Journal of Medicinal Chemistry

Article

Discovery of 2-((*R*)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)-2-methylpiperazin-1-yl)-*N*-((1*R*,2*s*,3*S*,5*S*,7*S*)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide (SKI2852): A Highly Potent, Selective, and Orally Bioavailable Inhibitor of 11#-Hydroxysteroid Dehydrogenase Type 1 (11#-HSD1)

Je Ho Ryu, Jung A Lee, Shinae Kim, Young Ah Shin, Jewon Yang, Hye Young Han, Hyun Joo Son, Yong Hyuk Kim, Joon Ho Sa, Jae-Sun Kim, Jungeun Lee, Jeeyeon Lee, and Hyeung-Geun Park

J. Med. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.jmedchem.6b01122 • Publication Date (Web): 31 Oct 2016

Just Accepted

ACS Publications

Journal of Medicinal Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Discovery of 2-((*R*)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)-2-methylpiperazin-1-yl)-*N*-((1*R*,2*s*,3*S*,5*S*,7*S*)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide (SKI2852): A Highly Potent, Selective, and Orally Bioavailable Inhibitor of 11β-Hydroxysteroid Dehydrogenase Type 1 (11β-HSD1)

Je Ho Ryu,[†,‡] Jung A Lee,[†] Shinae Kim,[†,§] Young Ah Shin,[†] Jewon Yang,[‡] Hye Young Han,[†] Hyun Joo Son,[†] Yong Hyuk Kim,[†] Joon Ho Sa,[†] Jae-Sun Kim,[†,∥] Jungeun Lee,[‡] Jeeyeon Lee,[‡] and Hyeung-geun Park[*,‡]

[†]Life Science R&D Center, SK Chemicals, Seongnam-Si, Bundang-Gu, Sampyeong-Dong 686, Gyeonggi-Do, 463-400, Korea

[‡]Research Institute of Pharmaceutical Science and College of Pharmacy, Seoul National University, Seoul, 151-742, Korea

ABSTRACT

A series of picolinamide- and pyrimidine-4-carboxamide-based inhibitors of 11β-hydroxysteroid dehydrogenase type 1 was synthesized and evaluated to optimize the lead compound **9**. The combination of the replacement of a pyridine ring of **9** with a pyrimidine ring and the introduction of an additional fluorine substituent at the 2-position of the phenyl ring resulted in the discovery of a potent, selective, and orally bioavailable inhibitor, **18a** (SKI2852), which demonstrated no CYP and PXR liabilities, excellent PK profiles across species, and highly potent and sustainable PD activity. Repeated oral administration of **18a**

significantly reduced blood glucose and HbA1c levels and improved the lipid profiles in *ob*/*ob* mice. Moreover, the HbA1c-lowering effect of metformin was synergistically enhanced in combination with **18a**.

INTRODUCTION

An estimated 285 million people worldwide suffered from diabetes in the year 2010, and this number is expected to rise to 438 million by the year 2030.[1] The majority of these cases are defined as type 2 diabetes mellitus, which is a combination of metabolic abnormalities, such as hyperglycemia and insulin resistance. Metabolic syndrome is a prediabetic state that consists of central obesity, glucose intolerance, insulin resistance, dyslipidemia, hypertension, and inflammatory or prothrombotic states.[2] When left untreated, metabolic syndrome progresses to type 2 diabetes and results in serious complications, including cardiovascular disease, diabetic retinopathy, renal failure, nerve damage, and ischemic stroke.

Recent studies have implicated aberrant glucocorticoid signaling as a cause of the development of several phenotypes that are associated with metabolic syndrome.[3] Elevated levels of active glucocorticoids in the liver and adipose tissue can lead to insulin resistance, impairment of glucose uptake, enhanced hepatic gluconeogenesis, and increased lipolysis. In this respect, an attractive therapeutic target is 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1).[4-7] 11β-HSD1 is a key enzyme that acts as an NADPH-dependent reductase and converts inactive glucocorticoids (cortisone in humans and 11-dehydrocorticosterone in rodents) into the receptor-active glucocorticoids (cortisol in humans and corticosterone in rodents). This enzyme is highly expressed in metabolically active tissues, including the liver and adipose tissue, and regulates tissue-specific glucocorticoid levels.[8-11]

The connection between 11β-HSD1 and metabolic syndrome has been demonstrated in several studies that use a genetic mouse model. Transgenic mice overexpressing 11β-HSD1 in only the liver or adipose tissues showed features of metabolic syndrome, such as abdominal obesity, glucose intolerance, insulin resistance, dyslipidemia, and hypertension.[12-14] In contrast, 11β-HSD1-deficient mice demonstrated a reduction in body weight, improved lipid profiles and glucose tolerance, and increased insulin sensitivity when maintained on a high-fat diet.[15,16] These findings suggest that 11β-HSD1 inhibition could be a promising strategy for the treatment of metabolic syndrome as well as type 2 diabetes.

In the last decade, extensive research by the pharmaceutical industry has identified various classes of 11β-HSD1 inhibitors,[17-19] and several compounds have reached the clinical-development phase. Incyte took the inhibitor INCB-13739[20] (structure not disclosed) as far as phase 2 trials as an add-on therapy to metformin for patients with type 2 diabetes exhibiting inadequate glycemic control with metformin alone. After 12 weeks of treatment, this compound resulted in significant reductions in HbA1c (-0.6%), fasting plasma glucose (-24 mg/dl), and HOMA-IR (-24%) compared with placebo.[20] Merck has progressed two compounds, **1** (MK-0916)[21,22] and **2** (MK-0736)[22] (Figure 1), into clinical trials. The administration of **1** to patients with type 2 diabetes and metabolic syndrome led to modest decreases in HbA1c (-0.3%), body weight, and blood pressure.[21] The compound **2** modestly improved secondary blood pressure endpoints, LDL-cholesterol, and body weight in overweight and obese patients with hypertension.[22] However, none of these compounds have progressed beyond phase 2 trials. Other companies, for example, Pfizer (**3**, PF-915275),[23,24] Amgen (**4**, AMG-221),[25] Astrazeneca (**5**, AZD-4017),[26] and Boehringer Ingelheim (**6**, BI 135585),[27] have also progressed compounds into the clinic, and the structures of them are shown in Figure 1.

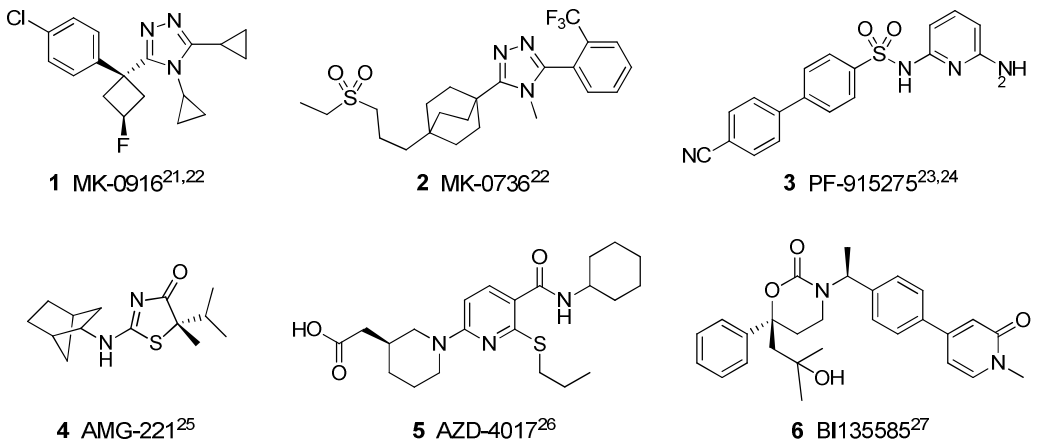


Figure 1. Chemical structures of 11β-HSD1 inhibitors that advanced into clinical trials

We have previously described a novel class of 11β-HSD1 inhibitors that contain the picolinamide core.[28,29] Structural modifications of the initial hit compound **7** resulted in the discovery of the highly potent and metabolically stable compound **8**. High potency was achieved by the incorporation of a hydroxy-adamantyl group, and the replacement of the piperidine ring with 1-(4-cyanophenyl)piperazine led to a significant improvement in metabolic stability.[28] Further optimization was performed to improve both the potency and pharmacokinetic (PK) profiles of **8**. The replacement of the cyano group at the 4-position of the phenyl ring with a methylsulfonyl group resulted in an increase in its biochemical and cellular potencies, and modifying the piperazine ring by introducing an (*R*)-methyl group substantially improved the PK properties. This lead compound **9** demonstrated excellent activity in a mouse *ex vivo* pharmacodynamic (PD) model and reduced the blood glucose, LDL cholesterol, and triglyceride levels in *ob*/*ob* mice after oral administration[29] (Figure 2).

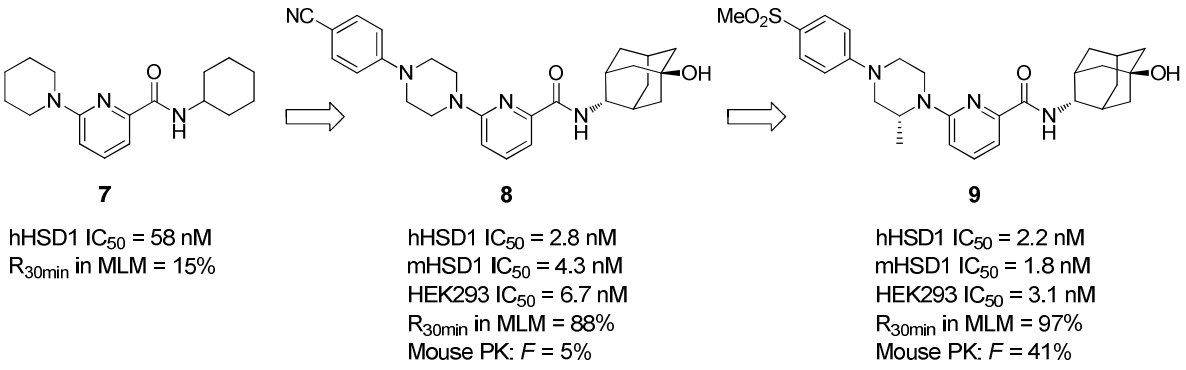


Figure 2. Progress of picolinamide 11β-HSD1 inhibitors from hit (**7**) to lead (**9**)

However, profiling in drug metabolism studies showed that compound **9** was a moderate-to-strong inhibitor of CYP3A4 and CYP2C19, exhibiting IC_{50} values of 0.97 μM and 3.7 μM, respectively. Therefore, in this report, we attempted further structural optimization of **9** to diminish the CYP liability while maintaining the high *in vitro* potency and *ex vivo* PD activity. Our strategy to reduce the interaction with CYP enzymes consisted in decreasing the lipophilicity of the molecule by introducing a more polar moiety to the left-hand side or replacing the central pyridine ring with a pyrimidine ring.

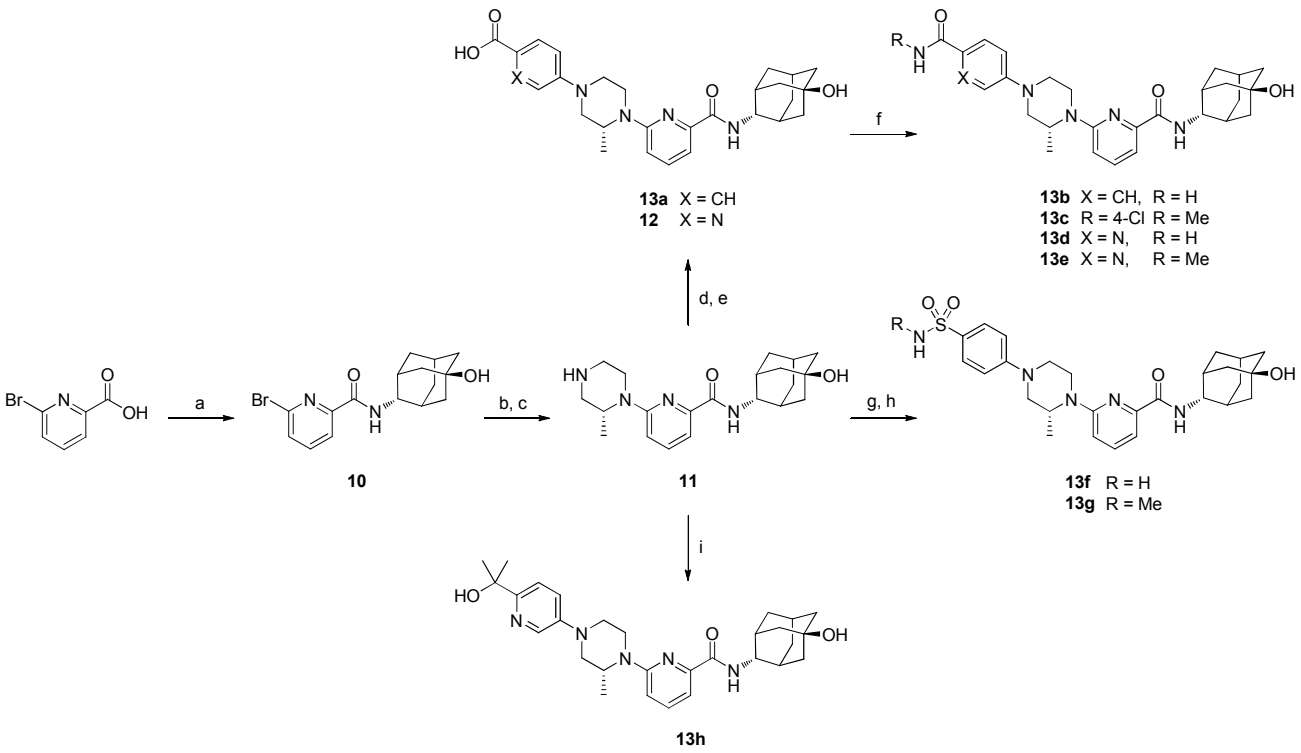
CHEMISTRY

Left-hand side-modified polar picolinamide analogs **13a-h** were synthesized via the routes that are outlined in Scheme 1. Coupling 6-bromopicolinic acid with *trans*-4-aminoadamantan-1-ol in the presence of HBTU yielded 6-bromopicolinamide **10**. A palladium-catalyzed cross-coupling reaction of **10** with (*R*)-4-*N*-BOC-2-methylpiperazine, followed by treatment with TFA, provided intermediate **11**. Carboxylic acid derivatives **12** and **13a** were obtained from the basic hydrolysis reaction of the ester intermediates, which were synthesized by the palladium-assisted coupling of **11** with methyl 4-bromobenzoate or methyl 5-bromopicolinate.[30] Compounds **12** and **13a** were then transformed into the amide derivatives

13b-e via HBTU coupling with the appropriate amine. The palladium-mediated reaction of **11** with 4-bromobenzenesulfonamides that were protected with *tert*-butyl groups produced the desired *N*-(*tert*-butyl) sulfonamide intermediates, which were treated with TFA to give sulfonamide analogs **13f** and **13g**. The reaction of **11** with 2-(5-bromopyridin-2-yl)propan-2-ol in the presence of $Pd_2(dba)_3$ and BINAP afforded derivative **13h**.

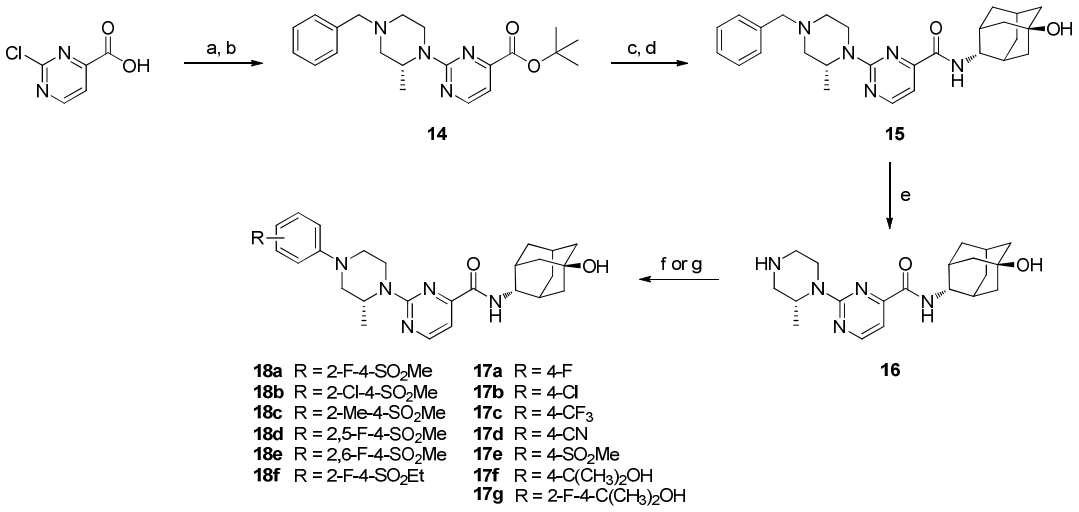
Pyrimidine-4-carboxamide compounds **17a-g** and **18a-f** were prepared as outlined in Scheme 2. 2-Chloropyrimidine-4-carboxylic acid was converted to the corresponding *tert*-butyl ester by using *p*-toluenesulfonyl chloride and *tert*-butanol.[31] Subsequently, a coupling reaction with (*R*)-1-benzyl-3-methylpiperazine yielded (*R*)-2-(4-benzyl-2-methylpiperazin-1-yl)pyrimidine **14**. The TFA-mediated removal of the *tert*-butyl group and the HBTU-assisted coupling with *trans*-4-aminoadamantan-1-ol produced carboxamide **15**, which was then hydrogenated to give intermediate **16**. The final compounds **17a-g** and **18a-c** were synthesized by the palladium-catalyzed reaction of **16** with the commercially available 4-substituted bromobenzenes.[32] Sulfonyl derivatives **18d-f**, whose corresponding bromobenzenes are not available, were prepared by the reaction of **16** with the appropriate 4-sulfonyl fluorobenzenes at high temperatures.

Scheme 1[a]



[a]Reagents and conditions: (a) *trans*-4-aminoadamantan-1-ol, HBTU, DIPEA, ACN, 85%; (b) (*R*)-*tert*-butyl 3-methylpiperazine-1-carboxylate, $Pd_2(dba)_3$, xantphos, NaO^tBu, toluene, 100 ºC, 54%; (c) TFA, DCM, 92%; (d) methyl 4-bromobenzoate or methyl 5-bromopicolinate, $Pd(OAc)_2$, xantphos, Cs_2CO_3, toluene, 100 ºC, 46-59%; (e) NaOH, MeOH, 74-88%; (f) RNH_2, HBTU, DIPEA, ACN, 55-78%; (g) 4-bromo-*N*-(*tert*-butyl)benzenesulfonamide or 4-bromo-*N*-(*tert*-butyl)-*N*-methylbenzenesulfonamide, $Pd[P(o\text{-tolyl})_3]_2Cl_2$, BINAP, Cs_2CO_3, toluene, 90 ºC, 38-96%; (h) TFA, DCM, 56-64%; (i) 2-(5-bromopyridin-2-yl)propan-2-ol, $Pd_2(dba)_3$, BINAP, NaO^tBu, toluene, 100 ºC, 29%.

Scheme 2[a]



[a]Reagents and conditions: (a) *p*-toluenesulfonyl chloride, pyridine, ^{t}BuOH, 62%; (b) (*R*)-1-benzyl-3-methylpiperazine, DIPEA, ACN, 100 ºC, 94%; (c) TFA, DCM, quantitative yield; (d) *trans*-4-aminoadamantan-1-ol, HBTU, DIPEA, ACN, 68%; (e) H_2, Pd/C, MeOH, 81%; (f) bromobenzenes, $Pd_2(dba)_3$, BINAP, NaO^{t}Bu, toluene, 100 ºC, 41-63% (for **17a-g** and **18a-c**); (g) fluorobenzenes, K_2CO_3, DMF, 130 ºC, 35-69% (for **18d-f**).

RESULTS AND DISCUSSION

The ability of all of the synthesized compounds to inhibit the 11β-HSD1 enzyme was evaluated by using a cell-based assay that utilized HEK293 cells stably transfected with human 11β-HSD1 cDNA. The metabolic stability of the compounds was also evaluated by determining the % remaining after a 30-min incubation with mouse liver microsomes (MLM). Potent compounds (IC_{50} values below 10 nM in a cell-based assay) with an acceptable metabolic stability (>50% remaining in MLM after 30 min) were selected for a mouse *ex vivo* PD assay.[33] In this study, male C57BL/6 mice were orally administered 10 mg/kg of compound, and the inhibition of 11β-HSD1 activity in liver and adipose tissues was assessed by using the liver and epididymal fat (EPF) pads that were collected at 2 h after dosing. In both the cell-based assay and *ex vivo* PD assay, the 11β-HSD1 enzyme activity was

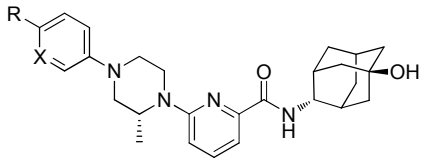
determined by measuring the conversion of cortisone to cortisol, the levels of which were quantified by an enzyme-linked immunosorbent assay (ELISA) method.

First, the introduction of a polar functional group, such as a carboxylic acid, amide, and sulfonamide, at the 4-position of the phenyl ring was attempted in order to reduce the CYP liability of compound **9** (Table 1). Because the left-hand side of this series of 11β-HSD1 inhibitors was positioned to face the solvent-exposed area in our previous docking study,[28] we expected that the introduction of a hydrophilic group on the phenyl ring would retain potency. As expected, the incorporation of an amide (**13b** and **13c**) or sulfonamide group (**13f** and **13g**) resulted in a cellular potency that was comparable to compound **9** (IC_{50} values below 10 nM). However, these compounds were metabolically less stable than **9** and exhibited poor pharmacodynamic activity in the mouse *ex vivo* PD assay. Interestingly, analog **13a** demonstrated a significantly reduced cellular potency, but we found that the biochemical potency of **13a** (hHSD1 IC_{50} = 3.2 nM) was similar to that of **9** (hHSD1 IC_{50} = 2.2 nM) in the human 11β-HSD1 enzyme assay. These results suggest that the carboxylic acid moiety is detrimental to the cell permeability of this class of 11β-HSD1 inhibitors.

We then planned a further modification of the left-hand side, replacing the phenyl ring with a pyridin-3-yl ring, and prepared a small set of derivatives. As shown in Table 1, the picolinamide analogs **13d** and **13e** were 2-3 times more potent in the cell-based assay than the corresponding benzamide compounds **13b** and **13c**, respectively. The cellular potency of the 2-(pyridin-2-yl)propan-2-ol-containing compound **13h** was also similar to those of **13d**, **13e**, and **9**. Except for compound **13d**, the metabolic stability of which was very poor, the derivatives **13e** and **13h** were evaluated in the *ex vivo* PD assay and substantially reduced the 11β-HSD1 enzymatic activities, showing an efficacy that was similar to that of **9** (>50% and >80% inhibition at 10 mg/kg in the liver and EPF, respectively), 2 h after oral administration.

However, the CYP issue was not clearly solved with these compounds. A CYP inhibition assay using human liver microsomes showed that analog **13e** was a much weaker CYP3A4 inhibitor than **9** but was a potent inhibitor of CYP2C19 metabolic activity (CYP2C19 IC_{50} = 0.7 μM). On the other hand, compound **13h** was still a moderate CYP3A4 inhibitor with an IC_{50} value of 5.4 μM, although it did not inhibit CYP2C19 (Table 3).

Table 1. *In vitro* and *ex vivo* data for picolinamide derivatives[a]



Compd	R	X	HEK293[b] IC_{50} (nM)	MLM MST[c] ($\%R_{30min}$)	Mouse PD[d] (%inh. at 2 h)	
					Liver	EPF
9	SO_2Me	CH	3.1 ± 0.6	97 ± 2	70	86
13a	CO_2H	CH	97 ± 23	71 ± 11		
13b	$CONH_2$	CH	8.2 ± 1.8	57 ± 5	0	26
13c	CONHMe	CH	9.2 ± 1.4	61 ± 6	0	34
13d	$CONH_2$	N	3.7 ± 0.7	23 ± 13		
13e	CONHMe	N	2.8 ± 0.8	66 ± 5	52	85
13f	SO_2NH_2	CH	9.8 ± 2.7	65 ± 7	0	11
13g	SO_2NHMe	CH	4.3 ± 1.1	83 ± 4	12	33
13h	$C(CH_3)_2OH$	N	3.5 ± 0.9	76 ± 6	63	87

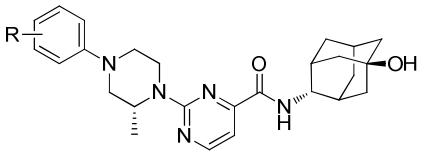
[a]Cellular potency and metabolic stability data are reported as an average of at least three replicates ± standard error of the mean (SEM). [b]Cellular assay utilizing HEK293 cells stably transfected with human 11β-HSD1 cDNA. [c]Metabolic stability test using mouse liver microsomes. [d]Dosed po at 10 mg/kg; 0.5% methylcellulose and 1% Tween80 was used as vehicle.

We next attempted to replace the central pyridine ring of **9** with a pyrimidine ring (Table 2). The hydroxy-adamantyl group and (*R*)-2-methyl-4-phenylpiperazin-1-yl moiety were maintained in the novel pyrimidine-4-carboxamide derivatives, and diverse functional groups were introduced at the 4-position of the phenyl ring (**17a-f**). Similar to the results of our previous SAR study on picolinamide analogs,[29] the compounds that were substituted with hydrophilic groups (**17d-f**) were approximately 2 times more potent in the cellular assay than the derivatives with hydrophobic substituents (**17a-c**). Among them, compound **17e** showed the highest cellular potency, good metabolic stability, and acceptable activity in the *ex vivo* PD assay (48% and 81% inhibition at 10 mg/kg in the liver and EPF, respectively). Moreover, **17e** did not inhibit 5 major human CYP isozymes, suggesting that the pyridine ring was the main contributor to the CYP interaction in compound **9** (Table 3).

In the human 11β-HSD1 enzyme assay, the pyrimidine-4-carboxamide **17e** exhibited comparable potency (hHSD1 IC_{50} = 2.7 nM) to the corresponding picolinamide inhibitor **9**. However, the cellular potency and oral bioavailability of **17e** (HEK293 IC_{50} = 8.5 nM and F = 25% in mouse) were inferior to those of compound **9** (HEK293 IC_{50} = 3.1 nM and F = 41% in mouse). We hypothesized that the much lower cLogP value of **17e** (cLogP = 1.73) relative to that of **9** (cLogP = 2.33) caused a reduction in cell permeability and oral bioavailability, resulting in lower PD activity compared to **9**. Increasing the lipophilicity of derivative **17f** by incorporating an additional fluorine substituent on the phenyl ring (**17g**) improved both the potency in the cell-based assay and *ex vivo* PD activity. Encouraged by this result, we sought to introduce a small lipophilic group, such as a halogen (**18a** and **18b**) or methyl group (**18c**), at the 2-position of the phenyl ring of compound **17e**. To further increase the lipophilicity of **17e**, difluorinated derivatives (**18d** and **18e**) and an ethylsulfonyl analog with a fluorine group

(**18f**) were also explored. As shown in Table 2, these compounds, except for **18e**, were more potent than **17e** in the cellular assay and demonstrated improved PD activities, especially in the liver. In the best case, the incorporation of a single fluorine atom (**18a**) led to an approximately 2-fold increase in cellular potency (IC_{50} = 4.4 nM) and an improvement in the metabolic stability (98% remaining in MLM after 30 min) and PD activity (86% and 88% inhibition at 10 mg/kg in the liver and EPF, respectively) in comparison with those of compound **17e**. The PD activity of **18a** was even superior to the picolinamide lead compound **9**, despite having a lower cLogP value (cLogP = 1.98) than that of **9**. Moreover, the pyrimidine-4-carboxamide compound **18a** neither inhibited 5 major CYP isozymes nor activated PXR, a nuclear receptor that upregulates genes involved in drug metabolism (e.g., CYP3A4),[34] suggesting that **18a** has a low potential for CYP-mediated drug-drug interactions (Table 3).

Table 2. *In vitro* and *ex vivo* data for pyrimidine-4-carboxamide derivatives[a]



Compd	R	HEK293[b] IC_{50} (nM)	MLM MST[c] ($\%R_{30min}$)	Mouse PD[d] (%inh. at 2 h)	
				Liver	EPF
17a	4-F	22 ± 3	82 ± 5		
17b	4-Cl	21 ± 4	78 ± 9		
17c	4-CF_3	18 ± 2	90 ± 5		
17d	4-CN	9.7 ± 1.3	86 ± 7	6	12
17e	4-SO_2Me	8.5 ± 0.6	92 ± 3	48	81
17f	4-$C(CH_3)_2OH$	9.2 ± 0.8	99 ± 2	32	46
17g	2-F, 4-$C(CH_3)_2OH$	8.8 ± 0.7	98 ± 3	43	74
18a	2-F, 4-SO_2Me	4.4 ± 0.5	98 ± 2	86	88
18b	2-Cl, 4-SO_2Me	7.6 ± 0.9	96 ± 4	77	82
18c	2-Me, 4-SO_2Me	8.1 ± 1.1	90 ± 2	64	77
18d	2,5-F, 4-SO_2Me	7.5 ± 1.5	92 ± 5	80	85
18e	2,6-F, 4-SO_2Me	12 ± 3	95 ± 3		
18f	2-F, 4-SO_2Et	4.8 ± 0.6	91 ± 6	79	82

[a]Cellular potency and metabolic stability data are reported as an average of at least three replicates ± standard error of the mean (SEM). [b]Cellular assay utilizing HEK293 cells stably transfected with human 11β-HSD1 cDNA. [c]Metabolic stability test using mouse liver microsomes. [d]Dosed po at 10 mg/kg; 0.5% methylcellulose and 1% Tween80 was used as vehicle.

Table 3. CYP inhibition and PXR activation data for selected compounds

Compd	CYP[a] IC_{50} (μM)					PXR[b] (% activation at 10 μM)
	1A2	2C9	2C19	2D6	3A4	
9	>10	>10	3.7	>10	0.97	32.7
13e	>10	>10	0.7	>10	>10	
13h	>10	>10	>10	>10	5.4	
17e	>10	>10	>10	>10	>10	
18a	>10	>10	>10	>10	>10	0.0

[a]Assays were performed in pooled human liver microsomes. [b]Data are expressed as a percent of control where 100% of control is equivalent to the activity achieved with 10 μM rifampicin.

To examine the binding mode of **18a** in the active site of 11β-HSD1, we carried out a docking study using the flexible molecular docking program Surflex-Dock. As shown in Figure 3, compound **18a** docked into the active site cavity of 11β-HSD1 well with a V-shape binding mode. The amide carbonyl group of **18a** established a central hydrogen bond interaction with the hydroxyl side chain of Ser170, one of the key residues (Ser170, Tyr183, and Lys 187) that define the catalytic triad for 11β-HSD1 activity.[35,36] 11β-HSD1 has large hydrophobic pockets (pocket I and II) on both sides of these key hydrogen-bonding residues. The adamantyl ring of **18a** occupied hydrophobic pocket I, and the hydroxyl group attached to the adamantyl ring formed a hydrogen bond with the carbonyl oxygen of the backbone of Thr124. The phenyl-piperazine moiety of **18a** formed hydrophobic interactions with pocket II consisting of Leu126, Tyr177, Val227, and Val231. As expected, the methylsulfonyl group was positioned toward the solvent-exposed area of the dimer interface region of the protein.

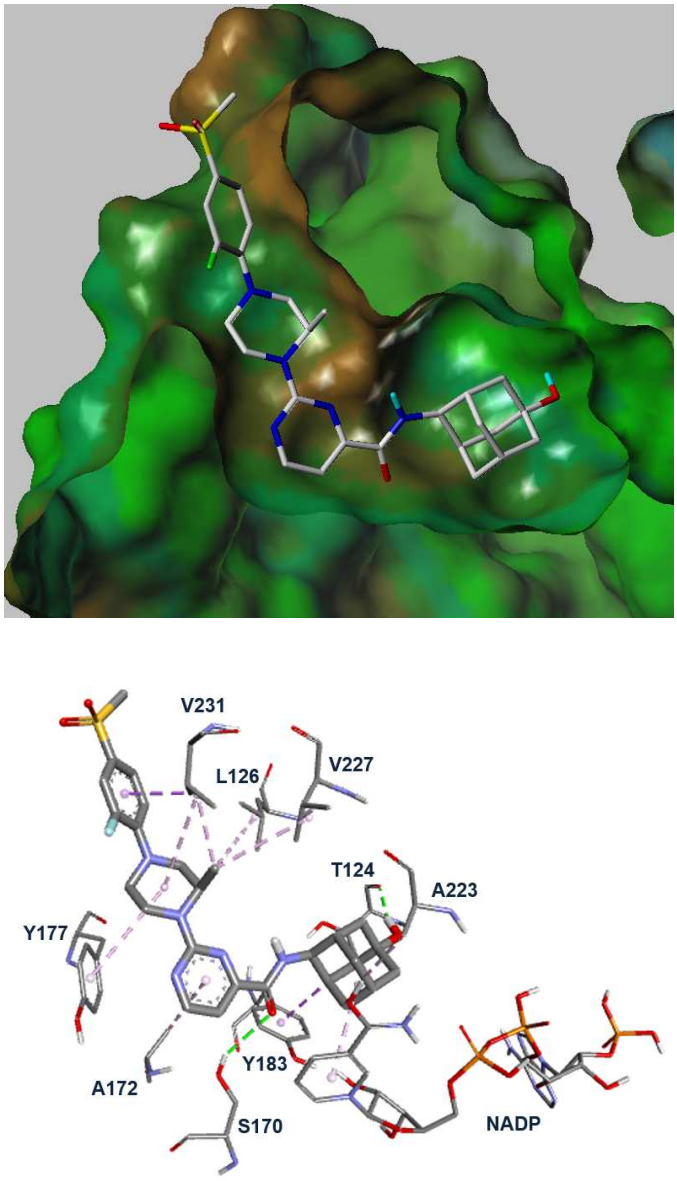


Figure 3. Docking pose of compound **18a** in the active site of human 11β-HSD1. The key hydrogen bonding interactions of **18a** to the enzyme are shown with the green dashed lines. Purple and pink dashed lines indicate π-σ and alkyl hydrophobic interactions, respectively. The protein structure was taken from 2ILT. The predicted binding mode of **18a** was generated by Surflex-Dock.

Based on the results of the SAR study, compound **18a** was selected for further biological evaluations, which included human and mouse 11β-HSD1 enzyme assays, *in vitro* selectivity assays, *in vivo* PK studies, and a dose-dependent PD study. The biochemical enzyme assays

were performed using microsomal fractions that overexpressed 11β-HSDs as the enzyme sources, and **18a** showed inhibition at low nanomolar concentrations for human (hHSD1) and mouse 11β-HSD1 (mHSD1) enzyme activities (hHSD1 IC_{50} = 2.9 nM, mHSD1 IC_{50} = 1.6 nM) in accordance with its nanomolar cellular potency. On the other hand, **18a** demonstrated only negligible inhibitory activity for human 11β-HSD2 (hHSD2), with 6% and 17% inhibition at 1 and 10 μM concentrations, respectively (hHSD2 IC_{50} > 10 μM). These results indicate an over 3000-fold selectivity for 11β-HSD1 over 11β-HSD2, where inhibition of the latter can result in undesirable sodium retention, hypokalemia, and hypertension.[37] Compound **18a** showed weak activity against the glucocorticoid and mineralocorticoid receptors in both agonist and antagonist formats (EC_{50} values above 5 μM). A good selectivity profile of **18a** was also observed versus a panel of 82 enzymes related to adverse reactions (MDS Pharma Services), with only three weak hits (UGT1A1 IC_{50} = 5.6 μM, PDE3 IC_{50} = 5.4 μM, PDE4 IC_{50} = 5.2 μM).

The pharmacokinetic profile of compound **18a** was examined in other species (mouse, rat, and dog), and the results are summarized in Table 4. As expected from its high activity in the *ex vivo* mouse PD assay, the PK study of **18a** in mice showed an oral bioavailability of 96% with a high systemic exposure of 11.26 μg × h/mL after oral administration of a 5 mg/kg dosage. Moreover, across all three species, **18a** exhibited consistently good PK properties characterized by moderate clearances, high exposures, and excellent oral bioavailabilities (F > 60%). To determine if compound **18a** can reach the tissues where 11β-HSD1 is highly expressed, we performed a tissue distribution study with **18a** in mice. C57BL/6 mice received a single oral dose of **18a** (10 mg/kg) and were sacrificed 2 h after dosing. To measure the compound exposure levels, brain, liver, adipose, and plasma samples were collected from the animals. Consistent with the observed *ex vivo* PD effect, **18a** was well distributed in the liver

and adipose, key target tissues for the treatment of metabolic diseases (Table 5). In contrast, the concentration of **18a** in the brain was relatively low, although the extent of free brain penetration cannot be assessed due to the lack of data concerning the free brain-to-free plasma concentration ratios ($K_{p,uu}$).[38] The total plasma compound concentration was over 10 μM, and we have previously determined that 99% of **18a** is protein bound in both human and mouse plasma. Hence, the free compound level in plasma was approximately 100 nM, which is >50-fold higher than the IC_{50} value of **18a** against mouse 11β-HSD1. This is also consistent with the >80% enzyme inhibition at 10 mg/kg in the target tissues.

Table 4. *In vivo* PK data for compound **18a**

Species	IV[a]				PO[b]			
	CL (L/kg/h)	V_{ss} (L/kg)	$t_{1/2}$ (h)	AUC (μg×h/mL)	C_{max} (μg/mL)	t_{max} (h)	AUC (μg×h/mL)	*F* (%)
Mouse[c]	0.42	1.1	1.7	2.35	2.21	1.0	11.26	96
Rat[c]	0.93	2.1	1.8	1.12	1.02	1.3	3.39	60
Dog[d]	0.36	2.4	4.7	1.47	1.12	2.1	11.52	98

[a]10% hydroxylpropyl-β-cyclodextrin was used as vehicle. [b]0.5% methylcellulose and 1% Tween80 was used as vehicle. [c]Dosed iv at 1 mg/kg, po at 5 mg/kg. [d]Dosed iv at 0.5 mg/kg, po at 4 mg/kg.

Table 5. Tissue distribution of compound **18a** in mice[a]

Tissue	Brain	Liver	Adipose	Plasma
Concentration (nmol/g)	0.41	31.0	6.64	10.6
Tissue/Plasma ratio	0.04	2.94	0.62	1

[a]Animals were dosed po with 10 mg/kg dissolved in 0.5% methylcellulose and 1% Tween80. Tissues were collected upon sacrifice at 2 h post-dose.

To evaluate the detailed pharmacodynamic profile of compound **18a**, C57BL/6 mice were orally administrated 3, 10, or 30 mg/kg of **18a**, once, and sacrificed at 2 or 6 h post-dose for an *ex vivo* analysis. As shown in Table 6, **18a** significantly reduced the 11β-HSD1 enzymatic activities in both the liver and EPF after 2 and 6 h in a dose-dependent manner. The activity of 11β-HSD1 was reduced by over 90% in animals that were treated with 30 mg/kg of **18a** and was inhibited in both tissues, even at 3 mg/kg (74% and 86% inhibition in the liver and EPF, respectively) after 2 h. Moreover, these PD activities were maintained for up to 6 h after administration. The prolonged PD activity of **18a** was beyond that expected based on its pharmacokinetic profile ($t_{1/2}$ value of 1.7 h in mouse), and these results suggest that **18a** is a potent 11β-HSD1 inhibitor with a long duration of action in target tissues that is suitable for once-daily dosing.

Table 6. *Ex vivo* mouse PD data for compound **18a**

Dose	*Ex vivo* mouse PD[a] (%inh.)			
	Liver		EPF	
	2 h	6 h	2 h	6 h
30 mg/kg	91	92	92	93
10 mg/kg	86	87	88	93
3 mg/kg	74	71	86	84

[a]Dosed po at indicated dose; 0.5% methylcellulose and 1% Tween80 was used as vehicle.

In the safety pharmacology studies of **18a**, no abnormal changes were observed in the cardiovascular and respiratory systems of telemetered dogs that were given oral doses of up to 400 mg/kg, or in the central nervous system of mice that were given oral doses of up to 1000

mg/kg. The whole-cell patch-clamp technique was used to investigate the effects of **18a** on hERG channels stably expressed in CHO cells, and the IC_{50} value was estimated to be 8.0 μM. Considering that the human and mice plasma protein binding levels of **18a** are both 99%, the expected unbound C_{max} of **18a** at the effective dose is >30-fold lower than 8.0 μM, indicating a low risk of cardiac toxicity. The genotoxic potential of **18a** was found to be negative in a reverse mutation assay, a chromosome aberration assay, and an *in vivo* mouse bone marrow erythrocyte micronucleus test. In a 4-week repeated oral-dose toxicity study in mice, **18a** was administered once daily at doses of 40, 100, 250, and 625 mg/kg, and the NOAEL was 625 mg/kg in both males and females. In a 4-week repeated oral-dose toxicity study in dogs, **18a** was administered once daily at doses of 25, 100, and 400 mg/kg, and the NOAEL was 400 mg/kg in both sexes. Toxicokinetic studies showed that systemic exposures (AUC and C_{max}) of **18a** were increased in dose-dependent manners in both mice and dogs, although they were not dose proportional (Supporting Information).

On the basis of its favorable *in vitro*, pharmacokinetic, pharmacodynamic, and toxicologic profiles, compound **18a** (SKI2852)[39] was selected as our final candidate. To examine the therapeutic efficacy of **18a** for type 2 diabetes and metabolic syndrome, we conducted various *in vivo* disease model studies, and the results were previously reported.[39] Repeated oral administrations of **18a** significantly lowered body-weight gains in *ob*/*ob* mice and partially improved lipid profiles in DIO, *ob*/*ob*, and KK-A^y mice models. It also efficiently reduced postprandial glucose and/or blood HbA1c levels in these mice and suppressed hepatic mRNA levels of gluconeogenic enzymes in DIO mice. Moreover, **18a** clearly enhanced hepatic and whole-body insulin sensitivities in a hyperinsulinemic-euglycemic clamp experiment in DIO mice.[39]

Metformin is a first-line oral anti-diabetic agent with a documented glucose-lowering effect in subjects with type 2 diabetes,[40] and it is commonly prescribed in combination with other anti-diabetic drugs, such as sulfonylureas, thiazolidinediones, and DPP-4 inhibitors.[41] To evaluate the effects of the potent 11β-HSD1 inhibitor **18a**, alone or combined with metformin, on glycemic control and lipid profiles, we performed an additional pharmacological study using the *ob*/*ob* mice model. As illustrated in Figure 4, after 25 days of once-daily oral administration of the compounds, a significant effect of **18a** and metformin on glycemic control was observed; the glycosylated hemoglobin (HbA1c) level was decreased by 0.70%, 1.20%, and 1.67% (vehicle corrected) in the metformin (300 mg/kg), **18a** (20 mg/kg), and combined **18a** plus metformin treatment groups, respectively. Compound **18a** alone or in combination with metformin significantly reduced the non-fasting blood glucose levels by 26% and 33%, respectively, compared with the vehicle control group, whereas metformin alone did not change the level. Although there were no statistically significant difference between the **18a** and combined groups, the effect of metformin on glycemic control was significantly enhanced in combination with compound **18a**. The LDL and total cholesterol levels were also significantly decreased in all treatment groups and were much lower in mice that were treated with compound **18a** or **18a** plus metformin than in the metformin monotherapy group (Table 7). These results suggested that the coadministration of **18a** and metformin could have an additive or synergistic effect on metabolic disorders in animal models of type 2 diabetes, which could further expand the concept of combination therapy with an 11β-HSD1 inhibitor and metformin in clinical practice.

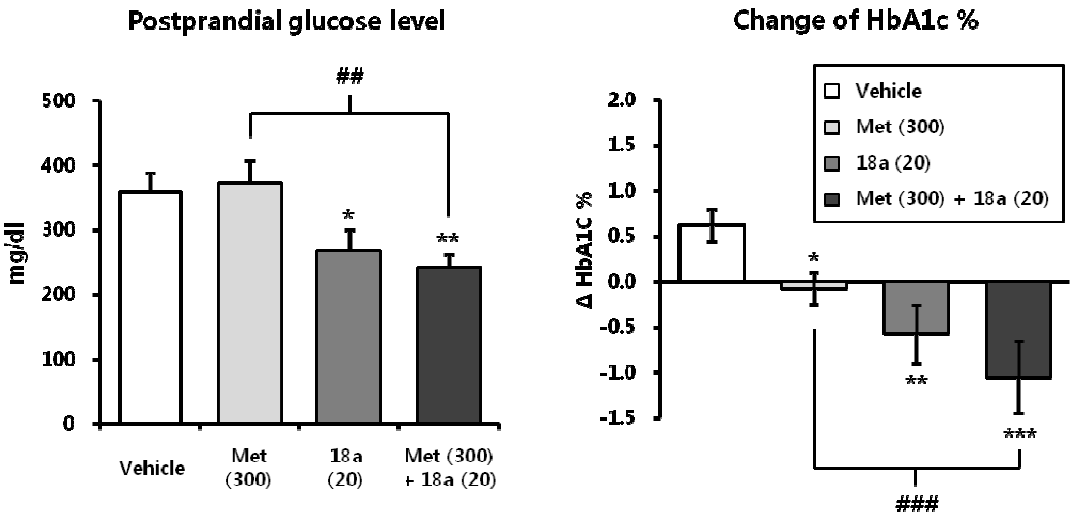


Figure 4. The effect of metformin, compound **18a**, and the combination thereof on glucose levels in *ob*/*ob* mice. Compounds were orally administrated to *ob*/*ob* mice, at the indicated dose (mg/kg), once daily for 25 days. Sterile water containing 0.5% methylcellulose and 1% Tween80 was used as vehicle. Data are expressed as the means ± SE of n = 10. Statistical analysis was performed by one-way ANOVA followed by the Tukey test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. vehicle, ## $P < 0.01$, ### $P < 0.001$ vs. metformin.

Table 7. The effect of metformin, compound **18a**, and the combination thereof on lipid profiles in *ob*/*ob* mice[a]

Group	LDL cholesterol (mg/dl)	Total cholesterol (mg/dl)	Triglyceride (mg/dl)
Vehicle	30.3 ± 0.8	286.6 ± 6.3	90.9 ± 5.5
Metformin	23.9 ± 0.9***	252.6 ± 7.4**	99.9 ± 6.3
Compd **18a**	17.1 ± 1.2***	230.6 ± 8.3***	83.4 ± 6.5
Metformin + Compd **18a**	17.2 ± 0.7***	235.0 ± 5.6***	84.1 ± 5.7

[a]Data are expressed as the means ± SE of n = 10. Statistical analysis was performed by one-way ANOVA followed by the Tukey test. ** $P < 0.01$, *** $P < 0.001$ vs. vehicle.

CONCLUSION

In order to diminish the CYP liability, further structural modifications of the lead compound **9** were performed and resulted in the discovery of a series of pyrimidine-4-carboxamide derivatives as novel 11β-HSD1 inhibitors. The replacement of the pyridine ring of **9** with a pyrimidine ring led to a slight decrease in the cellular potency and PD activity, which were, however, substantially improved by introducing an additional fluorine substituent at the 2-position of the phenyl ring. This compound, 2-((*R*)-4-(2-fluoro-4-(methylsulfonyl)phenyl)-2-methylpiperazin-1-yl)-*N*-((*E*)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide (**18a**), was identified as a potent and selective inhibitor of 11β-HSD1 with no CYP and PXR issues. The compound **18a** also exhibited excellent PK profiles across species and a dose-dependent, highly potent, and sustainable PD activity that was superior to that of **9**. Finally, **18a** significantly reduced the blood glucose and HbA1c levels and improved the lipid profiles in *ob*/*ob* mice after oral administration. Moreover, the HbA1c-lowering effect of metformin was synergistically enhanced when combined with **18a** in these mice. Compound **18a** was selected as the final candidate for IND-enabling studies. Further details of these investigations will be reported in due course.

EXPERIMENTAL SECTION

Chemistry. *General methods.* All commercial solvents and chemicals were of reagent grade and were used without further purification. All reactions were monitored for completion by TLC using Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm). Flash column chromatography was carried out using Merck silica gel (Kieselgel 60, 230-400 mesh) or prepacked silica cartridges from Redisep with an Isco Companion system. ^{1}H NMR spectra were recorded on a Varian UNITY 300 (300 MHz), a Bruker AMX 500 (500 MHz), JEOL

JNM-ECA 600 (600 MHz), or Bruker AMX 800 (800 MHz) instruments and were determined in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (0.00 ppm) or solvent peaks as the internal reference, and coupling constant (*J*) values are reported in hertz (Hz). ^{13}C NMR spectra were recorded on a Bruker AMX 500 (125 MHz), JEOL JNM-ECA 600 (150 MHz), or Bruker AMX 800 (200 MHz) instrument. All ^{13}C NMR spectra were determined in DMSO-d_6 and assigned in ppm relative to the central DMSO-d_6 peak (39.50 ppm). High-resolution mass spectra (HRMS) were measured on a JEOL JMS 700 or JEOL JMS 600-W spectrometer. Melting points were measured on a Büchi B-540 melting point apparatus and were not corrected. The purity of all final compounds was determined to be >95% by HPLC (Waters ACQUITY UPLC® BEH C18 column, 2.1 x 100 mm, 1.7 μm) with gradient of 30-80% acetonitrile in 0.01 M disodium hydrogen orthophosphate buffer adjusted to pH 7.6 with phosphoric acid.

*6-Bromo-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)picolinamide (**10**).* To a solution of 6-bromopicolinic acid (17.5 g, 86.6 mmol) and *trans*-4-aminoadamantan-1-ol (17.4 g, 104 mmol) in acetonitrile (500 mL) were added *N,N*-diisopropylethylamine (18.1 mL, 104 mmol) and HBTU (39.4 g, 104 mmol). The reaction mixture was stirred at ambient temperature for 15 h and then concentrated under reduced pressure. The mixture was diluted with EtOAc (600 mL), washed with saturated aqueous NH_4Cl (200 mL) and brine (200 mL), dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 70% EtOAc in hexanes) to afford **10** (26.1 g, 85%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (dd, J = 0.9, 7.5 Hz, 1H), 8.12 (brs, 1H), 7.72 (dd, J = 7.5, 7.8 Hz, 1H), 7.62 (dd, J = 0.9, 7.8 Hz, 1H), 4.22-4.16 (m, 1H), 2.25 (brs, 3H), 1.99-1.88 (m, 3H), 1.86-1.78 (m, 5H), 1.61-1.53 (m, 2H), 1.43 (s, 1H). MS (ESI) *m*/*z*: 351 $[M+H]^+$.

*N-((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)-6-((R)-2-methylpiperazin-1-yl)picolinamide (**11**).* A mixture of **10** (1.0 g, 2.85 mmol), (*R*)-*tert*-butyl 3-methylpiperazine-1-carboxylate (855 mg, 4.27 mmol), $Pd_2(dba)_3$ (52 mg, 0.057 mmol), xantphos (99 mg, 0.171 mmol), sodium *tert*-butoxide (410 mg, 4.27 mmol), and toluene (20 mL) was stirred at 100 ºC for 3 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, and saturated aqueous NH_4Cl was added. The mixture was extracted with CH_2Cl_2 (40 mL x 2), and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 90% EtOAc in hexanes) to afford (*R*)-*tert*-butyl 4-(6-(((1*R*,2*s*,3*S*,5*S*,7*S*)-5-hydroxyadamantan-2-yl)carbamoyl)pyridin-2-yl)-3-methylpiperazine-1-carboxylate (720 mg, 54%) as a pale yellow solid. MS (ESI) *m*/*z*: 471 $[M+H]^+$.

To a solution of (*R*)-*tert*-butyl 4-(6-(((1*R*,2*s*,3*S*,5*S*,7*S*)-5-hydroxyadamantan-2-yl)carbamoyl)pyridin-2-yl)-3-methylpiperazine-1-carboxylate (715 mg, 1.52 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (10 mL). After being stirred at ambient temperature for 3 h, the reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (40 mL x 2). The organic layers were discarded, and the aqueous layer was basified with 5 N aqueous NaOH and extracted with 5% MeOH in CH_2Cl_2 (40 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford **11** (516 mg, 92%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 9.0 Hz, 1H), 7.62 (dd, J = 7.2, 8.7 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 6.77 (d, J = 8.7 Hz, 1H), 4.44-4.37 (m, 1H), 4.22-4.15 (m, 1H), 3.95-3.88 (m, 1H), 3.19-3.08 (m, 3H), 3.00-2.89 (m, 2H), 2.23 (brs, 3H), 1.99-1.92 (m, 2H), 1.85-1.77 (m, 6H), 1.62-1.52 (m, 2H), 1.26 (d, J = 6.6 Hz, 3H). MS (ESI) *m*/*z*: 371 $[M+H]^+$.

*5-((R)-4-(6-(((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)carbamoyl)pyridin-2-yl)-3-methylpiperazin-1-yl)picolinic acid (**12**).* A mixture of **11** (190 mg, 0.513 mmol), methyl 5-bromopicolinate (133 mg, 0.615 mmol), $Pd(OAc)_2$ (7 mg, 0.0308 mmol), xantphos (18 mg, 0.0308 mmol), cesium carbonate (251 mg, 0.769 mmol), and toluene (8 mL) was stirred at 100 ºC for 15 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 0-3% MeOH in CH_2Cl_2, gradient elution) to afford methyl 5-((*R*)-4-(6-(((1*R*,2*s*,3*S*,5*S*,7*S*)-5-hydroxyadamantan-2-yl)carbamoyl)pyridin-2-yl)-3-methylpiperazin-1-yl)picolinate (119 mg, 46%) as a yellow solid. MS (ESI) *m*/*z*: 506 $[M+H]^+$.

To a solution of 5-((*R*)-4-(6-(((1*R*,2*s*,3*S*,5*S*,7*S*)-5-hydroxyadamantan-2-yl)carbamoyl)pyridin-2-yl)-3-methylpiperazin-1-yl)picolinate (100 mg, 0.198 mmol) in MeOH (2 mL) was added 2 N aqueous NaOH (0.5 mL). After being stirred at ambient temperature for 20 h, the pH of the reaction mixture was adjusted to 6-7 with 1 N aqueous HCl. The mixture was extracted with CH_2Cl_2 (10 mL x 4), and the combined organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 5-15% MeOH in CH_2Cl_2, gradient elution) to afford **12** (86 mg, 88%) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39 (d, J = 3.0 Hz, 1H), 8.29 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.74 (dd, J = 7.2, 8.7 Hz, 1H), 7.38 (dd, J = 3.0, 9.0 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 4.62-4.52 (m, 1H), 4.50 (s, 1H), 4.12-4.03 (m, 1H), 4.02-3.90 (m, 3H), 3.49-3.16 (m, 3H), 2.06 (brs, 3H), 1.79-1.64 (m, 8H), 1.54-1.45 (m, 2H), 1.21 (d, J = 6.3 Hz, 3H). MS (ESI) *m*/*z*: 492 $[M+H]^+$.

*4-((R)-4-(6-(((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)carbamoyl)pyridin-2-yl)-3-methylpiperazin-1-yl)benzoic acid (**13a**).* Compound **13a** was prepared according to the

procedure of **12** from intermediate **11** and methyl 4-bromobenzoate in 44% yield (two steps). Mp: 278 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.72 (dd, J = 7.2, 8.7 Hz, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 4.60-4.52 (m, 1H), 4.50 (brs, 1H), 4.10-4.03 (m, 1H), 3.98-3.94 (m, 1H), 3.91-3.82 (m, 2H), 3.45-3.29 (m, 2H), 3.18-3.09 (m, 1H), 2.11-2.03 (m, 3H), 1.80-1.64 (m, 8H), 1.54-1.45 (m, 2H), 1.20 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.29, 162.94, 156.54, 153.66, 147.61, 138.96, 130.92, 118.90, 112.64, 110.24, 110.16, 65.36, 51.66, 50.45, 48.10, 46.18, 45.19, 44.26, 33.49, 30.50, 29.08, 14.61. MS (FAB) m/z: 491 $[M+H]^+$. HRMS (FAB) m/z: calcd for $C_{28}H_{35}N_4O_4$ 491.2658, found 491.2654.

*6-((R)-4-(4-Carbamoylphenyl)-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)picolinamide (**13b**).* To a solution of **13a** (60 mg, 0.122 mmol) in acetonitrile (2 mL) were added ammonia (0.5 M solution in dioxane, 0.49 mL, 0.244 mmol), *N,N*-diisopropylethylamine (0.043 mL, 0.244 mmol), and HBTU (56 mg, 0.146 mmol). The reaction mixture was stirred at ambient temperature for 3 h, and saturated aqueous NH_4Cl was added. The mixture was extracted with 10% MeOH in CH_2Cl_2 (15 mL x 2), and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 5% MeOH in CH_2Cl_2) to afford **13b** (47 mg, 78%) as a pale yellow solid. Mp: 261 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.73 (dd, J = 7.2, 8.6 Hz, 1H), 7.71 (brs, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 7.00 (brs, 1H), 6.97 (d, J = 8.8 Hz, 2H), 4.61-4.54 (m, 1H), 4.50 (s, 1H), 4.12-4.05 (m, 1H), 3.98-3.93 (m, 1H), 3.90-3.79 (m, 2H), 3.42-3.33 (m, 1H), 3.25-3.20 (m, 1H), 3.07-3.00 (m, 1H), 2.12-2.03 (m, 3H), 1.79-1.64 (m, 8H), 1.54-1.46 (m, 2H), 1.21 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.63, 162.94, 156.61, 152.79, 147.60, 138.96, 128.90, 123.08, 112.99, 110.33, 110.17,

65.35, 51.65, 51.14, 47.92, 46.60, 45.19, 44.26, 33.48, 30.50, 29.07, 14.30. MS (FAB) *m*/*z*: 490 $[M+H]^+$. HRMS (FAB) *m*/*z*: calcd for $C_{28}H_{36}N_5O_3$ 490.2818, found 490.2820.

N-((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)-6-((R)-2-methyl-4-(4-(methylcarbamoyl)phenyl)piperazin-1-yl)picolinamide ***(13c)***. Compound **13c** was prepared according to the procedure of **13b** from benzoic acid **13a** and CH_3NH_2 (2.0 M solution in THF) in 70% yield. Mp: 227 °C. ^{1}H NMR (800 MHz, DMSO-d_6) δ 8.31 (d, J = 8.3 Hz, 1H), 8.14 (q, J = 4.5 Hz, 1H), 7.74-7.72 (m, 3H), 7.29 (d, J = 7.2 Hz, 1H), 7.08 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 8.9 Hz, 2H), 4.60-4.55 (m, 1H), 4.50 (s, 1H), 4.11-4.04 (m, 1H), 3.98-3.94 (m, 1H), 3.88-3.84 (m, 1H), 3.83-3.79 (m, 1H), 3.39-3.35 (m, 1H), 3.23-3.20 (m, 1H), 3.05-3.00 (m, 1H), 2.75 (d, J = 4.5 Hz, 3H), 2.10 (brs, 1H), 2.06 (brs, 2H), 1.78-1.71 (m, 4H), 1.69-1.65 (m, 4H), 1.53-1.47 (m, 2H), 1.21 (d, J = 6.6 Hz, 3H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 166.28, 162.94, 156.61, 152.66, 147.60, 138.97, 128.33, 123.43, 113.16, 110.36, 110.18, 65.36, 51.65, 51.22, 47.87, 46.65, 45.19, 44.26, 33.48, 30.50, 29.07, 26.09, 14.25. MS (FAB) *m*/*z*: 504 $[M+H]^+$. HRMS (FAB) *m*/*z*: calcd for $C_{29}H_{38}N_5O_3$ 504.2975, found 504.2979.

6-((R)-4-(6-Carbamoylpyridin-3-yl)-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)picolinamide ***(13d)***. Compound **13d** was prepared according to the procedure of **13b** from picolinic acid **12** and ammonia (0.5 M solution in dioxane) in 78% yield. Mp: 237 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32-8.27 (m, 2H), 7.86 (d, J = 8.8 Hz, 1H), 7.77 (brs, 1H), 7.73 (dd, J = 7.1, 8.7 Hz, 1H), 7.43 (dd, J = 2.7, 8.8 Hz, 1H), 7.31 (brs, 1H), 7.30 (d, J = 7.1 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 4.61-4.55 (m, 1H), 4.50 (s, 1H), 4.12-4.06 (m, 1H), 3.98-3.87 (m, 3H), 3.46-3.39 (m, 1H), 3.36-3.31 (m, 1H), 3.18-3.11 (m, 1H), 2.12-2.03 (m, 3H), 1.79-1.64 (m, 8H), 1.54-1.46 (m, 2H), 1.21 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.27, 162.94, 156.55, 148.09, 147.62, 139.33, 138.97, 134.42, 122.47, 120.07, 110.33, 110.26, 65.35, 51.68, 50.32, 47.90, 46.06, 45.18, 44.25, 33.46, 30.50,

29.07, 14.40. MS (FAB) *m*/*z*: 491 $[M+H]^+$. HRMS (FAB) *m*/*z*: calcd for $C_{27}H_{35}N_6O_3$ 491.2771, found 491.2765.

N-((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)-6-((R)-2-methyl-4-(6-(methylcarbamoyl)pyridin-3-yl)piperazin-1-yl)picolinamide ***(13e)***. Compound **13e** was prepared according to the procedure of **13b** from picolinic acid **12** and CH_3NH_2 (2.0 M solution in THF) in 55% yield. Mp: 163 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.39 (d, J = 4.8 Hz, 1H), 8.32-8.27 (m, 2H), 7.85 (d, J = 8.8 Hz, 1H), 7.73 (dd, J = 7.2, 8.7 Hz, 1H), 7.43 (dd, J = 2.7, 8.8 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 4.62-4.55 (m, 1H), 4.50 (s, 1H), 4.12-4.04 (m, 1H), 3.98-3.86 (m, 3H), 3.46-3.38 (m, 1H), 3.35-3.29 (m, 1H), 3.17-3.09 (m, 1H), 2.79 (d, J = 4.8 Hz, 3H), 2.11-2.03 (m, 3H), 1.79-1.63 (m, 8H), 1.54-1.45 (m, 2H), 1.21 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.62, 162.95, 156.56, 148.07, 147.62, 139.40, 138.97, 134.46, 122.22, 120.23, 110.34, 110.28, 65.36, 51.69, 50.40, 47.86, 46.13, 45.18, 44.25, 33.47, 30.50, 29.07, 25.80, 14.38. MS (FAB) *m*/*z*: 505 $[M+H]^+$. HRMS (FAB) *m*/*z*: calcd for $C_{28}H_{37}N_6O_3$ 505.2927, found 505.2937.

N-((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)-6-((R)-2-methyl-4-(4-sulfamoylphenyl)piperazin-1-yl)picolinamide ***(13f)***. A mixture of **11** (30 mg, 0.081 mmol), 4-bromo-*N*-(*tert*-butyl)benzenesulfonamide (28 mg, 0.097 mmol), $Pd[P(o\text{-tolyl})_3]_2Cl_2$ (1 mg, 0.00081 mmol), BINAP (3 mg, 0.0049 mmol), cesium carbonate (26 mg, 0.081 mmol), and toluene (5 mL) was stirred at 90 ºC for 15 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 5% MeOH in CH_2Cl_2) to afford 6-((*R*)-4-(4-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-2-methylpiperazin-1-yl)-*N*-((1*R*,2*s*,3*S*,5*S*,7*S*)-5-hydroxyadamantan-2-yl)picolinamide (45 mg, 96%) as a pale yellow solid. MS (ESI) *m*/*z*: 582 $[M+H]^+$.

To a solution of 6-((*R*)-4-(4-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-2-methylpiperazin-1-yl)-*N*-((1*R*,2*s*,3*S*,5*S*,7*S*)-5-hydroxyadamantan-2-yl)picolinamide (40 mg, 0.069 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at ambient temperature for 15 h and then concentrated under reduced pressure. The mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (5 mL). The organic layer was discarded, and the aqueous layer was basified with saturated aqueous $NaHCO_3$ and extracted with 10% MeOH in CH_2Cl_2 (10 mL x 2). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 5% MeOH in CH_2Cl_2) to afford **13f** (23 mg, 64%) as a pale yellow solid. Mp: 243 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (d, J = 8.3 Hz, 1H), 7.73 (dd, J = 7.2, 8.4 Hz, 1H), 7.64 (d, J = 8.9 Hz, 2H), 7.30 (d, J = 7.2 Hz, 1H), 7.08-7.03 (m, 5H), 4.60-4.53 (m, 1H), 4.50 (s, 1H), 4.11-4.04 (m, 1H), 3.98-3.94 (m, 1H), 3.91-3.82 (m, 2H), 3.44-3.37 (m, 1H), 3.33-3.27 (m, 1H), 3.14-3.06 (m, 1H), 2.12-2.03 (m, 3H), 1.79-1.64 (m, 8H), 1.54-1.46 (m, 2H), 1.20 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.94, 156.55, 152.73, 147.60, 138.97, 132.17, 127.17, 112.93, 110.29, 110.19, 65.36, 51.66, 50.73, 48.02, 46.40, 45.18, 44.26, 33.48, 30.50, 29.07, 14.48. MS (FAB) *m*/*z*: 526 $[M+H]^+$. HRMS (FAB) *m*/*z*: calcd for $C_{27}H_{36}N_5O_4S$ 526.2488, found 526.2487.

*N-((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)-6-((R)-2-methyl-4-(4-(N-methylsulfamoyl)phenyl)piperazin-1-yl)picolinamide (**13g**).* Compound **13g** was prepared according to the procedure of **13f** from intermediate **11** and 4-bromo-*N*-(*tert*-butyl)-*N*-methylbenzenesulfonamide in 21% yield (two steps). Mp: 264 °C. ^{1}H NMR (800 MHz, DMSO-d_6) δ 8.31 (d, J = 8.3 Hz, 1H), 7.73 (dd, J = 7.2, 8.5 Hz, 1H), 7.58 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 7.2 Hz, 1H), 7.10-7.07 (m, 4H), 4.59-4.55 (m, 1H), 4.50 (s, 1H), 4.09-4.05 (m, 1H), 3.98-3.94 (m, 1H), 3.91-3.83 (m, 2H), 3.45-3.40 (m, 1H), 3.36-3.31 (m, 1H), 3.16-3.12

(m, 1H), 2.35 (d, *J* = 5.1 Hz, 3H), 2.09 (brs, 1H), 2.06 (brs, 2H), 1.78-1.71 (m, 4H), 1.69-1.65 (m, 4H), 1.53-1.47 (m, 2H), 1.20 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 162.93, 156.53, 153.04, 147.60, 138.98, 128.33, 126.36, 112.94, 110.27, 110.19, 65.36, 51.66, 50.41, 48.05, 46.18, 45.19, 44.26, 33.48, 30.50, 29.07, 28.63, 14.60. MS (FAB) *m*/*z*: 540 $[M+H]^+$. HRMS (FAB) *m*/*z*: calcd for $C_{28}H_{38}N_5O_4S$ 540.2645, found 540.2647.

*N-((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)-6-((R)-4-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-2-methylpiperazin-1-yl)picolinamide (**13h**).* A mixture of **11** (130 mg, 0.351 mmol), 2-(5-bromopyridin-2-yl)propan-2-ol (91 mg, 0.421 mmol), $Pd_2(dba)_3$ (6 mg, 0.0070 mmol), BINAP (13 mg, 0.021 mmol), sodium *tert*-butoxide (51 mg, 0.526 mmol), and toluene (7 mL) was stirred at 100 ºC for 15 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 0-10% MeOH in CH_2Cl_2, gradient elution) to afford **13h** (51 mg, 29%) as a pale yellow solid. Mp: 135 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29 (d, *J* = 8.2 Hz, 1H), 8.23 (d, *J* = 2.6 Hz, 1H), 7.73 (dd, *J* = 7.2, 8.7 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.39 (dd, *J* = 2.6, 8.7 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 5.05 (s, 1H), 4.64-4.58 (m, 1H), 4.50 (s, 1H), 4.16-4.10 (m, 1H), 3.98-3.93 (m, 1H), 3.81-3.75 (m, 1H), 3.67 (d, *J* = 12.0 Hz, 1H), 3.35-3.27 (m, 1H), 3.07-3.01 (m, 1H), 2.90-2.83 (m, 1H), 2.06 (brs, 3H), 1.79-1.64 (m, 8H), 1.54-1.45 (m, 2H), 1.40 (s, 6H), 1.24 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.96, 158.31, 156.71, 147.63, 145.15, 138.95, 135.78, 122.96, 118.37, 110.52, 110.30, 71.87, 65.35, 52.71, 51.70, 47.80, 47.33, 45.17, 44.25, 33.45, 30.80, 30.50, 29.07, 13.59. MS (FAB) *m*/*z*: 506 $[M+H]^+$. HRMS (FAB) *m*/*z*: calcd for $C_{29}H_{40}N_5O_3$ 506.3131, found 506.3137.

*(R)-Tert-butyl 2-(4-benzyl-2-methylpiperazin-1-yl)pyrimidine-4-carboxylate (**14**).* To a solution of 2-chloropyrimidine-4-carboxylic acid (500 mg, 3.15 mmol) in 2-methylpropan-2-

ol (20 mL) were added pyridine (3 mL) and *p*-toluenesulfonyl chloride (1.2 g, 6.31 mmol). After being stirred at ambient temperature for 4 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and concentrated under reduced pressure. The residue was taken up in water (10 mL), and the resulting precipitate was filtered, washed with water, and dried in vacuo to afford *tert*-butyl 2-chloropyrimidine-4-carboxylate (420 mg, 62%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, J = 4.8 Hz, 1H), 7.85 (d, J = 4.8 Hz, 1H), 1.63 (s, 9H). MS (ESI) m/z: 215 $[M+H]^+$.

To a solution of *tert*-butyl 2-chloropyrimidine-4-carboxylate (206 mg, 0.96 mmol) and (*R*)-1-benzyl-3-methylpiperazine (183 mg, 0.96 mmol) in acetonitrile (5 mL) was added *N,N*-diisopropylethylamine (0.334 mL, 1.92 mmol). After being stirred at 100 ºC for 15 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Then, water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (15 mL x 2). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 1% MeOH in CH_2Cl_2) to afford **14** (334 mg, 94%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 4.8 Hz, 1H), 7.40-7.24 (m, 5H), 7.01 (d, J = 4.8 Hz, 1H), 4.94-4.85 (m, 1H), 4.60-4.52 (m, 1H), 3.60 (d, J = 13.2 Hz, 1H), 3.43 (d, J = 13.2 Hz, 1H), 3.33-3.24 (m, 1H), 2.95-2.87 (m, 1H), 2.73 (d, J = 11.1 Hz, 1H), 2.21 (dd, J = 3.9, 11.1 Hz, 1H), 2.17-2.08 (m, 1H), 1.59 (s, 9H), 1.30 (d, J = 6.6 Hz, 3H). MS (ESI) m/z: 369 $[M+H]^+$.

*2-((R)-4-Benzyl-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide (**15**).* To a solution of **14** (2.49 g, 6.76 mmol) in CH_2Cl_2 (40 mL) was added trifluoroacetic acid (40 mL). The reaction mixture was stirred at ambient temperature for 24 h and then concentrated in vacuo to afford the crude (*R*)-2-(4-benzyl-2-

methylpiperazin-1-yl)pyrimidine-4-carboxylic acid, which was used without purification in the following reaction.

To a solution of the crude (*R*)-2-(4-benzyl-2-methylpiperazin-1-yl)pyrimidine-4-carboxylic acid in acetonitrile (40 mL) were added *trans*-4-aminoadamantan-1-ol (1.34 g, 8.11 mmol), *N,N*-diisopropylethylamine (7 mL, 40.1 mmol), and HBTU (3.08 g, 8.11 mmol). The reaction mixture was stirred at ambient temperature for 15 h and then concentrated under reduced pressure. The mixture was diluted with EtOAc (100 mL), washed with saturated aqueous NH_4Cl (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3% MeOH in CH_2Cl_2) to afford **15** (2.12 g, 68%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 4.8 Hz, 1H), 8.24 (d, J = 8.1 Hz, 1H), 7.41-7.28 (m, 5H), 7.26 (d, J = 4.8 Hz, 1H), 4.83-4.74 (m, 1H), 4.47-4.39 (m, 1H), 4.19-4.12 (m, 1H), 3.61 (d, J = 13.2 Hz, 1H), 3.48 (d, J = 13.2 Hz, 1H), 3.33-3.24 (m, 1H), 2.99-2.91 (m, 1H), 2.78 (d, J = 11.4 Hz, 1H), 2.27 (dd, J = 3.9, 11.4 Hz, 1H), 2.22-2.11 (m, 4H), 1.97-1.90 (m, 2H), 1.83-1.70 (m, 6H), 1.62-1.56 (m, 2H), 1.32 (d, J = 6.9 Hz, 3H). MS (ESI) *m*/*z*: 462 $[M+H]^+$.

*N-((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)-2-((R)-2-methylpiperazin-1-yl)pyrimidine-4-carboxamide (**16**).* To a solution of **15** (2.1 g, 4.55 mmol) in MeOH (40 mL) was added 10% palladium on activated carbon (500 mg), and the mixture was stirred at ambient temperature for 15 h under a hydrogen atmosphere. The reaction mixture was then filtered through Celite, and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 15% MeOH in CH_2Cl_2) to afford **16** (1.37 g, 81%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.58 (d, J = 4.8 Hz, 1H), 7.19 (d, J = 4.8 Hz, 1H), 4.89-4.81 (m, 1H), 4.56-4.48 (m, 1H), 4.08 (brs, 1H), 3.23-3.11 (m,

2H), 3.03-2.98 (m, 2H), 2.84-2.74 (m, 1H), 2.19 (brs, 3H), 1.93-1.78 (m, 8H), 1.65-1.57 (m, 2H), 1.30 (d, J = 6.9 Hz, 3H). MS (ESI) m/z: 372 $[M+H]^+$.

2-((R)-4-(4-Fluorophenyl)-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide ***(17a)***. Compound **17a** was prepared according to the procedure of **13h** from intermediate **16** and 1-bromo-4-fluorobenzene in 41% yield. Mp: 119 °C. ^{1}H NMR (800 MHz, DMSO-d_6) δ 8.64 (d, J = 4.7 Hz, 1H), 8.22 (d, J = 7.9 Hz, 1H), 7.14 (d, J = 4.7 Hz, 1H), 7.08-7.05 (m, 2H), 7.01-6.99 (m, 2H), 4.90-4.86 (m, 1H), 4.53-4.49 (m, 1H), 4.50 (s, 1H), 3.97-3.93 (m, 1H), 3.68-3.64 (m, 1H), 3.58-3.54 (m, 1H), 3.38-3.34 (m, 1H), 2.95-2.91 (m, 1H), 2.76-2.71 (m, 1H), 2.11-2.05 (m, 3H), 1.78-1.72 (m, 4H), 1.68-1.64 (m, 4H), 1.50-1.45 (m, 2H), 1.28 (d, J = 6.6 Hz, 3H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 162.15, 160.70, 160.07, 157.23, 156.68, 155.51, 148.20, 117.53, 115.30, 106.31, 65.33, 53.93, 52.16, 48.89, 46.80, 45.13, 44.19, 38.60, 33.20, 30.38, 29.04, 14.37. MS (FAB) m/z: 466 $[M+H]^+$. HRMS (FAB) m/z: calcd for $C_{26}H_{33}FN_5O_2$ 466.2618, found 466.2625.

2-((R)-4-(4-Chlorophenyl)-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide ***(17b)***. Compound **17b** was prepared according to the procedure of **13h** from intermediate **16** and 1-bromo-4-chlorobenzene in 62% yield. Mp: 98 °C. ^{1}H NMR (800 MHz, DMSO-d_6) δ 8.64 (d, J = 4.7 Hz, 1H), 8.22 (d, J = 7.9 Hz, 1H), 7.25-7.23 (m, 2H), 7.14 (d, J = 4.7 Hz, 1H), 6.99-6.97 (m, 2H), 4.88-4.83 (m, 1H), 4.50 (s, 1H), 4.49-4.46 (m, 1H), 3.96-3.93 (m, 1H), 3.74-3.70 (m, 1H), 3.66-3.63 (m, 1H), 3.43-3.38 (m, 1H), 3.05-3.01 (m, 1H), 2.85-2.80 (m, 1H), 2.10-2.05 (m, 3H), 1.78-1.72 (m, 4H), 1.68-1.64 (m, 4H), 1.49-1.45 (m, 2H), 1.25 (d, J = 6.7 Hz, 3H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 162.11, 160.69, 160.03, 157.20, 150.01, 128.62, 122.16, 116.82, 106.31, 65.32, 52.41, 52.14, 47.68, 47.02, 45.13, 44.18, 38.45, 33.20, 30.37, 29.03, 14.57. MS (FAB) m/z: 482 $[M+H]^+$. HRMS (FAB) m/z: calcd for $C_{26}H_{33}ClN_5O_2$ 482.2323, found 482.2319.

*N-((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)-2-((R)-2-methyl-4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)pyrimidine-4-carboxamide (**17c**).* Compound **17c** was prepared according to the procedure of **13h** from intermediate **16** and 1-bromo-4-(trifluoromethyl)benzene in 50% yield. Mp: 156 °C. ^{1}H NMR (800 MHz, DMSO-d_6) δ 8.64 (d, J = 4.7 Hz, 1H), 8.23 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 4.7 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 4.85-4.80 (m, 1H), 4.50 (s, 1H), 4.46-4.41 (m, 1H), 3.97-3.93 (m, 1H), 3.89-3.81 (m, 2H), 3.55-3.50 (m, 1H), 3.31-3.27 (m, 1H), 3.09-3.04 (m, 1H), 2.09 (brs, 3H), 1.79-1.73 (m, 4H), 1.69-1.64 (m, 4H), 1.50-1.45 (m, 2H), 1.24 (d, J = 6.6 Hz, 3H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 162.11, 160.71, 159.99, 157.19, 153.17, 126.21, 125.71, 124.37, 113.45, 106.32, 65.33, 52.14, 50.37, 47.53, 46.37, 45.14, 44.18, 38.40, 33.21, 30.37, 29.04, 15.01. MS (FAB) m/z: 516 $[M+H]^+$. HRMS (FAB) m/z: calcd for $C_{27}H_{33}F_3N_5O_2$ 516.2586, found 516.2590.

*2-((R)-4-(4-Cyanophenyl)-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide (**17d**).* Compound **17d** was prepared according to the procedure of **13h** from intermediate **16** and 4-bromobenzonitrile in 63% yield. Mp: 160 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.64 (d, J = 4.8 Hz, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.9 Hz, 2H), 7.15 (d, J = 4.8 Hz, 1H), 7.01 (d, J = 8.9 Hz, 2H), 4.81-4.74 (m, 1H), 4.49 (s, 1H), 4.41-4.36 (m, 1H), 3.97-3.93 (m, 1H), 3.90-3.84 (m, 2H), 3.60-3.54 (m, 1H), 3.43-3.37 (m, 1H), 3.19-3.13 (m, 1H), 2.08 (brs, 3H), 1.79-1.71 (m, 4H), 1.69-1.63 (m, 4H), 1.50-1.44 (m, 2H), 1.21 (d, J = 6.4 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.06, 160.66, 159.92, 157.16, 152.99, 133.33, 120.10, 113.12, 106.32, 97.40, 65.30, 52.11, 49.35, 47.84, 45.78, 45.12, 44.17, 38.36, 33.21, 30.36, 29.03, 15.23. MS (FAB) m/z: 473 $[M+H]^+$. HRMS (FAB) m/z: calcd for $C_{27}H_{33}N_6O_2$ 473.2665, found 473.2667.

*N-((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)-2-((R)-2-methyl-4-(4-(methylsulfonyl)phenyl)piperazin-1-yl)pyrimidine-4-carboxamide (**17e**).* Compound **17e** was prepared according to the procedure of **13h** from intermediate **16** and 1-bromo-4-(methylsulfonyl)benzene in 58% yield. Mp: 230 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.64 (d, J = 4.8 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 8.9 Hz, 2H), 7.15 (d, J = 4.8 Hz, 1H), 7.07 (d, J = 8.9 Hz, 2H), 4.83-4.77 (m, 1H), 4.49 (s, 1H), 4.43-4.38 (m, 1H), 3.97-3.94 (m, 1H), 3.93-3.86 (m, 2H), 3.60-3.54 (m, 1H), 3.42-3.37 (m, 1H), 3.19-3.13 (m, 1H), 3.09 (s, 3H), 2.08 (brs, 3H), 1.79-1.72 (m, 4H), 1.69-1.64 (m, 4H), 1.51-1.45 (m, 2H), 1.22 (d, J = 6.4 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.07, 160.68, 159.94, 157.17, 153.62, 128.60, 127.68, 112.64, 106.32, 65.32, 52.12, 49.69, 47.76, 46.05, 45.13, 44.28, 44.17, 38.41, 33.22, 30.37, 29.04, 15.19. MS (FAB) m/z: 526 $[M+H]^+$. HRMS (FAB) m/z: calcd for $C_{27}H_{36}N_5O_4S$ 526.2488, found 526.2492.

*N-((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)-2-((R)-4-(4-(2-hydroxypropan-2-yl)phenyl)-2-methylpiperazin-1-yl)pyrimidine-4-carboxamide (**17f**).* Compound **17f** was prepared according to the procedure of **13h** from intermediate **16** and 2-(4-bromophenyl)propan-2-ol in 47% yield. Mp: 173 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.63 (d, J = 4.8 Hz, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 4.8 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 4.91-4.85 (m, 1H), 4.81 (s, 1H), 4.53-4.48 (m, 1H), 4.49 (s, 1H), 3.97-3.93 (m, 1H), 3.73-3.68 (m, 1H), 3.62-3.57 (m, 1H), 3.40-3.33 (m, 1H), 2.95-2.90 (m, 1H), 2.76-2.70 (m, 1H), 2.09 (brs, 3H), 1.79-1.72 (m, 4H), 1.69-1.64 (m, 4H), 1.51-1.44 (m, 2H), 1.39 (s, 6H), 1.28 (d, J = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.12, 160.66, 160.08, 157.19, 149.45, 141.33, 125.11, 115.17, 106.24, 70.21, 65.32, 53.36, 52.15, 48.48, 46.86, 45.13, 44.18, 38.67, 33.20, 32.01, 30.38, 29.03, 14.44. MS (FAB) m/z: 505 $[M^+]$. HRMS (FAB) m/z: calcd for $C_{29}H_{39}N_5O_3$ 505.3053, found 505.3051.

*2-((R)-4-(2-Fluoro-4-(2-hydroxypropan-2-yl)phenyl)-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide (**17g**).* Compound **17g** was prepared according to the procedure of **13h** from intermediate **16** and 2-(4-bromo-3-fluorophenyl)propan-2-ol in 54% yield. Mp: 140 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.63 (d, J = 4.6 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.21 (dd, J = 1.8, 14.2 Hz, 1H), 7.16 (dd, J = 1.8, 8.3 Hz, 1H), 7.14 (d, J = 4.6 Hz, 1H), 6.98 (t, J = 8.9 Hz, 1H), 5.01 (s, 1H), 4.93-4.87 (m, 1H), 4.58-4.53 (m, 1H), 4.49 (s, 1H), 3.97-3.93 (m, 1H), 3.43-3.39 (m, 1H), 3.36-3.29 (m, 2H), 2.90-2.86 (m, 1H), 2.80-2.74 (m, 1H), 2.11-2.05 (m, 3H), 1.78-1.71 (m, 4H), 1.69-1.63 (m, 4H), 1.50-1.44 (m, 2H), 1.39 (s, 6H), 1.32 (d, J = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.14, 160.66, 160.09, 157.23, 155.37, 153.76, 145.81, 137.80, 120.55, 118.65, 112.40, 106.34, 70.13, 65.32, 55.38, 52.19, 49.96, 46.55, 45.13, 44.18, 38.78, 33.17, 31.77, 30.37, 29.02, 14.04, MS (FAB) m/z: 523 [M^+]. HRMS (FAB) m/z: calcd for $C_{29}H_{38}FN_5O_3$ 523.2959, found 523.2960.

*2-((R)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide (**18a**).* Compound **18a** was prepared according to the procedure of **13h** from intermediate **16** and 1-bromo-2-fluoro-4-(methylsulfonyl)benzene in 50% yield. Mp: 197 °C. ^{1}H NMR (800 MHz, DMSO-d_6) δ 8.64 (d, J = 4.8 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.68 (dd, J = 2.2, 12.4 Hz, 1H), 7.65 (dd, J = 2.2, 8.5 Hz, 1H), 7.25 (t, J = 8.5 Hz, 1H), 7.16 (d, J = 4.8 Hz, 1H), 4.93-4.88 (m, 1H), 4.56-4.52 (m, 1H), 4.49 (s, 1H), 3.96-3.93 (m, 1H), 3.67-3.63 (m, 1H), 3.59-3.56 (m, 1H), 3.41-3.37 (m, 1H), 3.20 (s, 3H), 3.14-3.11 (m, 1H), 3.01-2.98 (m, 1H), 2.10-2.05 (m, 3H), 1.78-1.72 (m, 4H), 1.68-1.63 (m, 4H), 1.49-1.44 (m, 2H), 1.29 (d, J = 6.7 Hz, 3H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 162.11, 160.71, 160.02, 157.25, 153.70, 152.47, 144.26, 132.51, 124.32, 118.90, 115.09, 106.50, 65.33, 53.99, 52.21, 48.87, 46.66, 45.13, 44.19, 43.70, 38.43,

33.19, 30.37, 29.03, 14.11. MS (FAB) *m*/*z*: 544 $[M+H]^+$. HRMS (FAB) *m*/*z*: calcd for $C_{27}H_{35}FN_5O_4S$ 544.2394, found 544.2386.

2-((R)-4-(2-Chloro-4-(methylsulfonyl)phenyl)-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide ***(18b)****.* Compound **18b** was prepared according to the procedure of **13h** from intermediate **16** and 1-bromo-2-chloro-4-(methylsulfonyl)benzene in 41% yield. Mp: 142 °C. ^{1}H NMR (800 MHz, DMSO-d_6) δ 8.65 (d, J = 4.7 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 2.2 Hz, 1H), 7.83 (dd, J = 2.2, 8.5 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 4.7 Hz, 1H), 4.98-4.93 (m, 1H), 4.62-4.58 (m, 1H), 4.49 (brs, 1H), 3.96-3.93 (m, 1H), 3.54-3.49 (m, 2H), 3.40-3.36 (m, 1H), 3.24 (s, 3H), 3.02-2.98 (m, 1H), 2.94-2.90 (m, 1H), 2.09 (brs, 2H), 2.07 (brs, 1H), 1.78-1.72 (m, 4H), 1.68-1.63 (m, 4H), 1.49-1.44 (m, 2H), 1.36 (d, J = 6.7 Hz, 3H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 162.16, 160.71, 160.02, 157.30, 153.38, 135.15, 129.18, 127.26, 127.16, 121.31, 106.51, 65.32, 54.82, 52.25, 50.37, 46.70, 45.13, 44.19, 43.58, 38.58, 33.16, 30.38, 29.03, 14.05. MS (FAB) *m*/*z*: 560 $[M+H]^+$. HRMS (FAB) *m*/*z*: calcd for $C_{27}H_{35}ClN_5O_4S$ 560.2098, found 560.2090.

N-((1R,2s,3S,5S,7S)-5-Hydroxyadamantan-2-yl)-2-((R)-2-methyl-4-(2-methyl-4-(methylsulfonyl)phenyl)piperazin-1-yl)pyrimidine-4-carboxamide ***(18c)****.* Compound **18c** was prepared according to the procedure of **13h** from intermediate **16** and 1-bromo-2-methyl-4-(methylsulfonyl)benzene in 63% yield. Mp: 208 °C. ^{1}H NMR (800 MHz, DMSO-d_6) δ 8.65 (d, J = 4.8 Hz, 1H), 8.19 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.70 (dd, J = 2.2, 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 4.8 Hz, 1H), 4.95-4.90 (m, 1H), 4.60-4.55 (m, 1H), 4.49 (s, 1H), 3.96-3.93 (m, 1H), 3.40-3.36 (m, 1H), 3.32-3.29 (m, 1H), 3.25-3.21 (m, 1H), 3.16 (s, 3H), 2.96-2.93 (m, 1H), 2.83-2.79 (m, 1H), 2.09 (brs, 2H), 2.06 (brs, 1H), 1.77-1.71 (m, 4H), 1.68-1.63 (m, 4H), 1.49-1.44 (m, 2H), 1.37 (d, J = 6.6 Hz, 3H). ^{13}C NMR (200

MHz, DMSO-d_6) δ 162.19, 160.71, 160.06, 157.30, 155.85, 134.34, 132.70, 129.51, 125.86, 119.30, 106.43, 65.34, 55.38, 52.24, 50.94, 46.75, 45.13, 44.19, 43.84, 38.85, 33.16, 30.38, 29.02, 18.23, 14.03. MS (FAB) *m*/*z*: 540 $[M+H]^+$. HRMS (FAB) *m*/*z*: calcd for $C_{28}H_{38}N_5O_4S$ 540.2645, found 540.2643.

*2-((R)-4-(2,5-Difluoro-4-(methylsulfonyl)phenyl)-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide (**18d**).* To a solution of **16** (50 mg, 0.135 mmol) and potassium carbonate (56 mg, 0.405 mmol) in DMF (1.5 mL) was added 1,2,4-trifluoro-5-(methylsulfonyl)benzene (85 mg, 0.405 mmol). The reaction mixture was stirred at 130 ºC for 18 h and then cooled to room temperature. The mixture was diluted with EtOAc (10 mL), washed with saturated aqueous NH_4Cl (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3% MeOH in CH_2Cl_2) to afford **18d** (52 mg, 69%) as a pale yellow solid. Mp: 212 °C. ^{1}H NMR (800 MHz, DMSO-d_6) δ 8.64 (d, J = 4.8 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.50 (dd, J = 6.6, 12.4 Hz, 1H), 7.17-7.14 (m, 2H), 4.91-4.86 (m, 1H), 4.52-4.48 (m, 1H), 4.49 (s, 1H), 3.96-3.93 (m, 1H), 3.75-3.71 (m, 1H), 3.68-3.64 (m, 1H), 3.44-3.40 (m, 1H), 3.28 (s, 3H), 3.24-3.20 (m, 1H), 3.09-3.05 (m, 1H), 2.10-2.05 (m, 3H), 1.78-1.72 (m, 4H), 1.68-1.63 (m, 4H), 1.49-1.44 (m, 2H), 1.26 (d, J = 6.7 Hz, 3H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 162.09, 160.72, 159.96, 157.25, 156.43, 155.19, 149.07, 147.86, 145.96, 117.88, 116.01, 106.67, 106.54, 65.33, 53.36, 52.20, 48.56, 46.78, 45.13, 44.19, 43.92, 38.26, 33.19, 30.37, 29.04, 14.24. MS (FAB) *m*/*z*: 562 $[M+H]^+$. HRMS (FAB) *m*/*z*: calcd for $C_{27}H_{34}F_2N_5O_4S$ 562.2300, found 562.2303.

*2-((R)-4-(2,6-Difluoro-4-(methylsulfonyl)phenyl)-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide (**18e**).* Compound **18e** was prepared according to the procedure of **18d** from intermediate **16** and 1,2,3-trifluoro-5-

(methylsulfonyl)benzene in 35% yield. Mp: 197 °C. ^{1}H NMR (800 MHz, DMSO-d_6) δ 8.64 (d, J = 4.8 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H), 7.64-7.61 (m, 2H), 7.15 (d, J = 4.8 Hz, 1H), 4.92-4.87 (m, 1H), 4.55-4.51 (m, 1H), 4.49 (s, 1H), 3.96-3.92 (m, 1H), 3.54-3.51 (m, 1H), 3.43-3.39 (m, 1H), 3.38-3.35 (m, 1H), 3.34-3.31 (m, 1H), 3.30-3.27 (m, 1H), 3.27 (s, 3H), 2.09 (brs, 2H), 2.06 (brs, 1H), 1.77-1.71 (m, 4H), 1.67-1.62 (m, 4H), 1.48-1.43 (m, 2H), 1.29 (d, J = 6.7 Hz, 3H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 162.15, 160.67, 160.16, 157.27, 156.48, 155.24, 133.67, 132.76, 111.91, 106.51, 65.34, 54.83, 52.25, 50.04, 46.80, 45.13, 44.19, 43.24, 38.96, 33.15, 30.36, 29.02, 13.67. MS (FAB) m/z: 562 $[M+H]^+$. HRMS (FAB) m/z: calcd for $C_{27}H_{34}F_2N_5O_4S$ 562.2300, found 562.2296.

*2-((R)-4-(4-(Ethylsulfonyl)-2-fluorophenyl)-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide (**18f**).* Compound **18f** was prepared according to the procedure of **18d** from intermediate **16** and 4-(ethylsulfonyl)-1,2-difluorobenzene in 60% yield. Mp: 227 °C. ^{1}H NMR (800 MHz, DMSO-d_6) δ 8.65 (d, J = 4.8 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.64-7.60 (m, 2H), 7.26 (t, J = 8.5 Hz, 1H), 7.16 (d, J = 4.8 Hz, 1H), 4.93-4.89 (m, 1H), 4.56-4.52 (m, 1H), 4.49 (s, 1H), 3.96-3.93 (m, 1H), 3.69-3.65 (m, 1H), 3.61-3.58 (m, 1H), 3.42-3.38 (m, 1H), 3.27 (q, J = 7.4 Hz, 2H), 3.16-3.13 (m, 1H), 3.03-2.99 (m, 1H), 2.11-2.06 (m, 3H), 1.78-1.72 (m, 4H), 1.68-1.64 (m, 4H), 1.49-1.45 (m, 2H), 1.30 (d, J = 6.6 Hz, 3H), 1.10 (t, J = 7.4 Hz, 3H). ^{13}C NMR (200 MHz, DMSO-d_6) δ 162.13, 160.72, 160.02, 157.27, 153.71, 152.48, 144.36, 129.93, 125.25, 118.89, 115.73, 106.51, 65.33, 53.94, 52.21, 49.28, 48.81, 46.68, 45.14, 44.19, 38.43, 33.18, 30.37, 29.03, 14.13, 7.20. MS (FAB) m/z: 558 $[M+H]^+$. HRMS (FAB) m/z: calcd for $C_{28}H_{37}FN_5O_4S$ 558.2550, found 558.2549.

11β-HSD1 Inhibition Assays. *In vitro* 11β-HSD1 assays were performed using procedures that were previously described.[28,39] For the biochemical enzyme assays, HEK293

cell lysates overexpressing human or mouse 11β-HSD1 were mixed with cortisone and different doses of test compounds in sodium phosphate buffer that contained the cofactor NADPH in a regenerating-system solution (BD Gentest™; BD Biosciences, San Jose, CA). These mixtures were incubated at 37°C for 1 h, and the supernatants were harvested for cortisol measurement. For the cell-based assay, HEK293 cells stably transfected with human 11β-HSD1 cDNA were pretreated with test compounds for 30 min, followed by incubation with cortisone for 2 h, and the culture media were collected for cortisol measurement. The activity of 11β-HSD1 was determined by measuring the conversion of cortisone to cortisol using a commercially available cortisol enzyme-linked immunosorbent assay (ELISA) kit (Assay Designs, Ann Arbor, MI). Relative cortisol levels were plotted as the percent inhibition, and the half maximal inhibitory concentration (IC_{50}) values were calculated using Prism software (GraphPad, San Diego, CA) with the sigmoidal dose-response curve-fitting option.

CYP Inhibition Assay. The test compound (0.1 μM - 10 μM) was incubated with human liver microsomes (1 mg/mL) and NADPH (1 mM) in the presence of a cytochrome P450 isoform-specific probe substrate (Phenacetin for CYP1A2, diclofenac for CYP2C9, mephenytoin for CYP2C19, dextromethorphan for CYP2D6, and midazolam for CYP3A4) in a 37ºC water bath for 10 min. The reactions were terminated by adding ice cold acetonitrile containing an internal standard followed by vortex-mixing. The samples were then centrifuged at 13,000 rpm for 10 min at 4ºC to precipitate the microsomal proteins. After centrifugation, the supernatants were analyzed by an LC-MS/MS system (API4000 Qtrap, AB SCIEX). For each isoform, except for CYP1A2, a selective inhibitor (sulfaphenazole for CYP2C9, ticlopidine for CYP2C19, quinidine for CYP2D6, and ketoconazole for CYP3A4) was used as a positive control. The IC_{50} values were calculated by non-linear regression

analysis from the plotted remaining metabolic activity at each test compound concentration using GraphPad Prism 4.0.

Animal Husbandry. Eight-week old male C57BL/6 and C57BL/6-*Lep*^{ob} (*ob*/*ob*) mice (Charles River Laboratories Japan, Yokohama, Japan) were used in this study. All the mice were housed in a controlled environment with 22±2 °C temperature, 50±10% humidity, and lights on 07:00-19:00 h. Food and drinking water were available *ad libitum*. All of the animal-experiment protocols were approved beforehand, and all experiments were conducted in accordance with the Guides for Care and Use of Laboratory Animals provided by the Institutional Animal Care and Use Committee of SK Chemicals.

Pharmacodynamic Assay. The *ex vivo* assay was performed using a procedure that was previously described.[33,39] Briefly, male C57BL/6 mice were orally administered, once, the vehicle (sterile water containing 0.5% methylcellulose and 1% Tween80) or test compounds. The animals were sacrificed at 2 or 6 h after administration, and liver and epididymal fat pads were collected. The inhibition of 11β-HSD1 enzyme activity in liver and epididymal fat tissues was assessed by measurement of cortisone-to-cortisol conversion in tissue-culture media that contained cortisone using a commercially available cortisol enzyme-linked immunosorbent assay (ELISA) kit (Assay Designs, Ann Arbor, MI).

***Ob/ob* Mouse Model Study**. Eight-week old male *ob*/*ob* mice were subjected to oral administrations, once a day for 25 days, of vehicle (sterile water containing 0.5% methylcellulose and 1% Tween80), compound **18a** (20 mg/kg) alone, metformin (300 mg/kg) alone, or a combination of compound **18a** plus metformin. The initial postprandial glucose (GM9 glucose analyzer; Analox Instruments, London, UK) and blood HbA1c (DCA Vantage Analyzer; Siemens Healthcare, Erlangen, Germany) levels were measured from blood samples that were collected via tail veins prior to the start of compound administration to

verify that these levels were not different among mice. At the end of the study, the postprandial glucose and blood HbA1c levels were measured, and circulating levels of lipids (total cholesterols, LDL cholesterols, and triglycerides) were analyzed by a biochemical analyzer (AU480; Beckman Coulter, Brea, CA) using trunk blood samples that were collected from vena cava or cardiac puncture.

ASSOCIATED CONTENT

Supporting Information

Spectroscopic data of final compounds and toxicokinetic data of **18a** can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Phone: +82 2 880 7871. Fax: +82 2 872 9129. E-mail: hgpk@snu.ac.kr.

Present Addresses

[§]For S. K.: New Drug Development Center, Daegu-Gyeongbuk Medical Innovation Foundation, Daegu, 41061, Korea. E-mail: shinaekim@dgmif.re.kr.

[||] For J.-S. K.: J2H Biotech, Ansan-Si, Danwon-Gu, Sandan-Ro 349, Gyeonggi-Do, Korea. E-mail: jsbach@j2hbio.com.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. Gildon Choi for generating and providing HEK293 cells that were stably transfected with 11β-HSD1 and Hyun Jung Lee for the cell biology contributions.

ABBREVIATIONS USED

11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; ACN, acetonitrile; AUC, area under the curve; BINAP, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; CL, clearance; CYP, cytochrome P450; DCM, dichloromethane; DIO, diet-induced obesity; DIPEA, *N*,*N*-diisopropylethylamine; DMF, *N*,*N*-dimethylformamide; DPP-4, dipeptidyl peptidase-4; ELISA, enzyme-linked immunosorbent assay; EPF, epididymal fat; HbA1c, glycosylated hemoglobin; HBTU, *N,N,N′,N′*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate; HEK, human embryonic kidney; IND, investigational new drug; LDL, low-density lipoprotein; MLM, mouse liver microsome; MST, metabolic stability test; NADPH, nicotinamide adenine dinucleotide phosphate; NOAEL, no-observed-adverse-effect level; PD, pharmacodynamic; PDE, phosphodiesterase; PK, pharmacokinetic; PXR, pregnane X receptor; SAR, structure-activity relationship; SE, standard error; TFA, trifluoroacetic acid; UGT, uridine diphosphate glucuronosyltransferase.

REFERENCES

(1) *Diabetes Atlas*, 4th ed.; International Diabetes Federation (IDF): Brussels, Belgium, 2009.

(2) Day, C. Metabolic syndrome, or what you will: definitions and epidemiology. *Diabetes Vasc. Dis. Res*. **2007**, *4*, 32-38.

(3) Walker, B. R.; Seckl, J. R. 11β-Hydroxysteroid dehydrogenase type 1 as a novel therapeutic target in metabolic and neurodegenerative disease. *Expert Opin. Ther. Targets* **2003**, *7*, 771-783.

(4) Andrews, R. C.; Rooyackers, O.; Walker, B. R. Effects of the 11β-hydroxysteroid dehydrogenase inhibitor carbenoxolone on insulin sensitivity in men with type 2 diabetes. *J. Clin. Endocrinol. Metab.* **2003**, *88*, 285-291.

(5) Alberts, P.; Nilsson, C.; Selen, G.; Engblom, L. O. M.; Edling, N. H. M.; Norling, S.; Klingstrom, G.; Larsson, C.; Forsgren, M.; Ashkzari, M.; Nilsson, C. E.; Fiedler, M.; Bergqvist, E.; Ohman, B.; Bjorkstrand, E.; Abrahmsen, L. B. Selective inhibition of 11β-hydroxysteroid dehydrogenase type 1 improves hepatic insulin sensitivity in hyperglycemic mice strains. *Endocrinology* **2003**, *144*, 4755-4762.

(6) Stulnig, T. M.; Waldhausl, W. 11β-Hydroxysteroid dehydrogenase type 1 in obesity and type 2 diabetes. *Diabetologia* **2004**, *47*, 1-11.

(7) Joharapurkar, A.; Dhanesha, N.; Shah, G.; Kharul, R.; Jain, M. 11β-Hydroxysteroid dehydrogenase type 1: potential therapeutic target for metabolic syndrome. *Pharmacol. Rep.* **2012**, *64*, 1055-1065.

(8) Tomlinson, J. W.; Walker, E. A.; Bujalska, I. J.; Draper, N.; Lavery, G. G.; Cooper, M. S.; Hewison, M.; Stewart, P. M. 11β-Hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. *Endocr. Rev*. **2004**, *25*, 831-866.

(9) Seckl, J. R.; Walker, B. R. 11β-Hydroxysteroid dehydrogenase type 1 as a modulator of glucocorticoid action: from metabolism to memory. *Trends Endocrinol. Metab*. **2004**, *15*, 418-424.

(10) Draper, N.; Stewart, P. M. 11β-Hydroxysteroid dehydrogenase and the pre-receptor regulation of corticosteroid hormone action. *J. Endocrinol*. **2005**, *186*, 251-271.

(11) Thieringer, R.; Hermanowski-Vosatka, A. Inhibition of 11β-HSD1 as a novel treatment for the metabolic syndrome: do glucocorticoids play a role? *Expert Rev. Cardiovasc. Ther*. **2005**, *3*, 911-924.

(12) Masuzaki, H.; Paterson, J.; Shinyama, H.; Morton, N. M.; Mullins, J. J.; Seckl, J. R.; Flier, J. S. A transgenic model of visceral obesity and the metabolic syndrome. *Science* **2001**, *294*, 2166-2170.

(13) Masuzaki, H.; Yamamoto, H.; Kenyon, C. J.; Elmquist, J. K.; Morton, N. M.; Paterson, J. M.; Shinyama, H.; Sharp, M. G.; Fleming, S.; Mullins, J. J.; Seckl, J. R.; Flier, J. S. Transgenic amplification of glucocorticoid action in adipose tissue causes high blood pressure in mice. *J. Clin. Invest.* **2003**, *112*, 83-90.

(14) Paterson, J. M.; Morton, N. M.; Fievet, C.; Kenyon, C. J.; Holmes, M. C.; Staels, B.; Seckl, J. R.; Mullins, J. J. Metabolic syndrome without obesity: hepatic over-expression of 11β-hydroxysteroid dehydrogenase type 1 in transgenic mice. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 7088-7093.

(15) Morton, N. M.; Holmes, M. C.; Fievet, C.; Staels, B.; Tailleux, A.; Mullins, J. J.; Seckl, J. R. Improved lipid and lipoprotein profile, hepatic insulin sensitivity, and glucose tolerance in 11β-hydroxysteroid dehydrogenase type 1 null mice. *J. Biol. Chem*. **2001**, *276*, 41293-41300.

(16) Morton, N. M.; Paterson, J. M.; Masuzaki, H.; Holmes, M. C.; Staels, B.; Fievet, C.; Walker, B. R.; Filler, J. S.; Mullins, J. J.; Seckl, J. R. Novel adipose tissue-mediated resistance to diet-induced visceral obesity in 11β-hydroxysteroid dehydrogenase type 1-deficient mice. *Diabetes* **2004**, *53*, 931-938.

(17) Morgan, S. A.; Tomlinson, J. W. 11β-Hydroxysteroid dehydrogenase type 1 inhibitors for the treatment of type 2 diabetes. *Expert Opin. Invest. Drugs* **2010**, *19*, 1067-1076.

(18) Sun, D.; Wang, M.; Wang, Z. Small molecule 11β-hydroxysteroid dehydrogenase type 1 inhibitors. *Curr. Top. Med. Chem*. **2011**, *11*, 1464-1475.

(19) Scott, J. S.; Goldberg, F. W.; Turnbull, A. V. Medicinal chemistry of inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). *J. Med. Chem*. **2014**, *57*, 4466-4486.

(20) Rosenstock, J.; Banarer, S.; Fonseca, V. A.; Inzucchi, S. E.; Sun, W.; Yao, W.; Hollis, G.; Flores, R.; Levy, R.; Williams, W. V.; Seckl, J. R.; Huber, R. The 11-β-hydroxysteroid dehydrogenase type 1 inhibitor INCB13739 improves hyperglycemia in patients with type 2 diabetes inadequately controlled by metformin monotherapy. *Diabetes Care* **2010**, *33*, 1516-1522.

(21) Feig, P. U.; Shah, S.; Hermanowski-Vosatka, A.; Plotkin, D.; Springer, M. S.; Donahue, S.; Thach, C.; Klein, E. J.; Lai, E.; Kaufman, K. D. Effects of an 11β-hydroxysteroid dehydrogenase type 1 inhibitor, MK-0916, in patients with type 2 diabetes mellitus and metabolic syndrome. *Diabetes, Obes. Metab.* **2011**, *13*, 498-504.

(22) Shah, S.; Hermanowski-Vosatka, A.; Gibson, K.; Ruck, R. A.; Jia, G.; Zhang, J.; Hwang, P. M. T.; Ryan, N. W.; Langdon, R. B.; Feig, P. U. Efficacy and safety of the selective 11β-HSD-1 inhibitors MK-0736 and MK-0916 in overweight and obese patients with hypertension. *J. Am. Soc. Hypertens*. **2011**, *5*, 166-176.

(23) Bhat, B. G.; Hosea, N.; Fanjul, A.; Herrera, J.; Chapman, J.; Thalacker, F.; Stewart, P. M.; Rejto, P. A. Demonstration of proof of mechanism and pharmacokinetics and pharmacodynamic relationship with 4'-cyano-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide (PF-915275), an inhibitor of 11β-hydroxysteroid dehydrogenase type 1, in cynomolgus monkeys. *J. Pharmacol. Exp. Ther*. **2008**, *324*, 299-305.

(24) Courtney, R.; Stewart, P. M.; Toh, M.; Ndongo, M. N.; Calle, R. A.; Hirshberg, B. Modulation of 11β-hydroxysteroid dehydrogenase (11βHSD) activity biomarkers and

pharmacokinetics of PF-00915275, a selective 11βHSD1 inhibitor. *J. Clin. Endocrinol. Metab*. **2008**, *93*, 550-556.

(25) Veniant, M. M.; Hale, C.; Hungate, R. W.; Gahm, K.; Emery, M. G.; Jona, J.; Joseph, S.; Adams, J.; Hague, A.; Moniz, G.; Zhang, J.; Bartberger, M. D.; Li, V.; Syed, R.; Jordan, S.; Komorowski, R.; Chen, M. M.; Cupples, R.; Kim, K. W.; St. Jean Jr., D. J.; Johansson, L.; Henriksson, M. A.; Williams, M.; Vallgarda, J.; Fotsch, C.; Wang, M. Discovery of a potent, orally active 11β-hydroxysteroid dehydrogenase type 1 inhibitor for clinical study: identification of (*S*)-2-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-ylamino)-5-isopropyl-5-methylthiazol-4(5*H*)-one (AMG 221). *J. Med. Chem*. **2010**, *53*, 4481-4487.

(26) Scott, J. S.; Bowker, S. S.; deSchoolmeester, J.; Gerhardt, S.; Hargreaves, D.; Kilgour, E.; Lloyd, A.; Mayers, R. M.; Mc Coull, W.; Newcombe, N. J.; Ogg, D.; Packer, M. J.; Rees, A.; Revill, J.; Schofield, P.; Selmi, N.; Swales, J. G.; Whittamore, P. R. O. Discovery of a potent, selective, and orally bioavailable acidic 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor: discovery of 2-[(3*S*)-1-[5-cyclohexylcarbamoyl)-6-propylsulfanylpyridin-2-yl]-3-piperidyl]acetic acid (AZD4017). *J. Med. Chem*. **2012**, *55*, 5951-5964.

(27) Hamilton, B. S.; Himmelsbach, F.; Nar, H.; Schuler-Metz, A.; Krosky, P.; Guo, J.; Guo, R.; Meng, S.; Zhao, Y.; Lala, D. S.; Zhuang, L.; Claremon, D. A.; McGeehan, G. M. Pharmacological characterization of the selective 11β-hydroxysteroid dehydrogenase 1 inhibitor, BI 135585, a clinical candidate for the treatment of type 2 diabetes. *Eur. J. Pharmacol*. **2015**, *746*, 50-55.

(28) Ryu, J. H.; Kim, S.; Han, H. Y.; Son, H. J.; Lee, H. J.; Shin, Y. A.; Kim, J.-S.; Park, H.-g. Synthesis and biological evaluation of picolinamides as potent inhibitors of 11β-

hydroxysteroid dehydrogenase type 1 (11β-HSD1). *Bioorg. Med. Chem. Lett*. **2015**, *25*, 695-700.

(29) Ryu, J. H.; Kim, S.; Lee, J. A.; Han, H. Y.; Son, H. J.; Lee, H. J.; Kim, Y. H.; Kim, J.-S.; Park, H.-g. Synthesis and optimization of picolinamide derivatives as a novel class of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1679-1683.

(30) Tasler, S.; Mies, J.; Lang, M. Applicability aspects of transition metal-catalyzed aromatic amination protocols in medicinal chemistry. *Adv. Synth. Catal*. **2007**, *349*, 2286-2300.

(31) Suich, D. J.; Mousa, S. A.; Singh, G.; Liapakis, G.; Reisine, T.; Degrado, W. F. Template-constrained cyclic peptide analogues of somatostatin: subtype-selective binding to somatostatin receptors and antiangiogenic activity. *Bioorg. Med. Chem*. **2000**, *8*, 2229-2241.

(32) Wan, Z.-K.; Chenail, E.; Xiang, J.; Li, H.-Q.; Ipek, M.; Bard, J.; Svenson, K.; Mansour, T. S.; Xu, X.; Tian, X.; Suri, V.; Hahm, S.; Xing, Y.; Johnson, C. E.; Li, X.; Qadri, A.; Panza, D.; Perreault, M.; Tobin, J. F.; Saiah, E. Efficacious 11β-hydroxysteroid dehydrogenase type 1 inhibitors in the diet-induced obesity mouse model. *J. Med. Chem*. **2009**, *52*, 5449-5461.

(33) Johansson, L.; Fotsch, C.; Bartberger, M. D.; Castro, V. M.; Chen, M.; Emery, M.; Gustafsson, S.; Hale, C.; Hickman, D.; Homan, E.; Jordan, S. R.; Komorowski, R.; Li, A.; McRae, K.; Moniz, G.; Matsumoto, G.; Orihuela, C.; Palm, G.; Veniant, M.; Wang, M.; Williams, M.; Zhang, J. 2-Amino-1,3-thiazol-4(5*H*)-ones as potent and selective 11β-hydroxysteroid dehydrogenase type 1 inhibitors: enzyme-ligand co-crystal structure

and demonstration of pharmacodynamic effects in C57Bl/6 mice. *J. Med. Chem*. **2008**, *51*, 2933-2943.

(34) Xie, W.; Uppal, H.; Saini, S. P. S.; Mu, Y.; Little, J. M.; Radominska-Pandya, A.; Zemaitis, M. A. Orphan nuclear receptor-mediated xenobiotic regulation in drug metabolism. *Drug Discovery Today* **2004**, *9*, 442-449.

(35) Filling, C.; Berndt, K. D.; Benach, J.; Knapp, S.; Prozorovski, T.; Nordling, E.; Ladenstein, R.; Jörnvall, H.; Oppermann, U. Critical residues for structure and catalysis in short-chain dehydrogenases/reductases. *J. Biol. Chem.* **2002**, *277*, 25677-25684.

(36) Hosfield, D. J.; Wu, Y.; Skene, R. J.; Hilgers, M.; Jennings, A.; Snell, G. P.; Aertgeerts, A. Conformational flexibility in crystals structures of human 11β-hydroxysteroid dehydrogenase type 1 provide insights into glucocorticoid interconversion and enzyme regulation. *J. Biol. Chem.* **2005**, *280*, 4639-4648.

(37) Van Uum, S. H.; Lenders, J. W.; Hermus, A. R. Cortisol, 11β-hydroxysteroid dehydrogenases, and hypertension. *Semin. Vasc. Med*. **2004**, *4*, 121-128.

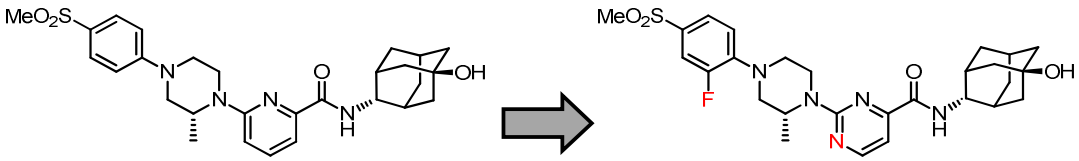
(38) Rankovic, Z. CNS Drug Design: Balancing physicochemical properties for optimal brain exposure. *J. Med. Chem.* **2015**, *58*, 2584-2608.

(39) Oh, H.; Jeong, K.-H.; Han, H. Y.; Son, H. J.; Kim, S. S.; Lee, H. J.; Kim, S.; Sa, J. H.; Jun, H.-S.; Ryu, J. H.; Choi, C. S. A potent and selective 11β-hydroxysteroid dehydrogenase type 1 inhibitor, SKI2852, ameliorates metabolic syndrome in diabetic mice models. *Eur. J. Pharmacol*. **2015**, *768*, 139-148.

(40) Inzucchi, S. E.; Bergenstal, R. M.; Buse, J. B.; Diamant, M.; Ferrannini, E.; Nauck, M.; Peters, A. L.; Tsapas, A.; Wender, R.; Matthews, D. R. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. *Diabetes Care* **2012**, *35*, 1364-1379.

(41) Bailey, C. J.; Day, C. Fixed-dose single tablet antidiabetic combinations. *Diabetes Obes. Metab*. **2009**, *11*, 527-533.

Table of Contents graphic



9

hHSD1 IC_{50} = 2.2 nM
mHSD1 IC_{50} = 1.8 nM
HEK293 IC_{50} = 3.1 nM
Mouse PK: *F* = 41%
CYP3A4 IC_{50} = 0.97 μM
CYP2C19 IC_{50} = 3.7 μM

18a

hHSD1 IC_{50} = 2.9 nM
mHSD1 IC_{50} = 1.6 nM
HEK293 IC_{50} = 4.4 nM
Mouse PK: *F* = 96%
CYP3A4 IC_{50} > 10 μM
CYP2C19 IC_{50} > 10 μM