Novel Bicyclic Piperazine Derivatives of Triazolotriazine and Triazolopyrimidines as Highly Potent and Selective Adenosine A_{2A} Receptor Antagonists

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A series of bicyclic piperazine derivatives of triazolotriazine and triazolopyrimidines was synthesized. Some of these analogues show high affinity and excellent selectivity for adenosine A_{2a} receptor versus the adenosine A_1 receptor. Structure−activity-relationship (SAR) studies based on octahydropyrrolo[1,2-*a*]pyrazine and octahydropyrido[1,2-*a*]pyrazine with various capping groups are reported. Among these analogues, the most potent and selective A_{2a} antagonist **26h** has a K_i value of 0.2 nM and is 16 500-fold selective with respect to the A_1 receptor. Among a number of compounds tested, compounds **21a** and **21c** exhibited significantly improved metabolic stability. Compounds **21a**, **21c**, and **18a** showed good oral efficacy in rodent catalepsy models of Parkinson's disease.

Introduction

The adenosine A_{2a} receptor is one of the four adenosine receptors (A_1, A_{2a}, A_{2b}, A_3) that have been identified in mammals. It belongs to the seven-transmembrane G-protein-coupled receptor (GPCR) superfamily and is highly expressed in the striatum, nucleus accumbens, and olfactory tubercle areas of the brain. Stimulation of the A_{2a} receptor was found to reduce the binding affinity of dopamine D2 receptors for dopamine and to counter the actions of both D1 and D2 receptors on behavior, gene expression, and secondary messenger systems.[1,2] Consequently, blockade of the adenosine A_{2a} receptor could compensate for the lack of dopamine D2 receptor-mediated control of striato-Gpe neurons.[1] Therefore, adenosine A_{2a} receptor antagonists may serve as a treatment for Parkinson's disease (PD), which arises from the progressive degeneration of dopaminergic neurons in the nigrostriatal pathway.[1−3]

Significant effort and progress have been made in the development of small-molecule A_{2a} receptor antagonists over the past few years.[4] The most advanced A_{2a} antagonist, KW-6002, is a xanthine[5] that has been reported to alleviate Parkinsonian symptoms in animal models[6] and has been evaluated in clinical trials for Parkinson's disease.[3,7] A number of non-xanthine A_{2a} antagonists, such as ZM241385 and SCH58261 (**1** and **2**, Figure 1), have also been extensively studied.[8,9] Although some progress have been made in improving the oral bioavailability of non-xanthine A_{2a} antagonists,[10−13] considerable challenge remains in the development of metabolically stable and orally active A_{2a} antagonists, with good potency, selectivity, and in vivo efficacy, as a potential alternative to the classic dopaminergic treatment of Parkinson's disease.

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As represented by BIO-10370 (**3**, Figure 1), we recently disclosed a series of piperazinyl[1,2,4]triazolo[1,5-*a*]triazines as A_{2a} antagonists that showed excellent in vitro potency and selectivity, as well as good oral efficacy in rodent models for Parkinson's disease.[14] However, the metabolic stability and oral bioavailability for **3** were low. We now report the preparation and biological profile of a series of bicylic piperazine derivatives of triazolotriazine and triazolopyrimidines as potent A_{2a} receptor antagonists with improved metabolic stability and good oral efficacy in rodent catalepsy models of Parkinson's disease.

Chemistry

Scheme 1 illustrates the syntheses of the octahydropyrido[1,2-*a*]pyrazine-derived [1,2,4]triazolo[1,5-*a*]triazines (**12a**), [1,2,4]triazolo[1,5-*c*]pyrimidines (**12b**), and [1,2,4]triazolo[1,5-*a*]pyrimidines (**12c**) capped as ethers. Scheme 2 represents the octahydropyridopyrazine-derived triazolotriazines capped as amines. The synthetic routes for heterocyclic templates (**5**−**7**)[8a,12,13] has been reported in detail previously. Following the literature procedures,[15,16] (7,9a)-*cis*- and (7,9a)-*trans*-(octahydropyridopyrazin-7-yl)methanol (**8**[15a] and **9**[15b]) were prepared from dimethyl 2,5-pyridinedicarboxylate, while the (6,9a)-*cis*-(octahydropyridopyrazin-6-yl)methanol (**10**[16]) was prepared from dimethyl 2,6-pyridinedicarboxylate. As shown in Scheme 1, sulfone **5** was condensed with 1 equiv of the diamine in DMF and the alcohol was mesylated to afford **11**. Phenols or heterocycles, such as imidazole, were deprotonated (NaH/DMF, 50 °C) and reacted with dried mesylate **11** (100 °C, 24 h) to afford the capped octahydropyridopyrazine **12a**. Syntheses of compounds of general structures **12b** and **12c** followed the same procedures, except that the S_NAr reaction was carried out in the presence of CsF in DMSO.

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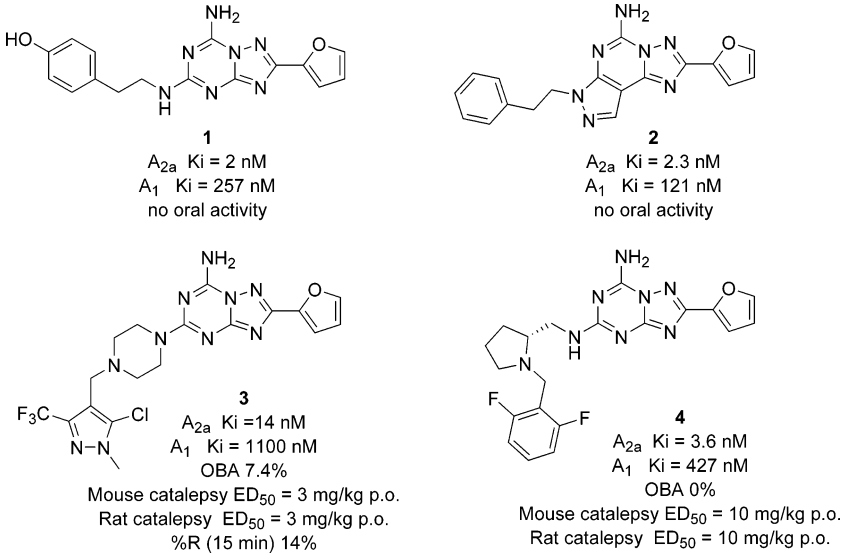
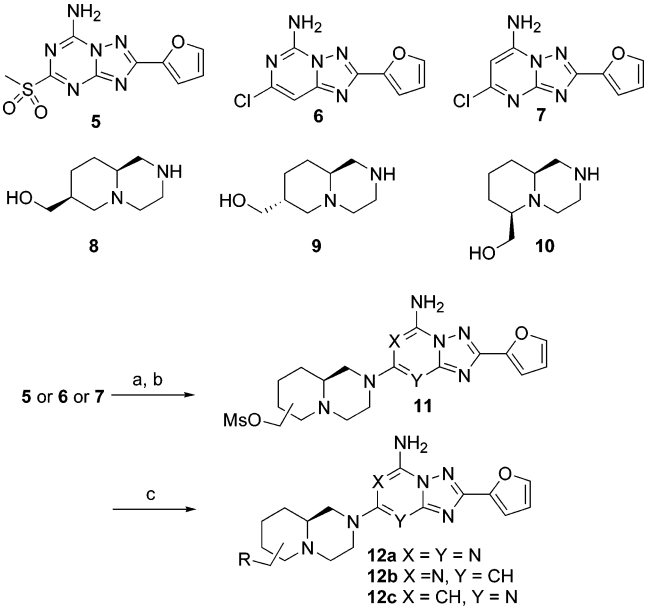


Figure 1. Representative non-xanthine A_{2a} antagonists.

Scheme 1[a]

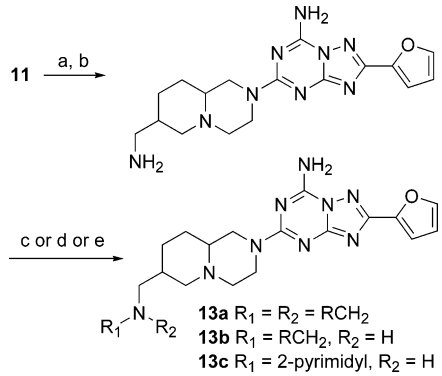


[a] Reagents and conditions: (a) for **12a**, **5**, alcohols (**8**−**10**, 1 equiv), DMF, 85 °C, 2 h; for **12b** and **12c**, **6** and **7**, respectively, alcohols (**8**−**10**, 1 equiv) CsF, DMSO, 100−120 °C, 15 h. (b) MsCl (1.5 equiv), triethylamine (4 equiv), DMF, 0 °C, 2 h. (c) NaH (4 equiv), phenols or heterocycles (1.3 equiv), DMF, 100 °C, 24 h. See Table 2 for structures of R groups.

Alternatively, mesylates **11** were converted to the azides (NaN_3/DMF, 100 °C) (Scheme 2). After purification by chromatography, the resulting azides were reduced to the corresponding amines using polymer-supported PPh_3. Reductive alkylation [aldehydes, $NaBH(OAc)_3$, or $Ti(O\text{-}^iPr)_4/NaBH_4$] afforded the disubstituted (**13a**) or monosubstituted (**13b**) derivatives. Nucleophilic aromatic displacement at the 2-position of 2-chloropyrimidine afforded compound of structure **13c**. (Scheme 2)

Schemes 3 and 4 represent the syntheses of the inversely capped bicyclic piperazine derivatives **14a**−**d** and **15a**,**b**. As shown in Scheme 3, *cis*-bicyclic diamino alcohol **8** was capped at the N-2 position under different conditions with phenyl, benzyl, pyrimidyl, and pyrazinyl groups. The resulting alcohols were converted to the

Scheme 2[a]



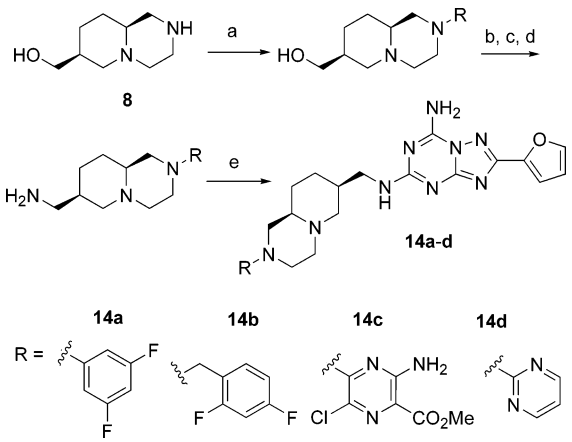
[a] Reagents and conditions: (a) NaN_3 (4 equiv), DMF, 100 °C; (b) polymer-supported PPh_3 (4 equiv), THF/H_2O; (c) for **13a**, RCHO (4 equiv), $NaBH(OAc)_3$ (1.5 equiv), TCE; (d) for **13b**, RCHO (1 equiv), $Ti(OiPr)_4$ (1.7 equiv), $NaBH_4$ (1.5 equiv), THF/MeOH; (e) for **13c**, 2-chloropyrimidine (1 equiv), K_2CO_3 (2 equiv), DMSO, 85 °C, 4 h. See Table 3 for structures of R groups.

corresponding amines, which were coupled to template **5** to afford compounds **14a**−**d**. As shown in Scheme 4, an alternative route was used for synthesizing compounds **15a**,**b** with the trans configuration. Alcohol **9** was protected at the N-2 position with Boc before the alcohol was converted to an amine. The resulting primary amine was then coupled to a heterocyclic template, such as **5**. After deprotection, the secondary amine end was capped through reductive amination of an aldehyde or through nucleophilic aromatic displacement at the 2-position of 2-chloropyrimidine to afford compound **13c**.

Results and Discussion

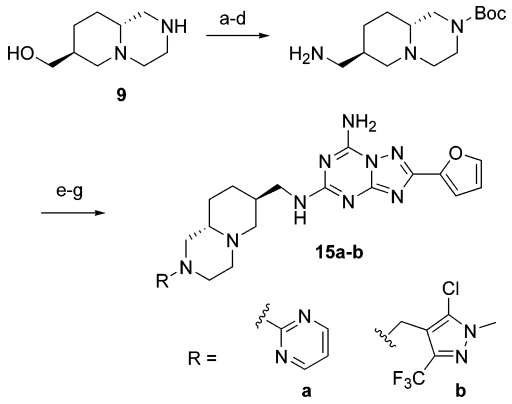
Compounds **3**[14] and **4**[17] (Figure 1) are potent adenosine A_{2a} receptor antagonists with the required subtype selectivity. While both compounds exhibited good oral efficacy in rodent models for Parkinson's disease, **3** and **4** do not possess the desired metabolic stability and oral bioavailablity. The discrepancy between the pharmacokinetic and pharmacodynamic profiles is presumably due to the presence of active metabolites, and we summarized that metabolism may occur through N-

Scheme 3[a]



[a] Reagents and conditions: (a) for **14a**, 1,3,5-trifluorobenzene (1 equiv), CsF, DMSO, 95 °C, overnight; for **14b**, 2,4-difluorobenzylbromide (1 equiv), Na_2CO_3 (1.5 equiv), THF, rt, overnight; for **14c**, methyl 3-amino-5,6-dichloro-2-pyrazinecarboxylate (1 equiv), TEA, i-PrOH, 80 °C; for **14d**, 2-chloropyrimidine (1 equiv), Na_2CO_3 (1.5 equiv), H_2O, 95 °C, overnight; (b) MsCl (1.5 equiv), triethylamine (4 equiv), CH_2Cl_2, 0 °C, 30 min; (c) NaN_3 (2 equiv), DMF, 100 °C, 24 h; (d) polymer-supported PPh_3 (3 equiv), THF/H_2O; (e) **5** (1 equiv), DMSO, 80 °C, 2 h.

Scheme 4[a]



[a] Reagents and conditions: (a) Boc_2O (2 equiv), 1,4-dioxane/5 N NaOH; (b) MsCl (2 equiv), triethylamine (5 equiv), CH_2Cl_2, 0 °C, 30 min; (c) NaN_3 (2 equiv), DMF, 100 °C, 3 h; (d) PPh_3/solid support (4 equiv), THF/H_2O; (e) **5** (1equiv), DMF, 75 °C, 2 h; (f) 10%TFA/CH_2Cl_2; (g) for **15a**, 2-chloropyrimidine (1 equiv), Na_2CO_3, acetonitrile, 80 °C; for **15b**, 5-chloro-1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carbaldehyde (1 equiv), $NaBH(OAc)_3$ (1.5 equiv), CH_2Cl_2, AcOH.

dealkylation of the capping group. We therefore sought to use a fused bicyclic piperazine system[18,19] (Table 1) to improve metabolic stability. In addition, the bicycle moiety should also provide reduced molecular flexibility, which often correlates with good oral bioavailability[20] and central nervous system (CNS) penetration.[21]

In hope of improving the pharmacological properties of **3** and **4**, a series of analogue with a constrained bicyclic piperazine was synthesized (Tables 1−4). We maintained the structural characteristics that have been considered critical for the binding affinity of our reference compounds, mainly the triazolotriazine or triazolopyrimidine templates, the furan ring, and the free amine at the 7-position of the aromatic templates. We decided to introduce octahydropyridopyrazine or octahydropyrrolopyrazine in the place of the piperazine or 2-(aminomethyl)pyrrolidine in our reference compounds. Parts a and b of Figure 2 show the superposition of an

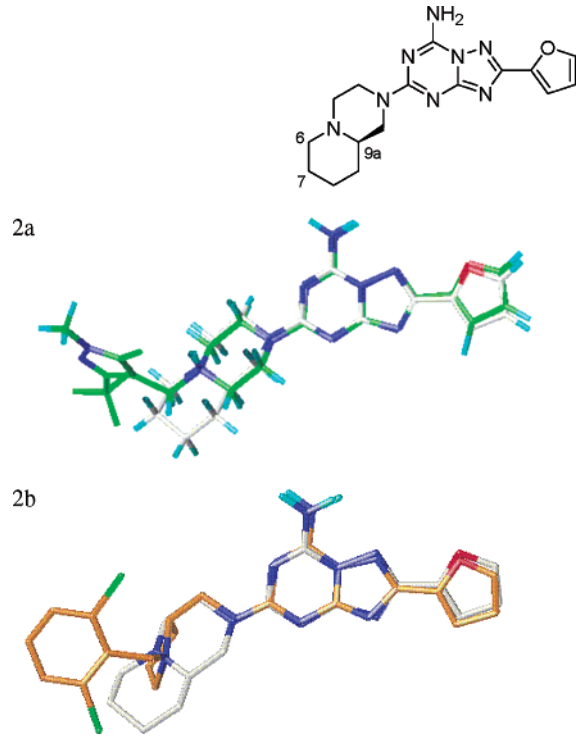


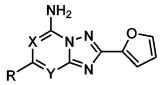
Figure 2. 3D structural alignment of *R*-**12c** (white) with **3** (green, 2a) and **4** (gold, 2b).[22]

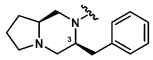
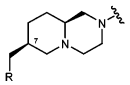
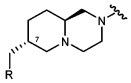
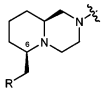
octahydropyridopyrazine derivative (white) with the low-energy conformations of **3** (green) and **4** (gold), respectively.[22] These models suggest that substitution at the 7- or 6- position with a *cis*-configuration may approximate the orientation of the capping groups of **3** and **4**. Since alcohols **8**−**10**[15,16] (Scheme 1) are relatively straightforward to prepare, we decided to use these as a starting point to investigate the SAR of 7- or 6-substituted octahydropyridopyrazines. The results are summarized in Table 2 (oxygen atom linkage) and Table 3 (nitrogen atom linkage).

Binding to adenosine A_{2a} and A_1 receptors was determined by competition binding assays, using [^{3}H]-ZM-241385 and [^{3}H]DPCPX, respectively, as radioligands. The methods have been described in detail in a previous report[14] and are summarized below in the Experimental Section. Most of the compounds showed binding affinity for the A_{2a} receptor in the nanomolar range with different degrees of selectivity versus the A_1 receptor (Tables 1−4).

Table 1 outlines the A_{2a} and A_1 receptor binding affinities for the uncapped octahydropyridopyrazine or octahydropyrrolopyrazine derivatives of three heterocyclic templates, along with that of the uncapped piperazine **16**[17] for comparison. It had been previously established that capping of the piperazine-NH is essential for A_{2a} inhibition.[14] In the bicyclic amine analogues, the piperazine moiety is intrinsically capped by the fused ring system; significantly improved binding to A_{2a} relative to **16** (Table 1) demonstrates that the fused ring recapitulates the improved activity of caps described in earlier reports.[14,17] The triazolotriazines (Table 1, column 4, X = N, Y = N) are generally more potent A_{2a} antagonists than their triazolo[1,5-*c*]pyrimidine (Table 1, column 2, X = N, Y = CH) and triazolo-[1,5-*a*]pyrimidine (Table 1, column 3, X = CH, Y = N) counterparts. With small polar substitution, such as an

Table 1. A_{2A} Affinity and Selectivity of Compounds **16**–**25c**



Bicyclic Diamines (R)		Compound No. and Ki (nM)					
		triazolo[1,5-c]pyrimidine X = N, Y = CH		triazolo[1,5-a]pyrimidine X = CH, Y = N		triazolotriazine X= N, Y = N	
						16	> 5000 (A_{2a})
			-		-		NT (A_1)
		**17a**	140 (A_{2a})	**17b**	38 (A_{2a})	**17c**	12 (A_{2a})
			> 500 (A_1)		> 500 (A_1)		860 (A_1)
		**18a**	63 (A_{2a})		-	**18c**	30 (A_{2a})
			1100 (A_1)				1200 (A_1)
		**19a**	110 (A_{2a})	**19b**	170 (A_{2a})	**19c**	46 (A_{2a})
			> 500 (A_1)		> 500 (A_1)		> 500 (A_1)
			-		-	**20c**	490 (A_{2a})
							> 1000 (A_1)
	R = OH	**21a**	96 (A_{2a})	**21b**	230 (A_{2a})	**21c**	45 (A_{2a})
			> 500 (A_1)		> 500 (A_1)		660 (A_1)
	R = NH_2	**22a**	56 (A_{2a})	**22b**	110 (A_{2a})	**22c**	16 (A_{2a})
			> 500 (A_1)		> 500 (A_1)		> 500 (A_1)
	R = OH	**23a**	240 (A_{2a})	**23b**	860 (A_{2a})	**23c**	71 (A_{2a})
			> 1000 (A_1)		> 1000 (A_1)		6100 (A_1)
	R = NH_2		-	**24b**	370 (A_{2a})	**24c**	2 (A_{2a})
					> 500 (A_1)		3500 (A_1)
	R = OH	**25a**	110 (A_{2a})	**25b**	610 (A_{2a})	**25c**	3 (A_{2a})
			> 500 (A_1)		> 500 (A_1)		1300 (A_1)

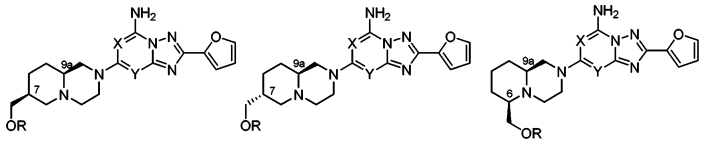
[a] For the A_{2a} receptor, membrane was prepared from rat brain tissues and the radioligand binding assay was performed using [^{3}H]ZM-241385. For the A_1 receptor, membranes were prepared from rat cerebral cortex and the radioligand binding assay was performed using [^{3}H]DPCPX. As a control for these radioligand binding assays, we routinely employed SCH-58261, which had a A_{2a} K_i of 37 nM and a A_1 K_i of 390 nM. K_i values were calculated from binding curves generated from the mean of three determinations per concentration, with variation in individual values of <15%.

amino or hydroxyl group on the bicycles, the least favored template is triazolo[1,5-*a*]pyrimidine (column 2, X = CH, Y = N, Table 1), as exemplified by the poor potency of compounds **21b**, **22b**, **23b**, **24b**, and **25b** as compared to their triazolotriazine and triazolo[1,5-*c*]-pyrimidine congeners.

The 5,6-bicyclic piperazine can be viewed as a constrained analogue of 2-(aminomethyl)pyrrolidine (see compound **4** in Figure 1), an excellent diamine to replace piperazine[17] for achieving high A_{2a} affinity. The fact that the (*R*)-enantiomer **18c** (A_{2a}, K_i = 30 nM, Table 1) is more potent than the (*S*)-enantiomer **19c** is consistent with our recently reported observation that **4** is more potent than its *S* counterpart[17] Benzyl substitution on octahydropyrrolopyrazine (**20c**, A_{2a}, K_i = 490 nM) led to substantial loss of affinity compared to the parent compound **19c** (A_{2a}, K_i = 46 nM). Small polar substitutions on the 6,6-bicyclic system are well-tolerated in the triazolotriazine derivatives **21c**, **22c**, **23c**, **24c**, and **25c**. In particular, (7,9a)-*trans*-amine **24c** (A_{2a}, K_i = 2 nM, A_1/A_{2a} ratio = 1750, Table 1) and (6,9a)-*cis*-alcohol **25c** (A_{2a}, K_i = 3 nM, A_1/A_{2a} ratio = 433, Table 1) are most favored.

As shown in Tables 2 and 3, capping groups were introduced at the 7- or 6-position to optimize the A_{2a} inhibitory potency, selectivity, and potentially pharmacological properties. In general, antagonists with the 7-cis configuration were more potent and selective for A_{2a} than their 7-trans or 6-cis counterparts.[23] Interestingly, the better potency and selectivity observed for

Table 2. A_{2A} Affinity and Selectivity of Compounds **26a**−**28c**



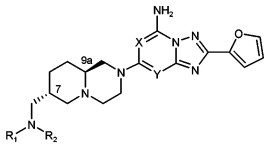
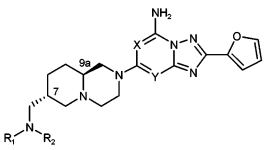
Compd.	Configuration	X	Y	R	A_{2a} Ki (nM)	A_1 Ki (nM)
26a	7-cis	N	N		21	> 500
26b	7-cis	CH	N		45	> 500
26c	7-trans	N	N		53	> 500
26d	6-cis	N	N		13	> 500
26e	7-cis	N	N		35	> 500
26f	7-trans	N	N		70	> 500
26g	7-cis	N	N		0.9	> 500
26h	7-cis	N	N		0.2	3300
26i	7-trans	N	N		53	960
26j	7-cis	N	N		4	> 500
26k	7-cis	N	N		70	> 500
27a	7-cis	N	N		0.6	3500
27b	6-cis	CH	N		830	> 500
27c	6-cis	N	N		76	> 1000
27d	7-cis	N	N		6	3500
27e	7-trans	N	N		73	210
27f	7-cis	N	N		20	> 1000
27g	7-trans	N	N		41	> 500
27h	7-trans	N	N		7	> 1000
27i	7-cis	N	N		36	> 1000
27j	7-trans	N	N		130	710
27k	7-cis	N	N		0.3	1400
27l	6-cis	CH	N		80	> 500
27m	7-cis	N	N		25	>1000
27n	7-trans	N	N		81	>1000
27o	7-cis	N	N		19	> 500
27p	7-trans	N	N		37	> 1000
27q	7-cis	N	N		5	> 500
				OR =		
28a	7-cis	N	N		0.3	1200
28b	7-cis	N	N		4	> 500
28c	7-cis	N	N		14	> 500

[a] Refer to Table 1 for membrane preparation and details regarding the radioligand binding assay. K_i values were calculated from binding curves generated from the mean of 3 determinations per concentration, with variation in individual values of <15%.

7-cis analogues are consistent with our hypothesis, based on structural superposition (Figure 2), that cis substitution is preferred over the trans.

On the phenyl ring, fluoro substitution (see compounds **26g** and **26h** Table 2) was more favorable than electron-donating OMe group (see compound **26e**). In particular, 3-fluorophenyl rendered **26h** (A_{2a}, K_i = 0.2 nM, Table 2) the most potent A_{2a} binder, with greater than 16 500-fold selectivity over the A_1 receptor. As shown in Table 2, compounds **27a** (A_{2a}, K_i = 0.6 nM,

Table 3. A_{2A} Affinity and Selectivity of Compounds **29a**−**n**

Compd.	Stereo	X	Y	R_1	R_2	A_{2a} Ki (nM)	A_1 Ki (nM)
29a	7-cis	N	N			> 500	>1000
29b	7-cis	N	N		H	2	1100
29c	7-cis	N	N			180	> 1000
29d	7-cis	N	N		H	30	> 500
29e	7-cis	N	N			47	> 1000
29f	7-cis	N	N			9	> 500
29g	7-cis	N	N			2	> 1000
29h	7-trans	N	N			4	7800
29i	7-cis	N	N		H	51	> 500
29j	7-cis	N	N			3	6000
29k	7-cis	N	N		H	36	> 500
29l	7-cis	N	N		H	9	1500
29m	7-trans	N	N		H	45	> 1000
29n	7-cis	N	CH		H	47	> 1000

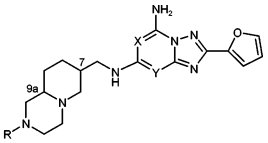
[a] Refer to Table 1 for membrane preparation and details regarding the radioligand binding assay. K_i values were calculated from binding curves generated from the mean of 3 determinations per concentration, with variation in individual values of <15%.

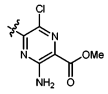
A_1/A_{2a} ratio = 5833) and **27d** (A_{2a}, K_i = 6 nM, A_1/A_{2a} ratio = 583) exhibited potent A_{2a} binding, presumably due in part to the electron-withdrawing effect of the nitrogen atom in the 6-quinolinyl and 5-isoquinolinyl capping groups, suggesting that these relatively bulky groups are well-accommodated at the 7-cis position. In contrast, similar substitutions with the 6-cis configuration led to substantial loss of potency in compounds **27b** (A_{2a}, K_i = 830 nM) and **27c** (A_{2a}, K_i = 76 nM). The relatively weak affinity of compound **27b** likely arises from the triazolo[1,5-*a*]pyrimidine, which also renders compound **21b** (A_{2a}, K_i = 610 nM, Table 1) significantly less potent than its analogues (**25c**, **25a**, Table 1). Among the 6-cis analogues, the phenyl-substituted **26d** (A_{2a}, K_i = 13 nM, Table 2) is more potent than those capped with polar groups (**27b**, **27c**, and **27l**, Table 2). However, none of these compounds is superior to the parent alcohol **25c** (A_{2a}, K_i = 3 nM, Table 1), suggesting that these capping groups are not favored at the 6-postion of the *cis*-bicyclic system.

Among the three pyridines, **27f**, **27k**, and **27m** (Table 2), the 3-pyridyl **27k** exhibited the best potency (A_{2a}, K_i = 0.3 nM, A_1/A_{2a} ratio = 4666). The enhanced A_{2a} inhibitory activity of 2-quinolinyl **27h** (A_{2a}, K_i = 7 nM, Table 2) as compared with 3-pyridyl **27g** (A_{2a}, K_i = 41 nM, Table 2) suggests that the fused phenyl ring in 2-quinolinyl is favored. The 4-quinazolines **27o** and **27p** exhibited A_{2a} binding affinity comparable to the 2-pyridyl and 4-pyridyl derivatives. Increased polarity, as in pyrazolopyrimidine **27q**, enhanced A_{2a} affinity (A_{2a}, K_i = 5 nM, Table 2) as compared to **27o**. Among the compounds directly capped with five-membered heterocycles through a nitrogen atom, imidazole **28a** showed higher affinity (A_{2a}, K_i = 0.3 nM, A_1/A_{2a} ratio = 4000, Table 2) than the triazole (**28b**, A_{2a}, K_i = 4 nM) and the tetrazole (**28c**, A_{2a}, K_i = 14 nM).

Table 3 summarizes the octahydropyridopyrazine-derived A_{2a} antagonists with nitrogen-linked capping groups. Interestingly, two opposing trends of A_{2a} binding affinity were observed for disubstituted vs monosubsti-

Table 4. A_{2A} Affinity and Selectivity of Compounds **14a**−**15b**



Compd.	Stereo	X	Y	R_1	A_{2a} Ki (nM)	A_1 Ki (nM)
14a	7-cis	N	N		49	> 500
14b	7-cis	N	N		130	> 500
14e	7-cis	N	CH		230	> 1000
14c	7-cis	N	N		34	> 1000
14d	7-cis	N	N		0.3	1600
15a	7-trans	N	N		230	> 1000
15b	7-trans	N	N		> 500	> 1000

[a] Refer to Table 1 for membrane preparation and details regarding the radioligand binding assay. K_i values were calculated from binding curves generated from the mean of 3 determinations per concentration, with variation in individual values of <15%.

tuted analogues. With highly hydrophobic capping groups such as difluorobenzyl, the monosubstituted antagonist **29b** (A_{2a}, K_i = 2 nM, A_1/A_{2a} ratio = 550, Table 3) is significantly more potent against A_{2a} receptor than its disubstituted counterpart **29a** (A_{2a}, K_i > 500 nM, Table 3). The more polar caps such as the pyrazolyl and furfuryl groups significantly improved the binding affinity of the disubstituted derivatives **29c** (A_{2a}, K_i = 179 nM) and **29e** (A_{2a}, K_i = 47 nM, Table 3) as compared to **29a**. However, monosubstitution is still more favored in the pyrazolyl case **29d** (A_{2a}, K_i = 30 nM, Table 3). When it comes to the pyridylmethyl derivatives (**29f**−**k**, Table 3), the trend is reversed completely; the disubstituted compounds **29g** (A_{2a}, K_i = 2 nM) and **29j** (A_{2a}, K_i = 3 nM, A_1/A_{2a} ratio = 2000) are more active than their monosubstituted counterparts, **29i** and **29m**, suggesting the possible existence of an additional hydrophilic pocket on the receptor. The 2-pyrimidyl capping group is well-tolerated in compound **29l** (A_{2a} K_i = 9 nM, A_1/A_{2a} ratio = 166), while the trans analogue **29k** and the one with the triazolo[1,5-*c*]pyrimidine template, **29n**, were less potent. The selectivity of this series of A_{2a} antagonists is generally good with some analogues (**29h**,**j**), achieving 2000-fold selectivity over the A_1 receptor.

Table 4 summarizes potency and selectivity of inversely capped octahydropyridopyrazine **14a**−**15b**. Compounds with a cis configuration exhibited good binding affinity as exemplified by 3,5-diflurophenyl **14a** (A_{2a}, K_i = 49 nM, Table 4), substituted pyrazine **14c** (A_{2a}, K_i = 34 nM), and 2-pyrimidyl **14d** (A_{2a}, K_i = 0.3 nM, A_1/A_{2a} ratio = 533). In contrast, the 2,4-difluorobenzyl cap was less favored, as in compounds **14b** and **14e**. The trans piperazines such as **15a** (A_{2a}, K_i = 230 nM) and **15b** (A_{2a}, K_i > 500 nM) are poorly tolerated.

Table 5. In Vitro Metabolic Stability of Selected A_{2A} Antagonists

	%*R*				%*R*		
compd	15 min	30 min	60 min	compd	15 min	30 min	60 min
14d	89	65	43	**21b**	97	81	51
18c	67	75	61	**21c**	100	100	100
19c	69	54	36	**26h**	57	36	12
21a	100	100	85	**27a**	42	25	16

[a] Compounds (2 μM final concentration) were incubated in rat liver microsomes. The percentage of parent compound remaining (%*R*) was measured after 15, 30, and 60 min. See Experimental Section for detail.

The metabolic stability of selected compounds was tested in an in vitro metabolic assay with rat liver microsomes and expressed as a percentage of parent compound remaining (%*R*) after 15−60 min. As shown in Table 5, the octahydropyridopyrazinyl methanols **21a**−**c** (see structures in Table 1) were found to be the most stable compounds in the study. The triazolo[1,5-*a*]triazine **21c** exhibited 100% parent remaining after 60 min. In contrast, the [1,2,4]triazolo[1,5-*c*]pyrimidine **21a** and [1,2,4]triazolo[1,5-*a*]pyrimidine **21b** were less stable with %*R* of 85% and 51%, respectively, at 60 min. Octahydropyrrolopyrazine **18c** and **19c** (see structures in Table 1) were moderately stable (%*R* at 30 min = 75% and 54%, respectively). Not surprisingly, capped compounds, such as **26h** and **27a**, were metabolized more readily in the rat liver microsomes (%*R* at 30 min = 36% and 25%, respectively). All of these tested compounds exhibited improved in vitro metabolic stability as compared to BIO-10370 (Figure 1, %*R* at 15 min = 14%), presumably due to the reduced susceptibility of the fused piperazines to oxidative metabolism. The inversely capped octahydropyridopyrazine **14d** (see

structure in Table 4) exhibited 43% parent remaining after 60 min.

To assess the in vivo efficacy of the bicyclic piperazine derivatives, rodent catalepsy models were used as a preliminary evaluation of both oral efficacy and CNS activity. In these models, an immobile state of catalepsy, in which Sprague−Dawley rats or CD-1 mice were unable to correct an externally imposed unnatural posture, was induced by subcutaneous injection of haloperidol into the animals. These models approximate the impaired motor activity observed in Parkinsonian patients and has been widely used to assess the anti-Parkinsonian properties of novel compounds. The efficacy of a test compound was determined by its ability to correct haloperidol-induced immobility in a "bar test"[14,24] after oral administration of the compound. Among a limited number of compounds[26] tested in the rodent PD model, three A_{2a} antagonists exhibited good efficacy. With a 3 mg/kg dosage, both compounds **21c** and **21a** (see Table 1) exhibited greater than 50% reduction of haloperidol-induced mouse catalepsy within 30 min of oral administration in the test, and the effect lasted for more than 60 min. However, these two compounds did not show efficacy in the more stringent rat catalepsy model with the 3 mg/kg dosage. Among a small selection of compounds studied at the 3 mg/kg dose in the rat catalepsy model, only the octahydropyrrolopyrazine derivative of triazolo[1,3-c]pyrimidine **18a** (see Table 1) exhibited greater than 50% reduction of haloperidol-induced rat catalepsy within 30 min of oral administration, and the effect lasted for more than 120 min. This encouraging result warrants additional efficacy studies in this series and provides a new platform for further optimizing the potency, selectivity, metabolic stability, and in vivo efficacy of this series.

Conclusion

In summary, a group of octahydropyridopyrazine and octahydropyrrolopyrazine derivatives of triazolo[1,5-*a*]-triazine, triazolo[1,3-*c*]pyrimidine, and triazolo[1,3-*a*]-pyrimidine have been identified as high-affinity adenosine A_{2a} antagonists with excellent selectivity over the adenosine A_1 receptor. Triazolotriazine template is most favored in providing in vitro binding potency. It was also found that antagonists with a cis bicyclic piperazine were generally more potent and selective than their trans counterparts. We have shown that a variety of capping groups linked to the bicyclic piperazine either through an oxygen atom or a nitrogen atom are well-tolerated, as exemplified by the potency of compounds **26h**, **27a**, **27k**, **27q**, **28a**, **29b**, **29g**, **29j**, and **14d**. The selectivity of this series of A_{2a} antagonists is generally good, with some analogues exhibiting greater than 5000-fold selectivity over the A_1 receptor. Two compounds (**21c** and **21a**) showed significantly improved metabolic stability in the in vitro rat liver microsomal study and oral efficacy in the mouse catalepsy model at 3 mg/kg. The octahydropyrrolopyrazine derivative of triazolo[1,3-*c*]pyrimidine **18a** exhibited good oral efficacy at 3 mg/kg, po, in the more stringent rat catalepsy model. The present study confirms the efficiency of the chosen aromatic heterocyclic templates and demonstrated the value of bicyclic piperazines as new pharmacophores for A_{2a} receptor for improving selectivity and in vitro metabolic stability.

Experimental Section

Gerneral Information. All proton magnetic resonance spectra were determined in the indicated solvent using a 400 MHz Bruker NMR spectrometer with the appropriate internal standard. Low-resolution mass spectra were obtained on a Micromass/single quadrupole/eletrospray platform. High-resolution mass spectra were obtained on a MALDI-TOF MS (Voyager-DE STR, Perseptive Biosystems) in the reflector mode with delayed extraction and an accelerating voltage of 20 kV. Each spectrum was an average of 100 laser shots and the experimental monoisotopic $M^+ + H$ value was calculated by averaging five spectra. Optical rotations were taken on a AUTOPOL IV automatic polarimeter. Elemental analyses were carried out at Quantitative Technology, Inc. (QTI, Whitehouse, NJ). The homogeneity of all the compounds was routinely checked by HPLC−MS and also by TLC on silica gel plates. Unless indicated otherwise, reagent-grade chemicals and solvents were purchased from Aldrich, Lancaster, Fisher, or Maybridge. Sulfone **5** and chlorides **6** and **7** were synthesized according to literature procedures.[8a,12,13] (7,9a)-*cis*- And (7,9a)-*trans*-(octahydropyridopyrazin-7-yl)methanols **8** and **9** and (6,9a)-*cis*-(octahydropyridopyrazin-6-yl)methanol **10** were prepared by following literature procedures.[15,16] (*R*)-Octahydropyrrolo[1,2-*a*]pyrazine (bicyclic diamine precursor for compounds **18a** and **18b**) was synthesized according to a literature procedure.[25] (±)-Octahydropyrido[1,2-*a*]pyrazine, (*S*)-octahydropyrrolo[1,2-*a*]pyrazine, and (*S,S*)-3-benzyloctahydropyrrolo-[1,2-*a*]pyrazine (bicyclic diamine precursors for **17a**−**c**, **19a**−**c**, and **20c**) were purchased from CNH Technologies, Inc. Analytical HPLC analysis was carried out using a HP 1100 series, with a 100 × 4.6 mm i.d. YMC column with S-5 μM packing (cat # AM-301). Preparative HPLC was carried out using a Gilson platform equipped with UV/visible detector and an automatic fraction collector. Preparative HPLC columns were 50 × 20 mm IC YMC column with S-5 μM packing. HPLC solvents (H_2O and CH_3CN) were buffered with 0.1% TFA.

Syntheses of Compounds 17a−21c, 23a−c, and 25a−c (Table 1): Method 1. The starting material, 2-furan-2-yl-5-methanesulfonyl[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-ylamine (**5**, 1 equiv), along with an appropriate bicyclic diamine (1−2 equiv), was dissolved in DMF. The mixture was stirred at 80 °C for 2 h. The solution was cooled to room temperature and filtered, and the solvent was removed in a Genevac evaporator. The residue was chromatographed on a silica gel column using 5−10% MeOH/CH_2Cl_2 as eluant to afford the desired product.

(±)-2-Furan-2-yl-5-(octahydropyrido[1,2-*a*]pyrazin-2-yl)[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-ylamine (17c). Using method 1 and (±)-octahydropyrido[1,2-*a*]pyrazine, compound **17c** was obtained as a white amorphous powder: yield 90%; ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (d, J = 2.0 Hz, 1H), 7.05 (d, J = 3.5 Hz, 1H), 6.53 (dd, J = 3.5, 2.0 Hz, 1H), 4.96 (d, J = 14.5 Hz, 1H), 4.89 (d, J = 14.5 Hz, 1H), 3.42 (brd, J = 12.0 Hz, 2H), 3.23 (m, 1H), 3.11 (m, 2H), 2.95 (m, 2H), 1.88 (m, 3H), 1.75 (m, 1H), 1.54 (m, 2H) ppm; MS m/z = 341 amu ($M^+ + H$). Anal. ($C_{16}H_{20}N_8O$) C, H, N.

(*S*)-2-Furan-2-yl-5-(hexahydropyrrolo[1,2-*a*]pyrazin-2-yl)[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-ylamine (19c). Using method 1 and (*S*)-octahydropyrrolo[1,2-*a*]pyrazine, compound **19c** was obtained as a light yellow amorphous powder: yield 90%; $[\alpha]^{20}_D$ −13.5° (*c* 1.1, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 3.5 Hz, 1H), 6.53 (dd, J = 3.5, 2.0 Hz, 1H), 5.12 (m, 1H), 4.13 (m, 1H), 3.85 (m, 1H), 3.66 (m, 1H), 3.48 (m, 1H), 3.35 (m, 1H), 3.07 (m, 2H), 2.09 (m, 3H), 1.80 (m, 1H) ppm; MS m/z = 327 amu ($M^+ + H$). Anal. ($C_{15}H_{18}N_8O$) C, H, N.

(7*RS*,9a*RS*)-[2-(7-Amino-2-furan-2-yl[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-5-yl)octahydropyrido[1,2-*a*]pyrazin-7-yl]-methanol (21c). Using method 1 and *cis*-(octahydropyrido[1,2-*a*]pyrazin-7-yl)methanol (**8**), compound **21c** was obtained as a white amorphous powder: yield 88%; ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 3.5 Hz, 1H),

6.62 (dd, J = 3.5, 2.0 Hz, 1H), 4.75 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.5 Hz, 1H), 3.82 (dd, J = 10.5, 7.5 Hz, 1H), 3.74 (dd, J = 10.5, 7.5 Hz, 1H), 3.11 (dt, J = 13.0, 3.0 Hz, 1H), 2.93 (d, J = 11.5 Hz, 1H), 2.78 (d, J = 11.5 Hz, 1H), 2.68 (dd, J = 13.0, 10.5 Hz, 1H), 2.22 (dd, J = 11.5, 3.0 Hz, 1H), 2.14 (dt, J = 12.0, 3.0 Hz, 1H), 1.93 (m, 1H), 1.85 (brd, J = 12.0 Hz, 2H), 1.60 (m, 1H), 1.43 (m, 2H) ppm; MS m/z = 371 amu ($M^+ + H$). Anal. ($C_{17}H_{22}N_8O_2 \cdot 0.2H_2O$) C, H, N.

(7*RS*,9a*SR*)-[2-(7-Amino-2-furan-2-yl[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-5-yl)octahydropyrido[1,2-*a*]pyrazin-7-yl]-methanol (23c). Using method 1 and *trans*-(octahydropyrido-[1,2-*a*]pyrazin-7-yl)methanol (**9**), compound **23c** was obtained as a white amorphous powder: yield 85%; ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (d, J = 1.5 Hz, 1H), 7.06 (d, J = 3.5 Hz, 1H), 6.53 (dd, J = 3.5, 1.5 Hz, 1H), 4.96 (t, J = 5.0 Hz, 2H), 3.48 (m, 3H), 3.34 (dd, J = 11.0, 7.0 Hz, 1H), 3.23 (m, 1H), 3.10 (m, 2H), 2.96 (dd, J = 15.0 Hz, 11.0 1H), 2.75 (t, J = 12.0 Hz, 1H), 1.97 (m, 2H), 1.84 (brd, J = 12.0 Hz, 1H), 1.56 (m, 1H), 1.35 (m, 1H) ppm; MS m/z = 371 amu ($M^+ + H$); HRMS calcd for $C_{17}H_{22}N_8O_2$ ($M^+ + H$) 371.1944, found 371.1940.

(6*RS*,9a*RS*)-[2-(7-Amino-2-furan-2-yl[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-5-yl)octahydropyrido[1,2-*a*]pyrazin-6-yl]-methanol (25c). Using method 1 and *cis*-(octahydropyrido[1,2-*a*]pyrazin-6-yl)methanol (**10**), compound **25c** was obtained as a white amorphous powder: yield 85%; ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 3.5 Hz, 1H), 6.65 (dd, J = 3.5, 2.0 Hz, 1H), 5.08 (brd, J = 15.0 Hz, 1H), 4.94 (brd, J = 15.0 Hz, 1H), 4.08 (dd, J = 12.0, 3.5 Hz, 1H), 3.90 (brd, J = 12.0 Hz, 1H), 3.62 (brd, J = 12.5 Hz, 1H), 3.36 (m, 2H), 3.16 (m, 3H), 1.98 (m, 4H), 1.67 (m, 2H) ppm; MS m/z = 371 amu ($M^+ + H$). Anal. ($C_{17}H_{22}N_8O_2$) C, H, N.

Method 2. The starting material, 7-chloro-2-furan-2-yl-[1,2,4]triazolo[1,5-*c*]pyrimidin-5-ylamine (**6**, 1 equiv), along with an appropriate bicyclic diamine (1−2 equiv) and CsF (1−2 equiv), was dissolved in DMSO. The mixture was stirred at 120 °C for 18 h. The solution was cooled to room temperature and filtered and the solvent was removed in a Genevac evaporator. The residue was chromatographed on a silica gel column using 5−10% $MeOH/CH_2Cl_2$ as eluant to afford the desired product.

(*R*)-2-Furan-2-yl-7-(hexahydropyrrolo[1,2-*a*]pyrazin-2-yl)[1,2,4]triazolo[1,5-*c*]pyrimidin-5-ylamine (18a). Using method 2, compound **18a** was obtained as a white amorphous powder: yield 90%; $[\alpha]^{20}_D$ +11.5° (c = 0.1, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (d, J = 2.0 Hz, 1H), 7.17 (d, J = 3.5 Hz, 1H), 6.59 (dd, J = 3.5, 2.0 Hz, 1H), 6.06 (s, 1H), 4.23−2.88 (m, 9H), 2.20 (m, 1H), 2.08 (m, 2H), 1.81 (m, 1H) ppm; MS m/z = 326 amu ($M^+ + H$); HRMS calcd for $C_{15}H_{18}N_8O$ ($M^+ + H$) 327.1682, found 327.1693.

(7*RS*,9a*RS*)-[2-(5-Amino-2-furan-2-yl[1,2,4]triazolo-[1,5-*c*]pyrimidin-7-yl)octahydropyrido[1,2-*a*]pyrazin-7-yl]methanol (21a). Using method 2 and *cis*-octahydropyrido-[1,2-*a*]pyrazin-7-yl)methanol (**8**), compound **21a** was obtained as a white amorphous powder: yield 80%; ^{1}H NMR (400 MHz, CD_3OD): δ 7.71 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 3.5 Hz, 1H), 6.63 (dd, J = 3.5, 2.0 Hz, 1H), 5.99 (s, 1H), 4.26 (d, J = 13.5 Hz, 1H), 4.19 (d, J = 13.5 Hz, 1H), 3.83 (dd, J = 10.5, 7.5 Hz, 1H), 3.74 (dd, J = 10.5, 7.5 Hz, 1H), 3.04 (dt, J = 12.5, 3.0 Hz, 1H), 2.95 (d, J = 12.0 Hz, 1H), 2.80 (d, J = 11.0 Hz, 1H), 2.62 (dd, J = 12.5, 10.5 Hz, 1H), 2.22 (m, 2H), 1.98 (m, 1H), 1.86 (brd, 12.0 Hz, 2H), 1.62 (m, 1H), 1.50−1.42 (m, 2H) ppm; MS m/z = 370 amu ($M^+ + H$). Anal. ($C_{18}H_{23}N_7O_2 \cdot 0.2H_2O$) C, H, N.

Method 3. The starting material, 5-chloro-2-furan-2-yl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ylamine (**7**, 1 equiv), along with the appropriate bicyclic diamine (1−2 equiv) and CsF (1−2 equiv) was dissolved in DMSO. The mixture was stirred at 100 °C for 18 h. The solution was cooled to room temperature and filtered, and the solvent was removed in a Genevac evaporator. The resulting residue was chromatographed on a silica gel column using 5−10% $MeOH/CH_2Cl_2$ as eluant to afford the desired product.

(7*RS*,9a*RS*)-[2-(7-Amino-2-furan-2-yl[1,2,4]triazolo-[1,5-*a*]pyrimidin-5-yl)octahydropyrido[1,2-*a*]pyrazin-7-yl]methanol (21b). Using method 3 and *cis*-(octahydropyrido-[1,2-*a*]pyrazin-7-yl)methanol (**8**), compound **21b** was obtained as a white amorphous powder: yield 80%; ^{1}H NMR (400 MHz, CD_3OD) δ 7.69 (d, J = 2.3 Hz, 1H), 7.10 (d, J = 3.5 Hz, 1H), 6.61 (dd, J = 3.5, 2.3 Hz, 1H), 5.73 (s, 1H), 4.32 (d, J = 13.5 Hz, 1H), 4.24 (d, J = 13.5 Hz, 1H), 3.82 (dd, J = 10.5, 7.5 Hz, 1H), 3.74 (dd, J = 10.5, 7.5 Hz, 1H), 3.10 (dt, J = 12.5, 3.2 Hz, 1H), 2.94 (d, J = 11.5 Hz, 1H), 2.79 (d, J = 11.5 Hz, 1H), 2.67 (dd, J = 13.0, 10.5 Hz, 1H), 2.21 (m, 2H), 1.96 (m, 1H), 1.85 (brd, 12.0 Hz, 2H), 1.60 (m, 1H), 1.47 (m, 2H) ppm; MS m/z = 370 amu ($M^+ + H$). Anal. ($C_{18}H_{23}N_7O_2$) C, H, N.

Syntheses of Compounds 22a−c and 24b−c (Table 1): Method 4. In a typical procedure, a solution of an amino alcohol derivative (1 equiv), obtained from method 1, 2, or 3, and triethylamine (2 equiv) in DMF was treated with methansulfonyl chloride (2 equiv) at 0 °C for 30 min. The reaction was then warmed to room temperature. To the reaction solution was added sodium azide (5 equiv), and the resulting mixture was stirred at 100 °C for 24 h. Then the solvent was removed, and the residue was purified by silica gel column chromatography using 5% $MeOH/CH_2Cl_2$ to afford the corresponding azide. A suspension of the azide (1 equiv) and polymer-supported PPh_3 (4 equiv, 3 mmol/g loading) in THF was shaken at room temperature overnight. Then water was added, and the resulting mixture was shaken at room temperature for 2 h. The suspension was filtered and the filter cake was washed with THF and water. The filtrates were combined and lyophilized to give the corresponding amine as an oil. Purification by preparative HPLC using aqueous CH_3CN (buffered with 0.1% TFA) afforded the desired product.

(7*RS*,9a*RS*)-5-(7-Aminomethyloctahydropyrido[1,2-*a*]-pyrazin-2-yl)-2-furan-2-yl[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-ylamine (22c). Using method 4 and alcohol **21c**, compound **22c** was obtained as a white amorphous powder: yield 70%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.68−2.28 (m, 4H), 2.30 (m, 1H), 3.13−3.69 (m, 9H), 4.67−4.79 (m, 2H), 6.69 (dd, J = 1.8, 3.4 Hz, 1H), 7.07 (d, J = 3.4 Hz), 7.88 (d, J = 1.8 Hz), 7.97 (m, 3H), 8.49 (m, 2H) ppm; MS m/z = 370 amu ($M^+ + H$); HRMS calcd for $C_{17}H_{23}N_9O$ ($M^+ + H$) 370.2103, found 370.2097.

Syntheses of Compounds 26a−k and 27a−q (Table 2): Method 5. In a typical procedure, a solution of an amino alcohol derivative (1 equiv), obtained using method 1, 2, or 3, and triethylamine (4 equiv) in DMF was treated with methansulfonyl chloride (2 equiv) at 0 °C. After 2 h, the reaction was quenched with ice and basified with 1 M NaOH, and the mixture was extracted with methylene chloride. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the corresponding mesylate. In the case of triazolotriazine derivatives, the mesylate precipitated out of solution during extraction and was collected and combined with the extracted product. The mesylate was used without further purification in the next reaction.

A solution of an appropriate hydroxyl-substituted phenyl or heterocycle (1.5 equiv) in DMF was treated with sodium hydride (60% oil dispersion, 4 equiv), for 2 h at 50 °C. Then a solution of a mesylate (1 equiv, obtained from previous step) in DMF was added. The mixture was then heated at 100 °C for 24 h. The solvent was removed, and the residue dissolved in DMSO, filtered, and purified by preparative HPLC using aqueous CH_3CN (buffered with 0.1% TFA) to afford the desired product.

(7*RS*,9a*RS*)-2-Furan-2-yl-5-[7-(quinolin-6-yloxy-methyl)octahydropyrido[1,2-*a*]pyrazin-2-yl][1,2,4]triazolo-[1,5-*a*][1,3,5]triazin-7-ylamine (26a). Using method 5 and 6-hydroxylquinoline, compound **26a** was obtained as a white amorphous powder: yield 75%; ^{1}H NMR (400 MHz, CD_3OD) δ 8.81 (d, J = 3.5 Hz, 1H), 8.72 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.78 (m, 1H), 7.63 (dd, J = 9.0, 3.0 Hz, 1H), 7.57 (brs, 1H), 7.50 (d, J = 2.5 Hz, 1H), 7.00 (d, J = 3.5 Hz, 1H), 6.48 (dd, J = 2.5, 3.5 Hz, 1H), 4.86 (m, 2H), 4.36 (m, 1H), 4.24 (m, 1H), 3.70 (dd, J = 12.5, 3.0 Hz, 1H), 3.45 (m, 1H), 3.28 (m, 1H), 3.19 (m, 1H), 3.06 (m, 2H), 2.55 (m, 1H), 1.95 (m, 3H), 1.82 (m, 2H); MS m/z = 498 amu ($M^+ + H$). Anal. ($C_{26}H_{27}N_9O_2$) C, H, N.

(7*RS*,9a*RS*)-2-Furan-2-yl-5-(7-imidazol-1-ylmethyloctahydropyrido[1,2-*a*]pyrazin-2-yl)[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-ylamine (28a). Using method 5 and imidazole, compound **23a** was obtained as a white amorphous powder: yield 70%; ^{1}H NMR (400 MHz, CD_3OD) δ 9.09 (s, 1H), 7.75 (brs, 1H), 7.73 (brs, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.17 (d, J = 3.0 Hz, 1H), 6.64 (dd, J = 3.0, 2.0 Hz, 1H), 5.00 (m, 3H), 4.61 (m, 2H), 3.10−3.57 (m, 7H), 1.95 (m, 3H), 1.74 (m, 1H); MS m/z = 421 amu (M^+ + H). Anal. ($C_{20}H_{24}N_{10}O$) C, H, N.

Syntheses of compounds 29a−n(Table 3): Method 6. In a typical procedure, a solution of an amine (1 equiv), obtained from method 4, and an appropriate aldehyde (3 equiv) in dichloroethene was treated with sodium triacetoxyborohydride (3 equiv) and AcOH (3 equiv). The mixture was shaken at room temperature for 24 h. The solvent was removed and the residue was purified by preparative HPLC using aqueous CH_3CN (buffered with 0.1% TFA) to afford the desired product.

(7*RS*,9a*RS*)-5-{7-[(Bispyridin-4-ylmethylamino)-methyl]octahydropyrido[1,2-*a*]pyrazin-2-yl}-2-furan-2-yl[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-ylamine (29j). Using amine **24b**, pyridine-4-carbaldehyde, and method 6, compound **29j** was synthesized as a white amorphous powder: yield 85%; ^{1}H NMR (400 MHz, CD_3OD) δ 1.01−1.32 (m, 1H), 1.50−2.49 (m, 4H), 2.55−3.45 (m, 9H), 3.57−4.03 (m, 4H), 4.55−4.79 (m, 2H), 6.70 (dd, J = 1.8, 3.3 Hz, 1H), 7.08 (d, J = 3.3 Hz, 1H), 7.76 (d, J = 4.5 Hz, 4H), 7.89 (d, J = 1.8 Hz, 1H), 8.43−8.62 (m, 2H), 8.73 (d, J = 4.5 Hz, 4H) ppm; MS m/z = 552 amu (M^+ + H); HRMS calcd for $C_{29}H_{33}N_{11}O$ (M^+ + H) 552.2947, found 552.2938.

Method 7. In a typical procedure, a solution of an amine (1 equiv), obtained from method 4, and an appropriate aldehyde (1 equiv) in anhydrous THF was treated with titanium(IV) isopropoxide (1.7 equiv) 60 °C for 5 h. Then, anhydrous methanol was added followed by careful addition of $NaBH_4$ (1.5 equiv). After 1 h, the reaction was completed as indicated by HPLC analysis. The solvent was removed and the residue was purified by preparative HPLC using aqueous CH_3CN (buffered with 0.1% TFA) to afford the desired product.

(7*RS*,9a*RS*)-2-Furan-2-yl-5-(7-{[(pyridin-4-ylmethyl)-amino]methyl}octahydropyrido[1,2-*a*]pyrazin-2-yl)[1,2,4]-triazolo[1,5-*a*][1,3,5]triazin-7-ylamine (29k). Using amine **24b**, pyridine-4-carbaldehyde, and method 7, compound **29k** was obtained as a white amorphous powder: yield 80%; ^{1}H NMR (400 MHz, CD_3OD) δ 1.77−2.11 (m, 4H), 2.66 (m, 1H), 3.78−3.05(m, 11 H), 4.46(bs, 2 H), 6.65 (dd, J = 1.8, 3.4 Hz, 1H), 7.18 (d, J = 3.4 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.88 (d, J = 6.0 Hz, 2H), 8.81 (d, J = 6.0 Hz, 2H) ppm; MS m/z = 461 amu (M^+ + H); HRMS calcd for $C_{23}H_{28}N_{10}O$ (M^+ + H) 461.2525, found 461.2519.

Method 8: In a typical procedure, a solution of an amine (1 equiv), obtained from method 4, and 2-chloropyrimidine (2 equiv) in DMSO was treated with K_2CO_3 (2 equiv). The mixture was stirred at 85 °C for 4 h. The reaction mixture was filtered, and the filtrate was concentrated and purified by preparative HPLC using aqueous CH_3CN (buffered with 0.1% TFA) to afford the desired product.

(7*RS*,9a*RS*)-2-Furan-2-yl-5-[7-(pyrimidin-2-ylamino-methyl)octahydropyrido[1,2-*a*]pyrazin-2-yl][1,2,4]triazolo-[1,5-*a*][1,3,5]triazin-7-ylamine (29l). Using method 8 and amine **24b**, compound **29l** was obtained as a white amorphous powder: yield 90%; ^{1}H NMR (400 MHz, CD_3OD) δ 1.60−1.86 (m, 4H), 2.21−2.30 (bs, 1H), 3.05−3.32 (m, 4H), 3.33−3.52 (m, 4H), 3.56−3.72 (m, 1H), 4.62−4.83 (m, 2H), 6.63 (t, J = 4.8 Hz, 1H), 6.69 (dd, J = 1.8, 3.4 Hz, 1H), 7.08 (d, J = 3.4 Hz, 1H), 7.41 (t, J = 5.6 Hz, 1H), 7.89 (d, J = 1.8 Hz, 1H), 8.32 (d, J = 4.8 Hz, 2H), 8.40−8.65 (m, 2H) ppm; MS m/z = 447 amu (M^+ + H). HRMS calcd for $C_{21}H_{25}N_{11}O$ (M^+ + H) 448.2321, found 448.2314.

Syntheses of compounds 14a−d (Table 4): Method 9. Alcohol **8** (1 equiv), along with 1,3,5-trifluorobenzene (1 equiv) and CsF (1 equiv), was suspended in DMSO. The mixture was stirred at 95 °C overnight. The solvent was removed, and the residue was subjected to silica gel column chromatography using 5% MeOH/CH_2Cl_2 to afford (7*RS*,9a*RS*)-[2-(3,5-difluorophenyl)octahydropyrido[1,2-*a*]pyrazin-7-yl]methanol as a colorless oil.

A solution of the above-mentioned product (1 equiv) and triethylamine (2 equiv) in CH_2Cl_2 was treated with methansulfonyl chloride (1.5 equiv) at 0 °C for 20 min. The reaction was quenched with 2 M Na_2CO_3 aqueous solution, and the mixture was extracted with methylene chloride. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the corresponding mesylate as a yellow oil. This material was used without further purification.

A solution of the above-mentioned mesylate (1 equiv) and sodium azide (2 equiv) in DMF was stirred at 90 °C for 24 h. The solution was cooled to room temperature, diluted with water, and extracted with methylene chloride. The combined organic layers was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the corresponding azide as a yellow oil. This material was used without further purification.

A suspension of the above-mentioned azide (1 equiv) and polymer-supported PPh_3 (4 equiv, 3 mmol/g loading) in THF was shaken at room temperature overnight. Then water was added, and the resulting mixture was shaken at room temperature for 2 h. The suspension was filtered and the filter cake was washed with THF and water. The filtrate was lyophilized to give the corresponding amine as a yellow oil. This material was used in the following step without further purification.

(7*RS*,9a*RS*)-N^5-[2-(3,5-Difluorophenyl)octahydropyrido-[1,2-*a*]pyrazin-7-ylmethyl]-2-furan-2-yl[1,2,4]triazolo[1,5-*a*][1,3,5]triazine-5,7-diamine (14a). The amine obtained in method 9 was coupled to sulfone **5** according to procedures described in method 1 to afford compound **14a** as a white amorphous powder: yield 50%; ^{1}H NMR (400 MHz, CD_3OD) δ 7.60 (brs, 1H), 6.96 (d, J = 3.0 Hz, 1H), 6.57 (d, J = 8.0 Hz, 2H), 6.52 (dd, J = 3.0, 1.0 Hz, 1H), 6.35 (t, J = 8.0 Hz, 1H), 3.90 (brd, J = 13.0 Hz, 1H), 3.73 (m, 3H), 3.30 (m, 5H), 3.14 (m, 3H), 2.22 (m, 1H), 1.90 (m, 2H), 1.80 (m, 1H) ppm; MS m/z = 482 amu (M^+ + H). Anal. ($C_{23}H_{25}F_2N_9O$) C, H, N.

(7*RS*,9a*RS*)-N^5-[2-(2,4-Difluorobenzyl)octahydropyrido-[1,2-*a*]pyrazin-7-ylmethyl]-2-furan-2-yl[1,2,4]triazolo[1,5-*a*][1,3,5]triazine-5,7-diamine (14b). Alcohol **8** (1 equiv), along with 2,4-difluorobenzyl bromide (1 equiv) and Na_2CO_3 (1 equiv), was suspended in THF. The mixture was stirred at 35 °C overnight and then filtered. The filtrate was concentrated and purified by silica gel column chromatography using 5% MeOH/CH_2Cl_2 to afford (7*RS*,9a*RS*)-[2-(2,4-difluorobenzyl)-octahydropyrido[1,2-*a*]pyrazin-7-yl]methanol as a colorless oil. This product was converted to the corresponding mesylate, azide, and amine sequentially according to the procedures described in method 9. The resulting amine was then coupled to sulfone **5** according to the procedures described in method 1 to afford compound **14b** as a white amorphous powder: yield 60%; ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (brs, 1H), 7.40 (m, 1H), 7.04 (d, J = 3.0 Hz, 1H), 6.89 (m, 2H), 6.55 (dd, J = 3.0, 1.0 Hz, 1H), 3.75 (brs, 2H), 3.64 (m, 1H), 3.28 (m, 5H), 3.02 (m, 3H), 2.93 (m, 1H), 2.60 (m, 1H), 2.16 (m, 1H), 1.81 (m, 2H), 1.72 (m, 2H) ppm; MS m/z = 496 amu (M^+ + H). Anal. ($C_{24}H_{27}F_2N_9O$) C, H, N.

(7*RS*,9a*RS*)-3-Amino-5-{7-[(7-amino-2-furan-2-yl[1,2,4]-triazolo[1,5-*a*][1,3,5]triazin-5-ylamino)methyl]octahydropyrido[1,2-*a*]pyrazin-2-yl}-6-chloropyrazine-2-carboxylic Acid Methyl Ester (14c). Alcohol **8** (1 equiv), along with methyl 3-amino-5,6-dichloro-2-pyrazinecarboxylate (1 equiv) and triethylamine (1 equiv), was suspended in i-PrOH. The mixture was stirred at 80 °C overnight. The solvent was removed, and the residue was suspended in 5% MeOH/CH_2Cl_2 and filtered. The filtrate was concentrated and subjected to silica gel column chromatography using 5%−10% MeOH/CH_2Cl_2 to afford (7*RS*,9a*RS*)-3-amino-6-chloro-5-(7-hydroxymethyloctahydropyrido[1,2-*a*]pyrazin-2-yl)pyrazine-2-carboxylic acid methyl ester as a brown oil. This product was converted to the corresponding mesylate, azide, and amine sequentially according to the procedures described in method 9. The

resulting amine was then coupled to sulfone **5** according to procedures described in method 1 to afford compound **14c** as a light brown amorphous powder: yield 55%; ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (brs, 1H), 7.03 (d, J = 3.0 Hz, 1H), 6.52 (dd, J = 3.0, 1.0 Hz, 1H), 4.39 (d, J = 14.0 Hz, 2H), 3.96 (m, 1H), 3.78 (s, 3H), 3.72 (m, 1H), 3.39 (m, 2H), 3.29−3.07 (m, 5H), 2.18 (m, 1H), 1.80 (m, 4H) ppm; MS m/z = 556 amu (M^+ + 2H). Anal. ($C_{23}H_{27}Cl\ N_{12}O_3$) C, H, N.

(7*RS*,9a*RS*)-2-Furan-2-yl-*N*^{5}-(2-pyrimidin-2-yloctahydropyrido[1,2-*a*]pyrazin-7-ylmethyl)[1,2,4]triazolo[1,5-*a*]-[1,3,5]triazine-5,7-diamine (14d). Alcohol **8** (1 equiv), along with 2-chloropyrimidine (1 equiv) and Na_2CO_3 (1 equiv), was dissolved in water. The mixture was stirred at 95 °C overnight. The solution was cooled to room temperature and extracted with methylene chloride. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give (7*RS*,9a*RS*)-(2-pyrimidin-2-yloctahydropyrido-[1,2-*a*]pyrazin-7-yl)methanol as a white solid. Without further purification, this alcohol was converted to the corresponding mesylate, azide, and amine sequentially according to the procedures described in method 9. The resulting amine was then coupled to sulfone **5** according to method 1 to give compound **14d** as a white amorphous powder: yield 60%; ^{1}H NMR (400 Hz, DMSO-d_6) δ 8.52 (d, J = 5.0 Hz, 1H), 7.94 (brs, 1H), 7.10 (d, J = 3.0 Hz, 1H), 6.84 (t, J = 5.0 Hz, 1H), 6.75 (dd, J = 3.0, 1.0 Hz, 1H), 4.84 (m, 2H), 3.64−3.19 (m, 8H), 3.13 (m, 1H), 2.30 (m, 1H), 1.88 (m, 2H), 1.80 (m, 2H) ppm; MS m/z = 448 amu (M^+ + H). Anal. ($C_{21}H_{25}N_{11}O$) C, H, N.

Syntheses of Compounds 15a,b (Scheme 4, Table 4). (7*RS*,9a*SR*)-*N*^{5}-[2-(5-Chloro-1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-ylmethyl)octahydropyrido[1,2-*a*]pyrazin-7-ylmethyl]-2-furan-2-yl[1,2,4]triazolo[1,5-*a*][1,3,5]triazine-5,7-diamine (15a). To a solution of (7*RS*,9a*SR*)-(octahydropyrido[1,2-*a*]pyrazin-7-yl)methanol (9, 1 equiv) in 1,4-dioxane was added 5 N KOH until pH = 9, and then a solution of Boc_2O (2 equiv) in 1,4-dioxane was added. The mixture was stirred at room temperature overnight, after which the solvent was removed and the residue was diluted with water and extracted with methylene chloride. The combined organic phases was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford (7*RS*,9a*SR*)-7-hydroxymethyloctahydropyrido-[1,2-*a*]pyrazine-2-carboxylic acid *tert*-butyl ester as a white solid.

Without further purification, the above-mentioned crude product was converted to the corresponding mesylate, azide, and amine sequentially according to the procedures described in method 9. The resulting amine was then coupled to sulfone **1** according to the procedures described in method 1 to afford (7*RS*,9a*SR*)-7-[(7-amino-2-furan-2-yl[1,2,4]triazolo[1,5-*a*][1,3,5]-triazin-5-ylamino)methyl]octahydropyrido[1,2-*a*]pyrazine-2-carboxylic acid *tert*-butyl ester as an yellow oil. This material was used without further purification.

To a solution of the above-mentioned product (1 equiv) in methylene chloride was added trifluoroacetic acid to reach a final concentration of 10% TFA. The mixture was stirred at room temperature for 2 h, after which the solvent was removed under reduced pressure, and the residue was dissolved in acetonitrile. To the resulting solution was added 2-chloropyrimidine (1 equiv) and Na_2CO_3 (2 equiv). The mixture was stirred at 80 °C overnight, after which, the solvent was removed and the residue was purified by preparative HPLC using aqueous CH_3CN (buffered with 0.1% TFA) to afford compound **15a** as a white amorphous powder: yield 65%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 4.7 Hz, 2 H), 7.70 (d, J = 2 Hz, 1 H), 7.12 (d, J = 3.6 Hz, 1 H), 6.72 (t, J = 4.7 Hz, 1H), 6.62 (dd, J = 2, 3.6 Hz, 1 H), 4.97 (d, J = 14.1 Hz, 2 H), 3.34−3.58 (m, 4 H), 3.11−3.24 (m, 3 H), 2.82−3.03 (m, 2 H), 2.33 (m, 1 H), 2.10 (d, J = 14.1 Hz, 1H), 2.02 (d, J = 13.2 Hz, 1 H), 1.60−1.69 (m, 1 H),1.39−1.49 (m, 1 H); MS m/z = 448 amu (M^+ + H); HRMS calcd for $C_{21}H_{25}N_{11}O$ (M^+ + H) 448.2322, found 448.2325.

(7*RS*,9a*SR*)-2-Furan-2-yl-*N*^{5}-(2-pyrimidin-2-yloctahydropyrido[1,2-*a*]pyrazin-7-ylmethyl)[1,2,4]triazolo[1,5-*a*]-[1,3,5]triazine-5,7-diamine (15b). The intermediate obtained in the above-mentioned procedure of Boc deprotection was dissolved in methylene chloride. To this solution was added 5-chloro-1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carbaldehyde (1.0 equiv), sodium triacetoxyborohydride (1.5 equiv), and acetic acid (1.5 equiv). The reaction was stirred at room temperature overnight. After the solvent was removed, the residue was purified by preparative HPLC using aqueous CH_3-CN (buffered with 0.1% TFA) to afford compound **15b** as a white amorphous powder: yield 55%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (d, J = 5.0 Hz, 1 H), 7.12 (d, J = 3.6 Hz, 1 H), 6.62 (m, 1 H), 4.51 (s, 3 H), 4.50 (s, 2 H), 3.39−3.53 (m, 4 H), 3.00−3.12 (m, 4 H), 2.80−2.86 (m, 1 H), 2.37−2.43 (m, 1 H), 2.21−2.27 (m, 2H), 1.94−1.97 (m, 2 H), 1.53−1.58 (m, 1 H), 1.30−1.44 (m, 1 H); MS m/z = 568 amu (M^+ + H); HRMS calcd for $C_{23}H_{27}N_{11}OClF_3$ (M^+ + H) 566.2119, found 566.2132.

Biological Assays. Radioligand Binding Assay and Data Analysis. A detailed description for membrane preparation and radioligand binding assay has been reported previously.[14,20] Briefly, membranes were prepared from rat brain tissues purchased from Pel-Freez for A_{2a} receptor. For A_1 receptor, the membranes were prepared from rat cerebral cortex isolated from freshly euthanized rats. Membranes (40−70 μg membrane protein), radioligands ([^{3}H]DPCPX for A_1 receptors, [^{3}H]ZM241385 A_{2a} receptors), and varying concentration of competing ligands were incubated in triplicates in 0.1 mL of buffer HE plus 2 units/mL adenodine deaminase for 2.5 h at 21 °C. Binding assays were terminated by filtration over Whatman GF/C glass-fiber filters using a BRANDEL cell harvester. Filters were rinsed three times with 3−4 mL of ice-cold 10 mM Tris-HCl, pH 7.4, and 5 mM $MgCl_2$ at 4 °C and were counted in a Wallac β-counter. Competition binding data were fit to a single-site binding model using Prizm GraphPad for K_i determination. The Cheng−Prusoff equation, K_i IC_{50}/(1+[I]/K_D), was used to calculate K_i values from IC_{50} values, wherein K_i is the affinity constant for the competing ligand, [I] is the concentration of the free radioligand, and K_D is the dissociation constant for the radioligand.

Rat Liver Microsome Stability Study. Compounds of interest (2 μM final concentration) were incubated in rat liver microsomes and their metabolic stability determined by the percent of parent compound remaining after 15, 30, and 60 min. Experimental details: Potassium phosphate buffer (425 μL, 66 mM, pH 7.4) was first added into a 1.2-mL cluster 96-well plate (Costar). The testing compounds (20 μL of 50 μM stock in DMSO) were then added into the buffer solution followed by solution A (25 μL, 26 mM $NADP^+$ + 66 mM glucose-6-phosphate + 66 mM $MgCl_2$) and solution B (5 μL, 40 U/mL Glucose-6-phosphate dehydrogenase in 5 mM sodium citrate buffer). The incubation plate was then equilibrated in a 37 °C water bath for 5 min, and Sprague−Dawley rat liver microsomes (25 μL, 20 mg of protein/mL) were added. The reaction plate was incubated in a 37 °C water bath with shaking, and aliquots (100 μL) of the reaction mixture were pipetted out at 0, 15, 30, and 60 min time points and added to another 1.2-mL cluster 96-well plate, containing the quench solution 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) (Sigma, 100 μL of 100 ng/mL stock in acetonitrile). The DPCPX acted as the internal standard against which the percent of the compounds of interest remaining were calculated in the LC/MS analysis. Activity of the rat liver microsome used in our assay was tested/verified by its ability to metabolize the two standard compounds, alprazolam (Sigma) and propranolol (Sigma), under exact conditions described above.

Catalepsy Experiments. Male Sprague−Dawley rats (225−275 g) were injected with haloperidol (1 mg/kg) to induce immobility. Every 30 min for the next 3 h, catalepsy was measured using the bar test.[23] In this test, the mice's forelimbs were placed on an aluminum bar (1 cm in diameter) suspended horizontally 10 cm above the surface of the bench. The elapsed time until the mouse placed the forepaw back was measured, with a maximum time of 120 s allowed. Once rats showed a stable baseline cataleptic response (about 3 h after haloperidol injection), a test compound or vehicle alone is administered by oral gavage, and catalepsy was measured by the bar test

every 30 min for the next 2 h. Data were analyzed by one-factor analysis of variance with Dunnett's *t* test used to make post-hoc comparisons. The method was identical for mice (CD-1; 25−30 g), except that the dose of haloperidol was 3 mg/kg sc, and the bar was suspended 4.5 cm above the surface of the bench.

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Supporting Information Available: Spectroscopic data for additional compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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