SUPPORTING INFORMATION

Identification of a selective SCoR2 inhibitor that protects against acute kidney injury

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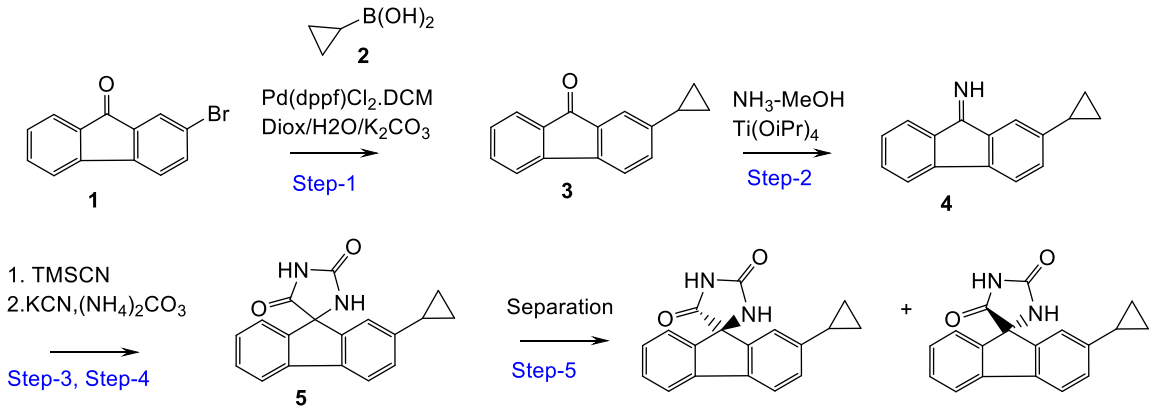


Figure S1. Synthesis of Compound JSD26.

Step-1 (Synthesis of compound 3): To a stirred solution of compound 1 (1 g, 3.86 mmol) and compound 2 (0.996 g, 11.53 mmol) in Dioxane: Water (20 mL: 5 mL) was added K_2CO_3 (1.6 g, 11.58 mmol) under N_2 atmosphere. The reaction mixture was degassed with N_2 over 15 min followed by addition of Pd(dppf)Cl_2.DCM (0.315 g, 0.386 mmol) and again degassed for another 10 min , heated to 80 °C for 16 h. After completion, reaction mixture was filtered through a small pad of Celite, washed with ethyl acetate, water was added, extracted with ethyl acetate, washed with water followed by brine, dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure to afford the crude mass that was purified by column chromatography (10% EA/HEX) to afford the desired compound 3 (800 mg, 94%) as a yellow gum.

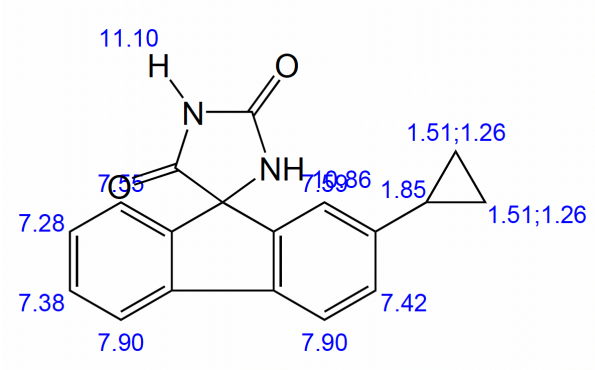
Step-2 (Synthesis of compound 4): To the stirred solution of compound 3 (1g, 4.54 mmol) in methanolic ammonia (5 ml), titanium isopropoxide (1.5 ml, 13.63 mmol) was added at 0 °C in a sealed tube and the reaction mixture was then allowed to stir at 60 °C for 12 h. After complete consumption of the starting material (monitored by TLC), it was filtered and the crude compound 4 taken to the next step without workup.

Step-3 and Step-4 (Synthesis of compound 5): To the above stirred solution of crude compound 4 (2 g) in methanolic ammonia (10 ml), TMSCN (3.42 ml, 27.27 mmol) was added slowly, purged with N_2 and stirred for 2 h at RT followed by heating at 60 °C for 12 hr in a sealed tube. The reaction mixture was diluted with ethyl acetate and water, and the resulting slurry was filtered through celite pad, filtrate thus collected dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure to afford crude compound 5 (1.8 g) which was used directly in the next reaction. To a stirred solution of compound 5 in methanol was added KCN (1.77 g, 27.27 mmol) and ammonium carbonate (8.73 g, 90.90 mmol) in a sealed tube and heated at 80 °C for 48 h. After complete consumption of the starting material (monitored by TLC), the reaction mass was quenched with 3N HCl until acidic and diluted with water and ethyl acetate. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 100 ml), washed with water followed by brine, dried over anhydrous sodium sulfate, filtered, evaporated under

reduced pressure to afford the crude mass which was purified by column chromatography (30% EA/HEX) to afford the desired compound 6 (400mg, 20%) as a white solid. ^{1}H NMR (DMSO-D6): 0.75 (2H, m), 1.0 (2H, m), 1.9-2.1 (1H, m), 7.15 (1H, m), 7.20 (1H, s), 7.30 (1H, m) 7.35-7.45 (2H, m), 7.75 (1H, d), 7.80 (1H, d), 8.5 (1H, s), 11.2 (1H, s).

Step 5 Enantiomers of compound 5 (JSD26) were separated by chiral HPLC (Chiralpak IC (4.6 x 250 mm), 5µ, mobile phase – Hexane / EtOH / isopropylamine : 80/20/0.1, flow rate - 1.0 ml/min, run time – 15 min, wave length – 282 nm.

A



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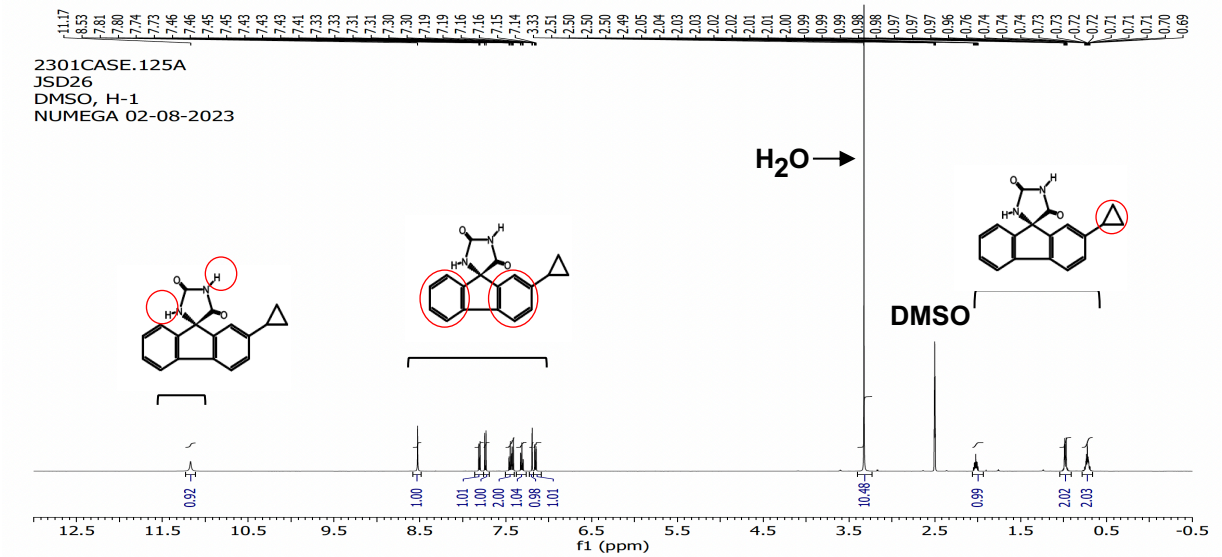
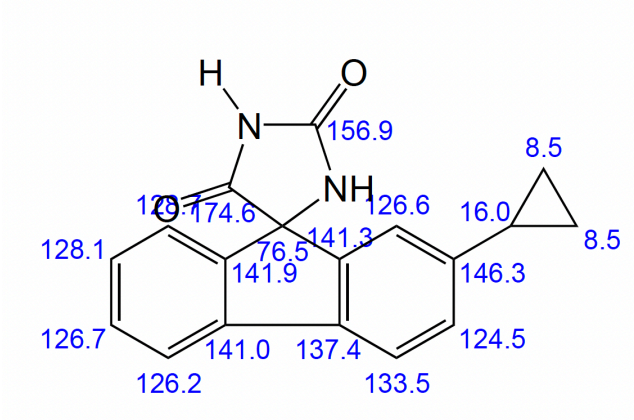


Figure S2. ^{1}H-NMR spectrum of JSD26.
A: Predicted ^{1}H-NMR chemical shifts in Parts Per Million (PPM) for each proton in JSD26 from ChemOffice software. **B:** ^{1}H-NMR spectrum of JSD26 with annotation of clusters of peaks.

A



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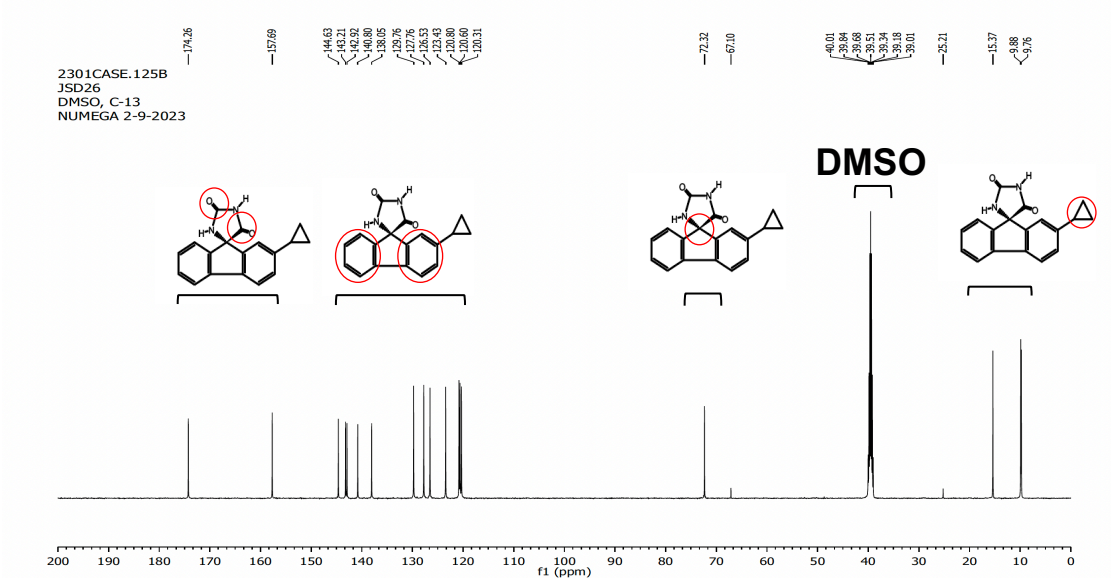

Figure S3. ^{13}C-NMR spectrum of JSD26.
A: Predicted ^{13}C-NMR chemical shifts in Parts Per Million (PPM) for each carbon in JSD26 from ChemOffice software. **B:** ^{13}C-NMR spectrum of JSD26 with annotation of clusters of peaks.

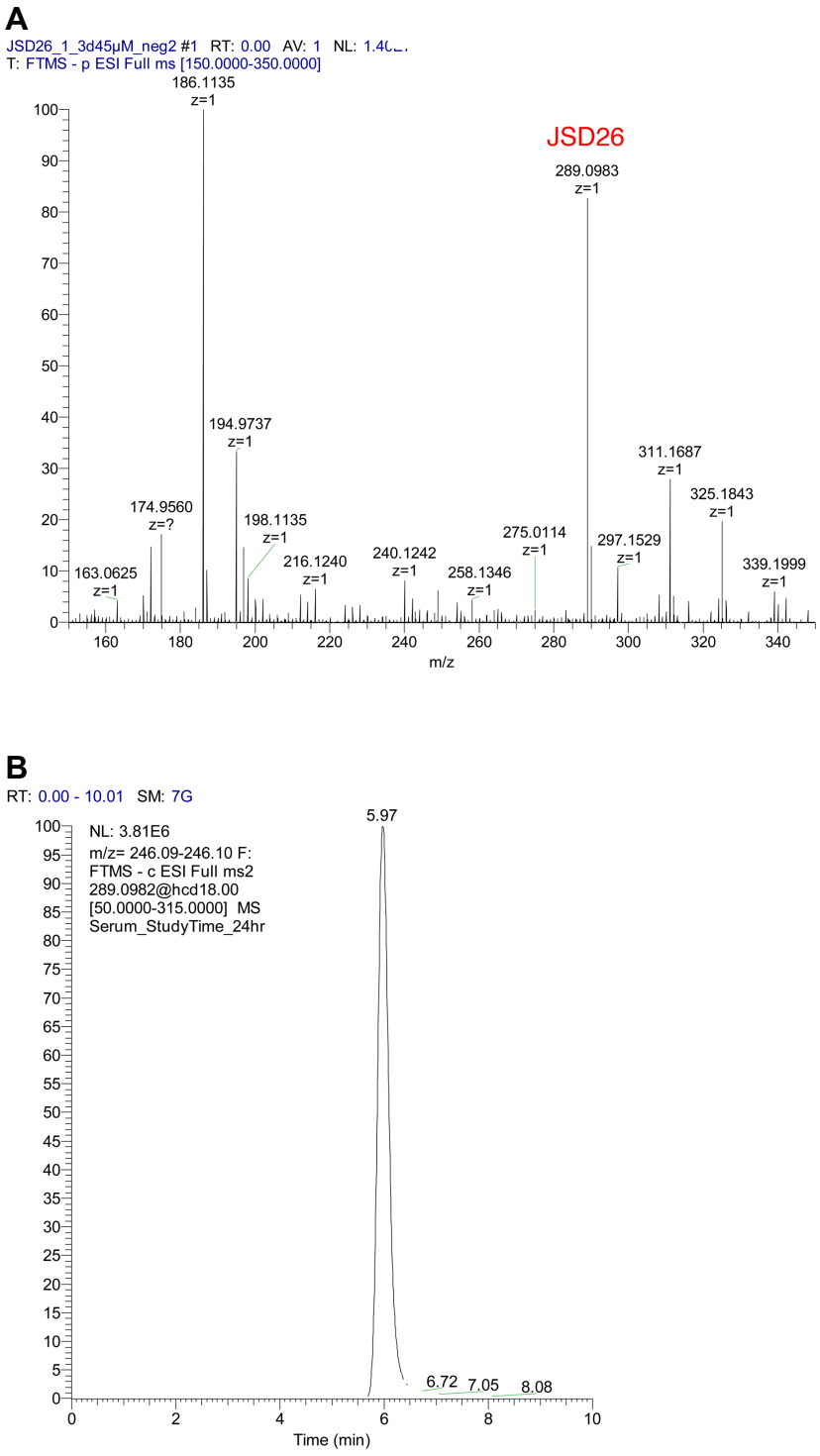

Figure S4. Detection of JSD26 in serum after i.p. dosing.
A: JSD26 (3.45μM) detected by mass spectroscopy after HPLC. JSD26 was dissolved in DMSO, then diluted in 50% acetonitrile solvent for injection. **B:** HPLC trace demonstrating JSD26 in serum collected 24 hours post-injection (120 mg/kg body weight, i.p.).

Table S1: IC_{50} Values of Initial SCoR2 Inhibitors (substrate = DL-glyceraldehyde)

Number	**C2**	**C3**	**C4**	**C7**	**SCoR2 IC_{50} (nM)**
Imirestat (1)	F	H	H	F	45
2	H	H	H	H	216
3	CH_3	H	H	H	708
4	Et	H	H	H	1002
5-1* **(JSD26)**	Cyclopropyl	H	H	H	93
5-2*	Cyclopropyl	H	H	H	3,800
6	OCH_3	H	H	H	403
7	$CH=CH_2$	H	H	H	653
8	OH	H	H	H	855
9	Cl	H	H	H	125
10	OCH_2CH_2OH	H	H	H	521
11	Br	H	H	H	155
12	CF_3	H	H	H	622
13	OCH_2CO_2H	H	H	H	155
14	OCH_2CHF_2	H	H	H	571
15	Et	H	H	F	386
16	Cyclopropyl	H	H	F	67
17-1*	Cyclobutyl	H	H	F	194
17-2*	Cyclobutyl	H	H	F	103
18	OH	H	H	F	241
19	Br	H	H	F	116
20	Cl	H	H	F	60
21	$CONH_2$	H	H	H	>5,000
22	$CONH(Et)_2$	H	H	H	>5,000
23	Pyrazol-3-yl	H	H	H	>5,000
24	1-Methyl-pyrazol-3-yl	H	H	H	>5,000

25	1-Methyl-pyrazol-5-yl	H	H	H	>5,000
26	Pyridin-2-yl	H	H	H	>5,000
27	2-Pyrazin-yl	H	H	H	>5,000
28	2-Chloropyrimidin-5-yl	H	H	H	>5,000
29	H	H	OCH_3	H	192
30	H	H	F	H	111
31	H	Br	H	H	155
32	H	OCH_3	H	H	243
33	F	Cyclopropyl	H	F	40
34	H	OCH_3	H	F	96
35	H	OH	H	F	256
36	H	OCH_2CHF_2	H	F	126
37	H	$OCH_2CH_2N(CH_3)_2$	H	F	447
38	H	H	F	F	64
39	CH_3	H	H	CH_3	>2,000
40	Et	H	H	Et	>5,000
41	Cl	H	H	Cl	433
42	Br	H	H	Br	>5,000
43	Cyclopropyl	H	H	Cyclopropyl	>5,000
44	1-Methyl-pyrazol-4-yl	H	H	1-Methyl-pyrazol-4-yl	>5,000

*individual enantiomers

Table S2: IC_{50} Values of Secondary SCoR2 Inhibitors (substrate = DL-glyceraldehyde)

Number	**C2**	**C3**	**C4**	**C7**	**SCoR2 IC_{50} (nM)**
45	H	OCH_2CO_2H	H	F	118
46	H	OCH_2CH_2OH	H	F	133
47-1*	F	OH	CH_2CO_2H	F	95
47-2*	F	OH	CH_2CO_2H	F	142
48-1*	F	OCH_2CO_2H	H	F	38
48-2*	F	OCH_2CO_2H	H	F	43
49-1*	F	H	CH_2CO_2H	F	16
49-2*	F	H	CH_2CO_2H	F	19
50	F	2-azetidin-1-yl-2-oxoethoxy	H	F	23
51	F	H	2-(azetidin-1-yl)-2-oxoethoxy	F	27
52	F	H	1-cyclopentyl-1H-1,2,3-triazol-4-yl	F	16
53	F	(Oxetan-3-yl)oxy	H	F	46

*individual enantiomers