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Discovery of AMG 232, a Potent, Selective, and Orally Bioavailable MDM2−p53 Inhibitor in Clinical Development

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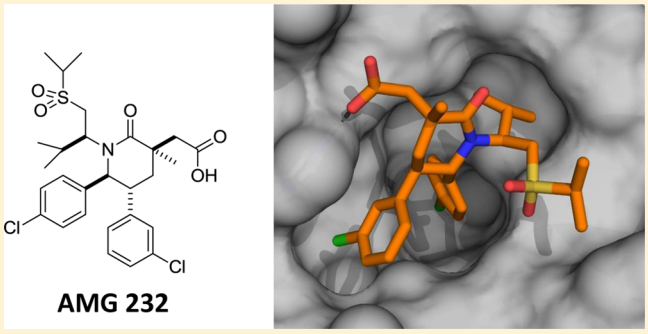
Supporting Information

ABSTRACT: We recently reported the discovery of AM-8553 (**1**), a potent and selective piperidinone inhibitor of the MDM2−p53 interaction. Continued research investigation of the *N*-alkyl substituent of this series, focused in particular on a previously underutilized interaction in a shallow cleft on the MDM2 surface, led to the discovery of a one-carbon tethered sulfone which gave rise to substantial improvements in biochemical and cellular potency. Further investigation produced AMG 232 (**2**), which is currently being evaluated in human clinical trials for the treatment of cancer. Compound **2** is an extremely potent MDM2 inhibitor (SPR K_D = 0.045 nM, SJSA-1 EdU IC_{50} = 9.1 nM), with remarkable pharmacokinetic properties and in vivo antitumor activity in the SJSA-1 osteosarcoma xenograft model (ED_{50} = 9.1 mg/kg).



INTRODUCTION

The tumor suppressor protein p53 plays a pivotal role in growth suppression and apoptosis of cancer cells,[1,2] and p53 pathway inactivation may be required for advanced tumor formation.[3] Roughly half of human cancers have wild-type p53, whose functions are regulated by human murine double minute 2 (MDM2).[4−6] MDM2 directly binds to and blocks the N-terminal transcriptional activation domain of p53, promotes export of p53 from nucleus to the cytoplasm, and induces degradation of p53 via ubiquitination through its E3 ligase activity.[1,2] As a result, the disruption of the MDM2−p53 interaction has been regarded as an attractive strategy for the activation of the p53 pathway.[7] In fact, studies with small molecule inhibitors of the MDM2−p53 interaction have yielded significant reductions in tumor growth both in vitro and in vivo.[8−11] Recently, several of these MDM2 inhibitors have advanced into clinical trials for the treatment of cancer (Figure 1).[12]

RESULTS AND DISCUSSION

Previously, we reported the discovery of AM-8553 (**1**; Figure 2)[13] as a potent and selective piperidinone inhibitor of the MDM2−p53 interaction. Compound **1** inhibited the MDM2−p53 interaction in a biochemical HTRF assay[14] with an IC_{50} of 1.1 nM. Its activity on the human SJSA-1 tumor cell line ranged from an IC_{50} of 0.072 μM in an EdU cell proliferation assay[14] to an IC_{50} of 0.76 μM in a p21 induction assay[14] in the presence of 10% human serum. Furthermore, this compound demonstrated tumor growth inhibition in the SJSA-1 xenograft model.

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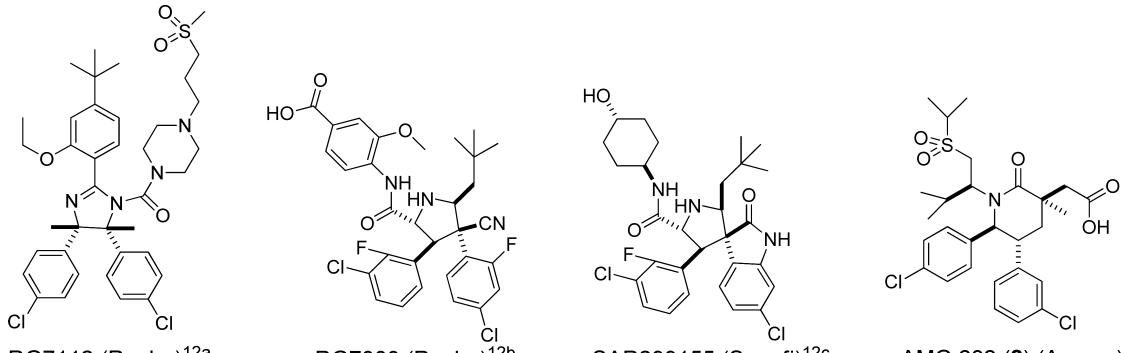

Figure 1. Chemical structures and potencies of RG7112, RG7388, SAR299155, and **2**. [a]K_D in the surface plasmon resonance (SPR) spectroscopy binding assay.[14] [b]IC_{50} in the EdU proliferation assay (SJSA-1, 10% human serum).[14]

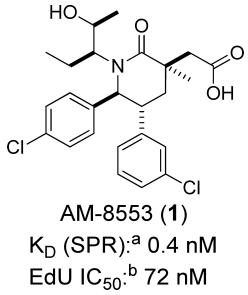

Figure 2. Chemical structure and potency of **1**. [a]K_D in the surface plasmon resonance (SPR) spectroscopy binding assay.[14] [b]IC_{50} in the EdU proliferation assay (SJSA-1, 10% human serum).[14]

The cocrystal structure of **1** with human MDM2 protein is shown in Figure 3.[13] The potency of **1** was improved with a focus on the three critical hydrophobic binding pockets and an interaction with H96. The C5 aryl group fills the $Leu26_{(p53)}$ pocket and engages in a face-to-face π-stacking interaction with H96, while the C6 aryl group occupies the $Trp23_{(p53)}$ binding cavity. The hydroxyl group is exposed to solvent and the ethyl group directed into the $Phe19_{(p53)}$ pocket by the conformational constraint induced by the α-substitution. In addition, the conformation of the piperidinone ring is stabilized by incorporation of a methyl group at the C3 position. Finally, the carboxylate of **1** interacts with the adjacent, presumably, charged imidazole of the H96 side chain of MDM2.

Analysis of our own in-house MDM2 cocrystal structures along with those in the literature suggested a region of the MDM2 protein which, while not accessed to a significant extent by inhibitors published to date, might serve as a potential source for improved binding affinity. The right side of Figure 3 depicts this shallow, predominantly hydrophobic cleft adjacent to the Phe19 binding pocket and to the right of the *N*-alkyl group of **1**. It is bordered on the edges by F55, N59, and M62. In this paper, we designate this region the "glycine shelf", as G58 serves as the approximate center and entry point to this extended, relatively flat part of the protein surface. While hydrophobic, this section of the binding site in the cocrystal structure is shallow and largely solvent exposed. We felt that additional research investigation of the *N*-alkyl group in **1**, especially in this shelf region, might offer an opportunity to increase potency while maintaining favorable selectivity and low intrinsic clearance in human hepatocytes. In this article, we report the continued investigational efforts which

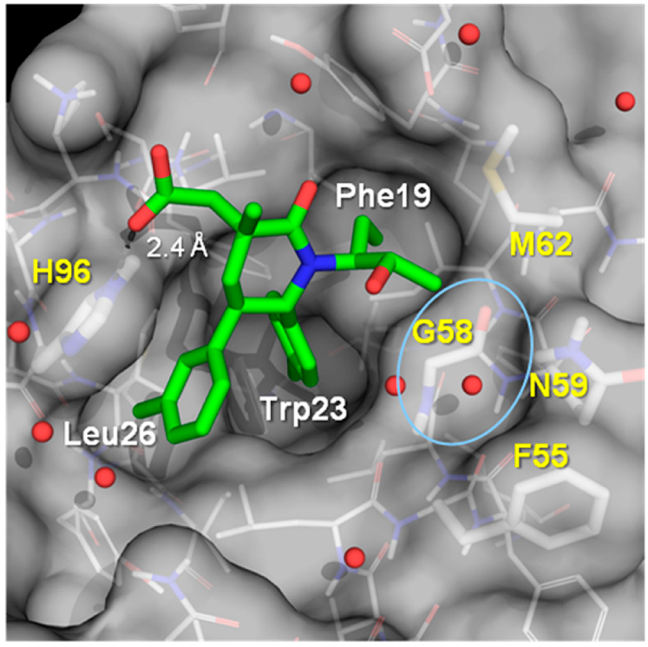

Figure 3. Cocrystal structure of **1** bound to human MDM2 (17−111) at 2.0 Å resolution and depicting proposed electrostatic interactions with H96 and G58 "shelf" region (circled). White labels indicate the positions normally occupied by key p53 residues. MDM2 residues H96, G58, M62, N59, and F55 are labeled in yellow. Cocrystallized water molecules are shown in red. PDB code: 4ERF.

led to the discovery of AMG 232 (**2**, Figure 1), a highly potent MDM2 inhibitor (K_D = 0.045 nM, EdU IC_{50} = 9.1 nM), with remarkable pharmacokinetic properties and in vivo efficacy in the SJSA-1 osteosarcoma xenograft model (ED_{50} = 9.1 mg/kg).

The investigation began with the replacement of the secondary alcohol in **1** with various alcohol or nitrile groups (Table 1). The tertiary alcohols **3** and **4** were potent in the biochemical assay in the absence of human serum but suffered a larger potency decrease than **1** upon addition of human serum. Compound **5**, containing a two-carbon spacer between the tertiary alcohol moiety and the carbon adjacent to the ring nitrogen, exhibited a similar potency as **1** in both the biochemical and the cell-based assays. Changing from the tertiary alcohol to a secondary alcohol (**6** and **7**)[15] slightly improved the biochemical potency but decreased the cellular potency. Similarly, replacing the secondary

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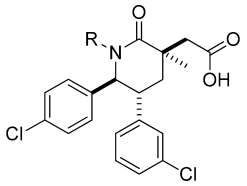
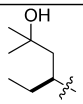
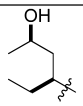
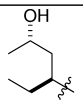
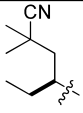
Table 1. Initial Modification of the *N*-Alkyl Group



Compd	R	Biochemical Potency		Cellular Potency (SJSA-1)	
		HTRF IC_{50} (nM)[a]	HTRF (15% HS[b]) IC_{50}(nM)[a]	p21 (10% HS[b]) IC_{50} (nM)[a]	EdU (10% HS[b]) IC_{50} (nM)[a]
1		1.1 ± 0.5	4.1 ± 1.6	760 ± 250	72 ± 14
3		1.4 ± 0.4	32.0 ± 9.8	2600 ± 410	490 ± 400
4		1.0 ± 0.2	62.4± 2.6	3200 ± 740	5500 ± 310
5		1.4 ± 0.3	4.7 ± 0.3	470 ± 190	100 ± 21
6		0.4± 0.08	5.6 ± 0.2	1100 ± 210	150 ± 62
7		0.7± 0.04	6.5 ± 0.6	880 ± 250	240 ± 91
8		1.2 ± 0.1	22± 8.1	2800 ± 1	630 ± 350
9		1.2 ± 0.1	22 ± 8.1	950 ± 130	120 ± 8

[a]Potency data are reported as the mean and standard deviation of at least two runs. [b]HS = human serum.

alcohol with a cyanomethyl or 2-cyano-2-methylpropanyl group resulted in a potency loss in the EdU assay (**8** and **9** vs **1**).

To improve the binding affinity to the MDM2 protein, we incorporated a sulfonamide moiety to search for additional interactions with the glycine shelf. As shown in Table 2, sulfonamide **10** had similar biochemical potency but weaker cellular potency in the presence of human serum as compared to **1**. Increasing the *S*-alkyl group size from methyl to *t*-butyl or cyclopropyl results in a substantial improvement in cellular potency (**11** and **12** vs **10**). *N*-Methylation of sulfonamide **11** was well tolerated (**13**), while *N*-methylation of **12** resulted in 2-fold improvement in the EdU cellular assay (IC_{50} for **14** of 16 nM vs IC_{50} for **12** of 37 nM). Furthermore, expanding the ethyl group (Phe19 pocket) attached to the carbon adjacent to the ring nitrogen to a cyclopropyl or an isopropyl group resulted in the sulfonamides **15** and **16**, which were 2−3-fold more potent than **14** in the EdU assay (IC_{50} for **15** of 5.3 nM and IC_{50} for **16** of 6.5 nM vs IC_{50} for **14** of 16 nM). Unfortunately, the majority of these sulfonamides proved to be less stable than **1** in human hepatocytes[16] and exhibited moderate to high clearance in rat (Table 2).[17] Reversing the sulfonamide orientation provided compounds **17**, **18**, and **19**, which maintained potency but yielded no improvement in metabolic stability.[18]

Encouraged by the increased potency imparted by the sulfonamide functionality, we decided to explore the less polar and potentially more stable sulfone moiety to maintain the

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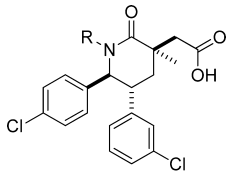
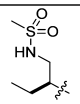
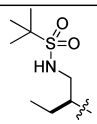
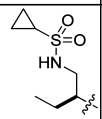
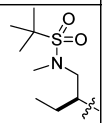
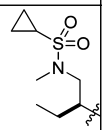
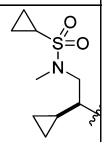
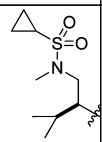
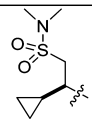
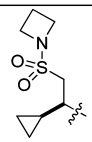
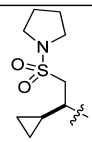
Table 2. Sulfonamide and Reverse Sulfonamide Piperidinone Derivatives



Compd	R	Biochemical Potency HTRF IC_{50} (nM)[a]	Cellular Potency (SJSA-1) EdU (10% HS[b]) IC_{50} (nM)[a]	*h*Hep CL_{int} (μL/min/10^6 cells)	Rat PK (iv, 0.5 mg/kg) CL(L/h/kg)/$t_{1/2}$(h)
1		1.1 ± 0.5	72 ± 14	3.0	1.2/3.5
10		0.7 ± 0.5	240 ± 110	11	5.5/1.2
11		1.3 ±1.6	37 ±26	17	6.6/0.41
12		0.5 ±0.17	37 ±13	14	4.0/3.0
13		0.7 ± 0.1	37 ±6.0	17	1.6/6.0
14		0.9 ± 0.3	16 ± 5	14	1.7/4.0
15		0.20 ± 0.16	5.3 ± 2.3	16	1.9/1.3
16		0.2 ± 0.06	6.5 ± 3.0	7.3	3.2/2.5
17		0.2 ± 0.02	3.4 ±1.6	11	4.3/1.4
18		0.1 ±0.07	6.0 ±1.2	17	5.5/1.6
19		0.1 ± 0.02	4.4 ±0.66	14	6.2/1.6

[a]Potency data are reported as the mean and standard deviation of at least two runs. [b]HS = human serum.

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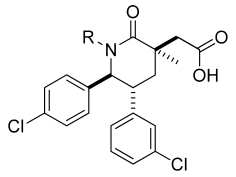
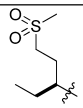
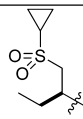
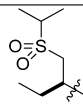
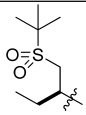
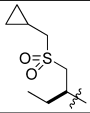
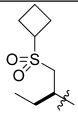
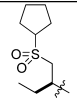
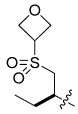
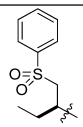
Table 3. Sulfone Piperidinone Derivatives



Compd	R	Biochemical Potency		Cellular Potency (SJSA-1)	
		HTRF IC_{50} (nM)[a]	HTRF (15%HS[b]) IC_{50} (nM)[a]	p21 (10% HS[b]) IC_{50} (nM)[a]	EdU (10% HS[b]) IC_{50} (nM)[a]
1		1.1 ± 0.5	4.1 ± 1.6	760 ± 250	72 ± 14
20		0.30± 0.08	1.6 ± 0.0	170 ± 74	9.5 ± 2.5
21		1.3 ± 0.5	3.4 ± 1.2	1400 ± 150	65 ± 64
22		0.30±0.05	1.6 ± 0.2	100 ± 23	5.7 ± 2.8
23		0.20 ± 0.09	1.70 ± 0.01	73 ± 10	3.8 ± 1.8
24		0.20 ± 0.03	1.4 ± 0.2	110 ± 96	6.0 ± 4.1
25		0.10 ± 0.04	1.1 ± 0.5	49 ± 29	3.0 ± 0.8
26		0.2 ± 0.09	1.8 ± 0.4	94 ± 27	5.6 ± 2.9
27		0.20 ± 0.02	1.1 ± 0.2	49 ± 10	4.7 ± 2.3
28		0.30 ± 0.00	1.6 ± 0.08	96 ± 22	8.3 ± 2.4
29		0.2 ± 0.01	1.3 ± 0.3	1100± 32	5.1 ± 1.5
30		0.3 ± 0.01	3.8 ± 1.7	110 ± 13	20 ± 7.5

[a]Potency data are reported as the mean and standard deviation of at least two runs. [b]HS = human serum.

favorable interaction with the glycine shelf and improve the stability in human hepatocytes and high clearance in rat. As revealed in Table 3, compound **20**, containing a one-carbon tethered sulfone, was noticeably more potent in both the biochemical assay and the cell-based assay than **1** and **21** which contains a two-carbon spacer. With the one-carbon tethered

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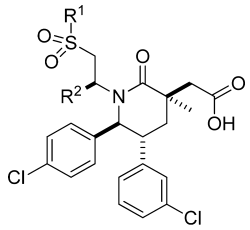
Table 4. Combination of Alkyl Groups at R^1 and R^2



Compd	R^1	R^2	biochemical potency HTRF IC_{50} (nM)[a]	cellular potency (SJSA-1) EdU (10%HS) IC_{50} (nM)[a]	*h*Hep CL_{int} (μL/min/10^6 cells)	Rat PK (iv, 0.5 mg/kg) CL(L/h/kg)/$t_{1/2}$ (h)
1			1.1 ± 0.5	72 ± 14	3.0	1.2/3.5
25	*t*-Bu	Et	0.10 ± 0.04	3.0 ± 0.8	11	0.47/3.4
31	*t*-Bu	CF_3CH_2	0.10 ± 0.03	8.1 ± 0.04	26	n/d
32	*t*-Bu	Me	0.1 ± 0.03	4.3 ± 1.2	n/d	0.62/3.9
33	*t*-Bu	*i*-Pr	0.6 ± 0.02	7.1 ± 4.3	7.9	0.78/7.5
34	*t*-Bu	*t*-Bu	0.5 ± 0.1	7.5 ± 2.3	4.6	0.19/18
35	*t*-Bu	*c*-Pr	0.10 ± 0.01	1.6 ± 0.8	16	1.1/3.8
36	*t*-Bu	*c*-Bu	0.1 ± 0.02	4.8 ± 0.6	12	n/d
24	*i*-Pr	Et	0.20 ± 0.03	6.0 ± 4.1	11	0.85/6.7
37	*i*-Pr	Me	0.2 ± 0.05	14 ± 1.8	4.1	2.1/3.8
2	*i*-Pr	*i*-Pr	0.6 ± 0.4	9.1 ± 2.8	6.3	0.66/2.4
38	*i*-Pr	*t*-Bu	0.4 ± 0.3	8.8 ± 5.2	6.3	0.78/8.0
39	*i*-Pr	*c*-Pr	0.20 ± 0.03	2.5 ± 1.5	20	0.96/8.7
40	*i*-Pr	*c*-Bu	0.1 ± 0.01	3.4 ± 0.8	20	1.4/3.7
20	Me	Et	0.30 ± 0.o8	9.5 ± 2.5	9.2	4.5/0.35
41	Me	Me	0.9 ± 0.1	110 ± 15	n/d	n/d
42	Me	*i*-Pr	0.30 ± 0.08	3.4 ± 0.9	11	2.7/9.0
43	Me	*c*-Pr	0.10 ± 0.04	4.0 ± 2.5	6.1	0.94/7.7

[a]Potency data are reported as the mean and standard deviation of at least two runs. [b]HS = human serum.

sulfone as the key feature required for potent inhibition, numerous sulfone derivatives were synthesized to define the optimum alkyl group in the sulfone side chain. In general, sulfones were more potent than sulfonamides as illustrated in Table 3. Many of the sulfone derivatives **22**–**30** were typically 10–20-fold more potent than **1** in both the p21 induction and the EdU proliferation assays. The *t*-butyl sulfone **25** was the most potent compound among the piperidinone sulfone derivatives, with an IC_{50} of 3.0 nM in the EdU assay.

On the basis of the observations exemplified in Tables 2 and 3, we explored combinations of alkyl groups at R^1 and R^2 (compounds **31**–**43**, Table 4) in order to improve pharmacokinetic properties while maintaining favorable potency. Importantly, many of those compounds not only maintain favorable cellular potency but also display low intrinsic clearance in human hepatocytes and in vivo clearance in rat. To discover a molecule suitable for preclinical development, the highly potent sulfone inhibitors in Table 4 were profiled in the CYP inhibition, time dependent inhibition (TDI) of CYP 3A4, and PXR induction assays. Compounds **2**, **25**, and **43** were found to have minimal liabilities in these assays. However, both compound **25** and **43** had moderate to high clearance and poor oral exposure in the cynomolgus monkey. Gratifyingly, compound **2** exhibited excellent pharmacokinetic properties in cynomolgus monkey (CL = 0.51 L/h/kg, %*F* = 51), allowing it to be selected for further development.

The dissociation constant (K_D) of **2** was measured as 0.045 nM in a surface plasmon resonance (SPR) spectroscopy binding assay.[14] Compound **2** was an extremely potent MDM2 inhibitor in all assays, especially in the EdU proliferation assay (IC_{50} = 9.1 nM). The selectivity of **2** was evaluated by examining its effect on the proliferation of HCT116 $p53^{wt}$ and $p53^{-/-}$ tumor cells in vitro[19] as previously reported for compound **1**.[13] HCT116 $p53^{wt}$ and $p53^{-/-}$ tumor cells were incubated with **2** for 16 h, and the percentage of cell-growth inhibition was measured in a BrdU proliferation assay. The BrdU selectivity data demonstrated that **2** has remarkable p53-dependent cellular inhibition (Figure 4). It displayed substantial growth inhibition of wild-type p53 cells (IC_{50} = 10 nM) and no growth inhibition of p53-deficient cells (IC_{50} > 25 μM).

In the pharamacodynamic assay[20] with MDM2-amplified SJSA-1 osteosarcoma tumor cells, compound **2** demonstrated

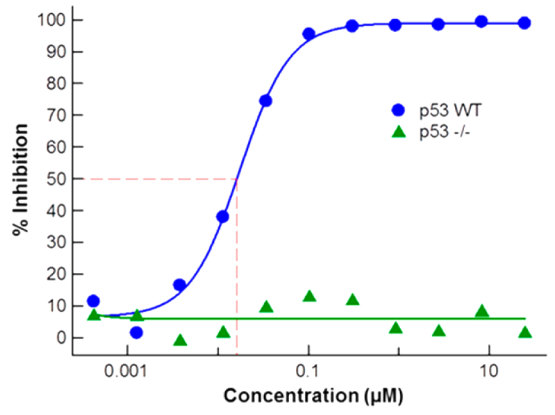


Figure 4. Cell activity of **2** is p53 dependent. In HCT116 $p53^{wt}$ and $p53^{-/-}$ cells, the percentage of BrdU positive cells was measured 16 h post compound treatment by flow cytometry. DMSO control was designated as 0% inhibition.

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significant time and concentration dependent p21 induction relative to the vehicle control, consistent with observations previously reported for compound **1**.[13] A 30-fold induction of p21 mRNA was observed 4 h after the last dose after QD adminstration for 4 days at 50 mg/kg (Figure 5). This data indicated that compound **2** achieves an on-target activation of the p53 pathway.

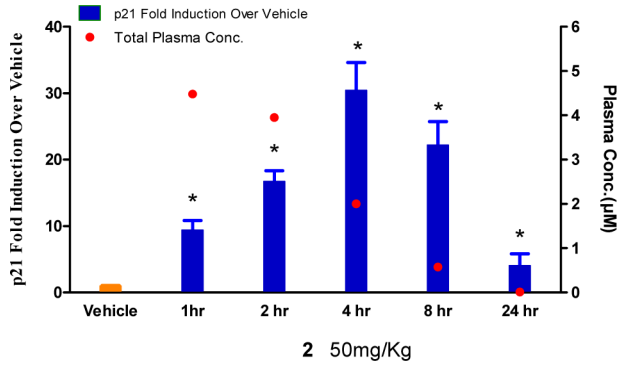

Figure 5. Pharmacodynamic study: treatment with **2** caused time and concentration dependent induction of p21 mRNA in SJSA-1 tumor xenografts. *p < 0.05. Female athymic nude mice were implanted subcutaneously with 5×10^6 SJSA-1 cells. When tumors reached ~175 mm^3, 50 mg/kg of **2** or vehicle was administered orally once daily (QD) for 4 days. Mice were sacrificed on day 4 at 1, 2, 4, 8, and 24 h postdose (n = 5/group). Tumors were immediately removed and snap-frozen. p21 mRNA levels were measured by quantitative RT-PCR. Tumors treated with vehicle served as a negative control and indicated the baseline p21 mRNA level. Data are represented as mean p21 fold induction over vehicle and error bars represent SEM of data from five mice. Concentrations in plasma were analyzed by LC/MS/MS.

In the SJSA-1 osteosarcoma xenograft model, treatment with **2** significantly inhibited tumor growth at each dose compared to the vehicle with an ED_{50} of 9.1 mg/kg (Figure 6). Unbound EC_{50} associated with ED_{50} was calculated as 2.8 nM.[21] The 60 mg/kg QD dose of **2** caused complete tumor regression in 10 of 12 mice.

While cocrystallization attempts of **2** with human MDM2 protein unfortunately proved unsuccessful, the cocrystal structure of **25**, an analogue of **2**, was obtained by X-ray

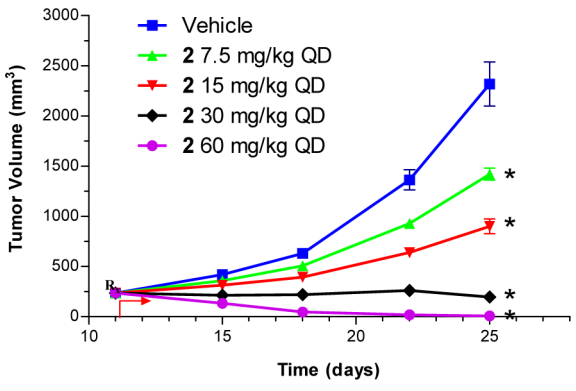

Figure 6. Treatment with **2** inhibited the growth of SJSA-1 tumors in vivo. * p < 0.05. SJSA-1 cells (5×10^6) were implanted subcutaneously into female athymic nude mice. Treatment with vehicle or **2** at 7.5, 15, 30, or 60 mg/kg QD by oral gavage began on day 11 when tumors had reached ~200 mm^3 (n = 12/group). Tumor sizes were measured twice per week. Data represent mean tumor volumes, and the error bars represent SEM of data from 12 mice.

crystallography to a resolution of 1.7 Å (Figure 7).[22] **25** occupies the three critical binding pockets as was seen with the earlier

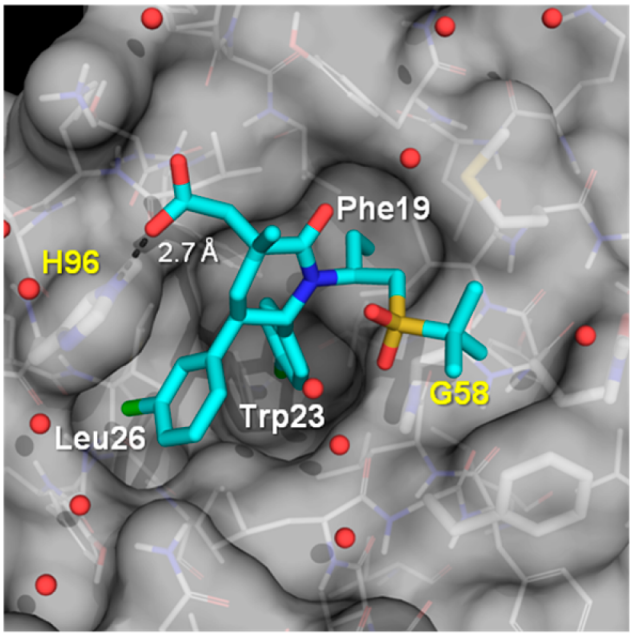

Figure 7. Cocrystal structure of **25** bound to human MDM2 (17−111) at 1.7 Å resolution. White labels indicate positions normally occupied by key p53 residues. H96 and G58 are labeled in yellow. Cocrystallized water molecules are shown in red. PDB code: 4OAS.

structures with **1** and other piperidinone compounds.[13] The C5 aryl group fills the Leu26 $_{(p53)}$ pocket and engages in a face-to-face π-stacking interaction with H96, while the C6 aryl group occupies the Trp23 $_{(p53)}$ binding cavity. The ethyl group is directed into the Phe19 $_{(p53)}$ pocket by the conformational constraint induced by the α-substitution. Additionally, the carboxylate of **25** interacts with the imidazole on the H96 side chain of MDM2.

The lactam side chain plays an important role in the enhanced potency of **25**, as illustrated in the bound structure. The sulfone moiety properly projects the t-butyl group to the glycine shelf region to maximize the hydrophobic contact while the ethyl moiety binds to the $Phe19_{(p53)}$ pocket. In addition, the sulfone function is situated ca. 3.5 Å from the α-carbon of G58, suggesting a CH···O type interaction with this residue.[23]

To confirm the absolute and relative stereochemical assignments of **2**, the single crystal structure was obtained, and the unit cell containing **2** and ethanol is shown in Figure 8 with a resolution of 0.84 Å.[24] Superimposition of **2** onto the cocrystal structure of **25** (Figure 9) illustrates that the binding conformation of **25** is essentially identical to the conformation of **2** crystallized in the absence of protein. The sulfone side chain is bound in the extended low energy conformation. This observation confirms and validates our previously reported efforts to stabilize the conformation of both the core and substituents in this piperidinone class of inhibitors,[13] predisposing the inhibitor for optimal MDM2 binding with minimal conformational cost.

CHEMISTRY

The synthesis of alcohol and nitrile derivatives (**3**−**9**) is described in Schemes 1−3. Aldehyde intermediate **44** was obtained via an asymmetric synthetic route reported previ-

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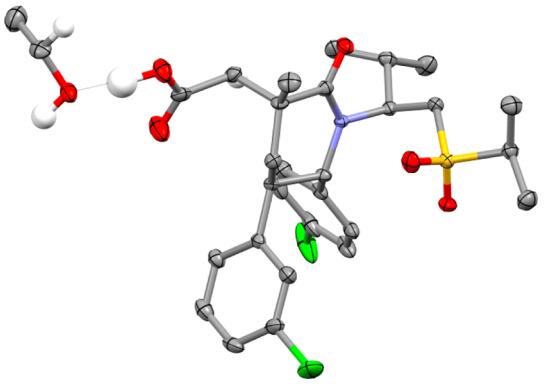


Figure 8. Single crystal structure of **2** with ethanol highlighting an intermolecular hydrogen bond between the two components.

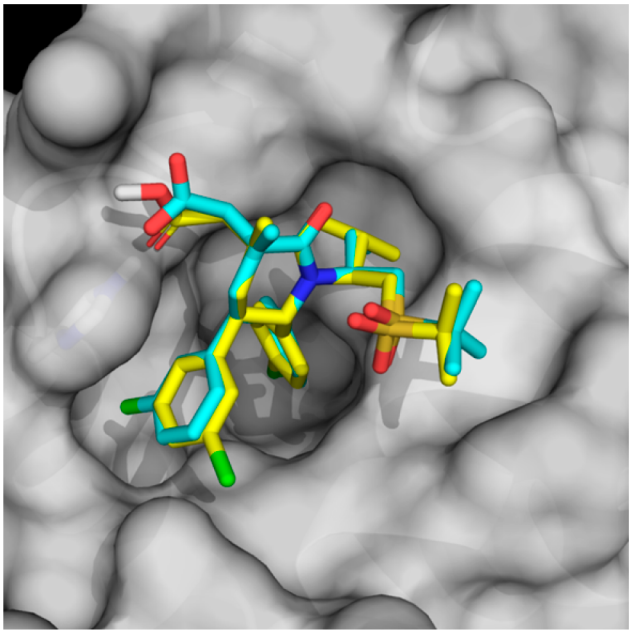


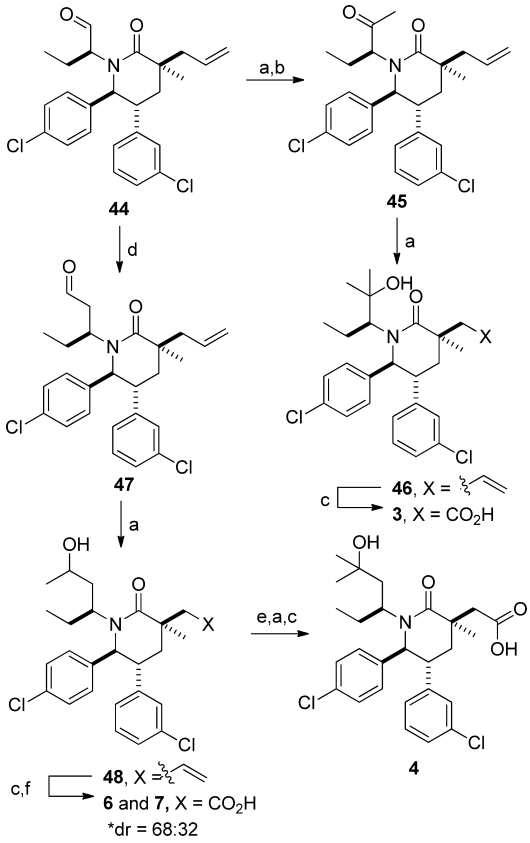
Figure 9. Single crystal structure of **2** aligned with cocrystal structure of **25** with MDM2 (PDB: 4OAS). **2** is shown in yellow and **25** is shown in blue.

ously.[25] Grignard reaction of **44** with CH_3MgBr, followed by a Swern oxidation, afforded ketone **45**. Grignard reaction of **45** with CH_3MgBr and oxidative cleavage of the alkene in **46** with catalytic ruthenium tetraoxide provided acid **3**. In a similar manner, conversion of **44** to the homologated aldehyde **47** via vinyl ether formation was followed by sequential transformations to yield alcohols **4**, **6**, and **7** (Scheme 1).

Similarly, the two-carbon homologated tertiary alcohol **5** was synthesized from the aldehyde **47** via methyl ketone **49** (Scheme 2). Conversion of **47** into the primary amide **50**, followed by dehydration under $(CF_3CO)_2O$ and TEA conditions, provided nitrile **8** (Scheme 2).

The synthesis of α,α-dimethyl cyano compound **9** started with oxidation of the alkene of **51**[13] to a 1,2-diol. Protection of the diol as its acetonide, followed by conversion of the ester to the aldehyde, gave **52**. Finally, compound **9** was obtained by a Horner–Wadsworth–Emmons reaction of **52** with diethyl cyanomethylphosphonate, followed by reduction of the alkene, methylation of the cyanide, deprotection of the acetonide group, and oxidation of the diol (Scheme 3).

Scheme 1[a]



[a]Reagents and conditions: (a) CH_3MgBr, 25 °C, 43–100%; (b) $(COCl)_2$, TEA, DMSO, −60 °C, 100%; (c) $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$, 22–78%; (d) KHMDS, $Ph_3P^+CH_2OCH_3Cl^-$; 3 N aq HCl, 90%; (e) Dess–Martin periodinane, 79–93%; (f) $NaBH_4$, 91%.

Sulfonamides **10**–**16** were synthesized as shown in Scheme 4. Reductive amination of aldehyde **44** with $PMBNH_2$, followed by removal of the PMB group afforded primary amine **54**. Sulfonylation of the amine in **54** with MsCl and oxidative cleavage of the alkene gave methyl sulfonamide **10**. Alternatively, Mitsunobu reaction of primary alcohols **55**–**57** with various sulfonamides ($R^1SO_2NHR^2$) in the presence of CMBP[26] provided compounds **11**–**16**. The synthesis of primary alcohol **55** was previously reported.[25] Alcohols **56**–**57** and **61**–**64** were prepared according to the procedures described for the synthesis of **55**, replacing (*S*)-(+)-2-amino-1-butanol with the appropriate amino alcohols.[27]

Scheme 5 describes the synthesis of the reverse sulfonamides **17**–**19**. Protection of the primary alcohol **56**, followed by conversion of the alkene to the methyl ester, gave **58**. Mitsunobu reaction of **58** with benzyl mercaptan in the presence of CMBP provided benzyl sulfide **59**. Transformation of benzyl sulfide **59** into a sulfonyl chloride in the presence of iodosobenzene and HCl[28] was followed by the reaction of this sulfonyl chloride with the various amines to afford compounds **17**–**19**.

Sulfone derivatives (**2**, **20**, and **22**–**43**), having a one carbon spacer between the sulfone moiety and the methine adjacent to the ring nitrogen, were synthesized either via a Mitsunobu reaction of primary alcohols **55**–**57** and **61**–**64** with various thiols in the presence of CMBP (Scheme 6) or via a nucleophilic ring-opening reaction of the bicyclic iminium ether[25] derived

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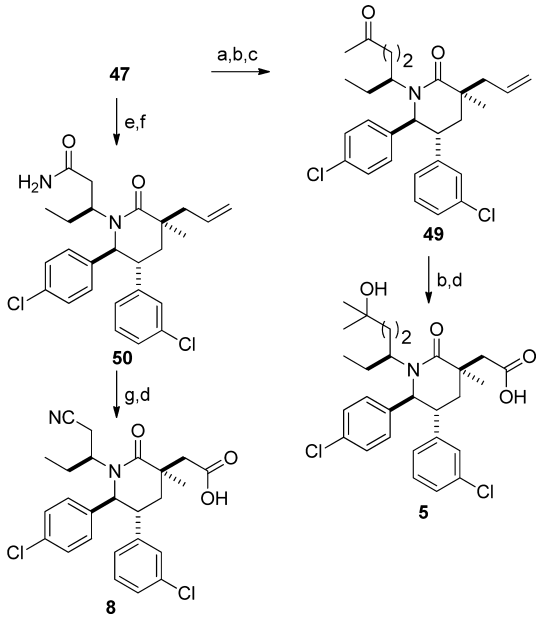
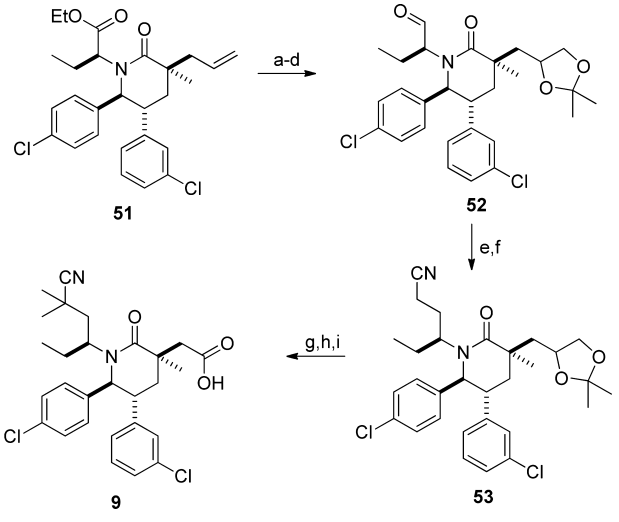
Scheme 2[a]



[a]Reagents and conditions: (a) KHMDS, $Ph_3P^+CH_2OCH_3Cl^-$; 3 N aq HCl, 76%; (b) MeMgBr, 25 °C, 98−100%; (c) Dess−Martin periodinane, 97%; (d) $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$, 55−75%; (e) NaH_2PO_4, $NaClO_2$, 27%; (f) isobutyl chloroformate, *N*-methylmorpholine, NH_4OH, 98%; (g) $(CF_3CO)_2O$, TEA, 56%.

Scheme 3[a]

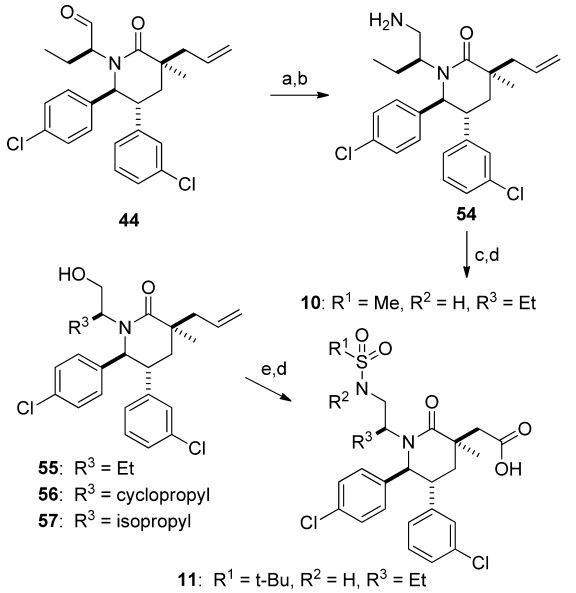


[a]Reagents and conditions: (a) OsO_4, NMO, 66%; (b) 2,2-dimethoxypropane, TsOH monohydrate, 91%; (c) $LiBH_4$, 100%; (d) Dess−Martin periodinane, 85%; (e) diethyl cyanomethylphosphonate, DMPU, NaH, 96%; (f) H_2, Pd/C, 58%; (g) CH_3I, LiHMDS, 63%; (h) 3 N aq HCl, 100%; (i) $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$, 65%.

from the primary alcohols **55**−**57** and **61**−**63**, with either thiolates or sulfinic acid sodium salts (Scheme 7).

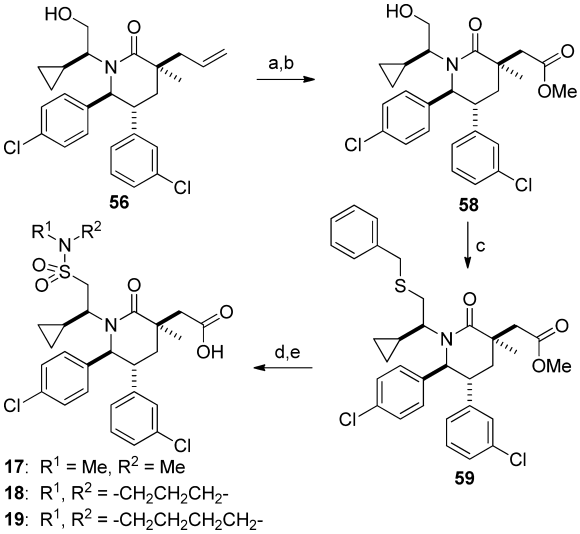
Finally, compound **21**, a sulfone derivative containing a two-carbon spacer, was prepared from a Horner−Wadsworth−Emmons reaction of **52** with diethyl methylsulfonylmethyl-phosphonate, followed by hydrogenation and removal of the acetonide group (Scheme 8).

Scheme 4[a]



[a]Reagents and conditions: (a) $PMBNH_2$, $NaBH(OAc)_3$, DCE, 100%; (b) ceric ammonium nitrate, H_2O/CH_3CN, 53%; (c) MsCl, pyridine, 47%; (d) $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$, 32−62%; (e) $R^1SO_2NHR^2$, CMBP, toluene, 50−90%.

Scheme 5[a]



[a]Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 92%; (b) $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$, 2 M (trimethylsilyl)diazomethane in Et_2O, 1 M TBAF in THF, 53%; (c) $PhCH_2SH$, CMBP, toluene, 81%; (d) iodosobenzene, HCl, R_1R_2NH, 54−79%; (e) LiOH, 56−71%.

CONCLUSION

In summary, research investigation of **1** led to the discovery of sulfone analogues that feature substantial improvements in biochemical and cellular potency. The enhanced potency of the sulfone-derived inhibitors can be rationalized by the favorable

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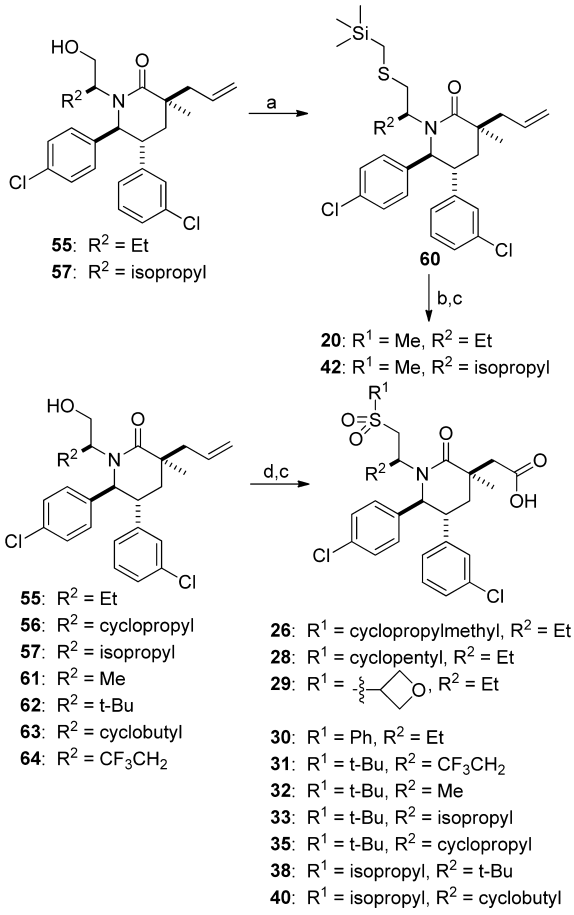
Scheme 6[a]



55: R^2 = Et
57: R^2 = isopropyl

20: R^1 = Me, R^2 = Et
42: R^1 = Me, R^2 = isopropyl

55: R^2 = Et
56: R^2 = cyclopropyl
57: R^2 = isopropyl
61: R^2 = Me
62: R^2 = t-Bu
63: R^2 = cyclobutyl
64: R^2 = CF_3CH_2

26: R^1 = cyclopropylmethyl, R^2 = Et
28: R^1 = cyclopentyl, R^2 = Et
29: R^1 = , R^2 = Et

30: R^1 = Ph, R^2 = Et
31: R^1 = t-Bu, R^2 = CF_3CH_2
32: R^1 = t-Bu, R^2 = Me
33: R^1 = t-Bu, R^2 = isopropyl
35: R^1 = t-Bu, R^2 = cyclopropyl
38: R^1 = isopropyl, R^2 = t-Bu
40: R^1 = isopropyl, R^2 = cyclobutyl

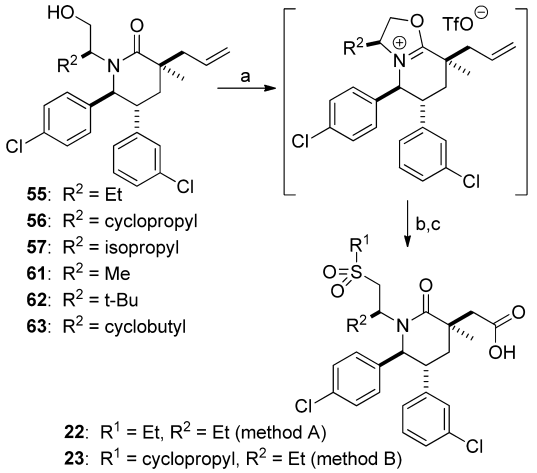
[a]Reagents and conditions: (a) $TMSCH_2SH$, CMBP, toluene, 40−50%; (b) 1 M TBAF in THF, 45−57%; (c) $NaIO_4$, $RuCl_3$, CH_3CN/CCl_4/H_2O, 30−62%; (d) R^1SH, CMBP, toluene, 32−91%.

hydrophobic interaction between the alkyl sulfone and the glycine shelf, which was observed in the cocrystal structure of **25** with MDM2. Further investigation efforts produced **2**, a highly potent MDM2 inhibitor (SPR K_D = 0.045 nM, EdU IC_{50} = 9.1 nM), with remarkable pharmacokinetic properties and in vivo antitumor activity in the SJSA-1 osteosarcoma xenograft model (ED_{50} = 9.1 mg/kg). Compound **2** is being evaluated in human clinical trials for the treatment of cancer.[12]

EXPERIMENTAL SECTION

General Chemistry. All reactions were conducted under an inert gas atmosphere (nitrogen or argon) using a Teflon-coated magnetic stir bar at the temperature indicated. Commercial reagents and anhydrous solvents were used without further purification. Removal of solvents was conducted by using a rotary evaporator, and residual solvent was removed from nonvolatile compounds using a vacuum manifold maintained at approximately 1 Torr. All yields reported are isolated yields. Preparative reversed-phase high pressure liquid chromatography (RP-HPLC) was performed using an Agilent 1100 series HPLC and Phenomenex Gemini C18 column (5 μm, 100 mm × 30 mm i.d.), eluting with a binary solvent system A and B using a gradient elusion (A, H_2O with 0.1% trifluoroacetic acid (TFA); B, CH_3CN with 0.1% TFA) with UV detection at 220 nm. All bioassayed compounds were purified to ≥95% purity as determined by an Agilent 1100 series HPLC with UV detection at 220 nm using the following method: Zorbax SB-C8 column (3.5 μm, 150 mm × 4.6 mm i.d.); mobile phase, A = H_2O with 0.1% TFA, B = CH_3CN with 0.1% TFA; gradient, 5−95% B (0.0−15.0 min); flow rate, 1.5 mL/min. Low-resolution mass spectral (MS) data were

Scheme 7[a]

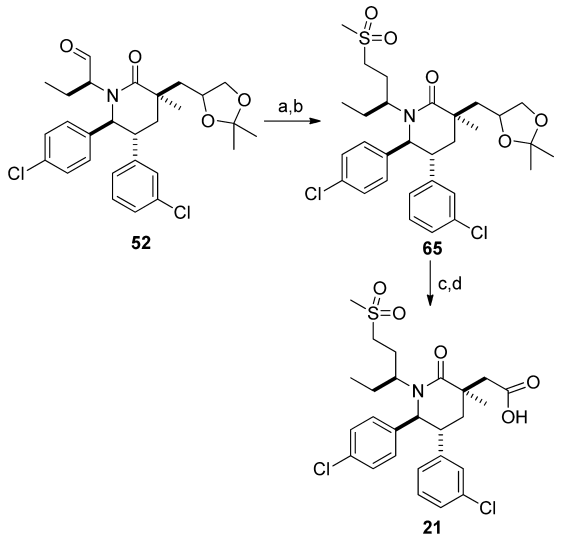


55: R^2 = Et
56: R^2 = cyclopropyl
57: R^2 = isopropyl
61: R^2 = Me
62: R^2 = t-Bu
63: R^2 = cyclobutyl

22: R^1 = Et, R^2 = Et (method A)
23: R^1 = cyclopropyl, R^2 = Et (method B)
24: R^1 = isopropyl, R^2 = Et (method C w/ Cs_2CO_3)
25: R^1 = t-Bu, R^2 = Et (method C w/ K_2CO_3)
27: R^1 = cyclobutyl, R^2 = Et (method B)
34: R^1 = t-Bu, R^2 = t-Bu (method C w/ NaH)
36: R^1 = t-Bu, R^2 = cyclobutyl (method C w/ K_2CO_3)
37: R^1 = isopropyl, R^2 = Me (method C w/ NaH)
2: R^1 = isopropyl, R^2 = isopropyl (method B)
39: R^1 = isopropyl, R^2 = cyclopropyl (method C w/ Na_2CO_3)
41: R^1 = Me, R^2 = Me (method B)
43: R^1 = Me, R^2 = cyclopropyl (method B)

[a]Reagents and conditions: (a) Tf_2O, 2,6-dimethylpyridine, −40 to 0 °C, 100%; (b) method A, R^1SNa, DMF, 82%; method B, $R^1S(O)ONa$, AcCN, 37−80%; method C, R^1SH, base, DMF, 27−84%; (c) $NaIO_4$, $RuCl_3$, CH_3CN/CCl_4/H_2O, 37−68%.

Scheme 8[a]



52

65

21

[a]Reagents and conditions: (a) *n*-BuLi, diethyl methylsulfonylmethylphosphonate, 70%; (b) H_2, Pd/C, 83%; (c) TFA, THF, 64%; (d) $NaIO_4$, $RuCl_3$, CH_3CN/CCl_4/H_2O, 55%.

determined on an Agilent 1100 series LCMS with UV detection at 254 nm and a low resolution electrospray mode (ESI). High-resolution mass spectra (HRMS) were obtained on an Agilent 6510 Q-TOF MS with a Agilent 1200 LC on the front end. ^1H NMR spectra were obtained on a Bruker Avance III 500 (500 MHz) or Bruker Avance II 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s =

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single; d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad.

(3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-2-oxopentan-3-yl)piperidin-2-one (45). To a solution of **44** (258 mg, 0.581 mmol) in THF (5.8 mL) was added methylmagnesium bromide (1.4 M in toluene/tetrahydrofuran (75/25), 1.24 mL, 1.74 mmol) at 0 °C. The reaction was allowed to warm to 25 °C. After being stirred at 25 °C for 3 h, the reaction was quenched (satd NH_4Cl), extracted (3 × EtOAc), and washed (2 × water and 1 × brine). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 30%, 40%, and 50% EtOAc/hexanes) to provide (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((3*S*)-2-hydroxypentan-3-yl)-3-methylpiperidin-2-one (200 mg, 0.434 mmol, 75%) as a mixture of two diastereomers. MS (ESI) 460.0 $[M + H]^+$.

To a solution of oxalyl dichloride (78.0 μL, 0.869 mmol) in DCM (1.5 mL) at −60 °C was added a solution of DMSO (93.0 μL, 1.30 mmol) in DCM (1.5 mL) under nitrogen. After being stirred for 2 min, a solution of the alcohol above (200 mg, 0.434 mmol) in DCM (1.5 mL) was added and the resulting solution was stirred for 15 min at −60 °C. Triethylamine (305 μL, 2.17 mmol) was added to the reaction solution. After being stirred at 25 °C for 20 min, the reaction was quenched (water), extracted (2 × EtOAc), washed (2 × brine), and dried (Na_2SO_4). The organic solution was concentrated under reduced pressure and the residue was purified by flash column chromatography (SiO_2, 20% and 30% EtOAc/hexanes) to provide **45** (200 mg, 0.436 mmol, 100%) as a colorless foam. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.23 (d, J = 8.8 Hz, 2 H), 7.07−7.17 (m, 2 H), 6.91−7.07 (m, 3 H), 6.78 (dt, J = 7.4, 1.6 Hz, 1 H), 5.80−5.94 (m, 1 H), 5.16−5.24 (m, 2 H), 4.52 (d, J = 10.8 Hz, 1 H), 3.32 (ddd, J = 13.6, 10.7, 3.1 Hz, 1 H), 3.11 (dd, J = 7.0, 5.7 Hz, 1 H), 2.62 (d, J = 7.4 Hz, 2 H), 2.20 (t, J = 13.7 Hz, 1 H), 2.15 (s, 3 H), 2.05−2.13 (m, 1 H), 1.98 (dd, J = 13.8, 3.2 Hz, 1 H), 1.79 (ddd, J = 14.0, 7.9, 5.7 Hz, 1 H), 1.27 (s, 3 H), 0.64 (t, J = 7.5 Hz, 3 H). MS (ESI) 458.0 $[M + H]^+$.

(3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-2-hydroxy-2-methylpentan-3-yl)-3-methylpiperidin-2-one (46). A solution of methylmagnesium bromide (1.4 M in toluene, 0.623 mL, 0.873 mmol) was added to a solution of **45** (0.100 g, 0.218 mmol) in THF (4 mL) was added at 0 °C. The reaction was allowed to warm to 25 °C. After being stirred at 25 °C for 4 h, an additional methylmagnesium bromide (0.156 mL, 0.218 mmol) was added and the reaction was stirred for another 2 h. The reaction was quenched (satd NH_4Cl), and extracted (EtOAc). The combined organic layers were washed (brine), dried ($MgSO_4$), and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 40% EtOAc/hexanes) to provide **46** (44.0 mg, 43%) as a light-yellow oil. MS (ESI) 474.2 $[M + H]^+$.

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-2-hydroxy-2-methylpentan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (3). To a rapidly stirring solution of **46** (0.044 g, 0.093 mmol) in H_2O/CCl_4/MeCN (0.9 mL:0.45 mL:0.45 mL) was added sodium periodate (0.079 g, 0.371 mmol), followed by ruthenium(III) chloride hydrate (2.09 mg, 9.27 μmol). After being stirred vigorously for 36 h, the reaction was acidified (10% citric acid) and diluted (DCM). The insoluble material was filtered through Celite to remove. The filtrate was extracted (2 × DCM) and the combined organic layers were washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 40% EtOAc/hexanes) to give **3** (10.0 mg, 22%) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.21−7.38 (m, 2 H), 7.01−7.21 (m, 4 H), 6.95 (m, 1 H), 6.73 (dt, J = 1.52, 7.53 Hz, 1 H), 4.40 (d, J = 10.56 Hz, 1 H), 3.24−3.37 (m, 1 H), 2.78−2.95 (m, 2 H), 2.44−2.55 (m, 1 H), 2.10−2.31 (m, 3 H), 1.68 (m, 1 H), 1.50 (s, 3 H), 1.35 (s, 3 H), 1.10 (s, 3 H), 0.37 (t, J = 7.63 Hz, 3 H). HRMS (ESI) m/z 492.1708 $[M + H]^+$ ($C_{26}H_{31}Cl_2NO_4$ requires 492.1703).

(*S*)-3-((3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)pentanal (47). To a solution of dried (methoxymethyl)triphenylphosphonium chloride (1.96 g, 5.71 mmol) in THF (10 mL) was added KHMDS (0.5 M in toluene, 10.2 mL, 5.08 mmol) at −78 °C. The color of the solution turned blood red. After the mixture was stirred at 0 °C for 30 min, a solution of **44** (564 mg, 1.27 mmol) in THF (10 mL) was added at 0 °C dropwise. After being stirred at 25 °C for 12 h, the reaction was quenched (satd NH_4Cl), extracted (2 × EtOAc), and washed (brine). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 15% and 20% EtOAc/hexanes) to provide a crude vinyl ether.

To a solution of the crude product above in acetonitrile (7.8 mL) was added 3 N hydrochloric acid (4.4 mL, 13.0 mmol), and the resulting solution was stirred at 25 °C for 1.5 h. The reaction was extracted (2 × EtOAc) and washed (brine). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide **47** (2.09 g, 90%) as a pale-yellow film. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.82 (s, 1 H), 7.24 (d, J = 8.4 Hz, 2 H), 7.08−7.18 (m, 2 H), 7.05 (d, J = 7.8 Hz, 2 H), 6.99 (s, 1 H), 6.80 (d, J = 7.2 Hz, 1 H), 5.76−5.95 (m, 1 H), 5.09−5.24 (m, 2 H), 4.74 (d, J = 10.6 Hz, 1 H), 3.46−3.63 (m, 1 H), 3.06−3.24 (m, 2 H), 2.45−2.69 (m, 3 H), 1.97 (d, J = 19.6 Hz, 1 H), 1.81−1.94 (m, 2 H), 1.33−1.47 (m, 1 H), 1.19 (s, 3 H), 0.46 (t, J = 7.5 Hz, 3 H). MS (ESI) 458.0 $[M + H]^+$.

(3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((3*S*)-5-hydroxyhexan-3-yl)-3-methylpiperidin-2-one (48). To a solution of **47** (540 mg, 1.18 mmol) in THF (12 mL) was added methyl magnesium bromide (1.4 M in toluene, 2.52 mL, 3.53 mmol) at 0 °C. The reaction was allowed to warm to 25 °C and stirred for 3 h. The reaction was quenched (satd NH_4Cl), extracted (2 × EtOAc), and washed (brine). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide **48** (558 mg, 100%) as a mixture of diastereomers.

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((3*S*,5*R*)-5-hydroxyhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)-acetic Acid (6) and 2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((3*S*,5*S*)-5-hydroxyhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (7). 2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((*S*)-5-oxohexan-3-yl)piperidin-3-yl)acetic acid was prepared as a white foam from **48** according to a similar procedure described for the synthesis of **3**. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.23−7.27 (m, 2 H), 7.06−7.17 (m, 4 H), 7.00 (t, J = 1.8 Hz, 1 H), 6.81 (s, 1 H), 4.92 (d, J = 10.8 Hz, 1 H), 3.54−3.63 (dd, J = 12.0, 12.0 Hz,1 H), 3.07 (m, 3 H), 2.67 (d, J = 15.8 Hz, 1 H), 2.50−2.60 (dd, J = 4.0, 12.0 Hz, 1 H), 2.19 (s, 3 H), 2.12 (t, J = 12.0 Hz, 1 H), 1.97−2.07 (m, 1 H), 1.88−1.96 (m, 1 H), 1.39 (s, 3 H), 1.21−1.32 (m, 1 H), 0.37 (t, J = 7.5 Hz, 3 H). MS (ESI) 490.0 $[M + H]^+$, 488.0 $[M - H]^-$.

To a solution of the keto acid above (24.0 mg, 0.049 mmol) in ether (0.4 mL) and MeOH (0.1 mL) was added sodium borohydride (9.26 mg, 0.245 mmol) at 0 °C. The reaction was allowed to warm to 25 °C. After being stirred at 25 °C for 1 h, the reaction was quenched (10% citric acid) and extracted (2 × EtOAc). The combined organic layers were washed (brine), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by RP-HPLC (30−70% A/B, gradient elution) to provide **6** as the more polar isomer. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.22−7.27 (m, 2 H), 7.07−7.19 (m, 2 H), 6.95−7.06 (m, 3 H), 6.71 (dt, J = 7.6, 1.6 Hz, 1 H), 4.57 (d, J = 10.2 Hz, 1 H), 3.77−3.89 (m, 1 H), 2.99−3.15 (m, 2 H), 2.69 (d, J = 14.9 Hz, 1 H), 2.23 (t, J = 13.6 Hz, 1 H), 1.81−1.99 (m, 2 H), 1.52−1.64 (m, 1 H), 1.47 (s, 3 H), 1.39 (d, J = 2.0 Hz, 1 H), 1.28 (m, 1 H), 1.19 (d, J = 6.3 Hz, 3 H), 0.60 (t, J = 7.4 Hz, 3 H). HRMS (ESI) m/z 492.1709 $[M + H]^+$ ($C_{26}H_{31}Cl_2NO_4$ requires 492.1703). Further elution provided **7** as the less polar isomer. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.04−7.27 (m, 5 H), 6.91−7.04 (m, 2 H), 6.70 (dt, J = 7.7, 1.5 Hz, 1 H), 4.47 (d, J = 10.4 Hz, 1 H), 3.75 (ddd, J = 12.4, 6.1, 0.7 Hz, 1 H), 3.15−3.27 (m, 1 H), 2.96 (d, J = 14.5 Hz, 1 H), 2.76 (d, J = 14.7 Hz, 1 H), 2.18 (t, J = 13.8 Hz, 1 H), 2.02−2.09 (m, 1 H), 1.59−1.71 (m, 2 H), 1.50 (s, 3 H), 1.26 (dd, J = 16.8, 6.8 Hz, 1 H), 1.08−1.21 (m, 1 H), 0.99−1.07 (m, 3 H), 0.89 (s, br, 3 H). HRMS (ESI) m/z 492.1709 $[M + H]^+$ ($C_{26}H_{31}Cl_2NO_4$ requires 492.1703).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-5-hydroxy-5-methylhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (4). To a solution of **48** (100 mg, 0.211 mmol) and water (5.70 μL, 0.316 mmol) in DCM (2.3 mL) was added Dess−Martin periodinane (134 mg, 0.316 mmol) at 25 °C. After being stirred at 25 °C

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for 40 min, the reaction was quenched (1 M $Na_2S_2O_3$, 2 mL), extracted (2 × DCM), and washed (2 × satd $NaHCO_3$ and brine). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 25% and 30% EtOAc/hexanes) to afford (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-5-oxohexan-3-yl)-piperidin-2-one (93.0 mg, 93%) as a colorless film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 2 H), 7.03−7.17 (m, 4 H), 6.93−7.01 (m, 1 H), 6.84 (s, 1 H), 5.78−5.94 (m, 1 H), 5.18 (d, J = 3.9 Hz, 1 H), 5.15 (s, 1 H), 4.80 (d, J = 10.8 Hz, 1 H), 3.55−3.68 (m, 1 H), 2.98−3.20 (m, 2 H), 2.58 (s, 3 H), 2.18 (s, 3 H), 1.93−2.05 (m, 1 H), 1.83−1.92 (m, 2 H), 1.28−1.37 (m, 1 H), 1.18 (s, 3 H), 0.40 (t, J = 7.5 Hz, 3 H). MS (ESI) 472.1 $[M + H]^+$.

Compound **4** was prepared as a white foam from ((3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-5-oxohexan-3-yl)piperidin-2-one according to a similar procedure described for the synthesis of **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25 (d, J = 7.8 Hz, 2 H), 6.98−7.18 (m, 4 H), 6.95 (t, J = 1.8 Hz, 1 H), 6.70 (d, J = 7.6 Hz, 1 H), 4.90−5.38 (m, 2 H), 4.67−4.81 (m, 1 H), 3.51 (s, 1 H), 2.98−3.13 (m, 2 H), 2.70 (d, J = 15.1 Hz, 1 H), 2.19 (t, J = 13.8 Hz, 1 H), 1.93 (d, J = 13.3 Hz, 2 H), 1.48 (s, 4 H), 1.16−1.28 (m, 7 H), 0.53 (s, br, 3 H). HRMS (ESI) m/z 506.1862 $[M + H]^+$ ($C_{27}H_{33}Cl_2NO_4$ requires 506.1859).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-6-hydroxy-6-methylheptan-3-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (5). Compound **5** was prepared as a white solid from **47** according to a similar procedure described for the synthesis of **4**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25 (d, J = 8.4 Hz, 2 H), 7.16 (dd, J = 1.9, 1.1 Hz, 1 H), 7.11 (d, J = 7.6 Hz, 1 H), 6.94 (t, J = 1.8 Hz, 3 H), 6.70 (d, J = 7.6 Hz, 1 H), 5.01−5.25 (m, 2 H), 4.37 (d, J = 10.4 Hz, 1 H), 3.06 (d, J = 15.3 Hz, 2 H), 2.93−3.03 (m, 1 H), 2.71 (d, J = 15.3 Hz, 1 H), 2.20 (s, 1 H), 2.02 (s, 1 H), 1.78−1.97 (m, 2 H), 1.37−1.56 (m, 6 H), 1.22 (d, J = 5.5 Hz, 6 H), 0.55 (t, J = 7.5 Hz, 3 H). HRMS (ESI) m/z 520.2024 $[M + H]^+$ ($C_{28}H_{35}Cl_2NO_4$ requires 520.2016).

(*S*)-3-((3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)pentanamide (50). To a solution of **47** (147 mg, 0.321 mmol) in 2-methylpropan-2-ol/2-methyl-2-butene (3: 1, 4.4 mL) was added a solution of sodium chlorite (290 mg, 3.21 mmol) and dihydrogen sodium phosphate (17.3 μL, 0.289 mmol) in water (1.6 mL). After being stirred at rt for 20 min, the reaction was quenched (satd NH4Cl), diluted (EtOAc), washed (brine), dried ($MgSO_4$), and concentrated to give (*S*)-3-((3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)-pentanoic acid (41.0 mg, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25 (m, 2 H), 7.00−7.20 (m, 4 H), 6.95 (s, 1 H), 6.75 (d, J = 8.0 Hz, 1 H), 5.85 (m, 1 H), 5.15−5.25 (m, 2 H), 4.65 (d, J = 8.0 Hz, 1 H), 3.35 (m, 1 H), 3.10−3.25 (m, 2 H), 2.63 (m, 2 H), 2.50 (dd, J = 4.0, 12.0 Hz, 1 H), 1.85−2.10 (m, 3 H), 1.45 (m, 1 H), 1.25 (s, 3 H), 0.50 (t, J = 8.0 Hz, 3 H).

To a solution of the acid above (40.0 mg, 0.084 mmol) and 1-methylmorpholine (13.0 μL, 0.118 mmol) in THF (0.5 mL) was added isobutyl chlorocarbonate (13.1 μL, 0.101 mmol) followed by aqueous ammonium hydroxide (28%, 11.2 mL, 0.169 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the reaction was quenched (satd NH_4Cl), diluted (EtOAc), washed (brine), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (SiO_2, 30−50% EtOAc/hexanes, gradient elution) to give **50** (39.0 mg, 98%). MS (ESI) 473.2 $[M + H]^+$.

(*S*)-3-((3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)pentanenitrile (8). A solution of **50** (39.0 mg, 0.082 mmol) and triethylamine (57.3 μL, 0.412 mmol) in THF (1.2 mL) was treated with trifluoroacetic anhydride (28.8 μL, 0.206 mmol) at 0 °C. After being stirred at 0 °C for 1.5 h, the reaction was warmed to 25 °C and stirred for another 1 h. The reaction was quenched (satd NH_4Cl), extracted (EtOAc), washed (brine), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (SiO_2, 20% EtOAc/hexanes) to provide (*S*)-3-((3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)pentanenitrile (21.0 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.20−7.28 (m, 2 H), 7.10−7.20 (m, 2 H), 6.95−7.08 (m, 2 H), 6.93 (s, 1 H), 6.84 (d, J = 8.0 Hz, 1 H), 5.88 (m, 1 H), 5.15−5.25 (m, 2 H), 4.65 (d, J = 8.0 Hz, 1 H), 3.45 (dd, J = 8.0, 12.0 Hz, 1 H), 3.19 (m, 1 H), 2.94 (m, 1 H), 2.63 (m, 2 H), 2.35 (dd, J = 4.0, 12.0 Hz, 1 H), 2.22 (t, J = 12 Hz, 1 H), 1.95−2.15 (m, 1 H), 1.95 (dd, J = 4.0, 12 Hz, 1 H), 1.55 (m, 1 H), 1.32 (s, 3 H), 0.50 (t, J = 8.0 Hz, 3 H).

Compound **8** was prepared from the nitrile above according to a similar procedure described for the synthesis of **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.20−7.28 (m, 2 H), 7.00−7.18 (m, 4 H), 6.95 (s, 1 H), 6.82 (d, J = 8.0 Hz, 1 H), 4.65 (d, J = 8.0 Hz, 1 H), 3.42 (dd, J = 8.0, 12.0 Hz, 1 H), 3.20 (m, 1 H), 2.90−3.05 (m, 3 H), 2.42 (dd, J = 4.0, 12.0 Hz, 1 H), 2.32 (t, J = 12 Hz, 1 H), 2.00−2.15 (m, 1 H), 1.95 (dd, J = 4.0, 12 Hz, 1 H), 1.52 (m, 1 H), 1.52 (s, 3 H), 0.48 (t, J = 8.0 Hz, 3 H). HRMS (ESI) m/z 473.1403 $[M + H]^+$ ($C_{25}H_{26}Cl_2N_2O_3$ requires 473.1393).

(2*S*)-2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-methyl-2-oxopiperidin-1-yl)butanal (52). To a solution of **51** (1.06 g, 2.23 mmol) and 4-methylmorpholine 4-oxide (393 mg, 3.35 mmol) in DCM (15.8 mL) was added osmium(VIII) oxide polymer-bound, 1% DVB (56.8 mg, 2.23 μmol). After being vigorously stirred at 25 °C for 48 h, additional osmium(VIII) oxide polymer-bound, 1% DVB (56.8 mg, 2.23 μmol) was added and the resulting solution was vigorously stirred at 25 °C for another 48 h. The resin was filtered and washed (DCM). The combined organic layers were washed (brine), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 53% and 63% EtOAc/hexanes) to provide the diol (746 mg, 66%). MS (ESI) 508.0 $[M + H]^+$.

To a solution of the product above (749 mg, 1.47 mmol) in DCM (8.2 mL) was added *p*-toluenesulfonic acid monohydrate (14.0 mg, 0.074 mmol) and 2,2-dimethoxypropane (8.15 mL, 66.3 mmol). After being stirred at 25 °C for 3 h, the reaction mixture was concentrated under reduced pressure and the residue was dissolved (EtOAc and satd $NaHCO_3$) and extracted (3 × EtOAc). The combined organic layers were washed (brine), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 27% and 37% EtOAc/hexanes) to provide the protected diol as a colorless film (732 mg, 91%). MS (ESI) 548.0 $[M + H]^+$.

To a solution of the crude product above (734 mg, 1.34 mmol) in ether (12 mL) was added lithium borohydride (58.3 mg, 2.68 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the reaction was quenched (ice cold 10% citric acid), extracted (2 × EtOAc), and washed (brine). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide (3*R*,5*R*,6*S*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1-((*S*)-1-hydroxybutan-2-yl)-3-methylpiperidin-2-one as a colorless film (693 mg, 100%). MS (ESI) 518.0 $[M + H]^+$. The crude product was used in the next step without further purification.

Compound **52** was prepared from (3*R*,5*R*,6*S*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1-((*S*)-1-hydroxybutan-2-yl)-3-methylpiperidin-2-one according to a similar procedure described for the synthesis of **49**. MS (ESI) 518.0 $[M + H]^+$.

(4*S*)-4-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-methyl-2-oxopiperidin-1-yl)hexanenitrile (53). To a solution of diethyl cyanomethylphosphonate (126 μL, 0.799 mmol) and DMPU (480 μL, 3.99 mmol) in THF (1.3 mL) was added 60% sodium hydride in mineral oil (24.0 mg, 0.599 mmol) at 0 °C. The mixture was stirred for 30 min and then treated with a solution of **52** (207 mg, 0.399 mmol) in THF (1.33 mL). After being stirred for 4 h, the reaction was quenched (water), extracted (2 × EtOAc), and washed (brine). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 30−40% EtOAc/hexanes, gradient elution) to provide the conjugated nitrile (218 mg, 96%) as a colorless liquid. MS (ESI) 541.2 $[M + H]^+$.

To a solution of the product above (208 mg, 0.384 mmol) in EtOH (13 mL) was added 10% palladium on activated carbon (40.9 mg, 0.038 mmol). The reaction mixture was stirred under a hydrogen balloon. After being stirred at 25 °C for 1.5 h, the catalyst was filtered using a short plug of silica gel and washed (EtOAc). The combined organic solutions were concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 35% and 40% EtOAc/

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hexanes) to provide **53** (120 mg, 58%) as a colorless film. MS (ESI) 543.1 $[M + H]^+$.

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-5-cyano-5-methylhexan-3-yl)-3-methyl-2-oxopiperidin-3-yl)-acetic Acid (9). To a solution of **53** (120 mg, 0.221 mmol) in THF (1.1 mL) was added lithium diisopropylamide (2 M in heptane/THF/ethylbenzene, 552 μL, 1.10 mmol) at −78 °C. After being stirred for 5 min at −78 °C, iodomethane (94.0 μL, 1.51 mmol) was added and the resulting solution was stirred at −78 °C for 30 min. The reaction was allowed to warm to 25 °C and stirred for 12 h. The reaction was quenched (satd NH_4Cl) and extracted (2 × EtOAc), and the combined organic layers were washed (brine), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 30% and 40% EtOAc/hexanes) to provide a mixture of dimethylated product and monomethylated product, which was resubjected to the methylation conditions described below.

To a solution of the crude product above in THF (1.1 mL) was added lithium diisopropylamide (2 M in heptane/THF/ethylbenzene, 552 μL, 1.10 mmol) at −78 °C. After being stirred for 5 min at −78 °C, iodomethane (94 μL, 1.51 mmol) was added and the resulting solution was stirred at −78 °C for 30 min. The reaction was allowed to warm to 25 °C and stirred for 12 h. The reaction was quenched (satd NH_4Cl) and extracted (2 × EtOAc), and the combined organic layers were washed (brine), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by RP-HPLC (60−90% A/B, gradient elution) to afford the tertiary nitrile (77.0 mg, 63%). MS (ESI) 557.2 and 571.2 $[M + H]^+$.

To a solution of the product above (77.0 mg, 0.135 mmol) in THF (2.7 mL) was added 3 N hydrochloric acid in water (1.35 μL, 4.04 mmol) at 25 °C. After being stirred at 25 °C for 4 h, the reaction was diluted (brine) and extracted (2 × EtOAc). The combined organic layers were washed (brine), dried (Na_2SO_4), and concentrated under reduced pressure to provide the corresponding diol (71.6 mg, 100%) as a colorless foam. MS (ESI) 531.2 $[M + H]^+$.

Compound **9** was prepared as a white solid from (4*S*)-4-((3*R*,5*R*,6*S*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-(2,3-dihydroxypropyl)-3-methyl-2-oxopiperidin-1-yl)-2,2-dimethylhexanenitrile according to a similar procedure described for the synthesis of **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27 (m, 2 H), 7.00−7.20 (m, 4 H), 6.97 (t, J = 1.7 Hz, 1 H), 6.82 (dt, J = 7.4, 1.4 Hz, 1 H), 4.82 (d, J = 10.6 Hz, 1 H), 3.12 (m, 1 H), 3.01 (d, J = 15.1 Hz, 1 H), 2.75 (m, 3 H), 2.54 (t, J = 12.0 Hz, 1 H), 2.03−2.12 (m, 1 H), 2.01 (s, 1 H), 1.90 (dd, J = 14.0, 2.6 Hz, 1 H), 1.52 (s, 3 H), 1.43 (s, 3 H), 1.35−1.41 (m, 1 H), 1.31 (s, 3 H), 1.23 (d, J = 13.9 Hz, 1 H), 0.33 (t, J = 7.3 Hz, 3 H). HRMS (ESI) m/z 515.1869 $[M + H]^+$ ($C_{28}H_{32}Cl_2NO_3$ requires 515.1863).

(*S*)-2-((3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butan-1-ammonium 2,2,2-trifluoroacetate (54). To a solution of **44** (300 mg, 0.675 mmol) and (4-methoxyphenyl)methanamine (131 μL, 1.01 mmol) in DCE (4.5 mL) was added sodium triacetoxyborohydride (429 mg, 2.03 mmol) at 0 °C in several portions. After being stirred at 25 °C for 18 h, the reaction was quenched (ice-cold satd aqueous $NaHCO_3$) and extracted (2 × DCM). The combined organic layers were washed (brine) and concentrated under reduced pressure to provide the PMB-protected amine (382 mg, 100%), which was used in the next step without further purification. MS (ESI) 565.2 $[M + H]^+$.

To a solution of the crude amine above (370 mg, 0.654 mmol) in acetonitrile (8 mL) and water (1.6 mL) was added ceric ammonium nitrate (2.87 g, 5.23 mmol) at 25 °C. After being stirred at rt for 2 days, the reaction was quenched (brine), extracted (3 × EtOAc), and washed (brine). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by RP-HPLC (35−70% A/B, gradient elution) to provide **54** (158 mg, 53%) as a pale-yellow powder. MS (ESI) 445.1 $[M + H]^+$.

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-1-(methylsulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic Acid (10). Lithium hydroxide (2 N aqueous solution, 0.340 mL, 0.680 mmol) was added to a solution of **54** (74.0 mg, 0.140 mmol) in DCM at 0 °C, and the resulting solution was stirred for 5 min at 0 °C. The solution was extracted (2 × DCM), washed (brine), dried (Na_2SO_4), and concentrated under reduced pressure to give the free amine. To a solution of the amine above in DMF (0.34 mL) was added methanesulfonyl chloride (53.0 μL, 0.680 mmol) and pyridine (66.0 μL, 0.820 mmol) successively at 0 °C. After being stirred at 25 °C for 12 h, the reaction was acidified (10% citric acid) and extracted (2 × EtOAc) and washed (brine). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by RP-HPLC (45−80% A/B, gradient elution) to provide *N*-((*S*)-2-((3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)butyl)methanesulfonamide (33.7 mg, 47%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.23 (d, J = 8.4 Hz, 2 H), 7.10−7.19 (m, 2 H), 7.02 (d, J = 7.0 Hz, 2 H), 6.93−6.98 (m, 1 H), 6.85 (dd, J = 6.7, 1.7 Hz, 1 H), 5.73−5.99 (m, 1 H), 5.12−5.25 (m, 2 H), 4.84−4.97 (m, 1 H), 4.71 (d, J = 10.6 Hz, 1 H), 3.53−3.68 (m, 1 H), 3.05−3.24 (m, 3 H), 2.98 (s, 3 H), 2.62 (d, J = 7.2 Hz, 2 H), 2.09−2.24 (m, 1 H), 1.90 (dd, J = 13.7, 3.1 Hz, 2 H), 1.44−1.62 (m, 1 H), 1.27 (s, 3 H), 0.58 (t, J = 7.5 Hz, 3 H). MS (ESI) 523.0 $[M + H]^+$.

Compound **10** was prepared from *N*-((*S*)-2-((3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)-butyl)methanesulfonamide according to a similar procedure described for the synthesis of **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25 (d, J = 8.2 Hz, 2 H), 7.10−7.18 (m, 2 H), 7.00−7.10 (m, 2 H), 6.97 (s, 1 H), 6.83 (d, J = 7.2 Hz, 1 H), 4.87−4.97 (m, 1 H), 4.74 (d, J = 10.4 Hz, 1 H), 3.44−3.65 (m, 1 H), 3.10−3.33 (m, 2 H), 3.02−3.09 (m, 1 H), 2.99 (s, 3 H), 2.96 (m, 1 H), 2.77 (d, J = 12.0 Hz, 1 H), 2.36 (d, J = 12.0 Hz, 1 H), 1.94−2.05 (m, 1 H), 1.77−1.92 (m, 1 H), 1.52−1.59 (m, 1 H), 1.50 (s, 3 H), 0.58 (t, J = 7.3 Hz, 3 H). HRMS (ESI) m/z 541.1333 $[M + H]^+$ ($C_{25}H_{30}Cl_2N_2O_5S$ requires 541.1325).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(1,1-dimethylethylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (11). **55** (203 mg, 0.454 mmol) and 2-methylpropane-2-sulfonamide (130 mg, 0.948 mmol) were dissolved in anhydrous toluene (4.5 mL). Cyanomethylenetributylphosphorane (451 mg, 1.68 mmol) was transferred to the reaction vessel via syringe. The reaction mixture was stirred 40 °C in a preheated oil bath, and an additional 2-methylpropane-2-sulfonamide (130 mg, 0.948 mmol) was added. After being stirred at 40 °C for 48 h, the mixture was partitioned between ethyl acetate and satd ammonium chloride. The aqueous phase was extracted (2 × EtOAc), washed (brine), dried (Na_2SO_4), and filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, 0−30% EtOAc/hexanes, gradient elution) to give *N*-((*S*)-2-((3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)-butyl)-2-methylpropane-2-sulfonamide (201 mg, 78%) as an off-white solid. MS (ESI) m/z = 565 $[M + H]^+$.

Compound **11** was prepared from *N*-((*S*)-2-((3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-1-yl)-butyl)-2-methylpropane-2-sulfonamide according to a similar procedure described for the synthesis of **3**. ^{1}H NMR (500 MHz, CD_3OD-d_4) δ 6.79−7.45 (m, 8 H), 4.94−5.05 (m, 1 H), 3.86−4.05 (m, 1 H), 3.32−3.40 (m, 1 H), 2.97−3.07 (m, 1 H), 2.88−2.97 (m, 1 H), 2.72−2.83 (m, 1 H), 2.64 (d, J = 13.45 Hz, 1 H), 2.33−2.49 (m, 1 H), 1.96−2.10 (m, 1 H), 1.75−1.89 (m, 1 H), 1.52−1.66 (m, 1 H), 1.45 (s, 3 H), 1.30−1.42 (m, 9 H), 0.46 (t, J = 7.58 Hz, 3 H). HRMS (ESI) m/z 583.1802 $[M + H]^+$ ($C_{28}H_{36}Cl_2NO_5S$ requires 583.1795).

Compounds **12**−**16** were prepared from **55**, **56**, and **57**, respectively, according to a similar procedure described for the synthesis of **11**, substituting methanesulfonylchloride for the appropriate sulfonyl chloride.

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(cyclopropanesulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (12). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.23 (m, 2 H), 6.90−7.18 (m, 5 H), 6.78−6.90 (m, 1 H), 4.76 (d, J = 10.56 Hz, 1 H), 3.61 (m, 1 H), 3.01−3.28 (m, 3 H), 2.92 (d, J = 14.09 Hz, 1 H), 2.77 (d, J = 14.28 Hz, 1 H), 2.28−2.49 (m, 2 H), 1.96−2.07 (m, 1 H), 1.77−1.92 (m, 1 H), 1.39−1.64 (m, 4 H), 1.08−1.23 (m, 2 H), 0.92−1.08 (m, 2 H), 0.54 (t, J = 7.53 Hz, 3 H).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(*N*,2-dimethylpropan-2-ylsulfonamido)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (13). ^{1}H NMR (500 MHz,

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CD_3OD-d_4) δ 7.10−7.40 (m, 5 H), 6.96−7.09 (m, 3 H), 4.79 (d, J = 10.76 Hz, 1 H), 4.40 (s, br, 1 H), 3.32−3.35 (m, 1 H), 2.88−3.01 (m, 4 H), 2.71−2.88 (m, 2 H), 2.63 (d, J = 13.20 Hz, 1 H), 2.43 (t, J = 13.69 Hz, 1 H), 1.94−2.06 (m, 1 H), 1.78−1.92 (m, 1 H), 1.58−1.71 (m, 1 H), 1.32−1.48 (m, 12 H), 0.51 (t, J = 7.21 Hz, 3 H). HRMS (ESI) m/z 597.1955 $[M + H]^+$ ($C_{29}H_{38}Cl_2N_2O_5S$ requires 597.1951).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-1-(*N*-methylcyclopropanesulfonamido)butan-2-yl)-2-oxopiperidin-3-yl)acetic Acid (14). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.24 (s, br, 2 H), 7.10−7.17 (m, 2 H), 6.80−7.09 (m, 4 H), 4.79 (d, J = 10.8 Hz, 1 H), 4.13−4.30 (m, 1 H), 2.99−3.12 (m, 2 H), 2.89 (s, 3 H), 2.64−2.81 (m, 2 H), 2.45 (t, J = 13.8 Hz, 1 H), 2.33 (m, 1 H), 1.88 (dd, J = 13.9, 2.7 Hz, 2 H), 1.54−1.66 (m, 1 H), 1.50−1.54 (m, 3 H), 1.22 (d, J = 4.5 Hz, 2 H), 1.02 (dd, J = 8.0, 3.9 Hz, 2 H), 0.51 (t, J = 7.4 Hz, 3 H). HRMS (ESI) m/z 581.1643 $[M + H]^+$ ($C_{28}H_{34}Cl_2N_2O_5S$ requires 581.1638).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-cyclopropyl-2-(*N*-methylcyclopropanesulfonamido)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (15). ^{1}H NMR (400 MHz, CD_3OD-d_4) δ ppm 7.31 (s, br, 2H), 7.11 (m, 3H), 7.02−7.05 (m, 3H), 4.82 (d, J = 8 Hz, 1H), 4.40 (s, br, 1H), 3.42 (m, 1H), 3.07 (m, 1H), 2.99 (d, J = 12 Hz, 1H), 2.94 (s, 3H), 2.70 (d, J = 12 Hz, 1H), 2.57 (s, br, 1H), 2.35 (t, J = 8 Hz, 1H), 2.20 (s, br, 1H), 2.08 (m, 1H), 1.73 (s, br, 1H), 1.44 (s, 3H), 1.06 (d, br, 4H), 0.40 (s, br, 1H), 0.29 (s, br, 1H), −0.28 (s, br, 1H), −0.71 (s, br, 1H.; HRMS (ESI) m/z 593.1642 $[M + H]^+$ ($C_{29}H_{34}Cl_2N_2O_5S$ requires 593.1638).

2-((3*R*,5*R*,6*S*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-3-methyl-1-(*N*-methylcyclopropanesulfonamido)-butan-2-yl)-2-oxopiperidin-3-yl)acetic Acid (16). ^{1}H NMR (500 MHz, CD_3OD-d_4) δ ppm 7.29 (s, br, 4 H), 7.07−7.16 (m, 2 H), 6.98−7.06 (m, 2 H), 4.97 (d, J = 11.0 Hz, 1 H), 4.13−4.40 (m, 1 H), 3.48 (ddd, J = 13.8, 11.0, 3.1 Hz, 1 H), 3.01 (d, J = 13.5 Hz, 1 H), 2.87−2.96 (m, 4 H), 2.60−2.71 (m, 2 H), 2.51−2.60 (m, 1 H), 2.38 (t, J = 13.7 Hz, 1 H), 2.23 (dquin, J = 9.5, 6.7 Hz, 1 H), 2.07 (dd, J = 13.7, 3.2 Hz, 1 H), 1.40 (s, 3 H), 0.95−1.22 (m, 4 H), 0.69 (d, J = 6.60 Hz, 3 H), 0.63 (d, J = 6.60 Hz, 3 H). HRMS (ESI) m/z 595.1799 $[M + H]^+$ ($C_{29}H_{36}Cl_2N_2O_5S$ requires 595.1795).

Methyl 2-((3*R*,5*R*,6*S*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-cyclopropyl-2-hydroxyethyl)-3-methyl-2-oxopiperidin-3-yl)acetate (58). To a solution of **56** (1.15 g, 2.51 mmol) and imidazole (0.439 g, 6.45 mmol) in DMF (6.5 mL) was added *tert*-butylchlorodiphenylsilane (0.963 mL, 3.76 mmol) via syringe. The yellow solution was stirred at 25 °C for 12 h under nitrogen. The reaction was quenched (water) and extracted (diethyl ether). The combined organic layers and washed (brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash column chromatography (SiO_2, 0−10% EtOAc/hexanes, gradient elution) gave the crude product (1.60 g, 92%). MS (ESI) 696.2 $[M + H]^+$.

2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-Butyldiphenylsilyloxy)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid was prepared as a pale-yellow foam from the TBDPS protected alcohol according to a similar procedure described for the synthesis of **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.62 (ddd, J = 7.2, 5.9, 1.4 Hz, 4 H), 7.37−7.49 (m, 8 H), 7.12−7.26 (m, 3 H), 7.05 (s, 1 H), 6.97 (s, 1 H), 6.60−6.69 (m, 1 H), 4.67−4.78 (m, 1 H), 4.26−4.40 (m, 1 H), 3.43−3.58 (m, 1 H), 3.12−3.23 (m, 1 H), 2.96−3.12 (m, 1 H), 2.72 (s, 1 H), 2.40−2.56 (m, 1 H), 2.24−2.35 (m, 1 H), 1.95−2.07 (m, 1 H), 1.52 (s, 3 H), 1.39−1.48 (m, 1 H), 1.15 (s, 9 H), 0.21 to −0.34 (m, 2 H), −0.4 to −0.31 (m, 1 H), −0.95−0.76 (m, 1 H). MS (ESI) 714.3 $[M + H]^+$.

To a solution of the acid above (1.40 g, 1.96 mmol) in MeOH (3.1 mL) and benzene (13 mL) was added 2.0 M (trimethylsilyl)-diazomethane in hexanes (1.96 mL, 3.92 mmol) at 0 °C dropwise. After being stirred at 0 °C for 1 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 10% and 20% EtOAc/hexanes) to provide methyl 2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butyldiphenylsilyloxy)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetate (992 mg, 70%) as a pale-yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.64 (ddd, J = 11.2, 8.0, 1.4 Hz, 4 H), 7.34−7.49 (m, 8 H), 7.15−7.21 (m, 2 H), 7.10−7.13 (m, 1 H), 7.02 (s, 1 H), 6.95 (s, 1 H), 6.61−6.67 (m, 1 H), 4.68−4.73 (m, 1 H), 4.37−4.47 (m, 1 H), 3.69 (s, 3 H), 3.47−3.56 (m, 1 H), 3.17−3.28 (m, 1 H), 2.91 (m, 1 H), 2.85 (m, 1 H), 2.33−2.46 (m, 1 H), 2.05−2.23 (m, 2 H), 1.47 (s, 3 H), 1.14 (s, 9 H), 0.15−0.28 (m, 2 H), −0.46 to −0.33 (m, 1 H), −0.89 to −0.69 (m, 1 H). MS (ESI) 728.2 $[M + H]^+$.

To a solution of the methyl ester above (578 mg, 0.793 mmol) in THF (3.2 mL) was added TBAF (1 M in THF, 2.40 mL, 2.38 mmol) at 0 °C, and the reaction mixture was allowed to warm to 25 °C for 6 h. The reaction was quenched (satd NH_4Cl), extracted (2 × EtOAc), and washed (brine). The combined organic layers were dried (Na_2SO_4) and concentrated under the reduced pressure. The residue was purified by flash column chromatography (SiO_2, 10% and 50% EtOAc/hexanes) to provide **58** (388 mg, 100%) as a colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.99−7.26 (m, 7 H), 6.77 (d, J = 7.4 Hz, 1 H), 4.87 (d, J = 10.0 Hz, 1 H), 3.70 (s, 3 H), 3.58 (dd, J = 11.0, 4.5 Hz, 1 H), 3.32−3.47 (m, 1 H), 3.14 (t, J = 10.5 Hz, 2 H), 2.75−2.93 (m, 2 H), 2.06−2.23 (m, 2 H), 1.40 (s, 3 H), 0.77−0.94 (m, 1 H), 0.61 (dd, J = 4.6, 3.8 Hz, 2 H), 0.16−0.33 (m, 1 H), 0.00−0.13 (m, 1 H). MS (ESI) 490.0 $[M + H]^+$.

Methyl 2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(Benzylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetate (59). A mixture of **58** (0.213 g, 0.434 mmol), phenylmethanethiol (0.102 mL, 0.869 mmol), and 2-(tributylphosphoranylidene)acetonitrile (0.233 mL, 0.869 mmol) was heated at 100 °C for 2 h. The reaction mixture was cooled to 25 °C, and diluted (EtOAc), washed (satd NH_4Cl and brine), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (SiO_2, 0−50% EtOAc/hexanes, gradient elution) to provide **59** (210 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.00−7.60 (m, 12 H), 6.95 (d, J = 8.0 Hz, 1 H), 4.82 (d, J = 10.6 Hz, 1 H), 3.92 (s, 2 H), 3.85 (s, 3 H), 3.50 (m, 1 H), 3.35 (m, 1 H), 3.08 (d, J = 12 Hz, 1 H), 3.00 (d, J = 12 Hz, 1 H), 2.62 (m, 2 H), 2.35 (dd, J = 4.0, 12.0 Hz, 1 H), 2.20 (dd, J = 4.0, 12.0 Hz, 1 H), 1.65 (s, 3 H), 1.65 (m, 1 H), 0.75 (m, 1 H), 0.45 (m, 1 H), 0.05 (m, 1 H), −0.65 (m, 1 H). MS (ESI) 596.0 $[M + H]^+$.

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-cyclopropyl-2-(*N*,*N*-dimethylsulfamoyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (17). To a heterogeneous mixture of **59** (0.03 g, 0.05 mmol) and iodosobenzene (0.037 g, 0.166 mmol) in ether (30 mL) was added hydrogen chloride (2.0 M in ether, 3.60 mL, 7.20 mmol) gradually with vigorously stirring. The resulting mixture was stirred for 30 min and concentrated under reduced pressure. The solution of the dried residue in DCM (2 mL) was added to a mixture of dimethylamine (0.011 g, 0.251 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.032 g, 0.251 mmol) in DCM (1 mL). The resulting mixture was stirred at 25 °C for 1 h and was diluted (DCM), washed (water and brine), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 20−70%, gradient elution) to give methyl 2-((3*R*,5*R*,6*S*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-cyclopropyl-2-(*N*,*N*-dimethylsulfamoyl)-ethyl)-3-methyl-2-oxopiperidin-3-yl)acetate (23.0 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27 (s, br, 3 H), 7.07−7.16 (m, 3 H), 6.95 (s, 1 H), 6.83−6.89 (m, 1 H), 4.83 (d, J = 10.56 Hz, 1 H), 4.19 (t, J = 12.42 Hz, 1 H), 3.07−3.19 (m, 2 H), 2.90 (s, 6 H), 2.73−2.84 (m, 2 H), 2.60 (s, br, 1H), 2.50 (t, J = 13.79 Hz, 1 H), 1.87 (dd, J = 13.79, 2.84 Hz, 2H), 1.53 (s, 3 H), 0.18−0.44 (m, 2 H), −0.28 (s, br, 1 H), −1.07 (s, br, 1 H). MS (ESI) 567.0 $[M + H]^+$.

To a solution of the sulfonamide above (0.023 g, 0.04 mmol) in THF/H_2O (3: 1, 3.0 mL) was added lithium hydroxide (0.079 mL, 0.079 mmol). The reaction mixture was stirred at 25 °C for 4 h. The reaction was quenched (satd NH_4Cl), extracted (2 × EtOAc), and washed (brine). The residue was purified by RP-HPLC (10−90% A/B, gradient elution) to provide **17** (16.0 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.10−7.19 (m, 2 H), 7.02−7.08 (m, 4 H), 6.88 (m, 1 H), 6.78 (m, 1 H), 4.77 (m, 1 H), 4.10 (m, 1 H), 3.02−3.10 (m, 2 H), 2.79 (s, 6 H), 2.64−2.70 (m, 2 H), 2.32−2.55 (m, 2 H), 1.70−1.81 (m, 2 H), 1.45 (s, 3 H), 0.30 (s, br, 1 H), 0.18 (s, br, 1 H), −0.32 (s, br, 1 H), −1.18 (s, br, 1 H). HRMS (ESI) m/z 567.1487 $[M + H]^+$ ($C_{27}H_{32}Cl_2N_2O_5S$ requires 567.1482).

Compounds **18** and **19** were prepared from **59** according to a similar procedure described for the synthesis of **17**, substituting dimethylamine for pyrrolidine, azetidine, respectively.

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2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-cyclopropyl-2-(pyrrolidin-1-ylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (18). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.21−7.37 (m, 3 H), 7.07−7.19 (m, 3 H), 6.98 (s, 1 H), 6.89 (d, J = 6.65 Hz, 1 H), 4.84 (d, J = 10.56 Hz, 1 H), 4.00 (m, 4 H), 2.30−3.305 (m, 10 H), 1.81 (s, br, 1 H), 1.52 (s, 3 H), 0.17−0.42 (m, 2 H), −0.28 (s, br, 1 H), −1.08 (s, br, 1 H). HRMS (ESI) m/z 579.1482 $[M + H]^+$ ($C_{28}H_{32}Cl_2N_2O_5S$ requires 579.1482).

2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(Azetidin-1-ylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (19). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.24−7.28 (m, 3 H), 7.07−7.17 (m, 3 H), 6.97 (m, 1 H), 6.81−6.88 (m, 1 H), 4.82 (d, J = 10.56 Hz, 1 H), 3.45−3.65 (m, 4 H), 3.10−3.20 (m, 2 H), 2.80−2.95 (m, 2 H), 2.45−2.80 (m, 2 H), 1.80−2.10 (m, 6 H), 1.80 (s, br, 1 H), 1.51 (s, 3 H), 0.18−0.44 (m, 2 H), 0.28 (s, br, 1 H), −1.07 (s, br, 1 H). HRMS (ESI) m/z 593.1644 $[M + H]^+$ ($C_{29}H_{34}Cl_2N_2O_5S$ requires 593.1638).

(3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-1-(((trimethylsilyl)methyl)thio)butan-2-yl)-piperidin-2-one (60). To a solution of **55** (125 mg, 0.280 mmol) in toluene (1 mL) was added cyanomethylenetributylphosphorane (300 μL, 1.12 mmol) and (trimethylsilyl)methanethiol (150 μL 1.12 mol) at 25 °C. The mixture was heated to 110 °C for 2 h. The reaction was cooled down to rt, quenched (satd NH_4Cl), extracted (2 × EtOAc), and washed (brine). The combined organic layers were dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 10, 20, 40% EtOAc/hexanes) to provide **60** (65.0 mg, 42%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.20−7.25 (m, 2 H), 7.05−7.20 (m, 2 H), 6.90−7.05 (m, 3 H), 6.75 (d, J = 8.0 Hz, 1 H), 5.88 (m, 1 H), 5.14−5.20 (m, 2 H), 4.67 (d, J = 8.0 Hz, 1 H), 3.40 (dd, J = 8.0, 12.0 Hz, 1 H), 3.11 (m, 1 H), 2.83 (m, 1 H), 2.60 (m, 2 H), 2.48 (dd, J = 4.0, 12 Hz, 1 H), 2.13 (t, J = 12.0 Hz, 1 H), 2.05 (m, 1 H), 1.89 (dd, J = 4.0, 12 Hz, 1 H), 1.82 (d, J = 12.0 Hz, 1 H), 1.73 (d, J = 12.0 Hz, 1 H), 1.57 (m, 1 H), 1.27 (s, 3 H), 0.50 (t, J = 8.0 Hz, 3 H), 0.16 (s, 9 H).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-1-(methylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic Acid (20). **60** (60.0 mg, 0.118 mmol) was dissolved in a solution of tetrabutylammonium fluoride (1 M in THF, 3.5 mL, 3.50 mmol) at 25 °C. After the resulting solution was stirred at 25 °C for 16 h, the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 10, 20, 40% EtOAc/hexanes) to provide (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-1-(methylthio)butan-2-yl)piperidin-2-one (32.0 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.14−7.21 (m, 2 H), 7.05−7.15 (m, 2 H), 6.95−7.05 (m, 3 H), 6.76 (d, J = 8.0 Hz, 1 H), 5.85 (m, 1 H), 5.15−5.20 (m, 2 H), 4.62 (d, J = 8.0 Hz, 1 H), 3.35 (dd, J = 8.0, 12.0 Hz, 1 H), 3.12 (m, 1 H), 2.85 (m, 1 H), 2.60 (m, 2 H), 2.48 (dd, J = 4.0, 12 Hz, 1 H), 2.13 (s, 3 H), 1.95−2.20 (m, 2 H), 1.89 (dd, J = 4.0, 12 Hz, 1 H), 1.56 (m, 1 H), 1.28 (s, 3 H), 0.52 (t, J = 8.0 Hz, 3 H).

Compound **20** was prepared from (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-1-(methylthio)butan-2-yl)piperidin-2-one according to a similar procedure described for the synthesis of **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27 (m, 2 H), 7.12 (m, 4 H), 6.95 (s, 1 H), 6.84 (d, J = 8.0 Hz, 1 H), 4.90 (d, J = 8.0 Hz, 1 H), 4.24 (m, 1 H), 3.37 (m, 1 H), 3.13 (m, 1 H), 2.99 (s, 3 H), 2.97 (m, 1 H), 2.90 (d, J = 12 Hz, 1 H), 2.76 (d, J = 16 Hz, 1 H), 2.37 (t, J = 16.0 Hz, 1 H), 2.14 (m, 1 H), 1.90 (d, J = 12 Hz, 1 H), 1.48 (s, 3 H), 1.45 (m, 1 H), 0.42 (t, J = 8.0 Hz, 3 H). HRMS (ESI) m/z 526.1217 $[M + H]^+$ ($C_{25}H_{29}Cl_2NO_5S$ requires 526.1216).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-3-methyl-1-(methylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic Acid (42). Compound **42** was prepared from **57** according to a similar procedure described for the synthesis of **20**. ^{1}H NMR (500 MHz, CD_3OD-d_4) δ ppm 7.29 (s, br, 4 H), 7.08−7.16 (m, 2 H), 7.03−7.08 (m, 1 H), 6.98 (dt, J = 7.2, 1.4 Hz, 1 H), 5.09 (d, J = 11 Hz, 1 H), 4.07 (dd, J = 13.9, 10.5 Hz, 1 H), 3.56 (ddd, J = 13.8, 10.9, 2.9 Hz, 1 H), 3.32−3.35 (m, 1 H), 3.20−3.29 (m, 1 H), 3.09 (s, br, 3 H), 2.99 (d, J = 13.5 Hz, 1 H), 2.62 (d, J = 13.5 Hz, 1 H), 2.29 (t, J = 13.6 Hz, 1 H), 2.18 (dq, J = 14.2, 6.9 Hz, 1 H), 2.05 (dd, J = 13.8, 3.1 Hz, 1 H), 1.37 (s, 3 H), 0.67 (d, J = 6.6 Hz, 3 H), 0.50 (d, J = 6.9 Hz, 3 H); MS (ESI) 540.2 $[M + H]^+$.

Compounds **26**, **28**−**33**, **35**, **38**, and **40**, were prepared from **55**−**57**, and **61**−**64**, respectively, according to a similar procedure described for the synthesis of **20**.

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-((cyclopropylmethyl)sulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (26). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.23−7.27 (m, 2 H), 7.00−7.22 (m, 4 H), 6.94−6.98 (m, 1 H), 6.85 (dt, J = 7.1, 1.5 Hz, 1 H), 4.95 (d, J = 10.8 Hz, 1 H), 4.17 (t, J = 12.1 Hz, 1 H), 3.35 (t, J = 9.7 Hz, 1 H), 3.13 (ddd, J = 13.6, 10.9, 2.7 Hz, 1 H), 2.83−3.07 (m, 4 H), 2.77 (d, J = 14.9 Hz, 1 H), 2.39 (t, J = 13.8 Hz, 1 H), 2.07−2.22 (m, 1 H), 1.91 (dd, J = 13.9, 2.7 Hz, 1 H), 1.48 (s, 3 H), 1.40−1.47 (m, 1 H), 1.12−1.25 (m, 1 H), 0.75−0.85 (m, 2 H), 0.37−0.48 (m, 5 H). HRMS (ESI) m/z 566.1538 $[M + H]^+$ ($C_{28}H_{33}Cl_2NO_5S$ requires 566.1529).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(cyclopentylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (28). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25 (m, 2 H), 7.12 (m, 4 H), 6.96 (s, 1 H), 6.85 (d, J = 8.0 Hz, 1 H), 4.97 (d, J = 8.0 Hz, 1 H), 4.10 (t, J = 12 Hz, 1 H), 3.36 (m, 2 H), 3.12 (m, 1 H), 3.00 (d, J = 16 Hz, 1 H), 2.76 (d, J = 16.0 Hz, 2 H), 2.40 (t, J = 12 Hz, 1 H), 2.09 (m, 5 H), 1.80−1.95 (m, 3 H), 1.70 (m, 2 H), 1.49 (s, 3 H), 1.46 (m, 1 H), 0.40 (t, J = 8.0 Hz, 3 H). HRMS (ESI) m/z 580.1692 $[M + H]^+$ ($C_{29}H_{35}Cl_2NO_5S$ requires 580.1686).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-1-(oxetan-3-ylsulfonyl)butan-2-yl)-2-oxopiperidin-3-yl)acetic Acid (29). ^{1}H NMR (400 MHz, CD_3OD-d_4) δ ppm 7.28 (s, br, 3 H), 7.07−7.22 (m, 3 H), 7.00−7.07 (m, 1 H), 6.97 (dt, J = 6.65, 1.76 Hz, 1 H), 4.94−5.01 (m, 2 H), 4.87−4.93 (m, 4 H), 4.55−4.76 (m, 1 H), 3.94−4.20 (m, 1 H), 3.41 (ddd, J = 13.60, 10.96, 2.84 Hz, 1 H), 2.98−3.07 (m, 1 H), 2.95 (d, J = 13.69 Hz, 1 H), 2.61 (d, J = 13.69 Hz, 1 H), 2.29 (t, J = 13.69 Hz, 1 H), 2.02−2.10 (m, 2 H), 1.46−1.63 (m, 1 H), 1.34−1.43 (m, 3 H), 0.39 (t, J = 7.63 Hz, 3 H). HRMS (ESI) m/z 568.1326 $[M + H]^+$ ($C_{27}H_{31}Cl_2NO_6S$ requires 568.1322).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxo-1-((*S*)-1-(phenylsulfonyl)butan-2-yl)piperidin-3-yl)acetic Acid (30). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.93 (d, J = 8 Hz, 2 H), 7.71 (m, 1 H), 7.61 (m, 2 H), 7.27(m, 2 H), 7.14 (m, 4 H), 6.99 (s, 1 H), 6.88 (d, J = 8.0 Hz, 1 H), 5.04 (d, J = 8.0 Hz, 1 H), 4.24 (dd, J = 16, 12 Hz, 1 H), 3.41 (m, 1 H), 3.15 (m, 1 H), 3.05 (d, J = 16 Hz, 1 H), 2.88 (dd, J = 16 Hz, 1 H), 2.79 (d, J = 16 Hz, 1 H), 2.50 (t, J = 16 Hz, 1 H), 2.08 (m, 1 H), 1.94 (dd, J = 12, 4 Hz, 1 H), 1.58 (s, 3 H), 1.46 (m, 1 H), 0.37 (t, J = 8 Hz, 3 H). HRMS (ESI) m/z 588.1378 $[M + H]^+$ ($C_{30}H_{31}Cl_2NO_5S$ requires 588.1373).

2-((3*R*,5*R*,6*S*)-1-((*S*)-1-(*tert*-Butylsulfonyl)-4,4,4-trifluorobutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (31). ^{1}NMR (400 MHz, $CDCl_3$) δ ppm 7.27 (s, 2 H), 7.03−7.23 (m, 4 H), 6.97 (s, 1 H), 6.87 (dt, J = 7.0, 1.6 Hz, 1 H), 5.07 (d, J = 10.8 Hz, 1 H), 4.11 (dd, J = 13.2, 11.2 Hz, 1 H), 3.86 (t, J = 10.3 Hz, 1 H), 3.09−3.27 (m, 2 H), 2.98 (dd, J = 13.2, 2.1 Hz, 1 H), 2.78−2.90 (m, 2 H), 2.41 (t, J = 13.8 Hz, 1 H), 2.11−2.28 (m, 1 H), 1.95 (dd, J = 13.9, 2.7 Hz, 1 H), 1.49 (s, 3 H), 1.43 (s, 9 H). HRMS (ESI) m/z 622.1401 $[M + H]^+$ ($C_{28}H_{32}Cl_2F_3NO_5S$ requires 622.1403).

2-((3*R*,5*R*,6*S*)-1-((*S*)-1-(*tert*-Butylsulfonyl)propan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (32). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.21−7.28 (m, 2 H), 7.08−7.15 (m, 4 H), 6.94−6.99 (m, 1 H), 6.83 (d, J = 7.1 Hz, 1 H), 4.95 (d, J = 10.8 Hz, 1 H), 4.24 (dd, J = 13.2, 11.3 Hz, 1 H), 3.70 (1 H, m), 3.00−3.10 (m, 2 H), 2.72 (d, J = 15.2 Hz, 1 H), 2.66 (dd, J = 2.45, 12.5, 1 H), 2.41 (t, J = 13.7 Hz, 1 H), 1.88 (d, J = 13.7 Hz, 1 H), 1.49 (s, 3 H), 1.43 (s, 9 H), 1.27 (d, J = 6.85 Hz, 3 H). HRMS (ESI) m/z 554.1539 $[M + H]^+$ ($C_{27}H_{33}Cl_2NO_5S$ requires 554.1529).

2-((3*R*,5*R*,6*S*)-1-((*S*)-1-(*tert*-Butylsulfonyl)-3-methylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (33). ^{1}H NMR (500 MHz, CD_3OD-d_4) δ ppm 7.18−8.01 (m, 3 H), 7.04−7.17 (m, 3 H), 6.98−7.03 (m, 1 H), 5.15 (d, J = 11.3 Hz, 1 H), 3.96 (dd, J = 13.8, 10.4 Hz, 1 H), 3.57 (ddd, J = 13.6, 11.1, 2.9 Hz, 1 H), 3.25−3.29 (m, 1 H), 3.10 (dd, J = 13.7, 1.71 Hz, 1 H), 2.99 (d, J = 13.7 Hz, 1 H), 2.61 (d, J = 13.5 Hz, 1 H), 2.30 (t, J = 13.7 Hz, 1 H), 2.11−2.25 (m, 1 H), 2.01−2.10 (m, 1 H), 1.45 (s, 9 H),

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1.37 (s, 3 H), 0.65 (d, J = 6.6 Hz, 3 H), 0.51 (d, J = 6.9 Hz, 3 H). HRMS (ESI) m/z 582.1845 $[M + H]^+$ ($C_{29}H_{37}Cl_2NO_5S$ requires 582.1842).

2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (35). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.20−7.26 (m, 3 H), 7.03−7.17 (m, 3 H), 6.93−6.97 (m, 1 H), 6.82−6.92 (m, 1 H), 4.95 (d, J = 10.6 Hz, 1 H), 4.30 (t, J = 12.0 Hz, 1 H), 3.14 (ddd, J = 13.6, 10.8, 2.6 Hz, 1 H), 3.07 (d, J = 15.1 Hz, 1 H), 2.92 (d, J = 11.9 Hz, 1 H), 2.79 (d, J = 15.1 Hz, 1 H), 2.72 (t, J = 9.6 Hz, 1 H), 2.45 (t, J = 13.8 Hz, 1 H), 1.88 (dd, J = 13.6, 2.4 Hz, 2 H), 1.50 (s, 3 H), 1.44 (s, 9H), 0.30−0.44 (m, 1 H), 0.17−0.30 (m, 1 H), −0.37 to −0.26 (m, 1 H), −1.15 to −1.05 (m, 1 H). HRMS (ESI) m/z 580.1692 $[M + H]^+$ ($C_{29}H_{35}Cl_2NO_5S$ requires 580.1686).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylsulfonyl)-3,3-dimethylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (38). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.36 (s, 1H), 7.81 (br s, 1H), 7.48 (s, br, 1H), 7.25 (s, br, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.15 (ddd, J = 7.8. 2.0, 0.7 Hz, 1H), 7.04 (t, J = 1.7 Hz, 1H), 7.00 (d, br, J = 7.8 Hz, 1H), 5.05 (d, J = 11.2 Hz, 1H), 3.90 (dd, J = 13.7, 11.0, 2.6 Hz, 1H), 3.70 (ddd, J = 13.7, 11.0, 2.6 Hz, 1H), 3.45 (m, 2H), 3.12 (dd, J = 13.4, 2.0, 1H), 2.97 (d, J = 13.9 Hz, 1H), 2.14 (t, J = 13.2 Hz, 1H), 2.03 (dd, J = 13.4 Hz, 1H), 1.32 (d, J = 6.8 Hz, 3H), 1.31 (d, J = 6.6 Hz, 3H), 1.23 (s, 3H), 0.62 (s, 9H). HRMS (ESI) m/z 582.1845 $[M + H]^+$ ($C_{29}H_{37}Cl_2NO_5S$ requires 582.1842).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-cyclobutyl-2-(isopropylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (40). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.24−7.30 (m, 2 H), 7.08−7.15 (m, 4 H), 6.98 (m, 1 H), 6.87 (d, J = 7.0 Hz, 1 H), 5.02 (d, J = 10.0 Hz, 1 H), 3.99 (t, J = 12.1 Hz, 1 H), 3.49 (m, 1 H), 2.95−3.18 (m, 6 H), 2.65−2.80 (m, 2 H), 2.42 (t, J = 12.0 Hz, 1 H), 1.80−1.95 (m, 3 H), 1.58 (m, 1 H), 1.46 (s, 3 H), 1.44 (d, J = 5 Hz, 6 H), 0.81 (m, 1 H). HRMS (ESI) m/z 580.1691 $[M + H]^+$ ($C_{29}H_{35}Cl_2NO_5S$ requires 580.1686).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(ethylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)-acetic Acid (22). To a solution of **55** (300 mg, 0.652 mmol) in DCM (6 mL) was added triethylamine (270 μL, 1.96 mmol) and methanesulfonic anhydride (170 mg, 0.977 mmol) successively at 0 °C. After being stirred at 25 °C for 2 h, the reaction was quenched with 10% aqueous citric acid and extracted (DCM), and the combined extracts were washed (water), dried (Na_2SO_4), and filtered. The filtrate was concentrated to give (3*S*,5*S*,6*R*,8*S*)-8-allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-ethyl-8-methyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-*a*]-pyridin-4-ium trifluoromethanesulfonate. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.95 (s, br, 1 H), 7.34−7.60 (m, 2 H), 7.18−7.34 (m, 4 H), 7.13 (dt, J = 7.5, 1.3 Hz, 1 H), 5.88 (m, 1 H), 5.37 (dd, J = 16.8, 1.6 Hz, 1 H), 5.28 (dd, J = 10.0, 2.0 Hz, 1 H), 5.16 (d, J = 10.8 Hz, 1 H), 5.06 (t, J = 9.8 Hz, 1 H), 4.78 (dd, J = 9.5, 7.1 Hz, 1 H), 4.45 (m, J = 2.7 Hz, 1 H), 3.88−3.98 (m, 1 H), 2.66−2.85 (m, 2 H), 2.33 (t, J = 13.4 Hz, 1 H), 1.99 (dd, J = 13.7, 3.4 Hz, 1 H), 1.32 (s, 3 H), 0.94 (m, 1 H), 0.59 (t, J = 7.2 Hz, 1 H), 0.41−0.53 (m, 1 H). MS (ESI) 428.2 $[M + H]^+$.

Method A: To a solution of the trifluoromethanesulfonate above (86.0 mg, 0.150 mmol) in DMF (0.7 mL) was added sodium ethanethiolate (38.0 mg, 0.450 mmol). After being stirred at 25 °C for 1.5 h, the reaction was quenched (satd NH_4Cl), extracted (2 × EtOAc), and washed (2 × brine). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 10% and 20% EtOAc/hexanes) to provide (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophen(yl)-6-(4-chlorophenyl)-1-((*S*)-1-(ethylthio)butan-2-yl)-3-methylpiperidin-2-one (60.0 mg, 82%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.22 (d, J = 8.4 Hz, 2 H), 7.08−7.18 (m, 2 H), 6.90−7.03 (m, 3 H), 6.72−6.81 (m, 1 H), 5.76−5.98 (m, 1 H), 5.18 (d, J = 4.5 Hz, 1 H), 5.15 (s, 1 H), 4.64 (d, J = 10.6 Hz, 1 H), 3.32−3.45 (m, 1 H), 3.13 (m, 1 H), 2.73−2.90 (m, 1 H), 2.49−2.68 (m, 5 H), 2.14 (t, J = 13.7 Hz, 1 H), 1.98−2.10 (m, 1 H), 1.89 (dd, J = 13.5, 3.1 Hz, 1 H), 1.57 (dd, J = 6.9, 2.6 Hz, 1 H), 1.24−1.33 (m, 6 H), 0.52 (t, J = 7.5 Hz, 3 H). MS (ESI) 490.2 $[M + H]^+$.

Compound **22** was prepared from (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(ethylthio)butan-2-yl)-3-methylpiperidin-2-one according to a similar procedure described for the synthesis of **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.24−7.26 (m, 2 H), 7.01−7.20 (m, 4 H), 6.93−6.98 (m, 1 H), 6.85 (d, J = 7.0 Hz, 1 H), 4.94 (d, J = 10.6 Hz, 1 H), 4.15 (t, J = 12.1 Hz, 1 H), 3.24−3.37 (m, 1 H), 2.92−3.18 (m, 4 H), 2.71−2.82 (m, 2 H), 2.38 (t, J = 13.8 Hz, 1 H), 2.06−2.21 (m, 1 H), 1.92 (dd, J = 13.7, 2.7 Hz, 1 H), 1.48 (s, 3 H), 1.42−1.46 (m, 1 H) 1.44 (t, J = 7.5 Hz, 3 H), 0.41 (t, J = 7.5 Hz, 3 H). HRMS (ESI) m/z 540.1378 $[M + H]^+$ ($C_{26}H_{31}Cl_2NO5S$ requires 540.1373).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(cyclopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (23). Method B: To a solution of (3*S*,5*S*,6*R*,8*S*)-8-allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-ethyl-8-methyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-*a*]pyridin-4-ium trifluoromethanesulfonate (75.0 mg, 0.130 mmol) in acetonitrile (1.3 mL) was added cyclopropanesulfinic acid sodium salt (50.0 mg, 0.390 mmol) at 25 °C. After being stirred at 90 °C for 1 day, the reaction was quenched (satd NH_4Cl) and extracted (2 × EtOAc), and the combined organic layers were washed (2 × brine), dried (Na_2SO_4), and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 35% and 45% EtOAc/hexanes) to provide (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(cyclopropylsulfonyl)butan-2-yl)-3-methylpiperidin-2-one (55.3 mg, 80%) as a colorless liquid.

Compound **23** was prepared from (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(cyclopropylsulfonyl)butan-2-yl)-3-methylpiperidin-2-one according to a similar procedure described for the synthesis of **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.22−7.26 (m, 2 H), 6.99 −7.19 (m, 4 H), 6.91−6.97 (m, 1 H), 6.76−6.89 (m, 1 H), 4.91 (d, J = 10.8 Hz, 1 H), 4.21 (dd, J = 13.5, 11.3 Hz, 1 H), 3.31 (t, J = 10.3 Hz, 1 H), 3.12 (ddd, J = 13.6, 10.9, 2.6 Hz, 1 H), 2.88−3.02 (m, 2 H), 2.76 (d, J = 14.9 Hz, 1 H), 2.31−2.49 (m, 2 H), 2.06−2.24 (m, 1 H), 1.90 (dd, J = 13.7, 2.7 Hz, 1 H), 1.40−1.56 (m, 1 H), 1.47 (s, 3 H), 1.23−1.36 (m, 2 H), 1.01−1.16 (m, 2 H), 0.42 (t, J = 7.5 Hz, 3 H). HRMS (ESI) m/z 552.1377 $[M + H]^+$ ($C_{27}H_{31}Cl_2NO_5S$ requires 552.1373).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (24). Method C: To a solution of (3*S*,5*S*,6*R*,8*S*)-8-allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-ethyl-8-methyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-*a*]pyridin-4-ium trifluoromethanesulfonate (61.0 mg, 0.105 mmol) in DMF (0.5 mL) was added cesium carbonate (206 mg, 0.633 mmol) and 2-propanethiol (59.2 μL, 0.633 mmol). After being stirred at 25 °C for 1.5 h, the recation was quenched (satd NH_4Cl), extracted (2 × EtOAc), and washed (2 × brine). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 7% and 15% EtOAc/hexanes) to provide (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylthio)butan-2-yl)-3-methylpiperidin-2-one (26.5 mg, 50%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.22 (d, J = 8.6 Hz, 2 H), 7.07−7.18 (m, 2 H), 6.86−7.05 (m, 3 H), 6.77 (dt, J = 7.4, 1.4 Hz, 1 H), 5.69−5.96 (m, 1 H), 5.06−5.23 (m, 2 H), 4.66 (d, J = 10.6 Hz, 1 H), 3.42 (dd, J = 12.6, 10.9 Hz, 1 H), 3.12 (ddd, J = 13.6, 10.6, 3.1 Hz, 1 H), 2.90 (dt, J = 13.4, 6.7 Hz, 1 H), 2.68−2.80 (m, 1 H), 2.52−2.67 (m, 3 H), 2.10−2.19 (m, 1 H), 1.99−2.09 (m, 1 H), 1.88 (dd, J = 13.5, 3.1 Hz, 1 H), 1.56−1.61 (m, 1 H), 1.31 (d, J = 6.6 Hz, 3 H), 1.30 (d, J = 6.6 Hz, 3 H), 1.26−1.29 (m, 3 H), 0.51 (t, J = 7.5 Hz, 3 H). MS (ESI) 504.2 $[M + H]^+$.

Compound **24** was prepared from (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylthio)butan-2-yl)-3-methylpiperidin-2-one according to a similar procedure described for the synthesis of **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.22−7.26 (s, br, 2 H), 7.02−7.21 (m, 4 H), 6.92−6.94 (s, 1 H), 6.85 (d, J = 7.0 Hz, 1 H), 4.97 (d, J = 10.8 Hz, 1 H), 4.10 (t, J = 11.7 Hz, 1 H), 3.27−3.42 (m, 1 H), 2.98−3.16 (m, 3 H), 2.70−2.78 (m, 2 H), 2.40 (t, J = 13.9 Hz, 1 H), 2.08−2.26 (m, 1 H), 1.86−1.93 (m, 1 H), 1.49 (s, 3 H), 1.43 (d, J = 6.8 Hz, 3 H), 1.43 (d, J = 6.8 Hz, 3 H), 1.40−1.50 (m, 1 H) 0.41 (t, J = 7.5 Hz, 3 H). HRMS (ESI) m/z 554.1533 $[M + H]^+$ ($C_{27}H_{33}Cl_2NO_5S$ requires 554.1529).

2-((3*R*,5*R*,6*S*)-1-((*S*)-1-(*tert*-Butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (25). Compound **25** was prepared from **55** according to

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a similar procedures described in method C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.21−7.26 (m, 2 H), 7.01−7.20 (m, 4 H), 6.92−6.94 (m, 1 H), 6.85 (d, J = 7.1 Hz, 1 H), 4.99 (d, J = 10.8 Hz, 1 H), 4.04 (dd, J = 13.2, 11.2 Hz, 1 H), 3.33 (t, J = 10.4 Hz, 1 H), 3.03−3.15 (m, 2 H), 2.80 (dd, J = 13.2, 2.0 Hz, 1 H), 2.72 (d, J = 15.4 Hz, 1 H), 2.43 (t, J = 13.8 Hz, 1 H), 2.08−2.23 (m, 1 H), 1.86 (dd, J = 13.7, 2.4 Hz, 1 H), 1.50 (s, 3 H), 1.46−1.49 (m, 1 H), 1.44 (s, 9 H), 0.41 (t, J = 7.6 Hz, 3 H). HRMS (ESI) m/z 568.1687 $[M + H]^+$ ($C_{28}H_{35}Cl_2NO_5S$ requires 568.1686).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(cyclobutylsulfonyl)butan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (27). To a suspension of magnesium (306 mg, 12.6 mmol) in ether (7.4 mL) was added a solution of bromocyclobutane (1.00 g, 7.41 mmol) in ether (7.4 mL) in several small portions at 25 °C. After the initial exotherm had ceased, the mixture was further heated to reflux for 1 h. The suspension was added in small portions to an ice-cold solution of sulfuryl dichloride (3.00 g, 22.2 mmol) in DCM (12 mL). The suspension was warmed to rt, and the volatiles were removed under reduced pressure. The residue was dried under a vacuum and then extracted with hexane (80 mL). The hexane suspension was filtered, and the filter cake was washed with hexanes. The combined filtrates were dried (Na_2SO_4) and concentrated under reduced pressure to give crude cyclobutanesulfonyl chloride. The crude cyclobutanesulfonyl chloride (1.15 g, 7.44 mmol) was added to a suspension of sodium sulfite (2.16 g, 17.1 mmol) in water (9.7 mL) and sodium carbonate (1.42 g, 13.4 mmol). The resulting suspension was heated to reflux for 1 h and then cooled and lyophilized to remove water. Ethanol (50 mL) was added to the residue, and the resulting mixture was heated under reflux for 2 h. The mixture was filtered and the filtrate was concentrated under the reduced pressure to give the crude cyclobutanesulfinic acid.

Compound **27** was prepared from **55** according to a similar procedure described in method B, substituting cyclopropanesulfinic acid for cyclobutanesulfinic acid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.21−7.27 (m, 2 H), 7.00−7.21 (m, 4 H), 6.93−6.97 (s, 1 H), 6.86 (d, J = 7.1 Hz, 1 H), 4.97 (d, J = 10.8 Hz, 1 H), 3.98 (t, J = 12.2 Hz, 1 H), 3.76 (quin, J = 8.3 Hz, 1 H), 3.31 (t, J = 9.9 Hz, 1 H), 3.12 (ddd, J = 13.6, 10.9, 2.7 Hz, 1 H), 2.99 (d, J = 14.9 Hz, 1 H), 2.75 (d, J = 14.9 Hz, 1 H), 2.50−2.69 (m, 3 H), 2.27−2.46 (m, 3 H), 2.04−2.19 (m, 3 H), 1.91 (dd, J = 13.7, 2.7 Hz, 1 H), 1.48−1.52 (m, 3 H), 1.41−1.47 (m, 1 H), 0.40 (t, J = 7.6 Hz, 3 H). MS (ESI) 566.2 $[M + H]^+$.

2-((3*R*,5*R*,6*S*)-1-((*S*)-1-(*tert*-Butylsulfonyl)-3,3-dimethylbutan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (34). Compound **34** was prepared from **62** according to a similar procedure described in method C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.48 (s, br, 1 H), 7.38 (s, br, 1 H), 7.12−7.23 (m, 2 H), 7.05−7.11 (m, 2 H), 7.01 (1 H, s), 6.93−6.97 (m, 1 H), 5.23 (d, J = 11.2 Hz, 1 H), 3.99 (dd, J = 13.2, 11.5 Hz, 1 H), 3.70 (m, 1 H), 3.45 (m, 1 H), 3.00 (d, J = 15.2 Hz, 1 H), 2.77−2.84 (m, 2 H), 2.47 (t, J = 13.8 Hz, 1 H), 1.90 (dd, J = 13.9, 2.9 Hz, 1 H), 1.48 (s, 9 H), 1.45 (s, 3 H), 0.67−0.73 (m, 9 H). HRMS (ESI) m/z 596.2003 $[M + H]^+$ ($C_{30}H_{39}Cl_2NO_5S$ requires 596.1999).

2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-Butylsulfonyl)-1-cyclobutylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (36). Compound **36** was prepared from **63** according to a similar procedure described in method C. ^{1}H NMR (400 MHz, CD_3OD-d_4) δ ppm 7.29 (m, 3 H), 7.08−7.18 (m, 3 H), 7.04 (s, 1 H), 6.95−7.00 (m, 1 H), 5.06 (d, J = 10.96 Hz, 1 H), 3.87−4.00 (m, 1 H), 3.39−3.51 (m, 2 H), 2.89−3.07 (m, 3 H), 2.62 (d, J = 13.50 Hz, 1 H), 2.29 (t, J = 13.69 Hz, 1 H), 2.02 (dd, J = 13.60, 3.03 Hz, 1 H), 1.81−1.92 (m, 1 H), 1.48−1.61 (m, 1 H), 1.44 (s, 9 H), 1.32−1.39 (m, 5 H), 1.29 (m, 1 H), 0.80−0.96 (m, 1 H). HRMS (ESI) m/z 594.1848 $[M + H]^+$ ($C_{30}H_{37}Cl_2NO_5S$ requires 594.1842).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylsulfonyl)propan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (37). Compound **37** was prepared from **61** according to a similar procedure described in method C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.25 (m, 2 H), 7.02−7.16 (m, 4 H), 6.95 (s, 1 H), 6.83 (d, J = 7.3 Hz, 1 H), 4.93 (d, 10.8 Hz, 1 H), 4.27 (dd, J = 13.0, 11.2 Hz, 1 H), 3.66−3.75 (m, 1 H), 3.03−3.11 (m, 2 H), 3.00 (d, J = 14.9 Hz, 1 H), 2.74 (d, J = 14.9 Hz, 1 H), 2.64 (dd, J = 13.2, 2.4 Hz, 1 H), 2.39 (t, J = 13.7 Hz, 1 H), 1.89 (dd, J = 13.8, 2.6 Hz, 1 H), 1.49 (s, 3 H), 1.42 (d, J = 6.8 Hz, 6 H), 1.26 (d, J = 6.8 Hz, 3 H). HRMS (ESI) m/z 540.1374 $[M + H]^+$ ($C_{26}H_{31}Cl_2NO_5S$ requires 540.1373).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (2). Compound **2** was prepared from **57** according to a similar procedure described in method B. ^{1}H NMR (500 MHz, CD_3OD-d_4) δ ppm 7.00−7.23 (m, 7 H), 7.03 (m, 1 H), 5.13 (d, J = 11 Hz, 1 H), 4.01 (dd, J = 13.7, 10.5 Hz, 1 H), 3.49−3.65 (m, 1 H), 3.32−3.37 (m, 1 H), 3.25−3.29 (m, 1 H), 3.11 (d, J = 13.7 Hz, 1 H), 2.99 (d, J = 13.7 Hz, 1 H), 2.61 (d, J = 13.5 Hz, 1 H), 2.31 (t, J = 13.7 Hz, 1 H), 2.18 (dq, J = 14, 6.9 Hz, 1 H), 2.05 (dd, J = 13.6, 2.8 Hz, 1 H), 1.41 (d, J = 6.9 Hz, 6 H), 1.37 (s, 3 H), 0.65 (d, J = 6.6 Hz, 3 H), −0.50 (d, J = 6.9 Hz, 3 H). MS (ESI) 568.0 $[M + H]^+$.

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-cyclopropyl-2-(isopropylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (39). Compound **39** was prepared from **56** according to similar procedure described in method C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.23−7.26 (m, 3 H), 7.04−7.20 (m, 3 H), 6.93−6.97 (m, 1 H), 6.84−6.88 (m, 1 H), 4.93 (d, J = 10.8 Hz, 1 H), 4.34 (m, 1 H), 3.05−3.18 (3 H, m, 3 H), 2.86 (d, J = 13.3 Hz, 1 H), 2.77 (d, J = 15.3 Hz, 2 H), 2.46 (t, J = 13.8 Hz, 1 H), 1.86 (dd, J = 13.5, 2.5 Hz, 2 H), 1.51 (s, 3 H), 1.44 (d, J = 6.8 Hz, 6 H), 0.31−0.44 (m, 1 H), 0.18−2.80 (m, 1 H), −0.35−0.23 (m, 1 H), −1.15−1.02 (s, br, 1 H). HRMS (ESI) m/z 566.1536 $[M + H]^+$ ($C_{28}H_{33}Cl_2NO_5S$ requires 566.1529).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-1-(methylsulfonyl)propan-2-yl)-2-oxopiperidin-3-yl)acetic Acid (41). Compound **41** was prepared from **61** according to a similar procedure described in method C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.21−7.28 (m, 2 H), 7.08−7.15 (m, 4 H), 6.94−6.99 (m, 1 H), 6.83 (d, J = 7.1 Hz, 1 H), 4.95 (d, J = 10.8 Hz, 1 H), 4.44 (dd, J = 13.2, 11.3 Hz, 1 H), 4.14 (m, 1 H), 3.70 (m, 1 H), 3.00−3.10 (m, 1 H), 2.77 (dd, J = 2.45, 12.5, 1 H), 2.34 (t, J = 13.7 Hz, 1 H), 1.92 (d, J = 13.7 Hz, 1 H), 1.43 (s, 3 H), 1.27 (d, J = 6.85 Hz, 3 H). HRMS (ESI) m/z 512.1065 $[M + H]^+$ ($C_{24}H_{27}Cl_2NO_5S$ requires 512.1060).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-cyclopropyl-2-(methylsulfonyl)ethyl)-3-methyl-2-oxopiperidin-3-yl)acetic Acid (43). Compound **43** was prepared from **56** according to a similar procedure described in method C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27 (m, 4 H), 7.07−7.20 (m, 2 H), 6.96 (s, 1 H), 6.81−6.92 (m, 1 H), 4.87 (d, J = 10.56 Hz, 1 H), 4.44 (s, br,1 H), 3.01−3.24 (m, 3 H), 3.00 (s, 3 H), 2.78 (m, 2 H), 2.43 (t, J = 13.79 Hz, 1 H), 1.71 1.97 (m, 2 H), 1.51 (s, 3 H), 0.33−0.49 (m, 1 H), 0.27 (s, br,1 H), −0.26 (s, br,1 H), −1.03 (s, br, 1 H). HRMS (ESI) m/z 538.1223 $[M + H]^+$ ($C_{26}H_{29}Cl_2NO_5S$ requires 538.1216).

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-1-(methylsulfonyl)pentan-3-yl)-2-oxopiperidin-3-yl)acetic Acid (21). To a solution of diethyl methylsulfonylmethylphosphonate (48.8 mg, 0.212 mmol) in THF (1.2 mL) was added butyllithium (1.6 M in THF, 127 μL, 0.203 mmol) at −78 °C under nitrogen. Thirty minutes later, a solution of **52** (100 mg, 0.193 mmol) in THF (0.8 mL) was added dropwise. After being stirred at −78 °C for 3 h, the reaction was quenched (*i*PrOH, EtOAc, and water). The reaction was warmed to 25 °C, and the aqueous layer was extracted (2 × EtOAc). The combined organics were washed (brine), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2, 0−75% EtOAc/hexanes, gradient elution) provided (3*R*,5*R*,6*S*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-methyl-1-((*E*)-1-(methylsulfonyl)pent-1-en-3-yl)piperidin-2-one (80.0 mg, 70%). MS (ESI) 594.2 $[M + H]^+$.

The conjugated sulfone above (60.0 mg, 0.101 mmol) was dissolved in ethanol (1.0 mL, 0.101 mmol) at 25 °C. Pd/C (5.37 mg, 5.05 μmol) was added, and the reaction was allowed to stir under a hydrogen balloon. The solvents were removed and flash column chromatography (SiO_2, 0−2% MeOH/DCM, gradient elution) provided **62** (50.0 mg, 83%).

To a solution of **62** (75.0 mg, 0.126 mmol) in THF (1.2 mL) was added 2,2,2-trifluoroacetic acid (71.7 mg, 0.629 mmol) at 25 °C. After being stirred for 2 h, the reaction was concentrated under reduced pressure. Flash column chromatography (SiO_2, 10% MeOH/DCM) provided (3*R*,5*R*,6*S*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-(2,3-di-

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hydroxypropyl)-3-methyl-1-(1-(methylsulfonyl)pentan-3-yl)piperidin-2-one (45.0 mg, 64%).

To a solution of the diol above (45.0 mg, 0.081 mmol) and tempo (5.57 mg, 0.036 mmol) in acetonitrile (8 mL) and pH 6.7 buffer (0.5 mL) at 35 °C were added solutions of sodium chlorite (23.8 mg, 0.210 mmol) in water (0.2 mL) and sodium hypochlorite (0.804 μL, 0.013 mmol) in water (0.2 mL) consecutively. After being stirred for 4 h, the reaction was quenched (1N HCl and EtOAc). The aqueous layer was extracted (EtOAc), and organics were washed (brine), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (SiO_2, 10% MeOH/DCM) to provide 2-((3*R*,5*R*,6*S*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-1-((*S*)-1-(methylsulfonyl)pentan-3-yl)-2-oxopiperidin-3-yl)acetic acid (7.00 mg, 16%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.23−7.27 (m, 2 H), 7.14−7.18 (m, 1 H), 7.09−7.14 (m, 1 H), 7.05 (d, J = 4.89 Hz, 2 H), 6.95 (s, 1 H), 6.75 (d, J = 7.58 Hz, 1 H), 4.58 (d, J = 10.51 Hz, 1 H), 3.40 (m, 1 H), 3.00−3.20 (m, 3 H), 2.82 (d, J = 12.0 Hz, 1 H), 2.92 (s, 3 H), 2.15−2.25 (m, 2 H), 2.05−2.10 (m, 1 H), 2.04 (m,1 H), 1.98 (s,1 H), 1.86 (m, 1 H), 1.51−1.57 (m, 1 H), 1.49 (s, 3 H), 0.61 (t, J = 7.34 Hz, 3 H). HRMS (ESI) m/z 540.1374 $[M + H]^+$ ($C_{26}H_{31}Cl_2NO_5S$ requires 540.1373).

Determination of the Single Crystal Structure of 2. First, 0.75 mL of 60% EtOH/H_2O was added to 100 mg of material with stirring at 25 °C. After a couple of minutes the foam was replaced by white crystalline material. The mixture was heated at reflux and then cooled to rt slowly and allowed to stand without stirring. After a few days, large crystals had formed. The material was collected by vacuum filtration to provide colorless needles.

A colorless rectangular rod of $C_{30}H_{41}Cl_2NO_6S$, approximate dimensions 0.17 mm × 0.24 mm × 0.45 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 100(2) K on a Bruker Kappa APEX II system equipped with a graphite monochromator and a CuKα fine-focus sealed tube (λ = 1.54178 Å) operated at 1.2 kW power (40 kV, 30 mA). The detector was placed at a distance of 5.0 cm from the crystal.

A total of 2464 frames were collected with a scan width of 0.5° in ω and φ and an exposure time of 10 s/frame. The total data collection time was 11 h. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a tetragonal cell yielded a total of 9052 reflections to a maximum θ angle of 66.53° (0.8405 Å resolution), of which 4449 were independent (redundancy 3.46), completeness = 92.1% (R_{int} = 5.21%, R_{sig} = 6.70%) and 4290 (96.4%) were greater than >2σ(I) σ(F^2). The final cell constants of a = 9.6944(4) Å, b = 9.6944(4) Å, c = 34.0641(15)Å, α = 90°, β = 90°, γ = 90°, volume = 3201.4(2) Å^3, are based upon the refinement of the XYZ-centroids of 6233 reflections above 20 σ(I) with 5.188° < 2θ < 133.077° . Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.53. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.2653 and 0.5046.

The structure was solved and refined using the Bruker SHELXTL (version 6.1) software package, using the space group $P4(3)$, with Z = 4 for the formula unit, $C_{30}H_{41}Cl_2NO_6S$. The final anisotropic full-matrix least-squares refinement on F^2 with 377 variables converged at $R1$ = 4.11%, for the observed data and wR^2 = 10.98% for all data. The goodness-of-fit was 1.058. The largest peak on the final difference electron density synthesis was 0.524 e−/Å^3 and the largest hole was −0.327 e−/Å^3 with an RMS deviation of 0.050 e−/Å^3 On the basis of the final model, the calculated density was 1.275 g/cm^3 and F(000), 1304 e−.

■ ASSOCIATED CONTENT

Supporting Information

In vitro biological assays, in vivo study protocols, determination of cocrystal structures of **25** with MDM2. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

The coordinates of **25** with MDM2 have been deposited in the PDB with accession codes 4OAS.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

AcCN, acetonitrile; Boc, *tert*-butoxycarbonyl; BrdU, 5-bromo-2-deoxyuridine; CMBP, cyanomethylenetributylphosphorane; CL, clearance; CYP3A4, cytochrome P450 3A4; DCM, dichloromethane; DMF, *N*,*N*-diemethylformamide; DMSO, dimethylsulfoxide; dr, diastereoselectivity ratio; EdU, 5-ethynyl-2′-deoxyuridine; EtOAc, ethyl acetate; hPXR, human pregnane X receptor; HTRF, homogous time-resolved fluorescence; KHMDS, potassium bis(trimethylsilyl)amide; MDM2, murine double minute 2; MsCl, methanesulfonyl chloride; NMO, *N*-methylmorpholinine *N*-oxide; QD, once a day dosing; qRT-PCR, quantitative reverse transcription polymerase chain reaction; SEM, standard error of mean; SPR, surface plasmon resonance; TBAF, tetrabutylammonium fluoride; TDI, time dependent inhibition; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran

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