Supporting Information

Spirocyclic Thiohydantoin Antagonists of F877L and Wild-Type Androgen Receptor for Castration-Resistant Prostate Cancer

Zhuming Zhang*[1]; Peter J. Connolly[1]; Luis Trabalón Escolar[2]; Christian Rocaboy[2]; Vineet Pande[3]; Lieven Meerpoel[3]; Heng-Keang Lim[1]; Jonathan R. Branch[1]; Janine Ondrus[1]; Ian Hickson[1†]; Tammy L. Bush[1]; James R. Bischoff[1§]; Gilles Bignan*[1]

(1) Janssen Research and Development, Spring House, Pennsylvania 19477, USA; (2) Eurofins Villapharma, 30320 Fuente Alamo, Murcia, Spain; (3) Janssen Research and Development, Turnhoutseweg 30, B-2340 Beerse, Belgium

KEYWORDS: androgen receptor, spirocyclic, thiohydantoin, resistance, apalutamide, LBD, prostate cancer

zzhang85@its.jnj.com; GBignan@its.jnj.com

Table of Contents

S-1. LNCaP AR WT and F877L Transcriptional Reporter Assay

LNCaP AR (cs) and LNCaP F877L luciferase cell lines were generated by transduction of each cell line (description of cell line generation Joseph JD, Lu N, Qian J, Sensintaffar J, Shao G, Brigham D, Moon M, Maneval EC, Chen I, Darimont B, Hager JH. A clinically relevant androgen receptor mutation confers resistance to second-generation antiandrogens enzalutamide and ARN-509. Cancer Discov 2013; 3:1020-1029) with an Androgen Response Element Firefly Luciferase lentiviral construct at a MOI (multiplicity of infection) of 50 following the manufacturer's instructions (Qiagen). A stable pooled-population cell line was generated using puromycin (Life Technologies) selection at 1:10,000 v/v. The protocol below was used for both cell lines and for testing of the compounds of Formula (I) of the present invention.

LNCaP cells were grown to about 80% confluence, media removed and cells rinsed in Hank's balanced salt solution prior to separation from the plate with 0.05% Trypsin EDTA. Cells were lifted and trypsin negated in complete CSS (charcoal stripped serum) culture media. CSS was maintained on cells for 24 h prior to assay, at which time 5,000cells/20µL were seeded in Greiner 384 well White/White Tissue Culture Treated Plates and incubated for a further 1-2 hours at 37 °C, 5% CO_2, prior to addition of 10µL of 4x Test Compounds (compounds described herein) or Assay Controls (all diluted in complete media containing 10% css). A further 10µL of 4x R-1881 Agonist Challenge (antagonist assay) or Buffer (agonist assay) was then added (all diluted in complete media containing 10% css). Agonist challenge was at 400pM for WT assay and 600pM for F877L assay. Plates containing cells and compounds herein were incubated for a further 20-24 hours at 37 °C, 5% CO_2 before addition of 40µL/well of Steady-Glo Luciferase Assay System Reagent (Promega# E2520). After 1 h, plates were read for luminescence on a BMG Pherastar.

EC/IC50 calculations were achieved utilizing calculated RLU data and data fitting macros. Data were fit using least-squares methods to the following formula:

$$Y_{[fit]} = Y_{[low\ cmpd]} + \frac{(Y_{[high\ cmpd]} - Y_{[low\ cmpd]}) * Y_{[cmpd]}^{Hill}}{Y_{[cmpd]}^{Hill} + IC50^{Hill}}$$

wherein

$Y_{[low\ cmpd]}$ = Y value with inactive compound

$Y_{[high\ cmpd]}$ = Y value with fully active compound effector

Hill = Hill coefficient

EC/IC_{50} = concentration of compound with 50% effect

S-2. Glucocorticoid Receptor Pathway GAL4 Reporter (Luc) Assay

The Glucocorticoid Receptor Pathway GAL4 Reporter (Luc) – HEK293 Cell Line contains a firefly luciferase gene under the control of glucocorticoid receptor ligand binding domain that is fused to the DNA binding domain (DBD) of GAL4 (GAL4 DBD-GR) stably integrated into HEK293 cells. This fusion construct activates firefly luciferase expression under the control of a multimerized GAL4 upstream activation sequence (UAS). This allows for specific detection of glucocorticoid-induced activation of the glucocorticoid receptor without the need for individual transcriptional targets and with low cross-reactivity for other nuclear receptor pathways.

GR Pathway GAL4 Reporter(luc)-HEK293 cells are grown in DMEM (no Phenol Red) (HyClone # SH30604.01), 10% FBS (Invitrogen # 16000-044), 1x NonEssential Amino Acids, 1x L-Glutamine, 1x Penicillin/Streptomycin, 1x Sodium Pyruvate, 400ug/ml Geneticin G418, 50ug/ml Hygromycin B. Maintain cell line at 1:3 split ratio; split 2x/week.

Cell Plating, Compound Treatment & Read: Remove culture media from flasks. Add 2ml of cell stripper to each flask to lift cells, rinse over monolayer. Stop with 7ml complete css culture media. Count cells via Cedex and Dilute to: 0.5 x 106 cells/ml (10,000 cells/20uL). Dispense 20uL/well of cell suspension in White/White Tissue Culture Treated Plate using Tempest (Greiner #781080). Incubate for 1-2 hours at 37 ^{o}C, 5% CO_2. Add 10uL of 4x Test Compounds or Assay Controls (all diluted in complete media containing 10% css). Add 10uL of 4x 20nM Dexamethasone Agonist Challenge or Buffer (all diluted in complete media containing 10% css). Incubate for 20- 24 hours at 37 ^{o}C, 5% CO_2. After final incubation, add 40 uL/well of Steady-Glo Luciferase Assay System Reagent (Promega# E2520). Wait 1 hour & Read 384 well Luminescence on BMG Pherastar.

RLU results will be collected and used directly for data calculation.

EC/IC50 calculations are achieved utilizing calculated RLU data and data fitting macros:

Data were fit using least-squares methods to the following formula:

$$Y_{[fit]} = Y_{[low\ cmpd]} + \frac{(Y_{[high\ cmpd]} - Y_{[low\ cmpd]}) * Y_{[cmpd]}^{Hill}}{Y_{[cmpd]}^{Hill} + IC50^{Hill}}$$

Where:

$Y_{[low\ cmpd]}$ = Y value with inactive compound

$Y_{[high\ cmpd]}$ = Y value with fully active compound effector

Hill = Hill coefficient

EC/IC50 = concentration of compound with 50% effect

An additional parameter is registered, called “Net Terminal Effect”:

NTV (%) = $\frac{(Y_{[high\ cmpd]} - Y_{[low\ cmpd]})}{(Y_{[saturating\ control\ cmpd]} - Y_{[infinite\ dilution\ of\ control\ cmpd]})} * 100$

S-3. Androgen Dependent Proliferation

VCaP cells were counted and seeded into black 384-well plates with clear bottoms at a concentration of 125,000 cells per mL in phenol red-free DMEM containing 10% Charcoal Stripped Serum. 16µL of the suspension was added per well and incubated for 48 h to allow the cells to adhere. After 48 hours, a 12 point serial semilog dilution of each compound was added to the cells in 16µL at a final concentration of 100 µM to 0.0003 µM. The compounds were also run in antagonist mode using 30 pM R1881 in which 8µL of the compound was added to the cells followed by 8µL of R1881. After 5 days of incubation at 37 ^{o}C, 16µL Of CellTiter-Glo (Promega) was added to the cells and the relative luminescence units (RLUs) of each well determined using the Envision. The percent stimulation and percent inhibition were determined for each sample and plotted using GraphPad Prism.

S-4. Hershberger assay

The effect of AR antagonists on androgen dependent signaling *in vivo* was assessed using the Hershberger assay. In this assay, peripubertal castrated male Sprague-Dawley rats were administered AR antagonists described herein in the presence of testosterone (0.4 mg/kg testosterone propionate) and the weights of androgen dependent organs measured. Dosing was continued for 10 days and measurements taken 24 h after the last dose. The extent of antagonism of AR and consequent inhibition of organ growth was evaluated by comparison to the castration control. Compounds were dosed orally QD and an endpoint assessment made by change in weight of 5 androgen sensitive organs (ASO): Paired Cowper's Glands (CG), Seminal Vesicles with Fluids and Coagulating Glands (SVCG), Glans Penis (GP), Ventral Prostate (VP) and Levator Ani-Bulbocavernosus Complex (LABC)). According to assay guidelines, statistically significant suppression of ASO is required in 2 of 5 organs for a compound to be classified as an anti-androgen (analysis was performed by t-test/ Mann-Whitney).

Unless otherwise stated, compounds defined herein were administered at 30 mg/kg and flutamide (FT), positive control, at 3 mg/kg. All compounds were co-administered with testosterone propionate (TP, 0.4mg/kg) which was also administered alone, untreated control, (castrated only rats served as the control for complete androgen blockade). A statistically significant change in ASO achieved in at least 2 of 5 organs was indicative of an active compound. Administration of Compound 43 resulted in significant reduction in ASO versus TP control ($p \leq 0.05$) in all 5 organs. Data for the inhibition of growth of the Seminal Vesicle

and Coagulating Glands (SVCG) and Ventral Prostate (VP) was reported for all studies (mean organ weight (% of TP control) ± SD (n=6)).

S-5. Tumor xenograft efficacy studies

Castrate six to seven-week-old male SCID Hairless Outbred mice (SHO, Charles Rivers Laboratories) were used as the host strain for xenograft studies. LNCaP SRαF876L cells were cultured as 3-D spheroids and expanded prior to subcutaneous injection on the flank of the animals (supplied post castration). Briefly, 5 ml of cells in media + 5 ml of cultrex were premixed prior to plating of 500 µl = 2 x 10^5 cells per well of a 24-well plate. Plates were incubated @ 37 °C for 30 min before addition of complete media on top and returned to incubator for growth of 3-D colonies. After 7 days, media was removed, plates chilled and contents of each well, 500 µl cultrex and cells, injected into flank of a recipient mouse. Tumor volume (length x width2/2) was monitored weekly. When tumors reached an average volume of ~200 mm^3, animals were randomized into treatment groups. During the treatment period tumor volume was monitored bi-weekly. At study end, tumor growth inhibition (TGI) was calculated: 100 – (Treated/Control*100). At the termination of study tumors were collected and stored for further analyses. Tumor volumes were calculated using the formula: Tumor Volume (mm^3) = (a x b^2/2); where 'a' represents the length, and 'b' the width.

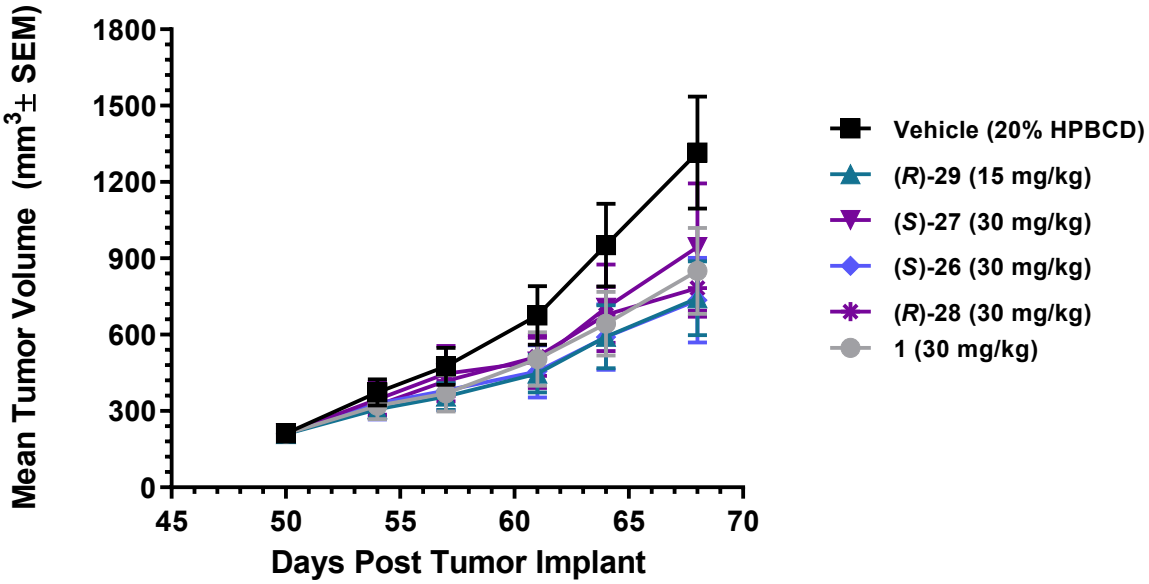


Figure S1. Oral *in vivo* efficacy profile of (*R*)-**29,** (*S*)-**27,** (*S*)-**26,** and (*R*)-**28** compared to **1** (enzalutamide) in castrated male SHO mice implanted with LNCaP F877L tumors cells. Tumors were measured twice weekly and the results presented as the average tumor volume, expressed in mm^3 ± SEM of each group.

S-6 GSH Screen for Phenolic Metabolites of Androgen Receptor Antagonists

The bioactivation of potential phenolic metabolites of androgen receptor antagonists were evaluated by modification of trapping procedure previously reported by Lim et al., 2008. Briefly, incubation of each potential phenolic metabolite was conducted in a final volume 1-mL in a test tube, containing 10 μM test compound, 1 mg/mL dog liver microsomes, 5 mM glutathione mixture (GSH: [$^{13}C_2$, ^{15}N-glycine]GSH 2:1), and 1 mM NADPH in 0.1M phosphate buffer. The control sample contained all except the NADPH cofactor. The samples were incubated for 60 minutes. Once the incubations were completed, the reaction was quenched with 5.0 mL of 1:1 ratio of acetonitrile and isopropyl alcohol containing 0.1% formic acid. The resulting mixture was vortex mixed and sonicated, followed by centrifugation at 3000xg for 10 minutes at 5°C. The supernatants were transferred into clean tubes and dried under nitrogen at room temperature to dryness. The residue was dissolved in 300 μL of 4:1 ratio of 0.1% formic acid and acetonitrile, sonicated and filtered through 0.45μm Nylon filters prior to LC-MS analysis.

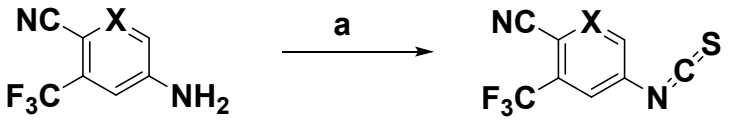
The glutathione conjugate was detected by isotopic pattern triggered data-dependent multiple-stage high resolution accurate mass analysis. The mining for glutathione conjugates was by high resolution accurate mass isotopic pattern filtering (MsMetrix, The Netherlands) of full scan MS data. The product ion mass spectra were used to elucidate the site of bioactivation.

S-7. Chemistry

All commercial reagents and anhydrous solvents were purchased and used without further purification, unless otherwise specified. Mass spectra (MS) were obtained on a SHIMADZU LCMS-2020 MSD or Agilent 1200\G6110A MSD using electrospray ionization (ESI) in positive mode unless otherwise indicated. Calculated (calcd.) mass corresponds to the exact mass. Nuclear magnetic resonance (NMR) spectra were obtained on Bruker model AVIII 400 spectrometers. Definitions for multiplicity are as follows: s = singlet, d = doublet, t= triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, dt = doublet of triplets, spt = septet, quin = quintet, m = multiplet, br = broad. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane as a standard. ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane as a standard. Normal-phase silica gel chromatography (FCC) was

performed on silica gel (SiO_2) using prepacked cartridges. Enzalutamide (**1** (MDV-3100)) was obtained from commercially available source. All compounds sent for biological tests were confirmed with purity >95% in quantitative HPLC analysis [method: Gilson GX-281-RP-HPLC with Phenomenex Gemini C18 (10µm, 150 x 25mm), or Waters XBridge C18 column (5µm, 150 x 30mm), mobile phase of 5-99% ACN in water (10mM NH_4HCO_3) over 10 min and then hold at 100% ACN for 2 min, at a flow rate of 25 mL/min] in addition to LC-MS & ^{1}H NMR.

Procedures for Synthesis of Isothiocyanate Intermediates 35a, 35b



35a X = N
35b X = CH

[a]Reagents and Conditions: (a) $C(=S)Cl_2$, $CHCl_3/H_2O$, rt.

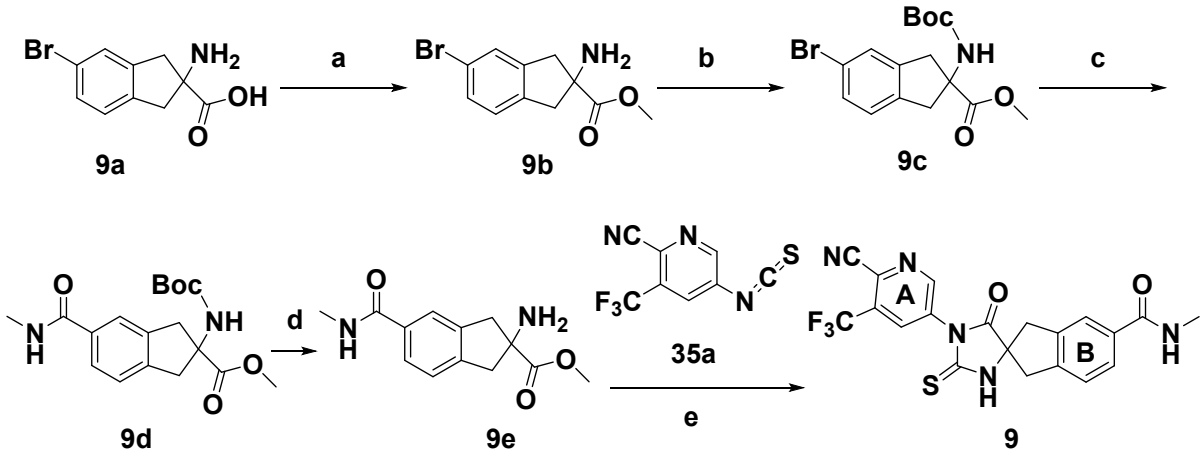
5-isothiocyanato-3-(trifluoromethyl)picolinonitrile, 35a (X = N):

To a stirred biphasic mixture of 5-amino-3-(trifluoromethyl)picolinonitrile (9.5 g, 50.8 mmol) in $CHCl_3$ (250 mL), water (100 mL) and DMA (25 mL) was added thiophosgene (6.97 mL, 91.4 mmol). The resulting reaction mixture was stirred at room temperature for 0.5 h. The mixture was diluted with DCM (100 mL). The two layers were separated, and the aqueous layer was extracted with DCM (100 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and dried *in vacuo* to afford crude 5-isothiocyanato-3-(trifluoromethyl)picolinonitrile (11.6 g, 100%), which was used directly in the next step as the crude product without further purification.

4-isothiocyanato-2-(trifluoromethyl)benzonitrile, **35b** (X = CH):

To a stirring mixture of 4-mmino-2-trifluoromethyl-benzonitrile (93 mg, 0.5 mmol) in dichloromethane (4.4 mL), and aqueous $NaHCO_3$ solution (1.8 mL) at room temperature was added thiophosgene (0.057 mL, 0.75 mmol). The reaction mixture was stirred for 30 min. then diluted with dichloromethane. The organic layer was separated, dried over $MgSO_4$, and concentrated to afford the crude product, which was used directly in the next step without further purification (124 mg, 100%).

Preparation of 1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 9



[a]Reagents and Conditions: (a) conc. H_2SO_4, MeOH, reflux; (b) Boc_2O, TEA, DCM, rt; (c) MeNHOMe.HCl, $W(CO)_6$ (cat.), $Pd(OAc)_2$ (cat.), Xantphos (cat.), DMAP, K_3PO_4, 1,4-dioxane, microwave, 120 ^oC; (d) TFA, DCM, rt; (e) TEA, THF, DMF, 80 ^oC.

Step A. Methyl 2-amino-5-bromo-2,3-dihydro-1H-indene-2-carboxylate, **9b**:

To a mixture of 2-amino-5-bromo-2,3-dihydro-1H-indene-2-carboxylic acid (Enamine, 2.56 g, 10 mmol) in methanol (22 mL) was added sulfuric acid solution (5%). The reaction mixture was heated at reflux for 15 h. The mixture was poured onto ice-water (50 mL) and neutralized to "pH" 7 by careful addition of aqueous NaOH solution (1 M). The mixture was extracted with dichloromethane (50 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to afford the crude product (2.19 g, 81%). MS: mass calcd. for $C_{11}H_{12}BrNO_2$, 269.0; m/z found, 270.0 $[M+H]^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.39 (s, 1H), 7.31 (d, J = 8.25 Hz, 1H), 7.15 (d, J = 8.25 Hz, 1H), 3.66 (s, 3H), 3.15-3.43 (m, 2H), 2.80 (dd, J = 13.75, 15.95 Hz, 2H), 2.13 (s, 2H) ppm.

Step B. Methyl 5-bromo-2-((tert-butoxycarbonyl)amino)-2,3-dihydro-1H-indene-2-carboxylate, **9c**:

To a solution of di-tert-butyl dicarbonate (786 mg, 3.6 mmol) in dichloromethane (6 mL) was added a solution of methyl 2-amino-5-bromo-2,3-dihydro-1H-indene-2-carboxylate (650 mg, 2.40 mmol) and triethylamine (0.667 mL, 4.8 mmol) in dichloromethane (19 mL). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with dichloromethane (25mL) and washed with brine (30 mL). The organic layer was separated

and concentrated. The residue was purified by flash chromatography. The pure fractions were combined and concentrated, and then dried to give the desired product (651 mg, 73%). MS: mass calcd. for $C_{16}H_{20}BrNO_4$, 369.0; m/z found, 270.0 $[M\text{-Boc}+H]^+$.

Step C. Methyl 2-((tert-butoxycarbonyl)amino)-5-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate, **9d**:

To a suspension of methyl 5-bromo-2-((tert-butoxycarbonyl)amino)-2,3-dihydro-1H-indene-2-carboxylate (0.8 g , 2.16 mmol), N,N-dimethylaminopyridine (1.5 g, 4.05 mmol), potassium phosphate (2.8 g, 13 mmol) and N,O-dimethylhydroxylamine hydrochloride (0.63 g, 6.5 mmol) in 1,4-dioxane (40 mL) in a autoclave vial was added tungsten hexacarbonyl (0.25 g, 0.71 mmol), Xantphos (0.18 g, 0.3 mmol) and palladium (II) acetate (35 mg, 0.16 mmol). The vial was sealed under air and irradiated under microwave at 120ºC for 20 min. The mixture was diluted with ethyl acetate (25 mL) and washed with brine (15 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) afforded the desired product (0.35 g, 46%). MS: mass calcd. for $C_{18}H_{24}N_2O_5$, 348.2; m/z found, 371.1 $[M+Na]^+$.

Step D. Methyl 2-amino-5-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate, **9e**:

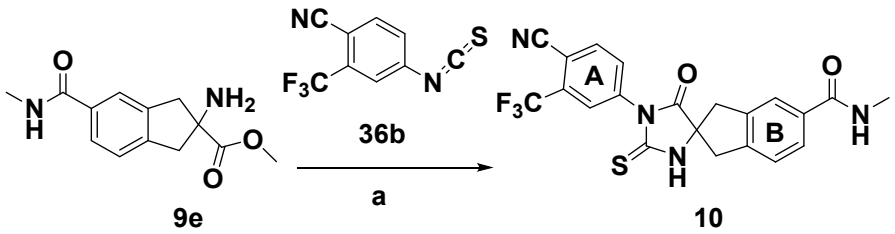
To a solution of methyl 2-((tert-butoxycarbonyl)amino)-5-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate (348 mg, 0.99 mmol) in dichloromethane (6 mL) was added trifluoroacetic acid (3 mL). The reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure, then toluene was added (10 mL) and the mixture was concentrated twice. The resulting crude residue was dissolved into ethyl acetate, washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated to give the desired product (183 mg, 74%). MS: mass calcd. for $C_{13}H_{16}N_2O_3$, 248.1; m/z found, 249.0 $[M+H]^+$.

Step E. 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, **9**:

To a suspension of methyl 2-amino-5-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate (0.183 g, 0.73 mmol) in tetrahydrofuran (8 mL) and N,N-dimethylformamide (8 mL) was added triethylamine (0.62 mL, 4.4 mmol). The mixture was stirred for 5 min, then 5-isothiocyanato-3-(trifluoromethyl)picolinonitrile (0.22 g, 0.96 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature and poured onto aqueous $NaHCO_3$ solution (25 mL) and extracted with ethyl acetate (40 mL). The combined organic extract was washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2,

EtOAc-heptane gradient) to afford the product as a white solid (147 mg, 45%). MS: mass calcd. for $C_{20}H_{14}F_3N_5O_2S$, 445.1; m/z found, 446.1 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{20}H_{14}F_3N_5O_2S$ $[M+H]^+$ 446.0899; m/z found, 446.0897; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.36 (s, 1H), 9.21 (d, J = 1.96 Hz, 1H), 8.77 (d, J = 1.47 Hz, 1H), 8.39 (br d, J = 4.40 Hz, 1H), 7.76 (s, 1H), 7.72 (d, J = 7.83 Hz, 1H), 7.37 (d, J = 8.31 Hz, 1H), 3.64 (br d, J = 17.12 Hz, 2H), 3.38 (br dd, J = 1.47, 17.12 Hz, 2H), 2.78 (d, J = 4.89 Hz, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.5, 175.9, 167.0, 154.2, 142.7, 139.8, 136.1, 134.3, 133.6, 129.3, 129.1, 129.0, 126.7, 124.6, 123.6, 120.7, 114.8, 70.1, 43.1, 26.7 ppm

Preparation of 1-(4-cyano-3-(trifluoromethyl)phenyl)-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 10

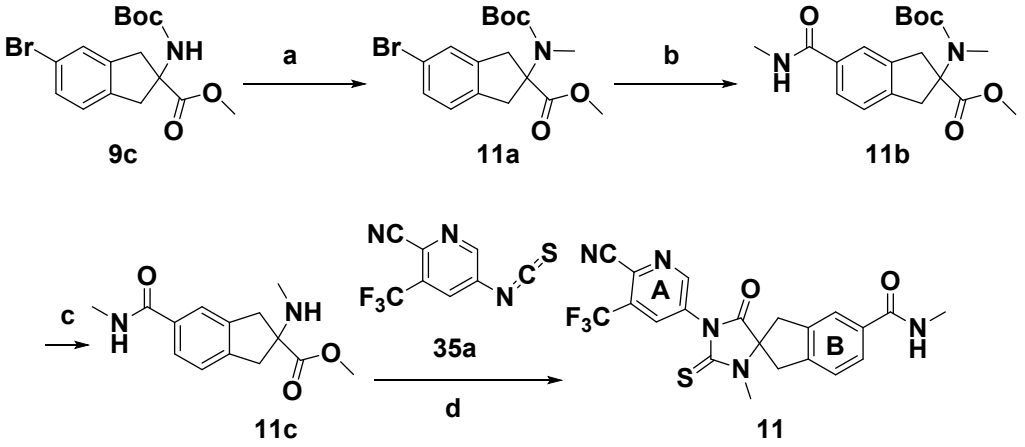


[a]Reagents and Conditions: (a) TEA, THF, DMF, 80 °C.

To a suspension of methyl 2-amino-5-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate (0.177 g, 0.71 mmol) in tetrahydrofuran (8 mL) and N,N-dimethylformamide (8 mL) was added triethylamine (0.6 mL, 4.3 mmol). The mixture was stirred for 5 min, then 4-isothiocyanato-2-(trifluoromethyl)benzonitrile (0.21 g, 0.93 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature and poured onto aqueous $NaHCO_3$ solution (25 mL) and extracted with ethyl acetate (40 mL). The combined organic extract was washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the product as a off-white solid (103 mg, 33%). MS: mass calcd. for $C_{21}H_{15}F_3N_4O_2S$, 444.1; m/z found, 445.0 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{21}H_{15}F_3N_4O_2S$ $[M+H]^+$ 445.0946; m/z found, 445.0942; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15-11.27 (m, 1H), 8.39 (q, J = 4.56 Hz, 1H), 8.34 (d, J = 8.31 Hz, 1H), 8.25 (d, J = 1.96 Hz, 1H), 8.03 (dd, J = 1.96, 8.31 Hz, 1H), 7.73 (s, 1H), 7.65-7.72 (m, 1H), 7.35 (d, J = 8.07 Hz, 1H), 3.61 (d, J = 17.12 Hz, 2H), 3.31 (br d, J = 2.69 Hz, 2H), 2.77 (d, J = 4.40 Hz, 3H)

ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 180.0, 176.2, 167.0, 142.9, 139.9, 138.4, 136.4, 134.3, 131.2, 128.4, 126.7, 124.6, 124.1, 123.5, 121.4, 115.6, 108.7, 69.9, 43.1, 26.7 ppm

Preparation of 1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-N,3-dimethyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 11



[a]Reagents and Conditions: (a) MeI, NaH, DMF, rt; (b) MeNHOMe.HCl, $W(CO)_6$ (cat.), $Pd(OAc)_2$ (cat.), Xantphos (cat.), DMAP, K_3PO_4, 1,4-dioxane, microwave, 120 °C; (c) TFA, DCM, rt; (d) TEA, THF, DMF, 80 °C..

Step A. Methyl 5-bromo-2-((tert-butoxycarbonyl)(methyl)amino)-2,3-dihydro-1H-indene-2-carboxylate, **11a**:

To a solution of methyl 5-bromo-2-((tert-butoxycarbonyl)amino)-2,3-dihydro-1H-indene-2-carboxylate (**10c**, 651 mg, 1.76 mmol) in N,N-dimethylformamide (6 mL) was added sodium hydride (60%, 141 mg, 3.51 mmol). The mixture was stirred for 5 min, and then iodomethane (0.219 mL, 3.51 mmol) was added. The reaction mixture was stirred at room temperature for 20 h. The mixture was poured into brine (25ml) and extracted with ethyl acetate (2x 45 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the desired product (364 mg, 55%). MS: mass calcd. for $C_{17}H_{22}BrNO_4$, 383.1; m/z found, 405.9 $[M+Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.35 (m, 2H), 7.05 (d, J = 8.25 Hz, 1H), 3.71 (s, 3H), 3.51-3.66 (m, 2H), 3.21-3.38 (m, 2H), 2.91 (s, 3H), 1.45 (s, 9H) ppm.

Step B. Methyl 2-((tert-butoxycarbonyl)(methyl)amino)-5-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate, **11b**:

To a suspension of 5-bromo-2-((tert-butoxycarbonyl)(methyl)amino)-2,3-dihydro-1H-indene-2-carboxylate (876 mg , 2.28 mmol), N,N-dimethylaminopyridine (557 mg, 4.56 mmol), potassium phosphate (2.90 g, 13.7 mmol) and N,O-dimethylhydroxylamine hydrochloride (75 mg, 0.768 mmol) in 1,4-dioxane (3 mL) in a autoclave vial (20 mL) was added tungsten hexacarbonyl (667 mg, 6.84 mmol), Xantphos (370 mg, 0.640 mmol) and palladium (II) acetate (37 mg, 0.164 mmol). The vial was sealed under air and irradiated under microwave at 120ºC for 20 min. The mixture was diluted with ethyl acetate (25 mL) and washed with brine (15 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) afforded the two products.

methyl 2-((tert-butoxycarbonyl)(methyl)amino)-5-(methoxy(methyl)carbamoyl)-2,3-dihydro-1H-indene-2-carboxylate (600 mg, 67%). MS: mass calcd. for $C_{20}H_{28}N_2O_6$, 392.2; m/z found, 415.0 $[M+Na]^+$.

The title compound: methyl 2-((tert-butoxycarbonyl)(methyl)amino)-5-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate (297 mg, 36%). MS: mass calcd. for $C_{19}H_{26}N_2O_5$, 362.2; m/z found, 363.0 $[M+H]^+$.

Step C. Methyl 5-bromo-2-((tert-butoxycarbonyl)(methyl)amino)-2,3-dihydro-1H-indene-2-carboxylate, **11c**:

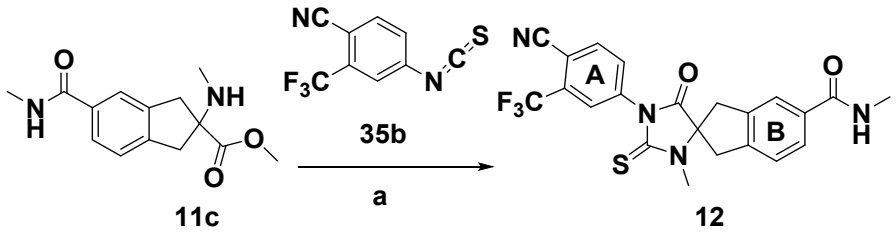
To a solution of methyl 2-((tert-butoxycarbonyl)(methyl)amino)-5-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate (297 mg, 0.819 mmol) in dichloromethane (4.91 mL) was added trifluoroacetic acid (3.27 mL). The reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure, then toluene was added (10 mL) and the mixture was concentrated twice. The resulting crude residue was used directly to next step without further purification (0.819 mmol, 100%). MS: mass calcd. for $C_{14}H_{18}N_2O_3$, 262.1; m/z found, 263.0 $[M+H]^+$.

Step D. 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-N,3-dimethyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, **11**:

To a suspension of methyl 2-(methylamino)-5-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate (162 mg , 0.62 mmol) in tetrahydrofuran (7 mL) and N,N-Dimethylformamide (7 mL) was added triethylamine (0.51 mL, 3.6 mmol). The mixture was stirred for 5 min, then 5-isothiocyanato-3-(trifluoromethyl)picolinonitrile (0.15 g, 0.66 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature and poured onto aqueous $NaHCO_3$ solution (25 mL) and extracted with ethyl acetate (60 mL). The combined organic extract was washed with water (15 mL), brine (15 mL), dried

over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the product as a white solid (258 mg, 90 %). MS: mass calcd. for $C_{21}H_{16}F_3N_5O_2S$, 459.1; m/z found, 460.0 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{21}H_{16}F_3N_5O_2S$ $[M+H]^+$ 460.1055; m/z found, 460.1057; ^1H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, *J* = 1.96 Hz, 1H), 8.35 (d, *J* = 1.96 Hz, 1H), 7.77 (s, 1H), 7.68 (d, *J* = 8.31 Hz, 1H), 7.37 (d, *J* = 7.82 Hz, 1H), 6.15 (br d, *J* = 4.40 Hz, 1H), 3.81 (d, *J* = 17.12 Hz, 2H), 3.39 (dd, *J* = 4.65, 17.36 Hz, 2H), 3.12 (s, 3H), 3.04 (d, *J*= 4.89 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 174.4, 170.4, 167.7, 153.9, 152.1, 148.8, 141.5, 138.8, 135.2, 133.8, 126.7, 124.4, 123.4, 73.0, 42.4, 41.0, 30.7, 27.0 ppm

Preparation of 1-(4-Cyano-3-(trifluoromethyl)phenyl)-N,3-dimethyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 12

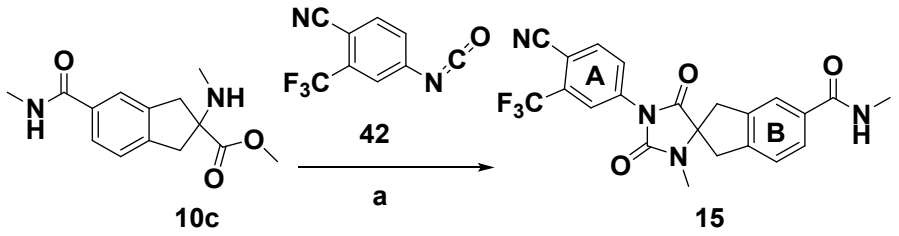


[a]Reagents and Conditions: (a) TEA, THF, DMF, 80 °C.

To a suspension of methyl 2-(methylamino)-5-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate (215 mg , 0.819 mmol) in tetrahydrofuran (9 mL) and N,N-Dimethylformamide (9 mL) was added triethylamine (0.686 mL, 4.9 mmol). The mixture was stirred for 5 min, then 4-isothiocyanato-2-(trifluoromethyl)benzonitrile (0.243 g, 1.065 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature and poured onto aqueous $NaHCO_3$ solution (25 mL) and extracted with ethyl acetate (60 mL). The combined organic extract was washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the product as a white solid (235 mg, 63 %). MS: mass calcd. for $C_{22}H_{17}F_3N_4O_2S$, 458.1; m/z found, 459.0 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{22}H_{17}F_3N_4O_2S$ $[M+H]^+$ 459.1103; m/z found, 459.1101; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.31 Hz, 1H), 7.95 (d, *J* = 1.96 Hz, 1H), 7.83 (dd, *J* = 2.08, 8.19 Hz, 1H), 7.76 (s, 1H), 7.67 (d, *J* = 8.31 Hz, 1H), 7.36 (d, *J* = 8.07 Hz, 1H), 6.15 (br d, *J* = 4.16 Hz, 1H), 3.79 (d, *J* = 17.36 Hz, 2H), 3.37 (dd, *J* = 4.40, 17.36 Hz, 2H), 3.11 (s, 3H), 3.04 (d, *J* = 4.89 Hz,

3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 174.6, 167.7, 141.6, 139.0, 137.1, 135.2, 135.1, 133.8, 133.4, 132.0, 126.6, 124.4, 123.3, 114.8, 110.2, 72.8, 42.4, 42.3, 30.6, 27.0 ppm.

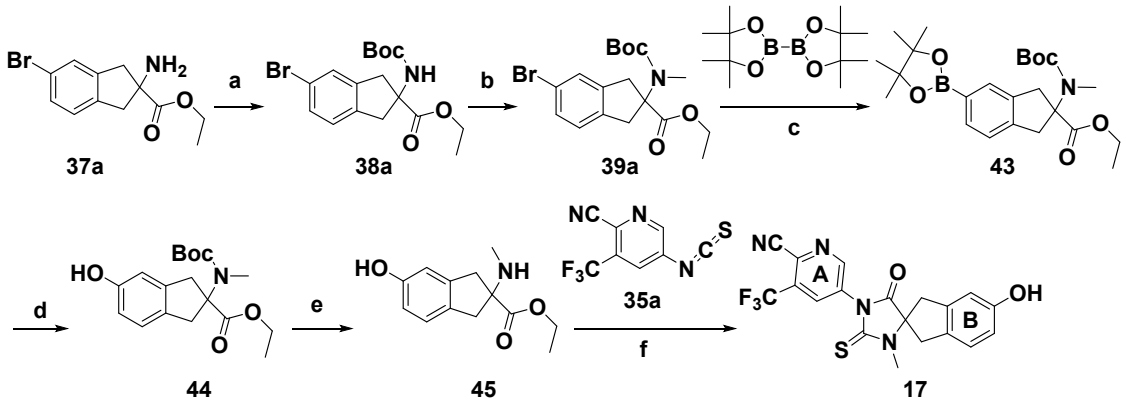
Preparation of 1-(4-cyano-3-(trifluoromethyl)phenyl)-N,3-dimethyl-2,5-dioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 15



[a]Reagents and Conditions: (a) TEA, THF, DMF, 80 ^{o}C.

To a suspension of methyl 2-(methylamino)-5-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate (72 mg , 0.28 mmol) in tetrahydrofuran (3 mL) and N,N-Dimethylformamide (3 mL) was added triethylamine (0.23 mL, 1.66 mmol). The mixture was stirred for 5 min, then 4-isocyanato-2-(trifluoromethyl)benzonitrile (0.243 g, 1.065 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature and poured onto aqueous $NaHCO_3$ solution (25 mL) and extracted with ethyl acetate (60 mL). The combined organic extract was washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the product as a white solid (17 mg, 14%). MS: mass calcd. for $C_{22}H_{17}F_3N_4O_3$, 442.1; m/z found, 443.0 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{22}H_{17}F_3N_4O_3$ $[M+H]^+$ 443.1331; m/z found, 443.1330; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.99-8.06 (m, 1H), 7.94 (br d, J = 8.56 Hz, 1H), 7.75 (br s, 1H), 7.65 (br d, J = 7.82 Hz, 1H), 7.35 (br d, J = 7.83 Hz, 1H), 6.14 (br s, 1H), 3.75 (br d, J = 16.87 Hz, 2H), 3.29 (br dd, J = 4.40, 17.12 Hz, 2H), 3.03 (br d, J = 4.89 Hz, 3H), 2.78 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 167.8, 152.3, 142.0, 139.3, 136.3, 135.4, 134.9, 127.9, 126.5, 124.2, 123.2, 123.0, 115.0, 108.5, 70.2, 42.1, 42.0, 27.0, 25.9 ppm.

Preparation of 5-(5'-hydroxy-3-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-3-(trifluoromethyl)picolinonitrile, 18



[a]Reagents and Conditions: (a) Boc_2O, TEA, DCM, rt; (b) MeI, NaH, DMF, rt; (c) $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, 80 °C; (d) oxone, acetone, rt; (e) TFA, DCM, rt; (f) TEA, THF, DMF, 80 °C.

Step A. Ethyl 5-bromo-2-((tert-butoxycarbonyl)amino)-2,3-dihydro-1H-indene-2-carboxylate, **38a**:

A solution of di-tert-butyl dicarbonate (35.9 g, 164.7 mmol) in dichloromethane (200 mL) was added to a solution of ethyl 2-amino-5-bromo-2,3-dihydro-1H-indene-2-carboxylate (**37a**) (23.4 g, 82.35 mmol) and triethylamine (23 mL, 164.7 mmol) in dichloromethane (200 mL). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with dichloromethane (250 mL) and washed with brine (300 mL). The organic layer was separated and concentrated. The residue was purified by flash chromatography. The pure fractions were combined and concentrated, and then dried to give the desired product (13g, 41%). MS: mass calcd. for $C_{17}H_{22}BrNO_4$, 383.1; m/z found, 284.0 $[M\text{-}Boc+H]^+$.

Step B. Ethyl 5-bromo-2-((tert-butoxycarbonyl)(methyl)amino)-2,3-dihydro-1H-indene-2-carboxylate, **39a**:

To a solution of ethyl 5-bromo-2-((tert-butoxycarbonyl)amino)-2,3-dihydro-1H-indene-2-carboxylate (7.3 g, 19 mmol) in N,N-dimethylformamide (57 mL) was added sodium hydride (60%, 1.52 g, 38 mmol). The mixture was stirred for 5 min, and then iodomethane (2.36 mL, 38 mmol) was added. The reaction mixture was stirred at room temperature for 20 h. The mixture was poured into brine (250 ml) and extracted with ethyl acetate (2 x 450 mL). The combined organic extracts were washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the desired product (7.17 g, 94.7 %). MS: mass calcd. for $C_{18}H_{24}BrNO_4$, 397.1; m/z found, 297.9 $[M\text{-}Boc+H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-

7.35 (m, 2H), 7.06 (d, *J* = 7.70 Hz, 1H), 4.17 (q, *J* = 7.15 Hz, 2H), 3.54-3.70 (m, 2H), 3.23-3.37 (m, 2H), 2.93 (s, 3H), 1.46 (s, 9H), 1.20-1.29 (m, 3H) ppm.

Step C. Ethyl 2-((tert-butoxycarbonyl)(methyl)amino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indene-2-carboxylate, **43**:

To a solution of ethyl 5-bromo-2-((tert-butoxycarbonyl)(methyl)amino)-2,3-dihydro-1H-indene-2-carboxylate (2.0 g, 5.02 mmol), bis(pinacolate)diboron (1.53 g, 6.03 mmol) and potassium acetate (0.986 g, 10.04 mmol) in anhydrous 1,4-ioxane (30 mL) was added [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.205 g, 0.251 mmol) while the mixture was degassed by bubbling nitrogen. The reaction mixture was heated in a sealed tube at 80 ºC for 14 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (45 mL), washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (SiO2, EtOAc-heptane gradient) to afford the desired product (2.20 g, 98%). MS: mass calcd. for $C_{24}H_{36}BNO_6$, 445.3; m/z found, 468.3 $(M+Na)^+$.

Step D. Ethyl 2-((tert-butoxycarbonyl)(methyl)amino)-5-hydroxy-2,3-dihydro-1H-indene-2-carboxylate, **44**:

To a solution of ethyl 2-((tert-butoxycarbonyl)(methyl)amino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indene-2-carboxylate (2.20 g, 4.9 mmol) in acetone (30 mL) was added an aqueous solution (75 mL) of oxone (1.67 g, 5.44 mmol) dropwise. The reaction mixture was stirred at room temperature for 15 min, then quenched with aqueous sodium metabisulfite solution (10%, 10 mL). The mixture was extracted with dichloromethane (250 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated to give the crude product (1.617 g, 97%). MS: mass calcd. for $C_{18}H_{25}NO_5$, 335.2; m/z found, 236.2 $[M\text{-}Boc+H]^+$.

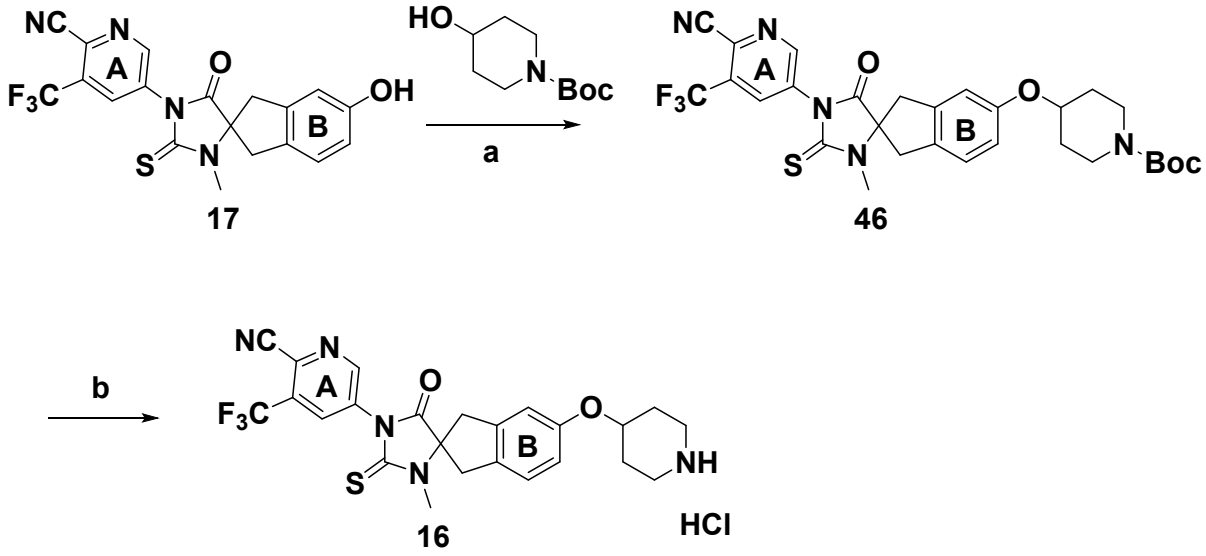
Step E. Ethyl 5-hydroxy-2-(methylamino)-2,3-dihydro-1H-indene-2-carboxylate, **45**:

To a solution of ethyl 2-((tert-butoxycarbonyl)(methyl)amino)-5-hydroxy-2,3-dihydro-1H-indene-2-carboxylate (1.617 g, 4.82 mmol) in dichloromethane (29 mL) was added trifluoroacetic acid (19 mL). The reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure, then toluene was added (40 mL) and the mixture was concentrated twice. The resulting crude residue was used directly to next step without further purification (4.82 mmol, 100%). MS: mass calcd. for $C_{13}H_{17}NO_3$, 235.1; m/z found, 236.0 $[M+H]^+$.

Step E. 5-(5'-Hydroxy-3-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-3-(trifluoromethyl)picolinonitrile, **17**:

To a suspension of ethyl 5-hydroxy-2-(methylamino)-2,3-dihydro-1H-indene-2-carboxylate (2.16 g, 9.18 mmol) in tetrahydrofuran (101 mL) and N,N-Dimethylformamide (101 mL) was added triethylamine (7.69 mL, 55.1 mmol). The mixture was stirred for 5 min, then 5-isothiocyanato-3-(trifluoromethyl)picolinonitrile (11.93 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature and poured onto aqueous $NaHCO_3$ solution (250 mL) and extracted with ethyl acetate (400 mL). The combined organic extract was washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the product as a white solid (2.86 g, 74%). MS: mass calcd. for $C_{19}H_{13}F_3N_4O_2S$, 418.1; m/z found, 418.9 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{19}H_{13}F_3N_4O_2S$ $[M+H]^+$ 419.0790; m/z found, 419.0782; ^1H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, *J* = 1.96 Hz, 1H), 8.36 (d, *J* = 2.20 Hz, 1H), 7.15 (d, *J* = 8.80 Hz, 1H), 6.75-6.82 (m, 2H), 4.97 (br s, 1H), 3.71 (dd, *J* = 12.72, 17.12 Hz, 2H), 3.26 (dd, *J* = 5.14, 16.87 Hz, 2H), 3.15 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 174.6, 156.0, 153.2, 152.1, 140.1, 139.7, 133.8, 129.8, 125.2, 117.0, 115.5, 113.7, 111.3, 73.5, 42.6, 42.0, 30.7 ppm.

Preparation of 5-(3-methyl-5-oxo-5'-(piperidin-4-yloxy)-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-3-(trifluoromethyl)picolinonitrile hydrochloride, 16



[a]Reagents and Conditions: (a) DEAD, PPh_3, THF, 60 °C; (b) HCl, 1,4-dioxane, rt.

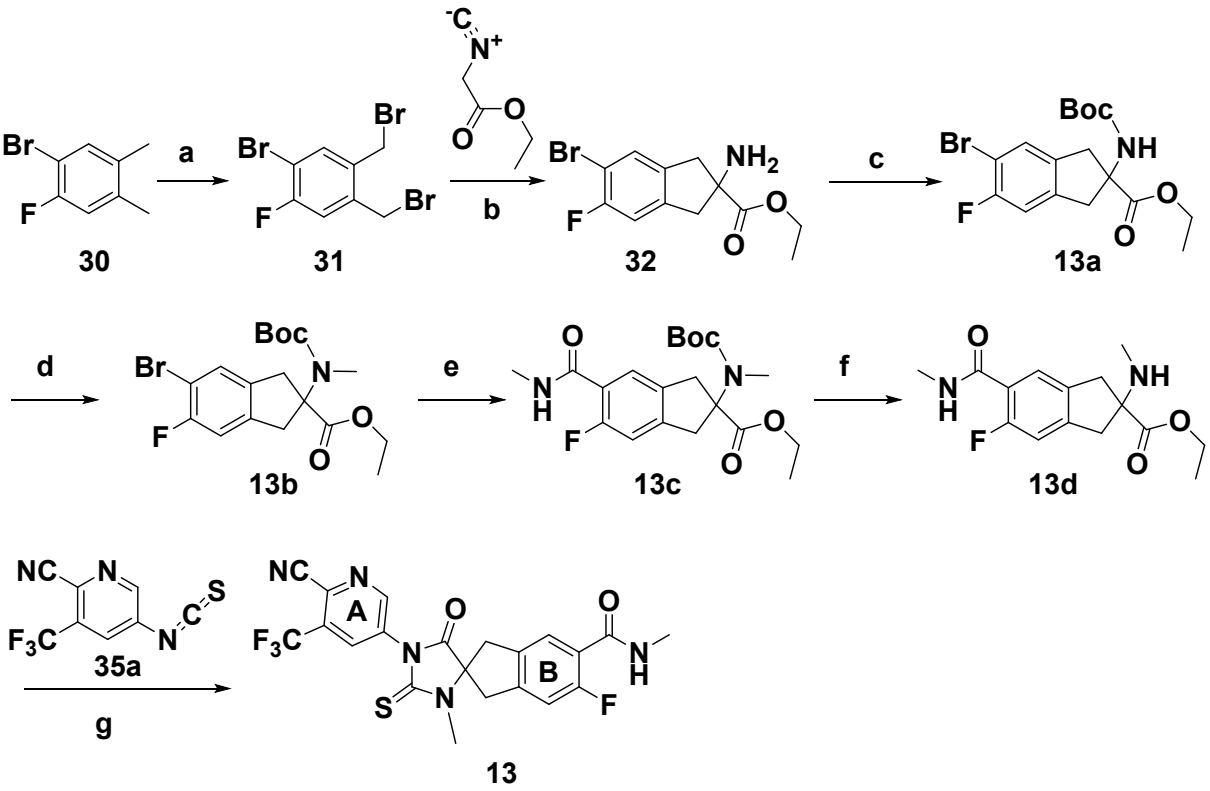
Step A. *tert*-Butyl 4-((1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-5'-yl)oxy)piperidine-1-carboxylate, **46**:

To a solution of 5-(5'-hydroxy-3-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-3-(trifluoromethyl)picolinonitrile (**17**, 2.43 g, 5.81 mmol), 1-boc-4-hydroxypiperidine (1.29 g, 6.4 mmol) and triphenylphosphine (3.36 g, 12.8 mmol) in tetrahydrofuran (20 mL) at 60 ºC was added a solution of diethyl azodicarboxylate (2.3 mL, 11.6 mmol) in tetrahydrofuran (10 mL) dropwise. The reaction mixture was stirred at 60 ºC of 4 h. The mixture was cooled to room temperature and diluted with ethyl acetate (50 mL). The mixture was washed with saturated aqueous $NaHCO_3$ solution (25 mL) and brine (25 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient, 5% to 30%) to afford the desired product (3.5 g, 99%). MS: mass calcd. for $C_{29}H_{30}F_3N_5O_4S$, 601.2; m/z found, 501.9 $[M\text{-Boc}+H]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ 9.09 (d, J = 1.65 Hz, 1H), 8.36 (d, J = 1.65 Hz, 1H), 7.20 (br d, J = 7.70 Hz, 1H), 6.80-6.92 (m, 2H), 4.42-4.53 (m, 1H), 3.66-3.80 (m, 4H), 3.22-3.44 (m, 4H), 3.16 (s, 3H), 1.86-2.00 (m, 2H), 1.68-1.84 (m, 2H), 1.48 (s, 9H) ppm.

Step B. 5-(3-Methyl-5-oxo-5'-(piperidin-4-yloxy)-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-3-(trifluoromethyl)picolinonitrile hydrochloride, **16**:

To a solution of *tert*-butyl 4-((1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-3-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-5'-yl)oxy)piperidine-1-carboxylate (3.49 g, 5.8 mmol) in dichloromethane (45 mL) at 0 ºC was added an anhydrous 1,4-dioxane solution (4 N) of HCl (14.5 mL, 58 mmol). The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure, and the residue was triturated with ethyl acetate and diisopropyl ether mixture. The resulting white solid was filtered, washed with diisopropyl ether and heptane, dried *in vacuo* to afford the desired product (1.81 g, 58%). MS: mass calcd. for $C_{24}H_{22}F_3N_5O_2S$, 501.1; m/z found, 502.1 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{24}H_{22}F_3N_5O_2S$ $[M+H]^+$ 502.1525; m/z found, 502.1527; ^1H NMR (400 MHz, DMSO-d_6) δ 9.22 (d, J = 1.96 Hz, 1H), 8.96 (br s, 2H), 8.78 (d, J = 2.45 Hz, 1H), 7.23 (d, J = 8.31 Hz, 1H), 7.00 (d, J = 1.96 Hz, 1H), 6.90 (dd, J = 2.45, 8.31 Hz, 1H), 4.63 (tt, J = 3.48, 7.27 Hz, 1H), 3.38-3.56 (m, 4H), 3.18-3.27 (m, 2H), 3.16 (s, 3H), 3.01-3.11 (m, 2H), 2.04-2.19 (m, 2H), 1.84 (br d, J = 8.80 Hz, 2H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.4, 175.4, 156.8, 154.2, 141.0, 136.1, 133.9, 131.7, 129.1, 125.6, 123.4, 120.7, 116.0, 114.8, 112.2, 77.5, 73.3, 69.7, 41.5, 41.0, 30.6, 27.7 ppm

Preparation of 1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-6'-fluoro-N,3-dimethyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 13



[a]Reagents and Conditions: (a) NBS, AIBN (cat), CCl_4, 85 °C; (b) K_2CO_3, 18-Crown-6, MeCN, rt; then aq. HCl, rt; (c) Boc_2O, TEA, DCM, rt; (d) MeI, NaH, DMF, rt; (e) MeNHOMe.HCl, $W(CO)_6$ (cat.), $Pd(OAc)_2$ (cat.), Xantphos (cat.), DMAP, K_3PO_4, 1,4-dioxane, microwave, 120 °C; (f) TFA, DCM, rt; (g) TEA, THF, DMF, 80 °C..

Step A. 1-Bromo-4,5-bis(bromomethyl)-2-fluorobenzene, **31**:

To a solution of 1-bromo-2-fluoro-4,5-dimethylbenzene (28 g, 138 mmol) in carbon tetrachloride (260 mL) at reflux (85 ºC) were added N-bromosuccinimide (51.5 g, 289.5 mmol) and AIBN (2.26 g, 13.8 mmol) in four portions over a period of 3 h. The reaction mixture was stirred at reflux temperature (85 ºC) for 2 h, then filtered through a pad of celite and the pad was washed with carbon tetrachloride. The combined filtrate was concentrated to afford the crude product, which was used in next step without further purification (138 mmol, 100%).

Step B. Ethyl 2-amino-5-bromo-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate, **32**:

To a solution of 1-bromo-4,5-bis(bromomethyl)-2-fluorobenzene (49.5 g, 137 mmol) in acetonitrile (800 mL) under nitrogen were added 18-Crown-6 (3.6 g, 13.7 mmol) and K_2CO_3 (113.6 g, 822 mmol), followed by the addition of ethyl isocyanoacetate (15 mL, 138 mmol). The reaction mixture was stirred at room temperature for 24 h. The mixture was filtered through a short pad of celite, and the filtrate was concentrated. The crude residue (42.7 g, 138

mmol) was dissolved into dichloromethane (950 mL) and ethanol (158 mL). The mixture was cooled at 0 ºC, and then concentrated aqueous HCl (35%, 11 mL) was added. The reaction mixture was stirred at 0 ºC for 4 h, then stirred at room temperature for 14 h. The mixture was diluted with water (400 mL), followed by the careful addition of $NaHCO_3$ (30 g) with stirring. The organic layer was separated, washed with brine (250 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, dichloromethane-MeOH) to afford the desired product (22.4 g, 54 % yield for 3 steps). MS: mass calcd. for $C_{12}H_{13}BrFNO_2$, 301.0; m/z found, 301.9 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 6.60 Hz, 1H), 6.99 (d, *J* = 8.80 Hz, 1H), 4.24 (q, *J* = 7.15 Hz, 2H), 3.50 (d, *J* = 16.50 Hz, 2H), 2.83 (d, *J* = 16.50 Hz, 2H), 1.71 (br s, 2H), 1.24-1.36 (m, 3H) ppm.

Step C. Ethyl 5-bromo-2-((tert-butoxycarbonyl)amino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate, **13a**:

A solution of di-tert-butyl dicarbonate (2.7 g, 12.6 mmol) in dichloromethane (25 mL) was added to a solution of ethyl 2-amino-5-bromo-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (1.9 g, 6.3 mmol) and triethylamine (1.3 g, 12.6 mmol) in dichloromethane (25 mL). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with dichloromethane (250 mL) and washed with brine (300 mL). The organic layer was separated and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient). The pure fractions were combined and concentrated, and then dried to give the desired product (0.57 g, 22%). MS: mass calcd. for $C_{17}H_{21}BrFNO_4$, 401.0; m/z found, 301.9 $[M\text{-}Boc+H]^+$.

Step D. Ethyl 5-bromo-2-((tert-butoxycarbonyl)(methyl)amino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate, **13b**:

To a solution of ethyl 5-bromo-2-((tert-butoxycarbonyl)amino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (1.6 g, 4.0 mmol) in N,N-dimethylformamide (73 mL) was added sodium hydride (60%, 0.32 g, 8.0 mmol). The mixture was stirred for 5 min, and then iodomethane (0.5 mL, 8.0 mmol) was added. The reaction mixture was stirred at room temperature for 20 h. The mixture was poured into brine (250 ml) and extracted with ethyl acetate (2 x 450 mL). The combined organic extracts were washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the desired product (0.79 g, 48 %). MS: mass calcd. for $C_{18}H_{23}BrFNO_4$, 415.1; m/z found, 315.8 $[M\text{-}Boc+H]^+$.

Step E. Ethyl 2-((tert-butoxycarbonyl)(methyl)amino)-5-fluoro-6-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate, **13c**:

To a suspension of ethyl 5-bromo-2-((tert-butoxycarbonyl)(methyl)amino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (546 mg , 1.31 mmol), N,N-dimethylaminopyridine (320 mg, 2.6 mmol), potassium phosphate (1.67 g, 7.87 mmol) and N,O-dimethylhydroxylamine hydrochloride (384 mg, 3.93 mmol) in 1,4-dioxane (18 mL) in a autoclave vial was added tungsten hexacarbonyl (138 mg, 0.39 mmol), Xantphos (114 mg, 0.197 mmol) and palladium (II) acetate (22 mg, 0.098 mmol). The vial was sealed under air and irradiated under microwave at 120ºC for 20 min. The mixture was diluted with ethyl acetate (25 mL) and washed with brine (15 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) afforded the title compound (368 mg, 71%). MS: mass calcd. for $C_{15}H_{19}FN_2O_3$, 294.1; m/z found, 295.0 $[M+H]^+$.

Step F. Ethyl 5-fluoro-2-(methylamino)-6-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate, **13d**:

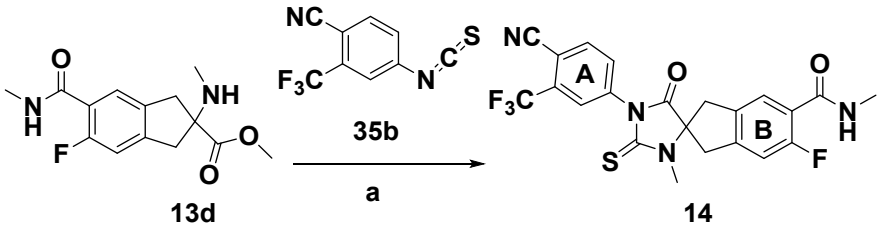
To a solution of ethyl 2-((tert-butoxycarbonyl)(methyl)amino)-5-fluoro-6-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate (369 mg, 0.93 mmol) in dichloromethane (5.5 mL) was added trifluoroacetic acid (3.7 mL). The reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure, then toluene was added (10 mL) and the mixture was concentrated twice. The resulting crude residue was used directly to next step without further purification (275 mg, 100%).

Step G. 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-6'-fluoro-N,3-dimethyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, **13**:

To a suspension of ethyl 5-fluoro-2-(methylamino)-6-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate (165 mg , 0.55 mmol) in tetrahydrofuran (5 mL) and N,N-Dimethylformamide (5 mL) was added triethylamine (0.47 mL, 3.3 mmol). The mixture was stirred for 5 min, then 5-isothiocyanato-3-(trifluoromethyl)picolinonitrile (0.127 g, 0.56 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature and poured onto aqueous $NaHCO_3$ solution (25 mL) and extracted with ethyl acetate (60 mL). The combined organic extract was washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the product as a white solid (104 mg, 39%). MS: mass calcd. for $C_{21}H_{15}F_4N_5O_2S$, 477.1; m/z found, 478.0 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{21}H_{15}F_4N_5O_2S$ $[M+H]^+$ 478.0961; m/z found, 478.0957; ^1H NMR (400 MHz, $CDCl_3$) δ 9.08 (br d, J = 1.96 Hz, 1H), 8.35 (br d, J = 1.96 Hz, 1H), 8.06 (br d, J = 6.85 Hz, 1H), 7.10 (br d, J = 11.25 Hz, 1H), 6.74 (br d, J = 4.40 Hz, 1H), 3.68-3.86 (m,

2H), 3.37 (br d, *J*=17.61 Hz, 2H), 3.14 (s, 3H), 3.05 (br d, *J*=4.89 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 174.1, 163.4, 162.1, 159.6, 152.1, 143.6, 134.6, 133.8, 132.3, 130.6, 130.3, 130.0, 127.6, 122.6, 121.3, 113.7, 112.3, 112.0, 73.2, 42.4, 41.7, 30.7, 27.0 ppm.

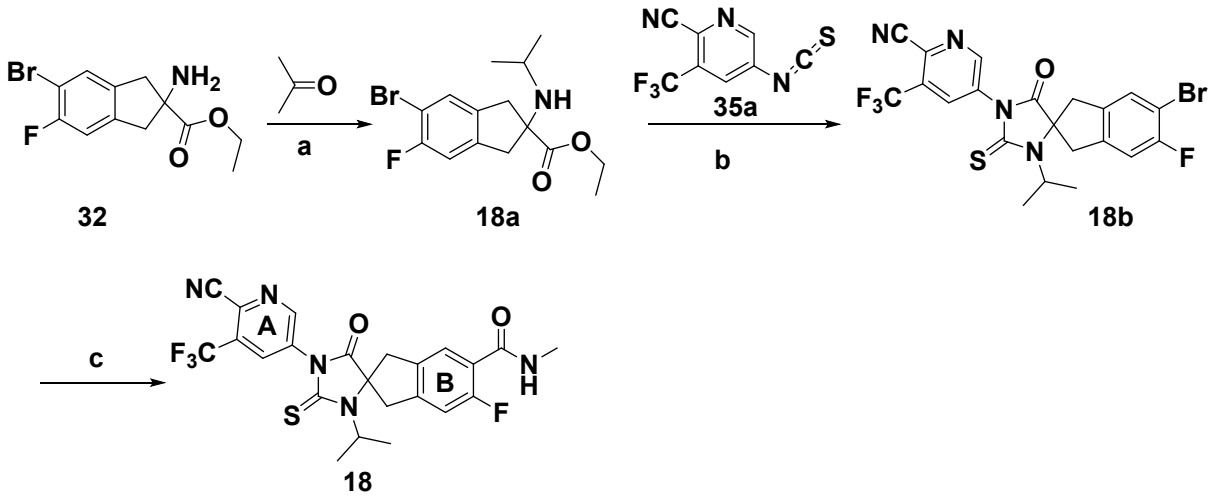
Preparation of 1-(4-cyano-3-(trifluoromethyl)phenyl)-6'-fluoro-N,3-dimethyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 14



[a]Reagents and Conditions: (a) TEA, THF, DMF, 80 ^{o}C.

To a suspension of ethyl 5-fluoro-2-(methylamino)-6-(methylcarbamoyl)-2,3-dihydro-1H-indene-2-carboxylate (**13d**, 163 mg , 0.55 mmol) in tetrahydrofuran (6 mL) and N,N-Dimethylformamide (6 mL) was added triethylamine (0.47 mL, 3.3 mmol). The mixture was stirred for 5 min, then 4-isothiocyanato-2-(trifluoromethyl)benzonitrile (0.127 g, 0.56 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature and poured onto aqueous $NaHCO_3$ solution (25 mL) and extracted with ethyl acetate (60 mL). The combined organic extract was washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the product as a white solid (104 mg, 39 %). MS: mass calcd. for $C_{22}H_{16}F_4N_4O_2S$, 476.1; m/z found, 477.0 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{22}H_{16}F_4N_4O_2S$ $[M+H]^+$ 477.1008; m/z found, 477.1007; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, *J* = 8.31 Hz, 1H), 8.27 (d, *J* = 1.47 Hz, 1H), 8.20 (br dd, *J* = 2.69, 4.16 Hz, 1H), 8.05 (dd, *J* = 1.96, 8.31 Hz, 1H), 7.56 (d, *J* = 6.85 Hz, 1H), 7.21-7.29 (m, 1H), 3.54 (br d, *J* = 19.07 Hz, 4H), 3.15 (s, 3H), 2.77 (d, *J* = 4.40 Hz, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.1, 175.3, 164.5, 158.1, 144.2, 138.7, 136.5, 135.6, 134.4, 131.3, 128.4, 126.0, 123.4, 121.3, 115.5, 112.8, 112.5, 108.9, 73.1, 41.2, 30.5, 26.8 ppm.

Preparation of 1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 18



[a]Reagents and Conditions: (a) $NaBH(OAc)_3$, DCE, rt; (b) TEA, THF/DMF, 80 °C; (c) $MeNH_2.HCl$, $W(CO)_6$ (cat.), $Pd(OAc)_2$ (cat.), Xantphos (cat.), TEA, 1,4-dioxane, 80 °C.

Step A. Ethyl 5-bromo-6-fluoro-2-(isopropylamino)-2,3-dihydro-1H-indene-2-carboxylate, **18a**:

To a solution of ethyl 2-amino-5-bromo-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (**32**, 22.4 g, 74.1 mmol) in 1,2-dichloroethane (250 mL) was added acetone (21.7 mL, 296.5 mmol), followed by the addition of sodium triacetoxyborohydride (47.1 g, 222.4 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was poured onto saturated aqueous $NaHCO_3$ solution (200 mL) and extracted with dichloromethane (200 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2, dichloromethane-methanol gradient). The pure fractions were combined, concentrated, and dried *in vacuo* to give the desired product (12.3 g, 48%). MS: mass calcd. for $C_{15}H_{19}BrFNO_2$, 343.1; m/z found, 344.0 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 6.60 Hz, 1H), 6.93 (d, J = 8.80 Hz, 1H), 4.18 (q, J = 7.15 Hz, 2H), 3.41 (br d, J = 15.95 Hz, 2H), 2.97 (d, J = 16.50 Hz, 2H), 2.82 (td, J = 6.32, 12.65 Hz, 1H), 1.69 (s, 1H), 1.27 (t, J = 7.15 Hz, 3H), 1.04 (d, J = 6.60 Hz, 6H) ppm.

Step B. 5-(5'-Bromo-6'-fluoro-3-isopropyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-3-(trifluoromethyl)picolinonitrile, **18b**:

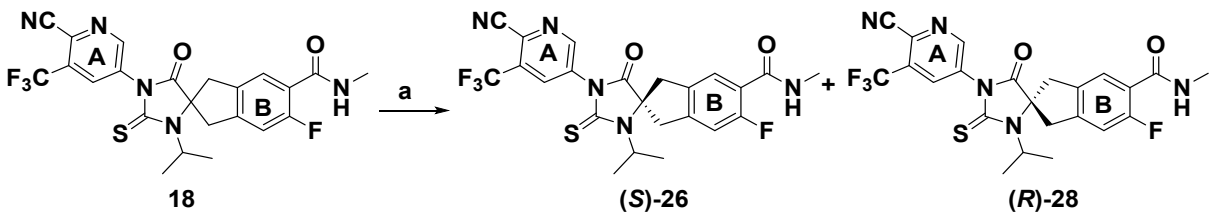
To a suspension of ethyl 5-bromo-6-fluoro-2-(isopropylamino)-2,3-dihydro-1H-indene-2-carboxylate (11.1 g, 32.3 mmol) in tetrahydrofuran (160 mL) and N,N-Dimethylformamide (160 mL) was added triethylamine (27 mL, 194 mmol). The mixture was stirred for 5 min, then 5-isothiocyanato-3-(trifluoromethyl)picolinonitrile (9.6 g, 42 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature

and poured into saturated aqueous $NaHCO_3$ solution (500 mL) and extracted with ethyl acetate (300 mL). The combined organic extract was washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the product as a white solid (12.6 g, 74%). MS: mass calcd. for $C_{21}H_{15}BrF_4N_4OS$, 526.0; m/z found, 527.0 $[M+H]^+$.

Step C. 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, **18**:

To a suspension of 5-(5'-bromo-6'-fluoro-3-isopropyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-3-(trifluoromethyl)picolinonitrile (1.3 g , 2.5 mmol), triethylamine (2.8 mL, 20 mmol) and methylamine hydrochloride (505 mg, 7.5 mmol) in 1,4-dioxane (20 mL) was added tungsten hexacarbonyl (438 mg, 1.25 mmol), xantphos (144 mg, 0.25 mmol) and palladium (II) acetate (77 mg, 0.25 mmol). The vial was sealed and heated at 80 ºC for 15 h. The mixture was diluted with ethyl acetate (50mL) and washed with brine (15 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) afforded the desired product (0.5 g, 40%). MS: mass calcd. for $C_{23}H_{19}F_4N_5O_2S$, 505.1; m/z found, 505.9 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{23}H_{19}F_4N_5O_2S$ $[M+H]^+$ 506.1274; m/z found, 506.1276; ^1H NMR (300 MHz, $CDCl_3$) δ 9.02 (d, J = 1.96 Hz, 1H), 8.29 (d, J = 1.96 Hz, 1H), 8.05 (d, J = 6.85 Hz, 1H), 7.08 (d, J = 11.25 Hz, 1H), 6.75 (br dd, J = 4.89, 12.72 Hz, 1H), 3.83 (td, J = 6.91, 14.06 Hz, 1H), 3.69-3.78 (m, 2H), 3.45-3.52 (m, 2H), 3.06 (d, J = 3.91 Hz, 3H), 1.62 (d, J = 6.85 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 174.6, 163.5, 162.0, 159.6, 152.6, 144.1, 135.1, 134.5, 131.9, 130.6, 130.0, 127.6, 121.1, 113.7, 112.3, 112.0, 74.3, 50.4, 42.7, 41.9, 27.0, 19.9 ppm.

Preparation of (S)-1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, (*S*)-**26; and (R)-1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide,** (*R*)-**28**



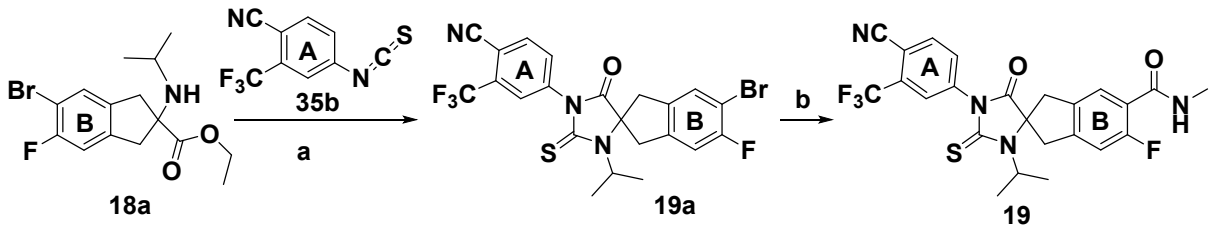
18 **(*S*)-26** **(*R*)-28**

[a]Reagents and Conditions: (a) SFC chiral separation.

The chiral separation of 1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide (Compound **18**, 4.9 g) was performed via chiral SFC (Stationary phase: ChiralPak AD, 300×50mm I.D., 10 um, Mobile phase: 50% CO2, 50% EtOH; Flow Rate: 200 mL/min; Pressure: 100 bar, also see SI section S-11) to give the first peak as (R)-1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, (*R*)-**28** (2.4 g, 49%, 100%ee). Absolute stereochemistry assigned as (*R*) with 90% confidence by VCD (BioTools, Jupiter, FL, see SI section S-9). MS: mass calcd. for $C_{23}H_{19}F_4N_5O_2S$, 505.1; m/z found, 506.1 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{23}H_{19}F_4N_5O_2S$ $[M+H]^+$ 506.1274; m/z found, 506.1274; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 2.45 Hz, 1H), 8.29 (d, *J* = 1.96 Hz, 1H), 8.05 (d, *J* = 7.34 Hz, 1H), 7.08 (d, *J* = 11.74 Hz, 1H), 6.75 (br dd, *J* = 4.89, 12.72 Hz, 1H), 3.83 (td, *J* = 6.85, 13.69 Hz, 1H), 3.68-3.79 (m, 2H), 3.40-3.54 (m, 2H), 3.05 (d, *J* = 4.40 Hz, 3H), 1.62 (d, *J* = 6.85 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 174.6, 163.5, 162.0, 159.6, 152.6, 144.0, 135.1, 134.5, 131.9, 130.6, 130.2, 127.6, 121.1, 113.8, 112.3, 112.0, 74.3, 50.4, 42.7, 41.9, 27.0, 19.9 ppm.

(*S*)-1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, (*S*)-**26** was isolated as the second peak (2.5 g, 51%, 99.5%ee). Absolute stereochemistry assigned as (*S*) with 90% confidence by VCD (BioTools, Jupiter, FL, see SI section S-9). MS: mass calcd. for $C_{23}H_{19}F_4N_5O_2S$, 505.1; m/z found, 506.1 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{23}H_{19}F_4N_5O_2S$ $[M+H]^+$ 506.1274; m/z found, 506.1274; ^{1}H NMR (401 MHz, $CDCl_3$) δ 9.02 (d, *J* = 1.96 Hz, 1H), 8.30 (d, *J* = 1.96 Hz, 1H), 8.05 (d, *J* = 7.34 Hz, 1H), 7.08 (d, *J* = 11.25 Hz, 1H), 6.75 (br dd, *J* = 4.65, 12.96 Hz, 1H), 3.83 (td, *J* = 7.03, 13.82 Hz, 1H), 3.67-3.79 (m, 2H), 3.44-3.54 (m, 2H), 3.06 (d, *J* = 4.89 Hz, 3H), 1.63 (d, *J* = 6.85 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 174.6, 163.5, 162.0, 159.6, 152.6, 144.0, 135.1, 134.5, 131.9, 130.6, 130.2, 127.6, 121.1, 119.9, 113.8, 112.3, 112.0, 74.3, 50.4, 42.7, 41.9, 27.0, 19.9 ppm.

Preparation of 1-(4-cyano-3-(trifluoromethyl)phenyl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 19



[a]Reagents and Conditions: (a) TEA, THF/DMF, 80 °C; (b) $MeNH_2$.HCl, $W(CO)_6$ (cat.), $Pd(OAc)_2$ (cat.), Xantphos (cat.), TEA, 1,4-dioxane, 80 °C.

Step A. 4-(5'-Bromo-6'-fluoro-3-isopropyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-2-(trifluoromethyl)benzonitrile, **19a**:

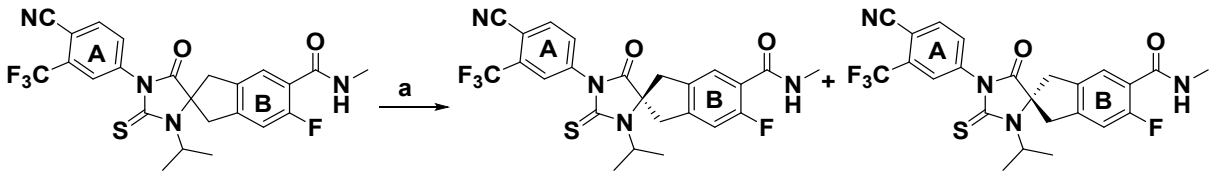
To a suspension of ethyl 5-bromo-6-fluoro-2-(isopropylamino)-2,3-dihydro-1H-indene-2-carboxylate (**18a**, 11.9 g, 34.6 mmol) in tetrahydrofuran (200 mL) and N,N-Dimethylformamide (200 mL) was added triethylamine (29 mL, 208 mmol). The mixture was stirred for 5 min, then 4-isothiocyanato-2-(trifluoromethyl)benzonitrile (10.2 g, 45 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ solution (500 mL) and extracted with ethyl acetate (300 mL). The combined organic extract was washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the product, which was crystallized from a mixture of dichloromethane and heptane as a white solid (16.6 g, 91%). MS: mass calcd. for $C_{22}H_{16}BrF_4N_3OS$, 525.0; m/z found, 525.7 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87-8.00 (m, 2H), 7.76-7.84 (m, 1H), 7.49 (d, J = 6.60 Hz, 1H), 7.08 (d, J = 8.25 Hz, 1H), 3.89 (td, J = 6.87, 13.75 Hz, 1H), 3.60-3.75 (m, 2H), 3.35-3.49 (m, 2H), 1.64 (d, J = 6.60 Hz, 6H) ppm.

Step B. 1-(6-Cyano-3-(trifluoromethyl)phenyl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, **19**:

To a suspension of 4-(5'-bromo-6'-fluoro-3-isopropyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-2-(trifluoromethyl)benzonitrile (1.7 g , 3.23 mmol), triethylamine (3.6 mL, 25.8 mmol) and methylamine hydrochloride (654 mg, 9.7 mmol) in Dioxane (20 mL) in a autoclave vial (50 mL) was added tungsten hexacarbonyl (568 mg, 1.61 mmol), xantphos (187 mg, 0.323 mmol) and palladium (II) acetate (100 mg, 0.323 mmol). The vial was sealed and heated at 80 ºC for 15 h. The mixture was diluted with ethyl acetate (50mL) and washed with brine (15 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) afforded the desired product (0.52 g, 40%). MS: mass calcd. for

$C_{24}H_{20}F_4N_4O_2S$, 504.1; m/z found, 505.1 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{24}H_{20}F_4N_4O_2S$ $[M+H]^+$ 505.1321; m/z found, 505.1321; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.34 Hz, 1H), 7.96 (d, *J* = 7.82 Hz, 1H), 7.90 (d, *J* = 1.96 Hz, 1H), 7.78 (dd, *J* = 1.96, 8.31 Hz, 1H), 7.07 (d, *J* = 11.25 Hz, 1H), 6.75 (br dd, *J* = 4.65, 12.96 Hz, 1H), 3.85 (td, *J* = 6.85, 13.69 Hz, 1H), 3.66-3.77 (m, 2H), 3.42-3.50 (m, 2H), 3.05 (dd, *J* = 0.98, 4.89 Hz, 3H), 1.61 (d, *J* = 6.85 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 174.8, 163.5, 162.0, 159.5, 144.3, 136.7, 135.1, 133.7, 133.3, 132.6, 127.5, 121.0, 114.8, 112.2, 111.9, 110.2, 74.1, 50.3, 42.7, 41.8, 27.0, 20.0 ppm.

Preparation of (S)-1-(4-cyano-3-(trifluoromethyl)phenyl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, (*S*)**-27; and (R)-1-(4-cyano-3-(trifluoromethyl)phenyl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide,** (*R*)**-29**



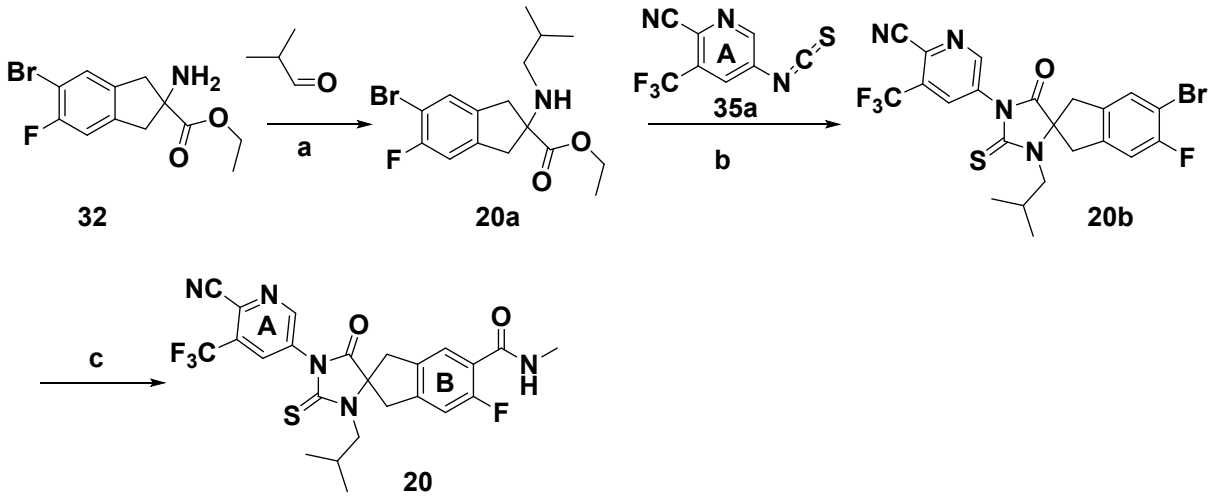
[a]Reagents and Conditions: (a) SFC chiral separation.

The chiral separation of 1-(4-cyano-3-(trifluoromethyl)phenyl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide (Compound **19**, 6.39 g) was performed via chiral SFC (Thar 350 preparative SFC; Stationary phase: ChiralPak AD, 300×50mm I.D., 10 um; Mobile phase: 65% CO_2, 35% iPrOH; Flow Rate: 200 mL/min; Pressure: 100 bar, also see SI section S-10) to give the first peak as (*S*)-1-(4-cyano-3-(trifluoromethyl)phenyl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide (3.04 g, 48%, 99.5%ee). Absolute stereochemistry assigned as (*S*) with 99% confidence by VCD (BioTools, Jupiter, FL, see SI section S-8). MS: mass calcd. for $C_{24}H_{20}F_4N_4O_2S$, 504.1; m/z found, 505.0 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{24}H_{20}F_4N_4O_2S$ $[M+H]^+$ 505.1321; m/z found, 505.1325; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.34 Hz, 1H), 7.96 (d, *J* = 8.31 Hz, 1H), 7.90 (d, *J* = 1.47 Hz, 1H), 7.78 (dd, *J* = 1.96, 8.31 Hz, 1H), 7.07 (d, *J* = 11.25 Hz, 1H), 6.69-6.81 (m, 1H), 3.85 (td, *J* = 6.85, 13.69 Hz, 1H), 3.72 (dd, *J* = 11.25, 17.61 Hz, 2H), 3.40-3.52 (m, 2H), 3.05 (d, *J* =4 .40 Hz, 3H), 1.61 (d, *J* = 6.85 Hz, 6H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.3, 174.7, 163.5, 162.0, 159.5, 144.3, 136.7, 135.1, 133.6, 133.3, 132.5, 127.5, 121.0, 120.9, 114.8, 112.2,

111.9, 110.2, 74.1, 50.2, 42.6, 41.8, 26.9, 19.9 ppm.

(*R*)-1-(4-cyano-3-(trifluoromethyl)phenyl)-6'-fluoro-3-isopropyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide was isolated as the second peak (3 g, 47%, 99.5%ee). Absolute stereochemistry assigned as (*R*) with 99% confidence by VCD (BioTools, Jupiter, FL, see SI section S-8). MS: mass calcd. for $C_{24}H_{20}F_4N_4O_2S$, 504.1; m/z found, 505.0 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{24}H_{20}F_4N_4O_2S$ $[M+H]^+$ 505.1321; m/z found, 505.1325; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.34 Hz, 1H), 7.96 (d, *J* = 8.31 Hz, 1H), 7.90 (d, *J* = 1.96 Hz, 1H), 7.78 (dd, *J* = 1.96, 8.31 Hz, 1H), 7.07 (d, *J* = 11.25 Hz, 1H), 6.75 (br dd, *J* = 4.40, 12.72 Hz, 1H), 3.85 (td, *J* = 6.66, 13.57 Hz, 1H), 3.72 (dd, *J* = 11.74, 17.61 Hz, 2H), 3.40-3.52 (m, 2H), 3.05 (d, *J* = 4.89 Hz, 3H), 1.61 (d, *J* = 7.34 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 174.8, 163.5, 162.0, 159.5, 144.3, 136.7, 135.2, 133.5, 132.6, 127.5, 121.0, 120.5, 114.8, 112.2, 111.9, 110.2, 74.1, 50.3, 42.7, 41.8, 27.0, 20.0 ppm.

Preparation of 1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-6'-fluoro-3-isobutyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 20



[a]Reagents and Conditions: (a) $NaBH(OAc)_3$, DCE, rt; (b) TEA, THF/DMF, 80 °C; (c) MeNHOMe.HCl, $W(CO)_6$ (cat.), $Pd(OAc)_2$ (cat.), Xantphos (cat.), DMAP, K_3PO_4, 1,4-dioxane, microwave, 120 °C

Step A. Ethyl 5-bromo-6-fluoro-2-(isobutylamino)-2,3-dihydro-1H-indene-2-carboxylate, **20a**:

To a solution of ethyl 2-amino-5-bromo-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (**32**, 400 mg, 1.3 mmol) in 1,2-dichloroethane (10 mL) was added isobutyraldehyde (0.12 mL, 1.3

mmol), followed by the addition of sodium triacetoxyborohydride (561 mg, 2.6 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was poured onto saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2, 0-10% methanol in dichloromethane gradient). The pure fractions were combined, concentrated, and dried *in vacuo* to give the desired product (470 mg, 99%). MS: mass calcd. for $C_{16}H_{21}BrFNO_2$, 357.1; m/z found, 357.9 $[M+H]^+$.

Step B. 5-(5'-Bromo-6'-fluoro-3-isobutyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-3-(trifluoromethyl)picolinonitrile, **20b**:

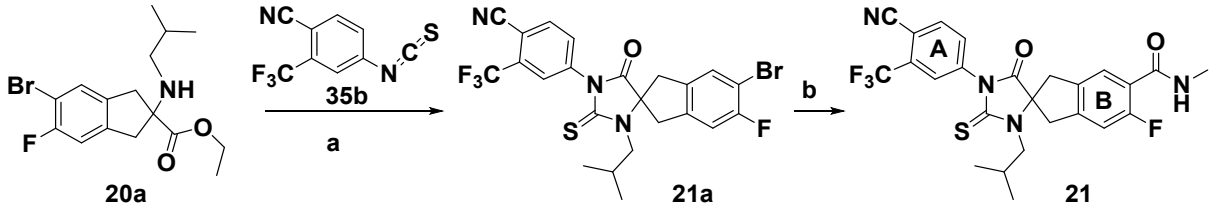
To a suspension of ethyl 5-bromo-6-fluoro-2-(isobutylamino)-2,3-dihydro-1H-indene-2-carboxylate (0.358 g, 1 mmol) in tetrahydrofuran (11 mL) and N,N-Dimethylformamide (11 mL) was added triethylamine (0.83 mL, 6 mmol). The mixture was stirred for 5 min, then 5-isothiocyanato-3-(trifluoromethyl)picolinonitrile (0.3 g, 1.3 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extract was washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the product as a white solid (0.237 g, 44%). MS: mass calcd. for $C_{22}H_{17}BrF_4N_4OS$, 540.0; m/z found, 541.2 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 9.08 (d, J = 1.65 Hz, 1H), 8.34 (d, J = 2.20 Hz, 1H), 7.51 (d, J = 6.05 Hz, 1H), 7.10 (d, J = 8.25 Hz, 1H), 3.66-3.79 (m, 2H), 3.44 (dd, J = 4.95, 7.70 Hz, 2H), 3.32 (d, J = 17.05 Hz, 2H), 1.96 (td, J = 6.74, 14.02 Hz, 1H), 0.88 (br d, J = 6.60 Hz, 6H) ppm.

Step C. 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-6'-fluoro-3-isobutyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, **20**:

To a suspension of 5-(5'-bromo-6'-fluoro-3-isobutyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-3-(trifluoromethyl)picolinonitrile (50 mg , 0.09 mmol), N,N-dimethylaminopyridine (23 mg, 0.19 mmol), potassium phosphate (0.12 g, 0.55 mmol) and N,O-dimethylhydroxylamine hydrochloride (27 mg, 0.28 mmol) in 1,4-dioxane (3 mL) in a autoclave vial was added tungsten hexacarbonyl (9.8 mg, 0.03 mmol), Xantphos (8 mg, 0.01 mmol) and palladium (II) acetate (2 mg, 0.007 mmol). The vial was sealed under air and irradiated under microwave at 120ºC for 90 min. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) afforded the title compound (20 mg, 41%). MS: mass calcd. for $C_{24}H_{21}F_4N_5O_2S$,

519.1; m/z found, 520.0 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{24}H_{21}F_4N_5O_2S$ $[M+H]^+$ 520.1430; m/z found, 520.1433; ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, *J* = 1.96 Hz, 1H), 8.33 (br d, *J* = 1.96 Hz, 1H), 8.08 (br d, *J* = 6.60 Hz, 1H), 7.09 (br d, *J* = 11.49 Hz, 1H), 6.69-6.84 (m, 1H), 3.69-3.85 (m, 2H), 3.27-3.47 (m, 4H), 3.06 (br d, *J* = 4.65 Hz, 3H), 1.89 (td, *J* = 6.94, 14.24 Hz, 1H), 0.84 (br d, *J* = 6.60 Hz, 6H) ppm;

Preparation of 1-(4-cyano-3-(trifluoromethyl)phenyl)-6'-fluoro-3-isobutyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 21



[a]Reagents and Conditions: (a) TEA, THF/DMF, 80 °C; (b) MeNHOMe.HCl, $W(CO)_6$ (cat.), $Pd(OAc)_2$ (cat.), Xantphos (cat.), DMAP, K_3PO_4, 1,4-dioxane, microwave, 120 °C

Step A. 4-(5'-Bromo-6'-fluoro-3-isobutyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-2-(trifluoromethyl)benzonitrile, **21a**:

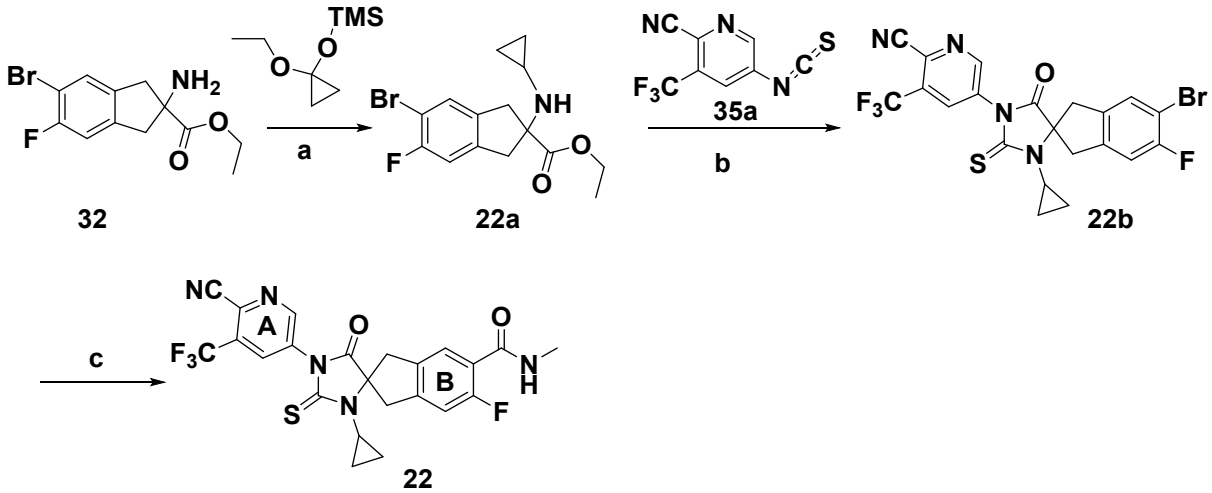
To a suspension of ethyl 5-bromo-6-fluoro-2-(isobutylamino)-2,3-dihydro-1H-indene-2-carboxylate (0.466 g, 1.3 mmol) in tetrahydrofuran (14 mL) and N,N-Dimethylformamide (14 mL) was added triethylamine (1.09 mL, 7.8 mmol). The mixture was stirred for 5 min, then 4-isothiocyanato-2-(trifluoromethyl)benzonitrile (0.39 g, 1.7 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extract was washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the product (0.5 g, 71%). MS: mass calcd. for $C_{23}H_{18}BrF_4N_3OS$, 539.0; m/z found, 539.8 $[M+H]^+$.

Step B. 1-(4-Cyano-3-(trifluoromethyl)phenyl)-6'-fluoro-3-isobutyl-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, **21**:

To a suspension of 4-(5'-bromo-6'-fluoro-3-isobutyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-2-(trifluoromethyl)benzonitrile (400 mg , 0.74 mmol), N,N-dimethylaminopyridine (181 mg, 1.48 mmol), potassium phosphate (0.94 g, 4.4 mmol) and N,O-dimethylhydroxylamine hydrochloride (220 mg, 2.2 mmol) in 1,4-dioxane

(12mL) in a autoclave vial was added tungsten hexacarbonyl (78 mg, 0.22 mmol), Xantphos (64 mg, 0.11 mmol) and palladium (II) acetate (12.5 mg, 0.06 mmol). The vial was sealed under air and irradiated under microwave at 120ºC for 90 min. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) afforded the title compound (133 mg, 34%). MS: mass calcd. for $C_{25}H_{22}F_4N_4O_2S$, 518.1; m/z found, 519.0 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{25}H_{22}F_4N_4O_2S$ $[M+H]^+$ 519.1478; m/z found, 519.1478; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.34 Hz, 1H), 7.97 (d, *J* = 8.31 Hz, 1H), 7.93 (d, *J* = 1.96 Hz, 1H), 7.82 (dd, *J* = 2.20, 8.07 Hz, 1H), 7.08 (d, *J* = 11.52 Hz, 1H), 6.71-6.85 (m, 1H), 3.75 (t, *J* = 16.87 Hz, 2H), 3.41 (dd, *J* = 5.62, 7.58 Hz, 2H), 3.32-3.38 (m, 2H), 3.06 (d, *J* = 3.82 Hz, 3H), 1.82-1.98 (m, 1H), 0.84 (dd, *J* = 0.98, 6.85 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0, 174.2, 163.4, 159.6, 144.1, 137.2, 135.0, 135.2, 133.8, 133.4, 132.2, 127.6, 127.1, 123.2, 120.8, 114.8, 112.1, 111.9, 110.2, 74.2, 52.4, 43.2, 42.5, 28.4, 27.0, 20.4 ppm

Preparation of 1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclopropyl-6'-fluoro-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 22



32 22a 22b 22

[a]Reagents and Conditions: (a) $NaBH_3CN$, MeOH/AcOH, molecular sieves 4A, 70 °C; (b) TEA, THF/DMF, 80 °C; (c) MeNHOMe.HCl, $W(CO)_6$ (cat.), $Pd(OAc)_2$ (cat.), Xantphos (cat.), DMAP, K_3PO_4, 1,4-dioxane, microwave, 120 °C

Step A. Ethyl 5-bromo-2-(cyclopropylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate, **22a**:

To a solution of ethyl 2-amino-5-bromo-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (**32**, 1.4 g, 4.6 mmol) in methanol (56 mL) was added acetic acid (2.65 mL, 46 mmol) , followed by the addition of molecular sieves 4A (5.6 g), (1-ethoxy-cyclopropoxy)-trimethyl-silane (1.86 mL, 9.27 mmol), and sodium cyanoborohydride (0.58 g, 9.27 mmol) sequentially. The reaction mixture was heated under nitrogen at 70 ºC overnight. The mixture was filtered. The filtrate was diluted with ethyl acetate (100 mL) and washed with aqueous $NaHCO_3$ saturated solution (75 mL). The organic layer was separated and concentrated. The residue was purified by flash chromatography (SiO_2, dichloromethane-methanol-ammonia gradient). Pure fractions were combined and concentrated to dryness to afford the product (255 mg, 16%). MS: mass calcd. for $C_{15}H_{17}BrFNO_2$, 341.0; m/z found, 341.9 $[M+H]^+$.

Step B. 5-(5'-Bromo-3-cyclopropyl-6'-fluoro-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-3-(trifluoromethyl)picolinonitrile, **22b**:

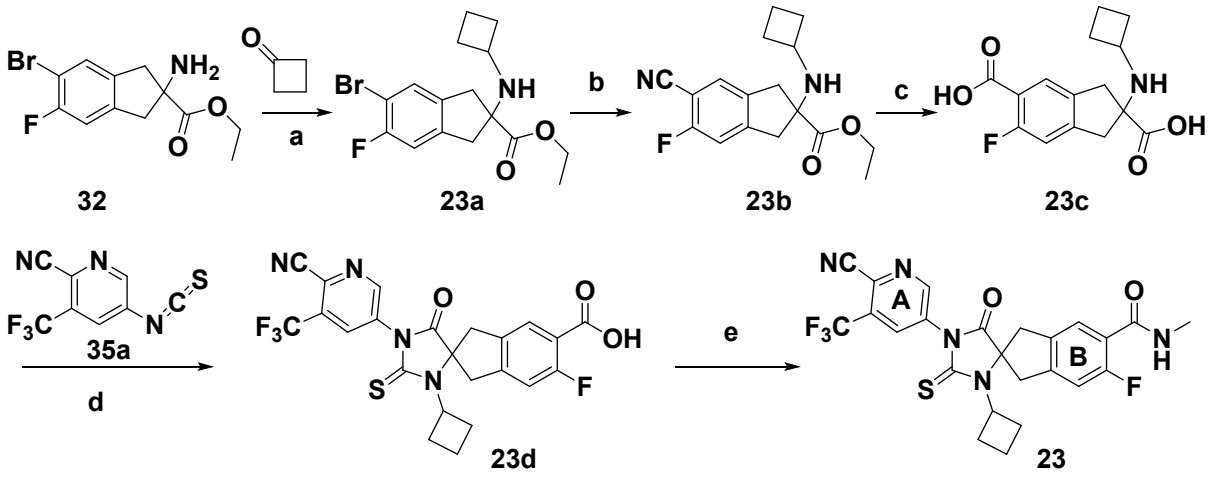
To a suspension of ethyl 5-bromo-2-(cyclopropylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (0.485 g, 1.42 mmol) in tetrahydrofuran (4 mL) and N,N-Dimethylformamide (4 mL) was added triethylamine (0.66 mL, 4.7 mmol). The mixture was stirred for 5 min, then 5-isothiocyanato-3-(trifluoromethyl)picolinonitrile (0.42 g, 1.8 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extract was washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) to afford the product as a white solid (0.584 g, 78%). MS: mass calcd. for $C_{21}H_{13}BrF_4N_4OS$, 524.0; m/z found, 524.8 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 9.02-9.10 (m, 1H), 8.31 (d, J = 1.65 Hz, 1H), 7.49 (d, J = 6.05 Hz, 1H), 7.08 (d, J = 7.70 Hz, 1H), 3.64-3.81 (m, 2H), 3.22-3.46 (m, 2H), 2.53-2.74 (m, 1H), 0.83-0.96 (m, 4H) ppm.

Step C. 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclopropyl-6'-fluoro-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, **22**:

To a suspension of 5-(5'-bromo-3-cyclopropyl-6'-fluoro-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-inden]-1-yl)-3-(trifluoromethyl)picolinonitrile (477 mg , 0.91 mmol), N,N-dimethylaminopyridine (222 mg, 1.82 mmol), potassium phosphate (1.16 g, 5.42 mmol) and N,O-dimethylhydroxylamine hydrochloride (266 mg, 2.72 mmol) in 1,4-dioxane (7 mL) in a autoclave vial was added tungsten hexacarbonyl (112 mg, 0.32 mmol), Xantphos (105 mg, 0.18 mmol) and palladium (II) acetate (112 mg, 0.32 mmol). The vial was sealed under air and irradiated under microwave at 120ºC for 20 min. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was separated, dried over $MgSO_4$ and

concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc-heptane gradient) afforded the title compound (104 mg, 23%). MS: mass calcd. for $C_{23}H_{17}F_4N_5O_2S$, 503.1; m/z found, 503.8 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{23}H_{17}F_4N_5O_2S$ $[M+H]^+$ 504.1117; m/z found, 504.1119; ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (br d, J = 2.20 Hz, 1H), 8.32 (br d, J = 2.20 Hz, 1H), 8.04 (br d, J = 7.09 Hz, 1H), 7.07 (br d, J = 11.49 Hz, 1H), 6.69-6.86 (m, 1H), 3.64-3.89 (m, 2H), 3.33-3.52 (m, 2H), 3.06 (br d, J = 4.65 Hz, 3H), 2.55-2.73 (m, 1H), 0.74-0.97 (m, 2H), 0.55-0.77 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 174.5, 163.5, 162.0, 159.4, 152.3, 144.4, 135.4, 134.0, 132.3, 130.7, 130.0, 127.3, 120.8, 113.8, 112.0, 111.8, 74.7, 43.4, 42.8, 28.2, 27.0, 7.5 ppm.

Preparation of 1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclobutyl-6'-fluoro-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 23



[a]Reagents and Conditions: (a) $NaBH(OAc)_3$, DCE, rt; (b) $Zn(CN)_2$, Pd_2dba_3, PPh_3, DMA, 120 °C; (c) aqueous conc. HCl, 135 °C; (d) TEA, THF/DMF, 80 °C; (e) NH_4Cl, HBTU, DIPEA, DMAP (cat.), DMF, rt.

Step A. Ethyl 5-bromo-2-(cyclobutylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate, **23a**:

To a solution of ethyl 2-amino-5-bromo-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (**32**, 1.4 g, 4.6 mmol) in 1,2-dichloroethane (35 mL) was added cyclobutanone (0.69 mL, 9.27 mmol), followed by the addition of sodium triacetoxyborohydride (3.9 g, 18.5 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was poured onto saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2, 0-10% methanol in dichloromethane gradient). The pure

fractions were combined, concentrated, and dried *in vacuo* to give the desired product (689 mg, 42%). MS: mass calcd. for $C_{16}H_{19}BrFNO_2$, 355.1; m/z found, 355.9 $[M+H]^+$.

Step B. Ethyl 5-cyano-2-(cyclobutylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate, **23b**:

A suspension of ethyl 5-bromo-2-(cyclobutylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (689 mg, 1.93 mmol), triphenylphosphine (609 mg, 2.32 mmol) and zinc dust (152 mg, 2.3 mmol) in N,N-dimethylacetamide (37 mL) was bubbled with nitrogen for 5 min. tris(dibenzylideneacetone)dipalladium(0) (177 mg , 0.193 mmol) was then added. The mixture was stirred under nitrogen for 10 min, then zinc cyanide (1.82 g, 15.5 mmol) was added. The mixture was heated under nitrogen at 110 ºC for 16 h. The mixture was cooled to room temperature, poured into aqueous $NaHCO_3$ (45 mL) and extracted with ethyl acetate (2x60 ml). The combined organic extracts were washed with water (15 mL), brine (15 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, ethylacetate-heptane gradient) to afford the product as a white solid (464 mg, 79%). MS: mass calcd. for $C_{17}H_{19}FN_2O_2$, 302.1; m/z found, 303.0 $[M+H]^+$.

Step C. 2-(Cyclobutylamino)-6-fluoro-2,3-dihydro-1H-indene-2,5-dicarboxylic acid, **23c**:

To a flask charged with ethyl 5-cyano-2-(cyclobutylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (464 mg, 1.53 mmol)) was added hydrochloric acid (37%, 3.9 mL). The reaction mixture was heated at 135 ºC overnight. The mixture was concentrated to afford the crude product (450 mg), which was directly used in the next step without further purification.

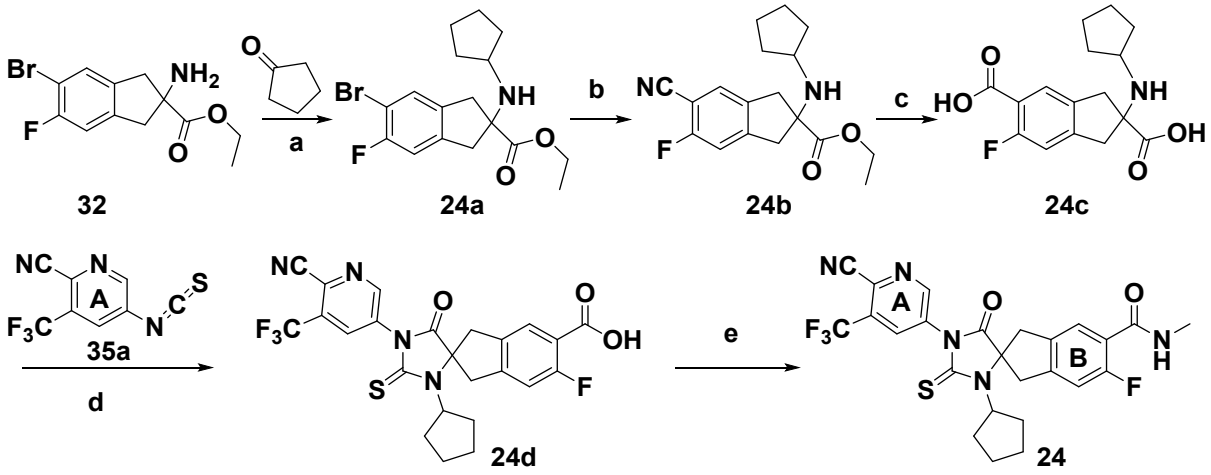
Step D. 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclobutyl-6'-fluoro-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxylic acid, **23d**:

To a suspension of 2-(cyclobutylamino)-6-fluoro-2,3-dihydro-1H-indene-2,5-dicarboxylic acid (0.225 g, 0.77 mmol) in tetrahydrofuran (8 mL) and N,N-Dimethylformamide (8 mL) was added triethylamine (0.64 mL, 4.6 mmol). The mixture was stirred for 5 min, then 5-isothiocyanato-3-(trifluoromethyl)picolinonitrile (0.23 g, 1 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature, poured into a mixture of water and acetic acid, and then extracted with ethyl acetate. The combined organic extract was washed with water, brine, dried over $MgSO_4$, and concentrated to afford the crude product, which was used directly in the next step without further purification (387 mg, 100%). MS: mass calcd. for $C_{23}H_{16}F_4N_4O_3S$, 504.1; m/z found, 505.0 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 9.05 (d, J = 1.65 Hz, 1H), 8.31 (d, J = 2.20 Hz, 1H), 7.97 (d, J = 6.60 Hz, 1H), 7.15 (d, J = 9.90 Hz, 1H), 4.29-4.52 (m, 1H), 3.66-3.89 (m, 2H), 3.37-3.60 (m, 3H), 2.69-2.95 (m, 2H), 2.29 (q, J = 8.25 Hz, 2H), 1.59-1.96 (m, 2H) ppm.

Step E. 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclobutyl-6'-fluoro-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, **23**:

To a suspension of 1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclobutyl-6'-fluoro-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxylic acid (0.267 g, 0.53 mmol), ammonium chloride (0.107 g, 1.59 mmol) and diisopropylethylamine (0.46 mL, 2.65 mmol) in N,N-dimethylformamide (12 mL) was added HBTU (0.6 g, 1.59 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with ethyl acetate (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (30 mL), brine (3x15 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, dichloromethane-methanol gradient), and the product was further purified by RP-HPLC to afford the title compound as a white solid (110 mg, 40%). MS: mass calcd. for $C_{24}H_{19}F_4N_5O_2S$, 517.1; m/z found, 517.8 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{24}H_{19}F_4N_5O_2S$ $[M+H]^+$ 518.1274; m/z found, 518.1276; ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J* = 2.20 Hz, 1H), 8.30 (d, *J* = 2.20 Hz, 1H), 8.04 (d, *J* = 7.09 Hz, 1H), 7.08 (d, *J* = 11.49 Hz, 1H), 6.67-6.84 (m, 1H), 4.29-4.53 (m, 1H), 3.66-3.88 (m, 2H), 3.41-3.60 (m, 2H), 3.06 (d, *J* = 4.3 Hz, 3H), 2.74-2.91 (m, 2H), 2.14-2.32 (m, 2H), 1.76-1.88 (m, 1H), 1.64-1.75 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 175.1, 163.5, 152.4, 144.1, 135.1, 134.3, 132.0, 130.0, 127.7, 121.2, 121.1, 113.7, 112.3, 112.1, 72.9, 51.8, 43.4, 42.7, 28.4, 28.2, 27.0, 15.4 ppm.

Preparation of 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclopentyl-6'-fluoro-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 24



[a]Reagents and Conditions: (a) $NaBH(OAc)_3$, DCE, rt; (b) $Zn(CN)_2$, Pd_2dba_3, PPh_3, DMA, 120 ^oC; (c) aqueous conc. HCl, 135 ^oC; (d) TEA, THF/DMF, 80 ^oC; (e) NH_4Cl, HBTU, DIPEA, DMAP (cat.), DMF, rt.

Step A. Ethyl 5-bromo-2-(cyclopentylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate, **24a**:

To a solution of ethyl 2-amino-5-bromo-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (**32**, 1.4 g, 4.6 mmol) in 1,2-dichloroethane (34 mL) was added cyclopentanone (1.64 mL, 18.5 mmol), followed by the addition of sodium triacetoxyborohydride (5.89 g, 27.8 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was poured onto saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2, 0-10% methanol in dichloromethane gradient). The pure fractions were combined, concentrated, and dried *in vacuo* to give the desired product (696 mg, 41%). MS: mass calcd. for $C_{17}H_{21}BrFNO_2$, 369.1; m/z found, 369.9 $[M+H]^+$.

Step B. Ethyl 5-cyano-2-(cyclopentylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate, **24b**:

A suspension of ethyl 5-bromo-2-(cyclopentylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (696 mg, 1.88 mmol), triphenylphosphine (592 mg, 2.26 mmol) and zinc dust (148 mg, 2.26 mmol) in N,N-dimethylacetamide (10 mL) was bubbled with nitrogen for 5 min. tris(dibenzylideneacetone)dipalladium(0) (172 mg , 0.188 mmol) was then added. The mixture was stirred under nitrogen for 10 min, then zinc cyanide (1.77 g, 15.0 mmol) was added. The mixture was heated under nitrogen at 110 ºC for 16 h. The mixture was cooled to room temperature, poured into aqueous $NaHCO_3$ (45 mL) and extracted with ethyl acetate (2x60 ml). The combined organic extracts were washed with water (15 mL), brine (15 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, ethylacetate-heptane gradient) to afford the product as a white solid (510 mg, 86%). MS: mass calcd. for $C_{18}H_{21}FN_2O_2$, 316.2; m/z found, 317.0 $[M+H]^+$.

Step C. 2-(Cyclopentylamino)-6-fluoro-2,3-dihydro-1H-indene-2,5-dicarboxylic acid, **24c**:

To a flask charged with ethyl 5-cyano-2-(cyclopentylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (510 mg, 1.61 mmol)) was added hydrochloric acid (37%, 5 mL). The reaction mixture was heated at 135 ºC overnight. The mixture was concentrated to afford the crude product (495 mg), which was directly used in the next step without further purification.

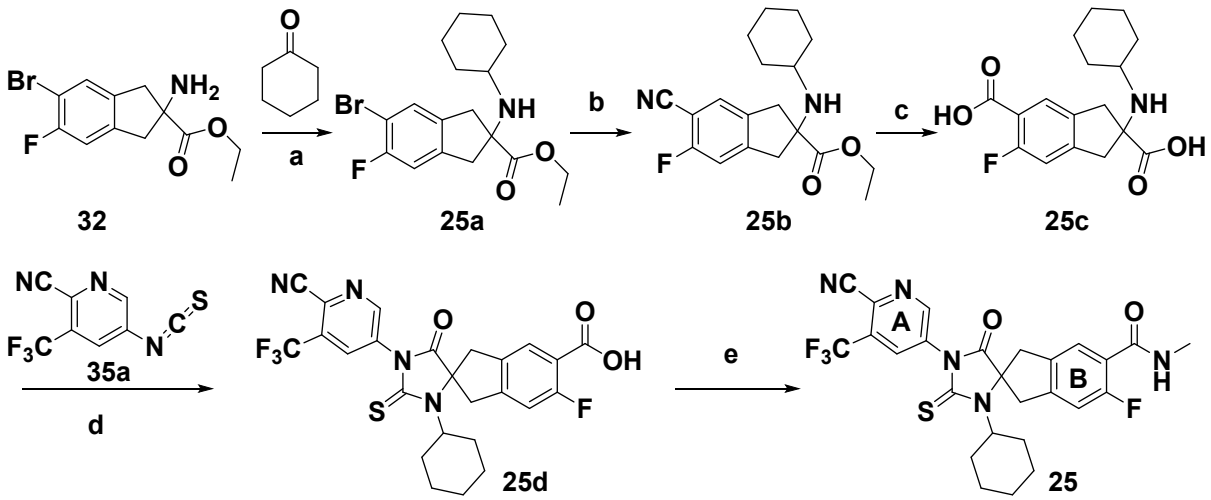
Step D. 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclopentyl-6'-fluoro-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxylic acid, **24d**:

To a suspension of 2-(cyclopentylamino)-6-fluoro-2,3-dihydro-1H-indene-2,5-dicarboxylic acid (0.248 g, 0.81 mmol) in tetrahydrofuran (11 mL) and N,N-Dimethylformamide (11 mL) was added triethylamine (0.68 mL, 4.8 mmol). The mixture was stirred for 5 min, then 5-isothiocyanato-3-(trifluoromethyl)picolinonitrile (0.24 g, 1 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature, poured into a mixture of water and acetic acid, and then extracted with ethyl acetate. The combined organic extract was washed with water, brine, dried over $MgSO_4$, and concentrated to afford the crude product, which was used directly in the next step without further purification (375 mg, 90%). MS: mass calcd. for $C_{24}H_{18}F_4N_4O_3S$, 518.1; m/z found, 518.8 $[M+H]^+$.

Step E. 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclopentyl-6'-fluoro-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, **24**:

To a suspension of 1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclopentyl-6'-fluoro-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxylic acid (0.375 g, 0.72 mmol), ammonium chloride (0.15 g, 2.2 mmol) and diisopropylethylamine (0.76 mL, 4.3 mmol) in N,N-dimethylformamide (11 mL) was added HBTU (0.69 g, 1.8 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with ethyl acetate (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (30 mL), brine (3x15 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, dichloromethane-methanol gradient), and the product was further purified by RP-HPLC to afford the title compound as a white solid (55 mg, 14%). MS: mass calcd. for $C_{25}H_{21}F_4N_5O_2S$, 531.1; m/z found, 532.0 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{25}H_{21}F_4N_5O_2S$ $[M+H]^+$ 532.1430; m/z found, 532.1440; ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J* = 2.20 Hz, 1H), 8.30 (d, *J* = 2.20 Hz, 1H), 8.04 (d, *J* = 7.09 Hz, 1H), 7.08 (d, *J* = 11.49 Hz, 1H), 6.71-6.85 (m, 1H), 3.59-3.93 (m, 3H), 3.44 (d, *J* = 17.85 Hz, 2H), 3.05 (d, *J* = 4.65 Hz, 3H), 2.64 (td, *J* = 8.93, 17.36 Hz, 2H), 1.89-2.01 (m, 2H), 1.71-1.86 (m, 2H), 1.41-1.54 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 174.6, 163.5, 162.0, 159.5, 152.6, 144.0, 135.1, 134.4, 131.9, 130.6, 127.6, 121.2, 113.8, 112.3, 112.0, 73.8, 58.4, 43.1, 42.3, 28.5, 28.4, 27.0, 25.1 ppm.

Preparation of 1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclohexyl-6'-fluoro-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, 25



[a]Reagents and Conditions: (a) $NaBH(OAc)_3$, DCE, rt; (b) $Zn(CN)_2$, Pd_2dba_3, PPh_3, DMA, 120 ^oC; (c) aqueous conc. HCl, 135 ^oC; (d) TEA, THF/DMF, 80 ^oC; (e) NH_4Cl, HBTU, DIPEA, DMAP (cat.), DMF, rt.

Step A. Ethyl 5-bromo-2-(cyclohexylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate, **25a**:

To a solution of ethyl 2-amino-5-bromo-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (**32**, 1.4 g, 4.6 mmol) in 1,2-dichloroethane (35 mL) was added cyclohexanone (0.96 mL, 9.27 mmol), followed by the addition of sodium triacetoxyborohydride (3.9 g, 18.5 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was poured onto saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2, 0-10% methanol in dichloromethane gradient). The pure fractions were combined, concentrated, and dried *in vacuo* to give the desired product (996 mg, 56%). MS: mass calcd. for $C_{18}H_{23}BrFNO_2$, 383.1; m/z found, 383.9 $[M+H]^+$.

Step B. Ethyl 5-cyano-2-(cyclohexylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate, **25b**:

A suspension of ethyl 5-bromo-2-(cyclohexylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (996 mg, 2.59 mmol), triphenylphosphine (816 mg, 3.11 mmol) and zinc dust (203 mg, 3.11 mmol) in N,N-dimethylacetamide (15 mL) was bubbled with nitrogen for 5 min. tris(dibenzylideneacetone)dipalladium(0) (237 mg , 0.26 mmol) was then added. The mixture was stirred under nitrogen for 10 min, then zinc cyanide (2.44 g, 20.7 mmol) was added. The mixture was heated under nitrogen at 110 ºC for 16 h. The mixture was cooled to room temperature, poured into aqueous $NaHCO_3$ (45 mL) and extracted with ethyl acetate (2x60 ml). The combined organic extracts were washed with water (15 mL), brine (15 mL),

dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, DCM-MeOH gradient) to afford the product as a white solid (683 mg, 80%). MS: mass calcd. for $C_{19}H_{23}FN_2O_2$, 330.2; m/z found, 331.0 $[M+H]^+$.

Step C. 2-(Cyclohexylamino)-6-fluoro-2,3-dihydro-1H-indene-2,5-dicarboxylic acid, **25c**:

To a flask charged with ethyl ethyl 5-cyano-2-(cyclohexylamino)-6-fluoro-2,3-dihydro-1H-indene-2-carboxylate (683 mg, 2.07 mmol)) was added hydrochloric acid (37%, 5 mL). The reaction mixture was heated at 135 ºC overnight. The mixture was concentrated to afford the crude product (664 mg), which was directly used in the next step without further purification. MS: mass calcd. for $C_{17}H_{20}FNO_4$, 321.1; m/z found, 321.9 $[M+H]^+$.

Step D. 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclohexyl-6'-fluoro-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxylic acid, **25d**:

To a suspension of 2-(cyclohexylamino)-6-fluoro-2,3-dihydro-1H-indene-2,5-dicarboxylic acid (0.337 g, 1.05 mmol) in tetrahydrofuran (121 mL) and N,N-Dimethylformamide (12 mL) was added triethylamine (0.88 mL, 6.3 mmol). The mixture was stirred for 5 min, then 5-isothiocyanato-3-(trifluoromethyl)picolinonitrile (0.31 g, 1.4 mmol) was added. The reaction mixture was stirred at 80 ºC for 4 h. The mixture was cooled to room temperature, poured into a mixture of water and acetic acid, and then extracted with ethyl acetate. The combined organic extract was washed with water, brine, dried over $MgSO_4$, and concentrated to afford the crude product, which was used directly in the next step without further purification (559 mg, 100%). MS: mass calcd. for $C_{25}H_{20}F_4N_4O_3S$, 532.1; m/z found, 532.9 $[M+H]^+$.

Step E. 1-(6-Cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclohexyl-6'-fluoro-N-methyl-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxamide, **25**:

To a suspension of 1-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-3-cyclohexyl-6'-fluoro-5-oxo-2-thioxo-1',3'-dihydrospiro[imidazolidine-4,2'-indene]-5'-carboxylic acid (0.559 g, 1.05 mmol), ammonium chloride (0.21 g, 3.2 mmol) and diisopropylethylamine (1.1 mL, 6.3 mmol) in N,N-dimethylformamide (15 mL) was added HBTU (1 g, 2.6 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with ethyl acetate (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (30 mL), brine (3x15 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, dichloromethane-methanol gradient), and the product was further purified by RP-HPLC to afford the title compound as a white solid (8 mg, 3%). MS: mass calcd. for $C_{26}H_{23}F_4N_5O_2S$, 545.1; m/z found, 546.0 $[M+H]^+$; HRMS (ESI-TOF): mass calcd. for $C_{26}H_{23}F_4N_5O_2S$ $[M+H]^+$ 546.1587; m/z found, 546.1590; ^1H NMR (400 MHz, $CDCl_3$) δ 9.02

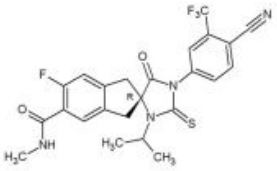
(d, J = 2.20 Hz, 1H), 8.28 (d, J = 2.20 Hz, 1H), 8.06 (d, J = 7.09 Hz, 1H), 7.08 (d, J = 11.49 Hz, 1H), 6.77 (br dd, J = 4.65, 12.72 Hz, 1H), 3.65-3.77 (m, 2H), 3.43-3.53 (m, 3H), 3.06 (d, J = 4.6 Hz, 3H), 2.63-2.75 (m, 2H), 1.70-1.90 (m, 6H), 1.18-1.32 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 174.6, 152.7, 144.2, 142.2, 140.5, 137.7, 136.0, 135.1, 134.5, 132.0, 130.0, 127.6, 121.1, 120.9, 113.7, 112.2, 111.9, 74.2, 59.1, 41.0, 29.7, 29.5, 27.0, 26.2, 24.7 ppm.

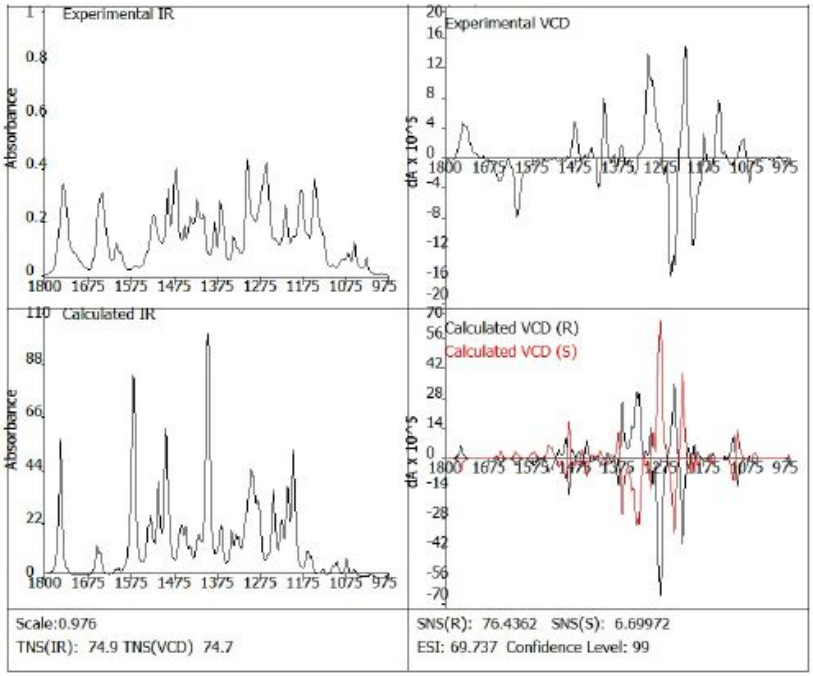
S-8. The absolute configuration of compound (*R*)-29 (and (*S*)-27) by VCD experiment

The VCD experiments were conducted in BioTools, Inc. 17546 Bee Line Hwy, Jupiter, Florida 33458, USA.

GENERAL INFORMATION	
Customer	Janssen
Sample code (Our ref.)	**(*R*)-29**
VCD-spectrometer	ChiralIR w/ Dual*PEM*
RESULTS	
Absolute Configuration of **27** is (S) Absolute Configuration of **29** is (R)	Confidence Level: **99%**
MEASUREMENT PARAMETERS	
Concentration	3.7 mg/0.1 mL
Solvent	$CDCl_3$
Resolution	4 cm^{-1}
PEM setting	1400 cm^{-1}
Number of scans/Measurement time	12 hours
Sample cell	BaF_2
Path length	100 µm
CALCULATION DETAILS	
Gaussian version	Gaussian 09
Total low-energy conformers used for Boltzmann sum	14
Methodology and basis set for DFT calculations	B3LYP/6-31G(d)
Enantiomer used for calculation	(R)
Total calculated conformers	49
Number of low-energy conformations shown in report	1
COMMENTS	
The confidence level is a measure of the degree of congruence between a calculated and measured spectrum. If identical spectra are being compared the confidence level is 100%. The confidence level (CL) is not the likelihood that the assignment is correct. Rather it's a measure of quality or degree of agreement between calculated and measured spectra.	

Structure of Compound (*R*)-**29**:



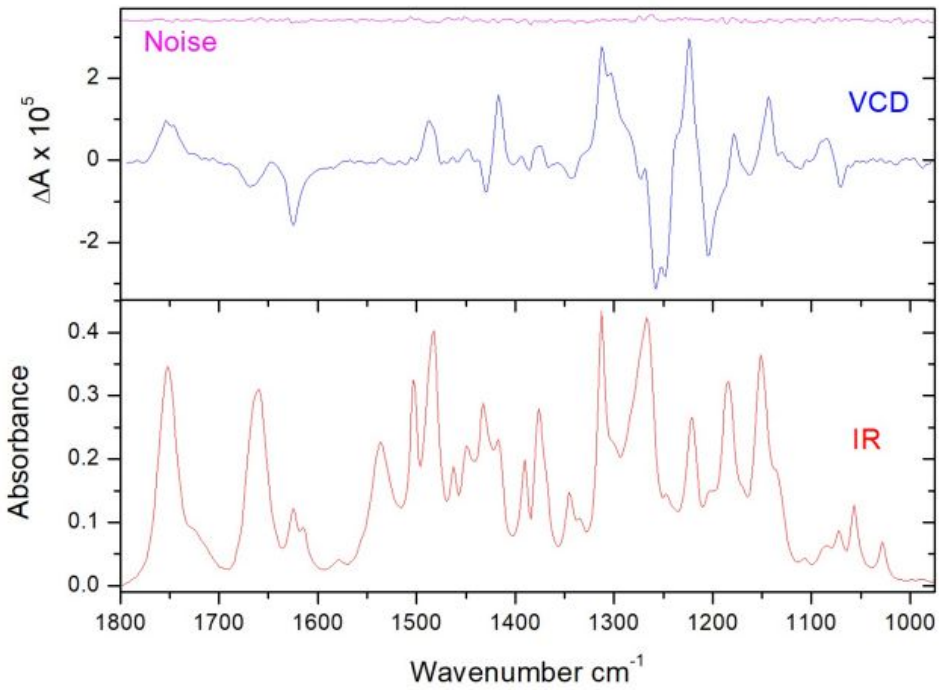


CompareVOA Results.
Please note: In this plot the frequency scaling factor is not applied.

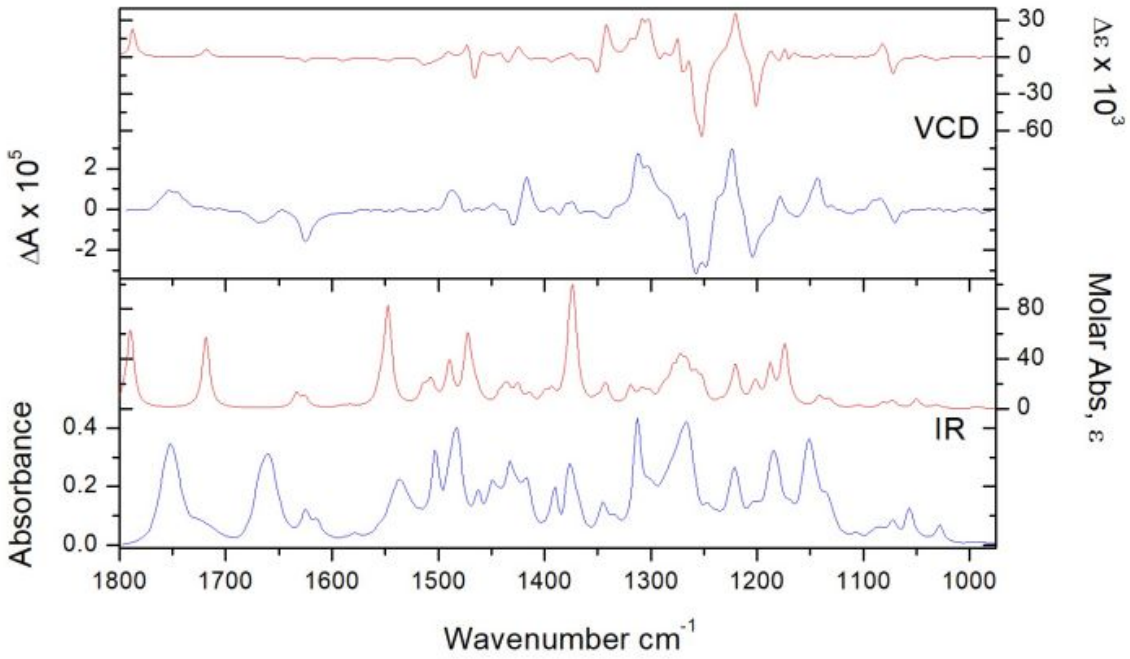
Table 1. Numerical comparison describing the similarity in the range of 975 - 1800 cm^{-1} between the calculated IR and VCD spectra for the **(*R*)** enantiomer at the B3LYP/6-31G(d) level and the observed IR and VCD spectra for **(*R*)-29**.

Cal. ($975\text{-}1800\ cm^{-1}$)	Numerical comparison	Observed **(*R*)-29**
(R)	scaling factor	0.976
	IR similarity (%)	74.9
	[a]∑ (%)	76.4362
	[b]Δ (%)	69.737
	Confidence Level (%)	99

[a]∑: single VCD similarity, gives the similarity between the calculated and observed VCD spectra.
[b]Δ: enatiomeric similarity index, gives the difference between the values of ∑ for both enantiomers of a given diastereoisomer.



IR (lower frame) and VCD (upper frame) spectra of (***R***)-**29** in $CDCl_3$ (3.7mg / 0.1mL); 0.1mm path-length cell with BaF_2 windows; 12 h collection for enantiomer and solvent; instrument optimized at 1400 cm^{-1}. Solvent subtracted IR and enantiomer subtracted VCD spectra are shown. Uppermost trace is the VCD noise spectra.



IR (lower frame) and VCD (upper frame) spectra observed for (***R***)-**29** (left axes) compared with Boltzmann-averaged spectra of the calculated conformations for the (***R***) configuration, (right axes).

S-9. The absolute configuration of compound (*S*)-26 (and (*R*)-28) by VCD experiment

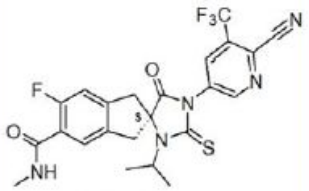
The VCD experiments were conducted in BioTools, Inc. 17546 Bee Line Hwy, Jupiter, Florida 33458, USA.

GENERAL INFORMATION	
Customer	Janssen
Sample description (Your ref.)	**(*S*)-26 / (*R*)-28**
VCD-spectrometer	ChiralIR w/ Dual*PEM*
RESULTS	
Absolute Configuration of Compound 28 is (R) Absolute Configuration of Compound 26 is (S)	Confidence Level: **90%**
MEASUREMENT PARAMETERS	
Concentration	6mg / 110uL
Solvent	$CDCl_3$
Resolution	4 cm^{-1}
PEM setting	1400 cm^{-1}
Number of scans/Measurement time	20 hours per enantiomer
Sample cell	BaF_2
Path length	100 µm
CALCULATION DETAILS	
Gaussian version	Gaussian 09
Total low-energy conformers used for Boltzmann sum	18
Methodology and basis set for DFT calculations	B3LYP-D3 / 6311G** PCM
Enantiomer used for calculation	S
Total calculated conformers	30
Number of low-energy conformations shown in report	0

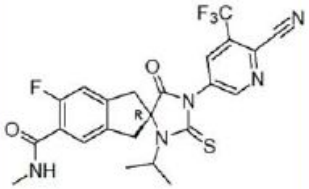
COMMENTS

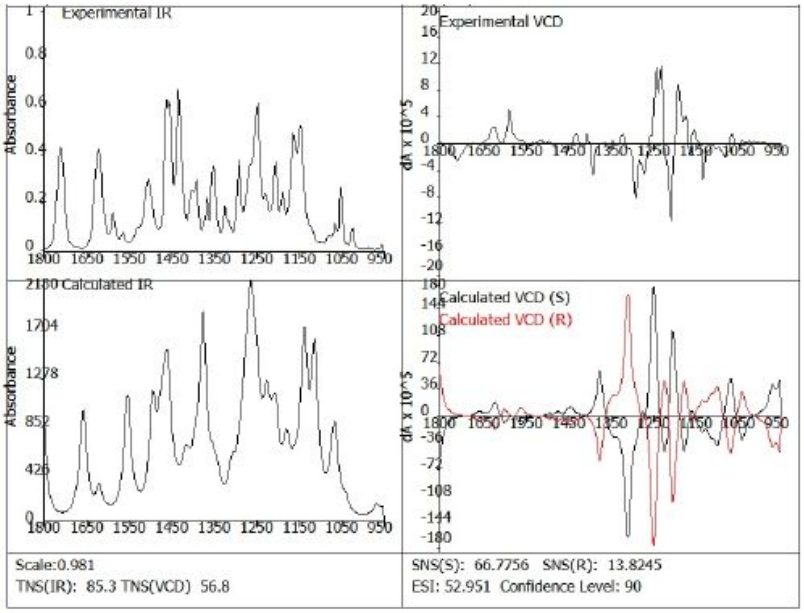
The confidence level is a measure of the degree of congruence between a calculated and measured spectrum. If identical spectra are being compared the confidence level is 100%. The confidence level (CL) is not the likelihood that the assignment is correct. Rather it's a measure of quality or degree of agreement between calculated and measured spectra. With a CL of 90% for this molecule, the visual agreement between measured and calculated spectra is very good – this is a high confidence assignment. The calculation was done by the customer in this case. We also compare the experimental VCD spectra to a very similar derivative ((*S*)-27).

Structure of (*S*)-26:



Structure of (*R*)-28:



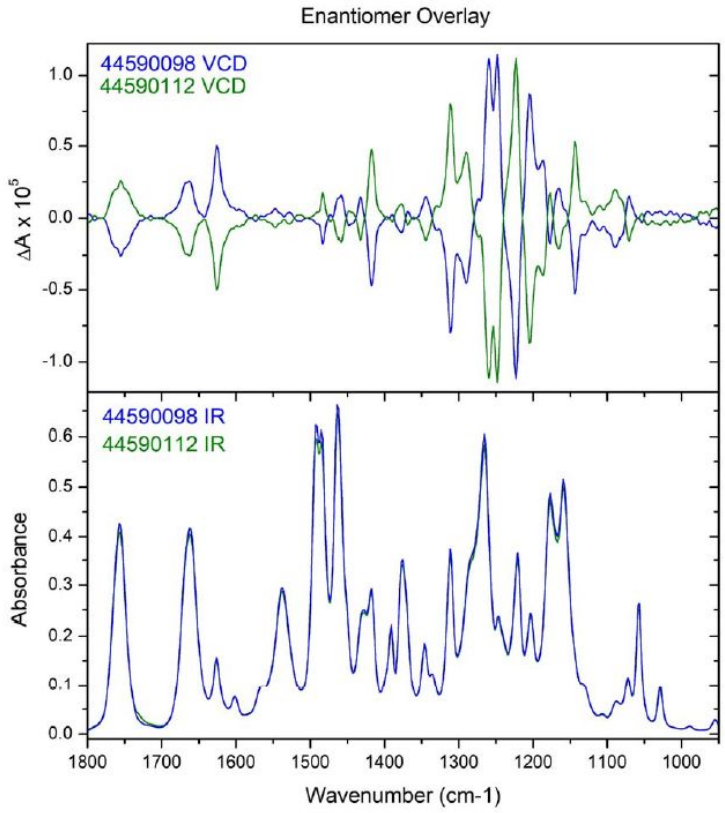


CompareVOA Results.
Please note: In this plot the frequency scaling factor is not applied.

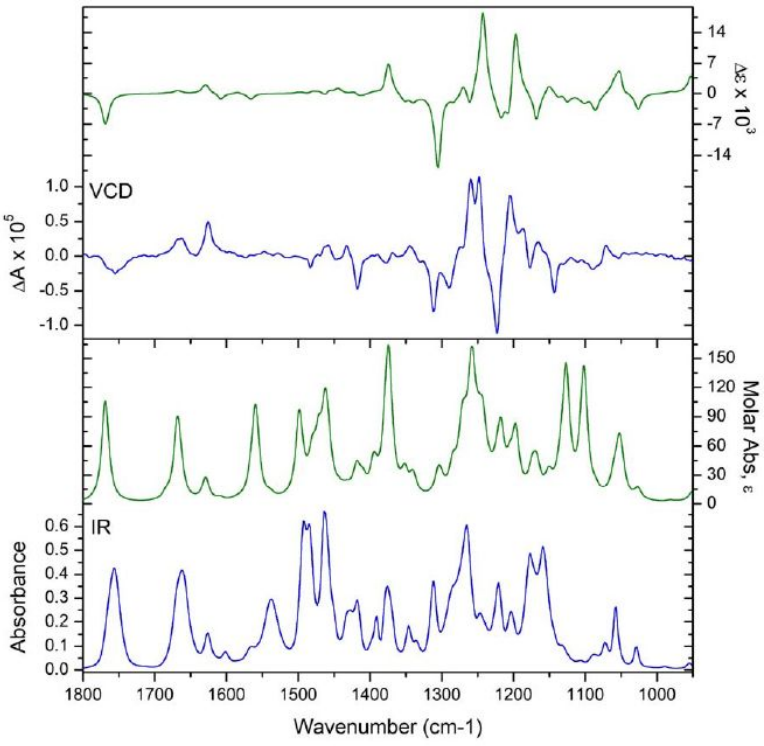
Table 1. Numerical comparison describing the similarity in the range of 950 - 1800 cm^{-1} between the calculated IR and VCD spectra for the **(*S*)** enantiomer at the B3LYP-D3 / 6311G** PCM level and the observed IR and VCD spectra for **(*S*)-26**.

Cal. (950-1800cm^{-1})	Numerical comparison	Observed **(*S*)-26**
(S)	scaling factor	0.981
	IR similarity (%)	85.3
	[a]∑ (%)	66.7756
	[b]Δ (%)	52.951
	Confidence Level (%)	90

[a]∑: single VCD similarity, gives the similarity between the calculated and observed VCD spectra.
[b]Δ: enatiomeric similarity index, gives the difference between the values of ∑ for both enantiomers of a given diastereoisomer.



Overlay of both enantiomers, **(*S*)-26 (JNJB-44590098)** and **(*R*)-28 (JNJB-44590112)**. The IR spectra are nearly identical. The VCD are mirror images due to the half difference processing (E1 – 2.E2) /



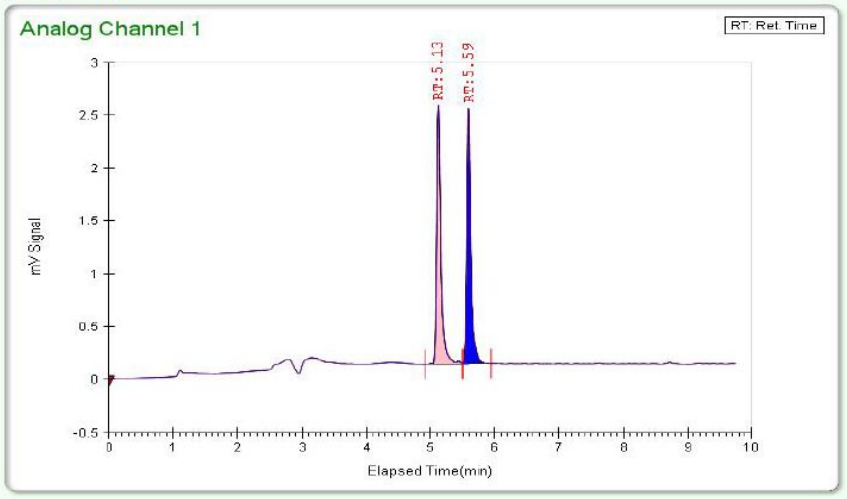
IR (lower frame) and VCD (upper frame) spectra observed for **(*S*)-26** (left axes) compared with Boltzmann-averaged spectra of the calculated conformations for the **(*S*)** configuration, (right axes).

S-10. SFC traces, LCMS, ^{1}H NMR of compounds (*S*)-27 and (*R*)-29

SFC trace of racemic compound 19 before chiral separation:

Method Name	Method-5-40_2.4ml_10min.met
Report Date	7/13/2015

Injection Volume	1
Co-Solvent %	5
Column	AD-3
Co-Solvent	IPA(0.05%DEA)
Total Flow	2.4
Wavelength	220
Injection Info	



Peak Name	**St. (min)**	**End (min)**	**RT (min)**	**Area %**
Peak1	4.9148	5.4878	5.13	49.0097
Peak2	5.4966	5.9411	5.59	50.9903

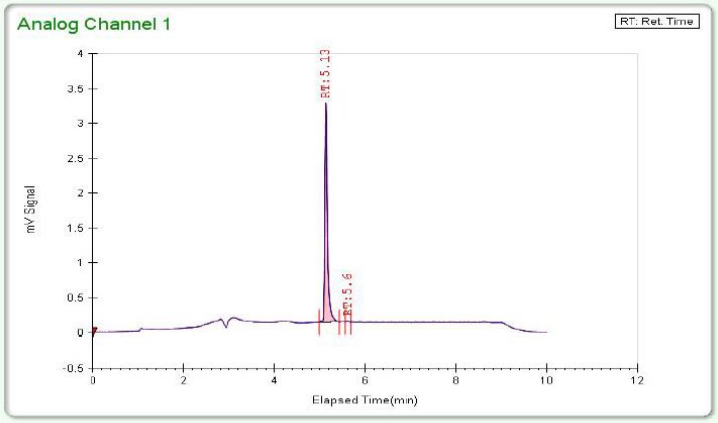
Theoretical Plates	**Resolution Peak1**	**Resolution Peak2**	**Height**
40267.4655	0	4.709	2.4537
57846.0541	-4.709	0	2.4198

Peak Info

SFC trace of (S)-27:

Method Name	Method-5-40_2.4ml_10min.met
Report Date	7/20/2015

Injection Volume	1
Co-Solvent %	5
Column	AD-3
Co-Solvent	IPA(0.05%DEA)
Total Flow	2.4
Wavelength	220
Injection Info	



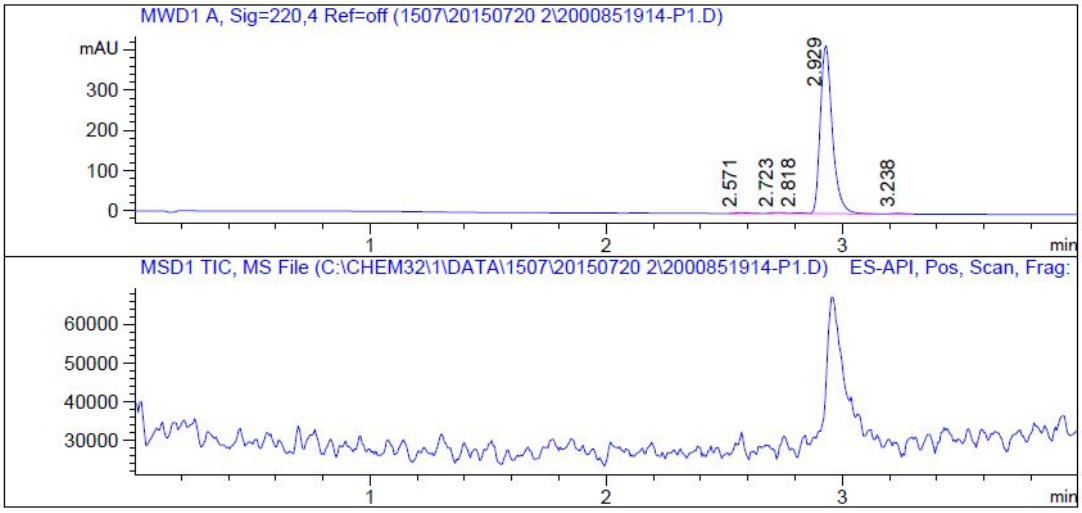
Peak Name	**St. (min)**	**End (min)**	**RT (min)**	**Area %**
Peak1	4.9914	5.418	5.13	99.7883
Peak2	5.5492	5.6641	5.6	0.2117

Theoretical Plates	**Resolution Peak1**	**Resolution Peak2**	**Height**
60233.1167	0	6.2489	3.1462
118474.7723	-6.2489	0	0.0097

Peak Info

LC-MS of (S)-27:

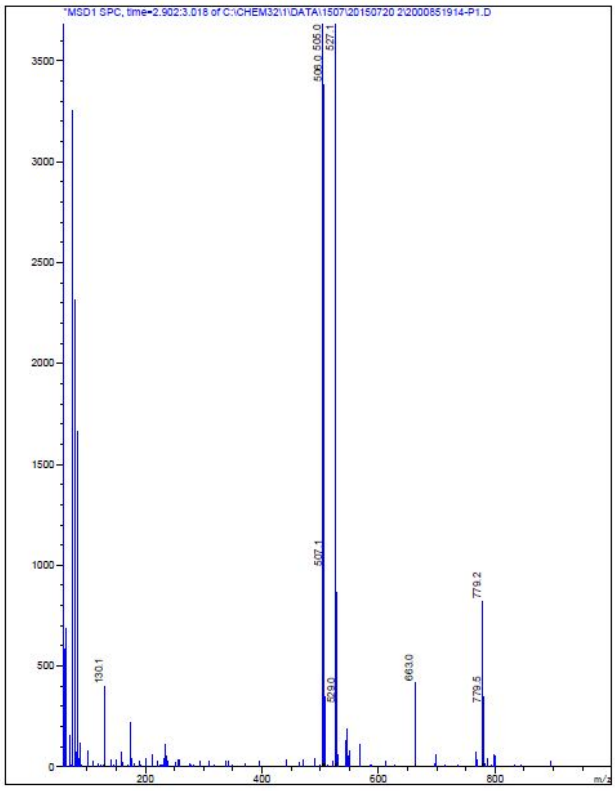
```
Acq   Method      : C:\Chem32\1\DATA\1507\20150720 2\10-80CD_4MIN.M
Data Filename     : C:\CHEM32\1\DATA\1507\20150720 2\2000851914-P1.D
Instrument        :  LCMS 12-102
```



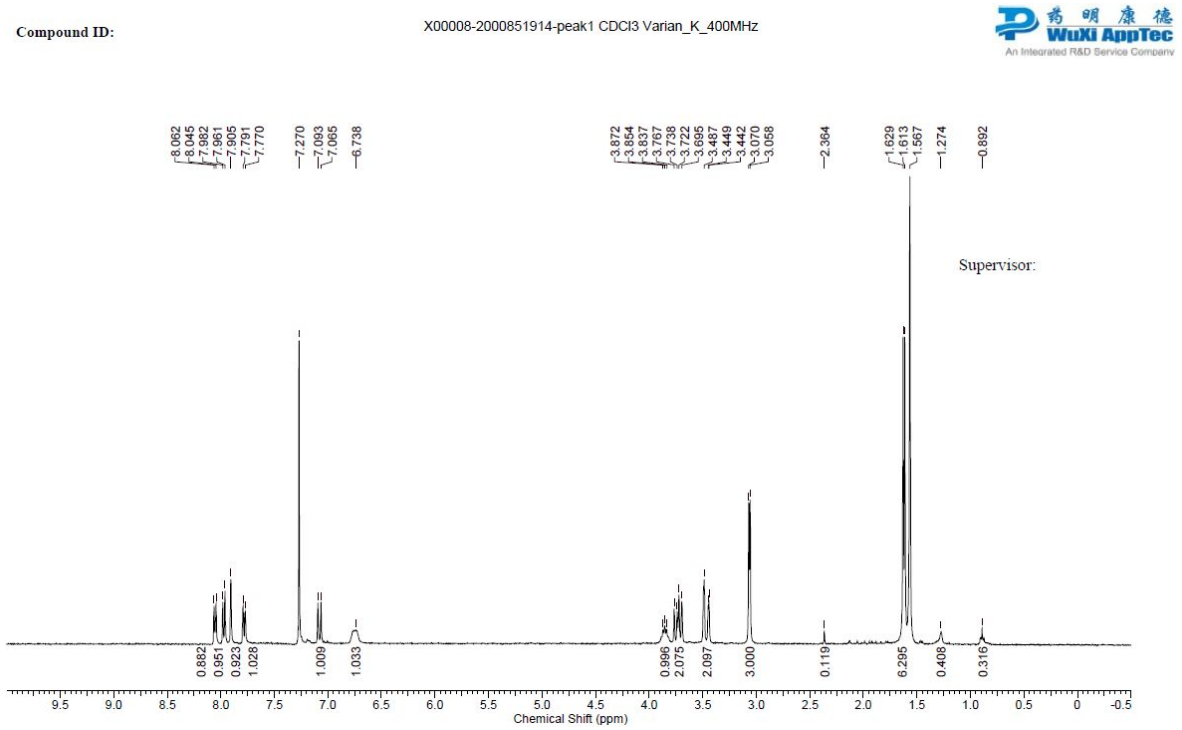
Report

Signal 1 : MWD1 A, Sig=220,4 Ref=off

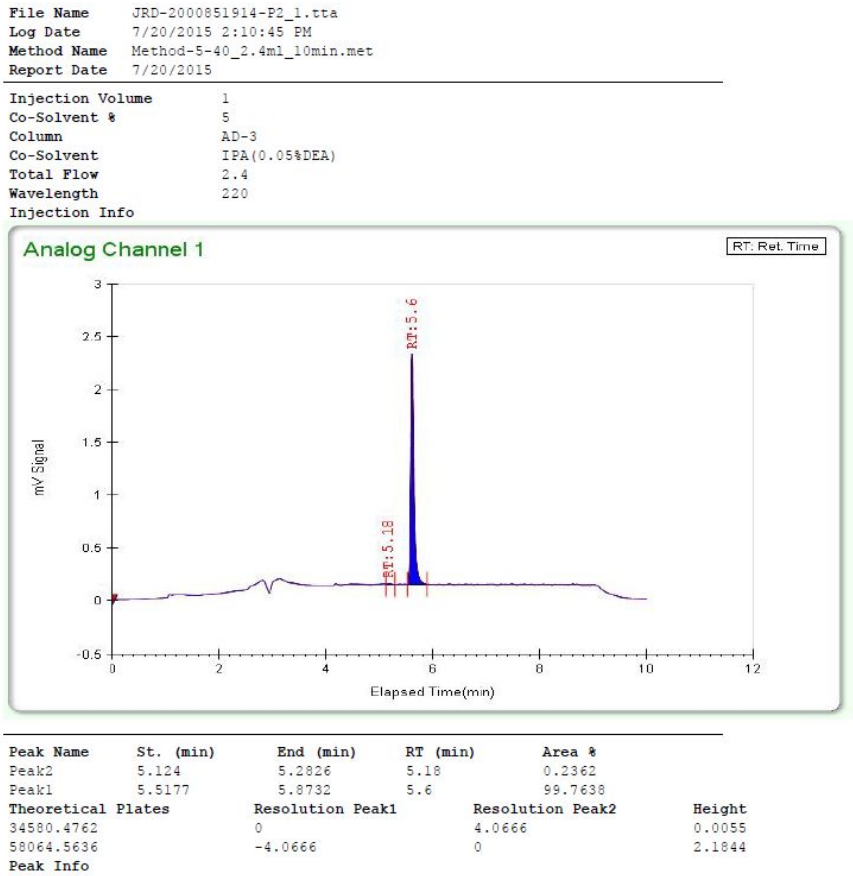
#	Meas. Ret.	Height	Width	Area	Area %
1	2.571	1.824	0.069	7.546	0.500
2	2.723	2.641	0.047	7.437	0.493
3	2.818	1.620	0.043	4.216	0.279
4	2.929	421.540	0.059	1484.181	98.379
5	3.238	1.747	0.050	5.263	0.349



^{1}H NMR of (S)-27:

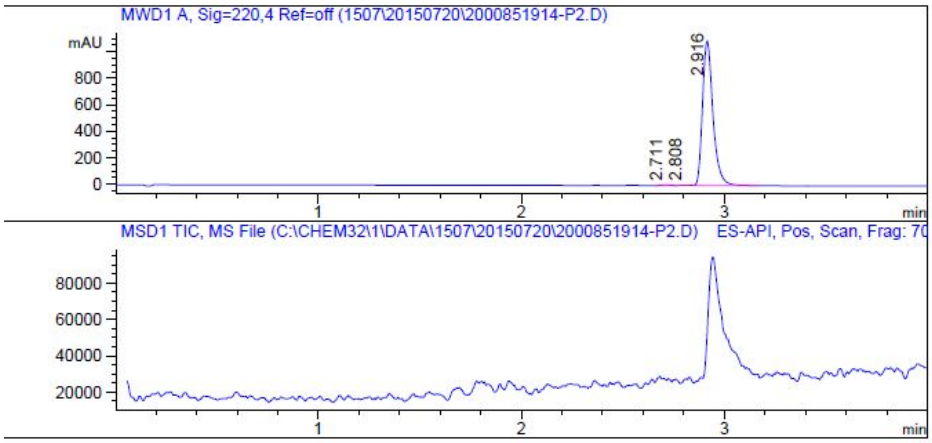


SFC trace of (R)-29:



LC-MS of (R)-29:

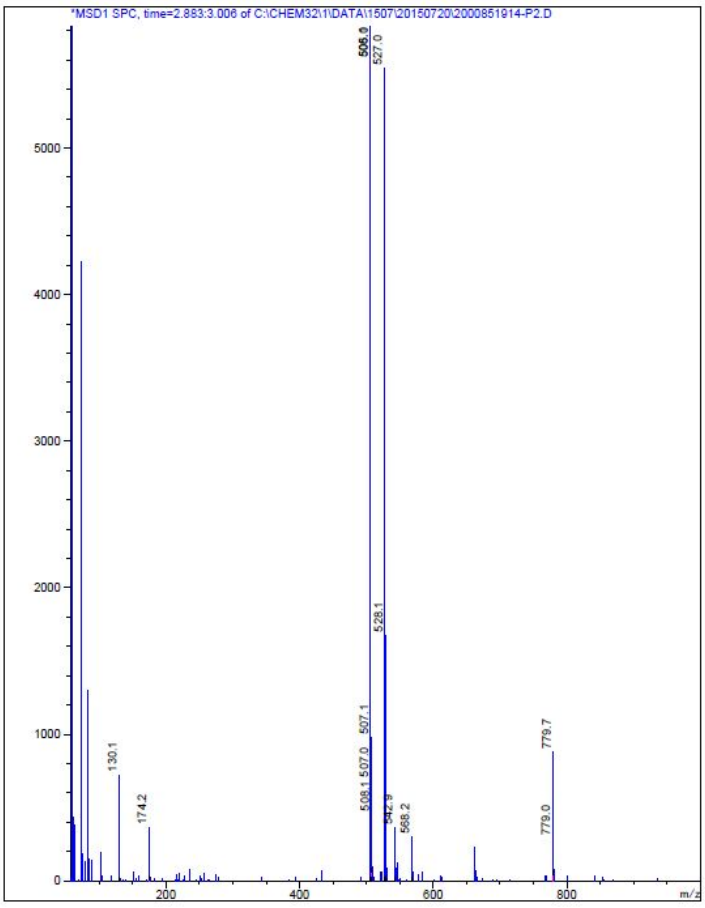
```
Compound ID      :
Sample ID        : 2000851914-P2
Injection Date   : Mon, 20. Jul. 2015
Location         : P1-F-04
Acq   Method     : C:\Chem32\1\DATA\1507\20150720\10-80CD_4MIN.M
Data Filename    : C:\CHEM32\1\DATA\1507\20150720\2000851914-P2.D
Instrument       :  LCMS 12-102
```



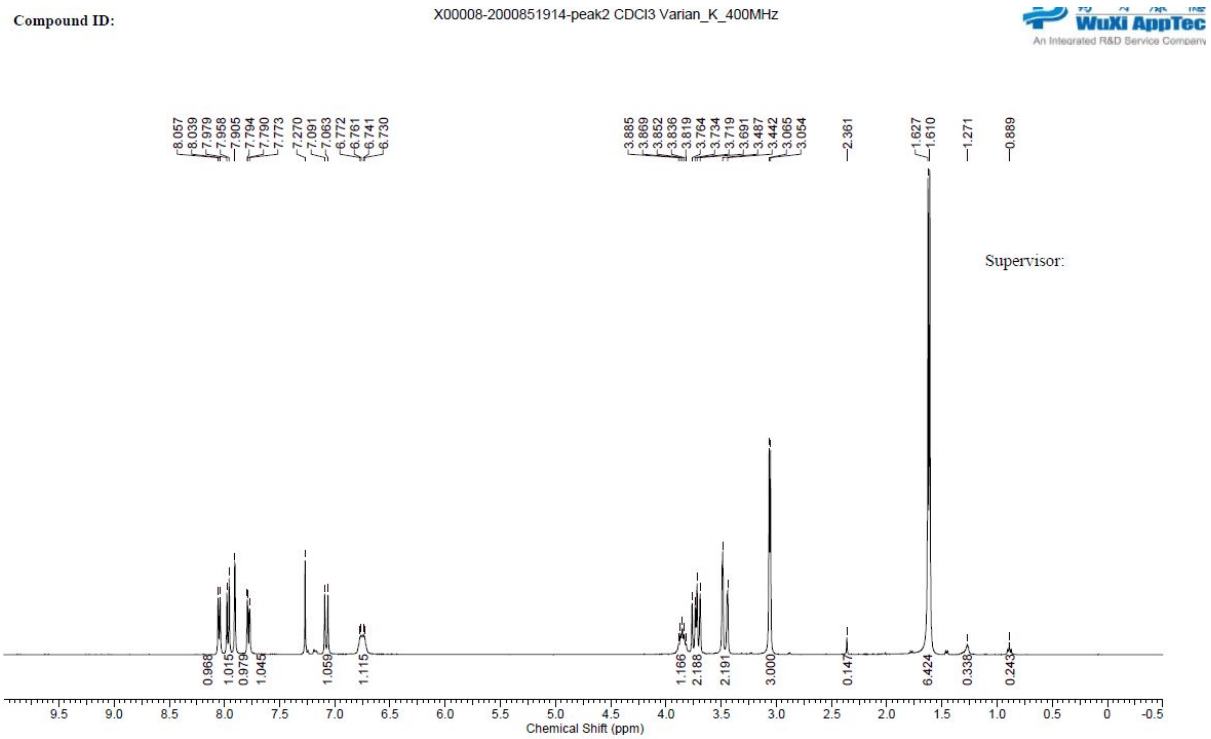
Report

Signal 1 : MWD1 A, Sig=220,4 Ref=off

#	Meas. Ret.	Height	Width	Area	Area %
1	2.711	4.495	0.050	13.452	0.343
2	2.808	0.758	0.037	1.687	0.043
3	2.916	1101.376	0.059	3903.397	99.614



^{1}H NMR of (R)-29:

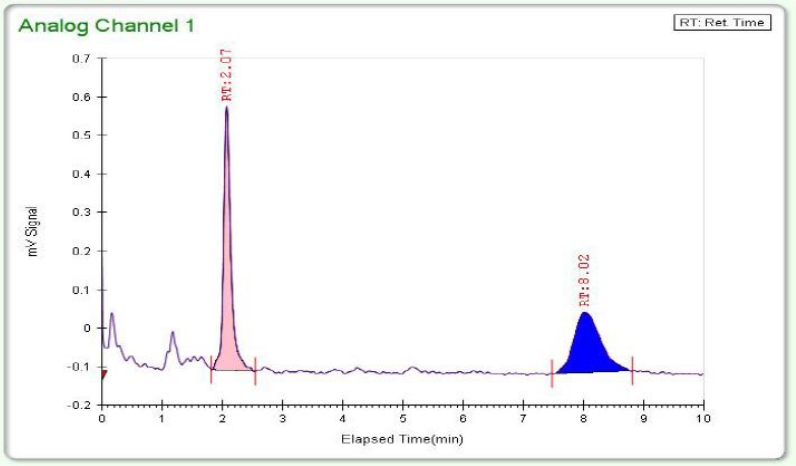


S-11. SFC traces, LCMS, ^{1}H NMR of compounds (*R*)-28 and (*S*)-26

SFC trace of racemic compound 18 before chiral separation:

File Name	2000851831_1.tta
Log Date	6/9/2015 5:11:38 PM
Method Name	Method-40_2.4ml.met
Report Date	6/9/2015

Injection Volume	1
Co-Solvent %	40
Column	AD-3
Co-Solvent	ETOH(0.05%DEA)
Total Flow	2.4
Wavelength	220
Injection Info	



Peak Name	St. (min)	End (min)	RT (min)	Area %
Peak2	1.8133	2.5424	2.07	54.702
Peak1	7.4763	8.806	8.02	45.298

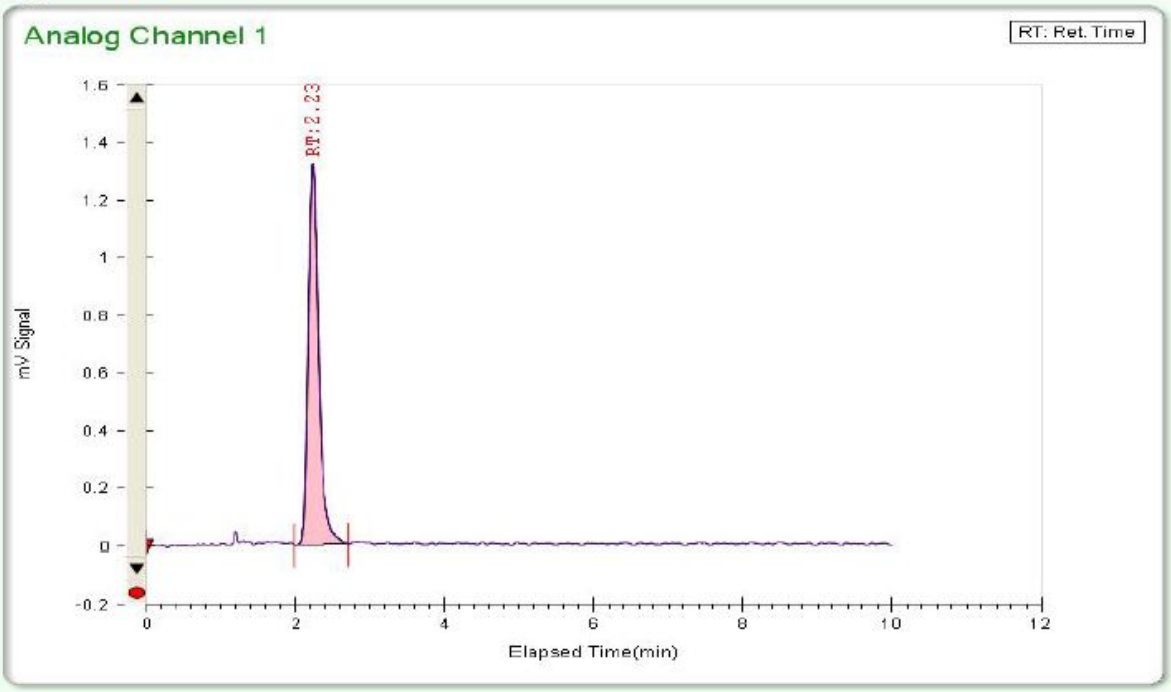
Theoretical Plates	Resolution Peak1	Resolution Peak2	Height
1800.7249	0	12.0922	0.6847
1655.5781	-12.0922	0	0.1574

Peak Info

SFC trace of (R)-28:

File Name	20000851831-P1_1.tta
Log Date	6/25/2015 11:11:07 AM
Method Name	Method-40_2.4ml.met
Report Date	6/25/2015

Injection Volume	1
Co-Solvent %	40
Column	AD-3
Co-Solvent	ETOH(0.05%DEA)
Total Flow	2.4
Wavelength	220
Injection Info	



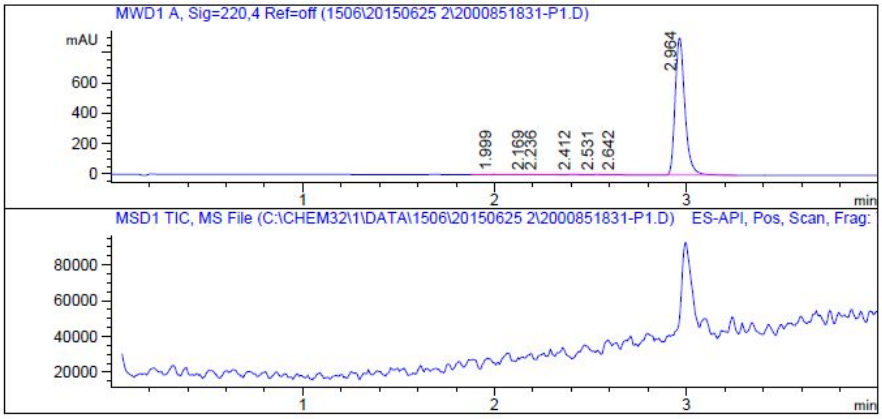
Peak Name	**St. (min)**	**End (min)**	**RT (min)**	**Area %**
Peak1	1.9906	2.6976	2.23	100

Theoretical Plates	**Resolution Peak1**	**Height**
1603.3091	0	1.3231

Peak Info

LC-MS of (R)-28:

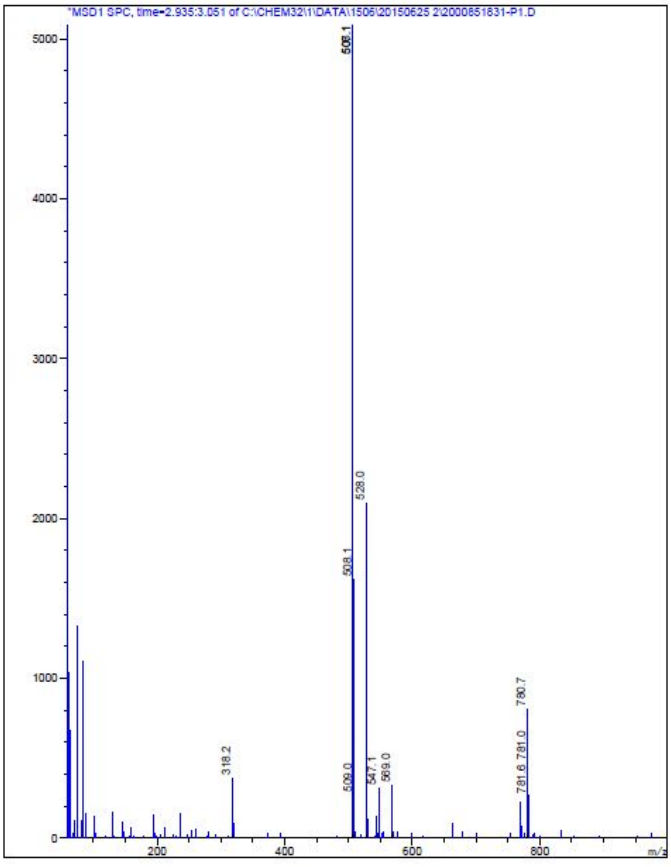
```
Compound ID      :
Sample ID        : 2000851831-P1
Injection Date   : Thu, 25. Jun. 2015
Location         : P1-E-03
Acq   Method     : C:\Chem32\1\DATA\1506\20150625 2\10-80CD_4MIN.M
Data Filename    : C:\CHEM32\1\DATA\1506\20150625 2\2000851831-P1.D
Instrument       :  LCMS 12-102
```



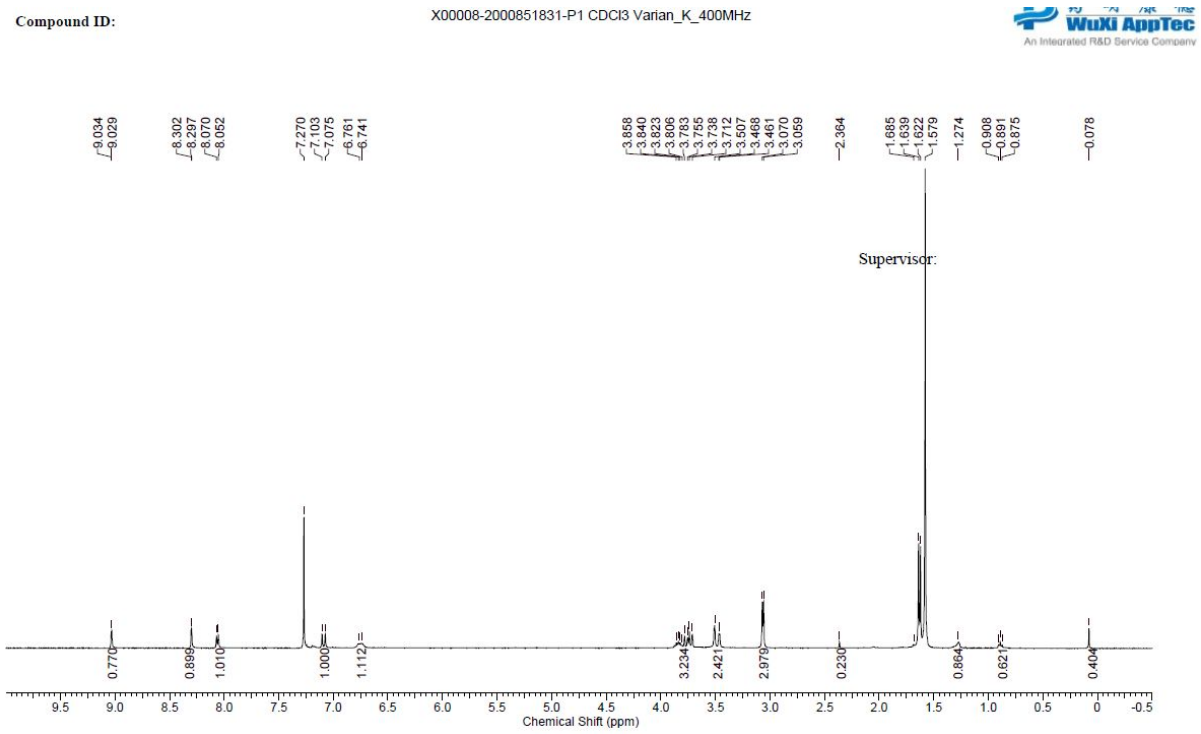
Report

Signal 1 : MWD1 A, Sig=220,4 Ref=off

#	Meas. Ret.	Height	Width	Area	Area %
1	1.999	1.530	0.103	11.414	0.349
2	2.169	1.803	0.061	7.020	0.214
3	2.236	1.557	0.050	5.040	0.154
4	2.412	3.695	0.076	19.682	0.601
5	2.531	3.313	0.053	11.761	0.359
6	2.642	1.553	0.067	7.295	0.223
7	2.964	915.334	0.058	3212.600	98.100



^{1}H NMR of (R)-28:

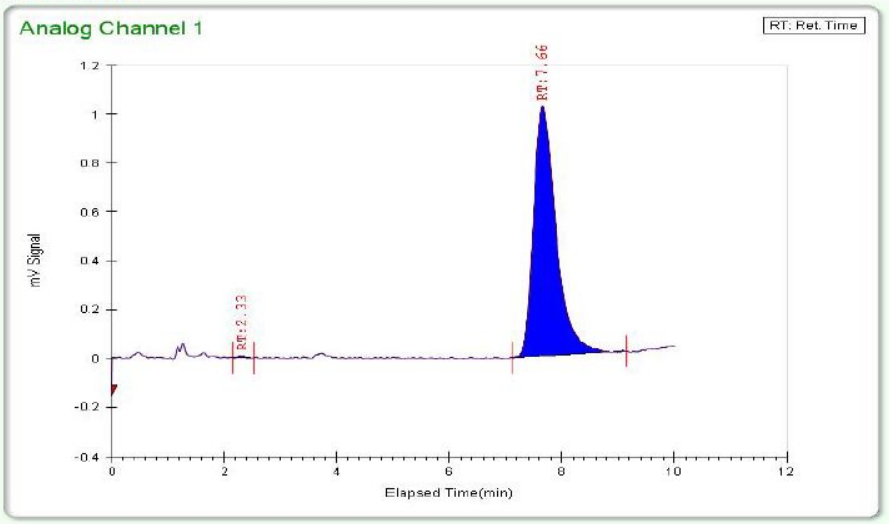


SFC trace of (S)-26:

File Name	20000851831-P2_1.tta
Log Date	6/25/2015 1:27:10 PM
Method Name	Method-40_2.4ml.met
Report Date	6/25/2015

Injection Volume	3
Co-Solvent %	40
Column	AD-3
Co-Solvent	ETOH(0.05%DEA)
Total Flow	2.4
Wavelength	220

Injection Info



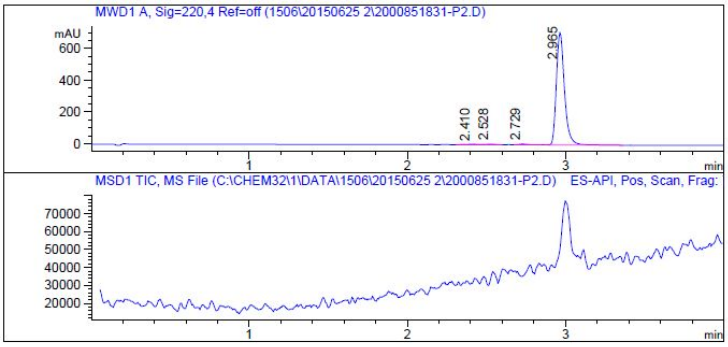
Peak Name	St. (min)	End (min)	RT (min)	Area %
Peak2	2.156	2.5279	2.33	0.222
Peak1	7.1143	9.1476	7.66	99.778

Theoretical Plates	Resolution Peak1	Resolution Peak2	Height
1739.2021	0	11.8231	0.0084
2037.7599	-11.8231	0	1.0231

Peak Info

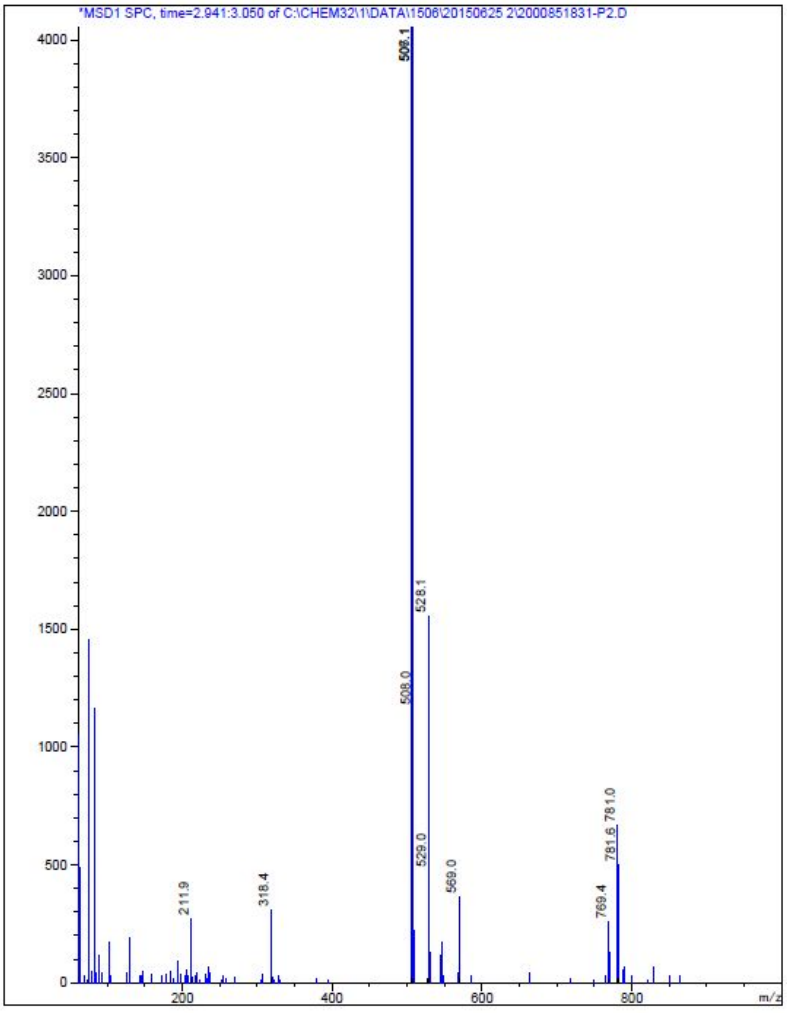
LC-MS of (S)-26:

```
Compound ID      :
Sample ID        : 2000851831-P2
Injection Date   : Thu, 25. Jun. 2015
Location         : P1-E-04
Acq   Method     : C:\Chem32\1\DATA\1506\20150625 2\10-80CD_4MIN.M
Data Filename    : C:\CHEM32\1\DATA\1506\20150625 2\2000851831-P2.D
Instrument       :  LCMS 12-102
```

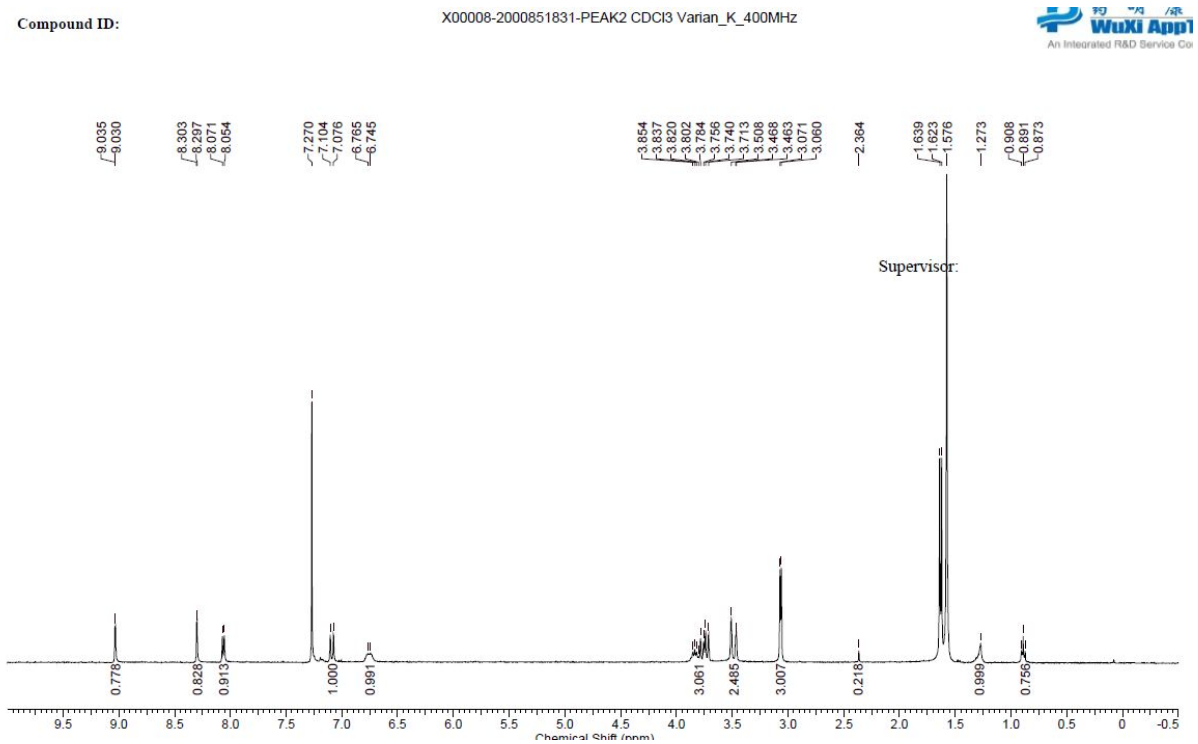


Report

```
==================================================================
   Signal 1 : MWD1 A, Sig=220,4 Ref=off
    #  Meas. Ret.   Height    Width       Area       Area %
   ------------------------------------------------------------
     1      2.410      3.473   0.073         17.509    0.681
     2      2.528      3.805   0.052         12.965    0.504
     3      2.729      5.060   0.055         18.636    0.724
     4      2.965    711.097   0.055       2523.305   98.091
   ------------------------------------------------------------
```



^{1}H NMR of (S)-26:


Compound ID:
X00008-2000851831-PEAK2 CDCl3 Varian_K_400MHz
Supervisor:
9.035
9.030
8.303
8.297
8.071
8.054
7.270
7.104
7.076
6.765
6.745
3.854
3.837
3.820
3.802
3.784
3.756
3.740
3.713
3.508
3.468
3.463
3.071
3.060
2.364
1.639
1.623
1.576
1.273
0.908
0.891
0.873
0.778
0.828
0.913
1.000
0.991
3.061
2.485
3.007
0.218
0.999
0.756
Chemical Shift (ppm)

S-12. Molecular Modeling

Helix 12 in AR has a role in modulating the pharmacology of AR as depicted in Figure S2 and published elsewhere [2-4]. Additionally, we modelled and hypothesized that ligand conformational flexibility in bicalutamide might play a role in antagonist to agonist switch, although with a different mutation W742L (Figure S3), which would work in conjunction with helix 12 dynamics- where an open conformation would be antagonistic whereas a closed one, agonistic (Figure S4 [1]). The same paradigm is then proposed for other antagonists such as apalutamide (Figure S5 [1]). Consequently, we used the homology model reported in [1] and ligand based alignment to hypothesize that conformational flexibility in the compounds reported here may play a role in agonist/antagonist switches as the spirocyclic moiety would not allow further adjustments in the ligand to stabilize it in the putative agonistic AR conformation (Figure S6).

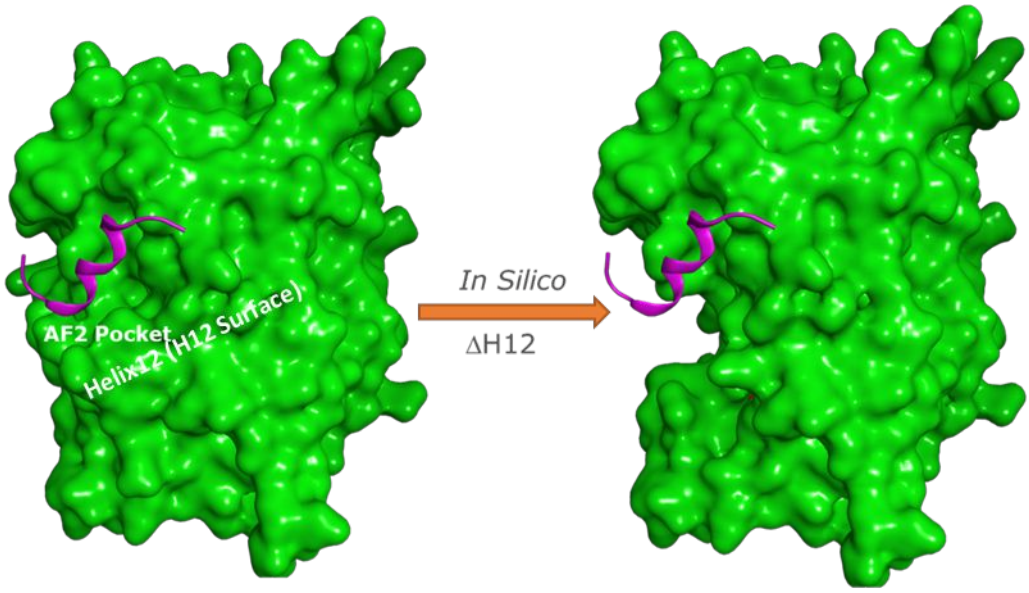
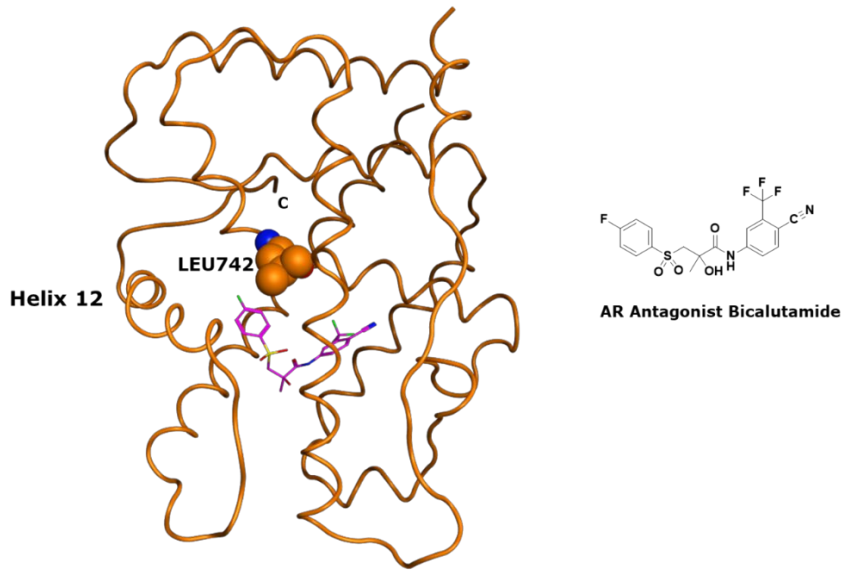
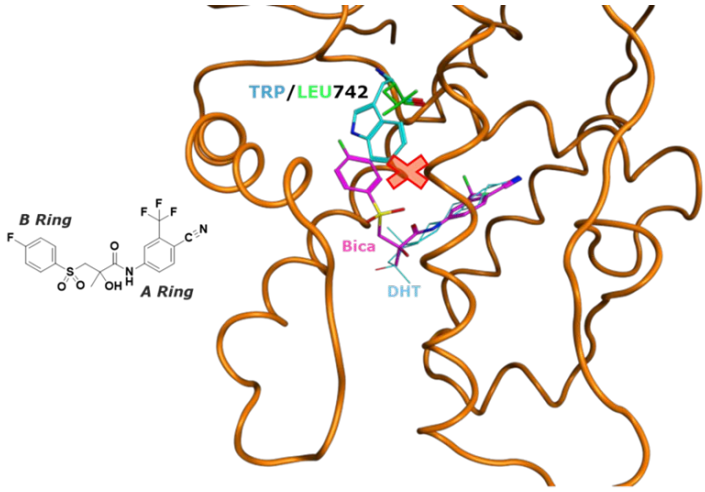


Figure S2. *In Silico* deletion of helix 12 disrupts the cofactor binding pocket (PDB ID: 1T73). In the image above, a helical fragment of cofactor (magenta ribbon) is superimposed with full-length androgen receptor (green) or ΔH12 androgen receptor (green).

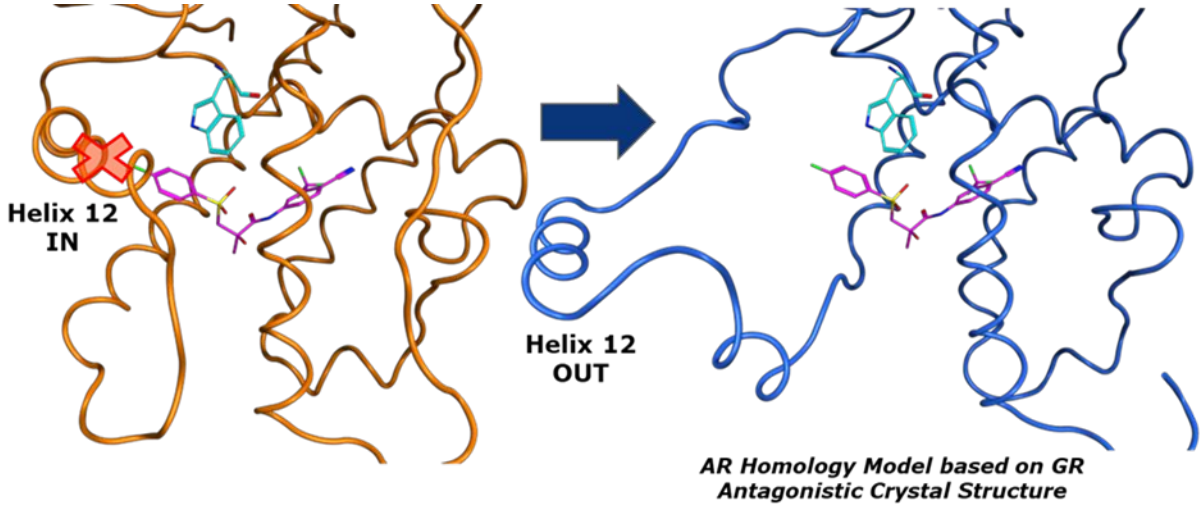


(A)

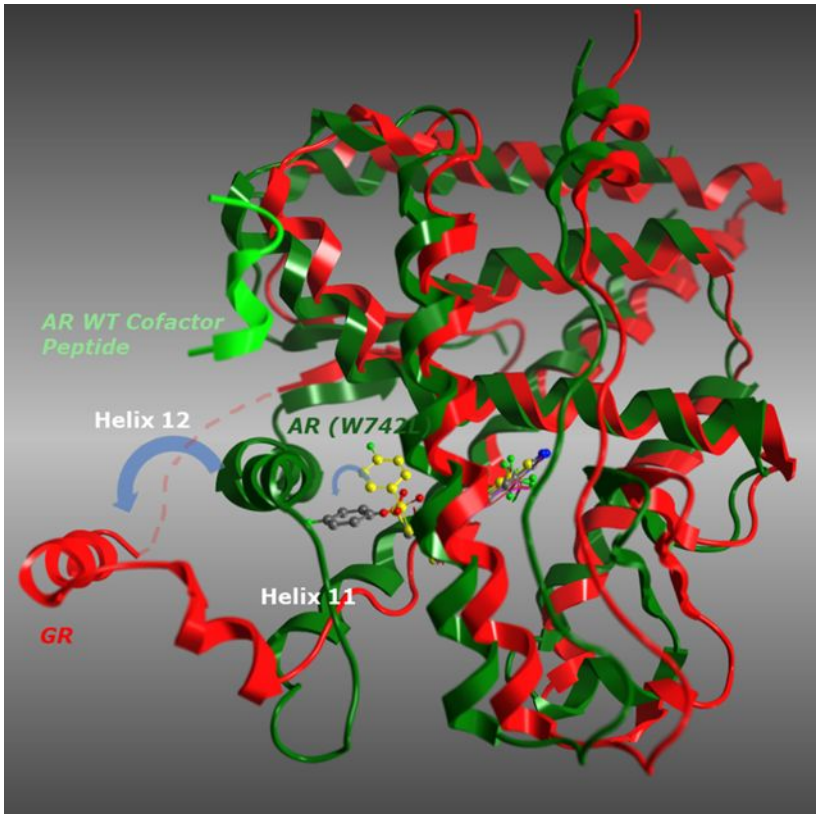


(B)

Figure S3. ***(A)*** AR LBD (W742L mutant): bicalutamide crystal structure; PDB ID: 1Z95, ***(B)*** **B** ring of bicalutamide would clash with WT W742 in an agonistic conformation. Our early homology models used crystal structures of either related proteins such as GR or AR with other point mutations (e.g. bicalutamide and the W742L mutation, which turns bicalutamide from an antagonist to an agonist)



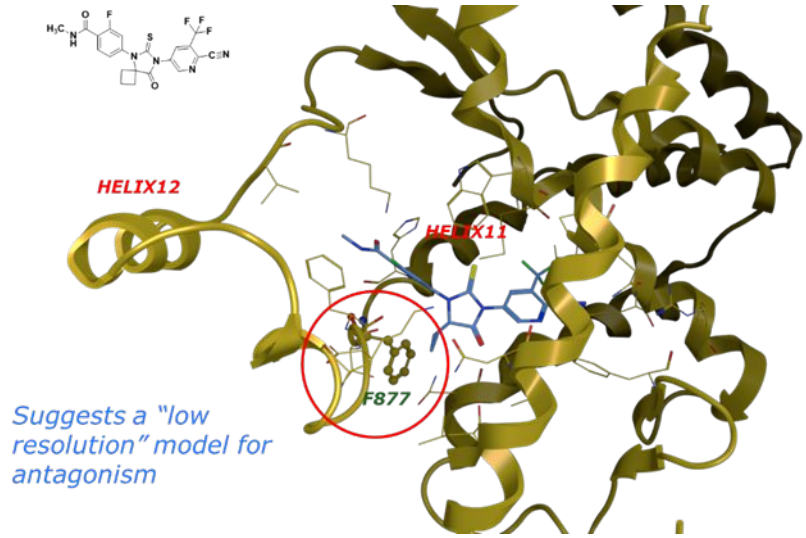
(A)-(B)



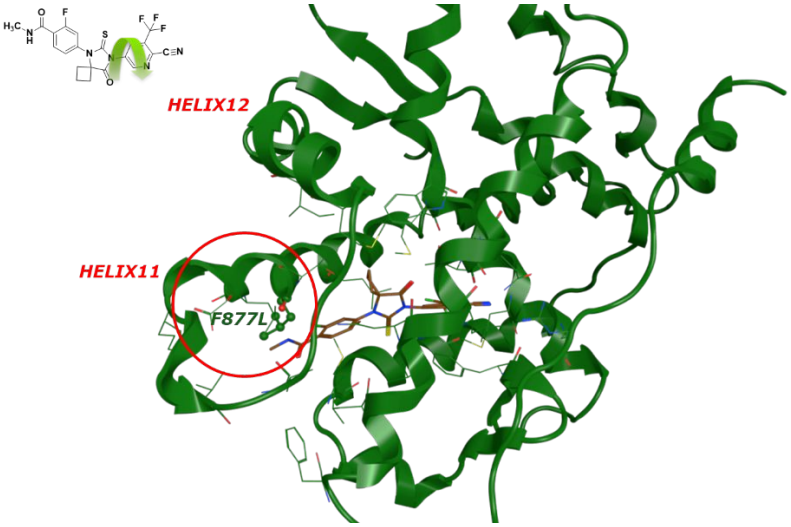
(C)

Figure S4. ***(A)*** Bicalutamide ligand dynamics (with single bond torsions) may lead to a low(er) energy conformer that would not stabilize agonistic/closed Helix12 conformation, ***(B)*** Comparable to GR, Helix 12 would move out to accommodate bicalutamide in an antagonistic conformation, ***(C)*** A summary of this model of putative ligand dynamics. We hypothesized that conformational dynamics in bicalutamide between ring B and the central

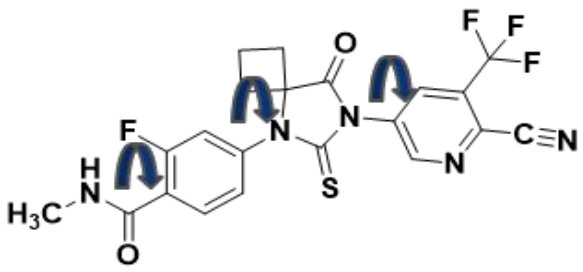
core might be responsible for the helix 12 switch as well as in stabilizing an agonistic conformation in the W742L mutant.



(A)

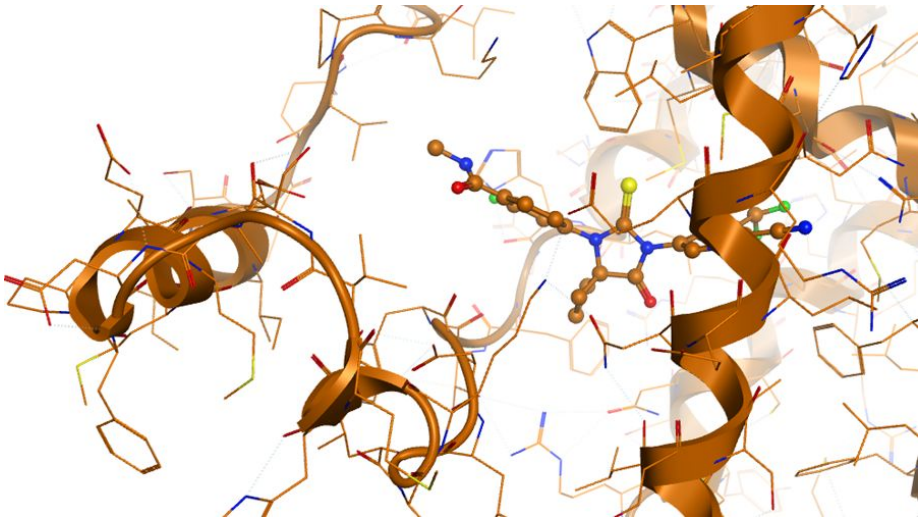


(B)

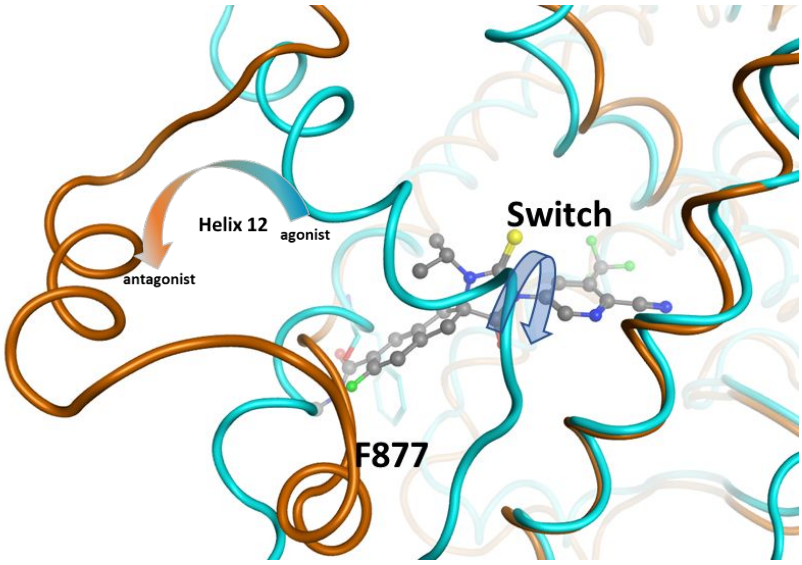


(C)

Figure S5. Apalutamide manually docked and ligand dynamics modelled with analogies from figure S4; ***(A)*** antagonistic, ***(B)*** agonistic, and ***(C)*** potential torsions that render ligand flexibility. We built this hypothesis on the role of ligand and protein conformations with our recently reported compounds [1] by illustrating a potential role for ligand torsion (e.g. between Ring A and central core) as a predictive model.



(A)



(B)

Figure S6. ***(A)*** Manual docking model of apalutamide prepared based on the antagonistic model previously reported [1] and ***(B)*** Ligand based overlay of compound (*R*)-**28** on apalutamide docked conformation, followed by introduction of a manual torsion (labeled

"switch") to demonstrate the hypothesis of a potential agonistic conformation of the ligand. This hypothesis laid the foundation for our design concept to employ spirocycles to create such torsional restrictions and probe further through synthesis and bioassays

REFERENCES

[1] Zhang, Z.; Connolly, P. J.; Lim, H. K.; Pande, V.; Meerpoel, L.; Teleha, C.; Branch, J. R.; Ondrus, J.; Hickson, I.; Bush, T.; Luistro, L.; Packman, K.; Bischoff, J. R.; Ibrahim, S.; Parrett, C.; Chong, Y.; Gottardis, M. M.; Bignan, G. Discovery of JNJ-63576253: a clinical stage androgen receptor antagonist for F877L mutant and wild-type castration resistant prostate cancer (mCRPC). *J. Med. Chem*. **2021**, 64(2), 909-924

[2] Liu, H.; Han, R.; Li, J.; Liu, H.; Zheng, L. Molecular mechanism of R-bicalutamide switching from androgen receptor antagonist to agonist induced by amino acid mutations using molecular dynamics simulations and free energy calculation. *J. Comput. Aided Mol. Des*. **2016**, 30(12), 1189-1200.

[3] Liu, H. L.; Zhong, H. Y.; Song, T. Q.; Li, J. Z. A Molecular Modeling Study of the Hydroxyflutamide resistance mechanism induced by androgen receptor Mutations. *Int. J. Mol. Sci.* **2017**, 18(9), pii: E1823.

[4] Balbas, M. D.; Evans, M. J.; Hosfield, D. J.; Wongvipat, J.; Arora, V. K.; Watson, P. A.; Chen, Y.; Greene, G. L.; Shen, Y.; Sawyers, C. L. Overcoming mutation-based resistance to antiandrogens with rational drug design. *Elife*. **2013**, 2, e00499