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Design and Synthesis of Pyrimidinone and Pyrimidinedione Inhibitors of Dipeptidyl Peptidase IV†

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The discovery of two classes of heterocyclic dipeptidyl peptidase IV (DPP-4) inhibitors, pyrimidinones and pyrimidinediones, is described. After a single oral dose, these potent, selective, and noncovalent inhibitors provide sustained reduction of plasma DPP-4 activity and lowering of blood glucose in animal models of diabetes. Compounds **13a**, **27b**, and **27j** were selected for development.

Introduction

It is estimated that 246 million people worldwide have diabetes and that by 2025, 380 million will be afflicted. In addition, 3.8 million people die each year from diabetes. This is about the same number as those dying from HIV/AIDS.[1]

One approach to the treatment of type 2 diabetes is the use of incretin-based therapies. Glucagon-like-peptide-1 (GLP-1[a]) is an incretin hormone released in the gut following meals. Through activation of its G-protein-coupled receptor, this peptide stimulates insulin secretion, inhibits the release of glucagon, delays gastric emptying, and reduces food intake, among other effects.[2] As early as 1999, researchers in the area suggested that GLP-1-based therapies would be useful in the treatment of diabetes.[3] However, active GLP-1 is rapidly inactivated by the serine protease DPP-4, thus limiting its therapeutic practicality. Enhancing the duration of GLP-1 action is accomplished either through the use of stable GLP-1 analogues or by inhibiting the degradation of endogenous GLP-1 with DPP-4 inhibitors.[2] Indeed, drugs directed to these two approaches have been approved by the FDA (exenatide[4] and liraglutide,[5] GLP-1 analogues; sitagliptin[6] and saxagliptin,[7] both DPP-4 inhibitors).

Results and Discussion

As part of an effort to discover novel DPP-4 inhibitors, we applied high-throughput crystallography to solve the human DPP-4 protein structure. Our group was among the first with access to this important structure.[8] We were also able to solve numerous structures of small molecules from 14 different chemotypes bound to the DPP-4 active site.

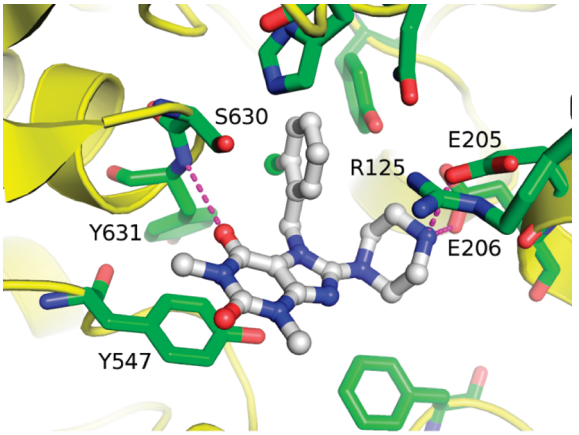

Figure 1. Cocrystal structure of **1** in the DPP-4 active site.

One of the approximately 80 cocrystal structures obtained was that of xanthine **1** (Figure 1).[9,10] This compound inhibits DPP-4 with an IC_{50} value of 2 μM. Our refined X-ray data revealed a hydrogen bond between Tyr631 and the carbonyl of the heterocycle, good occupancy of the S1 pocket by the chlorophenyl group, a salt bridge between the NH of the piperazine and Glu205/Glu206, and a π-stacking interaction between Tyr547 and the xanthine.

Xanthine **2**[11] inhibits DPP-4 with an IC_{50} value of approximately 5 nM. A cocrystal structure of **2** in the DPP-4 active site is shown in Figure 2.[12] Our data reveal differences between this cocomplex and that of **1** including a polar interaction between the cyano group and Arg125, and a bidentate salt bridge between the primary amino group at the 3-position of the piperidine and the protein. Taken together, these changes account for an improvement in potency of approximately 400-fold. To determine the preferred stereochemistry

†Crystal structures of cocomplexes with DPP-4 for compounds **1**, **2**, **13c**, and **27b** have been deposited into the Protein Data Bank: PDB codes 3G0C, 3G0D, 3G0G, and 3G0B.

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[a] Abbreviations: DPP-4, dipeptidyl peptidase IV; GLP-1, glucagon-like-peptide-1; RLM, rat liver microsomes; HLM, human liver microsomes; NT, not tested; PCM, Polarizable Continuum Model; AM1, Austin Model 1; VAMP, Vienna Ab Initio Molecular Dynamics Package; GAMESS-US, General Atomic and Molecular Electronic Structure System-United States; ALS, Advanced Light Source; 3-*R*-AP, 3-(*R*)-aminopiperidinyl.

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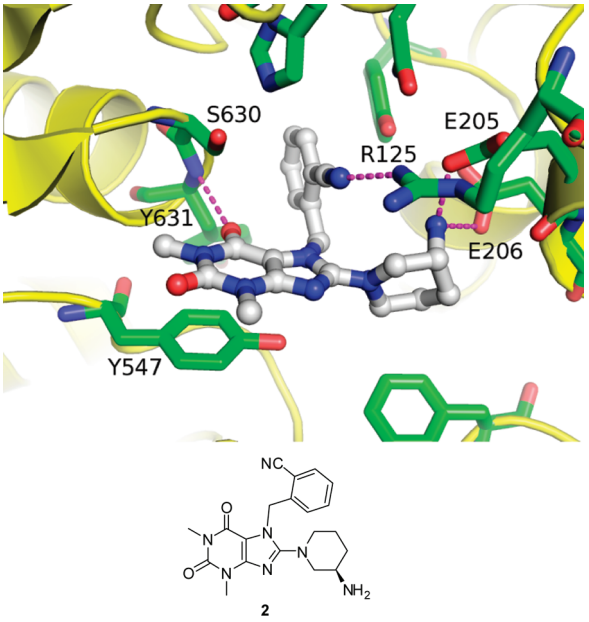


Figure 2. Cocrystal structure of **2** in the DPP-4 active site.

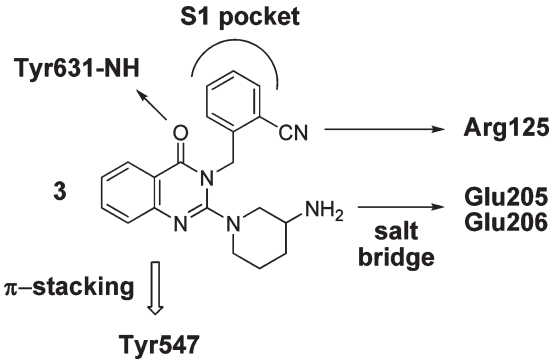


Figure 3. Structure-based design of compound **3**.

at the 3-position of the aminopiperidine, we prepared both enantiomers of **2**. We found the *R*-isomer to be approximately an order of magnitude more potent than the *S*-isomer.

Using this information and that from other cocrystal structures, we hypothesized that a quinazolinone scaffold could effectively display DPP-4 pharmacophores. Shown schematically in Figure 3, placing the aminopiperidine motif at C2 could provide the critical salt bridge to Glu205/Glu206, while a cyanobenzyl group at N3 was expected to effectively fill the S1 pocket (formed by Val656, Tyr631, Tyr662, Trp659, Tyr666, and Val711) and simultaneously interact with Arg125. The carbonyl at C4 was anticipated to provide an important hydrogen bond to the backbone NH of Tyr631, and the bicyclic heterocycle was predicted to π-stack with Tyr547.

Our hypothesis was borne out when **3** was found to have an IC_{50} of 10 nM against DPP-4. While **3** (Figure 4) and related quinazolinones were potent and selective inhibitors of DPP-4, they also resulted in cytochrome P450 inhibition and hERG blockade.[13] In an effort to find compounds having more favorable properties, we prepared a series of pyrimidinone DPP-4 inhibitors described by structure **4** (Figure 4). In addition, we examined replacement of the pyrimidinone ring with a pyrimidinedione ring as in structure **5** (Figure 4).

Compounds **13a**−**k** and **14** were synthesized according to the method depicted in Scheme 1. 2,4-Dichloropyrimidines **7** were readily synthesized from pyrimidinediones by chlorination with $POCl_3$. Selective hydrolysis with sodium hydroxide gave the chloropyrimidinones **8**. Alkylation of **8** with 2-cyanobenzyl bromide using the conditions of Curran and co-workers[14] gave a mixture of regioisomers, consistent with results from similar pyrimidinone alkylation methods.[15] The desired N3-alkylation products **9** were obtained, along with O-alkylation products **10** and N1-alkylation products **11**. The product distribution of this reaction was dependent on the substitution at R5 and R6. Higher ratios of desired N3-alkylation isomer were seen with less electron-deficient groups at R5. N1-Alkylation was not observed for compounds with substitution at R6. It was determined that the O-alkylated product was a kinetic product and could be minimized or eliminated with increasing reaction times. Finally, compounds **13a**−**k** were generated from compounds **9** by chloride displacement with 3-(*R*)-aminopiperidine.

The bromo compounds **13c** and **13d** served as versatile intermediates for the synthesis of a number of derivatives, without the need for amine protection prior to use (Scheme 2). Debromination of compound **13c** by way of a tributyltin hydride-mediated reduction led to compound **12**. Attempts at this transformation using hydrogenation led to debenzylation, even under mild reductive conditions. Aryl compounds **15a**−**g** were made using conventional Suzuki coupling conditions.[16] Compound **16** was synthesized by the direct displacement of bromide with pyrrolidine. Acetylene compounds **17a**−**d** were prepared using Sonogashira or Stille reactions.[16b] Vinylic compounds **18a**−**d** were made utilizing either Suzuki or Stille methods. Compounds **19**−**23** were prepared using the conditions developed for the synthesis of **13a**−**k**.

The pyrimidinedione inhibitors were prepared as shown in Scheme 3. Selective alkylation of **24b**,[14] methylation of **25b**, and displacement of chloride with 3-(*R*)-aminopiperidine gave **27b**. Compounds **27a** and **27c**−**p** were prepared in an analogous manner.

Data on the DPP-4 inhibitory potency, selectivity with respect to DPP-8 and metabolic stability for the pyrimidinones are shown in Table 1. At the outset of work on the pyrimidinones, it was not clear whether removal of the fused phenyl ring of the quinazolinone would result in a reduction in potency. However, as shown in Table 1, the pyrimidinones are potent inhibitors of DPP-4. Various groups at R5 were found

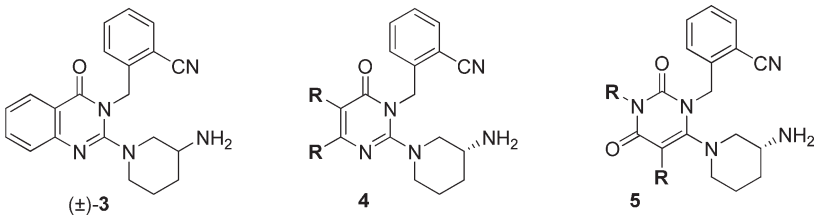
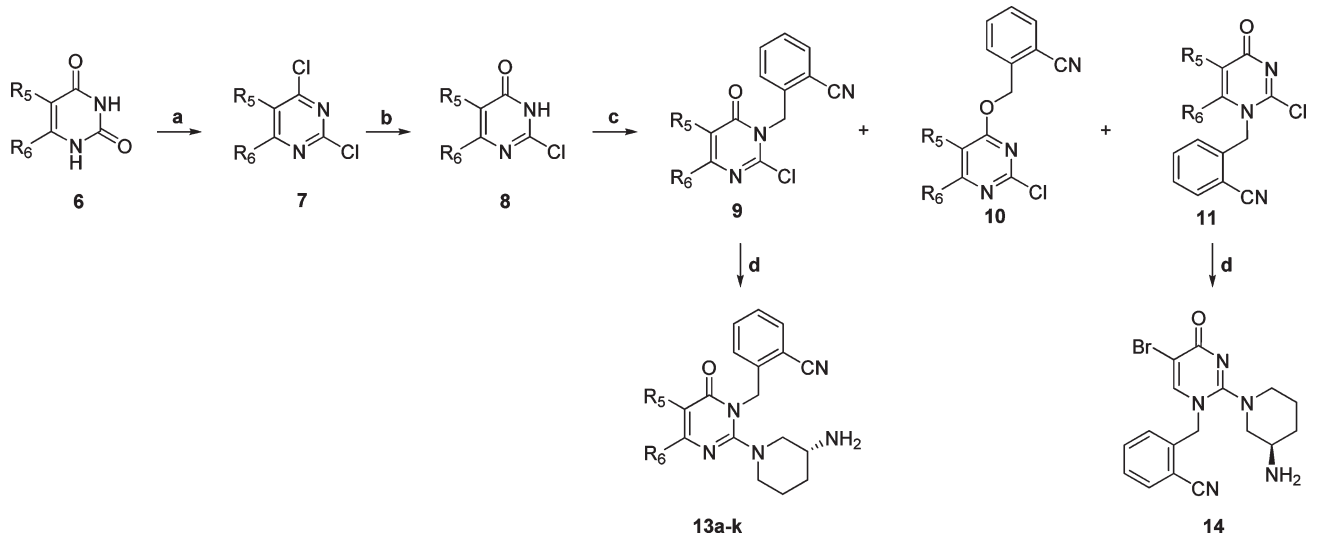


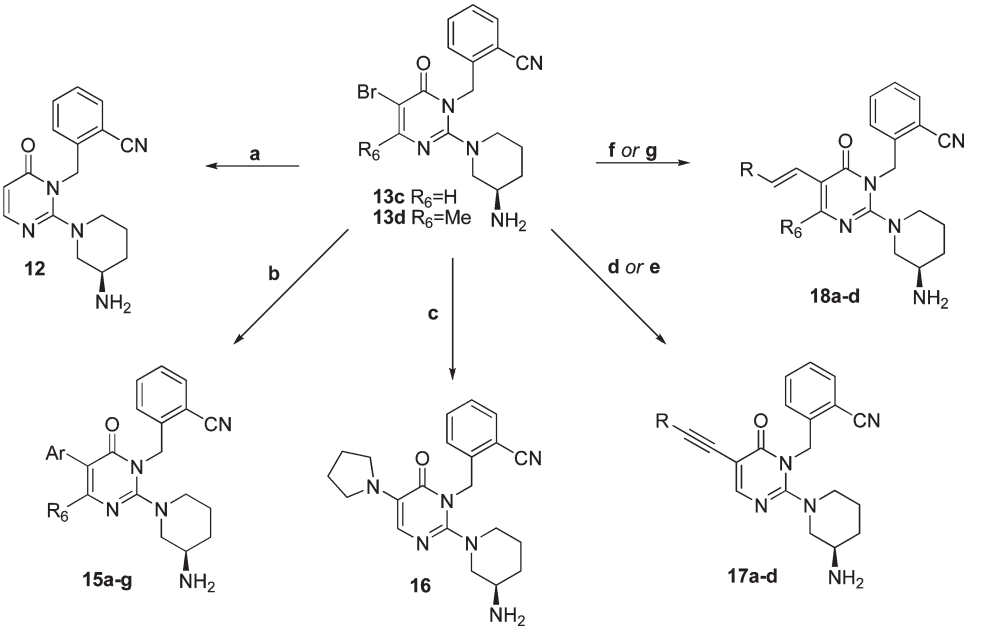
Figure 4. Quinazolinone, pyrimidinone, and pyrimidinedione inhibitors of DPP-4.

Scheme 1. Synthesis of Compounds **13a**−**k** and **14**[a]



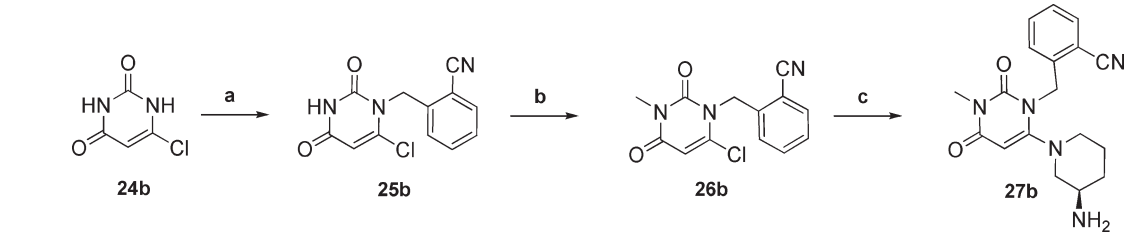
[a] Reagents: (a) $POCl_3$, dimethylaniline, reflux; (b) NaOH; (c) NaH, LiBr, 2-CN-benzyl bromide; (d) 3-(*R*)-aminopiperidine, $NaHCO_3$, 60 °C.

Scheme 2. Synthesis of Compounds **12** and **15a**−**18d**[a]



[a] Reagents: (a) Bu_3SnH, $Pd(Ph_3P)_4$, AIBN; (b) Ar-$B(OH)_2$, $Pd(Ph_3P)_4$, Na_2CO_3, DME; (c) pyrrolidine, 150 °C; (d) R-acetylene, Et_3N, Ph_3P, $PdCl_2(Ph_3P)_2$, CuI; (e) R-acetylenyl-$SnBu_3$, $Pd(Ph_3P)_4$, dioxane; (f) R-vinyl-$SnBu_3$, $Pd(Ph_3P)_4$, dioxane; (g) R-vinyl-$B(OH)_2$, $Pd(Ph_3P)_4$, Na_2CO_3, DME.

Scheme 3. Synthesis of Compound **27b**[a]

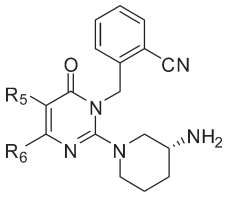


[a] Reagents: (a) NaH, 2-CN benzyl bromide, LiBr, DMF, DMSO, 54%; (b) NaH, CH_3I, THF, DMF, 72%; (c) 3-(*R*)-aminopiperidine, $NaHCO_3$, 100 °C, 70−76%.

to be well tolerated. Addition of a second substituent at R6 resulted in significant potency reduction (compare **15a**/**15b**, **15e**/**15f**).

N1-Alkylated regioisomers **14** were formed as minor side products in the synthesis of the desired N3-alkylated inhibitors **13**. When assessed for DPP-4 inhibition, the N1-alkylated

Table 1. Selected Data for Pyrimidinone Analogues



compd	R_5	R_6	DPP-4 IC_{50}, μM	DPP-8 IC_{50}, μM	RLM/HLM $t_{1/2}$, min
12	H	H	0.014 ± 0.004	> 100	131/ > 200
13a	F	H	0.006 ± 0.002	> 100	> 200/ > 200
13b	Cl	H	0.007 ± 0.001	> 100	199/ > 200
13c	Br	H	0.005 ± 0.001	> 100	94/ > 200
13d	Br	Me	0.008 ± 0.000	> 100	23/ > 200
13e	Br	*t*-Bu	7.400 ± 1.900	NT	NT/NT
13f	I	H	0.006 ± 0.002	> 100	59/161
13g	Me	Me	0.010 ± 0.001	> 100	10/ > 200
13h	Et	H	0.017 ± 0.000	NT	7/ > 200
13i	OMe	H	0.004 ± 0.000	> 100	20/ > 200
13j	H	Ph	0.023 ± 0.003	> 100	12/119
13k	$-(CH_2)_4-$		0.013 ± 0.000	NT	6/83
15a	Ph	H	0.023 ± 0.000	> 100	1/70
15b	Ph	Me	0.54 ± 0.19	NT	NT/NT
15c	2-F Ph	H	0.240 ± 0.068	> 100	NT/NT
15d	2-OMe Ph	H	0.99 ± 0.38	NT	NT/NT
15e	furan-3-yl	H	0.012 ± 0.004	> 100	4/56
15f	furan-3-yl	Me	0.077 ± 0.026	> 100	NT/NT
15g	pyrrol-3-yl	H	0.005 ± 0.001	> 100	71/61
16	pyrrolidin-1-yl	H	0.200 ± 0.055	NT	NT/NT
17a	ethyn-1-yl	H	0.005 ± 0.001	> 100	> 200/ > 200
17b	propyn-1-yl	H	0.005 ± 0.001	> 100	> 200/ > 200
17c	3-OH 1-propynyl	H	0.020 ± 0.006	> 100	> 200/ > 200
17d	3,3-dimethyl 1-butynyl	H	0.570 ± 0.130	NT	NT/NT
18a	ethen-1-yl	H	0.008 ± 0.000	> 100	6/164
18b	(*E*)-2-(phenyl)ethen-1-yl	Me	0.022 ± 0.003	25 ± 3.0	34/ > 200
18c	(*E*)-2-(4-F-phenyl)ethen-1-yl	H	0.021 ± 0.005	20 ± 5.5	> 200/186
18d	(*E*)-2-(pyrid-3-yl)ethen-1-yl	H	0.006 ± 0.001	84 ± 0	27/ > 200

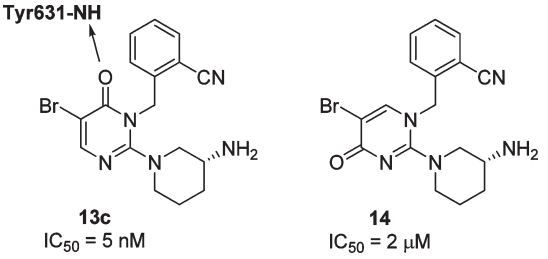


Figure 5. Activity of N1- vs N3-alkylated pyrimidinone isomers.

isomers were found to be much less potent than their N3-alkylated counterparts. This can be attributed, at least in part, to the loss of the hydrogen bond between the inhibitor carbonyl and the backbone NH of tyrosine 631 (Figure 5). This interaction is observed in the cocrystal structure of **13c** and DPP-4 (Figure 6).[17]

Several alternatives to the N3 cyanobenzyl group were examined in the pyrimidinone series (Table 2). While the 3-CN, 2-thiophenylmethyl group provided excellent potency, it suffered from reduced stability in the presence of rat liver microsomes. A fluorine atom at the 5-position of the benzyl group was well tolerated, while 4-position substitution was not.

The pyrimidinones proved to be highly selective for DPP-4 over related proteases such as DPP-8. This was important

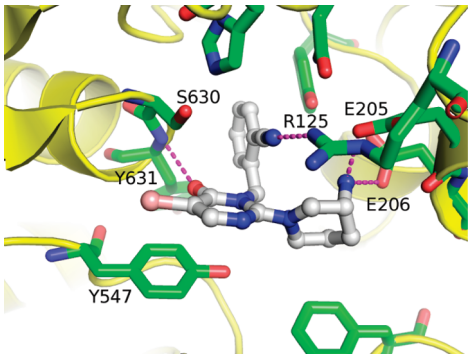


Figure 6. Cocrystal structure of **13c** in the DPP-4 active site.

given the reports of significant animal toxicity observed for compounds that inhibit DPP-8/DPP-9.[18]

Several of the pyrimidinones were tested in PK-PD experiments.[19] In general, these compounds displayed high oral bioavailability, good exposures (AUCs), and sustained levels of DPP-4 inhibition. Dog PK-PD data for compounds **13a** and **13c** are shown in Figures 7 and 8. PK parameters for several pyrimidinones are shown in Table 3.

Data for the pyrmidinedione analogs are shown in Table 4. At R1, H and methyl were equally well tolerated while ethyl substitution resulted in a 10-fold reduction in potency. A variety of benzyl groups at R2 were tolerated, with the 2-cyano,

5-fluoro-substituted analogue (**27j**) providing the best potency. Placement of a chlorine atom at R3 provided no advantage. No beneficial modification of the 3-aminopiperidine moiety was uncovered; however, quaternization of the 3-position with a methyl group provided an inhibitor with potency similar to that of its parent (Table 4, **27p**). The selectivity of these compounds for DPP-4 over the related protease DPP-8 is excellent. In addition, the in vitro metabolic stability of these compounds suggested they might enjoy long half-lives in vivo.

The cocomplex of **27b** in the active site of DPP-4 is shown in Figure 9.[20] The aminopiperidine forms a salt bridge to Glu205/Glu206, while the cyanobenzyl group effectively fills the S1 pocket (formed by Val656, Tyr631, Tyr662, Trp659, Tyr666, and Val711) and interacts with Arg125. The 2-position carbonyl participates in an important hydrogen bond with the backbone NH of Tyr631, and the uracil ring π-stacks with Tyr547.

In this cocomplex and in those of related compounds (e.g., **13c**, vide supra), we noted a preference for the axial orientation of the 3-amino group on the piperidine. To support this assignment, ab initio calculations were carried out on both the axial and equatorial conformations. The axial ligand coordinates were extracted from the cocomplex and hydrogens added and initially relaxed using the Austin Model 1[21] (AM1) method within the Vienna Ab Initio Molecular Dynamics Package[22] (VAMP). All hydrogens were free to relax while all heavy atoms were constrained in order to allow moderate relaxation but not to disturb the cocomplex conformation significantly. This structure was then subjected to a DFT/B3LYP (6-31++G**) energy calculation within the General Atomic and Molecular Electronic Structure System[23] (GAMESS-US) in order to obtain the in vacuo heat of formation. An identical protocol was followed for the equatorial conformation, albeit with a weaker constraint on the aminopiperidine ring to allow a more realistic relaxation to occur.

In order to measure the contribution to the intramolecular stabilization of the nitrile−amine interaction, the two conformers were constructed and simulated without the cyanophenyl group (Figure 10). Again, the above protocol was followed

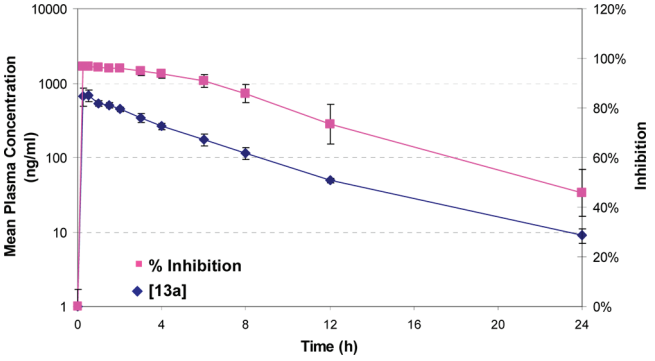


Figure 7. Plasma concentrations and DPP-4 inhibition in dogs for **13a** (HCl salt, 2.7 mg/kg po, single dose).

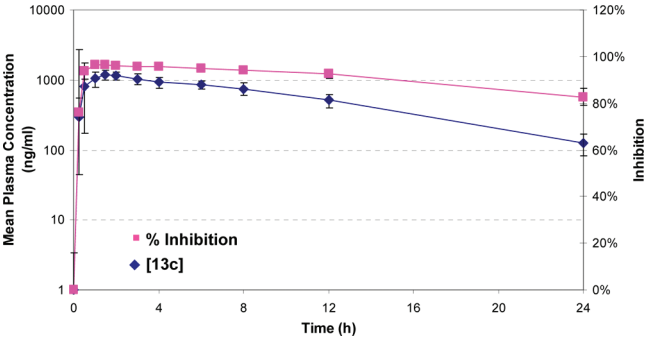
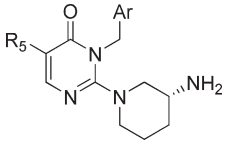


Figure 8. Plasma concentrations and DPP-4 inhibition in dogs for **13c** (HCl salt, 3.0 mg/kg po, single dose).

Table 2. Selected Data for Pyrimidinone Analogues: Cyanobenzyl Group Modifications

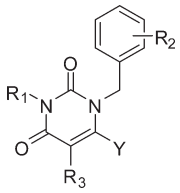


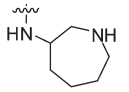
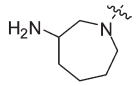
compd	R_5	Ar	DPP-4 IC_{50}, μM	DPP-8 IC_{50}, μM	RLM/HLM $t_{1/2}$, min
19	Br	3-CN,2-thiophenyl	0.003 ± 0.000	> 100	15/ > 200
20	F	2-CN,4-F-Ph	0.430 ± 0.089	NT	NT/NT
21	F	2-CN,5-F-Ph	0.008 ± 0.003	> 100	> 200/ > 200
22	Cl	2-CN,5-F-Ph	0.008 ± 0.002	> 100	122/ > 200
23	Br	2-CN,5-F-Ph	0.006 ± 0.001	> 100	41/ > 200

Table 3. Selected PK Parameters for Compounds **12**, **13a**, **13b**, and **13c**

compd	salt form	species	dose, iv/oral (mg kg^{-1})	iv $t_{1/2}$ (h)	oral $t_{1/2}$ (h)	AUC_{po} (μg h mL^{-1})	V_{dss} (mL kg^{-1})	F (%)
12	TFA	rat	1.4/14	0.74 ± 0.03	1.0 ± 0.21	1.2 ± 0.08	4800 ± 790	54 ± 4
12	TFA	dog	0.52/1.8	2.4 ± 0.11	2.8 ± 0.74	1.4 ± 0.44	3000 ± 200	78 ± 27
13a	TFA	rat	0.71/14	1.5 ± 0.03	1.5 ± 0.07	3.8 ± 0.70	4200 ± 230	73 ± 13
13a	HCl	dog	0.85/2.7	4.6 ± 0.48	4.5 ± 0.16	3.2 ± 0.20	3500 ± 500	80 ± 5
13a	tartrate	monkey	1.6/2.1	4.0 ± 1.2	5.7 ± 1.3	3.1 ± 0.86	3200 ± 500	110 ± 30
13b	HCl	rat	0.8/11	1.3 ± 0.44	1.3 ± 0.28	2.8 ± 0.47	3000 ± 540	65 ± 11
13b	HCl	dog	0.8/2.5	5.2 ± 0.71	4.8 ± 1.1	8.4 ± 2.5	1900 ± 310	90 ± 27
13c	HCl	rat	2.0/10	1.1 ± 0.40	1.7 ± 0.40	2.4 ± 1.1	3200 ± 220	74 ± 34
13c	HCl	dog	1.0/3.0	5.3 ± 0.32	6.1 ± 0.78	14.7 ± 3.3	1700 ± 340	105 ± 23
13c	free base	monkey	1.1/7.6	4.2 ± 2.1	5.4 ± 0.59	8.2 ± 2.0	4200 ± 1500	112 ± 17

Table 4. Selected Data for Pyrimidinediones **27a**−**p**



compd	R1	R2	R3	Y	DPP-4	DPP-8	RLM	HLM
					IC_{50} (μM)		$t_{1/2}$ (min.)	
27a	H	2-CN	H	3-(*R*)-aminopiperidinyl (3-*R*-AP)	0.004 ± 0.001	>100	>200	129
27b	Me	2-CN	H	3-*R*-AP	0.007 ± 0.002	>100	200	121
27c	Me	2-CN	Cl	3-*R*-AP	0.057 ± 0.006	NT	56	164
27d	Et	2-CN	H	3-*R*-AP	0.068 ± 0.019	NT	32	>200
27e	H	2-Br	H	3-*R*-AP	0.036 ± 0.007	>100	>118	>200
27f	Me	2-Br	H	3-*R*-AP	0.012 ± 0.001	>100	82	>200
27g	Me	2-Br, 5-F	H	3-*R*-AP	0.008 ± 0.001	>100	16	90
27h	Me	2-Cl, 5-F	H	3-*R*-AP	0.014 ± 0.002	>100	53	>200
27i	Me	2-Cl, 4-F	H	3-*R*-AP	0.890 ± 0.160	NT	67	>200
27j	Me	2-CN, 5-F	H	3-*R*-AP	0.004 ± 0.001	>100	>200	>200
27k	Me	2,5-diCl	H	3-*R*-AP	0.027 ± 0.007	86 ± 12	10	165
27l	Me	2-Cl, 3,6-diF	H	3-*R*-AP	0.830 ± 0.230	NT	NT	NT
27m	Et	2-CN	H	$NH_2CH_2CH_2NH$	17 ± 4.4	NT	NT	NT
27n	Me	2-CN	H		0.590 ± 0.130	NT	NT	NT
27o	Me	2-CN	H		3.800 ± 0.470	NT	NT	NT
27p	Me	2-CN, 5-F	H	3-(*R*)-amino-3-methylpiperidinyl	0.010 ± 0.003	>100	35	>200

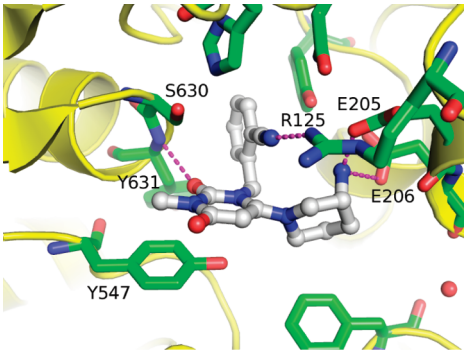


Figure 9. Compound **27b** in the active site of DPP-4 with key interactions shown.

to obtain heats of formation. The axial conformer (**27b-ax**) is 13.2 kcal/mol more stable than its equatorial conformer (**27b-eq**), while the des-cyanophenyl axial conformer (**28-ax**) is only 4.0 kcal/mol more stable than its equatorial conformer (**28-eq**). Comparing the results of these calculations, we clearly see there is significant stabilization (around 9 kcal/mol) of the axial conformation by the nitrile−amine interaction.

The observed electron density and the binding site environment support only the axial conformer where the piperidine ring is in a chair form. However, the equatorial conformer where the piperidine ring is in a boat or twist-boat form (Figure 10, molecule **27b-ax boat**) may also conceivably fit the density and site, albeit not as well as the axial with the piperidine ring in a chair form. The heat of formation of the equatorial boat form was calculated using the same protocol already described. This conformer was found to be 2.4 kcal/mol less stable than the axial chair form and minimizes to a noticeably poorer fit to the binding site, again supporting the assignment of the axial chair conformer to the electron density observed. Finally, the Polarizable Continuum Model[24] (PCM) was applied to each conformer/isomer to assess solvent effects. The results of these calculations do not alter the energetic preferences observed, merely the magnitude of the enthalpies.

As shown in Figure 11, **27j** provides a sustained pharmacodynamic effect, with a 7 mg/kg oral dose giving >80% inhibition of DPP-4 activity after 24 h. The favorable PK-PD of **27j** in dogs is also observed in rats (data not shown) and monkeys (Figure 12 and Table 5). In animal efficacy models, compound **27j** improved glucose tolerance and increased postprandial plasma insulin levels in Zucker *fa*/*fa* rats (Figure 13).

Given their in vivo profiles, **13a**, **27b**, and **27j** were selected for preclinical development. As part of the evaluation of these compounds, they were tested for their ability to inhibit cytochrome P450 enzymes (1A2, 2C19, 2C9, 2D6, and 3A4). None of these compounds was found to have an IC_{50} value lower than 10 μM against any of these isoforms. In addition, none of the compounds was found to block the hERG channel at concentrations up to 30 μM. Profiling of these compounds in a safety pharmacology screen gave very favorable results. Following scale-up, GLP toxicology studies in rat and dog demonstrated all three compounds to be well tolerated.

13a, **27b**, and **27j** were selected for clinical development. In trials, **27b** was safe and demonstrated favorable human PK,

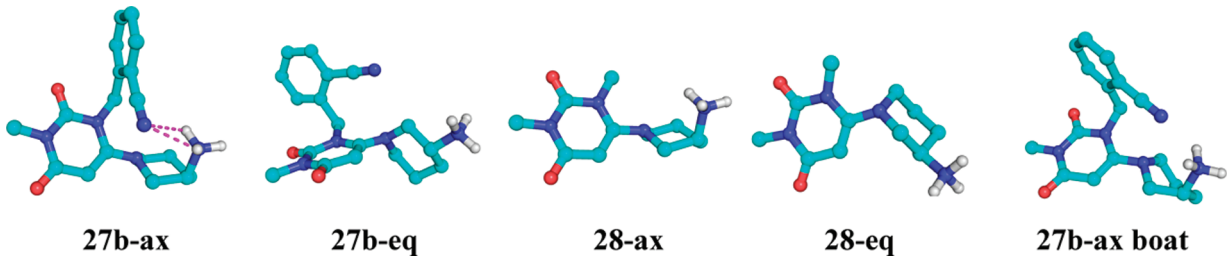


Figure 10. Molecules investigated by ab initio calculations.

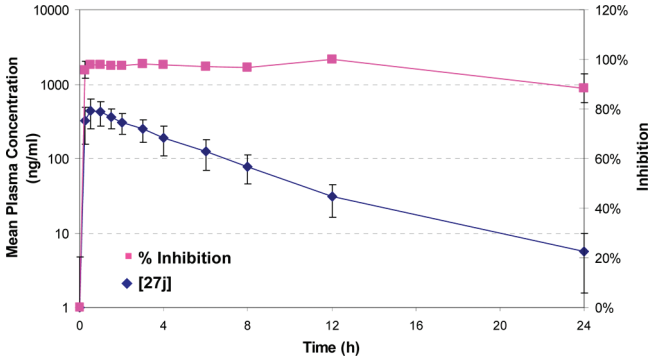


Figure 11. Plasma concentrations and DPP-4 inhibition in dogs for **27j** (TFA salt, 2.7 mg/kg po).

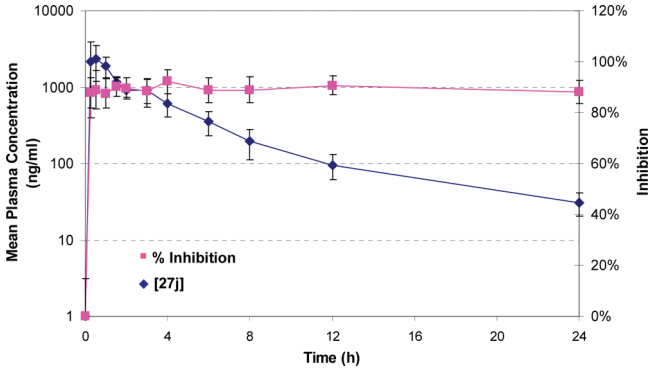


Figure 12. Plasma concentrations and DPP-4 inhibition in cynomologous monkeys for **27j** (HCl salt, 5 mg/kg po).

sustained DPP-4 inhibition, and lowering of glycosylated hemoglobin (HbA1c) in type 2 diabetics.[25]

Summary

The pyrimidinone and pyrimidinedione DPP-4 inhibitors described here are potent, selective, orally bioavailable, and efficacious in vivo. These compounds possess favorable pharmaceutical properties and exhibit a wide safety margin in animals. Clinical development of these compounds is underway.

Experimental Section

General. Figures 1, 2, 6, 9, and 10 were prepared using the program PyMol.[26]

All references to ether or Et_2O are to diethyl ether. Brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions conducted under an inert atmosphere at room temperature unless otherwise noted.

^{1}H NMR spectra were recorded on a Bruker Avance 400. Chemical shifts are expressed in parts per million (ppm). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

All compounds reported are of at least 95% purity. Compound purity data and unit-resolution mass spectra were acquired either on a Waters ZQ LC/MS single quadrupole system equipped with electrospray ionization (ESI) source, UV detector (220 and 254 nm), and evaporative light scattering detector (ELSD) or on a Waters Acquity UPLC/MS system equipped with a UPLC binary pump, a SQD 3100 mass spectrometer with electrospray ionization (ESI) source, a PDA detector (210−400 nm), and an evaporative light scattering detector (ELSD).

Thin-layer chromatography was performed on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid, ninhydrin, or *p*-anisaldehyde solution. Flash column chromatography was performed on silica gel (230−400 mesh, Merck).

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (12). 2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-bromo-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile (**13c**) (80 mg, 0.21 mmol) and tributyltin hydride (83 μL, 0.31 mmol) were stirred in dry toluene (5 mL) under nitrogen. Tetrakis(triphenylphosphine)palladium(0) (36 mg, 0.013 mmol) and a catalytic amount of AIBN were added, and the mixture was stirred at 108 °C for 24 h. Concentration in vacuo and purification by preparative HPLC gave 51.8 mg (59%) of **12** as the TFA salt. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (br s, 3H), 7.71 (d, 1H, J = 6.4 Hz), 7.63 (d, 1H, 7.6 Hz), 7.57 (t, 1H, J = 7.6 Hz), 7.40 (t, 1H, J = 7.6 Hz), 7.33 (d, 1H, J = 7.6 Hz), 6.25 (d, 1H, J = 6.4 Hz), 5.36 (AB q, 2H, J = 113.2, 15.2 Hz), 3.47−3.59 (m, 3H), 3.21−3.28 (m, 2H), 1.95−2.05 (m, 2H), 1.80−1.91 (m, 1H), 1.60−1.71 (m, 1H). MS (ES) [M + H] calcd for $C_{17}H_{19}N_5O$, 310; found 310.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-fluoro-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (13a). 2-Chloro-5-fluoro-3*H*-pyrimidin-4-one (**8a**) was prepared in 56% yield from 2,4-dichloro-5-fluoropyrimidine (**7a**) according to the procedure for 5-bromo-2-chloro-3*H*-pyrimidin-4-one (**8c**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.98 (br s, 1H), 8.14 (d, 1H, J = 3.2 Hz).

2-(2-Chloro-5-fluoro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9a**) was prepared in 44% yield from 2-chloro-5-fluoro-3*H*-pyrimidin-4-one (**8a**) according to the procedure for 2-(5-bromo-2-chloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9c**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.74 (dd, 1H, J = 7.6, 1.2 Hz), 7.59 (td, 1H, J = 7.6, 1.2 Hz), 7.45 (t, 1H, J = 7.6 Hz), 7.15 (d, 1H, J = 7.6 Hz), 5.67 (s, 2H). MS (ES) [M + H] calcd for $C_{12}H_7ClFN_3O$, 264, 266; found 264, 266.

Also obtained from the reaction were impure fractions of the less polar O-alkylated isomer (**10a**) and the more polar N3-alkylated isomer (**11a**).

13a was prepared in 68% yield from 2-(2-chloro-5-fluoro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9a**) according to the general procedure outlined for **13c** and was isolated as the TFA salt. ^{1}H NMR (400 MHz, CD_3OD): δ 7.99 (d, 1H, J = 0.8 Hz), 7.85 (d, 1H, J = 7.2 Hz), 7.64 (t, 1H, J = 7.6 Hz), 7.47

Table 5. Selected PK Parameters for Compound **27j**

species	salt form	dose, iv/oral (mg kg^{-1})	iv $t_{1/2}$ (h)	oral $t_{1/2}$ (h)	AUC_{po} (μg h mL^{-1})	CL (mL kg^{-1} min^{-1})	V_{dss} (mL kg^{-1})	F (%)
dog	TFA	0.90/2.7	1.5 ± 0.06	4.8 ± 1.1	2.2 ± 0.85	18 ± 63	4400 ± 590	90 ± 35
monkey	HCl	0.93/4.6	5.6 ± 0.16	6.2 ± 0.76	8.0 ± 2.0	10 ± 2.3	3300 ± 550	105 ± 27

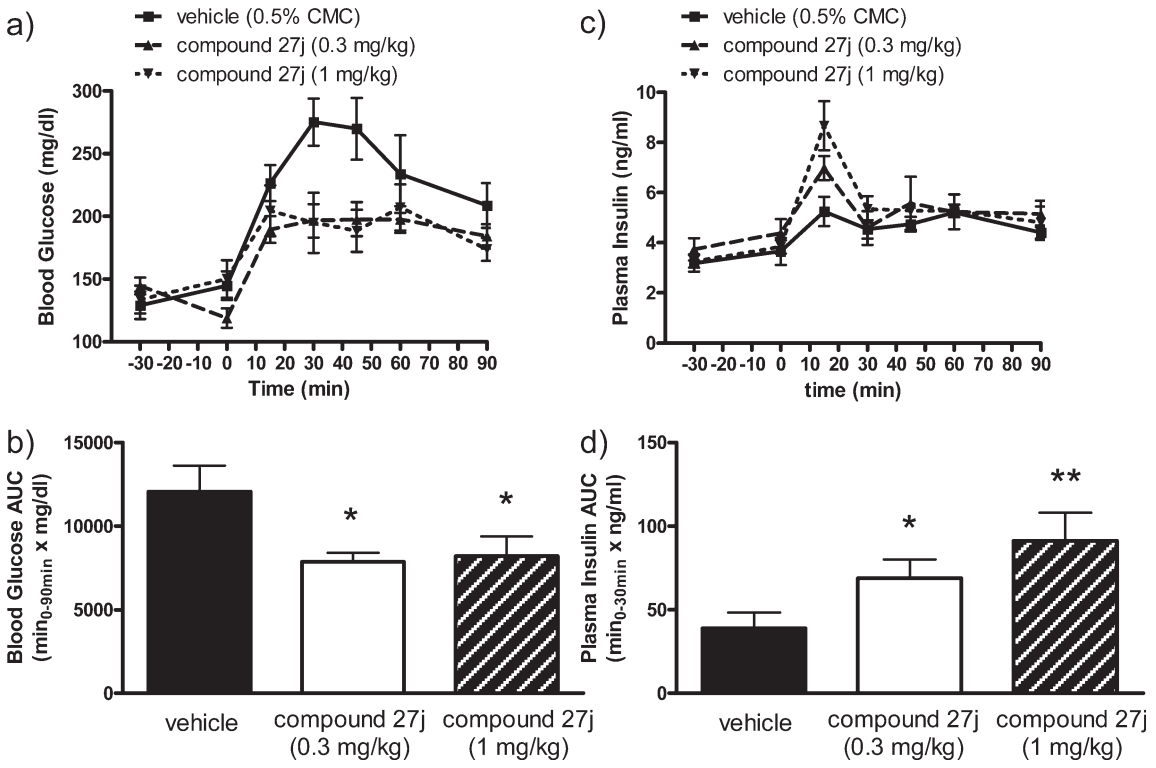


Figure 13. Effect of a single oral dose of compound **27j** on blood glucose levels (a), baseline-adjusted $AUC_{0-90min}$ of blood glucose levels (b), plasma insulin levels (c), and baseline-adjusted $AUC_{0-30min}$ of plasma insulin levels (d) after oral glucose load in Zucker *fa/fa* rats. Animals were fasted overnight then administered a single dose of vehicle alone (0.5% carboxymethylcellulose) or compound **27j** by oral gavage. At 30 min postdose, the rats were given a glucose solution (1 g/kg). Blood samples were collected prior to dosing (−30 min), prior to glucose load (0 min), and at 15, 30, 45, 60, and 90 min. Data are the mean ± SE (n = 8): (*) $p < 0.05$ and (**) $p < 0.01$ (vs vehicle control using an unpaired Student's t test).

(t, 1H, J = 7.6 Hz), 7.20 (d, 1H, J = 7.6 Hz), 5.33 (s, 2H), 3.49−3.58 (m, 1H), 3.10−3.19 (m, 1H), 2.68−2.76 (m, 2H), 2.48−2.58 (m, 1H), 1.60−1.80 (m, 2H), 1.41−1.51 (m, 1H), 1.10−1.19 (m, 1H). MS (ES) [M + H] calcd for $C_{17}H_{18}FN_5O$, 328; found 328.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-chloro-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (13b). 2,5-Dichloro-3*H*-pyrimidin-4-one (**8b**) was prepared in 76% yield from 2,4,5-trichloropyrimidine (**7b**) according to the procedure for 5-bromo-2-chloro-3*H*-pyrimidin-4-one (**8c**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.40 (br s, 1H), 8.24 (s, 1H). MS (ES) [M + H] calcd for $C_4H_2Cl_2N_2O$, 165, 167; found 165, 167.

2-(2,5-Dichloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9b**) was prepared in 40% yield from 2,5-dichloro-3*H*-pyrimidin-4-one (**8b**) according to the procedure for 2-(5-bromo-2-chloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9c**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.73 (dd, 1H, J = 7.6, 1.2 Hz), 7.59 (dt, 1H, J = 7.6, 1.2 Hz), 7.45 (t, 1H, J = 7.6 Hz), 7.16 (d, 1H, J = 7.6 Hz), 5.69 (s, 2H). MS (ES) [M + H] calcd for $C_{12}H_7Cl_2N_3O$, 280, 282; found 280, 282.

Also obtained from the reaction were impure fractions of the less polar O-alkylated isomer (**10b**) and 41% yield of the more polar N3-alkylated isomer (**11b**).

13b was prepared in 55% yield from 2-(2,5-dichloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9b**) according to the general procedure outlined for **13c**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.09 (d, 1H, J = 6.8 Hz), 7.69 (br s, 3H), 7.64 (dt, 1H, J = 7.6, 1.2 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.27 (d, 1H, J = 7.6 Hz), 5.29 (AB q, 2H, J = 48.0, 15.2 Hz), 3.49−3.58 (m, 1H), 3.16−3.36 (m, 2H), 2.86−3.02 (m, 2H), 1.89−1.96 (m, 1H), 1.72−1.81 (m, 1H), 1.43−1.64 (m, 2H). MS (ES) [M + H] calcd for $C_{17}H_{18}ClN_5O$, 344, 346; found 344, 346.

2-((2-(3-(*R*)-Aminopiperidin-1-yl)-5-bromo-6-oxopyrimidin-1(6*H*)-yl)methyl)benzonitrile (13c). 5-Bromo-2,4-dichloropyrimidine (**7c**, 5.0 g, 22 mmol) was stirred in THF (10 mL) with 1 N NaOH (30 mL) at room temperature for 3 h. The solution was made slightly acidic with 1 N HCl and was extracted with $CHCl_3$. Organics were dried ($MgSO_4$) and concentrated in vacuo. Precipitation from 20% $CHCl_3$/hexanes and collection by filtration gave 2.92 g (64%) of 5-bromo-2-chloro-3*H*-pyrimidin-4-one (**8c**) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.33 (br s, 1H), 8.35 (s, 1H). MS (ES) [M + H] calcd for $C_4H_2BrClN_2O$, 209, 211, 213; found 209, 211, 213.

5-Bromo-2-chloro-3*H*-pyrimidin-4-one (**8c**) (1.88 g, 9.0 mmol) was stirred in DME (25 mL)/DMF (5 mL) under nitrogen at 0 °C. Sodium hydride (95%, 238 mg, 9.4 mmol) was added in portions. After 10 min, lithium bromide (1.56 g, 17.9 mmol) was added and the mixture stirred for 15 min at room temperature. α-Bromo-*o*-tolunitrile (3.5 g, 17.9 mmol) was added, and the mixture was stirred at 65 °C for 8 h. The solution was diluted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by silica gel chromatography (1:1:1 EtOAc/hexanes/$CHCl_3$) gave 997 mg (34%) of

2-(5-bromo-2-chloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9c**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.73 (dd, 1H, J = 7.6, 1.2 Hz), 7.58 (dt, 1H, J = 7.6, 1.2 Hz), 7.45 (t, 1H, J = 7.6 Hz), 7.16 (d, 1H, J = 7.6 Hz), 5.69 (s, 2H). MS (ES) [M + H] calcd for $C_{12}H_7BrClN_3O$, 324, 326, 328; found 324, 326, 328.

Also obtained from the reaction were impure fractions of the less polar O-alkylated isomer (**10c**) and 1.06 g (36%) of the more polar N3-alkylated isomer (**11c**).

2-(5-Bromo-2-chloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9c**) (189 mg, 0.58 mmol), 3-(*R*)-aminopiperidine dihydrochloride (128 mg, 0.74 mmol), and sodium bicarbonate (195 mg, 2.32 mmol) were stirred in ethanol (5 mL) at 60 °C for 90 min. The mixture was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by silica gel chromatography (5% MeOH/$CHCl_3$) gave 139 mg (62%) of the target compound (**13c**) as a clear oil. This was converted to the solid TFA salt by subjection to TFA in CH_2Cl_2 and concentration in vacuo. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.98 (br s, 3H), 7.82 (d, 1H, J = 6.8 Hz), 7.64 (dt, 1H, J = 7.6, 1.2 Hz), 7.47 (t, 1H, J = 7.2 Hz), 7.27 (d, 1H, J = 7.6 Hz), 5.29 (AB q, 2H, J = 42.8, 15.2 Hz), 3.52−3.57 (m, 1H), 3.30−3.39 (m, 1H), 3.15−3.24 (m, 1H), 2.88−3.05 (m, 2H), 1.90−1.99 (m, 1H), 1.75−1.83 (m, 1H), 1.49−1.63 (m, 2H). MS (ES) [M + H] calcd for $C_{17}H_{18}BrN_5O$, 388, 390; found 388, 390.

2[2-(3-(*R*)-Aminopiperidin-1-yl)-5-bromo-4-methyl-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (13d). 5-Bromo-2-chloro-6-methyl-3*H*-pyrimidin-4-one (**8d**) was prepared in 63% yield from 5-bromo-6-methyl-1*H*-pyrimidine-2,4-dione (**6d**) utilizing a method analogous to the preparation of 2-chloro-5,6-dimethyl-3*H*-pyrimidin-4-one.[27] ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H). MS (ES) [M + H] calcd for $C_5H_4BrClN_2O$, 223, 225, 227; found 223, 225, 227.

2-(5-Bromo-2-chloro-4-methyl-6-oxo-6*H*-pyrimidin-1-ylmethyl)-benzonitrile (**9d**) was prepared in 52% yield from 5-bromo-2-chloro-6-methyl-3*H*-pyrimidin-4-one (**8d**) according to the procedure outlined for 2-(5-bromo-2-chloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9c**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (dd, 1H, J = 7.6, 1.2 Hz), 7.67 (dt, 1H, J = 7.6, 1.2 Hz), 7.52 (t, 1H, J = 7.6 Hz), 7.26 (d, 1H, J = 7.6 Hz), 5.50 (s, 2H), 2.41 (s, 3H). MS (ES) [M + H] calcd for $C_{13}H_9BrClN_3O$, 338, 340, 342; found 338, 340, 342.

13d was prepared in 52% yield from 2-(5-bromo-2-chloro-4-methyl-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9d**) according to the procedure outlined for **13c**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (br s, 3H), 7.81 (d, 1H, J = 7.2 Hz), 7.63 (t, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 7.2 Hz), 7.23 (d, 1H, J = 7.6 Hz), 5.27 (AB q, 2H, J = 42.0, 15.2 Hz), 3.50−3.55 (m, 1H), 3.31−3.40 (m, 1H), 3.13−3.20 (m, 1H), 3.00−3.06 (s, 1H), 2.85−2.92 (m, 1H), 2.33 (s, 3H), 1.90−1.99 (m, 1H), 1.75−1.83 (m, 1H), 1.49−1.63 (m, 2H). MS (ES) [M + H] calcd for $C_{18}H_{20}BrN_5O$, 402, 404; found 402, 404.

2-((2-(3-(*R*)-Aminopiperidin-1-yl)-5-bromo-4-*tert*-butyl-6-oxopyrimidin-1(6*H*)-yl)methyl)benzonitrile, TFA salt (13e). To a suspended mixture of 2-amino-6-*tert*-butylpyrimidin-4(3*H*)-one (1.0 g, 5.9 mmol), bromine (1.0 g), and CuBr (1.01 g, 7.1 mmol) in $CHCl_3$ (50 mL) were slowly added Br_2 (1.0 g) and 97% isoamyl nitrite (2.9 g mL) in $CHCl_3$ (5 mL) at the same time over 10 min. The mixture was stirred under reflux for 2 h, diluted with DCM, washed with saturated Na_2SO_3, dried over Na_2SO_4, concentrated, and purified by chromatography to give 2,5-dibromo-6-*tert*-butylpyrimidin-4(3*H*)-one.

2,5-Dibromo-6-*tert*-butylpyrimidin-4(3*H*)-one (200 mg) was converted to **13e** in two steps according to the procedures outlined for **13c** and was isolated as the TFA salt (41% yield). ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1) δ 7.68−7.74 (d, J = 7.5 Hz, 1H), 7.62 (t, J = 8.5 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H), 5.57 (q, J = 13.6 Hz, 2H), 4.80 (d, J = 11.4 Hz, 1H), 4.40 (d, J = 12.6 Hz, 1H), 3.29 (m, 1H), 3.15−3.26 (m, 1H), 3.02 (t, J = 11.4 Hz, 1H), 2.16 (d, J = 8.1 Hz, 1H), 1.80 (d, J = 12.4 Hz, 1H), 1.53 (d, J = 13.4 Hz, 2H), 1.41 (s, 9H). MS (ES) [M + H] calcd for $C_{21}H_{27}BrN_5O$, 444; found 444.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-iodo-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (13f). The title compound was prepared in 15% yield from 2,4-dichloro-5-iodopyrimidine (**7f**) according to the procedure outlined for **13c**. ^{1}H NMR (400 MHz, CD_3OD): δ 8.27 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.63 (m, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 5.34−5.46 (AB q, J = 15.2 Hz, 2H) 3.65−3.72 (m, 1H), 3.49−3.58 (m, 1H), 3.28−3.34 (m, 1H), 3.14−3.22 (m, 1H), 3.05−3.09 (m, 1H), 2.07−2.17 (m, 1H), 1.60−1.90 (m, 3H). MS (ES) [M + H]: 436.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-4,5-dimethyl-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (13g). 2-(2-Chloro-4,5-dimethyl-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9g**) was prepared in 64% yield from 2-chloro-5,6-dimethyl-3*H*-pyrimidin-4-one[27] according to the procedure for 2-(5-bromo-2-chloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9c**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 1H, J = 7.6 Hz), 7.55 (dt, 1H, J = 7.6, 1.2 Hz), 7.41 (t, 1H, J = 7.6 Hz), 7.12 (d, 1H, J = 7.6 Hz), 5.63 (s, 2H), 2.32 (s, 3H), 2.10 (s, 3H). MS (ES) [M + H] calcd for $C_{14}H_{12}ClN_3O$, 274, 276; found 274, 276.

Also obtained from the reaction was 30% yield of the less polar O-alkylated isomer (**10g**).

13g was prepared in 74% yield from 2-(2-chloro-4,5-dimethyl-6-oxo-6*H*-pyrimidin-1ylmethyl)benzonitrile (**9g**) according to the general procedure outlined for **13c**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (br s, 3H), 7.81 (d, 1H, J = 7.6 Hz), 7.61 (dt, 1H, J = 7.6, 1.2 Hz), 7.44 (t, 1H, J = 7.6 Hz), 7.09 (d, 1H, J = 7.6 Hz), 5.26 (AB q, 2H, J = 45.2, 15.2 Hz), 3.29−3.42 (m, 2H), 2.91−3.08 (m, 2H), 2.71−2.80 (m, 1H), 2.19 (m, 3H), 1.89−1.96 (m, 1H), 1.83 (s, 3H), 1.72−1.81 (m, 1H), 1.46−1.61 (m, 2H). MS (ES) [M + H] calcd for $C_{19}H_{23}N_5O$, 338; found 338.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-ethyl-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (13h). 2-Chloro-5-ethyl-3*H*-pyrimidin-4-one (**8h**) was prepared in 67% yield from 5-ethyl-1*H*-pyrimidine-2,4-dione (**6h**) utilizing a method analogous to the preparation of 2-chloro-5,6-dimethyl-3*H*-pyrimidin-4-one.[27] ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.21 (br s, 1H), 7.90 (br s, 1H), 2.39 (q, 2H, J = 7.6 Hz), 1.08 (t, 3H, J = 7.6 Hz). MS (ES) [M + H] calcd for $C_6H_7ClN_2O$, 159, 161; found 159, 161.

2-(2-Chloro-5-ethyl-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9h**) was prepared in 20% yield from 2-chloro-5-ethyl-3*H*-pyrimidin-4-one (**8h**) according to the procedure for 2-(5-bromo-2-chloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9c**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, 1H, J = 7.6, 1.2 Hz), 7.65 (d, 1H, J = 1.2 Hz), 7.55 (dt, 1H, J = 7.6, 1.2 Hz), 7.40 (t, 1H, J = 7.6 Hz), 7.10 (d, 1H, J = 7.6 Hz), 5.63 (s, 2H), 2.51 (dq, 2H, J = 7.6, 1.2 Hz), 1.20 (dt, 3H, J = 7.6, 1.2 Hz). MS (ES) [M + H] calcd for $C_{14}H_{12}ClN_3O$ 274, 276; found 274, 276.

Also obtained from the reaction were impure fractions of the less polar O-alkylated isomer (**10h**) and 38% yield of the more polar N3-alkylated isomer (**11h**).

13h was prepared in 54% yield from 2-(2-chloro-5-ethyl-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9h**) according to the general procedure outlined for **13c**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (br s, 3H), 7.81 (dd, 1H, J = 7.6, 1.2 Hz), 7.69 (s, 1H), 7.61 (dt, 1H, J = 7.6, 1.2 Hz), 7.44 (t, 1H, J = 7.6 Hz), 7.10 (d, 1H, J = 7.6 Hz), 5.26 (AB q, 2H, J = 48.0, 15.2 Hz), 3.29−3.42 (m, 2H), 2.91−3.08 (m, 2H), 2.75−2.84 (m, 1H), 2.25 (q, 2H, J = 7.2 Hz), 1.89−1.96 (m, 1H), 1.72−1.81 (m, 1H), 1.46−1.61 (m, 2H), 1.00 (t, 3H, J = 7.2 Hz). MS (ES) [M + H] calcd for $C_{19}H_{23}N_5O$, 338; found 338.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-methoxy-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA Salt (13i). 2-Chloro-5-methoxy-3*H*-pyrimidin-4-one (**8i**) was prepared in 8% yield from 5-methoxy-1*H*-pyrimidine-2,4-dione[28] (**6i**) utilizing a method analogous to the preparation of 2-chloro-5,6-dimethyl-3*H*-pyrimidin-4-one.[27] ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.58 (s, 1H), 3.74 (s, 3H). MS (ES) [M + H] calcd for $C_5H_5ClN_2O_2$, 161, 163; found 161, 163.

2-(2-Chloro-5-methoxy-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9i**) was prepared in 33% yield from 2-chloro-5-methoxy-3*H*-pyrimidin-4-one (**8i**) according to the general procedure outlined for 2-(5-bromo-2-chloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)-benzonitrile (**9c**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 1H, J = 7.2 Hz), 7.55 (t, 1H, J = 7.2 Hz), 7.42 (t, 1H, J = 7.2 Hz), 7.34 (s, 1H), 7.12 (d, 1H, J = 7.2 Hz), 5.66 (s, 2H), 3.89 (s, 3H). MS (ES) [M + H] calcd for $C_{13}H_{10}ClN_3O_2$, 276, 278; found 276, 278.

13i was prepared in 49% yield from 2-(2-chloro-5-methoxy-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9i**) according to the general procedure outlined for **13c** and was isolated as the TFA salt. ^{1}H NMR (400 MHz, CD_3OD): δ 7.71 (d, 1H, J = 7.2 Hz), 7.59 (t, 1H, J = 7.2 Hz), 7.47 (s, 1H), 7.42 (t, 1H, J = 7.2 Hz), 7.19 (d, 1H, J = 7.2 Hz), 5.46 (s, 2H), 3.79 (s, 3H), 3.31−3.40 (m, 1H), 3.02−3.21 (m, 2H), 2.72−2.85 (m, 2H), 1.92−2.02 (m, 1H), 1.61−1.82 (m, 2H), 1.38−1.48 (m, 1H). MS (ES) [M + H] calcd for $C_{18}H_{21}N_5O_2$, 340; found 340.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-6-oxo-4-phenyl-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (13j). 2-(2-Chloro-6-oxo-4-phenyl-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9j**) was prepared in 49% yield from 2-chloro-4-phenyl-3*H*-pyrimidin-4-one[29] according to the procedure for 2-(5-bromo-2-chloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9c**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, 2H, J = 7.6 Hz), 7.73 (d, 1H, J = 7.6 Hz), 7.41−7.60 (m, 5H), 7.21 (d, 1H, J = 7.6 Hz), 6.92 (s, 1H), 5.69 (s, 2H). MS (ES) [M + H] calcd for $C_{18}H_{12}ClN_3O$, 322, 324; found 322, 324.

Also obtained from the reaction were impure fractions of the less polar O-alkylated isomer (**10j**).

13j was prepared in 72% yield from 2-(2-chloro-6-oxo-4-phenyl-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9j**) according to the general procedure outlined for **13c** and was isolated as the HCl salt. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.51 (s, 3H), 8.06−8.14 (m, 2H), 7.81 (d, 1H, J = 7.6 Hz), 7.62 (t, 1H, J = 7.6 Hz), 7.39−7.51 (m, 4H), 7.23 (d, 1H, J = 7.6 Hz), 6.69 (s, 1H), 5.33 (AB q, 2H, J = 36.8, 15.2 Hz), 3.67−3.76 (m, 1H), 3.35−3.45 (m, 1H), 3.15−3.26 (m, 2H), 2.90−3.00 (m, 1H), 1.95−2.05 (m, 1H), 1.78−1.88 (m, 1H), 1.53−1.70 (m, 2H). MS (ES) [M + H] calcd for $C_{23}H_{23}N_5O$, 386; found 386.

(*R*)-2-{[2-(3-Aminopiperidin-1-yl)-4-oxo-5,6,7,8-tetrahydroquinazoline-3(4*H*)-yl]methyl}benzonitrile, TFA salt (13k). 2-Chloro-5,6,7,8-tetrahydroquinazoline-4(3*H*)-one (**8k**) was prepared in 47% yield from 5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione[30] (**6k**) utilizing a method analogous to the preparation of 2-chloro-5,6-dimethyl-3*H*-pyrimidin-4-one.[27] ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.20 (br s, 1H), 2.58−2.72 (m, 4H), 1.75−1.92 (m, 4H). MS (ES) [M + H] calcd for $C_8H_9ClN_2O$ 185, 187; found 185, 187.

2-[(2-Chloro-4-oxo-5,6,7,8-tetrahydroquinazolin-3(4*H*)-yl)-methyl]benzonitrile (**9k**) was prepared in 59% yield from 2-chloro-5,6,7,8-tetrahydroquinazoline-4(3*H*)-one (**8k**) according to the procedure outlined for 2-(5-bromo-2-chloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9c**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, 1H, J = 7.6, 1.2 Hz), 7.55 (td, 1H, J = 7.6, 1.2 Hz), 7.41 (t, 1H, J = 7.6 Hz), 7.14 (d, 1H, J = 7.6 Hz), 5.62 (s, 2H), 2.59−2.65 (m, 2H), 2.50−2.58 (m, 2H), 1.71−1.87 (m, 4H). MS (ES) [M + H] calcd for $C_{16}H_{14}ClN_3O$ 300, 302; found 300, 302.

13k was prepared in 68% yield from 2-[(2-chloro-4-oxo-5,6,7,8-tetrahydroquinazolin-3(4*H*)-yl)methyl]benzonitrile (**9k**) according to the procedure outlined for **13c**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (br s, 3H), 7.82 (d, 1H, J = 7.6 Hz), 7.61 (t, 1H, J = 7.6 Hz), 7.44 (t, 1H, J = 7.6 Hz), 7.09 (d, 1H, J = 7.6 Hz), 5.26 (q_{AB}, 2H, J = 44.8, 15.2 Hz), 3.25−3.40 (m, 2H), 2.90−3.08 (m, 2H), 2.70−2.80 (m, 1H), 2.48 (br s, 2H), 2.23 (br s, 2H), 1.89−1.98 (m, 1H), 1.42−1.80 (m, 7H). MS (ES) [M + H] calcd for $C_{21}H_{25}N_5O$ 364; found 364.

2-{[2-(3-(*R*)-Aminopiperidin-1yl)-5-bromo-4-oxopyrimidine-1(4*H*)-yl]methyl}benzonitrile, TFA salt (14). 14 was prepared in 58% yield from 2-[(5-bromo-2-chloro-4-oxopyrimidin-1(4*H*)-yl)methyl]benzonitrile (**11c**) according to the procedure outlined for **13c**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (br s, 3H), 7.95 (s, 1H), 7.90 (dd, 1H, J = 7.6, 1.2 Hz), 7.75 (t, 1H, J = 7.6 Hz), 7.56 (t, 1H, J = 7.6 Hz), 7.45 (d, 1H, J = 7.6 Hz), 5.28 (AB q, 2H, J = 46.8, 15.6 Hz), 3.50−3.55 (m, 1H), 3.24−3.35 (m, 2H), 2.83−3.00 (m, 2H), 1.92−2.02 (s, 1H), 1.76−1.84 (m, 1H), 1.50−1.64 (m, 2H). MS (ES) [M + H] calcd for $C_{17}H_{18}BrN_5O$, 388, 390; found 388, 390.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-6-oxo-5-phenyl-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (15a). 2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-bromo-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile (**13c**, 70 mg, 0.18 mmol), phenylboronic acid (33 mg, 0.27 mmol), and sodium carbonate (57 mg, 0.54 mmol) were stirred in DME (2 mL)/ H_2O (0.3 mL) in a flask purged with nitrogen. Tetrakis-(triphenylphosphine)palladium(0) (31 mg, 0.03 mmol) was added, and the mixture was stirred at 88 °C for 2 h. The mixture was diluted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by silica gel chromatography (5% MeOH/$CHCl_3$) followed by conversion to the TFA salt with TFA/CH_2Cl_2 gave 76 mg (85%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (s, 1H), 7.93 (br s, 3H), 7.82 (d, 1H, J = 7.2 Hz), 7.63 (dt, 1H, J = 7.6, 1.2 Hz), 7.56 (d, 2H, J = 8.4 Hz), 7.45 (t, 1H, J = 7.6 Hz), 7.24−7.37 (m, 4H), 5.34 (AB q, 2H, J = 40.0, 15.2 Hz), 3.53−3.59 (m, 1H), 3.36−3.45 (m, 1H), 3.18−3.25 (m, 1H), 2.80−3.08 (m, 2H), 1.92−2.00 (m, 1H), 1.79−1.85 (m, 1H), 1.51−1.67 (m, 2H). MS (ES) [M + H] calcd for $C_{23}H_{23}N_5O$, 386; found 386.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-4-methyl-6-oxo-5-phenyl-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (15b). 15b was prepared in 64% yield from phenylboronic acid and 2-[2-(3-(*R*)-aminopiperidin-1-yl)-5-bromo-4-methyl-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile (**13d**) according to the general procedure outlined for **15a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.09 (br s, 3H), 7.81 (d, 1H, J = 7.6 Hz), 7.64 (dt, 1H, J = 7.6, 1.2 Hz), 7.44 (t, 1H, J = 7.6 Hz), 7.14−7.37 (m, 6H), 5.30 (AB q, 2H, J = 43.2, 15.2 Hz), 3.51−3.57 (m, 1H), 3.33−3.42 (m, 1H), 3.12−3.20 (m, 1H), 3.10−3.19 (m, 1H), 2.85−2.93 (m, 1H), 2.08 (s, 3H), 1.92−2.00 (m, 1H), 1.79−1.85 (m, 1H), 1.51−1.67 (m, 2H). MS (ES) [M + H] calcd for $C_{24}H_{25}N_5O$, 400; found 400.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-(2-fluorophenyl)-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (15c). 15c was prepared in 48% yield from 2-fluorophenylboronic acid according to the procedure outlined for **15a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (br s, 3H), 7.85 (s, 1H), 7.71 (d, 1H, J = 7.2 Hz), 7.54 (t, 1H, J = 7.6 Hz), 7.35 (t, 1H, J = 7.6 Hz), 7.06−7.27 (m, 5H), 5.23 (AB q, 2H, J = 40.4, 15.2 Hz), 3.47−3.54 (m, 1H), 3.36−3.45 (m, 1H), 3.12−3.20 (m, 1H), 2.93−3.02 (m, 1H), 2.83−2.90 (m, 1H), 1.22−1.90 (m, 1H), 1.70−1.78 (m, 1H), 1.42−1.58 (m, 2H). MS (ES) [M + H] calcd for $C_{23}H_{22}FN_5O$, 404; found 404.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-(2-methoxyphenyl)-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (15d). 15d was prepared in 42% yield from 2-methoxyphenylboronic acid according to the procedure outlined for **15a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (br s, 3H), 7.80−7.84 (m, 2H), 7.66 (t, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.12−7.31 (m, 3H), 6.99 (d, 1H, J = 8.4 Hz), 6.91 (t, 1H, J = 7.6 Hz), 5.33 (AB q, 2H, J = 43.2, 15.2 Hz), 3.58 (s, 3H), 3.49−3.56 (m, 1H), 3.36−3.45 (m, 1H), 3.15−3.21 (m, 1H), 3.01−3.09 (m, 1H), 2.89−2.96 (m, 1H), 1.92−1.99 (m, 1H), 1.75−1.84 (m, 1H), 1.50−1.65 (m, 2H). MS (ES) [M + H] calcd for $C_{24}H_{25}N_5O_2$, 416; found 416.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-furan-3-yl-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (15e). 15e was prepared in 64% yield from 3-furanylboronic acid according to the procedure outlined for **15a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.16 (s, 1H), 8.05 (br s, 3H), 7.82 (d, 1H, J = 7.2 Hz), 7.68 (s, 1H), 7.62 (t, 1H, J = 7.6 Hz), 7.44 (t, 1H, J = 7.6 Hz), 7.19 (d, 1H, J = 7.6 Hz), 7.01 (s, 1H), 5.36 (AB q, 2H, J = 41.6, 15.2 Hz), 3.49−3.56 (m, 1H), 3.36−3.45 (m, 1H), 3.13−3.21 (m, 1H), 3.01−3.09 (m, 1H), 2.86−2.93 (m, 1H), 1.92−1.99 (m, 1H), 1.76−1.84 (m, 1H), 1.50−1.65 (m, 2H). MS (ES) [M + H] calcd for $C_{21}H_{21}N_5O_2$, 376; found 376.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-furan-3-yl-4-methyl-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (15f). 15f was prepared in 64% yield from 3-furanylboronic acid according to the general procedure outlined for **15a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (br s, 3H), 7.79−7.84 (m, 2H), 7.59−7.67 (m, 2H), 7.44 (t, 1H, J = 7.6 Hz), 7.17 (d, 1H, J = 7.6 Hz), 6.62 (d, 1H, J = 1.2 Hz), 5.29 (AB q, 2H, J = 40.4, 15.2 Hz), 3.49−3.56 (m, 1H), 3.33−3.41 (m, 1H), 3.01−3.17 (m, 2H), 2.82−2.89 (m, 1H), 2.30 (m, 3H), 1.92−1.99 (m, 1H), 1.76−1.84 (m, 1H), 1.50−1.65 (m, 2H). MS (ES) [M + H] calcd for $C_{22}H_{23}N_5O_2$, 390; found 390.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-6-oxo-5-(1*H*-pyrrol-3-yl)-6*H*-pyrimidin-1-ylmethyl]benzonitrile (15g). 15g was prepared in 71% yield using 1-(triisopropylsilyl)pyrrole-3-boronic acid in the general procedure outlined for **15a**, followed by TBAF deprotection according to the procedure for **17a**. ^{1}H NMR (400 MHz, CD_3OD): δ 8.09 (s, 1H), 7.71 (d, 1H, J = 7.2 Hz), 7.58 (t, 1H, J = 7.2 Hz), 7.36−7.47 (m, 2H), 7.14 (d, 1H, J = 7.2 Hz), 6.74 (d, 1H, J = 4.4 Hz), 6.47 (d, 1H, J = 4.4 Hz), 5.50 (s, 2H), 3.36−3.42 (m, 1H), 3.00−3.18 (m, 2H), 2.72−2.88 (m, 2H), 1.92−2.02 (m, 1H), 1.61−1.82 (m, 2H), 1.29−1.39 (m, 1H). MS (ES) [M + H] calcd for $C_{21}H_{22}N_6O$, 375; found 375.

2-((2-(3-(*R*)-Aminopiperidin-1-yl)-6-oxo-5-(pyrrolidin-1-yl)pyrimidin-1(6*H*)-yl)methyl)benzonitrile, TFA salt (16). 16 was prepared by heating **13c** with pyrrolidine at 150 °C for 20 min using a microwave. The crude product was purified by HPLC and was isolated in 35% yield as the TFA salt. ^{1}H NMR (400 MHz, CD_3OD): δ 7.71 (d, J = 7.6 Hz, 1H), 7.60 (t, J = 7.6, 8.0 Hz, 1H), 7.43 (t, J = 8.0, 7.2 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 5.30 (AB q, J = 15.6, 24.0 Hz, 2H), 3.71−2.90 (m, 8H), 2.28−1.57 (m, 9H). MS (ES) [M + H] calcd for $C_{21}H_{26}N_6O$, 379; found 379.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-ethynyl-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile (17a). 2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-bromo-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile (**13c**, 189 mg, 0.49 mmol), trimethylsilylacetylene (103 μL, 0.73 mmol), triphenylphosphine (4 mg, 0.02 mmol), and triethylamine (102 μL, 0.73 mmol) were stirred in THF (4 mL) in a flask purged with nitrogen. Dichlorobis(triphenylphosphine)palladium(II) (17 mg, 0.024 mmol) was added, and after 10 min copper iodide (2 mg) was added. The mixture was stirred for 18 h at room temperature. The solution was diluted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by silica gel chromatography (5% MeOH/$CHCl_3$) gave 168 mg (85%) of 2-[2-(3-(*R*)-aminopiperidin-1-yl)-5-trimethylsilylethynyl-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile as a clear oil. MS (ES) [M + H] calcd for $C_{22}H_{27}N_5OSi$, 406; found 406.

Deprotection of 2-[2-(3-(*R*)-aminopiperidin-1-yl)-5-trimethylsilylethynyl-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile (168 mg) was carried out by stirring the intermediate in THF (2 mL) with TBAF (1 N in THF, 0.8 mL, 0.8 mmol) for 1 h. The mixture was purified by silica gel chromatography (4−8% MeOH/$CHCl_3$) to give 98 mg (71%) of **17a** as a faintly yellow oil/foam. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (s, 1H), 7.81 (dd, 1H, J = 7.6, 1.2 Hz), 7.63 (dt, 1H, J = 7.6, 1.2 Hz), 7.45 (t, 1H, J = 7.6 Hz), 7.19 (d, 1H, J = 7.6 Hz), 5.22 (AB q, 2H, J = 16.4, 15.2 Hz), 4.13 (s, 1H), 3.25−3.46 (m, 2H), 2.82−2.89 (m, 1H), 2.70−2.77 (m, 1H), 2.58−2.63 (m, 1H), 1.74−1.82 (m, 1H), 1.63−1.71 (m, 1H), 1.45−1.57 (m, 1H), 1.11−1.19 (m, 1H). MS (ES) [M + H] calcd for $C_{19}H_{19}N_5O$, 334; found 334.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-prop-1-ynyl-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile (17b). 2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-bromo-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile (**13c**) (120 mg, 0.31 mmol) and tributyl(1-propynyl)tin (140 μL, 0.46 mmol) were stirred in dioxane (5 mL) in a flask purged with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (54 mg, 0.046 mmol) was added, and the solution was stirred at 96 °C for 40 h. Concentration in vacuo and purification by silica gel chromatography (16% MeOH/$CHCl_3$) gave 82 mg (76%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, CD_3OD): δ 7.82 (s, 1H), 7.64 (d, 1H, 7.6 Hz), 7.53 (t, 1H, J = 7.6 Hz), 7.36 (t, 1H, J = 7.6 Hz), 7.16 (d, 1H, J = 7.6 Hz), 5.30 (s, 2H), 3.40−3.48 (m, 1H), 3.21−3.30 (m, 1H), 2.78−2.89 (m, 2H), 2.58−2.66 (m, 1H), 1.91 (s, 3H), 1.85−1.93 (m, 1H), 1.52−1.74 (m, 2H), 1.18−1.27 (m, 1H). MS (ES) [M + H] calcd for $C_{20}H_{21}N_5O$, 348; found 348.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-(3-hydroxyprop-1-ynyl)-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile (17c). 17c was prepared in 66% yield using propargyl alcohol in the procedure outlined for 2-[2-(3-(*R*)-aminopiperidin-1-yl)-5-trimethylsilylethynyl-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile. ^{1}H NMR (400 MHz, CD_3OD): δ 7.90 (s, 1H), 7.63 (d, 1H, 7.6 Hz), 7.52 (t, 1H, J = 7.6 Hz), 7.36 (t, 1H, J = 7.6 Hz), 7.19 (d, 1H, J = 7.6 Hz), 5.28 (s, 2H), 4.24 (s, 2H), 3.48−3.54 (m, 1H), 3.31−3.38 (m, 1H), 2.78−2.89 (m, 2H), 2.61−2.69 (m, 1H), 1.85−1.93 (m, 1H), 1.52−1.74 (m, 2H), 1.19−1.28 (m, 1H). MS (ES) [M + H] calcd for $C_{20}H_{21}N_5O_2$, 364; found 364.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-5-(3,3-dimethylbut-1-ynyl)-6-oxo-6*H*-pyrimidin-1-ylmethyl]benzonitrile (17d). 17d was prepared in 51% yield using 3,3-dimethyl-1-butyne in the procedure outlined for **17a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (s, 1H), 7.82 (d, 1H, 7.2 Hz), 7.54 (t, 1H, J = 7.6 Hz), 7.45 (t, 1H, J = 7.2 Hz), 7.15 (d, 1H, J = 7.6 Hz), 5.22 (s, 2H), 3.20−3.40 (m, 2H), 2.71−2.76 (m, 2H), 2.53−2.59 (m, 1H), 1.46−1.82 (m, 3H), 1.20 (s, 9H), 1.10−1.19 (m, 1H). MS (ES) [M + H] calcd for $C_{23}H_{27}N_5O$, 390; found 390.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-6-oxo-5-vinyl-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (18a). 18a was prepared in 56% yield using tributylvinyltin in the general procedure outlined for **17b** and was isolated as the TFA salt. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (br s, 3H), 7.78 (s, 1H), 7.62 (d, 1H, 7.6 Hz), 7.56 (t, 1H, J = 7.6 Hz), 7.39 (t, 1H, J = 7.6 Hz), 7.29 (d, 1H, J = 7.6 Hz), 6.49 (dd, 1H, J = 30.4, 11.6 Hz), 6.03 (d, 1H, J = 17.6 Hz), 5.37 (AB q, 2H, J = 100.8, 14.8 Hz), 5.33 (d, 1H, J = 11.6 Hz), 3.47−3.59 (m, 3H), 3.16−3.26 (m, 2H), 1.95−2.05 (m, 2H), 1.80−1.90 (m, 1H), 1.60−1.71 (m, 1H). MS (ES) [M + H] calcd for $C_{19}H_{21}N_5O$, 336; found 336.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-4-methyl-6-oxo-5-*trans*-styryl-6*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (18b). 18b was prepared in 64% yield from *trans*-2-phenylvinylboronic acid according to the general procedure outlined for **15a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (br s, 3H), 7.83 (d, 1H, J = 7.2 Hz), 7.61−7.66 (m, 2H), 7.42−7.50 (m, 3H), 7.31 (t, 2H, J = 7.6 Hz), 7.17−7.22 (m, 2H), 7.00 (d, 1H, J = 16.4 Hz), 5.30 (AB q, 2H, J = 38.4, 15.2 Hz), 3.51−3.58 (m, 1H), 3.34−3.42 (m, 1H), 3.03−3.19 (m, 2H), 2.85−2.93 (m, 1H), 2.43 (m, 3H), 1.92−1.99 (m, 1H), 1.76−1.84 (m, 1H), 1.50−1.65 (m, 2H). MS (ES) [M + H] calcd for $C_{26}H_{27}N_5O$, 426; found 426.

2-{2-(3-(*R*)-Aminopiperidin-1-yl)-5-[2-*trans*-(4-fluorophenyl)-vinyl]-6-oxo-6*H*-pyrimidin-1-ylmethyl}benzonitrile, TFA salt (18c). 18c was prepared in 62% yield from *trans*-2-(4-fluorophenylvinyl-boronic acid according to the procedure outlined for **15a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.09 (s, 1H), 8.01 (br s, 3H), 7.82 (d, 1H, J = 7.2 Hz), 7.63 (t, 1H, J = 7.6 Hz), 7.43−7.54 (m, 4H), 7.22 (d, 1H, J = 7.6 Hz), 7.14 (t, 2H, J = 8.8 Hz), 6.92 (d, 1H, J = 16.4 Hz), 5.33 (AB q, 2H, J = 38.4, 15.2 Hz), 3.51−3.59 (m, 1H), 3.36−3.45 (m, 1H), 3.15−3.23 (m, 1H), 3.01−3.09 (m, 1H), 2.89−2.96 (m, 1H), 1.92−1.99 (m, 1H), 1.77−1.84 (m, 1H), 1.51−1.65 (m, 2H). MS (ES) [M + H] calcd for $C_{25}H_{24}FN_5O$, 430; found 430.

2-[2-(3-(*R*)-Aminopiperidin-1-yl)-6-oxo-5-((*E*)-2-pyridin-3-yl-vinyl)-6*H*-pyrimidin-1-ylmethyl]benzonitrile (18d). 3-Ethynylpyridine (1.03 g, 10 mmol) and tributyltin hydride (3.2 mL, 12 mmol) were stirred in dry THF (10 mL) with a catalytic amount of AIBN at 50 °C for 18 h. The solution was concentrated in vacuo and purified by silica gel chromatography (10% EOAc/hexanes) to give 2.09 g (53%) of 3-((*E*)-2-tributylstannanylvinyl)pyridine as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.61 (s, 1H), 8.45 (d, 1H, J = 3.2 Hz), 7.75 (d, 1H, J = 7.6 Hz), 7.25−7.29 (m, 1H), 6.93 (AB q, 2 H, J = 57.2, 19.6 Hz), 1.49−1.59 (m, 6H), 1.28−1.39 (m, 6H), 0.87−1.00 (m, 15H).

Also obtained from the reaction was 0.91 g (23%) of the less polar 3-((*Z*)-2-tributylstannanylvinyl)pyridine. ^{1}H NMR

(400 MHz, DMSO-d_6): δ 8.48−8.52 (m, 2H), 7.53−7.58 (m, 2H), 7.24−7.27 (m, 1H), 6.38 (d, 1H, J = 14.0 Hz), 1.35−1.45 (m, 6H), 1.20−1.30 (m, 6H), 0.78−0.90 (m, 15H).

18d was prepared in 55% yield using 3-((*E*)-2-tributylstannanylvinyl)pyridine in the general procedure outlined for **17b**. ^{1}H NMR (400 MHz, CD_3OD): δ 8.53 (d, 1H, J = 1.6 Hz), 8.32 (d, 1H, J = 4.8 Hz), 8.04 (s, 1H), 7.92 (d, 1H, J = 7.6 Hz), 7.70 (d, 1H, J = 7.6 Hz), 7.50−7.61 (m, 2H), 7.31−7.47 (m, 2H), 7.24 (d, 1H, J = 7.6 Hz), 7.00 (d, 1H, J = 16.4 Hz), 5.41 (s, 2H), 3.51−3.58 (m, 1H), 3.29−3.37 (m, 1H), 2.81−2.99 (m, 2H), 2.70−2.78 (m, 1H), 1.90−1.99 (m, 1H), 1.62−1.79 (m, 2H), 1.26−1.36 (m, 1H). MS (ES) [M + H] calcd for $C_{24}H_{24}N_6O$, 413; found 413.

2-[2-(3-(*R*)-Aminopyrimidin-1-yl)-5-bromo-6-oxo-6*H*-pyrimidin-1-ylmethyl]thiophene-3-carbonitrile, TFA salt (19). 2-Methylthiophene-3-carbonitrile[31] (1.36 g, 11 mmol), *N*-bromosuccinimide (2.56 g, 14.4 mmol), and a catalytic amount of benzoyl peroxide were stirred in benzene (30 mL) at 80 °C for 2 h. The solution was diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by silica gel chromatography (10% EtOAc/hexanes) gave 1.03 g (46%) of 2-bromomethylthiophene-3-carbonitrile as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.39 (d, 1H, J = 5.6 Hz), 7.17 (d, 1H, J = 5.6 Hz), 4.79 (s, 2H).

2-(5-Bromo-2-chloro-6-oxo-6*H*-pyrimidin-1ylmethyl)thiophene-3-carbonitrile was prepared in 58% yield from 2-chloro-5-bromo-3*H*-pyrimidin-4-one (**8c**) and 2-bromomethylthiophene-3-carbonitrile according to the general procedure outlined for 2-(5-bromo-2-chloro-6-oxo-6*H*-pyrimidin-1-ylmethyl)benzonitrile (**9c**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.40 (d, 1H, J = 5.6 Hz), 7.21 (d, 1H, J = 5.6 Hz), 5.74 (s, 2H). MS (ES) [M + H] calcd for $C_{10}H_5BrClN_3OS$, 330, 332; found 330, 332.

19 was prepared in 66% yield from 2-(5-bromo-2-chloro-6-oxo-6*H*-pyrimidin-1ylmethyl)thiophene-3-carbonitrile according to the general procedure outlined for **13c** and was isolated as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18 (s, 1H), 8.00 (br s, 3H), 7.69 (d, 1H, J = 5.6 Hz), 7.37 (d, 1H, J = 5.6 Hz), 5.45 (AB q, 2H, J = 28.0, 15.2 Hz), 3.26−3.52 (m, 3H), 2.80−2.95 (m, 2H), 1.92−2.02 (m, 1H), 1.62−1.81 (m, 2H), 1.41−1.51 (m, 1H). MS (ES) [M + H] calcd for $C_{15}H_{16}N_5OSBr$, 394, 396; found 394, 396.

2-((2-(3-(*R*)-Aminopiperidin-1-yl)-5-fluoro-6-oxopyrimidin-1(6*H*)-yl)methyl)-5-fluorobenzonitrile, TFA salt (20). A solution of 2-methyl-5-fluorobenzonitrile (3.4 g, 25.2 mmol), NBS (4.63 g, 26 mmol), and 100 mg of AIBN was refluxed for 2 h under nitrogen. After the mixture was cooled to room temperature, the solvent was removed and the residue was purified by column chromatography to give 2-bromomethyl-5-fluorobenzonitrile (2.7 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51−7.59 (m, 1H), 7.26−7.39 (m, 2H), 4.61 (s, 2H).

2-((5-Fluoro-2-chloro-6-oxopyrimidin-1(6*H*)-yl)methyl)-5-fluorobenzonitrile was prepared in 45% yield from 2-bromomethyl-5-fluorobenzonitrile according to the procedure outlined for **9c**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.32−7.48 (m, 2H), 5.63 (s, 1H). MS (ES) [M + H] calcd for $C_{12}H_6ClF_2N_3O$, 282; found 282.

20 was prepared in 36% yield from 2-((5-fluoro-2-chloro-6-oxopyrimidin-1(6*H*)-yl)methyl)-5-fluorobenzonitrile according to the general procedure outlined for **13c** and was isolated as the TFA salt. ^{1}H NMR (400 MHz, CD_3OD): δ 7.85 (d, J = 4 Hz, 1H), 7.37−7.59 (m, 3H), 5.40 (AB q, J = 16.0, 28.0 Hz, 2H), 3.47−3.64 (m, 2H), 2.91−3.25 (m, 3H), 1.57−1.91 (m, 4H). MS (ES) [M + H] calcd for $C_{17}H_{17}F_2N_5O$, 346; found 346.

2-((2-(3-(*R*)-Aminopiperidin-1-yl)-5-fluoro-6-oxopyrimidin-1(6*H*)-yl)methyl)-4-fluorobenzonitrile, TFA salt (21). A mixture of 2-bromo-5-fluorotoluene (3.5 g, 18.5 mmol) and CuCN (2 g, 22 mmol) in DMF was refluxed overnight. After cooling to room temperature, the mixture was diluted with water and extracted with hexane. The extract was dried over $MgSO_4$, and the solvent was removed. The residue was purified by column chromatography to give 4-fluoro-2-methylbenzonitrile (1 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 5.6, 8.8 Hz, 1H), 6.96−7.06 (m, 2H), 2.55 (s, 3H).

A solution of 4-fluoro-2-methylbenzonitrile (4.8 g, 25.4 mmol), NBS (4.5 g, 25.4 mmol), and 100 mg of AIBN was refluxed for 2 h under nitrogen. After the mixture was cooled to room temperature, the solvent was removed and the residue was purified by column chromatography to give 2-bromomethyl-4-fluorobenzonitrile in 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 5.2, 8.4 Hz, 1H), 7.28 (d, J=2.4, 8.8 Hz, 1H), 7.10−7.6 (m, 1H), 4.60 (s, 2H).

2-((5-Fluoro-2-chloro-6-oxopyrimidin-1(6*H*)-yl)methyl)-4-fluorobenzonitrile was prepared from 2-bromomethyl-4-fluorobenzonitrile and 2-chloro-5-fluoropyrimidin-4(3*H*)-one (**8a**) according to the procedure outlined for **9c**. This material was used in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 0.8 Hz, 1H), 7.73−7.78 (m, 1H), 7.13−7.20 (m, 1H), 6.88 (dd, J = 2.4, 8.8 Hz, 1H), 5.66 (s, 2H). MS (ES) [M + H] calcd for $C_{12}H_6ClF_2N_3O$, 282; found 282.

21 was prepared from 2-((5-fluoro-2-chloro-6-oxopyrimidin-1(6*H*)-yl)methyl)-4-fluorobenzonitrile according to the general procedure outlined for **13c** and was isolated in 31% yield as the TFA salt. ^{1}H NMR (400 MHz, CD_3OD): δ 7.75−7.88 (m, 2H), 7.18−7.27 (m, 2H), 5.42 (AB q, J = 15.2, 31.6 Hz, 2H), 3.47−3.64 (m, 2H), 2.89−3.23 (m, 3H), 1.57−2.17 (m, 4H). MS (ES) [M + H] calcd for $C_{17}H_{17}F_2N_5O$, 346; found 346.

2-((2-(3-(*R*)-Aminopiperidin-1-yl)-5-chloro-6-oxopyrimidin-1(6*H*)-yl)methyl)-4-fluorobenzonitrile, TFA salt (22). 22 was prepared in 33% yield from 2,5-dichloro-3*H*-pyrimidin-4-one (**8b**) and 2-bromomethyl-4-fluorobenzonitrile according to the general procedure outlined for **13c** and was isolated as the TFA salt. ^{1}H NMR (400 MHz, CD_3OD): δ 8.01 (s, 1H), 7.76−7.82 (m, 1H), 7.20−7.27 (m, 2H), 5.39 (AB q, J = 14.8, 24.0 Hz, 2H), 3.52−3.73 (m, 2H), 3.0−3.33 (m, 3H), 1.62−2.18 (m, 4H). MS (ES) [M + H] calcd for $C_{17}H_{17}ClFN_5O$, 362; found 362.

2-((2-(3-(*R*)-Aminopiperidin-1-yl)-5-bromo-6-oxopyrimidin-1(6*H*)-yl)methyl)-4-fluorobenzonitrile, TFA salt (23). 2-((5-Bromo-2-chloro-6-oxopyrimidin-1(6*H*)-yl)methyl)-4-fluorobenzonitrile was prepared in 35% yield from 2-bromomethyl-4-fluorobenzonitrile according to the procedure outlined for **9c**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.71−7.77 (m, 1H), 7.12−7.19 (m, 1H), 6.88 (dd, J = 2.4, 4.8 Hz, 1H), 5.66 (s, 2H). MS (ES) [M + H] calcd for $C_{12}H_6BrClFN_3O$, 341.9, 343.9; found 341.9, 343.9.

23 was prepared in 80% yield from 2-((5-bromo-2-chloro-6-oxopyrimidin-1(6*H*)-yl)methyl)-4-fluorobenzonitrile according to the general procedure outlined for **13c** and was isolated as the TFA salt. ^{1}H NMR (400 MHz, CD_3OD): δ 8.13 (s, 1H), 7.76−7.82 (m, 1H), 7.20−7.27 (m, 2H), 5.39 (AB q, J=14.2, 26.6 Hz, 2H), 3.67−3.73 (m, 2H), 3.02−3.32 (m, 3H), 1.62−2.17 (m, 4H). MS (ES) [M + H] calcd for $C_{17}H_{17}BrFN_5O$, 406, 408; found 406, 408.

2-(6-Chloro-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl)-benzonitrile (25b). To a solution of 6-chlorouracil (20 g, 122 mmol) in a mixture of DMF−DMSO (6:1, 600 mL) under nitrogen at 0 °C was added sodium hydride (60%, 5.5 g, 137 mmol) in portions. After 0.5 h, lithium bromide (8 g, 96 mmol) was added to the mixture and stirred for 15 min at 0 °C. A solution of α-bromo-*o*-tolunitrile (25.1 g, 128 mmol) in DMF (30 mL) was added dropwise and stirred at this temperature for 1 h and then room temperature overnight. The mixture was evaporated and coevaporated with water in vacuo to remove most of DMF and then poured into ice−water (1 L). The precipitate was collected by filtration. The crude product was suspended in hot AcOEt−$CHCl_3$ and sonicated for 5 min, allowed to stand at 0 °C for 1 h, and then filtered to give a white solid of the title compound (19 g) in 54% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.82 (s, 1H), 7.87 (d, 1H, J = 7.6 Hz), 7.71 (t, 1H, J = 7.6 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.37 (d, 1H, J = 8 Hz), 6.06 (s, 1H), 5.31 (s, 2H). MS (ES) [M + H] calcd for $C_{12}H_9ClN_3O_2$, 262; found 262.

2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl)benzonitrile (26b). To a cold (0 °C) solution of benzylated

6-chlorouracil **25b** (10 g, 38 mmol) in DMF−THF (1:1, 300 mL) under nitrogen was added NaH (60%, 1.6 g, 39.9 mmol) in portions, followed by addition of LiBr (2 g). The mixture was stirred at room temperature for 20 min. After addition of iodomethane (5.4 mL, 76 mmol), the flask was sealed and the mixture stirred at this temperature for 10 min, at room temperature for 2 h, and at 35 °C overnight and then concentrated in vacuo. The residue was dissolved in $CHCl_3$ and washed with water and brine, dried (Na_2SO_4), and filtered and then concentrated in vacuo. The crude product was crystallized from THF−hexanes to give 7.6 g (72%) of the title compound **26b**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (d, 1H, J = 7.6 Hz), 7.70 (t, 1H, J = 7.6 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.40 (d, 1H, J = 8 Hz), 6.21 (s, 1H), 5.38 (s, 2H), 3.28 (s, 3H). MS (ES) [M + H] calcd for $C_{13}H_{11}ClN_3O_2$, 276; found 276.

2-{6-[3(*R*)-Aminopiperidin-1-yl]-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl}benzonitrile, TFA salt (27a). 27a was prepared in 80% yield from compound **25b** by the procedure used in preparation of compound **27b**. ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1): δ ppm 7.65 (d, J = 7.5 Hz, 1 H), 7.58 (t, J = 7.8 Hz, 1 H), 7.39 (t, J = 7.5 Hz, 1 H), 7.27 (d, J = 7.8 Hz, 1 H), 5.32 (s, 1 H), 5.13−5.13 (ABq, 2H, J = 30.0, 15.0 Hz), 3.39 (m, 2 H), 2.95 (m, 2 H), 2.69 (m, 1 H), 2.12 (m, 1 H), 1.85 (m, 1 H), 1.64 (m, 2 H). MS (ES) [M + H] calcd for $C_{17}H_{20}N_5O_2$, 326; found, 326.

2-{6-[3(*R*)-Aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl}benzonitrile, TFA salt (27b). 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl)-benzonitrile (330 mg, 1.08 mmol), (*R*)-3-aminopiperidine dihydrochloride (246 mg, 1.4 mmol), and sodium bicarbonate (500 mg, 5.4 mmol) were stirred with 200 mg of activated molecular sieves (4 Å) in dry MeOH (5 mL) at 100 °C for 2 h. The mixture was filtered through Celite, concentrated in vacuo, and then diluted with $CHCl_3$, and washed with water. The water phase was extracted with $CHCl_3$, and the combined organic phases were washed with water, dried (Na_2SO_4), and filtered. TFA (1 mL) was added to the solution which was then concentrated in vacuo. The residue was dissolved in a small amount of MeOH, and Et_2O was added to force precipitation. The mixture was allowed to stand at room temperature overnight. Solvents were decanted, and the solid was washed with Et_2O twice to give 270 mg of product (56%) as off-white powder. ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1): δ 7.82 (d, 1H, J = 7.6 Hz), 7.65 (t, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 8.0 Hz), 5.42 (s, 1H), 5.50−5.00 (ABq, 2H, J = 41.6, 15.2 Hz), 3.30 (m, 2H), 3.16 (s, 3H), 2.91 (m, 1H), 2.76 (m, 2H), 1.93 (m, 1H), 1.79 (m, 1H), 1.51 (m, 2H). MS (ES) [M + H] calcd for $C_{18}H_{22}N_5O_2$, 340.2; found, 340.2.

2-{6-[3(*R*)-Aminopiperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl}benzonitrile, TFA salt (27c). Compound **27b** (40 mg, 0.1 mmol) in THF (2 mL) was treated with 1 M HCl in Et_2O (200 μL) at room temperature for 2 h, concentrated, and then purified by LC−MS to give the title compound in 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1): δ ppm 7.73 (d, J = 7.6 Hz, 1 H), 7.64 (t, J = 7.6 Hz, 1 H), 7.45 (t, J = 7.6 Hz, 1 H), 7.14 (d, J = 8.1 Hz, 1 H), 5.32−5.42 (m, 2 H), 3.43 (s, 3 H), 3.33−3.40 (m, 2 H), 3.17 (m, 2 H), 2.87 (s, 1 H), 2.08 (m, 1 H), 1.70 (m, 1 H), 1.32−1.43 (m, 2 H). MS (ES) [M + H] calcd for $C_{18}H_{21}ClN_5O_2$, 374; found, 374.

2-{6-[3(*R*)-Aminopiperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl}benzonitrile, TFA salt (27d). 27d was prepared in 38% yield using the procedures described in the preparation of **27b** except that ethyl bromide was used in place of iodomethane. ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1): δ ppm 7.66 (d, J = 7.8 Hz, 1 H), 7.59 (td, J = 7.8, 1.4 Hz, 1 H), 7.40 (t, J = 7.6 Hz, 1 H), 7.26 (d, J = 7.6 Hz, 1 H), 5.41 (s, 1 H), 5.13−5.23 (ABq, 2H, J = 41.6, 15.2 Hz), 3.91 (q, J = 7.1 Hz, 2 H), 3.37 (m, 2 H), 2.87−2.98 (m, 2 H), 2.70 (m, 1 H), 2.12 (m, 1 H), 1.88 (m, 1 H), 1.67 (m, 2 H), 1.15 (t, J = 6.9 Hz, 3 H). MS (ES) [M + H] calcd for $C_{19}H_{24}N_5O_2$, 354; found, 354.

6-[3-(*R*)-Aminopiperidin-1-yl]-1-(2-bromobenzyl)-1*H*-pyrimidine-2,4-dione, TFA salt (27e). 27e was prepared in 65% yield using the procedure for compound **27b** except that the methylation step was skipped and 2-bromobenzyl bromide was used in the place of α-bromo-*o*-tolunitrile. ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1): δ ppm 7.52 (d, J = 8.1 Hz, 1 H), 7.24 (t, J = 7.8 Hz, 1 H), 7.10 (t, J = 7.8 Hz, 1 H), 6.89 (d, J = 7.579 Hz, 1 H), 5.27 (s, 1 H), 4.92−5.04 (ABq, J = 34.1, 15.0 Hz, 2H), 3.27 (bd, J = 10.4 Hz, 1 H), 3.09−3.18 (m, 1 H), 2.89 (m, 1 H), 2.70 (t, J = 10.9 Hz, 1 H), 2.48 (t, J = 12.0 Hz, 1 H), 2.03 (m, 1 H), 1.60−1.71 (m, 1 H), 1.42−1.53 (m, 2 H). MS (ES) [M + H] calcd for $C_{16}H_{20}BrN_4O_2$, 379; found, 379.

6-[3-(*R*)-Aminopiperidin-1-yl]-1-(2-bromobenzyl)-3-methyl-1*H*-pyrimidine-2,4-dione, TFA salt (27f). 27f was prepared from compound **27e** in 61% yield using the methylation procedure for compound **26b**. ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1): δ 7.45 (d, J = 7.8 Hz, 1 H), 7.16 (t, J = 7.5 Hz, 1 H), 7.03 (t, J = 7.2 Hz, 1 H), 6.80 (d, J = 7.3 Hz, 1 H), 5.28 (s, 1 H), 4.93−5.05 (ABq, 2H, J = 36.4, 16.4 Hz), 3.22 (m, 1H), 3.19 (m, 3 H), 3.09 (m, 1 H), 2.84 (d, J = 12.6 Hz, 1 H), 2.63 (t, J = 10.5 Hz, 1 H), 2.42 (t, J = 10.9 Hz, 1 H), 1.97 (d, J = 11.1 Hz, 1 H), 1.58−1.69 (m, 1 H), 1.38−1.48 (m, 2 H). MS (ES) [M + H] calcd for $C_{17}H_{22}BrN_4O_2$, 393; found, 393.

6-[3-(*R*)-Aminopiperidin-1-yl]-1-(2-bromo-5-fluorobenzyl)-3-methyl-1*H*-pyrimidine-2,4-dione, TFA salt (27g). 27g was prepared in 46% yield using the procedure for compound **27b** except that 2-bromo-5-fluorobenzyl bromide was used in the place of α-bromo-*o*-tolunitrile. ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1) δ ppm 7.46 (dd, J = 8.7, 5.2 Hz, 1 H), 6.82 (td, J = 8.3, 2.9 Hz, 1 H), 6.59 (dd, J = 9.1, 3.0 Hz, 1 H), 5.28 (s, 1H), 4.99−5.06 (ABq, J = 41.7, 16.7 Hz, 2H), 3.28 (m, 1H), 3.23 (s, 3 H), 3.13−3.21 (m, 1 H), 2.86 (bd, J = 12.6 Hz, 1 H), 2.71 (t, J = 10.5 Hz, 1 H), 2.47 (t, J = 11.0 Hz, 1 H), 2.00−2.08 (m, 1 H), 1.65−1.74 (m, 1 H), 1.42−1.53 (m, 2 H). MS (ES) [M + H] calcd for $C_{17}H_{21}FBrN_4O_2$, 411; found, 411.

6-[3-(*R*)-Aminopiperidin-1-yl]-1-(2-chloro-5-fluorobenzyl)-3-methyl-1*H*-pyrimidine-2,4-dione, TFA salt (27h). 27h was prepared in 48% yield using the procedure for compound **27b** except that 2-chloro-5-fluorobenzyl bromide was used in the place of α-bromo-*o*-tolunitrile. ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1): δ ppm 7.34−7.40 (dd, J = 8.5, 5.1 Hz, 1 H), 6.97 (td, J = 8.3, 2.9 Hz, 1 H), 6.72 (dd, J = 9.0, 2.9 Hz, 1 H), 5.41 (s, 1 H), 5.11−5.19 (ABq, J = 41.7, 16.7 Hz, 2H), 3.37 (s, 1 H), 3.32 (s, 3H), 3.23−3.30 (m, 1 H), 2.96 (d, J = 12.1 Hz, 1 H), 2.81 (t, J = 10.2 Hz, 1 H), 2.59 (t, J = 11.1 Hz, 1 H), 2.13 (d, J = 10.4 Hz, 1 H), 1.76−1.86 (m, 1 H), 1.52−1.63 (m, 2 H). MS (ES) [M + H] calcd for $C_{17}H_{21}ClFN_4O_2$, 367; found 367.

6-[3-(*R*)-Aminopiperidin-1-yl]-1-(2-chloro-4-fluorobenzyl)-3-methyl-1*H*-pyrimidine-2,4-dione, TFA salt (27i). 27i was prepared in 45% yield using the procedure for compound **27b** except that 2-chloro-4-fluorobenzyl bromide was used in the place of α-bromo-*o*-tolunitrile. ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1) δ ppm 7.15 (dd, J = 8.211, 2.400 Hz, 1 H), 6.95−7.06 (m, 2 H), 5.40 (s, 1 H), 5.09−5.18 (ABq, J = 37.7, 15.9 Hz, 2H), 3.33−3.39 (m, 1 H), 3.30 (s, 3 H), 3.23−3.29 (m, 1 H), 2.98 (bd, J = 12.9 Hz, 1 H), 2.79 (t, J = 10.4 Hz, 1 H), 2.55−2.66 (t, J = 11.2 Hz, 1 H), 2.13 (m, 1 H), 1.78−1.88 (m, 1 H), 1.55−1.65 (m, 2 H). MS (ES) [M + H] calcd for $C_{17}H_{21}ClFN_4O_2$, 367; found 367.

2-[6-(3-Aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl]-4-fluorobenzonitrile, TFA salt (27j). A mixture of 3-methyl-6-chlorouracil (0.6 g, 3.8 mmol), 2-bromomethyl-4-fluorobenzonitrile (0.86 g, 4 mmol), and K_2CO_3 (0.5 g, 4 mmol) in DMSO (10 mL) was stirred at 60 °C for 2 h. The mixture was diluted with water and extracted with EtOAc. The organics were dried over $MgSO_4$, and the solvent was removed. The residue was purified by column chromatography to give 0.66 g of 2-(6-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl)-4-fluorobenzonitrile (60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, J = 7.2, 8.4 Hz, 1H), 7.26 (d, J = 4.0 Hz, 1H), 7.11−7.17 (m, 1H), 6.94 (dd, J = 2.0, 9.0 Hz, 1H), 6.034 (s, 2H), 3.39 (s, 3H). MS (ES) [M + H] calcd for $C_{13}H_9ClFN_3O_2$, 293; found 293.

2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl)-4-fluorobenzonitrile (300 mg, 1.0 mmol), 3-(*R*)-aminopiperidine dihydrochloride (266 mg, 1.5 mmol), and sodium bicarbonate (500 mg, 5.4 mmol) were stirred in a sealed tube in EtOH (3 mL) at 100 °C for 2 h. The final compound (367 mg, 81% yield) was obtained as a TFA salt after HPLC purification. ^{1}H NMR (400 MHz, CD_3OD): δ 7.77−7.84 (m, 1H), 7.16−7.27 (m, 2H), 5.46 (s, 1H), 5.17−5.34 (ABq, 2H, J = 35.2, 15.6 Hz), 3.33−3.47 (m, 2H), 3.22 (s, 3H), 2.98−3.08 (m, 1H), 2.67−2.92 (m, 2H), 2.07−2.17 (m, 1H), 1.82−1.92 (m, 1H), 1.51−1.79 (m, 2H). MS (ES) [M + H] calcd for $C_{18}H_{20}FN_5O_2$, 357; found, 357.

6-[3-(*R*)-Aminopiperidin-1-yl]-1-(2,5-dichlorobenzyl)-3-methyl-1*H*-pyrimidine-2,4-dione, TFA salt (27k). 27k was prepared in 38% yield using the procedure for compound **27b** except that 2,5-dichlorobenzyl bromide was used in the place of α-bromo-*o*-tolunitrile. ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1): δ ppm 7.50 (d, J = 8.6 Hz, 1 H), 7.39 (dd, J = 8.3, 2.526 Hz, 1 H), 7.22 (d, J = 2.5 Hz, 1 H), 5.41 (s, 1 H), 5.01−4.93 (ABq, J = 41.9, 16.2 Hz, 2H), 3.25 (m, 2 H), 3.10 (s, 3H), 2.85 (m, 1 H), 2.76 (m, 1 H), 2.67 (m, 1 H), 1.91 (m, 1 H), 1.75 (m, 1 H), 1.45 (m, 2 H). MS (ES) [M + H] calcd for $C_{17}H_{21}Cl_2N_4O_2$, 383; found 383.

6-[3-(*R*)-Aminopiperidin-1-yl]-1-(2-chloro-3,6-difluorobenzyl)-3-methyl-1*H*-pyrimidine-2,4-dione, TFA salt (27l). 27l was prepared in 43% yield using the procedure for compound **27b** except that 2-chloro-3,6-difluorobenzyl bromide was used in the place of α-bromo-*o*-tolunitrile. ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1) δ ppm 6.98−7.06 (m, 1 H), 6.90 (m, 1 H), 5.31 (s, 1 H), 5.01−5.20 (ABq, J = 24.2, 14.4 Hz, 2H), 3.28−3.37 (m, 2 H) 3.13 (s,3H), 3.01−2.94 (m, 1 H), 2.6−2.9 (m, 2 H), 2.10 (m, 1 H), 1.92 (m, 2 H), 1.73 (s, 1 H), 1.6−1.75 (m, 2 H). MS (ES) [M + H] calcd for $C_{17}H_{20}ClF_2N_4O_2$, 385; found 385.

2-[6-(2-Aminoethylamino)-3-ethyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl]benzonitrile, TFA salt (27n). 27n was prepared in 42% yield using the procedure for compound **27b** except that ethyl bromide was used in the place of methyl iodide and ethylene diamine was used in the place of the aminopiperidine. ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1) δ ppm 7.70 (d, J = 7.8 Hz, 1 H), 7.58 (t, J = 7.7 Hz, 1 H), 7.40 (t, J = 7.4 Hz, 1 H), 7.12 (d, J = 8.1 Hz, 1 H), 5.37 (s, 2 H), 3.95 (q, J = 6.8 Hz, 2 H), 3.45 (t, J = 5.9 Hz, 2 H), 3.11 (t, J = 6.1 Hz, 2 H), 1.19 (t, J = 6.8 Hz, 3 H). MS (ES) [M + H] calcd for $C_{16}H_{20}N_5O_2$, 314; found 314.

2-{6-[Azepan-3(±)-ylamino]-3-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl}benzonitrile, TFA salt (27n) and 2-{6-[3(±)-Aminoazepan-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl}benzonitrile, TFA salt (27o). 27n (11% yield) and **27o** (50% yield) were prepared from compound **26b** (70 mg, 0.27 mmol) and azepan-3-ylamine (70 mg, 0.61 mmol) using the procedure for compound **27b**. Both compounds were purified by HPLC and isolated as TFA salts.

27n: ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1) δ ppm 7.77 (d, J = 7.8 Hz, 1 H), 7.66 (t, J = 7.6 Hz, 1 H), 7.47 (t, J = 8.0 Hz, 1 H), 7.36 (d, J = 8.1 Hz, 1 H), 5.54 (s, 1 H), 5.49 (s, 1 H), 5.27−5.36 (ABq, J = 26.0, 16.4 Hz, 2H), 3.50 (m, 2 H), 3.37 (s, 2 H), 3.26 (s, 3 H), 3.12 (m, 1H), 3.04 (m, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.60−1.71 (m, 3H). MS (ES) [M + H] calcd for $C_{19}H_{24}N_5O_2$, 354; found, 354.

27o: ^{1}H NMR (400 MHz, $CDCl_3$−CD_3OD 10:1) δ ppm 7.77 (d, J = 8.1 Hz, 1 H), 7.63 (t, J = 7.6 Hz, 1 H), 7.46 (t, J = 8.0 Hz, 1 H), 7.19 (d, J = 7.6 Hz, 1 H), 5.48 (s, 1H), 5.44−5.52 (ABq, J = 61.9, 18.4 Hz, 2H), 3.80 (s, 1 H), 3.58−3.50 (m, 1 H), 3.39−3.39 (m, 1 H), 3.26 (s, 3 H), 3.13 (m, 1 H), 2.89 (t, J = 12.4 Hz, 1 H), 2.04 (m, 1 H), 1.93 (m, 1 H), 1.86 (m, 2 H), 1.59−1.70 (m, 2 H). MS (ES) [M + H] calcd for $C_{19}H_{24}N_5O_2$, 354; found, 354.

2-((6-(3-(*R*)-Amino-3-methylpiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-4-fluorobenzonitrile, TFA salt (27p). 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl)-4-fluorobenzonitrile (300 mg, 1.0 mmol), 3-(*R*)-amino-3-methylpiperidine dihydrochloride (266 mg, 1.4 mmol), and sodium bicarbonate (500 mg, 5.4 mmol) were stirred in a sealed tube in EtOH (3 mL) at 100 °C for 2 h. The final compound was obtained (360 mg, 80% yield) as the TFA salt after HPLC purification. ^{1}H NMR (400 MHz, CD_3OD): δ. 7.78−7.83 (m, 1H), 7.14−7.26 (m, 2H), 5.47 (s, 1H), 5.12−5.36 (ABq, 2H, J = 105.2, 15.6 Hz), 3.21 (s, 1H), 2.72−3.15 (m, 4H), 1.75−1.95 (m, 4H), 1.39 (s, 3H). MS (ES) [M + H] calcd for $C_{19}H_{22}FN_5O_2$, 372; found, 372.

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Supporting Information Available: X-ray diffraction data, DPP-4 assay procedure, microsomal stability procedure, and purity data. This material is available free of charge via the Internet at http://pubs.acs.org.

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