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Design and Synthesis of Diazatricyclodecane Agonists of the G-Protein-Coupled Receptor 119

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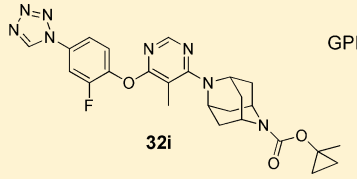
Supporting Information

ABSTRACT: A series of GPR119 agonists based on a 2,6-diazatricyclo[3.3.1.1~3,7~]decane ring system is described. Also provided is a detailed account of the development of a multigram scale synthesis of the diazatricyclic ring system, which was achieved using a Hofmann–Löffler–Freytag reaction as the key step. The basis for the use of this complex framework lies in an attempt to constrain one end of the molecule in the "agonist conformation" as was previously described for 3-oxa-7-aza-bicyclo[3.3.1]nonanes. Optimization of carbamate analogues of the diazatricylic compounds led to the identification of **32i** as a potent agonist of the GPR119 receptor with low unbound human liver microsomal clearance. The use of an agonist response weighted ligand lipophilic efficiency (LLE) termed AgLLE is discussed along with the issues of applying efficiency measures to agonist programs. Ultimately, solubility limited absorption and poor exposure reduced further interest in these molecules.



GPR119 cAMP EC_{50} = 22 nM 101%IA
K_i = 15 nM
AgLLE = 4.4

INTRODUCTION

The incidence of diabetes continues to grow globally with recent estimates of 384 million cases worldwide.[1] Generally diagnosis is determined by measurement of fasting plasma glucose (FPG), but recently an international recommendation has been made for the use of glycosylated hemoglobin (HbA_{1c}) as a time integrated marker of glucose levels.[2] Current pharmacologic treatment of diabetes is largely characterized by modulation of the pathway for the endogenous hormone insulin either by increasing its secretion or by sensitizing the target tissues to its action.[3,4] Although an orthogonal mechanism that addresses glucose directly by increasing its disposal in urine is currently in development,[5] the insulin pathway continues to receive attention, particularly with respect to achieving glycemic control with reduced risk of hypoglycemia or for exhausting the ability of the pancreas to secrete insulin.

Interest in the non-peptide G-protein-coupled receptor 119 (GPR119) can be traced to the success of glucagon-like peptide 1 (GLP-1) injectable drugs such as exenatide[6] and the oral small molecule inhibitors that act by increasing the circulating levels of active GLP-1 by blocking its enzymatic degradation by dipetidyl dipeptidase IV (DPPIV).[7] Theoretically a GPR119 agonist could provide the benefits of the former in an oral agent through the stimulation of GPR119 receptors in the gastrointestinal tract.[8,9] In addition, stimulation of GPR119 receptors in the islet is proposed to have beneficial effects on the health of islets.[10] These theoretical attributes have thus far been a challenge to demonstrate clinically, and the potential of GPR119 agonists remains unanswered.[11−13]

Although early GPR119 structures showed a high prevalence of a piperidine carbamate on one end of the molecule (the "head") and a sulfone on the other (the "tail"), it is now apparent that other structural motifs are tolerated.[14−18] Interestingly, synthetic agonist ligands are structurally distinct from the growing number of "endogenous" ligands of the receptor.[19,20]Accompanying the evolution of GPR119 agonist structures has been an increasing understanding of the structural features that drive an agonist response. Previously we described a conformational hypothesis to explain the differences in human agonist pharmacology for oxaazabicyclo[3.3.1]nonane head pieces.[21] Herein we describe the extension of this hypothesis to a novel series of bridged cyclic structures.

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RESULTS AND DISCUSSION

Design and Synthesis of the "Cage". As shown in Figure 1, the approach was to constrain the piperidine head piece as in

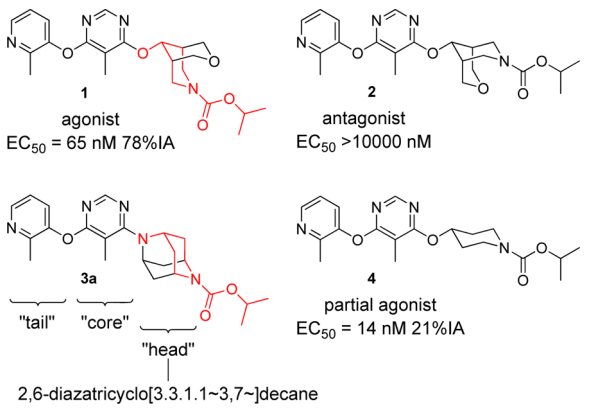
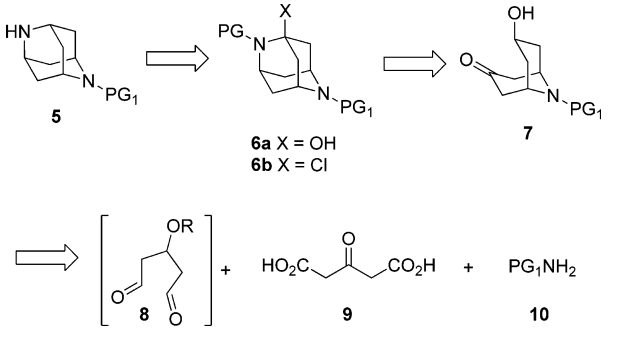


Figure 1. Functional profile for bridged cyclic vs unbridged structures.

the oxoazabicyclo[3.2.1]octanes **1** and **2**.[21] At the same time the aim was to ensure that the preferred conformation locks this part of the molecule into the "agonist conformation". The ring system we planned to use for achieving this was a 2,6-diazatricyclo[3.3.1.1~3,7~]decane, informally referred to as the "cage".[22] While the carbamate placement would closely match that of compound **1** and provide a level of confidence in achieving an agonist profile, the switch to a nitrogen linkage between the headgroup and the "core" central pyrimidine ring would have less predictable consequences. One of the concerns with the change centered on the added carbons near the pyrimidine ring and the impact they may have on the torsion to the central pyrimidine, particularly one bearing a methyl group as in **3a**. From a calculated physicochemical perspective, the diazatricyclo[3.3.1.1~3,7~]decane system has a similar ClogP to the oxoazabicyclo[3.2.1]octane in the context of structures **1**–**3** (ClogP(**3a**) = ClogP(**1**) = 3.3). By far the biggest concern with the proposal, however, was how to address the synthesis challenge presented by the complex cage structure.

To fully test how well the cage structures fit our conformational hypothesis, we needed to enable an efficient and scalable synthesis of a versatile intermediate such as **5** (Scheme 1) to access bridged-cyclic structures such as **3a** (Figure 1). Several synthetic strategies for the synthesis of the requisite cage intermediate were explored. Our first attempt is outlined retrosynthetically in Scheme 1. In this scheme the cage template **5** would ultimately result from a hydrodechlorination

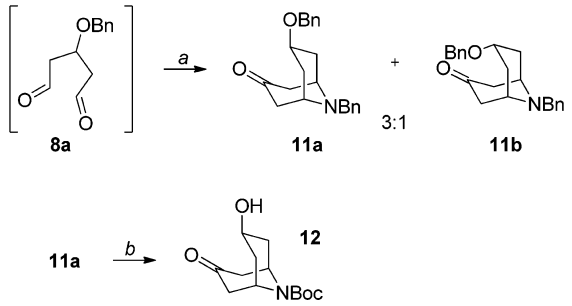
Scheme 1. Retrosynthetic Analysis of the 2,6-Diazatricyclo[3.3.1.1~3,7~]decane Ring System



of intermediate **6b**.[23] In turn, this intermediate would arise from chlorination of the corresponding aminal **6a**. An oxidation of the hydroxyl group in **7** and reductive amination with hydride delivery from the convex face would be required to produce **6a**. Bicyclic **7** would then be accessed via a double Mannich reaction on the iminium species formed from **8** and **10** (Scheme 1).

As shown in Scheme 2, the synthetic sequence used to pursue this approach began with the Mannich reaction of

Scheme 2. Mannich/Reductive Amination Approach[a]

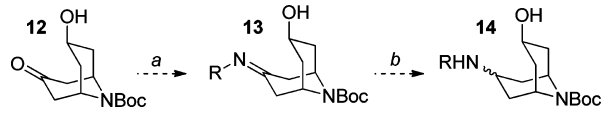


[a]Reagents and conditions: (a) 1,3-acetonedicarboxylic acid, $BnNH_2$, conc HCl, H_2O, 50 °C (35%); (b) H_2, $Pd(OH)_2$, Boc_2O, MeOH, 23 °C (quant).

bisaldehyde **8a**,[24] benzylamine, and acetone-1,3-dicarboxylic acid.[25] This provided a 3:1 mixture of isomers favoring the enolate addition to the face of the iminium opposite that of the benzyl ether. Hydrogenolysis of the major isomer **11a** in the presence of di-*tert*-butyl dicarbonate provided bicyclic ketone **12**.

Installation of the second nitrogen via a two-step reductive amination protocol was then attempted following the conditions shown in Table 1. Only recovered starting material

Table 1. Reductive Amination Conditions



step a	step b	pressure (bar)	temp (°C)	reducing agent
NH_3/EtOH	EtOH	40	40	Raney Ni
$BnNH_2$/EtOH	EtOH	70	70	Raney Ni
$MeNH_2$/EtOH	EtOH/NH_4OAc	10	25	PtO_2
NH_2OH·HCl, NaOAc/MeOH	THF		30–40	$LiAlH_4$

was obtained after attempted reductive amination via sequential treatment of **12** with NH_3/MeOH and Raney nickel.[26] The use of benzylamine[27] or methylamine with PtO_2 as catalyst[28] yielded similar results. Condensation of the C-3 ketone with hydroxylamine followed by LAH reduction of the oxime resulted in decomposition of the oxime to a complex mixture that was not investigated further.[29] The lack of success in installing the C-3 amine in this fashion necessitated exploring a different approach to the cage intermediate.

An alternative approach was to exploit the work of Rassat et al. who, in 1974, disclosed the synthesis of a 2,6-diazatricyclo-[3.3.1.1~3,7~]decane (2,6-diazaadamantane) derivative via Hofmann–Löffler–Freytag (HLF) ring closure (Scheme 3).[30]

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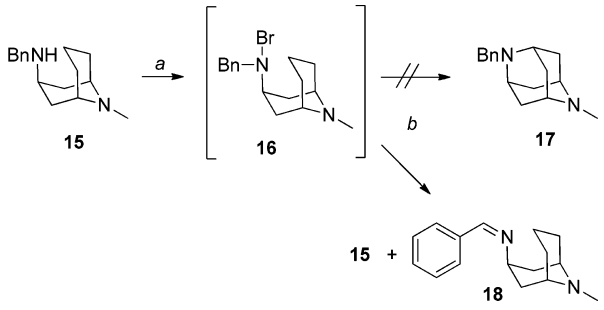
Despite the fact that Li[31] failed to reproduce the Rassat work, the simplicity of the approach compelled us to further explore this free radical chain cyclization process.

Scheme 3. Rassat's Route to 2,6-Diazaadamantane Derivatives[a]

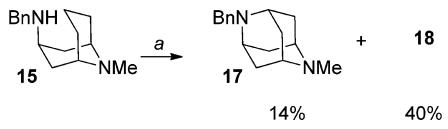


[a]Reagents and conditions: (a) Br_2, cyclohexane, 0 °C; (b) 84% H_2SO_4, 65 °C, 30 min (**15**, 30%, **18**, 33%).

Consistent with the work of Li, our attempts to follow the sequence in Scheme 3 using the published conditions with Br_2 or *N*-bromosuccinimide failed to provide any of the desired **17**. In both cases, the compounds isolated from the reaction were benzaldimine **18** arising from the formal loss of HBr and recovered starting material. Presumably if **18** was formed from the aminyl radical derived from homolytic cleavage of the N–Br bond, the rate of hydrogen atom abstraction from the benzylic methylene must be greater than that of the cross-ring abstraction required to form **17**. It is also possible that under the reaction conditions in Scheme 3, no homolytic bond cleavage occurs, only elimination of HBr.

Although studies have shown that homolytic cleavage of *N*-chloroamines under acidic conditions leads to protonated aminyl radicals that are less prone to disproportionation/dimerization and undergo more efficient HLF reaction,[32] we did not try this acidic halide variation. Instead, we explored the acid free conditions reported by Ban as shown in Scheme 4.[33]

Scheme 4. Initial Hofmann–Löffler–Freytag Reaction[a]



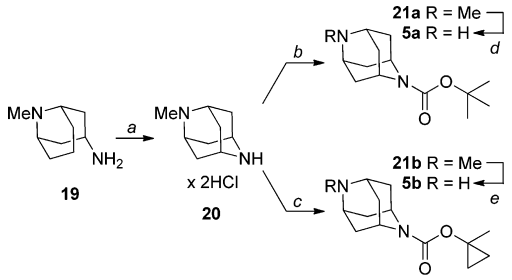
[a]Reagents and conditions: (a) NCS, Et_2O, 0 °C, 5 min; then Et_3N, hν, 0 °C, 45 min (**17**, 29%; **18**, 40%).

In this case *N*-chlorosuccinimide was used to N-chlorinate **15** and homolysis was achieved by first addition of triethylamine followed by photolysis. Substantial amounts of the benzaldimine **18** were still obtained. However, for the first time, small amounts of the desired cage compound **17** were produced. While this was an encouraging result, significant improvements in yield would be needed to supply sufficient quantities of **17** for the rapid synthesis of analogues.

To improve the yield of the cyclization step, we needed to identify an HLF precursor less prone to unproductive side reactions. One possibility was to replace the troublesome *N*-benzyl with a more inert protective group. The more efficient approach was to forego a protective group altogether.[34]

As shown in Scheme 5, treatment of commercially available endo-3-amino-9-methyl-9-azabicyclo[3.3.1]nonane **19** with *t*-

Scheme 5. Optimization of the Hofmann–Löffler–Freytag Reaction[a]



[a]Reagents and conditions: (a) *t*-BuOCl, Et_2O, 23 °C, 15 min; then hν, 35 °C, 60 min, (68%) of 3:1 mix **20**/**19**; (b) Boc_2O, Et_3N, MeOH, 23 °C, 30 min (54%, steps a and b); (c) 1-methylcyclopropyl 4-nitrophenylcarbonate, Et_3N, CH_2Cl_2, 16 h, (44%, steps a and c); (d) $KMnO_4$, NaOH (1.5 N), THF, 68 h (90%); (e) ACE-Cl, 1,2-DCE, 90 °C, 1.5 h; MeOH, 90 °C, 1.5 h (93%).

BuOCl, followed by ultraviolet irradiation of the mixture, provided a 68% yield of a 3:1 mixture of **20** and starting material as a hygroscopic solid. Switching to *t*-BuOCl eliminated the succinimide byproduct formed when *N*-chlorosuccinimide was used as the chloronium source and simplified the isolation of the product. The cage intermediate **20** was easily converted to the *tert*-butyl (**21a**) and 1-methylcyclopropyl (**21b**) carbamate derivatives in 54% and 44% yield, respectively, from **19**. To complete the synthesis of the cage intermediate needed for our analogue work, we needed to demethylate **21a** and **21b**. Compound **21b** was demethylated with 1-chloroethyl chloroformate (ACE-Cl) using the standard conditions to provide **5b** in 93% yield.[35] For the demethylation of **21a**, we used an alternative method because of concerns with the HCl content of commercial sources of ACE-Cl and the acid instability of the Boc group. Thus, intermediate **21a** was demethylated under oxidative conditions with $KMNO_4$ to afford **5a** in 90% yield.[36]

Synthesis and SAR of Cage Analogues. With an efficient and scalable method to prepare 2,6-diazatricyclo-[3.3.1.1~3,7~]decane derivatives we were ready to investigate the impact of this novel piperidine surrogate on human GPR119 pharmacology. The compounds shown in Table 2 were synthesized using the general sequence shown in Scheme 6. The synthesis of **25a–c** began with the addition of 2-fluoro-4-(methylsulfonyl)phenol to 4,6-dichloro-5-methylpyrimidine

Table 2. In Vitro Human GPR119 Pharmacology for 25a–c and 26

compd	cAMP EC_{50} (nM)[a]	IA (%)	K_i (nM)[a]	ClogP (ElogD)[b]
25a	40 ± 12	87 ± 8	41 ± 24	3.2
	n = 6		*n* = 5	(4.6)
25b	121 ± 34	74 ± 4	141 ± 71	2.8
	n = 9		*n* = 5	(4.4)
25c	169 ± 49	91 ± 8	131 ± 45	2.8
	n = 4		*n* = 4	(4.3)
26	29 ± 28	49 ± 7	53 ± 56	2.8
	n = 24		*n* = 9	(4.5)

[a]See ref 21 for assay conditions. [b]See ref 38.

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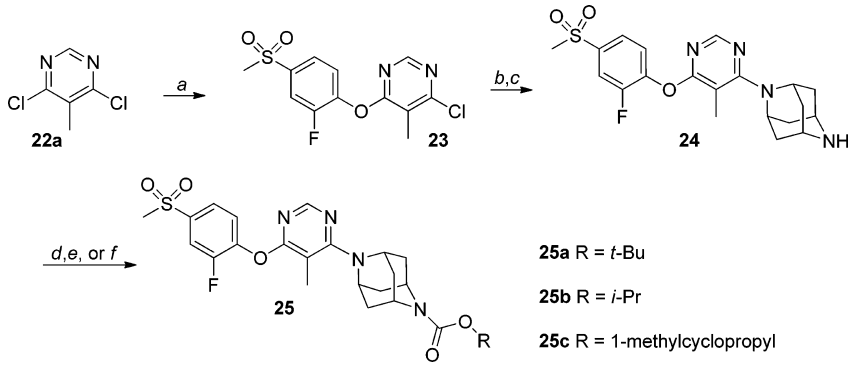
Scheme 6. Addition of the 2,6-Diazatricyclo[3.3.1.1~3,7~]decane to Biaryl Chloropyrimidine via S_NAr[a]



[a]Reagents and conditions: (a) 2-fluoro-4-(methylsulfonyl)phenol, Cs_2CO_3, CH_3CN, microwave 120 °C, 1.5 h (57%); (b) 2-methyl-2,6-diazatricyclo[3.3.1.1~3,7~]decane, Cs_2CO_3, CH_3CN, microwave 180 °C, 1 h (57%); (c) ACE-Cl, 1,2-DCE, 90 °C, 1.5 h; MeOH, 90 °C, 1.5 h; (d) Boc_2O, Et_3N, CH_2Cl_2, 23 °C, 30 min (17%, steps c and d); (e) isopropyl chloroformate, DIPEA, CH_2Cl_2, 23 °C, 18 h (74%); (f) 1-methylcyclopropyl 4-nitrophenylcarbonate, DIPEA, CH_2Cl_2, 16 h (57%).

22a. The resulting biaryl ether **23**[37] underwent nucleophilic aromatic substitution with the Boc-cage derivative **20** followed by N-demethylation to provide pyrimidine **24**. The desired carbamates derivatives **25a–c** were then obtained by standard acylation. The pharmacology of these analogues was compared with that of the unbridged piperidine analogue **26**[37] (Figure 2).

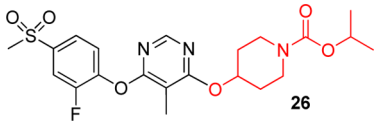


Figure 2. Piperidinol comparator.

Consistent with our hypothesis, direct comparison of **25b** and **26** showed that the cage analogue indeed elicits a greater agonist response than its piperidinol counterpart in our 3′,5′-cyclic adenosine monophosphate (cAMP) functional assay. To investigate whether the conformational disposition of the cage group resembles the conformation of the oxoazabicyclo[3.2.1]-octane headgroup we explored earlier, we obtained a single crystal X-ray structure for **25b**.

As seen in Figure 3, the cage structure places the "crown" methine in a similar torsional arrangement as in the case of the piperidinol,[21] just out of plane with one of the pyrimidine

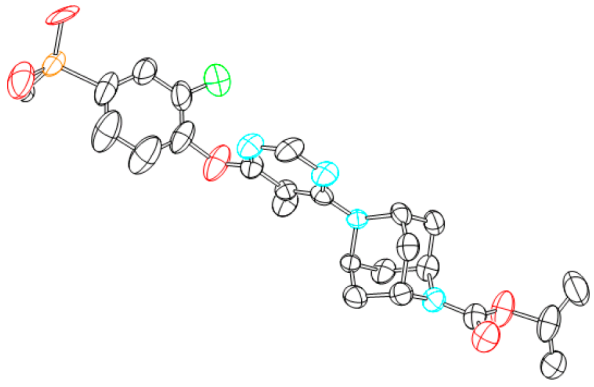


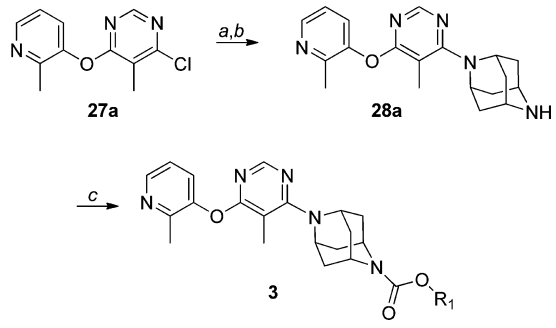
Figure 3. ORTEP of **25b** with ellipsoids drawn at the 50% confidence level.

nitrogens. In effect this places the carbamate in the same area as the "agonist" conformation of **1**.

To make the comparison with analogues in the oxoazabicyclo[3.2.1]octane series, we next wanted to incorporate the methylpyridyloxy tail. Our experience showed that the methylpyridyloxy group generally provides a lower agonist response relative to the fluoro(methylsulfonyl)phenoxy group. Having a baseline comparator with near 50% of the maximal response would allow both positive and negative changes in intrinsic activity (IA) to be readily assessed, thus revealing the contribution of various cage groups on agonist response. Also, methylpyridyloxy analogues exhibit superior aqueous solubility relative to those having fluoro(methylsulfonyl)phenoxy tails.[21,39]

The synthesis of the methylpyridyloxy analogues is shown in Scheme 7. Nucleophilic aromatic substitution reaction between

Scheme 7. Synthesis of 2,6-Diazatricyclo[3.3.1.1~3,7~]decane Pyridyloxypyrimidine Analogues[a]



[a]Reagents and conditions: (a) *tert*-butyl 2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate **5a**, Na_2CO_3, CH_3CN, 1200 °C, 42 h (53%); (b) 4 N HCl/1,4-dioxane, MeOH, 20 °C, 16 h; (c) $R_1OC(O)X$, Et_3N, CH_2Cl_2, 23 °C, 12–16 h (31–94%, steps b and c).

5a and commercially available chloropyrimidine **27a** followed by Boc cleavage provided the pyrimidine derivative **28a**, which was used for the synthesis of the carbamate analogues **3a–i** in Table 3.

Given the apparent positional contribution of the carbamate on the functional profiles of **1** and **2**, enforced by their distinct conformations, we also wanted to explore the nature of the

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Table 3. In Vitro Human GPR119 Pharmacology for 3a−i

compd	R_1, Scheme 7	cAMP EC_{50} (nM)[a]	IA (%)	K_i (nM)	ClogP (ElogD)[b]
3a	isopropyl	559 ± 1128	64 ± 16	2233 ± 1608	3.3
		n = 10		n = 5	(3.8)
3b	Et	5562 ± 2223	56% at 10 μM	1970 ± 914	3.0
		n = 3		n = 4	
3c	1-methylcyclopropyl	636 ± 1201	81 ± 10	586 ± 668	3.4
		n = 21		n = 4	(4.0)
3d	cyclobutyl	130 ± 59	53 ± 6	682 ± 409	3.4
		n = 5		n = 3	
3e	*tert*-butyl	40 ± 11	61 ± 13	486 ± 204	3.7
		n = 3		n = 3	(4.3)
3f	isobutyl	88 ± 75	27 ± 5	231 ± 78	3.9
		n = 7		n = 5	(4.5)
3g	(*R*)-*sec*-butyl	145 ± 59	44 ± 7	290 ± 53	3.9
		n = 3		n = 3	(4.4)
3h	(*S*)-*sec*-butyl	155 ± 62	45 ± 4	493 ± 24	3.9
		n = 3		n = 3	(4.4)
3i	1-methylcyclobutyl	75 ± 19	46 ± 3	136 ± 41	3.9
		n = 3		n = 3	(4.5)

[a]See ref 21 for assay conditions. [b]See ref 38.

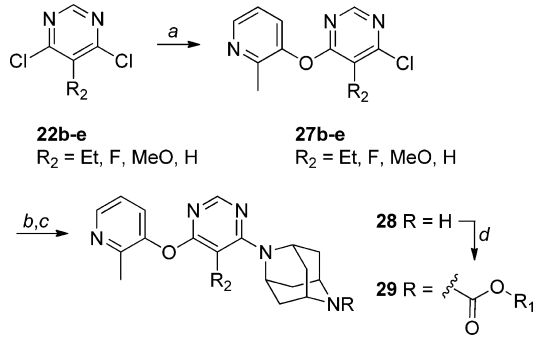
carbamate on the functional response. As shown in Table 3, branching near the carbamate oxygen led to the compounds with the highest agonist response. Interestingly, the methylpyridyloxy tail did not lower the IA relative to the sulfone-based tail to the extent anticipated with some overlap remaining in the standard deviation for the maximal agonist response. With the exception of **3b**, a lower agonist response could not be ascribed to reduced binding affinity. The aqueous solubility of the representative **3c** (0.5 μg/mL, phosphate buffered saline, pH 7.4, and 6.8 mg/mL at pH 1.2) suggested the potential for good aqueous solubility at low pH. The in vitro human liver microsomal clearance for the compounds tracked with lipophilicity. Of the compounds tested in Table 3, only compounds with ClogP greater than 3.7 demonstrated scaled apparent intrinsic clearance ($Cl_{int,app,scaled}$) greater than 30 mL min^{-1} kg^{-1} in human liver microsomes.

Unfortunately, when straightforward changes to the terminal nitrogen of the cage headgroup were employed, it was not possible to obtain a sufficiently potent full agonist using the methylpyridyloxy tail. While we had demonstrated that the cage was beneficial for eliciting an agonist response, it was at the cost of adding molecular weight and limited options for easy substitutions. Unable to overcome the lower IA for the methylpyridyloxy tail with changes to the cage head, alternative tail−core combinations would be needed to achieve the desired pharmacologic profile and would potentially limit options for retaining desirable physicochemical properties.

Next we explored the impact of different substitution on the core pyrimidine ring. As mentioned previously, there was concern that such changes would create a more congested environment around the cage headgroup relative to the piperidinol.

Scheme 8 describes the synthesis of the modified core analogues. As shown in Table 4, changes to R_2 on the central pyrimidine ring generally resulted in weaker agonists compared to compounds where R_2 is methyl. In certain cases, such as when R is H, this is a consequence of a loss in binding affinity to the receptor. No additional effort was applied to this region of the molecule.

Scheme 8. Synthesis of C-5 Substituted Pyrimidine Derivatives[a]



[a]Reagents and conditions: (a) 2-methylpyridin-3-ol, KO-*t*-Bu, THF/DMF, 0−23 °C (81−90%); (b) *tert*-butyl 2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate **5a**, Na_2CO_3 or $NaHCO_3$, DMF or DMA, 80−120 °C, 1−16.5 h (51−87%); (c) 4 N HCl/1,4-dioxane, MeOH or TFA, CH_2Cl_2, 23 °C, 1.25−3 h; (d) $R_1OC(O)X$, Et_3N, CH_2Cl_2, 23 °C, 12−16 h (7−93%, steps c and d).

Finally, the tail portion of the molecule was explored starting with **22a**, attaching the tail piece and then coupling to cage **5a** (Scheme 9). Cage **5a** was selected because removal of a Boc group rather than a methyl was anticipated to provide greater flexibility in the choices of tail groups. As shown in Table 5, we explored a number of phenoxy groups terminated with motifs that would project a hydrogen bond acceptor in a position similar to that of the sulfonyl compounds **25a−c**. With the possible exception of the 4-cyano-2-fluorophenoxy group, the changes led to a higher maximal agonist response than that associated with the methylpyridyloxy tail. Indeed, in some instances the IA was greater than that seen for the prototype sulfone analogues **25a−c**. In comparing the various five-membered heterocycles examined, both the tetrazole and triazole isomers led to examples with some of the better agonist profiles. Interestingly, methyl substitution on the 1,2,4-triazole was poorly tolerated (see **32m**; cf. **32g**). The reduced binding affinity and corresponding loss in functional activity with this change suggest a disruption to the coplanarity of the phenyl

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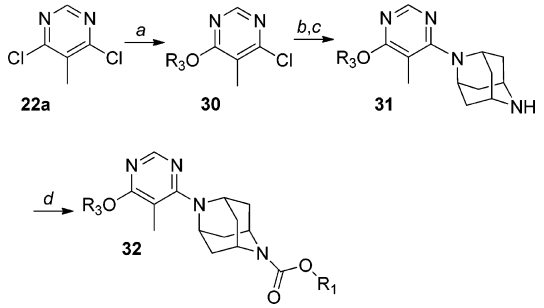
Table 4. In Vitro Human GPR119 Pharmacology for 29a–j

compd	R_1, Scheme 8	R_2, Scheme 8	cAMP EC_{50} (nM)[a]	IA (%)	K_i (nM)	ClogP (ElogD)[b]
29a	1-methylcyclopropyl	H	>10000		>8148	2.9
			$n = 3$		$n = 1$	
29b	*tert*-butyl	H	>10000		>8148	3.2
			$n = 3$		$n = 2$	
29c	isopropyl	Et	164 ± 153	36 ± 0.2	197 ± 55	3.9
			$n = 3$		$n = 3$	(4.3)
29d	1-methylcyclopropyl	Et	49 ± 21	52 ± 5	123 ± 33	3.9
			$n = 6$		$n = 3$	(4.4)
29e	*tert*-butyl	Et	16 ± 7	37 ± 4	18 ± 6	4.3
			$n = 5$		$n = 3$	
29f	1-methylcyclopropyl	F	>10000		>7318 ± 1027	2.8
			$n = 3$		$n = 3$	
29g	*tert*-butyl	F	>3014 ± 4665	47 ± 3	814 ± 569	3.2
			$n = 4$		$n = 3$	
29h	isopropyl	OMe	691 ± 184	28 ± 5	1496 ± 103	3.0
			$n = 3$		$n = 3$	(3.6)
29i	1-methylcyclopropyl	OMe	1028 ± 482	43 ± 4	3123	3.1
			$n = 3$		$n = 1$	
29j	*tert*-butyl	OMe	144 ± 71	35 ± 7	163 ± 33	3.4
			$n = 3$		$n = 3$	

[a]See ref 21 for assay conditions. [b]See ref 38.

Scheme 9. Synthesis of 2,6-Diazatricyclo[3.3.1.1–3,7~]decane Analogues with Tail Variations[a]



[a]Reagents and conditions: (a) R_3OH, Cs_2CO_3 or K_2CO_3, CH_3CN or DMF, 23–120 °C, 1–24 h (43–90%); (b) *tert*-butyl 2,6-diazatricyclo-[3.3.1.1–3,7~]decane-2-carboxylate **5a**, $NaHCO_3$, Cs_2CO_3, or DIPEA, DMF, DMSO, or CH_3CN, 60–120 °C, 2–64 h, (13–72%); (c) TFA, CH_2Cl_2, 23 °C, 3 h; (d) $R_1OC(O)Cl$, Et_3N, CH_2Cl_2, 23 °C, 12–16 h (24–72%, steps c and d).

ring and the terminal triazole and/or a steric clash between the added methyl group and the receptor.

Selection and Characterization of Compound 32i as a Potential Candidate. Ultimately, identifying the most compelling agonist in the cage series was not difficult since relatively few full agonists with EC_{50} below 100 nM were identified. The tetrazole-containing compounds (**32d,e,f,h,i,j**) proved to be the best at providing a low EC_{50} and a relatively full agonist response. Among these, **32i** was one of the most potent agonists that retained good human liver microsomal stability ($Cl_{int,app,scaled}$ < 9.5 mL min^{-1} kg^{-1}).

Others have reportedly[15,39] optimized their GPR119 agonists by tracking a property termed ligand lipophilic efficiency (LLE),[40,41] a combined measure of potency and lipophilicity. Although we did not use this methodology to identify our best agonists, we performed a retrospective analysis of the compounds in this manuscript using LLE to highlight the limitations of such efficiency measures when applied to agonist programs. We also present an agonist weighted alternative.[42]

Over the past decade a number of calculated terms that integrate physicochemical or molecular properties and primary pharmacology have been reported. These include ligand efficiency (LE),[43,44] LLE, and the related term LipE.[45,46] The widespread use of these terms can be understood from the way in which they indirectly relate to efficacious concentration and unbound clearance, two major determinants of dose. Although the increased use of these properties has made for "ready reckoners"[44] or easier visualization of superior compounds in plots and tables of compounds, it has increased the potential for users of these concepts to forget the parameters that form their basis.

LipE, although introduced with an agonist program using the agonist EC_{50} for the potency contribution, was done in the context of the unusual situation where all the compounds apparently achieved the same full agonist response (100% IA).[45] No correction would therefore be needed. The concept of LLE was originally introduced specifically using pIC_{50} and pK_i presumably to avoid the complication of agonist pharmacology. However, it was later[15] expanded to include pEC_{50} as well and in so doing exposed the issue of how to appropriately treat partial agonists.

Clearly, the weighing of the agonist response can be applied in different ways, but penalizing poor agonists would have to be the consistent outcome of any correction factor. As recently introduced,[42] one solution is to correct LLE for IA to derive the "agonist lipophilic ligand efficiency" (AgLLE) as shown in eq 1.

$$\text{agonist LLE} = \text{AgLLE} = (\text{pEC}_{50} - \text{ClogP})(\text{IA}/100\%) \quad (1)$$

As with many agonist programs, our GPR119 functional data were derived from a comparison to control agonists having the same pharmacology. The IA of a test compound is thus the fractional efficacy[47] relative to the maximum response of the control agonist chosen. The choice of control agonist is an important decision particularly for an orphan G-protein-

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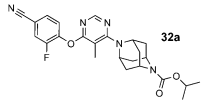
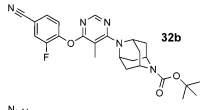
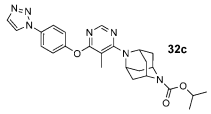
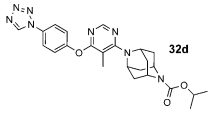
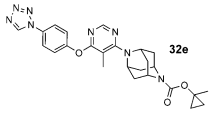
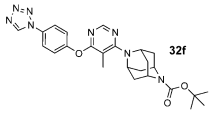
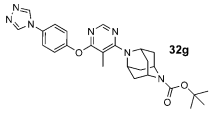
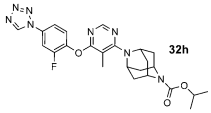
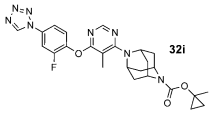
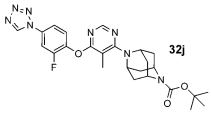
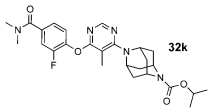
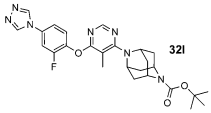
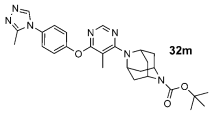
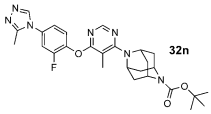
Table 5. In Vitro Human GPR119 Pharmacology for 32a−n

Compound (Scheme 9)	cAMP EC_{50} (nM)[a]	IA (%)	Ki (nM)	ClogP (ElogD)[b]
 **32a**	274±245 n=3	47±3	912±370 n=3	3.7
 **32b**	144±87 n=5	68±19	133±68 n=3	4.1
 **32c**	202±89 n=4	80±5	294±54 n=3	3.9 (4.4)
 **32d**	100±33 n=4	90±17	94±39 n=3	3.3 (4.4)
 **32e**	39±6 n=4	88±8	48±2 n=3	3.3 (4.3)
 **32f**	17±3 n=4	94±8	21±20 n=3	3.7
 **32g**	140±21 n=3	79±2	125±41 n=3	3.6
 **32h**	34±16 n=8	96±8	18±5 n=3	3.3 (4.6)
 **32i**	22±9 n=13	101±10	15±6 n=3	3.3 (4.6)
 **32j**	13±4 n=3	88±8	7±5 n=4	3.7
 **32k**	1049±552 n=4	89±11	1148±823 n=3	2.8
 **32l**	96±24 n=3	80±5	33±20 n=3	3.5
 **32m**	>8510±1294 n=3	93±10	948±496 n=3	3.9
 **32n**	300±178 n=3	64±1	507±390 n=3	3.8

[a]See ref 21 for assay conditions. [b]See ref 38.

coupled receptor (GPCR) where the endogenous ligand is not firmly established or unknown. In the case of our GPR119 program the control molecules we selected achieve the same maximal response as oleleoylethanolamide (OEA).[48]

The results of the analysis for the compounds reported in this manuscript are plotted Figure 4. The 45° lines trace the indicated LLE values. On the basis of a straightforward LLE analysis, better compounds should map to the upper left quadrant of the plot. However, from an accounting for the agonist response, a very different picture emerges and it is no longer true that only better agonists will be found in the upper left region. This can be visualized in Figure 4 where the diameters of the circles are sized according to AgLLE. Bigger circles equate to better agonists and better (larger) AgLLE values; smaller circles equate to poor agonists and smaller AgLLE values. The upper left quadrant is, in fact, populated with compounds with poor IA, thereby underscoring why LLE should not be used in agonist programs for assessing compounds. The use of AgLLE correctly distinguishes agonists from partial agonists and antagonists. In fact, the full spectrum of functional activity from inverse agonists (negative AgLLE) to superagonists (IA > 100%) can be accommodated by this term.

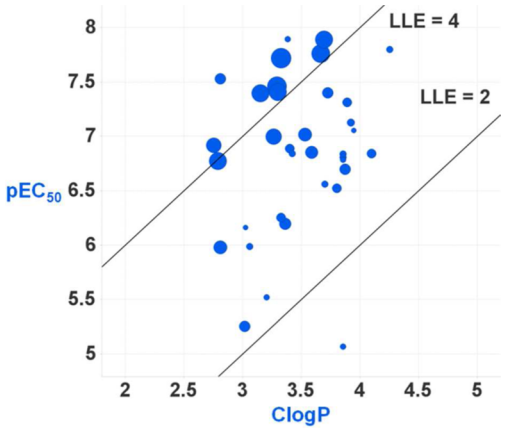


Figure 4. Plot of pEC_{50} vs ClogP sized by AgLLE with lines of constant LLE.

Interestingly, **32i** has the highest AgLLE value (4.4) of all the cage compounds,[49] as well as having one of the top LLE values (4.3). On the basis of LLE, the top compound in the data set is actually **26** (LLE = 4.7; AgLLE = 2.3), a partial agonist. It is perhaps not surprising to have partial agonists result in high LLE scores. For two compounds that trace the same agonist response curves, differing only in their maximum response, the lower EC_{50} will be associated with the compound with the lower IA.

Having profiled **32i** as a compound of interest in vitro, we proceeded to characterize the molecule in vivo. Given the inherent risks associated with species differences in pharmacology, especially translation of agonism to human, our priorities were to project human oral exposure and prepare for high dose toxicology studies rather than to demonstrate preclinical efficacy.[50] On the basis of our own experience, as well as the work of others working on GPR119 agonists, the potential for low solubility and hence solubility limited absorption was a concern.[39,51] Thus, before in vivo studies were run, it was

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Table 6. Oral and Intravenous Pharmacokinetics for 32i in Sprague–Dawley Rats

route and formulation	dose (mpk)[a]	AUC [b,h] (ng·h/mL)	$T_{1/2}$ [h] (h)	Cl [h] (mL min^{-1} kg^{-1})	V_{ss} [h] (L/kg)	C_{max} [b,h] (ng/mL)	T_{max} [h] (h)	F [c] (%)
iv[d]	1	1360 ± 592	4.34 ± 0.79	13.2 ± 5.6	3.96 ± 2.0			
po 0.5% MC[e]	3	312 ± 139				24.2 ± 8.5	3.00 ± 1.41	7.6
nanomilled[f]	3	3180 ± 695				255 ± 75.0	4.7 ± 1.2	78
nanomilled	30	12533 ± 289				912 ± 39.0	6.0 ± 0.0	31
SDD[g]	3	6137 ± 1577				484 ± 172	4.7 ± 1.2	>100
SDD[g]	30	49133 ± 9279				3490 ± 825	4.0 ± 0.0	>100

[a]Milligram per kilogram (mpk). [b]All concentrations are reported as total drug; the fraction unbound in rat plasma is 1.0%. [c]F calculations are based on 1 mpk rat iv PK data. [d]iv vehicle = 10% *N*-methylpyrrolidone and 90% sulfobutyl ether–β-cyclodextrin (SBE-CD) solution prepared at 30%. [e]Per os (po) dosing in 0.5% methylcellulose (MC). [f]po dosing of milled material in 0.5% MC. [g]po at 0.6 mL/kg as 25% SDD in 20 mM Tris buffer with 0.5% MC + 0.5% HPMCAS-HF, pH 7.4. [h]Data reported are the mean ± SD for studies conducted in three animals.

Table 7. Oral and Intravenous Pharmacokinetics for 32i in Male Beagle Dogs[a]

route and formulation	dose (mpk)[b]	AUC [c] (ng·h/mL)	$T_{1/2}$ (h)	Cl (mL min^{-1} kg^{-1})	V_{ss} (L/kg)	C_{max} [c] (ng/mL)	T_{max} (h)	F [d] (%)
iv[e]	1	4730	26.8	1.74	3.7	515		
po SDD[f]	3	8580	20.0			812	1	60
po SDD[g]	10	41000				1950	1	87
po SDD[g]	30	76800				3750	1	54
po SDD[g]	100	151000				6030	1.5	32

[a]PK parameters reported are the mean values obtained from two animals. [b]Milligram per kilogram (mpk). [c]All concentrations are reported as total drug; the fraction unbound in dog plasma is 1.4%. [d]F calculations are based on 1 mpk dog IV pk data. [e]1 mg/kg iv at 2 mL/kg in 5% dimethylacetamide (DMA)/75% polyethylene glycol 200 (PEG200)/20% (30% SBE-CD). [f]po at 0.6 mL/kg as 25% SDD in 20 mM Tris buffer with 0.5% MC + 0.5% HPMCAS-HF, pH 7.4. [g]10, 30, or 100 mpk po at 5 mL/kg as 25% SDD in 20 mM Tris buffer in 0.5% MC and 0.5% HPMCAS-HF, pH 7.4.

important to first check the thermodynamic solubility of crystalline **32i**. Consistent with the high melting point (234 °C, determined by differential scanning calorimetry) the thermodynamic solubility of **32i** in aqueous media was poor (solubility at pH 7.4 is 0.7 μg/mL; that at pH 1.2 is 4.8 μg/mL). This suggested a need for using solubilizing formulations to administer the compound.

The baseline intravenous (iv) and oral rat pharmacokinetics (PK) for **32i** are shown in Table 6. The poor bioavailability (F) at the lowest oral dose could be overcome by reducing the average particle size by milling (2–25 μm premilling to approximately 190 nm postmilling). This was consistent with a problem of poor solubility and not permeability. This notion is supported by the apparent permeability (P_{app}) for **32i**, which at 3.5×10^{-6} cm/s was indicative of moderate flux.[52] Unfortunately, there was a limit to the increases in exposure and bioavailability achievable using nanomilled material. Further increases in exposure with increasing dose was achieved by preparing an amorphous spray dried dispersion (SDD)[53] of the molecule with HPMCAS-HF (hydroxypropylmethylcellulose acetate succinate high fine). By use of SDD, an added 3-fold increase in maximum plasma concentrations (C_{max}) and area under the curve (AUC) over nanomilled material was achieved.

A similar PK evaluation was conducted in dog as shown in Table 7. In this instance SDD was used straight away. In general the exposure was similar to rat. As another indicator of solubility-driven exposure, the best bioavailability was achieved at low doses with the larger dosing volumes. Disappointingly, the bioavailability in dog was substantially reduced with increasing dose (cf. 10–100 mpk).

The major concern with these exposure data was how they compared to our projected efficacious concentration for human. On a free exposure basis, the 30 mpk SDD doses in rat and dog only achieve between 69 and 104 nM free drug at C_{max}. Absent actual human efficacy data for comparison and mindful of the theoretical risk of receptor desensitization, our target trough efficacious drug concentration was set at approximately 75% receptor activation from the cAMP assay. For compound **32i** this is estimated to be 50–70 nM. Therefore, even at the highest dose used in dog (100 mpk) only an approximate 3-fold margin above our projected efficacious concentration was achieved at C_{max} (167 nM free drug). Furthermore, the decline in bioavailability with increasing dose would make it hard to achieve greater multiples over the projected efficacious concentration. Given the challenge of trying to further develop this compound, we chose to abandon the cage series.

In summary we have described an efficient synthesis of the complex 2,6-diazatricyclo[3.3.1.1~3,7~]decane system and have demonstrated the benefits of this conformationally restricted framework on eliciting an agonist response from the human GPR119 receptor. In spite of the advantages of this cage group, achieving the desired overlap in agonist pharmacology and metabolic stability was only possible with larger substituents on the tail end of the molecule. Smaller compounds such as **3c** with superior solubility characteristics did not have the desired agonist properties. It was also shown that the direct use of LLE is not sufficient to identify more desirable agonists. The application of AgLLE, which applies a simple correction for IA to LLE, makes it possible to use this concept to triage potentially more interesting compounds. Compound **32i** was shown to be one of the better cage agonists overall. However, interest in this cage series diminished when it was established that it would be difficult to progress **32i** because of challenges in achieving adequate exposure relative to the projected efficacious concentration.

EXPERIMENTAL SECTION

Commercial reagents were used without further purification. All final compounds were purified using flash chromatography on Isco Combiflash systems or by preparative HPLC on a Waters Sunfire C_{18} column (19 mm × 100 mm, 5 μm particle size), eluting with a

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H_2O/CH_3CN, using NH_4OH or TFA as a modifiers. Compounds of pharmacologic interest are greater than 95% pure as judged by five separate UPLC methods, using the method reporting the largest percent impurity. Except where indicated, reactions were magnetically stirred and monitored by thin-layer chromatography using Merck silica gel 60 F254 by fluorescence quenching under UV light or by LC/MS detection. NMR spectra were obtained on a Varian INOVA spectrometer (400 or 500 MHz). Chemical shifts are expressed in δ (ppm) units relative to solvent residual peak, and peak multiplicities are expressed as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), multiplet (m), broad singlet (br s). Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane (TMS), and coupling constants (J) are in hertz (Hz). The synthesis of representative compounds is given below.

(1*R*,5*S*,7*r*)-9-Benzyl-7-(benzyloxy)-9-azabicyclo[3.3.1]nonan-3-one (11a) and (1*R*,5*S*,7*s*)-9-Benzyl-7-(benzyloxy)-9-azabicyclo[3.3.1]nonan-3-one (11b). To a stirred solution of 4-(benzyloxy)cyclopentane-1,2-diol[16] (8.50 g, 40.82 mmol) in H_2O (88.0 mL) was added $NaIO_4$ (4.41 mg, 20.4 mmol) at 23 °C. After 18 h, CH_3CN (60 mL) was added and stirring was continued for an additional 30 min. The mixture was filtered, and the filtrate was concentrated. Acetonitrile (60 mL) was added. The mixture was filtered and the filtrate was concentrated to provide a clear oil. To the crude oil in H_2O (40 mL) were added acetone-1,3-dicarboxylic acid (6.15 g, 40.8 mmol) and concentrated HCl (2.2 mL), followed by dropwise addition of benzylamine (3.6 mL, 33.6 mmol). The mixture was stirred for 1.5 h at 23 °C, then heated at 50 °C for 6 h. After cooling, the mixture was placed in an ice bath and basified to pH >9 using 1 N NaOH. The basic solution was extracted 3× with CH_2Cl_2 (60 mL). The organic phase was dried over K_2CO_3, filtered, and the filtrate was concentrated to dryness. The resulting brown viscous oil was purified by silica gel chromatography using 40% EtOAc/heptanes to provide **11a** (3.59 g, 10.7 mmol) as a semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85−1.95 (m, 4H), (m, 2H), 2.31 (d, J = 16.4 Hz, 2H), 2.73 (dd, J = 6.8 Hz, J = 16.6 Hz, 2H), 3.45 (br s, 2H), 3.64−3.75 (m, 1H), 3.92 (s, 2H), 4.47 (s, 2H), 4.69 (d, J = 5.87 Hz), 7.24−7.39 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.7, 44.9, 53.7, 56.6, 65.6, 70.1, 127.2, 127.9, 128.6, 128.8, 138.7, 139.2, 141.1, 210.3. LCMS: 336.1 (M + 1). Compound **11b** (1.198 g, 3.57 mmol) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (d, J = 13.7 Hz, 2H), 1.95−2.05 (m, 2H), 2.37 (d, J = 17.8 Hz, 2H), 2.62 (dd, J = 7.3 Hz, J = 17.6 Hz, 2H), 3.28 (br s, 2H), 3.77 (s, 1H), 3.88 (s, 2H), 4.40 (s, 2H), 7.20−7.40 (m, 10 H). ^{13}C NMR (CDCl3, 100 MHz) δ 32.2, 42.4, 50.5, 57.0, 69.2, 70.9, 127.4, 127.6, 127.9, 128.5, 128.7, 138.7, 206.5. LCMS: 336.1 (M + 1).

(1*R*,3*r*,5*S*)-*tert*-Butyl 3-Hydroxy-7-oxo-9-azabicyclo[3.3.1]-nonane-9-carboxylate (12). To a solution of **11a** (3.20 g, 9.54 mmol) in EtOH (48 mL) was added di-*tert*-butyl dicarbonate (4.21 g, 19.1 mmol). Hydrogenolysis of the material was achieved via a continuous flow process on an ThalesNano H-Cube apparatus with a long $Pd(OH)_2$ cartridge as the metal catalyst at 70 bar and 70 °C for 1 h. The mixture was concentrated and purified by silica gel chromatography using a gradient elution of 10−90% EtOAc/heptanes over 40 min to give **12** (2.4 g, 9.50 mmol) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H), 1.55−1.65 (m, 2H), 1.90−2.00 (m, 2H), 2.32 (s, 2H), 2.36 (s, 2H), 2.48−2.61 (m, 3H), 3.89 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6, 40.0, 45.7, 45.8, 47.6, 48.7, 80.9, 153.8, 208.6. LCMS: 256.1 (M + 1).

(1*R*,3r,5*S*,*Z*)-*N*-Benzylidene-9-methyl-9-azabicyclo[3.3.1]-nonan-3-amine (18). To a solution of **15** (5.2 g, 21.3 mmol) in cyclohexane (100 mL) and 12% NaOH (15 mL) was added a solution of Br_2 (1 mL) in cyclohexane (150 mL) dropwise over 1.5 h. During the addition the mixture was cooled in an ice bath. The cyclohexane solution of the bromoamine intermediate was separated, and the aqueous layer was extracted with cyclohexane (20 mL). The extracts were combined, washed with 12% NaOH (50 mL), dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The *N*-bromoamine **16** (6.2 g) thus obtained was used in the next step without purification. The *N*-bromoamine **16** was dissolved in 70 mL of cold 84% H_2SO_4 (80 mL of concentrated sulfuric acid, 20 mL of H_2O). The solution was then heated at 65−70 °C for 30 min. After cooling, the mixture was added to 200 mL of ice−water, rendered strongly alkaline with 50% NaOH solution, and then extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4, filtered, and the filtrate was concentrated to yield 4 g of a crude viscous oil. This crude mixture was purified by silica gel chromatography using 1:7 Et_3N/EtOAc to give SM **15** (1.56 g, 30%) as a clear oil and **18** (1.70 g, 33%) as an off-white gel. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09−1.13 (m, 2H), 1.49−1.55 (m, 1H), 1.66−1.74 (m, 2H), 1.97−2.05 (m, 2H), 2.18−1.25 (m, 2H), 2.30−2.41 (m, 1H), 2.54 (s, 3H), 3.06 (d, J = 10.98 Hz, 2H), 3.74−3.81 (m, 1H), 7.40 (dd, J = 3.17 Hz, 3H), 7.74−7.75 (m, 2H), 8.36 (s, 1H). GCMS (m/z): 242.

2-Benzyl-6-methyl-2,6-diazatricyclo[3.3.1.1~3,7~]decane (17). To *N*-benzyl-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine **15** (5.15 g, 21.1 mmol) dissolved in Et_2O (250 mL) in a Pyrex flask, under nitrogen, was added recrystallized *N*-chlorosuccinimide (5.68 g, 42.1 mmol) at 23 °C with stirring. After 13 min, Et_3N (11.7 mL, 84.3 mmol) was added rapidly and the mixture was irradiated for 50 min using a mercury lamp (450 W). The mixture was cooled to 23 °C and filtered through a Pall GHP filter (0.45 μm). The solid was rinsed with Et_2O, and the filtrate was concentrated to dryness under vacuum. The residue was purified by chromatography on 120 g silica gel (50−100% ethyl acetate in heptanes for 3 min, followed by 1:7 Et_3N/EtOAc) to afford the title compound as a yellow oil (1.46 g, 29%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83−1.97 (m, 8H), 2.57 (s, 3H), 2.88 (br s, 2H), 2.92 (br s, 2H), 3.87 (s, 2H), 7.17−7.44 (m, 5H). GCMS (m/z): 242.

2-Methyl-2,6-diazatricyclo[3.3.1.1~3,7~]decane·2HCl (20). To a stirred, cold (0 °C) solution of *endo*-3-amino-9-methylazabicyclo-[3,3,1]nonane **19** (4.85 g, 31.47 mmol) in Et_2O (1 L) in a 2 L Pyrex round-bottom flask was added *tert*-butyl hypochlorite dropwise under a nitrogen atmosphere. During the addition the mixture became a milky color. The bath was removed, and the mixture was stirred for 15 min at 23 °C. The flask was equipped with a reflux condenser and placed in a plastic bucket that was wrapped in aluminum foil. The mercury lamp (450 W) photoreactor equipped with a quartz jacketed cooling condenser was placed next to the 2 L flask inside the bucket. A pump was used to circulate ice cold H_2O through the inner well of the photoreactor and the reflux condenser of the flask. Aluminum foil was used to wrap the bucket and condenser to prevent light exposure. The mixture was irradiated for 45 min over which time the mixture became light orange with some solids present. The power supply was shut off, and after 5 min a small aliquot of the reaction mixture was taken and analyzed by GCMS. The mixture was filtered, and the resulting filter cake (somewhat hygroscopic) was collected, dried, and analyzed by GCMS. The crude material contained a 3:1 mixture of the title compound **20** to SM. A small aliquot was purified by silica gel chromatography using 1:7 Et_3N/EtOAc for characterization. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.87 (d, J = 12.93 Hz, 4H), 2.07 (d, J = 12.93 Hz, 4H), 2.44 (s, 3H), 2.87 (br s, 2H), 3.60 (br s, 2H), 9.13 (br s, 1H). GCMS (m/z): 152.

***tert*-Butyl 6-Methyl-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (21a).** To a stirred solution of crude (3:1) 2-methyl-2,6-diazatricyclo[3.3.1.1~3,7~]decane·2HCl **20** (3.25 g, 21.4 mmol) in MeOH (100 mL) was added Et_3N (6.72 mL, 48 mmol) followed by di-*tert*-butyl dicarbonate (5.10 g, 23.4 mmol). The reaction was complete after 1 h, but the mixture was stirred at 23 °C under nitrogen for 13 h. The yellow suspension was reduced to dryness under vacuum and diluted with 1 N NaOH (30 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated to dryness under vacuum. The residue was purified by silica gel chromatography with a gradient elution (20% of (1:9) Et_3N/EtOAc solution in heptanes to 100% (1:9) Et_3N/EtOAc) to give the title compound as a light yellow oil that solidified under vacuum (2.91 g, 54%). Product R_f = 0.23 in 75% (1:9, Et_3N/EtOAc)/heptane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.66 (d, 4H), 2.04 (t, 4H), 2.56 (s, 3H), 2.93 (br s, 2H), 4.28 (br s, 1H), 4.39 (br s, 1H). ^{13}C NMR (500 MHz,$CDCl_3$) δ 28.5, 30.6, 31.8, 41.2, 45.2, 46.4, 51.8, 79.2, 154.3. GCMS (m/z): 252.

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***tert*-Butyl 2,6-Diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (5a).** *tert*-Butyl 6-methyl-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **21a** (2.59 g, 10.28 mmol) was dissolved in THF (8.6 mL) and cooled to 0 °C. A solution of 1.5 N NaOH (206 mL, 308 mmol) was added slowly by addition funnel. To the resulting white suspension was added in four portions solid $KMNO_4$ (12.20 g, 77.10 mmol). The mixture was stirred at 0 °C for 10 min and then stirred at 23 °C for 68 h. Additional $KMNO_4$ (3.05 g, 19.28 mmol) and H_2O (50 mL) were added, and the reaction mixture was stirred for another 8 h. The mixture was then extracted with CH_2Cl_2 (3 × 75 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated to dryness under vacuum to afford the title compound as a colorless oil that became a white solid under vacuum (2.207 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.77−2.00 (m, 8H), 3.30 (s, 2H), 4.36 (s, 1H), 4.48 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 28.5, 35.6, 35.7, 45.4, 45.9, 46.8, 79.2, 154.6. GCMS (*m*/*z*): 238. LCMS (ES+): 239.3 (M + 1).

1-Methylcyclopropyl-6-methyl-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate (21b). To a stirred solution of crude 2-methyl-2,6-diazatricyclo[3.3.1.1~3,7~]decane **20** in CH_2Cl_2 (525 mL) at 0 °C was added Et_3N (26.4 mL, 189 mmol), followed by 1-methylcyclopropyl 4-nitrophenylcarbonate (37.4 g, 158 mmol). After 15 h, the mixture was concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2, poured into a 2 L separatory funnel, followed by the addition of a 1:1 mixture of 1 N NaOH and saturated NH_4Cl (500 mL). The mixture was shaken, and the CH_2Cl_2 layer was removed. More CH_2Cl_2 (200 mL) was added, and the procedure was repeated twice. The combined organic phase was concentrated to dryness under reduced pressure and adsorbed onto silica gel. This silica gel was loaded atop a 330 g ISCO column and eluted using 9:1 (EtOAc/10% NH_4OH in MeOH) to give 17 g (44%) of the title compound **21b** as an amber oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.64 (dd, *J* = 5.85, 7.07 Hz, 2H), 0.88 (t, *J* = 6.59 Hz, 2H), 1.57 (t, 3H), 1.6−1.7 (m, 4H), 2.01−2.10 (m, 4H), 2.57 (s, 3H), 2.94 (br s, 2H), 4.24 (br s, 1H), 4.42 (br s, 1H). GCMS (*m*/*z*): 250.

Preparation of 1-Methylcyclopropyl-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate (5b). To a stirred, cold (0 °C) solution of 1-methylcyclopropyl-6-methyl-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate **21b** (17.0, 64.8 mmol) in 1,2-dichloroethane (324 mL) was added dropwise 1-chloroethyl chloroformate (8.47 mL, 77.7 mmol). After 10 min at 0 °C, the ice bath was removed and the yellow reaction mixture was allowed to warm to 23 °C over 5 min. The reaction mixture was heated at reflux (~90 °C) for 1.5 h and then allowed to cool to 23 °C. The solvent was removed under reduced pressure, and MeOH (324 mL) was added. The mixture was heated at 90 °C for 1 h. The reaction mixture was cooled to 23 °C and concentrated under reduced pressure. To the resulting residue was added a 1:9 mixture of MeOH/Et_2O. Upon addition a tan solid began to precipitate. The solid was collected and washed with Et_2O to give the title compound **5b** as a tan solid, 14 g (93% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.67 (t, *J* = 7.32 Hz, 2H), 0.88 (t, *J* = 6.34 Hz, 2H), 1.50−1.65 (m, 7H) 1.86−1.96 (m, 4H) 2.90 (br s, 2H), 3.52 (s, 1H) 4.35 (br s, 1H), 4.55 (br s, 1H). GCMS (*m*/*z*): 236.

4-Chloro-6-(2-fluoro-4-(methylsulfonyl)phenoxy)-5-methylpyrimidine (23).[37] To a solution of 4,6-dichloro-5-methylpyrimidine (700 mg, 4.29 mmol) and 2-fluoro-4-methylsulfonylphenol (743 mg, 3.91 mmol) and CH_3CN (15.8 mL) in a 20 mL microwave vial was added Cs_2CO_3 (1.65 g, 5.07 mmol). The vial was capped and irradiated at 120 °C for 40 min using a microwave. The reaction mixture was passed through a pad of Celite, and the filtrate was diluted with EtOAc (25 mL) and H_2O (15 mL). The layers were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered, and the filtrate was evaporated. The crude material was purified by flash chromatography using an 80 g ISCO column with a gradient elution of 20−50% EtOAc/heptanes over 20 min and then an isocratic elution of 50% EtOAc/heptanes to afford the title compound **23** (775 mg, 57%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.10 (s, 3H), 7.44 (dd, *J* = 6.64, 8.40 Hz, 1H), 7.78−7.83 (m, 2H), 8.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1, 44.8, 116.9, 117.1, 117.4, 124.6, 125.2, 154.8, 161.9. LCMS: 317.0 (M + 1).

2-{6-[2-Fluoro-4-(methylsulfonyl)phenoxy]-5-methylpyrimidin-4-yl}-6-methyl-2,6-diazatricyclo[3.3.1.1~3,7~]decane (24). A solution of 2-benzyl-6-methyl-2,6-diazatricyclo[3.3.1.1~3,7~]decane **17** (456 mg, 1.88 mmol) in MeOH (12.0 mL) was passed through a long Pd/C cartridge on a ThalesNano H-Cube apparatus at full hydrogen pressure and 60 °C. The mixture was circulated through the instrument for a total of 4 h. The mixture was concentrated to give 288 mg of hydrogenolysis product (crude). A 0.1 M solution of the crude material and 4-chloro-6-[2-fluoro-4-(methylsulfonyl)phenoxy]-5-methylpyrimidine **23** in CH_3CN (14 mL) was prepared in a 20 mL microwave vial, and Cs_2CO_3 (766 mg, 2.35 mmol) was added. The vial was capped and irradiated in the microwave at 180 °C for 1 h. The crude material was concentrated and purified by silica gel chromatography using 14% Et_3N/EtOAc as the eluent to give the title compound as an off-white foam (387 mg, 57%). Product R_f = 0.2 in 14% Et_3N/EtOAc. LCMS (ES+): 433.2 (M + 1).

***tert*-Butyl 6-{6-[2-Fluoro-4-(methylsulfonyl)phenoxy]-5-methylpyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (25a).** To a stirred, cold (0 °C) solution of 2-{6-[2-fluoro-4-(methylsulfonyl)phenoxy]-5-methylpyrimidin-4-yl}-6-methyl-2,6-diazatricyclo[3.3.1.1~3,7~]decane **24** (361 mg, 0.835 mmol) in 1,2-dichloroethane (8.35 mL) was added dropwise 1-chloroethyl chloroformate (244 mg, 1.67 mmol). The solution was stirred for 10 min, and the ice bath was removed. The mixture was placed in a DrySyn heating vessel and heated at reflux for 2 h. The mixture was cooled and concentrated. Methanol (10.0 mL) was added, and the mixture was heated at reflux for 2 h. The crude mixture was concentrated to dryness. Dichloromethane (10.0 mL) was added, followed by di-*tert*-butyl dicarbonate (552 mg, 2.50 mL) and triethylamine (422 mg, 4.18 mmol) at 23 °C. After 2 h, the mixture was concentrated to dryness. Purification of the crude residue was performed on silica gel using 50% EtOAc/heptanes as the eluent to give the title compound as a white solid (84 mg, 17%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.87 (app t, *J* = 12.1 Hz, 4H), 1.98−2.08 (m, 4H), 2.18 (s, 3H), 3.07 (s, 3H), 4.27 (s, 2H), 4.43 (s, 2H), 4.56 (s, 1H), 7.4 (t, *J* = 7.80 Hz, 1H,), 7.72−7.78 (m, 2H), 8.19 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.6, 28.7, 34.0, 34.2, 44.8, 46.4, 49.3, 79.8, 102.0, 116.7, 116.9, 124.4, 125.1, 138.2, 138.3, 145.7, 145.9, 153.2, 154.2, 154.5, 155.8, 166.3, 167.2. LCMS (ES+): 519.0 (M + 1).

Isopropyl-6-{5-methyl-6-[(2-fluoro-4-methanesulfonylphenyl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]-decane-2-carboxylate (25b). To a stirred suspension of *tert*-butyl 6-{5-methyl-6-[(2-fluoro-4-methanesulfonylphenyl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (28 mg, 0.054 mmol) in MeOH (0.50 mL) was added 2.0 M HCl in Et_2O (0.40 mL, 0.80 mmol). The resulting solution was stirred for 16 h at 23 °C. The solvents were removed under vacuum to give the amine intermediate as a white solid (29.5 mg) which was used without further purification. ^{1}H NMR (500 MHz, CD_3OD) δ 2.28 (s, 3H), 2.29−2.38 (m, 8H), 3.15 (s, 3H), 3.93 (br s, 2H), 4.36 (br s, 2H), 7.49 (t, *J* = 7.81 Hz, 1H), 7.53 (d, *J* = 2.20 Hz, 1H), 7.78−7.85 (m, 2H), 8.24 (s, 1H). LCMS (ES+): 419.5 (M + 1).

To a stirred suspension of crude 2-{5-methyl-6-[(2-fluoro-4-methanesulfonylphenyl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane·HCl **25a** (14 mg, 0.028 mmol) in CH_2Cl_2 (0.5 mL) was added *N*,*N*-diisopropylethylamine (20.0 μL, 0.112 mmol), and the resulting solution was stirred at 23 °C for 10 min. Isopropyl chloroformate (31.00 mL, 0.031 mmol) was added, and the yellow mixture was stirred at 23 °C for 1 h. The solvent was evaporated to give 20 mg (92%) of a pale yellow solid which was purified by silica gel chromatography, eluting with a linear gradient of 40−80% EtOAc/heptanes to afford the title compound as a white solid (10.5 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, 6H), 1.92 (d, *J* = 9.27 Hz, 4H), 2.02−2.12 (m, 4H), 2.22 (s, 3H), 3.11 (s, 3H), 4.31 (br s, 2H), 4.53 (br s, 1H), 4.63 (br s, 1H), 4.9−5.04 (m, 1H), 7.41−7.47 (m, 1H), 7.80 (ddd, *J* = 2.07, 6.34, 8.42 Hz, 2H), 8.22 (s, 1H). LCMS (ES +): 505.5 (M + 1).

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1-Methylcyclopropyl-6-{5-methyl-6-[(2-fluoro-4-methanesulfonyl-phenyl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate (25c). To a stirred suspension of 2-{5-methyl-6-[(2-fluoro-4-methanesulfonylphenyl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane·HCl (14 mg, 0.028 mmol) in CH_2Cl_2 (0.5 mL) was added *N*,*N*-diisopropylethylamine (20.0 μL, 0.112 mmol), and the resulting solution was stirred at 23 °C for 10 min. 1-Methylcyclopropyl 4-nitrophenylcarbonate (7.5 mg, 0.031 mmol) was added, and the yellow mixture was stirred at 23 °C for 18 h. Additional *N*,*N*-diisopropylethylamine (10.0 μL, 0.056 mmol) and 1-methylcyclopropyl 4-nitrophenyl carbonate (3.6 mg, 0.015 mmol) were added, and the mixture was stirred at 23 °C for another 18 h. The reaction was quenched with 0.5 N NaOH (2 mL), and extraction was with CH_2Cl_2 (4 mL). The aqueous layer was extracted two additional times with CH_2Cl_2 (4 mL). The combined organic layers were washed with a 0.5 N NaOH. The organic layer was dried over Na_2SO_4, filtered, and the filtrate was evaporated to give 15.5 mg of a pale yellow solid which was purified by preparative reverse phase HPLC on a Waters Sunfire C_{18} column (19 mm × 100 mm, 5 μm particle size), eluting with a gradient of H_2O/CH_3CN (0.05% TFA modifier) to afford 8.1 mg (57%) of the title compound. Analytical LCMS: retention time 3.35 min (Atlantis C_{18} 4.6 mm × 50 mm, 5 μm particle size; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN for 4.0 min with a hold at 5% H_2O/CH_3CN to 5.0 min; 0.05% TFA modifier; flow rate 2.0 mL/min). LCMS (ES+): 517.25 (M + 1).

4-Chloro-5-methyl-6-((2-methylpyridin-3-yl)oxy)pyrimidine (27a). To a stirred solution of 2-methylpyridin-3-ol (6.29 g, 57.6 mmol) in THF (45 mL) and DMF (30 mL) at 23 °C was added KO-*t*-Bu (57.6 mmol, 57.6 mL) in one portion to give a brown solution. In a separate flask, a stirred solution of 4,6-dichloro-5-methylpyrimidine (8.95 g, 54.9 mmol) in THF (120 mL) under N_2 was heated to 70 °C. The potassium salt solution was added via cannula to the stirred pyrimidine solution in a slow steady stream. After the addition was complete, the mixture became brownish white. After 1.5 h at 70 °C, the heating bath was removed and the mixture was allowed to cool to 23 °C. The solvents were removed under reduced pressure, and the remaining residue was diluted with 0.1 M KOH (100 mL) and MTBE (150 mL). The layers were separated, and the basic aqueous layer was extracted with MTBE (2 × 50 mL). The MTBE layers were combined, washed with brine, dried over Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure to a clear colorless oil. The colorless oil was crystallized from heptanes to give the title compound as a white solid (5.5 g, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 2.48 (s, 3H), 7.25−7.28 (m, 1 H), 7.41 (d, J = 10.0 Hz, 1 H), 8.36 (s, 1 H), 8.47 (d, J = 4.64 Hz, 1H). LCMS (ES+): 236.2 (M + 1).

***tert*-Butyl 6-{5-Methyl-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (3e).** To a mixture of *tert*-butyl 2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate (400 mg, 1.70 mmol) **5a**, 4-chloro-5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidine (404 mg, 1.70 mmol), and Na_2CO_3 (214 mg, 2.55 mmol) in a 10 mL microwave vial was added *N*,*N*-dimethylacetamide (4.2 mL). The vial was sealed, and the resulting suspension was stirred at 120 °C for 42 h. The mixture was cooled to 23 °C and then poured into H_2O (80 mL) that was externally cooled by an ice bath. After the resulting mixture was stirred for 5 min, the ice bath was removed and stirring was continued for an additional 90 min. The solids that formed were collected by filtration on a Pall GHP filter (0.45 μm), rinsed with H_2O, and dried for 30 min under a stream of nitrogen. The solid was dissolved in EtOAc and saturated brine. The aqueous mixture was extracted with EtOAc (2 × 20 mL), and the combined extracts were dried over Na_2SO_4, filtered, and the filtrate was dried under vacuum to give an off-white solid that was purified by chromatography on silica gel (40−100% EtOAc/heptanes, followed by a period of 2% MeOH/EtOAc) to give the title compound as a white solid (391 mg, 53%). Product R_f = 0.36 in 70% EtOAc/heptanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 1.80−1.98 (m, 4H), 1.99−2.14 (m, 4 H), 2.22 (s, 3 H), 2.43 (s, 3 H), 4.27 (br s, 2 H), 4.46 (br s, 1 H), 4.59 (br s, 1H), 7.21 (dd, J = 8.05, 4.88 Hz, 1 H), 7.39 (d, J = 7.07 Hz, 1 H), 8.22 (s, 1 H), 8.40 (d, J = 3.66 Hz, 1 H). LCMS (ES+): 438.4 (M + 1).

2-{5-Methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane·HCl (28a). To a stirred solution of *tert*-butyl 6-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **3e** (132 mg, 0.30 mmol) in MeOH (2.3 mL) was added 4 N HCl in 1,4-dioxane (1.13 mL, 4.53 mmol), dropwise. The mixture was stirred for 16 h at 20 °C before the solvents were removed under vacuum to give the title compound as a hygroscopic, yellow solid (165 mg). This material was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03−2.19 (m, 8H), 2.22 (s, 3H), 2.43 (s, 3H), 3.56 (br s, 2H), 4.29 (br s, 2H), 7.21 (dd, J = 4.64, 8.05 Hz, 1H), 7.39 (d, J = 8.05 Hz, 1H), 8.22 (s, 1H), 8.40 (d, J = 3.66 Hz, 1H). LCMS (ES+): 338.3 (M + 1).

The free base of the above compound was prepared as follows.

To a stirred solution of *tert*-butyl 6-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **3e** (389 mg, 0.89 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.9 mL, 11.6 mmol). The reaction mixture was stirred at 23 °C for 5 h and then concentrated to dryness under vacuum. The residue was dissolved in 1 N NaOH solution and extracted with CH_2Cl_2 (3 × 20 mL) and then with 2-butanol (3 × 20 mL). The combined extracts were pooled, dried over a mixture of $MgSO_4$, filtered, and the filtrate was concentrated to dryness under vacuum. The resulting solid was dissolved in a mixture of EtOAc and THF and was filtered. The filtrate was concentrated to give the title compound as a white solid (306 mg), which was used in the subsequent steps without purification. ^{1}H NMR (500 MHz, CD_3OD) δ 2.20 (d, J = 13.42 Hz, 4H), 2.29 (s, 3H), 2.31−2.43 (m, 7H), 3.94 (br s, 2H), 4.33 (br s, 2H), 7.36 (dd, J = 4.88, 8.29 Hz, 1H), 7.54 (d, J = 8.05 Hz, 1H), 8.15 (s, 1H), 8.33 (d, J = 4.63 Hz, 1H). LCMS (ES+): 338.3 (M + 1).

Isobutyl 6-{5-Methyl-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (3f). To a stirred suspension of 2-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane·HCl salt (20 mg, 0.05 mmol) in dichloromethane (0.25 mL) was added triethylamine (27 mg, 0.27 mmol) followed by isobutyl chloroformate (7 μL, 0.05 mmol). The mixture was stirred at 23 °C for 2 h. Water was added to the reaction mixture, and it was extracted with dichloromethane (3 × 2 mL). The combined extracts were washed with half saturated brine, dried over sodium sulfate, filtered, and the filtrate was concentrated to dryness under vacuum to give the title compound as a tan solid (17.8 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (d, J = 6.83 Hz, 6H), 1.86−2.03 (m, 5H), 2.10 (d, J = 12.20 Hz, 4H), 2.22 (s, 3H), 2.43 (s, 3H), 3.93 (d, J = 6.59 Hz, 2H), 4.29 (br s, 2H), 4.55 (br s, 1H), 4.64 (br s, 1H), 7.21 (dd, J = 4.64, 8.05 Hz, 1H), 7.39 (d, J = 7.81 Hz, 1H), 8.22 (s, 1H), 8.40 (d, J = 4.15 Hz, 1H). LCMS (ES+): 438.3 (M + 1).

Alternatively, the crude material was purified by preparative reverse phase HPLC on a Waters Sunfire C_{18} column (19 mm × 100 mm, 5 μm particle size), eluting with a gradient of H_2O/CH_3CN (0.05% TFA modifier) to afford the title compound as the TFA salt. Analytical LCMS: retention time 2.59 min (Atlantis C_{18} 4.6 mm × 50 mm, 5 μm particle size; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN for 4.0 min with a hold at 5% H_2O/CH_3CN to 5.0 min; 0.05% TFA modifier; flow rate 2.0 mL/min). LCMS (ES+): 438.2 (M + 1).

Ethyl 6-{5-Methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (3a). The title compound was prepared from 2-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane (12 mg, 0.03 mmol) in a manner similar to that described for the preparation of isobutyl 6-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **3f**. The crude material was purified by preparative reverse phase HPLC on a Waters Sunfire C_{18} column (4.6 mm × 100 mm, 5 μm particle size), eluting with a gradient of H_2O/CH_3CN (0.05% formic acid modifier) to afford 4.8 mg of the title compound. Analytical LCMS: retention time 2.31 min (Atlantis C_{18} 4.6 mm × 50 mm, 5 μm particle size; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN for 4.0

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min with a hold at 5% H_2O/CH_3CN to 5.0 min; 0.05% formic acid modifier; flow rate 2.0 mL/min). LCMS (ES+): 410.1 (M + 1).

Isopropyl 6-{5-Methyl-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (3b). To a mixture of isopropyl 2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate (50 mg, 0.22 mmol), 4-chloro-5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidine (53 mg, 0.22 mmol), and Na_2CO_3 (28 mg, 0.36 mmol) in a 5 mL microwave vial was added *N*,*N*-dimethylformamide (1.1 mL). The vial was sealed, and the resulting suspension was stirred at 120 °C for 45 h. The mixture was cooled to 23 °C, diluted with H_2O (20 mL) and aqueous 10% LiCl solution (5 mL), and extracted with EtOAc (3 × 15 mL). The combined extracts were washed with aqueous 10% LiCl solution (15 mL), dried over Na_2SO_4, filtered, and the filtrate was dried under vacuum to yield a white solid that was purified by silica gel chromatography (with a gradient elution of 50−100% EtOAc/heptanes, followed by a period of 2% MeOH/EtOAc) to give the title compound as a white solid (56 mg). This material was further purified by stirring the solid in 50% EtOAc/heptanes (3 mL) for 3 days, filtering, and rinsing the solid with 50% EtOAc/heptanes (2 × 1 mL) to give the title compound as a white solid (30 mg, 31%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, J = 6.10 Hz, 6H), 1.81−2.00 (m, 4H), 2.02−2.15 (m, 4H), 2.22 (s, 3H), 2.43 (s, 3H), 4.28 (br s, 2H), 4.52 (br s, 1H), 4.63 (br s, 1 H), 4.91−5.07 (m, 1H), 7.21 (dd, J = 4.88, 8.05 Hz, 1H), 7.39 (d, J = 7.81 Hz, 1H), 8.22 (s, 1H), 8.40 (d, J = 4.39 Hz, 1H). LCMS (ES+): 424.3 (M + 1).

1-Methylcyclopropyl 6-{5-Methyl-6-[(2-methylpyridin-3-yl)-oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (3c). To a stirred solution of *tert*-butyl 6-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate **3e** (400 mg, 0.91 mmol) in CH_2Cl_2 (3 mL) was slowly added TFA (1.0 mL) at 23 °C. After 2 h, toluene (10 mL) was added and the reaction mixture was reduced to dryness under vacuum. The residue was diluted with 6 mL of toluene, and the mixture was sonicated. The solvent was again removed under vacuum to give a light yellow residue. This residue was dissolved in CH_2Cl_2 (5 mL), and to the resulting solution were added Et_3N (0.67 mL, 4.81 mmol) and 1-methylcyclopropyl 4-nitrophenylcarbonate (251 mg, 1.06 mmol). The mixture was stirred for 16 h at 40 °C. The mixture was cooled to 23 °C, and additional Et_3N (0.3 mL) and 1-methylcyclopropyl 4-nitrophenylcarbonate (46 mg, 0.18 mmol) were added. The mixture was heated at 40 °C for another 3.5 h. The mixture was cooled to 23 °C, diluted with 1 N NaOH solution (20 mL), stirred for 10 min, and extracted with CH_2Cl_2 (three times, 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was reduced to dryness under vacuum, giving a light yellow solid which was purified by silica gel chromatography (with a gradient elution of 40−100% EtOAc/heptanes, followed by a period of 2% MeOH/EtOAc) to give the title compound as a white solid (395 mg, 94%). This solid was suspended in EtOAc (4 mL) and was stirred for 20 h. The mixture was filtered through a Pall GHP 0.45 μm membrane. The solid was rinsed with cold EtOAc (3 mL) and dried under a stream of nitrogen for 30 min. The solid was further dried under vacuum to give the title compound as a white, crystalline solid (309 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.60−0.73 (m, 2H), 0.84−0.97 (m, 2H), 1.59 (s, 3H), 1.76−1.98 (m, 4H), 1.99−2.14 (m, 4H), 2.21 (s, 3H), 2.42 (s, 3H), 4.27 (br s, 2H), 4.41 (br s, 1H), 4.61 (br s, 1H), 7.21 (dd, J = 4.88, 8.05 Hz, 1H), 7.38 (d, J = 7.81 Hz, 1H), 8.21 (s, 1H), 8.39 (d, J = 3.90 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 13.0, 19.5, 21.7, 33.8, 34.0, 45.3, 46.2, 48.9, 56.5, 102.1, 121.9, 129.5, 145.8, 148.2, 151.9, 154.3, 154.6, 166.1, 167.5. LCMS (ES+): 436.4 (M + 1).

Cyclobutyl 6-{5-Methyl-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (3d). The title compound was prepared from 2-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane **28a** (15 mg, 0.05 mmol) in a manner similar to that described for the preparation of 1-methylcyclobutyl 6-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate **3c** but with a heating time of 18 h. The crude material was purified by preparative reverse phase HPLC on a Waters Sunfire C_{18} column (19 mm × 100 mm, 5 μm particle size), eluting with a gradient of H_2O in CH_3CN (0.05% TFA modifier) to afford 17.3 mg of the title compound as the mono-TFA salt. Analytical LCMS: retention time 2.55 min (Atlantis C_{18} 4.6 mm × 50 mm, 5 μm particle size; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN for 4.0 min with a hold at 5% H_2O/CH_3CN to 5.0 min; 0.05% TFA modifier; flow rate 2.0 mL/min). LCMS (ES+): 436.3 (M + 1).

3-Methyl-1-({[(1*R*)-1-methylpropyl]oxy}carbonyl)-1*H*-imidazol-3-ium Iodide. To a stirred solution of (*R*)-2-butanol (80 mg, 1.08 mmol) in toluene (2.8 mL) was added 1,1′-carbonyldiimidazole (175 mg, 1.08 mmol). The mixture was stirred 1 h at 23 °C. The mixture was then diluted with Et_2O (20 mL), and the organic layer was washed with 0.1 N HCl solution (23 mL). The aqueous layer was again extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give 1-({[(1*R*)-1-methylpropyl]oxy}carbonyl)-1*H*-imidazole as a clear, colorless oil (60 mg, 32%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, J = 7.44 Hz, 3 H), 1.41 (d, J = 6.34 Hz, 3 H), 1.65−1.88 (m, 2 H), 5.08 (m, 1 H), 7.08 (s, 1 H), 7.43 (s, 1 H), 8.14 (s, 1 H). GCMS (m/z): 168. To a solution of crude imidazole (22 mg, 0.13 mmol) in CH_3CN (0.5 mL) in a sealable vial, under an N_2 atmosphere, was added methyl iodide (0.1 mL, 2.0 mmol). The vial was sealed and heated at 50 °C for 42 h. The solvent was removed under vacuum to give a light yellow solid that was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, J = 7.44 Hz, 3H), 1.54 (d, J = 6.10 Hz, 3H), 1.78−1.89 (m, 1H), 1.92−2.03 (m, 1H), 4.34 (s, 3H), 5.21 (m, 1H), 7.47 (s, 1H), 7.77 (s, 1H), 10.83 (s, 1H). LCMS (ES+): 183.1 (M).

(1*R*)-1-Methylpropyl 6-{5-Methyl-6-[(2-methylpyridin-3-yl)-oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (3g). To a stirred solution of the crude 3-methyl-1-({[(1*R*)-1-methylpropyl]oxy}carbonyl)-1*H*-imidazol-3-ium iodide (22 mg, 0.12 mmol) in CH_2Cl_2 (0.5 mL) was added Et_3N (0.028 mL, 0.20 mmol) followed by 2-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane (41 mg, 0.12 mmol). The amber colored solution was stirred for 2 h, diluted with H_2O, and extracted with CH_2Cl_2 (3 × 3 mL). The combined extracts were dried over Na_2SO_4, filtered, and the filtrate was concentrated to dryness under vacuum to give a tan solid that was purified by preparative reverse phase HPLC on a Waters Sunfire C_{18} column (19 mm × 100 mm, 5 μm particle size), eluting with a gradient of H_2O/CH_3CN (0.05% TFA modifier) to afford 22.5 mg of the title compound as the mono-TFA salt. Analytical LCMS: retention time 2.81 min (Atlantis C_{18} 4.6 mm × 50 mm, 5 μm particle size; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN for 4.0 min with a hold at 5% H_2O/CH_3CN to 5.0 min; 0.05% TFA modifier; flow rate 2.0 mL/min). LCMS (ES+): 452.4 (M + 1).

(1*S*)-1-Methylpropyl 6-{5-Methyl-6-[(2-methylpyridin-3-yl)-oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (3h). The title compound was prepared from crude 3-methyl-1-({[(1*S*)-1-methylpropyl]oxy}carbonyl)-1*H*-imidazol-3-ium iodide and 2-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane **28a** (41 mg, 0.12 mmol) in a manner similar to that of 1-methylpropyl 6-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]-decane-2-carboxylate **3g**. The crude material was purified by chromatography on silica gel, eluting with EtOAc/heptanes to give the title compound as a white solid (22 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.44 Hz, 3H), 1.26 (d, J = 6.34 Hz, 3H), 1.50−1.73 (m, 2H), 1.82−2.00 (m, 4H), 2.08 (d, J = 8.05 Hz, 4H), 2.22 (s, 3H), 2.46 (s, 3H), 4.29 (br s, 2H), 4.54 (br s, 1H), 4.63 (br s, 1H), 4.82 (m, 1H), 7.22−7.29 (m, 1H), 7.44 (d, J = 7.81 Hz, 1H), 8.21 (s, 1H), 8.40 (d, J = 4.64 Hz, 1H). LCMS (ES+): 438.2.

1-Methylcyclobutyl 6-{5-methyl-6-[(2-methylpyridin-3-yl)-oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (3i). To a stirred suspension of 2-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane·HCl salt **28a** (20 mg, 0.05 mmol) in CH_2Cl_2

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(0.25 mL) was added Et_3N (27 mg, 0.27 mmol) followed by 1-methylcyclobutyl 4-nitrophenylcarbonate (14 mg, 0.05 mmol). After 4.5 h at 45 °C the reaction mixture was cooled to 23 °C, diluted with 1 N NaOH, and extracted with CH_2Cl_2 (3 × 2 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated to dryness to produce a yellow solid. The crude material was purified by preparative reverse phase HPLC on a Waters Sunfire C_{18} column (19 mm × 100 mm, 5 μm particle size), eluting with a gradient of H_2O/CH_3CN (0.05% TFA modifier) to afford 14.1 mg of the title compound as the mono-TFA salt. Analytical LCMS: retention time 2.63 min (Atlantis C_{18} 4.6 mm × 50 mm, 5 μm particle size; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN for 4.0 min with a hold at 5% H_2O/CH_3CN to 5.0 min; 0.05% TFA modifier; flow rate 2.0 mL/min). LCMS (ES+): 450.2 (M + 1).

***tert*-Butyl 6-{6-[(2-Methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (29b).** To a 5 mL microwave vial charged with *tert*-butyl 2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate (200 mg, 0.90 mmol) **5a**, 4-chloro-5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidine (215 mg, 0.90 mmol), and Na_2CO_3 (114 mg, 1.35 mmol) was added *N*,*N*-dimethylformamide (4.5 mL). The mixture was stirred, put under an N_2 atmosphere, sealed, and heated at 120 °C for 16.5 h. The mixture was cooled to 23 °C, diluted with H_2O (80 mL), 10% aqueous LiCl (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with 10% aqueous LiCl (40 mL), dried over Na_2SO_4, filtered, and the filtrate was reduced to dryness under vacuum. The residue was suspended in heptane, and the solvent was removed under vacuum. The process was repeated to give 393 mg of crude material as an orange solid. The crude material was purified by chromatography on 25 g silica, eluting with EtOAc/heptanes using a linear gradient from 25% to 85% EtOAc over 18.5 min, followed by a linear gradient from 85% to 100% EtOAc over 2.6 min, then a period of EtOAc for 10 min to give the title compound as a white foam (332 mg, 87%). Product R_f = 0.24 in 70% EtOAc/heptanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 9H), 1.85−2.00 (m, 8H), 2.43 (s, 3H), 4.46 (br s, 1H), 4.59 (br s, 1 H), 6.02 (s, 1H), 7.21 (dd, J = 4.88, 8.05 Hz, 1H), 7.39 (d, J = 7.07 Hz, 1H), 8.28 (s, 1H), 8.41 (d, J = 3.66 Hz, 1H). LCMS (ES+): 424.3 (M + 1).

1-Methylcyclopropyl 6-{6-[(2-Methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (29a). The title compound was prepared from **29b** in a manner similar to **3c** from **3e**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.60−0.73 (m, 2H), 0.84−0.97 (m, 2H), 1.60 (s, 3H), 1.75−1.98 (m, 8H), 2.46 (s, 3H), 4.42 (br s, 1H), 4.62 (br s, 1H), 6.02 (s, 1H), 7.21 (dd, J = 4.88, 8.05 Hz, 1H), 7.38 (d, J = 7.81 Hz, 1H), 8.28 (s, 1H), 8.39 (d, J = 3.90 Hz, 1H). LCMS (ES+): 422.3 (M + 1).

4-Chloro-5-ethyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidine (27b). The title compound was prepared from 4,6-dichloro-5-ethylpyrimidine (783 mg, 4.42 mmol) in a manner similar to that used to prepare 4-chloro-5-methyl-6-((2-methylpyridin-3-yl)oxy)-pyrimidine. The title compound was obtained as a tan solid (892 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (t, J = 7.56 Hz, 3H), 2.42 (s, 3H), 2.95 (q, J = 7.40 Hz, 2H), 7.22−7.30 (m, 1H), 7.41 (d, J = 8.05 Hz, 1H), 8.35 (s, 1H), 8.47 (d, J = 4.64 Hz, 1H). LCMS (ES+): 250.2 (M + 1).

***tert*-Butyl 6-{5-Methoxy-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (29e).** The title compound was prepared from 4-chloro-5-ethyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidine (100 mg, 0.40 mmol) in a manner similar to that used to prepare *tert*-butyl 6-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate **3e**. Silica gel chromatography was carried out using EtOAc/heptanes followed by a second chromatography using EtOAc/CH_2Cl_2. The title compound was isolated as a white solid (107 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, J = 7.32 Hz, 3H), 1.50 (s, 9H), 1.85−1.98 (m, 3H), 2.02−2.14 (m, 3H), 2.54 (br s, 2H), 2.63 (d, J = 7.56 Hz, 2H), 3.50 (d, J = 2.20 Hz, 3H), 4.27 (br s, 2H), 4.41−4.50 (m, 1H), 4.54−4.64 (m, 1H), 7.21−7.37 (m, 1H), 7.44−7.61 (m, 1H), 8.19 (s, 1H), 8.42 (d, J = 4.88 Hz, 1H). LCMS (ES+): 452.2 (M + 1).

Isopropyl 6-{5-Ethyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (29c). To a stirred solution of *tert*-butyl 6-{5-ethyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **29e** (20 mg, 0.044 mmol) in MeOH (0.3 mL) was added 4 N HCl in 1,4-dioxane (0.33 mL, 1.32 mmol), and the mixture was stirred for 75 min. The solvent was removed under vacuum, and the residue was dissolved in CH_2Cl_2 (1 mL) and Et_3N (0.031 mL, 0.22 mmol). The reaction mixture was cooled to 0 °C, at which point 1 M isopropyl chloroformate in toluene (0.048 mL, 0.048 mmol) was added dropwise. The mixture was stirred for 1 h at 0 °C and then allowed to warm to 23 °C. After a total of 15 h, the reaction mixture was diluted with 1 N NaOH and extracted with CH_2Cl_2 (2×). The combined extracts were pooled, dried over Na_2SO_4, filtered, and the filtrate was concentrated to dryness. The residue was dissolved in DMSO (0.9 mL) and purified by preparative reverse-phase HPLC on a Waters Sunfire C_{18} 19 mm × 100 mm, 0.005 mm column, eluting with a linear gradient of 90% H_2O/CH_3CN (0.05% TFA modifier) to 0% H_2O/CH_3CN in 8.5 min and holding at 0% H_2O/CH_3CN for 1.5 min (flow rate, 25 mL/min) to give the title compound as the mono-TFA salt (19 mg, 78%). Analytical LCMS: retention time 2.61 min (Waters Atlantis C_{18} 4.6 mm × 50 mm, 0.005 mm column; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN over 4.0 min and held at 5% H_2O/CH_3CN for 1.0 min; 0.05% TFA modifier; flow rate 2.0 mL/min). LCMS (ES+): 438.1 (M + 1).

1-Methylcyclopropyl 6-{5-Ethyl-6-[(2-methylpyridin-3-yl)-oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (29d). The title compound was prepared using *tert*-butyl 6-{5-ethyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **29e** (20 mg, 0.044 mmol) in a manner similar to that used to prepare 1-methylcyclopropyl 6-{5-methyl-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **3c**. The residue was dissolved in DMSO (0.9 mL) and purified by preparative reverse-phase HPLC on a Waters Sunfire C_{18} 19 mm × 100 mm, 0.005 mm column, eluting with a linear gradient of 90% H_2O/CH_3CN (0.05% TFA modifier) to 0% H_2O/CH_3CN in 8.5 min and holding at 0% H_2O/CH_3CN for 1.5 min (flow rate, 25 mL/min) to give the title compound as the mono-TFA salt (23.1 mg, 93%). Analytical LCMS: retention time 2.60 min (Waters Atlantis C_{18} 4.6 mm × 50 mm, 0.005 mm column; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN over 4.0 min and held at 5% H_2O/CH_3CN for 1.0 min; 0.05% TFA modifier; flow rate 2.0 mL/min). LCMS (ES+): 450.1 (M + 1).

4-Chloro-5-fluoro-6-[(2-methylpyridin-3-yl)oxy]pyrimidine (27c). The title compound was prepared from 4,6-dichloro-5-fluoropyrimidine (300 mg, 1.77 mmol) in a manner similar to that used to prepare 4-chloro-5-methyl-6-((2-methylpyridin-3-yl)oxy)-pyrimidine. The title compound was obtained as a clear, colorless oil (382 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.22−7.33 (m, 1H), 7.47 (d, J = 8.05 Hz, 1H), 8.29 (s, 1H), 8.50 (d, J = 4.88 Hz, 1H). LCMS (ES+): 240.1 (M + 1).

***tert*-Butyl 6-{5-Fluoro-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (29g).** To a microwave vial charge with *tert*-butyl 2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **5a** (47 mg, 0.20 mmol), 4-chloro-5-fluoro-6-[(2-methylpyridin-3-yl)oxy]pyrimidine **27c** (47 mg, 0.20 mmol), and $NaHCO_3$ (25 mg, 0.29 mmol) was added *N*,*N*-dimethylformamide (0.49 mL). The vial was capped, and the resulting suspension was stirred at 90 °C for 1 h, then 80 °C for 6 h. The mixture was cooled to 23 °C, diluted with H_2O (25 mL), and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with 10% aqueous LiCl (15 mL), dried over Na_2SO_4, filtered, and the filtrate was dried under vacuum to give an off-white solid that was purified using silica gel chromatography, eluting with an EtOAc/heptanes gradient. The title compound was obtained as a white solid (67 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 9H), 1.90−2.06 (m, 8H), 2.50 (s, 3H), 4.46 (br s, 1H), 4.59 (br s, 1H), 4.90 (br s, 2H), 7.25 (br s, 1H), 7.42−7.54 (m, 1H), 7.99 (s,

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1H), 8.43 (br s, 1H). LCMS (ES+): 442.3 (M + 1). Product R_f = 0.20 in 60% EtOAc/heptanes.

1-Methylcyclopropyl 6-{5-Fluoro-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (29f). To a stirred solution of *tert*-butyl 6-{5-fluoro-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate **29g** (15 mg, 0.034 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.2 mL). After being stirred at 23 °C for 3 h, the mixture was concentrated to dryness under vacuum. The residue was dissolved in CH_2Cl_2 (0.5 mL) and Et_3N (0.024 mL, 0.13 mmol). 1-Methylcyclopropyl 4-nitrophenylcarbonate (10 mg, 0.044 mmol) was added, and the mixture was heated to 45 °C. After 18 h, the reaction mixture was cooled to 23 °C, diluted with 1 N NaOH, and extracted with CH_2Cl_2 (3 × 2 mL). The combined extracts were pooled, dried over Na_2SO_4, filtered, and the filtrate was concentrated to dryness under vacuum. The residue was dissolved in DMSO (0.9 mL) and purified by preparative reverse-phase HPLC on a Waters XBridge C_{18} 19 mm × 100 mm, 0.005 mm column, eluting with 60% H_2O/CH_3CN (0.03% NH_4OH modifier) holding for 1 min, then a linear gradient of 60% H_2O/CH_3CN to 40% H_2O/CH_3CN in 5.75 min, followed by a linear gradient of 40% H_2O/CH_3CN to 0% H_2O/CH_3CN in 0.25 min and holding at 0% H_2O/CH_3CN for 1.0 min (flow rate 30 mL/min) to obtain the title compound (3.4 mg, 23%). Analytical LCMS: retention time 2.58 min (Waters Atlantis dC_{18} 4.6 mm × 50 mm, 0.005 mm column; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN over 4.0 min and a hold at 5% H_2O/CH_3CN for 1 min; 0.05% TFA modifier; flow rate 2.0 mL/min). LCMS (ES+): 440.1 (M + 1).

4-Chloro-5-methoxy-6-[(2-methylpyridin-3-yl)oxy]-pyrimidine (27d). The title compound was prepared from 4,6-dichloro-5-methoxypyrimidine (500 mg, 2.79 mmol) in a manner similar to that used to prepare 4-chloro-5-methyl-6-((2-methylpyridin-3-yl)oxy)pyrimidine. The title compound was obtained as a white solid (607 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 4.10 (s, 3H), 7.24−7.29 (m, 1 H), 7.44 (d, J = 8.05 Hz, 1 H), 8.23 (s, 1H), 8.48 (dd, J = 1.22, 4.64 Hz, 1H). LCMS (ES+): 252.1 (M + 1).

***tert*-Butyl 6-{5-Methoxy-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (29j).** To a microwave vial charged with *tert*-butyl 2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (95 mg, 0.40 mmol) **5a**, 4-chloro-5-methoxy-6-[(2-methylpyridin-3-yl)oxy]pyrimidine **27d** (100 mg, 0.40 mmol), and $NaHCO_3$ (50 mg, 0.60 mmol) was added *N*,*N*-dimethylacetamide (1.0 mL). The vial was capped, and the resulting suspension was stirred at 120 °C for 15 h. The mixture was cooled to 23 °C, diluted with H_2O, and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with 10% aqueous LiCl, dried over Na_2SO_4, filtered, and the filtrate was dried under vacuum. The residue was purified by silica gel chromatography, eluting with an EtOAc/heptanes gradient. The title compound was obtained as an off-white solid (90 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 1.85−2.10 (m, 8 H), 2.52 (s, 3H), 3.87 (s, 3H), 4.36−4.48 (m, 1H), 4.51−4.63 (m, 1H), 5.01 (br s, 2H), 7.23−7.30 (m, 1H), 7.43−7.51 (m, 1H), 8.02 (s, 1H), 8.41 (d, J = 4.88 Hz, 1 H). LCMS (ES+): 454.2 (M + 1). Product R_f = 0.17 in 75% EtOAc/heptanes.

Isopropyl 6-{5-Methoxy-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (29h). To a stirred solution of *tert*-butyl 6-{5-methoxy-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate **29j** (21 mg, 0.047 mmol) in CH_2Cl_2 (0.3 mL) was added TFA (0.1 mL). After being stirred at 23 °C for 3 h, the mixture was concentrated to dryness under vacuum. The residue was dissolved in CH_2Cl_2 (0.5 mL) and Et_3N (0.040 mL, 0.24 mmol) before isopropyl chloroformate (1 M in toluene, 0.056 mL, 0.056 mmol) was added. After 2 h, the reaction mixture was cooled to 23 °C, diluted with 1 N NaOH, and extracted with CH_2Cl_2 (2×). The combined organic extracts were pooled, dried over Na_2SO_4, filtered, and the filtrate was concentrated to dryness under vacuum. The residue was purified using silica gel chromatography, eluting with EtOAc/heptanes. The title compound was isolated as a white solid (10 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, J = 6.34 Hz, 6H), 1.87−2.15 (m, 8H), 2.55 (br s, 3H), 3.87 (s, 3H), 4.47−4.55 (m, 1H), 4.57−4.65 (m, 1H), 4.95−5.06 (m, 3H), 7.22−7.33 (m, 1 H), 7.43−7.58 (m, 1H), 8.02 (s, 1H), 8.42 (d, J = 4.63 Hz, 1H). LCMS (ES+): 440.2 (M + 1).

1-Methylcyclopropyl 6-{5-Methoxy-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (29i). To a stirred solution of *tert*-butyl 6-{5-methoxy-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate **29j** (20 mg, 0.045 mmol) in CH_2Cl_2 (0.3 mL) was added TFA (0.1 mL). After being stirred at 23 °C for 3 h, the mixture was concentrated to dryness under vacuum. The residue was dissolved in CH_2Cl_2 (0.5 mL) and Et_3N (0.031 mL, 0.23 mmol) before 1-methylcyclopropyl 4-nitrophenylcarbonate (13 mg, 0.054 mmol) was added. The mixture was heated to 50 °C for 19 h. The reaction mixture was cooled to 23 °C, diluted with 1 N NaOH, and extracted with CH_2Cl_2 (2×). The combined organic extracts were pooled, dried over Na_2SO_4, filtered, and the filtrate was concentrated to dryness under vacuum. The residue was dissolved in DMSO (0.9 mL) and purified by preparative reverse-phase HPLC on a Waters XBridge C_{18} 19 mm × 100 mm, 0.005 mm column, eluting with a linear gradient of 85% H_2O/CH_3CN (0.03% NH_4OH modifier) to 0% H_2O/CH_3CN in 8.5 min and holding at 0% H_2O/CH_3CN for 1.5 min; flow rate 25 mL/min, to obtain the title compound (1.4 mg, 7%). Analytical LCMS: retention time 2.43 min (Waters Atlantis C_{18} 4.6 mm × 50 mm, 0.005 mm column; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN over 4.0 min and a hold at 5% H_2O/CH_3CN for 1 min; 0.05% TFA modifier (flow rate 2.0 mL/min). LCMS (ES+): 452.2 (M + 1).

***tert*-Butyl 6-[6-(4-Cyano-2-fluorophenoxy)-5-methylpyrimidin-4-yl)]-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (32b).** *Step 1: 4-(6-Chloro-5-methylpyrimidin-4-yloxy)-3-fluorobenzonitrile.* To a stirred solution of 4,6-dichloro-5-methylpyrimidine (3.92 g, 24.1 mmol) and 3-fluoro-4-hydroxybenzonitrile (3.0 g, 22.0 mmol) in CH_3CN (75 mL) was added Cs_2CO_3 (9.27 g, 28.4 mmol). The reaction mixture was heated at reflux under nitrogen for 18 h. The reaction mixture was cooled to 23 °C, filtered, and the filtrate was evaporated under reduced pressure. The residue was taken up in EtOAc (200 mL) and H_2O (100 mL), and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated to a cream-colored solid. This material was purified by silica chromatography (120 g silica, 25% EtOAc/heptanes as eluent, using a 25g silica precolumn) to give the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.39 (t, J = 8.0 Hz, 1H), 7.53−7.58 (m, 1H), 8.37 (s, 1H). LCMS (ES+): 305.1 (M + 1 + formic acid).

Step 2. A microwave vial was charged with *tert*-butyl 2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **5a** (125 mg, 0.52 mmol), 4-(6-chloro-5-methyl-pyrimidin-4-yloxy)-3-fluorobenzonitrile (138 mg, 0.52 mmol), $NaHCO_3$ (66.0 mg, 0.786 mmol), and dry *N*,*N*-dimethylformamide (2.5 mL). The vial was sealed and heated at 120 °C for 18 h. The mixture was cooled to 23 °C and diluted with EtOAc (50 mL) and H_2O (50 mL). The aqueous layer was separated and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica chromatography (12 g silica, eluting with 25% EtOAc/heptanes). The product fractions were combined and evaporated to a white solid (126.7 mg, 51.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.84−1.90 (m, 4H), 2.00−2.04 (m, 4H), 2.18 (s, 3H), 4.26 (br s, 2H), 4.43 (br s, 1H), 4.56 (br s, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.45−7.50 (m, 2H), 8.17 (s, 1H). LCMS (ES+): 466.2 (M + 1).

Isopropyl 6-[6-(4-Cyano-2-fluorophenoxy)-5-methylpyrimidin-4-yl]-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (32a). To a stirred solution of 4-[6-(2,6-diazatricyclo[3.3.1.1~3,7~]-dec-2-yl)-5-methylpyrimidin-4-yloxy]-3-fluorobenzonitrile·HCl (prepared from Boc cleavage of **32b**) (40 mg, 0.10 mmol) in dry CH_2Cl_2 (1.0 mL) and diisopropylethylamine (51.7 mg, 0.40 mmol)

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was added isopropyl chloroformate (1 M in toluene, 0.12 mL, 0.12 mmol) at 23 °C. The reaction vessel was sealed, and the mixture was stirred for 2.5 h. The reaction mixture was diluted with CH_2Cl_2 and H_2O and shaken. The organic layer was separated and filtered through an Alltech filter, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative reverse-phase HPLC on a Waters Sunfire C_{18} column (19 mm × 100 mm, 5 μm particle size), eluting with a gradient of H_2O/CH_3CN (0.05% TFA modifier) to afford the title compound (10.9 mg, 24%). Analytical LCMS: retention time 3.72 min (Atlantis C_{18} 4.6 mm × 50 mm, 5 μm particle size; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN for 4.0 min with a hold at 5% H_2O/CH_3CN to 5.0 min; 0.05% TFA modifier; flow rate 2.0 mL/min). LCMS (ES+): 452.1 (M + 1).

***tert*-Butyl 6-{5-Methyl-6-[4-(3-methyl-4*H*-1,2,4-triazol-4-yl)-phenoxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]-decane-2-carboxylate (32m).** *Step1: 4-Chloro-5-methyl-6-[4-(3-methyl-4H-1,2,4-triazol-4-yl)phenoxy]pyrimidine.* The title compound was prepared from 4-(3-methyl-4*H*-1,2,4-triazol-4-yl)phenol (234 mg, 1.34 mmol) in a manner similar to that used to prepare 4-chloro-5-methyl-6-[4-(4*H*-1,2,4-triazol-4-yl)phenoxy]pyrimidine (step 1 of **32g** preparation). Heating was carried out at 100 °C for 1 h. The title compound was obtained as a white solid (360 mg, 90%). ^{1}H NMR (500 MHz, CD_3OD) δ 2.46 (s, 3H), 2.54 (s, 3H), 7.44−7.50 (m, 2H), 7.60−7.66 (m, 2H), 8.35 (s, 1H), 8.90 (s, 1H). LCMS (ES+): 302.0 (M + 1). TLC: R_f = 0.27 in 5% $MeOH/CH_2Cl_2$.

Step 2. A mixture of 4-chloro-5-methyl-6-[4-(3-methyl-4*H*-1,2,4-triazol-4-yl)phenoxy]pyrimidine (100 mg, 0.33 mmol), *tert*-butyl 2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **5a** (79 mg, 0.33 mmol), and *N*,*N*-diisopropylethylamine (0.115 mL, 0.66 mmol) in CH_3CN (0.33 mL) was heated at 100 °C for 24 h in a sealed tube. The reaction mixture was cooled to 23 °C, diluted with H_2O and brine, and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. A portion of the orange residue was dissolved in DMSO (0.9 mL) and purified by preparative reverse-phase HPLC on a Waters XBridge C_{18} 19 mm × 100 mm, 0.005 mm column, eluting with a linear gradient of 85% H_2O/CH_3CN (0.03% NH_4OH modifier) to 0% H_2O/CH_3CN in 8.5 min and holding at 0% H_2O/CH_3CN for 1.5 min (flow rate, 25 mL/min) to give the title compound (6.0 mg). Analytical LCMS: retention time 2.85 min (Waters XBridge C_{18} 4.6 mm × 50 mm, 0.005 mm column; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN over 4.0 min and a hold at 5% H_2O/CH_3CN for 1 min; 0.03% NH_4OH modifier; flow rate 2.0 mL/min). LCMS (ES+): 504.2 (M + 1). TLC R_f = 0.16 in 10% $MeOH/CH_2Cl_2$.

***tert*-Butyl 6-{5-Methyl-6-[4-(4*H*-1,2,4-triazol-4-yl)phenoxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (32g).** *Step 1: 4-Chloro-5-methyl-6-[4-(4H-1,2,4-triazol-4-yl)phenoxy]pyrimidine.* To a mixture of 4,6-dichloromethylpyrimidine (212 mg, 1.30 mmol) and 4-(4*H*-1,2,4-triazol-4-yl)phenol (200 mg, 1.24 mmol) in CH_3CN (5 mL) in a 2−5 mL microwave vial was added Cs_2CO_3 (526 mg, 1.61 mmol). The vial was sealed and heated at 80 °C for 2 h. The reaction mixture was cooled to 23 °C and adsorbed onto 2 g of silica gel. This silica was place on top of a silica gel column and eluted with a $MeOH/CH_2Cl_2$ gradient to give the title compound as a white solid (316 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.34−7.41 (m, 2H), 7.55 (d, J = 7.32 Hz, 2H), 8.40 (s, 1H), 8.71 (br s, 2H). LCMS (ES+): 288.2 (M + 1). TLC: R_f = 0.22 in 5% $MeOH/CH_2Cl_2$.

Step 2. The title compound was prepared using 4-chloro-5-methyl-6-[4-(4*H*-1,2,4-triazol-4-yl)phenoxy]pyrimidine (100 mg, 0.35 mmol) in a manner similar to that used to prepare *tert*-butyl 6-{5-methyl-6-[4-(3-methyl-4*H*-1,2,4-triazol-4-yl)phenoxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **32m** (step 2 of **32 m** preparation). This mixture was heated for 64 h instead of 24 h. A small portion of the crude product was dissolved in DMSO (0.9 mL) and purified by preparative reverse-phase HPLC on a Waters XBridge C_{18} 19 mm × 100 mm, 0.005 mm column, eluting with a linear gradient of 85% H_2O/CH_3CN (0.03% NH_4OH modifier) to 0% H_2O/CH_3CN in 8.5 min and holding at 0% H_2O/CH_3CN for 1.5 min (flow rate, 25 mL/min) to give the title compound (9.2 mg). Analytical LCMS: retention time 2.83 min (Waters XBridge C_{18} 4.6 mm × 50 mm, 0.005 mm column; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN over 4.0 min and a hold at 5% H_2O/CH_3CN for 1 min; 0.03% NH_4OH modifier; flow rate 2.0 mL/min). LCMS (ES+): 490.2 (M + 1).

Isopropyl 6-[5-Methyl-6-(4-[1,2,3]triazol-1-ylphenoxy)-pyrimidin-4-yl]-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (32c). A sealed 8 dram tube charged with 4-chloro-5-methyl-6-(4-[1,2,3]triazol-1-yl-phenoxy)pyrimidine (29.6 mg, 0.10 mmol), isopropyl 2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (23 mg, 0.1 mmol), $NaHCO_3$ (13 mg, 0.16 mmol), and dry *N*,*N*-dimethylformamide (0.5 mL) was heated at 120 °C for 18 h. The mixture was cooled to 23 °C and diluted with EtOAc (20 mL) and H_2O (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated to a yellow solid (53 mg). This solid was purified by preparative reverse-phase HPLC on a Waters Sunfire C_{18} column (19 mm × 100 mm, 5 μm particle size), eluting with a gradient of H_2O/CH_3CN (0.05% TFA modifier) to give the title compound (19.8 mg, 41%). Analytical LCMS: retention time 3.28 min (Atlantis C_{18} 4.6 mm × 50 mm, 5 μm particle size; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN for 4.0 min with a hold at 5% H_2O/CH_3CN to 5.0 min; 0.05% TFA modifier (flow rate 2.0 mL/min). LCMS (ES+): 476.1 (M + 1).

***tert*-Butyl 6-{5-Methyl-6-[4-(1*H*-tetrazol-1-yl)phenoxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (32f).** *Step 1: 4-Chloro-5-methyl-6-[4-(1H-tetrazol-1-yl)phenoxy]pyrimidine.* A mixture of 4-(1*H*-tetrazol-1-yl)phenol (4.80 g, 30 mmol), 4,6-dichloro-5-methylpyrimidine (5.71 g, 33 mmol), and potassium carbonate (8.50 g, 62 mmol) in *N*,*N*-dimethylformamide (60 mL) was stirred at 23 °C for 18 h. The mixture was then diluted with EtOAc (500 mL), washed with brine (2 × 100 mL), dried over Na_2SO_4, and filtered. While the filtrate was concentrated under vacuum, a solid began to precipitate. The solid was triturated with petroleum ether and was filtered. The filter cake was washed with 10% EtOAc/petroleum ether, and the collected solid was further dried under vacuum to afford the title compound as a brown solid (5 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.39 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.8 Hz, 2H), 8.39 (s, 1H), 9.00 (s, 1H). GCMS: m/z 288.8.

Step 2. A microwave vial was charged with *tert*-butyl 2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **5a** (41 mg, 0.17 mmol), 4-chloro-5-methyl-6-[4-(1*H*-tetrazol-1-yl)phenoxy]pyrimidine (50 mg, 0.17 mmol), $NaHCO_3$ (22 mg, 0.26 mmol), and *N*,*N*-dimethylformamide (0.43 mL), capped, and heated at 90 °C for 16 h. After cooling to 23 °C, the reaction mixture was diluted with H_2O (25 mL) and a 10% aqueous LiCl (5 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with 10% aqueous LiCl (15 mL), dried over Na_2SO_4, filtered, and the filtrate was concentrated to dryness under vacuum. The residue was purified by silica gel chromatography, eluting with an $EtOAc/CH_2Cl_2$ gradient. The title compound was isolated as an off-white solid (18 mg, 21%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 9H), 1.84−1.99 (m, 4H), 2.01−2.13 (m, 4H), 2.22 (s, 3H), 4.32 (br s, 2H), 4.42−4.52 (m, 1H), 4.55−4.66 (m, 1H), 7.33−7.39 (m, 2H), 7.71−7.78 (m, 2H), 8.29 (s, 1H), 8.97 (s, 1H). LCMS (ES+): 491.2 (M + 1). Product R_f = 0.16 in 30% $EtOAc/CH_2Cl_2$.

Isopropyl 6-{5-Methyl-6-[4-(1*H*-tetrazol-1-yl)phenoxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (32d). The title compound was prepared from *tert*-butyl 6-{5-methyl-6-[4-(1*H*-tetrazol-1-yl)phenoxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **32f** (15 mg, 0.031 mmol) in a manner similar to that used to prepare isopropyl 6-{5-methoxy-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **29h**. The residue was dissolved in DMSO (0.9 mL) and purified by preparative reverse-phase HPLC on a Waters XBridge C_{18} 19 mm × 100 mm, 0.005 mm column, eluting with a linear gradient of 60% H_2O/CH_3CN (0.03%

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NH_4OH modifier) to 40% H_2O/CH_3CN in 10.5 min, linear to 0% H_2O/CH_3CN for 0.5 min, and a hold at 0% H_2O/CH_3CN for 1.0 min (flow rate 25 mL/min) to give the title compound (5.0 mg, 33%). Analytical LCMS: retention time 3.25 min (Waters Atlantis dC_{18} 4.6 mm × 50 mm, 0.005 mm column; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN over 4.0 min and a hold at 5% H_2O/CH_3CN for 1 min; 0.05% TFA modifier; flow rate 2.0 mL/min). LCMS (ES+): 477.2 (M + 1).

1-Methylcyclopropyl 6-{5-Methyl-6-[4-(1*H*-tetrazol-1-yl)-phenoxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]-decane-2-carboxylate (32e). The title compound was prepared from *tert*-butyl 6-{5-methyl-6-[4-(1*H*-tetrazol-1-yl)phenoxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **32f** (14 mg, 0.029 mmol) in a manner similar to that used to prepare 1-methylcyclopropyl 6-{5-methoxy-6-[(2-methylpyridin-3-yl)oxy]-pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **29i**. The residue was dissolved in DMSO (0.9 mL) and purified by preparative reverse-phase HPLC on a Waters XBridge C_{18} 19 mm × 100 mm, 0.005 mm column, eluting with a linear gradient of 85% H_2O/CH_3CN (0.03% NH_4OH modifier) to 0% H_2O/CH_3CN in 8.5 min and holding at 0% H_2O/CH_3CN for 1.5 min (flow rate 25 mL/min) to give the title compound (5.3 mg, 37%). Analytical LCMS: retention time 3.23 min (Waters Atlantis dC_{18} 4.6 mm × 50 mm, 0.005 mm column; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN over 4.0 min and a hold at 5% H_2O/CH_3CN for 1 min; 0.05% TFA modifier (flow rate 2.0 mL/min). LCMS (ES+): 489.2 (M + 1).

***tert*-Butyl 6-{6-[2-Fluoro-4-(1*H*-tetrazol-1-yl)phenoxy]-5-methylpyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (32j).** *Step 1: 4-Chloro-5-methyl-6-[2-fluoro-4-(1H-tetrazol-1-yl)phenoxy]pyrimidine.* A mixture of 2-fluoro-4-(1*H*-tetrazol-1-yl)phenol (1.00 g, 5.6 mmol), 4,6-dichloro-5-methylpyrimidine (1.09 g, 6.7 mmol), and K_2CO_3 (1.20 g, 8.4 mmol) in *N*,*N*-dimethylformamide (15 mL) was stirred at 70 °C for 3 h. The mixture was then diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated to dryness under vacuum. The residue was purified by silica gel chromatography, eluting with EtOAc/petroleum ether. The title compound was obtained as a white solid (1.00 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 7.62 (m, 1H), 7.83 (m, 1H), 7.96 (m, 1H), 8.36 (s, 1H), 9.82 (s, 1H). GCMS: *m*/*z* 306.8.

Step 2. A mixture of *tert*-butyl 2,6-diazatricyclo[3.3.1.1~3,7~]-decane-2-carboxylate (78 mg, 0.33 mmol), 4-chloro-5-methyl-6-[2-fluoro-4-(1*H*-tetrazol-1-yl)phenoxy]pyrimidine (100 mg, 0.33 mmol), and $NaHCO_3$ (41 mg, 0.49 mmol) was suspended in *N*,*N*-dimethylformamide (0.82 mL) in a microwave vial. The vial was capped and heated at 60 °C for 14 h. The temperature was increased to 70 °C, and the mixture was heated an additional 26 h. The mixture was cooled to 23 °C, diluted with H_2O and 10% aqueous LiCl, and extracted with EtOAc (2 × 20 mL). The organic extracts were combined, washed with 10% aqueous LiCl (15 mL), dried over Na_2SO_4, filtered, and the filtrate was concentrated to dryness under vacuum. The residue was purified by silica gel chromatography, eluting with an EtOAc/heptanes gradient. The title compound was isolated as a white solid (36 mg, 22%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 9H), 1.84−1.98 (m, 4H), 2.00−2.13 (m, 4H), 2.24 (s, 3H), 4.31 (br s, 2H), 4.46 (br s, 1H), 4.60 (br s, 1H), 7.46 (d, *J* = 8.05 Hz, 1H), 7.52−7.58 (m, 1H), 7.64 (dd, *J* = 2.56, 9.88 Hz, 1H), 8.23 (s, 1H), 8.99 (s, 1H). LCMS (ES+): 509.2 (M + 1).

Isopropyl 6-{6-[2-Fluoro-4-(1*H*-tetrazol-1-yl)phenoxy]-5-methylpyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (32h). The title compound was prepared from *tert*-butyl 6-{5-methyl-6-[2-fluoro-4-(1*H*-tetrazol-1-yl)phenoxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **32j** (18 mg, 0.035 mmol) in a manner similar to that used to prepare isopropyl 6-{5-ethyl-6-[(2-methylpyridin-3-yl)oxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **29c**. The residue was dissolved in DMSO (0.9 mL) and purified by preparative reverse-phase HPLC on a Waters Sunfire C_{18} 19 mm × 100 mm, 0.005 mm column, eluting with a linear gradient of 70% H_2O/CH_3CN (0.05% TFA modifier) to 30% H_2O/CH_3CN in 10.5 min, linear to 0% H_2O/CH_3CN in 0.5 min, and holding at 0% H_2O/CH_3CN for 1 min (flow rate 25 mL/min) to give the title compound as the free base (10 mg, 59%). Analytical LCMS: retention time 3.36 min (Waters Atlantis dC_{18} 4.6 mm × 50 mm, 0.005 mm column; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN over 4.0 min and held at 5% H_2O/CH_3CN for 1.0 min; 0.05% TFA modifier (flow rate 2.0 mL/min). LCMS (ES+): 495.2 (M + 1).

1-Methylcyclopropyl 6-{6-[2-Fluoro-4-(1*H*-tetrazol-1-yl)-phenoxy]-5-methylpyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate (32i). *Step 1: 4-(6-Chloro-5-methylpyrimidin-4-yloxy)-3-fluoroaniline.* To a stirred mixture of 4,6-dichloro-5-methylpyrimidine (24.3 g, 149 mmol) and Cs_2CO_3 (48.7 g, 149 mmol) in CH_3CN (299 mL) was added 4-amino-2-fluorophenol (19.0 g, 149 mmol) at 23 °C. The mixture was allowed to stir at 23 °C for 4 h. The mixture was then filtered through Celite, rinsing the filter cake with EtOAc. The filtrate was concentrated to dryness and adsorbed onto silica. The charged silica was place on top of a 330 g silica gel column and purified by chromatography using an isocratic elution with 30% EtOAc/heptanes to give 19 g (50%) of the title compound as a tan solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.80 (br s, 2H), 6.49 (dd, *J* = 11.7 Hz, 21.5 1H), 6.97 (t, *J* = 17.6 Hz, 1H), 8.38 (s, 1H). LCMS (ES+): 254.0 (M + 1). TLC: R_f = 0.30 in 30% EtOAc/heptanes.

Step 2: 1-Methylcyclopropyl 6-(6-{4-[Amino]-2-fluorophenoxy}-5-methylpyrimidin-4-yl)-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate. A 250 mL flask was charged with 4-(6-chloro-5-methylpyrimidin-4-yloxy)-3-fluoroaniline (17.8 g, 82.5 mmol), 1-methylcyclopropyl-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (19.5 g, 82.5 mmol), $NaHCO_3$ (17.9 g, 211 mmol), and DMSO (82.6 mL). The reaction mixture was equipped with a reflux condenser and heated at 160 °C for 18 h. The reaction mixture was cooled to 23 °C, and H_2O was added. A tan solid precipitated from the solution. This solid was filtered and dried. The solid material was adsorbed onto silica gel with the aid of CH_2Cl_2. The charged silica was loaded on top of a silica gel column and was purified by chromatography using 50% EtOAc/CH_2Cl_2 to give the title compound as an off-white solid (23 g, 72%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.58−0.65 (m, 2H), 0.76−0.83 (m, 2H), 1.50 (s, 3H), 1.67−1.82 (m, 4H), 1.89−2.02 (m, 4H), 2.11 (s, 3H), 4.18 (br s, 2H), 4.25 (br s, 1H), 4.37 (br s, 1H), 5.27 (s, 2H), 6.35 (dd, *J* = 2.44, 8.54 Hz, 1H), 6.42 (dd, *J* = 2.56 Hz, 13.05, 1H), 6.87 (t, *J* = 8.90 Hz, 1H), 8.12 (s, 1H). LCMS (ES+): 454.3 (M + 1). TLC: R_f = 0.21 in 60% EtOAc/heptanes.

Step 3. A mixture of 1-methylcyclopropyl 6-[6-(4-amino-2-fluorophenoxy)-5-methylpyrimidin-4-yl]-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate (23.0 g, 50.7 mmol), NaN_3 (3.64 g, 55.8 mmol), triethyl orthoformate (25.8 mL, 152 mmol), and acetic acid (23.3 mL, 406 mmol) was heated at 80 °C. After 2 h, the suspension became a yellow solution before transitioning to a very thick slurry, which was loosened with the addition of acetic acid (20 mL). The mixture was heated at 80 °C for an additional 2 h. After cooling to 23 °C, the mixture was diluted with H_2O and was extracted with EtOAc (200 mL). The aqueous layer was extracted again with EtOAc (2 × 100 mL), and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated to dryness under vacuum. The crude residue was purified by silica gel chromatography using 40% EtOAc/CH_2Cl_2 as the eluent to give 19 g (75%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.63−0.70 (m, 2H), 0.87−0.94 (m, 2H), 1.59 (s, 3H), 1.80−1.98 (m, 4H), 2.00−2.13 (m, 4H), 2.23 (s, 3H), 4.29 (br s, 2H), 4.42 (br s, 1H), 4.62 (br s, 1H), 7.42−7.48 (m, 1H), 7.52−7.58 (m, 1H), 7.63 (dd, *J* = 2.44, 9.76 Hz, 1H), 8.22 (s, 1H), 8.99 (s, 1H). LCMS (ES+): 507.3 (M + 1). TLC R_f = 0.70 in EtOAc/CH_2Cl_2.

***tert*-Butyl 6-{6-[2-Fluoro-4-(4*H*-1,2,4-triazol-4-yl)phenoxy]-5-methylpyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (32l).** The title compound was prepared using 4-chloro-5-methyl-6-[2-fluoro-4-(4*H*-1,2,4-triazol-4-yl)phenoxy]-pyrimidine (88 mg, 0.29 mmol) in a manner similar to that used to prepare *tert*-butyl 6-{5-methyl-6-[4-(3-methyl-4*H*-1,2,4-triazol-4-yl)-

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phenoxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **32g**. This mixture was heated for 64 h instead of 24 h. A small portion of this residue was dissolved in DMSO (0.9 mL) and purified by preparative reverse-phase HPLC on a Waters XBridge C_{18} 19 mm × 100 mm, 0.005 mm column, eluting with a linear gradient of 85% H_2O/CH_3CN (0.03% NH_4OH modifier) to 0% H_2O/CH_3CN in 8.5 min and holding at 0% H_2O/CH_3CN for 1.5 min (flow rate 25 mL/min) to give the title compound (10 mg). Analytical LCMS: retention time 2.93 min (Waters XBridge C_{18} 4.6 mm × 50 mm, 0.005 mm column; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN over 4.0 min and a hold at 5% H_2O/CH_3CN for 1 min; 0.03% NH_4OH modifier; flow rate 2.0 mL/min). LCMS (ES+): 508.1 (M + 1).

***tert*-Butyl 6-{6-[2-Fluoro-4-(3-methyl-4*H*-1,2,4-triazol-4-yl)-phenoxy]-5-methylpyrimidin-4-yl}-2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate (32n).** The title compound was prepared using 4-chloro-5-methyl-6-[2-fluoro-4-(3-methyl-4*H*-1,2,4-triazol-4-yl)phenoxy]pyrimidine (74 mg, 0.31 mmol) in a manner similar to that used to prepare *tert*-butyl 6-{5-methyl-6-[4-(3-methyl-4*H*-1,2,4-triazol-4-yl)phenoxy]pyrimidin-4-yl}-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate **32m**. A small portion of this residue was dissolved in DMSO (0.9 mL) and purified by preparative reverse- phase HPLC on a Waters XBridge C_{18} 19 mm × 100 mm, 0.005 mm column, eluting with a linear gradient of 85% H_2O/CH_3CN (0.03% NH_4OH modifier) to 0% H_2O/CH_3CN in 8.5 min and holding at 0% H_2O/CH_3CN for 1.5 min (flow rate, 25 mL/min) to give the title compound (6.3 mg). Analytical LCMS: retention time 2.93 min (Waters XBridge C_{18} 4.6 mm × 50 mm, 0.005 mm column; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN over 4.0 min and a hold at 5% H_2O/CH_3CN for 1 min; 0.03% NH_4OH modifier; flow rate 2.0 mL/min). LCMS (ES+): 522.2 (M + 1).

Isopropyl 6-[6-(4-Dimethylcarbamoyl-2-fluorophenoxy)-5-methylpyrimidin-4-yl]-2,6-diazatricyclo[3.3.1.1~3,7~]decane-2-carboxylate (32k). *Step 1: 4-(6-Chloro-5-methylpyrimidin-4-yl oxy)-3-fluoro-N,N-dimethylbenzamide.* To a solution of 4,6-dichloro-5-methylpyrimidine (202 mg, 1.24 mmol) and 3-fluoro4-hydroxy-*N*,*N*-dimethylbenzamide (205 mg, 1.12 mmol) in CH_3CN (5.0 mL) was added Cs_2CO_3 (476 mg, 1.46 mmol). The reaction mixture was heated at reflux under nitrogen for 18 h. The mixture was cooled to 23 °C and diluted with H_2O (30 mL) and EtOAc (40 mL). The aqueous layer was separated and extracted once with EtOAc (20 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated. The residue was purified by silica gel chromatography (12 g silica, 30% EtOAc/heptanes linear gradient to 70% EtOAc/heptanes). The product fractions were combined, evaporated, and dried under high vacuum to give the title compound as an off-white solid (150.8 mg, 43%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.07 (s, 3H), 3.17 (s, 3H), 7.25−7.33 (m, 4H). LCMS (ES+): 310.2 (M + 1).

Step 2. 4-(6-Chloro-5-methylpyrimidin-4-yloxy)-3-fluoro-*N*,*N*-dimethylbenzamide (32 mg, 0.10 mmol), isopropyl 2,6-diazatricyclo-[3.3.1.1~3,7~]decane-2-carboxylate (23 mg, 0.1 mmol), and $NaHCO_3$ (13 mg, 0.16 mmol) were heated at 120 °C in a sealed 8 dram tube in dry *N*,*N*-dimethylformamide (0.5 mL) for 18 h. The mixture was cooled to 23 °C, diluted with EtOAc (20 mL) and H_2O (20 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and the filtrate was evaporated to a yellow solid (53 mg). This solid was purified by preparative reverse-phase HPLC on a Waters Sunfire C_{18} column (19 mm × 100 mm, 5 μm particle size), eluting with a gradient of H_2O/CH_3CN (0.05% TFA modifier) to afford the title compound (6.7 mg, 13%). Analytical LCMS: retention time 3.19 min (Atlantis C_{18} 4.6 mm × 50 mm, 5 μm particle size; 95% H_2O/CH_3CN linear gradient to 5% H_2O/CH_3CN for 4.0 min with a hold at 5% H_2O/CH_3CN to 5.0 min; 0.05% TFA modifier (flow rate 2.0 mL/min). LCMS (ES+): 498.1 (M + 1).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray experimental conditions for the structure determination of **25b** and the results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

GPR119, G-protein-coupled receptor 119; GLP-1, glucagon-like peptide 1; DPPIV, dipetidyl dipeptidase IV; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; GPCR, G-protein-coupled receptor; cAMP, 3′,5′-cyclic adenosine monophosphate; IA, intrinsic activity; OEA, oleoylethanolamide; LLE, ligand lipophilic efficiency; LE, ligand efficiency; AgLLE, agonist ligand lipophilic efficiency; C_{max}, maximum plasma concentration; AUC, area under the curve; iv, intravenous; po, per os; UPLC, ultrahigh pressure liquid chromatography; mpk, milligram per kilogram; *F*, bioavailability; SDD, spray dried dispersion; HPMCAS-HF, hydroxypropylmethylcellulose acetate succinate high fine; MC, methylcellulose; DMA, dimethylacetamide; PEG200, polyethylene glycol 200

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