Supporting Information for Design, Synthesis, Molecular Modeling and Bioactivity Evaluation of 1,10-Phenanthroline and Prodigiosin (Ps) Derivatives and Their Copper(I) Complexes against mTOR and HDAC Enzymes as Highly Potent and Effective New Anticancer Therapeutic Drugs

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Section A. Materials / General Methods / Instrumentation

All chemicals and reagents were purchased from commercial suppliers (Aldrich, Alfa Aesar or Fisher) and used without further purification. Anhydrous dichloromethane (DCM) and acetonitrile were separately distilled over CaH$_2$ under nitrogen. Dioxane was separately distilled over Na/benzophenone under nitrogen. Thin layer chromatography (TLC) was performed on silica gel 60 F254 (E. Merck). Column chromatography was carried out on silica gel 60F (Merck 9385, 0.040–0.063 mm). Ligands ($L_1$-$L_6$) (Cetin, 2017; Dietrich-Buchecker and Sauvage, 1990; Zhong et al., 2010; Kang et al., 2014; Kohler et al., 2016; Kohler et al., 2017; Hayes et al., 2018; Hayes et al., 2018; Schmittel et al., 1997; Cetin et al., 2017; Cetin et al., 2020) precursors (Cetin, 2017; Kang et al., 2014; Cetin et al., 2017; Cetin et al., 2020; Melvin et al., 2002; Kang et al., 2008) for ligands ($L_7$-$L_{15}$), and complexes ($C_1$-$C_{15}$) (Cetin, 2017; Dietrich-Buchecker and Sauvage, 1990; Kang et al., 2014; Cetin et al., 2017; Cetin et al., 2020; Kang et al., 2008) were prepared according to previous literature procedures with slight/moderateCOMPLETE modifications. All details for synthetic procedures are described in the Section B.

Proton and carbon nuclear magnetic resonance ($^1$H, $^{19}$F and $^{13}$C NMR) spectra were recorded on JEOL ECS–400 or a Varian Unity Inova 500 spectrometer, with working frequency of 400 or 500 MHz for $^1$H, 100 or 125 MHz for $^{13}$C, and 376 or 471 MHz for $^{19}$F nuclei, respectively. Chemical shifts are reported in ppm relative to the signals corresponding to the residual non–deuterated solvent (CDCl$_3$ (99.9% D with 0.05% v/v TMS): $\delta = 7.24$ ppm for $^1$H NMR, and (CDCl$_3$ (99.9% D with 0.05% v/v TMS): $\delta = 77.16$ ppm for $^{13}$C NMR). Coupling constants, $J$, are reported in hertz. High-resolution ESI mass spectrometry was performed on an Exactive-Orbitrap mass spectrometer at Texas Tech University (Lubbock, TX). Flash
chromatography was performed using Silicycle UltraPure Flash Silica Gel (60 Å, 40-63 μm). Thin layer chromatography (TLC) was performed using EMD HPTLC plates, silica gel 60, F254. All reaction vessels were flame-dried under vacuum and filled with nitrogen prior to use. All reactions were performed under a nitrogen atmosphere as a routine practice, not as an essential requirement.

**Section B. Synthetic Protocols**

The detailed synthetic procedures and the structural characterization data for the intermediates and target compounds are presented below.

![Scheme S1](image)

**Scheme S1** Synthesis of the copper(I) complexes (C1-C6) — 2:1 ligand-to-metal complexes, as PF$_6^-$ salts — from their respective 1,10-phenanthroline-based ligand derivatives (L$^1$-$L^6$).
**Scheme S2** Synthesis of the Prodigiosin (Ps) derivatives ($L^7$-$L^{15}$) and their respective 2:1 ligand-to-metal copper(I) complexes (C7-C15), as PF$_6^-$ salts.

**Synthesis of 4-methoxy-5-(5-ethyl-1H-pyrrol-2-ylmethylidene)-1,5-dihydropyrrol-2-one:**

To a solution of 2-formyl-5-ethylpyrrole (0.500 grams, 4.06 mmol) and 4-methoxy-3-pyrroline-2-one (0.920 grams, 8.13 mmol) in 20 mL DMSO was added 2N aq. NaOH (15 mL) and the mixture was stirred at 60 °C for 8 hours. After dilution with 100 mL DI-water, the suspension was extracted with 300 mL dichloromethane (3 x 100 mL). The organic phase was washed (shaken) with saturated brine and DI-water, dried over Na$_2$SO$_4$, and evaporated to dryness. The crude was dissolved in 2-3 mL dichloromethane and then excess hexane (50 mL) was added. The solution was evaporated under vacuum at 45 °C until 15-20 mL hexane was left. The black solid formation occurred. It was filtered and solid was collected over the filter paper. Then it was dissolved in 2-3 mL dichloromethane again and excess hexane (50 mL) was added into it. The solution was started to concentrate by evaporating under vacuum at 45 °C until 15-20 mL hexane was left again. Formation of brown solid was observed. The solid was collected over filter paper, dried, and left under vacuum overnight. After checking the proton NMR of the solid, 0.696 grams (78%) pure
product was obtained. $^1$H NMR (400 MHz, CDCl$_3$, 25 ºC) δ 10.8 (s, 1H), 10.31 (s, 1H), 6.37 (t, $J$ = 3.2 Hz, 1H), 6.32 (s, 1H), 5.99 (t, $J$ = 2.7 Hz, 1H), 5.10 (d, $J$ = 2.0 Hz, 1H), 3.90 (s, 3H), 2.79 (q, $J$ = 15 and 7.3 Hz, 2H), 1.34 (t, $J$ = 7.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$, 25 ºC) δ 173.13, 168.00, 141.98, 125.63, 123.98, 117.38, 107.01, 102.75, 90.12, 58.18, 21.30, 13.71.

**Synthesis of 2-trifluoromethansulfonyloxy-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrole (Key Intermediate):**

To a solution of 4-methoxy-5-(5-ethyl-1H-pyrrol-2-ylmethylidene)-1,5-dihydropyrrol-2-one (0.696 grams, 3.19 mmol) in dichloromethane (55 mL) at 0-5 ºC was added Tf$_2$O (0.1.80 grams (0.650 mL), 6.37 mmol) dropwise under nitrogen atmosphere. After stirring at this temperature for 30 minutes, the reaction mixture was poured into a 2% aq. NaHCO$_3$ solution, and extracted with ethyl acetate (2 x 50 mL). Then solvent was removed and the crude was left under vacuum for 2-3 hours. After dissolving the crude in ethyl acetate (50 mL), the solution was washed with saturated brine solution. After separating the organic layer, it was dried over anhydrous Na$_2$SO$_4$ and evaporated to the dryness. The crude was chromatographed on silicagel eluting with 50:50 hexane:dichloromethane solvent mixture. The pure 2-trifluoromethansulfonyloxy-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrole was obtained (1.03 grams, 92%); $^1$H NMR (400 MHz, CDCl$_3$) δ 10.8 (s, 1H), 7.03 (s, 1H), 6.66 (d, $J$ = 3.6 Hz, 1H), 6.07 (d, $J$ = 3.7 Hz, 1H), 5.40 (s, 1H), 3.88 (s, 3H), 2.74 (q, $J$ = 15 and 7.3 Hz, 2H), 1.32 (t, $J$ = 7.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.07, 161.21, 146.65, 132.44, 128.54, 123.20, 122.20, 120.39, 109.75, 87.18, 58.82, 21.61, 12.73.; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -72.7 (s, -CF$_3$).
**Synthesis of 2-(1-Boc-pyrrol-2-yl)-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrrole:**

An oxygen-free solution of 2-trifluoromethansulfonyloxy-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrrole (0.142 g, 0.404 mmol) in dry and freshly distilled 1,4-dioxane (30 mL) was treated in sequence with 1-Boc-pyrrole-2-boronic acid (0.341 g, 1.62 mmol), K$_2$CO$_3$ (0.446 g, 3.23 mmol). The solution purged with nitrogen for 10 mins and then Pd(PPh$_3$)$_4$ (23.3 mg, 5mol%) was added, and then the reaction mixture was heated to 90 °C under nitrogen atmosphere with stirring for 24 hours. After cooling to room temperature, the reaction mixture was poured into ice-water (50 mL) and extracted with ethyl acetate (4 x 50 mL). The organic phase was washed (shaken) with saturated brine solution and DI-water, then dried over anhydrous sodium sulfate. Then it was evaporated to dryness and kept under vacuum for 2-3 hours. The crude was then columned with alumina (activated) by eluting 100 % hexane (300 mL) and then hexane:ethyl acetate (85:15) to purify the product. It was columned over activated alumina twice to get pure product (67.7 mg, 46%); $^1$H NMR (400 MHz, CDCl$_3$) δ 6.84 (s, 1H), 6.72 (s, 1H), 6.68 (dd, $J = 3.7$ and 1.4 Hz, 1H), 6.49 (d, $J = 3.6$ Hz, 1H), 6.17 (t, $J = 2.3$ Hz, 1H), 6.04 (s, 1H), 5.89 (d, $J = 3.7$ Hz, 1H), 3.96 (s, 3H), 3.67 (s, 1H), 2.30 (q, $J = 15$ and 7.3 Hz, 2H), 1.26 (s, 9H), 1.05 (t, $J = 7.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.95, 145.30, 128.75, 128.74, 122.74, 120.64, 115.95, 112.78, 110.31, 108.13, 95.59, 58.52, 37.50, 32.02, 29.79, 22.78, 20.31, 14.22, 13.36.

**Synthesis of dimethylated macrocycle ($L^1$):**

In a flame-dried round-bottom flask, a mixture of dimethylated diphenol (10.0 g, 25.4 mmol) and 1,14-diodo-3,6,9,12-tetraoxatetradecane (12.4 g, 27.0 mmol) in DMF (400 mL) was added drop wise within 24 hours under efficient stirring to a nitrogen flushed suspension of Cs$_2$CO$_3$ (25.6 g, 72.6 mmol) in DMF (150 mL) kept at 55-60 °C. At the end of the addition, stirring was continued for another 48 hours at the same temperature. DMF was removed under reduced pressure with a rotary evaporator. The yellowish residue was dissolved in 150 mL of DCM, washed with saturated...
aq. NH₄Cl (3 x 100 mL), dried over anhydrous Na₂SO₄ and filtered. The solvent was evaporated under reduced pressure by a rotary evaporator to leave a yellow solid that was purified on silica gel by flash column chromatography using DCM-methanol (99.5:0.5) to provide dimethylated macrocycle L₁ (12.5 g, 82%) as a bright yellow solid, m.p. 153.8-155.1 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.37 (dd, 2.0, 2.0 Hz, 2H), 8.26-8.24 (m, 4H), 8.07 (d, J = 8.0 Hz, 2H), 7.74 (s, 2H), 7.15 (d, J = 8.5 Hz, 2H), 4.34 (t, J = 5.0 Hz, 5.5 Hz, 4H), 3.84 (t, J = 5.5 Hz, 5.0 Hz, 4H), 3.75-3.69 (m, 12H), 2.42 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) 158.37, 156.40, 145.88, 136.53, 132.35, 130.14, 127.64, 127.27, 126.51, 125.41, 119.04, 112.95, 71.02, 70.66, 70.56, 69.52, 68.28, 16.69; HRMS (ESI) calcd for C₃₆H₃₉N₂O₆ [M+H]+ m/z 595.2803, found m/z 595.2800; Anal. calcd. for C₃₆H₃₈N₂O₆: C, 72.71; H, 6.44; N, 4.71; found: C, 72.33; H, 6.51; N, 4.66.

**General procedure for the syntheses of complexes:**

A solution of the ligand (L₂-L₁₅) (0.250 mmol) in DCM (10 mL) and acetonitrile (10 mL) was prepared at room temperature under a nitrogen atmosphere. The light yellow-colored solution was stirred until the ligand was dissolved completely. To this solution, tetrakis(acetonitrile)copper(I) hexafluorophosphate (0.125 mmol) was added and the solution was stirred for 20 minutes at room temperature. The color of the solution turned to a dark brown-red-black. Concentration of the mixture under reduced pressure using a rotary evaporator provided the crude product. Purification on silica gel by flash column chromatography, using DCM–methanol (99:1) as eluent, afforded the corresponding copper(I) complex, [Cu(Lⁿ)₂]PF₆ (C₂-C₁₅), where Lⁿ = L₂-L₁₅.

In the synthesis of C₁, to a solution of dimethylated macrocycle L₁ (205 mg, 0.362 mmol) in dichloromethane (10 mL) and acetonitrile (10 mL) at room temperature under nitrogen was added tetrakis(acetonitrile)copper(I) hexafluorophosphate (123 mg, 0.463 mmol) and stirred for 20 min.
A dichloromethane (5 mL) and acetonitrile (5 mL) solution of \( \text{L}^2 \) (142 mg, 0.362 mmol) was added from another Schlenk flask under nitrogen via cannula. The reaction mixture was stirred for two hours at room temperature under nitrogen followed by concentration of the mixture under reduced pressure by a rotary evaporator. Purification on SEC column chromatography using DCM as eluent afforded the partially oxidized complex \([\text{CuL}^1\text{L}^2]\text{PF}_6\) (C1). The partially oxidized product was dissolved in 10 mL DCM, and 5 mg sodium dithionite (90%), and five drops of 2N aqueous sodium hydroxide were added to the solution and the mixture was stirred for 30 min at room temperature. After 30 min, the solution was filtered through a fritted-funnel which was filled with 1 cm height of Celite 545 and 1 cm height of anhydrous \( \text{Na}_2\text{SO}_4 \) to provide reduced and pure \([\text{CuL}^1\text{L}^2]\text{PF}_6\) (C1) (400 mg, 98%) as a red glassy solid, m.p. 252.4-253.0 °C; \(^1\text{H} \text{NMR (500 MHz, CDCl}_3) \delta 8.64 \text{ (d, J = 8.5 Hz, 2H)}, 8.46 \text{ (d, J = 8.0 Hz, 2H)}, 8.22 \text{ (s, 2H)}, 8.00 \text{ (s, 2H)}, 7.89 \text{ (d, J = 8.0 Hz, 2H)}, 7.80 \text{ (d, J = 8.0 Hz, 2H)}, 7.51 \text{ (d, J = 8.5 Hz, 4H)}, 7.18 \text{ (d, J = 8.5 Hz, 2H)}, 6.95 \text{ (s, 2H)}, 6.08 \text{ (d, J = 8.5 Hz, 4H)}, 5.81 \text{ (d, J = 8.0 Hz, 2H)}, 3.88 \text{ (s, 4H)}, 3.76-3.74 \text{ (m, 4H)}, 3.67-3.64 \text{ (m, 8H)}, 3.61-3.59 \text{ (m, 4H)}, 3.52 \text{ (s, 6H)}, 1.51 \text{ (s, 6H)}; \(^{13}\text{C} \text{NMR (125 MHz, CDCl}_3) \delta 160.28, 157.24, 157.06, 155.74, 143.46, 137.81, 136.86, 132.22, 131.20, 130.30, 129.28, 129.28, 128.16, 127.84, 127.20, 126.56, 126.09, 125.85, 124.19, 112.58, 112.58, 109.38, 71.31, 71.06, 71.06, 69.52, 67.52, 55.38, 15.88 \}; \text{HRMS (ESI) calcd for C}_{62}\text{H}_{58}\text{CuN}_4\text{O}_8 \text{[M-PF}_6]^+ \text{ m/z 1049.3545, found m/z 1049.3521; Anal. calcd. for C}_{62}\text{H}_{58}\text{CuF}_6\text{N}_4\text{O}_8\text{P: C, 62.28; H, 4.89; N, 4.69; found: C, 62.35; H, 4.69; N, 4.62.}
Section C. NMR Spectroscopy

$^1$H NMR Spectrum of 4-methoxy-5-(5-ethyl-1H-pyrrol-2-ylmethylidene)-1,5-dihydropyrrol-2-one

Figure S1 | Annotated $^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 4-methoxy-5-(5-ethyl-1H-pyrrol-2-ylmethylidene)-1,5-dihydropyrrol-2-one.

$^{13}$C NMR Spectrum of 4-methoxy-5-(5-ethyl-1H-pyrrol-2-ylmethylidene)-1,5-dihydropyrrol-2-one

Figure S2 | Annotated $^{13}$C NMR spectrum (100 MHz, CDCl$_3$, 25 °C) of 4-methoxy-5-(5-ethyl-1H-pyrrol-2-ylmethylidene)-1,5-dihydropyrrol-2-one.
$^1H$ NMR Spectrum of 2-trifluoromethansulfonyloxy-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrole (Key Intermediate):

Figure S3 | Annotated $^1H$ NMR spectrum (400 MHz, CDCl$_3$, 25 ºC) of 2-trifluoromethansulfonyloxy-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrole.

$^{13}C$ NMR Spectrum of 2-trifluoromethansulfonyloxy-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrole (Key Intermediate):

Figure S4 | Annotated $^{13}C$ NMR spectrum (100 MHz, CDCl$_3$, 25 ºC) of 2-trifluoromethansulfonyloxy-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrole.
$^1$H NMR Spectrum of 2-(1-Boc-pyrrol-2-yl)-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrole:

Figure S5 | Annotated $^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 ºC) of 2-(1-Boc-pyrrol-2-yl)-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrole.

$^{13}$C NMR Spectrum of 2-(1-Boc-pyrrol-2-yl)-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrole:

Figure S6 | Annotated $^{13}$C NMR spectrum (100 MHz, CDCl$_3$, 25 ºC) of 2-(1-Boc-pyrrol-2-yl)-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrole.
$^1$H NMR Spectrum of dimethylated macrocycle (C1)

**Figure S7** Annotated $^1$H NMR spectrum (500 MHz, CDCl$_3$, 25 °C) of dimethylated macrocycle (C1).

$^{13}$C NMR Spectrum of dimethylated macrocycle (C1)

**Figure S8** Annotated $^{13}$C NMR spectrum (125 MHz, CDCl$_3$, 25 °C) of dimethylated macrocycle (C1).
# Section D. Computational Calculations and Molecular Modeling Studies

Table S1: Calculated binding energies (in kcal/mol) and inhibition constants (in μM, except C7 being in mM) for commercially available Taxol, Ps, ligands L2-L15 and copper(I) complexes C1-C15.

| Compound ID | mTOR Binding Energies (kcal/mol) | mTOR Inhibition Constants (μM) | HDAC1 Binding Energies (kcal/mol) | HDAC1 Inhibition Constants (μM) |
|-------------|---------------------------------|-------------------------------|-----------------------------------|---------------------------------|
| Taxol (commercial) | −4.63 | 405.16 | −4.72 | 348.25 |
| Ps |
| L2 |
| L3 |
| L4 |
| L5 |
| L6 |
| L7 |
| L8 |
| L9 |
| L10 |
| L11 |
| L12 |
| L13 |
| L14 |
| L15 |
| C1 |
| C2 |
| C3 |
| C4 |
| C5 |
| C6 |
| C7 |
| C8 |
| C9 |
| C10 |
| C11 |
| C12 |
| C13 |
| C14 |
| C15 |

S13
Table S2 | Three-dimensional (3D) images generated via molecular docking of Ps, ligands \( \text{L}_7 \) and \( \text{L}_{14} \) and copper(I) complexes C1 and C14, and two-dimensional (2D) images generated via molecular docking of Ps, ligands \( \text{L}_7 \) and \( \text{L}_{14} \) into mTOR and HDAC1 enzymes.

| Compound ID | mTOR | HDAC1 |
|-------------|------|-------|
| Ps          | ![3D Image](image1.png) | ![3D Image](image2.png) |
| Ps (2D)     | ![2D Image](image3.png) | ![2D Image](image4.png) |
| C1          | ![3D Image](image5.png) | ![3D Image](image6.png) |
| \( \text{L}_7 \) | ![3D Image](image7.png) | ![3D Image](image8.png) |
Table S3 | Primary anticancer activity screening of compounds (L₁⁴, L⁹, C₁⁴, C⁹, L₁³, L₁⁵, L₁⁰, C₁⁵, C₁₃, C₈, C₁₀, L⁷, Ps, Taxol (Paclitaxel)) on different cell lines.

**L₁⁴:**

| cell line | 7.90E-10  | 7.90E-09  | 7.90E-08  | 7.90E-07  | 7.90E-06  | 7.90E-05  | Positive | Negative |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|---------|---------|
| 231BR     | 0.628     | 0.596     | 0.573     | 0.589     | 0.603     | 0.319     | 0.623   | 0.160   |
|           | 0.604     | 0.568     | 0.596     | 0.597     | 0.318     | 0.624     | 0.162   |
|           | 0.653     | 0.577     | 0.601     | 0.573     | 0.314     | 0.635     | 0.161   |
|           | 0.614     | 0.673     | 0.641     | 0.635     | 0.623     | 0.316     | 0.607   | 0.162   |
|           | 0.638     | 0.608     | 0.56      | 0.611     | 0.593     | 0.305     | 0.625   | 0.164   |
|           | 0.629     | 0.636     | 0.622     | 0.609     | 0.619     | 0.317     | 0.642   | 0.159   |
| average   | 0.628     | 0.610     | 0.599     | 0.602     | 0.602     | 0.315     | 0.626   | 0.161   |
| deviation (SD) | 0.0173   | 0.0392   | 0.0300   | 0.0213   | 0.0165   | 0.0051   | 0.0119 | 0.0018 |
| Inhibition ratio | -0.0036 | 0.0351 | 0.0584 | 0.0513 | 0.0509 | 0.6692 | SD 3.89E-06 |

| cell line | 7.90E-10  | 7.90E-09  | 7.90E-08  | 7.90E-07  | 7.90E-06  | 7.90E-05  | Positive | Negative |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|---------|---------|
| HTB22     | 0.325     | 0.319     | 0.333     | 0.331     | 0.351     | 0.349     | 0.343   | 0.122   |
|           | 0.335     | 0.321     | 0.317     | 0.327     | 0.332     | 0.329     | 0.341   | 0.127   |
|           | 0.264     | 0.331     | 0.314     | 0.295     | 0.343     | 0.344     | 0.347   | 0.126   |
|           | 0.336     | 0.352     | 0.328     | 0.333     | 0.332     | 0.332     | 0.318   | 0.127   |
|           | 0.337     | 0.329     | 0.32     | 0.329     | 0.335     | 0.335     | 0.336   | 0.126   |
|           | 0.345     | 0.335     | 0.32     | 0.348     | 0.345     | 0.345     | 0.35    | 0.124   |
| average   | 0.324     | 0.331     | 0.322     | 0.327     | 0.340     | 0.339     | 0.339   | 0.125   |
| deviation (SD) | 0.0299 | 0.0119 | 0.0071 | 0.0174 | 0.0078 | 0.0081 | 0.0114 | 0.0020 |
| Inhibition ratio | 0.0717 | 0.0366 | 0.0794 | 0.0553 | -0.0031 | 0.0000 |

| cell line | 7.90E-10  | 7.90E-09  | 7.90E-08  | 7.90E-07  | 7.90E-06  | 7.90E-05  | Positive | Negative |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|---------|---------|
| CRL       | 1.784     | 1.674     | 1.667     | 1.667     | 1.682     | 1.061     | 1.763   | 0.161   |
|           | 1.748     | 1.672     | 1.641     | 1.639     | 1.655     | 1.006     | 1.784   | 0.165   |
|           | 1.715     | 1.499     | 1.585     | 1.602     | 1.586     | 1.053     | 1.67    | 0.169   |
|           | 1.715     | 1.611     | 1.636     | 1.759     | 1.662     | 1.059     | 1.771   | 0.165   |
|           | 1.737     | 1.818     | 1.684     | 1.698     | 1.629     | 1.023     | 1.81    | 0.17    |
|           | 1.875     | 1.865     | 1.87      | 1.833     | 1.785     | 1.016     | 1.789   | 0.165   |
| average   | 1.762     | 1.690     | 1.681     | 1.700     | 1.667     | 1.036     | 1.765   | 0.166   |
| deviation (SD) | 0.0608 | 0.1344 | 0.0988 | 0.0844 | 0.0668 | 0.0241 | 0.0490 | 0.0033 |
| Inhibition ratio | 0.0017 | 0.0470 | 0.0528 | 0.0409 | 0.0616 | 0.4557 |
### C14:

| Cell Line | 3.85E-08 | 3.86E-07 | 3.85E-06 | 3.85E-05 | 3.85E-04 | Positive Control | Negative Control | Drug Control |
|-----------|----------|----------|----------|----------|----------|------------------|------------------|-------------|
| HTB131    | 1.259    | 1.580    | 1.546    | 0.719    | 2.079    | 1.487            | 0.078           | 0.147       |
|           | 1.878    | 1.523    | 1.960    | 0.791    | 1.934    | 0.101            | 0.077           | 0.150       |
|           | 1.555    | 1.385    | 1.537    | 0.648    | 2.010    | 1.381            | 0.079           | 0.162       |
|           | 1.478    | 1.147    | 1.304    | 0.711    | 2.122    | 1.474            | 0.076           | 0.469       |
|           | 1.039    | 1.366    | 1.407    | 0.645    | 2.191    | 1.541            | 0.079           | 0.835       |
|           | 1.765    | 2.030    | 2.143    | 0.763    | 1.901    | 1.378            | 0.076           | IC50 > 2.28E-05 M |

### C14:

| Cell Line | 3.85E-08 | 3.86E-07 | 3.85E-06 | 3.85E-05 | 3.85E-04 | Positive Control | Negative Control | Drug Control |
|-----------|----------|----------|----------|----------|----------|------------------|------------------|-------------|
| HTB131    | 1.259    | 1.580    | 1.546    | 0.719    | 2.079    | 1.487            | 0.078           | 0.147       |
|           | 1.878    | 1.523    | 1.960    | 0.791    | 1.934    | 0.101            | 0.077           | 0.150       |
|           | 1.555    | 1.385    | 1.537    | 0.648    | 2.010    | 1.381            | 0.079           | 0.162       |
|           | 1.478    | 1.147    | 1.304    | 0.711    | 2.122    | 1.474            | 0.076           | 0.469       |
|           | 1.039    | 1.366    | 1.407    | 0.645    | 2.191    | 1.541            | 0.079           | 0.835       |
|           | 1.765    | 2.030    | 2.143    | 0.763    | 1.901    | 1.378            | 0.076           | IC50 > 2.28E-05 M |

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### Positive versus Negative

| Positive | Negative |
|----------|----------|
| Control  | Control  |

### 231BR

| Positive | Negative |
|----------|----------|
| Control  | Control  |

### HTB22

| Positive | Negative |
|----------|----------|
| Control  | Control  |

### CRL

| Positive | Negative |
|----------|----------|
| Control  | Control  |

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### Drug Concentration (M)

| Positive | Negative |
|----------|----------|
| Control  | Control  |

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### Average

| Positive | Negative |
|----------|----------|
| Control  | Control  |

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### SD

| Positive | Negative |
|----------|----------|
| Control  | Control  |

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### Inhibition Rate

| Positive | Negative |
|----------|----------|
| Control  | Control  |

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### IC50

- 2.28E-05 M
- 3.85E-06 < IC50 < 3.85E-05
- 2.41E-06
| Cell Line | drug concentration (M) | Positive Control | Negative Control | Drug Control |
|-----------|------------------------|------------------|------------------|--------------|
| **CRL**   |                        |                  |                  |              |
|           | 3.85E-08               | 2.333            | 0.726            | 2.370        |
|           | 3.86E-07               | 2.333            | 2.149            | 2.370        |
|           | 3.85E-06               | 2.441            | 1.136            | 2.441        |
|           | 3.85E-05               | 2.441            | 2.114            | 2.441        |
|           | 3.85E-04               | 2.441            | 2.202            | 2.441        |
|           | 2.444                   | 2.441            | 0.906            | 2.441        |
|           | 2.444                   | 2.441            | 2.315            | 2.441        |
|           | 2.444                   | 2.441            | 0.867            | 2.441        |
|           | 2.444                   | 2.441            | 2.302            | 2.441        |
|           | 2.444                   | 2.441            | 0.888            | 2.441        |
|           | 2.444                   | 2.441            | 2.219            | 2.441        |
|           | 2.444                   | 2.441            | 0.852            | 2.441        |
|           | 2.444                   | 2.441            | 2.270            | 2.441        |
|           | 2.444                   | 2.441            | 0.443            | 2.441        |
|           | 2.444                   | 2.441            | 1.382            | 2.441        |
|           | **Average**             | **2.316**        | **0.896**        | **2.655**    |
|           | **SD**                  | **0.1446**       | **0.1030**       | **0.0517**   |
|           | **Inhibition rate**     | **-0.0236**      | **-0.0824**      | **-0.0327**  |

| **31BR**  |                        |                  |                  |              |
|           | 3.85E-08               | 0.653            | 0.460            | 1.007        |
|           | 3.86E-07               | 0.653            | 0.500            | 2.019        |
|           | 3.85E-06               | 0.500            | 0.520            | 2.182        |
|           | 3.85E-05               | 0.500            | 0.729            | 0.717        |
|           | 3.85E-04               | 0.500            | 0.538            | 2.108        |
|           | 2.238                   | 0.500            | 0.536            | 2.242        |
|           | 2.238                   | 0.500            | 0.784            | 0.130        |
|           | **Average**             | **0.707**        | **0.695**        | **0.134**    |
|           | **SD**                  | **0.0681**       | **0.0974**       | **0.0723**   |
|           | **Inhibition rate**     | **0.0476**       | **0.0687**       | **-0.2270**  |

| **231**   |                        |                  |                  |              |
|           | 3.85E-08               | 0.575            | 0.432            | 2.106        |
|           | 3.86E-07               | 0.575            | 0.429            | 2.179        |
|           | 3.85E-06               | 0.575            | 0.398            | 2.146        |
|           | 3.85E-05               | 0.575            | 0.448            | 2.134        |
|           | 3.85E-04               | 0.575            | 0.538            | 2.154        |
|           | 2.435                   | 0.575            | 0.536            | 2.242        |
|           | 2.435                   | 0.575            | 0.784            | 0.130        |
|           | **Average**             | **0.613**        | **0.595**        | **0.078**    |
|           | **SD**                  | **0.0495**       | **0.0279**       | **0.0366**   |
|           | **Inhibition rate**     | **0.0153**       | **0.0150**       | **-0.1056**  |

| **MCF10A**|                        |                  |                  |              |
|           | 3.85E-08               | 0.492            | 0.579            | 1.113        |
|           | 3.86E-07               | 0.492            | 0.604            | 1.228        |
|           | 3.85E-06               | 0.492            | 0.551            | 1.174        |
|           | 3.85E-05               | 0.492            | 0.646            | 1.298        |
|           | 3.85E-04               | 0.492            | 0.607            | 1.229        |
|           | 2.490                   | 0.492            | 0.668            | 1.189        |
|           | 2.490                   | 0.492            | 0.466            | 0.607        |
|           | **Average**             | **0.462**        | **0.609**        | **1.205**    |
|           | **SD**                  | **0.0191**       | **0.0214**       | **0.0024**   |
|           | **Inhibition rate**     | **-0.0110**      | **0.0687**       | **-0.3266**  |
| Cell Line | drug concentration (M) | Positive Control | Negative Control | Drug Control |
|-----------|------------------------|------------------|------------------|--------------|
| HTB131    | 5.60E-08               | 1.738            | 0.374            | 1.498        |
|           | 5.60E-07               | 1.566            | 0.433            | 2.081        |
|           | 5.60E-06               | 1.817            | 0.439            | 2.311        |
|           | 5.60E-05               | 1.576            | 0.472            | 1.962        |
|           | 5.60E-04               | 1.502            | 0.488            | 2.232        |
|           | Control                | 1.777            | 0.393            | 1.707        |
|           |                       |                  |                  |              |
| CRL       | 5.60E-08               | 1.763            | 0.457            | 1.860        |
|           | 5.60E-07               | 1.898            | 0.499            | 1.788        |
|           | 5.60E-06               | 2.078            | 0.441            | 1.983        |
|           | 5.60E-05               | 2.161            | 0.555            | 2.561        |
|           | 5.60E-04               | 2.276            | 0.534            | 2.268        |
|           | Control                | 2.036            | 0.463            | 2.344        |
|           |                       |                  |                  |              |
| 231BR     | 5.60E-08               | 0.679            | 0.566            | 0.666        |
|           | 5.60E-07               | 0.745            | 0.719            | 0.688        |
|           | 5.60E-06               | 0.642            | 0.627            | 0.648        |
|           | 5.60E-05               | 0.625            | 0.579            | 0.739        |
|           | 5.60E-04               | 0.631            | 0.535            | 0.810        |
|           | Control                | 0.745            | 0.502            | 0.716        |
|           |                       |                  |                  |              |
| 231       | 5.60E-08               | 0.646            | 0.563            | 0.636        |
|           | 5.60E-07               | 0.664            | 0.541            | 0.573        |
|           | 5.60E-06               | 0.587            | 0.479            | 0.595        |
|           | 5.60E-05               | 0.621            | 0.484            | 0.597        |
|           | 5.60E-04               | 0.599            | 0.493            | 0.632        |
|           | Control                | 0.770            | 0.482            | 0.693        |

**Approximate average**

| Cell Line | drug concentration (M) | Positive Control | Negative Control | Drug Control |
|-----------|------------------------|------------------|------------------|--------------|
| HTB131    | 1.663                  | 5.60E-08         | 5.60E-07         | 5.60E-06     |
|           | 1.566                  | 5.60E-05         | 5.60E-04         | 5.60E-03     |
|           | 1.635                  | 5.60E-02         | 5.60E-01         | 5.60E-00     |
|           | 1.942                  |                  |                  |              |
| CRL       | 1.735                  | 5.60E-08         | 5.60E-07         | 5.60E-06     |
|           | 1.820                  | 5.60E-05         | 5.60E-04         | 5.60E-03     |
|           | 1.784                  | 5.60E-02         | 5.60E-01         | 5.60E-00     |
|           | 1.784                  |                  |                  |              |
| 231BR     | 1.763                  | 5.60E-08         | 5.60E-07         | 5.60E-06     |
|           | 1.837                  | 5.60E-05         | 5.60E-04         | 5.60E-03     |
|           | 1.589                  | 5.60E-02         | 5.60E-01         | 5.60E-00     |
|           | 1.589                  |                  |                  |              |
| 231       | 1.763                  | 5.60E-08         | 5.60E-07         | 5.60E-06     |
|           | 1.642                  | 5.60E-05         | 5.60E-04         | 5.60E-03     |
|           | 1.641                  | 5.60E-02         | 5.60E-01         | 5.60E-00     |
|           | 1.641                  |                  |                  |              |
| Cell Line | 5.60E-08 | 5.60E-07 | 5.60E-06 | 5.60E-05 | 5.60E-04 | Control | Control | Control |
|-----------|---------|---------|---------|---------|---------|---------|---------|---------|
| MCF10A    | 0.458   | 0.443   | 0.418   | 0.242   | 0.408   | 0.445   | 0.180   | 0.184   |
|           | 0.474   | 0.464   | 0.425   | 0.249   | 0.426   | 0.466   | 0.185   | 0.181   |
|           | 0.441   | 0.438   | 0.412   | 0.249   | 0.425   | 0.476   | 0.183   | 0.187   |
|           | 0.434   | 0.446   | 0.402   | 0.252   | 0.438   | 0.455   | 0.182   | 0.240   |
|           | 0.485   | 0.439   | 0.411   | 0.248   | 0.434   | 0.499   | 0.184   | 0.402   |
|           | 0.487   | 0.443   | 0.396   | 0.244   | 0.412   | 0.474   | 0.177   |         |
| average   | 0.463   | 0.446   | 0.411   | 0.247   | 0.424   | 0.469   | 0.182   | 0.184   |
| deviation | 0.02250 | 0.00952 | 0.01050 | 0.00367 | 0.01184 | 0.01873 | 0.00293 |         |

| Inhibition Rate | 0.02033 | 0.08188 | 0.20325 | 0.180   | 0.184   | 0.474   | 0.464   | 0.425   |
|                | 0.441   | 0.438   | 0.412   | 0.249   | 0.425   | 0.476   | 0.183   | 0.187   |
|                | 0.434   | 0.446   | 0.402   | 0.252   | 0.438   | 0.455   | 0.182   | 0.240   |
|                | 0.485   | 0.439   | 0.411   | 0.248   | 0.434   | 0.499   | 0.184   | 0.402   |
|                | 0.487   | 0.443   | 0.396   | 0.244   | 0.412   | 0.474   | 0.177   |         |

| Approximate  | 0.463 | 0.446 | 0.411 | 0.247 | 0.424 | 0.469 | 0.182 | 0.184 |
|              | 0.02250 | 0.00952 | 0.01050 | 0.00367 | 0.01184 | 0.01873 | 0.00293 |         |

| IC50        | 1.14E-05 M | 5.6E-06 < IC50 < 5.6E-05 M | SD   | 1.11E-06 |

**Drug Concentration (M):**
- Positive
- Negative
- Drug

**Approximate deviation (SD):**
- 0.02250
- 0.00952
- 0.01050
- 0.00367
- 0.01184
- 0.01873
- 0.00293

**IC50:**
- 1.14E-05 M
- 5.6E-06 < IC50 < 5.6E-05 M
- SD 1.11E-06

**Inhibition Rate:**
- 0.02033
- 0.08188
- 0.20325
- 0.180
- 0.184
- 0.474
- 0.464
- 0.425

**Drug Concentration (M):**
- Positive
- Negative
- Drug

**Approximate deviation (SD):**
- 0.04979
- 0.01513
- 0.03897
- 0.00404
- 0.01277
- 0.03009
- 0.00208

**IC50:**
- 3.1E-06 M

**Inhibition Rate:**
- 0.05802
- 0.04691
- 0.51235
- 0.98230
- 0.99630

**Drug Concentration (M):**
- Positive
- Negative
- Drug

**Approximate deviation (SD):**
- 0.02919
- 0.03372
- 0.02003
- 0.02950
- 0.01114
- 0.02042
- 0.00058

**IC50:**
- 3.2E-05 M

**Inhibition Rate:**
- -0.04491
- -0.00577
- 0.02555
- 0.82283
- 0.98146

**Drug Concentration (M):**
- Positive
- Negative
- Drug

**Approximate deviation (SD):**
- 0.01852
- 0.03995
- 0.05679
- 0.05590
- 0.00400
- 0.02043
- 0.00153

**IC50:**
- 2.85E-04 M

**Inhibition Rate:**
- -0.02847
- -0.01542
- 0.08541
- 0.01265
- 0.59549

**Drug Concentration (M):**
- Positive
- Negative
- Drug

**Approximate deviation (SD):**
- 0.01154
- 0.02042
- 0.00058

**IC50:**
- 3.1E-06 M

**Inhibition Rate:**
- -0.02847
- -0.01542
- 0.08541
- 0.01265
- 0.59549

**Drug Concentration (M):**
- Positive
- Negative
- Drug

**Approximate deviation (SD):**
- 0.01852
- 0.03995
- 0.05679
- 0.05590
- 0.00400
- 0.02043
- 0.00153

**IC50:**
- 2.85E-04 M

**Inhibition Rate:**
- -0.02847
- -0.01542
- 0.08541
- 0.01265
- 0.59549

**Drug Concentration (M):**
- Positive
- Negative
- Drug

**Approximate deviation (SD):**
- 0.01852
- 0.03995
- 0.05679
- 0.05590
- 0.00400
- 0.02043
- 0.00153

**IC50:**
- 2.85E-04 M

**Inhibition Rate:**
- -0.02847
- -0.01542
- 0.08541
- 0.01265
- 0.59549

S20
| Cell Line | drug concentration (M) | Positive Control | Negative Control | Drug Control |
|----------|------------------------|------------------|------------------|-------------|
|          | 3.70E-08   | 3.70E-07   | 3.70E-06   | 3.70E-05   | 3.70E-04   |
| 231BR    | 1.051      | 1.025      | 0.929      | 0.599      | 1.451      |
|          | 1.042      | 0.986      | 0.934      | 0.496      | 1.437      |
|          | 1.041      | 1.020      | 0.882      | 0.424      | 1.300      |
| average  | 1.045      | 1.010      | 0.915      | 0.506      | 1.396      |
| deviation (SD) | 0.005508 | 0.021221 | 0.087956   | 0.083433   | 0.022605   |
| Inhibition Rate | 0.000385 | 0.040077 | 0.030777   | 0.03667    | 0.001155   |

IC50 3.19E-05 M

**C8:**

| Cell Line | drug concentration (M) | Positive Control | Negative Control | Drug Control |
|----------|------------------------|------------------|------------------|-------------|
|          | 2.50E-08   | 2.50E-07   | 2.50E-06   | 2.50E-05   | 2.50E-04   |
| 231BR    | 1.296      | 1.219      | 1.095      | 0.878      | 0.499      |
|          | 1.297      | 1.223      | 1.089      | 0.867      | 0.510      |
|          | 1.246      | 1.239      | 1.089      | 0.838      | 0.509      |
| average  | 1.280      | 1.227      | 1.091      | 0.861      | 0.506      |
| deviation (SD) | 0.02916  | 0.01058   | 0.00346   | 0.02066    | 0.00608    |
| Inhibition Rate | -0.04203 | 0.00866   | 0.13956   | 0.36092    | 0.75938    |

IC50 4.85E-05 M

**C13: (Batch 1)**

| Cell Line | drug concentration (M) | Positive Control | Negative Control | Drug Control |
|----------|------------------------|------------------|------------------|-------------|
|          | 1.60E-08   | 1.60E-07   | 1.60E-06   | 1.60E-05   | 1.60E-04   |
| 231BR    | 1.204      | 1.259      | 1.254      | 0.905      | 0.906      |
|          | 1.281      | 1.271      | 1.236      | 0.913      | 0.916      |
|          | 1.263      | 1.217      | 1.205      | 0.898      | 0.962      |
| average  | 1.249      | 1.249      | 1.232      | 0.905      | 0.928      |
| deviation (SD) | 0.04028  | 0.02835   | 0.02479   | 0.00751    | 0.02987    |
| Inhibition Rate | 0.02027  | 0.02058   | 0.03679   | 0.19052    | 0.96352    |

IC50 2.78E-05 M

**C13: (Batch 2)**

| Cell Line | drug concentration (M) | Positive Control | Negative Control | Drug Control |
|----------|------------------------|------------------|------------------|-------------|
|          | 1.65E-08   | 1.65E-07   | 1.65E-06   | 1.65E-05   | 1.65E-04   |
| 231BR    | 1.238      | 1.239      | 1.124      | 0.340      | 1.396      |
|          | 1.263      | 1.285      | 1.224      | 0.354      | 1.366      |
|          | 1.161      | 1.293      | 1.214      | 0.339      | 1.210      |
| average  | 1.221      | 1.272      | 1.187      | 0.344      | 1.324      |
| deviation (SD) | 0.05316  | 0.02914   | 0.05508   | 0.00839    | 0.09986    |
| Inhibition Rate | 0.01855  | -0.03103  | 0.05054   | 0.75016    | 0.83877    |

IC50 1.12E-05

**C15:**

| Cell Line | drug concentration (M) | Positive Control | Negative Control | Drug Control |
|----------|------------------------|------------------|------------------|-------------|
|          | 2.50E-08   | 2.50E-07   | 2.50E-06   | 2.50E-05   | 2.50E-04   |
| 231BR    | 1.296      | 1.219      | 1.095      | 0.878      | 0.499      |
|          | 1.297      | 1.223      | 1.089      | 0.867      | 0.510      |
|          | 1.246      | 1.239      | 1.089      | 0.838      | 0.509      |
| average  | 1.280      | 1.227      | 1.091      | 0.861      | 0.506      |
| deviation (SD) | 0.02916  | 0.01058   | 0.00346   | 0.02066    | 0.00608    |
| Inhibition Rate | -0.04203 | 0.00866   | 0.13956   | 0.36092    | 0.75938    |

IC50 4.85E-05 M
| Drug concentration (M) | Positive | Negative | Drug | Control | Control | Control |
|------------------------|----------|----------|------|---------|---------|---------|
| 7.50E-10               | 1.030    | 0.941    | 0.486 | 0.383   | 0.363   | 0.902   |
| 7.50E-09               | 1.028    | 0.955    | 0.513 | 0.391   | 0.358   | 0.935   |
| 7.50E-08               | 1.035    | 0.958    | 0.536 | 0.407   | 0.365   | 1.000   |
| 7.50E-07               | 1.064    | 0.966    | 0.520 | 0.429   | 0.370   | 0.970   |
| 7.50E-06               | 1.020    | 0.928    | 0.548 | 0.422   | 0.370   | 0.943   |
| 7.50E-05               | 1.045    | 1.034    | 0.563 | 0.424   | 0.372   | 1.005   |
| 7.50E-04               | 1.035    | 0.955    | 0.529 | 0.411   | 0.367   | 0.962   |
| Control                |          |          |      |         |         |         |
| Control                |          |          |      |         |         |         |
| Control                |          |          |      |         |         |         |

**Approximate deviation (SD):**
0.007594 0.010424 0.015777 0.015341 0.003559 0.029428 0.001708

**IC50:** 7.5E-08 M

Inhibition Rate:
1.084131 0.991877 0.497824 0.360603 0.309545

**SD:** 3.78E-09

| Drug concentration (M) | Positive | Negative |
|------------------------|----------|----------|
| 4.80E-08               | 1.256    | 1.264    |
| 4.80E-07               | 1.255    | 1.260    |
| 4.80E-06               | 1.219    | 1.226    |
| 4.80E-05               | 1.243    | 1.250    |
| 4.80E-04               | 0.02108  | 0.02088  |
| Control                |          |          |
| Control                |          |          |
| Control                |          |          |

**Approximate:**
1.255 1.260 0.322 0.237 1.844 1.234 0.196 0.204

**IC50:** 1.2E-06 M

Inhibition Rate:
0.00349 -0.00286 0.88032 0.96635 1.18730

**IC50:** 7.5E-08 M

Inhibition Rate:
1.084131 0.991877 0.497824 0.360603 0.309545

**SD:** 3.78E-09

| Drug concentration (M) | Positive | Negative |
|------------------------|----------|----------|
| 2.695                  | 2.614    | 2.435    |
| 2.568                  | 2.403    | 1.415    |
| 2.510                  | 2.281    | 1.385    |
| 2.560                  | 2.425    | 1.448    |
| 2.565                  | 2.427    | 1.394    |
| 2.641                  | 2.441    | 1.386    |
| 2.577                  | 2.423    | 1.399    |
| Control                |          |          |
| Control                |          |          |
| Control                |          |          |

**Approximate:**
2.651 2.577 2.423 1.400 1.224 1.202 1.204 1.216

**IC50:** 7.5E-07 < IC50 < 7.5E-06 M

Inhibition Rate:
0.05677 0.02505 0.01370 0.01226 0.02691 0.02186 0.00096

**SD:** 3.78E-09

| Drug concentration (M) | Positive | Negative |
|------------------------|----------|----------|
| 2.695                  | 2.614    | 2.435    |
| 2.568                  | 2.403    | 1.415    |
| 2.510                  | 2.281    | 1.385    |
| 2.560                  | 2.425    | 1.448    |
| 2.565                  | 2.427    | 1.394    |
| 2.641                  | 2.441    | 1.386    |
| 2.577                  | 2.423    | 1.399    |
| Control                |          |          |
| Control                |          |          |
| Control                |          |          |

**Approximate:**
2.651 2.577 2.423 1.399 1.386 1.378 1.369 1.358

**IC50:** 7.5E-07 < IC50 < 7.5E-06 M

Inhibition Rate:
1.11461 1.08086 1.01029 0.54192 0.04827
| Cell Line | drug concentration (M) | Positive | Negative |
|-----------|------------------------|----------|----------|
|           | 7.50E-10 | 7.50E-09 | 7.50E-08 | 7.50E-07 | 7.50E-06 | Control | Control |
| HTB131    |          |          |          |          |          |         |         |
|           | 1.463    | 1.143    | 0.695    | 0.546    | 0.264    | 1.125   | 0.139   |
|           | 1.280    | 1.212    | 0.858    | 0.665    | 0.290    | 1.222   | 0.144   |
|           | 1.145    | 1.317    | 0.958    | 0.536    | 0.262    | 1.169   | 0.138   |
|           | 1.093    | 1.110    | 0.707    | 0.607    | 0.287    | 1.109   | 0.137   |
|           | 1.207    | 1.205    | 0.798    | 0.573    | 0.241    | 1.143   | 0.134   |
|           | 1.230    | 1.173    | 0.686    | 0.534    | 0.221    | 0.947   | 0.132   |
| average   | 1.216    | 1.183    | 0.765    | 0.566    | 0.264    | 1.137   | 0.137   |
| deviation (SD) | 0.05601 | 0.03175 | 0.07746 | 0.03178 | 0.01881 | 0.02574 | 0.00216 |
| inhibition rate | 1.125 | 0.139 | 1.280 | 1.212 | 0.858 | 0.665 | 0.264 | 1.137 | 0.137 |
| IC50      |          |          |          |          |          |         |         |
| HTB22     |          |          |          |          |          |         |         |
|           | 0.732    | 0.712    | 0.444    | 0.401    | 0.274    | 0.737   | 0.170   |
|           | 0.696    | 0.756    | 0.464    | 0.381    | 0.276    | 0.720   | 0.166   |
|           | 0.778    | 0.715    | 0.465    | 0.419    | 0.284    | 0.757   | 0.182   |
|           | 0.733    | 0.696    | 0.493    | 0.372    | 0.258    | 0.708   | 0.170   |
|           | 0.747    | 0.715    | 0.457    | 0.387    | 0.279    | 0.660   | 0.168   |
|           | 0.723    | 0.552    | 0.444    | 0.375    | 0.278    | 0.717   | 0.166   |
| average   | 0.734    | 0.710    | 0.458    | 0.386    | 0.277    | 0.721   | 0.169   |
| deviation (SD) | 0.00991 | 0.00911 | 0.00968 | 0.01114 | 0.00222 | 0.01212 | 0.00191 |
| inhibition rate | 1.0994 | 0.98007 | 0.52355 | 0.39402 | 0.19611 | 0.01135 | 0.00129 |
| IC50      |          |          |          |          |          |         |         |
| MCF10A-Core |          |          |          |          |          |         |         |
|           | 1.239    | 1.139    | 0.776    | 0.653    | 0.351    | 1.140   | 0.182   |
|           | 1.267    | 1.167    | 0.825    | 0.684    | 0.361    | 1.141   | 0.189   |
|           | 1.299    | 1.238    | 0.832    | 0.703    | 0.366    | 1.255   | 0.190   |
|           | 1.267    | 1.159    | 0.733    | 0.638    | 0.342    | 1.237   | 0.191   |
|           | 1.256    | 1.130    | 0.745    | 0.649    | 0.353    | 1.151   | 0.192   |
|           | 1.316    | 1.126    | 0.719    | 0.623    | 0.334    | 1.133   | 0.240   |
| average   | 1.272    | 1.149    | 0.770    | 0.656    | 0.352    | 1.196   | 0.191   |
| deviation (SD) | 0.01857 | 0.01717 | 0.04105 | 0.01971 | 0.00780 | 0.05834 | 0.00129 |
| inhibition rate | 1.07583 | 0.95301 | 0.57608 | 0.46295 | 0.11114 | 0.05834 | 0.00129 |
| IC50      |          |          |          |          |          |         |         |
drug concentration (M)

| cell line  | 7.5xE-10 | 7.5xE-9 | 7.5xE-8 | 7.5xE-7 | 7.5xE-6 | 7.5xE-5 | Positive  | Negative | Drug  |
|------------|----------|---------|---------|---------|---------|---------|-----------|----------|--------|
| 231BR      | 0.98     | 0.825   | 0.78    | 0.456   | 0.411   | 1.162   | 0.119     |          |        |
|            | 0.999    | 0.976   | 0.915   | 0.756   | 0.413   | 0.927   | 0.126     |          |        |
|            | 1.024    | 0.969   | 0.963   | 0.795   | 0.403   | 0.93    | 0.123     |          |        |
|            | 0.821    | 0.869   | 0.87    | 0.76    | 0.413   | 0.943   | 0.12      |          |        |
|            | 0.979    | 0.979   | 0.945   | 0.768   | 0.391   | 0.918   | 0.123     |          |        |
|            | 1.077    | 1.039   | 0.942   | 0.842   | 0.413   | 0.98    | 0.245     | Approximate |       |
| average    | 0.9373   | 0.9483  | 0.9413  | 0.7698  | 0.4100  | 0.9450  | 0.1230    | IC50     | 7.5E-07 < IC50 < 7.5E-06 M |
| deviation  | 0.0211   | 0.0530  | 0.0198  | 0.0176  | 0.0048  | 0.0243  | 0.0024    |          |        |
| inhibition rate | 0.9907 | 1.0040 | 0.9954 | 0.7868 | 0.3491 |          |          |          |        |

| cell line  | 7.5xE-10 | 7.5xE-9 | 7.5xE-8 | 7.5xE-7 | 7.5xE-6 | 7.5xE-5 | Positive  | Negative | Drug  |
|------------|----------|---------|---------|---------|---------|---------|-----------|----------|--------|
| 361        | 1.362    | 0.985   | 1.183   | 1.238   | 1.167   | 1.25    | 0.138     |          |        |
|            | 1.408    | 1.181   | 1.054   | 1.111   | 1.231   | 1.24    | 0.139     |          |        |
|            | 1.334    | 1.213   | 1.095   | 1.323   | 1.253   | 1.253   | 0.139     |          |        |
|            | 1.35     | 1.264   | 1.192   | 1.118   | 0.138   | 1.143   | 0.133     |          |        |
|            | 1.466    | 0.982   | 1.182   |         |         | 1.143   | 0.133     |          |        |
|            | 1.438    | 1.332   | 1.26    |         |         | 1.142   | 0.137     | Approximate |       |
| average    | 1.3895   | 1.1608  | 1.1953  | 1.1763  | 1.2403  | 1.1938  | 0.1380    | IC50     | > 7.5E-06 M |
| deviation  | 0.0409   | 0.1221  | 0.0456  | 0.0636  | 0.0784  | 0.0593  | 0.0008    |          |        |
| inhibition rate | 1.1854 | 0.9687 | 1.0015 | 0.9835 | 1.0441 |          |          |          |        |

| cell line  | 7.5xE-10 | 7.5xE-9 | 7.5xE-8 | 7.5xE-7 | 7.5xE-6 | 7.5xE-5 | Positive  | Negative | Drug  |
|------------|----------|---------|---------|---------|---------|---------|-----------|----------|--------|
| CRL        | 2.644    | 2.631   | 2.393   | 1.187   | 0.582   | 2.496   | 0.213     |          |        |
|            | 2.642    | 2.595   | 2.31    | 1.265   | 0.619   | 2.433   | 0.215     |          |        |
|            | 2.512    | 2.542   | 2.324   | 1.225   | 0.6     | 2.277   | 0.213     |          |        |
|            | 2.51     | 2.631   | 2.36    | 1.317   | 0.649   | 2.562   | 0.22      |          |        |
|            | 2.58     | 2.464   | 2.303   | 1.256   | 0.671   | 2.507   | 0.214     |          |        |
|            | 2.593    | 2.556   | 2.264   | 1.16    | 0.562   | 2.499   | 0.213     | Approximate |       |
| average    | 2.58175  | 2.581   | 2.32425 | 1.23325 | 0.6125  | 2.48375 | 0.21375   | IC50     | 7.5E-07 < IC50 < 7.5E-06 M |
| deviation  | 0.0536   | 0.0402  | 0.0254  | 0.0353  | 0.0286  | 0.0342  | 0.0010    |          |        |
| inhibition rate | 1.0432 | 1.0428 | 0.9297 | 0.4491 | 0.1757 |          |          |          |        |

| cell line  | 7.5xE-10 | 7.5xE-9 | 7.5xE-8 | 7.5xE-7 | 7.5xE-6 | 7.5xE-5 | Positive  | Negative | Drug  |
|------------|----------|---------|---------|---------|---------|---------|-----------|----------|--------|
| HTB131     | 1.297    | 1.202   | 0.872   | 0.465   | 0.381   | 1.18    | 0.146     |          |        |
|            | 1.117    | 1.222   | 1.051   | 0.558   | 0.432   | 1.288   | 0.147     |          |        |
|            | 1.21     | 1.286   | 1.04    | 0.51    | 0.414   | 1.251   | 0.148     |          |        |
|            | 1.264    | 1.307   | 1.034   | 0.415   | 0.468   | 1.309   | 0.145     |          |        |
|            | 1.192    | 1.067   | 0.949   | 0.705   | 0.459   | 1.312   | 0.146     |          |        |
|            | 1.263    | 1.172   | 0.976   | 0.513   | 0.435   | 0.972   | 0.149     | Approximate |       |
| average    | 1.23225  | 1.2205  | 0.99975 | 0.5115  | 0.435   | 1.257   | 0.14675   | IC50     | 7.5E-07 < IC50 < 7.5E-06 M |
| deviation  | 0.0368   | 0.0483  | 0.0445  | 0.0380  | 0.0185  | 0.0567  | 0.0010    |          |        |
| inhibition rate | 0.9777 | 0.9671 | 0.7683 | 0.3285 | 0.2596 |          |          |          |        |
### Taxol (Paclitaxel):

| Cell Line | 7.50E-10 | 7.50E-09 | 7.50E-08 | 7.50E-07 | 7.50E-06 | Positive Control | Negative Control |
|-----------|---------|---------|---------|---------|---------|-----------------|-----------------|
| HTB131    | 1.559   | 0.96    | 1.15    | 0.365   | 0.703   | 1.587           | 0.148           |
|           | 1.869   | 0.98    | 0.873   | 0.512   | 0.363   | 1.744           | 0.148           |
|           | 1.727   | 1.277   | 1.17    | 0.591   | 0.593   | 1.521           | 0.145           |
|           | 1.704   | 1.152   | 1.088   | 0.539   | 0.778   | 1.827           | 0.146           |
|           | 1.742   | 1.053   | 1.017   | 0.522   | 0.899   | 1.818           | 0.149           |
|           | 1.794   | 1       | 1.06    | 0.507   | 0.856   | 1.841           | 0.149           |
| average  | 1.733   | 1.070   | 1.060   | 0.506   | 0.699   | 1.723           | 0.148           |
| SD       | 0.103   | 0.122   | 0.108   | 0.075   | 0.198   | 0.137           | 0.002           |
| inhibition rate | -0.006 | 0.414 | 0.421 | 0.772 | 0.650 |

| Cell Line | 7.50E-10 | 7.50E-09 | 7.50E-08 | 7.50E-07 | 7.50E-06 | Positive Control | Negative Control |
|-----------|---------|---------|---------|---------|---------|-----------------|-----------------|
| CRL       | 1.158   | 0.812   | 0.657   | 0.497   | 0.386   | 1.579           | 0.19            |
|           | 1.378   | 0.601   | 0.571   | 0.566   | 0.573   | 1.572           | 0.185           |
|           | 1.38    | 1.03    | 0.651   | 0.513   | 0.545   | 1.633           | 0.189           |
|           | 1.602   | 0.695   | 0.48    | 0.609   | 0.484   | 1.565           | 0.188           |
|           | 1.578   | 0.801   | 0.696   | 0.67    | 0.605   | 1.626           | 0.187           |
|           | 1.713   | 0.996   | 0.705   | 0.497   | 0.522   | 1.61            | 0.188           |
| average  | 1.468   | 0.823   | 0.627   | 0.559   | 0.519   | 1.598           | 0.188           |
| SD       | 0.201   | 0.167   | 0.086   | 0.070   | 0.077   | 0.029           | 0.002           |
| inhibition rate | 0.092 | 0.550 | 0.689 | 0.737 | 0.765 |

| Cell Line | 7.50E-10 | 7.50E-09 | 7.50E-08 | 7.50E-07 | 7.50E-06 | Positive Control | Negative Control |
|-----------|---------|---------|---------|---------|---------|-----------------|-----------------|
| 231BR     | 0.641   | 0.577   | 0.452   | 0.449   | 0.423   | 0.654           | 0.256           |
|           | 0.606   | 0.556   | 0.502   | 0.483   | 0.493   | 0.822           | 0.258           |
|           | 0.605   | 0.607   | 0.52    | 0.458   | 0.43    | 0.722           | 0.256           |
|           | 0.685   | 0.604   | 0.531   | 0.503   | 0.459   | 0.762           | 0.249           |
|           | 0.726   | 0.582   | 0.53    | 0.479   | 0.448   | 0.786           | 0.262           |
|           | 0.835   | 0.605   | 0.562   | 0.522   | 0.441   | 0.935           | 0.288           |
| average  | 0.683   | 0.589   | 0.516   | 0.482   | 0.449   | 0.780           | 0.262           |
| SD       | 0.080   | 0.019   | 0.034   | 0.025   | 0.023   | 0.087           | 0.012           |
| inhibition rate | 0.187 | 0.370 | 0.509 | 0.575 | 0.639 |

### HTB131 Cell Line

- **Drug concentration (M)**: 7.5xE-10, 7.5xE-9, 7.5xE-8, 7.5xE-7, 7.5xE-6, 7.5xE-5, Control
- **Positive inhibition rate**: 0.9250, 0.9232, 0.7656, 0.3439, 0.1231
- **Negative inhibition rate**: 0.198, 0.593, 0.694, 0.167, 0.025
- **SD**: 3.9E-08 M
- **IC50**: 7.5E-07 < IC50 < 7.5E-06 M

### CRL Cell Line

- **Drug concentration (M)**: 7.50E-10, 7.50E-09, 7.50E-08, 7.50E-07, 7.50E-06, Control
- **Positive inhibition rate**: 0.441, 0.601, 0.812, 0.599, 0.383
- **Negative inhibition rate**: 0.358, 0.398, 0.426, 0.595, 0.73
- **SD**: 1.587, 1.744, 1.521, 1.827, 1.818
- **IC50**: 5.7E-08 M

### 231BR Cell Line

- **Drug concentration (M)**: 7.50E-10, 7.50E-09, 7.50E-08, 7.50E-07, 7.50E-06, Control
- **Positive inhibition rate**: 0.641, 0.606, 0.605, 0.605, 0.685
- **Negative inhibition rate**: 0.423, 0.493, 0.458, 0.458, 0.479
- **SD**: 0.256, 0.258, 0.256, 0.256, 0.249
- **IC50**: 3.9E-08 M

- **SD**: 0.674, 0.674, 0.696, 0.696, 0.696
- **SD**: 0.025, 0.167, 0.167, 0.167, 0.167
- **SD**: 0.080, 0.080, 0.080, 0.080, 0.080

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| Cell Line | drug concentration (M) | Positive control | Negative control |
|-----------|------------------------|------------------|-----------------|
| 231       | 7.50E-10 | 7.50E-09 | 7.50E-08 | 7.50E-07 | 7.50E-06 | Control | Control |
|           |          |          |          |          |          | 0.703   | 0.429   | 0.399   | 0.391   | 0.363   | 0.747   | 0.211   |
|           |          |          |          |          |          | 0.624   | 0.455   | 0.37    | 0.379   | 0.363   | 0.723   | 0.212   |
|           |          |          |          |          |          | 0.615   | 0.448   | 0.369   | 0.347   | 0.344   | 0.679   | 0.213   |
|           |          |          |          |          |          | 0.661   | 0.472   | 0.371   | 0.349   | 0.358   | 0.717   | 0.238   |
|           |          |          |          |          |          | 0.65    | 0.469   | 0.36    | 0.352   | 0.361   | 0.707   | 0.218   |
|           |          |          |          |          |          | 0.652   | 0.57    | 0.358   | 0.304   | 0.401   | 0.762   | 0.223   |
| average   |          |          |          |          |          | 0.651   | 0.484   | 0.371   | 0.354   | 0.365   | 0.723   | 0.219   |
| SD        | 0.031    | 0.045    | 0.015    | 0.030    | 0.019    | 0.029   | 0.010   |
| inhibition rate | 0.142 | 0.473 | 0.698 | 0.733 | 0.710 |

| Cell Line | drug concentration (M) | Positive control | Negative control |
|-----------|------------------------|------------------|-----------------|
| MCF10A    | 7.50E-10 | 7.50E-09 | 7.50E-08 | 7.50E-07 | 7.50E-06 | Control | Control |
|           | 0.425    | 0.37    | 0.356    | 0.35    | 0.313    | 0.45    | 0.179   |
|           | 0.424    | 0.44    | 0.367    | 0.354   | 0.353    | 0.464   | 0.184   |
|           | 0.405    | 0.367    | 0.368    | 0.351   | 0.346    | 0.426   | 0.178   |
|           | 0.411    | 0.379    | 0.349    | 0.337   | 0.35    | 0.419   | 0.181   |
|           | 0.425    | 0.374    | 0.363    | 0.334   | 0.346    | 0.442   | 0.182   |
|           | 0.411    | 0.369    | 0.362    | 0.332   | 0.333    | 0.469   | 0.179   |
| average   | 0.417    | 0.383    | 0.361    | 0.343   | 0.340    | 0.445   | 0.181   |
| SD        | 0.009    | 0.028    | 0.007    | 0.010   | 0.015    | 0.020   | 0.002   |
| inhibition rate | 0.107 | 0.234 | 0.319 | 0.386 | 0.397 |

| Cell Line | drug concentration (M) | Positive control | Negative control |
|-----------|------------------------|------------------|-----------------|
| 361       | 7.50E-10 | 7.50E-09 | 7.50E-08 | 7.50E-07 | 7.50E-06 | Control | Control |
|           | 3.247    | 3.147    | 2.67     | 2.501   | 2.601    | 3.618   | 0.156   |
|           | 3.159    | 2.865    | 2.36     | 2.443   | 2.49     | 3.27    | 0.158   |
|           | 3.074    | 3.033    | 2.444    | 2.399   | 2.693    | 3.416   | 0.159   |
|           | 3.378    | 3.239    | 2.44     | 2.455   | 2.506    | 3.269   | 0.152   |
|           | 3.593    | 3.137    | 2.437    | 2.444   | 2.335    | 3.33    | 0.156   |
|           | 3       | 3.039    | 2.567    | 2.312   | 2.221    | 3.264   | 0.156   |
| average   | 3.292    | 3.077    | 2.486    | 2.426   | 2.474    | 3.361   | 0.156   |
| SD        | 0.182    | 0.129    | 0.112    | 0.065   | 0.172    | 0.139   | 0.002   |
| inhibition rate | 0.022 | 0.089 | 0.273 | 0.292 | 0.277 |

| cell line | drug concentration (M) | Positive control | Negative control | Drug control |
|-----------|------------------------|------------------|-----------------|-------------|
| HTB22     | 7.50E-10 | 7.50E-9 | 7.50E-8 | 7.50E-7 | 7.50E-6 | 7.50E-5 |
|           | 0.753    | 0.672    | 0.682    | 0.516   | 0.739    | 0.676   | 0.125   |
|           | 0.689    | 0.666    | 0.648    | 0.495   | 0.709    | 0.648   | 0.157   |
|           | 0.671    | 0.672    | 0.652    | 0.503   | 0.702    | 0.696   | 0.157   |
|           | 0.697    | 0.674    | 0.645    | 0.492   | 0.711    | 0.704   | 0.155   |
|           | 0.684    | 0.663    | 0.642    | 0.498   | 0.711    | 0.653   | 0.154   |
|           | 0.688    | 0.664    | 0.654    | 0.514   | 0.757    | 0.637   | 0.154   |
| average   | 0.6895   | 0.6685   | 0.64975  | 0.5025  | 0.70825  | 0.66825 | 0.155   |
| deviation | 0.0083   | 0.0041   | 0.0040   | 0.0083  | 0.0043   | 0.0222  | 0.0014  |
| inhibition rate | 1.0414 | 1.0005 | 0.9640 | 0.6771 | 0.5390 |
### Table S4: Secondary cytotoxicity tests of L13, C10, L7, C1, and Ps, respectively, on different cancer cell lines.

#### L13:

| Cell Line | drug concentration (M) | Positive Control | Negative Control | Drug Control |
|-----------|------------------------|------------------|------------------|--------------|
| 231BR     | 3.90E-07               | 7.80E-07         | 1.56E-06         | 1.33E-06     |
|           | 6.25E-06               | 1.25E-05         | 2.10E-05         | 4.20E-05     |
|           |                        |                  |                   | SD 9.47E-07  |
| CRL       | 1.83                  | 1.67              | 1.67              | 1.74         |
|           | 1.69                  | 1.49              | 0.27              | 0.21         |
|           | 1.71                  | 0.33              | 0.20              | 0.34         |
|           | 1.65                  | 0.47              | 0.32              | 0.32         |
|           | 1.42                  | 0.31              | 0.26              | 0.30         |
|           | 0.0050                | 0.0476            | 0.0727            | 0.0125       |
| Inhibition Rate | 0.0601 | 0.0119 | 0.0480 | 0.9165 | 0.98600 | 0.97254 |

#### IC50 5.06E-06 M

| Cell Line | drug concentration (M) | Positive Control | Negative Control | Drug Control |
|-----------|------------------------|------------------|------------------|--------------|
| 3.90E-07  | 7.80E-07               | 1.56E-06         | 1.33E-06         | 6.25E-06     |
|           | 1.25E-05               | 2.10E-05         | 4.20E-05         | SD 3.84E-07  |
| HTB131    | 1.98                  | 1.83              | 1.70             | 1.41         |
|           | 1.41                  | 1.35              | 0.91             | 0.23         |
|           | 1.37                 | 1.37              | 0.30             | 0.23         |
|           | 1.34                 | 1.34              | 0.32             | 0.32         |
|           | 0.1241                | 0.09351           | 0.07410          | 0.0125       |
| Inhibition Rate | -0.1622 | -0.08112 | -0.00929 | 0.03082 | 0.20304 | 0.34421 | 0.87310 | 0.93700 |

#### IC50 1.26E-05 M

| Cell Line | drug concentration (M) | Positive Control | Negative Control | Drug Control |
|-----------|------------------------|------------------|------------------|--------------|
| 3.90E-07  | 7.80E-07               | 1.56E-06         | 1.33E-06         | 6.25E-06     |
|           | 1.25E-05               | 2.10E-05         | 4.20E-05         | SD 3.84E-07  |
| 231       | 0.635                  | 0.619             | 0.593            | 0.528        |
|           | 0.385                  | 0.251             | 0.214            | 0.248        |
|           | 0.244                  | 0.201             | 0.199            | 0.252        |
|           | 0.241                  | 0.198             | 0.196            | 0.249        |
|           | 0.0125                 | 0.03031           | 0.00071          | 0.00971      |
| Inhibition Rate | 0.09937 | 0.16038 | 0.21761 | 0.31950 | 0.61195 | 0.86541 | 0.99811 | 0.98050 |

#### SD 1.03E-07

#### SD 2.59E-07
### Table 1: Inhibition Rates and IC50 Values for Different Drug Concentrations

| Cell Line | 3.75E-07 | 7.50E-07 | 1.50E-06 | 3.00E-06 | 6.00E-06 | 1.20E-05 | 2.40E-05 | 4.80E-05 |
|-----------|----------|----------|----------|----------|----------|----------|----------|----------|
| CRL       | 1.839    | 1.251    | 0.972    | 0.569    | 0.202    | 0.177    | 0.185    | 0.190    |
|           | 1.847    | 1.493    | 0.931    | 0.563    | 0.212    | 0.186    | 0.183    | 0.189    |
|           | 1.675    | 1.403    | 0.944    | 0.519    | 0.212    | 0.181    | 0.184    | 0.192    |
|           | 1.765    | 1.544    | 0.972    | 0.535    | 0.215    | 0.195    | 0.183    | 0.205    |
|           | 1.768    | 1.434    | 0.961    | 0.568    | 0.210    | 0.208    | 0.187    | 0.200    |
|           | 1.885    | 1.656    | 1.010    | 0.651    | 0.219    | 0.198    | 0.183    | 0.199    |
| average   | 1.797    | 1.464    | 0.965    | 0.568    | 0.212    | 0.191    | 0.184    | 0.196    |
| deviation (SD) | 0.07584 | 0.13718 | 0.02733 | 0.04561 | 0.00568 | 0.01162 | 0.00160 | 0.00643 |
| Inhibition Rate | 0.00154 | 0.20659 | 0.51355 | 0.75831 | 0.97742 | 0.99025 | 0.99436 | 0.98717 |
| IC50     | 0.160E-06 |
| SD       | 8.42E-08 |

### Table 2: Inhibition Rates and IC50 Values for Different Drug Concentrations

| Cell Line   | 3.75E-07 | 7.50E-07 | 1.50E-06 | 3.00E-06 | 6.00E-06 | 1.20E-05 | 2.40E-05 | 4.80E-05 |
|-------------|----------|----------|----------|----------|----------|----------|----------|----------|
| HT13B1      | 1.534    | 1.577    | 0.653    | 0.661    | 0.446    | 0.124    | 0.118    | 0.132    |
|             | 1.536    | 1.493    | 0.656    | 0.600    | 0.435    | 0.132    | 0.118    | 0.134    |
|             | 1.578    | 1.491    | 0.676    | 0.638    | 0.439    | 0.122    | 0.120    | 0.137    |
| average     | 1.549    | 1.520    | 0.662    | 0.633    | 0.440    | 0.126    | 0.119    | 0.134    |
| deviation (SD) | 0.02485 | 0.04908 | 0.01250 | 0.03081 | 0.00557 | 0.00529 | 0.00115 | 0.00252 |
| Inhibition Rate | 0.00046 | 0.02054 | 0.61519 | 0.63504 | 0.76870 | 0.98615 | 0.99123 | 0.98869 |
| IC50     | 0.17E-06 |
| SD       | 1.00E-07 |

### Table 3: Inhibition Rates and IC50 Values for Different Drug Concentrations

| Cell Line   | 3.75E-07 | 7.50E-07 | 1.50E-06 | 3.00E-06 | 6.00E-06 | 1.20E-05 | 2.40E-05 | 4.80E-05 |
|-------------|----------|----------|----------|----------|----------|----------|----------|----------|
| 3B          | 0.640    | 0.679    | 0.597    | 0.438    | 0.242    | 0.132    | 0.116    | 0.121    |
|             | 0.631    | 0.649    | 0.601    | 0.440    | 0.237    | 0.130    | 0.111    | 0.120    |
|             | 0.675    | 0.685    | 0.615    | 0.466    | 0.264    | 0.135    | 0.115    | 0.128    |
| average     | 0.649    | 0.671    | 0.604    | 0.448    | 0.248    | 0.132    | 0.114    | 0.123    |
| deviation (SD) | 0.02325 | 0.01929 | 0.00945 | 0.01156 | 0.01436 | 0.00252 | 0.00265 | 0.00436 |
| Inhibition Rate | 0.11436 | 0.07805 | 0.18645 | 0.44065 | 0.76640 | 0.95393 | 0.98374 | 0.99350 |
| IC50     | 0.286E-06 |
| SD       | 2.13E-07 |
| Cell Line | drug concentration (M) | Positive | Negative | Drug |
|-----------|------------------------|----------|----------|------|
| MCF10A    | 1.143 1.906 0.216 0.202 1.904 1.513 0.181 0.180 |
|           | 1.164 1.192 0.217 0.197 1.803 1.173 0.183 0.193 |
|           | 1.196 1.263 0.220 0.197 1.813 1.283 0.183 1.486 |
| average   | 1.168 1.184 0.218 0.199 1.840 1.203 0.182 |
| deviation (SD) | 0.02669 0.08381 0.00208 0.00289 0.05565 0.07000 0.00115 |
| Inhibition Rate | 0.03736 0.02177 0.96329 0.98181 0.65497 |

**L7:**

| Cell Line | drug concentration (M) | Positive | Negative |
|-----------|------------------------|----------|----------|
| 361       | 5.86E-08 1.17E-07 2.34E-06 2.34E-05 9.83E-06 1.88E-05 1.35E-05 1.35E-04 |
| 231BR     | 5.86E-09 1.17E-08 2.34E-07 2.34E-06 9.83E-06 1.88E-05 1.35E-05 1.35E-04 |
| CRL       | 5.86E-08 1.17E-07 2.34E-06 2.34E-05 9.83E-06 1.88E-05 1.35E-05 1.35E-04 |
| HTB 131   | 2.93E-09 5.86E-09 1.17E-08 2.34E-07 2.34E-06 9.83E-06 1.88E-05 1.88E-04 |

| Cell Line | drug concentration (M) | Positive | Negative | Drug |
|-----------|------------------------|----------|----------|------|
| 361       | 5.86E-08 1.17E-07 2.34E-06 2.34E-05 9.83E-06 1.88E-05 1.35E-05 1.35E-04 |
| 231BR     | 5.86E-09 1.17E-08 2.34E-07 2.34E-06 9.83E-06 1.88E-05 1.35E-05 1.35E-04 |
| CRL       | 5.86E-08 1.17E-07 2.34E-06 2.34E-05 9.83E-06 1.88E-05 1.35E-05 1.35E-04 |
| HTB 131   | 2.93E-09 5.86E-09 1.17E-08 2.34E-07 2.34E-06 9.83E-06 1.88E-05 1.88E-04 |

**SD 1.51E-07**
| Cell Line | Inhibition Rate | SD | IC50 | 7.58E-06 M | 27.8186 ng/mL |
|---|---|---|---|---|---|
| 231 | -0.00800 | 0.03222 | 0.02003 | 0.03122 | 0.02906 |

C1:

| Cell Line | Inhibition Rate | SD | IC50 | 9.7E-07 M | 3.2E-08 |
|---|---|---|---|---|---|
| 231BR | 0.00174 | 0.02159 | 0.01209 | 0.00442 | 0.00044 |

SD: 9.7E-07
| Cell Line | drug concentration (M) | Positive Control | Negative Control | drug concentration (M) | Positive Control | Negative Control | Inhibition Rate | SD |
|-----------|------------------------|------------------|------------------|------------------------|------------------|------------------|----------------|-----|
| HTB131    | 1.24E-08               | 2.47E-08         | 4.94E-08         | 9.88E-08               | 1.98E-07         | 3.95E-07         | 7.90E-07       |     |
|           | 1.592                  | 1.416            | 1.224            | 1.288                  | 0.733            | 0.695            | 0.714           |     |
|           | 1.585                  | 1.328            | 1.347            | 1.113                  | 0.651            | 0.682            | 0.654           |     |
|           | 1.587                  | 1.550            | 1.625            | 1.272                  | 0.674            | 0.727            | 0.646           |     |
| average   | 1.588                  | 1.431            | 1.399            | 1.224                  | 0.686            | 0.701            | 0.671           |     |
| deviation (SD) | 0.03606             | 0.111791         | 0.205432         | 0.096749               | 0.042297         | 0.023159         | 0.037166       |     |
| Inhibition Rate | 0.076825             | 0.176296         | 0.197037         | 0.307725               | 0.649524         | 0.639788         | 0.658836       |     |
|           | 7.58095                | 0.041885         | 0.001000         | 2.28E-07  M            | 1.11E-08         |
| 231       | 1.24E-08               | 2.47E-08         | 4.94E-08         | 9.88E-08               | 1.98E-07         | 3.95E-07         | 7.90E-07       |     |
|           | 0.7619                 | 0.06964          | 0.06429          | 0.07857                | 0.09762          | 0.60417          | 0.79643        |     |
| MCF10A    | 1.58E-08               | 1.58E-07         | 1.58E-06         | 1.58E-05               | 1.58E-04         | 1.58E-03         | 1.58E-02       |     |
|           | 1.286                  | 0.938            | 0.774            | 0.209                  | 0.271            | 1.257            | 0.181          |     |
|           | 1.286                  | 0.973            | 0.715            | 0.202                  | 0.270            | 1.261            | 0.183          |     |
|           | 1.211                  | 0.901            | 0.752            | 0.207                  | 0.247            | 1.310            | 0.183          |     |
| average   | 1.261                  | 0.937            | 0.747            | 0.206                  | 0.263            | 1.276            | 0.289          |     |
| deviation (SD) | 0.04330             | 0.03600          | 0.02982          | 0.00361                | 0.01358          | 0.02951          | IC50 1.0E-06 M |
| Inhibition Rate | 0.01371              | 0.30957          | 0.48355          | 0.97806                | 0.94180          | IC50 6.5E-06 M  |
| 361       | 1.58E-08               | 1.58E-07         | 1.58E-06         | 1.58E-05               | 1.58E-04         | 1.58E-03         | 1.58E-02       |     |
|           | 4.163                  | 3.463            | 2.892            | 0.726                  | 0.296            | 3.363            | 0.156          |     |
|           | 4.160                  | 3.184            | 2.707            | 0.869                  | 0.396            | 3.133            | 0.155          |     |
|           | 4.105                  | 3.344            | 2.881            | 0.876                  | 0.343            | 3.255            | 0.153          |     |
|           | 4.107                  | 3.518            | 2.827            | 0.914                  | 0.349            | 3.509            | 0.155          |     |
|           | 4.090                  | 3.325            | 2.603            | 0.846                  | 0.329            | 3.056            | 0.154          |     |
|           | 4.160                  | 3.119            | 2.681            | 0.823                  | 0.369            | 3.363            | 0.158          |     |
| average   | 4.131                  | 3.326            | 2.765            | 0.842                  | 0.347            | 3.280            | 0.155          |     |
| deviation (SD) | 0.03358             | 0.15425          | 0.11840          | 0.06465                | 0.03415          | 0.16651          | IC50 7.15E-07  |
| Inhibition Rate | -0.27227             | -0.01456         | 0.16475          | 0.78005                | 0.93856          | 0.142           | 0.183          |     |

**Ps:**
### Table 1: IC50 and Inhibition Rate

| Cell Line | IC50 (M) | Increased drug concentration (mg/mL) | Positive Control | Negative Control |
|-----------|----------|--------------------------------------|-----------------|-----------------|
| CRL       | 5.86E-07 | 1.17E-07 2.34E-06 4.69E-06 9.38E-06 1.88E-05 3.75E-05 7.50E-05 | 1.376 0.195 | 1.301 0.203 |
| HTB131    | 5.86E-08 | 1.17E-07 2.34E-07 4.69E-07 9.38E-07 1.88E-06 3.75E-06 7.50E-06 | 0.324 0.397 | 0.348 0.397 |
| 231       | 5.86E-08 | 1.17E-07 2.34E-07 4.69E-07 9.38E-07 1.88E-06 3.75E-06 7.50E-06 | 1.397 0.194 | 1.397 0.194 |

### Table 2: Average Inhibition Rate

| Cell Line | Inhibition Rate | Positive Control | Negative Control |
|-----------|----------------|-----------------|-----------------|
| CRL       | 0.948029       | 0.817441 0.939881 0.495265 0.256772 0.173530 0.174411 0.243338 | 0.324 0.397 | 0.348 0.397 |
| HTB131    | 1.046811       | 0.965658 0.960957 0.920074 0.808258 0.516149 0.386549 0.340352 | 0.159750 | 0.197507 |
| 231       | 1.025816       | 0.986712 1.002278 0.923690 0.765756 0.526955 0.416856 0.333713 | 0.77408  | 0.77408 |

### Table 3: SD and SD (M)

| Cell Line | SD | SD (M) |
|-----------|----|--------|
| CRL       | 3.20E-07 | (1504.70 mg/mL) |
| HTB131    | 3.20E-07 | (910.16 mg/mL) |
| 231       | 7.74E-08 | (510.86 mg/mL) |
| Cell Line | 5.86E-07 | 1.17E-06 | 2.34E-06 | 4.69E-06 | 9.38E-06 | 1.88E-05 | 3.75E-05 | 7.50E-05 | Positive | Negative | Control | Control |
|-----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|---------|---------|
| MCF10A    | 1.187    | 1.079    | 0.814    | 0.819    | 0.793    | 0.787    | 0.693    | 0.573    | 1.533    | 0.182    |
|           | 1.244    | 1.135    | 0.822    | 0.813    | 0.816    | 0.793    | 0.673    | 0.608    | 1.455    | 0.186    |
|           | 1.317    | 1.063    | 0.820    | 0.831    | 0.748    | 0.797    | 0.689    | 0.591    | 1.414    | 0.186    |
|           | 1.234    | 1.102    | 0.821    | 0.794    | 0.768    | 0.686    | 0.653    | 0.469    | 1.450    | 0.180    |
|           | 1.244    | 1.056    | 0.761    | 0.752    | 0.765    | 0.760    | 0.636    | 0.578    | 1.346    | 0.184    |
|           | 1.341    | 0.961    | 0.709    | 0.737    | 0.788    | 0.689    | 0.627    | 0.568    | 1.510    | 0.186    |
| average   | 1.261    | 1.066    | 0.791    | 0.791    | 0.780    | 0.752    | 0.662    | 0.565    | 1.451    | 0.184    |
| deviation (SD) | 0.057129 | 0.058924 | 0.046594 | 0.038247 | 0.024172 | 0.051614 | 0.027542 | 0.048952 | 0.067254 | 0.002530 |
| Inhibition Rate | 0.149829 | 0.303867 | 0.520784 | 0.529916 | 0.551697 | 0.622862 | 0.699684 | 0.002530 | 0.067254 |
| IC50      | 8.75E-06 M (2839.91 ng/mL) | 2.98E-07 |
Section F. Crystallographic Characterization

All the crystallographic data for the 2-trifluoromethansulfonfonyloxy-4-methoxy-5-[(5-ethyl-2H-pyrrol-2-ylidene)methyl]-1H-pyrrole (Key Intermediate) structure reported in this paper have been deposited to the Cambridge Crystallographic Data Centre (CCDC) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. CCDC deposition number and all data for the compound can be found in Tables S5–S10.

Table S5 | Crystallographic data and structure refinement for the Key Intermediate.

|                                | CCDC# 2160302 |
|--------------------------------|---------------|
| **Empirical Formula**          | C_{13}H_{13}F_{3}N_{2}O_{4}S |
| **Mol. Weight**                | 350.31        |
| **Temperature / K**            | 100(2)        |
| **Crystal System**              | Monoclinic    |
| **Space Group**                | C2/c          |
| **a, b, c (Å)**                 | 24.822(11), 4.954(2), 23.601(10) |
| **α, β, γ (°)**                 | 90, 93.027(5), 90 |
| **Volume (Å³)**                | 2898(2)       |
| **Z**                          | 8             |
| **ρcalc / mg mm⁻³**            | 1.606         |
| **μ / mm⁻¹**                   | 0.280         |
| **F(000)**                     | 1440          |
| **Crystal Size / mm³**         | 0.350 × 0.095 × 0.010 |
| **2Θ Range for Data Collection** | 1.643 to 25.641° |
| **Index Ranges**               | -30 ≤ h ≤ 30, -6 ≤ k ≤ 6, -28 ≤ l ≤ 28 |
| **Reflections Collected**      | 12659         |
| **Independent Reflections**    | 2727[R(int) = 0.0530] |
| **Data/Restraints/Parameters** | 2727/0/214    |
| **Goodness-of-fit on F²**      | 1.056         |
| **Final R Indexes [I>2σ (I)]** | R₁ = 0.0421, wR₂ = 0.1020 |
| **Final R Indexes [All Data]** | R₁ = 0.0604, wR₂ = 0.1108 |
| **Largest Diff. Peak/Hole / e Å⁻³** | 0.372/-0.492 |
**Crystallographic Data of the Key Intermediate**

**Method:** Single crystals of C$_{13}$H$_{13}$F$_3$N$_2$O$_4$S were submitted. A suitable crystal was selected (a Zeiss Stemi 305 microscope was used to identify a suitable specimen) and the crystal was mounted on a MiTiGen holder in Paratone oil on a Bruker Kappa APEX-II CCD diffractometer (operated at 1500 W (50kV, 30 mA) to generate (graphite monochromated) Mo Kα radiation (λ = 0.71073 Å)). The crystal was kept at 100 K during data collection. Using Olex2 (Dolomanov et al., 2009), the structure was solved with the XT (Sheldrick, 2015) structure solution program using Intrinsic Phasing and refined with the XL (Sheldrick, 2007) refinement package using Least Squares minimization.

**Crystal Data:** For C$_{13}$H$_{13}$F$_3$N$_2$O$_4$S ($M = 350.31$): monoclinic, space group C2/c (no. 15), $a = 24.822(11)$ Å, $b = 4.954(2)$ Å, $c = 23.601(10)$ Å, $\alpha = 90^\circ$, $\beta = 93.027(5)^\circ$, $\gamma = 90^\circ$, $V = 2898(2)$ Å$^3$, $Z = 8$, $T = 100(2)$ K, $\mu$(MoKα) = 0.280 mm$^{-1}$, $D_{calc} = 1.606$ g/mm$^3$, 12659 reflections measured (1.643° ≤ 2Θ ≤ 25.641°), 2727 unique ($R_{int} = 0.0530$) which were used in all calculations. The final $R_1$ was 0.0421 (I > 2σ(I)) and $wR_2$ was 0.1108 (all data).

**Refinement Details:** After data collection, the unit cell was re-determined using a subset of the full data collection. Intensity data were corrected for Lorentz, polarization, and background effects using the Bruker program APEX 3. A semi-empirical correction for adsorption was applied using the program SADABS (Krause et al., 2014). The SHELXL-2014 (Sheldrick, 2007), series of programs was used for the solution and refinement of the crystal structure. Hydrogen atoms bound to carbon atoms were located in the difference Fourier map and were geometrically constrained using the appropriate AFIX commands. The hydrogen atom bound to N2 (H2A) was last major peak found in the difference Fourier map and was allowed to refine both its position and thermal displacement parameter.
Figure S9 | Single crystal X-ray structures of the **Key Intermediate**.

Table S6 | Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\AA^2 \times 10^3$) for **Key Intermediate**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized Uij tensor for the **Key Intermediate**.

|   | x       | y       | z       | U(\text{eq}) |
|---|---------|---------|---------|-------------|
| S(1)| 4689(1) | 7266(1) | 6443(1) | 24(1)       |
| F(1)| 5300(1) | 4339(3) | 5793(1) | 33(1)       |
| F(2)| 4454(1) | 4241(3) | 5584(1) | 42(1)       |
| F(3)| 4912(1) | 7752(3) | 5385(1) | 46(1)       |
| O(1)| 5079(1) | 9725(3) | 6507(1) | 27(1)       |
| O(2)| 4802(1) | 5311(4) | 6866(1) | 29(1)       |
| O(3)| 4170(1) | 8362(4) | 6333(1) | 32(1)       |
| O(4)| 6701(1) | 11156(4)| 7681(1) | 28(1)       |
| N(1)| 5944(1) | 7780(4) | 6551(1) | 25(1)       |
| N(2)| 6581(1) | 3847(5) | 6053(1) | 26(1)       |
| C(1)| 5607(1) | 9460(5) | 6756(1) | 24(1)       |
| C(2)| 5790(1) | 11114(5)| 7213(1) | 24(1)       |
| C(3)| 6316(1) | 10326(5)| 10326(5)| 23(1)       |
| C(4)| 6418(1) | 8219(5) | 6892(1) | 25(1)       |
| C(5)| 6886(1) | 6852(5) | 6833(1) | 26(1)       |
| C(6)| 6973(1) | 4782(5) | 6435(1) | 25(1)       |
| C(7)| 7441(1) | 3366(5) | 6330(1) | 27(1)       |
| C(8)| 7318(1) | 1607(5) | 5881(1) | 28(1)       |
| C(9)| 6781(1) | 1934(5) | 5710(1) | 26(1)       |
| C(10)| 6441(1)| 607(6)  | 5257(1) | 32(1)       |
| C(11)| 6748(1)| -1408(6)| 4910(1) | 34(1)       |
| C(12)| 6538(1)| 13191(5)| 8070(1) | 28(1)       |
| C(13)| 4859(1)| 5817(5) | 5759(1) | 28(1)       |
Table S7 | Bond lengths [Å] and angles [°] for the Key Intermediate.

| Bond lengths [Å] | Bond angles [°] | Bond lengths [Å] | Bond angles [°] |
|------------------|-----------------|------------------|-----------------|
| S(1)-O(2)        | 1.4075(18)      | N(1)-C(1)-O(1)   | 120.6(2)        |
| S(1)-O(3)        | 1.4096(19)      | C(2)-C(1)-O(1)   | 121.2(2)        |
| S(1)-O(1)        | 1.5589(19)      | C(3)-C(2)-C(1)   | 102.5(2)        |
| S(1)-C(13)       | 1.836(3)        | C(3)-C(2)-H(2B)  | 128.7           |
| F(1)-C(13)       | 1.317(3)        | C(1)-C(2)-H(2B)  | 128.7           |
| F(2)-C(13)       | 1.323(3)        | O(4)-C(3)-C(2)   | 131.0(2)        |
| F(3)-C(13)       | 1.315(3)        | C(2)-C(3)-C(4)   | 107.6(2)        |
| O(1)-C(1)        | 1.413(3)        | C(5)-C(4)-N(1)   | 123.9(2)        |
| O(4)-C(3)        | 1.342(3)        | C(5)-C(4)-C(6)   | 126.2(2)        |
| O(4)-C(12)       | 1.435(3)        | C(5)-C(4)-C(3)   | 127.3(2)        |
| N(1)-C(1)        | 1.292(3)        | N(1)-C(4)-C(3)   | 108.8(2)        |
| N(1)-C(4)        | 1.406(3)        | C(4)-C(5)-C(6)   | 126.2(2)        |
| N(2)-C(9)        | 1.357(3)        | C(4)-C(5)-H(5)   | 116.9           |
| N(2)-C(6)        | 1.372(3)        | C(6)-C(5)-H(5)   | 116.9           |
| N(2)-H(2A)       | 0.79(3)         | N(2)-C(6)-C(7)   | 106.5(2)        |
| C(1)-C(2)        | 1.410(3)        | N(2)-C(6)-C(5)   | 123.6(2)        |
| C(2)-C(3)        | 1.369(3)        | C(7)-C(6)-C(5)   | 129.9(2)        |
| C(2)-H(2B)       | 0.9500          | C(6)-C(7)-C(8)   | 107.4(2)        |
| C(3)-C(4)        | 1.452(3)        | C(6)-C(7)-H(7)   | 126.3           |
| C(4)-C(5)        | 1.360(4)        | C(8)-C(7)-H(7)   | 126.3           |
| C(5)-C(6)        | 1.415(4)        | C(9)-C(8)-C(7)   | 108.6(2)        |
| C(5)-H(5)        | 0.9500          | C(9)-C(8)-H(8)   | 125.7           |
| C(6)-C(7)        | 1.391(3)        | C(7)-C(8)-H(8)   | 125.7           |
| C(7)-C(8)        | 1.393(4)        | N(2)-C(9)-C(8)   | 106.6(2)        |
| C(7)-H(7)        | 0.9500          | N(2)-C(9)-C(10)  | 121.9(2)        |
| C(8)-C(9)        | 1.382(4)        | C(8)-C(9)-C(10)  | 131.6(2)        |
| C(8)-H(8)        | 0.9500          | C(9)-C(10)-C(11) | 113.4(2)        |
| C(9)-C(10)       | 1.481(4)        | C(9)-C(10)-H(10A) | 108.9       |
| C(10)-C(11)      | 1.523(4)        | C(11)-C(10)-H(10A) | 108.9      |
| C(10)-H(10A)     | 0.9900          | C(9)-C(10)-H(10B) | 108.9       |
| C(10)-H(10B)     | 0.9900          | C(11)-C(10)-H(10B) | 108.9      |
| C(11)-H(11A)     | 0.9800          | H(10A)-C(10)-H(10B) | 107.7   |
| C(11)-H(11B)     | 0.9800          | C(10)-C(11)-H(11A) | 109.5     |
| C(11)-H(11C)     | 0.9800          | C(10)-C(11)-H(11B) | 109.5     |
| C(12)-H(12A)     | 0.9800          | H(11A)-C(11)-H(11B) | 109.5    |
| C(12)-H(12B)     | 0.9800          | C(10)-C(11)-H(11C) | 109.5    |
| C(12)-H(12C)     | 0.9800          | H(11A)-C(11)-H(11C) | 109.5    |
| O(2)-S(1)-O(3)   | 122.87(11)      | H(11B)-C(11)-H(11C) | 109.5    |
| Bond                  | Distance (Å) | Bond                  | Distance (Å) |
|-----------------------|--------------|-----------------------|--------------|
| O(2)-S(1)-O(1)        | 111.72(11)   | O(4)-C(12)-H(12A)    | 109.5        |
| O(3)-S(1)-O(1)        | 105.90(11)   | O(4)-C(12)-H(12B)    | 109.5        |
| O(2)-S(1)-C(13)       | 107.88(12)   | H(12A)-C(12)-H(12B)  | 109.5        |
| O(3)-S(1)-C(13)       | 103.76(12)   | O(4)-C(12)-H(12C)    | 109.5        |
| O(1)-S(1)-C(13)       | 102.68(11)   | H(12A)-C(12)-H(12C)  | 109.5        |
| C(1)-O(1)-S(1)        | 121.66(15)   | H(12B)-C(12)-H(12C)  | 109.5        |
| C(3)-O(4)-C(12)       | 115.28(19)   | F(3)-C(13)-F(1)      | 109.5(2)     |
| C(1)-N(1)-C(4)        | 103.0(2)     | F(3)-C(13)-F(2)      | 108.8(2)     |
| C(9)-N(2)-C(6)        | 111.0(2)     | F(1)-C(13)-F(2)      | 107.9(2)     |
| C(9)-N(2)-H(2A)       | 121(2)       | F(1)-C(13)-S(1)      | 109.97(18)   |
| C(6)-N(2)-H(2A)       | 127(2)       | F(1)-C(13)-S(1)      | 113.17(18)   |
| N(1)-C(1)-C(2)        | 118.1(2)     | F(2)-C(13)-S(1)      | 107.43(17)   |

Symmetry transformations used to generate equivalent atoms

Table S8 | Anisotropic displacement parameters (Å² x 10³) for the Key Intermediate. The anisotropic displacement factor exponent takes the form: $-2 \pi² [h² a*² U^{11} + ... + 2 h k a* b* U^{12}]$

| U11   | U22   | U33   | U23   | U13   | U12   |
|-------|-------|-------|-------|-------|-------|
| S(1)  | 26(1) | 26(1) | 21(1) | -1(1) | 10(1) |
| F(1)  | 30(1) | 37(1) | 31(1) | -9(1) | 11(1) |
| F(2)  | 33(1) | 51(1) | 43(1) | -22(1)| 3(1)  |
| F(3)  | 74(1) | 43(1) | 23(1) | 7(1)  | 16(1) |
| O(1)  | 30(1) | 23(1) | 28(1) | -2(1) | 4(1)  |
| O(2)  | 30(1) | 32(1) | 24(1) | 6(1)  | 10(1) |
| O(3)  | 27(1) | 36(1) | 33(1) | -2(1) | 5(1)  |
| O(4)  | 26(1) | 32(1) | 26(1) | -6(1) | 8(1)  |
| N(1)  | 27(1) | 24(1) | 23(1) | 1(1)  | 11(1) |
| N(2)  | 24(1) | 30(1) | 26(1) | 0(1)  | 12(1) |
| C(1)  | 27(1) | 24(1) | 21(1) | 4(1)  | 5(1)  |
| C(2)  | 29(1) | 22(1) | 21(1) | -1(1) | 11(1) |
| C(3)  | 28(1) | 24(1) | 18(1) | 2(1)  | 11(1) |
| C(4)  | 28(1) | 24(1) | 23(1) | 2(1)  | 11(1) |
| C(5)  | 27(1) | 28(1) | 24(1) | 1(1)  | 12(1) |
| C(6)  | 26(1) | 25(1) | 25(1) | 2(1)  | 12(1) |
| C(7)  | 26(1) | 26(1) | 30(1) | 0(1)  | 10(1) |
| C(8)  | 27(1) | 28(1) | 29(1) | 1(1)  | 13(1) |
| C(9)  | 31(1) | 24(1) | 23(1) | 1(1)  | 12(1) |
| C(10) | 30(1) | 36(2) | 31(2) | -5(1) | 9(1)  |
| C(11) | 34(2) | 37(2) | 31(2) | -8(1) | 15(1) |
| C(12) | 31(1) | 28(1) | 26(1) | -5(1) | 9(1)  |
| C(13) | 32(1) | 30(2) | 24(1) | -1(1) | 7(1)  |

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Table S9 | Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for the Key Intermediate.

|   | x      | y      | z      | U(eq) |
|---|--------|--------|--------|-------|
| H(2A) | 6282(12) | 4380(60) | 6006(12) | 28(8) |
| H(2B) | 5596   | 12441  | 7410   | 28    |
| H(5)  | 7184   | 7333   | 7082   | 31    |
| H(7)  | 7782   | 3562   | 6528   | 32    |
| H(8)  | 7562   | 388    | 5720   | 33    |
| H(10A) | 6283  | 2010   | 5000   | 38    |
| H(10B) | 6140  | -340   | 5432   | 38    |
| H(11A) | 6504  | -2186  | 4613   | 51    |
| H(11B) | 6893  | -2849  | 5158   | 51    |
| H(11C) | 7046  | -485   | 4734   | 51    |
| H(12A) | 6843  | 13661  | 8331   | 43    |
| H(12B) | 6241  | 12502  | 8286   | 43    |
| H(12C) | 6418  | 14800  | 7857   | 43    |

Table S10 | Hydrogen bonds for the Key Intermediate.

| D-H     | d(D-H) | d(H..A) | <DHA  | d(D..A) | A   |
|---------|--------|---------|-------|---------|-----|
| N2-H2A  | 0.791  | 2.461   | 159.77| 3.215   | F1  |
| N2-H2A  | 0.791  | 2.304   | 122.23| 2.806   | N1  |
Section G. References

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