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Novel Inhibitors of the MDM2-p53 Interaction Featuring Hydrogen Bond Acceptors as Carboxylic Acid Isosteres

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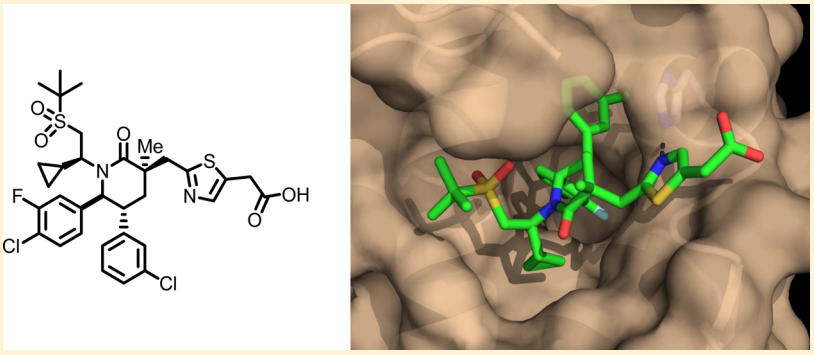
Supporting Information



ABSTRACT: We previously reported the discovery of potent and selective morpholinone and piperidinone inhibitors of the MDM2-p53 interaction. These inhibitors have in common a carboxylic acid moiety that engages in an electrostatic interaction with MDM2-His96. Our continued search for potent and diverse inhibitors led to the discovery of novel replacements for these acids uncovering new interactions with the MDM2 protein. In particular, using pyridine or thiazole as isosteres of the carboxylic acid moiety resulted in very potent analogues. From these, AM-6761 (**4**) emerged as a potent inhibitor with remarkable biochemical (HTRF IC_{50} = 0.1 nM) and cellular potency (SJSA-1 EdU IC_{50} = 16 nM), as well as favorable pharmacokinetic properties. Compound **4** also shows excellent antitumor activity in the SJSA-1 osteosarcoma xenograft model with an ED_{50} of 11 mg/kg. Optimization efforts toward the discovery of these inhibitors as well as the new interactions observed with the MDM2 protein are described herein.

INTRODUCTION

Activation of the pro-apoptotic protein p53 is a promising and highly sought out approach toward cancer treatment.[1] Upon cellular stress, p53 activation leads to the transcription of multiple downstream genes that regulate cell cycle control, apoptosis, DNA repair, and senescence.[2−4] About half of all human cancers progress either by mutation or deletion of p53.[5] However, for the remaining half that retains wild-type p53 activity, survival is achieved by other mechanisms such as upregulation of its natural antagonists. Amplified in many tumor tissues, MDM2 (murine double minute 2) has been identified as p53's main negative regulator.[6−8] Many research programs, including our own, aim to design small molecules that bind to MDM2 at its p53 active site, impeding MDM2's interaction with p53. This results in increased levels of unbound p53 and reactivation of its pathways. From these efforts, several inhibitors have recently emerged and are now being tested in the clinic, most of which were registered within the past two years.[9−13] Consequently, this is arguably one of the most exciting times in over 30 years of research on the p53 pathway.[13−17]

Recently, we reported on a series of piperidinone-derivatives as potent and selective inhibitors of the MDM2-p53

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interaction. Our optimization efforts within this series led to the discovery of AMG 232 (**1**, Figure 1), which is currently being

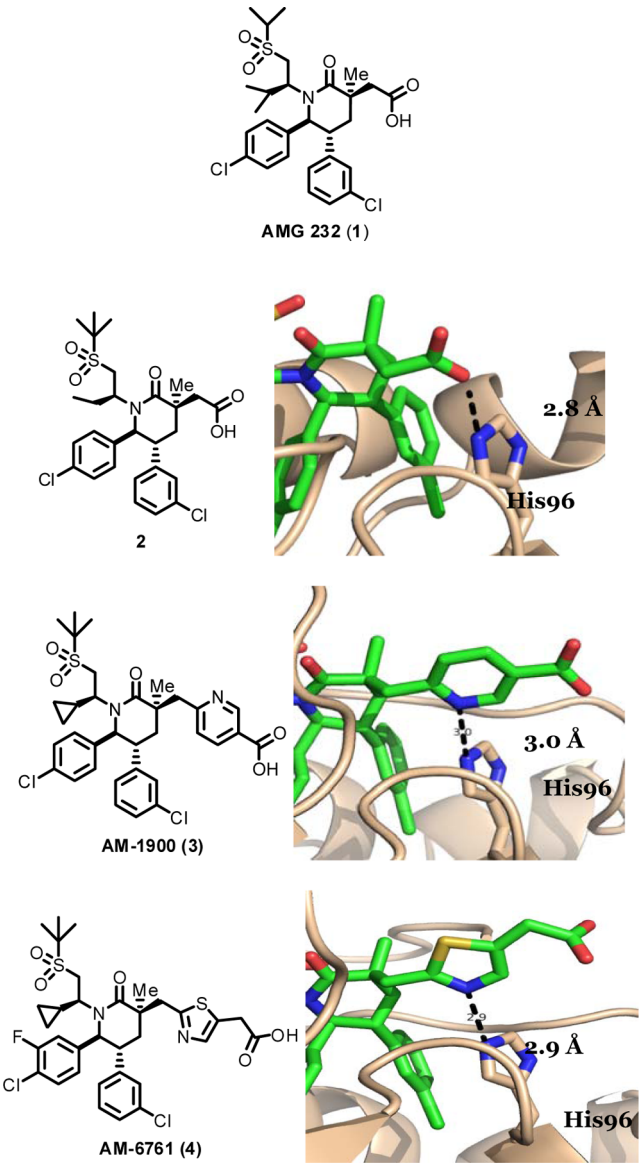


Figure 1. Co-crystal structures of potent piperidinone inhibitors bound to human MDM2 (6–110) highlighting their interaction to MDM2-His96. Coordinates for compounds **2** (PDB code: 4OAB), **3** (PDB code: 4OGN), and **4** (PDB code: 4ODE) bound to MDM2 have been deposited in the PDB.

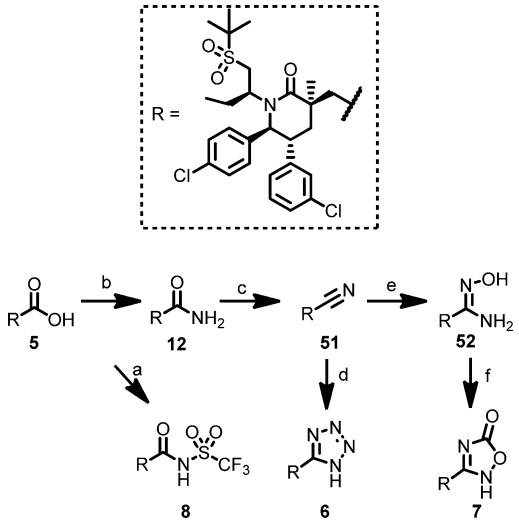
tested in the clinic.[17,18] Inhibitor **1** is highly potent (K_d = 0.045 nM; SJSA-1 EdU IC_{50} = 9.1 nM)[19] with remarkable pharmacokinetic properties (*h*Hep CL_{int} = 6.3 μL/min/10^6 cells) and in vivo efficacy in the SJSA-1 osteosarcoma xenograft model (ED_{50} = 9.1 mg/kg).[17,20] Because **1** is among the most potent inhibitors of the MDM2/p53 interaction reported to date and has good pharmacokinetic properties in preclinical models, with this work, we aim to identify compounds with distinct metabolic profiles to **1** should a compound with a different metabolite profile or clearance route is needed.

Crystallographic analysis of analogous inhibitors such as **2** bound to MDM2 shows that the carboxylate interacts with the imidazole of the His96 side chain of MDM2.[20] This unique interaction resulted in a nearly 100-fold improvement in binding affinity.[18e] The amide of the oxindole-derived MDM2 inhibitors was reported to engage in similar interactions with His96.[16,18e] Thus, we set out to explore this and other acid replacements within our series. In this article, we described our efforts to identify acid replacements, which led to the discovery of **4**, an exquisitely potent thiazolyl-containing inhibitor of the MDM2-p53 interaction. Inhibitor **4** also exhibits excellent pharmacokinetic properties (*h*Hep CL_{int} = 5.5 μL/min/10^6 cells) and in vivo efficacy in the SJSA-1 osteosarcoma xenograft model (ED_{50} = 11 mg/kg).

CHEMISTRY

The route to the isosteres of acid **5**, compounds **6**–**8**, and **12** is depicted in Scheme 1. Many acid-containing heterocycles were

Scheme 1[a]



[a]Reagents and conditions: (a) trifluoromethanesulfonamide, DIEA, HATU, DMF, rt, 5 h, 41%; (b) *N*-methylmorpholine, 28% NH_3/H_2O, isobutyl chloroformate, THF, 0 °C, 3 h, 75%; (c) trifluoroacetic anhydride, TEA, 0 °C, 1 h, 92%; (d) NaN_3, DMF, 90 °C, 5 days, 65%; (e) $NaHCO_3$, NH_4OH, MeOH, 70 °C, 12 h, quant.; (f) CDI, DBU, dioxane, 100 °C, 2 days, 15% (last two steps).

synthesized from common nitrile intermediate **53** (Scheme 2). From **53**, addition of ethanol under acidic conditions resulted in imidate **54** that was taken directly to iminium **55** by the addition of ammonia. Intermediate **55** can be transformed to either imidazole inhibitor **45** or pyrimidine **27** through the sequential reaction of **55** with ethyl-3-oxo-propionate or 4-chloroacetic acid methyl ester, respectively, followed by saponification.

Alternatively, nitrile intermediate **53** could be converted to thioamide **56** with phosphorus pentasulfide. From **56**, a variety of thiazole isomers could be synthesized by the addition of the corresponding ester reagent followed by saponification of the resulting ester to give inhibitors **32**, **33**, and **37**.

Synthesis of pyrazole inhibitor **31** (Scheme 3) commenced by C3-alkylation of piperidinone intermediate **57** with (2-chloromethyl)ethyltrimethylsilane giving ether **58**. Intermediate **58** was then transformed to primary alcohol **59** with boron trifluoride and then to mesylate **60** by reaction with methanesulfonic anhydride. The mesylate moiety of **60** could then be displaced with hydrazine to give **61** that was converted to pyrazole **62** by the addition of ethyl-2-formyl-3-oxo-

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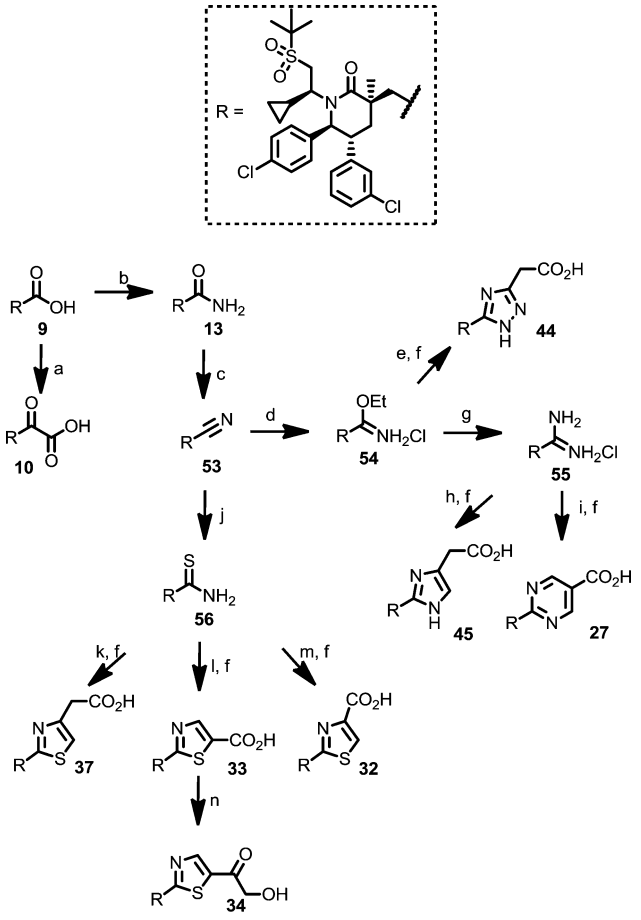
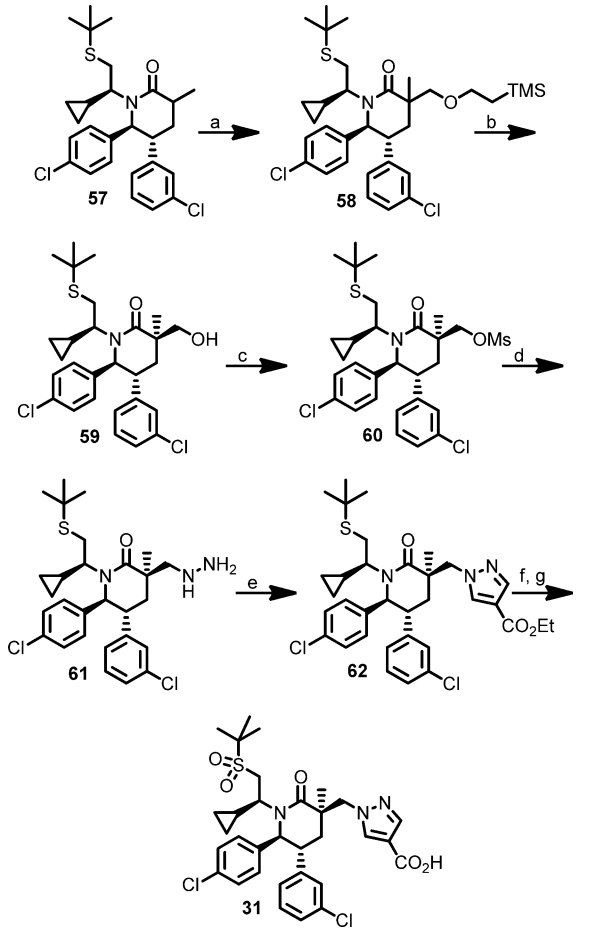
Scheme 2[a]



[a]Reagents and conditions: (a) 1-(cyanomethyl)tetrahydro-1-*H*-thiophene-1-ium bromide, DIEA, HATU, DCM, rt, 4 h, quant.; then, oxone, DMF/H_2O, rt, 3 h, 64%; (b) NH_3, DIEA, HATU, 55 °C, 1 h, 88%; (c) trifluoroacetic anhydride, TEA, 0 °C, 1 h, 90%; (d) HCl, ethanol, 1 h, rt, quant.; (e) ethyl 3-hydrazinyl-3-oxopropanoate, EtOH, 12 h, 63%; (f) LiOH, MeOH/THF/H_2O, 50 °C, 1 h; (g) NH_3, ethanol, 12 h, rt, 100%; (h) ethyl trans-4-oxo-2-butenoate, 130 °C, 1 h, 8%; (i) ethyl-2-formyl-3-oxo-propionate, DMA, 100 °C, 2 h, 66%; (j) P_2S_5, ethanol, 70 °C, 12 h, 66%; (k) 4-chloroacetic acid methyl ester, EtOH, 90 °C, 3 h, 57% (both steps); (l) ethyl-2-chloro-3-oxopropanoate, toluene, 100 °C, 5 h, 66%; (m) ethyl bromo pyruvate, dioxane, 3 h, rt; then, pyridine and TFA, 12 h, rt, 22%; (n) oxalyl chloride, DMF, 1 h; then, tris(trimethylsilyloxy)ethylene, 90 °C, 12 h, 10%.

Scheme 3[a]



[a]Reagents and conditions: (a) (2-chloromethoxy)ethyltrimethylsilane, LDA, THF, −78 °C, 1 h, 52%; (b) BF_3−OEt_2, DCM, 0 °C, 3 h, 33%; (c) methanesulfonic anhydride, NEt_3, DCM, 30 min, rt, quant.; (d) hydrazine, EtOH, 90 °C, 12 h, 40% conversion; (e) ethyl-2-formyl-3-oxo-propionate, 100 °C, DMA, 2 h, 38%; (f) mCPBA, DCM, 0 °C, 30 min, 30%; (g) LiOH, MeOH/THF/H_2O, 50 °C, 1 h, 30% (last two steps).

propionate. Finally, inhibitor **31** was obtained through oxidation of the *tert*-butyl thioether to its corresponding sulfone followed by saponification of the ethyl ester to the acid.

Addition of triphenylphosphine and carbon tetrabromide to alcohol **59** yields alkylbromide **63** (Scheme 4). This intermediate undergoes displacement by 2-mercaptopyrimidine to form thioether **64**. Oxidation of **64** to bis-sulfone **65** proceeded smoothly with mCPBA. Finally, inhibitor **14** was formed by reaction of **65** with hydroxylamine-*O*-sulfonic acid.

Highlighted in Schemes 5 and 6 are the synthetic routes used to access some of our most potent thiazole inhibitors. Coupling between acid **9** and ethyl 4-(bis(trimethylsilyl)amino)but-2-ynoate in the presence of TBAF produced propargylamide **67** that could then undergo one pot cyclization to thiazole **68** by refluxing in toluene in the presence of Lawesson's reagent (Scheme 5). From **68**, alkylation α to the ester moiety with either methyl iodide or 1,2-dibromoethane resulted in inhibitors **39** and **40** after saponification of the ethyl ester.

Alternatively, coupling of acid **69** with glycine methyl ester followed by saponification provided intermediate **70** (Scheme 6). Addition of methyl potassium malonate to **70** followed by decarboxylation resulted in the formation of β-keto ester **71** that, similar to **67**, can undergo cyclization to thiazole **72** in the presence of Lawesson's reagent. Reaction of **72** with *N*-fluorobenzenesulfonimide resulted in fluorination at the α carbon to the ester, but the reaction was sluggish and not chemoselective providing a mixture of **41** and **42** that could be separated via preparative HPLC. Oxazole **43** was formed from cyclization of **71** in the presence of Burgess' reagent.

Morpholinone inhibitors **46** and **47** were synthesized starting from C2-Me morpholinone **73** (Scheme 7). Alkylation with methyl (6-bromomethyl)nicotinate yields C2-disubstituted **74** as a nearly 1:1 mixture of epimers at C2. Deprotection of silylether, Mitsunobu reaction, and oxidation of the resulting thioether to the corresponding sulfone produced **76** that can be easily transformed to a mixture of **46** and **47** by saponification. The isomers were separated by preparative HPLC.

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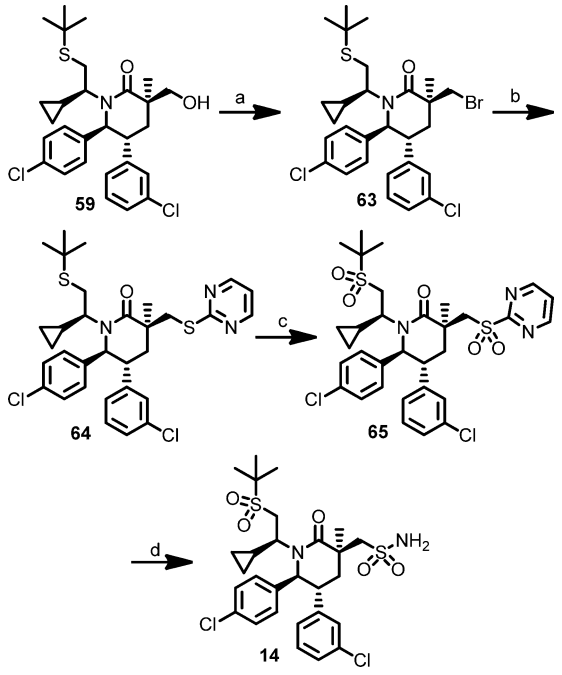
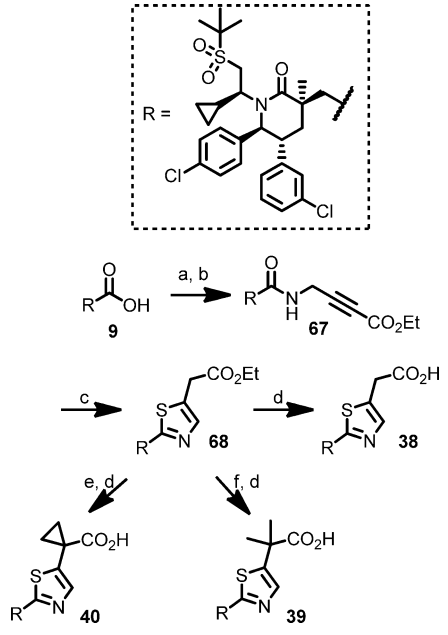
Scheme 4[a]



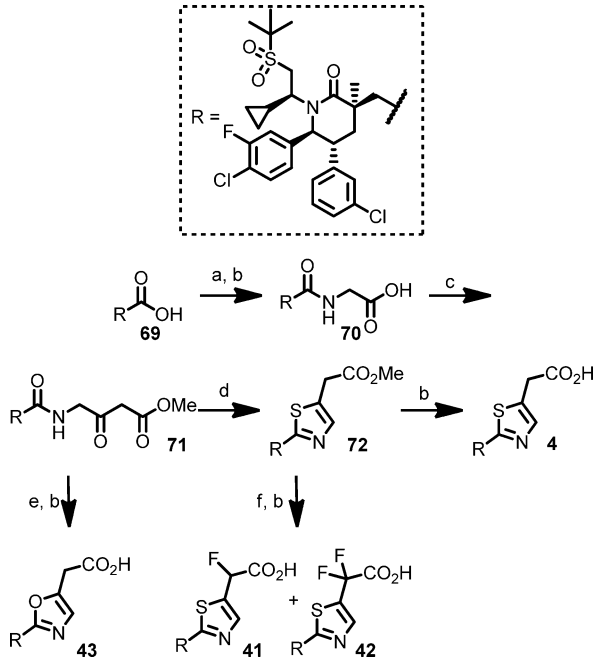
[a]Reagents and conditions: (a) triphenylphosphine, CBr_4, MeCN, 55 °C, 5 h, 86%; (b) 2-mercaptopyrimidine, K_2CO_3, DMF, rt, 12 h; (c) oxone, THF/H_2O, rt, 12 h, 48% (last two steps); (d) hydroxylamine-*O*-sulfonic acid, K_2CO_3, MeOH, 12 h, rt, 46%.

Scheme 5[a]



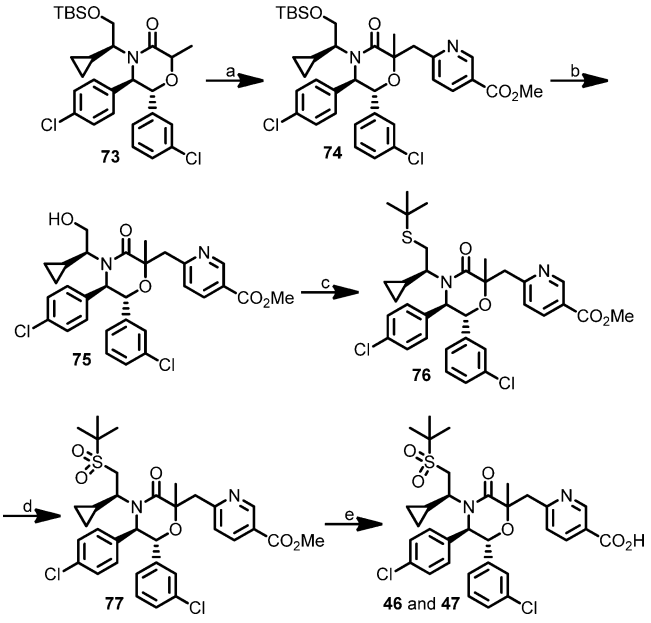
[a]Reagents and conditions: (a) oxalyl chloride, THF, DMF, rt, 1 h, quant.; (b) ethyl 4-(bis(trimethylsilyl)amino)but-2-ynoate, TBAF, THF, rt, 12 h; then, HCl/water, 72%; (c) Lawesson's reagent, toluene, 60 °C, 3 h, 63%; (d) LiOH, MeOH/THF/H_2O, 50 °C, 1 h; (f) MeI, NaO^{t}Bu, DMF, 0 °C, 30 min, 62%; (e) 1,2-dibromoethane, NaO^{t}Bu, DMF, 0 °C, 30 min, 80%.

Scheme 6[a]



[a]Reagents and conditions: (a) glycine methyl ester hydrochloride, EDC, HOAt, $NaHCO_3$, DMF, 40 °C, 3 h, quant.; (b) LiOH, MeOH/THF/H_2O, 50 °C, 1 h; (c) $MgCl_2$, CDI, methyl potassium malonate, 50 °C, 12 h, 63%; (d) Lawesson's reagent, toluene, 100 °C, 3 h, 71%; (e) Burgess' reagent, DCE, 120 °C, 7 h, 62%; (f) *N*-fluorobenzenesulfonimide, NaO^{t}Bu, DMF, 0 °C, 1 h; then step b, **41**, 11%; **42**, 4%.

Scheme 7[a]



[a]Reagents and conditions: (a) methyl (6-bromomethyl)nicotinate, LDA, THF, −78 °C, 2 h, 78%, 1:1 d.r.; (b) TBAF, THF, rt, 12 h, 60%; (c) ^{t}BuSH, cyanomethyltri-*N*-butylphosphorane, 110 °C, 12 h, 61%; (d) mCPBA, DCM, 30 min, 0 °C, quant.; (e) LiOH, MeOH/THF/H_2O, 50 °C, 1 h.

Finally, many of the nicotinic acid analogues were synthesized through simple alkylation of **57** with the corresponding alkylbromide (Scheme 8). Alkylation with 5-bromo-2-(bromomethyl)pyridine results in **78** that can be functionalized to inhibitors such as **23** through standard Pd-mediated coupling conditions.

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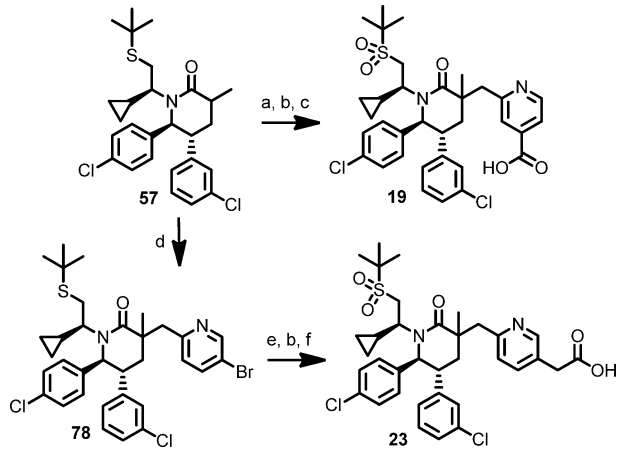
Scheme 8[a]



[a]Reagents and conditions: (a) *tert*-butyl-2-(bromomethyl)-isonicotinate, LDA, THF, −78 °C, 4 h, 71%, 3:1 d.r.; (b) mCPBA, DCM, 30 min, 0 °C, quant.; (c) LiOH, MeOH/THF/H_2O, 50 °C, 1 h; (d) 5-bromo-2-(bromomethyl)pyridine, LDA, THF, −78 °C, 2 h, 18% (single isomer); (e) $Pd(dba)_2$, Q-phos, (2-(*tert*-butoxy)-2-oxoethyl)zinc(II) chloride, THF, 60 °C, 4 h, 37%; (f) formic acid, 6 h, 75%.

RESULTS AND DISCUSSION

Piperidinone Inhibitors. Table 1 briefly summarizes our initial efforts to replace the carboxylic acid moiety with a variety of functional groups.[21] At first, we examined known acid isosteres or functionalities that could form an electrostatic interaction with MDM2-His96. Analogues featuring tetrazole (**6**) and 1,2,4-oxadiazolone (**7**) as acid isosteres demonstrated potency similar to that of the parent carboxylic acid (**5**) in the MDM2-p53 biochemical assay (HTRF-based neutralization assay measuring inhibition of the interaction between MDM2 and p53) and cell proliferation assays (EdU using SJSA-1 tumor cells). However, unlike **5**, compounds **6** and **7** are moderate inhibitors of CYP3A4. Acylsulfonamide analogues such as **8** showed a substantial reduction in potency in the biochemical and cell based assays and also displayed moderate CYP3A4 inhibition. Substitution of the carboxylic acid with an α-keto acid (**10**) provided an inhibitor with a profile similar to that of the corresponding acid (**9**) in the in vitro assays (Table 1) but also displayed poor pharmacokinetic properties in vivo in preclinical models (data not shown). The carboxylic acid **5** and the α-hydroxyl ketone **11** afford similar activity in the HTRF assay suggesting that an ionized group is not essential for potent binding to MDM2. Encouraged by this result, we explored amides as replacements for the carboxylic acid (**12** and **13**, Table 1). It was reassuring to observe that **13** had potency similar to that of the analogous carboxylic acid **9** in the HTRF assay, although **12** and **13** are approximately 10-fold less potent in the cell proliferation assay compared to their parent acids **5** and **9**, respectively, and give rise to the aforementioned CYP3A4 inhibition liability. A great variety of amides and amides isosteres, such as sulfonamide **14**, provided less potent compounds and also carried the CYP3A4 inhibition. Our efforts to improve potency by engaging additional residues on the MDM2 protein such as Lys94 led us to synthesize pyrrolidines **15** and **16** containing an appended carboxylic acid. These inhibitors have potency similar to that of the carboxylic acid analogue (**9**) in the MDM2-p53 HTRF assay and no activity in the CYP3A4 inhibition assay. We hypothesized that the pyrrolidineamide moiety of **15** and **16** bind to MDM2 through a hydrogen bond interaction with MDM2-His96. Since **15** and **16** are epimers at the stereocenter bearing the carboxylic acid moiety and have similar potency in the biochemical assay, it was postulated that this group was not making a specific interaction with the protein; however, the appending acid facilitated the decrease in CYP3A4 inhibition. Therefore, it was hypothesized that heterocyclic derivatives could similarly interact with MDM2-His96 serving as viable replacements of the carboxylic acid moiety. Indeed, pyridine **17** has potency similar to that of the carboxylic acid **9** in the biochemical assay (HTRF IC_{50} in the serum free assay for **17** and **9** is 0.30 ± 0.01 and 0.10 ± 0.01 nM, respectively; Table 1). Notably, the phenyl-analogue **18** was 30-fold less potent than **17**, presumably due to the loss of the hydrogen bond interaction between the pyridine nitrogen and the imidazole moiety on MDM2-His96. Although encouraged by the intrinsic affinity of **17** toward MDM2 in the HTRF assay, it was necessary to address its potent inhibition of CYP3A4. Thus, we introduced a carboxylic acid with the intention to achieve a similar decrease in CYP3A4 inhibition as previously observed with pyrrolidine amides **15** and **16**. This led to the discovery of isonicotinic acid **19**, which shows significant improvement in the biochemical and cell based assays while displaying no activity in the CYP3A4 inhibition assay. Exploration of other heterocycles led to the discovery of thiazole **20**, a highly potent inhibitor of the MDM2-p53 interaction in the HTRF and cell proliferation assays with negligible CYP3A4 inhibition. As a result, we decided to explore other heterocycles including nicotinic acid isomers of **19** as well as thiazole inhibitors such as **20**.

First, we probed the position of the carboxylic acid on the pyridine ring. To this end, inhibitors **19**, **21**, and **3** were synthesized (Table 2). Notably, the meta (**19**)- and para-substituted (**3**) analogues offer similar potency in the MDM2-p53 biochemical assay. However, **3** is significantly more potent than **19** in the cell based assays, including the mechanism based p21 assay with SJSA-1 cells (p21 IC_{50} for **3** and **19** of 5 nM and 47 nM, respectively). Unfortunately, **3** also features an increased potential for drug−drug interactions by time-dependent inhibition of CYP3A4 (TDI, 61% inhibition at a concentration of 10 μM; Table 2).[22] Co-crystal structure of **3** bound to human MDM2 (17−111) shows a hydrogen bond interaction between the pyridine moiety and MDM2-His96 confirming our hypothesis for the binding of these inhibitors (Figure 1). Our measurements show the hydrogen bond between the pyridine and the imidazole moieties to be classical in nature (C−C−N-H ∠ 170°) with little to no π-hydrogen bond contribution.[23] Introduction of the *meta*-fluoro substituent at the C6-arene (**22**) resulted in a 10-fold increase in potency in the serum-free HTRF assay when compared to that of parent **3**. However, this increase in potency did not materialize when **22** was tested in the same assay run in the presence of 15% human serum or the cell based assay. Homologation of the carboxylic acid to acetic acid gave inhibitor **23**, which was 2-fold less potent in the HTRF-serum free assay and 3-fold less potent in the cell proliferation assay relative to **3** but had improved stability in the hepatocytes assay as well as decreased CYP3A4 TDI (Table 2). We sought to further improve metabolic stability by hindering the carboxylic acid on **23**. Thus, **24** was synthesized and evaluated in vitro for metabolic stability. Rewardingly, **24** was noticeably more stable (*h*Hep CL_{int} = <0.1 μL/min/10^6 cells) compared to the α-unsubstituted acid **23** (*h*Hep CL_{int} = 3.4 μL/min/10^6 cells) in

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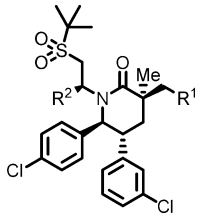
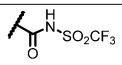
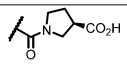
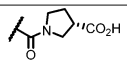
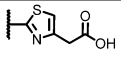
Table 1. Carboxylic Acid Replacements



Compd.	R^1	R^2	HTRF[a] Serum Free IC_{50} (nM)[e]	HTRF[b] 15% HSA IC_{50} (nM)[e]	SJSA-1 EdU[c] IC_{50} (nM)[e]	CYP3A4 IC_{50} (μM)[d]
5		Et	0.10 ± 0.05	1.1 ± 0.5	3 ± 1	>27
6		Et	0.1 ± 0.01	0.8 ± 0.1	5 ± 1	2.5
7		Et	0.2 ± 0.01	1.3 ± 0.2	8 ± 1	1.2
8		Et	3.1 ± 1.0	23 ± 8	897 ± 20	3.8
9		cPr	0.10 ± 0.01	1.1 ± 0.1	2 ± 1	>27
10		cPr	0.10 ± 0.05	1.9 ± 0.7	3.3 ± 0.6	>27
11		Et	0.6 ± 0.2	3.7 ± 0.3	11.7 ± 0.2	0.7
12		Et	0.5 ± 0.2	2.1 ± 0.4	43 ± 3	1.3
13		cPr	0.10 ± 0.05	1.8 ± 0.5	33 ± 1	1.2
14		cPr	1.1 ± 0.2	14 ± 3	547 ± 35	0.5
15		cPr	0.10 ± 0.01	1.8 ± 0.5	15 ± 1	>27
16		cPr	0.10 ± 0.01	0.7 ± 0.1	27 ± 3	>27
17		cPr	0.30 ± 0.01	6.7 ± 0.7	418 ± 17	0.7
18		cPr	137	7.6	14500 ± 1	1.7
19		cPr	0.10 ± 0.04	1.4 ± 0.2	47 ± 15	>27
20		cPr	0.20 ± 0.03	1.1 ± 0.1	25 ± 1	>27

[a]IC_{50} in the biochemical assay using serum free buffer. [b]IC_{50} in the biochemical assay using buffer containing 15% human serum. [c]Cellular potency in SJSA-1 osteosarcoma tumor cells in the presence of 10% human serum. [d]Estimated CYP3A4 inhibition IC_{50}, Midazolam, at 3 μM. [e]Mean and standard deviation of at least two runs.

our in vitro human hepatocyte assay. Attempts to introduce methyl substituents on the nicotinic acid core caused a decrease in potency (**25** and **26**, Table 2). Replacing the pyridine by either a pyrimidine (**27** and **28**, Table 2) or a pyrazine (**29**) yielded inhibitors with similar potency in the biochemical and cellular assays. Notably, the pK_a of the nitrogen in these

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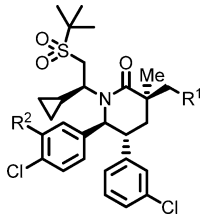
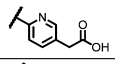
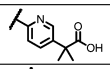
Table 2. Optimization of the Pyridine Series and Other Six-Membered Heterocyclic Analogues



Compd.	R^1	R^2	HTRF[a] Serum Free IC_{50} (nM)[f]	HTRF[b] 15% HS IC_{50} (nM)[f]	SJSA-1 EdU[c] IC_{50} (nM)[f]	TDI, % Inhibition of CYP3A4[d]	hHep CL (μL/min per 10^6 cells)[e]
19		H	0.10 ± 0.01	1.4 ± 0.2	47 ± 15	30	---
21		H	1.2 ± 0.6	24 ± 11	730 ± 66	62	---
3		H	0.10 ± 0.01	0.8 ± 0.2	5 ± 3	61	10
22		F	0.10 ± 0.01	0.5 ± 0.1	6± 2	67	7.8
23		H	0.20 ± 0.02	2.0 ± 0.2	17 ± 1	26	3.4
24		H	0.20 ± 0.01	1.7 ± 0.5	13 ± 3	33	< 0.1
25		H	0.40 ± 0.06	5.3 ± 1.2	87 ± 2	49	26
26		H	0.30 ± 0.02	5.9 ± 4.2	62 ± 1	47	5.1
27		H	0.10 ± 0.03	0.8 ± 0.1	18 ± 7	49	10
28		F	0.10 ± 0.03	0.9 ± 0.1	11 ± 2	42	14
29		H	0.10 ± 0.05	0.7 ± 0.1	8 ± 1	44	25
30		H	3 ± 1	39 ± 4	522	---	---

[a]IC_{50} in the biochemical assay using serum free buffer. [b]IC_{50} in the biochemical assay using buffer containing 15% human serum. [c]Cellular potency in SJSA-1 osteosarcoma tumor cells in the presence of 10% human serum. [d]Time-dependent inhibition, % CYP3A4 activity of Rifampin, 30 min, at 10 μM. [e]Human hepatocyte stability. [f]Mean and standard deviation of at least two runs.

heterocycles (pyridine pK_a, ∼5.2; pyrimidine pK_a, ∼1.3; and pyrazine pK_a, ∼0.6) has little to no effect on the CYP3A4 TDI of the inhibitors. Finally, benzoic acid **30** was 150-fold less potent than **3** in the serum-free biochemical assay (Table 2), confirming the importance of the hydrogen bond interaction observed in the cocrystal structure of **3** between the pyridine nitrogen and MDM2-His96 (Figure 1). A similar observation was previously made when we compared the pyridine derivative **17** (HTRF serum free IC_{50} = 0.30 ± 0.01 nM) to its phenyl analogue **18** (HTRF serum free IC_{50} = 137 nM) (Table 1).

We investigated other nitrogen-containing heterocycles, many of which exhibited good potency (Table 3). For example, the pyrazole **31** afforded potency similar to that of the carboxylic acid analogue **9** in the biochemical and cell-based assays, but again presented a considerable CYP3A4 TDI liability. Both thiazole-4-carboxylic acid **32** and thiazole-5-carboxylic acid **33** were synthesized, **33** being 4- and 40-fold more potent than **32** in the biochemical (HTRF, serum free) and cell based assays, respectively, showing that the position of the carboxylic acid substituent plays an important role in potency (Table 3). As previously observed, hydroxy ketone **34** had similar potency compared to that of the parent acid (**33**) suggesting that the ionizable carboxylic acid group was not essential for affinity to MDM2 or potent cellular activity. However, **34** has poor metabolic stability in human hepatocytes and high CYP3A4 inhibition (IC_{50} = 0.8 μM). The reduced activity of the unsubstituted thiazole, **36**, in the CYP3A4 TDI assay compared to that of the analogous thiazole-5-carboxylic acid derivative, **35**, suggested that the acid was in part responsible for the observed time-dependent inhibition of CYP3A4 and that changes around the carboxylic acid could help address this potential liability.

Thus, as observed within the nicotinic acid series (**3** and **23**, Table 2), homologation of the acid gave inhibitor **37**, which is 2-fold more potent than the corresponding thiazole-4-carboxylic acid (**32**) in the p53-MDM2 HTRF assay and is devoid of CYP3A4 TDI activity. Likewise, **38** and **4** show significantly less CYP3A4 TDI (Table 3).

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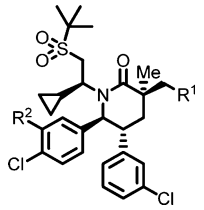
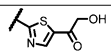
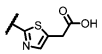
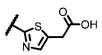
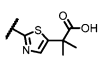
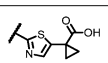
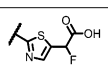
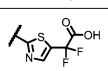
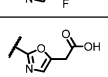
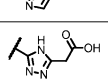
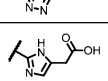
Table 3. Optimization of the Thioazole Series and Other Five-Membered Heterocyclic Derivatives



Compd.	R^1	R^2	HTRF[a] Serum Free IC_{50} (nM)[f]	HTRF[b] 15% HS IC_{50} (nM)[f]	SJSA-1 EdU[c] IC_{50} (nM)[f]	TDI, % Inhibition of CYP3A4 (%)[d]	hHep CL (μL/min per 10^6 cells)[e]
31		H	0.10 ± 0.01	1.0 ± 0.1	4 ± 1	64	2.8
32		H	0.40 ± 0.10	8.1 ± 0.1	164 ± 20	50	1.8
33		H	0.10 ± 0.01	0.7 ± 0.2	4 ± 1	70	8.7
34		H	0.10	1.7	19.0 ± 0.3	---	47
35		F	0.10 ± 0.01	0.7 ± 0.2	4 ± 1	60	10.0
36		F	0.30 ± 0.01	5.5 ± 0.1	219 ± 50	9	14.0
37		H	0.20 ± 0.03	1.1 ± 0.1	25 ± 1	<1	5.3
38		H	0.10 ± 0.01	1.1 ± 0.3	10 ± 1	---	5.8
4		F	0.10 ± 0.01	0.8 ± 0.1	16 ± 1	26	5.5
39		H	0.20 ± 0.01	2.1 ± 0.5	23 ± 1	32	3.6
40		H	0.20 ± 0.01	2.3 ± 0.1	22 ± 1	35	7.7
41		F	0.10 ± 0.01	2.0 ± 0.3	36 ± 1	26	---
42		F	0.10 ± 0.01	1.3 ± 0.2	157 ± 6	51	4.7
43		F	0.10 ± 0.01	1.3 ± 0.1	16 ± 3	26	4.3
44		H	0.10 ± 0.03	1.0 ± 0.2	70 ± 7	36	10.0
45		H	0.20 ± 0.03	1.5 ± 0.4	213 ± 13	74	5.0

[a]IC_{50} in the biochemical assay using serum free buffer. [b]IC_{50} in the biochemical assay using buffer containing 15% human serum. [c]Cellular potency in SJSA-1 osteosarcoma tumor cells in the presence of 10% human serum. [d]Time-dependent inhibition, % CYP3A4 activity of Rifampin, 30 min, at 10 μM. [e]Human hepatocyte stability. [f]Mean and standard deviation of at least two runs.

A cocrystal structure of **4** bound to human MDM2 (Figure 2) demonstrates that this inhibitor binds to MDM2 filling the critical pockets naturally occupied by the three key residues of p53: Leu26, Trp23, and Phe19.9 The 3-chlorophenyl occupies the Leu26 pocket, engaging in a $\pi-\pi$ stacking interaction with the imidazole of the His96. The 3-fluoro-4-chlorophenyl is buried in the Trp23 pocket. The small lipophilic cyclopropyl group projects toward the Phe19 pocket, while the *tert*-butyl sulfone is within van der Waals distance from the "glycine shelf", named after Gly58 on MDM2, maximizing hydrophobic contact with the protein. Finally, the thiazole-nitrogen forms a hydrogen bond (2.9 Å) with the imidazole-NH of His96.

Introducing substituents α to the carboxylic acid of **4** or **38** did not critically alter the overall profile of the inhibitors (**39**–**42**, Table 3). Finally, other heterocycles such as oxazole (**43**), triazole (**44**), and imidazole (**45**) were also synthesized and evaluated. While many of these substitutions were tolerated, they did not lead to increased potency (Table 3).

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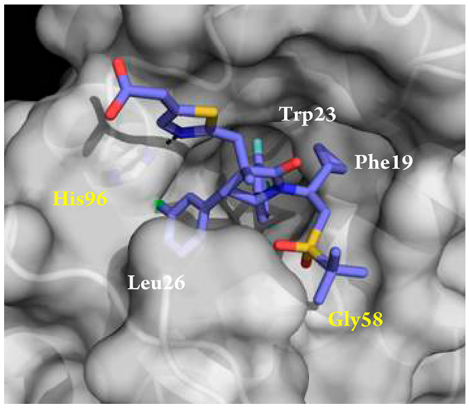


Figure 2. Co-crystal structure of **4** bound to human MDM2 (6−110). White labels indicate positions normally occupied by key p53 residues. MDM2 residues His96 and Gly58 are labeled in yellow. Coordinates for compound **4** (PDB code: 4ODE) bound to MDM2 have been deposited in the PDB.

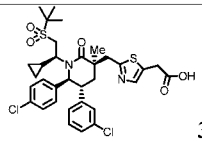
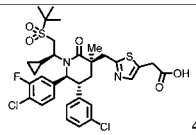
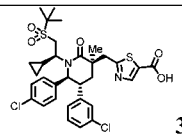
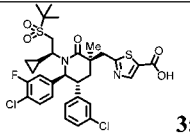
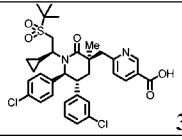
Compounds **3**, **4**, **33**, **35**, and **38** were selected for their potency and evaluated in rodent pharmacokinetic experiments (Table 4). The majority of these inhibitors exhibit low clearance in rodent species. The addition of a *meta*-fluoro substituent at the C5-arene on **4** and **35** (Table 4) improved their metabolic stability in rat and mouse and increased oral bioavailability compared to that of the *des*-fluoro derivatives. These results, together with good cellular potency, favorable in vitro stability in human hepatocytes, and reduced liability to cause potential drug−drug interactions through inhibition of CYP3A4, lead to the selection of **4** for further evaluation in our tumor xenograft model.

First, we confirmed that the cytotoxicity observed with **4** is attributable to activation of the p53 pathway. Thus, we evaluated the ability of **4** to inhibit the proliferation of HCT116 $p53^{wt}$ and $p53^{-/-}$ tumor cells in vitro (Figure 3).[24] Compound **4** displayed robust dose-dependent cell growth inhibitions of HCT116 wild-type p53 cells (IC_{50} = 11 nM) and no inhibition of p53 deficient cells at doses <10 μM. Similarly, **4** also exhibited a dose-dependent increase of p21 mRNA, a direct transcriptional readout of p53 activity, in HCT116 $p53^{wt}$ cells (IC_{50} = 58 nM). No induction was observed when HTC116 $p53^{-/-}$ tumor cells were treated with **4** at concentrations up to 10 μM.

In a pharmacodynamic in vivo xenograft assay with SJSA-1 osteosarcoma tumor cells, **4** demonstrated significant time-dependent p21 induction over the vehicle (Figure 4). A maximum 15-fold induction of p21 mRNA was observed 4 h after dosing QD for 4 days at 25 mg/kg. These data indicated that **4** achieved an on-mechanism inhibition of MDM2 and induction of p53 signaling, and provided dose-selection guidance for the xenograft study.

We tested the ability of **4** to inhibit tumor growth in a mouse xenograft model bearing the same SJSA-1 osteosarcoma tumor used in the pharmacodynamic assay (Figure 5).[25] In this study, **4** caused robust dose-dependent tumor growth inhibition with the highest dose of 50 mg/kg causing 6% tumor regression. The calculated ED_{50} was 11 mg/kg. Figure 6 compares the cellular potency of inhibitor **4** to other known inhibitors that are currently in the clinic for the treatment of cancer.

Table 4. Rodent PK Profiles of Selected Compounds

Compound	Rat[a] (iv, 0.5 mg/kg)			Mouse[a] (iv, 0.5 mg/kg)			Mouse[b] (po, 5 mg/kg)
	Cl (L/h/kg)	$t_{1/2}$(h)	Vss (L/kg)	Cl (L/h/kg)	$t_{1/2}$(h)	Vss (L/kg)	F%
 **38**	1.37	1.81	0.74	0.43	2.01	0.72	10
 **4**	0.23	4.4	0.27	0.15	3.2	0.35	56
 **33**	0.19	3.6	0.18	0.35	3.3	0.67	18
 **35**	0.09	2.3	0.41	0.15	4.1	0.53	36
 **3**	0.36	1.8	0.41	0.23	2.8	0.57	60

[a]Rat/mouse iv vehicle: 10.0% DMAC, 10.0% EtOH, 30.0% propylene glycol, and 50.0% saline (0.45% NaCl/49.55% water). [b]Mouse iv vehicle: 0.5% methyl cellulose, 1% Tween 80, and 98.5% water.

dx.doi.org/10.1021/jm401911v | J. Med. Chem. 2014, 57, 2963−2988

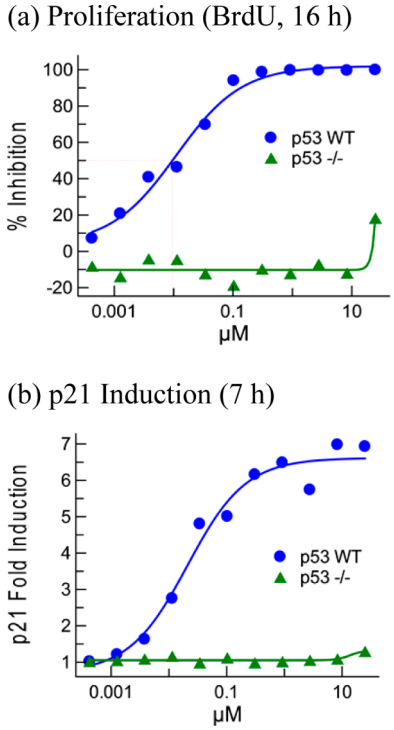


Figure 3. Cell activity of **4** is p53-dependent. (a) In HCT116 $p53^{wt}$ and $p53^{-/-}$ cells, the percentage of BrdU positive cells was measured 16 h postcompound treatment by flow cytometry. The DMSO control was designated as 0% inhibition. (b) In HCT116 $p53^{wt}$ and $p53^{-/-}$ cells, total RNA was extracted 7 h postcompound treatment, and p21 mRNA was measured by quantitative RT-PCR.

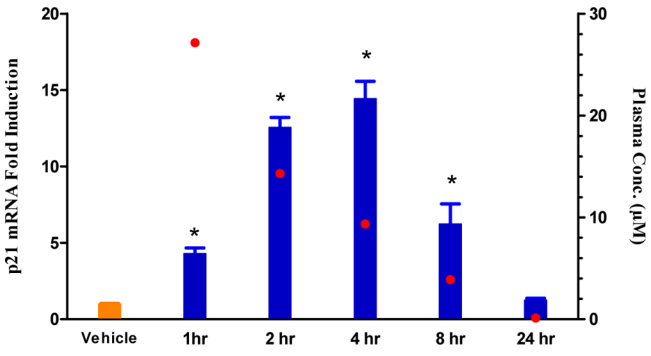
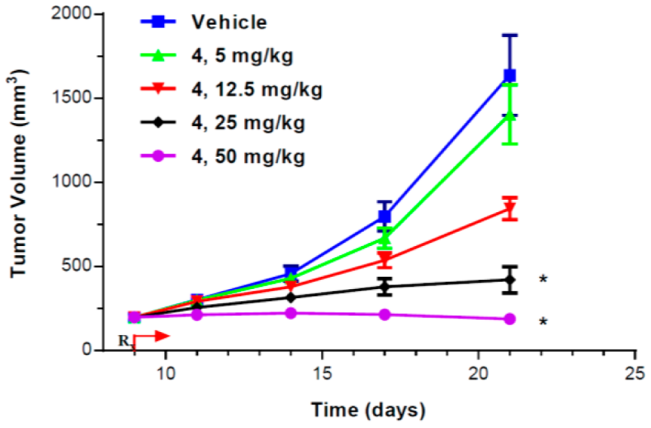


Figure 4. PD study results of **4** in the SJSA-1 tumor xenograft: Female athymic nude mice (n = 4/group) were implanted subcutaneously with 5×10^6 SJSA-1 cells. When tumors reached ~175 mm^3, 25 mg/kg of **4** or the vehicle was administered orally once daily (QD) for 4 days. Mice were sacrificed on day 4 at 1, 2, 4, 8, and 24 h postdose. 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 the mean p21 fold induction over vehicle, and error bars represent standard error of the mean (SEM) of data from five mice. Concentrations in plasma (red dots) were analyzed by LC/MS/MS. *p < 0.001.

To better understand its metabolism, inhibitor **4** was incubated in hepatocytes (10^6 cells/mL) from five different species and its degradation products were evaluated by LC-MS/MS (Figure 7). The reported chromatograms show that oxidative metabolites **M1**, **M2**, and **M3** are generated across species, including human hepatocytes.[26] The acyl glucuronide metabolite of **4** was not observed in this experiment.



Group	
Vehicle	%TGI = 0.0
4- 5 mg/kg	%TGI = 16.3
4- 12.5 mg/kg	%TGI = 55.2
4- 25 mg/kg	%TGI = 84.6
4- 50 mg/kg	% Regression = 5.6

Figure 5. SJSA-1 cells (5×10^6) were implanted subcutaneously into female athymic nude mice. Treatment with vehicle or **4** at 5, 12.5, 25, or 50 mg/kg QD by oral gavage began on day 9 when tumors had reached ~200 mm^3 (n = 10/group). Tumor sizes and body weights were measured twice per week. Data are represented as the mean tumor volumes, and the error bars represented the SEM of data from 10 mice. * p < 0.005.

Interestingly, this contrasts from **1** for which metabolite profiles were qualitatively similar across species with only it is acyl glucuronide observed in these incubates.[27] Therefore, glucuronidation of **1** is predicted to be the primary metabolic pathway in humans.

Morpholinone Inhibitors. Recently, we disclosed our efforts toward the optimization of potent morpholinone inhibitors. From these studies, we concluded that whereas morpholinone inhibitors are about 3- to 5-fold less potent than piperidinones, this core substitution had a profound effect on the in vitro and in vivo metabolic stability of these analogues, giving them divergent metabolism.[28]

Thus, we decided to explore some of the most potent acid replacements encountered thus far on the morpholinone core. To this end, nicotinic acid inhibitor **46** was synthesized. A direct comparison between inhibitors **3** and **46** (Table 5) shows morpholinone **46** to be, as expected, 3- to 5-fold less potent than piperidinone **3** in the EdU cell assay. Surprisingly, its C2-epimer **47** turned out to be 2-fold more potent than **46** (EdU assay, Table 5). The cocrystal structures of **46** and **47** bound to MDM2 (Figure 8) allowed us to confirm the relative configuration of these inhibitors. The structure of **46** bound to MDM2 (Figure 8a) depicts the pyridine nitrogen engaging in a hydrogen bond interaction with the imidazole-NH of His96 similar to that observed with inhibitors **3** and **4** (Figure 1). In contrast, the binding of **47** to MDM2 shows interactions that have yet to been seen in the nicotinic acid series (Figure 8b). In this case, there is no hydrogen bond observed between the inhibitor and His96. However, there are direct hydrogen

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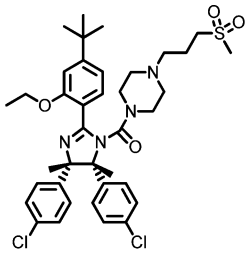
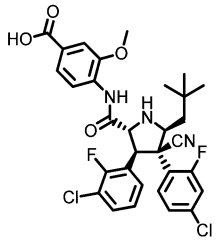
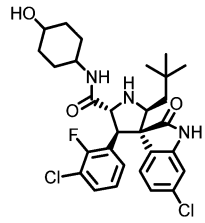


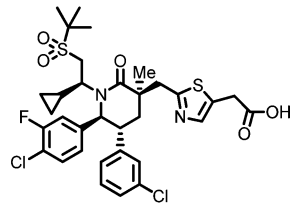
RG7112 (Roche)[13a]
EdU[a] IC_{50} = 581 nM



RG7388 (Roche)[13b]
EdU[a] IC_{50} = 45 nM



SAR299155 (Sanofi)[13c]
EdU[a] IC_{50} = 214 nM



4
EdU[a] IC_{50} = 16 nM

Figure 6. Chemical structures and potencies of some known MDM2 inhibitors currently being tested in the clinic: RG7112, RG7388, SAR299155, and **4**. [a] IC_{50} in the EdU cell proliferation assay (SJSA-1 and 10% human serum).

bonds observed between the acid in **47** and the backbone NH and side chain hydroxyl of Ser17. Furthermore, there is a water mediated hydrogen bond between this acid and the side chain of Gln18. The enhanced potency of **47** can be rationalized by these new interactions offsetting the loss of the hydrogen bond to His96.

Our previous studies on the morpholinone series showed that, in general, the C2-*R* isomer is more potent than its C2-*S* epimer. This can be best exemplified by comparing epimeric morpholinone inhibitors **48** (SJSA-1 EdU IC_{50} = 38 nM) and **49** (SJSA-1 EdU IC_{50} = 247 nM) (Figure 8c-d). Notably, in this case, the carboxylate moiety of both **48** and **49** interacts with the imidazole moiety of His96.

We also synthesized **50** (Table 5), a piperidinone inhibitor with S-stereochemistry at C3 (Table 5). Crystallographic data of **50** bound to MDM2 (1.85 Å resolution) was obtained, but we were unable to identify a defined density for the nicotinic acid moiety. Evidently, in this case, the piperidinone core precludes the nicotinic acid from picking up the hydrogen bonds with either His96 or Ser17. This finding is in agreement with the observed loss in potency of **50** (SJSA-1 EdU IC_{50} = 238 nM) compared to **3** (SJSA-1 EdU IC_{50} = 5 nM).

CONCLUSIONS

Evaluation of the carboxylic acid moiety of **1** identified known acid isosteres such as tetrazole (**6**), oxadiazolone (**7**), and α-keto acid (**10**) as viable replacements, maintaining potency similar to that of **1** in the biochemical and cell based assays. However, these analogues are moderate inhibitors of CYP3A4. Insights into the binding of these inhibitors to MDM2 (**2**, Figure 1) led us to hypothesize that the electrostatic interaction between MDM2 and the carboxylic acid moiety could be replaced by a dipole−dipole interaction with a hydrogen bond donor or acceptor. Further studies led to the discovery that replacement of the acid with hydrogen bond acceptor moieties, such as amides (**13**, **15**, and **16**) and heterocycles like pyridine (**3**), pyrimidine (**28**), pyrazine (**29**), thiazole (**4**), pyrazole (**31**), oxazole (**43**), triazole (**44**), and imidazole (**45**), provide potent inhibitors of the MDM2-p53 interaction. Notably, phenyl analogues **18** and **30**, which cannot engage in a hydrogen bond binding interaction with MDM2-His96, have significantly less affinity for the protein than their corresponding pyridine analogues (**17** and **3** respectively), corroborating the importance of this interaction for potent binding. The aforementioned interaction of these novel heterocyclic inhibitors with MDM2-His96 was confirmed with the MDM2 cocrystal structures of pyridine **3** and thiazole **4** (Figure 1). Although heterocycles are not often thought of as carboxylic acids isosteres, there is precedence for the successful use of pyridines as replacements of carboxylic acids.[29]

Among these new analogues, compound **4** shows excellent biochemical potency (HTRF IC_{50} = 0.1 nM, Table 4), cellular potency (SJSA-1 EdU IC_{50} = 16 nM), and MDM2 selectivity over MDMX (MDMX HTRF IC_{50} > 100 μM), as well as good pharmacokinetic properties.[30,31] Compound **4** also shows robust antitumor activity in the SJSA-1 osteosarcoma xenograft study with a calculated ED_{50} of 11 mg/kg. Compounds **4** and **1** exhibit comparable potency and efficacy. However, while glucuronidation is the main route of metabolism of **1**, inhibitor **4** is cleared primarily by oxidative pathways. Thus, **4** could provide for a viable alternative to **1** should a compound with a different metabolic profile or clearance mechanism be desired.

EXPERIMENTAL SECTION

General Chemistry. Reactions were conducted under an inert gas atmosphere (nitrogen or argon) at the temperature indicated. Commercial reagents and anhydrous solvents were used without further purification. Analytical thin layer chromatography (TLC) was performed on Analtech silica gel with organic binder 250 μm TLC plates. 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 final 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 and B = CH_3CN with 0.1% TFA; gradient: 5−95% B (0.0−15.0 min); and flow rate, 1.5 mL/min. Low-resolution mass spectral (MS) data were 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 = single; d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, and br = broad.

2-((3R,5R,6S)-1-((S)-1-(tert-Butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)-acetamide (12). To a solution of **5** (213 mg, 0.375 mmol) and *N*-

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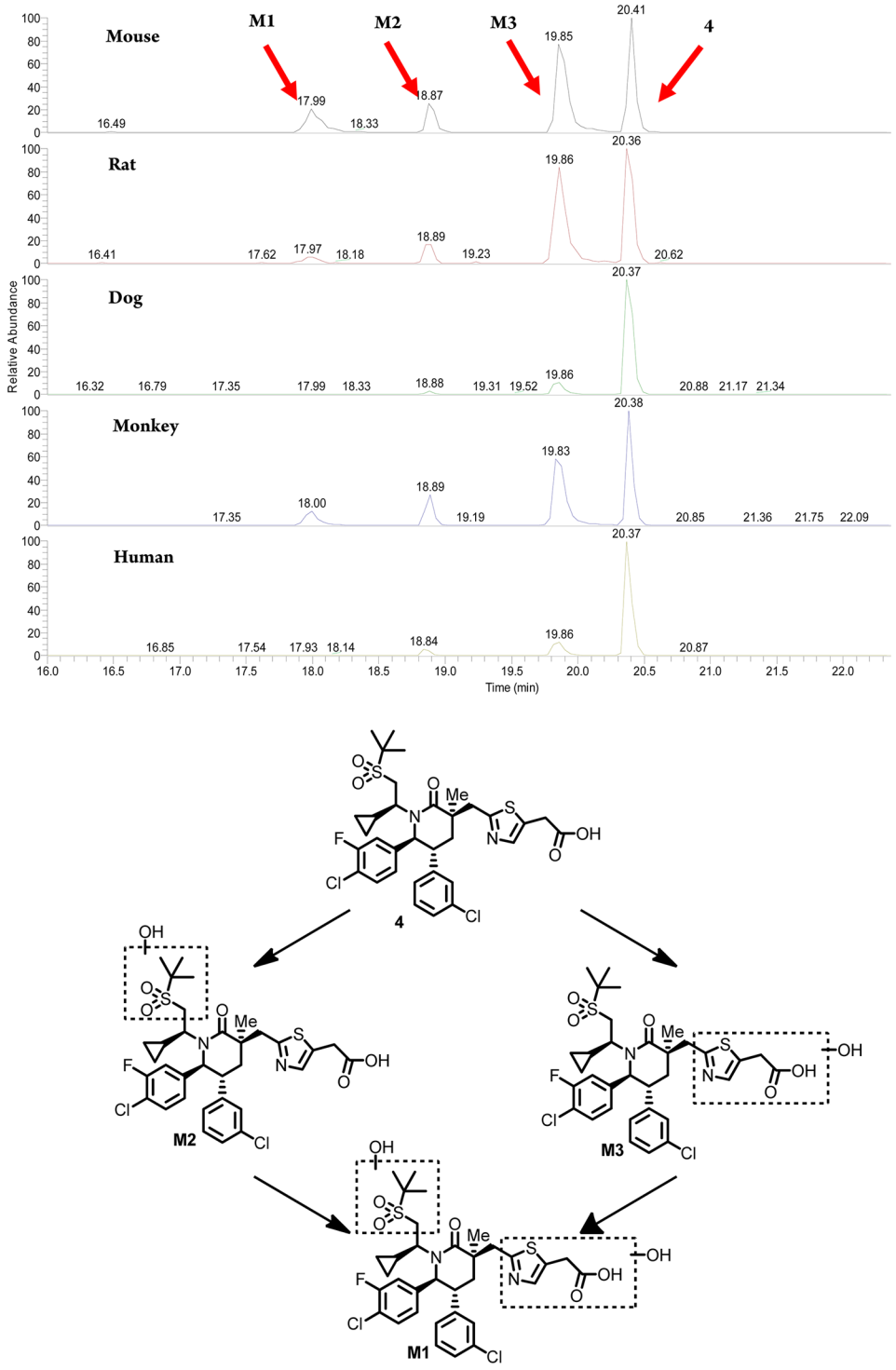

Figure 7. Metabolite profiles of **4** from hepatocyte incubation at 10 μM after 2 h.

methylmorpholine (57.7 μL, 0.524 mmol) in THF (1.87 mL) was added isobutyl chloroformate (58.8 μL, 0.450 mmol) at 0 °C. The cloudy colorless solution was stirred at 0 °C for 1 h. Then, 28% ammonia in water (50.6 μL, 0.749 mmol) was added to the mixture at 0 °C, and the resulting mixture was stirred at 0 °C for 3 h. The reaction mixture was extracted with ethyl acetate and water. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide a crude product as a pale yellow solid. Purification by RP-HPLC (40% to 55% CH_3CN/H_2O in 25 min, flow rate = 45 mL/min) provided 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)acetamide (160 mg, 0.282 mmol, 75% yield) (**12**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.26 (m, 2H), 7.05−7.21 (m, 3H), 6.96−7.02 (m, 1H), 6.87 (dt, J = 6.4, 2.0 Hz, 1H), 6.79 (br. s., 1H), 6.27 (br. s., 1H), 4.99 (d, J = 10.8 Hz, 1H), 4.08 (dd, J = 13.2, 11.1 Hz, 1H), 3.21−3.37 (m, 2H), 2.74−2.84 (m, 2H), 2.56−2.70 (m, 1H), 2.35 (t, J = 13.7 Hz, 1H), 2.14 (ddd, J = 14.2, 9.8, 7.2 Hz, 1H), 2.02 (dd, J = 13.7, 2.9 Hz, 1H), 1.49 (td, J = 7.0, 2.9 Hz, 1H), 1.44 (s, 9H), 1.43 (s, 3H), 0.41 (t, J = 7.5 Hz, 3H). Mass spectrum (ESI) m/z = 567.2 $[M + H]^+$. HRMS (ESI) m/z found 567.1841 $[M + H]^+$, calcd for $C_{28}H_{36}Cl_2N_2O_4S$ 567.1851.

2-((3R,5R,6S)-1-((S)-1-(tert-Butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)-N-

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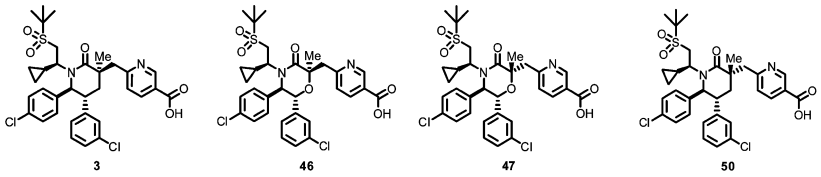
Table 5. Comparison between Nicotinic Acid Inhibitors Derived from the Piperidinone and Morpholinone Scaffolds



Biochemical Potency				
HTRF Serum Free IC_{50} (nM)[b]	0.10 ± 0.01	0.10 ± 0.05	0.10 ± 0.01	0.50 ± 0.10
HTRF 15% HS IC_{50} (nM)[b]	0.8 ± 0.2	1.5 ± 0.5	1.0 ± 0.2	8.0. ± 2.7
Potency in SJSA-1 cells				
EdU IC_{50} (nM)[a, b]	5 ± 3	23 ± 1	12 ± 2	240 ± 90

[a]Assays conducted in the presence of 10% human serum. [b]Mean and standard deviation of at least two runs.

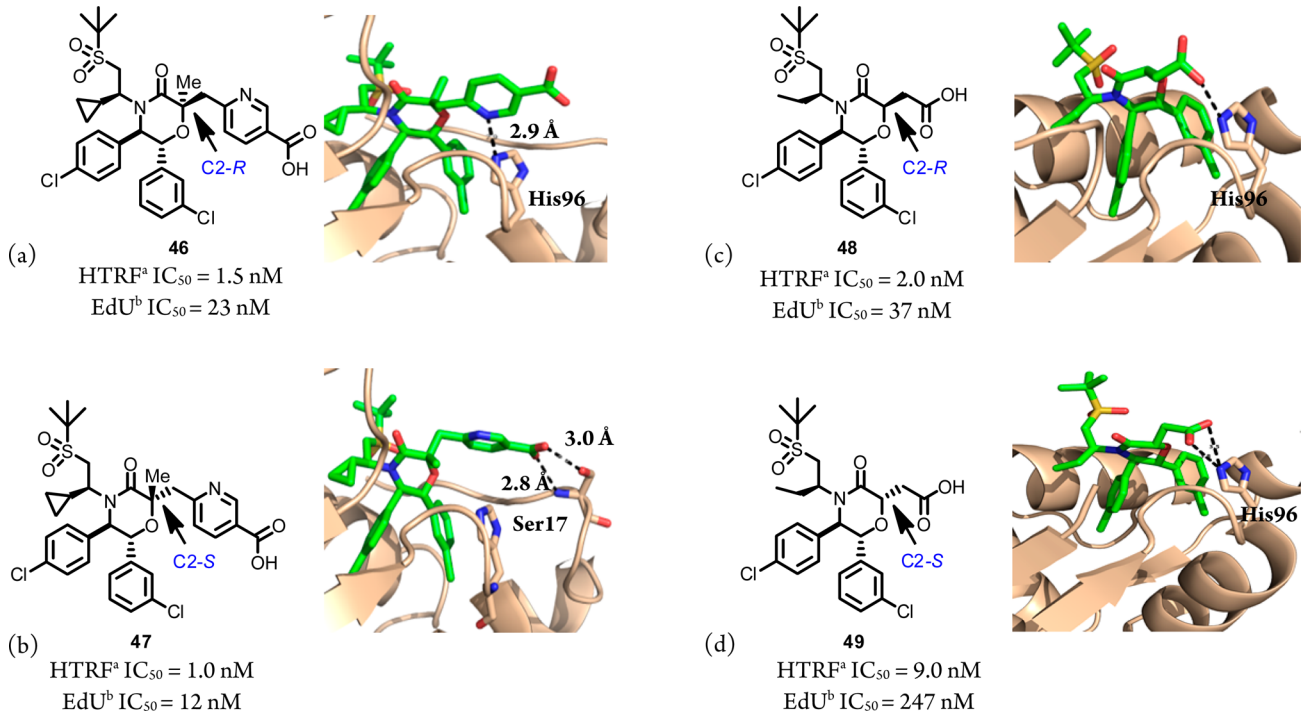


Figure 8. Co-crystal structures of (a) **46**, (b) **47**, (c) **48**, and (d) **49** bound to human MDM2 (**46**, **47** MDM2, 6−110; **48**, **49** MDM2, 17−111). [a] IC_{50} in the biochemical assay using buffer containing 15% human serum. [b] Cellular potency in SJSA-1 osteosarcoma tumor cells in the presence of 10% human serum. Coordinates for compounds **46** (PDB code: 4OGT), **47** (PDB code: 4ODF), **48** (PDB code: 4OCC), and **49** (PDB code: 4OGV) bound to MDM2 have been deposited in the PDB.

*((trifluoromethyl)sulfonyl)acetamide (**8**).* A solution of **5** (50 mg, 0.088 mmol) and trifluoromethanesulfonamide (52.4 mg, 0.32 mmol) in DMF (0.281 mL) was treated with HATU (134 mg, 0.352 mmol) and diisopropylethylamine (0.092 mL, 0.528 mmol) successively. Then, the reaction was stirred at room temperature for 5 h. After this period, the crude mixture was diluted in 5 mL of 1 N HCl, then 30 mL of water, and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the filtrate was concentrated under vacuum. Purification by RP-HPLC (25−75% AcCN/H_2O in 30 min) provided 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)-*N*-((trifluoromethyl)sulfonyl)acetamide (**8**) (25 mg, 0.036 mmol, 41% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 4H), 7.05−7.18 (m, 2H), 6.94 (s, 1H), 6.78−6.86 (m, 1H), 4.92−5.11 (m, 1H), 3.95−4.13 (m, 1H), 3.30−3.44 (m, 1H), 3.19−3.29 (m, 1H), 2.92−3.08 (m, 1H), 2.77−2.86 (m, 1H), 2.60−2.71 (m, 1H), 2.45−2.58 (m, 1H), 2.11−2.27 (m, 1H), 1.78−1.89 (m, 1H), 1.51 (s, 3H), 1.45 (s, 9H), 0.42 (t, J = 7.53 Hz, 3H). Mass spectrum (ESI) m/z = 699.0 $[M + H]^+$. HRMS (ESI) m/z found 699.1346 $[M + H]^+$, calcd for $C_{29}H_{35}Cl_2F_3N_2O_6S_2$ 699.1344.

*2-((3R,5R,6S)-1-((S)-1-(tert-Butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)-acetonitrile (**51**).* A solution of 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)acetamide (**12**) (180 mg, 0.317 mmol) and triethylamine (221 μL, 1.586 mmol) in THF (2.64 mL) was

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treated with 2,2,2-trifluoroacetic anhydride (113 μL, 0.793 mmol) at 0 °C. After being stirred at 0 °C for 90 min, the reaction was quenched (sat. aq. NH_4Cl), extracted (2 × EtOAc), and washed (brine). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by combi-flash (24 g SiO_2, 30% EtOAc/Hex) provided 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)acetonitrile (**51**) (160 mg, 0.291 mmol, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.26 (m, 2H), 7.06−7.21 (m, 4H), 6.99 (s, 1H), 6.85−6.90 (m, 1H), 4.99 (d, *J* = 10.8 Hz, 1H), 4.07 (dd, *J* = 13.3, 11.0 Hz, 1H), 3.20−3.36 (m, 2H), 2.95 (d, *J* = 16.8 Hz, 1H), 2.77 (dd, *J* = 13.2, 2.2 Hz, 1H), 2.72 (d, *J* = 16.8 Hz, 1H), 2.42 (t, *J* = 14.0 Hz, 1H), 2.13 (ddd, *J* = 14.3, 9.9, 7.3 Hz, 1H), 2.05 (dd, *J* = 14.1, 2.9 Hz, 1H), 1.47−1.54 (m, 1H), 1.46 (s, 3H), 1.43 (s, 9H), 0.41 (t, *J* = 7.5 Hz, 3H). Mass spectrum (ESI) *m*/*z* = 549.2 $[M + H]^+$.

*(3R,5R,6S)-3-((1H-Tetrazol-5-yl)methyl)-1-((S)-1-(tert-butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (**6**).* To a solution of 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)acetonitrile (**51**) (57 mg, 0.104 mmol) in DMF (259 μL) was added sodium azide (67.4 mg, 1.037 mmol) and ammonium chloride (55.5 mg, 1.037 mmol). The resulting mixture was stirred at 90 °C for 5 days. Then, the reaction was acidified (aq. 10% citric acid), extracted (2 × EtOAc), and washed (brine). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by RP-HPLC (40% to 55% CH_3CN/H_2O, 0.1% TFA each, in 25 min, flow rate = 45 mL/min) provided (3*R*,5*R*,6*S*)-3-((1H-tetrazol-5-yl)methyl)-1-((*S*)-1-(*tert*-butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (**6**) (40 mg, 0.068 mmol, 65% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.27 (m, 2H), 7.10−7.17 (m, 2H), 7.00 (d, *J* = 1.8 Hz, 3H), 6.88 (d, *J* = 6.7 Hz, 1H), 5.03 (d, *J* = 10.6 Hz, 1H), 4.10 (t, *J* = 12.0 Hz, 1H), 3.55−3.62 (m, 1H), 3.42 (d, *J* = 16.0 Hz, 1H), 3.3−3.39 (m, 1H), 3.14 (t, *J* = 11.3 Hz, 1H), 2.84 (d, *J* = 13.3 Hz, 1H), 2.57 (t, *J* = 13.8 Hz, 1H), 2.10−2.24 (m, 1H), 1.95−2.02 (m, 1H), 1.46 (s, 9H), 1.36−1.43 (m, 1H), 1.32 (s, 3H), 0.42 (t, *J* = 7.5 Hz, 3H). Mass spectrum (ESI) *m*/*z* = 592.2 $[M + H]^+$. HRMS (ESI) *m*/*z* found 592.1913 $[M + H]^+$, calcd for $C_{28}H_{35}Cl_2N_5O_3S$ 592.1916.

*2-((3R,5R,6S)-1-((S)-1-(tert-Butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)-N′-hydroxyacetimidamide (**52**).* A round-bottomed flask equipped with a reflux condensor was charged with a suspension of 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)acetonitrile (**51**) (0.100 g, 0.182 mmol) and hydroxyammonium chloride (0.011 mL, 0.273 mmol) in MeOH (4 mL). Then, sodium hydrogencarbonate (0.023 g, 0.273 mmol) was added. The reaction was refluxed overnight. The reaction was cooled to room temperature and quenched (sat. aq. NH_4Cl), extracted (2 × EtOAc), and washed (brine). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The compound was used on the next step without further purification. Mass spectrum (ESI) *m*/*z* = 582.2 $[M + H]^+$.

*3-(((3R,5R,6S)-1-((S)-1-(tert-Butylsulfonyl)butan-2-yl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)-1,2,4-oxadiazol-5(4H)-one (**7**).* To a solution of 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)-*N*′-hydroxyacetimidamide (**52**) (0.090 g, 0.154 mmol) in dioxane (2 mL) was added DBU (0.069 mL, 0.463 mmol) via syringe followed by 1,1′-carbonyldiimidazole (0.075 g, 0.463 mmol). The reaction was refluxed for 2 days. After this period, the reaction mixture was allowed to cool to room temperature. The crude was quenched with water (25 mL). Extracted with EtOAc (100 mL) and the organic layer washed with brine (10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by reversed phase preparatory HPLC (GeminiTM Prep C18 5 mm column; Phenomenex, Torrance, CA) (eluent, 40−65% CH_3CN/H_2O, 0.1% TFA each, 30 min) to provide 3-(((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)methyl)-1,2,4-oxadiazol-5(4*H*)-one (**7**) (0.014 g, 0.023 mmol, 15% yield over last two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.27 (m, 4H), 7.09−7.20 (m, 2H), 6.96 (s, 1H), 6.85 (d, *J* = 7.09 Hz, 1H), 5.00 (d, *J* = 10.76 Hz, 1H), 4.02 (t, *J* = 12.10 Hz, 1H), 3.34 (m, 1H), 3.22 (d, *J* = 15.65 Hz, 1H), 3.06 (ddd, *J* = 13.69, 10.88, 2.57 Hz, 1H), 2.74−2.84 (m, 2H), 2.58 (t, *J* = 13.82 Hz, 1H), 2.14 (ddd, *J* = 14.12, 9.84, 7.58 Hz, 1H), 1.87 (dd, *J* = 13.82, 2.57 Hz, 2H), 1.30−1.54 (m, 12H), 0.42 (t, *J* = 7.46 Hz, 3H). Mass spectrum (ESI) *m*/*z* = 608.2 $[M + H]^+$. HRMS (ESI) *m*/*z* found 608.1758 $[M + H]^+$, calcd for $C_{29}H_{35}Cl_2N_3O_5S$ 608.1753.

*3-((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)-2-oxopropanoic Acid (**10**).*[32] Part A: A solution of 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 (**9**) (300 mg, 0.517 mmol) and 1-(cyanomethyl)tetrahydro-1*H*-thiophen-1-ium bromide (161 mg, 0.775 mmol) in DCM (5167 μL) was treated with HATU (236 mg, 0.620 mmol) and DIEA (269 μL, 1.550 mmol) at room temperature. The reaction was stirred at this temperature for 4 h. After this period, the reaction was quenched (sat. aq. NH_4Cl), extracted (2 × EtOAc), and washed (brine). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by combi-flash (12 g SiO_2, 0% to 70% acetone/ethyl acetate) provided the intermediate cyanosulfur ylide (356 mg, 0.516 mmol, 100% yield). Mass spectrum (ESI) *m*/*z* = 689.2 $[M + H]^+$.

Part B: To a solution of the sulfur ylide formed in part A (356 mg, 0.516 mmol) in DMF (3.44 mL) and water (1.72 mL) was added oxone (635 mg, 1.032 mmol) at room temperature. The reaction was stirred for 2.5 h. After this period, the reaction was quenched (2.5 mL, 1 N aq. HCl), extracted (2 × EtOAc), and washed (brine). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by RP-HPLC (45 to 65% CH_3CN/H_2O, both containing 0.1% TFA, in 30 min, flow rate = 45 mL/min) provided 3-((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)-2-oxopropanoic acid (**10**) (200 mg, 0.329 mmol, 64% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−8.09 (m, 1H), 7.51 (m, *J* = 12.5 Hz, 1H), 6.69−7.16 (m, 6H), 4.91 (d, *J* = 10.6 Hz, 1H), 4.13−4.21 (m, 1H), 4.03 (d, *J* = 11.0 Hz, 1H), 3.29−3.41 (m, 1H), 2.85 (d, *J* = 12.5 Hz, 1H), 2.66−2.79 (m, 1H), 2.50 (t, *J* = 13.1 Hz, 1H), 2.23 (d, *J* = 11.2 Hz, 1H), 1.67−1.85 (m, 2H), 1.43 (br. s., 3H), 1.41 (s, 9H), 0.25−0.46 (m, 2H), −0.45− −0.24 (m, 1H), −1.19− −1.01 (m, 1H). Mass spectrum (ESI) *m*/*z* = 608.2 $[M + H]^+$. HRMS (ESI) *m*/*z* found 608.1630 $[M + H]^+$, calcd for $C_{30}H_{35}Cl_2NO_6S$ 608.1640.

*2-((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)-acetamide (**13**).* To a solution of 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 (**9**) (300 mg, 0.517 mmol), HATU (393 mg, 1.033 mmol) and *N*,*N*-diisopropylethylamine (0.270 mL, 1.550 mmol) in DMF (1.00 mL) was added a 7 N ammonia solution in methanol (0.369 mL, 2.58 mmol). The reaction was stirred at 40 °C for 1 h. The crude material was concentrated and absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (40 g), eluting with a gradient of 0% to 40% acetone/MeOH (9:1) in DCM, to provide 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)-acetamide (**13**) (264 mg, 0.456 mmol, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (s, 2H), 7.04−7.18 (m, 2H), 6.96−7.04 (m, 1H) 6.92−6.96 (m, 1H), 6.71−6.92 (m, 1H), 6.43−6.63 (m, 1H), 5.44−5.63 (m, 1H), 4.96 (d, *J* = 10.8 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 1H), 3.32 (s, 1H), 2.96 (s, 1H), 2.89 (s, 1H), 2.81 (s, 1H), 2.57−2.80 (m, 3H), 2.38 (s, 1H), 2.05 (s, 2H), 1.97−2.08 (m, 1H), 1.36−1.51 (m, 12H), 1.27 (t, *J* = 7.2 Hz, 2H). Mass spectrum (ESI) *m*/*z* = 579.0 $[M + H]^+$.

HRMS (ESI) m/z found 579.1851 $[M + H]^+$, calcd for $C_{29}H_{36}Cl_2N_2O_4S$ 579.1851.

*2-((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)-acetonitrile (**53**).* A solution of 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)acetamide (**13**) (125 mg, 0.216 mmol) and triethylamine (0.150 mL, 1.078 mmol) in tetrahydrofuran (3 mL) was treated with trifluoroacetic anhydride (0.075 mL, 0.539 mmol) at 0 °C. After being stirred at 0 °C overnight, the reaction was quenched with water (10 mL), extracted (3 × 10 mL EtOAc), and washed with brine (10 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (acetone/hexanes: 0−50%) to give 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)-acetonitrile (**53**) (92 mg, 0.164 mmol, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (s, 2H), 7.11−7.20 (m, 3H), 7.11 (s, 1H), 6.94−7.05 (m, 1H), 6.86−6.94 (m, 1H), 4.95 (d, J = 10.5 Hz, 1H), 4.13 (d, J = 7.1 Hz, 1H), 3.20 (s, 1H), 2.98 (s, 1H), 3.01 (s, 1H), 2.80 (s, 1H), 2.84 (m, 2H), 2.48 (s, 1H), 2.05 (s, 1H), 2.03 (dd, J = 13.9, 3.2 Hz, 2H), 1.48 (s, 3H), 1.44 (s, 9H), 1.27 (t, J = 7.2 Hz, 2H). Mass spectrum (ESI) m/z = 561.2 $[M + H]^+$.

*Ethyl 2-((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetimidate (**54**).* A solution of 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)acetonitrile (**53**) (90 mg, 0.160 mmol) in ethanol (1.603 mL) was bubbled with HCl for 15 min. The reaction was stirred overnight reaching complete conversion. The crude was concentrated and used in the next step without further purification. Mass spectrum (ESI) m/z = 607.2 $[M + H]^+$.

*1-Amino-2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)ethaniminium (**55**).* A solution of **54** (0.097 g, 0.160 mmol) in ethanol (1.6 mL) was bubbled with ammonia for 30 min. The reaction was allowed to stir for 3 h at room temperature when complete conversion to the desired product was observed. The crude was concentrated and used in the next step without further purification. Mass spectrum (ESI) m/z = 578.3 $[M + H]^+$.

*2-((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)-ethanethioamide (**56**).* To a solution of 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)acetonitrile (**53**) (100 mg, 0.178 mmol) in ethanol (1.781 mL) was added diphosphorus pentasulfide (0.076 mL, 0.712 mmol), and the reaction was allowed to stir at 90 °C overnight. After this period, the crude material was concentrated and adsorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (40 g), eluting with a gradient of 0% to 100% acetone in DCM, to provide 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)ethanethioamide (**56**) (70 mg, 0.118 mmol, 66% yield). Mass spectrum (ESI) m/z = 595.0 $[M + H]^+$.

*2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)pyrimidine-5-carboxylic Acid (**28**).* Part A: A solution of 1-amino-2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)ethaniminium (45 mg, 0.075 mmol) and ethyl-2-formyl-3-oxopropionate (0.109 mL, 0.753 mmol) in dimethylacetamide (1 mL) was heated in the microwave at 100 °C for 2 h. After this period, the reaction was concentrated, and the crude material was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (12 g), eluting with a gradient of 0% to 50% 9:1 acetone/MeOH in DCM to provide ethyl 2-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)pyrimidine-5-carboxylate (35 mg, 0.050 mmol, 66% yield) as a yellow oil. Mass spectrum (ESI) m/z = 704.2 $[M + H]^+$.

Part B: To a solution of ethyl 2-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)pyrimidine-5-carboxylate (35 mg, 0.050 mmol) in THF (2 mL) and MeOH (1 mL) was added lithium hydroxide (1.0 mL, 2 M). The solution was stirred at 50 °C for 30 min. After this period, the reaction was neutralized (2 mL/1 M HCl), concentrated, and diluted with MeOH (2 mL). Purification by prep HPLC (25−75% acetonitrile/water both solvents containing 0.1% TFA, in 30 min, flow rate =45 mL/min) provided 2-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)pyrimidine-5-carboxylic acid (**28**) (25 mg, 0.037 mmol, 74% yield) as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 2H), 6.95−7.26 (m, 6H), 5.03 (d, J = 10.56 Hz, 1H), 4.37 (t, J = 11.84 Hz, 1H), 3.71 (d, J = 12.13 Hz, 1H), 3.44−3.56 (m, 1H), 3.38 (s, 1H), 2.91 (d, J = 11.74 Hz, 1H), 2.57−2.72 (m, 1H), 2.42 (t, J = 13.69 Hz, 1H), 1.81−1.94 (m, 2H), 1.75 (dd, J = 3.23, 13.60 Hz, 1H), 1.44 (s, 3H), 1.42 (s, 9H), 0.25−0.50 (m, 2H), −0.27 (br. s., 1H), −0.95 (br. s., 1H). Mass spectrum (ESI) m/z = 676.0 $[M + H]^+$. HRMS (ESI) m/z found 676.1809 $[M+H]^+$, calcd for $C_{33}H_{36}Cl_2FN_3O_5S$ 676.1815.

*2-(((3R,5R,6S)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)pyrimidine-5-carboxylic Acid (**27**).* Compound **27** was prepared according to a similar procedure described for the synthesis of **28**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 2H), 7.04−7.27 (m, 3H), 6.88−7.04 (m, 2H), 6.69−6.88 (m, 2H), 6.56−6.69 (m, 1H), 4.56 (d, J = 10.8 Hz, 1H), 4.52 (s, 1H), 3.57 (d, J = 12.7 Hz, 1H), 3.45 (d, J = 12.7 Hz, 1H), 3.17 (br. s., 1H), 3.03−3.14 (m, 1H), 2.88 (d, J = 13.7 Hz, 1H), 2.50 (d, J = 13.4 Hz, 1H), 2.24−2.41 (m, 1H), 1.95−2.18 (m, 3H), 1.26−1.53 (m, 9H), 1.14−1.34 (m, 2H), 0.86−1.05 (m, 1H), 0.63−0.86 (m, 1H). Mass spectrum (ESI) m/z = 658.2 $[M + H]^+$. HRMS (ESI) m/z found 658.1913 $[M + H]^+$, calcd for $C_{33}H_{37}Cl_2N_3O_5S$ 658.1909.

*2-(2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)-1H-imidazol-4-yl)acetic Acid (**45**).* To a solution of 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)-acetimidamide (**55**) (80 mg, 0.138 mmol) in acetonitrile (1 mL) was added ethyl trans-4-oxo-2-butenoate (21.26 μL, 0.166 mmol), and the mixture was heated to 130 °C for 1 h in the microwave. The reaction was concentrated and diluted in THF (1 mL) and MeOH (1 mL), and LiOH (1 mL, 2 M) was added, and the reaction was stirred at 50 °C for 1 h. After this period, the reaction was cooled and concentrated, diluted in MeOH, and filtered. Purification by RP-HPLC (25−75% CH_3CN/H_2O both solvents containing 0.1% TFA, 30 min, flow rate = 45 mL/min) provided **45** (8 mg, 8% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10−7.56 (m, 1H), 6.87 (d, J = 12.13 Hz, 7H), 4.58−4.83 (m, 1H), 3.92−4.21 (m, 2H), 3.40−3.73 (m, 3H), 3.05−3.32 (m, 2H), 2.49−2.80 (m, 2H), 2.11−2.39 (m, 1H), 1.42−1.68 (m, 2H), 1.07−1.36 (m, 12H), −0.16−0.28 (m, 2H), −0.74− −0.43 (m, 1H), −1.55− −1.16 (m, 1H). Mass spectrum (ESI) m/z = 660.2 $[M + H]^+$.

*2-(5-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)-4H-1,2,4-triazol-3-yl)acetic Acid (**44**).* Part A: A solution of ethyl 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)acetimidate (**55**) (95 mg, 0.156 mmol) and ethyl 3-hydrazinyl-3-oxopropanoate (27.4 mg, 0.188 mmol) in EtOH was heated to 75 °C and stirred overnight. The crude material was concentrated and absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (12 g), eluting with a gradient of 0% to 40% acetone/MeOH (9:1) in DCM, to provide ethyl 2-(5-(((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)methyl)-4*H*-1,2,4-triazol-3-yl)acetate (68 mg, 0.099 mmol, 63% yield) as a light-yellow solid. Mass spectrum (ESI) m/z = 689.0 $[M + H]^+$.

Part B: To a solution of ethyl 2-(5-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chloro-

phenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)-4*H*-1,2,4-triazol-3-yl)-acetate (68 mg, 0.099 mmol) in THF (0.5 mL)/methanol (0.5 mL)/water (0.5 mL) was added lithium hydroxide (1 mL, 2 M). The reaction was stirred for 30 min at 50 °C. After this time, the reaction was quenched with 10% citric acid solution (5 mL), diluted in water (10 mL), and washed with ether (3 × 15 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by RP-HPLC (25−75% CH_3CN/H2O both solvents containing 0.1% TFA, 30 min, flow rate = 45 mL/min) provided 2-(5-(((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)methyl)-4*H*-1,2,4-triazol-3-yl)acetic acid (**44**) (47 mg, 0.071 mmol, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.75 (bs, 2H), 6.89−7.25 (m, 6H), 4.96 (d, J = 10.56 Hz, 1H), 4.27 (t, J = 12.03 Hz, 1H), 4.06 (br. s., 3H), 3.34−3.68 (m, 2H), 2.91 (d, J = 12.72 Hz, 1H), 2.64−2.83 (m, 1H), 2.44 (t, J = 14.28 Hz, 1H), 1.75−1.90 (m, 2H), 1.58−1.73 (m, 1H), 1.44 (s, 9H), 1.40 (br. s., 3H), 1.31−1.37 (m, 1H), 0.31−0.49 (m, 1H), 0.05−0.29 (m, 1H), −0.50− −0.18 (m, 1H), −1.48− −0.99 (m, 1H). Mass spectrum (ESI) m/z = 661.0 $[M + H]^+$.

*2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazole-4-carboxylic Acid (**32**).* To a mixture of 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)-ethanethioamide (**56**) (90 mg, 0.151 mmol) and potassium bicarbonate (121 mg, 1.209 mmol) was added dry dioxane (1 mL) and ethyl bromopyruvate (0.0568 mL, 0.453 mmol). The reaction was allowed to stir under argon for 3 h. After this period, the mixture was cooled to 0 °C, and a solution of trifluoroacetic acid anhydride (0.084 mL, 0.604 mmol) and pyridine (0.111 mL, 1.360 mmol) in dioxane (1 mL) was added. The reaction was allowed to warm to room temperature overnight. The crude was washed with brine (30 mL) and diethyl ether (3 × 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (12 g), eluting with a gradient of 0% to 50% acetone in DCM, to provide the intermediate ester (Mass spectrum (ESI) m/z = 691.2 $[M + H]^+$). This material was diluted with THF (2 mL), MeOH (1 mL), and LiOH (1 mL, 2 M). The mixture was stirred at 50 °C for 1 h, then cooled, neutralized with 1 M HCl (2 mL), and concentrated. Purification of the crude product by RP-HPLC (45 to 65% AcCN/H2O, both containing 0.1% TFA, in 30 min, flow rate = 45 mL/min) provided 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)methyl)thiazole-4-carboxylic acid (**32**) (22 mg, 0.033 mmol, 22% yield over the last two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.08−7.17 (m, 1H), 6.99−7.06 (m, 3H), 6.94 (s, 2H), 6.68−6.86 (m, 2H), 4.92 (d, J = 10.56 Hz, 1H), 4.21−4.39 (m, J = 12.52 Hz, 1H), 3.61 (d, J = 14.28 Hz, 1H), 3.41 (d, J = 14.28 Hz, 1H), 3.04−3.19 (m, J = 16.43 Hz, 1H), 2.85 (d, J = 13.89 Hz, 1H), 2.26 (t, J = 13.89 Hz, 2H), 1.65−1.91 (m, 2H), 1.36 (s, 9H), 1.33 (s, 3H), 0.25−0.43 (m, 1H), 0.05−0.23 (m, 1H), −0.54− −0.24 (m, 1H), −1.31− −0.98 (m, 1H). Mass spectrum (ESI) m/z = 663.0 $[M + H]^+$. HRMS (ESI) m/z found 663.1518 $[M + H]^+$, calcd for $C_{32}H_{36}Cl_2N_2O_5S_2$ 663.1521.

*2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazole-5-carboxylic Acid (**33**).* Part A: A solution of 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)-ethanethioamide (**56**) (100 mg, 0.168 mmol) and ethyl 2-chloro-3-oxopropanoate (50.6 mg, 0.336 mmol) in toluene (1 mL) was stirred at 100 °C in the microwave for 5 h. After this period, the crude was concentrated and absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (40 g), eluting with a gradient of 0% to 40% acetone in DCM, to provide ethyl 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)-methyl)thiazole-5-carboxylate (77 mg, 0.111 mmol, 66% yield) as a light yellow solid. Mass spectrum (ESI) m/z = 691.0 $[M + H]^+$.

Part B: To a solution of methyl 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)methyl)thiazole-5-carboxylate (77 mg, 0.114 mmol) in THF (2 mL) and MeOH (1 mL) was added lithium hydroxide (2 mL, 2 M). After this period, the reaction was neutralized (4 mL, 1 M HCl) and concentrated. Purification of the crude product by RP-HPLC (45% to 65% AcCN/H_2O, both containing 0.1% TFA, in 30 min, flow rate = 45 mL/min) provided 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)-methyl)thiazole-5-carboxylic acid (**33**) (64 mg, 0.096 mmol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.28 (br. s., 4H), 7.11 (d, J = 4.50 Hz, 2H), 7.01 (s, 1H), 6.90 (br. s., 1H), 5.00 (d, J = 10.76 Hz, 1H), 4.29−4.51 (m, J = 13.50 Hz, 1H), 3.72 (d, J = 14.08 Hz, 1H), 3.56 (d, J = 13.89 Hz, 1H), 3.24 (t, J = 12.91 Hz, 1H), 2.95 (d, J = 13.50 Hz, 1H), 2.64−2.79 (m, 1H), 2.35 (t, J = 13.79 Hz, 1H), 1.75−2.06 (m, 2H), 1.40−1.50 (m, 12H), 0.24−0.48 (m, 2H), −0.28 (br. s., 1H), −1.00 (br. s., 1H). Mass spectrum (ESI) m/z = 663.0 $[M + H]^+$. HRMS (ESI) m/z found 663.1522 $[M + H]^+$, calcd for $C_{32}H_{36}Cl_2N_2O_5S_2$ 663.1521.

*2-(2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-4-yl)acetic Acid (**37**).* Part A: To a solution of 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)-ethanethioamide (**56**) (70 mg, 0.118 mmol) in ethanol (1.2 mL) was added 4-chloroacetoacetic acid methyl ester (70.8 μL, 0.470 mmol), and the mixture was stirred at 90 °C for 3 h. The crude was concentrated and taken onto the next step without further purification. Mass spectrum (ESI) m/z = 691.0 $[M + H]^+$.

Part B: To a solution of methyl 2-(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)methyl)thiazol-4-yl)acetate (from Part A) in MeOH (1 mL) and THF (1 mL) was added lithium hydroxide (1 mL, 2 M) and stirred at 50 °C for 1 h. After this period, 2 mL of 1 N HCL was added, and the crude was concentrated. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (12 g), eluting with a gradient of 0% to 40% MeOH/acetone (1:9 with 1% acetic acid) and DCM, to provide 2-(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)methyl)thiazol-4-yl)acetic acid (**37**) (45 mg, 0.066 mmol, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81−7.25 (m, 8H), 4.97 (d, J = 10.76 Hz, 1H), 4.24−4.55 (m, 1H), 3.86 (d, J = 1.37 Hz, 2H), 3.68 (d, J = 14.09 Hz, 1H), 3.41 (d, J = 14.09 Hz, 1H), 3.13−3.26 (m, 1H), 2.87−2.96 (m, 1H), 2.62−2.73 (m, 1H), 2.20−2.29 (m, 1H), 2.15−2.19 (m, 1H), 1.76−1.85 (m, 1H), 1.43 (s, 9H), 1.38 (s, 3H), 0.10−0.45 (m, 2H), −0.56− −0.21 (m, 1H), −1.22− −0.95 (m, 1H). Mass spectrum (ESI) m/z = 677.0 $[M + H]^+$. HRMS (ESI) m/z found 677.1682 $[M + H]^+$, calcd for $C_{33}H_{38}Cl_2N_2O_5S_2$ 667.1677.

*2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazole-5-carboxylic Acid (**35**).* Compound **35** was prepared in a manner similar to a procedure described for the synthesis of **33**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.09−7.18 (m, 1H), 7.02 (dd, J = 1.37, 3.72 Hz, 2H), 6.90−6.96 (m, 1H), 6.76−6.86 (m, 1H), 6.34−6.73 (m, 3H), 4.91 (d, J = 10.56 Hz, 1H), 4.32 (t, J = 12.03 Hz, 1H), 3.63 (d, J = 13.89 Hz, 1H), 3.43 (d, J = 13.89 Hz, 1H), 3.06 (t, J = 11.64 Hz, 1H), 2.86 (d, J = 12.32 Hz, 1H), 2.60 (t, J = 9.19 Hz, 1H), 2.23 (t, J = 13.89 Hz, 1H), 1.87 (br. s., 1H), 1.36 (s, 9H), 1.35 (br. s., 3H), 0.30 (br. s., 2H), −0.34 (br. s., 1H), −1.05 (br. s., 1H). Mass spectrum (ESI) m/z = 681.0 $[M + H]^+$. HRMS (ESI) m/z found 681.1429 $[M + H]^+$, calcd for $C_{32}H_{35}Cl_2FN_2O_5S_2$ 681.1427.

*(3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-3-(thiazol-2-ylmethyl)piperidin-2-one (**36**).* Compound **36** was obtained as a side product during the synthesis of **41** and **42**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.97 (m, 1H), 7.31−7.53 (m, 3H), 7.10 (br. s., 5H), 4.96 (d, J = 10.37 Hz, 1H), 4.26−4.42 (m, J = 9.00 Hz, 1H), 3.77 (d, J

= 10.76 Hz, 1H), 3.48−3.66 (m, 1H), 3.02−3.25 (m, 1H), 2.92 (d, J = 16.24 Hz, 1H), 2.60−2.76 (m, 1H), 2.18−2.36 (m, 1H), 1.88−2.05 (m, 1H), 1.44 (s, 12H), 0.36 (br. s., 2H), −0.28 (br. s., 1H), −0.97 (br. s., 1H). Mass spectrum (ESI) m/z = 637.0 $[M + H]^+$. HRMS (ESI) m/z found 637.1531 $[M + H]^+$, calcd for $C_{31}H_{35}Cl_2FN_2O_3S_2$ 637.1528.

*(5R,6S)-1-((S)-2-(tert-Butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((2-(trimethylsilyl)ethoxy)methyl)piperidin-2-one (**58**).* In a 25 mL round-bottomed flask evacuated and filled with argon was added THF (2 mL) and then diisopropylamine (0.703 mL, 5.02 mmol). This solution was cooled to −78 °C. At this temperature, butyllithium (2.0 mL, 4.89 mmol, 1 M) was added, and the mixture was allowed to stir for 30 min. In a separate flask, also evacuated and filled with argon, (5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (**57**) (600 mg, 1.223 mmol) was placed and diluted with THF (2 mL), and this solution was also cooled to −78 °C. To this, the solution of freshly produced LDA was added maintaining the temperature at −78 °C. The solution was allowed to slowly reach room temperature overnight. After this period, the mixture was quenched with sat. aq. ammonium chloride (50 mL) and was washed with diethyl ether (3 × 50 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (80 g), eluting with a gradient of 0% to 50% acetone in hexanes, to provide (5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((2-(trimethylsilyl)ethoxy)methyl)piperidin-2-one (**58**) (393 mg, 0.633 mmol, 52% yield) as white oil and a 2:1 mixture of isomers. Mass spectrum (ESI) m/z = 620.2 $[M + H]^+$.

*(3R,5R,6S)-1-((S)-2-(tert-Butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-(hydroxymethyl)-3-methylpiperidin-2-one (**59**).* To a mixture of (5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((2-(trimethylsilyl)ethoxy)methyl)piperidin-2-one (**58**) (2:1 mixture of isomers) (0.393 g, 0.633 mmol) in DCM (6.33 mL), under argon, at 0 °C, was added $BF_3{\cdot}OEt_2$ (0.241 mL, 1.899 mmol). After 3 h, the crude was diluted with sat. aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate, and concentrated. Purification by flash chromatography, (80 g) eluting with 10% to 20% acetone/hexanes, provided first (3*S*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-(hydroxymethyl)-3-methylpiperidin-2-one (56 mg, 0.108 mmol, 17% yield) (fastest eluting isomer) and then (3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-(hydroxymethyl)-3-methylpiperidin-2-one (**59**) (110 mg, 0.211 mmol, 33% yield) (slowest eluting isomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04−7.41 (m, 7H), 6.90 (d, J = 7.24 Hz, 1H), 4.78 (d, J = 9.59 Hz, 1H), 3.82−4.08 (m, 1H), 3.81−4.15 (m, 1H), 3.38−3.63 (m, 2H), 2.44−3.01 (m, 2H), 2.21−2.37 (m, 1H), 2.05−2.16 (m, 1H), 1.52−1.99 (m, 2H), 1.37−1.45 (m, 9H), 1.33−1.37 (m, 3H), 0.44−0.61 (m, 1H), 0.29−0.43 (m, 1H), 0.01 (dd, J = 4.30, 8.80 Hz, 1H), −0.69 (br. s., 1H). Mass spectrum (ESI) m/z = 520.2 $[M + H]^+$.

*((3R,5R,6S)-1-((S)-2-(tert-Butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl Methanesulfonate (**60**).* (3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-Butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-(hydroxymethyl)-3-methylpiperidin-2-one (**59**) (100 mg, 0.192 mmol) was dissolved in DCM (0.768 mL). Then, methanesulfonic anhydride (41.8 mg, 0.240 mmol) and triethylamine (0.0335 mL, 0.240 mmol) were added at room temperature. After stirring for 30 min, the crude was diluted with sat. aq. $NaHCO_3$ (10 mL) and extracted with DCM (2 × 20 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The product was used in the next step without further purification (quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03−7.24 (m, 7H), 6.79−6.85 (m, 1H), 4.54−4.76 (m, 2H), 4.25 (d, J = 9.78 Hz, 1H), 3.77−3.98 (m, 1H), 3.26−3.44 (m, 1H), 3.06−3.17 (m, 3H), 2.50−2.62 (m, 1H), 2.37 (br. s., 1H), 2.09−2.27 (m, 1H), 1.20−1.41 (m, 12H), 0.36−0.57 (m, 1H), 0.15−0.34 (m, 1H), −0.20− −0.05 (m, 1H), −0.95− −0.67 (m, 1H). Mass spectrum (ESI) m/z = 598.2 $[M + H]^+$.

*1-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)-1H-pyrazole-4-carboxylic Acid (**31**).* Part A: To a solution of ((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl methanesulfonate (**60**) (115 mg, 0.192 mmol) in EtOH (2 mL) was added hydrazine (0.181 mL, 5.76 mmol), and the mixture was stirred in the microwave at 90 °C for 36 h. The conversion was about 40% toward the desired product (**61**). The reaction mixture was concentrated from toluene (10 mL). The concentrate was taken to the next step without further purification assuming 40% yield. Mass spectrum (ESI) m/z = 534.2 $[M + H]^+$.

Part B: A solution of (3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-(hydrazinylmethyl)-3-methylpiperidin-2-one (**61**) (45 mg, 0.077 mmol) (containing starting material from the last step) and ethyl-2-formyl-3-oxopropionate (0.111 mL, 0.770 mmol) in dimethylacetamide (1 mL) was heated in the microwave at 100 °C for 2 h. After this period, the reaction was concentrated, and the crude material was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (12 g), eluting with a gradient of 0% to 50% 9:1 acetone/MeOH in DCM to provide ethyl 1-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)-1*H*-pyrazole-4-carboxylate (**62**) (19 mg, 0.030 mmol, 38% yield) as a yellow oil. Mass spectrum (ESI) m/z = 642.1 $[M + H]^+$.

Part C: To a solution of **62** (19 mg, 0.031 mmol) in DCM (1 mL) was added 3-chloroperoxybenzoic acid, (77%) (13.86 mg, 0.062 mmol) at 0 °C. After stirring for 30 min at this temperature, the reaction was quenched with sat. aq. sodium bicarbonate (2 mL), extracted with dichloromethane (3 × 10 mL), and brine (10 mL), and the combined organic layer was dried over magnesium sulfate. The crude mixture was concentrated.

The crude was then diluted in THF (2 mL) and MeOH (1 mL), and then lithium hydroxide (2 mL, 2 M) was added. After this period, the reaction was neutralized (4 mL, 1 M HCl) and concentrated. Purification of the crude product by RP-HPLC (45% to 65% AcCN/H2O, both containing 0.1% TFA, in 30 min, flow rate = 45 mL/min) provided 1-(((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)methyl)-1H-pyrazole-4-carboxylic acid (**31**) (6 mg, 9.28 μmol, 30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 9.39 Hz, 2H), 6.83−7.22 (m, 7H), 6.71−6.80 (m, 1H), 4.93 (d, J = 10.56 Hz, 1H), 4.81 (d, J = 13.89 Hz, 1H), 4.29−4.39 (m, 1H), 4.24 (d, J = 13.89 Hz, 1H), 2.92 (d, J = 11.35 Hz, 1H), 2.71 (t, J = 10.27 Hz, 1H), 2.34−2.47 (m, 1H), 2.24 (t, J = 13.79 Hz, 1H), 1.94−2.10 (m, 2H), 1.44 (s, 9H), 1.36−1.40 (m, 3H), 0.37 (d, J = 7.63 Hz, 2H), −0.33 (br. s., 1H), −0.94 (br. s., 1H). Mass spectrum (ESI) m/z = 646.2 $[M + H]^+$. HRMS (ESI) m/z found 646.1906 $[M + H]^+$, calcd for $C_{32}H_{37}Cl_2N_3O_5S$ 646.1909.

*(3S,5R,6S)-3-(Bromomethyl)-1-((S)-2-(tert-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (**63**).* (3*S*,5*R*,6*S*)-1-((*S*)-2-(*tert*-Butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-(hydroxymethyl)-3-methylpiperidin-2-one (**59**) (326 mg, 0.626 mmol), carbon tetrabromide (312 mg, 0.939 mmol), and triphenylphosphine (246 mg, 0.939 mmol) were stirred in CH_3CN (1.25 mL). After stirring overnight, the mixture was heated at 55 °C for 5 h. The resulting thick oil was diluted in DCM and concentrated onto silica gel. This was purified by flash chromatography (SiO_2, 24 g), eluted with 0% to 15% ethyl acetate/hexanes, to provide (3*S*,5*R*,6*S*)-3-(bromomethyl)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (**63**) (313 mg, 0.536 mmol, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05−7.25 (m, 5H), 6.90−7.03 (m, 2H), 6.83 (td, J = 1.49, 7.38 Hz, 1H), 4.68 (d, J = 10.37 Hz, 1H), 4.00 (d, J = 10.37 Hz, 1H), 3.78 (d, J = 10.37 Hz, 1H), 3.59 (t, J = 11.35 Hz, 1H), 3.05 (dt, J = 5.97, 10.51 Hz, 1H), 2.61 (dd, J = 4.50, 12.13 Hz,

1H), 2.12−2.23 (m, 2H), 1.39−1.43 (m, 3H), 1.33−1.37 (m, 9H), 1.30 (s, 2H), 0.35−0.51 (m, 1H), 0.16−0.30 (m, 1H), −0.15 (qd, J = 4.92, 9.88 Hz, 1H), −0.96− −0.82 (m, 1H). Mass spectrum (ESI) m/z = 584.0 $[M + H]^+$.

*(3S,5R,6S)-1-((S)-2-(tert-Butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((pyrimidin-2-ylthio)methyl)piperidin-2-one (**64**).* (3*S*,5*R*,6*S*)-3-(Bromomethyl)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (**63**) (104 mg, 0.178 mmol), 2-mercapto-pyrimidine (19.99 mg, 0.178 mmol), and potassium carbonate (29.6 mg, 0.214 mmol) were stirred in DMF (0.5 mL). After stirring overnight, additional 12 mg of 2-mercaptopyrimidine and 30 mg of potassium carbonate were added. After 2 h, this was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to provide (3*S*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((pyrimidin-2-ylthio)methyl)-piperidin-2-one (**64**) (quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 4.89 Hz, 1H), 8.50 (d, J = 4.89 Hz, 2H), 7.01−7.25 (m, 6H), 6.80 (t, J = 1.86 Hz, 1H), 6.63−6.68 (m, 1H), 4.64 (d, J = 10.37 Hz, 1H), 4.19 (d, J = 14.09 Hz, 1H), 4.13 (q, J = 7.04 Hz, 1H), 3.52−3.87 (m, 1H), 3.30−3.45 (m, 1H), 2.60 (dd, J = 4.70, 12.13 Hz, 1H), 2.09−2.22 (m, 2H), 1.43 (s, 3H), 1.35 (s, 9H), 1.29 (s, 2H), 0.36−0.47 (m, 1H), 0.17−0.29 (m, 1H), −0.15 (dd, J = 4.70, 9.59 Hz, 1H), −0.91 (d, J = 4.89 Hz, 1H). Mass spectrum (ESI) m/z = 614.2 $[M + H]^+$.

*(3S,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((pyrimidin-2-ylsulfonyl)methyl)piperidin-2-one (**65**).* (3*S*,5*R*,6*S*)-1-((*S*)-2-(*tert*-Butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((pyrimidin-2-ylthio)methyl)piperidin-2-one (**64**) (119 mg, 0.194 mmol) was dissolved in THF (2 mL), and water (1 mL) and oxone (714 mg, 1.162 mmol) were added. After stirring overnight, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude was purified by preparatory TLC eluting with 30% acetone in hexanes to provide (3*S*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((pyrimidin-2-ylsulfonyl)methyl)piperidin-2-one (**65**) (62 mg, 0.091 mmol, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, J = 4.89 Hz, 2H), 7.55 (t, J = 4.89 Hz, 1H), 7.14−7.25 (m, 4H), 7.06−7.12 (m, 2H), 6.89−7.01 (m, 2H), 4.97 (d, J = 10.76 Hz, 1H), 4.25 (t, J = 12.42 Hz, 1H), 4.00−4.18 (m, 1H), 3.59 (dt, J = 4.11, 11.74 Hz, 1H), 2.88 (d, J = 14.48 Hz, 1H), 2.73 (br. s., 1H), 2.31−2.49 (m, 2H), 1.61 (s, 3H), 1.56 (br. s., 2H), 1.43 (s, 9H), 0.14−0.39 (m, 2H), −0.34 (br. s., 1H), −1.07 (br. s., 1H). Mass spectrum (ESI) m/z = 678.1 $[M + H]^+$.

*((3S,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)-methanesulfonamide (**14**).* (3*S*,5*R*,6*S*)-1-((*S*)-2-(*tert*-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-((pyrimidin-2-ylsulfonyl)methyl)piperidin-2-one (**65**) (24 mg, 0.035 mmol) and potassium carbonate (25 mg, 0.181 mmol) were stirred in MeOH (0.5 mL). After stirring overnight, complete conversion to the sulfinic acid was observed. Then, hydroxylamine-*o*-sulfonic acid (31 mg, 0.053 mmol) was added. After stirring overnight, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude was purified by preparative TLC eluted with 30% acetone/hexanes to provide ((3*S*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methanesulfonamide (**14**) (10 mg, 0.016 mmol, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05−7.24 (m, 6H), 7.00 (s, 1H), 6.89 (br. s., 1H), 5.38 (br. s., 2H), 4.96 (d, J = 10.56 Hz, 1H), 4.34 (t, J = 11.44 Hz, 1H), 3.45−3.74 (m, 2H), 3.31 (t, J = 11.15 Hz, 1H), 2.91 (d, J = 13.69 Hz, 1H), 2.73 (br. s., 1H), 2.46 (t, J = 13.60 Hz, 1H), 1.95 (dd, J = 2.93, 13.89 Hz, 1H), 1.90 (br. s., 1H), 1.60 (s, 3H), 1.44 (s, 9H), 0.19−0.47 (m, 2H), −0.32 (br. s., 1H), −1.08 (br. s., 1H). Mass spectrum (ESI) m/z = 615.1 $[M + H]^+$. HRMS (ESI) m/z found 615.1523 $[M + H]^+$, calcd for $C_{28}H_{36}Cl_2N_2O_5S_2$ 615.1521.

*2-(2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)acetic Acid (**38**).* Part A: To a solution of 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)acetyl chloride (196 mg, 0.327 mmol) in THF (1.15 mL) was added ethyl 4-(bis(trimethylsilyl)amino)but-2-ynoate (89 mg, 0.327 mmol) and then tetra-*N*-butylammonium fluoride, 1 M solution in THF (0.052 mL, 0.052 mmol). The solution was stirred at room temperature overnight. After this period, the reaction was acidified with 1 M HCl (5 mL), then extracted with diethyl ether (3 × 30 mL) and brine (30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (40 g), eluting with a gradient of 0% to 40% acetone in DCM, to provide ethyl 4-(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)acetamido)but-2-ynoate (**67**) (162 mg, 0.235 mmol, 72% yield) as a white solid. Mass spectrum (ESI) m/z = 688.3 $[M]^+$.

Part B: A solution of ethyl 4-(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)acetamido)but-2-ynoate (**67**) (162 mg, 0.235 mmol) and Lawesson's reagent (47.5 mg, 0.117 mmol) in toluene (0.435 mL) was stirred at 60 °C for 3 h. The reaction was then cooled and concentrated. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (40 g), eluting with isocratic 15% acetone in DCM to provide ethyl 2-(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)methyl)thiazol-5-yl)-acetate (**68**) (105 mg, 0.149 mmol, 63% yield) as a white solid. Mass spectrum (ESI) m/z = 704.2 $[M]^+$.

Part C: To a solution of ethyl 2-(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)methyl)thiazol-5-yl)acetate (**68**) (33 mg, 0.047 mmol) in THF (2 mL) and MeOH (1 mL) was added lithium hydroxide (1 mL, 2 M). The reaction was stirred at 50 °C for 1 h. Purification of the crude product by RP-HPLC (25 to 75% CH_3CN/H_2O, both containing 0.1% TFA, in 30 min, flow rate = 45 mL/min) provided 2-(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)methyl)thiazol-5-yl)acetic acid (**38**) (18 mg, 0.027 mmol, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 6.96−7.26 (m, 6H), 6.79−6.92 (m, 2H), 4.94 (d, J = 10.76 Hz, 1H), 4.24−4.45 (m, 1H), 3.92 (s, 2H), 3.64−3.77 (m, 1H), 3.55 (br. s., 1H), 3.24 (t, J = 11.93 Hz, 1H), 2.91 (d, J = 12.72 Hz, 1H), 2.71 (br. s., 1H), 2.31 (t, J = 13.69 Hz, 1H), 1.74−1.95 (m, 2H), 1.43 (s, 9H), 1.42 (br. s., 3H), 0.34 (br. s., 1H), 0.22 (br. s., 1H), −0.35 (br. s., 1H), −1.06 (br. s., 1H). Mass spectrum (ESI) m/z = 677.2 $[M + H]^+$. HRMS (ESI) m/z found 677.1673 $[M + H]^+$, calcd for $C_{33}H_{38}Cl_2N_2O_5S_2$ 677.1677.

*2-(2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)-2-methylpropanoic Acid (**39**).* Part A: To a solution of ethyl 2-(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)methyl)thiazol-5-yl)acetate (**68**) (50 mg, 0.071 mmol) in DMF (0.269 mL) was added sodium *tert*-butoxide (18 mg, 0.203 mmol) at 0 °C. After stirring for 15 min, methyl iodide (0.00836 mL, 0.135 mmol) was added. The reaction was quenched with sat. aq. ammonium chloride (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (40 g), eluting with a gradient of 0% to 40% acetone in DCM, to provide ethyl 2-(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)-methyl)thiazol-5-yl)-2-methylpropanoate (32 mg, 0.044 mmol, 62% yield). Mass spectrum (ESI) m/z = 733.2 $[M + H]^+$.

Part B: To a solution of ethyl 2-(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)methyl)thiazol-5-yl)-2-methylpropanoate (32 mg, 0.044 mmol) in THF (2 mL) and MeOH (1 mL) was added lithium hydroxide (1 mL, 2 M). The solution was stirred at 50 °C for 30 min. After this period, the reaction was neutralized (2 mL, 1 M HCl) and concentrated. Purification of the crude product by RP-HPLC (25 to 75% CH_3CN/H2O, both containing 0.1% TFA, in 30 min, flow rate =45 mL/min) provided 2-(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)methyl)thiazol-5-yl)-2-methylpropanoic acid (**39**) (23 mg, 0.033 mmol, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.02−7.26 (m, 6H), 6.96 (s, 1H), 6.81−6.90 (m, 1H), 4.94 (d, J = 10.76 Hz, 1H), 4.37 (t, J = 11.84 Hz, 1H), 3.73 (d, J = 14.28 Hz, 1H), 3.45 (d, J = 14.28 Hz, 1H), 3.07−3.22 (m, 1H), 2.61−2.77 (m, 2H), 2.27 (t, J = 13.79 Hz, 1H), 1.89−1.99 (m, 1H), 1.84 (d, J = 11.93 Hz, 1H), 1.72 (d, J = 0.98 Hz, 6H), 1.44 (s, 9H), 1.43 (s, 3H), 0.13−0.45 (m, 2H), −0.34 (br. s., 1H), −1.03 (br. s., 1H). Mass spectrum (ESI) m/z = 705.0 $[M + H]^+$. HRMS (ESI) m/z found 705.2002 $[M + H]^+$, calcd for $C_{35}H_{42}Cl_2N_2O_5S_2$ 705.1990.

*1-(2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)cyclopropanecarboxylic Acid (**40**).* Compound **40** was synthesized through a procedure similar to that described for the synthesis of **39**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.43 (m, 1H), 6.84 (s, 6H), 6.74 (s, 1H), 6.63 (d, J = 6.26 Hz, 1H), 4.71 (d, J = 10.76 Hz, 1H), 4.01−4.20 (m, J = 8.02 Hz, 1H), 3.49 (d, J = 13.11 Hz, 2H), 3.27 (d, J = 13.89 Hz, 2H), 2.82−3.03 (m, 1H), 2.48 (br. s., 1H), 2.06 (t, J = 13.79 Hz, 1H), 1.68 (br. s., 4H), 1.25−1.30 (m, 1H), 1.21 (s, 12H), −0.08−0.22 (m, 2H), −0.57 (br. s., 1H), −1.26 (br. s., 1H). Mass spectrum (ESI) m/z = 703.0 $[M + H]^+$.

*2-(2-((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)acetic Acid (**70**).* Part A: A solution of 2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (**69**)[17] (22.00 g, 36.8 mmol) and glycine methyl ester hydrochloride (11.54 g, 92 mmol) in DMF (100.0 mL) was treated with EDC (17.62 g, 92 mmol), HOAT (12.51 g, 92 mmol), and sodium hydrogencarbonate (15.44 g, 184 mmol) successively at room temperature. The reaction was stirred at 40 °C overnight. After this period, the reaction was diluted (1 N aq. HCl), extracted (2 × EtOAc), and washed (1 × sat. aq. $NaHCO_3$, and 2 × brine). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The product of this step was used in the next process without further purification. Mass spectrum (ESI) m/z = 669.2 $[M + H]^+$.

Part B: To a solution of methyl 2-(2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)acetate (see part A) (24.60 g, 36.7 mmol) in THF (40 mL), MeOH (40 mL), and H_2O (80 mL) was added lithium hydroxide (4.40 g, 184 mmol). The reaction was stirred at room temperature.

The reaction was quenched with ice-cold 1 N aq. HCl, extracted with EtOAc, and washed with brine. The combined organic layer were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product crystallized with 60 mL of EtOAc/50 mL hexanes, and the mother liquor was purified by flash column chromatography: 220g SiO_2, with a gradient of 35% to 50% acetone in hexanes, over 15 min to give 2-(2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)acetic acid (**70**) (21.6 g, 32.9 mmol, 90% yield over the last two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (br. s., 1H), 7.14−7.37 (m, 2H), 7.09−7.15 (m, 2H), 7.03 (s, 1H), 6.90−6.97 (m, 1H), 4.98 (d, J = 10.51 Hz, 1H), 4.29 (t, J = 11.49 Hz, 1H), 4.07−4.18 (m, 2H), 3.25−3.39 (m, 1H), 3.06 (d, J = 13.45 Hz, 1H), 2.87−2.94 (m, 1H), 2.83 (d, J = 13.45 Hz, 1H), 2.68 (br. s., 1H), 2.21−2.48 (m, 2H), 1.84 (br. s., 1H), 1.44 (s, 9H), 1.37 (s, 3H), 0.19−0.45 (m, 2H), −0.27 (br. s., 1H), −1.08 (br. s., 1H). Mass spectrum (ESI) m/z = 655.2 $[M + H]^+$.

*Methyl 2-(2-(((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)acetate (**71**).* Part A: To a 200-mL round-bottomed flask was added methyl potassium malonate (4.76 g, 30.5 mmol) and magnesium chloride (2.178 g, 22.88 mmol) in 30 mL of THF. This mixture was allowed to stir at 50 °C for 4 h.

2-(2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)acetic acid (**70**) (5.00 g, 7.63 mmol) was dissolved in THF (40 mL). Then, 1,1′-carbonyldiimidazole (4.33 g, 26.7 mmol) was added portionwise to the solution. The mixture was stirred for 2 h at 50 °C. After this period, the above mixture was added to the methyl magnesium malonate suspension at 50 °C, and the reaction was allowed to stir at 50 °C overnight. The reaction mixture was diluted with EtOAc and washed with 1 M sodium bisulfate. The aqueous layer was extracted twice with EtOAc and washed with sat. aq. $NaHCO_3$ and brine. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (120 g SiO_2, 25% to 40% acetone/hexanes gradient over 15 min) to give methyl 4-(2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-3-oxobutanoate (**71**) (3.40 g, 4.78 mmol, 63% yield). Mass spectrum (ESI) m/z = 711.2 $[M + H]^+$.

Part B: To a 500-mL round-bottomed flask was added methyl 4-(2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-3-oxobutanoate (**71**) (4.00 g, 5.62 mmol) and Lawesson's reagent (2.273 g, 5.62 mmol) in toluene (50 mL). The mixture was heated at reflux for 3 h. After this time, the reaction was cooled and concentrated under reduced pressure. The crude product was purified by flash column chromatography (330 g SiO_2, 35% to 50% EtOAc/hexanes gradient over 20 min) to give methyl 2-(2-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)acetate (**72**) (2.8 g, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.03−7.14 (m, 3H), 6.96 (s, 4H), 4.95 (d, J = 10.76 Hz, 1H), 4.38 (t, J = 11.98 Hz, 1H), 3.89 (s, 2H), 3.69 (d, J = 14.18 Hz, 1H), 3.32 (d, J = 14.18 Hz, 1H), 3.01 (br. s., 1H), 2.93 (d, J = 12.72 Hz, 1H), 2.60−2.76 (m, 1H), 2.23 (t, J = 13.82 Hz, 1H), 2.18 (s, 3H), 2.00 (br. s., 1H), 1.90 (dd, J = 2.32, 13.57 Hz, 1H), 1.44 (s, 9H), 1.40 (s, 3H), 0.26−0.46 (m, 2H), −0.29 (d, J = 3.18 Hz, 1H), −1.00 (br. s., 1H). Mass spectrum (ESI) m/z = 709.2 $[M + H]^+$.

*2-(2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)acetic Acid (**4**).* To a solution of methyl 2-(2-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)acetate (**72**) (5.70 g, 8.03 mmol) in THF (60 mL), MeOH (40 mL), and H_2O (80 mL) was added lithium hydroxide (0.962 g, 40.2 mmol). The reaction was stirred at room temperature for 1.5 h. The reaction was quenched with ice-cold 1 N aq. HCl, extracted with EtOAc, and washed with brine. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (220 g SiO_2, 40% to 50% acetone/hexanes gradient over 10 min) to provide 2-(2-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)-acetic acid (**4**) (5.10 g, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (br. s., 1H), 6.96−7.17 (m, 5H), 6.89 (d, J = 6.60 Hz, 1H), 4.96 (d, J = 10.51 Hz, 1H), 4.34 (t, J = 11.86 Hz, 2H), 3.96 (s, 2H), 3.67−3.82 (m, 2H), 3.61 (br. s., 1H), 2.91 (d, J = 12.96 Hz, 1H), 2.69 (br. s., 1H), 2.32 (t, J = 13.94 Hz, 1H), 1.80−1.97 (m, 2H), 1.44 (s, 9H), 1.26 (s, 3H), 0.37 (d, J = 4.16 Hz, 2H), −0.29 (br. s., 1H), −0.98 (br. s., 1H). ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ 175.4, 171.9, 165.8, 158.9,

158.6, 144.2, 141.9, 141.6, 133.3, 131.9, 130.9, 127.7, 127.4, 126.6, 119.6, 119.5, 118.7, 116.7, 114.8, 69.9, 59.9, 58.7, 58.6, 44.4, 43.9, 43.6, 41.2, 38.2, 33.4, 26.5, 14.6, 7.3, 4.6. Mass spectrum (ESI) m/z = 695.2 $[M + H]^+$. HRMS (ESI) m/z found 695.1584 $[M + H]^+$, calcd for $C_{33}H_{37}Cl_2FN_2O_5S_2$ 695.1583.

*2-(2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)-2-fluoroacetic Acid (**41**) and 2-(2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)-2,2-difluoroacetic Acid (**42**).* Part A: To a solution of ethyl 2-(2-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)acetate (**72**) (21 mg, 0.029 mmol) in DMF (0.269 mL) was added sodium *tert*-butoxide (5.86 mg, 0.061 mmol) at 0 °C. After stirring for 15 min, *N*-fluorobenzenesulphonimide (19.21 mg, 0.061 mmol) was added. After 30 min, LCMS showed a mixture of compounds containing unreacted starting material, mono-, difluorination, and deacetylation products. The crude mixture was quenched (0.5 mL water), concentrated, and taken into the next step without further purification.

Part B: The mixture from the previous step was diluted in THF (2 mL), MeOH (1 mL), and 1 mL of 2 M LiOH and heated and 50 °C for 30 min. After this period, the reaction was cooled, quenched with 1 N HCl (2 mL), and concentrated. Purification by preparative HPLC (25−75% CH_3CN/H_2O both solvents containing 0.1% TFA) provided, in order of elution, first 2-(2-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)-2-fluoroacetic acid (**41**) (2.4 mg, 3.36 μmol, 12% yield) as a 1:1 mixture of isomers; then, 2-(2-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)thiazol-5-yl)-2,2-difluoroacetic acid (**42**) (0.8 mg, 4% yield, Mass spectrum (ESI) m/z = 731.0 $[M + H]^+$); and then, (3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-3-(thiazol-2-ylmethyl)piperidin-2-one (**36**) (3 mg, 16% yield), as white amorphous solids.

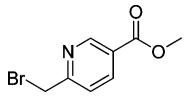
*Characterization of **41**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−8.03 (m, 1H), 7.10 (d, J = 1.96 Hz, 7H), 5.95−6.30 (m, 1H), 4.86−5.11 (m, 1H), 4.24−4.44 (m, 1H), 3.64−3.79 (m, 1H), 3.34−3.54 (m, 1H), 3.06−3.21 (m, 1H), 2.88−3.02 (m, 1H), 2.18−2.39 (m, 1H), 1.78−2.08 (m, 2H), 1.44 (s, 12H), 0.38 (br. s., 2H), −0.26− −0.24 (m, 1H), −0.38− −0.19 (m, 1H), −0.99 (br. s., 1H). Mass spectrum (ESI) m/z = 713.0 $[M + H]^+$. HRMS (ESI) m/z found 713.1489 $[M+H]^+$, calcd for $C_{33}H_{36}Cl_2F_2N_2O_5S_2$ 713.1486.

*2-(2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)oxazol-5-yl)acetic Acid (**43**).* Part A: To a solution of methyl 4-(2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-3-oxobutanoate (**71**) (19 mg, 0.027 mmol) in DCE (1.3 mL) was added (methoxycarbonylsulfamoyl)triethyl-ammonium hydroxide (25.4 mg, 0.107 mmol). The solution was stirred for 5 h in the microwave. The reaction did not reach completion; thus, additional (methoxycarbonylsulfamoyl)triethyl-ammonium hydroxide (25.4 mg, 0.107 mmol) was added, and the reaction was set again in the microwave for 2 more hours, after which period only the desired product was observed. The crude mixture was concentrated and absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column (40 g), eluting with a gradient of 5% to 60% acetone in hexanes, to provide methyl 2-(2-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)oxazol-5-yl)acetate (12 mg, 0.017 mmol, 65% yield) as a white solid. Mass spectrum (ESI) m/z = 693.0 $[M + H]^+$.

Part B: To a solution of ethyl 2-(2-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)oxazol-5-yl)-acetate (12 mg, 0.017 mmol) in THF (2 mL) and MeOH (1 mL) was added lithium hydroxide (1 mL, 2 M). The solution was stirred at 50 °C for 30 min. After this period, the reaction was neutralized (2 mL, 1 M HCl) and concentrated. Purification by preparative HPLC (25−75% acetonitrile/water both solvents containing 0.1% TFA) provided 2-(2-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)oxazol-5-yl)acetic acid (**43**) (8 mg, 0.012 mmol, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 2H), 7.14 (d, J = 5.28 Hz, 2H), 7.02 (s, 2H), 6.91−6.98 (m, 1H), 5.00 (d, J = 10.37 Hz, 1H), 4.39 (t, J = 12.03 Hz, 1H), 3.78 (s, 2H), 3.25−3.48 (m, 2H), 3.07−3.23 (m, 1H), 2.94 (d, J = 13.89 Hz, 1H), 2.68 (t, J = 10.76 Hz, 1H), 2.29 (br. s., 2H), 1.87−2.01 (m, 1H), 1.73 (d, J = 14.09 Hz, 1H), 1.46 (s, 9H), 1.42 (s, 3H), 0.38 (br. s., 2H), −0.26 (br. s., 1H), −0.98 (br. s., 1H). Mass spectrum (ESI) m/z = 679.0 $[M + H]^+$. HRMS (ESI) m/z found 679.1812 $[M + H]^+$, calcd for $C_{33}H_{37}Cl_2FN_2O_6S$ 679.1812.

*Methyl 6-(((2S,5R,6R)-4-((S)-2-((tert-butyldimethylsilyl)oxy)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)methyl)nicotinate and methyl 6-(((2R,5R,6R)-4-((S)-2-((tert-butyldimethylsilyl)oxy)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)methyl)nicotinate (**74**).* Part A: Lithium bis(trimethylsilyl)amide (1.0 M solution in tetrahydrofuran, 17.3 mL, 17.3 mmol) was added to an oven-dried, 3-neck round-bottom flask containing (5*R*,6*R*)-4-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)morpholin-3-one[28] in tetrahydrofuran at −78 °C under argon. Methyl iodide (1.08 mL, 17.3 mmol) in tetrahydrofuran was added subsequently. After stirring at −78 °C for 1 h, the reaction was quenched with sat. aq. ammonium chloride (20 mL), extracted with ethyl acetate (2 × 30 mL), and washed with brine (30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, gradient elution of 0% to 80% ethyl acetate in hexanes) afforded (2*S*,5*R*,6*R*)-4-((*S*)-2-((*tert*-butyldimethylsilyl)-oxy)-1-cyclopropylethyl)-6-(3-chloro-phenyl)-5-(4-chlorophenyl)-2-methylmorpholin-3-one and (2*R*,5*R*,6*R*)-4-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)-1-cyclopropylethyl)-6-(3-chloro-phenyl)-5-(4-chlorophenyl)-2-methylmorpholin-3-one (**73**) as a 2:1 mixture of diastereomers. Mass spectrum (ESI) m/z = 533.2 $[M + H]^+$.

Methyl 6-(bromomethyl)nicotinate.



In a round-bottomed flask equipped with a reflux condenser, a mixture of methyl 6-methyl nicotinate (10.0 g, 66.2 mmol), *N*-bromosuccinimide (7.1 g, 39.7 mmol), and benzoyl peroxide (1.6 g, 6.62 mmol) in carbon tetrachloride was stirred under nitrogen at 75 °C for 2 days. The cooled reaction mixture was filtered, the filter cake was washed with dichloromethane, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel column, gradient elution of 5% to 25% ethyl acetate in hexanes) afforded methyl 6-(bromomethyl)nicotinate as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, J = 1.56 Hz, 1H), 8.31 (dd, J = 2.15, 8.02 Hz, 1H), 7.54 (d, J = 8.22 Hz, 1H), 4.59 (s, 2H), 3.97 (s, 3H). MS (ESI) m/z: 230.0 $[M + H]^+$.

Part B: A three-necked, oven-dried, round-bottomed flask was cooled under argon and charged with diisopropylamine (2.48 mL, 17.7 mmol) and tetrahydrofuran (20 mL) and cooled to 0 °C. *n*-Butyllithium (2.5 M in hexanes, 7.08 mL, 17.70 mmol) was added dropwise, and the reaction was stirred for 10 min at 0 °C. The reaction mixture was cooled to −78 °C, and a solution of (2*S*,5*R*,6*R*)-4-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)-1-cyclopropylethyl)-6-(3-chloro-phenyl)-5-(4-chlorophenyl)-2-methylmorpholin-3-one and (2*R*,5*R*,6*R*)-4-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)-1-cyclopropylethyl)-6-(3-chloro-phenyl)-5-(4-chlorophenyl)-2-methylmorpholin-3-one (**73**) in tetrahydrofuran (30 mL), also at −78 °C, was added. After stirring at −78 °C for 15 min, a solution of methyl 6-(bromomethyl)nicotinate (4.07

g, 17.70 mmol) in tetrahydrofuran (20 mL) at −78 °C was added. The reaction was stirred at this temperature for 1 h.

The resulting mixture was quenched with saturated ammonium chloride (50 mL), extracted with ethyl acetate (3 × 50 mL), and washed with water (50 mL) and brine (50 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated. Purification of the residue by flash column chromatography (silica gel column, gradient elution of 0% to 25% acetone in hexanes) afforded **74**.

*Methyl 6-(((2R,5R,6R)-4-((S)-2-((tert-butyldimethylsilyl)oxy)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)methyl)nicotinate (**74a**, Faster Eluting Isomer).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 2.15 Hz, 1H), 8.10 (d, J = 7.63 Hz, 1H), 7.23 (d, J = 8.22 Hz, 1H), 7.11 (d, J = 8.22 Hz, 2H), 7.00−7.08 (m, 2H), 6.92 (t, J = 7.83 Hz, 1H), 6.71−6.86 (m, 2H), 6.53 (d, J = 7.63 Hz, 1H), 4.85 (d, J = 9.78 Hz, 1H), 4.69 (d, J = 9.98 Hz, 1H), 4.20 (t, J = 9.98 Hz, 1H), 3.84 (s, 3H), 3.77 (d, J = 13.50 Hz, 1H), 3.38−3.43 (m, J = 4.50 Hz, 1H), 3.33 (d, J = 14.28 Hz, 1H), 2.04−2.18 (m, 1H), 1.52 (s, 3H), 0.87 (s, 9H), 0.81 (d, J = 0.78 Hz, 1H), 0.25−0.32 (m, 2H), 0.00 (s, 3H), −0.04 (s, 3H), −0.34− −0.26 (m, J = 8.80 Hz, 1H), −0.63 (dd, J = 4.21, 9.29 Hz, 1H). Mass spectrum (ESI) m/z = 683.2 $[M + H]^+$.

*Characterization Data for the Slowest Eluting Isomer, Methyl 6-(((2S,5R,6R)-4-((S)-2-((tert-butyldimethylsilyl)oxy)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)methyl)nicotinate (**74b**, Slower Eluting Isomer).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20−9.25 (m, 1H), 8.21−8.28 (m, 1H), 7.43 (d, J = 8.02 Hz, 1H), 7.24 (br s, 2H), 7.11−7.19 (m, 3H), 7.02 (t, J = 7.83 Hz, 1H), 6.92−6.98 (m, 1H), 6.86−6.91 (m, 1H), 6.52 (d, J = 7.83 Hz, 1H), 4.78 (d, J = 9.78 Hz, 1H), 4.62 (d, J = 9.78 Hz, 1H), 3.98−4.06 (m, 1H), 3.96 (s, 3H), 3.89−3.95 (m, 1H), 3.73 (d, J = 13.50 Hz, 1H), 3.46−3.52 (m, J = 5.67, 10.17 Hz, 1H), 1.76 (s, 3H), 1.31−1.43 (m, 1H), 0.91 (s, 9H), 0.28−0.48 (m, 2H), 0.05 (s, 3H), 0.02 (s, 3H), −0.15− −0.02 (m, 1H), −0.56− −0.38 (m, 1H). Mass spectrum (ESI) m/z = 683.1 $[M + H]^+$.

*Methyl 6-(((2R,5R,6R)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-4-((S)-1-cyclopropyl-2-hydroxyethyl)-2-methyl-3-oxomorpholin-2-yl)methyl)nicotinate (**75a**).* Tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 0.70 mL, 0.70 mmol) was added to a solution of **74a** (300 mg, 0.44 mmol) in tetrahydrofuran (5 mL) and stirred at ambient temperature overnight. The resulting mixture was quenched with saturated ammonium chloride (10 mL) and washed with ethyl acetate (3 × 15 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated. Purification of the residue by flash column chromatography (silica gel column, gradient elution of 0% to 25% ethyl acetate in hexanes) afforded **75a** (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (dd, J = 0.78, 2.15 Hz, 1H), 8.16−8.24 (m, J = 5.87 Hz, 1H), 7.29 (d, J = 8.22 Hz, 1H), 7.17−7.25 (m, 3H), 7.11 (t, J = 1.66 Hz, 1H), 7.07 (t, J = 7.92 Hz, 1H), 6.91−7.02 (m, 2H), 6.61 (d, J = 7.63 Hz, 1H), 4.85−4.92 (m, 1H), 4.73−4.82 (m, 1H), 3.95 (s, 3H), 3.82 (s, 1H), 3.56−3.66 (m, 1H), 3.34−3.48 (m, 2H), 3.12−3.25 (m, 2H), 1.60 (s, 3H), 0.68−0.78 (m, 1H), 0.48−0.68 (m, 2H), 0.21−0.31 (m, 1H), 0.04−0.19 (m, 1H). Mass spectrum (ESI) m/z = 569.0 $[M + H]^+$.

*Methyl 6-(((2R,5R,6R)-4-((S)-2-(tert-butylthio)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)methyl)nicotinate (**76a**).* Cyanomethylenetributylphosphorane (0.356 g, 1.48 mmol) and *tert*-butanethiol (0.133 g, 1.48 mmol) were added to a solution of **75a** (210 mg, 0.37 mmol) in toluene (2 mL), and the mixture was stirred at 70 °C overnight. The resulting mixture was cooled and concentrated. Purification of the residue by flash column chromatography (silica gel column, gradient elution of 0% to 35% ethyl acetate in hexanes) afforded **76a** (61%). Mass spectrum (ESI) m/z = 641.1 $[M + H]^+$.

*6-(((2R,5R,6R)-4-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)methyl)nicotinic Acid (**46**).* Part A: 3-Chloroperbenzoic acid (77 wt.%, 0.031 g, 0.14 mmol) was added to a solution of **76a** (60 mg, 0.07 mmol) in dichloromethane (3 mL) at 0 °C. The reaction was quenched after 30 min with 1 N sodium thiosulfate (5 mL) and washed with ethyl acetate (3 × 10 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated. Purification of the residue by flash column chromatography (silica gel column, gradient elution of 0% to 40% acetone in hexanes) afforded **77a**. Mass spectrum (ESI) m/z = 673.0 $[M + H]^+$.

Part B: Lithium hydroxide (1 mL, 2 M solution) was added to a solution of **77a** (30 mg, 0.045 mmol) in methanol (1 mL) and tetrahydrofuran (1 mL) at room temperature. The resulting mixture was heated at 50 °C for 1 h. The reaction mixture was cooled, quenched with a 10% citric acid solution (5 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. Purification of the residue by flash column chromatography (silica gel column, gradient elution of 0% to 100% ethyl acetate in hexanes) afforded **46**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.56 (d, J = 8.61 Hz, 1H), 7.63 (d, J = 8.22 Hz, 1H), 7.19−7.26 (m, 2H), 7.11−7.18 (m, 3H), 7.04 (t, J = 8.12 Hz, 2H), 6.82 (d, J = 7.63 Hz, 1H), 5.17 (d, J = 9.78 Hz, 1H), 5.06 (d, J = 9.78 Hz, 1H), 4.15−4.27 (m, J = 12.72 Hz, 1H), 3.89 (d, J = 13.11 Hz, 2H), 3.72 (d, J = 13.30 Hz, 1H), 2.92 (d, J = 13.50 Hz, 1H), 2.71 (t, J = 9.68 Hz, 1H), 1.81−1.97 (m, 1H), 1.68 (s, 3H), 1.40 (s, 9H), 0.31−0.54 (m, 2H), −0.33− −0.20 (m, 1H), −0.79− −0.59 (m, 1H). Mass spectrum (ESI) m/z = 659.0 $[M + H]^+$. HRMS (ESI) m/z found 659.1748 $[M+H]^+$, calcd for $C_{33}H_{36}Cl_2N_2O_6S$ 679.1749.

*6-(((2S,5R,6R)-4-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-6-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-3-oxomorpholin-2-yl)methyl)nicotinic Acid (**47**).* Compound **47** was synthesized in a manner similar to that for **46** starting from **74b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.56 (d, J = 8.61 Hz, 1H), 7.63 (d, J = 8.22 Hz, 1H), 7.27 (br s, 4H), 7.11−7.17 (m, 2H), 7.04 (t, J = 8.12 Hz, 1H), 6.82 (d, J = 7.63 Hz, 1H), 5.17 (d, J = 9.78 Hz, 1H), 5.06 (d, J = 9.78 Hz, 1H), 4.13−4.28 (m, J = 11.74 Hz, 1H), 3.89 (d, J = 13.11 Hz, 2H), 3.72 (d, J = 13.30 Hz, 1H), 2.91 (d, J = 13.89 Hz, 1H), 2.62−2.79 (m, 1H), 1.80−1.98 (m, 1H), 1.68 (s, 3H), 1.40 (s, 9H), 0.27−0.54 (m, 2H), −0.36− −0.19 (m, 1H), −0.75− −0.59 (m, 1H). Spectrum (ESI) m/z = 659.0 $[M + H]^+$. HRMS (ESI) m/z found 659.1755 $[M + H]^+$, calcd for $C_{33}H_{36}Cl_2N_2O_6S$ 679.1749.

*2-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)isonicotinic Acid (**19**).* Part A: An oven-dried, cooled under Argon, round-bottomed flask was charged with diisopropylamine (0.065 mL, 0.459 mmol) and THF (1 mL), and then butyllithium (0.287 mL, 0.459 mmol) was added at 0 °C. The reaction was stirred at this temperature for 10 min. The reaction solution was then cooled to −78 °C. To this, a solution of (5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (**57**) (150 mg, 0.306 mmol) was added in THF (1 mL) at −78 °C. The reaction was stirred at −78 °C for 15 min, then warmed up to −20 °C and stirred at this temperature for an additional 15 min. The reaction was then cooled again to −78 °C, and a solution of *tert*-butyl 2-(bromomethyl)isonicotinate (125 mg, 0.459 mmol) in THF (1 mL) was added. The reaction was stirred for 4 h at −78 °C. After this time, the reaction mixture was diluted with EtOAc and washed with sat. NH_4Cl, water, brine. The crude was purified by column (silica gel, eluting with ethyl acetate and hexanes) to give a 3:1 mixture of isomers of *tert*-butyl 2-(((5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)isonicotinate (147 mg, 0.216 mmol, 71% yield). Mass spectrum (ESI) m/z = 681.2 $[M + H]^+$.

Part B: To a solution of *tert*-butyl 2-(((5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)isonicotinate in *N*,*N*-dimethylformamide (1.5 mL) was added 3-chloroperoxybenzoic acid, 75% max. (145 mg, 0.647 mmol) at 0 °C. The reaction was allowed to stir for 40 min after which it was quenched (1.5 mL of 1 M aq. $Na_2S_2O_3$), extracted (EtOAc), and washed (1 × sat. aq. $NaHCO_3$, 1 × water, and 1 × brine). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a crude of *tert*-butyl 2-(((5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)isonicotinate (167 mg, 0.234 mmol, quantitative

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yield). The crude was used on the next reaction without further purification. Mass spectrum (ESI) m/z = 713.2 $[M + H]^+$.

Part C: To a solution of *tert*-butyl 2-(((5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)isonicotinate (154 mg, 0.216 mmol) in DCM (3 mL) was added TFA (3 mL), and the reaction was stirred at room temperature for 3 h. Concentration gave a residue, which was purified by preparative HPLC to give 2-(((3*S*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)isonicotinic acid (22 mg, 0.033 mmol, 16% yield), and then 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)methyl)isonicotinic acid **19** (96 mg, 0.146 mmol, 68% yield). Characterization for **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (br. s., 1H), 8.02−8.19 (m, 2H), 7.05−7.26 (m, 5H), 7.03 (s, 1H), 6.90 (d, J = 5.28 Hz, 1H), 5.00 (d, J = 10.76 Hz, 2H), 4.33 (t, J = 11.84 Hz, 1H), 3.80 (d, J = 13.50 Hz, 1H), 3.29−3.53 (m, 2H), 2.89 (d, J = 13.50 Hz, 1H), 2.77 (br. s., 1H), 2.45 (t, J = 13.79 Hz, 1H), 1.90 (d, J = 12.72 Hz, 1H), 1.82 (br. s., 1H), 1.42 (s, 9H), 1.38 (s, 3H), 0.33 (d, J = 6.65 Hz, 2H), −0.34 (br. s., 1H), −0.95 (br. s., 1H). Mass spectrum (ESI) m/z = 657.2 $[M + H]^+$. HRMS (ESI) m/z found 657.1951 $[M + H]^+$, calcd for $C_{34}H_{38}Cl_2N_2O_6S$ 657.1957.

*(3R,5R,6S)-3-((5-Bromopyridin-2-yl)methyl)-1-((S)-2-(tert-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (**78**).* An oven-dried 10 mL flask equipped with a stir bar and rubber inlet was fitted with a needle and argon balloon. The flask was filled with THF (1.2 mL) and submerged in an ice−water bath. Diisopropylamine (82 μL, 0.587 mmol) was added, followed by butyllithium (235 μL, 0.587 mmol). After 2 h, at −78 °C, a solution of (5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (**58**) (192 mg, 0.391 mmol) in THF (1.2 mL) was added dropwise via a plastic syringe under an argon atmosphere over 5 min. After 1 h, the reaction was warmed to −40 °C and a solution of 5-bromo-2-(bromomethyl)pyridine (147 mg, 0.587 mmol) in THF (1.2 mL) was added to the reaction mixture. After stirring for 3 h at this temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and partitioned with EtOAc. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was dissolved in DCM and loaded onto a dry silica gel cartridge and eluted on a 25 g gold-capped ISCO Redisep silica gel column with 0−40% EtOAc/hexanes to give **79** (45 mg, 18% yield). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.58 (d, J = 2.4 Hz, 1H), 7.78 (dd, J = 2.4, 8.3 Hz, 1H), 7.20 (d, J = 8.3 Hz, 3H), 7.16−7.10 (m, 2H), 7.08 (s, 1H), 6.95 (br. s., 2H), 6.88−6.85 (m, 1H), 4.73 (d, J = 10.5 Hz, 1H), 3.47 (t, J = 11.0 Hz, 1H), 3.42 (d, J = 12.7 Hz, 1H), 3.37−3.30 (m, 1H), 3.11 (d, J = 13.0 Hz, 1H), 2.54 (dd, J = 5.1, 12.0 Hz, 1H), 2.41−2.22 (m, 1H), 2.06 (t, J = 13.4 Hz, 1H), 1.85 (dd, J = 3.2, 13.7 Hz, 1H), 1.65−1.59 (m, 1H), 1.31 (s, 9H), 1.25 (s, 3H), 0.47−0.37 (m, 1H), 0.32−0.22 (m, 1H), −0.06− −0.17 (m, 1H), −0.74− −0.89 (m, 1H). Mass spectrum (ESI) m/z = 661.0 $[M + H]^+$.

*2-(6-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)pyridin-3-yl)acetic Acid (**23**).* Part A: To a vial containing (3*R*,5*R*,6*S*)-3-((5-bromopyridin-2-yl)methyl)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (**78**) (13.0 mg, 0.020 mmol) was added Q-Phos (0.839 mg, 1.181 μmol) and tris(dibenzylideneacetone)-dipalladium(0) (2.163 mg, 2.362 μmol). The solids were diluted in THF (98 μL), and (2-(*tert*-butoxy)-2-oxoethyl)zinc(II) chloride (47.2 μL, 0.024 mmol) was added. The vial was placed on a hot plate at 60 °C. After 4 h, the reaction mixture was diluted with DCM and loaded onto a 4 g gold-capped ISCO silica gel column that had been preflushed with hexanes. The column was eluted with a gradient of 0−100% EtOAc/hexanes to give *tert*-butyl 2-(6-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylthio)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)pyridin-3-yl)acetate (5.0 mg, 37%). Mass spectrum (ESI) m/z = 695.2 $[M + H]^+$.

Part B: To a vial containing *tert*-butyl 2-(6-(((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)methyl)pyridin-3-yl)-acetate (obtained with a procedure similar to that depicted for the synthesis of **19**, part B) (4.0 mg, 5.50 μmol) was added formic acid (0.211 μL, 5.50 μmol). The vial was heated on a hot plate at 40 °C for 6 h. The reaction mixture was concentrated. The compound was loaded onto a Uniplate Silica Gel HLF (catalog number 47521; 250 μm) plate and eluted with 50% acetone/hexanes. The most polar band was cut and eluted with 6 mL of EtOAc. The eluent was concentrated to give 2-(6-(((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)methyl)pyridin-3-yl)acetic acid (**23**) (2.77 mg, 4.12 μmol, 75%) as a white pellet. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.48 (d, J = 2.0 Hz, 1H), 7.62 (dd, J = 2.3, 7.9 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.23−7.03 (m, 5H), 7.03−6.94 (m, 1H), 6.94−6.81 (m, 1H), 4.92 (d, J = 10.8 Hz, 1H), 4.36 (br. s., 1H), 3.67 (s, 2H), 3.48 (d, J = 12.7 Hz, 1H), 3.21 (ddd, J = 2.9, 10.8, 13.7 Hz, 1H), 3.10 (d, J = 12.7 Hz, 1H), 2.94 (d, J = 12.5 Hz, 1H), 2.61 (br. s., 1H), 2.20−2.09 (m, 1H), 1.93 (br. s., 1H), 1.81 (dd, J = 2.9, 13.4 Hz, 1H), 1.40 (s, 9H), 1.27 (s, 3H), 0.33 (br. s., 1H), 0.24 (br. s., 1H), −0.32 (br. s., 1H), −1.05 (br. s., 1H). Mass spectrum (ESI) m/z = 671.2 $[M + H]^+$.

*(3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-3-(pyridin-2-ylmethyl)-piperidin-2-one (**17**).* Compound **17** was synthesized in a manner similar to that described for the preparation of **19**. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.55 (dd, J = 0.9, 4.8 Hz, 1H), 7.65 (dt, J = 1.8, 7.6 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.25−7.16 (m, 4H), 7.16−7.06 (m, 3H), 7.03−7.00 (m, 1H), 6.91 (td, J = 1.7, 6.8 Hz, 1H), 4.94 (d, J = 10.8 Hz, 1H), 4.45−4.26 (m, 1H), 3.50 (d, J = 12.7 Hz, 1H), 3.32 (ddd, J = 3.2, 10.8, 13.6 Hz, 1H), 3.10 (d, J = 12.7 Hz, 1H), 2.94 (d, J = 13.2 Hz, 1H), 2.10 (t, J = 13.6 Hz, 1H), 1.93 (br. s., 1H), 1.77 (dd, J = 2.8, 13.3 Hz, 1H), 1.40 (s, 9H), 1.26 (s, 3H), 0.34 (br. s., 1H), 0.23 (br. s., 1H), −0.31 (br. s., 1H), −1.07 (br. s., 1H). Mass spectrum (ESI) m/z = 613.2 $[M + H]^+$. HRMS (ESI) m/z found 613.2058 $[M + H]^+$, calcd for $C_{33}H_{38}Cl_2N_2O_3S$ 613.2058.

*4-(((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-Cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)-methyl)benzoic Acid (**30**).* Compound **30** was synthesized in a manner similar to that described for the preparation of **19**. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.06 (d, J = 8.3 Hz, 2 H), 7.42 (d, J = 8.3 Hz, 2 H), 7.26−7.05 (m, 4 H), 6.95−6.78 (m, 3 H), 6.78−6.74 (m, 1 H), 4.89 (d, J = 10.8 Hz, 1 H), 4.37 (br. s., 1 H), 3.42−3.33 (m, 1 H), 3.00 (d, J = 13.2 Hz, 1 H), 2.98−2.90 (m, 2 H), 2.60 (br. s., 1 H), 2.24 (t, J = 13.8 Hz, 1 H), 1.80 (dd, J = 3.1, 13.8 Hz, 1 H), 1.43−1.36 (m, 10 H), 1.27 (s, 3 H), 0.36 (br. s., 1 H), 0.29 (br. s., 1 H), −0.32 (br. s., 1 H), −1.02 (br. s., 1 H). Mass spectrum (ESI) m/z = 656.2 $[M + H]^+$. HRMS (ESI) m/z found 656.2014 $[M + H]^+$, calcd for $C_{35}H_{39}Cl_2NO_5S$ 656.2004.

*(3R,5R,6S)-3-Benzyl-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methylpiperidin-2-one (**18**).* Compound **18** was synthesized in a manner similar to that described for the preparation of **19**. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.40−7.29 (m, 6 H), 7.08−7.05 (m, 2 H), 6.86−6.72 (m, 5 H), 4.84 (d, J = 10.8 Hz, 1 H), 4.37 (br. s., 1 H), 3.38 (d, J = 13.2 Hz, 1 H), 2.98−2.84 (m, 2 H), 2.81 (d, J = 13.2 Hz, 1 H), 2.59 (br. s., 1 H), 2.22−2.12 (m, 1 H), 1.83 (dd, J = 2.7, 13.7 Hz, 1 H), 1.40 (s, 10 H), 1.28 (s, 3 H), 0.34 (br. s., 1 H), 0.27 (br. s., 1 H), −0.34 (br. s., 1 H), −1.04 (br. s., 1 H). Mass spectrum (ESI) m/z = 612.2 $[M + H]^+$.

*6-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)-methyl)picolinic Acid (**21**).* Compound **21** was synthesized in a manner similar to that described for the preparation of **19**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 7.63 Hz, 1H), 8.02 (t, J = 7.63 Hz, 1H), 7.57−7.67 (m, 1H), 7.61 (d, J = 7.63 Hz, 1H), 7.07−7.25 (m, 6H), 6.97 (s, 1H), 6.76−6.86 (m, 1H), 4.98 (d, J = 10.56 Hz, 1H), 4.38 (t, J = 11.84 Hz, 1H), 3.35−3.55 (m, 2H), 3.12−3.28 (m, 1H), 2.93 (d, J = 13.11 Hz, 1H), 2.70 (br. s., 1H), 2.44 (t, J = 13.79 Hz, 1H), 1.84 (dd, J = 2.35, 13.89 Hz, 2H), 1.44 (s, 9H), 1.32 (s, 3H), 0.23−0.52 (m, 2H), −0.31 (br. s., 1H), −1.05 (br. s., 1H). Mass

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spectrum (ESI) m/z = 657.2 $[M + H]^+$. HRMS (ESI) m/z found 657.1962 $[M + H]^+$, calcd for $C_{34}H_{38}Cl_2N_2O_5S$ 657.1957.

*6-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)nicotinic Acid (**3**).* Compound **3** was synthesized in a manner similar to that described for the preparation of **19**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.67 (d, J = 7.63 Hz, 1H), 7.74 (d, J = 8.22 Hz, 1H), 6.98−7.25 (m, 6H), 6.84−6.93 (m, 1H), 5.00 (d, J = 10.76 Hz, 1H), 4.26 (t, J = 12.13 Hz, 1H), 3.92 (d, J = 13.30 Hz, 1H), 3.39−3.55 (m, 1H), 3.28 (d, J = 13.30 Hz, 1H), 2.86 (d, J = 12.91 Hz, 1H), 2.76 (t, J = 9.59 Hz, 1H), 2.52 (t, J = 13.79 Hz, 1H), 1.87 (d, J = 12.52 Hz, 1H), 1.80 (br. s., 1H), 1.41 (s, 13H), 0.35 (d, J = 6.85 Hz, 2H), −0.34 (br. s., 1H), −0.92 (br. s., 1H). Mass spectrum (ESI) m/z = 657.2 $[M + H]^+$. ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ 175.4, 166.7, 163.5, 162.7, 159.9, 158.6, 158.5, 158.3, 149.9, 144.7, 139.5, 137.7, 132.7, 132.1, 130.9, 128.8, 127.8, 127.2, 126.6, 125.5, 125.3, 118.8, 114.9, 69.1, 59.6, 58.8, 45.5, 44.6, 44.2, 43.7, 38.7, 25.8, 14.6, 2.0. HRMS (ESI) m/z found 657.1954 $[M + H]^+$, calcd for $C_{34}H_{38}Cl_2N_2O_5S$ 657.1957.

*6-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)nicotinic Acid (**22**).* To a mixture of (3*R*,5*R*,6*S*)-3-((5-bromopyridin-2-yl)methyl)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methylpiperidin-2-one (27 mg, 0.038 mmol), tripotassium phosphate (9.28 mg, 0.044 mmol), palladium(II) acetate (1.450 mg, 6.46 μmol), and 1,3-bis(dicyclohexylphosphino)propane bis(tetrafluoroborate) (4.65 mg, 7.60 μmol) was added DMSO (0.463 mL), followed by DBU (0.00916 mL, 0.061 mmol) and water (0.021 mL, 1.140 mmol). The reaction vial was evacuated and backfilled with carbon monoxide 4 times. Then, the reaction was heated at 80 °C overnight. The crude reaction mixture was filtered using a 25 mm GD/X disposable siringe filter (Whatman catalog number 6878-2504), washed with DCM, and concentrated. The concentrated crude was then diluted with MeOH. Purification by RP-HPLC (25 to 75% CH_3CN/H_2O in 30 min, both solvents containing 0.1% TFA, flow rate = 45 mL/min) provided 6-(((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)nicotinic acid (**22**) (13 mg, 0.019 mmol, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.58 (d, J = 6.85 Hz, 1H), 7.65 (d, J = 6.65 Hz, 1H), 6.98−7.25 (m, 6H), 6.93 (d, J = 2.93 Hz, 1H), 5.01 (d, J = 10.37 Hz, 1H), 4.16−4.41 (m, 1H), 3.76 (br. s., 1H), 3.28−3.57 (m, 2H), 2.88 (d, J = 13.50 Hz, 2H), 2.71 (d, J = 4.11 Hz, 1H), 2.44 (t, J = 13.60 Hz, 1H), 1.85 (d, J = 12.72 Hz, 2H), 1.41 (s, 9H), 1.40 (br. s., 3H), 0.40 (d, J = 6.26 Hz, 2H), −0.28 (br. s., 1H), −0.89 (br. s., 1H). Mass spectrum (ESI) m/z = 675.1 $[M + H]^+$.

*2-(6-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)pyridin-3-yl)-2-methylpropanoic Acid (**24**).* Compound **24** was synthesized in a manner similar to that described for the preparation of **19**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82−8.95 (m, 1H), 8.12 (d, J = 8.80 Hz, 1H), 7.57 (d, J = 8.41 Hz, 1H), 7.07 (s, 6H), 6.80−6.94 (m, 1H), 4.94 (d, J = 10.76 Hz, 1H), 4.30 (t, J = 10.86 Hz, 1H), 3.63 (d, J = 12.91 Hz, 1H), 3.43 (d, J = 13.30 Hz, 1H), 3.33 (t, J = 11.15 Hz, 1H), 2.82−2.96 (m, 1H), 2.66−2.77 (m, 1H), 2.32−2.43 (m, 2H), 1.74−1.94 (m, J = 19.95 Hz, 2H), 1.69 (s, 6H), 1.42 (s, 9H), 1.37 (s, 3H), 0.29 (br. s., 2H), −0.34 (br. s., 1H), −0.95 (br. s., 1H). Mass spectrum (ESI) m/z = 699.2 $[M + H]^+$. HRMS (ESI) m/z found 699.2410 $[M + H]^+$, calcd for $C_{37}H_{44}Cl_2N_2O_5S$ 699.2426.

*6-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)-2-methylnicotinic Acid (**25**).* Compound **25** was synthesized in a manner similar to that described for the preparation of **19**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 7.83 Hz, 1H), 7.48−7.69 (m, 2H), 6.96−7.23 (m, 6H), 6.91 (br. s., 1H), 5.00 (d, J = 10.56 Hz, 1H), 4.17−4.32 (m, 1H), 3.92 (br. s., 1H), 3.47 (t, J = 11.64 Hz, 1H), 3.27 (d, J = 14.09 Hz, 1H), 2.99 (s, 3H), 2.88 (d, J = 12.91 Hz, 1H), 2.78 (br. s., 1H), 2.49 (t, J = 14.28 Hz, 1H), 1.83 (d, J = 13.89 Hz, 2H), 1.41 (s, 9H), 1.38 (br. s., 3H), 0.35 (br. s., 2H), −0.32 (br. s., 1H), −0.88 (br. s., 1H). Mass spectrum (ESI) m/z = 671.2 $[M + H]^+$. HRMS (ESI) m/z found 671.2119 $[M + H]^+$, calcd for $C_{34}H_{38}Cl_2N_2O_5S$ 671.2113.

*6-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)-4-methylnicotinic Acid (**26**).* Compound **26** was synthesized in a manner similar to that described for the preparation of **19**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.47−7.63 (m, 2H), 6.91−7.24 (m, 6H), 6.88 (d, J = 5.67 Hz, 1H), 4.97 (d, J = 10.56 Hz, 1H), 4.24 (t, J = 12.03 Hz, 1H), 3.87 (d, J = 13.11 Hz, 1H), 3.43 (t, J = 11.54 Hz, 1H), 3.21 (d, J = 12.72 Hz, 1H), 2.86 (s, 3H), 2.74 (d, J = 10.96 Hz, 3H), 1.86 (d, J = 13.89 Hz, 1H), 1.80 (br. s., 1H), 1.43 (s, 3H), 1.40 (s, 9H), 0.35 (d, J = 6.85 Hz, 2H), −0.35 (br. s., 1H), −0.91 (br. s., 1H). Mass spectrum (ESI) m/z = 671.2 $[M + H]^+$.

*5-(((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)methyl)pyrazine-2-carboxylic Acid (**29**).* Compound **29** was synthesized in a manner similar to that described for the preparation of **19**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.59 (s, 1H), 7.16 (br. s., 5H), 7.11−7.15 (m, 2H), 7.05 (s, 1H), 6.93−7.01 (m, 1H), 5.02 (d, J = 10.76 Hz, 1H), 4.36 (t, J = 12.03 Hz, 1H), 3.34−3.65 (m, 3H), 2.91 (d, J = 11.54 Hz, 1H), 2.68 (br. s., 1H), 2.38 (t, J = 13.69 Hz, 1H), 1.81 (br. s., 1H), 1.76 (dd, J = 3.03, 13.60 Hz, 1H), 1.43 (s, 9H), 1.31 (s, 3H), 0.22−0.45 (m, 2H), −0.30 (d, J = 3.52 Hz, 1H), −0.99 (br. s., 1H). Mass spectrum (ESI) m/z = 658.2 $[M + H]^+$. HRMS (ESI) m/z found 658.1902 $[M + H]^+$, calcd for $C_{33}H_{37}Cl_2N_3O_5S$ 658.1909.

*(3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((5-(2-hydroxyacetyl)thiazol-2-yl)methyl)-3-methylpiperidin-2-one (**34**).* Part A: To 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)methyl)thiazole-5-carboxylic acid (**33**) (0.061 g, 0.091 mmol) in THF (0.913 mL) was added oxalyl chloride (0.01215 mL, 0.137 mmol) and one drop of DMF. After 1 h, the crude was concentrated under vacuum and taken into the next step without further purification.

Part B: To 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)methyl)thiazole-5-carbonyl chloride (62 mg, 0.091 mmol) was added tris(trimethylsilyloxy)ethylene (90 μL, 0.272 mmol). The reaction was stirred at 90 °C. After stirring overnight, the reaction was cooled and charged with 1.8 M aqueous HCl (1 mL) and THF (1 mL). The mixture was diluted with water (10 mL) extracted with ethyl acetate (2 × 20 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography (gradient elution 30 to 100% EtOAc in hexanes) afforded (3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-((5-(2-hydroxyacetyl)thiazol-2-yl)methyl)-3-methylpiperidin-2-one (**34**) (6 mg, 8.85 μmol, 10% yield over the last two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.03 (d, J = 5.28 Hz, 8H), 4.90 (d, J = 10.76 Hz, 1H), 4.70 (d, J = 1.76 Hz, 2H), 4.30 (t, J = 11.93 Hz, 1H), 3.61 (d, J = 13.89 Hz, 1H), 3.39−3.51 (m, 1H), 3.11−3.25 (m, J = 2.93 Hz, 1H), 2.84 (d, J = 15.06 Hz, 1H), 2.52−2.68 (m, 1H), 2.24 (t, J = 13.50 Hz, 1H), 1.61−1.70 (m, 2H), 1.36 (s, 9H), 1.32 (s, 3H), 0.25−0.36 (m, 1H), 0.08−0.23 (m, 1H), −0.39 (br. s., 1H), −1.09 (br. s., 1H). Mass spectrum (ESI) m/z = 677.0 $[M + H]^+$.

*3-((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)-2-oxopropanoic Acid (**11**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (br. s., 2H), 7.03−7.20 (m, 4H), 6.97 (s, 1H), 6.86 (dt, J = 6.5, 1.9 Hz, 1H), 4.97 (d, J = 10.8 Hz, 1H), 4.22−4.39 (m, 2H), 4.07 (dd, J = 13.2, 10.9 Hz, 1H), 3.14−3.34 (m, 3H), 2.71−2.93 (m, 3H), 2.32 (t, J = 13.8 Hz, 1H), 2.08−2.20 (m, 1H), 2.00 (dd, J = 13.9, 2.9 Hz, 1H), 1.48−1.55 (m, 1H), 1.43 (s, 9H), 1.41 (s, 3H), 0.41 (t, J = 7.5 Hz, 3H). Mass spectrum (ESI) m/z = 582.2 $[M + H]^+$. HRMS (ESI) m/z found 582.1855 $[M + H]^+$, calcd for $C_{29}H_{37}Cl_2NO_5S$ 582.1848.

*(R)-1-(2-((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetyl)pyrrolidine-3-carboxylic Acid (**15**).* Part A: To a solution of methyl β-*dl*-prolinate-HCl (133 mg, 1.033 mmol) in DMF (1 mL) was added 2-((3*R*,5*R*,6*S*)-1-((*S*)-2-(*tert*-butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperi-

din-3-yl)acetic acid (**9**) (200 mg, 0.344 mmol), HATU (262 mg, 0.689 mmol), and DIEA (0.481 mL, 2.76 mmol). After stirring overnight, this was diluted with ethyl acetate and washed twice with water. The mixture of isomers were separated via SFC, 20% isopropanol (NH_4OH)/CO_2 (100 bar), IC (2 × 15 cm), and 3 mL/min to provide in order of elution (stereochemistry arbitrarily assigned); (*R*)-methyl 1-(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)acetyl)pyrrolidine-3-carboxylate (38 mg, 0.055 mmol, 16%, Mass spectrum (ESI) m/z = 691.3 $[M + H]^+$) and then (*S*)-methyl 1-(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)-acetyl)pyrrolidine-3-carboxylate (42 mg, 0.061 mmol, 18% yield). Mass spectrum (ESI) m/z = 691.3 $[M + H]^+$.

Part B: To a mixture of (*R*)-methyl 1-(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)acetyl)pyrrolidine-3-carboxylate (fastest eluting isomer) (38 mg, 0.055 mmol) in MeOH (0.500 mL) and THF (1 mL) was added 1.0 M aq. LiOH (0.330 mL, 0.330 mmol) solution. After 90 min, the reaction mixture was acidified with 5% aq. HCl, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to provide (*R*)-1-(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)acetyl)pyrrolidine-3-carboxylic acid (**15**) (36 mg, 0.053 mmol, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (br. s., 4H), 7.08 (d, J = 5.09 Hz, 2H), 7.00 (s, 1H), 6.93 (br. s., 1H), 4.94 (dd, J = 3.03, 10.86 Hz, 1H), 4.35 (br. s., 1H), 3.91 (d, J = 7.04 Hz, 1H), 3.83 (t, J = 7.53 Hz, 1H), 3.62−3.75 (m, 1H), 3.31−3.62 (m, 2H), 3.07−3.29 (m, 1H), 2.77−3.02 (m, 3H), 2.71 (br. s., 1H), 2.16−2.45 (m, 4H), 1.90 (br. s., 1H), 1.44 (s, 9H), 1.41 (d, J = 3.33 Hz, 3H), 0.13−0.48 (m, 2H), −0.31 (br. s., 1H), −1.04 (br. s., 1H). Mass spectrum (ESI) m/z = 677.2 $[M+H]^+$). HRMS (ESI) m/z found 677.2223 $[M + H]^+$, calcd for $C_{34}H_{42}Cl_2N_2O_6S$ 677.2219.

*(S)-1-(2-((3R,5R,6S)-1-((S)-2-(tert-Butylsulfonyl)-1-cyclopropylethyl)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetyl)pyrrolidine-3-carboxylic Acid (**16**).* Compound **16** was synthesized in a manner similar to that described for the preparation of **15** from the slowest eluting isomer in part A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (br. s., 4H), 7.08 (d, J = 4.89 Hz, 2H), 6.99 (br. s., 1H), 6.93 (t, J = 4.11 Hz, 1H), 4.94 (d, J = 10.56 Hz, 1H), 4.34 (br. s., 1H), 3.60−4.04 (m, 3H), 3.35−3.60 (m, 2H), 3.07−3.27 (m, 1H), 2.75−3.00 (m, 3H), 2.71 (br. s., 1H), 2.15−2.40 (m, 4H), 1.90 (br. s., 1H), 1.44 (s, 9H), 1.41 (d, J = 3.13 Hz, 3H), 0.15−0.44 (m, 2H), −0.31 (br. s., 1H), −1.06 (br. s., 1H). Mass spectrum (ESI) m/z = 677.2 $[M + H]^+$). HRMS (ESI) m/z found 677.2210 $[M + H]^+$, calcd for $C_{34}H_{42}Cl_2N_2O_6S$ 677.2219.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

In vitro biological assays, in vivo protocols, determination of cocrystal structures of **3**, **4**, and **46**−**49** bound to MDM2. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

Coordinates for compounds **3** (PDB code: 4OGN), **4** (PDB code: 4ODE), **46** (PDB code: 4OGT), **47** (PDB code: 4ODF), **48** (PDB code: 4OCC), and **49** (PDB code: 4OGV) bound to MDM2 have been deposited in the Protein Data Bank.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

Boc, *tert*-butoxycarbonyl; BrdU, 5-bromo-2-deoxyuridine; CL, clearance; CYP3A4, cytochrome P450 3A4; DCM, dichloromethane; DMBCl, 2,4-dimethoxybenzyl chloride; DMF, *N*,*N*-diemethylformamide; DMP, Dess-Martin periodinane; DMSO, dimethylsulfoxide; dr, diastereoselectivity ratio; EdU, 5-ethynyl-2′-deoxyuridine; EtOAc, ethyl acetate; FACS, fluorescence-activated cell sorting; hPXR, human pregnane X receptor; HTRF, homogeneous time-resolved fluorescence; LiHMDS, lithium bis(trimethylsilyl)amide; MDM2, murine double minute 2; MsCl, methanesulfonyl chloride; NaHMDS, sodium bis(trimethylsilyl)amide; 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; TES, triethylsilyl; TESCl, triethylsilyl chloride; TFA, trifluoroacetic acid; THF, tetrahydrofuran

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