

## SUPPORTING INFORMATION

# Discovery of Spiro oxazolidinediones as Selective, Orally Bioavailable Inhibitors of p300/CBP Histone Acetyltransferases

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## IN-VITRO BIOLOGY

### P300 HAT Domain Enzyme Inhibition Assay.

P300 HAT inhibitory activity was assessed using a radiometric scintillation proximity assay measuring the transfer of a 3H-Acetyl group from 3H-Acetyl-CoA to a biotinylated peptide by purified p300-HAT domain, as previously described.

Reactions were performed in a 40 µL volume in polypropylene 96 well 300 µL plates (Greiner) in reaction buffer (100 mM HEPES buffer; pH 7.9, 80 µM EDTA, 40ug/mL BSA, 100 mM KCl, 1 mM DTT, 0.01% triton X-100 and 5% DMSO). The test compounds were dissolved in DMSO to generate 10 mM stocks and further diluted with 10mM HEPES, pH 7.8 with 20% DMSO to make 4X intermediate concentrations. Compounds were tested from 120 µM to 2 nM in 3-fold dilutions. 10 µL of the compound stock was added to 20 µL of p300 HAT enzyme at 10 nM (2x of final concentration) and incubated at room

temperature for 30 minutes. The reaction was initiated by adding 10  $\mu\text{L}$  of a 4X substrate mix consisting of a biotinylated synthetic Histone H4 Peptide (Biotin-C6-GRGKGGKGLGKGGAK) at 100  $\mu\text{M}$ , 1.8  $\mu\text{M}$  cold acetyl coenzyme A (Moravek) and 0.6  $\mu\text{M}$  tritiated acetyl coenzyme A (Sigma). The reaction was incubated for one hour at room temperature and terminated with the addition of 160  $\mu\text{L}$  of 0.5 N HCl. The reaction contents were then transferred to a 96 well streptavidin and scintillant-coated microplate (Perkin Elmer), incubated for 1 hour, and counted in a Top Count (Perkin Elmer) microplate scintillation counter at one minute per well. IC<sub>50</sub> values were generated based on percent inhibition calculated from the scintillation counter readings.

#### **Cellular Inhibition assay : Inhibition of H3K27 Ac in PC-3 cells.**

The ability of compounds to inhibit p300 in cells was assessed by measuring inhibition of H3K27 Acetylation levels via high content microscopy , as previously disclosed.

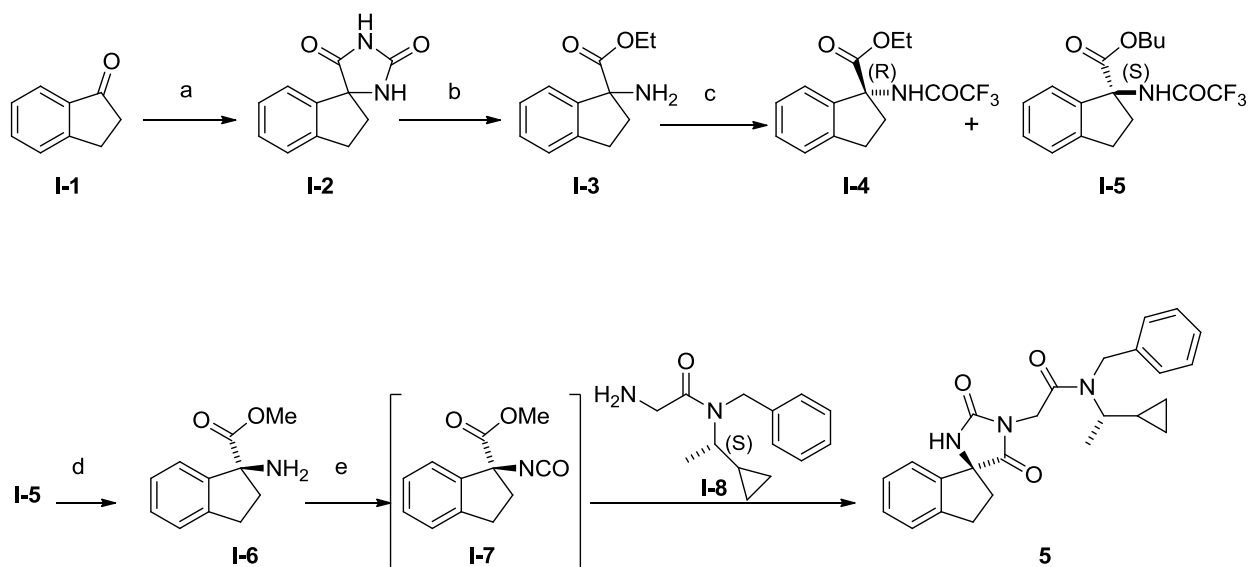
PC-3 cells were plated in Collagen I coated 96-well view plates (Perkin Elmer Cat #: 6005810) then treated with an 8 point half-log dose response of compound starting at 10  $\mu\text{M}$  for 3 h. Cells were fixed in 10% formaldehyde (Polysciences, Inc. #04018) at room temperature for 10 min, washed in PBS, and then permeabilized in 0.1% Triton X-100 for 10 min. Cells were then blocked in 1% BSA for 1 h and incubated with the incubated antibodies in antibody dilution buffer (0.3% BSA in PBS) overnight at 4 °C. Cells were washed three times in PBS and then incubated with a mixture of Alexa Fluor488-conjugated goat anti-rabbit IgG antibodies (Life Technologies, #A-11029), Alexa Fluor555-conjugated goat anti-mouse IgG (Life Technologies, #A-21424) antibodies, and Hoechst 33342 (Life Technologies, #H3570) for 1 h at room temperature. After washing four times in PBS, plates were scanned within 24 h of processing on a ThermoFisher CellInsight using the target activation algorithm acquiring 15 fields per well. Fluorescence intensities were quantified using the average mean intensity function. EC<sub>50</sub> values for H3K27Ac, H3K18Ac, and H3K9Ac inhibition were calculated using a sigmoidal fit of the concentration/inhibition response curves using Prism GraphPad 5.

## **CHEMISTRY**

## General Experimental

### Synthesis of enantiomerically pure hydantoins 5-8.

#### Representative Synthesis of Compound 5



Supplemental Scheme 1. (a)  $(\text{NH}_4)_2\text{CO}_3$ , NaCN, rt.; (b)  $\text{Ba}(\text{OH})_2$ , 150 °C ;(c) 1. CAL-B,  $\text{BuOCOCBu}$ ; 2.TFAA; (d) 1. HCl, 2.  $\text{SOCl}_2$ , MeOH; (e)  $\text{Et}_3\text{N}$ , triphosgene

#### **2',3'-dihydrospiro[imidazolidine-4,1'-indene]-2,5-dione (I-2)**

A solution of **I-1** (9.0 g, 68.0 mmol) in water (90 mL) and ethanol(90 mL) was treated with  $(\text{NH}_4)_2\text{CO}_3$  (65.3 g, 680 mmol) and NaCN (10.0 g, 204 mmol) at room temperature, then heated at 70 °C overnight. After being cooled to room temperature and concentrated, the residue was purified by silica gel column chromatography eluting with 100% EtOAc/Hexane to afford **I-2** (8.92 g, 65%). LC-MS:  $m/z$  = 203.2  $[\text{M}+\text{H}]^+$

#### **ethyl 1-amino-2,3-dihydro-1H-indene-1-carboxylate (I-3)**

A suspension of Intermediate **I-2** (5.70 g, 27.80 mmol) and  $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$  (13.50 g, 42.71 mmol) in distilled water (114 mL) was heated at 150 °C in a sealed steel reactor for 72 h. The reaction mixture was cooled to room temperature and acidified to pH 1.6 with  $\text{H}_2\text{SO}_4$ , (1 M). The precipitate was filtered off and the filtrate was evaporated to dryness. The residue was suspended in EtOH (200 mL), cooled to 0

°C, treated with SOCl<sub>2</sub> (2.47 mL, 33.82 mmol) then heated to reflux for 24 h, before being evaporated to dryness. Water (80 mL) was then added and the pH was adjusted with aqueous NH<sub>4</sub>OH (25%) to pH 9–10 (indicated by pH paper). The aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×50 mL) and the combined organic layers were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated, affording **I-3** (4.18 g, 20.39 mmol, 73%). LC-MS:  $m/z = 206.0[M+H]^+$

**(R)-ethyl 1-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-indene-1-carboxylate (I-4) and (S)-butyl 1-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-indene-1-carboxylate (I-5)**

CAL-B (4.5 g, 50 mg/mL) was added to a solution of **I-3** (0.90 g, 4.39 mmol) and BuCO<sub>2</sub>Bu (6.34 g, 44.00 mmol) in isopropyl ether (90.0 mL) in the presence of 4 Å MS (30 mg/mL). The reaction was stopped at 49% conversion by filtering off the enzyme after 24 h. (CF<sub>3</sub>CO)<sub>2</sub>O (5.26 g, 21.80 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) was added to the above filtrate and the reaction mixture was stirred for 2 h before evaporating the solvent. The residue was purified on a silica gel column (petroleum ether/EtOAc, 20:1), affording **I-4** ( $R_f = 0.10$ ; 0.62 g, 2.06 mmol, 47%, 92% *ee*). LC-MS:  $m/z = 302.2[M+H]^+$  and **I-5** ( $R_f = 0.17$ ; 0.69 g, 0.70 mmol, 48%, 99% *ee*). LC-MS:  $m/z = 330.2[M+H]^+$  as oils.

**(S)-methyl 1-amino-2,3-dihydro-1H-indene-1-carboxylate (I-6)**

Hydrolysis of **I-5** (81.0 mg, 0.17 mmol) in aqueous HCl (6 M) for 2 days at reflux produced (S)-1-amino-2,3-dihydro-1H-indene-1-carboxylic acid hydrochloride (42.0 mg, 0.24 mmol, 98%). LC-MS:  $m/z = 178.0[M+H]^+$

To a stirring solution of (S)-1-amino-2,3-dihydro-1H-indene-1-carboxylic acid hydrochloride (0.2 g, 1.13 mmol) in MeOH (10 mL) was added SOCl<sub>2</sub> (266 mg, 2.26 mmol) at 0 °C and the reaction mixture was stirred at r.t. for 30 min. The solvent was removed under reduced pressure to afford **I-6** (0.20 g, 93%) as an oil. TLC: 50% EtOAc/hexane ( $R_f$ : 0.2)

**N-benzyl-N-[(1S)-1-cyclopropylethyl]-2-[(4S)-2,5-dioxo-2',3'-dihydro-1H-spiro[imidazolidine-4,1'-inden]-1-yl]acetamide (5)**

A solution of **I-6** (45 mg, 0.24 mmol) in 10 mL CH<sub>2</sub>Cl<sub>2</sub> was cooled to 0 °C, then treated with triethylamine (25 mg, 0.24 mmol) and triphosgene (24 mg, 0.08 mmol). The resulting mixture

was stirred overnight at r.t. and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc and the precipitate was filtered off. The EtOAc extract was concentrated to give 43 mg of the crude product (*R*)-methyl 1-isocyanato-2,3-dihydro-1*H*-indene-1-carboxylate (**I-7**), which was used directly in next step. **I-7** (43 mg, 0.2 mmol) and amine **I-8** (46 mg, 0.2 mmol) were dissolved in 10 mL CH<sub>2</sub>Cl<sub>2</sub> and stirred at room temperature for 3 h and the solvent was removed under reduced pressure. The residue was dissolved in 5 mL of THF and treated with a solution of LiOH.H<sub>2</sub>O (10 mg) in 1 mL water added dropwise. After stirring for 1 h, the reaction mixture was concentrated *in vacuo*, purified by column using 50% 20 EtOAc in petroleum ether to provide 35 mg of desired product **5**. (42% yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 120 °C) δ 8.28 (s, 1H), 7.41 – 7.06 (m, 9H), 4.66 (s, 2H), 4.24 (s, 2H), 3.76 (s, 1H), 3.60 (s, 1H), 3.52 – 3.40 (m, 1H), 2.57 (dt, *J* = 13.4, 6.7 Hz, 1H), 2.23 (dt, *J* = 13.4, 7.7 Hz, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 0.96 (ddt, *J* = 10.5, 5.0, 2.5 Hz, 1H), 0.53 – 0.41 (m, 1H), 0.24 (dtt, *J* = 14.5, 5.3, 3.4 Hz, 3H). MS (ESI<sup>+</sup>) *m/z* 418 (M+H)<sup>+</sup>.

Compounds **6-8** were prepared in similar fashion starting with either **I-4** or **I-5** and coupling with either (S) or (R) 2-amino-*N*-benzyl-*N*-(1-cyclopropylethyl)acetamide.

**N-benzyl-N-[(1S)-1-cyclopropylethyl]-2-[(4R)-2,5-dioxo-2',3'-dihydro-1H-spiro[imidazolidine-4,1'-inden]-1-yl]acetamide (6)**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.28 (s, 1H), 7.39 – 7.14 (m, 9H), 4.66 (s, 2H), 4.33 – 4.16 (m, 2H), 3.61 (s, 1H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.57 (dt, *J* = 13.4, 6.7 Hz, 1H), 2.23 (dt, *J* = 13.3, 7.7 Hz, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.03 – 0.87 (m, 1H), 0.55 – 0.40 (m, 1H), 0.35 – 0.11 (m, 3H). MS (ESI<sup>+</sup>) *m/z* 418 (M+H)<sup>+</sup>.

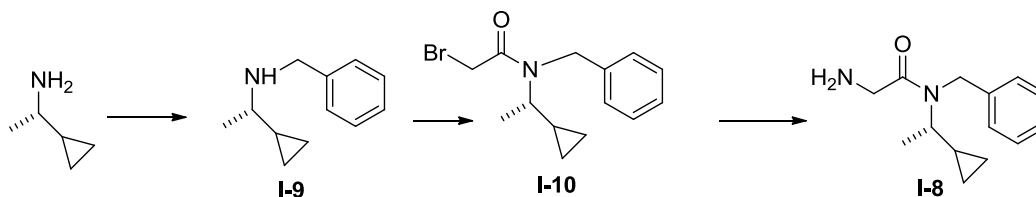
**N-benzyl-N-[(1R)-1-cyclopropylethyl]-2-[(4S)-2,5-dioxo-2',3'-dihydro-1H-spiro[imidazolidine-4,1'-inden]-1-yl]acetamide (7)**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.28 (s, 1H), 7.39 – 7.14 (m, 9H), 4.66 (s, 2H), 4.33 – 4.16 (m, 2H), 3.61 (s, 1H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.57 (dt, *J* = 13.4, 6.7 Hz, 1H), 2.23 (dt, *J* = 13.3, 7.7 Hz, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.03 – 0.87 (m, 1H), 0.55 – 0.40 (m, 1H), 0.35 – 0.11 (m, 3H). MS (ESI<sup>+</sup>) *m/z* 418 (M+H)<sup>+</sup>.

**N-benzyl-N-[(1R)-1-cyclopropylethyl]-2-[(4R)-2,5-dioxo-2',3'-dihydro-1H-spiro[imidazolidine-4,1'-inden]-1-yl]acetamide (8)**

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ,  $120^\circ\text{C}$ )  $\delta$  7.38 – 7.11 (m, 8H), 4.65 (s, 2H), 4.23 (s, 2H), 3.04 (t,  $J$  = 7.2 Hz, 2H), 1.14 (d,  $J$  = 6.7 Hz, 3H), 0.32 – 0.14 (m, 3H). MS (ESI $^+$ )  $m/z$  418 (M+H) $^+$ .

**Preparation of intermediate chiral amine I-8**



**(S)-N-benzyl-1-cyclopropylethanamine (I-9)**

A stirring solution of (S)-1-cyclopropylethanamine (3.0 g, 35.2 mmol) in MeOH (30 mL) at r.t. was treated with benzaldehyde (2.0 g, 18.8 mmol) followed by NaBH(OAc)<sub>3</sub> (4.0 g, 18.5 mmol). The reaction mixture was stirred at r.t. overnight, then diluted with 1 N NaOH (50 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. Combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 5% MeOH/ CH<sub>2</sub>Cl<sub>2</sub> to afford compound I-9 (5.1 g, 90%). LC-MS:  $m/z$  = 176.2 [M+H] $^+$

**(S)-N-benzyl-2-bromo-N-(1-cyclopropylethyl)acetamide (I-10)**

A solution of I-9 (70 mg, 0.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) cooled to 0 °C was treated with 2-bromoacetyl bromide (0.1 g, 0.48 mmol), the mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction mixture was partitioned between saturated NaHCO<sub>3</sub> solution and CH<sub>2</sub>Cl<sub>2</sub>. (extracted twice). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to obtain crude product 3 (0.13 g, 88%), which was used to the next step without any other purification. LC-MS:  $m/z$  = 296.2/298.2 [M+H] $^+$

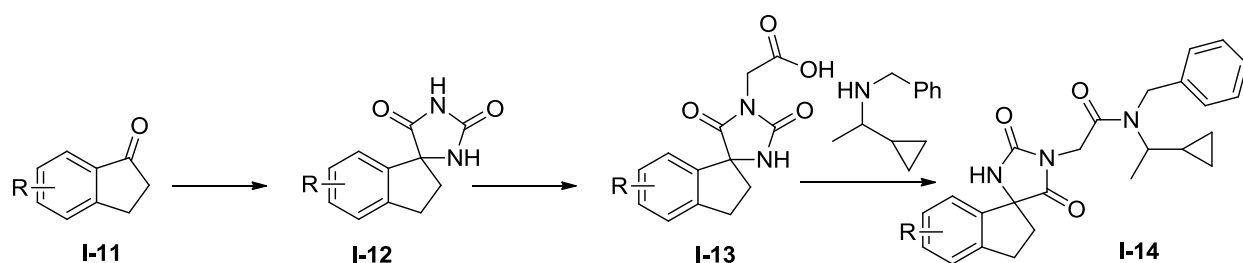
**(S)-2-amino-N-benzyl-N-(1-cyclopropylethyl)acetamide (I-8)**

A solution of (S)-N-benzyl-2-bromo-N-(1-cyclopropylethyl)acetamide 3 (70 mg, 0.25 mmol) in DMSO (20 mL) was treated with NaN<sub>3</sub> (34 mg, 0.3 mmol) then stirred at room temperature for 1 h. The reaction mixture was diluted with cold water and extracted twice with EtOAc. Combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to obtain crude

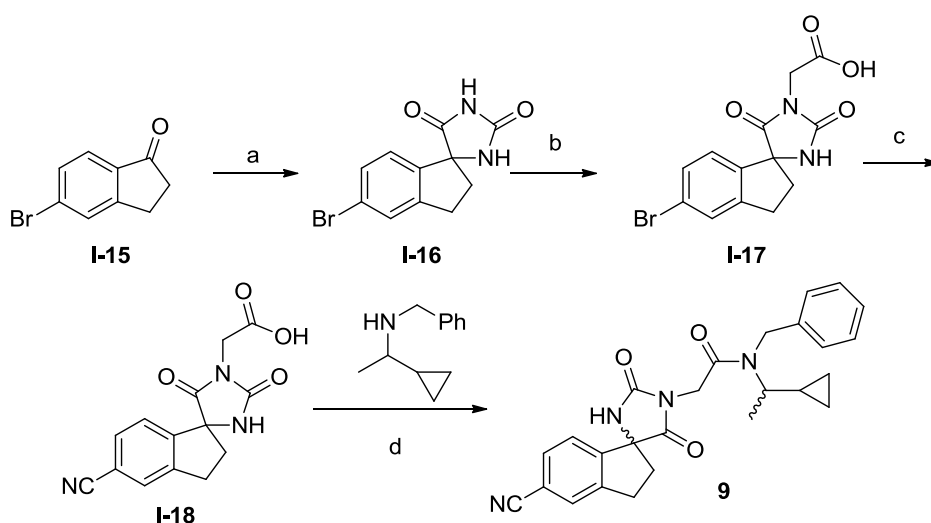
product (S)-2-azido-N-benzyl-N-(1-cyclopropylethyl)acetamide (0.1 g, 93%), which was used to the next step without any other purification. LC-MS:  $m/z = 259.1[M+H]^+$

To a stirring solution of the azide from the previous step (0.1 g, 0.25 mmol) in 80% THF/H<sub>2</sub>O (5 mL) was added PPh<sub>3</sub> (0.12 g, 0.3 mmol) at 40 °C and stirred for 1 h. The reaction mixture was diluted with cold water and extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. Combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography to afford the amine **I-8** (70 mg, 87%) as a yellow oil. LC-MS:  $m/z = 233.2[M+H]^+$

### General synthesis of hydantoins (compounds 9-19)



### Representative Synthesis of Compound 9



Supplemental Scheme 2. (a) (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub>, KCN ; (b) 1. BrCH<sub>2</sub>COOtBu, 2. TFA; (c) Zn(CN)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>; (d) HATU

**5'-bromo-2',3'-dihydrospiro[imidazolidine-4,1'-indene]-2,5-dione (I-16):**

A solution of indanone **I-15** (11.7 g, 55.4 mmol) in 60% EtOH/H<sub>2</sub>O (80 mL) was treated with (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> (15.9 g, 0.17 mol) followed by potassium cyanide (5.4 g, 83.5 mmol) at r.t. The reaction mixture was heated to 70 °C for 16 h, then cooled to r.t. diluted with water and extracted twice with EtOAc. The combined organic layers was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford compound **I-16** (12.7 g, 81%). LC-MS: *m/z* = 281.1/283.1 [M+H]<sup>+</sup>

**2-(5'-bromo-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-indene]-1-yl)acetic acid (I-17)**

A solution of **I-16** (1.0 g, 3.5 mmol) in DMF (20 mL) at r.t. was treated with tert-butyl-2-bromoacetate (0.73 g, 3.7 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.0 g, 7.1 mmol) then stirred at room temperature overnight. The reaction mixture was diluted with water and extracted twice with EtOAc. Combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to obtain crude product tert-butyl 2-(5'-bromo-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-indene]-1-yl)acetate (1.6 g, 95%), which was used to the next step without any other purification. LC-MS: *m/z* = 395.1/397.1 [M+H]<sup>+</sup>

A solution of the product from above (1.6 g, 4.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) at 0 °C was treated with trifluoroacetic acid (4 ml) , then stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to obtain crude product, which was used to the next step without any other purification as compound **I-17** (1.3 g, 90%) as an off-white solid. LC-MS: *m/z* = 339.1/341.1 [M+H]<sup>+</sup>

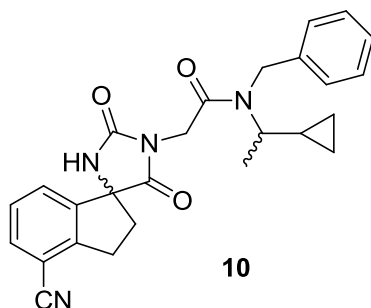
**2-(5'-cyano-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-indene]-1-yl)acetic acid (I-18)**

A solution of compound **I-17** (0.3 g, 0.9 mmol) in DMF (4 mL) was treated with Pd(PPh<sub>3</sub>)<sub>4</sub> (0.1 g, 0.1 mmol) and Zn(CN)<sub>2</sub> (0.1 g, 0.9 mmol) and stirred at 160 °C under microwave for 1 hour. After consumption of the starting material (by TLC), the reaction mixture was diluted with water and extracted with EtOAc. Combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to obtain crude product used to the next step without any other purification as compound **3** (0.12 g, 41%)

**N-benzyl-2-(5'-cyano-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-N-(1-cyclopropylethyl)acetamide (9)**

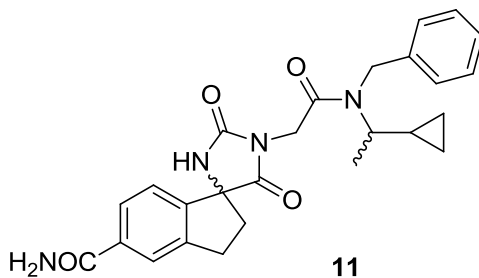


To a stirring solution of **I-18** (100 mg, 0.35 mmol) in DMF (10 mL) was added racemic N-benzyl-1-cyclopropylethanamine (61 mg, 0.35 mmol) and DIPEA (55 mg, 0.43 mmol) at room temperature and stirred for 2 mins, then HATU (0.15 g, 0.38 mmol) was added and the reaction mixture was stirred at r.t. for 1 h. The solvent from the reaction was concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography to afford **9** (15 mg, 18%) as an off-white solid. LC-MS:  $m/z = 443.1[M+H]^+$  at RT 1.68 (100% purity).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.92 (d,  $J = 18.2$  Hz, 1H), 7.86(s, 1H), 7.79-7.77 (m, 1H), 7.57 – 7.44 (m, 1H), 7.47 – 7.32 (m, 2H), 7.25 (dt,  $J = 18.9, 9.7$  Hz, 3H), 4.85 – 4.56 (m, 2H), 4.53 – 4.24 (m, 1H), 4.26 – 4.11 (m, 1H), 3.73 (dd,  $J = 16.6, 7.6$  Hz, 1H), 3.10 (dd,  $J = 13.8, 6.8$  Hz, 2H), 2.69 – 2.55 (m, 1H), 2.27 (ddd,  $J = 20.9, 13.0, 7.9$  Hz, 1H), 1.30 – 1.04 (m, 3H), 0.93 (d,  $J = 7.6$  Hz, 1H), 0.49 (d,  $J = 8.2$  Hz, 1H), 0.42 – 0.06 (m, 3H).



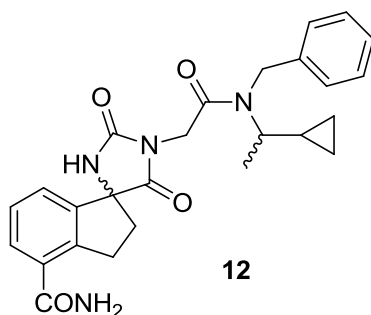
**N-benzyl-2-(4'-cyano-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-N-(1-cyclopropylethyl)acetamide (10)**

Compound **10** was prepared in similar fashion as **9**, starting with 4-bromo-2,3-dihydro-1H-inden-1-one in place of **I-15**. LC-MS:  $m/z = 443[M+H]^+$  at RT 1.61 (96.4% purity).  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ ):  $\delta$  8.91 (d,  $J = 17.7$  Hz, 1H), 7.84 (d,  $J = 7.6$  Hz, 1H), 7.70 – 7.62 (m, 1H), 7.51 (dd,  $J = 15.8, 7.9$  Hz, 1H), 7.44 – 7.16 (m, 5H), 4.75 (s, 1H), 4.63 (d,  $J = 6.6$  Hz, 1H), 4.52 – 4.10 (m, 2H), 3.73 (d,  $J = 9.2$  Hz, 1H), 3.37 (d,  $J = 6.9$  Hz, 1H), 3.30 – 3.12 (m, 2H), 2.65 (dd,  $J = 14.0, 6.0$  Hz, 1H), 2.38 – 2.24 (m, 1H), 1.25 – 1.05 (m, 3H), 0.94 (s, 1H), 0.58 – 0.08 (m, 4H).



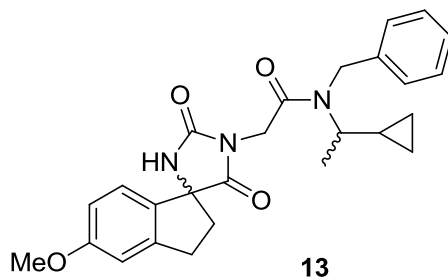
**1-(2-(benzyl(1-cyclopropylethyl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-indene]-5'-carboxamide (11)**

A solution of compound **9** (40 mg, 0.1 mmol) in MeOH (4 ml) was treated with NaOH (36 mg, 1 mmol) followed by H<sub>2</sub>O<sub>2</sub> (2 mL), and the resulting mixture was stirred at room temperature for 3 h then extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to obtain compound **11** as white solid (15 mg, 34%). LC-MS:  $m/z$  = 461.1[M+H]<sup>+</sup> at RT 1.44 (100% purity). <sup>1</sup>H NMR (400 MHz, DMSO *d*<sub>6</sub>)  $\delta$  8.83 (d, *J* = 17.5 Hz, 1H), 8.05 – 7.69 (m, 3H), 7.52 – 7.10 (m, 5H), 4.72–4.60 (m, 2H), 4.35 (ddd, *J* = 27.4, 15.8, 7.2 Hz, 1H), 4.20 (d, *J* = 3.6 Hz, 1H), 3.73 (s, 1H), 3.17 – 2.97 (m, 2H), 2.65 – 2.54 (m, 1H), 2.28 (m, 1H), 1.30 – 1.04 (m, 3H), 0.91 (d, *J* = 33.0 Hz, 1H), 0.47 (s, 1H), 0.42 – 0.07 (m, 3H).



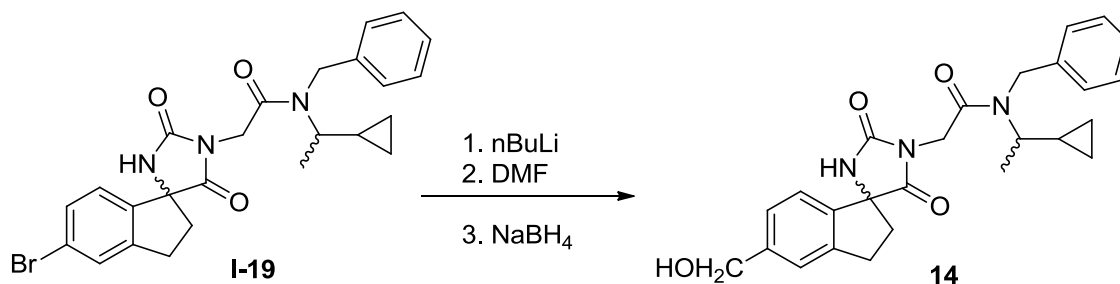
**1-(2-(benzyl(1-cyclopropylethyl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[indene-4,1'-indene]-4'-carboxamide (**12**)**

Compound **12** was prepared from **10**, as described for **11**. LC-MS:  $m/z$  = 461[M+H]<sup>+</sup> at RT 1.44 (96.4% purity). <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>): $\delta$  8.83 (d, *J* = 17.1 Hz, 1H), 7.85 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.52 – 7.13 (m, 7H), 4.75 (s, 1H), 4.63 (d, *J* = 5.5 Hz, 1H), 4.51 – 4.13 (m, 2H), 3.73 (dd, *J* = 16.2, 7.0 Hz, 1H), 3.44 – 3.36 (m, 1H), 3.32 – 3.16 (m, 2H), 2.55 (d, *J* = 5.2 Hz, 1H), 2.27 – 2.12 (m, 1H), 1.25 – 1.06 (m, 3H), 0.94 (s, 1H), 0.57 – 0.07 (m, 4H).



**N-benzyl-N-(1-cyclopropylethyl)-2-(5'-methoxy-2,5-dioxo-2',3'-dihydrospiro[indene-4,1'-inden]-1-yl)acetamide (**13**)**

Compound **13** was prepared in similar fashion as **9**, starting with 5-methoxy-2,3-dihydro-1H-inden-1-one in place of **I-15**. LC-MS:  $m/z = 448.2[M+H]^+$ .  $^1H$  NMR (400MHz, DMSO- $d_6$ ):  $\delta$  8.73 (d,  $J = 16.6$  Hz, 1H), 7.39 (q,  $J = 8.1$  Hz, 2H), 7.33 – 7.13 (m, 4H), 6.89 (s, 1H), 6.83 (dd,  $J = 10.3, 4.2$  Hz, 1H), 4.74 (s, 1H), 4.62 (s, 1H), 4.48 – 4.11 (m, 2H), 3.75 (d,  $J = 2.7$  Hz, 3H), 3.39 (d,  $J = 7.3$  Hz, 1H), 3.00 (d,  $J = 6.5$  Hz, 2H), 2.58 (d,  $J = 7.5$  Hz, 1H), 2.25 – 2.13 (m, 1H), 1.22 – 1.06 (m, 3H), 0.93 (d,  $J = 9.5$  Hz, 1H), 0.57 – 0.43 (m, 1H), 0.41 – 0.06 (m, 3H).

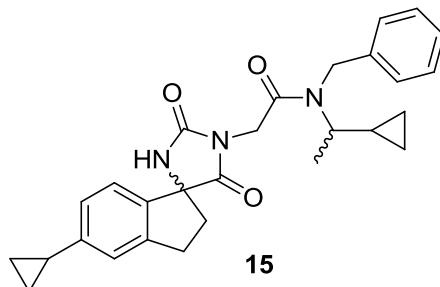


**N-benzyl-N-(1-cyclopropylethyl)-2-(5'-(hydroxymethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)acetamide (**14**)**

A solution of N-benzyl-2-(5'-bromo-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-N-(1-cyclopropylethyl)acetamide (0.48 g, 0.96 mmol- prepared by coupling **I-17** with racemic N-benzyl-1-cyclopropylethanamine) in THF (20 mL) was cooled to  $-78^\circ\text{C}$  and treated with 2.5 M n-BuLi (1.2 mL, 2.88 mmol) , stirred for 15 min at  $-78^\circ\text{C}$ , then treated with DMF (0.14 g, 1.92 mmol). The reaction mixture was stirred for 30 min at  $-78^\circ\text{C}$ , then quenched by addition of water and extracted twice with EtOAc. The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 50% EtOAc /petroleum ether to afford N-benzyl-N-(1-cyclopropylethyl)-2-(5'-formyl-2,5-dioxo-2',3'- dihydrospiro[imidazolidine-4,1'-indene]-1-yl)acetamide (0.22 g, 51%).LC-MS:  $m/z = 446.2$   $[M+H]^+$

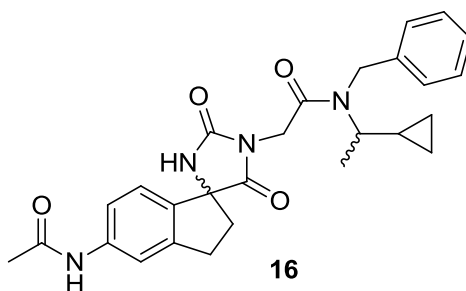
A solution of the formate from above (220 mg, 0.49 mmol) in  $\text{CH}_3\text{OH}/\text{THF}$  (10mL/1 mL, V/V) was treated with  $\text{NaBH}_4$  (37 mg, 0.98 mmol) at  $0^\circ\text{C}$  stirred at r.t. for 30 min then diluted with water and extracted twice with EtOAc. The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to obtain crude product, which was purified by Prep-HPLC to afford compound **14** (0.15 g, 68%). **LC-MS**:  $m/z = 448.2$   $[M+H]^+$  at RT 3.97 (98.11% purity)  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.76 (d,  $J = 12.9$  Hz, 1H), 7.45 – 7.06 (m, 15 8H), 4.67 (d,  $J = 36.8$  Hz, 2H), 4.51 – 4.25 (m, 3H), 4.18 (d,  $J = 2.3$  Hz, 1H), 3.75-3.68

(s,0.5H), 3.42 – 3.31 (m, 0.5H), 3.01 (dd, J = 11.4, 6.9 Hz, 2H), 2.61 – 2.51 (m, 1H), 2.20(dd, J = 13.3, 7.7 Hz, 1H), 1.21 – 1.04 (m, 3H), 0.97-0.92 (m, 1H), 0.52 – 0.09 (m, 4H).



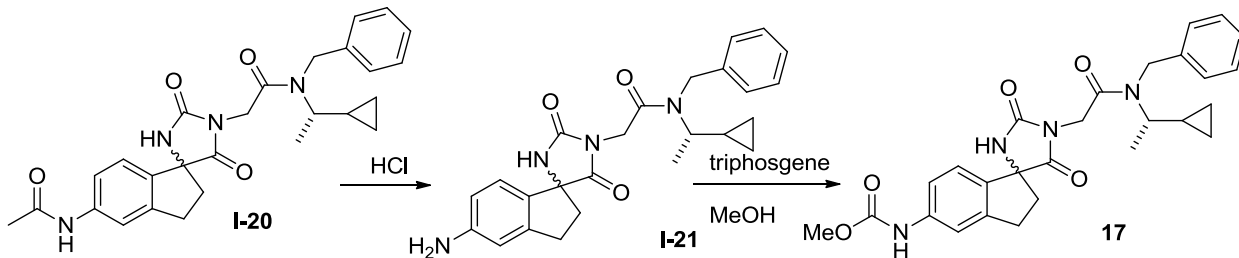
**N-benzyl-2-(5'-cyclopropyl-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-N-(1-cyclopropylethyl)acetamide (15)**

Compound **15** was prepared in similar fashion as **9**, starting with 5-cyclopropyl-2,3-dihydro-1H-inden-1-one in place of **I-15**. LC-MS:  $m/z = 458.0[M+H]^+$  at RT 5.081 (98.03% purity).  $^1H$  NMR (400 MHz, DMSO):  $\delta$  8.72 (d, J = 16.6 Hz, 1H), 7.63 – 6.86 (m, 8H), 4.90 – 4.06 (m, 4H), 3.71 (s, 0.6H), 3.38 (s, 0.4H), 3.17 – 2.83 (m, 2H), 2.27 – 2.07 (m, 1H), 1.92 (d, J = 3.3 Hz, 1H), 1.30 – 1.04 (m, 3H), 0.94 (d, J = 8.3 Hz, 3H), 0.66 (s, 2H), 0.57 – 0.04 (m, 5H).



**2-(5'-acetamido-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-N-benzyl-N-(1-cyclopropylethyl)acetamide(16)**

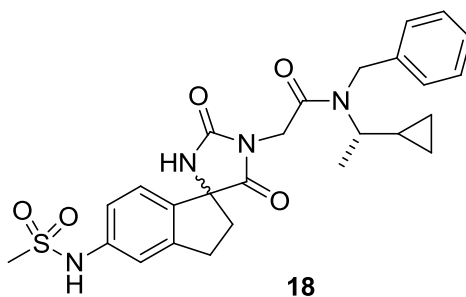
Compound **16** was prepared in similar fashion as **9**, starting with N-(1-oxo-2,3-dihydro-1H-inden-5-yl)acetamide in place of **I-15** LC-MS:  $m/z = 475[M+H]^+$  at RT 1.38 (98.96% purity).  $^1H$  NMR (400MHz, DMSO-d<sub>6</sub>):  $\delta$  9.99 (s, 1H), 8.74 (d, J = 16.9 Hz, 1H), 7.64 (d, J = 4.6 Hz, 1H), 7.50 – 7.13 (m, 3H), 4.74 (s, 1H), 4.62 (s, 1H), 4.47 – 4.11 (m, 1H), 3.80 – 3.66 (m, 1H), 3.45 (m, 1H), 3.00 (dd, J = 13.2, 6.4 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.27 – 2.14 (m, 1H), 2.06 (d, J = 14.4 Hz, 1H), 1.26 – 1.04 (m, 2H), 0.94 (s, 1H), 0.52 – 0.09 (m, 2H).



**Methyl (1-(2-(benzyl((S)-1-cyclopropylethyl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)carbamate (**17**)**

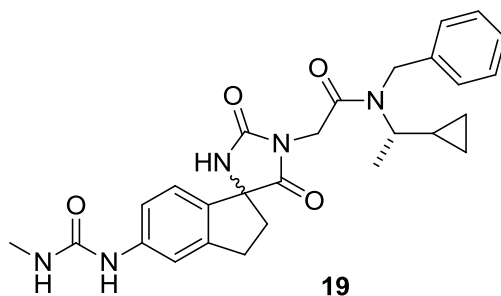
A solution of **I-20** [2-(5'-Acetamido-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-indene]-1-yl)-N-benzyl-N-((S)-1-cyclopropylethyl)acetamide- prepared by reacting 2-(5'-acetamido-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)acetic acid with enantiomerically pure (S) N-benzyl-1-cyclopropylethanamine] (150 mg, 0.316 mmol) in MeOH (4 mL) was treated with con. HCl (1 mL) followed by H<sub>2</sub>O (1 mL) at r.t. The reaction mixture was heated to 80 °C for 1 h then cooled to room temperature, neutralized with 4M NaOH solution and the resulting precipitate was filtered and dried to afford 2-(5'-Amino-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-indene]-1-yl)-N-benzyl-N-((S)-1-cyclopropylethyl)acetamide (**I-21**) (85 mg, 62%) as an yellow solid. LC-MS:  $m/z$  = 433[M+H]<sup>+</sup>

A solution of **I-21** (39 mg, 0.0903 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) at 0 °C was treated with triphosgene (10.7 mg, 0.03612 mmol) followed by Et<sub>3</sub>N (10.9 mg, 0.1084 mmol) , then allowed to warm up to r.t., stirred an additional 2 h, then diluted with MeOH (3 mL) and stirred at r.t. for 2 h. The reaction mixture was concentrated under reduced pressure to obtain the crude product, which was purified by Prep-TLC eluting with 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford **17** (20 mg, 45%) as a white solid. LC-MS:  $m/z$  = 491.0[M+H]<sup>+</sup>. <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>): δ 9.72 (s, 1H<sup>+</sup>), 8.73 (d, J = 16.6 Hz, 1H), 7.52 – 7.07 (m, 8H), 4.74 (s, 1H), 4.62 (s, 1H), 4.47 – 4.15 (m, 2H), 3.69 (d, J = 16.0 Hz, 3H), 3.38 (s, 1H), 2.99 (dd, J = 13.0, 6.6 Hz, 2H), 2.54 (d, J = 7.0 Hz, 1H), 2.28 – 2.11 (m, 1H), 1.21 – 1.06 (m, 3H), 0.94 (s, 1H), 0.56 – 0.12 (m, 4H).



**N-benzyl-N-((S)-1-cyclopropylethyl)-2-(5'-(methylsulfonamido)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)acetamide (18)**

A solution of **I-21** (0.05 g, 0.115 mmol), in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) was cooled to 0 °C, treated with triethylamine (35 mg, 0.345 mmol) followed by CH<sub>3</sub>SO<sub>2</sub>Cl (26 mg, 0.23 mmol), then stirred at 0 °C for 1 h. The solvent from the reaction mixture was removed under reduced pressure, the residue was diluted with brine and extracted with EtOAc. Combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to obtain crude bis sulfonylated product N-benzyl-N-((S)-1-cyclopropylethyl)-2-(5'-(N-(methylsulfonyl)methylsulfonamido)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)acetamide. The crude product was dissolved in THF (5 mL) and water (5 mL), treated with K<sub>2</sub>CO<sub>3</sub> (35 mg, 0.255 mmol), stirred for 2 h, then concentrated under reduced pressure. The residue was diluted with brine and extracted with EtOAc. Combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to obtain crude product, which was purified by Prep-HPLC [H<sub>2</sub>O-ACN(0.05%TFA)] to afford compound **18** (0.016 g, 37%) as a white liquid. <sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>): δ 7.49 – 7.10 (m, 8H), 4.81 – 4.34 (m, 4H), 3.82 (dd, J = 6.6, 3.4 Hz, 1H), 3.14 (t, J = 6.8 Hz, 2H), 2.97 (s, 3H), 2.79 – 2.70 (m, 1H), 2.40 – 2.30 (m, 1H), 1.33 – 1.21 (m, 3H), 0.97 (d, J = 4.4 Hz, 1H), 0.64 – 0.54 (m, 1H), 0.42 – 0.24 (m, 3H). LC-MS: *m/z* = 510.9[M+H]<sup>+</sup> (96.6% purity, 214nm)

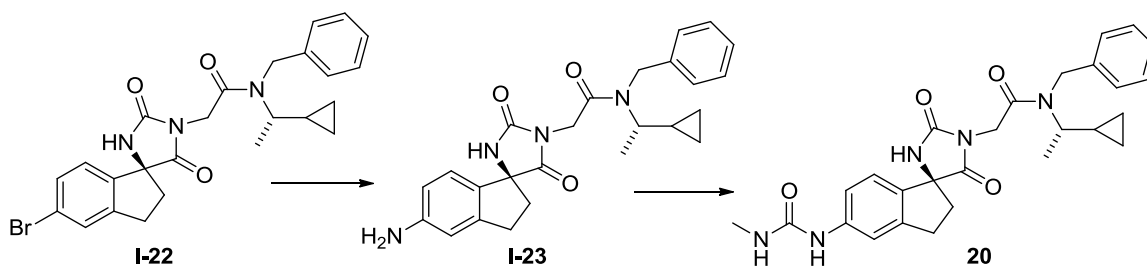


**N-benzyl-N-((S)-1-cyclopropylethyl)-2-(5'-(3-methylureido)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)acetamide (19)**

To a stirring solution of compound **I-21** (39 mg, 0.0903 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added triphosgene (10.7 mg, 0.03612 mmol) followed by Et<sub>3</sub>N (10.9 mg, 0.1084 mmol) at 0 °C and the resulting mixture was stirred at r.t. for 3 h, then treated with 2 M methylamine in THF (0.05 mL, 0.1 mmol) and stirred at r.t. for an additional 1 h. The reaction was concentrated under reduced pressure and the residue was purified by Prep-TLC eluting with 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford **19** (5 mg, 11%) as a white solid. LC-MS: *m/z* = 490.2[M+H]<sup>+</sup>. <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>): δ 8.69 (d, J = 16.7 Hz, 1H), 8.56 (s, 1H), 7.50-7.00 (m,

8H), 6.01 (s, 1H), 4.73 (s, 1H), 4.62 (s, 1H), 4.50-4.15 (m, 2H), 3.71 (s, 1H), 3.36 (s, 1H), 3.02 – 2.91 (m, 2H), 2.65 – 2.52 (m, 3H), 2.18 (dd,  $J = 20.4, 10.5$  Hz, 1H), 1.20 – 1.06 (m, 3H), 0.93 (s, 1H), 0.50-0.30 (m, 2H), 0.29 – 0.14 (m, 2H).

**N-benzyl-N-((S)-1-cyclopropylethyl)-2-((S)-5'-(3-methylureido)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)acetamide (20)**



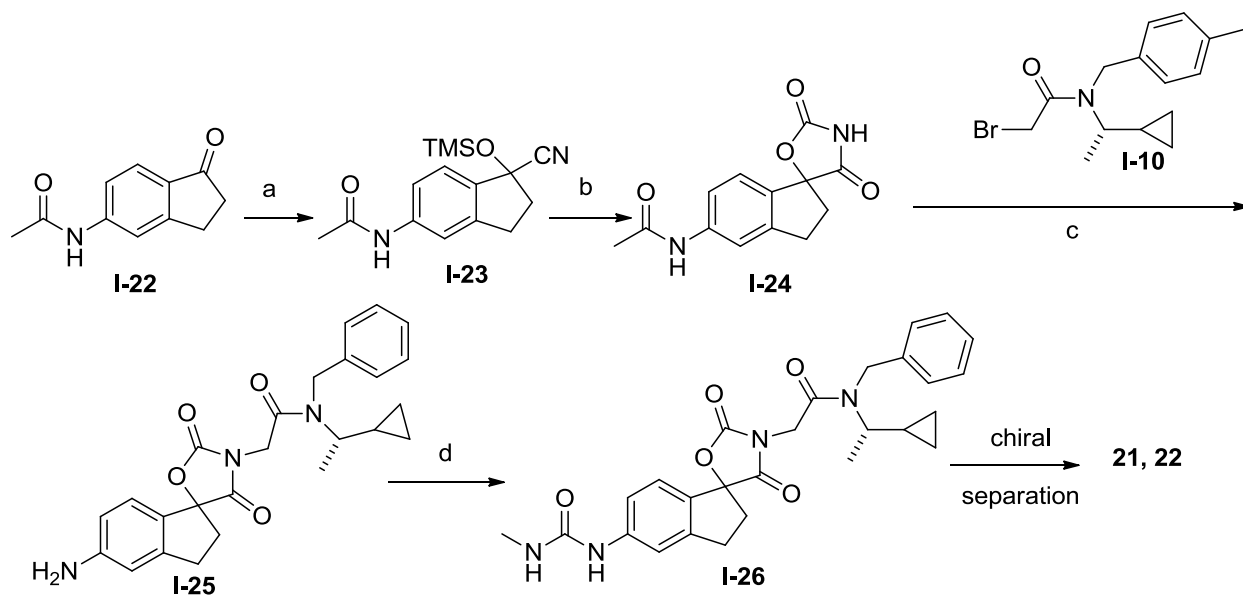
To a suspension of N-benzyl-2-((S)-5'-bromo-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-N-((S)-1-cyclopropylethyl)acetamide (**I-22**) (0.1 g, 0.2 mmol) (prepared from 5-bromo-2,3-dihydro-1H-inden-1-one following the procedures for compound **5**) and diphenylmethanimine (0.072 g, 0.4 mmol) in toluene (20 mL) was added  $\text{Pd}_2(\text{dba})_3$  (18 mg, 0.02 mmol), BINAP (25 mg, 0.04 mmol) and *t*-BuONa (58 mg, 0.6 mmol) under  $\text{N}_2$  and the reaction mixture was stirred at 100 °C for 4 h. Cooled to r.t. and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography (EtOAc/ Hexane 1: 2) to afford benzyl-N-((S)-1-cyclopropylethyl)-2-((S)-5'-(diphenylmethyleneamino)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-indene]-1-yl)acetamide (0.12 g, 100%) as white solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 – 7.67 (m, 2H), 7.53 – 7.35 (m, 5H), 7.33 – 7.22 (m, 5H), 7.11 (dd,  $J = 7.4, 2.1$  Hz, 3H), 6.75 – 6.52 (m, 3H), 4.74 – 4.61 (m, 2H), 4.38 (s, 1H), 4.23 (d,  $J = 3.5$  Hz, 1H), 4.04 – 3.94 (m, 1H), 2.87 – 2.66 (m, 2H), 2.31 – 2.16 (m, 2H), 1.21 (dd,  $J = 14.7, 5.3$  Hz, 3H), 0.86 – 0.75 (m, 1H), 0.58 – 0.47 (m, 1H), 0.41 – 0.20 (m, 3H). LC-MS:  $m/z = 596.7[\text{M}+\text{H}]^+$  (90% purity)

This imine (120 mg, 0.2 mmol) was dissolved in THF (15 mL), treated with 1 N HCl ( 3 mL), stirred at r.t. for 2 h then concentrated under reduced pressure to obtain the crude product, which was purified by silica gel column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  20: 1) to afford **I-23** (65 mg, 75%) as brown solid.

A suspension of **I-23** (31 mg, 0.07 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was treated with triphosgene (7.2 mg, 0.024 mmol) and triethylamine (8.5 mg, 0.084 mmol) at 0 °C under  $\text{N}_2$ , stirred at r.t. for 4 h, then

treated with MeNH<sub>2</sub> (1 N in THF, 0.35 mL), and stirred at r.t under N<sub>2</sub> for an additional 2 h and concentrated under reduced pressure to obtain the crude product, which was purified by Prep-HPLC (MeCN/H<sub>2</sub>O 2: 1) to afford **20** (20 mg, 59%) as white solid. LC-MS:  $m/z$  = 490.0[M+H]<sup>+</sup> at RT 3.65 (99.32% purity). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.88 – 6.77 (m, 8H), 4.83 – 4.68 (m, 2H), 4.47 (d,  $J$  = 7.1 Hz, 1H), 4.32 (s, 1H), 3.81 (dd,  $J$  = 9.6, 6.9 Hz, 1H), 3.08 (s, 2H), 2.75 (d,  $J$  = 8.2 Hz, 3H), 2.72 – 2.61 (m, 1H), 2.40 – 2.22 (m, 1H), 1.25 (dd,  $J$  = 24.6, 6.7 Hz, 3H), 0.94 (dd,  $J$  = 12.6, 8.8 Hz, 1H), 0.66 – 0.50 (m, <sup>1</sup>H), 0.48 – 0.12 (m, 3H).

#### Synthesis of oxazolidinediones 21-22 via chiral HPLC separation



Supplemental Scheme 3. (a) TMSCN, ZnI<sub>2</sub>; (b) 1. HCl, 2. Triphosgene; (c) 1. K<sub>2</sub>CO<sub>3</sub>, DMF, 2. HCl; (d) triphosgene, MeNH<sub>2</sub>.

#### N-(1-cyano-1-(trimethylsilyloxy)-2,3-dihydro-1H-inden-5-yl)acetamide (I-23)

To a stirring solution of *N*-(1-oxo-2,3-dihydro-1H-inden-5-yl)acetamide (1.125 g, 6 mmol) in toluene and MeCN (25 mL/5 mL) was added ZnI<sub>2</sub> (200 mg, 0.6 mmol) and TMSCN (0.9 g, 9 mmol) and the resulting mixture was heated to 60 °C for 3 h. The solvent from reaction mixture was removed under reduced pressure and the residue was diluted with NaHCO<sub>3</sub> aqueous and extracted twice with EtOAc. The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced



pressure to obtain crude product, which was purified by silica gel column chromatography to afford compound **I-23** (1.2 g, 70%) as a yellow liquid.

***N*-(2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-ozazolidine]-5-yl)acetamide (I-24)**

Compound **I-23** (1 g, 3.5 mmol) was dissolved with EtOH (30 mL), the mixture was cooled to 0 °C and excess of HCl gas was bubbled in and the mixture was stirred for 2 h. The solvent from reaction mixture was removed under reduced pressure and the crude ethyl 5-acetamido-1-hydroxy-2,3-dihydro-1H-indene-1-carbimide was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), then treated with TEA (0.4 g, 4 mmol) and a solution of triphosgene (0.24 g, 0.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and the mixture was stirred for 3 h. The mixture was controlled to pH=5, stirred for 1 hour and the solvent from reaction mixture was removed under reduced pressure. Obtained residue was purified by silica gel column chromatography to afford intermediate **I-24** (0.28 g, 31%) as a yellow solid. TLC: 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. LC-MS:  $m/z = 261[M+H]^+$

**2-(5-amino-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-ozazolidine]-3'-yl)-N-benzyl-N-((S)-1-cyclopropylethyl)acetamide (I-25)**

A solution of *N*-(2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-ozazolidine]-5-yl)acetamide **I-24** (1 g, 3.85 mmol), (S)-*N*-benzyl-2-bromo-*N*-(1-cyclopropylethyl)acetamide **I-10** (1.14 g, 3.85 mmol) and K<sub>2</sub>CO<sub>3</sub> (1 g, 7.7 mmol) in DMF (20 mL) was stirred for 2 h. The reaction mixture was diluted with sat NaCl aqueous and extracted twice with EtOAc. Combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography to afford (S)-2-(5-acetamido-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-ozazolidine]-3'-yl)-*N*-benzyl-*N*-(1-cyclopropylethyl)acetamide (1.35 g, 73%) as a yellow liquid.

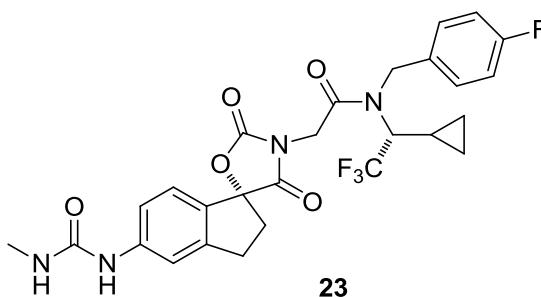
The product from the previous step (1.35 g, 2.85 mmol) was dissolved with MeOH/THF/H<sub>2</sub>O (10 mL/10 mL/10 mL) treated with 37% HCl (4 mL), then heated to 60 °C for 2 h. The solvent from reaction mixture was removed under reduced pressure and the residue was diluted with sat NaCl aqueous and extracted twice with EtOAc. Combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography to afford intermediate **I-25** (1 g, 81%) as a yellow liquid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.65 (d, *J* = 18.2 Hz, 1H), 7.51 – 7.08 (m, 7H), 6.56 – 6.41 (m, 2H), 4.75 – 4.20 (m, 5H), 4.13 – 3.54 (m, 1H), 3.52 – 2.74 (m, 2H), 2.74 – 2.33 (m, 1H), 1.42 – 1.00 (m, 3H), 1.02 – 0.84 (m, 1H), 0.56 – 0.16 (m, 4H). LC-MS:  $m/z = 434.10[M+H]^+$  (91.53% purity, 214 nm)

**N-benzyl-N-((S)-1-cyclopropylethyl)-2-((S)-5-(3-methylureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)acetamide (21) and**

**N-benzyl-N-((S)-1-cyclopropylethyl)-2-((R)-5-(3-methylureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)acetamide (22)**

A solution of intermediate **I-25** (433 mg, 1 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) at  $0^\circ\text{C}$  was treated with triphosgene (149 mg, 0.5 mmol) followed by  $\text{Et}_3\text{N}$  (304 mg, 3 mmol) and the resulting mixture was stirred at r.t for 1.5 h. then treated with methylamine (2M in THF, 2.5 mL, 5 mmol and stirred at r.t for 0.5 h. The reaction mixture was diluted with water and extracted twice with  $\text{CH}_2\text{Cl}_2$ . Combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to obtain crude product (343 mg, 70%), which was purified by SFC (column: CHIRALCELL OD-H; Manufacturer: DAICEL CHIRAL TECHNOLOGIES (CHINA) CO., LTD;  $\text{EtOH}/\text{CO}_2$  (3:7, 0.2% FA and 0.2% diethylamine in  $\text{EtOH}$ ) ) to afford compound **21** (89 mg, 52%) and compound **22** (92 mg, 54%) as a white solid. **21**: LC-MS:  $m/z = 491.0$   $[\text{M}+\text{H}]^+$  at RT 4.68 (100% purity).  $^1\text{H}$  NMR (301 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52 – 7.28 (m, 5H), 7.25 – 6.95 (m, 3H), 4.73 – 4.69 (m, 2H), 4.34 (s, 2H), 4.05 – 3.83 (m, 1.5H), 3.39 – 3.07 (m, 2.5H), 2.78 (s, 3H), 2.59 – 2.48 (m, 1H), 1.41 – 1.28 (m, 3H), 0.95 – 0.83 (m, 1H), 0.58 – 0.24 (m, 4H).

**22**: LC-MS:  $m/z = 491.0$   $[\text{M}+\text{H}]^+$  at RT 8.74 (100% purity).  $^1\text{H}$  NMR (301 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54 – 7.27 (m, 5H), 7.23 – 6.92 (m, 3H), 4.75 – 4.69 (m, 2H), 4.51 – 4.33 (m, 2H), 4.07 – 3.82 (m, 1.5H), 3.33 – 3.04 (m, 2.5H), 2.79 (s, 3H), 2.57 – 2.45 (m, 1H), 1.38 – 1.25 (m, 3H), 0.89 – 0.74 (m, 1H), 0.57 – 0.22 (m, 4H).

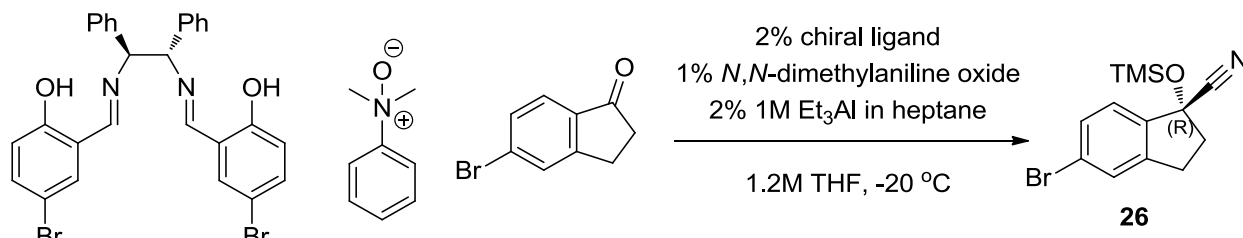


**N-((R)-1-cyclopropyl-2,2,2-trifluoroethyl)-N-(4-fluorobenzyl)-2-((R)-5-(3-methylureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)acetamide (23)**

Compound **23** was prepared in a similar fashion to **22** except substituting (R)-2-bromo-N-(1-cyclopropyl-2,2,2-trifluoroethyl)-N-(4-fluorobenzyl)acetamide for **I-10**. Racemic product was purified by SFC (column: CHIRALPAK AS-H; Manufacturer: DAICEL CHIRAL TECHNOLOGIES (CHINA) CO., LTD; condition:  $\text{EtOH}/\text{CO}_2$  (3:7, 0.2% of FA and 0.2% Diethylamine in  $\text{EtOH}$ )). The second eluent LC-MS:  $m/z = 563.1$   $[\text{M}+\text{H}]^+$  at RT 4.02 (98.78% purity).  $^1\text{H}$  NMR (301 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.71 (s, 1H), 7.64 – 7.39

(m, 2H), 7.35 – 7.05 (m, 4H), 6.16 – 6.03 (m, 1H), 5.11 – 4.77 (m, 2H), 4.65 – 4.03 (m, 3H), 3.20 – 2.89 (m, 2H), 2.79 – 2.54 (m, 4H), 2.46 – 2.34 (m, 1H), 1.40 – 1.14 (m, 1H), 0.86 – 0.63 (m, 2H), 0.48 – 0.14 (m, 2H).

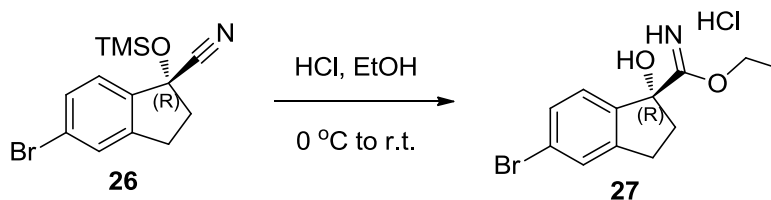
### Enantioselective Synthesis of 24 (A-485).



### **(R)-5-bromo-1-((trimethylsilyl)oxy)-2,3-dihydro-1H-indene-1-carbonitrile (26)**

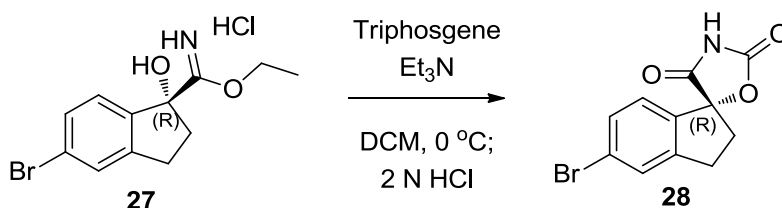
A 1000 mL, 4-neck jacketed flask fitted with an internal temperature probe was charged with 2,2'-((1*E*,1'*E*)-(((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis(4-bromophenol) (5.48 g, 9.48 mmol) and tetrahydrofuran (200 mL) under argon. To the resulting yellow solution was added triethylaluminum (1M solution in heptane, 9.48 mL, 9.48 mmol) drop-wise over 10 min. The mixture was stirred for 1 h. 5-bromo-2,3-dihydro-1H-inden-1-one (100 g, 474 mmol) was then added in one portion. After stirring for 15 min, the reaction was cooled to  $-20\text{ }^\circ\text{C}$  with a Huber 230 Ministat. Separately, a 500 mL flask was charged with *N,N*-dimethylaniline oxide (0.650 g, 4.74 mmol) and tetrahydrofuran (200 mL) under argon. To this solution was added TMSCN (125 mL, 948 mmol) drop-wise over 20 minutes and then was stirred for 1 hour and then was transferred via cannula under nitrogen to an addition funnel and added to the triethylaluminum suspension at  $-20\text{ }^\circ\text{C}$  drop-wise over 90 minutes maintaining the internal temperature less than  $-19.0\text{ }^\circ\text{C}$ . The resulting yellow suspension was stirred under argon at  $-20\text{ }^\circ\text{C}$  for 92 h. A small sample was removed and quenched with saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The sample was analyzed by LC/MS and NMR. No starting material was detected. The reaction was quenched by the drop-wise addition of saturated aqueous sodium bicarbonate (425 mL) solution. The mixture was then warmed to ambient

temperature and transferred to a separatory funnel. The mixture was diluted with more saturated aqueous sodium bicarbonate (575 mL) aqueous solution and water (1000 mL) and then extracted with EtOAc (2x). The combined organics were dried over sodium sulfate and filtered through Celite. The combined filtrate and washes were concentrated to a yellow oil to give 151.4 g of the crude product. The crude oil was purified via chromatography to obtain 134.52 g (92%) of compound **26**.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.60 (dq,  $J$  = 1.6, 0.8 Hz, 1H), 7.54 (ddt,  $J$  = 8.1, 1.6, 0.8 Hz, 1H), 7.44 (d,  $J$  = 8.1 Hz, 1H), 3.11 – 3.02 (m, 1H), 3.01 – 2.91 (m, 1H), 2.72 (ddd,  $J$  = 13.5, 7.8, 5.8 Hz, 1H), 2.40 (ddd,  $J$  = 13.4, 7.8, 5.6 Hz, 1H), 0.16 (s, 9H). MS (DCI)  $m/e$  326.9 ( $M+\text{NH}_4$ ) $^+$ .



**(*R*)-ethyl 5-bromo-1-hydroxy-2,3-dihydro-1H-indene-1-carbimidate hydrochloride (**27**)**

A jacketed 3 L 3-neck round bottom flask equipped with an internal temperature probe, Huber Ministat (constant temperature control), HCl gas inlet (through a trap to a gas dispersion tube), nitrogen inlet and gas outlet was charged with **26** (207.81 g, 670 mmol) and ethanol (1300 mL). The almost colorless solution was cooled to 0 °C and anhydrous hydrogen chloride (gas) was added (90 min) until the mixture was saturated and the reaction was complete by TLC. The temperature was kept below 10 °C by controlling the gas flow. The reaction mixture was stirred overnight at 0 °C. TLC analysis of an aliquot of the reaction indicates starting material consumption. The reaction mixture was concentrated by rotary evaporation and the resulting yellow tan solid foam weighed 203 g. The foam was scraped loose from the walls under argon and the solid was triturated with diethyl ether (600 mL). The diethyl ether was decanted and the flask was returned to the rotovap and then dried under high vacuum to give 192.07g of crude (*R*)-ethyl 5-bromo-1-hydroxy-2,3-dihydro-1H-indene-1-carbimidate hydrochloride. This material was used in the next step without further purification.

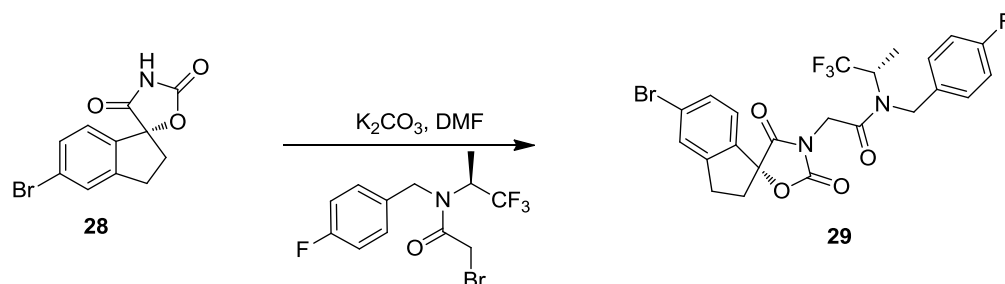


**(R)-5-bromo-2,3-dihydrospiro[indene-1,5'-oxazolidine]-2',4'-dione (28)**

**[CAUTION: Triphosgene is highly toxic and should be handled in a fume hood.]**

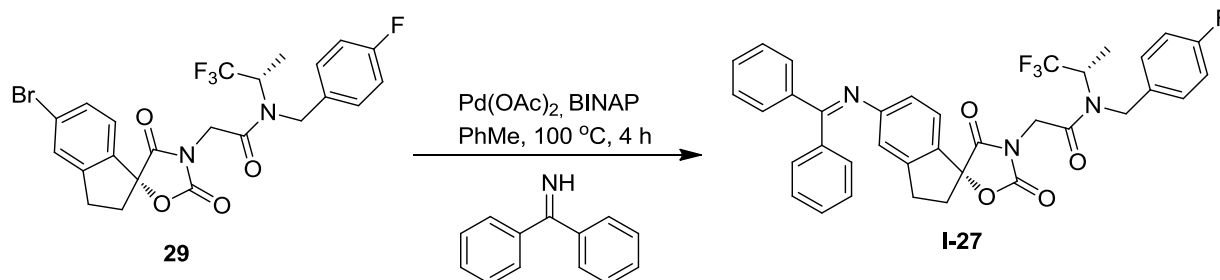
(R)-ethyl 5-bromo-1-hydroxy-2,3-dihydro-1H-indene-1-carbimidate hydrochloride (140 g, 437 mmol) (Sticky, hygroscopic foam) was suspended in tetrahydrofuran (1747 mL) and cooled to 2-5 °C. Triethylamine (183 mL, 1310 mmol) was added and the mixture was cooled to 3-7 °C with an ice bath. To the thick, difficult to stir slurry, triphosgene (51.8 g, 175 mmol) (**CAUTION - TOXIC - weighed out in hood**) was added portion-wise as a solid (5-10 g at a time). **There is a 15-20 °C exotherm associated with this addition** but it can be controlled well with an ice bath. After the addition was complete, the reaction mixture (light yellow suspension) was allowed to stir at 3-5 °C for about 2.0 h. The reaction temperature was maintained at about 5 °C using an ice-bath and the reaction was overwhelmed with 2 N HCl (**carefully at first - sharp exotherm**). The mixture remained a light yellow color and after 30 - 45 min, LCMS showed product as the main peak with small amounts of by-products. EtOAc was added (ca 200 mL), stirred for 10 min and then all was poured into a separatory funnel. The layers were separated, the aqueous layer was extracted with EtOAc (2x) and the combined organics were dried (MgSO<sub>4</sub>), treated with activated charcoal, filtered through a plug of silica gel and concentrated by rotary evaporation to give a light yellow sticky solid which was placed on the high vacuum for 2 h. At this point, the material was about 77% ee. The following is the enantiomeric enrichment process: Direct crystallization did not work on material less than 90% ee. After drying, 4 L of toluene was added to the flask and the mixture was stirred for about 1 h. Stirring was stopped and the solids were allowed to settle before decanting off the toluene solution. The white solids were washed out of the flask with toluene and collected by filtration. These solids were washed one more time with 2 L toluene, filtered and dried to give 18.5 g of white solids that were essentially racemic. The toluene washes were concentrated by rotary evaporation to give 90 g of a yellow solid. This material was crystallized (to remove impurities) from 650 mL toluene (105 °C) and allowed to cool overnight. The solids were collected by filtration providing 80 g of white solids (92% ee). The mother liquor was concentrated and chromatographed (300 g silica gel, 0-65% heptanes: EtOAc) to give 7.6 g product (92% ee). This material was combined and recrystallized from hot toluene: 87.6 g was dissolved in 2.5 L toluene and heated to 72 °C upon which time, a solution formed. After cooling to 45 °C, the solids were collected by filtration to give 33 g (99.8% ee). The mother liquors were concentrated and the solids were stirred with 2 L PhMe for 2 h. The solids were removed by filtration and the toluene removed by rotary evaporation.

The recrystallization / toluene wash was repeated 2 x, providing (*R*)-5-bromo-2,3-dihydrospiro[indene-1,5'-oxazolidine]-2',4'-dione (73 g, 259 mmol, 59% over 2 steps, >99% ee).



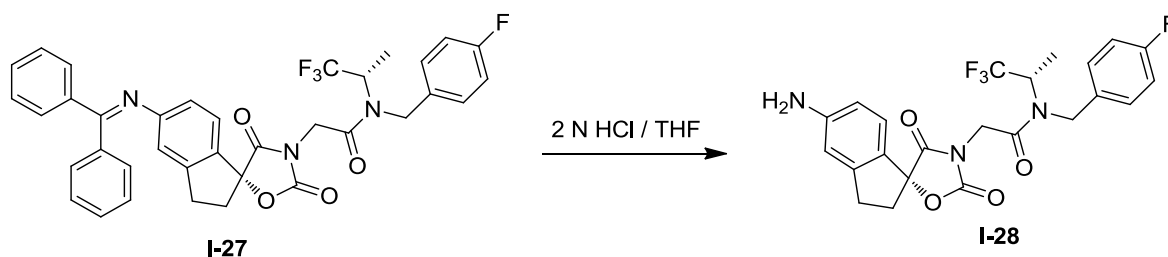
**2-((*R*)-5-bromo-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (29)**

(*S*)-2-bromo-N-(4-fluorobenzyl)-N-(1,1,1-trifluoropropan-2-yl)acetamide (33.4 g, 98 mmol) was taken up in DMF and added to a 3-neck 500 mL Morton fit with thermocouple / JKEM, magnetic stirring and nitrogen in and out. (*R*)-5-bromo-2,3-dihydrospiro[indene-1,5'-oxazolidine]-2',4'-dione (26 g, 92 mmol, 99.8% ee) was added as a solid and the clear, colorless solution was cooled to 3.3 °C. Potassium carbonate (25.5 g, 184 mmol) was added as a solid all at once and the temperature went down to about 2.8 °C. The mixture was allowed to stir for 10 min, warmed to 20 °C, stirred for 2 h and then poured into 2 L of water. The resulting slurry was stirred for 20 min and filtered. The filter cake was allowed to dry overnight to give 50 g of 2-((*R*)-5-bromo-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide which was used in the next step without further purification.



**2-((*R*)-5-((diphenylmethylene)amino)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (I-27)**

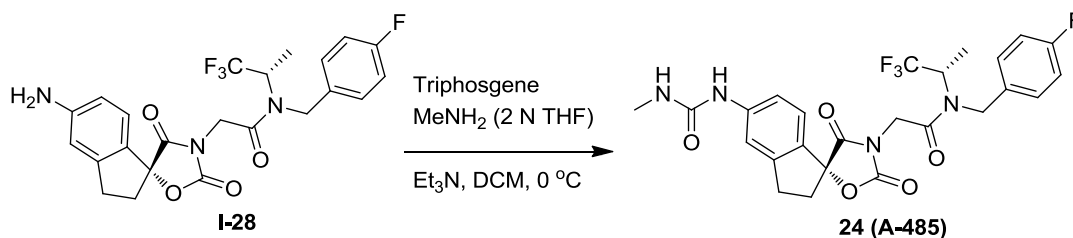
2-((R)-5-bromo-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (48.5g, 89 mmol), diphenylmethanimine (19.47 mL, 116 mmol), Cs<sub>2</sub>CO<sub>3</sub> (40.7 g, 125 mmol), BINAP (5.00 g, 8.03 mmol) and Toluene (298 mL) were combined and sparged (subsurface) with nitrogen for 20 min. Pd(OAc)<sub>2</sub> (0.802 g, 3.57 mmol) was added and the mixture was further sparged for 10 min. The reaction was heated at 96-102 °C for 3.5 - 4 h, (turned a dark brownish red) at which time the reaction was complete by LCMS. The reaction was cooled to room temperature and mercapto silica gel and charcoal were added and stirred for about 30 min. The mixture was filtered through a pad of silica gel (800 g), eluting with 50% EtOAc : Heptanes. The filtrate was stirred again with charcoal and mercapto silica gel, filtered through a pad of celite and concentrated by rotary evaporation to give 2-((R)-5-((diphenylmethylene)amino)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide as an orange foam which was used in the next step without purification.



**2-((R)-5-amino-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (I-28)**

2-((R)-5-((diphenylmethylene)amino)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (58 g, 90 mmol, orange foam) was dissolved in THF (500 mL). 2 N HCl (180 mL, 360 mmol) was poured in, the temperature rose to 25-27 °C and the solution color turns from orange to light yellow. After about 20 min, a saturated solution of sodium bicarbonate was added until the reaction mixture was basic and the mixture was then extracted twice with EtOAc. The combined organics were dried (MgSO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (330 g silica gel, 0-60% step wise Hep:EA) to give 2-((R)-5-amino-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (36 g, 75 mmol, 76% yield over 3 steps) as an off-white solid.

High temperature NMR resolved the rotamers seen at room temperature:  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ , 120 °C)  $\delta$  7.33 (dd,  $J$  = 8.5, 5.4 Hz, 2H), 7.12 (t,  $J$  = 8.8 Hz, 2H), 7.03 (d,  $J$  = 8.2 Hz, 1H), 6.58 – 6.47 (m, 2H), 5.18 (t,  $J$  = 7.8 Hz, 1H), 5.00 (s, 2H), 4.82 (d,  $J$  = 17.6 Hz, 1H), 4.66 – 4.51 (m, 2H), 4.36 (d,  $J$  = 16.8 Hz, 1H), 3.02 (dt,  $J$  = 15.4, 7.5 Hz, 1H), 2.88 (ddd,  $J$  = 16.2, 8.8, 4.1 Hz, 1H), 2.61 (ddd,  $J$  = 14.3, 8.7, 6.7 Hz, 1H), 2.40 (ddd,  $J$  = 14.4, 8.3, 3.9 Hz, 1H), 1.37 (d,  $J$  = 7.1 Hz, 3H), MS (ESI)  $m/e$  958.8 (2M+H) $^+$ .



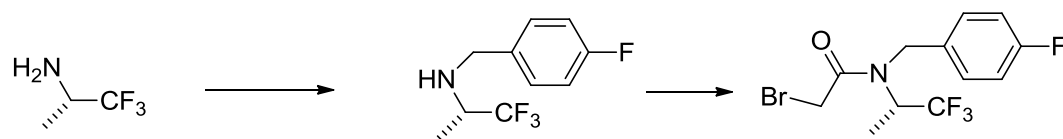
**N-(4-fluorobenzyl)-2-((R)-5-(3-methylureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (24)**

2-((R)-5-amino-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (10 g, 20.86 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (316 mL). Triethylamine (8.72 mL, 62.6 mmol) was added and the reaction solution was cooled in an ice-bath (internal temperature 0.8 °C). Triphosgene (2.79 g, 9.39 mmol) was added as a solid all at once and the temperature rose to 7.0 °C quickly. The reaction was allowed to cool back down to near 0 °C and stirred at that temp for 2 h. Methylamine (2N THF, 31.3 mL, 62.6 mmol) was added via syringe at 0.3 °C and the temperature rose to about 4.0 °C. The reaction was allowed to stir at 1 - 2 °C for 1 h and at that time, LCMS indicated complete reaction. HCl (1N, 300 mL) was added and the layers were separated. The aqueous layer was extracted once with  $\text{CH}_2\text{Cl}_2$  and the combined organics were dried ( $\text{MgSO}_4$ ), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Silica gel, 330 g, 0-100% EA:Hep) to give N-(4-fluorobenzyl)-2-((R)-5-(3-methylureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (10.1 g, 18.83 mmol, 90 % yield) as a white solid. High temperature NMR resolved the rotamers seen at room temperature:  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ , 120 °C)  $\delta$  8.29 (s, 1H), 7.51 (t,  $J$  = 1.2 Hz, 1H), 7.36 (dd,  $J$  = 8.4, 5.4 Hz, 2H), 7.26 (d,  $J$  = 1.7 Hz, 2H), 7.15 (t,  $J$  = 8.7 Hz, 2H), 5.87 (d,  $J$  = 5.4 Hz, 1H), 5.31 – 5.12 (m, 1H), 4.86 (d,  $J$  = 17.7 Hz, 1H), 4.74 – 4.54 (m, 2H), 4.40 (d,  $J$  = 16.8 Hz, 1H), 3.22 – 3.07 (m, 1H), 3.02 (ddd,  $J$  = 16.3, 8.7, 4.2 Hz, 1H), 2.75 – 2.61 (m, 4H), 2.50 – 2.43 (m, 2H), 1.40 (d,  $J$  = 7.1 Hz, 3H); MS (ESI)  $m/e$  1072.9 (2M+H) $^+$ ;  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ , 120 °C)  $\delta$  174.04, 167.67, 163.18, 160.75,



156.23, 154.35, 146.54, 143.73, 133.74, 130.33, 128.68, 127.38, 124.47, 117.96, 115.63, 114.39, 94.60, 46.31, 42.14, 35.60, 35.56, 30.26, 26.50; HRMS ( $m/z$ ):  $[M+H]^+$  calcd for  $C_{25}H_{25}F_4N_4O_5$ , 537.1756 ; found, 537.1733.  $[\alpha]_D^{20} + 46.1^\circ$  (c 0.74, MeOH); HPLC purity: 100% PA at 254 nm (Condition 1, Phenomenex Luna 5  $\mu$ m, C18(2), 100 Å, 4.6 x 250 mm, room temperature, 1 h gradient (H<sub>2</sub>O (0.1% TFA) : Acetonitrile 10-95% gradient). HPLC purity: 99% PA at 254 nm (Condition 2, Waters XBridge 3.5  $\mu$ m, C18, 4.6 x 150 mm, room temperature, 1 h gradient (H<sub>2</sub>O (0.1% H<sub>3</sub>PO<sub>4</sub>) : Acetonitrile 10-95% gradient).

#### Synthesis of (S)-2-bromo-N-(4-fluorobenzyl)-N-(1,1,1-trifluoropropan-2-yl)acetamide



#### (S)-1,1,1-trifluoro-N-(4-fluorobenzyl)propan-2-amine:

To a solution of (S)-1,1,1-trifluoropropan-2-amine (37 g, 327 mmol) and 1-(bromomethyl)-4-fluorobenzene (74.3 g, 393 mmol) in DMF (500 mL) was added K<sub>2</sub>CO<sub>3</sub> (135 g, 981 mmol). The reaction mixture was stirred at room temperature for overnight, quenched with water, extracted with EtOAc, washed with water and brine, dried and concentrated under reduced pressure. The crude product was purified by silica gel (methanol: CH<sub>2</sub>Cl<sub>2</sub> = 1:20) to afford (S)-1,1,1-trifluoro-N-(4-fluorobenzyl)propan-2-amine (55 g, 76%) as oil. LC-MS:  $m/z$  = 222.0  $[M+H]^+$  To a stirring solution of (S)-1,1,1-trifluoro-N-(4-fluorobenzyl)propan-2-amine (38.6 g, 175 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (500 mL) was added 2-bromoacetyl bromide (70.4 g, 350 mmol). The resulting mixture was stirred at RT for 2 h, quenched with NaHCO<sub>3</sub>, extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried and concentrated and purified by silica gel (petroleum ether:ethyl acetate = 1:1) to give **5** (49.5 g, 83%) as oil. LC-MS:  $m/z$  = 342.0/344.0  $[M+H]^+$