Structure−Activity Relationships of 2,N^6,5′-Substituted Adenosine Derivatives with Potent Activity at the A_{2B} Adenosine Receptor

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2, N^6, and 5′-substituted adenosine derivatives were synthesized via alkylation of 2-oxypurine nucleosides leading to 2-arylalkylether derivatives. 2-(3-(Indolyl)ethyloxy)adenosine **17** was examined in both binding and cAMP assays and found to be a potent agonist of the human A_{2B}AR. Simplification, altered connectivity, and mimicking of the indole ring of **17** failed to maintain A_{2B}AR potency. Introduction of N^6-ethyl or N^6-guanidino substitution, shown to favor A_{2B}AR potency, failed to enhance potency in the 2-(3-(indolyl)-ethyloxy)adenosine series. Indole 5″- or 6″-halo substitution was favored at the A_{2B}AR, but a 5′-*N*-ethylcarboxyamide did not further enhance potency. 2-(3″-(6″-Bromoindolyl)ethyloxy)adenosine **28** displayed an A_{2B}AR EC_{50} value of 128 nM, that is, more potent than the parent **17** (299 nM) and similar to 5′-*N*-ethylcarboxamidoadenosine (140 nM). Compound **28** was a full agonist at A_{2B} and A_{2A}ARs and a low efficacy partial agonist at A_1 and A_3ARs. Thus, we have identified and optimized 2-(2-arylethyl)oxo moieties in AR agonists that enhance A_{2B}AR potency and selectivity.

Introduction

There are four subtypes of adenosine receptors (ARs): A_1, A_{2A}, A_{2B}, and A_3.[1] Three of these subtypes already possess selective and potent agonists and antagonists.[2] Only the A_{2B}-AR remains without a selective agonist. It should be noted, however, that highly potent and selective antagonists have been reported for this subtype.[3−8] A_{2B}AR antagonists are directed toward clinical use for treating asthma and diabetes. Conversely, a selective A_{2B}AR agonist would provide a useful pharmacological probe for exploring the role of receptor activation. Activation of the A_{2B}AR is known to induce angiogenesis,[9] reduce vascular permeabilization,[10] increase production of the anti-inflammatory cytokine IL-10,[11] increase chloride secretion in epithelial cells,[12−14] and increase release of inflammatory mediators from human and canine mast cells.[15,16] A_{2B}AR agonists have been proposed for the treatment of septic shock[17] and cystic fibrosis,[18] and cardiac,[19] pulmonary,[20] and kidney[19] diseases associated with remodeling and hyperplasia. Thus, such an agonist may be useful in preventing restenosis. The A_{2B}AR mediates vasodilation in the corpus cavernosum of rabbit and agonists, therefore, may be useful in treating erectile dysfunction.[21] Recently, Yang et al. described a proinflammatory phenotype resulting from deletion of the gene encoding the A_{2B}-AR in the mouse, suggesting that activation of the A_{2B}AR can have anti-inflammatory effects.[22] Activation of the A_{2B}AR also promotes postconditioning salvage of ischemic myocardium.[23]

Modulation of A_{2B}AR potency has been achieved through structural changes at several sites on the adenosine molecule. R-PIA (R-N^6-(phenylisopropyl)adenosine) **1** was one of the earliest potent agonists to be extensively investigated at ARs and was one of the nucleosides used initially to distinguish the low affinity A_{2B} and high affinity A_{2A}ARs.[24] It was found to activate the A_{2B}AR with a micromolar potency and later was noted to bind to the A_3AR with nearly the same affinity as at the A_{2A}AR.

For several decades, NECA (5′-*N*-ethylcarboxamidoadenosine) **2** was considered to be the most potent known agonist at the A_{2B}AR, with an EC_{50} of 140 nM.[25−27] A survey of structurally diverse adenosine derivatives as agonists of the human A_{2B}AR failed to identify a lead that surpassed the potency of **2**.[28] Cristalli and co-workers have explored the SAR (structure−activity relationship) of 2-substituted 5′-uronamide adenosine derivatives such as (*S*)-PHP-NECA **4** (EC_{50} = 220 nM) as potent but relatively nonselective agonists of the A_{2B}AR.[29−31]

Recent reports provided new insights into the SAR of agonists of the A_{2B}AR. A 3-fold enhancement in potency at the A_{2B}AR was achieved by combining **2** with the N^6-guanidino modification in **3**.[32] This structural change produced a 3-fold gain in potency at the A_3AR, a 300-fold loss of potency at the A_{2A}AR, and no change at the A_1AR. Also, while 2-ether derivatives of adenosine were characterized as potent A_{2A}AR agonists, specific 2-(2-arylethyloxy) ethers were also noted to be particularly potent at the A_{2B}AR.[26] In the present study we characterized the SAR of potent A_{2B}AR agonists based on compound **17**. In particular, 5″ or 6″-functionalization on the indole moiety of **17** led to the achievement of new AR agonists with enhanced potency at the A_{2B}AR and reduced potency at other AR subtypes. Moreover, we have used molecular modeling of the human A_{2B}AR to propose a mode of docking of the potent 2-substituted derivatives.

Results

Chemical Synthesis. The structures of the target adenosine 2-ether derivatives **5**−**40** appear in Chart 1 and Table 1. Compounds **5**−**7** and **9**−**16** were studied previously at the human A_{2B}AR.[26] Routes to the synthetic intermediates for the 2-ether component are shown in Schemes 1 and 2. The novel 2-alkoxyadenosines **8** and **17**−**36**, N^6-guanidino-2-(3-indolyl)-ethyloxy)adenosine derivatives **37** and **38**, N^6-ethyl-2-(3-indolyl)ethyloxy)adenosine **39** and 5′-*N*-ethylcarboxamido-2-(3-indolyl)ethyloxy-adenosines **40** were prepared via alkylation of 2-oxypurine nucleosides using arylalkyl/alkyl iodides as shown in Schemes 3−5.

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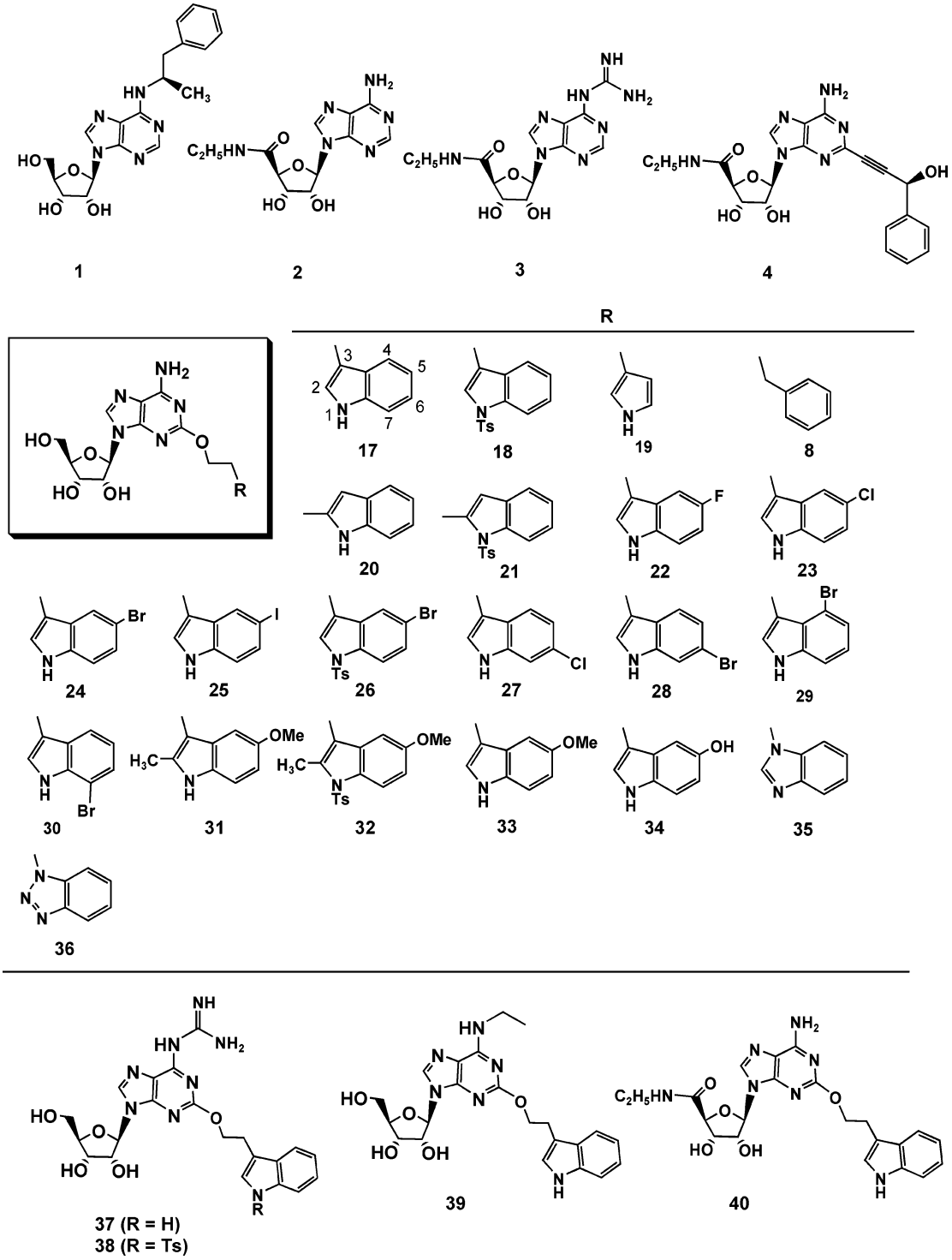
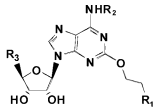
Chart 1. Chemical Structures of Selected Adenosine Derivatives **1**−**4** Previously Used as Pharmacological Reference Compounds for Characterization of the A_{2B}AR and Novel Adenosine Derivatives **8**, and **17**−**40**[a]



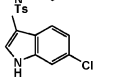
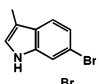
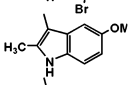
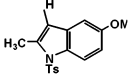
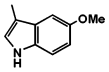
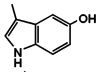
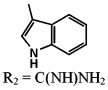
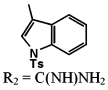
[a] The remaining adenosine derivatives in the series, **5**−**7** and **9**−**16** (structures in Table 1), were reported previously.[26]

The various arylalkyl iodides used in this study, when not commercially available, were synthesized by the routes shown in Schemes 1 and 2. Tryptophol (3-(2-hydroxyethyl)indole) **41**, 5-methoxytryptophol **42**, and 5-hydroxy-tryptophol **43** were converted to the corresponding tosylates **44**−**46**, respectively, followed by iodination with NaI to give the iodides **47**−**49**. Indole-3-acetic acid analogues **50**−**52** having a functional group at the 2- and/or 5-position were transformed to the corresponding esters, which were reduced with lithium aluminum hydride to give the alcohols **53**−**55**. Tosylation of the alcohols **53**−**55** followed by iodination with sodium iodide gave the corresponding iodides **59**−**61**. Furthermore, other 5- or 6-substituted tryptophols **67**−**70** were prepared by refluxing the corresponding phenylhydrazine hydrochloride salts **63**−**66** and 2-ethoxytetrahydrofuran **62** to effect a Fischer indole ring cyclization.[34] Compounds **67**−**70** were converted to the corresponding iodides **74**−**77**, respectively, by using the conventional method mentioned above. Compounds **78** and **79** were transformed to the ethyl glyoxylate derivatives **80** and **81**, which were reduced with lithium aluminum hydride to give the corresponding tryptophol

Table 1. Potency of Various Adenosine Derivatives in Activation of the Human A_{2B}AR Expressed in CHO Cells[a]



5 – 40, R_2= H, R_3 = CH_2OH, unless noted

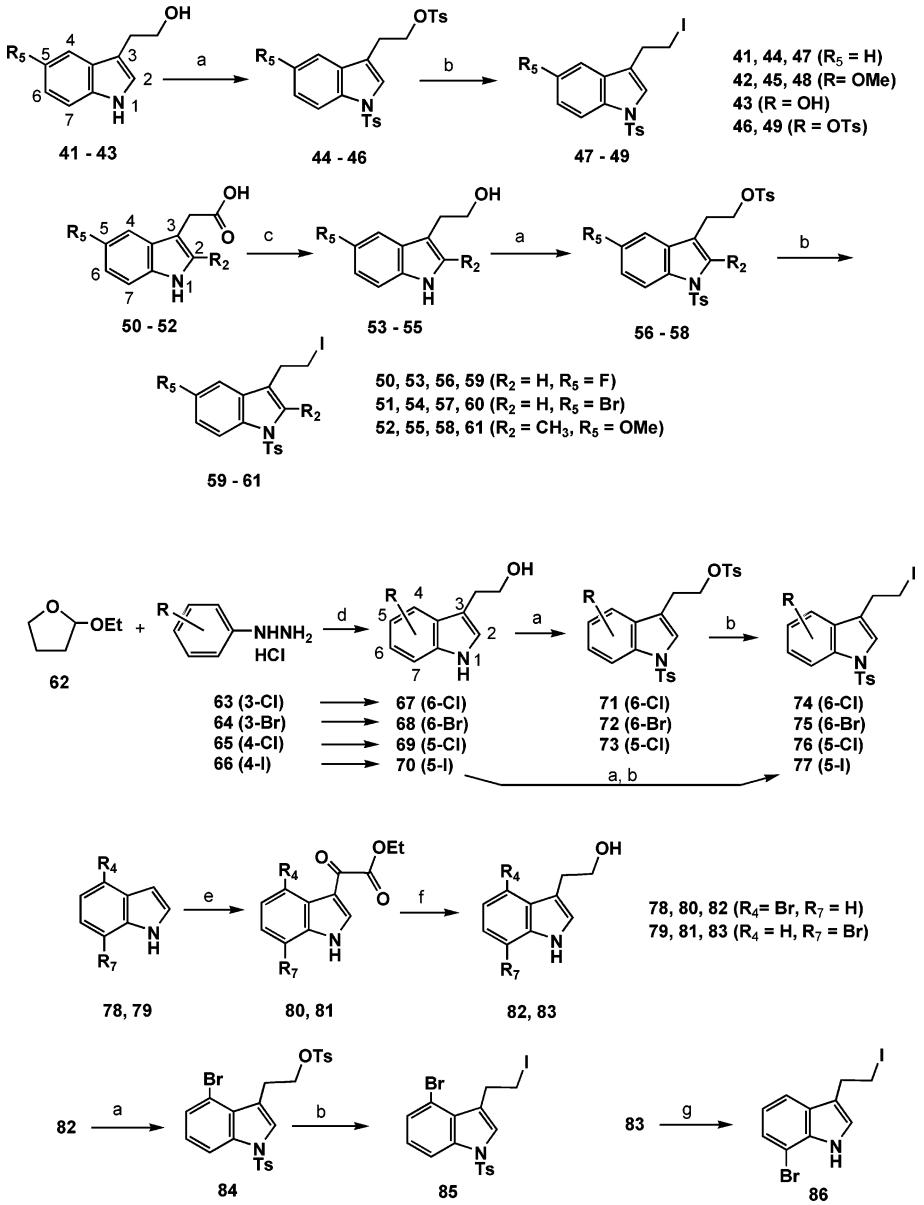
Compound	Name/Substitution	EC_{50} at $A_{2B}AR$ (nM) (or % activation)	K_i at A_1AR (nM) or % inhib.[b]	K_i at $A_{2A}AR$ (nM) or % inhib.[b]	K_i at A_3AR (nM) or % inhib.[b]	Efficacy, A_3AR %
Reference Agonists						
1	R-PIA	1680±500	2.0±0.3	884±188	8.7±0.9	102±6
2	NECA	140±19	6.8±2.4	2.2±0.6	16.0±5.4	100
3[c]	6-guanidino-NECA	54.5±13.3	7.0±1.0	628±39	5.1±1.3	100
4[d]	(*S*)-PHP-NECA	220	2.1	2.0	0.75	
2-Ethers	R_1 =					
5[e]	H	*(-1%)*	2640±540	360±139	568±205	99±4
6[e]		*(36%)*	*(36%)*	579±250	578±182	52±3
7[e]		3490±1490	221±57	9.3±2.9	54.2±14.3	71±3
8		*(29%)*	960±95	500±50	66 ± 3	42±8
9[e]		*(3%)*	2060 ± 630	519 ± 41	352 ± 66	37±8
10[e]		*(13%)*	1560 ± 250	413 ± 37	312 ± 47	18±8
11[e]		*(12%)*	331±22	58.1±24.9	77.8±13.5	45±5
12[e]		*(64%)*	312 ± 24	69.3 ± 4.7	119 ± 8	50±7
13[e]		*(11%)*	467±100	56.8±16.3	112±16	74±5
14[e]		1440±70	141±51	16.1±7.0	130±8	45±9
15[e]		1780±260	174±20	10.9±4.8	93.3±16.8	80±5
16[e]		*(9%)*	280±72	13.3±4.1	101±34	62±15
17[c]		299±45	148±19	45.0±11.6	232±54	17±3
18		*(43%)*	*(39±6%)*	2670±630	1340±230	0±3
19		2580	218±55	95±18	104±40	75±1
20		*(49%)*	197±47	373±71	513±84	37±8
21		*(32%)*	*(47±2%)*	2570±670	622±19	30±1
22		767	150±50	370±80	490±60	-1±1
23		2180	130±40	390±110	296±8	-4±1
24[c]		365±73	358±1	502±32	234±24	1±2
2-Ethers	R_1 =					
25		1870	350±60	900±200	110±20	-5±2
26		*(30%)*	*(38±2%)*	*(54±8%)*	8730±340	-1±5
27		216±59	145±6	29.3±13.7	92.3±7.9	2±5
28[c]		128±32	253±3	150±20	90±15	20±1
29		*(16%)*	443±82	39.7±14.4	260±19	-5±1
30		*(43%)*	210±19	252±109	142±17	-8±5
31		*(48%)*	579±88	*(64±2%)*	599±3	13±4
32		*(24%)*	*(20±2%)*	*(26±4%)*	*(66±5%)*	3±2
33		1250	1820±330	1400±300	360±50	-3±3
34		896	310 ± 90	450±8	120 ± 20	24±3
35		*(0%)*	*(18±4%)*	3870±497	2070 ± 700	3±2
36		*(0%)*	*(41±5%)*	*(46±2%)*	1920 ± 470	13±4
37		*(40%)*	73.6 ± 8.0	277 ± 74	90 ± 10	58±8
38		*(42%)*	*(52±2%)*	344 ± 72	457 ± 40	24±7
39		3270	640±110	40±4%	30±10	54±12
40		989	190±20	250±30	110±20	102±2

[a] Values are expressed either as the EC_{50} (nM) or the percent stimulation at 10 μM (in parentheses). For comparison, binding affinities of the adenosine derivatives at human A_1, A_{2A}, and A_3ARs expressed in CHO cells (expressed as K_i value or percent displacement at 10 μM) and maximal agonist effects at 10 μM at the A_3AR. Values for compounds **5**−**7** and **9**−**16** are from ref 26. [b] All experiments were performed using adherent CHO cells stably transfected with cDNA encoding a human AR. Percent activation of the human A_{2B} or A_3AR was determined at 10 μM. Binding at A_1, A_{2A}, and A_3ARs was carried out as described in Experimental Procedures. The A_3 receptor activation results were from three separate experiments. The K_i and EC_{50} values from the present study are expressed as mean ± s.e.m., $N = 3-5$. [c] Compounds **3**, MRS3218; **17**, MRS3534; **24**, MRS3854; and **28**, MRS3997. [d] Data from refs 29 and 31. [e] Data from ref 26.

derivatives **82** and **83**, respectively. Compounds **82** and **83** were converted to the corresponding iodides **85** and **86** by using conventional methods.

A tosylated 2-tryptophol **88** was prepared by the palladium-mediated heteroannulation of 2-iodoaniline with 3-butyn-1-ol (Scheme 2). The amino group of 2-iodoaniline **87** was activated

Scheme 1[a]



[a] Reagents and conditions: (a) TsCl, NaH, THF, 0 °C−rt; (b) NaI, DMF, 60 °C; (c) (i) TsOH-H_2O, MeOH, 60 °C; (ii) LAH, THF, 4 °C−rt; (d) EtOH, reflux; (e) oxalyl chloride, Et_2O, EtOH; (f) LAH, THF, reflux; (g) I_2, PPh_3, imidazole, benzene.

by the strong electron-withdrawing sulfonyl group, and the indole cyclization occurred in one pot to give the tosylated 2-tryptophol **88**.[35] Compound **88** was converted to the corresponding iodide **89** with iodine, triphenylphosphine, and imidazole.

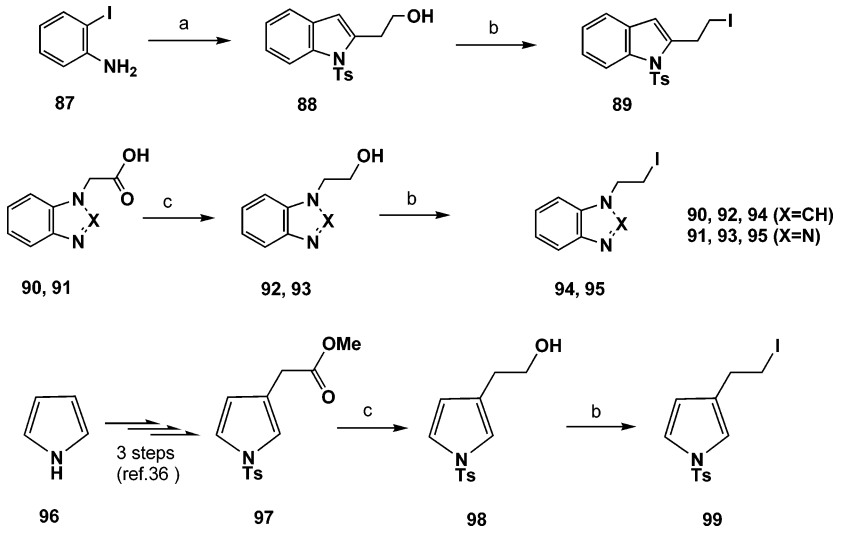
Reduction of benzoimidazol-1-yl-acetic acid **90** and benzotriazol-1-yl-acetic acid **91** with lithium aluminum hydride followed by iodination gave the corresponding iodides **94** and **95**, respectively.

N-Tosyl-3-pyrrolylacetic acid methyl ester **97** was synthesized from pyrrole by the known method[36] involving Friedel−Crafts acylation followed by a Willgerodt−Kindler reaction. Reduction of **97** with lithium aluminum hydride produced the alcohol **98**, which was converted to the corresponding iodide **99** by using iodine, triphenylphosphine, and imidazole.

The synthesis of the 5′-CH_2OH analogues (Scheme 3) started from 2-amino-6-chloro-9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)purine **100**, which was converted to 6-chloro-2-hydroxy-9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)purine **101**, as reported.[33] Reaction of the hydroxyl group at the 2-position of **101** with various iodides **47**−**49**, **59**−**61**, **74**−**77**, **85**, **86**, 1-iodo-3-phenylpropane, **89**, **94**, **95**, and **99**, respectively, was carried out in the presence of cesium carbonate to give compounds **102**−**118**. Simultaneous removal of the acetyl group and amination at the 6-position of **102**−**118** by using saturated ammonia in ethanol solution afforded compounds **18**, **119**−**121**, **26**, **32**, **122**−**126**, **30**, **8**, **21**, **35**, **36**, and **127**, respectively. Deprotection of the *N*-tosyl group of the indole or pyrrole ring of **18**, **119**−**121**, **26**, **32**, **122**−**126**, **21**, and **127** was conducted using potassium hydroxide in methanol to give compounds **17**, **33**, **34**, **22**, **24**, **31**, **27**, **28**, **23**, **25**, **29**, **20**, and **19**, respectively.

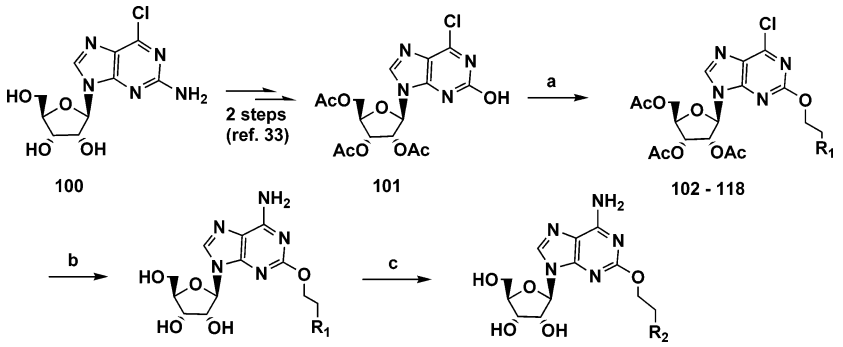
Synthesis of N^6-guanidino derivatives **37** and **38** began with compound **102** (Scheme 4). The guanidinolysis of **102** in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded **37** and the tosylate **38**. Treatment of **102** with ethyl amine and *N*,*N*-diisopropylethylamine in DMF at 140 °C followed by removal of the tosyl group with potassium hydroxide gave the N^6-ethyl derivative **39**.

Scheme 2[a]



[a] Reagents and conditions: (a) (i) TsCl, pyridine, CH_2Cl_2; (ii) 3-butyn-1-ol, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 70 °C; (b) I_2, PPh_3, imidazole, Et_2O−MeCN, rt; (c) LAH, THF, 0 °C−rt.

Scheme 3[a]



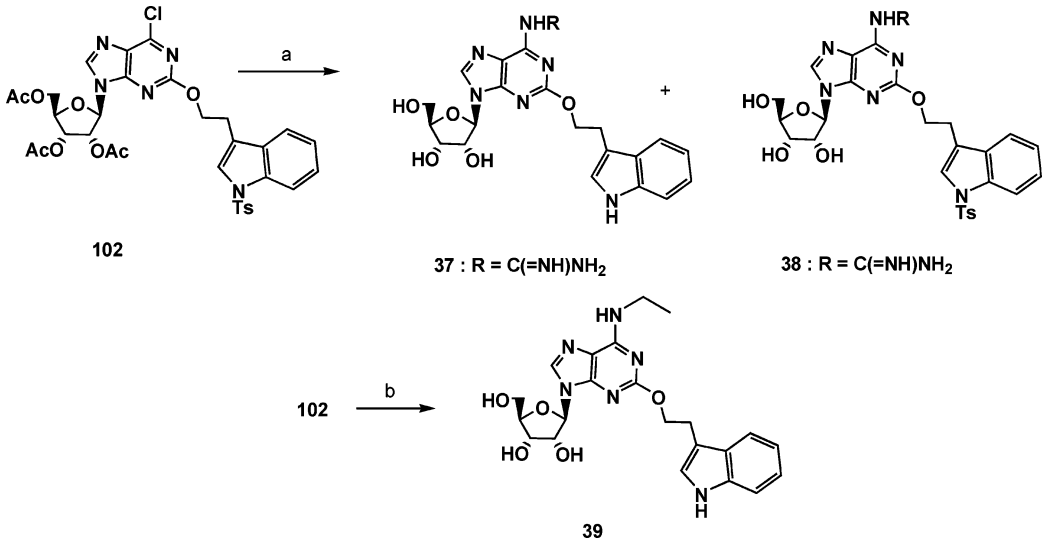
102	18 R_1 = 3"-(N-Ts-Indolyl-)	17 R_2=3"-indolyl-
103	119 R_1 = 3"-(5"-MeO-N-Ts-Indolyl-)	33 R_2 = 3"-(5"-MeO-Indolyl-)
104	120 R_1 = 3"-(5"-TsO-N-Ts-Indolyl-)	34 R_2 = 3"-(5"-OH-Indolyl-)
105	121 R_1 = 3"-(5"-F-N-Ts-Indolyl-)	22 R_2 = 3"-(5"-F-Indolyl-)
106	26 R_1 = 3"-(5"-Br-N-Ts-Indolyl-)	24 R_2 = 3"-(5"-Br-Indolyl-)
107	32 R_1 = 3"-(5"-MeO-2"-Me-N-Ts-Indolyl-)	31 R_2 = 3"-(5"-MeO-2"-Me-Indolyl-)
108	122 R_1 = 3"-(6"-Cl-N-Ts-Indolyl-)	27 R_2 = 3"-(6"-Cl-Indolyl-)
109	123 R_1 = 3"-(6"-Br-N-Ts-Indolyl-)	28 R_2 = 3"-(6"-Br-Indolyl-)
110	124 R_1 = 3"-(5"-Cl-N-Ts-Indolyl-)	23 R_2 = 3"-(5"-Cl-Indolyl-)
111	125 R_1 = 3"-(5"-I-N-Ts-Indolyl-)	25 R_2 = 3"-(5"-I-Indolyl-)
112	126 R_1 = 3"-(4"-Br-N-Ts-Indolyl-)	29 R_2 = 3"-(4"-Br-Indolyl-)
113	30 R_1 = 3"-(7"-Br-Indolyl-)	
114	8 R_1 = $PhCH_2$-)	
115	21 R_1 = 2"-(N-Ts-Indolyl-)	20 R_2 = 2"-Indolyl-
116	35 R_1 = 1"-Imidazolyl-	
117	36 R_1 = 1"-Triazolyl-	
118	127 R_1 = 3"-(N-Ts-Pyrrolyl-)	19 R_2 = 3"-Pyrrolyl-

[a] Reagents and conditions: (a) $R_1CH_2CH_2$−I (**47**−**49**, **59**−**61**, **74**−**77**, **85**, **86**, 1-iodo-3-phenylpropane, **89**, **94**, **95**, and **99**, respectively), Cs_2CO_3, DMF, rt; (b) saturated NH_3 in EtOH, 120 °C; (c) deprotection of tosyl group of **18**, **119**−**121**, **26**, **32**, **122**−**126**, **21**, and **127**; KOH, MeOH 70−90 °C.

Synthesis of the 5′-*N*-ethylcarboxamido derivative **40** began with **100** (Scheme 5). Protection of the 1,2-diol of **100** afforded the acetonide **128**. Oxidation of **128** with potassium permanganate gave the corresponding carboxylic acid derivative **129**, which was converted to the 5′-*N*-ethylcarboxamide derivative **130** using benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP). Diazotization of **130** with *t*-butyl nitrite followed by hydrolysis gave the 2-hydroxy derivative **131** in 47% yield. Coupling of **131** with the iodide **47** in the presence of cesium carbonate in DMF gave the 2-*O*-alkylated derivative **132**, which was followed by displacement of the 6-chloro moiety with ammonia to give **133**. Removal of the 2′,3′-*O*-isopropylidene group of **133** with 80% acetic acid aqueous solution afforded compound **134**. Treatment of **134** with potassium hydroxide in methanol resulted in the desired 5′-*N*-ethyluronamide derivative **40**.

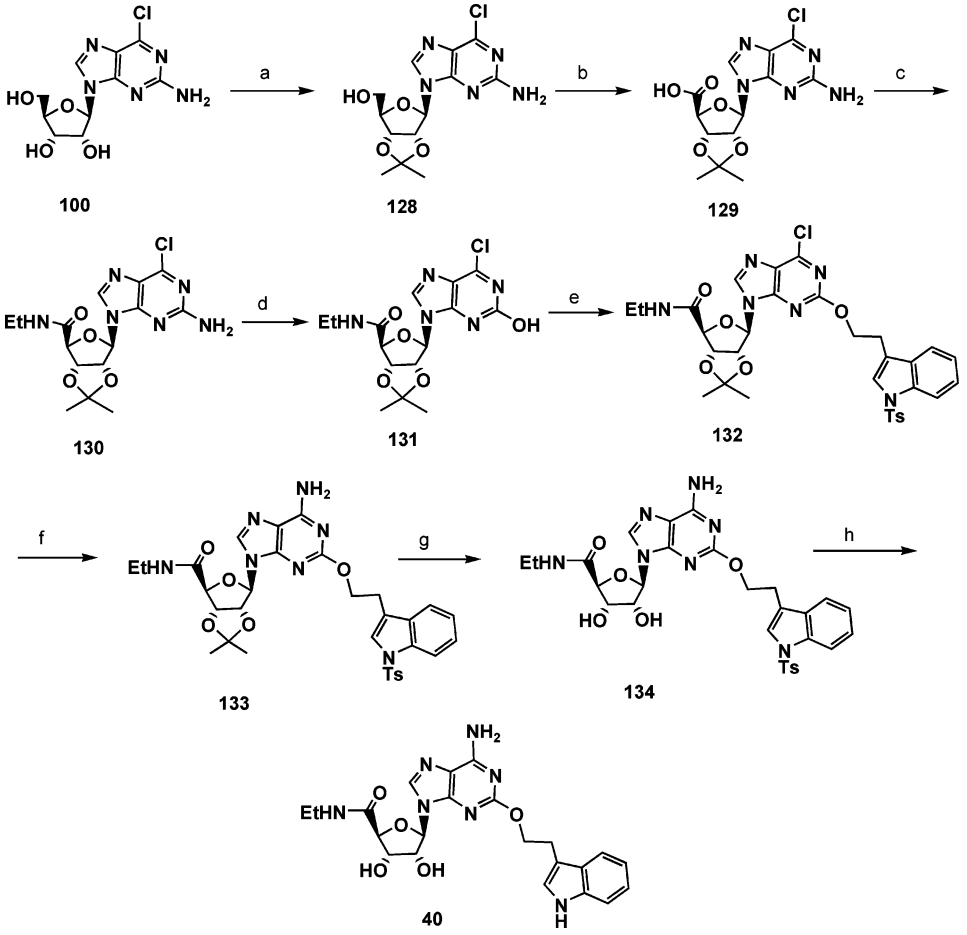
Biological Evaluation. The AR binding affinities of novel compounds **8** and **17**−**40** were investigated in comparison to known (**1**−**4**, **5**−**7**, and **9**−**16**) nucleosides (Table 1). The SAR proceeded from known agonists with high potency at the A_{2B}-AR, that is, **1**−**4**. A previous difficulty has been targeting the A_{2B}AR potency distinctly from the usually more potent activity

Scheme 4[a]



[a] Reagents and conditions: (a) guanidine solution,[32] DABCO, EtOH, 110 °C; (b) (i) $EtNH_2$·HCl, DIPEA, DMF, 140 °C; (ii) KOH, MeOH, 80 °C.

Scheme 5[a]



[a] Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-TsOH-H_2O, DMF; (b) $KMnO_4$, KOH, H_2O; (c) PyBop, DIPEA, $EtNH_2$ HCl, DMF; (d) *t*-butyl nitrite, 2-PrOH/H_2O (1:1); (e) iodide **47**, Cs_2CO_3, DMF, rt; (f) saturated NH_3, EtOH, 120 °C; (g) 80% AcOH, 80 °C; (h) KOH, MeOH, 70 °C.

at the A_{2A}AR. Compound **4** was reported as a potent A_{2B}AR agonist; nevertheless, it remained two orders of magnitude selective for the A_{2A}AR in comparison to the A_{2B}AR.[31] Among 2-substituted derivatives, 2-ethers were more potent than the corresponding amines or thioethers.[26] A 2-phenylethyl ether **7** was only 2-fold less potent than R-PIA **1** at the A_{2B}AR. Nevertheless, the affinity in binding to the A_{2A}AR was nearly 400-fold greater than the A_{2B}AR functional potency. Therefore, great improvement was necessary to approach A_{2B}AR selectivity.

Elongation of the spacer alkyl chain beyond ethyl weakened the affinity against all ARs, as shown in **7**−**9**. Compound **10** is a variation of **8** in which a methyl group is branched in the alkyl chain and its affinity was reduced in comparison to **8**.

The effect of fluoro substitution of the phenyl ring was also probed. The 2-F **11**, 3-F **12**, and 4-F **13** analogues were invariant in affinity at A_1, A_{2A}, and A_3 ARs, with K_i values at these subtypes ranging from 60 to 500 nM. These three analogues were also nearly inactive at the A_{2B}AR.

Three other aromatic moieties in 2-(2-arylethyloxy) ethers **14**−**16** were reported in a previous study.[26] 2-Naphthyl and 2-thienyl moieties were tolerated at the A_{2B}AR, while a 3-thienyl group resulted in inactivity at that subtype. Those modifications produced relatively minor changes at A_1, A_{2A}, and A_3ARs in comparison to the phenyl analogue **7**.

Interestingly, the 3-indolyl analogue **17** (a tryptophol ether) was 12-fold more potent than **7** at the A_{2B}AR and 4−5-fold less potent than **7** in binding to the A_{2A} and A_3ARs. Also, **17** was only 2-fold less potent than **2** at the A_{2B}AR. This considerable enhancement was exploited in subsequent SAR exploration. The corresponding *N*-tosyl derivative **18**, as for similar *N*-tosyl derivatives, was considerably less potent at all ARs.

The 3-pyrrolyl derivative **19** was the simplest analogue in this study, whose pyrrole ring moiety is a critical component of an indole ring. Compound **19** was tolerated at the A_{2B}AR, with a potency close to that of the 2-thienyl derivative **15**, leading to 1.4-fold and 8-fold decreased potency at the A_1 and A_{2A}ARs, respectively, and similar potency at A_3AR.

On the other hand, the corresponding 2-indolyl derivative **20** decreased markedly A_{2B}AR potency compared to **17**. Thus, the 3-position was clearly the favored connection point and was utilized in subsequent synthesis. Its *N*-tosyl derivative **21** was less potent at all ARs, similar to results with **18**.

It is known from SAR studies of A_{2B} agonists that substitution of the 4′-hydroxymethyl group of an adenosine analogue with a 5′-*N*-ethylcarboxamido group often yields compounds endowed with higher affinity than the parent compound.[31,37] Based on these findings, we have prepared the 5′-*N*-ethyluronamido analogue **40** of **17**. Unexpectedly, **40** was 3-fold less potent than the parent 5′-CH_2OH compound **17** at the A_{2B}AR and showed a 2-fold increased potency at only the A_3AR.

Cristalli and colleagues have established that the N^6-ethyl analogue of (*S*)-PHP-adenosine was more potent than the N^6-methyl and N^6-isopropyl derivatives at the A_{2B} subtype.[31] These findings were applied to 3-indolyl analogue **17**, leading to the N^6-ethyl analogue **39**. Compound **39** was somewhat tolerated at A_{2B}AR and 7-fold more potent than the parent compound **17** at the A_3AR.

Another N^6-functionalization for **17** was also investigated at ARs. Recently the N^6-guanidino derivative **3** was reported to display a 3-fold potency enhancement over the parent 5′-*N*-ethyluronamide **2** at the A_{2B}AR.[32] However, introduction of a N^6-guanidino group to **17** led to derivative **37** and its tosyl derivative **38** with decreased A_{2B} potency compared to the parent compounds. Compound **37** showed a 2-fold increased potency at A_1 and A_3 ARs. Thus, the effect of N^6-guanidinylation to enhance A_{2B}AR selectivity is not always compatible with other beneficial structures.

Benzoimidazole and benzotriazole analogues **35** and **36** are simple congeners of **17**, in which the indole ring was substituted with an imidazole or triazole ring, respectively. Compounds **35** and **36** showed low potency at all AR subtypes.

The effect of substitution of the indole ring moiety was tested. A 2″-methyl-5″-methoxy indolyl derivative **31** showed reduced potency compared to **17**, especially at the A_{2B}AR. Its *N*-tosyl derivative **32** lost potency at all ARs. A 5″-methoxy derivative **33** was tolerated at A_{2B}AR, but the affinities against A_1, A_{2A}, and A_3ARs were significantly reduced. 5″-Hydroxy analogue **34** was more potent than the 5″-methoxy analogue **33** at all ARs. Bulkiness of the substituent at the 5″-position might be related to the reduced affinity.

The effect on the 5″-halo-substitution of the indole moiety was also investigated. The corresponding 5″-halo analogues **22**−**25** were well tolerated by the A_{2B}AR. Of these analogues, the 5″-bromo analogue **24** was equipotent to **17** at the A_{2B}AR, but was 11-fold less potent than **17** in binding to the A_{2A}AR. Compound **24** was roughly equipotent at all four ARs, however, its selectivity was improved compared to the parent compound **17**. This series of 5″-halo derivatives showed a tendency toward increased K_i values at A_1 and A_{2A}ARs, depending on the bulkiness of halogen atom.

The importance of bromo-substitution of **26** for A_{2B}AR potency prompted us to design the positional isomers of bromo-substituted indole, leading to the 4″-, 6″-, or 7″-bromo derivatives **28**−**30**. Of these bromo analogues, surprisingly, compound **28** surpassed the A_{2B}AR potency of the 5″-bromo analogue **24**, the parent compound **17**, and even **2**. Also, **28** displayed improved selectivity compared to **17** and **2**. On the other hand, the 5″-chloro analogue **27** showed a decreased potency at A_{2B}AR compared to **28**.

Activation curves were determined for **28** in comparison to **2** at the A_1, A_{2A}, A_{2B}ARs, and A_3AR (Figure 1). Compound **28** was a partial agonist at A_1 and A_3ARs and a full agonist at A_{2A} and A_{2B}ARs.

Molecular Modeling. A recently published rhodopsin-based molecular model of the human A_{2B}AR[38] was adapted to study the binding mode of compound **28** after docking and energy optimization using Monte Carlo multiple minimum (MCMM) calculations.[39] The position of the adenosine moiety of **28** in the A_{2B}AR obtained after MCMM calculations was found to be similar to its initial position. Furthermore, it was observed that the 2-(6-bromoindol-3-yl)-ethyloxy substituent fits the binding site well (Figure 2). In the resulting model, the oxygen atom of this moiety was found in proximity to the side chain amino group of Asn254 (6.55) and seemed to be involved in H-bonding with this residue. The indole ring occupied a pocket formed by several residues located in TM3 and EL2. In particular, the NH-group of the indole ring was found near the OH-group of Ser165 (EL2). Although, a H-bond between the NH-group of the indole ring and Ser165 was not observed in the model, a formation of this bond seems to be possible due to the rotation of the side chain of Ser165.

Discussion

The goal was to prepare novel A_{2B}AR agonists having high potency and selectivity. Although the most potent agonist **28** is not truly selective for the A_{2B}AR, it is effectively a mixed A_{2A}AR/A_{2B}AR agonist, with minimal ability to activate A_1 and A_3ARs.

Initially, we found a novel lead compound **17** in which adenosine is substituted with a 3-indolylethyloxy functional group at the 2-position as an A_{2B}AR agonist having favorable pharmacological properties. The A_{2B}AR potency (299 nM) of compound **17** was similar to that of **2** (140 nM). These promising findings encouraged us to optimize the A_{2B}AR activity and selectivity of **17** by derivatization at the indole 2-position and by modification at the ribose 5′-position or the purine 6-position. Generally, substitution of the 2-position of adenosine is not well tolerated by the A_{2B}AR; however, (*S*)-PHP-Ado and (*S*)-PHP-NECA **4** were known to show higher A_{2B}AR potencies compared to **2**.[31] Distinct from the 2-ethynyl substituent of **4**, exploration of the SAR of a 2-(3-indolylethyloxy) substituent could provide novel insights to molecular recognition at the A_{2B}-

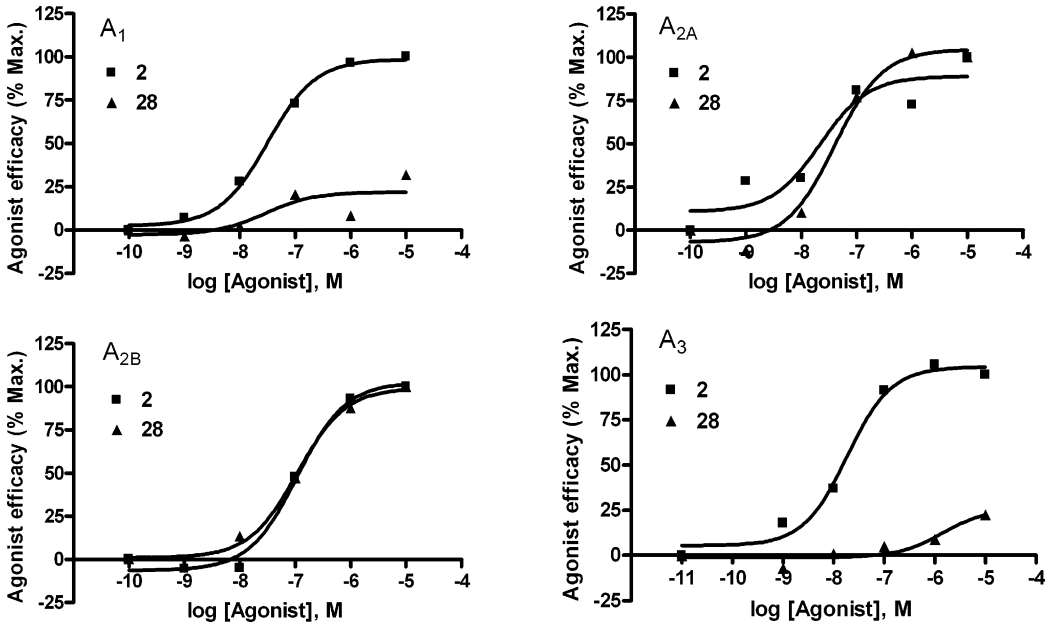


Figure 1. Functional effects of compound **28** on adenylate cyclase in CHO cells stably expressing the human ARs. Compound **28** was a full agonist at the A_{2A} and A_{2B}ARs to stimulate cAMP production. In the curves shown, the EC_{50} values for **2** were 21.9 (A_{2A}) and 110 (A_{2B}) nM, and for **28**, the EC_{50} values of 39.7 (A_{2A}) and 109 (A_{2B}) nM were obtained. The relative maximal efficacy of **28** at the A_1 and A_3ARs to inhibit cAMP production was 31.8% and 20.2 ± 1.0% of the full agonist **2**, respectively.

AR. We can speculate that the lack of an additive effect on A_{2B} potency of combining the 3-(indolyl)ethyloxy- and 5′-*N*-ethyluronamido fragments (i.e., **40** in comparison to **2** and **17**) may be due to an unfavorable change in the conformation or position of the ribose ring inside the ligand binding site.

First, we focused on the simplification, altered connectivity, and mimicking of the indole ring of **17**, as shown in the case of compounds **19**, **8**, **20**, **35**, and **36**. Unfortunately, these approaches failed to maintain the A_{2B}AR potency. Next, we tried to transform the 4′-hydroxymethyl moiety to an ethylcarboxamide, which was expected to favorably increase A_{2B}AR potency. However, the 5′-*N*-ethyluronamide analogue **40** showed only a 2-fold increased potency at the A_3AR compared to **17**. In this respect, **40** has quite different pharmacological characteristics from (S)-PHP-NECA **4**. Also, the 6′ modification of **17**, as shown in the case of compound **37** and **39**, did not improve potency at the A_{2B}AR. Finally, we focused on functionalization of the indole moiety. Even minor modifications were examined because of the lack of a prior pharmacological precedent for the indole ring moiety at this position.

Eventually, through probing a relatively restrictive SAR, we achieved the new A_{2B} agonist **28** that gained an advantage over the parent compounds **17** and **2** for the A_{2B}AR in both potency and selectivity. In addition, compound **28** produced quite a different selectivity from (*S*)-PHP-NECA **4** and 6-guanidino-NECA **3**. Compound **4** showed a high potency/affinity at each AR (Table 1).[31] Compound **3** displayed a selectivity at A_1 and A_3ARs.[32] Compound **28** showed the improved selectivity compared to compounds **2**−**4**, providing a novel type of potent A_{2B}AR agonist. Molecular modeling results with **28** docked in the human A_{2B}AR demonstrated that, in addition to all interactions proposed for adenosine,[38] the 2-(6-bromoindol-3-yl)-ethyloxy fragment can provide additional favorable interactions of the ligand with a distal region of the putative agonist binding site of the receptor.

Experimental Procedures

Chemical Synthesis. Materials and Instrumentation. 2-Amino-6-chloropurine-9-riboside, tryptophol, 1-iodo-3-phenylpropane, 5-bromoindole-3-acetic acid, 5-methoxyindole-3-acetic acid, and other reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO), and 5-fluoroindole-3-acetic acid was purchased from Wako Chemicals U.S.A., Inc. (Richmond, VA). Compound **69** was prepared as reported.[34]

^{1}H NMR spectra were obtained with a Varian Gemini 300 spectrometer using $CDCl_3$ and CD_3OD as solvents. Chemical shifts are expressed in δ values (ppm) with tetramethylsilane (δ 0.00) for $CDCl_3$ and (δ 3.30) for CD_3OD.

The purity of the nucleosides submitted for biological testing was checked using a Hewlett−Packard 1100 HPLC equipped with a Luna 5μ RP-C18(2) analytical column (250 × 4.6 mm; Agilent Technologies, Santa Clara, CA). System A: linear gradient solvent system, CH_3CN/H_2O from 20/80 to 40/60 in 20 min; the flow rate was 1 mL/min. System B: linear gradient solvent system, CH_3CN/H_2O from 20/80 to 60/40 in 20 min; the flow rate was 1 mL/min. System C: linear gradient solvent system, CH_3CN/5 mM TBAP from 20/80 to 60/40 in 20 min; the flow rate was 1 mL/min. System D: linear gradient solvent system, CH_3CN/5 mM TBAP from 5/95 to 80/20 in 20 min; the flow rate was 1 mL/min. Peaks were detected by UV absorption with a diode array detector. All derivatives tested for biological activity showed >98% purity in the HPLC systems.

TLC analysis was carried out on glass precoated with silica gel F_{254} (0.25 mm) from Aldrich. Low-resolution mass spectrometry was performed with a JEOL SX102 spectrometer with 6-kV Xe atoms following desorption from a glycerol matrix or on an Agilent LC/MS 1100 MSD with a Waters (Milford, MA) Atlantis C18 column. High-resolution mass spectroscopic (HRMS) measurements were performed on a proteomics optimized Q-TOF-2 (Micromass-Waters) using external calibration using polyalanine. Observed mass accuracies are those expected based on known performance of the instrument as well as trends in masses of standard compounds observed at intervals during the series of measurements. Reported masses are observed masses uncorrected for this time-dependent drift in mass accuracy.

General Tosylation Procedure for the Synthesis of 3-Iodoethylindole Derivative 44−46, 56−58, 71−73, and 84. To a solution of the alcohol in THF (tetrahydrofuran) was added sodium hydride (60%, 3 equiv) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. To the suspension was added tosyl chloride (3 equiv) at 0 °C, and the reaction mixture was stirred at room

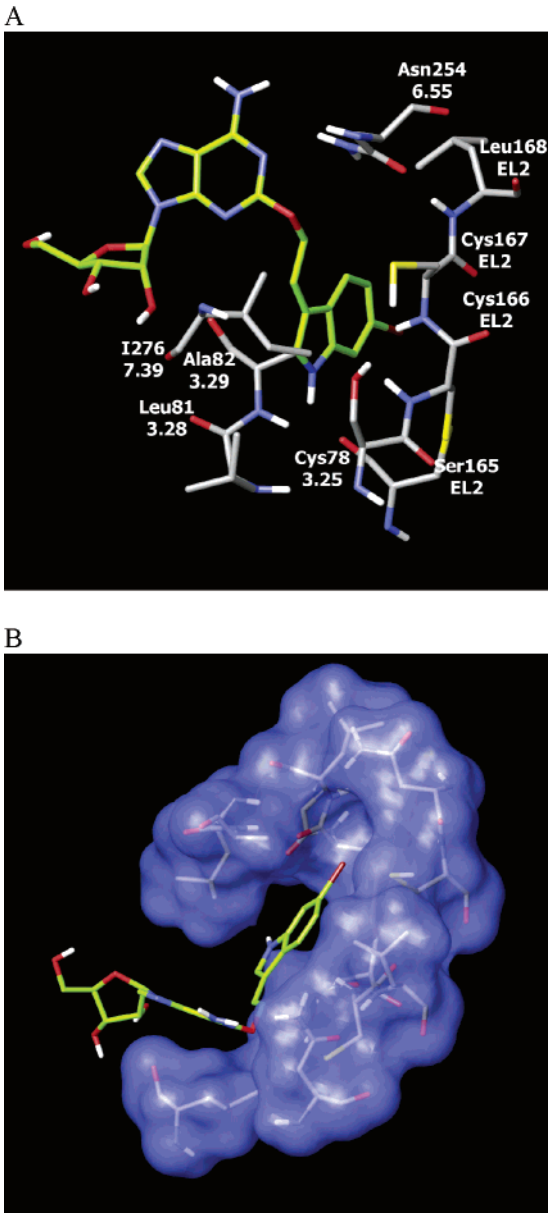


Figure 2. Docking model of compound **28** in the binding site of the human A_{2B}AR, showing residues in proximity (A) and the Van der Waals surface of the receptor (B).

temperature overnight. The reaction mixture was diluted with ethyl acetate and washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a crude oil, which was subjected to column chromatography on silica gel. Elution with a mixture of toluene and acetone (40:1) gave the tosylated derivative.

General Iodination Procedure for the Synthesis of Compounds 47−49, 59−61, 74−77, and 85. A solution of the tosylate and sodium iodide (3.5 equiv) in *N*,*N*-dimethylformamide was stirred overnight at 60 °C. The reaction mixture was diluted with ethyl acetate and washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a crude oil, which was subjected to column chromatography on silica gel. Elution with a mixture of hexanes and ethyl acetate (4:1) gave the iodide.

3-(*p*-Toluenesulfonyloxyethyl)-1-(*p*-toluenesulfonyl)indole (44). The yield was 62%: ^{1}H NMR ($CDCl_3$) δ 7.93 (1H, d with small coupling, J = 8.0 Hz), 7.74 (2H, d, J = 8.2 Hz), 7.56 (2H, d, J = 8.5 Hz), 7.12−7.34 (7H, m), 4.24 (2H, t, J = 6.6 Hz), 3.01 (2H, t, J = 6.6 Hz), 2.38 (3H, s), 2.32 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{24}H_{23}NO_5S_2Na$ $(M+Na)^+$, 492.0915; found, 492.0914.

5-Methoxy-3-(*p*-toluenesulfonyloxyethyl)-1-(*p*-toluenesulfonyl)-indole (45). The yield was 56%: ^{1}H NMR ($CDCl_3$) δ 7.82 (1H, d, J = 9.1 Hz), 7.71 (2H, d with small coupling, J = 8.5 Hz), 7.53 (2H, d with small coupling, J = 8.2 Hz), 7.27 (1H, s), 7.21 (2H, dd, J = 0.6 and 8.8 Hz), 7.15 (2H, dd, J = 0.6 and 8.5 Hz), 6.89 (1H, dd, J = 2.5 and 9.1 Hz), 6.71 (1H, d, J = 2.2 Hz), 4.23 (2H, t, J = 6.6 Hz), 3.77 (3H, s), 2.97 (2H, dt, J = 0.8 and 6.6 Hz), 2.39 (3H, s), 2.32 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{25}H_{26}NO_6S_2$, 500.1202 $(M+H)^+$; found, 500.1207.

1-(*p*-Toluenesulfonyl)-3-(*p*-toluenesulfonyloxyethyl)-5-(*p*-toluenesulfonyloxy)indole (46). The yield was 57%: ^{1}H NMR ($CDCl_3$) δ 7.80 (1H, d, J = 9.1 Hz), 7.71 (2H, d with small coupling, J = 8.5 Hz), 7.82 (2H, d with small coupling, J = 8.5 Hz), 7.58 (2H, d, with small coupling, J = 8.2 Hz), 7.36 (1H, s), 7.31 (2H, dd, J = 0.6 and 8.5 Hz), 7.25 (2H, d, J = 8.4 Hz), 7.19 (2H, d, J = 8.2 Hz), 6.97 (1H, d, J = 2.2 Hz), 6.84 (1H, dd, J = 2.3 and 8.9 Hz), 4.18 (2H, t, J = 6.5 Hz), 2.90 (2H, t, J = 6.5 Hz), 2.46 (3H, s), 2.40 (3H, s), 2.35 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{31}H_{30}NO_8S_3$ $(M+H)^+$, 640.1134; found, 640.1099.

3-Iodoethyl-1-(*p*-toluenesulfonyl)indole (47). The yield was 70%: ^{1}H NMR ($CDCl_3$) δ 7.98 (1H, d with small coupling, J = 8.2 Hz), 7.76 (2H, dt, J = 1.9 and 8.5 Hz), 7.45 (2H, m), 7.32 (1H, ddd, J = 1.3, 7.1, and 8.4 Hz), 7.23 − 7.28 (2H, m), 7.20 (2H, d with small coupling, J = 8.0 Hz), 3.41 (2H, t with small coupling, J = 7.1 Hz), 3.24 (2H, t with small coupling, J = 7.3 Hz), 2.33 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{17}H_{17}NO_2SI$ $(M + H)^+$, 426.0025; found, 426.0016.

3-Iodoethyl-5-methoxy-1-(p-toluenesulfonyl)indole (48). The yield was 74%: ^{1}H NMR ($CDCl_3$) δ 7.74 (1H, d with small coupling, J = 9.1 Hz), 7.73 (2H, d with small coupling, J = 8.2 Hz), 7.40 (1H, s), 7.20 (2H, dd, J = 0.7 and 8.7 Hz), 6.92 (1H, dd, J = 2.5 and 9.2 Hz), 6.85 (1H, d, J = 2.5 Hz), 3.82 (3H, s), 3.40 (2H, dt, J = 0.7 and 7.6 Hz), 3.20 (2H, t, J = 7.3 Hz), 2.33 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{18}H_{19}NO_3SI$ $(M + H)^+$, 456.0130; found, 456.0135.

3-Iodoethyl-1-(*p*-toluenesulfonyl)-5-(*p*-toluenesulfonyloxy)indole (49). The yield was 83%: ^{1}H NMR ($CDCl_3$) δ 7.85 (1H, d, J = 9.1 Hz), 7.73 (2H, d with small coupling, J = 8.5 Hz), 7.68 (2H, d with small coupling, J = 8.2 Hz), 7.47 (1H, s), 7.30 (2H, d, J = 8.3 Hz), 7.23 (2H, d, J = 8.3 Hz), 7.02 (1H, d, J = 2.5 Hz), 6.91 (1H, dd, J = 2.3 and 8.9 Hz), 3.26 (2H, t with small coupling, J = 7.4 Hz), 3.12 (2H, t with small coupling, J = 7.1 Hz), 2.46 (3H, s), 2.36 (3H, s); APCI-MS (*m*/*z*) 596.0 $(M + H)^+$.

General Procedure for the Synthesis of 3-Hydroxyethylindole Derivatives 53−55. Esterification and Reduction: To a solution of a 2- and/or 5-substituted-indole-3-acetic acid in methanol was added *p*-toluenesulfonic acid monohydrate (3 equiv), and the reaction mixture was stirred at 60 °C overnight. After neutralization with 1 N aqueous NaOH, the solvent was evaporated leaving an oily residue, which was dissolved in ethyl acetate. The solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated leaving an oily residue, which was subjected to column flush chromatography on silica gel. Elution with a mixture of toluene and acetone (5:1) gave the corresponding ester.

To a solution of the ester in THF was added lithium aluminum hydride (2.8 equiv) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h. After addition of ethyl acetate, the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate and washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated, leaving an oily residue that was subjected to column chromatography on silica gel. Elution with a mixture of toluene and acetone (3:1) gave the pure alcohol.

5-Fluoro-tryptophol (53). Compound **53** was identical to the known compound reported by Mewshaw et al.[40]

5-Bromo-tryptophol (54). Compound **54** was identical to the commercially available compound.

3-Hydroxyethyl-5-methoxy-2-methylindole (55). The yield was 81%: ^{1}H NMR ($CDCl_3$) δ 7.27 (1H, br s), 7.16 (1H, d, J = 8.8 Hz), 6.97 (1H, d, J = 2.2 Hz), 6.78 (1H, dd, J = 2.5 and 8.5 Hz), 3.78−3.88 (2H, m overlapped with OCH_3), 3.85 (3H, s), 2.94 (2H, t, J = 6.5 Hz), 2.39 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{12}H_{16}NO_2$, 206.1181; found, 206.1190.

5-Fluoro-1-(*p*-toluenesulfonyl)-3-(*p*-toluenesulfonyloxyethyl)-indole (56). The yield was 58%: ^{1}H NMR ($CDCl_3$) δ 7.87 (1H, dd, J = 4.1 and 9.1 Hz), 7.72 (2H, d with small couplings, J = 8.5 Hz), 7.55 (2H, d with small coupling, J = 8.2 Hz), 7.36 (1H, S), 7.24 (2H, d with small coupling, J = 8.0 Hz), 7.16 (2H, dd, J = 0.7 and 8.7 Hz), 7.00 (1H, dt, J = 2.4 and 9.0 Hz), 6.89 (1H, dd, J = 2.2 and 8.5 Hz), 4.22 (2H, t, J = 6.5 Hz), 2.95 (2H, t, J = 6.5 Hz), 2.39 (3H, s), 2.34 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{24}H_{23}NO_5S_2F$ $(M + H)^+$, 488.1002; found, 488.0995.

5-Bromo-3-(*p*-toluenesulfonyloxyethyl)-1-(*p*-toluenesulfonyl)-indole (57). The yield was 63%: ^{1}H NMR ($CDCl_3$) δ 7.80 (1H, d with small coupling, J = 9.6 Hz), 7.73 (2H, d with small coupling, J = 8.2 Hz), 7.52 (2H, d with small coupling, J = 8.5 Hz), 7.32−7.39 (3H, m), 7.25 (2H, d, J = 8.0 Hz), 7.13 (2H, d, J = 8.0 Hz), 4.23 (2H, t, J = 6.3 Hz), 2.95 (2H, dt, J = 0.8 and 6.5 Hz), 2.39 (3H, s), 2.34 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{24}H_{22}NO_5S_2$-BrLi $(M + Li)^+$, 554.0283; found, 554.0292.

5-Methoxy-2-methyl-3-(*p*-toluenesulfonyloxyethyl)-1-(*p*-toluenesulfonyl)indole (58). The yield was 30%: ^{1}H NMR ($CDCl_3$) δ 8.02 (1H, d, J = 9.1 Hz), 7.58 (2H, d with small coupling, J = 8.2 Hz), 7.48 (2H, d with small coupling, J = 8.2 Hz), 7.18 (2H, dd, J = 0.7 and 8.7 Hz), 7.13 (2H, dd, J = 0.6 and 8.5 Hz), 6.84 (1H, dd, J = 2.8 and 9.1 Hz), 6.64 (1H, d, J = 2.5 Hz), 4.11 (2H, t, J = 6.7 Hz), 3.79 (3H, s), 2.90 (2H, t, J = 6.7 Hz), 2.43 (3H, s), 2.39 (3H, s), 2.33 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{26}H_{27}$-NO_6S_2Na $(M + Na)^+$, 536.1178; found, 536.1186.

3-Iodoethyl-5-fluoro-1-(*p*-toluenesulfonyl)indole (59). Yield 70%: ^{1}H NMR ($CDCl_3$) δ 7.92 (1H, ddd, J = 0.6, 4.3 and 9.1 Hz), 7.74 (2H, dt, J = 1.9 and 8.5 Hz), 7.48 (1H, s), 7.22 (2H, d, J = 8.0 Hz), 7.09 (1H, dd, J = 2.5 and 8.5 Hz), 7.04 (1H, dt, J = 2.5 and 9.1 Hz), 3.39 (2H, dt, J = 0.7 and 6.8 Hz), 3.19 (2H, t, J = 7.3 Hz), 2.35 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{17}H_{15}$-NO_2FS $(M - I)^+$, 316.0808; found, 316.0810.

5-Bromo-3-Iodoethyl-1-(*p*-toluenesufonyl)indole (60). The yield was 65%: ^{1}H NMR ($CDCl_3$) δ 7.85 (1H, d, J = 8.8 Hz), 7.74 (2H, d with small coupling, J = 8.2 Hz), 7.57 (1H, d, J = 1.9 Hz), 7.45 (1H, s), 7.41 (1H, dd, J = 1.9 and 8.8 Hz), 7.22 (2H, d, J = 8.2 Hz), 3.88 (2H, t, J = 7.0 Hz), 3.19 (2H, t, J = 7.3 Hz), 2.35 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{17}H_{15}NO_2SBrI$ $(M + H)^+$, 502.9025; found, 502.9036.

3-Iodoethyl-5-methoxy-2-methyl-1-(*p*-toluenesufonyl)indole (61). The yield was 85%: ^{1}H NMR ($CDCl_3$) δ 8.07 (1H, d, J = 9.1 Hz), 7.58 (2H, dt, J = 1.8 and 8.5 Hz), 7.17 (2H, d, J = 8.2 Hz), 6.87 (1H, dd, J = 2.5 and 9.1 Hz), 6.79 (1H, d, J = 2.5 Hz), 3.84 (3H, s), 3.26 (2H, m), 3.14 (2H, m), 2.52 (3H, s), 2.33 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{19}H_{21}NO_3IS$ $(M + H)^+$, 470.0287; found, 470.0294.

General Synthetic Procedure for 3-Hydroxyethylindole Derivatives 67−70 via Fischer Indole Ring Preparation. A solution of substituted phenylhydrazine hydrochloride and ethoxytetrahydrofuran (1.5 equiv) in 95% ethanol was refluxed overnight. The reaction mixture was filtered through celite. The filtrate was evaporated to give a crude solid. The solid was dissolved in ethyl acetate, and the solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a crude oil, which was subjected to column chromatography on silica gel. Elution with a mixture of toluene and acetone (2:1) gave the alcohol.

6-Chloro-tryptophol (67),[41] **6-Bromo-tryptophol (68),**[42] **and 5-Chloro-tryptophol (69).**[34] Compounds **67**−**69** are identical to the known compounds.

5-Iodo-tryptophol (70). The yield was 32%: ^{1}H NMR ($CDCl_3$) δ 8.07 (1H, br s), 7.95 (1H, m), 7.45 (1H, dd, J = 1.7 and 8.5 Hz), 7.16 (1H, d, J = 8.5 Hz), 7.06 (1H, d, J = 2.2 Hz), 3.89 (2H, br s), 2.98 (2H, dt, J = 0.8 and 6.3 Hz), 1.45 (1H, br s); APCI-MS (*m*/*z*) 288.0 $(M + H)^+$.

6-Chloro-3-(*p*-toluenesulfonyloxyethyl)-1-(*p*-toluenesulfonyl)-indole (71). Yield 32%: ^{1}H NMR ($CDCl_3$) δ 7.94 (1H, d, J = 1.7 Hz), 7.74 (2H, d with small coupling, J = 8.5 Hz), 7.51 (2H, d with small coupling, J = 8.2 Hz), 7.29 (2H, d, J = 8.5 Hz), 7.25 (1H, s), 7.19 (1H, d, J = 8.2 Hz), 7.10−7.16 (3H, m), 4.27 (2H, t, J = 6.3 Hz), 2.97 (2H, t, J = 6.3 Hz), 2.40 (3H, s), 2.35 (3H, s); APCI-MS (*m*/*z*) 504.1 $(M + H)^+$.

6-Bromo-3-(*p*-toluenesulfonyloxyethyl)-1-(*p*-toluenesulfonyl)-indole (72). The yield was 30%: ^{1}H NMR ($CDCl_3$) δ 8.10 (1H, d, J = 1.4 Hz), 7.74 (2H, d with small coupling, J = 8.2 Hz), 7.51 (2H, d with small coupling, J = 8.2 Hz), 7.23−7.30 (5H, m), 7.13 (2H, dd, J = 1.7 and 8.2 Hz), 4.23 (2H, t, J = 6.3 Hz), 2.97 (2H, t, J = 6.3 Hz), 2.40 (3H, s), 2.35 (3H, s); APCI-MS (*m*/*z*) found 548.0 $(M + H)^+$.

5-Chloro-3-(*p*-toluenesulfonyloxyethyl)-1-(*p*-toluenesulfonyl)-indole (73). The yield was 30%: ^{1}H NMR ($CDCl_3$) δ 7.85 (1H, dd, J = 0.6 and 8.8 Hz), 7.73 (2H, dt, J = 2.1 and 8.7 Hz), 7.53 (2H, dt, J = 1.8 and 8.5 Hz), 7.36 (1H, s), 7.21−7.26 (3H, m), 7.19 (1H, dd, J = 0.6 and 1.9 Hz), 7.14 (2H, dd, J = 0.5 and 8.5 Hz), 4.23 (2H, t, J = 6.5 Hz), 2.95 (2H, dt, J = 0.8 and 6.5 Hz), 2.39 (3H, s), 2.34 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{24}H_{22}$-NO_5NaS_2Cl $(M + Na)^+$, 526.0526; found, 526.0535.

6-Chloro-3-iodoethyl-1-(*p*-toluenesulfonyl)indole (74). The yield was 67%: ^{1}H NMR ($CDCl_3$) δ 8.00 (1H, d, J = 1.7 Hz), 7.76 (2H, d with small coupling, J = 8.5 Hz), 7.43 (1H, s), 7.36 (1H, d, J = 8.5 Hz), 7.25∼7.28 (2H overlapped with $CHCl_3$), 7.22 (1H, dd, J = 1.8 and 8.4 Hz), 3.39 (2H, t with small coupling, J = 7.3 Hz), 3.21 (2H, t, J with small coupling, J = 7.3 Hz), 2.38 (3H, s); APCI-MS (*m*/*z*) 460.0 $(M + H)^+$.

6-Bromo-3-iodoethyl-1-(*p*-toluenesulfonyl)indole (75). The yield was 67%: ^{1}H NMR ($CDCl_3$) δ 8.16 (1H, d, J = 1.7 Hz), 7.76 (2H, dd, J = 1.9 and 8.5 Hz), 7.42 (1H, br s), 7.36 (1H, dd, J = 1.7 and 8.5 Hz), 7.30 (1H, d, J = 8.2 Hz), 7.25 (2H, d, J = 8.5 Hz), 3.38 (2H, t with small coupling, J = 7.4 Hz), 3.21 (2H, t with small coupling, J = 7.3 Hz), 2.36 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{17}H_{15}BrINO_2S$ $(M)^+$, 502.9052; found, 502.9066.

5-Chloro-3-iodoethyl-1-(*p*-toluenesulfonyl)indole (76). The yield was 60%: ^{1}H NMR ($CDCl_3$) δ 7.90 (1H, dd, J = 0.6 and 8.8 Hz), 7.74 (2H, d with small coupling, J = 8.2 Hz), 7.47 (1H, s), 7.41 (1H, dd, J = 0.6 and 1.9 Hz), 7.24−7.29 (1H overlaped with $CHCl_3$), 7.22 (2H, d, J = 8.3 Hz), 3.39 (2H, dt, J = 0.8 and 7.3 Hz), 3.20 (2H, t, J = 7.3 Hz), 2.35 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{17}H_{16}NO_2ICl$S $(M + H)^+$, 459.9635; found, 459.9625.

5-Iodo-3-iodoethyl-1-(*p*-toluenesulfonyl)indole (77). The yield was 68%: ^{1}H NMR ($CDCl_3$) δ 7.77 (1H, d, J = 1.6 Hz), 7.74 (1H, d, J = 8.8 Hz), 7.73 (2H, d with small coupling, J = 8.5 Hz), 7.58 (1H, dd, J = 1.7 and 8.5 Hz), 7.41 (1H, s), 7.22 (2H, d, J = 8.2 Hz), 3.83 (2H, t, J = 7.2 Hz), 3.19 (2H, t, J = 7.3 Hz), 2.35 (3H, s); APCI-MS (*m*/*z*) 551.9 $(M + H)^+$.

Ethyl 4-Bromo-3-indolylglyoxylate (80). To a solution of **78** (2.94 g, 15.0 mmol) in diethyl ether (60 mL) was added oxalyl chloride (3.01 mL, 34.5 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 10 h. After evaporation, ethanol (30 mL) was added to the solids, and the solution was stirred at room temperarure overnight. The solvent was evaporated to give a solid. This residue was dissolved in ethyl acetate, washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a crude solid, which was subjected to column chromatography on silica gel. Elution with a mixture of hexanes and ethyl acetate (1:1) gave **80** (2.3 g, 52%). ^{1}H NMR ($CDCl_3$) δ 9.55 (1H, br s), 8.24 (1H, d, J = 3.3 Hz), 7.50 (1H, dd, J = 0.8 and 7.7 Hz), 7.42 (1H, dd, J = 0.8 and 8.3 Hz), 7.13 (1H, t, J = 8.0 Hz), 4.41 (2H, q, J = 7.1 Hz), 1.40 (3H, t, J = 7.1 Hz); APCI-MS (*m*/*z*) 296.0 $(M + H)^+$.

Ethyl 7-Bromo-3-indolylglyoxylate (81). Compound **81** was obtained from **79** by the similar procedure for the preparation of **80** (yield 70%). ^{1}H NMR ($CDCl_3$) δ 8.96 (1H, br s), 8.55 (1H, d, J = 3.3 Hz), 8.39 (1H, dd, J = 0.6 and 8.0 Hz), 7.48 (1H, dd, J = 0.8 and 8.0 Hz), 7.23 (1H, t, J = 7.8 Hz), 4.43 (2H, q, J = 7.1 Hz), 1.44 (3H, t, J = 7.1 Hz); APCI-MS (*m*/*z*) 296.0 $(M + H)^+$.

4-Bromo-tryptophol (82). To a solution of **80** (20 mg, 0.0675 mmol) in THF (1.4 mL) was added lithium aluminum hydride (17.4 mg, 0.459 mmol), and the reaction mixture was refluxed for 2 h. The mixture was diluted with ethyl acetate and washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a crude oil, which was subjected to preparative TLC developed

with a mixture of hexanes and ethyl acetate (1:1) to give **82** (10 mg, 63% yield). ^{1}H NMR ($CDCl_3$) δ 8.12 (1H, br s), 7.32 (1H, dd, J = 0.8 and 7.7 Hz), 7.28 (1H, dd, J = 0.8 and 7.7 Hz), 7.14 (1H, d, J = 2.5 Hz), 7.02 (1H, t, J = 7.8 Hz), 3.97 (2H, q, J = 6.1 Hz), 3.29 (2H, dt, J = 0.6 and 6.5 Hz), 1.46 (1H, t, J = 5.6 Hz); HRMS (ESI-MS m/z) calcd for $C_{10}H_{11}BrNO$ $(M + H)^+$, 240.0024; found, 240.0028.

7-Bromo-tryptophol (83). Compound **83** was obtained from **81** by the similar procedure for the preparation of **82** (yield 52%). ^{1}H NMR ($CDCl_3$) δ 8.82 (1H, br s), 7.57 (1H, d, J = 8.0 Hz), 7.36 (1H, d, J = 8.0 Hz), 7.16 (1H, d, J = 2.2 Hz), 7.02 (1H, t, J = 7.8 Hz), 3.91 (2H, q, J = 6.2 Hz), 3.02 (2H, dt, J = 0.5 and 6.3 Hz), 1.46 (1H, t, J = 6.0 Hz); HRMS (ESI-MS m/z) calcd for $C_{10}H_{11}NOBr$ $(M + H)^+$, 240.0024; found, 240.0031.

4-Bromo-3-(*p*-toluenesulfonyloxyethyl)-1-(*p*-toluenesulfonyl)-indole (84). The yield was 41%: ^{1}H NMR ($CDCl_3$) δ 7.91 (1H, dd, J = 0.8 and 8.2 Hz), 7.75 (2H, d with small coupling, J = 8.5 Hz), 7.55 (2H, d with small coupling, J = 8.2 Hz), 7.41 (1H, s), 7.28 (1H, dd, J = 1.0 and 7.8 Hz), 7.25 (2H, d, J = 8.2 Hz), 7.11 (2H, d, J = 8.0 Hz), 7.09 (1H, t, J = 8.0 Hz), 4.32 (2H, t, J = 6.5 Hz), 3.25 (2H, t, J = 6.3 Hz), 2.34 (6H, s); APCI-MS (m/z) 548.0 $(M + H)^+$.

4-Bromo-3-iodoethyl-1-(*p*-toluenesulfonyl)-indole (85). The yield was 67%: ^{1}H NMR ($CDCl_3$) δ 7.96 (1H, dd, J = 0.8 and 8.2 Hz), 7.76 (2H, d with small coupling, J = 8.5 Hz), 7.52 (1H, s), 7.38 (1H, dd, J = 0.8 and 8.0 Hz), 7.23 (2H, dd, J = 0.6 and 8.5 Hz), 7.13 (1H, t, J = 8.1 Hz), 3.45 (4H, s), 2.35 (3H, s); HRMS (ESI-MS m/z) calcd for $C_{17}H_{16}NO_2IBrS$ $(M + H)^+$, 509.9130; found, 509.9114.

7-Bromo-3-iodoethylindole (86). The yield was 88%: ^{1}H NMR ($CDCl_3$) δ 8.21 (1H, br s), 7.52 (1H, dd, J = 0.8 and 8.0 Hz), 7.36 (1H, d, J = 7.7 Hz), 7.16 (1H, d, J = 2.2 Hz), 7.02 (1H, t, J = 7.7 Hz), 3.39−3.46 (2H, m), 3.29−3.37 (2H, m); HRMS (ESI-MS m/z) calcd for $C_{10}H_{10}NBrI$ $(M + H)^+$, 349.9041; found, 349.9036.

2-Hydroxyethyl-1-(*p*-toluenesulfonyl)-indole (88). To a solution of 2-iodoaniline (1.0616 g, 4.84 mmol) in dichloromethane (20 mL) were added pyridine (1.17 mL, 14.5 mmol) and tosyl chloride (1.10 g, 5.81 mmol), and the reaction mixture was stirred overnight. The mixture was diluted with chloroform, washed with water, dried over $MgSO_4$ and filtered. The filtrate was evaporated to give crude solids which were subjected to column chromatography on silica gel. Elution with a mixture of hexane and ethyl acetate (5:1) gave *N*-tosyl-2-iodoaniline (1.40 g, 77%). To a solution of *N*-tosyl-2-iodoanilide (1.172 g, 3.14 mmol) in DMF were added 3-butyn-1-ol (1.42 mL, 18.8 mmol), copper iodide (119 mg, 0.628 mmol), triethyl amine (13.56 mL, 97.3 mmol), and $Pd(PPh_3)_2Cl_2$ (220.3 mg, 0.314 mmol), and the reaction mixture was stirred at 70 °C overnight. The reaction mixture was diluted with ethyl acetate. The solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give an oil, which was subjected to column chromatography on silica gel. Elution with a mixture of hexanes and ethyl acetate (1:1) gave **88** (820 mg, 83%). ^{1}H NMR ($CDCl_3$) δ 8.16 (1H, d, J = 8.2 Hz), 7.61 (2H, d with small coupling, J = 8.2 Hz), 7.42 (1H, dd, J = 1.7 and 7.4 Hz), 7.28 (1H, dt, J = 2.2 and 7.6 Hz), 7.23 (1H overlapped with Ph), 7.18 (2H, d, J = 8.5 Hz), 6.50 (1H, s), 4.01 (2H, t, J = 6.1 Hz), 3.29 (2H, t, J = 6.2 Hz), 2.33 (3H, s); APCI-MS (m/z) 316.0 $(M + H)^+$.

2-Iodoethyl-1-(*p*-toluenesulfonyl)-indole (89). To a solution of **88** (638 mg, 2.02 mmol) in a mixture of diethylether (24 mL) and acetnitrile (8 mL) were added triphenylphosphine (1.589 g, 6.06 mmol), imidazole (439 mg, 6.46 mmol), and iodine (1.639 g, 6.46 mmol), and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with ethyl acetate. The solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give an oil, which was subjected to column chromatography on silica gel. Elution with a mixture of hexanes and ethyl acetate (4:1) gave **89** (847 mg, 98%). ^{1}H NMR ($CDCl_3$) δ 8.14 (1H, d with small coupling, J = 8.2 Hz), 7.60 (2H, dt, J = 2.0 and 8.6 Hz), 7.45 (1H, dd, J = 1.0 and 6.7 Hz), 7.30 (1H, dt, J = 1.5 and 8.0 Hz), 7.23 (1H, dd, J = 1.2 and 7.6 Hz), 7.18 (2H, d with small coupling, J = 8.0 Hz), 6.50 (1H, s), 3.46−3.60 (4H, m), 2.33 (3H, s); HRMS (ESI-MS m/z) calcd for $C_{17}H_{17}NO_2IS$ $(M + H)^+$, 426.0025; found, 426.0035.

Benzoimidazol-1-yl-ethanol (92). To a solution of benzoimidazol-1-yl-acetic acid (893 mg, 5.06 mmol) in THF (20 mL) was added lithium aluminum hydride (672 mg, 17.7 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 5 h. After dilution with ethyl acetate, the solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a crude oil, which was subjected to column chromatography on silica gel. Elution was with a mixture of chloroform and methanol (8:1) to give **92** (620 mg, 76%). ^{1}H NMR ($CDCl_3$) δ 7.63 (1H, s), 7.38 (1H, dt, J = 1.0 and 8.2 Hz), 7.31 (1H, dt, J = 1.0 and 8.0 Hz), 7.17 (1H, ddd, J = 1.0, 7.1, and 8.1 Hz), 7.06 (1H, ddd, J = 1.1, 7.1, and 8.1 Hz), 4.22 (2H, t, J = 4.9 Hz), 3.99 (2H, t, J = 4.8 Hz); HRMS (ESI-MS m/z) calcd for $C_9H_{11}N_2O$ $(M + H)^+$, 163.0871; found, 163.0880.

Benzotriazol-1-yl-ethanol (93). The procedure used for the preparation of **93** from **91** was similar to those used for the preparation of **92** from **90**; amorphous solid, the yield was 59%. ^{1}H NMR ($CDCl_3$) δ (1H, d with small coupling, J = 8.5 Hz), 7.61 (1H, d with small coupling, J = 8.2 Hz), 7.50 (1H, ddd, J = 1.1, 7.0 and 8.1 Hz), 7.36 (1H, ddd, J = 1.2, 6.9 and 8.1 Hz), 4.75 (2H, t, J = 5.1 Hz), 4.25 (2H, dd, J = 5.9 and 10.3 Hz), 2.55 (1H, t, J = 6.0 Hz); HRMS (ESI-MS m/z) calcd for $C_8H_{10}N_3O$ $(M + H)^+$, 164.0824; found, 164.0812.

Benzoimidazol-1-yl-ethyliodide (94). To a solution of **92** (22 mg, 0.134 mmol) in a mixture of acetonitrile (0.3 mL) and diethylether (0.9 mL) were added triphenylphosphine (105 mg, 0.402 mmol), imidazole (29 mg, 0.428 mmol), and iodine (108 mg, 0.428 mmol) at 0 °C, and the reaction mixture was stirred for 2 h. The mixture was diluted with ethyl acetate, washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a crude oil, which was subjected to preparative TLC developed with a mixture of toluene and acetone (2:1) to give **94** (32.3 mg, 88%). ^{1}H NMR ($CDCl_3$) δ 7.97 (1H, s), 7.80−7.87 (1H, m), 7.28−7.42 (3H, m), 4.58 (2H, t, J = 7.0 Hz), 3.51 (2H, t, J = 7.1 Hz); APCI-MS (m/z) 273.0 $(M + H)^+$.

Benzotriazol-1-yl-ethyliodide (95). The procedure used for the preparation of **95** from **93** was similar to those used for the preparation of **94** from **92**; amorphous solid, the yield was 88%. ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, dt, J = 1.0 and 8.3 Hz), 7.50 − 7.60 (2H, m), 7.40 (1H, ddd, J = 1.8, 6.3, and 8.1 Hz), 5.02 (2H, t, J = 7.3 Hz), 3.67 (2H, t, J = 7.3 Hz); HRMS (ESI- MS m/z) calcd for $C_8H_9N_3I$ $(M + H)^+$, 273.9841; found, 273.9833.

3-Hydroxyethyl-1-(*p*-toluenesulfonyl)pyrrole (98). To a solution of **97** (1.24 g, 4.21 mmol) in THF (20 mL) was added lithium aluminum hydride (340 mg, 6.32 mmol) at 0 °C. The reaction mixture was stirred for 2 h. After addition of ethyl acetate, the mixture was stirred for 30 min. The mixture was diluted with ethyl acetate, washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a crude oil, which was subjected to column chromatography on silica gel. Elution with a mixture of chloroform and methanol (20:1) gave **98** (692 mg, 62%). ^{1}H NMR δ 7.74 (2H, d, J = 8.4 Hz), 7.28 (2H, d, J = 8.7 Hz), 7.10 (1H, t, J = 2.7 Hz), 6.99 (1H, m), 6.19 (1H, dd, J = 1.5 and 3.3 Hz), 3.74 (2H, t, J = 6.5 Hz), 2.64 (2H, t, J = 6.5 Hz), 2.40 (3H, s); HRMS (ESI-MS m/z) calcd for $C_{13}H_{16}NO_3S$ $(M + H)^+$, 266.0851; found, 266.0837.

3-Iodoethyl-1-(*p*-toluenesulfonyl)pyrrole (99). The procedure used for the preparation of **99** from **98** is similar to those used for the preparation of **89** from **88**; the yield was 62%. ^{1}H NMR ($CDCl_3$) δ 7.73 (2H, d, J = 8.2 Hz), 7.29 (2H, d, J = 8.5 Hz), 7.08 (1H, t, J = 2.8 Hz), 6.99 (1H, m), 6.16 (1H, dd, J = 1.6 and 3.3 Hz), 3.24 (2H, t, J = 7.3 Hz), 2.96 (2H, t, J = 7.6 Hz), 2.40 (3H, s); HRMS (ESI-MS m/z) calcd for $C_{13}H_{15}NO_2SI$ $(M + H)^+$, 375.9868; found, 375.9857.

General Synthetic Procedure for 2-Substituted Adenosine Derivatives. To a solution of 6-chloro-2-hydroxy-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl) purine in *N*,*N*-dimethylformamide were added iodide (1.8 equiv) and Cs_2CO_3 (2.7 equiv) at room temperature, and the reaction mixture was stirred overnight. After dilution

with ethyl acetate, the solution was washed with water twice, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a crude oil that was purified by column chromatography or preparative TLC on silica gel. Elution or developing with a mixture of toluene and acetone (4:1) gave the 2-substituted 2′,3′,5′-triacetyl-6-chloroadenosine derivative.

A solution of 2-substituted 2′,3′,5′-triacetyl-6-chloroadenosine derivative in saturated ammonia ethanol solution was stirred in sealed tube overnight at 110−120 °C. The solvent was evaporated to give an oil, which was subjected to preparative TLC developed with a mixture of chloroform and methanol (8:1) to give the 2-substituted adenosine derivative.

In case of deprotection of the tosyl group of the 2-substituent, the tosylated adenosine derivative was treated with KOH (20 equiv) in methanol overnight at 70 °C in a sealed tube. The reaction mixture was concentrated to a small amount of solution, which was subjected to preparative TLC developed with a mixture of chloroform and methanol (5:1) to give the final product.

6-Chloro-2-(3″-(1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)-3′,4′,5′-triacetyladenosine (102). The yield was 86%: ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, s), 7.98 (1H, d with small coupling, J = 6.6 Hz), 7.76 (2H, d with small coupling, J = 8.2 Hz), 7.61 (1H, d with small coupling, J = 7.1 Hz), 7.53 (1H, s), 7.14 − 7.36 (4H, m), 6.13 (1H, d, J = 4.7 Hz), 5.93 (1H, t, J = 5.1 Hz), 5.65 (1H, t, J = 5.5 Hz), 4.71 (2H, m), 4.39 − 4.49 (2H, m), 4.32 (1H, dd, J = 4.7 and 12.6 Hz), 3.24 (2H, t, J = 7.0 Hz), 2.32 (3H, s), 2.14 (3H, s), 2.09 (3H, s), 2.05 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{33}H_{32}N_5O_{10}$-ClSNa $(M + Na)^+$, 748.1456; found, 748.1455.

6-Chloro-2-(3″-(5″-methoxy-1″-(*p*-toluenesulfonyl)indolyl)-ethyloxy)-3′,4′,5″-triacetyladenosine (103). The yield was 72%: ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, s), 7.86 (1H, dd, J = 9.1 Hz), 7.73 (2H, d, J = 8.5 Hz), 7.48 (1H, s), 7.20 (2H, d, J = 8.2 Hz), 7.03 (1H, d, J = 2.5 Hz), 6.92 (1H, dd, J = 2.3 and 8.9 Hz), 6.12 (1H, d, J = 4.7 Hz), 5.93 (1H, t, J = 5.1 Hz), 5.66 (1H, t, J = 5.6 Hz), 4.69 (2H, ddd, J = 3.8, 7.4, and 14.3 Hz), 4.40 − 4.49 (2H, m), 4.31 (1H, dd, J = 4.4 and 12.6 Hz), 3.85 (3H, s), 3.19 (2H, t, J = 6.7 Hz), 2.32 (3H, s), 2.14 (3H, s), 2.09 (3H, s), 2.05 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{34}H_{35}N_5O_{11}SCl$ $(M + H)^+$, 756.1742; found, 756.1735.

6-Chloro-2-(3″-(5″-(*p*-toluenesulfonyloxy)-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)-3′,4′,5′-triacetyladenosine (104). The yield was 51%: ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, s), 7.83 (1H, d, J = 8.5 Hz), 7.72 (2H, d with small coupling, J = 8.5 Hz), 7.68 (2H, d with small coupling, J = 8.2 Hz), 7.57 (1H, s), 7.25−7.31 (3H, m), 7.22 (2H, d, J = 8.0 Hz), 6.83 (1H, dd, J = 2.3 and 8.9 Hz), 6.12 (1H, d, J = 4.4 Hz), 5.94 (1H, dd, J = 4.7 and 5.5 Hz), 5.67 (1H, t, J = 5.4 Hz), 4.64 (2H, m), 4.40−4.50 (2H, m), 4.31 (1H, dd, J = 5.1 and 12.8 Hz), 3.13 (2H, t, J = 6.7 Hz), 2.42 (3H, s), 2.34 (3H, s), 2.15 (3H, s), 2.08 (3H, s), 2.03 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{40}H_{39}ClN_5O_{13}S_2$ $(M + H)^+$, 896.1674; found, 896.1638.

6-Chloro-2-(3″-(5″-fluoro-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)-3′,4′,5′-triacetyladenosine (105). The yield was 59%: ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, s), 7.91 (1H, dd, J = 4.4 and 9.1 Hz), 7.74 (2H, d with small coupling, J = 8.5 Hz), 7.57 (1H, s), 7.25−7.31 (1H overlapped with $CHCl_3$), 7.22 (2H, d, J = 8.0 Hz), 7.04 (1H, dt, J = 2.6 and 9.0 Hz), 6.11 (1H, d, J = 4.7 Hz), 5.94 (1H, t, J = 4.9 Hz), 5.67 (1H, t, J = 5.5 Hz), 4.69 (2H, m), 4.40−4.50 (2H, m), 4.31 (1H, dd, J = 4.9 and 12.9 Hz), 3.18 (2H, t, J = 6.9 Hz), 2.33 (3H, s), 2.15 (3H, s), 2.09 (3H, s), 2.04 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{32}H_{23}N5O_{10}SFCl$ $(M + H)^+$, 744.1542; found, 744.1522.

2-(3″-(5″-Bromo-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)-6-chloro-3′,4′,5′-triacetyladenosine (106). The yield was 47%: ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, s), 7.84 (1H, d, J = 8.8 Hz), 7.75 (1H, s), 7.73 (2H, d with small coupling, J = 6.6 Hz), 7.54 (1H, s), 7.40 (1H, dd, J = 1.8 and 8.9 Hz), 7.22 (2H, d, J = 8.5 Hz), 6.13 (1H, d, J = 4.7 Hz), 5.94 (1H, t, J = 4.9 Hz), 5.67 (1H, t, J = 5.4 Hz), 4.69 (2H, t, J = 6.6 Hz), 4.40−4.50 (2H, m), 4.31 (1H, dd, J = 5.2 Hz), 3.19 (2H, t, J = 6.7 Hz), 2.33 (3H, s), 2.15 (3H, s), 2.09 (3H, s), 2.03 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{33}H_{32}N_5O_{10}SClBr$ $(M + H)^+$, 804.0742; found, 804.0752.

6-Chloro-2-(3″-(5″-methoxy-2″-methyl-1″-(*p*-toluenesulfonyl)-indolyl)ethyloxy)-3′,4′,5′-triacetyladenosine (107). The yield was 72%: ^{1}H NMR ($CDCl_3$) δ 8.08 (1H, s), 8.07 (1H, d, J = 9.6 Hz), 7.60 (2H, d with small coupling, J = 8.5 Hz), 7.17 (2H, d, J = 8.0 Hz), 6.98 (1H, d, J = 2.5 Hz), 6.87 (1H, dd, J = 2.8 and 9.1 Hz), 6.12 (1H, d, J = 5.0 Hz), 5.83 (1H, t, J = 5.2 Hz), 4.36 − 4.54 (5H, m), 4.31 (1H, dd, J = 4.1 and 12.4 Hz), 3.86 (3H, s), 3.13 (2H, t, J = 7.8 Hz), 2.61 (3H, s), 2.32 (3H, s), 2.13 (3H, s), 2.06 (3H, s), 2.05 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{35}H_{37}N_5O_{11}$-SCl $(M + H)^+$, 770.1899; found, 770.1895.

6-Chloro-2-(3″-(6″-chloro-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)-3′,4′,5′-triacetyladenosine (108). The yield was 70%: ^{1}H NMR ($CDCl_3$) d 8.09 (1H, s), 7.99 (1H, d, J = 1.9 Hz), 7.76 (2H, d with small coupling, J = 8.5 Hz), 7.53 (1H, d, J = 8.5 Hz), 7.52 (1H, s), 7.20−7.28 (3H, m), 6.11 (1H, d, J = 4.7 Hz), 5.95 (1H, t, J = 4.9 Hz), 5.66 (1H, t, J = 5.5 Hz), 4.68 (2H, m), 4.38−4.50 (2H, m), 4.31 (1H, dd, J = 4.5 and 12.2 Hz), 3.20 (2H, t, J = 6.9 Hz), 2.35 (3H, s), 2.14 (3H, s), 2.09 (3H, s), 2.06 (3H, s); APCI-MS (*m*/*z*) 760.1 $(M + H)^+$.

2-(3″-(6″-Bromo-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)-6-chloro-3′,4′,5′-triacetyladenosine (109). The yield was 45%: ^{1}H NMR ($CDCl_3$) δ 8.15 (1H, d, J = 1.6 Hz), 8.09 (1H, s), 7.76 (2H, d with small coupling, J = 8.2 Hz), 7.50 (1H, s), 7.49 (1H, d, J = 9.1 Hz), 7.38 (1H, dd, J = 1.7 and 8.5 Hz), 7.25 (2H, d, J = 8.2 Hz), 6.11 (1H, d, J = 4.7 Hz), 5.95 (1H, t, J = 4.9 Hz), 5.66 (1H, t, J = 5.5 Hz), 4.68 (2H, m), 4.18−4.50 (2H, m), 4.31 (1H, dd, J = 4.5 and 12.5 Hz), 3.20 (2H, t, J = 7.0 Hz), 2.35 (3H, s), 2.14 (3H, s), 2.09 (3H, s), 2.06 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{33}H_{32}N_5O_{10}SCl$ Br $(M + H)^+$, 804.0742; found, 804.0760.

6-Chloro-2-(3″-(5″-chloro-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)-3′,4′,5′-triacetyladenosine (110). The yield was 46%: ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, s), 7.89 (1H, d, J = 9.1 Hz), 7.73 (2H, d with small coupling, J = 8.2 Hz), 7.59 (1H, d, J = 2.2 Hz), 7.24−7.30 (2H, m), 7.22 (2H, d, J = 8.0 Hz), 6.12 (1H, d, J = 4.4 Hz), 5.94 (1H, t, J = 5.1 Hz), 5.67 (1H, t, J = 5.4 Hz), 4.69 (2H, m), 4.40−4.49 (2H, m), 4.31 (1H, dd, J = 4.9 and 13.2 Hz), 3.18 (2H, t, J = 6.7 Hz), 2.33 (3H, s), 2.15 (3H, s), 2.09 (3H, s), 2.04 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{33}H_{31}N_5O_{10}SCl_2Na$ $(M + Na)^+$, 782.1066; found, 782.1071.

6-Chloro-2-(3″-(5″-iodo-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)-3′,4′,5′-triacetyladenosine (111). The yield was 45%: ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, s), 7.93 (1H, d, J = 1.7 Hz), 7.73 (3H, m), 7.57 (1H, dd, J = 1.8 and 8.7 Hz), 7.50 (1H, s), 7.22 (2H, d, J = 8.0 Hz), 6.13 (1H, d, J = 4.7 Hz), 5.94 (1H, t, J = 5.1 Hz), 5.67 (1H, t, J = 5.4 Hz), 4.68 (2H, t, J = 7.0 Hz), 4.40−4.48 (2H, m), 4.31 (1H, dd, J = 5.1 and 13.3 Hz), 3.18 (2H, t, J = 6.9 Hz), 2.33 (3H, s), 2.15 (3H, s), 2.09 (3H, s), 2.04 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{33}H_{32}N_5O_{10}SClI$ $(M + H)^+$, 852.0603; found, 852.0566.

6-Chloro-2-(3″-(4″-bromo-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)-3′,4′,5′-triacetyladenosine (112). The yield was 40%: ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, s), 7.95 (1H, dd, J = 0.8 and 8.2 Hz), 7.75 (2H, d with small coupling, J = 8.5 Hz), 7.59 (1H, s), 7.39 (1H, dd, J = 0.8 and 8.0 Hz), 7.23 (2H, d, J = 8.5 Hz), 7.12 (1H, t, J = 8.1 Hz), 6.13 (1H, d, J = 5.0 Hz), 5.92 (1H, t, J = 5.1 Hz), 5.64 (1H, t, J = 5.4 Hz), 4.75 (2H, m), 4.38−4.50 (2H, m), 4.33 (1H, dd, J = 4.7 and 12.9 Hz), 3.53 (2H, t, J = 7.0 Hz), 2.34 (3H, s), 2.13 (3H, s), 2.09 (3H, s), 2.05 (3H, s); APCI-MS (*m*/*z*) 806.1 $(M + H)^+$.

6-Chloro-2-(3″-(7″-bromoindolyl)ethyloxy)-3′,4′,5′-triacetyladenosine (113). The yield was 10%: ^{1}H NMR ($CDCl_3$) δ 8.06 (1H, s), 7.66 (1H, d, J = 8.0 Hz), 7.35 (1H, d, J = 7.7 Hz), 7.27 (1H overlapped with $CHCl_3$), 7.03 (1H, t, J = 7.7 Hz), 6.11 (1H, d, J = 5.0 Hz), 5.91 (1H, t, J = 5.2 Hz), 5.64 (1H, t, J = 5.2 Hz), 4.70 (2H, m), 4.37−4.46 (2H, m), 4.32 (1H, dd, J = 5.4 and 13.1 Hz), 3.30 (2H, t, J = 7.1 Hz), 2.13 (3H, s), 2.07 (3H, s), 2.07 (3H, s); APCI-MS (*m*/*z*) 672.1 $(M + Na)^+$.

6-Chloro-2-phenypropoxy-3′,4′,5′-triacetyladenosine (114). The yield was 63%: ^{1}H NMR ($CDCl_3$) δ 8.08 (1H, s), 7.16−7.34 (5H,

m), 6.14 (1H, d, J = 4.9 Hz), 5.91 (1H, t, J = 5.4 Hz), 5.63 (1H, t, J = 5.2 Hz), 4.38−4.52 (5H, m), 4.31 (1H, dd, J = 3.8 and 11.8 Hz), 2.85 (2H, dd, J = 7.4 and 8.0 Hz), 2.12−2.24 (2H, m), 2.15 (3H, s), 2.10 (3H, s), 2.09 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{25}H_{27}N_4O_8ClLi$ $(M + Li)^+$, 553.1677; found, 553.1661.

6-Chloro-2-(2″-(1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)-3′,4′,5′-triacetyladenosine (115). The yield was 40%: ^{1}H NMR ($CDCl_3$) δ 8.16 (1H, d, J = 8.2 Hz), 8.09 (1H, s), 7.63 (2H, d, J = 8.5 Hz), 7.42 (2H, d, J = 7.1 Hz), 7.15−7.32 (3H, m), 6.59 (1H, s), 6.16 (1H, d, J = 5.0 Hz), 5.87 (1H, t, J = 5.2 Hz), 5.61 (1H, t, J = 5.2 Hz), 4.83 (2H, m), 4.40−4.48 (2H, m), 4.34 (1H, dd, J = 4.9 and 13.2 Hz), 3.58 (2H, t, J = 6.6 Hz), 2.33 (3H, s), 2.12 (3H, s), 2.08 (3H,s), 2.07 (3H,s); HRMS (ESI-MS *m*/*z*) calcd for $C_{33}H_{33}N_5O_{10}ClS$ $(M + H)^+$, 726.1637; found, 726.1640.

6-Chloro-2-(3″-(benzoimidazol-1″-yl)ethyloxy)-3′,4′,5′-triacetyladenosine (116). The yield was 51%: ^{1}H NMR (CD_3OD) δ 8.09 (2H, d, J = 8.0 Hz), 7.79 (1H, dd, J = 1.4 and 7.1 Hz), 7.55 (1H, dd, J = 1.1 and 7.1 Hz), 7.34 (1H, dt, J = 1.4 and 7.4 Hz), 7.28 (1H, dt, J = 1.4 and 7.5 Hz), 6.05 (1H, d, J = 4.7 Hz), 5.92 (1H, t, J = 4.9 Hz), 5.67 (1H, t, J = 5.4 Hz), 4.82 (2H, m), 4.66 (2H, t, J = 5.4 Hz), 4.39−4.48 (2H, m), 4.27 (1H, dd, J = 5.2 and 13.2 Hz), 2.16 (3H, s), 2.09 (3H, s), 2.02 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{25}H_{26}N_6O_8Cl$ $(M + H)^+$, 573.1501; found, 573.1503.

6-Chloro-2-(3″-(benzotriazol-1″-yl)ethyloxy)-3′,4′,5′-triacetyladenosine (117). The yield was 53%: ^{1}H NMR ($CDCl_3$) δ 8.08 (1H, s), 8.03 (1H, dt, J = 0.8 and 8.5 Hz), 7.72 (1H, dt, J = 0.8 and 8.5 Hz), 7.52 (1H, ddd, J = 1.0, 7.1 and 8.1 Hz), 7.36 (1H, ddd, J = 1.1, 7.1 and 8.2 Hz), 6.07 (1H, d, J = 4.4 Hz), 5.89 (1H, dd, J = 4.7 and 5.5 Hz), 5.62 (1H, t, J = 5.4 Hz), 5.11 (2H, m), 5.00 (2H, m), 4.40−4.48 (2H, m), 4.26−4.34 (1H, m), 2.15, 2.10 and 2.05 (each 3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{24}H_{25}N_7O_8Cl$ $(M + H)^+$, 574.1453; found, 574.1456.

6-Chloro-2-(3″-(1″-*p*-toluenesulfonyl)pyrrolyl)ethyloxy)-3′,4′,5′-triacetyladenosine (118). The yield was 61%: ^{1}H NMR ($CDCl_3$) δ 8.08 (1H, s), 7.73 (1H, d, J = 8.5 Hz), 7.27 (2H, d overlapped with $CHCl_3$), 7.08 (2H, m), 6.28 (1H, dd, J = 1.9 and 3.0 Hz), 6.13 (1H, d, J = 5.0 Hz), 5.91 (1H, t, J = 5.1 Hz), 5.63 (1H, t, J = 5.4 Hz), 4.57 (1H, dd, J = 2.8 and 7.4 Hz), 4.53 (1H, dd, J = 3.0 and 7.7 Hz), 4.38−4.45 (2H, m), 4.32 (1H, dd, J = 4.3 and 12.2 Hz), 2.95 (2H, t, J = 7.0 Hz), 2.40 (3H, s), 2.15 (3H, s), 2.09 (3H, s), 2.07 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{29}H_{31}N_5O_{10}SCl$ $(M + H)^+$, 676.1480; found, 676.1450.

2-(3″-(5″-Methoxy-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)-adenosine (119). The yield was 56%: ^{1}H NMR (CD_3OD) δ 8.14 (1H, s), 7.81 (1H, d, J = 9.3 Hz), 7.67 (2H, dt, J = 1.9 and 8.5 Hz), 7.52 (1H, s), 7.15 (2H, dd, J = 0.6 and 8.5 Hz), 7.02 (1H, d, J = 2.5 Hz), 6.89 (1H, dd, J = 2.8 and 8.8 Hz), 5.89 (1H, d, J = 6.0 Hz), 4.72 (1H, t, J = 5.6 Hz), 4.55 (2H, dt, J = 1.1 and 6.3 Hz), 4.33 (1H, dd, J = 3.3 and 5.0 Hz), 4.12 (1H, q, J = 3.0 Hz), 3.88 (1H, dd, J = 2.7 and 12.4 Hz), 3.78 (3H, s), 3.74 (1H, dd, J = 3.2 and 12.5 Hz), 3.11 (2H, t, J = 6.3 Hz), 2.25 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{28}H_{31}N_6O_8S$ $(M + H)^+$, 611.1924; found, 611.1899.

2-(3″-(5″-(*p*-Toluenesulfonyloxy)-1″-(*p*-toluenesulfonyl)indolyl)-ethyloxy)adenosine (120). The yield was 63%: ^{1}H NMR (CD_3OD) δ 8.15 (1H, s), 7.86 (1H, d, J = 8.8 Hz), 7.71 (2H, d with small coupling, J = 8.5 Hz), 7.64 (1H, s), 7.60 (2H, d with small coupling, J = 8.2 Hz), 7.28 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.0 Hz), 7.08 (1H, d, J = 2.5 Hz), 6.93 (1H, dd, J = 2.2 and 9.1 Hz), 5.90 (1H, d, J = 6.1 Hz), 4.71 (1H, t, J = 5.6 Hz), 4.42 (2H, t, J = 6.6 Hz), 4.33 (2H, t, J = 6.6 Hz), 4.33 (1H, dd, J = 3.2 and 5.1 Hz), 4.14 (1H, q, J = 3.0 Hz), 3.90 (1H, dd, J = 2.8 and 12.6 Hz), 3.74 (1H, dd, J = 3.2 and 12.5 Hz), 3.00 (2H, t, J = 6.6 Hz), 2.34 (3H, s), 2.29 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{34}H_{35}N_6O_{10}S_2$ $(M + H)^+$, 751.1856; found, 751.1819.

2-(3″-(5″-Fluoro-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)adenosine (121). The yield was 55%: ^{1}H NMR (CD_3OD) δ 8.13 (1H, s), 7.91 (1H, dd, J = 4.4 and 9.1 Hz), 7.70 (2H, d with small coupling, J = 8.5 Hz), 7.64 (1H, s), 7.29 (1H, dd, J = 2.5 and 8.8 Hz), 7.16 (2H, d, J = 8.0 Hz), 7.05 (1H, dt, J = 2.5 and 9.1 Hz), 5.89 (1H, d, J = 6.0 Hz), 4.73 (1H, t, J = 5.5 Hz), 4.54 (2H, t, J = 6.2 Hz), 4.33 (1H, dd, J = 3.3 and 5.2 Hz), 4.12 (1H, q, J = 3.0 Hz), 3.89 (1H, dd, J = 2.7 and 12.4 Hz), 3.74 (1H, dd, J = 3.2 and 12.5 Hz), 3.10 (2H, t, J = 6.3 Hz), 2.26 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{27}H_{28}N_6O_7SF$ $(M + H)^+$, 599.1724; found, 599.1714.

2-(3″-(6″-Chloro-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)adenosine (122). The yield was 51%: ^{1}H NMR (CD_3OD) δ 8.13 (1H, s), 7.92 (1H, d, J = 1.7 Hz), 7.72 (2H, d with small coupling, J = 8.2 Hz), 7.61 (1H, s), 7.58 (1H, d, J = 8.5 Hz), 7.25 (1H, dd, J = 1.9 and 8.5 Hz), 7.21 (2H, dd, J = 0.7 and 8.7 Hz), 5.89 (1H, d, J = 6.1 Hz), 4.72 (1H, t, J = 5.5 Hz), 4.55 (2H, m), 4.33 (1H, dd, J = 3.3 and 5.2 Hz), 4.12 (1H, q, J = 2.9 Hz), 3.88 (1H, dd, J = 2.8 and 12.4 Hz), 3.74 (1H, dd, J = 3.3 and 12.4 Hz), 3.12 (2H, t, J = 6.5 Hz), 2.28 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{27}H_{28}N_6O_7SCl$ $(M + H)^+$, 615.1429; found, 615.1413.

2-(3″-(6″-Bromo-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)adenosine (123). The yield was 50%: ^{1}H NMR (CD_3OD) δ 8.13 (1H, s), 8.08 (1H, d, J = 1.7 Hz), 7.71 (2H, dt, J = 2.1 and 8.5 Hz), 7.60 (1H, s), 7.53 (1H, d, J = 8.2 Hz), 7.38 (1H, dd, J = 1.7 and 8.2 Hz), 7.21 (2H, d with small coupling, J = 8.2 Hz), 5.89 (1H, d, J = 6.1 Hz), 4.72 (1H, t, J = 5.5 Hz), 4.54 (2H, m), 4.33 (1H, dd, J = 3.3 and 5.2 Hz), 4.12 (1H, q, J = 3.0 Hz), 3.88 (1H, dd, J = 2.7 and 12.4 Hz), 3.74 (1H, dd, J = 3.3 and 12.4 Hz), 3.12 (2H, t, J = 6.5 Hz), 2.28 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{27}H_{28}N_6O_7BrS$ $(M + H)^+$, 659.0924; found, 659.0910.

2-(3″-(5″-Chloro-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)adenosine (124). The yield was 62%: ^{1}H NMR (CD_3OD) δ 8.13 (1H, s), 7.90 (1H, d, J = 8.8), 7.71 (2H, d with small coupling, J = 8.8 Hz), 7.64 (1H, s), 7.57 (1H, d, J = 1.9 Hz), 7.27 (1H, dd, J = 1.9 and 8.8 Hz), 7.18 (2H, d, J = 8.2 Hz), 5.89 (1H, d, J = 5.8 Hz), 4.73 (1H, t, J = 5.6 Hz), 4.55 (2H, t, J = 6.5 Hz), 4.33 (1H, dd, J = 3.3 and 5.2 Hz), 4.12 (1H, q, J = 3.1 Hz), 3.89 (1H, dd, J = 2.7 and 12.6 Hz), 3.74 (1H, dd, J = 3.2 and 12.5 Hz), 3.11 (2H, t, J = 6.3 Hz), 2.27 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{27}H_{28}N_6O_7SCl$ $(M + H)^+$, 615.1429; found, 615.1401.

2-(3″-(5″-Iodo-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)adenosine (125). The yield was 71%: ^{1}H NMR (CD_3OD) δ 8.14 (1H, s), 7.89 (1H, d, J = 1.7 Hz), 7.73 (1H, d, J = 9.1 Hz), 7.71 (2H, d with small coupling, J = 8.5 Hz), 7.58 (1H, s), 7.57 (1H, dd, J = 1.8 and 8.7 Hz), 7.18 (2H, d, J = 8.2 Hz), 5.89 (1H, d, J = 5.8 Hz), 4.73 (1H, t, J = 5.5 Hz), 4.54 (2H, t, J = 6.3 Hz), 4.34 (1H, dd, J = 3.3 and 5.2 Hz), 4.12 (1H, q, J = 3.0 Hz), 3.89 (1H, dd, J = 2.9 and 12.5 Hz), 3.75 (1H, dd, J = 3.3 and 12.4 Hz), 3.10 (2H, t, J = 6.3 Hz), 2.27 (3H, s); APCI-MS (*m*/*z*) 707.0 $(M + H)^+$.

2-(3″-(4″-Bromo-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)adenosine (126). The yield was 43%: ^{1}H NMR (CD_3OD) δ 8.13 (1H, s), 7.95 (1H, dd, J = 0.7 and 8.4 Hz), 7.73 (2H, d with small coupling, J = 8.5 Hz), 7.69 (1H, s), 7.39 (1H, dd, J = 0.8 and 7.7 Hz), 7.19 (2H, dd, J = 0.6 and 8.5 Hz), 7.15 (1H, t, J = 8.1 Hz), 5.89 (1H, d, J = 6.1 Hz), 4.74 (1H, t, J = 5.5 Hz), 4.61 (2H, m), 4.33 (1H, dd, J = 3.3 and 5.2 Hz), 4.12 (1H, q, J = 3.1 Hz), 3.89 (1H, dd, J = 2.8 and 12.4 Hz), 3.75 (1H, dd, J = 3.3 and 12.4 Hz), 3.44 (2H, m), 2.27 (3H, s); APCI-MS (*m*/*z*) 659.1 $(M + H)^+$.

2-(3″-(1″-(*p*-Toluenesulfonyl)pyrrolyl)ethyloxy)-adenosine (127). The yield was 69%: ^{1}H NMR (CD_3OD) δ 8.12 (1H, s), 7.72 (2H, d with small coupling, J = 8.5 H), 7.29 (2H, d, J = 8.5 Hz), 7.08−7.14 (2H, m), 6.30 (1H, dd, J = 1.7 and 3.2 Hz), 5.88 (1H, d, J = 6.0 Hz), 4.71 (1H, t, J = 5.5 Hz), 4.41 (2H, t, J = 6.7 Hz), 4.32 (1H, dd, J = 3.4 and 5.1 Hz), 4.11 (1H, q, J = 3.2 Hz), 3.86 (1H, dd, J = 2.6 and 12.5 Hz), 3.73 (1H, dd, J = 3.3 and 12.7 Hz), 2.85 (2H, t, J = 6.5 Hz), 2.36 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{23}H_{27}N_6O_7S$ $(M + H)^+$, 531.1662; found, 531.1667.

(2*R*,3*S*,4*S*,5*R*)-2-(2′-Amino-6′-chloropurin-9′-yl)-5-hydroxymethyl-3, 4-*O*-isopropylidene-tetrahydrofuran (128). To a solution of 2-amino-6-chloropurine-9-riboside (100 mg, 0.331 mmol) in *N*,*N*-dimethylformamide (2 mL) were added 2,2-dimethoxypropane (0.242 mL, 1.97 mmol) and *p*-toluenesulfonic acid monohydrate (188 mg, 0.993 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction was diluted with ethyl acetate, washed with water, dried over $MgSO_4$, and filtered. The

filtrate was evaporated to give an oil, which was subjected to preparative TLC developed with a mixture of toluene and acetone (1:1) to give **128** (56 mg, 50%). ^{1}H NMR ($CDCl_3$) δ 7.81 (1H, s), 5.79 (1H, d, J = 4.9 Hz), 5.68 (1H, dd, J = 1.4 and 11.3 Hz), 5.14−5.24 (3H, m), 5.08 (1H, dd, J = 1.4 and 6.0 Hz), 4.51 (1H, d, J = 1.7 Hz), 3.97 (1H, d with small coupling, J = 12.6 Hz), 3.78 (1H, ddd, J = 1.9, 11.3 and 13.2 Hz), 1.64 (3H, s), 1.38 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{13}H_{17}N_5O_4Cl$ $(M + H)^+$, 342.0969; found, 342.0979.

(2*R*,3*S*,4*S*,5*R*)-2-(2′-Amino-6′-chloropurin-9′-yl)-5-carboxy-3,4-*O*-isopropylidene-tetrahydrofuran (129). To a solution of **128** (16.9 mg, 0.0494 mmol) in water (4.5 mL) were added potassium permanganate (70.3 mg, 0.445 mmol) and potassium hydroxide (25 mg, 0.444 mmol), and the reaction mixture was stirred for 1 h. After addition of isopropanol, the reaction mixture was filtered. The filtrate was neutralized with 0.1 N hydrochloric acid aqueous solution and evaporated to give a crude solid, which was subjected to preparative TLC developed with a mixture of chloroform, methanol, and saturated aqueous ammonia (2: 1: 0.3) to give **129** (9 mg, 51%). ^{1}H NMR (CD_3OD) δ 8.29 (1H, s), 6.18 (1H, d, J = 1.2 Hz), 5.52 (1H, dd, J = 1.7 and 6.2 Hz), 5.37 (1H, d, J = 6.0 Hz), 4.59 (1H, d, J = 1.7 Hz), 1.55 (3H, s), 1.39 (3H, S); HRMS (ESI-MS *m*/*z*) calcd for $C_{13}H_{13}N_5O_5Cl$ $(M - H)^-$, 354.0605; found, 354.0622.

(2*R*,3*S*,4*S*,5*R*)-2-(2′-Amino-6′-chloropurin-9′-yl)-5-ethylcarboxyamide-3,4-*O*-isopropylidene-tetrahydrofuran (130). To a solution of **129** (11.9 mg, 0.0334 mmol) in *N*,*N*-dimethylformamide (0.8 mL) were added ethylamine hydrochloride (8.1 mg, 0.100 mmol), *N*,*N*-diisopropylethylamine (0.035 mL, 0.200 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (22.5 mg, 0.0434 mmol), and the reaction mixture was stirred overnight. The mixture was diluted with ethyl acetate, washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a crude oil, which was subjected to preparative TLC developed with a mixture of chloroform and methanol (10:1) to give **130** (10 mg, 78%). ^{1}H NMR (CD_3OD) δ 8.16 (1H, s), 6.27 (1H, s), 5.73 (1H, dd, J = 1.9 and 6.3 Hz), 5.43 (1H, d, J = 6.3 Hz), 4.62 (1H, d, J = 1.7 Hz), 2.91 (1H, dt, J = 6.0 and 13.3 Hz), 2.80 (1H, dt, J = 6.0 and 13.3 Hz), 1.55 (3H, s), 1.40 (3H,s), 0.61 (3H, t, J = 7.3 Hz); HRMS (ESI- MS *m*/*z*) calcd for $C_{15}H_{20}N_6O_4Cl$ $(M + H)^+$, 383.1235; found, 383.1229.

(2*R*,3*S*,4*S*,5*R*)-5-Ethylcarboxyamide-2-(2′-hydroxy-6′-chloropurin-9′-yl)-3,4-*O*-isopropylidene-tetrahydrofuran (131). To a solution of **130** (10 mg, 0.026 mmol) in a mixture of 2-propanol (0.4 mL) and water (0.4 mL) was added *t*-butylnitrite (13.3 μL, 0.115 mmol) at 4 °C, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a crude oil, which was subjected to preparative TLC developed with a mixture of chloroform and methanol (10:1) to give **131** (5 mg, 50%). ^{1}H NMR ($CDCl_3$) δ 7.99 (1H, s), 6.37 (1H, br t, J = 6.1 Hz), 6.11 (1H, d, J = 1.6 Hz), 5.72 (1H, dd, J = 1.7 and 6.1 Hz), 5.36 (1H, dd, J = 1.7 and 6.0 Hz), 4.75 (1H, s), 3.05 (2H, m), 1.61 (3H, s), 1.41 (3H, s), 0.77 (3H, t, J = 7.3 Hz); APCI-MS (*m*/*z*) 384.1 $(M + H)^+$.

(2*R*,3*S*,4*S*,5*R*)-5-Ethylcarboxyamide-2-2′-(3″-(1″-(*p*-toluenesufonyl)indolyl)ethyloxy)-6′-chloropurin-9′-yl)-3, 4-*O*-isopropylidene-tetrahydrofuran (132). To a solution of **131** (19.4 mg, 0.0505 mmol) in *N*,*N*-dimethylformamide (0.8 mL) was added iodide **47** (43 mg, 0.101 mmol) and cesium carbonate (49.3 mg, 0.151 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a crude oil, which was subjected to preparative TLC developed with a mixture of toluene and acetone (4:1) to give **132** (24 mg, 70%). ^{1}H NMR ($CDCl_3$) δ 7.99 (1H, s), 7.98 (1H, d, J = 8.2 Hz), 7.77 (2H, d with small coupling, J = 8.5 Hz), 7.61 (1H, d with small coupling, J = 7.7 Hz), 7.56 (1H, s), 7.24−7.35 (2H, m), 7.21 (2H, d, J = 8.5 Hz), 6.27 (1H, t, J = 6.0 Hz), 6.14 (1H, d, J = 2.2 Hz), 5.52 (1H, dd, J = 1.9 and 6.1 Hz), 5.39 (1H, dd, J = 2.1 and 6.2 Hz), 4.60−4.80 (3H, m), 3.27 (2H, t, J = 6.7 Hz), 2.97 (2H, m), 2.32 (3H, s), 1.61 (3H, s), 1.35 (3H, s), 0.69 (3H, t, J = 7.3 Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{32}H_{33}N_6O_7SClNa$ $(M + Na)^+$, 703.1718; found, 703.1732.

(2*R*,3*S*,4*S*,5*R*)-5-Ethylcarboxyamide-2-(6′-amino-2′-(3″-(1″-(*p*-toluenesufonyl)indolyl)ethyloxy)-purin-9′-yl)-3,4-*O*-isopropylidene-tetrahydrofuran (133). A solution of **132** in saturated ammonia ethanol solution was stirred at 120 °C overnight. The solvent was evaporated to give an oil, which was subjected to preparative TLC developed with a mixture of chloroform and methanol (10:1) to give **133** (17 mg, 88% yield). ^{1}H NMR ($CDCl_3$) δ 7.96 (1H, d, J = 7.7 Hz), 7.77 (2H, d, J = 8.2 Hz), 7.68 (1H, s), 7.54−7.60 (2H, m), 7.30 (1H, dt, J = 1.6 and 7.7 Hz), 7.24 (1H, overlapped with $CHCl_3$), 7.19 (2H, d, J = 8.5 Hz), 6.44 (1H, t, J = 5.9 Hz), 6.07 (1H, d, J = 1.9 Hz), 5.59 (1H, br s), 5.51 (1H, dd, J = 1.9 and 6.0 Hz), 5.43 (1H, dd, J = 1.8 and 6.2 Hz), 4.70 (1H, d, J = 1.9 Hz), 4.61 (2H, m), 3.18 (2H, t, J = 6.7 Hz), 2.96 (2H, m), 2.31 (3H, s), 1.64 (3H, s), 1.31 (3H, s), 0.69 (3H, t, J = 7.3 Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{32}H_{36}N_7O_7S$ $(M + H)^+$, 662.2397; found, 662.2374.

(2*R*,3*S*,4*S*,5*R*)-5-Ethylcarboxyamide-2-(6′-amino-2′-(3″-(1″-(*p*-toluenesufonyl)indolyl)ethyloxy)-purin-9′-yl)-tetrahydrofuran (134). A solution of **133** (13.4 mg, 0.0202 mmol) in 80% acetic acid aqueous solution was stirred at 80 °C for 63 h and evaporated to give an oil, which was subjected to preparative TLC developed with a mixture of chloroform and methanol (8:1) to give **134** (9 mg, recovery yield 85%). ^{1}H NMR (CD_3OD) δ 8.09 (1H, s), 7.94 (1H, d, J = 7.7 Hz), 7.69 (2H, d with small coupling, J = 8.5 Hz), 7.56 (1H, d with small coupling, J = 7.7 Hz), 7.52 (1H, s), 7.30 (1H, dt, J = 1.3 and 7.7 Hz), 7.16−7.26 (3H, m), 5.93 (1H, d, J = 7.4 Hz), 4.54−4.76 (2H, m), 4.42 (1H, d, J = 1.9 Hz), 4.31 (1H, dd, J = 1.8 and 4.8 Hz), 3.00−3.18 (4H, m), 2.28 (3H, s), 0.83 (3H, t, J = 7.1 Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{29}H_{32}N_7O_7S$ $(M + H)^+$, 622.2084; found, 622.2095.

2-Phenylpropoxyadenosine (8). The yield was 66%: ^{1}H NMR (CD_3OD) δ 8.11 (1H, s), 7.10−7.28 (5H, m), 5.88 (1H, d, J = 6.1 Hz), 4.72 (1H, t, J = 5.5 Hz), 4.30−4.34 (1H overlaped with CH_2), 4.29 (2H, t, J = 6.6 Hz), 4.10 (1H, q, J = 3.2 Hz), 3.85 (1H, dd, J = 2.9 and 12.5 Hz), 3.72 (1H, dd, J = 3.3 and 12.4 Hz), 2.78 (2H, t, J = 7.7 Hz), 2.06 (2H, dt, J = 6.4 and 15.3 Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{19}H_{24}N_5O_5$ $(M + H)^+$, 402.1777; found, 402.1771; HPLC (system A) 14.1 min (99%), (system C) 10.7 min (99%).

2-(3″-Indolylethyloxy)adenosine (17). The yield was 72%: ^{1}H NMR (CD_3OD) δ 8.12 (1H, s), 7.60 (1H, d with small coupling, J = 7.7 Hz), 7.32 (1H, d with small coupling, J = 7.7 Hz), 7.15 (1H, s), 7.07 (1H, dt, J = 1.2 and 7.5 Hz), 7.01 (1H, dt, J = 1.2 and 7.3 Hz), 5.90 (1H, d, J = 5.5 Hz), 4.71 (1H, t, J = 5.5 Hz), 4.58 (2H, m), 4.31 (1H, dd, J = 3.6 and 5.2 Hz), 4.11 (1H, q, J = 3.2 Hz), 3.85 (1H, dd, J = 2.8 and 12.4 Hz), 3.73 (1H, dd, J = 3.4 and 12.2 Hz), 3.24 (2H, t, J = 7.3 Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{20}H_{23}N_6O_5$ $(M + H)^+$, 427.1730; found, 427.1711; HPLC (system A) 11.4 min (99%), (system C) 9.3 min (99%).

2-(3″-(1″-(*p*-Toluenesulfonyl)indolyl)ethyloxy)adenosine (18). The yield was 60%: ^{1}H NMR (CD_3OD) δ 8.14 (1H, s), 7.93 (1H, d with small coupling, J = 7.4 Hz), 7.70 (2H, d with small coupling, J = 8.2 Hz), 7.59 (2H, m), 7.29 (1H, dt, J = 1.7 and 8.1 Hz), 7.23 (1H, dt, J = 1.5 and 8.1 Hz), 7.17 (2H, d, J = 8.0 Hz), 5.90 (1H, d, J = 6.0 Hz), 4.73 (1H, t, J = 5.6 Hz), 4.57 (2H, m), 4.33 (1H, dd, J = 3.2 and 5.1 Hz), 4.12 (1H, q, J = 3.0 Hz), 3.88 (1H, dd, J = 2.8 and 12.4 Hz), 3.74 (1H, dd, J = 3.3 and 12.4 Hz), 3.14 (2H, t, J = 6.3 Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{27}H_{29}N_6O_7S$ $(M + H)^+$, 581.1818; found, 581.1797; HPLC (system B) 16.5 min (99%), (system C) 16.7 min (99%).

2-(3″-Pyrrolylethyloxy)adenosine (19). The yield was 57%: ^{1}H NMR (CD_3OD) δ 8.11 (1H, s), 6.63 (2H, d, J = 2.2 Hz), 6.04 (1H, t, J = 2.1 Hz), 5.88 (1H, d, J = 5.8 Hz), 4.72 (1H, t, J = 5.5 Hz), 4.42 (2H, t, J = 7.4 Hz), 4.31 (1H, dd, J = 3.4 and 5.1 Hz), 4.10 (1H, q, J = 3.2 Hz). 3.85 (1H, dd, J = 3.0 and 12.4 Hz), 3.73 (1H, dd, J = 3.6 and 12.4 Hz), 2.91 (2H, t, J = 7.3 Hz); HRMS

(ESI-MS *m*/*z*) calcd for $C_{16}H_{21}N_6O_5$ $(M + H)^+$, 377.1573; found, 377.1577; HPLC (system A) 4.5 min (99%), (system C) 4.7 min (99%).

2-(2″-Indolylethyloxy)adenosine (20). The yield was 32%: ^{1}H NMR (CD_3OD) δ 8.08 (1H, s), 7.37 (1H, d with small couplings, $J = 7.4$ Hz), 7.25 (1H, d with small coupling, $J = 8.0$ Hz), 6.97 (1H, dt, $J = 1.4$ and 7.1 Hz), 6.88 (1H, dt, $J = 1.1$ and 7.2 Hz), 6.21 (1H, d, $J = 0.8$ Hz), 5.86 (1H, d, $J = 5.8$ Hz), 4.69 (1H, t, $J = 5.5$ Hz), 4.57 (2H, t, $J = 6.6$ Hz), 4.30 (1H, dd, $J = 3.3$ and 5.2 Hz), 4.08 (1H, q, $J = 3.3$ Hz), 3.83 (1H, dd, $J = 2.9$ and 12.2 Hz), 3.72 (1H, dd, $J = 3.3$ and 12.4 Hz), 3.18 (2H, t, $J = 6.7$ Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{20}H_{23}N_6O_5$ $(M + H)^+$, 427.1730; found, 427.1735; HPLC (system A) 14.6 min (99%), (system C) 10.9 min (99%).

2-(2″-(1″-(*p*-Toluenesulfonyl)indolyl)ethyloxy)adenosine (21). The yield was 55%: ^{1}H NMR ($CDCl_3$) δ 8.10 (1H, d, $J = 8.2$ Hz), 7.57−7.64 (3H, m), 7.37 (1H, d, $J = 7.7$ Hz), 7.11−7.26 (4H, m), 6.52 (1H, s), 5.71 (1H, d, $J = 6.9$ Hz), 5.66 (2H, br s), 5.03 (1H, t, $J = 6.9$ Hz), 4.62 (1H, m), 4.46 (2H, m), 4.27 (1H, s), 3.89 (1H, d, $J = 11.5$ Hz), 3.74 (1H, d, $J = 11.5$ Hz), 3.43 (2H, m), 3.19 (1H, br s), 2.30 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{27}H_{29}N_6O_7S$ $(M + H)^+$, 581.1818; found, 581.1802; HPLC (system A) 23.0 min (99%), (system C) 16.7 min (99%).

2-(3″-(5″-Fluoro-indolyl)ethyloxy)adenosine (22). The yield was 80%: ^{1}H NMR (CD_3OD) δ 8.12 (1H, s), 7.20∼7.30 (3H, m), 6.83 (1H, dt, $J = 2.5$ and 9.1 Hz), 5.89 (1H, d, $J = 5.8$ Hz), 4.72 (1H, t, $J = 5.5$ Hz), 4.55 (2H, t, $J = 7.0$ Hz), 4.31 (1H, dd, $J = 3.3$ and 5.2 Hz), 4.11 (1H, q, $J = 3.3$ Hz), 3.86 (1H, dd, $J = 2.8$ and 12.4 Hz), 3.73 (1H, dd, $J = 3.6$ and 12.4 Hz), 3.16 (2H, t, $J = 7.1$ Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{20}H_{21}N_6O_5FNa$ $(M + Na)^+$, 467.1455; found, 467.1479; HPLC (system A) 13.1 min (99%), (system C) 10.2 min (99%).

2-(3″-(5″-Chloro-indolyl)ethyloxy)adenosine (23). The yield was 54%: ^{1}H NMR (CD_3OD) δ 8.12 (1H, s), 7.55 (1H, d, $J = 1.9$ Hz), 7.28 (1H, dd, $J = 0.5$ and 8.5 Hz), 7.22 (1H, s), 7.03 (1H, dd, $J = 1.9$ and 8.5 Hz), 5.89 (1H, d, $J = 6.0$ Hz), 4.71 (1H, t, $J = 5.5$ Hz), 4.56 (2H, t, $J = 7.0$ Hz), 4.31 (1H, dd, $J = 3.6$ and 5.2 Hz), 4.11 (1H, q, $J = 3.2$ Hz), 3.86 (1H, dd, $J = 2.9$ and 12.5 Hz), 3.73 (1H, dd, $J = 3.3$ and 12.4 Hz), 3.17 (2H, t, $J = 7.0$ Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{20}H_{22}N_6O_5Cl$ $(M + H)^+$, 461.1340; found, 461.1332; HPLC (system A) 16.6 min (99%), (system C) 11.8 min (99%).

2-(3″-(5″-Bromo-indolyl)ethyloxy)adenosine (24). The yield was 70%: ^{1}H NMR (CD_3OD) δ 8.12 (1H, s), 7.70 (1H, d, $J = 1.9$ Hz), 7.24 (1H, d, $J = 8.8$ Hz), 7.20 (1H, s), 7.15 (1H, dd, $J = 1.8$ and 8.7 Hz), 5.89 (1H, d, $J = 5.8$ Hz), 4.71 (1H, t, $J = 5.5$ Hz), 4.56 (2H, t, $J = 7.0$ Hz), 4.32 (1H, dd, $J = 3.6$ and 5.2 Hz), 4.11 (1H, q, $J = 3.2$ Hz), 3.86 (1H, dd, $J = 2.8$ and 12.4 Hz), 3.73 (1H, dd, $J = 3.6$ and 12.4 Hz), 3.17 (2H, t, $J = 6.9$ Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{20}H_{22}N_6O_5Br$ $(M + H)^+$, 505.0835; found, 505.0822; HPLC (system A) 15.2 min(98%), (system C) 12.2 min (98%).

2-(3″-(5″-Iodo-indolyl)ethyloxy)adenosine (25). The yield was 56%: ^{1}H NMR (CD_3OD) δ 8.12 (1H, s) 7.89 (1H, dd, $J = 0.6$ and 1.7 Hz), 7.32 (1H, dd, $J = 1.7$ and 8.5 Hz), 7.16 (1H, s), 7.15 (1H, dd, $J = 0.6$ and 8.5 Hz), 5.89 (1H, d, $J = 5.8$ Hz), 4.71 (1H, t, $J = 5.5$ Hz), 4.55 (2H, t, $J = 7.0$ Hz), 4.32 (1H, dd, $J = 3.6$ and 5.2 Hz), 4.11 (1H, q, $J = 3.2$ Hz), 3.86 (1H, dd, $J = 2.8$ and 12.4 Hz), 3.73 (1H, dd, $J = 3.3$ and 12.4 Hz), 3.16 (2H, t, $J = 6.9$ Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{20}H_{22}N_6O_5I$ $(M + H)^+$, 553.0696; found, 553.0681; HPLC (system A) 19.0 min (98%), (system C) 13.1 min (98%).

2-(3″-(5″-Bromo-1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)adenosine (26). The yield was 68%: ^{1}H NMR (CD_3OD) δ 8.14 (1H, s), 7.86 (1H, dd, $J = 0.6$ and 8.8 Hz), 7.68−7.74 (3H, m), 7.63 (1H, s), 7.40 (1H, dd, $J = 1.8$ and 8.8 Hz), 7.18 (2H, d with small coupling, $J = 8.5$ Hz), 5.89 (1H, d, $J = 6.0$ Hz), 4.73 (1H, t, $J = 5.6$ Hz), 4.55 (2H, t, $J = 6.3$ Hz), 4.33 (1H, dd, $J = 3.3$ and 5.2 Hz), 4.12 (1H, q, $J = 3.0$ Hz), 3.89 (1H, dd, $J = 2.9$ and 12.5 Hz), 3.74 (1H, dd, $J = 3.3$ and 12.4 Hz), 3.11 (2H, t, $J = 6.2$ Hz), 2.27 (3H, s); HRMS (ESI MS *m*/*z*) calcd for $C_{27}H_{28}N_6O_7BrS$ $(M + H)^+$, 659.0924; found, 659.0921.

2-(3″-(6″-Chloro-indolyl)ethyloxy)adenosine (27). The yield was 54%: ^{1}H NMR (CD_3OD) δ 8.08 (1H, s), 7.52 (1H, d, $J = 8.5$ Hz), 7.27 (1H, d, $J = 1.7$ Hz), 7.13 (1H, s), 6.95 (1H, dd, $J = 1.9$ and 8.5 Hz), 5.86 (1H, d, $J = 6.0$ Hz), 4.67 (1H, t, $J = 5.5$ Hz), 4.51 (2H, m), 4.28 (1H, dd, $J = 3.4$ and 5.1 Hz), 4.07 (1H, q, $J = 3.2$ Hz), 3.81 (1H, dd, $J = 2.8$ and 12.4 Hz), 3.69 (1H, dd, $J = 3.3$ and 12.4 Hz), 3.14 (2H, t, $J = 7.0$ Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{20}H_{22}N_6O_5Cl$ $(M + H)^+$, 461.1340; found, 461.1339; HPLC (system A) 15.7 min (99%), (system C) 11.9 min (99%).

2-(3″-(6″-Bromo-indolyl)ethyloxy)adenosine (28). The yield was 71%: ^{1}H NMR (CD_3OD) δ 8.12 (1H, s), 7.52 (1H, d, $J = 8.5$ Hz), 7.48 (1H, d, $J = 1.7$ Hz), 7.17 (1H, s), 7.12 (1H, dd, $J = 1.7$ and 8.5 Hz), 5.90 (1H, d, $J = 5.8$ Hz), 4.71 (1H, t, $J = 5.5$ Hz), 4.56 (2H, m), 4.31 (1H, dd, $J = 3.3$ and 5.2 Hz), 4.11 (1H, q, $J = 3.2$ Hz), 3.85 (1H, dd, $J = 3.4$ and 12.2 Hz), 3.73 (1H, dd, $J = 3.4$ and 12.2 Hz), 3.21 (2H, t, $J = 7.2$ Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{20}H_{22}N_6O_5Br$ $(M + H)^+$, 505.0835; found, 505.0840; HPLC (system A) 18.1 min (98%), (system C) 12.6 min (98%).

2-(3″-(4″-Bromo-indolyl)ethyloxy)adenosine (29). The yield was 44%: ^{1}H NMR (CD_3OD) δ 8.11 (1H, s), 7.31 (1H, dd, $J = 0.8$ and 8.0 Hz), 7.24 (1H, s), 7.16 (1H, dd, $J = 0.8$ and 7.4 Hz), 6.93 (1H, t, $J = 7.8$ Hz), 5.89 (1H, d, $J = 6.0$ Hz), 4.71 (1H, t, $J = 5.5$ Hz), 4.60 (2H, m), 4.31 (1H, dd, $J = 3.6$ and 5.0 Hz), 4.10 (1H, q, $J = 3.2$ Hz), 3.85 (1H, dd, $J = 2.9$ and 12.5 Hz), 3.73 (1H, dd, $J = 3.4$ and 12.5 Hz), 3.47 (1H, t, $J = 7.1$ Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{20}H_{22}N_6O_5Br$ $(M + H)^+$, 505.0835; found, 505.0843; HPLC (system A) 15.3 min (99%), (system C) 11.7 min (99%).

2-(3″-(7″-Bromo-indolyl)ethyloxy)adenosine (30). The yield was 27%: ^{1}H NMR (CD_3OD) δ 8.12 (1H, s), 7.60 (1H, d, $J = 8.0$ Hz), 7.25 (1H, d, $J = 7.4$ Hz), 7.24 (1H, s), 6.95 (1H, t, $J = 7.8$ Hz), 5.90 (1H, d, $J = 5.8$ Hz), 4.71 (1H, t, $J = 5.6$ Hz), 4.58 (2H, m), 4.31 (1H, dd, $J = 3.6$ and 4.9 Hz), 4.11 (1H, q, $J = 3.2$ Hz), 3.85 (1H, dd, $J = 2.9$ and 12.2 Hz), 3.73 (1H, dd, $J = 3.3$ and 12.4 Hz), 3.20 (2H, t, $J = 6.9$ Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{20}H_{22}N_6O_5Br$ $(M + H)^+$, 505.0835; found, 505.0837; HPLC (system A) 15.9 min (99%), (system C) 12.1 min (99%).

2-(3″-(5″-Methoxy-2″-methylindolyl)ethyloxy)adenosine (31). The yield was 29%: ^{1}H NMR (CD_3OD) δ 8.13 (1H, s), 7.10 (1H, dd, $J = 0.6$ and 8.8 Hz), 6.96 (1H, d, $J = 2.2$ Hz), 6.65 (1H, dd, $J = 2.3$ and 8.7 Hz), 5.90 (1H, d, $J = 5.8$ Hz), 4.68 (1H, t, $J = 5.5$ Hz), 4.47 (2H, m), 4.30 (1H, dd, $J = 3.6$ and 5.2 Hz), 4.10 (1H, q, $J = 3.2$ and 6.5 Hz), 3.84 (1H, dd, $J = 2.9$ and 12.2 Hz), 3.72 (1H, dd, $J = 3.3$ and 12.4 Hz), 3.13 (2H, t, $J = 7.3$ Hz), 2.37 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{22}H_{26}N_6O_8Na$ $(M + Na)^+$, 493.1812; found, 493.1792; HPLC (system A) 11.8 min (98%), (system C) 9.4 min (98%).

2-(3″-(5″-Methoxy-2″-methyl-1″-(p-toluenesulfonyl)indolyl)-ethyloxy)adenosine (32). The yield was 71%: ^{1}H NMR (CD_3OD) δ 8.12 (1H,s), 7.96 (1H, d, $J = 9.1$ Hz), 7.52 (2H, d, $J = 8.5$ Hz), 7.11 (2H, d, $J = 8.5$ Hz), 6.92 (1H, d, $J = 2.5$ Hz), 6.82 (1H, dd, $J = 2.5$ and 9.1 Hz), 5.87 (1H, d, $J = 6.0$ Hz), 4.66 (1H, t, $J = 5.6$ Hz), 4.41 (2H, m), 4.29 (1H, dd, $J = 3.2$ and 5.1 Hz), 4.10 (1H, q, $J = 2.9$ Hz), 3.82 (1H, dd, $J = 2.8$ and 12.4 Hz), 3.77 (3H, s), 3.70 (1H, dd, $J = 3.2$ and 12.5 Hz), 3.06 (2H, t, $J = 6.6$ Hz), 2.56 (3H, s), 2.21 (3H, s); HRMS (ESI-MS *m*/*z*) calcd for $C_{29}H_{33}N_6O_8S$ $(M + H)^+$, 625.2081; found, 625.2079; HPLC (system B) 17.3 min (99%), (system C) 17.6 min (99%).

2-(3″-(5″-Methoxy-indolyl)ethyloxy)adenosine (33). The yield was 54%: ^{1}H NMR (CD_3OD) δ 8.12 (1H, s), 7.20 (1H, d, $J = 8.8$ Hz), 7.12 (1H, s), 7.05 (1H, d, $J = 2.5$ Hz), 6.73 (1H, dd, $J = 2.5$ and 8.8 Hz), 5.89 (1H, d, $J = 5.8$ Hz), 4.71 (1H, t, $J = 5.5$ Hz), 4.56 (2H, t, $J = 7.1$ Hz), 4.31 (1H, dd, $J = 3.3$ and 5.2 Hz), 4.10 (1H, q, $J = 3.2$ Hz), 3.84 (1H, dd, $J = 2.8$ and 12.4 Hz), 3.72 (1H, dd, $J = 3.3$ and 12.4 Hz), 3.18 (2H, t, $J = 7.1$ Hz); HRMS (ESI-MS *m*/*z*) calcd for $C_{21}H_{25}N_6O_6$ $(M + H)^+$, 457.1836; found, 457.1815; HPLC (system A) 10.7 min (98%), (system C) 8.8 min (98%).

2-(3″-(5″-Hydroxyindolyl)ethyloxy)adenosine (34). The yield was 31%; ^{1}H NMR (CD_3OD) δ 8.12 (1H, s), 7.15 (1H, dd, J = 0.6 and 8.8 Hz), 7.09 (1H, s), 7.01 (1H, dd, J = 0.5 and 2.5 Hz), 6.65 (1H, dd, J = 2.3 and 8.4 Hz), 5.90 (1H, d, J = 5.8 Hz), 4.72 (1H, t, J = 5.6 Hz), 4.54 (2H, t, J = 7.4 Hz), 4.31 (1H, dd, J = 3.3 and 5.2 Hz), 4.11 (1H, q, J = 3.2 Hz), 3.86 (1H, dd, J = 2.7 and 12.4 Hz), 3.74 (1H, dd, J = 3.3 and 12.4 Hz), 3.13 (2H, t, J = 7.3 Hz); HRMS (ESI-MS m/z) calcd for $C_{20}H_{22}N_6O_6Na$ $(M + Na)^+$, 465.1499; found, 465.1471; HPLC (system A) 5.5 min (98%), (system C) 5.3 min (98%).

2-(3″-(Benzoimidazole-1″-yl)ethyloxy)adenosine (35). The yield was 57%: ^{1}H NMR (CD_3OD) δ 8.22 (1H, s), 8.10 (1H, s), 7.62 (2H, d with small coupling, J = 8.2 Hz), 7.31 (1H, dt, J = 1.2 and 7.6 Hz), 7.24 (1H, dt, J = 1.3 and 7.6 Hz), 5.84 (1H, d, J = 5.8 Hz), 4.63 − 4.74 (5H, m), 4.31 (1H, dd, J = 3.2 and 5.1 Hz), 4.11 (1H, q, J = 3.0 Hz), 3.86 (1H, dd, J = 2.8 and 12.4 Hz), 3.73 (1H, dd, J = 3.0 and 12.4 Hz); HRMS (ESI-MS m/z) calcd for $C_{19}H_{22}N_7O_5$ $(M + H)^+$, 428.1682; found, 428.1691; HPLC (system A) 4.9 min (99%), (system D) 8.3 min (99%).

2-(3″-(Benzotriazole-1″-yl)ethyloxy)adenosine (36). The yield was 40%: ^{1}H NMR (CD_3OD) δ 8.10 (1H, s), 7.93(1H, dt, J = 1.0 and 7.4 Hz), 7.80 (1H, dt, J = 0.8 and 8.2 Hz), 7.52 (1H, ddd, J = 1.0, 7.1 and 8.1 Hz), 7.38 (1H, ddd, J = 1.0, 7.1 and 8.1 Hz), 5.83 (1H, d, J = 5.8 Hz), 5.13 (2H, m), 4.82−4.92 (2H, m, overlapped with HDO), 4.64 (1H, t, J = 5.6 Hz), 4.31 (1H, dd, J = 3.3 and 5.2 Hz), 4.10 (1H, q, J = 3.1 Hz), 3.83 (1H, dd, J = 2.8 and 12.6 Hz), 3.72 (1H, dd, J = 3.3 and 12.4 Hz); HRMS (ESI-MS m/z) calcd for $C_{18}H_{21}N_8O_5$ $(M + H)^+$, 429.1635; found, 429.1642; HPLC (system A) 4.7 min (99%), (system C) 4.8 min (99%).

6-Guanidino-2-(3″-indolylethyloxy)adenosine (37) and 6-Guanidino-2-(3″-(1″-(*p*-toluenesulfonyl)indolyl)ethyloxy)adenosine (38). To a solution of guanidine hydrochloride (98 mg, 1.02 mmol) in acetonitrile (2.2 mL) and *N*,*N*-dimethylformamide (1.1 mL) was added sodium hydride (60%; 41.2 mg, 1.02 mmol) at room temperature, and the reaction mixture was stirred overnight. This guanidine solution was added to a mixture of compound **102** (46 mg, 0.0633 mmol) and 1,4-diazabicyclo[2.2.2]octane (14 mg, 0.0126 mmol), and the resulting mixture was stirred overnight at 110 °C and filtered. The filtrate was evaporated to give a crude oil, which was subjected to preparative TLC developed with a mixture of chloroform, methanol, and saturated aqueous ammonia (2:1:0.3) to give **37** (2.3 mg, 8%) and **38** (9 mg, 23%) as an amorphous solid.

37: ^{1}H NMR (CD_3OD) δ 8.09 (1H, s), 7.60 (1H, d with small coupling, J = 7.7 Hz), 7.32 (1H, d with small coupling, J = 7.2 Hz), 7.16 (1H, s), 7.08 (1H, dt, J = 1.3 and 7.6 Hz), 7.01 (1H, dt, J = 1.2 and 7.3 Hz), 5.90 (1H, d, J = 6.0 Hz), 4.73 (1H, t, J = 5.5 Hz), 4.54 (2H, t, J = 7.1 Hz), 4.32 (1H, dd, J = 3.3 and 4.9 Hz), 4.12 (1H, q, J = 3.0 Hz), 3.87 (1H, dd, J = 2.8 and 12.6 Hz), 3.73 (1H, dd, J = 3.3 and 12.4 Hz), 3.24 (2H, t, J = 7.4 Hz); HRMS (ESI-MS m/z) calcd for $C_{21}H_{25}N_8O_5$ $(M + H)^+$, 469.1948; found, 469.1952; HPLC (system B) 8.9 min (97%), (system D) 7.5 min (97%).

38: ^{1}H NMR (CD_3OD) δ 8.25 (1H, s), 7.93 (1H, dd, J = 1.4 and 7.4 Hz), 7.71 (2H, d with small coupling, J = 8.5 Hz), 7.61 (1H, dd, J = 1.4 and 7.1 Hz), 7.59 (1H, s), 7.30 (1H, dt, J = 1.2 and 7.6 Hz), 7.24 (1H, dt, J = 1.2 and 7.6 Hz), 7.18 (2H, d with small coupling, J = 8.5 Hz), 5.96 (1H, d, J = 6.0 Hz), 4.74 (1H, t, J = 5.5 Hz), 4.59 (2H, t, J = 6.5 Hz), 4.35 (1H, dd, J = 3.4 and 5.1 Hz), 4.13 (1H, q, J = 3.2 Hz), 3.89 (1H, dd, J = 2.9 and 12.5 Hz), 3.76 (1H, dd, J = 3.6 and 12.4 Hz), 3.18 (2H, t, J = 6.5 Hz), 3.26 (3H, s); HRMS (ESI-MS m/z) calcd for $C_{28}H_{31}N_8O_7S$ $(M + H)^+$, 623.2036; found, 623.2045; HPLC (system A) 16.3 min (97%), (system C) 8.7 min (97%).

6-Ethylamino-2-(3″-indolyl)ethyloxy)adenosine (39). To a solution of **102** (28.3 mg, 0.0389 mmol) in DMF (1.4 mL) in a sealed tube were added ethylamine hydrochloride (63.5 mg, 0.779 mmol) and *N*,*N*-diisopropylethylamine (0.271 mL), and the reaction mixture was stirred at 140 °C overnight and evaporated to give an oil. The oil was dissolved in methanol (1 mL), KOH (14.6 mg, 0.261 mmol) was added, and the reaction mixture was stirred for 42 h at 80 °C. The solvent was evaporated to give a crude solid that was subjected to preparative TLC developed with a mixture of chloroform and methanol (5:1) to give **39** (2.2 mg, 28% yield in two steps). ^{1}H NMR (CD_3OD) δ 8.05 (1H, s), 7.60 (1H, d with small coupling, J = 7.1 Hz), 7.32 (1H, d with small coupling, J = 7.7 Hz), 7.14 (1H, s), 7.07 (1H, dt, J = 1.3 and 7.6 Hz), 7.00 (1H, dt, J = 1.1 and 7.4 Hz), 5.87 (1H, d, J = 6.0 Hz), 4.71 (1H, t, J = 5.6 Hz), 4.60 (2H, t, J = 7.0 Hz), 4.30 (1H, dd, J = 3.2 and 5.1 Hz), 4.11 (1H, q, J = 3.0 Hz), 3.86 (1H, dd, J = 2.6 and 12.5 Hz), 3.73 (1H, dd, J = 3.2 and 12.5 Hz), 3.50−3.66 (2H, br m), 3.22 (2H, t, J = 7.1 Hz), 1.26 (3H, t, J = 7.3 Hz); HRMS (ESI-MS m/z) calcd for $C_{22}H_{27}N_6O_5$ $(M + H)^+$, 455.2043; found, 455.2063; HPLC (system A) 19.5 min (99%), (system C) 13.5 min (99%).

(2*R*,3*S*,4*S*,5*R*)-6-Amino-5-ethylcarboxyamide-2-(3″-indolyl)-ethyloxy)-purin-9-yl)-tetrahydrofuran (40). Potassium hydroxide (12.6 mg, 0.025 mmol) was added to a solution of **134** (7.0 mg, 0.0112 mmol) in methanol (1.5 mL), and the reaction mixture was stirred at 70 °C overnight. The mixture was evaporated to a small amount of solution that was subjected to preparative TLC developed with a mixture of chloroform and methanol (5:1) to give **40** (1.7 mg, 33% yield). ^{1}H NMR (CD_3OD) δ 8.06 (1H, s), 7.56 (1H, d with small coupling, J = 8.0 Hz), 7.32 (1H, d with small coupling, J = 8.0 Hz), 7.11 (1H, s), 7.08 (1H, dt, J = 1.2 and 8.1 Hz), 7.00 (1H, dt, J = 1.1 and 8.1 Hz), 5.91 (1H, d, J = 7.4 Hz), 4.74 (1H, dd, J = 4.8 and 7.3 Hz), 4.61 (2H, m), 4.41 (1H, d, J = 1.9 Hz), 4.30 (1H, dd, J = 1.7 and 4.9 Hz), 3.15−3.26 (4H, m), 0.99 (3H, t, J = 7.2 Hz); HRMS (ESI MS m/z) calcd for $C_{22}H_{26}N_7O_5$ $(M + H)^+$, 468.1995; found, 468.2015; HPLC (system A) 15.7 min (98%), (system C) 11.4 min (98%).

Pharmacological Methods. [^{125}I]N^6-(4-amino-3-iodobenzyl)-adenosine-5′-*N*-methyluronamide (I-AB-MECA; 2000 Ci/mmol), [^{3}H]CCPA (2-chloro-N^6-cyclopentyladenosine, 42.6 Ci/mmol), [^{3}H]-CGS21680 (2-[*p*-(2-carboxyethyl)phenylethylamino]-5′-*N*-ethylcarboxamido-adenosine, 47 Ci/mmol), and [^{3}H]cyclic AMP (40 Ci/mmol) were from Amersham Pharmacia Biotech (Buckinghamshire, U.K.).

Cell Culture and Membrane Preparation. CHO (Chinese hamster ovary) cells expressing the recombinant human ARs[26] were cultured in DMEM supplemented with 10% fetal bovine serum, 100 units/mL penicillin, 100 μg/mL streptomycin, 2 μmol/mL glutamine, and 800 μg/mL geneticin. Cells were harvested by trypsinization. After homogenization and suspension, cells were centrifuged at 500 *g* for 10 min, and the pellet was resuspended in 50 mM Tris-HCl buffer (pH 8.0) containing 10 mM $MgCl_2$, 1 mM EDTA, and 0.1 mg/mL CHAPS. The suspension was homogenized with an electric homogenizer for 10 s and was then recentrifuged at 20 000 *g* for 20 min at 4 °C. The resultant pellets were resuspended in buffer in the presence of 3 units/mL adenosine deaminase, and the suspension was stored at −80 °C until the binding experiments. The protein concentration was measured using the Bradford assay.[43]

Binding Assay. Human A_1 and A_{2A} Receptors: For binding to human A_1 receptors, [^{3}H]CCPA (1 nM) was incubated with membranes (40 μg/tube) from CHO cells stably expressing human A_1 receptors at 25 °C for 60 min in 50 mM Tris-HCl buffer (pH 7.4; $MgCl_2$, 10 mM) in a total assay volume of 200 μL. Nonspecific binding was determined using 10 μM of CPA. For human A_{2A} receptor binding, membranes (20 μg/tube) from HEK-293 cells stably expressing human A_{2A} receptors were incubated with 15 nM [^{3}H]CGS21680 at 25 °C for 60 min in 200 μL of 50 mM Tris-HCl, pH 7.4, containing 10 mM $MgCl_2$. NECA (10 μM) was used to define nonspecific binding. Reaction was terminated by filtration with GF/B filters.

Human A_3 Receptor: For competitive binding assay, each tube contained 100 μL of membrane suspension (20 μg protein), 50 μL of [^{125}I]I-AB-MECA (0.5 nM), and 50 μL of increasing concentrations of the nucleoside derivative in Tris-HCl buffer (50 mM, pH 7.4) containing 10 mM $MgCl_2$ and 1 mM EDTAPRIVATE. Nonspecific binding was determined using 10 μM of Cl-IB-MECA in the buffer. The mixtures were incubated at 25 °C for 60 min.

Binding reactions were terminated by filtration through Whatman GF/B filters under reduced pressure using a MT-24 cell harvester (Brandell, Gaithersburgh, MD). Filters were washed three times with 9 mL of ice-cold buffer. Radioactivity was determined in a Beckman 5500B γ-counter.

Cyclic AMP Accumulation Assay. Intracellular cyclic AMP levels were measured with a competitive protein binding method.[44,45] CHO cells that expressed recombinant human A_3ARs were harvested by trypsinization. After centrifugation and resuspension in medium, cells were plated in 24-well plates in 1.0 mL of medium. After 24 h, the medium was removed and cells were washed three times with 1 mL of DMEM, containing 50 mM HEPES, pH 7.4. Cells were then treated with agonists and/or test compounds in the presence of rolipram (10 μM) and adenosine deaminase (3 units/mL). After 45 min, forskolin (10 μM) was added to the medium, and incubation was continued an additional 15 min. The reaction was terminated upon removal of the supernatant, and cells were lysed upon the addition of 200 μL of 0.1 M ice-cold HCl. The cell lysate was resuspended and stored at −20 °C. For determination of cyclic AMP production, protein kinase A (PKA) was incubated with [^{3}H]cyclic AMP (2 nM) in K_2HPO_4/EDTA buffer (K_2HPO_4, 150 mM; EDTA, 10 mM), 20 μL of the cell lysate, and 30 μL of 0.1 M HCl or 50 μL of cyclic AMP solution (0−16 pmol/200 μL for standard curve). Bound radioactivity was separated by rapid filtration through Whatman GF/C filters and washed once with cold buffer. Bound radioactivity was measured by liquid scintillation spectrometry.

Statistical Analysis. Binding and functional parameters were calculated using Prism 4.0 software (GraphPAD, San Diego, CA). IC_{50} values obtained from competition curves were converted to K_i values using the Cheng−Prusoff equation.[46] Data were expressed as mean ± standard error.

Molecular Modeling. A published molecular model of the human A_{2B}AR in which (*S*)-PHP-NECA was docked[38] was utilized to study the binding mode of **28**. Toward this goal, the ribose and adenine moieties of **28** were superimposed upon the corresponding moieties of (*S*)-PHP-NECA located inside the binding site. Then (*S*)-PHP-NECA was removed from the receptor. The obtained complex of the A_{2B}AR with **28** was subjected to MCMM calculations using MacroModel software.[39] The MCMM calculations were performed for **28** and all residues located within 5 Å from the ligand, using a shell of residues located within 2 Å. The following parameters were used: MMFFs force field, water was used as an implicit solvent, a maximum of 1000 iterations of the Polak−Ribier conjugate gradient (PRCG) minimization method was used with a convergence threshold of 0.05 kJ·mol^{-1}·Å^{-1}, the number of conformational search steps = 100, and the energy window for saving structures = 1000 kJ·mol^{-1}.

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