.86 (s, 3H), 3.96 (s, 2H), 3.99 (s, 2H),

4.34 (t,  $J = 8.46$  Hz, 2H), 6.09 (br.s, 2H), 7.04 (s, 1H), 7.16 – 7.23 (m, 4H), 7.27 – 7.32 (m, 2H), 7.48 (dd,  $J = 2.16, 7.99$  Hz, 1H), 8.07 (d,  $J = 8.22$  Hz, 1H), 8.26 (s, 1H), 8.42 (d,  $J = 1.47$  Hz, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  24.61, 31.73, 38.82, 45.66, 49.32, 101.19, 109.42, 113.56 (d,  $J = 3.23$  Hz), 116.36 (d,  $J = 12.91$  Hz), 119.07 (d,  $J = 24.29$  Hz), 123.97, 126.48, 126.66, 128.82, 128.98, 131.08, 135.33, 137.47, 139.72, 145.38 (d,  $J = 8.20$  Hz), 147.30, 149.54, 149.74, 152.49, 154.79, 157.16, 168.83; HRMS (ESI)  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{29}\text{H}_{25}\text{FN}_6\text{O}$  493.2147, found 493.2154.

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-phenylpyridin-2-yl)ethan-1-one (29)*. General procedure C with 5-(4-fluoroindolin-5-yl)-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride **17** (0.100 g, 0.281 mmol) and 2-(5-phenylpyridin-2-yl)acetic acid **47** (0.072 g, 0.337 mmol) to obtain 1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(5-phenylpyridin-2-yl)ethan-1-one (0.055 g, 0.115 mmol, 41 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  3.25 (t,  $J = 8.4$  Hz, 2H), 3.73 (s, 3H), 4.11 (s, 2H), 4.36 (t,  $J = 8.4$  Hz, 2H), 6.04 (br. s, 2H), 7.19 (t,  $J = 8.0$  Hz, 1H), 7.26 (s, 1H), 7.38 – 7.56 (m, 4H), 7.69 – 7.77 (m, 2H), 7.93 (d,  $J = 8.2$  Hz, 1H), 8.07 (dd,  $J = 2.5, 8.1$  Hz, 1H), 8.13 (s, 1H), 8.82 (d,  $J = 2.1$  Hz, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  24.02, 30.79, 44.69, 48.73, 100.78, 107.03, 112.21 (d,  $J = 3.0$  Hz), 117.08 (d,  $J = 15.0$  Hz), 118.92 (d,  $J = 23.1$  Hz), 124.36, 125.25, 126.81, 128.07, 129.17, 130.91 (d,  $J = 2.0$  Hz), 133.77, 134.66, 136.99, 144.53 (d,  $J = 8.3$  Hz), 147.07, 150.18, 151.67, 154.38, 155.23 (d,  $J = 244.6$  Hz), 157.19, 168.55; HRMS (ESI)  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{28}\text{H}_{23}\text{FN}_6\text{O}$  479.1990, found 479.1976.

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(4-fluorophenyl)ethan-1-one (30)* General procedure C with 5-(2,3-dihydro-1H-indol-5-yl)-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride **17** (0.06 g, 0.17 mmol) and 2-(4-fluorophenyl)acetic acid (0.060 g, 0.190 mmol) to obtain 1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(4-fluorophenyl)ethan-1-one (0.012 g, 0.029 mmol, 17 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  3.24 (t,  $J = 7.8$  Hz, 2H), 3.73 (s, 3H), 3.88 (s, 2H), 4.29 (t,  $J = 8.5$  Hz, 2H), 6.02 (s, 2H), 7.12 – 7.22 (m, 3H), 7.26 (s, 1H), 7.33 (t,  $J = 7.2$  Hz, 2H), 7.92 (d,  $J = 8.3$  Hz, 1H), 8.13 (s, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  24.47, 31.22, 41.49, 48.89, 101.22, 107.46, 112.60 (d,  $J = 3.7$  Hz), 115.43 (d,  $J = 21.2$  Hz), 117.44 (d,  $J = 14.3$  Hz), 119.23 (d,  $J = 23.1$  Hz), 125.68, 129.59, 131.34 (d,  $J = 2.6$  Hz), 131.58 (d,  $J = 3.1$  Hz), 131.98 (d,  $J = 8.0$  Hz), 145.05 (d,  $J = 8.0$  Hz), 150.61, 152.10, 156.02

(d,  $J = 242.5$  Hz), 157.62, 160.37, 162.78, 169.69; HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{23}H_{19}F_2N_5O$  420.1630, found 420.1642.

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(4-chlorophenyl)ethan-1-one (31)* General procedure C with 5-(2,3-dihydro-1H-indol-5-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine dihydrochloride **17** (0.060 g, 0.170 mmol) and 2-(4-chlorophenyl)acetic acid (0.030 g, 0.190 mmol) to obtain 1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(4-chlorophenyl)ethan-1-one (0.025 g, 0.057 mmol, 34 % yield).  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.09 – 3.25 (m, 2H), 3.72 (s, 3H), 3.89 (s, 2H), 4.17 – 4.40 (m, 2H), 6.01 (br.s, 2H), 7.09 – 7.49 (m, 6H), 7.84 – 7.97 (m, 1H), 8.13 (s, 1H);  $^{13}C$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  24.47, 31.23, 41.64, 48.90, 101.22, 107.43, 112.60 (d,  $J = 2.9$  Hz), 117.47 (d,  $J = 15.0$  Hz), 119.26 (d,  $J = 23.1$  Hz), 125.68, 128.65, 131.35 (d,  $J = 2.6$  Hz), 131.76, 132.05, 134.50, 145.01 (d,  $J = 8.1$  Hz), 150.61, 152.11, 156.01 (d,  $J = 242.8$  Hz), 157.62, 169.44; HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{23}H_{19}ClFN_5O$  436.1335, found 436.1335.

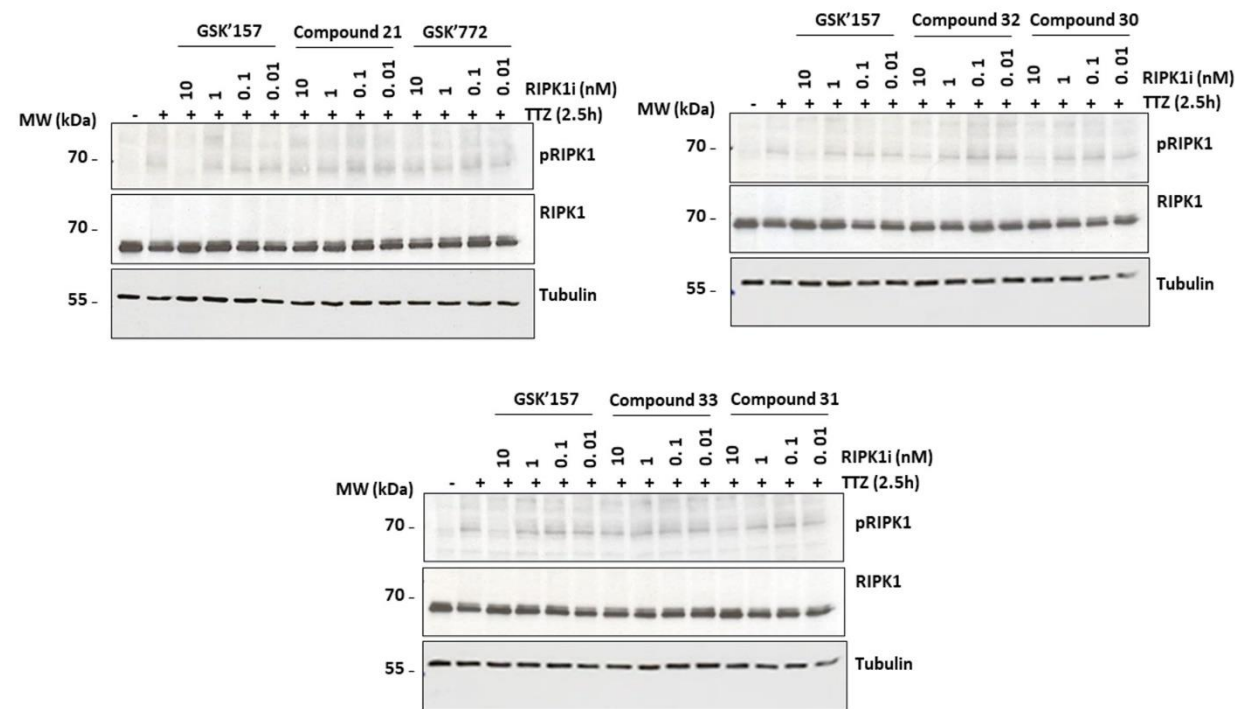
*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(4-bromophenyl)ethan-1-one (32)* General procedure C with 5-(2,3-dihydro-1H-indol-5-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine dihydrochloride **17** (0.060 g, 0.170 mmol) and 2-(4-bromophenyl)acetic acid (0.040 g, 0.190 mmol) to obtain 1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(4-bromophenyl)ethan-1-one (0.180 g, 0.375 mmol, 22 % yield).  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.24 (t,  $J = 8.5$  Hz, 2H), 3.73 (s, 3H), 3.88 (s, 2H), 4.28 (t,  $J = 8.2$  Hz, 2H), 6.01 (br. s, 2H), 7.33 – 7.09 (m, 4H), 7.53 (d,  $J = 7.9$  Hz, 2H), 7.91 (d,  $J = 8.3$  Hz, 1H), 8.14 (s, 1H);  $^{13}C$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  24.47, 31.25, 41.71, 48.90, 101.20, 107.49, 112.00 – 112.96 (m), 117.51, 119.15, 119.36 (d,  $J = 3.6$  Hz), 120.26, 125.56 – 125.85 (m), 131.35 (d,  $J = 2.0$  Hz), 131.57, 132.43, 134.91, 144.46, 151.25 (d,  $J = 140.8$  Hz), 153.65 (d,  $J = 232.3$  Hz), 157.51, 169.37; HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{23}H_{19}BrFN_5O$  480.0830, found 480.0852.

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(p-tolyl)ethan-1-one (33)* General procedure C with 5-(2,3-dihydro-1H-indol-5-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine dihydrochloride **17** (0.06 g, 0.17 mmol) and 2-(p-tolyl)acetic acid (0.030 g, 0.190 mmol) to obtain 1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(p-tolyl)ethan-1-one (0.022g, 0.053 mmol, 31 % yield).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  2.34 (s, 3H), 3.24 (t,  $J = 8.5$  Hz, 2H), 3.79 (s, 2H), 3.86 (s, 3H), 4.18 (t,  $J = 8.5$  Hz, 2H), 5.98 (br. s, 2H), 7.04 (s, 1H), 7.12 – 7.26 (m, 5H), 8.12 (d,  $J = 8.4$  Hz, 1H), 8.28 (s, 1H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  20.90,

24.36, 31.37, 43.02, 48.65, 100.93, 108.93, 113.19 (d,  $J = 3.7$  Hz), 116.10 (d,  $J = 14.7$  Hz), 118.34 (d,  $J = 21.1$  Hz), 125.99 (d,  $J = 2.7$  Hz), 126.00, 128.70, 128.81, 129.38, 130.31, 136.72, 130.85 (d,  $J = 2.1$  Hz), 145.10 – 145.26 (m), 147.49, 149.46, 154.78, 169.47; HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{24}H_{22}FN_5O$  416.1881, found 416.1871.

*1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(4-(trifluoromethyl)phenyl)ethan-1-one (34)* General procedure C with 5-(2,3-dihydro-1*H*-indol-5-yl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dihydrochloride **17** (0.1 g, 0.28 mmol) and 22-(4-(trifluoromethyl)phenyl)acetic acid (0.06 g, 0.281 mmol) to obtain 1-(5-(4-amino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(4-(trifluoromethyl)phenyl)ethan-1-one (0.077 g, 0.164 mmol, 58 % yield).  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.25 (t,  $J = 8.4$  Hz, 2H), 3.73 (s, 3H), 4.02 (s, 2H), 4.31 (t,  $J = 8.4$  Hz, 2H), 6.04 (br. s, 2H), 7.19 (t,  $J = 8.0$  Hz, 1H), 7.26 (s, 1H), 7.52 (d,  $J = 7.9$  Hz, 2H), 7.71 (d,  $J = 7.9$  Hz, 2H), 7.91 (d,  $J = 8.2$  Hz, 1H), 8.14 (s, 1H);  $^{13}C$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  24.47, 31.25, 42.05, 48.91, 101.18, 107.50, 112.60 (d,  $J = 2.4$  Hz), 117.47 (d,  $J = 14.9$  Hz), 119.31 (d,  $J = 23.3$  Hz), 125.49 (q,  $J = 3.5$  Hz), 125.77, 126.24, 127.76 (d,  $J = 31.6$  Hz), 131.12, 131.36 (d,  $J = 1.8$  Hz), 140.45, 144.98 (d,  $J = 8.5$  Hz), 150.55, 151.91, 156.02 (d,  $J = 242.5$  Hz), 157.47, 169.17; HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{24}H_{19}F_4N_5O$  470.1598, found 470.1589.

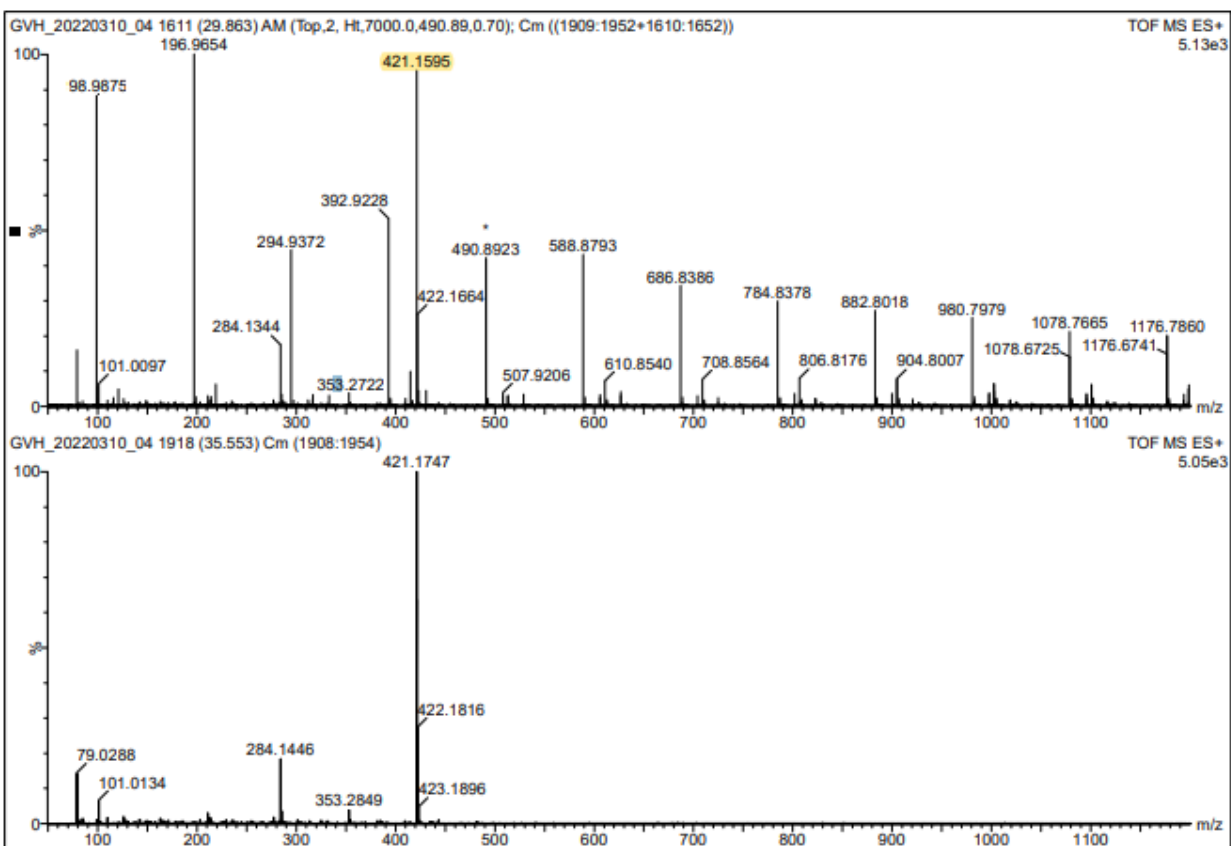
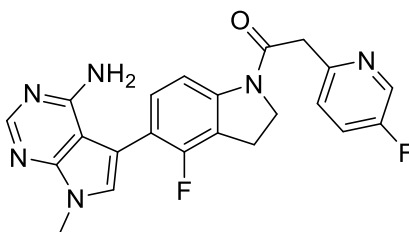
2 Western blot figure of non selective compounds 21, 30-33



**Figure S1.** Western blot to compare GSK'157 with compounds 21 and 30– 33 active on PERK for the prevention of RIPK1 phosphorilation. Immortalized MEFs were pretreated for 30 min with ZVAD-fmk (50 μM), TAK1-inh (1 μM) and the indicated compounds and then stimulated for 2.5 h with hTNF (20 ng/ml).

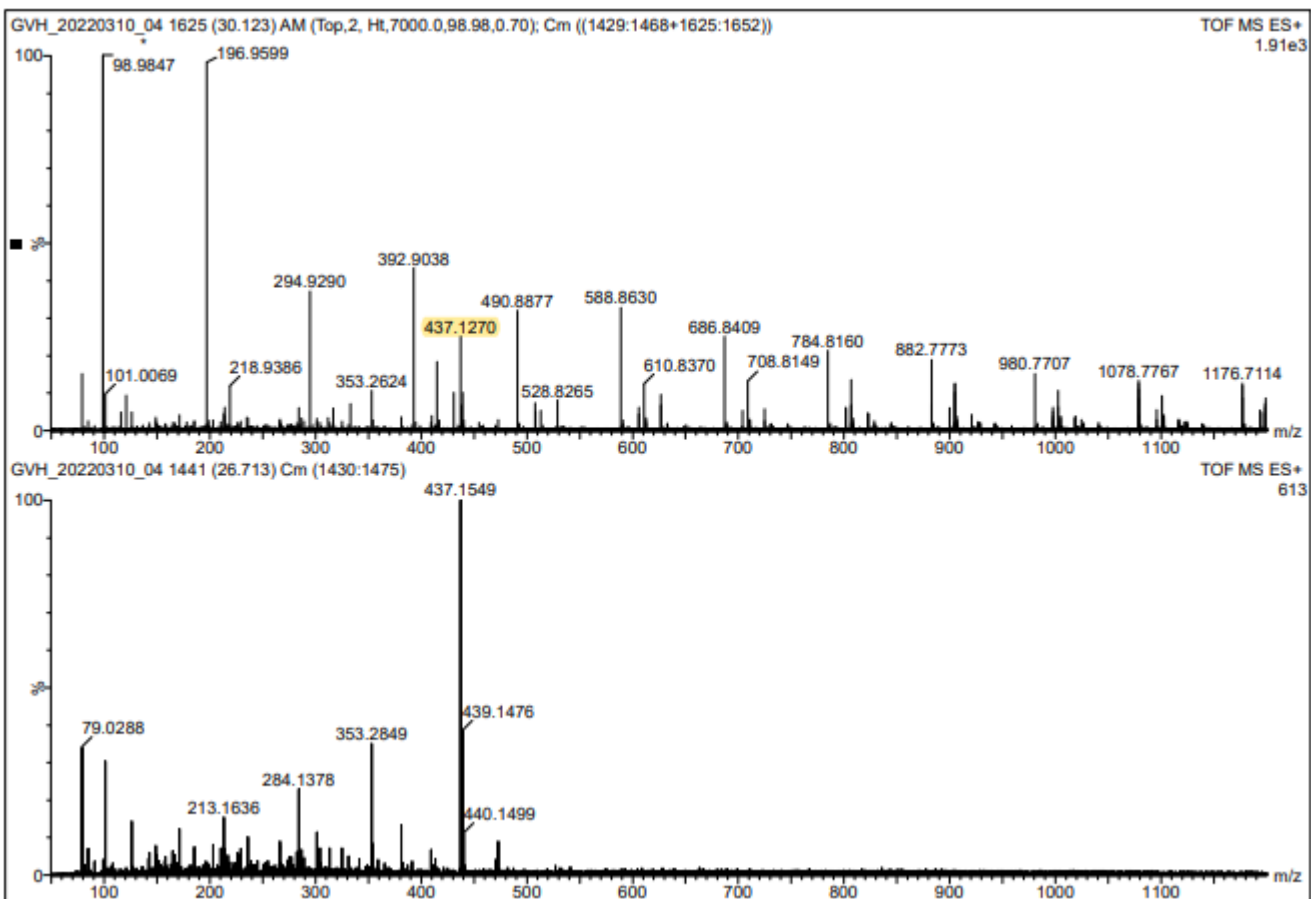
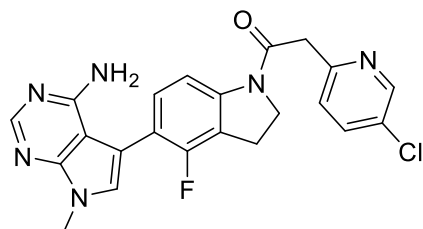
### 3 HRMS spectra

#### Compound 18

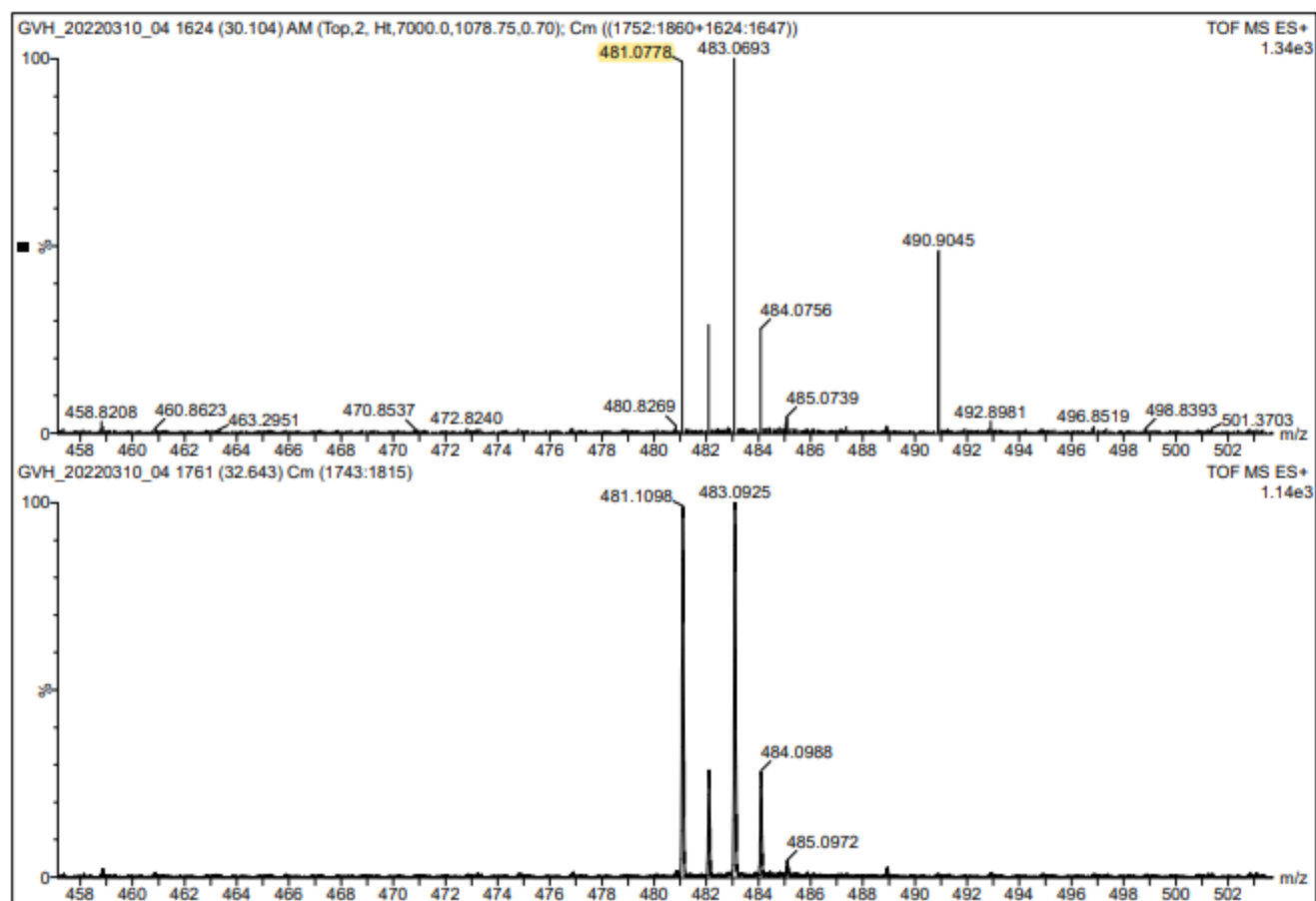
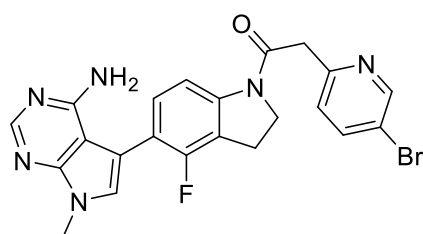




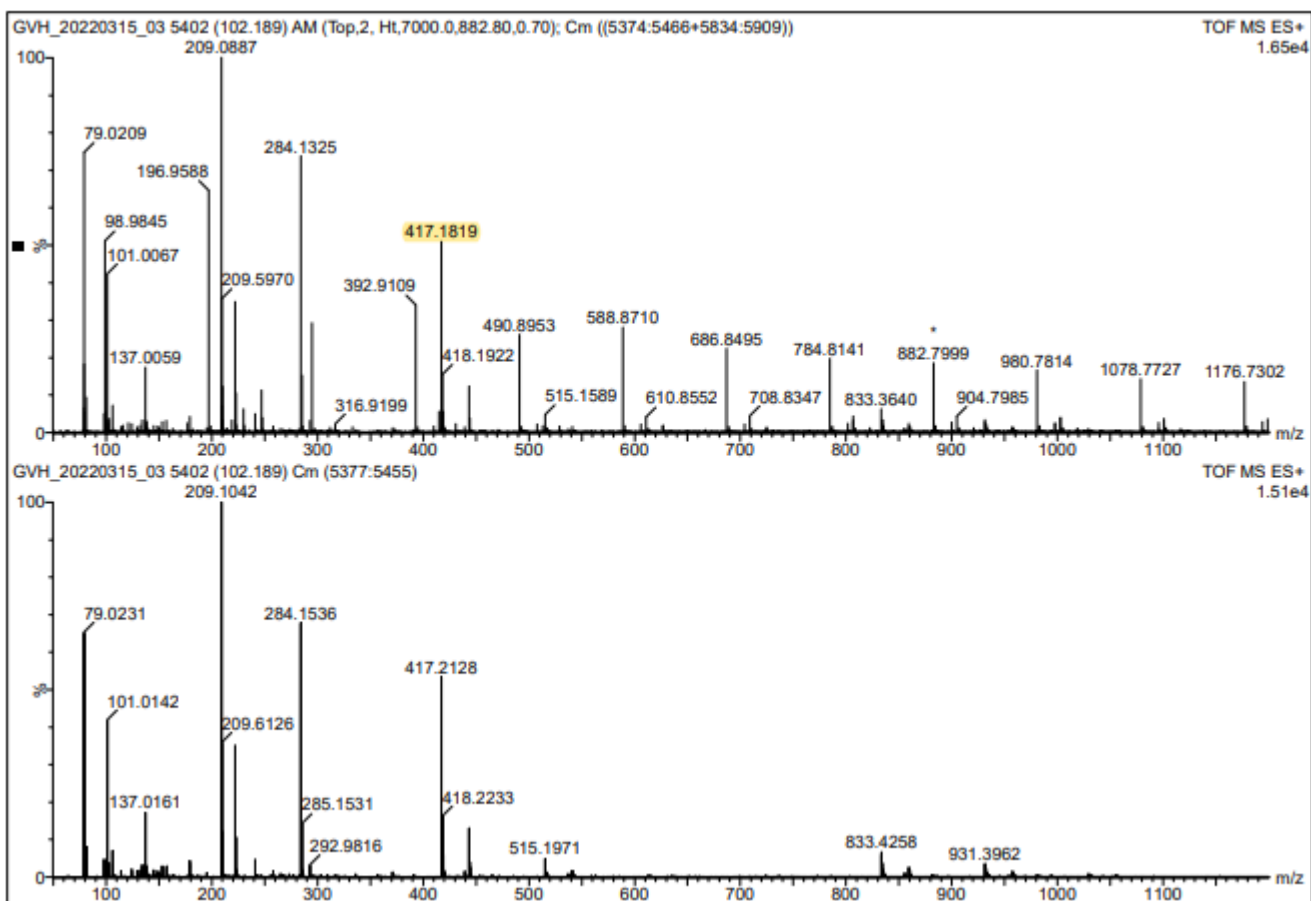
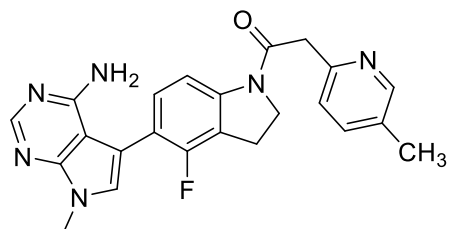
## Compound 19



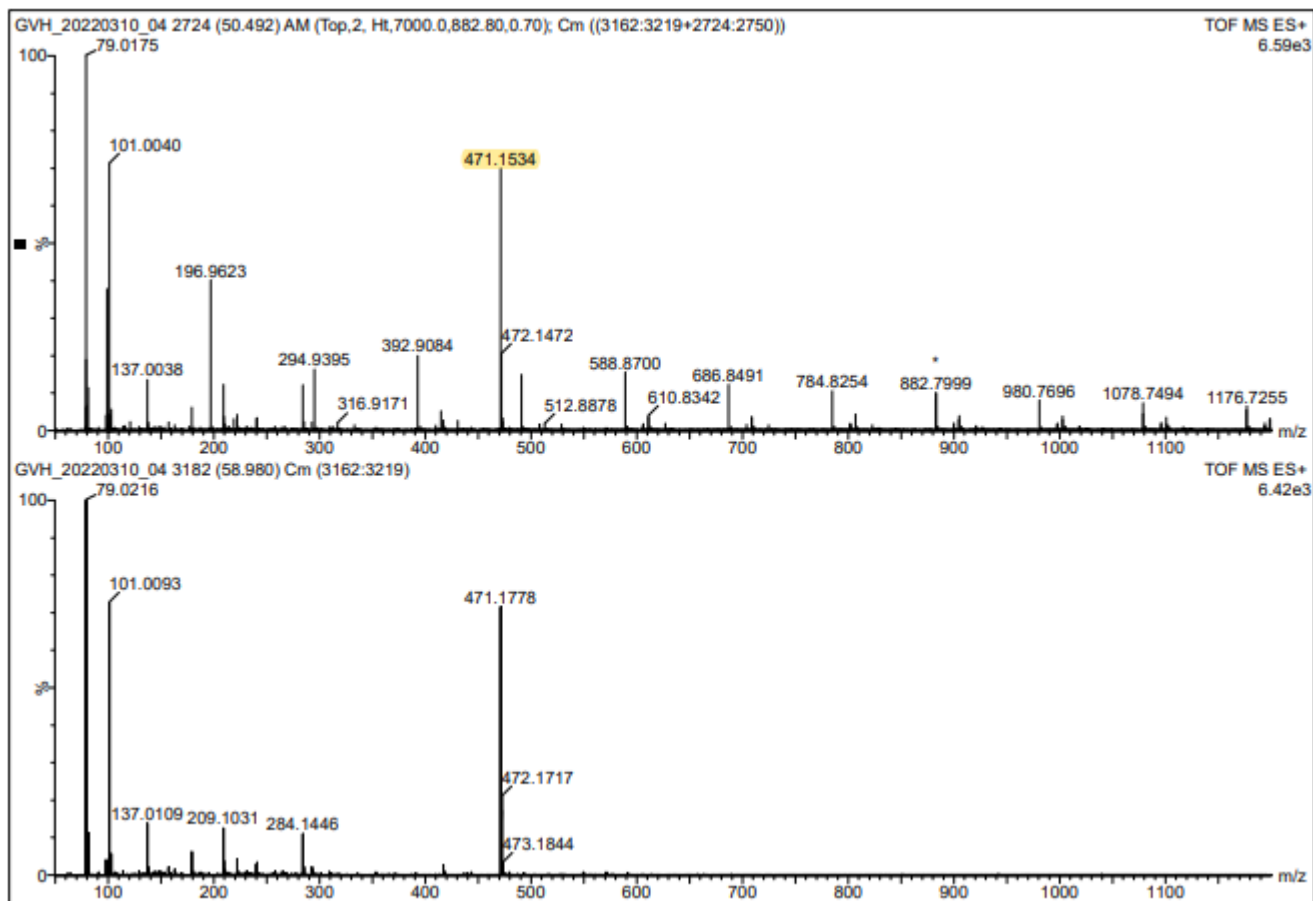
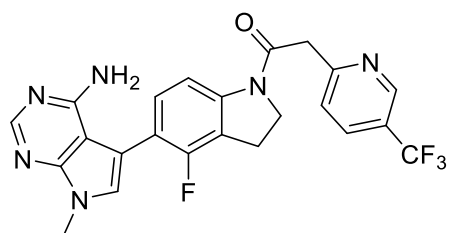
## Compound 20



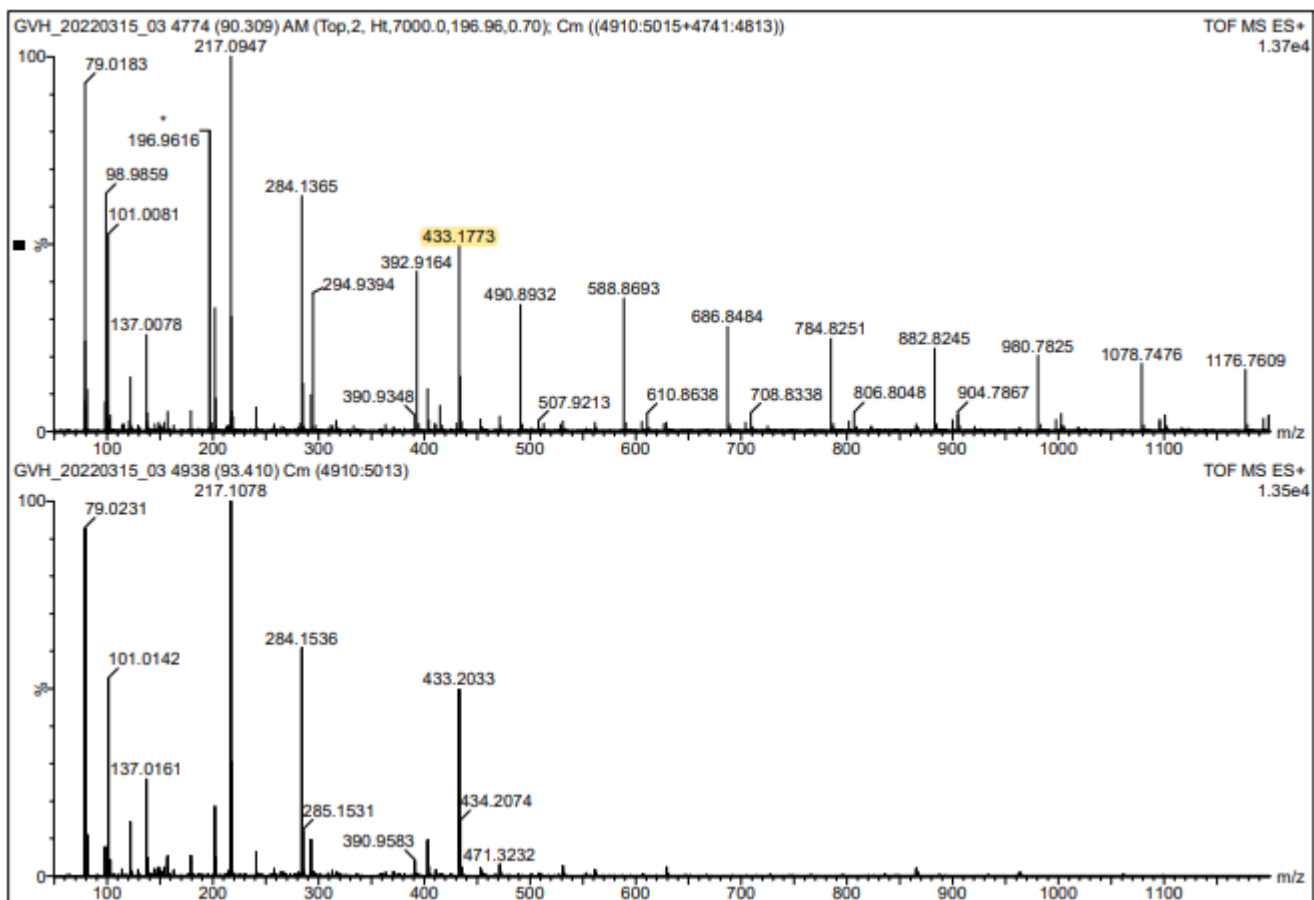
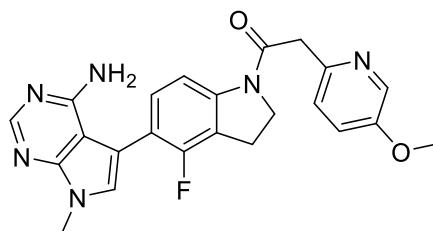
# Compound 21



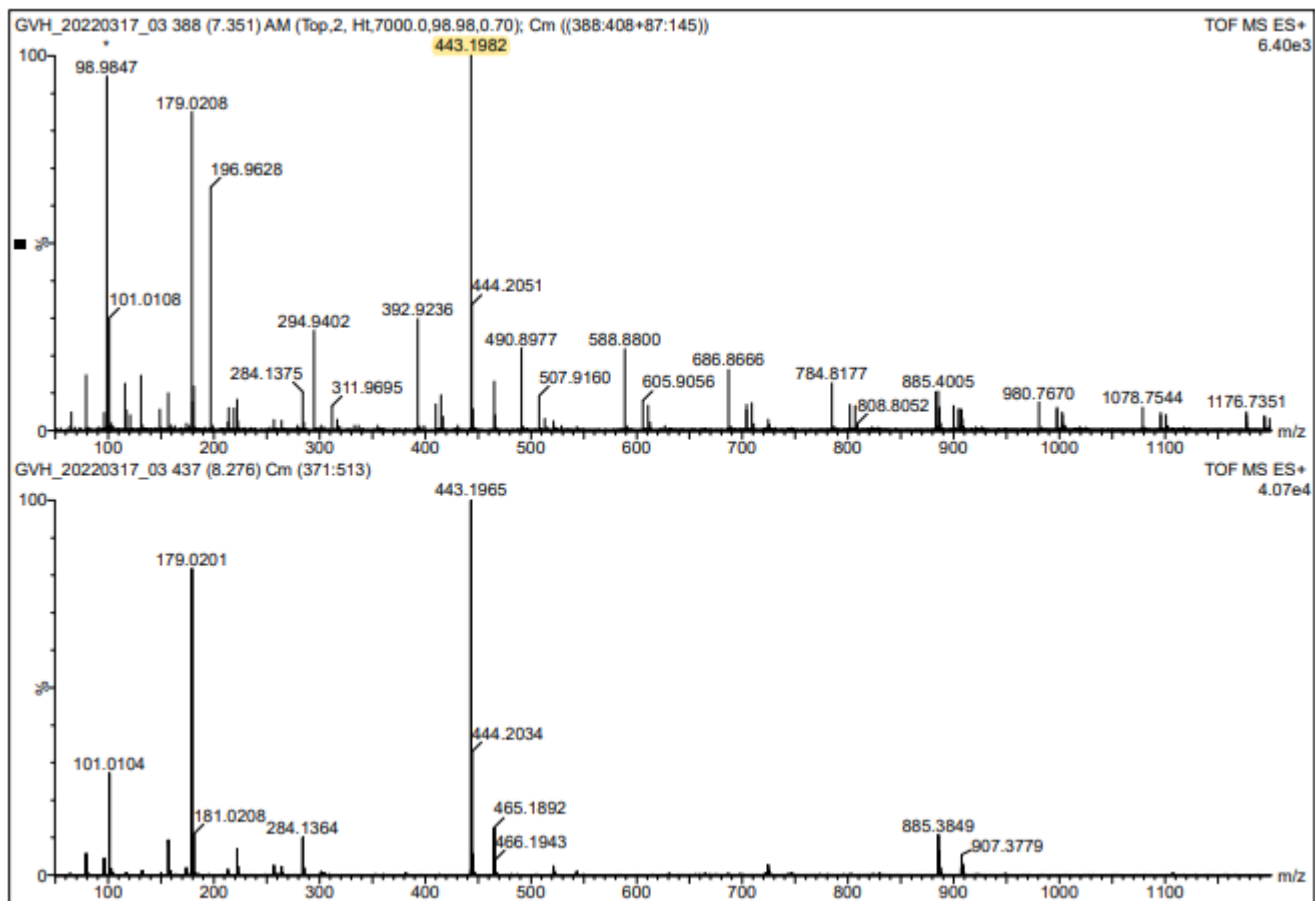
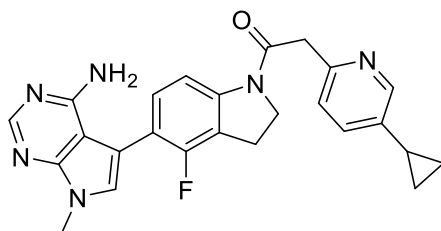
## Compound 22 (UAMC-3861)



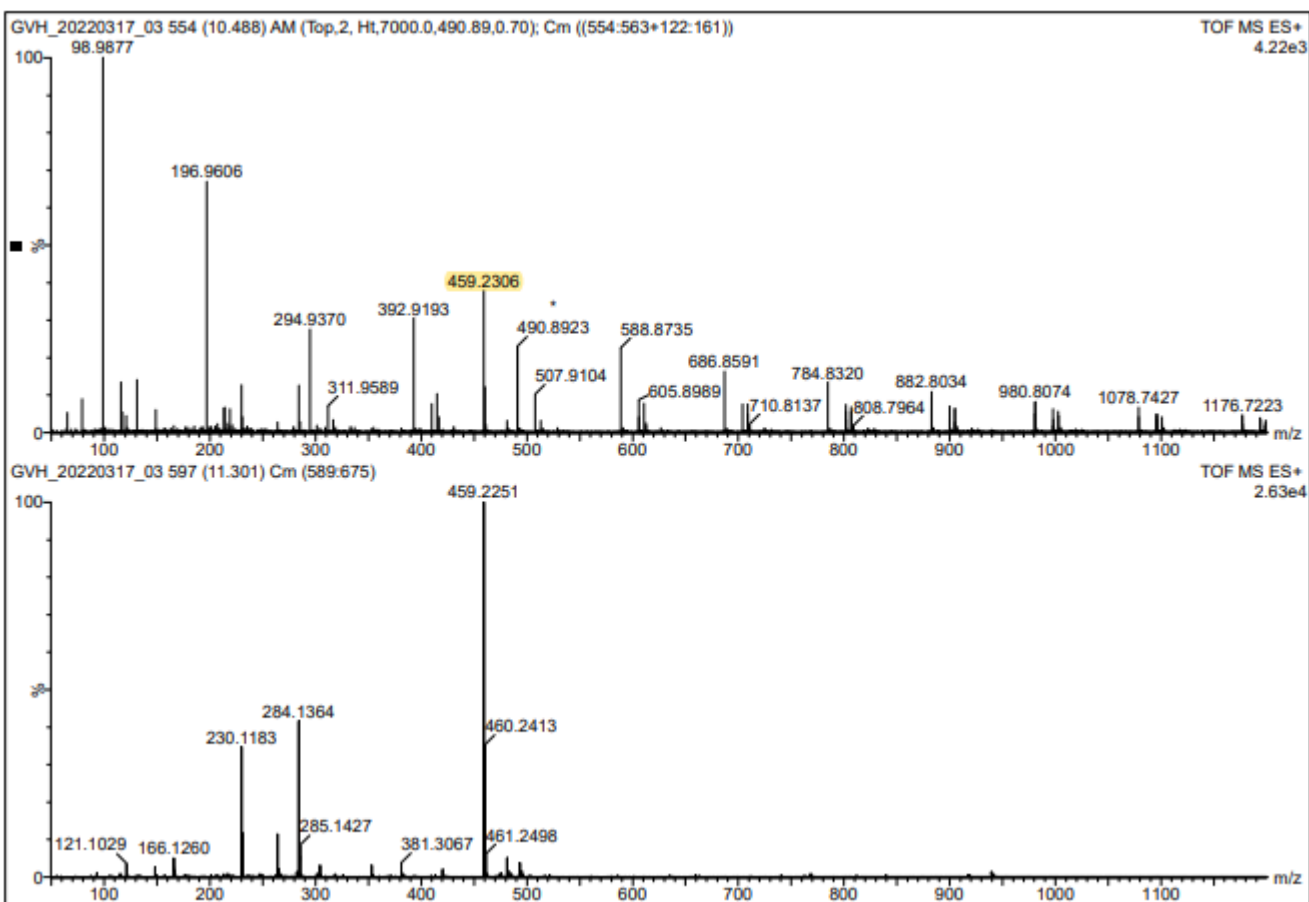
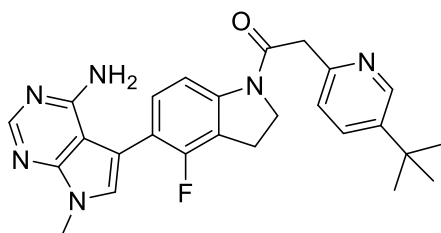
## Compound 23



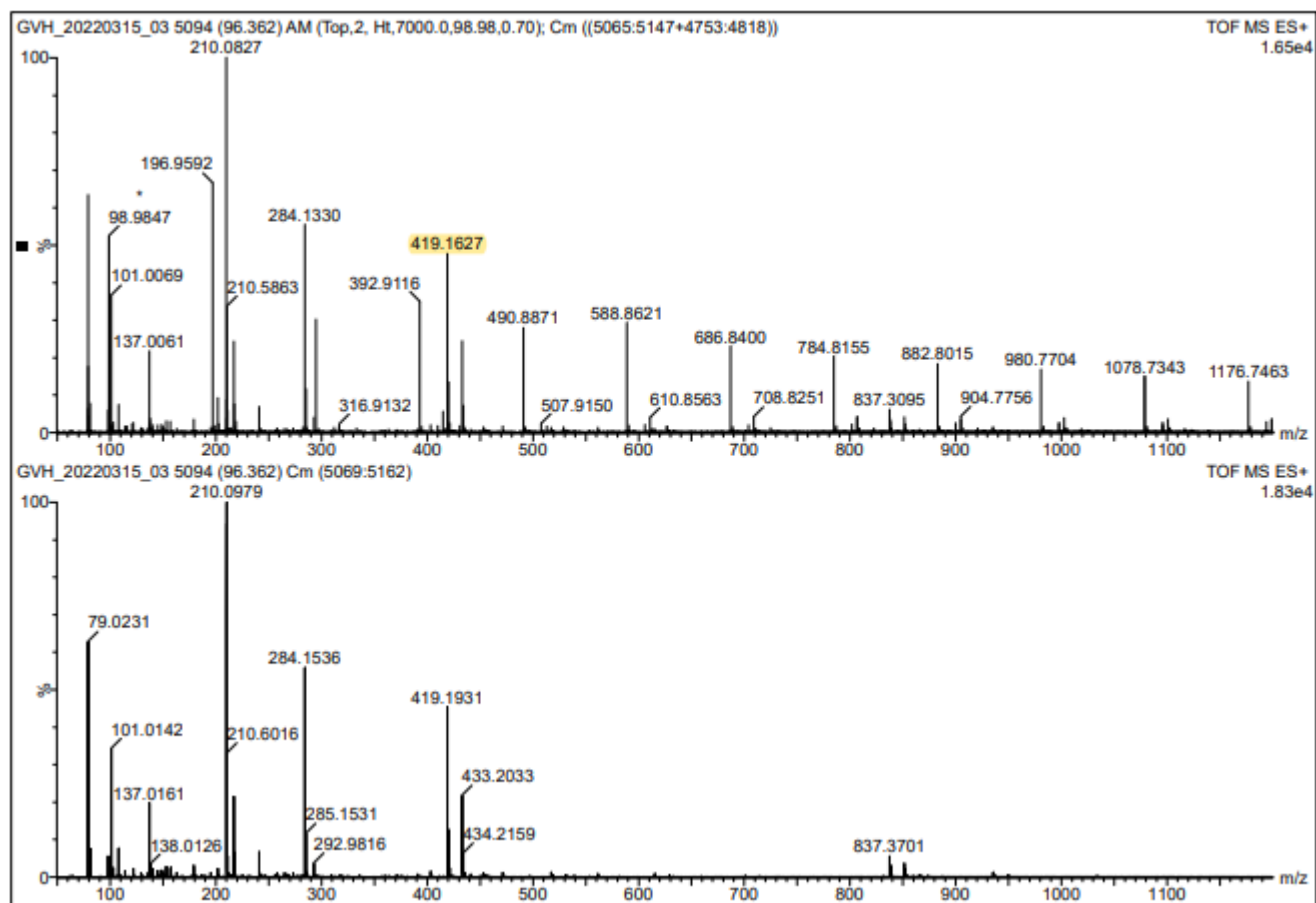
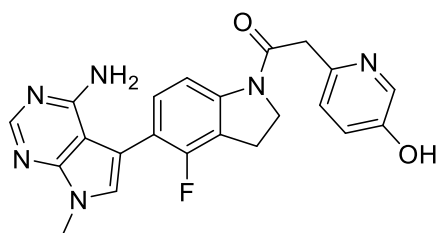
## Compound 24



# Compound 25

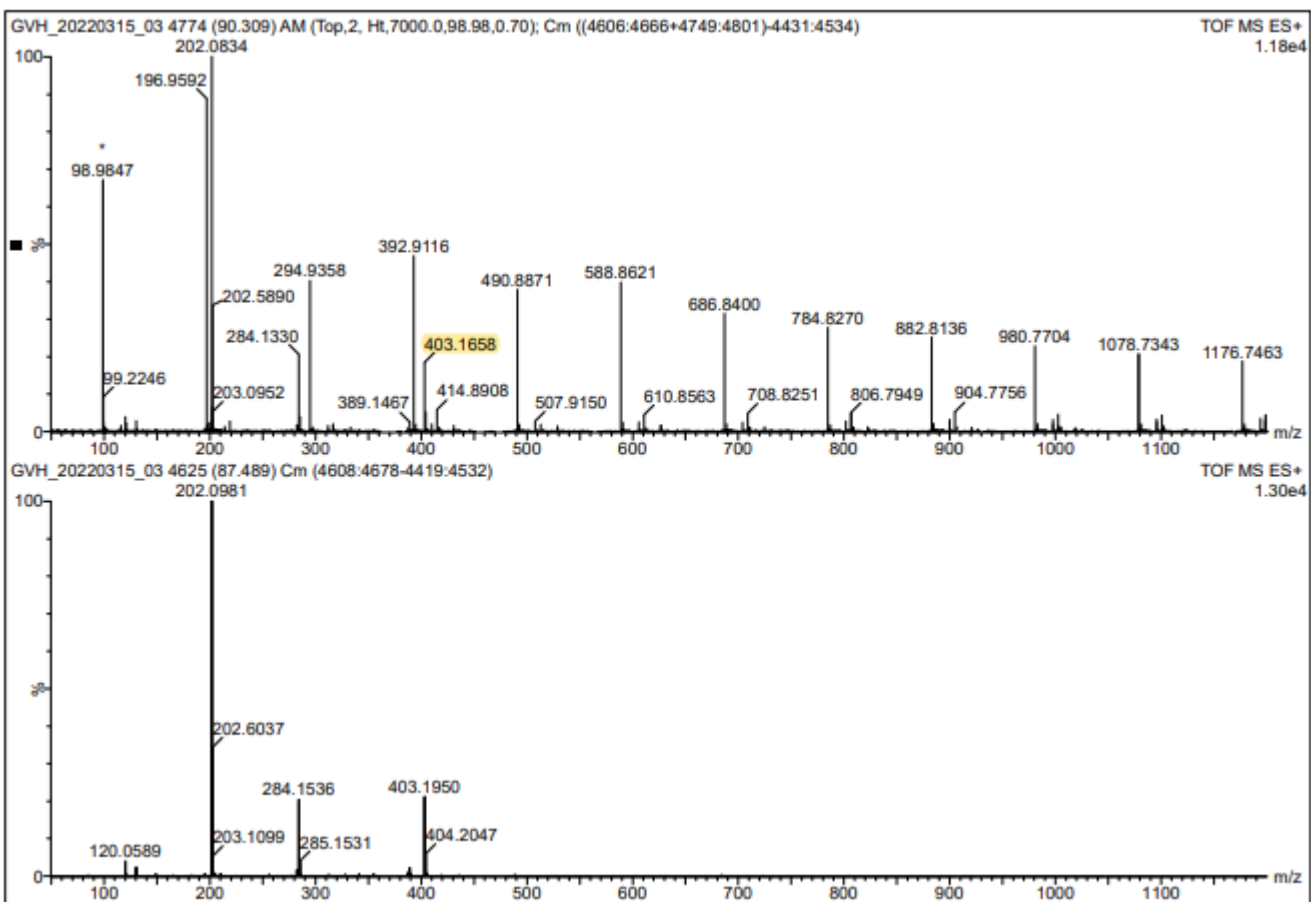
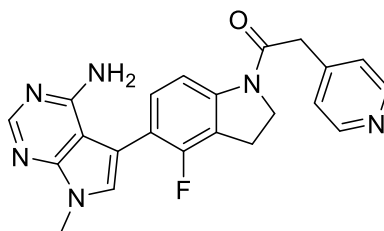


## Compound 26

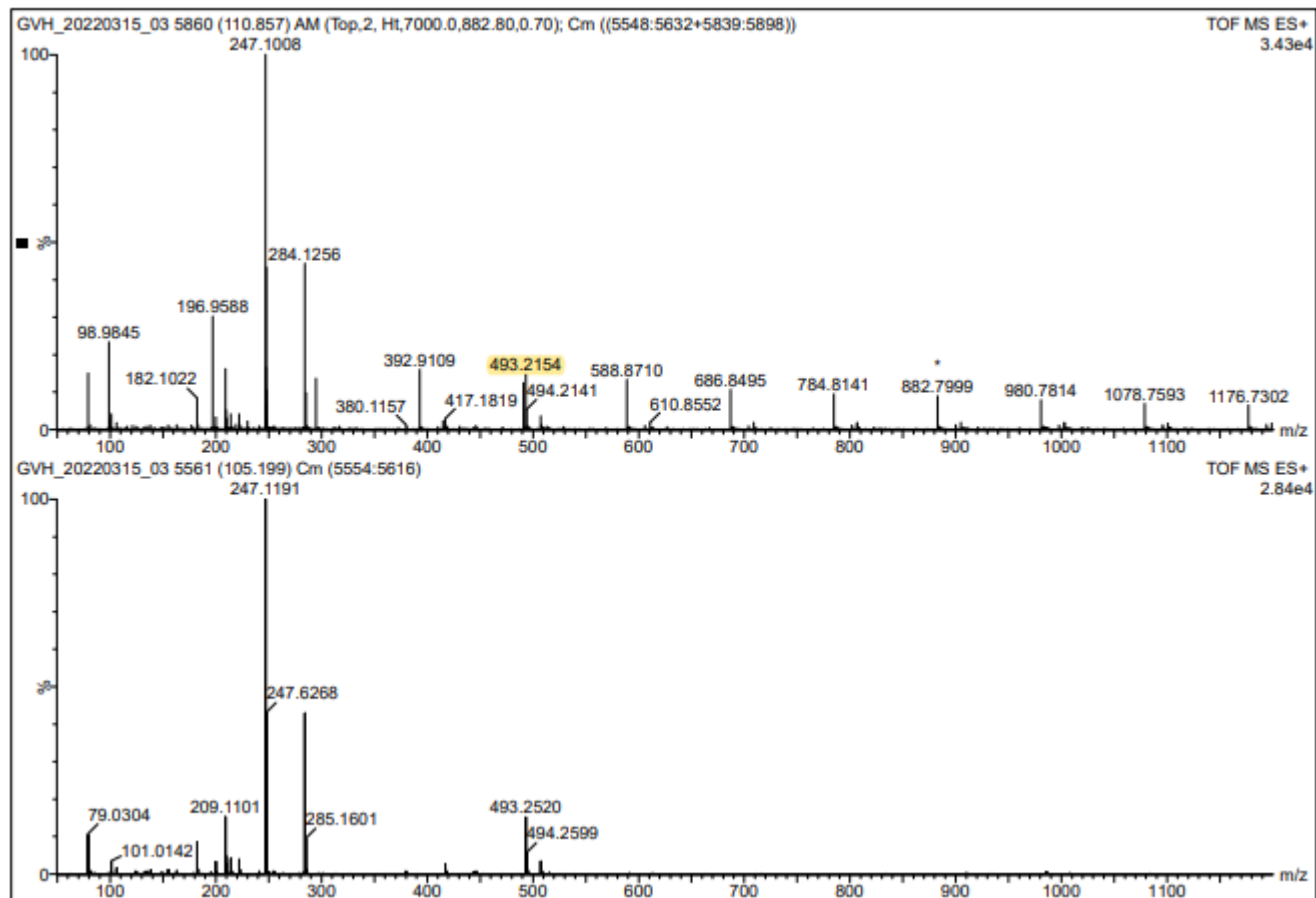
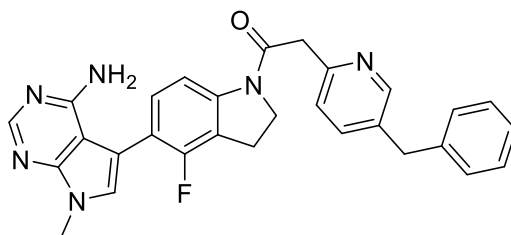




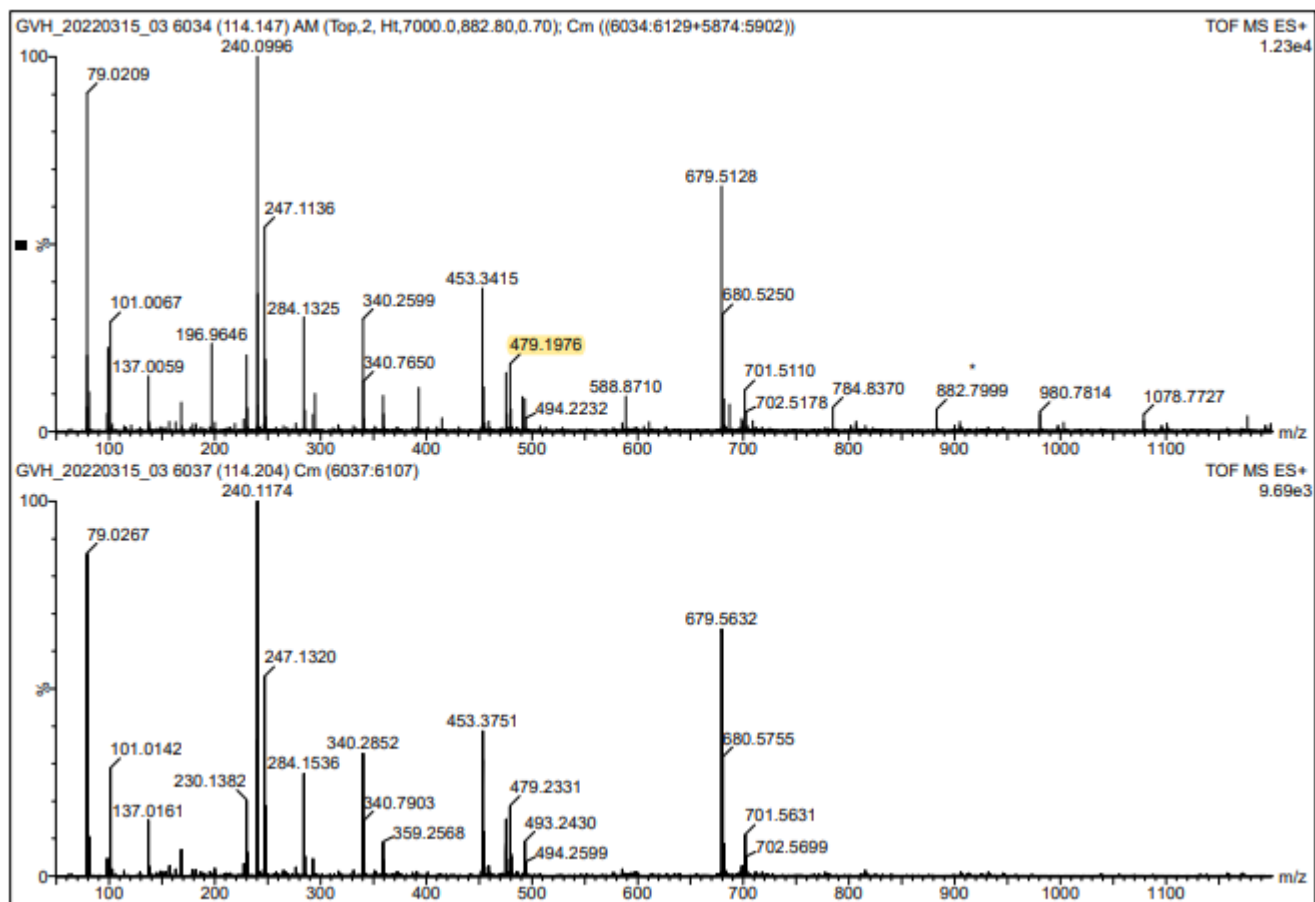
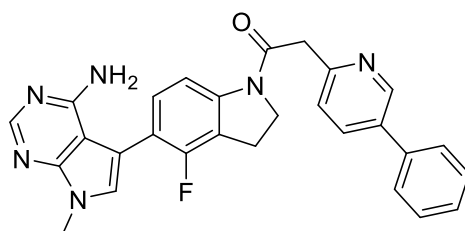
## Compound 27



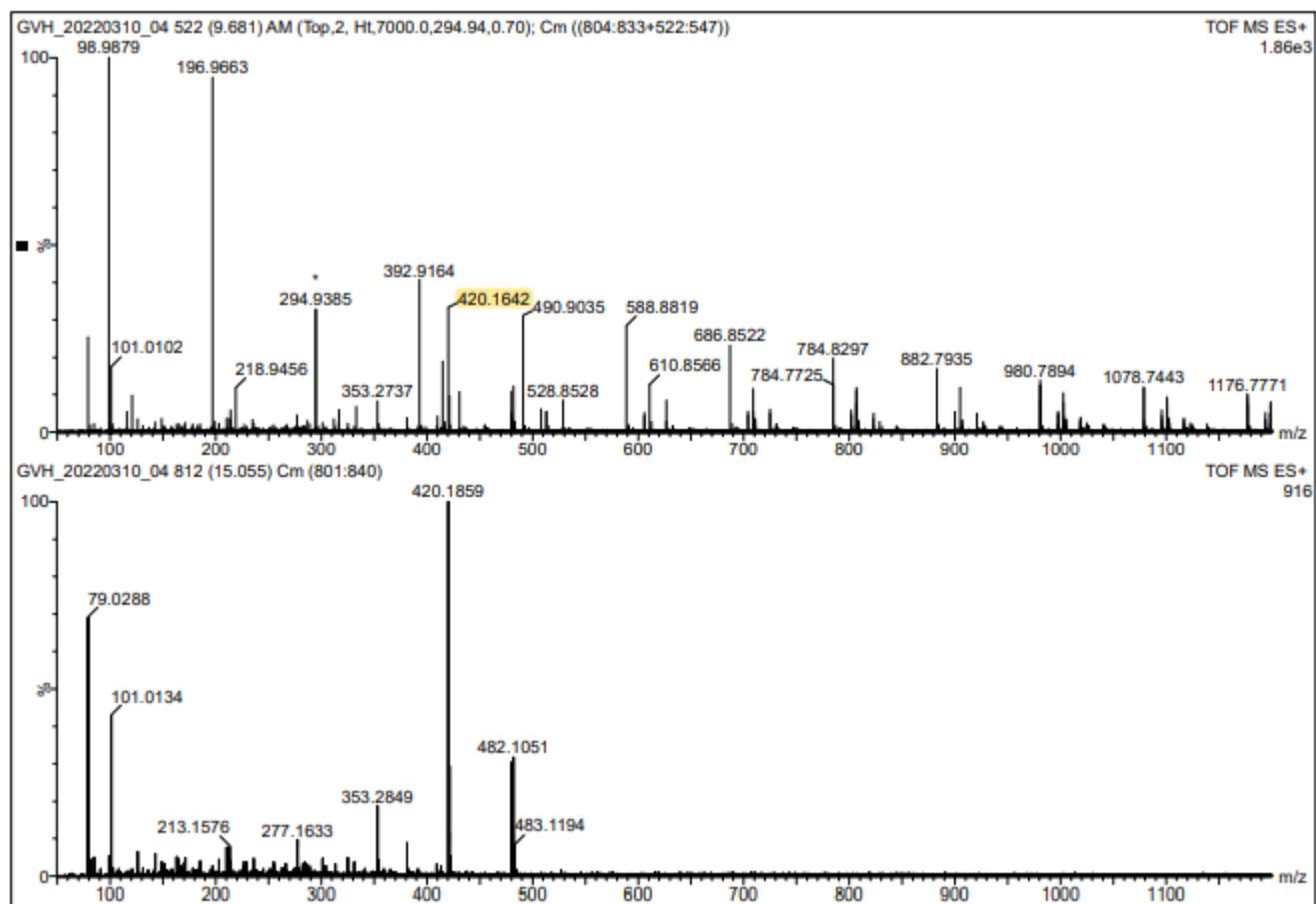
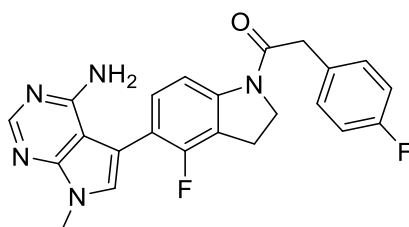
## Compound 28



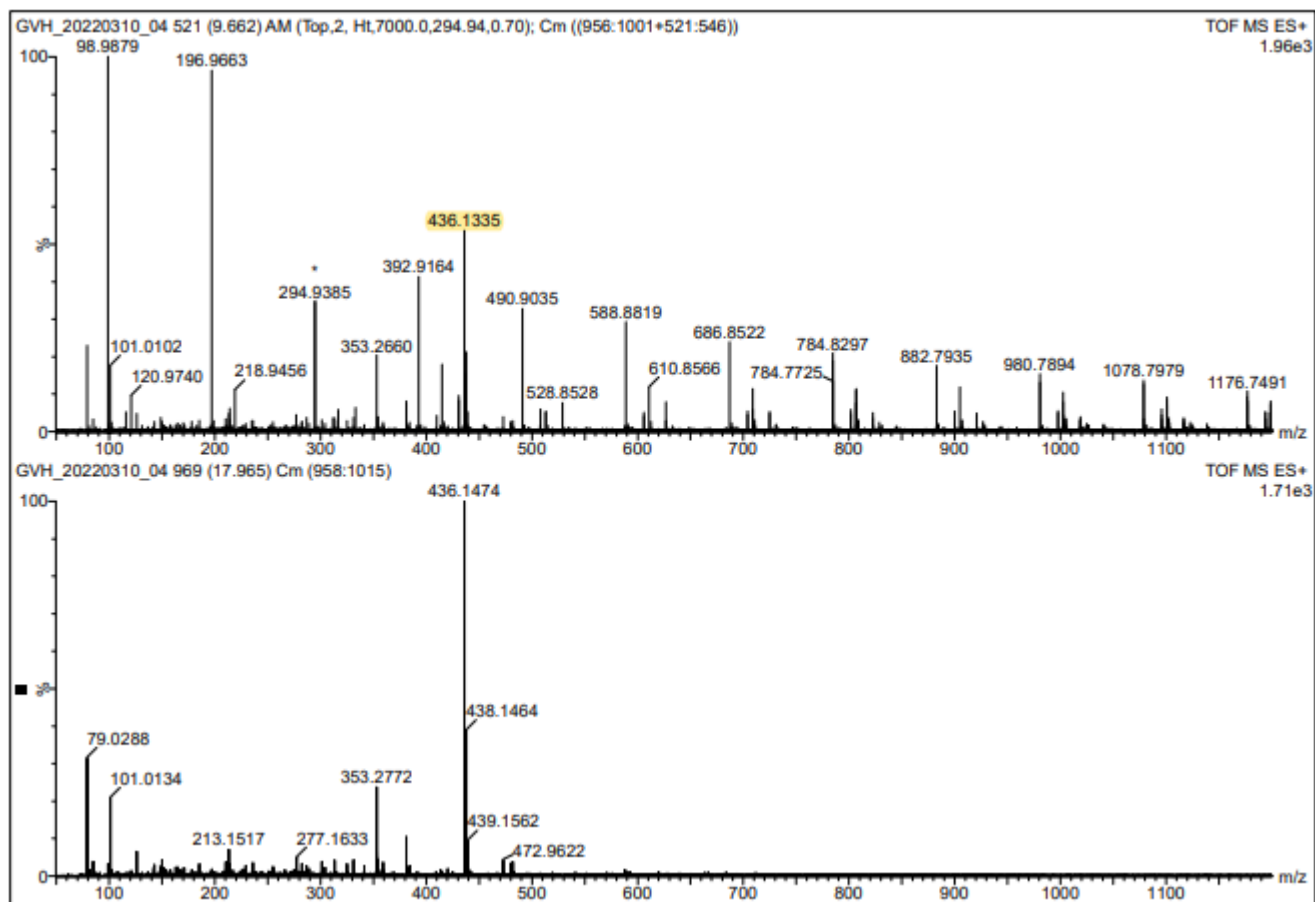
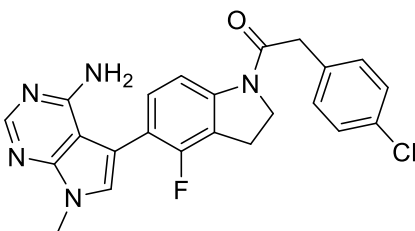
## Compound 29



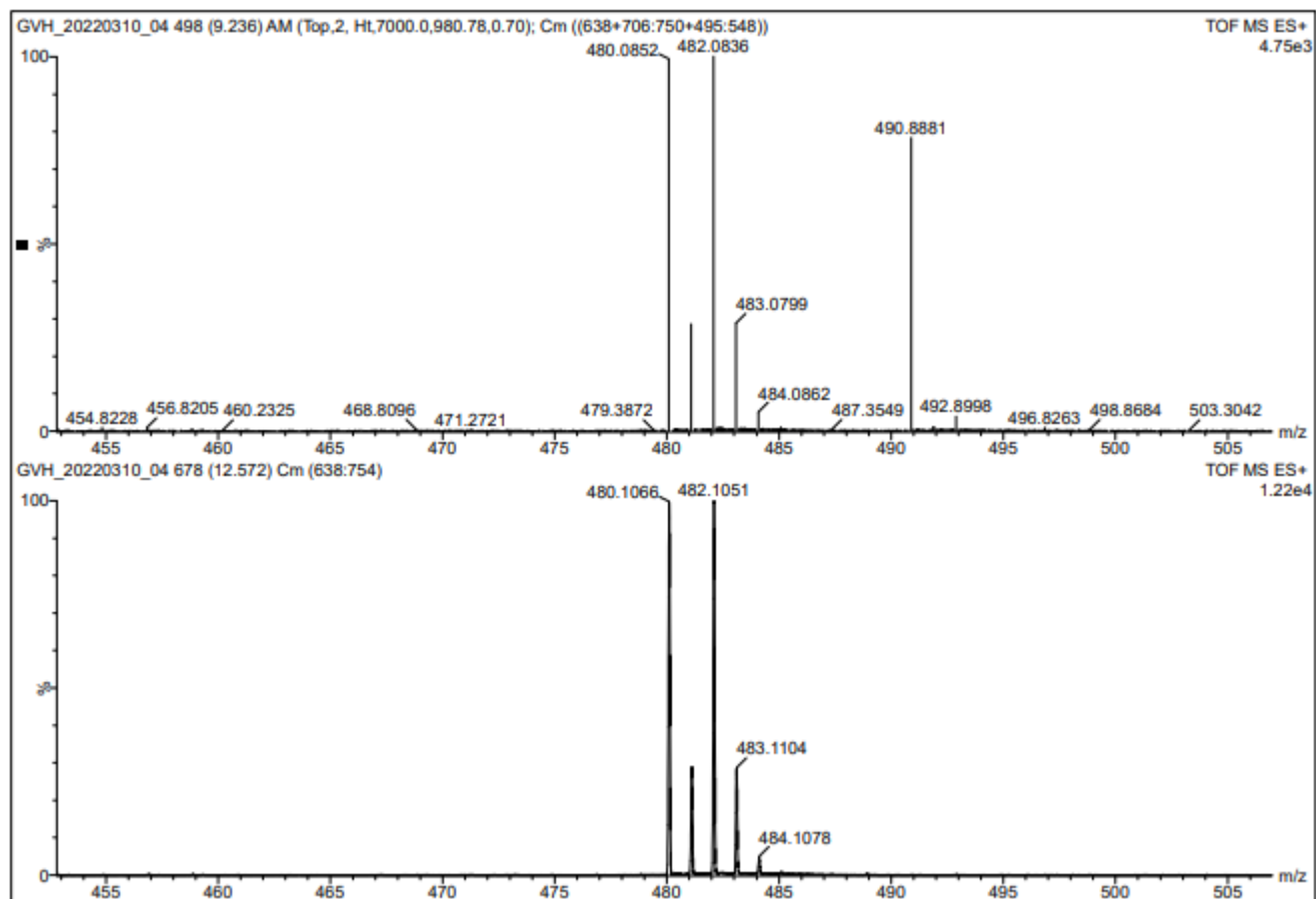
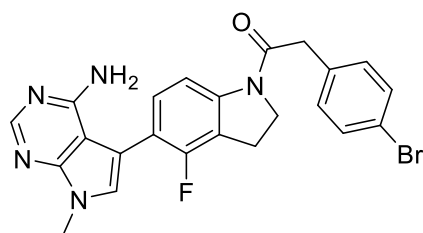
## Compound 30



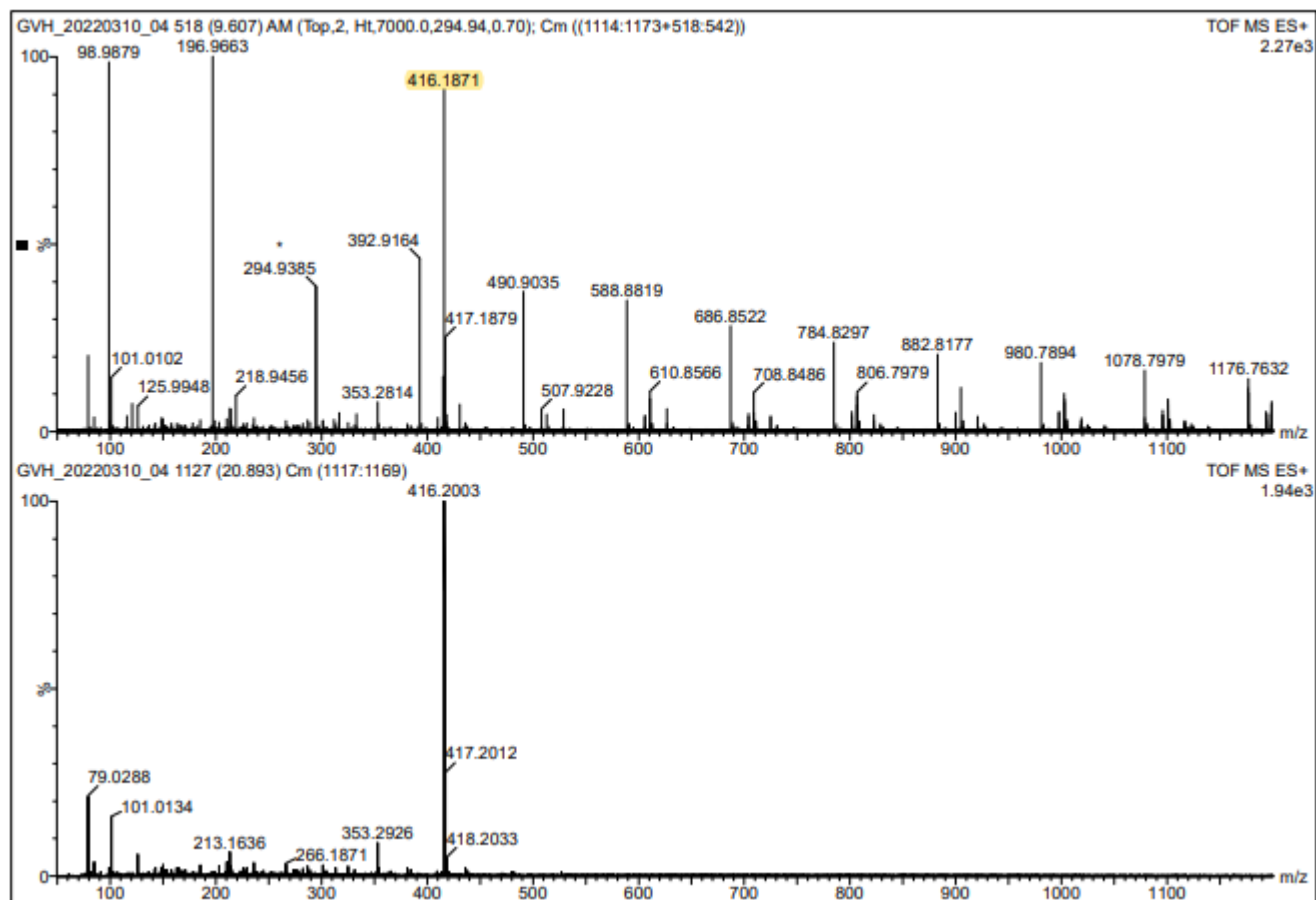
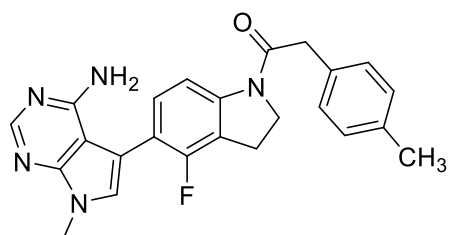
### Compound 31



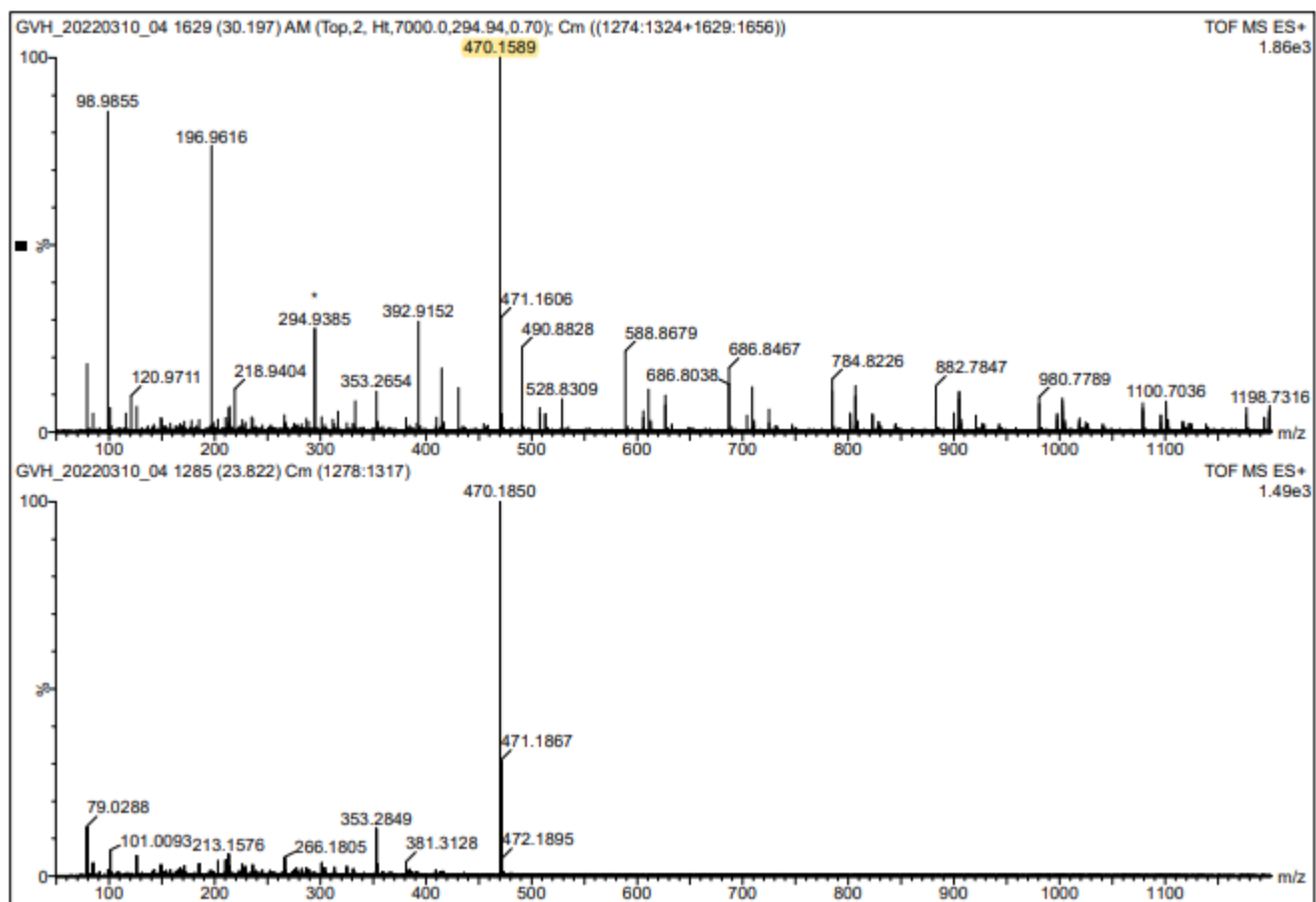
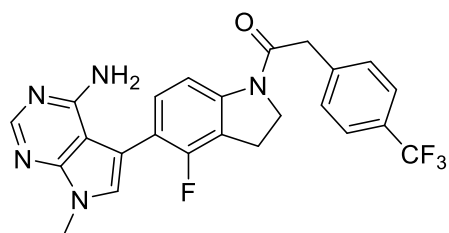
## Compound 32



# Compound 33

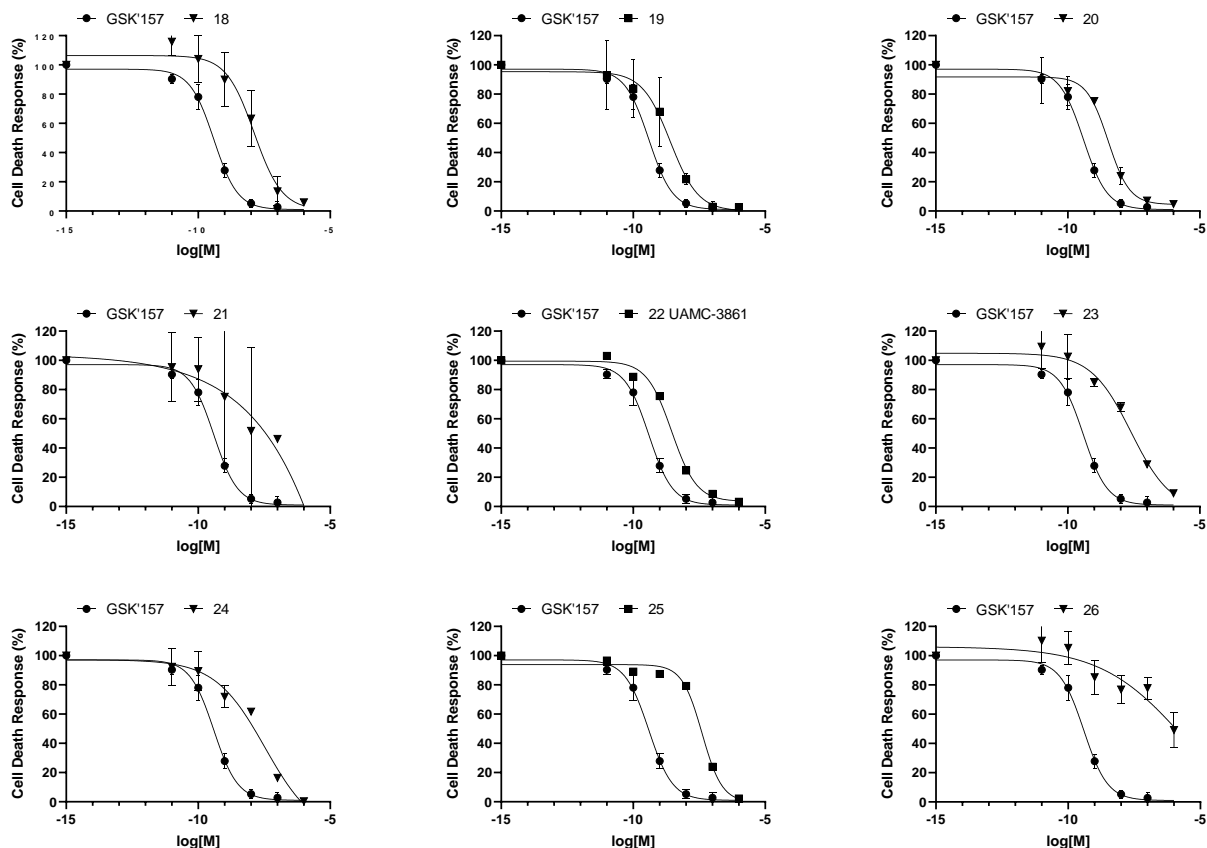


## Compound 34

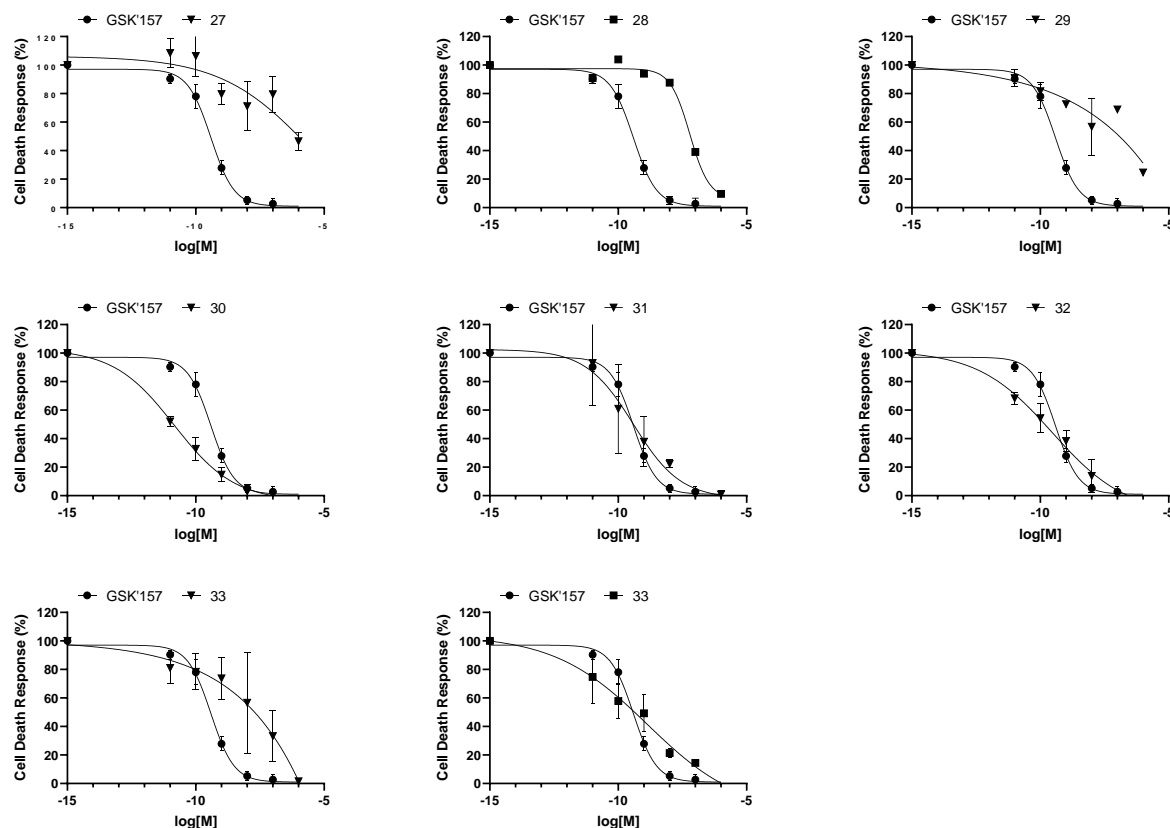




#### 4 Dose-response curve for compounds 18-34



**Figure S2. Representation of the single curve for each compound in comparison with GSK'157.** RIPK1 kinase-dependent necroptosis was induced in immortalized MEFs by 30 min pretreatment with pan-caspases inhibitor ZVAD-fmk (50  $\mu$ M) and increasing concentrations of the indicated compounds then stimulated by hTNF (20 ng/ml). The TNF-mediated necroptosis was measured at 24 h post-stimulation by SytoxGreen positivity tested



**Figure S3. Representation of the single curve for each compound in comparison with GSK'157.** RIPK1 kinase-dependent necroptosis was induced in immortalized MEFs by 30 min pretreatment with pan-caspases inhibitor ZVAD-fmk (50  $\mu$ M) and increasing concentrations of the indicated compounds then stimulated by hTNF (20 ng/ml). The TNF-mediated necroptosis was measured at 24 h post-stimulation by SytoxGreen positivity tested

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